TAB OFFICE OF TECHNOLOGY ASSESSMENT AT THE GERMAN BUNDESTAG

SYNTHETIC BIOLOGY – THE NEXT PHASE OF BIOTECHNOLOGY AND GENETIC ENGINEERING

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Summary

- Scientific and technological progress allows to genetically redesign natural organisms in ever more profound ways (synbio in the broader sense). In the long term, the aim is to create artificial biological systems (synbio in the narrow sense).
- Application areas are chemical and energy production, environmental protection as well as the medical sector. Considering the current, early state of research and development, it is impossible to forecast reliably which approaches of synbio will prevail against procedures that make use of the available biological diversity or that are limited to more subtle interventions.
- Risk assessment and the evaluation of substantially modified organisms will require the development and exploration of new methods and procedures.
- Opportunities for different societal groups to participate in the responsible development of synbio are ranging from stakeholder involvement in setting research agendas to DIY biology.
- Dealing with intellectual property within the framework of an increasingly digital economy will also represent a major challenge for the future use of synbio.

What it is about

For more than ten years now, the term »synthetic biol-ogy« (synbio for short) refers to research projects, methods and procedures dealing with the **»redesign« of natural organisms** that goes far beyond what has been possible so far by »traditional« genetic engineering. The approaches involved are envisioned to ultimately give rise to the creation of (completely) artificial »biological« systems. Synbio is the subject of a multitude of studies and opinions from political advisory bodies, ethics commissions, academies and funding organizations. In the public, however, the term is almost unknown. A main reason for this is that there exists no clear-cut, scientifically recognized demarcation to genetic engineering, let alone one that is (easily) understandable to non-experts. As a consequence, it is inherently difficult to examine and to discuss the possible impacts of synbio. For this reason, the TAB report introduces a **basic differentiation** between **synbio in the narrow sense** and **synbio in the broader sense** (see boxes on pages 2 and 3).

Applications of **synbio i. n. s.**, i. e. of artificial, completely »designed« (complex) biological systems or organisms, are still a distant dream. Their **social and political relevance in the years to come** is thus considered to be small. The situation is quite different for **synbio i. b. s.** – which is considered here as the next phase of biotechnology and genetic engineering. Due to increasingly simpler and faster techniques for targeted molecular-biological modification of organisms, a **large number of applications** is expected for the near future. Whereas synbio projects primarily focused on the modification of micro-organisms for industrial and medical use so far, the scientific and regulatory debate from spring 2015 onwards concentrated also on applications of new genetic modification technologies in plants, animals and humans.

So far, the recently developed so-called **genome editing techniques** (such as CRISPR/Cas) have hardly been dealt with under the label of synbio. Their potential for innovation is not so much linked to the visionary notion to completely redesign organisms, but to the simplicity and speed in the targeted modification of genomes – including the human genome. In 2015, it became apparent that a **new round of the debate on genetic engineering** is imminent or has already started at the international and national level. As regards the responsible, further development and potential regulation, it appears evident that **synbio** (at least i. b. s.), »by definition«, **cannot elude this debate.**

Client and topic initiative

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Fields of application

Many research and development approaches of synbio focus on the use of renewable instead of fossil raw materials in chemical and energy production and thus on the **core notion of the (future) »bioeconomy«.** Furthermore, there are potential applications in medicine as well as in the field of environmental sensing and remediation. The objective is always to use synbio in order to overcome or at least extend some of the limitations inherent in biological processes.

Chemical and energy production: A whole series of **new bio-based production processes** has been successfully established by means of synbio i. b. s., particularly regarding high-value aromatic substances, fragrances and other ingredients for the food, cosmetics and detergents industry (such as vanillin or a palm oil substitute). For this, genes from various organisms are typically combined in a recipient organism (yeasts, algae, bacteria) to generate a new optimized metabolic pathway. On a **pre-commercial scale**, this approach has also been used for producing important **commodity chemicals** for the production of polymers (1,3-Propanediol, 1,4-Butanediol), biodegradable plastics (polylactides, polyhydroxyalkanoates) as well as of high-quality **biofuels** (butanol, biodiesel, farnesenes). In Brazil, synthetic diesel fuel is already being tested in local public transport.

Moreover, in the energy sector, research efforts focus on the conversion of raw materials, mainly **lignocellulosic biomass** – the material which represents the largest part of plant biomass and which is not edible (e. g. corn stalks and leaves). The aim is to avoid direct competition with food production and, at the same time, tap a source of raw materials which is available in large quantities.

