Introduction:

Bioelectronics is the application of electrical engineering principles to biology, medicine, behavior or health. It advances the fundamental concepts, creates knowledge for the molecular to the organ systems levels, and develops innovative devices or processes for the prevention, diagnosis, and treatment of disease, for patient rehabilitation, and for improving health.

Bioelectromagnetic, instrumentation, neural networks, robotics, and sensor technologies are some of the disciplines necessary to develop new understanding and products in this area.

Bioelectronic medicine is a new approach to treating and diagnosing disease and injury that has emerged from the Feinstein Institutes' labs. It represents a convergence of molecular medicine, neuroscience and bioengineering. Bioelectronic medicine uses device technology to read and modulate the electrical activity within the body's nervous system, opening new doors to real-time diagnostics and treatment options for patients.

work to generate knowledge of the mechanisms of organ control by tapping into neural pathways, develop technology that delivers safe and effective therapies with fewer adverse effects, and rapidly advance our knowledge into clinical practice along a streamlined medical device regulatory pathway.

Bioelectronic medicine may change the way we treat diseases, injuries and conditions such as rheumatoid arthritis, Crohn's disease, diabetes, paralysis, bleeding, and even cancer. We are working to develop devices to control the electrical signal used by the nervous system.

how does it work:

Bioelectronics (or electroceuticals) are implanted devices that stimulate the nervous system using electrical impulses to prevent or treat severe chronic diseases.

They consist of tiny electrodes attached directly to a nerve, connected through a wire to a pulse generator, which stimulates the nerve's activity. This is called neuromodulation. The pulse generator, along with a data processing and data storage unit, is contained within a case that is about the size of a watch. This case sits under the skin in the breast area, where it controls the nerve impulses and monitors nerve activity.

Simple non-feedback, 'open-loop' devices are already in use to treat Parkinson's disease, depression, epilepsy, and other conditions. These use consistent, pre-programmed nerve stimulations to targeted regions of the brain or peripheral nerves. However, newer state-of-the-art 'closed loop' bioelectronics are being developed that adjust treatment based on the detection of pathological nerve activity. These may provide more precise and personalized treatment than 'open loop' systems.

Recently, a woman was successfully treated for depression with an experimental closed-loop implant. But the potential for these bioelectronic devices extends far beyond psychiatric and neurological disorders. By developing bioelectronics that can target specific regions of the peripheral nerves (as well as the brain) the approach can be expanded to a wide range of complex and common diseases.

Bioelectronic devices with a simple two-channel electrode are already on the market," explains Robert Spoelgen, our Head of Bioelectronics, "but these only deliver a predetermined electrical impulse and don't monitor nerve activity or respond to feedback. We aim to develop more sophisticated bioelectronic devices that have multiple channels allowing us to target precise sub-regions of the nerve. The goal is to first record nerve activity to find the relevant physiological area of the nerve linked to certain disorders and then subsequently precisely stimulate only this sub-segment.

Bioelectronics have the potential to stimulate various nerves, but we are focusing on the vagus nerve. Running from the back of the brain via the neck and chest down to the abdomen, this major nerve carries an extensive range of signals from the internal organs to the brain and vice versa.

