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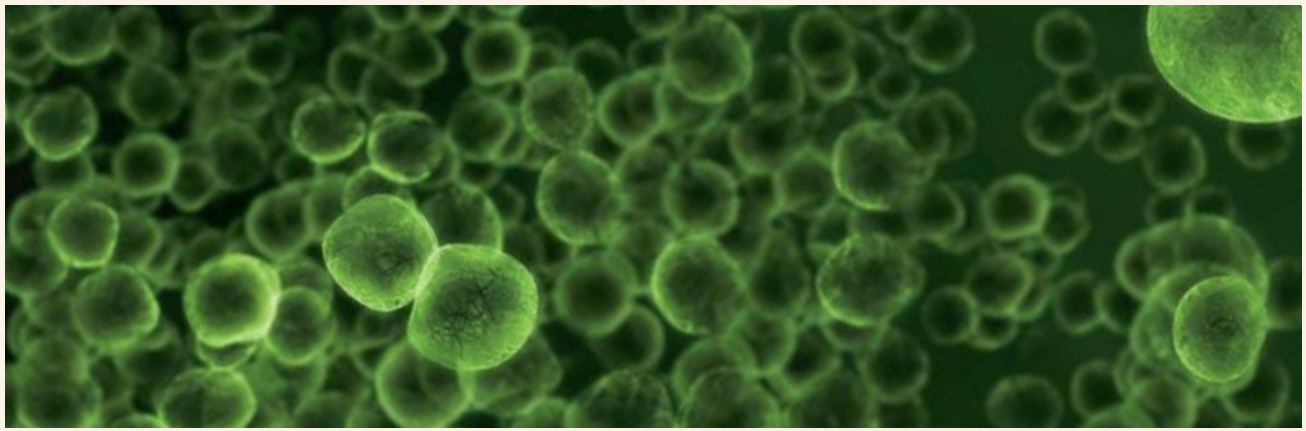
SYNTHETIC BIOLOGY PROJECT / SYNBIO 3

Ethical Issues in SYNTHETIC BIOLOGY

An overview of the debates



SYNBIO 3 / JUNE 2009

Synthetic BIOLOGY PROJECT

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Synthetic BIOLOGY PROJECT

Preface

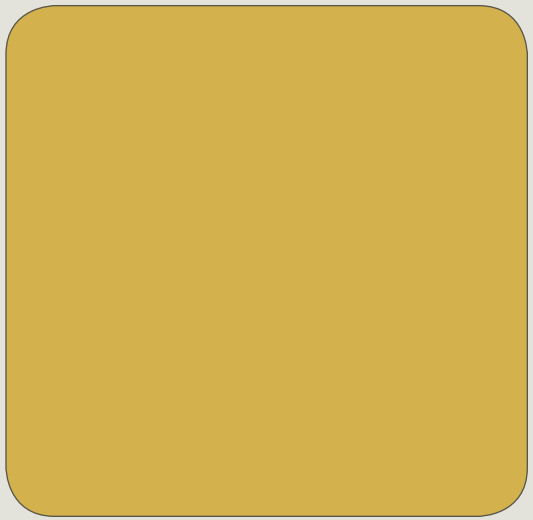
Synthetic biology will allow scientists and engineers to create biological systems that do not occur naturally as well as to re-engineer existing biological systems to perform novel and beneficial tasks. This emerging field presents a number of opportunities to address ethical issues early and proactively.

With synthetic biology, scientists are literally getting to the basis of life itself, but concerns about whether or not humans should be "playing god" are only part of the equation. Concerns have already been voiced about patents, oversight, and possible inequitable access to new and potentially powerful synthetic biology innovations in areas ranging from medicine to energy production.

This report by Erik Parens, Josephine Johnston, and Jacob Moses of the Hastings Center, a bioethics research institute in Garrison, New York, presents a framework for addressing the social and ethical issues surrounding the emerging field of synthetic biology. The paper explores current frameworks for evaluating ethical issues and proposes an approach where such topics are divided into two broad categories: concerns about physical and non-physical harms. While physical harms often trigger debates about how to proceed among researchers, policymakers, and the public, non-physical harms present more difficult conundrums. These non-physical concerns range from equitable distribution of benefits to fundamental beliefs about our place in the natural world.

Ethical concerns are too often addressed after investments in science have been made and technologies are already mature and in the marketplace. At that point, neither the research community nor policymakers have a strong incentive to address ethical issues for fear that any debate may stifle technological advance and innovation. But given the rate at which new technologies are emerging and converging, this paper argues that a comprehensive ethical approach is needed early to best foster the wide public acceptance and support of new technologies such as synthetic biology.

—David Rejeski
Director, Synthetic Biology Project



Executive Summary

- To advance knowledge and create products that can promote human welfare, synthetic biologists seek to create biological systems that do not occur naturally as well as to re-engineer biological systems that do occur naturally.

- Synthetic biology can be considered an extension of genetic engineering, which, as it advances, will increasingly converge with nano and information technologies. Several putatively distinct areas of emerging science and technology are converging, making it ever less useful to try to draw clear borders among them.

- As emerging technologies converge, it becomes clearer that the ethical issues raised by these technologies are at core similar and familiar. It would be a waste of resources to take up the ethical questions in parallel; i.e., it is not profitable to invent a "new kind" of ethics for each new technology. Instead, we need to get better at productively engaging the familiar ethical questions that cut across those emerging—and converging—technologies. It is time to go from speaking about hyphenated ethical enterprises (gen-ethics, nano-ethics, neuro-ethics, synbio-ethics) to speaking about **the ethics of emerging technologies.**

- We can expect that ethical concerns will arise with the advent of any emerging technology. These concerns can crudely be divided into two large categories: concerns about **physical harms** and concerns about **non-physical harms.** Because "non-physical harms" captures such a wide range of concerns, it can be helpful to further divide non-physical harms into two groups: those that seem to have gained traction among the researchers closest to the action (e.g., concerns about how to fairly distribute the tools needed to do synthetic biology and how to fairly distribute the benefits of synthetic biology) and those that have not gained traction among the researchers and scholars closest to the action (primarily concerns about the appropriate attitude to adopt toward ourselves and the rest of the natural world).

- We can also anticipate that people will often (though not always and not necessarily) think about these ethical concerns using, crudely speaking, two frameworks: a **“pro-actionary”** or a **“pre-cautionary”** framework. People using each framework can give reasons for their views, but no one proceeds from reasons alone. Noticing that people can proceed from different ethical frameworks can help us better appreciate the disagreements regarding whether the risks of physical and non-physical harms are serious and what actions should be taken in response to those risks.

- So far, the literature on synthetic biology contains significant work on safety and security (i.e., physical harms), in which the pro-actionary stance has been winning the day. That literature also shows some recognition of the importance of the first kind of non-physical harm and a few measures to address some of these harms (for instance, calls for making patentable inventions open-source). But there has been little meaningful engagement with the second kind of non-physical harm, which depends on even more deeply contested views about the appropriate role of humans in relation to themselves, other creatures and the environment. Some go so far as to argue that it is not worth engaging with these concerns.

- There is a need to identify and engage with both physical and non-physical harms, including those that are deeply contested. Such an engagement will lead to greater mutual understanding, which is both a good in itself and carries practical benefits.

- With few exceptions, in the United States we have required policy makers to consider concerns about physical harms, but expected them to remain largely silent regarding non-physical harms. Given the ardency with which concerns about non-physical harms continue to bubble up in the public conversation about emerging technologies, it is time to have a systematic look at the question, what role can concerns about non-physical harms play in the policy world? We do not fully answer that question in this document, but take it to be central for our future research.

Who is doing what, where are they doing it and how is this current work funded?

