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Synthetic Biology: Building a Nation's Inspiration: Interdisciplinary Research Team Summaries

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The National Academies Keck Futures Initiative

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THE NATIONAL ACADEMIES
KECK FUTURES INITIATIVE

SYNTHETIC BIOLOGY
BUILDING ON NATURE'S INSPIRATION

INTERDISCIPLINARY RESEARCH TEAM SUMMARIES

Conference
Arnold and Mabel Beckman Center
Irvine, California
November 20–22, 2009

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NOTICE: The Interdisciplinary Research (IDR) team summaries in this publication are based on IDR team discussions during the National Academies Keck *Futures Initiative* Conference on Synthetic Biology held at the Arnold and Mabel Beckman Center in Irvine, California, November 20-22, 2009. The discussions in these groups were summarized by the authors and reviewed by the members of each IDR team. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the IDR teams and do not necessarily reflect the view of the organizations or agencies that provided support for this project. For more information on the National Academies Keck *Futures Initiative* visit www.keckfutures.org.

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The National Academies Keck *Futures Initiative*

The National Academies Keck *Futures Initiative* was launched in 2003 to stimulate new modes of scientific inquiry and break down the conceptual and institutional barriers to interdisciplinary research. The National Academies and the W. M. Keck Foundation believe that considerable scientific progress will be achieved by providing a counterbalance to the tendency to isolate research within academic fields. The *Futures Initiative* is designed to enable scientists from different disciplines to focus on new questions, upon which they can base entirely new research, and to encourage and reward outstanding communication between scientists as well as between the scientific enterprise and the public.

The *Futures Initiative* includes three main components:

Futures Conferences

The *Futures* Conferences bring together some of the nation's best and brightest researchers from academic, industrial, and government laboratories to explore and discover interdisciplinary connections in important areas of cutting-edge research. Each year, some 150 outstanding researchers are invited to discuss ideas related to a single cross-disciplinary theme. Participants gain not only a wider perspective but also, in many instances, new insights and techniques that might be applied in their own work. Additional pre- or post-conference meetings build on each theme to foster further communication of ideas.

Selection of each year's theme is based on assessments of where the

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intersection of science, engineering, and medical research has the greatest potential to spark discovery. The first conference explored *Signals, Decisions, and Meaning in Biology, Chemistry, Physics, and Engineering*. The 2004 conference focused on *Designing Nanostructures at the Interface between Biomedical and Physical Systems*. The theme of the 2005 conference was *The Genomic Revolution: Implications for Treatment and Control of Infectious Disease*. In 2006 the conference focused on *Smart Prosthetics: Exploring Assistive Devices for the Body and Mind*. In 2007 the conference explored *The Future of Human Healthspan: Demography, Evolution, Medicine and Bioengineering*. In 2008 the conference focused on *Complex Systems*. The 2009 conference explored *Synthetic Biology: Building on Nature's Inspiration* and the 2010 conference will focus on Imaging Science.

Futures Grants

The *Futures* Grants provide seed funding to *Futures* Conference participants, on a competitive basis, to enable them to pursue important new ideas and connections stimulated by the conferences. These grants fill a critical missing link between bold new ideas and major federal funding programs, which do not currently offer seed grants in new areas that are considered risky or exotic. These grants enable researchers to start developing a line of inquiry by supporting the recruitment of students and postdoctoral fellows, the purchase of equipment, and the acquisition of preliminary data—which in turn can position the researchers to compete for larger awards from other public and private sources.

NAKFI Communications

The Communication Awards are designed to recognize, promote, and encourage effective communication of science, engineering, medicine, and/or interdisciplinary work within and beyond the scientific community. Each year the *Futures Initiative* awards $20,000 prizes to those who have advanced the public's understanding and appreciation of science, engineering, and/or medicine. The awards are given in four categories: books, magazine/newspaper, online, and film/radio/TV. The winners are honored during *Futures* Conferences.

NAKFI cultivates science writers of the future by inviting graduate students from six science writing programs across the country to attend the

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conference and develop IDR team discussion summaries and a conference overview for publication in this book. Students are selected by the department director or designee, and prepare for the conference by reviewing the Podcast tutorials and suggested reading, and selecting an IDR team in which they would like to participate. Students then work with NAKFI's science writing student mentor to finalize their reports following the conferences.

Facilitating Interdisciplinary Research Study

During the first 18 months of the Keck *Futures Initiative*, the Academies undertook a study on facilitating interdisciplinary research. The study examined the current scope of interdisciplinary efforts and provided recommendations as to how such research can be facilitated by funding organizations and academic institutions. *Facilitating Interdisciplinary Research* (2005) is available from the National Academies Press (www.nap.edu) in print and free PDF versions.

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Preface

At the National Academies Keck *Futures Initiative* Conference on Synthetic Biology, participants were divided into twelve Interdisciplinary Research (IDR) teams. The teams spent nine hours over two days exploring diverse challenges at the interface of science, engineering, and medicine. The composition of the teams was intentionally diverse, to encourage the generation of new approaches by combining a range of different types of contributions. The teams included researchers from science, engineering, and medicine, as well as representatives from private and public funding agencies, universities, businesses, journals, and the science media. Researchers represented a wide range of experience—from postdoc to those well established in their careers—from a variety of disciplines that included science and engineering, medicine, physics, biology, math/computer science and behavioral science.

The teams needed to address the challenge of communicating and working together from a diversity of expertise and perspectives as they attempted to solve a complicated, interdisciplinary problem in a relatively short time. Each team decided on its own structure and approach to tackle the problem. Some teams decided to refine or redefine their problems based on their experience.

Each team presented two brief reports to all participants: (1) an interim report on Saturday to debrief on how things were going, along with any special requests; and (2) a final briefing on Sunday, when each team:

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- Provided a concise statement of the problem;
- Outlined a structure for its solution;
- Identified the most important gaps in science and technology and recommended research areas needed to attack the problem; and
- Indicated the benefits to society if the problem could be solved.

Each IDR team included a graduate student in a university science writing program. Based on the team interaction and the final briefings, the students wrote the following summaries, which were reviewed by the team members. These summaries describe the problem and outline the approach taken, including what research needs to be done to understand the fundamental science behind the challenge, the proposed plan for engineering the application, the reasoning that went into it and the benefits to society of the problem solution. Due to the popularity of some topics, two teams were assigned to explore the subjects.

Eleven Podcasts were launched throughout the summer to help bridge the gaps in terminology used by the various disciplines. Participants had the opportunity to ask questions of the Podcast speakers during the panel discussion, which took place immediately prior to the IDR team discussions.

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APPENDIXES

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Conference Summary

Cassandra Brooks

Synthetic biology is an innovative and growing field that unites engineering and biology. It builds on the powerful research that came about as a result of recombinant DNA technology and genome sequencing and appears to be one of the most important extensions of that work—a perfect example of science building on what came before. The goal of synthetic biologists is nothing short of building a biological system from the ground up.

By definition, synthetic biology is an interdisciplinary enterprise comprising biologists of many specialties, engineers, physicists, computer scientists, and others. It promises a fundamentally deeper understanding of how living systems work and the capacity to recreate them for medicine, public health, and for the environment, including renewable energy. By building synthetic biological systems, scientists seek an unprecedented level of insight and knowledge about how various parts of biological systems function in isolation and as whole organisms or even whole ecosystems.

The National Academies Keck *Futures Initiative* in 2009 focused on Synthetic Biology to generate new ideas about how to program and control both simple and complex biological systems. The possibilities synthetic biology offer are clear but challenges are significant because, as one participant said, "We cannot yet program cells the way we can program computers," and that is what needs to happen.

To explore the engineering, scientific and social aspects of synthetic biology, researchers, as well as individuals from funding, industry, and government agencies who participated in the *Futures Initiative* on Synthetic

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Biology joined one of 12 Interdisciplinary Research (IDR) teams comprising about a dozen leading researchers whose job was to think creatively, outside the proverbial "box" about how to move the field forward.

IDR teams 1a and 1b each discussed new foundational technologies and tools required to make biology easier to engineer. The teams came up with many clever ideas, including creating a "smart Web-cam" that could be inserted into a cell to observe and record cellular processes without disturbing the cell's function. They also explored creating a futuristic "photocopying machine" that could copy cells, tissues, organelles and whole organisms. This would allow synthetic biologists to efficiently produce useful products in large quantities. The group also stressed the importance of increasing the number of cell types with open protocols. For example, access to thermophilic bacteria that live in extremely hot environments for carrying out reactions at high temperatures would lead to innovative avenues of research.

IDR team 2 was asked to consider whether there are ethical considerations unique to synthetic biology. After much deliberation, the team of scientists and bioethicists concluded that synthetic biology does not pose any unique problems when compared to previous cutting edge advances in science. Yet, they warned, this new field does deserve the same level of careful attention and monitoring devoted to previous technologies. They recommended that synthetic biology should borrow from the existing regulatory framework to protect the public while allowing the science to move forward.

IDR teams 3a and 3b asked how synthetic biology could lead to an understanding of the principles underlying natural genetic circuits and to the discovery of new ways to make use of that knowledge. Half of the group approached the problem by asking if a failed or noisy synthetic circuit could help scientists better understand natural circuits and locate missing genes, proteins or chemical reactions. The group proposed a noise "decomposer" that could track the randomness in zebrafish stem cells as they become the various parts of the animal. Moreover, they proposed assembling a "deviance library" where a scientific failure (i.e., a synthetic circuit that intentionally produces caffeine in *E. coli* but arsenic in staphylococcus) could lead to another's deliberate design.

The other half of the group debated how synthetic biology could be used to answer fundamental biological questions such as how proteins assemble, bind to DNA and regulate transcription. They also suggested borrowing techniques from electrical engineering: for example, sending the

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equivalent of a pulse or oscillating wave into a biological circuit and then devising ways to measure the output. By finding tools to precisely disturb natural systems, scientists could gain tremendous insight into how these systems operate.

IDR team 4 tackled how cellular collaboration and communication could be used in synthetic biology for specialization and division of labor. The team proposed specific ways that cell communities could be used to clean up waste, improve health, keep plants fed and watered, and even explore Earth or other planets in the future. One clever idea proposed was a "land and pond rover" based on the life cycle of the slime mold *Dictyostelium discoideum,* or Dicty for short. The team proposed that mobile Dicty-like slugs could be engineered to search for arsenic or gold and then sprout into their readily visible mushroom-like form to indicate where hazardous or valuable materials are located.

IDR team 5 thought about why human-designed biological circuits and devices are fragile and inaccurate relative to their natural counterparts. To kick off the discussion, they considered whether the rigidity of engineered systems is the source of fragility. Although biology is noisy, it works well and should not be considered an undesired element when engineering biological systems. Instead synthetic biologists should consider how to engineer biological robustness, including redundancy, plasticity, adaptability and flexibility. In the end they worried that "the inherent complexity of biological systems defies reliable engineering."

Despite this, the team came up with some theoretical tools for constructing more robust systems. They suggested that the equivalent of a biological wind tunnel could be used to carefully examine each genetic circuit in a one-at-a-time way to test its strengths and flaws. In contrast, the researchers also proposed a "rapid comparison" approach. This entailed bombarding combinatorial circuits into the cell and then assessing which was most robust.

IDR team 6 pondered how genomics could be leveraged to develop coherent approaches for rapidly exploring the biochemical diversity in and engineering of new model organisms, to augment studies that currently rely on well studied organisms. They decided that the most pertinent problem is figuring out ways to most efficiently and effectively search the biosphere for new genes and to elucidate their specific functions. Because genetic diversity is presumed to correlate with biodiversity, the team recommended sampling soil from different ecological zones throughout the world. Once regions of highest diversity are found, biopropsecting efforts could be focused on

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those regions. This should include toxic waste sites, where an organism's ability to deal with toxins could potentially be exploited to clean up other polluted environments.

IDR teams 7a and 7b each investigated how to move beyond genetics to use chemical and physical approaches to synthetic biology. Half of the team explored means for developing new tools to exploit the evolution of biological systems and use that knowledge to renew systems that are failing. They identified several goals based on orthogonal functions, meaning those entirely separate from and not interacting with existing biological functions. These included generating cells that include macromolecules with new and desirable functions, programming new molecules to encode information, designing sub-cellular pathways that are separate from the cell's machinery, and engineering molecular interactions with organic or engineered devices.

The other half of the team focused on creating biotic and abiotic devices that could act on the host cell without altering its DNA, which would offer research an incredible advantage over current techniques of genetic engineering. First, the team proposed building simpler synthetic transporter proteins that, when injected into cells, could stimulate a desired response immediately. Moreover, the transporter would be designed to self-destruct after completing its task in order to "do no harm." Second, they proposed building a cellular radio that could be inserted into a cell and remotely controlled with incredible power and precision. The radio could theoretically be used to produce heat, mechanical vibrations, or hydrolysis. The heat, for example, could be used to destroy cancer cells.

IDR team 8 considered the role of evolution in synthetic biology. They pointed out the necessity of developing methods to accelerate evolution and get a desired result faster, but also having a kill switch for these evolutionary processes once the experiment was finished. Yet, this will only be possible by engineering strains of bacteria in which the mutation rate can be controlled, making it significantly more reliable and malleable.

IDR team 9 focused on explaining synthetic biology to the public and on encouraging young scientists to enter the field. The team worked to define some of the educational, institutional and communication barriers that may inhibit the progress of synthetic biology. They concluded that part of the solution is to train young scientists in new ways, break

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down divisions in academic institutions, and to improve general science communication.

As all the groups gathered on the final day of the conference to present their ideas, it became clear that most individuals were both challenged and inspired. During the final large group discussion, many participants commented that the conference changed the way they will do their research, will inspire their teaching, foster new collegial connections and bolster existing ones.

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IDR Team Summary 1

What new foundational technologies and tools are required to make biology easier to engineer?

CHALLENGE SUMMARY

The engineering of biological systems holds great promise for developing solutions to many global challenges, including renewable energy production, material synthesis, and medical advancement. Synthetic biology is a rapidly growing, interdisciplinary field that involves the design, construction, and optimization of biological functions and systems. One of the long-term goals of synthetic biology is to make the engineering of biological systems easier and more reliable. Toward these goals, core activities of synthetic biology have focused on the engineering of complex biological systems and the development of engineering frameworks and foundational technologies that support the reliable programming of biological function.

Synthetic biology builds upon other more mature disciplines and most notably the field of genetic engineering. Genetic engineering began as a field more than thirty years ago and was largely developed around a set of foundational technologies that allowed researchers to amplify pieces of DNA, build relatively simple synthetic DNA elements by piecing together DNA fragments, and place those synthetic DNA elements into living systems to encode relatively simple, novel biological functions. However, the foundational technology set associated with genetic engineering does not scale readily to the engineering of large-scale integrated biological systems, such that biotechnology and medical technologies have not seen an increase in the complexity of reliably-operating biological systems that can be designed and constructed at a pace that is similar to the growth observed in other technology sectors. In addition, the knowledge-base supporting the design

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of biological circuits that perform specified functions reliably is not well developed. As one example, there is not a comprehensive knowledge-base that guides the selection between transcriptional, post-transcriptional, or posttranslational control schemes or layering of these schemes to achieve a desired circuit performance.

The engineering of microbial chemical factories provides important case examples of engineering complex biological systems. Researchers are successfully engineering complex metabolic pathways (comprising up to 10-20 synthetic enzymatic steps) in microorganisms to achieve bioremediation and green synthesis strategies, the latter directed to the synthesis of various specialty drugs and chemical commodities, including biofuels. One recent example is based on the engineering of microorganisms, such as yeast and bacteria, to produce a cure for malaria based on the natural product artemisinin. Artemisinin is a molecule that is naturally produced in the plant *Artemisia annua* and is obtained through extraction from the plant material. Currently, the drug is expensive and thus does not allow effective treatment of malaria in the third world countries most afflicted with this disease. Researchers developed a solution to this problem by engineering a microorganism that can be grown cheaply, quickly, and in very large volumes to produce Artemisinin at nearly one-tenth of its current price. However, the success of this single engineering effort (and the current design, construction, and optimization processes in place) required a very large amount of dedicated resources and time. Therefore, the investment required to apply this strategy anew to every chemical and material we would like to produce is unrealistic with current technologies. As such, the ability of newly developed foundational technologies that will make these approaches cheaper, faster, and more reliable is critical to the broader application of synthetic biology.

