The ethical landscape: identifying the right way to think about the ethical and societal aspects of synthetic biology research and products

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1. INTRODUCTION

For most areas of significant innovation in science and technology a subtle balance needs to be established when it comes to the governance of new knowledge and novel inventions (see the series of studies since Nelkin 1979). Proponents typically make strong claims about the novelty, excitement and potential impact of their emerging field or area of technological advance. This reflects the genuine enthusiasm they feel for their projects, but also helps to mobilise funding and investment, and to excite political support (see Wright 1994: 115). There is always competition for research funding and for investment by universities, and new areas can only win significant backing through insistence and clear claims about the rewards they can bring. At the same time, the more novel the area, the greater the potential demands for regulatory intervention usually are (see Jasanoff 1990: 2-9). Innovators are generally anxious about excessive regulation and therefore their claims about novelty are commonly complemented by assertions that regulatory issues are negligible or have already been taken into account.

Synthetic biology fits this generalisation almost perfectly. The area can make a very plausible case for its innovative qualities. Of course, the science itself has great novelty. The idea of finding a minimal "operating system" for life for example, or of investigating how biological parts function in novel "circuits", or even of creating living cells and cell systems based not on DNA but around peptide nucleic acid (PNA) chains need no exaggeration or rhetorical boosterism to appear highly significant. But there are also additional ways in which synthetic biology's novelty is manifest.

There is firstly the matter of the potential applications of the technology. Though the potential uses in the short term seem limited (and mostly to resemble existing techniques of genetic engineering), proponents offer visions in which highly innovative biological systems are engineered to produce hydrogen or other fuels. There are also ideas about the engineering of biological systems to synthesise medically important molecules and even to deliver them to specific locations within living organisms. Other suggestions hinge on developing bacteria or other simple biological entities that can clean up environmental toxins or remediate contaminated land. In a period when governments the world over are concerned about finding

technological routes to avoid carbon dependence, the idea of efficient biological factories for hydrogen production is inevitably attractive.

Alongside these ideas about practical interventions there is also a procedural novelty about synthetic biology: the way that it can take advanced genetic engineering to the 'garage' level. At least among some exponents – and in a sense institutionalised in the celebrated annual iGEM (international Genetically Engineered Machine) competition which involves undergraduates and even high-school students across the world – one finds the idea that genuinely novel work can be done by relatively untrained people using commonly available equipment and materials. Just as in the world of IT and electronics where a number of powerful and commercially successful initiatives have been initiated outside the academy and beyond the walls of established corporations, synthetic biology could potentially be undertaken by enthusiasts in informal 'laboratories'. As commercial sources of oligonucleotides proliferate and as DNA synthesisers fall in cost and rise in speed, the feasibility of these claims only increases (see Vriend 2006).

The exact implications of this potential are contested and, in detail, unforeseeable but in the IT world such garage practitioners have given rise to enormously innovative firms and tremendous creativity, as well as to hackers and persistent distributors of viruses. There seems no reason to suppose that biological research could not develop along similar lines. And the already-demonstrated capacity to synthesise actual viruses from biological precursors suggests that the unwanted side of this move to 'garage production' is as likely as the positive one, even in the case of synthetic biology.

To summarise this introduction therefore, in the case of synthetic biology there are strong arguments about the scientific and intellectual novelty of the area, about the potential range of applications which could likely result, and even about the wide range of potential practitioners that could become involved. But directly corresponding to each of these is a kind of regulatory concern. If the entry barriers are low for a form of scientific practice with dramatic implications then - arguably - the need for regulatory control over access is great since no one wants unlicensed operators releasing experimental organisms. If there are likely to be extensive opportunities for application within the human body and in the open environment (for energy production or novel forms of bioremediation) then the release and safetytesting implications are potentially enormous. Lastly, if this technology does give people new power over the fabrication of entirely new forms of life (truly intelligent design as some have guipped) then this might eclipse the ethical and moral concern over granting licences for experiments on admixed embryos which was so conspicuous in the UK in 2008.

