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The four Fs of the knowledge-based BioEconomy – A homage to Christian Patermann

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ABSTRACT

Every discourse about the knowledge-based BioEconomy (KBBE) leads to identification of specific products that can be manufactured through advanced biology-based processes in a fashion more environmentally-friendly, more sustainable and more economically appealing than earlier procedures. Such products can be grouped in at least four types of tangible goods, the reference names of each of which—as entertained by Christian Patermann—starting by an F: food, feed, fuel, fibre. Since the first elaborations of the KBBE to the present time, major conceptual developments and scientific technologies have impacted the biotechnological practices and endowed the four Fs with possibilities that were not anticipated at the time. New scenarios have also emerged—paramount among which is climate crisis. In this context, what started as a strategy to backup the existing industrial system might end up being a phenomenal tool for a much needed revision of our mutuality with the natural world.

Introduction

The onset of modern biotechnology can be tentatively fixed by the mid-late 1970s, during the time of development of recombinant DNA technology (Cavalier-Smith, 1982). Five decades are already long enough to have witnessed a number of major local and global socioeconomic changes (e.g. globalization), game-changing technologies (e.g. the internet) and the onset of planet-wide threats (e.g. climate crisis). Such developments have been accompanied in the realm of Life Sciences research by awesome discoveries and novel methodologies that reach out to this day. Just to mention a few examples, the polymerase chain reaction (PCR; Bartlett and Stirling, 2003), the production of recombinant antibodies (Winter, 2019) and CRISPR-based genome editing (Strzyz, 2020), each of these having deserved respective Nobel Awards in 1993, 2018 and 2020. In parallel, the narrative of biotechnology has also undergone an evolution from being just an anecdotal complement to an otherwise established pharmaceutical and chemical industry to being considered one of the pillars of the so-called 4th Industrial Revolution (Skilton and Hovsepian, 2018). Such a transition has been accompanied by key conceptual developments that have facilitated a growing mutual appeal between the biotechnological and the industrial worlds. One of them is the notion of *Cell Factories*, a concept that was developed in the early 1990s elicited by the work of Jay Bailey and his proposition that microbial cells could be considered actual—not metaphoric—industrial units amenable to the same formal analyses and methodologies than their human-made counterparts (Khosla et al., 2018). The term/concept, initially thought for microorganisms, quickly propagated towards other types of cells (plants, animals) and found its way also into the jargon of funding agencies and research organizations. Over the years, the idea of a factory in miniature performing complex chemical reactions in a small tridimensional space has been nothing but confirmed. The very conception of microbes-as-factories has two immediate consequences. One, that it is possible to transfer to a biological platform production of different types of molecules of interest that were otherwise the exclusive competence of the chemical industry (Gong et al., 2017). And second, that live microorganisms can deliver activities and/or compounds *in situ* to locations of interest. These features have opened immense biotechnological possibilities in agriculture and environmental management and have given birth to a new epoch in the annals of biotechnology (Nikel et al., 2016).

From genetic engineering to bioengineering and the KBBE

One can operatively map the era of what could be termed *traditional* genetic engineering (GE) within the 33 years that go from publication in 1973 of the first report of the cloning of a DNA segment (Cohen et al., 1973) to the article in 2006 describing production of the antimalarial drug precursor artemisinic acid in yeast (Ro et al., 2006). The route between these two milestones was punctuated by a large number of success stories—mostly in the biomedical field—such as the bulk production of recombinant hormones and bioactive drugs that were otherwise difficult to manufacture. But a new stage of biotechnology followed that was marked by 3 seminal articles published in year 2000 which are often considered the birth of what was later called *synthetic biology*. One

Abbreviations: KBBE, Knowledge-based bioeconomy; PCR, Polymerase chain reaction; CRISPR, Clustered regularly interspaced short palindromic repeats; BE, Bioengineering; GE, Genetic engineering; EFSA, European food safety authority; GMO, Genetically modified organism; EU, European union; SCP, single cell protein; CG, crude glycerol; MFCs, microbial fuel cells; PET, polyethylene terephthalate; PNAs, peptide nucleic acids; HVO, hydrogenated vegetable oil; AIDS, acquired immunodeficiency syndrome; ELM, engineered living materials.

