From Bioelectronics to Nanobioelectronics: The Biomedical Electronics Translational Research Center

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ELECTRICAL NEUROMODULATION is an evolving therapy featuring the targeted delivery of constant voltage stimulation or constant current stimulation (CCS) to specific neurological sites to enable the alteration of nerve activities. It can influence nerves by releasing transmitters, such as dopamine, and other chemical messengers, including peptides, that can modulate the excitatory and inhibitory functions of neural circuits. The end effect is the normalization of a neural network function from its perturbed state. The presumed mechanisms of electrical neuromodulation could include a depolarizing blockade, the stochastic normalization of neural firing, an axonal blockade, the reduction of neural firing keratosis, and the suppression of neural network oscillations [1]. Although the exact mechanisms of electrical neuromodulation are not known, the procedure's empirical effectiveness has led to numerous clinical applications.

Electrical neuromodulation using implantable devices was first achieved in the 1980s. Its technologies and applications have continued to develop and expand. Existing and emerging treatments have been applied to neural disorders, including drug-resistant epilepsy, chronic pain, and Parkinson's disease. They have also been used to improve sensory deficits, such as via cochlear implants for hearing and retinal implants for vision, as well as functional therapies, such as bladder and bowel control. Electrical neuromodulation therapy has been investigated for other chronic conditions, including dementia, Alzheimer's disease, depression, and rheumatoid arthritis. It is also called *bioelectronic medicine*, which can "turn off" chronic diseases and disorders by harnessing electricity. Bioelectronic medicine has great potential to be widely used in the future.

In general, implantable electrical neuromodulation systems consist of electrodes and an implanted pulse generator (IPG) with associated external components. Electrodes can be epidural, subdural, and parenchymal, and they can be placed via minimally invasive needle techniques, open surgery, and stereotactic implants. Depending on the distance from the electrode access point, an extension cable may be added to the system. An IPG can have a nonrechargeable battery that needs replacement every 2–5 years, depending on the stimulation parameters, or a rechargeable battery that is replenished via an external inductive charging system.

Although most systems operate in an open loop through the delivery constant stimulation, we are now at the advent of so-called closed-loop, or feedforward, stimulation, where a device's activation is contingent on a physiological event, such as an epileptic seizure. In this circumstance, the device is activated to deliver a desynchronizing pulse to the cortical area where the problem is located. Closed-loop stimulation is likely to become more prevalent as physiological markers of targeted diseases and neural disorders are discovered and verified [2]. On-demand, closed-loop stimulation may contribute to longer battery life if the system's sensing and signal processing demands are sufficiently efficient in power usage. New electrode designs could yield more efficient and precise stimulation, requiring less current and minimizing unwanted side stimulation. Wireless power transfers to recharge implanted batteries and wireless bidirectional data transceivers to communicate with implanted devices have been adopted in neuromodulation systems [3], [4].

In addition, to leverage advanced CMOS nanoelectronics technologies, complex algorithms in the implanted medical devices to judge symptoms can quickly execute to give responses. Thus, in-time treatment through electrical stimulation can alleviate neurological disorder symptoms. In addition, the power consumption of systems on chip (SoC) fabricated through nanoscale CMOS technologies can be significantly reduced to get longer battery life. Thus, nanobioelectronic medicine will become increasingly attractive.

BIOMEDICAL ELECTRONICS TRANSLATIONAL RESEARCH CENTER

The Biomedical Electronics Translational Research Center (BETRC) at National Yang Ming Chiao Tung University, Hsinchu, Taiwan, established in 2004, focuses on the research and development of implantable medical electronic systems using SoC technology and biocompatible materials, especially for closed-loop neuromodulation for the treatment of disorders through electrical voltage/current stimulations. The mission and vision of the BETRC include 1) treating intractable neurological disorders by conducting interdisciplinary research to develop multidisciplinary technology platforms, 2) exploring the frontier of neural sciences,

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and 3) incubating start-up companies to produce neural prosthetic devices. Technologies for biomedical devices and diagnosis equipment require many semiconductor chips and biomaterials, which can be developed and manufactured in Taiwan, with strong industrial support. Figure 1 illustrates the relationships among medical applications and technology platforms at the BETRC. The center's research team poses in Figure 2.

