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Synthetic biology confronts publics and policy makers: challenges for communication, regulation and commercialization

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The novelty of synthetic biology lies in the use of synthesized parts that can be arranged to make useful products. Such advanced, high-throughput genetic engineering projects redesign and fabricate existing biological systems as well as new biological parts, devices and systems that do not occur in nature. This Opinion discusses challenges raised by synthetic biology for public acceptance, regulation, commercialization and the emerging global issue of access to genetic resources and information. As with all new fields of research, maintaining the trust of the public and policy regulators is paramount. Hype and exaggerated claims are counterproductive to developing adaptive and ethically sound regulatory models responsive to stakeholder concerns.

Synthetic biology

The emerging interdisciplinary field of synthetic biology brings an engineering approach to biology [1]. Individual parts can be readily synthesized and combined in different biological arrangements to make useful products such as biopharmaceuticals and biofuels [2]. Synthetic biology spans from advanced genetic engineering, which redesigns and fabricates existing biological systems [3], to the construction of new biological parts, devices and systems that do not occur in nature [4–6]. Thus, framing synthetic biology is a combination of the old and the new, with a change in mindset towards engineered systems [7].

History has shown that although new frames for technological advances may capture the imagination of funding agencies, politicians and investors, there is a concomitant risk of raising ethical and legal issues that reverberate beyond the scope of the technology and the researcher community. Thus, framing synthetic biology as revolutionary could feed the cycle of hype common with new technologies [8] and lead to disproportionate social, ethical and regulatory responses. In this vein, the Presidential Commission for the Study of Bioethical Issues, in its 2010 report on synthetic biology, cites information accuracy as a key recommendation for this emerging field. It cautions that '[t]he use of sensationalist buzzwords and phrases ... may initially increase attention to the underlying science and its implications for society, but ultimately such words impede ongoing understanding of both the scientific and ethical issues at the core of public debates on these topics' [9]. This Opinion focuses on potential public acceptance responses, as well as regulatory and commercialization issues.

The media, public opinion and public engagement

Like other controversial technologies before it, synthetic biology is piquing public and media interest, which, in turn, can have important consequences for its trajectory (Box 1) [10]. Experience with other technologies shows that the media will play an important role in framing the emergence of synthetic biology in the public arena [11]. Frames are storylines that help the lay person interpret an issue – why it may be a problem, who or what is responsible, and what should be done. They are an unavoidable part of communication processes, but, given their power, need to be given much thought by researchers and policy makers who want to be more effective in communicating with diverse audiences [11]. Two frames for synthetic biology may be particularly consequential: (i) the (re)design of nature and the merging of biology with engineering raise the natural versus unnatural debate; and (ii) researchers are viewed as 'playing God' [12,13]. For the public, the anchoring heuristics during the early stages of the technology will include past experiences with controversial technologies such as agricultural biotechnology [14], cloning and stem cell research [8]. Such associations of synthetic biology with preceding gene technologies are already being made in the media [10,14], and, experience shows, will probably be an important influence on emerging public opinion of this new technology (Box 1).

Much of the initial coverage has emphasized potential benefits over risks, but issues of biosecurity and biosafety are already emerging as key concerns in this coverage [15]. As the technology matures, the public will assess its specific features such as the potential applications, risk–benefit trade-offs and other social–ethical dimensions most closely associated with the relation between humans and nature.

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Box 1. Media coverage and public opinion of controversial science: debunking the deficit model

After formal education, the main information source for the public on science issues is the media. Television dominates, followed by the Internet [39]. Quantity and quality of science coverage vary markedly within and between media, with print sources generally providing higher quality coverage than television news [11]. Current trends for media fragmentation in the digital sphere and the rise of ideologically driven news sources enable audiences to self-select according to social values or avoid science coverage altogether. Although media effects on public opinion are generally overstated, the media can focus public attention on or away from specific issues (agenda setting) and can frame issues to the benefit or detriment of specific stakeholders.

The deficit model of public understanding, which posits that increasing knowledge of scientific facts or familiarity with a technology will increase public support, has been widely discredited [11,22]. Knowledge is only one factor that influences public opinion about controversial fields of science such as genetic modification, stem cell research, nanotechnology, climate change and evolution [11,40]. Although knowledgeable individuals tend to be more supportive of research and more deferential to expert authority, knowledge may be the effect rather than the cause – motivated individuals who seek out knowledge may do so because they are already supportive of and interested in science.

