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An implantable translational platform
enabling clinical investigation of unexplored
adaptive stimulation

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A dissertation proposal
submitted in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy

University of Washington

2025

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Abstract

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Adaptive stimulation has cultivated growing interest due to its potential for improving the therapeutic efficacy of neuromodulation in a variety of neurorehabilitative applications. In utilizing neuronal activity to drive neuromodulation delivery, adaptive stimulation may induce synaptic plasticity changes that could result in enhanced functional connectivity and potentially towards improved patient outcomes. While advances in sensing and stimulation capabilities of neuromodulation systems have facilitated research thrusts in investigating preliminary adaptive stimulation design, there are still limitations in the types of algorithms that can be explored by current systems. These limitations present a gap in the technological capabilities currently available for investigating novel adaptive paradigms. This technological limitation also impedes investigation into the nature of neuroplasticity and its relationship towards improving therapeutic outcomes from neurological conditions.

In this thesis, we address this gap by developing a neuromodulation research platform capable of realizing novel adaptive stimulation algorithms not currently supported by clinical systems. Building around the investigational CorTec Brain Interchange, we develop a research software interface capable of implementing customized neuromodulation therapies and providing full access to the features of the investigational device. This work aims to support continued growth within

the adaptive neuromodulation space by expanding the types of adaptive algorithms that can be designed and investigated within the clinical research space.

To thoroughly assess this platform, we introduce a benchtop evaluation tool, the NeuroTest, to verify the functionalities and increase confidence in its abilities. We specifically focus on the ability of the platform to sense cortico-cortical evoked potentials, a recognized metric for measuring neural connectivity. With the NeuroTest, we simulate cortico-cortical evoked potential experiments and characterize the platform’s behavior under the presence of stimulation. We also assess the efficacy of signal processing techniques to identify cortico-cortical evoked potentials activity and extend this initial verification work by performing cortico-cortical evoked potentials experiments with the proposed platform in vivo. In verifying the platform and processing pipeline for cortico-cortical evoked potentials applications, we develop a comprehensive understanding of the Brain Interchange’s capabilities, identifying limitations and ideal configurations to optimize performance with the research platform.

Finally, we utilize the proposed research platform to implement and execute a temporally-driven adaptive stimulation paradigm. We establish the platform’s ability to perform the adaptive paradigm robustly with the NeuroTest environment and following these promising feasibility outcomes, we demonstrate preliminary plasticity induction via cortico-cortical evoked potentials modulation with the implemented paradigm in vivo. While future efforts will aim to characterize the influence of these plasticity effects on behavior, these outcomes demonstrate the platform’s potential to be an effective research tool for supporting clinical neuroplasticity investigations.

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Acknowledgements

There are numerous people I would like to acknowledge who have made a significant impact as I navigated my academic journey.

First, I would like to thank my advisor, Jeffrey Herron, for his mentorship throughout my PhD and guidance for future pursuits. Your transparency and encouragement have been instrumental in making the most of my graduate experience. Having the opportunity to achieve what I set out to do and more with your mentorship has helped me grow as an engineer and researcher. I'm eternally grateful for your support and for always helping me approach challenges with a new perspective.

Working with a multidisciplinary group has been a phenomenal experience, and I'm privileged to have worked alongside peers of the GRIDLab, AMP Lab, and Neural Systems Lab. In particular, I'd like to thank Adrià Robert Gonzalez for the journal club, engaging research chats, and candid conversations. I'd also like to thank the clinical team at UW, including Dr. Jeffrey Ojemann, Dr. Andrew Ko, and Dr. Ben Grannan.

I would also like to thank my previous mentors- Mark Howell and Brett Campbell. To Mark, I'm very lucky to have your resolute support. From the very beginning and throughout every milestone, thank you for always having my back. To Brett, so much of my foundation within this research space was made possible because of you. Your patience and insight have been invaluable in helping me get to where I am now.

Thank you to my family for supporting me and always helping me find the drive to put my all in anything I do. To my friends, thank you for your creativity, infectious excitement, and helping me explore new ways to find joy.

Finally, I'd like to give my sincerest thanks to my partner, Alex. There isn't a single doubt that this journey wouldn't have been nearly as fulfilling without you. Thank you for helping me ground myself through difficult times, cherishing wins both big and small, and always making me laugh.

Chapter 1

Introduction

The brain’s ability to restructure and modify neural connections, known as neuroplasticity, has significant impact on behaviors, such as learning and cognition. In addition to its role in development [1], this neuroplasticity property of the central nervous system has significant impact towards functional rehabilitation from neurological disorders and injury [2], [3]. Considering the impact of neuroplasticity on motor recovery from neural injury, there is great interest in understanding its underlying mechanisms and how to effectively drive targeted neural plasticity changes to improve motor outcomes from conditions such as stroke and spinal cord injury. Utilizing what is currently understood of its mechanisms, researchers are exploring strategies to more effectively modulate neuroplasticity and induce network connectivity changes. With more targeted means to drive neuroplasticity, those affected from neural injury may experience improved therapeutic outcomes, enhancing their abilities to overcome functional challenges, gain independence to perform typical activities of daily living, and improve overall quality of life.

One promising approach to modulate neuroplasticity has been via neuromodulation. Symptoms associated with a variety of neurological and psychiatric disorders have been shown to improve with stimulation therapy [4], [5], [6]. While the therapeutic mechanisms of neuromodulation are not well understood, neural plasticity may play a role in the beneficial outcomes from this intervention by its effects on modulating relevant neural networks [7], [8]. Despite the therapeutic efficacy of open-loop stimulation, this intervention is still limited by efficacy and efficiency. Tradeoffs of open-loop stimulation include unwelcome side effects, such as paresthesia and dysarthria [9], [10]. Additionally, variations in symptoms between clinical visits can result in partial efficacy since patients are often limited in their ability to adjust settings until a clinician adjusts their stimulation. This partial efficacy may reflect the natural fluctuations of neural activity and the suboptimal efforts of open-loop methods to engage with neural plasticity effectively.

To address these limitations of open-loop methods, there have been efforts towards developing alternative approaches for delivering stimulation. One method of particular interest is closed-loop or adaptive stimulation. This closed-loop model utilizes chronic sensing that reflects patient state and can be used as feedback to modulate stimulation delivery. Design considerations for adaptive neuromodulation are extensive, not only focusing on the types of feedback or biomarkers effective for driving stimulation delivery, but also the nature of the parameters of the delivered stimulation output. Various clinical studies have demonstrated the promise of adaptive stimulation methods for improving therapy efficacy, comparable to traditional open-loop methods [11], [12], [13]. However, with closed-loop stimulation, the complexity of stimulation algorithms increases, considering the large parameter space that can be configured within a closed-loop model. To support the clinical investigation of more complex and customizable stimulation paradigms, advances in the capabilities of these neuromodulation devices have been crucial to progress novel adaptive stimulation research.

In particular, investigational systems, devices approved for human-use research applications, play a major role in characterizing the translational potential of adaptive stimulation paradigms. Fully implantable investigational systems, such as the Summit RC + S [14], [15] and DyNeuMo [16], have demonstrated system feasibility of closed-loop stimulation within clinical populations and have helped identify key biomarkers reflecting patient state. Most of these adaptive stimulation algorithms center around the investigational devices' abilities to perform spectral analysis and extract the power of neural oscillations as reliable biomarkers, as seen with Parkinson's disease [11], [12], [15], essential tremor [17], [18], and epilepsy [19], [20], [21]. Another algorithmic approach focusing on time-dependent stimulation, such as phase-triggered stimulation where stimulation is timed to a certain phase of neural oscillations, is of particular interest. This timing-specificity of stimulation delivery builds on growing evidence that temporal dynamics of neuron populations may have a role in modulating synaptic plasticity [22]. In considering the dynamic nature of neural oscillatory activity, these adaptive stimulation algorithms may be more effective in modulating brain connectivity, compared to open-loop methods that utilize fixed stimulation parameters. This approach may result in more effective cortical reorganization and potentially improve recovery after neural injury such as stroke [23], [24] or spinal cord injury [25].

Despite this interest in timing specificity to drive potentially therapeutic stimulation delivery, these paradigms utilize processing and timing sensitivity not currently supported by available devices. These technological drawbacks pose a research limitation that restricts adaptive neuromodulation investigation. Additionally, given the wide parameter space for developing adaptive algorithms, there is a need for systems that enable flexible exploration of algorithmic design to expand efforts investigating neural plasticity mechanisms and its role in behavior.

To overcome the barrier in a more thorough and broad exploration of the adaptive stimulation design space, the efforts presented in this work are guided by three specific aims. First, I will develop a clinical research platform that would allow clinical investigation into timing-dependent stimulation algorithms. In implementing and evaluating a temporally driven adaptive stimulation paradigm, this platform demonstrates design flexibility not supported by currently available investigational devices.

Next, the second aim will assess the platform’s ability to capture neural plasticity effects. Though cortico-cortical evoked potentials serve as an established method for connectivity mapping within a neural site, the means to evaluate a system’s ability to measure these signals are limited. Verification of this platform’s ability to capture these data minimizes ambiguity and ensures reliable characterization of connectivity changes induced by adaptive stimulation paradigms.

The final aim then builds on the previous two aims by investigating neuroplasticity changes with the administration of the temporally driven adaptive paradigm. By observing potential neuroplasticity effects characterized by neural biomarkers, this system demonstrates its readiness to support neural plasticity research and the characterization of the role of neural plasticity towards functional outcomes.

1.1 Research Aims

1.1.1 Aim #1: Develop and evaluate an investigational research platform capable of enabling exploration of adaptive stimulation

Consideration of stimulation timing requirements may reveal new insights on the induction of more targeted plasticity effects, which could lead to more therapeutic outcomes for a wide variety

of neurological disorders. However, the lack of investigational tools that can incorporate timing-oriented design to determine the delivery of stimulation limits researchers' abilities to assess timing optimization of closed-loop stimulation and its effects on neuroplasticity.

Chapter 4 focuses on the development and characterization of a research platform that can support expansive adaptive algorithm development, particularly those that require timing specificity for driving stimulation delivery. These efforts are initiated through the application of a proposed software framework to interface with an implantable neurostimulator to inform the architecture design utilized in this research platform. This interface is then developed in order to enable custom stimulation algorithm design, resulting in an investigational distributed neuromodulation platform that allows users to take full advantage of the functionalities of the investigational device and incorporate more complex processing techniques to realize paradigms of interest. With this interface, a variety of stimulation paradigms, both open and closed-loop will be implemented, demonstrating the versatility of the research platform. In addition, evaluation of the platform's recording capabilities within an in-human case will be performed through intraoperative recordings.

1.1.2 Aim #2: Characterize the platform's ability to assess neuroplasticity changes

In addition to realizing temporally-driven adaptive algorithms, this system must also establish its ability to capture measures of neuroplasticity. With the means to drive and measure neural connectivity changes, this platform becomes a comprehensive tool researchers can use for neural plasticity research.

While there are various measures to assess connectivity within the brain, one well-established approach for evaluating neural connectivity is cortico-cortical evoked potentials. Cortico-cortical evoked potentials provide a targeted means of understanding relationships between brain regions of interest. Additionally, measurement of the oscillatory components comprising a cortico-cortical evoked potential is an effective quantitative method for evaluating neural plasticity effects. Through controlled benchtop testing, Chapter 5 centers on determining the platform's ability to capture this metric, explores signal processing techniques to isolate oscillations of interest, and highlights nuances to note when utilizing this platform in order to best obtain these biomarkers

of interest.

1.1.3 Aim #3 Assess the platform's ability to investigate a novel approach to modulating neuroplasticity outcomes

The final aim is to utilize the fully implantable platform to investigate a novel approach to neuroplasticity modulation within patients. Evaluating the investigational platform will build on the verified functionalities from the two prior aims: administer a temporally adaptive stimulation paradigm and characterize changes in cortico-cortical evoked potentials.

In chapter 6, we will take an adaptive, timing-specific paradigm, beta phase-triggered stimulation, and evaluate its performance within in vivo experiments. This chapter will provide preliminary results of the interactions between temporal neural dynamics and stimulation by delivering single pulses of stimulation to particular phases of patients' beta activity. Prior to and following the delivery of this stimulation paradigm, we will record cortico-cortical evoked potentials. These biomarkers will direct how to tune stimulation delivery and serve as quantitative measures of the neuroplasticity effect of this phase-specific stimulation.

Chapter 2

Overview of Neuroplasticity

2.1 Characterizing neuroplasticity

Neuroplasticity is a phenomenon characterizing the changes the brain undergoes in response to stimuli. This encompasses a variety of processes, such as the manipulation of neuronal connections and functional reorganization, within the brain that have a role in functions such as learning, memory, and recovery from neural injury. While neuroplasticity is prevalent in neural development and behavior, the exact mechanisms of neuroplasticity are not well characterized and is an ongoing focus within research. To properly contextualize the work presented here, we will focus on neuroplasticity specifically within the context of neural injury.

2.1.1 Neuroplasticity within neural injury

When neural injury occurs, disruptions in neural pathways can lead to significant impairments, depending on numerous factors like lesion location and size. For weeks following the injury event, there is a period of heightened neuroplasticity. These effects drive recruitment of remaining neural tissue to form new connections around the lesion and compensate for the damaged area, resulting in neural reorganization [26], [27]. While there can continue to be neuroplastic changes following the initial months after the injury, these plasticity changes begin to slow [28]. This denotes a critical time window during which the nervous system is most receptive to learning and adaptation. It is important to highlight that the effects of neuroplasticity changes during this period do not necessarily translate to beneficial recovery. Maladaptive changes may take effect, leading to the development of compensatory behavior that inhibits rehabilitation of the affected side that may result in suboptimal functional outcomes [29], [30]. This highlights the need to understand how to effectively engage with neuroplasticity in order to maximize the potential recovery from neural injury during the acute state post-injury.

2.1.2 Synaptic plasticity and its mechanisms

While the exact nature of neural plasticity is not yet clearly understood, there are theories about certain mechanisms that can help drive neural plasticity effects. One mechanism, synaptic plasticity [1], describing how neuroplasticity takes effect through changes in synapses between neurons. Long-term potentiation and long-term depression describe the persistent strengthening and weakening, respectively, that can occur within synaptic connections. These changes in synaptic connections are theorized to be governed by spike-timing-dependent plasticity (STDP) [31], [32], [33], which describes the relative and precise timing (<20 ms) relationship that induces this bidirectional effect in the synaptic connection between two neurons [34]. Commonly known as “Neurons that fire together, wire together”, this Hebbian principle [35] outlines how the firing of a presynaptic neuron contributes to the firing of a postsynaptic neuron, leading to long-term potentiation (LTP). Subsequently, the phrase, “Neurons that fire out of sync, lose their link”, reflects long-term depression (LTD), where the connection is weakened, as the presynaptic neuron’s activity is not causal towards the postsynaptic neuron’s firing.

2.2 Methods to engage with neuroplasticity

2.2.1 Physical therapy

The primary treatment utilized in clinical practice to promote recovery from neural injury is physical therapy. Physical therapy interventions aim to restore patients’ abilities to carry out activities of daily living and maximize their long-term independence post neural injury. The field of physical rehabilitation encompasses various activities and custom protocols centered around specific activity-based exercises, such as constraint-induced movement therapy [36] and locomotor training [37], [38], [39]. Alongside physical therapy, technologies including robotics [40], [41], [42], exoskeleton devices [43], [44], and virtual reality platforms [45], [46] have been incorporated to assist with motor training and potentially enhance the environment to improve neurorehabilitation outcomes. A series of principles provide guidance on how physical therapy should be designed, taking into account the opportunity provided by this heightened plasticity state, to maximize improved functional outcomes [47]. These exercises promote the use of affected limbs during the subacute phase and take advantage of the enhanced learning to improve motor recovery. In taking

advantage of the increased adaptability during this time critical window, physical therapy can be particularly effective, as it utilizes learning facilitated by lesion-induced plasticity to assist with reorganization.

However, despite physical rehabilitation being a critical component towards overcoming functional loss from neural injury, it is important to highlight the limitations of the efficacy of this intervention. These limitations are primarily realized by variances in functional outcomes of patients who undergo physical therapy. A majority of patients experience partial recovery that yields suboptimal improvements, where factors such as the severity of the neural injury and timing of physical therapy relative to injury significantly impact recovery [48], [49], [50]. This may reflect limited capacity of surviving connectivity to engage in neuroplasticity via physical therapy methods alone. Furthermore, it should be noted that physical therapy is often limited to the acute period poststroke, and while it takes advantage of the heightened plasticity state, this intervention does not necessarily drive neuroplastic effects. While there has been exploration of chronic physical therapy to continue recovery [51], improvement gains are significantly diminished [52]. While physical therapy by itself may provide some functional benefits to patients, additional methods to supplement physical rehabilitation may enable further improvements and potentially extend the window to observe those improvements, enhancing the quality of life for patients.

2.2.2 Open-loop stimulation

One method to consider pairing with physical therapy is the use of neurostimulation. Neurostimulation provides one avenue to more intentionally induce specific and repeated coincident firing of neurons, following the Hebbian mechanism to induce LTP and LTD. With a more targeted means of inducing neuroplastic effects, the potential for motor recovery from neural injury provides an opportunity for additional functional gain within the chronic phase of stroke. A variety of stimulation modalities, both noninvasive and invasive, have been demonstrated to modulate connectivity within clinical populations and are actively used in research efforts to explore the efficacy of plasticity changes and therapeutic outcomes. Brain stimulation methods that have been applied towards improving rehabilitation outcomes and observed therapeutic improvements from neural injury include:

Transcranial magnetic stimulation (TMS): Magnetic coils placed over the scalp deliver magnetic pulses that can activate corticospinal tracts and induce muscle contractions. TMS has the ability to target specific cortical regions. Applications of TMS include repetitive TMS [53], [54], theta burst stimulation (TBS) [55], and intermittent TBS [56]. Prior efforts with TMS towards improving stroke rehabilitation have utilized concurrent delivery of various TMS paradigms to promote cortical excitability in the perilesional cortex and inhibition of the contralesional cortex to counter compensation and promote plastic changes in the perilesional area [57], [58] .

Transcranial direct current stimulation (tDCS): Large electrode pads are placed over the scalp and utilize low-intensity stimulation to modulate excitability depending on current direction, resulting in increased excitability with anodal stimulation and inhibition with cathodal stimulation [59]. While less precise in stimulation delivery relation to TMS, tDCS can similarly target subregions within the cortex. Similarly to TMS, applications of tDCS aim to excite the perilesional site [60], inhibit the contralesional cortex [61], [62], or utilize bihemispheric stimulation to induce both stimulation strategies [63].

Epidural cortical stimulation (ECS): Electroencephalography grids implanted on the cortical surface of the motor cortex delivered electrical stimulation, enabling increased spatial resolution. Relative to noninvasive methods like TMS and tDCS, ECS provided higher spatial resolution, enabling specificity to activate select neuronal populations. Rows of electrodes on the implanted grid were selected as the cathode and anode for continuous stimulation delivery to promote excitability around the lesion [64], [65], [66]. Similar to the noninvasive techniques introduced previously, cortical stimulation may be encouraging specific recruitment of nearby, non-affected areas surrounding the lesion to enhance post injury recovery.

Deep brain stimulation (DBS): Recent work has utilized DBS, a treatment typically used for movement disorders [67], [68], [69], to deliver low-frequency, continuous stimulation to the cerebellar dentate nucleus. Using the dentatothalamocortical pathway [70], stimulation of the cerebellar dentate nucleus provides a potential alternative target for modulating excitability of the ipsilesional cortex and extending the window for improved functional outcomes.

While both noninvasive and invasive neuromodulation approaches have reported promising therapeutic potential, there have also been mixed outcomes on the efficacy of these interventions regardless of modality. Applications of both continuous and intermittent TBS showed no major improvement in motor function compared to sham stimulation [71]. Similarly, initial Phase I and II clinical trials [65], [66], [72] reported therapeutic efficacy of ECS for stroke when combined with physical rehabilitation, but outcomes of a larger Phase III clinical trial [6] did not observe similar functional improvements.

One possible reason is that the use of stimulation at this point has been performed in an open-loop manner, where stimulation parameters are pre-determined and remain constant throughout stimulation delivery. These mixed findings of open-loop stimulation efficacy may be attributed to factors such as stimulation location and stimulation timing relative to motor training, in addition to variables associated with the limitations of physical therapy, like injury severity. However, one aspect to highlight about open-loop methods is the use of preprogrammed paradigms and how such approaches do not necessarily factor in the timing mechanisms to effectively induce neuroplasticity. One such example of an open-loop, temporally driven stimulation paradigm is paired associative stimulation [73], [74], typically employing TMS and peripheral nerve stimulation. Aiming to elicit STDP mechanisms, this method highlights the significance of precise timing for inducing LTP and LTD effects more efficiently. While a stimulation approach like paired associative stimulation may better account for timing specificity, its efficacy is still limited as it does not consider the dynamic nature of the brain when delivered in an open-loop fashion.

2.2.3 Closed-Loop Stimulation

One alternative to traditional open-loop stimulation is closed-loop or adaptive stimulation, where the sensing and processing of real-time data modulates stimulation output. The use of various biomarkers that aim to drive stimulation delivery has yielded promising therapeutic outcomes for disorders including Parkinson’s disease [11], [12], [15], essential tremor [17], [18], and epilepsy [19], [20], [21]. While the mechanisms behind therapeutic adaptive neurostimulation have yet to be fully understood, there is a growing focus on the role of neural plasticity in clinical outcomes and how adaptive paradigms may more thoroughly induce plasticity effects. This is likely due to the

timing precision incorporated when triggering stimulation with naturally occurring activity. As discussed in 2.1.2, the mechanisms to engage neural plasticity are driven by temporal dynamics and emphasize the critical firing timing of neurons [32], [33] and the repeated coincident activity of these neurons [31], [75] to observe notable connectivity changes in neuronal populations.

With this closed-loop model, the complexity of these paradigms exponentially increases due to the expansion in design parameters to consider. This includes a biomarker that can reliably reflect the state of interest, the control policy that determines how changes in the biomarker inform stimulation output, and the stimulation parameters that are modulated in order to maintain therapeutic outcomes. Due to the myriad of adaptive algorithms that can be realized, adaptive stimulation algorithms, effective closed-loop designs continue to be an active area of interest.

Despite the many different possible designs of adaptive stimulation, adaptive paradigms ultimately improve upon the timing precision needed by triggering stimulation with naturally occurring activity to invoke Hebbian plasticity. In the context of neural injury, utilizing and processing real-time bio-electric activity to time stimulation to patients' states or actions during motor training presents a unique opportunity to induce plasticity effects within surviving connectivity involved in motor function.

