



Concept note

Synthetic Biology

Risks and opportunities of an emerging field

Preface

IRGC is an independent organisation whose purpose is to help the understanding and management of emerging global risks that have impacts on human health and safety, the environment, the economy and society at large. IRGC's work includes developing concepts of risk governance, anticipating major risk issues and providing risk governance policy recommendations for key decision makers.

IRGC's work programme is deliberately focused on the governance of risks and their associated opportunities. In addition to ongoing work on the concept and practice of risk governance itself, IRGC's work programme encompasses all emerging, global risks of a systemic nature. IRGC is currently addressing the governance of a number of risks and opportunities posed by the mitigation of and adaptation to the effects of climate change, the security of energy supply, unconventional crises, and innovative technologies, and has identified synthetic biology as a new technology where there may be significant deficits in risk governance structures and processes.

Every IRGC project commences with the writing of a "concept note" to provide an overview of the particular topic being addressed and of its associated risks and opportunities. This is the objective of the following document, which is not intended to be a complete and in-depth description of the current status of synthetic biology and of the associated debate but, rather, merely provides a brief summary of synthetic biology and of the issues it raises and suggests a number of questions relating to its risk governance. The document thus seeks to inform and guide any future work by the IRGC on the subject.

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Introduction

Synthetic biology is one of a range of technology developments that IRGC has identified as raising unresolved challenges for risk governance. In life sciences and nanotechnology, for example, scientific knowledge is progressing very rapidly and speculation about potential novel applications of path-breaking discoveries and their risk governance begins many years before actual products emerge from the inevitably long research and development process.

Some of these potential innovative products and processes raise risk issues for which there is no clear regulatory precedent. And yet, effective risk regulation is usually a pre-requisite for financial investment in developing a particular technology. National and international regulatory systems thus often struggle to develop timely and effective responses to the challenges raised by products emerging from fundamental discoveries in science, medicine and engineering.

Several aspects relevant to innovative technologies have yet to be explicitly addressed by IRGC – for example:

- Linking risk governance and regulation to the requirements of commercially based innovation systems for the further development of novel scientific discoveries, including:
 - the inhibiting effect of uncertainty about future regulatory systems, particularly for products with long lead times for delivery from conception to market
 - how different forms of regulation (enabling / constraining; discriminating / indiscriminate) interact with innovation processes (Tait, et al., 2008) to determine the fate of individual innovations and also the relative competitive advantage of companies and even countries
 - the potential for a lack of harmonisation between different national regulatory systems, leading to potential trade-related and other conflicts
- The effectiveness and wider implications of existing regulatory approaches in encouraging the provision of public benefits from innovative technology without compromising on workplace, environmental or product safety or inhibiting industry competitiveness;
- The nature of stakeholder needs and concerns and the processes by which competing and sometimes conflicting perspectives can be reconciled, including:
 - the problems of stakeholder and public engagement about innovations where there is ignorance or at best uncertainty about the eventual nature of new products and processes;
 - the volatile nature of public opinion about innovative technology so that decisions based on the balance of stakeholder attitudes today may face a very different set of public opinions in ten years' time; and
 - the need to take decisions on an inclusive basis, particularly where there is irreconcilable ideologically-based conflict over innovative technology and its application (Tait, 2007).

By addressing synthetic biology, IRGC is thus responding to a need for the development of guiding principles for the risk governance of a broad range of innovative technologies that are internationally applicable and are based on a

thorough understanding of how risk regulatory and governance approaches interact with innovation processes. This study of synthetic biology is seen as a test case for such a development.

The purpose of this concept note is to raise some of the risk governance issues associated with synthetic biology. It is important to consider these issues even at this early stage of the field's development, because the kind of policy instrument that is adopted can have serious implications. Regulation can shape the future development of the science, guide product development in certain directions, and potentially generate conflict between stakeholder groups. Rather than providing concrete recommendations, the purpose of this note is to provide a background to and a stimulus for further discussion.

The concept note starts by addressing the issue of how synthetic biology is defined, because this has implications for how it should be regulated. It explores the distinctions between synthetic biology and genetic engineering, and looks at the relationship of synthetic biology to systems biology. It examines the three most prominent areas of research activity that go on under the heading of 'synthetic biology' and then turns to the environmental, health and industrial applications of the field. It examines the risks of synthetic biology in the areas of biosafety, biosecurity and intellectual property, and it also addresses ethical issues, particularly concerning the distinction between the 'natural' and 'unnatural'. Finally, it turns to the present regulatory context, and considers some of the suggestions that have been put forward for the regulation of synthetic biology in the areas of biosecurity and biosafety. It also explores proposals for self-governance – such as voluntary codes of practice – and the objections raised to these initiatives.

1. Background/definitions

What is synthetic biology?

It is hard to provide a precise definition of any new and emerging scientific field, but defining synthetic biology is particularly difficult because it incorporates a number of disparate research activities under its banner. However, the way synthetic biology is defined will have important implications for how it is regulated. For example, if one concludes that synthetic biology is merely an extension of genetic engineering then it may make sense to apply the existing regulatory thinking on genetic engineering to synthetic biology. If one were to decide that it is a completely different type of activity then it may demand regulations for which there are no precedents.

