

Synthetic biology and biosecurity

From low levels of awareness to a comprehensive strategy

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Synthetic biology has become one of the most dynamic research fields in the life sciences. In reality, though, the term is used to cover a host of different approaches rather than a single defined discipline; these range from the large-scale assembly of DNA segments to the development of new tools and technology platforms, and to the search for the minimal cell and the origins of life. The evolution of the field has also been accompanied by the recognition that the concomitant shift in biology from a descriptive to a predictive science, and the technologies that will ensue, bring with them a range of potential societal implications and dangers.

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Taking these dangers seriously seems to be warranted given past misuses of advances in the life sciences; major scientific breakthroughs have repeatedly informed offensive state-level biological weapons programmes (Dando, 1999). These abuses have been relevant across the board, from bacteriology in the late nineteenth century to aerobiology and virology in the mid-twentieth century, and to the early stages of genetic engineering, which found its way into the clandestine Soviet biological weapons programme of the 1970s and 1980s. This pattern of misuse raises the spectre that governments or terrorist groups might also abuse future advances in the life sciences to produce biological warfare agents.

It should be self-evident that the different subfields of synthetic biology have different kinds of security implications, which are already relevant or will become so at different points in time. Clearly, the potential security implications of synthetic genomics—with its capacity to generate rapidly large DNA molecules—are of more immediate concern than those of some future minimal cell construct that could act as a chassis for nefarious applications even further down the line.

The potential risks inherent in powerful new technologies have been a recurrent topic among synthetic-biology practitioners, commentators, and national and international institutions. The 2005 New and Emerging Science and Technology (NEST) High-Level Expert Group commissioned by the European Commission (Brussels, Belgium), for example, acknowledged that “genetic manipulation of organisms can be used or can result by chance in potentially dangerous modifications of human health or the environment. The possibility of designing a new virus or bacterium *à la carte* could be used by bioterrorists to create new resistant pathogenic strains or organisms, perhaps even engineered to attack genetically specific sub-populations” (de Oliveira & Krassnig, 2007).

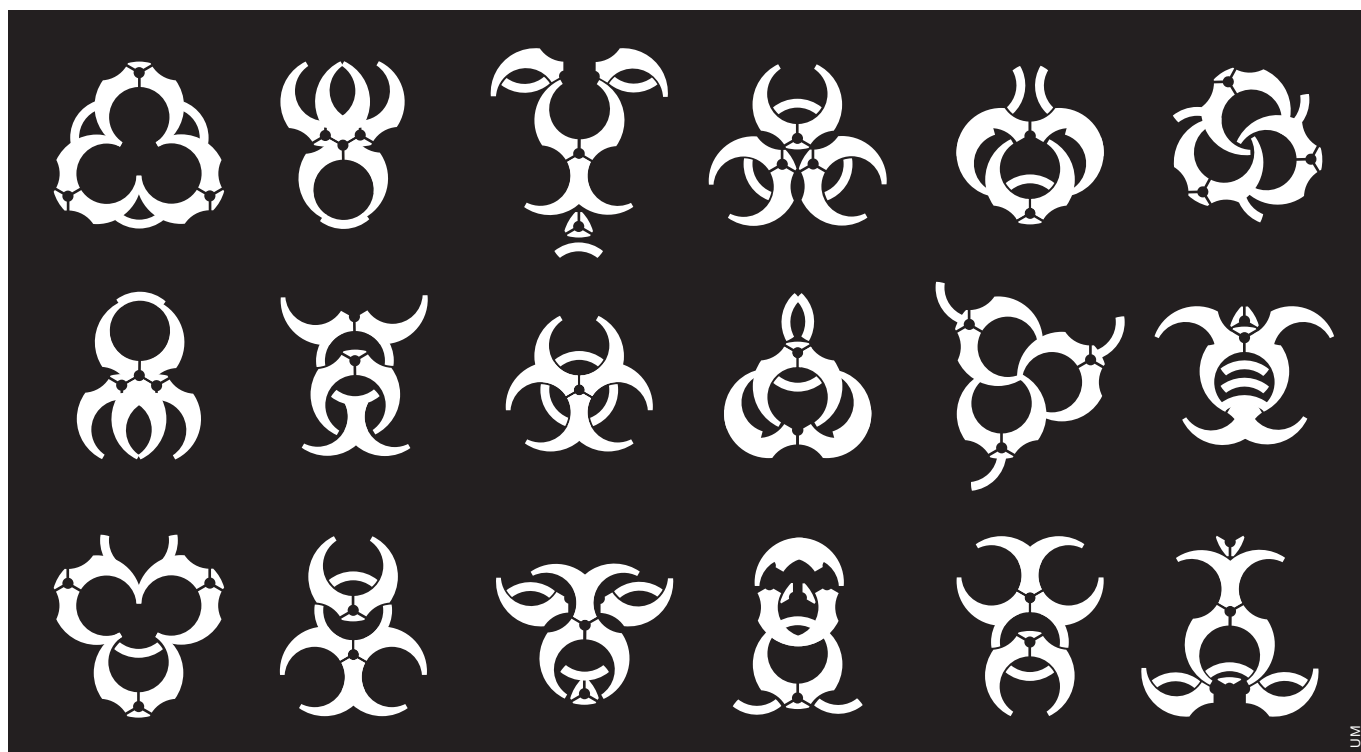
More recently, the chairman of the NEST group cautioned that existing “hurdles and the engineering challenges they currently represent may [...] be overcome in some near future by further advances in science and we need thus to keep vigilant” (Serrano, 2007). This assessment was shared by Garfinkel *et al*, who concluded that “in the near future [...] the risk of nefarious use will rise because of the increasing speed and capacity” of synthetic genomics, which

