Current ethical issues in Synthetic Biology: Where should we go from here?

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Abstract:
Synthetic Biology (SynBio) is an emerging scientific field which has quickly established momentum and visibility. Although no single definition of SynBio prevails, the field broadly encompasses the application of engineering principles to biology; re-designing biological materials and using them as new substrates to create products and entities not otherwise found in nature. This paper first reviews SynBio, highlighting the novel aspects of this technology. It then synthesises ethical issues highlighted in the literature to date and makes some initial claims that research on the ethical aspects of SynBio should: avoid creating a new sub-type of bioethics, concentrate on novel concepts and problems and be situated within a context of cooperative inter-disciplinary investigation.

Keywords: Synthetic biology, ethical issues, regulation, creating life.

Introduction

The convergence of methodologies and techniques in biotechnology, chemistry and engineering has given rise to the emergent field of synthetic biology (SynBio), which broadly aims to re-design biological materials and using them as new substrates to create novel entities and products in a variety of contexts. SynBio has rapidly gained a presence in the literature and is attracting increasing research funding. The field now also appears to be moving from a phase of broad manifestos to defined research projects and early outputs (Rabinow & Bennett, 2009). The possible applications of SynBio are broad, including products for use in bioremediation, biofuels and health care.

Given the convergence of methodologies and the myriad and undefined applications SynBio may give rise to, the presence of an ethical dimension is unsurprising. Indeed, a notable feature of this field is that researchers in SynBio have been keen to engage with the ethical, legal and social implications of their work from the outset; perhaps to avoid the problems previously experienced in other research domains. There have been sessions dedicated to ethical issues at all major SynBio conferences and several multi-disciplinary collaborations have been established and attracted research funding. There is also a burgeoning literature on the implications of this technology (Bhutkar, 2005; de Vriend, 2006; Tucker and Zilinskas, 2006; Balmer & Martin, 2008; Parens *et al*, 2009; European Group on Ethics, 2009; Royal Academy of Engineering, 2009). Policy-makers have been engaged in SynBio for some time (European Commission 2005), yet with one exception (ETC Group, 2007), non-governmental organisations have not yet shown significant interest in SynBio; perhaps because its applications remain somewhat ill-defined.

This paper will provide an overview of SynBio and its ethical implications, broadly construed. The scope, development and putative applications of SynBio will first be described, focussing on the novel aspects of this technology. The established and emerging ethical issues will then be synthesised. Most such issues are likely to emerge at what may be called the 'functional' or 'self-

organisation' stage of SynBio, rather than from the core scientific research methodologies that have driven the development of this discipline. Bearing in mind the long-standing tension between bioethics and the social sciences, some initial claims will then be made as to how research on the implications of SynBio should proceed. These are that research on the ethics of SynBio should: avoid creating a new sub-type of bioethics, concentrate on novel concepts and problems and be situated within a context of multi-disciplinary investigation.

Definitions and applications of SynBio

Although several definitions have been suggested for SynBio (see, for example: European Group on Ethics, 2009; Deplazes, 2009; BBSRC & EPSRC, 2010), no single descriptor has been, or is likely to be, accepted by the entire SynBio research community. This diversity of views is likely due to the varying technical emphases and approaches prevalent in SynBio. However SynBio can broadly be thought of as the application of engineering principles (including abstraction, standardisation and modularisation) to biology, to provide a rational and systematic approach to the design or re-design of robust, stable, predictable and novel biological parts or systems. It is a discipline of converging technologies; involving engineering, biotechnology, chemistry and computational modelling, among others.

SynBio does seem to differ in kind from the technologies it has developed from. The novelty of this scientific approach is that:

> ...synthetic biology starts from an integrated approach with the aim to create something fundamentally new. Its goal far exceeds that of conventional biotechnology. Synthetic biologists... aim at producing living machines or completely artificial organisms...[.] (Deplazes *et al,* 2009, p73).