At this stage my argument does not depend on any of these claims about the intellectual or practical aspects of synthetic biology being correct or likely to take place; the point is that once these assertions about far-reaching novelty or widespread applicability are made the regulatory implications are hard to avoid. The more strongly the claims are put forward, the more powerful the apparent regulatory logic. Proponents of synthetic biology need to make

claims about its startling novelty and wide-ranging implications if they are to win support, yet they cannot make these claims without simultaneously raising questions about suitable safety and regulatory standards.

In this case the regulatory demand has been recognised and acknowledged within the synthetic biology community (or perhaps 'communities') itself. In the UK and Europe the analogy with the public controversies over GMO plants and foodstuffs has been widely noted. There is a concern to avoid the polarisation of views which characterised that controversy (see Yearley 2005: 159-74). In the US the analogy with the Asilomar Conference on Recombinant DNA in 1975 has been at least as much to the fore, and the topic has also been widely discussed in the light of the increased terrorist threat this century and the response in terms of Homeland Security and the regulations that go with it. As is well known, a key feature of the Asilomar meeting was that the scientific community developed its own protocols on biosafety in advance of external regulation. The meeting was able to put forward its own biosafety methodology (essentially the proposal was to match the containment strategy to the level of risk posed by the material being worked on, using a straightforward classification of risk levels (Bennett et al 1986: 12)) and to advance ideas about how a national policy advisory body should be constituted: as an advisory body to the NIH (Wright 1994: 154).

Already, ethical and social issues relating to synthetic biology have been acknowledged by many of the leading research entities and some forms of ethical reflection have been set up alongside research initiatives: in the USA, the NSF Synthetic Biology Engineering Research Center (SynBERC) has a human practices "thrust" (alongside thrusts on chassis, on parts and on devices), iGEM now includes a component on ethical and social reflection, the EU synthetic biology programme has a funded project entitled Synbiosafe, and in the UK the BBSRC commissioned its own social and ethical challenges review (Balmer and Martin 2008). Clearly, it is impressive that the awareness of the possible implications is sufficiently advanced that researchers have taken this initiative, though of course it is also a smart move in pragmatic terms both to anticipate regulatory review and to display one's concern with such matters. As Wright noted of the intense debates at Asilomar, 'Being regulated by one's colleagues troubled some researchers, but that it might preempt externally administered controls acted as a powerful pressure toward achieving consensus' (1994: 153).

Recognising the role for this kind of review and even deciding to undertake the process is one thing, but there remains the question of what such a review should look like. What counts as an adequate ethical and social review in such an area and where can one turn for a template or pattern? Moreover, how does one establish the integrity of such an undertaking? In the next sections of this paper what I propose to do is to analyse one well known example cited by leading synthetic biologists. I shall consider both the nature of the arguments in this example and the model for ethical review that appears to inform it. Then I shall consider this example in the light of the tradition of institutionalised bioethical review as it has developed in the last two decades. Finally, in the fourth section, I shall specify how insights drawn

from the case of bioethics can be helpfully applied in reflecting on the case of synthetic biology.

2. ETHICAL CONSIDERATIONS IN SYNTHESIZING A MINIMAL GENOME

In his 2007 UK tour to promote his then newly published autobiography (2007), and thus his whole synthetic biology enterprise, Craig Venter responded to concerns about the societal and human implications of his version of synthetic biology by, among other things, noting that he and his colleagues were alert to these issues, even to the extent that they had commissioned a review – published in *Science* – of 'Ethical considerations in synthesizing a minimal genome' (Cho et al 1999). This is indeed an uncommon move for a research scientist to make.

Though this paper was published in 1999, Venter was still invoking it as evidence of his engagement with the societal implications of his research several years later and thus it is worth commenting on the suitability of the work undertaken in that paper for the purposes that Venter apparently had in mind. While Cho et al's publication is well known, it is worth reviewing its contents briefly here for two reasons. First, it is interesting to see what kinds of issue are taken to fall within the areas of 'ethical considerations' as Cho et al construe them and thus to identify what kind of template or model for ethical review inform their work. Second, it is important to assess how much purchase the reasoning about these ethical considerations has on the conclusions and policy recommendations of that paper.

