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Designing Synthetic Biology

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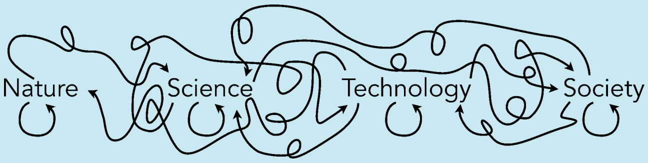

ABSTRACT: Synthetic biology is frequently defined as the application of engineering design principles to biology. Such principles are intended to streamline the practice of biological engineering, to shorten the time required to design, build, and test synthetic gene networks. This streamlining of iterative design cycles can facilitate the future construction of biological systems for a range of applications in the production of fuels, foods, materials, and medicines. The promise of these potential applications as well as the emphasis on design has prompted critical reflection on synthetic biology from design theorists and practicing designers from many fields, who can bring valuable perspectives to the discipline. While interdisciplinary connections between biologists and engineers have built synthetic biology via the science and the technology of biology, interdisciplinary collaboration with artists, designers, and social theorists can provide insight on the connections between technology and society. Such collaborations can open up new avenues and new principles for research and design, as well as shed new light on the challenging context-dependence—both biological and social—that face living technologies at many scales. This review is inspired by the session titled "Design and Synthetic Biology: Connecting People and Technology" at Synthetic Biology 6.0 and covers a range of literature on design practice in synthetic biology and beyond. Critical engagement with how design is used to shape the discipline opens up new possibilities for how we might design the future of synthetic biology.

KEYWORDS: *synthetic biology, engineering, design, design principles, context*

■ SYNTHETIC BIOLOGY: CONNECTING SCIENCE AND TECHNOLOGY

Synthetic biology is the science of designing biological systems. The term "synthetic biology" has been used during the past century to describe a wide range of projects that bring an engineering mindset to biology.[1] These include the formation of biological shapes by the osmotic motion of inks in salt solutions,[2,3] the achievements of recombinant DNA technology,[4,5] the synthesis of non-native biological chemistry[6] or "never born proteins,"[7] the construction of protocells,[8] and the identification of a minimal gene set for a free-living bacterium.[9] Today, synthetic biology is characterized primarily by three distinct research programs related to the design of biological systems: the large scale synthesis of microbial genomes,[10] the production of commodity chemicals through the redesign of metabolic pathways,[11] or the rational design of genetic logic devices from modular DNA parts.[12,13] This review covers literature on the diverse intersections of biology and design in contemporary synthetic biology, providing new perspectives on biological design in cellular, technological, and social context.

The diversity of synthetic biologies over the past 100 years reflects the diversity of ways that conventional experimental biology intersects with biological engineering and design.[14] The science of biology and the practice of engineering (*knowing* and *making*[15]) are especially connected in parts-based synthetic biology, where many engineers and scientists seek to "build life to understand it" through the assembly of standardized genetic modules.[16] The synthetic biology "toolbox" is populated with genetic parts that depend on the knowledge of biological systems that has accumulated through decades of analytic research in biochemistry, molecular, and cellular biology.[17] These parts are recombined into designs that could be useful as industrial technologies but also as tools for further scientific inquiry, used to explore the logic of gene expression, cellular metabolism, or signal transduction, among other systems.[18] Design and design principles in synthetic biology thus create a positive feedback loop between knowledge of biological science and the engineering of new biological technologies.

