COMPUTING WITH THE STUFF OF LIFE

Researchers are taking inspiration from the workings of human organism when it comes to developing next-generation switches, sensors and chipsets.
By **Christine Evans-Pugh**, **Aasha Bodhani** and **James Hayes**.

THE INVENTION of the silicon transistor brought us the computer-centric world we live in, and now scientists are applying the principles of computing to biology in ways that could be equally revolutionary over the next 50 years. Whole new ways are being discovered, for example, of creating computing building blocks from prokaryotic microorganisms and DNA. Elsewhere, cognitive computing chips are being designed to create working models of human brain-functions.

Researchers have the idea to create tiny computers from networks of nucleic acid molecules such as DNA and RNA, using high and low concentrations of molecules as signals, rather than the high and low voltages in electronics.

Successful proofs of principle of nucleic acid computers have already been built, and researchers are working on more complex systems. Scientists at the California Institute of Technology (Caltech) have, for instance, built a DNA-based neural network that operates like a tiny brain.

Milan Stojanovic of the Medical Centre at Columbia University in New York has developed a kind of DNA FPGA. A group at the Swiss Federal Institute of Technology in Zurich led by Yaakov Benenson has created a circuit to detect cervical cancer markers in cells and destroy the cancerous cells.

At the heart of these systems is Watson-Crick base pairing, the chemical 'Velcro' that binds the two strands of the DNA double helix together. Methods to exploit this phenomenon vary but the common factor is that input molecules enter a computational network and output molecules emerge that are a mathematical function of the input.

GLOW IMAGES

Soup-er computers

Over the years, Erik Winfree's Caltech group has built combinations of structures such as AND, OR and NOT gates from scratch using nucleic acid strands that interact by strand-displacement (see box, right) in a kind of computational soup.

The project to build a 'brain in a test tube', led by postdoctoral scholar Lulu Qian, involved developing a soup of 112 different types of DNA structures called 'seesaw gates', 'threshold gates' and 'fuel molecules' that could sum input signals, apply positive or negative weights to different inputs, and set thresholds using strand-displacement. The researchers made four fully-connected artificial neurons from these elements, based on a simple model of a neuron, called a linear threshold function, in which a neuron fires and communicates with its neighbours when the sum of signals it receives is above a certain threshold.

To show that this 'brain' could recognise things based on incomplete patterns, the group concocted a question-game to identify one of four scientists, each represented by a set of answers to four yes-or-no questions. A human player would add to the test tube some of the DNA strands corresponding to one set of answers. Fluorescent signals triggered by the presence of particular output strands indicated which scientist the circuit had guessed. It answered correctly every time, according to Qian. This circuit could, in theory, work in a volume of one cubic micron, which is smaller than a single transistor.

Dr Milan Stojanovic at Columbia University is making

strand-displacement computing circuits in a slightly different way using catalytic DNA enzymes, known as deoxyribozymes, that act on other DNA strands. Most recently his group built a multi-purpose molecular circuit that works like an electronic field programmable gate array (FPGA). The design is such that a series of DNA soup circuits all containing identical DNA logic structures can be made to operate in many ways by activating them with differently sequenced 'training' strands.

Computer-in-a-cell

Yaakov Benenson and his team in Zurich, working with MIT professor Ron Weiss, are creating circuits inside cells using the ready-made machinery of cellular enzymes, which nature uses to switch genes on and off and make Boolean logic-like systems that compute molecular answers in response to environmental stimuli. Benenson's group has developed a technique using RNA interference to make one of the most complex cell-based computers ever built, although it is still much simpler than Caltech's 'soup' circuits.

RNA interference is a process by which short pieces of RNA, called microRNAs, inhibit the activity of certain messenger RNA within cells. Cells have many regulation mechanisms but RNA interference is the most amenable to synthetic engineering. It can be combined in parallel, in cascade and in various other ways that enable it to perform complex computations.

Benenson and his team identified five microRNAs characteristic of cervical cancer **>**

Brain work: IBM Synapse researchers Paul Merolla and John Arthur.

BUILDING ORGANISMIC ELECTRONICS

One aspect of biological computing has recently shown that intestinal bacteria and even DNA can form the basis of 'logic gates' – devices that can be switched between two opposing states – using chemical triggers.

Biological logic gates could, think researchers at the Department of Bioengineering and the Faculty of Natural Sciences at Imperial College London, be used as 'processors' in microscopic 'biological computers'. They would take form of sensors designed to detect and address pollutants and toxic substances in at-risk environmental situations, such as places with a risk of toxin leakage.

The four-year-long project – 'Engineering modular and orthogonal genetic logic gates for robust digital-like synthetic biology' – built a type of biological logic gate called an AND gate from an E Coli sample with modified DNA, which reprogrammed it to perform a 'near-digital' on-and-off switching process when stimulated by chemicals.

"In the test system we used small, simple, naturally occurring sugars as primary signals to turn on the genes," says Professor Martin Buck of Imperial College. "These sugars can be used by bacteria for growth, and we employed the regulatory systems that control the sugar utilisation genes as primary building blocks."

