An introduction to start-ups in synthetic biology

September 15 2015, by Aditya Kunjapur

When did you first hear the phrase "synthetic biology"? Was it many years ago, or did it just happen when you clicked on this blog?

Synthetic biology — or SynBio — involves the engineering of biological systems to create useful products or functions through thoughtful tinkering with DNA. Commercial applications span several industries: energy, chemicals, materials, pharma, food, agriculture, diagnostics, probiotics, antibiotics, and gene therapy — just to name a few. According to one analysis from 2014, the global SynBio market was valued at $3.0 billion in 2013 and is estimated to reach $38.7 billion by 2020.

I first heard about SynBio in 2009 and am now a researcher in this field. In this post, I will describe a representative set of SynBio start-ups alongside a personal narrative of my expanding interest in the field. Despite what little I know, I will also speculate on what may lie ahead. If you are a fan of science, a SynBio student or practitioner, or an investor in start-ups, then this post is especially for you.

Fuels and SynBio Start-ups v1.0

In 2004, I wrote to the Houston Museum of Natural Science about my desire to help cure what I called "The Black Plague of Black Gold." I was a high school junior in the Energy Corridor of West Houston and wanted to help end our reliance on petroleum.

Five years later, I worked part-time in a lab at the University of Texas cultivating strains of algae that naturally accumulate oil. We wanted to harvest the oil as a potential biofuel, and I wondered how we could coax the algae into producing more of it. I was a chemical engineering major and did not know much about biology. But then I heard about a start-up that was doing "synthetic biology" to make renewable fuels. The six year old company was Amyris.

Amyris genetically engineers yeast to produce a chemical called farnesene from sugar. Farnesene can be used as biodiesel or as jet fuel. I was amazed at the time to see that they also engineer yeast to produce artemisinic acid, an immediate precursor to an antimalarial drug. Natural yeast strains do not contain farnesene, artemisinic acid, or anything chemically similar.

Over the next few weeks, I found out about other start-ups that engineer microbes ranging from algae to E. coli in order to produce biofuels from sugar. Among these companies are Synthetic Genomics, Solazyme, Joule Unlimited, and LS9 (now REG Life Sciences).

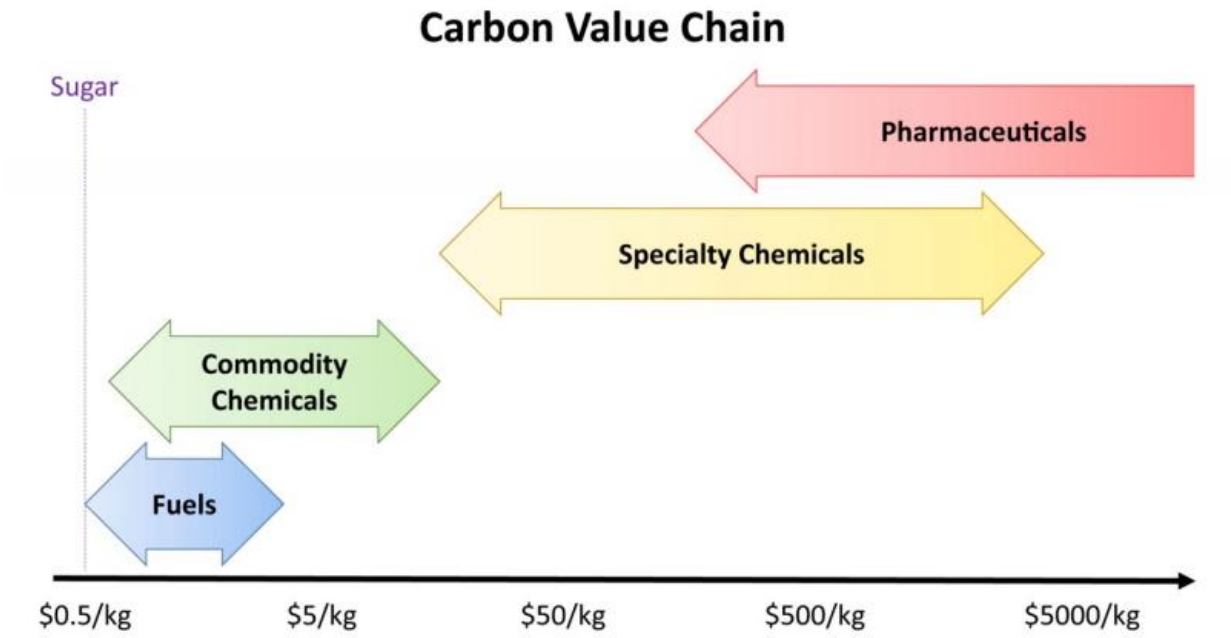
SynBio fuel efforts seemed to receive validation in the marketplace. For example, in June 2009, oil and gas giant ExxonMobil invested $300 million into Synthetic Genomics as part of an R&D partnership to develop biofuels. Amyris became publicly traded the following year.

Higher Value Products and SynBio Start-ups v2.0

The apparent commercial success of SynBio fuel start-ups influenced my decision to join a SynBio lab in graduate school in early 2011. Once there, I realized that microbes could be engineered to produce essentially any of the numerous products that are ordinarily derived from petroleum. And in order to provide a path towards complete independence from petroleum, it is important to find sustainable routes

to make these products in addition to fuels. The use of microbes that are engineered to efficiently convert renewable inputs to products at high yields is an elegant strategy for many products. However, based on rough economic considerations, I gradually began to question whether fuels were practical targets for SynBio start-ups.

