SENCER
APPLYING THE SCIENCE OF LEARNING TO THE LEARNING OF SCIENCE

Synthetic Biology

A SENCER BACKGROUNDER FOR DISCUSSION AT SSI 2014

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I. Introduction

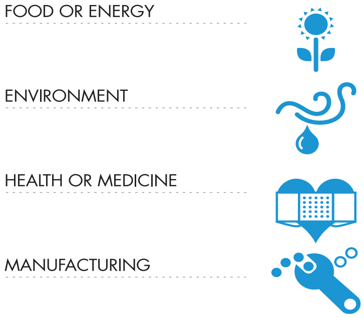

Image credit: Karen Ingram
Icons for some broad topic areas that could be addressed with a biotechnology.

A telling question was posed in the introduction to the backgrounder on nanotechnology that was published by SENCER in 2003.[1] This impressive article by Dr. Kulinowski of Rice University asked: what would random people identify as the most pressing global challenges of today and of the future, challenges that might be solved with a technology? Notably, the answers offered then are the same answers we'd hear today, more than 10 years later. The list then, as now, includes the need for clean energy and water, cures to diseases like cancer, reduced environmental pollution, better national security, and improved computing power. These persistent challenges in medicine and health, in environmental sustainability, in manufacturing, and in security have driven the research agenda of the nation for a generation or more. Great progress has been achieved, yet, to a first approximation, the challenges remain unsolved. And while nanotechnology was cited in 2003 as the technical field whose research products stood poised to develop solutions for all the grand challenges that were identified, it is the field of synthetic biology that, a decade later, presents itself as this era's agent for positive change.

In this backgrounder, the field of synthetic biology will be introduced, first through a brief description of its roots, and then through some illustrative examples of its contributions to science and engineering. The examples have been chosen to emphasize the achievements of the field as well as to show how much good work there is left to do. The societal aspects of this emerging discipline raise the kinds of complex, contested and unresolved questions that "fit" the SENCER teaching approach.

The similarity between synthetic biology now with nanotechnology 10 years ago can be further observed when we consider a second question posed in the nanotechnology backgrounder, a question probing public awareness of the field. Kulinowski reports on research from the National Science Foundation[2] that suggests two kinds of answers to the question: what is nanotechnology? Most respondents reported no awareness of the field. A smaller fraction could answer with some application idea, saying that nanotechnology had something to do with "tiny machines that fix things" for example. Thus, the public awareness was found to be either nonexistent or slight, despite the societal benefits promised by nanotechnology research.

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[1] Kulinowski, 2003

[2] Bainbridge, 2002, and later Cobb and Macoubrie, 2004

Current data that speaks to the public's awareness of synthetic biology mirrors the findings for nanotechnology from 2003.[3] Most of the individuals polled had never heard of synthetic biology, and those who knew something about it associate the work with things that are "man-made," "artificial," and "unnatural." A majority of the people polled who had heard about synthetic biology felt that the benefits of the research were equal to its risks. Thus, synthetic biologists—whether they know it or not-- are currently in a social "sweet spot" where most of the public is unaware of their field, and people who know about it have initial impressions that balance the potential positive and negative outcomes. If other emerging technologies offer any lessons, however, the field will not fly under the radar for long and the public's judgment will hinge on an early application or captivating news story. Some possibilities for these are detailed in Section 3 (below).

At its core, synthetic biology tries to change the way we view our relationship to the living world. A Polish scientist, Waclaw Szybalski, is credited with first articulating the concept of synthetic cells as ones that "can serve our needs as if they were tiny machines we had programmed *de novo*".[4] His idea was to leverage the tools and findings of molecular biology, which advanced descriptive science, to build entirely new genetic arrangements that suit our purposes and goals. He imagined putting "new better control circuits" inside cells and proposed building a "new better mouse." He believed there was a limitless pool of ideas to be explored once genetics, understood to the molecular level, was combined with DNA sequence information and the tools for recombining and manipulating the DNA code inside living cells. Defined in this way, the field of synthetic biology is the living application of nanotechnology's goals, in which the nanomaterial both encodes and fabricates itself. Interestingly, Szybalski's ideas about programming living cells harken back to an earlier idea proposed by Sephane Leduc about "synthetic cells." Leduc, in the early part of the 20th century, simulated the properties of living cells using precipitates and India ink. He did this to explain the origins and operations of life rather than to apply his uderstanding to meet any defined need, but through his effort to produce living things from non-living materials, he was attempting to debunk the notion that the synthesis of life had a necessary element of magic.

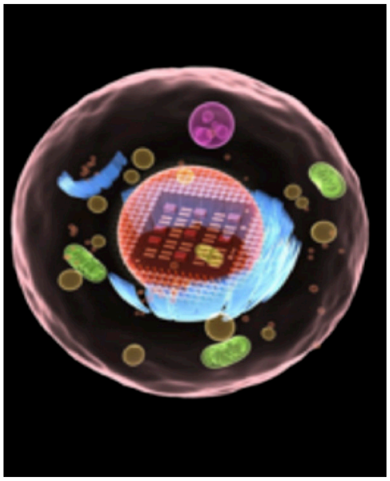

Image credit: Christine Daniloff
A cell depicted as a programmable object, with a microprocessor embedded in the nucleus.