One recent example of the exchange between knowing and making in synthetic biology is the refactoring of the nitrogen fixation operon in *Klebsiella oxytoca*.[19] The operon was redesigned from the bottom up, replacing naturally occurring cryptic and overlapping regulatory components with a design that was human-understandable and machine-readable. This streamlining produced a more engineerable operon but at the initial expense of system robustness and a drastically reduced fixed nitrogen output. However, improved engineerability allows for the iterative testing of new designs, providing valuable information about the function or expression of individual members of the operon that can feed back into principles for improved designs of future iterations. This iterative refinement of the refactored operon led to a detailed mapping of the genetic

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design space and an engineered pathway that produced wild-type levels of nitrogen fixation.[20]

In the literature of synthetic biology, this exchange between analytic science and synthetic technology, bridged by engineering design, forms the foundation of technoscientific innovations. Design principles from engineering such as standardization and abstraction of modular parts and the decoupling of design from fabrication are intended to speed these iterative cycles of exchange,[21] in order to develop better tools for "plug-and-play" synthetic biology based on off-the-shelf parts.[22] The positive feedback between science and engineering in synthetic biology has been compared to the history of other disciplines and industries, such as aviation[23] or synthetic chemistry.[24] Discussions of the potential for industrializing synthetic biology frequently refer to the trajectories of these other industries as a model for the future design of biological technologies.[25] As these discussions make evident, the industrialization of synthetic biology has been seen as potentially transformative for a range of fields, and this apparent potential has been a driver of the growth of synthetic biology over the past decade.

Design, however, can offer much more to synthetic biology beyond principles for streamlining and industrialization. In order to understand the role that design might play in the future of synthetic biology, we should also turn to a different kind of design, one that engages not only with the technological contexts of synthetic biology at the industrial scale, but with the social and cultural context of technologies at the human scale.

■ VOCABULARIES OF SCIENCE, ENGINEERING, AND DESIGN

The promise that synthetic biology will transform how we practice medicine, produce energy and food, and manage the environment has inspired a great deal of attention and enthusiasm for the field among students, policymakers, funders, and the media. This promise and the framing of biology as a design medium has also attracted the attention of many designers from fields outside of biological science, such as product design, industrial design, or interaction design. Conversation and collaboration between these designers and synthetic biologists has opened up many avenues for discussion and research at different scales.[26]

Collaboration across different disciplines first requires developing a shared vocabulary and translation of jargon to facilitate communication. For conversations between synthetic biology and other design fields, misunderstandings can arise not only over specialist language but also over shared terms that have different meanings in different contexts. Alexandra Daisy Ginsberg, a designer and artist whose work explores the future potential of synthetic biology and a speaker on the design panel at SB6.0 has written about the role such terms play in conversations between designers and scientists:

> *In art and design, I use the "experiment" as an open-ended process to open up and reveal potential ideas; in science, the "experiment" is a tool to generate data to test a hypothesis. Repeating an experiment and achieving the same results is key to the scientific method, whereas the experimental process in art often seeks out the exceptional or unique. Artifacts may emerge from experiments. In science, the "artifact" is an outlying bit of data—an erroneous, often human-induced thing that can be ignored, like the distortion caused by the curvature of a lens. Conversely, for the artist or designer, the artifact is the focus of our attention: We are actively making things.*[26]

Defining these words can clear potential misunderstanding, but exploring the differences can also be productive, providing new perspectives for research and design between the disciplines that meet in synthetic biology, from biology and engineering to art and design. For synthetic biology, the discussion of "experiments" and "artifacts" can call out aspects of the practice we do not usually focus on: the identification of new problems[27] and the production of material artifacts at a human scale. While synthetic biologists are indeed concerned with the production of useful things, the emphasis is largely on the function of genetic circuits inside of the cell rather than artifacts at the scale that a product designer, interaction designer, or even an architect might focus on. Consideration of these differences offers new perspectives for how we might collaboratively open up the design of novel experiments/tools and the design of technologies/artifacts in synthetic biology.