One primary approach employing utilizes voluntary activity to initiate stimulation delivery. Motor output has driven functional electrical stimulation, yielding improved therapeutic recovery [76], [77], [78], [79]. However, one key limitation of this approach is its reliance on voluntary motor output, an ineffective source signal for those with severely limited or abnormal motor capability. To address this shortcoming, noninvasive electrophysiology has also been used to initiate stimulation [80], [81], [82]. However, both of these methodologies lack the necessary spatiotemporal resolution to satisfy the strict timing needed to initiate Hebbian plasticity and more susceptible to noise. This limitation may indicate that invasive modalities are more suitable for this stimulation strategy and warrants consideration.

Another alternative adaptive paradigm of interest is phase-triggered stimulation, an algorithm centered on the timing precision and consideration of oscillatory activity to induce neural plasticity changes in a more effective and targeted manner. Phase-triggered stimulation has demonstrated

targeted modulation of plasticity in both noninvasive [83] and invasive applications [22], though additional studies are needed to evaluate the implications towards functional outcomes. This temporally driven paradigm implements the timing constraints described by Hebbian mechanisms to induce LTP and LTD, presenting a potentially more effective means to induce cortical reorganization that may improve recovery outcomes from neural injury, even within the chronic stage.

2.3 Methods to measure neuroplasticity

With active efforts to investigate interventions to improve patients’ functional gains from neural impairment, it is critical to highlight the importance of surviving connectivity and how that residual connectivity changes when approaching an improved recovery state. Though neuroplasticity effects are tied to therapeutic outcomes, it is unclear how exactly changes in connectivity relate to improved behavioral outcomes. Numerous approaches, including imaging, stimulation, and recording technologies, have been developed to characterize the different facets of neural connectivity and how neuroplasticity realizes connectivity changes. This variety of techniques allows researchers to assess neuroplasticity changes more extensively and in a quantifiable manner to better characterize neuroplasticity and its relationship with recovery from neural injury. Here, we will discuss two key neurophysiological biomarkers that provide insight into the strength and nature of the effective connectivity of brain networks of interest.

2.3.1 Motor evoked potentials

Motor evoked potentials (MEPs) capture the activation of corticospinal tracts connecting the primary motor cortex and targeted contralateral muscle from stimulation. Stimulation is typically administered by TMS [84], [85] or direct cortical stimulation [86], [87] and captured using electromyography (EMG). As MEPs reflect motor-cortical connectivity, multiple studies have utilized changes in MEP amplitudes to characterize the effects of various stimulation-based interventions on plasticity [88], [89] and observed changes in MEPs in conjunction with functional improvements [90], [91]. Additionally, the absence of MEPs has been identified as an indicator of a lack of surviving connectivity, a proposed contributor behind a failure to meet clinical outcomes from a Phase III trial pairing direct cortical stimulation with physical rehabilitation compared to

the success of the intervention observed in previous preclinical and Phase I and II trials [6], [92].

2.3.2 Cortico-cortical evoked potentials

Another technique to investigate effective connectivity is cortico-cortical evoked potentials (CCEPs). Electrical stimulation delivered at one neural site can trigger a response at another neural site. The detected CCEP responses reflect the connection between the two sites, with larger responses reflecting stronger cerebral connections. Use of ECoG or intracranial electrodes provide spatiotemporal resolution when recording CCEPs, in addition to localization of stimulation to a specific cortical site. Historically, CCEPs have been utilized for mapping of networks and understanding the information flow of brain regions [93], [94], [95]. However, CCEPs are gaining traction as a potential biomarker to characterize brain states [96] and empirically assess changes in these states in response to plasticity-inducing conditions [22]. One advantage of CCEPs is the potential to illustrate directional connectivity in vivo and give insight into the causal effect of one cortical site on another. This is particularly beneficial as other non-interventional approaches or neuroimaging techniques are unable to or limited in measuring directionality.

Chapter 3

Neurotechnologies supporting adaptive stimulation

3.1 Developing effective adaptive stimulation algorithms

Considering the potential of closed-loop paradigms for improving traditional open-loop approaches, there is increased motivation to investigate adaptive neuromodulation and utilize adaptive methods to drive therapeutic outcomes. Adaptive stimulation is built on the theory that an optimal amount of stimulation is delivered based on when patients need this intervention. However, determining the conditions for optimal stimulation delivery is still rather exploratory. This is attributable to the fact that the design of effective adaptive stimulation is complex and requires additional design considerations relative to traditional open-loop methods. Beyond the stimulation parameters themselves, such considerations include identifying the biomarker or feature of interest, characterizing how biomarkers relate to patient state, and assessing how electrical stimulation can drive towards a therapeutic state. Characterization of these considerations has yielded promising therapeutic outcomes of adaptive stimulation paradigms for neurological disorders, including Parkinson’s disease [11], [12], [15], essential tremor [17], [18], and epilepsy [19], [20], [21].

However, there are unique technical hurdles ascribed to the development of adaptive paradigms. Challenges such as enabling concurrent sensing and stimulation, increased computational complexity, and bidirectional communication have resulted in advances of the hardware capabilities of these research devices. Consequently, the research software for interfacing with these investigational hardware devices has also increased in complexity, raising design questions on how to best enable full access to these hardware functionalities for developers and researchers within the field. And while these developments are critical components for supporting exploration of novel adaptive paradigms, there are still technological limitations to continual investigation of the adaptive algorithm space.

To better understand the current capabilities available, in this chapter I review the current landscape of the neurotechnologies facilitating adaptive neuromodulation research. Considering interest in assessing the clinical impact of adaptive stimulation, this chapter will focus on implantable neurostimulators and design considerations towards developing these investigational research platforms.

3.2 Current landscape of adaptive neuromodulation systems

3.2.1 Implantable neurostimulation hardware

Driven by continuous research interest in adaptive stimulation, advances in the neural interfaces have supported more thorough investigation into potential biomarkers, how they reflect patient state, and protocols to better tune therapeutic stimulation and improve clinical symptoms of neurological disorders. A wide range of implantable devices have been developed specifically for realizing adaptive stimulation paradigms with some systems having received approval for clinical use [97], [98]. However, the technical capabilities of these commercial systems are very specific, often streamlining/black boxing behind the scenes steps constituting the adaptive algorithms. Furthermore, adjustable parameters and outcomes from neural signal processing are streamlined, minimizing the technical complexity for simplified usability.

However, this highly specialized scope of commercial systems limits research initiatives within the adaptive neuromodulation space. Investigational devices, or hardware that have been approved for in-human research use, provide an alternative avenue towards supporting novel research efforts. Often accompanied with research tools, investigational devices expand the functionalities available for use and can manifest customized signal processing and algorithm development. Some commercial devices, including NeuroPace’s RNS system [99], [100], Medtronic’s Percept [101], [102], [103], and the DyNeuMo [16], [104], [105], have on-board adaptive algorithms, with certain design parameters modifiable with a clinician programmer. Other investigational neuromodulation systems, such as Medtronic’s Activa PC + S [106], [107], and Summit RC + S [108], [109], are accompanied with research application programming interfaces (APIs) to take full advantage of on-board capabilities, enabling more sophisticated processing pipelines and use of device features when developing adaptive neuromodulation algorithms.

It should be noted that all of the aforementioned systems are fully implantable devices. These fully implantable platforms pose a key limitation: the computational capabilities of these systems are constrained to the specialized functionalities of the on-board hardware. Processing functionalities available on these systems typically include filtering, FFT computations, time-frequency analysis, and classification. These capabilities primarily encompass spectral analysis of neural activity, and have facilitated clinical investigation of using pathological neural activity [107], [109], [110], [111], [112], circadian rhythms [104], [113], and external sensors [17], [18], [114] to drive therapeutic stimulation. One system, the NeuroPace RNS, is capable of performing time domain analysis. However, these functionalities are designed for pattern detection to trigger limited bursts of stimulation, and while effective for detecting temporal changes in activity, are not suitable for realizing timing-sensitive algorithms or the delivery of continuous, adaptive therapy [115].

Moreover, the nature of communication for these fully implantable systems poses limitations on the responsiveness of the adaptive algorithms. For example, packetization, as observed with the Summit RC + S where intervals of packets contain 50 ms of data on average [108], presents additional difficulties in satisfying the timing sensitivity that would be required for certain adaptive control policies. In addition, given the nature of wireless communication, packet loss is inevitable during operation. Considering the nature of current communication protocols, packet loss can potentially result in the loss of hundreds of milliseconds, significantly impacting the performance of timing-sensitive processing and stimulation. As currently available devices are not designed with the abilities needed to precisely tune stimulation delivery, investigators are unable to implement these alternative paradigms for investigational applications. This translates to limited tools available for researchers to thoroughly explore the diverse nature of the therapeutic adaptive neuromodulation landscape.

3.2.2 Design challenges for interfacing with implantable hardware

Alongside improvements in hardware, research software plays a pivotal role in supporting adaptive stimulation research. Providing a layer to interface with investigational hardware capabilities is crucial to leveraging these advanced functionalities and implementing algorithms of interest. As

mentioned in the previous section, some investigational devices come with application programming interfaces (APIs), which have proved to be particularly pivotal in creating customizable software applications for research use of these devices. While APIs have facilitated this flexibility in interfacing with neuromodulation hardware, a lack of a standardized framework for creating these interfaces has resulted in a fragmented ecosystem. Differences in research software, such as design architecture and programming language, have become barriers to rapid adoption and extension, impeding scientific advances utilizing these implantable neuromodulation systems with redundant development efforts.

For example, the typical approach to building these software interfaces has been to develop monolithic applications. BCI2000 is a prime example of a general-purpose monolith application with established use in BCI [116]. A monolithic approach, while straightforward to develop and deploy, can become difficult to scale with increased complexity. In the context of adaptive neuromodulation research, continuous updates to a monolithic application for various neuromodulation paradigms can be challenging, as functionalities may not be written in a way that allows reusability and may require writing from scratch. Furthermore, any errors that arise during deployment result in the entire application failing, potentially disrupting critical operations of the device.

Another consideration to keep in mind is the foreseeable software incompatibility with future implantable systems. It is inevitable that continual neurotechnology development will result in

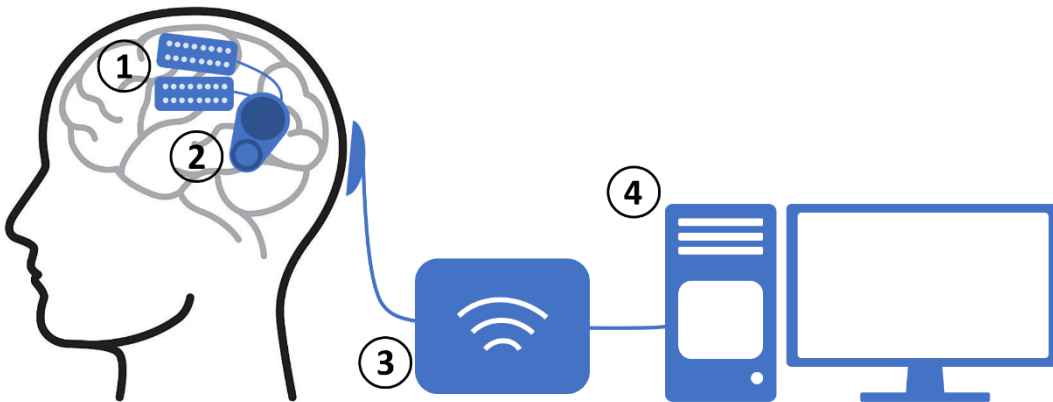


Fig. 3. 1 Intended use diagram for the CorTec Brain Interchange (BIC) system. The implant consists of a 1) cortical grid that supports up to 32 contacts and an 2) electronics unit for power and communication. The 3) external unit supplies power and connects to a 4) PC with the proprietary API.

more research tools being released into the field. However, the differences in supported programming languages accompanying future hardware pose a higher risk to rewriting research software, a burdensome and time-consuming task that potentially limits researchers' abilities to take advantage of novel features of up-to-date technology. Roarr et al. [117] identified an example of this issue, highlighting how Medtronic, a key manufacturer of implantable neurostimulation devices, changed the supported programming language of their software development tools between devices. In addition to rewriting software, efforts to pursue replication or expansion works are less robust due to possible differences in technical foundation of re-written software. This presents another prominent challenge research software development faces in the neuromodulation space.

3.3 Emerging solutions diversifying the adaptive neurotechnology landscape

3.3.1 CorTec Brain Interchange

The CorTec Brain Interchange (BIC) [CorTec GmbH, Freiburg, Germany] is a wireless investigational system that consists of an implant, external communication unit, and personal computer as shown in Fig. 3.1 The implant consists of a power receiving coil and electrode connections that can contain up to 32 ECoG channels that are designed for stimulation and recording up to a 1 kHz sampling rate. The implant connects to a communication unit via a magnetic head piece which provides power inductively and communicates via broad-band radio. This external communication unit then connects to a personal computer (PC) via USB, enabling bidirectional communication where data from the implant can be streamed and logged to the PC and commands from the personal computer can be sent to the implant.

Additionally, the BIC has an accompanying API compatible with C, C++, and Python. This API enables custom design of stimulation algorithms and monitoring of neural data, alongside other system diagnostics like power, temperature, and humidity. Via the API, users can utilize a computer-in-the-loop framework to leverage the BIC's functionalities to develop adaptive neuromodulation paradigms. This distributed framework enables developers to make full use of the PC's computational capabilities for performing real-time processing, allowing a wider array of processing methods that can be implemented with the BIC. Relative to devices with dedicated,

yet limited, on-board capabilities, a distributed system extends the scope of adaptive algorithms that can be realized. A constraint with a distributed system approach is the physical tether required in order to maintain communication and receive power from the PC. However, with continuous advances in the miniaturization of electronics, distributed systems may not impose significant mobility restrictions despite the tether.

An early version of the BIC implant demonstrated preliminary feasibility outcomes with sensing and closed-loop stimulation [118]. However, additional technical developments of the BIC have since yielded a more up to date system. The BIC benchtop development kit, which emulates the implantable BIC system, has also been made available for research and development work exploring possible applications of the system. Recent efforts with the BIC have already evaluated the recording abilities, in both a fully implanted case with a canine model [119], and in comparison to other clinically approved electrophysiology systems [120]. Outcomes from these initial investigations demonstrate promising sensing performance with the BIC.

3.3.2 Open-Mind Neuromodulation Interface

An alternative approach to designing research software utilizes a microservice architecture. Focusing on modularity, a microservice-based design loosely couples features of an application into independent services. While this approach is technically more complex to deploy and introduces more points of failure, a microservice design increases technical robustness in the face of errors by preventing crashing of the entire system. The development of a microservice architecture relies on the same APIs used to build monolithic applications, enabling communication with implantable hardware and providing users access to system-unique functionalities such as stimulation and recording. This design would also facilitate reusability, as common functionalities can be used across different applications, minimizing development investment.

To overcome the current challenges attributed to the fragmented research software landscape and potentially standardize software design for in-human use systems, the Open-Mind Neural Interface (OMNI) architecture [117] was introduced as a proposed framework for designing software interfaces to work with implantable neuro-stimulators (INS). OMNI is a microservice-based

architecture that aims to accelerate neuromodulation research by establishing a common technical foundation while still enabling INS-specific functionalities. OMNI provides an API framework definition for common features available across different implantable neuromodulation devices. The services are divided into the Bridge API, Device API, and Info API. The Bridge service provides an abstraction layer for telemetry-related functionality such as device discovery and communication status. The Device service enables an application to access the implanted device's configuration and control stimulation. Finally, the Info API supplies information about the microservice itself including version number and supported devices.

This framework is also programming-language agnostic, employing gRPC (gRPC Remote Procedure Call), an open-source remote procedure call framework that enables communications across different programming languages. By enabling software interoperability, research groups can utilize their preferred programming languages, easing the translation of new investigational devices towards research applications. Additionally, the gRPC microservice runs in its own sandboxed instance, providing a layer of security by which user-mode code errors or crashes are isolated from implant-interfacing code in the server. Ensuring an isolated environment to run application code maintains stability and improves robustness by minimizing potential security threats to the system. This microservice structure provides several advantages for both developers and users, such as allowing developers more flexibility to avoid getting locked into outdated technology and sandboxed execution environments to prevent user-code related application crashes from impacting critical implant interfacing software.

Chapter 4

System development of an adaptive neuromodulation platform

As the capabilities of investigational neuromodulation systems grow, there will be a keen interest to interface with these systems and leverage their functionalities. These devices provide a prime opportunity to implement adaptive stimulation paradigms that have yet to be investigated within the clinical space. However, there is no standardized approach for interfacing with investigational hardware and many design challenges to consider when determining the customized software tool to communicate with an investigational device. This variability is particularly concerning within the research space, where dissemination and flexibility to enable replication expansion efforts are highly valued to thoroughly assess the efficacy of novel paradigms.

In this chapter, we will review the efforts aiming to minimize fragmentation and development barriers while also expanding support for investigational systems. Technologies that have been introduced to the field, as discussed in Chapter 3, will be used to develop a flexible, implantable research platform that can be used to develop temporally driven adaptive stimulation paradigms. We will also introduce a benchtop evaluation platform to enable controlled, in vitro testing of neuromodulation systems and how it's utilized to characterize the proposed research platform. This chapter includes published material in [121], and work in collaboration with Jeremiah Morrow and Alik Widge at the University of Minnesota, and Moaad Benjaber and Tim Denison at the University of Oxford.

4.1 OMNI-BIC: A software interface for the BIC

4.1.1 Design and Implementation of OMNI-BIC

To enable potential users to develop their own customizable neuromodulation paradigms, we applied the OMNI framework, discussed in Chapter 3, to the design and implementation of a microservice for the BIC system, named here as the OMNI-BIC. The gRPC protocol created a flexible research ecosystem using our OMNI-BIC framework, allowing the implementation of custom algorithms. To create the OMNI-BIC framework, shown in Fig. 4.1, we used the provided

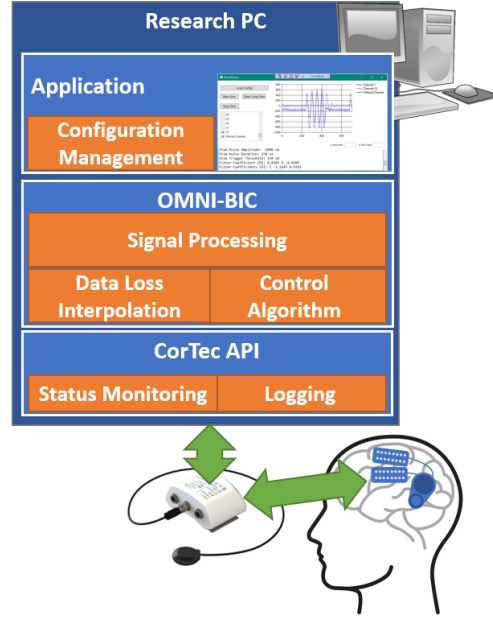


Fig. 4. 1 Block diagram of the features of the software components comprising the proposed research platform with the BIC.

C++ API to control the BIC device. Additions to the protobuf file, which provides the programming-agnostic definitions of microservice-provided functions and messages, beyond the general OMNI specifications allow the use of the BIC's specific functionalities which include status monitoring, sensor streaming, data logging, and stimulation.

To perform stimulation with the CorTec API, we first created a waveform definition request. We subsequently created pulse functions with characteristics such as amplitude and period that can then be added to the waveform. Once the waveform of interest was populated with the desired pulse functions, the waveform was then enqueued before a start stimulation command was sent to the system. The BIC has different stimulation enqueueing modes including persistent function, allowing selection of a specific pulse function of a waveform for delivery, persistent command, where a stimulation waveform is sent and the same waveform is retained for subsequent stimulation, and volatile command, where after delivery of the stimulation waveform the initial waveform is reset and must be defined again prior to subsequent stimulation. In approaching the implementation of various stimulation paradigms, we used the persistent command preloading method as all enqueued functions were delivered.

Desired data processing steps, such as thresholding and filtering, can be integrated into the

microservice through C++ to isolate and detect neural biomarkers of interest. Additional microservice features include missing data interpolation to account for missing data caused by communication dropouts, client-side stimulation waveform definition, and reporting of system characteristics such as temperature and humidity.

To demonstrate the versatility of the OMNI-BIC, we implemented several example neuromodulation paradigms based on previously published work by integrating the required functionality directly into the microservice. By choosing to integrate stimulation triggering and adaptive algorithms into the microservice directly, system developers can ensure that their operation is uninterrupted by user-mode application crashes. Implemented paradigms include open loop stimulation and two investigated adaptive stimulation algorithms: a beta burst paradigm [11] and a phase-triggered stimulation paradigm [22].

4.1.2 Open-loop stimulation

As the BIC system does not have an innate open-loop stimulation functionality, we designed an open-loop subcomponent in the microservice. To implement open-loop stimulation, a 20 Hz waveform with a maximum of 255 repetitions was defined to ensure that our open-loop stimulation pattern will run as long as possible each time stimulation is triggered. The waveform definition encompassed defining the stimulation pulse and an interpulse interval indicative of the overall frequency of the desired stimulation. This pattern was then uploaded as a persistent waveform. Given our targeted open-loop frequency of 20 Hz and using the maximum of 255 waveform repetitions, we continuously delivered open-loop stimulation by using a dedicated thread which stops stimulation on a stimulation frequency-defined interval before re-triggering the delivery of this repeated waveform. While this results in short periods of inactivity between each trigger, these periods where no stimulation was sent did not significantly impact the overall delivery of open-loop stimulation given the overall high duty-cycle.

4.1.3 Beta burst stimulation

The beta burst paradigm [11] aimed to detect bursts of beta activity, neural oscillations typically ranging between 12 and 30 Hz, and respond with a burst of stimulation for the duration of elevated

beta activity. Characterizing online beta activity used a moving average filter followed by rectification, smoothing, and thresholding, functionalities not currently available in clinical systems. To replicate this paradigm, incoming neural samples from a selected channel were processed using a two-pole infinite impulse response (IIR) bandpass filter with a passband frequency of 15-25 Hz. This filtered data was then rectified and smoothed using an IIR low pass filter. The resulting processed signal was then monitored to identify when it was above a certain threshold and responded with a burst of stimulation. When the processed signal was below the set threshold, stimulation was discontinued.

4.1.4 Beta phase-triggered stimulation

The phase-triggered paradigm [22] targeted the depolarizing phase of ongoing oscillatory beta activity for stimulation. Neural activity was band-pass filtered to isolate oscillations of interest and a dual time-amplitude window discriminator helped generate triggers for stimulation on specific phases of the filtered oscillations. Current clinical systems are typically limited to spectral analysis and are unable to apply additional temporal processing needed for this algorithm. To implement the phase-triggered paradigm with the OMNI-BIC, data was similarly filtered using an IIR bandpass filter with a passband frequency of 15-25 Hz. The maxima of the filtered signal were then identified and used to trigger stimulation output. The maxima were used to account for time delays of the system to ensure stimulation delivery during the proper phase of the filtered waveform.