There are five BETRC project teams working on the following: 1) photovoltaic-powered subretinal prostheses for patients with retinitis pigmentosa and age-related macular degeneration, 2) closed-loop seizure control systems for patients with epilepsy and dementia, 3) bone-guided cochlear prostheses for patients that have high-frequency hearing loss, 4) closed-loop deep-brain stimulation (DBS) systems for Parkinson's disease, and 5) electroencephalogram–transcranial dc stimulation systems for the neurological rehabilitation of stroke patients. Moreover, the BETRC invites partner universities to join the integrated engineering–biomedicine joint research platform in Taiwan. It also promotes international collaborations with top research centers, institutions, and enterprises.

The center's research projects have been partially supported by the Taiwan Ministry of Education's Aim for the Top University Project, from 2006 to 2015, and Featured Areas Research Center Program within the Higher Education Sprout Project, since 2015. Moreover, partial long-term support is provided by the country's National Science Council and Ministry of Science and Technology as well as National Chiao Tung University (which is now National Yang-Ming Chiao-Tung University).

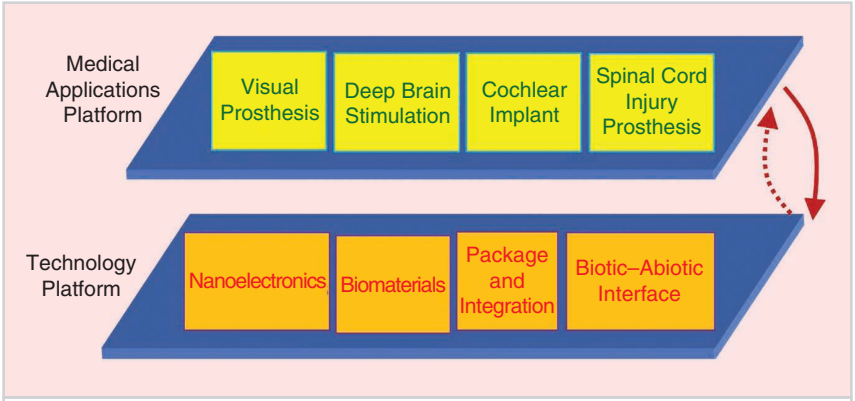

FIGURE 1 The integration of medical applications and technology platforms at the BETRC.

FIGURE 2 The BETRC research team. Front row, center-right: Ming-Dou Ker. Front row, center-left: Chung-Yu Wu.

In 2013, research work on the closed-loop epileptic seizure control SoC was published at the IEEE International Solid-State Circuits Conference, where it received the Distinguished Technical Paper Award. In 2016, a start-up company, A-Neuron Electronic, was established by transferring BETRC technologies related to photovoltaic-powered subretinal prostheses and closed-loop epileptic seizure control systems. A-Neuron Electronic will commercialize the technologies into two major medical products.

Figure 3 shows the closed-loop epileptic seizure control SoC and its external control system, fabricated in 0.18-μm CMOS process technology [3]. The key elements of the SoC include a low-noise electrocorticography (ECoG) acquisition unit with an input protection circuit to share electrodes with stimulators, a biosignal processor for accurate and fast seizure detection, a biphasic CCS of up to 3 mA that has an adaptive power supply, and wireless power and bidirectional data telemetry in a single pair of coils. When an epileptic seizure is detected, the biphasic CCS stimulates the brain and stops the event before it becomes severe. The wireless power transfer is used for battery charging, and the bidirectional data telemetry transfers the ECoG out and the control signal in. This is the first SoC for human closed-loop epileptic seizure control.