Cho et al's paper begins by noting that 'Efforts to create a free-living organism with a minimal genome ... provide an opportunity for proactive identification and debate of the associated ethical issues' (p. 2087) because the capability of making such organisms is thought to be a long way off. In other words, precisely because we are only at the development stage (this is 1999), there is a valuable opportunity to lay out and refine the relevant ethical issues. The paper spends the first few hundred words on the nature of this space for work on a minimum genome. It then turns to conceivable applications and the social or policy implications they might have.

This section consists principally of a listing of possible implications: that synthesised alien species could 'wreak ecological havoc' (p. 2088) as imported species sometimes have; that restrictive patenting could cause serious problems for a field that requires the 'use of large numbers of genes simultaneously' (p. 2088); and the danger of use of synthetic biology knowledge for biological weapons production (p. 2088). Though the potential problems are outlined reasonably well and even-handedly, no assessment nor ethical conclusion is provided. Instead comments are made such as 'we need to give serious thought to monitoring and regulation at the level of national and international public policy' (p. 2088). Although the authors highlight things that people may have ethical concerns about, the paper does not set out or determine what the ethical analysis might conclude.

The next section focuses on what might be termed more existential issues. It is concerned with the implications for our understanding of life of the reductionist project of which the 'attempt to model and create a minimal genome represents the culmination' (p. 2089). The authors note the possible worry that reductionist approaches could limit the ways that 'life' is understood in the biological sciences. It may also have implications for broader philosophical notions about the nature of human life: the reader is reminded that 'at least since Aristotle, there has been a tradition that sees life as something more than merely physical' (p. 2089). This too appears to be a rather minimal claim, unless a lot is concealed in what the term 'merely physical' might mean. People (or indeed philosophers) might readily agree that life is something more than merely physical without at all agreeing about what is to be valued in life. Though the authors do not say this explicitly, one of their chief concerns seems to be that a theory or even heuristic of reductionism in synthetic biology studies might get mistaken for the metaphysical reality of reductionism; in other words they seem to worry that will conclude that synthetic biology has shown that all the important aspects of living systems are to be found at the molecular level. Thirdly, they suggest that reductionism might have implications for debates about when life begins. A reductionist view - they suggest - might lead one to think there has to be a scientific answer to the question of when life originates, whereas other views of life might indicate that there is no point in trying to resolve the question in purely scientific terms.

There then follows a section on religious beliefs. The authors stress that science and religion need not be at odds but indicate that one area of potential conflict could be over the issue of 'playing God' by engineering life when the making of life might be viewed as a divine prerogative or as hubristic for humans. They suggest that a 'good steward' view of humans might allow a sensible position between pessimism and over confidence: 'Moving forward with caution requires that the scientific communities be in continual conversation with the entire [sic] society, working together to address key ethical and religious concerns' (p. 2090).

This review of ethical conclusions concludes that:

The prospect of constructing minimal and new genomes does not violate any fundamental moral precepts or boundaries, but does raise questions that are essential to consider before the technology advances further. How does work on minimal genomes and the creation of new free-living organisms change how we frame ideas of life and our relationship to it? How can the technology be used for the benefit of all, and what can be done in law and social policy to ensure that outcome? The temptation to demonize this fundamental research may be irresistible. However, the scientific community and the public can begin to understand what is at stake if efforts are made now to identify the nature of the science involved and to pinpoint key ethical, religious, and metaphysical questions so that debate can proceed apace with the science. The only reason for ethics to lag behind this line of research is if we choose to allow it to do so (p. 2090).