4.2 Enabling custom user application development

4.2.1 Enabling high-level interfacing with BIC

In implementing functions within the microservice, we have developed APIs that not only handle core device functionalities, such as communication and device configuration, but also are capable of features such as real-time data streaming and processing of data for adaptive stimulation. With the programming language agnosticism of gRPC, developers can write using their programming language of choice when building user interfaces. This flexibility is particularly powerful when considering the design scope of applications for specific neuromodulation experiments. Equipped

with these APIs, developers working with OMNI-BIC can create high-level applications that enable researchers bidirectional interfacing with the BIC and implemented features of OMNI-BIC.

4.2.2 Overview of user applications developed via OMNI-BIC

Following stimulation implementation, we wrote several user applications to enable high-level interfacing with these functions within OMNI-BIC. The C# programming language was selected for its flexibility and versatility, in addition to its ability to accept JSON files for configuration of parameters for the closed-loop control algorithm, such as filtering and stimulation, and stimulus waveform for evoked potential experiments. Modifiable stimulation variables include amplitude and duration values for the pulses within a biphasic waveform, and the channels that sense neural activity and observe stimulation output. While the stimulation characteristics are determined by a user, the distributed algorithm determines the timing of the stimulation pulse through processing and identification of key biomarkers. Processing parameters, such as filtering coefficients and thresholding values, can also be set through the imported configuration file. The customization of implemented processing functionalities through multiple JSON configurations allows various control paradigms to be explored and tuned for patient specificity. The applications are also

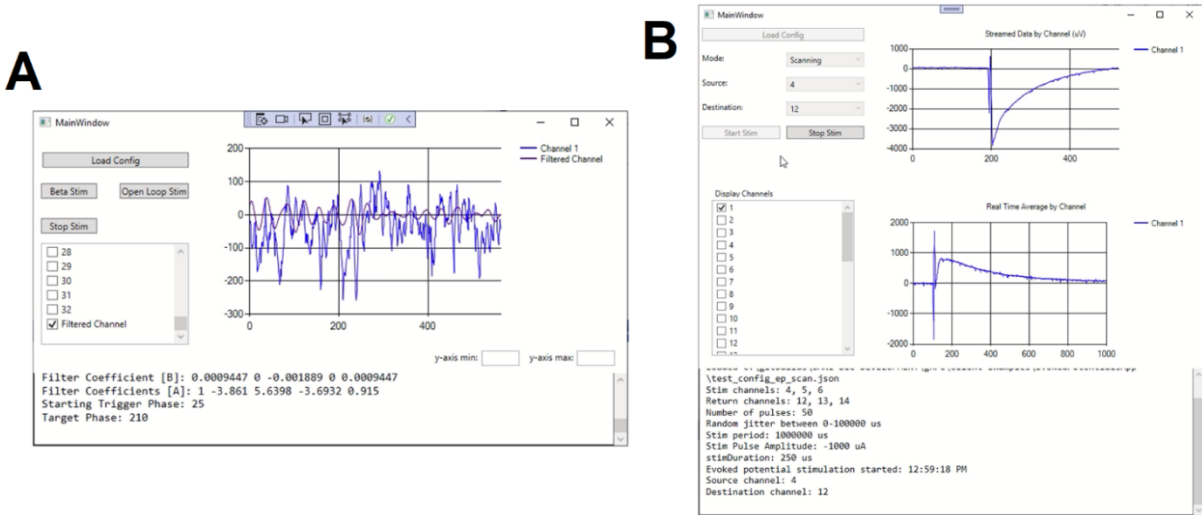


Fig. 4. 2 Example user applications developed via OMNI-BIC. User applications interface with specific functionalities implemented with OMNI-BIC and the BIC system. A) An application to perform open-loop and beta phase-triggered stimulation with customized configuration parameters inputted via a JSON file. Raw streamed data and filtered beta activity can also be visualized to allow for real-time monitoring. B) A second application used to deliver single pulse stimulation for evoked potential experiments. Users can similarly customize the stimulus waveform and perform multiple evoked potential experiments via a single configuration file.

capable of logging raw and interpolated data, in addition to timing data to allow synchronization between data logged by the CorTec API and interpolated data from the microservice.

Considering the wide variety of possible experiments within the neuromodulation space, various high-level user applications were developed to illustrate the versatility of the OMNI-BIC interface. Examples of the applications created using OMNI-BIC are shown in Fig. 4.2:

Stimulation Therapy: To assess the efficacy of various stimulation paradigms on driving neuroplasticity effects, this application allows users to deliver both open-loop and adaptive beta phase-triggered stimulation. Parameters for open and adaptive stimulation are configurable via JSON, and neural data is streamed to a real-time visualization window.

Evoked Potentials: Specifically for single-pulse experiments, this program allows a high-degree of stimulation waveform customization for CCEP. In addition to streaming of neural data, there is real-time averaging, allowing users to receive feedback during the experiment. This feature helps immediately identify configurations that generate CCEP activity and can also assist with troubleshooting of stimulation experiments.

Motor Threshold and Motor Evoked Potentials: For evaluating corticospinal tract connectivity, this application delivers two types of stimulation patterns: an open-loop 50 Hz paradigm and bursts of trains of stimulation, for motor thresholding and motor evoked potentials, respectively.

Impedances: This application initiates the BIC device to perform an impedance check to assess the integrity of electrode placement and identify potentially noisy channels that may influence the quality of neural recordings. Impedance measurements are immediately stored in a CSV format for later reference.

4.3 Initial evaluation of the OMNI-BIC interface

4.3.1 Benchtop setup

The benchtop experiment used to assess performance of the system is pictured in Fig. 4.3. A signal generator served as neural input to the system and delivered bursts of 20 Hz sine waves into a

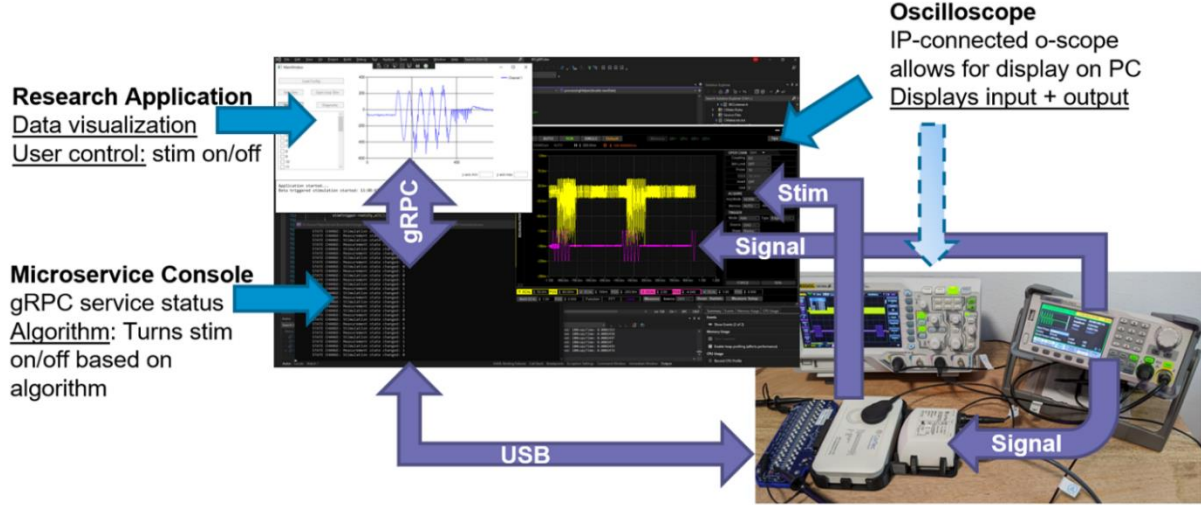


Fig. 4. 3 Benchtop demonstration setup to perform various implemented control algorithms within OMNI-BIC. The testing setup used to evaluate implemented stimulation paradigms. The client application and microservice start, allowing a user to load configuration parameters and monitor incoming and filtered data. A signal generator sends in bursts of 20 Hz sine waves to the electrode model module connected to the BIC to provide simulated beta burst input. The PC (not shown) determines the stimulation control paradigm. Meanwhile, an oscilloscope monitors stimulation output and an in-phase, but higher amplitude version of the original input into the system.

channel on the BIC's breakout board, which utilizes a resistor-capacitor based model to replicate biophysical properties of neurons, replacing a tissue phantom model. An oscilloscope was connected to observe stimulation output alongside a second sine wave generated in-phase, but with higher amplitude, to the original input to assess timing. Upon starting the client, a JSON configuration file designated the sensing and output channels, the stimulation waveform parameters, and the filtering coefficients for a 15-25 Hz bandpass filter. This test setup was used to evaluate the performance of the open loop stimulation and adaptive stimulation algorithms implemented into the OMNI-BIC; specifically, the system's ability to identify specified biomarkers of interest and respond with stimulation.

Another facet of system performance assessed was communication robustness. As the BIC is a wireless system, we were interested in characterizing packet loss during system operation. We compared packet loss by categorizing packets into two categories. First is a critical loss, which is an instance when there are more than 9 consecutive missing packets. This threshold was selected as interpolating more than 9 lost data points at the system's native sampling rate of 1 kHz results in an effective Nyquist rate below a desired minimum of 50 Hz which ensures an oversampling of

the beta frequency range of interest by at least two. The second category is a recoverable packet loss, which is when there are 9 or fewer dropped packets, in which case linear interpolation is used to preserve signal processing and filtering functionality despite the lost data.

4.3.2 Stimulation performance

Open loop stimulation and the two adaptive stimulation paradigms were tested and the output of the OMNI-BIC system for each is shown in Fig. 4.4. The top subplot in each figure shows data logged by the OMNI-BIC system while the bottom subplot shows the observed measurements from the oscilloscope. Recordings from the OMNI-BIC were time synchronized with data collected by an oscilloscope. Input signals and stimulation output aligned between the data streams, verifying the reliability of the system's data collection abilities. Approximately 10 min sessions were performed for each paradigm and the recorded input signal was then compared to the recorded active stimulation signal to assess system performance. For all paradigms, there were periods of absent or irregular stimulation output. Encountered exceptions were logged for all three paradigms and time-aligned to determine the result of encountered exceptions during stimulation. Two types of DLL exceptions were logged: type I and type II. Type I exceptions were returned

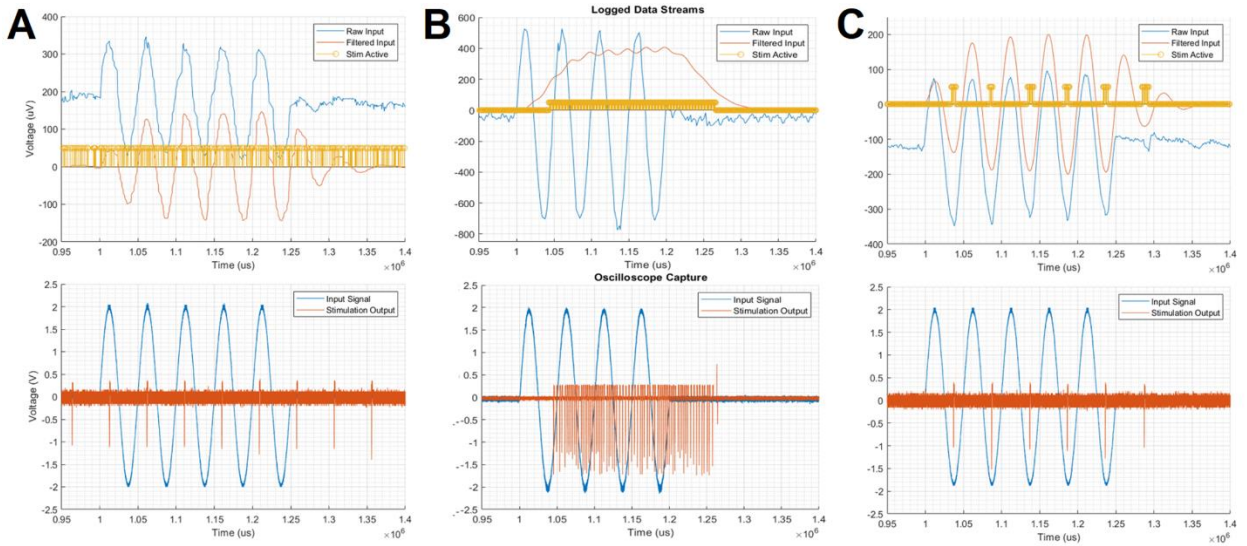


Fig. 4. 4 Stimulation algorithm demonstration: Time synchronized data as reported by the OMNI-BIC system and recording oscilloscope are shown in the top and bottom plots respectively for the a) open-loop, b) beta-burst, and c) phase-triggered paradigms. The bursts of sine wave input connected to the oscilloscope was in-phase with the input into the OMNI-BIC system but of higher amplitude in order to assess timing.

Condition	Total Packets	Critical Events	Recoverable Events	Average Loss per Event
Recording only	664500	0	6509	1.99
Open-loop	678600	0	28898	1.57
Beta-burst	666700	0	27091	2.46
Phase-locked	669200	0	15892	1.83

Table 4. 1 Comparison of communication loss observed for 10 min periods of different stimulation paradigms implemented within OMNI-BIC.

when the device was in an invalid state and cannot start stimulation due to a recent stop stimulation command. Type II exceptions were reported when there was no response (a timeout) from the device when trying to start stimulation.

For the open-loop paradigm, there were 124 exceptions encountered during testing. 121 instances of Type I exceptions were logged while 3 instances of Type II exceptions were recorded. In all cases, the system was able to automatically retry the stimulation command to resolve the issue and continue with open-loop stimulation.

The beta burst algorithm was assessed only if triggering points resulted in stimulation. Of 619 triggering points, 618 elicited a burst of stimulation. Latency between the triggering point and onset of stimulation was characterized by having a median of 22.75 ms. Most latencies ranged between 21.81 ms and 23.99 ms. 2 exceptions were logged, and all were recorded as Type II. Bursts of stimulation affected by exceptions were observed to have fewer than the expected number of pulses.

For the phase-triggered stimulation paradigm, identified peaks did not always trigger a stimulation response. In a recording with 3830 identified peaks, 3818 of those peaks triggered a stimulation response. The stimulation responses were then subdivided into hits (stimulation delivered during the depolarizing phase) and misses (those that were delivered past the depolarizing phase). 3372 peaks were classified as hits while 446 peaks were classified as misses. OMNI-BIC's performance of the phase-triggered paradigm was further assessed through characterizing latency between a triggering peak and onset of stimulation. The median latency for the phase-triggered paradigm was 21.80 ms with most latencies ranging from 20.06 ms to 23.34 ms. Five Type II exceptions were logged.

4.3.3 Communication robustness

Packet loss characterization for all stimulation paradigms and passive recording was assessed. While there is packet loss due to the wireless communication nature of the system, there is also loss expected during stimulation. For every stimulation pulse, 2 packets are lost. However, as the number of lost packets is below the threshold for data interpolation, these samples are recovered. A distribution of the types of losses observed is shown in Table 4.1. While conditions were performed in 10 min sessions, the total time, including setup and shutdown, sometimes resulted in 11 min recordings being used for communication analysis. Across all paradigms, no critical events were observed, indicating that all data loss was minor enough to be mitigatable through interpolation. The passive recording session observed about 1.94% of total packets as interpolated packets. For the open-loop paradigm, 6.67% of total packets were interpolated. In the beta-burst paradigm, 9.99% of total packets were interpolated. The phase-locked paradigm observed 4.35% of total packets as recoverable.

4.3.4 Discussion

Further expansion of promising research tools for the neuromodulation sphere provides opportunities for future studies to investigate novel adaptive paradigms. Specifically, providing the means to test temporal driven methods towards closed-loop stimulation diversifies the approaches to selective and effective stimulation therapy. Developing the OMNI-BIC has shown successful application of the OMNI architecture to the CorTec Brain Interchange for high performance of time sensitive processing for closed-loop neuromodulation. OMNI offers standardized functionalities to interface with devices while still allowing customization to realize unique applications and algorithms, allowing researchers to replicate and build off previous work.

While our experience working with the preliminary development kit for the Brain Interchange system showed it is generally robust for adaptive stimulation applications, there are still technical limitations to be considered when designing system software for the Brain Interchange device. As observed with the beta burst and phase locked paradigms, there was a delay between data received and the stimulation response. Furthermore, we identified instances where stimulation commands were rejected or dropped by the API, resulting in no stimulation pulses generated despite a

request. However, these instances are rare and, as the system is able to recover and eventually send stimulation, do not significantly impact the regularity of accurate stimulation delivery. Wireless communication dropouts such as these are common across implantable devices and system developers must take care to evaluate the proper actions to take upon an API function's time-out. However, the choice by the BIC developers to stream 1000 Hz neural data with one data point per packet at low-latency (which include all 32 channels at each sampled time point) allows for easy interpolation of lost data in the case of a short drop-out to preserve processing functionality. While data interpolation was high in the case of the beta-burst paradigm, packet loss is expected to vary depending on stimulation activity of the system, as demonstrated by interpolation observed in the open-loop and phase-locked paradigms.

Although some of these development hurdles are addressed by applying the OMNI framework, there is still user effort required to develop algorithms of research interest. Functionalities embedded into the Brain Interchange system are limited, so features that are not already implemented in the OMNI-BIC microservice or provided applications will require user effort and familiarity with the CorTec API before running OMNI-BIC with the desired abilities. Still, OMNI-BIC has the potential to ease developer effort in other ways by allowing researchers to create applications with their programming languages of choice and to provide greater opportunity for sharing and reusing code.

It should be noted of course that the demonstrations performed with the OMNI-BIC utilized benchtop equipment, and do not fully encompass the system's technological capabilities as a neuromodulation research platform. Utilizing this system in vivo will help better characterize system performance, such as stimulation artifact, and potential barriers that would not be encountered when using benchtop instruments. Future work will focus on evaluating the system in a saline tank environment using upcoming application-specific electrodes prior to using the system with a patient. Conditions from additional testing within a saline tank will more likely match those when performing recordings in a patient. Testing and observing the results in saline can potentially serve as feedback to see how well the OMNI-BIC system would perform in a patient and how to improve the performance when the OMNI-BIC is used with a patient. Additionally, while the stability of wireless communication in the demonstration is robust, there

is room for stability variability between recording sessions. The use of data interpolation to recover dropped packets preserves the integrity of recorded data and helps counter the impact of dropped packets. However, so far, we have only implemented linear interpolation and more sophisticated interpolation methods may further improve the quality of signal processing during minor data loss events. Future updates to the Brain Interchange, such as system configurations allowing selection of the most stable frequency channel for wireless communication will further reduce packet loss.

By implementing various stimulation paradigms in a single system, we have demonstrated the flexibility of the OMNI-BIC system to explore novel stimulation approaches. We believe the OMNI-BIC has great potential in enabling research opportunities for algorithms that have yet to be explored in current implantable systems. In addition, the OMNI-BIC presents avenues to incorporate additional sensors for more complex data collection and processing. Previous literature [16], [122] has shown the therapeutic application of sensor data in closed-loop stimulation. Integration of sensor data is feasible through additions to the microservice or custom user application and could be used to expand the feedback utilized to deliver stimulation beyond neural biomarkers. Furthermore, due to the low latency of the system from current processing, additional steps can be added to our processing pipeline. We believe that stimulation artifact rejection algorithms can be applied as data is streamed to maintain the stability of neural recordings. Minimization of the effect of stimulation artifact can enable more precise delivery of closed-loop stimulation and ease post-collection analysis of data.

4.4 Preliminary validation of the OMNI-BIC and BIC platform

4.4.1 Initial application of the OMNI-BIC

The efforts presented in this chapter have evaluated the performance of the OMNI-BIC interface to communicate and enable research functionalities, such as recording and stimulation, with the BIC system. However, this work has utilized the BIC development kit within a laboratory environment. While this development kit emulates the implantable BIC system, discrepancies between use within a laboratory environment and a fully implanted case may introduce differences in performance. To assess the performance of the proposed investigational platform, during clinical implantation of the BIC, we captured and analyzed intraoperative resting state activity to validate

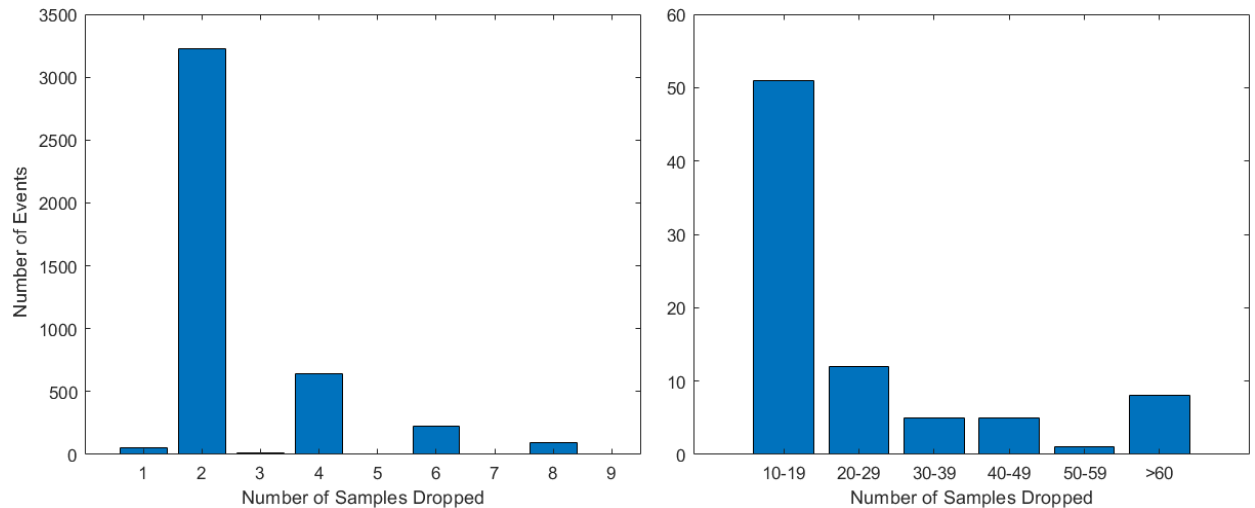
the recording functionality of the OMNI-BIC.

4.4.2 Patient overview

One subject with a history of stroke provided informed consent for implantation of the Cortec BIC at Harborview Medical Center. This was an elective surgical procedure as part of enrollment in a clinical study approved by the University of Washington Institutional Review Board and following Investigational Device Exemption regulations. Post-surgical imaging depicting the implanted device and localization of the ECoG grid electrodes are depicted in Fig. 4.5A.

