Exploring technological change in the German pharmaceutical industry

A history-friendly model of technological change and technology adoption in a science-based industry

Zur Erlangung des akademischen Grades eines Doktors der Wirtschaftswissenschaften

(Dr. rer. pol.)

von der Fakultät für Wirtschaftswissenschaften der Universität Fridericiana zu Karlsruhe

genehmigte

Dissertation

von

lic. rer. pol. Iciar Dominguez Lacasa

Tag der mündlichen Prüfung: 17. Juli 2005
Referent: Prof. Dr. Hariolf Grupp
Koreferent: Prof. Dr. Hagen Lindstädt

E R K L Ä R U N G

(gemäß §4, Abs. 4 der Promotionsordnung vom 21. April 1989)

Ich versichere wahrheitsgemäß, die Dissertation bis auf die in der Abhandlung angegebe Hilfe selbständig angefertigt, alle benutzten Hilfsmittel vollständig und genau angegeben und genau kenntlich gemacht zu haben, was aus Arbeiten anderer und aus eigenen Veröffentlichungen unverändert oder mit Abänderungen entnommen wurde.

Acknowledgements

The driving ideas for this project came from a working paper my supervisor gave me from the Danish Research Unit for Industrial Dynamics (DRUID). Already on the first pages I found a family of economic terms that were quite new for an economist with a strong neo-classical background like me: complex dynamics, behavioural patterns, invention, innovation, selection mechanisms, simulation model etc. Both, my curiosity to find out more about these terms and my interest for the economics of technological change motivated the learning process I have been involved in the last 4 years. This document is the result of this intellectual adventure. There are a number of people that have been important and I would like to thank here.

First, I would like to express my special thanks to Hariolf Grupp for providing me with enough intellectual freedom and guidance when I needed it to complete this effort. The support of Hagen Lindstädt and his comments in the final stage of my work have been very valuable as well.

I am also grateful to the research programme "Innovation Culture in Germany", funded by the German Federal Ministry for Education and Research, for giving me the opportunity to develop my work in an interdisciplinary context.

During the empirical field work with archival material I obtained guidance from Hans-Hermann Pogarell, Christina Sehnert, Christine Berghausen, Sabine Bernschneider-Reif and Manuela Kuhl. An important part of this project would have not been possible without the access to the historical archives of the corporations I have studied.

Additionally, I have benefit from discussions and lectures during the European Doctoral Training Program ETIC 2001 organised by Patrick Llerena. I am especially grateful to Esben Sloth Andersen and to Marco Valente for their intellectual support and for teaching me how to develop a simulation model. Moreover, a Marie Curie Fellowship from the European Commission has given me the opportunity to participate in interesting seminars and obtain useful comments from the researchers at CESPRI at Bocconi University and from the members of the IKE Group at Aalborg University. Their influence can be found throughout the next pages.

During my PhD I was very fortunate to work at the Fraunhofer Institute for Systems and Innovation Research (ISI) where I learnt a lot from Thomas Reiss and Ulrich Schmoch. My colleagues at the Emerging Technologies Department have supported me since the beginning of the project with exceptional working conditions and good humour. Stefan

Wörner, Bernhard Bührlen and Ralf Lindner have given me stimulating comments on earlier drafts of my work. My literature requests had been greatly managed by Martina Fuchs-Blum and Silvia Rheinemann. Silke Just has strongly supported me with the final layout. It is a great pleasure to acknowledge their encouragement and support and to thank them for it.

I would also like to thank the other PhD students at Fraunhofer ISI for their interest and encouragement during the project and especially in the days before my exam. Without their support I would have never been able to prepare a 30-minutes-talk for defending my work in July 2005. They have all been excellent colleagues and I have very much enjoyed working with them.

My last words of thanks go to Christoph Bayer for distracting and inspiring me with his pioneer projects. Dealing with my mood in the in the last stages of my PhD was a fantastic achievement and I thank him for his patience.

Iciar Dominguez Lacasa
Karlsruhe, December 2005

List of contents Page

List of tables i

List of figures iii

1 Introduction 1

1.1 Technological change in the pharmaceutical industry 1

1.2 Technological change from an evolutionary perspective 3

2 Theoretical and methodological framework 7

2.1 Introduction 7

2.2 The building blocks of evolutionary economics 8

2.2.1 The Austrian School 9

2.2.2 Institutional Economics: the legacy of Thorstein Veblen and the developments of new Institutional Economics 10

2.2.3 Neo-Schumpeterian Economics: the work influenced by Schumpeter 11

2.3 A conceptualisation of the nature of technology 15

2.3.1 General principles to characterise technology 17

2.4 Technological change from an evolutionary perspective 19

2.4.1 The emergence of technologies (or the search for alternative technological solutions and the creation of variety) 21

2.4.2 Technology diffusion (or the ex-post selection mechanisms in the process of technological change) 24

2.4.3 Taxonomies of technological change 25

2.4.3.1 Taxonomies focusing on the direction of technological change and on its paradigmatic basis 26

2.4.3.2 Taxonomies focusing on the impact of technological change on organisational capabilities 26

2.4.3.3 The impact of technological change on the whole economy 28

2.5 The firm in the process of technological change 29

Page

2.5.1 Theory of the firm in the Nelson and Winter approach 29
2.5.2 The knowledge-based view to the theory of the firm 31
2.5.2.1 The building blocks of a firm's knowledge base 31
2.5.2.2 Accumulation of knowledge for technological change: Organisational learning 32
2.5.2.3 Firm's performance in dynamic environments 33
2.6 Simulation models to explore technological change 36
2.6.1 Simulation models in socio-economic research 36
2.6.2 Value of simulation for the evolutionary approach to technological change 37
2.6.3 The Nelson and Winter simulation models 40
2.6.4 Evolutionary history-friendly modelling 41
2.6.5 Examples of evolutionary history-friendly models 43
2.7 Towards a history-friendly model of technological change and technology adoption in the German pharmaceutical industry 46

3 An appreciative theory of technological change and technology adoption in the German pharmaceutical industry during the 20th century 51

3.1 Introduction 51
3.2 Tracing the development of organic chemical synthesis and biotechnology 52
3.2.1 Organic chemical synthesis 55
3.2.2 Biotechnology 57
3.3 Technological change in the German pharmaceutical industry during the 20th century 60
3.4 The recognition and exploitation of modern biotechnology by 4 German drug producers 70
3.4.1 Organisational technological capabilities in the second half of the 20th century 72
3.4.2 Research traditions 73

Page

3.4.3 Attitudes towards the application of traditional biotechnology 75
3.4.4 Investment in research and development 77
3.4.5 Internal capabilities 78
3.4.6 Strategic collaboration....80
3.4.7 Discussion....81
3.5 Issues for a history-friendly model of technological change and technology adoption in the German pharmaceutical industry 83

4 A history-friendly model of technological change and technology adoption in the German pharmaceutical industry 91

4.1 Introduction 91
4.1.1 The search space....94
4.1.2 The technologies....95
4.1.3 The knowledge environment 97
4.1.4 Characterisation of the firm 98
4.1.5 Accumulation of technological capabilities 100
4.1.6 Firm's perception of discontinuities in the knowledge environment and adoption of the new technological opportunities 101
4.1.7 Collaboration....103
4.1.8 The innovation process 104
4.1.9 The selection environment 106
4.1.10 The transition dynamics 107
4.2 Simulation experiments....108
4.2.1 The history-friendly scenario 109
4.2.1.1 Exogenous discontinuities, firm entry and collaboration....111
4.2.1.2 Parameter setting regarding firms' strategic paradigms 113
4.2.1.3 Parameter setting regarding the technological regimes 114
4.2.1.4 History-friendly simulation results 116

Page

4.2.2 Counterfactuals: history-divergent scenarios 121
4.2.2.1 Scenario 1: Absence of discontinuities in the biotechnology knowledge base 123
4.2.2.2 Scenario 2: Firms focus on one type of learning 127
4.2.2.3 Scenario 3: Absence of adoption costs versus high level of adoption costs 131
4.2.2.4 Scenario 4: Absence of firm entry 136

5 Summary and conclusions 141

6 References 153

Annex 167

Annex 1: Case studies 169

Introduction 171
Case study 1: Hoechst 173
Case study 2: Bayer 180
Case study 3: Merck 186
Case study 4: Schering 192

Annex 2: Quantitative indicators for the case studies 201

Patent publications 203
Corporate expenditures in research and development 205
Human capital 207
Strategic collaborative arrangements 210

Annex 3: Parameter setting in the history-friendly scenario 219

Annex 4: Model's source code 225

List of tables Page

Table 1: Main schools of economic thought contributing to the development of evolutionary economics 8

Table 2: Taxonomy of firm's learning processes 32

Table 3: Levels of aggregation in evolution 47

Table 4: The biotechnological trajectory. 53

Table 5: German drug producers at the beginning of the 20th century 74

Table 6: Investment volume in research and development in pharmaceuticals (in million German Mark and as a percentage of pharmaceutical sales)....77

Table 7: The exploitation of biotechnology by German drug producers and indicators to capture the adjustment to the advent of modern biotechnology 81

Table 8: Relevant parameters for the characterisation of the conditions for technological change in the different phases of the German pharmaceutical industry....85

Table 9: Firms' strategic paradigms: Variables for the characterisation of the firms in history-friendly simulation runs 113

Table 10: Relevant parameters for the characterisation of the technological regimes in the different phases of the industry in the history-friendly scenario 115

Table 11: History-friendly scenario: Firms' reaction to discontinuities in the knowledge environment (average over 100 simulation runs) 118

Table 12: Counterfactual scenario 2: Firms' reaction to discontinuities in the knowledge environment (100 simulation runs)....129

Table 13: Counterfactual scenario 3: Firms' reaction to discontinuities in the knowledge environment (100 simulation runs)....133

Table A 1: Patent classes for sector and technology definition 203

Table A 2: Patent data 204

Table A 3: Investment volume in research and development (in million German Mark and as a percentage of the total sales). 206

Page

Table A 4:	Human capital profile: Employees holding an academic degree according to their academic qualification (disciplines)	209
Table A 5:	Strategic collaborative arrangements per year and type	211
Table A 6:	Research partners Bayer	212
Table A 7:	Research partners Hoechst	214
Table A 8:	Research partners Merck	217
Table A 9:	Research partners Schering	218
Table A 10:	Parameter values history-friendly scenario	221
Table A 11 :	Initial values of variables that need to be initialised	223

List of figures

Page

Figure 1: Logic of simulation....36

Figure 2: System with micro-macro relationships....38

Figure 3: Micro-macro relationships in a model of technological change....47

Figure 4: Shares of biotechnology and organic chemistry-related patent documents in the total patent outcome....55

Figure 5: Patent documents in pharmaceuticals. Shares of biotechnology and organic chemistry-related patents....60

Figure 6: Direct project funding for biotechnology-related research in Germany (1970-2000)....68

Figure 7: Corporate patent documents in pharmaceuticals. Share of biotechnology and organic chemistry-related patent documents in the pharmaceutical corporate patent portfolio of Schering, Bayer, Hoechst and Merck and their main subsidiaries....72

Figure 8: Relevant achievements with the application of biotechnology and biotechnology research projects of Schering, Merck, Bayer and Hoechst....76

Figure 9: Human capital at Schering, Merck, Hoechst and Bayer: Qualification of the employees holding an academic degree....79

Figure 10: Number of biotechnology-related strategic agreements per patent application in pharmaceuticals....80

Figure 11: Artificial pharmaceutical industry: the basic structure of the model....92

Figure 12: Firm's decisions and its interactions within the system....93

Figure 13: The search space of drug candidates....95

Figure 14: Technologies to explore the search space. Technology B determines the firm's error of observation (σ_{jt}). Technology S determines the range of search space the firm can explore (S_{jt})....96

Figure 15: Probability to perceive and adopt new technological opportunities....102

Figure 16: Probability to innovate W_j^I....105

Page

Figure 17: Transition dynamics in the model 108

Figure 18: History-friendly scenario: Technological change in the industry (100 simulation runs and average) 117

Figure 19: History-friendly scenario: Technological capabilities of the incumbent firms (average 100 simulation runs) 118

Figure 20: History-friendly scenario: Number of collaborations of incumbent firms (average 100 simulation runs) 119

Figure 21: History-friendly scenario: Quality of firm's superior product candidates (average 100 simulation runs) 120

Figure 22: History-friendly scenario: Size of firm's product portfolio (average 100 simulation runs) 120

Figure 23: History-friendly scenario: Firm's reward from the selection environment (average 100 simulation runs) 121

Figure 24: Selected research issues for counterfactual analysis 122

Figure 25: Counterfactual scenario 1: Technological change in the industry (100 simulation runs and average) 123

Figure 26 Counterfactual scenario 1: Technological capabilities of incumbent firms (average 100 simulation runs) 124

Figure 27 Counterfactual scenario 1: Quality of firm's superior product candidates (average 100 simulation runs) 125

Figure 28 Counterfactual scenario 1: Size of firm's product portfolio (average 100 simulation runs) 125

Figure 29 Counterfactual scenario 1: Firm's reward from the selection environment (average 100 simulation runs) 126

Figure 30 Counterfactual scenario 2: Technological change in the industry (100 simulation runs and average) 127

Figure 31 Counterfactual scenario 2: Technological capabilities of the incumbent firms (average 100 simulation runs) 128

Figure 32 Counterfactual scenario 2: Quality of firm's superior product candidates (average 100 simulation runs) 129

Figure 33 Counterfactual scenario 2: Firm's reward from the selection environment (average 100 simulation runs) 130

Page

Figure 34 Counterfactual scenario 3: Technological change in the industry (100 simulation runs and average) 132

Figure 35 Counterfactual scenario 3: Technological capabilities of the incumbent firms (average 100 simulation runs).....133

Figure 36 Counterfactual scenario 3: Quality of firm's superior product candidates (average 100 simulation runs).....134

Figure 37 Counterfactual scenario 3: Firm's reward from the selection environment (average 100 simulation runs) 135

Figure 38 Counterfactual scenario 4: Technological change in the industry (100 simulation runs and average) 136

Figure 39 Counterfactual scenario 4: technological capabilities of the incumbent firms (average 100 simulation runs).....137

Figure 40 Counterfactual scenario 4: Quality of firm’s superior product candidates (average 100 simulation runs).....137

Figure 41 Counterfactual scenario 4: Size of firm's product portfolio (average 100 simulation runs) 138

Figure 42 Counterfactual scenario 4: Firm's reward from the selection environment (average 100 simulation runs) 138

1 Introduction

1.1 Technological change in the pharmaceutical industry

In simple words the pharmaceutical industry links activities and business accomplishing the discovery, development, production and commercialisation of drugs (i. e. products with therapeutic properties). Accordingly, product innovation is based on the search and development of molecules that may have desirable therapeutic effects. Basically new drugs can be developed either with the application of organic chemical synthesis or from the separation of compounds produced by natural microorganisms, which as an application of biotechnology[1]. The development of these technologies (chemical synthesis and biotechnology) during 19th and 20th centuries has tremendously changed the conditions for innovation in the pharmaceutical industry. An interesting aspect of the pharmaceutical industry is the interaction between science and technology. Scientific advances have contributed to the development of the knowledge base underlying drug discovery and development. Indeed, the pharmaceutical industry can be considered an extreme case of a science-based industry (Gambardella 1995). Accordingly, to exploit innovative opportunities, the companies in this industry (the drug producers) have been forced to develop new competencies for the application of the novel scientific advances (Santos 2003; Galambos, Sturchio 2003).

During the establishment of the modern pharmaceutical industry in the last decades of the 19th century, the scientific principles of organic chemistry guided drug discovery without providing understanding about the biological processes of diseases. However, this constraint did not prevent drug producers from developing promising drugs by synthesising compounds which could be tested for therapeutic properties using animal models. The German drug producers mastered this technology, which allowed them to dominate the industry until World War II.

In contrast, after a period of successful application at the beginning of the 20th century, biotechnology for drug production remained more or less a niche technology in pharmaceuticals until the 1960s.[2] Scientific advances in molecular biology and

1 Biotechnology refers to the processing of materials with biological agents to provide goods and services (Bull et al. 1982). The revolutionary discoveries in the 1970s of artificially controlled recombinant DNA (rDNA) enabled the direct manipulation of genetic material of biological agents involved in the processing of goods and services. The techniques of rDNA are the basis of modern biotechnology, which has created enormous expectations for industrial applications. The body of literature on innovation studies often uses the term "biotechnology revolution" to refer to this technological development. However, biotechnology has a long historical record (Bud 1993).

2 At the beginning of the 20th century microbiological applications and a large number of biotechnological processes had already been introduced. Waste water treatment, distillery, brewery, vinegar

biochemistry provided drug discovery with scientific knowledge on protein structure and on the function of proteins. To describe the contributions of biochemistry and of molecular biology in pharmaceuticals scholars refer to a transition from a chemical/ random screening to a biological drug design model (Gambardella 1995; Henderson et al. 1999). Moreover, after the 1970s, with the discoveries of recombinant DNA (rDNA) and monoclonal antibodies, biotechnology became a key tool for drug discovery and development and production. However, German actors in the pharmaceutical industry had problems in adjusting to the dynamics of the knowledge environment of the industry. Germany's innovative performance in the pharmaceutical industry in the last half of the 20th century has been very disappointing, especially if compared with the strength of the industry before World War I.

Due, on the one hand, to the revolutionary character of the rDNA discovery (which provided encouraging prospects of being able to develop complex protein-based drugs and understanding its effects) and on the other hand, to the emergence of a biotechnology industry in the west and east coasts of the USA (which appeared to facilitate the access to skills in genetic engineering to those actors not involved in academic research), the emergence of modern biotechnology in the 1970s has attracted increasing attention of policy-makers and social scientists for these developments.

Contributions to innovation studies and explorations of industry dynamics and processes of creative destruction have chosen the advent of modern biotechnology in the pharmaceutical to study, among other issues, the reactions of incumbents in the pharmaceutical industry to the shift in their knowledge environment. However, in general terms, the studies analysing the reactions of incumbent drug producers to the new technological opportunities after the 1970s do not consider explicitly the historical conditioning of technological change, a process where history matters. An exception is Henderson (1994), who traces the development of the competencies of pharmaceutical companies involved in drug discovery in the last quarter of the 20th century.

This contribution aims at exploring technological change in the German pharmaceutical industry to unfold the mechanisms underpinning the changes in the relative importance of technologies, to identify the factors driving these transitions and the consequences for industry incumbents. The study aims at understanding the processes, develop a model formalising them and testing the outcomes against historical experience.

production, wine production, creamery, tannery, fertilizers, sugar production and production of organic acids were some of the fields and production processes were biotechnology was first applied (Marschall 2000).

1.2 Technological change from an evolutionary perspective

How does technological change in the pharmaceutical industry occur? Which are the mechanisms shaping the relative importance of technologies and their development paths? How do firms contribute to these processes? How do firms react when new technologies emerge outperforming the technologies they master?

This study attempts to understand these processes guided by evolutionary theory. Dosi and Nelson (1994, p. 154) use the term “evolutionary” to define theories, models or arguments with the following characteristics:

i. The analysis is explicitly dynamic. The purpose is to explain why something is what it is a certain moment in time in terms of how it got there.

ii. The explanation involves random elements which generate some variation in the variables in question.

iii. The models involve some processes of imperfect (mistake-ridden) learning and discovery and some selection processes.

iv. The selection processes imply the identification of a unit of selection (profit, price, quality etc.) and certain mechanisms through which selection operates.

Evolutionary theories, models or arguments may match these features more or less precisely, depending on the issues explored and on the authors analysing them. However, the term “evolutionary” in economic models explicitly rejects the neo-classical scenario of general equilibrium and its assumption of rational agents following profit maximising patterns.

There are several reasons why we consider the evolutionary framework as appropriate to explore technological change.

Firstly, it provides comprehensive theoretical explanations suggesting that the aggregate pattern of technological change at the industry level draws on mechanisms at lower levels of aggregation such as the level of the firm. Additionally, it provides the conceptual tools to explore technological change as a process relying on the accumulation and transmission of knowledge, skills, and behaviour among the actors involved. Moreover, the evolutionary approach to explore technological change admits its historical conditioning. Hence, from an evolutionary perspective historical reconstruction needs to be merged with the analysis of the process of technological change. The acknowledgement of history dependent processes of technological change at an aggregate level (such as the level of the industry or the economy) does not necessarily imply the need of the historical characterisation of micro behaviours. History de-

pendence at the system level can be the outcome of an invariant choice process subject to some sorts of externality, dynamic increasing returns, multiple locally stable equilibria etc. However, the analysis of technological change can very much profit from the historical-characterisation of micro behaviours. Which technologies emerge and how they develop and diffuse cannot generally be considered independently from the particular sequence of actions of their developers and adopters (Dosi et al. 1992, p. 4.) Finally, formal modelling plays a significant role, but it is not central. Nelson and Winter (1982, pp. 154-155) make the distinction between "formal" and "appreciative" theorising. Different from formal theory, appreciative theory is strongly influenced from empirical findings. Hence, appreciative theorising involves verbal explanations based on empirical findings. These explanations challenge formal theory and modelling, which are meant to act as a formalisation tool to identify gaps in the verbal stories or to test there logic. Additionally, formal modelling may identify new research questions reorienting empirical research. From this perspective, formal theory is hence supposed to provide guidance and a conceptual framework to empirical study (Hodgson 1993, p. 166).

This contribution aims at combining appreciative theorising and formal modelling by developing a history-friendly model of technological change and technology adoption to study technological change German pharmaceutical industry during the 20th century.

The challenge of history-friendly models is to select research phenomena on firms and industries, generate hypothesis about the process of technological change using empirical facts (qualitative and quantitative) and to set up a model specification to test the outcome against the historical experience in a rigorous manner. Thus, the methodological approach of evolutionary history-friendly models draws on appreciative theorising and includes (i) a set of stylised facts characterising the phenomenon to be explored, (ii) verbal logic on how the processes occur, (ii) formal representation of the verbal logic in a model, and finally (iii) the implementation of a numerical computer simulation replicating the phenomenon explored.

The contribution is structured as follows:

The next chapter introduces the theoretical and methodological frameworks. Drawing on a literature review, the discussion starts by giving a presentation on the main schools of economic thought contributing to develop evolutionary thinking. Next, chapter 2 specifies a conceptualisation of technology and elaborates on the main seminal contributions and concepts put forward by evolutionary scholars that can be useful for answering the research questions regarding technological change and the role of the firm in this process. The goal is to put together a toolbox to explore the technological

transitions in the German pharmaceutical industry and firms' performance. The chapter includes an introduction to simulation models and their value for evolutionary analysis of socio-economic phenomena. Chapter 2 ends with the presentation of history-friendly models and key methodological issues of the approach relevant for the purposes of this contribution.

Chapter 3 aims at specifying the research phenomenon. In other words, it presents the empirical analysis of the major changes in the knowledge base underlying drug discovery and development since the establishment of the modern pharmaceutical industry in the last quarter of the 19th century and the implications for the industry and for the German drug producers. The analysis considers the historical conditioning of technological change and takes a historical perspective. The findings are combined with a quantitative analysis using patent indicators. Additionally, at the organisational level, a case study approach is followed to analyse the ability of four German drug producers to exploit the technological opportunities of biotechnology after the advent of modern biotechnology in the 1970s. The complete material collected for the case studies is included in the annexes. However, all relevant results for our purposes are included in chapter 3.

Chapter 3 identifies the stylised facts specifying the mechanisms underpinning technological change in the German pharmaceutical industry during the 20th century and putts forward interesting issues to be explored with a history-friendly model. Together with the theoretical concepts discussed in chapter 2, the findings elaborated in chapter 3 build the ground for the specification of the simulation model presented in chapter 4.

Chapter 4 draws, to some extent, on previous models of technological change in the evolutionary tradition discussed in chapter 2. The goal is to build an artificial environment to explore the logic of the appreciative theory and the role of relevant processes and variables identified in the empirical analysis. The model includes the four characteristics outlined by Dosi and Nelson (1994, p. 154) to define evolutionary models given at the beginning of this section: the specification is dynamic, it includes random elements, discovery and selection processes and mechanisms through which selection operates.

Finally chapter 5 summarises the main findings and draws the conclusions.

2 Theoretical and methodological framework

2.1 Introduction

The idea of evolutionary technological change comes largely, on the one side, from historical and sociological research traditions and, on the other side, from evolutionary economics (Nelson, Nelson 2002, p. 265; McKelvey 1996, p. 36).

From a historical perspective Vicenti (1990) for instance, explores the way technology evolves. Drawing on empirical evidence from the aircraft industry he analyses engineers' strategies on solving technical problems and on improving technical solutions. He proposes a blind trial and error process to compare the different technological alternatives to improve planes. This process leads to the identification of what ex-post can be defined as the better technology. The criteria determining the superior technology could emerge from an evaluation mechanism which is innate in the technological problem, thus the criterion is based on technical parameters such as speed or power. An additional evaluation mechanism he considers is the set of beliefs and opinions of the technological community contributing to solve the technological problems. Hence Vicenti's approach suggests that technology development is the result of a search process shaped by technological possibilities and the shared knowledge and practices of communities of engineers.

On the other hand, evolutionary economists explore technological change in the context of economic development and market dynamics. According to Kwasnicki (1999, pp. 18-19) in the most general understanding the term evolutionary economics is used to emphasise the role of change in socio-economic processes in opposition to an analysis focussed on static equilibrium properties. In a narrow sense, "evolutionary" relates to a socio-economic analysis based on analogies and metaphors borrowed from theories of biological evolution.[3] However, the term "evolutionary economics"

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3 The theory of biological evolution is associated with the name Charles Darwin. The Darwinian theory of biological evolution states that evolutionary change in a heterogeneous population is due to natural selection of organisms according to their suitability to the environment in which they interact. Organisms hold a genetic make-up (genotype) that results in different morphological structures and behavioural characteristics (phenotype) that may be suitable or not for their environment. The poor adopters perish but the best adopters survive passing their genetic information to their offspring. The mechanism of selection and information transfer can be "Lamarckian" (if novelty is intentional and organisms develop variations in order to adapt to environmental conditions, passing on such adaptations to their offspring) or "Darwinian" (if novelty is random and genetic variations are produced through a random process. The environment may affect organisms but the results of these effects can not be transmitted to the offspring). Even though there is no clear evidence for a Lamarckian selection mechanism in biological evolution, this type

applies to a confusingly wide array of approaches analysing socio-economic phenomena.

The following section presents the main schools of economic thought contributing to the development of evolutionary economics. Next, a conceptualisation of the nature of technology and its implications for the analysis of technological change from an evolutionary perspective is presented in section 2.3. Section 2.4 covers the issues of technology emergence and diffusion in decentralised economies and presents relevant taxonomies of technological change. The role of firms in driving technological change from an evolutionary perspective is discussed in section 2.5. Finally, the chapter closes with the introduction of computer simulation as a method to explore technological change and technology adoption from an evolutionary perspective.

2.2 The building blocks of evolutionary economics

This strand of economic theory emphasises the relevance of dynamic analysis in the study of socio-economic phenomena and the need to build realistic assumptions about human agency (i. e. about how decision-making processes work). Hodgson (1999, pp. 127-129) and Kwasnicki (1999, pp. 18-19) identify at least three main schools of economic thought which can be grouped under the umbrella phrase “evolutionary economics”: the Austrian School, Institutional Economics and the work influenced by Schumpeter (or the so called neo-Schumpeterian economics).[4]

Table 1: Main schools of economic thought contributing to the development of evolutionary economics

Schools of economic thought	Important exponents	Selected general concepts
Austrian School	Friedrich Hayek	• Rejection of equilibrium theorising; • Human action is considered purposeful; • Emphasis on the role of knowledge in economic analysis; • Biological idea of social evolution.

of mechanism is most suitable for the exploration of socio-economic development (Hodgson 1988, pp. 141-144).

4 To this selection Hodgson (1999, pp. 127-129) adds three additional approaches associated with the word "evolutionary": (i) The economics of writers such as Adam Smith, Karl Marx, Alfred Marshall and others, (ii) developments in mathematical economics under the phrase "evolutionary game theory" inspired by related work in theoretical biology and (iii) work typically developed at the Santa Fe Institute (http://www.santafe.edu) in the USA described as "complexity theory". The approach draws on application of chaos theory and various types of simulation approaches such as replicator dynamics and genetic algorithms.

Table 1 continued

Schools of economic thought	Important exponents	Selected general concepts
Institutional Economics	Thorstein Veblen	• Rejection of equilibrium analysis to explore processes of change; • Human action is considered purposeful, rationally bounded and coevolves with its environment; • Darwinian metaphor of economic evolution involving institutions (i. e. habits, roles and conventional behaviour).
neo-Schumpeterian Economics	Nelson and Winter	• Rejection of equilibrium analysis to explore processes of change; • Human action is rationally bounded and shaped by institutions; • Lamarckian metaphor of economic evolution involving institutions (i. e. routines).

Table 1 sketches a selection of relevant conceptual aspects. The next sections elaborate briefly on the main characteristics of these strands of economic theory.

2.2.1 The Austrian School

The fundamental premise of the Austrian School is the rejection of both equilibrium theorising and the existence of rigid preference functions determining agents' decision-making processes. Its members explicitly recognise that human action is purposeful.[5] Therefore, an agent's choice is not determined by the environment in the sense that his or her goals are not predetermined. Additionally, the work of the Austrian School puts great emphasis on problems of information and the role of knowledge in the economic process.

The contributions of Hayek in the 20th century represent one of the most developed and important applications of the evolutionary analogy (Hodgson 1993, p.153). Hayek's work is grounded, on the one side, on the purposeful behaviour of agents (already stressed in his early writings). However, according to Hodgson (1989, p. 258), Hayek recognised that individuals' goals and tastes were not predetermined, he considered that the formation and moulding of individual tastes and preferences were beyond the scope of economic analysis. Moreover, Hayek develops in his later writings a modern biological idea of social evolution.

5 "Purposeful behaviour" assumes that agents have the capacity to change both behaviour and goals without external stimulus. In contrast, orthodox economic theory assumes "goal-directed behaviour" in which agents' goals and preferences are exogenously given and agents do not have a will (Hodgson 1988, p. 11).

2.2.2 Institutional Economics: the legacy of Thorstein Veblen and the developments of new Institutional Economics

This school draws on the intellectual heritage created and developed by early twentieth-century economists such as Thorstein Veblen.[6] His work aimed at developing an alternative to the orthodox theoretical framework. Veblen's critique of the orthodox approach focused on its inadequacy for the theoretical purpose of analysing the process of change and transformation in the economy. Under Veblen's point of view, the relevant research question lies on why innovations take place (and not on the conditions for equilibrium after new technological possibilities have been established).

Nelson and Nelson (2002, p. 266) suggest that in Veblen's work institutional analysis (in the sense of the exploration of the set of factors moulding and defining human interaction) and evolutionary analysis of socio-economic development were intertwined.

Regarding the institutional aspects of his work on the exploration of agents' behaviour, Veblen stresses that human nature or preference functions are not given for granted. Both, circumstances and character of an individual are involved in the cumulative process of change. Hence, both the agent and the environment are the outcome of a cumulative process. To elaborate this idea he introduces the role of institutions in the analysis of human behaviour. Economic institutions are seen as complexes of habits, roles and conventional behaviour. In contrast with the Austrian idea that all action is purposeful, and with the neoclassical idea that all action is determined by preference functions, in the sense of Veblen habits are essentially non-deliberative and even unconscious. Moreover, breaking with the orthodox picture of the agent's maximising behaviour (and in reminiscence of the idea of Simon (1957) of bounded rationality or limited computational capacity) he recognises the agent's problems of global calculation of maximisation opportunities.

With regard to Veblen's elaboration of evolutionary concepts, his work presents an attempt to develop a theory of socio-economic evolution using the Darwinian evolutionary metaphor (where institutions and habits of thought act as genes in the biological sense). In this sense, Veblen suggests a mechanism specifying the sustenance and procreation of action and institutions as units of selection.[7]

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6 This school uses very often the terms "evolutionary" and "institutional" as synonyms. For instance, in the USA the school is represented by the Association for Evolutionary Economics (AFEE) and in Europe by the European Association for Evolutionary Political Economy (EAEPE).

7 See footnote 3 for a short elaboration of the concept of Darwinian evolutionary processes. Veblen described himself as Darwinian because he puts greater emphasis on the selection

The contributions of the Institutionalist school of Veblen and his colleagues built up a prominent paradigm among American economists in the 1920s and 1930s which emerged largely out of their critique of orthodox assumptions regarding the behaviour of agents embedded in a socio-economic system. However, the fundamentals of their work defining human agency and their methodological approach (largely based on empirical work on the nature and function of institutions) were not able to compete with the formalistic and mathematical developments pushing the neo-classical approach after World War II (Hodgson 1989).

In the 1970s, institutions were placed again in the centre of economic analysis by the strand called new Institutional Economics. Its best known exponents are Williamson (1985, 1993) (developing organisational theory) and North (1990) (who takes a historical perspective). Even though they try to break with neoclassical theory, their work embraces much of the core neoclassical fundamentals (Hodgson 1989). For instance, even though new Institutional Economics admit the bounded rationality of agents, they include optimising exercises (by minimising transaction costs) in agents' decision-making processes. Edquist and Johnson (1997, pp. 44-45) point out that Williamson's contribution largely draws on the transaction cost theory put forward by Cose (1937). The central aim of Williamson's transaction costs economics is to explain the nature and existence of economic institutions such as markets and firms using concepts of opportunism and transaction costs involved in trading. The organisation of firms and markets can be explained in terms of existing transaction costs and the search for organisational structures minimising them. North develops a theory of the development of institutions involving the concept of transaction costs and a theory of property rights.

2.2.3 Neo-Schumpeterian Economics: the work influenced by Schumpeter

A continually growing body of literature under the umbrella phrase neo-Schumpeterian economics has been modelling economic processes inspired by Schumpeter's work in the last 30 years.

Saviotti and Metcalfe (1991) summarise the fundamentals of Schumpeters' work as follows. Schumpeter's main research interest was to explain the phenomena of "economic evolution". In his view, "economic evolution" corresponds to economic change

process through which some institutions prosper and others decline. Whether Veblen's theory was really Darwinian (in the sense that he excluded purposeful behaviour and the possible transmission of adaptations to the environment) is unclear. His work leaves room for different interpretations (Hodgson 1993, pp. 134-135).

driven by innovation and all its effects (including the responses from the economic system).[8] Additionally, he stresses the non-equilibrium aspects of economic development in capitalist economies. For Schumpeter "evolution" means the denial that equilibrium can be attained as a permanent state of rest, and the assertion of constant novelty and change. In his view, evolution is hence a disturbance of existing structures and more likely a series of explosions than a moderate transformation.[9] Finally, regarding the entrepreneurial act, Schumpeter suggests a conception of behaviour as fundamentally rule-governed, rejecting rationality (Langlois 2002, p. 14).

Schumpeter's early writings focus on the role of the entrepreneur as main responsible for technological change by seizing upon exogenously given inventions and transforming them into economic innovations without explicit planning of innovative activities. Innovations disequilibrate and alter hence the given market structure. However, the emergence of inventions was not explored in his early work. Basic inventions are treated more or less as exogenous to the economic system. On the other hand, his later work, *Capitalism, Socialism and Democracy,* was mainly concerned with the role of large corporations, their rational calculation when planning research and development, and the effects of monopolistic practices on innovation and economic development. In these writings invention becomes a purposeful and, to some extent, planned activity carried out by large firms. Due to the different pictures of technological change presented in Schumpeter's writings, his work has been often classified as Schumpeter I (referring to its early writings, or the 1934 English translation

8 Schumpeter's concept of innovation goes far beyond technological change in a narrow sense. The concept includes the introduction of a new good, a new method of production, the opening of a new market, the involvement of new sources of raw material, and the enforcement of a new industrial organisation such as the taking up of a monopoly position (Schwitalla 1993).

9 However, the evolutionary character of Schumpeter's work is not explicit. Hodgson (1993) points out that Schumpeter's own notion of "economic evolution" is explicitly distanced from evolution of in a biological sense and excludes any suggestion of a Darwinian or a Lamarckian process of selection and information transfer. For Schumpeter, "economic evolution" meant change in general. His idea clearly accepts structural, qualitative and cultural change. However, according to Hodgson, his notion is too broad for an implicit evolutionary analogy in the biological ubnderstanding, which should include elements of selection. Challenging Hodgson's view, Andersen (1995) supports the evolutionary character of Schumpeter's work and appeals to consider Schumpeter's own distinction between the analytic tools available to him and his evolutionary vision. According to Andersen, "Schumpeter formulated his evolutionary theory in connection to a (pseudo)-Walrasian framework (…) Schumpeter's sole reliance on innovation rather than selection should instead be seen as reflecting the inadequate tools available to him" (Andersen 1995, pp.6-7).

of his *Theory of Economic Development*) and Schumpeter II (referring to his work *Capitalism, Socialism and Democracy*) (Schwitalla 1993; Freeman 1982).[10]

Schumpeterian analysis experienced a renaissance in the 1980s with the work of Nelson and Winter (1982), which at the same time opened up the development of formal evolutionary modelling. Inspired by Schumpeter, Nelson and Winter (1982) stress the role of technological change as the motor of economic growth and emphasise the role of firms in this process. In addition, they explicitly adopt a biological metaphor considering industries as populations of profit-seeking firms. The market represents the selection environment and determines the definition of firm's success. Firms try to adapt to market conditions in order to fulfil this definition. As in biological selection, firms that best adapt to the conditions of competition are able to survive. In the spirit of Veblen, Nelson and Winter introduce institutionalist concepts in their analysis of technological change and industry evolution with the notion of *routines*, which store essential information for the organisation such as how to accomplish certain processes or how to interpret market signals. In their biological metaphor to illustrate industry evolution organisational routines act as "genes". However, for Nelson and Winter industry evolution allows for the inheritance of acquired characteristics through a "Lamarckian" process of information transfer (Nelson, Winter 1982, pp. 134-136).[11] Finally, using formal methods and computer simulations, the evolutionary model of economic growth elaborated in chapter 9 of their 1982 contribution generates standard macroeconomic series describing growth were all three elements (labour productivity, real wages and capital intensity) increase. As Hodgson (1993, p. 166) puts forward, in the early 1990s their work was still "the most extensive and rigorous application of the application of the evolutionary metaphor from biology in economics".

10 The literature of technological change offers a conventional interpretation of the differences between Schumpeter I and II according to which Schumpeter changed his fundamental position on the nature of innovation because of trends he saw developing in 20th century US-American capitalism. Langlois (2002) emphasises that the interpretation of different fundamental positions in Schumpeter's work is wrong. According to him, Schumpeter's ideas are consistent with different stages of capitalist economies where the access of agents to knowledge changes. The early Schumpeter writings are based on an economic framework in which the access of agents to knowledge is limited, rationality is bounded and hence innovation can not be planed. In this context, progress depends on entrepreneurship, i. e. on taking risks and transforming resources in unconventional directions. His later writings, on the other hand, draw on an economic framework in which the bounds of rationality are broken, limits to knowledge are disappearing and a planned economic activity (far away from conditions of perfect competition) can lead to innovation and growth.

11 See footnote 3 for a description of "Lamarckian" evolutionary mechanisms of selection and information transfer.

The neo-Schumpeterian literature developing Nelson and Winter's approach considers economic phenomena as dynamic, historical processes in which macroeconomic characteristics are the result of economic agents' activity at the micro-level. Heterogeneity of agents is a fundamental feature of economic evolutionary processes where selection and search for innovation are the two basic mechanisms of development (Kwasnicki 1999).

A key difference between neo-Schumpeterian economics and the Institutionalist and Austrian Schools introduced above is their methodological approach. According to Kwasnicki (1999, p. 22), neo-Schumpeterian economics are characterised by the wide application of formal modelling and simulation tools for economic analysis, while the Institutionalist and Austrian Schools make use of verbal and graphical representations to describe and analyse economic phenomena.

However, Nelson and Nelson (2002, pp. 266-267) suggest that the Institutionalist and neo-Schumpeterian schools share important theoretical premises regarding human action in the sense of Veblen (i. e. the consider human action as the result of shared habits of action and thought). Additionally, both approaches try to understand the determinants of economic performance and why performance differs across countries. Most importantly, recent developments have seen the strands of Institutional and neo-Schumpeterian economics converge. For instance, some of the scholars contributing to the development and establishment of neo-Schumpeterian economics and its formalisation have also elaborated heuristic frameworks to integrate institutions as the main factors moulding technologies used by societies. The results are empirical studies of technology and industry evolution as well as approaches like National Innovation Systems, Sectoral Innovation Systems and Technological Systems.[12] While these heuristic approaches have been able to account for institutions in their analysis of technological change, the pure formal neo-Schumpeterian approaches are still developing conceptual and methodological tools to integrate institutional aspects in their analysis (Nelson, Nelson 2002).[13]

12 This section skips a review of the extensive literature on the Systems of Innovation approach and its main exponents. Freeman (1988) and Nelson (1988) introduced the concept of National Systems of Innovation which was further developed by Lundvall (1992), Nelson (1993) and Edquist (1997). Carlsson and Stankiewicz (1991) propose the concept of Technological Systems and Breschi and Malerba (1997) use the concept of Sectoral Systems of Innovation.

13 Schwitalla (1993, pp. 40-41) already pointed out these different developments in the neo-Schumpeterian strand of evolutionary economics. Grupp (1998) introduces this aspect in his overview of theoretical approaches exploring the innovation process as well. He speaks of *Institutional* neo-Schumpeterian innovation theories to refer to neo-Schumpeterian economists explicitly embracing and developing the institutional approach in concepts such

Even though technological change is considered to be the main driver of economic development, the focus of neo-Schumpeterian economics remains mostly on economics-related questions such as economic growth, industrial dynamics and firms' strategies. McKelvey (1996), who has analysed the relevance of evolutionary patterns of technological change for evolutionary economic theories stresses that “economists often assume that technical change is evolutionary without exploring the issue” (McKelvey 1996, p.36).

The next sections discuss more deeply the issue of evolutionary technological change from a neo-Schumpeterian perspective. The aim is to set the theoretical and methodological framework to explore technological change and technology adoption in the German pharmaceutical industry. This theoretical framework combines institutional and evolutionary elements in their narrower meaning. Accordingly, the presentation aims (i) at conceptualising the nature of technology and its implications for the analysis of technological change, (ii) at including search and selection mechanisms in the processes of technological change, (iii) at emphasising the role of institutions in firms' decision-making[14], and finally (iv) at identifying the processes underpinning the acquisition and transmission of knowledge at the level of the firm.

2.3 A conceptualisation of the nature of technology

A key step towards the characterisation of technology is the recognition of its imposed function, which determines how technology should behave or the task it should accomplish. For instance, if I had an air-conditioning system in my office I would expect it to control the room temperature and cool it if it gets too hot; hence this is the imposed function of the air-conditioning technology. Therefore, technology involves a transformation of the world in order to reach a predefined behaviour (Nightingale 1998, 2004).

Metcalfe puts forward a dualistic approach to technology according to which technologies have two dimensions: the artefact dimension and the knowledge dimension (Metcalfe, Boden 1992).

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as innovation systems. While the neo-Schumpeterian approaches developing formal models and stressing fundamentals of behavioural theories at the micro level to explore macroeconomic processes are referred to in Grupp’s work as *Evolutionary* neo-Schumpeterian innovation theories. Grupp applies the adjectives *Institutiona*l and *Evolutionary* in their narrow sense (Grupp 1998, pp. 68-76).

14 "Institution" here refers to the "the sets of common habits, routines, established practices, rules, or laws that regulate the relations and interactions between individuals and groups" (Edquist, Johnson 1997, p. 46).

The artefact dimension refers to the physical devices articulating the transformation process of inputs into outputs. Moreover, it embodies the physical achievements in the development of a technology which can be captured in terms of performance of outputs (for instance functional or qualitative performance) or of production processes applied (in terms of necessary equipment and its costs or environmental criteria, for example).

On the other side, technology as knowledge refers to the concepts, theories and practices underlying the transformation process and the actions that enable its operation. Technology involves different types of knowledge such as tacit knowledge (which can not be easily articulated and communicated) and codified knowledge (which can be expressed in symbolic form and easily articulated).[15] Nelson and Winter (1982) suggest that real life knowledge can often be placed on a continuum between perfectly codified and tacit knowledge. Moreover, the nature of knowledge in terms of degree of "codifiability" may change overtime (Saviotti, Metcalfe 1991).

An important issue in innovation studies and in science and technology policy is the interaction between technology and science. To explore this interaction it is necessary to understand the differences between science and technology.[16]

In simple words, science provides understanding about the world. Accordingly, scientific activities involve experimental practices in order to match scientists' ideas about the world with the facts they observe under specific conditions. Science provides understanding of how phenomena occur. In contrast to technology, science is not supposed to work correctly (since it does not involve an imposed function). Science is supposed to deliver statements that match the evidence (Nightingale 1998, 2004). Metcalfe and Boden have stressed the differences between science and technology by focussing on their problem-solving nature. A technological problem is solved with the development of an artefact that works, or when the performance standards of an artefact are improved (Metcalfe, Boden 1992, p.60). Therefore, technological problem-

15 Polanyi (1962) analysed the role of tacit knowledge. This type of knowledge that can't be easily articulated is embodied in skills and is accumulated through experience.

16 For a literature review on the body of research developing theory on the distinctiveness and complementarities of science and technology see Metcalfe (1998, pp. 108-111). He starts by discussing the traditional linear model of innovation, which considers technology as merely applied science and science as the driver of technological change. This perspective served as rationale for public science investments for at least three decades after the publication of the Vannevar Bush Report “Science – The endless Frontier” in 1945. In the 1980s a new body of research established an alternative approach to the interactions of science and technology recognising their different and independent nature. According to this perspective, both science and technology contribute to economic growth and the role of science and technology policy is to support their interaction.

solving is subject to a test which is shaped in an economic or social context. On the other side, scientific explanations are judged by the truthfulness of the knowledge in explaining observed phenomena under specified conditions.

For these reasons technology is not applied science (Pavitt 1987). Technologies can exist without science (because we may be able to make a fire without understanding the fundamentals of combustion processes). Therefore, technology and science are independent bodies of knowledge. In some cases science contributes to technology development by guiding technological problem solving (Nelson 1982), even though scientific results can't be applied by users at no cost. For instance, companies willing to apply scientific results need, at least, to cover the costs of employees with the capabilities of understanding those results and adapting them to the specific processes and products of the firm (Pavitt 1987; Nightingale 1998, 2004). Moreover, there is strong empirical evidence sustaining that interaction between science and technology varies across industries (Grupp, Schmoch 1992; Meyer-Krahmer, Schmoch 1998). Finally, technology may also complement science (even stimulate it) by providing it with new phenomena to be explained or with new engineering solutions unveiling new questions for scientific research (Nelson, Rosenberg 1993, p. 9; Rosenberg 1990).

2.3.1 General principles to characterise technology

The issues discussed above raise the challenge of drawing general principles that characterise technology and of deriving implications for the analysis of technological change. Since the 1980s, the evolutionary perspective of technological change has produced valuable contributions to the understanding and conceptualisation of technology. From this perspective and in general terms, technology is specific, complex (which makes it unpredictable), cumulative in its development and frequently tacit.[17]

Technology is specific

Most technological activity is carried out in firms where intentional research and development tries to improve products and processes. Consequently, firms aim at accumulating codified knowledge and skills and articulate them in new product or process artefacts (or in improvements of artefacts that already exist). There is strong empirical evidence for the similarities of the knowledge base of firms within the same industry (Pavitt 1998). However, the articulation of firms' knowledge bases into useful technological solutions leads to artefacts with different characteristics across firms. In

17 See for example Pavitt (1987) or Metcalfe (1998). This section is largely inspired by these contributions.

other words, each firm has a more or less unique way of transforming inputs into outputs. At the level of the industry the specific nature of technology is not so obvious, however, the closer we get to the firm and to the product, the more specific technology is.

Technology is complex

To reproduce its imposed function technology draws on the combination of different bodies of knowledge from different sources. There interaction "makes things work". A strong implication of complexity is *ex-ante* uncertainty in the application of technology (Dosi 1982), which makes an early assessment of either the performance or utility of an innovation impossible. To capture this characteristic of technology, Nightingale (2004) refers to the unpredictability of technology.

Efforts to advance technology are to a large extent "blind" because, even though research and experimental activities devoted to improve technological solutions have an intention and draw on a large body of different types of knowledge; whether the efforts to articulate the interaction of knowledge will be successful from a technological and/or economic point of view remains uncertain. Success is determined through ex-post competition, after technology is confronted with alternatives.

Technology is cumulative in its development

As already mentioned, most technological activity is carried out by profit-seeking firms. They carry out technological activity by building up incrementally from what they already know. Their technological experimental activity is therefore constrained by what they have learned in the past. In many cases this constraint can be loosened with the contribution of firm's extramural knowledge base (which involves knowledge and experiences of firms they purchase or they collaborate with and knowledge available from university research and public research institutions). Even though technological activity may not necessarily result in a better solution, experimental processes enhances firm's existing knowledge base.[18] In the words of Nelson and Winter, "the result of today's searches is a natural starting point for the searches of tomorrow" (Nelson, Winter 1982, p. 257).

18 Accordingly, even though innovative effort may have diminishing returns in the short run (as performance improves it takes progressively more effort to achieve further improvements), the additional knowledge created through the experimental processes becomes part of the knowledge available for the next periods and, in the long run, the process of technical advance becomes less demanding in terms of effort (Metcalfe, Georghiou 1998, p. 116). In other words, the long run can be characterised by increasing returns to expenditures in research and development.

Partial tacitness of technology

Technology can not be completely codified. While many elements of design and problem-solving activity may be easily articulated and even public (such as scientific inputs), the specific transformation of these elements into useful technological solutions (product or process artefacts) is largely tacit and hard to imitate. Technologies can be hence characterised in terms of their degree of "tacitness" versus "publicness". Technological accumulation therefore involves learning through experience, example and training, especially if the degree of tacitness is large. As technology becomes easier to articulate (i. e. less tacit), the extent to which it can be transferred and reproduced increases.

Once the cumulative, firm-specific, complex and tacit nature of technology are recognised, technology can't be considered as generally applicable, easy to reproduce and reuse. Technology development, whether in terms of knowledge or in terms of artefacts, is costly. Users and adopters may have to undertake technological modifications or obtain additional knowledge in order to use or integrate a technology in their production processes. Even borrowers of technology need to develop their own skills and make their own expenditures on research, development and production engineering to be able to reproduce technology's imposed function properly. Inventing around other people's patents can not be done at no cost. Innovation and imitation are often indistinguishable, both in their inputs and in their outputs (Nelson, Winter 1982).

Consequently, technological change can't be conceptualised as a process in which firms help themselves from a stock of technological knowledge freely available to find technological solutions. Neither can technological change be considered a random process. Observed patterns of technological change account for a certain ordered nature and, moreover, search and discovery activities around a technological problem are relatively limited to a small subset in the space of technological solutions that a technician can think of (Dosi 1988a).

Given these considerations, and taking into account that technological change is the result of interactions among individuals, populations and environments over time, the following section discusses the process of technological change from an evolutionary perspective.

2.4 Technological change from an evolutionary perspective

In non-planed economies most technological activity is carried out in incentive driven organisations which conduct trial and error experiments (sometimes guided by

scientific knowledge) in order to solve technological problems or to improve existing technological solutions. Technological activity may provide organisations with high rewards as long as they are able to develop successful innovations. Consequently, competition in technological activities is to a large extent innovation driven.

Traditionally the so called "technology push" and "demand pull" theories have attempted to explain the drivers and patterns of technological change by focussing either on the supply factors shaping new technological opportunities to be exploited (such as scientific development) or, alternatively, on the needs of users and beneficiaries of technology as main drivers of technological activities.

Dosi (1982) points out that both approaches have different understandings of the role of market signals in the process of technology development and, moreover, they fail to provide a theoretical framework for technological change.

On the one hand, the demand-pull approach implies a-priory recognition of the needs of technology users (Mowery, Rosenberg 1979). This assumption contradicts the uncertain nature of technology discussed above. Even if technology developers were able to identify a priori the needs of technology users, the range of products or processes satisficing their needs may be unknown. Even in the best case - that is, if these artefacts were known - the scientific and socio-economic environment might set strong constraints to develop them. Technological solutions are not readily available (Rosenberg 1976, p. 63). In other words, market signals alone are not able to drive technology development.

On the other hand, the technology-push approach is not reconcilable with the obvious fact that socio-economic factors (and not technological and scientific conditions exclusively) are important in shaping the direction of the innovation process. Users of technology, for instance, have a strong influence on the path of technological change.

To conciliate the independence of technology development from socio-economic mechanisms (suggested by the technology push approach) and their relevance shaping technological change (suggested by the demand-pull approach), evolutionary economists point out that technological change does not happen at once, it is rather a gradual process. Tentative models aiming at explaining this process should consider that technological change involves firstly the emergence of possible technological solutions (in other words, the generation of variety or the establishment of a set of alternative technological solutions to solve a problem). This process is followed by further selection procedures in a socio-economic context that limit the set of alternative solutions, determine their relative importance over time and the direction of technological development.

From an evolutionary perspective in capitalist economies technological change is a complex dynamic process of *search* for possible technological solutions and *selection* among them. In the generation of variety (i. e. the search of possible technological solutions) profit-seeking actors operate in a wider institutional matrix. This matrix involves institutions and mechanisms shaping the variety creation process by determining the set of technological solutions or opportunities available. Accordingly, elements such as beliefs of technicians, experience, skills, scientific explanations, theories, etc. shape the search process of technicians when the technological solutions are emerging. This is the phase of technology emergence or variety creation. After the set of technological solutions has been created, socio-economic forces shape what we could call the ex-post selection process (since the technological options are jet known) by stimulating specific solutions, rewarding their developers and, in consequence hindering the development of alternative technological solutions. Moreover, the process of variety creation and technological selection ex-post influence each other in complex feed back mechanisms.[19] McKelvey (1996) stresses that for technology developers the selection process is not deterministic. Since selection processes are fundamentally processes of social interaction between market forces, government decisions, public debate, and the state of relevant scientific knowledge, technology developers can not accurately predict what users want or what competitors will do.

2.4.1 The emergence of technologies (or the search for alternative technological solutions and the creation of variety)

In this framework, technological change involves first the exploration of alternative directions in which to search for novel technological solutions or technological improvements. However, this choice is not random. Technicians in their problem-solving activities develop beliefs about what is worth attempting, or to which extent certain improvements may be feasible or not. This range of possible directions of development based on technicians' assessments has been called by Nelson and Winter a *technological regime* (Nelson, Winter 1977). Most importantly, technicians have their own specific understandings regarding the potentials (the boundaries) of these regimes.

Within a technological regime some directions of technology development may appear more obvious than others. Nelson and Winter (1977, p. 57) called these sometimes almost "inevitable" development paths in the eyes of technicians *natural trajectories.* Nelson and Winter specified the following characteristics of natural trajectories:

19 See for example Dosi (1982), Dosi (1988) or De Liso and Metcalfe (1996).

- Natural trajectories can be complementary;
- While natural trajectories have special elements associated with a particular technology, certain natural trajectories can be common to a wide range of technologies (such as the progressive exploitation of economies of scale and the increasing mechanisation of hand operations);
- Underlying the movement along natural trajectories is a body of knowledge. In some cases this knowledge is well articulated knowledge;
- The extent to which scientific understanding can contribute to technology development along natural trajectories differs across industries.

The contribution of Nelson and Winter is very broad and relies largely on technicians' assessment to develop both the concept of technological regime (as scheme setting up the possible development paths of technology) and the natural trajectories technologies may follow on the ground of a regime.

Building on the theoretical conceptualisation put forward by Nelson and Winter, and by drawing on an empirical analysis of the semiconductor industry, Dosi tries to be more specific in the identification of the factors shaping technician's beliefs, their criteria to select among different technological solutions and the role of social, institutional and economic factors in guiding technological change. His starting point is an analogy with the notion of the scientific paradigm of Kuhn (1962). Dosi introduces the concept of technological paradigm.[20] In simple words, Dosi's technological paradigms shape technological activity (which he presents as a problem-solving activity) by specifying the following elements:

- The problem to be solved or the generic task to be accomplished;
- The technologies involved;
- The technological or economic dimensions experimentation should focus on.

Most importantly, such paradigms embody guidance on the direction technological change should follow and on which technological options should be neglected. Accordingly, a paradigm is a focusing device; a set of heuristics embodying prescriptions. These direct the search towards certain technological solutions and cause a degree of blindness with respect to potential alternatives. Examples of technological paradigms are the combustion engine, oil-based synthetic chemistry or semiconductors. Dosi defines a technological paradigm "as a 'model' and a 'pattern' of solution

20 Despite the broad analogy between science and technology Dosi explicitly states that the analogy should not be taken as an entity (Dosi 1982, p. 152).

of *selected* technological problems, based on *selected* principles derived from natural sciences and on *selected* material technologies" (Dosi 1982, p. 152).

Given this set of rules defining problems and suggesting workable solutions, problem solving is supposed to follow a pattern which Dosi (1982, pp. 154-155) defines as technological trajectory. Technological trajectories present the following characteristics:

- Trajectories might be more general or more specific as well as more or less powerful (in terms of the number of trajectories they exclude);
- Trajectories can complement each other to the extent that developments in one technology may foster developments in other technologies;
- It is possible to determine a technological frontier which corresponds to the highest level of the most relevant technological or economic dimension reached by a technological solution;
- Technical progress retains some cumulative features in the sense that future advances may depend on the technological level reached vis-à-vis the existing technological frontier;
- If the technological paradigm guiding problem-solving changes, the problem-solving activity has to be restarted almost from the beginning. For this reason it might be difficult to change from one trajectory to an alternative one;
- Due to the uncertain nature of research and experimentation activities, the objective comparison of alternative technological paths can only be carried out ex-post (even if objective criteria or indicators are available).

Dosi's work systematically develops the concept of technological regime proposed by Nelson and Winter by specifying the factors and mechanisms shaping technicians' assessment on the technological options that might be worth developing and the conditions determining the set of possible technological solutions. The concepts presented (technological regimes and paradigms) aim at identifying the elements guiding creative activities in the process of searching for technological solutions. Both approaches agree on the existence of focusing devices which shape the set of technological solutions firms are most likely to consider. In addition, it is suggested that firms' problem solving does not occur in isolation. In the process of searching and identifying potential technological solutions firms are embedded in a set of institutions. Firms draw on a set of knowledge, experiences, specific and uncodified capabilities and apply search modes. These elements guiding technological activity are shared and supported to a large extent by a body of actors.

Furthermore, both approaches (the Nelson and Winter approach and Dosi’s approach) point out the complementary nature of technologies and their different degrees of specificity in the sense that some technologies can be apply to solve a large range of

different problems while others are specific to the problem under consideration. However, while Nelson and Winter remark the knowledge dimension of technology and the role of scientific knowledge in technology development, Dosi brings up the implications of the cumulative nature of technology development and the implications for experimentation in alternative directions. This cumulative aspect is directly related to the difficulty of adopting new technologies for problem solving instead of the ones already adopted in the past, even though the conditions for problem solving might have changed.

2.4.2 Technology diffusion (or the ex-post selection mechanisms in the process of technological change)

At a certain point, when the set of alternative technological solutions is better known by the institutions involved, the solutions undergo a monitoring process that determines their relative importance and the pattern of technological changed observed. Thus selection environments frame the processes of competition and technological accumulation, determining the technological improvements that become innovations and their relative importance over time.

They do this by monitoring technological solutions and rewarding technology developers that are better able to fulfil the criteria of the monitoring mechanism. The extent to which technology developers are capable to fulfil the selection criteria will lead to changes over time in the relative importance of the technological solutions. The process of technological experimentation and competition may persist until a dominant design emerges (Utterback, Abernathy 1975). A selection environment draws hence on the definition of "worth" or "merit" of a technological solution, the criteria according to which technological developers are rewarded or penalised. The users/beneficiaries of the technological solutions can play a key role in the selection environment since these may impose some restrictions to the technology and influence these criteria.

Selection environments differ greatly in the structure of the demanders and monitors and in the manner and strength in which these mould and constrain the behaviour of firms (Nelson, Winter 1977). But most importantly, selection environments involve factors shaping investment decisions of firms (such as incentive structures) and conditions for knowledge sharing among firms (which may facilitate or hamper imitation and knowledge diffusion and influence the possibility of firms to appropriate the economic returns of their research and development efforts). An important phenomenon influencing how selection environments shape technological change are externalities arising in the process of technology selection and development. These are, for instance, information flows, interdependencies among sectors, technologies

and firms that result in inducements or constraints for the selection of technologies or for technology development in certain directions. Dosi (1988a) notes that "technological progress along any trajectory is linked with (a) the development of *specific infrastructures*; (b) *system scale economies*; (c) complementary technologies; and (d) *particular technical standards* that positively feed upon specific patterns of innovation" (Dosi 1988a, p. 1146). Dosi emphasises the influence of network externalities and increasing returns to scale on the direction of technology development. These ideas belong to the path-dependence perspective of technological change put forward by Paul David (1985) and Brian Arthur (1988).

According to the path dependence perspective, once a technology is some what ahead of the others in the selection environment, a variety of factors will reinforce the development of this technology. Moreover, this relative importance of a technology over the alternatives can become stable since these factors can influence the choice for one technology in future periods. If this occurs, the process is said to be path dependent. Arthur (1988) identifies the following sources of path dependence: (a) learning by using; (b) network externalities; (c) scale economies in production; (d) informational increasing returns; and (e) technological interrelatedness.

To sum up, after the set of possible technological solutions is known it undergoes a monitoring process based on the definition of worth or merit determined by the selection environment where firms compete to seize innovation opportunities. The monitoring process selects which technological solution develops further and diffuses. However, this endogenous competition of technologies and problem-solving methods in the selection environment is influenced by network externalities and forms of dynamic increasing returns. For instance, the development of particular technologies and the development of specific problem solving-methods increase the capabilities of firms in these specific directions, increasing the incentives to do so in the future. Experience and incentives of firms in the selection environment are hence important factors determining technological change. The same holds for the existence of complementary technologies or standards. These elements may prevent firms to deviate from established technological solutions and from experimenting along alternative technological trajectories.

2.4.3 Taxonomies of technological change

The exploration of the impact of technological change on organisational, institutional and socio-economic environments has motivated empirical and theoretical studies to suggest more or less established taxonomies or different types of technological change according to the nature and degree of its impact. This section summarises the main

theoretical conceptualisations which provide qualitative criteria to explore the nature of technological change.[21] These approaches can be classified in three blocks: (i) approaches focusing on the direction of technological change and on the changes in its paradigmatic basis, (ii) approaches exploring the impact of technological change on the environment for innovation and the consequences for the profit-seeking organisations carrying out technological activities and (iii) approaches exploring the impact of technological change on the whole economy.

2.4.3.1 Taxonomies focusing on the direction of technological change and on its paradigmatic basis

Dosi, for instance, refers to two main types of technological change: technological change along the same technological trajectory guided by the set of rules of a technological paradigm and extraordinary technological attempts related to the search for new technological directions and the establishment of new technological paradigms. The first ones can be motivated by technology-push and demand-pull factors in interaction or in isolation. The latter emerge either in relation to new opportunities opened up by scientific developments or to the increasing difficulty in going forward on a given technological direction (for technological, economic reasons or both). Changes in the socio-economic environment (demand-pull mechanisms) usually are not able to establish new technological paradigms (Dosi 1982, p. 157). De Liso and Metcalfe (1996, pp. 79-80) note that in many cases a new paradigm does not replace or overcome the previous ones: old and new technological paradigms can coexist. It is only their relative degree of economic and social application that determines the extent to which a technological revolution occurs. Moreover, due to the artefact and knowledge dimension of technologies, it is difficult to distinguish between incremental and revolutionary forms of technological change. A radical change in the knowledge dimension of technology may be articulated in incremental changes in the artefact dimension (since the articulation of the new forms of knowledge into artefacts may need a time lag or require new communities of practitioners to articulate the new paradigm).

2.4.3.2 Taxonomies focusing on the impact of technological change on organisational capabilities

Focusing on the artefact dimension of technology and using empirical material from the minicomputer, cement and airline industries, Tushman and Anderson (1986) explore

21 Empirical contributions have also developed quantitative methodological approaches to capture the nature of technological change and innovation. For a detailed see Grupp (1998, chapter 3).

the impact of technological change (new or improved product and process artefacts) on the environment for innovation.[22] They put forward the differentiation between incremental technological changes versus technological discontinuities.

Incremental technological changes are continuous improvements of established product or process artefacts. In this sense, they reinforce the established technical order. They occur through the interaction of many organisations, in most cases driven by the prospect of economic returns. On the other hand, technological discontinuities are far reaching advances, dramatic technological shifts that incorporate a major competitive progress compared with alternative technologies. Technological discontinuities can be competence enhancing (in the sense that build on existing know-how and result in over-magnitude improvements and increases of efficiency in the established core technology) and competence destroying (in the sense that the emerging technological advances are so fundamentally different from previous dominant technologies that the skills and knowledge base required to operate the core technology shift). Tushman and Anderson (1986) attempt to demonstrate that technology evolves through periods of incremental change punctuated by technological breakthroughs that either enhance or destroy the competence of firms in an industry. Competence-enhancing technological breakthroughs are initiated by existing firms and are associated with decreased environmental turbulence, while competence-destroying technological breakthroughs are initiated by new firms and associated with increased environmental turbulence.

Henderson and Clark (1990) explore different types of technological change in terms of their impact on the capabilities of the firm. Their unit of analysis is a manufactured product. By choosing a systems perspective they distinguish between the product as a whole (the system) and the product in its parts (the components).[23] Accordingly, successful product development requires two types of knowledge, component knowledge on the particular components and architectural knowledge on the ways the components are linked together. In this framework the traditional categorisation of technological change as either incremental or radical is incomplete. Henderson and Clark (1990) propose 4 types of technological change:

(i) Radical innovation: it establishes a new dominant design, a set of new components linked together in a new architecture;

22 They focus on three aspects of the environment for innovation: the degree of uncertainty, the opportunities for economic growth and the entry and exit rate of firms in an industry.

23 Component is defined in the sense of Clark (1985) as “a physically distinct proportion of the product that embodies a core design concept and performs a well-defined function” (Henderson, Clark 1990).

(ii) Incremental innovation: it improves or extends an existing design. Individual components might be refined but the underlying core design concepts and the links between them remain the same;

(iii) Modular innovation: it changes the core design concepts of a technology (such as replacement of analogue with digital telephones) without changing the product architecture;

(iv) Architectural innovation: it reconfigures an established system to link components in a new way.

In line with Tushman and Anderson (1986), Henderson and Clark (1990) suggest that radical innovations destroy the usefulness of the existing capabilities of established firms while incremental innovations tend to reinforce their positions. Architectural innovations present a challenge for established firms since the firm's component knowledge may be very valuable but the architectural knowledge available in the organisation may handicap the firm. Due to the fact that architectural innovations are not as explicit as radical innovations, organisations may have difficulties in capturing the true dimension of the innovation and acquiring the new architectural knowledge that it needs.

Finally, Abernathy and Clark (1985) have drawn a distinction between innovation that challenges the technical capabilities of an organisation and innovation that challenges the organisation's knowledge of the market and of customers needs.

2.4.3.3 The impact of technological change on the whole economy

From a broader perspective than the approaches presented above, and attempting to explore the impacts of technological change on the economy as a whole, Freeman and Perez (1988) introduce a taxonomy of innovations based on empirical work carried out at the Science Policy Research Unit (SPRU) in the United Kingdom. According to them, innovations (technological improvements that are rewarded in a selection environment) can be incremental, radical, they may involve changes of the technology system or, with their stronger impact, involve changes in what Freeman and Perez call the "techno-economic paradigm".

In the framework of Freeman and Perez "incremental innovations" occur more or less continuously. They are not the result of deliberate research activities but improvements suggested by those involved in production or by users. These innovations contribute to productivity growth but can't have dramatic effects. "Radical innovations" on the other hand are usually the result of a deliberate research activity. They often combine product, process and organisational innovation, bringing about productivity improvements together with structural change (in the sense that they usually largely stimulate

industrial activity and large flows of investments such as the development of nylon or oral contraceptives). However, unless they occur together with other radical innovations, they have no impact on the aggregate economy as a whole as in the development of the semiconductor or synthetic materials industry. These so called "changes of the technology system" are further reaching changes that affect several branches of the economy and give rise to entirely new sectors. Some of the changes in the technology systems are so far reaching that they influence drastically the behaviour of the entire economy. Changes in the so called "techno-economic paradigm", as Perez (1983) suggests, are very broad, reaching beyond technological trajectories or new directions of research (as captured in Dosi´s concept of new technological paradigm). Thus, a new "techno-economic paradigm" affects the input cost structure, conditions for production and distribution and modes of growth throughout the system, influencing the technological capability and limitations of the economic system, organisation forms of firms and forms of cooperation and competition (Freeman, Perez 1988, pp. 45-57).

2.5 The firm in the process of technological change

The body of neo-Schumpeterian research exploring technological change in the last 30 years has provided comprehensive theoretical explanations suggesting that the aggregate pattern of technological change that has been discussed in the previous sections draws on mechanisms at lower levels of aggregation such as the level of the organisation. From this perspective firms are the carriers of technologies and the driving force behind innovation.

The seminal work of Nelson and Winter introduced in section 2.1 was a tentative of explaining how the strategies of heterogeneous firms in the pursuit of competitive advantage are significant factors determining the rate and direction of technological change (Nelson, Winter 1982).

2.5.1 Theory of the firm in the Nelson and Winter approach

Drawing on organisational and behavioural concepts (such as bounded rationality and satisficing behaviour) developed by March and Simon (1958) and Cyert and March (1992), the main assumptions of Nelson and Winter regarding the behaviour of the firm deal with the question of why firms do what they do, or in other words, which are the factors shaping firms' decision-making.

