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**Could optogenetics be the technology that allows us to unlock the workings of the brain?**

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**Attempts to create machine intelligence that could match or exceed our own – so called strong AI – have been going on for decades, almost since the first computers emerged. Strong AI contrasts with weak AI, which typically concentrates on specific tasks to match or beat human performance – chess playing being one of the best examples.**

In the early days, advocates of Strong AI were ludicrously optimistic. If their predictions had been right, Strong AI would be with us now; and it certainly is not. Today, future gazers like Ray Kurzweil are predicting it will arrive within the next few decades, when a 'singularity' will happen – machines will be intelligent enough to design better versions of themselves and so on, leading to an 'intelligence explosion', a term coined by statistician IJ Good in 1965. There is even a Singularity Institute for AI, which says its purpose is to 'reduce the risk of a catastrophe' if the singularity occurs.



However, many remain unconvinced and there is one glaring fact supporting the sceptics: we already have billions of working examples of strong AI – ourselves – but we hardly have any detailed, specific knowledge of how we do it! While we have made a start, thanks to huge improvements in brain scanning over the last two to three decades, that work typically tells us mostly about what areas of the brain are working when we perform cognitive acts like talking or understanding images.

We know from this that our brains work in a modularised way, with areas specialising in language or vision, for example. But we still know little about what is actually going on. The fundamental question is: what do the vast assemblies of neurons actually do to enable us to perform intelligent actions?

To answer this, it looks as if a radically new kind of brain monitoring and control technique is going to be needed – and it may just have arrived. A new field of study called optogenetics – a combination of electronics, optics and genetics – looks to have the potential to both analyse in extraordinary detail how the brain operates and to control it. The hope is it will, ultimately, reveal what happens for intelligence to emerge.

If it does this, we will surely then be in a far more powerful position to create truly intelligent machines. And, potentially, we will also be able to solve major problems with our own brains Ed Boyden explains. Boyden, together with Karl Deisseroth, is one of the pioneers of optogenetics. The two first developed the approach at Stanford University, and Boyden has since become principal investigator in MIT's Synthetic Neurobiology group.

"We are inventing new tools for analysing and engineering brain circuits ... devising technologies for controlling specific neural circuit elements, to understand their causal contribution to normal and pathological neural computations," he says. "Our inventions include 'optogenetic' tools, developed for activation and silencing of neural circuits with light, and noninvasive devices using novel physical principles to control neural activity."

As he says, the group's work is making possible a new systematic approach to neuroscience, revealing how entire neural circuits operate to generate behaviour, in the process hopefully developing new therapeutic strategies for neurological and psychiatric disorders.

Optogenetics is based on the use of light sensitive proteins called rhodopsins, which are related to proteins found in the human retina. The rhodopsins used in optogenetics can change the electrical properties of nerve cells. Introduced into neurons, they insert themselves into the membrane and make them sensitive to light. Then, using lasers, it becomes possible to activate or inhibit specific sets of neurons with millisecond scale precision.

From a genetic point of view, this is radically different because most genetic manipulation is far slower, from hours or days to months. By using optogenetics to add or delete precise activity patterns in neuronal assemblies of living, intact animals, it should be possible to analyse exactly what is happening and how it enables the creature's behaviour.

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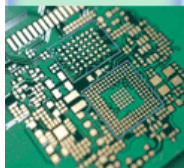
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There are several steps to the optogenetics process. First, a genetic construct is made that contains the rhodopsin gene and other elements that control its expression. Then it is packaged into a virus, which infects many neurons and delivers the construct, although the gene is only activated in targeted cells. With the rhodopsin proteins now in the appropriate cells' membranes, it is possible to trigger or silence them with light of a specific wavelength, usually delivered through an optical fibre threaded through the skull.

Optogenetics' precision is potentially far greater than other brain techniques, like a needle compared with a hammer. For example, when electrodes are inserted into brains to stimulate neurons, they typically operate on hundreds of thousands at once; far too many for really detailed analysis. The same applies to drugs or lesions. Optogenetics can turn far smaller numbers of neurons on or off.

Even though optogenetics dates back only a few years, some remarkable things have been achieved. It helped rescue breathing capacity after spinal cord injury (reference 1), restore vision in blind mice (reference 2), and control movements in creatures such as nematode worms and fruit flies (reference 3).