So although it may seem that other scientific methodologies are similar, the interests that drive many of the researchers working on SynBio extend beyond those encountered in 'traditional' molecular biology. SynBio brings together previously unconnected scientific disciplines; faster more reliable and cheaper DNA synthesis and improved computing power. The design of novel components, parts, systems or entities also allows for a great deal of creativity. These features collectively allow frontiers to be explored that were not previously thought to be feasible or possible, such as the creation of 'designer genomes' from scratch. Moreover, the ready availability of scientific tools also means that one does not necessarily need to have access to a laboratory environment to undertake SynBio work.

Within SynBio there are already several distinctions as to approach, which differ depending on methodology, materials and objectives. To this end, various classes and groupings of SynBio are emerging (see, eg: Deplazes, 2009; O'Malley *et* al, 2008). O'Malley *et al* (2008) have defined three broad approaches to SynBio: (i) DNA-based device construction; (ii) genome-driven cell engineering and (iii) protocell creation; each of which is briefly discussed further below. They suggest that each of these approaches encompasses different views about concepts such as genetic determinism and complexity and each will also give rise to different issues in domains such as intellectual property. Characterising SynBio into these categories offers an opportunity to begin to conceive of its many layers and will be important to any identification, synthesis and normative determination over the ethical issues that will arise (Deplazes, 2009).

DNA-based device construction, as its name suggests, utilises DNA synthesis as a primary tool to design and build deliberately engineered biological systems (O'Malley, *et al* 2008, p57). Natural complexity is removed and replaced by a catalogue of standardised parts which are then used to perform discrete tasks or create devices. The biological systems in which these parts and devices might operate are de-emphasised in favour of inter-changeability. The best known example of this

approach is the Registry of Standard Biologial Parts ('BioBricks': http://partsregistry.org), an open-access library of standardised biological parts and devices.

Genome-driven cell engineering focuses on the entire genome. The aims of this approach include reducing existing genomes to the minimum necessary to sustain life and synthesising whole genomes from scratch. These can then be transplanted into host cells to investigate functional attributes and develop a host 'chassis' to assist with eventual device implantation (O'Malley *et al*, 2008, p59). This approach therefore takes a genome-centric view of biological causation. Examples of the synthesis approach include re-creating the 1918 pandemic flu virus through purchasing commercially available DNA sequences (Tumpey *et al*, 2005) and the synthetic genome of *Mycoplasma genitalium* (Gibson *et al*, 2008).

Protocell creation is perhaps the most ambitious, and therefore least established, approach to SynBio. This approach aims to construct an artificial minimal cell and to eventually use this to develop novel artificial cellular systems (including artificial tissues and organs). Researchers working with this approach are first attempting to create many of the biological components that will be necessary for protocell life and investigating how they interact and function in the lab (Forster and Church, 2006). In 2010, the same team that created *M genitalium* published their claim to the first synthetically produced cell, in which a synthetically created chromosome was transplanted into a bacterial cell chassis: *Mycoplasma mycoides* (Gibson *et al*, 2010).

Drawing together the various conceptions of and approaches to SynBio, a range of practical applications may be possible. If SynBio researchers substantiate current hype, these outputs will be robust, novel and will have predictable properties. Applications could include devices or parts for use in bioremediation, biofuel production and health care (notably biosensors, novel or better targeted drugs, new medical devices for tissue repair and synthetic vaccines (European Commission, 2005)).

Good progress is already being made towards some of these applications. Perhaps the best-known example is work on a synthetic form of amorphadiene, the precursor to the chemical compound artemisinin – a next-generation anti-malarial drug (Ro *et al*, 2006). Artemisinin is a rare naturally occurring plant and is therefore expensive to produce. Synthetic production of its precursor will enable its production costs to be reduced dramatically, hopefully providing benefits for countries with low resources but high malaria prevalence. However, it has also been recognised that such scale-up of SynBio production will affect the livelihood of those living in developing countries who currently harvest artemisinin (Balmer and Martin, 2008).

