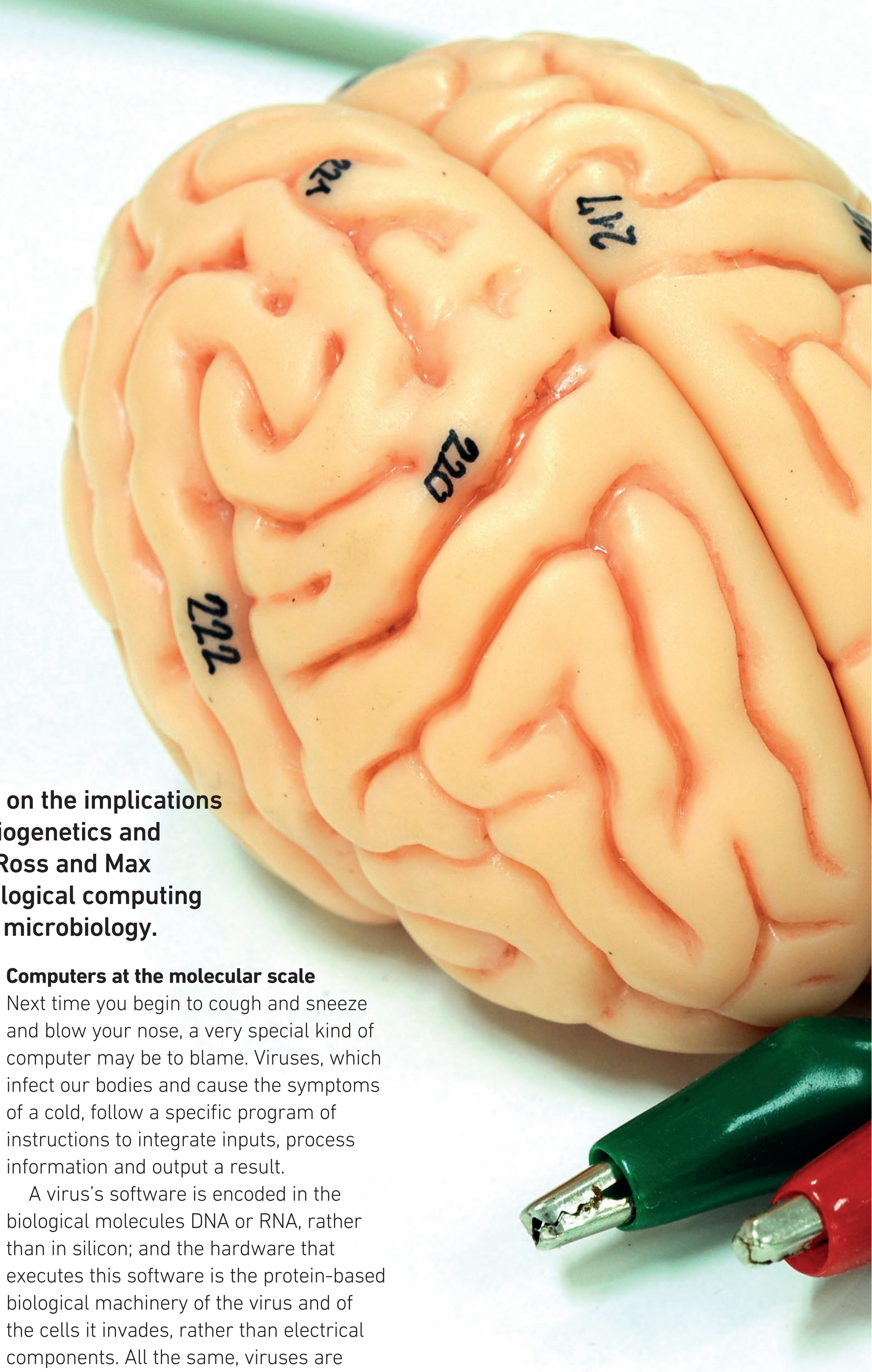


The third in a series of four articles on the implications of the convergence of computing, biogenetics and cognitive neuroscience by Charles Ross and Max Jamilly looks at the new field of biological computing and swapping microprocessors for microbiology.

Traditionally, computers and biology do not mix. Computers are made of silicon and organisms are made of cells. Computers were invented and organisms evolved.