Increasing knowledge does not necessarily improve opinion of particular avenues of research or its applications, nor does it enhance deference to expert opinion. Counter to the deficit model, countries with high levels of scientific literacy may be strongly opposed to some technologies, such as GM food. Other attributes guide how individuals reach judgments about controversial science and perceive its risks, including demographic and socioeconomic characteristics, social identity, ideology and trust. For example, individuals respond divergently to information about nanotechnology and stem cell research based on cultural worldviews and religiosity [11,40].

It is impossible to be informed on all debates, and therefore individuals rely on heuristics – sets of mental shortcuts, values and emotions – to decide on issues in the absence of knowledge. Decisions may be reinforced by information that reflects pre-existing beliefs or may be based on past experiences with new technologies, such as GMOs. Portrayals in popular culture of technologies such as genetic enhancement, nanotechnology and cloning are also influential. Finally, digital media give prominence to opinion leaders, such as religious figures, nongovernmental organizations and politicians, who may frame controversial science in a manner that contradicts scientific consensus or runs contrary to the interests of organized science [11].

Given the importance of public opinion in supporting or pillorying technological advances, there remains a paucity of studies on public perceptions of synthetic biology. The few studies indicate that most people – over eight in ten – have not yet heard of this field in the United States [16,17] or in Europe [18], and, at this early stage, the familiarity of survey respondents was not strongly associated with risks and benefits [10]. At the same time, European respondents felt it important to know more about the possible risks, the claimed benefits, who would benefit, and who would bear the risks [18].

Although the media are important as information sources (Box 1) and play a role in influencing public opinion, more important will be for the public to engage in the debate over synthetic biology. Public involvement will help to shape the trajectory of synthetic biology with meaningful upstream input into the research agenda as well as regulatory responses to research, development and products as these reach the market. These new initiatives recognize that stakeholders who benefit but also bear the risks of new technologies deserve input into decision-making processes (Box 2).

Principled and adaptive regulation of synthetic biology

Principled regulation with public engagement

As awareness grows, the institutional conditions for public confidence in a technology will play an increasingly important role in supportive or adverse public opinion. Trust in regulatory systems and their perceived competence in risk mitigation play significant roles in eliciting

Box 2. Models for upstream public engagement

New models are emerging for publics to engage with science debates, enabling a plurality of views to inform research priorities and policy [11,41]. These models reflect theories on responsive and responsible democratic processes, where citizens who bear the risks and potential benefits of new technologies participate in making decisions about their development and regulatory trajectories. The goal is to move these engagement models upstream in research and development to counter criticism that most engagement exercises serve a public relations function, occurring once products are ready for market. Indeed, public deliberations 'should be an honest effort at relationship- and trust-building rather than persuasion, with mechanisms for actively incorporating the input of lay participants into decision-making' [11], which may run contrary to the self-interests of scientists.

Calls for public engagement, especially in Europe, have arisen from debates about the impact of new technologies, questions about the equitable distribution of risks and benefits, and the nature of control [41]. Emerging deliberative fora recognize the limits of scientific expertise and the uncertainties inherent in complex, multidisciplinary research and development. They have arisen from a confluence of factors: a history of flawed initiatives where public outrage has resulted from decisions that exclude those who predominantly bear the risks, for example, of large energy projects; and the growing influence of social movements that provide alternative sites of expertise.

A variety of models span a spectrum of venues and media [23,41,42]. A commonality is the recognition of the importance to decision making of sociocultural factors external to the scientific considerations of conventional risk analysis. The Internet is increasingly becoming an open arena for informal participation or for structured participation events such as deliberative polls; for example, the EU project SYNBIOSAFE carried out an open e-conference to stimulate debate on the societal issues around synthetic biology [12]. However, more common are in-person events such as, *cafés scientifiques,* citizen juries and consensus conferences. These activities represent a spectrum of participation from question–answer sessions with experts and consultations requiring feedback through participation in identifying problems and appropriate solutions to empowerment where participation extends from defining the problem to determining the solution. The deployment of these various public engagement and deliberative activities represents social experiments in the making, particularly as controversies around biotechnology have occurred worldwide and governments have grappled with public engagement by many means, with different aims and to different effects. Emerging technologies such as nanotechnology and, more recently, synthetic biology have taken lessons from these precedents, with more upstream forethought given to considerations of publics and their participation and expectations of more robust science policy.

and maintaining confidence in a technology [19], although these impacts are modulated by prior attitudes of individuals and can be influenced by specific events [20] (Box 1). At present, public unease following regulatory failures, such as the failure of dikes during Hurricane Katrina in the USA and the bovine spongiform encephalopathy crisis in the UK, has resulted in a general mistrust of government regulators and politicians.

