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Synthetic biology

Life 2.0

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The new science of synthetic biology is poised between hype and hope. But its time will soon come

Get article background

IN 1965 few people outside Silicon Valley had heard of Gordon Moore. For that matter, no one at all had heard of Silicon Valley. The name did not exist and the orchards of Santa Clara county still brought forth apples, not Macintoshes. But Mr Moore could already discern the outlines. For 1965 was the year when he published the paper that gave birth to his famous "law" that the power of computers, as measured by the number of transistors that could be fitted on a silicon chip, would double every 18 months or so.

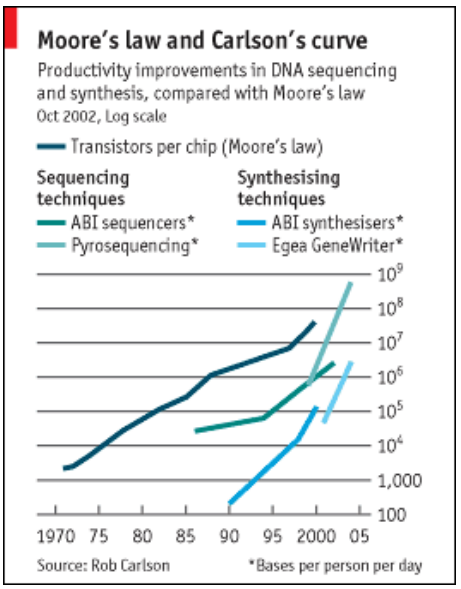
Four decades later, equally few people have heard of Rob Carlson. Dr Carlson is a researcher at the University of Washington, and some graphs of the growing efficiency of DNA synthesis that he drew a few years ago look suspiciously like the biological equivalent of Moore's law. By the end of the decade their practical upshot will, if they continue to hold true, be the power to synthesise a string of DNA the size of a human genome in a day.

At the moment, what passes for genetic engineering is mere pottering. It means moving genes one at a time from species to species so that bacteria can produce human proteins that are useful as drugs, and crops can produce bacterial proteins that are useful as insecticides. True engineering would involve more radical redesigns. But the Carlson curve (Dr Carlson disavows the name, but that may not stop it from sticking) is making that possible.

In the short run such engineering means assembling genes from different organisms to create new metabolic pathways or even new organisms. In the long run it might involve re-writing the genetic code altogether, to create things that are beyond the range of existing biology. These are enterprises far more worthy of the name of genetic engineering than today's tinkering. But since that name is taken, the field's pioneers have had to come up with a new one. They have dubbed their fledgling discipline "synthetic biology".

Truly intelligent design

One of synthetic biology's most radical spirits is Drew Endy. Dr Endy, who works at the Massachusetts Institute of Technology, came to the subject from engineering, not biology. As an engineer, he can recognise a kludge when he sees one. And life, in his opinion, is a kludge.



No intelligent designer would have put the genomes of living organisms together in the way that evolution has. Some parts overlap, meaning that they cannot change jobs independently of one another. Others have lost their function but have not been removed, so they simply clutter things up. And there is no sense of organisation or hierarchy. That is because, unlike an engineer, evolution cannot go back to the drawing board, it can merely play with what already exists. Biologists, who seek merely to understand how life works, accept this. Engineers such as Dr Endy, who wish to change the way it works, do not. They want to start again.

So Dr Endy has developed an idea invented by Tom Knight, one of his colleagues at MIT. Dr Knight calls the idea "BioBricks". His inspiration was a children's toy called Lego. What makes Lego successful is that any part can attach to any other via a universal connector. A BioBrick is a strand of DNA that has universal connectors at each end. BioBricks can thus be linked together to form higher-level components and also joined into the DNA of a cell so that they can control its activity.

Dr Endy likes BioBricks because they promise the synthetic biologist the standardised set of parts that has been one of the advantages enjoyed by the electronic engineers behind Moore's law. If an engineer wants a particular component for a job, he can go to a catalogue, find a widget with the right parameters and order it from a supplier. He does not have to design it himself. He does not even have to know how it works. Dr Endy thinks BioBricks can put biologists in the same position.

The DNA of a BioBrick contains a combination of genes that acts as a standardised component. When translated into protein in a cell, it makes that cell do something—and that something is often more than just "make more of protein X". In particular, Dr Endy is interested in switches and control systems that regulate other genes. Such switches are the basis of electronics and he hopes they may one day become the basis of an industrialised synthetic biology.