Key Questions

- What are the most important experimental and computational technologies and tools that will support the engineering of biological systems?
- What new technologies are required to support increased efficiencies and scaling in design, construction, and optimization of biological processes?
- What tools are most needed to address the growing gap between our ability to construct and our ability to design large-scale integrated biological systems?

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- What is the knowledge-base required to support the design of biological circuits and systems that operate reliably?
- How can we most effectively build the required knowledge-base?
- What are effective means for assessing newly-developed tools?

Reading

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Due to the popularity of this topic two groups explored this subject. Please be sure to review the second write-up, which immediately follows this one.

IDR TEAM MEMBERS—GROUP A

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- Shota Atsumi, University of California, Davis
- Randy Bartels, Colorado State University
- Steven Boxer, Stanford University
- Richard Braatz, University of Illinois at Urbana-Champaign
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IDR TEAM SUMMARY—GROUP A

By Frederik Joevling, Graduate Science Writing Student, New York University

The engineering of biological systems could help develop solutions to some of the biggest global challenges, such as renewable energy production, material synthesis, and specialized drug manufacture. Synthetic biology is the rapidly growing, interdisciplinary area that involves the design, construction, and optimization of biological systems and functions. The field also promises an improved understanding of life, just like building a clock from scratch teaches you more about its inner workings than merely prying one apart.

But so far, the vision of what synthetic biology might accomplish remains beyond today's technological prowess. Much scientific progress depends on technology to enable researchers to see in new ways and to collect data to which they previously did not have access. For example, when a few years ago it became possible to rapidly sequence the genomes of entire communities of organisms—the so-called metagenomics—the doors were suddenly thrown wide open to a microbial terra incognita. In the same way, an important element to the success of synthetic biology is the development of new tools and technology.

At the 2009 National Academies Keck *Futures Initiative* Conference, an IDR Team, comprising chemists, engineers, computer scientists, and others (Interdisciplinary Research Team 1A) met to identify the kinds of tools that will be needed to accelerate the design cycle of new biological systems, allowing researchers to test and execute their ideas fast and efficiently. The group categorized its recommendations according to different

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levels of abstraction, moving from computer-based modeling to wetware implementation.

Advances in the Application of Computer Science to Synthetic Biology Are Essential to Moving the Field Forward

Synthetic biology should be described in a language that is usable by biologists and readily executable on a computer. Researchers already have good representations for protein structures and DNA sequences, but it is necessary to find a way to describe cellular processes and functions with equal precision. With such a description—encompassing everything from chemical reactions in a single cell to biological interactions in a community of cells—scientists would be able to simulate entire biological systems as well as their operations on them. In computer science, this type of language is known as an "executable specification language." It should be compositional, meaning that the properties of any given system can be derived entirely from the properties of its parts. It should also be curated and validated, and experimentalists should to be able to add descriptions of various biological components in order to expand its functionality.

Along with a new computational language, researchers need better predictive models to describe dynamic behavior at different levels of biological organization, including molecules, organelles, cells, organs, organisms and ecosystems. The models should account for multiple interactions between the components of a biological system as well as internal feedback loops in which the end products of certain biochemical pathways influence their own synthesis. Finally, new mathematical approaches to analyzing biological systems could prove useful, but there was no consensus as to the nature of these approaches, nor the exact problem they would address.

Cells are inherently complex and noisy milieus. One might imagine—indeed, hope—that a great deal of this information can be safely ignored when using them as backdrops for new gene circuits; methods are needed to determine the necessary and sufficient set of parameters that specify their context and biological state.

Sensing, Diagnostic, and Actuating Systems Are Crucial for Synthetic Biology

Given their complex and adaptive nature, engineered cells also tend to do what is best for them and not necessarily what scientists want them

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to do. Therefore it is essential to be able to analyze, predict and design for stability and robustness that will ensure reliable performance in a complex environment. And if unwanted change does occur, measures should be taken to ensure self-repair. The synthesized biological system should also include a sensing and diagnostic apparatus to inform us of errors that cannot be automatically corrected; just like the checkpoints included in the code of a computer program can help debug it, signals inserted at critical points in a biological circuit would reveal when and where the error occurred. An actuator system should also be coupled to this sensing and diagnostic apparatus to carry out the repair.

Of course, scientists should have means of interacting with the cells, of sensing their state and of manipulating and controlling them. Imagine that cells were engineered to produce a certain level of insulin in the pancreas of patients with type 1 diabetes in response to a blood sugar spike. If somehow these cells became corrupted and started secreting too much insulin, which could kill the patient by fatally lowering blood sugar levels, there needs to be an easy fix. Because extracting the cells directly is at best cumbersome—and at worst impossible—inserting a "kill switch" in the cells that scientists can control might be a solution.

To facilitate this interaction between scientists and cells, a variety of interfaces should be developed between biological and chemical, electronic, optical, thermal, and mechanical signals. In the case of insulin production in the pancreas, the engineered cells could be designed to respond to a synthetic chemical injected intravenously. In drug-manufacturing cell systems that function outside the body, on the other hand, an easy way to control production would be by making the cells sensitive to temperature. The sensors should report in real time on the state of the biological system, at various levels of organization and in terms of both time and space.

High-Throughput Screening Methods Integrated with Computational Modeling Are Necessary

Ultimately, the goal of these technologies is to improve the design cycle of synthetic systems, leading to rapid prototyping of new designs. To enhance the process further, it would be useful to have large collections, or libraries, of biological components and systems that could be screened and evaluated fast. The elements in the library should be well designed, for instance based on computer models, high-throughput experimental systems or a combination of both.

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Advances in the Wet Lab Are Needed to Complete the Design Cycle of New Biological Systems

When it comes to the cells themselves, there are a variety of ways researchers could optimize the design cycle. It would be interesting to determine the theoretical limits of how fast cells can reproduce, for example, in order to create cells that multiply as fast as possible and thus enable experiments to be carried out quickly. Increasing the number of cell types with open protocols and useful characteristics would also be useful. So far, researchers have relied largely on *E. coli* as their model organism, but other species may have more suitable properties for a specific purpose—for instance, thermophilic bacteria that thrive in very hot environments could prove useful in carrying out reactions requiring high temperatures.

At present, the success of a single engineering effort—such as the production of artemisinin, an anti-malarial drug that is now being produced cheaply by engineered microorganisms—requires a very large amount of resources and time. Synthetic biologists would want to create minimal cells by developing methods to quickly determine the cellular components sufficient to achieve a particular objective. Different cell lines might then be optimized in a task-specific manner for ideal performance. Today, most synthetic systems rely on tinkering with natural cell components, but it would clearly be useful to create entirely artificial cells with known functionality, the paragon of synthetic biology.

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IDR TEAM SUMMARY—GROUP B

By Lauren Whaley, Graduate Science Writing Student, University of Southern California

Science is often driven by the technology available to it. At the 2009 National Academies Keck *Futures Initiative* on Synthetic Biology, an Interdisciplinary Research (IDR) team of researchers with experience in bioengineering, pharmacology, chemical engineering, genomics, computer technology and other disciplines came together to discuss what tools and technologies could support the engineering of biological systems. The team came up with ideas.

Before looking at the list, it is useful to step back and consider the IDR team's definition of synthetic biology as the discipline in which humans *make* biology into useful things for society, such as drought-resistant food, drugs, and environmentally applicable organisms, such as a coral that sequesters carbon. Synthetic biology encompasses BOTH the *design* and construction of new biological parts (such as DNA) and systems (such as cells and entire organisms) as well as the *re-design* of existing systems (reconfiguring a cell so it behaves how the scientist wants it to). By creating new life and redesigning things that are already living, synthetic biologists will create anything they want.

To determine what tools would advance such a multidisciplinary and complicated field the team decided that examining Systems Biology would be a useful starting point. Systems Biology studies complex biological systems as integrated wholes, using many different tools, including DNA sequencing, epigenetics (looking at cells that have the same genotype, but a different phenotype), and protein-to-protein interactions. By understanding how *natural* biological systems work, synthetic biologists will be able to use them as parts or models for their *made* systems.

Dr. Wendell A. Lim said at the opening of the conference that by using synthetic biology as a model for natural biology, humans could begin to understand why and how things—like cells—break down and will learn a better way to design them so they don't. Lim is a professor of Pharmacology and Biochemistry at the University of California, San Francisco.

As an organizational strategy, the IDR team decided to organize its tool list into Requests for Applications (RFAs), much as science foundations do. The team recognized that creating new tools will require funding, and that funding will likely come from grants. One of the major problems with

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advancing the field has to do with finding financial backing for projects. Arranging the tool wish list into a request for applications seemed like a logical way to proceed. The IDR team's goal in framing its report in terms of potential grants will encourage novel collaborations, and therefore, novel results, from scientists across many disciplines who may not currently work together.

Some characteristics of new tools include cheaper and faster ways to sequence and synthesize DNA. Sequencing is the process of finding out what series of base-pairs makes up a piece of DNA, while synthesis is the process of actually making the DNA from separate base pairs.

The IDR team also hoped for the creation of a "smart Web-cam" that could be inserted into a cell to see and understand everything that was going on without disturbing any of the cell's function. Such an advancement would make it possible to understand how the system of a cell functions down to every working part, so that new or modified cells could be reliably produced.

The scientists also wanted to create a futuristic "photocopying machine" that could copy cells, tissues, organelles and whole organisms. This technology would be invaluable in making synthetic biology "scalable"—that is, able to produce useful products in large quantities.

Building on that, the team agreed that the ultimate accomplishment would be to develop a computer algorithm to mimic a cell. If such code existed, it could be typed into another item on the scientists' wish list, a machine that could read that code and produce the cell it requested. A researcher imagines a cell and types its characteristics into a futuristic machine. Then, that machine, call it a "Star Trek replicator," would rumble and shake and finally swing open its doors, revealing the physical form of cell or tissue the scientist had imagined. The machine would also print out an ingredient and recipe list to go along with the made concoction. One group member summed it up when he asked, "What could be more enabling than that?"

The IDR team organized its Request for Applications wish list into three categories: Synthesis, Analysis and Modeling.

1. *Methods to reduce cost, increase length, and increase fidelity of DNA synthesis.*

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- Target: Reduction in the cost of DNA synthesis.
  - Ideally, costs would go down to $.005 / base pair. Right now, synthesis costs are about $1 per base pair.
- Includes methods focused on oligos on a chip, new chemistry for DNA synthesis, very long length reads, and engineering epigenetic DNA.
- Technologies for cheaper DNA synthesis that are currently in the Research and Development pipeline include: microfluidics, new chemistries, chip-based or bead-based techniques, novel polymerization and single-molecule sequencing.

2. *New approaches to enable the synthesis of a broad range of biological entities, beyond simple polymers such as DNA and RNA.*

Synthesis targets include the following cellular entities:

- Proteins
- Bacterial and archaeal cells
- Subcellular machines
- Eukaryotic cells
- Organelles
- Tissues
- Viruses

3. *Methods to measure composition and biophysical states of biological systems. This includes the measurements of genes, proteins, metabolites, and interactions among biological molecules.*

Ideally, the methods should be highly multiplexed, at high spatial and temporal resolution, and minimally invasive to the system.

Examples of technologies needed include:

- Novel detection methods, including reagent generation.
- Multi-parameter measurements with single molecule sensitivity (proteins, genes, metabolites, etc.).
- Development of organic/inorganic interfaces.
- Systems for measurement of endogenous interactions such as protein to protein, protein to nucleic acid, protein to small molecule, and nucleic acid to small molecule, particularly in living cells.

4. a. *A tool that would design cells from scratch, using knowledge of natural cells.*

Currently, the ability to synthesize exceeds science's ability to model in

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advance. The capacity to design cells from scratch would vastly increase the chances that one could create useful organisms for both medical and environmental uses. In order to design such cells, we need to more completely understand such things as protein to protein interactions and phenotype to genotype prediction.

b. Development of systems models via combined experimental and modeling approaches; methods to enable in silico *design of cells.*

The ultimate goal here would be to predict a genome sequence that would completely encode a cell with desired capabilities. In the near term, the group wants predictive cell re-design methods. Experimental data generation will be integrated with the modeling. Models should be formatted in ways that can be readily communicated to and implemented across the whole community. The information could be shared using common computer language, such as Systems Biology Markup Language (SBML).

The *in silico* design of cells could include:

- Introduction of whole pathways into cells, including transport between organisms.
- Aiding in the tuning of synthetic circuits.
- Elucidating the relationship between promoter sequence and protein expression.
- Remodeling a well-studied pathway, modulation of various parameters such as promoter strength, operons, terminator strength, etc.
- Methods for predicting toxic effects of small molecules.
- Harnessing high-throughput computational technology (e.g., Graphic Processing Unit) to solve previously untenable computational problems.

5. Additional ideas

In addition to discussing tools that can be used now and tools they'd like to use now, the members of the IDR team also imagined technologies that seemed a bit far-fetched, but that if made, would really help them engineer biology. One of those ideas is the Safety/Kill Switch.

The team would like to see the construction of a fail-safe mechanism to ensure regulatory compliance and public acceptance of cells made using synthetic biology. We seek proposals to develop genetic fail-safe mechanisms for use in prokaryotic and eukaryotic cells that would cause cell death.

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- Prokaryotic and Eukaryotic devices to terminate synthetic cells.
- Eukaryotic devices that, for instance, might be used in therapeutic stem cells.
- Examples of fail-safe device activation could include chemical treatment, cell-division counters, and auxotrophy. Auxotrophy is when a cell dies because it is not being "fed" by the scientist. These synthetic cells could be engineered to only survive in very specific environments. If they escaped said environments, they would terminate.

If the scientists of the IDR team had their druthers, they would design every bit of DNA that goes into an organism so that they—the scientists—know exactly how it would behave now and in the future.

The more tools that can make what is currently hard easy, the more quickly scientists will see rapid increases in productivity and development. The scientists want all of this to advance medicine, come up with alternative energy sources, create food and develop more and more remarkable materials that could enhance human life on earth.

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IDR Team Summary 2

What are the significant differences, if any, between risk assessment capacity and religious analyses of the moral permissibility for synthetic biology applications and other biotechnology applications?

CHALLENGE SUMMARY

The Hastings Center, one of several bioethics think tanks, recently announced that it is doing a study on ethical issues in synthetic biology, noting that "this rapidly advancing technology raises ethical questions about benefits and harms that have not been thoroughly addressed." But because synthetic biology is a part of the continuum of research in the broad field of biotechnology, most of the ethical and policy issues it might raise are at least somewhat familiar. The challenge is to identify those issues, if any, that are quantitatively or qualitatively different for this field.

Synthetic biology is not limited to engineering specific changes in existing naturally occurring cells and organisms. Rather, it is predicted to be capable of constructing powerful and problematic organisms from scratch. When researchers announced that they had synthesized the deadly and virulent polio virus—for the purpose, they said, of showing how easy it would be to construct new bioweapons from off the shelf materials—scientists and ethicists were alarmed and the National Academies initiated a study on ways to prevent the destructive use of biotechnology. The familiar safety issues raised by biotechnology were now qualitatively altered to include bioterrorism, leading to extended discussions about scientific freedom versus the asserted need to prohibit some forms of research or to censor some forms of scientific communication.

More generally, risk assessment is a generic problem for all new technologies. In the area of biotechnology, early experiments were the subject of vociferous public debate, leading a few jurisdictions to ban the work

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entirely within their borders. Even where permitted, it was accompanied by extraordinary safety measures and enhanced oversight. Much of this was due to a combination of factors—the novelty of recombinant DNA techniques (which was the impetus for the unprecedented Asilomar Conference, during which time a diverse audience of nearly 150 biologists and other scientists, physicians, and lawyers met to draw up voluntary guidelines to ensure the safety of recombinant DNA technology); the concerns about new traits or organisms escaping from the controlled environment and affecting flora and fauna on a large scale; the fear that it would be a temptation to undue tinkering with nature; and the prospect of altering the economics of agriculture. Synthetic biology's predicted capacity to expand the range of organisms that can be constructed may make risk assessments so complex that current methodologies will prove inadequate. In discussing the benefits and potential risks associated with the creation of synthetic organisms, scientists should take care to use language that is direct but not inflammatory.

