# Producing food from $CO_2$ using microorganisms: Lots to do, little to lose!

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## 1. Abstract

Background: For the first time, the recently held United Nations Climate Change Conference (COP 28) involved a summit leaders' declaration to include global food production in their action plan to fight climate change. Reducing meat consumption is the primary way to take this fight seriously, nevertheless the global supply of people with high-quality protein is one of the central challenges of the coming decades. Producing microbial protein from $CO_2$ (aka single cell protein, SCP) offers the unique opportunity to recycle both, $CO_2$ from the atmosphere and food side streams, into consumer-oriented foods - an innovative path to a zero-carbon footprint diet.

Scope and approach: The importance of utilizing $CO_2$ as a substrate for microbial food production is underscored by comparative environmental footprint studies of various protein sources. This *commentary* systematically discusses the opportunities and technical challenges in realizing this vision.

Key findings and conclusions: The herein proposed acetate-based $CO_2$-to-food framework carries the potential to decrease the environmental footprint of food production by several orders of magnitude in terms of greenhouse gas emission, water, and land usage. While all relevant process steps are already advanced to a high technological readiness level, the key engineering challenges encompass their consolidation to a circular process, scale-up and product formulation.

**Keywords:** microbial fermentation, circularity; decarbonization; sustainability; microbial protein

## 1. Introduction

Climate change and population growth are the grand challenges of our time. Ending world hunger through improved food security, quality, and sustainability is a top priority on the United Nations agenda of the Sustainable Development Goals. According to two renowned studies from 2018 and 2021, food production contributes to one third of all anthropogenic global greenhouse gas (GHG) generation, such as carbon dioxide ($CO_2$) and methane ($CH_4$) (Poore and Nemecek 2018; Crippa et al. 2021). Processes involved in meat and dairy production are responsible for almost 60% of this emission (Poore & Nemecek, 2018). The *status quo* of the global food production capacity could potentially provide the 7,400 trillion kcal demand for the projected 10 billion world population by 2050 already today. Following this naïve fallacy would however require a 100% plant-based diet. Since a purely vegan diet is neither socially accepted nor politically enforced at the moment this narrative is made to fail. In addition, higher living standards also include a craving for meat above the average requirement, opening a global 100 Mt protein gap (Noorman, 2023).

Nevertheless, there is a growing willingness to reduce or abstain from meat and dairy products for a more environmentally friendly lifestyle in western countries, also in the light of ethical concerns regarding factory farming (Zimmerman, 2024). Plant-based meat substitutes currently have the biggest market impact for vegan or vegetarian food products. Whilst these products outperform the environmental footprint of animal protein, their metrics still mostly reside in the same order of magnitude (Figure 1). Hence, scaling the present global food infrastructure is destined to destabilize the system Earth beyond habitability. Yet, the food industry fuels the worst-case scenario with contributions to global GHG emissions (34%), deforestation (24%), eutrophication (78%), and freshwater scarcity (70%), to name only a few (Crippa et al., 2021; Poore & Nemecek, 2018). Consequences such as rising global temperature and increased likelihood of extreme weather events pose further pushbacks toward securing a stable food supply. Obviously, ‘no innovation’ is a ‘no go’ since a vicious cycle calls for disruptive measures. Several meat and dairy alternatives other than plants implied by the umbrella term ‘alternative protein’ (AP) carry the potential to be this disruptive force. Cultivated meat, cellular agriculture and myco- or single-cell protein are candidates to fill the protein gap with a minimal ecological footprint (Matassa et al., 2020). Replacing meat and dairy with AP formulations in our diet also comes with certain health benefits, even though consumer resentments are often biased toward the opposite (Hartmann et al., 2022). How can this promise become reality when current microbial food processes still depend on agricultural substrates limiting environmental benefits? $CO_2$-based decoupling from agriculture can present itself as an enabling technology for disrupting the *status quo* of protein production, potentially reducing GHG emissions by one order of magnitude (red squares in Figure 1).

While pushing for new food technologies one has to bear in mind that approximately one billion people's lives are entrenched in the livestock industry and associated value chains. Thus, solving the food crisis unfolds as a multilayered problem. The first piece of the puzzle is to overall reduce meat consumption to take pressure from the livestock market, which will also enable more sustainable meat production.

In this *commentary*, we will explore the potential of a fermentation-based framework dedicated to produce microbial food from $CO_2$ (

Figure **2**). Here, the central idea is to use acetogenic gas fermentation in bacteria to convert $CO_2$ from different sources into a few select platform substrates. This aligns with the concept of an acetate-based bioindustry, easing potential synergies and global scaling. In the next step, single food ingredients will be produced from platform substrates by means of biomass or precision fermentation. In theory, leveraging microorganisms for protein production seems an obvious choice for sustainable food production. Closed fermentation systems possess by far superior water, carbon and nitrogen efficiencies *versus* open plant and animal value chains. Microbial biomass proliferates at time scales of minutes to days instead of months to years, and there is no ethical concern around microbial well-being (Choi et al., 2022). Furthermore, fermentation is independent of climate, arable land, sunlight and most supply chains, if $CO_2$ can be upgraded to a raw material. Unsurprisingly, $CO_2$-to-food has therefore recently become a highly anticipated discipline across research, industry, investment, and policy agencies (Marcellin et al., 2022; Noorman, 2023).