In the Nelson and Winter framework, firms are heterogeneous profit-seeking actors aiming at improving their position vis-à-vis their competitors. In this context, the

possible behaviour of a firm is determined by its so called "routines". Routines may be considered as collective rules or procedures that programme the behaviour of firms over which the selection environment will operate. Rather than the result of optimisation problems, strategies are hence shaped by these behavioural and cognitive regularities.[24] Agency can influence the evolution and implementation of routines. However, rather than a "maximising" behaviour (as proposed by orthodox economic approaches) agents, in their decision-making process, display what Nelson and Winter called "satisficing" behaviour (Nelson, Winter 1982, p. 211). Even though firms aim at enlarging their profits, their decisions are not the result of a profit-maximisation analysis, since firms do not have enough information to optimise solutions (incomplete information on their environment) and are not able to compute alternatives (due to uncertainty and complexity inherent to the process of technological change). Under these conditions firms try to develop more effective means of production, or solutions to technological problems, relative to their current practice and relative to the practice of the industry. Moreover, firms have an incentive of applying modes of problem solving that have been successful in the past (in the sense of "good enough" rather than optimal).

Routines store hence essential information of the organisation which are remembered (or transferred between individuals). Due to the context-dependence of the problem-solving activity and the influence of firm's collective experience, routines have a path-dependent character. Accordingly, they provide some stability of behaviour, making it to some extent predictable. However, routines only depict potential patterns of firm behaviour over time. The complex and unpredictable environment where firms are embedded determines (ex-post) the firms' behavioural patterns we observe. The current characteristics of firms and their strategies to articulate knowledge into useful artefacts are hence the expression of firm’s routines in their competitive environment (Nelson, Winter 1982, pp. 134-136).[25] In an evolutionary framework, those firms whose behaviour is best suited to prosper in the environment become dominant, and with them, their problem-solving schemes.

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24 As pointed ou by Becker (2004) the concept of "routine" as Nelson and Winter proposed it is not associated with the every-day meaning of the term in many languages. Variation and change are phenomena that are not in opposition to the concept of routines.

25 Despite the enormous impact of the notion of firm's routines in various disciplines, the concept of routine remains unclear. For a discussion on this issue see for example Cohendet and Llerena (2003). Becker (2004) presents a review of the literature that has contributed to develop the notion of routines, what they are and the effect they have on organisations.

A large number of contributions have further developed the theory of the firm suggested by Nelson and Winter. These theoretical and empirical frameworks have brought about a large body of literature and the proliferation of terms and concepts that can be clustered under the so-called organisational capabilities approach or knowledge-based theory of the firm.[26]

2.5.2 The knowledge-based view to the theory of the firm

This section discusses the role of firms in shaping technological change at the aggregate level from the perspective of the knowledge-based view of the firm. Under this framework the firm can be defined through its knowledge base and is considered an organisation aiming at generating and applying knowledge (Grant 1996).

2.5.2.1 The building blocks of a firm's knowledge base

The body of literature drawing on Nelson's and Winter's concept of routines has introduced further terms conceptualising the knowledge base of the firm. These are mainly "organisational capabilities", "core competencies" and "skills".

According to Dosi et al. (2000), capabilities are know-how (embodied knowledge) that enables organisations to perform activities such as designing a new product, offering services or organising a marketing campaign. In a pharmaceutical company, capabilities are the forms of embodied organisational knowledge that account for the organisation’s ability to identify and develop new pharmaceuticals. With regard to the differences with routines, capabilities are usually larger units of analysis in the sense that routines are the building blocks of capabilities. Moreover, routines do not usually have an explicit purpose, while a main feature of a capability is the output that it is supposed to enable. In this sense, a capability is shaped by a conscious decision in its development and deployment and involves organised activity. A routine does not.

Prahalad and Hamel (1990) speak of core competencies instead of capabilities. According to Dosi et al. (2000), the concept of core competence is narrower than the concept of capability since it covers only the areas of “hard technology". The know-how required for accomplishing activities such as logistics, marketing or distribution are not included in the concept of competencies.

26 According to Foss (2003) the organisational capabilities approach comprises capability, dynamic capability, and competence approaches as well as the evolutionary theory of the firm. In a recent contribution, Foss and Klein (2005) refer to this body of literature as the knowledge-based approach of the firm.

Finally, individual skills are knowledge at the level of the individual. The skills of the organisation are the collectivity of skills possessed by individuals in the organisation and represent the building blocks of the organisational routines.

2.5.2.2 Accumulation of knowledge for technological change: Organisational learning

In creating, acquiring and adapting knowledge over time, organisations are performing something that in the management literature is referred to as organisational learning. Inspired by a group of contributions that stressed the role of knowledge in the absorption and generation of new technologies by firms, Malerba (1992, pp. 847-848) advances a conceptualisation of learning by firms with the following propositions:

(i) Learning is a costly and targeted process that takes place within the firm;

(ii) Learning is linked to different sources of knowledge that might be either internal or external to the firm. The different sources of knowledge can be accessed with different types of learning processes;

(iii) Learning is a cumulative process increasing the firm's stock of knowledge. The type of learning process determines the types of knowledge that can be accumulated through time;

(iv) The firm's specific stock of knowledge generates mostly local and incremental innovations. [27]

From the second proposition Malerba derives a taxonomy of learning processes which can be grouped in two main categories: learning internal to the firm and learning external to the firm. The taxonomy is presented in Table 2.

Table 2: Taxonomy of firm's learning processes

Learning internal to the firm	Learning external to the firm
• Learning by doing	• Learning from advances in science and technology
• Learning by using	• Learning from inter-industry spill-overs
• Learning by searching	• Learning by interacting

Source: Malerba (1992)

27 Malerba (1992) draws on contributions to the knolwedge-based approach such as Cohen and Levinthal (1989), Teece (1986) and Winter (1987) among others.

Learning internal to the firm is related to activities taking place within the firm and related to production (learning by doing), to the use of products, machinery and inputs (learning by using) or mainly related to formalised activities aiming at generating knowledge such as research and development. On the other hand, learning external to the firm is related to the absorption of new developments in science and technology, to what other actors in the industry are doing or to the interaction with suppliers, users or other firms in the industry. The knowledge-based approach of the theory of the firm views interaction as a channel to exploit complementary assets and to create new capabilities.[28]

The distinction between tacit and codified knowledge introduced in section 2.3 is essential in the context of organisational learning. The ability of firms to integrate knowledge outside their boundaries decreases the higher the degree of tacitness of knowledge.

2.5.2.3 Firm's performance in dynamic environments

In the knowledge-based approach, firms are different because they have different knowledge bases and different strategies to articulate their knowledge into innovations. An important consequence of the difference in knowledge bases across firms is that (even though firms may interact in the same industry and face the same signals) firms can interpret the signals differently and develop different patterns of actions (Cohendet et al. 2001). A relevant issue for firm strategy is the extent to which firms are able to interpret the signals and react adequately.

To stress the cognitive differences between firms in the way they perceive signals from their environment (or from their current technological regime in the sense of Nelson and Winter or technological paradigm in the sense of Dosi), interpret them and react to reach their business objectives (given the companies' technological capabilities), Metcalfe and Boden (1992) put forward the concept of "strategy paradigm", which

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28 In the last two decades at least 3 theoretical approaches have focussed on the role of cooperations in the innovation process. Transaction cost economics (Williamson 1985), the knowledge-based approach of the dynamic capabilities of the firms (Teece, Pisano 1994) and network theories (Håkansson 1989; Powell et al. 1996) agree that cooperation plays a central role in the innovative process. However, these theoretical frameworks present different rationales for collaboration. Both transaction cost economics and the dynamic capabilities perspective present collaboration as an alternative to internalising activities within the firm. The first focuses on cost reduction and opportunism arguments whereas the latter on the exploitation of complementary assets. On the other side, network theories present collaboration as an asset and not as a substitute for in-house activities. They argue that the knowledge gained within the innovation network can hardly be generated with existing firm capabilities, especially in fast evolving sectors.

relates to the competitive process at the level of the organisation. Firms competing in the same technological regime articulate their knowledge in different ways, take different bets. The crucial role of the strategy paradigm of a business unit is hence the generation of hypotheses at the interface of a selection environment and the technological capabilities of the firm (Metcalfe, Boden 1992, p. 65). In contrast to the notion of technological paradigm introduced in section 2.4.1, the strategy paradigm is firm specific and is embodied in the decision-making process of the firm by establishing the technological alternatives that can be considered, the technological options and the implementation model to develop them. The behaviour of firms in a dynamic environment is hence very much determined by their strategy paradigm.[29]

For Teece et al. (1997) a firm's success in competitive environments depends on the bodies of knowledge within the firm that differentiate it from its competitors strategically and are difficult to imitate. Therefore, the innovative opportunities of a firm are rather constrained by the set of firm-specific assets. As we have seen, according to Tushman and Anderson (1986) in a dynamic environment technological change can enhance or destroy firms' competencies. In some cases firm-specific assets can boost up development and incremental innovation as long as (after the shift) the industry remains in the same technological regime; or in other words, as long as the technological advance reinforces the established technological order. However, if these are technological discontinuities, firm-specific assets can foster incumbent inertia not only because these are difficult to change (since the adjustment may require a strong mobilisation of resources), but because firm-specific assets reflect accumulated behaviours and beliefs based on early corporate success that shape organisational culture and norms (Leonard-Barton 1992).

Theoretical contributions suggest that, under such circumstances, the innovative strength of the corporations in dynamic environments draws on their ”combinative capabilities”, i. e. the ability to acquire and synthesise knowledge resources and build new applications from those resources (Kogut, Zander 1992). Similarly, the "dynamic capabilities" approach, emphasises the ability to integrate, build and reconfigure internal and external competencies as the key to address rapidly changing environments (Teece et al. 1997).

If we consider the work of Cohen and Levinthal (1990), the strength of the combinative or dynamic capabilities of a firm draws probably on how firms equilibrate and complement external and internal learning processes. With the concept of "absorptive

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29 Also Witt (1999) stresses that firms can shape the cognitive structures of their employess by imposing them business conceptions that guide their problem solving strategies.

capacity" Cohen and Levinthal put forward the interrelation of these types of learning and their relevance for firms competing in rapidly changing knowledge environments. Absorptive capacity refers to the firm's ability to recognise the new technological opportunities and assimilate them. The important aspect of this concept is that absorptive capacity is a function of the knowledge of the firm. In other words, the extent to which firms are able to articulate knowledge from internal and external sources into useful innovations depends on firms' knowledge bases. Moreover, considering that firm's ability to acquire new knowledge and develop new capabilities is not independent from the history of the firm, absorptive capacity is hence path-dependent (Dosi et al. 1992). We can conclude that firms which have been able to perceive and integrate changes in their knowledge environment in the past are more likely to be able to do so in the future.

These contributions focusing on the role of firms shaping technological change are only a short review of the extensive literature in this subject from the knowledge-based view of the firm. However, due to the diversity of concepts and authors shortly discussed, the presentation demands a brief paragraph stressing the main ideas:

(i) From an evolutionary perspective firms are the carriers of technology. Firms display the novelty that is monitored in the selection environment introduced in section 2.4.2. In this process, due to the uncertainty and complexity inherent to the innovation process, the way firms do things is not part of a maximising exercise.

(ii) An important aspect of the knowledge-based view of the firm is heterogeneity. Firms are different because they embody different knowledge bases and have different strategies to articulate their knowledge into specific artefacts.

(iii) In their problem solving activities firms draw on internal and external sources of knowledge. Accordingly, the process of knowledge accumulation (organisational learning) can be external and internal to the firm.

(iv) Firms compete in dynamic environments and perceive signals from their environment in different manners and react as well differently. Their knowledge bases and their abilities to perceive and react to their environment build on experience.

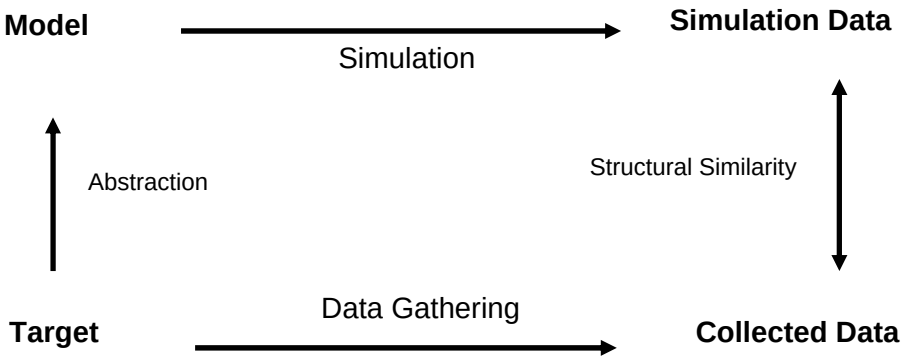
(v) Experience and knowledge accumulation allows firms to develop capabilities, competencies and skills that distinguish them from their competitors. However, in dynamic environments these firm-specific assets may need to be reconfigured to adapt to the new conditions. In this case, the ability to recognise new knowledge sources and integrate them is essential for firm's competitive strength. This ability is not independent from the history of the firm.

2.6 Simulation models to explore technological change

2.6.1 Simulation models in socio-economic research[30]

In simple words, computer implemented simulation models are artificial environments defining entities and relations between them which aim at representing real dynamic phenomena. However, a model of a real phenomenon remains a simplified, idealised and approximate representation of the phenomenon under consideration. The construction and analysis of simulation models can be applied (i) to understand and explain (ii) to forecast and (iii) to support decision-making. However, in socio-economic research the goal is understanding qualitative developments and pattern formation rather than developing accurate models from a quantitative perspective. In general terms, the use of simulation models allows researchers in socio-economic fields to explore dynamic phenomena including stochastic processes. Moreover, research may require the exploration of non-linear systems that can not be solved through analytic reasoning. In this case numerical approaches are effective tools for experimentation in socio-economic research.

Figure 1: Logic of simulation



Source: Drawn from Gilbert and Troitzsch (1999, p. 16)

Figure 1 sketches the logic of simulation. The implementation of a model and the simulation require the definition of a target, in other words, the specification of a phenomenon to be represented and explored by the model. In socio-economic research the target is dynamic. Usually the definition of a target entails hence the development of a theory of how the process works. Given the target, the model is the

30 This section is largely based on Gilbert and Troitzsch (1999, Chapter 2)

result of an abstraction and formalisation process that specifies (i) the relevant entities of the phenomenon, (i) their relationships (which may include random elements) and (iii) their change over time. The process of formalisation involves being precise in the definition of the entities and their relationships. However, complex models may require the development of assumptions regarding the way specific processes involved occurred or in terms of the parameters (input values). Input values may need to be assumed, not measured. Nonetheless, the logic of how the phenomenon occurs needs to be complete and coherent. Next, through real data gathering, empirical observations need to be collected that describe the output of the processes of interest or behaviour to be explored.

Through simulation the model should hence be able to reproduce the collected real data. If not, the model needs to be improved by better specifying and formalising the entities involved and their relationships. In some cases the improved specification of the model may require further empirical research and analysis of the real phenomenon. Accordingly, the process of model building, before the simulation experiments are carried out, entails already a process of improving researcher's understanding of how real phenomena work. This process does not end until the model can be relied on to reflect the behaviour of the target. Therefore, the data collected from the target (the real data) are the reference to validate the model. If the model includes random elements it is necessary to keep in mind that computers work with pseudo-random numbers and the result of just one simulation run is not reliable. Therefore it is necessary to test whether the results are robust with respect to different random values. Once the model is validated, a sensitivity analysis is carried out by varying selected parameters of the model and observing the differences in the outcomes. The aim is to find out whether the behaviour of the simulation model is sensitive to the assumptions that have been made.

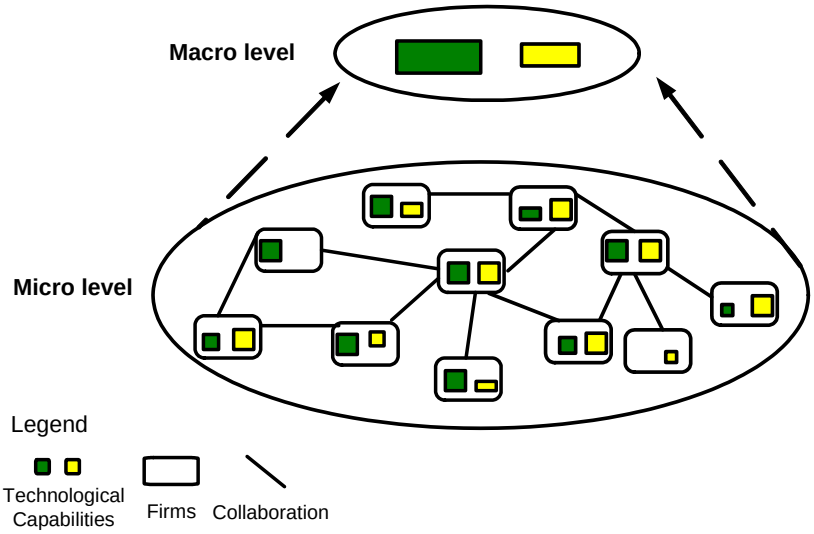
2.6.2 Value of simulation for the evolutionary approach to technological change

The potential of simulation models to explore economic growth and technical change has been emphasised by evolutionary scholars. The development of computer-implemented simulation models has been indeed an important factor fostering the wave of neo-Schumpeterian evolutionary modelling (Kwasnicki 1999, pp. 20-21; Dosi, Nelson 1994, p. 154). The usefulness of simulation models builds mainly on their ability to deal with the complexity of the evolutionary process of technological change, its fundamental uncertainty and the requirement to consider heterogeneity between firms.

To illustrate how complexity influences the analysis of evolutionary processes we draw on social theoretical investigations. Gilbert (1998) points out how, even if the behaviour of individuals may follow very simple rules, their interactions can create systems of great complexity (Gilbert 1998, p. 11). Complexity can be linked to the existence of emergent properties in economic and innovation processes.[31] In capitalistic economies, industries, for instance, have emergent properties because, even though their existence draws on the interaction of firms, the interesting properties and patterns of development (such as size distribution of firms or the relative importance of technologies) can't be described from the perspective of the individual agents interacting in them. The properties of the industry are the output of decentralised behaviour of individual firms. They flow from the mechanisms at the micro level, which might involve stochastic processes. However, the subject of analysis is not the individual firm but rather the industry.

Pyka and Faggiolo (2005) translate this concept to neo-Schumpeterian economics by describing socio-economic systems as systems with micro-macro relationships. Figure 2 sketches such a system that could be used to analyse a process of technological change (i. e. the changes in the relative importance of technologies over time).

Figure 2: System with micro-macro relationships



31 "Emergence occurs when interactions among objects at one level give rise to different types of objects at another level. More precisely, a phenomenon is emergent if it requires new categories to describe it which are not required to describe the behaviour of the underlying components" (Gilbert 1998, p. 12).

The micro-level contains heterogeneous entities (firms for instance) with different characteristics (such as the stock of capabilities in two different technologies represented in the figure with dark and light squares). Repeated interactions among these firms and their performance in a selection environment change the micro-economic patterns (their stock of capabilities in each technology). The aggregation of these micro patterns generates macro dynamics for the aggregate variable of interest (capabilities of the industry in each technology represented in the figure with a dark and light square in the macro level). The behaviour at the macro level is generated from the behaviour of entities at the micro level. The behaviour at the macro level is hence an emergent property.

The problem of processes presenting emergent properties is their exploration. Computer-implemented simulation models can be given the necessary structure to link the interaction of heterogeneous agents to the development of variables at a higher level of aggregation (such as the industry or the economy) (Lane 1993a; Lane 1993b). Given that from an evolutionary perspective, in decentralised economies firms are the carriers of technology, the exploration of technological change at the industry level involves the exploration of a system with micro-macro relationships.

If we consider the nature of technology we must also outline the fundamental element of uncertainty in the process of technological change. As pointed out in section 2.3, an implication of the complexity of technology is the ex-ante uncertainty in its application. However, as Dawid (2004, p. 5) points out, uncertainty not only flows from the unpredictability in the articulation of different bodies of knowledge into useful artefacts, but also from the reaction of competitors to the new artefacts. Also Dosi (1988b) puts forward that innovation involves “the search for new products, new production processes and new organisational set-ups”. By definition the outcome of the search activity can not be predicted before the exploration has started. This fundamental uncertainty does not come from lack of information but mainly because the impossibility of “precisely tracing consequences to actions” (Dosi 1988b, p. 222). As discussed in section 2.5, to make constraints on computability explicit and to restrict the information of the agents to what is available evolutionary modelling takes a behavioural view with rule-based decision-making processes. Simulation models can be design to incorporate sets of rules to determine investment or technology adoption decisions (Dawid 2004, pp. 5-6).

As discussed in section 2.5, technological change (with regard to the relative importance of technologies in industries or economies) is an aggregate behaviour drawing on the heterogeneity of knowledge and capabilities held by different firms in an industry. Firms drive innovation to distinguish themselves from their competitors or to

imitate them hoping to improve their position in the selection environment vis-à-vis their competitors. Consideration of heterogeneity of firms seems essential to understand the processes governing technological change. Simulation models can be designed to include heterogeneous agents with different strategies (in which heterogeneity is not only induced by differences in the endowments of firms but also by differences in behaviour) without having to reduce the analysis to a representative agent (Dawid 2004, p. 6).

2.6.3 The Nelson and Winter simulation models

As already pointed out in section 2.1, the strand of new evolutionary economics has increasingly relied on computer simulation models to explore economic processes. The work of Nelson and Winter (1982) was a strong impulse in this direction. This seminal work included the joint efforts of the authors to explore macroeconomic patterns breaking with heterodox assumptions on firm behaviour such as rationality, perfect information and optimising behaviour. Their assumption of macroeconomic properties flowing from microeconomic behaviour of agents was the basic reason for the necessity of using computer simulation models (Nelson, Winter 1982, pp. 207-208).

In their seminal contribution Nelson and Winter (1982) present an evolutionary model of economic growth (chapter 9) and a model to explore the interactions among market structure, R&D spending, technical change and certain firm's behavioural rules relevant for the process of improving production techniques (chapter 12) in an industry producing an homogenous good. The latter has been called a model of "Schumpeterian competition".

The firm is the key unit in the specification of their models. However, the interesting processes to be explored occur at the level of the population (the industry). The condition of the industry at any moment *t* is described by the capital stock and the behavioural rules of each firm (which involve the productivity of capital). Through search and selection processes the firms evolve over time, changing the productivity of capital. However, search and selection are stochastic processes. The firm's investment rate determines the stochastic realisation of a change in productivity of capital. In other words, investment rates in period t determine the probability distribution for innovation and hence the productivity of capital in period t+1. Moreover, it is assumed that the state of the economy prior to period t does not influence the transition probability between t and t+1 (Nelson, Winter 1982, p. 19).

Successful innovations increase productivity and tend to enhance the profitability of a firm. Accordingly, firms compete to develop the best technology. The market introduces

selection forces which apply to those firms who are less profitable, or, in other words, to those firms who are not able to keep up with the pace of technological progress of their competitors. Firm's profitability determines whether firms expand or contract.

The key idea behind the transition mechanism from one state of the industry to the next one in the Nelson and Winter models is that the state of the economy in any period determines the probability distribution of the state of the economy in the next period. The models contain hence a complete specification of the transition from the state at t to the state at t+1 which has the character of a stochastic Markov process.

The consideration of different scenarios characterised by different scenarios of conditions for innovation (such as different degrees of difficulty of imitation, speed in the growth of knowledge or degree of variety of innovations) or firm's strategies (in terms of investment rules of firms) allows evaluating the extent to which technological change and industry concentration are sensitive to the scenario considered.

Nevertheless, certain aspects are highly simplified. For instance, firms never adapt their decision rules. This aspect was improved by Winter (1984) who extends the Nelson and Winter approach by specifying adaptive innovation strategies (in terms of spending in innovative and imitative research and development) and firm entry.

Moreover, innovation probabilities in the Markov process only depend on current investments. There is neither accumulation of research investment nor explicit role for knowledge accumulation at the firm. Llerena and Oltra (2002) develop the Nelson and Winter approach to include this aspect. Firm's innovation probabilities depend on the stock of accumulated knowledge rather than on current investment. Also Pyka (Pyka 1999) develops an approach specifying spill-overs and the role of firm's absorptive capacity to integrate them in the innovation process.

Finally, the representation of technological change is very rudimentary. The Nelson and Winter models do not specify how research and development funds result in productivity increases.

2.6.4 Evolutionary history-friendly modelling

The Nelson and Winter models have had great influence on evolutionary modelling. Following the theoretical and methodological approach of Nelson and Winter, and in some cases extending it in different directions, the field of new evolutionary economics has advanced since the 1980s in the development of general theory of economic growth and industrial dynamics. Important followers of Nelson and Winter are among others Winter (1984), Silverberg et al.(1988) and Silverberg and Verspagen (1994).

Evolutionary simulation models have been able to generate plausible patterns of economic growth or changes in the concentration of industries. However, there has been little effort to use simulation models to generate hypothesis about technology development and to test outcomes against historical experience in a rigorous manner (Ruttan 2001, p. 107). On the other side, the neo-Schumpeterian strand embracing Institutional Economics and recognising the range of institutions involved in technological change has elaborated a large body of empirical and historical case studies (Nelson 1995). As already discussed in section 2.2, even though this strand of neo-Schumpeterian contributions lacks mathematical abstraction, it explicitly explores the role of institutions in shaping technological change, economic growth and differences between regions, countries and industries.

Attempting to fill up the gap between formal modelling to build general theories and empirical analysis of specific cases, Malerba et al. (1999) put forward the history-friendly model approach. In this framework simulation models aim at reproducing observed patterns of socio-economic change. Most importantly, the theory underpinning the models draws on empirical regularities (i. e. stylised facts) and verbal causal relationships (i. e. appreciative theory) explicitly considering the role of institutions in shaping the phenomena under exploration.

In their approach Malerba et al. (1999) develop appreciative theorising as suggested by Nelson and Winter (1982, p. 46). The appreciative theory of a phenomenon is the verbal logic explaining it with causal arguments and descriptive explanations. History friendly models draw hence on appreciative theorising and include (i) a set of stylised facts characterising the phenomenon to be explored, (ii) verbal logic on how the processes occur, (ii) formal representation of the verbal logic in a model and (iii) the implementation of a numerical computer simulation replicating the phenomenon explored.

In the history-friendly framework, formal modelling should be considered firstly as an attempt to asses the consistency of the verbal arguments that constitute the appreciative theory. This assessment involves, on the one side, verifying that the model can generate the historical patterns observed. On the other side, assessing the consistency of the appreciative theory involves testing whether parameter settings contradicting the accepted stylised facts yield to "history divergent" results (Malerba et al. 1999, pp. 4-5). Given the consistency of the appreciative theory, the models can be validated and used as experimental environments to explore the same phenomenon under different conditions (Orsenigo 2003).

To sum up, history-friendly model building attempts to reconcile formal and appreciative theorising of economic evolution. It requires firstly the identification of stylised facts describing a phenomenon of interest and the understanding of the factors and mechanisms shaping the processes observed. How these factors and mechanisms shape the process observed needs to be articulated with verbal arguments. Secondly, the verbal arguments are formalised in a model and implemented in a computer simulation in order to replicate the patterns observed. Even though the specification and parameterisation of history-friendly models is largely based on empirical findings (i. e. stylised facts of highly qualitative nature), the architecture of the models is similar to the Nelson and Winter type of models. The firms, their behavioural rules and the transition dynamics defining the evolution from state t to state t+1 (including selection mechanisms and stochastic processes) constitute the fundamental structure of the models.

2.6.5 Examples of evolutionary history-friendly models

Evolutionary history-friendly models developed so far focus on issues of industrial dynamics. The phenomena considered refer to changes in terms of concentration, firm's entry and exit and the formation of hybrid forms of industry structures such as networks. In their first attempt Malerba et al. (1999) centre their approach in the computer industry and the changes in its structure since the 1950s. Using the same methodological framework, Malerba and Orsenigo (2002) explore the factors and dynamic processes accounting for the evolution of the pharmaceutical industry and biotechnology. Pyka and Saviotti (2005) develop a history-friendly model representing the emergence of a new industrial organisation in the so called biotechnology-based sectors (pharmaceuticals, agriculture, food, environment etc.).

Before elaborating the issues concerning a history-friendly model of technology adoption and technological change in the pharmaceutical industry, the next paragraphs describe briefly the main aspects and results of the modelling efforts that have already applied the history-friendly approach.

With regard to the history-friendly model exploring the computer industry, Malerba et al. (1999) start by elaborating an appreciative theory of how the industry has evolved, in particular the transitions of the industry in terms survival of incumbent firms and success of new entrants as new technologies emerged in the industry (from transistor to microprocessor technology) and new markets emerged (from mainframe computers, minicomputers through personal computers). The new technologies had a competence destroying effect in the market segments where a few dominant firms held the stronger market shares. New firms enter the industry carrying the new technologies and opening

up new market segments. The "old" established leaders will manage to enter the new markets segments but will not be able to sweep away the newcomers nor to reach the strong positions they held in their original market.

After elaboration of the verbal logic involving factors and mechanisms shaping this process, the next step is the development of the simulation model and its implementation. The authors formalise the following aspects nested in the competitive dynamics of industries:

- Interacting heterogeneous firms, their investment and price decisions and the evolution of their technological capabilities. The representation of firm behaviour is very simple, relying on fix percentage investment rules. Firms' strategies are assumed to be fixed;
- Adoption of new technologies by incumbent firms and their diversification into new markets. These actions follow simple probabilistic rules;
- Different user types of computers shaping different market segments.

Finally, by considering empirical observations from the computer industry in a highly qualitative way (i. e. stylised facts, the authors choose a set of parameter values (difficulty of market entry, technology adoption and diversification costs, customer sensibility to quality etc.) to run the model and try to “replicate” the historical patterns observed in terms of industry structure and firm entry during the transition from one technology to another (from transistor to microprocessor technology). In order to test the logic of the appreciative theory the model is based on, the authors specify a set of parameters that produce ‘history-divergent’ results. This exercise brings insights to the mechanisms shaping the evolution of the computer industry, especially the role of demand, and the conditions for technology adoption, market diversification and firm entry in the structure of the computer industry. In a latter contribution Malerba et al. (2001) extend their descriptive analysis to explore the effect on the market structure of antitrust measures in the computer industry and of several measures to support firm diversification and firm entry as new markets emerge.

In their exploration of the pharmaceutical and biotechnology industries Malerba and Orsenigo (2002) identify stylised facts largely based on the experience of American pharmaceutical companies. Drawing mainly on the American experience, their appreciative theory (or verbal account of the changes in the industry) establishes 3 major epochs: the period between 1850 and 1945 (in which little new drug development occurred and minimal research was conducted with primitive methods)[32],

32 In Europe, especially in Germany, the industrialisation of research and development in the pharmaceutical industry occurred already in the first quarter of the 20th century. German

the period between 1945 and 1970 (characterised by the institution of industrial R&D laboratories and faster rates of new drug introduction based on random screening procedures) and the period after the 1970s (which was characterised by the influence of molecular biology in research and the transition from a different search regime in drug discovery: drug discovery by design). The key aspects defining the specification of their model are:

- The absence of economies of scale and scope in pharmaceutical innovation.
- The exogenous "advent of science" which enlarges the opportunities for innovation and introduces a technological discontinuity. The technological discontinuity is specified exogenously through the variation of the possible behaviour of incumbent pharmaceutical firms in their innovation activities and allowing for the entry of companies with the ability to exploit the new opportunities for innovation.
- Biotechnology firms challenge the industrial position of large pharmaceutical companies. The incumbent pharmaceutical companies do not react immediately to the discontinuity; they learn gradually and seize collaborative arrangements with the new entrants.

Their analysis concentrates on the role of market fragmentation and the level of opportunities for innovation (before and after the technological discontinuity) to explain the observed patterns of industry evolution (in terms of industry concentration). Even though the model introduces some aspects of a science-based industry, the relationships between science and innovation, the role of scientific knowledge and the process of knowledge accumulation within the firm to develop capabilities for innovation are not included in the model specification. Using highly qualitative data to set the parameters and define the probabilistic distributions the history-friendly model replicates key historical features of the industry structure and dynamics such as low degree of industry concentration and weak impact of the emergence of the biotechnology industry in the concentration of the pharmaceutical industry. This is mainly due to the inability of biotechnology companies to replace incumbent pharmaceutical firms and the development of collaborative arrangements between large pharmaceutical firms and biotechnology companies.

The contribution of Pyka and Saviotti (2005) develops a history-friendly model replicating the emergence of networks in the so called biotechnology-based sectors (pharmaceuticals, agriculture, food, environment etc.). Their analysis focuses on the importance of knowledge generation and accumulation featuring the biotechnology field. Based on the empirical findings and on the existing case studies on the

dyestuff companies developing drugs followed science-based strategies in their drug discovery processes (see section 3.4.2).

biotechnology-based sectors, the authors develop a formal representation of the development of the industry structure. The authors admit that the analysis leaves open the issue of the asymmetries among countries and the different roles Dedicated Biotechnology Firms (DBFs) may play in each region. The results give insight to:

- The two roles of the DBFs as translators (to cover the competence-gap of the established companies at early stages) and *explorers* (to investigate the scientific fields that established companies are not willing to enter in an irreversible way);
- The existence of innovation networks in the biotechnology-based sectors as stable phenomena and efficient forms of industrial organisation against the traditional dichotomy between the market and hierarchical organisations.

2.7 Towards a history-friendly model of technological change and technology adoption in the German pharmaceutical industry

The evolutionary history-friendly models introduced in the previous section are bottom-up approaches exploring industrial dynamics. In other words, by specifying the behaviour of heterogeneous firms at the micro level and the competitive environment where they interact, the models explore the structure of the industry over time in terms of degree of concentration and network formation. Malerba et al. (1999) and Malerba and Orsenigo (2002) introduce technological change in the history-friendly models by allowing for entry of firms in the industry mastering a new technology and changing the conditions for innovation. Incumbent firms can adopt the new technology or not.

Apart from important assumptions at the organisational level (such as rejection of maximising behaviour and the implicit specification of routines), the evolutionary aspect of history-friendly models of industrial dynamics lies on the exploration of industry evolution with specification of search and selection mechanisms involving random processes. Moreover, the transition dynamics from the stage of the industry at time t to the stage at time t+1 are specified (implicitly) through Markov processes.

The analogy between these models of industrial dynamics and biological evolution is sketched in Table 3. While history-friendly models of industry evolution choose the population of firms as unit of evolution, this contribution proposes a history-friendly model of technological change. Accordingly, as sketched Table 3, the unit of evolution is the body of technological capabilities constituting the pharmaceutical industry. The unit of selection is the firm (as carrier of technological capabilities). Firms will hence face a selection environment where they are rewarded (or not) according to their adaptability to the environment. Inspired by the theory of the firm suggested by Nelson

and Winter (see section 2.5), firms' adaptability will be determined by the expression of their routines in the selection environment.

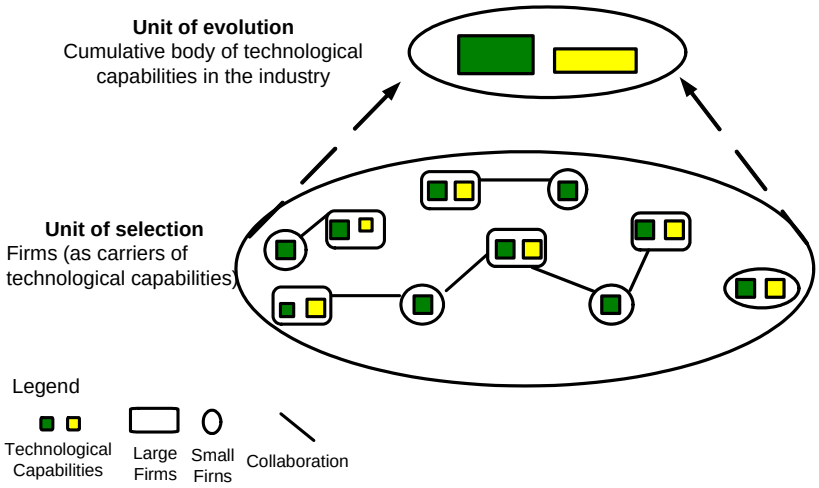
Table 3: Levels of aggregation in evolution

Level of aggregation	Biology	Industrial Dynamics	Technological Change
Unit of variation	Genotype (units accumulating and transferring information)	Routines (behavioural and cognitive regularities storing and transferring information)	Routines (behavioural and cognitive regularities storing and transferring information and building up the technological capabilities of the firms)
Unit of selection	Phenotype (organisms)	Firms	Firms (as carriers of technological capabilities)
Unit of evolution	Pool of genes	Population of firms constituting industries or national economies	Cumulative body of technological capabilities constituting industries or national economies

Source: Adapted from McKelvey (1996)

The evolutionary analogy can be represented by a system with micro-macro relationships as the one give in Figure 3.[33]

Figure 3: Micro-macro relationships in a model of technological change



In the history-friendly model of technological change proposed in this contribution, the phenomenon to explore is the relative importance of capabilities in two technologies

33 See section 2.6.2 for a short elaboration on systems with micro-macro relationships.

(synthetic organic chemistry and biotechnology) in the aggregate level of capabilities of the German pharmaceutical industry over time. This phenomenon is the unit of evolution in Figure 3, where the capabilities of the industry in each technology are represented with a dark and a light square. Taking the neo-Schumpeterian perspective that the aggregate pattern of technological change draws on mechanisms at lower levels of aggregation such as the level of the organisation, the exploration of technological change demands hence the consideration of heterogeneous firms as carriers of technologies. German drug producers are considered the heterogeneous agents carrying technologies, interacting and facing a selection environment (i. e. unit of selection in Figure 3). Firms are heterogeneous because they have different "routines" (behavioural and cognitive regularities, in simple words modes of carrying out their business and of managing their research and development activities). As a model of technological change, the focus lies on the technological capabilities firms apply to adapt to their environment and on the processes underpinning the accumulation of these capabilities. Capabilities are represented in Figure 3 with a dark and a light square in each firm and determine, to a large extent, adaptability to the competitive environment[34]. Due to the science-based character of the pharmaceutical industry, the development of technological capabilities to discover and develop medicines draws on the understanding and application of scientific results. Therefore, the knowledge environment of the firms (i. e. firms extramural knowledge base) and its dynamics plays an important role in the process of technological change we are exploring.

Taking this basic structure as staring point to define the phenomenon to explore, the next step is the specification of how the knowledge environment changes and how firms interact to acquire knowledge and develop capabilities. History friendly models specified these elements on the ground of appreciative theorising. Accordingly, an empirical analysis identifies stylised facts of the industry and describes the observed pattern of technological change.

In this contribution the empirical analysis to develop an appreciative theory will concentrate firstly on the study of the environment where firms interact and subsequently on firms' strategies for acquiring and developing technological capabilities to adapt to the requirements imposed by the selection environment. The analysis will focus on the following aspects of the German pharmaceutical industry:

(i) The knowledge environment shaping technology development;

---

34 The nature capabilities is discussed in section 2.5.2.1.

(ii) The implications of changes in the knowledge environment for the conditions for innovation in the pharmaceutical industry;

(iii) Firms' strategies to integrate knowledge and develop technological capabilities.

With regard to the first aspects concerning the knowledge environment of firms, the concepts of technological regimes and technological trajectories put forward by Nelson and Winter (1977) and Dosi (1988b) introduced in section 2.4.1 provide a theoretical basis to explore the knowledge environment shaping technology development and the implications for the conditions for innovation in the pharmaceutical industry. Malerba and Orsenigo (1993, pp. 47-49) make these concepts operational for empirical analysis and define technological regimes according to the following dimensions:[35]

(i) Innovation opportunity conditions: These refer to the effort needed to develop new successful solutions to a technological problem.

(ii) Characteristics of the knowledge base underpinning technological change: The knowledge base of a technological regime can be largely tacit and firm specific, or rather codified and universal. Moreover, it can present different degrees of complexity in respect to the disciplines contributing to its development or in respect to the number of competences needed to develop technological solutions.

(iii) Appropriability conditions: These reflect the extent to which firms are able to protect their innovations and appropriate the innovation rents (in other words the ease of imitation or the existence of knowledge spill-overs).

(iv) Degree of cumulativeness of technological knowledge: Extent to which technology improvements within a technological regime demand experience and accumulation of knowledge.

The empirical analysis focusing on biotechnology and organic chemical synthesis and on the extent to which they have shaped drug discovery and development should be able to identify these dimensions and their changes over time. Due to the difficulties in measuring these dimensions however, the analysis will be highly qualitative and asses the dimensions as been "high" or "low" in different periods of evolution of the pharmaceutical industry. Moreover, the empirical results should specify whether the dimensions differ across the trajectories under consideration: biotechnology and the organic chemical synthesis.

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35 Malerba and Orsenigo (1993) use the concept of technological regime to explore the adequacy of firm's strategies to the environments they operate in.

With regard to firms' strategies to integrate knowledge and develop technological capabilities to adapt to dynamic environments, the empirical analysis will take an organisational perspective. At this point the empirical exploration will draw on the theoretical concepts put forward in the presentation of the knowledge-based theory of the firm sketched in section 2.5.2. Accordingly, considering that firms are different with regard to their knowledge bases and their interpretation of the environment, the empirical effort will try first to gain insights on the knowledge bases of the German drug producers in terms of routines and capabilities and their changes over time. Next, drawing on the categorisation of firm's learning processes presented in Table 2 in section 2.5.2.2, the stylised facts should be able to characterise firms' patterns of internal and external learning in the processes of accumulating technological capabilities. Finally, the appreciative theory will explore the ability of industry incumbents in recognising changes in their dynamic knowledge environment. Given that the phenomenon to explore deals with technological change in a science-based industry with strong discontinuities in its scientific knowledge base, the stylised facts at the organisational level should give insight to the processes shaping technology adoption by German drug producers after the advent of modern biotechnology in the 1970s.

After the empirical effort is accomplished and stylised facts are identified, the appreciative theory of technological change and technology adoption in the German pharmaceutical industry will be formalised in a model and implemented in a numerical computer simulation following the steps sketched in section 2.6.1.

3 An appreciative theory of technological change and technology adoption in the German pharmaceutical industry during the 20th century

3.1 Introduction

The aim of this chapter is to identify the main variables and causal relationships shaping technological change and technology adoption in the German pharmaceutical industry during the 20th century. In other words, the goal is to develop a verbal explanation of how the interesting processes have occurred. For this purpose the exploration draws on a literature review in the fields of history of technology and empirical industrial dynamics and innovation research. Moreover, the analysis uses quantitative and qualitative indicators to study selected issues.

As discussed in chapter 2, from an evolutionary perspective the aggregate pattern of technological change that can be observed at level of the economy or at the level of the industry draws on mechanisms at a lower level of aggregation (such as the level of the firm) and on the features of the knowledge environment where firms conduct their profit-driven activities. Accordingly, the attempt of developing an appreciative theory to explain verbally the process of technological change in the German pharmaceutical industry during the 20th century demands the consideration of the complex interaction between (i) the knowledge environment shaping technology development, (ii) the industry (as selection environment) and the implications of changes in the knowledge environment for the conditions for innovation and finally (iii) the strategies of the firms to develop capabilities to accomplish their risk-taking and profit-driven activities in a dynamic knowledge environment.

Therefore, to develop an appreciative theory of technological change, this chapter explores the German pharmaceutical industry in the 20th century from three perspectives: (i) the knowledge environment perspective, (ii) the industrial perspective and (iii) the organisational (or the firm) perspective.

From the perspective of knowledge environment section 3.2 focuses on the development of two technologies (organic chemical synthesis and biotechnology) and their scientific knowledge bases. This short excursion in the history of these technologies does not intend to provide new insights on their emergence and development. The presentation draws on contributions to the history of technology and presents the main facts relevant for understanding the changes in the bodies of knowledge shaping their development and their influence in the German pharmaceutical industry.

Section 3.3 presents the evolution of the pharmaceutical industry in Germany with special attention to the changes in the knowledge base for drug discovery and development induced by the possibilities to apply synthetic organic chemistry and biotechnology. The exploration points out the successful innovative performance of German drug producers during the first half of the 20th century applying the principles of organic chemistry and the problems of the industry in adapting to the paradigmatic change towards the application of biotechnology in drug discovery and development after World War II.

Finally, from the organisational perspective, section 3.4 explores the strategies for adjustment of the German drug producers to the changes in the knowledge base after the revolutionary discoveries in molecular biology in the 1970s. The analysis presented considers the historical conditioning of the adjustment of firms to this technological discontinuity taking into account that the German corporations active in drug discovery and production come traditionally from two different sectors: the traditional pharmacy and the coal-tar dyestuff industry. Until the 1950's both sub-sectors of the pharmaceutical industry were different in their organisational capabilities, their product lines and most importantly their attitudes towards the application of biotechnology. Section 3.4 follows a case study approach combining qualitative and quantitative tools.[36]

Section 3.5 closes the chapter with a short discussion of the main findings (in relation to the theoretical concepts introduced in chapter 2 and a presentation of the main issues to be explored in the history-friendly model to be developed in chapter 4.

3.2 Tracing the development of organic chemical synthesis and biotechnology

The following are two basic definitions of chemical synthesis and biotechnology relevant for the exploration that follows:

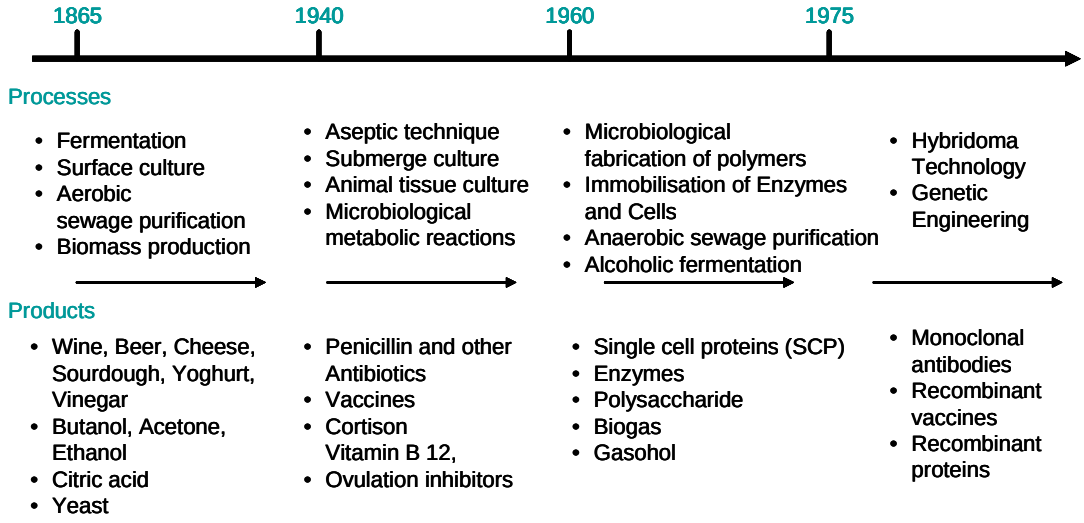
> The chemical synthesis combines chemical elements or simple chemical compounds to produce complex substances.
>
> Biotechnology is the application of scientific and engineering principles to the

36 The chapter does not include the qualitative company case studies carried out for the analysis. It presents only the main qualitative findings and the empirical results. The qualitative case studies are included in annex I.

processing of materials by biological agents to provide goods and services (Bull et al. 1982).[37]

According to the theoretical discussion in the previous chapter, a key characteristic of a technology is its imposed function. The technologies we are considering in this section have a common imposed function: the production of substances which can provide goods and services, however, while the organic chemical synthesis draws on the combination of chemical elements or simple chemical compounds to produce complex substances, biotechnology draws on the processing of materials by biological agents. For our purposes, this characteristic (the processing of materials by biological agents) is the main feature of biotechnology. Most importantly, this is the feature allowing us tracing a continuous (bio-)technology trajectory during the 20th century and beyond. This trajectory covers a large range of techniques ranging from fermentation processes in the 19th century to the application of recombinant DNA techniques developed in the 1970s. These techniques are presented in Table 4.

Table 4: The biotechnological trajectory.



Source: Adapted from Fonds der Chemischen Industrie (1989).

37 In a broad sense biological agents can be microorganisms, enzymes or plants. The agents may or may not be modified by genetic engineering. Among the several definitions of biotechnology this one proposed by the Organisation for Economic Co-operation and Development (OECD) has been influential in both academic and government circles and is the ground for the international statistics available on the development and application of this technology.

An interesting aspect of biotechnology and organic chemical synthesis is the strong influence that advances in different scientific disciplines and in engineering have had on the development and diffusion of these technologies. In their origins chemical synthesis and biotechnology were applied without any understanding of the processes underlying the transformation of chemical compounds or biological agents into products with desired properties. Technology application was an experimental trial-and-error process. Scientific and engineering advances during the 19th and 20th century have revolutionised these technologies by providing additional knowledge that has expanded their possibilities and improved their control. Krimsky (1991, p. 25) points out that the demarcation between analytic[38] and synthetic chemistry is similar to the distinction between pre- and post-1970 biotechnology. With the development of organic chemical synthesis it became possible to produce unique compounds. With modern biotechnology, genetic information could be transferred to produce organisms with desired properties. However, the time path in which new forms of knowledge have shaped the technologies providing them with new possibilities has been quite different, influencing hence the periods of their development and diffusion.

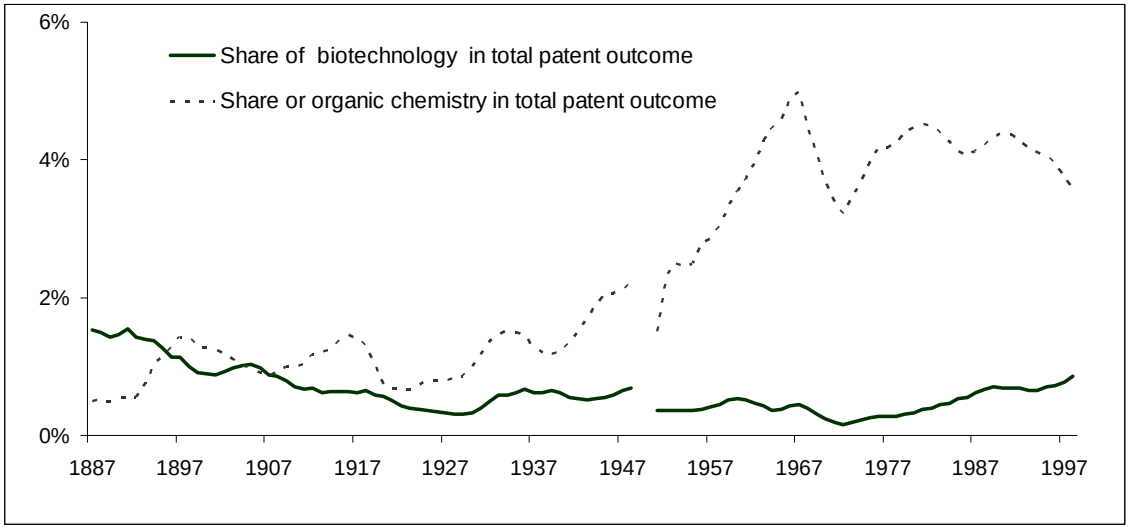
As regard to biotechnology, at the beginning of the 20th century the application of traditional biotechnology was an alternative to organic chemistry in the development and production processes of primary products. Despite the empirical nature of biotechnology, a large number of biotechnological processes had already been introduced in the industry. Waste water treatment, distillery, brewery, vinegar production, wine production, creamery, tannery, fertilizers, sugar production and production of organic acids were some of the fields and production processes where biotechnology was first applied. However, biotechnology (with its strong empirical character) could not compete with the development of the organic chemical synthesis (already drawing on a strong science base) and lost importance after World War I. The advent of the new scientific discoveries in the field of molecular biology in the 1950s changed the development path of biotechnology. The interdisciplinary advances in its science base during the 20th century have provided the technology with new possibilities that have promoted its application in different economic sectors.

On the other side, already in the late 19th century the chemical synthesis was guided by the scientific developments in organic chemistry and started to be applied by the dyestuff producers who developed strong scientific capabilities in organic chemistry. The application of the organic chemical synthesis was not only supported by its strong

38 Analytic chemistry is a collection of techniques that allows exact laboratory determination of the composition of a given sample of material.

science base. The development of the Haber-Bosch process in the 1910s influenced dramatically the application of chemical synthesis and the focus of the chemical industry on the application of this technology to produce complex substances. The organic chemical synthesis dominated the processing of materials until the last quarter of the 20th century. These historical stylised facts matched remarkably well with historical
patent indicators presented on Figure 4.

Figure 4: Shares of biotechnology and organic chemistry-related patent documents in the total patent outcome



Sources: Own calculations using data from PLUSPAT and PATDPA from the vendor Questel[39]

The next sections explore in detail the influence of the science base and advances in complementary technologies on the development paths of these technologies.

39 Data: 5-year moving average of German patent applications filed at the German and European patent offices with Germany as designation country. The database PLUSPAT provides the back file patent documentation used by the examiners of the European Patent Office (EPO) in their examination processes. This documentation is retrospectively reclassified according to the latest European Patent Classification's (ECLA) revision. Accordingly, the PLUSPAT database offers a suitable research tool to cope with the reclassification problems that appear in historical time series of patent indicators. For methodological issues on the elaboration of historical time series of patent indicators see Dominguez Lacasa et al. (2003).

3.2.1 Organic chemical synthesis

In the 18th century the chemical synthesis practice was carried out without a theoretical understanding of the chemical structure of the substances produced. Moreover, by the late 18th century the artificial production of organic substances by means of combining inorganic compounds seemed impossible.[40]

Advances in the elemental analysis of organic substances provided chemists with new insights about their composition and properties. Especially the experiments of Lavoisier (1743-1794) gave impetus to a systematic analysis of organic substances. Further experimental results suggested that the chemical laws governing the composition and behaviour of inorganic substances could be applied to organic substances as well.[41] With the new discoveries organic substances lost their special status of being produced by an “intangible life force” and became the compounds of carbon. Most importantly, the new understanding of the composition of organic substances set the ground for their artificial production through chemical synthesis (by combining the right elements, organic and sometimes inorganic, in the right amount and under the right conditions).

In 1846 the German chemists Frankland and Kolbe synthesised the organic compound acetic acid from inorganic substances that could be prepared directly from pure elements. After this discovery increasingly complex organic compounds were analysed. Already in the second half of the 19th century the synthetic structures of fruit and lactic acid were identified, and a large number of natural dyes, flavouring agents and the first medicines had been synthesised.

Kekulé's discovery of the ring structure of benzene in 1865, advances in physical chemistry (concerned with the physical properties of materials, such as their electrical and magnetic behaviour) together with a successive creation of new institutes with modern laboratories and an increasing number of skilled chemists contributed to the development of the organic chemistry and its application for industrial purposes.

Organic chemistry became the theoretical basis for the production of organic compounds available in nature (like benzene or ethylene) and its transformation through subsequent processing to obtain products with desired characteristics. The synthesis of organic substances was first applied for the production of dyes. Instead of

40 The distinction between organic and inorganic substances was important since chemists assumed that organic compounds could only be produced by an “intangible life force” present in plants and animals (Schorlemmer 1979).

41 Important chemists in this phase of development of the organic chemical synthesis were Gay-Lussac (1778-1850), Berzelius (1779-1848) and v.Liebig (1803-1873).

relying on the fortunate coincidence to discover new dyes, those producers skilled in organic chemistry had the possibility of imitating dyes that could be found in nature (or even inventing new ones). As pioneers of the application of the scientific principals of organic chemistry for industrial purposes, the dyestuff producers performed large investments in research and development that would determine their competitive capabilities in the years after (Andersen 1996).

During the 20th century the application of organic chemical synthesis reached most sub-sectors of the chemical industry in Germany like the production of nylon and polyester fibres, the production of plastics, pharmaceuticals, and the production of artificial sweeteners. A technological breakthrough in engineering in the 1910s, the development and application of the Haber-Bosch process for the production of ammonia, influenced dramatically the application of the chemical synthesis (Hughes 1975). With the high pressure synthesis of the Haber-Bosch process, the chemical industry intensified its strategy of chemically synthesising natural materials or replacing them by chemical supplements. The starting raw material was coal and Germany had enough coal reserves at that time. For instance, the IG Farben decided to specialise on coal-based products. By shaping the technological capabilities of the German chemical companies this breakthrough in engineering partly determined the technological orientation of the chemical companies towards the application of the organic chemical synthesis in all their segments (including pharmaceuticals) (Buchholz 1979; Marschall 2000).

3.2.2 Biotechnology

Even though biotechnology needed to wait until the 20th century to have the status of a science-based technology, already in the 19th century it was applied in different industrial activities from the biological production of fertilizers up to the production of rubber, fuel, lactic acids and in waste water treatment. Biotechnology had the advantage of being an inexpensive production method that relied on the availability of carbohydrate-based raw materials. According to Marschall (2000), despite its empirical nature, the years between 1900 and the World War I were of most prosperity for the industrial biotechnology in Germany. The data given in Figure 4 support her assessment.

The development of biotechnology during the 20th century to become the technology with the possibilities it has today is the result of the advance in understanding biological processes and of the development of a variety of skills and forms of knowledge to control them. These advances have provided a continuously growing knowledge base influencing the possibilities of the processing of materials by biological agents.

According to Abir-Am (2003), this development has come along with transdisciplinary research strategies to explore and control biological processes. [42]

All along the 20th century, biology has gone through a process of progressive colonisation by the so called exact sciences (i. e. chemistry, physics, mathematics, and engineering). Furthermore, this progressive colonisation has created hybrid fields or transdisciplinary outcomes which have found institutional stabilisation along the 20th century: first biochemistry, later on molecular biology, and at in the last quarter of the 20th century genetic engineering.

In the 19th century biotechnology relied on a scarce science base resulting from the alliance of biology, physiology and chemistry to explore biological and physiological problems with techniques of organic chemistry. Depending on whether the emphasis was on chemistry or biology, this alliance took different disciplinary formulations such as microbiology, bacteriology or biochemistry (Bud 1993, p. 7).

The institutionalisation of biochemical research began in the early 20th century with the chemical investigation and explanation at the molecular level of biological processes such as growth, respiration, nourishment, digestion, movement, sensation and reproduction (Kamminga 2003). The studies focused on the role of enzymes, vitamins and hormones in biological processes. [43]

In the 1930s the crucial role played by enzymes in regulating and coordinating metabolic reactions generated enormous interest in the structure of these substances. It was soon learned that enzymes are proteins[44]. Because of proteins' involvement in life processes, the exploration and complete resolution of their chemical and spatial structures seemed to be holding a key to understand the processes of life (Kamminga 2003). Due to the proteins' complexity, the problem of protein structure posed a

42 According to Mittelstraß (2004) given a disciplinary order and a problem, the research strategies to solve the problem can be transdisciplinary in the sense that different scientific disciplines collaborate to solve it "resulting in a lasting and systematic order that alters the disciplinary order itself" (Mittelstraß 2004).

43 Enzymes are protein molecules in plant or animal that affect the speed rate of specific metabolic reactions without being permanently altered or destroyed. They are responsible for bringing about all of the biochemical reactions in living organisms. Vitamins are organic substances that occur in many foods. They are necessary in trace quantities for the normal physiologic and metabolic function of the body. Hormones are biological substances that are produced by a certain cell or tissue and that cause a specific biological change or activity in another cell or tissue located elsewhere in the body (Morris 1992).

44 Proteins are complex organic compounds. They are widely distributed in plants and animals being responsible for every function in the living cell (Morris 1992). They are involved in life processes including respiration, digestion, and reproduction.

transdisciplinary challenge, which required, among others, physical and physico-chemical techniques, ranging from x-ray crystallography to the ultracentrifuge, electrophoresis, chromatography and electron microscopy. Even though proteins were the research focus of biochemists, the protein structure became a research object that could not be explored within the boundaries of biochemistry. The research question did not fit in the given disciplinary order because biochemists did not have tools to solve the spatial structure of proteins.

The research problems (and the strategies to solve them) reinforced in the late 1930s the transition from the era of biochemistry to the era of molecular biology, which explored the structures of viruses, proteins and nucleic acids (DNA and RNA)[45]. Between the mid 1940s and 1960s scientists discovered that the form and the function of a living cell derive from the information enclosed in its DNA. Furthermore, scientists learnt how this information was processed in the cell in order to produce proteins with a certain function. The transition process reached its peak in the 1960s with the academic stabilisation of molecular biology (Abir-Am 2003). However, as we will see in the next sections there were major regional differences with regard to the institutionalisation process of molecular biology.

Finally, in 1974 molecular biologists made public a new technological breakthrough, the phenomenon of artificially controlled recombinant DNA, which enabled the direct manipulation of the genetic material and the formation of new forms of life.[46] In 1975 scientists reported on the hybridoma technique and the production of monoclonal antibodies. These scientific techniques of genetic modification opened up the era of modern biotechnology, revolutionising the scientific knowledge base biotechnology draws on and its possibilities. These developments created enormous expectations for the industrial applications of biotechnology.[47]

45 In simple words DNA constitutes the genetic material of living organisms, which is present in every cell of every living organism. Each gene in the DNA contains the information for the composition of a particular protein and the necessary signals for the production of that protein. The RNA is the nucleic acid in the cell responsible for decoding the genetic information of the DNA for producing the proteins.

46 Recombinant DNA is a hybrid DNA molecule created by the in vitro combination of DNA from different sources. The recombinant DNA technology allows separating and recombining segments of DNA or genes (Morris 1992).

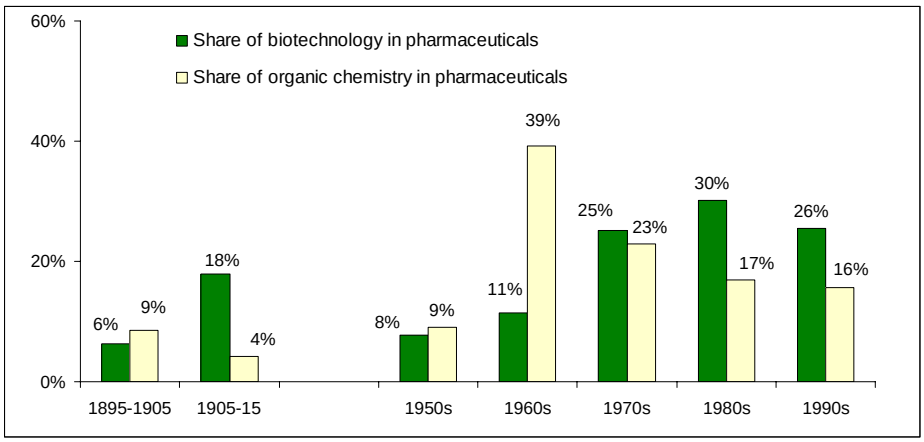
47 Sharp (1995) presents a short but clear overview of the applications of biotechnology. Her contribution focuses on the biotechnology applications after the revolutionary discoveries of the 1970s.

3.3 Technological change in the German pharmaceutical industry during the 20th century

After reviewing the development of chemical synthesis and biotechnology we face the challenge of capturing their relevance for drug discovery and development in Germany. Due to the great dependence of the pharmaceutical industry on the patent system for the appropriation of returns from research and development, the use of patent counts to capture the flows of codified knowledge in this sector seems to be adequate (Levin et al. 1987; Santos 2003).

Based on counts of patent documents Figure 5 presents the extent to which organic chemical synthesis and biotechnology have shaped the research and development process in drug discovery and development. Despite the relative importance of biotechnology in pharmaceuticals in terms of the share in the patent counts at the beginning of the 20th century, chemical synthesis dominated the sector in the 1950s and 1960s and until the last quarter of the 20th century. The scientific discoveries in the field of molecular biology in the 1950s seem to influence the development path of these technologies. According to the data, since the 1970s biotechnology plays an important role in pharmaceuticals. The empirical evidence speaks for the strong and increasing influence of biotechnology in the development of pharmaceuticals in Germany, especially since the 1980s.

Figure 5: Patent documents in pharmaceuticals. Shares of biotechnology and organic chemistry-related patents



Source: Own calculations based on data from the databases PLUSPAT PATDPA of the data base vendor Questel[48].

48 Data: German patent applications filed at the GPO and EPO with Germany as designation country. For methodological issues on the elaboration of historical time series of patent indicators see Dominguez Lacasa et al.(2003).

This pattern of technological change is the output of the interaction of the development of the firm's extramural knowledge base, the structure and competitive forces of the industry and government influences. The next paragraphs explore this interaction along late 19th and 20th centuries. The presentation draws on contributions to the development of the pharmaceutical industry in general, without a national focus and on studies concentrating on the American pharmaceutical industry. Therefore, many of the general aspects discussed are not specific for the German experience. However, the analysis aims at highlighting those aspects relevant for the German case. The aim is to describe the environment German drug producers were facing in terms of knowledge base and conditions for innovation.

Phase I (1880s-1950s): the establishment of the modern pharmaceutical industry

Before the formation of the modern pharmaceutical industry in Germany in the last decades of the 19th century the process of drug discovery and development was carried out by apothecaries in small traditional pharmacies. The responsibilities of doctors and pharmacists were clearly defined. The German state guaranteed the pharmacists the responsibility of producing and commercialising the medicaments prescribed by the doctors. Already in the first half of the 19th century the analytical chemistry became the tool to isolate from plants those compounds with therapeutic character. Nonetheless, the successful isolation of these compounds and the (unexplainable) therapeutic effectiveness raised the questions of how to disseminate the drugs to as many persons as possible and how to make sure that the medicines had homogenous standards. Some of the apothecaries recognised the need for large scale production and standardisation measures. From the technical point of view there were no major constraints for the large scale production of the known compounds, however the lack of infrastructure for transportation limited the regional area the pharmacists could supply with medicaments. The traditional small pharmacies developed into medium size companies like Schering or E. Merck, which produced alkaloids and medicinal chemicals extracted from animals and plants. It was the first impulse towards the formation of the modern pharmaceutical industry in Germany.

The second impulse towards the formation of the modern pharmaceutical industry came from the chemical sector. The largest German dyestuff producers were established between 1863 and 1873.[49] They started their activities by copying the dyes of French and British manufactures. However, already in 1877 half of the dyestuff world

49 Bayer Farbenfabrik (in the city of Wuppertal, 1863); Farbwerke Meister, Lucius und Bruening (in Hoechst, 1863), Aktiengesellschaft fuer Anilin-Fabrikation -Agfa- (in Berlin, 1873).

production had German origin (Murmann, Landau 1998).[50] During the 1880s the medicinal effects of dyestuffs and other organic chemicals were discovered. German chemical companies such as Hoechst AG and Bayer leveraged their technical competencies in organic chemical synthesis to manufacture drugs (Marschall 2000). Besides the strong competencies in organic chemistry the chemical companies strengthened their competencies through intensive research collaborations with academic scientists.

With the impulse from the dyestuff producers the German pharmaceutical industry became the largest source of medicinal innovations. Dyestuff firms (such as Bayer and Hoechst) and traditional drug producers (such as E. Merck and Schering) built up in the last decades of the 19th century the modern German pharmaceutical industry, which dominated the world market for new chemical drugs until World War I (Murmann, Landau 1998).

This prosperous period of the German pharmaceutical industry matches with the foundation of drug research, which found its institutional setting in the industrial research laboratories of the German drug producers.[51] In this period drug research was strongly influenced by the principles of the organic chemical synthesis. By the end of the 19th century analytic and synthetic chemistry had reached a high degree of maturity and were moving hand in hand with drug discovery and development (Drews 2003). Many examples illustrate the alliance of organic chemistry and medicine. The origins of chemotherapy, for instance, drew on the search for chemical compounds, which had the ability of destroying pathogens and could hence be used against infectious diseases like bacterial infections and, later on, against fungal and protozoa infections. Additionally, the scientific principles of organic chemistry allowed the synthesis of hundreds of compounds in the laboratory that could be tested for therapeutic effects against parasites (source of infectious diseases) in animal models and systematically manipulated to reach desired properties (Issekutz 1971). Even though this strategy for drug discovery very much relied on serendipity, this random

50 The dyestuff industry in Germany developed from the large scale production of illuminating gas. This production process produced a major by-product, the “coal tar”. This black mass seemed at first to have no significant industrial use; however it turned out to contain compounds of great interest for the production of dyes. Instead of being extracted from animal or vegetable sources, dyes could be developed "artificially" from the coal tar. This was the solution to satisfy the demand for dyes in the rapid growing textile industry at that time.

51 In other regions such as in the US and in the UK, formal science entered the drug factories in the mid-20th century after the discovery of the therapeutic properties of penicillin (Henderson et al. 1999).

screening worked very well for the German companies for many years. The opportunities for innovation were large since the companies faced an open field where most therapeutic solutions were waiting to be discovered.[52] Even though this strategy did not provide any biological understanding of the disease, drug discovery became an analytical process based on the accurate variation of the structure of organic compounds for designing and synthesising promising drugs. With chemotherapy diseases like syphilis or sleeping sickness could be treated with synthetic substances.[53] In the 1920s substances against malaria and streptococcus were successfully synthesised. In the 1930s the medical effects of sulphonamide to treat bacterial infections (streptococcus or staphylococcus infections) were discovered.[54] Again, even though organic synthesis did not provide any understanding of the biological process by which sulphonamide was able to achieve a bacteriological cure, the discovery of sulphonamide started the era of antibacterial chemotherapy.

Based on historical sources, Achilladelis (1999) points out that between 1880 and 1930 the modern German pharmaceutical industry was the source of more than 50 % of the medicinal innovations. Until the 1930s the application of synthetic organic chemistry had led German drug producers to innovative products that relieved the symptoms of diseases rather than their causes. These types of drugs were analgesics and antipyretics. Later on, organic chemical synthesis led to drugs that fought against the disease-causing agents such as protozoa or bacteria. In the 1940s the structure of a large range of natural substances with antiseptic characteristics to treat bacterial infections was discovered and synthesised in the laboratory by organic chemists.

