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Advancing Neuromodulation Using a Dynamic Control Framework

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Abstract— The current state of neuromodulation can be described using a classical dynamic control framework such that the nervous system is the classical "plant", the neural stimulator is the controller, tools to collect clinical data are the sensors, and the physician's judgment is the state estimator. This framework characterizes the types of opportunities available to advance neuromodulation. In particular, technology can address two dominant factors limiting the performance of the control system: "observability," the ability to observe the state of the system from output measurements, and "controllability," the ability to drive the system to a desired state using control stimulation. Improving sensors and stimulation methods are necessary to address these factors. Equally important in achieving the desired therapy outcome is improving state estimation by understanding the neural processes underlying diseases. Technological advancements in neuromodulation using the control framework enable not only improvements in therapies for neurologic diseases but also research into the dynamic properties of the nervous system and mechanisms of action of therapies. In this paper, we provide an overview of the control system framework for neuromodulation, its practical challenges, and two investigational devices applying this framework for specific applications. To help motivate future efforts, we describe a chronically implantable, low-power neural stimulation system, which integrates sensing, stimulation, and state estimation. This research system has been implanted and used in an ovine to address novel research questions.

I. INTRODUCTION

INNOVATION in neuromodulation can be facilitated by modeling the interaction between device and the nervous system in a dynamic control framework. Progress has already taken place in sensing [1],[2], improving therapy delivery [3],[4], and understanding the pathophysiology of the disease state [5]-[7]. We argue that dynamic control theory provides a mature paradigm to further advance the field of neuromodulation (Fig. 1). A classical control paradigm consists of a "plant" (the nervous system), the controller (neural "stimulator"), the sensor (clinical data), and the state estimator (patient assessment). In this context, the controller consists of any device or method that modulates the activity of a set of neurons. We call these "stimulators" for simplicity. Currently most stimulators operate in an open-loop fashion, requiring an operator to change therapy settings. Clinical observations and tests serve as sensors to generate the data used by physicians to assess the patient. In the future, neuromodulation aims to improve patient outcomes with ongoing therapy adjustment that minimizes clinical and patient burden. In a dynamic control framework, this goal points toward the following:

- Define the patient's desired state using objective criteria (Fig. 1a).
- Improve controllability through more sophisticated neural stimulator parameters, such as lead and electrode selection, field steering, selective stimulation, stimulation frequencies and amplitudes, and understand how these parameters affect the desired state (Fig. 1b);
- Understand the nervous system and the pathophysiology of diseases as the foundation for realizing a control strategy (Fig. 1c).
- Improve disease state observability through measurement of relevant biomarkers (Fig. 1d) and accurate estimation of the patient state (Fig 1e).

This framework allows neuromodulation to leverage well-understood dynamic control principles. Technologies should be used to minimize time delay in the control loop by providing timely feedback and control automation from sensing and state estimation. We also need to clearly understand the sensing-stimulation interaction and minimize the impact of direct feedthrough in the control loop. In addition, healthcare providers will be critical to optimize control parameters to ensure judicious use of the therapy for patients.

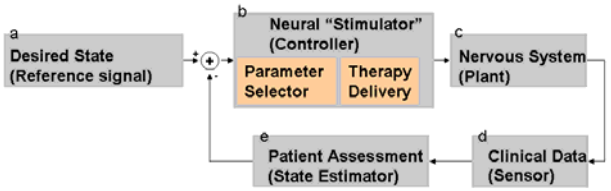

Fig. 1. The dynamic control framework for neuromodulation. a. Desired disease state is the reference signal, b. neural "stimulator" is the controller, c. the nervous system is the plant, d. tools to collect clinical data are the sensors, and e. patient assessment is the state estimator. In current clinical practice, the difference between a physician's estimate of the desired state and the patient assessment drives parameter changes in the neural "stimulator".