Ethical issues arising in SynBio

The early ethical issues arising in Synthetic Biology have been well documented (see, for example: Balmer and Martin, 2008; Deplazes *et al*, 2009) and the literature in this field continues to increase. There are also a burgeoning number of funded projects that aim to investigate the ethical, legal and social issues arising in SynBio. However these ethical deliberations remain at an early stage, with little substantive analysis yet emerging to address the issues in depth.

As mentioned in the introduction to this paper, one feature of these early debates on SynBio is that lab-based researchers have taken great interest in ethical discussions. Research funders have also recognised the potential sensitivities of this research and many funding schemes have either encouraged or mandated the involvement of ethics or social science researchers (such as the UK research council-funded networks in synthetic biology). Policy-makers are also monitoring the field and several committees have been established. There have also been several early public engagement activities.

Presenting an in-depth description and analysis of all of the ethical issues arising in SynBio is beyond the scope of this paper (and has already been published elsewhere; see for example Parens *et al*, 2009). It is however important to summarise these briefly, as they influence two other key questions: (i) is there anything new here? and (ii) how should deliberations over the ethical, legal and social aspects of SynBio proceed? This is not to say that the issues identified here are (or will remain) objectively contentious as they are all subject to challenge – some may disappear with sound oversight and control, while others might be resolved through ethical reasoning and debate.

As with any ethical deliberation, various taxonomies to classify the issues in SynBio can be proposed. One such classification has been proposed by Parens *et al* (2009) – physical harms and non-physical harms.

Like many of the debates over SynBio, reasoning about harms tends to be consequentialist (Schmidt *et al*, 2008; Swierstra and Rip, 2007); perhaps because identifying outcomes and endpoints is more amenable to scientific engagement than is a discussion of principles, duties or virtues which may lack tangibility or practical context. A consequentialist approach also naturally lends itself to considerations of harm, which can then provide a useful 'hook' into discussions over policy-making for SynBio.

Physical harms are those which threaten the actual safety and security of humans or the environment. Two such harms that have been discussed at length in SynBio are biosafety and biosecurity (Kelle, 2009). Biosafety considers the potential negative effects of synthetic or artificial organisms on the environment or human beings, say for example if a synthetic entity were to be released beyond the laboratory and interact with or alter the environment in an unexpected way. While novel or highly modified organisms are unlikely to survive in an environment outside the laboratory or could be engineered to ensure this is not possible (Garfinkel *et al*, 2008), there may also be situations where there will be a need for trade-offs between benefits and risks. Yet biosafety does not solely concern the substantive issues of safety or containment, which to some extent are a matter of careful oversight and responsible scientific practice. Debates over biosafety also include determining what is 'safe' in SynBio (Garfinkel *et al,* 2008) and who should determine this. While there is general agreement that rigorous standards are required, there is less agreement on what these should be.

Biosecurity issues arise over the possible uses of the products of SynBio by those who wish to commit harmful acts such as bioterrorism (Bugl *et al*, 2007). This concern has been more widely discussed in North America than Europe, perhaps because the USA has already seen a successful biological attack. Much of the concern with biosecurity arises from the relative ease of obtaining materials necessary for baseline SynBio research outside of the more regulated environment of a university or research institute. Examples such as the synthesis of the virus that led to the 1918 influenza pandemic and the polio virus by way of procuring DNA sequences online from commercial providers, although undertaken by responsible scientists, illustrate that an individual with mal-intent or a nefarious state may be able to inflict harm to many. It also gives rise to concerns about 'dual use' problems in emerging technologies; by which the same application of SynBio could give rise to both beneficial and harmful consequences. There is some industrial self-oversight over sequencing orders, but there are concerns about whether, when or how other forms of monitoring should take place.

One further issue which overlaps with biosecurity and biosafety as physical harms is that of professional ethics within SynBio. Given that SynBio research involves professionals from a range of scientific disciplines working together for the first time, they may come together with different

codes of conduct or expectations as to what constitutes responsible research. While it is important to recognise that researchers already appreciate the possible implications of their field, monitoring professional integrity may become a more pressing problem as the field advances. This also gives rise to questions around regulation; a consideration that is briefly returned to below.

