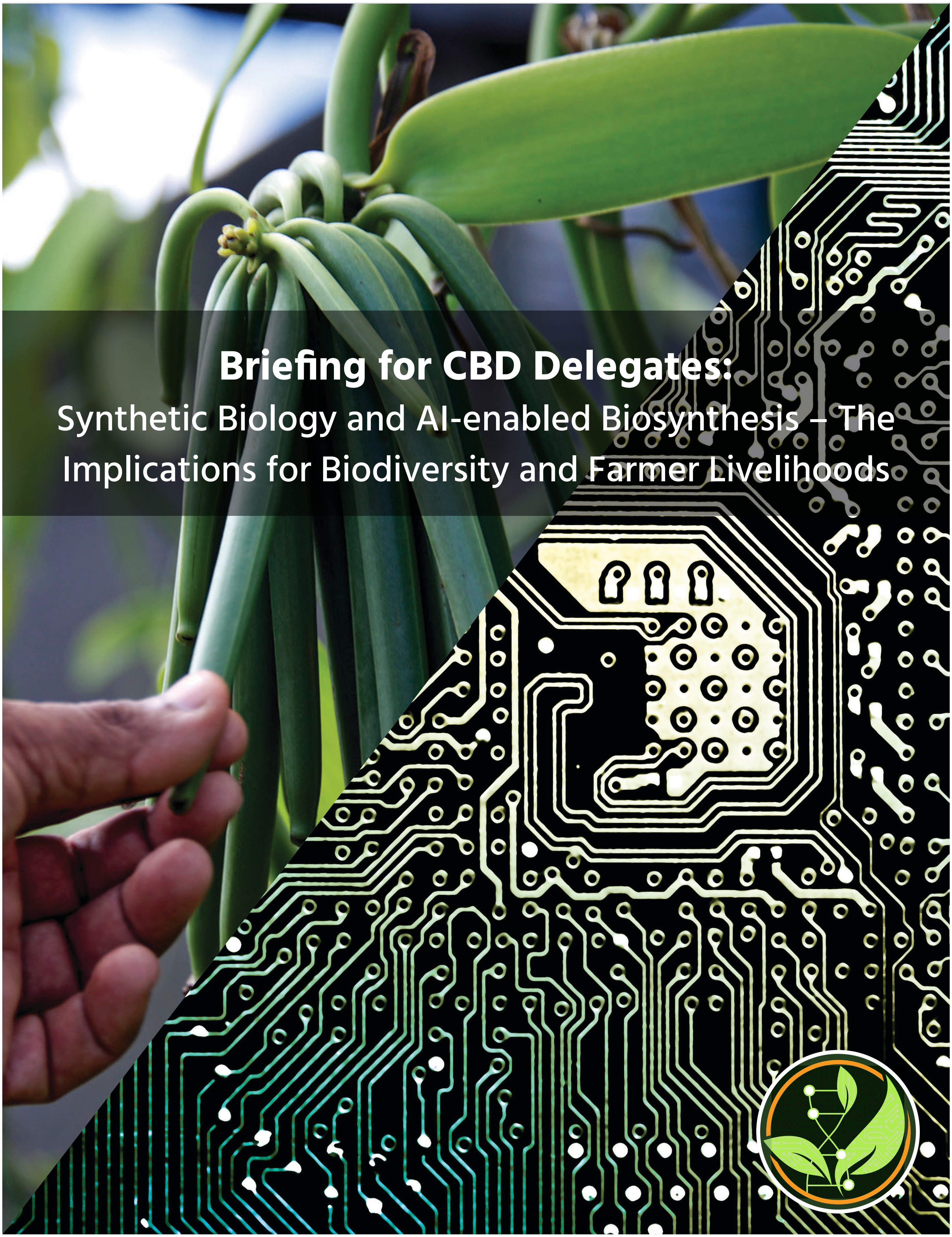

Briefing for CBD Delegates:

Synthetic Biology and AI-enabled Biosynthesis – The Implications for Biodiversity and Farmer Livelihoods

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2018

About African Centre for Biodiversity: The African Centre for Biodiversity (ACB) is committed to dismantling inequalities in the food and agriculture systems in Africa and our belief in people's right to healthy and culturally appropriate food, produced through ecologically sound and sustainable methods, and their right to define their own food and agricultural systems. (Please note: On 7 April 2015 the African Centre for Biosafety officially changed its name to the African Centre for Biodiversity. This name change was agreed on through consultation within the ACB to reflect the expanded scope of our work over the past few years. All ACB publications prior to this date will remain under our old name of African Centre for Biosafety and should continue to be referenced as such.)

About ETC Group: ETC Group works to address the socioeconomic and ecological issues surrounding new technologies that could have an impact on the world's marginalized people. It operates at the global political level and works closely with partner civil society organizations (CSOs) and social movements, especially in Africa, Asia and Latin America. ETC Group is headquartered in Val David, Canada, and Davao, Philippines, with offices in Mexico City and Guelph, Canada.

About Third World Network: Third World Network (www.twn.my) is an independent non-profit international network of organizations and individuals involved in issues relating to sustainable development, the South and North- South relations. TWN's goal is to deepen the understanding of the development dilemmas and challenges facing developing countries and to contribute to policy changes in pursuit of just, equitable and ecologically sustainable development. TWN's International Secretariat is in Penang (Malaysia) with offices in Kuala Lumpur (Malaysia) and Geneva (Switzerland). There are researchers based in Beijing, Delhi, Jakarta, Manila and New York. The Latin America Regional Secretariat is located in Montevideo (Uruguay) and the African Regional Secretariat is in Accra (Ghana).

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Visit www.synbiogovernance.org for more information and translations.

Layout: Cheri Johnson

Building International Capacity in Synthetic Biology Assessment and Governance

Briefing for CBD Delegates: Synthetic Biology and AI-enabled Biosynthesis – The Implications for Biodiversity and Farmer Livelihoods

It is now almost a decade since the Convention on Biological Diversity first began tracking developments in synthetic biology. At the time, prominent synthetic biologists boasted that any compound that was produced by a plant could now be synthesized in a vat of engineered microbes. While that was theoretically true a decade ago, it is now becoming truer: the field of synthetic biosynthesis has become more significant because of capabilities in artificial intelligence and automation are rapidly converging. These developments have serious implications for the conservation and sustainable use of biodiversity.

In the face of ever-increasing numbers of syn bio-derived organisms and compounds, there is now an urgent need for governments to better get a handle on an emerging 'biosynthesis' industry and to address the disruption that may be felt by millions of traditional farm producers and pickers and the biodiversity that they steward.