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The rest of the paper is structured as follows. Section II will discuss the challenges in each aspect of the dynamic control system in Fig. 1. Section III will review two investigational devices using this dynamic control framework. Section IV describes our development of an implantable platform system for chronic neural sensing, stimulation, and state estimation. Section V will provide examples of utilizing this system to address novel research questions. Section VI discusses future applications of this technology approach in neuromodulation.

II. Challenges in the Dynamic Control System

A. Desired State (Reference Signal)

The desired state, analogous to the reference signal in the control paradigm, represents the state of the neural network that the clinician would like to achieve with optimal therapy. For example, a patient with Parkinson's disease desires to be in the "on" state, meaning that the patient is optimally controlled with medications and/or deep brain stimulation (DBS). An epileptic patient may have a desired state of "homeostasis" in which neural activity is free of the ictal neural state. Precise definition of the desired state continues to be a challenge. Currently, the desired state is largely subjective, changes over time for a given patient, and varies between patients.

Improved understanding of neurologic diseases will provide more objective measures of defining the desired state. Recent research in Parkinson's disease [1], epilepsy [5], and depression [6] has revealed possibilities for defining and quantifying these signals.

B. Neural "Stimulator" (Controller)

Current neural "stimulators," which are effectively electric pulse generators, have an associated set of parameters, such as stimulation parameters (i.e., frequency, amplitude, and pulse width) and electrode location. Currently, the physiologic relationships between stimulation parameters and the nervous system are not well understood, leading to parameter selection procedures that may not ensure maximal patient benefit. Increasingly complex therapy delivery paradigms (such as greater number of electrodes [8] and wider parameter ranges) will further complicate parameter selection, and efficient parameter selection methods will be needed for optimal therapeutic benefit.

One method of improving feedback on parameter selection involves visualizing the volume of tissue activated (VTA) of neural stimulation (Fig. 2) [9]. This approach allows visualization of the anatomical regions receiving stimulation to optimize therapy to the desired targets. VTA serves as a useful tool to investigate the relationships between stimulators, stimulation parameters, and the structure and function of the nervous system.

Another set of challenges relates to the delivery of therapy. Currently, neural "stimulators" and their associated electrodes are limited in how they change neural electrical potentials. Stimulation volume is imprecise compared to the scale of neurons, and control over neural membrane potentials is imprecise compared to physiological membrane potentials. Advancements in electrode technology will enable more specific neural stimulation [8]. In the future, neural "stimulators" may utilize cellular and genetic techniques thereby enabling more nuanced mechanisms for modulating neural activity. One example is optogenetics, which uses gene therapy to allow unprecedented control over neural electric potentials [5].

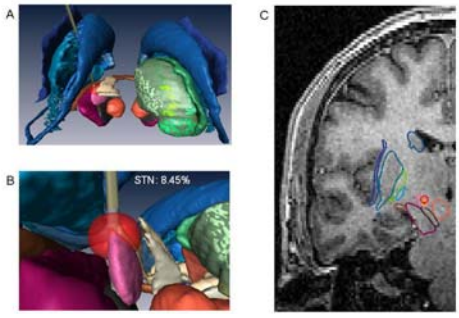

Figure 2: Visualization toolkit to enable clinicians to provide visual feedback in parameter selection. Examples of Visualization feature set: A) 3D anatomy of the atlas (not patient-specific) with a lead located in a default position and a VTA B) zoom-in onto STN including the volume intersection of VTA and STN C) the same atlas represented as 2D outline on the top of the atlas MRI (not patient MRI)

C. Nervous System (Plant)

The representation and temporal dynamics of the disease state in the nervous system, or "plant," are important in understanding the relationship between "stimulator" and observed sensor data. However, dynamic system identification to describe the nervous system and its non-linear relationship to therapy remains a formidable challenge. Neural models by Hahn and McIntyre [10] and Tass *et al* [7] demonstrate examples of using physiology based representations to help describe the dynamic effects of neural stimulation.

Improved understanding of the nervous system at the cellular and network levels together with increased computing power may improve the ability to characterize the plant and enable robust and precise neural stimulation and state observation strategies.

