Policy Brief

Guidelines for the Appropriate Risk Governance of Synthetic Biology

international risk governance council

Abbreviations used in the text:

ATC	Air Traffic Control
BWC	Biological Weapons Convention
CCS	Carbon Capture and Storage
COP	Conference of the Parties
CBD	Convention on Biological Diversity
DNA	Deoxyribonucleic acid
ENMOD	Environmental Modification Convention
EPA	US Environmental Protection Agency
EU	European Union
FAO	UN Food and Agriculture Organization
FDA	US Food and Drug Administration
GATT	General Agreement on Tariffs and Trade
GM	Genetically modified
GMO	Genetically modified organism
GURTs	Genetic use-restriction technologies
IASB	International Association for Synthetic Biology
ICGEB	International Centre for Genetic Engineering and Biotechnology
ICT	Information and communication technologies
IP	Intellectual property
IRGC	International Risk Governance Council
LMO	Living modified organism
NIH	US National Institutes of Health
NGO	Non-Governmental Organisation
OECD	Organisation for Economic Co-operation and Development
RNA	Ribonucleic acid
SRM	Solar Radiation Management
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UN	United Nations
US	United States of America
USDA	US Department of Agriculture
WTO	World Trade Organization

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Preface

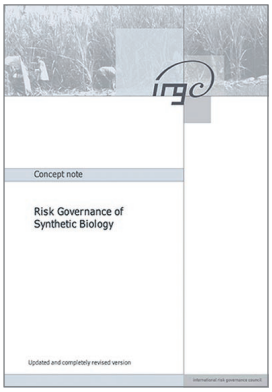
The International Risk Governance Council (IRGC) aims to improve the governance of emerging, systemic risks through helping decision-makers, particularly governments, to anticipate and understand such risks and the options for managing them before they become urgent policy priorities. IRGC's risk governance recommendations are communicated to policymakers to inform their work in designing policies and regulations, drawing their attention to aspects of the issue that might be inappropriately neglected or ignored.

IRGC's core process in working on synthetic biology comprised the following:

- Analysing the scientific and technological developments and their associated opportunities and risks, as well as the institutions and risk governance structures and processes that are currently in place for assessing and managing these;
- Identifying potential issues of concern at the earliest possible time;
- Identifying and understanding risk governance deficits which appear to hinder the efficacy of the existing risk governance structures and processes;
- Developing guidelines that address these deficits.

This policy brief on synthetic biology is part of IRGC's work on the risk governance of innovative technologies. Previous IRGC projects on such technologies include work on nanotechnology, carbon capture and storage (CCS) and solar radiation management (SRM). IRGC has identified synthetic biology as a new technology for which there may be significant deficits in risk governance structures and processes, in part because of uncertainties about the directions that the technology might take.

Of particular concern to IRGC is that important social and economic benefits offered by innovative technologies are not compromised by inadequate risk governance, which could result in unduly restrictive regulation. Synthetic biology has the potential to provide potential solutions to some of the challenges that the world faces in the fields of environmental protection (e.g., detecting and removing contaminants), health (e.g., diagnostics, vaccines and drugs) and energy and industry (e.g., biofuels). At the same time, IRGC aims to ensure that risks are not underestimated by those developing the field, and it recognises that some potentially severe risks might demand the recommendation of new precautionary measures.



In October 2009, IRGC organised a multi-stakeholder workshop in Geneva entitled 'Risk Governance of Synthetic Biology', at which many of the issues raised in this policy brief were discussed. It was attended by 24 participants from the United States (US), Canada, China and many European countries, including experts from academia, governments, non-governmental organisations (NGOs) and the private sector. An IRGC concept note [IRGC, 2009b] was published as a briefing document for this workshop (available on IRGC's website, www.irgc.org.)

This policy brief does not intend to propose a wide and exhaustive review of the field of synthetic biology, but to reflect and elaborate on the discussions at the workshop and subsequent risk governance developments in the field. Moreover, IRGC recognises that governments, industry and other sectors are already seeking ways to resolve the uncertainties associated with the risk governance of synthetic biology. The aim of this policy brief is to provide guidance to decision-makers to achieve this goal.

Executive summary

Synthetic biology is a new scientific discipline emerging from the convergence of biotechnology, genetics and advances in the systems-scale fundamental understanding of living organisms, along with aspects of physics, chemistry and computer science. It is predicated on an engineering approach to biology: an understanding of the mechanisms by which living cells function, coupled to the availability of tools for intervening in and altering these functions at the genetic level – or even for rebuilding some biological entities and processes from scratch using chemical methods. This is making it possible to 'design' life in much the same way as we might design an automobile or an electronic circuit. Instead of relying on haphazard tinkering or small-scale genetic modification to direct living systems towards new objectives, it may become possible to radically alter what cells and organisms can achieve in a rational, systematic way.

This discipline offers great promise in areas such as health and medicine, chemical manufacturing and energy generation and conversion. But there are attendant risks, not just in terms of the safety of engineered or 'synthetic' organisms but also in a broader sense of how such a powerful technological capacity might transform the environment and society, affect economic development, and alter existing power relationships between basic science, industry, consumers, governments, and nations.

This document develops the concept of *appropriate risk governance:* one that is *enabling* of innovation, *minimises* risk to people and the environment, and *balances* the interests and values of all relevant stakeholders. It provides suggestions for how an appropriate trade-off between these factors might be attained, and argues that regulation must not simply prohibit or restrict any development for which potential risks can be adduced but should seek the right balance between potential social benefits and dangers – even though these may both be uncertain and speculative at this early stage in the field's evolution.

Some of the near-term research in and applications of synthetic biology will be already governed by existing regulatory frameworks. However, these are not always mutually compatible or consistent, and there are some areas of potential conflict between different aims and priorities. Moreover, such frameworks have shortcomings and loopholes when applied to some of the potential outcomes of synthetic biology – for example, safety risks for genetically modified organisms might not be best judged from the behaviour of the parent organism, once modification is pursued at the 'deep' systemic level that synthetic biology should enable. The objective here is to seek ways of addressing such risk governance deficits that allow a voice to all relevant stakeholder groups.

With this in mind, the policy brief offers a series of guidelines for policymakers involved in regulating or otherwise guiding or affecting the course of synthetic biology. The guidelines address factors ranging from biosecurity risks in the fundamental research and development stages, to the question of how to balance transparency against the need for commercial confidentiality. Among the key considerations are that new regulations should not repeat the mistakes of existing ones, that they should take care not to foreclose future advances that could be of significant social benefit, and

that there should be an international effort to standardise procedures and regulations while recognising that particular regions and nations may have specific requirements or vulnerabilities.

Furthermore, an effective approach to risk governance of synthetic biology must be capable of evolving as scientific and technical knowledge expands and as lessons are learned about the most appropriate forms of regulation and governance: for example, if and how the technology can regulate itself, and how intellectual-property frameworks might best stimulate innovation in a sustainable way. This requires flexibility in the face of uncertainty about the eventual applications, products, processes, benefits and risks, while recognising the dangers of irreversible harms.

Introduction

Synthetic biology is one of a range of developments in science and technology that IRGC has identified as raising challenges for risk governance. Building on developments in the life sciences over the past several decades, in essence it involves the repositioning of biology as an engineering discipline, so that living organisms become amenable to rational design and synthesis. Advances in biotechnology and genetic engineering in the past several decades have presaged the emergence of this new field, but it now promises to take their approach to a new level in our ability to plan, control and manipulate living systems.

Synthetic biology represents just one illustration of how rapid advances in the life sciences are opening up a host of potentially dramatic new applications in medicine and healthcare, agriculture, industrial chemistry and energy production, among other fields. These developments also introduce possible new risks that are necessarily speculative and hard to assess. Yet there is often pressure for decision-making about risk governance and regulation to begin many years before actual products appear on the market. Errors of judgement at these early stages can have a major impact on the trajectory of a new technology, as well as on the effectiveness and efficiency of risk governance itself [Tait, 2007].

Such decisions, taken in a context of high uncertainty, also affect the investment environment for innovative technology. Complex regulatory systems give rise to long lead times for new products and thus to the need for long-term investment to support development. But investors are reluctant to commit funding without knowing what future regulatory systems will look like – and thus what the likely costs of compliance will be.

These pressures on policy-makers to take early decisions about risk governance, based on incomplete or merely speculative information about the scale of the actual risks, make it difficult to apply conventional risk governance approaches. There is a need for flexibility, including a capacity to modify early decisions in the light of emerging evidence about risks and opportunities. Such an adaptive approach must, however, also acknowledge the need to identify and avoid potential irreversible harms, which cannot be ameliorated by later adjustments in policy.

The concept of risk governance that we adopt here takes a broad view of risk. It includes both what has been termed ‘risk management’ or ‘risk analysis’, as well as considering ‘how risk-related decision-making unfolds when a range of actors is involved, requiring coordination and possibly reconciliation between a profusion of roles, perspectives, goals and activities’ [IRGC, 2005]. Our goal is to develop guidelines for appropriate risk governance of innovative technology that integrate in-depth, independent understanding of three key areas and their interactions: (i) strategies for scientific research and innovation strategies in the public and private sectors; (ii) regulation and governance of new technology; and (iii) the interests and perspectives of the public and other stakeholders [Wield, 2008]. It has long been understood that decisions on risk regulation are determined by interactions among these three constituencies; here

we aim to assess their outcomes in terms of societal benefits delivered or foregone. The target audience for this policy brief includes policymakers, politicians, companies and researchers with interests in biotechnology, energy, health, agriculture, climate, environment, trade and security.

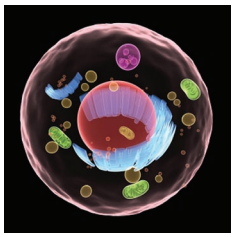
Policy-makers and regulators can increasingly be seen as shaping, rather than responding to, innovative science and technology. They may influence the future development of the science, guide product development in certain directions, and either generate or diminish conflict between stakeholder groups. The guidelines proposed here focus on what policy-makers and regulators can achieve in this context. While we cannot predict how the field will evolve, some regulatory rethinking may be needed if synthetic biology is to grow into a mature, safe and accepted set of technologies, with innovative and socially valuable products brought to market [Rodemeyer, 2009].

Section 1 of this policy brief outlines the scope and meaning of synthetic biology, and Section 2 describes current developments and potential applications. Section 3 considers the associated risks, and Section 4 outlines the existing regulatory frameworks for handling these and identifies potential risk governance deficits. In Section 5 we consider the issue of appropriate risk governance of synthetic biology and suggest approaches or guidelines for risk assessment and management that could enable the potential benefits of synthetic biology to be delivered while avoiding or minimising associated risks and ensuring proper accountability. Section 6 then proposes a set of guidelines to support policy decision-making. Two previous concept notes [IRGC, 2008; 2009b], and also an IRGC workshop involving diverse experts in synthetic biology, have provided background material.

1. What is synthetic biology?

Synthetic biology applies the principles of engineering to living organisms, regarding them as systems that are amenable to design and fabrication for predictable and closely specified functions. By tailoring the 'parts' of an organism – the genetic instructions, the molecules and molecular assemblies, and the interactions between different genes, molecules and cells – it aims to create organisms that function and behave in ways quite different from the natural species on which they are based.