A report from the 2017 meeting of the CBD's Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology noted this new accelerated pace of synthetic biology development [para 14] and indeed highlighted the increasing technological capacity to produce novel, modified organisms.[1] The AHTEG noted: "Approaches such as machine learning, artificial intelligence, robotics and those related to 'big data' […] are expected to enable rapid prototyping and testing of highly novel organisms" [para 15]. The AHTEG also noted that "combining new biotechnology tools and automation allows the more rapid production of modified organisms" [para 15]. The AHTEG identified challenges that a proliferation of novel organisms could bring, including in the areas of detection, identification and monitoring and noted that gaps in technical infrastructure and capacity in some countries could increase those challenges [paras 32-37].

This briefing is intended to provide CBD delegates with more information about the state of research, development and commercialization of synthetic biology (syn bio) as applied to biologically synthesizing products for the marketplace in order to inform their discussions and consideration of potential actions.

Key Points:

> Socio Economic harms must be addressed:

Addressing the potential social, economic and indirect harms to biodiversity from replacement of natural products by biosynthesis should be a high priority for the CBD. In its recent report, the AHTEG highlighted "the importance of addressing the potential socio-economic impacts of the commercialization of products of synthetic biology that replaced naturally occurring products" [para 57] as well as "the need to take into account the socio-economic impacts, perspectives, rights and lands of indigenous peoples and local communities when considering the possible release of organisms developed through synthetic biology into the lands and territories of indigenous peoples and local communities" [para 53].

> Safety, traceability, recall, liability:

Public and private entities are accelerating the pace of organism design and proposing to release syn bio-synthesized ingredients into the market. They must ensure means to test their products for safety, to ensure traceability for integrity in the marketplace and the ability to recall their products and remediate if necessary. Products of synthetic biology differ from those produced through chemical synthesis and should be labelled, regulated and carefully tested.

As a way forward, the AHTEG offers that those commercializing "products and organisms resulting from synthetic biology…could be made responsible for providing validated tools, relevant sequence data and reference materials, in an accessible manner, that would facilitate the detection, identification and monitoring of such organisms and products" [para 38].

> No false natural claims:

Biosynthesized products also should not be obscured by misleading marketing claims: While the technologies involved may "hijack" natural processes for production, the products of synthetic biology are not naturally produced. Claims of "natural" are not justified and they are misleading to government regulators as well as consumers. The CBD SBSTTA should explicitly reject the "natural" label for the biosynthesized products of synthetic biology.

Introduction: What is Synthetic Biology and Biosynthesis?

More than a decade ago, civil society characterized synthetic biology as "genetic engineering on steroids" to highlight a new and dramatic increase in the technological capacity for biological manipulations.[2] Synthetic biology (or syn bio, for short) brought together engineering, bioinformatics and the life sciences with an aim to tweak existing biological systems or to construct entirely new biological parts, devices and systems ("*de novo*"); syn bio reflects an attempt to apply a predictive engineering approach to biology. The ascendant application of syn bio is the targeted engineering and construction of "metabolic pathways," which are inserted into microorganisms that are then fed a carbon-based food. The metabolism process produces a high-value substance as a by-product – in effect, turning individual cells into "living factories"[3] to "retrofit" at will, depending on the desired end product. A convergence of biological engineering, automation technologies, robotics, data mining and artificial intelligence is once more exploding the technological capacity to manipulate existing organisms and design new ones.

The commercial exploitation of microbes is not in itself new; commercial-scale fermentation processes that result in yogurt and beer are common examples. We're all familiar with baker's yeast that feeds on sugar and secretes carbon dioxide and alcohol as a waste product of metabolism. When an engineered metabolic pathway (constructed from synthetic DNA) is inserted into a cell, however, the fermentation process can be altered both on the feedstock end and the by-product end. The term *biosynthesis* puts the accent on the by-product: fuels, pharmaceuticals, fragrances, foods and food ingredients have all been biosynthesized using synthetic biology techniques, and new products of biosynthesis are being announced regularly. A group of scientists in China recently reported on efforts to produce breviscapine– a medicine to treat heart disease, traditionally botanically sourced – by inserting new engineered metabolic pathways into yeast feeding on glucose[4]; a company in the UK, Isobionics, is feeding sugar to engineered *E. coli* bacteria to produce patchouli fragrance.[5] Research groups and start-ups around the world have re-engineered microorganisms to produce a variety of valuable substances – biosynthesizing squalane (formerly found in olives or shark livers), jet fuel, sandalwood oil, even spider silk, to name just a few.

Some of the world's largest corporations – companies whose trade has traditionally depended on nature's biodiversity, both plants and animals – are eager to partner with synthetic biology startups because of the alluring possibility of cheaper, more uniform, stable and accessible sources of raw materials and products. In the words of one syn bio company's promotional literature, the technology promises to solve "the supply chain issues of nature" including "lack of convenience factors," and it offers the opportunity to "improve and customize products"[6] – to eliminate allergens, for example. Manufacturing via synthetic biology is expected to impact virtually every industrial sector; in turn, producers and other workers along the supply chain of virtually every industrial sector could be affected, with potentially dire consequences – especially for those small-scale producers and workers who are already vulnerable. (See Annex.)

"We'd all love to imagine a world where we could adapt biology to manufacture any product renewably, quickly and on demand," Michael Jewett, synthetic biologist, Northwestern University, Illinois (USA) and Principal Investigator, *Clostridia* Foundry for Biosystems Design (*c*BioFAB), quoted in *Nature*.[7]

In the hyped, early days of metabolic pathway engineering for fermentation-based biosynthesis, companies focused on producing biofuels and bioplastics, but technically-sound and cost-effective commercial scale-up remained elusive. Even colossal fermentation tanks – 200,000 liters – could not compete with petroleum refineries on volume or cost. "Production can be fickle and can be hard to control in a vat the size of a bus," explained Mark Bünger, a market analyst.[8] Most syn bio companies that attracted initial investment and philanthropic grant money with promises to create a "green" alternative to fossil fuels have now adopted a new business model or have filed for bankruptcy. Once-celebrated syn bio startups that failed to compete in the biofuel marketplace include Solazyme, LS9, INEOS Bio, Joule Unlimited and Amyris, Inc. As one syn bio executive explained: "Challenged by cheap oil, investor fatigue, and technical hurdles, many biofuel companies pivoted to produce alternative chemical products through fermentation. We looked for products with lower costs, lower volume, and higher value…"[9]

