Concept note

Risk Governance of Synthetic Biology

Updated and completely revised version

international risk governance council

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Abbreviations used in the text:

BBSRC	Biotechnology and Biological Sciences Research Council (UK)
DNA	Deoxyribonucleic acid
ESRC	Economic and Social Research Council (UK)
EU	European Union
GM	Genetically Modified
iGEM	International Genetically Engineered Machines competition
Innogen	ESRC Centre for Social and Economic Research on Innovation in Genomics
IP	Intellectual Property
IRGC	International Risk Governance Council
NGO	Non-Governmental Organisation
NIH	National Institutes of Health (US)
NSF	National Science Foundation (US)
OECD	Organisation for Economic Cooperation and Development
SynBERC	Synthetic Biology Engineering Research Center (US)
SYNBIOSAFE	Safety and Ethical Aspects of Synthetic Biology (EU-funded) project
UK	United Kingdom of Great Britain and Northern Ireland
US	United States of America

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Preface

The International Risk Governance Council (IRGC) is an independent organisation whose purpose is to help the understanding and governance of emerging global risks that have impacts on human health and safety, the environment, the economy and society at large. IRGC believes that important opportunities for social and economic development may be foregone through inadequate risk governance.

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 developing recommendations for improving the governance of emerging, global risks of a systemic nature. IRGC 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.

This is the second concept note in which IRGC has addressed this particular topic. The first, published in May 2008, provided the background to discussion at an exploratory workshop held in Geneva the following month. One of the conclusions drawn by IRGC from that workshop was that IRGC should conduct project work to develop recommendations for improving the risk governance of synthetic biology. IRGC is now beginning that work.

Such has been the pace of developments in the field that IRGC recognised a need for a completely revised and updated document, to provide a brief summary of some of the issues that will be addressed in the course of the future project work. This is the purpose of this document, which is therefore not intended to be a complete and in-depth description of the current status of synthetic biology and of the associated debate.

Comments are welcome on how IRGC's project on the risk governance of synthetic biology can make a constructive contribution to the work of policymakers and regulators responsible for its governance.

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Contents

Introduction

This concept note has as its primary purpose to inform discussion at an expert workshop on October 26 and 27, 2009. The workshop is an integral element in a project in which IRGC will develop recommendations for improving the risk governance of synthetic biology. The project is itself part of IRGC's contribution to the appropriate risk governance of innovative technology.

Research in the field of synthetic biology is expanding rapidly. However, the commercial development of useful applications is potentially hampered by an uncertain policy and regulatory environment as well as by the complexity of the associated societal challenges. This IRGC project will conclude with the publication of an IRGC policy brief for policymakers and other interested parties in which IRGC will provide recommendations for improving risk governance in this important area of scientific development.

Synthetic biology is an emerging field at the intersection between life sciences and engineering, offering the potential for trans-sectoral impacts in areas such as energy, health and the environment. The technology is already raising political, legal and ethical concerns, and may give rise to risks to health and the environment. Effective risk governance is therefore key to enabling innovation in this new area of scientific endeavour as well as to assuring due consideration of relevant risks and benefits.

This concept note provides an overview of the science and innovation potential of the field and of the benefits it offers and the risks it may pose. The document also seeks to stimulate discussion on the regulation and governance of synthetic biology and appropriate models of public and stakeholder engagement, including how and when to incorporate stakeholder concerns and opinions into decision-making about future developments. In this concept note IRGC has not attempted to give a comprehensive review or commentary on all the existing literature pertaining to synthetic biology – this will later be undertaken as part of the research and drafting of the forthcoming policy brief. Readers are encouraged to suggest relevant papers and reports for inclusion in that review.

There have been numerous recent conferences and workshops on synthetic biology, alongside reports from national and international bodies [Balmer and Martin, 2008; Gaisser, et al., 2008; Garfinkel, et al., 2007; NEST, 2007; POST, 2008; National Academies, OECD and Royal Society, 2009; Rodemeyer, 2009; Royal Academy of Engineering 2009; Royal Society 2008, 2009]. The list of issues raised in these reports is beginning to stabilise around a limited set of concerns for which few concrete solutions have yet emerged:

- The fact that synthetic biology involves the production of novel living organisms which will be self-replicating and therefore potentially uncontrollable;
- The increasingly routine nature of many synthetic biology procedures which makes them more readily accessible to those without specialist training;
- The ability to engineer or re-engineer potential human, animal or plant pathogens;
- Issues around the patenting of novel life forms or their components, including questions of trade and global justice; and
- Questions of the morality of creating novel life forms.

Additionally, there are concerns regarding biosafety risks and, particularly in the United States, a number of aspects of the biosecurity risks posed by synthetic biology. The synthesis of several pathogenic viruses has led to concerns that the degree of regulatory oversight applied is not commensurate with the risks. A range of options have been suggested, from the reinforcement of existing norms against the use of biotechnology to do deliberate harm in specific contexts [Steinbruner, 2009], to a ban on all uses of synthetic biology in the open environment until a risk assessment can be conducted for each proposed application [Tucker and Zilinskas, 2006]. A fundamental problem for risk governance is that the beneficial and hostile applications of synthetic biology cannot be disentangled at the level of basic research.

Precedents for the governance issues raised by synthetic biology can be found in several other areas of life science and decision-making needs to be informed by an understanding of how risk governance and engagement approaches interact with innovation processes. IRGC's project on synthetic biology will build on prior work by IRGC on the concept and practice of risk governance [IRGC, 2005; Renn and Walker, 2007] and on risk governance deficits [IRGC, 2009] and on research at the ESRC Innogen Centre on appropriate risk governance of innovative technologies [Tait and Chataway, 2007; Tait, et al., 2008; Tait 2009a].