The term 'synthetic biology' is the dominant one which is attached to most of the conferences and funding initiatives in the field.¹ Some scientists and commentators use the term 'synthetic genomics' (e.g. Garfinkel et al. 2007), but their focus is usually on narrower issues to do with the synthesis of DNA, whereas 'synthetic biology' includes research which extends beyond the synthesis of genetic material alone. From this perspective, 'synthetic genomics' falls within the broader category of 'synthetic biology'.

The word 'synthetic' is ambiguous since it can mean either 'constructed' or 'artificial'. The former meaning is preferred by synthetic biologists (BBSRC/EPSC 2007), but it is inevitable that the 'artificial' aspect of synthetic is to some extent associated with the name. In fact, attempts have been made to avoid the word 'synthetic' by naming the field 'constructive biology' or 'intentional biology' (Carlson 2006), but these names have not become widely adopted.

Most definitions of synthetic biology have two parts: synthetic biology is defined as the construction of completely novel biological entities, and the re-design of already existing ones. For example, a group of leading scientists in the field defines synthetic biology as "the design and construction of new biological parts, devices, and systems and the re-design of existing, natural biological systems for useful purposes".² A high-level expert group similarly describes synthetic biology as "the engineering of biological components and systems that do not exist in nature and the re-engineering of existing biological elements" (NEST 2005).

The emphasis on engineering in the above definition is important, because synthetic biology has been described as 'the engineer's approach to biology' (Breithaupt 2006). This arguably distinguishes the field from previous more 'biologically' oriented activities. Some synthetic biologists are explicit about the engineering approach, saying that their aspiration is to make biology into an engineering discipline (Endy 2005, Arkin and Fletcher 2006), something that requires the reduction of biological complexity (Pleiss 2006). The engineering approach to biology, combined with synthetic biology's heavy reliance on information technologies, makes the field intrinsically interdisciplinary.

¹ See for example the series of conferences Synthetic Biology 1.0, 2.0 and 3.0, which took place in MIT, Berkeley and Zurich respectively (<http://www.syntheticbiology3.ethz.ch>)

² <http://syntheticbiology.org>

Some commentators think that synthetic biology is a new discipline that will emerge out of biology like electrical engineering emerged from physics (De Vriend 2006). Parallels are often drawn between today's synthetic biology and the early days of the nascent computer industry, with the intended implication that the technological revolution that synthetic biology brings will be as important as the revolution in ICTs brought about by electrical engineering (NEST 2005, Royal Society 2008a).

Comparison to genetic engineering

Synthetic biologists usually want to distinguish their work from genetic engineering (De Vriend 2006). This is not surprising, since excitement and funding often accompanies the start of something that is considered to be new. It might also be beneficial for synthetic biologists to distance themselves from some of the negative perceived social implications of genetic engineering.

There are two ways in which synthetic biology is often distinguished from genetic engineering. The first is in terms of the methods that are adopted. Synthetic biology involves the use of standardised parts and follows a formalised design process (Arkin and Fletcher 2006). Here, the tools and intellectual approach of engineering are being applied in synthetic biology in a way which distinguishes it from previous genetic engineering. As one prominent synthetic biologist has put it: "Genetic engineering doesn't look or feel like any form of engineering" (Endy quoted in De Vriend 2006).

The second way of distinguishing synthetic biology is in terms of the sophistication and complexity of the work. For example, in genetic engineering one gene at a time is inserted into an existing biological system, but in synthetic biology a whole specialised metabolic unit can be constructed (Stone 2006). This is because synthetic biology is not restricted to using genetic material from existing organisms (POST 2008), and involves "tinkering with the whole system instead of individual components" (Breithaupt 2006:22). Arguably this sophistication is only possible because of developments in knowledge of the underlying science, and it is often said that what is special about synthetic biology is that it is informed by a *systems* biology perspective (Barrett et al. 2006).

Relationship to systems biology

Systems biology makes use of computational tools and mathematical modelling in an attempt to integrate and analyse the vast amounts of data that have been generated by genome sequencing and other high through-put data gathering projects. According to some synthetic biologists, the emergence of systems biology has led to a change in mind-set which has allowed synthetic biology to focus on the assembly of parts, rather than just the parts alone (Panke 2007). Some scientists think that the most important role of synthetic biology will be to provide a hard test case for the theories and models developed in systems biology (Benner and Sismour 2005). If it is possible to build an actual functioning synthetic biological system from a systems biology model then this is good evidence that the model is correct.

The close relationship between systems and synthetic biology helps explain why synthetic biology is emerging now, since it is heavily dependent on scientific developments such as the availability of the DNA sequences of a number of entire organisms and a better understanding of how biological systems function (De Vriend 2006), as well as improved computational power. A more specific development which has contributed directly to the emergence of synthetic biology is the increasing speed and ease of gene synthesis (Garfinkel et al. 2007).

Types of synthetic biology

The different types of activity which go on under the broad heading of 'synthetic biology' can be divided into three areas: DNA-based device construction, genome-driven cell engineering, and protocell creation (O'Malley et al. 2008). These areas of research are connected and interrelated.