Another long-running debate concerns intellectual property and the status of elements of living systems, such as gene sequences or altered organisms. For decades, U.S. law has granted patent rights for these products of biotechnology research and innovation, but whether this has achieved the goals of the patent system—incentivizing investment, inducing open disclosure, and speeding technological advances—has been debated unrelentingly since the first patent was granted for an altered bacterium. Recently the debate has intensified, with a legal challenge to the patents held by Myriad Genetics that are used for testing BRCA mutations that may increase a person's risk of breast and ovarian cancer. Certainly the prospect of modular elements allowing a wider range of people to participate in the construction of new organisms may change the way the patent system's incentives actually function, and may lead to rethinking the use of patents in this area.

More dramatic, however, is the fact that synthetic biology represents the ability to construct artificial life forms. The sheer ability to construct a living organism is a fundamental break with history of the human species, one that may lead to profound questioning of deeply held religious and cultural beliefs about the origins and meaning of life. As one observer noted wryly, "God has competition." If life is not a mystery but rather a predictable consequence of combining elements of the material world, it bespeaks a mastery over creation that has led to deep distress in public debates surrounding IVF in the 1980s and cloning in the 1990s. It taps into fundamental divisions among major world religions in their views on the proper domain of human activity, and it even affects notions of human exceptionalism, whether in the

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context of debates on evolution or speculation about life on other planets. But the extent to which these debates are changed as one moves from cloning to synthetic biology is not yet understood.

Bioethics is not a discipline aimed at slowing or stopping scientific inquiry and technological progress. It is, however, a discipline that aims to begin with accurate science, incorporate emotional and political realities into debates, and use political and moral philosophy to guide us to more carefully reasoned arguments about whether and when a technological application is good or bad, and when a governmental response is or is not justified.

Key Questions

- What are the significant differences, if any, in risk assessment capacity for synthetic biology applications as opposed to other biotechnology applications? Do current regulatory structures and ethical analyses adequately capture the uncertainties associated with synthetic biology?
- What are the significant differences, if any, in religious analyses of the moral permissibility or implications of creating life synthetically, as opposed to the use of cloning or IVF?
- What is the current state of thinking about the net effects of granting intellectual property rights over engineered organisms? Is this analysis affected by introducing synthetic biology into the discussion?
- What can be learned from Asilomar?

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IDR TEAM SUMMARY

By Lynne R. Peeples, Graduate Science Writing Student, New York Univrsity

The Interdisciplinary Research (IDR) team, comprising 13 scientists and bioethicists, considered ethical and policy issues at the National Academies Keck *Futures Initiative* Conference on Synthetic Biology in 2009. The team concluded that synthetic biologists should heed the accumulated wisdom from decades of advances in biotechnology and remain alert to new developments as the field progresses.

A number of policies and regulations are already in place to prevent both safety and ethical lapses in the application of recombinant DNA technology. The challenge for this team was to identify those issues, if any, which were quantitatively or qualitatively different for synthetic biology. Is there anything special about this emerging field?

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The IDR team thoughtfully concluded that, at this early stage in the field's development, synthetic biology currently poses no unique problems that previous cutting edge advances in science have not. However, the team recommended that it deserves the same level of careful attention. They believe the new discipline should borrow from the existing regulatory frameworks to protect the public and allow the science to proceed, for now. New approaches to ethics training, risk assessment, monitoring and public communication should be developed along the way to address the innovations of a burgeoning discipline.

Risks and Benefits

Many existing technologies lie along the biotechnology continuum, such as the genetic modification of organisms for agriculture, assisted reproduction, and the capacity to sequence the human genome. These have already spurred the exploration of a range of questions about ethics and regulatory policy.

Synthetic biology is another incremental step forward on that continuum. And, like its precursor technologies, the risks and benefits can be categorized as intentional and unintentional—requiring regulations to keep sensitive tools, techniques, and resources out of the hands of bad people and harmful products from getting out of the laboratory.

To that end, similar oversight should be applied to both the final products and processes used in their manufacturing. Regulation should continue to be based primarily on products' properties, suggested the team, regardless of how they are made, or what percentage of natural and synthetic components are involved. If a toxic or otherwise dangerous creation results from synthetic biology, it should be regulated just like any other hazardous material. The team acknowledged, however, that the blurred border between natural and synthetic properties, and the potential for products of synthetic biology to evolve, could complicate intellectual property frameworks in the future.

Precautionary interventions are necessary throughout the production process. Again, policies already in place could be used as guidelines for improved ethics training for students and scientists; monitoring of key tools, techniques and resources to keep tabs on who is doing what with the technology and where; maintaining academic journal standards that scrutinize submitted papers for security implications; and proper disposal of lab waste. The team could not agree, however, whether synthetic organisms should

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include self-destruct mechanisms to prevent uncontrolled spread in the environment. The issue of self-evolvability was also raised, but consensus was not reached as to whether future synthetic biology products could pose unique risks if they evolved at an unprecedented pace and in unexpected directions.

Because developments in technology during recent decades are now routinely used not only in high tech laboratories but in high school classrooms, the tools that can be used for experiments in synthetic biology are widely available. A doctoral degree in science isn't necessary to know how to mix and match genes. Some scientists suggest building new organisms with genetic blocks may be easier than brewing your own beer—or could even be done while drinking that brew. So, in addition to academic scientists, high school students and do-it-yourself garage labs have the potential to create synthetic organisms. The team was unable to agree whether these amateur scientists could, or should, be closely monitored and subject to regulation.

The team recommended that funding agencies continue to support the study of ethical issues related to new science by setting aside about 5 percent of all grant money for examining these and many more issues that could arise—from risks to humans and the environment to possible limitations on its applications imposed by public wariness of the field.

Public Perception and Cultural Context

Public perception will continue to play a major role in the way people respond to news about progress in synthetic biology. The popular media frequently reminds us—and often exaggerates—the risks associated with manipulating nature. The villain in a recent episode of the popular television show, CSI Miami, is an ear of genetically engineered corn; the plot of Jurassic Park was based on genetic engineering gone awry.

While these kinds of portrayals may not accurately reflect the truth, scientists must communicate with the public to alleviate apprehensions that will inevitably arise. People frequently fear what they don't understand. Natural compounds may sound more benign than artificial ones even though the most harmful toxins are completely natural. The team recommends allocating resources toward risk assessment and communication to ensure the public has the right facts, and that the benefits of the new science—from its potential in curing diseases to creating new renewable fuel sources to cleaning up environmental messes—are presented along with theoretical or real risks.

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IDR Team Summary 3

Reconstructing gene circuitry: How can synthetic biology lead us to an understanding of the principles underlying natural genetic circuits and to the discovery of new biology?

CHALLENGE SUMMARY

Genetic circuits have traditionally been studied using genetics and biochemistry. These studies underpin our current understanding of the regulatory wiring diagrams of organisms. They have also revealed that biological components like regulatory elements in DNA, genes, and proteins are intrinsically modular in nature. However, even when we believe we know the list of circuit components and their interactions, this knowledge often fails to explain/recapitulate the mechanism of the circuit. What is missing from these circuit diagrams? How can we infer those missing components if they have not been revealed by traditional experimentation? How can we test what parts of a given circuit are sufficient for a particular behavior? How different are potential circuit designs, that we imagine, from the actual circuit designs that have evolved to solve biological problems?

Due to an enormous expansion in our knowledge about genetic components and interactions in a number of model systems, we are now in a position to pursue a complementary approach to understanding natural gene circuits, based on *reconstruction of genetic circuits.* Specifically, we can engineer synthetic genetic circuits out of well-characterized genetic components and analyze their behavior in cells and organisms. These circuits can be based on their natural counterparts or on theories of how natural processes might work. Equally important, they can be engineered to operate as independently as possible from the corresponding endogenous cellular circuits. Circuits can also be created by "rewiring" existing circuits (adding, deleting, or changing regulatory connections). The goals of studying such

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reconstructed genetic circuits are to understand how different aspects of circuit architecture contribute to function, to determine what functional tradeoffs are inherent in the design of the circuit, and to establish the sufficiency of particular circuit designs for given biological functions. More generally, they provide a complementary path to identifying both particular circuit interactions and general principles of gene circuit operation.

A reconstructive approach to genetic circuits may allow us to design circuits with unique properties and may provide insight into their underlying mechanisms. With a synthetic approach, it may be possible to construct a replica of a particular natural genetic circuit out of well-understood components and monitor its exact function in living cells. Using a synthetic approach, we could test the sufficiency of an arbitrary circuit made up of well-characterized components for generating a particular function. A major advantage to this approach is that we may be able to study the circuit mechanism without impairing cellular functions or inducing downstream consequences which are often drawbacks of traditional perturbation approaches. Finally, different circuit designs with similar functions can be directly compared to determine the precise properties each design grants a network as well as their relative advantages and disadvantages in particular cellular contexts. Ultimately, these studies may provide us with a deep enough understanding that we can design circuits that perform novel biological functions and we can exploit synthetic circuitry to reveal basic principles about natural circuit design.

Nonetheless, the synthetic approach faces many obstacles. For example, while we often know the components in a circuit, we frequently do not have *in vivo* information regarding kinetic parameters (affinities, binding and degradation rates, etc.). How can we infer these values if we cannot or have not measured them directly? Additionally, the intracellular environment is intrinsically "noisy," and small copy numbers of molecular species limit the predictability of biochemical reactions. How can we interpret or predict circuit functions in the face of such noise? Can we devise synthetic circuits that suppress such noise to operate reliably, or take advantage of such noise to enable probabilistic cellular behaviors?

Key Questions

- What are the major advantages and limitations of synthetic circuits as a means of understanding the principles of genetic circuit design?

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- How do we determine the basic principles underlying which circuit architectures can generate particular functions in cells and organisms?
- How do we identify missing components from natural circuits if they have not been revealed by traditional experimentation? How can we infer *in vivo* kinetic values if we cannot or have not measured them directly?
- To what extent can we analyze genetic circuits without comprehensive knowledge of all components and interactions?
- How can we evaluate how a circuit operates in the context of a complete organism?
- What new challenges and opportunities do particular classes of circuits present? In particular, what can synthetic biology do to better understand probabilistic behaviors, developmental circuits, neural circuits, immune circuits, and plant circuits?
- Can we delete natural circuits and replace them with synthetic counterparts within organisms?
- How can we engineer circuits that perform robustly in a noisy environment?
- If synthetic circuits completely fail to work, or work exactly as expected, they may appear to have taught us nothing. How do we develop synthetic projects that are as informative as possible?

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Due to the popularity of this topic, two groups explored this subject. Please be sure to review the second write-up, which immediately follows this one.

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IDR TEAM SUMMARY—GROUP A

By Daniel Strain, Graduate Science Writing Student, University of California, Santa Cruz

It's time for biologists to stop worrying about failure.

The world is a knotty and complex place, and biology in all its criss-crossing parts is the knottiest of all. Synthetic biologists often think they know a genetic circuit, a network of genes that interact to stimulate or repress each other, only to find that in living cells, their lab-built imitations tend to fizzle.

At the National Academies Keck *Futures Initiative* Conference on Synthetic Biology, an Interdisciplinary Research (IDR) team examined how synthetic biologists might stop this fizzle, designing circuits that generate

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the right products at the right time, all the time. But it also explored how scientists can use the unexpected results of a circuit experiment to their advantage. The group asked if a "failed" synthetic circuit could help scientists better understand natural circuits and locate missing genes, proteins or chemical reactions. Can failures help untie the knots?

In many cases, context leads to unpredictability. Two separate cells, for instance, may express even the simplest synthetic circuits in different ways. A circuit that works just fine in muscle cells might shut down when it is expressed in a skin cell. Considerable research in synthetic biology focuses on bypassing the influences of context with modular circuits, circuits that produce dependable, or "robust," results in many contexts.

While complete modularity may not be realistic, there are techniques that biologists can use to make synthetic circuits more robust. Redundancy is one of them. *E. coli* and *staphylococcus* bacteria might like to gobble the same sugar molecule but because they have different promoters, they respond differently to the same stimulus. Many synthetic biologists spend months at the computer or hand-to-pipette designing promoters that respond similarly to the same sugary treat.

But what if scientists want to learn more about context, not bypass it? Context, after all, makes a muscle cell a muscle cell and not a skin cell. The unexpected results of synthetic circuit experiments—which, though unexpected, can certainly not be called failures—can provide important information on the intracellular and extracellular hubbub that makes a muscle cell what it is.

Take a circuit in a hypothetical "grad student" bacterium. In this microbe, morning sunlight activates gene A, which turns on gene B, which turns on gene C, which produces an enzyme that secretes caffeine into the grad student's environment. The benefits of such a bacterium are obvious. From genetic experimentation, researchers already know a little bit about A and C. Their screens found gene B but didn't place it in the caffeine circuit. For all the researchers know, the caffeine circuit consists only of genes A and C. To understand this natural circuit better, the researchers make a proxy circuit, tying a synthetic mimic of A to a mimic of C in such a way that these genes effectively produce caffeine. But before they celebrate over espressos, the researchers want to find out if their synthetic circuit is anything like the real deal.

To do so, the group decided, the researchers will need to swap their synthetic circuit for the natural circuit and see what happens. The group developed a technique called genetic photocopying to achieve this swap.

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In photocopying, researchers give a synthetic circuit a fitness benefit to bacteria, antibiotic resistance, for instance, so that bacteria will prefer the researchers' circuit to their own. As the experimental colony grows and evolves, the synthetic and beneficial A and C will slowly replace the redundant but natural A and C in the bacterial genomes. After the experiment, researchers can take a look at these genomes to see which segments of DNA went missing.

This synthetic proxy technique can show scientists what genes, at minimum, are sufficient to complete a particular cellular function and what the DNA sequences of those genes are. It can't, however, reveal that there's still a missing component to the circuit, gene B. To learn more, scientists need to run a "parameter screen."

Every genetic circuit works within a range of environmental conditions. Viruses like the lambda phage have simple genomes that function like circuits and can only infect certain cell types.

If scientists think they understand the circuitry of a virus like lambda, they can create a synthetic lambda and let it run free among a range of bacteria. If the synthetic virus lyses just as successfully as the natural lambda, it's likely an accurate model. But if it's less effective, scientists will know there's still a missing piece to the puzzle. Scientists can also use the synthetic lambda in reverse—as a probe. If they know it only infects cells with certain types of receptors, they can find these receptors by seeing which cells the virus infects.

The idea of the synthetic circuit as probe isn't limited to viruses and cellular receptors. Scientists can use synthetic circuits as signaling devices for many stimuli across a range of cell types.

The group developed the probe system to look for "noise" in gene expression. Noise describes the random fluctuation in genetic activity that occurs within every cell. It results from the game of chance that governs how often the molecules and proteins that form the machinery of gene expression bump into genes or mRNA strands, setting them in motion. Some cells are noisier than others, and the level of noise can change over time like when a cell undergoes stress or starvation.

Synthetic biologists often consider noise a hassle, making finely constructed synthetic circuits fizzle. But such randomness may be critical to cellular function. The group proposed to test whether the type of random fluctuations of cellular contents changes as an embryonic stem cell differentiates into another type of cell, such as a muscle or skin cell.

The group proposed a noise "decomposer" made of three separate

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circuits that biologist could plunk into a variety of locales, such as zebra fish stem cells. Say biologists have a catalogue of circuits whose functions they know—from previous experiments that went kaput or didn't work according to plan—are either sensitive or insensitive to noise. Scientists could engineer an insensitive circuit to produce a decaying red fluorescent protein in response to chaotic cellular environments, such as unpredictable fluctuations in ribosome abundance. They would then train two increasingly sensitive circuits to produce green and yellow glowing proteins, respectively, in response to medium and low noise levels. Because the fluorescent markers dim over time, scientists can use them to track the randomness in stem cells as they become part of the fish's tail or slippery skin.

