Market Formation of the Bioeconomy in the UK

Professor Richard Kitney
Professor Paul Freemont

Co-directors UK National Innovation and Knowledge Centre for Synthetic Biology SynbiCITE, Imperial College London, UK

Paul Freemont is Professor of Structural Biology, Fellow of the Royal Society of Biology; member of European Molecular Biology Organization, member of AHTEG Group on synthetic biology UN-Convention for Biological Diversity.
Richard Kitney is Professor of Biomedical Systems Engineering, Fellow of the Royal Academy of Engineering, Fellow of the Royal Society of Edinburgh, member of the UK's Ministerial Leadership Council for Synthetic Biology.

**Please note that the views expressed in this presentation are our own, and do not necessarily represent the opinions of Imperial College or the UK government.*

Introduction

Petroleum has played an important role in the social, economic and political history of the world. Since the nineteenth century petroleum has been used as a source of energy production, which with developments in synthetic chemistry at the start of the 20th century, led to an industrial revolution in petrochemicals. The petrochemical industry is by far the largest of the industrial chemicals sectors, accounting for about 40% of the global chemicals market of around $3 trillion representing the majority of all chemicals shipped between the continents of the world. Basic petrochemicals such as olefins, aromatics and methanol, together with plastics, are the key building blocks for the manufacturing of a vast and wide variety of durable and nondurable consumer goods. Such products include the clothes we wear, the houses and offices we live and work in, the household appliances and electronic equipment we use, the food and drink packaging we consume, and many products used for transporting us around the planet never mind the energy required from petroleum to do so. The concept of "make-use-dispose" is not sustainable as is the over-reliance on oil, coal and gas for global energy production. Given the growing global population, the widespread effects of climate change and the growing environmental pollution problem - including non-degradable plastic waste products - now requires a complete re-think on how to sustain human activity for the future. One growing area which aims to address these challenges is the concept of the Bioeconomy - underpinned by rapid technology advances in synthetic biology. In this article we will describe the strategy, policy and methodology for implementing the Bioeconomy from a UK perspective - taking into account the recent UK government's investment in synthetic biology research, training and translation.

The Bioeconomy – what is it?

The European Commission defines the Bioeconomy as "the production of renewable biological resources and the conversion of these resources and waste streams into value added products, such as food, feed, bio-based products and bioenergy"[1]. The application of innovative bio-based technologies to primary production processes, health and industry could result in the development of a Bioeconomy, where biotechnology contributes to significant economic growth and output. The overall strategy for the EU is to become a resource-efficient and sustainable economy (more innovative and low-emissions). This would be an economy based on more sustainable agriculture and fisheries, food security, and the sustainable use of renewable biological resources for industrial purposes - whilst ensuring biodiversity and environmental protection[2]. The EU Bioeconomy is estimated to be worth €2.2 trillion and employs 18.6 million people and there is a major

[1] EU Report - Innovating for Sustainable Growth

[2] https://ec.europa.eu/research/bioeconomy/index.cfm?pg=policy

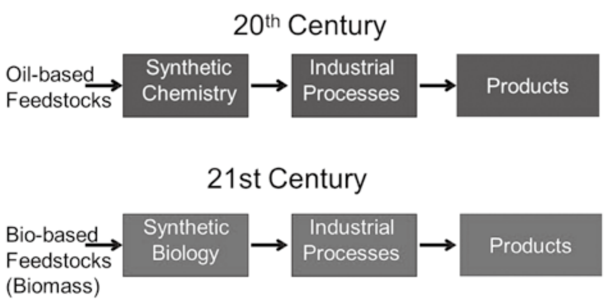
opportunity for growth[3]. The UK is currently developing a Bioeconomy strategy which will be launched in 2018 - with the Bioeconomy contributing ~£220 billion to the overall UK economy involving 5.2 million jobs and is expected to grow by ~13% in the next decade[4]. The working definition of the UK Bioeconomy is aligned with the strategy of other governments and is - "all economic activity derived from bio-based products and processes which contributes to sustainable and resource-efficient solutions to the challenges we face in food, chemicals, materials, energy production, health and environmental protection"[5]. Growing the UK Bioeconomy also offers strategic opportunities for investment in research and development. A key underpinning technology will be synthetic biology (see below).

A Fourth industrial revolution using biotechnology?