Phase II (1950s-1970s): From random to guided drug discovery

Parallel to the successful synthesis of innovative drugs, biotechnology was experiencing a strong development, opening possibilities to understand biological processes of diseases and to produce medicines with microbiological methods at a large scale.

52 Achilladelis and Antonakis (2001) present data on innovation counts in the pharmaceutical industry since the 19th century. According to their data German corporations were until World War II the major introducers of innovations in the pharmaceutical sector.

53 Important substances of this type were Atoxil and Salvarsan. Salvarsan was the first effective chemotherapy. It was brought to the market by the German dye manufacturer Hoechst, with whom the scientist Paul Ehrlich collaborated.

54 The first marketing drug of this type was called Prontosil. It was brought to the market by the German dyestuff manufacturer Bayer in 1932.

As discussed in section 3.2.2 since the 1930s biology was being transformed by the exact sciences. The alliance of biology, physiology and organic chemistry (bio-chemistry) was providing new diagnostic procedures and means of intervening in disease processes at the chemical level (Kamminga 2003). Moreover, between the mid 1940s and 1960, advances in molecular biology provided the screening procedures to search for substances that attack biological targets with certain selectivity (Drews 2003, p. 80). In other words, these first advances in molecular biology set the ground for the understanding of the mechanisms by which drugs affect the body and allowed latter to developed techniques of "rational drug discovery" or "drug discovery by design" (Henderson 1994, pp. 14-16; Gambardella 1995, pp. 23-25).

Additionally, regarding the application of biotechnology in production processes, in the mid 1940s the development of bio-reactors offered unpredictable new possibilities. It was the beginning of the aseptic and aeration technique for the microbiological production at large scale. The development of the bio-reactor made the industrial application of microbiological processes possible (Metz 1995).

The German pharmaceutical industry had difficulties exploiting the technological opportunities offered by the new scientific advances in the disciplines emerging from biology (such as microbial biochemistry and enzymology). For instance, after the properties of penicillin to treat bacterial infections had been discovered in the late 1930s and its production by fermentation processes optimised, American and Swiss drug companies started to establish departments of microbiology and fermentation units. However, in Germany penicillin was only known from the scientific literature. Its therapeutic features were not very well known. Few research institutes and companies were carrying out research on penicillin production (Metz 1995). While in the 1940s American drug producers were producing penicillin to go through clinical trials German chemical engineers kept trying to synthesise sulphonamides for the treatment of bacterial diseases (Marschall 2000).[55]

Especially in the USA, pharmaceutical producers embarked on a period of massive investment in research and development. This period of institutionalisation of science in the American pharmaceutical industry was supported by strong investments of public research organisations in medical research in the United States (Pisano 2002). The penetration of biochemistry, microbiology and molecular biology into drug research was responsible for the drug revolution that in the 1950s and 1960s produced an

55 For a detailed historical analysis of the reasons why German drug producers disregarded the changes in the knowledge base underlying drug discovery in the 1940s see Marschall (2000, chapter 4.2).

abundance of new medicines such as psycho-pharmaceuticals, beta-blockers, calcium antagonists, diuretics, anaesthetics and anti-inflammatory preparations (Drews 2003).

The German pharmaceutical industry lost its leading position after the World War II. According to Achilladelis (1999) this was not a consequence of the war damage since in other sectors of the chemical industry companies such as Hoechst and Bayer re-emerged to become world leaders in the 1970s. In the pharmaceutical sector the weakness was mainly technological. After World War II, German drug producers restarted their activities with research and development strategies that had made them successful in the previous period and building on their chemical capabilities. In the 1960s they were not building up capabilities, which would have allowed them to conduct medical research on the function of hormones, the cardiovascular and the central nervous systems, anti-inflammatory drugs or vitamins (Buchholz 1979). Industry's disregard for biotechnology research and development in the 1960s was accompanied by a weak commitment of German public research institutions and universities in the biotechnology-relevant scientific fields. Zarnitz (1968, pp. 83-84) analysis the research activities of German research institutes and universities in the 1960s and identifies serious gaps with regard to the process of institutionalisation of molecular biology in German universities. Research fields such as protein research, cell and virus research, immune biology or molecular genetics at that time were mainly concentrated on selected institutes of the Max Planck society. However, according to Buchholz (1979), the biotechnology-relevant scientific developments and the industrial application of biotechnology in the 1960s occurred mainly in the Anglo-Saxon regions, in Switzerland, in Japan and in Sweden. Interestingly, Nobel prices in the fields of medicine and physiology in the period between 1946 and 1964 were granted for achievements in research on molecular biology. The national origin of the scientists was USA (6), Sweden (2), UK (7) and Germany (1) (Zarnitz 1968, pp. 54-55).[56]

The knowledge base of the industry was changing mainly beyond the German borders and the German corporations were not able to match the advances of their competitors based on the application of microbiology, biochemistry and later on, of molecular biology.

56 The figures in brackets represent the number of scientists with the given nationality. In some years the Nobel price was granted to more than one scientist.

Phase III (1970s-1990s): the era of modern biotechnology in the pharmaceutical industry

Since the mid 1960s and during the last quarter of the 20th century the breakthroughs in molecular biology and the revolutionary discoveries of recombinant DNA and monoclonal antibodies radically changed the drug discovery and development process. Their contribution to the process of drug discovery has been twofold. On the one hand they have helped to understand diseases and to determine the optimal molecular target for drug intervention. On the other, they have provided the tools for manufacturing proteins with known therapeutic value at a large scale, allowing their distribution as therapeutic agents (Gambardella 1995; Henderson 1994).

The scientific development was accompanied by strong institutional changes as the new assortment of genetic and cellular techniques was transferred from academic to commercial laboratories.[57] This institutional process motivated the use of the term Biotechnology to describe an emergent industry in the United States in the late 1970s and later on in Europe (Kenney 1986; Krimsky 1991). Moreover, due to the widespread expectations of the application of modern biotechnology for medicinal purposes, academics, consultants, industry stakeholders and government have promoted the term "biotech revolution" to refer to the scientific and institutional changes in the 1970s and 1980s. The expectations have brought about an increasing volume of research and development expenditures in drug discovery and development. Whether modern biotechnology has been able to produce the expected revolutionary improvements in medicines and health care services is part of a current controversial debate (Nightingale, Martin 2004).

Senker (1998) and Acharya et al (1998) have studied the differences of the emergence and development of modern biotechnology and its commercialisation among different regions, especially between the US and Europe. Their contributions stress how Europe, maybe with the exception of the U.K., was much slower in developing and exploiting the biotechnology knowledge base. Besides the strength of the American biotechnology knowledge base, the US has traditionally had a more adequate institutional climate for the commercialisation of modern biotechnology than Europe. Patenting and regulatory issues have been identified as the most significant differences between the US and Europe influencing the commercial exploitation of modern biotechnology (Senker et al. 1998).

57 For a detailed presentation of the interaction between industry and academia in the commercial exploitation of genetic engineering see McKelvey (1996, pp. 100-110).

For the global pharmaceutical industry, the emergent biotechnology industry in the USA brought about a new industrial organisation presenting (i) three type of actors: incumbent large diversified firms (LDFs), public research institutions (university or R&D Laboratories) and knowledge/science-intensive small and medium-sized enterprises called Biotechnology Dedicated Firms (BDFs) and (ii) constantly growing inter-institutional collaboration agreements between the new entrants and incumbents (Saviotti 1998; Orsenigo 1989).

Regarding the role of DBFs in the pharmaceutical industry, two stylised interpretations can be made One the one hand, DBFs can be explained in terms of a life cycle industry model[58]. There are two main reasons why an industry life cycle scenario does not perfectly fit to the pharmaceutical industry. Firstly, drug producers have survived the emergence of modern biotechnology and some of them continue to be industrial leaders. Furthermore, incumbents and small entrants have built a co-operative behaviour at various stages of R&D and production (Acharya et al. 1998, p. 89).

An alternative explanation of the emergent industrial organisation in the pharmaceutical industry after the advent of modern biotechnology builds upon the strong science-based and interdisciplinary nature of modern biotechnology. These features favour the collaboration between actors and the establishment of innovation networks (Orsenigo 1989; Pisano 1991).

Within the borders of the Federal Republic of Germany, the development of the biotechnology knowledge base and the creation of DBFs followed a slower pace. Buchholz (1979, p. 71) has pointed out the underdevelopment of the German Federal Republic in the 1970s in what concerned both the development of the biotechnology knowledge base and its industrial exploitation.

This underdevelopment vis-à-vis the United States and the UK in the knowledge base, the difficulties of the German innovation system in fostering the establishment of DBFs together with the large investments of important German drug producers in research and development projects with American public research institutions[59] motivated major political concern about Germany's technological weakness in biotechnology. Moreover,

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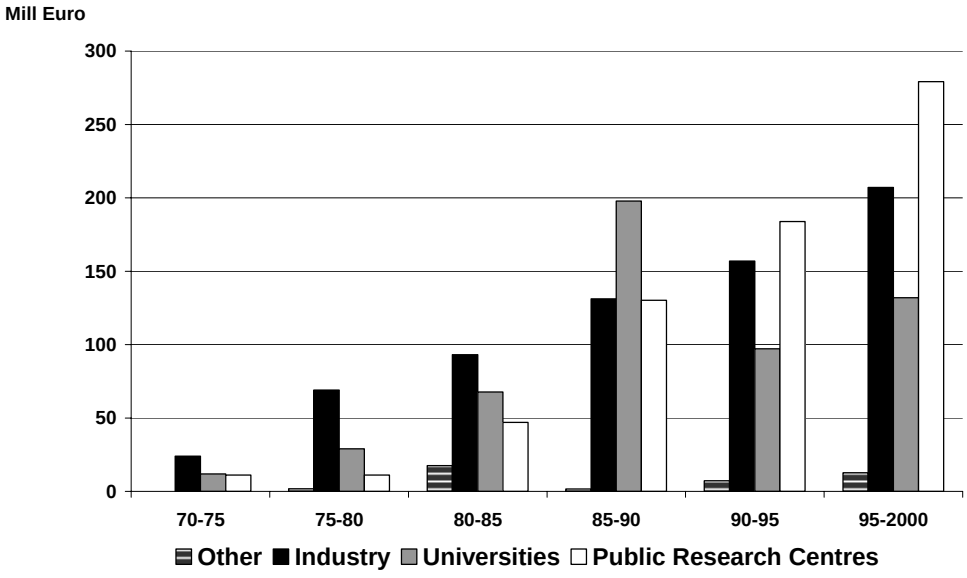
58 The industry life cycle model relates industrial dynamics with technological change. The coming up of a new technology fosters market entry for small innovative firms in terms of product innovation. The incumbent firms have problems in adapting to the new paradigm. As the technology matures market entry becomes harder. The industry settles down to a set of established firms where the early innovators have swept away the formal industry leaders.

59 The strategy of Hoechst with research and development investments in the USA is the most well-known example. See annex I for a short presentation.

due to the widespread expectations that biotechnology would revolutionise drug discovery and development, policy-makers were concerned about the possible negative implications of the German underdevelopment for the competitiveness of the German pharmaceutical industry and other industrial sectors (Giesecke 2001).

The major conscious policy contribution to the development of biotechnology in Germany was probably the introduction of the Genetic Engineering Act in 1989 to set the legal framework for the activities involving genetic engineering. However, the government concern for the support of biotechnology in Germany had already began in the 1970s. Policy has taken several forms and tackled issues regarding the regulatory framework, the development of the knowledge base through direct project funding (with special emphasis on research that can be directly applied), the establishment of science-based dedicated biotechnology firms network formation between industry and academia and the creation of regional clusters (Buchholz 1979; Giesecke 2000; Dominguez Lacasa, Reiss 2004).

Figure 6: Direct project funding for biotechnology-related research in Germany (1970-2000) [60]



60 Source: Public Promotion Catalogue of the Bundesministerium für Bildung und Forschung (BMBF Federal Ministry of Research and Education). The figures include only the federal investments classified as biotechnology activities by the German Federal Ministry of Research and Education and does not consider expenditures in medical, health and environmental research that may directly support biotechnology but do not appear in the ministry's biotechnology statistics. Block grants and other types of institutional funding such as the biotechnology funding of the Deutsche Forschungsgemeinschaft (German Research Council) are not included either.

Figure 6 presents the public direct project funding in biotechnology since 1970. The figures give evidence for the increasing policy concern for biotechnology in Germany in terms of project funding between the years 1970 and 2000. Research and technology policy have explicitly targeted the development of the biotechnology science base and its industrial exploitation. In terms of project funding industry actors have been an important target of the policy measures during the entire period under consideration. At the beginning of the 1970s, firms beneficiated the most from public promotion programmes. However, since the 1980s public funding has increasingly targeted fundamental research by supporting public research centres who have became the most important target group of direct project funding followed by industry actors who have kept a quite large stake of public funding. According to the public budget allocation among actors, in 2000 companies and non-university research institutes received more than 75 % of the direct project funding for biotechnology.

With regard to the development of the biotechnology industry, policy intervention in Germany during the 1990s supported the creation of biotechnology start-ups and a number of measures to promote the availability of venture capital and private investments were implemented. By 2000 the German biotechnology industry was already the largest in Europe in terms of numbers of biotechnology dedicated firms (Dominguez Lacasa, Reiss 2004).

The underdevelopment of the German biotechnology science base in the 1980s compared to the USA and the almost inexistent German biotechnology industry have probably augmented the costs of recognition and exploitation of modern biotechnology by the German drug producers. There is strong empirical evidence for the delay of German drug producers in entering into the biotechnology networks (Hullman 2000, pp. 92-94). There have been different types of arrangements for linking up to dedicated biotechnology firms, ranging from research collaborations and licenses, equity investments and acquisitions. Moreover, as other European corporations in the pharmaceutical industry, German drug producers have relied mainly on American DBFs to access to biotechnology capabilities. Regarding the collaborations with public research institutions, in the early 1990s German public health research institutions played an important role for German companies. However, in the second half of the 1990s the importance of North American and other European universities and public research institutions beyond the German borders increased (Hinze et al. 2001, pp. 58-61).

3.4 The recognition and exploitation of modern biotechnology by 4 German drug producers

After the study of the knowledge environment of the pharmaceutical industry in Germany, we go on to explore the process shaping the recognition and exploitation of technological opportunities. The next paragraphs concentrate on the experience of German drug producers in adapting to the advent of modern biotechnology after the 1970s.

A number of contributions to innovation studies and explorations of industry dynamics and processes of creative destruction have already chosen the advent of modern biotechnology in the 1970s to study, among other issues, the reactions of incumbents in the pharmaceutical industry to the shift in their knowledge environment. Pisano (1991), Senker and Sharp (1997), Galambos and Sturchio (1998), Rothaermel (2001) and Santos (2003) focus on the establishment of collaborative arrangements between large firms and biotechnology companies for the transfer biotechnology capabilities after the revolutionary discoveries of the 1970s. As a reaction to the changes in the knowledge environment, Zucker and Darby (1997) stress the resource mobilisations of pharmaceutical corporations within the firm (through hiring new scientists) and the access to external capabilities (through non contractual collaboration between large firms and academic research groups). From a different perspective, Kaplan et al. (2003) explore the role of management models in the recognition of the technological discontinuity after the 1970s.

In general terms, these contributions do not consider explicitly the historical conditioning of technological change and, more specifically, the influence of firms' past decisions and experience in the process of recognising and exploiting technological opportunities. An exception may be the contribution of Henderson (1994) who explores the development of the competencies of pharmaceutical companies involved in drug discovery in the last quarter of the 20th century.

From a historical perspective, one of the interesting aspects of the exploration of the adjustment by German drug producers is their successful innovative record during the first half of the 20th century applying synthetic organic chemistry. As we have seen, in the era of random screening the German drug producers dominated the pharmaceutical industry in terms of innovation. Among other factors their innovation success drew indeed on the application of organic chemical synthesis. Given the dynamics in the underlying knowledge base of the pharmaceutical industry, especially with the scientific advances in molecular biology in the 1950s and the developments that followed during the last quarter of the 20th century, this sections aims at deepening into the question whether the firm-specific technological competencies in organic

chemical synthesis of the German drug producers can have inhibited an adjustment to the external shifts in the knowledge base.

The German corporations active in drug discovery and production facing the revolutionary discoveries of the 1970s come traditionally from two different sectors: the traditional pharmacy and the coal-tar dyestuff industry. Until the 1950's both sub-sectors of the pharmaceutical industry (the more traditional pharmaceutical companies and the pharmaceutical companies from the coal-tar sector) were different in their organisational capabilities, their product lines and most importantly their attitudes towards the application of biotechnology during the 20th century.

The study explores the reaction to the advent of modern biotechnology by two diversified chemical companies coming from the coal-tar dyestuff industry (Hoechst AG[61] and Bayer) and two representatives of the traditional pharmaceutical industry (Schering AG and E. Merck[62]), both companies with a strong tradition in the application of microbiology and enzymatic processes for drug development and production. The goal is to unfold the organisational variables and processes shaping the adjustment to the emergence of modern biotechnology.

Patent indicators are used to capture the development of the technological capabilities of the firms in biotechnology and organic chemical synthesis. Given these results, the next step will be to disclose the process of perception and adoption of the possibilities of biotechnology after the 1970s. Guided by the theoretical framework sketched in chapter 2, the study focuses on the following issues and indicators:

(i) Research traditions (in terms of science-based or empirical trial-and-error strategies);

(ii) Attitudes towards the application of traditional biotechnology and focus on synthetic organic chemistry (to capture the technological roots of the firms);

(iii) Research and development investments (to measure the extent to which firms are research-based);

61 Since 1999, after the merger with Rhone Poulenc, the company's name is Aventis and has its headquarters in Strasbourg, France. In 2003 Aventis was acquired by the French pharmaceutical company Sanofi-Synthelabo and is now called Sanofi-Aventis.

62 Since 1995 and after several corporate reorganisations during the 20th century the company has the name Merck KGaA and is located in Darmstadt, Germany. Today Merck KGaA has no connection with Merck & Co. of Whitehouse Station, New Jersey. Even though the historical roots are the same this branch was confiscated by the US government during World War I and in 1917 became the independent company Merck & Co (Bernschneider-Reif et al. 2002).

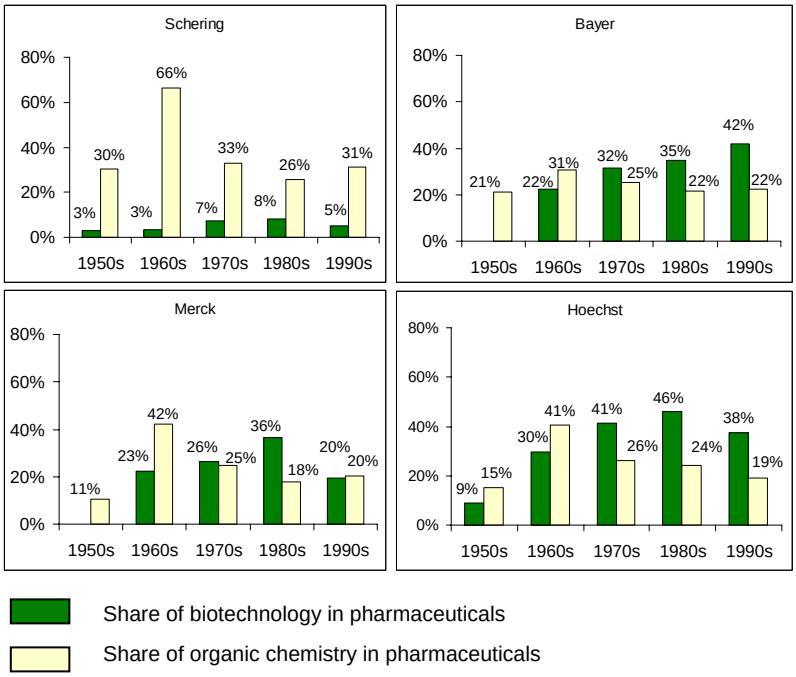
(iv) Educational statistics (to capture the disciplinary profiles of the employees and its development);

(v) Strategic collaborative agreements, (to capture the extent to which firms aim at exploiting the extramural knowledge base).

3.4.1 Organisational technological capabilities in the second half of the 20th century

Patent documents draw on research and development activities regardless of the innovative impact of the potential invention. Granstrand et al. (1997) or Mowery et al. (1996) have already successfully applied patent statistics as indicators to analyse organisational technological capabilities. Therefore, this indicator can unfold the extent to which the corporations develop and apply biotechnology and organic chemical synthesis in their research and development efforts.

Figure 7: Corporate patent documents in pharmaceuticals. Share of biotechnology and organic chemistry-related patent documents in the pharmaceutical corporate patent portfolio of Schering, Bayer, Hoechst and Merck and their main subsidiaries[63]



Sources: Annex II.

63 Data: German patent applications filed at the German and European patent offices with Germany as designation country. The criteria to classify the patent documents were based on the European Patent Classification (EPC).

The indicators based on patent documents are presented in Figure 7. The data historical time series used for our analysis has been gathered from the online databases PLUSPAT and PATDPA of the database vendor Questel.

The indicators present counts of German patent applications of the four corporations and their main subsidiaries filed at the German and European patent offices with Germany as designation country. Using the European Patent Classification (ECLA), pharmaceutical-related patents of the corporations have been categorised in two groups: those involving the application of biotechnology and those involving the application of organic chemical synthesis.[64] The results suggest a considerably better performance of Bayer and Hoechst than the traditional drug producers in perceiving and exploiting the possibilities of biotechnology in the period under consideration. For the period 1960s-80s Merck presents a rather similar share of biotechnology-related pharmaceutical patents than the best adopters, however biotechnology at Merck does not reach the share obtained in the pharmaceutical patents of Bayer and Hoechst. In the 1990s the share decreases slightly. Schering has a very low share of biotechnology-related patents in pharmaceuticals throughout the whole period considered.

The next sections aim at exploring some of the forces driving these developments.

3.4.2 Research traditions

Marschall (2000) and Achilladelis (1999) point out that until the 1950's the two sub-sectors of the pharmaceutical industry (the traditional pharmaceutical companies and the pharmaceutical companies from the dyestuff sector) were quite different. As presented in Table 5, these differences concerned their size and their product lines[65], the skills of the employees and most importantly their research strategies and criteria for technology adoption. On the one hand, the traditional pharmaceutical companies applied trial-and-error base principles to develop new drugs. Accordingly, the German traditional pharmaceutical companies (such as E. Merck, A. Knoll and Schering AG) were quite slow in shifting their emphasis from extraction of natural products to the

64 The definitions of pharmaceuticals-related patent documents and those documents involving biotechnology and organic chemical synthesis are based on codes of the ECLA classification (see annex II).

65 In general the traditional pharmaceutical companies developed organic acids with the application of traditional biotechnology and enzymes, vitamins and hormones, which in the early phases of the pharmaceutical industry were isolated from natural raw materials. On the other hand the dyestuff producers concentrated on the development of innovative synthetic products.

organic synthesis of drugs. On the other hand, guided by the principles of organic chemistry, the strategies of the dyestuff manufacturers had already became science-based by the 1880s (Marschall 2000).[66] This science-based strategy shaped their learning processes, which were characterised by (i) the institutionalisation of industrial scale R&D activities, (ii) large supply of well-trained university chemists and (iii) interaction with research institutes and universities.

Table 5: German drug producers at the beginning of the 20th century

Coal-tar dyestuff companies	Traditional pharmaceutical companies
• Large diversified companies;	• Small and medium enterprises arising from traditional pharmacies;
• Chemists in charge of the drug discovery activities;	• Pharmacists responsible for the drug discovery activities;
• Science-based strategies guided their research and development activities;	• Empirical "trial-and-error" guided their research and development strategies;
• Conscious choice of the organic chemical synthesis in drug discovery until the 1960s.	• Extraction of drugs from natural compounds and application of traditional biotechnology.

Sources: Marschall (2000) and Achilladelis (1999).

Moreover, the innovation flow (in terms of products) maintained by the German coal-tar dyestuff companies occurred parallel to the establishment of industrial scientific laboratories to exploit the industrial application of scientific principles (Marsch 1994). The research and development activities that used to be carried out in laboratories at a small scale were then performed at large industry scale. This transition from laboratory to industrial scale research and development activities was possible through the institutionalisation of science in the industry. The enlargement of research capabilities

66 As Marschall (2000) has put forward, in its origins the research and development practices of the dyestuff companies had an empirical fundament, that is trial-and-error exercises guided the process of developing synthetic dyes from the coal tar. The chemical structure of the synthetic dyes remained unknown until the advances in the structural analyses of organic compounds, which led to the first synthesizes of organic compounds based on the understanding of their molecular structure. The scientific advances in organic chemistry transformed the discovery of dyestuffs from an empirical into a theory driven procedure. In the 1880s dyestuff producers diversified into pharmaceuticals applying the same science-based strategies that they were using in the discovery and development of dyestuffs. With this strategy the dyestuff companies were able to develop a large portfolio of innovative drugs.

demanded large investments in infrastructure for research and development.[67] These corporate research activities were strongly influenced by the German university and the polytechnic institutes (Beer 1959).

The dyestuff companies complemented this organisational innovation with the recruitment of workers with experience in scientific research. At the Bayer company for instance, already in 1897 all research chemists in the main laboratory held a Ph.D. in chemistry and the majority had research experience at the university (Meyer-Thurow 1982, p. 376). Achilladelis (1999) and Beer (1959) also stress the ability of dyestuffs producers in the pharmaceutical industry to build in house R&D capabilities and to interact and cooperate with academic researchers, universities and polytechnic institutes.

3.4.3 Attitudes towards the application of traditional biotechnology

According to Marschall (2000) the traditional pharmaceutical companies applied traditional biotechnological methods with great success in the production of basic chemicals (like butyric acid, acetic acid or lactic acid). The Schering company produced organic acids in the early 1900s with the application of micro-organisms, Luitpold was active in 1931 in the biotechnological production of enzymes and Knoll in the production of Ephedrin since 1930. Roehm and Boehringer Ingelheim are other examples of early adopters of biotechnology. After World War II, Boehringer Ingelheim and Merck were leaders in microbial transformation technology.

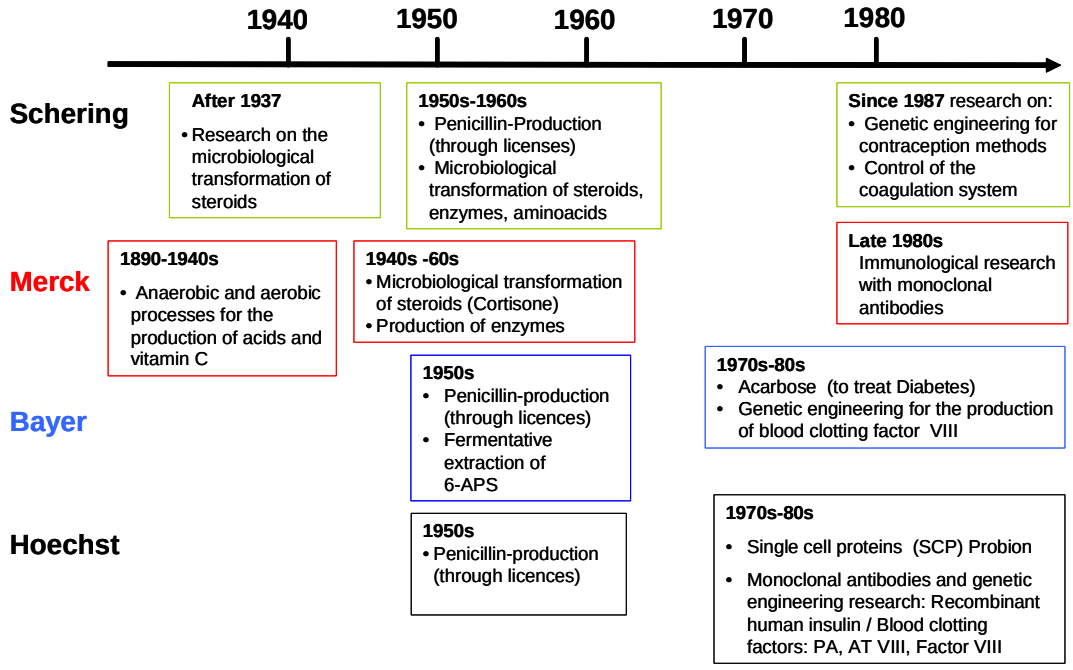
On the other hand, the companies of the coal-tar dyestuff sector were less interested in developing and applying biotechnology methods. The leading players in the sector (Bayer, BASF, and Hoechst) reacted very cautiously and sceptically (even with prejudice) to the possibilities offered by biotechnology. The strong innovation flow of the dyestuff producers at the beginning of the 20th century was rooted in the application of scientific principles. The successful research strategy of the dyestuff producers supported the establishment of implicit principles that would shape their technological decisions in the future by guiding their perception, assessment and selection of technologies. These implicit principles favoured science-based technologies and rejected empirical (i. e. trial-and error guided) technologies (Marschall 2000).

67 Liebenau (1988) points out that there is little evidence that cost/benefit calculations were done in anything more than a rudimentary way. According to him, the decisions taken by German corporations leading to the creation of the industrial laboratories were not the result of a systematic analysis leading to the conclusion that the company would profit from the establishment of laboratories.

Only after the discovery of the therapeutic importance of penicillin, the improvement of microbiological production methods and their relevance after World War II, did the companies from the dyestuff sector start to produce penicillin under US licences (Buchholz 1979).

Figure 8 sketches the main achievements of the drug producers under study in exploring and exploiting the technological possibilities of biotechnology. These findings are a result of the cases studies included in Annex I. The case studies use historical sources to describe the biotechnology research achievements of the firms and their process of building up biotechnology research capabilities.

Figure 8: Relevant achievements with the application of biotechnology and biotechnology research projects of Schering, Merck, Bayer and Hoechst



Source: Annex I

The corporations present a different profile in the exploitation of biotechnology in the 20th century. While the representatives of the traditional pharmaceutical industry had accumulated experience with the application of what we have defined as traditional biotechnology, the dyestuff producers started its application using licences for the production of penicillin.

However, according to the findings, traditional pharmaceutical companies did not further develop their capabilities. In the 1970s dyestuff producers started their activities

in modern biotechnology while the traditional pharmaceutical companies waited until the late 1980s. Surprisingly dyestuff producers had been faster in recognising the possibilities of the technology after the revolutionary scientific discoveries of the 1970s.

3.4.4 Investment in research and development

To capture the extent to which firms are research-based and engage in creating and accumulating knowledge and in developing their absorptive capacity, data on research and development expenditures in pharmaceuticals for the period 1955-1995 are presented in Table 6. The historical data have been gathered from the corporate historical archives using annual reports and relevant documents covering the pharmaceutical segment of the corporations. The internationalisation of corporations in the pharmaceutical industry during the 20th century makes the consistent analysis of trends in financial data over long periods of time quite difficult. The data for the period 1955-1970 refer to pharmaceutical research and development of the corporation (*Mutterkonzern*). For the period 1975-1995 the data refer to the global group *(Welt oder Gruppe).*

Table 6: Investment volume in research and development in pharmaceuticals (in million German Mark and as a percentage of pharmaceutical sales)

	Merck		**Schering**		**Hoechst**		**Bayer**		
	mio DM	%	mio DM	%	mio DM	%	mio DM	%	
1955							12	9 %	**1955**
1960					21	7 %	23	10 %	**1960**
1965			27.3	6 %	43	9 %	37	11 %	**1965**
1970		13 %	60.4	10 %	109	11 %	61	10 %	**1970**
1975	55	8 %			352	10 %			**1975**
1980	67	8 %	194	14 %	503	10 %	290	6 %	**1980**
1985			380	18 %	972	14 %			**1985**
1990	205	12 %	543	17 %	1182	13 %	986	12 %	**1990**
1995	439	13 %	845	18 %	2018	18 %	1517	14 %	**1995**

Source: Material from the historical corporative archives other sources (see annex II).

The data presented in Table 6 show that the differences between the companies in terms of size remained in the 20th century. As in the period of establishment of the pharmaceutical industry, in 1980 (about 100 years later) Merck and Schering were much smaller than their competitors Hoechst and Bayer in terms of investment volume in pharmaceutical research and development. Economies of scale in research seem to play a role in the adjustment to the external shift in the knowledge base. This result is

consistent with Kaplan et al. (2003) who find evidence for the hypothesis that the adjustment process is also driven by economies of scale. In terms of investment ratio however, the differences are not as clear. All 4 corporations are very research intensive and until 1995 they seem to have quite stable R&D investment behaviour. According to the data available, in the last quarter of the 20th century Schering was investing the largest share of its pharmaceutical sales in R&D activities, but the differences are not significant.

3.4.5 Internal capabilities

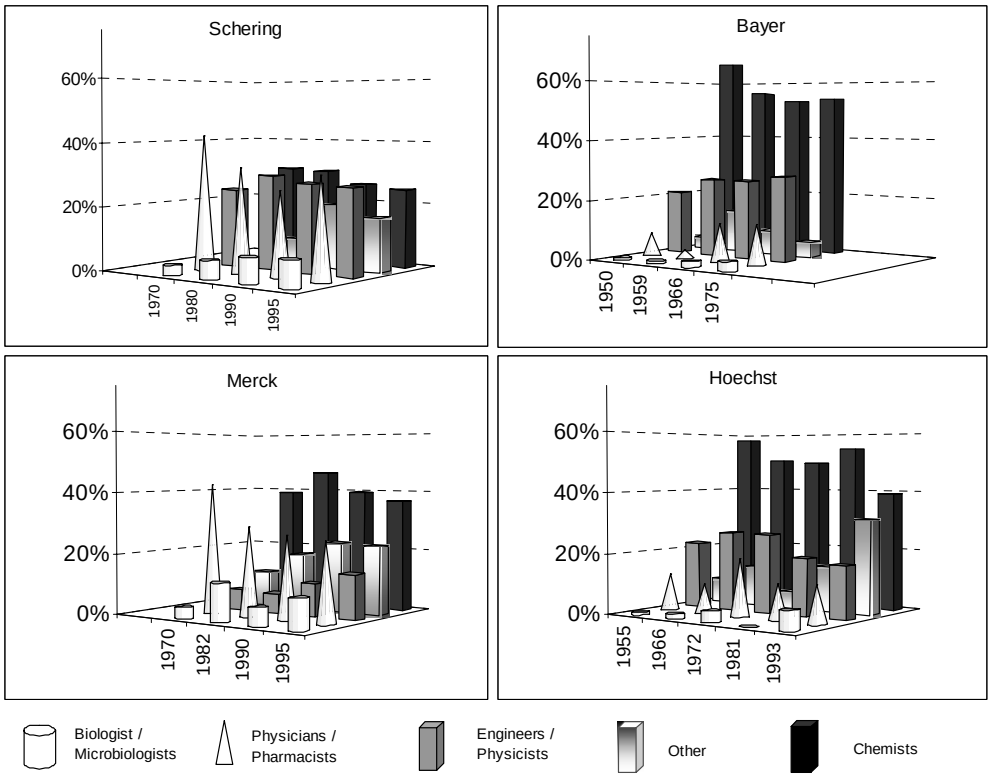
To explore the internal capabilities of the firms we use educational statistics. Jacobsson and Oskarsson (1995) put forward the educational statistics approach to trace the technological base of firms. The analysis in this section explores educational background of the staff before the advent of modern biotechnology to capture the extent to which the internal capabilities of the companies were appropriate to recognise the possibilities of modern biotechnology and adopt it.

Figure 9 presents the data for the corporations we are considering. Subsidiary-companies have not been included in the analysis. Again the data have been gathered from the historical corporate archives using historical material from the corporate staff departments on employee qualification. Due to problems of data availability, building up consistent time series for the 4 corporations for the same period was a challenging exercise. The raw data are structured in academic groups with a classification from company to company presenting different degrees of aggregation. For the purposes of the analysis five academic groups have been built for each firm:

- Biologists and microbiologists;
- Physicians and pharmacists;
- Chemists;
- Engineers and physicists;
- other disciplines (which include disciplines such as psychologist, mathematics, law, or business administration).

Unfortunately the data available do not allow making an accurate comparison between the corporations. However, an interesting observation can be drawn. In terms of the employee qualification the companies in the 1970s seem to maintain the profile of the beginning of the 20th century presented in Table 5. Chemists are the most important group of employees with an academic degree in the dye-stuff companies Hoechst and Bayer. At Merck chemists and the group integrating pharmacists and physicians, are comparable in size while at Schering chemists do not play a leading role at all.

Figure 9: Human capital at Schering, Merck, Hoechst and Bayer: Qualification of the employees holding an academic degree



Source: Historical corporative archives[68].

According to employee qualifications, by the 1970s the employees of the German corporations under consideration had weak skills to develop understanding on the biological processes of diseases. While Schering and Merck seemed to have strong skills on pharmacology and medicine, Hoechst and Bayer had mostly competencies in chemistry. The profile of employee qualifications seems to be quite persistent. Even in the era of modern biotechnology, skills in biology either play a secondary role or were clearly underrepresented among the employees with an academic degree of the corporations we are considering (for Bayer we have no evidence to make an assessment of the development of employee qualification).

Considering that the data refer to the whole corporations (and not just to the pharmaceutical business units) the differences in the employees' academic profiles

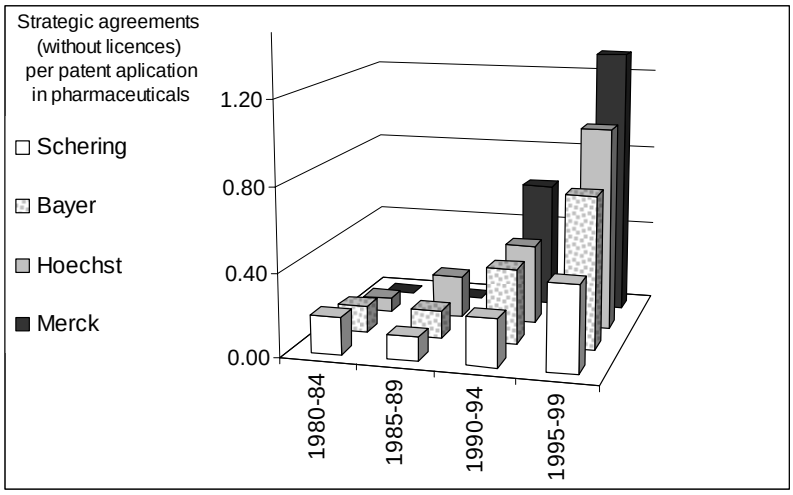
68 Comments to the data: For Schering in the year 1970 the data refer to the pharmaceutical activities only. Data for Hoechst in the years 1981 and 1993 refer to the Hoechst AG, for the other years the data refers to the Hoechst Group. The data for Bayer refers to Bayer Farbenfabrik. For detail see annex II.

could be explained by the fact that the dye-stuff producers were very much diversified in the chemical sector while the traditional pharmaceutical companies mainly focused on pharmaceuticals. However, according to the corporate annual reports, in 1975 Merck and Schering had developed into diversified chemical companies reaching 55 % and 45 % of their sales, respectively, in industries of the chemical sector other than pharmaceuticals. Accordingly, the differences in the scientific skills of the employees (measured in terms of share of academic degrees in selected disciplines) and their persistence demonstrate to a large extent different paths in the accumulation of internal (i. e. firm-specific) technological capabilities.

3.4.6 Strategic collaboration

To explore the strategies of the corporation to access extramural knowledge and skills outside the firms, we examine the strategic collaborative agreements of the firms. Figure 10 presents the biotechnology-related contractual agreements of the companies (and their major subsidiaries). These include equity and non equity inter-firm agreements (except for licensing activities) and major strategic collaborative arrangements between the firm under consideration and public research institutions aiming at enhancing the technological capabilities of the firms. To control for the size of the companies the data have been related to the number of patent applications in pharmaceuticals.

Figure 10: Number of biotechnology-related strategic agreements per patent application in pharmaceuticals



Source: Peter (2002) and own desk research using annual reports, secondary literature and firm information (see annex II).

In the 1980s the corporations present a similar collaborative intensity in terms of agreements per patent application in pharmaceuticals. In the 1990s all companies increase the collaboration rate; however Schering seems to rely largely on its internal firm-specific assets to develop research and development capabilities in the new knowledge environment.

3.4.7 Discussion

As presented in previous sections the emergence of modern biotechnology in the 1970s has changed the institutional and knowledge environment of the pharmaceutical industry. The industry incumbents have faced the challenge of adjusting to the new conditions for innovation in drug discovery and development. Drawing on the theoretical framework of the organisational capabilities of the firm (or knowledge-based approach to the firm) this section has aimed at describing the knowledge bases of the German drug producers, at characterising their strategies for the acquirement and development of capabilities and most importantly, at exploring their adjustment to the shift in their knowledge environment after the emergence of modern biotechnology.

Table 7: The exploitation of biotechnology by German drug producers and indicators to capture the adjustment to the advent of modern biotechnology

	Merck	**Schering**	**Hoechst**	**Bayer**
Research tradition in the early 20th century	empirical (trial-and-error) strategies	empirical (trial-and-error) strategies	science-based strategies	science-based strategies
Biotechnology in drug development and production **before the 1970s**	successful applications of BT since the 19th century	successful applications of BT since the 1930s	focus on chemical synthesis applications of BT after 1950 (through licensing)	focus on chemical synthesis applications of BT after 1950 (through licensing)
R&D investment in pharmaceuticals in % of pharm. sales (average 1970-95)	11 %	15 %	13 %	11 %
Disciplinary orientation of employees' qualification by the 1970s	Medicine / Pharmacology	Medicine / Pharmacology	Chemistry	Chemistry
Biotech. strategic agreements per pharmaceutical patent (average 1980-99)	0.48	0.23	0.41	0.34
Modern biotechnology **Biotechnology in drug discovery and development after the 1970s**	**research starts in the late 1980s**	**research starts in the late 1980s**	**first applications in the early 1980s**	**first applications in the early 1980s**

The analysis has tried to be consistent with the historical conditioning of technological change and the fact that the decisions of firms on technology adoption and development are not independent from the history of the organisations in which corporate strategies and capabilities develop.

By considering the organisational factors shaping the innovation activities of the 4 firms and their experience with the application of biotechnology in the first half of the 20th century we have explored the exploitation of modern biotechnology by the 4 German drug producers in the second half of the 20th century. The overall results of the analysis are given in Table 7. A key aspect of the study is the different heritage of the corporations: Merck and Schering are representatives of the traditional pharmaceutical industry while Hoechst and Bayer are rooted in the coal tar dyestuff industry.

With regard to their research tradition, the representatives of the traditional pharmaceutical industry were characterised by empirical (trial-and-error-based) strategies. On the other hand, the coal tar dyestuff producers followed a science-based strategy characterised by a large supply of well trained university chemists and strong collaboration patterns with research institutes and universities.

Contributions to the history of technology and to the exploration of the pharmaceutical industry have pointed out that these research traditions influenced the application of biotechnology in the first half of the 20th century. As shown in Table 7, the empirical character of biotechnology (compared with the science-base character of organic chemical synthesis) prevented the coal tar dyestuff companies from applying it in drug development. They did not apply biotechnology until the sterile technique for the production of penicillin in the 1950s had been developed and successfully applied by their American and Swiss counterparts. At this time the progressive colonisation of biology by the exact sciences was providing biotechnology with a continuously growing scientific knowledge base. According to the empirical analysis of technological capabilities through patent counts presented in Figure 7, during the second half of the 20th century the accumulation of biotechnological capabilities at Hoechst and Bayer went hand in hand with the transformation of biotechnology into a science-based technology. The values and norms shaping the technology adoption of drug producers may have played a role in this development.

In terms of share of investment in research and development the companies behave quite similarly. Schering, which is probably the largest investor in this group in relative terms, does not exploit the new technological opportunities of biotechnology in the second half of the 20th century. However, the total volume of research and development investments given in Table 6 discloses considerable differences in size

between the corporations. Interestingly the largest firms (Bayer and Hoechst) seem to have been faster in recognising and exploiting the new technological opportunities after the emergence of modern biotechnology. Economies of scale in research seem to play a role in the adjustment to the external shift in the knowledge base.

The companies maintain a constant profile of in-house scientific skills suggesting that (in the absence of mergers, acquisitions or buyouts) changes in the internal capabilities of the firms do not occur rapidly. Additionally, the data on employee qualification suggest that, before the emergence of modern biotechnology the dyestuff companies did not have the skills to develop capabilities for understanding the biological process of diseases.

As for the strategies to access the extramural knowledge base through the interaction with dedicated biotechnology firms, the relatively large share of contractual agreements of Bayer and Hoechst demonstrates their engagement aiming at identifying and accumulating additional capabilities in biotechnology. Merck presents a similar profile in terms of collaboration, even though according to the patent indicators presented in Figure 10 the exploitation of biotechnology is not as strong as at Bayer and Hoechst. Moreover, its reaction to the advent of modern biotechnology is slower (see Figure 8).

As for Schering, its engagement in biotechnological research and development during the first half of the 20th century, its relatively large share of investment in research and development in pharmaceuticals and its firm-specific capabilities in medicine and pharmacology (which seem more appropriate for the rational model of drug discovery enhanced by the emergence of modern biotechnology) have not resulted in the adoption of the new technological opportunities. The interactions to accumulate external capabilities seem to be missing.

The existence of research and development activities, the science-based research tradition together with interactions to access the extramural knowledge base of the firms seem to have been crucial in the perception and adoption of the new technological possibilities of biotechnology after the 1970s, rather than prior competence in biotechnology or the employees with the skills to develop the capabilities to exploit it.

3.5 Issues for a history-friendly model of technological change and technology adoption in the German pharmaceutical industry

In the previous sections we have introduced important facts to develop an appreciative theory of technological change in the German pharmaceutical industry by focusing the

development and diffusion of the organic chemical synthesis and the biotechnology during the 20th century. For this purpose we have taken three perspectives: the knowledge environment, the industrial and the organisational perspective.

From the perspective of the knowledge environment underpinning firms' activities and technological change we have focused on the development of two technologies: organic chemical synthesis and biotechnology. The stylised facts introduced in the previous sections suggest that the scientific advances in the knowledge bases underlying these two technologies have very much influenced their diffusion in the pharmaceutical industry. However, the development of the scientific knowledge bases of these technologies has followed different paces. The scientific base of the organic chemical synthesis was developed in the second half of 19th century, providing scientific theories (codified knowledge) about how to manipulate compounds to create new substances. The complexity of analytical chemistry and the principles guiding organic chemical synthesis (in terms of scientific disciplines contributing to its development) were moderate.

The development of biotechnology presents a different profile. While at the end of the 19th century the application of biotechnology was mainly a handcraft activity and its scientific base still in its infancy, during the 20th century scientific advances have changed the nature of the biotechnology-relevant science base. This process started already in the 1950s with the development of molecular biology and culminated in the 1970s with the revolutionary discoveries of rDNA and the production of monoclonal antibodies. With scientific development the knowledge base underlying biotechnology has gradually gain in complexity and the technology has become less tacit (easier to articulate).

The exploration of the influences of these developments for the pharmaceutical industry reveals three different phases in the pharmaceutical industry. The stylised facts identified in the 3 phases of development of the German pharmaceutical industry together with the changes in the development of organic chemical synthesis and biotechnology allow us to identify the parameters describing the technological regimes shaping technological change in the industry. As put forward in section 2.5.2, according to Malerba and Orsenigo (1993) the relevant parameters are (i) the level of opportunity conditions, (ii) the appropriability conditions, and (iii) the degrees of cumulativeness of technological knowledge and (iv) the characteristics of the knowledge base. The estimations are given in Table 8.

Table 8: Relevant parameters for the characterisation of the conditions for technological change in the different phases of the German pharmaceutical industry

Description	Phase (I)	Phase (II)	Phase (III)
Innovation opportunity conditions	high	high	very high
Appropriability conditions	middle	middle	low
Cumulativeness of the knowledge base	middle	large	large
Volume of scientific knowledge provided by public sector research institutions relevant for the organic chemical synthesis	large	large	large
Degree of tacitness of the chemical synthesis	low	low	low
Degree of complexity of chemical synthesis	middle	middle	middle
Volume of scientific knowledge provided by public sector research institutions relevant for biotechnology	low	large	large
Degree of tacitness of biotechnology	high	middle	low
Degree of complexity of biotechnology	middle	high	very high

Phase I covers the establishment of the modern pharmaceutical industry from the 1880s until World War II. In this period both biotechnology and organic chemical synthesis competed in the processing of materials until World War I. The dominance of the dyestuff companies in the German pharmaceutical industry supported the technological option for the organic chemical synthesis in the drug discovery and development processes. However, at this point drug discovery did not draw on the understanding of the biological processes of diseases. Drug discovery was based on random experimentation with the application or principles of organic chemistry. The degree of cumulativeness of the knowledge base was moderate since, even though successful innovation was based on the accumulation of capabilities in organic chemistry, the capabilities for innovation were embedded in large in-house research and development infrastructures to complete screening procedures. The innovation opportunity conditions were high since most diseases were waiting for a therapeutic treatment and the incentives to carry out research and development were large. The need of random experimentation provided the innovation environment with possibilities to appropriate the profits from innovation. Accordingly, even though in Germany patent law did not protect medicines and their therapeutic until the 1960s, appropriability conditions were moderate. Serependity in drug discovery made innovation around well known chemical compounds with therapeutic properties difficult, since the light variation of a compound did not guarantee therapeutic effects.

Phase II in the development of the pharmaceutical industry in Germany began with the termination of World War II. This phase saw the transition from random towards guided

drug discovery). After Wold War II biotechnology gradually becomes the key for innovation in the drug discovery and development processes. The understanding of biological process starts influencing drug discovery. even though innovation continues to draw on the accumulation of knowledge, capabilities in organic chemical synthesis are not enough for successful innovations. Microbiology, biochemistry, physiology and pharmacology become key disciplines for drug discovery and development. The innovation opportunity conditions were still large, and the development of the knowledge opened up gradually new areas of therapeutic application. However, with this gradual transformation of the knowledge environment German drug producers lost their innovative strength in the second half of the 20th century. Imitation was not straightforward since even though the knowledge underpinning biotechnology was becoming gradually codified, its transfer and was still very much based on observing interacting and training. The appropriability conditions were moderate.

Finally, **Phase III** starts with the advent of modern biotechnology in the 1970s, the emergence of a biotechnology industry in the United States and the strategic orientation of German drug producers towards this region in what concerned research and development activities. Scholars have already referred to the emergence of modern biotechnology in the pharmaceutical industry as a competence destroying technological advance in the sense of Tushman and Anderson[69], a new technological trajectory in Nelson and Winter's sense[70] or a new paradigm in Dosi's sense[71]. The stylised facts provide evidence for a transformation of the knowledge environment shaping drug discovery and development and its industry structure with the entrance of biotechnology dedicate firms ant the creation of networks of innovation. The innovation opportunity conditions increase since modern biotechnology brings about enormous expectations for drug discovery with regard to the understanding of diseases and the manufacturing of proteins. Regarding the appropriability conditions, the private appropriation of the profits deriving from innovation was however difficult (appropriability conditions were low). On the one side, and particularly in the early stages, the relevant knowledge base could in principle be codified and was hence easily transferable. Moreover, there was great confusion in what concerned the patentability of biotechnology-related novel technological advances. Regarding the cumulativeness of the knowledge base, drug discovery became even more research and development intensive. The scientific discoveries underpinning modern

69 See for example Freeman (1995, p. 14) or Pisano (1991, p. 239).

70 See for example Nelson et al. (1982).

71 See for example Dosi (1988a).

biotechnology forced German drug producers to acquire and develop new capabilities which were largely being developed beyond the German innovation system. During the last two decades of the 20th century strong policy engagement was directed towards the promotion of the industrial application of biotechnology, the creation of biotechnology companies and the interaction between industry and academia within the German borders.

All in all, the emergence of modern biotechnology and the increasing importance of the role of understanding diseases for innovation have transformed the knowledge environment and the research and development activities; however, the pharmaceutical industry in Germany and in other regions is still largely based on the application of chemical principals. It seems that, in the sense of De Liso and Metcalfe (1996, pp. 79-80.) biotechnology has not replace or overcome the chemical paradigm in the pharmaceutical industry, both paradigms coexist. Regarding the radical dimension of modern biotechnology, we concur with Nightingale and Martin (2004) in that even though the developments at the level of the knowledge base in the 1970s were rather radical than incremental, the articulation of these scientific advances into innovative products with therapeutic properties has not fulfilled jet the expectations created in the 1970s. While the knowledge dimension of the technology has experienced radical improvement, the artefact dimension of the technology (in terms of medicines and therapies) seems to be following an incremental path of change.

Given this development of the knowledge environment of the pharmaceutical industry, the analysis has tried to disclose, at the level of the firm, the process of recognition and adoption of the technological possibilities of modern biotechnology after the 1970s by German drug producers. The empirical exercise has considered the theoretical discussion on the role of the firm in the process of technological change and the main concepts developed by the knowledge-based view of the firm identified in section 2.5: firm heterogeneity, absence of maximising behaviour in their decision processes, historical conditioning of firm behaviour, the contribution of internal and external learning to knowledge accumulation and the importance of being able to reconfigure firm capabilities to survive in dynamic knowledge environments.

Given that the companies hold a similar share of R&D investments per pharmaceutical sales, the qualitative and quantitative innovation indicators used have tried to identify:

(i) the research traditions (in terms of science-based versus empirical research strategies),

(ii) the technological roots of the firms (in terms of previous experience with biotechnology and focus on the application of organic chemical synthesis),

(iii) the availability of internal skills to develop capabilities in biotechnology (in terms of the academic profile of the employees), and

(iv) the interaction to access the extramural knowledge base of the firms (in terms of number of strategic cooperations per patent application).

Science-based research strategies together with interactions to access the extramural knowledge base of the firms (learning external to the firm) have been crucial in the perception and adoption of the new technological possibilities of biotechnology after the 1970s.

These results suggest that in dynamic environments it is not enough for entrepreneurs to manage their internal knowledge bases and allocate their resources effectively. Additionally, to be aware of the changes in their knowledge environments and adapt adequately, entrepreneurs seem to be forced to manage their interface between internal and external knowledge bases.

This analysis of the German pharmaceutical industry has identified variables and depicted causal relationships to unfold the process of technological change and technology adoption. The argumentation has been developed in a verbal way. As discussed in section 2.6.4, the next step is to asses the logic of the argumentation by formalising the processes and variables identified in a formal model and explore the conditions for technological change and technology adoption running simulation experiments, i. e. varying selected parameters and observing the results.

The following issues could be explored with a history-friendly model:

Firstly, the development of the knowledge base, especially after World War II, seems to play an important role in the diffusion of biotechnology in the German pharmaceutical industry. The historical stylised facts speak for a development of the knowledge base and the industrial exploitation especially in the US. This geographical dimension of the knowledge base (i. e. the access for German drug producers was more difficult than for other actors), together with its increasing complexity has probably played a role in the application of biotechnology in the German pharmaceutical industry. Accordingly, a simulation model could serve as platform to test technological change and technology adoption under different characteristics of the knowledge base.

Moreover, the barriers for industrial exploitation of biotechnology in Germany have probably augmented the costs of perceiving and adopting the new technological opportunities by the German pharmaceutical industry. A history-friendly model can explore the influence of adoption costs in the adoption and development of biotechnology in the German pharmaceutical industry.

Additionally, given their technological traditions, firms' learning strategies (in terms of internal and external learning) seem to have been determinant to perceive and adopt the new technological opportunities, especially after the 1970s, when the biotechnology science base experienced a radical change in terms of complexity. Given the development of the knowledge base and the set of factors determining the level of adoption costs, a history-friendly model can serve as artificial environment to test the influence of firms' strategies on technological change and technology adoption.

4 A history-friendly model of technological change and technology adoption in the German pharmaceutical industry

4.1 Introduction

Guided by the appreciative theory introduced in the previous chapter, the history-friendly model put forward in the next sections intends to draw the process of technological change in the German pharmaceutical industry driven by the scientific advances of molecular biology in the mid 20th century and the emergence of modern biotechnology in the 1970s.

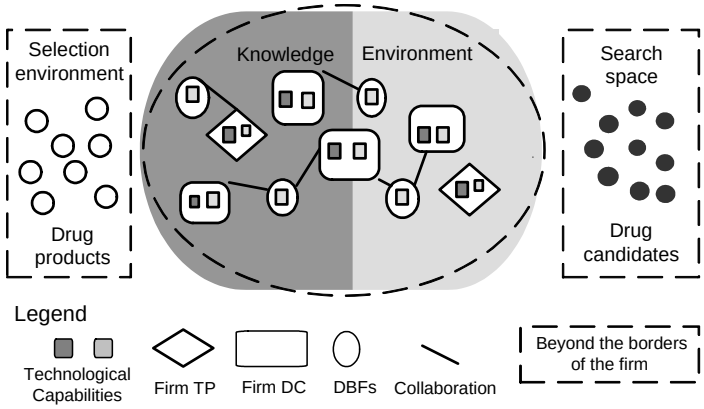
The aim of this exercise is to create an artificial environment to explore technological change in a science-based industry by focusing on the nature of the science base (in terms of volume and complexity), on the conditions for technology adoption, on firms' strategies to build up technological capabilities and, finally, on the influence of collaboration as mechanism for knowledge transfer.

At the micro level the model specifies (i) the activities of heterogeneous firms nested in the competitive dynamics of drug discovery and development, (ii) firms' decision-making process regarding research and technology development and (iii) the evolution of firms' technological capabilities. Additionally, the science-based character of the industry is explicitly modelled by defining technology development at the firm level as a function of the ability of firms to perceive, develop and articulate scientific results available in their knowledge environment. However, the interesting phenomenon the model aims at exploring is at the industry level, i. e. at a higher level of aggregation than the level of the firm. The development of technologies at the industry level is simulated by modelling the creation and development of technological capabilities at the firm level. As discussed in section 2.6.2, the model presents micro-macro relationships and technological change is hence the collective result of the individual actions of firms.

Figure 11 presents the basic structure of the model with an artificial drug industry where companies compete to find the best drug candidates and to develop them into drug products.

Drawing on the neo-Schumpeterian tradition the model involves heterogeneous firms with bounded rationality, search and selection processes and a knowledge environment firms can draw on to improve their routines.

Figure 11: Artificial pharmaceutical industry: the basic structure of the model



The firms

Based on the appreciative theory the model presents three types of companies: Traditional Pharmaceutical companies (Firm Type TP), Dyestuff companies (Firm Type DC) and Dedicated Biotechnology Firms (DBFs). However, DBFs enter the industry at a later stage, after a discontinuity in the knowledge environment bringing about new technological opportunities. Therefore, firms of type TP and DC are considered incumbent firms in the industry while DBFs are considered new entrants with the capabilities to exploit the new technological opportunities.

Search processes

Firms face a search space of potential medicines which may have therapeutic properties (drug candidates on the right side in figure 11). Their goal is to find the best potential drug candidates, develop them into drug products and bring them to the market (on the left side in figure 11). Therefore firms compete (i) to search for drug candidates and (ii) to develop them into products. In their search and development processes firms can apply two technologies: technology B and technology S (which represent biotechnology and organic chemical synthesis, respectively). The imposed function of these technologies is to ease the search and development processes. Effectiveness of the search process depends on the level of technological capabilities of the firms.

Selection processes

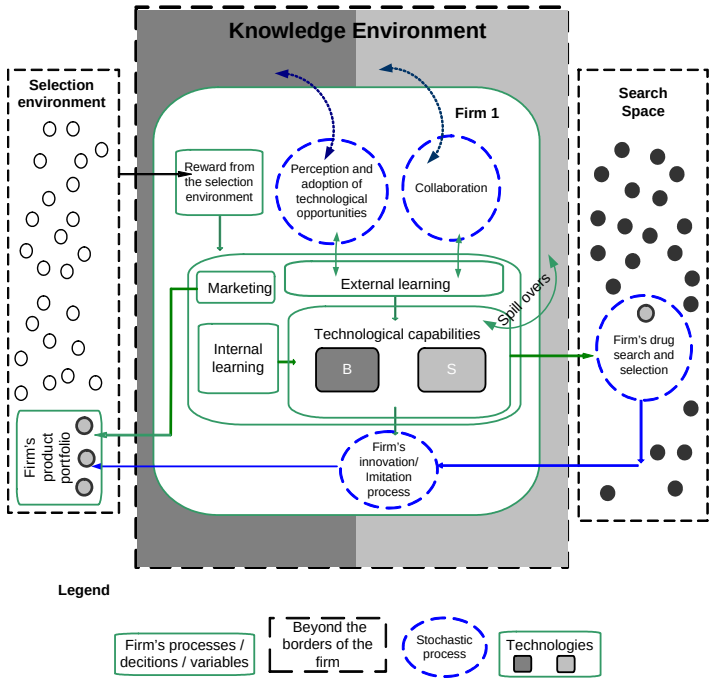
Firms face additionally a selection environment which represents the market for medicines. Success is specified according to ability of firms to market the products developed (discoveries or imitations). Therefore, firms' adaptability to the selection environment (firms' fitness in an evolutionary sense) is determined according to the relative performance of their products vis-à-vis the product portfolio of their competitors. Good performance provides best adaptors with relatively higher rewards

that can be used to develop their capabilities and search modes further and improve adaptability, while bad adaptors are forced to constraint their development due to lower rewards.

The knowledge environment

Firms interact in their knowledge environment carrying out learning processes external and/or internal to the firm to accumulate technological capabilities. The model emphasises the knowledge dimension of technologies by assuming that technology development draws on the accumulation of technological capabilities. Technological capabilities are the main assets of firms (since they determine the effectiveness of the search and development processes of products and, consequently, firm's adaptability to the competitive environment). Moreover, firm's performance in the selection environment will influence the extent to which firms are able to develop their technological capabilities further, applying their superior search modes and learning strategies. Therefore, if the conditions for innovation do not change (i. e. the conditions in the selection environment), adaptability of firms at time t depends on the extent to which they were able to adapt to the environment and obtain rewards in the past.

Figure 12: Firm's decisions and its interactions within the system



The model presents the following major simplifications:

- Two technologies: technology B and technology S;
- Three types of firms: Traditional Pharmaceutical Companies (Firm Type TP), Dyestuff Companies (Firm Type DC) and Dedicated Biotechnology Firms (DBFs);
- The selection environment with a constant budget to reward firms represents the market dynamics;
- Firms' knowledge environment involves two knowledge bases (one for each technology) which are independent from each other and to some extent exogenous. The knowledge bases develop with the input of public research institutions (exogenously) and with intra-industry spill-overs (endogenously);
- Absence of firm exit in the industry.

Figure 12 outlines the main decisions, variables and processes shaping the activities of a sample firm and its interactions with the knowledge environment. The next sections elaborate on the main issues.

4.1.1 The search space

To specify the process of drug discovery in the model a search space is modelled where firms look for potential medicines (or drug candidates) i. As given in Eq 1, in the search space each potential medicine i is defined by a parameter q_i (representing its quality) and a variable p_{it} indicating whether the potential drug is still waiting to be discovered, it has already been developed or is available for imitation. Imitation of products is only possible if the patent protection has expired (20 periods after the discovery of the drug).

Eq 1 $$i \equiv (q_i, p_{it}) \quad i = \{1 \ldots N\};$$

q_i := Quality of the potential drug i;

p_{it} := Intellectual property rights variable;

$$p_{it} = \begin{cases} 0 & \text{if the drug has not been discovered jet;} \\ 1 & \text{if the drug has been developed and is protected from imitation;} \\ 2 & \text{if the period for protection from imitation is over.} \end{cases}$$

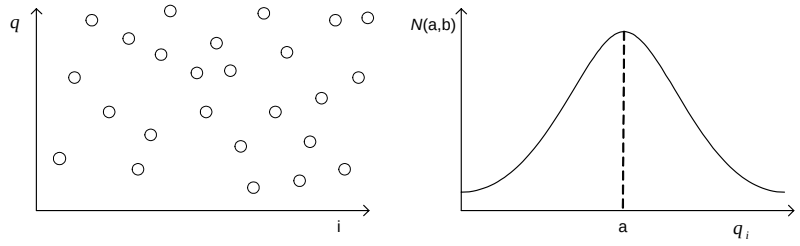
The number of potential drugs N is exogenously given. The quality q_i assigned to each potential drug i in the search space is determined in the first period of the simulation trough a random process as given in Eq 2:

Eq 2 $$q_i \sim N(a, b).$$

Figure 13 presents the search space of potential products that the companies face in the process of drug discovery.

The firms search and compete for potential drugs with the highest quality in the search space. The goal is to discover or imitate drug candidates with a high therapeutic quality. The selection environment only accepts products with a therapeutic quality level over a given standard q^*. In the search and selection process firms have bounded rationality which prevents them from accessing the entire search space and from recognising the true quality of the drug candidates. The accuracy of their search process depends on their technological capabilities. Additionally, the area of the search space they have access to is also a function of their technological capabilities.

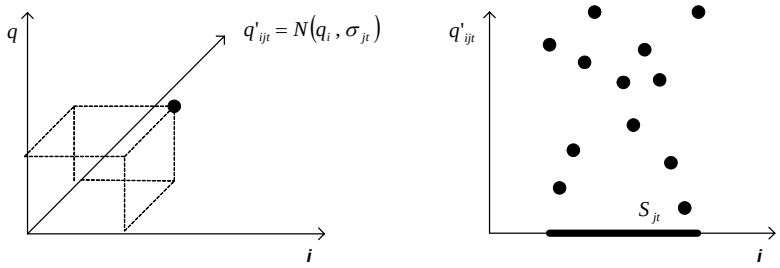
Figure 13: The search space of drug candidates



4.1.2 The technologies

Technologies ease the search process by allowing firms to approach the search space in a more effective way. The search process involves the application of two technologies: technology "S" (which represents organic chemical synthesis and determines the extension of the landscape of compounds a firm can access) and technology "B", given by σ_{jt} in Eq 3, (which represents biotechnology and determines the observation error of the companies in the search process). Technology effectiveness is firm specific. In other words, firms have different level of technological capabilities, which determine firm's technological achievements and the extent to which they are able to exploit technologies effectively. Therefore, firms are heterogeneous since the conditions under which they access the search space are not the same for every firm. Figure 14 presents a graphic representation of technology specification in the formal model.

Figure 14: Technologies to explore the search space. Technology B determines the firm's error of observation (σ_{jt}). Technology S determines the range of search space the firm can explore (S_{jt}).



Given the true quality of a drug candidate q_i and the error of observation of firm j in the search process (technological level reached by the firm in period t in technology B σ_{jt}, Eq 3 gives the quality of the drug candidate perceived by firm *j*:

Eq 3 $$q'_{ijt} = N\left(q_i , \sigma_{jt}\right).$$

Given the starting position within the search space where firms start searching in each period, the achievement in technology S (S_{jt}) gives the scope of the search space firms have access to. The starting point in every period is given by a uniform probability distribution.

The maximum effectiveness a technology can reach is given by its technological frontier. Technological frontiers in each technology F^S and F^B are exogenous and determine firm's technological gaps G^S_{jt} and G^B_{jt}, which are defined by the distance of firm's technological performance in each technology S_{jt} and σ_{jt} to the respective technological frontiers and given in Eq 4:

Eq 4 $$G^S_{jt} = F^S_t - S_{jt} \text{ with } F^S_t \geq S_{jt};$$
$$G^B_{jt} = \sigma_{jt} - F^B_t \text{ with } \sigma_{jt} \leq F^B_{jt}.$$

The model stresses the knowledge dimension of technologies, which implies that in order to make a technology work, knowledge is needed. The larger the capabilities available to make a technology work are, the nearest the technological achievements of the firm to the technological frontier. Accordingly, technology development at the firm level draws on learning processes that yield to the accumulation of capabilities.

Drawing on Malerba et al. (2002), the rates of technological change r_{jt} are firm specific and depend on the stock of technological capabilities of the company K_{jt} and on its

technological gap G_{jt} (i. e. distance of the technological achievement of the firm to the technological frontier F) in each technology, respectively. As firm's performance nears the technological frontier, technical improvement requires more capabilities. Moreover, this process is not totally deterministic. To stress the uncertain character of technological change, a stochastic term e is included in the equations giving the rates of technological development r_{jt}.

The rates of technological change at the firm level are given in equations Eq 5 and Eq 6:

Eq 5 $S_{jt} - S_{jt-1} = r_{jt}^{S}$ with S_{j0} the initial technological level of firm j;

$r_{jt}^{S} = \theta^{S} \cdot \left[G_{jt}^{S}\right]^{a_1} \cdot \left[K_{jt}^{S}\right]^{a_2} \cdot e$;

θ^{S} := Scaling parameter; $e \sim U(0.8\ ,\ 1.2)$; $a_1 < a_2 < 1$;

Eq 6 $\sigma_{jt} - \sigma_{jt-1} = -r_{jt}^{B}$ with σ_{j0} the initial technological level of firm j;

$r_{jt}^{B} = \theta^{B} \cdot \left[G_{jt}^{B}\right]^{b_1} \cdot \left[K_{jt}^{B}\right]^{b_2} \cdot e$

θ^{B} := Scaling parameter; $e \sim U(0.8\ ,\ 1.2)$; $b_1 < b_2 < 1$.

Technological improvements in technology S enlarge the area of the search space S_{jt} a firm has access to. Technological improvements in technology B reduce the error of observation of the firm σ_{jt} in the selection of drug candidates with high therapeutic qualities.

4.1.3 The knowledge environment

In their learning processes firms can access the knowledge environment. The model specifies two knowledge bases external to the firm (i. e. two extramural knowledge bases). These are brought about (i) by the effort of public research organisations conducting scientific research driven by the incentive of understanding processes and disseminating their research results, (ii) by the volume of knowledge firms are willing to share through cooperative research or licensing activities and (iii) by knowledge and technology intra-industry spill-overs (since normally the conditions of the technological regimes can not guarantee the technicians' appropriation of his or her technological advances).

