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Roundtable on Synthetic Biology

Visions and Challenges in Redesigning Life

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Interest in synthetic biology has grown remarkably over the last few years. In Britain, the Royal Society issued a call for views on it in summer 2007, and convened a Synthetic Biology Policy Coordination Group following on from that to exchange information on national and international developments, identify gaps in current policy activities and stimulate policy activities to encourage the development of synthetic biology. It held a two-day open discussion meeting on developments and applications of synthetic biology in early June 2008, and is co-organizing a two-day international symposium on the opportunities and challenges of synthetic biology with the US National Academies and the Organization for Economic Co-operation and Development to take place in the United States in late 2008. The Royal Academy of Engineering has also established a working group to undertake a policy study on synthetic biology, while the Royal Society of Chemistry has identified this topic as one of its key strategic areas and held a one-day seminar on 'Engineering life: The emerging field of synthetic biology' in April 2008 together with the Institute of Physics and the Institute of Biology.

Gaymon Bennett is Director of Ethics at the Synthetic Biology Engineering Research Center (SynBERC), UC Berkeley (http://synberc.org/thrusts.html). His work concerns the interactions of religion, politics and science, with a focus on bioethics. He is the author, with Paul Rabinow, of 'Toward Synthetic Anthropos: Remediating Concepts' (available at www.anthropos-lab.net/documents).

Jef Boeke is Professor of Molecular Biology and Genetics and Director of the High Throughput Biology Center at Johns Hopkins University School of Medicine. He headed the GeneDesign project, which developed a web-based, automated computer program that greatly simplifies the time-consuming and error-prone process of manually designing artificial pieces of DNA.

Drew Endy is Assistant Professor in Bioengineering at Stanford University. With Thomas Knight, Gerald Jay Sussman and other researchers at MIT, he is working on synthetic biology and the engineering of standardized biological components, devices and parts, collectively known as BioBricks. Endy is also known for his opposition to limited ownership and support for free access to genetic information. He has been one of the early promoters of open source biology, and helped start the BioBricks Foundation, a not-for-profit organization that will work to support open-source biology. He is also a co-founder of Codon Devices, a biotechnology start-up company that is aiming to commercialize DNA synthesis.

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Paul Rabinow is Professor of Anthropology at the University of California Berkeley, Director of the Anthropology of the Contemporary Research Collaboratory (ARC), and Director of Human Practices for the Synthetic Biology Engineering Research Center (SynBERC), where he is part of a collaborative effort to re-think the relationship between ethics and science within this NSF-funded Engineering Research Center. His major works include *Marking time: On the anthropology of the contemporary* (2007), *Anthropos today: Reflections on modern equipment* (2003), *French DNA: Trouble in purgatory* (1999), *Essays on the anthropology of reason* (1996), *Making PCR: A story of biotechnology* (1993).

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Funders too are showing a keen interest. The Biotechnology and Biological Sciences Research Council (BBSRC) has a working group dedicated to synthetic biology. Following a two-day workshop in February 2007, the BBSRC issued a call for proposals for networks in synthetic biology in partnership with the Engineering and Physical Science Research Council (EPSRC) and the Economic and Social Research Council. In January 2008 the BBSRC published an independent review of the UK's position in synthetic biology and the key societal issues raised by new research capabilities and the likely trajectory of the research, and building on the call for networks it is increasingly offering an expanded array of grant support for work in this area. The EPSRC has also identified synthetic biology as an important area for future development, and along with the BBSRC, co-sponsored the 2007 BioSysBio conference in Manchester, and supported Summer Vacation Bursaries for graduates to participate in the iGEM (international Genetically Engineered Machines) competition. The Wellcome Trust is organizing a workshop in November 2008 to inform the development of its funding strategy in this area, and the National Endowment for Science, Technology and the Arts is interested in developing models and projects to facilitate interdisciplinary research and has identified synthetic biology as a good platform for development.

