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Ethics and Synthetic Biology: Four Streams, Three Reports

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Josep Egozcue Lectures

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Introduction

A couple of years ago, Craig Venter and his team were able to synthesise the DNA of an organism, creating what they called "the first synthetic cell". The news was a hot topic around the world and headlines were quick to announce that life had been created artificially, for the first time. Although the content of the story was immediately contested by the first scientists who were consulted, the matter was far from trivial and raised a number of ethical issues. The first and most general of these issues is that the discovery in question was one of the possibilities of synthetic biology, a new concept that still requires definition and understanding, as well as establishing which benefits and risks may arise from it. Synthetic biology is defined as "biological engineering", a term that encompasses various techniques with different objectives, ranging from new therapies for curing illnesses that are currently incurable to new biological systems and genetic engineering techniques. The second ethical issue posed by innovations such as those that are grouped together under the umbrella term of synthetic biology is how the news is spread and how people are informed of the new discoveries and the possible benefits and risks these may bring. Information on Venter's discovery was unlucky; it alarmed the population and it seems that one of the first to be alarmed was the President of the United States, Barack Obama. Obama's immediate reaction was to request that the Presidential Commission for the Study of Bioethical Issues to produce a report on synthetic biology and all the different foreseeable conflicts – ethical, political legal and social. The Commission got to work and one year later, in 2011, it presented an excellent report that clarified the concept, analysed the possible applications of the various techniques and contrasted those applications with fundamental ethical values. It is safe to say that, since then, almost every national bioethics committee has been interested in the issue and contributed some observation regarding synthetic biology. For example, the Spanish Bioethics Committee, together with the Conselho Nacional de Ética para as Ciências da Vida (the Portuguese bioethics committee) recently produced a report with the same purpose of clarifying and enriching the debate on the future of synthetic biology.

The Víctor Grífols i Lucas Foundation used the context of the annual Josep Egozcue Conferences to introduce this subject and spark discussion about the various issues. The speaker chosen to open the conference was Thomas Murray who was, until recently, the President of the prestigious Hastings Center in New York. Murray is one of the people who appeared before the United States Commission to discuss the issue and put forth the points of view of the institution he was directing. As a first-hand participant in the drafting of the report, Murray knew better than anyone the content of that document, which he explained during his speech, while introducing his personal opinion on the ethical attitude that must be adopted in the face of synthetic biology. The Conferences took place at the Faculty of Communication of the Pompeu Fabra University (Barcelona), with the intention of putting particular emphasis on the issue of disclosure and information regarding scientific discoveries. Thomas Murray's lecture was followed by a round table attended by scientists Luis Serrano and Ricard Solé, jurist Carlos Romeo Casabona and journalist Milagros Pérez Oliva. The first two analysed synthetic biology from scientific and technical perspectives, Romeo Casabona addressed, in particular, the issue of patents and Pérez Oliva discussed the disadvantages and challenges of making public such complex issues through media that seek, above all, immediacy, simplicity and sensation.

Ethics questions scientific innovations from two viewpoints: the consequences and principles. As regards the former, it is necessary to employ the principle of precaution and ensure that the risks of new techniques do not outweigh the benefits. It is also necessary to consider who will be the main beneficiaries of the possible applications of synthetic biology, bearing in mind the requirements of the principle of justice which demands, first and foremost, that it must benefit the underprivileged and those who need it most. As regards principles, it is necessary to consider and contemplate what the limits should be on controlling nature and creating new living organisms. Everybody – scientists, governments and citizens – must be involved with these two viewpoints, because everybody is partly responsible for shaping the future of humanity. It is clear that biomedicine works with the ultimate objective of improving people's lives and providing better quality of life. However, it is not always easy to determine what "improving" and "better quality" mean, in the same way that it is not easy to manage advances in science in order to solve the most serious social problems.

"Good ethics begin with good facts," is a mantra from The Hastings Center with which Murray began his speech. Without knowing the facts, without analysing what synthetic biology is, ethical reflection is a speculation about concepts that is not in touch with reality and is of no use to anyone. That is why the Víctor Grífols i Lucas Foundation seeks to promote interdisciplinary debate when dealing with matters that are ethically controversial. That is the intention of this new publication from the Josep Egozcue Conferences.

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Ethics and Synthetic Biology: Four Streams, Three Reports

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Understanding what synthetic biology requires from citizens, institutions, and governments requires answering three questions. First, in keeping with The Hastings Center's principle that good ethics begins with good facts, we must ask what synthetic biology is. Is it something distinctly new as its proponents claim, or is it better understood as an incremental step in scientific and technological developments in biology broadly understood to include molecular biology, genetic engineering, genomics and other scientific frontiers in the life sciences? For that matter, is synthetic biology one thing or many things brought together under an umbrella label?

Second, what benefits does synthetic biology—as its advocates describe it—promise, how likely are they to be realized and what are the principal risks provoking concern among knowledgeable commentators? Scientific and technological innovations routinely bring potential benefits and risks. Wise public policy seeks to support the rapid development of beneficial applications while at the same time minimizing or managing the risks.