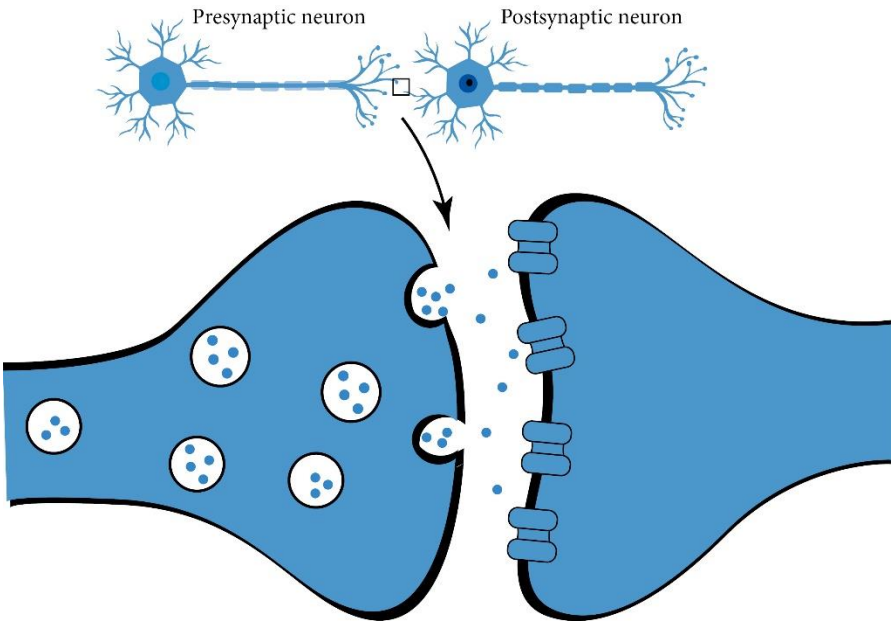
The vagus nerve is involved in a biological feedback loop called the 'inflammatory reflex. In this feedback process, the vagus nerve senses the presence of inflammatory molecules and then signals to the brain to regulate their production through immune cells produced by the spleen. In other words, it is thought to play a key role in regulating inflammation in the body. This is important as research has shown that chronic inflammation is linked with diseases such as heart disease, diabetes, and multiple sclerosis.

The vagus nerve has been implicated in many diseases and disorders, but our initial goal is to focus on its role in chronic inflammatory disorders, to see if we can develop bioelectronics that can precisely downregulate the chronic inflammation that causes symptoms like pain."

Early clinical studies in rheumatoid arthritis have shown that stimulating the vagus nerve with simple bioelectronic devices could offer an exciting new approach for treating patients with this disease. Results suggest the use of these devices not only reduce the levels of pro-inflammatory molecules, but also improve patient-reported pain and mobility.

Electrical Signaling in Biology:

One of the most important and widely known electrical signals in biology is the neuronal action potential. The neurons are specialized cells in the brain that carry the fundamental bit of information. Although the action potential is often described as a current that travels along the neuron, it is purely ionic. The driving force is the membrane potential, the difference in ionic concentration between intracellular and extracellular environment. The ionic current is generated when specialized proteins on the cell membrane, the ion channels, are activated, enabling exchange between cations and anions inside and outside of the cell. The action potential travels along the neuron without losing its amplitude because the signal is regenerated throughout the axon by the activation of adjacent ion channels. When the signal reaches the end of the axon, it triggers the release of neurotransmitters that are chemical messengers able to diffuse and reach the adjacent neuron, inducing an action potential. The action potential is triggered only if the transmembrane potential reaches a threshold and, therefore, is also called an “all or nothing event.” Communication between neurons occurs across a small gap known as the synapse, where nerve impulses are relayed electrically or chemically from the axon of a presynaptic (sending) neuron to the dendrite of a postsynaptic (receiving) neuron.



Motor neurons can also form synapses at neuromuscular junctions with muscle fibers and, in this way, control their contractions. The neurotransmitters that are released from the neuron attach to the cell membrane of the muscle fiber, causing membrane depolarization, and after a cascade of reactions, there is contraction of the fiber.