Throughout the twentieth century, cell biologists have steadily characterised the molecular components of life in increasing detail. It is apparent that life arises from the interactions of these parts: genes encoded in DNA, proteins encoded in genes, as well as cellular compartments, ions and other substances in the cell fluid (cytoplasm), small RNA molecules also encoded in the genome, and other components. How those interactions are orchestrated remains one of the big questions of molecular biology, in particular how information and organisation are transmitted throughout a hierarchy of size scales from individual molecules to the whole organism.



A typical animal cell with its specialised compartments

At the same time, biologists have sought to intervene in and to modify these interactions, changing an organism's function and physiology – to influence human health, for example, or to alter the properties of agricultural crops, or to confer useful technological behaviours on micro-organisms. These efforts have resulted in a view of life's mechanisms that owes a strong debt to engineering. The use of terms such as bioengineering and genetic engineering testifies to the way the engineering paradigm, which invokes principles of design and control, has already imposed itself on the life sciences. Nonetheless, on the whole our interventions in biology have tended to be directed towards either crude 'sabotage' of the processes of life – preventing micro-organisms or cancer cells from proliferating, say – or minor, ad hoc modifications of existing behaviours in which much of the 'mechanics' remains a 'black box'.

Synthetic biology aims to apply basic design principles in order to produce predictable and robust biological systems with novel functions and properties that do not exist in nature

Synthetic biology now aims to use the engineering paradigm for much more dramatic and systematic intervention in biology: to applying basic design principles in order to produce predictable and robust biological systems with novel functions and properties that do not exist in nature. It has been described as 'the engineer's approach to biology' [Breithaupt, 2006] and some synthetic biologists claim that their aspiration is to make biology into an engineering discipline [Endy, 2005; Arkin and Fletcher, 2006], something that requires a reductionist understanding of biological complexity [Pleiss, 2006]. This engineering approach to biology, combined with synthetic biology's heavy reliance on information technologies, makes the field intrinsically interdisciplinary. Although some researchers approach synthetic biology as a 'discovery science' – a tool for investigating how nature works – it is ultimately likely to become a manufacturing technology, offering new synthetic routes to such things as medicines, new materials and fuels, environmental or physiological sensors, and micro-organisms that clean up pollutants.

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Several of the fundamental scientific issues and current applied objectives of synthetic biology overlap with those in other, more mature fields, especially *biotechnology and*

There is no consensus about where the boundaries of synthetic biology lie or what form it might most productively take

systems biology. Traditionally, biotechnology involves the manipulation of biological molecules, cells or whole organisms to address technological challenges. But the degree of modification involved has tended to be small and often based on a strongly empirical approach that does not redesign an organism or component at a deep level. For example, there are now well developed ways to introduce genes from one species into the genomes of another and to stimulate the expression of those foreign genes to produce an excess of the protein product. But when a naturally synthesised compound involves the coordinated action of many genes, these techniques struggle to achieve the required coordination in time and space, in part because the interactions of genes are poorly understood. This limits the scope of what biotechnology can do.

It is hoped that much of the understanding needed for more dramatic interventions and redesign of biological systems will come from the discipline of systems biology [Ideker, 2004; Kitano, 2002]. This involves the mapping of pathways and networks of interaction between genes, proteins and other biomolecular components, so as to ascertain the 'logic circuitry' of natural organisms at the level of cells and sub-cellular compartments, tissues and the whole organism. While cell and molecular biology and genetics have been largely concerned so far with studying individual components and small groups of them in isolation, systems biology aims to discover how they all fit together in a robust, functional system. As such, it should provide the analytical framework in which synthetic biology will operate. Simulation tools and models developed in systems biology will be used in synthetic biology to design and engineer novel circuits or components [Barrett et al., 2006]. In this respect, synthetic biology will involve using systems biology not for 'pure understanding' of natural systems but for practical design of semi-synthetic, and ultimately perhaps wholly synthetic, ones.

Synthetic biology involves 'tinkering with the whole system instead of individual components'

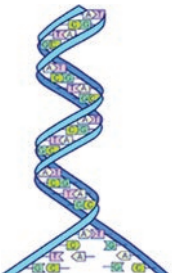
It is important to emphasise that, as is common for an emerging technology, there is no consensus about where the boundaries of synthetic biology lie or what form it might most productively take. It may (and at present, generally does) involve the use and modification of existing organisms; but the *de novo* design and synthesis of organisms is also a goal of some researchers. It is widely believed that the design element should involve the use of standardised parts and follow a formalised design process [Arkin and Fletcher, 2006] that takes it beyond the capabilities of previous forms of genetic engineering. Greater sophistication and complexity might thereby be achieved, offering the ability to move from inserting one gene at a time into an existing biological system to the construction and insertion of whole specialised metabolic units [Stone, 2006]. Synthetic biology is not restricted to using genetic or other biological material from existing organisms [POST, 2008], and involves 'tinkering with the whole system instead of individual components' [Breithaupt, 2006: 22].

Despite the diversity and fluid definitions of synthetic biology, four inter-related research areas can be identified that currently contribute its major themes:

1. Electronic devices are designed to perform in a well-defined way when inserted into any circuit. It is widely thought that the 'gene circuit components' of synthetic

biology, which might for example turn other genes on and off or otherwise modulate their activity, will have to be similarly standardised and reliable, so that they can be simply plugged into circuits and perform predictably. The engineering principles of standardisation, decoupling and abstraction [Endy, 2005] may be adopted to develop biological components that are interchangeable, functionally discrete and capable of being easily and reliably combined in a modular fashion to enable predictable performance in a wide variety of organisms.

2. Genome-driven cell engineering focusses on the design and synthesis of whole genomes – something that has been made possible by advances in chemical technology that will rapidly synthesise long stretches of DNA with a specified sequence (the linear order of the basic chemical units, which encodes genetic information). DNA synthesis is now a commercial technology and offers DNA sequences approaching the length of entire bacterial genomes. To use these constructs for synthetic biology involves either 'editing' the genomic sequences of existing genomes to make a more streamlined and efficient genetic 'chassis', which could provide a platform for making organisms with new genomes [Gibson et al., 2010], or (more ambitiously) the wholly de novo design and synthesis of genomes.



DNA double helix

3. The chemical creation of 'protocells' with lifelike functions such as replication and metabolism, for example by inserting natural or modified biomolecular components into artificial, hollow, cell-like sacs called vesicles [Szostak et al., 2001].

4. More revolutionary research approaches include attempts to create an alternative genetic alphabet with new nucleotides beyond the four found in natural DNA. This could lead to pseudo-biomolecules or even synthetic proto-organisms that are 'invisible' to natural biological systems, as well as suggesting ways of commandeering natural cellular machinery to make substances with a chemical basis different from those found in nature.

Some of these areas are explained in more detail in the next section.

Box: Genetics and molecular biology

In the traditional picture of genetics developed since the discovery of DNA's chemical structure in 1953, the double-helical molecule of DNA encodes in its sequence of chemical building blocks (called nucleotide bases) the information needed to construct a protein molecule from amino acids. Most of these proteins are enzymes that enable biochemical processes in the cell to take place. Each protein is encoded by a separate gene, and the nucleotide sequence of a gene on DNA is translated ('expressed') by cellular molecular machinery into a sequence of amino acids that determines the corresponding protein's shape and function (Figure 1). Thus DNA was seen as a repository of encoded protein structures.

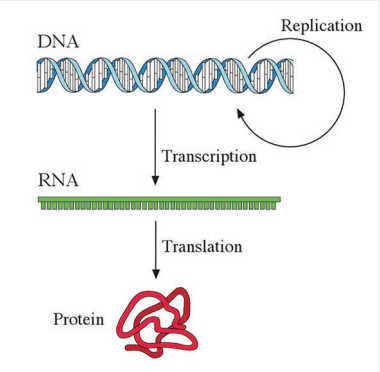


Figure 1: The traditional picture of genetics: how genetic information of DNA is converted, via RNA, into protein structures with a well-defined shape and function.

While this basic picture still holds, it is now complicated in many ways. Most importantly, the interaction of genes and proteins is two-way: some proteins will attach themselves (bind) to DNA to regulate the way other genes are expressed (turning a gene 'on' or 'off', say), so that in effect genes can influence other genes. This cross-talk between genes means that they are linked into a complex network of interactions, leading some researchers to describe genetics using metaphors such as a 'society' of genes, rather than the traditional picture of a 'book' of information (Figure 2). Tracing these interaction networks – in effect, deducing the 'wiring diagram' of the cell's genetic circuitry (Figure 3) – is a key aim of systems biology, and this information is essential if we are to design new 'gene networks' with specific functions, which can be inserted into genomes using the cutting and splicing tools of biotechnology.

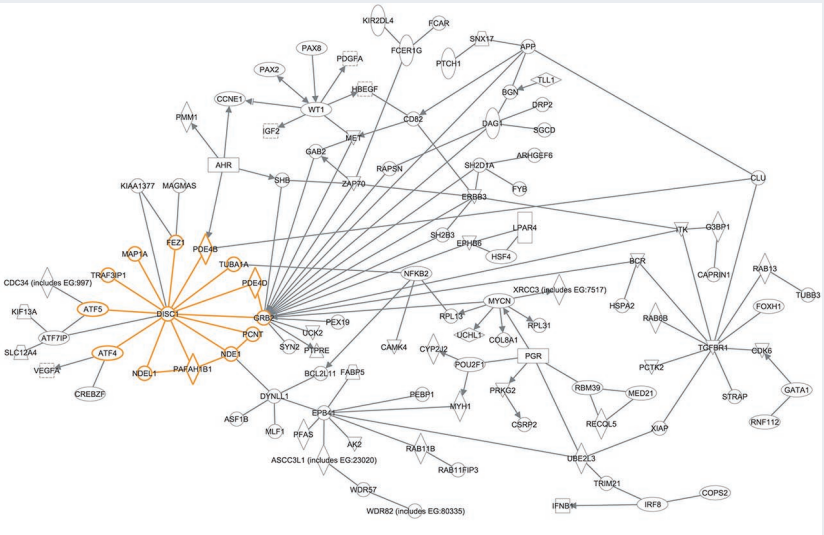


Figure 2: Part of the network of genes related to the function of a protein called DISC1, which plays a variety of roles in the functioning of cells. Most genes and their corresponding proteins are embedded in networks of interaction like this one. [Copyright: © 2009 Hennah, Porteous; original source: http:// www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0004906]

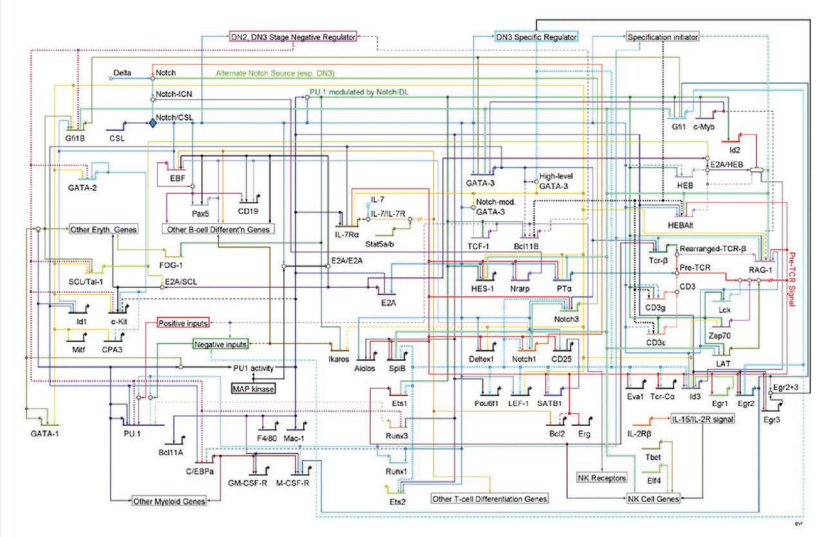


Figure 3: The gene network that regulates the behaviour of T cells, involved in the immune response. The feedbacks and interactions are analogous to those in computer logic circuits [From Georgescu et al., 2008; Copyright (2008) National Academy of Sciences, USA]

2. Current developments in synthetic biology

Parallels have been drawn between today's synthetic biology and the early days of the computer industry. On the one hand, this implies that the technological revolution brought by synthetic biology will be as important as the revolution in information and communication technologies (ICT) brought about by electrical engineering [NEST, 2005; NEST, 2007; Royal Society, 2008]. On the other hand, it suggests that the precise form and content of that revolution is as hard to predict at this moment as it was for ICT in the 1970s.