was one of the key technologies identified by the NEST High-Level Expert Group (Garfinkel *et al*, 2007).

The distinction between biosafety and biosecurity has also been discussed, for instance, during the annual meetings of the states that are party to the Biological and Toxin Weapons Convention (BWC). During the 2006 meeting, the German representative, speaking on behalf of the European Union, provided the following characterization of the two concepts: “[w]hile a biosafety risk classification system is based on the inherent capability of micro-organisms to cause disease, of greater or lesser severity, in humans, animals and plants, a biosecurity risk classification system is founded on the potential of a micro-organism or toxin to be used as a weapon” (Germany on behalf of the European Union, 2006).

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The use of the terms biosafety and biosecurity often draws on guidelines from the World Health Organization (WHO; Geneva, Switzerland) concerning laboratory biosafety and laboratory biosecurity (WHO, 2004, 2006). Pursuing biosafety goals and biosecurity goals are mostly complementary activities with a large area of overlap. However, in certain instances, approaches to achieve biosecurity and biosafety might be at odds with each other. One such example is the idea of engineering biosafety mechanisms into synthetic organisms to make them depend on nutrients that are unavailable in nature. Yet, the principal problem with such a safety system



is that someone with malicious intent could possibly short-circuit the fail-safe mechanism. Although some biosafety strategies might go some way to addressing biosecurity concerns, there certainly is not a complete overlap. Biosecurity issues therefore need to be addressed in their own right.

Most of the governance approaches that have been proposed for synthetic biology rely on some form of involvement of the scientific community (Maurer & Zoloth, 2007). One of the key prerequisites of any degree of involvement is, of course, awareness of the relevant issues. This applies in particular to the realm of biosecurity, as there has been no previous engagement with this issue on the part of the scientific community when discussing ethical, legal and social issues, such as during the past debates on genetically modified organisms (de Vriend, 2006). To assess the level of awareness of the unfolding biosecurity discourse, I interviewed 20 leading European synthetic biologists between June and October 2007. These interviews aimed to investigate the awareness of European scientists of dual-use issues and of six key proposals to address the security implications of research in the life sciences.

The work of the Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology, which is known as the Fink Committee, was a reaction to increasing concerns in the USA that research in the life sciences might be misused for bioterrorist or biowarfare purposes (National Research Council, 2004). Against this background, the Fink Committee was specifically tasked to “recommend changes in [...] practices that could improve US capacity to prevent the destructive application of biotechnology research while still enabling legitimate research to be conducted” (National Research Council, 2004). The recommendations of the Fink Committee are as follows: to educate the scientific community, to review plans for experiments, to review manuscripts before publication, to create a national science advisory board for biodefence, to adopt additional elements to protect against misuse, to achieve a more active role for the life sciences in efforts to prevent bioterrorism and biowarfare, and to harmonize international oversight. Of the 20 interviewees, only seven had heard of the report, and only one interviewee was able to give an opinion on its recommendations.