While the distinction between them is somewhat blurry, *non-physical harms* broadly encompass those aims or applications of SynBio that could harm the well-being of individuals or communities (Parens *et al*, 2009). A potential non-physical harm in SynBio is the role that humans have in creating new entities and how this may affect conceptions of the self and relationships to the environment (Royal Academy of Engineering, 2009, p43). Creating novel life forms is a key aim of SynBio and there has been some discussion over whether creating a novel entity such as a microorganism is indeed creating life or merely a biological machine (Schmidt *et al*, 2008). However if SynBio does move on to more complex applications, new entities may require evaluation as to their moral status. This could require a reconsideration of the concept of 'life,' its creation and the 'natural,' as well as whether creating life is acceptable.

Creating entities from biological components or the bases of DNA could also lead to a mechanistic understanding of life and a de-emphasis on biological interaction in the generation of complexity. However, some commentators claim that while an important point of discussion, such a concern should not limit the development of entities such as minimal genomes (Cho *et al*, 1999). An emerging question is how the concepts of life and its creation should be used in normative reasoning about the development of SynBio (Deplazes *et al*, 2009).

The fair allocation of the benefits of SynBio is another putative non-physical harm. A significant benefit of SynBio is that it is anticipated that the scale-up and manufacture of devices, entities or processes developed in the lab may not be as expensive as for other emerging technologies. This is because SynBio can exploit the in-built proliferation mechanisms of 'living' entities (Schmidt *et al*, 2008). However existing issues around the necessary infrastructure to translate these technologies for beneficial use for all will exist for SynBio just as they do for other technologies. Deliberation is therefore necessary to try to establish at the outset how the scale-up of SynBio processes can be undertaken to deliver benefit in an equitable manner.

A further possible non-physical harm from SynBio, which may give rise to a conflict with fair allocation, is deriving commercial benefit. Just like any other scientific discipline, there is a need to reward and encourage innovation in SynBio while being mindful of the restrictions that too much intellectual property can give rise to. Some patents are already being applied for (such as Venter's *Mycoplasma genitalium*), while several component parts of BioBricks and the pathway to developing artemisinin are already patented (Henkel and Maurer 2007, cited by O'Malley *et al,* 2008). Concerns have been expressed about patent thickets (multiple patent holders) and the development of an 'anti-commons' in which numerous patent owners all effectively block each other from innovating (Royal Academy of Engineering, 2009, p44). Some groups have suggested an outright ban on patenting in SynBio (ETC Group, 2007), but this may be difficult due to the technical limitations in differentiating SynBio products from others arising in biotechnology (Rutz, 2009). One mechanism to ameliorate concerns may be to offer different levels of intellectual property protection for distinct synthetic entities; with greater protection for more complex entities. However it is not yet certain how this might work in practice or in conjunction with the current patents system (Royal Academy of Engineering, 2009). The 'morality clause' in EU patent law is also likely to be relevant to SynBio (Rutz, 2009).

While these issues are far from resolved, both kinds of harm arising from SynBio might be mitigated through appropriate regulation, governance or oversight. However, questions will also arise as to

what form of regulation may be needed and who should determine this. The European Group on Ethics has recently observed that many applications of SynBio are covered by existing European regulations (European Group on Ethics, 2009). However, assuming that SynBio does give rise to applications (or even entities) that move beyond current mechanisms of regulation and governance, questions will arise as to what means of oversight are appropriate, what kind of entity should create them and at what level (Garfinkel *et al*, 2007; Weir and Selgelid 2009; Samuels *et al* 2009).

