Strategies for synbio success

Michael Holman, research vice president of global primary research and technology innovator, Lux Research.

Synthetic biology (synbio) has emerged as an alternative to traditional petrochemical synthesis for applications in agrifood; beauty and personal care; chemicals; and consumer products. *MechChem Africa* presents findings from the executive summary of a report by lead analyst, Gihan Hewage, and research vice president, Michael Holman, from global primary research and technology innovator, Lux Research.

According to Gihan Hewage and Michael Holman, writing in the executive summary of Lux Research's Synbio strategy report, effectively using synbio capabilities requires understanding the right strategy for each of the distinct value propositions it can offer, including marketing benefits, environmental benefits, novel products, and cheaper and more flexible production.

As the next decade unfolds, synbio strategy will evolve from creating niche products with 'green' credentials, to creating new molecules not accessible with current technology and new capital-light business models based on strain development and fermentation as a service.

With respect to synthetic biology's potential for producing chemicals, the authors note that while traditional petrochemical synthesis has led to the commercial-scale production of numerous chemicals and materials, the limitations of the technology, as well as both real and perceived ill effects, have led researchers to prefer to explore biological routes.

"Biological catalysts (enzymes), however, offer better reaction rates, selectivity and yields; they don't require high temperatures or pressures; and can convert biomass, waste or other more environmentally friendly feedstocks – using only reactants of 'natural' biological origin," argue Hewage and Holman.

"Over the past decade, biological tools from genetic engineering to DNA synthesis have been developed to enable the creation of organisms that use fermentation to produce a variety of desired molecules from sugars or other biological feedstock. As a result, interest and activity in this approach, called synthetic biology (or synbio), has grown, creating billion-dollar companies and generating a flurry of innovations," they add.

But synbio isn't a panacea, warn the Lux researchers. "Not all syntheses are amenable to fermentation and targeted use might not be a fit for one of two reasons:

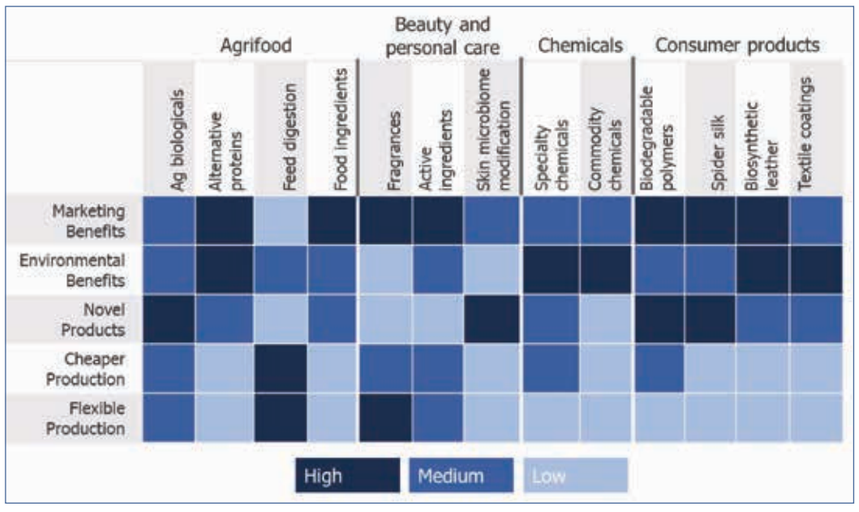
- "Microorganisms may not be able to metabolise the desired feedstock. While this may provide a challenge for some feedstocks, such as crude oil, microbes naturally metabolise sugar to produce a wide variety of chemical targets – and many types of biomass can be converted to sugars.
- "Genes may not exist to produce the target compound. Although microbes can be readily genetically modified to produce a wide variety of compounds, some lack the genetic code for production. It may be possible to develop the necessary genes, but some molecules are more accessible than others."

They argue that synbio works particularly well for:

- Naturally occurring products. If genes for the target are found in nature, they require less effort to make via microbial fermentation.
- Enantiopure products, that is, substances consisting of two mirror image components. Biological catalysts are highly effective at producing just one of the two possible mirror images of a molecule, which is often important for drugs and other active ingredients.

On the other hand, synbio does not work as well for:

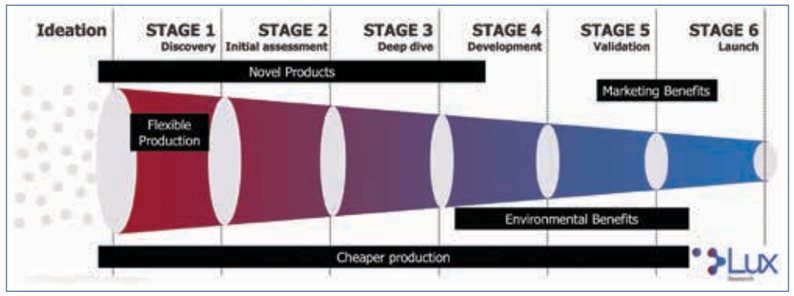
- Inorganic compounds. Microbes are generally best at converting a carbon source to a carbon-containing product.
- Hydrocarbons. Most fermentation feedstocks – from sugars to CO_2 – are oxygenated carbon compounds. Making pure hydrocarbons is less efficient due to the need to remove oxygen.