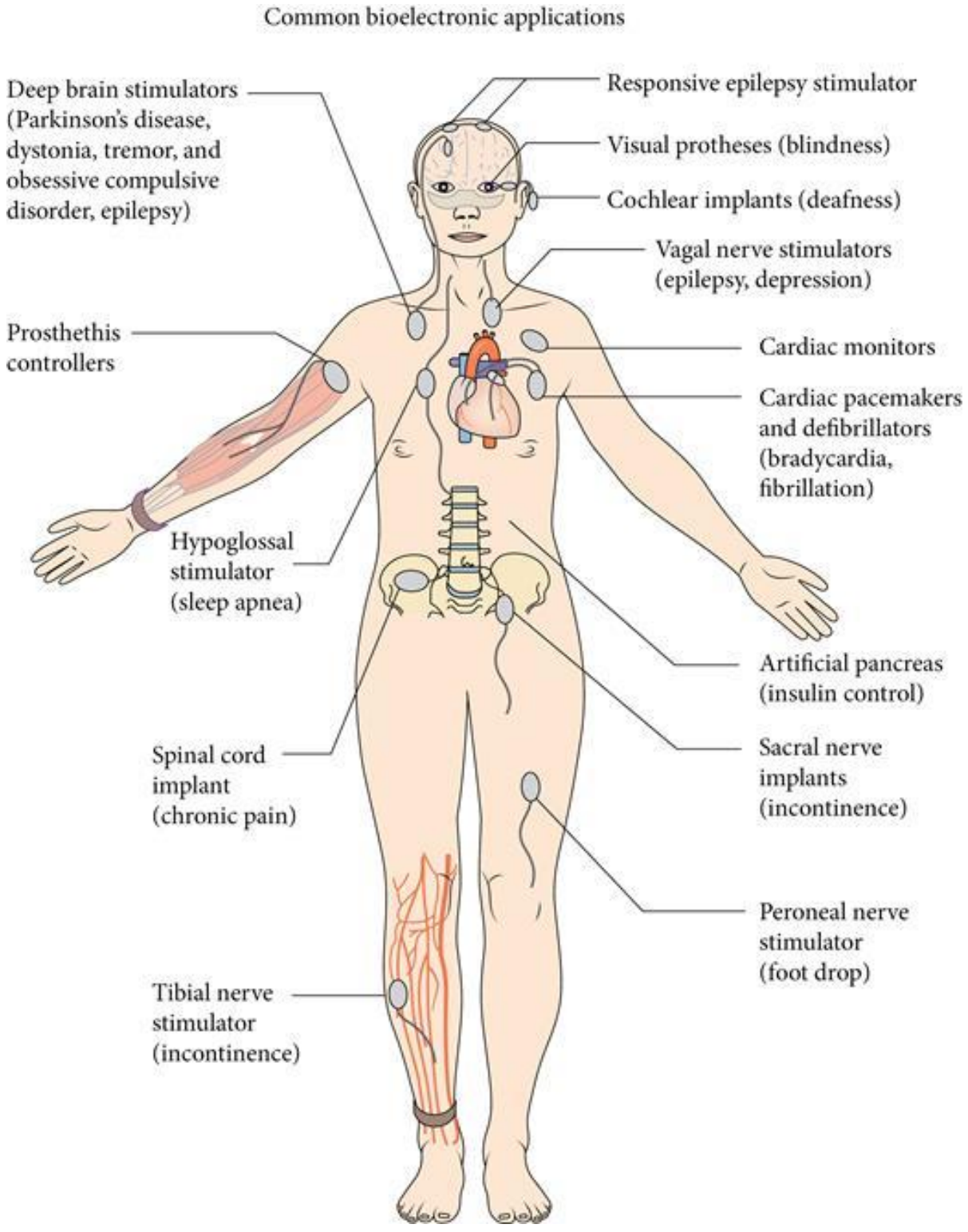
The heart function is controlled by electrical signals as well. However, the cardiomyocyte contraction is not controlled directly from neurons but from specialized cells, the cardiac pacemaker's cells. These cells depolarize spontaneously and through gap junctions initiate the depolarization of adjacent cells. The gap junctions are specialized connections between the intracellular space of two cells, enabling the electrical signal to travel from one cell to the other.

There are examples where electrons play a vital role in biological reactions as well in the form of electrochemical redox reactions. However, these reactions are usually very localized, and electrons are exchanged within molecules in proximity. An example is the generation of reactive oxygen species (ROS) in oxidative stress.