The recent development of synthetic biology/engineering biology as a new and interdisciplinary field has come about due to several factors. Firstly, the foundations of synthetic biology are based on our ability to manipulate biological systems at the genetic level and over a short period of forty years (between 1950 and 1990) a step-change took place in our understanding of the molecular basis of life. During this period we were able to understand how genetic materials are stored and coded in the form of a molecule called DNA and how this code is replicated and translated into proteins. Developments in molecular biology techniques allowed the movement of pieces of DNA between organisms (called molecular cloning). This was quickly followed by technology developments that allowed the code to be read (DNA sequencing) and chemically written (DNA synthesis). Synthetic biology, which utilises these foundational advancements also encapsulates the engineering principles of modularity, standardisation and reproducibility. Together, this is leading to a paradigm shift in how to design and construct biological systems for specific applications. At the centre is the engineering Design-Build-Test-Learn (DBTL) cycle. This enables automation, computational modelling, part modularity and robust metrology allowing rapid prototyping of biological designs using systematic protocols and automated processes (see below). These developments have led to the recent establishment of 'biofoundries', including the London DNA Foundry[6] that contain integrated infrastructure (e.g. liquid handling robots, analytical instruments) to facilitate the DBTL cycle. At a recent meeting at Imperial College London, fifteen global foundries came together to discuss how they could form a global alliance to enable closer working, sharing and collaboration[7]. The speed of these developments has been driven by the adoption of an engineering design cycle which has to lead to the idea of a fourth industrial revolution, driven by synthetic biology and biotechnology, combined with the need to adopt bio-based feedstock models for sustainable industrial production and economic growth.

Alternative model based on bio-based feedstocks

Figure 1 illustrates the traditional model for industrialisation developed in the late 19th and 20th centuries. This comprises oil-based feedstocks as its input and the use of synthetic chemistry - leading to industrial processes and products. The model forms the basis of many of today's major industries. An alternative, sustainable industrial model, based on synthetic biology, comprises



Source: Kitney and Freemont. Engineering biology: a key driver of the bio-economy

Figure 1 Transition to Bio-based synthetic biology processes

[3] The BioEconomy in the EU in Numbers - Factsheet

[4] Report - Evidencing the BioEconomy

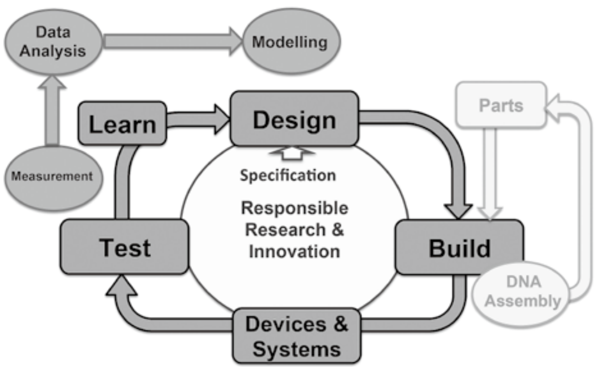
[5] https://bbsrc.ukri.org/research/briefings/bioeconomy/

[6] http://www.londondnafoundry.co.uk/

[7] http://www.synbicite.com/news-events/2018/jun/25/global-biofoundry-meeting-london-june-2018/

bio-based feedstocks (biomass) as its input and synthetic biology – leading to industrial processes and products. The basic elements of the synthetic biology/engineering biology approach comprise the confluence of synthetic biology with engineering science and the application of the engineering principles of modularity, characterisation and standardisation. These are normally implemented according to a hierarchy comprising BioParts (consisting of sections of DNA), standard devices and standard systems which in a biological context relates to designed genetic regulators and multi-gene operons or "circuits".

Central to the whole approach is biodesign. This is normally implemented according to a design paradigm consisting of the DBTL cycle. The paradigm is usually incorporated into a design cycle (illustrated in Figure 2). Referring to the figure, the core comprises the development of a design, based upon modelling. A design aims to use standard components (BioParts) that reside in a database - known as a registry, although parts can be obtained virtually by bioinformatics searches of existing DNA sequence databases. The DNA components can then be assembled by a build process to create the physical DNA design that has been specified. Once this has been built, it is tested either *in vitro* cell-free extracts or in living cells and assessed using analytical measurement techniques (such as mass spectrometry and data analysis). The design is then compared, in terms of its function and performance, with the specification and, if necessary, a second cycle of the process is undertaken. This systematic approach is complimentary to alternative high-throughput screening methods where optimal target functions like product yields from biosynthetic pathways are optimised. Biodesigns can also involve very large DNA regions including whole genomes or even chromosomes as in the Yeast Sc2.0 project[8].