As given in Eq. 7, the model includes two extramural knowledge bases (one per technology) involving the action of public research institutions z, the intra-industry knowledge spill-overs (determined by the rate of spill-overs ϕ) and the knowledge available through collaborative activities Ω_{jt}:

Eq 7

$$Z_{jt}^{S} = z^{S} + \phi \sum_{\substack{J \\ J \neq j}} K_{Jt}^{S} + \Omega_{jt}^{S};$$

$$Z_{jt}^{B} = z^{B} + \phi \sum_{\substack{J \\ J \neq j}} K_{Jt}^{B} + \Omega_{jt}^{B}.$$

The scientific knowledge provided by public sector research institutions is exogenous and constant in every period. The knowledge available through collaborative arrangements is endogenous, firm specific and depends on the collaborative activities of the firm (see Eq 21 below). Moreover, the ability to access the extramural knowledge bases depends on the absorptive capacity of the firms (see Eq 11 bellow). These two last characteristics of the model regarding firms' extramural knowledge base emphasise the evolutionary perspective of the firm according to which firms are heterogeneous and, even if firms are embedded in the same knowledge environment, their ability to exploit it varies across firms.

4.1.4 Characterisation of the firm

As given in Figure 12 at the beginning of the chapter, the model includes firms concentrating on two activities: learning and marketing. The aim of firm's learning is to create technological capabilities that enable them the effective search for products in the search space. Learning processes can be external or internal to the firm (Malerba, Orsenigo 1993; Santos 2003). External learning enables, on the one side, awareness of existence of new technological opportunities through the exploration of the science base and, on the other side, collaboration and knowledge transfer between the firm and actors shaping the articulation of the science base into useful technological processes (see Figure 12). Firm's marketing activities, on the other hand, aim at promoting the image of the firm's product portfolio.

The extent to which a firm engages in learning or in marketing activities is the result of firm's decision-making process determined by the strategic paradigms of the firms. From an evolutionary perspective this is considered a path dependant process in the sense that firms can not change their strategic paradigms easily or at no cost (see section 2.5.2.3).

Firm's strategic paradigms shape hence its learning strategy and determine its preference for a technological trajectory.

Firm's learning strategy

Firm's learning strategy is given by the variables $\beta_{jt} \leq 1$ and $\lambda_{jt} \leq 1$, which determine the budget invested in learning ($\beta_{jt} \cdot B_{jt}$) and the share of the learning budget directed to

external learning ($\lambda_{jt} \cdot \beta_{jt} \cdot B_{jt}$). The budget invested in external learning serves to accumulate capabilities for exploring the science base, for collaborating with other companies or public research organisations and for acquiring licences. The budget that is not invested in learning $(1-\beta_{jt})$ is planned for marketing activities.

Eq 8 gives the budgets invested in internal and external learning in every period (L_{jt}^{W} and L_{jt}^{E}), where B_{jt} represents the total budget available to finance firm's activities.

Eq 8
$$L_{jt}^{W} = (1-\lambda_{jt}) \cdot \beta_{jt} \cdot B_{jt};$$
$$L_{tj}^{E} = \lambda_{jt} \cdot \beta_{jt} \cdot B_{jt}.$$

Firm's technological trajectory

In the model proposed firms develop a technological strategy determined in every period by the variable α_{jt}, which represents the firm's bet on the technology being worth developing in-house (Malerba et al. 1999). The larger α_{jt}, the greater the budget share invested in technology S. The budget share invested din technology B is hence $1-\alpha_{jt}$.

To capture bounded rationality in decision-making the variables β_{jt}, λ_{jt} and α_{jt} are uniform randomly distributed. To capture firm heterogeneity and path dependence the upper and lower bounds of the uniform distributions $U(\beta_j^1, \beta_j^2)$, $U(\lambda_j^1, \lambda_j^2)$ and $U(\alpha_j^1, \alpha_j^2)$ are firm specific and constant.[72]

To sum up, firm's technological capabilities in every period are created through internal and external learning: New technological capabilities in each technology developed in every period by firm's internal learning l_{jt}^{W} are given by Eq 9. The variable α_{jt} determines firm's technological focus. The logarithmic function implies decreasing returns of investment in learning in the short term:

72 For reasons of simplicity, the specification of the investment decisions does not follow the satisficing behaviour rules put forward by Nelson and Winter (Nelson, Winter 1982). In their history-friendly models Malerba et al. (Malerba et al. 1999, p. 13) also choose this strategy of simplifying the investment decisions and model investment decisions with constant investment rates.

Eq 9
$$l_{jt}^{W,S} = \log\left(1+\alpha_{jt}\cdot L_{jt}^{W}\right);$$
$$l_{jt}^{W,P} = \log\left(1+(1-\alpha_{jt})\cdot L_{jt}^{W}\right).$$

On the other side, firm's investment in external learning L_{jt}^{E} contributes to the accumulation of organisational capabilities l_{jt}^{E} to exploit extramural knowledge. This stock of organisational capabilities is accumulated according to the expression given in Eq 10:

Eq 10
$$l_{jt}^{E} = \log\left(1+\omega\cdot l_{jt-1}^{E}+L_{jt}^{E}\right) \text{ with } \omega<1.$$

This stock of organisational capabilities shape the "absorptive capacity" γ_{jt} of the firm, which determines the extent to which firm *j* is able to integrate and exploit its extramural knowledge base (Cohen, Levinthal 1989). The model uses the functional specification of absorptive capacity put forward by Llerena and Oltra (2002) given in Eq 11, where φ stands for the degree of complexity of the extramural knowledge base:

Eq 11
$$\gamma_{jt} = 1-\left(\frac{2\cdot\varphi}{\sqrt{l_{jt}^{E}}}\right) \text{ with } 4\varphi^{2} \le l_{jt}^{E} \le \infty.$$

Accordingly, besides the creation of technological capabilities through internal learning given by Eq 9, external learning provides the firm in every period with the technological capabilities l_{jt}^{E} in each technology as given by Eq 12. These are a function of the absorptive capacity (γ_{jt}) of the firm and firm's extramural knowledge base Z_{jt} in each technology:

Eq 12
$$l_{jt}^{E,S} = \gamma_{jt}\cdot Z^{S};$$
$$l_{jt}^{E,B} = \gamma_{jt}\cdot Z_{jt}^{B}.$$

4.1.5 Accumulation of technological capabilities

The technological capabilities created in every period can be accumulated over time. Both, capabilities created through external and internal learning l_{jt}^{E} *and* l_{jt}^{W} contribute to this accumulation process. However, capabilities in both technologies depreciate over time at a rate δ; so that in order to maintain an adequate level of technological capabilities firms need to invest constantly in learning activities. The capabilities accumulation processes in technology S and technology B of firm *j* at time *t* are given

in Eq 13. Both stocks of capabilities determine the total stock of technological capabilities in drug discovery and development K_{jt} of firm *j* at time *t*:

Eq 13
$$K_{jt}^{S} = \left(1-\delta^{S}\right)\cdot K_{jt-1}^{S} + l_{jt}^{W,S} + l_{jt}^{E,S};$$
$$K_{jt}^{B} = \left(1-\delta^{B}\right)\cdot K_{jt-1}^{B} + l_{jt}^{W,B} + l_{jt}^{E,B};$$
$$K_{jt} = K_{jt}^{S} + K_{jt}^{B}.$$

Technology development at industry level is given by the simple aggregation of the stock of technological capabilities of the firms in the industry (which includes only those firms holding a drug portfolio)[73] in every period as given in Eq 14 and Eq 15:

Eq 14
$$I_{t}^{S} = \sum_{j} K_{jt}^{S};$$

I_{t}^{S} := Stock of capabilities in technology S at industry level in period t;

K_{jt}^{S} :=Stock of capabilities of firm j in technology S in period t;

Eq 15
$$I_{t}^{B} = \sum_{j} K_{jt}^{B};$$

I_{t}^{B} := Industrial stock of capabilities in technology B in period t;

K_{jt}^{B} :=Industrial stock of capabilities of firm j in technology B in period t.

4.1.6 Firm's perception of discontinuities in the knowledge environment and adoption of the new technological opportunities

The knowledge environment can experiment discontinuities brought about by scientific advances. Due to the science-based character of the industry, scientific advances contribute to technological change. However, the model presents firms as the carriers of technology and, therefore, technology development draws on firms exploiting and developing the new technological opportunities offered by scientific discontinuities. Consequently firms need to become aware of scientific discontinuities and decide

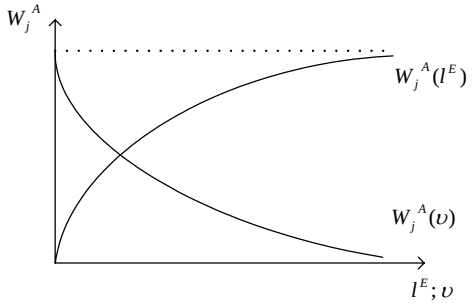
73 Firms make part of the industry (and hence contribute to the accumulation of capabilities at the industry level) as long as they are able to successfully develop products and compete in the selection environment. Other wise their capabilities are not considered in the aggregation process of the industry since they are not consider as "pharmaceutical companies".

whether or not integrate them in their technology development processes. In the tradition of Nelson and Winter (1982) this decision is implemented as a stochastic process with probability W_{jt}^{A} given by the Eq 16:

Eq 16 $$W_{jt}^{A} = 1 - \exp\left(\frac{-\eta \cdot l_{jt}^{E\,2}}{\upsilon}\right);$$ with η :=Scaling parameter.

The probability W_{jt}^{A} of perceiving and adopting the discontinuities in the knowledge environment is a function of the stock of organisational capabilities of the firm for external learning l_{jt}^{E} and the expected additional costs of integrating the new scientific discoveries υ. Figure 15 illustrates how these factors and the parameter influence the probability.

Figure 15: Probability to perceive and adopt new technological opportunities



Again, the process is stochastic. The firm accesses an adoption "lottery" where the adoption decision is taken as long as the probability is larger than the so called "adoption draw" $b_t \sim U(0,1)$ and the level of capabilities of the firm for external learning in period t l_{jt}^{E} is larger enough than the adoption costs υ.

Eq 17 $$A_{jt} = \begin{cases} 1 & adoption\ \ if \quad W_{jt}^{A} \geq b_t \ \ and \ \ l_{jt}^{E} > 2\upsilon; \\ 0 & disregard\ \ if \quad W_{jt}^{A} < b_t. \end{cases}$$

Due to the specificities of the discontinuity in the knowledge base (in terms of the complexity for instance) and the novelty of the underlying scientific results, the adoption and integration of the scientific advances available imply additional costs υ for the firm. These costs burden the firm (by diminishing its profits) for a certain number of periods. The burden decreases in every period at rate θ, after the firm has started to explore the new technological opportunities offered by the discontinuity.

4.1.7 Collaboration

Scientific advances may bring about radical technological change. According to the appreciative theory previously discussed, in the case of the pharmaceutical industry, the revolutionary discoveries of recombinant DNA for instance provoked the emergence of modern biotechnology and the entrance of new firms mastering the new technological opportunities offered by biotechnology (DBFs). Incumbent firms entered into collaborative arrangements with the new entrants.

Accordingly, the model specifies the possibility for incumbent firms having perceived technological discontinuity of entering into collaborative arrangements with the new entrants. The process of entering into collaborative arrangement is modelled as a stochastic process. The probability $W_{jzt}^{\ A}$ that two firms (an incumbent *j* and a new entrant *z*) achieve a collaborative agreement is a function of the stock of capabilities for external learning of the incumbent firm l_{jt}^{E} (which captures the extent to which the research strategy of the firm considers the active interaction with the actors involve in shaping its knowledge environment) and the distance between the two firms in the search space of potential drugs π_{jzt} (which represents the extent to which the potential partners may have the same research objectives). The probability is given by Eq 18:

Eq 18 $$W_{jzt}^{C} = 1 - \exp\left(\frac{-\nu \cdot l_{jt}^{E\,2}}{\pi_{jzt}}\right);$$ with ν representing a scaling parameter.

Again, the firms enter into a "collaboration lottery" given in Eq 19 to determine whether the collaboration occurs or not.

Eq 20 $$C_{jzt} = \begin{cases} 1 \quad collaboration \quad if \quad W_{jzt}^{C} \geq d_t; \\ 0 \quad if \quad W_{jzt}^{C} < d_t; \end{cases}$$

C_{jzt} := result at time t of the process of collaboration between firm j and z;

$d_t \sim U(0,1).$

After two periods the termination of a collaboration agreement is considered by activating the same stochastic process, (after updating two variables: the location of the firms in the search space and the engagement of the incumbent firm in interacting with its environment). For reasons of simplicity the model specification does not allow a DBF to hold more than a collaborative agreement simultaneously. Incumbent firms however, can have several collaboration partners.

A collaborative arrangement between incumbent firm *j* and a DBF *z* has two main implications. Firstly, the incumbent firm has access to a share of the technological capabilities ϑK_{zt}^{B} of its collaboration partner. Given that the incumbent firm may have many collaboration partners, the technological capabilities that add up to the extra mural knowledge of incumbent firm j in every period Ω_{jt}^{B} are given by Eq 21:

Eq 21 $$\Omega_{jt}^{B} = \vartheta \sum_{z} K_{zt}^{B} .$$

As part of the firm extramural knowledge, the extent to which firm *j* is able to absorb the capabilities of its collaboration partners and integrate them in its search and development activities depends on its absorptive capacity.[74] Moreover, incumbent firms have the possibility to licence the potential drug candidate of highest quality within the portfolio of drug candidates of the DBF partner. Moreover, after a licensing agreement incumbent firms can exploit the drug candidate even after the collaboration has been terminated. Accordingly, after successful development, licensed products enlarge the product portfolio of incumbent firms in the selection environment as their own products. Drugs of DBFs can be licensed only once.

4.1.8 The innovation process

Firms innovate when they are able to develop drug candidates (new discoveries, imitations or licensed drug candidates of their partners) that are not included jet in their product portfolio and reach the quality standards required by the selection environment.

In every period firms move in the search space looking for an attractive drug candidate as given in Figure 12 (or by collaborating with new entrants if a technological transition has taken place). The selection is based on the quality of the potential drug (which is unknown and can only be estimated by the application of technology B). These drugs might be totally new for the selection environment or imitations. New products are protected from imitation for 20 simulation periods. The extent to which the innovation process succeeds depends on the stock of technological capabilities accumulated by the firm. However, the result of the innovation process remains a stochastic process (Nelson, Winter 1982). By accumulating capabilities in drug discovery and development K_{jt} firms can increase the probability of successful innovation/imitation W_{jt}^{I} which is given by Eq 22 and sketched in Figure 16:

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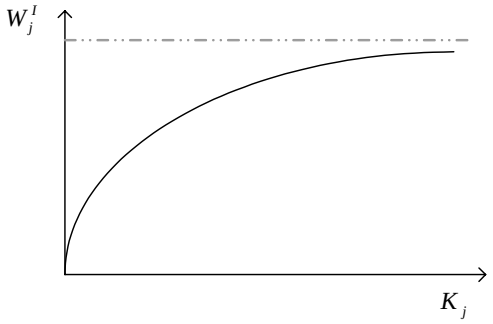
74 See Eq 7 and Eq 12 for related equations giving the extramural knowledge base of the firm and the extent to which this on is integrated in the technological capabilities of the firm.

Eq 22 $W_{jt}^{I} = 1 - \exp\left(-\mu \cdot K_{jt}\right)$; with μ := Scaling parameter.

Figure 16: Probability to innovate W_j^I



Accordingly, the model specifies the cumulative character of technology in the innovation process since the accumulated stock of technological capabilities (and not the new technological capabilities created in every period) influence the probability to successfully develop new products or imitate them.

With this probability to successfully develop potential drugs selected from the search space or licensed into products, firm *j* accesses in each period the so called "innovation lottery" which determines the success of the innovation process I_{ijt}. The random draw in the innovation lottery of firm j at time t is given by a uniform random distribution $a_{jt} \sim U(0,1)$.

Eq 23
$$I_{ijt} = \begin{cases} 1, & \textit{succesfull innovation process} \quad \textit{if } W_{jt}^{I} \geq a_{jt} \textit{ and} \quad q_{ijt} \geq q^{*}; \\ 0, & \textit{failed innovation process} \quad \textit{if } W_{jt}^{I} < a_{jt}; \end{cases}$$

with I_{ijt} := result of the process of developing the drug candidate i by the firm j at period t.

A successful innovation implies that the firm's portfolio of products increases in one drug and the selection environment has an additional product against diseases. This happens only if the novel drug selected (or the generic developed) reaches the minimum quality determined by the standards q^{*} in the selection environment.

Once a product is accepted by the selection environment the firm supports it with marketing campaigns to improve the product's image. The aim of the firm's marketing campaign is to increase the "merit" of the product which determines the reward the firm obtains from the selection environment. This volume of marketing efforts M_{jt} to reach

a desirable product image is given in equation Eq 24, where β_j stands for the investment share for learning activities and B_{jt} for firm's budget.

Eq 24 $$M_{jt} = (1-\beta_{jt}) \cdot B_{jt}.$$

4.1.9 The selection environment

Drawing on the evolutionary tradition firms face a selection environment that evaluates the products (drugs) they develop and commercialise. In each period companies approach the selection environment with their portfolio of products developed so far. Accordingly, the products available in the selection environment are those discovered and developed by all the firms in the industry. The selection environment only accepts products that reach certain quality standards. In other words, as in the pharmaceutical industry is the case, products can be introduced in the selection environment as long as they reach a minimum level of quality set by the system.

Firms are rewarded by the selection environment according to the "aggregate merit" of their product portfolio compared to the aggregate merit reached by the industry. For this purpose the selection environment has a budget ψ .The reward from the selection environment is used to finance firm's activities.

The products in the selection environment are evaluated and given a certain "merit". Drawing on Malerba and Orsenigo (2002) in every period the merit of product developed by the firm j U_{ijt} depends on three factors:

(i) the true quality of the product q_{ij} ,

(ii) its expected return on investment r_i , which is higher for novel products than for generics and

(iii) its image c_{ijt} , which in turn depends on the marketing investment of the firm for that particular drug $M_j(t_{ij})$.

The relevant expressions concerning these variables are given in Eq 25 and Eq 26:

Eq 25 $$U_{ijt} = m_0 \cdot q_{ij}^{\,m_a} \cdot (1/r_i)^{m_b} \cdot c_{ijt}^{\,m_c}$$; with m_0 :=scaling parameter and $m_a < m_b < m_c$.

Eq 26 $$c_{ijt} = \begin{cases} 0 & if\ t < t_{ij} \\ M_j(t_{ij}) \cdot \exp\{\rho \cdot (t - t_{ij})\} & if\ t \geq t_{ij} \end{cases};$$

where ρ represents the rate of erosion of the image of a product.

The merit share reached by firm j in each period F_{jt} is given by the aggregated merit of the products developed by firm *j* related to the aggregated merit of the products in the selection environment.

Eq 27 $$F_{jt} = \frac{\sum_{i} U_{ijt}}{\sum_{ij} U_{ijt}};$$

As given in Eq 28, the budget to reward firms ψ and the merit share of the firm *j* F_{jt} determine firm's revenue in period t.

Eq 28 $$R_{jt} = F_{jt} \cdot \psi \ .$$

Finally, the profit π_{jt} of firm j in each period is determined by the sum of the non expended budget (after considering the current investment research and technology development L_{jt}, the marketing investments for launching a new product M_{jt} in the periods where a medicine is offered to the health system and the costs of adopting new technological opportunities T_{jt} in the periods where these activities take place) and the revenue R_{jt}. Eq 29 gives the relevant expression:

Eq 29 $$\pi_{jt} = B_{jt} - L_{jt} - M_{jt} - T_{jt} + R_{jt} \ ;$$

The profit is reinvested in the activities of drug discovery and development and marketing. The budget of a firm is given by Eq 30:

Eq 30 $$B_{jt} = \begin{cases} B_{jo} & if \quad t = 0 \\ \pi_{jt-1} & if \quad t > 0; \end{cases}$$

B_{jt} := Budget for drug discovery, drug development and marketing activities;

π_{jt} :=Profit of firm j at time t.

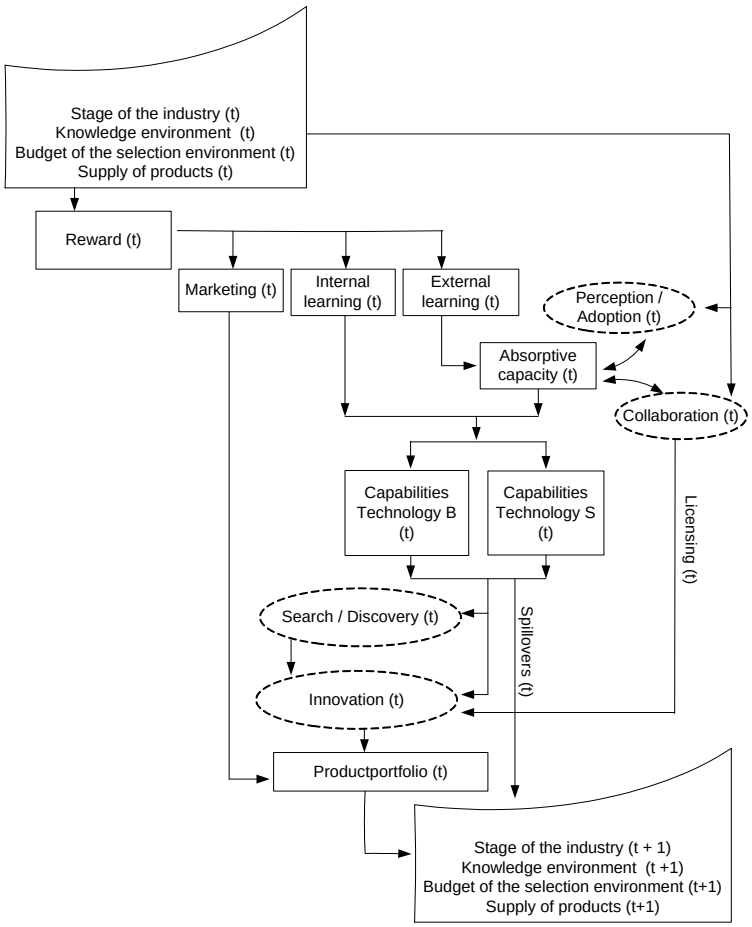
4.1.10 The transition dynamics

The model is dynamic. Accordingly the specification defines the transition from stage t to stage t+1 as given in Figure 17.

The transition dynamics include stochastic processes. These are represented in Figure 17 with circles. In the spirit of the Nelson and Winter models, the state of the

industry in any period determines the probability distribution of the state of the industry in the next period. The specification of the transition from the state at time t to the state at time t+1 has the character of a stochastic Markov process. However, inspired by Llerena and Oltra (2002), probabilities do not depend on current variables (such as in the Nelson and Winter models). In the model put forward in this contribution, the probability to innovate, to perceive discontinuities in the knowledge environment and to collaborate depend on the stock of accumulated capabilities rather than on current investment.

Figure 17: Transition dynamics in the model



4.2 Simulation experiments

According to Malerba (1999), to test the logic of an appreciative theory as the one presented in chapter 3 it is necessary to demonstrate that a stylised formal model

incorporating the appreciative theory is able to reproduce the observed historical patterns.

The first step is to implement the model described in the previous section in a numerical simulation model. The implementation of the simulation model has been done using object-oriented programming. This approach allows building models with a structure made of a set of objects. Objects are abstract entities, referred to with a name or label, which can contain either other objects or numerical variables. Objects are devoted to present entities of the reality the model aims at simulating like, for example, market, firms, capabilities, products etc. Stochastic and deterministic functions and numerical parameters specify initial conditions, object interaction and transition dynamics from one stage to the next (Valente 1998).[75]

Next, to replicate the pattern of technological change of the industry described in chapter 3, a parameter setting will be specified capturing the key stylised facts given in the appreciative theory. Additionally, the simulation environment allows building counterfactual scenarios by specifying alternative parameter settings that might contradict the main assumptions of the appreciative theory. This procedure enables, on the one side, to prove the logic of the theory developed. If the logic is coherent, a parameter setting that does not correspond to the basic stylised facts of the appreciative theory should produce history divergent results. Finally, the results can have relevant policy implications.

Section 4.2.1 discusses the specification of the history-friendly scenario and presents the results of the simulation runs replicating the pattern of technological change in the German pharmaceutical industry in the 20th century driven by the development of biotechnology and synthetic organic chemistry and discussed in chapter 3. The counterfactual analysis is presented in section 4.2.2

4.2.1 The history-friendly scenario

The history-friendly scenario aims at reproducing the historical patterns of technological change presented in chapter 3. The empirical analysis carried out from the industrial and organisational perspectives (sections 3.3 and 3.4) constitute the basis for the parameter setting of the model. More specifically, the value of the parameters related to the technological regimes, such as complexity of the scientific knowledge base,

75 The software used has been the Laboratory for Simulation Development (LSD), freely available at http://www.business.aau.dk/lsd/lsd.html. The parameters and important parts of the programming code are included in annex III and IV.

appropriability conditions (spill-overs) or the cumulativeness of technological capabilities in terms of level (high or low) draw on the analysis carried out in section 3.5. On the other hand, the selection of the parameters related to the characterisation of the firms draw on the organisational analysis carried out in section 3.4.7.

An important aspect of the parameter setting of history-friendly models is the fact that the level of the parameters is not grounded on econometric or statistical analysis. The values of the parameters need to be numerically coherent with the model specification and match the stylised facts of the appreciative theory. However, the numerical values themselves do not represent an accurate empirical result in absolut terms.[76]

A simulation run includes 100 periods. In each period the cycle specified in Figure 17 updates the stage of the industry in terms of level of technological capabilities (Eq 14 and Eq 15). This process includes the update of variables at the organisational level such as firms' investment decisions and research, learning and marketing activities as specified in the previous sections, as well as their performance regarding collaboration and innovation. It is assumed that firms in their real managerial activities revise such decisions yearly. Accordingly, a simulation period corresponds to a year.

The next section presents the main assumptions concerning the parameter setting replicating the historical pattern of technological change given in the appreciative theory and summarised in section 3.5. The discussion of the parameter setting starts with a general description of the main exogenous events introduced in the simulation concerning the knowledge environment and firm entry. Next, a detail specification of the parameters determining firm's strategic paradigms is presented. Moreover, the arguments behind the parameters influencing the technological regimes and their changes are discussed in detail.

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76 For instance, to capture the stylised fact based on the empirical analysis that the revolution of molecular biology in the 1950s brought about a change in the nature of biotechnology's science base and moreover, that the emergence of modern biotechnology involved revolutionary scientific advances, two exogenous discontinuities specified in the simulation increase the degree of complexity of the firms' extramural biotechnology knowledge base φ^B (see Eq 11). The appreciative theory developed in chapter 3 does not allow us to assign an accurate value to the parameter φ^B (degree of complexity of the knowledge base) after the discontinuities occur, but it does allow us to put forward an increase of complexity after the scientific advances.

4.2.1.1 Exogenous discontinuities, firm entry and collaboration

The stylised facts distinguished 3 phases in the evolution of the German pharmaceutical industry from the 1880s to the end of the 20th century. The history-friendly model introduced in this chapter covers the three phases and involves 2 main exogenous discontinuities in the knowledge environment. Accordingly, in a simulation run (100 periods) exogenous discontinuities are introduced in the periods t=50 and t=75. The discontinuity at t=75 allows for firm entry and the establishment of collaborative agreements between industry incumbents and new entrants.

First discontinuity (t=50)

This event tries to capture the effects of the revolution of molecular biology in the 1950s in the German pharmaceutical industry. It involves the following changes in the knowledge environment:

- The knowledge base related to technology B expands due to novel scientific advances and to an increase in the volume of research results from foreign public research organisations (see Eq 7);
- The technological frontier of technology B moves to allow for further improvements of the firms in this technology (see Eq 4 and Eq 6). Additionally, the scientific knowledge base of technology B becomes more complex (see Eq 11);
- Only those firms perceiving the novel scientific advances exploit the new technological opportunities (depending on their level of absorptive capacity) and start trying to reach the new technological frontier (see section 4.1.6).

Second discontinuity (t=75)

This event represents the advent of modern biotechnology in the 1970s, the establishment of the biotechnology industry and innovation networks. This transition is specified as follows:

- The opportunity conditions for innovation increase. The landscape of molecules changes to include more potential drugs with higher therapeutic quality. However, again only those firms perceiving the new scientific advances and integrating them have access to additional drug candidates in the landscape of molecules. The opportunities for innovation increase hence only for these companies;
- The novel scientific advances turn the scientific knowledge base of technology B more complex. At the same time the technological frontier of technology B moves further to allow for additional technological improvements of the firms in this technology;

- The transition is to some extent competence destroying in the sense that it challenges the ability of incumbent firms to accumulate technological capabilities in technology B given the new conditions in the knowledge environment. The maintenance of the level of capabilities in technology B requires more effort since, due to novel scientific advances, in every period the share of capabilities in technology B becoming obsolete is larger than in the past (see Eq 13);
- Dedicated Biotechnology Firms (DBFs) enter the industry.

Firm entry and collaboration (t=75)

DBFs are characterised by their exclusive engagement in the development and application of technology B. Accordingly, the companies have no marketing capabilities. This handicap prevents them from bringing in potential drug candidates they have discovered into the selection environment and obtaining a reward. However, they have access to a fix budget in every period (capturing the access to venture capital or public subsidies of Dedicated Biotechnology Firms), which is the financial basis of their learning activities to develop technology B.

Regarding their technological performance in the application of technology B, DBFs enter the industry with a technological performance that equals the technological frontier. In other words, DBFs are able to fully exploit the technological opportunities offered by technology B when they enter the industry. In what concerns their technological achievement in technology S, they are far away from the technological frontier and therefore, compared to incumbent firms, they have access to a relatively narrow scope of the search space. Due to their exclusive engagement in the development of technology B they do not develop any capabilities in technology S and therefore, they do not experience any improvement in what concerns the application and development of this technology.

The simulation allows for the establishment of collaborative arrangements (i. e. the model specification allows for collaboration only after t=75). Incumbent firms have the possibility of entering collaborative arrangements with the new entrants (see section 4.1.7).

According to the model specification, t he role of DBFs is twofold. On the one hand, they act as potential collaboration partners for incumbent firms (firms of type DC and TP). For incumbent firms a collaboration agreement entails the possibility of acquiring additional knowledge to develop biotechnology capabilities (technology B). Therefore, DBFs can be considered as a source of knowledge in incumbents' extramural knowledge base. On the other hand, due to the excellence of DBFs in technology B, these may be able to develop products of higher therapeutic quality than incumbent

firms. Collaborative arrangements involve the possibility for incumbent firms of obtaining the rights for the commercial exploitation of products developed by DBFs.

4.2.1.2 Parameter setting regarding firms' strategic paradigms

With regard to the number of firms, at the beginning of the simulation the model presents an industry with 4 firms: two of firm type DC (representing dyestuff companies) and the other two firms of type TP (representing traditional pharmaceutical companies). In period t=75 the specification of the model allows for the entry of 14 firms of type DBF. Table 9 gives the relevant variables specifying firms' strategic paradigms and its values.[77]

Table 9: Firms' strategic paradigms: Variables for the characterisation of the firms in history-friendly simulation runs

Variables and description	Firm Type TP	DC	DBFs
β_{jt} := Investment share directed to learning	U (0.5 , 0.7)	U (0.5 , 0.7)	1
λ_{jt} := Investment share directed to external learning	U (0.1 , 0.2)	U (0.3 , 0.4)	1
α_{jt} := Company's bet on the technology being worth developing	U (0.3 , 0.5)	U (0.6 , 0.8)	0

This parameter setting at the level of the organisation aims at capturing, in an extreme form, the strategic paradigms of the firms, i. e. the different research traditions and technological roots of the firms in the industry.

As given in Table 9, three variables determine the behavioural and cognitive characteristics of a firm. On the one side, the variables β_{jt} and λ_{jt} determine its learning strategies. As introduced in section 4.1.4, firms' learning strategies aim at creating and accumulating technological capabilities to carry out search and development activities.

Companies of type TP and DC are assigned parameter values according to which the share of their budgets invested in learning in every period β_{jt} is uniformly distributed between 0.5 and 0.7. Even though the probabilistic distribution and its limits remain constant, the variable is updated in every period. The fact that the probability distribution and the limits of the stochastic parameters are time invariant is a strong simplification of the model.

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77 The complete list of parameters and their values are included in annex III.

The learning budget can be invested in internal and external learning. The share of investment for external learning λ_{jt} (which determines the share of the learning budget to finance activities promoting learning by searching and learning by interacting in the sense of Malerba (1993)) differs among companies. In accordance with the stylised facts discussed in section 3.4.7, the engagement of firms of type DC in external learning is stronger than in the case firms of type TP.[78] Again, the variable is uniformly distributed and is updated in every period even though the probabilistic distribution and its limits remain constant.

The variable α_{jt} captures companies' technological strategy (i. e. companies' bet on the technology being worth developing in-house). Firms of type DC have a preference for technology S while firms of type TP have a slight preference towards the development and application of technology B.

With regard to DBFs, this type of companies appears in the simulation at t=75. DBFs invest their entire budget in learning, which implicates that no resources are invested for marketing activities. Moreover, DBFs are exclusively engaged to external learning. Therefore, they are characterised by a deterministic parameter λ_j equal to 1. Additionally, to capture their exclusive engagement in technology B, α_j is deterministic and equal to zero.

4.2.1.3 Parameter setting regarding the technological regimes

The history-friendly model aims at replicating the stylised facts discussed after the establishment of the modern pharmaceutical industry. In this phase already two technological trajectories (biotechnology and synthetic organic chemistry) shaped drug discovery and development processes. Accordingly, the exploration does not cover the emergence of technologies. It focuses in their development and relative importance for the pharmaceutical industry over time.

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78 According to the stylised facts, the differences between dyestuff companies and traditional pharmaceutical companies in terms of R&D expenditures as share of their sales have not been significant. However, dyestuff companies were characterised by strong interaction with the knowledge environment in terms of collaboration and by following science-based research strategies. Traditional pharmaceutical companies, on the other hand, have traditionally empirical (trial-and error or learning by doing) research strategies and, to some extent, do not interact as much as their counterparts with the actors in their knowledge environment. Moreover, dyestuff companies were very much focused on the application of the organic chemical synthesis, while the representatives of the traditional pharmaceutical industry had positive attitudes towards the application of biotechnology, and had applied it and developed it in the first half of the 20th century.

To set the parameters characterising the dimensions of the technological regimes shaping the different phases of the pharmaceutical industry the analysis draws on the stylised facts elaborated in sections 3.3 and 3.4 of chapter 0. The relevant parameters capturing the staring situation and their changes have been discussed in the previous chapter and given in Table 8.

In the parameter setting of the history-friendly scenario given in Table 8 the changes in the technological regimes are driven by the development of the knowledge base underpinning the application and development of technology B. The main change corresponds to the volume of scientific knowledge provided in every period by public sector research institutions z^B after t=50. Additionally, the degree of complexity of the extramural knowledge base relevant for technology B φ^B increases. This effect aims to capture the changes in the nature of the knowledge base in terms of the number of disciplines contributing to its development. Moreover, the depreciation rate of technological capabilities in technology B δ^B increases to capture the difficulty of firms in keeping up with the intensive scientific development in technology B.

Table 10: Relevant parameters for the characterisation of the technological regimes in the different phases of the industry in the history-friendly scenario

Parameter and description	Phase (I) 0 <t<49	Phase (II) 50<t<74	Phase (III) 75<t
F^B := Technological frontier of technology B (min. search error)	1200	700	300
z^B := Scientific knowledge underpinning technology B provided in every period by public sector research institutions	1.5	5	5
φ^B := Degree of complexity of technology B extramural knowledge base	0.22	0.24	0.28
ϕ^B := Rate of intra-industry knowledge spill-overs in technology B	0.01	0.01	0.01
δ^B := Depreciation rate of technological capabilities in technology B	0.04	0.04	0.045
F^S := Technological frontier of technology S (max. search scope)	400	400	400
z^S := Scientific knowledge underpinning technology S provided in every period by public sector research institutions	3	3	3
φ^S := Degree of complexity of technology S extramural knowledge base	0.22	0.22	0.22
ϕ^S := Rate of intra-industry knowledge spill-overs in technology S	0.01	0.01	0.01
δ^S := Depreciation rate of technological capabilities in technology S	0.04	0.04	0.04

An important contribution of the advent of modern biotechnology for the pharmaceutical industry (technology B in our model) was the enlargement of the opportunity conditions for innovation. In the simulation model this changes is specified by giving firms

adopting and developing the new technological opportunities in technology B the possibility to discover new products with higher quality that were not available before. Accordingly, the search space varies for incumbent firms adopting the new technological opportunities available after t=75.

4.2.1.4 History-friendly simulation results

The next paragraphs and charts present the results of the history-friendly simulation runs. These match quite well the historical pattern of technological change described in chapter 3.

The discussion of the results will be carried out at two levels of aggregation: the level of the industry and the level of the organisation. As for the industry level, the analysis focuses on technological change in terms of the relative importance of technology B and technology S and the rate of development of industrial capabilities in these technologies. As for the organisational level, the results consider the differences in the types of firm (TP, DC or DBF) and analyse the following aspects of firm behaviour:

- Development of firms' technological capabilities
- Firms' reaction to changes in the knowledge environment
- Firms' collaborative behaviour
- Quality level reached by the best products (i. e. firm's superior products) developed by each firm
- Development of firms' product portfolio (in terms of number of products)
- Reward obtained by firms from the selection environment in each period

Figure 18 gives the results in terms of technological capabilities of the industry.[79] Technology S (representing the organic chemical synthesis) dominates the capabilities of the industry during the entire simulation. However, after the first discontinuity in the knowledge environment (t=50) technology S slows its development rate while the rate at which the industry develops capabilities in technology B increases. Next, after period t=75, the industry is not able to maintain the rate of development in creating capabilities in technology B. According to the specification of the model, the absorptive capacity of incumbent firms is weaken by the increased complexity of the extramural knowledge base relevant for technology B. However, the industry keeps developing capabilities in

79 At this point it is most important to note that the values in the Y-axis standing for the technological capabilities of the industry deserve only a qualitative interpretation (in terms of low of high). In neo-Schumpeterian evolutionary models data are the numerical results of the simulation and do not aim at capturing the absolute volume of capabilities of the industry. The pattern of change is of relevance, not the aboslute values per se. This holds for all the data presented in the next sections.

technology B at a larger rate than capabilities in technology S. The results match remarkably well the stylised facts presented in section 3.5 and speak for a forthcoming change in the dominance of technologies in the industry.

Figure 18: History-friendly scenario: Technological change in the industry (100 simulation runs and average) [80]

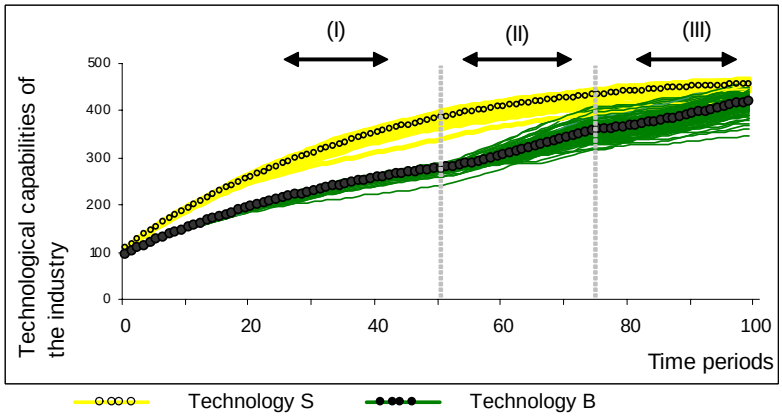


Figure 19 gives the level of technological capabilities of the 4 incumbent firms specified in the simulation. Drawing on the stylised facts, the initialisation of the simulation specifies firms of type TP with a higher level of capabilities in technology B than capabilities in technology S while firms of type DC are larger and hold a relatively larger share of capabilities in technology S (see annex III for details on the initialisation of these variables).

While the relative importance of the technological capabilities remains unchanged in the case of firms of type DC, firms of type TP experience a transformation in their technological identity. Even though the companies start the simulation with a large share of capabilities in technology B, already in period t=30 technology S dominates the capabilities for product search and development. Both types of companies accelerate the rate of development of technology B capabilities after t=50, even though in the case of firms of type TP the acceleration is weaker and it starts latter than in the case of firms of type DC.

80 A simulation run includes stochastic processes based on computer-generated random numbers. An algorithm produces the random numbers, so they are not really random. The algorithm needs a number to start with (the so called seed). Simulation runs with the same parameter setting drawing on different seeds produce different random numbers and hence different simulation results so that the simulation's result depends on the seed chosen. To eliminate this deterministic bias the simulation results given in the tables present the average results of 100 simulations each with a different seed.

Figure 19: History-friendly scenario: Technological capabilities of the incumbent firms (average 100 simulation runs)

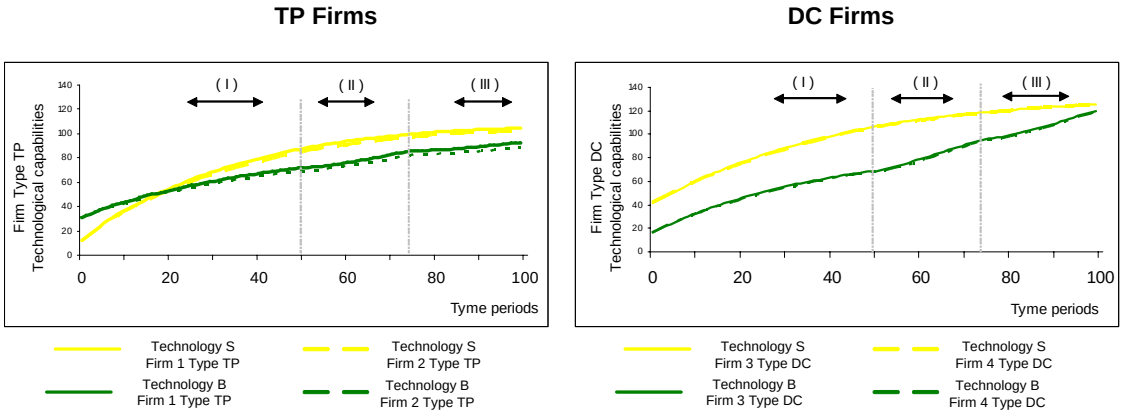


Table 11 gives detailed insight to the reaction of firms to discontinuities in the knowledge environment. Firms of type DC perceive the first technological discontinuity at a rate of 99 % and 98 %, respectively, while firms of type TP present lower average perception and adoption rates. The reactions to the next discontinuity are quite similar. Firms of type DC are better able to perceive and adopt the new technological opportunities. Adoption occurs in both cases often and faster in the case of the firms of type DC. These results are coherent with the specification of the model and with the logic of the appreciative theory. Commitment to external learning (as in the case of firms of type DC) enables perception and adoption of technological opportunities.

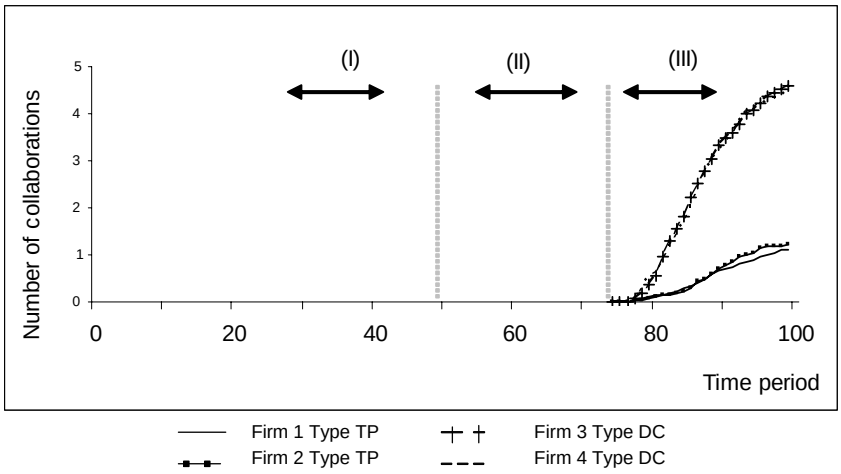
Table 11: History-friendly scenario: Firms' reaction to discontinuities in the knowledge environment (average over 100 simulation runs)[81]

		Firm Type TP		**Firm Type DC**	
		Firm 1	Firm 2	Firm 3	Firm 4
t=50	Perception / Adoption rate	81 %	83 %	99 %	98 %
	Average adoption period	69	67	60	61
t=75	Perception / Adoption rate	51 %	53 %	92 %	86 %
	Average adoption period	86	85	82	84

81 A perception / Adoption rate of 81 % in the case of firm 1 after the discontinuity at t=50 means that firm 1 has perceived and adopted the technological opportunities given by the discontinuity in the knowledge environment in 81 out of 100 simulation runs. In average, adoption took place in period t=69.

After the discontinuity at t=75, Dedicated Biotechnology Firms (DBFs) introduce changes in the structure of the industry. Firms of type TP and DC have now the opportunity of cooperating with the DBFs and herewith the access to additional sources of knowledge related to technology B. Figure 20 gives the number of collaborations of incumbent firms (firms of type TP and DC) with the new entrants after the second discontinuity in t=75. Compared to their counterparts, firms of type DC interact more with DBFs.

Figure 20: History-friendly scenario: Number of collaborations of incumbent firms (average 100 simulation runs)



Again, the results are coherent with the appreciative theory. Engagement in external learning (as in the case of firms of type DC) implicates larger number of collaborations with DBFs.

Figure 21 gives the quality of firms' superior product candidates. After period t=75, DBFs hold the drug candidates with the highest quality. Due to the fact that DBFs are at the technological frontier (that is, they carry out the search and selection process of product candidates in the search space with the lowest error of observation allowed) they are able to discover and (if already patented) imitate the potential drugs with the highest quality. However, these innovations remain drug candidates because DBFs have no marketing resources and hence they are not able to build up a drug portfolio and compete with incumbent firms.

As given in Figure 21, firms of type DC are able to increase continually the quality of their best product candidate. In phase III the maximum quality reached improves more radically. In the case of firms of type TP this improvement is more incremental. Regarding the capacity of firms to develop products and add them up to the product

portfolio provided to the selection environment Figure 22 gives the size of firm's drug portfolio.

Figure 21: History-friendly scenario: Quality of firm's superior product candidates (average 100 simulation runs)

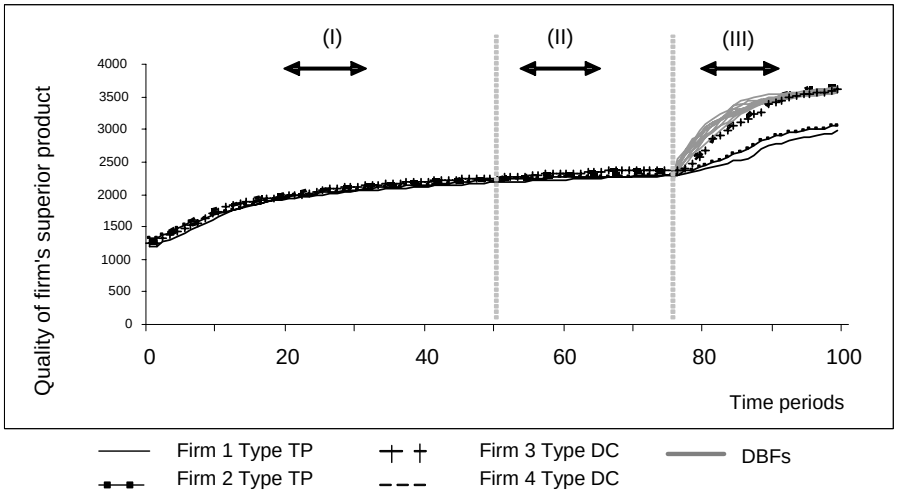
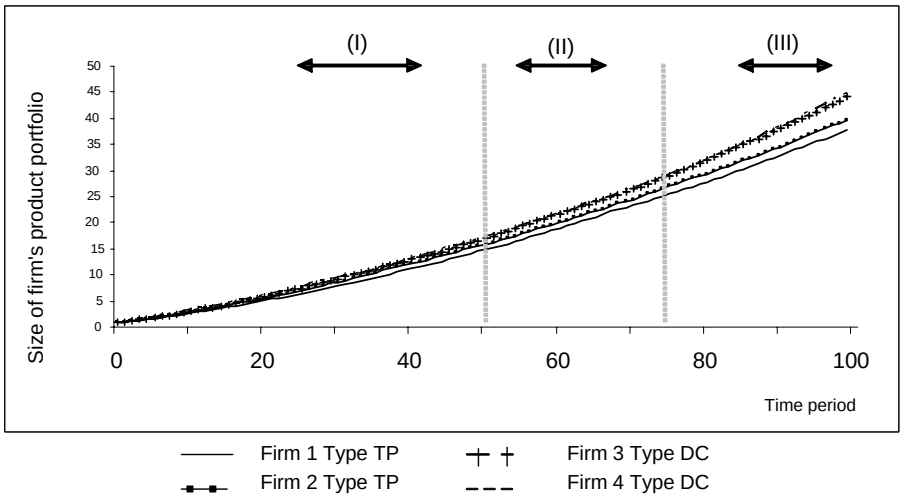
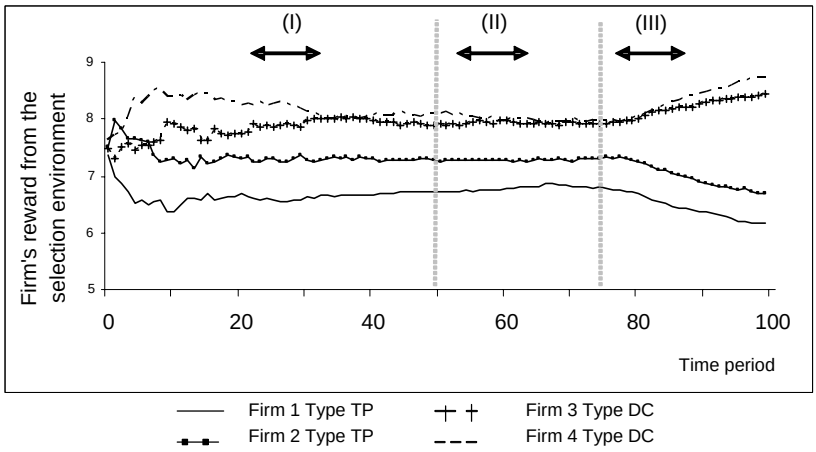


Figure 22: History-friendly scenario: Size of firm's product portfolio (average 100 simulation runs)



The results suggest that firms of type DC are more successful in bringing products to the selection environment. Their success is more evident in phase III. Even though firms of type DC start the simulation with a larger volume of capabilities, the results suggest that firms of type TP are able to follow them by introducing innovations at the same pace. In phase III the differences of performance are clearer. These results are consistent with the results regarding the reward that firms obtain from the selection environment presented in Figure 23.

Figure 23: History-friendly scenario: Firm's reward from the selection environment (average 100 simulation runs)



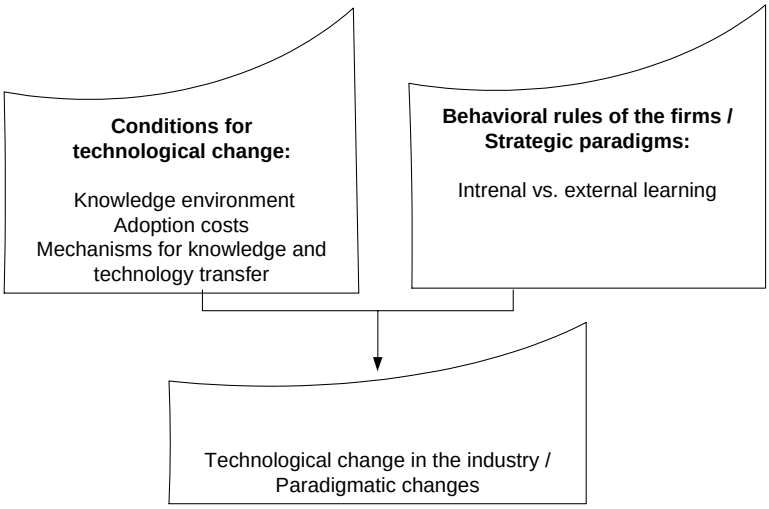
As discussed in section 4.1.9, in each period the companies provide the selection environment with their product portfolio. The selection environment rewards product developers according to the relative "merit" of the company's product portfolio (see Eq 27 and Eq 28). The results confirm that firms of type DC are able to collect the largest reward during almost the entire simulation. In phase III the dominance of firms of type DC is clear. In phase I industrial leadership seems to be related to technological strength in applying technology S. Moreover, engagement in external learning reinforces the ability to recognise discontinuities in the knowledge environment and to develop absorptive capacity in phase III. Therefore, firms of type DC enhance their performance by exploiting the possibilities provided by their knowledge environment and adapting to the selection environment. These results at the organisational level are coherent with the appreciative theory.

4.2.2 Counterfactuals: history-divergent scenarios

In this section we test the logic of the appreciative theory by running the simulation with parameter settings that contradict the appreciative theory. The results should be history-divergent, or in other words, they should not replicate the empirical stylised facts of technological change in the pharmaceutical industry.

Counterfactual analysis can be carried out to explore technological change in the industry from many different perspectives. This contribution chooses focusing on the influence of the conditions for knowledge accumulation and the role of the strategic paradigms of the firms on technological change. Figure 24 presents the selected research issues for counterfactual analysis.

Figure 24: Selected research issues for counterfactual analysis



The following scenarios are specified:

- Scenario 1: Absence of discontinuities in the biotechnology knowledge base

At t=50 (1950s) and t=75 (1970s) the parameter setting does not include discontinuities in the scientific knowledge base related to technology B (z^B). Accordingly, the scenario does not allow for the entry of DBFs at t=75 either.

- Scenario 2: Firms' strategic paradigms focus on one type of learning

Two parameter settings define alternative firms' learning strategies to the ones specified in the history-friendly scenario by modifying the limits of the probability distribution of the parameter controlling for external learning (see λ_{jt} in Eq 8 and Table 9).

- Scenario 3: Absence of adoption costs versus high level of adoption costs

Two parameter settings define alternative levels of technology adoption costs (υ) that firms need to cover if they aim at exploiting the new technological opportunities offered by major discontinuities in the firms' knowledge environment (see Eq 16).

- Scenario 4: Absence of firm entry

The parameter setting includes the discontinuities in the knowledge environment concerning technology B. However, the scenario does not allow for firm entry at t=75 (1970s). Incumbent firms can not enter into collaborative arrangements with DBFs.

The counterfactual analysis that follows in each scenario is carried out at two levels of aggregation: the level of the industry and the level of the organisation. As for the industry level, the analysis focuses again on technological change in terms of the relative importance of technology B and technology S and the rate of development of these technologies. As for the organisational level, the following aspects of firm performance in the different scenarios are analysed: development of firm's

technological capabilities, the quality level reached by the best products developed by each firm, firms' reaction to the changes in their knowledge environment and the reward obtained by the firms from the selection environment in each period.

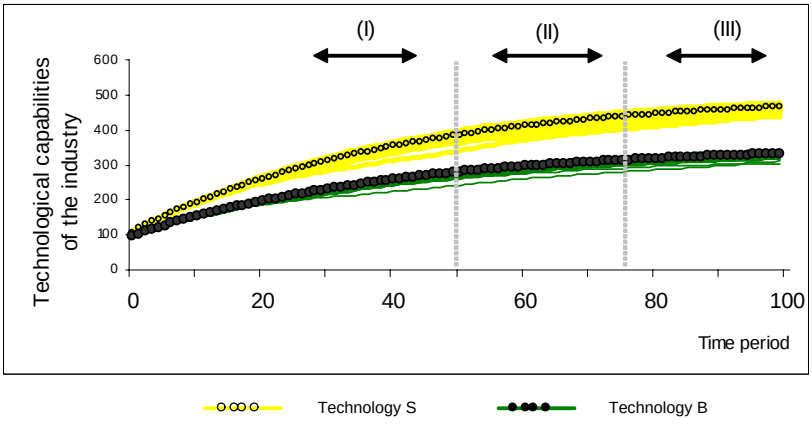
4.2.2.1 Scenario 1: Absence of discontinuities in the biotechnology knowledge base

To explore the influence of changes in the scientific knowledge base relevant for technology B a scenario is implemented where the knowledge environment develops without experiencing major discontinuities. The parameter setting maintains constant the starting values of the parameters given in Table 10 referring to the scientific knowledge provided by public sector research institutions relevant for technology B z^B, the degree of complexity of technology B extramural knowledge base φ^B, the rate of depreciation of capabilities of technology B ϕ^B and the depreciation rate of technological capabilities in technology B δ^B.

With regard to the appreciative theory, this scenario represents a situation where the two main scientific impulses for the development of biotechnology (technology B), the scientific advances of molecular biology between the 1940s and 1960s and the development of genetic engineering, do not occur. Furthermore, by preventing the scenario from allowing firm entry, it is assumed that major institutional changes enabling the transfer of scientific results from academia to the industry do not take place.

Figure 25 gives the average results of 100 simulation runs in terms of the level technological capabilities of the industry in technology B and in technology S.

Figure 25: Counterfactual scenario 1: Technological change in the industry (100 simulation runs and average)

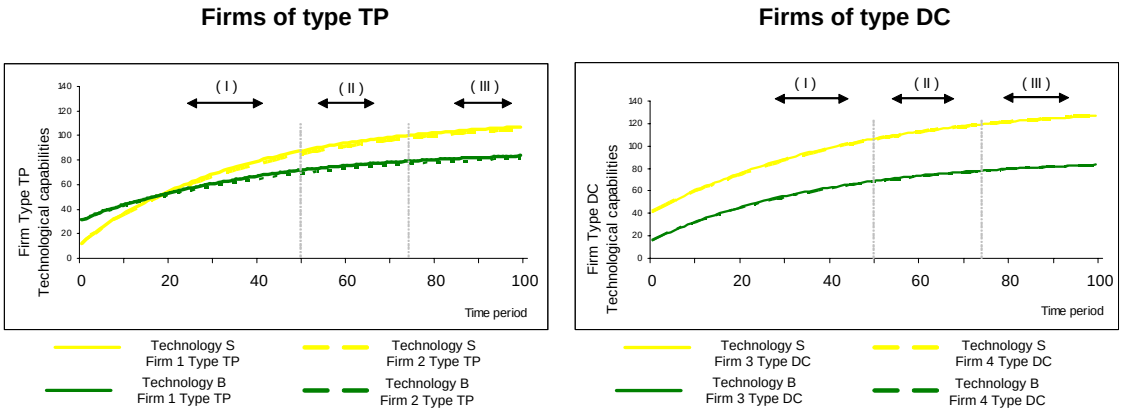


Phase I in Figure 25 presents the same pattern than the history-friendly scenario (Figure 18). However, due to the counterfactual parameter setting (based on assumptions that do not correspond with the stylised facts identified) a different (history-divergent) pattern of technological change emerges. Contradicting the observed pattern of technological change explored in chapter 3 and the history-friendly scenario, the industry does not change the rate of development of capabilities in technology B during phases II and III.

As for the results at the organisational level, the analysis starts with the accumulation of technological capabilities.

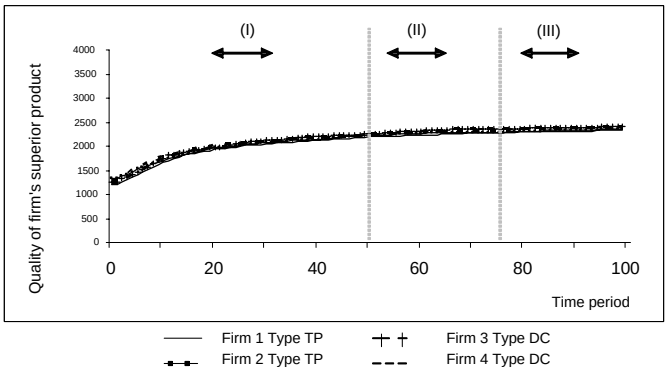
Figure 26 gives the average results of 100 simulation runs under scenario 1. As in the history-friendly scenario (Figure 19), firms of type TP change their technological identity at about period t=30 and herewith technology S becomes the dominant technology for both types of firms. However, technology development in phases II and III occurs differently than in the history-friendly scenario. While in the history-friendly scenario the development rate of capabilities in technology B increases in phases II and III, in this scenario the rate of development of technology B remains quite stable for both types of firms.

Figure 26: Counterfactual scenario 1: Technological capabilities of incumbent firms (average 100 simulation runs)



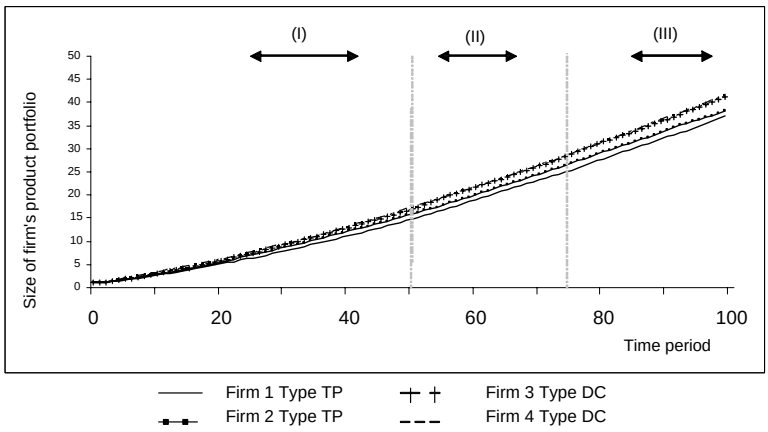
In what concerns product development, as given in Figure 27 the absence of discontinuities in the knowledge environment seems to have a strong influence on the quality level of the products developed and accepted by the selection environment. In phase I firms are able to increase incrementally the quality of their products. However, they do not reach the levels of the history-friendly scenario given in Figure 21 in phase III.

Figure 27: Counterfactual scenario 1: Quality of firm's superior product candidates (average 100 simulation runs)



Accordingly, the absence of scientific development in disciplines contributing to the development of technology B influences product quality in the industry. This is in line with the results in terms of the size of the product portfolio. In the absence of scientific advances firms' innovation performance in terms of number of new products is slightly weaker. However, the differences with the history-friendly scenario (Figure 22) are not as strong as in the case of product quality. These findings suggest that the changes in the knowledge environment do not result in radical change in the number of new products.

Figure 28: Counterfactual scenario 1: Size of firm's product portfolio (average 100 simulation runs)

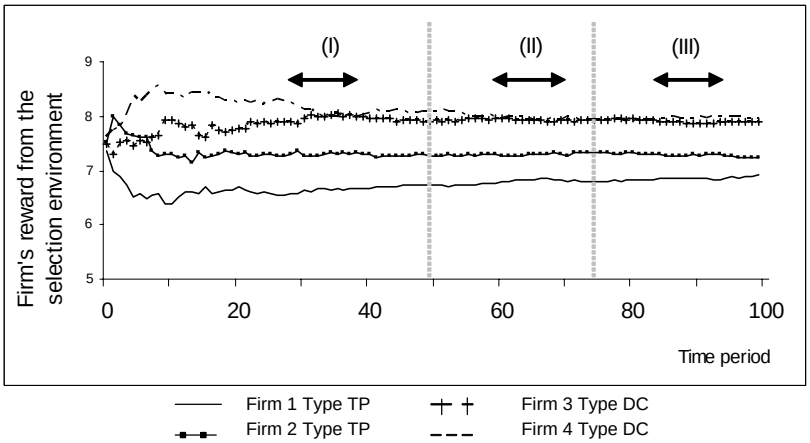


Due to the absence of discontinuities in firms' knowledge environment, the study of this scenario skips the analysis of firms' reactions to these events.

An additional aspect to be considered is firms' performance in terms of reward from the selection environment in each period. Figure 29 presents the average results of 100 simulation runs. As in the history-friendly scenario (Figure 23), in phase I firms of type DC are the best adaptors and receive the largest rewards. The reward levels do not

experience much variation after period t=30. The industrial leadership in terms of firm reward remains stable in phase II and phase III.

Figure 29: Counterfactual scenario 1: Firm's reward from the selection environment (average 100 simulation runs)



The results of the first counterfactual scenario are coherent with the assumption of the central role of the development of the science base in shaping and driving technological change in a science-based industry (in terms of knowledge underpinning search and innovation activities). However, as for the effects in the knowledge environment on the innovation rate of the industry, the results suggest that in a scenario without radical scientific advances in the knowledge environment, the innovative performance of the companies in terms of number of products brought to the market doesn't experience any remarkable differences compared to the history-friendly scenario. Nonetheless, in the scenario without discontinuities in the knowledge environment product quality is much lower.

As far as the experience of the German pharmaceutical industry, the development of the science base can explain the pattern of technological change in the pharmaceutical industry. The difficulties of German drug producers in developing biotechnology capabilities compared to the achievements to their American and European counterparts already in the 1960s (and in the 1980s after the advent of modern biotechnology) can be explained by the regional differences in the development of the knowledge base.

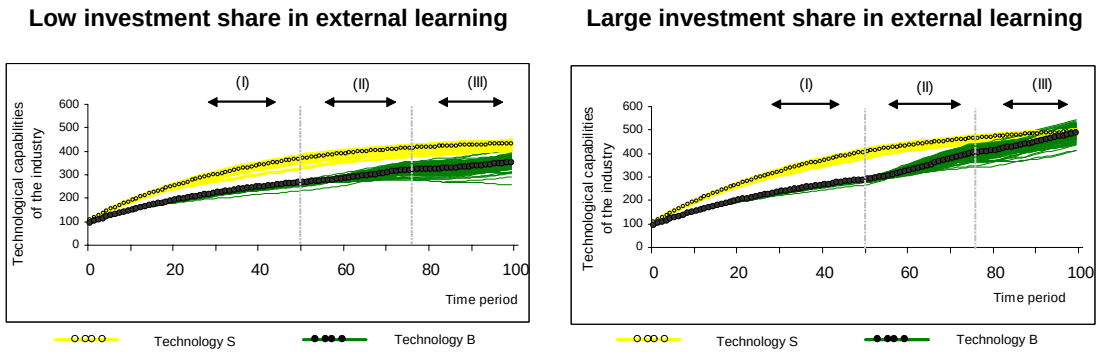
All in all, the results support the pattern of technological change according to which the development of biotechnology has brought about radical changes in the knowledge underlying search and innovation in the pharmaceutical industry. However, in terms of number of product innovations the discontinuity is more incremental.

4.2.2.2 Scenario 2: Firms focus on one type of learning

The next counterfactual analysis explores the influence of firms' learning strategies on the development of technological capabilities of the industry. In the model proposed, firms' learning strategies are specified (i) through investment decisions in learning activities and (ii) through the extent to which learning is internal or external. Drawing on the results presented in section 3.4.7, the history-friendly scenario has assumed that incumbent firms (firms of type DC and TP) implement different learning strategies in what concerns the balance between internal and external learning. As given in Table 9, in the history-friendly scenario firms of type DC present a higher commitment in external learning (i. e. learning from advances in science and spill-overs and learning by interacting) than their counterparts (firms of type TP).

In this section two alternative scenarios are implemented. Firstly, the parameter setting assumes weak commitment in external learning by all incumbent firms (the uniform distribution specifying variable λ_{jt} in each period is given the limits (0.10 , 0.15)). Alternatively, in a second scenario the parameter setting reflects strong commitment in external learning by all incumbent firms (the uniform distribution specifying variable λ_{jt} in each period is given the limits (0.40 , 0.50)). The analysis focuses firstly on the development of capabilities at the level of the industry. Figure 30 gives the results of 100 simulation runs and the average.

