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Unpackaging synthetic biology: Identification of oversight policy problems and options

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Abstract

The emerging field of synthetic biology (SB) is just entering policy debates. Reports from non-governmental organizations, such as the ETC Group and the International Risk Governance Council, have recently been issued, but there have been few systematic analyses of the policy problems that we will likely face as this area develops. Biosecurity issues are the most defined; other societal oversight issues and implications have not been well explored. Although SB could assist in addressing pressing global challenges, such as sustainable and renewable energy, there are considerable societal concerns that accompany its development and applications. This article is designed to anticipate and prepare for these concerns by identifying policy problems associated with SB oversight, upstream of its development. Projected applications of SB are reviewed and a typology of them is developed. Key oversight policy problems are then identified based on historical experiences with other emerging technologies, such as nanotechnology and biotechnology. Problems associated with biosecurity, biosafety, intellectual property, and ethics are discussed in relation to the typology of SB applications to identify applications of the highest potential concern. Finally, policy options for SB oversight are considered, preventative to promotional. We propose that different categories of SB application may warrant different oversight regimes: there might not be an appropriate "one size fits all" approach. We stop short of making specific recommendations, but suggest that the typology, problems, and oversight options identified in this article be used as a starting point for deliberative, democratic decisionmaking processes that take into account a wide range of perspectives about risk, economic impact, scientific progress, and moral reasoning in the design of oversight systems.

Keywords: oversight, policy, synthetic biology.

Introduction

Synthetic biology (SB) seeks "to discover and apply the operational principles of biological systems through the design and construction of biologically inspired parts, devices,

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and systems that do not exist in the natural world and to redesign existing, natural biological systems for useful purposes" (Engineering and Physical Sciences Research Council and National Science Foundation 2009). SB is expected to provide benefits to society in several sectors, including human health, agriculture and food production, environmental protection and remediation, bioenergy, chemical synthesis, and biosensor development, among others. Engineered cells may one day be used for the production of therapeutic chemicals to combat a range of diseases, including cancer (Gibbs 2004), malaria (Gibbs 2004), AIDS (Horne *et al.* 2009), and diabetes (Meredith 2003). They may also aid in the efficient production of carbon-neutral biofuels to combat climate change (Stephanopoulos 2007). Synthetic microorganisms may one day be released into the environment to digest or neutralize hazardous pollutants such as toxic chemicals and heavy metals (Lovley 2003). Artificial cells may one day have the capability to perform simple computations, sensing, and decisionmaking to create more effective drug delivery systems (Tu *et al.* 2007). Agricultural crops could be better protected through the design of SB pesticides. The chemical industry could gain the capability to produce novel chemicals as well as existing ones with greater efficiency through SB (Rincones *et al.* 2009). SB is just emerging and its potential is yet to be realized. However, with SB come significant societal oversight challenges.

The current research market for SB has been estimated at $600 million, with projected growth for 10 years estimated as more than $3.5 billion (Beachhead Consulting 2006). Lux Research predicts that by 2015, one-fifth of the chemical industry (now estimated at $1.8 trillion) could be dependent on SB (Lux Biosciences Intelligence 2009). The construction of a completely artificial cell is well underway (Gibson *et al.* 2008), and hundreds of biological parts for use in SB have been generated and catalogued (The BioBricks Foundation 2009). Several academic and other institutions have produced a library of standard genetic and biological components that perform specific functions and can be put together ("mixed and matched") to make SB systems or devices (called the Registry of Standard Biological Parts or BioBricks™) (The BioBricks Foundation 2009). With the current knowledge of genomics and systems biology and the developments in nanotechnology and information technology, it is clear that SB is a rapidly developing field.

But the same technology that offers potential for societal benefits is also capable of creating human and environmental hazards. Microorganisms exist in a highly complex environment of chemical signals. Naturally occurring cells derive their genetic functions through the process of evolution over millions of years of trial and error. Biologists are now embarking wholeheartedly on a mission to circumvent evolution by introducing human design into that process. But human error is a concern, especially when dealing with complex new technologies and, in biology, hazards are heightened by the ability of living organisms to reproduce and proliferate in a manner that is difficult for humans to control.

There is also the potential for intentional harm by malicious individuals who become skilled in SB. For example, the DNA for the polio and smallpox viruses has been sequenced, and the genome sequences currently exist as computer files in accessible online databases (National Institutes of Health [NIH] 2009; Sanger Institute 2009). Openly published knowledge and tools for SB could lead to populations of people with the knowledge and expertise to create harmful synthetic microorganisms (Relman 2006). As our understanding of synthetic genomics increases, so does the knowledge on how to create lethal pandemics.

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Synthetic biology has the potential to make a dramatic impact on society through its beneficial applications as well as its harmful misuses, mishaps, or unintended effects. This dilemma begs familiar oversight questions: How can we maximize the benefits of SB while minimizing the risks to society? How do we keep potentially dangerous technology out of the hands of people who wish us harm? How can the benefits of SB be equitably distributed? How can the values of individuals and societies be respected in the face of this powerful technology?

Synthetic biology now promises to provide us with a means to engineer living systems, perhaps even allowing us to bypass the process of evolution. The scale of this vision behooves us to look "upstream" prior to wide-scale deployment and use, to anticipate its possible social impacts. There has recently been a push to look upstream for other emerging technologies, such as nanotechnology, through a framework of anticipatory governance (Guston & Sarewitz 2002). Justifications cited to provide upstream assessments of emerging technologies include the need to enhance public confidence; the need for societal values to be incorporated into technology development process; the need for public engagement and transparency in the oversight development process; and the need to have oversight mechanisms and policies established for products prior to market introduction (Guston & Sarewitz 2002; Wilsdon & Willis 2004; Kuzma *et al.* 2008).