The government and its departments are also showing increasing attention to this topic. The Government Office for Science is maintaining a watching brief on it, while the Parliamentary Office of Science and Technology issued one of its POSTnotes on synthetic biology in January 2008. The Ministry of Defence (MoD) held a workshop on synthetic biology already in December 2006, and while participants did not see the field as posing particular threats or opportunities for the UK in the immediate future, longer-term threats and opportunities were identified. The MoD is currently undertaking a more detailed review of the emerging field and maintains a watching brief on the issue. The Departments of Health and of Food and Rural Affairs (Defra) are also monitoring developments, with particular interest in better, cheaper drugs and in biofuels, as well as in ensuring the safe application of the technology. Other regulators are involved too. The Health and Safety Executive's Horizon Scanning Intelligence Group produced a short report on synthetic biology, and its Science Advisory Committee for Genetic Modification has identified this as an area it will monitor closely. The Health and Safety Executive is also a member (along with Defra) of the European Union working group investigating the alignment of current GMO (genetically modified organisms) regulations with new technologies, including synthetic biology.

It is not only in Britain and on a national level that we are seeing this rapidly expanding interest in synthetic biology. Stakeholders are developing strategies, initiatives and networks at regional and international levels too. For instance, the European Commission's SYNBIOLOGY project, funded through its New and Emerging Science and Technology programme, looked at the synthetic biology sector in Europe and North America and analysed the main actors involved, the geographic distribution of research and the key sources of funding. The follow-up SYNBIOSAFE project, launched in January 2007, is the first European project to research the safety and ethical aspects of synthetic biology, and draws on experts from synthetic biology, biosafety, biosecurity, ethics, public perception, technology assessment and public awareness.

But what exactly is it that the synthetic biology stakeholders are getting so excited about? What is synthetic biology, and how might it change the way we think about life? In this inaugural 'roundtable forum' I speak to two of the key scientists involved in synthetic

biology, the engineer Drew Endy and the biologist Jef Boeke, whose ideas and imaginations are pushing and shaping this rapidly developing field to find out how they envision synthetic biology and what they think its major potentials and challenges are. I also speak to the anthropologist Paul Rabinow and the bioethicist Gaymon Bennett, who have both been following developments in synthetic biology over the last few years, to seek what they term 'second-order' insights on the science and to explore the role of social scientists in the synthetic biology debates. We spoke about different visions of synthetic biology, about some of the potentials of the field and some of its major challenges.

Filippa Lentzos: To start us off I thought we might consider what synthetic biology actually is, and whether, in your opinion, synthetic biology is really something novel, or, as some say, merely an extension of what is already being done in the field?

Drew Endy: Sure. The current technologies that let us sequence DNA or manipulate it via restriction endonucleases and polymerase chain reaction have been developed over the last 30 years or so, and synthetic biology is really the next big step in taking biotechnology forward. It is a direct extension of genetic engineering and genetics, and is primarily focused on making biology easy to engineer.

If we look at the field of biotechnology we could ask whether we have realized its promise: have we delivered on all of the applications that were scoped out as the field was getting going? The answer is no. While we do have production of therapeutic molecules in bacteria, things like insulin, we don't really have gene therapy working, we don't have nitrogen-fixing crops working. Synthetic biology is the technology that will enable us to deliver the solutions and products to these outstanding challenges.

So essentially synthetic biology is about problem-solving. It's about analysing the opportunities that will improve the process of delivering working biotechnological solutions to specific problems. Oftentimes these opportunities are coupled to new tools and technologies. So, for example, where we previously had recombinant DNA for cutting and pasting pre-existing fragments of genetic material, you can now work at your computer to design a DNA molecule; and when you want the physical DNA molecule, you don't go into the lab yourself and manually cut and paste DNA to try and produce it, you instead send that sequence information over a computer network to a machine, a DNA synthesizer, that, when you press the button, prints the DNA from scratch for you. Now, this makes it a lot easier if you wanted to go engineer some living organism because it would let some people specialize and become experts in designing DNA and other people specialize and become experts in building DNA, much like an architect or a contractor work together to produce an office building. So automatic construction of DNA becomes a new foundational technology that's very interesting in synthetic biology. This is the sort of work Ham Smith's team at the Venter Institute is doing, demonstrating that it's possible to construct ever longer fragments of genetic material. There are, of course, many other groups also working on the problem. Teams in Japan, for example, have constructed fragments of DNA that are 15 times as long as those that the Venter Institute has been constructing so far. So the automatic construction of DNA is one new tool that's been developed. There are two more tools where you see a lot of work in synthetic biology happening right now. One is what a computer scientist would call abstraction, and the other is what a mechanical engineer would call standardization.