Bioelectronic Technologies Used in the Clinic Today:

The application of bioelectronics in medicine is one of the most innovative and exciting directions in healthcare today. Bioelectronics is used to advance diagnosis and care for people suffering from an ever-growing range of challenging diseases and conditions. From treatment of heart problems (arrhythmias) to deafness to bladder control to chronic

pain, bioelectronic interventions have reshaped the lives of millions of patients. The global market for bioelectronics in medicine already exceeds $22 billion and is projected to grow to more than $60 billion by 2030 (Tsao, 2019). Below, we present a brief synopsis of a selection of the most prominent clinical-grade bioelectronic technologies today.



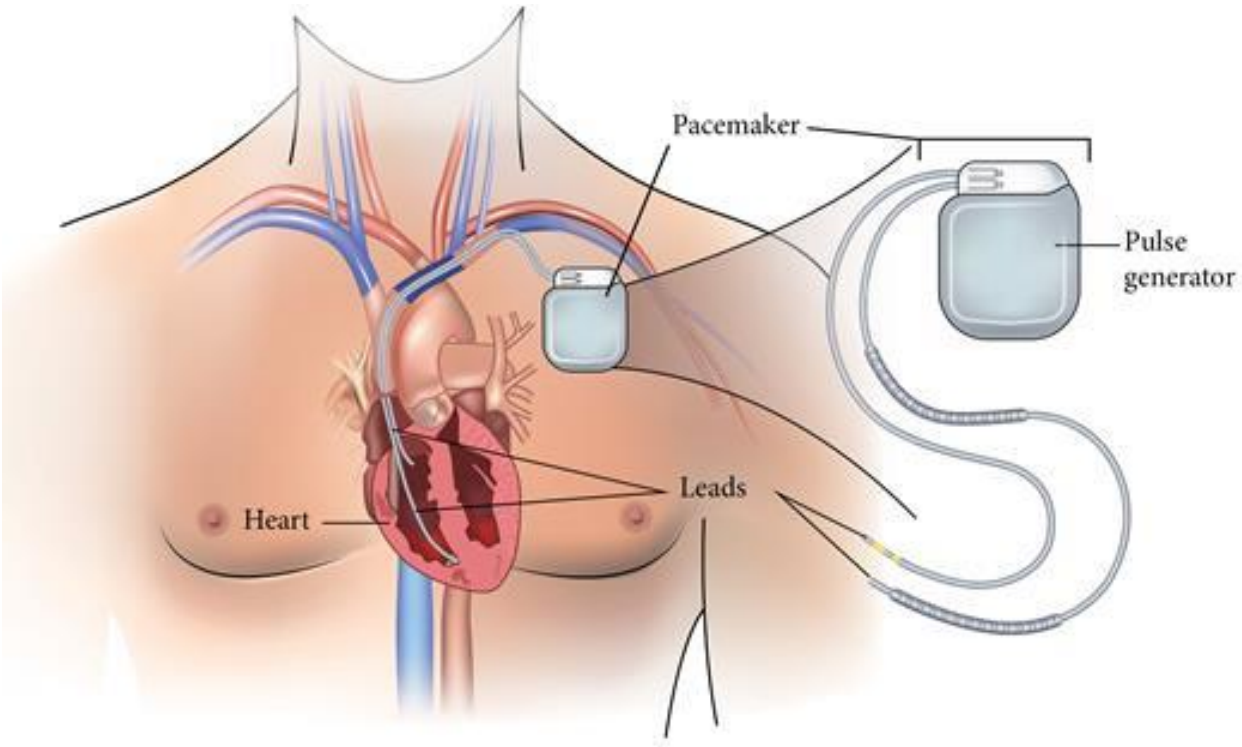
The cardiac pacemaker:

Over the centuries, there were examples of physicians or scientists who discovered a correlation between heartbeat and electric current, but it was not until the end of the 19th century, in the work of Aguste Desire Waller and Willem Einthoven, that the electrical activity of the heart was resolved with the use of the Lippman electrometer (Aquilina, 2006). Waller was the first to successfully record the electrocardiogram (ECG) in a clinical setting, but he did not realize the implications of his discovery in diagnosis and therapy. On the other hand, Eindhoven grasped the importance of ECG and developed the string galvanometer, which enabled a visualization of the ECG on a photographic plate. For his work on ECG and the string galvanometer, he was awarded the Nobel in Physiology and Medicine in 1924. Today, a 12-electrode system is used, which amplifies the signal, and it was developed in 1942 by E. Goldberg.