Source: Freemont and Kitney.
Figure 2 The Design, Build, Test, Learn cycle for synthetic biology

The whole biodesign approach, based on synthetic biology, is now possible because of the development of the ability to read DNA and write DNA chemically (sequencing and synthesis). Fundamentally, this arose from technology that was developed for the human genome project. The technology for reading and writing DNA is now reliable and inexpensive (in the case of sequencing) and reliable and relatively inexpensive (in the case of synthesis). Typically, DNA parts (BioParts) are ordered by synthetic biology companies from specialist companies (see below). They are then shipped back for assembly - prior to testing (a process known as characterisation). An important aspect of the design and build process is reproducibility and reliability. Increasingly, building and testing are undertaken using DNA foundries. These comprise multiple liquid handling robots and other associated analytical instruments, in the context of high levels of automation. DNA foundries facilitate the ability to build and test multiple designs variants in parallel with high levels of reproducibility and reliability.

Policy

The global synthetic biology market is estimated to reach $38.7 billion by 2020[9]. A number of international bodies - including the UK and US Governments, the EC and the OECD - are predicting that synthetic biology will have a significant impact on the economy, growth and jobs over the coming years. These are some of the key reasons why there is developing interest in creating strategy for the Bioeconomy in the UK. As previously discussed, the strategy is based on the implementation of the alternative, sustainable industrial model illustrated in the Figure 1. This

[8] http://www.syntheticyeastresource.com/main

[9] "Global Synthetic Biology Market (Products, Technologies, Applications and Geography) - Global Opportunity Analysis and Forecast - 2013 – 2020" (2014) Allied Market Research, Portland, OR, USA http://www.alliedmarketresearch.com/synthetic-biology-market

comprises an alternative industrial model based on bio-based feedstocks (biomass) the use of synthetic biology – leading to industrial processes and products.

The UK's original synthetic biology roadmap, published in July 2012[10], resulted in the creation of six new basic research centres in synthetic biology at the Universities of Bristol, Cambridge/John Innes Centre, Edinburgh, Manchester, Nottingham and Warwick - in addition to the original basic research centre at Imperial College. The Government's £300 million investment resulted in the centres working in different areas of synthetic biology: Bristol (biomolecules to biosystems), Cambridge/John Innes (agro-science and open technology development), Edinburgh (mammalian synthetic biology), Manchester (synthetic biology for fine and speciality chemicals), Nottingham (sustainable industrial production processes) and Warwick (engineering effectors systems in plants, biosynthetic pathways and microbial communities) - with Imperial College continuing to work on platform (or foundational) technology, with a range of applications. In addition, the UK government established the national industrial translation centre for synthetic biology (SynbiCITE) at Imperial College. The second phase of the development of synthetic biology strategy for the UK resulted in a new report (BioDesign for the Bioeconomy, published in February 2016)[11]. This report focused on a number of areas, but, principally, on: accelerating industrialisation and commercialisation; maximising the capability of the innovation pipeline; building an expert workforce; developing a supportive business environment; and building value for national and international partnerships.

The UK's strategic developments have resulted in an emergent UK industry involving start-ups and spinouts - as well as the creation and development of new technology opportunities that can be exploited by existing companies. These include emerging technologies and new market opportunities for large multinational companies, as well as small to medium companies (SMEs). To fully realise the potential that this opportunity presents to the UK, the gap between university-based research and industry needs to be bridged. Research outputs from academic institutions are usually classified at technology readiness level (TRL) 1 and 2; as such, they are not, typically, ready for development by industry. Technologies need to be matured and de-risked and potential products and markets defined to make them attractive for investment and product development, at TRL 5, by industry. Since its inception in October 2013, SynbiCITE, in concert with its industrial and academic partners, has established an industrial translation platform for research using synthetic biology. This combination is capable of advancing technologies (as diverse as protein therapeutics and gene therapy; fine and specialty chemicals; biofuels; the agriculture and bioremediation- see below) through TRLs 3 and 4, leading to investment and product development by industry at TRL 5 and beyond.