However, there are still significant challenges on the road ahead. For one, fixing $CO_2$ for food production does not automatically result in net-zero products, especially when respiring microorganisms are in play. Leveraging acetogenic fermentation, however, opens the possibility to recycle $CO_2$ from aerobic fermentation steps for a closure of the carbon cycle. In doing so, the global warming potential estimate for microbial protein will fall well below that of plant-based protein. Likewise, closing water and nutrient cycles between coupled fermentations will further reduce the environmental impact. In addition to considerations regarding sustainability, the cost of goods sold (COGS) has to decrease dramatically to achieve cost parity with meat and plant-based protein, which could be accomplished by increasing fermentation scale and TRY (titer, rate yield) metrics. As evident from Figure 1, the energy demand of microbial food is still and will be an issue in the foreseeable future. Utilizing renewable energy, as forecasted in the $CO_2$-based SCP scenarios, displays the potential to decrease energy-related environmental footprints. Finally, microbial food formulations have to attain taste and texture parity with meat products to be considered a 'buy' by the consumer (Hartmann et al., 2022). Setting up microbial platforms that produce single food ingredients beyond protein including carbohydrates, oils, vitamins, flavors, and colorants could further enable flexible and creative novel food formulations that directly address consumers’ cravings (Choi et al., 2022).

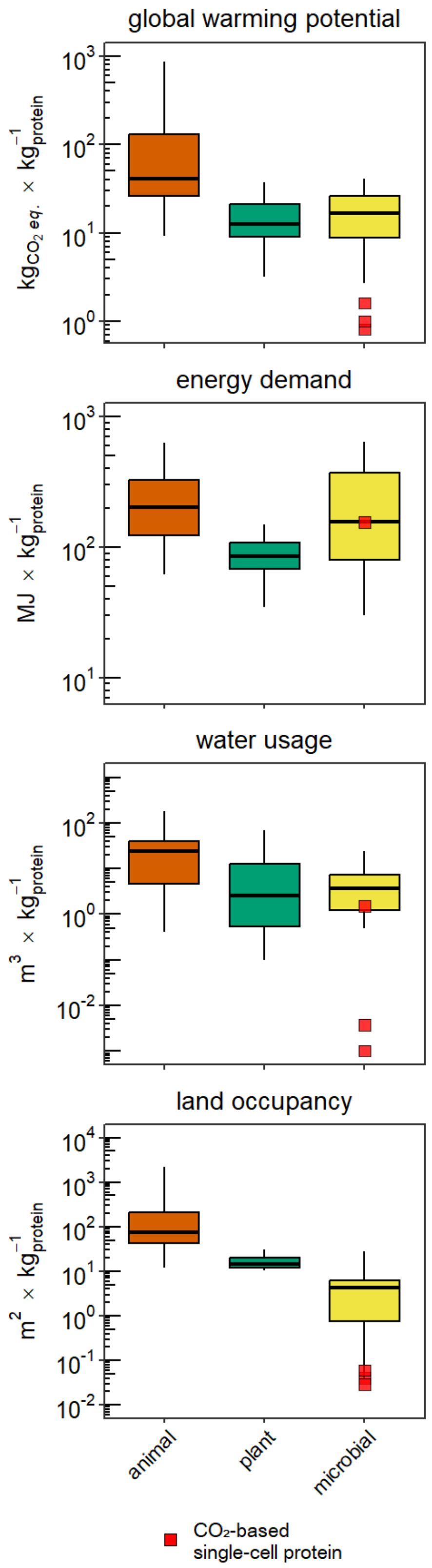

**Figure 1. Literature overview of environmental footprint studies on dietary protein sources.** The data originates from 44 life cycle assessment (LCA) articles and is harmonized to a per kg protein basis. The animal category contains LCA data for beef, pork, and poultry cases. The plant category contains tofu, tempeh, and processed plant-based meat alternative cases. The microbial category contains single-cell protein and mycoprotein cases. LCA data of $CO_2$-based microbial protein is additionally plotted as squares. The upper and lower hinges of the boxplots span the interquartile range (IQR), with the median indicated by black lines. Whiskers extend to a maximum of 1.5 times the IQR in both directions. The raw data and literature sources are available in Appendix A.

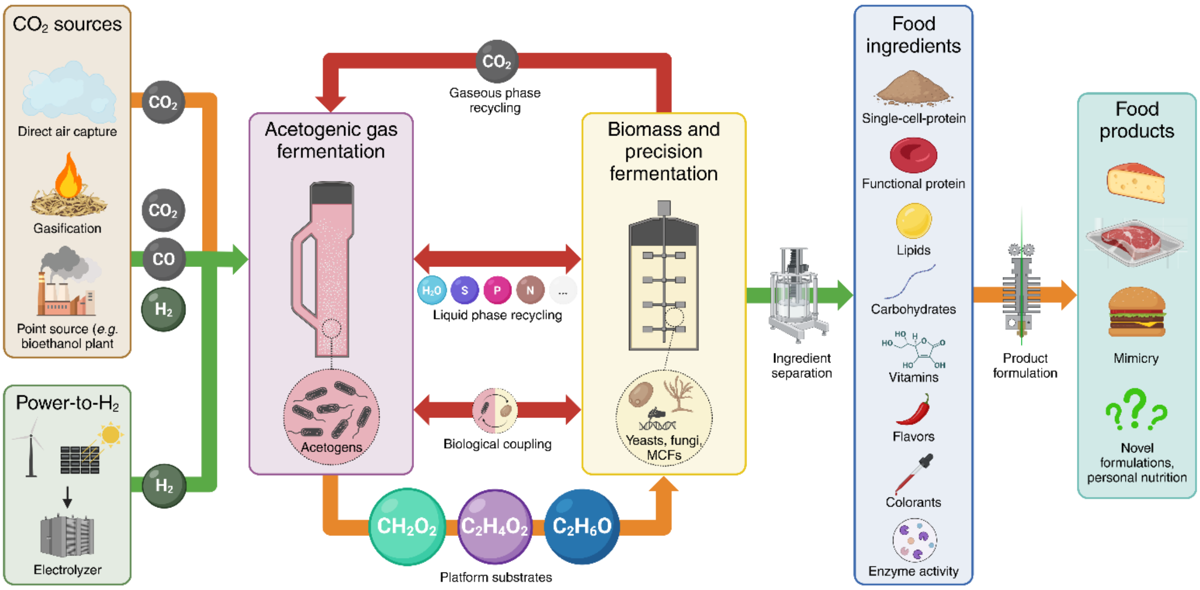

**Figure 2. $CO_2$-based food production framework using microbial fermentation technologies.** Green, orange, and red arrows indicate established, prototypical, and hypothetical processes, respectively. MCF, microbial cell factory.