The team also proposed assembling a catalogue of instances in which synthetic circuits produce unwanted or unpredictable results called a deviance library. If a research team designed a synthetic circuit that produced caffeine in *E. coli* but failed in *staphylococcus*, that observation could go in the library. The next team that wants to build a caffeine circuit would then know that they should modify the design to get it to work in staph. But the library wouldn't just record that a circuit had failed but also how it failed. With enough "how" data, biologists could begin to decode why circuits, in general, either move full steam ahead or grind to a halt.

A genetic mutation is a biological failure of sorts. Its effects can be good or bad but they're always unexpected. Over time, however, mutations can lead to handy new inventions like the opposable thumb or bat claw. This group concluded that biologists should take a tip from nature and use the frequent "failures" of synthetic genetic circuits as a learning tool.

While robust synthetic circuits have many applications, the best circuits for learning about the natural world aren't entirely predictable. Differences in the way the same synthetic circuit works across contexts, like muscle and skin cells, can help scientists understand what makes those contexts unique. They can help untangle what factors—like noise—make one cell good for running and another suited to a nice tan.

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IDR TEAM SUMMARY—GROUP B

By Tia Ghose, Graduate Science Writing Student, University of California, Santa Cruz

For many biological problems, the instruments used to uncover new connections are scattershot, and sometimes very blunt. To tease out the role of a certain gene, scientists often knock out its function completely, or send it into overdrive so that it produces far more protein than it would in nature. Others blast a cell with a huge amount of a chemical and then measure everything they can to see what turns up. At the 2009 National Academies Keck *Futures Initiative* Conference on Synthetic Biology, an Interdisciplinary Research Team (IDR) charged with "reconstructing gene circuitry" asked: what if synthetic biology could uncover what's really going on in biological systems, in a way that is more precise, informative, and systematic than anything we can do now? The team agreed that a toolbox of controls that precisely dial different parts of a biological system up or down would provide synthetic biologists with significant opportunities to discover new information about living systems.

The group consisted of a diverse set of physicists, engineers, developmental biologists, computational biologists, biochemists, and chemists. Its stated challenge was to determine how synthetic biology can lead to an understanding of the principles underlying natural genetic circuits and to the discovery of new biology. For instance, scientists believe they have a complete list of circuit components and their interactions, yet this knowledge often fails to capture exactly how the circuit works. The team was charged with using synthetic biology to determine what is missing from these circuit diagrams, and how to infer these missing components when traditional

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experimentation fails. The team was also tasked with devising a method to test what parts of a given circuit are sufficient for a particular behavior, and to imagine how circuit designs we construct differ from the actual circuit designs that have evolved to solve biological problems. To begin with, team members suggested several different ways that synthetic biology could answer fundamental biological questions. Can synthetic biology be used to determine the "minimal circuit," or the smallest number of elements and connections that can mimic the behavior of a real network in nature?

Ultimately the team rejected pursuing that path, because nature often creates a tangle of redundant or even dead-end connections between genes, proteins or transcription factors. This redundancy helps keep the network stable in response to changing conditions. So, the simplest network may reveal very little about natural systems. For instance, the fruit fly embryo develops in the presence of a protein called bicoid. A fly can develop normally, even if in the spatiotemporal distribution of bicoid in the embryo changes wildly, demonstrating that it is insufficient to know only that bicoid is important. Obviously there is more to it than that.

The team also raised the idea that synthetic biology could help determine underlying principles that govern cellular behavior. For instance, if all bacteria that use a gradient of chemicals to sense and move toward food rely on a certain fundamental set of genes, proteins, or chemical signals, synthetic biology might confirm that. And if the bacterial genes differ, perhaps the underlying type of network stays the same. Synthetic biology could provide tools to uncover these similarities.

Team members agreed that different scales are likely to play a role in the way network problems are studied. For instance, the approaches used for uncovering how the spinal cord assembles may be completely different from those needed to probe how individual *E. coli* in a biofilm talk to each other. Those will differ from techniques used to examine how proteins bind to each other, inactivate DNA, or change shape. This observation about scale helped the team focus its discussion.

Despite their divergent interests, each of the scientists longed to improve upon some of the sledgehammer approaches of some now traditional genetic technologies. They wanted instead to gently nudge biological systems from their ordinary states and then measure and analyze how these systems respond in real-time. To do that, they converged on the idea of using the electrical circuit as a metaphor for biological connections. Just as electrical engineers send a pulse or an oscillating wave into circuits and then use an oscilloscope to measure the output, biologists need a set of

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tools to precisely perturb natural systems and then observe and understand how they react. These artificial networks could be plugged in to the natural networks to send in different inputs, they suggested. Synthetic tools may also help scientists detect changes.

Tweaking the System

At the level of small molecules, biologists need a way to tune precisely the amount of each chemical in specific sites in the cell (such as the nucleus). They may also want to target molecules to a very specific place within the cell. Being able to control how fast chemicals respond, break down, or change state would also be useful. For instance, green fluorescent protein can take a while to fold into its functional shape, while light can activate chemicals in a flash. Researchers need a way to modulate the time-scale of these reactions, depending on what they are measuring. They need ways to easily modify how fast certain genes are transcribed and translated or how, in real time, promoter regions in genes respond to different stimuli.

On the level of individual circuits, researchers want to peer in as proteins assemble, bind to DNA and regulate its transcription, or when chemical modifications like phosphorylation occur.

For large networks, altering the input into a system without actually changing the way the network is configured is a key goal. Currently, the standard tools for changing gene networks are knockout or over-expression experiments. But these are more like all-or-nothing changes that can't be precisely controlled. Making a gene produce, say, a third as many copies of a protein for twenty minutes, then twice as many for five minutes, is not feasible right now. Because of current technological limitations, the team decided to focus on this smaller scale.

Sensing Changes

Sometimes scientists cannot see what's going on inside a living organism in real-time. If the new tools the team proposed could create subtle and dynamic changes on a fine scale, then scientists may also need better techniques to sense the system's response.

One step would be to remove what the team called the deconvolution problem. For instance, to find out if a certain protein is being made, biologists often add a snippet of DNA that encodes a green fluorescent protein linked to another protein to see if the target protein lights up. But it can

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take many minutes for the protein to be transcribed, translated, fold up, fluoresce, and be detected. Though scientists have rough ways of determining when transcription occurred, the team envisioned using synthetic techniques to know exactly when DNA was transcribed.

It's also important to check that proteins are actually working, not just that all the raw materials are present. For instance, when bacteria build their whip-like tails, it would be useful to know that the proteins are linked together and form functional structures, rather than simply pinpointing them to the same general region. The team envisioned creating a sensor or time-stamp that detected when proteins are assembled. The group's ultimate goal was a "synthetic oscilloscope"—a grab-bag of different techniques that can detect when and how changes occur inside the cell more easily and quickly.

Analyzing Results

With such precise control of what is sent into the system, the team wondered whether the existing tools for analyzing data and formulating experiments might be insufficient. Even though a scientist can test the system with a hundred different inputs, that process is often cumbersome and expensive. Given the explosion of new technologies that a synthetic tool box would provide, new analytical techniques may help researchers focus their efforts and design experiments more efficiently. When the inputs are more finely controlled, it may also be necessary to determine which of the numerous variables should be measured, and with what resolution. Once one experimental system is characterized, those results must be analyzed to help scientists plan future experiments.

Detecting a cell or a network's response may require modelers to develop new analyses of biophysical principles—or even uncover new principles. Another frequently raised issue was the "inverse problem." Many gene networks may make a fish blue, for instance. But once the scientist knows the fish is blue, it can be tricky to figure out which genes led to its coloring. Untangling the results from these much more complicated experiments may require mining existing analytical tools or even developing new ones.

Is Synthetic Biology a Hammer in Search of a Nail?

One question that came up repeatedly was whether synthetic biology is truly better than, or simply complementary to, existing technologies.

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Though existing tools are clearly insufficient for answering many biological questions, the team wondered whether synthetic biology was actually the best way to produce better tools. For instance, researchers could envision the usefulness of creating precise inputs using synthetic biology, but it was less clear that synthetic biology could produce better ways of detecting outputs from natural systems.

Synthetic Swiss Army Knife

The team developed a rough model of how synthetic networks could be linked into biological systems. Their "synthetic Swiss army knife" would be genetically encoded into a cell, complete with simple start and stop buttons that work reliably. These would attach to an oscillator or wave generator whose frequency could be tuned. The team also envisioned adding a noise filter which could make the signal sent into the cell more random. Scientists could link this tool to a real system at various points in the natural network.

By modulating the input functions, a researcher could very precisely control how much messenger RNA is made, how many changes like methylation or phosphorylation are added to a completed protein, or the concentration of proteins or ions in a cell. Many of these different components could be altered at once, or each change could be done sequentially. Using this system, the team could explore a larger range of behaviors in the natural networks, perhaps uncovering new principles along the way.

While synthetic biology is traditionally touted as a way to create tailor-made, artificial biology, its potential for understanding the natural world has not yet been realized. Though a multi-purpose, synthetic biology-based tool as envisioned by the team is still a long ways away, it could ultimately provide a deeper understanding of natural biological systems.

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IDR Team Summary 4

Designing communities of cells: how do we create communication and collaboration between cells to allow for specialization and division of labor?

CHALLENGE SUMMARY

Synthetic biology often focuses on engineering individual strains of microbial or other organisms to implement novel behaviors or metabolic functions in a cell autonomous manner. This approach, while powerful, appears to overlook one of the most basic aspects of biological systems: the ability of different species or cell types to interact with one another in order to generate behaviors that would be less feasible or impossible with a single genotype. In natural ecosystems, consortia of multiple species are commonplace, and many, perhaps most, species are non-culturable in isolation, requiring signals or nutrients from other species to grow. Some metabolic functions may be more efficient when divided between strains, compared to when implemented in a single genotype. Thus, multi-genotype/multi-cell type systems provide an opportunity for specialization and optimization not possible with homogeneous cultures. Two examples of such optimization include the ability to compartmentalize different biosynthetic reactions in different cells that are chemically incompatible with each other, and the ability to create coherent structures that are dramatically larger than the size limit imposed by the dimensions of a cell.

Nevertheless, polycultures present a number of unique challenges compared to monocultures, such as engineering ecological stability (preventing one genotype from taking over the population). Signaling between cells and populations is crucial to organize multiple populations. Clearly, expanding synthetic biology to polyculture systems will require better understanding and control of basic ecological principles, signaling systems, determinants

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of evolutionary stability, population synchronization, and the constraints inherent in complex metabolic pathways. In addition, problems inherent to all synthetic biology projects, such as uncertainty about the effects of a synthetic circuit on host growth rate, or uncertainty in biochemical parameters, could be even more challenging in the polyculture context.

Here we will discuss the key issues, opportunities, and challenges that we will face in efforts to make use of the "parallelism" inherent in polyculture systems.

Key Questions

- How can one engineer self-synchronizing populations, that behave coherently, despite cell-cell variability?
- How do we achieve effective cell communication over multiple length and time scales. For example, what are strategies for cell communication to nearest neighbors, over several cell layers and across an entire culture? How do we design cells to self-organize into defined three-dimensional structures (Example: organs). Temporally, how do we synchronize cell cycles or metabolic states?
- What kinds of metabolic processes are best carried out through the cooperative action of distinct strains, rather than consolidated in a single cell? Are there advantages to spreading out metabolic functions even when the individual pathways involved are chemically compatible with each other? (Example: Chris Voigt's research, www.voigtlab.ucsf.edu.)
- What are optimal strategies for engineering ecological systems that maintain programmable population fractions? How can such a system be made ecologically and evolutionarily stable (i.e., robust to invasion by "cheaters")? (Example: Alexander van Oudenaarden's research, http://web.mit.edu/biophysics; and Wenying Shou's COSMO, see reading reference below.) What applications might exist for controlled multi-population systems?
- Trojan horses: How do we engineer organisms that can invade and flourish in natural populations while altering the behavior of the affected organism/ecosystem in a controlled and desirable manner? (Example: Bruce Hay's work on making elements that invade and spread through mosquito populations while making them resistant to malaria, www.its.caltech.edu/~haylab.)

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IDR TEAM SUMMARY

By Olga P. Kuchment, Graduate Science Writing Student,
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Fixing a broken spine would be a routine operation if we could persuade bone, muscle, neurons, and other players to work together predictably and on cue. But though diverse communities of cells working together are common in nature, many mysteries remain about how they communicate constructively, and how best to work with them to encourage cellular communities to do things on command.

An Interdisciplinary Research (IDR) team comprising scientists in biochemistry, chemistry, computer science, and chemical, biological, and electrical engineering arrived at the 2009 National Academies Keck *Futures Initiative* Conference on Synthetic Biology to consider how synthetic biology might best harness the power of cellular collaboration.

They considered the following: Synthetic biology often focuses on putting into action novel behaviors in independent cells. But in biological systems, different species or cell types interact to generate behaviors that would be difficult or impossible otherwise. Many, perhaps most, species cannot survive in isolation, requiring signals or nutrients from other species to grow. The team discussed how research could best use such behaviors. They also discussed navigating the challenges unique to poly-cultures, in addition to the inherent challenges of all synthetic biology projects.

The team members at first proposed seemingly opposite approaches to the task of designing and engineering communities of cells. Some wanted first to ask what useful systems, machines, organs, or instruments could be built. Others wanted to first consider the properties of interacting pieces: cell types from complex organisms, microbes, enzymes, and structural molecules. Discussion ran the gamut of complexity and abstraction.

The team developed a framework for tackling the problem, and then proposed specific ways that cell communities could be used to clean up waste, improve health, keep plants fed, and explore the Earth or other planets in the next years and decades.

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Why Study and Build Cell Communities?

Cells do certain things well only in company: using hundreds of senses to navigate through life, differentiating from each other, and performing certain types of chemical reactions.

The "company" sometimes includes multicellular organisms or organs. Or it can entail several strains of single cells working together, such as the yeast and bacteria that help humans digest food. Or it might consist of cells all of the same strain, such as bioluminescent ocean bacteria that produce light only when many cells congregate.

Such communities hold frequent "town-hall meetings" to decide what to do, "talking" with each other and testing for a multitude of organisms and substances that a single cell could not detect. They emit light, repair parts, replicate themselves, or spawn off portions to do distinct tasks. Different strains of bacteria are known to produce food to sustain each other, or work together to carry out multi-step chemical reactions.

Working with these cellular companies could fill many gaps in understanding biological systems, team members argued. For instance, it is still not clear how these groups of cells arise in nature and what they need to stay together. Seemingly fragile components form surprisingly robust communities and emerge as symbionts. There are breaks in our knowledge about how such communities age, how they repair themselves, how their constituents interact to reach a common goal, and why one community flourishes while another flounders.

What Kinds of Things Might Be Built?

Communities of cells might help build tiny devices, organic irrigation systems, or textiles. They might help deliver antibiotics or help people grow hair. The group members split into three teams to discuss several practical applications in depth.

Some team members considered the many applications of groups of different species of microbe living in close contact in seawater, in the soil, or elsewhere, known as bacterial consortia. In these consortia, the population of different types of cells changes cyclically over time, but most of the component organisms never disappear entirely.