The time seems ripe for upstream analyses of potential policy problems and options. There is currently little public awareness of SB. One recent study has found that only 9% of Americans have "heard a lot or some" about the field of SB, while 22% have "heard just a little" and 67% have "heard nothing at all" (Hart 2008). Furthermore, the number of researchers in the field is limited. Also lacking is a clear consensus about how SB should be overseen. Although SB products will likely be regulated similar to the products of biotechnology, these past oversight regimes have been criticized for significant shortcomings in their handling of genetic and biological cross-contamination incidents, post-market monitoring, level of public engagement in decisionmaking, and transparency (Pew Initiative on Food and Biotechnology [PIFB] 2004; Kuzma *et al.* 2009; Rodemeyer 2009). SB, given its profound ethical and social dimensions, is likely to exacerbate the problems with current regulatory frameworks for biotechnology, and there is renewed interest in improving oversight to prepare for SB (Caruso 2008; Rodemeyer 2009).

This article looks upstream at the policy issues that are likely to become associated with SB as its applications enter into society. It is designed not to predict but to help prepare for a future with SB. In this analysis, we first develop a typology of the applications and products of SB. By drawing upon historical experiences with other emerging technologies, we then use the framework of policy analysis (Bardach 2000) to identify key policy problems that are likely to be associated with SB oversight. The analysis is based upon existing published evidence and scholarship and our previous interviews with experts and stakeholders to address biotechnology and nanotechnology oversight policy (Kuzma *et al.* 2009). We then draw on the literature to discuss different overarching policy approaches to address the problems. We propose that different categories of SB application may warrant different oversight regimes, and there might not be an appropriate "one size fits all" approach. We stop short of a full policy analytical approach (evaluation of particular options, tradeoffs, and outcomes) and argue that policy recommendations should be built from consultation with experts and stakeholders representing multiple disciplines, and developed in the presence of stakeholders and public citizens. Given the broader societal issues surrounding SB, which intersect with and lie outside of science

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and risk, wide-scale deliberative democratic processes should be conducted upstream of technological deployment to prepare for a future with SB.

Related emerging technologies and applications of SB

Synthetic biology is a conglomerate of different fields and approaches that draw upon various scientific disciplines. SB researchers and practitioners use many different strategies, research tools, and materials, but share the overall goal of creating new forms of biological systems, some of which could be synthetic forms of life (Balmer & Martin 2008; The Royal Society 2008; Synbiology 2009). SB has been described as "the engineer's approach to biology" (Breithaupt 2006). Most definitions for SB in the literature include the construction of novel biological entities and the engineering and redesign of existing natural biological systems for useful purposes (Benner & Sismour 2005; New and Emerging Science and technology [NEST] 2005; Luisi *et al.* 2006; O'Malley *et al.* 2008; Massachusetts Institute of Technology–Computational and Systems Biology [MIT–CSBi] 2009). However, there seems to be no consensus on a community definition of SB.

Synthetic biology is interdisciplinary: it is based on an engineering approach, draws on recent advances in systems biology, and interfaces with a variety of disciplines such as biology, chemistry, physics, computer science, and mathematics, among others (International Risk Governance Council [IRGC] 2008). Biotechnology and nanotechnology are two other emerging (or emergent) technologies that are interdisciplinary, and they converge with SB. Nanotechnology involves the control and manipulation of matter at the atomic and molecular scales. SB differs from nanotechnology in that it always involves some type of biological matter (DNA, RNA, protein, carbohydrate) whereas nanotechnology may not. However, when biological molecules are manipulated at the nanoscale, the two emerging technologies intersect. Biotechnology involves the manipulation of biological molecules such as DNA and protein. Genetic engineering, a subset of biotechnology, and to a lesser extent nanotechnology, are good starting points as historical precedents for examining the potential policy problems and options associated with SB, and they will be used in subsequent sections of this article. However, it should be noted that parallels between SB and other technologies, such as information technology and semiconductor technology, may also be instructive for formulating policies and programs for oversight.

One difference between conventional genetic engineering and SB is the level and extent of genetic transfer. Conventional genetic engineering involves the transfer of one or a few genes from one organism to another, whereas SB applies engineering principles to genetics, protein synthesis, and integration of bio-macromolecules to allow the construction of novel biological systems from genes or other biological parts, akin to the construction of electronic circuits (Tucker & Zilinskas 2006). Multiple genes may be transferred with SB, and the genetic material may not necessarily be derived from that found in nature (IRGC 2008). In essence, SB strives to lower the economic and practical barriers to entry into the field of genetic engineering through the development of standardized engineering and production methodologies. While today a genetically engineered organism (GEO) typically is a conventional organism enhanced by the transfer of a few genes from other organisms (e.g. Bt corn contains a pest resistance gene and a few other genetic elements for regulating this gene) (National Research Council [NRC] 2000), future bioengineered organisms may contain a large number of gene combinations

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intended to serve a wide array of functional purposes. The number of genetically engineered traits available will be limited only by DNA synthesis capability and human imagination.

It is worthwhile to consider the differences between SB and conventional genetic engineering technologies to help determine which policy issues will transcend both and which features of SB will require special attention. The following are themes found in literature that highlight the *distinguishing features* of SB and suggest technology-based criteria by which SB can be classified.