The concept of 'appropriate risk governance' builds on research conducted at the Innogen Centre [Wield, 2008] integrating in-depth understanding of three key areas: (i) science and innovation strategies in public and private sector organisations; (ii) regulation and governance of new technology; and (iii) public and stakeholder perspectives. Interactions among these three areas determine which scientific research and development is commercialised, which products are developed, and which companies and industry sectors – and even which countries – are able to participate in and benefit from product development.

In common with many other innovative technologies (e.g., nanotechnology), the development, commercialisation and risk governance of synthetic biology would benefit from the development of internationally-applicable guiding principles. Core issues that need to be addressed in the development of these principles include:

1) Linking risk governance and regulation to the requirements of commercially-based innovation systems for the further development of novel scientific discoveries, with due consideration of:

   - The inhibiting effect of uncertainty about future regulatory systems, particularly for products with long lead times from conception to market;
   - How different forms of regulation interact with innovation processes [Tait, et al., 2008] to determine the fate of individual innovations and the relative competitive advantage of companies and even countries; and
   - The potential for a lack of harmonisation across national regulatory systems, leading to potential trade-related and other conflicts.

2) The role of existing and future regulatory approaches in encouraging the provision of public benefits from innovative technology without compromising workplace, environmental or product safety.

3) The nature of stakeholder needs and concerns and the processes by which competing and sometimes conflicting perspectives can be reconciled, taking into account [Tait, 2009b]:

- The problems of stakeholder and public engagement about innovations where there is ignorance or uncertainty about the eventual nature of new products, processes, benefits and risks;
- The volatile nature of public opinion about innovative technology (in that decisions based on the balance of stakeholder attitudes now may not be consistent with public opinion in the future); and
- The need to take decisions on an inclusive basis in the face of concerns about national security, human and environmental safety and ethical concerns, particularly where there is an absence or dearth of scientific evidence and when there is irreconcilable conflict over the technology and its applications.

Regulation and governance of synthetic biology are in the very early stages of development and the approaches currently under consideration relate mainly to the risks attached to the research itself rather than to the products and other innovations that might eventually emerge from that research. In governing the risks of new technologies, there is a history of decisions taken at the very earliest stages of development having unforeseen and often counter-productive outcomes which are difficult to change in later stages. As a starting point for further discussions, the following general lessons for the better governance of innovative technology are relevant [Tait, et al., 2008]:

1) Regulatory initiatives can have major, rapid and positive influences on innovation processes and safety assurance. They can also, particularly when applied in areas beyond their original purpose, have unexpected negative impacts on research and product development. There is a need to use such insights from past examples to help design or re-design the regulatory systems of the future;
2) A regulatory policy that *enables* positive change in industry strategies and *discriminates* among products on the basis of societally and scientifically relevant criteria is likely to be more effective and efficient than one which is *indiscriminate* and attempts to *constrain* undesirable behaviour;
3) In point 2, the enabling criterion will affect the speed with which a particular regulatory policy is able to exert its influence, while the extent and appropriateness of its discrimination among products or processes will determine its effectiveness in guiding product development in particular directions;
4) In considering appropriate regulatory precedents for innovative technologies such as synthetic biology, a useful ground rule would be to consider first the regulatory system in operation for the industry sector or product range for which the innovation is path-dependent, rather than one for which it is path-breaking.

Policymakers and regulators hold the key to all these outcomes and should be seen as shapers of, rather than responders to, scientific developments and public and stakeholder responses. In other areas of life sciences, such as genetically modified (GM) crops and stem cells, the key to future evolution of the sector has been determined by early policy decisions on appropriate regulatory precedents. An ‘appropriate’ approach to risk governance would be one that is enabling of innovation, minimises risk to people and the environment, and balances the interests and values of relevant stakeholders [Tait, et al., 2008].

The discussion points proposed below reflect the need to think through how the benefits promised by synthetic biology can be delivered and how the associated risks can be recognised and minimised, by identifying and avoiding

risk governance deficits in three key areas: technology development; policy and regulation; and, public and stakeholder engagement.

Developing the field

- As synthetic biology develops, what governance structures and regulatory and accreditation processes would be applicable to, first, fundamental research, and, secondly, commercialisation by industry?
- What kind of governance system could enable commercialisation while assuring workplace and protecting product safety and product quality?

Managing emerging risks

- What are the risks associated with synthetic biology at its research stage?
- What are the potential risks generated by synthetic biology at its commercialisation stage?
- Do these risks interact?
- What should the balance be between private and public ownership of shared resources to enable innovation?
- What should the balance be between private and public responsibility for the associated risks?
- How can different intellectual property (IP) regimes and cultures be reconciled when stakeholder interests and incentives are only minimally aligned?
- Are current bioethics frameworks adequate for managing ethical concerns or is there a need to develop a broader form of societal review?

Governance and regulation

- What new governance issues are raised by synthetic biology as a whole?
- What governance issues are raised by different application areas of synthetic biology?
- Is there a role for self-governance initiatives for synthetic biology and, if so, what are their benefits?
- What regulatory precedents could policymakers focus on, how appropriate are they and what might be their pitfalls?
- What problems arise from international differences in regulatory approaches?
- What would be the impact on the development of synthetic biology of high regulatory barriers to market entry?

Public and stakeholder engagement

- What is the optimal form of debate about risk governance for a technology with very long time lines for product development and regulatory approval?
- Would ‘rules for engagement’ be useful (e.g., to set standards for the quality and breadth of evidence; to assure the willingness of all participants to listen to and respect the views of others)?
- What lessons are relevant from previous risk governance experiences?
- What are the potential benefits of synthetic biology that could suggest public support for development of the field?