As I noted above, in many ways Cho et al gives an interesting review of the field. But it spends much less time *doing* ethical analysis than in sketching the kinds of issues about which people might have ethical concerns. Though it is invoked by Venter as an example of an ethical review, it does not actually come to ethical conclusions nor use ethical principles to pass judgements on the likely ethical and social implications of synthetic biology. Instead it somewhat uncontroversially suggests that now (at least, 1999) would be a good time to hold such a review. Moreover, it is rather misleading about how straightforward such an exercise might be. As stated in the quote above, Cho et al call for 'scientific communities [to] be in continual conversation with the entire society'. Of course, it is a good ambition to consider the needs and maybe the views of all sectors of society, but the idea of continual conversation with the *entire society* is clearly Panglossian. It sounds reassuring and attractive, but is patently unrealistic and cannot represent a serious practical ambition.

Second, it is conspicuous that the report hovers uncertainly between giving a professional ethicist's analysis of the leading concerns and anticipating what the 'popular' ethical considerations may be. For example, the question about the connection between synthetic biology and debates over the point at which an individual's life begins might be expected to play a large part in public and political controversies over the new science and technology because of links to abortion politics. This is likely a shrewd estimation of how the public debate might take shape given, for example, the way in which policy towards embryonic stem cell work developed in the USA under President George W Bush. Opponents of embryonic stem cell research sometimes mobilised the argument that embryos were already living humans; they thus had a keen interest in debates over when life originates. But noting how these issues are deployed is not the same thing as an ethicist's evaluation of the key issues. No professional ethicist is going to follow the line of thinking about which the report warns; the ethical debate about abortion is already very rich, and ethicists (and activists) know all the intellectual moves that people are likely to make. The advent of synthetic biology will not change these. Yet the report lumps together the worries that ethicists are likely to regard as serious ethical concerns with other worries that members of society are likely to voice.

There is a third consideration here, not about the kinds of argument advanced but about the design of the ethical review process itself. The review does highlight some potential concerns and possible disadvantages around synthetic biology but it does not call for a halt to the development of synthetic biology (as some environmental NGOs have done) nor any farreaching restrictions. I am not arguing for such an outcome myself, but simply raising the question of what would have happened had this been the conclusion. There is inevitably a question about where one goes for a disinterested and an as-objective-as-possible assessment in such a controversial area. The key difficulty is this: given the scientific and commercial interests in favour of developing synthetic biology and the determined opposition of some environmental groups, where does one source warrantably impartial ethical advice and, supposing one could find it, would

the actors in the controversy accept its conclusions. The continuing close connection between the *commissioners* of such reviews and people *conducting* the review suggest that this is not an easy problem to resolve (see for example Garfinkel et al 2007).

To conclude this section, I have examined one widely-cited review. Though it is invoked as an ethical review, it – somewhat surprisingly – does not actually carry out much ethical reviewing. By being styled as an ethical review, Cho's paper looks as though it will offer some practical interventions in the same way that ethical reviews in medical contexts commonly do. In fact, however, it largely avoids coming to decisive ethical conclusions and mostly limits itself to calls for further dialogue over ethical matters. Furthermore, it mixes empirical issues (what people will likely worry about) with normative ones (what ethicists think people should worry about), and does not demonstrably deal with concerns about the objectivity and impartiality of the review process itself. It is time now to look in a different way at this very notion of an ethical review. I shall use the example of one areas where ethical review has been successfully institutionalised to see how some of these difficulties have been approached or addressed in a related field.

3. BIOETHICS AS A MODEL OF ETHICAL REVIEW FOR SYNTHETIC BIOLOGY

The challenge of trying to work out what an ethical review of a topic such as synthetic biology should comprise, and of who should undertake it, is not unprecedented. On the contrary, the question is similar to the more long-standing matter of how to conduct reflection and wise review in bioethics and biomedical policy more generally. Indeed, one could argue that the proposal for an 'ethical review' in the case of synthetic biology appeals precisely because the practice of ethical review has both been well established and apparently successful in the field of bioethics in the last decade and a half. Bioethics is now institutionalised in the US medical system, and elsewhere to a lesser extent, and has achieved a form of monopoly ethical authority.