INTRODUCTION

Naturally occurring biological systems are even more complex and difficult to manipulate than anyone imagined 10 or 20 years ago. There are myriad technical problems in getting these systems to act the way we want. With synthetic biology, however, scientists hope to leapfrog these problems. One of synthetic biologists' hopes is that by building biological systems from the ground up, they can create biological systems that will function like computers or factories, producing the products we want, when we want and in the amounts we want.[1,2] (Such industrial analogies are inescapable when talking about this work, and while they do not appropriately capture the "living" element of synthetic biology, they do exemplify the field's central goal: to make biology easier to engineer.[1]) Scientists also believe that creating these products through synthetic systems will be safer than merely trying to manipulate naturally occurring systems to produce them.[3-6]

It is difficult to find a hard-and-fast definition of synthetic biology, given both the range of activities it involves and the frequent overlap between synthetic biology and other fields of research and technology. One way to begin to understand this range of activity is to look at the work of the field's key players (indeed, the field is still young enough so that we can identify four of the key players). These individuals come from different disciplines (including engineering and genetics), have different sources of funding, approach the topic from different angles (creating biobricks out of DNA and other molecules, engineering whole genomes, creating cells)[7] and have different goals (from understanding the evolution of life to creating useful products like ethanol or artemisinin).[8]

Drew Endy, who left the Massachusetts Institute of Technology (MIT) for Stanford University in 2008, is one of those key players. Active not only in the scientific literature, Endy has been a leader in defining synthetic biology's goals and engineering approaches.[1] A civil engineer by trade, Endy founded the non-profit Biobricks Foundation and the International Genetically Engineered Machines competition (iGEM) for undergraduate students. He also co-founded the gene synthesis company Codon Devices. Codon Devices lists Flagship Ventures, Alloy Ventures, Khosla Ventures, Kleiner Perkins Caufield and Byers and Highland Capital as investors.[9]

Endy is working at what Maureen O'Malley et al. have called **DNA-based device construction**.[7] He is spearheading an effort to construct and catalogue a registry of what he calls "biobricks," which are made from DNA and other molecules and can in turn be used by other researchers (on an open-source basis) to build what they want.

Endy's catalogue of biobricks can be thought of as bio-*parts* that, for example, will reliably turn gene production on or off, or as bio-*tools* that, for example, will reliably measure the concentration of a particular gene product. As Endy sometimes puts it, his parts will be for the 21st century what screws and bolts were for the 19th, or what transistors and resistors were for the twentieth. He envisions that bio-industrialists will (for free), download the genetic information they need to synthesize the genetic tool or part they need to manufacture a given project.[1,10]

Craig Venter heads the J. Craig Venter Institute (JCVI), which has two locations, one in Rockville, Maryland, and the other in La Jolla, California. His institute's website describes JCVI as having more than 400 scientists and staff and more than 250,000 square feet of laboratory space. Synthetic biology (or what Venter sometimes calls synthetic genomics) is one of the institute's focus areas. The JCVI website does not contain information about how this work is funded, but we have found references to funding from the Department of Energy and National Institutes of Health (NIH), as well as "the public" and "major foundations." [11,12] The JCVI also receives funding from Synthetic Genomics, a private company founded by Venter in 2005. Synthetic Genomics reports energy company British Petroleum and investment firms Biotechonomy, Draper Fisher Jurvetson, Desarrollo Consolidado de Negocios, Genting Berhad and Meteor Group as investors, along with its founders.[13]

Venter and his staff are working at what O'Malley et al. have called genome-driven cell engineering. For example, they hope to use synthetic DNA to build a "minimal genome," which will include only the genetic material needed to sustain the life of a bacterium.[14] If successful, Venter could then insert the sort of bio-parts that Endy is working on into his minimal genome, which could enable that genome to code for a new product such as cheap biofuel. So far, Venter has shown that you can transplant a genome from one species of bacterium to another[15] and that you can synthesize a copy of a bacterial genome,[16] but he has not yet been able to take that synthesized copy and make it work in a cell.[17] Venter has applied for international patent rights on the minimal genome organism, dubbed *Mycoplasma laboratorium*, and hopes this will become the commercial chassis for synthetic biology applications.[18] Others, like Endy, advocate for a hybrid approach to intellectual property protection whereby bio-parts and bio-tools are freely available and only specific applications are patented.[19;20]

George Church, at Harvard University, is a molecular geneticist with a Ph.D. in biochemistry and molecular biology. He has received funding from a number of sources; his current funders appear to be the Department of Energy, the National Human Genome Research Institute, the Lipper Foundation and the National Cancer Institute.

Church's group is pursuing what O'Malley and her colleagues refer to as protocell creation.[7] Thus we can imagine that one of Venter's modified, minimal genomes could be inserted into one of the synthetic cells now being created by Church's group at Harvard.[21] Such a synthetic cell could be viewed as a mini-factory, producing various substances, from treatments for devastating diseases to weapons of terror.

Jay Keasling, at University of California, Berkeley, is the fourth researcher most frequently invoked in public conversations about synthetic biology. The Keasling lab is funded by the Department of Energy, the Institute for One World Health, the Bill & Melinda Gates Foundation, the NIH, the National Science Foundation (NSF), the Jane Coffin Childs Memorial Fund for Medical Research and the University of California, Berkeley Davis Toxic Substances Research & Teaching Program.[22]

Keasling's lab has already engineered bacteria to produce the anti-malarial artemisinin, which some are calling the "poster child" for synthetic biology.[23] (Keasling's lab is working to scale up production by 2010 through a partnership with the pharmaceutical company Sanofi-aventis.)[24] They are also working to engineer bacteria to break down pesticides and generate biofuels, among other goals. Keasling's work, however, resembles "traditional" genetic engineering more than the previous three examples, insofar as he is essentially transferring a suite of at least 14 genes into bacteria.[25] However, as Drew Endy would point out, what Keasling is doing is a significant step beyond the "cutting and pasting" of DNA done by "traditional" genetic engineers;[26] to some people, this step of transferring many genes instead of one qualifies Keasling's work as significantly different enough to warrant a new label like "synthetic biology."[2,5] (We say more about the relationship between genetic engineering and synthetic biology in just a moment.)

Keasling, Endy and Church are all part of the Synthetic Biology Engineering Research Center (or SynBERC), which is an NSF-funded, multi-institute effort "to lay the foundation for synthetic biology."[27] SynBERC does not aim only to turn synthetic biology research into industrial products and to train young scientists to become synthetic biologists. It also hosts a Human Practices Center, led by anthropologist Paul Rabinow and political scientist Ken Oye, which does research on "evolving ethical practices in synthetic biology and emergent related fields (e.g., nanotechnology in NSF-funded centers)."[28]

In addition to these key U.S.-based players and other U.S.-based research groups, there is an international community of scientists working on synthetic biology,[29,30] as well as a number of individuals and groups inside and outside the United States addressing ethical, legal and policy issues. For example, SYNBIOSAFE is a project supported by the European Commission and led by Markus Schmidt. It is "the first European project to research the safety and ethical aspects of synthetic biology, and aims to proactively stimulate a debate on these issues."[31] Schmidt is also the director of the Organization for International Dialogue and Conflict Management, which contributes to the analysis, communication and management of new bio- and energy technologies. SYNBIOSAFE held an "electronic conference" in spring 2008 with the stated goal to "stimulate a wider debate on the societal issues of synthetic biology in a proactive way." Brief descriptions of ethical, safety, security and other societal issues were posted on an online discussion board, allowing participants the opportunity to respond.[32]

How distinct is synthetic biology from other emerging areas of scientific and technological innovation?