Third, what can be done to provide a sophisticated, scientifically grounded assessment of the risks, and what governance measures can and should be used in order to strike the optimum balance between promoting the positive development of synthetic biology while keeping the risks that come with it in check?

Following a description of the major variants gathered under the umbrella label «synthetic biology» and its putative benefits and risks, we will consider three influential reports that illustrate the range of reactions. Two of the reports were produced by national bioethics bodies: one in the US, the other jointly between Spain and Portugal. The third report is credited to three civil society groups with more than one hundred additional organizations as signatories. Taken together, the three reports illustrate the principle dimensions along which ethical and policy analyses of synthetic biology are currently being arrayed.

Four Streams of Synthetic Biology

The European Commission's report on synthetic biology described it as «the engineering of biology: the synthesis of complex, biologically based (or inspired) systems which display functions that do not exist in nature. This engineering perspective may be applied at all levels of the hierarchy of biological structures… In essence, synthetic biology will enable the design of "biological systems" in a rational and systematic way».[1]

Other bodies have adopted similar accounts of synthetic biology, emphasizing an engineering approach to biological systems along with rational, systematic design. Astute observers will note that scientists have been practicing «genetic engineering» for decades. But swapping genes between organisms is a far more bespoke activity than the «engineering» label suggests. Scientists typically work with existing organisms rather than designing one from the bottom up. Even «simple» organisms may be complex enough to make hijacking their metabolism for human purposes more a matter of hit or miss tinkering than of the rational, systematic design associated with engineering. The first of the four streams included under the broad umbrella of synthetic biology least resembles the model of electronic or software engineering. Indeed, it is more directly a continuation of advances in molecular biology over the decades. Much of the sophisticated research in molecular biology now being done is not labeled as «synthetic biology» though some lines of work have been advertised as such. Call this stream: «contemporary genetic engineering as synthetic biology».

Contemporary genetic engineering as synthetic biology: Approximately 243 million people become symptomatic with malaria every year while roughly 863,000 die from the disease. More than 80 percent of those dying are children in sub-Saharan Africa.[2] The most potent therapies to treat malaria combine artemisinin-derived drugs with other anti-malaria compounds. The strategy known as artemisinin-combined therapy (ACT) is intended to delay or prevent the development of artemisinin-resistant strains of the malaria parasite.[3, 4]

As of June 2012, artemisinin is only available commercially through harvesting the Chinese Sweet Wormwood plant, which is grown in the developing world. The supply is subject to climate conditions and seasonal variations. A team of scientists led by Jay Keasling used the increasingly refined tools of traditional genetic engineering on yeast cells to coax them to produce artemisinic acid, a precursor that is readily converted via three chemical steps into artemisinin.[4, 5] Amyris Biotechnologies, which developed the metabolic pathway for synthetic artemisinin, claims commercial production will commence later this year or in 2013, with the cost per dose at 25 to 50 cents, significantly lower than the price of botanically derived artemisinin.[6]

Biosynthetic artemisinin is a solid candidate for the first significant therapeutic application being attributed to synthetic biology, indeed, the first significant large-scale production of any useful synthetic biology product. (It is important to acknowledge the difficulty in distinguishing between what contemporary molecular biologists who do not consider themselves to be practicing «synthetic biology» do and the artemisinin work that is being described as synthetic biology.) The same scientific team is using similar techniques in an effort to engineer microbes to make commercially viable biofuels.[7] These research and development programs, along with similar efforts by competing teams, exemplify the continuity with a tradition of biological experimentation with roots in Cohen's and Boyer's pioneering work on recombinant DNA in the early 1970s. If this were the entirety of what is now called synthetic biology, it would be very difficult to make the case that it represents revolutionary change rather than evolutionary development. But there are other strains of synthetic biology such as DNA-based device construction, which envisions biological systems very much in the model of engineering.

DNA-Based Device Construction: Electronics engineers have catalogues of parts from which they can design myriad devices. *Transistors, capacitors, resistors,* and other components can be assembled to accomplish whatever purpose the engineer desires. The early developers and proponents of synthetic biology proposed that biological systems could be imagined in an analogous fashion, conceiving of the dynamics of genetic expression using terms such as sensors, actuators, motors, and switches. The BioBricks movement, for example, is a collaborative effort to identify, characterize, catalogue and share biological «parts». The «Registry of Standard Biological Parts» was created at MIT in 2003.[8] It encourages users to also be contributors, following the principal «give some, get some». The BioBricks movement also embraces the open-source model of intellectual property characterized by software movements such as Linux and Firefox.

The vision animating the BioBricks movement and DNA-based device construction in general is bold: to create biological parts that are simplified and standardized and that can be assembled into systems that behave predictably and in conformance with the engineer's intentions. Whether this vision can be achieved is not yet known. Biological entities, even so-called «simple» intact organisms, are complex. While feedback loops occur in electronic systems, biological organisms are characterized by adaptation and evolution, which may pose great challenges to those who hope to redesign biological systems according to an engineering model.