Additionally, definitions of design itself vary between synthetic biologists and professional artists and designers. Like the term synthetic biology, "design" can refer to a wide range of activities. While some researchers have attempted to formally define "design,"[28] others remain more playful with the expansiveness of the term and its use in different contexts and as different parts of speech—a popular history of design states that "Design is to design a design to produce a design."[29] Other definitions focus on the way that designed objects mediate society's interactions with industrial production, with art,[30] with politics, and even with science and technology. Introducing the 2011 exhibition *Talk to Me: Design and the Communication Between People and Objects,*[31] Paola Antonelli, the Senior Curator of Architecture and Design at the Museum of Modern Art discusses her definition of design as a mediating force, bridging science and technology with society:

> *What designers do is they take revolutions that happen maybe in science or technology or politics, and they transform them into objects that you and I can use, that you and I can feel some familiarity or at least some curiosity about, so we can be drawn in and we can start a new life and a new behavioral pattern. And this idea of designers as the interface of progress, between progress and humanity, is what I try to stay with.*[32]

This definition of design as the interface between technology and society is analogous to the definition of design as the interface between science and technology in synthetic biology. Design principles in synthetic biology guide the exchange between the *science* of biology and the *technology* of biological engineering; the design projects presented in the *Talk to Me* exhibition represent a different kind of design transformation, one that translates technology from the engineering lab to wider *society*. Bridging the gap between these two kinds of design through discussion and collaboration can offer synthetic biologists new tools for designing biotechnologies at the human scale. As a first step, such collaborations can provide scientists and engineers with novel ways of conceiving the relationships between science, technology, and society.

■ THE "CENTRAL DOGMA" OF SCIENCE AND SOCIETY

A popular (but somewhat problematic) conception of these relationships is a pipeline, where knowledge from science informs the design of technologies that can then have an impact on society. This model is reminiscent of another two-step transformation: the flow of genetic information in the cell from DNA to RNA to protein. This "Central Dogma" of molecular biology, first articulated by Francis Crick in the 1950s[33] and reiterated in 1970[34] helped to guide significant research on how biological information is coded, processed, and expressed in the cell (an early draft of Crick's dogma is reproduced in Figure 1[35]).

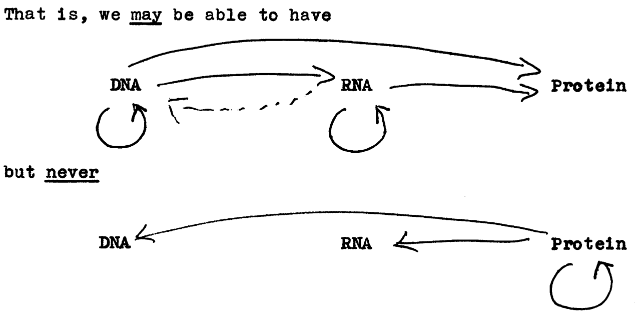

Figure 1. Excerpt from Francis Crick's 1956 sketch of the Central Dogma in "Ideas on Protein Synthesis."[35] Reproduced with permission from the Wellcome Library, London.

Since the Central Dogma was first described, many new types of arrows have been drawn on the classic diagram. Studies of the processes of post-translational protein modification, RNA catalysis, noncoding RNAs, and alternative splicing, transpositions, and horizontal gene transfers, prions, histone modification, methylation, and other mechanisms of epigenetic change have complicated the model of how genotypes translate to phenotypes.[36] Just as the Central Dogma has been complicated by unforeseen interactions between DNA, RNA, and proteins, so the simple pipeline of science to technology to society is more complicated than commonly understood. Instead of a linear model for the relationship between science, technology, and society (Figure 2), the metaphor of the Central Dogma applied to the relationship between science and society forces us to consider the ways that the many interrelationships between nature, science, technology, and society might shape one other in the design of synthetic biologies (Figure 3).

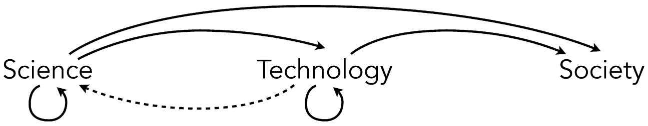

Figure 2. The central dogma of design? The connections between science, technology, and society are commonly understood as a pipeline, flowing linearly from scientific knowledge to technological design that impacts society. "Reverse transcription" between science and technology is important to the development of synthetic biology, but potential "epigenetic" connections between society and science or technology are rarely discussed in the field.