The use of electric current to modulate the heartbeat was shown in the 1930s independently by Doctors Mark Lidwell and Albert Hyman . Hyman's electromechanical device could stimulate the heart through a bipolar needle electrode that could be inserted through the skin. His method, though, was not widely accepted but rather seen with skepticism as it was interfering with natural processes. Furthermore, engineering problems rendered the method ineffective. In the 1950s, there were several examples of bulky stimulators with external controllers based on vacuum tubes and requirement for connection with a power outlet. The first truly portable stimulator was a battery-operated wearable pacemaker that was invented by Earl E Bakken, co-founder of Medtronic Inc., one of, if not the most, successful biomedical device companies that is still active. It required a 9.4 V mercury battery, and the stimulation was modulated via a transistor circuit. Surgeon C. Walton Lillehei applied the device on a patient only after 4 weeks of experimentation. This is something that would be impossible today due to strict regulations for translation of devices to the clinic. The first fully implantable pacemaker was designed by Swedish surgeon Ake Senning and physician and inventor Rune Elmqvist . Senning and Elmqvist wanted to minimize the risk of infection caused by the open route between electrodes and controllers in portable or wearable devices. Therefore, they designed a device that included the battery and the circuit within a box that could be placed in the abdominal wall. The battery could be recharged via induction with external coupling. The first fully

implantable pacemaker was implanted in Arne Lasson, but it operated only for a few hours, while the second one lasted for about a week. Arne Lasson went on to receive 26 pacemakers during his life and died in 2001 at the age of 86 due to a non-heart-related cause.

Following decades of technological development, pacemakers have evolved from being the last reserve of a surgeon to being a cornerstone of modern healthcare. Today, pacemakers are small enough to be implanted via a small catheter and can be designed to stimulate different chambers of the heart. Pacemakers have also been combined with implantable defibrillators for patients at high risk of cardiac arrest. The defibrillator sends a larger electrical stimulus to the heart that essentially “reboots” it to get it pumping again. Modern pacemakers are typically programmed to adjust the stimulation in response to the patient's needs, providing stimulus only when needed. If the device senses that the heart has missed a beat or is beating too slowly, it will intervene to restore a steady rhythm. Pacemakers may also incorporate sensors that monitor movement and/or breathing rates to better match stimulation patterns to activity.

