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Emerging Technology for Advancing the Treatment of Epilepsy Using a Dynamic Control Framework

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Abstract— **We briefly describe a dynamic control system framework for neuromodulation for epilepsy, with an emphasis on its practical challenges and the preliminary validation of key prototype technologies in a chronic animal model. The current state of neuromodulation can be viewed as a classical dynamic control framework such that the nervous system is the classical "plant", the neural stimulator is the controller/actuator, clinical observation, patient diaries and/or measured bio-markers are the sensor, and clinical judgment applied to these sensor inputs forms the state estimator. Technology can potentially address two main factors contributing to the performance limitations of existing systems: "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. In addition to improving sensors and actuator performance, methods and tools to better understand disease state dynamics and state estimation are also critical for improving therapy outcomes. We describe our preliminary validation of key "observability" and "controllability" technology blocks using an implanted research tool in an epilepsy disease model. This model allows for testing the key emerging technologies in a representative neural network of therapeutic importance. In the future, we believe these technologies might enable both first principles understanding of neural network behavior for optimizing therapy design, and provide a practical pathway towards clinical translation.**

I. INTRODUCTION

Improving the outcomes of therapy devices for epilepsy might be facilitated by better understanding the interaction between device and the nervous system. While initial therapies for movement disorders allowed for immediate observation of clinical effects from stimulation, epilepsy is more episodic and the linkage between stimulator settings and outcomes is not so immediately clear to the programming clinician. In addition, initial clinically-reported results from cycled "open-loop" systems and responsive systems appear quite similar [1, 2], suggesting that the leveraging of real-time information collected from the neural network has not yet been fully utilized. Finally, the relative importance of false positive and false negatives with respect to therapy and side effects in epilepsy may call for algorithms distinct from established cardiac devices.

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To help enhance outcomes, significant improvements are being explored in the technical and scientific understanding of device- and neural-circuit interactions. Progress has already taken place in sensing, improving therapy delivery, and understanding the pathophysiology of the disease state [3,4]. We argue that dynamic control theory provides a paradigm to further advance the field of neuromodulation, and in particular, the treatment of epilepsy (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. For simplicity, such devices will be referred to as neural "stimulators".

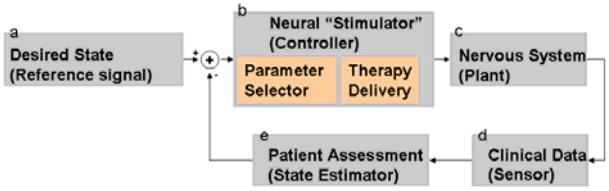

Fig. 1. The dynamic control framework for neuromodulation. Desired physiological state is the reference signal, the neural "stimulator" is the controller, the nervous system is the plant, clinical data is the sensor, and patient assessment is the state estimator.

The goal of neuromodulation is to provide quality disease control with ongoing therapy adjustment that minimizes clinical and patient burden. Viewing a typical therapy flow from a classical control framework, this goal points toward the following key technical blocks (ref Fig. 1):

- Define healthy and neurological disease states using objective criteria for assessing performance (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 better understand how these parameters affect the physiological state of the nervous system (Fig. 1b).
- Understand the nervous system and the nature of the disease state as the foundation of realizing a therapy control strategy (Fig. 1c).
- Improve disease state **observability** through measurement of pathophysiology biomarkers (Fig. 1d) and estimation of the physiological state (Fig 1e). Enhancements might include quantifiable diagnostics and translate to automated systems in the future.