Recently, the US sociologist John H Evans (2002) has carried out a study of the way in which a certain conception of bioethics became institutionalised and professionalised in the USA. What Evans observes is that there has been what he terms a 'thinning' of the ethical debate from the 1980s into the 2000s. Nowadays, he suggests, the principal participants argue over issues almost exclusively in terms of a restricted set of considerations. Many key participants no longer contest with each other in terms of ultimate goals but focus instead on a limited set of formal criteria, such as autonomy.

Rather than ascribe this thinning to a necessary accommodation to value differences in a multicultural and multi-faith society, Evans proposes that this strategy emerged as the unintended consequence of conflict between professional groups who were all seeking to gain influence in the world of human genetics, its governance and its interpretation. Out of governance arrangements such as those proposed at the Asilomar meeting came a regulatory landscape dominated by appointed advisory bodies. These bodies found it easy to work with an approach that came to be known as

'principlism', an intellectual strategy that focused on a principle-based system of ethics. Rather than argue about ultimate ethical ends, protagonists began to claim that their view (against or in favour of restrictions of work on human embryonic stem cells and so on) was superior in terms of accepted ethical principles. The four central principles are now known and taught worldwide: beneficence, nonmaleficence, autonomy and justice. Participants 'in the debate began to adopt this new form of argumentation largely because they thought it was the best way to make ethical decisions *in light of the new decision-makers*, the commissions' (2002: 37 original emphasis). Those who wanted to take part – philosophers, theologians, patients' activists, scientists and so on – increasingly restricted themselves to framing their arguments in 'principlist' terms. The arguers thinned their own arguments and 'like all processes of institutionalization, in time the form of argumentation took on a life of its own, somewhat independent of the social conditions of government advisory commissions that gave it birth' (2002: 37).

Evans is not primarily seeking to evaluate principlism in philosophical or ethical terms; rather, he is trying to explain how it came to be the dominant framing of bioethics issues in many public contexts, from hospitals and health practices right up to Federal research bodies. He argues that it has become a kind of *lingua franca* in which representatives of different perspectives try to win over the advisory bodies. But, by couching their arguments in these terms (rather than in more traditional religious terms or in terms, say, of promoting medical research for its own sake) the participants tend to reinforce this way of conceiving of bioethical arguments. From an ethical language that was chosen, it becomes *the way* to talk about bioethics; it even begins to look like the only commonsensical way to reflect on these issues. 'People who entered these debates and who adopted this new form of argumentation – or people who converted to it – began calling themselves "bioethicists" and not scientists, theologians, or philosophers. A new profession was born' (2002: 37).

But Evans does also have an ethical concern about where this new professional orthodoxy and the pervasiveness of principlism will lead. A long quote from his book indicates what he feels is at stake:

If one were to ask a focus group of people unfamiliar with the debate about germline human genetic engineering (HGE) to come up with arguments against the practice, they would probably not think to raise the argument that germline HGE is wrong because persons not yet born at the time of the research had not given their informed consent to risks to their own genome. Yet this was one of the few arguments against germline HGE considered *legitimate* in bioethical debate in the 1990s. I suspect that my imaginary focus group would think it odd to conceive of intergenerational responsibility through the language of consent, rather than responsibility, and they would likely find it pointless to enter a debate premised on getting impossible consent from not yet existing people (Evans 2002: 11).

In other words, people in the USA who wanted to fashion arguments about human genetic engineering for use in public contexts found that they had to construct their arguments out of the four building blocks of principlism, and they fastened onto autonomy. A way of expressing distaste with practices that would lead to changes to the germline was to claim that this impaired the autonomy of future people who might be affected by this change but could not – of course – consent. Evans's view is that something has been lost in moral discourse when participants have to go to such implausible lengths to construe their concerns in acceptable terms.