1. *High engineered complexity*. Genetic engineering today typically involves the insertion of a few genes into host organisms whereas SB involves higher engineered genetic complexity, extending even to the synthesis of entire genomes. The ultimate aim of SB is to understand and manipulate the genetic code to program living cells in a manner akin to the way electronics are now programmed by sophisticated software routines (Shapiro & Beneson 2006).
2. *Engineering and manufacturing standardization*. SB strives to create a knowledge base of reusable component parts and design methodologies to create engineering economies of scale resulting in enhanced productivity in development and production flows. An example of this is the MIT Registry of Standard Biological Parts (Gibbs 2004; The BioBricks Foundation 2009).
3. *Novel life forms*. SB endeavors to create novel microorganisms that do not exist in nature. While most applications for years to come will be manipulations of existing life forms, SB enables the creation of cells that have fully synthesized genomes and functions. The starting point for this is the self-sustaining minimal cell (Luisi 2002; Gibson *et al.* 2008; *Nature News* 2008).
4. *Systems scope to engineering*. Through advanced system modeling, SB enables the development of complex networks of engineered organisms that function and communicate in concert within complex biological environments to solve specific problems (Weiss *et al.* 2003; Tu *et al.* 2007).

Note that these criteria do not attach SB to specific biology-based taxonomical category (e.g. kingdom or species levels). Included in SB are the simplest of living microorganisms, such as viruses (although there is much debate over whether or not viruses can be truly classified as living organisms), as well as more complex microorganisms such as bacteria, systems of microorganisms, and plants. Biological components used in non-living SB applications can be derived from all kingdoms, including animals, and then altered, or they can be artificially generated.

Another way to type SB is by its products. Currently in the US, emerging technologies are regulated by product type and usage rather than by the methods by which they were created. The Coordinated Framework for the Regulation of Biotechnology (CFRB) was formulated in 1986 and was designed for the regulation of environmental release and use of GEOs outside of the laboratory (Office of Science and Technology Policy [OSTP] 1986). The CFRB instructed three US federal agencies, the Environmental Protection Agency, the Food and Drug Administration, and the Department of Agriculture, to use the Toxic Substances Control Act, Federal Insecticide, Fungicide, and Rodenticide Act, Federal Food Drug and Cosmetic Act, and the Federal Plant Pest Act to regulate the products of biotechnology and GEOs. The framework relied on the policies that the

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"product not process" should be the focus of regulation, and that no new laws were needed to cover GEOs and their products (OSTP 1986). The political will to adopt this framework stemmed in part from controversies, court cases, and Congressional hearings about the proposed release of a GEO, the "ice minus" bacterium, into the environment (US Congress 1983).

It is expected that SB products will also be treated on a product-by-product basis under the CFRB for environmental, agricultural, or market release. For laboratory experiments, SB will likely be overseen by the National Institute of Health's (NIH) Guidelines for Research Involving Recombinant DNA and its Recombinant DNA Advisory Committee (NIH 1978). As reviewed in the introduction to this article, SB can be applied to many areas, including fuel production, environmental remediation, agriculture and food, materials, consumer products, health, and medicine. Given the product basis for regulation and the different social and political contexts in the various sectors (e.g. with regard to power relationships, system organization and operation, stakeholders, and attitudes toward risk), policy issues surrounding SB will be dependent not only on the subset of technologies used, but also on the product and the sector in which it is deployed.

To anticipate these policy problems and grapple with ways to address them in the absence of knowledge about the exact uses of SB, in this article we develop a typology of the field of SB and its applications. The matrix presented in Table 1 categorizes applications of SB based on technologies (process) and sectors of deployment (product usage). Six categories of technology and six sectors are identified. There are many ways to characterize applications of SB, and it should be emphasized that the boundaries between the categories are not sharp. However, we present the typology as a framework by which to "unpackage" SB and more meaningfully discuss policy issues and options in subsequent sections of this article. The six sector (product) categories of SB proposed in Table 1 are defined below.

- Human medicine: drugs, devices, over-the-counter medicine, clinical therapies, etc.
- Consumer products: computers, sporting goods, cosmetics, etc.
- Energy: synthetic fuels, biofuels, electricity, hydrogen, etc.
- Food and agricultural production: pesticides, engineered crops, fertilizers, etc.
- Chemical production: industrial compounds, high-value compounds, plastics, etc.
- Environmental application: remediation, restoration, monitoring, detection, etc.

The following six categories of applications by SB technology, or process, are derived from a review of the SB literature and are based in part on the *distinguishing features* of SB discussed above.

- Non-living biological parts: engineered biological molecules (derived mostly from or inspired by nature) to perform a function.
- Systems of non-living biological parts: systems of many types of engineered biological parts to perform a function.
- Highly engineered living cells: complex genetic engineering of one cell type to perform a function.
- Highly engineered systems of living cells: complex genetic engineering of multiple types of cells linked in systems.

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Table 1 Draft typology of synthetic biology applications and their areas of concern

Technology (process criteria)	Sector (product type category)					
	Human medicine	Consumer products	Energy	Food and agricultural production	Chemical production	Environmental application
Non-living biological parts	IP				IP	
Systems of non-living biological parts	IP*	IP	IP	IP	IP*	IP
Highly engineered living cells	IP* Biosecurity* Ethical	IP Biosafety* Ethical*	IP Biosafety	IP Biosecurity Biosafety* Ethical*	IP* Biosafety Ethical*	IP Biosecurity Biosafety* Ethical
Highly engineered systems of living cells	IP* Biosecurity* Ethical	IP Biosafety* Ethical*	IP Biosafety	IP Biosecurity Biosafety* Ethical*	IP* Biosafety Ethical*	IP Biosecurity Biosafety* Ethical
Artificial living cells	IP* Biosecurity Ethical	IP Biosafety* Ethical*	IP Biosafety	IP Biosecurity Biosafety* Ethical*	IP* Biosafety Ethical*	IP Biosecurity Biosafety* Ethical
Systems of artificial living cells	IP* Biosecurity Ethical	IP Biosafety* Ethical*	IP Biosafety	IP Biosecurity Biosafety* Ethical*	IP* Biosafety Ethical*	IP Biosecurity Biosafety* Ethical

*Denotes an even higher level of concern.
IP, intellectual property.
Note, however, that these issues will affect all categories of application to some degree.