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of them was the description by M. Elowitz's team of the so-called repressilator (Elowitz and Leibler, 2000): a genetic circuit between three mutually inhibitory transcriptional repressors which behaved cyclically in a fashion that could be faithfully described by a mathematical model. A second article reported the rational design of a genetic toggle switch in a way that obeyed the rules imposed by its human composer (Gardner et al., 2000). And the third described simple genetic circuits endowed with artificially designed feedback loops (Becskei and Serrano, 2000). The take home message in each of these three cases was that engineering principles could be *rigorously* applied to living systems. Under this new paradigm, live entities are looked at from the perspective of the relational logic of their parts that makes them to work as they do, thereby enabling alternative and new configurations at user's will. Such a radical point of view facilitates also the import of interpretive frames and analyses tools which are characteristic of electric, mechanical and industrial engineering. In this context of biology-as-engineering it is not surprising that term *chassis* has been so quickly incorporated to the mainstream narrative of synthetic biology as a follow up of the earlier notion of Cell Factory. The concept of a chassis has been defined by the EFSA (More et al., 2020)[1] and is subject to considerable regulatory and conceptual debate as it somehow marks the transition between customary genetic engineering (GE) and a new period shaped by the onset of bona fide Bioengineering (BE). In reality, the switch GE→BE, which feeds on both synthetic and systems biology, is not just a methodological one, it has a large number of societal and economic/industrial ramifications. On one hand, BE ambitions to overcome the widespread view of GE as a mere instrument for increasing productivity (and profits for the cognate companies) which has resulted in a remarkable social backlash. Instead, BE pursues involvement of end-users at all stages of the processes that lead to new products or services. On the other hand, BE upgrades biotechnology from being a somewhat secondary aid for the big chemical, agronomical and manufacturing industry to become one of the pillars of its future. No wonder that the economic value of BE was quickly grasped by industrial and regulatory actors and translated into various initiatives to foster what has been since called bioeconomy, or more appropriately knowledge-based BioEconomy or KBBE (Aguilar et al., 2009; Patermann and Aguilar, 2018; Kircher, 2021; House, 2012; Singh, 2012). The notion has many implications, but the ones discussed below deal exclusively with what Christian Patermann called the four Fs of the KBBE (Fig. 1) i.e. *Food, Feed, Fuel* and *Fibre*, to which we can also add *Fever* (see below).

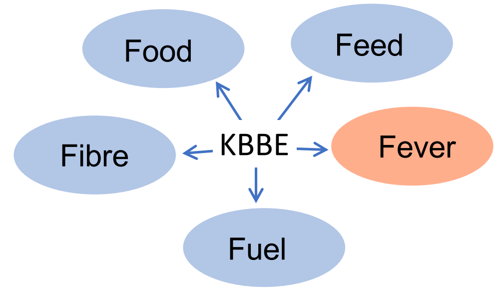

Fig. 1. The Fs of the Bioeconomy. The sketch summarizes the pillars on which contemporary systems-based and synthetic biology-based Biotechnology relies. Food encompasses all types of edible products of animal or vegetal origin as well as items fortified through the action of microorganisms (e.g. fermented food) and/or formulated with additives for a superior nutritional or physiological benefit. Feed includes both food for animals and feedstocks for the chemical industry which in either case can be derived from biological wastes and other types of biomass. Fibre is about production of biomaterials with preset physical properties that make them amenable to functionalization for the sake of the textile, high-tech and construction industries. Fuel comprises a large collection of high carbon density compounds and mixtures thereof intended to growingly replace fossil fuels by C-neutral alternatives and thus reducing emission of greenhouse gases. To this set of 4 canonical Fs (as proposed by Christian Patermann), one more key branch of present-day biotechnology can be added (fever) that signifies advanced approaches for tackling infectious diseases on the basis of new bioactive molecules and engineered live agents.

Food

The first wave of applications of recombinant DNA technology (and the most controversial thus far) to the food industry stemmed from the early technologies developed by van Montagu and Jeff Schell for transformation of vegetal cells and tissues for generating transgenic plants (Herrera-Estrella et al., 1983). One of the early outcomes was the design of major crops (soybean, cotton, corn) for herbicide resistance and/or defence of insect plagues and other diseases. Separate efforts with entirely different genetic technologies aimed also at increasing animal productivity, as exemplified by creation of large-size transgenic salmons (Sundström et al., 2015). Note however that these endeavours, clearly orientated to increase productivity turned a double-edged sword. On the one hand, more output meant more food, thereby pinpointing GE as one of the tools for combatting hunger—in particular by improving staple foods of developing countries e.g. cassava (Chavarriaga-Aguirre et al., 2016), resistant to pests. This includes not only editing of the plant genome proper, but also programming the associated microbiome for improved crop yields (Han and Yoshikuni, 2022) and draught resistance (Kour and Yadav, 2022). On the other hand, such engineered crops threatened biodiversity and made farming extremely dependant on the few companies able to put seeds and cognate herbicides in the market, which in several cases were designed to be operative only one season and thus avoid re-sowing. The somewhat greedy attitude of major seed providers (such as Monsanto) at that time elicited a considerable public criticism which was leveraged by environmental activists to make a general case against GM food which lasts to this day (Scoones, 2008). Alas, the legit debate about the multi-tiered pluses and minuses of such technologies has turned into a confrontational argument based more on feelings and beliefs than on evidence. But may we like it or not, these developments have given rise to two further scenarios with major consequences for the biotechnological agenda of the KBBE. The first is that the more recent endeavours in the field pursue not so much increasing production but adding value to the GM items in terms of consumer benefits. This goes from rice enriched in vitamin A (Pinkaew et al., 2014), tomatoes with higher levels of nutrients, or extended lifetime of the food in the refrigerator (Paduchuri et al., 2010). While still receiving some scepticism, in particular in the EU domain, GM edibles that deliver clear advantages to the final users will surely help removing barriers to acceptance. A second move fostered inter alia by the earlier GM debate is the spectacular growth of the organic food sector of the last 15 years (Sahota, 2009). The field bases its whole marketing on the avoidance not just of any genetic technologies but also of the pesticides and chemical fertilizers which are so characteristic of intensive agriculture. The ensuing biotechnological question is whether we can improve crops in quality and quantity without genetic and chemical approaches (considered by many as artificial) for the sake of a more natural and healthy lifestyle. The downsides or organic food include a lower net productivity (De Ponti et al., 2012) and very variable seasonality (Knapp and van der Heijden, 2018). Yet, if we leave aside ideological considerations about what is natural and what is not, reality is that the trend towards organic food not only creates a new market, but it also raises exciting research questions e.g. replacement of synthetic pesticides and growth promoters by e.g. fortification of the rhizosphere with selected microorganisms (Han and Yoshikuni, 2022),