- *DNA-based device construction.* DNA-based device construction is the most well-known area of synthetic biology. This approach draws on the engineering principles of standardisation, decoupling and abstraction (Endy 2005), with the objective of developing biological components that are interchangeable, functionally discrete and capable of being easily combined in a modular fashion (Andrianantoandro et al. 2006). This results in the creation of standardized biological parts, devices and systems, called 'BioBricks', which are available online in an open-access library called the Registry of Standard Biological Parts.³ BioBricks can be used to create genetic circuits such as logic gates and oscillators (showing the explicit analogies drawn with electronic engineering). This school of synthetic biology is notable for founding the Genetically Engineered Machine jamboree (iGEM), a competition where undergraduates use the BioBricks to develop their own synthetic biological devices.⁴
- *Genome-driven cell engineering.* Another group of activities in synthetic biology focuses on whole genomes. This involves both 'top down' attempts to strip excess DNA away from existing genomes to make more efficient 'chassis' which, it is hoped, will form a basis for new synthetic organisms (e.g. Glass et al. 2006), as well as 'bottom up' attempts to construct genomes from scratch, including the synthesis of viral genomes such as the polio virus (Cello et al. 2002), and the ϕ X174 phage (Smith et al. 2003).
- *Protocell creation.* The area of protocell creation has been somewhat sidelined by other approaches to synthetic biology. Rather than aspiring to reduce the complexity of biological systems to make them more amenable to engineering, this approach is more interested in trying to recreate living cells. This often involves inserting molecular components into lipid vesicles (see Deamer 2005). These molecular components can either be synthesised from scratch, or already existing genes and enzymes can be used (Luisi et al. 2006). This school of

³ <http://parts.mit.edu>

⁴ See http://parts.mit.edu/igem07/index.php/Main_Page

synthetic biology, perhaps more than any other, raises the question of what it is to create life.

There are activities going on under the heading of synthetic biology which do not fit easily under these three headings, such as attempts to create an alternative genetic alphabet with new nucleotides beyond the four found in nature (Pollack 2001). However, the three sub-headings capture most of the activities commonly called 'synthetic biology'.

The purpose of discussing the different definitions and areas of work in synthetic biology is to help with the question of how it should best be regulated. As mentioned above, it will be necessary to decide whether synthetic biology should be treated as a new area of research or not in order to decide whether it requires new forms of regulation. Since synthetic biology covers a range of different activities, it is unlikely that this decision could be made for the field as a whole. The demonstration of the diversity of activities called 'synthetic biology' suggests that different approaches in synthetic biology are likely to raise different governance issues.

2. Scientific developments and likely applications

The field of synthetic biology is diverse and so are the prospective opportunities offered by its potential applications. These fall into several different areas of technology, each of which may well require different forms of governance and regulatory oversight. Before turning to these applications it is necessary for a caveat. Most of the work taking place in synthetic biology today is far from commercial exploitation, as demonstrated by the fact that the majority of it is funded by public institutions, rather than companies (De Vriend 2006). It is estimated that no products will be seen for at least a decade (Garfinkel et al. 2007). Perhaps all that one can be sure of is that the increasing speed and decreasing cost of DNA synthesis will assist the progress of experimental research in the biological sciences (Endy 2005). For these reasons, the discussion of applications and their opportunities is rather speculative. Nonetheless, synthetic biologists are keen to highlight the applications to show the potential of their field and to support its further funding. The potential applications of synthetic biology are also the focus of the risk debate and some, themselves, give rise to broader public concerns about future developments in the field. In this section a selection of the many potential applications of synthetic biology are highlighted.

Environmental applications

- *Bioremediation.* Another area with potential environmental benefits is bioremediation. Microorganisms or even plants could be engineered to degrade pesticides and remove pollutants (Tucker and Zilinskas 2006).
- *Biosensors.* The area of biosensors also has potential environmental benefits. Although biosensors have a broad range of uses (including the production of photographic bacteria, see Levskaya et al. 2005), they can also be developed to detect toxic chemicals, such as arsenic (Chu 2007).

Health applications

- *In vivo applications.* There are a range of potential applications of synthetic biology which could monitor and respond to conditions in the human body. For example, regulatory circuits could be designed which trigger insulin production in diabetes (ITI Life Sciences 2007). Bacteria or viruses could be programmed to identify malignant cancer cells and deliver therapeutic agents (Serrano 2007). Viruses have also been engineered to interact with HIV-infected cells, which could prevent the development of AIDS (De Vriend 2006).
- *New drug development pathways.* One of the avenues of synthetic biology that has wide application is the development of alternative production routes for useful compounds, and one of the most discussed of these is the construction of an artificial metabolic pathway in *E. coli* and yeast to produce a precursor (artemisinic) for an anti-malarial drug (Martin et al. 2003, Ro et al. 2006). It has been suggested that an approach such as this could be used to produce

other therapeutically useful compounds for cancer and HIV treatment (Voigt 2005). Polyketides are another important class of drugs which could potentially be produced using synthetic biology (Heinemann and Panke 2006).

- *Synthetic vaccines.* The fact that synthetic biology can 'start from scratch' means that new synthetic vaccines could be produced in response to viruses that themselves evolve rapidly, such as those that cause severe acute respiratory syndrome (SARS) and hepatitis C (Garfinkel et al. 2007).

