Trend Summary – Synthetic Biology

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A summary for policy makers from MoRST's Futurewatch Programme.

Overview

Synthetic biology is an emerging multidisciplinary field that brings principles of engineering to biology. It shifts biotechnology from tinkering with existing organisms to being able to make more fundamental changes. It has been called by some critics "genetic modification on steroids".

Two approaches are seen in synthetic biology. The first, an extension of existing genetic engineering, involves modification of metabolic pathways rather than just one or two genes. Some conventional genetic modification is also being rebranded as synthetic biology.

The second, more ambitious, approach is reconstructing existing organisms or the creation of completely novel organisms. J. Craig Venter, an influential figure in this area, describes his own work as synthetic genomics – introducing a synthesised genome into an existing cell. Others are interested in building cells from scratch. Practitioners usually draw parallels between cells and computers, talking about genetic circuits, DNA software and cellular chassis.

Increasingly more complex viruses and bacteria are being re-created through synthetic genomics [1]. No novel genomes (or organisms) have yet been created from scratch, but are likely to be in the next few years.

Potential applications for both types of synthetic biology are being considered for environmental, biomedical, industrial, energy and military purposes (examples are given later). A major focus is on developing single celled organisms that can act as bio-factories to produce specific biological compounds or chemicals.

The field is experiencing rapid growth, at least with respect to research publications (Figure 1).

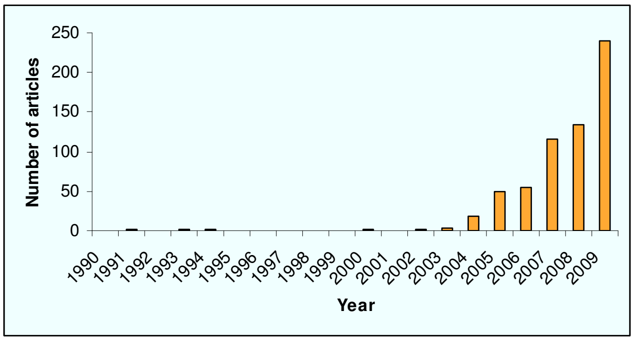


Figure 1. The number of published papers with the phrase "synthetic biology" in the title, abstract or used as key words from 1990-2009. Source: Scopus.

Currently synthetic biology is focussed on developing tools and techniques, with real applications being slow to emerge [2] [3].

Technological developments that will enable practical advancement of synthetic biology include an increasing understanding of genetic components and metabolic pathways, the provision of a wide range of inexpensive well-characterised biological components [4], and the development of affordable tools that can predict with greater accuracy the consequences of combining these components in a cell.

Taking a lead from the robotics field, competitions for students are being used to inspire current and future leaders in synthetic biology to develop applications [5].

Regulatory, moral and ethical implications of synthetic biology are the subject of a range of reports from government and non-government organisations. The main areas of discussion are whether, or to what extent, synthetic biology raises additional regulatory, moral and ethical concerns compared to other forms of genetic modification.

Figure 2 notes some of the recent key scientific developments in synthetic biology.

General implications

Synthetic biology accelerates the shift of biology from a field seeking to understand the natural world to one where desirable biological functions are engineered rather than tinkered with. In some regards it is an evolution of existing gene technologies, but the potential to create completely novel organisms gene by gene or manipulating complex metabolic pathways provides a significant change.

The J. Craig Venter Institute's recent successful synthesis of a bacterial genome and transplantation into a cell to create a self-replicating bacterium [1] is a significant proof of concept step for synthetic biology. It does not though represent the *de novo* creation of a new life form [18]. Such developments, however, cannot now be far off.

The extended capabilities of synthetic biology are likely to intensify societal debate and concerns over safety, commercial, moral and ethical issues associated with genetic modification. There is disagreement as to whether synthetic biology creates novel moral and ethical challenges [19]. However, there is likely to be a general view that the creation of new forms of life is a significant change from previous capabilities.