More recently, in 2017, there has been the publication of further UK government strategic documents that define a new industrial strategy: Building our Industrial Strategy – Green Paper;[12] Life Sciences Industrial Strategy;[13] and Industrial Strategy – Building a Britain Fit for the Future.[14] Other key international documents include: Industrialisation of Biology – US National Academies[15].

Platform technology enables multiple applications

The basic strategy for implementing synthetic biology translation in the UK is focused around the development and adoption of platform (or foundational) technology. As shown in Figure 3 synthetic biology platform technology can be applied to many different applications and market sectors including pharmaceuticals, chemicals, materials, energy and agriculture. The technology also allows novel product development particularly around biomaterials and natural product discovery and production. The public investment for developing platform technology has been

[10] Synthetic Biology Roadmap for the UK 2012

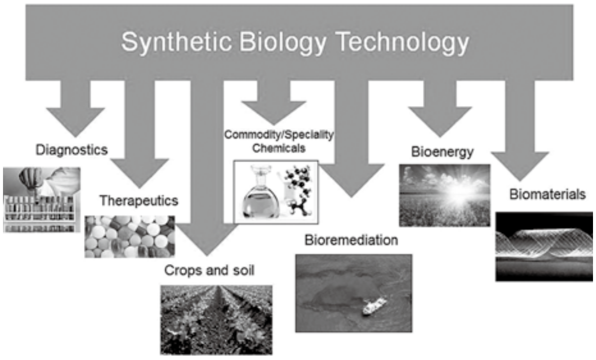
[11] Biodesign for the Bioeconomy - UK Synthetic Biology Strategic Plan 2016

[12] Building Our Industrial Strategy – Green Paper 2017

[13] Life Sciences Industrial Strategy, 2017

[14] Industrial Strategy - Building a Britain Fit for the Future, 2017

[15] Industrialization of Biology - National Academies Press



Source: Freemont and Kitney

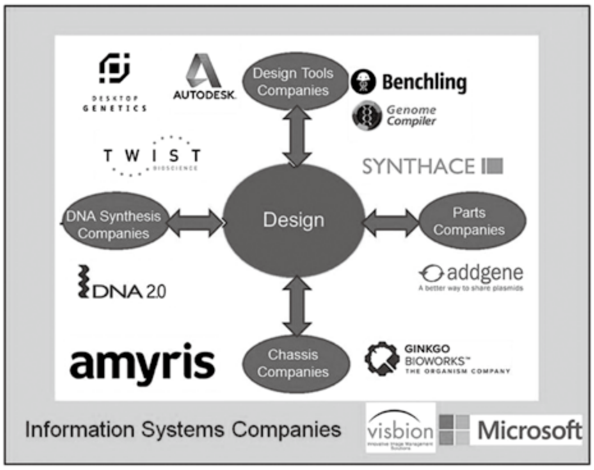
Figure 3 Applications enabled by synthetic biology platform technology

primarily focused around the UK seven synthetic biology research centres and four DNA foundries (see footnote 7), where biofoundries act as the prototyping environment for synthetic biology designs and processes. The global development of biofoundries also validates this strategy - where the systematic and industrial processes needed for the new biotechnology industries and value-chains that are developing will be driven by distributed biofoundries. With platform technology enabled at biofoundries, there is also real possibility that in the future much of the fabrication and testing of biodesigns and engineered organisms will be done in the Cloud by biofoundry service providers.

New products and value chains

As stated above, the development of platform technologies within Biofoundry service providers leads to the opportunity of new business models, value chains and products. At the centre of synthetic biology is Biodesign. This approach has already led to new supply companies for DNA synthesis, software tools, genetic part and chassis or organism companies. This is illustrated in Figure 4, where a number of US start-up companies (e.g. Ginkgo Bioworks, Zymergen, Amyris) have business models based on delivering engineered organisms for specific product production (e.g. fine and speciality chemicals like perfumes or cosmetic additives). In addition, specialist DNA synthesis providers (e.g. Twist, GeneArt/Thermo Fisher Scientific) supply these companies and the growing synthetic biology industry with raw material namely synthetic DNA.

