IMPLANTS CONNECT PATIENTS FOR BETTER, FASTER, MORE PERSONALISED CARE

In this article, Will Rosellini, JD, MBA, Chairman & Chief Executive Officer, Nexeon MedSystems, and Beth Rosellini, DDS, Consultant to Nexeon, describe the rapidly advancing area of local field potential recording of nervous system activity which, via brain-implanted devices, has the ability to record detailed patient data directly and, in conjunction with other devices including drug delivery devices, has the potential to form highly advanced connected and closed-loop systems, taking personalised care and the recording of biometric and other data to a new level of sophistication.

INTRODUCTION

The nervous system functions very much like a sophisticated symphony of interrelated nuances and bold activities, both passive undertones (parasympathetic and sympathetic nervous systems) and more conspicuous expressions (pain and motor nerves). The nervous system communicates via electrical signal to control almost every cell and organ of the body either directly or indirectly. Observation of correlated system stimuli and system reactions provided early intrigue into the power of tapping into or even controlling this communication pathway. Thus, the application of electrical impulses to biological and medical systems has grown in use throughout history to illicit therapeutic responses, and it continues to grow as the science and technology improve around it.

In the past few decades, modern medicine adopted electrical impulse therapy for the treatment of various medical conditions in the form of cardiac pacemakers, deep brain stimulators, among others. Nowadays, most bioelectronics are still limited in use to conditions refractory to traditional pharmacotherapy. But with exponential advancements in hardware, software, machine learning, and leveraging of big data analytics, it is reasonable to hypothesise that the engineering and technology will eventually prove to be more efficacious than prescribed medications and to present with fewer side effects as well.

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WHERE WE'VE BEEN: DISCOVERING THE WHERE & THE HOW

If you're familiar with the Steve Jobs and Bill Gates race to develop and capture the home computer market in the late 1980s, then you'll quickly be able to get a pulse on the progress that's been made in the field of neurostimulation. The focus over the last 15-20 years has been on development of hardware, and due to the substantial cost, regulatory hurdles, and other barriers to market entry, the majority of this traction has been executed by the largest players in the space: Medtronic (Minneapolis, MN, US), Boston Scientific (Marlborough, MA, US), and St Jude Medical (St Paul, MN, US).

With the capacity and knowledge available, researchers primarily investigated where this neurostimulation therapy could be effective; more specifically, on which nerves and in what parts of the brain to treat chronic neurological diseases such as epilepsy, Parkinson's disease, dystonia, overactive bladder, medication-resistant obsessive compulsive disorder, and others. The field primarily needed to develop and refine the "tools" by which to deliver stimulation inside the body. Secondarily, development of the "map" of the chronically diseased human body needed to be discovered to understand where best to employ these tools.

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Because of this preliminary thrust of research needed, learnings around the mechanisms of action for these neurostimulation pathways have been limited, and the current device-based systems are riddled with issues. Existing devices target large areas of tissue indiscriminately rather than honing in on specific groups of neurons within circuits. Therefore, prescribed dosages of stimulation must balance the benefits of stimulating the desired target tissues and the drawbacks of the side effects associated with stimulating the non-target tissues.

Other issues involve the arduous nature of initial and ongoing device programming as well as the need for follow-up surgeries for battery and device replacement every 3-5 years. Most patients require a bolus of post implantation time spent with their physician to program the device, and there is no accepted best care standard for ongoing monitoring of the therapy. And while patients maintain some degree of pharmacotherapy, the relationship between these intimate systems is vastly under-optimised.

So despite there being great progress in the where and how over the past 20 years in this field, recent scientific advances have made it apparent that there's much to be learned about the why. And the sophistication of the technology is directly proportional to the ability to understand and take action on new learnings.

WHERE WE ARE TODAY: STUDYING AND MASTERING THE WHY

The tremendous implications of this science has caused a proportionate amount of funding to innovate solutions and commercialise products in this space. With the introduction of competition, there have not only been device-centric inventions, but there has also been plenty of clinical application ingenuity as well as system optimisation activity for patients and physicians alike.

Components of the research being explored today in bioelectronics are comparable with learning a new language. Neuro-engineers and their partnering healthcare providers are learning to read and write the electrical signals that travel between the brain and the body's organs and also learning to deliver these messages in a more precise manner. Biometric data and personalised care are being explored and delivered in a way that has never been seen before, which is presenting a whole new frontier in treating disease.