Current conventional microbial and molecular techniques already have the potential to produce harmful organisms, and there have been several cases of conventional pathogens escaping from laboratories, so potential risks posed by synthetic biology need to be considered in context [3].

Some countries (such as the UK) are developing national policies to guide synthetic biology research and development. However, some

Progress in the development of wholly synthetic organisms		Progress in modifying metabolic pathways or the production of biological "components"
Successful completion of a 3-year effort to create a polio virus from scratch [6].	**2002**	
Recreation of the 5.3 kb bacteriophage ϕX174 in the lab in 14 days from commercially available pieces of DNA [7].	**2003**	Production of an anti-malarial drug using engineered bacteria [8].
	2004	
	2005	The BioBricks Foundation is formed – an organisation where DNA sequence information and other characteristics of standard biological components (BioBrick™) are available to the public free of charge [9].
	2006	Production of an anti-malarial drug using engineered yeast [10].
Successful genome transplantation in bacteria, with no trace of the original recipient genome after transplantation [11].	**2007**	
The J. Craig Venter Institute assembles a bacterium's entire genome (*Mycoplasma genitalium*) from chemically synthesized DNA segments in yeast in multiple steps or a single step [121] [13].	**2008**	
Transfer of the genome from one species of bacteria (*Mycoplasma mycoides*) into yeast, and then modified and transferred this genome into another species of bacteria (*Mycoplasma capricolum*) [14].	**2009**	Synthetic genetic counters developed that allow bacteria to count events such as repeated chemical exposure [15]. Creation of artificial active ribosomes (the particles within cells that are responsible for protein production) [16].
The genome of *Mycoplasma mycoides* (1.08 mega base pairs) is synthesised and inserted into a *M. capricolum* cell and is able to reproduce [1].	**2010**	Laboratory bacteria modified so that all cells in a population synchronously fluoresce [17]

Figure 2. Timeline outlining some recent key developments in synthetic biology research

commentators point out that the trans-national nature of modern science, including global access to biological information and concerns over bio-terrorism, render existing models of nation-specific regulation inadequate. Developments in synthetic biology will contribute to these challenges, rather than necessarily creating new challenges.

Potential opportunities

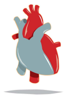
Transforming microorganisms into 'bio-factories' to produce specific biological compounds or chemicals is the main focus of synthetic biology, although modification of metabolic pathways in plants and animals is also being investigated. The objective is greater control and specificity of cellular metabolism.

The creation of artificial ribosomes [16] is likely to advance the development of wholly synthetic organisms, or artificial minimal cells. Such research could also lead to the production of engineered ribosomes specifically tailored for large-scale efficient protein production or the production of proteins used by industry that are less susceptible to degradation or have novel characteristics.

Synthetic biology also provides new tools and techniques to improve our understanding of biology by helping test biological principles in more directed ways.

Applications in specific fields are noted in the following sections.

A. Health



Synthetic biology is being explored as a means to improve health, through developing new and less costly treatments. The most well-known example of this is the production of the anti-malarial drug artemisinin. Artemisinin is an anti-malarial compound found in the sweet wormwood tree. Producing the compound in yeast is expected to be a more cost-effective than chemical synthesis or harvesting from the tree and could be used to produce other expensive drugs or chemicals [20].

Development of this synthetic form of artemisinin has been underway since 2002. Sanofi-Aventis hopes to make it commercially available in 2012. To be more effective, this slow customised approach to therapeutics will need to be replaced by a more rapid process that can build metabolic pathways using “off the shelf” components [3].

Other areas of active research include engineering microorganisms to produce biomaterials (such as *Salmonella* that can produce and secrete spider silk proteins) that could be potentially used in medical devices such as replacement arteries [21], engineering bacteria that can sense the microenvironment of a tumour and then respond by invading cancerous cells and releasing a cytotoxic agent [22] or producing biological sensors to detect infections or diagnose disease [23].