## 2. Microbial fermentation enables net zero food

The carbon source not only determines the cost of production but also the sustainability of microbial food. Unfortunately, more often than not, both these aspects correlate negatively—a challenge the bio-based fuel and commodity industries know only too well (Pfleger & Takors, 2023). So-called second-generation (2G) feedstocks mitigate carbon emissions and do not compete over farmable land with food crops by using renewable lignocellulosic biomass and other agricultural or industrial side streams. While 2G raw material is relatively cheap and abundant, bioprocess engineers deal with recalcitrant feedstock decomposition, which requires further processing steps, substantially adding to capital (CAPEX) and operational (OPEX) expenditure. Both feedstock complexity and variability impede the selection and/or engineering of a compatible microorganism or microbial community currently preventing the global scaling of the technology. In the end, decades of research and development efforts put into running fermentations with renewables still face fatal process upsets or even bankruptcies on a regular basis. Using renewable marine biomass (3G) is even further away from achieving industrial maturity (Pfleger & Takors, 2023). Thus, both the biofuel and food industries currently prefer crop-derived cellulosic (1G) sugar due to its low cost and high achievable TRY metrics.

1-3G feedstocks will and should have their rightful place in a circular bioeconomy, but reversing the carbon emission trend is only doable when $CO_2$ becomes an economically competitive raw material. Circumventing plant-derived sugars or organic acids as a microbial substrate further adds to food security through land, climate, and supply chain independence. After all, $CO_2$ is a virtually unlimited resource with an estimated one teraton excess in the atmosphere and an annual anthropogenic addition of 40 Gt (Lamboll et al., 2023). Several carbon capture and utilization (CCU) technologies aim to capitalize on this abundance either through direct air capture (DAC) or by tapping concentrated industrial point sources. Different CCU solutions are under active development or already deployed and have been reviewed elsewhere, also in regard to life cycle assessment (Artz et al., 2018; Grim et al., 2020). In the process, $CO_2$ must be reduced or upgraded to $C_{\geq 2}$ compounds for subsequent fermentative valorization as the molecule possesses zero reducing power. Cost-efficient and renewable energy can enable these processes either in a power-2-X context or from on-site power generators, both backed by the global energy transformation.

Though originally not envisioned for upstream integration into microbial food production, some CCUs at advanced technological readiness levels (TRL up to 9, Table 1) yield reclaimable substrates for aerobic bioprocesses (Grim et al., 2020). Suitable products from direct electrosynthesis are methanol, formic acid, ethanol, and acetic acid (Grim et al., 2020). While these reactions offer almost 100 % theoretical $CO_2$ conversion, their application is currently limited as long-term catalyst durability is an issue. Fortunately, the research area is vibrant and breeds more and more innovations. Hann and colleagues, for instance, recently reported an artificial photosynthesis concept using solar energy to convert $CO_2$ to acetic acid with a noticeable energy conversion efficiency exceeding that of plant photosynthesis (Hann et al., 2022).

An even closer look at mother nature offers a myriad of microbial $CO_2$ fixing pathways. Of those, the acetogenic Wood-Ljungdahl pathway (WLP) in bacteria is currently the most efficient $CO_2$ fixing mechanism described (Köpke & Simpson, 2020). Here, so called acetogens employ the water/gas shift (WGS) reaction to reduce $CO_2$ to CO using the reductive power of $H_2$ and produce mostly acetic acid, ethanol, formic or lactic acid in an anaerobic fermentation. The reversible key WGS enzyme CO-dehydrogenase allows acetogens to accept a range of $CO_2$:CO:$H_2$ ratios, opening the door for using variable syngas sources. Syngas, when originating from gasification or pyrolysis of 2-3G feedstocks, could overcome their troublesome reconstitution to a microbial substrate. Aerobic fixation with methano-, hydrogeno- or carboxydodrophic bacteria, on the other hand, displays superior ATP yields. This would allow a one-step SCP production, but significantly trails the energy efficiency of acetogenic conversion (Köpke & Simpson, 2020). Furthermore, microbial fermentations come with the merits of operating in ambient conditions, offering high product selectivity and high process durability (more in section 4) (Köpke & Simpson, 2020).

Fermentative $CO_2$ capture is therefore feasible at scale using industrial point sources that emit syngas. A leading example is LanzaTech, operating plants in China and, most recently, in Belgium to convert steel mill off-gas to biofuel. With policy changes regarding carbon credits, emission penalties, and tax incentives on the horizon, chemical and other industries are slowly getting on track to decarbonize their processes. $H_2$ from renewables will play a central role in accessing $CO_2$ from sources lacking a reductive component, such as aerobic fermentations or DAC. A promising approach is e.g. the production of $H_2$ on demand *via in situ* water electrolysis during fermentation. Direct electrification of the biocatalyst in so-called microbial fuel cells might be a future option, too (Fruehauf et al., 2020).

All in all, acetogenic fermentation technology finds itself positioned in an attractive setup to become a platform process for downstream microbial food production. Its advanced level of development meets a pressing demand for a sustainable bioeconomy. Of particular interest for food production is the ability to funnel several $C_1$ originations toward a select few fermentation substrates. Since acetic acid is on the verge of becoming a platform chemical entrenched in several bio-based industries, it will help to draw the attention of investors and policymakers alike.