Figure 1: The nervous system communicates via electrical signal to control almost every cell and organ of the body either directly or indirectly.

Known as local field potential recording (LFP recording), certain implantable devices now being rolled out are capable of sensing and interpreting nervous system activity at the site of stimulation. This feedback can be thought of as serving as a "stethoscope to the brain"; so while the brain is being stimulated to illicit a desired therapeutic response, the bidirectional system allows for feedback to be sent and evaluated. While it is relatively commonplace now to stream data from patients, to connect them more frequently and more conveniently to their healthcare providers, that data has been limited to basic biometrics. These newly developed and launched device solutions provide improved alternatives to manual collection of data by a patient either via a digital or manual journal or medical log.

Researchers are learning the language of these neural signals so that we can listen for signals of disease or injury. We are also using bio-electronic medicine technologies to record, stimulate, and block neural signals, which is essentially teaching the body how to heal itself. Real-time streaming of recorded deep brain activity increases the convenience, accuracy, and volume of patient information collected.

Deep brain stimulation therapy has been prescribed worldwide in over 135,000 patients with Parkinson's disease, yet the mechanism of action is not fully understood. The long-term implications of LFP recording include better disease management as well as data-based analysis of a disease and therapy that have been mysterious in many ways for decades. Beyond that, most of these patients do not suffer from only this one morbidity. In fact, many of these patients are burdened with other chronic neurological comorbidities such as depression, dementia, COPD, dysphagia, overactive bladder, to name a few. These comorbidities require a therapeutic pathway as well, but all pharmacotherapy, device-based therapy, and any other solutions, influence efficacy of the others. And whether these patients lack capacity or motivation, their ability to track the nuances of their multi-variable-related status is negligible relative to the passive automation of recording from an implanted device.

Today, we are on the precipice of a technological development and near-term

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deployment that we hypothesise will majorly advance our understanding of complex diseases and how those diseases can best be treated.

The contribution to this current phase of development has been both vast and exciting. Medical device manufacturers such as Medtronic and Nexeon MedSystems are working to make this data stream fast and easy to collect while not compromising the simultaneous delivery of stimulation therapy.

Nexeon is developing its Synapse deep brain neurostimulation system (Figure 2) which includes leads implanted into the deep part of the brain, an implantable pulse generator typically implanted in the subclavicular region, a patient controller, an external battery recharger, and the physician reprogrammer tablet.

As announced in late 2016, GlaxoSmithKline is leveraging devices (already built) to develop unique pathways for drug delivery. Elon Musk, PayPal Co-Founder and, more recently Co-Founder of Neuralink Corporation (San Francisco, CA, US), and Facebook CEO Mark Zuckerberg, have recently announced an investment in the software and big data development associated with the brain-computer interface. All thrusts are of vital importance and appear to be working towards the common vision of improving

Figure 2: Nexeon's Synapse deep brain neurostimulation system includes: leads implanted into the deep part of the brain (front); implantable pulse generator typically implanted in the subclavicular region (left); patient controller (center); external battery recharger (right); and the physician reprogrammer tablet (rear).

therapeutic outcomes for patients, easing the pathway in which a physician provides the care, and increasing collective knowledge to make higher quality and more accurate care decisions moving forward.

VISION FOR THE FUTURE: WHERE ARE WE HEADED NEXT?

To say the implications of these technological advancements and increased connectivity will be interesting for healthcare is an understatement. This is a field where the leaders are trained based on the experience of those that came before them as well as the research journals and continuing education courses they have sufficient capacity with which to engage. That capacity is only diminished when considering the government initiatives occuring globally to increase the total number of patients required to be serviced by the healthcare system but without making proportionate increases in the infrastructure that provides that service. Thus, the same number of doctors are seeing more and more patients.

Physicians and neuro-engineers are cautiously optimistic that this never-before collected data will provide the basis for adaptive (deep learning) closed-loop device systems, remote physician management systems with little to no disruption to patient quality-of-life, and individually-optimised therapies with minimised undesired side effects.