Industrial applications

- *Biofuels.* One of the most widely discussed areas of future application of synthetic biology research is biofuels. There are many ways of engineering microorganisms to produce carbon-neutral (or more environmentally friendly) sources of energy. For example, bacteria could be engineered to synthesise hydrogen or ethanol by degrading cellulose, although further work is needed to overcome technical barriers. Plants and algae could also be engineered to produce biodiesel (Shreeve 2006). The aspiration to develop new and more sustainable sources of energy was behind BP's \$500 million, 10 year research collaboration with the University of California, Berkeley, Lawrence Berkeley National Laboratory and the University of Illinois, which started in February 2007 (POST 2008).
- *Biobased manufacturing and chemical synthesis.* The development of alternative production routes (as in the artemisinin case above) does not have to be limited to health-related applications, but could also be used for the production of other useful compounds. For example, Du Pont and Tate & Lyle are involved in making corn produce a compound used in the textile industry (POST 2008). Plants have also been engineered to produce a synthetic analogue of spider silk which has qualities of extreme strength and elasticity (De Vriend 2006). Along similar lines, synthetic mollusc shells could lead to the production of material which is light but also strong (Academy of Medical Sciences & Royal Academy of Engineering 2007).

3. Risks related to synthetic biology

These potential applications of synthetic biology have to be viewed in the light of the possible risks. There are two factors which make the risk governance of synthetic biology potentially problematic. The first is that synthetic biology (like genetic engineering) involves the production of living organisms, which by definition are self-propagating. The second is that with the growth of the Internet and the routinisation of many biotechnological procedures, the tools for doing synthetic biology are readily accessible (Garfinkel et al. 2007).

This section will address some of the environmental risks (biosafety), social risks (biosecurity), economic risks (intellectual property), and ethical issues (natural/unnatural) raised by synthetic biology.

Environmental risks: biosafety

The major biosafety risk of synthetic biology is the accidental release of synthetic organisms, which could have unintended detrimental effects on the environment or on human health (De Vriend 2006). This could be a particular risk in the case of bioremediation, where synthetic organisms would be purposely released into the environment, for example to remove toxins from the soil. Not only are microorganisms living and self-propagating, but they also evolve rapidly, and they can exchange genetic material with each other across species boundaries.

Additionally, the flexibility of synthetic biology means that microorganisms could be created which are radically different from existing ones, and these microorganisms might have unpredictable and emergent properties (Tucker and Zilinskas 2006), making the risks of accidental release very difficult to assess in advance (De Vriend 2006).

Some scientists have pointed out that these problems are not imminent since it is currently much easier for a synthetic organism to survive in an artificial environment than in a natural environment (Benner and Sismour 2005). It has also been suggested that synthetic organisms could be made to be dependent on nutrients that are not found in nature (De Vriend 2006), or that they could have built-in safety features such as 'fail-fast' mechanisms (Endy 2005). Here arguments are being made that making synthetic organisms less natural will make them *less* risky, rather than more so.

Social risks: biosecurity

Biosecurity is the most heavily debated social risk associated with synthetic biology in the US. The potential for deliberate and malevolent misuse of synthesised organisms has led to concerns that 'biohackers' (Tucker and Zilinskas 2006) could recreate known pathogens and perhaps even make them more virulent. The level of attention paid to biosecurity issues has led to criticisms that these concerns have pushed aside other, equally pressing issues (ETC Group 2006).

Biosecurity concerns were initiated by the synthesis of several pathogenic viruses. In 2002 an infectious poliovirus was synthesised in a laboratory using

only published DNA sequence information and mail-ordered raw materials (Cello et al. 2002). In 2003 a virus that infects bacteria (called ϕ X174) was also synthesised in only two weeks. In 2005 the virus that was responsible for the 1918 influenza pandemic was re-constructed from scratch (Tumpey et al. 2005).

Although experts argue that there are currently much easier ways of obtaining pathogens than synthesising them, they also predict that the relative ease of synthesis will change with time (Garfinkel et al. 2007). Furthermore, the availability of DNA sequence data and explanations of molecular biology techniques online, combined with the ease of getting a DNA sequence synthesized by a specialised company, means that these technologies are becoming available to an increasingly wide range of people (Garfinkel et al. 2007, De Vriend 2006).

Economic risks: intellectual property

Intellectual property law, like other forms of law, can work on the basis of precedent and attempts to draw parallels with already existing technologies. This is problematic in the case of synthetic biology, which operates at the intersection of biotechnology, software and electronics (Rai and Boyle 2007). For these reasons, and because synthetic biology is such a new field, the intellectual property issues are still in flux. Commentators say that the main objective is to develop some form of protection of intellectual property “without stifling the openness that is so necessary to progress” (NEST 2007:15).

Patents already exist that could inhibit the progress of research in synthetic biology (including broad patents on foundational technologies, and narrower patents on biological functions encoded by BioBricks). Worries about these potentially restrictive patents in synthetic biology are closely linked to concerns about the monopolisation of the field by large companies (ETC Group 2007), issues which were very important in the GM debate.

