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Regulation of Synthetic Biology

Synthetic biology can be defined as the design and engineering of novel biologically-based parts, devices and systems or the redesign of existing biological systems.[1] It may deliver potential benefits across a wide range of applications. However, some future applications may raise social and ethical issues and challenge current regulatory systems. This POSTnote examines the potential benefits and challenges.

Overview

- Synthetic biology products are starting to be marketed as high value chemicals, food additives and therapeutics. A wide range of other applications are in development; these may deliver a wide range of benefits.
- A UK stakeholder engagement exercise[2] and recent reports[3] have identified some potential biosecurity, biosafety, environmental and social concerns.
- Most current synthetic biology activities are covered by existing EU directives and UK regulations on genetically modified organisms (GMOs).
- Some novel genome editing techniques, used in both synthetic biology and genetic modification are not necessarily covered by the current GMO regulations because the final product is indistinguishable from one where mutations have occurred naturally.

Background

Synthetic biology spans a wide range of activities, from well-established genetic modification to the creation of entirely novel (synthetic) organisms and everything in between. It involves using engineering principles and computational tools (Box 1) to optimise existing biological systems and design new ones (see POSTnote 298). The building blocks are genetic material (DNA or RNA) that confer specific, characterised functions (traits), for example, the ability to produce pharmaceuticals, flavourings, or respond to a specific environment. A future aim is to standardise the building blocks so that they can be easily joined together to construct systems and organisms with new or improved functions (Box 1).

The tools in Box 1 can be used in areas of research shown in Box 2. The main focus of research is on developing enabling technologies to confer new traits to a biological system or organism. However, synthetic biology also embraces other research such as attempts to define the minimal genome needed to sustain biological systems and modifying the components of the genetic code itself (Box 2).

The UK is recognised as a world leader in synthetic biology.[4] Research in this area has benefited from public and private funding. For instance, following the Synthetic Biology Roadmap in 2012,[1] the UK government has invested in six multi-disciplinary centres of research, a synthetic biology research hub, and in other infrastructure including that needed for technology translation. This has helped establish a vibrant community of small to medium sized companies working with large multinationals.

The first products from synthetic biology are beginning to reach the market. They include the anti-malarial drug artemisinin, the flavouring vanillin and other applications that may have a range of potential benefits such as pollution control, bioremediation, and reducing the dependence on non-renewable resources.[1,3] Such products may fall within the scope of existing regulations and risk assessment frameworks for genetically modified organisms (GMOs), food, chemical and medicines.[5,6] However, there is debate as to whether existing regulations will be appropriate for potential future applications in this rapidly emerging field.[7]

Finally, synthetic biology raises a number of potential environmental, ethical, legal and societal issues. Although public awareness of synthetic biology is not widespread, a UK public dialogue in 2010 highlighted that those consulted were not opposed to synthetic biology as such, but wanted to know more about the purpose and implications of the

Box 1. Enabling Technologies for Synthetic Biology

Computational Design Tools

Engineers and computer scientists are developing computer programs and other tools to help design the genetic code of novel organisms. Concepts from engineering may allow such tools to be used without specialist biological knowledge. However, the biological components must be characterised and standardised so that they can be applied to different circumstances.

DNA Synthesis and Assembly

DNA synthesis companies produce short sequences of DNA to order (including those not found in nature). By joining these sequences together researchers can create fully synthetic genomes. High profile examples include:

- the first 'synthetic organism' in 2010 where the genome of the bacterium *Mycoplasma mycoides* was edited digitally, synthesised and inserted into another bacterial cell which had had its genetic material removed to produce a self-replicating organism
- a whole synthetic yeast chromosome.

Genome Editing

Early methods of genome editing involved inserting selected DNA sequences into an organism's genome at random. This sometimes led to unexpected effects if the original genes were disturbed. New technologies, for example CRISPR-Cas9 and TALENS, allow the genome to be cut and new genes inserted at a specific position. This gives more predictable and reproducible results and allows for multiple traits to be introduced more rapidly.