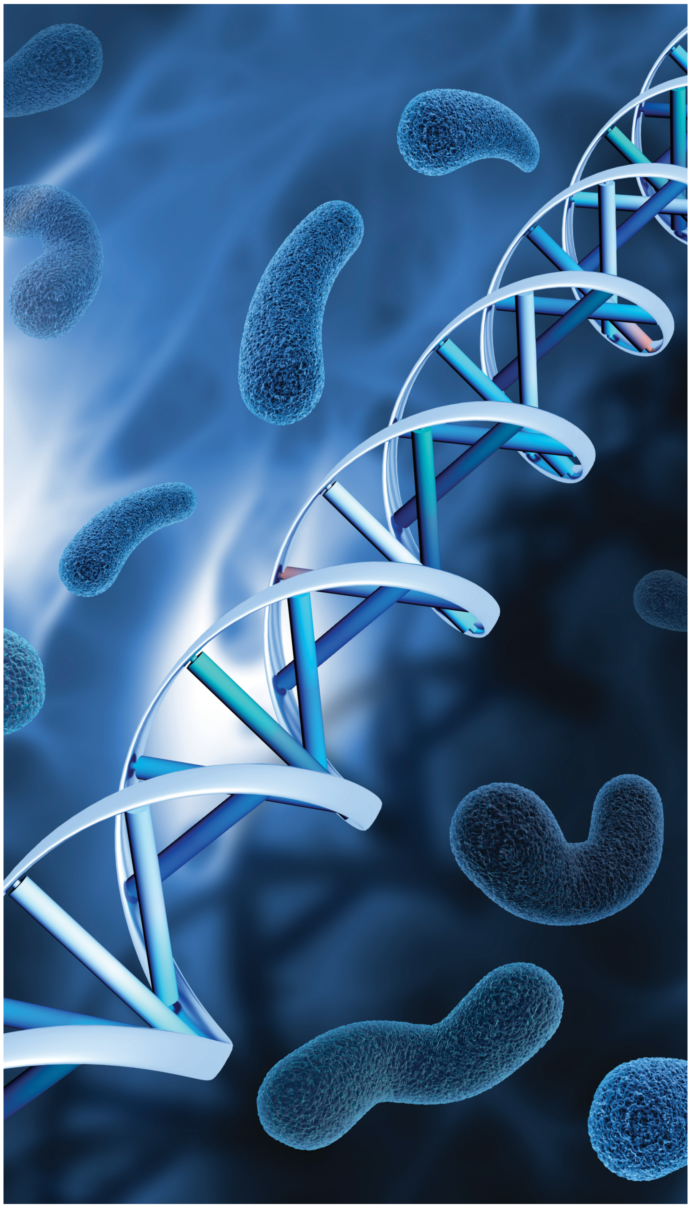
Targeting lower volume / higher value products brought the biotech upstart to the world of flavours, fragrances and cosmetic ingredients – a move which implicates the livelihoods of small agricultural producers around the world. (Some of those products are listed in Table 2, below.) The flavour and fragrance industry, as just one example, currently sources 200 to 250 different botanical

Table 1: Sectors with Active Synthetic Biology R&D and Selected Examples of Biosynthesized Products

Pharmaceuticals	Fashion	Flavours and Fragrances	Sweeteners	Cosmetics	Agribusiness Food/Feed	Fuels
Artemisinin* (malaria drug), Taxol (cancer drug), Cannabinoids (pain relievers)	Silk,* Leather Dyes PDO*	Vanilla / Vanillin,* Vetiver, Patchouli*, Rose oil * Nootkatone* (grapefruit)	Monk Fruit, Stevia	Shea Butter*, Resveratrol,* Squalane* Propanediol*	Meat, Fishmeal,* Milk (dairy), Seed Treatments,* Fertilizers*	Bio-diesel* Isobutanol*

* On market

For more information on biosynthesized ingredients incorporated into products, consult the Synbiowatch GMOs 2.0 Ingredients Database: http://database.synbiowatch.org/.



crops grown worldwide; the vast majority, an estimated 95%, are grown and harvested by small-scale farmers and agricultural workers, mostly in the global South.[10] An estimated 20 million people, including small-scale farmers, agricultural workers and other workers along the supply chain depend on botanical crops sourced for natural flavours and fragrances.[11] Some industry trade groups recognize that these botanicals are "highly important in terms of their socio-economic impact on rural populations and may also have important environmental benefits within agricultural systems."[12] Essential oils derived from botanicals, for example, "are typically categorized as 'minor crops,' [but] they are of major economic social and environmental importance to the communities that are involved in their production – and frequently represent the key cash crop (family income generator) in their farming mix that supports improvement in social indicators – notably health and education."[13] If even a small fraction of those botanically sourced flavours and fragrances are replaced by biosynthesized alternatives, the impact on livelihoods could be dire.

Automation and Artificial Intelligence (Machine Learning) Speed Up Biosynthesis in "Living Foundries"

Biosynthesis development – specifically, the number and variety of engineered organisms – has been accelerating because both public and private enterprises, largely in the United States, have been able to substantially reduce the cost and shorten the timeline for designing and producing organisms. They've done this by bringing together new genome engineering techniques such as CRISPR (for gene editing) and CRISPR interference (CRISPRi, for manipulating gene expression)[14] with data mining, automation, robotics and artificial intelligence (machine learning).

The US government's "Living Foundries" program – run by the Department of Defense's Advanced Research Projects Agency (DARPA) – claims that between 2012 and 2014 it achieved a greater than 7.5-fold acceleration and a greater than 4-fold decrease in cost for the "design-build-test cycle" for generating new "production strains" of organisms – that is, engineered organisms capable of industrially useful biosynthesis.[15] The US Department of Energy's "Agile BioFoundry" – a consortium involving nine government-run laboratories – aims to design, build and analyze more than 75,000 organisms by 2020.[16] The United Kingdom, Singapore, China, and Denmark are also building biofoundries.[17]

Ginkgo Bioworks, a private company (as of writing) headquartered in Boston, recently secured funding for its third "foundry" for designing, testing (i.e. experimenting) and scaling engineered organisms.[18] Ginkgo claims its new automation software will speed up product delivery and double its current monthly foundry output.[19] In order to produce all those novel organisms, Ginkgo put in an order for one billion base pairs of synthetic DNA from Twist Bioscience, a private company in San Francisco – "the largest volume supply agreement in the industry" equaling approximately one third of the global output of synthetic DNA, according to the two companies.[20] The new foundry will also house a new USD 100 million joint venture with Bayer to design and produce nitrogen-fixing microbes for agriculture.[21]