Craig Venter's team has filed for a patent on the smallest genome needed for a living organism (Glass et al. 2007), which also claims any method of hydrogen or ethanol production that uses the minimal genome. This patent has received considerable media attention because it has been interpreted as a patent on the ‘essence of life’ itself. However, analysts think it is unlikely to be granted on the grounds of lack of enablement (Nature Biotechnology 2007). The company Scarab Genomics has a patent on a reduced *E. coli* genome (Blattner et al. 2006), which, some argue, may prove to be more important (Nature Biotechnology 2007).

The BioBricks Foundation has been set up in an attempt to ensure that BioBricks are freely available in the public domain. The economic rationale for this is that since the products of synthetic biology are likely to require many different BioBricks, patenting them could lead to ‘patent thickets’. The BioBricks Registry is modelled on open source principles, meaning that anyone who takes a part from the Registry “must report any improvements and modifications and register new parts on the same terms” (POST 2008:3). But are there other ways of organising intellectual property around BioBricks? And is an open source model sustainable? This is currently an area of much debate (see for example Rai and Boyle 2007 and Henkel and Maurer 2007).

Synthetic biology encompasses more than just BioBricks, however, and there has been discussion about whether there should be different ownership regimes for different 'levels' of synthetic entity, such as parts, devices and systems. Some argue that since any organisms produced by synthetic biology will be the result of a great deal of effort, they should be subject to more stringent forms of intellectual property protection (Maurer 2006). This approach raises the question of whether it is possible to separate out different 'levels' of synthetic entity in a straightforward manner.

The intellectual property issues raised by synthetic biology are closely linked to ethical concerns about 'owning life'. Synthetic biology is very likely to involve the creation and the patenting of novel living organisms. The 'unnaturalness' of the creations in synthetic biology may actually make it easier to patent them, because they are clearly human inventions rather than products of nature.

Ethical issues: natural/unnatural

It is the perceived unnaturalness of synthetic biology which is most likely to give rise to ethical alarm. Statements to the effect that the next 50 years of DNA evolution will take place "not in Nature but in the laboratory and clinic" (Benner 2004:785), accompanied by inventions such as plants that produce spider silk, clearly challenge everyday understandings of nature and our place in it.

Synthetic biology raises ethical questions about where the line should be drawn between what is 'natural' and what is not. A key question here is whether risk analysis should distinguish between totally synthetic organisms and new organisms based on existing organisms (De Vriend 2006). But how can one decide whether or not something is a totally synthetic organism? For example, does putting a synthetic genome into an existing cell create a totally synthetic organism? If the focus is at the DNA level, then it may be necessary to say it does. Much synthetic biology adopts this DNA-centric perspective. For example, it is often assumed that if the synthesis of the genome of a virus or a bacterium constitutes the synthesis of the organism. This thinking also underlies concerns about Venter's minimal genome patent being a patent on the 'essence of life'. However, if one was to take the cellular context into account then the conclusion may be that the new cell is actually based on an existing organism, and is not, therefore, totally synthetic. The Ratheau Institute suggests introducing a measure of 'artificialness' of synthetic systems to assist regulation, which will involve developing guidelines about how to make distinctions between artificial systems and natural systems (De Vriend 2006).

4. Present regulatory and governance context

As there have, to date, been no specific regulations introduced that pertain to synthetic biology this section will examine some of the recommendations that have been put forward, including those for self-governance from the scientific community.

As mentioned above, most of the discussion of the risks of synthetic biology in the US has focused on the issue of biosecurity. Developments such as the synthesis of the poliovirus led to concerns about the potential misuse of the technology, and in 2004 the National Science Advisory Board for Biosecurity was established to provide advice “on ways to minimize the possibility that knowledge and technologies emanating from vitally important biological research will be misused to threaten public health or national security”.⁵

Another development in the biosecurity area was the publication in 2007 of the report ‘Synthetic Genomics: Options for Governance’ by the J. Craig Venter Institute, the Center for Strategic & International Studies, and the Massachusetts Institute of Technology (funded by a grant from the Sloan Foundation). This report considers different options for policy intervention in the area of DNA sequencing, suggesting various types of regulation of companies selling synthetic DNA and DNA synthesizers, owners of DNA synthesis technologies, and end-users of synthetic DNA. The report provides a range of regulatory options and includes suggestions such as the screening of customers by DNA synthesis companies (something that most of these companies do already), the education of scientists on biosecurity issues, the formation of a professional society for synthetic biology, and a biosafety manual for synthetic biology laboratories (Garfinkel et al. 2007).

Suggestions have also been made for dealing with biosafety issues to do with the accidental (rather than purposeful) release of synthetic organisms. Tucker and Zilinskas (2006), for example, think that the precautionary principle should be adopted with respect to synthetic biology saying that “it may be necessary to ban all uses in the open environment until a robust risk assessment can be conducted for each proposed application” (p.44). Others think that this step would make research expensive and restrict synthetic biology to a few labs (Garfinkel et al. 2007).