Standardisation and Parts Libraries

The British Standards Institute and Innovate UK are developing a set of standards for fully characterising the biological building blocks.[8] Information about their DNA sequence, function, and reliability can be stored in open source 'parts libraries', such as BioBrick, BIOFAB, SynBIS and OpenPlant so that selected building blocks can be joined together to form designer organisms. To encourage collaboration, OpenPlant suggests a "two-tier" model for intellectual property (IP) whereby the tools and biological parts are readily shared but IP rights may be sought on the final organism for specific applications.[9]

Box 2. Some Approaches to Synthetic Biology Research

Engineering Metabolic Pathways

The aim is to introduce biological components and systems into organisms in order to produce a response not normally found in that organism or to optimise a natural process. In practice, this might involve using simple organisms such as bacteria, yeast or algae. These have been used to develop biosensors (e.g. that change colour in the presence of toxins such as arsenic[14]) and 'cell factories' to produce high-value chemicals such as vanillin[15] and pharmaceutical products. These are the most promising products of synthetic biology in the near-term.[16] Longer-term targets include developing drought resistant crops,[17] and biological alternatives to antibiotics.[18]

Minimal Genome and Protocells

Where cells are used to produce chemicals, the removal of unnecessary metabolic pathways reduces the load on the cell and makes chemical production more efficient. One approach is to start with an existing genome and remove specific genes, characterising their effects until what is left is the minimum required to sustain the organism. An alternative is protocells – self-organising compartments of lipids made in the laboratory. At the moment, protocells cannot replicate and are not regarded as living but have potential uses as models for fundamental research and for chemical production.[9]

Xenobiology

DNA is a long chain containing molecules called bases. Combinations of bases code for specific amino acids that join together to form proteins essential for life. Xenobiology creates synthetic forms of these bases (known collectively as XNA) and their associated synthetic amino acids in the lab. These approaches may produce genetic material that is more stable in the environment for nano-devices such as catalysts.[19] The genetic code of an organism can also be altered so that it requires the synthetic amino acid to survive. This method of 'biocontainment' can be designed into the genome in order to ensure the organisms are unable to survive outside of the lab.[20]

research.[2] In order to engage stakeholders and build trust, a Responsible Research and Innovation (RRI) framework (see Box 3) was incorporated into the Synthetic Biology Roadmap and publically-funded synthetic biology research. In addition to intellectual property rights (see POSTnote 401)[10] the main concerns (discussed later) were biosecurity, biosafety, and environmental and social responsibility.

Current Governance and Regulation

Synthetic biology developed from the field of genetic engineering and so is covered by existing regulations for biotechnology. In the USA and Canada, regulation focuses on the novelty of the traits of the product itself (trait-based, regulation, see Box 4 and POSTnotes 482 and 483). The focus of EU regulation is more on the process of genetic modification used to make a product and whether or not the GMOs are released to the environment. The House of Commons Science and Technology Select Committee recently recommended the UK move towards trait-based regulation of genetically modified (GM) crops.[11]

Current EU Directives (see below) define a GMO as any organism "where the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination".[12,13] There is debate about whether or not this definition applies to the products of the genome editing techniques outlined in Box 1 because some of these techniques make use of naturally occurring gene modification and repair systems.[7,21,22,23] This is important because, among other things, it affects whether foods containing products of synthetic biology need to be labelled as GM foods. Other synthetic biology products, such as protocells (Box 2) may not fit this definition as they are chemical constructs and may be more appropriately regulated by chemical and biological safety regulations.[24]

EU Legislation

Risk assessment of synthetic biology research is covered by two EU GMO directives (other regulations cover marketing of products such as medicines, cosmetics and chemicals)[8]:

- The Contained Use Directive (2009/41/EC) which covers contained activities, such as those carried out in a laboratory.[26] These are regulated by the Health and Safety Executive in the UK, advised by the Scientific Advisory Committee for Genetic Modification.
- The Deliberate Release Directive (2001/18/EC) which covers the release of a GMO to the environment.[27] Defra is the lead UK department. Decisions on releases solely for research purposes are made at a national level following guidance from the Advisory Committee for Releases to the Environment. Applications to market an organism or for GM food or feed, are decided at EU level.

