include monetary issues, as well as training and transfer of technology and scientific information, so developing nations could profit from deep-sea research both commercially and scientifically. However, Newman thinks that benefit sharing should be weighted among different partners to cover the relative cost of those who contribute. Johnston added that being able to assess quantitatively where and how much deep-sea research is taking place will also improve the quality of environmental impact assessments.

Not surprisingly, industrial and academic parties have mixed reactions to the value of any future international policy. Mathur was more positive and commented that he was the first industry member to be invited to the UN conference on benefit sharing three years ago. He hopes industry representatives will be invited again to allow them to present their view before any global legislation is passed.

There is still the question whether the UN would be the right organization to oversee regulations of international deep-sea research and biodiscovery. For instance, Shank questioned the effectiveness of any UN policy because "scientists do not think about looking on a UN web page on a daily basis and most probably have not heard of the recent UN document." Similarly, Stetter conceded that he had not even heard of the UNU–IAS document and commented that any regulation by the UN "smells of bureaucracy". Newman questions whether a UN policy would have any effect if not all countries translate it into binding national law. He called the UN Convention on the Law of the Sea a "toothless tiger", which has not stopped overfishing because many nations do not enforce the policy. In addition, Distel pointed out that it will be a very complicated process to get all countries to adopt and adhere to a common policy: "The political and natural [borders] may conflict and complicate the issue of delineating protected areas."

While the scientists and lawmakers continue to debate whether the UN is the right organization to regulate research, most agree that the scientific community should be looking to the future. As Christoffersen pointed out, there may be much more commercial interest in the deep seas to come. "We don't have resorts and hotels in the deep sea yet and it will be decades before that might happen, [but] it is good that efforts for policy have been started because the currently limited deep-sea expedition traffic will probably increase in the next few decades."

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Laura Ruth

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The engineer's approach to biology

Engineers' interest and contributions to molecular biology have sparked a completely new research field: synthetic biology. Despite no commercial applications so far, the prospects for basic research are exciting

In 1998, computer scientist Ehud Shapiro returned to the Weizmann Institute in Rehovot, Israel, as a group leader after a five-year break as a software entrepreneur. At the peak of the Internet boom, it would have been easy to find an exciting topic to pursue in computer science. Instead, Shapiro became interested in the origin of life and began to train himself in molecular biology, which eventually sparked his idea to build computers from biological molecules. His team first constructed a molecular Turing machine based on DNA, restriction nuclease and ligase to perform simple computations (Benenson *et al*, 2001), soon followed by a more sophisticated system that performs stochastic computations using mRNA molecules as input (Benenson *et al*, 2004).

What seems merely to be the intellectual interest of an Israeli computer scientist—using biological compounds and systems to create logical circuits—has in fact become the hottest area in the biological sciences: synthetic biology. Other engineers are also dropping their soldering guns for micropipettes to rewire genes and genomes with the aim of reprogramming living organisms. "Synthetic biology is the other side of the coin of systems biology," commented Victor de Lorenzo, Vice Director of the National Centre of Biotechnology in Madrid, Spain. "What you want is to create or recreate systems that have some properties of life from engineering principles." This includes a range of techniques from recombinant cloning, to synthesizing genomes *de novo*, to creating completely new entities such as Shapiro's artificial systems. However, more interesting than the technology itself is the ability to create artificial metabolic and regulatory pathways and to

test their viability in living systems. It allows scientists to probe the complexity of an organism's innards and thus derive further insights into how cells work. As George Church, Professor of Genetics at Harvard Medical School (Cambridge, MA, USA), described it: "It obviously inherits all kinds of things from chemistry, engineering and genetic engineering but the larger thing is, it involves whole systems."

Tinkering with the whole system instead of individual components holds enormous potential for creating artificial organisms to serve the needs of humans. Synthetic biology could spawn a brave new world, free of the environmental or health problems that plague many industrial processes. Artificial bacteria could produce energy from sunlight, water and organic wastes. Cellular reactors could replace energy-intensive, wasteful multi-step chemical synthesis. Synthetic molecules produced by biocatalysts could create new avenues for drug and vaccine development. Genetically modified bacteria could constantly scan the environment for toxic pollutants and break them down into harmless compounds. Synthetic organisms in our bloodstream could monitor body cells for pathogenic derivations and synthesize therapeutic molecules to stop a disease in its tracks.

Although much of this is still science fiction, some applications are already in place. Genetically modified bacteria are already used to break down toxic pollutants in the environment (Cases & de Lorenzo, 2005). Bacteria could be modified to defuse land mines by breaking down their explosives (Williams *et al*, 2004). Scientists are testing modified plants to extract heavy metals and organic toxicants from polluted soils (Peuke & Rennenberg, 2005). Jay Keasling, Professor of Chemical Engineering at the University of California, Berkeley, USA, plans to create bacteria that synthesize amorphadiene—the precursor for the anti-malaria drug artemisin—the only source of which is the wormwood tree *Artemisia annua*. J. Craig Venter plans to produce, among other things, a hydrogen-producing organism as a cheap source of fuel. And

> Synthetic biology could spawn a brave new world, free of the environmental or health problems that plague many industrial processes

Shapiro's molecular computer is only the first step towards his main goal: to create an artificial system based on biological compounds that constantly monitors mRNA levels in the body and synthesizes therapeutic nucleotides to switch off gene activity if it detects any pathogenic derivations. As James Collins, Professor of Biomedical Engineering at Boston University (MA, USA), said: "It's a fascinating area. It's got everything: interesting characters, interesting science and some concerns."