This concept note is organised in three parts. Firstly, it defines synthetic biology and sets out the present regulatory and governance context. The second part provides an overview of emerging risks in four broad areas: biosafety, biosecurity, intellectual property, and ethics. The third part builds on IRGC’s work on risk governance deficits by identifying and developing an approach to avoiding potential governance deficits in the key areas of technology development; policy and regulation; and public and stakeholder engagement.

1. Definition and context

1.1 What is synthetic biology?

The wide variety of definitions of synthetic biology was summarised more fully in IRGC's first concept note on synthetic biology [IRGC, 2008]. In this document the term refers to two main activities: the design and construction of new biologically-based parts, novel devices and systems; and the re-design of existing, natural biological systems for useful purposes [Royal Academy of Engineering, 2009]. Synthetic biology is the dominant term attached to most of the conferences and funding initiatives in the field and it includes research which extends beyond the synthesis of genetic material alone. Synthetic genomics on the other hand focuses on narrower issues to do mainly with the synthesis of DNA [Garfinkel, et al., 2007]. Thus, synthetic genomics can be seen as falling within the broader category of synthetic biology.

The most widely-publicised strand of synthetic biology application involves the use of standardised parts, following a formalised design process [Arkin and Fletcher, 2006]. This has been described as 'the engineer's approach to biology' [Breithaupt, 2006], distinguishing the field from more 'biologically' oriented activities. Some synthetic biologists are very explicit about their aim to make biology into an engineering discipline [Endy, 2005], requiring the reduction of biological complexity [Pleiss, 2006]. An engineering approach to biology based on the principles of standardisation, decoupling and abstraction [Brent, 2004] and a heavy reliance on information technologies make the field inherently interdisciplinary.

Many of the short-term uses of synthetic biology resemble existing applications of genetic engineering, through a more rapid and extensive development methodology accessible to a wider range of people. Long-term visions involve highly innovative biological systems engineered to produce a range of practical interventions: environmental applications, such as bioremediation, where microorganisms or plants could be engineered to degrade pesticides and remove pollutants [Tucker and Zilinskas, 2006]; industrial applications in the area of biofuels and agricultural biotechnology; and health applications, such as the rapid development of new synthetic vaccines that could be produced in response to viruses that themselves evolve quickly [Garfinkel, et al., 2007].

Synthetic biology shows strong market potential. A recent market research report estimated the global market at $233.8 million in 2008 and predicted an increase to $2.4 billion by 2013 [BCC, 2009]. Production of chemicals and energy related developments so far represent the largest market segment for synthetic biology, valued at $80.6 million in 2008, and projected to reach $1.6 billion in 2013. The biotechnology and pharmaceuticals segment is the second-largest market sector, valued at approximately $80.3 million in 2008 and projected to reach $594 million in 2013. The majority of current research is funded by public institutions, although this is beginning to change [de Vriend, 2006].

1.2 Current regulatory and governance contexts

Despite the hybrid nature of synthetic biology, part biotechnology and part engineering, it appears to be following the biotechnology model where regulation is concerned in that it is subject to demands for a strong governance and regulatory structure. In Europe, the most common concern is to avoid the polarisation of views that characterised the public controversies over GM plants and foodstuffs. In the United States (US), the analogy with the Asilomar Conference on Recombinant DNA in 1975 has been noted and the biosecurity implications have also been discussed in light of the potential terrorist threat and the response in terms of homeland security [Garfinkel, et al., 2007].

Revisions have been proposed to the US National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules to cover synthetic nucleic acids [NIH Guidelines, 2009]. An exemption to the guidelines has been proposed for synthetic nucleic acids that cannot replicate, provided they are not used in human gene transfer. The risk assessment framework set out in the NIH guidelines is considered by regulators to be sufficient at present, although this may need to be reviewed as the technology develops. For example, the current framework uses the risk group of the parent organism as a starting point for determining the necessary containment level, but synthetic techniques may enable the development of more complex chimeras for which the parent organism is not obvious. In the European context, the general view is that the science as it stands is covered by the existing regulatory mechanisms for genetic modification and releases to the environment [Royal Academy of Engineering, 2009].

Within the synthetic biology community, there is considerable support for approaches to oversight that rely on measures developed and implemented by the community itself [Campos, 2009]. There is a difficult balance to be found between avoiding premature or inappropriate regulatory oversight, and the advocacy of minimal approaches to governance which could exacerbate public concerns. One of the lessons to be learned from the GM crops experience in Europe is that attempts by scientists and companies to minimise regulatory scrutiny of their activities is a powerful factor in legitimising the views of pressure groups in the eyes of the public and gives them a leading role in the framing of the technology [Tait, 1993].

At the Second International Meeting on Synthetic Biology (SynBio 2.0) in Berkeley in 2006 the participants put forward a declaration on the governance of the field, which focused on biosecurity issues and emphasised self-regulation. Although the declaration demonstrated that there was broad awareness of the risk issues that synthetic biology raises, the call for self-regulation met with a strongly negative response from civil society organisations and non-governmental organisations (NGOs) [ETC Group, 2006]. Synthetic biologists have also put forward technical risk governance proposals, such as building in self-destruct mechanisms to novel organisms with potential risks [Endy, 2005; Church, 2005].

In considering the current regulatory and governance context, it is important to be aware of the potential overlaps between synthetic biology and areas currently being discussed under the heading of nanotechnology, particularly where there is convergence between nanotechnology, information technology and biotechnology [European Commission, 2008; IRGC, 2007]. This could be another area where regulatory precedents and comparisons become important.