Depending on the context, synthetic biology is described either as radically new or comfortably familiar. Sometimes discussants stress the extent to which synthetic biology has been going on for almost 40 years in biotechnology, or even for millennia in human agriculture.[33-35] At other times (including when trying to attract investors or funders), discussants emphasize how radically different the technology is from existing approaches.[36] Simultaneous claims of novelty and familiarity can be difficult to process. As Jennifer Kuzma has noted in the nanotechnology context, "Developers should not tell the public that nanotechnology is unique and thus will provide great benefits, and then turn around and tell them that a special regulatory look is not necessary."[37] Putting aside for a moment the strategic benefits of a claim for newness or for familiarity, synthetic biology is, altogether unsurprisingly, closely connected with existing lines of science and technology.

SYNTHETIC BIOLOGY AND GENETIC ENGINEERING

The recombinant DNA (rDNA) technology, or "genetic engineering," that grew up in the 1970s was based on a central dogma that supposed that one discrete stretch of DNA produces one discrete stretch of RNA that produces one protein. That approach allowed for some important successes, such as "biosynthetic" insulin, which is now produced industrially by bacteria; the genetic "instructions" for human insulin are "pasted into" bacterial genomes, and out comes badly needed medicine.

However, many of the scientists who pioneered these early methods readily acknowledge its technical shortcomings: rDNA is expensive (parts and labor accounting for $1.5 billion of the NIH budget),[38] and, from an engineering perspective, messy. Employing rDNA requires a large technical knowledge base, which can be difficult to translate to other projects. Furthermore, there are some genetic dishes that rDNA cannot directly cook up. For example, there is no wild-type gene for a biofuel that can just be "cut and pasted"—or, as Endy sometimes says, "bashed"—into a bacterium. Instead, a new genetic dish must be created.

Beyond the technical shortcomings, there is a deeper conceptual problem with the old-fashioned approaches of the genetic engineers. It turns out that the central dogma was a significant simplification of the terrifically complex processes out of which most naturally occurring products emerge. While there is skepticism that synthetic biologists will successfully avoid those complexities by "starting from scratch,"[3,39] that is indeed what some synthetic biologists aim to achieve.

In contrast to the expensive methods of genetic engineering, commercial gene-synthesis companies are now able to manufacture virtually any DNA, built-to-order. Users can simply type a particular sequence into an Internet order form and in a week or two the DNA arrives by mail.[40] This advance effectively "black boxes" the DNA-manufacturing process by masking much of the complexity inherent in rDNA. More important, it is hoped that, in combination with computer modeling, the building of de novo proteins and the use of bioinformatics to predict and analyze those products, synthetic biologists will be able to create systems that

are not only less messy or complex than naturally occurring ones but also more efficient at producing the products we want.

Some have argued that "the involvement of several new, non-biological scientific and engineering disciplines is what *clearly distinguishes* synthetic biology from genetic engineering and 'classical biology'" (emphasis added).[2] Others describe genetic engineering as one of the tools of synthetic biology. We simply wish to observe that insofar as synthetic biology involves the manipulation and transfer of genes, it is intimately related to genetic engineering.

SYNTHETIC BIOLOGY AND NANOTECHNOLOGY

Nanotechnology refers to the scale at which a heterogeneous set of activities takes place. While synthetic biologists may for strategic reasons want to avoid the public attention that has surrounded nanotechnology, insofar as synthetic biology occurs at the nanoscale, it would not be unreasonable to consider it a form of nanotechnology. The large global nanotechnology community (dominated by chemists, physicists and engineers) is eyeing what the European Union terms in vitro synthetic biology as a means of providing the "production facilities" for nanoscale fabrication.[41] Already, nanoscientists are using viruses to construct battery parts. As Angela Belcher at MIT recently said, "We've been getting really good in the last couple of years at using biology and biological mechanisms to grow and assemble materials and functional devices."[42] As we will suggest below, it is exceedingly difficult (if not impossible) to distinguish between the ethical concerns that arise in the context of nanotechnology and those that arise in the context of synthetic biology (or for that matter, genetic engineering). Recognizing the interconnectedness of the science can also help us recognize the interconnectedness of the ethical issues.

SYNTHETIC BIOLOGY AND INFORMATION TECHNOLOGY

DNA can, of course, be viewed simply as information. And, according to synthetic biologists, cells can usefully be viewed as networks much like the information networks in information technology. To take the

"Recognizing the interconnectedness of the science can also help us recognize the interconnectedness of the ethical issues."

metaphor one step further, Endy and others envision a field where the information to be found on these networks should be available for free to all responsible researchers, much the way that some computer software is available for free (as "open source").[43] In theory, anyone who wants to use the parts or tools derived by synthetic biologists should be able to go to the shelf and use them for free. Not incidentally, the convergence with information technology has large implications for where and how production of synthetic parts and wholes can take place. Synthetic biology builds on a decades-long trend in flexible manufacturing. As one recent report explained, "DNA synthesis allows 'decoupling' the design of engineered genetic material from the actual construction of the material."[44] Once we place a genetic sequence in the global information network and combine it with remote and sophisticated production technologies, regulation of synthetic biology becomes very challenging.

"EMERGING TECHNOLOGIES"

The overall point we are driving at is that genetic engineering, nanotechnology, information technology and synthetic biology are so intimately interconnected that it might not make sense to spend much time making neat distinctions among them—at least for the sake of thinking about the ethical questions. We should add that it is equally hard to cleanly and consistently distinguish those just-mentioned fields from other areas of scientific inquiry, such as cognitive neuroscience or even stem cell research (some researchers have apparently begun to use nanomaterials as the vehicles to deliver genes to the nuclei of differentiated cells in an attempt to induce pluripotentiality).[45] A few years ago, this overlap and interconnectedness moved Mihail Roco and William Sims Bainbridge to begin speaking about the "convergence of emerging technologies."[46]

Viewing synthetic biology as an emerging technology that is converging with many others is not simply empirically accurate. It can also help in a practical way: it can save us the resources it would take to search for putatively new ethical questions. While the basic ethical questions are very similar from one area of technology or science to another, we do not dispute that some ethical questions may be more pressing in one context than in another; some ethical (or legal, or policy, or social) issues will be more difficult, more important or more contested in one area of science or at one time. Nevertheless, the core concerns, debate and values are familiar. In the best of all possible worlds we would learn from these previous debates and our previous successes and failures at responding to them, so as to better anticipate concerns and address problems. Recognizing synthetic biology as another emerging technology helps us avoid needlessly reinventing the ethical wheel each time we encounter a "new" area of science.[47;48] We acknowledge and understand that funders and grant writers might initially be tempted to describe the ethical issues surrounding synthetic biology as "new," but in the long run such a strategy can lead to disappointment.[47] A more prudent, if less dramatic, approach makes clear from the beginning that even if it makes sense to tackle the ethical issues as they arise with each field of science and technology, these issues are familiar and have been considered, although not necessarily resolved, in other contexts in the past.

Ethics: What harms and benefits are associated with synthetic biology?

The field of ethics is about the many facets of the question, what ought we to do? In the United States' democratic tradition, we aspire to eschew answers to that question that appeal to emotion or to any particular tradition's understanding of God or nature. Or, as it is sometimes put, we aspire to provide answers that appeal to public reason alone.

As noble as that aspiration may be, the last century-and-a-half of social analysis and natural science has taught us the respects in which it is, if not naïve, then based on an incomplete description of how animals like us make arguments and arrive at conclusions.[49] From Darwin through to the experiments of today's neuroscientists, we now understand ever more deeply just how intimately related reason and emotion are. From Marx through to those same neuroscientists, we understand how difficult it is to disentangle our own interests from the "facts." And from Durkheim through to Charles Taylor,[50] we understand that each of us brings residues from multiple intellectual traditions to each decision we make (even if one of them is the tradition of atheism).

