

Bio manufacturing and One Health

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Abstract

At a time when the scope of One Health is expanding, the term “biomanufacturing” has taken on new significance as a new route to more sustainable manufacturing in the face of the current overwhelming reliance on fossil resources for fuel, energy, and materials. This article looks at how One Health and biomanufacturing interact from policy, technical, and societal viewpoints. The biofoundry is explored as a missing link in the design phase of biomanufacturing and examples are given where the potential of biofoundries can be enhanced in selected environmental and human health applications.

The medical writer role

A clear role for medical writers will be to delineate change to regulatory systems necessitated by technologies that allow for the faster generation of candidate molecules and their filtering through technologies such as quantitative structure-activity relationships (QSARs). The medical writer role will become clearer while reading this article.

The OECD single definition for biotechnology

The Organization for Economic Cooperation and Development (OECD) leads policy discussions among its member countries, which span the globe from North and South America to Europe and Asia-Pacific. The OECD’s single definition of biotechnology is:

*The application of science and technology to living organisms, as well as parts, products, and models thereof, to alter living or non-living materials for the production of knowledge, goods, and services.*¹

The global policy landscape

To date, 195 member states of the United Nations Framework Convention on Climate Change (UNFCCC) are party to the Paris Agreement, the global agreement to slow climate change caused by carbon emissions that was signed in Paris in 2015. The plan is to achieve well below a 2°C rise in global temperature, a goal that requires net-zero carbon emissions by mid-century. The proximity to 2050 calls for very fast action, and many of the needed technologies to store and recycle carbon, and truly new, low-emissions industrial production systems, are not ready for deployment. After a long period of policy focus on fuels and energy, it has been realised that the effort will require all sectors in all countries.² While climate action is top priority in sustainability policy, it is part of the wider concept of sustainability, which has environmental as well as economic and social pillars. The concept is enshrined in One Health, where human, animal, and environmental health all intersect (Figure 1).

“Through Executive Order 14081, the Federal Government will deliver reports to the President on how biotechnology and biomanufacturing can further societal goals related to health, climate change and energy, food and agricultural innovation, resilient supply chains, and cross-cutting scientific advances.”⁴

EXECUTIVE ORDER OF U.S. PRESIDENT
JOSEPH R BIDEN, SEPT. 12, 2022

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Biotechnology is used in biomanufacturing, also known as bioproduction. Biomanufacturing and bioproduction are terms that are familiar to the pharmaceutical industry. Biomanufacturing is a more recent entrant in serious policy debates. It was thrust upon centre stage with the Biden Administration Executive Order (see above) on biomanufacturing issued on September 12, 2022. Since then, the Ministry of Science and Information and Communication Technology-ICT (MSIT) of Korea announced the National Synthetic Biology Initiative to enhance the country’s capabilities in biomanufacturing.⁵ One of four goals set is to

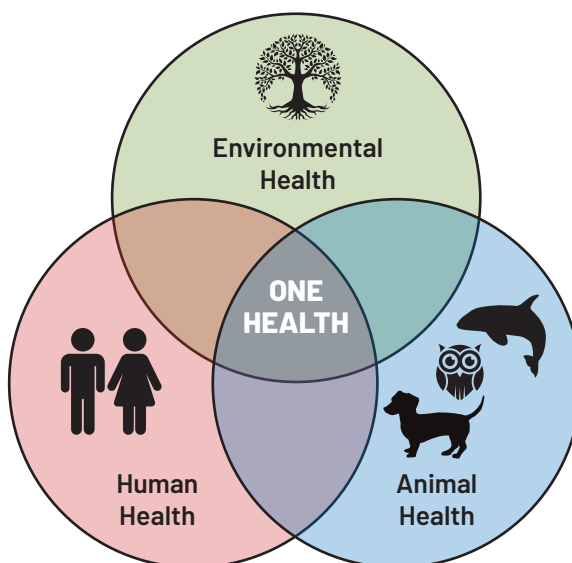


Figure 1. The intersection of human, animal, and environmental health is One Health