So after Szybalski's lofty proposition was made to engineer cells as if they were tiny machines to perform our bidding, what happened? In truth, nearly nothing resembling synthetic biology surfaced for 25 years. It took approximately a quarter century for the electrical engineers to step in and join the scientists to launch the field. Not coincidentally, electrical engineering and computer science were undergoing a transformation in this era as well. At the end of the 20th century, computing technologies revolutionized the way we process and think about information, attracting legions of brilliant engineers who wanted to contribute to the development of the field. Computers got cheaper, faster, and smaller thanks to advances in transistor technology on integrated circuits.[5] But as the industry approached the theoretical limit for miniaturization of the transistors that powered computers, a healthy number of the computer scientists turned to biological science to find the next solution for nanoscale manufacturing. They correctly saw how cells build themselves molecule by molecule, doing so with few environmental pollutants, with inexpensive starting materials and with reliable and enviable precision. The engineers started to learn a new programming language, one that was written in the genetic code: G, A, T, and C. It was the complementary but fundamentally different approach that engineers took to build cellular machines that launched the field of synthetic biology.

II. Some Science and Engineering

Many cite a pair of back-to-back papers published in 2000 in *Nature* as the publications that really kicked off the field of synthetic biology.[6] Superficially, these two papers

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[3] Hart Research Group, 2013

[4] Szybalski, 1974

[5] Moore, 1965

[6] Elowitz and Leibler, 2000; Gardner, Cantor, and Collins, 2000

appear to describe simple bacterial cells that could blink "green" and "not green"[7] under defined growth conditions. Oscillatory behavior of cells was not a new phenomenon in 2000, and so, unlike other scientific papers in that issue, these papers did not reveal any surprising discoveries. What made these blinking cells groundbreaking was how the authors had applied a "rational network design" framework to imagine, model, build, and then test them.

Rather than build these blinking systems to understand the precise details of how they worked, these bioengineers were eager to see if the behavior of the complex system they had designed was consistent with their design specifications. Just as engineers in any discipline would do, these synthetic biologists cycled through the design, building, and testing phases, including the prototyping of different designs to find the most promising direction. Their process resembled the scientific method, in which a researcher might cycle through hypotheses, experiments, and analysis, but rather than trying to understand the precise details of how their system works, these engineers were most interested in seeing if their prototype tested properly.

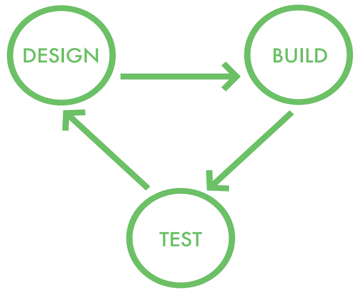

Image credit: Karen Ingram
A simplified depiction of the engineering design cycle.

The blinking circuits were constructed from simpler component "parts," genetic elements that had been defined through years of scientific research because they related to normal cellular activities like growth and gene expression. The parts were then re-deployed to perform a human-defined function, namely blinking a color on and off. The circuits elegantly and noticeably illustrated the complementary goals of "learning to build" — i.e., elucidating the design principles that would allow for the rational design of more complex genetic circuits — and "building to learn" — i.e., testing the limits of our understanding by successfully (or not!) constructing according to what we know. The spirit of this two-pronged approach, that embraces both the scientific urge to discover and the engineering drive to solve, has found its slogan in a quote from American physicist and Nobel laureate Richard Feynman, written on his blackboard at Caltech at the time of his death in 1988: "What I cannot create, I do not understand."

Several other illustrative examples and landmark publications have helped define synthetic biology in the past decade. A sampling of them shows a field in rapid development and reflects the diversity of approaches that are being used to engineer living cells.

Refactoring

This design approach comes from the realm of computer programming and refers to the process that engineers take to "clean up" computer code in a way that preserves its functions but also makes it more understandable to an outside reader.[8] Genomes have been refactored by synthetic biologists, notably by Drew Endy whose research group uncomplicated the genetic code for a bacterial virus, leaving an infective but more easily understood and studied sequence.[9] A second landmark example of refactoring efforts in synthetic biology is seen in the redesign of the right arm of an entire yeast chromosome (Chromosome IX in *Saccharomyces cerevisiae*). Dymond and colleagues (2011) followed three design principles, namely that the function of the genes on the refactored chromosome should be unchanged, that the destabilizing elements of the nearly 90,000 base pair chromosome should be removed, and that the final form of the refactored chromosome should be amenable to further study. Notably, the researchers took a similar approach to the refactoring of Chromosome III, but carried out the work in the context of a "build-a-genome" class for undergraduates at Johns Hopkins University.[10] That the refactoring of an entire chromosome could be carried out by minimally trained undergraduates in a semester speaks to a possible future of wide-spread bio-hacking by non-experts, making the engineering of living materials a topic that's even more complex and therefore appealing from a SENCER perspective.

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[7] Throughout this backgrounder, hyperlinks offer access to resources where readers can learn much more on specific topics (by clicking on the green underlined text).