**Table 1: $CO_2$ reduction and upgrading technologies yielding suitable substrates for aerobic fermentations with platform organisms and suitability for power-to-X integration.** Water electrolyzers are included as an intermediate for indirect methods using $CO_2$ and $H_2$. AE, aqueous electrolyzer; DSP, downstream processing; GDE; gas diffusion electrode; PEM, proton exchange membrane.

| technology | educts | main product | TRL | current limitation | main advantage | literature |
|---|---|---|---|---|---|---|
| **electrochemistry** | | | | | | |
| PEM | $H_2O$ | $H_2$ | 9 | durability | scaled technology | (Grim et al., 2020) |
| alkaline AE | | | 9 | stability against energy fluctuations | scaled technology | (Grim et al., 2020) |
| GDE | $CO_2$, $H_2O$ | methanol | 3 | durability, productivity, selectivity, energy efficiency | | (Stöckl et al., 2022) |
| | | formic acid | 4 | durability, scalability | Faradaic efficiency, selectivity | (Stöckl et al., 2022) |
| | | ethanol | 3 | durability, energy efficiency, selectivity | | (Stöckl et al., 2022) |
| | | acetic acid | 1-3 | durability, energy efficiency | selectivity | (Grim et al., 2020) |
| 2-step catalysis | $CO_2$, $H_2O$ | methanol | 9 | only feasible on $CO_2$ point sources | scaled technology | (Smith et al., 2019) |
| **direct bioelectrochemistry (microbial electrosynthesis)** | | | | | | |
| biofilm-based | $CO_2$, $H_2O$ | formic acid | 2-3 | low $CO_2$ reduction rate, stability, scalability, space-time-yield, selectivity, energy efficiency | continuous processing, easy product recovery, low overpotential | (Fruehauf et al., 2020) |
| | | ethanol | 2-3 | low $CO_2$ reduction rate, stability, scalability, space-time-yield, selectivity, energy efficiency | continuous processing, easy product recovery, low overpotential | (Fruehauf et al., 2020) |
| | | acetic acid | 2-3 | low $CO_2$ reduction rate, stability, scalability, space-time-yield | continuous processing, easy product recovery, low overpotential | (Fruehauf et al., 2020) |
| **indirect bioelectrochemistry** | | | | | | |
| gas fermentation | $CO_2$, $H_2$ | acetic acid | 4-7 | gas solubility, separation costs, lower theoretical energy efficiency, low product concentration | 100 % selectivity possible, theoretical ~100 % $CO_2$ conversion | (Heijstra et al., 2017) |
| | syngas ($CO_2$, CO, $H_2$) | ethanol | 7-9[a] | gas solubility, separation costs, low product concentration | 100 % selectivity possible, flexible syngas composition, scaled technology, theoretical ~100 % $CO_2$ conversion | (Heijstra et al., 2017) |
| **hybrid systems** | | | | | | |
| artificial photosynthesis | $CO_2$, $H_2O$ | acetic acid | 2-3 | scalability, durability, energy efficiency | high selectivity | (Hann et al., 2022) |
| $CO_2$-electrolyser + gas fermentation | | ethanol (as an intermediate toward Butyrate and hexanol) | 5-7 | scalability, energy efficiency | | (Fruehauf et al., 2020) |

[a] TRL is not explicitly mentioned in the referenced work and is based on self-assessment. TRL contextualization follows the specifications given by Buchner and colleagues (Buchner et al., 2019).

## 3. Finding the right microorganisms for improved process economics

Any biotech venture starts by choosing a suitable microorganism with a set of either native or engineered traits to achieve an economic goal. Regarding gas fermentation, various acetogens employ the WLP with nuanced genetic backgrounds, resulting in strain-specific combinations of substrate and product spectrum, growth rate, product selectivity, carbon yield, or cultivation parameters (Sun et al., 2019). For instance, *Moorella thermoacetica* reduces the contamination risk at cultivation temperatures above 50°C. *Acetobacterium woodii* is particularly efficient in utilizing $CO_2$:$H_2$ mixtures, while *Clostridium ljungdahlii* and *C. autoethanogenum* perform best on syngas. Yet, the merits of acetogens regarding their $CO_2$ fixing efficiency result in low biomass yields rendering this process step rather infeasible for direct SCP production. Furthermore, biomass derived from *Clostridia* is not food grade approved. Hence, a second, aetate-to-food step is therefore necessary.

The list of microbes for food production is extensive as virtually any food ingredient, from micro- to macronutrients, can be produced microbially (Choi et al., 2022; Shi et al., 2022). Biomass fermentation produces whole cells, while sophisticated microbial cell factories (MCF) release functional ingredients in precision fermentations at enhanced TRY metrics. The baker's yeast *Saccharomyces cerevisiae* is a prime MCF example for its proven track record of working at scale with an arsenal of genetic tools available to introduce various heterologous production pathways. Cellular agriculture values yeasts as expression hosts for producing extracellular plant and animal proteins (Dupuis et al., 2023). Impossible Foods Inc. patented an engineered *Komagataella phaffii* strain able to excrete leghemoglobin from soy, giving their plant-based burger patties a meaty note. Even the production of food colorants is possible, such as the recently published engineering work on a *Yarrowia lipolytica* strain able to produce beetroot red in a sustainable and economically feasible manner (Thomsen et al., 2023).

Clinging to known MCFs, however, sometimes limits the optimization potential of TRY metrics. Platform microbes often gained their status based on their century-long history of being a specimen in scientific labs rather than due to their compatibility with, *e.g.* a precision fermentation environment. Fortunately, nowadays it becomes increasingly more feasible to transfer genetic engineering tools to new genetic backgrounds. Hence, a dogmatic shift is in place to find new strains that meet substrate- or fermentation-specific demands before initiating process and strain engineering.