Biological systems have taught us invaluable lessons about computers, and computers have helped us to probe the depths of the brain and mind. The last two articles in this four-part series investigated how neuroscientists and computer scientists have used cutting-edge artificial intelligence and high-tech prosthetics to combine their two disciplines and explore new frontiers.

Yet perhaps computers and life were never truly distinct at all: scientists are learning that biology has been doing computing all along. Biological systems are even more specialised at processing complex information than the greatest supercomputers. The new field of biological computing allows us to swap microprocessors for microbiology, using our knowledge of computers to redesign the incredible, invisible architecture of living things as if they were machines. Human-machine interactions could be greater than we ever imagined.

Computers at the molecular scale

Next time you begin to cough and sneeze and blow your nose, a very special kind of computer may be to blame. Viruses, which infect our bodies and cause the symptoms of a cold, follow a specific program of instructions to integrate inputs, process information and output a result.

A virus's software is encoded in the biological molecules DNA or RNA, rather than in silicon; and the hardware that executes this software is the protein-based biological machinery of the virus and of the cells it invades, rather than electrical components. All the same, viruses are molecular computers. The term 'computer virus' may be more apt than it seems.

Next time you begin to cough and sneeze and blow your nose, a very special kind of computer may be to blame.

Although the modern definition of computers is limited to electronic devices, the earliest manmade computers were mechanical. From ancient devices like the Antikythera mechanism through to immediate precursors of modern computers like Charles Babbage's Difference Engine, these devices used protoypical hardware and software to apply Boolean logic and arithmetic in order to solve problems. And, in turn, all these wonderful machines came millions of

doi:10.1093/itnow/bww084

TOWARDS ARTIFICIAL PROSTHETIC BRAINS

years after the original computers – living organisms.

The precursor to life was some kind of self-replicating chemical system over four billion years ago. Many of the details are lost in prehistory but biochemists can spot remnants of those early life-forms in modern organisms and follow the trail back into the mists of time. Reconstructions suggest that these systems were capable of consistently executing specific programmes and, later, of separately storing these programmes and generating the hardware to maintain them. Modern-day viruses, possibly a close reflection of these ancient beginnings, are among the simplest molecular computers of all. More complex organisms, such as bacteria, yeast and multi-cellular organisms, can function entirely autonomously with exquisite computational power.

It is at a much smaller scale, inside every cell in every tissue of the body, that the architecture of life really mirrors that of a computer.

We are familiar with the idea that brains behave like computers and that computers behave like brains, but it is at a much smaller scale, inside every cell in every tissue of the body, that the architecture of life really mirrors that of a computer. Nature seems to have invented computers long before we did.

Reprogramming life: synthetic biology

Imagine you are a computer scientist who discovers a mysterious device. First of all, you would try to understand its hardware, then to decode its software. The ultimate test of your understanding of the device would be to build a new one from scratch. One of the hallmarks of any Turing machine is that it can be reprogrammed to perform any logical task. In the same way, our understanding of biological computers will reach its climax when we can reprogram them entirely.

A cell's genetic code, written in DNA, contains the basic blueprint for each cell's structure (its hardware), and also the instructions for its functions (software). In the second half of the twentieth century, biologists invented a remarkable array of techniques to read and modify this code. Only recently, though, has it become truly possible to treat cells like computers and make definite changes to the code.

The answer to reprogramming

organisms is synthetic biology, an exciting and cutting-edge new field which seeks to apply the principles of engineering to biology. Traditionally, biologists have been interested in studying existing organisms in order to find out how they work and how to fix them when they break. Synthetic biology, on the other hand, takes what we know and uses it to build new things.

The task for synthetic biology lies in creating biological parts which are modular enough to be built up into functional systems like electronic computers. By analogy to engineering, biologists are aiming to build parts whose function is so reliably predictable that they can simulate entire systems before they actually do the work of building them. But it remains a great challenge to design the right modules and create systems where these parts behave reliably and predictably.