(after Ratnadass and Deguine, 2021)³

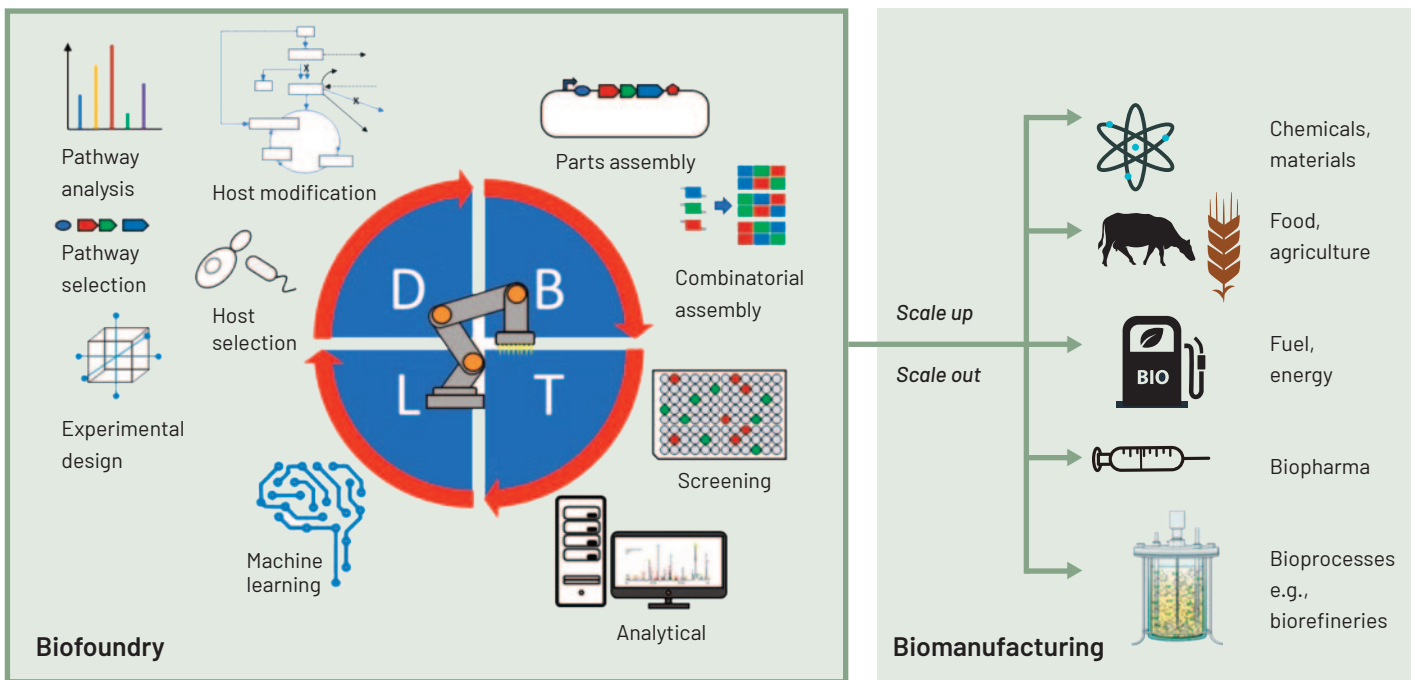


Figure 2. The biofoundry as the missing link in biomanufacturing: Automating the Design-Build-Test-Learn (DBTL) iteration cycle

Standards, automation, and machine learning are key to the success of this approach. As in modern manufacturing, the site of the design (the biofoundry) can be totally separated from the site of manufacturing (typically the biorefinery), using data transfer to dematerialise the process.

transition 30% of the manufacturing industry to a bio-based industry within the next 10 years.

And on November 14, 2022, EuropaBio, Europe’s largest biotechnology industry group, announced a new cross-sectoral Biomanufacturing Platform to strengthen the link between biotechnology and competitiveness, health, and sustainability across Europe. The platform has the mission to “represent biomanufacturing at the highest policy levels in Europe, to ensure that it is visible and recognised within the industrial strategy and Europe’s green and digital transitions.”⁶

Application across human, animal, and environmental health

Gurdo et al. (2022) “... argue that some of the solutions [...] could help consolidate a bioeconomy in times when alternatives to oil-based production (subjected to all sorts of political and economic sways) are urgently needed.”⁷

This article is themed on biomanufacturing as a future industrial production system. In human health, this is not so new, but for industrial production of fuels, chemicals, and materials, the goal is the gradual replacement of reliance on fossil resources like oil and gas. One of the major challenges of bio-based production systems like

fermentation is that the microorganisms used are not optimised for use in large-scale systems, which inhibits the fulfilment of industrial biotechnology as an engineering and manufacturing discipline. The most promising design tool to overcome this challenge is the biofoundry. Biofoundries are highly automated facilities that use laboratory robots (Figure 2) programmed for specific tasks defined in a workflow. It can be seen that the biofoundry is a platform technology applicable across many of the key sectors of relevance to One Health.