Most genetic engineering over the last 30 years has taken place at the level of DNA itself: the As, Ts, Cs and Gs. So if you wanted to be a genetic engineer you would have to be very familiar with DNA sequences that encode different functions when placed inside a cell: the 23 base pair sequence TAA, TA, CGA, CGC, ACT, ATA, GGG, AGA, for example that encodes a promoter for the T7RNA polymerase initiating transcription in bacteria. But if I had to do all my genetic programming at the level of sequences, that would be like programming a computer in zeros and ones in the machine language of that machine, in the same way that the As, Ts, Cs and Gs are the machine language of the cell. Very few computer programmers write programmes in machine language anymore. That's because computer software engineers and computer scientists have invented a hierarchy of programming languages, building up to ever more powerful functions without having those functions be ever more complex. So you can write a programme that calls upon a print statement, and when you use the print statement it causes something to be printed to your screen, a little read-out, and you never see that behind the scenes, inside your computer, that this high-level function is automatically compiled down to zeros and ones for you. So what happens when we invent new programming languages, this time not for programming silicon, but for programming wet-wear in genetic material? That's a whole area of research called abstraction. This deals with the tools for managing the information that goes into the DNA synthesizers. And that's where you see efforts like the BioBricks project, which aims to standardize biological parts and make them publicly available online.

The mechanical engineers, with their concern for standardization, then come along and say this is fine, you can build DNA and you can define abstract genetic objects, but how do you know that when you put them together they're going to work? And how do you know that what one person says is working is the same thing that you think is working? So this is like what happened when mechanical engineers all agreed to make nuts and bolts in accordance with a particular screw thread standard, or when the telegraph engineers laying the transatlantic cables invented a standard for measuring resistance through the wires (the ohm). Standardization is an agreement, basically, amongst many disparate people so they can coordinate their work. So each of these technologies—automation, standardization and abstraction—provides a platform for helping the process of engineering biology get better and better and better, and that's what synthetic biology is for me.

Jef Boeke: Yes, like Drew says, synthetic biology is in many ways an extension of what is already being done. The technology itself isn't really so radically new, gene synthesis technology has been around for years and years. What's new about synthetic biology is the scale on which it's being done.

Synthetic biology also enables you to do things on a far greater scale. So on the synthetic genomics side, for example, it enables you to contemplate synthesizing entire genomes as opposed to just one gene or operon at a time. And on the synthetic biodevice side, there's a new perspective on biology that's coming from the engineering community focused on how we can put individual genes or clusters of genes to work to solve specific biological problems that we might be wanting to solve.

Filippa Lentzos: So is synthetic biology somehow changing the way biologists think about life?

Drew Endy: I think it has to. For example, if you can build a piece of DNA and you're interested in studying how natural living systems work, being able to build any piece of DNA you want lets you test out all sorts of ideas. So genetics as a science will probably change quite dramatically as a result of construction technologies getting better, in the same way that genetics changed in response to sequencing technologies getting better. I don't think very many people understand this yet. There are certainly very few geneticists thinking about how genetics will take place in a post-synthesis era.

Filippa Lentzos: What do you think Paul?

Paul Rabinow: Having observed synthetic biology for the past few years now, I think we're seeing more than one vision of where the field is going.

One vision, the one that Drew champions, is of a new discipline emerging modelled on electronic engineering, with modularized parts that are fully interchangeable and a set of standards for how you put those parts together. Or in other words, a linear programme whereby you can take parts and simply add them to other parts in order to get device functions which you can then build into systems. So it's about making biology into an engineering discipline. Everything that came before in biology was interesting and things were learnt, but it was not yet engineering, and not yet therefore able to achieve the kind of control over biological processes that this new discipline will be able to achieve. The big question here of course is whether or not living systems are analogically close enough to the electronics industry, or indeed to the vision of nineteenth-century engineering and the standardized screw, to be directly applicable. Can the basic biological, evolutionary, non-linear aspects of living systems be engineered out?