Engineers are also designing biological circuits combined with tailor-made proteins as sensors to act as input/output devices, and genetic networks to calculate appropriate responses to a given input and to control gene activity. Their ultimate aim is to create a toolbox of biological circuits that can be combined in a living cell, much as standard circuits are put together on a computer motherboard (Ferber, 2004). Collins' team rewired two mutually inhibitory repressor genes to create what is known in electrical engineering as a 'flip-flop' circuit (Gardner *et al*, 2000), a switch that can alternate between two different states. Keasling's project to create artemisin-producing bacteria is ambitious as well, as it involves creating new biochemical pathways by inserting plant and yeast genes into the bacterial genome and placing them under the tight control of regulatory networks. Scientists have also managed to synthesize whole viruses from single nucleotides and cell-free extracts (Cello *et al*, 2002; Smith *et al*, 2003). Going one step further, the research group of Drew Endy at the Massachusetts Institute of Technology (MIT; Cambridge, MA, USA) redesigned the genome of bacteriophage T7 based on engineering principles and showed that this new organism—which they dubbed T7.1 in a nod to software developers—is viable and infectious (Chan *et al*, 2005). Synthetic biology is also finding its way into biology and engineering curricula. Students at MIT's Biological Engineering Division are challenged to reprogramme bacterial genomes to make *Escherichia coli* blink like a lighthouse—not a simple task given that students have to figure out how to make a single cell emit regular light bursts and make the bacteria communicate with each other so as to blink at the same time. Given that the ultimate goal is to create new organisms by rewriting their genomes, it is no wonder that synthetic biology has received much attention both in the scientific media and in the public press—"Pimp my genome", one headline put it (Davies, 2005).

Yet, scientists have tweaked and tinkered for decades with genes and whole biochemical and regulatory pathways to create products such as insulin-producing bacteria, plants that synthesize antibodies and other therapeutic molecules (Twyman *et al*, 2005) or bacteria that break down organic toxicants. "Synthetic biology is in a way not unlike what was done by recombinant cloning," commented Eckard Wimmer, Professor at the State University of New York, Stony Brook, USA. "Even changing 'circuits' had been done before. This is already synthetic biology." Church also sees it as an extension of earlier work. "[Synthetic biology] technology was seeded by earlier technologies" such as polymerase chain reaction, nucleotide synthesis, recombinant cloning and electrical engineering, he said. "The basic tools were around for decades but got more sophisticated."

Church added that reduced costs for DNA sequencing and synthesis have now made biology interesting for engineering approaches. Indeed, synthetic biology is largely driven by technologies to cheaply synthesize DNA molecules of up to several thousand base pairs—pioneered by Church's group (Tian *et al*, 2004), among others—which allows the creation of whole genomes or parts of genomes. "Now the technology is such that you can build entire genomes from single components," de Lorenzo said. "You can build chromosomes a la carte."

> "Synthetic biology is in a way not unlike what was done by recombinant cloning"

What is certainly different is the mindset that proponents of synthetic biology—many of whom come from engineering—bring to biology. "First, engineers are really good at building things. We can build things even if we don't understand how every detail of the system works," commented Collins. "Second, engineers in general are really good at dealing with complex systems… Third, engineers are really good at modelling." In fact, ignoring the unknown is a main idea behind synthetic biology. "You focus on parts of the science that you do understand and clean out the parts that you don't

understand," Church explained. "The paradigm shift is that you treat biology like engineering [and] work with the parts that you understand."

> …synthetic biology is largely driven by technologies to cheaply synthesize DNA molecules of up to several thousand base pairs…

Still, there is a difference between designing a bridge and designing a regulatory pathway in a living organism—even when ignoring parts that are not understood. "An engineer's approach to looking at a biological system is refreshing but it doesn't make it more predictable," Wimmer said. "The engineers can come and rewire this and that. But biological systems are not simple… And the engineers will find out that the bacteria are just laughing at them." Collins also conceded that the complexity of living organisms is a problem for straightforward engineering approaches: "If you have incomplete knowledge then it is highly possible that you are up for a few surprises."

This, however, has not impeded the commercial interest in synthetic biology. Attracting most of the media coverage is Synthetic Genomics (Rockville, MD, USA), founded by Venter and Hamilton Smith, who shared the 1978 Nobel Prize in Physiology or Medicine with Werner Arber and Daniel Nathans for their discovery of restriction endonucleases. According to the company's website, their goal is to create genetically tailor-made organisms for energy production and the environmentally friendly production of industrial chemicals. While the sky is obviously the limit for such synthetic life forms to synthesize or degrade complex compounds—hydrogen production being the 'Holy Grail' of synthetic biology according to de Lorenzo—others have more humble expectations for the nearer future. Church also sees a future market for drug and vaccine development, but in the short-term he expects commercial development driven mainly by a "tools industry" to produce genetic circuits. "You need a complete set of regulatory tools for a variety of organisms," he explained. "There is already a market for the synthetic genomics part." Church, together with Endy and Keasling, founded Codon Devices (Cambridge, MA, USA) to create such genetic circuits.