Regulatory responses to new technologies need to accord with three normative principles [21,22]: (i) proportionality – the response should be proportional in balancing the risks to health and the environment against the potential benefits of research and novel technologies; (ii) distributive justice – consideration should be given to the just distribution of benefits and burdens; and (iii) procedural justice – those who will benefit and those who will be adversely affected have input into decision-making processes (Box 3).

Effective public engagement models (Box 2) will be essential to address all three legal principles because evidence required for proportional balancing of risk and benefit is not only scientific, especially in novel fields where uncertainty is high, but also ethical and social [22]. Procedural justice demands meaningful engagement with all stakeholders and the inputs of publics will be essential in determining the ethical distribution of costs and benefits, especially in a global context. Experiences with other gene technologies, and more recently nanotechnologies, show that meaningful upstream public engagement has the added benefit of increased confidence in governance structures (Box 2) [23].

Characteristics of an adaptive governance regime

In addition to being principled, governance regimes for new technologies need to be adaptive. A recent analysis for nanotechnologies suggests that such a regime, in addition to being reflexive in identifying and addressing deficiencies, should also be informed by evidence of risk and benefit as this becomes available; transparent in its decision making for all stakeholders, including researchers, industry, and the public; and prospective in being able to anticipate the trajectory of the field to respond to newly foreseeable risks [22]. Nanotechnology is an appropriate comparator for synthetic biology because it also cuts across a broad swathe of product categories that have distinctive, but existing, regulatory regimes, governed by a range of statutory laws, regulations, and institutional policies.

One issue, therefore, is whether existing regulatory schemes have the capacity to regulate synthetic biology, or whether adaptation is required. Synthetic biology challenges the adequacy of existing regulation and practice in several areas (Table 1). As with nanotechnologies, the products of synthetic biology can also have unanticipated uses. For example, they may be used as biofuels (the current focus of Amyris Biotechnologies in partnership with Brazilian sugar producers) or for bioremediation, but could also be used by rogue states or non-state actors as bioweapons [24]. Concerns have been raised that the existing US Select Agent Regulation, which covers potentially harmful biological agents and toxins, does not cover the *de novo* synthesis of novel viral DNA, which could be pathogenic [25]. This necessitates new guidelines to respond to the threat of bioterrorism (Table 1). At present, the guidelines for screening purchasers of synthetic double-stranded DNA are voluntary, but if risks increase as the technology advances, this area may require a more forceful regulatory response with greater public engagement in its development. A similar response will be warranted for other applications, such as synthetic biological systems using standard parts as envisioned by the BioBricks Foundation, and the creation of the first 'synthetic' microorganism by Craig Venter in 2010. The evolution of the field will need to be closely monitored.

However, as for most emerging technologies, current applications are incremental advances on existing technologies and may more accurately be defined as advanced genetic engineering [4,6]. One example is described in an accompanying Opinion piece in this issue on a project that combines high-throughput plant metabolomics with

Box 3. Adaptive and principled regulation of new technologies

The central task for regulators is to adopt an adaptive and principled approach that acts to protect public health and the environment while promoting potentially beneficial research and innovation [22]. With new technologies, regulatory decisions must be made in the face of evidentiary uncertainty on the nature and extent of risks. Adaptation requires taking into account new information as it becomes available to ensure responses are made according to the best information. Principles act as constraints on regulatory responses. A number of overlapping principles have been articulated in prominent reports by the Presidential Commission for the Study of Bioethical Issues on synthetic biology and the Nuffield Council on public health and biofuels [9,21].

One principle that has gained prominence, especially in Europe, is the precautionary principle, which states that certainty of harm should not be required and causation need not be proven to justify regulatory intervention [43]. However, the principle is often criticized as vague, overly restrictive and, in some instances, paralyzing. The Nuffield Council suggests that it should be viewed as an approach rather than a rule for regulation [21].

However, other principles may be more helpful and include proportionality, distributive justice and procedural justice. Such a set of ethical principles should be used as a benchmark when evaluating new technologies and give 'far more direction to policy makers and other stakeholders regarding what to do in situations of *ex ante* uncertainty than would many of the precautionary approaches alone' [21]. Proportionality concerns the rightness of the response in balancing the risks and potential benefits and should consider public beneficence; impact on human rights, for example, on health, housing, water and security; responsible stewardship including environmental stewardship and impact on future generations; and just reward for labor and intellectual property. Distributive justice considers the equitable distribution of benefits and burdens.