B. Industrial/Energy

A second major area of interest for synthetic biology is the creation of organisms to increase the supply of renewable energy or the production of chemicals. For example, researchers have proposed that microorganisms could be engineered to convert agricultural products or carbon dioxide produced by coal or oil-fired power stations to biofuels [23]. Attempts are also underway to develop bacteria that can produce propanediol (normally obtained from corn syrup), which can be used to form polymers [24].

C. Food and Agriculture

Research is being directed to develop new types of seeds with specific applications such as for optimised food production or biofuel feedstocks, or for the production of agrofuels [23].

Potentially, synthetic biology could be used to develop new ruminant microbes or pasture plants, or the cattle or sheep themselves to help reduce greenhouse gas emissions.

Other research has shown that aspects of current food production can be manipulated using synthetic biology techniques. For example, the fermentation process can be engineered to delay yeast sedimentation [15] which can alter various characteristics of fermented products such as beer or wine.

D. Environment

Synthetic biology could be used to create organisms that are better at environmental remediation (eg, the degradation of environmental contaminants or pollutants to non-toxic substances). For example, researchers have engineered a *Pseudomonas* bacterium to degrade an organophosphate compound (which is used in pesticides) [25].

Other areas of active research are in developing microbes to act as biosensors (eg, the production of an engineered *E. coli* strain that can detect arsenic in drinking water [26]), and as producers of biodegradable packaging [23].

E. Security and Defence

Areas of research related to security and defence include the production of chemical or radiation biosensors to detect explosives or other hazardous substances [21].

The US Defense Advanced Research Projects Agency (DARPA) is investing in synthetic biology research to develop bio-based materials for military use (eg sensors, bio-fuels, cleanup of pollutants, long life cell-based medical treatments that are deployable on battlefields). DARPA are also looking at the feasibility of creating synthetic organisms that could self-destruct if they got into the wrong hands [27].

Challenges

There are a range of technical and policy challenges associated with synthetic biology. One of the most significant technical road blocks to the progression of synthetic biology is the complexity of biological systems. It can take many years to identify all the genes and control elements in a metabolic pathway. Even when all components may have been identified expression in another cell may not be stable or produce the expected compound(s) [23].

As with other forms of genetic modification, introduced DNA needs to overcome DNA repair and methylation systems in cells that may inactivate or change gene expression [1, 28].

As the recent creation of a synthesised genome indicated [1], chemical synthesis of DNA needs to be closely checked to ensure that inadvertent errors aren't introduced that will prevent proper functioning. In contrast to computer hacking, creation of synthetic organisms is likely to require for some time at least a highly trained and well funded team of researchers.

One approach attempting to overcome biological complexity is the development of basic biological "chassis" or minimal cells, that attempt to remove "non-essential" components from a cell [22, 23]. Specific genetic constructs could then be added in as desired to produce the product(s) of interest.

The development of predictive computer modelling platforms is likely to enable more rapid and reliable design of new metabolic pathways. Researchers from Boston University have developed a technology platform that could be used to guide gene network design in yeast [29].

Several research groups are working on the identification and construction of 'biobricks', standardised sequences of DNA that could be inserted to produce predictable effects. Many of the 'bio-parts' are freely available to the public by institutions such as Massachusetts Institute of Technology. However, the quality and usability of many of these bio-parts has been questioned, and standards are required to develop and properly characterise such genetic components [2].

In addition to compiling bio-parts, synthetic biology also needs a multidisciplinary approach, involving a range of scientific and engineering disciplines (and other stakeholders). These teams can be difficult to develop and support. Several countries are building synthetic biology multidisciplinary networks to foster such linkages [3].

Genetic systems are also being developed that use artificial (not natural) DNA bases or nucleic acids [30]. Such artificial systems may be used to prevent engineered organisms from reproducing outside of labs or factories.

