Can we fulfill the potential of microbial conversion for biofuels and biomanufacturing?

All life is fermentation

Microbes can convert everything from agricultural waste to urban refuse into molecules of great value – food, medicines, useful chemicals, and, perhaps most ambitiously, fuels. Not very long ago, a microbe that can use oil to grow helped clear a vast oil spill that was the result of the Deep horizon BP spill.[1] Meanwhile, another microbe converts milk to yoghurt and has been, since ancient times, an integral part of one of the most delicious and healthy foods known to humans. Microbial conversion may be our secret ally to clean water, better health, reliable environmental stewardship, and a strong bioeconomy.[2]

There are certainly impediments to the use of microbial platforms in industry, in biotechnology, and in the production of fuels, and the examples earlier provide us some insight into these challenges. The oil-consuming microbe showed an innate capability that surpassed human technology or intervention. However, to implement this ability in a reliable and scalable manner will require an extensive examination of the microbe as well as investment into the development of processes that use this capability.

In the case of yogurt, the bacterial strains used routinely today are the result of centuries of cultivation and optimisation. It is fair to say that we need to expedite our ability to develop scalable technologies that harness microbial manufacturing capabilities. The road-map for this work, and systematic approaches for this effort, are only just beginning to take shape.

Looking back

Human use of microbes in food and drink go back to ancient times, independently documented across the world from Greece to Asia. Use of budding yeast for wine, sake, and beer can be tracked back to these times. Our discovery of microbially derivable medicines is more recent, going back only a century or so to penicillin – debatably the most significant step forward towards the betterment of human health.[3] Even more recent is the development of microbial platforms that produce life-saving hormones like insulin.[4] These examples are encouraging to contemplate, but they also provide no clear path of how, as scientists, we can expedite the discovery and the development of efficient processes, especially for a product such as biofuel that must compete in the current petrochemical marketplace.


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Microbial cultures at the Advanced Biofuels and Bioproducts Process Demonstration Unit (ABPDU), Lawrence Berkeley National Lab

Development of microbial platforms for biomanufacturing commodity chemicals is a very young enterprise. In 2005-06 with crude oil prices inching towards record highs of over $60/barrel (€57.3) and its impact on the burgeoning energy dependent economies across the world, it was clearer than ever that our lives and our futures were inextricably dependent on petrochemically derived fuels and materials. This impacted our daily lives, our environment, our jobs, and the energy security of nations. At that time, biotechnology was primarily focused on human health. However, in 2007 federal agencies in the US, especially the Department of Energy (DOE), took a visionary and strategic step of investing in the development of biological platforms to generate alternate fuels.[5]

Key funding opportunity announcements were made on the topic of microbially converting cellulosic biomass to ethanol – the most prevalent biofuel at the time. Industry also made considerable investments into similar efforts during this time. The result was a massive stimulus investment in research that led to the development of microbe-based technologies that went beyond ethanol and led to processes to produce fungible advanced fuels – biopetrols, jet biofuels, and biodiesels. This was accomplished by leveraging and optimising key pathways such the isoprenoid, amino acid, fatty acid biosynthetic pathways in microbial strains that were then optimised for enhanced utilisation of carbon sources derivable from cellulosic biomass, and with characteristics required for resilience to process by-products and accumulation of final products.

These programmes have led to an incredible period in basic science where we advanced our understanding of plants, discovered mechanisms of novel enzymes to simplify plant materials to sugars and other monomers, and made important inroads into understanding microbial physiology and enhancing microbial metabolic and strain engineering. These developments are critical in achieving the primary purpose of the research – renewable advanced biofuel production – but are an equally important foundation for advancements in a range of other fields such as the production of chemicals, commodities, and pharmaceuticals, a variety of synthetic biology applications, and the development of energy crops.

The US situation

The federal stewardship of these programmes has positioned the US at the global forefront of these valuable technology advancements, is the backbone for this scientific progress, and has supported the training of hundreds of future scientists in biotechnology and microbial metabolic engineering. Equally importantly, the development of technologies in support of biofuel production have led to numerous broadly useful intellectual properties in biotech and an impressive surge in entrepreneurship. These start-up endeavours have received both federal, industrial, and private support.