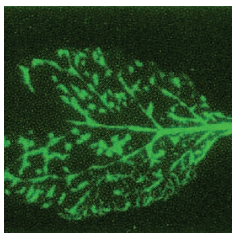
Parallels have been drawn between today's synthetic biology and the early days of the computer industry

Synthetic biology may be able to fulfil many of the promises that traditional biotechnology is still struggling to fulfil

Because of the fundamental change that it proposes to introduce in the methodology for modifying living organisms, synthetic biology may be able to fulfil many of the promises that traditional biotechnology is still struggling to fulfil, in such important areas as biomedicine, the synthesis of pharmaceuticals, the sustainable production of chemicals and energy, and safeguarding against bioterrorism. While traditional biotechnology has had some notable achievements in several of these areas, they have generally been slow and expensive to develop. In contrast, synthetic biology, with its rational, knowledge-based approach to biological design, might attain such goals more quickly and cheaply. It will also enable developments that are not obviously feasible with conventional biotechnological tools, such as the coordination of complex sequences of enzymatic processes in the cell-based synthesis of useful organic compounds. Thus, while 'first-generation' synthetic biology is likely to simply enable straightforward extensions of what today's biotechnology can achieve, ultimately its goals and its capabilities will not be mere extrapolations of this sort but may differ in qualitative ways, probably bringing about applications that we cannot yet envisage [IRGC, 2008]. Examples of some of the current achievements and projected aims are detailed below [see also NEST, 2005].

2.1 Current and past activities

2.1.1 Synthetic gene circuits



Green fluorescent protein expressed in the cells of a leaf

[From Santa Cruz et al ., 1996); Copyright (1996) National Academy of Sciences, USA

Most of the key early work in synthetic biology involved devising simple synthetic 'gene circuits' and using the techniques of biotechnology to insert them into bacterial genomes and look for the corresponding changes in the behaviour of the cells [Elowitz and Leibler, 2000; Gardner et al., 2000; Weiss, 2004]. Many of these circuits were inspired by those used in electronic engineering for the 'logic' operations of computation: for example, switches to turn other genes on or off, or oscillators that induce regular bursts of the production of certain proteins. In one instance, oscillations in the synthesis of a fluorescent protein produced by bacterial cells cause them to flash with a steady pulse when illuminated with ultraviolet light [Elowitz and Leibler, 2000].

As well as demonstrating a 'proof of principle' – the feasibility of designing gene circuits that can control cell biochemistry in pre-determined ways – these efforts might have genuine technological and biological applications. They might enable genes to be activated and reactivated at will, or in response to outside signals. They can be used to test theories of how 'information processing' works in natural cells – for example,

how the detection of particular chemical signals at the cell surface triggers a change in cell behaviour. Logic-processing operations in cells might also be used to develop new kinds of biological sensors that signal the presence of pollutants or biomolecules in the environment or the body, and to enable bacteria to communicate with one another in new ways [Butler et al., 2004]. The engineering of logic gates in mammalian cells might significantly extend the realm of synthetic biology to medical applications.

To develop these capabilities in a systematic way analogous to the evolution of microelectronic circuitry, it seems fruitful to learn the lessons of the electronics industry: to create standardised components (such as switches and oscillators) that can be reliably plugged into any circuit, for example, and to establish a library of well-characterised gene devices. Some standardised biological parts, devices and systems (sometimes called BioBricks) are being made freely available online in an open access library called the Registry of Standard Biological Parts. BioBricks can be used for creating genetic circuits, for example by using logic gates and oscillators, revealing direct analogies with electronic engineering [Lowrie, 2010].

New kinds of biological sensors that signal the presence of pollutants or biomolecules in the environment or the body

One example of the way such research might be applied is an attempt to develop a plant whose leaf shape or flower colour changes when a land mine is buried below it, by genetically altering the plant roots to detect explosives traces in the soil and to communicate that information to the leaves or flowers [Antunes et al., 2006].

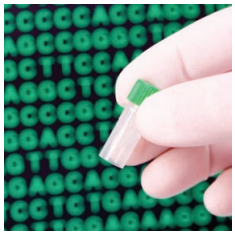
2.1.2 Creation of synthetic organisms

The announcement of a 'synthetic organism' in 2010 by Craig Venter and his co-workers [Gibson et al., 2010] highlighted, among other things, how ambiguous this term is. Venter and colleagues did not by any means build a bacterial cell from scratch; rather, they replaced the genome of an existing cell (a particularly simple form of bacteria of the genus Mycoplasma, which has an unusually small genome) with one designed and made by chemical methods. This new genome was based on the natural one, but with some additions and deletions. Thus the Mycoplasma cells were essentially 'reprogrammed' with a new set of genetic instructions, which had themselves been designed and made in the laboratory.

This was a natural and anticipated development in explorations of the concept of a 'minimal genome', which Venter's group and others had been pursuing for several years [Glass et al., 2006; Glass et al., 2007; Lartigue et al., 2007; Gibson et al., 2008]. The idea is that a genome stripped down to the bare minimum of genes needed to ensure the organism's survival could act as a 'chassis' on which new genomes could be designed and built to confer new functions – biosynthesis of a new fuel from natural sources, say – on the organism. The very notion of a minimal genome is itself ambiguous – what genes a cell needs may depend on what environmental challenges it will face – but the underlying concept that bacterial genomes can be simplified and tailored now seems to be vindicated. However, it remains to be seen whether we can understand the 'gene circuitry' of even these simple bacterial genomes well enough to enable wide-ranging and systematic design of new ones.

The underlying concept that bacterial genomes can be simplified and tailored now seems to be vindicated

2.1.3 Biological computation



The way in which genetic information is encoded and read out in cells is a kind of digital computation. This has led to suggestions that such 'logic' might be used both to control and modify biological processes in cells, for medicine say [Benenson et al., 2004], and to use biological systems for purely technological information processing, for example in sensor technologies. One group is exploring complex logic systems based on ribozymes (catalytic forms of RNA) that will enable external molecular signals to activate drugs [Stojanovic and Stefanovic, 2003]. Others have shown that artificial DNA molecules can be designed to perform logic operations, computations and controllable behaviour in general [LaBean et al., 1999; Seeman, 2003; Rothemund, 2006]. Synthetic biology might permit such systems, which have been made and investigated in vitro, to be incorporated in living cells.

2.1.4 Building artificial cells or compartments from scratch

Some researchers are pursuing the goal of making cell-like entities from scratch

In contrast to the 'top-down' re-engineering of natural organisms exemplified by the work of Craig Venter's group, some researchers are pursuing the goal of making cell-like entities from scratch, putting them together from either natural or synthetic molecular components [Szostak et al, 2001; see http://www.protocell.org]. This 'bottom-up' construction of artificial 'protocells' could offer a testing ground for ideas about how life began on Earth, for example by elucidating the minimal requirements of life-like systems that can grow, divide and evolve. Such 'cells' may also have practical applications, for example acting as 'factories' for the synthesis of biological molecules – much as genetically engineered micro-organisms can, except that such artificial systems would be much simpler and therefore easier to design, control, adapt and sustain. A system in which microscopic compartments (vesicles) that assemble themselves from the lipid molecules that constitute cell membranes encapsulate pared-down genetic machinery (DNA and RNA) has been shown to generate proteins when provided with the raw ingredients [Noireaux and Libchaber, 2004].

This 'bottom-up' construction could offer a testing ground for ideas about how life began on Earth

One key aim is to develop synthetic 'protocells' that can replicate and pass on genetic information, probably using modified forms of the genetic machinery of natural cells. Very simple forms of self-replication have already been reported, for example in vesicles like those mentioned above but made from self-assembling molecules whose formation is catalysed by the vesicles themselves [Luisi, 2006; Luisi et al., 2006].

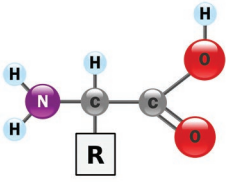
2.1.5 Materials and nanotechnology

One prominent theme in nanotechnology involves the mimicry of natural molecular systems that have evolved effective solutions to 'engineering' problems of a sort encountered in technology, such as storing information, harvesting light or making materials with atomic-scale precision. But it sometimes turns out that such natural systems can themselves be commandeered for that purpose, often with chemical modifications that might be implemented at the level of the genes that encode them. In this respect, synthetic biology potentially has much to offer molecular nanotechnology [Ball, 2005].

For example, protein-like molecules have been generated using 'directed evolution' of biosynthetic pathways that will recognise and bind to a range of inorganic materials (for example, semiconductors) and that can act as templates and 'adhesives' for assembling functional inorganic particles and thin films, providing a potential interface between the biological and inorganic worlds [Whaley et al., 2000; Sarikaya et al., 2003]. Molecular rotary motor proteins have been used to rotate microscopic metal blades [Soong et al., 2000], and the proteins responsible for transporting small packets and objects around in cells have been harnessed for the controlled transport of artificial small particles, offering 'molecular shuttles' that might be used to create complex materials, repair tiny defects on surfaces or in living cells, and to store and retrieve information [Hess et al., 2001]. Chemically modified viruses have been used as templates for crystallising metallic and magnetic nanowires [Mao et al., 2003]. All these uses of biological 'molecular parts' might gain in power and versatility from the use of synthetic biology to assist their synthesis in cells and their organisation.

2.1.6 Developing genomes from using non-natural nucleotides, proteins from non-natural amino acids

Although proteins and nucleic acids are astonishingly diverse in their structures and functions, they incorporate only a very limited range of basic building blocks: 20 (amino acids) for proteins, four (nucleotides) for DNA. It is possible that their repertoire of functions might be widened by including more diverse building blocks – for example, making proteins more water-repellent or temperature-resistant, or making DNA more electrically conducting. Expanding the genetic code of DNA could also allow new types of information to be encoded. Several groups have managed to incorporate non-natural amino acids into proteins [Wang et al., 2001; Chin et al., 2003, Montclare and Tirrell, 2006] and non-natural nucleotides into DNA and RNA [Kool, 2002]. One group has modified both bacterial and yeast cells to genetically encode non-natural amino acids so that they may be inserted into proteins at specified locations [Wang et al., 2001; Chin et al., 2003]. In some cases, the cells are able to make the new amino acids from simple raw ingredients in the environment.