Similarly, Collins founded Cellicon (Boston, MA, USA) to use the tools and technologies from systems and synthetic biology for drug development.

But basic research stands to profit first from this influx of engineers to biology. "To me, what is more fascinating is this interface with engineering [which] provides a concept or a framework of how a system works," de Lorenzo said. "Biology has to import this framework from different fields." In fact, although construction is still the primary focus of synthetic biology, engineers are beginning to explore fundamental questions, Collins said: "We are increasingly turning to basic science." This is why it acts as the other side of the coin of systems biology: by creating and putting together artificial metabolic and regulatory circuits, synthetic biology provides the experimental framework needed to understand how genes and their products interact in a living system and how this creates complexity. This approach makes even failures valuable, because they show where the gaps in understanding are and point researchers to interesting new questions. "You tackle important questions about the origin of life," de Lorenzo said, adding that this approach may revolutionize biology in the same way that physicists helped to establish molecular biology in the 1950s.

For any new technology, there are concerns about potential misuse and accidents—however, these are not new themes. "I would say that this is a deja vu of genetic engineering," de Lorenzo commented. The ability to synthesize or rewrite genomes of pathogens has both security experts and the public worried about the misuse of this technology for nefarious purposes (see the Viewpoint by Hamilton & Smith, p4 in this issue). Around 100 laboratories worldwide already have the capacity to synthesize smaller viruses, such as polio or flu, and the technology is advancing fast. "… [I]n five years you [could] have this synthesis facility in every university lab…With this technology you can make poliovirus for 50 cents," said Wimmer, who first synthesized the poliovirus from single nucleotides as a proof-of-principle and to warn society about the possibilities of this technology (Cello *et al*, 2002). "You cannot stop this technology because there is a great hunger for it from many biologists."

The problem is that the sequence information for many pathogens—polio, flu, smallpox, anthrax and others—is freely available on the Internet. Wimmer regards this as a main security concern, particularly for diseases that are being or have been eradicated, such as smallpox or polio, and against which humans have lost immune protection. "If some jerk then

takes the sequence of [a dangerous pathogen] and synthesizes it, we could be in deep, deep trouble," he said. However, he strongly opposes strict regulation or even control of this information, as was recently proposed in the USA by North Carolina Republican Senator Richard Burr, to create a government agency to control scientific information (Lee, 2005). "There is no way to bottle up this information… You may as well tell everybody about the dangers and tell society to do something about it," Wimmer said. Instead, he pointed out, scientists and the public should be aware of misuses and use these new technologies to design drugs and vaccines, which would also be extraordinarily beneficial for healthcare.

> …although construction is still the primary focus of synthetic biology, engineers are beginning to explore fundamental questions…

Similar concerns about accidental releases of engineered biocatalysts, which could create havoc with the environment, have been around since the 1975 Asilomar conference on the risks of recombinant cloning. While Church concedes that there are some legitimate concerns about safety that would require new rules and regulations, he pointed out that the new technologies might in fact be even safer. "Synthetic biology may not lead to releases of organisms into the environment, because synthetic biology is more sophisticated," he commented. Engineers could control their organisms by building in clocks that kill them after several cycles, by preventing the exchange of genes, or by using non-viable organisms with non-natural nucleotides, for instance. "There are all kinds of new safety systems you can make with synthetic biology," Church said. Collins pointed out that a sophisticated regulatory framework is already in place, for instance at the US Food and Drug Administration (FDA) or the Environmental Protection Agency (EPA). "FDA or EPA don't care whether it is synthetic biology or not," he said. "You are going to have to get clearance from them."

The synthetic biology community seems to be aware of these concerns and has begun to lead the debate. In 2004, Church wrote a white paper that proposes some regulation and oversight to reduce the danger of misuse (Church, 2004). In June 2005, MIT, the J. Craig Venter Institute (Rockville, MD, USA) and the Center for Strategic and International Studies (Washington, DC, USA) announced a joint project to examine the societal implications of synthetic biology with respect to risks and benefits as well as ways to prevent abuse. In fact, scientists need to learn from the debates over genetically modified organisms to avoid similar mistakes in the future, according to de Lorenzo. "I think the question of regulation should not be the first question…Let's first see what [the technology] is good for," de Lorenzo said. "If you first ask the question about risk, then you kill the whole field."

The future will show if synthetic biology, sparked by engineers' interest in molecular biology, marks a new era in biological research—and whether its commercial arm will develop all the exciting products. For now, amid increasing interest from the scientific community and the hype surrounding the field, it is refreshing to see someone inject some pragmatism. "The proof is in the results," Shapiro said. "If good results come out of it, it's good."

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Holger Breithaupt

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