The A-Z of the 2019 Graeme Clark Oration

Most, if not all, scientific disciplines have their fair share of jargon. Ahead of the 2019 Graeme Clark Oration with Professor Timothy Denison, we're here to help you understand some of the terms that are commonly used in the field of neural engineering.

NEUROMODULATION

Neuromodulation involves the direct stimulation of the nervous system with electrical signals to alter their active behaviour. It is used most commonly in patients with Parkinson's disease; epilepsy; ischaemia; cardiac, bowel and bladder dysfunction; spinal cord injuries and some psychiatric disorders. This helps them manage their chronic disease when pharmaceutical interventions are ineffective and, overall, improve quality of life.

Currently, there are three types of neuromodulation:

1. **Spinal cord stimulation - the nervous tissue in a specific area of the spinal cord is electrically stimulated to block pain signals to the brain;**
2. **Peripheral nerve stimulation - a specific nerve is targeted with electrical stimulation to activate the nerve or relieve pain in a local area of the body;**
3. **Deep brain stimulation - a highly targeted, mild electrical stimulation in areas of the brain to impact on movement control, epileptic seizures and psychiatric disorders.**

The process behind neuromodulation involves implanting a small device made up of three components: electrodes, a connecting lead and a neurostimulator. The neurostimulator is programmed to send electrical pulses via the lead to electrodes that electrically stimulate the neurons in the target area. In cases of pain, by disrupting signal transmission, these pulses can replace the painful feeling with a sensation some describe as gentle massaging; for some, neuromodulation completely eradicates the feeling of pain.

Research conducted over the years has shown that neuromodulation is safe, effective and long-lasting as a treatment for chronic pain, movement disorders and other conditions. It is also reversible and adjustable, making it powerful and flexible. Current research and development in the field is focused on improving these devices and investigating whether this concept can be applied to new therapeutic areas. For example, integrating novel digital technology, machine learning and algorithms into neuromodulatory devices may help personalise treatment to better suit the needs of individual patients as well as detecting physiological fluctuations and implementing rapid-response systems that can adjust pulses accordingly, known as closed-loop control.

DEEP BRAIN STIMULATION

Deep Brain Stimulation (DBS) is a specific form of neuromodulation and is most commonly used to manage the symptoms of Parkinson's disease, particularly motor symptoms such as stiffness, slowness and tremor.

Here, the neurostimulator is surgically implanted under the skin in the upper chest. The lead travels up under the skin, through the skull and to the brain, with the electrodes positioned within the targeted brain area, specifically the subthalamic nucleus, the internal globus pallidus or the ventral intermediate nucleus of the thalamus. These regions of the brain influence movement control.

How DBS works is not yet fully understood, but researchers believe that DBS disrupts the abnormal neuronal signalling patterns (which is how brain cells communicate with one another) that are responsible for motor symptoms in Parkinson's disease. However, DBS does not address all the different Parkinson's disease symptoms; more research and development is needed.

The latest research is seeking to improve DBS devices and surgical methods in hopes of making DBS more tailored and responsive to each individual's need, as well as expanding the number of people who could benefit from the therapy. This includes investigating targeting different areas of the brain to treat walking and balance problems. Recent clinical trials have tested targeting the fornix, a structure that connects the left and right hippocampi. This new treatment strategy also has the potential to diminish memory deficits associated with neurodegenerative diseases, including Alzheimer's disease, to improve the daily functioning of patients and to slow the progression of cognitive decline.

VAGUS NERVE STIMULATION

Vagus Nerve Stimulation (VNS) involves the use of a device to stimulate the vagus nerve, which is a nerve that connects the brain with the heart, lungs, digestive tract and many other parts of the body. VNS is used as a treatment for poorly controlled epilepsy, where antiepileptic drugs are ineffective.

Typically, in VNS, the neurostimulator is surgically implanted under the skin on the chest and the lead is threaded under the skin to connect to electrodes wrapped around the left vagus nerve. When activated, electrical pulses are sent from the device that stimulate the vagus nerve. The left vagus nerve is often used for VNS because it is less likely to have connections to the heart, which means that interference with the heart's own electrical signals is less likely.

