Summary, "Synthetic Biology: Hardware, Software, and Wetware"
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By: Catherine Baker

Vaccine factories that can rapidly respond to viral threats such as bird flu. Biologically produced photocells to meet energy demands. Plants that act as sensors for explosive materials. Houses of living wood that repair themselves. Self-producing pocket calculators. Bacteria that will pan for gold. These are some of the possibilities from the nascent field of synthetic biology.

But they are still dreams. To date the field's most significant accomplishments have been the creation of cell lines that produce therapeutic proteins and useful chemicals. "That's not bad for a start," said Dr. Pamela Silver, a professor in the Department of Systems Biology at Harvard Medical School. According to Dr. Silver, synthetic biology is also making a mark through its interdisciplinary nature and in the way in which those involved in the field are proactively engaging in dialogue about the ethical issues related to their work.

Dr. Silver spoke at a November 10, 2005, lecture sponsored by the Dialogue on Science, Ethics, and Religion (DOSER), a program of the American Association for the Advancement of Science (AAAS).

Dr. Silver defined synthetic biology as "a discipline that embraces aspects of engineering and computer science in an effort to design or redesign biological systems for practical applications and also to better understand how biology works."

Though the term "synthetic biology" is itself only about thirty years old, humans have been manipulating biological systems throughout history. The domestication of dogs and the development of corn are just two examples of the great many living organisms, both plant and animal, that have been created through human intervention.

Modern synthetic biology is based on recombinant DNA technology, also called gene splicing or genetic engineering: the piecing together in novel ways of DNA strands to create something new. According to Dr. Silver, one of the first real successes in synthetic biology was the creation of artificial insulin. The gene that encodes human insulin was inserted into bacteria cells, and as those cells reproduced they generated quantities of the protein used in the treatment of diabetes. The Harvard biologist called this a "fantastic" development for medicine, noting, “I don’t think I have read anything negative about those experiments.”

Other significant products that have been created through recombinant DNA include the blood product Factor 8, which is used for people infected with HIV, and various antibodies. Research in synthetic biology also has provided scientists with a far greater understanding of genetics. “More importantly,” added Dr. Silver, “synthetic biology presents us with new kinds of engineering possibilities that haven’t necessarily been embraced by the traditional engineering community.”

Discussions of ethics and responsibility have been a hallmark of this field since DNA recombination techniques were first discovered. In 1974 American scientists declared a moratorium on recombinant DNA experiments that, while controversial, was universally observed. A symposium, held at the Asilomar Conference Grounds near Monterey, California early the next year, helped establish standards of practice. According to Dr. Silver, the primary concern at the time was over the potential for accidental release into nature of biologically designed organisms; by contrast, the greatest concern today is terrorist use of synthesized organisms.

Back in 1974, scientists were using naturally occurring DNA as their source material. Today, raw material from any number of genomes — mouse, human, microbial, and more — is readily obtainable over the Internet. In addition, chemically synthesized DNA can be obtained from more than twenty different companies around the globe. MIT has created a Registry of Standard Biological Parts (parts.mit.edu) from which one can order “biobricks.” For example, one can order DNA sequences that enable an organism to light up, or fluoresce.

The ability to synthesize DNA is exceeding Moore’s law, according to Dr. Silver, which means a doubling of information approximately every 18 months. DNA costs about $1 per base pair, which means that a small bacterium of 1 million base pairs could be made for less than $1 million. Prices have dropped 50 percent in the last few years and are expected to keep falling. Even so, DNA is still pricey for the typical laboratory scientist, the biologist added.

The Harvard biologist acknowledged that while many of the experiments in synthetic biology are intriguing, not much progress has been made. The technology is not at the stage where long strands of DNA can be synthesized or where totally new genes or totally new proteins can be created. “Nonetheless, the opportunity is now here to begin to design entire genomes and to construct minimal genomes.” As an example, scientists recently rebuilt the polio vaccine and are in the process of rebuilding a bacterial phage. (The scientists who reconstructed the polio virus, Eckard Wimmer of the State University of New York at Stony Brook and his colleagues, claimed they did so to demonstrate that this kind of potentially dangerous project is possible.)

As a “stellar example” of the benefits from synthetic biology, Dr. Silver pointed to the work of Jay Keasling and colleagues at Lawrence Berkeley National Laboratory in California. These researchers are close to synthesizing artemisinin, a naturally occurring product that is highly effective against malaria but very difficult to extract from plants and extremely expensive (it is sold by Novartis). The Bill and Melinda Gates Foundation have provided $42.6 million in grants to advance this promising research.

According to Dr. Silver, synthetic biology has parallels to engineering in that scientists make use of tangible elements, use signal processing and communication, construct modularly, use assembly line processes to duplicate materials, and problem-solve, that is, they seek to produce products with practical applications.

Unlike conventionally engineered machines, however, biological machines are in theory at least capable of self-repair and evolution. Whether evolution in machinery will be a bane or a boon is not yet known. “It could end up being good: you could go from an inefficient biological machine to an efficient one by letting the cell do the work for you.”

Dr. Silver’s own work is in biologically based computing. She is working with yeast cells, which divide asymmetrically (by budding off a daughter cell from the mother cell). The yeast has been modified with DNA to trigger fluorescent activity during cell division; this makes the division countable. Applications that might result from such experiments include being able to count the number of times a cell has divided, being able to isolate cells of a specific age, and the development of drugs that affect cell aging.