Figure 30: Counterfactual scenario 2: Technological change in the industry (100 simulation runs and average)

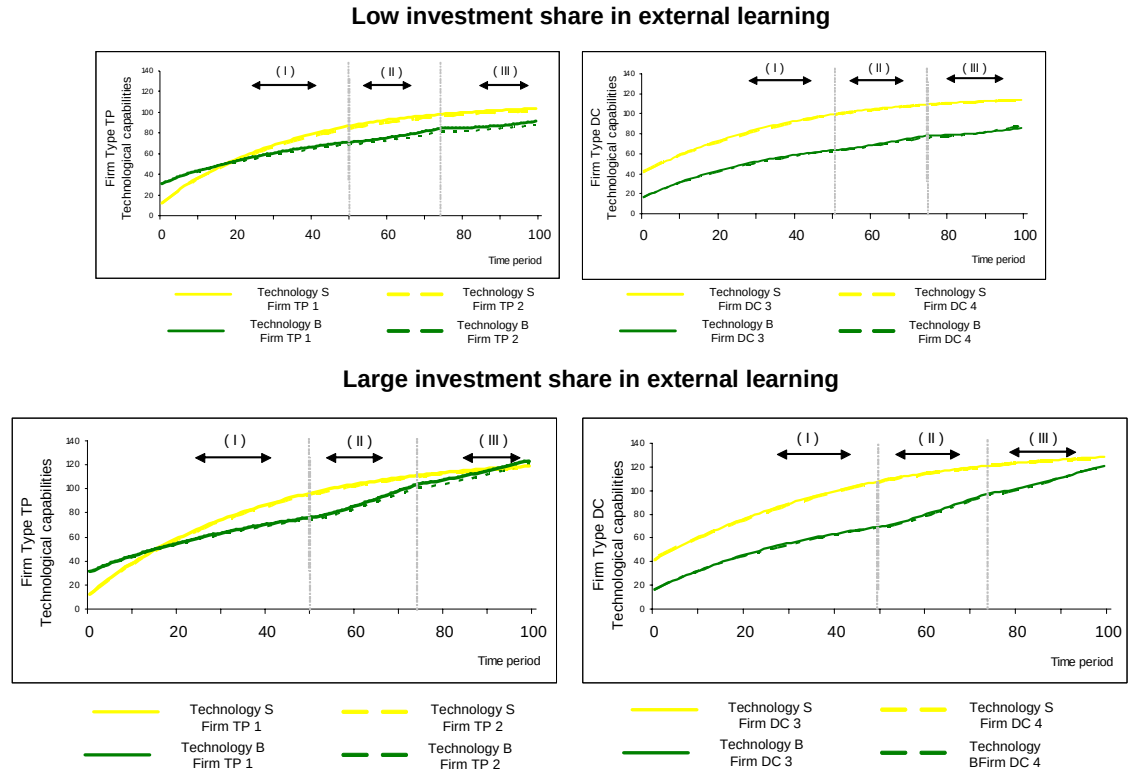


The results suggest that firms' commitment to external learning influence the aggregated pattern of technological change at the industry level. On the right hand side figure, the pattern of technological change is similar to the history-friendly scenario (Figure 18) in the sense that in phases II and III (characterised by changes in the extramural knowledge base) the level of technological capabilities in technology B grows in average at a faster rate than the level of capabilities in technology S. However, the rate of development of technology B in the last periods is higher in this

scenario. Accordingly in phase III technology B outperforms technology S in terms of relative importance leading to a paradigmatic change in the industry. This result is history divergent. While both technologies complement each other, their relative importance changes giving advantage to technology B. The figure in the left hand side gives the results of choosing a parameter setting assuming weak commitment in external learning by all incumbent firms. In this case, the level of technological capabilities of the industry is lower than the history-friendly scenario for both technologies.

As for the results at the firm level, Figure 31 gives the level of technological capabilities of firms of type DC and TP in both scenarios: low and large investment share in external learning.

Figure 31: Counterfactual scenario 2: Technological capabilities of the incumbent firms (average 100 simulation runs)



Again, the results suggest that large investment share in external learning (on the lower part of the figure) enhances the development of capabilities in technology B after the scientific advances at t=50 and t=75. Differently from the history-friendly scenario (Figure 19), firms of type TP (on the left side) invest more in external learning. This leads to a change in their technological identity in phases I and III, in the sense that the relative importance of the technologies in their volume of technological capabilities changes. As in the history-friendly scenario, firms of type DC also adapt the de-

velopment of technological capabilities to the changes in their knowledge environment. In case of firms of type DC, however, compared with the history-friendly scenario the parameter setting has not varied much.

Table 12: Counterfactual scenario 2: Firms' reaction to discontinuities in the knowledge environment (100 simulation runs)

Low investment share in external learning

		Firm Type TP		Firm Type DC	
		Firm 1	Firm 2	Firm 3	Firm 4
t=50	Perception / Adoption rate	85 %	84 %	86 %	87 %
	Average adoption period	69	67	67	69
t=75	Perception / Adoption rate	56 %	61 %	58 %	64 %
	Average adoption period	85	85	85	85

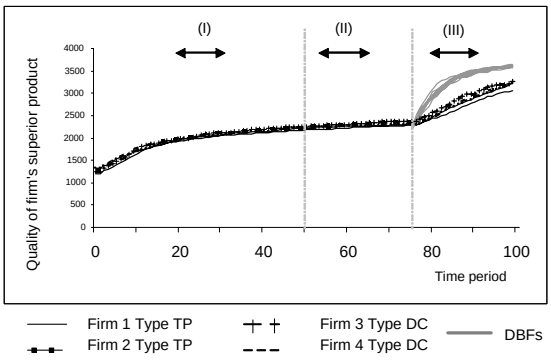
Large investment share in external learning

		Firm Type TP		Firm Type DC	
		Firm 1	Firm 2	Firm 3	Firm 4
t=50	Perception / Adoption rate	96 %	100 %	100 %	97 %
	Average adoption period	61	60	60	61
t=75	Perception / Adoption rate	83 %	88 %	89 %	84 %
	Average adoption period	83	84	82	84

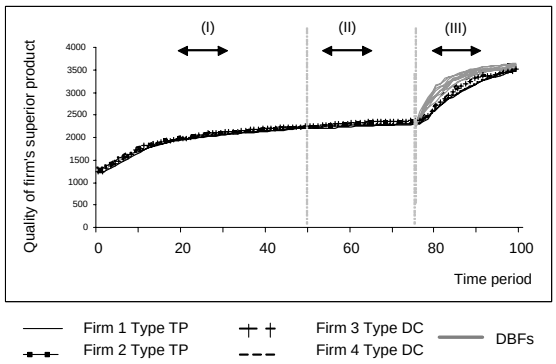
The results presented in Table 12 confirm the role of external learning in firms' reaction to changes in the knowledge environment. In the scenario with large share of investment in external learning incumbent firms perceive the discontinuity at t=50 in at least 96 % of the simulation runs. The average period of adoption of the new technological opportunities after t=50 lies between period t=60 and t=61. As for the discontinuity at t=75, the perception rates are again much higher (and adoption takes place faster) than in the low investment share scenario.

Figure 32: Counterfactual scenario 2: Quality of firm's superior product candidates (average 100 simulation runs)

Low investment share in external learning

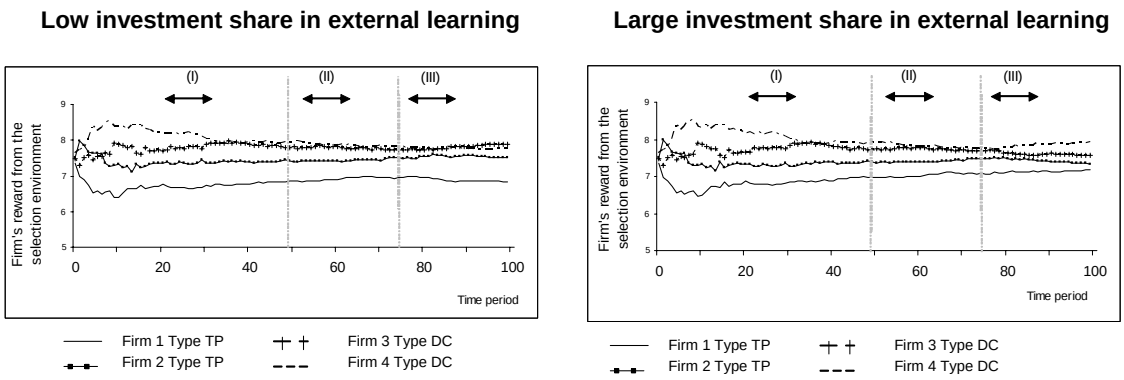


Large investment share in external learning



With regard to product quality, this scenario suggests that external learning has strong effects on the quality of the products developed by incumbent firms. In Figure 32, in the case of large investments in external learning, the best product candidates of incumbent firms match the quality of the best products discovered by DBFs. This is also the case for firms of type TP, which are not able to reach such high levels of quality in the history-friendly scenario (Figure 21). Considering that DBFs are located at the frontier of technology B (in other words, DBFs are able to exploit all technological opportunists offered by technology B in the search process) the achievement of incumbent firms by engaging in external learning is remarkable.

Figure 33: Counterfactual scenario 2: Firm's reward from the selection environment (average 100 simulation runs)



As shown in Figure 33, and compared with the history-friendly scenario in Figure 23, both scenarios present a similar profile in terms of firms' rewards in the selection environment. Especially, in the parameter setting specifying large investment in external learning by all incumbent firms (on the right hand side), performance in the selection environment converges among firms. In other words, in a dynamic environment, if all firms behave similarly (in terms of balance between external and internal learning) firm performance is not affected by discontinuities in the knowledge environment. Accordingly, the decision "internal versus external learning" seems to have a big influence in the adaptation of firms to the conditions of the selection environment and in the rewards they obtain from it..

An important implication of these results is that the development of technological capabilities in a science-based industry is not independent from the ability of firms to access their extramural knowledge base. As shown in scenario 1, the development of the scientific knowledge base is a necessary condition for technological change in the science-based industry. Additionally, this scenario suggests that, the extent to which industry actors are able to articulate scientific advances into technological innovations depends on the ability of firms to perceive changes in their extramural knowledge base

and exploit them. This ability depends on their engagement in external learning (i. e. learning from advances in science and technology, learning from industry spill-overs and learning by interacting). Moreover, in the presence of changes in the knowledge environment, this ability influences the quality improvement of the products they develop. Finally, similar firm behaviour in terms of strong commitment to external learning diminishes the differences in the performance of incumbent firms in the selection environment. A comparison of the results with the history-friendly scenario suggests that in a dynamic environment, differences in firm performance seem to be related to differences in their learning strategies with regard to the balance between internal and external learning.

As for the stylised facts in the German pharmaceutical industry the results confirm the appreciative theory: difficulties of the traditional pharmaceutical companies (represented by firms of type TP) in exploiting the technological opportunities after the advent of modern biotechnology can be explained through their learning strategies. Even though their technological tradition and internal technological capabilities in terms of human capital were better qualified to develop capabilities in modern biotechnology, their commitment to external learning was not strong enough to exploit the changes in the knowledge environment. On the other side, dyestuff companies committed traditionally to external learning have been better able to exploit the knowledge environment, despite their disadvantage in terms of internal core competences and technological tradition.

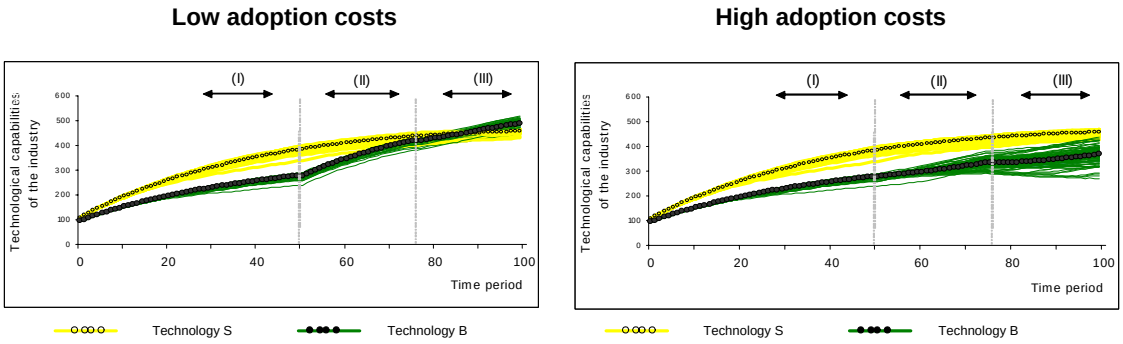
4.2.2.3 Scenario 3: Absence of adoption costs versus high level of adoption costs

Given the specification of the model as presented in section 4.1.6, firms do not have free access to the extramural knowledge base. Exploitation of scientific advances requires firstly the ability to perceive scientific advances or technological opportunities from the extramural knowledge base and additionally, covering an extra cost υ representing the effort of exploiting new technological opportunities (see Eq 16).

In the history-friendly scenario the parameter setting specifies the adoption costs with υ=1. This section introduces a scenario with low adoption costs (υ=0.01) and a scenario with high adoption costs (υ=2). The parameters characterising the knowledge environment and firms' behaviour correspond to the history-friendly scenario given in Table 9 and Table 10. Figure 34 gives the average results of 100 simulation runs regarding the technological capabilities of the industry under low (in the left hand side figure) and high adoption costs (in the right hand side figure).

The results given in the right hand side figure confirm that high adoption costs for firms imply a lower level of industrial capabilities in technology B after 100 periods. Despite the strong increase in the volume of scientific knowledge provided by public research institutions after t=50, the industry in phases II and III is not able to developed the level of technological capabilities reached in the history-friendly scenario (Figure 18). In the presence of high adoption costs for firms, the rate of development of technology B is slower than in the history-friendly scenario and the industry remains under strong influence of technology S. In the left hand side figure, the parameter setting assumes lower adoption costs than the history-friendly scenario. The pattern of technological change presents a change in the relative importance of technologies in phase III. The industrial level of capabilities in technology B develops faster in phase I and phase II than in the history-friendly scenario.

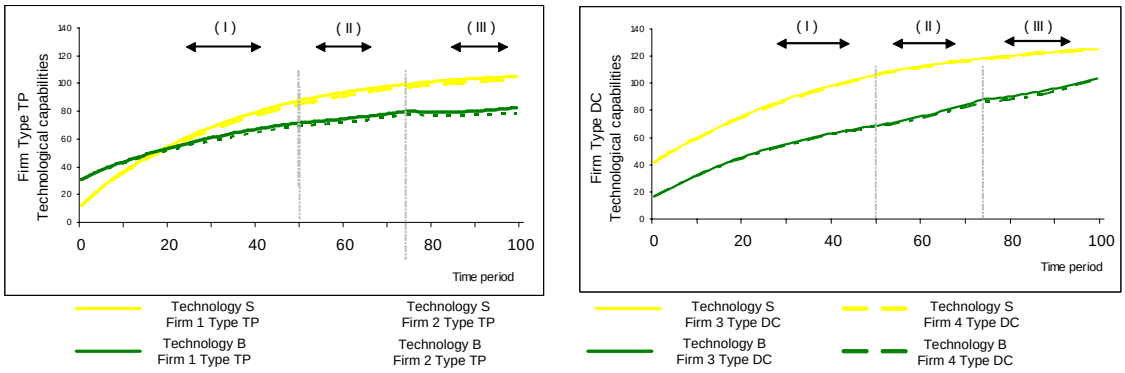
Figure 34: Counterfactual scenario 3: Technological change in the industry (100 simulation runs and average)



The results at the level of the firm given in Figure 35 suggest that adoption costs influence the extent to which firms react to the changes in their knowledge environment. In the case of low adoption costs both types of firms (TP in the left and DC in the right) develop capabilities in technology B to the extent that in phase III all firms present a higher absolute level of capabilities in technology B than in technology S. In this case search and innovation become processes mainly guided by technology B.

Figure 35: Counterfactual scenario 3: Technological capabilities of the incumbent firms (average 100 simulation runs)

Low adoption costs



High adoption costs

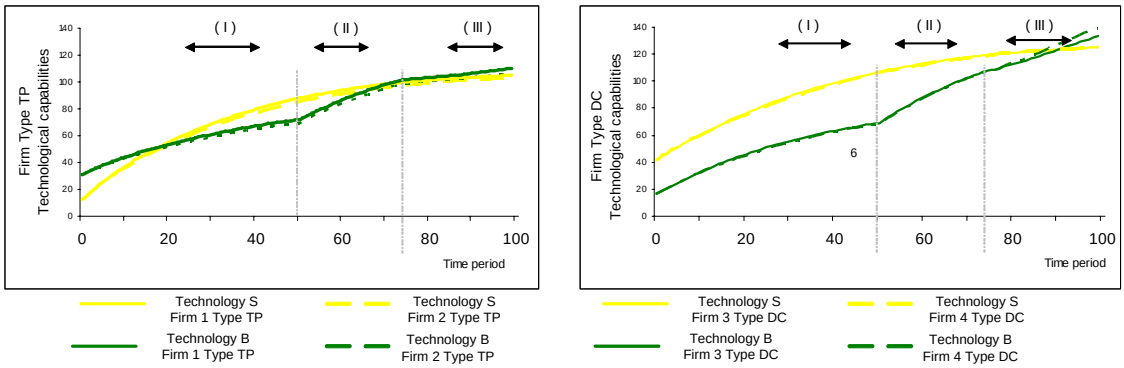


Table 13: Counterfactual scenario 3: Firms' reaction to discontinuities in the knowledge environment (100 simulation runs)

Low adoption costs

		Firm Type TP		Firm Type DC	
		Firm 1	Firm 2	Firm 3	Firm 4
t=50	Perception / Adoption rate	100 %	100 %	100 %	100 %
	Average adoption period	51	51	51	51
t=75	Perception / Adoption rate	100 %	100 %	100 %	100 %
	Average adoption period	76	76	76	76

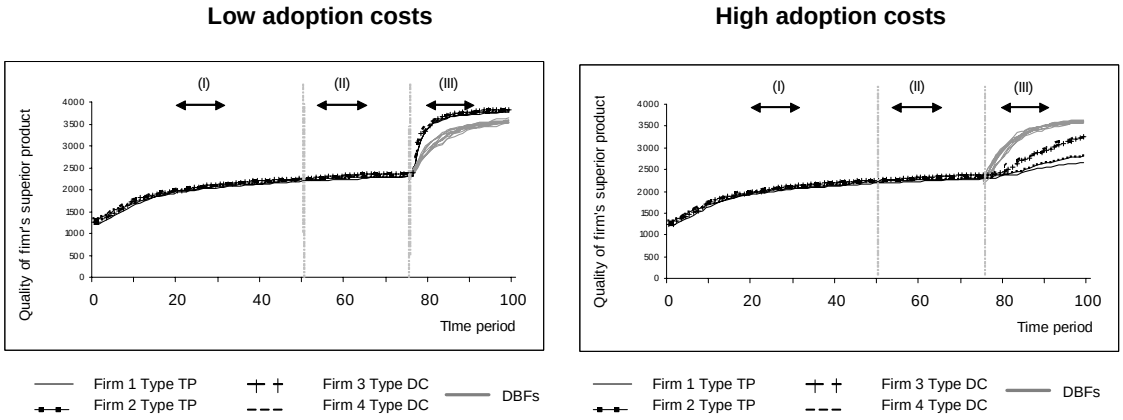
High adoption costs

		Firm Type TP		Firm Type DC	
		Firm 1	Firm 2	Firm 3	Firm 4
t=50	Perception / Adoption rate	48 %	53 %	82 %	83 %
	Average adoption period	72	73	64	68
t=75	Perception / Adoption rate	24 %	33 %	60 %	59 %
	Average adoption period	83	86	86	84

As given in Table 13, the rates of perception and adoption of technological opportunities by firms after the development of novel scientific advances underpinning technology B at t=50 and t=75 are extremely high in the low adoption costs scenario. These results are coherent with he logic of the model.

The results in Figure 36 regarding the quality of firms' superior products suggest that the development of capabilities in technology B by incumbent firms in the low adoption costs scenario allows all of them (independently of the type of firm TP or DC) to discover and develop products that outperform the product candidates of DBFs in terms of quality. DBFs count only with capabilities in technology B. Despite their superior technological achievement for the selection of products with high quality in the search space, the low adoption costs for incumbents prevent DBFs for maintaining the leading position in terms of quality of product candidates. In the low adoption cost scenario incumbents are able to develop large levels of capabilities of technology B which seem to complement their capabilities in technology S in the search process for potential products. The combination of capabilities enables them to outperform DBFs in terms of quality.

Figure 36: Counterfactual scenario 3: Quality of firm's superior product candidates (average 100 simulation runs)

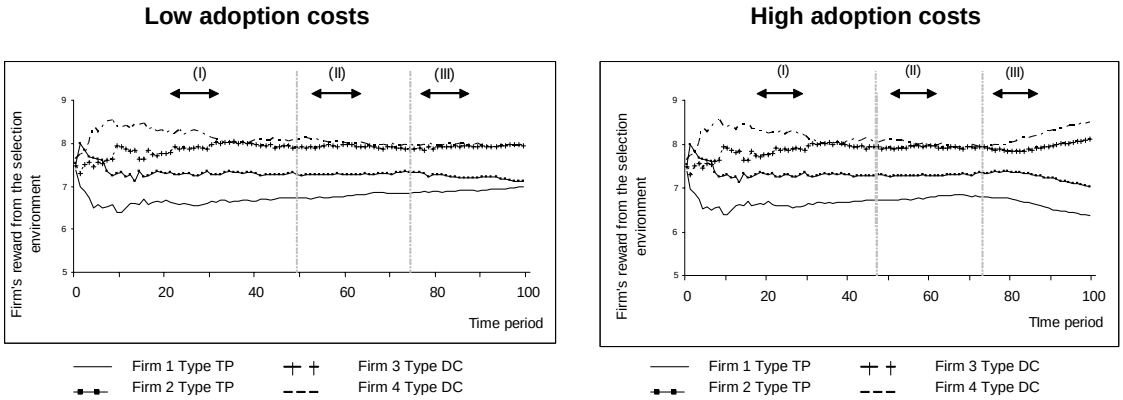


Moreover, the results provide insights into the competitive advantage of firms engaging in external learning. In the case of discontinuities in the knowledge environment with high adoptions costs (on the right hand side in Figure 36) firms of type DC reach higher levels of quality in their potential products than firms of type TP. Even though incumbent firms are not able to outperform DBFs, those engaging in external learning are more effective in their search process.

As for the results concerning firm performance in the selection environment, Figure 37 presents the rewards obtained by firms. In the presence of low adoption costs learning

strategies do not seem to influence firm performance and the relative position of firms in the selection environment does not change. In the case of large adoption costs, firms of type DC are better able to adapt than their competitors. This effect is quite remarkable in phase III. Accordingly, in the presence of high adoption costs, firms engaging in external learning adapt better to the selection environment.

Figure 37: Counterfactual scenario 3: Firm's reward from the selection environment (average 100 simulation runs)



Again, the counterfactuals explored in this section are coherent with the verbal logic of the appreciative theory of technological change in the German pharmaceutical industry. The costs of developing capabilities to exploit technological opportunities offered by novel scientific advances (i. e. adoption costs at the firm level) influence the pattern of technological change at the industry level. Apart from the knowledge required to exploit new technological opportunities, adoption costs may be reinforced by uncertainty about the possibilities of exploiting the new technological opportunities, by barriers to access the novel scientific results or by the costs of adapting firm's processes and infrastructure to the requirements of exploiting the new technological opportunities. Therefore, in the presence of high adoption costs for firms, the industry does not exploit new opportunities given by the knowledge environment. At the organisational level, firms engaging in external learning are better prepared to deal with barriers to adoption.

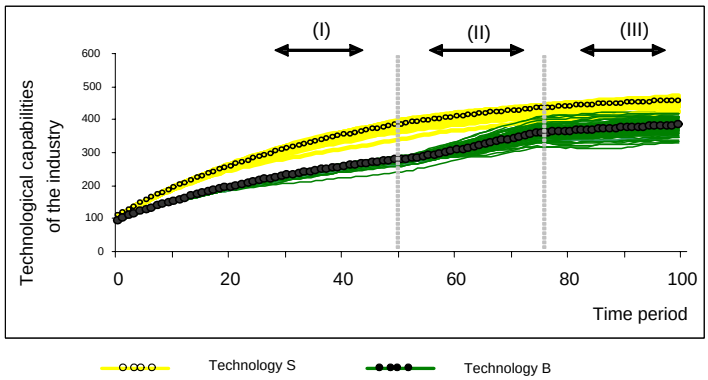
In the German case, the geographical dimension of scientific advances and public research in scientific disciplines relevant for the development of biotechnology (which took place beyond the German borders until the 1980s) increased the adoptions costs of German drug producers in relation to those of their American counterparts. Moreover, the institutional framework did not contribute to decrease adoption costs. Regarding the differences between German drug producers, in the presence of these high adoption costs, the engagement of dyestuff companies in external learning has given them an advantage in the adoption process.

4.2.2.4 Scenario 4: Absence of firm entry

In this section a history-divergent scenario is introduced by assuming that the advent of modern biotechnology in the mid 1970s (t=75), which opens phase III in the history-friendly scenario, did not involve the emergence of a biotechnology industry enhancing the transfer of the new scientific results from the academic to the industrial laboratories. The goal is to explore the role of Dedicated Biotechnology Firms (DBFs) in transferring capabilities to incumbent firms through collaborative agreements and industry spill-overs.

Figure 38 gives the average results of 100 simulation runs of the path of technological change of the industry. The results in terms of capabilities of the industry in technology B present a slightly different pattern of technological change than the history-friendly scenario (Figure 18).[82] In phase III the industry does not increase the level of capabilities in technology B as much as in the history-friendly scenario.

Figure 38: Counterfactual scenario 4: Technological change in the industry (100 simulation runs and average)

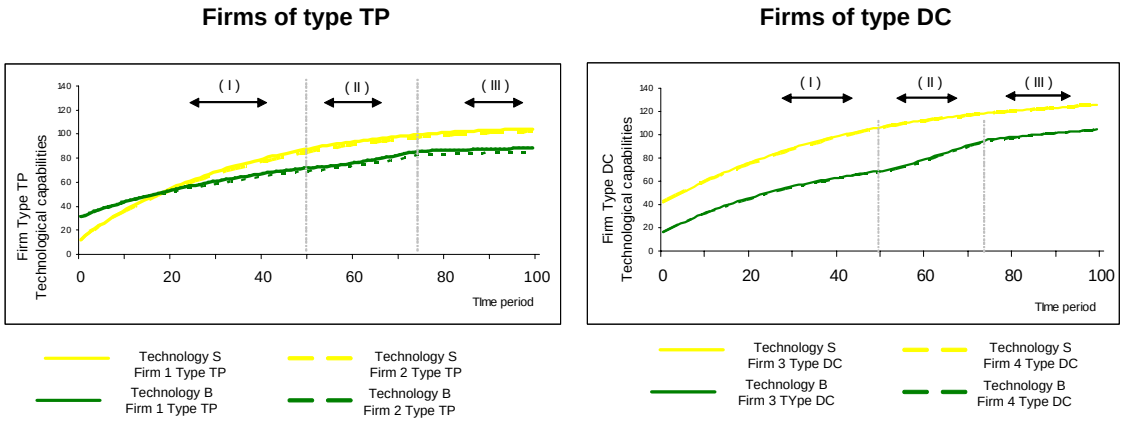


At the level of the firm (Figure 39), in the absence of DBFs and collaborative arrangements those firms engaging in external learning are not able to reach the level of capabilities of the history-friendly scenario (Figure 19). It seems that with the absence of DBFs the access to additional knowledge in technology B is limited to the existence of spill-overs and the rate of development of capabilities in incumbent firms is now lower. The pattern of development of technological capabilities in the case of firms of type TP does not vary much. Since the number of collaborative arrangements in the

82 Note that the history freindly scenario does not include the capabilities of DBFs in the aggregate level of technological capabilities of the industry. Only those actors reaching the selection environment are considered as industry members. DBFs discover products, however,, they never reach the selection environment due to their lack of marketing capabilities (see footnote 73).

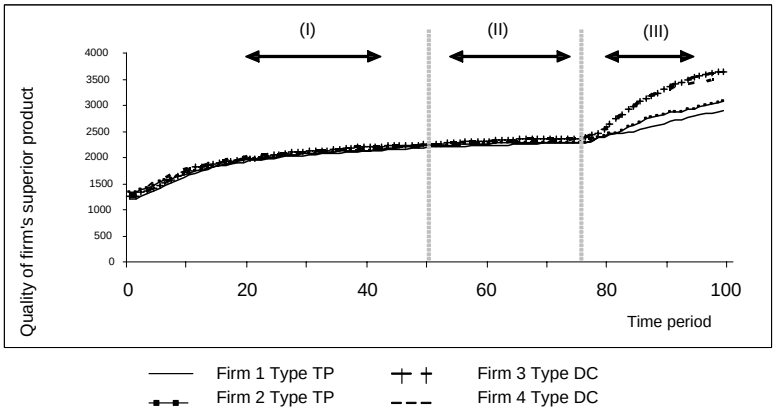
history-friendly scenario was also lower (see Figure 20), the absence of DBFs has not a great impact for them and their engagement in learning from their spill-overs (external learning) is also weak.

Figure 39: Counterfactual scenario 4: technological capabilities of the incumbent firms (average 100 simulation runs)



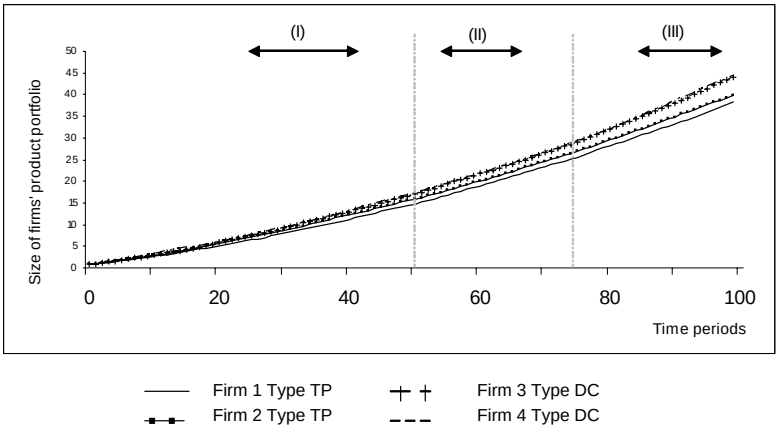
The results presented in Figure 40 regarding the quality of the best product candidates of incumbent firms suggest that product quality does not suffer from the absence of DBFs in the industry. Superior products of incumbent firms are able to reach the levels of quality of the history-friendly scenario (Figure 21) at the end of the simulation run.

Figure 40: Counterfactual scenario 4: Quality of firm's superior product candidates (average 100 simulation runs)



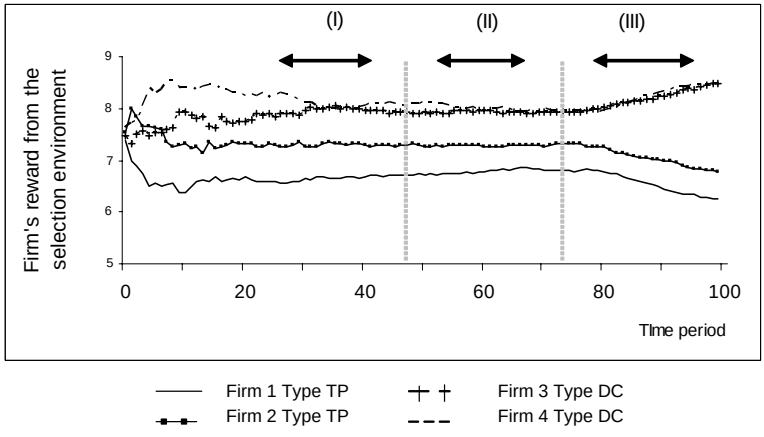
Moreover, in the absence of DBFs and collaborative arrangements, incumbent firms continue to enlarge their product portfolios (see Figure 41) without drawing on the extra volume of capabilities being transferred from DBFs. The innovation rate in terms of products increases incrementally as in the history-friendly model.

Figure 41: Counterfactual scenario 4: Size of firm's product portfolio (average 100 simulation runs)



Finally, rewards from the selection environment given in Figure 41 behave as in the history-friendly scenario (Figure 23). Firms of type TP clearly deteriorate their position in phase III and firms of type DC improve it. These findings are not surprisingly since reward depends on product quality. As seen above the absence of DBFs doesn't have large influence on product quality reach by incumbents.

Figure 42: Counterfactual scenario 4: Firm's reward from the selection environment (average 100 simulation runs)



Considering that technology B represents biotechnology, these results are consistent with the assumption of the appreciative theory according to which the historical pattern of technological change in the pharmaceutical industry after the 1970s drew on the institutional changes enhancing biotechnology knowledge transfer in the pharmaceutical industry. An important policy implication is hence the central role of firm entry for technology transfer science-based industries. However, in the history-friendly model specified, firm entry enhances knowledge transfer rather than product development. To

sum up, the absence of DBFs and collaborations seems to have strong impact in the development pattern of technological capabilities of the industry. However, the effect on product development is not as convincing.

The findings support the merit of DBFs in transferring knowledge and technology from the knowledge environment to the industry. Accordingly, DBFs play a role in the transformation of the technological capabilities of the industry. However, in terms of enabling product innovation to incumbent firms, DBFs aren't decisive. In the absence of DBFs incumbent firms do reach the quality level of the history-friendly scenario and continue to develop new products. The results suggest that the knowledge transfer carried out by DBFs is not articulated into products to the extent that it would be expected. These findings support the position discussed in section 3.5 according to which, the advent of modern biotechnology and the new institutional setting for innovation in the pharmaceutical industry has resulted into a transformation of the knowledge base underpinning drug discovery and development. However, the discontinuity in terms of products has a much incremental character.

With the regard to the German experience, the results can support the scenario of a delay in the German industry vis-à-vis the US in exploiting modern biotechnology due to the different framework conditions for firm creation and entry. However, due to the differences in the developments of the knowledge environment in both regions, the explanation does not allow to identify the institutional setting promoting firm creation as the only reason for this delay.

Nonetheless, the German experience shows how firm entry can be strongly promoted by policy intervention. In the few years between 1995 and 2000 Germany became the European country with the largest biotechnology industry in terms of DBFs. These firms entered the industry mainly through public support. Their problems in bringing products to the market made many of them unprofitable. Policy instruments were not designed to sustain the growth of these actors. Accordingly many of them disappeared or have been acquired by incumbents after a few years of activity.

Due to the role of DBFs for knowledge and technology transfer, an interesting issue for policy research is whether other measures than subsidised entry of DBFs exist to promote the transfer of knowledge from the academic to the industrial laboratory as effectively as the creation of small technology-based companies, but in a sustainable manner.

5 Summary and conclusions

This contribution explores technological change from an evolutionary perspective. The aim is to unfold the processes underpinning the changes in the relative importance of technologies in industries, the mechanisms driving these transitions and the consequences for industry incumbents.

The analysis concentrates on the experience of the German pharmaceutical industry and the changes in the relative importance of biotechnology and synthetic chemical synthesis in shaping drug discovery and production processes along the 20th century. The role played by German drug producers in this process, and the extent to which they have been able to perceive and contribute to these changes, are the main issues of study.

The theoretical framework

The evolutionary framework provides an adequate toolbox to explore the interrelation between the macro and micro-levels of the process of technological change since, from an evolutionary perspective, firms are the carriers of technology and, consequently, patterns of change at the level of the industry are the result of the collective interaction of firms. Moreover, in the last 30 years, a large body of literature has contributed to define firm behaviour in this context, even though the theoretical framework is still developing.

Evolutionary theorists consider firms as heterogeneous agents with bounded rationality in the sense that the constraints of their computational abilities prevent them from conducting any type of optimisation decision processes. In addition, firms in the same environment and facing the same type of market signals may interpret information differently and/or react in dissimilar ways. The main factors making firms different are their specific knowledge base, the conditions in which they have accumulated it and their strategies to articulate the knowledge into useful products or processes.

A further important aspect stressed by the evolutionary approach is that firms do not act in isolation. Thus, firms' decision-making is a process embedded in an institutional matrix in which institutions and firms' behavioural patterns coevolve. Evolutionary theorists use the concept of technological regimes or paradigms to refer to the set of institutions influencing firms' behaviour and firms' assessments about the technological options being worth taken, or about the superior strategies that should be applied and developed to solve managerial and technical problems. Accordingly, technological regimes or paradigms act as focusing devices for firms, tracing possible patterns of development and blinding out potential alternatives. Consequently, these influences

depict so called technological trajectories that underpin industrial activity. Technological trajectories may coexist, complement each other or compete.

Moreover, the evolutionary perspective imposes the recognition of the process of technological change in industries as a dynamic process. From this view, and in analogy to biological evolution, variety creation and selection (in the sense that firms may enter the industry but may be forced to disappear) lead to changes in the composition of the industry and in its aggregate patterns. Accordingly, taking into consideration that firms are the carriers of technologies, which technological trajectories shape an industry depends, to a large extent, on the performance of the firms developing and applying them in the selection environment. The technologies developed and applied by the best performers will hence outperformed alternative technologies in terms of importance. In this endogenous competition, process externalities and dynamic increasing returns may influence firms' behaviour, thus reinforcing the development of a technological trajectory or preventing experimentation in other directions.

All in all, changes in the relative importance of technological trajectories bring about technological change in terms of the technological capabilities underpinning industrial activity. These changes can have incremental or radical dimensions and impact incumbent firms by enhancing their competences or destroying them. In some cases they may lead to paradigmatic transitions within the industry turning the capabilities of incumbent firms inadequate for the new framework conditions and fostering the entrance of new firms. The knowledge-based theory of the firm explores the mechanisms enabling incumbent firms to adjust to these transitions. The approach puts forward concepts such as "absorptive capacity", "combinative capabilities" and "dynamic capabilities" to define the type of firms' capabilities enabling adjustment to discontinuities in the knowledge environment.

Simulation as a tool

Drawing on this theoretical toolbox, one strand of evolutionary economic theory has explored economic growth and technological change using simulation models inspired by the seminal work of Nelson and Winter (1982). The usefulness of simulation models builds mainly on their ability to deal with the fundamental uncertainty and the requirement to consider heterogeneity between firms. Moreover, computer simulation models enable the study of complex processes were macroeconomic properties are considered phenomena flowing from the interaction of microeconomic agents.

Evolutionary simulation models have been able to generate plausible patterns of economic growth or changes in the concentration of industries. However, evolutionary

scholars have concentrated on the exploration of these processes without testing the models' outcomes against historical experience in a rigorous manner. On the other hand, embracing institutional economics, a strand of neo-Schumpeterian research has elaborated a large body of empirical and historical case studies without mathematical abstraction, exploring explicitly the role of institutions in shaping technological change, economic growth and the differences between regions, countries and industries.

To reconcile formal modelling to build general theories with empirical analysis of specific cases, a group of scholars with a large record of contributions to the development of neo-Schumpeterian economics (including Nelson and Winter) have developed so called "evolutionary history-friendly models". In this framework, simulation models attempt at reproducing observed patterns of socio-economic change. The theory underpinning the models draws on stylised facts and verbal causal relationships (i. e. on an appreciative theory) considering the role of institutions in shaping the phenomena under exploration. Thus, in the history-friendly framework, formal modelling should be considered as an attempt to asses the consistency of the verbal arguments that constitute the appreciative theory explaining dynamic phenomena. History friendly models include (i) a set of stylised facts characterising the phenomenon to be explored, (ii) verbal logic on how the processes occur, (ii) formal representation of the verbal logic in a model and (iii) the implementation of a numerical computer simulation replicating the phenomenon explored.

A history-friendly model

This contribution chooses the approach of evolutionary history-friendly modelling to study technological change in the German pharmaceutical industry during the 20th century and the ability of German drug producers to adjust to the discontinuities in their knowledge environment. Empirical findings are the ground to develop an appreciative theory that explains verbally the phenomenon under consideration. Next, the appreciative theory has been specified in a formal model and implemented in a simulation to test the logic of the verbal explanations.

From an evolutionary perspective this endeavour demands the specification of an argument to explain technological change that deals with the complex interaction of (i) the knowledge environment shaping the conditions for technology emergence and development, (ii) a selection environment evaluating the technologies upon a unit of selection and determining the conditions for innovation, and finally (iii) firm's strategies in developing technologies to ease their risk-taking activities.

The stylised facts

Consequently, the efforts concentrate firstly on the empirical exploration of the changes in the knowledge environment, on the development of the industry, and on firms' strategies in adopting and developing new technologies.

From the perspective of the scientific knowledge environment shaping technology development, the study focuses on the knowledge bases of organic chemical synthesis and biotechnology. The stylised facts suggest that the scientific advances underlying these two technologies have very much influenced their application and diffusion in the pharmaceutical industry. However, the scientific development has followed different paces. While the scientific base of the organic chemical synthesis was developed in the second half of the 19th century, the scientific base of biotechnology at that time was still in its infancy. Along the 20th century, scientific advances have provided biotechnology with strong scientific base. This process started already in the 1950s with the development of molecular biology and was enhanced in the 1970s with the revolutionary discoveries of rDNA and the production of monoclonal antibodies.

At the level of the pharmaceutical industry both technologies competed in the processing of materials until the World War I. The dominance of the dyestuff companies in the German pharmaceutical industry supported the technological option for the organic chemical synthesis in the drug discovery and development processes. However, after Wold War II (especially after the 1970s) biotechnology has gradually become the key for innovation in the drug discovery and development processes. With this development, German drug producers lost their innovative strength in the second half of the 20th century. The path breaking discoveries in molecular biology in the 1950s, the advent of modern biotechnology in the 1970s together with the emergence of a biotechnology industry in the United States changed the knowledge environment of the industry and the institutional conditions for knowledge diffusion, especially in what concerned the transfer of knowledge from academic to industrial laboratories. Nonetheless, this development was at first very much localised in the USA. The strategic orientation of German drug producers towards this region in what concerned their research and development activities alarmed the German government. During the last two decades of the 20th century strong policy engagement was directed towards the promotion of the industrial application of biotechnology, the creation of biotechnology companies and the interaction between industry and academia within the German borders.

Given these processes at the level of the industry, we have explored the processes of technology adoption and development at the level of the firm. Specially, the ability of

German large firms to develop and exploit organic chemical synthesis and biotechnology. German drug producers can be classified in two different types of firms according to their technological traditions: the traditional pharmaceutical companies and the dyestuff producers. The strategies of these companies to build up capabilities for drug discovery and development along the 20th century seem to differ. To put it in an extreme way, traditional pharmaceutical companies have been more engaged in understanding the biological processes behind the diseases and in using biological products to treat them while dyestuff corporations were very much focused on the synthesis of potential drugs. The advent of modern biotechnology in the 1970s had a competence destroying character and forced the German drug producers to adopt new ways of drug discovery and development. In this process, the companies that traditionally came from the coal-tar dyestuff industry were faster in adjusting to the new framework conditions.

These empirical findings allow us to identify the following processes as key determinants of technological change in the German pharmaceutical industry:

Firstly, the entry of the dyestuff producers at the end of the 19th century with capabilities in organic chemical synthesis and the strength of the firms' knowledge environment supporting this technology determined the technological dominance of the organic chemical synthesis in the first half of the 20th century. However, the development of the knowledge environment after World War II, as the organic chemistry reached maturity and biotechnology developed further, contribute to the change in the relative importance of both technologies. By the last quarter of the 20th century drug discovery and development was increasingly being guided by biological principles.

The historical stylised facts speak for a strong development of the biotechnology knowledge base and its industrial exploitation especially in the USA. This geographical dimension of the knowledge base (together with its increasing complexity) has probably played a role in the industrial application of biotechnology in the German pharmaceutical industry by slowing the process of technological change compared to the USA. Moreover, the barriers for industrial exploitation of biotechnology in Germany in the early 1980s have probably prevented drug producers from perceiving and adopting the new technological opportunities of biotechnology.

Regarding the role of firms in this process, the leaders of the German pharmaceutical industry in the first half of the 20th century (the dyestuff producers) were embedded in the technological regime of the organic chemical synthesis. Their technological regime favoured science-based research strategies, where interaction with the knowledge environment (by learning from scientific advances and from interacting) played a

central role in technology development. Despite the exclusion of biotechnology until the 1950s, their ability to perceive the discontinuity in the knowledge environment allowed them to adjust faster to the emergence of modern biotechnology. On the other side, traditional pharmaceutical companies, with a historical record in the application of biotechnology and empirical (trial-and-error) guided research and development strategies have been much slower in the adoption process, even though the competence destroying nature of the discontinuity should have been less drastic for these type of firms.

The evolutionary model

These stylised facts have been used to specify an evolutionary history-friendly model which intends to draw the patterns of technological change observed.

In the neo-Schumpeterian tradition, the history-friendly model put forward specifies firms as the carriers of technology. Hence, technological change at the industry level is the result of firms' interaction in a selection environment. The aggregated pattern of mechanisms of technology adoption and development at the firm level determined the technological development of the industry. In this sense, technological change is the collective result of the individual actions of firms.

The formal model presents an artificial industry with companies searching and developing drugs in a knowledge environment. Firms face a search space of potential medicines which may have therapeutic properties (product candidates). The goal of firms is to find and develop best potential product candidates and offer them to the selection environment (which is a simplification of the health system or the market for pharmaceuticals). Firms are heterogeneous and are rewarded by the selection environment according to the “merit” (which is largely based on quality) of the products they have developed. Accordingly, firms' have different strategies aim at improving their technological capabilities to improve the merit of their products.

Two technologies enable the search process by reducing the observation error in the search process (technology B) and by expanding the range of possible drug candidates the can handle (technology S).The knowledge dimension of these technologies and its cumulative character are essential aspects of the model. Knowledge accumulation allows firms improving the merit of their products by enhancing technological achievements and by easing firms' problem solving activity.

Moreover, innovation is specified as a stochastic process where the stock of accumulated knowledge can increase the chances of innovating. Knowledge accumulation stands on learning processes which can be internal to the firm (by learning by doing for

instance) and external to the firm (learning by searching and interacting in the knowledge environment and from spill-overs).

Finally, the model is dynamic and the transition dynamics can be described with a Markov process where the stage of the industry at *t* influences the stage of the industry at *t+1*. Most importantly the specification of the accumulated stock of knowledge as a variable influencing the stochastic processes grants the model with "historicity" in the sense that the stage at *t* captures the results of the learning process in the past.

The simulation experiments try first to replicate the observed pattern of technological change in the pharmaceutical industry (the history-friendly scenario). For this purpose, the parameter settings aim at capturing in a extreme form the key stylised facts of the appreciative theory regarding (i) the nature of the knowledge environment shaping the different phases of the pharmaceutical industry and (ii) the characterisation of the firms. To capture the nature of the knowledge environment the dimensions of the technological regimes have been specified (i. e. technological frontier of technologies, volume of scientific knowledge, degree of complexity of knowledge, appropriability conditions in terms of spill-overs, and depreciation rate of technological capabilities). Additionally, the characterisation of the firms specifies 3 types of companies: Companies of firm type DC (representing the dyestuff companies), firm type TP (representing the traditional pharmaceutical companies) and firm type DBF (representing the dedicated biotechnology firms entering the industry a la later stage). These firms are different with regard to (i) the technology they believe is worth developing, (ii) in their engagement in learning and (iii) in their balance between internal and external learning.

In addition, the simulation environment has been used to experiment with alternative parameter settings that contradict the stylised facts of the appreciative theory. Apart from testing the logic of the appreciative theory and the stylised facts, the approach has led to the identification of relevant policy implications at the level of the industry and provided insights about firms' strategies in dynamic environments. The mechanisms and effects identified in the simulation experiments concern the level of the industry and the level of the firm.

Model results: Patterns of technological change at the level of the industry

The results in terms of technological capabilities of the industry in the history-friendly experiments match remarkably well the stylised facts. The origins of the industry are shaped by the dominance of firms of type DC (dyestuff producers) and the establishment of search and innovation processes drawing on technology S (organic chemical synthesis). Changes in the knowledge environment of the firms in two time periods (t=50) and (t=75) bring about an incremental application of technology B

(biotechnology). The exogenous specification of these changes is based on the stylised facts identified in chapter 3. These changes refer to the parameters describing the technological regime of the industry including the specific characteristics of the knowledge dimension of technology B (biotechnology) (innovation opportunity conditions, volume of scientific knowledge from the public sector, degree of complexity of knowledge, depreciation rate of technological capabilities) and entry of DBFs. After the discontinuities in the knowledge environment providing new technological opportunities, firms increase the accumulation of technology B. Accordingly the aggregate pattern of technological capabilities in the industry varies while technology B challenges the relative importance of technology S. Nonetheless, both technologies coexist.

With regard to the implications for the pharmaceutical industry in Germany, which is the ground of the empirical analysis, the pattern of development of technological capabilities described by the history-friendly scenario speaks for a forthcoming change in the dominance of organic chemical synthesis in the industry. The results suggest that the industry is still dominated by an organic chemical paradigm, however the application of biological principles in drug discovery and development play an increasingly important role and may displace chemical synthesis in the future.

The simulation experiments explore the role of developments in the knowledge environment in driving technological change of the industry. Considering that firms are the carriers of technology, and that technological opportunities have to be recognised and exploited by firms, the results support the central role of firms' knowledge environment in the pattern of technological change of the industry. Accordingly, the nature of the science base in terms of the complexity of knowledge, the speed of scientific development and the volume of research results available from public institutions can explain the pattern of technological change in the pharmaceutical industry and differences across regions. As far as the experience of the German pharmaceutical industry, the development of the science base can explain the pattern of technological change. Thus, the difficulties of German drug producers in developing biotechnology capabilities compared to the achievements to their American and European counterparts already in the 1960s (and in the 1980s after the advent of modern biotechnology) can be the result of the differences in the development of the national scientific knowledge bases.

The influence of firms' strategic paradigms (Metcalfe, Boden 1992) and the relevance of the dynamic capabilities of the firms (Teece et al. 1997) for technological change at the industry level has been analysed in the second counterfactual analysis (scenario 2). The results suggest that the development of technological capabilities in a science

base industry is not independent from the ability of firms to access their extramural knowledge base. The extent to which the industry is able to articulate scientific advances in technological solutions depends on the ability of firms to perceive changes in their extramural knowledge base and exploit them.

As for the role of technology adoption costs at the level of the firm, the results suggest that the investment firms need to undertake to integrate new scientific advances from the knowledge environment and to exploit new technological opportunities influence the development pattern of technological capabilities of the industry. Adoption costs involve the efforts to understand information from the knowledge environment and integrate it in the corporate research and development processes. Moreover, institutional and geographical barriers to access the novel scientific results can reinforce barriers to adoption. In the case of the German pharmaceutical industry, the geographical dimension of scientific advances and public research in scientific disciplines relevant for the development of biotechnology (which took place beyond the German borders until the 1980s) probably increased the adoptions costs of German drug producers in relation to those of their American counterparts.

Finally, the experiments analyse the role of mechanisms for knowledge and technology transfer. The findings support the merit of Dedicated Biotechnology Firms (DBFs) in transferring knowledge and technology from the knowledge environment to the industry. However, in terms of easing product innovation to incumbent firms, DBFs aren't so influential. These findings support the position discussed in section 3.5 according to which the advent of modern biotechnology and the new institutional setting for innovation in the pharmaceutical industry has resulted into a transformation of the knowledge base underpinning drug discovery and development. However, the discontinuity in terms of products has a much incremental character.

With the regard to the German experience, the results can support the scenario of a delay in the German industry vis-à-vis the US in exploiting modern biotechnology due to the different framework conditions for firm creation and entry. However, due to the differences in the developments of the knowledge environment in both regions, the explanation does not allow to identify the institutional setting promoting firm creation as the only reason for this delay.

Model results: The firm in the process of technological change

At the organisational level, the history-friendly scenario is able to reproduce the historical experience. Accordingly, firms of type TP (representing traditional pharmaceutical companies such as Merck KGaA and Schering AG with traditional technological experience with the application of technology B) have experienced a

transformation in their technological identity towards the accumulation of capabilities in technology S (organic chemicals synthesis). Regarding the perception and adoption of technological opportunities, firms of type DC (representing dyestuff companies such as Hoechst and Bayer) are better able to perceive and adopt the new technological opportunities from the knowledge environment. Moreover, compared to their counterparts, firms of type DC interact more with Dedicated Biotechnology Firms (DBFs). This ability is enhanced by their commitment to external learning (i. e. learning from advances in science and technology, learning from industry spill-overs and in learning by interacting). Moreover, in dynamic environments, differences in firms' performance seem to be related to differences in firms' learning strategies with regard to the balance between internal and external learning.

Therefore, regarding the experience of German drug producers, the findings put forward that the balance between internal and external learning can explain the difficulties of traditional pharmaceutical companies in exploiting technological opportunities after the advent of modern biotechnology. Despite their technological tradition in biotechnology and internal technological capabilities in pharmacology, biology and medicine in terms of human capital, their weak commitment to external learning seems to prevent them from perceiving and exploiting the changes in the knowledge environment. On the other hand, the dyestuff companies, with their technological roots in the synthetic organic chemistry but a long tradition in the application of science-based strategies and in collaboration, have been faster in reacting to the discontinuities in the knowledge environment. External learning seems to have compensated for the disadvantage of the corporations in terms of large firm-specific assets in organic chemistry (due to their traditional focus on this technology), which could have caused inertia in the adoption process.

The results are coherent with the notion of absorptive capacity (Cohen, Levinthal 1990) in that firms balancing external and internal learning appropriately are better prepared to deal with barriers to knowledge and technology adoption. Regarding the different reactions among German drug producers to the advent of modern biotechnology, in the presence of the high adoption costs characterising the German pharmaceutical industry, the companies with science-based research strategies have been better able to exploit the new technological opportunities.

Methodological issues

The study has deepened into the process of technological change in a science-based industry. The challenge has been to select a research phenomenon, generate hypothesis about the variables and mechanisms shaping it using qualitative and

quantitative empirical facts and verbal reasoning and finally, specified the logic in a formal model to test the outcome against the historical experience.

The task of formalising verbal explanations demands extraordinary diligence forcing the scientist to elaborate thoughts in a precise way, defining feed back mechanisms and complex relationships. Therefore, the formalisation of the logic followed by the implementation of the simulation experiments have lead to a better understanding of the process of technological change and technology adoption observed in the German pharmaceutical industry. Formal theory has contributed to the identification of gaps or mistakes in the verbal explanation, since the outcomes did not match the observed patter of change. In these cases, the empirical analysis had to be rethought. Additionally, simulation has provided an experimentation tool to test alternative hypothesis.

On the other side, the specification of the model regarding the parameter set to run the simulation remains a dangerous issue. As in the other history-friendly models put forward so far, the parameters draw on qualitative estimations and are coherent with the stylised facts. However, the values themselves do not represent a quantitative empirical result, neither are grounded on econometric or statistical analysis. For this reason, the justification of why to choose a model specification instead of other isn't straight forward.

In the case of this contribution, the function and parameter specification builds a numerically consistent model matching the stylised facts of the appreciative theory. The process of setting parameters has been diligently discussed in sections 3.5 and 4.2.1. Moreover, the results of the history-friendly scenario match the historical experienced, the counterfactuals are coherent with the verbal logic and account for the sensitivity of the results. Additionally, the results concern general trends rather than the forecasting of precise values. Nonetheless, a criticism is easily found to any argument supporting the given specification and not an alternative one.

Recent methodological contributions deal with this general problem of empirically based simulation-models and proposed a methodology to cope with specific characteristics of models in heterodox economics (Werker, Brenner 2004, 2005). These approaches are based on Critical Realism[83] as a methodology to infer models. The approach combines data on assumptions and implications based on empirical

83 According to Werker and Brenner (2005) Critical Realism sustains "that reality is the result of processes at a deeper level. Therefore it is not sufficiently to describe the relationships on the observed level. We need to understand these relationships on the basis of the processes of the underlying level".

findings to create classes of systems. Hence the approach leads beyond the common use of simulation models. Contributions of this kind give evidence on the increasing importance of simulation models in socio-economic analysis and the methodological gaps still needed to be filled. All in all, the results support the value of combining empirical work and formal modelling in order to understand socio-economic processes.

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Annex

Annex 1:
Case studies

Introduction

The case studies concentrate on four corporations of the German pharmaceutical industry. The corporations have been chosen among a list of German corporations represent two types of drug producers: diversified chemical companies coming from the coal-tar dyestuff industry and traditional pharmaceutical companies. After contacting the different corporations and their historical archives the selection of the four corporations depended on the extent to which qualitative and quantitative material to conduct the case studies seemed to be available. Accordingly the firms that could be considered for the case studies were Hoechst AG, Bayer, Schering AG and E. Merck.

The case studies concentrate on the biotechnology related activities of the corporations, their achievements in biotechnology research and development and on the biotechnology capabilities they accumulated in second half of the 20th century. The data presented in annex 2 on patent publications, corporate expenditures in research and development, human capital and collaborations complement the qualitative case studies that follow.

Case study 1: Hoechst

The case study focuses on the activities of the company in the second half of the 20th century.

The company's first activities began in 1863 with the setting up of a factory for coal tar dyes "Meister, Lucius & Co" at Höchst near Frankfurt am Main. In 1883 pharmaceuticals became part of the product portfolio supplied by the company. The small dyeworks factory grew to become a modern stock chemical corporation in the 1880s. After the devastating effects of World War I together with other German chemical companies the corporation created a larger community of interests in 1915/16 and finally merged in 1925 into the I.G Farbenindustrie AG[84]. With the break up of the I.G. Farbenindustrie AG after World War II the company was refunded as an independent chemical corporation in 1951 under the name "Farbwerke Hoechst AG vormals Meister Lucius & Brüning".[85]

Farbwerke Hoechst AG restarted its activities in 1951 with 5 business fields: Dyes, solvents, pharmaceuticals, organic chemicals and chemical preliminary products and other chemical products. However, the annual reports of the decade of the 1950s announced activities in all types of chemical products distributed in different organisational structures. Even though the corporation was quite diversified the management was very much centralised and had a clear strategic preference for the development of the business dealing with chemical gross products. Accordingly, in the 1950s the corporation focused on the production of chemical products such as plastics, solvents, fibre, and foils. The segments pharmaceuticals and dye stuffs lost progressively their importance in terms of sales and investments (Bartmann 2003, pp. 237-239).

The strong chemical focus of the corporation remained along the second half of the 20th century. However, the pharmaceutical segment gained progressively importance within the company in terms of sales. In the 1960s the management started focusing

84 The I.G. Farbenindustrie AG was funded in 1925. Its headquarters where in Frankfurt am Main. The corporation was the result of the merger of the 8 largest chemical companies in Germany. After World War II the Allies forced the corporation to go through a dismemberment process giving rise to entirely new and organisationally independent companies.

85 In 1974 the corporate name changed again to "Hoechst Aktiengesellschaft". Since 1999, after the merger with Rhone Poulenc, the company's name is Aventis and has its headquarters in Strasbourg, France. In 2003 Aventis was acquired by the French pharmaceutical company Sanofi-Synthelabo and is now called Sanofi-Aventis.

on the pharmaceutical segment and supporting its expansion with acquisitions and investments.

Despite the strong chemical tradition of the corporation, the responsible for drug discovery and development were aware of the existence of different strategies that could be followed in the process of drug discovery. The annual report of the year 1969 discusses the presence of two alternative research strategies in drug discovery. On the one side it refers to the "screening strategy" on the other to the "biological strategy":

> "In the screening strategy 30 compounds out of 4000 new synthetic compounds have qualified for further drug development and will go through the quality and security tests. Of these 30 compounds only 10 reached the stage of clinical trials and only one reaches the market. In the cancer research, for instance, hundreds of synthetic substances are screened each year. Apart from this screening strategy the company follows a biological research approach. However, results from the biological research approach are expected only in the long term" (Annual Report 1969, p. 36).

Despite the strong chemical research tradition, drug discovery responsibles at Hoechst in the 1970s seemed to be aware of the possibilities of applying other scientific principles than the organic chemical synthesis.

On the base of notes from interviews with researchers at Hoechst conducted for the purposes of an internal project of the company, we can put forward that in 1960s pharmaceutical research was still guided by chemical principles. These provided the tools for varying the structure of known medicines to synthesis new compounds which were tested for therapeutic properties. In the 1970s and 1980s the understanding of the biological mechanisms behind the effectiveness of medicines increased and the research tasks in drug discovery changed accordingly. Instead of "vary the structure" the slogan in drug discovery became "do beta-blockers" (Wicenec 1996).

Biotechnology research and achievements at Hoechst

The first relevant application of biotechnology for drug development was the penicillin production through microbiological processes. Already after World War II, Hoechst recognises the importance of strategic collaborations with companies in order to accomplish successful biotechnology-related projects. In 1947 started the first negotiations with the company Merck Rahway (USA) for the licensing of the penicillin production method (Hoechst 1985a; Schreier, Wex 1990). The license contract included the intensive collaborative activities with Merck including personal exchange. 2 employees from Merck spent 2 years in Germany to help building up the necessary

technological capabilities in house (Hoechst 1985b). A bio-reactor plant for the penicillin production was built at Hoechst in 1955 (Hoechst 1985b).

With the penicillin production researchers at Hoechst faced a challenging exercise since the production mainly drew on the control of biological process, which required different skills than the application of organic chemical synthesis. The activities demanded experience and some times also "a bit of luck" in order to obtain the expected results since the outcome of biological processes could not be forecasted and the secrets of the growth of fungus had not been disclosed. After this first step Hoechst continued in 1968 the next biotechnology-related activities with the production of Cephalosporine (an antibiotic) through enzymatic biotransformation processes in collaboration with Roussel-Uclaf (France) (Hoechst 1985b).

In the 1970s Hoechst restraint the line of chemotherapy-based cancer research. The serendipity-based screening strategy followed to developed chemotherapy treatments against cancer resulted quite ineffective. However, biological research activities on cancer were continued at the Behringwerke. In 1981 Hoechst was carrying out research in this location on the production of monoclonal antibodies for therapeutic and diagnostic purposes against cancer (Hoechst 1985b, pp. 46-48).

In the field of plant biotechnology Hoechst also seemed to be aware of the possibilities of applying biological principles in the production processes. In the annual report of 1975 Hoechst notifies that, apart from working on the traditional chemical pest control, the company also works on biological and biochemical applications for plant protection (such as the breeding and reproduction of virus, which attack exclusively harmful insects). These research activities were carried out with public support and in collaboration with universities.

In the 1970s different biotechnology applications were developed. In 1971 Hoechst had already achieved the production of single cell proteins (SCP) with the Probion (Kretzschmar et al. 1997). The research activities in the field of antibiotics were successful. In the family of the Cephalosporin (a highly effective antibiotic) a new semi-synthetic compound was produced together with Roussel Uclaf (Annual Report 1977). In 1979 hybridoma-cell lines were developed for the in vitro production of monoclonal antibodies at Behringwerke (Hoechst 1985b). Additionally, Hoechst produced large scale industrial production of ethanol from starch and sugary substances (Kretzschmar et al. 1997).

In the early 1980s annual reports announced optimistic perspectives for genetic research in different types of substances. Insulin, the vaccine therapy for viral diseases

Interferone, antibiotics and coagulants were some of the potential applications for genetic engineering in the pharmaceutical sector.[86]

The era of insulin at Hoechst had begun in 1971 with the peptide chemical modification of insulin. In the 1970s insulin research continued. However, the research work focused on the extraction of human insulin through the enzymatic transformation of animal insulin (pig insulin). In 1984 the research work results into the expression of a fusion protein reach in insulin (recombinant human insulin) (Hoechst 1985b; Obermeier 1997). The same year an application for the establishment of a production plant is submitted. In 1985 began the planning and establishment of a pilot plant for the production of recombinant human insulin (Obermeier 1997).

Regarding the application of genetic engineering for the development of coagulants, a number of research projects focused on genetic production of substances which could only be isolated from blood (blood-clotting Factor VIII und XIII and Antithrombin). In 1985 began the cultivation of genetically modified mammal animal cells for the production of blood-clotting factors. In 1991 biotechnological production of blood-clotting factor Hyrundin in large scale was successful and clinical trials started. According to the annual report of that year, the substance was produced through infiltration of the gene for Hyrundin in yeast cells.

Further achievements involving genetic engineering were the Recombinant Tissue Plasminogen Activator (or rTPA, commonly used in patients with myocardial infarction), which was successfully completed in 1985 at Behringwerke, the expression of Angiogenin at laboratory scale (completed in 1986 and produced at large scale in collaboration with the Harvard Medical School) and the production of recombinant human Erythropoietin. In 1988 Behringwerke requested a building-licence for the production plant of recombinant human Erythropoietin (rhu-EPO).

Biotechnology capabilities at Hoechst

The process of building up biotechnology capabilities at Hoechst has been shaped by a combination of accumulation of internal capabilities in German research locations, collaborative activities and internationalisation.

Already in 1970 foreign research locations of Hoechst were located in France, in the UK, in the US, in Japan, in India and in Egypt (Hoechst 1985b). At a first glance the internationalisation process of the company seems in the 1970s seems to follow the

86 Plant protection is also presented as a field of application for genetic engineering.

aim of building up biotechnology capabilities. However, at that point, internationalisation was not the result of an innovation strategy to search for capabilities and research infrastructure abroad. In 1981, 72 % of the pharmaceutical research and development costs were invested in the Germany.[87] As in the case of Bayer AG, the establishment of foreign locations in the 1950s and 1960s aimed at supporting the access to foreign markets (Bartmann 2003).

The pharmaceutical research capabilities of the corporation in Germany were distributed in 4 locations: Hoechst, Behringwerke, Cassella and Albert. However, the biotechnology capabilities were mostly located at Hoechst in Frankfurt and at the Behringwerke (in Marburg). Hoechst in Frankfurt was the home of the biochemical and microbiological departments. In 1977 research in the field of gene-technology was established as an integral part of research and development in this location (Obermeier 1997). Between 1979 and 1981 a research group on monoclonal antibodies and a gene technology group were established at Behringwerke (Hoechst 1985b). The research domains at Behringwerke focused on diagnostics, vaccines, growth and differentiation factors of the immune system, production processes for plasma proteins, blood-clotting factors and gene technology (Hoechst 1985b).

In the early 1980s the annual reports present gene technology as a new research focus. In 1983, 9 % of research investments in pharmaceuticals worldwide were directed to gene-technology activities (Hoechst 1985b, p. 54).

The internationalisation process in search for biotechnology capabilities began in the 1980s as the pharmaceutical business tried to strengthen its research capabilities in biotechnology abroad. An important step was the 10-years-collaboration agreement with the Molecular Biological Institute of the Massachusetts General Hospital, which received in 1981 37 million DM (5 % of the total R&D costs) (Hoechst 1985b, p. 55). According to the annual report of 1981, 5 million DM per year were planed to finance the research activities of the research group. It was the most important collaborative research project with a public research institution in terms of investment and length. In 1981 a 10 years collaboration agreement was signed (Hoechst 1985b; Schreier, Wex 1990).

Similarly, in 1984 Roussel Uclaf (which had been acquired by Hoechst) established a research institute for genetics and complex chemical synthesis. The institute was

87 This figure excludes the costs of the clinical trials and the R&D investment of Roussel Uclaf (in 1981 Hoechst was the largest share holder of the French company).

meant to be a platform for collaboration with the public research organisation CNRS (Schreier, Wex 1990).

In the 1990s the expansion of biotechnology capabilities abroad continues. In 1995 the establishment of a Drug Development Centre In Bridgewater/USA is planed. In 1997 a research centre for applied genome research was established together with ARIAD Pharmaceuticals in Cambridge (USA). Collaboration with the Harvard Medical School continued in the 1990s. In 1997 Hoechst announced a five-´years (16 million US$) joint-research-agreement to carry out research on bio-information engineering, cellular cycle regulation, cellular regeneration and bioinformatics. The same year an institute was established in Martinsried (Munich).

Important collaborators of Hoechst along the last quarter of the 20th century were the company Ciba (latter on with Ciba-Geigy AG until 1984) in the field arteriosclerosis and metabolic disorders, Roussel-Uclaf S.A. in the field of hormone research, Boehringer Mannheim in the field of antidiabetics and the Bayer AG in AIDS research together with the Georg-Speyer-Haus. Collaborative research and development with companies was intensified in the 1990s. In 1997 the annual report announces running cooperative projects in the pharmaceutical business with 12 different companies[88].

Acquisitions and Joint Ventures relevant for Hoechst's biotechnology activities

In the internationalisation process that started in the 1960s the management considers the acquisition of an American company with the aim of establishing a pharmaceutical location in USA. The company Lloid Brothers Pharmaceuticals Inc. was acquired. However, the acquisition did not bring the expected results. The successful acquisition for the pharmaceutical business took place in the 1990s with the incorporation of Marion Merrell (Bartmann 2003, p. 270).

Already in the 1960s the French company Roussel-Uclaf S.A. was an important research and business collaborator of Hoechst in the pharmaceutical business. In 1967 Hoechst acquires 20 % of the company and in 1972 increases its shares to obtain the majority of the shares (Hoechst 1985b). The expansion of the pharmaceutical business of Hoechst continues in 1995/1996 with the acquisition of Marion Merrel Dow (US). The American company was incorporated together with Roussel Uclaf and the

88 An important joint venture in plant biotechnology was AgrEvo-Joint Venture with the German company Schering.

pharmaceutical business of Hoechst into the new pharmaceutical company Hoechst Marion Roussel, which integrated the pharmaceutical activities of Hoechst AG.

Parallel to this development, relatively smaller acquisitions took place to reinforce the diagnostic business: in 1977 an American producer of enzyme-based diagnostics (Calbiochem, US) and in 1995 Syva (USA) also focused on the field of diagnostics. In 1997 a joint venture was planned with the American diagnostic producers Dade International of which Hoechst held a 32 % participation.

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Case study 2: Bayer

The case study reviews achievements of the company in biotechnology research and the development of capabilities in this field in the second half of the 20th century.

Similar to Hoechst, Bayer's origins are rooted in the production of dyes from coal-tar derivatives. In 1863 a partnership between two chemists was established with the aim of manufacturing and saling synthetic dyestuffs. As Hoechst, Bayer was able to develop strong capabilities in the production of dyes for the textile industry experimenting impressive growth in its early years. The partnership became a stock company called "Farbenfabriken vorm. Friedr. Bayer & Co." in 1881. Even though dyestuffs remained the company's largest division, between 1881 and 1913 new business fields built up a strong multinational with a world wide organisation and major research capabilities in Wuppertal-Elberfeld.

Together with Hoechst and other German chemical companies, Bayer created a larger community of interests in 1915/16 and finally merged in 1925 into the I.G Farbenindustrie AG[89] until the end of World War II.

As one of the successors of IG-Farben, Bayer was newly established in 1951. The management was strongly conditioned from the IG tradition and in the first years the chemical segments remained the focus of the corporate investments. Between 1948 and 1960 only 7.2 % of the investments in research laboratories and infrastructure for product development were directed towards the pharmaceuticals' segment (Bartmann 2003, pp. 299-300).

Both, the relatively manageable war-damages and the high reputation of the company allowed Bayer to restart its business without major problems. In the period from 1950 to 1960 Bayer had tripled its sales. However the discovery of the therapeutic properties of the penicillin (and its production and marketing by Bayer's competitors) drastically changed the innovative performance of the company. Bayer, which belonged to the pioneers of the industrial pharmaceutical synthesis, could not compete with its foreign competitors in microbiological production methods.

