A synthetic biology future, a synthetic biology crisis

Introduction - flying cars and future fears

Expectations have been set high for the synthetic biology future. From biosensors that detect and destroy disease to advanced biofuels and oil-free plastics[1], synthetic biology has certainly made some lofty promises. We need only remember stories of flying cars and robot butlers to know that any attempt to predict the future of a developing technology is likely to prove over-optimistic at best, and completely wrong at worst. Realistic or otherwise, such hopes for the future may also raise some very real fears. With this in mind, this paper will consider a 'disaster scenario' that takes place in some possible future where synthetic biology technologies are commonplace. In this way we hope to address concerns around synthetic biology by considering how we might respond if fears become reality. This paper is divided into three parts - Part 1, in which we summarize the regulation of the synthetic biology present; Part 2, in which we look at the near-term future of synthetic biology; and Part 3, in which we will examine our crisis scenario.

Part 1 – The synthetic biology present

The legal context

Before we can consider what synthetic biology might look like in the future, we must examine the synthetic biology present. In order to provide some legal context to our discussion we here present a brief summary of the existing legislation on deliberate release (when modified organisms are released from the lab for the purposes of a field trial or commercial application) and transboundary movement (the transport of modified organisms across national borders).

Deliberate release

In the EU, the deliberate release of GMOs is governed by a 2001 Directive[2], which states that an environmental risk assessment must be carried out and consent must be obtained from a 'competent authority' before a release. Member states are required to consult the public on proposed releases 'in order to give the public… the opportunity to express an opinion'. In the event of any modification to a previously released GMO which could have consequences for human health and the environment, or if new information becomes available on a risk posed by the GMO, the legislation states that the releaser 'must immediately take the measures necessary to protect human health and the environment'. In the event of such a situation, the competent authority is responsible for evaluating the available information and informing the public of possible risks, and it has the right to suspend or terminate the deliberate release.

Transboundary movement

The existing legislation relating to the transboundary movement of GMOs is derived from the 2001 Cartagena Protocol on Biosafety[3] which regulates the international trade, handling, and use of GMOs. It sets out procedures for moving GMO's across borders, including a requirement to for any country exporting GMOs to first obtain the informed

[1] The Royal Academy of Engineering (2009), "SyntheticBiology: scope, applications, and implications", May 2009, London: The Royal Academy of Engineering

[2] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, 2001, Official Journal of the European Communities, 17.4.2001, L 106, 1-38

[3] Secretariat of the Convention on Biological Diversity (2000) Cartagena Protocol on Biosafety to the Convention on Biological Diversity: text and annexes. Montreal, Canada. ISBN 92-807-1924-6

consent of the destination country.
However, this regulatory framework remains contested. The EU Directive is highly complex, controversial, and continuously subject to updates and amendments[4]. It should also be noted that several 'pro-GE' countries, including the US, Argentina, and Canada, have refused to ratify the Cartagena agreement.

Part 2 – Next steps

Out of the laboratory

As synthetic biology begins to move out of the laboratory towards industrial and commercial applications, there may come a time where SBOs are deliberately released into the environment. Many of the issues presented by environmental release have been well covered in discussions around genetically modified organisms, and we shall not attempt to revisit them here. Synthetic biology, however, raises new questions which must be addressed before we can consider a longer-term vision for the field.

Do we need new legislation on deliberate release?

The current consensus among scientists and legislators is that existing GMO legislations are adequate to regulate SBOs. Ignoring the practical problems with the current legislation, we must ask whether synthetic biology represents a significant enough shift from genetic engineering to warrant different regulation. It is true that in the near future the end-products of synthetic biology technology will look much like those of genetic engineering. Placing a new name on an old technology does not create a new hazard[5], and if synthetic biology is simply 'old wine in new bottles' then existing legislation should be perfectly adequate. Consider, though, the future possibilities raised by synthetic biology, and the field begins to look very different from its older relative. Where genetic engineering used genetic material found in nature, synthetic biology is looking towards using entirely new material like xeno-nucleic acids. Where genetic engineering modified existing organisms, synthetic biology aims to create entirely new kinds of lifeforms. And this is not to mention the issues of intellectual property and biosecurity that legislation applying to synthetic biology must begin to address. Just as the advent of the internet raised issues not present in older forms of broadcast media[6], new regulation is needed to handle the new ethical, legal, and social considerations that may be presented by this nascent field.