"If you're still using your hands, you won't be doing science." — Max Hodak, co-founder of Transcriptic, automation software maker and partner of Ginkgo Bioworks, describing the near future of synthetic biology in an era of robotics and automation[22]

A rival of Ginkgo Bioworks is California-based Zymergen, which relies on automation and machine learning (a.k.a. artificial intelligence) to "tune up" microbes that have already been engineered for biosynthesis. Companies send their industrial microbes to Zymergen with hopes that the company's automated systems can engineer a more productive version.[23] Zymergen begins with algorithms that come up with 1,000 or more possible changes to the microbe's genetic material to increase efficiency, and "that's when the robots take over, injecting the suggested DNA snippets into the specimens, testing their properties, collecting data about each new combination and feeding that information back into the data trove."[24] Zymergen's process is parallel (more than one microbe, or even more than one species of microbe, can be tested at the same time) and iterative (a version of a microbe undergoing optimization can be tested and analyzed, with the analytic results contributing to the next iteration, and so on). For now, Zymergen makes money by charging its clients subscription fees and taking a percentage of the improved profit margins achieved by the new, optimized microbes.[25] (Zymergen does not disclose its revenue or the names of its corporate clients.) In the future, Zymergen aims to focus on designing and building its own commercially profitable organisms.[26] To that end, Zymergen recently acquired Radiant Genomics, which holds "one of the largest fully-assembled and instantly-accessible catalogues of genetic diversity in the world."[27]

The Role of Big Data

Underlying all the recent synthetic biology developments is a dizzying amount of biological data. GenBank is a data repository that holds genomic sequence information on more than 400,000 species of plants, animals and microorganisms. Beyond genomic data, Pathguide (pathguide.org) provides a list of 702 separate resources (most of them databases) related to biological pathways and molecular interactions, and, at the beginning of 2018, the online Molecular Biology Database Collection identified 1,737 databases encompassing 15 categories and 41 subcategories.[28] No human brain could begin to sift through that amount of disparate and dispersed data, so data mining must necessarily become automated.

SyBiOntKB is a recently created knowledge-base specific to the design of synthetic organisms; biological data from different datasets in different formats were first integrated under a unified framework into a searchable "data warehouse" to enable searching for potentially useful genetic parts and devices in the creation of a synthetic organism.[29] The developers of SyBiOntKB hope their approach "will be useful to speed up synthetic biology design and ultimately help facilitate the automation of the biological engineering life cycle."[30] Another syn bio-specific data tool is Garuda (Genetic Automation: Recommendation Unit and Data Analyzer), which has been developed at Boston University with funding from DARPA's Living Foundries program.[31] Garuda consists of collections of data mining, pattern analysis, and machine-learning algorithms to potentially reveal information not stored explicitly stored by users and lead to "meaningful recommendations" in syn bio design or "debugging."[32]

Protein Biosynthesis: Start-ups Bet that Both "Greens" and Big Ag Will Embrace A New Food Supply Chain via "Cellular Agriculture"

Most current biosynthesis research and development (R&D) is focused on producing high value / low volume compounds that may traditionally have been botanically sourced such as those used in foods (as flavours), cosmetics or perfumes, or on bioactive compounds for the pharmaceutical and agribusiness sectors; however, other products of biosynthesis are beginning to gain attention and investment. Several companies around the world are trying to grow protein-rich foods in the lab via syn bio fermentation – sometimes called "cellular agriculture" – with animal welfare, food security, environmental sustainability and "clean" production cited as motives for the work. Some also see a "colossal market opportunity."[33]

Plant-based substitutes explicitly intended to replace cow's milk (e.g., soy milk) have been on the market since the early 20th century, as have plant-based foods aimed at simulating meat's texture and taste, but the newer, dairy-free (and cow-free) milks and "meat analogs" are something different: the products of synthetic biology. For example, Perfect Day Foods, based in Silicon Valley, has engineered yeast to ferment sugar to produce synthetic dairy proteins (casein and whey), from which a milk substitute is made. Perfect Day Foods is supported by New Harvest, a non-profit research institute that funds about a dozen so-called cellular agriculture projects around the world, including hen-free eggs and cow-free hamburger meat.[34] Other research teams are part of the DIYbio (do-it-yourself biology) movement, such as the Real Vegan Cheese project (https://realvegancheese.org/), whose funding is crowd sourced via Indiegogo.

Cellular agriculture start-ups have begun attracting investment from Big Ag players. Germany-based PHW Group, one of Europe's largest poultry producers, recently became a strategic partner of SuperMeat, a Tel Aviv start-up that aims to bring biosynthesized chicken to the market within the next three years.[35] SuperMeat started with an Indiegogo crowd-source campaign that raised more than USD 230,000 in pre-orders for its lab-grown chicken.[36] The Chinese government invests in SuperMeat as well as two other Israeli alt-meat companies – Future Meat Technologies and Meat the Future – as part of a USD 300 million bilateral trade deal backing so-called climate friendly high-tech.[37] Both Tyson Foods and Cargill (along with Bill Gates and Richard Branson) have invested in Memphis Meats, another Silicon Valley cellular agriculture start-up. Tyson's head of venture investing explains the move: "If disruptions take place in the way that food is going to be developed, or delivered in protein in particular, Tyson Foods is going to be there."[38]

In 2016, Cargill formed a joint venture with Calysta, a Silicon Valley biosynthesis company, called NouriTech, which produces protein to be used as a fish, livestock and pet feed ingredient. NouriTech broke ground on a new protein factory in Memphis, Tennessee (USA) in 2017, which the company expects to open in 2019; NouriTech already has a fermentation facility in northern England. NouriTech's product, known as FeedKind, is marketed as a sustainable and direct replacement for fishmeal and has been approved for use as an ingredient in organic systems for animal feed in the UK and Europe.[39] (Presumably, organic accreditation is possible because the microorganisms in this application are considered non-GMO for regulatory purposes; however it appears Calysta's microorganisms have undergone extensive "strain engineering," even if no foreign DNA has been introduced.[40]) According to Envision Intelligence, the global market for fishmeal and fish oil will reach USD 9.50 billion in 2018.[41]

Syn Bio's Fake Claim to "Natural"

One enticement for industry is the prospect that, in many jurisdictions, the products of synthetic biology might be legally described and labeled as "natural" because manufacturers can claim the microbiological process of fermentation is in itself 'natural' (regardless of the unnatural nature of the production organisms).[42] This means that syn bio ingredients could be very quietly introduced into natural products markets. Indeed, a handful of synthetic biology biosynthesized ingredients already misleadingly receive "The Natural Seal" – a 'natural' certification mark.[43] The use of the term *natural* is already fraught,[44] but syn bio's high-tech hijack of biology for industrial purposes will make it more so. Even companies steeped in traditional Big Ag commodities – companies like Cargill, which has partnered with Swiss-based Evolva to commercialize a biosynthesized stevia-like compound – are willing to invest in the possibility of a less expensive, more direct route to secure the agricultural commodities they trade, especially so if those commodities can be direct replacements with identical labeling. They will continue to source their products from the farm, possibly, but preferably from the lab if the price is right – in the interest of uniformity and a stable supply chain. For some products such as flavours and cosmetics ingredients, biosynthesized products are not only positioned to compete with their natural, botanically derived counterparts, but they will also have a market advantage over synthetic versions. Consumers routinely report that they prefer products that are natural to those that are artificial or synthetic.[45] For the majority of syn bio's products, however, consumers will have no way of knowing if the product labeled "natural" is derived from industrial, engineered microbes or from a traditional botanical or agricultural source.