4. FIGURING OUT A SUITABLE ETHICAL LANDSCAPE FOR SYNTHETIC BIOLOGY

It is clear that most of the leading actors in the world of synthetic biology recognise that they need to attend to the ethical and social aspects of their research. This appears to be both because they recognise that synthetic biology may indeed have enormous societal implications and because they appreciate – as Wright noted above – that regulating one's own community is probably less painful than being regulated.

What I have argued in this paper is that one obvious and superficially attractive way to do this is to conduct an ethical review, modelled approximately on the bioethical analyses which are now standardly conducted in healthcare and in medical research contexts. This approach is attractive for synthetic biologists for precisely the kinds of sociological reason that Evans outlines in the case of germline engineering and other topics. Bioethics seems to work, in that bioethicists help to make decisions at nearly every level in US biomedicine. Moreover, bioethics appears to have a sound and systematic foundation: it rests on the four pillars of principlism. Furthermore, many social groups, including mainstream theologians and activists, orientate themselves to this same ethical language. When they disagree with biomedicine's positions or policies, they commonly express their disagreements in principlist terms. Finally, the principles have a kind of affinity with scientific thinking. They are universalistic and as Evans notes (2002: 153) 'commensurable', in the sense that other ethical concerns can typically be re-cast in the language of the principles. As ethical arguments go, these look pretty much like the laws or principles that scientists are familiar with. Scientists and medics readily feel at ease with the principlist language of ethics.

However, despite these attractions, the bioethics review is a misleading model for social and ethical reflection about synthetic biology. Part of the reason for this is relatively straightforward. It is evident that some of the unease expressed about synthetic biology relates to concerns about allowing people (i.e. researchers and the enterprises they work for) to develop novel forms of life. Cho et al present this as primarily a worry about letting humans 'play God'. But other writers, such as the German sociologist Beck (1995), express this in a less other-worldly way. Beck notes that recent scientific and technological advances have, for example, freed societies from dependence on the vagaries of the weather but the same societies are now dependent for their security on the good behaviour of the operators of nuclear power stations. Vaccine programmes appear to have overcome many dread diseases, but the Cold War powers held on to, and even developed, new diseases. Our fear of 'natural' diseases has lessened, but we are left

dependent for our safety on the military controllers of stored viruses. His point is that where we once feared nature, we now worry about the dependability of organisations and regulatory systems. In this sense, he argues, nature has been humanised (1995: 55). Seen this way, worries about hubris and playing God are not religious or spiritual worries but are directly political and sociological anxieties. They are worries about whom to believe and how to check the power of the mighty and secretive. Precisely because the outlook of principlism is non-political, it fails to attend to this dimension of people's concerns.

The bioethics review is also a poor model for desirable kinds of review of synthetic biology because the assumption of the centrality of universal ethical principles is even less applicable to these startling areas of biological innovation than to the case of novel medical interventions. One might say that beneficence and nonmaleficence are reasonable guides to interacting with our natural environment. But in the case of the environmental release of synthetic organisms the main public concern is not the ethics of the matter but the uncertainty and unpredictability of environmental impacts. In an important sense, configuring the kind of review needed as an *ethical* one is already to limit the forms of public debate and dialogue that are appropriate.

Overall, my conclusion is that there is wide agreement that synthetic biology calls for care and oversight. But there is a risk of a precipitate move to organise reflection on this novel research using an inappropriate model, that of bioethics.

Organising an ethical review of synthetic biology using the template seemingly offered by bioethics will be misleading. It will lead reviewers to focus on too narrow a set of concerns, on ethics but not politics; and it will lead them to be over-confident about the universality of principlism. It may look like an objective and science-friendly approach, but this appearance of objectivity will be misleading. Going down this route will be inadequate in its own right. But it will also be counter-productive since the apparatus constructed to conduct the social and ethical review will come to look like a mere legitimatory cloak for synthetic biology's advance. I believe the need is not simply that synthetic biology be accompanied by some sort of ethical and social review, but that the review should be conducted in broader terms than those offered by the comfortable language of principlism.

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