[8] Kuldell and Lerner, 2009

[9] Chan, Kisouri, and Endy, 2005

[10] Dymond et al., 2009

Standardization for parts-based design

One analogy that has helped clarify the synthetic biologist's approach to the engineering of cells is that of DNA parts that can snap together like Legos™. Nearly everyone on the planet has played with, or at least seen, a Lego brick and knows that you do not need any formal training to put the bricks together. Moreover, there are nearly limitless combinations to make because they have uniform connections. Like Lego bricks, standardized biological parts could, in principle, enable an abundance of cellular design outcomes, and could empower a community of essentially untrained bioengineers to participate. Standardized biological parts have been cataloged and their sequence information is available to everyone with an Internet connection (see: Registry of Standard Biological Parts). The physical bits of DNA are distributed to teams of novice synthetic biologists each year through the iGEM competition.[11] Beyond the interesting projects that this competition has generated, iGEM has introduced the field of synthetic biology to thousands of students around the world, providing authentic insight into the excitement and potential of engineering careers. These iGEM students, working on their home campuses around the world, are challenged to build novel designs with standard biological parts and run the circuits in living cells. Some of the most charismatic and impressive of these student projects have been published in peer-reviewed journals, such as the Bacterial Photography System that was published in *Nature* in 2005.[12] Like the "build-a-genome" example cited above, the success of iGEM speaks to the fact that a community of relatively untrained teenagers can accomplish publishable research if they are given the scientific context and engineering tools to do so.

Synthetic cells

Craig Venter draws the spotlight from many, more modest efforts in synthetic biology with his efforts to "create" life from non-living components. When asked if he and his team of scientists at Synthetic Genomics, the world's largest private lab, were "playing God," Craig Venter quipped, "We're not playing".[13] The frenzy about his grand designs on life peaked with a publication in May 2010 that described a synthetic cell.[14]

The synthetic cell's genome had started as an online data file that cataloged the natural DNA sequence from an existing simple bacterium, *Mycoplasma mycoides*. The digital code was then converted to small segments of physical DNA material made on a DNA synthesizer, essentially a DNA printer that produces tangible bits of DNA based on the digital information that is typed into the computer. The short DNA segments were modified slightly with "watermarks" and philosophical quotes, including a quote from *American Prometheus* by Robert Oppenheimer ("See things not as they are but as they might be") and from James Joyce ("To live, to err, to fall, to triumph and to recreate life out of nonlife"). For synthetic biologists, though, the most resonant of all the quotes he added was that from Richard Feynman: "What I cannot create, I do not understand." The researchers then stitched together the synthesized DNA fragments with a combination of techniques, some of which included passaging the fragments through living cells. Finally, the assembled genome was inserted into an already living close cousin of the cell being synthesized. Because the technological tour-de-force was also presented as evidence for the "creation of life from non-life," the publication touched off a flurry of ethical discussions, including a study from the Presidential Commission for the Study of Bioethical Issues that examined the emerging field of synthetic biology, its governance, its social equity, and its potential for misuse.[15]

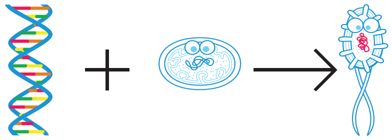

Image credit: Karen Ingram
DNA can be used to modify the cellular functions of an existing organism, giving rise to a novel living system.

Platforms for cellular redesign

The tools available for building often define engineering outcomes. By the 18th century, rebar was being used to improve construction with concrete, thereby enabling new civil engineering projects. More recently, integration techniques to print thousands of integrated circuits onto a single chip led to inexpensive and

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[11] Mitchell, Yehudit and Kuldell, 2011

[12] Levskaya et al., 2005

[13] Venter interview, 2008

[14] Gibson et al., 2010

[15] New Directions: The Ethics of Synthetic Biology and Emerging Technologies, 2010

improved computer science products. Along these lines, the construction tools for synthetic biology are developing in parallel with the tools and approaches for design.

Tools for building biology include DNA synthesis that was mentioned above in conjunction with synthetic cells. With DNA synthesis, new genetic elements can be "written" from scratch. Some in synthetic biology weave a scenario where DNA synthesis circumvents Darwinian evolution, removing the requirement for a living ancestor cell. In this futuristic vision, the desired DNA sequence could be typed into a computer, the DNA synthesizer could read the file and then compile it with actual nucleotides, and a 3D-printer could produce a living material encoded by the synthesized genome. The implications of this scenario are explored in multiple ways below.

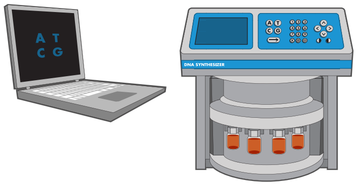

Image credit: Karen Ingram
Genomic information can be stored in digital form on computers (left) and converted to physical material with a DNA synthesizer (right).

Other platforms for cellular redesign include the MAGE technique that was developed in the laboratory of George Church.[16] This laboratory technique essentially accelerates natural evolutionary pressures and was used by these scientists to generate 4.3 **billion** combinatorial genomic variants of a bacterial cell in one day. To put that number in perspective, the normal rate of mutation is approximately 10^{-10} mutations/base pair in a bacterial genome,[17] meaning it would take more than 1,000 years to generate this many changes.

Image credit: Karen Ingram
By deliberately converting all natural stop codons (TAG) in a cell to a synonymous stop codon (TAA), the genetic code can be expanded and partially reprogrammed.