In addition, there is a yet untapped potential of undiscovered new microbial hosts, pathways, and enzymes, probably best reflected by the terms 'microbial dark matter' (MDM) and 'functional dark matter' (FDM). The former represents the around 99% of microorganisms that have not been cultivated to date while the latter refers to uncharacterized functions of protein-encoding genes (Kaster & Sobol, 2020). Both MDM and FDM are turning more and more into exploitable resources enabled by environmental sequencing, advanced *-omics* methodologies and the use of artificial intelligence (AI) (Ardern et al., 2023). There are already some noteworthy examples of food ingredient-producing strains originating from environmental probing. Nature's Fynd, for instance, is a company currently marketing a protein rich in fiber, vitamins, and amino acids derived from the filamentous fungi *Fusarium* strain *flavolapis,* which was isolated from hot springs in the Yellowstone National Park (Furey et al., 2022). Another example comes from Solar Foods, a Finnish producer of SCP that isolated its *Xanthobacter* strain from forest soil (Banks et al., 2022).

Examples of well-known microorganisms that produce food ingredients and can grow on acetate are listet in **Table 2**. Since the anticipated substrate displays a toxic effect as it changes the cellular pH upon dissociation once internalized, improved acetic acid tolerance above the natural 0.5% (w/w) threshold is, thus, essential. Recently the acetic acid tolerance of an already industrially deployed yeast  was engineered into a non-tolerant yeast using whole genome transformation (Stojiljkovic et al., 2022). Adaptive laboratory evolution is another technique where a selective pressure, such as exposure to acetic acid, is repeatedly applied to proliferating cells until mutants with superior tolerance levels prevail. Some cutting-edge concepts empower synthetic biology with AI and automation to create virtually any phenotype regarding a host's environmental compatibility, TRY metric, or engineered production pathway. Multiple iterations over design, build, test, and learn cycles in so-called biofoundries are employed until a desired trait is observed. These optimization routines have long found their way into the industry, speeding up strain engineering times considerably.

**Table 2. Examples of microbial food ingredients for human consumption.** The list focuses on processes at advanced technological readiness level (TRL) using microorganisms with the ability to grow heterotrophically on acetic acid.

| product | description | microbial producer | TRL | reference |
|---|---|---|---|---|
| **single-cell protein** | | | | |
| filamentous fungi | taste and texture component of meat alternatives | *Fusarium venenatum*[a], *Lentinula edodes* | 9 | (Banks et al., 2022) |
| yeast | savory ingredient, protein rich powder as food supplement | *Saccharomyces cerevisiae*, *Yarrowia lipolytica*[b] | 9 | (Chai et al., 2022) |
| bacteria | protein rich texturizer | proprietary *Xanthobacter tagetidis* strain (VTT-E-193585) | 7-8[c] | (Banks et al., 2022) |
| **functional proteins** | | | | |
| β-lactoglobulin | bovine whey protein substitute | *Trichoderma reesei* | 4-6[c] | (Banks et al., 2022) |
| leghemoglobin | soy-derived heme providing meaty taste and red color | *Komagataella phaffii* | 5-7[c] | (Shi et al., 2022) |
| myoglobin | mammal-derived heme providing meaty taste and red color | *Komagataella phaffii* | 5-7[c] | (Shi et al., 2022) |
| casein | milk protein substitute | *Komagataella phaffii* | 4-6[c] | (Banks et al., 2022; Dupuis et al., 2023) |
| collagen | structural/scaffolding protein | undisclosed yeast[d] | 8-9[c] | (Dupuis et al., 2023) |
| **lipids** | | | | |
| 17-eicosapentaenoic acid[e] (EPA) | omega-3 fatty acid source | *Yarrowia lipolytica* | 9 | (Chai et al., 2022) |
| 19-docosahexaenoic acid (DHA) | omega-3 fatty acid source | *Crypthecodinium cohnii*, *Schizochytrium* sp. | 9 | (Chai et al., 2022) |
| γ-linolenic acid (GLA) | omega-6 fatty acid source | *Mucor circinelloides* | 8[c] | (Ghazani & Marangoni, 2022) |
| palmitic, stearic, and oleic acid | cocoa-butter ingredients | *Cryptococcus curvatus* | 9 | (Ghazani & Marangoni, 2022) |
| **carbohydrates** | | | | |
| hyaluronic acid | thickening agent, dietary supplement | *Streptococcus zooepidemicus*, *Streptococcus equi* | 9 | (Shi et al., 2022) |
| xanthan | thickening agent | *Xanthomonas campestris* | 9 | (Sun et al., 2021) |
| cellulose | dietary fiber | *Gluconacetobacter xylinus* | 9 | (Shi et al., 2022) |
| erythritol | sweetener | *Moniliella Pollinis*, *Yarrowia lipolytica*, *Candida magnoliae*, and others | 9 | (Sun et al., 2021) |
| steviol glycosides | sweeteners | undisclosed yeast | | (Chai et al., 2022) |
| **vitamins** | | | | |
| riboflavin | vitamin $B_2$ and colorant | *Ashbya gossypii*, *Bacillus subtilis* | 9 | (Suri et al., 2024) |
| ascobic acid | vitamin C and antioxidant | *Gluconobacter*, *Acetobacter*, *Ketogulonicigenium*, *Pseudomonas*, *Erwinia*, and *Corynebacterium* species | 9 | (Suri et al., 2024) |
| cobalamin | vitamin $B_{12}$ | *Pseudomonas denitrificans* | 9 | (Suri et al., 2024) |
| **Flavors** | | | | |
| vanillin | vanilla flavor | *Saccharomyces cerevisiae* | 9 | (Chai et al., 2022) |
| nootkatone, valencene | citrus flavor | *Rhodobacter sphaeroides* | 9 | (Chai et al., 2022) |
| glutamate | umami flavor | *Corynebacterium glutamicum* | 9 | (Sun et al., 2021) |
| γ-decalactone | peachy flavor | *Yarrowia lipolytica* | 6-8 | (Chai et al., 2022) |
| **colorants** | | | | |
| betanin (beetroot red) | beetroot red with antioxidant properties | *Yarrowia lipolytica* | 4 | (Thomsen et al., 2023) |