D. Clinical Data (Sensors)

Sensors are a critical element to collecting physiological data from the patient. As sensors become smaller, cheaper, and more power efficient [11] it is becoming increasingly important to develop sensors specific to disease states. Chronic neural signals are a natural place to look for biomarkers of neurologic diseases. Work in Parkinson's disease has implicated the amplitude of neural activity in the beta band (10-30 Hz) in parts of the basal ganglia to be related to the degree of movement dysfunction. In these patients, beta band amplitude has been estimated to be on

the order of 1 μV_{RMS} in the local field potential (LFP) [1], which is more than 100 times smaller than cardiac pacemaker signals. This poses significant technical challenges to developing sensors aimed at resolving this and other important signals [8]. In addition to neural signals, it may be possible to infer disease state information from other physiologic markers (for example, limb movement, heart rate, respirations, and others) using sensors like accelerometers.

E. Patient Assessment (State Estimator)

In neuromodulation, state estimation refers to the process of translating sensor information into an estimate of the patient state. In classical control theory, there are many ways to perform state estimation including the well-known Kalman filters and support-vector machines. Challenges to getting good state estimation fall into several categories. First, there is not sufficient information about the physiology and pathophysiology of the nervous system to understand the relationship between sensed biomarkers and the disease state. This understanding is fundamental to adequately capture the complex relationships between sensor measurements and the desired disease state in order to deliver optimal therapy. Second, the process of data collection and algorithm deployment in the flow of patient care is not well characterized. Third, limited understanding of the "true" patient state complicates the process of state estimator validation.

III. Current State of Devices With A Dynamical Control Framework

Evidence for the application of the dynamic control framework can be found in two investigational technologies: the Medtronic RestoreSensor™ system, a spinal cord stimulator CE-marked for chronic pain and the Neuropace RNS® system, an implantable investigational device for treating epilepsy. Both technologies have ongoing research trials.

RestoreSensor™ utilizes the control theory framework to maintain a therapeutic level of stimulation by using accelerometer data (i.e., sensor) to estimate body posture and activity (i.e., state estimator) and adjusting stimulation amplitude accordingly (i.e., neural stimulator). Stimulation is specific to the individual patient and the patient's posture. This technology is useful to ensure constant therapeutic parasthesia by enabling real-time stimulation changes that account for variations in electrode-to-spinal cord position.

The RNS® system utilizes a control theory framework to treat epilepsy by using neural activity (i.e., sensor) to estimate the neural state of the patient (i.e., state estimator), and deliver therapy accordingly (i.e., neural stimulator). This therapy may be useful for a large number of patients for whom pharmacologic treatment inadequately controls their epilepsy.

These systems demonstrate proof of concept for using the dynamic control framework for specific applications. However, the fundamental unanswered questions of neurological diseases call for a flexible general platform to enable discoveries for therapy translation.

IV. Next Generation Research Platform

Given the need for this basic research, our group has been developing a general prototype platform for investigating the dynamics of the nervous system (Fig. 3). With the constraint of ensuring standard-of-care therapy, the platform was built on an existing neural stimulator with added sensors for recording biopotentials (i.e., LFPs), movement (i.e., accelerometer), and patient events (i.e., patient-defined button presses). The sensors are used as inputs to the user-defined state estimator, which contains two discrete stages of processing: a linear discriminator (LD) front-end and a derived statistics back-end.

Fig. 3 shows the information flow for the system in its typical mode of operation. The device records and transmits sensor information for analysis by the clinician-researcher. Sensor data and clinical judgment are used to create a state estimator that identifies patient events (for example, the presence of seizures). The LD is generated offline by calculating an optimal linear boundary between vectors of separable biomarkers. The derived statistics back-end uses user-selected parameters to determine patient state and initiate triggers. The back-end is meant to filter the results of the LD to balance the trade-off between sensitivity, specificity, and detection latency. Triggers can initiate device functions such as starting high-fidelity neural data recording. In the future, the state estimator can also be used to initiate or change therapy. Finally, triggers can be reviewed by the clinician-researcher to validate and improve the state estimator.