Box 3. Responsible Research and Innovation

The Engineering and Physical Sciences Research Council (EPSRC) has adopted a Responsible Research and Innovation (RRI), framework.[25,26] Rather than solely focussing on safety, RRI enables other factors to be considered such as economic or social concerns. Key to this is an iterative approach to assessing risk, involving social and natural scientists, NGOs, citizens and regulators.[27] The UK synthetic biology community has adopted this framework at each research centre, the national centre for technology transfer and in industry.[28,29] This involves researchers highlighting to regulators where work in the field pushes the boundaries of current regulations and provides a safe space for discussions.[1,30]

Risk Assessment

EU regulation of GMOs is based on a precautionary approach. This requires risk assessment which is based on three key concepts:[7,9]

- Case-by-case approach. All activities that involve GMOs are considered on a case-by-case basis depending on the scale of the activities, the nature of the manipulation and the specifics of the environment.
- Step-by-step principle. This is applied where the ultimate application of an organism involves its release to the environment. It involves gradually reducing containment and increasing scale when evaluation of human and environmental health indicate it is safe to do so.
- Comparative analysis. For release to the environment, the novel organism is compared against a 'wild-type' (non-GM) comparator in order to determine if there is a possibility of increased risk. For contained use, the characteristics of the parent organism and any introduced traits are used to estimate a risk level for the novel organism and select an appropriate level of containment.

Environmental, Ethical and Social Aspects

Biosecurity

As with many emerging technologies, there are potential concerns over dual-use.[31] This is when the same scientific work can be used to do good or be intentionally used unethically in civilian or military applications.[32] In the US, commonly cited examples include the use of DNA synthesis (Box 1) to produce copies of the polio and the 1918 flu viruses for vaccine research.[33,34] In the EU, regulation 388/2012 controls the export of potential dual-use items (updated annually) to non-EU countries.[35] In addition, the Biological and Toxic Weapons Convention prohibits: the development, production and stockpiling of microbial or biological agents and toxins, whatever their origin or method of production, for any purpose that is not peaceful; their transfer to other states; and helping other states to manufacture or acquire them.[36] The scope of the convention covers all foreseeable products from synthetic biology.[37] To prevent individuals ordering potentially harmful DNA from DNA synthesis companies, the Harmonised Screening Protocol sets guidelines for such companies to screen the genetic sequence of each order against a list of sequences of concern.[38,39] The companies also screen the customer, to ensure the order is coming from a legitimate source. About 80% of worldwide DNA synthesis capacity has signed up to this voluntary protocol.[40] However, as technologies become more accessible, it is likely that equipment will become more widely available for DNA synthesis. Some experts suggest that more emphasis should be placed on developing counter-measures to protect the population in the event of a biosecurity alert.[9]

Box 4. Regulation Outside the EU

In the US, biotechnology products and their release are governed by three regulatory agencies – the Department of Agriculture's Animal and Plant Health Inspection Service (APHIS), the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA). The majority of near-term work is covered by the current regulatory framework. However, some novel techniques in plant modification fall outside the current framework.[41] This means that some plants do not require regulatory review prior to release into the environment.[42,] Other concerns raised include the ability of the EPA to cope with an increasing number of applications for microbes for commercial use and environmental release.

Canada regulates all products from biotechnology, including those from synthetic biology, in the same way that it regulates other novel products. The trigger for regulation is the novelty of the trait of the product rather than the way it was introduced. This has the advantage that any new technology developments in the field would automatically be regulated, including genetic modification techniques (Box 1) and those that cannot be anticipated.

Biosafety

A group of 111 NGOs has called for the Convention on Biological Diversity (CBD, Box 5) to impose a global moratorium on the environmental release and commercial use of synthetic biology until more is known about the potential risks to human health and the environment.[43] In 2014, pressure from NGOs caused Ecover (a home and personal care products manufacturer) to put use of an algal oil alternative to palm oil on hold in order to allow further research, even though Ecover maintains that synthetic biology was not involved in the development of the oil.[44] However, some proponents of synthetic biology argue that the principle of 'safety-by-design' can potentially make synthetic biology safer than GM approaches. For example, xenobiology (Box 2) might be used to incorporate safety features that ensure the organism dies if it escapes from the lab.[45] Researchers suggest that such a moratorium would damage advances in the field of synthetic biology.[46]

In addition to the above, concerns have been expressed over the potential risks arising from DIYbio. This involves people who are not necessarily associated with an academic or industrial institution doing biology at home or in a 'biohacking' group, either purely for interest or with ambitions of creating commercial products. The movement is more advanced in the USA (particularly for synthetic biology) than in Europe.[7] This may be because EU GMO regulations apply to the practice of GM irrespective of where it is being carried out. In the US, DIYbio groups have produced commercial products for release into the environment, including a glowing plant.[47] The first DIYbio group in the UK to become a class 1 notified laboratory has recently gained approval to carry out contained GM work at the lowest risk level where there is negligible risk of causing harm to human, animal or environmental health.[48] One

potential concern is that the technology may become more available to DIYbio practitioners who have no awareness of their legislative responsibilities before they carry out any synthetic biology activity. Another is that practitioners may not be familiar with biological safety, risks and good laboratory practice.[49,50] Codes of conduct have been established within the DIYbio community by individuals who are aware that their behaviour reflects upon the community as a whole.[51,52] Online training courses and increased accessibility to risk assessment and management may be useful because they can be readily updated.[7]