We surely do not mean to suggest that we should give up the aspiration to give public reasons. Rather, we are suggesting the need for realism about the nature of the arguments we offer each other, and that we bear in mind that none of us comes to the debates about the ethics of synthetic biology from reason alone. Remembering this can help us respect those with views different from our own.

The four researchers mentioned above (Endy, Venter, Church and Keasling), along with many others, have come together in three conferences to discuss not only the science of synthetic biology but also the ethical, legal, social and policy issues that arise in the context of that science. The first conference, "Synthetic Biology 1.0," occurred in Cambridge, Massachusetts, in 2004. "Synthetic Biology 2.0" happened in Berkeley, California, in 2006, and was billed explicitly as an international conference. "Synthetic Biology 3.0" occurred in Zurich in 2007, and "Synthetic Biology 4.0" took place in October 2008 in Hong Kong.

The first conference, from which few materials are now available, included discussion of "ethics related to the engineering of biology" and "biological property rights," and featured a presentation by anthropologist Paul Rabinow critiquing the process for identifying ethical issues and questioning the validity of what is sometimes called the concern about nature.[51] Substantially more information is available about the second, third and fourth meetings which can be streamed over the Internet (available at http://syntheticbiology.org/Conferences.html).

One very important aspect of Synthetic Biology 2.0 was a failed attempt to pass a community resolution for self-governance that would describe "some principles for advancing this new field in a safe and effective way"[52] (see below for more detail). Unlike the second meeting, which included no strongly critical voice, the third meeting included a representative of ETC Group, an Ottawa-based environmental advocacy organization, who noted that one invitation to a scientific conference did not amount to the kind of societal engagement they believe is necessary. The fourth meeting also included some critical voices and one session devoted to a proposed consensus paper guiding the

development of synthetic biology, although no consensus document has yet emerged.

Other meetings, as well as discussions, online conferences and publications, have begun to consider the ethics of synthetic biology. One of the first, and for a long time one of the only, articles was written by a group of bioethics scholars brought together in the late 1990s at Venter's request to consider his specific goal of creating a minimal genome organism. The group considered the potential benefits to scientific knowledge and the practical applications of the minimal genome organism, the need for monitoring of biosecurity risks and potential intellectual property challenges. Group members expressed a fear that the reductionist approach to life could "lead science astray."[53] At the same time, they found no inherent objection by religious groups to the research that Venter was proposing and argued that it did not violate any existing fundamental moral precepts or boundaries. This paper, now nearly a decade old, did not purport to be a risk assessment, a ruling or the final word on the ethical issues raised by synthetic biology; nonetheless, it has been cited in support of claims that synthetic biology in general, and Venter's work in particular, is ethical.[7,17,54] More recently, several reports and articles, as well as an e-conference, have addressed ethical issues raised by synthetic biology.[2,32,55-57]

Below we aim to give a crude map of the basic ethical concerns and ethical frameworks that arose in these meetings, conferences and publications, and that we, based on prior experience with other emerging technologies, expect will arise in the future. We will distinguish between two sorts of ethical concerns: those that are first about physical harms, and then those that are first about non-physical harms. We also will distinguish between two sorts of ethical frameworks from which reasonable people can proceed to the debates about both physical and non-physical harms: we will suggest that when people are enthusiastic about synthetic biology, they tend to use the arguments at hand in the pro-actionary framework, and when critical they tend to use the arguments at hand in the pre-cautionary framework. People from each framework can give reasons for their views, but no one proceeds from reason alone. Noticing that reasonable people can proceed from different ethical frameworks can help us better appreciate the disagreements we will observe about the existence of both physical and non-physical harms and about what, if anything, should be done in response to these harms or risks of harm.

In the democratic tradition of the United States, one of the fundamental ethical questions is, what are the relevant harms and benefits associated with a proposed course of action? Before saying something about the different sorts of harms, we should say something about the potential benefits held out by synthetic biology.

POTENTIAL BENEFITS

The benefits of pursuing synthetic biology can be divided into two categories: advancing basic knowledge and creating new products. Needless to say, the distinction between basic knowledge and practical applications is hardly watertight. For example, to get his commercial venture of creating the minimal genome platform off the

ground, Venter and colleagues have to first do the basic scientific work of determining what are the minimal requirements for life. Nonetheless, it is a distinction often used in these discussions and has been described as a "central tension in synthetic biology."[7]

Advancing knowledge and understanding

One goal of synthetic biology is to better answer basic questions about the natural world and to elucidate complex biological processes—about how DNA, cells, organisms and biological systems function. How did life begin? How does a collection of chemicals become animated life? And, of course, what is life? Synthetic biologists take to heart the last words that the physicist Richard Feynman putatively wrote on his chalkboard: "What I cannot create I do not understand."[26]

One of the hopes is that, by engineering or reengineering living organisms in the lab, synthetic biologists will be able to understand how the biological world works in areas where earlier analytical approaches fell short. As the molecular biologist Steven Benner has suggested, the proof of the pudding may be in the making. Scientists like Benner hope that synthetic biology will allow for biological hypotheses to be tested more rigorously.[58]

Creating useful applications

A second sort of benefit of synthetic biology would come in the form of practical applications, such as the creation of new energy sources, new biodegradable plastics, new tools to clean-up environments, new ways of manufacturing medicines and new weapons.[8] It is hoped not only that these applications will create products that are completely new but also that their production will be cleaner, faster and cheaper than we can currently achieve.[59-61]

Perhaps precisely because many of the objections to "re-engineering nature" may stem from concerns about the environment, scientists and funders interacting with the press have particularly stressed the potential "green" synthetic biology applications: from biofuels[62] to carbon sequestration,[8] from oil spill remediation[63] to arsenic-sensing bacteria.[64]

To use an example that is closer to market, Keasling's work to engineer bacteria to produce artemisinic acid is notable not because this is a novel drug we do not know how to acquire; it is a naturally occurring product of the sweet wormwood herb. The problem, as Keasling sees it, is that the plant takes too many months to grow, and harvest yields are simply too small to meet the global need for effective malaria combination treatments. Even at around $2.40 per treatment, the parts of the world that need multi-course antimalarials most are least able to afford them.[65] By combining genes and molecular pathways from the wormwood plant, bacteria and yeast into a bacterial "chassis," Keasling trusts that the medication's cost can be driven down to pennies; his teams have already increased synthetic artemisinin output 10-million-fold since the first experiments in 1999.[66] Here the economic benefits of synthetic biology have the potential to have a positive impact on public health.

Many scientists see Keasling's work as only the beginning. Projects such as Endy's Biobricks Foundation and Venter's biological

specimens circumnavigation are creating massive genetic sequence repositories that will make it possible to avoid starting from square one with each new project. Researchers associated with these projects are working to describe existing, and to create new, bio-parts and bio-tools so that the next pharmaceutical does not take many tens of millions of dollars and hundreds of person-years of effort to produce. The iGEM competition for undergraduates was founded to show that it does not take a doctoral degree to design a biotechnology product. Much of the economic promise of synthetic biology rests in its rational approach to biological design, which could reduce research and development time.