Finally, procedural justice requires that those individuals and groups whose fundamental interests are profoundly impacted by a political decision are entitled to have input into decision-making processes [9,21]. At a minimum, the responsible use of political power requires the interests and well-being of those affected to be taken into account, even if they are not given formal standing in the decision-making process. However, this principle could be addressed through deliberative democracy initiatives by incorporating the public engagement models in Box 2, which may become fora for enabling greater procedural justice for all affected by regulatory decisions over emerging technologies.

Table 1. A comparison of representative laws, regulations and guidelines that may impact synthetic biology

	International	United States of America	Canada	Europe	Refs
Laboratory biosafety	WHO *Laboratory Biosafety Manual* does not explicitly cover synthetic DNA.	*NIH Guidelines for Research Involving Recombinant DNA* do not cover synthetic DNA except when joining to DNA molecules. Proposed changes cover synthetic nucleic acids synthesized chemically or otherwise.	*Laboratory Biosafety Guidelines* do not explicitly cover synthetic DNA.	*Directive on Contained Use of Genetically Modified Micro-organisms* does not explicitly cover synthetic DNA. Directive on *Biological Agents at Work* covers genetically modified microorganisms, but no explicit reference to synthetic microorganisms	[44–49]
Biosecurity	*Biological and Toxin Weapons Convention* covers biological agents or toxins, whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes.	*Select Agents Regulations (SAR)* regulates the possession, use and transfer of select agents. *Screening Framework Guidance for Producers of Double Stranded DNA* aims to cover potentially harmful synthetic biological agents and toxins that are not covered by the *SAR*.	*Human Pathogens and Toxins Act* covers listed human pathogens and toxins as well as pathogens within defined risk groups. 'Human pathogen' includes nucleic acids.	No EU-level legislation exists that has been specifically developed to address biosecurity.	[50–53]
Traditional medicinal botanicals	No international law governing safety, efficacy and quality of traditional medicinal botanicals.	No pre-market approval is required for dietary supplements under the *Dietary Supplement Health and Education Act*. According to *Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues* under the *Dietary Supplement Health and Education Act*, a synthetic copy of a constituent or extract of an herb or other botanical is not a dietary ingredient of a dietary supplement.	Traditional preparations of *Natural Health Products Regulations of the Food and Drugs Act* can be licensed based upon traditional use, but biosynthetic products are not traditional preparations. Non-traditional preparations require scientific evidence of safety.	*Directive on Traditional Herbal Medicinal Products* limits registration to traditional herbal substances and their preparations. Bioequivalence principles under the EMA *Guidelines on the Investigation of Bioequivalence* are not applicable to herbal medicinal products.	[29,30, 54–56]
Access to Genetic Resources and Benefit Sharing (ABS)	The *Convention on Biological Diversity* and the associated *Nagoya Protocol* call on signatory nations to develop national laws to govern ABS. Countries with strong ABS laws include Brazil, India, South Africa and China. These countries also restrict patenting of non-ABS compliant inventions.	Not a signatory to the *Convention on Biological Diversity*.	Not yet a signatory to the *Nagoya Protocol*.	The European Union is a signatory to the *Nagoya Protocol*, and some the European Community, Italy and Switzerland have ABS laws. Switzerland restricts patenting of non-ABS compliant inventions.	[35,36]

a synthetic biology yeast production platform for high-value products. These biotechnology-derived plant natural products are regulated based on their intended use (e.g. foods, drugs, pesticides, fragrances, cosmetics and fuels). There is an issue, however, as to whether regulations that apply to products that occur 'naturally' equally apply to biotechnology-derived versions of those products.

For example, regulators often evaluate the safety of one product by comparing it to another product that is known or assumed to be safe. In the case of novel foods, for instance, if there are no significant differences between the comparator and the novel food or if any differences do not adversely affect health, then the novel food is considered to be safe [26]. However, the goal of synthetic biology is to create new products rather than modify an existing product [4]. Here, there may be no comparator against which to judge the product as safe, forcing safety evaluations to focus on the attributes of the novel product itself. This result will necessitate significant adaptations to the current regulatory framework.

Another example of regulatory inadequacy lies in guidelines that regulate NIH-funded recombinant DNA research, but do not cover the creation of nucleic acid sequences by chemical synthesis. The NIH acknowledges that synthetic biology techniques could lead to rapid development of hitherto unknown products that may raise new and unanticipated biosafety risks [27], necessitating amendments to its guidelines.