Equally exciting to the biologist is her work using synthetic biology to train the next generation of scientists. She has been advisor to the Harvard teams participating in iGEM, the Intercollegiate Genetically Engineered Machines Competition, which encourages students to build simple biological machines. The competition is a way “of building a responsible field,” she asserted. The first iGEM took place in 2004 with five schools participating. The 2005 iGEM competition involved thirteen teams, with two from Europe. Some 30 teams are anticipated for the 2006 season.

The world’s first biological photographic film was created through iGEM 2004. Students from the University of Texas at Austin genetically modified *E. coli* bacteria with light-inducible protein elements, spread the bacterium into a thin film and then used stencil and light exposure to generate a picture of the words “Hello World.” (One can read about this work in the November 26, 2005 issue of *Nature*, which focuses on synthetic biology).

In another exciting project, a team from Harvard University created a “biowire” — a line of bacteria down which a signal can be propagated. Dr. Silver pointed out that this team featured a computer science student, and iGEM teams also have included students from the fields of math and physics and even a history of science major.

Concerns raised by synthetic biology research include fear of the accidental release of self-replicating synthetic organisms, hostile use of such organisms, and ecological contamination. An ethical question raised by the research is how the creation of synthetic cells affects our definition of life. In response to these concerns, choices are to halt further research in synthetic biology (“probably too late for this,” Dr. Silver noted), to provide some kind of partial control or monitoring, or to encourage a responsible, open-source research environment.

Dr. Silver encouraged those interested in learning more about synthetic biology to check the numerous web sites on the subject, in particular **syntheticbiology.org,** sponsored and maintained by members of the synthetic biology research community, and the Wikipedia encyclopedia listing at **en.wikipedia.org/wiki/Synthetic_biology**. Dr. Silver also maintains an “open wetware” website (openwetware.org/wiki/Silver_Lab), to promote the sharing of information among researchers and groups in synthetic biology.

A response to Dr. Silver’s remarks was provided by Lisa N. Geller, an attorney at Wilmer Cutler Pickering Hale and Dorr LLP. In addition to being a Ph.D. biologist and an attorney, Geller also is a member of the Genetic Screening Study Group, an independent group that has worked on scientific ethical issues, mostly dealing with genetic discrimination.

Dr. Geller noted that the expenses involved in synthetic biology are not going to prevent the research from going forward. While at the moment the cost to make a bacterium is about a million dollars, “let me remind you that a good pharmaceutical product — not a great one like Prozac or Viagra, just a run of the mill good one — is worth one million dollars a day, so a million to make a sequence is really not such a big deal. It just depends on who you are talking to, an academic or someone in industry.”

In Dr. Geller’s opinion, the ethical questions concerning stem cells, cloning, and other issues related to recombinant DNA technology have been handled piecemeal and inadequately. Furthermore synthetic biology presents a slightly different set of issues because it is as much technology as science. For that reason, the attorney points to technological fields for models of oversight. For example, engineers are licensed and they are governed by codes of ethics. She cautioned that such oversight might be resisted by scientists. As it stands now, “your license to practice molecular biology is your funding,” she said.

Dr. Geller also noted that in many scientific fields, ethics discussions are relegated to seminars for graduate and post-graduate students. The field of synthetic biology is the exception, however, with Dr. Silver and her colleagues taking the lead to promote discussion among themselves as well as with students coming into the field.

Work in synthetic biology does not fall under the same monitoring that experiments involving humans do, such as the monitoring from Internal Review Boards. The work, which is international in scale, also would require oversight that can cross international boundaries. Regulation and monitoring have costs, and it needs to be determined who will pay for it. “We’re probably not going to be willing to pay for it until something bad happens,” Dr. Geller noted.

In the United States, only scientists who make use of public money are regulated. Much of synthetic biology research occurs in privately funded labs; it would be a novel step to introduce oversight of privately funded researchers. Global enforcement of any practice standards also would be difficult, “but that doesn’t mean we don’t try,” said Dr. Geller.

During the question-and-answer period, discussion centered on the issue of who is funding synthetic biology research and how that might affect its regulation. Dr. Silver noted that her research is not supported by federal funds. “It’s not clear that if I wrote a grant to the NIH that I would get it, because there is still a philosophy at NIH that we should be doing hypothesis-driven research.” At the same time, her synthetic biology research strays close to engineering, which makes it less fundable as a science project. “The cancer genome, that’s the big thing now at NIH, but is that more valuable than the cell that can make hydrogen fuel 50 years from now?”

Dr. Geller commented, “If NIH doesn’t want to fund it, I know where the money’s coming from: put together industry or venture capitalists who want to be on the first floor. I have qualms about that myself, but that is more and more the trend: to move this kind of work to private funding. But remember, if it’s privately funded, right now we don’t regulate that very well.”

Other funding sources include defense agencies, the pharmaceutical industry, and the Linux open-network model of “lots of little biohackers, building something big,” according to Dr. Silver.

Both speakers pointed to the need for more effective education of the public. Dr. Geller suggested that a flu epidemic, and how that is handled, might serve as a “wedge” to force more negotiation on monitoring the field. She noted that it will not be smooth or easy to introduce regulation “into an area that has not had a lot of it before and always had ways of getting around it.”

A questioner noted that theologians and philosophers had not been mentioned by the speakers as participants in the ethical discussions surrounding synthetic biology. Dr. Silver responded that iGEM competitions field interdisciplinary teams and are one avenue for non-scientists to enter the scientific discussion. She said she would “love” to have Harvard divinity students on her iGEM team. “We’re trying to build a community where anyone can join the conversation, because personally I find that more interesting.”