There are various models for regulation, including legal oversight, codes of conduct, professionalization (Weir and Selgelid, 2009) or self-regulation. Each of these has benefits and problems: legal oversight can provide clarity but can be inflexible in light of scientific advances. Codes of conduct clearly stipulate responsibilities but can be difficult to monitor or enforce. Professionalization provides a good balance of internal and external regulation and collective responsibility, yet such a model is somewhat unusual for scientists working in biology. Self-regulation allows significant scientific freedom but may not engender public confidence (BBSRC & EPSRC, 2010, p42) and previous attempts at self-regulation in SynBio have failed. The unknown risks of SynBio will also pose regulatory challenges (BBSRC & EPSRC, 2010, p71).

Ultimately, a combination of regulatory models will likely be necessary for SynBio. However the emphasis or 'starting point' for such a framework will also need to be debated. Parens *et al* (2009) distinguish between 'precautionary' and 'proactionary' frameworks, although not all scholars believe it is valid to conceive of these as necessarily opposing approaches (personal communication, Professor Andrew Stirling, 25 November 2009). However leaving this concern to one side, a proactionary approach instead starts from a perspective of enthusiasm for the emerging technology. Supporters of this framework believe that a new technology should be considered safe and beneficial until proven otherwise – with the burden of proof on those who wish to slow the development of the technology (Parens *et al*, 2009, p18). A proactionary approach will maximise research freedom and commercial benefit to drive innovation and will involve minimal oversight.

A 'precautionary' approach would support a conservative approach to the development of a new technology until it is proven to be safe. This would involve the stricter of the regulatory models described above. While a precautionary approach to oversight of new and emerging technologies has tended to be criticised in bioethics literature, the nuances and uses have been defended in other domains such as law (Fisher, 2007). Additionally, Schmidt *et al* (2008) have reported that some scientists believe that the precautionary principle should have a role in debates over SynBio, particularly as we do not yet know what applications this technology may give rise to. Multi-disciplinary engagement specific to the putative benefits and harms of SynBio may help advance this debate.

How should ethical deliberations on SynBio proceed?

Given their diversity, bringing these various issues together to derive an 'ethics of SynBio' is not easy. Indeed, this may not even be appropriate. In this final section, three claims will be made about the future of ethical deliberation on SynBio. Research on the ethical aspects of SynBio should: (1) not lead to another sub-type of bioethics; (2) concentrate on novel concepts and problems; and (3) be situated within a context of cooperative inter-disciplinary investigation.

(1) Research on the ethics of SynBio should not lead to another sub-type of bioethics

A significant question arising in ethical analyses of all new technologies is whether there is anything specific to that technology which would warrant a distinct methodology for bioethical inquiry. To this end, bioethics already features sub-disciplines such as genethics, nanoethics and neuroethics. Some have argued that there is little about SynBio that would warrant another methodology. For example, Parens *et al* (2008, p1449) have argued that "further balkanization of bioethics would be a

mistake… [Considering] the convergence of scientific investigations [in SynBio], it is not logical to separate the associated ethical enquires." This sentiment has also been echoed by SynBio researchers (Schmidt *et al*, 2008). As an alternative, Parens *et al* (2008) claim that we instead need to be better able to address existing ethical questions in new scientific contexts than to derive a whole new sub-genre of bioethics. The challenges are how to achieve this and whether it would lead to anything interesting; points also considered at (2) below.

However it has also been argued there is something about SynBio that sets it apart from previous debates in bioethics. There have been claims that analogies to past debates have their limits (Boldt & Müller 2008; Schmidt *et al*, 2008), that "synthetic biology sets these issues in a new context" and goes beyond previous technologies (Deplazes *et al*, 2009, p66), that the socio-political context in SynBio is different (Lentzos, 2009) and that "something new and important is happening" (Balmer and Martin, p4, p29).

SynBio certainly has novel aspects, for example its scope for scientific creativity, the open-ended nature of what might be created and the potentially large scale of production. It also features a novel convergence of technologies and disciplines. But carving out another new sub-discipline could lead to a re-hashing of previous debates and further fragmenting a small discipline that is still finding its place in academe.

