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A modular, closed-loop platform for intracranial stimulation in people with neurological disorders

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Abstract

Neuromodulation systems based on electrical stimulation can be used to investigate, probe, and potentially treat a range of neurological disorders. The effects of ongoing neural state and dynamics on stimulation response, and of stimulation parameters on neural state, have broad implications for the development of closed-loop neuromodulation approaches. We describe the development of a modular, low-latency platform for pre-clinical, closed-loop neuromodulation studies with human participants. We illustrate the uses of the platform in a stimulation case study with a person with epilepsy undergoing neuro-monitoring prior to resective surgery. We demonstrate the efficacy of the system by tracking interictal epileptiform discharges in the local field potential to trigger intracranial electrical stimulation, and show that the response to stimulation depends on the neural state.

I. INTRODUCTION

Closed-loop neuromodulation systems that concurrently estimate brain state and deliver electrical stimulation or other feedback are a promising approach to investigation and therapy for neurological disease and injury [1–3]. One application of closed-loop stimulation is seizure control. Electrical stimulation in cortex, deep brain structures, and cranial nerves has been shown to limit seizure propagation and reduce seizure incidence [4]. A well-calibrated seizure detection system could predict or detect the early onset of a seizure, providing an early warning to the patient, or delivering direct electrical stimulation to disrupt seizure propagation and stop the seizure before the patient experienced any symptoms [2].

However, state-of-the-art clinical approaches remain limited: they require hand-tuning by care providers; they rely on relatively few electrodes with limited spatiotemporal resolution, they use retrospective statistical techniques to detect the likelihood of potentially heterogeneous seizures; and they deliver all-or-nothing stimulation responses to timevarying seizures. With these limitations, existing stimulation devices are effective but usually not curative [2, 3].

Programmable, dynamic control approaches to brain stimulation and seizure control have been proposed, but have not been translated to human research participants [5–7]. Cortical stimulation has been used to probe neural dynamics during interictal states in people with epilepsy, as an active assessment of the susceptibility of brain network dynamics to electrical pulse propagation, and by extension, seizures [8]. Because stimulation affects the neural state, and the ongoing neural state affects the response to stimulation, approaches that investigate and describe both ongoing neural states and stimulation effects are an important step towards dynamic intracranial stimulation with broad application potential.

We developed a closed-loop hardware-software research platform to acquire data from electrodes of varying spatial and temporal resolutions; to flexibly interchange signal processing and state estimation techniques; and to deliver stimulation conditioned on detected neural events and their features. We deployed this system to estimate neural state and stimulate electrically the brain of a person with epilepsy. Here, we describe design principles and technical details of this system. We illustrate the platform’s capabilities with intracranial electrical stimulation, conditioned to detection of interictal epileptiform discharges (IED), in an individual with focal epilepsy. Notably, the proposed modular architecture, suitable for use in humans, achieves substantially lower latencies than previously reported systems.

Although we focus on epilepsy, the applicability of the approach to other neurological and neuropsychiatric disorders is, in principle, broad. Electrical stimulation has been proposed as an effective component of implantable systems for Parkinson’s Disease, essential tremor, obsessivecompulsive disorder, depression, and motor-prosthetic braincomputer interfaces [9].

Our platform has been designed to make such extensibility feasible. It can be used to prototype closed-loop algorithms for detection and stimulation, and to actively probe neural dynamics in the context of a variety of neurological disorders.

II. METHODS

A. Participant

The participant was an adult male with pharmacologically intractable epilepsy who had depth electro-encephalographic electrodes placed for clinical monitoring prior to resective surgery at Massachusetts General Hospital. Stimulation experiments were approved by the Institutional Review Board at Massachusetts General Hospital. Subsequent analysis was approved by Institutional Review Boards at Massachusetts General Hospital, Brown University, and the Providence Veterans Affairs Medical Center.

B. Hardware and Software

Five computers running Windows, as well as an additional computer running a real-time operating system and three specialized neural signal processing and stimulation machines, were used in the architecture (Figure 1).