Syn Bio Variations: Different Microbes, Different Feedstocks, Focusing on the Energy Sector

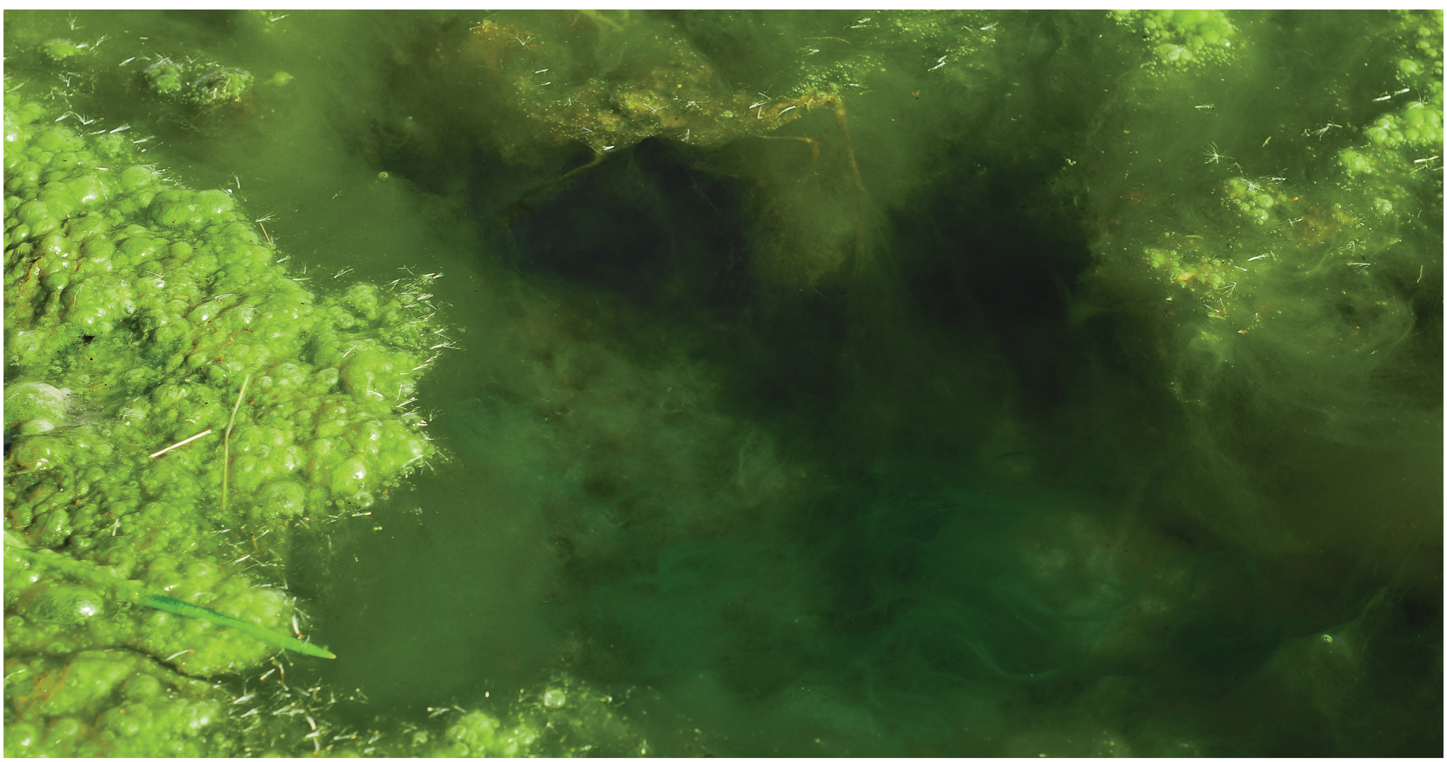
Calysta's fishmeal replacement, described above, follows the now-familiar pattern: engineered microorganisms are fed a carbon-based energy source and they undergo fermentation to produce a valuable commodity. But Calysta's syn bio-based fermentation process is different. First, the microorganisms themselves become the commercial product (whereas, in the usual case, it is the byproduct of fermentation that is of commercial value). Secondly, Calysta's microorganisms don't metabolize sugar; they are bacteria that metabolize methane, the principal component of natural gas and the second most abundant greenhouse gas in Earth's atmosphere. When the Calysta-Cargill fishmeal facility (NouriTech) comes online in Tennessee in 2019, it will get its methane piped in from the city of Memphis.[46]

Calysta has also engineered its methane-eaters, called methanotrophs, to produce lactic acid, a building block of bioplastics. Calysta and NatureWorks, a US-based company that currently makes bioplastics from GMO corn, have partnered to biosynthesize lactic acid using methanotrophs. The project is being supported by a USD 2.5 million grant-award from the US Department of Energy.[47] While theoretically atmospheric methane could be captured and used as a feedstock in production – and it is largely on this theoretical basis that the technology makes 'eco-friendly' claims– the bacteria that Calysta engineers to produce protein and lactic acid are currently fueled by natural gas. (There is little incentive to do otherwise since natural gas prices are at historic lows in the United States, largely due to abundant supplies from fracking.[48]) Other syn bio companies, such as LanzaTech, which operates in New Zealand, India, China and the United States, are aiming to use engineered methanotrophs in the production of ethanol using "waste carbon streams," including carbon monoxide effluent from steel mills; US-based Intrexon is using methanotrophs to convert natural gas to isobutanol.