Others specialist companies like Synthace and Desktop



Source: Kitney and Freemont

Figure 4 The Biodesign supply chain

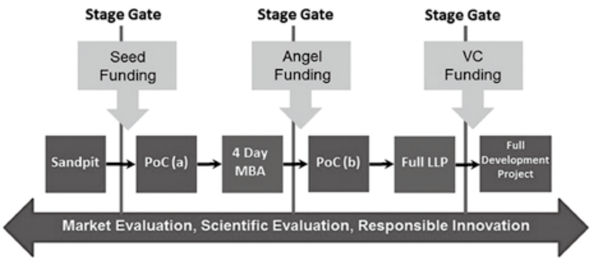
Genetics in the UK and Benchling in the US offer software tools to enable biodesign (BioCAD) and automation integration. Multinational software companies like Microsoft and Visbion are also developing information systems and tools to accelerate the whole biodesign process. In the UK synthetic biology start-up scene, there are a number of new companies which are building their business models around biodesign (both as tool and service providers) to product development companies (see Figure 4).

With the advent of synthetic biology tools and processes, there is a growing market opportunity in the area of biomaterials and consumer biotechnology products. This exciting market development has been pioneered by two US start-ups, Bolt Threads and Modern Meadow. Their business models are centred upon the sustainable production of insect and animal materials without using the source organism. By using synthetic biology to produce spider silk in Baker's yeast – and, more recently, mycelium cells to produce leather like material - Bolt Threads have launched a consumer spider silk tie product. Modern Meadow is producing collagen to make natural leather like materials that can be incorporated into luxury fashion products, recently receiving much fanfare and support from word-famous designer Stella McCartney. In the UK a Cambridge start-up Colorifix are using engineered bacterial cells to produce sustainable natural dye products such that material can be dyed by simply growing bacterial cells on the material. The growing market of sustainable material products for the fashion industry exemplifies the potential opportunity for a growing circular economy of re-use, repair and recycling driven by synthetic biology tools and processes.

SynbiCITE

As previously stated, SynbiCITE[16] is the UK's industrial translation centre for synthetic biology, based at Imperial College. It works with over 50 companies (of which the 11 are multinationals- and the rest are start-ups and SMEs) and over 20 UK universities. While SynbiCITE works with large companies on a range of projects, a principal focus of activity relates to start-ups and SMEs. SynbiCITE supports these types of companies in three ways: providing funding in support of projects and company development; providing technical support and facilities; and providing business courses. Figure 5 illustrates the SynbiCITE projects and funding pipeline. Referring to the figure, the first stage in the process comprises ideation, which may be via a sandpit or the development of an idea within a company. Using the example of a start-up company, once an idea has been developed, the next stage in the process is, typically, to fund a proof of concept (PoC)project – which may last 3 to 6 months.

This is normally funded at around £50,000, using public funds to provide seed funding. Once this phase of the project has been completed successfully from a scientific point of view, if it is judged to be worth developing, the next stage is for members of the company to undertake the SynbiCITE four-day MBA. The second phase of the development (PoC (b)) is normally funded from a combination of public and Angel Funds. This phase, depending on the project, can last a year and be funded at around £250,000 - depending on requirements. Once the scientific work for the phase has been completed, members of the company undertake a 12-week Lean LaunchPad (LLP) course. This is a customer facing course that is designed to align the results of the projects with potential customers and the market. The final phase of the pipeline comprises a full development project that is usually funded from venture capital sources.



Source: Kitney and Freemont

Figure 5 SynbiCITE project pipeline and funding

[16] http://www.synbicite.com/

UK Synthetic Biology Start-ups

In 2017, SynbiCITE undertook a survey of start-up companies in the UK in the area of synthetic biology. The survey covered the years between 2000 and 2016. The survey showed that UK has created more than 146 synthetic biology start-ups over the period. On average, the number of synthetic biology companies has been doubling every five years. More than half (54%, 79) of start-ups are tech transfer start-ups, with fewer (46%, 67) non-tech transfer start-ups produced over the same period. (Tech transfer companies are defined as companies that come out of universities via the Tech Transfer Office; whereas, non-tech transfer company start-ups are independent of any university.) However, over the last few years, non-tech transfer start-ups have been outpacing the more traditional tech transfer start-ups by 2:1. Currently, of the 146 companies surveyed, 111 remain active - representing 76% of the original total (8% were acquired and 16% are inactive). Over the period of the survey, £620 million has been raised from the private sector, of which £487 million went to tech transfer start-ups and £133 million to non-tech transfer start-ups.

Summary

The article addresses the Bioeconomy as a key area for economic growth – based on synthetic biology. With significant government investment the UK is now second to the US in terms of synthetic biology start-up companies, a sector which is expected to grow rapidly.