An amino acid

Part of the motivation for such work is fundamental: to explore the limits of biological information transfer or the 'structure space' of protein molecules. But these studies have important potential applications too: for example, drugs that interact with natural proteins and nucleic acids in new ways, or protein-based materials with new structures and properties. For example, one aim of some artificial genetic coding schemes that use non-natural nucleotides [Kool, 2002] is to use chemically modified DNA to detect the small genetic mutations that cause cancer and drug resistance. Artificial genes incorporated into microbes can encode non-natural proteins with interesting material properties (for example, ones that form liquid crystals and materials for tissue engineering), including some with non-natural amino acids [Tirrell et al., 1991].

2.1.7 In-cell synthesis of chemicals and materials

There is a well-established field called 'metabolic engineering', which aims to genetically

engineer the metabolic processes of simple organisms so that they produce useful chemicals on an industrial scale – some vitamins and fine chemicals, for example, are made this way. However, this has often relied on 'tinkering' rather than rational, design-based strategies, frequently leading to only minor changes to the cells' synthetic capabilities.

Synthetic biology could open up new and efficient routes to natural and non-natural compounds with medicinal and industrial value

Synthetic biology could give this approach the more rational flavour of true engineering. The ability to harness, combine, modify and adapt the genetically encoded routes by which cells make complex organic molecules will open up new and efficient routes to natural and non-natural compounds with medicinal and industrial value. These modules might be engineered into bacteria to greatly expand the power of the kinds of fermentation processes currently used with genetically modified bacteria to make pharmaceuticals. Some success with this approach has already been demonstrated with the engineering of E. coli bacteria to produce the antimalarial artemisinin, a natural product found in very small quantities in a species of plant [Martin et al., 2003; Withers and Keasling, 2007]. Because of the multi-stage nature of the synthesis of artemisinin in plants, this re-engineering of bacteria is beyond the reach of conventional genetic modification, requiring a complicated redesign of the bacterial genome.

Artemisia annua

2.2 Some potential future applications

The developments described above open up some new, often rather speculative, possibilities for synthetic biology. Some are as follows.

2.2.1 Biomedicine

A smart drug would be delivered to a patient like a regular drug, but would only become active in cells affected by a disease

A smart drug would be one that contains an autonomous diagnostic capability; it could directly sense molecular disease indicators, which may initiate drug activation or release. Ideally, a smart drug would be delivered to a patient like a regular drug, but would only become active in cells affected by a disease. The techniques and philosophy of synthetic biology have already been used to develop prototypes of such drugs based on a kind of computation performed by synthetic strands of DNA.

Synthetic biology could help in the design of biocompatible devices, e.g., small assemblies of molecules that will sense changes in particular biochemical signals such as hormones and will proceed to secrete a chemical or biological compound in response [Benenson et al., 2004]. This kind of device could be used to sense damage to body tissues such as blood vessels or bone, and to repair them. Synthetic biology could provide ways to generate these devices themselves *in situ* within cells in response to physiological signals of damage or distress.

Modified viruses are currently being explored as transport agents for gene therapy, which can penetrate cells and deliver 'healthy' genes to the target tissue in a way that promotes their integration with the cell's genome. Synthetic biology might offer great flexibility for the design and modification of such 'virus vectors'. They might, for example, be tailored to recognise specific cells and target them for drug delivery or destruction.

One vision of personalised medicine is to develop drugs that are adapted in their mode of action, formulation, dosage, and release rates to the individual requirements of the patient. But this is feasible only if such medicines with subtle differences can be manufactured reliably at a small scale. Synthetic biology might be used to devise cells that will manufacture such drugs according to precise genetic specifications.

It is possible that we will be able to modify human cells to give them new functions not present in our body. One might imagine, for example, cells involved in the immune response being programmed by design to recognise and attack specific viruses or bacteria. Not only would this address the growing problem of antibiotic-resistant pathogenic bacteria but it could also reduce the chance of resistance spreading rapidly.

Synthetic biology might be used to devise cells that will manufacture drugs according to precise genetic specifications

2.2.2 Applications of non-natural biopolymers

There is currently great interest in developing drugs from nucleic acids, such as small RNA molecules that interfere with the expression of genes. Modified nucleic acids with a non-natural chemical composition might be given advantageous characteristics from a pharmaceutical perspective, for example passing more easily across cell membranes. Organisms with an expanded genetic code that allows more than the 20 natural amino acids to be incorporated into proteins should likewise enable the manufacture of protein drugs with novel or enhanced properties, for example by lengthening their 'shelf-life' or making them less or more prone to interfere in unintentional ways with biochemical processes. Enzymes with non-natural amino acids might also show greater or less catalytic activity when used for the production of pharmaceuticals.

Pseudo-biomolecules with non-natural chemical structures could be designed to be 'invisible' to the natural chemistry of the cell, for example enabling the design of biomolecular sensors that operate independently from natural protein networks and pathways. Among the potential uses of such in vivo molecular sensors might be the very early detection of cancer signals. Encoding genetic information in non-natural nucleic acids might also reduce the risks of genetic modification of natural organisms, because the use of the added genes could then be made dependent on an external supply of the ingredients needed to make the non-natural nucleic acids: without them, the added genes could not be replicated. This would offer a simple way to switch the genetic modification 'on' and 'off', for example by withholding the necessary ingredients from a transgenic plant.

Nucleic acids have been recognised as versatile components for the synthesis of nanoscale structures and devices [Seeman, 2003; see above]. Expanded genetic alphabets should allow the cell-based synthesis and replication of DNA nanodevices with a wider range of properties: greater robustness, say, or the ability to interact with inorganic components.

One of the key aims of the 'minimal genome' approach to synthetic organisms is to design them to turn biomass into biofuels such as ethanol

2.2.3 Sustainable chemicals manufacturing and energy production

The inevitable dwindling of fossil-fuel reserves during this century will force industrial chemistry to find a new source of raw materials for making products such as drugs, fuels and plastics. One of the current goals in synthetic biology is to develop engineered micro-organisms that can generate useful carbon-based (organic) chemicals, of the sort currently obtained from petroleum, from new feedstocks such as biomass. This is a particularly valuable objective in the arena of fuel production, where microbial production could be based on renewable sources. One of the key aims of the 'minimal genome' approach to synthetic organisms [Glass et al., 2006] is to design them to turn biomass, perhaps especially the recalcitrant parts of plants that are not easily degraded by existing micro-organisms, into biofuels such as ethanol.

2.2.4 Environmental remediation

Bioremediation – the use of naturally occurring organisms such as bacteria and fungi to break down organic pollutants such as oil and sewage, or to concentrate toxic heavy metals from soils – has emerged in recent decades as one of the best techniques for decontaminating natural and man-made environments. Synthetic biology might enable such organisms to be rationally designed, both to improve their efficiency and to broaden the range of pollutants that they can degrade or remove.

2.2.5 Systems-scale molecular nanotechnology

As shown above, there are several ways in which engineered proteins, viruses and organisms might assist in the development of new materials, such as those used in biomedicine, microelectronics, mechanical engineering and energy conversion.

So far, much of the work in this area has demonstrated specific functions using individual biological components: for example, desalination or filtration using proteins that perform an analogous function in cell membranes, or transport of nanoparticles using motor proteins. But in living cells, such systems are tightly coupled to others in an integrated, autonomous molecular assembly that builds and repairs itself and generates its energy from ambient sources. It would be desirable to achieve this sort of integration in synthetic systems [Ball, 2005]. For example, coupling photosynthetic devices to motor proteins could enable light-driven molecular motion. It is conceivable that the best way to do this will be to incorporate all of the components into the genetic programs of engineered organisms. In other words, synthetic biology might help us to mimic not just some of the 'molecular engineering' principles of living cells but their systems-scale operation.

3. Risks of synthetic biology

Synthetic biology is an emerging discipline with huge potential and scope. However, there is no direct correspondence between the nature and extent of the benefits and the associated safety and security risks. Each new development will need to be assessed on its merits, balancing risks and benefits and, where necessary or appropriate, considering innovative approaches to enabling innovation while avoiding hazards to people or the environment.

Each new development will need to be assessed on its merits

IRGC has identified two 'frames' of synthetic biology development:

- **first-generation** 'evolutionary' synthetic biology that builds on existing applications of genetic engineering, deploying more rapid development methodologies accessible to a wider range of actors at reduced costs; and
- **second-generation** 'revolutionary' developments where feasible forms of innovation and application areas are less certain.

Each of these regimes will have a distinct set of risks, with the former obviously less speculative and more well-defined than the latter [Mukunda et al., 2009]. A distinction also needs to be made between the challenges of regulating the *conduct* of synthetic biology research itself and the need to regulate the *products and practical outcomes* of that research. For basic research and knowledge generation, risk governance should focus mainly on the research processes that are likely to give rise to hazards. For products and other applications arising from this knowledge, on the other hand, governance should focus less on the processes involved and more on the products and outcomes themselves.

- Regulating the *conduct* of synthetic biology research
- Regulating the *products* and *practical outcomes* of that research

In considering products and potential applications, this policy brief focuses on first-generation developments, for which we do have some information on likely future outcomes. However, comments on the conduct of basic research on synthetic biology would apply to both first- and second-generation developments.

Reports assessing potential risks associated with synthetic biology have been prepared by an exceptionally diverse set of organisations. These include official governmental bodies [NSABB, 2006; POST, 2008], national academies [Royal Academy of Engineering 2009; Royal Society 2008, 2009; DFG, 2009], foundation - and/or government - funded consortia [Balmer and Martin, 2008; Caruso, 2008; Gaisser, et al., 2008; Garfinkel, et al., 2007; NEST, 2007; Rodemeyer, 2009] and NGOs [Friends of the Earth, 2010; ETC, 2010]. These reports have focussed on the following areas:

1. Insufficient basic knowledge about the potential risks posed by designed and synthetic organisms. For example, a recent European Union (EU) report has raised questions about our ability to assess the safety of organisms that combine genetic elements from multiple sources, that contain genes and proteins that have never existed together in a biological organism, or that incorporate biological functions that do not exist in nature [European Commission, 2009].
2. Uncontrolled release of novel genetically modified organisms with potential environmental or human health implications, either arising from accidental release

into the environment or from applications entailing deliberate release (for example, bioremediation and some varieties of living therapeutics) [e.g. Friends of the Earth, 2010]. Are existing biosafety measures adequate? Who is responsible for ascertaining and quantifying risks, and for implementing any clean-up measures that might need to be undertaken?