I think the jury is out as to whether or not they're succeeding, so far at least. And there's a lot of scepticism in the labs about whether this is the right approach. That's not to say that the scientists we talk to don't think that you can standardize and modularize functions, up to a certain point; that you can achieve functional regularity, a certain degree of modularity, and so on. Jay Keasling, for example, who is head of the Berkeley Center for Synthetic Biology, has demonstrated that you can build pathways using Drew's type of language and type of strategy. But rather than building from the bottom up, Keasling takes very well known experimental organisms like *E. coli* and modifies their pathways to use them as 'chemical microbial factories', as he calls them, to produce specific molecules. And that seems to work. For example, one of his projects, funded by the Gates Foundation, was to produce artemisinin—the major remaining effective anti-malaria molecule that, in nature, comes from the bark of a Chinese yew tree. He has synthetically produced the molecule, or the precursor of the molecule, in both yeast and *E.coli,* in magnitudes and at lower cost such that it can now be produced industrially, modified to reduce the rapid growth of resistance, and then distributed—by a non-governmental organization, One World Health—at very low prices, while also taking into account that the Chinese yew tree farmers mustn't be put out of business. So Keasling has demonstrated that something like engineering biology is plausible.

But while in some ways this pathways approach is similar to Drew's parts-based approach, in other ways it's not, because Keasling has a problem-driven approach. He wants to produce very specific molecules of interest, and does that by redesigning pathways.

And so he may build parts, and modularize to a certain extent, but it's not to control the whole game, it's to build the pathways of interest. So the object under consideration, and therefore its relationship to biological considerations, is the nature of the pathway, and not the character of the individual parts that make up the pathway.

Many of the scientists we speak to don't think that the analogies from past engineering disciplines should set the standard for whether or not biology has achieved engineering. They want to move beyond those analogies and discover what are the engineering principles proper to dynamic living systems. So by and large they tend not to think that the linear programme is the only way to proceed, and/or that black boxing all the biology is really very likely to be a successful approach.

The other extreme vision of synthetic biology at the moment is of course the top-down approach often associated with Craig Venter, who works at the level of full genomes, in a top-down fashion, to create the minimal genome that will allow you to have a sort of plug-and-play set of functions.

Filippa Lentzos: Yes, we heard a lot about Venter's work on synthetic genomics at the London School of Economics panel discussion on synthetic biology last year [a transcript of which was published in *BioSocieties* vol. 3(1)]. I wonder whether, Drew, you might give us your thoughts on what you think some of the main benefits, or products and applications, might be of synthetic biology as you see it?

Drew Endy: That's a bit like asking somebody building one of the first electronic computers what all the applications of computers will be in the future. When computers were getting built in the United States during World War II and soon thereafter, the applications were to help us design hydrogen bombs by computing the trajectories of munitions. Are those the applications of computers we should be celebrating? Then, only 25 years later, by the mid-1970s people had become so excited about computing and so fed up with limited access to these centralized computing resources that they went ahead and invented the personal computer. Now, what's a personal computer good for? Well, it's whatever a person wants to do with it. And what do people want to do? All sorts of things. So maybe that's the way I think about synthetic biology.

What are the applications of synthetic biology? Well, it's whatever people want to do because as we make biology easier to engineer we make it more accessible, we make it more distributed. And biology can do a lot: from production of materials, to chemicals, to information processing, to energy; food for people, food for animals, food for vehicles, environmental sensing, detection or mediation, and so on and so forth. Art, beauty, design. What happens when you get the equivalent of graphic designers working in genetic material? We've seen this happen a little bit already, but the tools haven't really been there. So look at what happened with painting when all of a sudden paints became available in foil tubes at scale, so-called readymade paints? How did that change painting? Was it still art? Did more people start painting?

I could, of course, say that one application getting a lot of attention today is bioenergy. Carbon sequestration too could be an important contribution. And we could go through the whole space of charismatic applications, but for somebody in my position it's much more interesting to come in from a slightly different perspective and say, if we actually succeed

in making the engineering of biology easy, or at least easier, then the set of things that could come true are much more interesting than anything we can come up with here and now.

Filippa Lentzos: Sure. What do you see as some of the biggest challenges to synthetic biology then?

