Cortical Brain Computer Interface for Closed-Loop Deep Brain Stimulation

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Abstract— Essential Tremor is the most common neurological movement disorder. This progressive disease causes uncontrollable rhythmic motions—most often affecting the patient’s dominant upper extremity—that occur during volitional movement and make it difficult for the patient to perform everyday tasks. Medication may also become ineffective as the disorder progresses. Deep brain stimulation (DBS) of the thalamus is an effective means of treating this condition when medication fails. In current use, however, clinicians set the patient’s stimulator to apply stimulation at all times—whether it is needed or not. This practice leads to excess power use, and more rapid depletion of batteries that require surgical replacement. In the work described here, for the first time, neural sensing of movement (using chronically-implanted cortical electrodes) is used to enable or disable stimulation for tremor. Therapeutic stimulation is delivered only when the patient is actively using their effected limb, thereby reducing the total stimulation applied, and potentially extending the lifetime of surgically-implanted batteries. This work, which involves both implanted and external subsystems, paves the way for the future fully-implanted closed-loop deep brain stimulators.

Index Terms—DBS, BCI, Closed-Loop Systems, Essential Tremor

I. INTRODUCTION

ESSENTIAL Tremor (ET) is the most common neurological movement disorder [1] and it has a dramatic impact on patient quality of life [2]. ET causes uncontrollable rhythmic motions—most often affecting the patient’s dominant upper extremity—during volitional movement. These uncontrollable movements make it difficult to perform everyday tasks such as eating, drinking, writing, or other activities that require fine motor control. While pharmaceutical agents (e.g., propranolol) can help relieve symptoms for some individuals, medication is often ineffective or poorly tolerated in the long run: ET is a progressive disease, and its symptoms worsen over time [3]. Deep brain stimulation (DBS) of the thalamus is often used to give otherwise untreatable patients control of their limb and freedom from disabling tremor symptoms [4,5].

Current DBS treatment of ET is performed using a battery-powered, implantable pulse generator (IPG) surgically implanted in the chest which sends electrical stimulation to a lead inserted through a hole drilled in the skull to electrical contacts in the ventral intermediate (VIM) nucleus of the thalamus [5]. While the underlying causes of ET in the brain are unknown, and the means by which thalamic stimulation treats essential tremor are unknown [6], the effect of electrical stimulation can be remarkably effective for reducing tremor in ET patients [4,5].

However, DBS for ET comes with several drawbacks. Stimulation can cause unpleasant side-effects for patients, such as paresthesias (abnormal facial or extremity sensations like tingling), dysarthria (speech impairment), and ataxia (dyscoordination) [7]. Additionally, most IPGs are non-rechargeable and require surgical replacement when the battery is depleted. Current clinically- and FDA-approved DBS systems run in an “open-loop” manner, meaning that they deliver stimulation at a steady rate for as long as the device is running. Changes to this therapy require intervention by a clinician to adjust the amplitude, pulse width, and frequency of the stimulation waveform. This “open-loop” means of applying stimulation can lead to additional problems for the patient. Patient symptoms and side effects vary widely and are difficult to evoke consistently during bedside testing, and so it can be difficult to determine appropriate stimulation parameters for each patient [8]. The current practice of applying open loop stimulation, even at times when the stimulation is not necessary, is wasteful and can result in more frequent battery replacement surgeries or larger implanted devices than would otherwise be needed.

“Closed-loop” methods of applying stimulation, where IPGs use sensors to collect tremor data from the patient and automatically make stimulation adjustments as needed, are being investigated as a solution to these drawbacks. For example, in the case of many Essential Tremor patients, a system that only provides stimulation when the patient is moving the affected limb may be capable of treating tremor while preserving battery life and reducing side-effects. Prior
applications of closed-loop DBS for ET in human subjects have exclusively used wearable inertial sensors [9], or electromyography(EMG) to provide feedback for closed-loop DBS experiments [9,10].

While wearable sensors are appropriate for use in an experimental setting, there are significant barriers to translating wearables to a clinically deployable system. Externally sensed data and externally computed control actions must be transmitted to the IPG. The computations necessary are time-intensive and introduce latency into the system. Further, the telemetry required to maintain a wireless communication channel between the IPG and external sensors is power intensive, and it is possible that the power lost on wireless telemetry would negate much of the power savings that closed-loop stimulation would deliver. Additionally, patient acceptance may be a concern, as wearing a sensor for much of the day may be uncomfortable, cumbersome, or draw unwanted attention. One possible way to address these potential problems with wearable closed-loop systems is to use signals collected from an additional set of implanted electrodes [11]. This would allow an implanted IPG to collect the data required to make control decisions without the need for worn sensors, off-board computations, or telemetry.