4.4.3 Recording with OMNI-BIC

While the patient was under the effects of anesthesia and following placement of the BIC device and wound closure, communication with the implanted device was initiated. With the OMNI-BIC microservice and custom user application, impedance measurements were performed to confirm the integrity of the placed ECoG arrays. An electrode on the cortical grid was selected as the reference prior to collecting resting state. No significant packet drops were observed throughout the resting state recording. Following data collection, power spectral density (PSD) plots, depicted in Fig. 4.5B, were created and characterized to verify the resting state recordings. Notable attributes of these PSD plots included suppression of high-frequency activity due to the presence



-Fig. 4. 5 Characteristics of recoverable and critical loss observed during intraoperative resting state collection. Distribution of the number of samples observed during (left) recoverable and (right) critical loss events show that a majority of packet loss is concentrated on the lower ends of the ranges for number of samples dropped for each type of loss.

of anesthesia, elevated beta power detected by electrodes over the motor cortex, and diminished activity from electrodes around the stroke lesion site relative to nearby contacts over nondamaged tissue. These outcomes aligned with expected behavior, considering electrode location and the

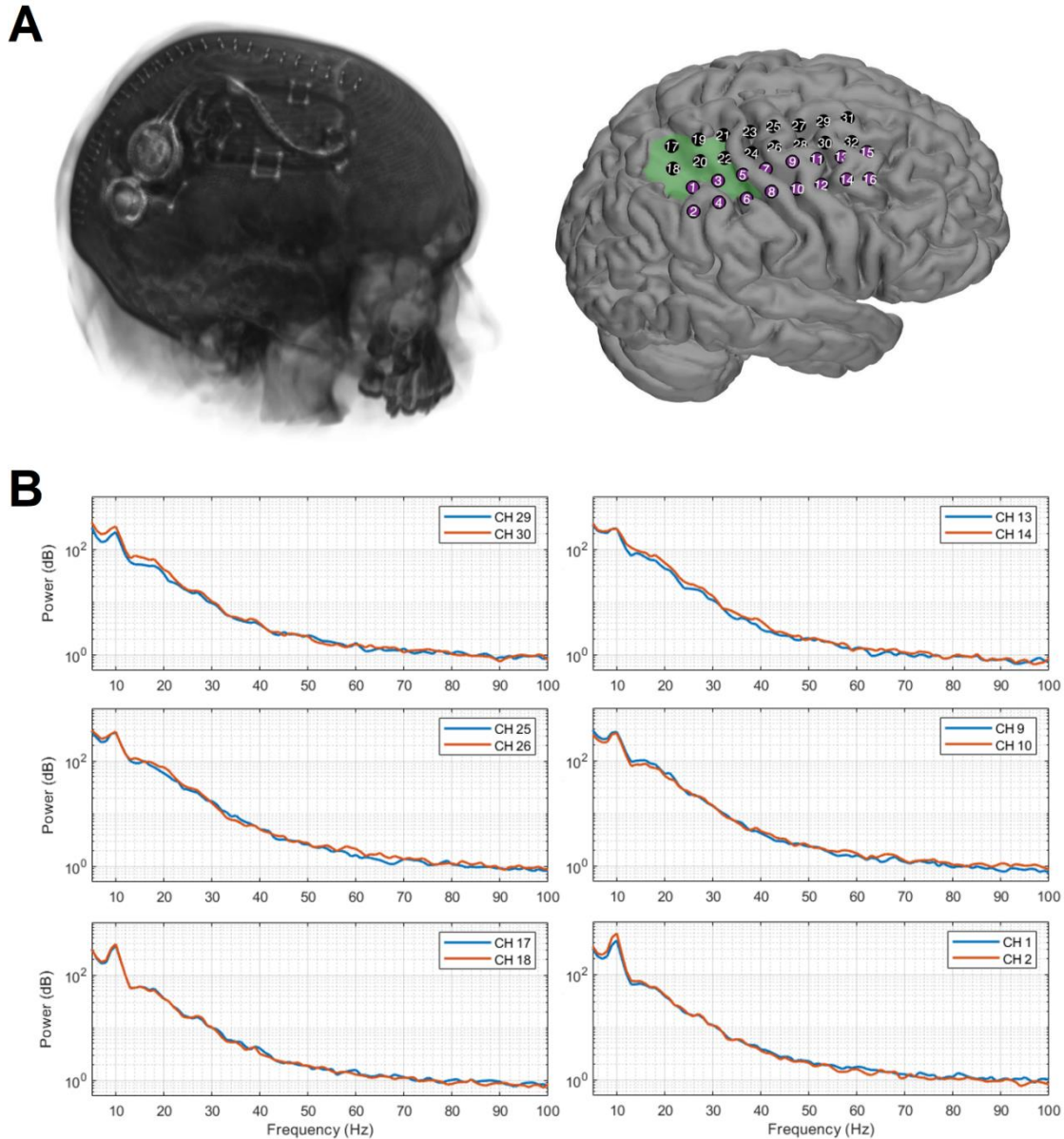


Fig. 4. 6 Outcomes following surgical implantation of the investigational BIC device. A) Postoperative imaging confirmed (left) BIC and (right) electrode placement. Coverage of the implanted ECoG grids include premotor, motor, sensory and parietal regions and the stroke lesion, shaded in green. The ground electrode of the device was placed in the subgaleal space. Channel 31, located on the premotor cortex, was selected as the reference electrode for subsequent recordings. B) PSD plots of select ECoG electrodes over (top) premotor, (middle) motor, and (bottom) parietal regions. Suppression of high-frequency activity and elevated alpha power across all areas reflect the influence of anesthesia over cortical activity.

presence of anesthesia, validating the recording capabilities of the OMNI-BIC and BIC platform.

4.4.4 Stability of intraoperative recordings

Data loss during intraoperative data collection was also assessed. As data was streamed from the BIC device, linear data interpolation was performed in response to smaller packet drops. The threshold for data interpolation was set to nine packets. Characteristics of both recoverable and critical loss from this recording are shown in Table 4.2 and Fig. 4.6. Packets recovered using linear interpolation composed 11.4% of total packets, with small packet loss primarily concentrated at 2 packets per recoverable event, as shown in Fig. 4.6B. Critical loss was also observed, resulting in 2.8% of total packets lost. The majority (62.2%) of critical loss events observed data drops ranging from 10 to 20 consecutive samples per event. However, there were also occasional instances of significant critical loss (11%), where more than 60 packets were lost, as shown in Fig. 4.6A. These instances of significant packet loss are likely due to the intraoperative environment, as the presence of clinical equipment may have contributed to instabilities when wirelessly communicating with the BIC device.

4.5 Revisiting the means to assess the OMNI-BIC and BIC

4.5.1 Advancing benchtop characterization of novel systems

Initial feasibility and safety assessments with novel systems and approaches are often achieved via preclinical models. While animal models enable biocompatibility assessments and scientific investigation within in vivo conditions, they also require significant investment (e.g., per diem costs, housing, investigator care/husbandry, etc). Furthermore, in vivo conditions can introduce factors that may complicate system troubleshooting. This is particularly relevant when characterizing the effects of stimulation artifacts on sensing functionalities of systems under test. These artifacts affect not only real-time processing pipelines for closed-loop algorithms, but also the detection of relevant biomarkers such as stimulation evoked potentials. Specifically, determining what in vivo attributes as opposed to what system characteristics may be responsible for unexpected outcomes can be a challenging confound.

The tools currently available to evaluate novel systems and adaptive algorithms are limited.

Traditional laboratory equipment is constrained in its ability to simulate biopotential activity and many neuroscience labs lack the expertise to assemble the appropriate pieces of equipment in-house. Many function generators strictly generate standard electrical waveforms while arbitrary waveform generators struggle to reproduce low-level signals typical of neural activity. Some proprietary signal generators that allow for playback of neuroelectric activity have facilitated benchtop evaluation with anticipated neural test signals. However, they present a limited set of signals available for playback, providing a narrow subset of test signals to evaluate novel algorithms. These systems are also typically purpose built around interfacing with a limited range of other devices, typically ones made by the same manufacturer. To expand on the features provided by these commercial solutions, more customizable simulators [123], [124] have been introduced that provide multichannel, low-noise, signal playback. These benchtop tools enable customized signal generation, greatly expanding the types of test signals to better capture the specific, target application of interest.

While these research technologies expand what is capable for benchtop evaluation, they also come with some limitations. These devices are designed to evaluate the sensing capabilities of other devices either through direct voltage injection or a resistive load setup. These test systems fail to account for the effects of the tissue-electrode interface, particularly the impact of stimulation on this interface and the sensing circuit. This is a critical oversight as the brain functions as an electrolyte medium in which ions serve as the charge carriers critical for neural function (as opposed to the electron flow present in hardwired devices such as a resistive load arrangement). Use of an electrolyte test medium also introduces a complex impedance setup, which better mimics in vivo conditions. The tissue-electrode interface therefore plays a key role in determining the performance of adaptive and closed-loop neural interfaces. Furthermore, voltage source or resistive load dependent systems typically do not allow for simultaneous recording of an evaluated device within saline, which could provide independent insight on what occurs during benchtop feasibility testing.

This work details the NeuroTest platform [125], [126], an in vitro benchtop testing system which supplements biopotential signal playback with its own recording capability and built-in waveform generation. A novel evoked potential mode enables simulation of stimulation evoked potentials

allowing researchers to conduct tests with reactive and/or closed-loop paradigms. These features allow for a more comprehensive benchtop characterization of the performance of novel neuromodulation technologies, helping users to be better informed about the nature of their devices prior to approaching in vivo experiments. Here, we describe the architecture, basic functions, and some simple applications of this platform for testing equipment used in neuromodulation research.

4.5.2 Introduction of the NeuroTest evaluation platform

The NeuroTest platform is a custom test bench setup designed to evaluate electrophysiology systems in vitro. It enables the characterization and testing of a device's ability to sense signals in the presence of electrical stimulation in an environment similar to the intended in vivo use case. Evaluation within an in vitro environment enables controlled testing of the impact of the tissue-electrode interface on the device's sensing circuit and assessment of how this varies with and without stimulation.

For this work, a gel electrophoresis chamber (BioRad Inc) was filled with a 0.9% saline solution in which the system under test was submerged. The use of a saline solution is critical as it mimics the electrolyte environment (i.e., brain or other tissue) in which devices will ultimately be implanted, allowing for a more meaningful and relevant evaluation of the sensing and stimulation functions of neural devices relative to hardwired systems. The tank features banana-plug connectors that are attached to wires submerged in the tank. These function as a cathode and an anode, enabling voltage or current to be injected across the entire tank.

The NeuroTest Board (NTB) is a custom hardware system designed to generate simulated biopotential signals, as well as to sense activity happening within an in vitro environment in parallel with a neural device under test. The NTB includes three main components: 1) a processing unit, 2) a precision arbitrary current source waveform generator (ACSWG), and 3) a precision sensing circuit. These three components of the NTB are galvanically isolated from each other in order to reduce noise, interferences, and ground loops between the different circuit functions. A system diagram of the NTB is illustrated in Fig. 4.7A and additional technical schematics of its components are shown in Fig. 4.7B. Further discussion of each component of the NTB follows below:

Processing unit: The first section of the NeuroTest board contains the microprocessor, a 32-bit Arm Cortex M7 clocked at 700 MHz which is programmed to be controlled and powered with a USB 2.0 connection, enabling communication speeds up to 480 Mbps. This section of the board also includes a microSD card that allows users to load large patient files to replay data. This microSD card can be used to save data observed during tests with the NTB, as well. The NTB is powered by a 5V supply via the USB connection. This connection also allows the user to update firmware on the NTB via the open-source Arduino IDE. Likewise, data can be streamed to the connected computer and visualized in the Serial Plot tool from Arduino or other data visualization softwares. The precision ACSWG and the precision sensing circuits are both powered from the same source as the processing unit using two galvanically isolated DC-DC converters, one $\pm 15\text{V}$ supply powers the ACSWG circuit, while the sensing circuit is supplied by an isolated 5V supply. All communication between the processor unit and the other two components are established using digital isolators.

Precision arbitrary current source waveform generator: This part of the NTB has two independent low-noise ACSWGs based on a Howland current source architecture (Fig. 4.7B). The current source circuit is designed to generate currents in the range of 0-10 mA with a 305 nA resolution driven by an ultra-low noise 16-bit digital-to-analog converter (DAC) combined with a low-noise, ultra-low offset amplifier. The current source has a voltage range of $\pm 14\text{ V}$ supplied from low-noise linear regulators (LDOs) to enable the system to maintain the required current delivery over a large range of impedances depending on the in vitro setup used.

The current circuit generator bandwidth is reduced from 10 MHz to 10 kHz using a feedback capacitor in order to reduce the injected noise by the NTB when connected in saline. We programmatically set the generator to have a range of 0.1 to 1000 Hz by default to enable simulation of a wide range of neural oscillatory events. We note that although the ACSWG is capable of generating up to 10 kHz signals, inadequate anti-aliasing filtering on the sensing circuit can cause high frequency noise to fold back from the current source. This can increase the noise floor of the system test, therefore we implement the cap of 1000 Hz programmatically.

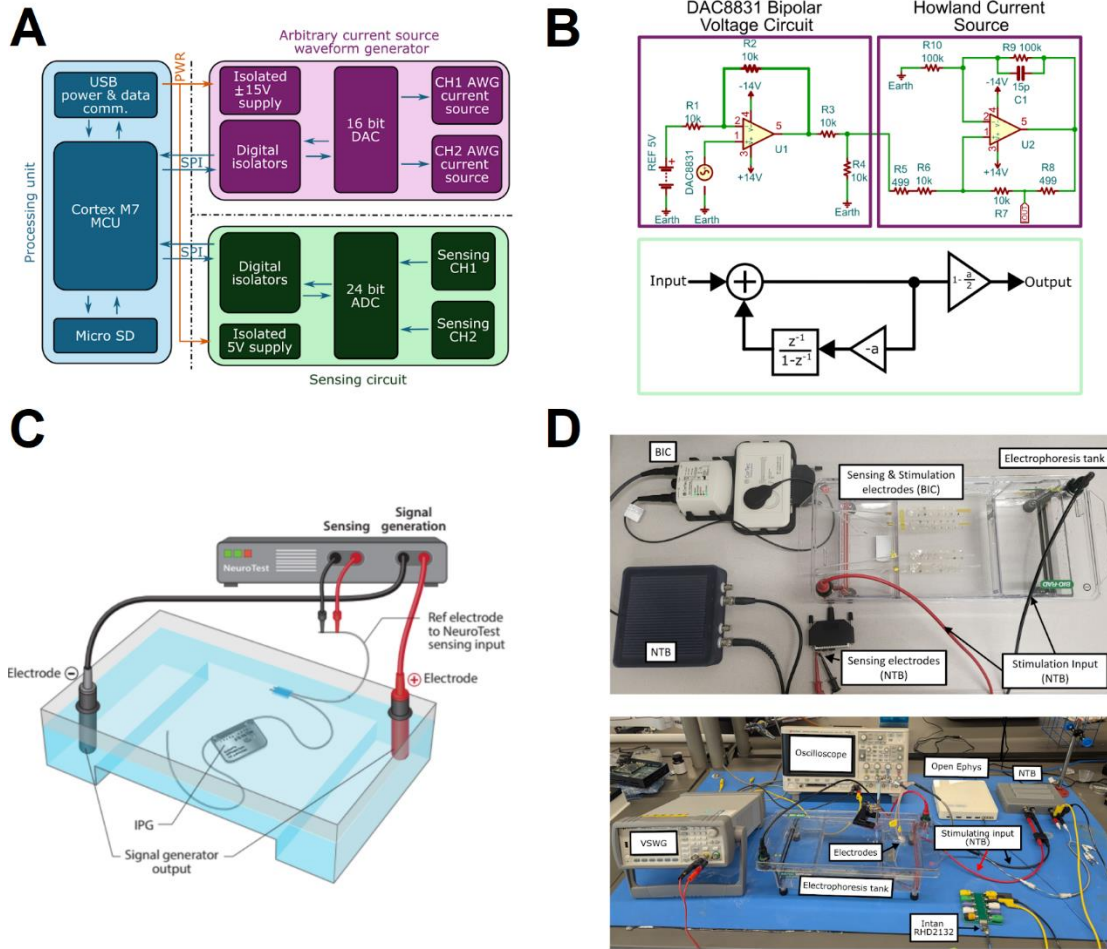


Fig. 4. 7 Technical overview of the NeuroTest platform. (A) Block diagram depicting the components of the NTB. The system is divided into three components: the processing unit (blue), the waveform generator (purple), and the sensing circuit (green). Power lines (PWR) are shown in orange while communication between the components is shown by the blue arrows. Serial peripheral interface cables (SPI) are used for bi-directional communication between the processing unit and the sensing circuit and waveform generator. (B) Design for system components of the NTB. Color coding follows the format shown in A. (Top) Circuit schematics of the current source waveform generator to drive constant current over a range of load resistances. (Bottom) Programmable high pass filter topology integrated with the sensing circuit. (C) Intended general use diagram of the NTB within a saline tank environment. (D) Site-specific testing environments with the NTB. (Top) Benchtop setup at the University of Washington. Sensing and stimulating electrodes from the BIC device are submerged in 0.9% saline in the electrophoresis tank. The sensing side of the NTB is connected to two ECoG grids using a modified D-sub connector. The waveform generator of the NTB is connected to the cathode and anode of the tank in both setups. (Bottom) Benchtop setup at the University of Minnesota. A voltage source waveform generator and oscilloscope were also connected for verification experiments. Up to six electrodes were submerged in saline and used for sensing or stimulation. Sensing electrodes are routed to the NTB (directly) or an Intan RHD2132 headstage (via a breadboard). The signal from the same electrodes can be split and routed to both systems (as shown here, yellow and black cables in the NTB).

Precision signal acquisition: The NTB features a two-channel, high-precision data acquisition circuit with a 24-bit resolution delta-sigma analog-to-digital converter (ADC) supplied by an isolated 5 V DC-DC converter. The data acquisition circuit has a theoretical noise floor of 1 μ V RMS at a 1 kHz bandwidth, when gain is set to 32 V/V and sampling frequency set to 2 kHz. The data acquisition circuit also offers a configurable sampling frequency up to 16 kHz, and configurable gain between 1 to 128 V/V.

The precision sensing circuit has a programmable high pass filter built into the ADC that can be configured to filter out DC offsets and low frequency noise. The range of the high pass filter is dependent on the sampling frequency set of the ADC for the NTB. For example, with a 2 kHz sampling rate, the high pass filter can be configured between 4 mHz – 90 Hz. The precision sensing circuit is fully controlled via the processing unit through the digital isolators. The sensing circuit is designed to be fully isolated from the other two parts of the NTB to reduce noise and crosstalk from the other two sections of the board. The ADC sampling frequency of the NTB can be programmatically set up to 20 kHz. However, as most bioelectrical field oscillations of interest occur between 0.1 and 500 Hz, the default value is set to 1 kHz.

With the design of the NTB, a key functionality of the NTB is its ability to play signals of interest (e.g., previously recorded neural activity) into saline. This neural playback functionality enables a benchtop alternative to in vivo experimentation, and for the case of the NTB, is augmented by the system’s recording functionality. Concurrent recording of benchtop activity enables the collection of ground truth data, providing a robust means to evaluate the recording capability of a system under test.

4.5.3 Benchtop testing environments

A diagram of an intended use setup with the NTB is visualized in Fig. 4.7C. Considering the various settings used within the neuromodulation space, it was integral to ensure that the system could be adaptable in order to best emulate disparate applications of interest. To demonstrate the versatility and reliability of the NTB, two distinct benchtop environments, were configured for assessments at two separate locations (the University of Minnesota and the University of

Washington). Testing performed at the University of Minnesota focused on preclinical applications (hereafter referred to as the “preclinical” site/setup) while evaluation done at the University of Washington site centered on clinical applications (hereafter referred to as the “clinical” site/setup). The preclinical benchtop setup sought to assess the characteristics of an Intan RHD2132 amplifier headstage (Intan Technologies) paired with the Open Ephys data acquisition system. The clinical testing environment used the investigational CorTec Brain Interchange (BIC) system.

Clinical Benchtop Environment: The benchtop environment with the BIC system, depicted in Fig. 4.7D, consisted of two sets of 32 channel electrocorticography (ECoG) grids submerged in a saline solution. A single set of ECoG electrodes consisted of two grids of 2x8 Platinum-Iridium circular contacts and ended in a D-Sub connector. A set of ECoG grids were connected to the BIC and NTB each. While the D-Sub connector directly connected to the implant module of the BIC development kit, additional connectors were used to connect the NTB to specific pins of the D-Sub connector. This connection scheme made it such that only 1 channel was used for sensing with the NTB. The output from the NTB was connected to the cathode and anode of the saline tank. An additional ground electrode, an optional lead hard-wired to the implant casing connected to the ECoG grids, was also submerged in saline. However, the ground electrode was not shorted to any contacts on the ECoG grid. These channels were not shorted together during subsequent testing to more realistically reflect noise characteristics to be found in vivo conditions.

Preclinical Benchtop Environment: In the preclinical setup, as seen in Fig. 4.7D, between six and twelve platinum-iridium electrodes (125 μm diameter, 1-20 kOhm impedances, AM Systems) were submerged in the 0.9% saline bath. These electrodes were wired to banana plugs, which were used to connect to various downstream devices. Simple banana to BNC adapters were used to connect wires to the sensing side of the NTB, a StimJim electrical stimulator (Open Ephys), or a Keysight digital oscilloscope (DSOX2004A, Keysight Technologies). A splitter was used to route parallel signals from the NTB sensing channel to a custom banana plug breakout board. This board was used to connect banana plugs to a 32-channel omnetics connector, which in turn allowed the electrodes to be routed through the Intan RHD2132 headstage. The headstage was then connected to an OpenEphys DAQ via a

serial peripheral interface (SPI) cable. Either a Keysight voltage source waveform generator (33500B, Keysight Technologies) or the precision arbitrary current source waveform generator of the NTB was connected to the cathode and anode of the electrophoresis tank using banana-to-banana plug connectors.

The Intan RHD series are silicon-based chips designed to detect and acquire weak electrical signals from living tissue. The RHD2132 used in these tests features a 16-bit ADC and 32 unipolar amplifiers with integrated analog filters. We shorted the reference and ground pins together and verified that any chips used were fully functional (no dead channels or unusual noise characteristics).

4.5.4 System assessments of the NeuroTest

Benchmark assessments were performed across both sites to evaluate the functionalities of the NTB prior to utilizing it for characterizing electrophysiology systems within in vivo applications.