Drew Endy: On a technical level, the field needs to demonstrate that the ideas of abstraction and standardization are actually going to be useful. Can we make a collection of standard biological parts? Sure, we can say we do that. We already have a couple of thousand in the BioBricks collection for example, but those parts aren't yet very well characterized and we don't know that when we snap any two parts together the behaviour of the resulting composite object will be as we expect. So demonstrating what a mechanical engineer would call reliable functional composition, that the function of the composite object is as you expect, that's got a lot of questions associated with it. Is biology too complicated to be simplified in this way? How much energy do we need to spend refining the materials, organizing the functions, adding in insulation so that when we combine things there aren't unexpected secondary effects? There are lots of research questions there, so there is a lot of good work to do.

Another area of uncertainty has to do with evolution. Most engineers have not looked at self-replicating machines before. If you think about your phone, laptop or car, these objects aren't capable of reproducing themselves. So the question arises, how do we design reproducing machines whose designs we can also understand? It's a new problem for most engineers, so figuring that one out is going to be pretty exciting.

Jef Boeke: Another technical hurdle we're facing is that when you contemplate doing something like synthesizing a yeast genome the price tag is still way too high. We really need a technology that will drop the price per base pair, not by 50 per cent, but by orders of magnitude. And once that happens, it's going to really change what can be done, because then we won't be contemplating building one genome but many genomes. That's when synthetic biology, or synthetic genomics, will really come into its own.

What we really need is to develop technologies for mixing and matching large numbers of genes in either a random or a semi-directed manner. One of the things that we've incorporated into our thinking is the ability to trigger large-scale genome re-arrangement at will. We've built in site-specific recombination signals throughout the genome that we're designing and—we haven't actually done this yet, but the idea is that we can then trigger low levels of the site-specific recombination to rearrange segments of the chromosomes and see what underlies genome structure and chromosome structure. Are there any rules to it or does anything go? Can you put any gene next to any other gene or is there a method to the madness of the way chromosomes are organized? So finding efficient and inexpensive ways to do experiments like this are also some of the technical challenges the field faces.

Drew Endy: On a broader socio-political level, I think the security situation is going to be very challenging. To date most people have considered issues of biosecurity at the level of nations, one country versus another, but as we make biology easier and easier to engineer we now have to consider what individuals might do. And I've not yet seen a biosecurity framework that strategically accounts for the fact that individuals are going to be able to

do things with biotechnology that just haven't been possible before. How do we prepare ourselves for a world where eventually somebody will design and construct a virus or another parasite or a pathogen which is designed to cause harm to other people or organisms or the ecosystem?

Filippa Lentzos: Yes, biosecurity has become a big concern in the US, and increasingly elsewhere, over the last few years. How realistic are biosecurity concerns with regard to synthetic biology do you think?

Jef Boeke: My initial reaction would be that, at this time, the risks are probably rather low. Not because I'm an expert on terrorism or anything like that, but just because I know how hard it is to do this stuff. And while, yes, all the parts are there if somebody wants to build smallpox from scratch or what have you, actually getting out there and doing it would require a large laboratory and quite a lot of infrastructure. So I think the notion of rogue terrorists being able to do this is rather unrealistic.

Synthesizing novel pathogens seems particularly unlikely at the moment to me. I would worry a lot more about people trying to recreate an existing one. It's relatively easy to make genes that just replicate something that's known to be out in nature and known to be dangerous. It's possible to make the sequences, particularly for viruses which are relatively small, that's no longer a challenge, you can order them online—although if the companies are screening you, you shouldn't receive them.

But fortunately, while constructing the DNA might be reasonably straightforward if one had a well-equipped laboratory, the challenge of actually turning it into something that could be used in the field, so to speak, would be non-trivial. Really, it would need a big operation. Even anthrax, for example, obviously it's been used to harm people in small numbers, but actually turning it into a 'bioweapon', as I understand it, which can be used with precision and with large-scale effects, is a very complicated business, and certainly not something that an average lab can do.

Filippa Lentzos: That the extent to which the 'know-how' involved in making biological weapons is equally as important from a non-proliferation point of view as addressing biological agents and equipment is a really important point that is so often missing from current policy and security discussions on this. And, of course, this 'know-how' encompasses more than the mere presentation of results and the methods sections in scientific publications. As you suggest, Jef, certain aspects of bioweapons knowledge rely on the unarticulated, personally held knowledge that is acquired through a practical hands-on process.