[1] *A SynBio chassis is an engineerable and reusable biological platform with a genome encoding a number of basic functions for stable self-maintenance, growth and optimal operation but with tasks and signal processing components optionally edited for strengthening performance under pre-specified environmental conditions* (EFSA definition)

optimizing soil composition (and general agricultural practices such as weed removal) for increased nutrient uptake and playing with photoperiods for e.g. enhancing underground tubercle growth (Martínez et al., 2018). Interestingly, such GM-free but highly technological approach has also reached out non-vegetal foods as the traditional kéfir (Blasche et al., 2021; Melkonian et al., 2019). The complex microbial community that generates this dairy product can be rationally manipulated on the basis of metabolic modelling and sophisticated culture conditions, but without any genetic change. Similarly, meat replacements based on all-natural vegetal components which are however heavily processed (Mejia et al., 2016; Morach et al., 2021). Such technologies showcase how customer demands may end up determining very successfully the research agenda.

In sum, granted that GM technologies as they were initially proposed may always be contested by an influential societal sector, the current trend is either making designer foods more appealing to consumers because of their benefits and/or avoiding altogether any recombinant DNA transactions. If the early food Biotech implicitly assumed the motto 'from field to fork', KBBE witnessed (and to an extent fostered) a mirror tendency 'from fork to field'. Under this frame, consumers' inclinations and societal mood are translated into specific demands for the biotechnological sector which in response, frame research priorities and manufacturing practices. Unlikely as it looks at the moment, it is possible that both the preoccupation towards natural, environmentally friendly food and advanced genetic technologies will eventually converge, for example in the field of animal-free meat. The growing trend towards vegetarianism has created a considerable market niche for edibles which keep most organoleptic properties of animal meat but are entirely alien to the sacrifice of farm animals. One key ingredient of the meaty flavour is haemoglobin, which is hardly obtainable from non-animal sources. However, unlimited amounts of the compound can be produced by metabolically engineered *E. coli* (Zhao et al., 2018) or yeast (Ishchuk et al., 2022) which can then be entered in the formulation of the vegetal meat. Whether or not these approaches will be eventually successful at large scale we cannot say at the moment, but they provide a good example of how two initially divergent fields may end up finding a common ground if the right narrative is developed. Similarly, the interest of increasing agricultural productivity by genetically stimulating photosynthesis and/or decreasing carbon loss through respiration may align well with the much needed capture of atmospheric CO_2 excess (Amthor et al., 2019; Jovine, 2022). In this sense, the recent genome-editing technologies (Langner et al., 2018; Wan et al., 2022) derived from CRISPR/Cas (and related) offer a good opportunity to replace the traditional and somewhat aggressive jargon of GM food (transgenic, manipulated etc.) with a better one reflecting a negotiation with the natural world instead of expressing a compulsion to subdue and dominate live systems. Alas, the first EU rules on this matter still considers CRISPR/Cas9-mediated genome plants identical to GM items (Stokstad, 2018; Shew et al., 2018). This is not only a serious scientific mistake, but also a major mishap in comprehension of social moods and a missed opportunity to take the conversation on genetic modifications to a different frame.

One additional trend that is under serious debate at present time is the exploitation of insects as a sustainable source of protein both for human food and animal feed (Van Huis, 2020). While some societies are already used to include some inspect species in their diet, there are considerable cultural barriers to their widespread adoption in Western eating habits. In any case, the pursuit of alternative protein which does not have an animal (at least, superior animal) origin goes well beyond the current and quite hyped development of synthetic meat (Fernandes et al., 2020).