Electronic circuits in modern computers depend on logic gates which perform Boolean logic to convert inputs into outputs: AND, OR, NOT and so on. Synthetic biologists build genetic circuits using the molecular equivalents of logic gates, molecules which interact in predictable ways to convert inputs to outputs. For example, consider the Boolean AND gate, which takes two inputs, both of which can be 0 or 1. The AND gate produces the output 0 unless both inputs are 1, in which case the output is 1. A biological equivalent of the AND gate is a genetic switch which controls a gene that makes a fluorescent protein. The switch needs two specific sugars to be turned on. If, and only if, both sugars are present, the switch activates the gene and the fluorescent molecule is produced. The earliest synthetic circuits combined logic gates like these to perform basic computational functions such as output switching or oscillation.

A group at MIT built a DNA-based digital-to-analog converter which integrates signals, stores them in memory, and uses logical decision-making to choose an output.

The risk of obsolescence is minimal... even after another sixty thousand years, and for however long humans survive, we will still have the biological machinery for reading DNA.

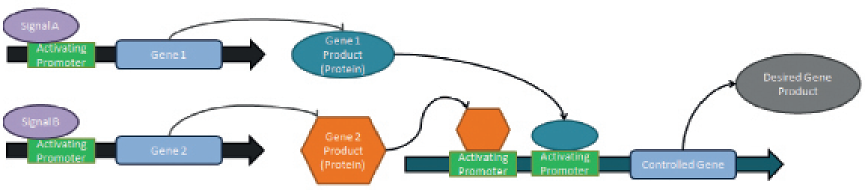
After a decade of research, synthetic biology has exploded into a vast, creative field that designs exquisite circuits to synthesise new biomolecules, detect chemical signatures or respond to the environment in real time. Researchers at Stanford have created the modular biological equivalent of a transistor, one of the key components of all modern computers; and a group at MIT built a DNA-based digital-to-analog converter which integrates signals, stores them in memory, and uses logical decision-making to choose an output. In 2016, another lab at MIT took an electronic design automation (EDA) program, normally used by electrical engineers to design integrated circuits, and repurposed it to specify genetic circuits which they built in real cells with a 75 per cent success rate. One of the products was the largest synthetic circuit ever built.

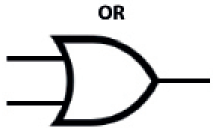
As synthetic biological parts become more reliable and complex, cells could become the new servers, but with one key difference: biological circuits offer far greater possibilities for integrating with the human brain.

Could biology overtake electronics?

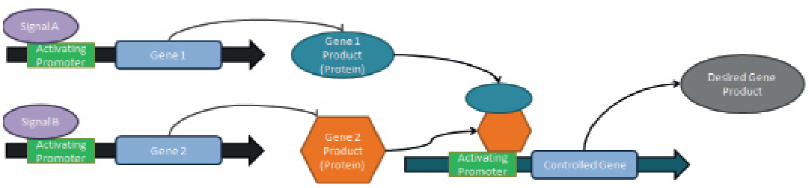
Synthetic biology is exciting but its potential remains unclear. Since most synthetic circuits are designed by analogy to electrical systems which already exist, how could the biological versions ever match them, let alone become elaborate enough to overtake them and support brain-computer convergence?

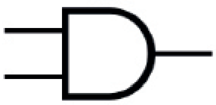
In fact, efforts to harness the computing power of biology began long before





input		output
A	B	OR
0	0	0
0	1	1
1	0	1
1	1	1





input		output
A	B	AND
0	0	0
0	1	0
1	0	0
1	1	1

Logical gates such as OR (top) and AND (bottom) can be encoded using genetic circuits. Next to each logical gate is its circuit symbol and a 'truth table' showing the possible inputs and outputs. Max Jamilly (CC) synthetic biology. Whereas synthetic biology attempts to harness existing cellular hardware to engineer new software, some biologists are making biological computers without cells at all. Leonard Adleman, one of the fathers of modern computer science, used the combinatorial power of DNA to solve the famous travelling salesman problem and other mathematical problems in his laboratory in the 1990s. Smaller and more efficient than electrical circuits, these chemical machines could have immense processing power.

Astonishingly, rat brains have been wired together to make a brain network which predicts the weather.

DNA has a natural tendency to pair with complementary molecules and form a hybrid 'duplex'. This has allowed researchers to develop a method called strand displacement, where an input DNA molecule interacts with a collection of DNA duplexes and, under certain conditions, can unzip a duplex to form its own hybrid, releasing another strand as output.