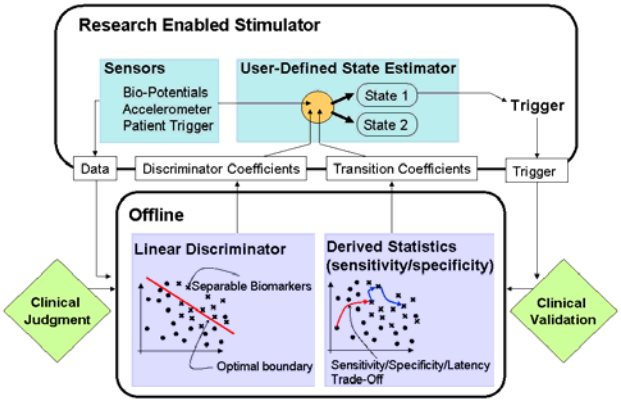

Fig. 3. A signal analysis flow model for the research platform to study and treat neurologic diseases. The research-enabled stimulator contains sensors to record biopotentials, acceleration, and patient triggers. A linear discriminator with derived statistical back-end triggers events, which can be used to validate the system.

V. Research Platform Enables Scientific Discovery

Early deployment of the prototype platform has already enabled the research discovery process. For example, the platform has been implanted and tested in an ovine with

leads placed in the hippocampus (HC) and anterior nucleus of the thalamus (ANT) [12]. Each lead was capable of both sensing and stimulation. The research system allowed investigators to stimulate the HC and simultaneously measure its effect on the neural network behavior. Fig 4 shows 4 bursts of HC stimulation at 120 Hz and between 2-2.5V. The research system revealed evidence of seizure-like activity during and after the second and fourth stimulation bursts. When stimulation is off, this activity can be observed as an after-discharge. The after-discharge manifests in the time-domain as a signal with higher than baseline amplitude, and in the frequency domain as delta/theta-band activity. When stimulation is on, seizure activity cannot be readily resolved in time domain since stimulation has >4 orders of magnitude higher power than the seizure activity. However, our system can clearly capture this level of activity within the stimulation, as shown in the "chirp" in the beta frequency band. The beta activity during seizure is not stimulation artifact, since it was not present when stimulations of similar levels were delivered (i.e., it does not appear during the first and third stimulation bursts). This experiment demonstrates that our system can capture signals of frequency and magnitude of human epilepsy in a biological model even in the presence of stimulation. This capability can help reveal network dynamics that were previously masked by stimulation.

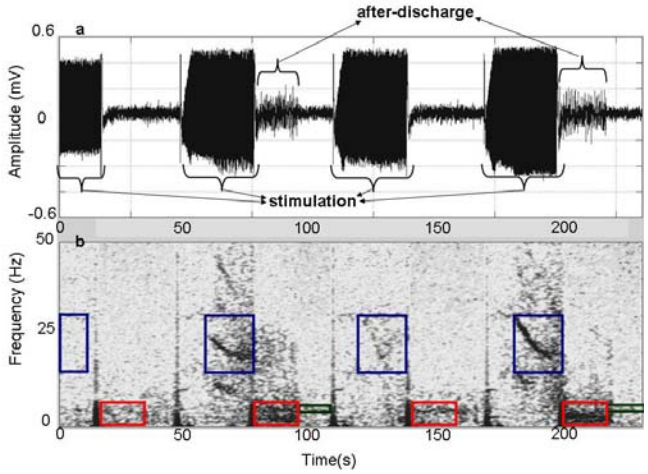

Fig. 4. Time domain graph (top) and spectrogram (bottom) recorded in the HC, showing 4 stimulation bursts of increasing amplitude (1.75V, 2V, 2.25V, and 2.5V) 120 Hz HC stimulation. Blue boxes highlight a 15-30Hz (beta band), red boxes highlight 0-6Hz (delta band), and green boxes highlight 5-7Hz (theta band).