Drew Endy, a leader of the BioBricks movement, had this to say: «if you consider nature to be a machine, you can see that it is not perfect and that it can be revised and improved».[9] Many biologists reject the premise of nature as a machine. Beyond that, the idea that nature can be «perfected» seems foreign to biology. Populations of organisms adapt to their environments--or they go extinct. Environments change. Species are more or less successful in their particular environmental niches, but it's difficult to imagine what «perfection» would consist of except as a metaphor for successful adaption to a particular environment at a particular time. More likely, Endy is referring to the redesign of a biological system to fulfill optimally some specific human purpose, perhaps producing biofuels or medicines, or acting as sensors that would provide early warnings of diseases such as cancers. The vision of DNA-based device construction brings with it a way of thinking about biological entities that has clear affinities with how biologists historically have understood and manipulated such entities; but the emphasis on such themes as standardization, interchangeability and perfectibility also suggest important differences in conceptual models and aspirations.

Creating a Minimal Cell: A third stream of synthetic biology works towards creating or recreating whole organisms. The most widely hailed recent accomplishment was the work of Craig Venter and colleagues to produce what they claimed was the first «synthetic cell».[10] After ascertaining the DNA sequence of a microbe with a relatively small genome (1.08 million base pairs), they commissioned a DNA synthesis company to produce 1078 relatively short lengths of DNA (each one was 1080 base pairs in length), which together replicated the full bacterial genome. Then the scientists used yeast cells to stitch the lengths of DNA together into ever longer strands until finally they had a complete chromosome with the full complement of *Mycoplasma mycoides's* DNA sequence, to which they added a few «texts»--the authors' names, some quotes and an email address. These can be described as genomic «tattoos»--decorative identifying marks with no effect on the organism's functional capacities. Finally, they inserted this synthesized genome into a closely related bacterium, *Mycoplasma capricolum*. An enzyme in the *M. capricolum* that protects it against invasion by foreign DNA had to be disabled. Eventually, the new chromosome was able to provide the genomic instructions necessary to keep the organism functioning.[11]

Venter and colleagues describe the resulting entity as a «synthetic cell»[10] on the grounds that over time, all of the bacteria's structures were replaced with ones specified by the inserted, synthesized genome. Other prominent scientists suggested that alternative descriptions were more accurate.[12] The functional genome was, in fact, that of an existing organism. In order to function it had to be inserted into an otherwise intact, closely related bacterial cell. One could just as well say that the cell «adopted» its new genome.

One of the potential uses of minimal cells is as a chassis on the model of an automotive chassis: a basic structure onto which other components can be added to build the particular vehicle desired. The same chassis could be built up into a passenger car, station wagon, SUV or pickup truck. For synthetic biology, such a chassis could be used as a foundation for the building of organisms performing a wide variety of different functions. It should be noted that the «chassis» metaphor could just as easily be applied to organisms such as *e. coli* and yeast that molecular biologists have long used as targets for new genes and combinations of genes.

Protocells: Ed Regis, a leader of the movement to create a new, completely synthetic biology describes its goal as creating «a genuinely new living entity, albeit one not based on biology and not made out of the customary biological ingredients: no DNA, no conventional biomolecules, no cell membrane of the ordinary type, no nucleus, no mitochondria, no endoplasmic reticulum or any of the other innumerable vital trappings of normal, orthodox biological cells».[13]

Protocell proponents aspire to redesign, synthesize and assemble the basic components of a cell, including the essential functions identified with life such as mechanisms for metabolism, control, organization, and replication. Ironically, it may be possible to create a «non-organic» biology. Whether this movement will succeed is far from certain.

Of the four streams, contemporary genetic engineering as synthetic biology is the closest to practical achievements. The introduction of biosynthetic artimisinin, when it can be produced in sufficiently large quantity at a low per-dose price, will mark the arrival of this stream of synthetic biology as a potentially significant contributor to human well being. But it must be noted that this stream is the most difficult to distinguish from a host of other developments in molecular biology that don't label themselves «synthetic» biology. The other three streams--DNA-based device construction, the creation of minimal cells as chassis, and the protocell movement--tell intriguing stories about their potential significance. But their accomplishments to date cannot tell us which if any will ultimately have major impacts on our lives or our planet.

Dueling Narratives: Continuity versus Radical Novelty

The four streams that comprise synthetic biology vary in how much they diverge from the main currents of molecular biology. The advanced genetic engineering that enabled the creation of yeast able to synthesize artemisinic acid comes directly from those long-established currents. Work on minimal cells and organismic chasses employing large-scale DNA synthesis and assembly may be an outgrowth of those well-established techniques, but its ambitions have more than a hint of novelty to them. DNA-based device construction represents even a sharper break with tradition, and the Protocell movement bursts the traditional bounds of biology in its quest for novel chemistries of life.

Whatever their differences from one another, the four streams of synthetic biology appear to share two features that begin to distinguish them from traditional molecular biology. First, they bring new communities of investigators and designers eager to make biological systems do what they wish, including engineers and the budding Do-It-Yourself (DIY) Bio movement. Communities of DIY biologists have emerged as technologies such as DNA sequencing and synthesis have become cheaper and more widely available.