Genetic manipulation of organisms can be used, or can result by chance, in potentially dangerous modifications for human health or the environment

3. Bio-terrorism, biological warfare and the construction of novel organisms designed to be hostile to human interests. Genetic manipulation of organisms can be used, or can result by chance, in potentially dangerous modifications for human health or the environment. Bioterrorists might, for example, create new pathogenic strains or organisms resistant to existing defences. It has even been suggested that pathogens might be engineered to attack only a particular genetic subset of a population [Garfinkel et al., 2007]. It is by no means clear that such abuses could be entirely eliminated, any more than they can be for other 'dual-use' technologies.
4. Aside from the risk of abuses coordinated by governments or organised groups, there are concerns about the emergence of a 'bio-hacker' culture in which lone individuals develop dangerous organisms much as they currently create computer viruses. The basic technologies for systematic genetic modification of organisms are widely available and are becoming cheaper, although it is easy to underestimate the degree of technical proficiency, experience and resources needed to make effective use of them. Many researchers in the field anticipate that the real harms that might be inflicted by such 'hacker' activities are probably small, but they nonetheless warrant careful consideration, and it is hard to see how they might be prevented – the question is more about law enforcement than scientific protocol. One suggestion is to aim to remove the 'glamour' which, by analogy with computer viruses, might become attached to bio-hacking.
5. Patenting and the creation of monopolies, inhibiting basic research and restricting product development to large companies.
6. Trade and global justice, for example exploitation of indigenous resources by enabling chemical synthesis of valuable products in industrial countries (e.g. artemisinin production for malaria treatment), or distorting land-use agendas for genetically engineered biomass [Friends of the Earth, 2010; ETC, 2010].
7. Claims that synthetic biology is involved in creating artificial life, and related philosophical and religious concerns. The accusation of 'playing God' [Peters, 2002] has already been levelled at synthetic biology in the wake of the first organism with a 'synthetic' genome [Gibson et al., 2010; Van den Belt, 2009]. As with reproductive technologies and stem-cell research, the lack of a shared conceptual framework makes it hard to debate this issue among the various interested parties: the science may have outstripped our ethical points of reference.

Many of these ethical and safety issues have already been acknowledged and discussed extensively by the synthetic-biology community [Schmidt, 2009b]. The increasingly active debate around the risks of synthetic biology focusses in Europe on the experience of similar debates about genetically modified (GM) crops [Tait, 2009b],

which have resulted in a de facto moratorium on many potential applications. In the US, public attitudes to GM crops have been much more permissive. An analogy is often made in the synthetic-biology community with the Asilomar Conference on Recombinant DNA in 1975, at which guidelines were agreed on how this technology might be used, and a voluntary moratorium was established on certain kinds of experiments, such as the cloning of DNA from pathogenic organisms.

It is easy for an enumeration of the potential risks of synthetic biology to sound alarming. But these must be weighed against the benefits

It is easy (and perhaps appropriate) for an enumeration of the potential risks of synthetic biology to sound alarming. But these must be weighed against the benefits, not least in the sense that there is an ethical component to the decision to forego a new technology too: there can be socially significant penalties to the seemingly 'safe' option of 'doing nothing.' For one thing, the powerful capabilities synthetic biology might provide for developing and manufacturing drugs, including ones sorely needed in developing countries, should not lightly be set aside, just as we do not prohibit all drugs that have side-effects. It is conceivable that in the long-term, synthetic biology might offer one of the most powerful approaches for ameliorating natural biological and ecological hazards such as the spread of infectious diseases [Mukunda et al., 2009].

Moreover, since the basic techniques necessary for conducting some form of synthetic biology already exist and are publicly accessible, curtailing scientific research in this area provides no guarantee against potential abuses. It is likely that misuse for the purposes of, say, bioterrorism and biowarfare might be most effectively prevented or remediated by the techniques of synthetic biology itself. (It could also offer new ways to counter already existing manifestations of these threats too.) In short, the genie is already out of the bottle: the technology might become its own best safeguard against some of its risks.

The technology might become its own best safeguard against some of its risks

4. Existing policy and regulatory frameworks, and their deficits

4.1 Regulatory and governance contexts

The Organisation for Economic Co-operation and Development (OECD) views synthetic biology as a potentially revolutionary technology that could transform biology and biotechnology from a largely scientific to an engineering discipline. In the near-term (to 2015), the OECD sees the use of metabolic-pathway engineering to produce chemicals that previously could not be produced biologically as the most likely commercial application of synthetic biology. In the longer-term, applications of synthetic biology in primary industrial manufacturing and in healthcare may become widespread. Commercialisation of these latter uses was considered unlikely before 2015, because such applications will be subject to the same regulatory procedures as other biotechnology products, which generally require a lead time of between 5 and 7 years [OECD, 2009a].

There is currently a complex array of national and international regulatory instruments that may be relevant for, or act as precedents for, the regulation of synthetic biology

There is currently a complex array of national and international regulatory instruments that may be relevant for, or act as precedents for, the regulation of synthetic biology, particularly first-generation products [e.g. Byers and Casagrande, 2010]. There is a history of decisions being taken in very early stages of product development that turn out to have unforeseen and often counter-productive outcomes which are then difficult to change. This is particularly evident where regulation has been designed to reassure the public rather than to address genuine expected risks, as was the case for GM crops in Europe. Also, where a regulatory regime has evolved over a long period of time in response to several generations of scientific development, it can become inflexible and difficult to modify in ways appropriate to the latest advances and opportunities [Byers and Casagrande, 2010]. This can unnecessarily limit opportunities for innovation and represent a governance deficit in itself [IRGC, 2009a]. The appropriate risk governance of innovative technologies thus needs to be informed by an understanding of how governance and engagement approaches interact with innovation processes.

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The European view on risk regulation in synthetic biology is that it will be covered by existing regulations for genetic modification and release of GM products to the environment [Royal Academy of Engineering, 2009]. However, these regulations are themselves controversial (see Section 5.2) and are already inhibiting the commercialisation of potentially beneficial GM products, such as pest- or drought-resistant crops [Wagner and McHughen, 2010].

International law has an important bearing on trade in biotechnological products, the most familiar example being the restrictions on trade in genetically modified organisms (GMOs) or products derived from them. Some regulations may be relevant to proposed applications of synthetic biology, such as the global moratorium on ocean fertilisation (for ameliorating climate change by promoting oceanic carbon dioxide uptake) under the Convention on Biological Diversity and the provisions of the Biological Weapons Convention (BWC). The next review conference of the BWC will be held in 2011, providing the opportunity for the international community to make binding decisions on the oversight of synthetic biology. The Environmental Modification Convention

(ENMOD), an international treaty prohibiting the military or other hostile use of environmental modification techniques such as alterations to weather patterns or ocean circulation, may also apply to some possible uses of synthetic biology.

The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) is the most comprehensive multilateral agreement on intellectual property, setting standards to be met in domestic patent law. Most applications and techniques of synthetic biology would be patentable under Article 27.3(b) of the agreement, which deals with intellectual property (IP) protection of genetic resources.

Limits on the exploitation of IP rights stem from other fields of law, such as human rights law and international environmental law. Trade-offs may be required where such issues as public access to innovative medicines are at stake. In this regard, compulsory licensing remains an option under the TRIPS agreement for patents in any field. In the 2001 Doha Declaration on TRIPS and Public Health, World Trade Organization (WTO) member governments stressed that it is important to implement and interpret the TRIPS Agreement in a way that supports public health.

There are potential conflicts between the TRIPS patenting regime and the Convention on Biological Diversity, as well as the International Undertaking on World Food Security negotiated at the United Nations Food and Agriculture Organisation (FAO). These conflicts are generally seen as political rather than legal, and may lead to dispute under the WTO dispute-settlement system.

The Cartagena Protocol on Biosafety to the Convention on Biological Diversity regulates international trade in genetically engineered products. The Protocol establishes core procedures and a set of standards relating to the import and export of living modified organisms (LMOs). Although the Cartagena Protocol recognises in its preamble that trade and environment agreements should be mutually supportive, it is grounded in a more robust application of the precautionary approach than the WTO rules. Currently, 157 national parties participate in the Protocol, including China, Brazil, India and most European nations, but not the US (where significant research and development in synthetic biology is taking place) or other potentially important international players such as Australia, Russia, Argentina and Canada.

There are clear areas of overlap between the Protocol and the WTO rules. In addition to TRIPS, the Agreement on Technical Barriers to Trade and the Agreement on the Application of Sanitary and Phytosanitary Standards are relevant. Article XX of the General Agreement on Tariffs and Trade (GATT) provides for exceptions from GATT rules in order to protect health or the environment. These agreements formed the basis of the dispute raised by the US, Canada and Argentina under the WTO system over the European Commission's regulation of GMOs. The different fundamental objectives of the international trade and environmental regimes may lead to conflicts in the regulatory measures taken to achieve these objectives. Strengthening the coherence of these two systems requires measures to be taken at national and supranational levels to ensure they are implemented in a mutually supportive manner.

Not enough is known at present for robust risk assessments related to containment of partially or wholly synthetic organisms

Developments in synthetic biology could lead to gaps in the risk assessment framework set out in the Cartagena Protocol, since established practices may not be capable of dealing with complex hybrids of genetic material (including some that are wholly synthetic in design and origin) and the properties and effects they display. The same problem is faced by non-participating states. In the US, the risk assessment framework in the National Institutes for Health Guidelines for Research involving Recombinant DNA Molecules [NIH Guidelines, 2009; Byers and Casagrande, 2010] is considered by regulators to be sufficient at present for handling risks that might arise in synthetic biology at the research stage. The 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 organisms for which the risks of the parent organism are not an appropriate precedent [Byers and Casagrande, 2010]. Not enough is known at present for robust risk assessments related to containment of partially or wholly synthetic organisms. There is also some concern that intellectual property rights claims could be used to restrict access to risk-related information and thereby compromise the credibility of risk assessments in future.

4.2 Risk Governance Deficits

There is concern that intellectual property rights claims could be used to restrict access to risk-related information and thereby compromise the credibility of risk assessments in future

Several aspects of risk governance relevant to innovative technologies are considered here in relation to synthetic biology:

- The uncertainty about future research and industrial developments, and thus about the actual opportunities and risks.
- The inhibiting effect on innovation of uncertainty about future regulatory systems, particularly for products with long lead times for delivery from conception to market.
- The need for a better understanding of how different regulatory approaches interact with innovation processes to determine the fate of innovations, including the relative competitive advantage gained by companies and countries operating in different regulatory regimes.
- The potential to adapt existing regulatory systems and to apply these to innovative technology, and in particular the importance of adopting the most appropriate regulatory precedent.
- The potential for lack of harmonisation between different national regulatory systems to lead to trade-related and other conflicts.
- Problems of stakeholder and public engagement about innovations where, for all parties involved in discussion and decision-making, 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 future public opinions.
- The need to take decisions on a balanced basis, particularly where there is irreconcilable or ideologically based conflict over innovative technology and its application.

These considerations suggest that any effective approach to risk governance of synthetic biology must be capable of evolving as scientific and technical knowledge expands, requiring flexibility in the face of uncertainty about the eventual nature of products, processes, benefits and risks. We have focussed here on the concept of risk governance deficits[1] – deficiencies or failures in risk governance processes or structures – and have aimed to identify weak spots in how risks are assessed and managed in the key areas of policy and regulation, innovation and technology development, and public and stakeholder engagement [IRGC, 2009a].