Finally, synthetic biology is taking a page from other more mature engineering disciplines, which model their systems before testing them. Just as civil engineers do not have to drive a heavy truck over a bridge to test its load, and how aerospace engineers do not have to fly a plane to know that a wing shape will provide enough lift, so are biological engineers and synthetic biologists working to model their systems before heading to the lab to build them.[18]

III. Applications

When the White House released its "blueprint for a bioeconomy," they promoted a handful of programs that, truth be known, were already underway. They chose to spotlight -- but not increase their funding for -- five strategic initiatives that they felt would promote research, innovation, social benefit, and economic prosperity through life-science technology.[19] Just how large did they report the bioeconomy to be? Using data from 2010, they estimated $100 billion in revenue for industrial biotechnology not related to agriculture and an additional $76 billion from genetically modified crops. Overall, the bioeconomy was estimated as 1-2% of GDP,[20] a percentage that is comparable to the contributions of mining or education services according to Wikipedia. And in the White House's blueprint, synthetic biology was cited as an emerging research area and future cornerstone of the technology-fueled bioeconomy.

The report justifies its optimism for synthetic biology with an often-cited success story, namely the production of an antimalarial drug in microbes.[21] The drug, derived from artemisinin, is naturally found in the sweet wormwood plant, *Artemisia annua*. To extract the compound from the plant's leaves is an expensive and labor-intensive process that is affected by local growth conditions and generates a drug of variable quality. Chemical engineer and synthetic biologist, Jay Keasling, wanted a reliable way to produce the drug in microbes and so his research group engineered a strain of baker's yeast to express the genes required to make the drug, turning an easily grown microbe into a cellular factory for the medicine. Keasling founded a company, Amyris, in 2003 to bring his research to market, and in partnership with a multinational pharmaceutical company, Sanofi, the large-scale microbial production of this drug began in April, 2013. Sanofi's plans is to

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[16] Wang et al., 2009

[17] Pray, 2008

[18] Chandran, Bergmann, Sauro, 2009; Beal et al., 2012

[19] National Bioeconomy Blueprint, 2012

[20] Carlson, 2007

[21] Ro et al., 2009; Paddon et al., 2013

produce 35 tons of artemisinin in 2013 and nearly twice as much in 2014, resulting in somewhere between 80 and 150 million anti-malarial treatments.

If the "bench to market" story for synthetic biology ended here, it would be conspicuously reminiscent of the generation-old story for recombinant DNA technology. In the 1970s, that emergent technology was used to improve the production of insulin, making it a safer, less expensive treatment for diabetes. However the findings about public perceptions of synthetic biology from the Wilson Center suggest that positive benefits from the field are not enough to offset the public's concern related to the potential risks of the field. Society's fears about synthetic biology (detailed in Section 4, below) include concern that the synthetic cells might behave in unexpected ways, might cause harm, and might fall into the wrong hands. One recent headline-grabbing application of synthetic biology, namely the "Glowing Plant" project, is illustrative of the precarious balance between benefits and risks the field faces.

Launched by a businessman and a scientist, the Glowing Plant project aimed to produce a plant that could provide natural lighting without electricity. The science behind the work is neither particularly novel nor particularly recognizable as synthetic biology, though it is being carried out by a bioengineer and an entrepreneur who have been associated with other efforts in the field. Some genes from fireflies and from bioluminescent bacteria are often moved from one type of organism to another and they can, under the right conditions, lead those recipient cells to glow, albeit dimly. Indeed high school biology students all over the country use a commercially available teaching kit that costs ~$100 to carry out the simple procedures needed to make a bacteria glow (pGLO lab kits).

The Glowing Plant project, however, captured the imagination of the public. Perhaps the initial appeal came from the glowing plants people remembered seeing in the movie *Avatar*. Perhaps the idea that biology is a sustainable approach to our planet's limited energy supply was attractive. These hyped ideas, however, remain far from commonplace. Nevertheless, they were promised as outcomes for the project once it was funded. The Glowing Plant project team launched a Kickstarter campaign in the spring of 2013 with hopes of raising $65,000 from the public. Well before the time had expired on their fundraising, they had secured more than $480,000. As an incentive for funding their project, the team offered a batch of glowing plant seeds for every $40 pledge. Another of the prizes was a do-it-yourself kit to carry out the genetic modifications at home, exposing a regulatory loophole around biotechnologies and raising liability questions for the distributors, should something go wrong. With nearly 5,000 backers at this pledge level, the promise, if fulfilled, appeared to be one of the largest uncontrolled releases of genetically modified plants in U.S. history, drawing concern from some about the environmental impact it could pose and concerns from others about the poor regulatory framework that oversees such work.[22] Because the work was being conducted in a "do-it-yourself" synthetic biology laboratory space (essentially a hobby shop for bioengineers), it seemed to be bypassing many of the public's presumed safeguards on who does such research and where.

The Glowing Plant project revealed a gap in the regulatory and ethical framework that applies to synthetic biology. This "policy vacuum" is like the one that was described for computer technology by Dartmouth College Professor James Moor in his prescient and applicable article "What is Computer Ethics?".[23] The emergence of technologies, like computer technology in the mid-20th century and synthetic biology in this era, enables things that were never possible before. With these new capabilities come new questions that have simply never arisen, but that must be considered in light of the new reality. To illustrate, Moor looks at the use of computer technology in elections. At first, computers were used to count votes, and they were an effective tool to carry out elections but did not fundamentally change the process. Soon, though, the computers collecting the votes could also be used to predict the outcome of the election before voting closed. This new capability, to know the result before everyone had voted, led to never-before-presented questions like: when should these predictions be revealed to the voting population? Such knowledge could influence the number and distribution of votes and in that way impact our process for fair elections. Because the opportunity to call the winner

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[22] Callaway, 2013

[23] Moor, 1985

before all the votes were cast was new, it revealed a "policy vacuum" for how to handle to the knowledge. As the Glowing Plant project intimates, synthetic biology will raise questions that we have no pre-existing framework for considering.