Other regulatory schemes such as the regulatory approval process for new drugs, including biologics, are probably more robust in adapting to products of synthetic biology [28,29]. However, this may not be the case for synthetic-biology-derived traditional medicinal plant products. In the USA, botanicals and their extracts are categorized as dietary supplements but synthetic-biology-derived 'traditional medicines' appear not to be so categorized because the

synthetic ingredient was never a constituent of the original, and was not extracted from it. Although the USA does not require government approval of a dietary supplement before it is sold, manufacturers of dietary supplements must ensure the safety of their products. In recent draft guidelines for industry, the Food and Drug Administration (FDA) opined that a synthetic copy of a constituent or extract of a herb or other botanical is not a dietary ingredient of a dietary supplement [30]. This suggests that the FDA may also deny that biotechnology-derived plant natural products are dietary ingredients. If so, then biotechnology-derived plant natural products that are bioequivalent to dietary supplements cannot be sold as dietary supplements and will either fall under the drug approval process or require a new regulatory framework.

Commercialization challenges and utilization of genetic resources

The principle of distributive justice arises most clearly in the context of commercialization, where policies on access to research tools and products through the management of intellectual property have global implications (Box 3). Commercialization issues arise in two contexts; first, the patenting or enclosure of information and, second, the global context for using genetic resources [31,32]. There is significant potential for blocking patents held by research institutions or companies that threaten the development of the field. Experience shows such patents are most likely to be over broad-based methods or other aspects of research platforms. To prevent such outcomes, research institutions in particular should follow best practices for licensing methods and research platforms, generally by licensing non-exclusively. In addition, institutions may ensure the free flow of information and materials through simplified conditions of use rather than onerous material transfer agreements [33]. The second threat is the potential for a patent thicket where a large number of overlapping patents make it difficult to aggregate permissions for use and further development of a platform or technology. The Biobricks Foundation is structured to mitigate potential patent thickets through the creation of a scientific commons for standard synthetic biological parts, available free of charge to the public via the Massachusetts Institute of Technology's Registry of Standard Biological Parts [4]. Individuals and organizations are invited to design, improve, and contribute to the registry. Placing parts in the public domain in this manner makes them unpatentable and undermines the patentability of minor improvements.

Finally, synthetic biology raises unique and boundary-challenging issues for the management and distribution of genetic resources. In a global context, increasing attention is being paid to the source of genetic material, which includes sequence data and plant metabolites [34–37], and the equitable distribution of benefits deriving from its exploitation (Table 1). International treaties suggest access to genetic resources should be granted, but the benefits from their utilization must be shared with the nation state where those genetic resources are endemic through, for example, transfer of technologies, rights over the resources, and/or monetary compensation. There has been some national implementation of access and benefit-sharing laws, but these have been patchy, occurring mainly in the Global South and mired in controversy at the international level [37,38].

Within the *Convention on Biological Diversity* and the associated *Nagoya Protocol* [36], synthetic biology is captured through the concept of derivatives (products derived from biotechnology) and examples of utilization of genetic resources, which include the 'use of genetic material as a "factory" to produce organic compounds'. Such concepts are also present in national access and benefit-sharing laws (e.g. Brazil, Thailand, and Philippines) and compliance with such laws is a prerequisite for patenting in some countries such as China (Table 1). Hence, synthetic biology researchers who rely on genetic material or sequence information from resources from the Global South will need to consider the impact of these laws.

Conclusion

In conclusion, recent developments in synthetic biology challenge current regulatory frameworks, international laws on research using genetic materials, and public opinion. As with all new fields of research, maintaining the trust of publics and regulators is paramount, and will, in large part, be determined by the behavior of early entrants. Researchers should be cautious in framing all incremental advances in the field as synthetic biology and avoid the potential for hype and exaggerated claims. Although not yet a prominent issue, the public is seeking balanced information on the risks and benefits of this new technology.

In developing an adaptive regulatory response to synthetic biology, policy makers should track scientific advances in the field and monitor emerging evidence of risks and benefits. To this should be added an analysis of the existing regulatory environment for the anticipated areas of application for synthetic biology, identifying potential gaps and overlap. Wherever possible, existing frameworks should be streamlined and modified, but some new technologies may also require novel regulatory responses. All responses should take into account, at a minimum, the three principles of proportionality, distributive justice and procedural justice, with all three requiring public engagement.

Upstream monitoring of the research and regulatory environments should recognize that in the face of novel technological innovation, not all evaluative criteria are scientific. Accordingly, public engagement processes should be established early so that stakeholders who will bear the risks and benefits of synthetic biology have the opportunity for meaningful input into the trajectory of this field. To be meaningful, public engagement must recognize that some avenues of research will not be acceptable and some products may be prevented from reaching the market.

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