Jef Boeke: One of the downsides of making gene synthesis 100-fold cheaper and automating it is of course, though, that that changes the picture somewhat. So as the technology improves and gene synthesis becomes simpler, the more of an issue biosecurity concerns become.

Drew Endy: Well just this year we've seen a group construct the genome of a bacterium from scratch. This is just under 600,000 base pairs long—i.e. a length of DNA greater than all known human viruses, including things like smallpox for which the sequence information is available freely over the internet. So 20 years from now you're telling me that it's

not going to have happened, that somebody will not have built the genome of a virus—it doesn't have to be as long as smallpox, it could be shorter—and released it? That would be really surprising to me. I certainly don't want to promote that sort of activity unnecessarily, but I think it would be naïve to not prepare for it.

To bring up some of the complexities around this issue, one could for instance ask whether the rapid expansion of classified biodefence research labs in the United States operating without public or international scrutiny, is good or bad with respect to biosecurity. Sure, there are some capabilities we might need to develop, but we also need to promote international transparency so that we don't inadvertently lead to a remilitarization of biological technology which, if one were to consider the technologies that are coming online, would be an absolute disaster. What would a person in a country outside the US think of the current, classified investments in biosecurity in the United States? Do you believe it's defensive? Should other countries have their own secret or classified biodefence research programmes? If you don't believe that it's defensive, what are you going to do? So I think this is an incredibly important question to bring up. I'm certainly not convinced that the way it's been approached in this country since the anthrax attacks on the US Congress in 2001 has been constructive, and I have yet to hear a coherent strategy for biosecurity.

Filippa Lentzos: Aside from biosecurity, do you see any other socio-political challenges to synthetic biology?

Drew Endy: Yes, there are obviously additional challenges to the field, and they're all very important, but to me they don't seem to have 'sticky problems' associated with them. I am not belittling these concerns, they're serious, but I see paths forward with them where, with the biosecurity one, I don't think the conversations have been strategic or mature enough to support it. So safety, for example, is an important challenge—researcher safety, public safety, ecological safety—but there's a tremendous set of lessons we can draw upon from earlier experiences and so these challenges aren't as heavy or as formidable to me. To my mind there are two main challenges with respect to biosafety and synthetic biology. The first is that most of the people coming into synthetic biology are young, which means they weren't around when the conversations took place about recombinant DNA. So basically you need to foment a generational transfer of knowledge about biosafety. The second challenge is that the majority of people coming into synthetic biology aren't biologists. They're physicists or computer scientists or electrical engineers and so they're just of a different culture. They don't have a lot of experience with microbiological safety. So you need to gain access or transmit knowledge across not just a generational gap, but across cultural divides. Both of those problems can be directly addressed. They're not trivial, but I don't think we need to debate at great length whether or not this should be done. Let's just go do it.

Jef Boeke: Yes, and in terms of environmental contamination, for example, the risks are really minimal because at the moment all gene synthesis is done in contained laboratories in relatively secure environments, and most of the things people are building wouldn't last in the environment for more than probably a nanosecond anyway.

But where synthetic biology could become a problem and where some regulation might be welcome is if there is scale up to a very large industrial scale or there is some kind of

outdoor type of release, say if you were going to engineer green algae to be a very efficient harvester of sunlight and producer of fuel and you were going to grow it in gigantic ponds. So, just like with recombinant DNA, there would need to be some regulation of very large scales and any kind of 'field trials'. But to my understanding, the current regulatory framework for genetic modification is one that can be adapted to monitor this type of work once we get to that point.

Paul Rabinow: I think the overall framing of synthetic biologists is that they would like to keep the Asilomar mode of regulation and of—pardon the Foucauldian jargon—objectivation in place. Which is to say that they regulate themselves, they teach responsible science, and they go about their business as if they were still in 1975. We don't think that makes much sense, for a number of reasons. First, that we live in a global world, with tens of thousands of world-class scientists around the world, in a way that wasn't the case in 1975. Second, the Internet, such that the production and dissemination of core technological and scientific knowledge is not restricted to the old boys' network in the way that it was in Asilomar. And then we live in a security environment, as we've already spoken about, which means that presumably, in the future, the kinds of considerations that cutting-edge engineering and science face are more than the safety considerations which Asilomar people succeeded in framing as the problem. Safety is not the only variable any more, security and preparedness are firmly on the agenda too. And although there's been a lot of talk about regulation so far, it has not been turned into concrete practices. Gaymon, you want to push that a little bit more?

