INNOVATIONS IN NEUROMODULATION

The field of neuromodulation lies at the intersection of a multiplicity of fields; in each, rapid innovation is underway. Consequently, this is one of the most exciting and, potentially, one of the highest impact technologies and fields of medicine. In this overview, the most prolific dimensions of innovation are discussed, and a sampling of some of the most promising and high-impact technologies and ventures is briefly presented.

The genesis of this presentation goes back to conversations that followed a more focused presentation given at NANS on neurosensing and neurocontrol in 2013, after which an invitation was extended to give a talk on high-impact technologies in neuromodulation that were “off the grid,” i.e., not yet on most neurosurgeons’ radar. This turned out to be a challenging task because most technologies that are “off the grid” are so because of one of two reasons: either they don’t work (at least not yet), or they do work—and work so well that their developers are keeping them under wraps.

The author worked as an Entrepreneur-in-Residence (EIR) at Santé Health Ventures, and actively sourced and vetted a multitude of novel technologies and ventures in the neurotechnology space in general and in the neuromodulation space in particular. From this experience and from a network of entrepreneurs and venture capitalists in the field, a reasonably thorough and in-depth view was gleaned of the upstream pipeline of new technologies poised to impact our field. Because of the implicit obligation of confidentiality, only information which was explicitly approved for disclosure (even if available to the public via other sources) by the corresponding CEOs was included in this presentation. As one might imagine, and as is fully appreciated by the author from days as the founding CEO of NeuroVista, this confidentiality limitation was a substantial filter on what could be presented. Nonetheless, some of the most high-impact ventures produced or published information that is of importance to our field and readership and thus is included here.

Dimensions of Innovation

By its nature as a technology-dependent and scientifically based specialty and industry, neuromodulation benefits directly from innovation through a rich set of disciplines. Neuromodulation synergistically combines technologies and science from the broad fields of (1) controlled and focal delivery of energy selected from various energy modalities for reversible modulation, comprising alternating and direct current electrical stimulation, magnetic stimulation, and optical stimulation, among others; (2) controlled and focal delivery of energy selected from various energy modalities for irreversible modulation—primarily by tissue ablation, comprising ultrasound, electrical energy, and optical energy, among others; (3) control theory, including simple open loop control, feedforward control, model reference control, and a plethora of forms of feedback control structures; (4) sensing, including invasive and non-invasive neural and physiological sensing modalities and sensor technologies; (5) algorithm development of neural state estimation as well as neural state prediction; (6) microelectronic miniaturization,
which facilitates the implementation of ever smaller neuromodulation interfaces and control systems which may be implanted and injected; (6) power optimization, including both development of lower power micro-electronic technologies as well as a stimulation paradigm amenable to lower power requirements; (7) power supply development, including higher energy density power systems as well as systems which extract energy from biological sources, such as kinetic and thermal modalities, provided by the user; (8) scientific advancements in neurophysiology and in functional neuroanatomy, which synergistically delineate with ever-increasing accuracy and fidelity the neural pathways of the CNS and PNS, including the autonomic nervous system, driving innovation along the organ system and indication dimension; (9) advancements in the broader field of medicine, which continue to demonstrate the ubiquitous influence of neural connections to various organs and their importance in the regulation and dysregulation of traditionally “non-neurological” diseases. Furthermore, (1) and (2) above contain the multidimensional aspects of parameter optimization, including those of frequency, temporal patterning, multimodal delivery, network modulation, and others.

Specific Examples of High-Impact Technologies
In the dimension of Sensing and Control, several technologies are poised to substantially advance the field. In the realm of neural state prediction, the technology developed by NeuroVista (disclosure: founded by the author as a junior resident) and presented by Cook et al. in 2013 is a potential game changer in the epilepsy field. In the first-in-man (FIM) study, 15 patients were implanted and followed for two years, and in a significant subset of these patients, clinically meaningful advance warning of impending seizures or high risk thereof, was achieved.\(^1\)\(^-\)\(^3\) In Figure 2, the advance warning provided by the system prior to seizure onset in this subject ranged from 90 minutes to two hours (Mark Cook, 2014, personal communication).

Chronic Neural Monitoring
With the introduction of chronic implanted monitoring technologies for seizure prediction and seizure termination, novel advancements in other areas, such as seizure surgical planning, have been demonstrated. In both the NeuroPace Pivotal Study for the Responsive Neurostimulator (RNS) and the NeuroVista first-in-man study on the Seizure Advisory System (SAS) (Figure 1), in patients for whom resective surgery was felt to not be an option, further chronic monitoring using the respective implanted systems provided additional localization information to substantiate resective surgery.\(^2\)^\(^-\)\(^4\)\(^5\) The first chronic ECoG-guided resection was planned and performed at Rush University Medical Center by Dr. Marvin Rossi and Dr. Richard Byrne in 2003 and reported in a case series of five patients with long-term follow up in 2014.\(^4\)
Closed-Loop Neuromodulation

The design and application of a closed-loop system architecture to the delivery of neuromodulatory was, to the best knowledge of the author, first described by DiLorenzo in 1998. In this system, a weighted combination of outputs from a model reference or other feedforward system and a closed-loop feedback driven system are used to provide an optimal control output. Various cost functions may be utilized to determine the control optimization, with such objectives as efficacy maximization (i.e., tremor minimization), side effect minimization, modulation energy minimization, power consumption minimization, or a combination of these or other objectives. Synergistic with closed-loop controller design, several investigators have defined and characterized a variety of neurophysiological biomarkers and their correlations with physiological signatures comprising combinations of signs and symptoms. A listing of a representative subset of these important studies is shown in Table 1.