2. Emerging benefits and risks

The potential industrial applications of synthetic biology research are diverse. As well as improving knowledge of biological systems and processes, many commentators believe the technology offers the potential for economic growth and wealth generation through the development of major new industries [Carlson, 2007]. The technology may also offer societal, environmental and medical benefits including [Garfinkel, et al., 2007]:

1) New and improved diagnostics, drugs and vaccines. Artemisinin is an effective anti-malarial drug currently obtained (albeit at high cost) through extraction from a plant. A $43 million project funded by the Gates Foundation has engineered new pathways in yeast that produce artemisinic acid, a precursor to the active drug [Ro, et al., 2006]. It is hoped that this potentially high-yield method will make the drug more widely available, perhaps within five years.
2) Biosensors. A team at the University of Edinburgh engineered bacteria as biological sensors for arsenic in water, principally for use in detecting arsenic in drinking water in developing countries. A sequence of genes in the bacteria stimulates them to produce acid if arsenic is present above the safe level for human consumption. The change in acidity can be read using existing pH test devices [Royal Academy of Engineering, 2009].
3) Bioremediation tools to process environmental contaminants. Researchers are using knowledge of natural processes to develop micro-organisms that can accumulate and/or degrade substances that are resistant to natural degradation and threaten the environment [POST, 2008]. For example, a team at Berkeley has engineered a strain of Pseudomonas putida (a soil bacterium) that can efficiently degrade an organophosphate compound (commonly used as a pesticide) and use it as a carbon, energy and phosphorus source [Mattuzzi, et al., 2006].
4) New biological production techniques for existing or novel materials and chemicals. Du Pont and Tate & Lyle produce a chemical commonly used in textiles from corn sugar using a synthetic biology process [POST, 2008]. There has been considerable interest in engineering organisms to produce hydrocarbons and many early potential applications of synthetic biology may be in the area of biofuels [Rodemeyer, 2009]. The University of California at Berkeley recently received $500 million from BP for bioenergy research in a deal that has been the subject of controversy [ETC Group, 2008].

Although most of the research taking place today is far from commercial exploitation, these examples demonstrate the potential benefits of synthetic biology.

In considering emerging risks under the headings in the remainder of this section, it is important also to pay attention to potential benefits and to make a balanced assessment of the benefits foregone in devising alternative approaches to risk governance, or in setting standards for research practices or for product or process safety. Going beyond the inherent properties of synthetic biology products and processes, an important consideration is the extent to which synthetic biology could render current risks (and associated risk governance systems) obsolete.

2.1 Biosafety risks

Present research with synthetic nucleic acids is, in most cases, considered as presenting biosafety risks that are comparable to those associated with recombinant DNA research. Current regulatory systems may be able to cope with many health-related applications of synthetic biology, but one concern is whether such systems can handle the risks associated with rapid vaccine development, or indeed whether they can reduce the risks associated with current methods of vaccine development.

One environmental biosafety risk that is currently hypothetical, but likely to give rise to public concerns and pressures on regulators, could arise from the presence in the open environment of novel synthetic organisms with unintended detrimental effects [de Vriend, 2006]. This risk could arise from the intentional introduction of living organisms for commercial or research purposes, as for example in soil bio-remediation, or from accidental escapes of organisms being developed in commercial-scale contained facilities or in laboratories. Living, self-propagating micro-organisms could be particularly difficult to control in themselves, and they can also evolve and exchange genetic material across species boundaries.

The flexibility of synthetic biology means that micro-organisms could be created with unpredictable emergent properties [Tucker and Zilinskas, 2006], making the risks of deliberate or accidental introduction into the environment difficult to assess in advance [de Vriend, 2006]. 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 been suggested that synthetic organisms could be made to be dependent on nutrients not found in nature [de Vriend, 2006], or that they could have built-in safety features such as 'fail-fast' mechanisms [Endy, 2005]. Here, the argument is that making synthetic organisms less natural will make them less risky.

To date, consideration of future biosafety risks seems somewhat simplistic, and is based only on comparisons with existing areas of biotechnology development that do not share synthetic biology's potential for synergistic interactions. The appropriate risk governance of synthetic biology will require that thinking extends beyond these current boundaries.

2.2 Biosecurity risks

Biosecurity is the synthetic biology-related risk of greatest concern in the US. Although this has a lower profile in Europe, the 'dual-use dilemma' is a recurrent theme in life sciences research [Royal Society, 2009]. The potential for malevolent misuse of synthesised organisms has led to concerns that 'bio-hackers' [Tucker and Zilinskas, 2006] could create novel pathogens or recreate known pathogens or perhaps make them more virulent. Such concerns began with 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 2005 the virus that was responsible for the 1918 influenza pandemic was synthesised [Tumpey, et al., 2005]. Carlson [2007] suggests that the 'coming bio-economy' will be based on inexpensive and highly-distributed technologies, which means that restricting access or practice will become increasingly untenable.

Although experts argue that there are currently 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 online explanations of molecular biology techniques, combined with the ease of purchasing a DNA sequence synthesised 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]. A recent news report in *Nature* [Hayden, 2009] suggests an international 'standards war' is emerging in the gene-synthesis industry over the screening of orders for hazardous materials, with two different sets of companies proposing different standards. In the absence of policy or guidance from governments or action by regulators, industry may move towards a minimum set of standards.