Gaymon Bennett: By working on the Asilomar model, or some kind of self-governance at least, synthetic biologists want to demonstrate that they're ethical scientists, and then allow that to be the warrant for them controlling their own game, as it were, with regard to ethical and other considerations. In the 1970s USA this played out pretty successfully for the scientists. They had the Asilomar conference, they set up the RAC (Recombinant DNA Advisory Committee), and then the first national commissions on bioethics were basically told that the safety considerations were taken care of and that they should find whatever slice of the pie was appropriate to bioethics. And so, if you read documents like *Splicing life* [US President's Commission, 1982], a good part of it is just speculation on the metaphysics of genetic engineering. And while I happen to be interested in metaphysical questions, and ontology in a more pragmatic way, the form that that took, under those circumstances, was really to reflect on the ontology of science fiction, and not the ontology of the science. So it was basically a division of labour, whereby bioethicists didn't get to deal with the manly questions about safety that the real tough scientists were going to deal with. And we just don't live in that world any more. There's now an increasing set of interfaces, and a diversity of interfaces, between the ethics community and emerging domains like synthetic biology. So, however this unfolds, Asilomar is not going to work; the bioethicists are not going to go into the next room and think about science fiction any more.

Another socio-political challenge to synthetic biology that I find particularly interesting is the extent to which industry is getting involved with the science today. The National Science Foundation mandate for our synthetic biology centre at Berkeley is that they be engaged with industry from the very start, and that within ten years they become

self-funded. We've just gone through a site review, in which the site review committee, which in 1975 would have been all 'distinguished scientists', was now at least half people from industry. And we hear this constant refrain 'Well, what would industry think?' As anthropologists, that's interesting; as citizens, it's a little bit less interesting and more troubling. Not that industry involvement is per se a bad thing, but there's an assemblage forming, in which the power of industry to make claims on what counts as science is very, very strong. And that's not something Paul Berg or Jim Watson would have accepted back in 1975.

Drew Endy: I agree, in certain areas of synthetic biology it's actually industry that's the leading source of innovation and progress. So, for example, if you were to take the DNA construction tool—let's get better at building DNA from scratch—I know of no coordinated public research programme supporting such work, which is unbelievable. For comparison, the amount of resources deployed in order to sequence DNA is quite impressive, both at the private scale and the public scale. But for synthesizing DNA it's almost all driven by private investment: the oligonucleotide synthesis companies, the gene synthesis companies and so on.

Now, you would think that the capability of starting with information in raw materials and compiling DNA, the stuff that programs the entire living world that we care about, that making that from scratch would be recognized as an important technology by public funding agencies, at least as important as DNA sequencing. Yet it's not. This asymmetry is very curious to me and also potentially problematic if we end up with a mismatch of interests, where the public interest isn't being represented in the development of the technology simply because there's no public support for its development.

Filippa Lentzos: You're raising a very interesting issue about the public interest not being represented because there's no public funding going into this. What role do you think scientists like yourself have in engaging with policy-makers and the public, or even with social scientists like myself?

Drew Endy: I don't see it as a role really. Rather, the work I'm trying to do is practically limited by the state of conversations, or the degree of understanding across many different actors and sectors, and most of these tend not to be my colleagues in research. So, for example, if I go and advocate that the United States government should make a public investment at the federal level to get better at building DNA, some of the people who might fund that work will say, well if we run a programme that helps improve DNA synthesis, more people will be able to synthesize pathogens, so we can't make this investment because it'll make the bioterrorism problem worse. The reason they think that way is because there's no national strategy for both developing biotechnology and mitigating issues of bioterrorism, which means that any individual federal agency or programme manager promoting such a programme would be exposed to undue political pressure.

We don't want to go through all the details of my own personal experience here, but my interest in biosecurity issues, my interest in the ownership, sharing and innovation framework, and my interest in the community and its organization all have to do with the practical limitations I've encountered in trying to do the work that I think is important. I'd like

to say that there's some noble instinct which says I have a duty to go talk to my good colleague Paul Rabinow, but in practice I'm driven to go talk to him and many other people because, if I don't, the things I'm trying to do will never become possible. They'll just be dead in the ground. So the issues of human practice occupy my time, and perhaps even the majority of my time, simply because they are the greatest limiting factors.