The second shared feature is what might be called a particular sort of engineering mindset, a way of thinking about biological systems that emphasizes standardization and control. Any effort to draw a sharp, categorical distinction between the goals and mindsets of scientists and engineers working in synthetic biology risks oversimplification and exaggeration. Perhaps it is more helpful to think of a continuum, with most investigators in synthetic biology falling somewhere between the endpoints. But it may nevertheless be useful to identify those endpoints and continua that help to define the dimensions within which synthetic biology operates.

Scientists, on the one hand, have as a primary goal to *understand*, engineers to *build, predict and control*. Molecular biologists seek to discover, molecular engineers to design. Scientists look to understand emergent properties and complexity even when that understanding entails creating simplifying abstractions or building novel biological entities; engineers aim to standardize in the service of efficiency. Tom Knight, a leader of the BioBricks movement, succinctly characterized this engineering mindset: «An alternative to understanding complexity is to get rid of it».[14]

There are other differences among the communities that may be relevant to the evolution and governance of synthetic biology. Biologists recognized, with the advent of recombinant DNA, that their science was acquiring new powers to do good--or harm. And with those powers came the moral responsibility to use them responsibly and to train coming generations of scientists to do the same. Engineers have also acknowledged that they have ethical obligations; but they have not had decades of experience with biological systems to learn what particular shape those obligations take when dealing with organisms capable of mutation, adaptation, and reproduction.

The primary sources of novelty for synthetic biology have mainly to do with mindset and the communities participating in it. So there are good reasons to favor the continuity narrative and to challenge those who wish to portray synthetic biology as something radically new.

Proponents of synthetic biology have many reasons to emphasize its novelty. New frontiers in science and technology spark interest. The annual iGEM competition, where college and high school students work to create new BioBricks and assemble them to perform some novel function, are popular and attract enthusiastic teams of young people.[15] Novelty can also help to attract funding in the form of government grants or investments in new companies. The long-unfulfilled promises of revolutionary advances in genetic engineering are less of a drag on public perception when scientists can declare that what they are doing is new and different.

Of course, novelty can also have its disadvantages. Fears about the dangers of genetic engineering that prompted scientists to declare a moratorium on research until the risks could be better assessed and strategies to minimize them devised have largely abated.[16, 17] To the extent that synthetic biology is a new enterprise, distinct from the decades-old methods and aims of genetic engineering, whatever reassurance might otherwise have been found in its safety record is not available. With novelty comes a fear of the unknown. Indeed, the most stringent criticisms of synthetic biology typically begin with assertions about its novelty, as in the recent report issued by a number of civil society groups. The US Presidential Commission for the Study of Bioethical Issues, on the other hand, emphasized synthetic biology's continuity with molecular biology and genetic engineering. Not surprisingly, they found less reason to fear it or to regulate it harshly.[18] I will discuss these reports, along with one issued jointly by the national Bioethics bodies of Spain and Portugal,[19] following a brief description of the most often touted benefits and risks.

Synthetic Biology: Risks and Benefits

Advocates for synthetic biology imagine an astonishing array of potential benefits. Along with synthetic artemisinin may come plentiful, cheap supplies of many other drugs, including some that are now expensive or in short supply and others yet to be imagined. Synthetic organisms may be able to convert agricultural wastes or other plant-based inputs into biofuels. Others envision ponds full of organisms that rely on photosynthesis to manufacture alternatives to petroleum-based fuels and other products. No more extraction of oil from tar sands, no need to transport oil across oceans or environmentally sensitive areas with the ever-present danger of toxic spills: advocates envision far more environmentally friendly sources of energy and new, ecologically gentle feed stocks for industry.

But there are risks as well. Among the first to come to the attention of policy makers was the prospect of the intentional creation of pathogens meant to cause grave harm to people, agriculture or the environment. Nation-states could try to use synthetic biology for the purpose of biowarfare. Nations can assemble the expertise necessary to create such pathogens, and nations can devise ways to weaponize them. To the extent that synthetic biology makes it easier for a rogue nation to create biological weapons, the vigorous enforcement of effective, binding international treaties and other agreements becomes ever more important.

As it becomes easier to manipulate organisms, a reality underscored by the recent rise of DIY biology (also known as «garage» biology), worries about malicious non-state actors making use of synthetic biology--bioterrorism--have increased. Security experts look for ways to deny terrorists the equipment, reagents, and information they would need to create pathogens. But the materials needed are likely to be increasingly available, and scientists are profoundly reluctant to censor information, as the recent concern over research that produced avian flu virus (H5N1) that was far more easily transmitted among ferrets (the preferred experimental analogue to humans) has shown.[20] Experts in biowarfare offer one reassuring piece of information: however easy it may become to create a pathogen, weaponizing it for delivery is immensely more difficult and likely to require the resources of a nation.[21]

Making a novel pathogen that could be effectively used in biological warfare has been regarded as quite difficult. The US National Science Advisory Board for Biosecurity (NSABB) reported in 2006 that: «Current scientific understanding reveals that it is often the combination or interaction of genetic elements that underlie these properties rather than one specific gene sequence. Furthermore, the harmful consequences of biological agents are dependent upon the coordination of multiple factors including host susceptibility, the agent's infectivity, transmissibility and virulence, and the availability of prophylactic or therapeutic interventions».[22] The recent H5N1 studies have altered the assessment of how difficult it is to modify a pathogen to increase its transmissibility, at the least.