Participants at the IRGC workshop on synthetic biology sought to find an appropriate balance between current scientific knowledge and uncertainty about future developments, and the need to realistically assess the potential of the field. A balance is also needed for policy and regulatory options, including the potential to transform existing policies and regulatory frameworks that may be difficult to adapt to the challenges raised by innovative technologies. The participants were concerned to ensure that the opportunities offered by synthetic biology as the technology develops be kept open, but also recognised that there is potential here to open up new models of public and stakeholder engagement.

One general theme to emerge from the workshop was the concern that 'synthetic biology' was already becoming too broad a set of developments to be dealt with under one heading. As is already the case with nanotechnology, this diversification will make it increasingly necessary to govern the area using a diverse and flexible set of regulatory precedents tailored to a range of specific hazards and the needs of different industry sectors.

The workshop discussions also explored potential interactions among risk regulatory processes, innovation systems, and stakeholder and public perspectives in relation to synthetic biology developments. They identified the following deficits [IRGC, 2009a, pp.64-65] as being most relevant to potential developments in synthetic biology (in order of perceived importance). The guidelines proposed in Section 6 are designed to help policy-makers and regulators to avoid or reduce these deficits.

Any effective approach to risk governance of synthetic biology must be capable of evolving as scientific and technical knowledge expands

Potential deficits in risk assessment:

- Lack of knowledge, including the probabilities of various discoveries, inventions and events and the associated economic, human health, environmental and societal consequences.
- Lack of knowledge about values, beliefs and interests and therefore about how risks are perceived by stakeholders.
- Failure to identify and involve relevant stakeholders in risk assessment in order to improve information input and confer legitimacy on the process.
- The provision of biased, selective or incomplete information.
- Lack of appreciation of the multiple dimensions of a risk and how inter-connected risk systems can entail complex and sometimes unforeseeable interactions.
- Failure to overcome cognitive barriers to imagining events outside of accepted paradigms.

(1) The concept and a list of the most commonly observed deficits in risk governance have been described in an IRGC report available at http://www.irgc.org/IMG/pdf/IRGC_rgd_web_final.pdf.

Diversification will make it increasingly necessary to govern the area using a diverse and flexible set of regulatory precedents

Potential deficits in risk management:

- Insufficient flexibility in the face of unexpected risk situations.
- Failure to balance transparency (which can foster stakeholder trust) and confidentiality (which can protect security and maintain incentives for innovation).
- Failure of the many organisations responsible for risk management to act cohesively.
- Failure to muster the will and resources to implement risk management policies and decisions.
- Failure to design risk management strategies that adequately balance alternatives.
- Failure of managers to respond and take action when risk assessors have determined from early signals that a risk is emerging.

5. Risk governance in synthetic biology

5.1 The concept of appropriate risk governance

IRGC defines 'appropriate risk governance' as that which, in the field of innovative technologies, *enables* innovation, *minimises* risk to people and the environment, and *balances* the interests and values of all relevant stakeholders [Tait, 2007], while avoiding simplistic comparisons across sectors and technologies. The IRGC risk governance framework [IRGC, 2005] has been applied very successfully to a range of risk issues, including for example 'Nanotechnology Applications in Food and Cosmetics' [IRGC, 2009c]. However, synthetic biology presents challenges for the usual approaches to risk governance. In its current, early developmental stage, both benefits and risks of synthetic biology are largely conjectural and most previous reports on this issue have therefore focussed on aspects that are covered only in the initial ('pre-assessment') phase of the IRGC framework – specifically,

- how risks are framed by stakeholders;
- whether there are any applicable legal or other existing rules or processes that cover technology developments;
- the scientific characteristics of the technology and its potential applications;
- the hopes and concerns of major stakeholder groups.

Regulation of basic research on synthetic biology should be considered separately from product regulation. Given the likely range of applications of synthetic biology in different industry sectors, however, it would be unwise to attempt to devise an overall framework for risk governance of synthetic biology. Instead, risk governance has to be approached on a product-by-product basis, paying particular attention to current regulatory approaches, the extent to which they are transferable to the new products, and the implications of such choices for the options for future development. For example, products that have applications to human or animal medicine, agricultural crop development and the production of biofuels will come under the scrutiny of different existing regulatory systems.

Risk governance has to be approached on a product-by-product basis, tailored to a range of specific hazards and the needs of different industry sectors

However, some areas of synthetic biology will not be covered by this approach. For example, trading in 'bio-bricks' (gene sequences that can be used by both researchers and commercial companies to develop new gene circuitry) can be dealt with using regulatory initiatives similar to those being developed to regulate the research stage. On the other hand, when synthetic biology is used to develop new processes for the manufacture of complex biological molecules, the resulting molecules themselves can be regulated by existing systems for drugs or other chemicals, but new regulation may also be needed for the novel organisms used in the production process.

5.2 Regulation and governance of first-generation synthetic biology

For some likely near-term applications of synthetic biology – for example, in biofuels and industrial applications, pharmaceuticals and health diagnostics, and genetic

The challenge is to choose the most appropriate regulatory precedent and to avoid reinforcing currently inadequate regulatory systems

modification of plants and organisms for agriculture and food production – well-developed risk governance approaches are already in place. The challenge is to choose the most appropriate regulatory precedent and to avoid reinforcing currently inadequate regulatory systems.

For example, the emerging consensus related to the use of synthetic biology to develop more sophisticated GM micro-organisms or plants, is that regulatory systems for existing GMOs will be the appropriate regulatory precedent. However, there are contentious differences between the US and EU approaches to GM risk governance. The latter is regarded by some to be unnecessarily demanding and inhibiting of innovation, while the former is seen as inadequate to deal with some of the risks emerging from current GM crop innovations, such as using GM food crops to produce pharmaceutical products. Ideally, the process of adapting these regulatory systems to accommodate the needs and opportunities presented by synthetic biology could at the same time resolve some of these outstanding and so far intractable issues arising from previous regulatory decisions.

Considering institutional and human dimensions to regulatory development, building regulatory capacity to deal with the issues presented by synthetic biology is both an experience issue and a skills issue. In terms of developing an appropriate knowledge base, the capacity to record 'near misses' is becoming recognised as a policy field in its own right and offers a structured approach to learning from early projects in order to develop adaptive governance frameworks [OECD, 2009b]. Furthermore, the risk assessment and governance of synthetic biology (in common with other areas of technological convergence) requires multi-disciplinary teams with skills across the scientific fields from which synthetic biology is emerging.

5.3 Policy and regulatory strategies in biosafety and biosecurity related to research, innovation and technology development

The ready availability of DNA sequence data and online explanations of the techniques of molecular biology, combined with the ease of purchasing a specified DNA sequence from the many commercial companies that now offer this service, means that these technologies can be readily acquired by amateur scientists or potential terrorists [Garfinkel, et al., 2007; de Vriend, 2006]. Even in the hands of legitimate and well-intentioned researchers, health and environmental risks could arise from unintended dispersion of modified organisms.

The synthetic biology community has generally supported approaches to oversight that rely on voluntary measures developed and implemented by the community itself [Campos, 2009]. In formalising such measures, decision-makers, particularly in the US and EU [Bennett, et al., 2009], are investigating approaches to screening all gene sequence orders sent by commercial DNA synthesis companies to

research laboratories or other commercial companies. This approach is supported by some scientists, who point out that the likely control of DNA synthesis and other key technologies by a small number of very efficient companies [Bhattacharjee, 2007] could make such monitoring relatively easy and reduce biosafety concerns.

As the gene-synthesis market has become more competitive, two groups of companies have proposed different standards for screening orders for gene sequences to enable identification of any that could present a potential biological hazard [Hayden, 2009]. The International Association for Synthetic Biology (IASB) code of conduct [IASB, 2009] includes a review step by an expert in the field, while DNA 2.0/Geneart has suggested an automated process. The Federation of American Scientists has considered this problem of multiple standards, and is working towards a consensus, at least among American scientists and companies [FAS, 2010], on how screening might be done. Guidelines for screening of DNA synthesis have been formulated by the US Department of Health and Human Services [DHHS, 2010], but these are voluntary, apply only to double-stranded DNA, and have been criticised by some researchers as representing no improvement to the security risk [Ledford, 2010].

Furthermore, if these technologies become ever more accessible [Carlson, 2010], so that gene sequences can be procured by means other than through companies with sophisticated screening procedures, this will create stiffer challenges for risk management. Some feel that the threat may be much greater from state-sponsored terrorism (for which DNA synthesis would be hard to control or monitor) than from amateur activities. However, it is important not to underestimate the difficulty of moving from research in a laboratory, let alone a 'bio-hacker's' garage, to a functioning product that can be disseminated widely. Incorporating engineering techniques into research on biology does not mean that the resulting products can be developed as if they were just another piece of hardware or software.

The synthetic biology community has generally supported approaches to oversight that rely on voluntary measures developed and implemented by the community itself

The dissemination of the technology, knowledge and capabilities involved in synthetic biology beyond the professional biotechnology community will have two (potentially overlapping) strands:

1. Professional groups such as engineers and computer scientists, educated in disciplines that do not routinely entail formal training in biosafety, may acquire these capabilities. In consequence, there needs to be a dialogue among all relevant researchers on what responsible conduct might entail in this field, and education about the risks of, and guidance on best practice for, biosafety principles and practices applicable to synthetic biology. A review of biosafety standards should also be conducted to identify differences between standards and actual laboratory practices.

2. Dissemination may extend beyond academic and professional circles as biological engineering becomes more accessible [Mukunda et al., 2009]. This may include less responsible individuals and organisations. Moreover, the most appropriate

The most appropriate balance between promoting innovation and containing risk will not be the same in all parts of the world

balance between promoting innovation and containing risk will not be the same in all parts of the world. Legitimate researchers can help governments and regulators to find ways to prevent other actors from using the technology for illicit purposes. An appropriate balance also needs to be found between top-down command and control and bottom-up education and awareness initiatives, including the fostering of a culture of responsibility and the de-glamorisation of the kind of antisocial activities already evident in the creation of computer viruses.

A summary of US Federal Regulations that relate to synthetic biology [Byers and Casagrande, 2010] has pointed to several inadequacies, including NIH Guidelines, EPA, USDA and FDA Regulations, Department of Commerce Regulations and Select Agent Rules, as currently applied to developments in synthetic biology that involve micro-organisms. The current approach to the definition and classification of organisms according to perceived hazard levels will not cover the range of possible modifications arising from synthetic biology, whether legitimate or malicious. The rules will need to be adapted to new circumstances.

One of the key issues, which lacks any current consensus, is to what extent avoidance of biosafety risks can be ensured by voluntary measures as opposed to top-down regulation

Policy-makers need to take a lead in developing and implementing standardised procedures and preferred practices for screening sequences and for mitigating biosecurity risks as a whole. The recently published US National Strategy for Countering Biological Threats [US National Security Council, 2009] is an important step in this direction. In the context of biological threats of all kinds, including any arising from synthetic biology, the strategy advocates an international, systemically organised approach that seeks to promote a 'culture of responsibility' in the life sciences, backed up by legal mechanisms, coupled with surveillance and improving intelligence on deliberate threats.