ADAPTIVE CLOSED-LOOP DBS SYSTEM FOR PARKINSON'S DISEASE

Parkinson's disease is a neurodegenerative disease of the motor nervous system that is estimated to affect about 1% of the population who is older than 60. Pathological evidence shows that the disease's essential feature concerns the degeneration of dopaminergic neurons in the substantia nigra. The substantia nigra is a part of the basal ganglia, which plays a crucial role in the motor control of voluntary movement. When the dopaminergic neurons in the

substantia nigra degenerate, the balance between the direct and indirect pathways of the basal ganglia is disrupted, causing Parkinson's symptoms. Patients may experience resting tremors, rigidity, and bradykinesia [5]. Treatment can alleviate the condition; however, long-term medication is susceptible to levodopa-induced dyskinesia, motor fluctuation, and other side effects.

Patients with advanced Parkinson's disease may choose DBS to treat drug-induced adverse effects. Conventional DBS (cDBS) is an open-loop system. The stimulator provides continuous electrical stimulation in the brain until its power is exhausted; usually, ~5 years later, a patient must undergo another surgery to replace it. Continuous electrical stimulation may cause negative effects, such as gait instability, dysarthria, and stimulation-induced dyskinesia. Continuous electrical stimulation not only inhibits abnormal neural functions but it interferes with normal neural functions. Could it be possible to detect unique disease biomarkers to be used as feedback control signals for electrical stimulation? This is the concept behind the closed-loop system, in which physicians and scientists are highly interested.

The local field potential (LFP) is the ensemble activity of the synaptic potentials surrounding the lead contacts, and it can reflect the synchronized behavior of a population of neurons. The LFP can be recorded in the subthalamic nucleus (STN) of Parkinson's patients when DBS leads are surgically implanted [6]. After spectral analysis, abnormal beta band oscillations (13–35 Hz) were observed in the STN [7]. This finding was similar to a recording in the internal globus pallidus of a parkinsonian rhesus monkey [8]. When patients received medical treatment or cDBS targeting the STN, the beta oscillations were significantly inhibited, and the Parkinson's symptoms improved. Therefore, an abnormal STN LFP can be used as a biomarker for Parkinson's disease.

If unique beta oscillation is used as a feedback control signal for electrical stimulation, a threshold can be set according to the suitable signal power. Brown's group first demonstrated the use of beta oscillation as a feedback control signal to control electrical stimulation in Parkinson's sufferers. The patients' motor symptom improvement scores were significantly better than those of people receiving continuous electrical stimulation (50% versus 29%; $p = 0.005$), and the required electrical stimulation time was only 44% of the total for continuous electrical stimulation [9]. A custom-built device was used to design different beta oscillation algorithms for closed-loop stimulation. According to the beta oscillation dynamic power change, the intensity of the stimulator was adjusted. Motor symptoms significantly improved compared with those in fixed-intensity electrical stimulation [10]. Such a closed-loop DBS, also known as *adaptive DBS* (*aDBS*), has passed clinical proof-of-principle trials.

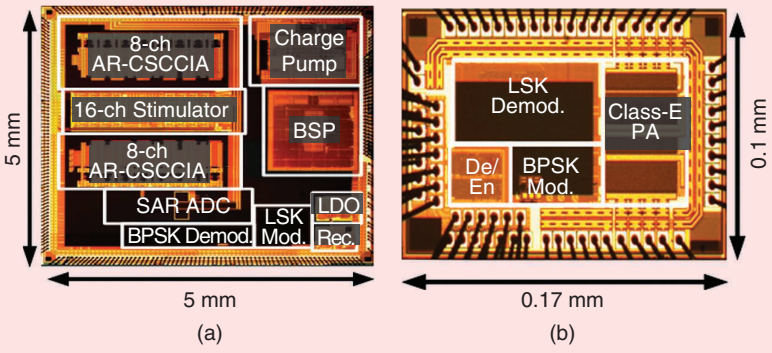

FIGURE 3 The (a) closed-loop epileptic seizure control SoC and (b) its external control system, fabricated in a 0.18-μm CMOS process technology [3].