Biowarfare and bioterror are not the only causes for concern; synthetic biology also raises the possibility of «bioerror»--the unintentional creation and release of something harmful. Bioerror is not of course an entirely new risk; biological researchers can cause unintended harms in many ways. The avian flu research just mentioned did not, in fact, rely on synthetic biology. Laboratory workers dealing with dangerous organisms can be infected through accidental needle sticks and carry the infection with them to their families and neighbors. Dangerous organisms can find their way into the environment through accidental failures of containment due to carelessness, systems failures or natural catastrophes such as earthquakes and floods.

If organisms created with the help of synthetic biology are used for environmental remediation or to clean up oils spills or industrial accidents, or if organisms meant to be contained in manufacturing vats or ponds escape into the environment, what are the risks? The PCSBI in one of its recommendations mentions «suicide genes» that would in theory kill any such organism. But a great deal of research remains to be done before we can be confident that such built-in safeguards would work as intended, or if synthetic biology organisms would behave like other living things, mutating, adapting, and exchanging genetic material with other microbes (a well-known phenomenon in biology we could call «microbial French-kissing».)[18]

In addition to these worries about health and the environment, some civil society groups raise additional concerns about cultural and economic dislocation and injustice.[17] They point out, for example, that the production of biosynthetic artemisinin is likely to affect the price developing world growers can get for Chinese Sweet Wormwood, potentially affecting their ability to make a living. I will take these issues up in the discussion of that report.

Policy and Governance

National bioethics bodies and civil society groups have offered a range of views on synthetic biology. Three that mark a spectrum from generally supportive to staunchly opposed are: *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*, from the US Presidential Commission for the Study of Bioethical Issues; *Synthetic Biology*, a joint report by the Spanish Bioethics Committee and the Portuguese National Ethics Council for the Life Sciences; and *The Principles for the Oversight of Synthetic Biology*, a report distributed by Friends of the Earth U.S., the International Center for Technology Assessment, and ETC Group, with the endorsement of over a hundred civil society organizations.[18, 19, 17] In the following discussion I will refer to these reports respectively as *New Directions, Synthetic Biology, and Principles for Oversight*.

The reports emphasize different subjects and embody different ways of organizing and presenting their findings and recommendations. But what they do--or do not--say about eight specific issues is revealing. The issues are: benefits; risks; governance/regulation; patents; the role of civil society; justice; ethical issues; and, underlying many of their particular judgments, where they stand on the continuity/radical discontinuity question.

Benefits: *New Directions* is in general quite optimistic about potential benefits from synthetic biology. Its first three recommendations urge the government to coordinate and evaluate public funding for synthetic biology, including research on risk assessment and ethical and social issues; use peer-review to identify the most promising research; and encourage innovation through licensing and sharing. *Synthetic Biology's* first recommendation says that the field «represents a potentially beneficial development for humankind in a wide variety of sectors, especially the health sector. Its development must therefore be supported though the necessary precautions must always be taken».[19] *Principles for Oversight*, on the other hand, calls synthetic biology an «extreme form of genetic engineering»[17] and makes no mention of possible benefits. Its focus is on risk, justice and governance.

Risks: *Principles for Oversight* asserts that synthetic biology «poses significant health, safety and environmental hazards, as well as profound social, economic and ethical challenges».[17] The report does not devote much effort to defending the claim about significant hazards beyond reciting well-rehearsed claims about synthetic biology and mentioning such particulars as the reassembled 1918 influenza and polio viruses and the Venter team's claim to have created a synthetic cell. The authors portray synthetic biology as something novel and therefore threatening. They urge that the Precautionary Principle be applied to synthetic biology. The report calls explicitly for new structures for oversight and regulation and for a moratorium «on the release and commercial use of synthetic organisms».[17]

The Spanish and Portuguese report also embraces what it calls the «principle of precaution» but expressly notes the principle's «flexible criteria».[19] This marks a sharp difference in tone from the *Principles for Oversight* report, not surprising because the latter document offers a far more ominous account of the risks likely to arise. In *Synthetic Biology*, risks such as dual use are acknowledged but regarded as appropriately dealt with by risk management, monitoring, and follow-up. For certain applications, the report suggests prior authorization would be advisable along with periodic monitoring and inspection. No new regulatory agencies are called for, and no moratorium is recommended.