Characterizing noise: To characterize system noise of the NTB, electrodes connected to the NTB and either the Intan RHD2132 or BIC were submerged in a saline solution. For these noise tests, a single sensing channel on the NTB was connected across a single pair of recording and reference electrodes that were submerged in the saline. Prior to recording, the NTB underwent calibration to ensure measurement reliability. With the aforementioned configurations, calibration consisted of injecting a known sinusoidal output with increasing peak to peak amplitude into saline while the NTB's input was connected to an electrode in saline. Once calibration was complete, the NTB and both systems under test were configured to record while no input was injected into the saline bath. After obtaining 2-minute long recordings with the above setup, root mean square (RMS) noise and noise floor were determined. To compute noise floor values, power spectral densities (PSDs) were calculated via Welch's method, using a 0.5 sec-long Hamming window and 50% overlap for the recording channel.

Assessing neural playback: To assess the NTB's biopotential generation and recording capabilities, electrophysiology collected in both preclinical and clinical contexts served as inputs to be played back by the system. Data for playback was re-sampled such that the

sampling rate was 2 kHz before being written to a CSV file. The CSV file was then loaded into a microSD card to be read by the NTB. Calibration was also performed prior to initiating biosignal playback. After both the NTB and systems under test captured 1 min of playback, cross-correlation was performed to compare the similarities between the original input and captured activity by the two systems.

4.5.5 Noise properties of the NeuroTest

A segment of these raw recordings from the NTB systems, Fig. 4.8A and 4.8B, and both systems under test, Fig. 4.8C and 4.8D, illustrate typical recordings without any injected input into saline. Despite distinct locations and setups, activity captured from the NTB and systems under test showed minimal noise fluctuation across sites. As seen in Fig. 4.8E, the NTB showed less line noise (i.e. 60Hz and harmonics) than the data collected with the Intan and Open Ephys. Data collected with the clinical benchtop environment also showed a similar decrease in the noise floor at all frequencies relative to the BIC, as shown in Fig. 4.8F. RMS values for the NTB were calculated across the entire 2-minute recording, yielding values of 4.06 μ V and 4.01 μ V at the preclinical and clinical sites, respectively. To assess the noise floors of the amplifiers, power spectral densities were calculated for the setups at each site. Due to differences between sampling frequencies for the NTB and BIC, the PSDs for each of these recordings reached a noise floor plateau at different frequencies. The PSDs determined at the clinical site showed the BIC plateauing around 500 Hz at -4 dB with the NTB settling near 1000 Hz around -24 dB. At the preclinical site, the PSD for the NTB also settled near 1000 Hz at -24 dB while the Intan setup settled near 600 Hz at -25 dB.

4.5.6 Evaluating neural playback outcomes

Both traditional electronic and biologically relevant electrophysiology signals were used to test the NTB's neural playback capability. First, both sites generated CSV files containing a 10 Hz, 1 mVpp sine wave and injected this signal via the neural playback function as an initial assessment of how well the ACSWG of the NTB reproduces the input signal. Fig. 4.9A shows data collected at the preclinical site. At both sites, the correlation between the input signal and the signal collected via the NTB and devices under test was very high (UMN: $r_{\text{NTB}} \geq 0.99$, $r_{\text{Intan}} \geq 0.99$;

UW: $r_{\text{NTB}} \geq 0.99$, $r_{\text{BIC}} = 0.96$).

Next, we sought to test the ACSWG with more complex signals. For the preclinical site, local field potential (LFP) data was collected from depth electrodes (Pt-Ir, $125 \mu\text{m}$ diameter, $<20\text{k}\Omega$) in the infralimbic cortex of a rat during a paradigm-free recording. Animals were placed inside a

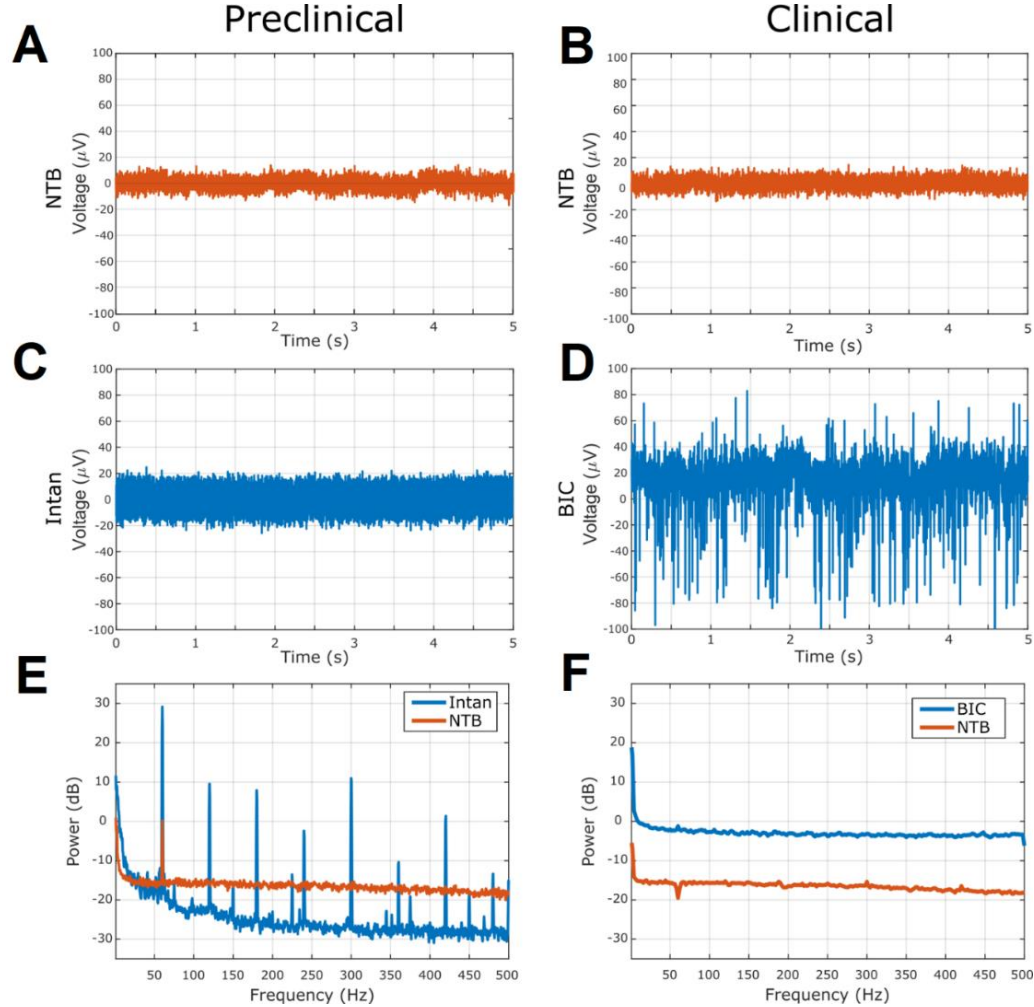


Fig. 4. 8 Noise floor characteristics of various data acquisition systems. Five seconds of data acquired from the NTB system at the (A) University of Minnesota and the (B) University of Washington. (C-D) Recordings collected with an (C) Intan RHD2132 headstage via an Open Ephys acquisition system and (D) CorTec BIC capturing the same activity depicted in (A) and (B), respectively. (E) Power spectral density plot comparing the spectral characteristics of the NTB and Open Ephys (Intan) data. While the Intan/Open Ephys data has less power at most frequencies, note the amplification of 60Hz harmonics. (F) Same as in (E) but comparing the NTB and the CorTec BIC. The BIC was found to have increased broad spectrum noise relative to the NTB. With the exception of 60 Hz noise and harmonics, due to differences in filter characteristics between the sites, the two NTB systems have nearly identical spectral characteristics.

non-conductive container located inside a faraday cage and allowed to freely explore the open space for the entirety of a 5-minute recording. Electrophysiology data were routed through a Brownlee amplifier (Model 440) to an Open Ephys DAC and sampled at 30 kHz. These data were downsampled to 2 kHz and injected into the electrophoresis tank using the neural playback function (Fig. 4.9B). Data were routed to both the sensing portion of the NTB and to an

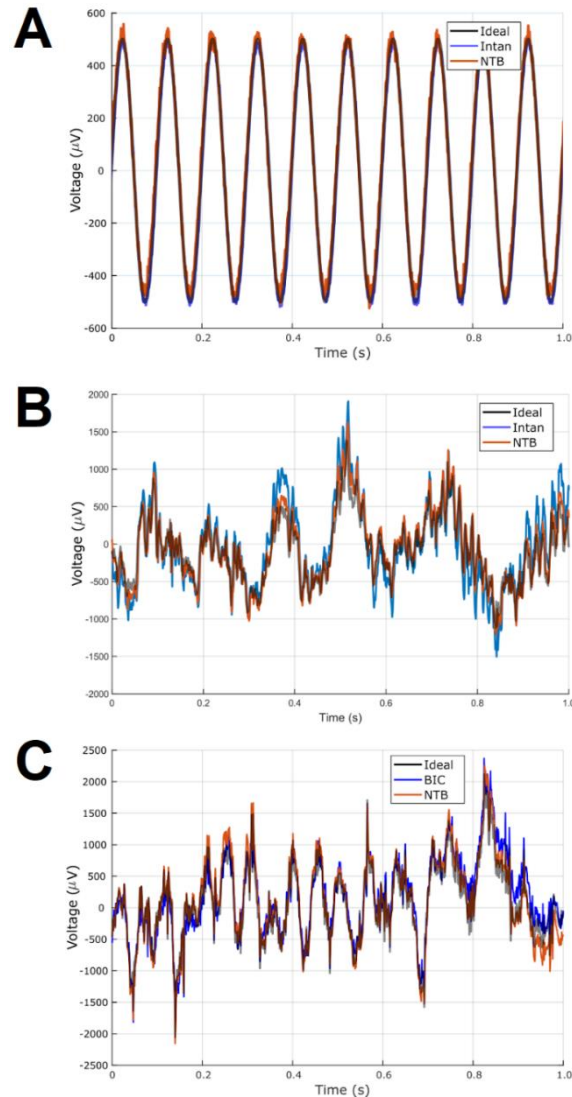


Fig. 4. 9 Accuracy of the current source waveform generator. (A) A 10Hz, 1 mVpp sine wave was injected into the saline tank for 1 s using the neural playback function. The input data (Ideal, black) is shown in black. The data recorded via the Intan chip (blue) and via the NTB (orange) is overlaid. (B) Neural activity collected from the rodent infralimbic cortex was injected into the UMN saline tank. One second of the recorded data is shown here comparing the ideal, Intan (Open Ephys), and NTB data streams. (C) Neural data collected from a patient with epilepsy was injected into the UW saline tank. One second of data comparing the Ideal, BIC (blue), and NTB (orange) is shown.

IntanRHD2132 headstage using a splitter, as described in the General Setup section above. The correlation between the input signal and the NTB recording was $r = 0.96$, while the correlation coefficient for the input signal and Intan data was $r = 0.87$.

With the clinical testing environment, stereoelectroencephalography (sEEG) recordings collected during intracranial monitoring of a human participant with epilepsy were used for playback. These resting state recordings were originally collected with the Cortec BIC system connected to a subset of the implanted sEEG electrodes through externalized extensions ending in clinical touch-proof connections. From the original recordings, a select channel located in the motor cortex served as the input signal to be played back by the NTB. Signal fidelity between the input and recorded signals was again high with the correlation coefficient between the original input and the sensed activity for the NTB being $r = 0.95$ while the BIC registered at $r = 0.86$ (Fig. 4.9C).

These data demonstrate the ability of the NTB to both generate and record complex signals while maintaining the integrity of the original dynamics of the input signal.

4.5.7 Discussion

With advances in the neuromodulation space, the need for evaluation tools will play a significant role in ensuring adequate preparation before starting in vivo research. Building from currently available evaluation systems, there will be more accessible means to assess electrophysiology equipment and experimental setups. Better informing users of the nuances of the systems they are utilizing in novel research efforts will guide upcoming experiment design and facilitate improved hardware design for future systems. By expanding the resources available to perform system evaluation work, researchers can raise confidence in the novel systems they are utilizing and support more rapid and reliable prototyping efforts within the neuromodulation space.

In this work, we present the NTB, a controlled, benchtop evaluation system that enables extensive device characterization to guide neuromodulation research efforts. The NTB and electrophoresis tank provide a platform that is designed to mimic bio-electric signals as well as the tissue-electrode interface, allowing for in vitro alternative to in vivo testing. Assessments across labs demonstrated highly consistent performance of the NTB despite distinct environments, including differences in the devices (i.e., Intan RHD2132 and CorTec BIC). Noise floor characteristics and signal

generation fidelity of the NTBs were nearly identical, establishing a reliable benchmark for assessing functionality of other devices. We further provide two separate use-cases of the neural playback functionality to assess stimulation artifacts in simulated evoked potential experiments. Taken together, these data demonstrate that the NTB can be used for critical testing and validation of brain stimulation technologies across sites, devices, and applications.

Reproducibility is critical for scientific research and the need for reliable benchmarks will only increase as electrophysiology experiments and related technologies become more complex. This reality is the core motivation for the creation of open-source devices like the NeuroDAC system [124] and our NTB. Having systems that can be used flexibly across many different applications and experimental setups allows for comparison across projects with disparate methodologies but overlapping scientific purposes. In our case, the teams at the University of Minnesota and University of Washington have similar end goals (i.e., developing new neuromodulation therapies for neurological and neuropsychiatric disorders); however, testing at the Minnesota site was done in a preclinical lab space while testing at the Washington site was done in a clinical laboratory environment. The Minnesota team used electrodes, simulators, and data acquisition systems common in preclinical research while the Washington team worked with a neuromodulation device in development for human use. We demonstrate that the NTB behaves predictably and similarly across these two laboratory setups despite their different methodological approaches.

The noise floors on our NTB devices follow a highly consistent and straightforward power-law scaling that starts sub 0 dB and bottoms out around -25 dB. We also observed general background noise in both systems to be ~ 4 μ V RMS. Given that neural oscillations recorded via intracranial electrodes generally have amplitudes in the 10 s to 100 s of microvolt range, these data show that the NTB can reliably detect even small simulated biopotentials. We further demonstrate the signal generator of the NTB exhibits extremely high fidelity replay capabilities both with simple signals, such as sine waves, and complex neural data from both rodents and humans. These data highlight the potential for this system to be used across the translational pipeline, from preclinical animal modeling to evaluation of investigational devices.

Despite the potential of this testbed to facilitate benchtop testing, the NTB has notable

limitations. Currently, the NTB only supports 2 input and output channels, placing a limit on the complexity that can be emulated in this testing environment. This configuration may not be appropriate for emulating more complex environments, particularly within applications exploring multi-source brain activity or investigating high spatio-temporal sensing configurations. Expansion of the current circuitry is relatively straightforward, though, and would mainly require duplication of the existing architecture. Another shortcoming of the proposed test-bench is the use of a microSD to load data available for playback. The number and size of data available for playback can be limited by the storage size of the microSD card, which may require more maintenance for a user when iterating through an array of signals to generate. While advances in memory technology have enabled significant increases in storage capacity, the process of modifying data for playback, reuploading the data to the memory card, and then physically mounting the card to the NTB can be laborious and serve as an inconvenient barrier for rapid iteration through various signals for testing. One alternative is to allow streaming of signals for playback, improving flexibility with the device that can be enabled with firmware and software development. Additionally, while the NTB can support a range of signals for playback, the device is constrained from generating high-frequency activity above 10 kHz. This ceiling limits emulation of some neural signals, particularly single-cell neural spiking activity. Likewise, the ADC is capped at 8 kHz, meaning that this device is optimized for applications involving meso- to macro-scale neural activity. Increasing these caps requires new hardware that would increase the price and computational demands of the system and should be weighed against broader purpose applications.

4.6 Conclusions

To address the technological limitations of current adaptive neuromodulation research systems, we developed a research platform that enables a high degree of customization, including the implementation of a wider array of adaptive stimulation paradigms. Performance assessments in both a benchtop environment and fully implanted case present promising outcomes for the proposed platform to be an instrumental tool towards continuing advances in the adaptive neuromodulation space. We also characterized a benchtop evaluation tool that emulates the tissue-electrode interface to more accurately assess novel systems and experimental approaches prior to

progressing to in vivo experimentation. With neural playback and recording functionalities, we believe that this controlled testing environment will facilitate verification work, assist debugging efforts, and raise confidence in the design of systems and algorithms supporting neuromodulation research.

Chapter 5

Evaluation of novel electrophysiology systems for CCEPs

In addition to having the means to induce neuroplasticity changes, another critical feature for clinical research systems is the ability to capture those changes reliably. As previously discussed in Chapter 2, various electrophysiological methods have been well-utilized to assess plasticity effects. CCEPs are a particularly prevalent biomarker for this application, however, the means to thoroughly characterize if a system can reliably capture CCEPs are not readily available. Within CCEP experiments, numerous variables may affect the ability to detect any evoked response. There may be physiological reasons behind the nature of an evoked potential response, such as the neural site of choice not being capable of generating an electrophysiological response. However, it's crucial to consider if any aspects of the electrophysiology system, such as sensing configurations and stimulation artifact, may also influence the detection of an evoked potential response. Additionally, signal processing techniques have been demonstrated to affect CCEP outcomes, further confounding what constitutes a “real” response [127]. These factors present challenging confounds when attempting to debug a system and identify system characteristics that may be responsible for unexpected outcomes. Currently, the lack of benchtop tools to assess systems' abilities to capture evoked potentials is a significant barrier towards validating a system's ability to capture a notable biomarker of neuroplasticity changes.

This chapter will focus on initiatives to assess the proposed platform's ability to capture CCEP activity. I will discuss a novel evoked potential functionality of the NeuroTest platform introduced in Chapter 4.4 and how this feature enabled simulation of CCEP experiments in saline. Characterization of stimulation artifact from these experiments were then used to identify signal processing approaches to mitigate the impact of post-stimulation artifact on sensing. These processing methods were then evaluated with saline and in vivo CCEP data to assess their efficacy.

This chapter includes work in collaboration with Jeremiah Morrow and Alik Widge at the University of Minnesota, and Moaad Benjaber and Tim Denison at the University of Oxford.

5.1 Introduction of NTB's ability to simulate EPs

To address this gap in evaluation tools and expand upon the NTB's capabilities introduced in Chapter 4, I present another unique feature of the NTB: its ability to simulate stimulation evoked potential experiments. In detecting activity above a user-defined threshold, the NTB responds with a series of oscillations with customizable parameters to more appropriately emulate an *in vivo* evoked response. In this stimulation context, the NTB's data acquisition capability is particularly relevant, as stimulation activity can overwhelm a system's amplifier, resulting in gaps of information on the impact of stimulation on capturing evoked neural activity. By having an independent monitor of what occurs in saline, the exact nature of stimulation can be characterized and not only inform the design of stimulation experiments, but also guide signal processing methods for post-hoc analysis.

Considering the variety of stimulation evoked activity, the NTB's evoked potential simulation functionality allows customization of the evoked response. Via a command interface,

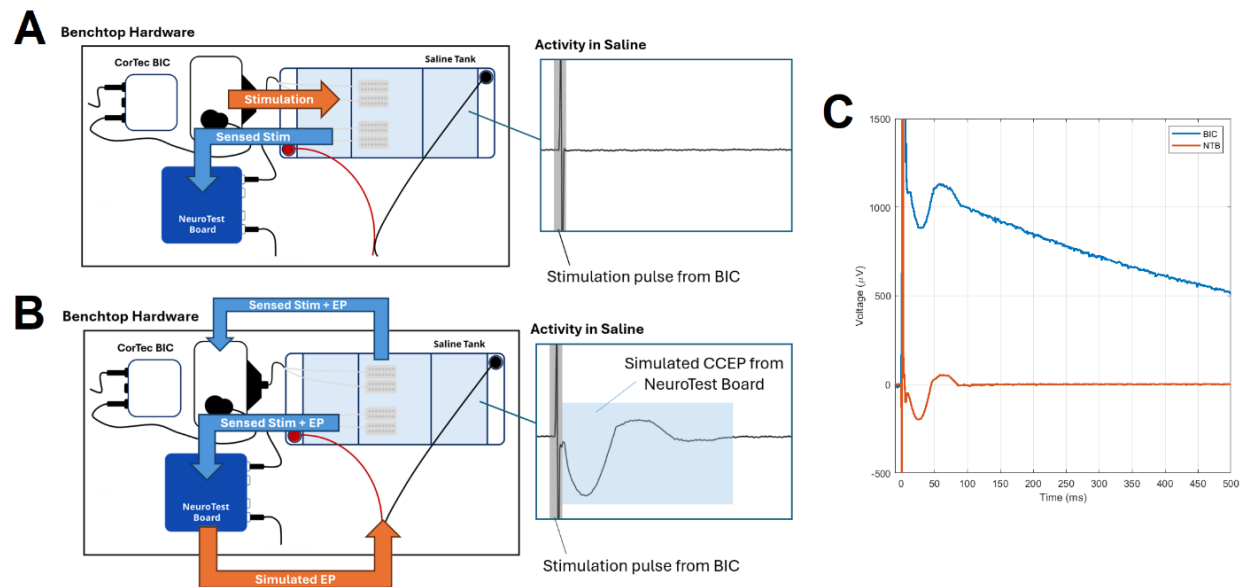


Fig. 5. 1 Benchtop testing environment used for simulating CCEP experiments. A) The CorTec BIC system delivers a stimulation pulse into saline which is detected by electrodes connected to the NTB. B) In response, the NTB responds to stimulation with a simulated CCEP response back into saline. This combined stimulation and CCEP response is captured by both the BIC and NTB systems. C) Simulated evoked response from the NTB is captured by both the BIC (blue) and NTB (orange). Homogeneity in the recordings of the injected signal demonstrates the use of the NTB as a reliable ground truth system for subsequent CCEP evaluation.

characteristics of the response can be created to better match the application of interest. As an initial demonstration of this feature, low-frequency stimulation pulses delivered by the BIC for the clinical benchtop environment, as seen in Fig. 5.1, triggered an evoked response from the NTB. Prior to stimulation, the evoked response generated by the NTB was configured via the serial command interface that communicates with the platform. Modifiable variables of the generated evoked response include frequency, amplitude, response delay, and morphology template of the response. Evoked activity highlighting these configurable parameters in response to low-frequency, single pulse stimulation are shown in Fig. 5.2.