These consortia could be used as "bucket brigades" to synthesize biofuels or to break down toxic waste, with different strains carrying out sequential reaction steps. They could form better probiotics, restoring microbial

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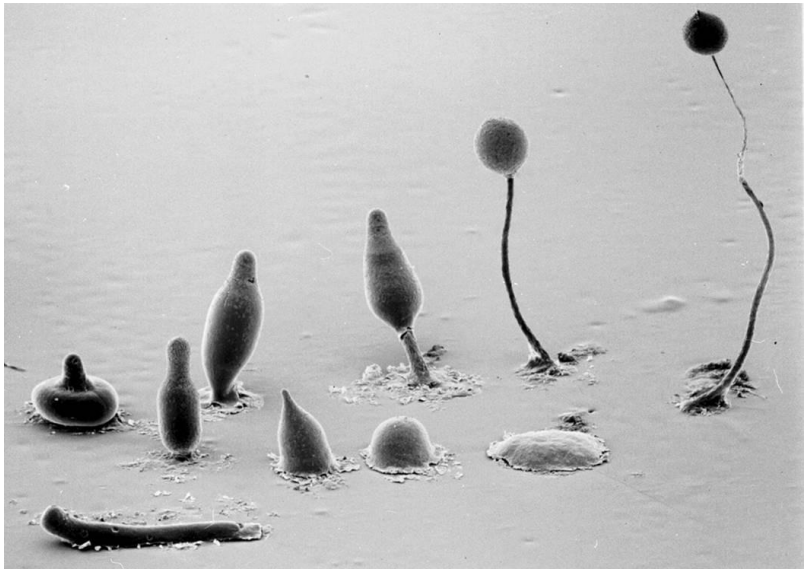
balance to the human gut and helping prevent obesity. Or, they could aid plant digestion, conferring drought resistance. Engineered consortia could serve as models of natural systems. They may also help educate the public about synthetic biology. School children could observe, for instance, how a consortium breaks down sugars at different temperatures and on different timescales.

Another idea is a "land and pond rover" based on the somewhat bizarre life cycle of the well-studied slime mold *Dictyosthelium discoideum,* Dicty for short. A Dicty's individual cells arise from spores scattered in the soil. These cells eat soil bacteria until the bacteria become scarce. The Dicty cells then coalesce into a slug and crawl toward light, heat, and humidity. When the "slug" finds a suitable resting place, its cells change, it develops a stalk and a hat, and eventually produces spores.

The team members predicted that during the next two years, Dicty-like slugs could be commissioned to search for arsenic or gold, then grow into their easily-visible mushroom-like form when they find the substances. During the next fifty years, researchers could engineer these cells to communicate over larger distances, to detect a larger variety of materials and



The life cycle of a Dicty. © Copyright, Mark Grimson and Larry Blanton, Electron Microscopy Laboratory, Department of Biological Sciences, Texas Tech University.

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collect samples, and to spawn off slugs to test for various things, including living organisms. They could test for biodiversity, profiling the cells they find and collecting samples.

The team considered building artificial organs. Engineered to be hypoallergenic, these could allow for a mass production of personalized organs. Their novel and broad functions could also be useful for medical testing. In a single artificial organ, one might screen potential drugs for both toxicity and permeability.

For instance, group members proposed the idea of a "kliver," a kidney-liver hybrid. An independent "kliver" could help filter bio-compounds out of drinking water. It could conceivably grow from an easily-shipped sample of a few cells that would regenerate when needed. One could also imagine how a riff on both organs' detox capabilities and the liver's ability to synthesize proteins could benefit a human body.

How Would We Build Them?

Having proposed the applications, the team considered anew whether what they envision would actually be possible. Potential building blocks might be mammalian and microbial cells and their products, such as slime, fibers, small molecules and proteins. The cells might be engineered to hold new electrical, mechanical, and chemical powers. For instance, their genetic circuits might allow the use of a laser or radio-waves to communicate with each other. The cells might be further changed and molded externally and internally, by engineering their environment and by synthetic parasites designed to accomplish specific cellular changes.

When placed together, the building blocks might be designed to become even more aware of each other, to communicate even more effectively. They might be taught to recognize invaders. The different cell populations might be designed to fluctuate, with the different components feeding off each other's byproducts and helping keep each others' populations in check. Cells would be programmed to degrade their organs and DNA if they began to invade other organisms or the environment. A genetic "kill switch" aims to stop contamination or infection.

The communities would be capable of things that singletons are not: They could generate force, specialize, rearrange, build large structures, spawn, and move as a collective. They would use these behaviors toward the overall goal.

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Moving Forward

The group decided that the field is ready to move forward, and that enough building blocks exist to begin work on the applications they suggested. Starting work would teach researchers about any additional requirements. The group members foresee building and exploring different architectures as an important challenge when moving toward their goals. They agreed to start work on simple proof-of-principle systems, but also to start moving from "toys to products"—creating commercial products to bring tangible benefits to society. They wondered what the first commercial product to employ communities of cells would be.

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IDR Team Summary 5

Why are human-designed biological circuits and devices fragile and inaccurate relative to their natural counterparts?

CHALLENGE SUMMARY

Three characteristic features of natural biological systems are robustness, adaptability, and redundancy. Natural systems are remarkably resistant to failure induced by changes in component abundance or activity (robustness), yet they maintain an underlying flexibility required to allow them to adjust to new environments (adaptability and redundancy). By contrast, many synthetic systems lack robustness, especially when compared to their natural counterparts that perform a similar task. Adaptability and redundancy are typically not considered. Two examples of synthetic systems that lack certain aspects of robustness are:

1. Ajo-Franklin et al. (see reading references) designed and characterized an elegant memory device in yeast that is based on a synthetic transcriptional cascade. This device does exhibit memory, but is sensitive to dilution of the autoactivator component during growth and requires "tuning" of growth rate by changes in media to maintain bistability.
2. Elowitz and Leibler (see reading references) constructed an oscillator based on a transcriptional cascade and found that only a fraction of cells exhibited oscillations; additionally, they observed significant variation in the period and amplitude between cells in a population. In comparison, the transcriptional oscillations associated with the circadian clock are far more robust.

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What can we learn from comparisons of designed systems and their natural counterparts?

Comparison of synthetic systems with those of their natural counterparts can be extremely informative—such studies sometimes provide insights that can be used to improve the function and design of engineered systems. Additionally, these comparisons can reveal the presence of previously unappreciated complexity and phenomena. Such an example comes from the Elowitz and Leibler study mentioned above, where these authors recognized that the oscillator was "noisy" and speculated that such noise might arise from stochastic fluctuations in transcription in cells. This observation was the motivation for the development of what turned out to be a highly influential method for quantifying stochastic fluctuations in gene expression, and the demonstration that transcription in *E. coli* is indeed noisy.

Can we harness the power of evolution to shape and design more robust systems?

The forces of evolution shape natural systems. In the process of natural selection, a population of cells or organisms effectively explores parameter space in a manner that allows for the discovery of biological circuits that are robust, adaptable and redundant. In contrast, many efforts in synthetic biology are engineering-based and exploit the modular nature of biology to assemble functioning circuits from sets of well-characterized component parts. It will be interesting to see if it is possible to use experimental evolution to discover or tune synthetic circuits that exhibit robustness, adaptability, and the redundancy seen in natural systems.

Key Questions

- What are "design principles" observed in natural circuits that have not been implemented in synthetic circuits and that may increase the reliability and robustness of engineered circuits?
- How can these new design principles be most effectively implemented into human-designed circuits? Are new tools required?
- Are new characterization methods and strategies required in order to measure properties such as robustness and adaptability?
- How can evolution be effectively integrated as a design principle into synthetic circuits?

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IDR TEAM SUMMARY

By Stephanie W. Schupska, Graduate Science Writing Student, University of Georgia

"The inherent complexity of biological systems defies reliable engineering today. Engineering needs iteration and debugging: It is too early for definitive comparisons to nature—and to make this judgment because we know too little about nature and how natural systems are designed. Our tools for synthetic systems are still rudimentary." This was the conclusion an Interdisciplinary Research (IDR) team came to after intense discussion

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coupled with creative tension and brainstorming to answer the question: Why are human devices fragile and inaccurate relative to their natural counterparts?

In addition to thinking about fragility, the IDR team also spent its time at the 2009 National Academies Keck *Futures Initiative* Conference comparing human-designed devices with the three characteristic features of natural biological systems: robustness, adaptability, and redundancy. Natural systems' resistance to failure is achieved by changes in component abundance or activity (robustness). At the same time, they maintain the flexibility they need to adjust to new environments (adaptability and redundancy). In contrast, many synthetic systems lack robustness, especially when compared to their natural counterparts that perform a similar task. Typically, adaptability and redundancy are not considered.

But the meeting of the minds—ranging from professional engineers, media lab scientists, physicists, synthetic biologists, and others—didn't stop with its conclusion that it's too early to compare synthetic systems with nature. The team went into detail about three specific areas likely to drive the field of synthetic biology in the future.

First, they discussed the trade-offs that could lead to fragility in human-designed circuits, which they said comes in part from unplanned interactions. This boiled down to the question of whether the engineering approach itself—and its rigidity—is the source of fragility.

Secondly, they considered how to systematically (and more efficiently) construct robust circuits. They decided a wind-tunnel-like testing ground and a rapid comparisons approach were the best route to take.

Finally, they decided that the study of the failure modes of existing systems was a good way to derive design rules.

The team also discussed the possibility of either holding a contest that would specifically address synthetic biology or funding a new section of the iGEM competition. iGEM, which stands for International Genetically Engineered Machine, is a biological challenge considered the premier student synthetic biology competition.

Source of Fragility

Synthetic biology is still in its earliest stages, much like the first bulky transistor compared to the current multi-trillion transistor model of today's Internet. Even now many scientists are unsure how the World Wide Web really works. In the same way, we've just barely begun to touch on what

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can be achieved through synthetic biology. Because there is still a deep gap between what can be envisioned and what can be accomplished, getting human-made circuits to work as well as natural ones continues to be a problem. Whether that is because the engineering methods for new circuits are still unreliable, or because the approaches themselves are basically faulty, remains to be seen.

For example, is modularity (a concept found extensively in complex engineered systems) the problem, or is it the specific ways that engineers want to introduce orderly structure into their designs? While biology exhibits a variety of forms of modularity, the discussion in the meeting focused more on whether the sort of modularity that engineers typically introduce in their designs might not be appropriate in synthetic biological systems.

When it comes to engineering new circuits, suboptimal design often results in decreased efficiency and performance. But does the modularity used in these designs lead to an increased fragility of the system? The group's answer was no. There's no obvious change in fragility as a result of modularity. However, they did consider whether more interfaces equal more fragility, but found that is a difficult question to answer, specifically because it is unknown what exactly confers robustness to natural systems.

The following options were considered in trying to understand robustness and what confers robustness on natural systems:

- Redundancy
- Distributed architecture
- Plasticity (adaptability)
- Flexibility/noisiness of individual parts

Nature is messy, but it works. Because nature often exploits variations in noise to get the job done, it's something that must be considered in synthetic biology, and considered not necessarily as a frustrating, undesired element but an essential (or useful) one.

Wind Tunnel

When it comes to making synthesized biological circuits more accurate and less fragile, the IDR team decided a more detailed analysis of the engineering approach is needed. But, first, let's take another look at the Internet example, and how a future system could work.

Scientists in the 1950s brought us the first transistor, a messy-looking

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system that somehow worked. About 1969, these tiny, interconnected devices brought us the beginning of the incredibly robust and useful Internet. Its path is a story that engineers constantly look to. The question they ask is "how are we going to do a similar engineering feat in the future?" The answer, many believe, lies in synthetic biology.

Right now, it's nearly impossible to take unreliable biological pieces and create extremely reliable systems from them, especially when scientists don't yet understand the biological pieces they are working with at the level of the first transistor. Understanding is more along the lines of Benjamin Franklin looking at a sparking Leyden jar, trying to figure out what causes electricity.

And they want to add a wind tunnel to the sparking jar. The goal is to understand what things can mess up a circuit by looking at each circuit in a one-at-a-time, principled way—perhaps in something like a wind tunnel.

Wind tunnels are commonly used to test aircraft, automobiles and other aerodynamic structures for both their strengths and their flaws. A wind tunnel in synthetic biology is still more of a concept than a real testing ground, but researchers are optimistic.

A wind tunnel would allow them to develop carefully characterized test environments for measuring the functionality of cell-free extracts, which are liquids that contain cell parts but no intact cells, and minimal cells, which are artificial cells that contain the smallest number of parts a cell needs to exist. They could systematically test designs in the presence of known troublemakers, such as more complex systems, and redesign based on an understanding of what went wrong.

They could also test the circuit they've built inside a cell, and, if it works, stop there. If not, they could update the environment around the cell to add in additional useful affects.

An example of this is in trying to develop a stable oscillator for mammalian cells. First, one would start with a few designs for oscillators. Next, these would be tested in a cell-free extract and then in increasingly complex environments until something breaks or meets the researchers' specifications. Finally, the circuit would be placed in an actual cell and tested. The "wind tunnel" test environment would be adjusted as needed.

Rapid Comparisons

Unlike the wind tunnel approach that looks at one circuit at a time, rapid comparisons would allow researchers to compare different compo-

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nents to see which work better. Using the stable oscillator for mammalian cells as an example, rapid comparison would look for combinations of circuit elements for oscillators. These could include activators, repressors and combinatorial promoters. Circuits would then be rapidly introduced into mammalian cells, in a way that allows comparisons (for example, control integration loci). The oscillators produced would go through a high throughput screen. A smaller number of the best oscillators would be selected and then analyzed in detail.

Oscillators aside, the process would work like this: Researchers would generate a component library and architectural alternatives for whatever function they desire. These would be a group of component properties and preselected architectures. They would construct all the possible combinatorial circuits from the library and architectures, introduce these into cells and check for function. They would then compare not only the performance of the circuit, but also look for robustness and other desired characteristics. Finally, they would analyze and explain the winning circuits.

Usually, with the outside forces of the directed evolutionary process, scientists don't know why a system works. There's no control over or full understanding of the final product, something that engineers (and many other scientists) find to be a frustrating challenge. The rapid comparisons approach would simplify the problem of what directed evolution did to the circuit.

The whole idea is wrapped in two answerable questions: Why is the winner robust, and why were the losers not?

Failure Modes

The group wanted to understand what a failure is in biological engineering by first defining success. It's not good enough if it gets me a publication, they said. The system has to meet a set of performance metrics.

So, what are performance metrics in synthetic biology? They include duration of operation, homogeneity, and robustness to external variations. Failure is when one or more of these are not met. Finding out why is the hard part.

Enter the systematic approach to failure analysis. How long will a system operate before failure and why does it fail are questions that need to be answered.

This mode of experimentation requires researchers to take a subset of engineered groups, run their systems until they break and examine why they

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break. Part of this approach's goal is to figure out what the cell's mechanisms are for breaking the systems that researchers are trying to build. The next step would be to redesign some of the systems and increase their genetic stability.

The failure mode frameworks they suggested involve performance timescales, metabolic load, noise, intrinsic versus extrinsic versus crosstalk failures and dependence on system size.

They suggest four types of experiments to test failure mode:

- Studies of genetic stability as a function of load.
- Comparison between analogous natural and synthetic systems.
- Case-by-case analysis of extrinsic interference.
- Host optimization to improve robustness.

Grand Challenge

In 2004, the DARPA (Defense Advanced Research Projects Agency) Grand Challenge dared contestants to build a vehicle that could make it across the Mohave Desert. The first year, everyone failed. The second year, five vehicles made it across. The third year, teams were faced with an even more complex problem: To drive an unmanned vehicle 60 miles through an urban area while obeying all traffic signals. The prize was $2 million. Six teams finished.

A biological challenge called iGEM already exists. For the contest, student teams work with a kit of biological parts and new parts they design to build biological systems and operate them in living cells. Unfortunately, the competition doesn't take aim at robustness, research on which is sorely needed in synthetic biology. The group proposed a contest based on robustness. It could either be incorporated as a part of iGEM or introduced as a new grand challenge.

It would involve, for example, students making an oscillator, placing it in a plasmid and then testing that oscillator in 10 different strains of *E. coli* and seeing which one works best. The challenge, like the DARPA Challenge, would be fine-tuned from year to year as progress is made.

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IDR Team Summary 6

How can genomics be leveraged to develop coherent approaches for rapidly exploring the biochemical diversity in and engineering of non-model organisms?