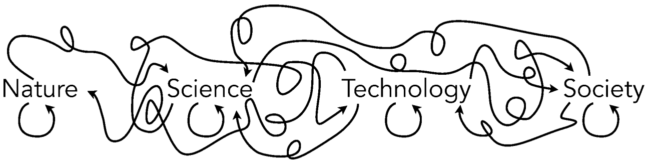

Figure 3. The reality of the interrelationship between nature, science, technology, and society is much more complicated than any linear metaphors can capture. Designing at the messy boundaries of these relationships can lead to the production of more successful and agile technologies for the real world.

Research in molecular biology over the past forty years has uncovered numerous environmentally influenced and protein-mediated mechanisms that influence the epigenetic function of biological systems. These mechanisms challenge the Central Dogma's central claim: that information can never flow in reverse from protein to DNA. Likewise, research over the past forty years in the field of Science, Technology, and Society (STS, also known as Science and Technology Studies) has uncovered many of the context-dependent mechanisms[37] by which we might challenge the unidirectional transfer of information from science to technology to society in our metaphorical Central Dogma.

Above, we saw how design in synthetic biology guides the "reverse transcription" between science and technology, shaping knowledge of biology through the making of genetic devices. Science and technology have strong influences on each other in many domains: new scientific knowledge influences technological capability, and new technologies shape the kinds of scientific questions that can be asked in turn.[38] In synthetic biology, we see this kind of exchange between technological tools and scientific questions often, and especially in the fields of DNA sequencing or synthesis. As these tools improve, technological capabilities change, leading to a different scale and scope of questions that can be asked.[39]

Design principles in synthetic biology also perform an "epigenetic" function, connecting the social world of engineers to the technologies being made. The design principles that synthetic biology is founded on work to organize the construction of genetic parts as well as to organize the relationships between practitioners in the field around certain core values. In particular, standardization has a long history of shaping engineering practices and communities.[40] In synthetic biology, standards for the assembly,[41] measurement,[42] and open source sharing of characterized parts[43] have been fundamental to the growth of the community and the organization of research programs.[44] Standards-based community building also drives the international Genetically Engineered Machines competition (iGEM), shaping the education of future synthetic biologists.[45] The field's other design principles can likewise influence the structure of funding of laboratories and of projects. For example, the principle of decoupling design, synthesis, and characterization of modular parts shapes the organization of the different companies and institutions that provide and use such services. Design principles thus affect not only the design and construction of genetic circuits but the specialization and organization of the people who make them.

■ HETEROGENEOUS ENGINEERING

This "engineering" of both social and technical factors in the development of new engineering disciplines is what the sociologist of technology John Law calls "heterogeneous engineering."[46] In order for an engineering project to be successful, it must be physically and technologically feasible but also economically viable and socially acceptable. Engineered systems are the result of many complex relationships among natural, technical, and social networks, reflecting the natural constraints provided by materials or the environment, the technical constraints of engineered systems, and also the organizational structure of the human institutions involved in the design and construction of new technologies. The relationships among designers, engineers, their clients, funders, and users[47] all shape the development of technologies.

The concept of heterogeneous engineering makes clear that engineering practice (and by extension, design) is never just about the function of a technology. For an engineering discipline in the making[48] such as synthetic biology, acknowledging the heterogeneous nature of engineering is important for developing principles that will enable successful design of reliable, effective, and acceptable technologies. The principles of synthetic biology as currently stated aim to transform genetic engineering from "ad-hoc tinkering" into a "true engineering discipline" through the construction of tools, practices, and organizations that promote the reliable assembly of well-characterized standard biological parts.[49] It is important to consider how these principles are used not only to organize genetic parts, but also how they organize the synthetic biology community around common goals and values and how they might shape and be shaped by other social, political, and economic factors involved in the creation of new technologies.