“No” to Status Quo Doesn’t Mean “Yes” to Syn Bio

Given the environmental and climate effects of industrial agriculture, the increase in global meat consumption and the proliferation of petroleum-derived plastics, it is not surprising that synthetic biology and biosynthesis have garnered media attention, private investment, government support and enthusiasm from some professed environmentalists. The point is not that the status quo should be preserved; however, if biosynthesis brings even a fraction of the market disruption envisioned, the socio-economic impacts will be monumental. Small producers are likely to be most affected and are least able to withstand upended markets. Even the prospect that a crop could be produced in an industrial vat could disrupt supply chains and cause farmers to reject opportunities for fear that there will be no buyers at harvest time.

When, in 2013, Amyris, Inc. and pharmaceutical giant Sanofi Aventis announced commercial production of syn bio-derived artemisinin – a key component of malarial treatment, which is botanically sourced from the sweet wormwood plant, *Artemisia annua* – it was hailed as “a triumph” for synthetic biology, as the test-case that proved the potential for an innovative start-up to create and distribute a finished, high-value product in collaboration with a multinational titan. It was also presented as a much-needed market stabilizer and an aid for those suffering from and needing treatment for malaria.[49] By 2015 however, the production of syn bio-derived artemisinin had been halted and by mid-2016, Sanofi had sold off its production facility. The reasons for the semi-synthetic product’s failure – or, at least, its “modest impact”[50] on the supply chain – are still being debated, but the bottom line is that it cost more to produce syn bio artemisinin than to grow and harvest sweet wormwood, at least in the timeframe of the corporate attention span: “If [the] price is already very low…there’s no reason to fire up a fermenter,” explained Jay Keasling, the technology’s inventor.[51] But that’s part of the lesson to learn from synthetic biology: the technology doesn’t have to ‘work’ to be profitable, to become a media and funding magnet, to disrupt markets for natural products and/or to divert funding from other (more) useful activities.



The Challenge to Biosafety Test, Detect, Monitor and Trace Syn Bio Organisms

It is worth noting that when synthetic biologists refer to the "design-build-test cycle," the "test" component does not refer to testing for safety; *test* refers to commercial utility: does the engineered organism produce (or become) the desired compound as designed? The aim is to accelerate the design-build-test cycle whenever possible.[52] With the increased use of artificial intelligence, including algorithms and machine learning, and robotics to speed up organism design and construction, we are likely to see *more* organisms produced *more* quickly and with *more* complexity – what one company refers to as the "directed creation of genetic diversity."[53]

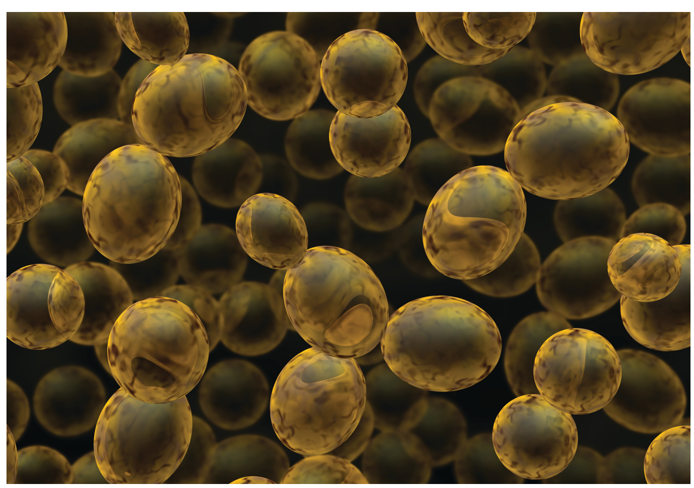
In its latest report, the CBD AHTEG on Synthetic Biology noted the potential increase in the complexity and abundance of engineered organisms through synthetic biology techniques [para 15] but concluded "that most living organisms already developed or currently under research and development…including organisms containing engineered gene drives…[fall] under the definition of LMOs [Living Modified Organisms] as per the Cartagena Protocol" [para 28]. The AHTEG then considered some of the potential shortcomings of the Protocol, including that the current tools for the detection, identification and monitoring of LMOs may need to be updated and adapted [para 32].

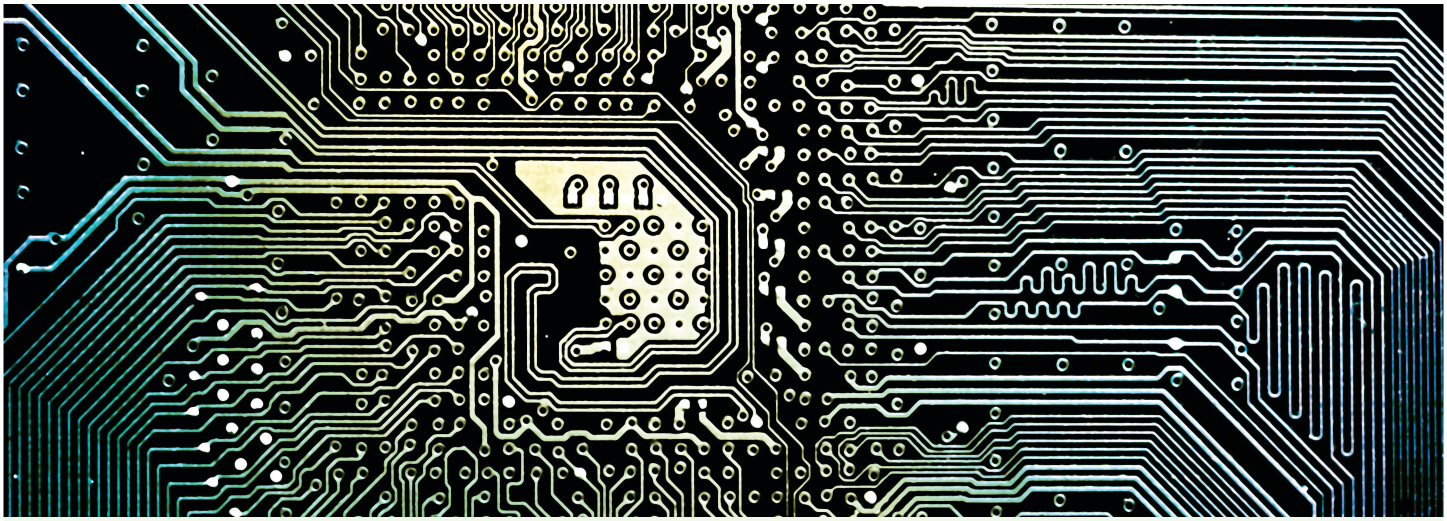
"When synthetic biologists announce they will treat microbes like tiny factories, investors and markets may be listening, but the microbes are not."[54] – Daniel Grushkin, science writer and co-founder of Genspace, a DIYbio lab

Especially given the anticipated commercial proliferation of synthetic organisms that aim to produce biosynthetic ingredients – some of which will be intentionally or unintentionally released in the environment or ingested by livestock and/or humans – current safety protocols are likely inadequate. Where they are in place, regulatory frameworks generally allow for "case by case" assessments of LMOs that have arrived at a regulator's door to be considered by human "experts."