|  |  |  |  |  |
|---|---|---|---|---|
| astaxanthin | red-violet pigment with antioxidant properties | *Xanthophyllomyces dendrorhous* | 9 | (Chai et al., 2022) |
| anthraquinone | red pigment (Arpink red$^{\mathrm{TM}}$) | *Penicillium oxalicum* | 9 | (Chai et al., 2022) |
| lycopene | red pigment with antioxidant properties | *Saccharomyces cerevisiae, Blakeslea trispora* | 6-8 | (Sun et al., 2021) |
| β-carotene | red-orange pigment with antioxidant properties, provitamin A | *Blakeslea trispora* | 9 | (Chai et al., 2022) |
| **enzymes** |  |  |  |  |
| chymosin | used for induction of protein coagulation in cheese production | *Aspergillus niger*, *Kluyveromyces lactis* | 9 | (Dupuis et al., 2023) |
| α-amylase | used for starch degradation | *Bacillus* species | 9 | (Raveendran et al., 2018) |
| glucose oxidase | used to improve shelf life and flavor | *Aspergillus niger* | 9 | (Raveendran et al., 2018) |
| proteases | used for meat tenderization | several bacterial and fungal hosts, *e.g. Aspergillus usamii* | 9 | (Raveendran et al., 2018) |

[a] Genome contains 6 uncharacterized acetyl-CoA synthetases with 100 % coverage of the acetyl-CoA synthetase from *Fusarium oxysporum*, which can grow on acetate (Panagiotou et al., 2008).

[b] *Y. lipolytica* SCP products are currently only sold for feed purposes, but were granted food-grade status by the Food and Drug Administration.

[c] TRL is not explicitly mentioned in the referenced work and is based on self-assessment. TRL contextualization follows the specifications given by Buchner and colleagues (Buchner et al., 2019) and commercialized processes are always classified as TRL 9.

[d] The related patent from Modern Meadow mentions a list of 6 possible yeasts genera (*Pichia*, *Candida*, *Komatagaella*, *Hansenula*, *Saccharomyces*, *Cryptococcus*, *Arxula*, *Ogataea*). The collagen currently produced by Evonik is intended for non-food purposes, such as cosmetics and artificial leather

[e] EPAs commercialization by DuPont is discontinued.

## 4. Bioprocess development, side-stream management and the challenge of scale

Despite its merits, including high biocompatibility and growing technological readiness, using acetic acid as an intermediate fermentation substrate comes with its very own challenges (Xu et al., 2017). Secondary food ingredient productions operate best under aerobic fed-batch conditions, where highly concentrated feed solutions well above 600 $g{\cdot}L^{-1}$ glucose are fed in a time-dependent manner to keep the producer in a TRY-maximizing sweet-spot. In contrast, the primary acetogenic fermentation step of the envisoned process framework may yield a continuous supply of acetic acid at a concentration as low as 10 $g{\cdot}L^{-1}$ (Perret et al., 2023). On a molar basis, 60 times more acetic acid effluent is required to feed the same quantity of carbon into the aerobic bioreactor, resulting in immense freshwater consumption and process design challenges. Concentrating acetic acid means adding a process step with high energetic demands appending some 20–30% to COGS (López-Garzón & Straathof, 2014). Furthermore, most concentration unit operations, such as anion exchange chromatography or electrodialysis, suffer from membrane fouling in long-term cultivations. Relying on the dilute substrate, on the other hand, calls for process intensification measures in the aerobic fermentation step that might also add to the cost of production. Low concentrated substrate streams further complicate feed-rate design since under-feeding might evoke culture starvation. Xu and colleagues solved this problem quite elegantly by using the primary feed as a pH-controlling agent (“pH-stat”) and adding a supporting, non-controlled feed at high biomass concentrations (Xu et al., 2017).

Freshwater usage calls for smart side-stream management, shifting from cascading to recycling. On that note, one of biotech’s grand challenges addresses reducing freshwater consumption to raise sustainability. Thus, closing the water loop by back-feeding the cell and oxygen-free broth to the acetogenic fermentation could reduce the freshwater footprint several-fold. This effect is shown by the lowest water usage datapoint in Figure 1, representing 80% water recycling. On the same page is the $CO_2$-rich off-gas stream generated by respiring cells that prevents a net-zero or -negative food production, putting the overall carbon footprint somewhere between that of the plant and animal production routes (Choi et al., 2022). Back-feeding $CO_2$ to the acetogens should therefore not only take $CO_2$ emission out of the equation but also increase the overall carbon efficiency of the process. So far, coupled bioprocesses with complete liquid and gas recycling have not emerged from blueprint to reality. Adding to technical challenges are the added CAPEX and OPEX required to condition side streams for the attached fermentation step.

Furthermore, it is an unexplored field of how coupled fermentation processes depend on each other. The product stream of an acetogenic gas fermentation is by no means stable throughout the process in terms of concentration and composition (Heijstra et al., 2017), and careful analyses and evaluation conciderations on how this affects the biological regulation in the aerobic step is required. At high cell densities, microorganisms further tend to excrete *quorum sensing* molecules that may trigger phenotypic shifts. After all, *quorum sensing* communication between acetogens and yeasts is not uncommon (Leeuwen et al., 2016). Before developing a sustainable and circular $CO_2$-to-food architecture, a series of biological and technical questions therefore need to be addressed. The economic constraint often preventing CAPEX- and OPEX-intensive technical solutions are, luckily, not as strict when producing food for human consumption, as its value resides one order of magnitude above that of feed or most biofuels.

