Driving industrial biomanufacturing with evolution

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Why do giraffes have long necks? At the University of Sheffield, Prof. Tuck Seng Wong applies Darwinian intrinsic research to the realm of industrial biomanufacturing

'Why do giraffes have long necks?'

Many children asked their parents this question as they wandered around the zoo and spotted the giraffes with their improbably long necks. My biology teacher told me this story when I was little.

'In the distant past, a group of giraffes inhabited an area. Some had long necks, while others had short necks. This diversity in neck length was a result of genetic variation within the population. The giraffes with long necks had an advantage as they could easily reach the high leaves on trees, ensuring their survival through adequate nutrition. Unfortunately, those with short necks struggled to feed themselves, often succumbing to starvation.'

The giraffe's neck, which can grow to as much as two metres in length, has been selected because it gives its owner exclusive access to the topmost leaves of the trees, and no other animal can reach them.

This adaptation allows giraffes to avoid competition for food with other species, a classical example of Charles Darwin's *'survival of the fittest'*. The process of natural selection states that within a population of organisms, those individuals with advantageous traits are more likely to survive and reproduce, passing down their advantageous traits to their offspring. Over time, these advantageous traits become more prevalent in the population, and the less advantageous traits become less common. This process leads to the evolution of species and the development of new adaptations that allow them to better survive in their environment. At the University of Sheffield, we adopt the Darwinian principle of diversity and selection, and apply it to the realm of industrial biomanufacturing.

Biological processes to produce industrial products

Industrial biomanufacturing involves the use of biological processes, such as fermentation and biocatalysis, to produce industrial products instead of traditional chemical synthesis. This interdisciplinary field combines biology and engineering to create high-value products such as chemicals, fuels, materials, pharmaceuticals, and food, using sustainable feedstocks such as plant-based materials and waste streams. The goal of industrial biomanufacturing is to decrease the environmental impact of chemical production by decreasing greenhouse gas emissions, reducing waste, and conserving resources. As a rapidly growing field, it has the potential to revolutionize the way industrial products are made. Industrial biomanufacturing has wide-ranging benefits for our society. One notable example of its applications is the production of beer, wine, and other alcoholic beverages, which are fermented using yeast.

Despite their potential, microorganisms and biocatalysts were not naturally evolved for the large-scale manufacture of biofuels, bioplastics, biopharmaceuticals, and other products. Additionally, they were not specifically designed to capture carbon dioxide, convert lignocellulosic waste into fermentable sugars, or utilize agro-industrial waste as carbon sources. Putting it simply, they are not fit for purpose! Frequently, the effective use of microorganisms and biocatalysts requires careful optimization to create a cost-competitive bioprocess that can rival traditional chemical processes. However, the complexity of biology presents significant challenges. To make rational advances, it is essential to first comprehend the functions of genes and the complex interactions between them. This task can prove extremely difficult, even for a seemingly 'simple' microorganism like *Escherichia coli*. Therefore, we turn to Darwin's principles of *diversity and selection* and allow nature to follow its course.

Using adaptive laboratory evolution in developing a biomanufacturing host

Our research team at the University of Sheffield, under my leadership along with Dr. Kang Lan Tee and Mr Joe Price, has repeatedly demonstrated the effectiveness of using adaptive laboratory evolution (ALE) in developing a biomanufacturing host that is fit for purpose. We have utilized the power of ALE to evolve *Cupriavidus necator* H16 to produce bioplastics from crude glycerol, a by-product of fat splitting [(1, 2)]. We have also evolved Escherichia coli, a widely used microorganism in industrial biomanufacturing, to thrive at a temperature of 46°C, which is nearly 10°C higher than its optimal growth temperature [(2)]. Additionally, we have evolved *Saccharomyces cerevisiae* to tolerate higher concentrations of isobutanol, a crucial trait for improving yeast productivity in biofuel production [(2)]. These are just a few examples of our team's success in utilizing ALE to enhance biomanufacturing processes.

While some may view the process of ALE as time-consuming and resource-intensive, our research team at Sheffield recognizes its potential for creating powerful biocatalysts. This led us to develop the Evolutor [(3)], a miniaturized bioreactor system that automates the entire workflow of ALE. The Evolutor comprises hardware, software, and biological tools that work in synergy to enable the parallel execution of multiple ALE experiments, streamlining the process and saving resources. Moreover, this system not only creates efficient biocatalysts but also provides valuable insights into the principles of evolution and biology, enabling us to digitize evolution and speed up the exploitation of biology.

Our vision extends beyond just the Evolutor

Our team's goal is to establish the world's first industrial-scale ALE factory in the North of England within the next 5 years. This facility will be equipped with towering bioreactor systems, referred to as the 'Galapagos towers'. In the language of Despicable Me, thousands of highly trained minions will work around the clock to produce highly efficient biocatalysts and gather unprecedented amounts of biological data in our ALE factory.

Our ambition is to revolutionize the biomanufacturing industry by combining cutting-edge technology and skilled expertise. Our aim is to establish a comprehensive repository of highly optimized microbes that can be seamlessly incorporated into any industrial biomanufacturing process, enabling the efficient production of a diverse array of products. This not only expedites the bioprocess development process but also provides significant cost savings for biomanufacturers globally.

As evolution experts, we are dedicated to exploring the limitless possibilities of evolution and revolutionizing the field of industrial biomanufacturing. We recognize its potential to address pressing global issues such as climate change, resource scarcity, feeding a growing population, and ensuring access to clean water. Our belief is that the future of industrial biomanufacturing is bound only by our imagination and ability to innovate. By pushing the boundaries of what is possible, we aim to create a more sustainable and equitable world for future generations.

References

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2. https://evolutor.bio/
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Grants:

- RAEng | The Leverhulme Trust Senior Research Fellowship (LTSRF1819\15\21) – FlexiChem: Feedstock Flexibility in Chemical Manufacturing
- Innovate UK ICURe follow on funding FY21 round 3 – Evolutor Microbe Optimization

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