Much about the Glowing Plant experiment is still uncertain. The team has hit several predictable scientific issues such as the limited amount of light actually produced by the genes they insert into plants. One outcome is clear, though. The project has provided a foretaste of the complexities that will need addressing once synthetic biology makes it easy for cells to be genetically programmed at will by anyone anywhere.

IV. Scientific and Social Concerns

Looking back again at the SENCER backgrounder on nanotechnology,[24] the author notes how the public's feeling of "wow" for a new technology can quickly turn to "yuck" as concerns about the impact of the technology are drawn out. The data from the Wilson Center supports this idea, showing that concerns about synthetic biology overtake optimism when the potential risks and benefits are described.[25] When a technology asks us to reconsider our place in the natural world, as synthetic biology does, that technology can quickly move from a place as the "cornerstone of a bioeconomy" and "solution to the world's persistent challenges" to "Frankenfood" and a poster child for the "Law of Unintended Consequences." When synthetic biologists describe cells — our cells! — as tiny machines or factories, they also ask us to question our own humanity.

The bio-error and the bio-terror scenarios are both high on the "yuck index" for synthetic biology. Programming a cell is not like programming a computer in that when a line of code for my laptop is written, that code must be deliberately altered to modify it. For example,

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for (i = 0) printf("hello");
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will print "hello" until someone decides to change it to

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for (i = 0) printf("good-bye");
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By contrast, the genome of living cells can mutate in response to environmental pressures, giving rise to genetic code that may resemble the original, but not perform identically to it. Visible evidence for the potential of spontaneous code revisions is found in the pathway for β-carotene. When mutations arise in a metabolic step for this biosynthetic pathway, the resulting product can be red, yellow or white in color. These differences are easily observed using standard microbial techniques.

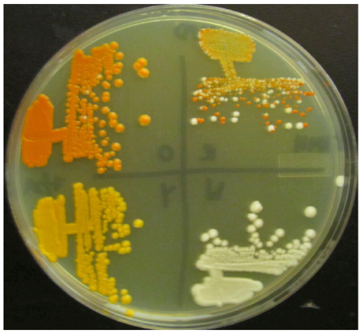

Image credit: Kathryn Hart
A petri dish with variants that spontaneously arise from a yeast strain originally programmed to produce β-carotene.

In the context of a synthetic cell that, say, enters our body to find and kill cancer cells, small genomic changes could be inconsequential or life threatening. Since they are based on the regulation of materials rather than information, the regulatory framework in the United States and elsewhere are insufficient for considering these differences. The EPA, for example, is in charge of toxic substances and pesticides, while the USDA oversees plant pests, and the FDA considers foods, drugs, and animal feed. The "policy vacuum" that Moor referred to in regard to computer technology[26] applies to synthetic biology now. No agency is prepared to consider the particulars of synthetic living organisms and their potential to mutate, either by accident or through the work of malevolent actors. It is unclear how soon the field of synthetic biology will be ready to deploy a living synthetic organism as a therapeutic or

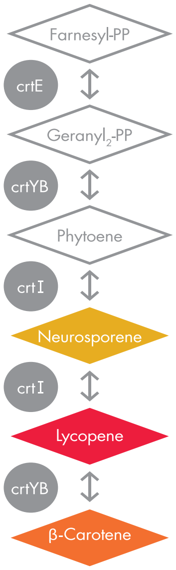

Image credit: Karen Ingram
A biosynthetic pathway that converts a common cellular precursor, farnesyl, to the Vitamin A precursor, β-carotene. The colors of the diamonds indicate the color of the compounds and the circles have the name of the enzyme that catalyzes each step in the pathway.

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[24] Kulinowski, 2003
[25] Hart Research Group, 2013
[26] Moor, 1985

into the environment. Much of the work in synthetic biology over the next few years will be to harness the power of genetics to find living solutions for grand challenges while controlling the further mutations in those solutions.

Bio-error is of further concern as we expand access to the crafting of biotechnologies and ask others to join in the rational engineering of cells. It used to be that only trained scientists in academic or commercial labs had access to the expertise, information and equipment needed to carry out biological research. Synthetic biology intentionally makes biology easier to engineer, removing the need for expert training of its practitioners and opening the door to enthusiasts just as the horticulture, astronomy and bird-watching communities have done in the past. In the same way that Legos provides widespread access to world-useable building materials, the availability of technical instruction and genetic sequence information on the Internet gives everyone who can connect to the Web access to the raw materials for planning experiments. The growing number of maker spaces and community laboratories can provide enthusiastic amateurs the equipment and space they need,[27] and for those without a local venue, they can order many kinds of used laboratory equipment through eBay or find parts on craigslist. The era of garage genomics may look to some like the era of garage computers, but to others it looks like an accident waiting to happen. Once a harmful microbe is made and released, even accidentally, we have essentially no ways to track it or selectively destroy it.

The destructive potential of biology has not escaped the notice of policy and defense experts. In July of 2013, author and former Microsoft CTO, Nathan Myhrvold wrote a backgrounder called "Strategic Terrorism." In it he makes the case that never before have so many people had access to such potentially destructive technologies.[28] Biology is just one possible weapon of mass destruction but it is, he argues, the one our nation is least prepared to deter, detect, or defend against. Though he does not cite synthetic biology per se, he talks about the need for strategic investment in counter-bioterrorism to combat the growing capabilities for anyone anywhere to engineer biology so as to meet their goals, be they good or evil.