An important, but often neglected topic regarding sustainable protein production is the nitrogen cycle. With an estimated 50% of the global food supply being enabled through the Haber-Bosch process, supplying nitrogen to the plant and animal industries contributes up to 2% of global GHG emissions. Nitrogen efficiencies of the open plant and animal systems do not exceed 16% (Matassa et al., 2020). This low value is caused by exuberant losses into the surroundings taking a further toll on the environment through eutrophication and ozone depletion. Using microbes with nitrogen efficiencies of nearly 100% could cause a plethora of positive second-order effects as nitrogen release in the environment can be completely avoided. Renewable alternatives to produce activated nitrogen are currently under development. The energy-intensive Haber-Bosch process for synthesizing ammonia from nitrogen and hydrogen can be made climate-neutral through technical modifications to use green hydrogen and renewable electricity. This is demonstrated by the first commercial plant for the production of green ammonia realized by the Spanish company Iberdrola in Puertollano. Alternative approaches are power-to-ammonia processes that work with new catalysts at significantly lower temperatures and pressures with new heat integration strategies substituting steam. They enable flexible and decentralised ammonia reactors and energy savings of up to 50% (Torrente-Murciano & Smith, 2023). Others are researching catalysis systems that use light as an energy source for ammonia production (Ashida et al., 2022). However, processes in which nitrogen is produced at room temperature using light, water and molybdenum catalysts are still far from industrial maturity.

The last but unarguably the highest hurdle is bringing a bioprocess to the commercial scale through the so-called valley of death (Witte et al., 2021). Process transfers from lab-scale testing to commercially relevant production tanks do not merely change the reactor volume. Several operational parameters, for instance, the volumetric power input, do not scale linearly with the reactor volume when perfect broth homogenization is the goal. Thus, compromises have to be made that boil down to a heterogeneous reaction space that, more often than not, deteriorates anticipated productivity and pushes a process out of the economic feasibility window (Crater & Lievense, 2018). Other scale-dependent effects include sterility issues, genetic instability due to extended numbers of generations required in large volumes to reach high cell densities, or a discrepancy between substrate preparation protocols across scales.

In reality, most process upsets stem from several superimposed scale-up effects, leaving process engineers dealing with a new reality that was not anticipated in the lab. Process transfer to commercial scale is often taken for granted while engineering the novel product, microorganisms, or process draws all the attention causing investors to bail when faced with the enormous costs of scaling up. Capital investment regarding scale-up unfolds in the range of $10^8$−$10^9$ € during empirical upscaling from pilot- to demo- to production scale—and industrial players rightfully keep their scale-up solutions a secret (Crater & Lievense, 2018). Currently, most precision fermentation companies with commercialized products scaled to medium-sized tanks up to 50 $m^3$. However, COGS start to dramatically decrease above the 50–100$m^3$ range (Synonym, 2023). Thus, bridging the valley of death is recognized as a pivotal problem to solve for a thriving bioeconomy. One way of tackling scale-up is through the so-called rational scale-down route. Here, critical scale-up effects such as concentration gradients are estimated by computational fluid dynamics and biokinetic modeling and translated to scale-down simulators that mimic the scale-up effect *a priori* (Haringa et al., 2018). Another strategy is to outsource the empirical upscaling through scale-up contractors.

## 5. Addressing consumers cravings

Microbial foods need to outperform legacy plant- and animal-derived products to become a disruptive force. So far, we discussed sustainability- and cost-related aspects and see the anticipated $CO_2$-to-food framework on the right path. However, to be accepted, innovative foods also need to convince a broader consumer base through taste and texture parity with meat or dairy (Boukid, 2020). Industry leaders seem to be confident estimating that in less than 20 years' time, the market share of animal meat will only make up 40% of the market (Warschun et al., 2020). Hence, the final challenge involves to create an appealing food product formulation *via* downstream processing.

The initial recovery step following either biomass or precision fermentation is fairly sophisticated from bacteria to algae and for a range of intra- and extracellular products. Some cell wall components of certain microbes require disruption as intact cells are rather indigestible for humans. However, more diet-compatible organisms, such as the fungus *Fusarium venenatum* or the algae *Euglena gracillis* can be consumed without further processing and even serve as a source of fiber (Dekkers et al., 2018). High RNA content, especially in fast-growing microorganisms is another issue since nucleic acids may cause gout or kidney stones but might be overcome by e.g. heat-inactivation.

Formulating a meat-like texture can be done following two paths. The first follows a bottom-up strategy assembling a muscle from scratch. Fibrous building blocks are gained from filamentous biomass or produced *via* wet or electrospinning of isolated protein. These structures are subsequently aligned and cross-linked to yield the structure of muscle cells. The top-down approach applies a force field, *e.g. via* extrusion, on pure or blended biopolymers to structure them toward a meat-like texture neglecting the fibrillar architecture. Dekker and colleagues reviewed the most common techniques, also providing examples of commercialized technologies from both approaches (Dekkers et al., 2018). Additive manufacturing is an emerging trend harnessing 3D-printing technology. The company NovaMeat presented a *faux steak* from the printer and claimed the cost of production to reside at 1.35 € per 50g (Lamb, 2020). Despite such appealing breakthroughs, the path to taste and texture parity is far from complete. Meat is still considered “the real deal” *versus* highly processed mimicries which some consumers regard as unnatural (Hartmann et al., 2022). In light of the complexity that gives meat its characteristic taste, more processing steps are likely required. A word of caution has to be said regarding the number of processing steps and sustainability. Thus, embedding the endeavor of taste parity in a $CO_2$-to-microbial food framework has yet to be addressed.