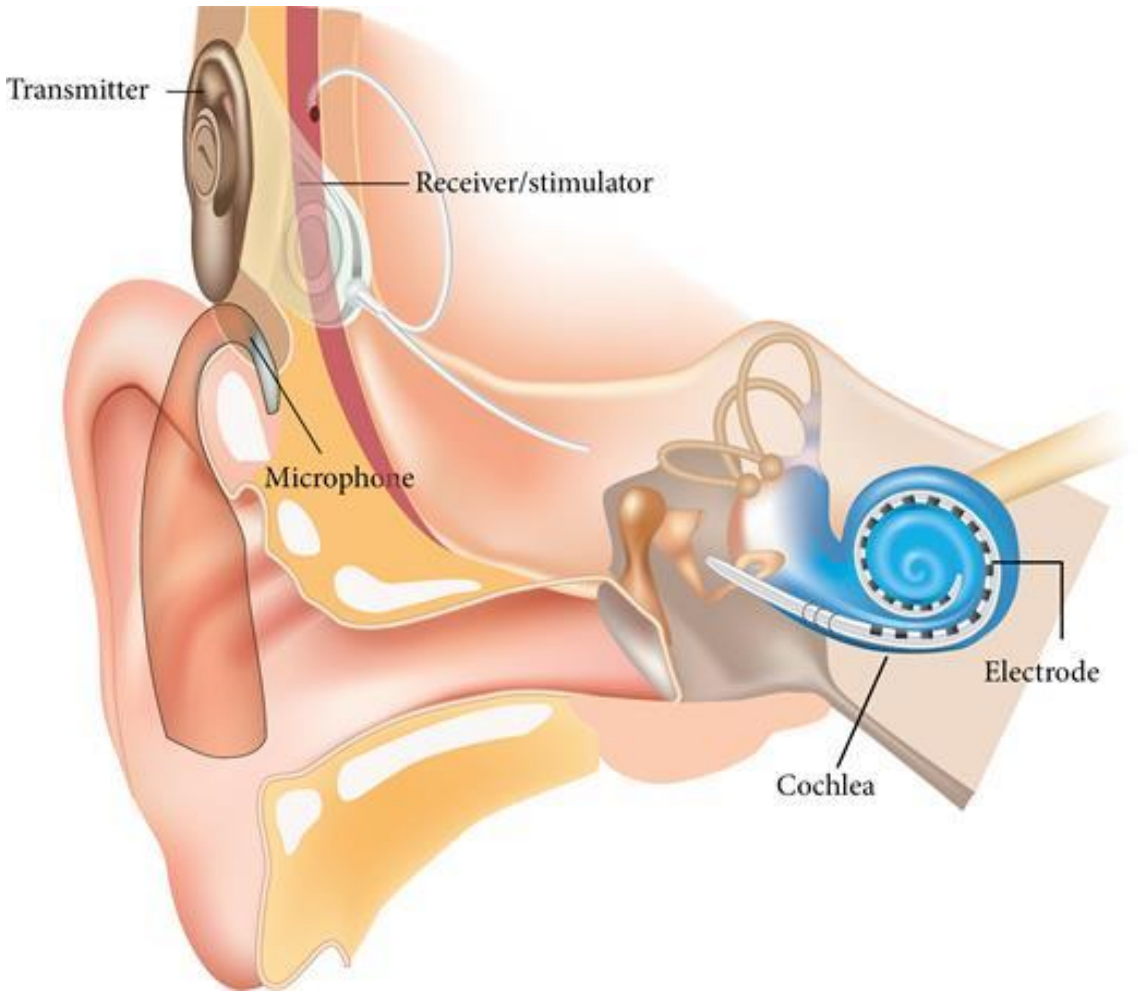


The Cochlear implant:

The inventor of the cochlear implant was William F. House, an American physician with a specialty in otology. He was very innovative, and despite the criticism he received by his peers, he stayed true to his beliefs and proceeded to the development of the cochlear implant. He performed the first implantation in 1961, but it was rejected by the patient. In 1969, the implantation was successful, and his design became commercial in 1972. House's cochlear implant was a single channel stimulator and was, therefore, not effective for detecting speech. This would require the stimulation of various locations in the inner ear in order for the patient to differentiate between low and mid-high frequencies. During the same period in Austria, electrical engineer Ingeborg J. Hochmair–Desoyer, together with physician Erwin Hochmair, developed the first multichannel cochlear implant at TU Vienna . Although their design consisted of eight stimulating electrodes instead of one, it was still questioned if it could achieve speech recognition considering the 20 000 hair cells of the inner ear. But surprisingly it worked, and the patient could detect speech. According to Hochmair–Desoyer, this could have been a result of the plasticity of the brain that learns to adapt. In Australia, in parallel with the Austrian team, Graeme Clark invented a 22 multichannel cochlear implant . Clark also faced criticism for his ambition but never quit, as he truly believed that it was the only way to restore hearing. Clark's invention was inspired by his deaf father. In 1978, Clark performed the first surgery, and together with his team, they were able to enable speech recognition to deaf people. Clark founded the Cochlear Limited to commercialize and make widely available his invention. Deafness is not a life-threatening condition, but deaf people can face a lot of struggles during their life. The cochlear implant is, therefore, an example of a bioelectronic device that can significantly improve the quality of life for patients.