VI. Technology Drives Advancements In Neuromodulation

New technology provides the tools necessary to investigate the next frontiers of neuroscience research. Our system allows researchers to chronically record and interpret neural activity in the presence of stimulation. This enables unprecedented study of neurological diseases. Current research in this field is limited by the capabilities of the state-of-the-art clinical recording technology, which largely restrict neural recording to the time during the surgical procedure. The latest work has allowed recording of neural local field potential signals 3-4 weeks post surgery [2] [13], but data collection was acute and restricted to the clinical environment.

By contrast, new general research platform will allow non-invasive recording and data transfer of neural signals for months to years post-surgery in both clinical and ambulatory settings. This may enable characterization of robust biomarkers that can be used as the feedback signal in the control loop. Furthermore, such capabilities could be a key enabler in understanding the mechanisms of action and therapeutic effects of currently available therapies. In the area of urinary incontinence, for example, chronic sensing and state estimation may enable closed-loop neural stimulation that is tailored to a patient's symptoms [14].

The ability to chronically perform sensing and patient state estimation using neural and non-neural biomarkers allows the study of the nervous system through a dynamic control framework. This framework facilitates both research into neurological diseases as well as more sophisticated therapies. Ultimately, it may be possible to perform continuous patient state monitoring and deliver neuromodulation with shorter time delays, improved patient outcomes, and reduced patient and clinical burden.

References

[1] F. Yoshida et al.; *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 81, no. 8, pp. 885-889, 2010.

[2] Rosa, M.; et al; *Exp Neurol*. Vol 222. No. 2. pp. 184-90. Apr 2010.

[3] Paralikar, K.; et al. "An Implantable Optical Stimulation Delivery System for Actuating an Excitable Biosubstrate," *Solid-State Circuits, IEEE Journal of* , vol.46, no.1, pp.321-332, Jan. 2011

[4] Diester, I.; Kaufman, M.T.; Mogri, M.; Pashaie, R.; Goo, W.; Yizhar, O.; Ramakrishnan, C.; Deisseroth, K.; Shenoy, K.V.; "An opotgenetic toolbox designed for primates." *Nature Neuroscience*. Vol. 14. pp. 387-397. Jan 2011.

[5] Osorio I, Frei MG, Wilkinson SB. *Epilepsia*, vol. 39, no. 6, pp. 615-627, June 1998.

[6] Craddock, C.R.; Holtzheimer, P.E.; Hu, X.P.; Mayberg, H.S.; *Magnetic Resonance in Medicine*, vol 62, no. 6. pp. 1619-1628. Dec. 2009.

[7] Tass, P. et al. *Journal of Neural Engineering*. Vol 7. pp. 1-16. 2010.

[8] Miyazawa, G.C.; Stone, R.; Molnar, G.F.; "Next generation deep brain stimulation therapy: modeling field steering in the brain with segmented electrodes". *Society for Neuroscience*, 693.21, San Diego, CA, 2007.

[9] Chaturvedi, A.; Butson, C.R.; Lempka, S.F.,; Cooper, S.E., McIntyre, C.C. *Brain Stimulation*. Vol 3. pp 65-77. 2010.

[10] Hahn, P.J.; McIntryre, C.C.; *Journal of Computational Neuroscience*. Dec 2008.

[11] Denison, T. ; Santa, W.; Molnar, G.; Miesel, K.; "Micropower Sensors for Neuroprosthetics." *IEEE Sensors*. Oct 2007.

[12] Stanslaski, S.; Stylpulkowski, P.; Giftakis, J.; Kemp, J.; Isaacson, B.; Cong, P.; Shafquat, A.; Afshar, P.; Denison, T.; "Preliminary validation of an implantable bi-directional neural interface for chronic, *in vivo*, investigation of brain networks." EMBS Cancun. April 2011.

[13] Ince, N.F.; et al.; *Neurosurgery*. Vol. 67. No. 2. pp. 390-397. Aug 2010.

[14] Wei, X.; et al. "Functional Electrical Stimulation as a Neuroprosthetic Methodology for Enabling Closed-loop Urinary Incontinence Treatment." EMBS Cancun. April 2011.