The ease of access to genetic information, the relatively low cost of

DNA synthesis and other lab procedures, and the possibility of "garage biology" or "biohacking" taking place (where the general public produce synthetic organisms at home) have generated concerns about the application of synthetic biology for bio-terrorism. In response to such concerns, the DNA synthesis sector has proposed self-regulation in controlling the distribution of synthetic DNA [31]. However, there is room for improvement in sharing information between the different companies and having clearer guidelines [32].

Some are sceptical that there is a biohacking "movement" similar to a computer hacking movement. Synthetic biology takes more than an individual with a computer and internet access, and while a few individuals may be promoting a biohacking trend, some consider that the complexities of cells will limit what people can do without access to molecular biology labs [33].

Due to the dependency on a range of technologies that need to cooperate or converge, some applications of synthetic biology may pose challenges in securing Intellectual Property rights [3]. As with other forms of biotechnology, appropriately recognising, protecting and rewarding the contribution of indigenous knowledge in applications will be required.

Non-government organisations, such as the ETC Group, have raised social, ethical and safety concerns over the development and use of synthetic organisms [34]. Various UK organisations have commissioned reports exploring the social and ethical challenges of synthetic biology [35], and public perceptions and reactions to synthetic biology [36].

Most discussions recognise that synthetic biology does not present new policy challenges separate from genetic modification in general. However, the potential to more radically alter organisms can make it more difficult to adequately assess risks, particularly if the intention is to release the organism into the environment.

Synthetic biology in New Zealand

Currently there is limited synthetic biology research occurring in New Zealand. Researchers from the Auckland Bioengineering Institute, at the University of Auckland have developed a mathematical modelling framework and models to aid in the design of synthetic biological systems [37].

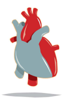
While most important developments will occur in other countries, fundamental research is moving relatively quickly and aspects may be taken up here. It can be anticipated that as the techniques develop, New Zealand researchers can be expected to also experiment with more sophisticated genetic modification in the laboratory.

The techniques used to create synthetic organisms mean that they are considered genetically modified organisms under New Zealand's regulatory system, and as such are subject to the same regulatory requirements as existing genetically modified organisms. As with current genetically modified organisms, the Hazardous Substances and New Organisms Act 1996 would regulate the creation and importation of synthetic organisms.

Implications for New Zealand

This section poses some hypothetical future developments to stimulate thinking about potential implications of developments in synthetic biology for New Zealand. As far as we are aware these scenarios do not reflect actual developments or applications at this time, but they may be feasible in the future.

A. Health



A synthetic minimal bacterium is developed to treat Crohn's disease. The organism uses artificial bases to prevent survival outside the body. Consequently, treatment includes ingesting the necessary artificial bases.

Is a different regulatory process required to assess the efficacy and safety of such a therapeutic product?

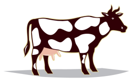
B. Industrial

A wood processing company switches to biological fermentation, using synthetic microbes, to produce higher value products from timber.

Are additional regulatory requirements necessary, compared to a conventional microbe used in fermentation?

What would public reaction be to such "contained" genetically modified organisms?

C. Food and Agriculture



A food company wants to market a pro-biotic food in New Zealand that contains a synthetic bacterium. The company claims it provides substantial nutritional benefits.

While not a medicine, should access to this type of food require a prescription?

D. Environment

Scientists want to develop and release an artificial virus in New Zealand designed to infect only possums and make the females sterile.

What would be required to minimise the chance of spread of the virus to other animals and to Australia?

What would public attitudes be to such an application?

E. Security and Defence

A self described "biohacker" inadvertently infects herself and ends up in hospital.

What could the consequences be for the control of microbiological and genetic research in New Zealand, and for our biosecurity procedures?

Figure 3 summarises some of the main trends and issues associated with synthetic biology.