The ethical questions raised by the computer revolution offer a helpful template for considering the ethics of synthetic biology. Computers became "personal" when they moved from number crunching machines to instruments that were useful for addressing user-specified problems and needs. In other words, computer technology became revolutionary when it became logically malleable, applicable to any ideas that could be framed as input/output functions.[29] With this change, issues of privacy, information crime, computerized decision making, and intellectual property arose. The mechanical application of other ethical theories left many computer-related questions unanswerable, leading experts to explicitly consider "computer ethics." For example, a SENCER model written by Professor Terrell Bynum allows for the teaching of computer ethics by engaging students in discussions, research, and writing about the issues raised by enhanced computer capabilities. New teaching models can address the modern policy vacuums created as the field of synthetic biology converts living systems into the next malleable substrate for answering user-specified problems and needs.

V. Connections to SENCER

Synthetic biology's application of scientific understanding in order to solve real world problems lends itself to numerous learning goals that have been defined as "essential" for success in the 21st century. Every example in this backgrounder, from refactored genomes and bacteria that serve as photographic pixels to glowing plants and synthetic cells, displays creative thinking, problem solving, evidence-based decision making, scientific and technological literacy, communication, and collaboration. Moreover, as an emerging technology, synthetic biology raises "complex, capacious" questions that are central to SENCER's educational models. It seems logical, then, that by engaging students with this field, they could develop nimble ways of thinking and working as well as learn some of the tools, skills and dispositions they will need for responsible living.

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[27] Kuiken, 2013

[28] Myhrvold, 2013

[29] Moor, 1985

Image credit: Justin Lo
Logo for MIT's project-based freshman class in biological engineering design.

Numerous classroom settings are natural places for featuring synthetic biology content. Introductory biology, microbiology, and biotechnology classes are using synthetic biology at the secondary and post-secondary levels. In most cases, synthetic biology is used to supplement existing curricula, offering modern examples or providing unsolved dilemmas to dig into. In some high schools, synthetic biology is offered as a senior elective class or as the basis of an after-school program. The success of the iGEM summer competition for college students around the planet speaks to the global interest and engagement in this engineering approach to problem solving and science. Clearly it is an intriguing point of departure for many curricula is to consider the natural world we have inherited in the context of the artificial or synthetic one we may be building.

One example of a college-level course that uses synthetic biology as a master organizing principle comes from my own teaching. At M.I.T., freshmen ordinarily take only the general institute requirements, but my class, 20.020, is one of a handful of project-based freshman classes that students can elect to add to their standard course load. Offered in the spring term, 20.020 gives students an opportunity to design and specify a biotechnology to solve a real world problem. The class is taught through interactive lectures, hands-on activities with existing synthetic systems, and long-blocks of "studio time" for team-based design work. Students focus first on a grand challenge area of their own interest, and I have deliberately kept their options completely open. It would certainly also be possible to frame a course around a single challenge (clean water, sustainable energy, etc.) and to further define the methods available for the students to achieve their goals. I have found, however, that by providing my students with a blank canvas and freeing them from the obligation of implementing their designs in the lab, they are happily unencumbered by the "it won't work" voices my more senior students hear. With a grand challenge area chosen, the students work through a bio-design framework to iteratively plan their living technology. I have seen creative and enthusiastic bio-design teams propose living systems for accelerating composting, stemming the red-tide algae blooms, harvesting lithium from ocean water, replacing defective genes in patients with muscular dystrophy, regulating iron levels in the blood of female athletes, and many, many more blue-sky project ideas. The ideas are based on extensively researched scientific understanding, but the teams are also granted some liberty in their designs, with imagined "black boxes" to mask the complexity of genetic functions that are, as of now, incompletely understood or as yet undiscovered.

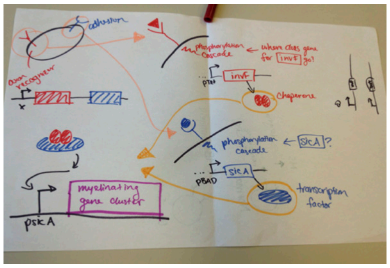

Image credit: Team Superfly, 20.020 Spring 2013
A genetic program designed to remyelinate cells, including DNA elements needed for the living therapeutic to recognize demyelated cells, to synthesize the myelin sheath proteins and to deposit of these proteins in a functional pattern.

As the term ends, many of my students have wanted to continue their work. Teams become so enamored of their ideas that they have wanted to build them. We have few opportunities today for them to do so given the persistent difficulty in assembling DNA even under the best of circumstances as well as the unknowns presented by the interdisciplinary work that the students are pioneering. In addition to the intellectual eagerness that my students have about their projects, they have also formed lasting social connections. They have learned to work with each other in healthy, deadline-respectful ways and they are sad to break up their teams as the term ends. As the field of synthetic biology matures, perhaps the fabrication and manufacturing of these imaginary solutions by teams of college freshmen will be possible. As exciting as that possibility is, not everyone is fully comfortable with it.