Microsoft Research, the blue-skies research division of Microsoft, has been leading the effort to build tools for programming DNA circuits using strand displacement. Logic gates built in this way have been used to compute square roots inside a test tube, solve a game of noughts and crosses, or even to make basic neural networks within less than $1x10^{-15}$ litres (which is very, very small).

Molecules never forget

Computer architecture depends on three key components: an input/output unit, a central processing unit (CPU) and memory. DNA in cells is nature's most ancient and highly adapted memory system. Stable, self-replicating, with a storage density millions of times greater than solid-state drives and ready-made cellular hardware for reading and writing,

DNA is a serious contender for the future of data storage. Some of the greatest modern computer scientists have moved to biological labs as they attempt to combine DNA-based memory with synthetic computational genetic circuits.

Data stored in DNA could last for a very long time. Sixty-thousand year-old DNA from woolly mammoths has been recovered intact. The risk of obsolescence is minimal, too. The electronic data storage standards of thirty years ago are forgotten today – how many people still have VCR players at home? – but even after another sixty thousand years, and for however long humans survive, we will still have the biological machinery for reading DNA. Amounts of DNA invisible to the naked eye have already been used to store HTML-formatted books, images, audio and computer programs. Highly stable DNA could form the basis for long-term archival data storage in the future. As DNA synthesis and sequencing become fast and cheap, accurately writing and reading huge amounts of data to DNA memory is already feasible.

Bringing it all together

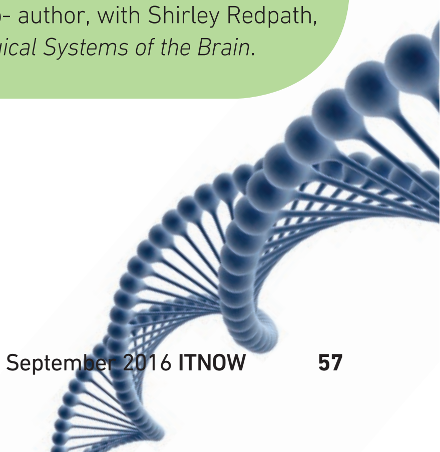
As promising as biological computers currently are, the holy grail of human prosthetic brains remains a long way off. Many of the systems described in this article can function inside the human body, such as circuits which detect the signature of a tumour in order to release a cancer drug. In order to decode signals from the brain and match patterns in synthetic circuits, however, we still need better algorithms and more robust circuits. Modular DNA parts for synthetic biology are still not sufficiently reliable; DNA storage still has very high latency.

Nonetheless, implanted prosthetic brains and advanced brain-machine interfaces are no longer the stuff of science fiction. Astonishingly, rat brains have been wired together to make a brain network which predicts the weather. Monkeys can learn to combine their mental processing capacity to solve virtual tasks. Synthetic circuits may provide the perfect interface for harnessing the power of human brains. Computers began with biology. Now we have come full circle, using the lessons learnt from electrical computers to design and build novel biological machines. Yet many hurdles remain before we can combine biological computers with the processing power of the human brain.

www.RealTimeClub.co.uk.
www.BrainMindForum.org

Max Jamilly is a PhD candidate on the BBSRC/EPSRC Synthetic Biology Centre for Doctoral Training at the University of Oxford. He holds a BA in Biological Natural Sciences and an MPhil in Biotechnology Enterprise from the University of Cambridge. His interests lie in the interface between engineering and biology, and in using biology to build new tools for computation, industry and therapeutics. Max has researched epigenetics in Cambridge, UK and gene assembly in Cambridge, US. You can follow his writing and research at **max.jamilly.com** and **twitter.com/UKsynbio**

Charles Ross has spent fifty eight years in both the entrepreneurial and research aspects of computing and has been associated with four world firsts in software design. He was elected a fellow of the BCS for his early work on software diagnostics and an Honorary Fellow for jointly launching *Computing* with Haymarket Press, and its subsequent sale. He assisted with the negotiations with the Oxford University Press (publishers of *ITNOW*), then managed the Quantum Computing in Europe Pathfinder Project- the only contract the BCS has obtained with the European Commission. He is a founder member of the Real Time Club and Chairman of the Brain Mind Forum. He is the co- author, with Shirley Redpath, of *Biological Systems of the Brain*.



Images: Thinkstock/Jezperklauzen