Shortly after the Fink Committee report was published, the US National Research Council (Washington, DC, USA) set up the Committee on Advances in Technology and the Prevention of their Application to Next Generation Bioterrorism and Biological Warfare Threats, which is known as the Lemon–Relman Committee. This committee developed a classification scheme for scientific and technological advances that contains four groups: technologies that seek to acquire novel biological or molecular diversity; technologies that seek to generate novel but predetermined and specific biological or molecular entities through directed design; technologies that seek to understand and manipulate biological systems in a more comprehensive and effective manner; and technologies that seek to enhance the production, delivery and ‘packaging’ of biologically active materials (National Research Council, 2006).

The report explicitly mentions synthetic biology in relation to the first two categories.

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In line with this reasoning, the committee made a recommendation to “adopt a broadened awareness of threats beyond the classical ‘select agents’ and other pathogenic organisms and toxins, so as to include, for example, approaches for disrupting host homeostatic and defense systems, and for creating synthetic organisms” (National Research Council, 2006).

In marked contrast to the increasingly careful monitoring and analysis of developments in synthetic biology by biosecurity experts (Choffnes *et al*, 2006), none of the interviewed European synthetic-biology practitioners had heard of the Lemon–Relman Committee, its report or any of the recommendations of the report.

As the draft Declaration of the Second International Meeting on Synthetic Biology (SB2.0) of May 2006 shows, the synthetic-biology community does take seriously the societal implications of its research. The declaration contains resolutions that clearly address some of the dual-use implications of DNA synthesis (Conferees SB2.0, 2006). In terms of practical steps, the draft proposes the formation of an open working group to improve existing software tools for screening DNA sequences, and the completion of a study to develop governance options for DNA-synthesis technology.

When asked about the draft declaration of SB2.0 and its contents, 12 of the 20 interviewees said that they were aware of it. This is a markedly higher level of awareness compared with the previous two studies. However, of the 12 positive respondents, only three were able to give an assessment of the four resolutions of the SB2.0 declaration.

Half of all interviewees were aware of the Center for Strategic and International Studies (CSIS)–Massachusetts Institute of Technology (MIT)–Venter draft report on Synthetic Genomics (Garfinkel *et al*, 2007), to which the SB2.0 declaration had made explicit reference. Some of the interviews were conducted during or after SB3.0, when the draft report was presented in the panel session on societal issues, which is likely to have affected these results; in fact, two interviewees made explicit reference to the presentation when answering the question. It is also noteworthy that only two of the respondents who had knowledge of the draft report were able to provide an assessment of the policy options that it put forward.

Following one of the recommendations contained in the Fink Committee report, the US government set up the National Science Advisory Board for Biosecurity (NSABB) in March 2004. One of the working groups created by the NSABB to address more specific issues has focused on synthetic biology. In the first phase of its work, this group sought to address the biosecurity implications of the *de novo* synthesis of select agents. A preliminary report was discussed during a NSABB meeting in October 2006, and has subsequently been submitted to the US government and made public (NSABB, 2006). Only three interviewees were aware of the NSABB activities and the report. Of those who had heard of the report, none were in a position to offer an assessment of its content or recommendations.

Since 2002, a group of scholars at the University of Maryland (Baltimore, MD, USA), led by John Steinbruner, has developed an oversight system for dangerous biological agents and research. The most elaborate version of this proposal was published as a monograph in Spring 2007 (Steinbruner *et al*, 2007). Starting from the dual-use dilemma that is inherent in most, if not all, research in the life sciences, Steinbruner and colleagues argue for “an oversight process designed to bring independent scrutiny to bear throughout the world without exception on fundamental research activities that might plausibly generate massively destructive or otherwise highly dangerous consequences” (Steinbruner *et al*, 2007).

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When asked whether they knew of the existence of the Controlling Dangerous Pathogens Project at the University of Maryland, six of the 20 interviewees responded positively. As with the previous reports, the level of detailed knowledge about the oversight system proposed by the University of Maryland group turned out to be low: only one interviewee felt in a position to provide an assessment of the work of the group.

In summary, the interviews demonstrate a low-to-medium level of awareness in quantitative terms among European synthetic-biology practitioners in relation to key developments and reports in the biosecurity area. In qualitative terms, the picture is even bleaker: only a few interviewees, if any at all, were in a position to give an assessment of the various committees, reports and recommendations. Even in the case of the SB2.0 declaration, the level of awareness dropped from 60% to 15%. This relatively superficial knowledge on the part of interviewees, who were in principle aware of the unfolding discourse, poses a considerable obstacle to a constructive participation by synthetic-biology practitioners in that very discourse.