Image credit: Natalie Kuldell
Students in MIT's biodesign class, 20.020, working together on the details of their system

There are tremendous risks associated with such complete success. Science and engineering are human endeavors, and they do not come with 100% safety (or satisfaction) guarantees, even when the research is done in academic and industrial lab settings. Indeed, some of the greatest bio-error and bio-terror events have come from academic, industrial, and government labs (see, for example, Wikipedia Anthrax Attacks). The spirit of transparency is widespread in synthetic biology, see for example the OpenWetWare and the BioBuilder websites that provide guidance to secondary schoolers who are engineering biology. This spirit makes technical knowledge openly available, which attracts bio-hobbyists and enthusiasts, leading to synthetic biology increasingly carried out in private hands and outside of supervised lab settings. The availability of technical information and the increasing ease of putting it to use expands the possibility of outcomes we do not desire. Knowledge and oversight of work done without institutional supervision is uncharted territory, at least for modern biological sciences.

Every technology has possible negative misapplications as well complex societal implications, and synthetic biology products are no different. As a society we may not be ready for the re-tasking of the living world to suit our needs, and we are certainly far from skilled at it yet. The human practice questions in synthetic biology are interdisciplinary, complex, and unsolved, making the field an attractive target for a SENCER teaching model.[30] Even this short backgrounder on synthetic biology has touched on numerous complexities, including questions about economics, social equity, national security, and the factors that affect awareness and opinion. The idea that synthetic biology could positively impact some of our planet's most persistent challenges is a "no brainer" for some and a "nonstarter" for others. A careful examination of the public statements regarding this field as well as our personal reactions to it can enrich classroom discussions and lead us to learn the underlying science and engineering principles.

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References

Bainbridge, W.S. (2002) "Public Attitudes Toward Nanotechnology" *Journal of Nanoparticle Research* 4: 561-571.

Beal, J., Weiss, R., Densmore, D., Adler, A., Appleton, E., Babb, J., Bhatia, S., Davidsohn, N., Haddock, T., Loyall, J., Schantz, R., Vasilev, V., and F. Yaman. (2012) "An end-to-end workflow for engineering of biological networks from high-level specifications" *ACS Synth Biol.* 1(8): 317-331. doi: 10.1021/sb300030d

BioBuilder Website http://biobuilder.org/

Bynum, T. SENCER Model: Computer Ethics http://serc.carleton.edu/sencer/computer_ethics/index.html

Callaway, E. (2013) "Glowing plants spark debate" *Nature* 498: 15–16. doi:10.1038/498015a

Carlson, R. (2007) "Laying the foundations for a bio-economy" *Syst Synth Biol* 1(3): 109–117. doi: 10.1007/s11693-007-9010-z

Chan, L.Y., Kosuri S., and D. Endy (2005) "Refactoring bacteriophage T7" *Molecular Systems Biology* vol 18. doi:10.1038/msb4100025

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[30] Kuldell, 2007

Chandran, D., Bergmann, F.T., and H.M. Sauro. "TinkerCell: modular CAD tool for synthetic biology" (2009) *Journal of Biological Engineering* 3: 19. doi:10.1186/1754-1611-3-19

Cobb, M.D. and J. Macoubrie (2004) "Public perceptions about nanotechnology: Risks, benefits and trust" *Journal of Nanoparticle Research* 6(4): 395-405

Dymond J.S., Scheifele, L.Z., Richardson, S., Lee, P., Chandrasegaran, S., Bader, J.S., and J.D. Boeke. (2009) "Teaching Synthetic Biology, Bioinformatics and Engineering to Undergraduates: The Interdisciplinary Build-a-Genome Course" *Genetics*. 181(1): 13–21. doi: 10.1534/genetics.108.096784

Dymond J.S., Richardson S.M., Coombes C.E., Babatz T., Muller H., Annaluru N., Blake W.J., Schwerzmann J.W., Dai J., Lindstrom D.L., Boeke A.C., Gottschling D.E., Chandrasegaran S., Bader J.S., and J.D. Boeke. (2011) "Synthetic chromosome arms function in yeast and generate phenotypic diversity by design." *Nature* 477(7365):471-476. doi: 10.1038/nature10403

Elowitz, M.B. and S. Leibler (2000) "A synthetic oscillatory network of transcriptional regulators" *Nature* 403: 335-338. doi:10.1038/35002125

Gardner, T.S., Cantor, C.R., and J.J. Collins (2000) "Construction of a genetic toggle switch in Escherichia coli" *Nature* 403: 339-342. doi:10.1038/35002131

Gibson D.G, et al. (2010) "Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome" *Science* 329(5987): 52-56. doi: 10.1126/science.1190719

Glowing Plant Project (2013) http://www.glowingplant.com/

Hart Research Group (2013) "Awareness and Impressions of Synthetic Biology" Wilson Center http://www.wilsoncenter.org/publication/awareness-impressions-synthetic-biology

Introduction to Biological Engineering Design, 20.020 class website http://openwetware.org/wiki/20.20(S13)

Kuiken, T., (2013) "DIYbio: Low Risk, High Potential" *The Scientist* http://www.the-scientist.com/?articles.view/articleNo/34443/title/DIYbio--Low-Risk--High-Potential/

Kuldell, N., (2007) "Authentic teaching and learning through synthetic biology" *Journal of Biological Engineering* 1:8. doi:10.1186/1754-1611-1-8

Kuldell, N., and N. Lerner, (2009) "*Genome Refactoring*" Synthesis Lectures on Synthetic Biology. Morgan and Claypool Publishers. ISBN-10: 1598299476