Feed

While humans live on diverse foods, both farm animals and industrial processes need to be supported in one case with grain, forage and fodder and in the other with chemical feedstocks. As long as animal feed is a variant of food, the same issues and developments discussed above are applicable here. Advanced genetic technologies can increase yields of typical crops used for animal nourishment and being fortified for key growth-promoting additives. One special and growingly interesting case is the use of some seaweed species (i.e. marine algae) as a supplement of animal feed (Morais et al., 2020) because of their high contents in useful metabolites, essential nutrient and minerals. Furthermore, open-ocean kelp farming does not compete with agricultural land, it grows very fast and it captures large amounts of CO_2. This makes algae (along with their associated microbiome; Krohn et al., 2022) one of the most promising inputs of the farming of the future. Yet, the growing demand for protein cannot be ultimately met because of the low efficiency of converting traditional, even fortified feed to meat and dairy products. Fortunately, single cell protein (SCP), i.e., protein produced in microbial and algal cells, is growingly becoming an appealing option, as microorganisms can convert waste streams (discarded raw materials, wastewater and chemicals) into proteins which can then be upgraded and eventually used in animal feed (Matassa et al., 2020; Sharif et al., 2021). Even human and animal waste (let alone lignocellulosic residues) offer potential for generation of edible food (Douglas et al., 2020). Sophisticated research projects on waste recycling that were initially entertained for supporting space travel can find a fertile application in more mundane scenarios for meeting the growing protein demand for farm animals. In between lays the immense challenge of global food waste i.e. the fact that over one-third of all current food production is lost or discarded in the way between the site of production and the consumer's garbage (Food and Agriculture Organization, 2013). This not only adds to the food crisis and to large economic loses (including water, energy and land resources wasted) but also to environmental problems (e.g. saturated landfills) and greenhouse gas emissions. Opportunely, a whole range of microorganisms are also capable of various upcycling operations to give such waste a second life. For example, by coupling anaerobic digestion and thermochemical gasification, it is possible to convert diverse biowaste to SynGas and/or other mixes of H_2, CH_2, CO_2, CO, NH_2, which can in turn be channelled into fermentative production of protein-rich microbial biomass and SCPs (Wainaina et al., 2018). One particularly interesting process is microbial conversion of CO_2 to formic acid (Roger et al., 2018), as it is then possible to channel this C1 compound towards either biomass production or a whole range of chemicals (Yishai et al., 2016; Claassens, 2021). These biological transformations can in turn be coupled to e.g. catalysed photo-splitting of water towards hydrogen and oxygen and subsequent methane activation to methanol (Zhang et al., 2022) or other products (Wang et al., 2022). As these processes are predominantly (micro)biological and thus ultimately dependant on DNA they can all be subject also to improvement with the conceptual and genetic tools of contemporary systems and synthetic biology, in particular with the growing number of assets available for microbiome engineering and assembly of complex live catalysts based on designer communities (Lawson, 2021).

The other major type of feed involves the entire collection of building blocks that serve the chemical industry and all its derivatives. The key source of such building blocks for over one century and a half has been petroleum. This fossil material is not only the origin (together with coal) of nearly all fuel consumed at present time (see below) for transportation but also the cradle of a very large number of chemical precursors for a plethora of synthetic materials that form part of our developed societies. While one can entertain ways of de-carbonising energy, replacement of the massive quantities of platform chemicals and building blocks extracted from oil is to this day a phenomenal challenge. But reality is that sooner or later, the oil reserves will come to an end (or their price will be prohibitive) and alternative sources of building blocks will be badly needed (Choi et al., 2015). For the time being, the only promise in this respect lays on biomass and high-energy bioproducts thereof e.g. starch, cellulose/hemicellulose, lignin, fats, waste protein and their mixtures. Ultimately, as is the case with oil, biomass is ultimately formed upon capturing solar energy in diverse types of chemical bonds. The cognate molecular structures can thus be leveraged (to an extent) as substitutes of staple chemicals (Chung et al., 2015). Note that bulk biomass most often appears as diverse type of solid polymers that need to be converted first to intermediate chemical platforms (e.g. cellulose to 6C and 5C sugars) which can then be fed to microbial catalysts for production of secondary chemicals and other intermediates. In some cases, microorganisms can run themselves biomass de-polymerization steps; in others, a physicochemical pre-treatment may be needed to reduce the size of the substrates for making them amenable to biotransformations (Yang et al., 2017a). In fact, it is remarkable that one of the foundational processes of the history of biotechnology involved production of acetone by fermentation of straw with Clostridia (Beesch, 1952). Modern systems and synthetic biology-based metabolic engineering have taken the approach to an unprecedented degree of efficacy and diversity of the molecules that can be produced for all types of industrial applications. This raises hopes that at least some of the bulk chemical intermediates that were formerly generated in oil refineries will be effectively produced in equivalent biorefineries able to process biomass into identical molecules of interest (Keasling, 2010).