CHALLENGE SUMMARY

The spectrum of biological organisms on earth provides an extraordinary repertoire of biochemical synthetic and signal processing systems that can be borrowed intact or modified to accomplish synthetic biological goals. Such efforts depend on a detailed understanding of the reactions that an organism carries out as well as the molecular players (e.g., proteins and metabolites) responsible for conducting these reactions. For compelling technical reasons, most molecular dissection of biological systems has focused on a bedrock group of five model organisms which include fruit flies, bakers yeast, roundworms, *E. coli*, and mice; the vast majority of breakthroughs in modern biology has come from work on these systems. There are a few other organisms like arabodopsis (mustard weed), zebrafish, and the frog *Xenopus laevis*. However, it requires a huge investment of time and resources to turn a wild organism into an experimentally tractable system, so researchers naturally try to get the most mileage out of the model organisms we already have. While understandable from a practical point of view, this focus comes at an enormous cost, as many of the most desirable reactions are not found in the common model organism. For example, none of the "big five" are able to directly harness energy from light through photosynthesis. Yet photosynthesis is the keystone of biofuels efforts.

The emerging field of metagenomics promises to help overcome this limitation and allow us to better exploit the full biological diversity of the world we live in. Metagenomics takes advantage of the revolution in DNA sequencing technologies to define genetic material recovered directly from

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environmental samples. Traditional microbiology studies cultivated clonal cultures. Metagenomics, in contrast, enables studies of organisms that are not easily cultured in a laboratory as well as studies of organisms in their natural environment. One of the first results to come from metagenomics was the realization that species identification efforts based on organisms that can be cultured had vastly underestimated the true level of biodiversity. While this conclusion is well accepted, identifying and exploiting the mass of information obtainable from these new life forms represents a major challenge and one that we are only now beginning to address.

Automated DNA synthesis has rapidly improved in fidelity, length, speed and cost. This enables the nucleotide information from sequencing and metagenomic efforts to be converted into a physical DNA sequence without the exchange of genetic or cellular material. So-called synthetic metagenomics refers to mining of databases for functional sequences, the "printing" of this information, and screening for function. This methodology will revolutionize enzyme/pathway/genetic circuit discovery, sequence-function mapping, and annotation of sequences. Novel bioinformatic methods will be needed to identify genes to be synthesized and to analyze the functional information.

A number of applications could require the forward programming of meta communities. Understanding the natural language and metabolic interdependencies of natural communities will aid in this process. Natural systems will yield more quorum sensing circuits that enable multiple channels by which cells can be programmed to communicate. Understanding the metabolic origins for symbiosis will enable multiple cells to be programmed to interact in a fermenter to achieve stable populations and predicable product titers.

Key Questions

- How do we identify environmental sources for metagenomics analyses that are most likely to contain organisms capable of novel biosynthetic strategies that will be of immediate value to synthetic biology efforts?
- How do we identify novel synthetic and signal transduction pathways from genomic information alone even when we are not able to culture a given organism? For example, comparative genomics, analysis of the environmental conditions in which organisms are found, metabolomics on polycultures.

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- Are there general strategies for increasing the spectrum of novel organisms that can be cultured?
- For those organisms that can be cultured, can we build a robust toolkit for establishing the basic infrastructure needed to carry out systematic functional analyses of that organism to identify novel biosynthetic pathways? For example, rapid strategies for creating collections of tagged and deleted strains. Integrated use of microarrays, proteomics, and metabolomics.
- When it is possible to identify valuable biosynthetic pathways, how can the machinery responsible for this new chemistry be systematically identified, transplanted and modified to enhance synthetic biology efforts?
- Are there general principles of polyculture life that can be revealed by metagenomics which will aid efforts to create robust, optimized polycultures for synthetic biology efforts?

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IDR TEAM SUMMARY

By James Berdahl, Graduate Science Writing Student,
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The field of genomics is in the midst of an explosion. As DNA sequencing becomes faster and cheaper, the genomes of various species are being completely sequenced in increasing numbers. New data are accumulating at astonishing rates. New techniques have given rise to new possibilities. Metagenomics, the analysis of genetic material gathered from environmental samples rather than from individual species, has given researchers the opportunity to look beyond the petri dish, beyond culturable cells, to the immense diversity of life in the world around them.

For compelling technological reasons, most molecular dissections of biological systems have focused on a bedrock group of five model organisms: fruit flies, baker's yeast, roundworms, *Escherichia coli* (*E. coli*), and mice. Scientists have accomplished a great deal despite these limitations—many breakthroughs in modern biology have come from work on these systems—but there is much left to explore. Only in the past decade, for example, has the genome of a photosynthetic plant been sequenced.

In the face of the great potential unlocked by metagenomics, an Interdisciplinary Research (IDR) team of scientists at the 2009 National Academies Keck *Futures Initiative* Conference on Synthetic Biology thought about how best to use the technique to explore the Earth's biosphere to discover its novel functions. The team began by reviewing issues that researchers have with gene databases, which already contain a wealth of undiscovered genes.

GenBank is one such database. Funded and maintained by the National Center for Biotechnology Information, it is a library of publicly known genetic sequences and the proteins they encode. It currently contains more than 100 billion nucleotide pairs from more than 150 million measured sequences; it is a valuable resource for researchers throughout the world of genomics and beyond. But it's far from perfect. Data are flooding in, though with no quick way of identifying functional sequences of DNA amidst the rest of the A's, T's, C's and G's, researchers are left with a tremendous amount of information to wade through. Within the database, annotations of gene function are often inaccurate, and though they can be corrected, doing so presents an awkward task that can further propagate errors. Complicating this, more than a third of GenBank consists of domains

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of unknown function, stretches of DNA that have yet to divulge their purposes, if they have any at all.

Current DNA sequencing techniques, which are still being improved, contribute to the problem because they sacrifice accuracy for efficiency. Error rates of one incorrect base pair for every 1000 seen in early sequencing methods have risen to as high as three for every 100 in more modern, faster techniques. Because just one erroneous nucleotide can radically alter a resultant protein's structure and function, such error rates can be difficult or impossible to work with. Complicating things further, repetitive DNA sequences in a genomic sample can combine with the short read lengths generated by these rapid techniques to produce overlapping sequences that aren't actually found in nature. But developing better DNA sequencing is hardly a new idea; the search for new techniques is ongoing, and the task itself wouldn't exist without the breakthroughs that have already been made.

Still, the massive accumulation of unchecked data in GenBank has led some researchers to refer to it, half jokingly, as a "write-only" database; only a small fraction of what pours in is currently ever recalled and used. Improved annotation methods would allow researchers to quickly locate proteins based on function, giving them the chance to properly explore the tremendous amounts of genetic information that we have already collected before they turn their attentions and resources to the genomes of the rest of the world.

The problem with annotation, however, is that it is difficult to verify. Sequences in GenBank are annotated either by the researchers submitting them or by automated software that determines their function based on similarities with other sequences. There's no guarantee against mistakes. The only way to know for sure what a given patch of DNA will do is through direct testing and wet biochemistry—inserting the sequence into the genomes of culturable cells and growing them to see what happens, then purifying whatever protein product might be produced and testing it *in vitro* to confirm or discredit a suspected function. Obviously, this presents something of a bottleneck when looking at billions of potential genes, so unless cheaper and faster methods of wet biochemistry are developed, a different approach is needed. The Holy Grail of automated annotation would be a program that could, given an input of A's, C's, T's and G's, use the physical properties of all the atoms involved to calculate the sequence, structure and function of the resultant protein, but such a program is a long way off, if it's possible at all. For the moment, it is prohibitively difficult to even model water at such

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a detailed level. A different approach in making annotations more effective would be to streamline the searching process by organizing proteins on an evolutionary basis, thus grouping classes of structure and function and making newcomers easier to identify. Again, though, this technique presents a bottleneck because researchers with special knowledge are needed to set up the database's new structure and classify the constant deluge of incoming data. For the immediate future, annotation might be most improved simply by making adjustments to the process itself, allowing users to more easily and concisely correct erroneous data that they find in GenBank.

Moving on from data management problems, the IDR team agreed that the most pertinent problem scientists face in adapting metagenomics for use in synthetic biology is the issue of how to best search the biosphere for new genes or those with specific genetic functions. The problems here are varied.

One technique would be bulk geographic sampling, taking metagenomic samples across a planetary grid or taking representative samples from different ecological regions, but the team deemed such a comprehensive method impractical at best; apart from being logistically intensive, it would simply be adding to the scores of unexplored genetic data that we already have, unless these data passed through the bottleneck of wet biochemistry. The question was also raised of how useful such a program would ultimately be. The extent to which the overall genetic picture varies from one environment to another is not known, so a metagenomic sample from a swamp in Brazil, say, wouldn't necessarily contain genes with much novel function compared to a field in Mongolia. But then again it could. Knowing how the diversity of genetic function relates to biodiversity is thus an important precursor to any attempts at more extensive environmental sampling.

The team outlined a straightforward plan to test this. By sampling a kilogram of soil from each of ten sites in differing ecological zones around the world, one would have a very rough approximation of the Earth's diversity. For more direct processing, these samples could be analyzed with metabolomics—analysis of the chemical signatures of the biological activity in the samples. Once such a test was completed, it would quickly divulge whether or not further geographical sampling might be an effective method of bioprospecting. It would also point to which, if any, environments harbor greater concentrations of genetic diversity.

It was generally agreed that such an experiment would find at least some differences in genetic function, so the team discussed which environments were most likely to harbor unique functions that would be useful for

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human application. These included toxic waste sites, where organisms living along a gradient of increased toxicity can evolve mechanisms to deal with the toxin in question. The functions of these organisms that allow them to survive could be exploited in other organisms to allow them to survive in similar environments, and even to clean up those environments.

In any case, the discussions of the IDR team touched upon many aspects of metagenomics, resulting in interesting suggestions for colleagues in synthetic biology to consider, from better database management and technology to the development of rational, inexpensive methods of targeted environmental sampling to exploit the diversity of the natural world. If better sense can be made of better incoming data, the field of metagenomics will come closer to realizing its incredible potential.

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IDR Team Summary 7

How do we move beyond genetics to engage chemical and physical approaches to synthetic biology?

CHALLENGE SUMMARY

The controlled manipulation of genetic information constitutes the "standard model" of synthetic biology. But biological behavior is subject to control at many levels, and biological systems respond to a wide range of chemical and physical stimuli. As cells and organisms adapt to their environments, they change the genes they express, the chemical substrates they use and the metabolites they produce. They respond to changes in temperature, pH, and ionic strength, to light and mechanical forces, and to many other chemical and physical signals. Researchers interested in creating new biological function can therefore draw on a set of tools that extends well beyond genetic manipulation.

Recent advances in chemistry, physics, and engineering have provided powerful new routes to novel biological behavior. Chemists have demonstrated the capacity of cells and organisms to use non-standard substrates, including amino acids, fatty acids and sugars that don't occur naturally. Non-standard nucleotides can be processed with high fidelity by DNA polymerase, non-canonical amino acids are readily incorporated into natural and artificial proteins, and novel sugars and fatty acids have been used to probe post-translational modification on a proteome-wide scale. Engineering of proteins and pathways has extended the diversity of substrates and products still further.

Physical tools such as patterning of cells on surfaces, microfabrication of three-dimensional cellular structures, and microfluidic delivery of proteins and other soluble factors also create significant opportunities

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for control of biological function. Such tools will become increasingly important as synthetic biology embraces more fully the design of complex multicellular systems.

Key Questions

- What are the most promising approaches to chemical and physical control of biological function? Inhibition or re-wiring of cellular pathways? Introduction of light-sensitive or mechanically-sensitive components? Others?
- Which cellular pathways are most promising with respect to control by chemical and physical means?
- What advantages might accrue from the development of novel chemical substrates (e.g., "abiological" nucleotides, amino acids, sugars, and other biosynthetic intermediates) for use in synthetic biology?
- Can we create organisms that prefer or even require altered sets of molecular substrates? If so, what kinds of biological behavior might emerge from such adaptations?
- To what extent can we change the properties of biological macromolecules? Will such changes allow us to overcome some of the most important limitations of macromolecular therapeutics or industrial enzymes (e.g., sensitivity to proteases, surfactants, or dehydration)?
- How can control of spatial relationships among cells contribute to the engineering of novel biological function?
- Are there advances in bioreactor design and micro- and nano-fluidic technologies that should be brought to bear on problems in synthetic biology?

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Due to the popularity of this topic, two groups explored this subject. Please be sure to review the second write-up, which immediately follows this one.

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IDR TEAM SUMMARY—GROUP A

By Sonya Collins, Graduate Science Writing Student, University of Georgia

The words MEN AT WORK alert passersby that construction is underway. While we see cranes conveying steel beams, concrete pouring forth from trucks, and people working, we are unconsciously aware that those at work here are not the ones who designed the building under construction. The building was designed by architects who constantly seek innovations to push the limits of what can be built.

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Synthetic Biology: Building a Nation's Inspiration: Interdisciplinary Research Team Summaries

Synthetic biologist Drew Endy, assistant professor of bioengineering at Stanford University, recommends that synthetic biology adopt the paradigm of building construction: that the work be divided between designers and builders working independently of one another. This analogy drove the discussions of an interdisciplinary research team (IDR) at the 2009 National Academies Keck *Futures Initiatives* Conference on Synthetic Biology that grappled with the challenge of devising chemical approaches to synthetic biology in order to push the limits of biology.

The construction analogy, in fact, serves multiple purposes in illustrating both the need for synthetic biology and the challenge to this team, which asked: How do we move beyond genetics to engage chemical and physical approaches to synthetic biology? While the "standard model" of synthetic biology is to manipulate genetic information, synthetic biology is not limited to this approach. One team member noted that construction once relied only on the elements found in nature—trees for lumber, mud for bricks, granite for blocks—and, thus, construction was restricted to what builders and designers could do with these materials. Today synthetic materials allow builders and designers literally to reach heights that nature has not: the construction of skyscrapers in cities and work stations on the moon.

Reliance solely on biological elements limits problem solving capacities in science as in construction. In addition to their capacity to reach beyond the limits of nature, synthetic materials possess predictable properties and, by definition, can be designed, engineered and programmed by man. The team explored means to develop new tools for synthetic biology, like new construction materials, with the goal of exploiting the renewability and evolvability of biology to synthesize non-biological materials that will improve the likelihood that synthetic biology will produce useful products for medicine, the environment, and other fields of endeavor.

The team approached the challenge by asking "What are the best ways to go beyond natural molecules to augment the central processes of life?" They identified several goals, each of which was based on orthogonal functions, meaning functions entirely separate from and not interacting with existing biological function. The goals were presented in a final presentation as follows:

- Orthogonal Performance: Augment cells to include new macromolecules with new and desirable functions.

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- Orthogonal Encoding: Program molecules other than DNA and RNA to encode information.
- Orthogonal Compartmentalization: Design sub-cellular compartments containing pathways separate from the cell's own machinery.
- Orthogonal Interactions: Engineer organisms and molecules to interact with each other or with engineered devices.

These goals are bound by the need for scientists to learn how to synthesize, evolve, and organize non-biological polymers efficiently and with high fidelity. Noting that research into orthogonal interactions is currently taking place, the team further explored the prospects of orthogonal performance and compartmentalization and recommended that orthogonal encoding is also worthy of future research.

Orthogonal Performance

An ability to code for and select a novel function of a synthesized molecule from a library of genetically encoded compounds could greatly assist in finding new therapeutics. Introducing new genetically encodable synthetic molecules into a cell to perform desired novel functions could allow for the production of new pharmaceuticals. For example, in order to achieve a therapeutic effect, a drug must be designed to resist degradation or rapid metabolism. Because the body tends to degrade natural biochemicals much faster than it does unnatural compounds, it is advantageous to incorporate unnatural chemical groups into drugs. For this to take place on the ribosome—the cell's protein factory where the compounds will be synthesized—incorporation of synthetic amino acids must be allowed. The ribosome possesses an amino acid-polymerizing active site that must be engineered, or mutated, to selectively accept new substrates with high efficiency.

Several areas, however, still need research. Because mutation of the ribosome polymerization center could kill the cell, the solution would require that ribosomes be synthesized in a cell-free system. However, *in vitro* transcribed ribosomal RNA from which ribosomes are made lacks between 1 and 6 critical chemical modifications required to synthesize ribosomes in a cell-free system (see figure). The team then proposed modifying *in vitro* transcribed ribosomal RNA with known and recently discovered enzymes (highlighted in the figure below)—or with crude cellular extract that contains these enzymes—then selecting desirable ribosome mutants based on their evolved function.