In theory the use of renewable carbon to make molecules identical to the products of the petrochemicals industry (so-called “drop-ins”) should lead to reductions in emissions. Much evidence seems to bear this out.^{8,9,10} From a human, animal and environmental health perspective, there are no more pertinent examples than the fossil-based thermoplastics, which are non-biodegradable over hundreds of years, but are subject to fragmentation into microplastics and nanoplastics in the oceans, the destination of many millions of tonnes per annum.

Point Nemo is the most remote area on Earth, more than 2,500 km from nearest land in all

directions. Water samples taken during the most recent yachting Ocean Race revealed 320 microplastic samples per cubic metre of water, up from 9 to 41 per cubic metre of water, depending on the source, in the previous race.¹¹ If accumulated in marine animals for human consumption, then there is the prospect of amplification to humans with the potential to cause health problems as yet unexplored. A more graphic illustration, however, is the consumption of “macroplastics” by seabirds, unable to distinguish plastics from food, which then die a wretched death filled with plastics (Figure 3).

Are microplastics an existential threat?

It has been estimated that there are 170 trillion pieces of plastic in the oceans.¹³ Does this pose some existential threat to all health (animal, plant, human, ecosystem)? There are at least two reasons why knowledge gaps need to be filled. First, nanoplastics have the potential to affect marine biota by ingestion. Second is the transfer of highly toxic chemicals, such as persistent organic pollutants (POPs) and endocrine disruptor chemicals (EDCs) along with the plastics. As hydrophobic materials, in the oceans they



Figure 3. A seabird killed by the consumption of plastics floating in the oceans

(Courtesy of Chris Jordan Photographic Arts, "Midway: Message from the Gyre")¹²

accumulate hydrophobic pollutants from ocean water, thus concentrating them on the plastics.¹⁴ The extent to which this causes harm to marine species is uncertain. And the threat is not restricted to the marine environment; microplastics have been found in raindrops and breathable air.¹⁵ The discovery of plastic particles in human blood¹⁶ surely warrants research on their fate and effects.

Why the biofoundry?

The demands of the DBTL cycle are not to be underestimated in terms of workload, time, and costs involved. Even today, much of the DBTL cycle in synthetic biology is semi-artisanal. The overarching function of the biofoundry is to accelerate and automate the cycle with increasing consistency and throughput while reducing labour (lumpen pipetting) and thus cost. Biofoundries mostly aim at streamlining the engineering of microbial chassis for chemical production. The key is throughput.

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The huge advances in genome sequencing, resulting in a current cost for a human genome of around USD600, have facilitated high-throughput design and build. It is now possible to automate the "test" phase as well though advances in technologies such as microfluidics.

Now the bottleneck lies in the "learn" phase of the DBTL cycle¹⁷ and machine learning holds out the hope of being able to further accelerate the cycle. Integrating machine learning into the DBTL cycle could, for example, aid in the development of accurate models for clinical studies and precision therapies, even leading to "diagnostic and therapeutic" microbes that can identify diseases *in situ* and produce drugs *in vivo* based on the diagnoses.¹⁸ In the chemical and environmental fields, similarly bacteria could be developed to break down cellulosic biomass, transport the produced sugars into the cell and then ferment those to a desired product, e.g., biofuels¹⁹ and bioplastics.²⁰ This consolidated bioprocessing has been a long time coming and

it looks like automation is the way to bring it to reality.