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- Artificial living cells: living cells derived from human synthesis.
- Systems of artificial living cells: systems of many types of living cells derived from human synthesis.

We hypothesize that some of the unresolvable dilemmas associated with SB oversight may be due to the conglomeration of a diversity of products, sectors, and technologies during policy debates. Thus, we consider the typology as a useful starting point and a way to unpackage SB for analysis and deliberation.

Identification of policy problems

Below we identify key policy problems associated with SB by drawing on historical experiences with other emerging technologies, and we examine illustrative examples of SB applications with respect to these problems. We use an overarching framework of "SB oversight." "Oversight" is defined as "watchful and responsible care" (*Merriam-Webster Dictionary* 2009) and is broader than regulations and statutes to govern risk. It includes, among other things, how laws are interpreted, voluntary measures, policies, and guidelines. Policies that guide oversight systems affect technological development and public confidence in products of emerging technologies (e.g. Rabino 1994; Macoubrie 2006; Siegrist *et al.* 2007). We use an oversight framework to capture a multitude of societal responsibilities and intersections among different kinds of policy issues.

The International Risk Governance Council (IRGC) has identified categories of "risks" raised by SB that need to be considered: (i) environmental (e.g. biosafety), (ii) social (e.g. biosecurity), (iii) economic (e.g. intellectual property), and (iv) ethical issues (e.g. natural/unnatural) (IRGC 2008). However, many policy issues related to oversight transcend these categories and not all are appropriately framed by "risk." For example, ethical issues are embedded in environmental risk assessment (Thompson 2007; Kuzma & Besley 2008) but are not themselves typically considered risk issues. The choice of intellectual property regime (open source, security classification, patent protection) can affect biosecurity and economic development, as well as pose difficult ethical dilemmas about "owning life." Thus, we use the categories of the IRGC but frame them more broadly as oversight issues and also consider the ways in which these areas intersect.

Intellectual property

For other emerging technologies, intellectual property (IP) protection, offered through patents, confidential business information (CBI), and trade secrets has clashed with public and stakeholder desires for access to research resources, transparency and engagement in decisionmaking, and affordable technological products (NRC 2000; PIFB 2006; Kumar and Rai 2006; Kuzma *et al.* 2009). Given the early stages of development of SB, it is an opportune time to examine the nexus of intellectual property and oversight before widespread technological deployment.

Existing IP law and policy may be tested by SB. It has been difficult for IP law to accommodate new technologies such as biotechnology, nanotechnology, and software. Rai and Boyle (2007) describe SB and IP issues as the "perfect storm," resulting from "flawed biotech law" meeting "flawed software law." There is an ongoing debate in the SB community between advocates of open source approaches and supporters of patent protection. Open source proponents argue that sharing of data and resources is essential

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to the growth of the SB community and for knowledge creation. The idea of a "synthetic biology commons," akin to the open source software movement, has arisen as an alternative to the push for proprietary SB products and information (Rai & Boyle 2007). However, others have argued that IP protection through trade secrets, CBI, and patents is necessary for investment into and growth of the field. A key dilemma is to provide some form of IP protection "without stifling the openness that is so necessary to progress" (NEST 2007, p. 15).

The treatment of IP is an important component of the oversight system for SB. Although there have been extensive analyses of the advantages and disadvantages of different IP regimes for SB from legal and technological development standpoints (Kumar & Rai 2006; Rai & Boyle 2007), several other diverse issues that intersect with the treatment of IP need to be considered for SB oversight. IP issues are intertwined with biosafety, ethical, and biosecurity issues and examples of these relationships will be discussed in subsequent sections focusing on these other elements of oversight.

Intellectual property regimes for SB are likely to affect the various categories of product identified in different ways (Table 1). The issue of "patent thickets" (Kumar & Rai 2006) may be most prominent in complex engineered systems of biological parts, where multiple patents on the different parts would need to be navigated and multiple licenses to use these parts obtained. However, the academic community seems to be taking an open source approach, as manifested by the Registry of Standard Biological Parts, which serves to develop an SB "commons" (Kumar & Rai 2006; The BioBricks Foundation 2009), so the typically high costs of patent thickets to technological development might not be so problematic. The development of highly engineered or artificial cells is likely to come with patent thickets on the parts used to create them and is thus classified of high concern for IP issues in Table 1. Significant IP policy issues are likely to permeate virtually all categories of SB application across all sectors, but especially those that can lead to the highest profit from IP protection (e.g. medicine, high-value chemicals).

Biosecurity

Currently in the US, the scientific community and research programs are placing a strong emphasis on the biosecurity aspects of SB, and there has been extensive treatment of SB biosecurity risks in the literature (e.g. Garfinkel *et al.* 2007). The potential for misuse of synthesized organisms has led to concerns that "biohackers" or bioterrorists could recreate known pathogens and perhaps even make them more virulent (Tucker & Zilinskas 2006). There is the potential for intentional harm by malicious individuals who become skilled in SB. As discussed in the introduction to this article, the DNA sequences for the polio and smallpox viruses currently exist in accessible online databases (NIH 2009; Sanger Institute 2009). Within the realm of SB, an increase in the open knowledge of pathogen genomics and biology generally increases the knowledge base for creating lethal pandemics or plagues on the environment if so desired by individuals or terrorist organizations.