After World War II the pharmaceutical business of Bayer focused on the development of chemotherapeutics. Until the 1970s the sales programme included mainly licensed

89 The I.G. Farbenindustrie AG was funded in 1925. Its headquarters where in Frankfurt am Main. The corporation was the result of the merger of the 8 largest chemical companies in Germany. After World War II the Allies forced the corporation to go through a dismemberment process giving rise to entirely new and organisationally independent companies.

products or own innovations introduced before the war. New drug developments were carried out and products such as Adalat (launched in 1972), Canesten (launched in 1974) and the penicillin derivatives (launched in 1977) turned to be strong block buster contributing to strengthen the pharmaceutical business (Bartmann 2003, p. 350).

Biotechnology research and achievements at Bayer

The first important project in which Bayer gets involved with the application of biotechnological methods was the production of penicillin after World War II. With American licences Bayer was able to apply microbiological methods for penicillin production in its location in Elberfeld. In the decades after Bayer intensified its work to develop own microbial and enzymatic processes for drug development (Benz et al. 1996). In the 1950s Bayer begins research to develop an enzymatic process for the extraction of the 6-APS, the basic compound of all derivatives of penicillin. The efforts took several years and in 1975 Bayer accomplished this research. At the end of the 1960s the experts in the field of metabolism entered upon a new research direction for the treatment of diabetes: the isolation and microbiological production of enzyme inhibitors (Alstaedter 1988). This research direction proved to be successful a decade latter when the development of "Acarbose" was completed. Biotechnological applications received increasing attention. For instance, in an internal report of 1979 the management of pharmaceutical research recognises the need of allocating resources for research exploring the biological processes dealing with the transfer of genetic information, especially for its application in the production of microbial agents. An important candidate to explore the possibilities of genetic engineering was the insulin production. The first research activities on the insulin synthesis had been carried together with Schering. Even though the collaboration did not succeed and the production of human insulin with recombinant DNA technology at Bayer was not completed, the management supports the strategy of building up progressively the necessary infrastructure to explore the applications of genetic engineering (Schütz 1977, p. 8).

In the first phase of research in genetic engineering at Bayer a quite important number of projects were carried out simultaneously. In July 1983 the research activities include 11 projects in Genetic Engineering including recombinant blood-clotting factors, the biological characterisation of the tissue plasminogen activator (t-PA) for the treatment of acute ischemic stroke and the enzyme inhibitor Val-15-Aprotinin (Auerswald 1983, p. 16). The activities were located mainly in American research locations of Bayer in Elkehart (location of Miles) and at the University of Rochester. Only 3 projects (among them the t-PA and Val-15-Aprotinin projects) were carried out in the German locations. The company realises that competitors already hold a technological advantage in all

products except for the Val-15-Aprotinin. The management tries to concentrate the activities on two main projects Val-15-Aprotinin und Factor VIIIc. The projects should be carried out together with other companies and institutions. In 1984 Bayer acquires a licence from Genentech for the production and marketing of the blood-clotting factor VIII. The company works on the improvement of the production of Factor VIII trough recombinant DNA technology.

In the second half of the 1980s and in the early 1990s Bayer is able to produce the first research results in the field of genetic engineering and bring them to the market. In 1986 the annual report announces important progress in the production of monoclonal antibodies for the targeted treatment of Pseudomonas-Infection. Another relevant achievement was the submission of the application to obtain the marketing approval in the US for the enzyme inhibitor Prolastin (Alpha-AT), a substance extracted from blood plasma to prevent pulmonary emphysema. In 1987 the product receives the marketing approval. In 1993 a blood clotting recombinant Factor VIII for the treatment of haemophilia is approved for marketing in the US. The brand name was Kogenate. Its development had taken 10 years of research activities and 300 million DM investment costs (Dolata 1994 p. 36).

In the 1990s Bayer advances towards the enrolment in the field of immunology and immunodiagnostics. These fields draw on molecular biology principals to develop treatments and diagnostic systems for disorders that involve the immune system (e. g., cancer, HIV disease, autoimmune diseases). In 1992 Bayer completes an important step in this field with the development of the analysis device Immuno 1. The annual report in 1991 announces the first positive results in the clinical trials of monoclonal antibodies against the tumour necrosefactor (TNF) causing arthritis.

Biotechnology capabilities at Bayer

The beginning of biotechnology research and development at Bayer was only possible though licensing and collaborative agreements with companies and research institutions. In 1949 Bayer entered into collaboration with the company Schenley to develop a modern plant for the production of penicillin G (Benz et al. 1996).

In order to grasp the state-of-the art in the applications of molecular biology and genetechnology for drug discovery and development Bayer held contacts at the beginning of the 1970s with the company Cetus and with Prof. Weil (from the University of Geneva) (Schütz 1977).

The process of building up in house capabilities to explore the applications of genetic engineering in drug discovery and development starts in the second half of 1970s with

the establishment of two research laboratories for the stem manipulation. The goal was to start building up an infrastructure which should be progressively enlarge latter on (Schütz 1977). The acquisition of Miles Corporation (US) in 1977 was a strong impulse in this direction. In 1979 Bayer expands the research facilities at Miles and upgrades its citric-acid production plant (Hauser 2004). In the German research facilities a research group for genetic engineering is established with 2 senior scientists and 4 technicians. Additionally the construction of a laboratory with approximately 300 square meters was planed for 1980 (Truscheit, Frommer 1979). The biotechnology-related research activities were concentrated in Elberfeld and in Elkhardt, the location of Miles Corporation (Hauser 2004). In 1983 fifteen PhDs were involved in genetic engineering within the pharmaceutical business unit, five in Germany and ten in the USA. The management admits not having enough intern capabilities to carry out the running projects in the new field of genetic engineering on their own (Auerswald 1983).

In the 1980s Bayer recognises that only the intensive contacts to external research institution and collaborative activities connected with the extension of intern screening capabilities and the appropriate expansion of the internal infrastructure for molecular biology research will enable Bayer the identification of promising products, its patent protection and its production with the application genetic engineering (Auerswald 1983).

In 1982 the annual report points out the importance of collaboration activities in the field of genetic engineering with academic institutions and research institutes in Germany and in the US. The report refers to the Max Planck Institute for Plant Breeding Research in Köln, the Genetic Institute at Köln University, the University of Rochester in NY and the Massachusetts Institute of Technology (MIT) in the US. Especially the University of Rochester in New York and the Yale University in New Heaven (Connecticut) were important research institutions for Bayer. In 1983 the company had 5 of its 11 projects in the field of genetic engineering being carried out to a large extent in the facilities of the University of Rochester (Auerswald 1983). The collaboration activities with the University of New Heaven were mainly motivated by the acquisition of Miles, which had research facilities in the same region.

Important collaborations with companies include the licensing contract with Genentech Inc. (US) in 1984. According to the Bayer's annual report of 1986 the companies worked together in the biosynthetic production of the blood-clotting Factor VIII. In this period Bayer and Hoechst AG cooperate in AIDS research.

The efforts to build up the necessary infrastructure continue in the years after. In 1988 a new research centre is established in West Haven (a location of Miles). According to

the annual report of 1987 the new research centre integrates 3 research units: Molecular Diagnostics Unit (specialised on diagnostic systems based on monoclonal antibodies), Molecular Therapeutics Unit (specialised on the treatment of immunological diseases such as Alzheimer and AIDS), and the Institute for autoimmune diseases (specialised on research on the therapy of rheumatic diseases).

In 1995 an additional research centre is established in Japan, in the Kasai Science City near Kyoto. Collaboration and licensing activities continue to be essential for the company in the 1990s. The main role of collaboration and research activities is the systemic search for chances of collaborative research with companies (Alsraedter, Foltin 1992).

Acquisitions and joint ventures relevant for Bayer's biotechnology activities

The process of building up internal capabilities of biotechnology research and development after World War II and, especially, since the 1970s was supported by a number of important acquisitions and joint ventures.

The first acquisition took place in 1974 with the integration of the activities of Cutter (US). The company was specialised in the production and sales of blood plasma-based products and veterinary products and most importantly, Cutter was carrying out pioneer research work in the field of blood fractionation. Hauser (2004) sustains that this acquisition was not the result of an strategic decision the expand the R&D activities but much more the logical consequence of Bayer business strategy of diversification of the sales programme to complement the products for human medicine with veterinary, dental and biomedical products. The acquisition of Cutter indented to reinforce the activities in the veterinary business.

In 1978 the purpose of acquiring a company located in the US was quite different. With the acquisition of Miles Laboratories, (USA) Bayer integrated a broad diversified company in the chemical-pharmaceutical sector. The business focus of Miles was the biological production of citric acid and enzymes. The acquisition of Miles was a clear attempt to build up own research capabilities in the US. According to Hauser (2004), the plans to secure the pharmaceutical business in Germany faced a few problems such as the high costs and the lack of qualified staff. The pharmaceutical research needed a second strong base and this should be located in the US. Accordingly by 1980 Bayer had 2 important research locations in the US: Elkhard (Indiana) which was the location of Miles and the research facilities of Cutter located in Berkley (California).

In the 1980s the strategy of expanding the research facilities towards the US continued with the establishment of two joint ventures in the West Haven: Molecular Diagnostics (in 1982) and Molecular Therapeutics (in 1985). The trend continued with the integration of Chiron Diagnostics in Bayer Diagnostics in 1987. Chiron Diagnostics provided Bayer with proprietary molecular diagnostics technology to be applied in the field of immunological diagnostics.

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Case study 3: Merck

The case study reviews achievements of the company in biotechnology research and the development of capabilities in this field in the second half of the 20th century.

The beginning of Merck is rooted in a family owned pharmacy in Darmstadt (Germany), which gradually reached industrial dimensions in the last quarter of the 19th century. By 1904 Merck's assortment included almost 50 specialties; about one half of these were preparations manufactured from animal organs and a wide variety of sera (Bernschneider-Reif et al. 2002, pp.52-54).

Even though Merck KGaA has became a diversified chemical company, with regard to its technological roots and research tradition it can be considered within the group of traditional pharmaceutical companies that started their activities exclusively in the pharmaceutical sector. There is large evidence for the identification of the company with the traditional pharmaceutical companies rather than with the diversified chemical corporations. For instance, at the beginning of the 20th century Merck established a community of interests (so called "Interessengemeinschaft") together with other traditional pharmaceutical companies. According to Bernschneider-Reif et al (2002, pp. 76) the idea behind this collaboration was to establish a counterbalance to the growing influence of the coal-tar dye factories, which themselves had joined forces to build two different community of interests years earlier". With the war the community of interests ended. However, in 1915 the companies Merck, Boehringer Mannheim and Knoll established a company officially called MBK to jointly produce a range of frequently prescribed tablets and ampoules. This community of interests continued to exist until 1971 (Bernschneider-Reif et al. 2002, p. 86).

Biotechnology research and achievements at Merck

Metz (1995) presents the application of traditional biotechnology along three phases. First, biotechnology was applied between 1893 and 1939 for the anaerobic bacteriological production of butyric and lactic acids. It was the integration of biotechnology in the drug development and production processes at Merck. Next, after1939 Merck focused on the synthesis of the ascorbic acid (vitamin C). In order to improve the yield of the basic substances involved in the synthesis, Merck developed a chemical process which integrated a step involving the bacteriological oxidation of sorbit into sorbose (the aerobic-sorbose-process). According to Metz, these first biotechnology production processes have to be considered more as empirical and handcraft-based work than as industrial. They required quite unique development and production strategies. The situation changed with the development of the bioreactor. The last phase of traditional biotechnology at Merck started with the establishment of a

bioreactor in 1956, which played a key role in the microbiological transformation of steroids.[90] Merck ventured into the cortisone business in 1953/1954 by buying manufacturing and marketing licenses (Bernschneider-Reif et al. 2002). The bioreactor allowed for the introduction of a microbiological transformation of steroids in the synthesis of Cortisone and Hydrocortisone, which made the process much more effective by reducing the synthesis from 32 to 13 steps. This technique (which had been discovered by Schering and further developed in the US) was integrated in Merck's development processes. Even though the company had a long tradition in the microbiological dehydrogenation of Sorbit to produce Sorbose, the process with Cortisone and Hydrocortisone required sterile reaction conditions. According to Brückner, who was responsible for carrying out this task, the technique was new for him and for the company (Brückner 1985).

In the following years the application of microbiological reactions was very successful. Until 1965 the microbiological transformation of steroids was a main focus of the development activities (Metz 1991). Almost all microbiological reactions known and needed were applied. Between 1956 and 1976 the company implemented more than 200 steroid and semi-finished steroid substances. The biotechnology capabilities built in this period were used for the applications in other fields and projects such as the sorbose process for the synthesis of the ascorbic acid, the vitamine B12, cell cultures and specially, during the third quarter of the 20th century, in the extraction of enzymes for diagnostic applications (Metz 1991, p. 44).

After 1972 the preparative biochemistry worked in the extraction of organ-specific iso-enzymes from the heart, brain and liver. The creation of antigen in animals as well as and the purification of antiserum for immunological use were additional projects demanding the further development of biotechnology capabilities in the company. It was the beginning of the immunological research at Merck. The work of the analytical biochemistry department complemented the activities of the diagnostic research programs. The microbiological group (apart from working o the production of GDH) worked primarily on the search for antibiotics out of staphylococci and through the specific selection of the microorganisms. The results in this research line were not very successful.

In the second half of the 1980s the company considers the possibility of broadening its indication portfolio to include immunological products for tumour therapy and tumour

90 Luitgard Marshall (2000) pp. 305-340 presents a detailed case study on the application of biotechnology in the production of vitamin C and the application of the bioreactor (i. e. the sterile technique) for production purposes at Merck.

diagnostics. The management had many doubts about undertaking research and allocating resources in this direction. On the one hand these activities were considered very risky and additionally, the available capabilities in immunological basic research and modern biotechnology were very narrow. Further more, issues of patent protection in this field were unclear. None the less the management saw strong innovation potential in this business line. New capabilities had to be built up for both research and development in the field of immunology (Merck 1987).

In 1993 three immunological research programs were pursued: the therapy of certain types of cancer using monoclonal antibodies, active immunisation and the prevention of metastases using adhesion receptors. Other biotechnology-related activities in the early 1990s involved the processing of thrombolytic proteins produced and the supply of reagents for molecular biology and biochemical purposes (such as gel material for nucleic acid electrophoresis or special enzymes for the isolation and purification of DNA and RNA) (Bernschneider-Reif et al. 2002).

Biotechnology capabilities at Merck

Merck set up its bacteriological department in 1895. Besides the production of antidiphteric serum and smallpox vaccine, the department carried out experiments to explore the possibilities of manufacturing additional biological-therapeutic products. This department grew rapidly and in 1902 a second location with a bacteriological department was established in Halle on the Saale (Germany). Animals were kept to guarantee the resources for the active constituents of the vaccines (Bernschneider-Reif et al. 2002).

The available sources do not provide with any evidence of establishment or expansion of research infrastructure to promote biotechnology-related activities in the first half of the 20th century.

The reestablishment of the research activities at Merck after World War II was slower than at other firms such as the successors of the IG-Farben, Bayer and Hoechst. That the annual reports of the company did not report any information on the research activities until 1957 could be a confirmation of the lack of interest on research and development activities from the management side (Brückner 1985).

In the 1950s professional contacts to research institutes in Germany in the microbiological field were very unusual. Microbiology and Biochemistry institutes in the German Universities were first created in the 1960s. Industrial problems were not of interest for the few University professors in the field at that time (Metz 1991).

At the end of the 1950s the research and development activities were distributed in three segments: the chemical research, the medical research (which included the pharmacological research department) and the biological station.

The microbiological capabilities were integrated in the pharmaceutical research segment. The work in the microbiological transformation of steroids demanded strong efforts in building up state-of-the-art in-house bacteriological capabilities to conduct the steroid-synthesis. In 1955 Merck built a bioreactor and microbiological laboratories for the application of microbiological processes in the steroid synthesis (Metz 1995).

The 1960s began with the establishment of a biochemical department by Dr. Hermann Lang after a visit in the US. The biochemical department was subordinated to the chemical research segment. In 1964 the technical microbiology group joined the biochemical department. The research focused on the exclusively microbiological synthesis of vitamin C and other projects on the microbiological production of enzymes. Already in 1967 the biochemical department was large enough to establish an independent biochemistry research unit with two departments: preparative biochemistry and analytical biochemistry. The microbiology research group belonged to the preparative biochemistry (Brückner 1985).

In 1975 the infrastructure for the development of microbiological production processes was modernised. The bioreactor was renovated to integrate a computerised data processor (Metz 1995).

Marshall points out the subordination of the microbiological research group to the exploration of chemical problems (Marschall 2000).[91] According to her, despite the critical mass in biotechnology capabilities at Merck and the successful achievements in the 1960s and the broad microbiological research portfolio, the company's activities in the 1960s and 1970s were mainly driven by chemical principles.

However available sources point out that in 1970 the importance of the screening activities for successful drug discovery was questioned by the management. Even though screening-based chemical strategy had led to a large number of more or less effective substances, only few of them had turned up to be really valuable for medical purposes. Screening activities had a strong weight in the drug discovery process and the probability to find a new substance with new therapeutic value was relatively low.

91 Her argument draws on the one side on the promising biotechnology-based products and processes that were not developed because they did not belong to the core business of steroids and enzymes and on the other, on the organisational structure of the research and development activities at Merck.

Additionally, the search process was quite superficial, leading to preliminary products that had trouble going through the required quality and safety controls. The logical consequence for the company management was to reorient drug discovery much more towards the diseases against which new therapeutic solutions should be developed, rather than focusing it on the synthesis of potential drug candidates. In an internal report the management pointed out the successful results of a "disease-oriented strategy" in liver-research and the need to allocate resources for drug discovery maintaining the resources for drug screening at a level not higher than the absolutely necessary (Merck 1970). The management seemed to be aware of the chances of understanding the biological causes of diseases for the discovery and development of appropriate therapies. In the mid 1980s biotechnology research and development was institutionalised.

In the 1970s professional contacts to research institutes were intensified. According to Metz (1991) after the strong political support of biotechnology in the 1970s there was an increasing number of university research institutes willing to cooperate with the industry[92]. Especially in the field of molecular genetics collaboration was very successful in different enzyme projects. For instance in the project *invertase* (yeast derived enzyme) and for genetic modifications of glucose-dehydrogenase the Merck worked together with Prof. Esser from the University of Bochum and Prof. Gassen.

In 1984 a biotechnology department was established by merging microbiology and the biochemistry research groups (Metz 1991). In 1986 the research activities included the development of monoclonal antibodies through animal cell cultures (Marschall 2000).

Already in the 1970s and 1980s the company considered the option of collaboration in the molecular genetic field with private companies. Metz (1991, p. 166) describes how in each case an assessment was necessary to decide whether to build in-house capabilities or to outsource research and development tasks.

In 1992 Merck bought an interest in the American company Biosite to strengthen its activities in the area of immunodiagnostics. In 1998 followed the joint venture BioMet Inc. USA and the acquisition of CN Biosciences, both in the USA. In 1999 the acquisition of Lexigen aimed at the expansion of biotechnology research, especially in order to secure the patent position of the company.

92 Metz describes how the framework conditions to carry out collaborative research changed. Apart from the increasing number of academic institutes, there was also a growing interest on working with problems arising from the industrial application of the scientific principals. Metz (1991, p. 164) sustains that this change in the willingness to cooperate had probably a lot to do with the criteria for the allocation of public funds in research.

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Case study 4: Schering

The case study reviews achievements of the company in biotechnology research and the development of capabilities in this field in the second half of the 20th century.

E. Schering was established in 1851 as family-owned pharmacy in Berlin. The pharmacy produced medicines and chemical products. The gradual conversion from a traditional pharmacy with a small laboratory into a pharmaceutical and chemical company led in 1871 to the change of corporate form to become a public limited company, the "Chemische Fabrik auf Aktien (vorm. E. Schering)". Even though the roots of the company were in a small pharmacy, along the first half of the 20th century the pharmaceutical business of Schering became a small part of a large conglomerate of business units (Bartmann 2003, pp. 384-386). In 1922 the company was acquired by a chemical corporation. The new mother company (with the stock market name Oberkoks) after a reorganisation of the holding company over took the name of one of its companies to become the Schering AG in 1937. Similar to the case of Bayer and Hoechst, the pharmaceutical business was a small unit of the corporation. In 1938 the pharmaceutical sales amounted less than the 15 % of the corporative sales. However, according to Bartmann (2003, p. 387), unlike the organisations of Bayer and Hoechst, the only large research infrastructure established at Schering was the pharmaceutical research department. The pharmaceutical research remained quite uninfluenced from the management, which was not interested in research and development. The research program focused since the early 1920s on physiological problems.

After World War II, Schering had lost a large part of its factories and infrastructure. Apart from the tremendous war damage, locations were lost with the new political frontiers established after the war. The reconstruction of the business drew on the development of the pharmaceutical activities[93].

Biotechnology research and achievements at Schering

Initial biotechnology-related activities at Schering were carried out in the bacteriological department. During the first decade of the 20th century the intensive research work in this department lead to patents for the production of prophylactics and remedies against tuberculosis (Scheringianum 1997a).

93 In the next paragraphs, unless otherwise indicated, the name Schering refers to the pharmaceutical activities of the current Schering AG .

In the first half of the 20th century pharmaceutical research at Schering focused on hormone research, especially on steroid hormones[94]. The work of the scientific research laboratory combined the efforts of understanding the functions of steroid hormones and their isolation with efforts of producing them through chemical synthesis.

In 1925 Schering applies the Allen-Dosi-Test for the assessment of hormones' effects. The first hormone products that were taken onto the market demanded expensive production processes. For instance, to produce the first hormone preparation for climacteric complaints the hormones had to be extracted from a placenta. To reduce the costs, the search for rational production processes by means of organic chemical synthesis was intensified. Chemists from university institutes were engaged in the late 1920s and mid 1930s to find the structural form of the hormones, which was the key to their synthesis in the laboratory (Berghausen et al. 1991, pp. 21-31).

In the late 1930s an alternative technique was explored by Schering to obtain sexual hormones: the microbiological transformation of hormones. In 1937 Schering patents a hydrogenation technique to produce testosterone drawing on the application of backer's yeast to the steroid hormone androstendion. This patent was the first description of a microbiological transformation of steroid hormones. However, at the time the process did not reach any relevance within the company since the production at industrial scale was not feasible. This discovery gave impulse to further activities involving the application of microbiology. A series of simple microbiological reactions with steroid hormones were described. This line of research and production was more or less disregarded until the end of the World War II. Schering did consider them economically attractive enough for their industrial application (Witzel 1983, pp.1-3).

Schering's experience with microbiological process was not an advantage for the company in the challenging penicillin production. Like most German drug producers after the 2nd WW, Schering was not able to produce antibiotics in an autonomous basis. In 1954 Schering brings onto the market the Antibiotic Erycinum, a preparation of Eli Lilly (Witzel 1983).

The management board member Dr. Clerc (mentor of the reconstruction of the company after the 2nd WW) promoted the research on projects combining techniques of

94 In 1905 the chief of the physiological research laboratory recognizes the effects of extracts from pancreas and sustains that patients of diabetes could be provided with this extract by a subcutaneous injection to activate the functions lost. Further research in this direction did not take place. Eighteen years later Canadian scientists developed insulin (Berghausen et al. 1991, p. 16).

organic chemical synthesis and microbiology to try to economise the production processes of steroids. After 1955 a small group of 3 scientists built up a first fermentor, which latter on would serve as pilot model for a bigger fermentation plant. In the 1960s the application of microbiology for steroids' processing had won recognition within the firm. These techniques were well established in drug production processes. The application of microbiology was not limited to the production of steroids, also enzymes, amino acids, and alkaloids were developed with the application microbiological principles (Ott 1994; Witzel 1983).

In 1987 the company considered exploring the possibilities of molecular biology, cell-biology and protein-chemistry. Schering announced the strategic decision of building up this line of research by further developing the available capabilities in microbiology and biochemistry (Scheringianum 1991, p. 3 year 1987).

The research work in biotechnology at this time focused on three main projects, one of them was the microbiological synthesis of steroids. In 1987 a project for the production of appropriate streams of bacteria to improve the microbiological steroid synthesis was launched. Additionally, Schering explored the application of genetic engineering for contraception methods and therapies against infertility. Finally, applications to improve the control of the coagulation system were part of the research program as well (Scheringianum 1990).

In the 1990s Schering makes important acquisitions to provide the company with additional capabilities. For instance, with the acquisition of the American biotechnology company Triton Biosciences Inc. in 1990 Schering incorporated strong biotechnology capabilities. In 1993 Betaferon, the first biotechnology product of the company was launched onto the market. The research work on the interferon-beta1 (Betaferon) had been carried out by Triton in the 1980s. The product became the block buster of Schering for the treatment of multiple sclerosis.

In 1997 the biotechnology-based product-pipeline included 5 projects. Only one of them was being carried out outside the US. In the field of cardiovascular diseases a project investigated the development of a recombinant product for the treatment of heart attacks. Additionally, the company worked in the Angiogenic Gene Therapy for cardiovascular diseases since 1996. For the treatment of Multiple Sclerosis (MS) Schering explored Glial Growth factors and lymphocyte / monocyte interactions. Finally, in the field of cancer therapy Schering carried out a project on ribosomes (Scheringianum 1997b).

Biotechnology capabilities at Schering

An analytical laboratory was built in 1883 and 10 years later the bacteriological department was established. However, the era of continuous research and development started in 1902, as the chemist and physiologist Max Dohrn became head of the new physiological laboratory. From the beginning Dohrn focused the research work on biological processes such as metabolism, hormone research and preparations extracted from animal's organs (Berghausen et al. 1991, p. 16).

The activities carried out at Schering in 1920s and 1930s in hormone research and in the microbiological transformation of steroids were supported by Prof. Butenandt and his student Luigi Mamolli who worked in the department of biological chemistry at the University of Göttingen and latter on at the University of Berlin and at Max Planck Institute for Biochemistry, Berlin-Dahlem (Ott 1994).

In penicillin production the American pharmaceutical company Squibb provided Schering with technological support in the early 1950s. In return Squibb was interested in the provision with steroid preliminary products from Schering for its activities in the steroid fermentation (Ott 1994; Wicenec 1996). In this period Schering built up the necessary in house capabilities to develop microbiological applications for production processes at large scale. Besides the establishment of a department for biochemistry in the pharmaceutical-chemical research unit, a microbiology department and a plant for the manufacture of corticoids were set up in the Charlottenburg works (Scheringianum 1971; Scheringianum 1983, p.3). In 1961 a large fermentor was built in Bergkamen. Two years later the company started the production with fermentation technique. In 1967 the capacity was enlarged. The plant was used for research and development (Witzel 1983).

In 1962 the research structure in the pharmaceutical unit explicitly distinguished between biological and chemical-pharmaceutical research. In the 1960s biological research plays an important role focusing on the exploration of biological processes. Issues of chemical physiology received special attention. The goal of this line of research was to increase the possibilities of the other research units involved in pharmaceutical research by providing orientation for a targeted development of therapies. In 1962 and 1963 this field experienced strong expansion in terms of personnel and capital investments (Scheringianum 1983, pp.24-25 and pp.44-45).

Even though Schering integrated biological research in the drug discovery and development processes, the capabilities for exploring the possibilities of modern biotechnology in the mid 1970s were quite short. The company waited until 1986 to build up capabilities in modern biotechnology and to consider the application of genetic

engineering for industrial purposes. In 1972 the company had began molecular genetic research. However, 1986 the capabilities for this activities integrated 5 scientists and 10 technical workers (Scheringianum 1986).

Since 1975 and almost without interruption Schering becomes public support from the Ministry of Research and Technology for research projects in the field of biotechnology. In the period between 1974 and 1985 the volume of public support amounted 4 million DM, covering 23 % of the total investments in microbiological and biochemical research[95] (Scheringianum 1986).

In the mid 1980s Schering undertakes organisational changes to impulse the activities in genetic engineering. Before 1986 biotechnology-related research was not subordinated to any business sector within the firm. This line of research was integrated in the area of fundamental research. Between 1986 and 1987 a research group called plant biotechnology was incorporated into the plant protection business unit. Additionally, another research group for fundamental research in biotechnology was integrated in the pharmaceutical business. This was the institute for biochemistry, which became in 1992 the institute for cell and molecular biology. Both institutes (in the plant and pharmaceutical business units) were established with the intention of promoting them to reach an adequate research infrastructure (Scheringianum 1992).

To build up capabilities in the field of genetic engineering Schering established in the mid 1980s two research institutes as platforms of access to the research results of public research institutions (Scheringianum 1993). In the period 1984-86 Schering established (and partly financed) the Institute for Gene-Biological Research in Berlin. It was created as an independent institution integrated in the location of the Max Planck Institute for Molecular Genetic in Berlin. The institute was connected with the University of Berlin (FU Berlin) through a collaboration contract and focused its work on cell biology research. Schering held a first refusal right on all research results.

The Institute of Diagnostic Research GmbH in Berlin was established in 1985 as a 100 % company of Schering. The institute worked as a normal profit center in the University Clinic in Charlottenburg (Berlin) and had direct contact to clinical research. The institute held a contract with the Berlin University (FU Berlin). The focus of the institute was applied research in the diagnostic field. Both Schering and the university held the first refusal rights on the research results.

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95 The investments do not include personnel costs.

In 1991 Schering launches an industry research consortium and establishes the clinic of the Albrecht-Ludwig University in Freiburg. In the project 3 companies were involved: Asta-Chemie (Frankfurt), Ciba Geigy (Basel) and Schering (Berlin). The goal of the clinic was the development and test of new methods for Tumour Diagnostics. The innovative aspect was the integration of oncology research, a clinic and a rehabilitation unit in one institution.

A further step towards the expansion of the biotechnology capabilities in Germany was the establishment in 1998 of the metaGen Gesellschaft für Genomforschung mbH in Berlin focusing on research on the human genome. The foundation was preceded by cooperation in 1996 between Schering and the Californian company Incyte Pharmaceuticals, which provided Schering with access to large DNA databases.

Acquisitions and joint ventures relevant for Schering's biotechnology activities

Schering's biotechnology activities at the end of the 1990s were mostly concentrated in the US. This situation was the result of the intensive acquisitive strategy followed by the corporation in the last quarter of the 20th century.

With the acquisition in 1979 of the internal medicine division of Cooper Laboratories in Palo Alto, Schering established Berlex Inc., a company with expertise in cardiovascular disease in the US.

The strategy of Schering in the 1990s was the incorporation of companies and research infrastructure to build up Berlex capabilities in the field of genetic engineering. To facilitate the acquisitions Schering establishes in the USA the Schering Berlin Venture Inc (New Jersey) with the aim of acquiring shares in companies conducting particularly innovative technologically research (Scheringianum 1971).

In 1990 Berlex Inc. acquired from the Schell Oil Company (Texas) the pharmaceutical research activities of Triton Biosciences Inc. (California). Experts estimate that the transaction reached the 100 million US$ value. Even though Triton did not have any product in the market at the time, the company had a research portfolio with very promising products (Lippold 2004). Additionally, Berlex expanded into biotechnology with the acquisition of Codon, also in the area of San Francisco. Both acquisitions added 250 employees working on biotechnology research.

In 1992 Berlex acquired for 85 million DM the research facilities of Chevron (US) in Richmond, California. This location involved 25 scientists working in the fields of

tumour therapy, cardiovascular diseases and the central nerve system. By 1993, all Berlex research was consolidated in Richmond, California (Lippold 2004).

The industrial Chemicals and Natural Substances Divisions were sold to the US American company Witco Corporation in New York (US) and the electroplating division was sold to the French company Elf Atochem SA, Paris (France). In 1994 the agrochemicals division is integrated in the joint venture AgreVo together with the Hoechst AG Schering held 40 % shares in this joint venture. With these operations in the first half of the 1990s Schering has set the ground for the future of Schering as a pharmaceutical company (Scheringianum 1971).

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Annex 2: Quantitative indicators for the case studies

Patent publications

Methodological issues

The patent data presents counts of the first publications of patent applications filed at the German patent office or European Patent Office with Germany as designation countries. The data until 1967 include all (foreign and German) published documents. From 1967 on, the time series include German documents only.

The data was gathered through online databases EDOC, PLUSPAT and PATDPA from the vendor Questel[96].

To deal with the problems of building historical time series of patent indicators the patent searches considered the approach put forward by Dominguez Lacasa et al. (2003)[97]. These problems concern the changes in the patent legislation and the publication rules, the use of consistent patent classifications over time and the limited comprehensive bibliographical information available in electronic form for patent documents published before 1968. Table A 1 gives the patent classes of the international patent classification (IPC) used for the sector and technology definitions. Regarding the counting of corporate patents, patent documents were recognised as pertaining to one of the corporations under consideration as long as the corporations' name, or the name of a major subsidiary, appeared as patent applicant. Changes in the corporations' name and possible errors due to companies with similar names in the US (for the case of Schering and Merck) were taken into account.

Table A 1: Patent classes for sector and technology definition

Sector / Technology	Patent Classes
Pharmaceuticals	A61K (except for A61K-007/EC), A61P
Organic chemistry	C07
Biotechnology	C12M; C12N, C12P, C12Q, C12S, A61K-039, A61K-048, C02F-003, G01N-033/48, G01N-033/49, G01N-033/5, G01N-033/6, G01N-033/7, G01N-033/8, G01N-033/9

96 www.questel.orbit.fr

97 Dominguez Lacasa, I.; Grupp, H.; Schmoch, U. (2003): Tracing technological change over long periods in Germany in chemicals using patent statistics. In: Scientometrics, 57 (2), pp. 175-195.

Patent data

Table A 2: Patent data

German Patent Ofice and European Patent office with Germany as designation country											
	Total number of patent documents published	Pharmaceuticals		Biotechnology		Organic chemical synthesis		Biotechnology in pharmaceuticals		Organic chemical synthesis in Pharmaceuticals	
		Total	%	Total	%	Total	%	Total	%	Total	%
1895-1905	73747	128	0.2%	101	0.1%	1131	1.5%	8	6.3%	11	8.6%
1905-1915	107423	258	0.2%	180	0.2%	1612	1.5%	46	17.8%	11	4.3%
1950s	227060	1123	0.5%	467	0.2%	9065	4.0%	87	7.7%	102	9.1%
1960s	283639	2157	0.8%	1246	0.4%	17918	6.3%	248	11.5%	846	39.2%
1970s	652679	6228	1.0%	5469	0.8%	36350	5.6%	1566	25.1%	1431	23.0%
1980s	861802	14764	1.7%	13842	1.6%	49899	5.8%	4462	30.2%	2504	17.0%
1990s	1242769	16672	1.3%	14618	1.2%	42972	3.5%	4260	25.6%	2598	15.6%

Bayer and main subsidiaries											
	Total number of patent documents published	Pharmaceuticals		Biotechnology		Organic chemical synthesis		Biotechnology in pharmaceuticals		Organic chemical synthesis in Pharmaceuticals	
		Total	%	Total	%	Total	%	Total	%	Total	%
1950s	2533	62	2.4%	15	0.6%	777	30.7%	0	0.0%	13	21%
1960s	3985	49	1.2%	41	1.0%	1588	39.8%	11	22.4%	15	31%
1970s	7416	190	2.6%	173	2.3%	2669	36.0%	60	31.6%	48	25%
1980s	12011	567	4.7%	474	3.9%	4821	40.1%	198	34.9%	123	22%
1990s	11314	423	3.7%	344	3.0%	3993	35.3%	177	41.8%	95	22%

Hoechst and main subsidiaries											
	Total number of patent documents published	Pharmaceuticals		Biotechnology		Organic chemical synthesis		Biotechnology in pharmaceuticals		Organic chemical synthesis in Pharmaceuticals	
		Total	%	Total	%	Total	%	Total	%	Total	%
1950s	1708	33	2%	15	1%	570	33.4%	3	9.1%	5	15%
1960s	2341	74	3%	37	2%	829	35.4%	22	29.7%	30	41%
1970s	5083	223	4%	137	3%	1790	35.2%	92	41.3%	58	26%
1980s	9475	625	7%	783	8%	3689	38.9%	288	46.1%	151	24%
1990s	9896	594	6%	572	6%	3282	33.2%	223	37.5%	114	19%

Schering and main subsidiaries											
	Total number of patent documents published	Pharmaceuticals		Biotechnology		Organic chemical synthesis		Biotechnology in pharmaceuticals		Organic chemical synthesis in Pharmaceuticals	
		Total	%	Total	%	Total	%	Total	%	Total	%
1950s	297	33	11.1%	3	1.0%	207	69.7%	1	3.0%	10	30.3%
1960s	370	62	16.8%	12	3.2%	224	60.5%	2	3.2%	41	66.1%
1970s	781	67	8.6%	51	6.5%	452	57.9%	5	7.5%	22	32.8%
1980s	1757	214	12.2%	118	6.7%	984	56.0%	17	7.9%	55	25.7%
1990s	2115	275	13.0%	76	3.6%	677	32.0%	14	5.1%	86	31.3%

Merck and main subsidiaries											
Merck	Total number of patent documents published	Pharmaceuticals		Biotechnology		Organic chemical synthesis		Biotechnology in pharmaceuticals		Organic chemical synthesis in Pharmaceuticals	
		Total	%	Total	%	Total	%	Total	%	Total	%
1950	217	19	8.8%	12	5.5%	115	53.0%	0	0.0%	2	10.5%
1960	548	71	13.0%	39	7.1%	384	70.1%	16	22.5%	30	42.3%
1970	745	117	15.7%	61	8.2%	456	61.2%	31	26.5%	29	24.8%
1980	1150	96	8.3%	76	6.6%	508	44.2%	35	36.5%	17	17.7%

Corporate expenditures in research and development

Data sources

The historical data have been gathered from the corporate historical archives using annual reports and relevant documents covering the pharmaceutical segment of the corporations. The data for the period 1955-1970 refer to pharmaceutical research and development of the corporation (*Mutterkonzern*). For the period 1975-1995 the data refer to the global group *(Welt oder Gruppe).*

Sources Hoechst

Annual reports (several years)

Bartmann, W. (2003): Zwischen Tradition und Fortschritt - Aus der Geschichte der Pharmabereiche von Bayer, Hoechst und Schering von 1935-1975, Stuttgart: Franz Steiner Verlag.

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Sources Schering

Annual reports (several years)

Archive Sch FuE Kennzahlen Grüne Mappe (1970-2002)

Archive Sch B01-0116/1, Archive Sch B01-263, Archive Sch B01-263 / 392

Archive Sch B01-520/2, Archive Sch B01-0268

Archive Sch B03 70-80-1025, Archive Sch Annex 1 70 80 1022

Sources Bayer:

Annual reports (several years)

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Sources Merck:

Annual reports (several years)

Archive Me J10 98

Archive Me J10 50

Archive Me J10 63, F1/1

Data

Table A 3: Investment volume in research and development (in million German Mark and as a percentage of the total sales).

	Merck		**Schering**		**Hoechst**		**Bayer**		
	mio DM	%	mio DM	%	mio DM	%	mio DM	%	
1955	n.a.	n.a.	0.3	0 %	69	5 %	62	4 %	**1955**
1960	10	5 %	12	7 %	113	4 %	125	4 %	**1960**
1965	22	7 %	33	9 %	204	4 %	193	5 %	**1965**
1970	50	9 %	69	11 %	420	6 %	355	6 %	**1970**
1975	*105*	*7 %*	163	9 %	930	4 %	803	5 %	**1975**
1980	134	7 %	281	9 %	1302	4 %	1241	4 %	**1980**
1985	208	6 %	575	11 %	2083	5 %	2134	5 %	**1985**
1990	303	9 %	802	14 %	2687	6 %	2738	7 %	**1990**
1995	565	9 %	845	18 %	3479	7 %	3258	7 %	**1995**

Human capital

Data sources and data

Human capital data gathering had the goal of building educational statistics as indicators of firm's internal capabilities. This approach allowing the identification of companies' core capabilities and their development has been put forward by Jacobsson and Oskarsson (1995)[98].

The data used in the analysis cover the educational background of the staff holding an academic degree according to their academic qualification. In order to capture the extent to which internal capabilities vary over time it is necessary to collect data at different points in time. Due to the historical perspective of the study, the data need to cover a time frame of at least 30 years. This means that in the case of for diversified companies the data is not differentiated according to the business segment.

The data have been collected from the corporative historical archives and, in some cases, directly from the personal departments of the companies under consideration. Annual reports and public corporate information do not give any relevant information for this purpose. Moreover, the personal departments of the 4 corporations have used, in most cases, different levels of aggregation to classify the academic disciplines. Accordingly, to obtain comparable data, the analysis has demanded a re-classification of the data available.

The data are given in Table A 4 For Schering in the year 1970 the data refer to the pharmaceutical activities only. Data for Hoechst in the years 1981 and 1993 refer to the Hoechst AG, for the other years the data refers to the Hoechst Group. The data for Bayer refers to Bayer Farbenfabrik.

The sources for the data are given bellow:

Schering

Scheringianum 3.1.2 "Belegschaftszahlen SA - Grüne Mappe". Personal Statistik / Anzahl Akademiker nach Fachrichtungen

Merck

Year	Source
1970	Archive file J10 98 "Akademische Berufe nach Fachrichtungen"
1982	Archive file: J10 565 "Akademische Berufe nach Fachrichtungen"
1990	Data from the personal department
1995	Data from the personal department
2000	Data from the personal department

98 Jacobsson, S.; Oskarsson, C. (1995): Educational statistics as indicators of technological activity. In: Research Policy, 25, pp. 127-136.

Hoechst

Year	Source
1955	Archive file 52 20 / 121110 Direktionsabteilung T Akademiker der Farbwerke Hoechst AG
1966	Jahresbericht 1966 Personal und Sozialbestand
1972	Archive file KPS 8 / 1972-1983 Veränderung des Stammpersonales . Stand nach Naturwissenschaftlern und Bestand nach Berufsgruppen.
1981	Personal und Sozialwessen Akademiker. Hoechst AG Naturwissenschaftler 1958-1981 (Graphik)
1993	Archive file. Akte R. Personalabteilung AT. Referat Naturwissenschaftler Einstellung von Akademikern. Beschäftigte Akademiker 1993

Bayer

Year	Source
1950	215/5.2 "Akademiker Stand 1.6.1950"
1959	215/5.2 "Beruflicher Gliederung akademischer Angestellten"
1966	265/8 "Zusammenstellung der akademischen Angestellten nach Berufsgruppen"
1975	Personalabteilung LA Personal "Bewegung der Akademiker mit naturw. und technische Ausbildung einschließlich Juristen"

Table A 4: Human capital profile: Employees holding an academic degree according to their academic qualification (disciplines)

	Schering			
	1970	**1980**	**1985**	**1995**
Physicians / Pharmacists	42%	32%	27%	31%
Biologists / Microbiologists	3%	6%	7%	8%
Chemists	30%	30%	28%	25%
Engineers /Physicists	0%	8%	15%	17%
Other	25%	30%	30%	27%

	Hoechst					
	1955	**1960**	**1966**	**1972**	**1981**	**1993**
Physicians / Pharmacists	12%	12%	10%	19%	12%	12%
Biologists / Microbiologists	1%	1%	2%	4%	n.a.	6%
Chemists	58%	55%	51%	50%	54%	39%
Engineers /Physicists	22%	23%	26%	26%	19%	17%
Other	8%	10%	14%	6%	15%	31%

	Merck			
	1970	**1982**	**1990**	**2000**
Physicians / Pharmacists	43%	29%	27%	23%
Biologists / Microbiologists	4%	13%	6%	12%
Chemists	39%	46%	40%	33%
Engineers /Physicists	7%	6%	11%	23%
Other	12%	18%	23%	22%

	Bayer			
	1950	**1959**	**1966**	**1975**
Physicians / Pharmacists	8%	3%	13%	13%
Biologists / Microbiologists	1%	1%	2%	3%
Chemists	67%	56%	53%	54%
Engineers /Physicists	21%	26%	26%	28%
Other	4%	14%	8%	5%

Strategic collaborative arrangements

Type of collaborative arrangements and data sources

Data gathering has concentrated on counting strategic collaborative arrangements of the corporations Bayer AG, Merck KGaA, Schering Aktiengesellschaft and Hoechst. In the case of Hoechst, due to the continuous corporative restructure processes, the data includes collaborative activities of the following companies and subsidiaries: Hoechst Marion Roussel (HMR), HMR Behringwerke, HMR Celanese, HMR Chiron Behring, HMR Hoechst Japan, HMR Hoechst Schering AgrEvo GmbH, Hoechst-Roussel, Marion Merrell Dow GmbH, HMR Roussel-Uclaf, Hoechst Schering AgrEVO, Hoechst-Ariad Genomics Center.

The strategic collaborative arrangements involve biotechnology-related activities of the following types:

- Research: unilateral transfer of fundamental research results
- Development: unilateral technology and product development services
- Co-development: joint development
- Collaboration: joint research
- Manufacturing
- Marketing
- Licensing
- Acquisition
- Share holding investment
- Joint Venture
- Other

The main sources for data gathering have been:

Lippold, M. (2004): Die Schaffung und Nutzung von Property Rights an Informationen: Zum Zusammenhang von Recht und Akteurshandeln im Bereich Biotechnologie. Online: http://www.biotechpropertyrights.uni-bremen.de/ (Accessed: 2004-05-01).

Peter, V. (2002): Institutionen im Innovationsprozess - Eine Analyse anhand der biotechnologischen Innovationssysteme in Deutschland und Japan, Heidelberg: Physica-Verl.

Material from the corporative archives of the corporations under consideration.

Desk research and literature review using corporate information (Internet and Annual Reports).

Strategic collaborative arrangements per year and type

Table A 5: Strategic collaborative arrangements per year and type

Bayer AG

Year	Research	Development	Codevelopment	Collaboration	Manufacturing	Marketing	Licensing	Acquisition	Share holding investment	Joint Venture	Other	Total collaboration	Total collaboration without licenses
1974								1				1	1
1978								1				1	1
1980	1			1								1	1
1982	1				1			1				2	2
1983	3			3								3	3
1984							2	1				3	1
1986	3	2	1		1	1	2					5	3
1987	1			1								1	1
1988	1			1			1					1	0
1989	1	2					1	1				5	4
1991	2	1		1						1	1	4	4
1992		3			2	3	4				1	8	4
1993		1			4	3	4					6	2
1994	3	1		2	4	4	3	1	2		3	10	7
1995	2	3		1	3		6		3		2	9	3
1996	3	7		2	2	1	6		1	1	1	11	5
1997	2	2		2	1	2	4					8	4
1998	7	7	1	4	5	3	8	2	2	3	2	23	15
1999					1	2						1	1

Hoechst

Year	Research	Development	Codevelopment	Collaboration	Manufacturing	Marketing	Licensing	Acquisition	Share holding investment	Joint Venture	Other	Total collaboration	Total collaboration without licenses
1977								1				1	1
1980		1										1	1
1981	1											1	1
1982					1							1	1
1984	1						1				1	1	0
1985	3	4			1		2				1	6	4
1986	3	3					1		3	1	2	6	5
1987	2	2					1		1		1	3	2
1988	2	3					3		1	1		7	4
1989	2	1			1		2		1			4	2
1990	1	3			2	1	6		4	3		7	1
1991	2	2			2	2	4		2			7	3
1992	1	4		1	2	2	7		3		3	11	4
1993	3	9		3	1	4	12	1	2		1	22	10
1994	2	2			1	5	8		1	1		15	7
1995	2	6		2	1	3	9	3	4	1	3	16	7
1996	2	3				2	7	1	2	1	3	15	8
1997	8	8	1	1	1	3	12		7	5	5	28	16
1998	2	7	3	1	2	6	9	6	2	1	4	32	23

Merck KGaA

Year	Research	Development	Codevelopment	Collaboration	Manufacturing	Marketing	Licensing	Acquisition	Share holding investment	Joint Venture	Other	Total collaboration	Total collaboration without licenses
1988		1			1		1					1	0
1990	2	3				2	4		2			4	0
1991		1				1			1	1		3	3
1992	1	2		2	1	1	2	1	1		1	6	4
1993	1			1								1	1
1994	1			1			1		1			1	1
1995						1			1			2	2
1996	1	2		1		2	3		1		1	5	2
1997		2					1			1		3	2
1998		1		1		1	2	1	1			13	11

Schering AG

Year	Research	Development	Codevelopment	Collaboration	Manufacturing	Marketing	Licensing	Acquisition	Share holding investment	Joint Venture	Other	Total collaboration	Total collaboration without licenses
1973		1										1	1
1977	4	4										4	4
1978												0	0
1979								1				1	1
1982	3	2					1					3	2
1984	1	1										1	1
1989								2			1	3	3
1990											1	1	1
1991							1					1	0
1993	3	2		1		2	4		3			8	4
1994	1	1		1		2	2					3	1
1995	2	4		1		3	6		3		1	7	1
1996	2	2		2			1	1				5	4
1997	1	1				3	3		2		1	5	2
1998	3	2		1	2	2	5	1	2		1	10	5
1999							1					1	0

Research partners per year

Bayer

Table A 6: Research partners Bayer

Year entering collaboration	Partner's name
1974	Cutter Laboratories
1978	Miles Laboratories
1980	Rochester University
1982	Molecular Diagnostics
1982	Synbiotics
1983	Genetic Systems, US
1983	Massachusetts Institute of Technology MIT
1983	Institut für Genetik der Universität Köln
1984	Genentech
1984	Standford University
1984	Molecular Therapeutics
1986	GBF Braunschweig
1986	Hoechst und Georg-Speyer-Haus
1986	Chiron Diagnostics
1986	Hygeia Pharmaceuticals
1986	Mast Immunosystems
1987	Yale University
1988	Hoechst
1988	Mitsubishi
1989	Calgene
1989	Technicon
1989	Chiron
1989	Elan
1989	Scios
1990	California Biotechnology
1991	Iterex Pharmaceuticals
1991	California Biotechnology
1991	ImClone Systems
1991	Trega Biosciences
1992	Celltech
1992	Kyoto Daiichi Kagaku
1992	Pharmaceutical Proteins
1992	Robert Pharmaceutical
1992	Saitex Pharmaceuticals
1992	Syntro
1992	Viagene
1992	Zeneca
1993	Bioprojet
1993	Centocor
1993	Eisai
1993	Fujirebio
1993	NABI
1993	Eisai
1994	Arris Pharmaceuticals Inc.
1994	Serologicals Corp.
1994	Axys Pharmaceuticals
1994	Heska
1994	Hycor Biomedical
1994	Onyx
1994	Schein Pharmaceutical
1994	SKB SmithKline
1994	Urgo
1994	Zeneca
1995	North American Biologicals
1995	Inex Pharmaceuticals
1995	Matritech
1995	Metra Biosystems
1995	Myriad Genetics
1995	NABI
1995	Pall
1995	Pharmacopeia
1995	Shaman Pharmaceuticals
1996	Pharmazia
1996	Oncogene Sciences
1996	Alza Corporation
1996	CV Therapeutics
1996	Fuisz Technologies
1996	Hoffmann-LaRoche

Year entering collaboration	Partner's name
1996	Immune Response
1996	MDL Information Systems
1996	OSI Pharmaceuticals
1996	Quidel
1996	Zeneca
1997	Alza Corporation
1997	Barr Laboratories
1997	Biomatrix
1997	Genome Therapeutics
1997	Genzyme
1997	Molecular Simulations
1997	Myriad Genetics
1997	Sequus
1998	Centeon
1998	Chiron Diagnostics
1998	Crompton & Knowles
1998	Exelixis Pharmaceuticals
1998	Fuisz Technologies
1998	Incyte Pharmaceuticals
1998	Lion bioscience
1998	Matritech
1998	Microtek International
1998	Microtek International
1998	Millennium Pharmaceuticals
1998	Molecular Simulations
1998	NicOx S.A.
1998	Novalon
1998	Oxford Asymmetry International
1998	Paradigm Genetics
1998	Proteomix (sub of NovaDX int, Vancouver)
1998	Sangamo BioSciences
1998	Scios
1998	Serologicals
1998	Symyx Technologies
1998	Stanford University
1998	Roche
1999	Cambridge NeuroScience

Hoechst

Table A 7: Research partners Hoechst

Year entering collaboration	Partner's name
1977	Callbiochem
1980	Cetus
1891	Massachusetts Hospital
1982	Biogen
1984	Scios
1985	Immunex
1985	Genex
1985	Citus
1985	Elan
1985	Nova Pharmaceutical
1985	Calgene
1986	Bayer und Georg-Speyer-Haus
1986	Synbiotics
1986	Chiron
1986	Celgene
1986	Codon
1986	Nova Pharmaceutical
1987	Integrated genetics
1987	IG Laboratories
1987	Cortech
1988	Calon
1988	Bayer AG
1988	Biomatrix
1988	Alza
1988	Creative BioMolecules
1988	Controlled Therapeutics
1989	Nippon Kayaku
1989	Genex
1989	Therion Biologics
1989	US Bioscience
1990	Transkaryotic Therapies
1990	Genzyme Transnational
1990	Sumitomo Metal
1990	Alteon
1990	Gensia Sicor
1990	DNARD
1990	ImmunoGen
1991	Bradley Pharmaceuticals
1991	Chiron
1991	Syntro
1991	Affymax
1991	Columbia Labs
1991	Ecogen
1991	EcoScience
1992	PGS International
1992	Polfa
1992	Triplex
1992	NABI
1992	Chapin Medical
1992	RPR
1992	Syntro
1992	ImmuLogic
1992	OSI Pharmaceuticals
1992	Scios
1992	Schering AG
1993	Oncogene Sciences
1993	Copley Pharmaceuticals
1993	Cortecs
1993	HMR
1993	HMR
1993	OSI Pharmaceuticals
1993	Kaketsuken-Mochida
1993	Roussel-Uclaf
1993	SKB
1993	Toyobo
1993	Biovail
1993	OSI Pharmaceuticals
1993	Bio-Imaging Technologies
1993	Mitsubishi Chemical
1993	Novopharm
1993	Rugby Group
1993	Sepracor
1993	SKB
1993	Synthelabo
1993	ABC Pharma
1993	Vertex

Year entering collaboration	Partner's name
1993	Toyobo
1994	Biopharm AG
1994	Deprenyl Animal Health
1994	Kyorin Pharmaceutical
1994	North China Pharmaceuticals
1994	Biomira
1994	Ixsys
1994	Biovail
1994	KV Pharmaceuticals
1994	Astra Merck
1994	Ostex International
1994	SKB
1994	Synthelabo
1994	Transkaryotic Therapies
1994	Suntory
1995	Transkaryotic Therapies
1995	Allelix Biopharmaceuticals
1995	Cell Genesys
1995	Incyte Pharmaceuticals
1995	Lynx Therapeutics
1995	MMD
1995	MPG
1995	ProScript
1995	Teva Pharmaceutical
1995	Zynaxis
1995	Syva
1995	Armour
1995	Ilex Oncology
1995	Pierre Fabre
1995	Selectide
1995	Ariad Pharmaceuticals
1996	Alza Corporation
1996	Transkaryotic Therapies
1996	Oncogene Sciences
1996	Alliance Pharmaceuticals
1996	BMS
1996	Cell Genesys
1996	Chiron
1996	Novartis Ciba-Geigy
1996	PGS International
1996	Pharmacyclis
1996	RPR
1996	Shire Pharmaceuticals
1996	Titan Pharmaceuticals
1996	Tripos
1996	North American Vaccine
1997	Fuisz Technologies Ltd
1997	Bayer Corporation
1997	Genentech
1997	VIA Medical Corporation
1997	Chiron Corporation
1997	SmithKline Beecham
1997	Incyte Pharmaceuticals
1997	Amgen
1997	Oncogene Science Inc
1997	Incyte Pharmaceuticals
1997	Dade International
1997	Cell Genesys
1997	Bavarian Science Foundation
1997	Cell Control GmbH
1997	MediGene Ag
1997	Alza
1997	Amylin Pharmaceuticals
1997	Ariad Pharmaceuticals
1997	Harvard University
1997	Kimeragen
1997	MediGene
1997	Nanogen
1997	OSI Pharmaceuticals
1997	Procter & Gamble
1997	Scriptgen
1997	Sugen
1997	Symyx Technologies
1997	Watson Pharmaceuticals
1998	Transgene
1998	3M Pharmaceuticals
1998	Advanta B.V.
1998	Cell Genesys
1998	Transkaryotic Therapies
1998	Amersham Pharmacia Biotech
1998	Ariad Pharmaceuticals
1998	Alza

Year entering collaboration	Partner's name
1998	Ariad Pharmaceuticals
1998	Harvard School of Public Health
1998	Procter & Gamble
1998	Chiron
1998	OSI Pharmaceuticals
1998	ProScript
1998	Quintiles Transnational
1998	Rhone-Poulenc
1998	Inhale Therapeutic Systems
1998	Pfizer
1998	Chiron
1998	Chiron Behring
1998	Genome Therapeutics
1998	Immunex
1998	Matrix
1998	Phylos
1998	Roberts Pharmaceutical
1998	Rugby Group
1998	Glaxo Wellcome
1998	Cargill
1998	Sapharco
1998	Cargill
1998	Gene Logic
1998	Pangea Systems

Merck

Table A 8: Research partners Merck

Year entering collaboration	Partner's name
1988	ImmunoGen
1990	Cygnus
1990	Dura Pharmaceuticals
1990	ImClone Systems
1990	Scios
1991	British Glaxo Group Ltd.
1991	Lipha
1991	Environmental Diagnostic
1992	Scripps Clinic, San Diego
1992	Strategic Diagnostics
1992	Biotrol
1992	Biosite Diagnostics
1992	Ligand Pharmaceuticals
1992	MGI Pharma
1993	Medical Research Council at Mill Hill.
1994	Medarex
1995	Amersham International
1995	Nycomed Amersham
1996	3-Dimensional Pharmaceuticals
1996	Etex
1996	Human Genome Sciences
1996	Neogen
1996	SKB SmithKline
1997	Biomet
1997	ImClone Systems
1997	Solvay
1998	CN Biosciences
1998	Argonaut Technologies
1998	ImClone Systems
1998	Lexigen Pharmaceuticals
1998	Abbott
1998	Argonaut Technologies
1998	Ariad Pharmaceuticals
1998	Astra AB
1998	DuPont
1998	Genetics Institute
1998	Merck Sharp and Dom
1998	RPR
1998	Sumitomo Pharma

Schering

Table A 9: Research partners Schering

Year entering collaboration	Partner's name
1973	Cetus
1974	Pfizer
1974	Hoffmann-La Roche
1974	World Health Organisation
1974	American National Institute of Health
1979	Cooper Laboratories
1982	FU Berlin
1982	Max Plank Gesellschaft
1982	Genex
1984	FU Berlin und MPG
1989	Condon
1989	Triton Bioscience
1989	Unigene Labs
1990	Liposome Company
1991	Molecular Biosystems
1993	Chiron
1993	Mallinckrodt
1993	NeXStar
1993	Nycomed Amersham
1993	Siemens
1993	Zonagen
1993	Bradley Pharmaceuticals
1993	PCS Health Systems
1994	Bioject
1994	Dr. Rentschler
1994	Novartis Ciba-Geigy
1995	3M
1995	Anthra Pharmaceuticals
1995	Ethical Holdings
1995	ImmuLogic
1995	Advanced Magnetics
1995	Argonaut Technologies
1995	Pharmacopeia
1996	Collateral Therapeutics
1996	Incyte Pharmaceuticals
1996	Jenapharm
1996	MDL Information Systems
1996	Novo Nordisk
1997	Alliance Pharmaceutical
1997	Kimeragen
1997	Ribozyme Pharmaceuticals
1997	Metra Biosystems
1997	Norland Medical Systems
1998	Cargill
1998	Cargill
1998	Gene Logic
1998	IntroGene B.V.
1998	Medarex
1998	Myriad Genetics
1998	Pharmacopeia
1998	Ribozyme Pharmaceuticals
1998	Vertex
1998	Cytogen

Annex 3: Parameter setting in the history-friendly scenario

Table A 10: Parameter values history-friendly scenario

	Parameter	Description	Value
	t*	Revolution of molecular biology	period 50
	t**	Emergence of modern biotech.	period 75
Search Space			
	N in Eq. 1	Size (number of potential drugs)	1200
		Patent duration	20
*before t***	*a in Eq. 2*	Drugs' quality average	1000
*before t***	*b in Eq. 2*	Drugs' quality stand. dev.	200
*after t***	*a in Eq. 2*	Drugs' quality average	2500
*after t***	*b in Eq. 2*	Drugs' quality stand. dev	200
Technology adoption			
	η *in Eq. 16*	Scaling parameter	0.05
	υ *in Eq. 16*	Max. adoption costs	1
	θ	Decreasing rate of υ after adoption	0.9
Collaboration (after t)**			
	ϑ *in Eq. 20*	Rate of knowledge flow	0.05
	ν *in Eq. 18*	Scaling parameter	10
Innovation			
	μ *in Eq. 21*	Scaling parameter	0.08
Organisational capabilities			
for external learning	ω *in Eq. 10*	Degree of depreciation	0.8
Technology B	**Technology diminishing firm's error of observation in the search process**		
	θ^B *in Eq. 6*	Scaling parameter	1
	b1 in Eq. 6	Growth rate parameter	0.1
	b2 in Eq. 6	Growth rate parameter	0.5
*before t**	F_1^B *in Eq. 4*	Technological frontier (min. error)	1200
*after t**	F_2^B *in Eq. 4*	Technological frontier (min. error)	700
*after t***	F_3^B *in Eq. 4*	Technological frontier (min. error)	300
*before t**	φ_1^B *in Eq. 11*	Complexity of knowledge base	0.22
*after t**	φ_2^B *in Eq. 11*	Complexity of knowledge base	0.24
*after t***	φ_3^B *in Eq. 11*	Complexity of knowledge base	0.28
*before t***	δ_1^B *in Eq. 13*	Degree of depreciation (tec. capb)	0.03
*after t***	δ_2^B *in Eq. 13*	Degree of depreciation (tec. capb)	0.045
	ϕ^B in Eq. 7	Intra-industry spill-over rate	0.01
*before t**	z_1^B *in Eq. 7*	Volume of public research	1.5
*after t**	z_2^B *in Eq. 7*	Volume of public research	5

Table A 10 continued

	Parameter	Description	Value
Technology S	**Technology increasing firm's scope in the search process**		
	θ^S *in Eq. 5*	Scaling parameter	0.3
	a1in Eq. 5	TC function's parameter	0.1
	a2in Eq. 5	TC function's parameter	0.5
	F^S *in Eq. 4*	Technological frontier (max. scope)	400
	φ^S *in Eq. 11*	Complexity of knowledge base	0.22
	δ^S *in Eq. 13*	Degree of depreciation (tec. capb)	0.04
	z^S *in Eq. 7*	Volume of public research	3
Products			
	m_0 *in Eq. 24*	Scaling parameter in the merit function	0.001
	m_a *in Eq. 24*	Parameter in the merit function	1.4
	m_b *in Eq. 24*	Parameter in the merit function	1
	m_c *in Eq. 24*	Parameter in the merit function	0.2
	r_i *in Eq. 24*	Expected return on investment (imitation)	0.7
	r_i *in Eq. 24*	Expected return on investment (innovation)	0.8
	ρ *in Eq. 25*	Product's image erosion rate	0.01
Selection environment			
	ψ_t *in Eq. 26*	Budget of the health system to reward firms	30
	q^* *in Eq. 22*	Quality standard of the health system	1100

Table A 11 : Initial values of variables that need to be initialised

Variable	Description	Value		
Search Space				
	Firm's search start position in the search space	U (1,1200)		
Firm's investment decisions		**Firm Type**		
		TP	**DC**	**DBF**
β_{jt} *in Eq. 8*	Share of investment in learning	U(0.5,0.7)	U(0.5,0.7)	1
λ_{jt} *in Eq. 8*	Share of investment in external learning	U(0.1,0.2)	U(0.3,0.4)	1
α_{jt} *in Eq. 9*	Technological trajectory	U(0.3,0.5)	U(0.6,0.8)	0
Firm's level of capabilities		**Firm Type**		
		TP	**DC**	**DBF**
K^{S}_{jto} *in Eq. 13*	in chemical synthesis at t=0	10	40	0
K^{B}_{jto} *in Eq. 13*	in biotechnology at t=0	30	15	25
l^{E}_{jto} *in Eq. 10*	in external learning at t=0	1	1	1
Firm's technological position at entry		**Firm Type**		
		TP	**DC**	**DBF**
σ_{jt0} in Eq. 6	Technological level in biotechnology at t=0	1200	1500	300
S_{jt0} in Eq. 5	Technological level in chemical synthesis at t=0	100	300	50

Annex 4:
Model's source code

Lsd Model: History-Friendly Model German Pharmaceutical Industry Version 2.1

Summary

Object Structure

```
Root->Root2->World->Industry->Firm->Portfolio->Drug
                  |                |
                  |                ->Scope_Tech
                  |                |
                  |                ->Precision_Tech
                  |                |
                  |                ->Network->col
                  |
                  ->Space->Mol
                  |
                  ->Knowledge_Base
```

List of Variables:
Abs_P(0), Abs_S(0), Adoption_Draw(0), Alpha(0), B(1), beta(0), col_Knowl(0), Collaboration(0), Delete(0), Divorce(0), DK(0), DP(1), DP_SO(0), DS(1), DS_SO(0), Entry_DBF(0), Ex(0), F(0), Fi(0), Generics(0), I(0), Image(0), Init2(0), Innovation_Draw(0), K(0), KP(1), KP_Share(0), KS(1), KS_Share(0), L_Budget(0), lambda(0), LB_Invest(1), LB_KK(1), LB_KP(0), LB_KS(0), LC_KP(0), LW_Invest(1), LW_KP(0), LW_KS(0), M_Expend(0), Max_Drug_q(0), Max_Drug_q_Industry(0), Merit(0), P_Adoption_De_1(0), P_Adoption_De_2(0), P_Knowl(0), P_SO(0), Precision(1), Precision_Gap(0), Precision_r(1), Precision_TP(0), Precision_V(1), Precision_WA(0), R(0), Rational_Phase_Industry(0), Rational_Phase_Knowlbase(0), S_Adoption_De(0), S_Knowl(0), S_SO(0), Scope(1), Scope_Gap(0), Scope_New_Knowlbase(0), Scope_r(1), Scope_TP(0), Scope_V(1), Scope_WA(0), Search(0), Start(1), U_Firm(0), U_Industry(0), V(0), WI(0)

List of Parameters:
a1, a2, a_u, Alpha_dbf, Alpha_f, ap, Approval, b1, b2, b_u, beta_f, c_u, col_date, col_DBF, col_divorce, col_divorce_date, col_j, col_knowl_r, col_KP, col_LF, col_number, cp, CW, DBF_Number, distance, DP_SO_p, Drug_C, Drug_d, Drug_del, Drug_i, Drug_l, Drug_lp, Drug_M, Drug_phase, Drug_q, Drug_qo,

Drug_Type, DS_SO_p, DW, fda, Firm_Type, HSB, i, Ip, ip, j, lambda_dbf, lambda_f, Mode, Mol_d, Mol_phase, o_u, Oligopol_size, P_complex, P_complex_2, P_complex_3, P_F1, P_F2, P_F3, P_Knowl_firm, P_PR_1, P_PR_2, P_sc, P_sc_2, P_SO_r, P_SO_r_2, P_td_1, P_td_2, Pd, Portfolio_Size, Precision_Adoption_1, Precision_Adoption_1_Date, Precision_Adoption_2, Precision_Adoption_2_Date, Precision_Max, Precision_Theta, pwa_power, q, q_average1, q_average2, q_st_dv1, q_st_dv2, qo, rho, S_complex, S_complex_2, S_F1, S_F2, S_PR_1, S_PR_2, S_sc, S_sc_2, S_SO_r, S_td, Scope_Adoption, Scope_Adoption_Date, Scope_Min, Scope_Theta, Size, t_entry_DBF, U, v, v_decr_rate, VentCap

Equation File: **fun_HFM_2.1.cpp**

Object Root

Containing Objects: Root2
List of Variables: (no Variables)
List of Parameters: (no Parameters)

Object Root2

Contained in Object: Root
Containing Objects: World
List of Variables: (no Variables)
List of Parameters: (no Parameters)
Description
This Object has been created to be able to build averages of 100 simulation runs. The implementation includes 100 Worlds and the main variables are analysed by creating average results of the 100 Worlds

'Root2' appears in the equation for: (Never Used).

Object World

Contained in Object: Root->Root2
Containing Objects: Industry, Space, Knowledge_Base
List of Variables: (no Variables)

List of Parameters: (no Parameters)
Description
This is the largest object in the model.

'World' appears in the equation for: (Never Used).

Object Industry

Contained in Object: Root->Root2->World
Containing Objects: Firm
List of Variables: Alpha(0), beta(0), Collaboration(0), Delete(0), Divorce(0), DK(0), DP(1), DS(1), Entry_DBF(0), Fi(0), Image(0), lambda(0), Max_Drug_q_Industry(0), Merit(0), Rational_Phase_Industry(0), Search(0), U_Industry(0)
List of Parameters: Alpha_dbf, col_knowl_r, DBF_Number, HSB, lambda_dbf, Mode, Oligopol_size, P_SO_r, P_SO_r_2, rho, S_SO_r, t_entry_DBF, VentCap
Description
The object industry includes incumbent companies developing products with therepeutic properties (drugs). The industry presents different types of firms according to their learning strategies (in terms of learning within the firm and beyond the firm), size and their technological strategies.

'Industry' appears in the equation for: (Never Used).

Object	Label	Comment
Industry	Mode (P)	'Mode' appears in the equation for: I. Innovation can be deterministic (Mode=0) or the result of a random process (Mode=1) Init. values If Mode=0 innovation is a draw which depends on the level of capabilities of the firms. If Mode=1 all innovate.
Industry	Search (0)	Search is an equation at the level of the system activitated in every period. It concerns every firm and activates the marketing and discovery and development processes of the firms. The firms, by appliying their technologies Scope and Precision, explore the search space of molecules to find the molecule with the best characteristics (highest quality) to develop a drug. If a drug is developed, marketing expenditures take place.