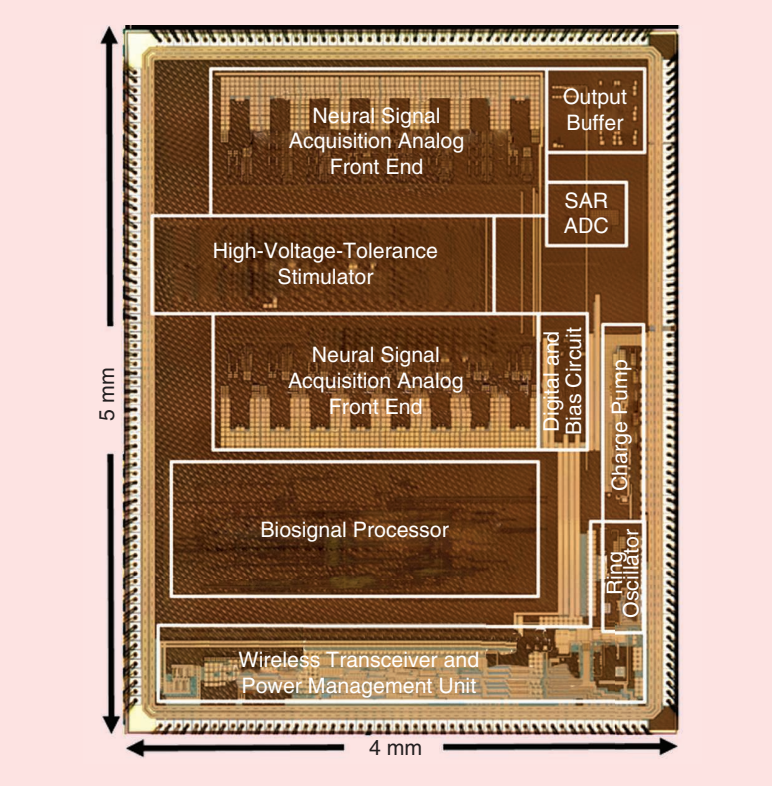

FIGURE 4 The SoC with adaptive deep-brain detection and stimulation for implantable medical devices, which is fabricated through a TSMC 0.18-μm CMOS process. SAR: successive approximation register; ADC: analog-to-digital converter.

Conventional devices used in aDBS were implemented through a system-on-board design. The latest aDBS device (the Medtronic Summit RC+S) adopts that architecture with several integrated circuit components to control differential functions via a printed circuit board. In our work, the SoC-based design can improve detection, computing, and stimulation performance. Moreover, it can effectively reduce power consumption. The SoC appears in Figure 4. Through integration with a neural signal acquisition analog front-end circuit and a high-voltage-tolerance stimulator circuit, artifact interference during electrical stimulation can be blocked from acquired neural signals. The SoC can simultaneously record LFP signals from 16 channels within implanted electrodes, convert the LFP signals to digital ones, and analyze them with a biosignal processor. The algorithm to evaluate Parkinson's symptoms, which was codeveloped with medical doctors, can operate in real time through the biosignal processor to judge whether electrical stimulation will be applied or not. Therefore, the SoC can efficiently execute closed-loop aDBS. The aDBS implemented with the SoC can increase the service life and therapeutic effect of the implanted stimulators. A biomedical device containing the SoC chip has been prepared for preclinical tests, including animal experiments, electrical safety evaluations, recognized medical device standards trials, and algorithm/software validation. After the safety certification and in vivo tests have been completed, clinical trials on humans will begin.

PERSPECTIVE

The implantable closed-loop epileptic seizure control devices and intelligent adaptive closed-loop DBS for Parkinson's disease are physics-based circuits and systems. The design incorporates CMOS SoCs and integrated circuits. In the future development of bioelectronic medicine, it is believed that more advanced CMOS nanoelectronics technologies, innovative circuit/system designs, and nanobioelectronics will be applied, greatly benefitting patients and leading to progress in neural science and engineering.

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