Different principles and values have guided the design of biological systems and the development of the discipline of synthetic biology, from defining standards to setting goals to educating young engineers. Throughout the development of synthetic biology's principles, projects, and institutions there have also been many social, political, and economic factors that have consistently emerged in discussions around the field, notably risk assessment and biosafety,[50,51] intellectual property and open source licensing,[52,53] and other factors that may influence the public acceptance of genetic technologies ready for deployment.[54,55] More than two decades after the Human Genome Project funded research into Ethical, Legal, and Social Implications (ELSI), researchers are working to reimagine the ELSI framework for synthetic biology and other disciplines,[56] bringing these concerns "upstream" in the governance and organization of research and industry,[57] and developing practices and principles for integrated design and a more reflexive heterogeneous engineering.

In a paper about public involvement in technology assessment, Andy Stirling, a scholar of Science and Technology Policy, notes the irony in continuing to use linear metaphors of "upstream/downstream" when addressing the interactions of technology and society.[58] Linear metaphors fail to capture the complex interrelations between science, technology, and society, "closing down" opportunities for discussion between engineers and a broader range of stakeholders. In synthetic biology, design principles such as standardization, abstraction, and decoupling, while useful for organizing researchers and designing genetic networks, can also close down debate by abstracting away the complexity of how biology works as well as how technologies are designed and developed in a complex social environment.[59] Stirling suggests a need for participatory technology assessment and analyses that can more accurately reflect the messy and ambiguous realities of technology in the real world, to "open up" a wider range of possibilities in the development, assessment, and consumer choice of new technologies. Refactoring synthetic biology's design practices and principles according to this sort of heterogeneity can likewise "open up" the field to new paradigms.

■ SPECULATIVE DESIGN

Synthetic biology has focused on producing basic tools, policies, and practices[60] with the idea that in the future, these tools will provide a foundation for engineering solutions to a wide range of potential problems. However, just what these problems and applications are or could be is underspecified. In a viewpoint article on standardization, Adam Arkin discusses how the standardization of parts has shaped the design of complex systems from planes to computer processors, and that, "Although we cannot quite yet imagine what synthetic biological applications might require the numbers and quality of elements on which these advanced technological systems rely, it is economically and socially important that we improve the efficiency, reliability, and predictability of our biological designs."[49] The true scope of these potential applications remains difficult to imagine, but as more applications in biosensing, drug delivery, and metabolic engineering are being designed with synthetic biology tools,[61] the promise of synthetic biology to address a range of problems grows. In an outlook piece targeted to a broad scientific audience, synthetic biologist James Collins writes that "Many of the major global problems, such as famine, disease, and energy shortages, have potential solutions in the world of engineered cells."[62] With this potential to solve problems but without the ability to fully and concretely imagine what these solutions might look like, it is crucial for designers, engineers, researchers, and policymakers to truly "open up" the discussion of these problems along with their proposed solutions.

Synthetic biologists can learn from the history of industrial design in addressing the complexity of problem finding and problem solving in situated practice. Since at least the 1971 publication of Victor Papanek's *Design in the Real World*, the profession of industrial design has turned a critical eye on its own work. Papanek begins his book bluntly and provocatively stating that, "There are professions more harmful than industrial design, but only a very few of them."[63] Harmful products result when designers are not engaged with the overlapping causes, contexts, and consequences of problems and their solutions, designing for a dangerous and unsustainable system of production and consumption. Problems and their synthetic biology solutions are likewise embedded in a range of overlapping and interacting contexts—social, technical, scientific, and natural (Figure 3). Engineers and designers often define themselves as problem solvers, but just as the practice of engineering is heterogeneous, with social values embedded in designs and products, the problems themselves are heterogeneous, emerging from the interaction of social, cultural, political, economic, environmental, biological, and technological factors. As the sociologist of technology Wiebe Bijker explained at SB6.0, the history of even the simplest technologies such as lightbulbs or bicycles shows that what might be a problem for one group of people might not be seen as a problem to another group with different values and different concerns.[64] If a new technology is to address problems, scientists and engineers must first be better at specifying problems, able to dynamically understand how problems and technologies are situated in a complex world.