5.2 Evaluating CCEPs in saline with the BIC

5.2.1 Influence of stimulation configuration

Neurostimulation typically utilizes either monopolar or bipolar configuration, depending on the application of interest. A monopolar configuration uses a single active contact of the implanted electrodes and a distant return electrode for stimulation. In a bipolar configuration, a pair of contacts on the implanted electrodes drive current flow. While both stimulation methods have been utilized for a variety of clinical applications, including functional mapping [94], [128], [129], [130], [131] and therapeutic intervention for a variety of disorders [132], [133], [134], the conditions to favor use of one configuration over another continues to be an active area of research. Considering that the desired nature of the electric fields generated and their effect on neuronal tissue will vary according to the application of interest, neuromodulation devices enable both stimulation configurations to extend their utility.

The BIC is capable of delivering stimulation with either of these stimulation configurations, in addition to a unique configuration denoted as bipolar with ground. The external, ground electrode of the BIC implant is incorporated as a third electrode, serving as an additional anode alongside the designated cathode and anode electrodes. Current flow between the designated anode and the ground electrode will distribute according to the impedances determined at each contact. As this configuration presents an alternative configuration when generating an electric field, a similar characterization will be performed to determine the conditions under which this would be preferable over a traditional bipolar configuration.

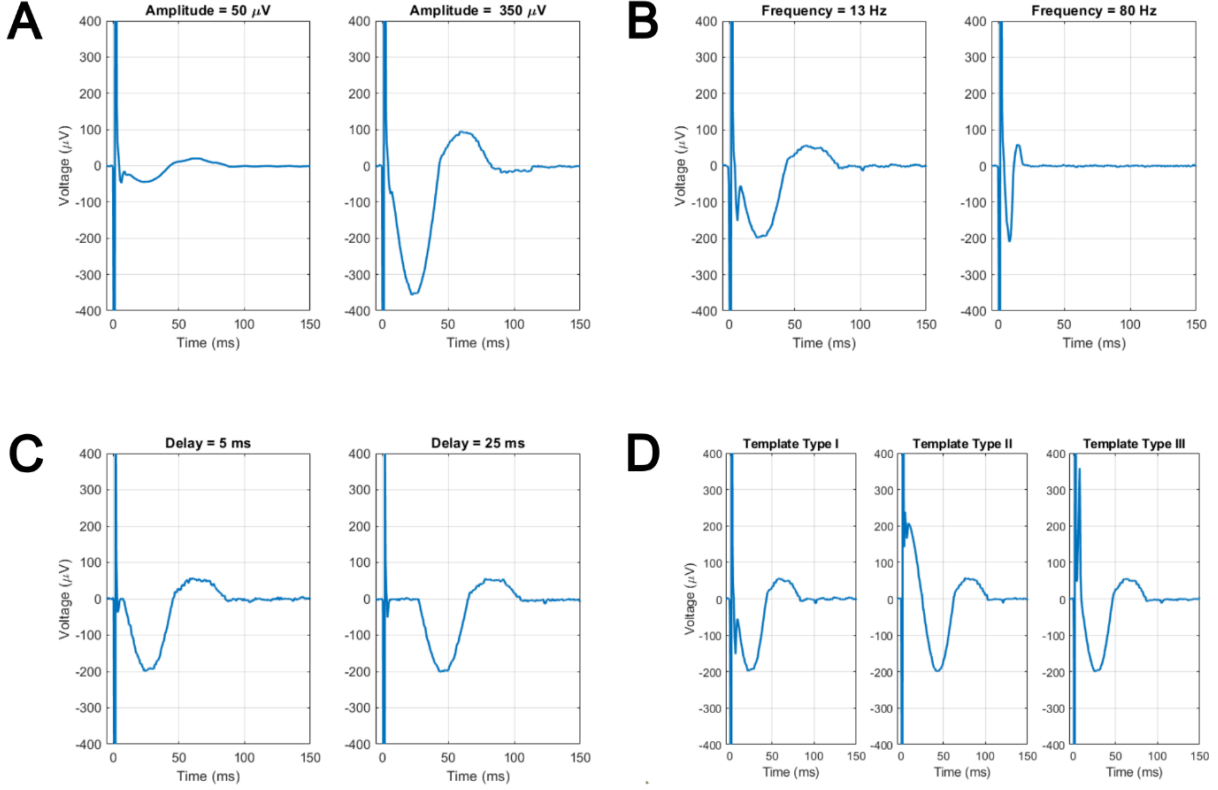


Fig. 5. 2 Time series plots demonstrating the customization possible with the NTB's EP simulation functionality. Configurable parameters include the A) frequency of oscillatory components, B) amplitude of components, C) delay between stimulation and the triggered evoked response, and D) morphology of the evoked response generated.

One aspect of stimulation configuration is its influence on the battery life [135] of implantable pulse generators, and for a fully implantable system, would be considered as another factor towards determining which configuration to utilize. However, as battery longevity is not a concern with the BIC, due to the nature of how the system is powered wirelessly via the magnetic headpiece, characterization will primarily focus on the impact of stimulation on sensing simulated electrophysiology signals.

5.2.2 Characterization of BIC's ability to capture evoked potentials

The NTB's evoked potential simulation feature facilitated assessments of the BIC's ability to reliably capture stimulation evoked activity and evaluate the efficacy of post-hoc cleaning techniques for isolating the evoked response of interest. Using the recording configuration described in Chapter 5.1 and the custom evoked potentials application described in Section 4.2.2,

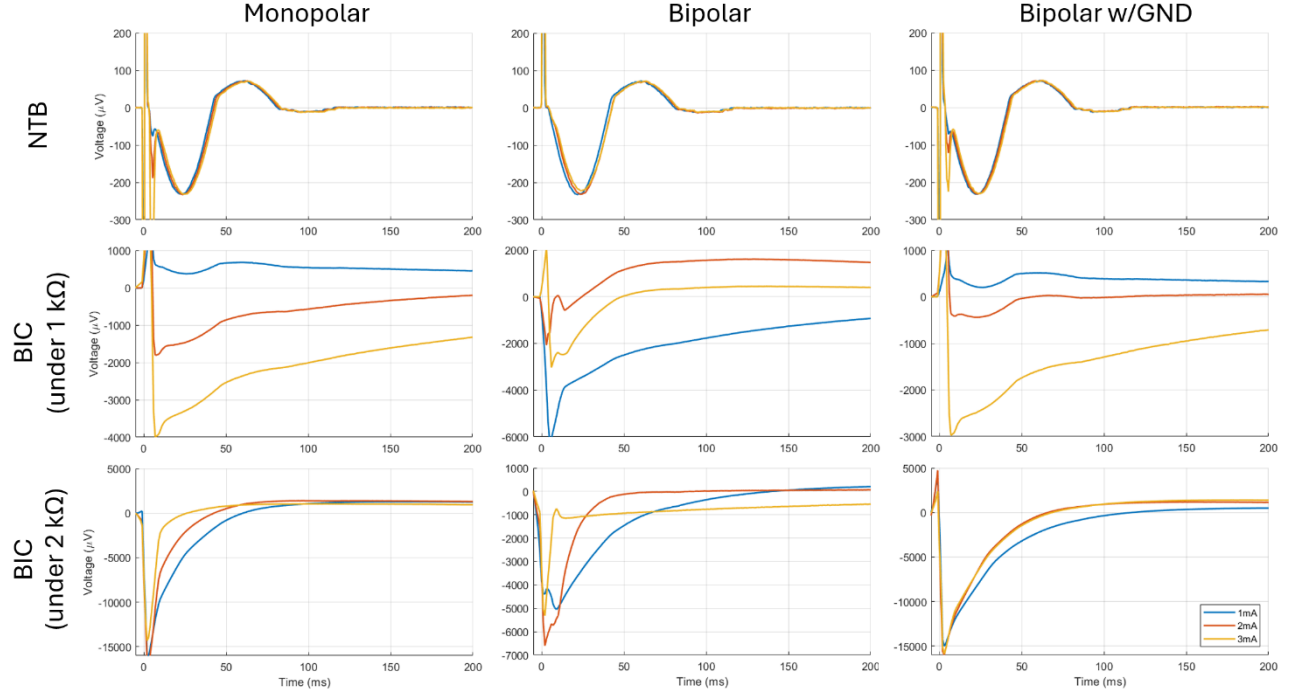


Fig. 5. 3 Raw averages from simulated benchtop CCEP experiments with the NTB and BIC systems with increasing stimulation amplitudes. (Top) Recordings from the NTB unequivocally show the injected simulated CCEP response present across all stimulation conditions. (Middle) Averaged activity from the BIC demonstrate the influence of the nonlinear trend following stimulation across various stimulation conditions. Oscillatory patterns composing the injected response from the NTB are more easily identifiable when utilizing stimulation configurations with a ground connection (i.e. monopolar and bipolar with ground). (Bottom) To demonstrate the impact of impedance on the nonlinear trend, impedance of the saline bath was increased until all values were reported to be between 1 - 2 k Ω . The same simulated CCEP experiments shown in the first two rows were repeated. The raw averages, even in the monopolar and bipolar with ground configurations, do not clearly show any simulated CCEP activity, as they are overwhelmed by the post-stimulation artifact.

low-frequency stimulation pulses were delivered by the BIC and triggered a consistent evoked response from the NTB. With the command interface, an oscillatory signal with 13 Hz frequency components was injected immediately upon detecting stimulation. This simulated evoked response contained an initial negative peak with an amplitude of approximately 250 μVpp around 25 ms, a smaller positive peak of around 60 μVpp about 60 ms, and subsequently smaller negative peak of 12 μVpp about 100 ms, all relative to the onset of the stimulation artifact. Throughout these stimulation experiments, both the BIC and NTB systems were set to record. For this characterization, 50 trials of stimulation were delivered with the BIC. Polarity reversals, where the cathode and anode for stimulation are inverted, were randomly performed throughout

stimulation delivery. Impedances as observed by the BIC were reported under 1 k Ω . These stimulation experiments were repeated with various stimulation configurations (i.e. monopolar, bipolar, and bipolar with ground) and with increasing stimulation amplitude. During post-hoc analysis, the trials were epoched and then averaged to generate a raw average evoked response waveform.

Trial data and their raw averages from this stimulation experiment can be seen for the NTB and BIC systems in the first two rows of Fig. 5.3. Across certain stimulation conditions, the raw average computed from the BIC recordings showed a nonlinear trend with varying time courses in the return to baseline. Under particular conditions, such as higher stimulation amplitude, the nature of this nonlinear trend overwhelmed the CCEP response. This was particularly significant within the bipolar stimulation condition, as the effects of stimulation were much more notable, and the higher-frequency nature of the return to baseline behavior made it challenging to fully appreciate the underlying evoked response.

Subsequent saline testing repeated these CCEP stimulation experiments, but under increased impedance of the saline bath. Impedances were increased until all submerged electrodes reported values between 1-2 k Ω . Raw averages from this additional testing are depicted in the bottom row of Fig. 5.3. These stimulation experiments observed the period of post-stimulation to substantially overwhelm the underlying simulated response across all stimulation conditions. For the monopolar and bipolar with ground conditions, this resulted in a considerable loss in appreciation of the injected signal prior to any additional processing, in contrast to the sub-1k Ω condition. This outcome is consistent with the effects of the electrode-tissue interface when injecting electrical stimulation, typically due to the product between the capacitive effects at this interface and resistance of the tissue [136]. However, these results do indicate a need for specific signal processing methods to target this nonlinear behavior.

Further inspection of individual single pulse trials yielded distinct distributions of post-stimulation artifact behavior. With the monopolar and bipolar with ground stimulation conditions, stimulation artifact was consistent and return to baseline activity was coupled closely across trials with small variations in the low-frequency return to baseline. However, individual trial outcomes with the

bipolar stimulation condition observed notably higher variability in stimulation artifact and return to baseline behavior, particularly within the first 150 ms following stimulation. In addition to having different time courses, post-stimulation activity did not follow a singular template and could be approximated by different nonlinear functions.

Recordings captured by the NTB show the stimulation artifact generated by the BIC and the preserved components of the generated evoked response. When evaluating the NTB and BIC trials

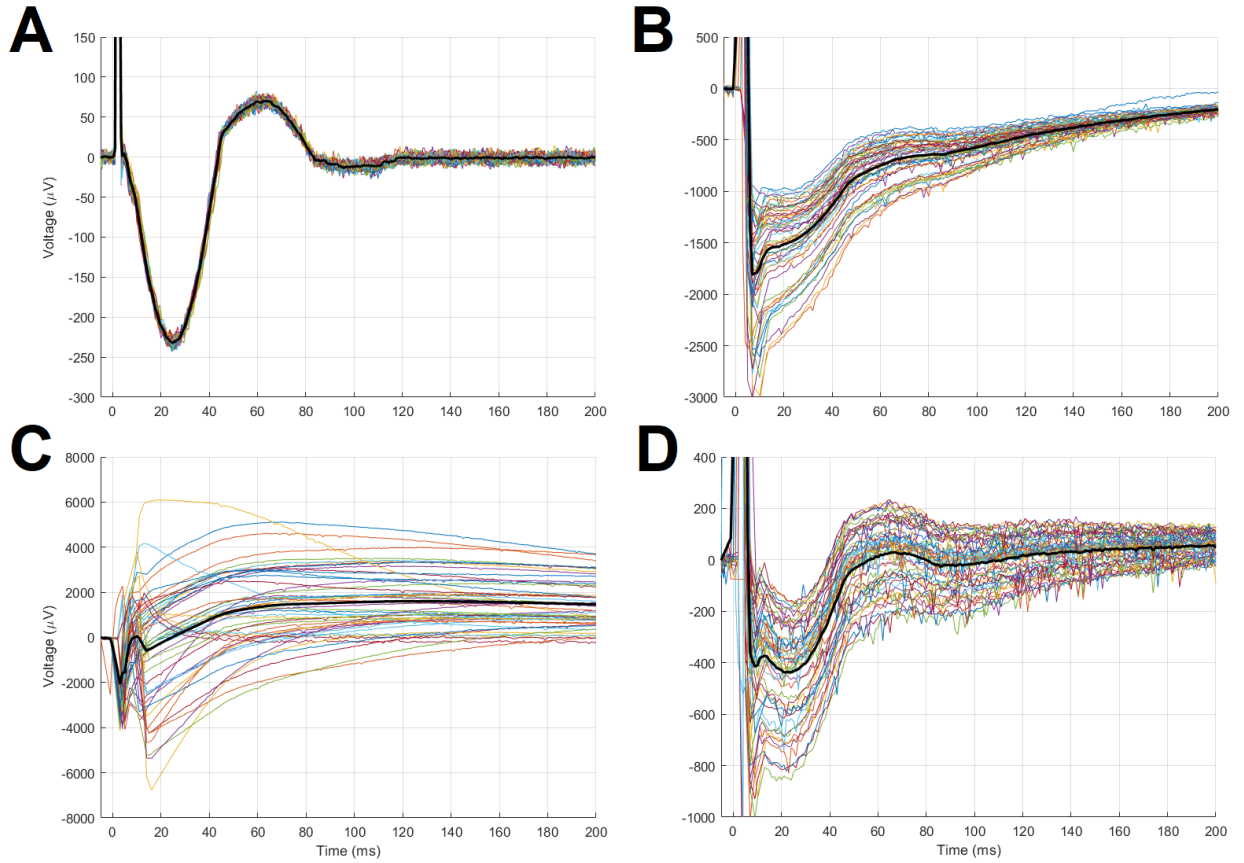


Fig. 5. 4 Demonstration of sensed post-stimulation artifact behavior across the NTB and BIC under various stimulation configurations. Colored traces reflect individual CCEP trials while the black is the raw average of those trials. A) Individual CCEP trials observed by the NTB are stable and consistent with a discernable CCEP response in the raw average. The simulated CCEP response from the NTB is triggered by stimulation from the BIC, using a 2 mA stimulation amplitude with impedances below 1 k Ω . Subsequent subplots show the same injected CCEP signal triggered by the same stimulation pulse captured by the BIC system in response to B) monopolar, C) bipolar, D) and bipolar with ground stimulation configurations. Return to baseline behavior across all stimulation configurations exhibit the nonlinear trend, in various degrees, affecting sensing of the injected CCEP response and were categorized into two types of post-stimulation artifact distributions.

and averages from these stimulation experiments, the variable nonlinear trend from stimulation was unique to the BIC dataset only, as shown in Fig. 5.4, indicating that this trend is specific to the sensing of the BIC device.

5.2.3 Need for targeted signal processing techniques for cleaning EPs

Overcoming the effects of stimulation artifact has been a long-standing challenge and several techniques have been proposed for targeting the stimulation artifact and recovering underlying neural activity [137]. However, in the context of CCEPs, signal processing techniques must not only limit the impact of stimulation, but also preserve meaningful electrophysiological oscillations due to interest in characterizing their temporal characteristics, such as their latencies and amplitudes. Typical methods utilized in cleaning electrophysiology data such as filters can distort evoked potential components, requiring careful consideration of which approaches to utilize in this particular use case [127]. Signal processing methods used previously in the context of CCEPs include model-based subtraction [136], [138], [139], [140], reverse polarity averaging [141], and independent component analysis [142], [143], [144].

Upon inspecting trial-by-trial outcomes from the in vitro experiment, polarity reversals did not yield notable stimulation artifact flip or distinct inverted return to baseline behavior across all conditions. The lack of this inverted artifact with a polarity reversal can likely be attributed to a combination of various hardware idiosyncrasies affecting the front-end sensing capabilities of the device. However, hardware modifications to the BIC device are beyond the scope of this work, so this return to baseline behavior serves as the primary signal processing challenge in assessing the BIC's ability to capture evoked potentials. Given that the reverse polarity averaging method relies on the condition that system-related influences will distinctly invert when switching cathode and anode channels during stimulation delivery, this technique will be excluded in subsequent post-hoc processing. Additionally, individual CCEP trials across all stimulation conditions indicate a consistent nonlinear trend immediately following stimulation. However, the nature of this trend varies according to stimulation configuration, as exemplified by Fig. 5.4B-D. Considering how this trend can manifest into two distinct distributions, various signal processing methods will be utilized according to the characteristics of the distribution of return to baseline behavior to better

extract the CCEP response of interest.

Two methods were applied to target this exponential trend and attempt recovery of the underlying response injected by the NTB: 1) a model-based subtraction (MBS) approach and 2) independent component analysis (ICA). The MBS approach involved fitting the return to baseline period following stimulation with an exponential function, y_{trend} . Exponential fits were modeled using the following equation:

$$y_{trend} = Ae^{bx} + Ce^{dx} \quad (5.1)$$

Constants A , C , b , and d were estimated to best reflect the characteristics of the resistive and capacitive effects of the electrode-tissue interface being emulated in the saline environment with the electrodes of the BIC device. This function was modeled to each trial before being subtracted from the trial data, due to slight variations between CCEP trials. The MBS method was used for CCEP datasets that mirrored the distribution of stimulation recovery behavior as seen in Fig. 5.4B and D- a closely coupled distribution of exponential trends with similar time course characteristics.

However, for datasets that have much higher variability and more complex characteristics in return to baseline behavior, similar to Fig. 5.4C, fitting Eq. 5.1 may be suboptimal and yield to poor fits. Poor fits can result in the creation of pseudo-oscillations that could be mistakenly interpreted as electrophysiological activity, and result in lower-fidelity recovery of true, underlying oscillations of interests. In these cases, ICA was applied to better recover the CCEP response. Prior efforts have utilized ICA for targeting artifacts and their distortions in various stimulation evoked response experiments utilizing TMS [143], [144]. Using the FastICA method [145], [146], ICA components reflecting stimulation artifact were selectively removed to minimize its overwhelming impact on the underlying evoked potential response. Because of the more distinct characteristics of the stimulation recovery behavior and considering potential frequency overlap between the return to baseline and oscillations of the simulated signal, components were manually identified prior to removal.

To assess the efficacy of these methods in extracting the injected CCEP responses, the NTB

outcomes, Y_O , were used as an effective ground truth dataset to compute the relative error of the cleaned signals, Y_C . Any activity immediately following stimulation, approximately 10 ms after stimulation onset, was ignored for this analysis. Relative error was calculated with the following equation:

$$Relative\ Error = \frac{\|Y_C - Y_O\|_2}{\|Y_O\|_2} * 100\% \quad (5.2)$$

where $\|x\|_2$ denotes the Euclidean norm of the signal, x .

5.2.4 Cleaning simulated CCEP datasets

The resulting signals from applying these cleaning methods across simulated CCEP experiment datasets are shown in Fig. 5.5 with relative error metrics to quantify the recovery of the CCEP response reported in Table 5.1. The MBS approach was applied towards all datasets in order to establish a baseline on CCEP signal recovery outcomes. However, this method yielded large relative error in signal recovery for the bipolar stimulation condition. ICA was subsequently applied to only the bipolar stimulation dataset to improve upon these initial recovery efforts. The resulting signals from ICA led to some improvements in the metric outcomes relative to MBS, but were still notably worse results compared to the outcomes observed with monopolar and bipolar with ground configurations.

Use of MBS towards recordings using a monopolar and bipolar with ground stimulation configurations was effective towards realizing the underlying oscillatory response. This approach was successful in offsetting the exponential trend without introducing pseudo-oscillations. Recovered CCEP activity generally maintained the morphology of the original injected signal. Latencies at which the initial negative and positive components of the recovered CCEP occurred were within 3 ms and 2 ms of the original negative and positive components, respectively. Greater variations were observed when recovering the second negative component, with recovered components occurring within 6 ms of the original. While latencies of these components were generally preserved in the cleaned responses, the most notable difference when compared to the ground truth signal was amplitude deviations, as quantified by the relative error metrics.