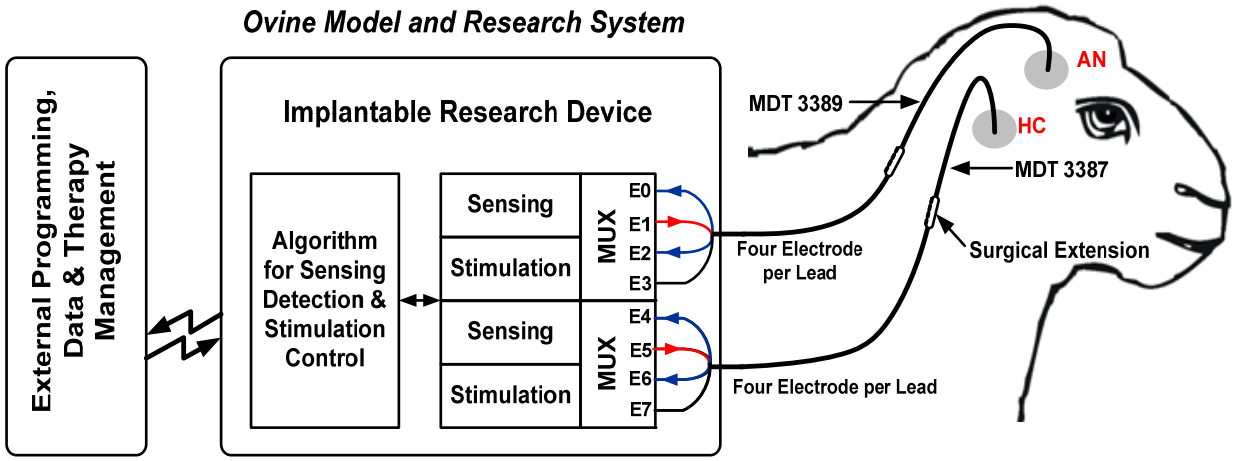

Fig 2: Ovine model for exploring the neural dynamics of the Circuit of Papez; leads are placed in the HC and ANT to probe dynamics in the thalamo-cortical network. Shown as stimulation (E1 to case) and Sensing (E0-E2)

The remainder of this paper is structured as follows. Section II will define the needed technology blocks within the control framework, and our initial validation of these blocks within a chronic animal protocol using an implantable research device. Section III will provide preliminary results of these experiments, with particular emphasis on validating controllability- and observability-focused technology blocks in the context of neural network behavior. Section IV will conclude the paper and discuss next steps.

II. Preliminary Exploration of Feedback Technology Concepts *In-vivo*

A. Chronic Protocol in Ovine Model for Epilepsy

A chronically implanted research tool [3] and protocol was used to initiate validation of the key functional blocks of a neuromodulation control system. The model for disease was the circuit of Papez in the ovine. The protocol and model were derived from Stypulkowski [5], and used the research device to explore some of the key design features related to the dynamic control framework described in this paper; the system block diagram is shown in Fig. 1:

- **Controllability**: validate the technology's ability to actuate a neural circuit and impact its state through stimulation
- **Observability**: validate the technology's ability to continuously resolve the neural network state. At minimum, this involves the ability to continuously sense the underlying physiological data with and without stimulation. The ultimate goal is to abstract this information using algorithms to determine high level brain state estimates on which to take action.

The study was conducted under an IACUC-approved protocol. Trajectories for a unilateral anterior nucleus of the thalamus (ANT) lead (Medtronic 3389) and unilateral hippocampus (HC) lead (Medtronic 3387) were planned, and leads implanted using a frameless stereotactic system (NexFrame). Intra-operative stimulation to confirm lead placement was delivered via a custom-designed system based upon implantable DBS hardware. Once lead placement was confirmed based upon these electrophysiological measures, model 37083 extensions were connected to the DBS leads and tunneled to a post-scapular pocket. The extensions were connected to the prototype instrumentation system in the thoracic pocket. Following closure of all incisions, anesthesia was discontinued and the animal was transferred to surgical recovery.

B. Controllability of Network Behavior

Following a two week recovery period, stimulation and recording sessions were conducted on a weekly basis for approximately two hour periods with the animal resting in a sling or freely moving. To ascertain the ability to modulate network activity, both low and high frequency stimulation of the ANT and HC lead to probe network connections and dynamics. This was performed both in ambulatory conscious animals, as well under anesthesia during surgical procedures.

Electrode impedance and evoked potentials by stimulation were collected at each session. The evoked potentials were tracked at the weekly monitors for more than six months post-implant, The protocol for evoked response testing was repeated with the implanted system to replicate results from Stypulkowski et al. chronically [5].

C. Observability of Network Behavior

Sensing and real-time classification of biopotential activity was accomplished in the presence of stimulation. Consistent with previous publications on sensing constraints during stimulation [3,6], measurements were taken from the two electrodes adjacent to the stimulation electrode, which was driven relative to the far-field case electrode in

monopolar mode. This provides sufficient symmetry for the brain sensing interface circuit to reject the stimulation as a common-mode perturbation. Far-field measurements from the stimulation source (ANT sensing during HC stim, and vice-versa) did not require this explicit symmetry constraint.

Recordings of the LFP data from the hippocampus were gathered representing ictal and non-inctal states and used to train a support vector machine discriminator [7]. In addition to monitor sessions, data was also collected at fixed time intervals using the embedded loop recorder and downloaded at the next monitor to help provide additional training data to the classifier. After analysis and supervised learning, the algorithm parameters were downloaded to the implanted device and detection was run in real-time. Classification results were then validated against observations.