At the moment, BioBricks, like Lego, are still a toy. They have been used for proof-of-principle studies such as taking photographs with films made of modified bacteria, but not yet for serious applications. But there are a lot of them around—many in the public domain at MIT's Registry of Standard Biological Parts. Such "open wetware" is one reason for the emergence of biohacking (see article).

Whether BioBricks will come to dominate the field remains to be seen. One difficulty they face is the cussed tendency of biological things to evolve. An electronic component, once designed, can be turned out reliably in a factory. BioBricks are bred, rather than made, and that introduces scope for error. Meanwhile, other researchers are content to work with things that more closely resemble natural components, although they still assemble them in unconventional ways.

A new synthesis

One of the leading proponents of this method is Jay Keasling, of the University of California, Berkeley, who also believes that synthetic biology will ultimately need standard, well-characterised parts if it is to thrive. But he is trying to get there via a practical project, rather than by generating lots of components and waiting for others to think of what to do with them.

Dr Keasling's project is to do biologically what no chemist has yet managed to accomplish—to synthesise an antimalarial drug called artemisinin cheaply. At the moment, artemisinin is a herbal remedy. It is extracted from *Artemisia annua*, a type of wormwood, and the best source is in China. Making artemisinin by standard chemistry requires so many steps that it is impractical. So Dr Keasling persuaded the Gates Foundation to back his idea for doing the job using synthetic biology.

For this, he has built a metabolic pathway in yeast cells that synthesises a chemical called artemisinic acid which chemists can easily convert into artemisinin. Some of the genes to do this have come from *Artemisia*, but others have been created from other sources.

Dr Keasling's project is not the only one to lay down artificial metabolic pathways. One goal of synthetic biology is to make what is known as cellulosic ethanol. At the moment, ethanol—whether for wine, beer or fuel—is made by fermenting sugar or starch. But even in crops such as sugar cane and maize, which have been bred for their high yields, a lot of the plant is wasted. Although yeast cannot digest cellulose or lignin, the molecules that form a plant's skeleton, some bacteria and other species of fungi are able to do the job. Identifying the genes for the enzymes that do this, modifying them and assembling them into new pathways would produce systems that could digest the whole plant and turn it into ethanol. Nancy Ho, of Purdue University, in Indiana, has already worked out a way to enable yeast cells to ferment the sugars produced by breaking down

cellulose—which natural yeast cannot do.

This is important stuff. Cellulosic ethanol is the great hope of many environmentalists since its carbon, unlike that in fossil fuels, comes from the atmosphere and thus cannot make a net contribution to global warming when it returns there.

The ultimate proof of the success of synthetic biology, though, would be not merely an artificial metabolic pathway, but an artificial organism. That is the goal of Craig Venter. Dr Venter, the man who first sequenced the entire genome of a living creature (a bacterium) and then went on to run a private-enterprise rival to the publicly funded Human Genome Project, has re-invented himself again. This time he is synthesising genomes, rather than analysing them. Three years ago he made the first viable synthetic virus from off-the-shelf chemicals. (It is a parasite of bacteria, not humans.) Now he has a bacterial genome in his sights.

To make the task easier, Dr Venter is first creating what he and Hamilton Smith, his collaborator at the Venter Institute in Rockville, Maryland, call the minimal genome. This is a stripped-down bacterial genome that contains the smallest set of genes consistent with life in the cushy environment of a laboratory. Such a genome would have several advantages for synthetic biologists. First, being small, it would be easier to make. Second, it would not survive in the big, bad world outside the laboratory, should it chance to escape. Third, it would not dissipate its biochemical effort on non-essential tasks. That means it could be used as a platform on which to bolt commercially useful pathways.

According to Dr Venter, the raw materials for those pathways are abundant. As he observes, half the mass of living organisms on the planet is made of bacteria and these bacteria are divided into zillions of species with countless unidentified genes. For the past couple of years he has been sampling the oceans and collecting bacterial genes. He has identified about 6m.

Among them are, for example, 20,000 genes for hydrogen-metabolising proteins. That is of particular interest, since Dr Venter sees synthetic biology as a source of new energy-generating technologies—and he has the backing of America's Department of Energy to prove the point. He has also found numerous genes for versions of rhodopsin. In vertebrates this protein is found in retinal cells, where it transduces the energy of light into a nerve signal to the brain. What it is doing in so many bacteria is not known, though one possibility is signalling how deep they are in the ocean as a consequence of how dark it is. Whatever the cause, the energy conversion that rhodopsin brings about is also of interest.