Self-governance initiatives and responses

The synthetic biology community is aware that their research has the potential to be extremely contentious, and many scientists regularly write about and publicly discuss regulatory issues. At the Second International Meeting on Synthetic Biology in Berkeley in 2006 the participants put forward a declaration on the governance of the field, which focused on biosecurity issues and emphasized self-regulation. Although the declaration demonstrated that there was broad awareness of the risk issues that synthetic biology raises, the call for self-regulation was driven by the agenda of the scientists and met with a strongly negative response from civil society organisations and NGOs. A global coalition of thirty-eight international organizations including scientists, environmentalists, trade unionists, biowarfare experts and social justice

⁵ <http://www.biosecurityboard.gov>

advocates wrote an open letter asking for the withdrawal of the declaration, saying “we believe that this potentially powerful technology is being developed without proper societal debate concerning socio-economic, security, health, environmental and human rights implications” (ETC Group 2006). It emphasised the necessity for broad and inclusive public debate on the implications of the field. This call for broader engagement with synthetic biology is found in other commentaries on the field. The Royal Society, for example, maintains that “Mechanisms need to be developed to encourage the responsible development of synthetic biology and a range of stakeholders (including publics) should be involved in discussing developments from an early stage” (Royal Society 2008b).

There are several ongoing synthetic biology projects which attempt to deal directly with societal issues and which involve stakeholders and policy makers. These include SYNBIOSAFE in Europe,⁶ and the Synthetic Society Working Group⁷ and the ‘Human Practices’ Thrust of SynBERC⁸ in the US.

⁶ www.synbiosafe.eu

⁷ http://openwetware.org/wiki/Synthetic_Society

⁸ <http://www.synberc.org>

5. Points for discussion

This concept note has attempted to provide a context for the discussion of the risk governance issues in synthetic biology. It started by examining the definition of synthetic biology and showing that how the field is defined has implications for how it is regulated, and for whether or not it is possible to transfer regulatory thinking from other areas (such as genetic engineering). Although synthetic biology can be broadly defined as the construction of completely novel biological parts and the re-design of existing ones, with an emphasis on the engineering of biology, it is a disparate field which includes DNA-based device construction, genome-driven cell engineering and protocell creation, amongst other activities. The applications of synthetic biology also cover a wide range, from biofuels and bioremediation to synthetic drug-delivery systems and novel synthetic pathways for useful compounds. The diversity of the applications of the field suggests that different regulatory guidelines may be needed for different areas of the technology. Applications within the human body, for example, will probably be subject to more stringent forms of regulation than where the synthetic organisms are easily contained (ITI Life Sciences 2007).

In the discussion of risks it was pointed out that the field raises particular concerns because it produces living, reproducing organisms, and because of the easy accessibility of the tools for doing synthetic biology. The areas of risk discussed were the accidental release of synthetic organisms, the malevolent use of the technology, and the different options for managing the creation of intellectual property in this emerging field. The discussion of ethical issues highlighted the fact that synthetic biology raises profound questions about the distinction between the 'natural' and the 'unnatural'. This has implications for risk governance, which, some have suggested, might benefit from introducing a measure of 'artificialness' of synthetic systems. The final section on the present regulatory context examined some of the suggestions that have been put forward for the risk governance of biosecurity and biosafety issues in synthetic biology. It also examined the self-governance initiative of the synthetic biology community and the response to this from NGOs, who stressed the importance of a more inclusive debate about the potential of this new technology. Such recommendations are relevant to the IRGC Risk Governance approach which emphasises the inclusiveness of the governance process, aspires to implement the principles of 'good' governance (such as transparency, effectiveness and efficiency, accountability and equity), and takes both the 'factual' and the 'socio-cultural' dimensions of risk into account (Renn 2005).

The aims of this report have been to provide a summary description of synthetic biology, to raise a number of important questions and to stimulate discussion. These discussions will take place in the wider context of the general questions about risk governance of innovative technology raised in the introduction. The following are specific questions which should be pursued in greater depth, both to inform risk-related decisions about synthetic biology itself and to contribute to the development of broader governance approaches and regulatory systems which meet the challenges raised by products emerging from fundamental discoveries in science, medicine and engineering:

- How should synthetic biology be defined for the purposes of risk governance?

- What should be included within the field of synthetic biology and what should be excluded from it? (For example, should protocell creation be treated similarly to work on BioBricks?)
- Can synthetic biology be treated as a form of genetic engineering or does it raise novel issues?
- Do the different application areas of synthetic biology raise different governance issues?
- Do different 'levels' of synthetic biological entity demand different levels of regulation? (For example, should BioBricks be regulated differently from synthetic organisms?)
- Should synthetic organisms be patentable?
- Would it be helpful to have a measure of 'artificialness' of synthetic systems?
- Is self-governance an adequate solution to the risk issues raised by synthetic biology?
- Would it be useful to have a more inclusive debate about the potential of the technology? If so, who should be part of this debate?
- Is international investment into the field of synthetic biology a good way of tackling pressing medical, environmental and social problems?
- What issues arise if different parts of the world develop different regulatory approaches, or if some regulate and some do not?