III. Results: Chronic In-Vivo Testing

A. Actuation: Exploring the "Controllability" of the Neural Network through Stimulation

The bi-directional capability of the neural interface allowed for dynamic measurements of the network's response to stimulation. This includes both time interleaved signals such as evoked potentials, as well as the capability to resolve neural signals in the presence of stimulation using spectral decoding techniques. Evoked signals were collected by stimulating one target (ANT) and measuring response the response in the other target (HC) per Fig 3. The evoked potential ~40ms post-stimulation was used for tracking network coupling chronically as this peak was observed during initial implant testing [5]. The measured latency for the evoked potential is consistent with the values seen acutely during implantation under anesthesia. The evoked potentials were tracked at the weekly monitors for > six months *in-vivo*, and demonstrated no monotonic trends in performance that would lead to concerns about network coupling. This work validates the initial feasibility of bi-directional coupling for modulation of network activity. Defining actuation constraints and degrees of freedom is ongoing, and requires observability to the network state.

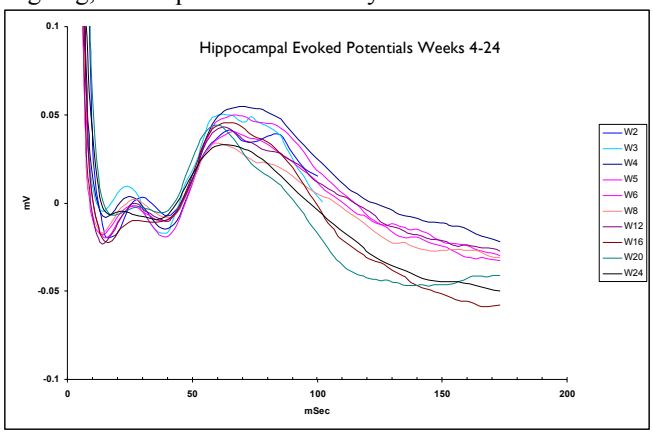

Fig 3. Chronic measurement of evoked potentials over six months; no systematic trending was observed, although week-to-week fluctuations were apparent.

B. Observability: Sensing Methods in Presence of Stimulation

An additional series of tests explored the observability of the neural network in terms of the ability of sensing during stimulation. A key issue is defining a repeatable physiological signal for sensing, especially in the presence of a strong stimulation background. We found that high amplitude, high frequency stimulation of the HC can induce an after-discharge that can be sensed in the hippocampus, as shown in Fig. 4. This signature was used to explore our measurement capability chronically *in-vivo*.

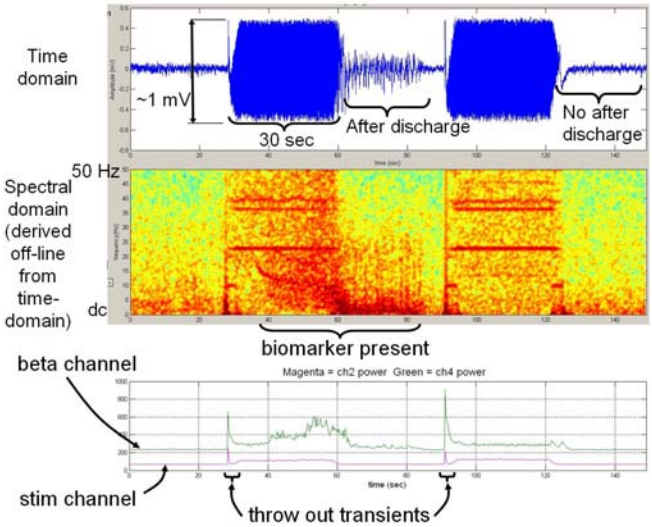

Fig. 4. Top: Time domain graph (upper) and spectrogram (lower) recorded in the HC, showing 2 stimulation bursts of 140 Hz, 2V HC stimulation. Bottom: On-line spectral processing in the research tool used for the detection algorithm: the beta band (physiology) and stim channel (monitor for artifact).

A key design goal of the implantable research tools is the ability to measure signals in the presence of stimulation. Following the methods presented in [3], we are able to resolve biomarkers embedded in artifact using frequency analysis. As shown in Fig. 4, the presence of an after-discharge is proceeded by a "wind-up" in the beta band of the HC LFP, which after stimulation drops in frequency to the theta-dominated spectral signature. The reasons for the frequency shift are not yet clear, but appear to be physiological. Test tones in a saline tank demonstrated the frequency translation is not an artifact. In addition,, biasing of the stimulation amplitude to a borderline zone where the after-discharge is generated with a random chance (~50%) showed that the stimulation artifact is high-Q and stationary versus the physiological response (ref second tone of Fig. 4).