Other efforts go beyond the "biofactory" models, which have been the bread and butter for the biotechnology industry since the development of biosynthetic drugs like insulin. Engineers at SynBERC, for example, are working to engineer a tumor-destroying bacterium.[67] Other groups, including the Defense Advanced Research Project Agency, have funded early projects to develop biological computers.[26] The Defense Science Board Task Force on Military Applications of Synthetic Biology is studying possible ways to apply synthetic biology to military technology.[68] De novo protein engineering could allow for the creation of wholly new gene products, for which no known natural template exists.[69] Instead of searching for a vaccine from known compounds, scientists hope to be able to design new targeted cures.[8] Proponents of human enhancement technologies such as Gregory Stock have written excitedly on the prospect of creating artificial chromosomes containing genes that would dramatically augment human traits—or create wholly new ones.[70]

POTENTIAL HARMS

In addition to describing benefits such as those just mentioned, the literature cites a number of potential harms surrounding synthetic biology. Some of those concerns are about potential physical harms, such as those that might be done to the health of persons or the environment if a synthesized molecule or organism mutated or escaped and contaminated someone or something outside of the controlled research setting.[20,23]

Some discussion of physical harms distinguishes between known harms (for example, we know that the synthetically engineered smallpox virus could be fatal to anyone exposed), unknown harms (for example, although we know that bacteria and viruses mutate rather quickly, we do not know how a synthetically engineered virus or bacterium will mutate) and unknown unknowns (that is, harms that, given the current state of our knowledge, we cannot yet anticipate).

Insofar as security measures aim to promote our safety and protect us from physical harms, concerns about security and safety fall squarely under this rubric of physical harm. Insofar as discussions about the rights and responsibilities of researchers and appropriate governance mechanisms are ultimately about how to protect us from physical harms, those discussions also fall under this rubric. There is often debate about whether a proposed means to respond to risk of physical harm is ethical.

For instance, one mechanism for dealing with security concerns, secrecy, has been

called both ethically necessary and unethical. Bill Joy and Ray Kurzweil have argued that some knowledge learned from synthetic biology should be kept secret (some scientific findings should be censored), such as the findings regarding the sequence of the genome of the 1918 flu virus, to protect people and the environment from the risk of physical harm.[71] Michael Selgelid also argues that with synthetic biology we may have to compromise our commitment to transparency to promote our security.[72]

Following publication of the papers that described how to synthesize the mousepox and polio genomes, concern grew about the risk of physical harm following publication.[73] In 2004 the federal government created the National Science Advisory Board for Biosecurity (NSABB). One of the issues on which the NSABB advises researchers and the government is the communication of the results of what the Board calls "dual-use research of concern."[73] Critics of the secrecy approach call it unrealistic and impractical, arguing that we simply will not be able to keep the knowledge secret.[38,44,74] Some argue that the best defense is a strong offense—that making the knowledge widely available will enable the development of antidotes and other strategies for managing dangerous substances.[75] Others argue that, as a matter of principle, secrecy is unethical.

It is perfectly reasonable that the risk of physical harms (threats to safety and security) has been a central topic of discussion at the international SynBio meetings and among ethicists speaking about these issues in general.[76-82] But as we mentioned above, many ethical concerns are about the risk of non-physical harms, or alternatively, what we might call harms to the well-being of individuals or communities. Concerns about non-physical harms focus on the possibility of harm to deeply held (if sometimes hard-to-articulate) views about what is right or good, including conceptions of fairness, equality, progress and the appropriate relationship of humans to themselves and the natural world.

For instance, among the many concerns about the patenting and commercialization of advances in synthetic biology are some that rest on deeply held but contested views about fairness (who should control and have access to inventions and for whose gain) and others that rest on views about the (in)appropriateness of owning patents on living organisms. Both kinds of concern about patents on synthetic biology inventions would fall under our rubric of non-physical harms, even though they are grounded in different fundamental concerns. Additionally, insofar as synthetic biology raises concerns about the distribution of risks and benefits, which also rest on deeply held but contested views of fairness and equality, those concerns also fall under our rubric of non-physical harms. And concerns about the prospect of using these technologies to enhance human traits and capacities return us to an ongoing debate about our appropriate relationship to our bodies. The concern that humans might be overreaching when we create organisms that never before existed can be a safety concern, but it also returns us to disagreements about what is our proper role in the natural world (a debate largely about non-physical harms or harms to well-being).

One way to respond to the risk of these and other non-physical harms is through regulation or oversight. While most

regulation or oversight seeks to address the risk of physical harm, it could also seek to address non-physical harms, although it seldom does. In United States' governance of emerging technologies, non-physical harms have received little policy attention, with a few small exceptions; for example, the Recombinant DNA Advisory Committee advises the NIH director on "scientific, ethical and legal issues raised by recombinant DNA technology and its basic and clinical research applications" and in this capacity has considered issues such as the equitable distribution of rDNA technologies;[83] and the recent Genetic Information Non-Discrimination Act,[84] which protects Americans from discrimination based on genetic information in the contexts of health insurance and employment. The National Bioethics Advisory Council and the President's Council on Bioethics have taken up non-physical harms, but purely in an advisory capacity—they were not able to make policy.

There is a straightforward sense in which we can all agree that preventing or reducing physical harms is a very important social goal. That is, we can agree that physical harm is undesirable. There is significant disagreement, however, about how we should do so, who should be responsible for setting standards or determining safety, who should bear the burden or risk or how much society should spend on reducing risks to humans and the environment. In the environmental context, there is even disagreement about whether a particular outcome amounts to harm.

There is also some, although often not as much, agreement that preventing or reducing non-physical harms is an important social goal. That is, we have some agreement at the level of core values that human flourishing is good; we should work to preserve equality, promote prosperity and uphold shared moral values. But compared with physical harms, there is significantly more disagreement about whether a particular activity threatens these values, how we should reduce non-physical harm, who should be responsible and what may be sacrificed along the way. We do not always agree about what counts as a non-physical harm, because we disagree about what is human well-being,

"It is crucial to recognize that, as with physical harms, we disagree about non-physical harms because we adopt different ethical frameworks."

or about how best to understand fairness, equality and our appropriate attitude toward nature. It is crucial to recognize that, as with physical harms, we disagree about non-physical harms because we adopt different ethical frameworks. In fact, we suggest here that the roots of the disagreements about physical and non-physical harms are often intimately related, if not the same.

The pro-actionary and pre-cautionary frameworks

As we just mentioned, we can all agree that the aim of preventing physical harms is good—that we ought to seek to prevent or ameliorate negative environmental impacts, contamination of naturally occurring genomes and the creation of deadly pathogens for the purpose of bioterror.[20] Different people, however, hold different views about which values we should emphasize (or give priority to) in preventing physical harms and promoting safety. They will therefore hold different views about how to prevent physical harm and about what is and is not acceptable to sacrifice along the way. To begin to get at the difference between these views, we will (somewhat crudely) distinguish between what we will call the "critics" and the "enthusiasts." (Our distinction is largely the same as Nikola Biller-Adorno's distinction between "the concerned" and "the cool."[76]) We understand that most people will find themselves somewhere between these two views or will fluctuate in their view depending on the particular facts under consideration.

Enthusiasts about emerging science and technology tend to approach synthetic biology with what might be called a pro-actionary approach.[85] The basic idea is that emerging science and technology should be considered safe, economically desirable and intrinsically good unless and until it is shown to be otherwise, which means that the burden of proof is on those who want to slow down a given line of research. Those who emphasize the pro-actionary attitude can appeal to fundamental ethical commitments to defend their framework, including commitments to the freedom of researchers and business people to pursue their work,[72,86,,87] economic growth,[8] American competitiveness,[75] and human health and well-being.[88,89] These appeals are especially powerful when the promised benefits of a particular line of scientific or technological enquiry include clean water, cheap food and cures for terrible diseases.

As hopeful as enthusiasts are about the potential for synthetic biology to do good, they are fearful about the prospect of the United States succumbing to what they take to be the huge European mistake in the context of genetically modified foods.[90] They fear that public skepticism could hinder uptake of consumer products and ultimately slow down the science.[8] And they fear another version of the embryonic stem cell troubles in the United States, where they believe that funding restrictions harmed American competitiveness and stymied scientific progress.[91] On this sort of pro-actionary view, one of the biggest "risks" facing our nation is that the technology will not go forward quickly enough and that the American public, American industry and the American economy will miss out on crucially important opportunities for growth and improvement.