For engineers, it is therefore important to understand and specify who is affected by the problem we are solving as well as who might benefit from a potential solution. Moreover, nuanced discussions of problems and their multifactorial causes and effects can help engineers better understand where a technological approach might or might not be appropriate, as well as what might count as a problem in the first place. For example, the "problem" of public acceptance of genetically modified organisms is frequently discussed within the synthetic biology community only in terms of the technical risks and rewards of a given technology.[65] Social science research such as Claire Marris's 2001 Public Acceptance of Agricultural Biotechnologies (PABE) project shows that public understanding and public acceptance of science and technology is, in reality, much more nuanced than the popular and polarizing myths of public ignorance circulating among engineers and anti-genetic engineering activist groups.[55] Understanding public understanding of science requires recognizing that "acceptance" is not a problem that can be solved with better technical safeguards or better outreach and education about technical factors and, in fact, might not be a "problem" that can and should be "solved" at all. Acceptance among different communities is based on complex consideration of the varied issues that can be technical but also cultural, political, and economic.[55] Engaging with these heterogeneous concerns in an open or participatory way at the design stage opens up opportunities for designing more acceptable, effective, safe, fair, and economically viable technologies.

Many contemporary designers work to broaden the scope of the problems they are addressing, to engage and work with broader communities, publics, and users, or to even question their role as problem solvers in the first place. Designers are engaged in active debates that draw on history, social theory and anthropology, economics, politics, as well as science and technology in order to develop a more nuanced picture of what causes certain problems and to open up new visions for possible solutions. The design theorist John Thackara writes in his book *In the Bubble: Designing in a Complex World* that, "To do things differently, we need to perceive things differently...We need to design macroscopes, as well as microscopes, to help us understand where things come from and why...Equipped with a fresh understanding of why our present situations are as they are, we can better describe where we want to be."[66] The large scale problems that synthetic biology has potential to address—problems facing the global systems of food, health, and energy—are complex problems caused as much by material constraints as by political and economic issues of inequality and the distribution of resources. These are macroscopic problems that need macroscopic solutions. In order for synthetic biology design to begin to address these challenges, we must be able to connect the microscopic world of engineered cells to the human scale.

In recent years, a new mode of design practice has emerged that focuses not on solving problems but on using fiction and speculation to ask new questions and open up new debates about emerging technologies. This field of critical, speculative design began with the work of Tony Dunn and Fiona Raby (the moderator of the SB6.0 design panel) and explores some of the nuance of emerging technology situated in cultural contexts and at human scales. In their design projects and those of their students in the Design Interactions program at the Royal College of Art in London, speculative scenarios are developed through narrative fictions and provocative objects that tell stories of the people who shape and are shaped by new technologies.[67] These designers often work in collaboration with scientists, engineers, and students to develop new vocabularies of design, imagine new applications, and engage broad publics in debates about the heterogeneous concerns involved in the development of technology. Alexandra Daisy Ginsberg and James King's *E. chromi* project (www.echromi.com) with its fictional disease-monitoring, pigment-producing gut health biosensor is an excellent example of how design collaborations with synthetic biologists—in this case the 2009 Cambridge University iGEM team—can lead to provocative and compelling scenarios of future applications that question the role that aesthetics, the human body, food cultures, health monitoring, and consumer products might have in the future of synthetic biology. Design practice that lies at the interface of technology and society can thus provide many examples for rethinking how synthetic biology imagines the problems to which engineering with standardized biological parts might be solutions, and the contexts through which they might be deployed.