C. Observability: State Classification in Presence of Stimulation (State Estimator)

Enabling a robust detection system requires algorithms that perform state estimation in real-time, in the presence or absence of stimulation artifact. Using the architecture defined in [3,7], sensors are used as inputs to the user-defined state estimator with two stages of processing: a

support vector machine (SVM) front-end and a derived statistics back-end.

To allow for training of an algorithmic detector of the after-discharge processes, we collected spectral powers in the device at the physiological bands (broad beta) associated with the observed seizure induction and after-discharge. A simple one-dimensional detector, however, would be confounded by stimulation artifact. To mitigate this we also sampled the artifact by tuning to a band (80 Hz) that provided a measure of stimulation energy coupling into the channel, but minimal physiological data. This allowed us to construct an algorithm that detected biomarkers in the presence and absence of stimulation.

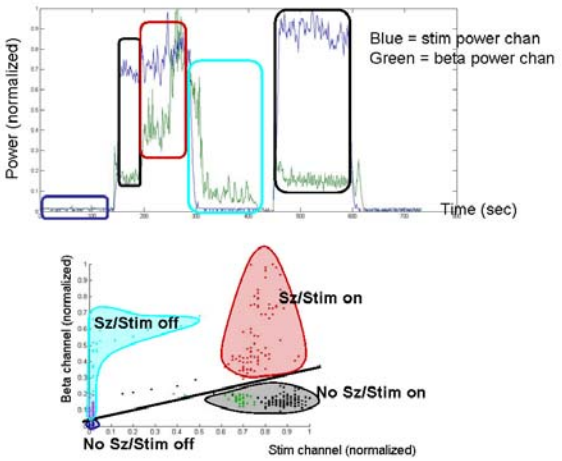

Fig. 5. Top: Power (physiological-beta, stim) annotated in the different states. The red and magenta are the "Sz-seizure" state, black represents background. Bottom: SVM-based boundary (solid line), with corresponding colored clusters.

Fig. 4 shows the flow of annotating the data for training. The area annotated "biomarker present" is labeled as one state, with the other areas forming the alternative state; edge transitions are kept out of the training set. Fig 5 zooms in on the two power channels of interest, illustrating how the states can be effectively separated using a *multi-dimensional* detector. The SVM is generated offline by calculating an optimal boundary, with the "stimulation" channel providing the key dynamic scaling of the boundary to account for the spectral leakage inherent in the sensor signal chain. The derived statistics back-end models physiological state transitions. The back-end "filters" the SVM to balance the trade-off between sensitivity, specificity, and detection latency, such as during stimulation on/off transitions. Fig. 6 illustrates the validation of the detector *in-vivo* after training; note that the validation data was taken two weeks after training, demonstrating promise for algorithm robustness.

IV. Discussion and Future Steps

Using the research tool chronically in-vivo, we have demonstrated key technology building blocks for exploring a dynamic control model for epilepsy therapy. This includes "controllability," where the model and implantable device provide a mechanism of actuating network activity, and "observability," where we have demonstrated the capability to sense neural state in the presence or absence of stimulation. This provides the ability to monitor the state of the network and potentially use an algorithm to control parameters such as duty cycle, etc, based on physiology.

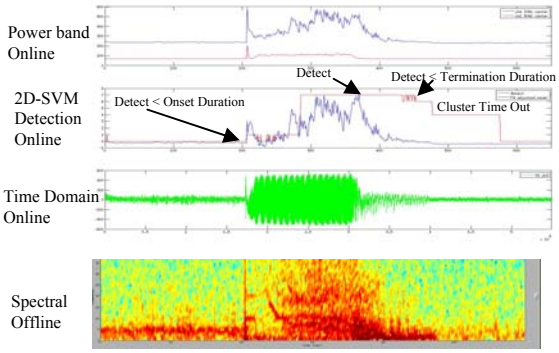

Fig. 6. Validation of the embedded detection algorithm detecting a seizure-induction state and after-discharge *in-vivo.*

The ultimate translation of these technology blocks into dynamic control schemes depends on the behavior of neural network dynamics. If network characteristics are relatively stationary, then an acceptable control scheme might be to provide patient-specific, physiologically based parameters for optimizing "open loop" cycled programming. If however, the network excitability is variable (circadian, etc), then the stimulation control might add in a degree of freedom such as an adjustable stimulation duty cycle to counteract network variations. In essence, this might take the form of a homeostatic feedback method that titrates to avoid seizure states, as opposed to attempting to abort ictal activity. First principles research will guide the solution.

Acknowledgements

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