Table 1: Biomarket characterization and Controlled DBS

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<tr>
<th>Indication</th>
<th>Biomarker Description</th>
<th>Investigator</th>
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<tbody>
<tr>
<td>Parkinson’s</td>
<td>Gpi Spikes – Oscillatory Activity</td>
<td>Hammond C, 2007</td>
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<tr>
<td>Parkinson’s</td>
<td>STN LFP - Oscillations</td>
<td>Kühn A, 2006</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>LFP (DBS Electrode)</td>
<td>Abosch A, 2012</td>
</tr>
<tr>
<td>PD &amp; ET</td>
<td>sEMG &amp; Accelerometer</td>
<td>Basu I, 2013</td>
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Organ System and Indication

Innovation along the multifaceted dimension comprising organ systems and indications is driving the discovery, validation or refutation, and clinical implementation of a multitude of potential new therapies for many years to come.

One of several areas the author believes holds particular promise to make a substantial clinical impact is neurocardiac therapeutics. One such technology, which was spun out from the Cleveland Clinic and is being developed by Cardionomic, involves modulation of the cardiac plexus for the treatment of acute decompensated heart failure. This technology facilitates augmentation of stroke volume and cardiac output without significant increase in heart rate or of systemic or pulmonary vascular
resistance, thereby providing enhanced cardiac performance without loss of efficiency encountered with many pharmacological agents.

**Modality—Monomodality and Multimodality**

An entirely new field is emerging around the application of high-frequency focal ultrasound (HIFU) in the treatment of a broad set of conditions, and involving ablation of central nervous system (CNS) and peripheral nervous system (PNS) targets.

<table>
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<th>Table 2: Innovations in Neuromodulation – Modality: HIFU Ablation of CNS Targets for Neurological Disease 12-15</th>
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<tr>
<td><strong>Indication</strong></td>
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<tr>
<td>Essential Tremor</td>
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<td>Trigeminal Neuralgia</td>
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<tr>
<td>Cerebrovascular</td>
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<td>Cerebrovascular</td>
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Furthermore, the use of HIFU has been shown to be effective in dissolution of thrombi in the treatment of ischemic cerebrovascular accidents (Newell, 2014 personal communication, unpublished data) as well as in clot lysis in the treatment of hemorrhagic cerebrovascular accidents.14-15

HIFU is being applied with some success to the ablation of peripheral neural targets in the treatment of systemic disease. Notwithstanding the failure in the Ardien renal nerve denervation hypertension trial to meet its primary endpoints, and its chilling effect on financing in the field, meaningful progress has continued. Kona Medical has shown efficacy with the use of a fully external focused ultrasound system in the ablation of renal nerves for the treatment of medically refractory hypertension (Dr. Michael Gertner, 2014 personal communication).16, 17

**Discussion and Future Directions**

This article represents only a brief snapshot of innovation in the field, and to the extent that these can be discussed within the size and scope constraints imposed, the following areas have substantial innovation potential:

1. Development of predictive algorithms will facilitate further advances in both the prediction and control of intermittently symptomatic neurological conditions such as epilepsy.
2. Chronic monitoring will provide a far more physiologically and anatomically accurate representation of neural source, node, and network behavior, thereby fundamentally changing the way epilepsy surgery is viewed, planned, and performed.
3. Neuromodulatory and resective surgery will be seen as potentially complementary approaches to influence network behavior, and the simplistic notion of a single source will give way to higher level concepts encompassing system stability, resonance and propagation, and characterization of signal latencies and dynamic behavior.

> WHILE STILL IN ITS FIGURATIVE INFANCY, NEUROMODULATION HAS ALREADY REVOLUTIONIZED THE TREATMENT OF SEVERAL NEUROLOGICAL CONDITIONS IN THE MOVEMENT DISORDERS AND PAIN FIELDS. SYNERGISTIC INNOVATION IN A BROAD SET OF INDICATIONS SPANNING NEUROPSYCHIATRIC, COGNITIVE, AND SYSTEMIC, COUPLED WITH COMPARABLY EXTENSIVE INNOVATION IN RELATED AND COMPLEMENTARY TECHNOLOGICAL AREAS, HOLDS THE POTENTIAL TO FUNDAMENTALLY CHANGE MEDICAL THERAPEUTICS. <
4. The role of signal processing and the underlying mathematical tools will play a role of growing importance in the research and clinical practice of epilepsy.

5. Closed-loop control is likely to transform neuromodulation in a more profound manner than demand pacing advanced the cardiac field. The benefits include continuous maximization of efficacy, stabilization of fluctuating symptoms, compensation for insidious disease progression, minimization of side effects, optimization of power efficiency, and truly customized and individualized therapy, among others.

6. Research and development of systems for modulating new organs and for new indications will continue, driven by physiological research and creativity.

7. HIFU has the potential to be a disruptive innovation in certain sets of indications and may offer a safe, practical, and cost effective alternative to reversible neuromodulation systems in specific applications.

8. The benefits of reversible modulation are likely to continue to out weigh those of HIFU in indications where the anatomy is unforgiving of small targeting errors—pathways subject to tachyphylaxis or habituation, pathways primarily requiring augmentation or stimulation rather than inhibition, and others.

While still in its figurative infancy, neuromodulation has already revolutionized the treatment of several neurological conditions in the movement disorders and pain fields. Synergistic innovation in a broad set of indications spanning neuropsychiatric, cognitive, and systemic, coupled with comparably extensive innovation in related and complementary technological areas, holds the potential to fundamentally change medical therapeutics.

Just as antibiotics changed the scope and impact of medicine by providing the capability to selectively kill invading organisms, neuromodulation will fundamentally change the efficacy and safety of medical therapeutics by focally and selectively regulating physiology in manners presently inconceivable within the domain of current pharmacology. The future is upon us.

References