The pro-actionary framework shapes not only how enthusiasts define and weigh the risks and benefits of synthetic biology but also what they think should be done in response to these risks and benefits. Two main activities—governance and public engagement—are often discussed in response to emerging technologies,[92-95] although the different frameworks have different understandings of what exactly these activities would amount to. When enthusiasts call for "public engagement," they often mean educational activities aimed at getting the public on board so that the benefits of the research are not diminished,

as they arguably were in the context of genetically modified foods. As Richard Jones, in the nanotechnology context, has (critically) suggested, "public education" can be interpreted as a way to diffuse opposition, a 'fig leaf' of public consent."[96]

Unsurprisingly, a pro-actionary attitude tends to correspond to a preference for minimal governance, usually in the form of "self-regulation."[92, 97,98] For example, Stephen Maurer and Laurie Zoloth argue in *Bulletin of the Atomic Scientists* that self-regulation is the only practical way to control the security risks posed by synthetic biology. "In this environment," they say, "initiatives developed by the synthetic biology community may be more effective than government regulation precisely because they are more likely to be respected and taken seriously. From a policy standpoint, too, building a nongovernmental body for implementing biosecurity policy seems like a good investment." They conclude that "protecting the public from the risks of synthetic biology depends on the scientific community's will, capacity, and commitment to regulate itself."

Some self-regulatory approaches can also be found in the Sloan Foundation–funded report, *Synthetic Genomics: Options for Governance*. Focusing on a particular set of risks (the possibilities of bioterrorism, harm to laboratory workers and harm to communities near laboratories), the project behind the report brought together individuals with a variety of policy, legal, scientific, ethical, business and social science expertise to identify areas for possible policy interventions and specific options for such interventions. The report was written by Drew Endy of MIT; two members of the J. Craig Venter Institute's Policy Center, Michele S. Garfinkel and Robert M. Friedman; and Gerald L. Epstein, who works at the Center for Strategic and International Studies. It compared 13 governance options. In addition to self-governance approaches (such as education or use of a clearinghouse for scientists to share information), a number of options that have an implied regulatory component (such as requiring commercial DNA synthesis firms to use approved screening software and to store sequence data from orders for potential forensic uses) were included. Although the report did not make any specific recommendations as to which option or options should be pursued, and although some of the options certainly amounted to more than simple self-regulation, the options are, on their face at least, far less restrictive than those sometimes proposed by more critical groups and individuals, such as bans on certain experiments or governance, including boundary setting, through a kind of intensive public engagement.[23]

Some advocates for self-regulation invoke the 1975 Asilomar Conference on Recombinant DNA (rDNA) as a shining example of scientists regulating themselves. Embroiled in controversies that rival the current synthetic biology debates, the 140 scientists at Asilomar sought to find a path to continue rDNA work, outline the potential risks of creating transgenic organisms and end the voluntary moratorium on rDNA experiments called for by molecular biologists in 1974, who expressed "serious concern that some of [the] artificial recombinant DNA molecules could prove biologically hazardous."[99] After a three-day discussion of the safety risks (the concerns we call the non-physical harms were deliberately left off the agenda[100]), the scientists at Asilomar agreed that it would

be safe to proceed under a set of laboratory guidelines. Experiments with known minimal risk would require only basic containment measures, such as wearing a lab coat. Work deemed riskier—such as experiments with animal viruses—would require greater safety measures, including using bacterial hosts unable to survive outside of the laboratory. Finally, experimentation on highly pathogenic organisms and "toxic genes" was determined to be too dangerous for current containment strategies.[101] These recommendations formed the basis of the 1976 NIH Guidelines for Research Involving Recombinant DNA Molecules, which were used by NIH's Recombinant DNA Advisory Committee (RAC) to oversee gene-transfer research.

Although the Asilomar conference led to guidelines used by an NIH committee, it is largely considered a success story for self-regulation, primarily because the conference brought a swift end to the moratorium and headed off more restrictive regulatory action. But perhaps most important, as a *Nature* editorial suggests, there was no "biological Chernobyl."[102]

The same *Nature* editorial, published in 2004, when the debates about synthetic biology were just ramping up, argued that public trust in synthetic biology might be "won" by following the Asilomar model.[102] In effect, the second Synthetic Biology meeting (Synbio 2.0) attempted to do this: a resolution was proposed to begin instituting a system of self-regulation in response to the concerns about physical harms. The resolution grew out of the Berkeley SynBio Policy Group, a joint project of Keasling's lab and the University of California, Berkeley's Goldman School of Public Policy and funded by the Carnegie and MacArthur Foundations.[92] After interviewing several scientists working in synthetic biology and holding a series of "town meetings," the group concluded that self-regulation ought to be the main response to developments in synthetic biology. The resolution tabled at Synbio 2.0 proposed screening synthetic DNA orders, articulated a commitment to addressing the "challenges to biological security and biological justice" and, perhaps most contentiously, singled out self-governance alone among possible policy responses.[103] The resolution was not passed for a number of reasons: an open letter signed by the ETC Group and other civil society organizations protesting their exclusion from the debate,[104] internal disagreements among the scientists at the meeting about whether the resolution was the next logical step (some proposed, for example, that a professional organization should be established before self-regulation is undertaken) and, apparently, the fact that it was tabled at the end of the meeting when many participants had left or were simply too tired to tackle the issue.[93] The resolution has not been resurrected at subsequent synthetic biology meetings.

Critics tend to be skeptical about the wisdom of relying on self-regulation. Mockingly, they characterize it as, "Trust us, we're the experts."[23] They tend to adopt instead a pre-cautionary attitude, which suggests that new substances should be considered dangerous until shown to be safe and that new technologies should be considered potentially threatening to ways of life and systems of meaning. Under a pre-cautionary approach, the burden of proof lies on those who might put the environment or public safety at risk or who might disrupt ways of living or systems

"The goal is to avoid repeating the mistakes of the past, where technologies like asbestos, chlorofluorocarbons, DDT and thalidomide were developed before their risks had been adequately assessed…"

of meaning,[89] which usually results in calls for more governance and public engagement and for a slower pace of research and development.

Critics of self-regulation point out that although members of the synthetic biology community seem to be aware of and concerned by the potential for public backlash (they fear a reprise of the controversy over genetically modified organisms), they have not yet paid much attention to the lessons from earlier and ongoing social science research. For instance, focus groups commissioned by the Woodrow Wilson Center's Project on Emerging Nanotechnologies found no public support for self-regulation of nanotechnology (nor, interestingly, for a moratorium on nanotechnology research). After receiving balanced scientific information, a majority of people in structured focus groups converged around three strategies to address the question "How can government and industry increase public trust around emerging technologies?" They recommended more transparency and disclosure by industry and government, pre-market testing before commercial products are introduced and more independent, third-party assessments of risks and benefits.[105] None of these options has yet been embraced by the synthetic biology enthusiasts.