Today, cochlear implants are regularly implanted in deaf and severely hearing-impaired patients starting within the first year of life. The implants that have up to 22 electrodes are designed to last a lifetime, though failures occasionally do occur, thereby necessitating a replacement surgery. Remarkably, cochlear implants enable many patients to have near 100% speech recognition when combined with lip reading in quiet environments. Nonetheless, even the most modern cochlear implants do not restore normal hearing. More complex sounds and noises, including music, are not well conveyed, and discerning speech in noisy

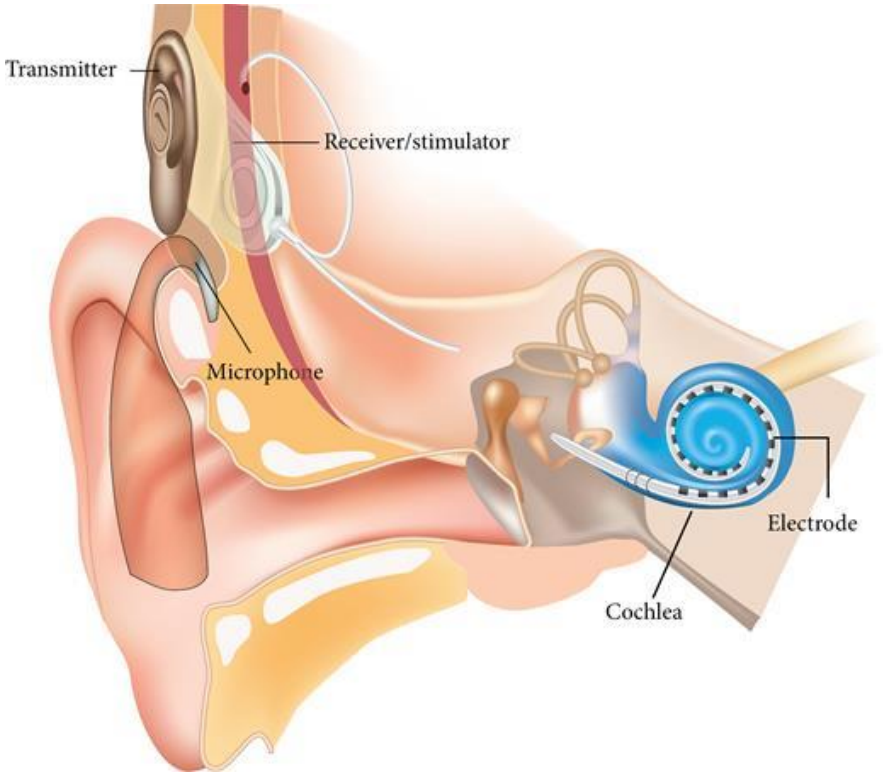
environments remains particularly challenging for cochlear patients. Despite these limitations, the cochlear implant is widely regarded as one of the most successful bioelectronic technologies.



Deep brain stimulator:

Electrical stimulation of the brain was used from the beginning of stereotactic neurosurgery. In 1947, neurologist Spiegel and neurosurgeon Wycis developed a stereotactic apparatus for brain surgery, which enabled them to target in a precise manner different brain areas. Initially, electrical stimulation was used to identify the area of the brain that would undergo lesioning. However, as early as 1952, it was proposed by Delgado and co-workers that an implantable recording and stimulation device can be therapeutic for psychotic patients. Indeed, electrical stimulation improved the condition of psychotic patients or ones with behavioral