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]. An excessive emphasis on biosecurity risks is counter-productive even from a security perspective, since constraining the dangers without impeding scientific research and innovation is as critical to national security as it is to economic prosperity [NRC, 2009]. Indeed, some applications of synthetic biology could assist in counteracting potential abuses [Mukunda, et al., 2009], for example through improved development and production of vaccines to counteract pathogens and novel methods of surveillance for bioweapons.

The challenge is to make biosecurity a positive and enabling framework for innovation, within which biology that is recognised as safe, secure and beneficial can be developed. Synthetic biologists can help governments and regulators to find ways to prevent other actors from using the technology for illicit purposes [Mukunda, et al., 2009] since neutralising a threat will require a speedy response. While the biological equivalent of an anti-virus firewall used in IT systems may not be a realistic prospect in the near term, legitimate researchers could be enabled to maintain a lead in the development of tools and applications to combat malicious usage.

2.3 Intellectual property and trade

Intellectual property rights and trade impacts are closely-linked issues which are influential in shaping public perceptions and acceptance of a technology. Public and stakeholder pressures arising from concerns about trade (often linked to concerns about 'global justice' and the North-South divide) tend to reinforce demands for more regulation and stricter governance. Policymakers' responses to these pressures can have counter-intuitive implications for innovation. A strict intellectual property regime, combined with high regulatory barriers to entry, leads to a sector being dominated by large companies. The governance of new areas of development in life sciences has in the past led to an increasingly onerous and lengthy regulatory process which adds to the obstacles facing new market entrants, and can eventually stultify the entire innovation system.

Biomedical technologies focus strongly on patents as a means to protect the very large amounts of financial investment needed to comply with regulatory regimes and bring a product to market [Maurer, 2006]. Patents that present overly-broad and ambitious claims, such as on foundational technologies and biological functions encoded by BioBricks, could inhibit research in synthetic biology. Craig Venter's team has filed for a patent on the smallest genome

needed for a living organism [Glass, et al., 2007]. The patent application also claims any method of hydrogen or ethanol production that uses this minimal genome. The Venter application is considered unlikely to be granted on the grounds of lack of enablement. Another company, Scarab Genomics, has a patent on a minimised E. coli genome [Blattner, et al., 2006] which, some argue, may prove to be more important [Nature Biotechnology, 2007].

Another dimension to the IP issue comes from the 'open source' approach that is modelled on the open software movement in information and communication technology [Heller and Eisenberg, 1998]. However, there are concerns about whether this model will be sustainable when it is translated over to life sciences or whether other ways of organising intellectual property will need to be developed [Rai and Boyle, 2007; Henkel and Maurer, 2007]. As synthetic biology moves towards commercial viability, it may become harder for synthetic biologists to maintain an open source approach. If so, there will then be a role for antitrust and competition law in creating and enforcing openness and access [Lemley, 2007].

Different IP cultures and worldviews are difficult to reconcile when stakeholder interests and incentives are not aligned. A key issue for risk governance is whether the synergisms enabled by open sharing can create incentives for rapid diffusion more effectively than the patent system, and what impact the framing of the debate as 'open source versus commercialisation' could have on public perceptions of the technology. Worries about potentially restrictive patents in synthetic biology, and attempts to create an open source ethos in synthetic biology research (if not the development of downstream products) are closely linked to concerns about the monopolisation of the field by commercial companies [ETC Group, 2007].

Oye and Wellhausen [2009] suggest that synthetic biology may be more vulnerable than most emerging technologies to the 'anti commons' problem, which has become shorthand for a broad class of issues where ambiguity in property rights both deters research and innovation and limits the utilisation of new discoveries. A range of different IP rights converge in synthetic biology and, in many cases, it is the 'bundle' of rights that matters rather than patents alone. There may be broad agreement on common ownership of parts, standards, and methods for basic research, and on private ownership of designs of assembled devices and systems close to commercialisation.

The framework of the 'semi commons' [Smith, 2000] has been suggested as a lens with which to view synthetic biology. This concept captures the dynamic interaction between private and shared uses of the same resources at different scales, and the potential for shifting demarcations over time [Fennell, 2009]. The current uncertainty over how such demarcations should be made may be typical of emerging technologies at such an early stage of development. Rather than representing a governance deficit, the time lag before some of the legal issues are resolved could lead to better outcomes than would result from decisions about IP frameworks being made too far in advance.

2.4 Ethical issues

The intellectual property issues raised by synthetic biology are closely linked to ethical concerns about creating and owning life. 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, but

this is also more likely to make them publicly controversial developments attracting strong, ideologically-based opinions. 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], accompanied by inventions such as Salmonella that produce spider silk, challenge everyday understandings of nature and the place of humans within it.

Synthetic biology raises questions about where the line should be drawn between what is natural and what is not. The Rathenau Institute suggests introducing a measure of 'artificialness' of synthetic systems to assist regulation. One question here is whether risk governance should distinguish between totally synthetic organisms and novel organisms based on existing organisms [de Vriend, 2006]. However, this distinction may be difficult to make in practice. It may also be unhelpful as, from the perspective of public concerns, the perceived novelty of the organism is unlikely to be related to the degree to which it is 'synthetic' and, likewise, the risks which it may present will be related to the nature rather than the degree of modification. This also raises the wider issue of whether risk governance and regulation should be based on products or processes.