Optoelectronics technology plays a central role in optogenetics and Boyden gives advice to potential fellow researchers as to how to build optical fibre and laser systems that can deliver light of various colours into the brain. These are often built from affordable, off the shelf components, but Boyden is constantly looking to advance the hardware associated with optogenetics.

"For in vivo experimentation, light can be delivered to the brain by insertion of the optical fibre through a cannula implanted in the brain. But this can be difficult to do and if the fibre were to break off in the cannula, for example, it could fill the implant and jeopardise the experiment. Also, inserting a very thin, 100 to 200µm wide fibre into a cannula in the brain of an awake, moving animal can be difficult."

To overcome this, Boyden suggests using a ferrule coupling system, which can be not only far easier to use but better for experimental success. Here, an optical fibre stripped down to the cladding is attached to a metal or ceramic ferrule, enabling the fibre to be implanted into the brain, with the ferrule sticking out. Just before the experiment, the ferrule attached to the implanted fibre is connected to a similar ferrule attached to the end of the fibre that goes back to the laser.

"To control the laser, a computer controlled d/a converter can be used, and pulse or function generators can control a TTL controllable laser," Boyden says. "Another popular strategy is to use Arduino boards, which are little programmable boards that take in lots of inputs (analogue and digital), can send out lots of outputs and are easy to program. Even if you don't know how to program, there are tons of examples of code online. They just plug into your computer over USB."

One significant technological advance Boyden has developed, with Zorzos et al, is a 'multiwaveguide probe' that emits light at several points, allowing larger areas of the brain to be targeted.

While an optical fibre is limited to delivering light to a single target within the 3d structure of the brain, a multiwaveguide probe can deliver light independently to multiple targets along the probe axis, enabling more versatile optical control of sets of distributed brain targets.

"The probe is 1.45cm long and microfabricated in the form of a 360µm wide array of 12 parallel silicon oxynitride multimode waveguides clad with SiO<sub>2</sub> and coated with aluminium," Boyden says. "The waveguide array accepts light from a set of sources at the input end and guides the light down each waveguide to an aluminium corner mirror that deflects light away efficiently from the probe axis. Light losses at each stage are small and a waveguide coupled, for example, to a 5mW source will deliver more than 1.5mW to a target at a depth of 1cm."

Boyden says he is taking an 'entrepreneurial approach to tackling clinically and philosophically important problems' and one form that takes is his involvement in Eos Neuroscience. Founded in 2007, Eos is targeting vision problems as its first major application of optogenetics.

According to the company, it is in preclinical development for a therapy to restore functional sight to patients blind from photoreceptor diseases, such as retinitis pigmentosa and macular degeneration, and is developing treatments for other neurodegenerative diseases. It has achieved proof of concept for this, working with mice, and is now in preclinical development.

Although optogenetics emerged only a few years ago, such is its potential that many researchers are now using the technique. At the University of California in San Francisco, Anselm Levskaya is studying the computational processes taking place in brain cells. Neurons work in hugely complex networks featuring hundreds of enzymes and signalling molecules. The precision of optogenetics makes it possible to monitor these interactions down to the level of individual dendrites: the tiny projections on neurons where signalling takes place.

At the Institute for Integrative Genomics at Princeton, researcher David Tank is analysing mice navigating a virtual reality environment and has succeeded in imaging, at the cellular level and in real time, the activity of the animals' cells that process spatial information.

This is not to say that there are no potential obstacles for optogenetics to overcome. One is the relatively poor penetration of light into deep within the brain, caused in part by the fact that blood absorbs blue and green light, the colours most commonly used. But Michael Lin at the University

of California in San Diego has described how this problem can be solved by 'red shifting' the proteins, making them more sensitive to red than blue or green.

Whilst optogenetics' first application area is neuroscience, it may prove to have even wider potential. In the brain it is ion channels that are light sensitive and acted on, but studies have shown that other signalling proteins can be used, called G-protein coupled receptors, which are found in nearly all kinds of cells – making almost any part of the body a potential target.

Not many techniques create a virtual new field of study, but optogenetics may well do that, which is why it has been described by Robert Desimone, director of the McGovern Institute for Brain Research at MIT as 'God's gift to neurophysiologists'. "Molecular techniques were always beyond us so this is our first opportunity. It's a revolution," he concluded.

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