It's life, Jim, but not as we know it

Dr Venter reckons he will be able to synthesise a working bacterial genome from scratch within two years. More complex genomes, of the sort that make plants, animals and fungi, will take longer. But they, he thinks, should be possible within a decade. Even this definitive erasure of the distinction between the living and non-living worlds is not, however, the most radical idea in synthetic biology. Some people want to go beyond the toolkit that evolution has provided and create biological systems that work with a chemistry that is not found in natural living things.

Biology's operating system relies on two sorts of molecule: nucleic acids and amino acids. Nucleic acids (DNA and its cousin, RNA) act as information stores. The information they store is how to assemble amino acids into proteins, which are chains of linked amino acids. Proteins then go on to do the work of sustaining life. They manufacture other sorts of biological molecules, such as fats and sugars. They process energy. They provide structural support for cells.

One of the recurrent principles of evolution is "if it ain't broke, don't fix it". That is why the kludges Dr Endy is trying to eliminate have endured across the millennia. Once the nucleic acid-amino acid operating system came into existence it could never be "fixed" into anything else by evolution, because the immediate consequences would have been so serious. But that does not mean it cannot be changed by an intelligent designer, and a number of such people are looking into how this might be done.

One obvious improvement would be to increase the number of amino acids that can be assembled into proteins. At the moment only 20 are used routinely in biology, but chemists can make thousands of others. Proteins containing those "non-biological" amino acids would have novel properties, and some of those properties might be useful. That, at least, is the thinking behind the attempt by Lei Wang, of the Salk Institute in La Jolla, California, to extend the amino-acid parts set. Dr Wang's starting point is the redundancy of the genetic code used by nucleic acids. This code is spelled out in the genetic "letters" A, C, G and T, which correspond to chemical sub-units of nucleic acids. The letters are grouped into three-letter "words" known as codons, meaning that there are 64 of them. All but three of the codons correspond to particular amino acids, and the order of the codons in the nucleic acid corresponds to the order of the amino acids in the protein. The remaining three are signals that the protein is complete.

But, with more codons than amino acids, many amino acids have more than one codon to describe them. There is also a superfluity of stop signals. Dr Wang has managed to reassign one of the stop codons in *E. coli*, the bacterial workhorse of geneticists, to recognise an unnatural amino acid. This can now be incorporated into proteins made by the bacterium.

Peter Carr of MIT and Farren Isaacs of Harvard Medical School have an even more ambitious plan. They intend to recode *E. coli* completely, eliminating the redundant codons. They have settled on one codon for each

natural amino acid and one for the stop signal and plan to go through the bacterium's entire genome replacing alternative codons with their chosen ones. The idea is that the cleaned up bacterium will be more efficient. That remains to be seen; natural selection has been working on *E. coli* for a long time, so whether two intelligent designers can do a better job is questionable. But if their new bacterium is at least viable, it will have 43 codons that can be re-assigned to other tasks.

The debate evolves

Where all this will lead is anybody's guess. But synthetic biologists themselves are aware of the risks. The most obvious is that somebody, whether a malicious biohacker or a political terrorist, will do something deliberately nasty. The other risk is that something will escape accidentally.

No technology is risk free, but synthetic biology has the twist that its mistakes can breed. Today the risks are not great. As David Baltimore, the president of the California Institute of Technology, observes, "nature is a very tough critic". Any organism modified in a laboratory is unlikely to make it in the outside world in competition with creatures toughened up by natural selection. Nevertheless, as knowledge increases, so will the risk that something truly nasty might be unleashed.

To avoid that and the opposite problem of hasty legislation to curb their activities, researchers are trying to get their retaliations in first by promoting public debate. Their historical model is the Asilomar conference of 1975, when the first biotechnologists met to agree on self-denying ordinances that went a long way towards establishing their credentials as responsible and trustworthy people. Despite initial fears, biotechnology has not, up to now, caused any serious problems.

A recent meeting of biosynthesists in Berkeley issued a discussion document; the Sloan Foundation has paid for a report, coming out soon, on the risks and social implications of synthetic biology. So far, perhaps surprisingly, the wider public has shown little interest. Perhaps it should.