		'Search' appears in the equation for: (Never Used).
Industry	Fi (0)	Budget of the health system to reward firms 'Fi' appears in the equation for: R.
Industry	HSB (P)	Budget of the health system to reward firms 'HSB' appears in the equation for: Fi. Init. values The value is set to 30. This parameter is a huge simplification of the demand side of the system
Industry	DS (1)	Scope capabilities (Technology S) at industry level. The capabilities of the DBFs are not computed. Only the capabilities og incumbent firms. 'DS' appears in the equation for: DK. Init. values
Industry	DP (1)	Precision capabilities (Technology B) at industry level. The capabilities of the DBFs are not computed. Only the capabilities og incumbent firms. 'DP' appears in the equation for: DK. Init. values
Industry	U_Industry (0)	Total drug merit in the industry 'U_Industry' appears in the equation for: F.
Industry	rho (P)	Rate of erotion of the image of the drug. 'rho' appears in the equation for: Image. Init. values
Industry	Merit (0)	This action update of the merit values of the drugs. The Merit function is a simplified version of Malerba & Orseniigo (2002), p.681 Merit= (TrueQuality)^a*(1/roi)^b*(MarkInvest)^c a=(1.2;1.4) like in Malerba (2002) b=(1.0;1.2) c=(0.1;0.2) roi=0.8 (in Malerba 0.2) for innovative

		products roi=0.7 (in Malerba 0.1) for immitative products roi is desired return of investment. Other things beeing equal, the higher ri, the will be the price and the lower the demand Annual Marketing invest-ment=LaunchCamp/20 'Merit' appears in the equation for: Search.
Industry	Image (0)	This variable updates the image values of the drugs 'Image' appears in the equation for: Search.
Industry	S_SO_r (P)	Spillover rate (Technology S) 'S_SO_r' appears in the equation for: S_SO. Init. values
Industry	P_SO_r (P)	Spillover rate (Technology B) 'P_SO_r' appears in the equation for: P_SO. Init. values
Industry	DK (0)	Capabilities at industry level 'DK' appears in the equation for: (Never Used).
Industry	Oligopol_size (P)	Number of DBFs that enter the industry in the second discontinuity (emergence of modern biotechnology) 'Oligopol_size' appears in the equation for: Entry_DBF. Init. values
Industry	Rational_Phase_Industry (0)	The technological discontinuity (emergence of modern biotechnology) changes the cummulativeness of the capabilities. 'Rational_Phase_Industry' appears in the equation for: (Never Used).
Industry	P_SO_r_2 (P)	Spillover rate after the second discontinuity

		in technology B. In this version of the model the spillover rate does not change after the discontinuity. The parameter has strong inflluence on the results. 'P_SO_r_2' appears in the equation for: (Never Used). Init. values All 50 instances equal to 0.02.
Industry	Entry_DBF (0)	Entry of biotech companies. The function is computed only once and then it is transformed in a parameter and never computed again. This equation sets the search space of molecules availiable for the drug producers to discover and develop drugs. 'Entry_DBF' appears in the equation for: (Never Used).
Industry	DBF_Number (P)	Number of Dedicated Biotechnology Firms 'DBF_Number' appears in the equation for: Entry_DBF. Init. values
Industry	lambda_dbf (P)	Investment share dedicated to external learning by DBFs 'lambda_dbf' appears in the equation for: Entry_DBF. Init. values
Industry	Alpha_dbf (P)	Company's bet on the technology being worth developing 'Alpha_dbf' appears in the equation for: Entry_DBF. Init. values
Industry	t_entry_DBF (P)	Period of entry of DBF 't_entry_DBF' appears in the equation for: Entry_DBF, LC_KP, col_Knowl, Collaboration, Divorce. Init. values All 100 instances equal to 75.
Industry	VentCap (P)	Amount of venture capital availiable for DBFs in every period

		'VentCap' appears in the equation for: B. Init. values
Industry	Delete (0)	This equation deletes the drugs of the DBFs after they have been added to the structure of the model. The variable has been included because the entry of firms in the model is implemented by selecting a firm that already exists and creating similar objects. However, new firms do not have products when they enter the industry. 'Delete' appears in the equation for: Entry_DBF.
Industry	Collaboration (0)	Activates the search of LFs (Firm Type 1 or 2) for collaborative partners (Firm type 3). The search starts after the discontinuity at t=70 has taken place. 'Collaboration' appears in the equation for: Search.
Industry	Divorce (0)	Evaluates the possibility of a collaboration to terminate. The termination of collaboration is a stochastic process after updating the location of the frims in the search space and the engagement of the incumbent firm in interacting with its environment. 'Divorce' appears in the equation for: (Never Used).
Industry	col_knowl_r (P)	Rate of capabilities that are transferred from the DBF to the incumbent firm in every period if a collaboration takes place 'col_knowl_r' appears in the equation for: Collaboration, Divorce. Init. values All 100 instances equal to 0.05.
Industry	beta (0)	Investment share directed to learning 'beta' appears in the equation for: M_Expend, L_Budget.
Industry	Alpha (0)	Company's bet on the technology being developed

		'Alpha' appears in the equation for: LW_KS, LW_KP, Abs_S, Abs_P.
Industry	lambda (0)	Company's investment share in the technology being developed 'lambda' appears in the equation for: LW_Invest, LB_Invest.
Industry	Max_Drug_q_Industry (0)	Max drug quality in the industry 'Max_Drug_q_Industry' appears in the equation for: (Never Used).

Object Firm

Contained in Object: Root->Root2->World->Industry
Containing Objects: Portfolio, Scope_Tech, Precision_Tech, Network
List of Variables: Abs_P(0), Abs_S(0), Adoption_Draw(0), B(1), col_Knowl(0), DP_SO(0), DS_SO(0), Ex(0), F(0), I(0), Innovation_Draw(0), K(0), KP(1), KP_Share(0), KS(1), KS_Share(0), L_Budget(0), LB_Invest(1), LB_KK(1), LB_KP(0), LB_KS(0), LC_KP(0), LW_Invest(1), LW_KP(0), LW_KS(0), M_Expend(0), Max_Drug_q(0), P_Adoption_De_1(0), P_Adoption_De_2(0), P_SO(0), R(0), S_Adoption_De(0), S_SO(0), Start(1), U_Firm(0), V(0), WI(0)
List of Parameters: a_u, Alpha_f, ap, Approval, b_u, beta_f, c_u, col_number, cp, CW, distance, DP_SO_p, DS_SO_p, Firm_Type, ip, j, lambda_f, o_u, P_Knowl_firm, Portfolio_Size, v, v_decr_rate
Description
The Firms are the actors in the industry and the carriers of technology.
Firms are heterogenous and have bounded rationality.

'Firm' appears in the equation for: Entry_DBF, Delete, Search, Image, Merit, DS_SO, DP_SO, DS, DP, Collaboration, Divorce.

Object	Label	Comment
Firm	R (0)	Reward of the company in each period. It depends on the quality reached by the molecule of the company and on the budget of the health system. 'R' appears in the equation for: Entry_DBF, B.
Firm	Start (1)	Action that determines in each period the location in the search space to start the search for the molecule with the highest quality.

		'Start' appears in the equation for: Entry_DBF, Search, Start, Collaboration, Divorce. Init. values All 4 instances set to integer random values drawn from a uniform in the range [200,1200].
Firm	LW_Invest (1)	Investment in learning within the firm. 'LW_Invest' appears in the equation for: Entry_DBF, LW_KS, LW_KP. Init. values All 4 instances equal to 3.
Firm	LB_Invest (1)	Investment in learning beyond the firm 'LB_Invest' appears in the equation for: Entry_DBF, LB_K, LB_KK. Init. values All 4 instances equal to 3.
Firm	LB_KK (1)	Stock of capabilities for learning beyond the firm 'LB_KK' appears in the equation for: Entry_DBF, LB_KK, Abs_S, Abs_P, Scope_WA, Precision_WA, Collaboration, Divorce. Init. values All 8 instances equal to 1.
Firm	LW_KS (0)	Internal research investment in the Scope technology (Technology S) 'LW_KS' appears in the equation for: Entry_DBF, KS.
Firm	LW_KP (0)	Internal research investment in the Precision Technology (Technology B) 'LW_KP' appears in the equation for: Entry_DBF, KP.
Firm	LB_KS (0)	Capabilities in the scope technology through learning outside the firm in the scope technology. 'LB_KS' appears in the equation for: Entry_DBF, KS.
Firm	LB_KP (0)	Capabilities in the precision technology through learning outside the firm in the precision technology. 'LB_KP' appears in the equation for: Entry_DBF, KP.
Firm	KS (1)	Capabilities in the scope technology (Technology S). Inspired by Lerena & Oltra p. 9.The acummulation of capabilities is a weighted average of past and new capabilities.

		'KS' appears in the equation for: Entry_DBF, DS_SO, DS, KS, K, KS_Share, Scope_r. Init. values All 4 instances equal to 0.
Firm	KP (1)	Accumulation of Capabilities in the Precision Technology (Technology B) Inspired by Llerena et Oltra p. 9.The acummulation of capabilities is a weighted average of past and new capabilities. 'KP' appears in the equation for: Entry_DBF, DP_SO, DP, KP, K, KP_Share, Collaboration, Divorce, Precision_r. Init. values All 4 instances equal to 0.
Firm	K (0)	Accumulation of Capabilities in both technologies. 'K' appears in the equation for: Entry_DBF, KS_Share, KP_Share, WI.
Firm	KS_Share (0)	Share of scope capabilities (Technology S) within the firm 'KS_Share' appears in the equation for: Entry_DBF.
Firm	KP_Share (0)	Share of precision capabilities (Technology B) within tne firm 'KP_Share' appears in the equation for: Entry_DBF.
Firm	I (0)	Innovation can be dterministic (Mode 0) or the result of a random process (Mode 1). 'I' appears in the equation for: Entry_DBF, Search.
Firm	WI (0)	Probability to Innovate. Different options to model this function. 'WI' appears in the equation for: Entry_DBF, I.
Firm	Portfolio_Size (P)	Number of products in the product portfolio. The parameter is updated every period according to the performance of every firm. 'Portfolio_Size' appears in the equation for: Entry_DBF, Search. Init. values All 4 instances equal to 1.
Firm	U_Firm (0)	Quality of the drug portfolio (by adding up product quality).

		'U_Firm' appears in the equation for: Entry_DBF, U_Industry, F.
Firm	F (0)	Merit share of the firm. This equation is used as performance indicator and is used to compute the reward of the firm from the system. 'F' appears in the equation for: Entry_DBF, R.
Firm	ap (P)	Scalling parameter in the stochastic adoption decition 'ap' appears in the equation for: Scope_WA, Precision_WA. Init. values All 8 instances equal to 0.05.
Firm	ip (P)	Scalling parameter in the stochastic innovation process 'ip' appears in the equation for: WI. Init. values All 4 instances equal to 0.005.
Firm	v (P)	Initial Adoption Cost 'v' appears in the equation for: S_Adoption_De, P_Adoption_De_1, P_Adoption_De_2, Scope_WA, Precision_WA, Precision_V, Scope_V. Init. values All 8 instances equal to 1.
Firm	B (1)	Budget for the activities of the firm 'B' appears in the equation for: Entry_DBF, B, M_Expend, L_Budget, S_Adoption_De. Init. values All 4 instances equal to 10.
Firm	M_Expend (0)	Expenditures in marketing activities 'M_Expend' appears in the equation for: Entry_DBF, Search, Ex.
Firm	a_u (P)	Parameter weigting Quality in the "Merit" function of a product 'a_u' appears in the equation for: Merit. Init. values All 4 instances equal to 1.4.
Firm	b_u (P)	Parameter weigting return on investment (roi) in the "Merit" function of a product 'b_u' appears in the equation for: Merit. Init. values All 4 instances equal to 1.

Firm	c_u (P)	Parameter weighting Image in the Merit function 'c_u' appears in the equation for: Merit. Init. values All 4 instances equal to 0.2.
Firm	o_u (P)	Scalling parameter in the Merit function 'o_u' appears in the equation for: Merit. Init. values All 4 instances equal to 0.001.
Firm	Abs_P (0)	Absorptive capacity for knowledge in technology P (precision) 'Abs_P' appears in the equation for: Entry_DBF, LB_KP, LC_KP.
Firm	Abs_S (0)	Absorptive capacity for knowledge in technology B (Scope) 'Abs_S' appears in the equation for: Entry_DBF, LB_KS.
Firm	Approval (P)	The parameter is set to one if the development of a drug in the previous period has been accepted in the selection environment 'Approval' appears in the equation for: Search, Ex. Init. values All 4 instances equal to 1.
Firm	Ex (0)	Expenditures. Part of the budget that has been spent 'Ex' appears in the equation for: Entry_DBF, B.
Firm	V (0)	Total adoption costs v[1]=p->cal("Scope_V",0); In the version of the model without "Entry of firms of type 2" make sure that this is included in the costs 'V' appears in the equation for: Entry_DBF, Ex.
Firm	Adoption_Draw (0)	The adoption draw determines the adoption succes of the firm. It is the same for all the firms. It is located at the industry level. 'Adoption_Draw' appears in the equation for: Entry_DBF, S_Adoption_De, P_Adoption_De_1, P_Adoption_De_2.
Firm	S_Adoption_De (0)	Scope Adoption Decition. This function determines whether a firm adopts new echnological opportunities after a discontinuity in

		the knolwedge base has taken place. This function is located at the level of the firm. 'S_Adoption_De' appears in the equation for: (Never Used).
Firm	P_Adoption_De_1 (0)	Precision Adoption Decition. This function determines whether a firm adopts new technological opportunities after a technological discontinuity (the transition from random to rational search has taken place. This function is located at the firm level. 'P_Adoption_De_1' appears in the equation for: (Never Used).
Firm	j (P)	Firm identification number 'j' appears in the equation for: Entry_DBF, DS_SO, DP_SO, Scope_V, Collaboration, Divorce. Init. values
Firm	v_decr_rate (P)	Decreasing rate of adoption costs. After adoption has take place adoption costs decrease with time. 'v_decr_rate' appears in the equation for: Precision_V, Scope_V. Init. values
Firm	Innovation_Draw (0)	The innovation draw determines the innovation succes of the firm. It is the same for all the firms. It is located at the industry level. 'Innovation_Draw' appears in the equation for: Entry_DBF, I.
Firm	L_Budget (0)	Amount of buget dedicated to learning 'L_Budget' appears in the equation for: Entry_DBF, Ex, LW_Invest, LB_Invest, P_Adoption_De_1, P_Adoption_De_2.
Firm	Firm_Type (P)	Firms can be large incumbent firms (of type 1 and 2) and Dedicated Biotechnology firms (of type 3) 'Firm_Type' appears in the equation for: Entry_DBF, Delete, DS_SO, DP_SO, DS, DP, B, beta, lambda, Alpha, LW_KP, Abs_P, col_Knowl, V, Collaboration,

		Divorce. Init. values
Firm	col_number (P)	Number of collaborations an incumbent firm has enter into. DBFs can have one collaboration partner only. 'col_number' appears in the equation for: col_Knowl, Collaboration, Divorce. Init. values All 4 instances equal to 0.
Firm	cp (P)	Scalling parameter in the collaboration and divorce stochastic functions 'cp' appears in the equation for: Collaboration, Divorce. Init. values All 4 instances equal to 10.
Firm	LC_KP (0)	Capabilities in the precision technology develop through collaboration 'LC_KP' appears in the equation for: KP.
Firm	CW (P)	Probability to collaborate. Collaboration is an stochastic decition. 'CW' appears in the equation for: Collaboration. Init. values All 4 instances equal to 0.
Firm	distance (P)	Distance between the incumbent firm and the DBF. Collaboration decition pf incumbent firms considers the distance of the firms in the search space. 'distance' appears in the equation for: Collaboration. Init. values All 4 instances equal to 0.
Firm	col_Knowl (0)	Addition of firm's capabilities in the precision technology acquired through colaboration 'col_Knowl' appears in the equation for: LC_KP.
Firm	Max_Drug_q (0)	Quality reached by the best product 'Max_Drug_q' appears in the equation for: Entry_DBF, Max_Drug_q_Industry.
Firm	P_Knowl_firm (P)	Part of the knowledge base a firm has access to. The knolwedge base is firm specific. 'P_Knowl_firm' appears in the equation for: P_Knowl,

		Entry_DBF. Init. values All 4 instances equal to 0.
Firm	Alpha_f (P)	Parameter of DBF. Bet on the technology being worth developing. 'Alpha_f' appears in the equation for: Entry_DBF, Alpha. Init. values All 4 instances equal to 0.
Firm	beta_f (P)	Parameter of DBF Investment share directed to learning 'beta_f' appears in the equation for: Entry_DBF, beta. Init. values All 4 instances equal to 0.
Firm	lambda_f (P)	Parameter of DBF Investment share directed to external learning 'lambda_f' appears in the equation for: Entry_DBF, lambda. Init. values All 4 instances equal to 0.
Firm	DP_SO_p (P)	Knowledge freely avaliable in technology B (Precision) 'DP_SO_p' appears in the equation for: DP_SO, P_SO. Init. values All 8 instances equal to 0.
Firm	DS_SO_p (P)	Knowledge freely avaliable in technology S (Scope) 'DS_SO_p' appears in the equation for: DS_SO, S_SO. Init. values All 8 instances equal to 0.
Firm	DS_SO (0)	Precision capabilities at industry level without the capabilities of the DBFs. This variable updates the level of Technology S (Scope) spillovers each firm may have access to "DP_SO_p". These do not consider capabilities of the DBFs. 'DS_SO' appears in the equation for: (Never Used).
Firm	DP_SO (0)	Precision capabilities at industry level without the capabilities of the DBFs. This variable updates the level of Technology B (Precision) spillovers each firm may have access to "DP_SO_p". These do not consider capabilities of the DBFs. 'DP_SO' appears in the equation for: (Never Used).

Firm	P_SO (0)	Spilovers in the Precision Technolgy a firm receives in each period. These depend on the knowledge freely avaliable and on the rate of spillovers 'P_SO' appears in the equation for: P_Knowl.
Firm	S_SO (0)	Spilovers in the Scope Technolgy a firm receives in each period. These depend on the knowledge freely avaliable and on the rate of spillovers 'S_SO' appears in the equation for: S_Knowl.
Firm	P_Adoption_De_2 (0)	Precision Adoption Decition. This function determines whether the firm adopt a new form of technology after a technological discontinuity (the transition from random to rational search has taken place. This function is located at the firm level. 'P_Adoption_De_2' appears in the equation for: (Never Used).

Object Portfolio

Contained in Object: Root->Root2->World->Industry->Firm
Containing Objects: Drug
List of Variables: (no Variables)
List of Parameters: (no Parameters)
Description
This object includes the products developed by the firm. It inludes object "Drug" which are added to the object according to the innovation , immitation and development performance of the firm.

'Portfolio' appears in the equation for: Search, Image, Merit.

Object Drug

Contained in Object: Root->Root2->World->Industry->Firm->Portfolio

List of Variables: (no Variables)
List of Parameters: Drug_C, Drug_d, Drug_del, Drug_i, Drug_l, Drug_lp, Drug_M, Drug_phase, Drug_q, Drug_qo, Drug_Type, U
Description
Drug is the product of the firm.

'Drug' appears in the equation for: Entry_DBF, Delete, Search, Image, Merit.

Object	Label	Comment
Drug	Drug_q (P)	Quality of the drug 'Drug_q' appears in the equation for: Entry_DBF, Search, Merit, Max_Drug_q, Collaboration. Init. values All 4 instances set to integer random values drawn from a uniform in the range [1200,1400].
Drug	Drug_i (P)	Drug's identification parameter 'Drug_i' appears in the equation for: Search. Init. values All 4 instances equal to 0.
Drug	Drug_qo (P)	Observed quality of the drug 'Drug_qo' appears in the equation for: Search. Init. values All 4 instances equal to 500.
Drug	Drug_d (P)	Period of launching the drug 'Drug_d' appears in the equation for: Entry_DBF, Search, Image, Merit, Collaboration. Init. values All 4 instances equal to 0.
Drug	Drug_Type (P)	'Type of Drug (= 1 new drug, =2 imitation) Drug_Type' appears in the equation for: Entry_DBF, Search, Merit. Init. values All 4 instances equal to 1.
Drug	U (P)	Merit of the drug. The parameter is updated in every period according to the image, the expected return on investment and the quality 'U' appears in the equation for: Entry_DBF, Merit, U_Firm. Init. values All 4 instances set to random values drawn from a uniform in the range [35,40].
Drug	Drug_phase (P)	After the second discontinuity in technology B (Precision) the search space changes and new drugs are avaliable for discovery. This parameter gives the phase in which the drug can be discovered.

		'Drug_phase' appears in the equation for: Search. Init. values
Drug	Drug_C (P)	Image of the drug once developed 'Drug_C' appears in the equation for: Entry_DBF, Image, Merit. Init. values All 4 instances equal to 4.
Drug	Drug_M (P)	Marketing Budget of the drug in the period of launching 'Drug_M' appears in the equation for: Entry_DBF, Search, Image. Init. values All 4 instances equal to 4.
Drug	Drug_del (P)	Parameter to allow objects to be deleted if needed 'Drug_del' appears in the equation for: Delete, Search. Init. values
Drug	Drug_l (P)	Drug liscensed parameter. A drug can only be liscensed once. If ==1 the drug is already liscenced. 'Drug_l' appears in the equation for: Collaboration. Init. values All 4 instances equal to 0.
Drug	Drug_lp (P)	Licensing partner parameter in the object drug 'Drug_lp' appears in the equation for: Collaboration. Init. values All 4 instances equal to 0.

Object Scope_Tech

Contained in Object: Root->Root2->World->Industry->Firm
List of Variables: Scope(1), Scope_Gap(0), Scope_r(1), Scope_TP(0), Scope_V(1), Scope_WA(0)
List of Parameters: a1, a2, Scope_Adoption, Scope_Adoption_Date, Scope_Theta
Description
Firms are the carriers of technologies.
technologies ease the search process by allowing firms to approach the search space in a more effective way. The Scope technology (or technology S) represents organic chemical synthesis and determines the extension of the landscape of compounds a firm can access).

'Scope_Tech' appears in the equation for: S_Adoption_De.

Object	Label	Comment
Scope_Tech	Scope (1)	Technological achievement of the firm in the scope technology. Time and firm specific 'Scope' appears in the equation for: Entry_DBF, Search, Scope, Scope_TP, Scope_Gap. Init. values All 4 instances equal to 15.
Scope_Tech	Scope_Gap (0)	Technological Gap. Distance of the technological level of the firm to the technological frontier. 'Scope_Gap' appears in the equation for: Scope_r.
Scope_Tech	Scope_Theta (P)	Scalling Parameter 'Scope_Theta' appears in the equation for: Scope_r. Init. values All 4 instances equal to 0.01.
Scope_Tech	Scope_r (1)	Rate of technological change of the scope technology. The variable is time and firm specific. Log linear function. 'Scope_r' appears in the equation for: Entry_DBF, Scope. Init. values All 4 instances equal to 0.
Scope_Tech	a1 (P)	Parameter in the technological change function of Technology S (Scope). Weight of technological Gap 'a1' appears in the equation for: Scope_r. Init. values All 4 instances equal to 0.1.
Scope_Tech	a2 (P)	Parameter in the technological change function of Technology S (Scope). Weight of capabilities 'a2' appears in the equation for: Scope_r. Init. values All 4 instances equal to 0.4.
Scope_Tech	Scope_TP (0)	Fraction of the distance to the technologi-

		cal frontier cover by the firm 'Scope_TP' appears in the equation for: Scope_WA.
Scope_Tech	Scope_WA (0)	Fraction of the distance to the technological frontier cover by the firm 'Scope_WA' appears in the equation for: S_Adoption_De.
Scope_Tech	Scope_Adoption (P)	Parameter signalling that the firm has perceived and adopted the technological opportunities offered by the discontinuity in the Scope technology. NOTE: This version of the model does not include any discontinuity in technology S 'Scope_Adoption' appears in the equation for: S_Knowl, Entry_DBF, S_Adoption_De, Scope_V, Scope, Scope_TP, Scope_Gap. Init. values
Scope_Tech	Scope_V (1)	The adoption expenditures for adopting advances in the scope technology. NOTE: This version of the model does not include any discontinuity in the Scope technology 'Scope_V' appears in the equation for: Scope_V. Init. values All 4 instances equal to 0.
Scope_Tech	Scope_Adoption_Date (P)	Date of adoption of the new technological opportunities in technology S 'Scope_Adoption_Date' appears in the equation for: S_Adoption_De, Scope_V. Init. values All 8 instances equal to 150.

Object Precision_Tech

Contained in Object: Root->Root2->World->Industry->Firm
List of Variables: Precision(1), Precision_Gap(0), Precision_r(1),

Precision_TP(0), Precision_V(1), Precision_WA(0)
List of Parameters: b1, b2, Precision_Adoption_1, Precision_Adoption_1_Date, Precision_Adoption_2, Precision_Adoption_2_Date, Precision_Theta, pwa_power
Description
'Precision_Tech' appears in the equation for: P_Adoption_De_1, P_Adoption_De_2.

Object	Label	Comment
Precision_Tech	Precision (1)	Technological Level of the firm in technology B (Precision). Firm and time specific 'Precision' appears in the equation for: Entry_DBF, Search, Precision, Precision_TP, Precision_Gap. Init. values All 4 instances equal to 1001.
Precision_Tech	Precision_Gap (0)	Precision Technological Gap. Distance to the technological frontier of the technology B. 'Precision_Gap' appears in the equation for: Precision_r.
Precision_Tech	Precision_Theta (P)	Scalling parameter in the function of technological change of technology B 'Precision_Theta' appears in the equation for: Precision_r. Init. values All 12 instances equal to 0.1.
Precision_Tech	Precision_r (1)	Rate of technological change in the precision technology. The variable is time and firm specific. Log linear function. If the min Precision is 1000 and the simulation has 100 runs I need a change of about 1% (0.01) a nd 2% (0.02)per period. 'Precision_r' appears in the equa-

		tion for: Entry_DBF, Precision. Init. values All 4 instances equal to 0.
Precision_Tech	b1 (P)	Parameter in the technological change function 'b1' appears in the equation for: Precision_r. Init. values All 4 instances equal to 0.3.
Precision_Tech	b2 (P)	Parameter in the technological change function 'b2' appears in the equation for: Precision_r. Init. values All 4 instances equal to 0.5.
Precision_Tech	Precision_TP (0)	Fraction of the distance to the frontier cover by the firm 'Precision_TP' appears in the equation for: Entry_DBF, Precision_WA.
Precision_Tech	Precision_WA (0)	The probability of adopting a technology after a technological discontinuity is a function of the level of capabilities in external learning, the technological position of the firm in the technology applied 'Precision_WA' appears in the equation for: Entry_DBF, P_Adoption_De_1, P_Adoption_De_2.
Precision_Tech	Precision_Adoption_1 (P)	Parameter signalling that the firm has perceived and adopted the technological opportunities offered by the discontinuity in technology B. 'Precision_Adoption_1' appears in the equation for: P_Knowl,

		Entry_DBF, P_Adoption_De_1, Precision_V, Precision, Precision_TP, Precision_Gap. Init. values All 8 instances equal to 0.
Precision_Tech	Precision_V (1)	The adoption expenditures for adopting advances in the precision technology 'Precision_V' appears in the equation for: Precision_V, V. Init. values
Precision_Tech	pwa_power (P)	Parameter in the stochastic adoption function. 'pwa_power' appears in the equation for: Precision_WA. Init. values All 4 instances equal to 2.
Precision_Tech	Precision_Adoption_1_Date (P)	Period for the first technological discontinuity in technolohy B 'Precision_Adoption_1_Date' appears in the equation for: P_Adoption_De_1, Precision_V. Init. values All 8 instances equal to 0.
Precision_Tech	Precision_Adoption_2 (P)	Parameter signalling that the firm has perceived and adopted the technological opportunities offered by the discontinuity in technology B. 'Precision_Adoption_2' appears in the equation for: Entry_DBF, Search, P_Adoption_De_2, Collaboration, Precision, Precision_TP, Precision_Gap. Init. values All 8 instances equal to 0.
Precision_Tech	Precision_Adoption_2_Date (P)	Period adopting the new technological opportunities after the second technological discontinuity.

		'Precision_Adoption_2_Date' appears in the equation for: P_Adoption_De_2. Init. values All 8 instances equal to 0.

Object Network

Contained in Object: Root->Root2->World->Industry->Firm
Containing Objects: col
List of Variables: (no Variables)
List of Parameters: (no Parameters)
Description
'Network' appears in the equation for: Collaboration, Divorce.

Object col

Contained in Object: Root->Root2->World->Industry->Firm->Network
List of Variables: (no Variables)
List of Parameters: col_date, col_DBF, col_divorce, col_divorce_date, col_j, col_KP, col_LF, DW
Description
'col' appears in the equation for: Collaboration, Divorce.

Object	Label	Comment
col	col_LF (P)	Id of the LF in the collaboration 'col_LF' appears in the equation for: Collaboration. Init. values All 40 instances equal to 0.
col	col_date (P)	Period the collaboration begins 'col_date' appears in the equation for: Collaboration, Divorce. Init. values All 40 instances equal to -1.
col	col_KP (P)	Capabilities in technology B (precision) transferred from the DBF to the LF in a collaboration

		'col_KP' appears in the equation for: col_Knowl, Collaboration, Divorce. Init. values All 40 instances equal to 0.
col	col_j (P)	'col_j' appears in the equation for: (Never Used). Init. values All 40 instances equal to 0.
col	col_DBF (P)	Id of the DBF in the collaboration 'col_DBF' appears in the equation for: Collaboration, Divorce. Init. values All 40 instances equal to 0.
col	col_divorce_date (P)	Period the collaboration ends 'col_divorce_date' appears in the equation for: Divorce. Init. values All 40 instances equal to 0.
col	DW (P)	The termination of a collaboration is a stochastic process. This is the probability that a collaboration terminates. Divorce is proofed every period. 'DW' appears in the equation for: Divorce. Init. values All 40 instances equal to 0.
col	col_divorce (P)	Parameter updated if the collaboration has elready ended up 'col_divorce' appears in the equation for: Divorce. Init. values All 40 instances equal to 0.

Object Space

Contained in Object: Root->Root2->World
Containing Objects: Mol
List of Variables: Generics(0), Init2(0)
List of Parameters: fda, Pd, Size
Description
Firms face a search space where they search for molecules to imitate or discover and develop into drugs.

'Space' appears in the equation for: (Never Used).

Object	Label	Comment
Space	Init2 (0)	Technical initialization function. It is computed only once and then it is transformed in a parameter and never computed again. This equation sets the search space of molecules availiable for the drug producers to discover and develop drugs. 'Init2' appears in the equation for: (Never Used).
Space	Size (P)	Number of incumbent firms in the industry 'Size' appears in the equation for: Init2, Search, Start. Init. values All 1 instances equal to 0.
Space	Pd (P)	Patent duration. This parameter determines the number of period a potential drug remains protected after discovery. 'Pd' appears in the equation for: Generics. Init. values
Space	Generics (0)	This action explores the search space every time is activated in order to vary the parameter Ip according to the statuts of the molecule (discovered or not) and if appropiate (according to the patent duration parameter) transform it into a drug that can be imitated. 'Generics' appears in the equation for: Search.
Space	fda (P)	Minimum quality level that a product needs to reach in order to be introduced in the market. 'fda' appears in the equation for: Search. Init. values

Object Mol

Contained in Object: Root->Root2->World->Space
List of Variables: (no Variables)
List of Parameters: i, Ip, Mol_d, Mol_phase, q, q_average1, q_average2, q_st_dv1, q_st_dv2, qo
Description
This object represents the molecules in the search space the firms move in. Molecules can be discovered or picked up for imitation.

'Mol' appears in the equation for: Init2, Generics, Search.

Object	Label	Comment
Mol	Ip (P)	The parameter gives statuts of the molecule (discovered or not) 'Ip' appears in the equation for: Init2, Generics, Search. Init. values
Mol	i (P)	Identification Parameter of the Molecule 'i' appears in the equation for: Init2, Search. Init. values
Mol	q_average1 (P)	Average quality of the molecules in phases 1 and 2 of the industry 'q_average1' appears in the equation for: Init2. Init. values
Mol	q_st_dv1 (P)	Standard deviation of the quality of the molecules in phases 1 and 2 of the industry 'q_st_dv1' appears in the equation for: Init2. Init. values All 100 instances equal to 500.
Mol	q (P)	Quality of the molecules asigned through an stochastic porcess at the beginning of the simulation 'q' appears in the equation for: Init2, Search. Init. values
Mol	qo (P)	Observed quality of the molecules (frim specific) 'qo' appears in the equation for: Search. Init. values
Mol	Mol_d (P)	Date of discovers of the molecule (relevant for the patent protection) 'Mol_d' appears in the equation for: Init2, Generics, Search. Init. values
Mol	Mol_phase (P)	Phase in which the molecule can be discovered (After the second discontinuity in the Precision Technology new molecules are avaliable) 'Mol_phase' appears in the equation for: Init2, Search. Init. values
Mol	q_average2 (P)	Average quality of the molecules in phase 3 of the industry 'q_average2' appears in the equation for: Init2.

		Init. values
Mol	q_st_dv2 (P)	Standard deviation of the quality of the molecules in phase 3 of the industry 'q_st_dv2' appears in the equation for: Init2. Init. values

---

Object Knowledge_Base

Contained in Object: Root->Root2->World
List of Variables: P_Knowl(0), Rational_Phase_Knowlbase(0), S_Knowl(0), Scope_New_Knowlbase(0)
List of Parameters: P_complex, P_complex_2, P_complex_3, P_F1, P_F2, P_F3, P_PR_1, P_PR_2, P_sc, P_sc_2, P_td_1, P_td_2, Precision_Max, S_complex, S_complex_2, S_F1, S_F2, S_PR_1, S_PR_2, S_sc, S_sc_2, S_td, Scope_Min
Description
The knolwedge base represents knowledge underlying technological development. Each technology has a specific knowledge base, which develops with the intra-industry spill-overs and the contributions from science and technology

of the firms 'Knowledge_Base' appears in the equation for: (Never Used).

Object	Label	Comment
Knowledge_Base	S_PR_1 (P)	Contribution to the knowledge base of technology S of public research before a discontinuity 'S_PR_1' appears in the equation for: S_Knowl. Init. values
Knowledge_Base	P_PR_1 (P)	Contribution to the knowledge base of technology B of public research before the discontinuity 'P_PR_1' appears in the equation for: P_Knowl. Init. values
Knowledge_Base	S_PR_2 (P)	Contribution to the knowledge base of technology S of public research after a discontinuity

		'S_PR_2' appears in the equation for: S_Knowl. Init. values
Knowledge_Base	P_PR_2 (P)	Contribution to the knowledge base of technology B of public research after the discontinuity 'P_PR_2' appears in the equation for: P_Knowl. Init. values
Knowledge_Base	S_F1 (P)	Technological Frontier of technology S after the first technological discontinuity. NOTE: This version of the model doea not include any discontinuities in technology S 'S_F1' appears in the equation for: Scope, Scope_TP, Scope_Gap. Init. values
Knowledge_Base	S_F2 (P)	Technological Frontier of technology S after the second technological discontinuity. NOTE: This version of the model doea not include any discontinuities in technology S 'S_F2' appears in the equation for: Scope, Scope_TP, Scope_Gap. Init. values
Knowledge_Base	P_F1 (P)	Technological Frontier of technology B after the first technological discontinuity 'P_F1' appears in the equation for: Precision, Precision_TP, Precision_Gap. Init. values All 1 instances equal to 998.
Knowledge_Base	P_F2 (P)	Technological Frontier of

		technology B after the second technological discontinuity 'P_F2' appears in the equation for: Precision, Precision_TP, Precision_Gap. Init. values All 2 instances equal to 500.
Knowledge_Base	S_td (P)	Period of the discontinuity in technology S. NOTE: This version of the model does not include any discontinuities in this technologies. 'S_td' appears in the equation for: Scope_New_Knowlbase, S_Adoption_De Init. values All 1 instances equal to 250.
Knowledge_Base	P_td_2 (P)	Period of the second discontinuity in technology P. 'P_td_2' appears in the equation for: Rational_Phase_Knowlbase, Rational_Phase_Industry, Search, P_Adoption_De_2. Init. values All 2 instances equal to 75.
Knowledge_Base	P_td_1 (P)	Period of the first discontinuity in technology P. 'P_td_1' appears in the equation for: Rational_Phase_Knowlbase, P_Adoption_De_1, Precision. Init. values All 1 instances equal to 250.
Knowledge_Base	Rational_Phase_Knowlbase (0)	The technological discontinuity with the revolution of molecular biology in the 1950s. Transition to rational drug discovery. 'Rational_Phase_Knowlbase'

		appears in the equation for: (Never Used).
Knowledge_Base	Scope_New_Knowlbase (0)	The technological discontinuity in the scope technology produces changes in the knowledge base. 'Scope_New_Knowlbase' appears in the equation for: (Never Used).
Knowledge_Base	Scope_Min (P)	Minimum level of technological achievement in technology S. 'Scope_Min' appears in the equation for: Scope_TP. Init. values
Knowledge_Base	Precision_Max (P)	Minimum level of technological achievement in technology P. 'Precision_Max' appears in the equation for: Precision_TP. Init. values
Knowledge_Base	S_Knowl (0)	Knowledge base underlying the scope technology. It is firm specific in the sense that it depends on whether the companies have perceived scientific advances or not. 'S_Knowl' appears in the equation for: LB_KS.
Knowledge_Base	P_Knowl (0)	Knowledge base underlying the precision technology. It is firm specific in the sense that it depends on whether the companies have perceived scientific advances or not. 'P_Knowl' appears in the equation for: LB_KP.
Knowledge_Base	S_complex (P)	Complexity of the knolwedge base underlying technology S

		'S_complex' appears in the equation for: Scope_New_Knowlbase, Abs_S. Init. values
Knowledge_Base	S_complex_2 (P)	Complexity of the knowledeg base underlying technology S after the technological discontinuity 'S_complex_2' appears in the equation for: Scope_New_Knowlbase. Init. values
Knowledge_Base	P_complex (P)	Complexity of the knolwedge base underlying technology B 'P_complex' appears in the equation for: Rational_Phase_Knowlbase, Abs_P. Init. values All 100 instances equal to 0.22.
Knowledge_Base	P_complex_2 (P)	Complexity of the knowledeg base underlying technology B after the technological discontinuity 'P_complex_2' appears in the equation for: Rational_Phase_Knowlbase. Init. values All 100 instances equal to 0.24.
Knowledge_Base	S_sc (P)	Speed of change (due to scientific advances) of the knowledge base underlying Technology S 'S_sc' appears in the equation for: Scope_New_Knowlbase, KS. Init. values
Knowledge_Base	S_sc_2 (P)	Speed of change (due to scien-

		tific advances) of the knowledge base underlying Technology S after the technological discontinuity 'S_sc_2' appears in the equation for: Scope_New_Knowlbase. Init. values
Knowledge_Base	P_sc (P)	Speed of change (due to scientific advances) of the knolwedge base underlying technology B 'P_sc' appears in the equation for: Rational_Phase_Industry, KP. Init. values
Knowledge_Base	P_sc_2 (P)	Speed of change (due to scientific advances) of the knowledeg base underlying Technology B after the technological discontinuity 'P_sc_2' appears in the equation for: Rational_Phase_Knowlbase, Rational_Phase_Industry. Init. values
Knowledge_Base	P_F3 (P)	Technological Frontier of technology B after the second technological discontinuity. 'P_F3' appears in the equation for: Precision, Precision_TP, Precision_Gap. Init. values All 2 instances equal to 300.
Knowledge_Base	P_complex_3 (P)	Complexity of the knowledeg base underlying technology B after the second technological discontinuity 'P_complex_3' appears in the equation for: Ra-

		tional_Phase_Knowlbase. Init. values All 50 instances equal to 0.28.

Initial Values

Object Structure

```
Root->Root2->World->Industry->Firm->Portfolio->Drug
                  |                |
                  |                ->Scope_Tech
                  |                |
                  |                ->Precision_Tech
                  |                |
                  |                ->Network->col
                  |
                  ->Space->Mol
                  |
                  ->Knowledge_Base
```

List of Variables:
B(1), DP(1), DS(1), KP(1), KS(1), LB_Invest(1), LB_KK(1), LW_Invest(1), Precision(1), Precision_r(1), Precision_V(1), Scope(1), Scope_r(1), Scope_V(1), Start(1)

List of Parameters:
a1, a2, a_u, Alpha_dbf, Alpha_f, ap, Approval, b1, b2, b_u, beta_f, c_u, col_date, col_DBF, col_divorce, col_divorce_date, col_j, col_knowl_r, col_KP, col_LF, col_number, cp, CW, DBF_Number, distance, DP_SO_p, Drug_C, Drug_d, Drug_del, Drug_i, Drug_l, Drug_lp, Drug_M, Drug_phase, Drug_q, Drug_qo, Drug_Type, DS_SO_p, DW, fda, Firm_Type, HSB, i, Ip, ip, j, lambda_dbf, lambda_f, Mode, Mol_d, Mol_phase, o_u, Oligopol_size, P_complex, P_complex_2, P_complex_3, P_F1, P_F2, P_F3, P_Knowl_firm, P_PR_1, P_PR_2, P_sc, P_sc_2, P_SO_r, P_SO_r_2, P_td_1, P_td_2, Pd, Portfolio_Size, Precision_Adoption_1, Precision_Adoption_1_Date, Precision_Adoption_2, Precision_Adoption_2_Date, Precision_Max, Precision_Theta, pwa_power, q, q_average1, q_average2, q_st_dv1, q_st_dv2, qo, rho, S_complex, S_complex_2, S_F1, S_F2, S_PR_1, S_PR_2, S_sc, S_sc_2, S_SO_r, S_td, Scope_Adoption, Scope_Adoption_Date, Scope_Min, Scope_Theta, Size, t_entry_DBF, U, v, v_decr_rate, VentCap

---

Object Industry Total instances = 1

Label	Initial values
Mode (P)	0
HSB (P)	30
DS Lag(1)	0
DP Lag(1)	0
rho (P)	0.01
S_SO_r (P)	0.01

P_SO_r (P)	0.01
Oligopol_size (P)	4
P_SO_r_2 (P)	0.01
DBF_Number (P)	10
lambda_dbf (P)	1
Alpha_dbf (P)	0
t_entry_DBF (P)	75
VentCap (P)	0.1
col_knowl_r (P)	0.05

Object Firm Total instances = 4

Label	Initial values
Start Lag(1)	616 292 957 730
LW_Invest Lag(1)	3 3 3 3
LB_Invest Lag(1)	3 3 3 3
LB_KK Lag(1)	1 1 1 1
KS Lag(1)	10 10 40 40
KP Lag(1)	30 30 15 15
Portfolio_Size (P)	1 1 1 1
ap (P)	0.05 0.05 0.05 0.05
ip (P)	0.005 0.005 0.005 0.005
v (P)	1 1 1 1
B Lag(1)	10 10 10 10
a_u (P)	1.4 1.4 1.4 1.4
b_u (P)	1 1 1 1
c_u (P)	0.2 0.2 0.2 0.2
o_u (P)	0.001 0.001 0.001 0.001
Approval (P)	1 1 1 1
j (P)	1 2 3 4
v_decr_rate (P)	0.9 0.9 0.9 0.9
Firm_Type (P)	1 1 2 2
col_number (P)	0 0 0 0
cp (P)	10 10 10 10
CW (P)	0 0 0 0

distance (P)	0 0 0 0
P_Knowl_firm (P)	0 0 0 0
Alpha_f (P)	0 0 0 0
beta_f (P)	0 0 0 0
lambda_f (P)	0 0 0 0
DP_SO_p (P)	0 0 0 0
DS_SO_p (P)	0 0 0 0

Object Drug Total instances = 4

Label	Initial values
Drug_q (P)	1205 1327 1296 1245
Drug_i (P)	1 1 1 1
Drug_qo (P)	500 500 500 500
Drug_d (P)	0 0 0 0
Drug_Type (P)	1 1 1 1
U (P)	37.0113 37.7765 38.3254 37.5898
Drug_phase (P)	0 0 0 0
Drug_C (P)	4 4 4 4
Drug_M (P)	4 4 4 4
Drug_del (P)	0 0 0 0
Drug_l (P)	0 0 0 0
Drug_lp (P)	0 0 0 0

Object Scope_Tech Total instances = 4

Label	Initial values
Scope Lag(1)	100 100 300 300
Scope_Theta (P)	0.3 0.3 0.3 0.3
Scope_r Lag(1)	0 0 0 0
a1 (P)	0.1 0.1 0.1 0.1
a2 (P)	0.5 0.5 0.5 0.5
Scope_Adoption (P)	1 1 1 1
Scope_V Lag(1)	0 0 0 0
Scope_Adoption_Date (P)	150 150 150 150

Object Precision_Tech Total instances = 4

Label	Initial values
Precision Lag(1)	1200 1200 1500 1500
Precision_Theta (P)	0.1 0.1 0.1 0.1
Precision_r Lag(1)	0 0 0 0
b1 (P)	0.3 0.3 0.3 0.3
b2 (P)	0.5 0.5 0.5 0.5
Precision_Adoption_1 (P)	0 0 0 0
Precision_V Lag(1)	0 0 0 0
pwa_power (P)	2 2 2 2
Precision_Adoption_1_Date (P)	0 0 0 0
Precision_Adoption_2 (P)	0 0 0 0
Precision_Adoption_2_Date (P)	0 0 0 0

Object col Total instances = 4

Label	Initial values
col_LF (P)	0 0 0 0
col_date (P)	-1 -1 -1 -1
col_KP (P)	0 0 0 0
col_j (P)	0 0 0 0
col_DBF (P)	0 0 0 0
col_divorce_date (P)	0 0 0 0
DW (P)	0 0 0 0
col_divorce (P)	0 0 0 0

Object Space Total instances = 1

Label	Initial values
Size (P)	1200
Pd (P)	20
fda (P)	1100

Object Mol Total instances = 1

Label	Initial values
lp (P)	0
i (P)	1
q_average1 (P)	1000
q_st_dv1 (P)	500
q (P)	0
qo (P)	0
Mol_d (P)	1000
Mol_phase (P)	1
q_average2 (P)	2500
q_st_dv2 (P)	500

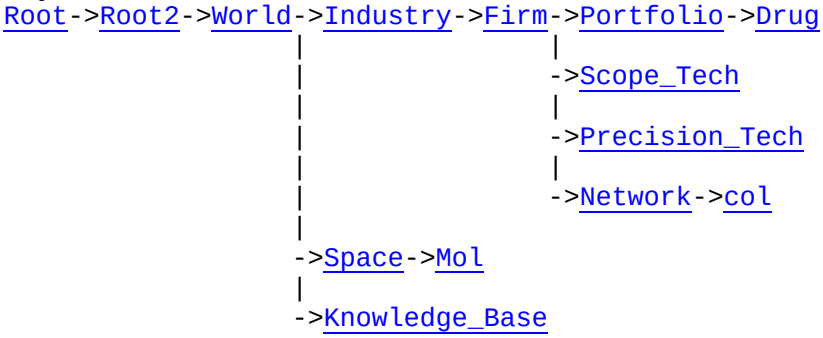
Object Knowledge_Base Total instances = 1

Label	Initial values
S_PR_1 (P)	2
P_PR_1 (P)	2
S_PR_2 (P)	3
P_PR_2 (P)	5
S_F1 (P)	400
S_F2 (P)	800
P_F1 (P)	1200
P_F2 (P)	700
S_td (P)	0
P_td_2 (P)	75
P_td_1 (P)	50
Scope_Min (P)	3
Precision_Max (P)	1500
S_complex (P)	0.22
S_complex_2 (P)	0.22
P_complex (P)	0.22
P_complex_2 (P)	0.24
S_sc (P)	0.04

S_sc_2 (P)	0.04
P_sc (P)	0.04
P_sc_2 (P)	0.045
P_F3 (P)	300
P_complex_3 (P)	0.26

Detailed Description

Object Structure



List of Variables:
Abs_P(0), Abs_S(0), Adoption_Draw(0), Alpha(0), B(1), beta(0), col_Knowl(0), Collaboration(0), Delete(0), Divorce(0), DK(0), DP(1), DP_SO(0), DS(1), DS_SO(0), Entry_DBF(0), Ex(0), F(0), Fi(0), Generics(0), I(0), Image(0), Init2(0), Innovation_Draw(0), K(0), KP(1), KP_Share(0), KS(1), KS_Share(0), L_Budget(0), lambda(0), LB_Invest(1), LB_KK(1), LB_KP(0), LB_KS(0), LC_KP(0), LW_Invest(1), LW_KP(0), LW_KS(0), M_Expend(0), Max_Drug_q(0), Max_Drug_q_Industry(0), Merit(0), P_Adoption_De_1(0), P_Adoption_De_2(0), P_Knowl(0), P_SO(0), Precision(1), Precision_Gap(0), Precision_r(1), Precision_TP(0), Precision_V(1), Precision_WA(0), R(0), Rational_Phase_Industry(0), Rational_Phase_Knowlbase(0), S_Adoption_De(0), S_Knowl(0), S_SO(0), Scope(1), Scope_Gap(0), Scope_New_Knowlbase(0), Scope_r(1), Scope_TP(0), Scope_V(1), Scope_WA(0), Search(0), Start(1), U_Firm(0), U_Industry(0), V(0), WI(0)

List of Parameters:
a1, a2, a_u, Alpha_dbf, Alpha_f, ap, Approval, b1, b2, b_u, beta_f, c_u, col_date, col_DBF, col_divorce, col_divorce_date, col_j, col_knowl_r, col_KP, col_LF, col_number, cp, CW, DBF_Number, distance, DP_SO_p, Drug_C, Drug_d, Drug_del, Drug_i, Drug_l, Drug_lp, Drug_M, Drug_phase, Drug_q, Drug_qo, Drug_Type, DS_SO_p, DW, fda, Firm_Type, HSB, i, Ip, ip, j, lambda_dbf, lambda_f, Mode, Mol_d, Mol_phase, o_u, Oligopol_size, P_complex, P_complex_2, P_complex_3, P_F1, P_F2, P_F3, P_Knowl_firm, P_PR_1, P_PR_2, P_sc, P_sc_2, P_SO_r, P_SO_r_2, P_td_1, P_td_2, Pd, Portfolio_Size, Precision_Adoption_1, Precision_Adoption_1_Date, Precision_Adoption_2, Precision_Adoption_2_Date, Precision_Max, Precision_Theta, pwa_power, q, q_average1, q_average2, q_st_dv1, q_st_dv2, qo, rho, S_complex, S_complex_2, S_F1, S_F2, S_PR_1, S_PR_2, S_sc, S_sc_2, S_SO_r, S_td, Scope_Adoption, Scope_Adoption_Date, Scope_Min, Scope_Theta, Size, t_entry_DBF, U, v, v_decr_rate, VentCap

Object Root

Containing: Root2
List of Variables: (no Variables)
List of Parameters: (no Parameters)

Object Root2

Contained in Object: Root
Containing: World
List of Variables: (no Variables)
List of Parameters: (no Parameters)

Object World

Contained in Object: Root->Root2
Containing: Industry Space Knowledge_Base
List of Variables: (no Variables)
List of Parameters: (no Parameters)

Object Industry

Contained in Object: Root->Root2->World
Containing: Firm
List of Variables: Alpha(0), beta(0), Collaboration(0), Delete(0), Divorce(0), DK(0), DP(1), DS(1), Entry_DBF(0), Fi(0), Image(0), lambda(0), Max_Drug_q_Industry(0), Merit(0), Rational_Phase_Industry(0), Search(0), U_Industry(0)
List of Parameters: Alpha_dbf, col_knowl_r, DBF_Number, HSB, lambda_dbf, Mode, Oligopol_size, P_SO_r, P_SO_r_2, rho, S_SO_r, t_entry_DBF, VentCap

Parameter **Mode**
In Object Industry
Used in: I
Go to: Description, Initial values, Model Structure

Variable **Search**
In Object Industry
Used in: (never used)
Using: Merit Image Collaboration Start I Portfolio_Size M_Expend Approval Drug_q Drug_i Drug_go Drug_d Drug_Type Drug_phase Drug_M Drug_del Scope Precision Precision_Adoption_2 Size Generics fda Ip i g go Mol_d Mol_phase P_td_2
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Search"))
{

/*
Search is an equation at the level of the system activitated in every
period.
It concerns every firm and activates the marketing and discovery and
development processes of the firms.
The firms, by appliying their technologies S (Scope) and B (Preci-
sion), explore the search space of
molecules to find the molecule with the best characteristics (highest
quality) to
develop a drug. If a drug is developed, marketing expenditures take
place.
*/

v[60]=p->cal("Generics",0);//Activates the process of revision of pat-
ent protection.
v[300]=p->cal("P_td_2",0);//biotech revolution period where the tech-
nological discontinuity affects the opportunities
CYCLE(cur3, "Firm")
 {
 cur3->write("Approval",0,0);//Setting the approval parameter to zero
 /* This parameter activates the planed marketing expenditures.
 If the approval is not sucessfull the planed marketing expenditures
can be reinvested in the next period.
 If in the previous period a drug has been approved the parameter has
been set to 1.
 BUT the parameter has to be reset to cero in every period in order to
make sure that the parameter
 varies according to the action of the firm in every period.
 */

 /*
 The next lines refer to the marketing activities of the firm
 */
 v[50]=cur3->cal("M_Expend",0);//Marketing budget for the potential
drug that can be developed.This budget is used only in the case the
drug is developed.
```

```
 /*
 Which are the search tools of the firm? Which is the achievement in
both technologies?
 Has the firm perceived and adopted the new technology?
 For every object "Firm" in the industry the area of the search space
to be explored
 is determined by the capabilities in Technology S , the start-point
in the
 search space and whether or not the firm has adopted the new Technol-
ogy B
 */

 v[0]=cur3->cal("Scope",0);//Technological achievement in the Technol-
ogy S
 v[1]=cur3->cal("Start",0);//Where does the search start?
 v[40]=cur3->son->cal("Precision_Adoption_2",1);
 // Has the firm perceived and adopted the new technology? f yes, the
search conditions change.

 /*
 The following lines make sure that the complete scope of exploration
of the
 firm is within the existing search space
 */

 v[29]=p->cal("Size",0);
 v[30]=v[0]+v[1];// Id of the last molecule of the field of explora-
tion
 v[31]=v[30]-v[29];//Differ. betw. the last Id of explor. and the last
Id
 if (v[31] > 0) //if outside of the search space
 v[32]= v[1]-v[31]; //the start point changes accordingly
 else //if within the search space
 v[32]=v[1];//nothing changes
 /*
 With the given part of the search space that can be explored the
search process
 for the molecule with the highest to develop the drug beginns
 */

 CYCLES(cur3,cur2,"Portfolio")
   {
    double maxQ = 0;
    cur1 = NULL;
    CYCLES(p->next,cur,"Mol")
    {

      v[3]=cur->cal("i",0);//Id of the molecule
      v[5]=cur->cal("Ip", 0);//Protection state of the molecule
      v[41]=cur->cal("Mol_phase",0);//Phase in which the molecule is
availiable.
      //1==random search 2==rational search
      v[21]=cur->cal("q",0);//True quality of the molecule
      v[20]=cur3->cal("Precision",0);
```

```
      v[22]=norm(v[21],v[20]);
      v[4]=round(v[22]);
      if (v[4]>0)
      cur->write("go",v[4],0);
      else
      cur->write("go",0,0);
      /*Be Carefull when controlling if the simulation works: Note
that at the end of the simulation the parameter
     "ObsQ" of the molecules in the search space will have the value
of the ObsQ of the molecule as observed by the
      last firm*/

      if (v[40]==0)
        //If the firm has not adopted the new perception technology
         {
           if(v[3] >= v[32] && v[3] < v[0] + v[32])
           /* This line determines the part of the search space to be
explored according
            to the technology S capabilities of the firm*/
            {
             if(v[4] >= maxQ && v[5] != 1 && v[41]==1) //Random search
             //The v[41] determines the type of molecules the firm has
acces to.
              {
               maxQ = v[4];
               cur1 = cur;
              }
            }
           v[3] = v[3] + 1;
         }

      if (v[40]==1 && t>v[300])//rational search and modern biotech
revolution
           //If the firm has adopted the new perception technology the
firm has
            //access to more molecules
          {
           if(v[3] >= v[32] && v[3] < v[0] + v[32])
           //This line determines the part of the search space to be
explored
            {
             if(v[4] >= maxQ && v[5] != 1 && v[41]!=0)
             //in this phase firms have access to both types of drugs
if they have adopted!
              {
                 maxQ = v[4];
                 cur1 = cur;
              }
            }
           v[3] = v[3] + 1;
          }

          //I have included this part to make a difference between DNA
revol (1950s)
           //and "modern biotech" with rDNA 1970s.

         if (v[40]==1 && t<v[300]) //rational search no modern biotech
```

```
            //If the firm has adopted the new perception technology but
the
              //time is bellow P_td_2(no modern biotech)
           {
             if(v[3] >= v[32] && v[3] < v[0] + v[32])
             //This line determines the part of the search space to be
explored
              according to the technology S capabilities of the firm
              {
               if(v[4] >= maxQ && v[5] != 1 && v[41]==1)
               //The v[41] determines the type of molecules the firm
has acces to.
                {
                 maxQ = v[4];
                 cur1 = cur;
                }
              }
             v[3] = v[3] + 1;
           }

    }
    v[51]=cur3->cal("I",0);
    /*
    v[51] activates the innovation function (see below) which deter-
mines whether the discovery
    and development processes are succesfull.
    */

    if(cur1 != NULL && v[51]==1)
      {
        v[7]=cur1->cal("q",0);
        // True quality of the selected object "Mol" with the maximum
observed quality
        v[200]=p->cal("fda",0);
        //Minimum Quality required for a drug to be launched into the
market
        if (v[7]>v[200])
        /*
        If an object Mol is selected wich satisfies the quality re-
striction determined by
        the minmum quality required:
        1) The approval parameter is updated accordingly activating
the marketing costs
        2) a new object "Drug" is added to the portfolio of the firm
        3) the parameters of the new drug are updated accordingly
        */
          {
            cur4=cur2->add_an_object("Drug", cur2->search("Drug"));
            cur3->write("Approval",1,0);
            cur3->increment("Portfolio_Size",1);
            cur1->write("Mol_d",(double)t,0);
            v[6]=cur1->cal("i",0); // Id of selected object "Mol" with
the maximum observed quality
            v[8]=cur1->cal("qo",0); // Observed quality of the se-
lected "Mol"
            v[9]=cur1->cal("Ip",0);
            // Type of molecule. If Ip==2, the molecule is an imita-
```

```
tion, if Ip==0 the molecule is
            //a new discovery
            v[10]=cur1->cal("Mol_phase",0);
            /*
            In the next lines the parameters of the new object "Drug"
of each firm are updated according
            to the results of "search" in the time step.
            */
            cur4->write("Drug_del",1,0);//Parameter to allow objects
to be deleted if needed.
            cur4->write("Drug_d",(double)t,0);//Period of launching
the drug
            cur4->write("Drug_i",v[6],0);//Identification parameter
            cur4->write("Drug_q",v[7],0);//Quality of the drug
            cur4->write("Drug_qo", v[8],0);//Observed quality of the
drug (implemented only for control purposes)
            cur4->write("Drug_phase", v[10],0);//Phase (1 or 2) in
which the drug was discovered
            cur4->write("Drug_M", v[50],0);//Marketing Budget for the
drug

            if (v[9]==0) //The molecule has been selected for the
first time.
            {
            cur1->write("Ip", 1, 0);
            //The discovered molecule will be protected from imitation
for the nex 20 periods.
            cur4->write("Drug_Type", 1, 0);//The drug is a new drug.
            }

            if (v[9]==2) //The selection is an imitation.
            cur4->write("Drug_Type", 2,0);//Generic drug

         }
      }
   }
 }
v[100]=p->cal("Image",0);//Activates the process of updating the image
value of each drug
v[101]=p->cal("Merit",0);//Activates the process of updating the merit
value of each drug
v[301]=p->cal("Collaboration",0);//Activates the process of updating
the merit value of each drug

res=1;
goto end;
}
```

Return

Variable **Fi**
In Object Industry
Used in: R
Using: HSB
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Fi"))
{
/*
Budget of the health system to reward firms
*/
v[0]=p->cal("HSB",0);
res=v[0];
goto end;
}
```
Return

Parameter **HSB**
In Object Industry
Used in: Fi
Go to: Description, Initial values, Model Structure

Variable **DS**
In Object Industry
Used in: DK
Using: KS Firm_Type
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"DS"))
{
/*
Technology S capabilities at industry level without the capabilities
of the DBFs
*/

  v[0]=0;
  for(cur1=p->search("Firm"); cur1!=NULL; cur1=go_brother(cur1) )
     {
      v[6]=cur1->cal("Firm_Type",0);
      if (v[6]==3)
            v[1]=0;
                  else
      v[1]=cur1->cal("KS",0);
                 v[0]=v[0]+v[1];
     }
res=v[0];
goto end;
}
```
Return

Variable **DP**
In Object Industry
Used in: DK
Using: KP Firm_Type
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"DP"))
{
/*
```

```
Technology B capabilities at industry level without the capabilities
of the DBFs
*/

  v[0]=0;
  for(cur1=p->search("Firm"); cur1!=NULL; cur1=go_brother(cur1) )
     {
      v[6]=cur1->cal("Firm_Type",0);
      if (v[6]==3)
      v[1]=0;
      else
      v[1]=cur1->cal("KP",0);


    v[0]=v[0]+v[1];
     }
res=v[0];
goto end;
}
```
Return

Variable **U_Industry**
In Object Industry
Used in: F
Using: U_Firm
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"U_Industry"))
{
/*
Total drug merit in the industry
*/

v[0]=p->sum("U_Firm",0);//Merit of the firms

res=v[0];
goto end;
}
```
Return

Parameter **rho**
In Object Industry
Used in: Image
Go to: Description, Initial values, Model Structure

Variable **Merit**
In Object Industry
Used in: Search
Using: a_u b_u c_u o_u Drug_q Drug_d Drug_Type U Drug_C
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Merit"))
```

```
{
/*
This action update of the merit values of the drugs.
The Merit function is a simplified version of Malerba and Orsenigo
(2002), p.681
*/
CYCLE(cur,"Firm")
  {
    // The relevant parameters are at the firm level
    v[0]=cur->cal("a_u",0);//parameter for Quality
    v[10]=cur->cal("b_u",0);//parameter for roi
    v[100]=cur->cal("c_u",0);//parameter for Image
    v[101]=cur->cal("o_u",0);//scaling parameter

    CYCLES(cur,cur1, "Portfolio")
     {
      CYCLES(cur1,cur2,"Drug")
        {
          v[2]=cur2->cal("Drug_d",0);//date
          v[3]=cur2->cal("Drug_C",0);//Image
          v[4]=cur2->cal("Drug_q",0);//Quality
          v[5]=cur2->cal("Drug_Type",0);//Generic(2) or New(1)

          v[6]=v[101]*pow(v[4],v[0])*pow((1/0.8),v[10])*pow(v[3],v[100
]);
          v[7]=v[101]*pow(v[4],v[0])*pow((1/0.7),v[10])*pow(v[3],v[100
]);

          if (v[5]==1)//If new drug
          cur2->write("U", v[6],0);//Updating of the parameter Merit!
          if (v[5]==2)//If generic drug
          cur2->write("U", v[7],0);//Updating of the parameter Merit!
        }
    }
  }
res=1;
goto end;
}
```

Return

Variable **Image**
In Object Industry
Used in: Search
Using: rho Drug_d Drug_C Drug_M
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Image"))
{
/*
Updating of the image values of the drugs
*/
CYCLE(cur,"Firm")
 {
  CYCLES(cur,cur1,"Portfolio")
  {
```

```
    CYCLES(cur1,cur2,"Drug")
    {
      v[6]=cur2->cal("Drug_M",0);//Marketing Budget of the drug in the
period of launching
      v[8]=cur2->cal("Drug_d",0);//Date of launch of the drug
      v[9]=p->cal("rho",0);//Rate of erotion of the image of the drug
      v[10]=cur2->cal("Drug_C",1);//Image of the drug

      if (t == v[8])
      cur2->write("Drug_C", v[6],0);//Drug image at time of launch

      if (t>v[8])
       {
        v[11]=v[10]*(1-v[9]);
        //Drug image after launching. It decreases according to the
rate of image erotion
        if (v[11]>0)
        cur2->write("Drug_C", v[11],0);
        else
        cur2->write("Drug_C", 0,0);//0.1
       }
    }
  }
 }
res=1;
goto end;
}
```

Return

Parameter **S_SO_r**
In Object Industry
Used in: S_SO
Go to: Description, Initial values, Model Structure

Parameter **P_SO_r**
In Object Industry
Used in: P_SO
Go to: Description, Initial values, Model Structure

Variable **DK**
In Object Industry
Used in: (never used)
Using: DS DP
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"DK"))
{
/*
Capabilities at industry level
*/
v[0]=p->cal("DP",0);
v[1]=p->cal("DS",0);
res=v[1]+v[0];
```

```
goto end;
}
```
Return

Parameter **Oligopol_size**
In Object Industry
Used in: Entry_DBF
Go to: Description, Initial values, Model Structure

Variable **Rational_Phase_Industry**
In Object Industry
Used in: (never used)
Using: P_td_2 P_sc P_sc_2
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"Rational_Phase_Industry"))
{
/*
The technological discontinuity changes the cummulativeness of the ca-
pabilities.
*/
v[0]=t;
v[2]=p->cal("P_td_2",0);
v[3]=p->next->next->cal("P_sc_2",0);

if (v[0] >= v[2])
p->next->next->write("P_sc",v[3], 0);

res=1;
goto end;
}
```
Return

Parameter **P_SO_r_2**
In Object Industry
Used in: (never used)
Go to: Description, Initial values, Model Structure

Variable **Entry_DBF**
In Object Industry
Used in: (never used)
Using: Oligopol_size DBF_Number lambda_dbf Alpha_dbf t_entry_DBF Delete R Start LW_Invest LB_Invest LB_KK LW_KS LW_KP LB_KS LB_KP KS KP K KS_Share KP_Share I WI Portfolio_Size U_Firm F B M_Expend Abs_P Abs_S Ex V Adoption_Draw j Innovation_Draw L_Budget Firm_Type Max_Drug_q P_Knowl_firm Alpha_f beta_f lambda_f Drug_q Drug_d Drug_Type U Drug_C Drug_M Scope Scope_r Scope_Adoption Precision Precision_r Precision_TP Precision_WA Precision_Adoption_1 Precision_Adoption_2
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Entry_DBF"))
{

 /*
  Entry of biotech companies. The function is computed only once and
then it is transformed in a parameter and never computed again. This
equation sets the search space of molecules availiable for the drug
producers to discover and develop drugs.
 */

v[0]=p->cal("t_entry_DBF",0);
if (t==v[0])
{
 v[3]=p->overall_max("j", 0);//highest Firm Id
 v[2]=p->cal("Oligopol_size",0);//Size of the oligopol
 v[21]=v[3]-v[2];//To make sure that we start at 0.
 v[1]=p->cal("DBF_Number",0);//Number of biotech companies
 cur=p->search_var_cond("j", v[3], 0);//Firm with the highest Firm Id
 v[6]=p->cal("lambda_dbf",0);//
 v[7]=p->cal("Alpha_dbf",0);//

 while (v[21]<v[1])
 {
  cur1=p->add_an_object("Firm",cur);
  cur1->write("Firm_Type", 3, v[0]);
  cur1->write("j", v[21]+v[2]+1, v[0]);
  cur1->write("Start",rnd_integer(1, 1200), v[0]-1);
  cur1->write("Portfolio_Size", 1, v[0]);

  cur1->write("lambda_f", v[6], v[0]);
  cur1->write("Alpha_f", v[7], v[0]);
  cur1->write("beta_f", 1, v[0]);

  cur1->write("WI", 0, v[0]);
  cur1->write("Adoption_Draw", 0, v[0]);
  cur1->write("Innovation_Draw", 0, v[0]);
  cur1->write("B", 0.1, v[0]);//no v[0]-1
  cur1->write("P_Knowl_firm", 0, v[0]);

  cur1->write("I", 0, v[0]);//no v[0]-1
  cur1->write("F", 0, v[0]);//no v[0]-1

  cur1->write("LB_KK", 1, v[0]);//no 1 and no v[0]-1
  cur1->write("K", 0, v[0]);//no v[0]-1
  cur1->write("KS_Share", 0, v[0]);//no v[0]-1
  cur1->write("KP_Share", 0, v[0]);//no v[0]-1

  cur1->write("KP", 25, v[0]-1);
  cur1->write("LW_KP", 0, v[0]);
  cur1->write("LB_KP", 0, v[0]);
  cur1->write("Abs_P", 0, v[0]);//no v[0]-1

  cur1->write("KS", 0, v[0]);//no v[0]-1
  cur1->write("LW_KS", 0, v[0]);//no v[0]-1
  cur1->write("LB_KS", 0, v[0]);//no v[0]-1
  cur1->write("Abs_S", 0, v[0]);//no v[0]-1
```

```
  cur1->write("Ex", 0, v[0]);
  cur1->write("M_Expend", 0, v[0]);
  cur1->write("L_Budget", 0, v[0]);
  cur1->write("LB_Invest", 0, v[0]);
  cur1->write("LW_Invest", 0, v[0]);
  cur1->write("R", 0, v[0]);


  cur1->son->next->next->write("Precision_Adoption_1", 1, v[0]-1);
    cur1->son->next->next->write("Precision_Adoption_2", 1, v[0]-1);
  cur1->write("V", 0, v[0]-1);
  cur1->son->next->write("Scope_Adoption", 1, v[0]-1);
  cur1->son->next->write("Scope", 100, v[0]); // no 50 //no v[0]-1
  cur1->son->next->write("Scope_r", 0, v[0]);//no v[0]-1
  cur1->son->next->next->write("Precision_r", 0, v[0]-1);
  cur1->son->next->next->write("Precision", 300, v[0]-1);
  cur1->son->next->next->write("Precision_TP", 0, v[0]);
  cur1->son->next->next->write("Precision_WA", 0, v[0]);


  cur1->write("U_Firm", 0, v[0]);//no v[0]-1
  cur1->write("Max_Drug_q", 0, v[0]);//no v[0]-1
  for(cur2=cur1->search("Drug"); cur2!=NULL; )
   {
   cur3=go_brother(cur2);
   cur2->write("Drug_q",rnd_integer(1500, 3000) , v[0]);
   cur2->write("Drug_d",v[0] ,v[0] );
   cur2->write("Drug_Type", 1, v[0]);
   cur2->write("Drug_C", 0, v[0]);//no 0.5
   cur2->write("Drug_d", v[0], v[0]);
   cur2->write("Drug_M", 1, v[0]);
   cur2->write("U",0, v[0]); // no rnd_integer(75, 100)
   cur2=cur3;
   }


  v[21]=v[21]+1;
 }
  v[11]=p->cal("Delete",0);


res=1;
param=1;
}

else
res=0;
 goto end;
}
```