In this paper, we demonstrate the first use of chronic electrocorticography (ECoG) to modulate an ET patient’s DBS in real-time through the use of movement-related cortical signals. This closed-loop system uses an investigational IPG with neural sensing capabilities to modulate stimulation amplitude based on motor cortex ECoG. We show that cortical movement-related beta-band desynchronization (during overt limb movement of the tremor-affected arm) can be used effectively to trigger deep brain stimulation in order to reduce tremor. We demonstrate the efficacy of this system while the patient performs standard drawing tasks that are a component of a widely-accepted clinical tremor assessment as well as a prompted movement task where the patient performs movements that predictably cause tremor. Our system successfully and accurately enables and disables stimulation during periods of movement and rest in these trials—and, as a result, the system reduces the power consumed by the IPG. That is, the system applies therapeutic stimulation to treat tremor only when the patient is actively using the limb, thereby reducing the total amount of stimulation applied, and consequently may extend the lifetime of surgically-implanted batteries. This work paves the way for the future fully-implanted closed-loop deep brain stimulators for use as therapeutic tools. It also facilitates investigation of closed-loop patient-device system dynamics.

II. METHODS

The experimental protocol used was approved by the Institutional Review Board at University of Washington Medical Center, and use of the Activa PC+S and Nexus D system was approved by the FDA through an Investigational Device Exemption. The experiments were performed in accordance with all relevant guidelines and regulations. The subject provided informed consent according to direction from the Institutional Review Board prior to enrollment in our study.

The patient is a 58-year-old right-handed man who experiences tremor during volitional movement of his right arm and leg. The patient consented to participate in our study.

Fig 1: Block diagram illustrating the experimental setup for our closed-loop DBS experiments. ECoG data, sensed by the Activa PC+S and streamed by the Nexus-D, is processed and classified on a laptop computer. When the Beta band-power crosses thresholds defined for movement and rest, the stimulation is turned on or off. Limb inertial and EMG recordings are logged and timestamped separate from the closed-loop.
to implant an investigational IPG developed by Medtronic, the Activa PC+S. This IPG has the capability to sense through implanted electrodes as well as provide traditional clinical therapeutic stimulation. The sensed data can be streamed to an external computational device, such as a laptop computer, through the use of the Nexus-D, another investigational device developed by Medtronic [[12]].

In addition to the DBS lead implanted in the VIM for therapy, we implanted a cortical strip of electrodes (the Resume II lead) on the surface of the brain overlying motor cortex and connected directly to the Activa PC+S. This strip of four electrodes allows for the chronic recording of neural signals from the cortex that have been shown to correlate with hand movement. Prior work with this patient demonstrated that limb movement may be detected using the Activa PC+S based on the onset of a decrease in beta power over sensorimotor cortex [[9]]. We also demonstrated the use of surface electromyography (EMG) from this patient’s arm muscles to trigger stimulation during movement. Using EMG to trigger stimulation only during muscle activation resulted in both power savings and suppression of tremor [[9]]. The innovation of the work reported here is the use of cortical signals to directly drive the closed-loop control system.

The overall experimental system is represented in the block diagram shown in Figure 1, which outlines each component of this first neural closed-loop DBS system for ET. The Activa PC+S digitizes neural signals at a rate of 422 samples per second. The Activa PC+S then streams the data to a laptop using the Nexus-D. Each packet contains 400ms (168 samples) of data. The laptop converts the time-domain data into the frequency domain, performing a 256-sample long FFT, with a Hann window and zero padding. When the patient moves, the beta-band (16-32Hz) component in the signal decreases, a well-described phenomenon known as cortical desynchronization [[13]]. When this beta band-power drops below a manually-tuned threshold, the system ramps stimulation up to the normal clinical setting, or “on” state, to deliver therapeutic stimulation and treat the tremor. Similarly, when the movement ends and the motor circuits re-synchronize, the beta band-power will rise. When it crosses a second manually-tuned threshold, the stimulation is turned off, thus conserving power when movement is not occurring.

To simplify the development of this proof of concept, we iteratively tuned the thresholds used to trigger stimulation changes. The two manually-tuned thresholds represented the movement-initiation band-power threshold and the rest initiation-band-power threshold. The movement-initiation threshold was calibrated while stimulation was off and the patient was constantly moving, and the rest-initiation was calibrated while stimulation was on and the patient was at rest. We averaged the beta band-power estimation across five packets (or two seconds) in order to gain better specificity for movement detection. However, averaging the feedback signal in this way introduces system delays that reduce overall system responsiveness.

There are several complicating factors that need to be considered when designing experimental code to perform this task. We noticed that there was a dramatic physiological effect of stimulation on the patient’s cortical beta-band signal, as shown in Figure 2. Fortunately, the magnitude of movement-related desynchronization was sufficient for use as a biomarker despite the noise in these signals and the reduction in band-power when stimulation is present. However, the fact that VIM stimulation suppressed cortical beta was a key rationale for the use of two separate manually-tuned thresholds instead of a single one.