Jef Boeke: Engaging with policy-makers or the public doesn't really come naturally to us, but as Drew says, it's something we have to do. We have a local community centre in the neighbourhood where I live, which happens to be near the undergraduate campus of Johns Hopkins, and I have, for example, suggested to them that we have a discussion involving myself and a local bioethicist, who's become interested in our project, to engage the people who live around Johns Hopkins University, so they know what kind of research is going on at John Hopkins and that there are some risks but that they can be put in perspective. So I think it's important to embrace opportunities to engage the public and to interact with the bioethics community. And, if there has to be regulation, it's important for us to work with policy-makers to try to minimize the impact that regulation might have in slowing down progress in biotechnology and the delivery of [potential] benefits to society.

Filippa Lentzos: And in terms of social scientist involvement in these debates, Paul and Gaymon, how do you see your role?

Paul Rabinow: Well, the one thing we're not going to do, and don't want to do, and couldn't even do, is give them technical solutions to their technical problems. So we're not here to do first-order problem-solving. But at the same time, we don't want to be so far outside the debate that we ironize about it. What we're trying to do is find a space in which we're fairly close to what's going on, but without providing first-order answers. So we want to get as close as possible to the emerging problem spaces in the public discussion—to the degree, after Marylin Strathern, that there is such a thing—that we can have some kind of impact on how this ramifies out. And one of the first things we need to do is think about critiques of the analogies used by synthetic biologists.

Gaymon Bennett: Let me just add a couple of things to that. If we go back to where we started from—what is synthetic biology, and what is it, or is it not, teaching us about life—we said there are a number of approaches to synthetic biology. Everybody in the game, though, agrees on two points. The first is we need to be able to provide rational design, from scratch, of biological systems, and the second is that these systems are going to be uniquely suited to address some of the world's most significant problems. So, at their best, what's recognized on both of those problems is that the existing scientific infrastructure, even with its connections to industry and government and so forth, really isn't suited to meeting either of those goals. On the first one, there's no existing expertise on how you would do this in biology. So then you have institutions like the synthetic biology centre in Berkeley, that we work for, that are trying to build collaborative models where they take experts from a number of different domains and put them into play together. With respect to the second problem, synthetic biologists recognize that the technical dimensions of the real-world problems they're working on are really rather small, and embedded in a much wider set of relationships. So again, there's a need for a new form of collaboration.

When Paul and I got into this game, through the synthetic biology centre at Berkeley, it was really under the auspices of this question about what new forms of collaboration would look like on common sets of problems, in which—in this emerging scientific field, where you recognize there are no forms of existing expertise—you'd begin to build productive and collaborative relationships among disciplines, and among scholars and institutions and labs, and so on and so forth. But the question you asked, what would the social sciences contribute to something like this, is actually a question that has remained open for us. We're a year in and we've been trying with a lot of energy and a lot of experimentation to find an answer to the question of what productive forms of collaboration look like, in which you identify problems in common, and begin to work on mutual forms of remediation around these problems. And I don't think we have an answer to that question yet. At best, the scientists are willing to talk to us about it; at worst, it evokes a lot of resistance. Because while at the manifesto level, the claim that synthetic biology needs new forms of collaboration is basically accepted, and people nod their heads at that, when these programmes get put into motion, collaboration demands a change of habits, and these scientists, for whatever reasons—funding constraints, the time of day, moods or careers, whatever the reasons are—resist that demand for a change of habit. So, whatever the answer is to the question, what would it look like to productively collaborate between the human sciences, the ethical sciences and biology, it's going to require more than goodwill. It's going to require some basic recalibration of the reward systems and so on and so forth, within these fields.

Filippa Lentzos: Developing new forms of collaboration, or indeed new spaces and forums in which disciplines and communities can meet, is certainly a challenge we're familiar with in *BioSocieties*. We hope that others will be provoked by reading this roundtable into contributing to the debate—this has been an excellent starting point, thank you all!

Reference

US President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1982). *Splicing life. A report on the social and ethical issues of genetic engineering with human beings*. Washington, DC.