How do we minimize the risks associated with deliberate release?

if 'the spectrum of biological risks encompasses naturally occurring, unintended, and deliberate risks'[7] then the kind of risk that we are concerned with when considering deliberate release is 'naturally occurring' risks, i.e. those that arise as a consequence of unforeseen circumstances. Naturally occurring risks are by definition impossible to predict and to prevent, but there are approaches that we may take to minimize them. Synthetic biology itself may provide the tools to do this, in the 'containment' or 'self-destruction' systems that attempt to render synthetic organisms unable to survive outside of the lab or to transfer their genetic material. Nevertheless, technology employed to manage risks brings its own risks of failure, and it would be foolish to rely on these mechanisms

[4] Gabriele Fontana (2010), "Genetically Modified Micro-Organisms: the EU regulatory framework and the new Directive 2009/41/EC on the contained use", AIDIC Biotech Working Group

[5] Benner, S.A. and Sismour, A.M, (2005). "Synthetic biology". Nature Reviews Genetics, 6: 533-543.

[6] Michael Rodemeyer (2009) New Life, Old Bottles: Regulating First-Generation Products of Synthetic Biology (PDF), Synthetic Biology Project, Woodrow Wilson International Center for Scholars, SynBio 2

[7] Royal Society Science Policy Centre (2009). "New Approaches to Biological Risk Assessment", July 2009, London: The Royal Society

alone. Other forms of risk management bring their own problems. For example, the open-sourcing of synthetic biology technology, as advocated by the iGEM competition and other users of the registry of standard biological parts, may help to reduce 'bioerror' by meaning that parts undergo thorough testing at the hands of many different researchers, but may increase the risk of 'bioterror' by making biological parts more easily available. How, then, is it possible to adequately manage the risks involved in deliberate release of synthetic organisms? We must accept that the only way to truly ensure that a release poses no risk is not to carry out the release at all, but then we must face the risks brought about by the loss of a potentially beneficial technology. In our opinion, the most sensible approach is to combine different risk management approaches, so that we may reduce risk to an acceptable level whilst continuing to enjoy the benefits that synthetic biology may bring.

PART 3 – Into the future

A synthetic biology crisis

For this final section we refer the reader to our 2030 Crisis Scenario as a concrete imagining of a disaster scenario. In using this specific example we aim to touch upon more general issues of liability, governance, and uncertainty in the event of a synthetic biology crisis.

Assigning liability

A disaster of this scale would impose a significant economic penalty on affected countries, and so we must consider who must be responsible for providing financial compensation. Under the current international agreement[8], the operator (the party in direct or indirect control) of the modified organism is held responsible for compensation in the event of the organism causing damage. Yet when there are so many different parties involved in the journey of a synthetic biology product from lab to market, is it always right to hold the operator liable? In the following paragraphs we will use the 2030 Crisis Scenario to explore which of the actors involved in the inception of a synthetic biology product we may consider to be truly responsible for its failure.

Firstly, let's consider the original creators of the GeneShield BioBricks. Can they be blamed for the failure of the parts that they created? Parts made available in the registry should be ready to use safely without requiring extensive modification, but in an open-source process, where numerous modifications may be made to the original part by many different parties, it is near impossible to assign blame for a particular fault. Further, creators of parts cannot be held responsible for the interactions of parts in the system into which they are eventually incorporated. If safety is viewed as a system-level property rather than a parts-level property, the end users of parts must be responsible for assuring their stability in a complete system.

If this is so, can we blame the scientists that initially developed the FertiBac system? Consider that what constitutes assurance of safety at field trial level is far less than that at industrial level, where the number of environmental variables is far higher, and therefore the responsibility for ensuring safety of the 'scaled up' system must lie not with the scientists but with the biotech company who manufactured the system for sale. Viewed differently, however, safeguards against mutations are an intrinsic part of any synthetic biology system designed for release into the environment, and therefore scientists must ensure they are present and correct at the earliest stages of design. What is clear is that efficient co-ordination between small and large-scale design is required to ensure

[8] Secretariat of the Convention on Biological Diversity (2010), Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety. Montreal, Canada. ISBN 92-9225-324-7

robustness of the system at all scales, something that may have been lacking in our scenario. Now we turn to the regulators who approved the system for sale. The use of open-sourced BioBrick parts in the FertiBac system should have raised alarm bells during the approvals process – while the parts might be more widely used than their private equivalents, giving assurance of quality through sheer prevalence, it may also be the case that the parts are never thoroughly tested, as no one person is truly accountable for them. In such a situation it is unclear how regulators may make a reliable judgement of safety.
There is not space here to consider the roles of others such as the chemical company. Clearly, further thought and further evidence will be required in order to attempt to ascribe blame to any single party.