■ COLLABORATION: UNDERSTANDING PROBLEMS AND DESIGNING SOLUTIONS

One frequently cited example of a synthetic biology application that demonstrates some of the successes as well as some of the challenges of designing for the micro- and macroscale is the arsenic biosensor developed by the 2006 University of Edinburgh iGEM team.[68] Arsenic is a naturally occurring pollutant in many groundwater wells, particularly in areas of Bangladesh. The biosensor was conceived as an easy to use, low-cost detector of arsenic contamination in drinking water, where an arsenate-responsive promoter activates the expression of genes that change the pH of the microbial growth media. At high arsenate concentrations, the pH of the media decreases, leading to a visible change of a colorimetric pH indicator. This easily detected pH change is a simple and elegant solution for minimizing the resources needed to test well water in remote areas.

The history of arsenic contaminated drinking water in Bangladesh, however, provides an important warning for would-be problem solvers—the shallow, arsenic contaminated tube-wells that provide water for much of the country's inhabitants were dug as part of a humanitarian response to waterborne diseases starting in the 1970s.[69] What was intended as a solution to one problem ended up causing a second public health catastrophe. This suggests first of all that inexpensive diagnosis of arsenic contamination will not be able to address the underlying problems of water infrastructure and management in Bangladesh. Second, this history demonstrates that looking at complex problems through a narrow, reductionist lens can lead to harmful designs with dangerous consequences. In order to safely and effectively deploy synthetic biology solutions to problems in the real world, we must design technologies for use in complex social, political, economic, and environmental contexts.

The arsenic detector is one of several case studies that have been used to develop collaborative and speculative tools for integrated technology assessment in synthetic biology, bridging industry, academia, regulatory policy, and a broader public. Engineering and design can never plan for all possible outcomes, but open dialogue[70] and creative, collaborative scenario planning,[71] can help engineers engage with the ways that technology and society intersect and to shape designs within these contexts. Several recent workshops have brought together synthetic biologists and environmental microbiologists, conservation biologists, ecologists, social scientists, and policy-makers to discuss the broad potential benefits and risks of new synthetic biology applications while projects are still at the design stage. The Woodrow Wilson International Center for Scholars has taken a leadership role in these discussions, sponsoring dialogues about many projects, including the arsenic detector. Other Wilson center dialogues have focused on the metabolic engineering of cyanobacteria[72,73] to be grown in open ponds, exploring new technical, ecological, and regulatory paradigms for their design.[74]

Dialogs of this type can help shape the design of a given application of synthetic biology or find new directions and new applications altogether. A unique conference was recently convened to open discussion of synthetic biology being applied in the context of species conservation.[75] During the SB6.0 design panel, Kent Redford, an organizer of the biodiversity conference, discussed his goals for collaborations between synthetic biologists and conservation biologists, illustrated with examples of applications where synthetic biology could help address biodiversity concerns, as well as potential risks arising from such work. While discussions of risk and biosafety typically involve isolation of engineered organisms from the environment, here environmental release and ecological impact are the intended outcome of the technology. For such applications, safety concerns often center around the potential risks of unintended gene flow and the long-term effectiveness of technologies that might prevent such transfers.[76] Discussion with ecologists and environmental microbiologists can help synthetic biologists to understand the potential for such gene-flow to occur and its consequences, but they can also help to shape the design of environmental applications in a much more fundamental way. Collaboration with ecologists or conservation biologists can point out new problems where synthetic biology may be able to offer solutions, in ecosystem services, pathogen control, or biodiversity.[75] Collaboration with environmental microbiologists and soil scientists can also help synthetic biologists design for the heterogeneous complexity of environmental ecologies, where the survival and function of an engineered organism depends on very different factors than it does in the controlled environment of the lab.[77] Through such conversations, synthetic biology designs can incorporate a deeper understanding of how engineered microbes live and behave in different contexts, inside and outside of the lab.