One of the key issues, which lacks any current consensus, is to what extent avoidance of biosafety risks can be ensured by voluntary measures (for screening of commercial DNA synthesis, say) as opposed to top-down regulation. For example, Mukunda et al. recommend the adoption of a 'safety hold' norm of the sort currently used by Air Traffic Control (ATC) systems, whereby any proposed change to ATC systems can be blocked by any member of the community who believes that they are likely to cause safety concerns [Mukunda et al., 2009].

A major plank of the strategy proposed here is the recognition that using the life sciences to combat both natural and malicious threats may be the best way to minimise harm, given that there is no foolproof way to forestall malicious use of the technology. This could include the use of methods in synthetic biology to develop improved disease diagnostics and vaccines. In this context, it is important to recognise that the risks to humanity from naturally occurring zoonoses (infectious diseases that can be transmitted from animals to humans) and other emerging pathogens are likely to be greater than those arising from malicious use of synthetic biology.

5.4 Intellectual property (IP) issues and maintaining incentives for innovation

In any innovative technology, the granting of limited exclusive rights in intellectual property can support innovation but carries the danger of creating a disproportionate concentration of market power. In areas of technological convergence, IP rights may be fragmented across many owners, and are sometimes given an excessively broad interpretation, which can pose obstacles to the development of the basic science. Moreover, where science is developing rapidly, the needs of the research community for IP protection are not necessarily aligned with those of product developers.

The needs of the research community for IP protection are not necessarily aligned with those of product developers

Many scientists working in synthetic biology have expressed a principled commitment to an 'open source' ethos, modelled on the open-software movement in ICT [Heller and Eisenberg, 1998]. Such strongly held views can make it more difficult to balance the societal trade-offs that need to be made between open access to information and commercial realities, particularly in the context of the lengthy and onerous regulatory processes that apply in many areas of life sciences (which tend to impose high development costs). The claim often made for open-source biotechnology – that it can realise the benefits of commercial technology transfer while creating a robust science and technology commons that can sustain innovation – has yet to be tested in cases like synthetic biology.

As well as a wholly open-access approach, various other options have been proposed for handling intellectual property in synthetic biology that go beyond the traditional option of patenting, typical of biotechnology and the pharmaceutical industry today [Rai and Boyle, 2007]. There could, for example, be provision for copyrighting of innovations, for contracts to govern their use, or for highly specific *sui generis* strategies. Each has advantages and disadvantages, and none is obviously preferable to the others. Oye and Wellhausen argue that current approaches can be distinguished both by the degree of public versus private ownership of IP and by the extent to which property rights are either clearly or ambiguously defined [Oye and Wellhausen, 2009]. They point out that there is no consensus on these issues among researchers in the field of synthetic biology, partly because there is no agreement on the extent to which private ownership is needed as an incentive to innovation. In the short-term, privatisation of IP may be imposed by the institutional demands of the researchers, but as applications of synthetic biology in areas such as energy and climate gain pace, international pressures may encourage a shift to a more commons-based approach.

For near-term applications that resemble those in current genetic engineering and which require large investments to bring a product to market, patenting seems likely to predominate. And as patent applications in the field of synthetic biology are likely to contain claims for biological molecules or micro-organisms, and for methods of producing and applying them, they will be mostly indistinguishable from similar applications in other areas of biotechnology. Patent authorities hold primary responsibility for ensuring

patent quality. Initiatives such as the 'Raising the Bar' programme of the European Patent Office aim to 'front-load' legal certainty by ensuring a high quality standard of patents granted [Nurton, 2009].

Various measures have been suggested for supporting the sharing of information in synthetic biology in the long-term while maintaining incentives for innovation [Henkel and Maurer, 2009]. Companies can be encouraged to use unpatented biological parts where possible and donate parts to the commons, and public funding institutions can exercise their influence on the licensing conditions for the resulting patents, so that for example where this funding is used to develop foundational tools and techniques, it carries an obligation to share information. However, this approach could still inhibit the commercial investment necessary to take a product to market.

IP rights should not be allowed to restrict access to the scientific data needed for risk assessment

Regulators have a range of tools to deal with, for example, the control of anti-competitive behaviour, and provisions for access to medicines and compulsory licensing remains an option under TRIPS. An important consideration in terms of balancing transparency and confidentiality is that IP rights should not be allowed to restrict access to the scientific data needed for risk assessment, as has happened in the US with some GM crop varieties [Scientific American, 2009]. This is particularly important where there is no de jure research exemption for the use of patented subject matter (although such an exemption may be recognised in practice).

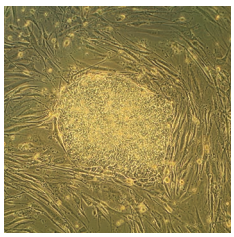
A more nuanced regulatory regime, rather than framing the debate as 'open source versus patenting and commercialisation', could take the needs of all parties into account so that policy responses favour researchers and product developers equally, allowing the flexibility that would enable interested parties to access information or biological parts on the terms which they require to conduct their research and/or investment. As the synthetic biology industry develops, more studies will be needed on the effects that patenting of inventions has on competition, including such phenomena as strategic patenting and patent clusters.

5.5 Risk regulation and barriers to innovation

Governance problems can arise if there is a failure to think through how the potential benefits can be delivered in a way that balances public and commercial needs and agendas

The shape of emerging synthetic-biology industries will be influenced by the regulatory and investment environments within which they operate. Governance problems can arise if there is a failure to think through how the potential benefits can be delivered in a way that balances public and commercial needs and agendas [Tait, 2009a]. Policy approaches often lack cross-functional coordination, for example between risk regulation, IP protection and stakeholder perspectives, and may not recognise some of the counter-intuitive implications that regulation might have for innovation. Regulation tends inevitably to be onerous and lengthy, which favours very large companies by raising high barriers to new market entrants. Large companies are often highly innovative, but only within the restricted area that supports their overall company strategy [Tait, 2007]. Synthetic biology is likely to offer ground-breaking opportunities for multinational companies, but it is precisely these developments that could be most

at risk from early regulatory initiatives. For example, the decision to categorise stem-cell therapies as 'drugs' for regulatory purposes militates against their development by small companies working with technology related to surgical procedures. Where there is a choice of regulatory systems, an appropriate precedent would be the system related to the industry sector for which the technology would be path-dependent [Tait, 2007].



Stem cells in culture

In general, the challenge is to find the appropriate balance between:

- the inhibiting effect of uncertainty about future regulatory systems on investment in new technology, particularly for products with long lead times from conception to market;
- regulation/innovation interactions that determine the fate of individual innovations and also the relative competitive advantage of companies in different sectors;
- the potential for a lack of harmonisation across national regulatory systems, which could create trade-related and other conflicts.

Because radical, path-breaking innovations generally require infrastructure changes, paving the way for them will often require concerted efforts to create a market, foresight research, and infrastructure investment. Regulators could consider streamlining market authorisation, for example by setting up a 'fast track' for products that satisfy a particular public demand or are capable of reducing the risks presented by current-generation products. A regulatory policy that *enables* positive change in industry strategies and *discriminates* among products on the basis of socially and scientifically relevant criteria is likely to be more effective and efficient than one which is *indiscriminate* and attempts merely to constrain undesirable behaviour [Tait, 2007].

5.6 Local, regional and international perspectives on regulatory oversight and risks

Divergent national approaches to the regulation of GM crops have created many problems for both large and small countries, with lessons for the governance of synthetic biology. Regulatory options for synthetic biology will have to take account of a complex, multi-layered regulatory environment (local, regional, national and supra-national) and various specialised regimes. The law uses various frameworks to regulate genetic technology, such as individual rights and duties, scientific regulation by administrative agencies, and legislative pre-emption. Each framework involves different decision-makers and is designed to oversee a different aspect of genetic technology.

International trade law can prevent some conflicts, but the trading system is not the appropriate place for harmonising environmental, social or other non-trade-related standards, or for determining its members' policies on biotechnology. While states must find their own appropriate balance on these matters (taking into account international legal obligations, especially multilateral environmental agreements such as the Cartagena Protocol), it is desirable that internationally applicable regulatory

principles and guidelines be established, along with ways to interface the approaches of different states.

Synthetic biology offers different opportunities and risks in different parts of the world

Synthetic biology offers different opportunities and risks in different parts of the world. An important consideration is how to coordinate the international planning and collaboration required for effective governance of an innovative life-science technology, while encouraging heterogeneity in a field with widely varying techniques and applications.

It is also vital to acknowledge varying capacities to administer complicated risk regulatory regimes

It is also vital to acknowledge varying capacities to administer complicated risk regulatory regimes: this might, for example, be more challenging in developing countries. These variations in capacity have been recognised as an impediment to the effective implementation of the risk assessment and risk management provisions of the Cartagena Protocol. To deal with these problems, developing countries will need support and access to technical resources. Building up the research capacity of developing countries, and fostering smaller start-up companies, could help these countries to reap the benefits that the technology offers while at the same time contributing to solving their pressing economic and social problems. Institutions such as the International Centre for Genetic Engineering and Biotechnology (ICGEB), which was created in 1983 to promote international cooperation in developing and applying peaceful uses of genetic engineering and biotechnology, may have a part to play in this. In any event, a failure to match the regulatory capacity of small countries with their technological capacity could create biosecurity risks.

It is not clear how countries that are currently undergoing rapid economic and technological development, such as China, India and Brazil, might function in the future as regulators, producers, and markets. To take just one example, in 2009 Amyris Biotechnologies opened a plant in Campinas, Brazil, for large-scale production of hydrocarbons from sugar cane processed using genetically engineered microbes [Bourzac, 2009]. These countries are moving towards stronger regulatory systems for products such as pharmaceuticals. Countries that already have robust regulatory systems should assist in this process, with the wider goal of improving all regulatory systems rather than allowing potential bottlenecks and flaws in existing models to be replicated in new systems.

5.7 Technological risk management options

Synthetic biology might create ways to mitigate some of the risks of products such as drugs or GM crops that are addressed by current regulatory frameworks, or to contribute to improved standards for biofuels. Some of the challenges posed by these technologies might become amenable to technological, rather than regulatory, solutions, and as a result synthetic biology might motivate regulatory reform and revision. Similarly, for some of the potential risks of synthetic biology, technological means to assure safety may be more appropriate than setting up a new regulatory system or extending an existing one.

The introduction of concepts from systems engineering, especially from safety engineering, to biology has been suggested as one way in which synthetic biology itself may help to overcome existing and possible future biosafety problems [Schmidt, 2009a]. To prevent the uncontrollable proliferation of novel organisms, for example, it might be feasible to make them dependent on nutrients not found in nature, or to equip them with self-destruct mechanisms [Endy, 2005; Church, 2005], or to incorporate multiple sources of dependency that will minimise their survivability in the wild. And making these organisms chemically distinct from natural ones, the possibilities for their interaction might be restricted. Proposals to build in safety by design are controversial, however, partly because of the de facto moratorium agreed on genetic use-restriction technologies (GURTs) in 2000 at the Fifth Conference of the Parties (COP) to the Convention on Biological Diversity (CBD) (Section III of Decision V/5 on Agricultural Biological Diversity).