Clearly, debates have moved on since these interviews took place. The extent to which this has led to an increased awareness is unclear; however, as no concerted effort at educating synthetic biologists or raising their awareness of biosecurity issues has been undertaken, any increase in the level of awareness is likely to be incremental. Therefore, any governance system will have to include measures to raise awareness in the scientific community. Over the course of the past few years, some proposals for such governance systems, or parts thereof, have been put forward by different scholars and institutions, which I briefly discuss here.

One of the earliest proposals to oversee synthetic biology was put forward by George Church at Harvard University (Cambridge, MA, USA; Church, 2004). He has suggested screening DNA and oligonucleotide orders for their similarity to specific, generally pathogenic, agents, and to license certain instruments and reagents, so as to limit their proliferation: both of these suggestions have been taken up by other groups or institutions. With respect to the oversight and regulation of these obligations, Church advocates setting up a clearing house with oversight assigned to one or more US government agencies.

By contrast, a White Paper that was circulated before the SB2.0 conference by Maurer *et al* puts greater emphasis on options that “can be implemented through community self-governance without outside intervention” (Maurer *et al*, 2006). The document contains several recommendations that were fed into the deliberations during SB2.0. The ‘Synthetic Genomics:

Options for Governance' report (Garfinkel *et al.*, 2007) addresses not only biosecurity issues based on the broad array of new capabilities provided by synthetic genomics, but also on environmental and biosafety risks. The most effective intervention point for preventing the misuse of synthetic genomics identified by the authors is at the level of DNA synthesis itself, that is, gene-synthesis firms, oligonucleotide manufacturers and DNA synthesizers.

This study on the governance of synthetic genomics has, in turn, influenced the work of two other groups. The International Consortium for Polynucleotide Synthesis (ICPS) has put forward a "tiered DNA synthesis order screening process" (Bügl *et al.*, 2007). This proposal puts DNA-synthesis companies and their industry association at the centre of a governance structure that would, however, not be a self-contained system of oversight, but rather would rely on "agreed-upon guidelines". Such guidelines would be put into practice, among other things, through lists of "select agents or sequences" that would determine whether and how to process DNA-synthesis orders.

The Industry Association Synthetic Biology (IASB) recently focused on several interrelated issues, and addressed these during a workshop on Technical Solutions for Biosecurity in Synthetic Biology (IASB, 2008). The workshop participants agreed on the adoption of five distinct work packages that include the following: the harmonization of screening strategies for DNA-synthesis orders; the establishment of a central virulence factor database; publishing an article on the status quo of synthetic biology; and the establishment of a technical biosecurity working group with members from both organizations, to "discuss improvements and next steps for biosecurity measures".

Current efforts to address biosecurity risks related to synthetic biology need to be broadened further, so as to include the different strands of this scientific field

The work packages and future efforts by the IASB and the ICPS will have the greatest impact when implemented by as many companies as possible. To this end, the fifth

Sidebar A | Potential biosecurity measures in the context of a 5P-strategy

Our proposed 5P-strategy allows for five policy intervention points at which steps can be taken to address biosecurity concerns. The following checklist gives an overview of the measures that can be implemented at each of these points, though we would not suggest that all are appropriate in all cases. By way of example, we have marked the fields that relate to activities already conducted by DNA-synthesis companies or their industry associations.

Potential biosecurity measures	Policy intervention points				
	Principal investigator	Project	Premises	Provider	Purchaser
Awareness raising	–	–	–	–	–
Education/training	–	–	–	–	–
Guidelines	–	–	–	✓	–
Codes of conduct	–	–	–	✓	–
Regulation	–	–	–	✓	–
National laws	–	–	–	✓	–
International treaty/agreement	–	–	–	✓	–

work package—the formulation of a code of conduct—is of particular relevance. The drafting of such a code was proposed during the April 2008 workshop, and an initial text was presented at the 2008 BWC meeting of state parties. The code seeks to establish high-standard biosecurity DNA-synthesis screening as best practice in industry, and will commit its signatories to keeping records of suspicious enquiries and positive screening hits, as well as to informing the authorities about such orders and enquiries that indicate illegal procurement activities.

In summary, two trends are discernible in the current proposals for the biosecurity governance of synthetic biology. The first is driven by DNA-synthesis companies and their industry associations, which focus their activities on technical solutions to the problem of potential misuse of DNA sequences. Here the emphasis is on the formulation and implementation of best practice across the industry. Oversight and enforcement of these standards, however, is not regarded as falling into the purview of industry itself, but rather as a governmental task. The second—not easily reconcilable—trend seems to be driven by those in the synthetic-biology community who are advocating self-governance by the scientific community as the prime or even sole approach (Maurer & Zoloth, 2007).