Return

Parameter **DBF_Number**
In Object Industry

Used in: Entry_DBF
Go to: Description, Initial values, Model Structure

Parameter **lambda_dbf**
In Object Industry
Used in: Entry_DBF
Go to: Description, Initial values, Model Structure

Parameter **Alpha_dbf**
In Object Industry
Used in: Entry_DBF
Go to: Description, Initial values, Model Structure

Parameter **t_entry_DBF**
In Object Industry
Used in: Entry_DBF LC_KP col_Knowl Collaboration Divorce
Go to: Description, Initial values, Model Structure

Parameter **VentCap**
In Object Industry
Used in: B
Go to: Description, Initial values, Model Structure

Variable **Delete**
In Object Industry
Used in: Entry_DBF
Using: Firm_Type Drug_del
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Delete"))
{
/*
This equation deletes the drugs of the DBFs after they have been added
to the structure of the model.
*/
last_update--;//repeat the computation any time is requested
if(c==NULL)//Avoids to be computed when the system activates the equa-
tion
{
res=-1;
goto end;
}
 CYCLE(cur2,"Firm")
   {
    v[4]=cur2->cal("Firm_Type",0);
    if (v[4]==3)
     {

       for(cur=cur2->search("Drug"); cur!=NULL; )
       {
```

```
       v[1]=cur->cal("Drug_del",0);
       cur1=go_brother(cur);
       if (v[1]==1)
       cur->delete_obj();
       cur=cur1;
       }

     }
   }
 v[3]=1;


res=v[3];
goto end;
}
```

Return

Variable **Collaboration**
In Object Industry
Used in: Search
Using: t_entry_DBF col_knowl_r Start LB_KK KP j Firm_Type col_number cp CW distance Drug_q Drug_d Drug_l Drug_lp Precision_Adoption_2 col_LF col_date col_KP col_DBF
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Collaboration"))
{
/*
This function activates the search of LFs (Firm Type 1 or 2) for col-
laborative partners (Firm type 3).
The search starts after the discontinuity at t=70 has taken place.
*/

v[0]=(double)t;
v[1]=p->cal("t_entry_DBF",0);
v[40]=p->cal("col_knowl_r",0);//rate of knowledge flow in the collabo-
rative arrangements
if (v[0]>v[1])

{
CYCLE (cur,"Firm")
 {
 v[2]=cur->cal("Firm_Type",0);
 v[17]=cur->cal("j",0);//Id of the firm
 v[3]=cur->cal("Precision_Adoption_2",0);
 v[4]=cur->cal("Start",0);
 v[16]=cur->cal("LB_KK",0);
 /*
 v[6]=cur->cal("KP_rank",0);
 */

   if (v[2] != 3 && v[3]==1)//Only incumbent firms that have adopted
the new technological opportunities
    {
```

```
   CYCLES (cur->up, cur1, "Firm")
     {
     v[5]=cur1->cal("Firm_Type",0);//DBF - Potential collaboration
partner
     v[14]=cur1->cal("KP",0);//DBF capabilities
     v[41]=v[40]*v[14];//DBF capabilities that can be transferred
     v[9]=cur1->cal("col_number",1);
     v[7]=cur1->cal("Start",0);
     v[15]=round(abs(v[7]-v[4]));

     if (v[15]==0)
     v[30]=0.1;
     else
     v[30]=v[15];
     cur1->write("distance",v[30],0);//Distance between the incumbent
firm and the DBF
     v[28]=cur1->cal("j",0);//Identification Number of the DBF

     v[31]=cur1->overall_max("Drug_q",0);//quality of max drug of DBF
     cur5=cur1->search_var_cond("Drug_q",v[31],0);//drug (object)with
highst quality of potential partner DBF
     v[34]=cur5->cal("Drug_l",0);//Is the drug already licensed? This
needs to be cheked
     v[32]=cur->overall_max("Drug_d",0);//date of jungest drug of LF
     cur6=cur->search_var_cond("Drug_d",v[32],0);//jungest drug (ob-
ject) of the incumbent LF searching for partner
     v[33]=cur6->cal("Drug_q",0);//quality of jungest drug of LF


     /*
     v[8]=cur1->cal("KP_rank_par",0);
     */
       if (v[30]<300)//only the ones that are "close"
        {
         v[10]=cur1->cal("cp",0);//Scalling parameter
         v[11]=(double)1-exp(-v[10]*pow(v[16],2)/v[30]);
         v[18]=UNIFORM(0,1);
         cur->write("CW",v[11],0);//Probability to collaborate

          if (v[11]>v[18] && v[5]==3 && v[9]!=1)//Closing licensing
agreement

            {
            if (v[33]<v[31] && v[34]!=1)//If the drug has not been
liscensed jet
            {
            //jungest drug (object) of the LF becomes the quality of
the best drug of   the DBF
            cur6->write("Drug_q",v[31],0);
            //Updating the "drug liscenced" parameter in the portfolio
of LF
            cur6->write("Drug_l",1,0);
            //Updating the licensing partner parameter in the drug
liscensed by the incumbent
            cur6->write("Drug_lp",v[28],0);
            cur5->write("Drug_l",1,0);//Updating the "drug liscenced"
```

```
parameter in the portfolio of the DBF
            }

            CYCLES(cur,cur2,"Network")
             {
             cur3=SEARCHS(cur2,"col");
             if(VS(cur3,"col_date")!=-1)
               cur3=cur2->add_an_object("col",cur3);
             cur1->write("col_number",1,0);//DBF level
             cur3->write("col_LF",v[17],0);//Id of the LF in the coll.
updated // Col level
             cur->increment("col_number",1);//Number of collaboration
of the LF updated // LF Level
             cur3->write("col_date",(double)t,0);//Date of collabora-
tion beginn updated// col level
             cur3->write("col_KP",v[41],0);//Capabilities transferred
from the DBF to the LF in the coll.//col level
             cur3->write("col_DBF",v[28],0);//Id of the DBF in the
coll. updated // Col level
             }
            }
         }
       }
      }
  }
}
res=1;
goto end;
}
```

Return

Variable **Divorce**
In Object Industry
Used in: (never used)
Using: t_entry_DBF col_knowl_r Start LB_KK KP j Firm_Type col_number cp col_date col_KP col_DBF col_divorce_date DW col_divorce
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Divorce"))
{
/*
Termination of collaboration.
Stochastic process after updating the location of the frims in the
search space and the engagement of the incumbent firm in interacting
with its environment.
*/
v[0]=(double)t;
v[1]=p->cal("t_entry_DBF",0);
v[40]=p->cal("col_knowl_r",0);

 if (v[0]>v[1])
 {
  CYCLE(cur,"Firm")
  {
  v[2]=cur->cal("Firm_Type",0);
```

```
  v[3]=cur->cal("col_number",0);
  v[6]=cur->cal("Start",0);
  v[8]=cur->cal("LB_KK",0);
  if (v[2]!=3 && v[3]>0)
  {
   CYCLES(cur,cur1,"Network")
   {
    CYCLES(cur1,cur2,"col")
     {
     v[4]=cur2->cal("col_DBF",0);
     v[22]=cur2->cal("col_date",0);
     if(v[22]==-1)
      break; //exit the cycle if it is not a real "col"
     cur3=cur1->up->search_var_cond("j",v[4], 0);
     v[5]=cur3->cal("Start",0);
     v[14]=cur3->cal("KP",0);
     v[41]=v[14]*v[40];
     v[7]=abs(v[5]-v[6]);
     if (v[7]==0)
     v[9]=0.1;
     else
     v[9]=v[7];
     v[10]=cur->cal("cp",0);
     v[11]=1-exp(-v[10]*pow(v[8],2)/v[9]);
     cur2->write("DW",v[11],0);//col level
     v[18]=UNIFORM(0,1);
     v[21]=cur2->cal("col_divorce",0);

     if (v[11]>v[18] && v[21]==0 && v[22]<v[0]-2)
       cur2->write("col_KP",v[41],0);//col level
     if (v[11]<=v[18] && v[21]==0 && v[22]<v[0]-2)
         {
         cur2->write("col_KP",0,0);//col level
         cur2->write("col_divorce_date",double(t),0);//col level
         cur3->write("col_number",0,0);
         cur2->write("col_divorce",1,0);//col level
        }
    }
  }
 }
}
}

res=1;
goto end;
}
```

Return

Parameter **col_knowl_r**
In Object Industry
Used in: Collaboration Divorce
Go to: Description, Initial values, Model Structure

Variable **beta**
In Object Industry

Used in: M_Expend L_Budget
Using: Firm_Type beta_f
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"beta"))
{
/*
Variable capturing investment decitions in learning
*/
last_update--;//repeat the computation any time is requested
if(c==NULL)//Avoids to be computed when the system activates the equa-
tion
{
res=-1;
goto end;
}

v[0]=c->cal("Firm_Type",0);
if (v[0]==1)
v[1]=UNIFORM(0.5,0.7);
if (v[0]==2)
v[1]=UNIFORM(0.5,0.7);
if (v[0]==3)
v[1]=1;

c->write("beta_f",v[1],0);
res=v[1];
goto end;
}
```

Return

Variable **Alpha**
In Object Industry
Used in: LW_KS LW_KP Abs_S Abs_P
Using: Firm_Type Alpha_f
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Alpha"))
{
/*
Variable capturing the technological bet of the firm
*/
last_update--;//repeat the computation any time is requested
if(c==NULL)//Avoids to be computed when the system activates the equa-
tion
{
res=-1;
goto end;
}


v[0]=c->cal("Firm_Type",0);
if (v[0]==1)
```

```
v[1]=UNIFORM(0.3,0.5);

if (v[0]==2)
v[1]=UNIFORM(0.6,0.8);

if (v[0]==3)
v[1]=0;

c->write("Alpha_f",v[1],0);
res=v[1];
goto end;
}
```
Return

Variable **lambda**
In Object Industry
Used in: LW_Invest LB_Invest
Using: Firm_Type lambda_f
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"lambda"))
{
/*
Variable capturing investment dections in external learning
*/
last_update--;//repeat the computation any time is requested
if(c==NULL)//Avoids to be computed when the system activates the equa-
tion
{
res=-1;
goto end;
}

v[0]=c->cal("Firm_Type",0);
if (v[0]==1)

v[1]=UNIFORM(0.10,0.15);//HFM scenario and Exp2_l scenario
/*
v[1]=UNIFORM(0.30,0.40);//Exp2_h scenario
*/

if (v[0]==2)
v[1]=UNIFORM(0.30,0.40);//HFM scenario and Exp2_h scenario

/*
v[1]=UNIFORM(0.10,0.15);//Exp2_l scenario
*/

if (v[0]==3)
v[1]=1;

c->write("lambda_f",v[1],0);
res=v[1];
```

```
goto end;
}
```
Return

Variable **Max_Drug_q_Industry**
In Object Industry
Used in: (never used)
Using: Max_Drug_q
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"Max_Drug_q_Industry"))
{
/*
Max drug quality in the industry
*/
v[2]=p->overall_max("Max_Drug_q", 0);
res=v[2];
goto end;
}
```
Return

Object Firm

Contained in Object: Root->Root2->World->Industry
Containing: Portfolio Scope_Tech Precision_Tech Network
List of Variables: Abs_P(0), Abs_S(0), Adoption_Draw(0), B(1), col_Knowl(0), DP_SO(0), DS_SO(0), Ex(0), F(0), I(0), Innovation_Draw(0), K(0), KP(1), KP_Share(0), KS(1), KS_Share(0), L_Budget(0), LB_Invest(1), LB_KK(1), LB_KP(0), LB_KS(0), LC_KP(0), LW_Invest(1), LW_KP(0), LW_KS(0), M_Expend(0), Max_Drug_q(0), P_Adoption_De_1(0), P_Adoption_De_2(0), P_SO(0), R(0), S_Adoption_De(0), S_SO(0), Start(1), U_Firm(0), V(0), WI(0)
List of Parameters: a_u, Alpha_f, ap, Approval, b_u, beta_f, c_u, col_number, cp, CW, distance, DP_SO_p, DS_SO_p, Firm_Type, ip, j, lambda_f, o_u, P_Knowl_firm, Portfolio_Size, v, v_decr_rate

Variable **R**
In Object Firm
Used in: Entry_DBF B
Using: Fi F
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"R"))
{
/*
Reward of the company in each period. It depends on the quality
```

```
reached by
the molecule of the company and on the budget of the health system.
*/
v[1]=p->cal("F",0);
v[2]=p->up->cal("Fi",0);
if (v[1]>0)
v[4]=v[1]*v[2];
else
v[4]=0;

res=v[4];
goto end;
}
```
Return

Variable **Start**
In Object Firm
Used in: Entry_DBF Search Start Collaboration Divorce
Using: Start Size
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"Start"))
{
/*
Action that determines in each period the location in the search space
to start the
search for the molecule with the highest quality.
*/

v[0]=(double)t;
if (v[0]==1)
{
 v[4]=p->cal("Size",0);
 v[3]=rnd_integer(0,v[4]);
}
else
{
 v[2]=rnd_integer(-50,50);
 v[1]=p->cal("Start",1);
 v[3]=abs(v[2]+v[1]);
}
res=round(v[3]);
goto end;
}
```
Return

Variable **LW_Invest**
In Object Firm
Used in: Entry_DBF LW_KS LW_KP
Using: lambda L_Budget
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"LW_Invest"))
```

```
{
/*
Investment in internal learning

*/
v[0]=p->cal("L_Budget",0);
v[1]=p->cal("lambda",0);//Investment in learning by interacting (ex-
ternal learning)

v[4]=v[0]*(1-v[1]);


res=v[4];
goto end;
}
```
Return

Variable **LB_Invest**
In Object Firm
Used in: Entry_DBF LB_KK
Using: lambda L_Budget
Go to: Description, Initial values, Model Structure
Equation Code:
```
if(!strcmp(label,"LB_Invest"))
{
/*
Investment in external learning
*/

v[0]=p->cal("lambda",0);//External learning parameter
v[1]=p->cal("L_Budget",0);//Leraning budget

v[3]=v[0]*v[1];


res=v[3];
goto end;

}
```
Return

Variable **LB_KK**
In Object Firm
Used in: Entry_DBF LB_KK Abs_S Abs_P Scope_WA Precision_WA Collaboration Divorce
Using: LB_Invest LB_KK
Go to: Description, Initial values, Model Structure
Equation Code:
```
if(!strcmp(label,"LB_KK"))
{
/*
Stock of learning beyond the firm
```

```
*/
v[1]=p->cal("LB_Invest",0);
v[2]=p->cal("LB_KK",1);
v[3]=0.8*v[2]+v[1];//0.8 depreciation of capabilities
v[5]=log(1+v[3]); //Abnehmende Skalenerträge or decreasing returns to
scale

res=v[5];
goto end;
}
```
Return

Variable **LW_KS**
In Object Firm
Used in: Entry_DBF KS
Using: Alpha LW_Invest
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"LW_KS"))
{
/*
Internal learning investment in the technology S
*/
v[1]=p->cal("LW_Invest",0);//Investment in learning within the firm
v[5]=p->cal("Alpha",0);//technological trayectory of the firm
v[3]=v[1]*v[5];//Investment in technology S

v[4]=log(1+v[3]);
/*
v[4]=pow(v[3],0.5);
*/
res=v[4];
goto end;
}
```
Return

Variable **LW_KP**
In Object Firm
Used in: Entry_DBF KP
Using: Alpha LW_Invest Firm_Type
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"LW_KP"))
{
/*
Internal research investment in technology B
*/
v[1]=p->cal("LW_Invest",0);//Investment in learning within the firm
v[5]=p->cal("Alpha",0);//Technological trayectory of the firm
v[10]=p->cal("Firm_Type",0);//Firm Type

if (v[10]==1)
```

```
{
v[6]=1-v[5];
v[12]=UNIFORM(0.3,v[6]);
}
if (v[10]==2)
{
v[6]=0.9-v[5];
v[12]=UNIFORM(0.3,v[6]);
}
if (v[10]==3)
v[12]=1;

v[3]=v[1]*v[12];//Investment in technology B

v[4]=log(1+v[3]);
res=v[4];
goto end;
}
```
Return

Variable **LB_KS**
In Object Firm
Used in: Entry_DBF KS
Using: Abs_S S_Knowl
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"LB_KS"))
{
/*
Capabilities in the technology S through external learning
*/

v[4]=p->cal("Abs_S",0);//Absorptive capacity
v[6]=p->cal("S_Knowl",0);// Extramural knowledge base
v[7]=v[4]*v[6];

res=v[7];
goto end;
}
```
Return

Variable **LB_KP**
In Object Firm
Used in: Entry_DBF KP
Using: Abs_P P_Knowl
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"LB_KP"))
{
/*
Capabilities in the technology B through external learning

*/
```

```
v[4]=p->cal("Abs_P",0);//Absorptive capacity
v[6]=p->cal("P_Knowl",0);
v[7]=v[4]*v[6];

res=v[7];
goto end;
}
```
Return

Variable **KS**
In Object Firm
Used in: Entry_DBF DS_SO DS KS K KS_Share Scope_r
Using: LW_KS LB_KS KS S_sc
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"KS"))
{
/*
Capabilities in technology S
Inspired by llerena et Oltra (1999)p. 9.
*/

v[0]=p->cal("KS",1);
v[1]=p->cal("LW_KS",0);//Cummulative research
v[2]=p->cal("LB_KS",0);//Non cummulative research
v[3]=p->cal("S_sc",0);//Depreciation of knowledge or Degree of cummu-
lativeness
v[4]=v[1]+v[2]+(1-v[3])*v[0];

res=v[4];
goto end;
}
```
Return

Variable **KP**
In Object Firm
Used in: Entry_DBF DP_SO DP KP K KP_Share Collaboration Divorce Precision_r
Using: LW_KP LB_KP KP LC_KP P_sc
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"KP"))
{
/*
Accumulation of Capabilities.
Inspired by llerena et Oltra (1999)p. 9.
The acummulation of capabilities is a weighted average of past and new
capabilities.
*/

v[0]=p->cal("KP",1);
v[1]=p->cal("LW_KP",0);//Learning internal to the firm
```

```
v[2]=p->cal("LB_KP",0);//Learning external to the firm
v[22]=p->cal("LC_KP",0);//Learning external to the firm
v[3]=p->cal("P_sc",0);//Depreciation of knowledge (or Degree of cummu-
lativeness)
v[4]=v[1]+v[2]+v[22]+(1-v[3])*v[0];

res=v[4];
goto end;
}
```
Return

Variable **K**
In Object Firm
Used in: Entry_DBF KS_Share KP_Share WI
Using: KS KP
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"K"))
{
/*
Accumulation of Capabilities of both technologies.
*/

v[1]=p->cal("KP",0);
v[2]=p->cal("KS",0);
v[3]=v[1]+v[2];
res=v[3];

goto end;
}
```
Return

Variable **KS_Share**
In Object Firm
Used in: Entry_DBF
Using: KS K
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"KS_Share"))
{
/*
Firm's share of technology S capabilities
*/

v[0]=p->cal("KS",0);
v[1]=p->cal("K",0);

res=v[0]/v[1];

goto end;
}
```
Return

Variable **KP_Share**
In Object Firm
Used in: Entry_DBF
Using: KP K
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"KP_Share"))
{
/*
Firm's share of capabilities in technology B
*/
v[0]=p->cal("KP",0);
v[1]=p->cal("K",0);

res=v[0]/v[1];
goto end;
}
```

Return

Variable **I**
In Object Firm
Used in: Entry_DBF Search
Using: Mode WI Innovation_Draw
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"I"))
{
/*
Innovation can be deterministic (Mode=0) or the result of a random
process (Mode=1).
*/
v[0]=p->cal("Innovation_Draw",0);
v[1]=p->cal("WI",0);
v[3]=p->up->cal("Mode",0);
/*
It determines the version of the model (all innovate or not). If
Mode=0 innovation is a
draw which depends on the level of capabilities of the firms. If
Mode=1 all innovate.
*/
if (v[3]==0)
 {
  if (v[0] < v[1])
  v[2]=1;
  else
  v[2]=0;
 }
else
v[2]=1;

res=v[2];
goto end;
}
```

Return

Variable **WI**
In Object Firm
Used in: Entry_DBF I
Using: K ip
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"WI"))
{
/*
Probability to Innovate. Different options to model this function.
*/
v[0]=p->cal("K",0);//Stock of capabilities
v[1]=p->cal("ip",0);//Scalling parameter
v[2]=1-exp(-v[1]*v[0]);

res=v[2];
goto end;
}
```

Return

Parameter **Portfolio_Size**
In Object Firm
Used in: Entry_DBF Search
Go to: Description, Initial values, Model Structure

Variable **U_Firm**
In Object Firm
Used in: Entry_DBF U_Industry F
Using: U
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"U_Firm"))
{
/*
Sum of the qualities of the drug portfolio.
*/
v[0]=p->son->sum("U",0);
res=v[0];
goto end;
}
```

Return

Variable **F**
In Object Firm
Used in: Entry_DBF R
Using: U_Industry U_Firm
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"F"))
{
/*
```

```
Merit share of the firm. This equation is used as performance indica-
tor and i
s used to operationalised the reward of the firm from the system.
*/
v[1]=p->cal("U_Firm",0);
v[3]=p->up->cal("U_Industry",0);
if (v[1]>0)
v[4]=(v[1]/v[3]);
else
v[4]=0;

res=v[4];
goto end;
}
```
Return

Parameter **ap**
In Object Firm
Used in: Scope_WA Precision_WA
Go to: Description, Initial values, Model Structure

Parameter **ip**
In Object Firm
Used in: WI
Go to: Description, Initial values, Model Structure

Parameter **v**
In Object Firm
Used in: S_Adoption_De P_Adoption_De_1 P_Adoption_De_2 Scope_WA Precision_WA Precision_V Scope_V
Go to: Description, Initial values, Model Structure

Variable **B**
In Object Firm
Used in: Entry_DBF B M_Expend L_Budget S_Adoption_De
Using: VentCap R B Ex Firm_Type
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"B"))
{
/*
Budget for the activities of the firm
*/

v[5]=p->cal("Firm_Type",0);
v[0]=p->cal("B",1);//Previous budget
v[1]=p->cal("R",0);//Reward
v[2]=p->cal("Ex",0);//Expenditure
v[6]=p->up->cal("VentCap",0);
if (v[5]==3)
/*
```

```
v[3]=v[6];
*/
v[3]=v[0]+v[1]-v[2]+v[6];
else
v[3]=v[0]+v[1]-v[2];


res=v[3];
goto end;
}
```
Return

Variable **M_Expend**
In Object Firm
Used in: Entry_DBF Search Ex
Using: beta B
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"M_Expend"))
{
/*
Expenditures in marketing activities
*/
v[0]=p->cal("beta",0);//Investment in learning
v[2]=p->cal("B",1);
v[3]=(1-v[0])*v[2];

res=v[3];
goto end;
}
```
Return

Parameter **a_u**
In Object Firm
Used in: Merit
Go to: Description, Initial values, Model Structure

Parameter **b_u**
In Object Firm
Used in: Merit
Go to: Description, Initial values, Model Structure

Parameter **c_u**
In Object Firm
Used in: Merit
Go to: Description, Initial values, Model Structure

Parameter **o_u**
In Object Firm

Used in: Merit
Go to: Description, Initial values, Model Structure

Variable **Abs_P**
In Object Firm
Used in: Entry_DBF LB_KP LC_KP
Using: Alpha LB_KK Firm_Type P_complex
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Abs_P"))
{
/*
Absorptive capacity for knowledge in technology B
*/

v[11]=p->cal("Alpha",0);//Technological trajectory
v[1]=p->cal("LB_KK",0);//External research level. It influences the
absorptive capacity of the firm
v[3]=p->cal("P_complex",0);//Complexity of technology S Knowledege
Base
v[10]=p->cal("Firm_Type",0);

 if (v[10]==1)
 {
 v[6]=1-v[11];
 v[12]=UNIFORM(0.3,v[6]);
 }
 if (v[10]==2)
 {
 v[6]=0.9-v[11];
 v[12]=UNIFORM(0.3,v[6]);
 }
 if (v[10]==3)
 v[12]=1;

v[7]=v[1];
if (v[7]<4*pow(v[3],2))
 v[8]=4*pow(v[3],2);
 else
 v[8]=v[7];
v[4]=1-(2*v[3]/sqrt(v[8]));//Absorptive capacity
if (v[4]<0)
 v[5]==0;
 else
 v[5]=v[4];

res=v[5];
goto end;
}
```

Return

Variable **Abs_S**
In Object Firm

Used in: Entry_DBF LB_KS
Using: Alpha LB_KK S_complex
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Abs_S"))
{
/*
Absorptive capacity of the technology S knowledge
s
*/
v[6]=p->cal("Alpha",0);//Technological trajectory
v[1]=p->cal("LB_KK",0);//External research level. It influences the
absorptive capacity of the firm
v[3]=p->cal("S_complex",0);//Complexity of technology S knowledege
Base
/*
v[7]=v[6]*v[1];
*/

v[7]=v[1];

if (v[7]<4*pow(v[3],2))
v[8]=4*pow(v[3],2);
else
v[8]=v[7];
v[4]= 1-(2*v[3]/sqrt(v[8]));//Absorptive capacity
if (v[4]<0)
v[5]==0;
else
v[5]=v[4];

res=v[5];
goto end;
}
```

Return

Parameter **Approval**
In Object Firm
Used in: Search Ex
Go to: Description, Initial values, Model Structure

Variable **Ex**
In Object Firm
Used in: Entry_DBF B
Using: M_Expend Approval V L_Budget
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Ex"))
{
/*
Expenditures. Part of the budget that has been spent
*/
```

```
v[1]=p->cal("L_Budget",0);//Learning investment
v[3]=p->cal("M_Expend",0);//Marketing Expenditures
v[4]=p->cal("Approval",0);//Development of a drug in the previous pe-
riod has been accepted
v[5]=p->cal("V",0);//Adoption costs


if (v[4]==1)//If in the period a drug has been admited for marketing
v[10]=v[1]+v[3]+v[5];
else
v[10]=v[1]+v[5];


res=v[10];
goto end;
}
```
Return

Variable **V**
In Object Firm
Used in: Entry_DBF Ex
Using: Firm_Type Precision_V
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"V"))
{
/*
Total adoption costs
v[1]=p->cal("Scope_V",0); In the version without Entry of firms
of type 2 make sure that this is included in the costs
*/

v[0]=p->cal("Firm_Type",0);
if (v[0]==3)
v[2]=0;
else
v[2]=p->cal("Precision_V",0);

res=v[2];
goto end;
}
```
Return

Variable **Adoption_Draw**
In Object Firm
Used in: Entry_DBF S_Adoption_De P_Adoption_De_1 P_Adoption_De_2
Using: (nothing)
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Adoption_Draw"))
{
```

```
/*
The adoption draw determines the adoption succes of the firm. It is
the same for
all the firms. It is located at the industry level.
*/

v[0]=UNIFORM(0,1);
res=v[0];
goto end;
}
```
Return

Variable **S_Adoption_De**
In Object Firm
Used in: (never used)
Using: v B Adoption_Draw Scope_WA Scope_Adoption Scope_Adoption_Date S_td
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"S_Adoption_De"))
{
/*
Technology S Adoption Decition. This function determines whether the
firm adopt
a new form of technology after a technological discontinuity has taken
place.
This function is located at the level of the firm
*/
v[0]=(double)t;
v[1]=p->cal("S_td",0);
if (v[0] > v[1])
  {
   v[2]=p->son->cal("Scope_Adoption",0);

//In the scenario "Entry DS_companies" make sure that this parameter
is set to "0" for the LFs form the traditional of Firm Type 1. In the
scenario with no entry DS_companies make sure that all companies have
this parameter set to "1".
   v[3]=p->son->cal("Scope_WA",0);
   v[4]=p->cal("Adoption_Draw",0);
   v[5]=p->son->cal("B",0);
   v[6]=p->up->cal("v",0);

     if (v[2] == 0 && v[3] > v[4] && v[5]>2*v[6])
       {
        cur1=p->search("Scope_Tech");
        cur1->write("Scope_Adoption",1,0);
        cur1->write("Scope_Adoption_Date",(double)t,0);
       }
 }
res=1;
goto end;
}
```
Return

Variable **P_Adoption_De_1**
In Object Firm
Used in: (never used)
Using: v Adoption_Draw L_Budget Precision_WA Precision_Adoption_1 Precision_Adoption_1_Date P_td_1
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"P_Adoption_De_1"))
{
/*
technology B Adoption Decition. This function determines whether the
firm adopt
a new form of technology after a technological discontinuity (the
transition from random to rational search
has taken place. This function is located at the firm level.
*/
v[0]=(double)t;

v[1]=p->cal("P_td_1",0);



if (v[0] > v[1])
  {
   v[2]=p->cal("Precision_Adoption_1",0);
   v[3]=p->cal("Precision_WA",0);
   v[4]=p->cal("Adoption_Draw",0);//At the level of the firm
   v[5]=p->son->cal("L_Budget",0);
   v[6]=p->up->cal("v",0);

     if (v[2] == 0 && v[3] > v[4] && v[5]>2*v[6])
       {
         cur1=p->search("Precision_Tech");
         cur1->write("Precision_Adoption_1",1,0);
         cur1->write("Precision_Adoption_1_Date",(double)t,0);
       }
  }
res=1;
goto end;
}
```

Return

Parameter **j**
In Object Firm
Used in: Entry_DBF DS_SO DP_SO Scope_V Collaboration Divorce
Go to: Description, Initial values, Model Structure

Parameter **v_decr_rate**
In Object Firm
Used in: Precision_V Scope_V
Go to: Description, Initial values, Model Structure

Variable **Innovation_Draw**
In Object Firm
Used in: Entry_DBF I
Using: (nothing)
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Innovation_Draw"))
{
/*
The innovation draw determines the innovation succes of the firm.
It is the same for all the firms. It is located at the industry level.
*/
v[1]=UNIFORM(0,1); //Random uniform value in the interval [0,1].
res=v[1] ;
goto end;
}
```

Return

Variable **L_Budget**
In Object Firm
Used in: Entry_DBF Ex LW_Invest LB_Invest P_Adoption_De_1 P_Adoption_De_2
Using: beta B
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"L_Budget"))
{
/*
Level of buget for learning
*/
v[1]=p->cal("B",1);
v[2]=p->cal("beta",0);//Learning parameter

res=v[1]*v[2];
goto end;
}
```

Return

Parameter **Firm_Type**
In Object Firm
Used in: Entry_DBF Delete DS_SO DP_SO DS DP B beta lambda Alpha LW_KP Abs_P col_Knowl V Collaboration Divorce
Go to: Description, Initial values, Model Structure

Parameter **col_number**
In Object Firm
Used in: col_Knowl Collaboration Divorce
Go to: Description, Initial values, Model Structure

Parameter **cp**
In Object Firm

Used in: Collaboration Divorce
Go to: Description, Initial values, Model Structure

Variable **LC_KP**
In Object Firm
Used in: KP
Using: t_entry_DBF Abs_P col_Knowl
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"LC_KP"))
{
/*
Capabilities in the technology B through through collaboration

*/

v[0]=(double)t;
v[1]=p->cal("t_entry_DBF",0);
if(v[0]>v[1])
{
v[4]=p->cal("Abs_P",0);//Absorptive capacity
v[6]=p->cal("col_Knowl",0);
v[7]=v[4]*v[6];
}
else
v[7]=0;
res=v[7];
goto end;
}
```

Return

Parameter **CW**
In Object Firm
Used in: Collaboration
Go to: Description, Initial values, Model Structure

Parameter **distance**
In Object Firm
Used in: Collaboration
Go to: Description, Initial values, Model Structure

Variable **col_Knowl**
In Object Firm
Used in: LC_KP
Using: t_entry_DBF Firm_Type col_number col_KP
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"col_Knowl"))
{
/*
Sum of firm's capabilities through colaboration in the technology B
```

```
*/

v[0]=(double)t;
v[1]=p->cal("t_entry_DBF",0);
v[2]=p->cal("Firm_Type",0);
v[3]=p->cal("col_number",0);
if(v[0]>v[1] && v[2]!=3 && v[3]>0)
v[7]=p->sum("col_KP",0);//capabilities transferred in all collabora-
tion
else
v[7]=0;
res=v[7];
goto end;
}
```
Return

Variable **Max_Drug_q**
In Object Firm
Used in: Entry_DBF Max_Drug_q_Industry
Using: Drug_q
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"Max_Drug_q"))
{
/*
Quality of the drug with highest quality level in the portfolio of the
firm
*/
v[0]=p->overall_max("Drug_q",0);
res=v[0];
goto end;
}
```
Return

Parameter **P_Knowl_firm**
In Object Firm
Used in: P_Knowl Entry_DBF
Go to: Description, Initial values, Model Structure

Parameter **Alpha_f**
In Object Firm
Used in: Entry_DBF Alpha
Go to: Description, Initial values, Model Structure

Parameter **beta_f**
In Object Firm
Used in: Entry_DBF beta
Go to: Description, Initial values, Model Structure

Parameter **lambda_f**
In Object Firm

Used in: Entry_DBF lambda
Go to: Description, Initial values, Model Structure

Parameter **DP_SO_p**
In Object Firm
Used in: DP_SO P_SO
Go to: Description, Initial values, Model Structure

Parameter **DS_SO_p**
In Object Firm
Used in: DS_SO S_SO
Go to: Description, Initial values, Model Structure

Variable **DS_SO**
In Object Firm
Used in: (never used)
Using: KS j Firm_Type DS_SO_p
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"DS_SO"))
{
/*
This variable updates the level of Technology B (precision) spillovers
each firm may have access to "DP_SO_p".
These do not consider capabilities of the DBFs.
*/


  v[10]=p->cal("j",0);
  v[0]=0;
  for(cur1=p->up->search("Firm"); cur1!=NULL; cur1=go_brother(cur1) )
     {
      v[6]=cur1->cal("Firm_Type",0);
      v[11]=cur1->cal("j",0);
      if (v[6]==3 || v[11]==v[10])
            v[1]=0;
                  else
      v[1]=cur1->cal("KS",0); //Technology S (Scope) capabilities at
firm level

      v[0]=v[0]+v[1];
      p->write("DS_SO_p",v[0],0);//Maximum amount of spillovers

     }

res=0;
goto end;
}
```

Return

Variable **DP_SO**
In Object Firm
Used in: (never used)
Using: KP j Firm_Type DP_SO_p
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"DP_SO"))
{
/*
This variable updates the level of Technology B (Precision) spillovers
each firm may have access to "DP_SO_p".
These do not consider capabilities of the DBFs.
*/

  v[10]=p->cal("j",0);
  v[0]=0;
  for(cur1=p->up->search("Firm"); cur1!=NULL; cur1=go_brother(cur1) )
     {
      v[6]=cur1->cal("Firm_Type",0);
      v[11]=cur1->cal("j",0);
      if (v[6]==3 || v[11]==v[10])//Firm type=3 are DBFs
      v[1]=0;
      else
      v[1]=cur1->cal("KP",0); //Technology B (precision) capabilities
at firm level
      v[0]=v[0]+v[1];
      p->write("DP_SO_p",v[0],0); //Spillovers availiable
     }

res=0;
goto end;
}
```

Return

Variable **P_SO**
In Object Firm
Used in: P_Knowl
Using: P_SO_r DP_SO_p
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"P_SO"))
{
/*
Spilovers in Technolgy B (Precision)
*/

v[1]=p->cal("DP_SO_p",0);//Volume of capabilities availiable
v[2]=p->cal("P_SO_r",0);//Spillover rate
res=v[1]*v[2];
goto end;
}
```

Return

Variable **S_SO**
In Object Firm
Used in: S_Knowl
Using: S_SO_r DS_SO_p
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"S_SO"))
{
/*
Spilovers in the Technolgy S (Scope)
*/

v[1]=p->cal("DS_SO_p",0);//Volume of capabilities availiable
v[2]=p->cal("S_SO_r",0);//Spillover rate
res=v[1]*v[2];
goto end;
}
```

Return

Variable **P_Adoption_De_2**
In Object Firm
Used in: (never used)
Using: v Adoption_Draw L_Budget Precision_WA Precision_Adoption_2 Precision_Adoption_2_Date P_td_2
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"P_Adoption_De_2"))
{
/*
Technology B Adoption Decition. This function determines whether the
firm adopt
a new form of technology after a technological discontinuity (the
transition from random to rational search
has taken place. This function is located at the firm level.
*/
v[0]=(double)t;

v[1]=p->cal("P_td_2",0);



if (v[0] > v[1])
  {
   v[2]=p->cal("Precision_Adoption_2",0);
   v[3]=p->cal("Precision_WA",0);
   v[4]=p->cal("Adoption_Draw",0);//At the level of the firm
   v[5]=p->son->cal("L_Budget",0);
   v[6]=p->up->cal("v",0);

     if (v[2] == 0 && v[3] > v[4] && v[5]>2*v[6])
       {
         cur1=p->search("Precision_Tech");
```

```
        cur1->write("Precision_Adoption_2",1,0);
        cur1->write("Precision_Adoption_2_Date",(double)t,0);
      }
  }
res=1;
goto end;
}
```
Return

Object Portfolio

Contained in Object: Root->Root2->World->Industry->Firm
Containing: Drug
List of Variables: (no Variables)
List of Parameters: (no Parameters)

Object Drug

Contained in Object: Root->Root2->World->Industry->Firm->Portfolio
Containing: (none)
List of Variables: (no Variables)
List of Parameters: Drug_C, Drug_d, Drug_del, Drug_i, Drug_l, Drug_lp, Drug_M, Drug_phase, Drug_q, Drug_qo, Drug_Type, U

Parameter **Drug_q**
In Object Drug
Used in: Entry_DBF Search Merit Max_Drug_q Collaboration
Go to: Description, Initial values, Model Structure

Parameter **Drug_i**
In Object Drug
Used in: Search
Go to: Description, Initial values, Model Structure

Parameter **Drug_qo**
In Object Drug
Used in: Search
Go to: Description, Initial values, Model Structure

Parameter **Drug_d**
In Object Drug
Used in: Entry_DBF Search Image Merit Collaboration
Go to: Description, Initial values, Model Structure

Parameter **Drug_Type**
In Object Drug
Used in: Entry_DBF Search Merit
Go to: Description, Initial values, Model Structure

Parameter **U**
In Object Drug
Used in: Entry_DBF Merit U_Firm
Go to: Description, Initial values, Model Structure

Parameter **Drug_phase**
In Object Drug
Used in: Search
Go to: Description, Initial values, Model Structure

Parameter **Drug_C**
In Object Drug
Used in: Entry_DBF Image Merit
Go to: Description, Initial values, Model Structure

Parameter **Drug_M**
In Object Drug
Used in: Entry_DBF Search Image
Go to: Description, Initial values, Model Structure

Parameter **Drug_del**
In Object Drug
Used in: Delete Search
Go to: Description, Initial values, Model Structure

Parameter **Drug_l**
In Object Drug
Used in: Collaboration
Go to: Description, Initial values, Model Structure

Parameter **Drug_lp**
In Object Drug
Used in: Collaboration
Go to: Description, Initial values, Model Structure

Object Scope_Tech

Contained in Object: Root->Root2->World->Industry->Firm
Containing: (none)
List of Variables: Scope(1), Scope_Gap(0), Scope_r(1), Scope_TP(0), Scope_V(1), Scope_WA(0)
List of Parameters: a1, a2, Scope_Adoption, Scope_Adoption_Date, Scope_Theta

Variable **Scope**
In Object Scope_Tech
Used in: Entry_DBF Search Scope Scope_TP Scope_Gap
Using: Scope Scope_r Scope_Adoption S_F1 S_F2
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"Scope"))
{
/*
Technological achievement of the firm in the Technology S . Time and
firm specific
*/
v[0]=p->cal("Scope",1);
v[2]=p->cal("Scope_r",1);
v[4]=p->cal("Scope_Adoption",0);

if (v[4]==0)//No adoption
  {
   v[1]=p->cal("S_F1",0);
   if (v[0]>=v[1])
   v[3]=v[1];
   else
   v[3]=v[0]+v[2];//No exponential growth
  }

else
  {
   v[1]=p->cal("S_F2",0);
   if (v[0]>=v[1])
   v[3]=v[1];
   else
   v[3]=v[0]+v[2];//No exponential growth
  }

res=int(v[3]);
goto end;
}
```

Return

Variable **Scope_Gap**
In Object Scope_Tech
Used in: Scope_r
Using: Scope Scope_Adoption S_F1 S_F2
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Scope_Gap"))
{
/*
Technological Gap. Distance of the technological level of the firm to
the
technological frontier.
*/

v[0]=p->cal("Scope",0);
v[4]=p->cal("Scope_Adoption",0);
if (v[4]==0)
v[2]=p->cal("S_F1",0);
else
v[2]=p->cal("S_F2",0);

v[3]=abs(v[2]-v[0]);

res=int(v[3]);
goto end;
}
```

Return

Parameter **Scope_Theta**
In Object Scope_Tech
Used in: Scope_r
Go to: Description, Initial values, Model Structure

Variable **Scope_r**
In Object Scope_Tech
Used in: Entry_DBF Scope
Using: KS Scope_Gap Scope_Theta a1 a2
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"Scope_r"))
{
/*
Rate of technological change of the Technology S . The variable is
time and
firm specific. Log linear function.
v[5]=v[0]*pow((1-v[1]),v[3])*pow(v[2],v[4]);
*/

v[0]=p->cal("Scope_Theta",0);//Scalling Parameter
v[1]=p->cal("Scope_Gap",0);
//Distance of the technological level achieved to the technological
frontier
```

```
v[2]=p->cal("KS",0);//Stock of capabilities in Technology S
v[3]=p->cal("a1",0);
v[4]=p->cal("a2",0);
v[5]=UNIFORM(0.8,1.2);


v[6]=v[0]*pow((v[1]),v[3])*pow(v[2],v[4])*v[5];//With random factor
/*
v[6]=v[0]*pow((v[1]),v[3])*pow(v[2],v[4]);
*/
v[7]=int(v[6]*1000);
res=v[7]/1000;
goto end;
}
```
Return

Parameter **a1**
In Object Scope_Tech
Used in: Scope_r
Go to: Description, Initial values, Model Structure

Parameter **a2**
In Object Scope_Tech
Used in: Scope_r
Go to: Description, Initial values, Model Structure

Variable **Scope_TP**
In Object Scope_Tech
Used in: Scope_WA
Using: Scope Scope_Adoption S_F1 S_F2 Scope_Min
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Scope_TP"))
{
/*
Fraction of the frontier cover by the firm
*/
v[0]=p->cal("Scope_Adoption",2);
v[1]=p->cal("Scope",0);
v[3]=p->cal("Scope_Min",0);

if (v[0]==0)
v[2]=p->cal("S_F1",0);
else
v[2]=p->cal("S_F2",0);

v[4]=(abs(v[1]-v[3])/abs(v[2]-v[3]));
v[5]=int(v[4]*10);

res=v[5]/10;
goto end;
```

```
}
```
Return

Variable **Scope_WA**
In Object Scope_Tech
Used in: S_Adoption_De
Using: LB_KK ap v Scope_TP
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Scope_WA"))
{
v[0]=p->cal("LB_KK",0);//Level of capabilities in extenal learning
v[1]=p->cal("Scope_TP",0);//Technological position of the firm
v[2]=p->cal("ap",0);//Scalling Parameter
v[3]=p->cal("v",0);//Uncertainty and other factors that influence the
adoption decition
/*
Uncertainty and other factors that influence the adoption decition.
The probability of adopting a technology after a technological discon-
tinuity is a
function of the level of capabilities in external learning, the tech-
nological position
of the firm in the technology applied.
*/

v[5]=1-exp(-v[2]*pow(v[0],2)*pow(v[1],0.1)/v[3]);
/*
v[6]=int(v[5]*10);

res=v[6]/10;
*/
res=v[5];
goto end;
}
```
Return

Parameter **Scope_Adoption**
In Object Scope_Tech
Used in: S_Knowl Entry_DBF S_Adoption_De Scope_V Scope Scope_TP Scope_Gap
Go to: Description, Initial values, Model Structure

Variable **Scope_V**
In Object Scope_Tech
Used in: Scope_V
Using: v j v_decr_rate Scope_Adoption Scope_V Scope_Adoption_Date
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"Scope_V"))
{
/*
The adoption expenditures for adopting advances in the Technology S
```

```
*/

v[0]=p->cal("Scope_Adoption",0);
v[1]=p->cal("Scope_Adoption_Date",0);
v[2]=p->cal("v",0);
v[3]=p->cal("Scope_V",1);
v[4]=(double)t-1;
v[6]=p->cal("v_decr_rate",0);
v[7]=p->cal("j",0);

if (v[0]!= 0)
  {
   if (v[1]==v[4])
   v[5]=v[2];
   else
   v[5]=v[6]*v[3];
  }
else
v[5]=0;

res=v[5];
goto end;
}
```

Return

Parameter **Scope_Adoption_Date**
In Object Scope_Tech
Used in: S_Adoption_De Scope_V
Go to: Description, Initial values, Model Structure

Object Precision_Tech

Contained in Object: Root->Root2->World->Industry->Firm
Containing: (none)
List of Variables: Precision(1), Precision_Gap(0), Precision_r(1), Precision_TP(0), Precision_V(1), Precision_WA(0)
List of Parameters: b1, b2, Precision_Adoption_1, Precision_Adoption_1_Date, Precision_Adoption_2, Precision_Adoption_2_Date, Precision_Theta, pwa_power

Variable **Precision**
In Object Precision_Tech
Used in: Entry_DBF Search Precision Precision_TP Precision_Gap
Using: Precision Precision_r Precision_Adoption_1 Precision_Adoption_2 P_F1 P_F2 P_td_1 P_F3
Go to: Description, Initial values, Model Structure

Equation Code:

```
if(!strcmp(label,"Precision"))
{
/*
Technological Level of the firm in the Technology B. Firm and time
specific
*/
v[0]=p->cal("Precision",1);
v[2]=p->cal("Precision_r",1);
v[4]=p->cal("Precision_Adoption_1",0);
v[41]=p->cal("Precision_Adoption_2",0);

v[7]=p->cal("P_td_1",0);
  if (v[4]==0 && v[41]==0)
  /*
  If the "if condition" in the previous line is true, the company has
not adopted
  */
    {
     v[5]=p->cal("P_F1",0);
     if (v[0]<=v[5])
     v[3]=v[5];
     else
     v[3]=v[0]-v[2];//No exponential growth
    }
  if (v[4]==1 && v[41]==0)
    {
     v[6]=p->cal("P_F2",0);
     if (v[0]<=v[6])
     v[3]=v[6];
     else
     v[3]=v[0]-v[2];//No exponential growth
    }
  if (v[4]==1 && v[41]==1)
        {
     v[6]=p->cal("P_F3",0);
     if (v[0]<=v[6])
     v[3]=v[6];
     else
     v[3]=v[0]-v[2];//No exponential growth
    }

res=int(v[3]);
goto end;
}
```

Return

Variable **Precision_Gap**
In Object Precision_Tech
Used in: Precision_r
Using: Precision Precision_Adoption_1 Precision_Adoption_2 P_F1 P_F2 P_F3
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Precision_Gap"))
{
```

```
/*
technology B Technological Gap.
Distance to the technological frontier of
the Technology B.
*/

v[0]=p->cal("Precision",0);
v[4]=p->cal("Precision_Adoption_1",0);
v[5]=p->cal("Precision_Adoption_2",0);

 if (v[4]==0 && v[5]==0)
 v[2]=p->cal("P_F1",0);
  if (v[4]!=0 && v[5]==0)
 v[2]=p->cal("P_F2",0);
 if (v[4]==1 && v[5]==1)
 v[2]=p->cal("P_F3",0);

v[3]=v[0]-v[2];

res=int(v[3]);
goto end;
}
```
Return

Parameter **Precision_Theta**
In Object Precision_Tech
Used in: Precision_r
Go to: Description, Initial values, Model Structure

Variable **Precision_r**
In Object Precision_Tech
Used in: Entry_DBF Precision
Using: KP Precision_Gap Precision_Theta b1 b2
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"Precision_r"))
{
/*
Rate of technological change in the Technology B. The variable is
time and firm specific. Log linear function. If the min Precision is
1000
and the simulation has 100 runs I need a change of about 1% (0.01) a
nd 2% (0.02)per period.
*/
v[0]=p->cal("Precision_Theta",0); //Scale-Parameter
v[2]=p->cal("KP",0); //Stock of capabilities in the Technology B
v[1]=p->cal("Precision_Gap",0); //Distance to the technological fron-
tier
v[3]=p->cal("b1",0);
v[4]=p->cal("b2",0);
v[6]=UNIFORM(0.8,1.2);

/*v[5]=v[0]*pow(v[1],v[3])*pow(v[2],v[4])*v[6];//With the precision
```

```
gap
*/
v[5]=v[0]*pow(v[1],v[3])*pow(v[2],v[4]);//With the precision gap with-
out random!

v[7]=int(v[5]*1000);
res=v[7]/1000;
goto end;
}
```
Return

Parameter **b1**
In Object Precision_Tech
Used in: Precision_r
Go to: Description, Initial values, Model Structure

Parameter **b2**
In Object Precision_Tech
Used in: Precision_r
Go to: Description, Initial values, Model Structure

Variable **Precision_TP**
In Object Precision_Tech
Used in: Entry_DBF Precision_WA
Using: Precision Precision_Adoption_1 Precision_Adoption_2 P_F1 P_F2 Precision_Max P_F3
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Precision_TP"))
{
/*
Fraction of the frontier cover by the firm
*/
v[0]=p->cal("Precision_Adoption_1",2);
v[4]=p->cal("Precision_Adoption_2",2);
v[1]=p->cal("Precision",0);
v[3]=p->cal("Precision_Max",0);



 if (v[0]==0 && v[4]==0)
 v[2]=p->cal("P_F1",0);
  if (v[0]!=0 && v[4]==0)
 v[2]=p->cal("P_F2",0);
 if (v[0]==1 && v[4]==1)
 v[2]=p->cal("P_F3",0);

v[4]=(abs(v[1]-v[3])/abs(v[2]-v[3]));
/*
v[5]=int(v[4]*10);
```

```
res=v[5]/10;
*/
res=v[4];
goto end;
}
```
Return

Variable **Precision_WA**
In Object Precision_Tech
Used in: Entry_DBF P_Adoption_De_1 P_Adoption_De_2
Using: LB_KK ap v Precision_TP pwa_power
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Precision_WA"))
{
/*
The probability of adopting a technology after a technological discon-
tinuity is a function of the level of capabilities in external learn-
ing, the technological position of the firm in the technology applied
*/

v[0]=p->cal("LB_KK",0);
v[1]=p->cal("Precision_TP",0);//Technological position of the firm
v[2]=p->cal("ap",0);//scalling parameter
v[3]=p->cal("v",0);//Uncertainty and other factors that influence the
adoption decition
v[7]=p->cal("pwa_power",0);//set to 2!!!
/*
v[5]=1-exp(-v[2]*pow(v[0],v[7])*v[1]/v[3]);
*/
v[5]=1-exp(-v[2]*pow(v[0],v[7])/v[3]);//without influence of the
TP!!!!


/*
v[6]=int(v[5]*10);
res=v[6]/10;
*/

res=v[5];
goto end;
}
```
Return

Parameter **Precision_Adoption_1**
In Object Precision_Tech
Used in: P_Knowl Entry_DBF P_Adoption_De_1 Precision_V Precision
Precision_TP Precision_Gap
Go to: Description, Initial values, Model Structure

Variable **Precision_V**
In Object Precision_Tech
Used in: Precision_V V
Using: v v_decr_rate Precision_Adoption_1 Precision_V Precision_Adoption_1_Date
Go to: Description, Initial values, Model Structure
Equation Code:

```
if(!strcmp(label,"Precision_V"))
{
/*
The adoption expenditures for adopting advances in the Technology B
*/

v[0]=p->cal("Precision_Adoption_1",0);
v[1]=p->cal("Precision_Adoption_1_Date",0);
v[2]=p->up->cal("v",0);//Initial Adoption cost
v[3]=p->cal("Precision_V",1);
v[4]=(double)t-1;
v[6]=p->cal("v_decr_rate",0);//decreasing rate of adoption costs

if (v[0] != 0)
  {
   if (v[1]==v[4])
   v[5]=v[2];
   else
   v[5]=v[6]*v[3];//The adoption cost decreses at the .9 rate
  }
else
v[5]=0;

res=v[5];
goto end;
}
```

Return

Parameter **pwa_power**
In Object Precision_Tech
Used in: Precision_WA
Go to: Description, Initial values, Model Structure

Parameter **Precision_Adoption_1_Date**
In Object Precision_Tech
Used in: P_Adoption_De_1 Precision_V
Go to: Description, Initial values, Model Structure

Parameter **Precision_Adoption_2**
In Object Precision_Tech
Used in: Entry_DBF Search P_Adoption_De_2 Collaboration Precision Precision_TP Precision_Gap
Go to: Description, Initial values, Model Structure

Parameter **Precision_Adoption_2_Date**
In Object Precision_Tech
Used in: P_Adoption_De_2
Go to: Description, Initial values, Model Structure

Object Network

Contained in Object: Root->Root2->World->Industry->Firm
Containing: col
List of Variables: (no Variables)
List of Parameters: (no Parameters)

Object col

Contained in Object: Root->Root2->World->Industry->Firm->Network
Containing: (none)
List of Variables: (no Variables)
List of Parameters: col_date, col_DBF, col_divorce, col_divorce_date, col_j, col_KP, col_LF, DW

Parameter **col_LF**
In Object col
Used in: Collaboration
Go to: Description, Initial values, Model Structure

Parameter **col_date**
In Object col
Used in: Collaboration Divorce
Go to: Description, Initial values, Model Structure

Parameter **col_KP**
In Object col
Used in: col_Knowl Collaboration Divorce
Go to: Description, Initial values, Model Structure

Parameter **col_j**
In Object col

Used in: (never used)
Go to: Description, Initial values, Model Structure

Parameter **col_DBF**
In Object col
Used in: Collaboration Divorce
Go to: Description, Initial values, Model Structure

Parameter **col_divorce_date**
In Object col
Used in: Divorce
Go to: Description, Initial values, Model Structure

Parameter **DW**
In Object col
Used in: Divorce
Go to: Description, Initial values, Model Structure

Parameter **col_divorce**
In Object col
Used in: Divorce
Go to: Description, Initial values, Model Structure

Object Space

Contained in Object: Root->Root2->World
Containing: Mol
List of Variables: Generics(0), Init2(0)
List of Parameters: fda, Pd, Size

Variable **Init2**
In Object Space
Used in: (never used)
Using: Size lp i g_average1 g_st_dv1 g Mol_d Mol_phase g_average2 g_st_dv2
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Init2"))
{
 /*
  Technical initialization function. It is computed only once and then
it is transformed in a parameter and never computed again. This equa-
tion sets the search space of molecules availiable for the drug pro-
ducers to discover and develop drugs.
```

```
 */
 cur=p->search("Mol");//Object
 v[0]=cur->cal("i",0);//Identification parameter
 v[1]=p->cal("Size",0);//Size or the search space

 while( v[0] < v[1] )
 {
   cur1=p->add_an_object("Mol",cur);
   cur1->write("i", v[0]+1, 0 );
   cur1->write("Ip", 0 , 0);
   /*Protection from imitation. Parameter for the protection status of
the molecule.
   The firm that first discovers it has a monopoly in its explotation
for a given
   number of periods. When the patent protection desapears the mole-
cule can be
   exploited by any firm as a generic.
   */

   /*
   The next two lines determine whether the molecule can be discovered
before the
   advent of modern biotech
   */
   v[20]=rnd_integer(1, 3);
   if (v[20]!=1)
   cur1->write("Mol_phase", 2, 0);
    //2==rational searching phase , the number of mols is larger to
capture the larger opportunities for innovation
   else
   cur1->write("Mol_phase", 1, 0);//1==random screening phase

   /*
   Mol_d is the date the molecule is discovered. This parameter is
useful to calculate
   the period in which the discovery looses patent protection. The pa-
rameter has the value
   1000 as long as the molecule has not been discovered. The value 0
is not used in order
   to make sure that the equation "Generics" works.
   */

   cur1->write("Mol_d", 1000, 0); //Patent protection

   /*
   True Quality of the Molecule. Is calculated for every molecule at
the beginning
   of the model and it does not change. It is determined by a random
process. The average
   depends on the phase the molecule can be discovered (phase 1 or 2).
   */

    if (v[20]!=1)
     {
     v[11]=p->cal("q_average2",0);//Quality average for drugs that can
be discovered in the rational searching phase
     v[12]=p->cal("q_st_dv2",0);//
```

```
     }
    else
     {
     v[11]=p->cal("q_average1",0);//Quality average for drugs that can
be discovered in the random screening phase
     v[12]=p->cal("q_st_dv1",0);
     }

   v[10]=norm(v[11],v[12]);
   v[13]=round(v[10]);//Quality of the potential drugs
   if (v[13]<0)
   cur1->write("q", 0 , 0); //True Quality can not be negative
   else
   cur1->write("q", v[13] , 0);

   v[0] = v[0] + 1;
 }

 param=1;
 res=0;
 goto end;
}
```

Return

Parameter **Size**
In Object Space
Used in: Init2 Search Start
Go to: Description, Initial values, Model Structure

Parameter **Pd**
In Object Space
Used in: Generics
Go to: Description, Initial values, Model Structure

Variable **Generics**
In Object Space
Used in: Search
Using: Pd Ip Mol_d
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Generics"))
{
/*
This action explores the search space every time is activated in order
to vary the parameter
Ip according to the statuts of the molecule (discovered or not) and if
appropiate (according
to the patent duration parameter) transform it into a drug that can be
imitated.
*/
last_update--;//repeat the computation any time is requested
if(c==NULL)//Avoids to be computed when the system activates the equa-
tion
```

```
 {
  v[0]=p->cal("Pd",0);//Patent duration
  CYCLE(cur, "Mol")
   {
    v[1]=(double)t;//Current period
    v[2]=cur->cal("Ip",0);//Protection Status
    v[3]=cur->cal("Mol_d",0);//Discovery date. If it has not been dis-
covered Mol_d=1000

    if (v[2] == 1 && v[1]-v[3] >= v[0])
    cur->write("Ip",2,0);
   }

  res=-1;
  goto end;
 }

res=1;
goto end;
}
```

Return

Parameter **fda**
In Object Space
Used in: Search
Go to: Description, Initial values, Model Structure

Object Mol

Contained in Object: Root->Root2->World->Space
Containing: (none)
List of Variables: (no Variables)
List of Parameters: i, Ip, Mol_d, Mol_phase, q, q_average1, q_average2, q_st_dv1, q_st_dv2, go

Parameter **Ip**
In Object Mol
Used in: Init2 Generics Search
Go to: Description, Initial values, Model Structure

Parameter **i**
In Object Mol
Used in: Init2 Search
Go to: Description, Initial values, Model Structure

Parameter **q_average1**
In Object Mol
Used in: Init2
Go to: Description, Initial values, Model Structure

Parameter **q_st_dv1**
In Object Mol
Used in: Init2
Go to: Description, Initial values, Model Structure

Parameter **q**
In Object Mol
Used in: Init2 Search
Go to: Description, Initial values, Model Structure

Parameter **qo**
In Object Mol
Used in: Search
Go to: Description, Initial values, Model Structure

Parameter **Mol_d**
In Object Mol
Used in: Init2 Generics Search
Go to: Description, Initial values, Model Structure

Parameter **Mol_phase**
In Object Mol
Used in: Init2 Search
Go to: Description, Initial values, Model Structure

Parameter **q_average2**
In Object Mol
Used in: Init2
Go to: Description, Initial values, Model Structure

Parameter **q_st_dv2**
In Object Mol
Used in: Init2
Go to: Description, Initial values, Model Structure

Object Knowledge_Base

Contained in Object: Root->Root2->World
Containing: (none)
List of Variables: P_Knowl(0), Rational_Phase_Knowlbase(0), S_Knowl(0), Scope_New_Knowlbase(0)
List of Parameters: P_complex, P_complex_2, P_complex_3, P_F1, P_F2, P_F3, P_PR_1, P_PR_2, P_sc, P_sc_2, P_td_1, P_td_2, Precision_Max, S_complex, S_complex_2, S_F1, S_F2, S_PR_1, S_PR_2, S_sc, S_sc_2, S_td, Scope_Min

Parameter **S_PR_1**
In Object Knowledge_Base
Used in: S_Knowl
Go to: Description, Initial values, Model Structure

Parameter **P_PR_1**
In Object Knowledge_Base
Used in: P_Knowl
Go to: Description, Initial values, Model Structure

Parameter **S_PR_2**
In Object Knowledge_Base
Used in: S_Knowl
Go to: Description, Initial values, Model Structure

Parameter **P_PR_2**
In Object Knowledge_Base
Used in: P_Knowl
Go to: Description, Initial values, Model Structure

Parameter **S_F1**
In Object Knowledge_Base
Used in: Scope Scope_TP Scope_Gap
Go to: Description, Initial values, Model Structure

Parameter **S_F2**
In Object Knowledge_Base
Used in: Scope Scope_TP Scope_Gap
Go to: Description, Initial values, Model Structure

Parameter **P_F1**
In Object Knowledge_Base
Used in: Precision Precision_TP Precision_Gap
Go to: Description, Initial values, Model Structure

Parameter **P_F2**
In Object Knowledge_Base
Used in: Precision Precision_TP Precision_Gap
Go to: Description, Initial values, Model Structure

Parameter **S_td**
In Object Knowledge_Base
Used in: Scope_New_Knowlbase S_Adoption_De
Go to: Description, Initial values, Model Structure

Parameter **P_td_2**
In Object Knowledge_Base
Used in: Rational_Phase_Knowlbase Rational_Phase_Industry Search P_Adoption_De_2
Go to: Description, Initial values, Model Structure

Parameter **P_td_1**
In Object Knowledge_Base
Used in: Rational_Phase_Knowlbase P_Adoption_De_1 Precision
Go to: Description, Initial values, Model Structure

Variable **Rational_Phase_Knowlbase**
In Object Knowledge_Base
Used in: (never used)
Using: P_td_2 P_td_1 P_complex P_complex_2 P_sc_2 P_complex_3
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"Rational_Phase_Knowlbase"))
{
/*
The technological discontinuity with the revolution of molecular biol-
ogy in the 1950s.
Transition to rational drug discovery.
*/
v[0]=(double)t;
v[1]=p->cal("P_td_1",0);//Phase II starts- Revolution of mol biol
1950s
v[11]=p->cal("P_td_2",0);//Phase III starts- Modern Biotech
v[2]=p->cal("P_complex_2",0);//complexity after the revolution of mol
biol
v[22]=p->cal("P_complex_3",0);//complexity after the emergence of mod-
ern biotech
v[3]=p->cal("P_sc_2",0);//Depreciation Rate of technological capabili-
ties after the revolution of mol biol

if (v[0] >= v[1] && v[0] < v[11])
{
 p->write("P_complex",v[2], 0);//complexity after the revolution of
mol biol
}
```

```
if (v[0] >= v[11])
 p->write("P_complex",v[22], 0);//complexity after the emergence of
modern biotech

res=1;
goto end;
}
```
Return

Variable **Scope_New_Knowlbase**
In Object Knowledge_Base
Used in: (never used)
Using: S_td S_complex S_complex_2 S_sc S_sc_2
Go to: Description, Model Structure
Equation Code:
```
if(!strcmp(label,"Scope_New_Knowlbase"))
{
/*
The technological discontinuity in the Technology S produces changes
in the knolwedge base.
Attention: In the version of the thesis there is no discontinuity in
the Scope Technology!!!
*/
v[0]=(double) t;
v[1]=p->cal("S_td",0);//not used in the version of the thesis. Set to
t=0.
v[2]=p->cal("S_complex_2",0);//complexity after the discontinuity
v[3]=p->cal("S_sc_2",0);//Depreciation Rate of technological capabili-
ties after the discontinuity

/*
if (v[0] >= v[1])it has been changed for the version without disconti-
nuity
*/

if (v[0] >= 0)
{
 p->write("S_complex",v[2], 0);//complexity
 p->write("S_sc",v[3], 0);//speed change
}

res=1;
param=1;
goto end;
}
```
Return

Parameter **Scope_Min**
In Object Knowledge_Base
Used in: Scope_TP
Go to: Description, Initial values, Model Structure

Parameter **Precision_Max**
In Object Knowledge_Base
Used in: Precision_TP
Go to: Description, Initial values, Model Structure

Variable **S_Knowl**
In Object Knowledge_Base
Used in: LB_KS
Using: S_SO Scope_Adoption S_PR_1 S_PR_2
Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"S_Knowl"))
{
/*
Knowledge base to develop the Technology S . It is firm specific in
the sense that
it depends on whether the companies have perceived discontinuities or
not.

In the version of the HFM model developed in the thesis technology S
does not experience any discontinuity.
*/

last_update--;//repeat the computation any time is requested
if(c==NULL)//Avoids to be computed when the system activates the equa-
tion
{
res=-1;
goto end;
}

v[0]=c->cal("S_SO",0);//Spillovers are firm specific

v[1]=c->cal("Scope_Adoption",0);//This parameter does not change since
in this version of the model there is no discontinuity in the scope
technology!!!!!
if (v[1]==0)
 v[2]=p->cal("S_PR_1",0);//Contribution to the knowledge base of tech-
nology S of public research before a doscontinuity
else
 v[2]=p->cal("S_PR_2",0);//Contribution to the knowledge base of tech-
nology S of public research after a discontinuity

res=v[0]+v[2];
goto end;
}
```

Return

Variable **P_Knowl**
In Object Knowledge_Base
Used in: LB_KP
Using: P_Knowl_firm P_SO Precision_Adoption_1 P_PR_1 P_PR_2

Go to: Description, Model Structure
Equation Code:

```
if(!strcmp(label,"P_Knowl"))
{
/*
Knowledge base to develop the Technology B. Knowledge base to develop
the Technology S. It is firm specific in the sense that it depends on
whether the companies have perceived discontinuities or not.
*/

last_update--;//repeat the computation any time is requested
if(c==NULL)//Avoids to be computed when the system activates the equa-
tion
{
res=-1;
goto end;
}

v[0]=c->cal("P_SO",0);// Spillovers are firm specific
v[1]=c->cal("Precision_Adoption_1",0);

if (v[1]==0)
 v[2]=p->cal("P_PR_1",0);//Contribution to the knowledge base of tech-
nology B of public research before the discontinuity
else
v[2]=p->cal("P_PR_2",0);//Contribution to the knowledge base of tech-
nology B of public research after the discontinuity

v[3]=v[0]+v[2];
c->write("P_Knowl_firm",v[3],0);
res=v[3];
goto end;
}
```

Return

Parameter **S_complex**
In Object Knowledge_Base
Used in: Scope_New_Knowlbase Abs_S
Go to: Description, Initial values, Model Structure

Parameter **S_complex_2**
In Object Knowledge_Base
Used in: Scope_New_Knowlbase
Go to: Description, Initial values, Model Structure

Parameter **P_complex**
In Object Knowledge_Base
Used in: Rational_Phase_Knowlbase Abs_P
Go to: Description, Initial values, Model Structure

Parameter **P_complex_2**
In Object Knowledge_Base
Used in: Rational_Phase_Knowlbase
Go to: Description, Initial values, Model Structure

Parameter **S_sc**
In Object Knowledge_Base
Used in: Scope_New_Knowlbase KS
Go to: Description, Initial values, Model Structure

Parameter **S_sc_2**
In Object Knowledge_Base
Used in: Scope_New_Knowlbase
Go to: Description, Initial values, Model Structure

Parameter **P_sc**
In Object Knowledge_Base
Used in: Rational_Phase_Industry KP
Go to: Description, Initial values, Model Structure

Parameter **P_sc_2**
In Object Knowledge_Base
Used in: Rational_Phase_Knowlbase Rational_Phase_Industry
Go to: Description, Initial values, Model Structure

Parameter **P_F3**
In Object Knowledge_Base
Used in: Precision Precision_TP Precision_Gap
Go to: Description, Initial values, Model Structure

Parameter **P_complex_3**
In Object Knowledge_Base
Used in: Rational_Phase_Knowlbase
Go to: Description, Initial values, Model Structure