These concerns have led scientists and policymakers to focus on issues surrounding the containment of SB knowledge and technology. So far, there seems to be a push toward self-regulation and open access to SB information (NRC 2004a; National Science Advisory Board for Biosecurity [NSABB] 2007). The NSABB is a key US federal advisory committee formed in 2004 that is currently grappling with SB and biosecurity. The Board focuses on how to minimize the risk from "dual-use" biological research (research that

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not only can be beneficial to society but also can be misused) and has created a working group to deal with synthetic genomics, a key component of SB (Relman 2006). The NSABB states that it "strongly supports the free and open exchange of information in the life sciences" and that "the best way to address concerns regarding dual use research is to raise awareness of the issue and strengthen the culture of understanding within the scientific community and public" (NSABB 2007, p. ii). However, the Board has suggested that some categories of experiment (e.g. increasing virulence or resistance of pathogens) should undergo more thorough review by institutional and federal oversight systems through existing channels, such as institutional biosafety committees or review boards, and the NIH Recombinant DNA Advisory Committee (NRC 2004a; NSABB 2007).

Some other policy options for dealing with access to harmful pathogens or DNA sequences for them have been proposed, including having gene synthesis companies screen whether orders are for pathogenic or dangerous sequences, investing in the development of software for more efficient screening of orders, establishing a confidential hotline for biosecurity issues, and affirming the ethical obligations of SB practitioners to report suspect behavior (reviewed in De Vriend 2006). Broader SB oversight options for biosecurity have been outlined, including governmental control, control by an independent authority, a hybrid of institutional and governmental control, institutional control, or control by individual scientists (Miller & Selgelid 2007). Currently, the US framework for dealing with biosecurity seems to be a mixture of these options, depending on the context of the research and the type of SB research or product development; however, it leans toward control by institutions and communities of scientists.

These US national efforts include, but do not necessarily focus on, the "lone perpetrator" who can order DNA synthesis and other biological research equipment and conduct the work in his or her own residence. Policies and programs to prevent such misuse are difficult to envision without intruding on personal privacy. One possibility is to limit the purchase of not only harmful gene sequences, but also any equipment that could be used to synthesize DNA. DNA synthesizers have recently been available for purchase on eBay (Relman 2006).

Biosecurity issues are also affected by IP regimes. For example, an open source movement in the SB community would allow for greater access to resources and information among a variety of researchers. Although this could help grow the field more quickly and equitably, such an approach to IP could increase national health and security threats from SB. With increasing openness there comes a greater chance of information getting into the hands of individuals or organizations that have malevolent intents; however, national organizations have stressed the importance of keeping science open for the most part so that the benefits can be derived and countermeasures to prevent misuse developed (NRC 2004a). Open publishing of SB work in academic journals is of increasing concern as biotechnology becomes more accessible (e.g. DNA synthesizers can be purchased on eBay and there are biotechnology kits for children to manipulate genes). Some have argued that open publication could put the knowledge and expertise to create harmful engineered microorganisms in the wrong hands (ETC 2006). Others note, however, that the creation of whole genomes is very complex and can only be accomplished by experts in the field (Vogel 2008). The National Research Council (NRC) argues for open publication of scientific research to advance the field and defense applications (NRC 2004b). Regardless, some journals have begun to develop guidelines for taking a

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closer look before publishing information about genetic sequences or the biology of dangerous pathogens (van Aken & Hunger 2009).

Although biosecurity is important for all categories of SB, the risk of harmful misuse is most pronounced for living organisms that can propagate, spread, and infect people, crops, livestock, pets, and organisms in ecosystems. Thus, in Table 1, the categories of highly engineered living cells, highly engineered systems of living cells, artificial living cells, and systems of artificial living cells are classified as having high concerns for biosecurity. The sector of deployment might also influence biosecurity risks. For example, synthetic organisms developed for medicine are likely to be more harmful for humans if misused, given their ability to survive in the human body. However, one can also imagine synthetic organisms altered to infect ecosystems and agricultural systems. These three sectors are classified as highest concerns for biosecurity. In the near term, it seems most urgent to consider the highly engineered organisms for biosecurity, as researchers have not yet been able to achieve the development of an artificial cell, and it is unlikely that artificial cells that can thrive outside laboratory conditions will be developed in the near future (i.e. five years).

Biosafety

Although biosecurity concerns are very important, the focus on them in policy domains has led to criticism that other, equally pressing issues are not being given adequate attention (ETC Group 2006). Biosafety issues are important for SB oversight and should also be considered in conjunction with biosecurity, IP, and other oversight issues. Biosecurity and biosafety issues are related in their emphasis on environmental and human health impacts; however, biosafety issues are defined not by malicious intent but rather by the risks of intended SB applications. Synthetic organisms that pose the threat of adverse effects on the environment or on human health could be accidentally or intentionally (e.g. in the case of bioremediation) released into the environment (De Vriend 2006; IRGC 2008).