Theoretically, these LMOs can be entered into the LMO-Unique Identifiers Registry (LMO-UIds) of the Biosafety Clearing-House, to provide relevant, public information including transformation events, genetic modifications, and the unique identification code (if available) for each record.[55] How will regulators keep up with the identification and then assessment of syn bio organisms produced by automated, AI-driven robots – especially those purported to be "nature-identical" – let alone monitor their biosafety? Will regulators then need to rely on AI-driven biosafety assessments to respond? How confident are we to relegate both the redesign of nature and the responsibility to ensure biosafety to automated systems?

Given these potential shortcomings, the AHTEG noted that those developing synthetic organisms for commercial use and products derived from such organisms "could be responsible for providing validated tools, relevant sequence data and reference materials, in an accessible manner, that would facilitate the detection, identification and monitoring of such organisms and products thereof, as was already the case for LMOs under some frameworks" [para 38]. Such tracking, identification and traceability would seem to be very lowest level of action required for the sake of precaution. The AHTEG further noted that risk management strategies and monitoring may also "need to be adapted and complemented in order to address specific characteristics of organisms developed through synthetic biology" [para 48].





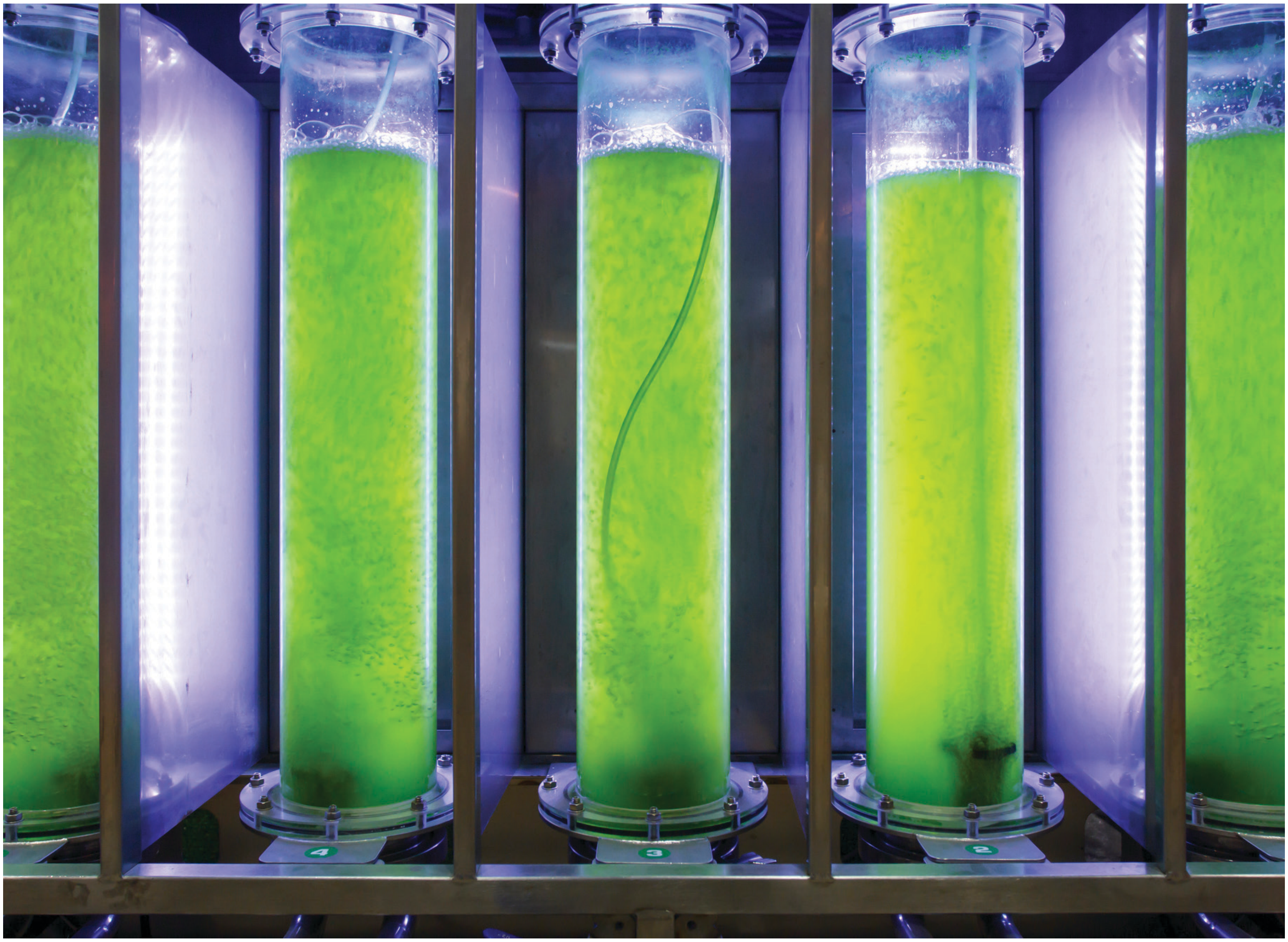
The problem of algorithmic governance

As the design and manufacture of novel organisms (and novel molecular byproducts) becomes increasingly driven by artificial intelligence and algorithmic decision making, a current hot controversy over the problem of algorithmic governance will start to become a challenge for biosafety regulators – just as it has for transport regulators addressing AI in self driving cars or justice officials in addressing AI in the legal system.

At the root of the algorithmic governance conundrum is the fact that current machine learning systems, trained using neural networks, may appear able to seize upon 'the right answer' to a problem with increasing precision but are unable to provide explanation for how they got there. In the case of self-driving cars for example, the decision by a neural net-trained AI to swerve around an accident or enter a bike lane is the result of the machines internal representation of the situation compared against previous data but may not be comprehensible to a human investigator. If the car should then hit a bystander or bicycle it is not clear where responsibility lies, since it is not possible to decode what, if any, logical mistake was made. This creates a vacuum for liability and governance in biotech as much as transport. This conundrum is leading to calls for AI developers to create 'explainable AI.'[68]

As more and more synthetic organisms are designed by machine learning algorithms that are not rules-based nor explainable, the same issues could arise in the life sciences. For example, AI biosynthesis firm Zymergen has admitted that it doesn't really understand how its design programmes decide on successful genetic alteration. In an interview with Science, Zymergen's founders admit that when their robots discover successful genetic changes that boost a chemical output they don't have a clue about the biochemistry behind their effects and may never understand it. "We get paid because it works, not because we understand why," explains Aaron Kimball, the company's chief technical officer. "An intriguing possibility is that we're closing the era of 'comprehensible' science," says Adrien Treuille, a computer scientist at Carnegie Mellon University in Pittsburgh, Pennsylvania, who works with molecular biologists.