References

Academy of Medical Sciences & Royal Academy of Engineering (2007) Systems biology: a vision for engineering and medicine. Academy of Medical Sciences and Royal Academy of Engineering: London

Anderson, JC, Clarke, EJ, Arkin, AP and Voigt, CA J. (2006) 'Environmentally Controlled Invasion of Cancer Cells by Engineered Bacteria' J. Mol. Biol. 355, 619–627

Anderson JC, Voigt CA, Arkin AP. (2007) 'Environmental signal integration by a modular AND gate' Mol Syst Biol 3 Article number 133 doi:10.10138/msb4100173

Arkin AP, Fletcher DA. (2006) 'Fast, cheap and somewhat in control' Genome Biol 7:114 doi:10.1186/gb-2006-7-8-114

Barrett CL, Kim TY, Kim HU, Palsson BØ, Lee SY. (2006) 'Systems biology as a foundation for genome-scale synthetic biology' Curr Opin Biotechnol 17: 1-5

BBSRC/EPSRC (2007) The Royal Society: call for views on synthetic biology. Joint BBSRC/EPSRC response, 22 Nov 2007; online at <http://royalsociety.org/document.asp?tip=0&id=7290> (accessed 25th February 2008)

Benner, SA (2004) 'Understanding nucleic acids using synthetic chemistry' Acc. Chem. Res. 37, 784-797

Benner SA, Sismour AM. (2005) 'Synthetic biology' Nat Rev Genet 6: 533-543

Blattner, FR, Posfai, G, Herring, CD, Plunkett, Guy, Glasner, JD (Inventors); Wisconsin Alumni Research Foundation (Assignee). 2006 January 26 'Bacteria with reduced genome' United States patent

Breithaupt H. (2006) 'The engineer's approach to biology' EMBO Rep 7: 21-24

Cello J, Paul AV, Wimmer E. (2002) 'Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template' Science 297: 1016-1018

Chu, J (2007) 'A Safe and Simple Arsenic Detector' Thursday, January 25, 2007 Technology Review; online at <http://www.technologyreview.com/Biotech/18103/> (accessed 25th February 2008)

Deamer D. (2005) 'A giant step towards artificial life?' Trends Biotechnol 23:336–338

De Vriend, Huib (2006) Constructing Life. Early social reflections on the emerging field of synthetic biology. The Hague: Rathenau Institute; Working Document 97; online at <http://www.rathenauinstituut.com/showpage.asp?stelID=2&item=2644> (accessed 25th February 2008)

Endy D. (2005) 'Foundations for engineering biology' *Nature* 438:449–453

ETC Group (2006) 'Global Coalition Sounds the Alarm on Synthetic Biology, Demands Oversight and Societal Debate' ETC Group News Release; online at http://www.etcgroup.org/en/materials/publications.html?pub_id=8 (accessed 25th February 2008)

ETC Group (2007) Extreme Genetic Engineering: An Introduction to Synthetic Biology; online at http://www.etcgroup.org/en/materials/publications.html?pub_id=602 on 13/08/07 (accessed 25th February 2008)

Garfinkel, MS, Endy, D, Epstein, GL and Friedman, RM (2007) Synthetic Genomics: Options for Governance. J. Craig Venter Institute, Rockville, MD, Center for Strategic & International Studies, Washington, DC and Massachusetts Institute of Technology, Cambridge, MA

John I. Glass, Nacyra Assad-Garcia, Nina Alperovich, Shibu Yooseph, Matthew R. Lewis, Mahir Maruf, Clyde A. Hutchison III, Hamilton O. Smith, and J. Craig Venter (2006) 'Essential genes of a minimal bacterium' *Proc Nat Acad Sci* 103: 425-430

Henkel J, Maurer SM. (2007) 'The economics of synthetic biology' *Mol Syst Biol* 3: 117 doi: 10.1038/msb4100161

ITI Life Sciences (2007) Synthetic Biology Foresighting: Technologies and Markets. October 2007, ITI Life Sciences: Dundee

Kumar, S and Rai, AK. (2007) 'Synthetic Biology: The Intellectual Property Puzzle' *Texas Law Review* 85:1745-1768

Glass JI, Smith HO, Hutchinson III CA, Alperovich NY, Assad-Garcia N, (Inventors); J. Craig Venter Institute, Inc. (Assignee). 2007, October 12. Minimal bacterial genome. United States patent application 20070122826

Heinemann M, Panke S. (2006) 'Synthetic biology – putting engineering into biology' *Bioinformatics* 22: 2790-2799, p 2793

Henkel J, Maurer SM. (2007) 'The economics of synthetic biology' *Mol Syst Biol* 3: 117 doi: 10.1038/msb4100161

Levskaya A, Chevalier AA, Tabor JJ, Simpson ZB, Lavery LA, et al. (2005) 'Engineering Escherichia coli to see light' *Nature* 438:441–442

Luisi PL, Ferri F, Stano P. (2006) 'Approaches to semi-synthetic minimal cells: a review' *Naturwissenschaften* 93:1–13

Martin VJJ, Pitera DJ, Withers ST, Newman JD, Keasling JD. (2003) 'Engineering a mevalonate pathway in Escherichia coli for production of terpenoids' *Nat Biotechnol* 21:796–802

Maurer, S (2006) 'Synthetic Biology/Economics Workshop: Choosing the Right IP Policy' Reporter notes. UC Berkeley Goldman School of Public Policy March 31, 2006; online at <http://gspp.berkeley.edu/iths/SynBio%20Workshop%20Report.htm> (accessed 25th February 2008)