These concerns about unintended effects were similarly associated with the initial creation of GEOs. In 1975, scientists working on GEOs convened the Asilomar Conference (Berg *et al.* 1975). Asilomar was an international meeting primarily of elite scientific experts who were concerned at the time about not only the health and environmental safety impacts of GEOs, but also the imminent governmental regulation of them. Thus, the Asilomar conversations centered on community self-regulation, and a self-imposed temporary moratorium on genetic engineering experiments. Soon after Asilomar, this moratorium was lifted, and the responsibility of GEO oversight was placed in the hands of the NIH's Recombinant DNA Advisory Committee for laboratory experiments (NIH 1978). Scholars have raised questions about whether Asilomar was the ideal way to initiate policy discussions about genetic engineering or whether it was a strategy for keeping debate confined to a select group of scientists more responsive to the concerns and interests of the scientific community than those of society at large (reviewed in De Vriend 2006).

Regardless, the SB community seems to be taking a self-regulatory path similar to the Asilomar Conference (NRC 2004a; De Vriend 2006). In 2006, at a key meeting of SB researchers (The Second International Synthetic Biology Conference, or "Synthetic Biology 2.0"), a group of SB researchers tried but failed to pass a community resolution for self-governance (Check 2006). This attempt to foster a climate of scientist self-governance was met with sharp criticism from non-government organizations (NGOs)

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such as the ETC Group, Greenpeace, the International Center for Technology Assessment, and the Third World Network, who believed that broader social dialogue was essential for SB oversight given its power and scope (ETC 2006). A few participants who were more critical of SB attended subsequent meetings of the SB community (Syn Bio 3.0 and 4.0), and sessions were held with them to develop a consensus statement (Parens *et al.* 2009). However, one did not emerge.

As previously discussed in this article, SB products meant for use in the environment, food, and agriculture will likely be regulated similarly to the products of GEOs under the CFRB (OSTP 1986). This oversight system has been the subject of considerable criticism with regards to its capability to provide adequate oversight, due to its patchwork structure of antiquated legislation and governmental agency jurisdiction (PIFB 2004; Rodemeyer 2009). It also has shortcomings in its handling of genetic and biological cross-contamination incidents, post-market monitoring, level of public engagement in decisionmaking, and transparency (Kuzma *et al.* 2009). Key oversight policy questions are whether oversight systems and human health and environmental risk analysis protocols for GEOs are adequate for living organisms resulting from SB, especially in light of their novelty and the uncertainty which accompanies their use (De Vriend 2006; Rodemeyer 2009).

As with biosecurity, biosafety concerns seem most prominent for applications and products of SB that involve living organisms. Thus, in Table 1, the categories of highly engineered living cells, highly engineered systems of living cells, artificial living cells, and systems of artificial living cells are categorized as being the highest concern for biosafety. However, unlike biosecurity, applications in the environment and agriculture seem to bear the most potential biosafety risk. Synthetic organisms developed for medicine are likely to be contained in laboratory and clinical settings, generally safe for human use (as approved by the Food and Drug Administration), and under strict laboratory handling and use protocols developed by the NIH Recombinant DNA Advisory Committee, institutional biosafety committees, and institutional review boards. Open market use through environmental, agricultural, and consumer product applications are likely to be of the highest concern. Contained laboratory manufacturing in energy sectors (e.g. synthetic algae for biofuels in photoreactors) and chemical synthesis (e.g. fermentation reactors in the lab) (Table 1) are also of significant concern, and are areas in which biosafety protocols and waste disposal processes will be critical.

Ethical considerations

Ethical concerns about SB have been raised, and a number of committees are presently examining the ethical implications of SB, focusing mainly on the creation and use of synthetic organisms (reviewed in IRGC 2008; Parens *et al.* 2009). SB raises fundamental ethical questions about manipulating and synthesizing life, the appropriate risk–benefit balance for individuals and communities, equitable distribution of the technology, and the basis for decisionmaking. Many of the ethical dimensions of SB present irresolvable ethical dilemmas. For example, there will be some stakeholders and citizens that are fundamentally opposed to tampering with or creating life on religious and moral grounds. An oversight system for SB cannot satisfy every value system that individuals and communities hold. However, space for open discussion and dialogue prior to deployment of SB technology can allow for increased understanding and respect for views from the other side.

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There have been previous calls for wide-scale "upstream public engagement" in decisionmaking about emerging technologies such as biotechnology and nanotechnology (Wilsdon & Willis 2004). These calls seem even more important for SB. However, significant barriers to upstream public engagement exist. Upstream public engagement might be a foreign concept in societies that are undemocratic, as policymakers do not necessarily operate on behalf of the people. But even in democracies such as the US, power relationships or a lack of information about SB may hinder deliberative, democratic processes.

Extensive claims of CBI in regulatory submissions have been identified as a problem in oversight systems because they prevent disclosure of information to stakeholders. For example, there has recently been public frustration over the amount of CBI claimed in company submissions to the Environmental Protection Agency's recent program for collecting risk information for nanomaterials (Goodman 2008; The Bureau of National Affairs 2008). For oversight of emerging technologies, which is often fraught with uncertainty and novelty, transparent and independent processes with opportunities for public input seem desirable. Transparency in oversight and adequate disclosure, especially for situations of "unique and wide impact" (NRC 1996), has been proposed as a cornerstone of the ethical principle of informed consent; important for public confidence trust, and legitimacy, and also for improving decisionmaking through external review, debate, or validation (NRC 1996; Macoubrie 2006; Kuzma & Besley 2008).

For GEOs, transparency in oversight and decisionmaking about products was low, and this affected public and stakeholder confidence in risk assessment for the products and the oversight system itself (Kuzma *et al.* 2009). Several cases are documented in which scholars or practitioners outside of industry and the regulatory agencies could not access information about the features of products in the research, development, and regulatory approval pipeline, and therefore, could not critically evaluate or contribute to the decisionmaking process (NRC 2000; PIFB 2006). A substantial amount of information submitted to regulatory agencies for GE products (e.g. risk relevant data and information) was claimed as CBI, preventing independent review by experts and stakeholders outside of industry and government regulators at crucial times in decisionmaking (NRC 2000; PIFB 2006; Kuzma & Besley 2008).