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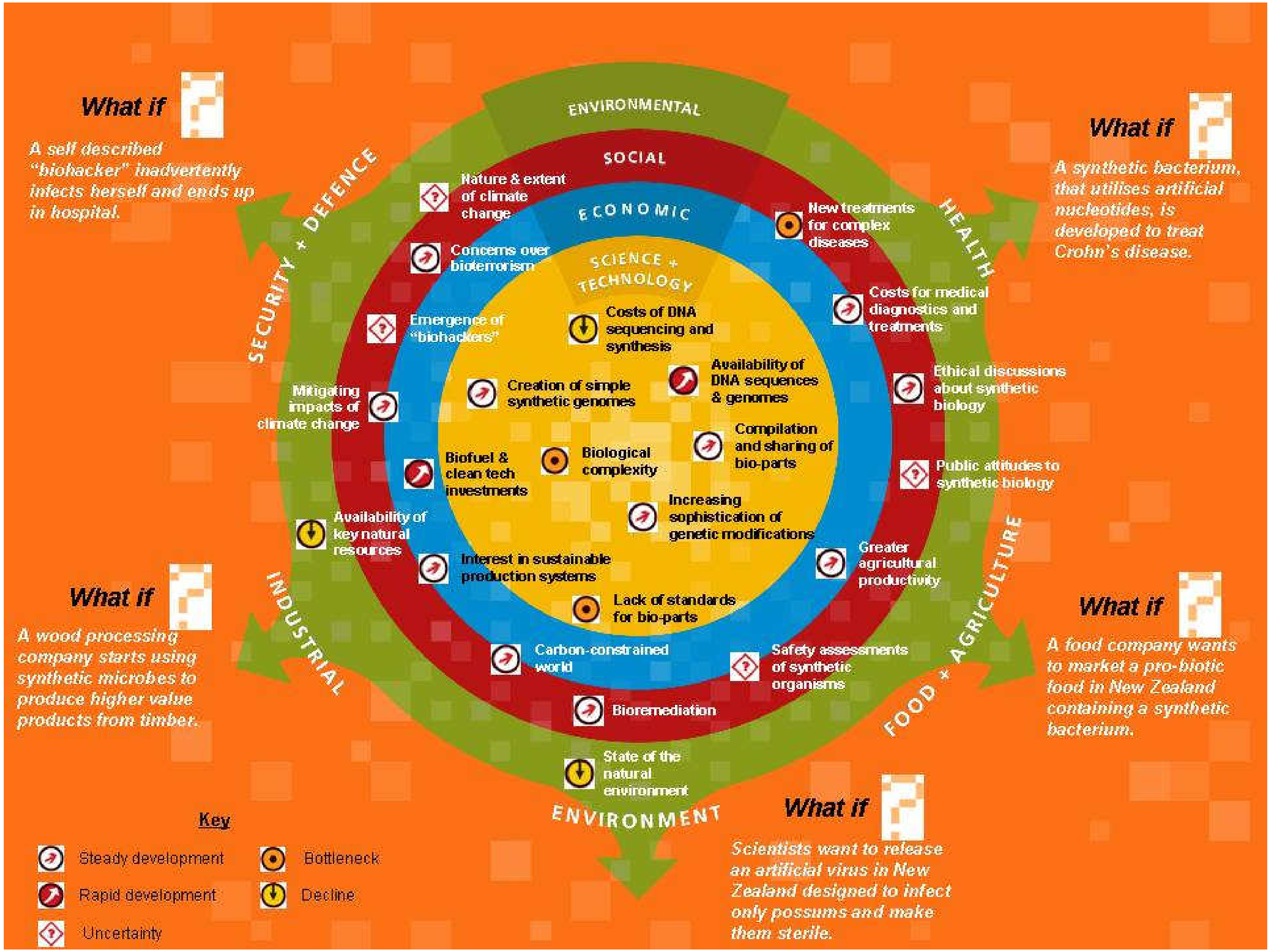

Figure 3. Some trends and related issues associated with synthetic biology using the Futurewatch Panoptic. Items are arranged into scientific, economic, social or environmental categories. Hypothetical future applications are given to stimulate thinking about policy implications. More information is given in the text. Additional information on the Panoptic is available from MoRST's website – http://www.morst.govt.nz/current-work/futurewatch/publications/#panoptic