Recommendation 4 in *New Directions* includes an explicit judgment about new agencies: «The Commission sees no need at this time to create additional agencies or oversight bodies focused specifically on synthetic biology».[18] The report recognizes the challenge posed by novelty and uncertainty in an emerging field for understanding risks, particularly the risks of events it describes as «low-probability, potentially high-impact»--catastrophes, as they are otherwise known. It calls for better coordination among government agencies in assessing risks as well as for an analysis of any gaps that may exist in how government would respond to proposed field releases of synthetic organisms. The report calls for safeguards and monitoring directed at preventing inadvertent releases of synthetic organisms, and for research on technical barriers that could be built into synthetic organisms to limit or prevent them from surviving if they should escape containment. In Recommendation 7, *New Directions* calls for risk assessment prior to intentional field releases--but opens the door to exceptions «in emergency circumstances or following a finding of substantial equivalence to approved products».[18] This is a notably large loophole framed as an either-or: *if* there is an emergency *or if* the synthetic organism is deemed substantially equivalent to one that exists, then a field release without prior risk assessment may be permissible. The authors and signatories to *Principles for Oversight* were likely horrified at this; the Spanish/Portuguese report does not offer any explicit recommendations regarding field releases but its endorsement of a moderate form of the Precautionary Principle and emphasis on prior authorization suggests the authors might take a more cautious stance than their counterparts in the US.

Governance: With respect to governance and oversight, the report from Spain and Portugal reminds «public and scientific authorities, companies, entrepreneurs, and media professionals [that they] must assume the responsibilities corresponding to their various tasks and duties, in such a way that they direct their actions towards benefiting the community and the general interest».[19] The report concludes that «self-regulation and transparency, insofar as they serve the general interest, are adequate for achieving an effective and efficient prevention of the risks associated with the use of synthetic biology, and for the protection of consumer's interests through the mechanisms of public participation».[19]

New Directions likewise places great faith in «a continued culture of individual and corporate responsibility and self-regulation...».[18] This report, however, pays substantial attention to DIY biology, recognizing that the institutional and cultural constraints built into academic and industrial research and development may not apply with equal force to the growing community of do-it-yourself synthetic biology developers. *New Directions* sees no immediate danger, but it encourages continuing scrutiny of and engagement with the DIY bio community, including by agencies such as the Department of Homeland Security and the Federal Bureau of Investigation. It also urges government to consider requiring certain oversight and reporting measures regardless of institutional status--public or private, large organization or DIY.

Principles for Oversight demands restrictive actions, including a prohibition of the «intentional release of synthetic organisms into the environment for such things as bio-remediation or other applications...»[17] The report also declares: «Until the above principles are incorporated into international, federal and local law as well as research and industry practices, there must be a moratorium on the release and commercial use of synthetic organisms».[17] The principles referred to constitute the body of the report and cover a very broad range of issues. They include: Employ the Precautionary Principle; Require mandatory synthetic biology-specific regulations; Protect public health and worker safety; Protect the environment; Guarantee the right-to-know and democratic participation; and, Require corporate accountability and manufacturer liability.

As a practical matter, a moratorium on any and all «release and commercial use of synthetic organisms»[17] until these six principles are incorporated into international, federal and local law as well as into practice would likely mean that no products of synthetic biology would be available for many, many years, if ever.

Patents and Intellectual Property: *Principles for Oversight* takes a dim view of patents in synthetic biology: «Patents on synthetic biology processes, synthetic organisms or products derived from synthetic biology could further the privatization and control of naturally occurring products and processes. Companies and researchers must not be permitted to patent synthetic versions of natural organisms. These patents could open up new avenues for bio-piracy and ways to circumvent access and benefit-sharing agreements. Transparency, public safety and environmental protection must take legal precedence over any patent or intellectual property protections».[17] The report offers no alternative account of how investment and development would take place in the absence of patents or other forms of intellectual property.

The report from Spain and Portugal asks «competent authorities» to evaluate new issues that may arise in patenting processes and products in synthetic biology. Their concern is that the potential economic impact of such patents «could violate the ethical principle of justice».[19]

The US Presidential Commission, in *New Directions* offers a sophisticated discussion of patents' impact on innovation but expressly «offers no specific opinion on the effectiveness of current intellectual property practices and policies in synthetic biology».[18] The Commission's concern is not so much justice, as in the other two reports, as it is access to basic research and the facilitating or dampening impact on innovation. The report notes with interest the open-source philosophy of the BioBricks movement but declines to endorse any particular approach, citing the conflicting testimony given on the relationship between intellectual property regimes and innovation.

Role of Civil society: All three reports call for engagement with the public. *New Directions* promotes «democratic deliberation» by encouraging «scientists, policy makers, and religious, secular, and civil society groups... to maintain an ongoing exchange» on synthetic biology with policy makers and the public. Scientists and policy makers are reminded to «respectfully take into account all perspectives relevant to synthetic biology».[18] The Commission then does something quite unusual for such bioethics bodies by urging everyone to «employ clear and accurate language» and to avoid «sensationalist buzzwords and phrases such as "creating life" or "playing God"...» on the grounds that such language impedes understanding. They go further to suggest a fact-checking mechanism, privately overseen, to vet claims about synthetic biology. Finally, the report recommends expanded educational activities directed at «students at all levels, civil society organizations, communities, and other groups» to be supported by government, private foundations, and grassroots organizations.[18]