A synthetic biology future – in the short term
When considering the first response to a synthetic biology crisis, there are two major challenges that must be faced, one of which is faced by all emergent fields and one of which is unique to synthetic biology. The former is the problem of governance in the face of uncertainty. An adequate response to any crisis requires careful analysis of existing evidence, taking into account any new insight gained in the light of the disaster, and often further long-term studies to determine safety. Gathering sufficient evidence to make the right judgements could take years. Yet in the aftermath of a disaster, governors may be working to timescales of hours, and the decisions they take in this time could have serious long-term consequences for public health and the environment. How can we assure safety without evidence? One general guideline that may be adopted in such situations is the precautionary principle. This principle states that when an activity raises a threat of harm to the environment or human health, precautionary measures should be taken even if proof of the threat cannot be established. In a synthetic biology crisis, then, the precautionary principle would recommend banning synthetic biology activities until their safety can be proved. However, this gives us no information as to the extent of the ban that should be established, or on what might constitute true 'proof' of safety.
The latter challenge is that of cross-borderness. Cross-borderness in synthetic biology may refer to geopolitical cross-borderness, which comprises the differing attitudes to and heterogeneous legislation of SBOs across different countries, or to the multi-disciplinary nature of the field[9], which I will discuss here. This type of cross-borderness renders decision-making even more complex, involving knowledge from many different disciplines, including biology, engineering, computer science and others. A multi-disciplinary team of scientific advisors may be employed to ensure that politicians have the knowledge required to understand the implications of their decisions. This approach, however, brings its own problems. Different scientific disciplines not only use different 'languages' but may have different ideas around what counts as knowledge, proof, or evidence[10]. Whilst this may be productive in the lab, in a crisis situation such cross-borderness may lead to conflict. Ultimately, no combination of scientists and politicians can ensure that the correct decision is taken on whether to ban a technology if there is a lack of sufficient evidence. Our short-term response to the 2030 Crisis Scenario therefore errs on the side of caution. We would recommend destruction of all crops fertilised with any brand of Fertibac-based fertilisers, and toxicity testing of any agricultural goods that come into contact with products incorporating SBOs. As the FertiBac mutation was induced by a combination of environmental circumstances that would not normally be found in a medical or industrial

[9] Zhang, J.Y., Marris, C., and Rose, N. (2011), "The Transnational Governance of Synthetic Biology", BIOS Working Paper no: 4. ISBN 1759-0620
[10] Fox-Keller, E. (2002). Making Sense of Life: explaining biological development with models, metaphors, and machines. Cambridge, Harvard University Press.

setting, we do not find it necessary to test other sorts of products incorporating SBOs. Given that the freely-available GeneShield technology or its variants may be incorporated into any organism intended for deliberate release, we would also establish a ban on the release of SBOs in any case where the party proposing the release is unable to prove the stability of its gene transfer prevention mechanism. Such severe initial restrictions, to be lifted with evidence of safety, are in our opinion the best way to balance the immediate concerns of the public with future economic, scientific and environmental interests.

A synthetic biology future – in the long term

Just as the Chernobyl and Fukushima disasters placed a question mark over the fate of nuclear power in many countries, so a synthetic biology disaster may prompt questions over its future role in society. However, unlike nuclear power, synthetic biology has applications in many fields – not only energy, but agriculture, medicine, and environmental applications - and so the long-term implications of a synthetic biology disaster are not so easy to predict. What is clear is that the eventual outcome must depend on the state of our scientific knowledge at that point in time. Perhaps it will be considered safer to push synthetic biology backwards, and ban all artificially synthesized genes, using only those taken from nature. Perhaps we must move it forwards, banning use of DNA in favour of xeno-nucleic acids. Rather than attempt to make specific predictions, then, we shall consider what seems to us to be a reasonably possible outcome: the banning of all deliberate release.

Whilst undoubtedly unsettling for the synthetic biology community, this need not mean the end for the field. Firstly, a ban on release of SBOs need not affect their use in academic, medical, or industrial settings. The sheer breadth of synthetic biology may be its best defence against any crisis. Secondly, synthetic biologists will have had to have overcome a huge number of obstacles in order to be permitted the deliberate release of SBOs, and they will not simply stand back and accept the destruction of all that they have worked for. Standing at the junction between biology and engineering, synthetic biologists are perfectly equipped to understand a problem and to build the solution, and this unique position ensures that synthetic biology will continue to evolve and adapt to the challenges that it may face in the years to come.

Conclusion

In 2010, the British Biotechnology and Biological Sciences Research Council conducted a large-scale synthetic biology dialogue involving consumer groups, industry representatives, and scientists as well as members of the public[11]. The dialogue, which aimed to 'explore people's hopes and fears for synthetic biology', concluded that there was public support for synthetic biology, but that it was conditional upon settling fears of governmental control and misuse. While synthetic biology remains at this stage a largely academic interest, we must ensure that we continue to acknowledge the concerns surrounding the field as it matures. We have been able to touch upon only a fraction of these issues in this position paper, yet in doing so we hope to have stimulated a process of discussion which may eventually lead to their resolution. Only then, and when the time is right, may we reap the benefits of the synthetic biology future.

[11] BBSRC/EPSRC (2010), Synthetic Biology Dialogue. Swindon, Biotechnology and Biological Sciences Research Council (BBSRC) and the Engineering and Physical Sciences Research Council (EPSRC), p.7.