Real-time software ran on the xPC Target operating system (Mathworks, Natick, MA). Custom code acquired neural data over an Ethernet connection from each of two Blackrock Neural Signal Processor (NSP) units every millisecond (Blackrock Microsystems, Salt Lake City, UT). Data from each NSP were also streamed to a computer for data storage. The Blackrock system is compatible with a variety of recording modalities at several concurrent sampling rates.

One computer was used as the primary interface for clinician and researcher interaction with the closed-loop system, providing status indicators and readouts of neural data. A minimum of one Windows computer is needed for the configuration, for operator control, stimulator control, and data storage.

A parallel port connection drove a digital trigger to a Blackrock Cerestim R96. Remaining commercial hardware and software, as well as low-latency infrastructure, are comparable to those reported in previous neuroprosthetic studies [10]. Interested readers can contact the authors for more details on the architecture and implementation.

C. Signal Processing

In this example case, data were sampled at 2ks/s and filtered between 0.3 and 1000 Hz. These “raw” neural data were saved for offline analysis. Higher sampling rates (e.g. 30 kHz), with concurrent computations of broadband field potentials and discrete neuronal ensemble spike trains, are also directly programmable.

D. Detection and Controls

In the example shown here, electrical stimulation was either triggered randomly or conditioned on a threshold crossing. A threshold on the LFP amplitude at -3 RMS was dynamically computed with a history of 30 seconds. To avoid contamination by the stimulation artifact, we excluded 100 milliseconds post-stimulation from the dynamic threshold estimate.

At each millisecond, regardless of whether or not an event was detected, a random draw with a mean positive rate of 10 events/second was performed. This defined one control case, in which no event was detected and a stimulation was issued. Stimulation was delivered a maximum of once every 2.5 seconds. To establish a second control case, in which an event was detected but no stimulation was issued, a Bernoulli draw with a probability of .9 determined if a given threshold crossing led to a stimulation pulse.

E. Stimulation

When stimulation was triggered, a single bipolar stimulation pulse at an amplitude of 1.25 mA was delivered with a duration of 90 μ s on the first electrode, an interphase of 53 μ s, and

90 μ s on the second electrode. More complex stimulation sequences are also possible. To compare the event-triggered stimulation to the control case we used a random permutation approach to estimate the chance level probability of measured maximum absolute difference between the responses in the two conditions (random label shuffling; 1000 random permutations).

Feasibility of the online system was confirmed by processing the neural data through a comparable offline signal processing pipeline. Processed neural data were then compared by the correlation between the two processed time series. Triggered events from the offline process were compared to triggered events from the online system.

Latencies were measured by an analog square wave driven into the NSP; the rising edge was detected in the realtime software, and a response trigger was driven back to the NSP. The lag time between the two rising edges characterizes the Ethernet delay and the processing delay, but some signal processing and estimation schemes may introduce further delays.

III. RESULTS

A. Latencies and Online-Offline Comparison

General technical features of the platform are as given in Table 1. The average time from event detection to delivery of electrical stimulation was 5ms. This latency includes the conduction time from brain to analog-digital conversion, Ethernet communication time of the neural signal, the signal processing time, and the time to stimulus delivery.

We examined the accuracy of the online detection by computing reconstructing the power and threshold offline from the raw 2ks/s data. The two approaches captured comparable events, demonstrating that the online system effectively detects neural events in real-time (Figure 2).

C. Random to Event-Triggered Response Comparison

Twenty-four minutes of stimulation data were collected. In subsequent offline analysis, events were grouped as event-triggered stimulation, event without stimulation, and randomly triggered, or baseline, stimulation. A hysteresis on the threshold was applied in the analysis such that random stimulation that occurred within 16.7% of the detection threshold were excluded from either stimulation category.

The evoked responses to event-triggered stimulation differed significantly from the randomly triggered stimulation at a remote site on the opposite hemisphere. This preliminary result suggests that evoked responses to stimulation, and propagation of those responses, depend on the occurrence of interictal epileptiform discharges (Figure 3). The result also demonstrates an experiment that could have been difficult to carry without the described infrastructure, which allows stimulation conditioned on ongoing brain states.

IV. DISCUSSION

We have presented here a proof-of-concept for a modular hardware-software platform for closed-loop stimulation based on tracking of brain states in the context of intracranial neural recordings and stimulation experiments in a person with epilepsy.