As we have a diversity of theoretical approaches to bioethics, so too should these prevail in deliberations over SynBio. No single ethical framework should prevail as this could stifle the breadth of arguments and conceptual analysis that would otherwise be possible – the perspectives of virtue ethics and duties-based approaches to the issues raise by creating life may well lead in different directions. Differing theoretical approaches are likely to lead to different arguments which can then be weighed against each other. This will necessitate an examination of the relevant issues or principles arising, rather than merely assessing the specific features of the technology (Swiestra and Rip, 2007). The goal needs to be to avoid scholarship that is too general or abstract to say anything meaningful about SynBio. Of course, as research continues it may be that a sub-discipline does emerge; but this would have been via an organic process of characteristic reasoning and argumentation over SynBio rather than an up-front proclamation.

(2) Bioethics research in SynBio should concentrate on novel concepts and problems
Prima facie, this claim seems obvious. After all, no research of any kind would be worth doing if it did not produce something novel. However there is some merit behind this statement as it applies to SynBio, in spite of claim (1) above. This claim is more about the substance of the inquiry rather than the taxonomy of the discipline.

Ethics researchers can either adopt an approach that applies previous genetic and biotechnology debates to SynBio (which may lead to reproducing existing discourse in a new context), or they can break new ground by developing and reasoning around interesting new questions. The latter can be drawn from what it is that SynBio researchers themselves claim is new about this scientific research - it involves taking the above claim of Parens *et al* (2008) but making sure that the questions answered are novel. To give an example, approaching the question of just distribution of the benefits of SynBio could lead to a re-consideration of existing problems in resource allocation. But it could also lead to new questions around managing potentially limitless synthetically produced resources, or allocating new living entities – should any form of moral status affect how a new entity is distributed?

Bioethics research within SynBio could therefore become one interesting exemplar for ethical analysis and conceptual reflection on emerging technologies. This way the issues can be scoped out

and room made for sound analysis and normative reasoning (particularly surrounding novel concepts and problems) while avoiding a superficial listing of the issues that arise or defining priorities and methodologies for ethics research too narrowly.

(3) Ethical analyses of SynBio need to be inter-disciplinary
This claim is perhaps the most difficult to defend without collapsing into the history, methodology and validity of the discipline of bioethics and its relationship to ethical theory, law and social science. To state that researchers in bioethics should not ignore the work of their colleagues in law and social science is obvious, yet appears glib without further substantiation. The claim being made here is a modest one: it is that the status quo in SynBio offers an excellent opportunity not only to determine what is required to substantially reason around the novel ethical issues arising, but also to consider how ethical, legal and social science approaches might best *integrate* to provide a rich reflection on SynBio and its future development. Achieving this will not be easy given that bioethics is often caricatured as a 'four principles' mantra or a consequentialist tick list. Likewise, bioethicists are surely guilty of misunderstanding the purpose and place of social science approaches, not least their puzzlement at the lack of normativity. It would be interesting and potentially very useful if academics in these related but mutually suspicious disciplines were able to use SynBio as something of a case study to gain a deeper understanding of the academic aims and conventions of their colleagues; rather than taking a 'straw man' example and using it to claim that one disciplinary approach trumps another. Yearley (2009) arguably fails to do this when he cites a short 'four principles' ethics paper as evidence to debunk the utility of the entire bioethics approach to SynBio.

Conclusion
Synthetic Biology research is continuing to grow and develop. As the applications of this emerging and converging approach become clearer, so too will the foci for ethical, legal and social deliberations that are required. A positive aspect of the debate to date is that it offers an excellent opportunity to examine the development of a new technology and shape wider reflection on its implications from the bottom-up, rather than assessing the problems that have arisen 'after the fact'. The engagement of scientists in SynBio is particularly welcome in this respect.

Therefore, research on the ethical, legal and social aspects of SynBio needs to: concentrate on novel concepts and problems, avoid simply segmenting a new sub-type of bioethics and be situated within a context of multi-disciplinary investigation. These three claims certainly require further work and are certainly open to rebuttal. However if they are prima facie valid then good attempts can be made to identify the substantive issues, principles and themes at stake in SynBio as well as encourage sound cooperation among researchers.

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