Like those comfortable with a pro-actionary attitude, those who emphasize the pre-cautionary attitude invoke fundamental ethical commitments, including the importance of protecting the environment from our well-intended mistakes and of safeguarding the public from the ill intentions of terrorists. On the view of the critics, one of the biggest "risks" is that science and technology will move forward too quickly, and there will be no chance to say no or to shape its development so that it serves the interests of all people and not simply the interests of scientists, investors or big business. While the ETC group has in fact advocated a ban on the release of de novo synthetic organisms,[23] most of the advocates for precaution suggest an important role for a variety of forms of governance. They therefore call for external regulation of emerging technologies[20] and for public engagement, in addition to self-

regulation. According to Jones, who is speaking about nanotechnology, critics tend to suggest methods such as consensus conferences, focus groups and citizen juries that both engage the public and govern the technology, although additional governance in the form of government regulation is also often embraced.[96]

When advocates of the pre-cautionary attitude call for "public engagement," they tend to mean allowing citizens to offer an upstream critique of science and technology.[106] The goal is to avoid repeating the mistakes of the past, where technologies like asbestos, chlorofluorocarbons, DDT and thalidomide were developed before their risks had been adequately assessed, and where technologies like genetically modified foods were brought to market before both their impact on human and environmental health and their impact on traditional farming practices and other well-being concerns had been carefully—and democratically—addressed.[39] This kind of public engagement will likely slow scientific and technological progress, but proponents believe that this price is worth paying.

O'Malley et al. argue that as biologists and engineers become ever more aware of the complexity of biological systems—and become ever more keenly aware of the deficiencies of the old-fashioned, simplistic, linear view that was expressed in the central dogma of genetics—we will move away from a model of downstream ethical, legal, and social implications (ELSI) research to a new "socioethics." As O'Malley and her colleagues put it, "A more valuable socioethical approach to systems biology would study systems biology as it develops, rather than waiting until the science has already set its course … [and, by engaging with scientists would] anticipate (and to some extent shape) the emerging social issues."[39] In so doing, René Von Schomberg suggests that because the effects of individual actions in the realm of emerging technologies could potentially have such far-reaching systemic and social effects, we need a "transformed notion of responsibility" that goes beyond the focus on individuals to a focus on "social institutional spheres."[107]

While we do not agree that ELSI or bioethics research has wholly failed to engage with science and technology upstream—indeed, upstream engagement was one goal of NIH funded ELSI research—the goal as described by O'Malley et al. is important and reasonable. Experience has shown, however, that it can be difficult to achieve, in part because the further upstream one goes the farther one moves away from concrete applications and other activities that will have a direct impact on individuals and communities. Nevertheless, upstream engagement could influence research priorities, provide critical feedback on hypothetical future applications and, perhaps most important, be used to establish and test processes and mechanisms that will respond to or deal with issues as they arise. On this understanding, public engagement becomes a kind of governance.

Competing—and potentially complementary—views about non-physical harms (harms to well-being)

While we have just discussed how enthusiasts and critics can hold very different views about how best to promote their shared aim of preventing physical harms, the debate about non-physical harms is still more complicated. That is because whereas we have something of a consensus about what physical harms are and that they should be avoided if possible, we do not have a similar consensus about what non-physical harms are or under what circumstances they should be avoided. This lack of consensus can lead to despair: some would say that because our understanding of what a non-physical harm is will always rest on a particular conception of what well-being is, and because well-being will always be contestable, we ought not waste our time discussing it.

Talking about the oft-expressed concern that humans are overreaching in their attempts to create life from scratch, Drew Endy asserted, "The questions of playing God or not are so superficial and embarrassingly simple that they're not going to be useful in discussion."[108] Or, as Laurie Zoloth suggested at the Synthetic Biology 3.0 meeting, it would be unprofitable to spend our time trying to come to agreement about conceptions of well-being, which draw on "incommensurate discourses" that include a large religious element. Zoloth argues that we cannot "solve these issues, even by logical argument." In the face of such deep disagreement, bioethics can only invoke what she calls "the ELSI liturgy" of "public discourse, open access, transparency, training, public education, collaboration, international codes, oversight, be careful, weapons are generally evil, and excessive profits are unfair."[77]

While we understand some of the frustration expressed by Endy and Zoloth, we believe that it is a conceptual and practical mistake to try to bracket discussion of competing conceptions of well-being—at least at this stage of the public conversation. For one thing, we have come some way in discussing some particular well-being concerns and can draw on those lessons in the context of synthetic biology. For example, we have developed a language for identifying and addressing concerns about the impact of patenting and licensing practices on the development of new technologies (a concern prominent in the embryonic stem cell debate in light of the breadth of the Thomson patents)[109] and about invasions of privacy and discrimination (prominent in the nanotechnology and genetic-testing debates). These concerns, while not universally shared, have achieved some traction among researchers and scholars due to their foundation in shared (if contested) notions of privacy, equality and fairness.

Further, while in past debates about emerging technologies we have thus far failed to get very far in our discussion of some of the other well-being concerns—such as concerns about human enhancement (prominent in debates over reprogenetics and neuroscience) and about altering living creatures or creating new kinds of living creatures (see the debates over germ-line gene therapy and creation of animal-human chimeras)—we do not think we should give up on these concerns.

If Zoloth meant that invoking the ELSI liturgy provides a way to circumvent a discussion of incommensurable values, then we believe she is making a conceptual mistake—at least insofar as she does not

"…although members of the synthetic biology community seem to be aware of and concerned by the potential for public backlash (they fear a reprise of the controversy over genetically modified organisms), they have not yet paid much attention to the lessons from earlier and ongoing social science research."

seem to acknowledge the extent to which our interpretations of the values enshrined in the ELSI liturgy will themselves depend on the particular ethical frameworks from which we proceed to the debate. For example, people who proceed from the pro-actionary and pre-cautionary frameworks will interpret terms like "public discourse" and "public education" and "unfair" differently because they proceed from different ethical values and premises. It is, we believe, a mistake to fail to appreciate the extent to which those differences in interpretation of the ELSI liturgy reflect differing conceptions of well-being.

When we give up on the difficult well-being concerns, we tend to subconsciously or reflexively privilege the pro-actionary

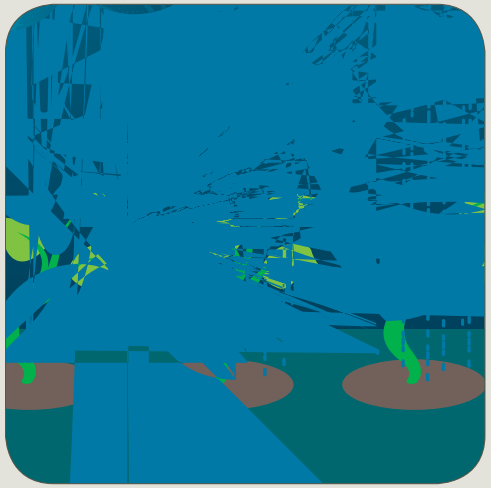
The most contested harms to well-being

Trying to engage those intuitions about this second class of non-physical harms and about the conceptions of well-being that they depend on, however, is difficult. Whereas we have a fairly well-developed public language to discuss physical harms, and an emerging language to talk about economic harms, invasions of privacy, discrimination and injustices (the first sort of non-physical harms), we still lack one to discuss concerns about creating new kinds of life or altering naturally occurring organisms, despite our experience with genetics, stem cell research, nanotechnology and neuroscience, among other areas. The appropriate attitude that humans ought to hold toward the natural world, including the extent to which we want to remake ourselves and the world around us, is a familiar concern, but we have not made much progress in exploring it.

For enthusiasts, the appropriate relationship of humans to nature is that of artists to their clay: we should see the natural world (including ourselves and our offspring) as ours to mold and modify as we want.[110] If we did not take that view, argue the enthusiasts, we would lack antibiotics, plentiful food and clean drinking water. If we observed such a deep respect for nature that we failed to change ourselves and our environment, we would remain victims of disease and slaves to our most basic needs; we would miss out on progress.