Unfortunately, researchers do not fully understand how VNS works. It is hypothesised that VNS may reshape nerve pathways, such as the ones involved in seizures. Regardless, studies have shown that in epilepsy patients, seizure control improves over time with VNS in some patients, with flow-on improvements in mood and overall quality of life.

Currently, researchers are working to better understand how VNS works and investigate its use for other conditions as well, such as inflammatory bowel disease. In fact, in Europe, new, non-invasive (meaning they do not require surgical implantation) VNS devices have been approved to treat epilepsy, depression and pain. In the USA, VNS has been approved for the treatment of cluster headaches.

BRAIN-COMPUTER INTERFACE

A Brain-Computer Interface (BCI) is a system that measures activity of the Central Nervous System (CNS) and converts it into artificial output that replaces, restores, enhances, supplements or improves the natural way that people interact with the world. BCI is a rapidly expanding technology that involves hardware and software that facilitate the interaction with computers or the control of external devices (such as wheelchairs or exoskeletons) through brain activity alone. BCI may sound like science fiction, but research into the possibilities of this technology began in the 1970s, but it wasn't until the mid-1990s when devices started appearing. The strongest breakthrough came in 2004 when the first human was implanted with an electrode array in the BrainGate research.

BCIs work by detecting the electrical signals that are produced by our brain cells and processing and interpreting these signals, which leads to an outcome (like a robotic arm moving). While this may sound simple, the electrical signals that brain cells produce are generally weak and often difficult to detect. This is often why devices need to be implanted - they need to be as close to the brain cells as possible. Also, understanding what these signals mean and how to translate them has also proved a difficulty, especially as there tends to be a lot of noise that needs to be filtered out. How can we assign a particular pattern of signals from a specific part of the brain to a movement or function? However, with machine learning and artificial intelligence, the accuracy of processing is improving. Emerging BCI technologies aim to address these current shortcomings.

CLOSED-LOOP CONTROL

A closed-loop controller adjusts its output (i.e., controlling signal) to ensure that the behaviour of the system that it is controlling remains is correct, consistent and robust. This form of system is commonly used in motor vehicles for cruise control.

Despite being well-used across many industrial applications, this type of system can also be translated into neurostimulators. Closed-loop control of stimulation of individual neurons or small groups of neurons is essential for delivery of targeted or focused stimulation with sensory prostheses, such as the bionic ear and eye, or with fine motor control of limbs and modulation of the activity of the brain. To build these systems, it is necessary to simultaneously record the activity of the neurons or the body while stimulating using the neurostimulator. When the activity strays from what is expected or what is required, the neurostimulator adjusts its stimulation to bring the activity closer to the target range. For example, the NeuroPace device, recording electrodes placed on the brain detect the start of an epileptic seizure which then activates a neurostimulator that attempts to stop the seizure using DBS.

ELECTROCEUTICALS

Electroceuticals is a general term used to describe an approach that treats a disease, disorder or illness with electrical impulses. Normally, electroceutical devices are implantable and deliver electrical stimulation to specific targets such as a nerve, brain region or organ. Such devices are already being used in people, including pacemakers for the heart arrythmias, bionic ears for deafness, bionic eyes for blindness and deep-brain stimulators for Parkinson's disease. Advances in vagus nerve stimulation and stimulating organs such as the pancreas will revolutionise electroceuticals, with devices set to become more versatile, more personalised and more powerful in their ability to treat a wider range of diseases, disorders and illnesses.

MEDICAL BIONICS

Medical Bionics is the broad term used to describe the multidisciplinary field of research that combines biology and electronics. This field, which draws from biomedical research, engineering and clinical research, is mainly focused on developing implantable devices that provide sensory or motor function that is long-term, safe and effective following nerve or muscle damage. From pacemakers to the bionic ear, the field of medical bionics has grown over the past decade due to the rapid development in materials science and electronics. As technology makes further advances, scientists working in this area hope that medical bionics could effectively help people with a variety of different sensory or neural-related disorders.

- *Professor David Grayden (University of Melbourne) and Dr Anna Chen (The Social Science) were consulted in the preparation of this document*

The Graeme Clark Oration

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