For some of the potential risks of synthetic biology, technological means to assure safety may be more appropriate than setting up a new regulatory system or extending an existing one

In principle, the incorporation of GURTs into transgenics is in keeping with the aims of the Cartagena Protocol (Article 2), since they would block gene flow. But the moratorium recommends that field testing and commercial use should not be approved at present. In March 2006, the COP 8 to the CBD rejected calls to regulate GURTs based on a case-by-case risk assessment approach (Decision VIII/23 of COP 8). Rather, parties were urged to "continue to undertake further research [...] on the impacts of genetic use-restriction technologies, including their ecological, social, economic and cultural impacts, particularly on indigenous and local communities". More needs to be known about GURTs and their potential value in developing containment strategies for synthetic biology.

5.8 Policy and regulatory strategies related to public and stakeholder dialogue

[For this paper, we define 'stakeholders' as organised representatives of particular constituencies with shared interests and/or values. This includes trade bodies representing companies, patient groups representing sufferers from particular diseases, and NGOs involved in advocacy related to health or environmental risks. The term 'public' refers to citizens acting as individuals who may or may not have an interest in synthetic biology and its products.]

A prominent theme at the IRGC workshop on synthetic biology was the 'fear of the fear of the public'

A prominent theme at the IRGC workshop on synthetic biology was the 'fear of the fear of the public' – a concern among those working on synthetic biology that the kind of public response to GM crops that emerged in Europe in the late 1990s would be transferred, perhaps in a more virulent form, to synthetic biology. Since the 1990s there have been major improvements in engagement approaches [Dietz and Stern, 2008; EPA, 2001]. However, it is still challenging to find ways of reconciling fundamentally conflicting values or ideologies [Tait, 2001]. Also, where there are strong differences of opinion at the outset of a debate, it is hard to manage the process in such a way as to avoid further polarisation of views and exacerbation of conflict [Sunstein, 2009].

It would be desirable to move from a paradigm in which innovative technologies are simply either rejected or accepted to a form of partnership that guides development

On the other hand, workshop participants also expressed the hope that some of the characteristics and potential applications of synthetic biology would enable it to avoid the ideologically motivated rejection that was, and still is, a prominent part of European opposition to GM organisms. For example, it would be desirable to move from a paradigm in which innovative technologies are simply either rejected or accepted to a form of partnership that guides development, such as occurs between patient groups and pharmaceutical companies in the development of new drugs.

Research in synthetic biology is thus likely to proceed within a context of open dialogue about its potential benefits and its social, economic and ethical implications, at a time when all of these outcomes will still be highly uncertain. This raises questions of how and when to incorporate stakeholder concerns into decision-making about future developments, what power and influence state and non-state actors (both expert and lay) should have, and how widely the dialogue should be framed. On this last point, there is a need to promote understanding not just of the science and technology involved but also of the processes of innovation and technology development, the relevant regulatory regimes, and how they interact with one another. A broader framing of public and stakeholder engagement is thus required that includes debate about these socioeconomic issues.

This is a complex task, but that in itself could encourage new forms of communication and dissemination that reach beyond the traditionally didactic approaches of the 'public understanding of science'. Some of the basic scientific issues in design and biosafety have already been presented in comic-strip form [Endy et al., 2005]; there is also now a wealth of experience that can be tapped in exploring the interactions of science, technology, policy and society using theatre, enactments and structured debate, in areas such as climate change, sustainability, health and genetics (see, for example, http://www.wellcome.ac.uk/Funding/Public-engagement/Funded-projects/Profiles/index.htm; http://www.kandu-arts.com/).

Innovation-related dialogue or engagement is particularly difficult, however, when there is ignorance or uncertainty *among all parties involved* about the eventual nature of new products, processes, benefits and risks. In such cases, the way the technology and its applications are framed can be highly speculative, and there is the danger of debating illusory risks based on assumptions and preconceptions more than on the directions the research is actually taking (compare, for example, early discussions of self-replicating 'nanobots', dubbed 'grey goo', in nanotechnology, which were never an explicit or immediately feasible objective).

Public and stakeholder engagement activities could be viewed in two stages:

- A structured dialogue between risk assessors, scientists, regulators and the full range of stakeholders to identify relevant developments, evaluate the appropriateness of current risk assessment and regulatory frameworks, and discuss potential risk management options and their interactions with technology development as a basis on which to build risk governance strategies.

- The knowledge base from the above process would inform a wider dialogue and engagement with citizens and stakeholders about emerging applications, making judgements on a broad basis related to perceived benefits and risks.

As noted above, engagement and dialogue can lead to polarisation of views and more entrenched conflict rather than consensus, and policymakers might consider whether clear 'rules for engagement' should be established [Tait, 2009b], for example on the standards of quality and breadth of evidence considered and the willingness of all participants to listen to and respect each others' views. Polarisation of views is much less likely to occur where all sides in a debate have a common interest in reaching consensus and will accommodate the needs and interests of others in order to reach that consensus: compare, for example, the discussions that regularly take place between patient groups and drug developers.

Dialogue around shared interests could lead to more creative regulatory solutions that take into account public demands and expectations but are not dominated by the views of vocal minorities or the degree of activism and political influence that stakeholders are able to mobilise. Ultimately, the policy aim should be to enable people, organisations, policymakers and governments to make informed choices within the constraints of effective regulatory systems, and to avoid the imposition of a single set of values that unnecessarily constrains the opportunities available to society at large.

Engagement and dialogue can lead to polarisation of views and more entrenched conflict rather than consensus, and policymakers might consider whether clear 'rules for engagement' should be established

6. Guidelines – Avoiding future risk governance deficits for synthetic biology

As noted in the Introduction, policymakers and regulators can increasingly be seen as shaping rather than reacting to innovative science and technology. With this in mind, we propose the following guidelines that should help policymakers and regulators avoid future risk governance deficits in research and technology development and public and stakeholder engagement.

Policymakers and regulators can increasingly be seen as shaping rather than reacting to innovative science and technology

The first set of guidelines relates particularly to research and technology development; the second to stakeholder engagement; and the third to systemic interactions across innovation, governance and stakeholder constituencies. The guidelines relate to the risk governance deficits identified in Section 4 and are based on a broad understanding of developments in synthetic biology, including discussions at IRGC workshops and with a wide range of experts in this area.

We have aimed to maintain balance, to base risk governance as far as possible on evidence of harm, and to accommodate the values and interests of all societal groups, maximising the scope for choice among a range of technology options. We want to help policymakers avoid irrevocable commitments to particular forms of regulation that will themselves lead to risk governance deficits in the future.

6.1 Guidelines relevant to research and technology development

6.1.1 Biosecurity risks

Guideline 1
Develop and implement internationally standardised procedures and preferred practices for mitigating biosecurity risks as a whole, and in particular for screening requests to commercial companies to supply gene sequences; and create an international, systemically organised approach to promoting a 'culture of responsibility', backed up by legal mechanisms, along with surveillance and intelligence on deliberate threats.

Guideline 2
In assigning hazard and containment levels to micro-organisms, consider both the properties of the parent organism (as in current provisions) and the nature of the modification, recognising that sufficiently extensive modification might result in the parent organism no longer being the appropriate point of reference.

Guideline 3
Conduct regular reviews of biosafety standards in synthetic biology laboratories to identify differences between mandated and actual laboratory practice.

Guideline 4
Avoid imposing restrictions on researchers that would, in the long run, inhibit society's capacity to respond both to natural and to intentional biosecurity threats; and support the use of synthetic biology to develop improved disease diagnostics and vaccines as a means of combating illicit use of this technology.

Guideline 5
For researchers working in synthetic biology who do not have previous training in biosafety: establish a dialogue on the nature of responsible conduct in this field, and provide education about experimental risks, including biosafety principles and practices.

6.1.2 Choosing an appropriate regulatory precedent

Guideline 6
For products arising from first-generation synthetic biology, choose the most appropriate regulatory precedent (e.g., for vaccines, diagnostic techniques, biofuels or plants) and avoid reinforcing regulatory systems that most important stakeholders currently find inadequate. This will entail careful evaluation of the extent to which such regulatory frameworks are transferable to new products from synthetic biology, and of the implications of such choices for future development options. Aim to use this opportunity to assess and improve current regulatory systems and to prevent potential bottlenecks and flaws in existing models from being replicated in new systems.

Guideline 7
Where new organisms capable of autonomous replication are used in production processes or where they are part of a final product, introduce design elements that restrict as far as possible their ability to survive in a natural environment. In this context, reconsider the circumstances under which the use of genetic use restriction technologies could be developed within the constraints set up by the Convention on Biological Diversity.

6.1.3 Balancing transparency and confidentiality

Guideline 8
Ensure that intellectual property rights claims cannot be used to restrict access to information needed for effective risk regulation.

6.1.4 The need for flexibility in the face of unexpected outcomes

Guideline 9
In the face of uncertainty about future risks, ensure flexibility in all interim regulatory initiatives, and include proposals for adaptation and revision on the basis of new evidence.

6.2 Guidelines relevant to public and stakeholder engagement

Guideline 10
Develop better procedures to involve a balanced range of stakeholders in dialogue about new developments in synthetic biology, including scientists, company managers, interest groups (for example, patients and farmers), NGOs and citizens. In addition to

dialogue with public groups motivated by shared values, ensure that equal prominence is given to groups with interests in the development of technology – for example, relevant patient groups in drug development.

Guideline 11
In addition to the usual focus on the science and risks of potential products, include in the dialogue discussion about innovation and regulatory processes and how these can safeguard against future risks (so that, for example, the 'slippery slope' argument that extrapolates into an imaginary landscape of risks and fears cannot be used to support unduly restrictive prohibitions at an early stage).

6.3 Systemic guidelines

Guideline 12
Encourage understanding among all relevant actors of the interactions between risk governance, regulation, market practices and innovation systems so that policymakers might aim to achieve a balanced resolution of various trade-offs, for example by explaining the risks of not doing as well as of doing. Where the development of certain products (such as new drugs) carries a strong potential social benefit, consider using policy incentives, such as market mechanisms, infrastructure investment or regulatory 'fast tracks', to avoid unnecessary delays on grounds of risk.

Guideline 13
Allow regulatory frameworks scope for adaptability to new knowledge and technical capability, while recognising the danger of irreversible harms that could not be redressed by future adjustments.

Guideline 14
Support international dialogue on regulatory oversight and the development of internationally applicable principles, particularly in relation to biosafety and biosecurity risks. An important part of this process will be to support the growth of knowledge, infrastructure and implementation capacity in developing countries.

Conclusion

Synthetic biology offers the potential to help us both further our understanding of natural biological systems and also develop new biologically-based systems to tackle pressing environmental and public health needs. In order to realise its full economic and social potential, the field needs to be subject to partnerships and international collaborations between technology developers, policymakers, regulators and public and stakeholder groups.

Credible, effective and appropriate governance systems are a key part of ensuring that the benefits of synthetic biology are realised while minimising risks. To devise such systems, policymakers need to make decisions that balance potential benefits and harms in the face of uncertainty about the eventual nature of products and processes. We hope these Guidelines will help to identify and promote policies and practices that assure responsible conduct of research and innovation in the field.

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IRGC believes that improvements in risk governance are essential if we are to develop policies that minimise risks and maximise public trust and effectiveness 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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