Synthetic Biology recommends creating commissions at national, community and local levels to monitor and supervise activities in synthetic biology and other emerging technologies. Depending on their legal remit, these commissions could exercise executive authority or be merely advisory.[19]

Public involvement is a key element for *Principles for Oversight*: «Governments must provide meaningful involvement for the public and workers throughout the entire decision-making process related to the development of synthetic biology and the products of synthetic biology, including setting the research agenda, the context and the scope of the risk assessment. This includes making sure that communities have access to independent scientific and legal opinions on the proposed projects».[17] In addition to this call for independent scientific advice, *Principles for Oversight* makes a distinctive claim for «traditional knowledge»: «Opportunities for participation in decisions on synthetic biology should not be narrowed to only scientific input. Other forms of knowledge including traditional knowledge as well as analysis of cultural, legal, social and economic considerations should also carry weight in decision-making processes».[17] The report insists that particular attention be paid to three categories of people: from communities, especially poor communities, where commercial facilities may be sited; labor unions and workplace safety groups concerned about work-related exposure; and communities concerned about social, cultural and economic implications related to land use or other relevant matters.

Justice: As its emphasis on public engagement with poor communities and workers makes clear, *Principles for Oversight* is deeply concerned with justice. The main axes of justice in its view are wealthy/poor and North/South. The endorsement it chose to place on the report's back cover, from Vandana Shiva, an environmental activist, displays clearly the worldview animating the report:
«Synthetic biology, the next wave of genetic engineering, allows seed, pesticide and oil companies to redesign life so that they can make more money from it. These companies now want to take over the forests and land of the Global South to make so called biofuels for planes and boats of the military or to make new cosmetics for the rich. Using synthetic biology, a biofuels dictatorship joins the food dictatorship wrought by the first kind of genetic engineering. The Principles for the Oversight of Synthetic Biology is an important tool to help people reign in these new technologies».[17]

As noted earlier, *Synthetic Biology's* concerns about justice center on injustices that might be caused through patenting. This report's advocacy for commissions at multiple levels appears to be directed primarily at risk and community benefit, but could just as easily boost procedural protections against injustice.

The last of the five principals articulated by the US Presidential Commission is «promoting justice and fairness». Applying it to synthetic biology, *New Directions'* final two recommendations urge that the risks of research and of commercial production «should not be unfairly distributed». The report goes on to address justice and fairness in benefits as well: «Manufacturers and others seeking to use synthetic biology for commercial activities should ensure that risks and potential benefits to communities and the environment are assessed and managed so that the most serious risks, including long-term impacts, are not unfairly or unnecessarily borne by certain individuals, subgroups, or populations. These efforts should also aim to ensure that the important advances that may result from this research reach those individuals and populations who could most benefit from them».[18]

The Commission is also mindful of the wealthy/poor and North/South axes so central to *Principles for Oversight*, but because it envisions potential benefits as well as risks its tone could hardly be in sharper contrast: «(...) much of the optimism surrounding synthetic biology stems directly from its potential to address some of the longstanding, significant problems associated with these disparities. Synthetic biology offers potential applications that may be particularly beneficial to less advantaged populations, including improved quality and access to vaccines against infectious diseases, medications, and fuel sources».[18]

Ethical considerations beyond consequences: One of the interesting features of synthetic biology is its ability to raise ethical issues beyond the usual terrain of consequences such as risks and benefits as well as justice. Scholars have explored questions about the appropriate limits to humankind's control over nature and the creation or re-creation of life.[23] A research project at The Hastings Center[24] considered several such questions and concluded (1) that they were cogent and should be taken seriously, and (2) that as long as synthetic biology was confined to working with no form of life more complex than single-cell microbes, such considerations did not pose any serious ethical barrier. That could change if and when synthetic biology took on more complex forms of life, especially human life.

Of the three reports, both *Principles for Oversight* and *Synthetic Biology* limit their attention to ethical issues to consequences such as risks and benefits and to justice. Neither report's recommendations address explicitly non-consequentialist concerns, although *Synthetic Biology* does raise them in the context of the Venter team's claims to have created a synthetic cell. This report notes that a claim such as this invites very important reflection...».[19] But the report's authors are not persuaded that life or a living cell was, in fact, created and so move quickly on to questions they believe to be more immediately relevant--questions about consequences and justice. *Principles for Oversight* remains steadfastly focused on risks and justice, making no mention of other categories of ethical concern.

New Directions, in contrast, recommends revisiting moral objections to synthetic biology as the field develops. They call for an «iterative, deliberative process» to be initiated, «particularly if fundamental changes occur in the capabilities of this science and its applications». In the commentary leading up to Recommendation 10, the authors expressly mention «intrinsic objections» as distinct from consequences per se or matters of justice.

Continuity/Radical discontinuity: Two of the reports under consideration here emphasize, on the whole, synthetic biology's continuity with earlier forms of biological science and technology. *New Directions* acknowledges that «revolutionary advances» may be on the horizon, but it also concluded that «the Venter Institute's research and synthetic biology are in the early stages of a new direction *in a long continuum of research in biology and* *genetics*».[18] [my emphasis]. The report is sensitive to the new entrants such as engineers and DIY biologists; but in its analysis and recommendations, the continuity account reigns.