An assessment of the relative benefits of synbio production for chemical products for different market sectors.

Value propositions in industrial and consumer applications

"The ability to engineer microbes to produce chemicals on command is heady stuff for a technologist, but what is the business case for using a synbio approach over long-established traditional synthetic chemistry? From our conversations with key players, ranging from startups to large companies across a variety of industries and regions, we've identified the following value," write the authors, noting that the full report dives into each of these key value propositions.



Lux Research's synbio innovation funnel of different value propositions at different stages of maturity.

- Marketing benefits: Products can be marketed as 'natural' or 'bio-based', without emphasising environmental advantages.
- Environmental benefits: New production routes have decreased environmental impacts over incumbent routes, especially with respect to decreased carbon footprints.
- Novel products: For certain applications, synbio can make products that have no existing manufacturing route. These products may have improved performance over incumbent products – but not necessarily.
- Cheaper production: Synbio routes can result in cheaper costs relative to incumbents.
- Flexible production: Simply switching out the microbes in a given fermenter means producing a new compound with equipment changes or plant redesign, allowing for small-volume production of numerous different compounds and/or changing production based on market demand.

Synbio fermentation processes use renewable feedstocks as opposed to fossil fuels, and production can have decreased environmental impacts, including a reduced CO_2 footprint and less use of toxic compounds.

In addition, reduced environmental impact has been used as a value proposition across most target industries for fermentation, notably chemicals, textiles and apparel, and agrifood.

There are challenges to overcome, however. "Companies have struggled to commercialise environmentally friendly products in the past, leading to challenges with internal interest. Some processes may use more energy and water than incumbent routes," the report notes as examples.

On the plus side, though, Impossible, the vegetarian meat substitute manufacturer, claims that synbio-derived leghemoglobin requires 96% less land, 87% less water and results in 89% fewer GHG emissions compared to beef production.

In addition, the bio-plastic producer, Braskem notes that fermentation-derived polyethylene (PE) effectively removes CO_2 from the atmosphere, making it a carbon sink.

For chemicals, environmental benefits stand out as the most applicable value proposition for fermentation routes. The prospect of using biomass as an input for chemical production can reduce CO_2 emissions and help drive adoption in an industry undergoing increasing scrutiny for poor environmental footprints.

Given that specialty products are smaller-volume, there is potential for cost reduction of existing products, exemplified by Genomatica, which uses cost reduction as a value proposition for its 1,4-butanediol and caprolactam.

There are also opportunities to develop novel chemicals using fermentation, such as succinic acid and furandicarboxylic acid (FDCA). Novel chemicals are, however, best targeted for specialty applications, as challenges with scale and market development have led to numerous failures for those targeting commodity chemicals from fermentation.

Key production strategies

There are two key strategies for flexible production. The first is imitating contract manufacturing organisations (CMOs) – or semiconductor fabs – in providing production services to other companies. Companies can specialise either in developing their own strains or in running those strains on fermenters in flexible facilities, maximising capital efficiency and leveraging each type of expertise separately.

The second is using synbio's flexibility to optimise and arbitrage one's own product portfolio, either using a single fermenter to make a year's worth of different products over a short amount of time or changing microbes at a given fermenter depending on market demands. The latter strategy would require either having a library of strains on hand or the ability to rapidly develop strains.

In addition, companies could use feedstock flexibility to expand to regions with different input availability.

Conagen: a case study

Strain developer, Conagen, recently announced it had developed strains to produce upwards of 20 rare lactones for flavours and fragrances. While the company has not yet produced any of these lactones at commercial scales, similar downstream processing conditions allow flexible production at scale.

Lux Research believes that Conagen is well-positioned to use the flexible production value proposition for its lactones, since these products are small-volume and used in the same applications. However, the biggest unknown is whether or not Conagen will need to use flexibility. If market demand is skewed toward a small fraction of the lactones, flexibility will become less relevant.

"Setting out a full synbio strategy requires understanding not just of how to act, but when. Different value propositions will be realised at different times, as the mapping to the innovation funnel shows," the report suggests, while pointing to its funnel diagram of the different value propositions at different stages of maturity.

Summarising the development pipeline, the report predicts that over the first half of the 2020s, small-volume products using marketing benefits as a label will continue to be launched. "Because production is not well-established, the two most important factors in this validation phase are feedstock and infrastructure. Players that can establish a feedstock source and production capacity will beat out those that are unable to secure either," the authors note.

Due to the relatively low numbers of players, the microbe and market will not matter as much – the players that bring products to market are not competing with other fermenters, but with established markets.

Small-volume applications with minimal regulatory hurdles, such as beauty and personal care, will be first to market. Others, such as food ingredients, will have opportunities to prosper if users can steer clear of regulatory issues, while markets must be developed for agricultural biologicals and biodegradable polymers, which are both applications that have downstream interest.

Marketing benefits will be the dominant value proposition, while environmental benefits will start becoming more important. Cheaper production will play a role in a few select cases where it's most easily achieved.

"At this stage of synbio's technical development, owning and operating a facility, rather than using contract manufacturing, will make the most sense. While outsourcing production is an appealing strategy that requires less upfront capital, the greater control and process knowledge from running one's own facility is more likely to be successful while the technology is less mature," is the concluding advice of the reports executive summary. ❑