In many fields, the design process depends on such deep engagements with diverse stakeholders and diverse issues in order to understand complex problems and imagine useful solutions. For synthetic biology, these conversations can help to reframe what we might think of as "barriers to innovation" between new technologies and their application in the real world.[65] By thinking of innovation in synthetic biology not as a linear flow from the lab to society but instead as a heterogeneous network of biological, technological, and social concerns about the potential benefits and risks of engineered organisms, we will be better able to choose good problems,[27] to understand the contexts of these problems, and to imagine how synthetic biology might be a part of the solution.

CONCLUSION: WHAT I DESIGN, I UNDERSTAND?

Many synthetic biologists take inspiration from a statement left on Richard Feynman's last blackboard at Caltech in 1988: "What I cannot create, I do not understand." This line captures well the exchanges of "reverse transcription" between science and technology that characterizes much of the current research in synthetic biology: synthetic biologists take apart and rebuild biological networks in order to better understand them. The irony, of course, is that Feynman was not an engineer but a theoretical physicist whose creations were not technologies but mathematical models. Reflecting on the ways that designs must engage with the complex interrelationships of different contexts—biological, technological, and social—we might rethink Feynman's point about the relationship between making and understanding in biological design.[78] The heterogeneity and complexity of these relationships means that we may not be able to fully understand, predict, and control the function of synthetic biologies[79] in a changing social and natural environment. Instead, we should approach the design of biological systems with more humility and with design principles that are more biological, emphasizing not control but adaptability, not streamlining but robustness, and not abstraction but complexity.

Such design approaches that incorporate uncertainty and biological adaptability have already played a significant role in the development of synthetic biologies at the cellular level. For the top-down, parts-based approach, the context dependence of biological systems and the complexity of the cellular environment lead to significant unpredictability in the function of even very simple synthetic gene networks. For example, empirical measurements of simple gene expression circuits determined that the composite design of regulatory components provided a more reliable range of expression outputs than the more rational, modular design.[80] A growing realization that noise in gene expression and other stochastic processes are fundamental to the robustness of biological systems[81] has also led many to consider a more systems-based approach to informing biological engineering,[82] and perhaps a revision of synthetic biology's design principles to enable a "second wave" of more complex, context-aware engineering.[83] These methods are enabled not strictly by rational assembly of well characterized parts but by a mixture of rational and irrational design tools that take advantage of biology's ability to iteratively improve function through directed evolution.[84,85]

These "irrational," biologically inspired design tools have also played a role in other industries, where designers have sought to make engineering more like biology—-adaptive, complex, robust, and sustainable.[86] This kind of biology-based design process in other domains of engineering such as architecture,[87] computer hardware,[88] or software,[89] may inform the philosophy of rational design that drives synthetic biology.[90] It may be more difficult to understand the things designed in this way,[91] but messy, holistic, biological designs may be able to function more effectively and sustainably in the real, messy, complex world of technologies in their social and environmental context.[92]

Likewise, the collaborative, speculative, context-dependent design tools described in this review will not be able to provide complete understanding or 100% accurate prediction of all the potential outcomes of biological technologies. Instead, such design experiments and speculative discussions can "assist with identifying areas of uncertainty and maintaining a degree of flexibility in response to unanticipated developments."[93] In synthetic biology, these sorts of open-ended strategies and creative methods for design have found their way into the lab through collaborations with designers from many other fields, bringing diverse approaches to the work of biological design.[26,94] Such collaborations offer engineers the opportunity to imagine new possibilities for how their work might be embedded into the human scale of everyday technology. Through design experiments and speculative prototyping, synthetic biologists can open up new directions for research, new questions, and new hypotheses, bridging the biological, the technological, and the social to communicate and question the potential benefits and risks of a new technology. The future of synthetic biology will impact our scientific understanding of biology, the design of biological technologies, and how we solve problems in the real world. Designing for the complex interrelationship of biology, technology, and society will open up new spaces for true innovation in synthetic biology.

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Notes

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