Although the proposals for technical solutions to DNA synthesis are certainly to be welcomed as useful building blocks for an overarching biosecurity governance structure, they do not represent an integrated approach that would, for a start, include a coherent set of measures to raise awareness across the synthetic-biology community. Furthermore, owing to the mostly technical

character of the solutions proposed and their focus on existing problems in a subfield of synthetic biology, these initiatives are not likely to be applicable to the full spectrum of synthetic biology, as many are still at the proof-of-principle stage.

What is needed is a broad approach that includes all stakeholders in the development of synthetic biology as a discipline and its potential future applications, and is also flexible enough to accommodate a range of scenarios about how the field might develop. To facilitate the development of such an overarching governance structure, I propose a '5P-strategy' that would focus on five points for policy intervention: the principal investigator, the project, the premises, the provider (of genetic material) and its purchaser.

At each of the five points, several measures are conceivable to address biosecurity concerns, depending on their severity. In principle, the biosecurity measures for synthetic biology range from raising awareness to education and training, codes of conduct, regulation, national laws and international treaties. Sidebar A provides an overview of potential combinations in the form of a checklist, and also notes those fields in which some activity is already discernible.

The most progress has been made by companies that synthesize DNA. On an international level, the screening of DNA orders is partly driven by the harmonized export controls imposed by states that are participating in the so-called Australia Group (AG). As part of its activities, the AG maintains common control lists that, among other things, require controls on the export of certain biological agents or parts thereof. These lists are being implemented through national

laws and regulations. As the IASB report has pointed out, “legislation for domestic orders is much more relaxed—both in the USA and the EU. Such legislation is much more focused on biosafety than biosecurity” (IASB, 2008). In addition, the harmonization of such guidelines is pursued through the formulation of a code of conduct by the IASB for the whole industry.

What are needed, in the first instance, are efforts to raise awareness and education. Furthermore, a systematic analysis is required to populate the empty fields in the checklist with adequate measures at different intervention points. Thus, the checklist in Sidebar A is not intended to suggest that all these boxes need to be ticked—instead, it can be a tool to analyse which ones should be ticked. It is likely that different strands of synthetic biology will require different sets of policy measures at the identified intervention points. On the basis of determining the range of adequate policy measures for the different branches of synthetic biology, a discussion of the content of such measures can be conducted.

On the basis of the realization that past breakthroughs in the life sciences have regularly been misused for weapons purposes, I have argued that the security implications of synthetic biology need to be taken seriously. For this to be done, it is initially necessary not to confuse or conflate the concepts of biosafety and biosecurity. The former deals with the inherent risk of a biological agent or material to its environment, whereas the latter is concerned with the misuse of a biological agent or material through, for example, loss, theft, diversion, intentional release or inadvertent research results.

A basic prerequisite for the formulation of meaningful and practical biosecurity measures is the involvement of all stakeholders, including first and foremost the synthetic-biology community. However, this community needs to be more aware of biosecurity issues to make a constructive contribution to the evolving discourse, as my study demonstrated (Kelle, 2007). Although some of these gaps will have been closed through the continuing debate about biosecurity considerations at conferences and meetings, such exposure is likely to have led to an incremental increase, not a huge leap forward, in terms of biosecurity awareness.

A review of existing proposals for the biosecurity governance of synthetic biology brought to the fore two main lines of reasoning and activities: one that puts a heavy emphasis on self-governance by the synthetic-biology community and one that emphasizes technical solutions. Although the latter is a necessary component of any governance or oversight system, it is by no means sufficient to address comprehensively the full range of biosecurity issues. It will therefore require attempts to formulate a code of conduct, awareness raising and educational activities to complement the more technically oriented supply-side control measures that DNA-synthesis companies and their industry associations are focusing on at present.

Current efforts to address biosecurity risks related to synthetic biology need to be broadened further, so as to include the different strands of this scientific field. To facilitate this, I proposed a 5P-strategy that would focus not only on the provider and purchaser of synthesized DNA, but also on the principal investigator, the project and the premises where the research is being conducted. Once the ideal policy-intervention points and the measures with which to address them are determined, a discussion involving the relevant stakeholders about possible measures can be started.

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