Yet not understanding the reason for a genetic modification or tracking its other side effects could be a recipe for disaster. Microbes engineered to biosynthesize ingredients for human ingestion have in the past caused significant harm and even death, in the case of the 1989 L-tryptophan incident where a tiny change in production levels for a common food supplement likely created an inadvertent toxin[69]. Considering the need to assure safety and act with precaution, putting 'black box' engineered organisms into commercial production would seem reckless.



Recommendations to SBSTTA

In light of the acceleration in number of compounds and organisms using synthetic biosynthesis, Parties to the CBD may wish to consider:

1. **Addressing the livelihood and biodiversity implications of biosynthesizing alternatives to natural products.**

The Parties to the CBD could consider developing mechanisms of horizon scanning, assessment, liability and redress by which Parties or communities can resolve situations where sustainable use of biodiversity is impacted by synthetic biology production, new algorithmic technologies or other associated innovations.

2. **Ensuring monitoring, testing, traceability and labelling of components, organisms and products of Synthetic Biology.**

As recommended by the AHTEG on Synthetic Biology, those commercializing “products and organisms resulting from synthetic biology…could be made responsible for providing validated tools, relevant sequence data and reference materials, in an accessible manner, that would facilitate the detection, identification and monitoring of such organisms and products” [para 38].

3. **Clarifying honest terminology**

Synthetic Biology (including gene-editing) is a genetic engineering technology within the field of modern biotechnology that gives rise to Living Modified Organisms. Therefore, it would be misleading and undermine transparency to label the products of synthetic biosynthesis as either ‘non-GMO’ or ‘natural.’

Annex: Natural Products Targeted for Biosynthesis, Selected

Natural Product Targeted for Replacement with Bio-synthesized Product	Market Status of Bio-synthesized Product	Companies Involved, Selected	National Economies Most Affected Potentially	Approx. Number of Producers Potentially Affected, if available	Global Market Value, US$, if available
Artemisia annua	Commercialized, but not currently in production	Amyris, Sanofi Aventis	China, Vietnam, Madagascar	~100,000	~27- 46 million
Medicinal Cannabinoids (occur naturally in cannabis plants)	Medicinal cannabinoids under development	Teewinot Life Sciences Corporation (USA)	Cannabis cultivation: Morocco, Mexico, Nigeria, Lebanon, Paraguay	n/a	12.67 billion[56] (for medicinal cannabinoids)
Nootkatone (occurs naturally in grapefruit)	On market	Evolva (Switzerland), Oxford Biotrans (UK), Isobionics (Netherlands)	Brazil, United States, Israel, Argentina, New Zealand	n/a	231 million (2016)[57]
Patchouli Oil	On market (Clearwood)	Isobionics (Netherlands), Evolva (Switzerland), Firmenich (Switzerland)	Indonesia, China, India	~50,000[58]	~100 million[59]

Natural Product Targeted for Replacement with Bio-synthesized Product	Market Status of Bio-synthesized Product	Companies Involved, Selected	National Economies Most Affected Potentially	Approx. Number of Producers Potentially Affected, if available	Global Market Value, US$, if available
Saffron	Under development	Evolva	Iran, India, Kashmir, Greece, China, Spain, Afghanistan, Morocco	> 150,000[60]	~646 million (2015)[61]
Sandalwood	Similar fragrance on market (Clearwood); others under development	Isobionics (Netherlands), Evolva (Switzerland), Firmenich (Switzerland)	India, Indonesia, Australia, South Africa, Tanzania, Kenya, China, Sri Lanka, Thailand, Cambodia	n/a	~27 billion
Squalene (occurs naturally in shark liver oil and olive oil)	On market	Amyris (USA), brand name Biossance, Croda (UK)	Olive – Spain, Israel, France, Italy, Greece, Portugal, Morocco, Syria, Algeria, Jordan, Tunisia, Turkey; Shark liver – India, Indonesia, United States, Belize[62]	n/a	110 million (2015)[63]

Natural Product Targeted for Replacement with Bio-synthesized Product	Market Status of Bio-synthesized Product	Companies Involved, Selected	National Economies Most Affected Potentially	Approx. Number of Producers Potentially Affected, if available	Global Market Value, US$, if available
Silk	Some products on market; others under development (scale-up)	Spiber, Inc. (Japan), AMSilk (Germany), Bolt Threads (USA), Kraig Biocraft Laboratories (USA)	China, India and 58 other countries	n/a (60 million households involved in production of natural fibers)	11.7 billion[64]
Stevia	Near-market (Cargill expects EverSweet on market in 2018); DSM has sought market approval for its stevia from EFSA in Europe and FDA in the United States; others under development	Evolva (Switzerland), DSM (Netherlands), Manus Biosynthesis (USA), Amyris (USA), Cargill (USA), PureCircle (USA), PepsiCo (USA), Coca Cola (USA)	Paraguay, Kenya, China, US, Vietnam, Brazil, India, Argentina, Colombia	n/a	~447.5 million[65] (2016)
Valencene (occurs naturally in orange peel)	On market	Evolva (Switzerland), Isobionics (Netherlands), FCI (France)	Brazil, Spain, United States, Israel, Italy, Morocco, Belize, Zimbabwe, Cypres	n/a	Unknown; worldwide citrus essential oil market ~3.2 billion[66] (2017)

Natural Product Targeted for Replacement with Bio-synthesized Product	Market Status of Bio-synthesized Product	Companies Involved, Selected	National Economies Most Affected Potentially	Approx. Number of Producers Potentially Affected, if available	Global Market Value, US$, if available
Vanilla	Biosynthesized vanillin on market	Symrise (Germany), IFF (USA) – using technology from Evolva (Switzerland), T. Hasegawa (Japan)	Madagascar, Comoros, Réunion; also grown in Indonesia, China, Mexico, East Africa, French Polynesia, India	~200,000	~1.3 billion[67] (2017)
Vetiver	Under development	Evolva	Haiti, Indonesia, Java, China, Japan, India, Brazil and Réunion	Unknown (27,000 farm families in Haiti alone)	~50 million

Endnotes

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