In a further screw turn, more feedstocks other than biomass have been added in recent times to the pipelines for microbial production of valuable compounds. One of them is the large volume of waste glycerol generated upon transesterification of fats or oils with an alcohol during the production of biodiesel (see below). Such a surplus of crude glycerol (CG) raises an opportunity to recycle what would otherwise be a discarded waste into a nutrient usable by natural or designed microorganisms for either production of other value-added chemicals or generation of SCPs for animal feeds (Dobson et al., 2012). Alas, CG from biodiesel is far from pure and it is mixed with a large number of toxic compounds (Samul et al., 2014). Not surprisingly, current research focuses both on upgrading CG into an edible substrate by microorganisms and on increasing stress resistance of the whole-cell catalysts involved. Finally, an unexpected feedstock has been recently added to the list of possible inputs to microbial-based biorefineries: plastic waste (Wierckx et al., 2015). Water and soil pollution by a very diverse collection of synthetic polymers (mostly PET, polyethylene and polystyrene) has been identified as one of the major agents of the ongoing environmental deterioration, second only to emissions of greenhouse gases and desertification (de Lorenzo, 2017). The main strategy available for tackling the issue thus far—apart of straight incineration—has been collection of waste and landfilling, a clearly non-sustainable solution. Although reports on bacteria able to grow on such polymers have peppered the literature for many years, it was not until 2016 that an effective enzyme for degradation of PET (the main component of plastic bottles) was described in detail (Yoshida et al., 2016; Han et al., 2017). Since then, the original PETase has been improved in many ways and new possibilities are opened to utilize the depolymerization products as nutrients for other engineered microorganisms for generation of valuable biologicals as before (Kaushal et al., 2021). At the time of writing this article, new reports in the literature describe plastic-munching larvae bearing microorganisms and enzymes in their gut able to degrade polyethylene (Brandon et al., 2018), polypropylene (Yang et al., 2021; Jeon et al., 2021) and polyurethane (Liu et al., 2022a), three polymers virtually considered recalcitrant to biological action. Although these reports should still be taken with some caution (Lear et al., 2022) they hold a huge potential for plastic waste upcycling and making biorefineries an effective complement (and perhaps a full alternative) to oil-processing plants.

Fuel

That the whole of the industry and the economic activity of our societies depends on coal, gas and petroleum is a fact that needs little explanation. Since the industrial revolution, we are altogether dependant on fossil fuels for meeting energy needs. Although current reserves are claimed to still be quite high, it is evident that they will be progressively less available and more expensive while they will continue releasing CO_2 to the atmosphere and accelerating the already unmanageable climate crisis. This state of affairs has fostered an urgent pursuit of alternatives for meeting the growing power needs. Bona fide decarbonisation is one of the preferred ways to go, in particular for electricity production. Wind and tidal energy, hydroelectric power and photovoltaic panels are already consolidated contributors to the power supply grid of many countries. At given times, electricity production from such renewable sources exceeds the levels generated by unsustainable fossil fuel combustion of thermal power stations and (in some countries) operation of nuclear power plants. De-carbonised energy growingly covers industrial and urban demands of electricity and it is progressively taking over the automobile sector, specifically for short-distance urban transport. Apart of such renewable energy suppliers, nuclear fusion power is proposed as the ultimate source energy for production of electricity (Mathew, 2022). Alas, while nuclear fusion is claimed to have many advantages over fission, a large number of fundamental issues have not been solved and therefore the choice is not yet at hand. Furthermore, other sectors of enormous economic importance (specially, long-distance transport of goods and air travel) still need high-energy liquid fuels for e.g. trucks or planes which thus far can be generated only from oil. This is because [i] storage of electric power in long-lasting, potent and light-weighted batteries is not yet a solved problem and [ii] the massic energy for delivering enough combustion potency to sustain operation of aircrafts and/or long-distance travel is to be found only in specialised gasolines and kerosenes. As a consequence, while much of the electricity-related demand of energy can be met without involving carbon, a large share of global economy relies on fluid fuels stemming from fossil sources. What answers to these challenges can be entertained from the realm of advanced life sciences research (Keasling et al., 2021)?

In reality, obtention of fuels from biological sources has been in the biotechnological agenda even before the era of recombinant DNA. One exemplary case is production of bioalcohol and its growing utilization as renewable liquid fuel (or part of fuel formulations thereof) for motor vehicles. The majority of cars in countries such as Brazil run on ethanol or in mixes containing the alcohol. Bioethanol is often produced through microbial fermentation of carbohydrates (Khaire et al., 2021). Favourite feedstocks for this process include sugar cane, beets cereal grains, which need to be processed to release fermentable substrates. On one hand, using bioethanol-blended fuels reduces consumption of fossil resources and reuses the CO_2 that is generated upon combustion. On the other hand, its massic energy is low, what makes it useful only for somewhat light operations. Finally, most bioethanol production relies on crops that occupy agricultural lands that could otherwise be used for food-making. As a consequence, much research is currently going on to utilize other non-feed raw materials such as waste lignocellulosic residues (Lin and Lu, 2021) and algal biomass (Das et al., 2021) which, once processed provide fermentable carbohydrates for production of ethanol and butanol. Along the same lines, a whole collection of what are generically called energy crops (Leontopoulos and Arabatzis, 2021) have been thriving in recent years. They include a (growing) number of plant species that can be planted in sites not amenable to food production and generating biomass that can be either used as energy source as such (e.g. pellets) or after processing deliver bioethanol, biogas or biodiesel usable as fuel for a diversity of applications.