However, for the bipolar stimulation condition, MBS was unable to recover the negative peak approximately 25 ms post-stimulation for stimulation amplitudes above 1 mA. This technique also began to introduce significant distortions to the first negative and positive peaks of the CCEP response with increasing stimulation amplitude, as shown in Fig. 5.5 B. Temporal characteristics of the CCEP response were notably affected. Peaks were reported to occur early and with higher

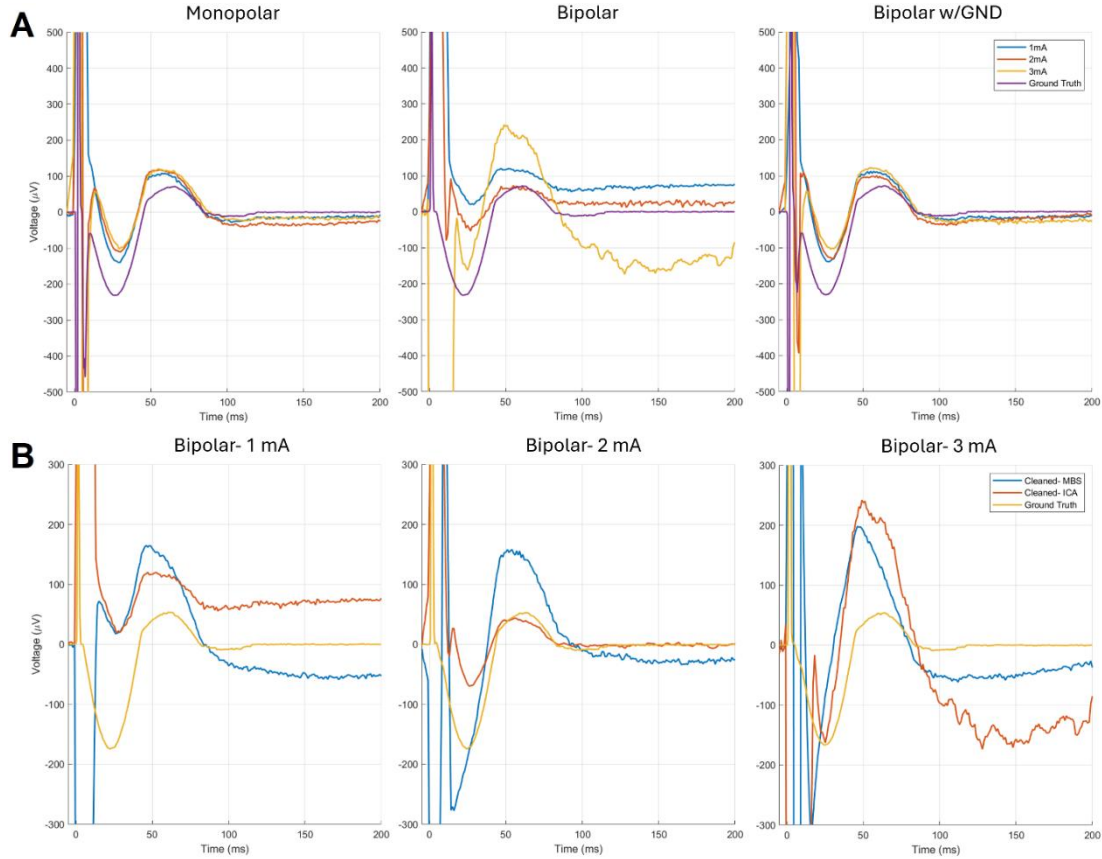


Fig. 5. 5 Outcomes from cleaning the simulated CCEP datasets collected with the BIC system. A) Recovered signals across all stimulation amplitudes and configurations from the data plotted in the middle row of Fig. 5.3. CCEP data collected using the monopolar and bipolar with ground configurations were recovered using the MBS method while signals from the bipolar configuration were recovered using ICA. While the same simulated CCEP response was injected in all stimulation experiments, the recovery of the underlying signal primarily varies between stimulation configurations. Stimulation amplitude also has some effect on CCEP recovery, though this is mainly observed in the bipolar stimulation configuration. Recovery in the monopolar and bipolar with ground configurations is relatively stable across all stimulation amplitudes. B) Additional comparisons between signal processing methods on all bipolar stimulation datasets. Signals recovered with both MBS and ICA observed various combinations of amplitude and latency distortion depending on stimulation condition, compared to monopolar and bipolar with ground outcomes in A).

Stimulation Configuration	Cleaning Method	Relative Error		
		1 mA	2 mA	3 mA
Monopolar	MBS	30.29 %	30.64 %	28.41 %
Bipolar	ICA	65.31 %	54.03 %	92.25 %
Bipolar	MBS	73.82 %	78.53 %	113.8 %
Bipolar w/GND	MBS	28.84 %	34.12 %	28.33 %

Table 5. 1 Metrics to assess the efficacy of recovery methods of underlying evoked potential responses during simulated CCEP experiments performed with the BIC.

amplitudes for the 2 mA and 3 mA, with the 3 mA case not being able to recover the first negative peak at all, distorting the original morphology of the CCEP signal. Additionally, across all stimulation amplitudes, MBS introduced a low-frequency trend approximately 85 ms after stimulation, effectively losing the small negative oscillation expected at 100 ms.

Outcomes from utilizing ICA on the bipolar stimulation dataset improved upon the results from MBS for the 1 mA and 2 mA cases. Under these specific amplitude conditions, ICA performed well in recovering the original morphology and latencies at which oscillatory activity occurred. This method also did not result in low-frequency activity 100 ms post-stimulation, as seen with MBS. While amplitude modulation of the CCEP components did occur with the ICA method, it was much less severe, resulting in lower relative error. However, for the 3 mA condition, ICA was not effective and yielded a similar signal to that returned with the MBS approach. While ICA was able to recover the first negative and positive oscillations that occurred, approximately within 5 ms of the original components, unwanted properties such as significant amplitude modulation and low-frequency drift following the CCEP response were also present. In contrast to the 1 mA and 2 mA cases, where frequency characteristics are still somewhat maintained through either curve-fitting or ICA approaches, outcomes with the 3 mA condition severely suffered from distortion effects despite the cleaning method. Though this may be an example where both signal processing approaches were ineffective towards extracting the signal of interest, it is also possible that bipolar stimulation with amplitudes of 3 mA and higher can introduce distortion effects due to front-end saturation of the device, resulting in subpar signal recovery from irreversible loss of signal information. ICA was not performed with any monopolar or bipolar with ground datasets as the MBS approach yielded good recovery results. In addition, ICA was unable to clearly separate the nonlinear trend and CCEP activity, resulting in inadequate cleaning outcomes.

5.2.5 Alternatives to overcoming saturation

Following application of signal processing methods to extract underlying CCEP activity, it's clear that there are nuances to consider when approaching stimulation experiments. Though these simulated CCEP experiments identify possible signal recovery approaches and conditions under which these methods may not be effective, there remains the question of how to address potential sensing challenges with the BIC device. With evidence of possible saturation occurring at the front-end amplifier and introducing distortion to the injected CCEP response, there is a need for alternatives to performing these CCEP stimulation experiments, especially under likely conditions such as increased impedance. The presence of saturation introduces the concern of whether there is a potential distortion or loss of components comprising the CCEP response, and while this does not occur for all stimulation conditions, this possible loss poses a major obstacle in reliably measuring a biomarker of interest to be used in measuring corticocortical neuroplasticity changes with the BIC platform.

From the outcomes of processing simulated CCEPs, it's clear that stimulation parameters and impedances are major contributors to observing saturation effects with the BIC. However, it is

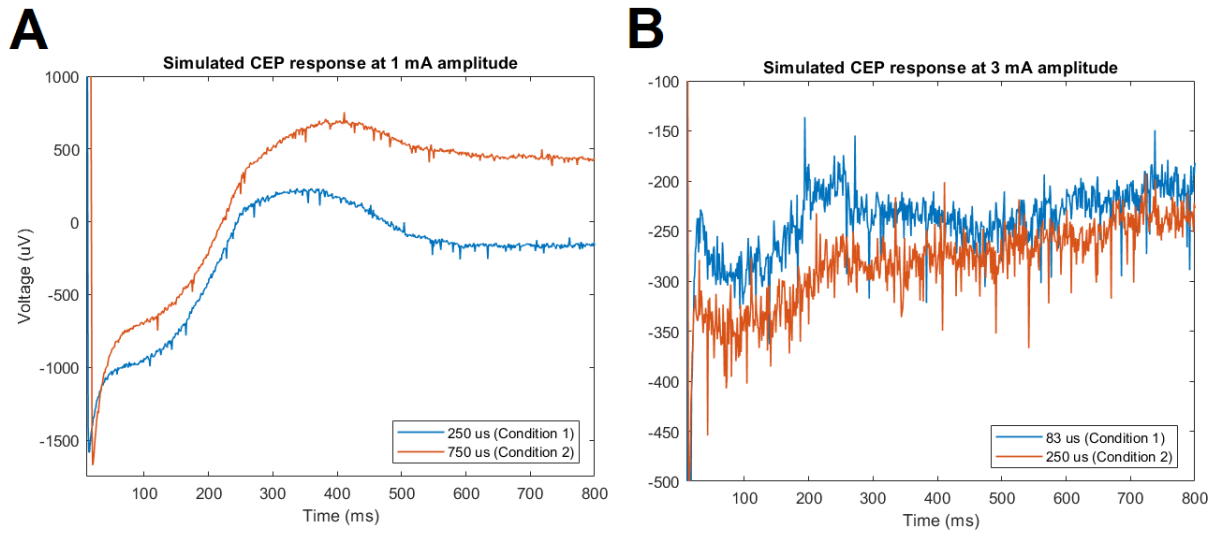


Fig. 5. 6 Simulated CCEP experiments to assess potential causes of saturation and sensing distortions. Similar saline CCEP experiments using stimulation parameters in Table 5.2 show that the visualization of a CCEP response is attainable with lower stimulation amplitude, despite differences in pulse width.

	Current amplitude	Pulse duration
Condition 1	1.0 mA	250 μ s
	3.0 mA	83 μ s
Condition 2	1.0 mA	750 μ s
	3.0 mA	250 μ s

Table 5. 2 Stimulation parameters to assess distortion conditions. Amplitude and pulse durations used for stimulation pulses during simulated CCEP experiments. Stimulation parameters are grouped under a condition based on the total amount of charge injected by the stimulus waveform.

important to note that impedances are subject to inflammatory responses upon placement within tissue [147], [148]. While surgical efforts strive to minimize impedances between electrodes and tissue, the reactive processes to implantation result in scar tissue that observe higher impedances following surgery [149], [150]. Given that electrode impedance is effectively an exogenous variable, in order to ensure that CCEP activity can continue to be observed long-term within a fully implanted case, it is important to consider how to redesign stimulation variables to address saturation concerns when approaching CCEP experiments.

To elucidate if these distortions are caused by specific stimulation amplitudes, charge build up, or some other aspect of the BIC system, additional experiments titrating stimulation parameters and preserving the total injected charge were performed. Pulse duration was adjusted such that the total charge injected by the BIC device using a low stimulation amplitude would match that at a higher stimulation amplitude. The same benchtop setup for initial CCEP experiments, described in Section 5.2.2, was used. Since a majority of saturation events occurred in the bipolar configuration, only bipolar stimulation was performed for these tests. The tested stimulation parameters for this follow-up experiment are shown in Table 5.2. The simulated CCEP responses using the tested stimulation settings are visualized in Fig. 5.6. Only under the 3 mA stimulation amplitude condition was saturation effects observed, Outcomes from these total charge experiments indicate that the distortion is exclusively stimulation amplitude dependent.

5.2.6 Discussion

As advances in technologies yield more complex systems for use within the neuromodulation space, it is critical to understand the capacity and what conditions these systems can be used for prior to in vivo research applications. With rising interest in characterizing evoked potentials as

biomarkers of neuroplasticity, it is critical to benchmark current and upcoming systems to ensure end user efforts are towards advancing research questions, raising confidence in the capabilities of these novel neuromodulation technologies, and minimizing endeavors towards debugging electrophysiology systems.

To better understand the capabilities of the BIC device to be applied towards adaptive stimulation, particularly in modulating neural plasticity, there was motivation to assess the device's ability to capture CCEPs, a relevant biomarker of neuroplasticity changes. Expansion of the NTB's functionalities allowed simulation of CCEP experiments, where the NTB responded to stimulation from the BIC with a customizable evoked signal into saline. Combined with the NTB's ability to record activity in the saline environment without being impacted by stimulation artifact, ground truth datasets were created alongside experimental recordings of the same activity observed by the BIC. This testing environment enabled post-hoc comparisons to directly assess the impact of stimulation on sensing the simulated CCEP response and evaluate signal processing pipelines to extract the signal of interest when working with BIC recordings.

The cleaning methods explored in this chapter served as preliminary efforts at extracting the underlying signals of interest. In comparing trial-by-trial differences in return to baseline behavior, distinct distributions of post-stimulation artifact were identified, resulting in the use of two techniques to target the low-frequency post-stimulation artifact. MBS was a reliable processing method for recovering the underlying signal of interest under consistent return to baseline behavior, with promising relative error metrics ranging from approximately 28-34% for the monopolar and bipolar with ground conditions. The efficacy of MBS can largely be attributed to the linear superimposition of the CCEP signal with the robust exponential trend across trials. The primary contributor to these error metrics was amplitude differences between the recovered and original signals. These differences are most likely to arise due to the approximation of the artifact recovery period. Although the exponential model provided good fits and allowed effective removal of this low-frequency trend, the exact characteristics of the RC product are unknown and subject to more complex impedance characteristics of the saline medium, resulting in amplitude modulation of the CCEP components.

Recovery performance for the bipolar stimulation was very poor, with relative error percentage ranging from 65-114%. Due to the more complex and variable return to baseline behavior, the MBS method proposed was not as effective at removing the post-stimulation artifact. While ICA was effective at recovering the timing characteristics of the oscillatory components at lower stimulation amplitudes, relative to MBS, its outcomes still suffered from amplitude modulation. These results are likely due to the time-dependency between the exponential return to baseline and simulated CCEP response. This time-dependency results in poor separation between post-stimulation artifact and the CCEP response, such that components identified with ICA still yield mixed measurements with the nonlinear trend and CCEP activity. Subsequent elimination of these components can result in removal of meaningful activity, resulting in the amplitude modulation observed in recovered responses. However, it is important to note that the trial variability observed in the bipolar stimulation dataset was advantageous when cleaning with ICA, as the nondeterministic nature of the artifact may have helped disrupt the time-locking relationship between the return to baseline and simulated CCEP response [143]. This is consistent with the suboptimal outcomes obtained when applying ICA towards the monopolar and bipolar datasets, where return to baseline behavior was consistent between trials, as shown in Fig. 5.4 A and C.

When transitioning to higher stimulation amplitudes, specifically with the bipolar stimulation configuration, there is evidence of saturation, as both amplitude and latency characteristics of the injected CCEP signal become distorted regardless of the cleaning method used. Although saturation was only observed within the bipolar condition in the presented data, it is reasonable to expect that under proper conditions like increased impedance, that saturation can occur with the monopolar and bipolar with ground conditions as well. These total charge experiments, elucidated that distortion is exclusively stimulation amplitude dependent. While a stimulus with high stimulation amplitude and short pulse width stimuli are more effective at eliciting greater CCEP response [151], using lower stimulation amplitudes with increased pulse duration is a possible alternative for executing CCEP experiments. This caveat implies that CCEP experiments with the BIC are still feasible, albeit limited as the duration of stimulation artifact may affect the visibility of early-latency components, which are believed to be reflective of effective connectivity [152], and must follow current density limitations to ensure non-damaging stimulation to tissue.

The NTB’s evoked potential functionality enabled extensive characterization of the BIC system’s ability to capture CCEP activity. This controlled, benchtop environment was key towards identifying specific characteristics to keep in mind when approaching CCEP collection with the BIC device. In addition to informing how to best program single-pulse stimulation experiments, the NeuroTest platform facilitated evaluation of signal processing methods for extracting CCEP signals, a biomarker of interest for assessing connectivity states. While the specific signal processing pipelines identified are only a small subset of possible techniques, the testing discussed in this work establish methods that can facilitate further assessment to determine effective post-hoc methods for identifying CCEP activity with the BIC system.

5.3 Evaluating CCEP collection in vivo

5.3.1 Transitioning from benchtop to in vivo

Insights from the benchtop testing outcomes in Chapter 5.2 with the BIC and NTB environment were used to validate the BIC and the proposed signal processing methods with in vivo CCEP data to determine their efficacy. As part of this validation, a research-grade neurophysiology

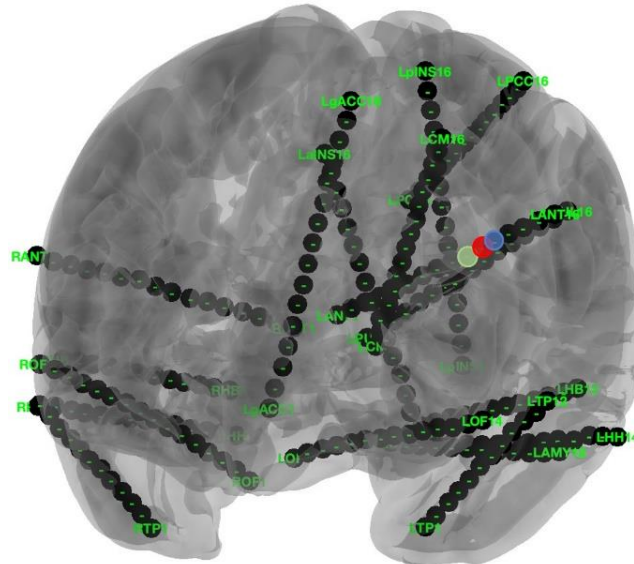


Fig. 5. 7 Electrode localization for in vivo CCEP data collection with the TDT and BIC systems. The cathode and anode electrodes used for stimulation are shaded in red and blue, respectively. The designation of cathode and anode contacts was inverted when performing polarity reversals throughout the stimulation experiment. While evoked potential activity was observed at various sEEG electrode sites, activity identified at the contact shaded in green was analyzed for the remainder of this chapter.

system- the Tucker Davis Technologies (TDT), was used to collect our ground truth dataset. The TDT system was composed of a PZ5 Neurodigitizer amplifier, an RZ5 BioAmp processor, and Subject Interface stimulator, enabling high density recordings, collecting 128 channels up to a sampling rate of 12 kHz, and customizable stimulation delivery. Both systems made use of a skull screw for a reference and a clinical monitoring system’s ground electrode for recordings. The TDT system was selected to collect ground truth data for comparison with the BIC as it has been well utilized to collect CCEP electrophysiology, demonstrating its reliability for this application [96], [127], [153], [154].

5.3.2 Patient Overview

Data was collected from a patient with epilepsy undergoing seizure monitoring at Harborview Medical Center. As part of standard clinical care, sEEG electrodes were implanted in neural regions relevant for clinical monitoring and the patient was moved to an epilepsy monitoring unit. The University of Washington Institutional Review Board approved data collection and patients were approached for consent to participate. Electrode localization for this patient is shown in Fig. 5.7.

5.3.3 Experimental setup

Recordings were obtained from implanted sEEG electrodes at the patient’s bedside via externalized extensions that ended in clinical touch-proof connectors. Both the BIC and TDT systems connected to a subset of the implanted sEEG electrodes for stimulation and recordings. A custom adapter was created to match the ends of these extensions and connect to the BIC development kit. The TDT system was utilized first to perform a CCEP sweep where stimulation was delivered to numerous adjacent contact pairs located within the motor cortex. Amplitude, pulse width, and frequency of the stimulation waveform remained constant throughout the sweep. Asymmetric, biphasic waveforms with a phase ratio of 4 were delivered in a bipolar fashion and 20 trials were collected per stimulation contact pair.

Data from the TDT sweep were then processed offline in order to identify a set of cathode and anode channels that elicited a notable CCEP response to stimulation. Once a complete set of stimulation parameters was identified within the TDT dataset, the following day, those

parameters were applied towards subsequent stimulation with the BIC. To ensure experimental consistency between the two systems, the stimulation waveform was preserved when transitioning from the TDT to BIC systems. From prior benchtop testing, the BIC used the bipolar with ground configuration for stimulation, as this setting maintained stability in capturing CCEPs for a wide range of stimulation amplitudes following post-hoc processing. Polarity reversals and jitter between individual stimulation pulses were also performed during CCEP stimulation in order to verify the presence of electrophysiological components comprising a potential CCEP response and minimize any entrainment effects. Following stimulation with the BIC device, data was similarly processed offline for an initial comparison. To minimize possible sources of variation, no additional data processing was applied to TDT or BIC-collected data, aside from averaging across evoked potential trials.

5.3.4 Outcomes from BIC vs TDT

Raw evoked potential responses identified in electrodes located in the left cerebral cortex, from both the BIC and TDT, are shown in Fig. 5.8. The TDT system produced a clear evoked potential response with positive peaks approximately 11 ms and 100 ms following stimulation, identified as P1 and P2, and a negative peak, identified as N1, about 35 ms post-stimulation. Meanwhile the raw average from the BIC was consistent with prior benchtop observations - a significant

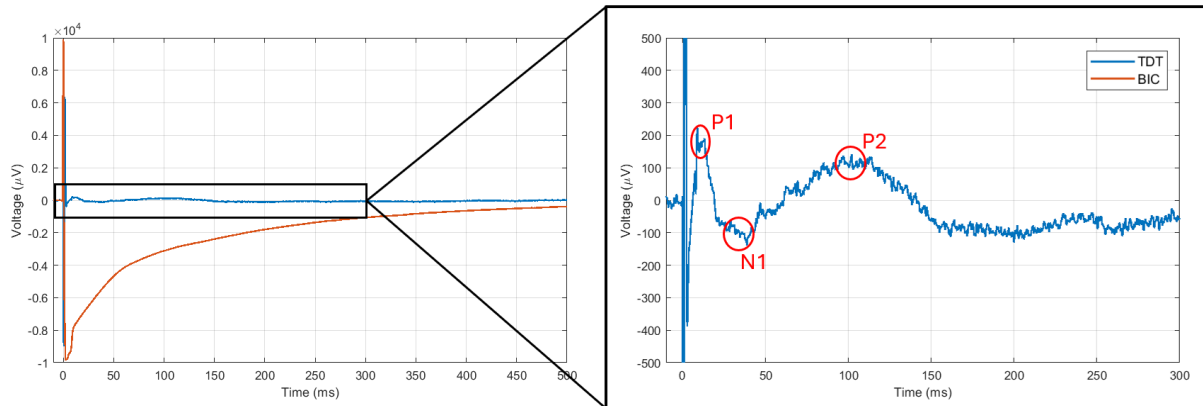


Fig. 5. 8 Raw averages of CCEP activity observed with the TDT and BIC systems. Zooming in within the first 300 ms following stimulation, evoked activity captured by the TDT system identifies notable oscillatory activity, identified as P1, N1, and P2. The BIC primarily shows the exponential trend after averaging, following expected behavior observed during saline benchtop testing.