The "carbon value chain" is a concept that categorizes carbon-containing products based on their price per mass. Although other variables, such as market size and maximum theoretical yield, are important, the carbon value chain offers quick insight into the largest margins that SynBio companies can realize on processes that generally all use sugar ($0.25-$0.50/kg) as an input. The image below depicts approximate current bulk prices for rough categories of potential SynBio products.



Some SynBio start-ups originally focused on producing chemicals with higher value than fuels. For example, Myriant Technologies and Lygos produce succinic acid (historically $3–5/kg) or malonic acid (historically $20–30/kg), respectively. Genomatica uses engineered strains to produce 1,4-butanediol, butadiene, and nylon intermediates. However, most SynBio start-ups, including fuel start-ups mentioned earlier, recently pivoted towards higher value chemicals to stay in business.

Some start-ups are aiming for sectors within higher value chemicals where may be consumer preference for biologically-derived goods, such as in textiles and flavors. Bolt Threads uses yeast to produce silk and high performance fabrics, and Evolva engineers yeast to produce several flavors and fragrances. Ginkgo Bioworks and Zymergen are two other companies that intend to produce flavors and fragrances but are more oriented towards building automated pipelines for industrial strain development. Many of these companies partner with other entities that grow the strains at commercial scale and purify the product.

In light of these industrial trends, my graduate research dabbled in improving biofuel production but had greater emphasis on engineering E. coli for production of higher value products. Some of my findings had clear commercial implications in the flavors and fragrances sector, where a surprisingly large percentage of products come from petroleum, including most vanilla in the market.

SynBio Start-ups Taking on Other Challenges

The discipline of chemical engineering focuses on developing or improving processes that produce chemicals. Despite having that background, I have been interested in the new generation of SynBio start-ups that are pursuing commercial applications beyond chemical manufacturing. For example, Sample6 brings SynBio into the realm of food safety by offering advanced detection of pathogens. SynLogic

develops therapeutic microbes for patients with inflammation and metabolic diseases. Synthorx produces novel proteins for life science applications by expanding the genetic alphabet.

Genome editing is an area of SynBio that has received more publicity lately. Breakthroughs achieved by the discovery and development of a gene editing technology known as CRISPR/Cas9 have resulted in start-ups such as Editas Medicine, Caribou Biosciences, Intellia Therapeutics, and CRISPR Therapeutics. All are geared towards developing treatments for genetic diseases.

SynBio is also advancing the development of alternatives to animal products. Pembient seeks to reduce poaching by fabricating rare wildlife products such as rhino horn and elephant ivory. Modern Meadow plans to use tissue engineering and 3D printing to fabricate leather and meat. Muufri plans to make animal-free milk and Clara Foods plans to make animal-free eggs. As a lifelong vegetarian due to animal welfare concerns, I find the objectives of these companies just as compelling as reduction of our dependence on petroleum or treatment of genetic diseases.

Given the wide range of commercial possibilities for SynBio, I sought to diversify my research experiences further by doing a post-doc in a genetics lab at a medical school. My current goal is to briefly step back from any particular application and instead focus more on the development of methods and tools that may later find use in several applications.

Pathways Ahead for SynBio Start-ups

Thus far in 2015, several SynBio start-ups have made headlines after earning investments from venture capital firms. For example:

- Bolt Threads: $32 million, Series B
- Caribou Biosciences: $11 million, Series A
- Editas Medicine: $120 million, Series B
- Ginkgo Bioworks: $45 million, Series B
- Twist Biosciences: $37 million, Series C
- Zymergen: $42 million, Series A

While large fundraising totals seem rosy, higher valuations may lead to more expectations from investors (the HBO Series Silicon Valley portrays this nicely). In addition to high expectations, several challenges lie ahead for SynBio start-ups. Prices of most petroleum-based products may drop now that crude oil prices have plummeted from $100/barrel to roughly $40/barrel. In the specialty chemicals arena, lots of small fragmented markets dominated by incumbents await new players. In food additives, consumer acceptance is an issue. In healthcare, new therapeutic modalities face regulatory hurdles.

Yet the upsides and opportunities seem to be bigger. Only a small fraction of the diversity of life on Earth has been genetically cataloged and even model organisms have significant room for functional annotation and for redesign to eliminate many unnecessary traits. Given this state, the field is ripe with potential for revolutionary discoveries of natural tools and products. The prices of DNA synthesis and sequencing declined at greater than exponential rates during the last decade and are expected to continue to do so. Commercial knowhow in SynBio is vastly increasing. Advances in machine learning, robotics, automation, and microfluidics all stand to decrease costs and time required for the design-build-test-learn cycle.

Now that start-ups have raised so much money, will the rate of innovation in the private sector start to outpace that of academic labs? Although start-up labs seem to have a lot more automation than academic labs, I personally think it will take many more years before

they become more innovative than academia given the potential of basic science research to suddenly result in groundbreaking and commercially relevant advancements (e.g. CRISPR/Cas9), as well as the difficulty for start-ups to devote resources to non-essential projects with long time-frames and high risks. My feeling of contentment in an academic setting is influenced by this opinion.

Overall, SynBio is an incredibly exciting field to be a part of because of its potential to address diverse societal problems and because our ability to engineer biological systems has so much room for improvement. Flush with capital and lessons from fuels, SynBio start-ups are uniquely poised at this moment to execute on their grand ideas. It will be fascinating to see what other SynBio start-ups emerge and how all of them begin to change the world, and I look forward to assisting them in some capacity when the time is right.

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