The case of biodiesel is of particular interest, as its production also predated the recombinant DNA era but its upgrading and improvement reach out the present time. As indicated above, this fuel results from a chemical reaction (transesterification) that coverts the triglycerides (fats) contained in oils into a liquid material able to replace petroleum-based diesel in suitable engines. The traditional process requires alkaline catalysis for making oils of vegetal or animal origin to react with alcohols (e.g. methanol and ethanol) and producing fatty acid methyl esters. The process has been further advanced more recently by using instead bacterial lipases (whether naturally-occurring or genetically improved) for bringing about the key transesterification step, what results in a fuel that is cleaner and easier to produce than the previous approaches

(Wang et al., 2021). Another variant of biodiesel is the so-called hydrogenated vegetable oil (HVO), which is produced by catalytic hydrogenation of vegetable oils and waste animal fats with hydrogen at high temperatures and pressures (Sonthalia and Kumar, 2019). The process releases a complex mix of hydrocarbons that can be further processed to produce kerosene usable as a component jet fuels (Hájek et al., 2021). Yet, note that the ultimate ambition of biofuel production is not to just add biological ingredients to basically *chemical* production pipelines, but to engineer microorganisms (and matching processes) able to produce effective replacements to oil-based fuels out of renewable carbon sources. Ethanol/butanol and biodiesel lead the way but large-scale biological production of advanced biofuels that meet the specifications and performance criteria of petrol and jet fuel is still quite an issue (Service, 2022). While a suite of microorganisms has been engineered to produce complex alkanes of interest (Liu et al., 2022b; Walls and Rios-Solis, 2020; Wang et al., 2019) and even polycyclopropanated high-energy biofuels for jet fuel formulations (Cruz-Morales et al., 2022), their manufacturing is for now exceedingly costly and the whole output still very limited for any significant substitution of equivalent oil-based counterparts in the near future. Yet, there seem to be no other choice but continuing research and innovation on this matter, as fossil resources are destined to be less and less accessible—let alone desirable in the context of climate crisis (Keasling et al., 2021).

Finally, hydrogen has been proposed repeatedly as a clean alternative to oil-based, C-rich fuels. For now, however, the vast majority of usable H_2 is produced through a high-temperature process in which a water steam is made to react with a hydrocarbon fuel (e.g. natural gas). H_2 can also be generated through electrolysis (including photoelectrochemical processes) and thermochemical water splitting (Kannah et al., 2021). All these methods operate at very high energy costs and therefore the pursuit of more sustainable and environmentally-friendly procedures for H_2 generation are badly needed. Once more, advanced biotechnologies may come to the rescue. Many known biological reactions release H_2 (Nandi and Sengupta, 1998) and a number of routes for large-scale production of the gas are being intensively studied e.g. direct or indirect biophotolysis, photofermentation or dark fermentation (or their combination thereof) and biocatalyzed electrolysis (Sharma, 2019). The one advantage of H_2 is that energy can be stored and transported in a liquid form, although there are still pending safety issues because of the explosive potential of the gas. Note also that besides direct use as fuel, H_2 is a major source or reductive power for a large number of chemical processes and biological transformations. It is thus no surprise that many entertain a future economy in which hydrogen basically replaces fossil fuels as the principal energy vector of the chemical industry and transportation sector (Dou et al., 2017).

Finally, microbial fuel cells (MFCs) have gained considerable attention as a mode of converting organic matter into electricity while purifying wastewater concurrently (Saravanan et al., 2021), achieving up to 50% chemical oxygen demand removal and power densities in the range of 420–460 mW/m^2 (Obileke et al., 2021). While these figures are is still very low for contributing significantly to the energy grid (Ramírez-Vargas et al., 2018), current research enables engineering of wetlands (Wang et al., 2020) with bacteria able to retrieve electrons from solid donors which then deliver *in situ* bioremediation activities for removal of nitrates, perchlorate, chlorinated compounds and many other spoilers of water quality.

Fibre

The immediate images brought by the term *fibre* include on one hand one vital component of human diet that eases intestinal transit and thus promotes a healthy physiology. On the other hand, fibre in its various forms is the material basis of textiles and other fabrics. But the notion can be further extended to include a whole collection of raw supplies that once processed acquire physical, tangible micro- and macro-properties of interest for both personal consumption and production of larger objects endowed with a degree of flexibility or malleability. Production, processing and fortification of edibles with dietary fibre falls within the domain of the food F above and will not be separately addressed here. However, there is a connection between plant-derived polymers (in particular cellulose) and one of the most active areas of activity of contemporary biotech: non-animal leather and functionalized textiles.