A. Relationship to Other Closed-Loop Systems

Previous neuromodulation systems have been used for brain stimulation in people with epilepsy. In the randomized NeuroPace study, in which stimulation was delivered in closed-loop fashion, 8% of subjects were seizure free after two years; the median reduction in seizures in a given patient was 53% [2]. These results indicate both the promise of neuromodulation approaches and the ongoing need to develop and test more effective closed-loop algorithms on programmable platforms.

Low latencies are likely to be a particularly important component of dynamic stimulators that respond to rapid changes in ongoing brain states. Approaches that involve a yes-or-no detection and an all-or-nothing feedback response can tolerate latencies of hundreds of milliseconds, but a dynamic approach is likely to require faster, more continuous feedback. Analogous approaches, moving from slow classification to rapid feedback, have been notably successful in neuroprosthetic control systems [10].

Other programmable stimulation platforms motivated by a dynamic control framework have previously been proposed [6, 7]. However, despite examples of responsive electrical stimulation in people and animals, we did not find a reported system in literature with the low latency, high channel throughput and sampling rate, and suitability for inpatient testing that characterizes our system.

B. Extensibility and Potential for Translation

The stimulation platform described here can be used for a range of task- and neural-event-triggered experiments, for investigation of mechanisms and therapies in epilepsy and a variety of other neurological and neuropsychiatric disorders. We are particularly interested in dynamic approaches to seizure prevention in which stimulation patterns are adjusted in real-time based on recent and current estimates of neural state; in actively probing the susceptibility of brain dynamics to seizure initiation and spread; and in the closed-loop identification of epileptogenic areas or other automated mapping procedures prior to resective surgery [11]. At this early stage, a rapidly programmable platform is advantageous: for instance, we have initiated work to trigger stimulation on other biomarkers at the same stimulation electrodes, to trigger different stimulation patterns on the same neural events, or to incorporate visual or auditory stimuli into the experimental paradigm.

Importantly, our system supports surface and depth electroencephalography as well as single-unit resolution micro-electrode array measurements. Given the promise of MEA-based seizure prediction and detection [12–14], this multi-modality allows concurrently for high fidelity recording and spatially distributed modulation in the inpatient research setting.

Detection and stimulation algorithms developed on this platform could be translated to an implantable device. A limitation of our approach is that it does not optimize for power consumption; the advantages of latency and throughput result in part from a system that is neither wireless nor chronically implanted. Clinically viable devices would likely be less flexible and more specialized, although improvements to the programmability of implantable devices will likely address these challenges over time. The approach proposed here is well-suited for flexible inpatient research, and could be extended to a range of investigative or therapeutic neuromodulation applications.

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Figure 1.

Overview of closed-loop neuromodulation architecture. Solid lines represent “hard” analog or digital connections, while dashed lines represent “soft” Ethernet or USB connections. A clinician or researcher interacts with the system from the Operator Control Windows computer. A real-time operating system runs on the Neural Interface Core computer for neural signal processing and event detection. Visual or auditory stimuli can be presented to a research participant on an additional Task computer, which was not used in the example study presented here.

Figure 2.

Recorded neural data with prominent interictal epileptiform discharges, overlaid with the dynamic RMS-based threshold. Above, black dots indicate online triggered stimulation, while magenta indicate offline-reconstructed stimulation. On the time series, physiologically triggered stimulation events marked in blue, un-stimulated events in green, and un-triggered stimulation in orange.

Figure 3.

Top: Coronal slice and axial slice showing locations of depth electrodes. Bottom: The left and right plots show the mean evoked responses to single-pulse stimulation near and distal (other hemisphere) to the stimulation site, respectively. We emphasize that the mean evoked responses in the distal site show a significant difference between IEDtriggered and baseline (random) stimulation conditions (permutation test at the point of maximum absolute difference, red dot, $p < .05$).

Table 1.

System technical properties.

<i>Property</i>	<i>Value</i>
Number of channels	Up to 256 electrodes
Loop latency	5ms +/- 1ms
Sampling rate	.5ks/s to 30ks/s