Next, a NOT gate was created, which was then combined with the AND gate to produce the more complex NAND gate. The research will attempt to develop more complex circuitry that comprises multiple logic gates. One challenge here is linking multiple logic gates together in a way similar to how electronic logic gates connect together to enable complex processing.

"Biological computing devices may include sensors that swim inside arteries to detect the build-up of plaque, and even to deliver medications to affected zones," says Professor Buck. Other applications posited include sensors capable of

detecting and destroying cancer cells.

The interdisciplinary team – which also included Professor Richard Kitney of Imperial's Centre for Synthetic Biology and Innovation and Department of Bioengineering, Dr Nicholas Joly of the Faculty of Natural Sciences, and Baojun Wang of the Faculty of Natural Science – say that its demonstrations show that biological logic gates can be linked: this suggests the possibility of modular biological processors.

"The difference with the Imperial project is that our devices are predictable and robust, and have been shown to work in differing environments," says Professor Kitney. "Discovering that we were able to control a naturally-occurring biological mechanism in the way we wanted to was something of a surprise. Establishing a biologically-based control system means that you can override cellular functions and start to look at ways to constraining a cell so that it operates in a desired way."

"The next research stage could lead to a type of circuitry for processing information," suggests Professor Buck, "complex biological circuitry processing information using chemicals, in the same way that our body uses them to process and store information. Bacterial and biological-based computers have to be seen as fundamentally different systems to silicon-based devices, and may never match the latter's instruction execution rate. They may match in memory, but these will much slower than electronic computers in speed of operation… [However] they may well excel in dealing with problems where it is unclear what instructions to give; complex problems could instead be evolved to an answer."

Bio-gates have more advantages over other synthesised techniques, says Professor Kitney: "They are better suited to functioning in harsh or unpredictable environments, and are able to draw energy from their local environments."

< and designed a 'classifier' circuit able to detect the markers and produce a protein output to destroy the cells. "We build the template in the form of synthetic genes and the cell turns them into components," says Benenson, "So we are hijacking the pathway that already exists, but we design new regulation mechanisms that utilise microRNA."

EDA for DNA

As research has progressed, it has become clear that software tools are needed to help design and debug such circuits. Lulu Qian, for instance, has written a compiler, which takes a specification of a logic circuit, converts it to DNA network representations, simulates it, and provides sequences for DNA molecules.

Microsoft Research in Cambridge UK is also active in this field with Luca Cardelli, head of the programming languages group, and Andrew Phillips, head of the biological computation group, working closely with experimentalists at Caltech, Washington, and Oxford Universities to develop a programming language and software tool called DNA Strand Displacement (DSD) model to simulate and analyse strand-displacement circuits.

"With DSD, the user can write down a description of DNA complexes, including how individual DNA strands are joined together and which regions are exposed," says Phillips, "and the tool generates the behaviour of the complexes over time."

Phillips' group, which is part of the computational science lab run by Stephen Emmott, also

'Biological gates are able to draw energy from their local environments'
Professor Richard Kitney

develops software for modelling systems in cells, including the Genetic Engineering of Cells (GEC) language. Work is underway to hook up different biological modelling languages in collaboration with local Cambridge researchers in synthetic biology.

"You could have a model of a DNA circuit written in DSD, which interfaces with a model of the cell machinery written in GEC, so that the DNA gets read by the cell and produces proteins, which could then act like smart drugs," says Phillips, "So the proteins would only
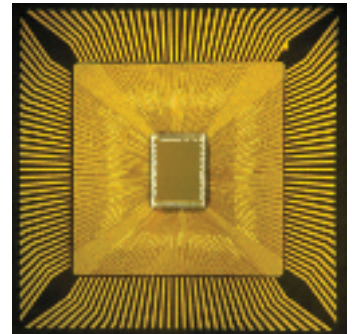

IBM's Synapse (Systems of Neuromorphic Adaptive Plastic Scalable Electronics)

be produced if the right conditions are detected by the DNA circuit."

Phillips and Cardelli predict that software tools for nucleic acid computing will rival the complexity and sophistication of those used by the computer industry, forming the foundation of a new wave of innovation. *

STRAND DISPLACEMENT COMPUTING

Inputs in strand-displacement computing are free-floating single nucleic acid strands. Logic gates are complexes of two or more strands, one of which is the potential output signal. Sticky overhanging tabs (or 'toeholds') on the gates allow passing input signals to latch-on (see upper diagram below). If an input signal has a base-pair sequence complementary to a gate, it binds to it, displacing the output strand..The free-floating output can then trigger a downstream gate so the circuit operates like a cascade (lower diagram below). Programming involves choosing the specific base sequences that make-up the different gates, and the number of types of gate and input strands.
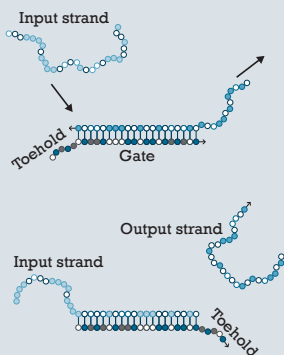
ETH Zurich's Yaakov Benenson:using RNA interference to make one of the most complex cell-based computers ever built