McAdams HH, Arkin AP, Shapiro L (Inventors); Leland Stanford Junior University Board of Trustees (Assignee). 1999 June 22 'System and method for simulating operation of biochemical systems' United States patent 5,914,891

Nature Biotechnology (2007) 'Editorial: Patenting the parts' Nature Biotechnology August 2007, 25 (8):822

NEST (2005) Synthetic Biology: Applying Engineering to Biology. Report of a NEST High-Level Expert Group Luxembourg: Office for Official Publications of the European Communities; online at ftp://ftp.cordis.europa.eu/pub/nest/docs/syntheticbiology_b5_eur21796_en.pdf (accessed 25th February 2008)

NEST (2007) Synthetic Biology: A NEST Pathfinder Initiative. Luxembourg: Office for Official Publications of the European Communities; online at <ftp://ftp.cordis.europa.eu/pub/nest/docs/5-nest-synthetic-080507.pdf> (accessed 25th February 2008)

Neumann G, Watanabe T, Ito H, Watanabe S, Goto H, Gao P, Hughes M, Perez DR, Donis R, Hoffmann E, Hoborn G, Kawaoka Y. (1999) 'Generation of Influenza A Viruses Entirely from Cloned cDNAs' Proceedings of the National Academy of Sciences USA 96: 9345-9350

O'Malley, M, Powell, A, Davies, J and Calvert, J (2008) 'Knowledge-making distinctions in synthetic biology' BioEssays, 30(1): 57–65

Panke, S (2007) 'Perspectives in synthetic biology' presentation at the Synthetic Biology Scoping Meeting, Genomics Forum, Edinburgh, UK, 3rd September 2007

Pleiss, J (2006) 'The promise of synthetic biology' Applied Microbiology and Biotechnology, 73: 735-739

Pollack, A (2001) 'Scientists Are Starting to Add Letters to Life's Alphabet' New York Times, 24 July 2001

POST (2008) Postnote: Synthetic Biology. January 2008, Number 298, London: The Parliamentary Office of Science and Technology; online at <http://www.parliament.uk/documents/upload/postpn298.pdf> (accessed 25th February 2008)

Rai A, Boyle J. (2007) 'Synthetic biology: caught between property rights, the public domain, and the commons' PLoS Biol 5: e58 doi:10.1371/journal.pbio.0050058

Renn, O (2005) White Paper No.1: Risk Governance – Towards an Integrative Approach. International Risk Governance Council: Geneva

Ro D-K, Paradise EM, Ouellet M, Fisher KJ, Newman KL, et al. (2006) 'Production of the antimalarial drug precursor artemisinic acid in engineered yeast' *Nature* 440:940–943

Royal Society (2008a) 'What is synthetic biology?' online at <http://royalsociety.org/page.asp?id=1231> (accessed 25th February 2008)

Royal Society (2008b) 'Synthetic biology: policy issues' online at <http://royalsociety.org/page.asp?id=5532> (accessed 25th February 2008)

Serrano (2007) 'Synthetic biology: promises and challenges' *Molecular Systems Biology* 3; doi:10.1038/msb4100202

Shreeve, J (2006) 'Redesigning Life to Make Ethanol' *Technology Review*, 21 Jul 2006; online at http://www.technologyreview.com/read_article.aspx?ch=specialsections&sc=biofuels&id=17052&a= (accessed 25th February 2008)

Smith HO, Hutchinson CA III, Pfanndoch C, Venter JC. (2003) 'Generating a synthetic genome by whole genome assembly: ϕ X174 bacteriophage from synthetic oligonucleotides' *Proc Natl Acad Sci USA* 100:15440–15445

Stone, M. (2006) 'Life redesigned to suit the engineering crowd' *Microbe* 1: 566-570. www.asm.org/microbe/index.asp?bid=47155

Tait, J. (2007). Risk Governance of Genetically Modified Crops: European and American Perspectives. In eds. O. Renn and K. Walker, *Global Risk Governance: Concept and Practice Using the IRGC Framework*. Dordrecht, NL: Springer Science and Business Media; pp 134-153.

Tait, J., Chataway, J and Wield, D. (2008) *Appropriate Governance of the Life Sciences – 2: the Case for Smart Regulation*. Innogen Policy Brief <http://www.genomicsnetwork.ac.uk/innogen/>

Tucker JB, Zilinskas RA. (2006) 'The promise and perils of synthetic biology' *New Atlantis* 12: 25-45

Tumpey TM, Basler CF, Aguilar PV, Zeng H, Solorzano A, Swayne DE, Cox NJ, Katz JM, Taubenberger JK, Palese P, Garcia-Sastre A. (2005) 'Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus' *Science* 310: 77-80

Voigt, C.A., et al. (2005) 'Programming Cellular Function' *Nature Chemical Biology*, Vol. 1, pp. 304–307

Acknowledgements

This IRGC concept note has been prepared for IRGC by Dr Jane Calvert, RCUK Academic Fellow, and Professor Joyce Tait, Scientific Adviser, both at the ESRC Innogen Centre, University of Edinburgh.

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