The novelty of SB and its focus on creating or altering biological systems seems to warrant increased public engagement and dialogue during oversight, but current regulatory policies for emerging technologies seem to privilege corporate confidentiality concerns over providing the public with information with which they can make choices or have input into decisionmaking. Understandably, there is resistance on the part of corporations and others to disclose information about their products in order to protect proprietary information and IP so that their substantial investments in technology development are recouped. However, for SB, it will be important to ensure that the public has access to the relevant information about the products prior to and during decisionmaking. On the other hand, open access to information will likely increase biosecurity risks, as discussed above. There seems to be a delicate balance, especially in the context of the special features of SB, among features of oversight (such as treatment of IP, transparency, and public engagement) and desired outcomes (such as biosafety, biosecurity, public confidence and trust, economic development, and research and innovation) (Fig. 1).

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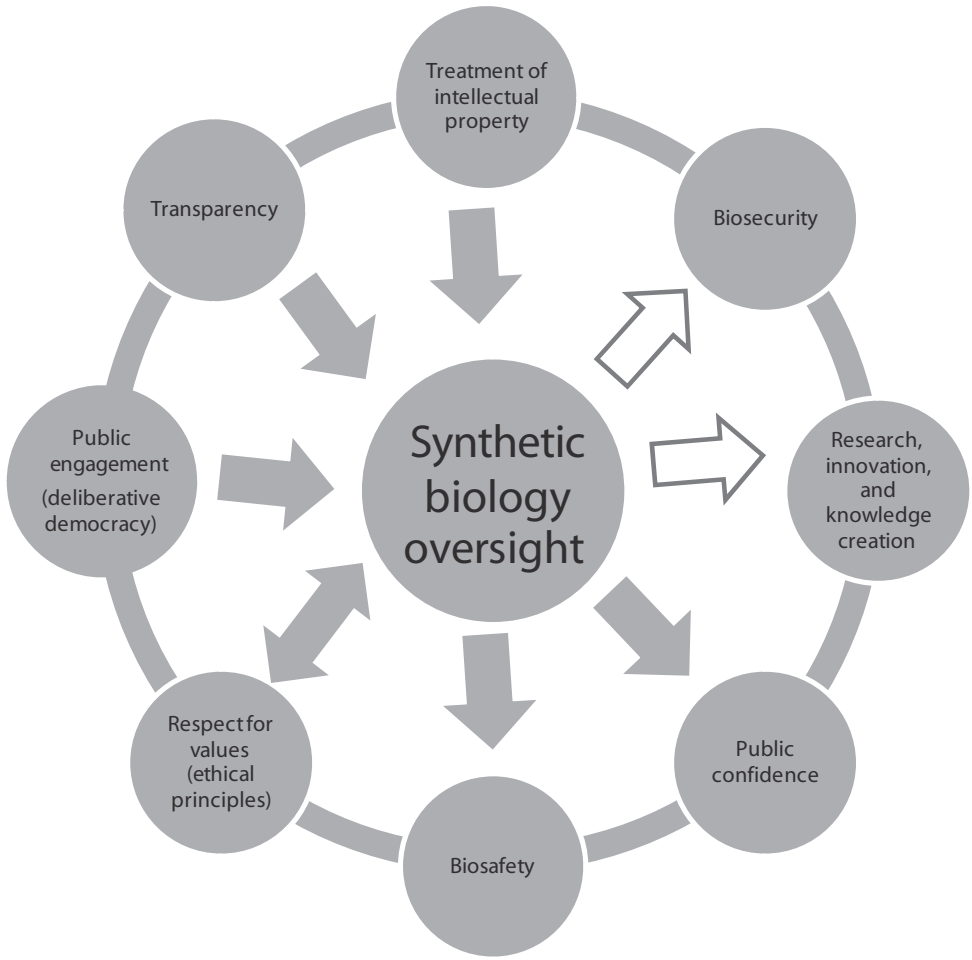

Figure 1 Conceptual model of synthetic biology oversight. Arrows pointing in to the center primarily represent features of oversight systems and those pointing out represent outcomes. Solid arrows indicate gaps in the synthetic biology literature.

Some applications of SB may warrant greater efforts in deliberation and public engagement in order to take into account a wider range of values than others. Ethical issues associated with living SB organisms seem more pronounced considering the fundamental objections some people will have to altering life (Table 1). However, the synthesis of biological parts or networks of them will also come with ethical issues, such as justice associated with the bearers of benefit and risk, global and equitable access to technology, and rights to know and choose products. Sectors of SB deployment that are likely to involve unjust risk–benefit distributions – such as in the chemical industry, manufacturing of consumer goods, and food and agricultural sectors, where large producers might bear the benefits but consumers will bear the risks (as was the case with the first generation of agricultural GEOs) – will also warrant particular attention to ethical issues through deliberation and engagement (Table 1). With regards to medical deployment of SB, it seems that if appropriate informed consent measures are taken, these ethical issues will not be as difficult to address.

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Policy options and conclusions

Synthetic biology poses a significant challenge for researchers and policymakers who strive to balance the need for a climate that is conducive to innovation for societal benefit with the need to prevent health and environmental harms and respect the values of diverse stakeholders and the public. There seems to be widespread consensus in the literature that SB needs oversight. However, the questions remain as to what type of oversight system would be most appropriate to achieve societal goals and how oversight systems can reconcile issues associated with IP, transparency, public engagement, biosecurity, biosafety, and incorporating values in decisionmaking. As we have tried to illustrate in this article, it might make most sense to "unpackage" SB in order to grapple with these significant policy challenges.