QSARs, machine learning, and the biofoundry

A goal of several decades has been the production at a competitive scale of biodegradable plastics that would be able to tackle the scourge of plastics in the oceans. There are several candidate molecules but little market penetration. Perhaps the biofoundry could be the design platform to increase the number of candidates. There would still be the bottleneck at testing and learning,



however. Here there may be a role for machine learning and AI to identify the most effectively degraded candidates under different conditions. Back in 1976, Klaus Kieslich published a 1,262 page volume on the microbial transformation of non-steroid cyclic compounds. Since then, electronic databases have replaced paper.²¹

The real power of electronics should be predictive capabilities. The most useful tools may be quantitative structure-activity relationships (QSARs), and their integration into biofoundry operations might provide this predictive power. AI/machine learning/deep learning models for

prediction, often using databases of QSARs, can now be used to predict the biodegradability of organic chemicals and bio-based plastics.²² It is speculated, then, that it may be possible to integrate these electronic models into the highly automated biofoundry to predict the biodegradability of new candidate molecules for biodegradable plastics.

The utility of QSARs in the biofoundry has potential way beyond biodegradable plastics. In human and environmental health a few examples are:

- *In vitro* and *in silico* toxicology testing before

clinical trials of a putative drug molecule.²³

- Predicting oxidative stress in humans caused by organic chemicals.²⁴
- Predicting the environmental toxicity of pollutant chemicals.²⁵

In drug design, virtual screening emerged as a powerful computational approach to screen large libraries of small molecules for new hits with desired properties that can then be tested experimentally. The underlying principle is that variations in structural properties cause different biological activities.²⁶ The ideal is to reduce the



number of candidates to be tested experimentally, and to rationalise their choice, in a similar manner to the rationalisation of choices of candidate bioplastics above. Among the virtual screening approaches, QSAR analysis is the most powerful method due to its high and fast throughput and good hit rate.²⁷ Yet there are still many constraints in drug design. Ensemble-based machine learning approaches have been used to overcome constraints and obtain reliable predictions.²⁸

Further downstream: scale-up and scale-out

While this article concentrates on upstream issues in design, it is worth mentioning some of the challenges on the right-hand side of Figure 2 relating to scaled-up manufacturing. The challenges are different for (bio)pharmaceuticals and chemicals/materials. For pharmaceuticals, the production volume is comparatively much smaller than, say, scaling up a bioplastic production to the point where it can compete in the marketplace. Pharmaceuticals have much higher added value than commodity chemicals, thus making small-scale production more easily profitable. While pharmaceuticals have a rigorous regulatory system, that is not to say regulation of chemicals and materials is trivial.

The sheer volume of production of a bio-based commodity chemical or a bioplastic creates major roadblocks to scaled production. Fermentation processes for such products generally have low titres, which necessitates expensive downstream processing to concentrate a dilute product from a bulk aqueous phase. And fermentation processes are generally much slower than petrochemical processes. This microbe-based manufacturing of commodity chemicals is thwarted by the fact that they are highly reduced and non-natural compounds relative to the carbohydrate feedstocks. Yim et al. (2011)²⁹ reported a successful metabolic engineering exercise to make 1,4-butanediol (BDO), a commodity chemical used in the annual manufacture of over 2.5 million tonnes of valuable polymers. That process has been successfully commercialised,³⁰ but there are

many more targets that need to be addressed: the chemicals industry manufactures at least 70,000 different products, the most important and highest volume being from petrochemistry.

Concluding remarks

It is possible, then, to make a link between the goals of the DBTL cycle, especially in the bottlenecked “learn” phase and the goals of QSARs. To date, this link is missing in the literature. As QSARs are mathematical models, in theory their integration into the complex software operations of biofoundries should not be impossible. They would represent a contribution to the learn phase of the DBTL cycle.

Finally, this short article points to much larger social, human health and environmental implications associated with the term One Health.

There is a coincidence in history of several Grand Challenges that make the immediate future of humans perhaps the most challenging of all time. Environmental health, human health, and animal health collide in myriad ways, making solutions difficult. As these Grand Challenges interact in complex ways rather like an ecosystem,³¹ the eventual solutions must also be interactive: a solution that acts on only one part of the interactive

ecosystem is likely to initiate other impacts elsewhere in the ecosystem.

A clear role for medical writers will be to delineate change to regulatory systems necessitated by technologies that allow for the faster generation of candidate molecules and their filtering through technologies such as QSARs.

Disclaimers

The views expressed are those of the author and are not necessarily those of the OECD or the governments of OECD member countries.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

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