Kulinowski, K. (2003) "Nanotechnology" SENCER backgrounder

Levskaya, A., Chevalier, A.A., Tabor, J.J., Simpson, Z.B., Lavery, L.A., Levy, M., Davidson, E.A., Scouras, A., Ellington, A.D., Marcotte, E.M., and C.A. Voigt. (2005) "Synthetic biology: Engineering Escherichia coli to see light" *Nature* 438: 441-442. doi:10.1038/nature04405

Mitchell, R., Yehudit, J.D., and N. Kuldell. (2011) "Experiential Engineering Through iGEM -- An Undergraduate Summer Competition in Synthetic Biology" *Journal of Science Education and Technology*. 20(2): 156- 160. doi:10.1007/s10956-010-9242-7

Moor J.M. (1985) "What is Computer Ethics?" *Metaphilosophy*. 16(4): 266-275

Moore G. E. (1965) "Cramming more components onto integrated circuits" *Electronics Magazine* pg: 114-117

Myhrvold, N. (2013) "Strategic Terrorism: A Call to Action" Lawfare Research Paper No. 2-2013. http://dx.doi.org/10.2139/ssrn.2290382

"National Bioeconomy Blueprint" (2012) from the Office of Science, Technology and Policy http://www.whitehouse.gov/administration/eop/ostp/library/bioeconomy

"New Directions: The Ethics of Synthetic Biology and Emerging Technologies" (2010) from the Presidential Commission for the Study of Bioethical Issues report http://bioethics.gov/synthetic-biology-report

OpenWetWare Wiki http://openwetware.org/wiki/Main_Page

Paddon, C.J., Westfall, P.J., Pitera, D.J., Benjamin, K., Fisher, K., McPhee, D., Leavell, M.D., Tai, A., Main, A., Eng, D., Polichuk, D.R., Teoh, K.H., Reed, D.W., Treynor, T., Lenihan, J., Fleck, M., Bajad, S., Dang, G., Dengrove, D., Diola, D., Dorin, G., Ellens, K.W., Fickes, S., Galazzo, J., Gaucher, S.P., Geistlinger, T., Henry, R., Hepp, M., Horning, T., Iqbal, T., Jiang, H., Kizer, L., Lieu, B., Melis, D., Moss, N., Regentin, R., Secrest, S., Tsuruta, H., Vazquez, R., Westblade, L.F., Xu, L., Yu, M., Zhang, Y., Zhao, L., Lievense, J., Covello, P.S., Keasling, J.D., Reiling, K.K., Renninger, N.S., and J.D. Newman. (2013) "High-level semi-synthetic production of the potent antimalarial artemisinin" *Nature* 496(7446): 528-532. doi: 10.1038/nature12051

pGLO kit from BioRad http://www.bio-rad.com/en-us/product/pglo-bacterial-transformation-kit

Pray, L. (2008) "Antibiotic Resistance, Mutation Rates and MRSA" *Nature Education* 1(1): 30

Registry of Standard Biological Parts http://parts.igem.org/Main_Page

Ro, D.K., Paradise, E.M., Ouellet, M., Fisher, K.J., Newman, K.L., Ndungu, J.M., Ho, K.A., Eachus, R.A., Ham, T.S., Kirby, J., Chang, M.C., Withersm S.T., Shiba, Y., Sarpong, R., and J.D. Keasling. (2006) "Production of the antimalarial drug precursor artemisinic acid in engineered yeast" *Nature* 40: 940-943 doi:10.1038/nature04640

Szybalski W. (1974) in *Control of Gene Expression* A. Kohn, A. Shatkay (Eds.) Plenum Press, New York pp. 23-24, 404-405, 411-412, 415-417.

Venter, J.C. interview by TED's Chris Anderson (2008) http://www.youtube.com/watch?v=nKZ-GjSaqgo

Wang, H.H., Isaacs F.J., Carr, P.A., Sun, Z.Z., Xu, G., Forest, C.R., and G.M. Church. (2009) "Programming cells by multiplex genome engineering and accelerated evolution" *Nature* 460(7257): 894-898. doi: 10.1038/nature08187

About the Author

Natalie Kuldell is an Instructor in the Department of Biological Engineering at Massachusetts Institute of Technology as well as Founder and President of the BioBuilder Educational Foundation. She graduated in 1987 magna cum laude from Cornell University with a B.A. in Chemistry and received her Ph.D. in Cell and Developmental Biology from Harvard University in 1994. After a post-doctoral fellowship at Harvard Medical School, she joined the faculty at Wellesley College where she taught and developed curriculum in the Department of Biological Sciences. In 2003, she was recruited to M.I.T. as they were launching a new major (Course 20) and new department in Biological Engineering. Her leadership in curriculum development and undergraduate education helped position MIT's program as a prime example of interdisciplinary engineering education, particularly in the area of synthetic biology. Serving as associate director of education for an NSF Engineering Research Center grant, Dr. Kuldell collaborated with award-winning high school teachers to collect her MIT synthetic biology teaching materials into modular curricular units appropriate for high school and early college settings. The resulting curriculum, and the non-profit organization that sustains it, is housed at BioBuilder.org.

Dr. Kuldell is spending her sabbatical year (2013-2014) as a visiting scholar with the National Center for Science and Civic Engagement, applying the SENCER model for teaching and learning to engineering education in high school and college settings.