One of the starting points of this field is the long-time observation that a whole variety of microorganisms produce and secrete cellulose fibres (Iguchi et al., 2000) as one of their assets to adhere to surfaces and/or forming biofilms. Bacterial cellulose is in itself an interesting material because of its superior strength as compared to the same of vegetal origin and its excellent performance in medical wound dressing and a suite of other small-scale applications (García and Prieto, 2019). One further development came from the observation that bacteria and other microorganisms that aerobically grown on fermented kombucha tea can form thick pellicles of cellulose at the liquid-air interface (Domskiene et al., 2019). Once dried and treated, such biofilms turn into a 2D material that has many of the properties and characteristics of animal leather. This occurrence has created an enormous interest in such a microbial matter not only because of its potential for replacement of unsustainable animal leather production for the clothing and footwear industries, but also for its promise to reduce skin damage upon direct contact and numerous possibilities of functionalization, both physical and biological. That production of microbial leather is ultimately determined by DNA opens possibilities of genetic programming of the cellulose-secreting cells, whether mono or multi-species, that are by no means possible with the animal counterpart. This scenario is in fact opening a brand new field of frontline biotechnological research: the pursuit of engineered living materials (ELMs). Although actual products have not reached out the market yet, the ELM field is one of the most fascinating areas of contemporary research (Gilbert and Ellis, 2018). Examples include derivatization of bacterial curli fibres with a variety of functionalized molecular decorations, incorporating e.g. inorganic-material-nucleating peptides, mussel foot proteins (for strong surface adhesion) or heavy-metal capturing motifs. But many other biological materials hold a great promise as source of new building blocks of genetically-programmable complex functions in nanomaterials e.g. diatoms as producers of silica-based microstructures or magnetotactic bacteria production of dipolar iron beads (Gilbert and Ellis, 2018).

Along the same line, a separate but related endeavour is about using microbial cell factories for production of a whole wealth of materials of interest that are naturally obtained only from animal sources. These include silk (both from silkworms and spiders (Dinjaski and Kaplan, 2016)) and muscle protein titin, a fibrous matter with extraordinary mechanical properties (Bowen et al., 2021). A way more advanced field is that of microbial production of bioplastics. The much earlier observation that many bacteria store carbon surplus in the form of intracellular inclusions of polyesters has evolved over the years into one of the most successful biotechnological industries of the last decade (García-Depraect et al., 2021). These polyesters have physico-chemical properties quite similar to counterparts of petrochemical origin. But, in contrast, their being of biological origin enables their composition and properties to be programable genetically, thereby giving rise to immense possibilities of functionalization for the sake of modifying their qualities, making them more or less biodegradable, biocompatible etc. Furthermore, as these materials are ultimately produced through metabolic reactions amenable to genetic engineering, it would be even feasible to entertain whole-cell catalysts able to degrade say *bad* plastics of petrochemical origin by *good* plastics with an environmentally friendly life cycle (Wierckx et al., 2015). In the meantime, some bioplastics of microbial origin are already in the markets and their demand will undoubtedly grow in years to come.

The hope of replacing unsustainable polymers by others of biological manufacture is in fact the subject of considerable research. But the ambition does not stop there and a branch of contemporary Biotech is already entertaining the use of biomaterials for large-scale construction and as a key asset of the architecture of the future. In reality, wood has been used as a primary construction material since the onset of humanity, but now an opportunity has materialized to explore other biologicals as resources for erecting all types of buildings. Just to mention a few possibilities under the radar of the construction industry: the use of fungal mycelia as insulation material (Yang et al., 2017b; Răut et al., 2021), bacterial production of nacre/mother of pearl (Spiesz et al., 2019) and the development of self-healing concrete (Seifan et al., 2016). Note that manufacture of cement accounts by itself for 8% of global CO_2 emissions and 10% of planet-wide drinking water. Therefore, any improvement in its production pipeline is expected to have important consequences.

One more F?

Although KBBE is generally considered the non-medical realm of present-day biotechnology, there is at least one area of overlap that is worth adding to the collection of subjects starting with an F: Fever. The word summarizes all types of issues that humans have with virulent microorganisms, whether bacteria, yeast, fungi or viruses (archaea are, distinctively non-pathogenic) from the perspective of advanced biotechnology. Note that the territory of this F is related, but independent, of medical biotechnology. Instead, it has to do with novel strategies to either find or improve antimicrobial drugs (or other bioactive agents against pathogens) development of vaccines, and strategies to monitor and combat antibiotic resistances. The overarching theme is scaled-up bioproduction of whatever biomolecule or active agent is identified as worth of application to infected patients. But this F stops short of running into actual clinical practices.