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**Previously Collected**

| Pre-Op | 4 Months Post-Op No Stimulation |

**Experiment (7 Months Post-Op)**

- No Stim
- Open Loop Stim
- Closed Loop Stim

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Fig 2: Normalized Cortical spectrogram showing patient rest with stimulation “off” on the left, and 140Hz stimulation “on” on the right after 4 seconds. Note lower beta-band (16-32Hz) power on the right relative to the left.

Fig 3: Patient drawn spirals collected as part of clinical tremor assessment. On the left are two spirals drawn with the dominant hand before and after DBS implant. On the right are spirals collected on the day of the experiment in each of the three stimulation states. Differences in tremor between no stimulation at four months post-op and experimental day are attributed to day to day tremor variation. Note tremor in the upper right and lower left quadrants of the spiral in the experimental no stimulation case. Comparatively there are few deviations from normal spirals in the open-loop and closed-loop cases.
To assess the experimental system, the patient performed two sets of tasks with no stimulation applied, open-loop stimulation, and closed-loop neural-triggered stimulation. The first were drawing tasks from the commonly-used Fahn-Tolosa-Marin tremor assessment [14], including the spiral draw, connecting dots, and sentence writing tasks. The patient was given short breaks in between the dot connecting and sentence writing tasks to give the researcher’s time to give the patient the next sheet of paper to work on. The patient was then asked to complete a series of computer-prompted tasks where he was instructed to alternate between resting his hand and bringing his hand to his mouth. This motion caused predictable tremor symptoms in this particular patient and facilitated a direct comparison of how each stimulation paradigm performed in a repeatable task. There were ten prompts each for movement and rest, with each prompt lasting for ten seconds. Each trial thus lasted a total of 200 seconds. The prompt was delivered through both visual cues presented on-screen to the patient and audio cues. While the patient was performing these tasks, we recorded data related to his arm movements with a wrist-worn accelerometer and surface electromyography.

Prior to closed-loop experiments, we characterized the side effect profile of stimulation amplitude ramping rates between “on” (2.4 volts) and “off” (0 volts) states. We asked the patient to report any unpleasant side-effects as stimulation was ramped with increasingly fast slew rates. The interval between stimulation setting updates was limited to the sensing packet rate (400ms) to avoid losing streamed data during the experiments with sensing enabled. When increasing the stimulation by 200mV every 400ms, the patient reported mild paresthesias that were not unpleasant. At 1000mV every 400ms, these sensations were more marked and surprising. Given his unpleasant reaction at the 1000mV level, we used 800mV/400ms as the ramping rate for closed-loop stimulation testing. This would result in the system being able to transition between the on and off states in a total 1.2 seconds.

III. RESULTS

The spirals from the tremor assessment drawn during no-stimulation, open-loop stimulation, and closed-loop stimulation are shown in Figure 3. The post-op no-stimulation spiral was selected as a representative example from previous tremor assessments. It is well known that the severity of tremor can vary day to day, but even during this low-amplitude session there are clear hallmarks of tremor in the spiral which were apparent in comparison to the open-loop case. The closed-loop case appears to be nearly identical to the open-loop results, indicating that the system was able to significantly reduce his tremor while writing.
All three tremor assessment tasks were performed for each stimulation paradigm, and the time-series plot of the closed-loop tremor assessment trial is shown in Figure 4. In the trial, the stimulation was turned off when the patient was at rest before the trials began, and during the short break in between the second and third tasks while the researchers switched pages. Stimulation was also correctly turned on for the duration of drawing spirals, connecting dots, and writing sentences.

The results from the movement-prompting task are shown in Figure 5. Each of the ten pairs of movement and rest periods were averaged together for each of the trials with the three different stimulation settings. The cumulative magnitude of the three axes of the inertial gyroscope is displayed in the top row of the figure. By analyzing the gyroscopic data, we can estimate how much tremor the patient experienced at a given moment. Due to patient reaction times and time to transition between states, initiation of movement is offset from the prompts at 0 and 10 seconds by approximately 1 second; this is indicated by the large discrete peaks that exceed the window bounds. Tremor appears as a noisy signal in-between the transient peaks, while the patient is holding his hand at his mouth. The strength of the tremor is estimated through spectral analysis to remove the influence of the transient peaks, as shown in the second row.

With no stimulation, there is tremor consistently throughout the prompted action and while at rest. The closed-loop system results in brief tremor at the start of the movement, followed by rapid reduction to the open-loop levels. In the third row, the average cortical beta-band power is shown. With stimulation off, there is a clear difference between the mean beta-band during rest and movement. Stimulation effects on the beta band make this distinction more difficult to see during open-loop stimulation.