disorders as it was reported in the following years. In the early years of deep brain stimulation (DBS) though, there were many controversial studies that raised ethical concerns. In the meantime, it was observed by several groups that high frequency (f > 50 Hz) stimulation could stop the tremor mimicking the therapeutic effect of brain lesioning, while many other studies focused on the treatment of chronic pain, epilepsy, and movement disorders. Initially, surgeons used modified cardiac pacemakers as neurostimulators to enable stimulation at higher frequencies. Because of the interest and promising results, Medtronics developed a neurostimulator device in 1968, and the term DBS was trademarked in 1975. In the late 1980s and early 1990s, the seminal work of Benabid et al. In 1997, DBS received FDA approval for the treatment of severe tremor in patients suffering from essential tremor or Parkinson's disease. In 2003, FDA allowed the use of DBS for the treatment of dystonia under the Humanitarian Device Exemption, while in 2009, the use of DBS for treating obsessive-compulsive disorder (OCD) was approved. DBS is safer than previous practices, which relied on lesional procedures, as it is not a permanent intervention, and it can change the brain activity in a controlled manner. Despite its use for treating several disorders, the exact mechanism has not yet been fully understood and is a subject of active research. Modern DBS systems use integrated sensors, most typically, electrophysiology recording electrodes, to feed back to the stimulator in a closed loop system. The first closed loop system was approved by the FDA in 2013 for the treatment of drug-resistant epilepsy. Closed loop systems are also being tested clinically for essential tremor, Parkinson's disease, depression, and chronic pain. In addition, to provide better patient outcomes (e.g., a greater reduction in seizures), closed loop systems significantly reduce stimulation time, thereby lowering power consumption and extending battery lifespan. It is widely anticipated that continued research and development into biomarkers and feedback algorithms will further improve the efficacy of DBS therapies in the coming decades.



The glucose biosensor:

Leland C Clark, an American biochemist, is considered the father of biosensors. He invented the Clark electrode, an amperometric sensor for detection of oxygen based on the current that is generated through oxygen reduction on an electrode surface. He soon realized that the concept can be used for the detection of various analytes with the use of oxidoreductase enzymes. Together with Lyons, they invented the glucose enzymatic biosensor in 1962 by modifying the oxygen electrode with glucose oxidase. Their invention of glucose biosensors practically opened the field of biosensing for medical diagnosis. Although the glucose electrochemical biosensor was invented in the 1960s, it was not until the 1990s that it became obvious to the medical field that people suffering from diabetes had to monitor and control their glucose levels daily. The first generation of devices relied on the detection of hydrogen peroxide and the use of a platinum electrode as the catalyst. The main limitations of these devices are the interference from other species, which can also be oxidized at the electrode, and their oxygen dependence. To minimize the interference, a semipermeable or charged membrane is used, which allows only glucose to diffuse to the electrode.

The second generation of electrochemical enzymatic biosensors replaced oxygen with another electron acceptor, an artificial mediator molecule, usually ferrocene or ferrocyanide. The enzyme is reoxidized by the mediator, while the oxidized mediator transfers the electron to the electrode. The first commercially available glucometer was a pen style device by Medisense Inc. in 1987. It relies on disposable enzyme electrode strips that use mediators and are fabricated with screen printing on a plastic substrate. A small blood drop from the finger is placed on the strip, which is then connected to the glucometer, providing a readout of the glucose concentration in less than 1 min.

Many commercially available glucose sensors are now able to continuously monitor glucose levels with data transmitted wirelessly at regular intervals. Such sensors measure interstitial glucose levels, which is the glucose found in the fluid between the cells. This is largely done using enzymatic glucose sensors that react with glucose molecules in the interstitial fluid to generate an electric current that is proportional to the glucose concentration. Fluorescence-based optical sensors that are implanted subcutaneously have also emerged as a promising alternative to enzymatic sensors particularly due to their extended lifetime compared with enzymatic sensors (10 vs 90 days). continuous glucose monitors are now used to provide real-time feedback to insulin pumps, which then autonomously inject insulin as needed to maintain blood sugar levels within the target range. Current commercial systems are considered a hybrid closed loop as meal-time boluses are still programmed manually. Nonetheless, many diabetes patients report that this semi-automated blood sugar control has been transformational, significantly improving the quality of life.