Status quo: synbio in the broader sense

Synbio i.b.s. refers to all currently pursued approaches regarding the molecular-biological modification of known organisms which are mostly application-oriented and **increasingly based on digital information**. So far, simple approaches for genetically modifying metabolic pathways of organisms (so-called metabolic engineering) were only based on the modification of a small number of genetic elements and often aimed at the optimization of (native) metabolic pathways already existing in natural organisms. But meanwhile **several genetic elements and genes** from different organisms are **combined** and transferred to suitable production organisms in order to produce chemicals by means of bio-synthesis, or to generate genetic circuits for new sensory and regulatory cell functions (see examples in the text). Furthermore, **computer-assisted design and modelling processes** are increasingly used to generate such complex biological functions.

Medical sector: Synbio offers a number of approaches for novel pharmaceuticals and vaccines, therapeutic treatment strategies and diagnostics. Most projects are still in early phases of research. But there are also clinical trials i. a. with **modified viruses for combating cancer**. Semi-synthetic **artemisinin**, an important ingredient of anti-malarial medicine, is already produced on a commercial scale in modified yeast. Moreover, large-scale field experiments for controlling dengue fever by means of **genetically modified mosquitoes** (synbio i. b. s.) are carried out.

Environmental sensing and remediation: As cell-based biosensors, genetically modified micro-organisms (GMMO) can allow an easy and cost-effective measurement of toxic substances in soil or water samples. A first commercially available product is the ARSOlux biosensor for determining the arsenic content in drinking water. If used properly, there will be no release of any GMMO. For the remediation of contaminated soils by means of GMMO, however, no approaches are known that are ready for application. Environmental release is likely to be inevitable and the effective control of the GMMO will pose a pivotal challenge.

Synbio: a key kechnology for the bioeconomy?

Earlier forecasts have seen the greatest potential of synbio in the production of bulk chemicals and in energy production. However, corresponding entrepreneurial activities and **large investments** have recently been **significantly reduced** as a consequence of the fluctuating and overall decreasing oil price. Both chemical and fuel production are addressing mass markets in which new procedures have to prevail against cost-optimized technologies, often established for decades.

Stakeholder engagement in developing the research agenda: resources are required

When it comes to define the orientation of research areas and agendas, European and German research policies increasingly strive to include CSO perspectives. Not only in view of future funding programs for research into the risks, safety and security of synbio, the involvement of representatives from civil society organizations dealing with environmental, developmental and social issues is of particular importance. Without **public funding**, however, a **continuous involvement** will be difficult for them, as they often have only few paid employees the work of whom is financed to a large extent by means of membership fees. For this reason, it appears sensible that research policy would make available funds not only sporadically, but with a long-term commitment regarding an organized participation of representatives from NGOs.

The (few) projects and products which may already become **competitive** today are **low-volume**, but **high-value specialty chemicals, flavoring substances, pharmaceuticals and vaccines.** For these, neither cost nor biosafety/biosecurity issues are playing a major role, because existing or alternative procedures are complex as well and because production processes are restricted to contained systems (bioreactors), or unintended side effects are accepted more readily (pharmaceuticals/therapeutics). With respect to medicines, vaccines or gene therapies in particular, prospects of success are hardly predictable; since very often the effectiveness and relative superiority become evident at rather late stages of development or during application only.

Vision of the future: synbio in the narrow sense

Synbio i.n.s. refers to the production of **cells or organisms** developed from scratch and **designed »de novo«** (or of cell-free biological or biochemical systems). These organisms are intended for the production of any, even completely novel substances or visionary applications in the fields of health, energy or the environment. Characteristic research approaches and methods in this context are the production of entire synthetic genomes, the construction of so-called »minimal cells« or »protocells« (either »top down« by reducing natural cells or »bottom up« or »from scratch« from basic biochemical components) as well as the use of non-natural molecules (»xenobiology«). Protocell approaches involving molecules not present in extant cells may also provide knowledge on the emergence of life (and its chemistry) on Earth.

The **future development** of synbio will on the one hand depend on the **commitment of public and private investors** and on **societal acceptance** on the other. Against this background, society's involvement in a responsible further development of synbio by means of different kinds of participation appears to be essential (see box).

Super-viruses from the synbio lab? Don't panic, but watch out!