The report from Spain and Portugal likewise judges that the work by Venter's team created a new "biotechnological tool," but fell far short of creating new life. The report states «(...) in science there is no such thing as discoveries that come out of nowhere, that do not have any predecessors or spring from a brain that is so privileged or original and intelligent that there is no need to consider what others have already discovered, described or intuited».[19] The report notes further that the ethical issues are likewise «in every way similar» to those that arise in a number of other technologies.[19] Again, the continuity account triumphs.

Principles for Oversight is the exception. Its depiction of synthetic biology as «extreme genetic engineering» gestures toward continuity, but the analysis and recommendations stress novelty and discontinuity. The report calls for thorough application of the Precautionary Principle and for «enforceable and prosecutable synthetic biology-specific regulations» as well as «the strictest levels of physical, biological and geographic containment as well as independent environmental risk assessment for each proposed activity or product».[17]

On the one hand it may seem that *Principles for Oversight* is embracing synbio exceptionalism--that is, for the purposes of policy and oversight, it treats synthetic biology as something very different from older technologies such as genetic engineering and therefore something that requires new and distinct means for controlling risk and assuring justice. But it may also be the case that the authors of this report are refighting older battles, hoping to convince readers that synthetic biology is sufficiently different from genetic engineering and genetically modified foods that ground lost in those engagements can be regained. It remains to be seen whether their calls for protecting workers' rights and health along with justice for communities in the Global South will find resonance in the context of synthetic biology.

Malaria, Artemisinin and Synthetic Biology

Do the differences in these reports matter? It would be unfair to reduce these three complex, multifaceted documents to caricatures or any simple ranking. While many issues are taken up in all three, the reports differ widely on the amount of attention they give to each; and some issues highlighted in one report receive little or no mention in the others. Rather than dealing in generalities, a case study may be more illuminating. An obvious candidate is the production of synthetic artemisinin to supplement or replace the artemisinin derived from its botanical source, the Chinese Sweet Wormwood plant, which is grown in several countries in the developing world.

New Directions tells the story of synthetic biology and artemisinin as one of good motives, savvy partnerships, and huge potential benefit to the hundreds of millions of people infected by the malarial parasite each year. The report describes the development of the capacity to produce synthetic artemisinin at industrial scale as «one example that demonstrates how academic, public, non-profit, and industry interests have come together to promote global well-being».[18] Referring to artemisinin and the possible production of biofuels, *New Directions* states: «There is great value in striving to pursue these and other applications and to ensure, if successful, that they reach those individuals and communities who would most benefit from them».[18]

Contrast this with the discussion around synthetic artemisinin in *Principles for Oversight*, which observes correctly that synthetic biology may «replace botanical production of natural plant-based commodities (e.g., rubber, plant oils, artemisinin) with vat-based production systems using synthetic microbes or to move production to genetically engineered plants».[17] *Principles for Oversight* then goes on to say that such developments «could have devastating economic impacts on farming, fishing and forest communities who depend on natural compounds for their livelihoods. These impacts and the impacts of biomass extraction and associated land grabbing must be considered in any assessment of risk. These assessments must include the full and active participation of the communities that will be impacted».[17]

Unless the laws of economics are suspended, Sweet Wormwood growers will find less demand for their crops if and when cheaper synthetic artemisinin is available in large quantities. Unless they can find alternative markets for Sweet Wormwood or switch to other crops that are equally profitable, their livelihoods will suffer. What will these communities, who see that they are likely to suffer major financial losses, say when they are consulted about the production of synthetic artemisinin? Perhaps they will be gracious and self-sacrificing. Perhaps they will say that it's more important to insure a cheap and plentiful supply to people with malaria than it is for them to make money. But what if they follow the path of self-interest? What if these communities, which might indeed be severely affected, object to the production or distribution of synthetic artemisinin? What weight should their voices have in the decision whether to produce enough to supply the world's needs at a far lower price?

Principles for Oversight attempts to stand up for the poor and the powerless, for workers, for the Global South, for people whose voices have long been ignored. For this, it deserves great credit. But in choosing not even to consider the possible benefits that might flow from synthetic biology, it lessens the report's usefulness. (A search for the word «malaria» failed to find a single instance in the report.) Nor can its well-considered recommendation to include «full and active participation»[17] of affected communities be expected to resolve all difficult issues.

Assuming it is as safe and effective as its botanical twin, whether to make and distribute artemisinin produced by synthetic biology is not a hard call: of course we should do it. It could benefit hundreds of millions of people in the Global South and elsewhere. Even if sweet wormwood growers protest. It would be far better to invest in ways to improve the health and livelihood of communities of wormwood growers than to insulate them against change at a staggering cost in health to others.

It is likely that other products of synthetic biology will present far more complicated balances of risks and benefits along with more complex problems in justice. There are nuggets of wisdom to be found in each of these three reports. We can hope that the global conversation about synthetic biology is informed by all of them.

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