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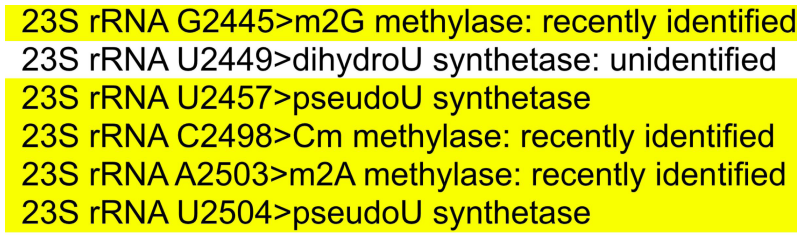

Figure adapted from Forster, A.C. and Church, G.M. (2006). Towards Synthesis of a Minimal Cell. *Molecular Systems Biology*, 2(45), 1-10.

Orthogonal Compartmentalization

Compartmentalization of biochemical pathways would provide a safety mechanism for compounds, such as therapeutics, manufactured using synthetic biology by ensuring that new synthesized functions would not interfere with the biological functions of the cell. The team recommends exploring and synthesizing novel molecules that promote orthogonal compartmentalization, such as a series of fluorolipids—fatty acid-like molecules that contain a fluorocarbon chain in place of a hydrocarbon chain—that would organize themselves into compartments and be easy to track inside cells. These lipids would differ in length, level of saturation, and level and position of fluorination. Researchers could test the extent to which each one is presented by, and sequesters on, the surfaces of mammalian cells. Once a set of fluorolipids with desirable properties is identified, the team proposes re-engineering lipid biosynthesis pathways to enable their biosynthesis. An alternate solution would be to engineer viral capsids that sequester biosynthetic pathways.

Additional Areas for Future Research

In addition to their exploration of orthogonal compartmentalization and performance, the team concluded with the following outline of areas for future research:

- Orthogonal information coding. Use synthetic (nucleic acid or protein) nanostructure to augment genomic information, for example, to create novel scaffolds for transport within the cell or to organize other molecules (such as a nonribosomal peptide synthetase pathway).

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- Adapt other biopolymers to possess an encoding function such as proteins with base pairs to organize their function.
- Design lipids that respond to enzymes, light, chemical signals, magnetic or electric fields and change their segregation properties.
- Develop modules that translate signals into genetic or regulatory events (much like the way membrane proteins sense changes in lipid structure).
- Develop morphogens that respond to an engineered device. Explore guiding cell fate in a spatially controlled way, perhaps even in three dimensions.
- Design orthogonal communication pathways. Explore developing a community controlled by nucleic acid sender-receiver systems.
- Develop specific surface interactions to direct connections between cells and engineered devices.

Synthetic biology is too young for us to know to what ends current research may one day be used. However, we do know that we are not bound by the limits of nature or genetics. The work of this team only begins to illustrate the ways in which synthetic biology can reach across disciplines to achieve greater control of biological functions and one day more fully reflect the design of complex multicellular systems.

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IDR TEAM SUMMARY—GROUP B

By Brandon R. Reynolds, Graduate Science Writing Student, University of Southern California

While genetic engineering presents many possibilities for programming cells, it must play by those very rules that govern biological development—namely, those that drive mutation and, by extension, evolution. A scientist can fabricate a totally unique cell, either by modifying existing genomes or inventing new ones, but every generation spun off that initial engineered one always runs the risk of taking off in some other direction: evolution up to its oldest trick. So as life tends to avoid stagnation through mutation and other variability, scientists must look for other strategies for influencing and controlling cellular behavior.

As physician and author Lewis Thomas wrote:

> The capacity to blunder slightly is the real marvel of DNA. Without this special attribute, we would still be anaerobic bacteria and there would be no music. Viewed individually, one by one, each of the mutations that have brought us along represents a random, totally spontaneous accident, but it is no accident at all that mutations occur; the molecule of DNA was ordained from the beginning to make mistakes.

With the unpredictability of genomics in mind, an Interdisciplinary Research Team (IDR) at the National Academies Keck *Futures Initiative* 2009 Conference on Synthetic Biology was asked: How can cells be influenced or controlled without rewriting their genetic blueprints?

It's a tricky question. As the team discovered in its discussions, the appeal of genetic engineering is strong. In proposing potential solutions to hypothetical problems, often the team found that manipulating DNA really is the easiest way to solve the problem. Consequently, their thinking got more creative and the two solutions proposed got fairly unorthodox.

It helped to think of the disadvantages of genetic engineering, and devise solutions around them. Aside from being prone to mutation, genes that are genetically modified can be very difficult to integrate into a cell. And once there, for better or worse, changes are heritable, and can be transmitted to future cellular generations. Lastly, the technology to create these changes is not portable; in other words, there is not a standard tool that will reliably engineer the same kind of change in each kind of cell's DNA.

The team's solutions involved creating agents to act on an existing host cell without altering its DNA. If that host is human, the advantage of not

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manipulating its DNA is clear—keeping humans as human as possible. The IDR team came up with two solutions, both of them more easily controlled, reversible, and portable than genetic engineering. One solution is biotic; the other is abiotic.

The Biotic Approach: Trojan Horses

Rather than build a whole new cell from the ground up, the team proposed building much simpler synthetic transporter proteins, synthetic organelles or intracellular bacteria that could infiltrate the cell to stimulate a response. This is a Trojan modulator. The benefit would be an immediate response—inject the modulator when the response is desired. No rewiring of the host is necessary.

This application of synthetic biology is excellent for existing organisms as opposed to creating new ones. A desired reaction simply requires a specific synthetic receptor. For example, an engineered T-cell receptor could be sent into a host to train a T-cell to react to cancer cells in a certain way. Growth factor receptors could be inserted to regulate stem cell or osteocyte division.

These organelles or bacteria could also be built with a feature that has been a staple of the synthetic biology conversation: the killswitch. Scientists in this field, as in others that deal with manipulating genes, want to make sure there's a way out of a situation—to make sure that genetic unpredictability, its ability to mutate or otherwise get out of control, can be regulated by pre-programmed destruction before a cell or its host is harmed. The Trojan modulators could be designed with an expiration date: an organelle made to self-destruct after completing its task, for example, so it will not be floating around the cell.

The Abiotic Approach: Cellular Radio

For even greater influence over a cell, with literal push-button timing, the IDR team discussed what is known as cellular radio—a carbon nanotube inserted into the cell and remotely controlled to create one of a few different reactions in the cell.

Less than a micron long and ten nanometers wide, the radio could be designed to respond to radio signals from outside the cell—outside the organism, even— and thereby remotely induce heat, mechanical vibrations, or hydrolysis in a region of the cells where the tube resides.

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The signal itself would have to be small to activate the nanotube, and be set at a specific wavelength (or combination of wavelengths) so the radio would recognize it—in effect, the radio would have its own channel. Once perfected, the cellular radio could be a new interface of genetic and electronic components—a bionic, biotic thing. A six-million-dollar cell.

A radio tuned to heat up the cell uncontrollably serves just one purpose: to destroy the cell, potentially handy for eliminating undesirable cells like cancer. Nanotube radio can also initiate electrolysis in surrounding water, producing protons which acidify the area around the nanotube. Though lethal in high doses, local acidification in specific organelles of the cell can potentially instruct the cell to perform other functions than just self-destruction. Cells change the pH of their organelles in many occasions. So, why not do it remotely via the radio?

A more complex action is to channel the action of the nanotube to influence just one biomolecule in the cell and to perform a specific function, such as stimulating production of calcium ions. Calcium has different functions at different times in different cells based on the function of the cell, so this one strategy represents many possibilities in regulating cell behavior, from neurotransmitter activation to muscular contraction. Activating the nanotube in leukocytes would excite the calcium ions to stimulate an immune response; and in some stem cells and progenitor cells, triggering the calcium burst by nanotube could activate cell division. Tissue homeostasis, then, could also be controlled remotely: Push a button, and the radio triggers cell division, leaving the radio in the original stem cell while the newly produced cell goes on to replicate over and over and become some kind of tissue. Need a new piece of pancreas? Tune in to cellular radio.

Beyond Genetics

As the IDR team discussions proved, genetic engineering is a staple of synthetic biology. Drawing up new genetic blueprints presents possibilities for new cells. But to make changes in existing cells, a subtler approach is sometimes required—something chemical or physical that can be controlled remotely. It's a whole different approach to synthetic biology, not intended to replace genetic manipulation, but to augment its possibilities without getting into the tricky wiring of the DNA. Because while genetic engineering presents better and better models for manipulating life, there is always the noise of evolution acting on the creation, the static of mutation threatening to change the engineered thing. At times like this, sometimes it's best to turn up the radio.

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IDR Team Summary 8

What is the role of evolution and evolvability in synthetic biology?

CHALLENGE SUMMARY

To circumvent the time-consuming, ad hoc nature of constructing new biological systems, some investigators have advocated efforts to "standardize" biological parts in such a way that their behavior in novel assemblies or environments becomes more predictable. The notorious complexity and context-dependency of the behavior of biological parts and systems, however, makes such standardization extremely challenging. For example, a biological device that is functional in one cell type may not exhibit the same behavior in another, even closely-related cell type. The stochastic nature of biochemical systems also presents a hurdle for prediction and standardization. It is unlikely in fact that biological parts can ever be fully standardized, and engineering methods that enable rapid optimization of synthetic biological systems will be needed. Nature's optimization algorithm is evolution: evolution fine-tunes the functions of parts in new contexts and optimizes their assemblies in nature. Can directed evolution be used to do the same in synthetic biology? Evolution is also the source of all biological parts—can directed evolution reliably generate useful parts, especially those unlikely to be found in Nature?

All biological systems evolve under the pressure of mutation and natural selection. Natural selection, however, leads to the destruction of synthetic systems that place the organism at a selective disadvantage relative to dysfunctional mutants. Synthetic biology will have to confront this ubiquitous feature of living systems.

A hallmark of biological systems is their ability to adapt to changing

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environments and challenges. Modularity appears to be a useful feature of evolvable, rapidly-adapting systems— some biological systems and even components are highly modular, such that components and sub-components can be rapidly swapped in and out to generate new functions. Eukaryotic signaling systems are a good example, but prokaryotes rely on much less modular systems that nonetheless serve them very well. Are there costs of evolvability in terms of system performance?

Key Questions

- When and how can evolutionary methods contribute to design of synthetic systems?
- How can evolutionary methods be best integrated with "rational" design, including computational design? What is the role of modeling?
- Are there design objectives that can be addressed *only* through evolutionary strategies? Are there objectives for which evolutionary strategies are unnecessary?
- What are the best targets for evolutionary optimization? Molecules? Circuits? Organisms?
- What technologies and tools will be needed for rapid, efficient evolutionary optimization?
- What strategies can we use to overcome the tendency of synthetic biological systems to mutate and escape programmed control?
- How do we design systems and host organisms to ensure genetic stability?
- How can we best understand mechanisms and consequences of mutation and develop routes for repair that enable designed functionality to be maintained?
- To what extent is it important to pursue strategies for designing evolvable systems? What are the key features?

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IDR TEAM SUMMARY

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It is widely accepted that organisms in the natural world evolve in order to adapt to changing environments and challenges. Evolution is a process that may take long periods to produce any observable change, and there is

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no easy way of predicting which organisms will evolve when faced with a challenge.

Synthetic biologists, however, are exploiting evolutionary principles in the laboratory to create new biological systems that may one day lead to breakthroughs in renewable energy, material synthesis and medicine.

The mission of synthetic biology is twofold: it involves the design and construction of new biological parts, devices and systems as well as the redesign of existing, natural biological systems for useful purposes.

To help facilitate the growth of the field, an Interdisciplinary Research (IDR) team of eleven scientists representing a variety of disciplines gathered at the 2009 National Academies Keck *Futures Initiative* Conference on Synthetic Biology to discuss the question: What is the role of evolution and evolvability in synthetic biology?

Using evolution in synthetic biology involves a combination of techniques and perspectives from both engineering and biology. Engineering principles provide methods for evaluating processes and how to monitor processes to achieve a desired outcome. For example, mechanical engineers design and implement sophisticated systems using machinery to create a specific outcome or product. Biology adds to this an understanding of the processes found in molecules, circuits and organisms within the natural world.

Through a process known as directed evolution, it is possible to introduce specific stresses that force components (molecules, for example) to evolve rapidly, eventually producing a biological system that is unique in both form and function.

But the attempts to marry engineering and biology are also fraught with difficulties. Members of the interdisciplinary research team observed that engineering generally relies upon consistency and predictability of processes, while biology is characterized by variation and diversification.

This disparity extends to the relationship between evolution and synthetic biology, because the results generated through directed evolution are sometimes difficult to replicate, and the components that evolve may continue to do so when placed in a new environment. The difficulties associated can lead to elevated lab cost, while continued evolution may result in an unstable system that behaves in ways that are unpredictable. Systems that function well in one cell type may not work the same way in others, even if the cells are closely related. Thus, systems that rely on directed evolution are not always the most stable.

With this in mind, the IDR team posed two hypothetical questions.

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1) Is synthetic biology successful when evolution is no longer needed and systems are created by rational (rule-based) design, or 2) is synthetic biology successful when scientists can effectively harness the unique features of evolution, making it a central tool through which systems are crafted?

Ultimately, there is not enough evidence to determine which of these outcomes is more likely. Several team members emphasized that the selection processes for synthetic biology and evolutionary biology are more of a craft than an industrial process, although to achieve some of synthetic biology's goals, creating organisms on an industrial scale will be necessary. Scientists must learn more before they use evolutionary principles for large-scale projects.

Indeed, directed evolution is such a boutique practice, proposals for advancement tend toward the conceptual rather than the concrete. As such, the group proposed a series of model problems identifying areas requiring additional research. Some of their model problems were:

1. To obtain a system that optimizes the output in financial terms (including the cost of setting up the system).

2. Obtain a robust enzyme circuit to do X, and to get the same behavior under various conditions (e.g. compounds, temperatures, media types and genetic background). That is, for directed evolution to have any broad application, we must create circuits that are not restricted to one function.

3. How does one initiate research when one cannot see the pathway from where we are to the final result? For example, how might one develop a bacterial population that spontaneously spells the word "HELP," or an *E. coli* that can play music? These unusual examples emphasize the point that we do not yet know how to begin research with a specific application in mind. If we are to design systems that fight cancer or enhance the immune system, we must develop ways to initiate research even if the exact process is unknown.

4. How do you make a system that is robust and can therefore search functional space more easily? Biologists often refer to the functionality of a particular agent in terms of a "fitness landscape," a graphical representation often conceived of as a series of peaks and valleys in which peaks represent the best outcomes for a given function. The group suggested a need to "smooth" the fitness landscape, meaning that we must find ways to reduce the number of "valleys," or poor functions, and make the overall selection process more consistent and predictable.

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Fundamentally, the team said it is necessary to develop methods to accelerate evolution to get to a desired result faster, while also developing ways to decelerate or stop evolutionary processes once the experiment reaches an end point.

To do so, biologists and engineers must develop more stable strains of bacteria into which end products of synthetic biology can be transferred or a strain where the mutation rate can be controlled. Ideally, this would prevent the over-mutation or under-mutation (i.e., evolution) of a system, thus making it significantly more reliable and malleable.

In addition scientists must create more robust systems in which swapping of components is seamless. That is, researchers must find a way to share evolved components without reengineering new components for each individual project.

The IDR team also suggested the creation of a universal fitness landscape readout from small molecules that applies across heterogeneous systems. This readout would apply to an overall fitness landscape. A universal fitness readout would simplify matters by allowing researchers to compare evolutionary processes for a variety of applications.

In order to create this kind of generalizability, the team argued that scientists must develop ways to predict and screen for sequences that are consistent with multiple objectives, what they called "multi-objective massively parallel optimization." This would require the creation of libraries from which scientists could choose components that they know would act in specific, predicable ways in a multitude of conditions.