Right from the beginning, the scientific and non-scientific debate on synbio has always been accompanied by issues of intentional misuse (»**biosecurity**«). These refer to a criminal (»**biocrime**«) or even malicious (»**bioterrorism**«) use of biological agents or of the underlying knowledge in public, private or illegal research laboratories. However, the most widely discussed risks have been related to medically and epidemiologically motivated research with highly pathogenic viruses carried out in high-level containment laboratories and which usually are not ascribed to synbio. In this context, an intensive debate on **dual use research of concern (DURC)** has emerged internationally and in Germany.

Besides recommending the creation of a national statutory DURC commission, the German Ethics Council particularly emphasized the necessity to systematically integrate the subjects of biosecurity and »dual use« into **university curricula and other training programs** in the life sciences and to create an overall culture of shared responsibility. This is a very challenging task, in particular with respect to universities and other research institutions, due to the high publication pressure and the often precarious employment situation.

If gene synthesis should become increasingly decentralized (and possibly significantly more efficient and less costly) it might also be necessary to deal with the question as to whether **registration and control of devices, their users** and specific **applications** (i.e. of the gene sequences produced) should be and can be performed. Malicious actors will try to elude such a control. For this reason, intelligence and security measures have to be considered as well without excessively restricting well-meaning actors.

Risk assessment will become (even more!) difficult – in need for further research

So far, the risk assessment of genetically modified organisms (GMO) is based on a case-by-case examination and on the comparison with largely similar (»substantially equivalent«) organisms which have been used for a long time already (which are »familiar«). In recent years, it has been pointed out that this procedure is put into question by several scientific and technological developments of synbio. The advances in genome editing techniques may significantly increase the pres-

DIY biology as active Citizen Science: support of »hackerspaces« and citizens' laboratories?

In recent years, projects of **Citizen Science** have been promoted in a targeted way by research policy. In this context, DIY biology represents a **particularly active variant** and combines **very heterogeneous interests** ranging from a mere leisure activity, a claim for participation based on democratic theory to the development of potential business concepts. At least some representatives – due to their combination of a certain affinity for biotechnology and social criticism – stand for a **new voice in the debate on genetic engineering and synbio**. The question is whether a comprehensive involvement of society in scientific progress in synbio should also include the support of bio-hackerspaces. It would also be possible to explore variants of »citizens' laboratories« which are more closely attached to university or research institutes, but are open for the ideas of their users.

sure to adapt risk assessment procedures. The central question is to **what extent and by means of which methods substantially modified** (or even largely »redesigned«) **organisms** capable of propagation and proliferation can be and must be characterized with a view to a **societally acceptable decision-making process regarding the use** of these organisms.

This would require a **new research policy agenda** for biosafety research with regard to synbio i. b. s.. In order to be able to develop this agenda, it would be necessary to reinvestigate the existing unresolved controversies concerning the risk assessment of »conventional« GMO and to carry out a comprehensive and especially **discursive balancing** with regard to the **weak points and controversial issues of risk assessment.** It may not be expected that the controversial issues will be resolved, but the objective should be to improve communication between the different actors with regard to the (still) open questions in biosafety research on GMO.

The relevant issues in the risk assessment of GMO are only partly linked to scientific aspects. Therefore, a future biosafety research program would also have to be **oriented towards social sciences and the humanities;** conceived **on the long term and across policy areas;** and offer **real opportunities for participation**, allowing to bring in the competences and interests of **all relevant societal stakeholders**. The coordination of such a process for developing a research program would have to be carried out by an institution or a (steering) body which is recognized as neutral and fair by as many actors involved as possible.

Points of reference for the sustainable development of synbio research and innovation

Expanding options for action and keeping them open: The most important principle of public R&D funding should be to broaden available options and to keep them open. This prohibits a premature commitment to specific technologies or processes – particularly in view of the complex challenges connected to a global sustainable bio-economy.

Solving problems instead of committing to technologies: The development of technologies – especially of those which are potentially controversial at the societal level – should be oriented towards solutions for societal challenges. The involvement of stakeholders outside the science system or the classical innovation system is of particular importance, as these stakeholders could bring in their expertise and everyday knowledge, e. g. on agricultural or healthcare issues which cannot be provided by scientific analyses and approaches alone.

Sustainable models for the protection and use of intellectual property related to digital data: There is an intense debate in the life sciences, but also beyond, on dealing with intellectual property (IP) within the framework of an increasingly digital economy. The objective is to make use of the increase of knowledge in a way which is as sustainable as possible, i. e. socially equitable, ecologically compatible and economically profitable in the long term. The development of innovative IP models is one of the major challenges for science, economy, society and politics and thus also for technology assessment in the years to come.

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Synthetische Biologie – die nächste Stufe der Bio- und Gentechnologie

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