Data-driven discovery and decision making provides much of the revolutionary platform upon which this proposed access to care can be delivered. With the progression of the technology, the big data management and outpouring of analytics will facilitate and expedite much of the physicians' process. Additionally it will eliminate the redundant or predictable decisions, such that the physicians' time can be streamlined to focus on what only they can do: diagnose, treatment plan, perform procedures, and care for patients. Additionally, leveraging big data from

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implanted patients has been assumed to be a valuable pathway to increasing the quality of care to patients in more rural areas. These smart devices could support physicians who are less experienced or less knowledgeable about a particular therapy by providing therapeutic parameters developed from the data of thousands of other patients managed by leading physicians from anywhere in the world.

The vision for the internet of medical things technology and the interconnectivity of drug delivery includes building and iterating upon all aspects of the current chronic disease therapy delivery model: from the very micro iteration of the type of material used to house the electrode in the deep part of the brain all the way to the macro, population-based trends detectable and actionable as related to disease comorbidity diagnosis and treatment. More specifically, beloware a few of many different ways in which patient therapeutic outcomes will be improved via the interconnectedness of medicine:

- Closed-loop devices. Deep learning and algorithm-based therapy adjustments will eliminate traditional medicine's approach to give "typical" dosage and then guess/check on how to adjust medications or therapy based on patient verbal feedback or physician observation of symptoms. Instead, we will be recording patients' unique responses, as well as many other influential biometrics, to fine tune the perfect drug dosages and/or supporting therapies. This establishes the swiftest pathway to achieving the best therapeutic window with minimal side effects.
- Connectivity of all variables. These devices, charged molecules, sensors, and microchips support an interconnected system in which drugs can be turned on and off, can be driven into specific tissues, and/or can be tracked for patient-specific efficacy in delivery. Data on all of these variables provide enhanced decision making related to ongoing management of the disease.
- Comorbidity management. Monitoring and sensing for closed-loop management of diseases and therapy will open the door to centralising care decisions and management. When a global system allows evaluation of everything from patient compliance to prescribed therapy success and failures, the healthcare provider can advise on best practices for improved outcomes.
- Reasonable hypotheses exist around the impact of big data analysis on multivariable biometrics of biological systems that have never been monitored before. Some in the field speculate that new trends, correlations and patterns will be discovered when connected technology facilitates rapid accumulation and deciphering of patient data points.
- More personalised care delivered via a more accurate process, while providing a platform for patient augmentation. As healthcare providers and patients are relieved of some of the burden of disease and therapy management, it will be interesting to observe how this technology and new capacity are employed beyond taking a patient from sick to healthier or healthy, but instead taking healthy patients to higher levels of performance. It may sound like science fiction, but we're edging closer to a future where precision electronic therapies sit alongside the medicines and vaccines we use today.

ABOUT THE AUTHORS

Will Rosellini, a former minor-league baseball pitcher, holds five masters degrees in addition to a law degree. He is a 15-year veteran of the neurotechnology space and has expertise in accelerating the development of emerging technologies with minimal at-risk capital. From 2005-2012, Rosellini was a founder and served as CEO of Microtransponder, a company developing vagal nerve stimulation for treatment of stroke and tinnitus. He left that position after being treated for and temporarily losing his voice from thyroid cancer. He went on to serve in other Board and C-level positions for various biomedical device companies and research programs, until he came on as Chairman and CEO of Nexeon MedSystems. Rosellini and his team are preparing for an early 2018 German commercial launch of this technology for the treatment of symptoms associated with Parkinson's disease.

Beth Rosellini joined her brother Will over four years ago in his pursuit to resolve much of the unmet needs of patients with chronic neurological disease as well as the healthcare providers who care for them. After studying chemistry and mathematics, Beth went on to get a Doctorate in Dental Surgery, with niche focus on head and neck-related emerging therapy research. In early 2 013, she founded and operated a telemedicine business delivering mobile dental care, clinical engineer service, and telecounselling support in long-term nursing care facilities. She concurrently engaged in various NIH-funded research programs related to neurostimulation in the head and neck as both Industry Expert and Principal Investigator. After exiting her telemedicine business in 2016, Dr Rosellini invested the proceeds into Nexeon and went on to serve in various roles in both clinical and research as well as business development functions. At the end of 2016, she left her position at Nexeon and founded VeloVerge, a medtech- and healthcare-focused business development consulting group that supports emerging therapies from innovative research to impactful commercialised product and ongoing service support. She maintains an ongoing relationship with Nexeon, consulting on various front-end related research and communication endeavours