However, maybe taste and texture parity with meat is not necessary after all. Food and taste are deeply related to cultural memory, and future generations might not miss the taste of meat and dairy products. In addition, we currently witness exciting times where the potential of new technology centered around AI enhanced by robotics and sensor technology is explored in almost any scientific or economic domain. In order to leverage AI for food structuring the variables underlying taste and texture need to be captured numerically. For instance, this gap may be closed by linking process data from the texturizing step, e.g. extrusion, to mechanistic product properties. Electronic microscopy or magnetic resonance imaging technology is under development in an attempt to capture structural properties without mechanistic knowledge. Bringing together information about texture with data related to health, consumer behavior and so on will train AI models enabling an reversed product design route. (Hassoun et al., 2024)

Nevertheless, the successful introduction of microbial food from $CO_2$ requires a deep understanding of product characteristics and the consumer perception that determine rejection or acceptance. The main drivers of AP perception are taste and health motives, familiarity, attitudes, food neophobia, disgust and social norms (Onwezen et al., 2021). Studies and research on strategies (*e.g.* nudging interventions) to motivate climate-friendly protein consumption are needed (Hartmann et al., 2022). Marketing and product framing also need to attend to the consumer’s motivators and demotivators for microbial foods to gain broad market acceptance. Otherwise, they risk failing in market roll-outs, as currently witnessed in the case of insect-based proteins. Pushing narratives such as *“Mouthwatering taste, texture and appearance”* coupled with engaging imagery, apparently, seems to be a strategy that works for plant-based companies (Motif FoodWorks Inc, 2023). A study on Instagram publications found that framing, however, requires careful evaluation of the targeted consumer groups to avoid the emergence of negative attitudes (Laviolette & Godin, 2024). Recently, Banovic and Grunert concluded that highlighting precision fermentation products as “natural” due to their relatedness to traditional fermentation products is currently the go-to motivator for customers to consider microbial foods in their everyday lives (Banovic & Grunert, 2023). The potential of microbial food to decrease the risk of suffering from first world health problems such as diabetes, colon cancer and cardiovascular disease should be addressed more publically, since healthiness is one of the main motivators to adopt a new product group (Onwezen et al., 2021). In addition, with environmental awareness of the consumer on the rise, unsustainable product choices are the second most important purchasing demotivator (Boukid, 2020). Once the environmental benefits of $CO_2$-derived foods become undeniable, the turn-off regarding unsustainable choices might put more pressure on the overall food industry to adopt more sustainable pathways.

## 6. Strategic considerations

A challenge transcending the microbial food industry is the manifesting divergence between the demand for biomanufactured goods and the global bioreactor capacity. This fermentation gap is recognized as a major obstacle since today’s global food-dedicated bioreactor capacity allows to provide 0.4 Mt alternative protein per year, undercutting the global protein demand by a factor of 500 (Noorman, 2023). Tubb and Seba forecasted that the investment landscape is on the right trajectory to fill this gap (Tubb & Seba, 2019). A supporting factor could also be the repurposing of *e.g.* biofuel fermentation capacity due to a shift in the transportation industry toward electric vehicles. However, repurposing the entire global existing bioreactor capacity towards microbial protein production would yield a mere 7-fold production capacity increase. Thus, in particular, the investing and regulatory bodies have to maintain and extend the current momentum around APs to enable a growing bioreactor capacity. Strategic governmental programs in key areas, such as the scale-up challenge, but also circular bioprocessing, host selection, and substrate sourcing should enable research breakthroughs to maintain said momentum. The European Union made a step in this direction by allocating part of its “Horizon Europe” program toward projects dedicated to scale-up. Incentivizing the consumer *via* product costs, of course, not only depends on production technology but also on pricing policies. In Germany, for instance, there is a current discussion on the fact that milk substitutes are taxed at a VAT rate of 19% whereas milk is taxed at 7% (Mridul, 2023). Similarly, enormous subsidies in the agricultural sector keep the price for animal-meat artificially low and thereby giving less incentive for consumers to opt for often more costly alternatives. In this regard, Funke and colleagues calculated a hypothetical tax to offset the environmental and social cost caused by animal meat production, which would increase current meat prices by 20−60% (Funke et al., 2021).

A look at the past is worthwhile to evaluate some risks from similar endeavors, for instance the introduction of SCP as feed starting in the late 1970s. Producing SCP from cheap and abundant substrates, such as methanol, seemed only logical at the time. However, rising methanol prices coupled with price competition from cheaper protein from soybeans ultimately resulted in a discontinuation of Pruteen, the first commercialized SCP product (Marcellin et al., 2022). A similar fate hit Statoil's SCP production line from methane that closed as it was not able to compete with the prices of fish meal in 2006 (Marcellin et al., 2022). To avoid a similar fate for microbially derived protein from $CO_2$, a favorable market momentum has to be preserved until cost parity is achieved. In the meantime, the 2–3-fold price premium that consumers have to pay for meat alternatives poses a realistic threat to the industry (Witte et al., 2021). Global economic slow-downs such as the high inflationary environment in 2023 can quickly turn existing customers away toward more affordable products. If a $CO_2$-to-microbial food infrastructure succeeds in the future, the costs of the carbon feedstock may be neglected leaving renewable energy as the main variable, next to water, influencing OPEX expenditure. This degree of feedstock independence may give this new sector an edge over the mentioned past failures, especially since renewable energy prices are set to stabilize between 3 and 5 ¢·$kWh^{-1}$ in the foreseeable future (Pfleger & Takors, 2023).

## 7. Conclusion

In summary, we find ourselves presented with an opportunity to establish a microbial food framework with a high mitigation potential for the grand challenges of our time: climate change and population growth. From a technical viewpoint, the parts of the sum, including acetogenic, biomass, and precision fermentation, as well as food texturizing technology, are available at high TRLs. Hence, combining existing technologies the proposed $CO_2$-to-food framework poses the key challenge. Overcoming engineering problems such as closing water and carbon cycles, scale-up, microbial efficiency, food texture, and taste will unlock a sustainable and carbon-neutral to negative food production.

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## Declaration of competing interest

None.

## Appendix A. Supplementary data

The following is the Supplementary data to this article.

[LINK]

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