Concerns about creating life may not be related to religious and philosophical anxieties about allowing humans to 'play God' [Cho, et al., 1999] but to a set of political concerns about the dependability of organisations and regulatory systems in managing risk from synthetic organisms. Yearley [2009] cautions that a focus on ethics but not politics could prove counter-productive, since the review apparatus comes to resemble a 'legitimatory cloak' for the science. He argues for a form of societal and ethical review that is broader than a template based only on bioethical principles allows. A sophisticated comparative understanding is needed in this area. Mandel, et al. [2008] found that hierarchical, conservative, and highly religious individuals in the US who are normally sceptical of claims of environmental risks are the most concerned about synthetic biology risks. The authors suggest that selective risk scepticism and risk sensitivity can convey a cultural commitment to traditional forms of authority. Clearly, issues of trust and authority are key factors in the risk debate around synthetic biology.

With an issue such as synthetic biology, which raises questions of an ideological nature, it is unlikely that there will ever be a society-wide consensus. Thus, decision-makers responsible for dealing with those questions must also give careful consideration to the circumstances under which the interests and values of one societal group should be allowed to over-ride those of others.

3. Avoiding risk governance deficits

The concept of risk governance deficits – deficiencies or failures within risk governance processes or structures – complements the use of the IRGC risk governance framework with an analytical tool designed to identify weak spots in how risks are assessed and managed [IRGC, 2009]. IRGC has identified 23 deficits as important because of their propensity to recur frequently over time and to impact on the effective governance of a wide range of risk types in many varying contexts and circumstances, with potential severe consequences. The deficits relevant to synthetic biology are summarised in Appendix 1.

The primary reasons for public investment in synthetic biology include improving our understanding of living systems and processes, the desire to establish a new high value-added life science industry sector or to contribute to those which already exist, and to develop potential solutions to currently intractable societal problems. However, while a lot of investment is made with these public benefits in mind, part of the governance problem is a failure to think through how benefits will be delivered [Tait, 2009a]. The success or failure of any innovative science, and the products and processes developed from it, will depend on the outcomes of a complex series of interactions among:

- Scientists, professionals and engineers developing the technology;
- Policymakers and regulators involved, either in promoting science and innovation, or in regulating its products; and
- Citizens and advocacy groups with concerns, either positive or negative, about the implications of the technology concerned.

Such are synthetic biology's potential benefits, potential risks, and speed of emergence of new developments, that it is a prime case for concerted international consideration of all three of the above components. The challenge is to identify and avoid governance deficits in the key areas of technology development; policy and regulation; and public and stakeholder engagement.

3.1 Technology development

At the present time most synthetic biology developments involve simple single-celled organisms like the bacterium E. coli or the yeast S. cerevisiae. In August 2009, researchers reported the successful transformation of one bacterium into a different strain. This was achieved by transferring the entire bacterial genome of the first strain into a second, related bacterial strain [J. Craig Venter Institute, 2009]. Many researchers anticipate the development of entirely artificial cells and the eventual expansion of synthetic biology to encompass multicellular organisms, which would greatly increase system complexity [Mohr, 2007]. The integration of different modules from different systems becomes a key challenge as developers build such complex entities.

In the medical field, for example, synthetic biology could aid the development of diagnostics, vaccines and cell-based or pharmacological therapeutics, but pharmaceutical companies are reluctant to invest in the technology without evidence of utility for human health. The extension of synthetic biology to target complex physiology will need an appreciation of system dynamics. Systems biology, which provides a higher-level understanding of physiology, is well-placed to provide this [Henney and Superti-Furga, 2008], particularly in the biomedical sector. Indeed, some commentators suggest that what is special

about synthetic biology is that it is informed by a systems biology perspective [Barrett, et al., 2006].

In the future, the research base for synthetic biology will change and develop, drawing selectively on many other areas of scientific research in response to new knowledge and new areas of potential application. Each such shift will open up new potential public benefits, create new commercial opportunities and raise different challenges for risk governance.

It is impossible to predict the outcomes of basic research projects currently under way. Equally, once the scientific research base for a potential new development exists, there will be many twists and turns in the path to the final product [Tait, 2009b]. It is therefore important both not to waste regulatory effort on developments which will not stand the test of time, and to remain alert to potential risk governance deficits arising from future development.

3.2 Policy and regulation

Regulation can shape the future development of the science, guide product development in certain directions, and either generate or diminish conflict between stakeholder groups. For synthetic biology a strong case can be made for international dialogue on the appropriate role of regulatory oversight. The difficulties that arise from piecemeal and divergent national approaches to the regulation of innovative technology in life sciences were very apparent in the case of GM crops, and this experience offers lessons for synthetic biology. However, these lessons are more complex than merely 'more and earlier stakeholder engagement' [Tait, 2009b]. Different issues arise (i) for the early-stage regulation of fundamental research in synthetic biology and (ii) for the regulation of the products of synthetic biology as they come to trial and market. Ideally, both should be co-ordinated at an international level.

At the product regulation stage, the joint goals of delivering public benefits from new technology, avoiding unnecessary risks, and allowing commercially-viable activity can be difficult to reconcile. An aspiring innovative technology such as synthetic biology has to get a lot of things right, and in the right order. For example, first it has to make the science work and to develop useful products that at least some people will want to buy; it has to generate positive market expectations some time before products are ready to appear on the market, but at the same time avoid the accusation of over-hyping the technology; it has to collaborate in the development of regulatory systems that will effectively control for foreseeable risks; and, it has to be ready with effective responses to the emergence of unexpected risks or to illegal behaviour by rogue developers.

This degree of planning and sequential activity, co-ordinated internationally, has so far eluded those involved in the governance of innovative technology. A key challenge is how to co-ordinate the planning and collaboration required for effective governance of an innovative technology while encouraging heterogeneity in a field with many different techniques and applications. Regulators are just one of the groups which need to be involved in this activity. Others include insurance companies and NGOs, who could both play a major role in identifying a broader spectrum of risks and in developing strategies to manage them.