An example is Zymergen, a data science-based microbial strain engineering start-up that has received significant Defense Advanced Research Projects Agency (DARPA; US Department of Defence) support, the latter relying in great part on similar microbial conversion biotechnology platforms for new and novel biosynthetic materials.

Even more recently, Lygos, another California-based company, received $13 million of private industry funding to carry their technology forward. Lygos, a biotech company that uses microbial conversion to manufacture Malonic acid, is an excellent example of a business that was founded on basic research conducted through federally funded National Lab programmes, and one that received the initial necessary support from several federal agencies, including the DOE, Department of Agriculture, and the National Science Foundation.

In other parts of the world, the Brazilian company Braskem is developing new materials for automotives and Praj Industries in India is setting up second-generation bioethanol plants, while American Genomatica is scaling up the production of its GENO BDO to 30,000 tonnes in Italy[6]. All of these are examples of microbial conversion processes. Bio-derived fuels from alternative sources have already begun to be tested for high performance engines by the US airforce.[7] Microbial fermentation and conversion platforms are now poised to provide drop-ins for an immense array of the chemicals that surround us, including plastics, polymers, adhesives, surfactants, lubricants, cleaners, flame retardants, and fuels.

From Stone Age to the future

Thomas Friedman, an economist, is known to quote Sheik Ahmed Zaki Yamani who said: "The Stone Age didn't end because we ran out of stones". We, as a culture, gravitate towards technologies that are better and are more efficient – despite pre-existing technologies and economies.

Microbial conversion is one such powerful technology for our future. The use of an optimised microbial platform serves at least three separate but important purposes:

1) Biological conversion uses less energy and generates less toxic waste
2) Biological conversion is more precise, benefiting from nature's elegant biological pathways
3) Biological conversion can be done anywhere using diverse starting materials – paving a path to decentralisation of manufacturing.

This is true of most platforms that use microbial conversion, if not all. To add to this list, the staggering diversity in biologically achievable molecules allows design of materials and compounds that cannot yet be achieved via the petrochemical route. The possibilities range from new polymers to new antibiotics. It is easy to argue that microbial conversion is worth research, development, and commercialisation investment.

But the endeavours to generate fuels via microbial conversions has only just begun. The lion's share of current research and development efforts have focused on discovery of novel catalytic activity naturally present in microbes, or that we can engineer into microbes to produce valuable products. For efficient biofuel production, specifically, the research community is actively focused on maximising the use of not only sugars but also the lignin in the plant and renewable biomass, understanding the impact of scaling on microbial cultures, developing biomass deconstruction methods that are highly efficient and can scale with rest of the process, and developing techno-economic and lifecycle models to assess the pinch points of the process.

Cost-effective biofuel production will entail an equally dedicated focus on high throughput strain engineering that goes hand-in-hand with process development – two aspects critical to scaling. Obtaining the most efficient strains for a product entails the optimisation of multiple genes in a pathway along with the rest of the host chassis to obtain relatively complex performance features. This is an endeavour that can be greatly assisted if we can couple high throughput strain engineering with analysis and machine learning. Data science is poised to play a key role in how fast these platforms mature and are usable in industry. Cost effective processes can also be realised by developing processes that leverage both chemistry and biology. These are inherently interdisciplinary areas of basic research – another aspect valued and supported by federal funding especially via their support of national labs.

New solutions

The biggest challenges of our times facing the US and the world are around energy, water, food, and disease. These are also the areas where new solutions will be found and new industries and jobs will be created. Biological microbial-based platforms provide solutions that decentralise and expand innovation, making it possible to be undertaken across regions and not only where fossil-based reserves are rich.

Microbial conversions are inherently scalable, broadly deployable manufacturing platforms. The discovery and basic science for this approach have great momentum and have demonstrated huge potential as a result of support from federal funds, as well as industry. As our mechanical understanding of the biological processes grows stronger and our ability to use large systematically collected data sets becomes more sophisticated, microbial conversion can provide powerful implementable solutions for large scale biomanufacturing for commodities, material, food, pharmaceuticals, and fuel.

Richard Feynman is reported to have said, "There, in wine, is found the great generalisation; all life is fermentation".[8] This may well prove true. ●

For more information:

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