During closed-loop stimulation, the beta-band tends to follow a more “normal” trend with low beta-band power during movement and higher beta-band power during rest. The average stimulation delivered in each trial is depicted in the final row. For the closed-loop stimulation trial, the average stimulation rose to clinical amplitudes during every movement and dropped to zero during every rest. The mean amplitude and quantile bounds reach 2.4 volts about five seconds after the prompt, indicating that for each and every movement period, stimulation reached clinical levels. The movement of the limb from the action to rest state also triggers stimulation, as can be seen in an average increase in the stimulation amplitude around 14 seconds. However, by the 18-second mark, prior to the next movement prompt, stimulation was off for all trials.

IV. DISCUSSION

The results show that the cortical movement-related beta-band desynchronization is an effective signal to trigger DBS in order to reduce tremor. While the patient performed drawing tasks, the system modulated the stimulation levels...
appropriately: the system applied stimulation while the patient moved his arm and turned stimulation off while he was at rest. During the prompted movement task, the system responded during every action and rest period to enable and disable stimulation appropriately during the tasks. The system also performed well despite changes in beta-band power observed during periods when stimulation was turned on.

Due to considerable system delays, this system was not able to prevent tremor at the beginning of the patient’s movement. Sensing packets are sent through the Nexus-D telemetry system every 400ms, and they take an additional 100ms to complete each transaction. Our signal processing method averages two seconds worth of beta band-power readings before comparing that average to a pre-determined threshold. Once the threshold is exceeded, the system must wait another 400ms before the communication channel is free (while the system downloads the next packet of data), before finally beginning to ramp the stimulation up to the clinical value over the course of 1.2 seconds. As such, system delays alone are on the order of around three seconds.

There are a number of ways to reduce this delay in the future iterations of this system. In a commercial system, the signal processing and control computations can be moved onto the implanted device, removing the need for serialization through a small-bandwidth telemetry system. This would eliminate all communication and packet-interval delays, which currently contribute nearly 1 second of delay. More sophisticated classifiers might also provide faster and more robust recognition of movement and rest. These classifiers could potentially remove the need for beta-band power averaging and thresholding. However, given the expected variability in the neural biomarkers of movement across patients, automated classifier training methods will need to be used in order for these closed-loop systems to translate into general clinical practice.

It is important to consider what a final designed system’s desired false-positive rate should be. Since existing systems stimulate constantly—at what can be thought of as a very high false-positive rate—any incremental reductions in stimulation time while maintaining tremor suppression is a clear improvement. By tuning the system to be more aggressive in applying stimulation, we may lose some specificity and have a higher false-positive rate, but obtain a reduced delay and thus do a better job of obtaining overall therapeutic benefit.

Another consideration is that other ECoG signals could be used for closed-loop control. For instance, prior work in the BCI field has identified that there are movement-related changes in both the beta and gamma bands [13,15]. While gamma signals are more localized on the motor cortex, and are more task specific then beta-band changes, gamma-band sensing may improve a system’s ability to determine when a patient is moving their limb and needs stimulation. Additionally, research conducted with Parkinson’s Disease patients suggests that some abnormal cortical signals may correspond to movement disorder symptoms [16]. Future work may find biomarkers that indicate when an essential tremor patient is experiencing tremors, and such a biomarker would allow us to limit stimulation only to periods when the patient is experiencing tremor.

When discussing system performance, it is important to consider the patient’s experience as modulation of stimulation parameters could have an impact on patient quality of life [8,17]. To gauge the potential impact of closed-loop control on the patient’s everyday experience, we conducted semi-structured interviews with the patient during each research visit [18]. When asked if the tremor at the beginning of movement is bothersome, the patient responded, “It’s not that big of a deal. You get used to it.” Given that by the time patients receive a DBS system they have often adapted to living with tremor for quite some time, the transient effects may be of less concern to many patients, as long as they reach their desired tremor-free state in a predictable time frame.

V. Conclusion

In conclusion, this paper documents the first successful demonstration of a fully-implanted sensing and stimulation platform for neural-triggered, closed-loop DBS in an ET Patient. To the best of the authors’ knowledge, this is the first use of intentional neural signals to drive therapeutic stimulation in real-time. Moreover, this technology, by providing access to simultaneous chronic recordings from deep and cortical structures, may enable increased understanding of the mechanisms of tremor and tremor suppression. While the current system uses an external computer for data logging, processing, and control, forthcoming versions of the IPG (from Medtronic) will likely be able perform these operations on hardware embedded within the implanted device, so that no external communication would be required. We have demonstrated here a system that is able to modulate delivery of deep brain stimulation by identifying intentional movement, providing tremor reduction in an Essential Tremor patient. Further work using this paradigm may realize a feasible, fully-implanted system for the delivery of demand-driven therapy for Essential Tremor.

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