3.3 Public and stakeholder engagement

In the increasingly active debate around the risks of synthetic biology, there is a strong focus on potential public and stakeholder questions and concerns and how and when to incorporate them into decision-making about future developments [IRGC, 2008]. A call for broader engagement with synthetic biology is found in several commentaries on the field, although product development is in the very early stages [Garfinkel, et al., 2007]. The Royal Society, for example, maintains that 'a range of stakeholders (including publics) should be involved in discussing developments from an early stage' [Royal Society, 2008]. On the other hand, upstream engagement has been described as offering 'compressed foresight' [Williams, 2006], whereby highly uncertain socio-technical prospects are presented as imminent and known, and Tait [2009b] has described a range of risk governance deficits inherent in some aspects of the upstream engagement process itself.

Several ongoing synthetic biology projects attempt to deal directly with societal issues and involve stakeholders and policymakers. In the US, the National Science Foundation (NSF) Synthetic Biology Engineering Research Center (SynBERC) has a human practices 'thrust' (alongside thrusts on chassis, on parts and on devices) and the International Genetically Engineered Machine competition (iGEM) includes a component on ethical and social reflection. There is a European Union (EU) funded project SYNBIOSAFE (Safety and Ethical Aspects of Synthetic Biology) and the Biotechnology and Biological Sciences Research Council (BBSRC) in the United Kingdom (UK) has commissioned its own social and ethical challenges review [Balmer and Martin, 2008]. However, it would be unwise to presume that engagement will, by itself, resolve the societal issues raised by synthetic biology.

Considering the European response to GM crops, failure by those developing the technology to consult with, and explain it to, the public at a sufficiently early stage in its development has been seen as an important contributor to public rejection. This was part of a wider picture that involved intense competition between multinational companies across a range of industry sectors, transatlantic political manoeuvres, and regulatory challenges and counter-challenges. Public values related to styles of food production and the role of new technology, 'tampering with our food' and globalisation were also a major part of the overall picture [Tait 2007].

At least as important for gaining public acceptance of synthetic biology would be having public advocacy groups who strongly support the development of the technology, for example as with the role of patient groups in supporting stem cell research. Having scientists tell a good-news story is not enough; in life sciences you seem to need public advocates to say 'We want it!' long before the products emerge in any market place.

IRGC's project will consider how such engagement dilemmas can be resolved to deliver good governance, as defined by public, commercial and national interest criteria.

Conclusions

As a nascent technology, synthetic biology must prove itself through the development and commercialisation of constructive practical applications. The market potential for synthetic biology products is considered to be high and growing rapidly. Although the field is expanding quickly, the commercial development of useful applications is hampered by an uncertain policy environment and the lack of concrete proposals to resolve societal challenges and manage emerging risks. In order to realise its full economic and social potential, synthetic biology needs to be subject to partnerships and international collaborations between technology developers, policymakers, regulators, and public and stakeholder groups.

There have been numerous recent conferences and reports on synthetic biology which have identified a number of recurring concerns but progress on resolving these has slowed. IRGC hopes to develop recommendations that will transcend the current impasse and move the debate forward. The discussion points cited earlier (see Introduction) have been chosen on the basis that there is a need to think through how the benefits that are promised by synthetic biology will be delivered in practice. Risks and benefits need to be considered jointly in forward-looking and dynamic governance systems to enable innovative developments that meet societal expectations and legitimate demands for product quality and safety.

With its project on the risk governance of synthetic biology, IRGC intends to develop recommendations for policymakers and regulators that will help them avoid making irrevocable commitments to particular forms of regulation that will lead to unforeseen downstream risk governance deficits.

Appendix

Summary of Potential Risk Governance Deficits

This list of risk governance deficits may be used as a checklist to evaluate a risk governance process, although it is not exhaustive and some deficits are interlinked.

Cluster/sub-cluster	Potential Deficit	Short description	Relevance to Synthetic Biology
A: Assessing and Understanding Risks			
Gathering and interpreting knowledge	A1: Early warning systems	Missing, ignoring or exaggerating early signals of risk	Early warning signals have been identified. There is no evidence of missing or ignoring early signals but there may be some exaggeration of emerging risks in relation to bio-safety and bio-security.
	A2: Factual knowledge about risks	The lack of adequate knowledge about a hazard, including the probabilities of various events and the associated economic, human health, environmental and societal consequences	Highly relevant. There is no factual knowledge about hazards and there is an even bigger gap in knowledge about the products that will be developed using the technology.
	A3: Perceptions of risk, including their determinants and consequences	The lack of adequate knowledge about values and interests and therefore about how risks are perceived by stakeholders	Relevant. There is little knowledge about public perceptions although public activist groups have expressed concerns about risks. Alongside the hype and exaggeration associated with any emerging technology, there is also evidence of 'downplaying' risks which, in the past, served to exacerbate public concerns in relation to genetically modified foods.
Disputed or potentially biased or subjective knowledge	A4: Stakeholder involvement	Failure to adequately identify and involve relevant stakeholders in risk assessment, in order to improve information input and confer legitimacy to the process	This is a potentially relevant future deficit, particularly regarding the need to involve stakeholders with relevant factual knowledge.
	A5: Evaluating the acceptability of the risk	Failure to consider variables that influence private risk appetite and public risk acceptance	This is a potentially relevant future deficit and its resolution is essential for the future viability of synthetic biology
Knowledge related to systems and their complexity	A7: Understanding complex systems	A lack of appreciation or understanding of the potentially multiple dimensions of a risk and of how interconnected risk	Highly relevant. There is a complex set of interactions between how the technology evolves and how the associated risks and their secondary impacts