Scholars have categorized broad oversight approaches to other emerging technologies as permissive, promotional, precautionary, and preventive in the literature. We used the definitions of Paarlberg (2000) to develop a spectrum of policy choices for IP, biosafety, biosecurity, and ethical considerations in SB oversight regimes. Policies that accelerate the spread of technologies are considered by Paarlberg as "promotional;" policies that are neutral toward new technologies, intending neither to speed nor to slow them, are considered "permissive;" policies that slow down the spread of technologies are "precautionary;" and those that tend to block or ban new technologies are considered "preventive" (Paarlberg 2000). We considered our typology of SB and our identification of policy issues of the highest concern for different SB application categories (Table 1) in the context of Paarlberg's framework of oversight approaches. In Table 2, we illustrate how different approaches to oversight might be chosen for different categories of SB application. It could be argued that for some applications of SB, such as the synthesis of biological parts or systems of parts that are non-living, permissive strategies will promote the greatest social welfare. For other applications, such as highly engineered living cells in medicine, food, agriculture, and the environment, more restrictive regimes seem appropriate.

We present the options in Table 2 not as prescriptive, as they were based solely on the knowledge, expertise, and views of the authors, but rather as starting points for deliberation. Anticipatory governance should be the cornerstone of SB development. Upstream public engagement (Wilsdon & Willis 2004) should be combined with real-time technology assessment, in which natural and social scientists work together during technological development to identify issues (Guston & Sarewitz 2002), and upstream oversight assessment, in which case studies of applications of technology in research and development stages are carefully examined with the public to consider the risk and oversight issues prior to commercialization (Kuzma *et al.* 2008). In a similar frame, Barben *et al.* (2008) describe the key elements of anticipatory governance as "engagement," "foresight," and "integration." Ideally, in the future, a revised and improved version of a SB application typology ("foresight") could be used in the presence of stakeholders, experts, and citizens for a more comprehensive evaluation of policy options for the various applications of SB ("engagement"). Although not explicitly addressed in that article, "integration" involves the inclusion of social science, values, and concerns with natural science in the technical process itself, at the conception of SB applications (Barben *et al.* 2008). Integrative programs that involve multidisciplinary teams and stakeholders have been developed in the field of nanotechnology and could be adopted for SB.

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Table 2 Broad oversight policy options for synthetic biology (SB) applications

	Preventative	Precautionary	Permissive	Promotional
Intellectual property	No access to information	Highly restricted access to information	Largely open access to information	Open access to information
Biosecurity	Control of information and tools by a few	Several have control of information and tools	Most have control of information and tools	Unrestricted access to information and tools
Biosafety	Ban on usage of SB products	Stringent, mandatory government regulation of environmental health and safety	Voluntary or flexible mandatory programs and standards for environmental health and safety	No specific SB provisions or standards for environmental health and safety
Ethics	Ban SB applications with moral objections	Widespread dialogue and deliberation before SB is deployed	Transparent decisionmaking with input from various non-expert stakeholders	Closed processes with little input outside of SB scientific community and decisionmakers
	Treatment of SB applications			
	Preventative	Precautious	Permissive	Promotional
	Highly engineered living cells or systems in food and agriculture and environment Artificial living cells or systems in food and agriculture and environment	Highly engineered living cells or systems in medicine and consumer products Artificial living cells or systems in medicine and consumer products	Systems of non-living biological parts (all sectors) Highly engineered living cells or systems in chemical synthesis or energy Artificial living cells or systems in chemical synthesis or energy	Non-living biological parts (all sectors)

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Specific policy options could be considered through an anticipatory governance approach. For example, a policy option suggested by our framework is to ban highly engineered or artificial living cells in the environment and restrict information about how these cells proliferate in different environmental contexts until there is rigorous premarket safety testing and widespread (national) deliberation. This option would fall toward the preventative and precautionary side of the spectrum in Table 2. Justification for this approach, in part, stems from public concern about GEOs in the environment and limited abilities to assess environmental risk (reviewed in Kuzma *et al.* 2009). GEOs already stretch the abilities of current biosafety risk assessments, and the complexity of SB applications in the environment will exacerbate the uncertainty.

Another example of a policy approach for consideration through a deliberative process is a voluntary, self-regulatory approach to non-living biological parts. Such an approach would also include open access to information and research tools (Table 2). This permissive or promotional approach resembles the one being taken right now by the natural science community (e.g. Registry of Standard Biological Parts). It is likely to encourage innovation in the field with minimal biosafety risks. However, access to knowledge and research tools for parts that are derived from dangerous pathogens might be restricted. There could be different levels of security on databases for parts derived from agents such as smallpox, anthrax, and influenza strains.

The typology and policy problems identified in this article are intended to be used as a starting point for deliberative, democratic decisionmaking processes (Guttman & Thompson 2004) that take into account a wide range of perspectives of risk, economic impact, scientific progress, and moral reasoning. Such an oversight approach, as a model of "watchful and responsible care" (*Merriam-Webster Dictionary* 2009), warrants broad participation and consideration of diverse issues and perspectives that lie outside the bounds of formal government regulation. Given the special features of SB and the issues its applications evoke (especially in the domain of living applications), we conclude that safe, adequate, just, and appropriate policies for oversight can only be designed through wide-scale deliberation.

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