As was the case with food, the potential of recombinant DNA technology for tackling these issues became evident short after the onset of the field in the mid/late 1970s. Following the first time cloning of a complete pathway for production of an antibiotic in 1984 (Malpartida and Hopwood, 1984), the field was opened for boosting production of antimicrobials at unprecedented levels, generation of new molecules through recombination and/or mutagenesis of existing biosynthetic routes and systematic survey of new inhibitors of microbial growth in the form not just of antibiotics proper, but also antifungal and antiviral molecules. The last two types of antimicrobials received considerable attention during the AIDS crisis of the 1990s, while the painful realization of the antibiotic resistance phenomenon elicited a constant demand of bioactive molecules. To this end, a plethora of methods for bioprospecting compounds of interest from the most diverse sources and locations has been developed over the years, in many cases sampling directly the metagenomic DNA and thus the genetic pool of environmental sites (Sekurova et al., 2019). Yet, while new antimicrobials will be certainly welcome (Bongaerts et al., 2022), the last few years have witnessed a clear lack of interest of pharmaceutical companies in their pursuit and eventual deployment. Since existing antibiotics still cover a very large portion of medical problems, development of new molecules seems to lack incentives. Yet, new types of antimicrobials could make a considerable difference. On one hand, the wealth of peptide antibiotics which can both be generated artificially (Torres and de la Fuente-Nunez, 2019) and also predicted from analyses of human proteomes (Torres et al., 2022). Also, designer antimicrobials are being created that combine in a single primary amino acid array the inhibitory power of peptide antibiotics with the immuno-modulating action of other sequences (Palmer et al., 2021). Finally, there is a renewed interest in antisense peptide nucleic acids (PNAs) that target mRNAs of essential bacterial genes (Popella et al., 2022). In any case, many if not most of the recent novelties for combatting infections come from the academic world and reach out clinical practices with different degrees of success. A clear trend of the last few years is to consider strategies not based on antibacterial drugs but capitalizing on inter-species interactions already existing in the microbial world. One that has received a considerable attention in recent times is phage therapy for those infections caused by bacteria altogether unresponsive to any antibiotic treatment (Gordillo Altamirano and Barr, 2019). Although the concept and even its practice has been around for a long time only more recently it has become a realistic strategy because of the ease or identifying effective phages for target strains and the possibilities of deep engineering of viral genomes brought about by synthetic biology (Lenneman et al., 2021). Another approach not based on antibiotics proper involves engineering bacterial *vigilantes* able to track virulent and/or antibiotic resistant members of a microbiome and leveraging horizontal gene transfer (López-Igual et al., 2019) or surface recognition (Ting et al., 2020) for delivery of killing devices to get rid of them. Each of these approaches hold a great promise, although for now they are mostly confined to experimental phases that still need to became mainstream.

The challenges and the means

The paragraphs above just provide a by no means exhaustive snapshot of the current state of affairs of the KBBE-related Fs. The obvious question is what will follow and what is needed to make it happen. The momentum initiated with the launch of KBBE years ago has possibly left behind the initial hype to start facing the realities of implementation along with the ensuing identification of bottlenecks that may have not been anticipated earlier. The greatest likely challenge of the KBBE is scaling up processes to the point of making them not just environmentally friendly and sustainable but also economically appealing and palatable to the big industry. In this respect, not each of the four Fs do as well as the others. Improvements of staple food production looks relatively easy to attain as existing agronomical practices can quickly adapt to new plants and animal variants. Also, organic farming will benefit immediately from the knowledge and the new GM-free technologies discussed above. But the type of advanced fork-to-field food that is often entertained as a major business sector of the future (e.g. non-animal replacements of meat) is still in its infancy and its eventual success depends on scaling up its production and reduction of costs to make it appealing to a growing number of customers. Something similar happens to new antimicrobial agents and vaccines: The existing fermentation facilities and downstream processing protocols of Pharma companies can be easily co-opted to manage strains and materials generated through advanced metabolic engineering for synthesis of high-added value bioactive molecules. But how to scale up the new items of the antimicrobial arsenal (e.g. phage therapy, microbiome vigilance, targeted depletion of pathogens) will surely require new production concepts and pipelines adapted to the biological actor and vice versa. One intriguing proposal in that respect is that of leveraging genetic programmability of microorganisms for biosynthesis of all types of compounds at the very site of demand (Cao et al., 2018). This could dramatically decentralize and make cheaper the synthesis of added value products—a notion not devoid of societal ramifications under the umbrella of what has been called frugal (bio)technologies (Reardon, 2013). Yet, the most challenging scale up endeavours remain within the other Fs: fuels, synthesis intermediates and new materials, as the extraordinary dimension at which they are needed cannot for now be met by any comparable production scheme. There is therefore an urgent need for upscaling technologies for biofabrication of such staple chemicals.

In the meantime, only molecules with a very high added value are thus far worth to produce in a typical bioreactor. This is because of the need of using sterile liquid medium, considerable downstream processing and release of large volumes of waste water. In this respect, most current bioreactors are not much different of what Egyptians used for beer production a few millennia ago: lots of liquid in a big recipient—not very appealing. It is time to rethink how new, effective platforms for large-scale generation of bioproducts and/or bulk chemicals could look like, surely getting inspiration of natural systems that release immediately usable bioproducts in an environmentally-friendly fashion (e.g. trees, udders). Reconsidering ways of industrial production in terms of conversation and negotiation with the natural world as well as learning from its longstanding problem-solving capacity might be ultimately more useful than trying to keep indefinitely domination and overexploitation of the Earth's resources (Chieza et al., 2022). This conversation should also be framed within the necessity to pursue a fair share the costs and benefits of mitigating climate crisis with less developed countries (Hickel and Slamersak, 2022). Only such an approach can make economic progress and environmental sustainability move forward hand to hand. Thanks Christian Patermann for pioneering this way of thinking—sometimes expressed in writing, often just shared through informal conversations—as a durable heritage of his amazing contribution to make Biotechnology one essential pillar of the society, economy and industry of the times to come.

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