		systems can imply complex and sometimes unforeseeable interactions	are understood and assessed.
	A8: Recognising fundamental or rapid changes in systems	Failure to re-assess in a timely manner fast and/or fundamental changes occurring in risk systems	This is a potentially relevant future deficit which could apply to fundamental or rapid changes in the underlying science and to the systems with which the science and its applications interact.
Knowledge and understanding are never complete or adequate	A10: Assessing potential surprises	Failure to overcome cognitive barriers in order to imagine events outside of accepted paradigms ("black swans")	Relevant in terms of both positive and negative surprises. The more that the debate about synthetic biology seeks to attribute boundaries to the extent of benefits and risks, the greater the risk of a potential surprise becomes.
B: Managing Risks			The following potential deficits need to be taken into account in risk management. Few are present at the current time, but they will need to be overcome in the future.
The preparation and decision of risk management strategies	B2: Designing effective risk management strategies	Failure to design policies that adequately balance policy alternatives	Highly relevant, as synthetic biology has no track record of risk assessment on which to base effective risk management strategies.
	B3: Considering a reasonable range of risk management options	Failure to consider a reasonable range of risk management options (and their negative or positive consequences) in order to meet set objectives	Risk management of synthetic biology should not be based solely on comparisons with existing areas of biotechnology development that do not show the potential for synergistic interactions that underlie many of the expected benefits.
	B4: Designing efficient and equitable risk management policies	Inappropriate risk management occurs when benefits and costs are not balanced in an efficient and equitable manner	Extremely difficult to overcome this deficit at the current time, as there is an absence of hard data on both benefits and costs.
	B6: Anticipating side-effects of risk management	Failure to anticipate, monitor and react to the outcomes of a risk management decision in the case of negative side effects	Successful risk management of synthetic biology requires anticipation of both the intended and unintended consequences of decisions, and rigorous monitoring of the effects of decisions. This includes benefits foregone in devising alternative approaches to risk governance.
	B7: Reconciling time horizons	An inability to reconcile the time frame of the risk with the time frames of decision-making and incentive schemes	The refinement and optimisation of foundational tools and techniques is vital for application development in synthetic biology. There is a need to reconcile time horizons between funding and support for tools for the long-term development of synthetic biology and funding for applications that offer near-term returns.
	B8: Balancing transparency and confidentiality	Failure to balance two of the necessary requirements of decision making: transparency, which can foster stakeholder trust, and confidentiality, which can protect security and	In synthetic biology, where there is incomplete factual knowledge about hazards, it may be difficult to achieve an appropriate balance between transparency and confidentiality in risk communication. For example, the drive for transparency in early

		maintain incentives for innovation	'upstream engagement' exercises may result in incomplete or non-consensual risk information being presented as fact.
Formulating responses, taking action and resolving conflicts	B1: Responding to early warnings	Failure of managers to respond and take action when risk analysts have determined from early signals that a risk is emerging	Formulating risk management strategies too early is also a deficit as circumstances may change and anticipated risks may never emerge or new risks may emerge.
	B11: Dealing with commons problems and externalities	A lack of understanding of the complex nature of commons problems and consequently also of the specific risk management tools required to address them	Commons problems are particularly relevant in relation to intellectual property in the context of synthetic biology. Identifying externalities is important to enable risk transfer capacity from the insurance industry.
	B12: Managing conflicts of interests, values and ideologies	A conflict may be negotiable or irreconcilable, and risk managers must have the capacity to distinguish between the two	GM foods raised issues that led to irreconcilable conflicts of interest in Europe. Synthetic biology has the potential to do the same, and elsewhere.
	B13: Acting in the face of the unexpected	Insufficient flexibility in the face of unexpected risk situations	Effective risk governance of synthetic biology lessens the likelihood of mistakes but also requires preparation for the mistakes that may happen with some developments. Risk managers must be able to act in the fact of such unexpected crises or emergency situations. This requires the flexibility and organisational capacity to make decisions in situations of uncertainty.
Organisational capacities for responding and monitoring	B5: Implementing and enforcing risk management decisions	Failure to muster the necessary will and resources to implement risk management policies and decisions	In the absence of policy/regulator action or guidance from government, the synthetic biology industry may be moving towards a minimum set of safety standards. There must be a mechanism to ensure that complying companies are not penalised by competitors not bearing the costs of compliance.
	B9: Organisational capacity	Failure to build or maintain an adequate organisational capacity to manage risk	A key issue in synthetic biology is identifying stakeholders and knowing which methods of stakeholder engagement are appropriate for a particular risk management issue. IRGC [2005] has described three dimensions to organisational capacity that need to be developed within an organisational 'risk culture': assets, skills and capabilities.
	B10: Dealing with dispersed responsibilities	Failure of the multiple departments or organisations responsible for management of a risk to act cohesively	The multiple applications of synthetic biology mean that its governance and regulation will be subject to oversight by different product regulators.

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The International Risk Governance Council (IRGC) is an independent organisation based in Switzerland whose purpose is to help the understanding and governance of emerging, systemic global risks. It does this by identifying and drawing on scientific knowledge and the understanding of experts in the public and private sectors to develop fact-based recommendations on risk governance for policymakers.

IRGC's goal is to facilitate a better understanding of risks; of their scientific, political, social, and economic contexts; and of how to manage them. IRGC believes that improvements in risk governance are essential if we are to develop policies that minimise risks and maximise public trust in the processes and structures of risk-related decision-making. A particular concern of IRGC is that important societal opportunities resulting from new technologies are not lost through inadequate risk governance.

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