These suggestions are merely the first steps toward the creation of a more unified practice of directed evolution. Members of the group recognize that many of the processes used in directed evolution experiments are in their technological infancy, but they maintained that additional research might generate the requisite knowledge to create robust yet flexible systems that work in harmony with biological circuits found in nature.

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IDR Team Summary 9

How do we maximally capitalize on the promise of synthetic biology?

CHALLENGE SUMMARY

The burgeoning field of Synthetic Biology offers the dual promise of solving some of the most profound challenges facing society as well as providing a fundamentally deeper understanding of the functioning of living systems. Synthetic Biology provides us a new view of biology, a view that offers an unprecedented level of knowledge about how parts of biological systems function in isolation and within natural or reconfigured living organisms. At present however, our ability to tackle the grandest challenges facing the field remain relatively primitive. Issues that need to be addressed to fully exploit what Synthetic Biology has to offer include technological, educational, institutional, and communication barriers to progress. To fully exploit the opportunities that lie ahead in Synthetic Biology, it is essential that we transform the currently existing cultures in scientific, educational, governmental, and communication institutions by embracing innovative new strategies for promoting this young field.

In terms of education, we need to train young scientists to view biology with fresh eyes. Starting at a young age (K-12), students need to understand that complex biological systems are not wholly reliant on their endogenous parts; rather, they can be evolved or engineered. Students need to know that biological systems can be understood through principles, not through memorization. We need to teach students that biological systems often have critical applications. Finally, our students need to appreciate that interdisciplinary knowledge lies at the heart of innovation.

It is also imperative that we break down "silos" in our academic insti-

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tutions. Synthetic Biology demands that biologists, chemists, physicists, and mathematicians work together with engineers. The deep philosophical divide between what might be called "pure science" and "engineering" must be bridged. In Synthetic Biology, understanding, manipulation, and application are intimately linked, and we need to provide an academic culture along with an appropriate infrastructure that allows academics to simultaneously explore multiple aspects of this field.

Another challenge is the gap that exists between academics and industry. This gap is most severe when one considers partnerships between basic sciences and industry, because the science fields lack the interface that engineering-based fields have traditionally had with industry. Mechanisms need to be put in place to enable academics, together with industry partners, to move from the proof of principle experiment in a petri plate (or the like) to the industrial scale.

Concurrent with the above, a shift must occur within the funding agency culture. Long-term strategic plans could be envisioned that both stimulate and incentivize cooperation among diverse disciplines and agencies to solve common foundational problems. Rigorous mechanisms for effectively evaluating new science coming from a new field need to be imagined.

Critically, we need a fundamental change in communication both within and outside the scientific community. Within the greater scientific community, Synthetic Biologists must move research beyond the border of a particular discipline. Going forward, scientists must be able to coherently explain the intellectual merit and relevant application of the work along with the technology and molecular mechanisms underpinning it to a broad scientific audience. Likewise, it is the job of the scientist to help non-scientists become good consumers of science. Outreach is especially critical in the Synthetic Biology field because the work can blur the distinction between animate and inanimate objects and therefore the research can potentially have an extreme ethical, religious, and social impact. Finally, our government needs to wrestle with balancing and promoting scientific innovation in Synthetic Biology with its serious safety and ethical considerations.

Key Questions

- How can Synthetic Biology be taught in schools in order to engage students in biology? How can we teach Synthetic Biology in a way that integrates it with other sciences and engineering?

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- How can academic institutions be restructured to promote the development of unique interdisciplinary sciences like Synthetic Biology?
- How can academic/industry partnerships be enhanced to catalyze Synthetic Biology applications?
- How can we maximize the efforts of government agencies to responsibly lay the foundation for Synthetic Biology?
- How can we prepare scientists to effectively engage with the diverse collections of people with interest in Synthetic Biology?

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Synthetic Biology: Building a Nation's Inspiration: Interdisciplinary Research Team Summaries

IDR TEAM SUMMARY

By Joseph B. Calamia, Graduate Science Writing Student,
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In one way, synthetic biology is a perspective. Seeing living systems as a series of parts, researchers craft new tools from basic biological components. Adding new genes to the workings of *E. coli*, for example, synthetic biologists have already transformed bacteria into anti-malarial drug factories. As researchers from diverse backgrounds, with training in fields from systems biology to computer engineering, collaborate to build increasingly complex biological systems, some hope to gain deeper insights into the details of how biology works. The 2009 National Academies Keck *Futures Initiative* Conference on Synthetic Biology asked an Interdisciplinary Research Team (IDR) of 13 scientists and engineers to discuss the best ways to realize this "dual promise" of synthetic biology, as a means both to solve important problems in biology and to enhance understanding of living systems. While leaving the technical details of synthetic biology to other IDR teams, this group defined some of the educational, institutional, and communication barriers to maximally capitalizing on the promises of synthetic biology. The IDR team concluded that part of the solution is to educate young scientists in new ways, to break down divisions within and across academic disciplines and institutions, and to improve general science communication.

Educating Scientists and Citizens

In November 2009, 110 teams of undergraduates, a total of 1,200 participants from around the world, came to the Massachusetts Institute of Technology to compete for a "Biobrick" trophy, the grand prize in the International Genetically Engineered Machine competition, known as iGEM (http://2009.igem.org/Main_Page).

At iGEM, teams design new biological systems (everything from banana-scented bacteria to arsenic biosensors) from a registry of "standard, interchangeable biological parts," including promoters, plasmids, and primers. The Grand Prize Winner of the 2009 competition, Cambridge University, created "*E. chromi*"—a modified version of *E. coli* that changes color when exposed to certain chemicals, and may lead to an easy-to-read test for certain diseases.

The IDR team saw iGEM as an ideal teaching model for synthetic biol-

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ogy and other multidisciplinary fields, and encouraged the creation of an iGEM competition for younger students. In general, they hoped for new, imaginative and inspirational ways to educate youth (K-12), through radio, television, and science-based games and competitions. Children should not be taught to see science as merely a corpus of facts to memorize and forget after an exam, but as a means to investigate the world. iGEM is one of many approaches to accomplishing that ideal.

Using synthetic biology as a model, teachers can demonstrate how scientists engineer biological systems and that interdisciplinary knowledge is a way toward innovation. As a field, synthetic biology will benefit from teachers who encourage young students to become future scientists and scientifically educated citizens. As pedagogical material, examples from synthetic biology will also provide a useful paradigm for educating students about other collaborative fields of research.

Undergraduate college courses that focus solely on memorizing facts turn many students away from additional scientific studies. The IDR team cited Elaine Seymour and Nancy M. Hewitt's book *Talking about Leaving: Why Undergraduates Leave the Sciences* (1997) and noted that almost 50 percent of first-year undergraduates intending to study hard sciences end up switching to other majors. "Science and Engineering Indicators," published every two years by the National Science Board, has more recently reported similar results. To encourage college students to study science and to create a more scientifically educated citizenry, the group encouraged active scientific investigation during students' early undergraduate careers and the creation of more opportunities for experimentation and laboratory experiences as part of introductory courses, including those for non-majors.

Turning to the education of professionals, the IDR team noted that even many research scientists have trouble defining the fledgling field of synthetic biology. Part of their difficulty may result from a "philosophical divide" between the pure sciences (such as biology) and applied sciences (such as engineering). To overcome communication hurdles between active researchers, the team suggested funding workshops to train across disciplines, aimed specifically at faculty, post-doctoral students, and graduate students—as this exercise would be helpful in any interdisciplinary pursuit. They also encouraged the creation of additional synthetic biology professional master's degree programs. This would continue the current trend to establish such degrees in a variety of scientific disciplines, as reported in the National Research Council's 2008 report *Science Professionals:*

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Master's Education for a Competitive World (http://www.nap.edu/catalog.php?record_id=12064).

Communicating Synthetic Biology

A misunderstanding of swine flu hurt pork sales. People sued the European Organization for Nuclear Research (CERN), fearing that the Large Hadron Collider would swallow Earth in a black hole. An advertisement for dress slacks that contained the word nanofibers engendered protests against nanotechnology. The public, the team believes, needs to be better educated about cutting-edge science so that it can better separate imagined risks from real ones.

The group suggested funding new "audience research surveys" to discover current public concerns and beliefs about synthetic biology and related fields. This research should allow scientists to recognize possible problems in how they frame their research. These surveys would also help researchers as they work with science communicators to develop new means for distributing lay descriptions of latest research to keep the public accurately informed. If the field hopes to attract younger generations, researchers' use of outlets such as Facebook, Twitter, and Wikipedia will be essential for communicating the results, implications, relevance, and excitement of new research. For example, the group suggested that graduate students publish lay summaries of major scientific papers in a public Internet source. Along these lines, the team encouraged researchers to collaborate with media and university press offices to increase the chances that their research receives accurate and prominent reportage.

As a final means to address possible public concerns, the team suggested actively developing a code of ethics for synthetic biology researchers, drawing on existing protocols regarding similar kinds of research, such as genetic engineering. An active approach to creating this code by gathering a summit of diverse stakeholders would help mitigate fears and also encourage funding for this new field. This summit might also provide a means to avoid reactionary government policymaking, which could inhibit the field's growth.

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Appendixes

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List of Synthetic Biology Podcast Tutorials

Engineering and Synthetic Biology
Podcast Released: August 13, 2009
Frances H. Arnold (NAS/NAE/IOM)
Dick and Barbara Dickinson Professor of Chemical Engineering and Biochemistry
California Institute of Technology

Gene Circuitry/Protein Circuits and Synthetic Biology
Podcast Released: August 20, 2009
Wendell A. Lim
Professor in the Departments of Pharmacology and Biochemistry
University of California, San Francisco
Investigator of the Howard Hughes Medical Institute

Chemistry and Synthetic Biology: Building Synthetic Tools
Podcast Released: August 27, 2009
David A. Tirrell (NAS/NAE)
Ross McCollum-William H. Corcoran Professor and former Chairman of the Division of Chemistry and Chemical Engineering at the California Institute of Technology

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National Security and Ethics and Synthetic Biology
Podcast Released: September 3, 2009
Jonathan D. Moreno (IOM)
David and Lyn Silfen University Professor of Ethics and Professor of Medical Ethics and of History and Sociology of Science, University of Pennsylvania

Overview of Synthetic Biology
Podcast Released: September 10, 2009
J. Craig Venter (NAS)
Founder, Chairman, and President
J. Craig Venter Institute

Gene Circuitry/Cell-to-Cell Communication and Synthetic Biology
Podcast Released: September 17, 2009
Ron Weiss
Associate Professor, Department of Biological Engineering and the Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology

Gene Circuitry/Fragility of Systems and Synthetic Biology
Podcast Released: September 24, 2009
Jim Collins
Boston University and Howard Hughes Medical Institute

Religion and Ethics and Synthetic Biology
Podcast Released: October 1, 2009
Laurie Zoloth
Director, Center for Bioethics, Science and Society and Professor of Medical Ethics and Humanities
Northwestern University

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Chemistry and Synthetic Biology: Metabolic Engineering, Building Pathways, Metagenomics and Applications
Podcast Released: October 8, 2009
Jay D. Keasling
Professor, Chemical Engineering and Bioengineering, University of California, Berkeley
Acting Deputy Laboratory Director, Lawrence Berkeley National Laboratory
CEO, Joint Bioenergy Institute

Engineering and Synthetic Biology
Podcast Released: October 15, 2009
Drew Endy
Assistant Professor, Bioengineering
Stanford University

Creative Problem Solving
Podcast Released: October 22, 2009
Richard N. Foster
Managing Partner of Millbrook Management Group, LLC and
Member of the W. M. Keck Foundation Board (Executive Committee)

All tutorials are available at www.keckfutures.org.

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Agenda

Friday, November 20, 2009

7:15 and 7:45 a.m.	Bus Pickup: Attendees are asked to allow ample time for breakfast at the Beckman Center; no food or drinks are allowed in the auditorium, which is where the welcome and opening remarks take place at 8:30.
7:30 a.m.	Registration (not necessary for individuals who attended Welcome Reception)
7:30 – 8:30 a.m.	Breakfast
8:30 – 8:45 a.m.	**Welcome and Opening Remarks** Harvey V. Fineberg, President, Institute of Medicine Bonnie L. Bassler, Chair, NAKFI Steering Committee on Synthetic Biology
8:45 – 9:45 a.m.	**Keynote Address** Ron Weiss, Professor, Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology

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	Wendell A. Lim, Professor, Departments of Pharmacology and Biochemistry, University of California, San Francisco; Investigator, Howard Hughes Medical Institute
9:45 – 10:00 a.m.	**Interdisciplinary Research Team and Grant Program Overview** (Bonnie Bassler)
10:00 – 10:30 a.m.	Break
	IDR Team Starters Meet to Review Assignments
10:30 a.m. – 12:00 p.m.	**Panel Discussion** *Moderator* • Joe Palca, Host of NAKFI's Preconference Podcast Tutorials *Panelists* • Frances H. Arnold (NAS/NAE/IOM), Dick and Barbara Dickinson Professor of Chemical Engineering and Biochemistry, California Institute of Technology • Michael Elowitz, Assistant Professor of Biology and Applied Physics at the California Institute of Technology • David A. Tirrell (NAS/NAE), Ross McCollum-William H. Corcoran Professor and former Chairman, Division of Chemistry and Chemical Engineering, California Institute of Technology • Laurie Zoloth, Director, Center for Bioethics, Science, and Society, Northwestern University
12:00 – 1:00 p.m.	Lunch
1:00 – 5:00 p.m.	Interdisciplinary Research Team Session 1
3:00 – 3:30 p.m.	Break

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5:00 – 6:00 p.m.	Reception
6:00 – 8:00 p.m.	Communication Awards Presentation and Dinner
8:00 p.m.	Bus Pickup
8:30 – 11:00 p.m.	Informal Discussions/Hospitality Room (optional)

Saturday, November 21, 2009

7:00 and 7:30 a.m.	Bus Pickup
7:15 – 8:00 a.m.	Breakfast
8:00 – 10:00 a.m.	Interdisciplinary Research Team Session 2
10:00 – 10:30 a.m.	Break
10:30 a.m. – noon	Interdisciplinary Research Team Reports (5 to 6 minutes per group)
Noon – 1:30 p.m.	Lunch
	Graduate Science Writing Students Meet with Barbara Culliton at Registration Desk for Lunch
12:45 – 1:30 p.m.	Related Interdisciplinary Research Team Discussion (Groups 1A-1B, 3A-3B, 7A-7B)
1:30 – 5:00 p.m.	Interdisciplinary Research Team Session 3
3:00 – 3:30 p.m.	Break
	Poster Set-Up: Attendees to setup posters for 5:00 p.m. poster presentation and reception

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5:00 p.m.	Final Presentation Drop-Off: Interdisciplinary Research Teams to drop off presentations at information/registration desk, or upload to FTP site prior to 7:00 a.m. Sunday morning.
5:00 – 6:30 p.m.	Poster Presentation and Reception All attendees are asked to stop by the registration desk to arrange for transportation if prearranged service does not work with schedule.
6:30 p.m.	Bus Pickup: Attendees brought back to hotel for free evening. Attendees will be reimbursed $40 to be applied toward dinner upon submission of Travel Expense Reimbursement form.

Sunday, November 22, 2009

7:00 and 7:30 a.m.	Bus Pickup: Attendees who are departing for the airport directly from the Beckman Center are asked to bring their luggage to the Beckman Center. Storage space is available.
7:15 – 8:00 a.m.	Breakfast
7:15 a.m.	Taxi Reservations: Attendees are asked to stop by the information/registration desk to confirm their transportation to the airport or hotel.
8:00 – 9:30 a.m.	Interdisciplinary Research Team Reports (10 to 12 minutes per group)
9:30 – 10:00 a.m.	Break
10:00 – 11:00 a.m.	Interdisciplinary Research Team Reports (10 to 12 minutes per group)
11:00 a.m. – noon	Q&A Across All Interdisciplinary Research Team Groups

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Noon – 1:30 p.m.	Lunch (optional)
Noon – 4:00 p.m.	Graduate Science Writing Students Meet with Barbara to Finalize First Draft of Paper
Noon and 1:30	Buses depart for Marriott and John Wayne Airport

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