Environmental and Social Responsibility

Synthetic biology may indirectly impact the environment. Some near-term applications use biomass to produce fuels, chemicals and pharmaceuticals. On the one hand, some NGOs have raised concerns that this may lead to increasing biomass production, which in turn may cause land-use change and could result in a decline in soil fertility and biodiversity.[3,53] On the other hand, an aim of synthetic biology is to improve the efficiency of production beyond that of conventional renewable energy from biomass.[54]

A report for the CBD (Box 5) has highlighted the potential for synthetic biology to have both positive and negative economic consequences.[3] It noted that developing countries may benefit from small scale, niche technologies, but also suggested that inequitable trends in trade may develop. For example, NGOs are applying pressure for ice-cream companies not to use vanillin from synthetic biology, arguing that it may replace natural vanillin and reduce vanilla farmers' incomes.[55] However, only around 1% of the 15,000 tonnes of vanillin sold globally in 2010 was isolated from vanilla pods; most of it was made synthetically.[56] Projects such as the 'Conversation on Novel Biotech' are exploring these concerns with stakeholders from academia, NGOs, industry, Government and regulators to understand the opportunities, problems and conflicting views that exist.[57]

Regulatory Issues

Much current synthetic biology activity is industrial biotechnology, using organisms such as bacteria, yeast or algae to produce products like fragrances or vaccines in contained facilities.[58] Such technologies are likely to be covered by the well-established regulatory framework for the contained use of GMOs. Expert opinion suggests that most synthetic biology activities in the UK and Europe fall within the limits of the Contained Use Regulations and that the current GMO risk assessment is sufficient, at least in the near-term.[37,57] However, some future work may pose new challenges to the regulatory process. These are discussed in more detail in this section.

Risk Assessment of Complex Novel Organisms

Synthetic biology allows researchers to create novel organisms containing many new traits from a variety of sources. This has the potential to make risk assessment difficult. For example, assessment of current GMOs involves comparing them with an equivalent non-GMO organism, a relatively straightforward task where there are only one or two traits involved. But as the number of traits and their sources increases, it becomes less obvious what comparator organism to use. Comparator organisms have been considered by the EU Scientific Committees.[7] Complex novel organisms are developed step-by-step, with researchers seeking regulatory approval for each new combination of traits. The committees suggested that a complex novel organism from an earlier point in the development chain (with a proven safety record) could be used as a comparator for assessing more complex versions of the organism.

Box 5. The 1992 Convention on Biological Diversity (CBD)

The CBD is a multinational treaty that aims to conserve biodiversity, ensure it is used in a sustainable manner and that its benefits are shared fairly.[59] It has given rise to two protocols potentially relevant to synthetic biology, both of which have been signed and ratified by the EU (but not the USA, among others):

- The Cartagena Protocol on Biosafety, which applies to organisms with novel genetic material as a result of modern biotechnology techniques.[60] It places controls on trans-boundary movements, transit, handling and use where they may have adverse effects on conservation and sustainable use of biodiversity and human health.
- The Nagoya Protocol aims to ensure that there is fair and equitable sharing of benefits derived from using genetic resources and associated traditional knowledge, where there is national legislation.[61] It does not apply to genetic resources obtained prior to the protocol coming into force. It is not clear if this will apply to synthetic DNA, BioBricks, or digital sequence information.

Volume and Complexity

There are concerns that synthetic biology may increase the burden on the current regulatory authorities.[7] This may occur in two main ways:

- the expansion of the range of technologies available and the speed at which modifications can be made could increase the volume of applications being handled
- the increasing complexity of the risk assessment process is likely to be more time consuming for regulators.

Route of Regulation

For some applications, it may not be clear if the synthetic biology product falls under the deliberate release or contained use regulations. [62] For example, a biosensor being developed by the Arsenic Biosensor Collaboration[19] uses GM bacteria contained within a secure casing, but is intended for use outside of the laboratory. Using GMOs in this way usually means getting approval through the deliberate release regulations. But the fact that the GMOs are contained (both physically and biologically) might make the contained use regulations more appropriate.

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