Critics often feel some level of unease with this attitude toward the natural world. While they might not be absolutists and therefore might agree that we should seek to fight disease and seek out new ways to produce food and fuel, they say that we should also look at the "deeper ethical issues."[2] One problem for the critics, however, is that they lack a fully adequate language for articulating these deeper ethical issues. This difficulty is apparent in an article by Joachim Boldt and Oliver Müller in a recent issue of *Nature Biotechnology*, which is thus far the most ambitious attempt to articulate these "nature" concerns in the synthetic biology literature.

Boldt and Müller argue that if we begin to create lower forms of life and to think of them as "artifacts" (as researchers in synthetic biology propose), then we "may in the (very) long run lead to a weakening of society's respect for higher forms of life."[55] That is, if we continue down this road, we risk undermining our respect for animals and, ultimately, humans as they naturally occur. They also argue that when creatures like us adopt the attitude of creators, we are making a category mistake—a mistake about the sorts of beings we really are. Less self-conscious, nonacademic authors would have used an unfashionable phrase about "playing God" to describe this mistake. While there are good reasons for rejecting language referring to God, we believe (as did Cho et al. in a much earlier piece in *Science*[53]) that we should not ignore a concern that continues to be widely shared.



Conclusion: Moving the debate forward

A variety of potential harms are being identified with synthetic biology. One way to carve up these potential harms is to distinguish between what we call "physical harms" and "non-physical harms." These potential harms are not unique to synthetic biology—they are familiar concerns that have been raised (and sometimes realized) in the context of other emerging technologies such as genetics, neuroscience, stem cell research and nanotechnology. In the literature, we observed fairly consistent agreement about what might be the potential physical harms of synthetic biology, although there is disagreement about how likely those harms are to eventuate and about what action, if any and at what cost, should be taken in order to prevent or remediate them.

Enthusiasts (those who are generally positive about advances in synthetic biology) tend to adopt a pro-actionary approach to the risk of physical harm, arguing that we should not seek to interfere with the development of an emerging technology unless we have very good cause to suspect that it will cause serious physical harm. And if we do interfere, many enthusiasts advocate minimal self-regulation rather than formal regulation through a federal agency. Alongside self-regulation, some enthusiasts also advocate the use of public funds for the kind of public engagement that seeks primarily or solely to educate the public about risks and benefits so that members of the public can become informed consumers of emerging technologies.

Critics (those who are concerned about advances in synthetic biology) tend to adopt a pre-cautionary view, arguing that we should be prepared to interfere with the development of an emerging technology if we have good cause to suspect that it might cause serious physical harm, and they generally see such a risk in synthetic biology. Critics advocate for regulation, oversight (usually external oversight) and the kind of public engagement that actually shapes the development of emerging technologies, such as is practiced in some European countries around genetically modified foods and other emerging technologies and is being employed and studied in the United States around nanotechnology.[111-115] Many people fall somewhere on the spectrum between critics and enthusiasts, finding themselves torn between the insights of each side.

On the question of non-physical harms, we observed some agreement among enthusiasts and critics that some non-physical harms are worth discussing, and possibly even addressing. While there is surely more work to do in conceptualizing, identifying and addressing these non-physical harms, there is already some acceptance, for example, of the legitimacy of the concern that patents might slow down research and of voluntary open-source practices as one way to address this concern (although there is not agreement about whether voluntary action is the best or only way to ensure the availability for further research of useful inventions).

However, there are non-physical harms that have thus far received short shrift in discussion of synthetic biology. There is very little agreement about the precise nature or legitimacy of these concerns, let alone what, if anything, might be done to address them. This group of non-physical harms centers around concerns about the appropriate relationship between humans and nature and

about whether humans ought to intentionally create new kinds of life.

We suggest that those who fund and lead synthetic biology seek to respectfully and carefully describe, and critically evaluate, concerns about both physical and non-physical harms. In so doing, they should draw on our experience of these concerns in the context of other emerging technologies, including genetics, neuroscience and nanotechnology. How were these concerns conceptualized, what values were appealed to in their description, how were the concerns addressed and what lessons can be critically applied to the case of synthetic biology? In some cases, these familiar concerns were better articulated and understood following funding of conceptual and empirical research on the ethical, legal and social implications of the science or technology in question. In all cases, individuals from outside the scientific community, including scholars and activists, were given a seat at the table, bringing their values, conceptual frameworks and suggested responses to the discussion. To adequately describe and address the risk of physical and non-physical harms, federal and private funders should undertake a coordinated research and outreach program that includes funding for conceptual and empirical research.

It will also be important, when examining concerns about physical and non-physical harms, to seek to respectfully and carefully describe, and critically evaluate, the various understandings of these concerns and suggested responses to them that are formulated from within both the pro-actionary and pre-cautionary frameworks.

In the realm of physical harms due to bioterrorism, we can already point to the reasonableness of the National Research Council's Committee on Research Standards and Practices to Prevent the Destructive Ability of Biotechnology, which seems to be headed for a hybrid approach that seeks to promote insights from both frameworks: they suggest ways to promote scientific and economic freedom while also protecting humans and the environment from security threats.[87] As synthetic biology moves out of the laboratory and is scaled up, existing regulations will likely be triggered, including the Toxic Substances Control Act, the Community Right-To-Know Act and various air, water, solid waste, worker safety and consumer protection statutes. As with nanotechnology, some research will likely be required to identify any gaps or mismatches in existing regulation as it applies to synthetic biology.[116]

In the realm of non-physical harms, we can point to the reasonableness of NIH's recommendations and guidelines regarding the patenting and licensing of research tools and genetic inventions[117,118] and some progress in accepting and understanding concerns about inequitable access to new technologies. But there is still a long way to go in understanding and addressing what we call here the second class of non-physical harms. There is a tendency, in fact, to ignore these concerns or dismiss them as irrational or of relevance only to people subscribing to a particular religion. As an empirical matter, this is false: many critics concerned about this second class of non-physical harms are rational and profess no religion at all.

Dismissal is premature. Instead, we need to begin to hybridize the strengths to be found in the pro-actionary and pre-cautionary

"By better understanding precisely what values are considered at play in the context of synthetic biology, we will be in a better position to understand what action would be reasonable to expect or recommend."

frameworks so as to better understand what critics are concerned about and what enthusiasts celebrate in synthetic biology. Through empirical and conceptual research, we need to better understand what individuals in our society mean when they cite a concern that some synthetic biology is against nature or is playing God. For those who believe that the job of human beings is to actively shape themselves and the rest of the natural world, synthetic biology is an obvious next step, and concerns about "playing God" are incoherent. While powerful, that understanding of our place in the world is but one very particular understanding. For those who believe that the job of human beings is to accept and "let be" some features of themselves and the rest of the natural world—and for the many of us who oscillate between these two intuitions[110]—those questions are worth taking seriously. By better understanding precisely what values are considered at play in the context of synthetic biology, we will be in a better position to understand what action would be reasonable to expect or recommend. As with other harms, we should draw on our experience of these concerns in the context of other emerging technologies, including genetics, neuroscience and nanotechnology.

We are confident that we can achieve some clarity about what specifically is feared will happen if humans become creators of new life forms—that is, about what we might lose when we "play God"—and we can begin to debate whether there are reasonable ways to address these fears. While we are unlikely to definitively answer the questions concerning the wisdom of shaping ourselves and the rest of the natural world, we can hope to better understand each other. When we listen carefully and respectfully to the concerns of others, we live up to a widely shared normative commitment to respect one another. We also allow for the possibility of some change, however slight, in our views and our practices. Understanding and respect can affect the selection of experiments and eventual products, the communication of results and the direction of publicly funded programs. It can also make more receptive those who might initially have opposed synthetic biology. The costs of this enhanced understanding are money—the research and outreach must be funded—and time—the progress of science might be slowed to keep pace with research and engagement. Experience with other emerging technologies strongly suggests that this would be time and money well spent.

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