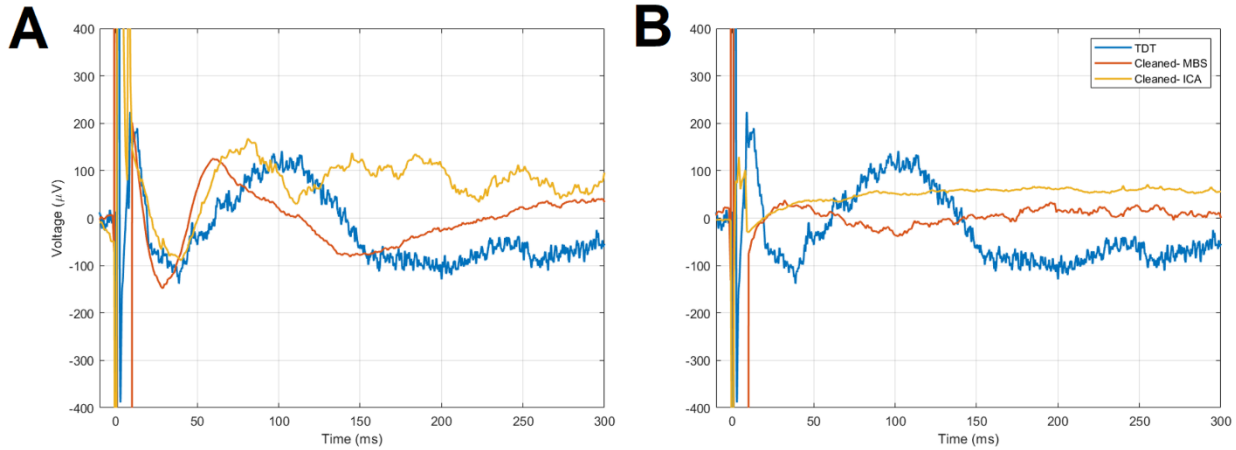


Fig. 5. 9 Application of different cleaning methods on identifying CCEP activity with the BIC. A) The CCEP response observed from the ground truth dataset (blue) is compared to outcomes from using model-based subtraction (orange) and ICA (yellow) to extract underlying activity. While there is identifiable oscillatory activity, there are temporal variations when comparing the cleaned results to the ground truth CCEP signal. B) Results from cleaning the CCEP trials performed with a polarity reversal. Unlike the signals obtained in A), there is no discernable evoked activity from stimulation.

exponential recovery period following stimulation immediately overwhelmed any possible evoked response observed by the BIC. ICA and MBS, as described in 5.2.3, were applied in an effort to recover the evoked response within the BIC dataset. Trials were separated according to stimulation polarity configuration and subsequently cleaned to verify the presence of electrophysiological oscillations in response to stimulation, as shown in Fig. 5.9.

Under the original polarity configuration, outcomes obtained from both ICA and MBS do not exactly mirror the CCEP response obtained with the TDT system, the ground truth dataset, but do contain oscillatory components similar to the morphology observed. Both cleaning methods do not capture the early-latency P1 component, but do resolve the subsequent N1 and P2 oscillations albeit with different temporal characteristics. The recovered N1 component has slight deviations in the latency at which it occurs while the P1 component shows greater variability in the latency. Temporal and amplitude characteristics of identified CCEP components are shared in Table 5.3. Both methods produced relative error metrics greater than 90%.

One idiosyncrasy with the BIC data was the notable lack of any evoked activity observed in trials performed with the reverse polarity configuration, as seen in Fig. 5.9B. Resulting signals from both signal processing approaches did not show any notable activity in response to stimulation.

	P1		N1		P2	
	Amplitude (μV)	Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)	Latency (ms)
TDT	178	11	104	35	121	100
MBS	N/A	N/A	82	36	145	61
ICA	N/A	N/A	150	38	122	78

Table 5. 3 Observed amplitude and latency components of CCEP responses obtained from the TDT system and following cleaning methods applied on data from the BIC device.

Considering the consistent outcomes from both of these cleaning techniques, it was determined that there was no CCEP observed with the inverted polarity configuration.

5.3.5 Discussion

Characterization of the sensing abilities of the BIC platform under the presence of stimulation facilitated the transition from simulating CCEP experiments via benchtop to conducting these single-pulse stimulation experiments with patients at the bedside. Performing stimulation experiments with the BIC and a research-grade electrophysiology system allowed tandem collection of experimental and ground truth datasets. Signal processing methods identified in Section 5.2.3 within benchtop experiments were then applied to extract the underlying CCEP activity. In applying the insights gained from initial benchtop testing, the efficacy of these recovery techniques were fully assessed within an in vivo application.

A key anomaly observed is the lack of any evoked response from stimulation performed with the polarity reversal configuration. One possible explanation behind this absence of activity is a difference in the electric fields generated between configurations. These stimulation experiments were performed using a bipolar with ground configuration, treating the ground contact as another return electrode and effectively creating a tripolar stimulation configuration. Differences in impedances of the stimulation paths between the designated return and ground electrodes may have resulted in distinct fields, resulting in disparate CCEP outcomes. However, the lack of an evoked response with the inverted polarity configuration does not indicate the response reported is artifactual. Oscillatory activity arising from stimulation would appear inverted, albeit smaller, even in the presence of a smaller electric field. However, since these trials depict stimulation artifact and an absence of any activity, the signal depicted in Fig. 5.9A is likely to be electrophysiological.

It should be noted that the recovered CCEP signals yielded varying characteristics in both latency and amplitude when compared between each other. While these discrepancies are similar to what was observed when comparing the outcomes of the two signal processing methods in Section 5.2.4, neither approach entirely matched the ground truth CCEP response collected with the TDT system. This inability to completely recover the ground truth CCEP signal may indicate the limitations of the tested techniques and a need to consider and evaluate additional methods for extracting CCEP activity.

However, one factor to note when deliberating why neither recovered signal entirely aligned with the ground truth signal is the possibility of CCEP differences between days. Fluctuations in CCEP responses between days have been reported and may be due to factors including medication and brain state [155]. Therefore, an outstanding question is whether the recovered signals are more closely aligned with the true CCEP response, compared to the denoted ground truth signal. Further testing may be needed to minimize this ambiguity, prior to concluding if the proposed signal processing approaches are robust strategies for identifying underlying CCEP signals.

This verification work at the patient bedside provided an opportunity to better characterize the nuances when utilizing the BIC system to approach in vivo CCEP data collection. From the presented outcomes, there may be a need for additional testing to further refine the processing pipeline and potentially explore alternative signal processing methods when collecting CCEPs. Evaluation with the benchtop testing environment yielded valuable insight towards elucidating observations from the EMU. Additionally, these outcomes provided feedback into additional avenues to explore to further characterize how best to utilize the BIC platform for CCEP collection.

5.4 Validating CCEP collection in a fully implanted case

5.4.1 Evaluation in a fully implanted case

While the work done in Chapter 5.3 facilitated evaluation of the BIC device for CCEP collection in vivo, the recording configuration consisted of connector solutions between implanted sEEG electrodes and the BIC development kit. Differences in the target stimulation and recording areas,

along with differences in recording configurations may yield different outcomes in capturing CCEP activity when the BIC is fully implanted. To validate the device’s capability of capturing CCEP activity, CCEP experiments were performed intraoperatively and utilized the signal processing methods from previous sections to identify potential CCEP responses.

5.4.2 Patient Overview

Data collection was performed with the same subject described in Section 4.4.2.

5.4.3 Collecting CCEPs intraoperatively

Following placement of the BIC device and wound closure, comprehensive single-pulse stimulation experiments were performed to identify the presence of CCEP activity. Impedances for all ECoG electrodes were observed to be below 1 k Ω . For the CCEP sweep, horizontally adjacent pairs of electrodes on both implanted ECoG grids were used to deliver bipolar stimulation. Stimulation was delivered using a 1 Hz frequency, 250 μ s pulse width, and 2.5 mA stimulation amplitude. A total of 50 trials were delivered for each contact pair and polarity reversals were randomly performed throughout stimulation.

5.4.4 Extending CCEP cleaning methods

To determine the possibility of the presence of CCEPs during intraoperative recordings, trials where stimulation was delivered to the motor cortex and channels capturing activity surrounding those stimulation contacts were prioritized for this preliminary analysis. Trials were grouped according to the stimulation polarity configuration used, prior to applying MBS and ICA methods to identify any evoked response to stimulation. An example of the raw and processed data from this procedure is shown in Fig. 5.10.

Upon comparing outcomes from these cleaning methods, no notable CCEP activity was observed. While it’s possible that this result is due to limited efficacy of the cleaning methods, as discussed in Section 5.3.6, another possible contribution behind a lack of CCEP responses is due to the influence of anesthesia. While CCEPs have been captured during the anesthetized state, higher stimulation amplitudes may be required to elicit a response and oscillatory components may be

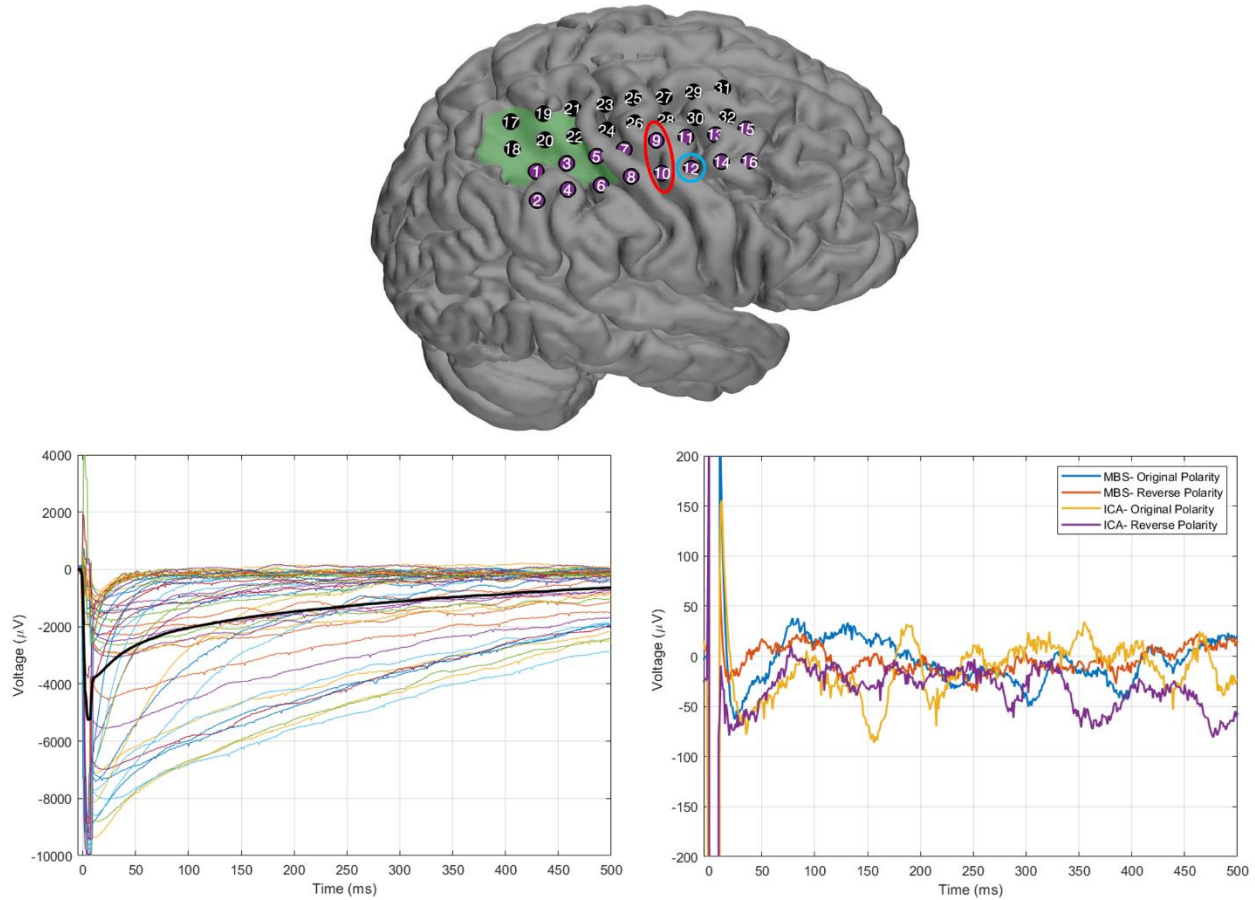


Fig. 5. 10 Example of preliminary intraoperative CCEP outcomes with the BIC system from a neighboring electrode (encircled in blue) following single pulse electrical stimulation over the motor cortex (encircled in red). (Lower left) Individual CCEP trials, depicted as colored traces, and their raw average, depicted in black, do not immediately show electrophysiological responses to stimulation. Characteristics of return to baseline behavior were similar to attributes observed during CCEP testing in saline. (Lower Right) Cleaning outcomes from applying MBS and ICA to better identify any CCEP activity. Individual trials were grouped according to polarity configuration and then both MBS and ICA were applied on categorized trials. Following both processing methods, no notable CCEP response was observed.

decreased compared to awake states [156], [157], [158]. Clinical time constraints posed limitations on the permutations of sweeps that could be performed to collect CCEPs. Future efforts will focus on validating the BIC's ability to capture CCEP activity by expanding the stimulation parameters used to provide more extensive stimulation sweeps while in the awake state. This will not only minimize the external factors influencing the presence of a CCEP, but also maximize the conditions under which an evoked response may occur.

5.5 Conclusions

In this chapter, we evaluated the research platform’s ability to capture CCEPs. simulations of CCEP experiments identified limitations of the BIC device and characterized its sensing functionality in the presence of stimulation. We determined that the time-course characteristic of the nonlinear post-stimulation artifact was dependent on stimulation configuration and impedance of the saline environment. Initial signal processing strategies to overcome the effects of stimulation and extract the CCEP signal were applied in both saline and in vivo datasets with mixed success. While additional testing will be required in order to fully assess the efficacy of the proposed signal processing techniques for robustly recovering CCEP activity, the methods presented establish initial feasibility of the proposed platform to observe neuroplasticity changes.

Chapter 6

Preliminary evaluation of neuroplasticity changes with a novel adaptive stimulation platform

As reviewed in Chapter 2, the mechanisms to engage neural plasticity are driven by temporal dynamics and emphasize the critical firing timing of neurons [32], [33] and the repeated coincident activity of these neurons [31], [75] to observe notable connectivity changes in neuronal populations. Considering how neurostimulation is one method to directly influence neuronal activity, a stimulation design considering oscillatory activity and centered around timing precision presents an approach that can induce neural plasticity changes in a more effective and targeted manner. The nature of these mechanisms motivates interest in adaptive, time-dependent stimulation. We previously introduced a beta phase-triggered stimulation paradigm, where stimulation is timed to a certain phase of neural oscillations, which has demonstrated targeted modulation of plasticity in both noninvasive [83] and invasive applications [22]. This adaptive algorithm approach demonstrates an improved stimulation delivery strategy to more effectively modulate brain connectivity as compared to open-loop methods that utilize fixed stimulation parameters. With the potential to be a more effective means to induce cortical reorganization, we will focus on further developing and evaluating this paradigm, by using the general use investigational platform and testbench introduced in previous chapters.

In this Chapter, I will discuss the implementation of a more robust design of the beta phase-triggered stimulation first implemented with OMNI-BIC in Chapter 4.1 Using the NeuroTest platform introduced in Chapter 4.4, I will review how we demonstrated the feasibility of performing the stimulation paradigm with the BIC in saline benchtop experiments. Following encouraging outcomes from this initial testing, beta phase-triggered stimulation was then performed at the patient bedside to explore the potential in modulating neuroplasticity mechanisms as captured by CCEP activity. The efforts presented in this Chapter aim to establish the potential to drive neuroplasticity effects but will not characterize functional or therapeutic outcomes from any observed plasticity changes. This Chapter includes published material in [125].

6.1 Implementation of beta phase-triggered stimulation

6.1.1 Design motivations

While the implementation of beta phase-triggered stimulation introduced in Section 4.1.3 yielded promising results in this preliminary evaluation, there are several limitations of this initial design to note:

Lack of stimulation artifact mitigation: The nature of stimulation artifact and its potential impact on extracting underlying activity of interest was not explored in the initial design proposed in Chapter 4.1. Considering the dominant influence of stimulation over neural activity and to account for the influence and distortion effects of stimulation, processing steps to mitigate the effects of stimulation artifact for reliable extraction of oscillations of interest must be incorporated.

Restriction to a limited frequency band: The fixed-point approach described previously to trigger stimulation is only effective for a very limited subset of frequencies. Due to the relatively wider range of the beta frequency band (12-30 Hz) and irregular nature of neural activity, this method would become ineffective when deviating from the regular 20 Hz test oscillation used prior. To better accommodate for any frequency within the beta band, alternative conditions for determining when to trigger stimulation must be identified.

Consideration of stimulation latency: From the preliminary benchtop testing, the reported stimulation latency range was about 3 ms [121]. While this stimulation paradigm targets a specific phase range of beta activity, allowing some tolerance with timing, higher beta band frequencies become less forgiving. As the target timing window for high beta becomes smaller, this latency variability becomes a limiting factor in stimulation performance. To maintain timing accuracy of stimulation delivery, the effect of stimulation latency and its variability must be considered.

Upon identifying these limitations, the goal of the second iteration of beta phase-triggered stimulation was to develop a more versatile and robust design for delivering this stimulation paradigm. Prior approaches have utilized online bandpass filters to extract oscillations of a target

frequency, and the Hilbert-Transform or zero-crossings to estimate the phase and trigger near-instantaneous stimulation along specific phases of neural activity [18], [159], [160], [161]. However, the CorTec BIC device introduces additional delays of approximately 22 ms [125] that minimize the feasibility of such approaches for targeting beta frequencies. Considerable delays are introduced from the stack of code and hardware between the application to trigger stimulation and the implanted device. These delays present the primary design and verification challenge in building a system capable of timing-dependent stimulation. The methods presented here automatically factor in the delay between stimulation command execution via the proprietary CorTec C++-API and generation of an electrical pulse.

6.1.2 Stimulation artifact mitigation

Due to the nature of large amplitude changes relative to neural activity, stimulation artifact can have significant impact on the performance of closed-loop stimulation delivery. Stimulation artifact removal and recovery from artifact continue to be challenging hurdles for isolating key biomarkers to carry out therapeutic closed-loop neuromodulation. Numerous solutions have been proposed to minimize the impact of stimulation artifact, including resilient front-end design, template subtraction, and computation-dependent processes [136], [137], [162]. However, some of these approaches are limited under specific conditions and may require certain hardware capabilities to employ these techniques. The BIC hardware design enables adjustable gain, allowing users to prevent saturation during stimulation. However, varying artifact morphology observed with the BIC device limits the use of techniques such as template subtraction, as signal distortion is likely to occur.

To mitigate the distortion effects of stimulation artifact while maintaining real-time performance, we applied a sample-and-hold approach, whereby individual samples associated with the stimulation artifact are removed and replaced with the sample prior to stimulation. Stimulation activity was detected by utilizing stimulation timing information provided by the CorTec API, which reflects the BIC’s stimulation state. In characterizing stimulation artifact in prior saline benchtop recordings, a stimulus waveform with an initial phase duration of 250 μ s generated 10-15 ms of artifact. For the purposes of this proof-of-concept, the blanking window was set to be 15 samples to ensure sufficient artifact removal.

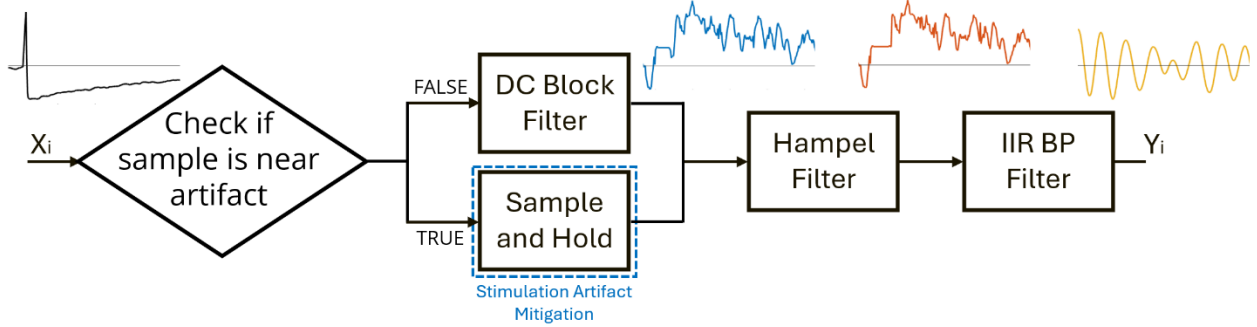


Fig. 6. 1 Block diagram of the signal processing pipeline. Raw samples (X_i) streamed from the BIC device are sent through this pipeline to determine underlying filtered beta activity (Y_i), sample by sample. Digital sample and holding was incorporated to mitigate stimulation artifact contamination. A segment of raw data with stimulation (black) and subsequent segments (blue, orange, and yellow) shows the outcomes of the segment after going through each signal processing component.

6.1.3 Signal processing

Stimulation artifact was observed to not only introduce distortion in samples close to stimulation onset but also introduce low-frequency fluctuations that influenced subsequent processing. Samples not close to stimulation onset were sent through a DC block filter with a 3 dB corner frequency of 8.75 Hz to minimize low-frequency fluctuations. A Hampel filter was then applied to identify and replace detected outliers with a moving window median. The signal then went through an infinite impulse response (IIR) bandpass filter to isolate neural activity within a frequency band of interest. We aimed to deliver stimulation during a particular phase of beta range frequencies, so beta activity within a particular peak frequency was extracted to execute beta phase-triggered stimulation. The IIR filter is a 2nd order Butterworth filter with a ± 5 Hz passband centered at the peak frequency. The complete signal processing pipeline, and the effects of each stage on a segment of neural data played back are visualized in Fig. 6.1.

6.1.4 Phase-locked loop design

To accommodate for this stimulation delay and deliver reliable beta phase-triggered stimulation, our approach is to utilize elements from a phase-locked loop (PLL) to dynamically adjust when to send the stimulation command during notable bursts of beta activity. PLL approaches have been previously utilized in phase-specific stimulation in both invasive [163], [164] and noninvasive applications [165], [166].

A block diagram of the implemented design via the OMNI-BIC is shown in Fig. 6.2. Our PLL design checked for two conditions prior to delivering stimulation. The first is an amplitude condition, such that stimulation is only delivered during persistent oscillatory periods. Filtered samples above a set, user-defined amplitude threshold satisfied the amplitude condition. Prior literature has set the threshold to be 3 times the standard deviation of filtered beta activity [22]. However, to assess feasibility, we lowered the threshold to be 1.5 times to ensure beta phase-stimulation would occur.

The second is a phase condition to control the delivery timing of a stimulation pulse. This phase condition determined if the phase of a filtered beta sample is close to the triggering phase, another parameter initialized by the user. As it was highly unlikely that the estimated phase of a sample would match the triggering phase, an updating history, with a window size of 3, containing the most recent filtered samples' phases was kept. If the oldest phase and most recent phase of that window were smaller and larger than the triggering phase, respectively, then the phase condition was satisfied. Bandpass filtered samples were used to estimate phase. Samples identified as positive zero-crossings were marked as the beginning of an oscillation and denoted as 0 degrees. Subsequent bandpass filtered samples then had their phase estimated using the average of estimated oscillation periods of recent beta activity and time difference from the preceding zero crossing. Due to

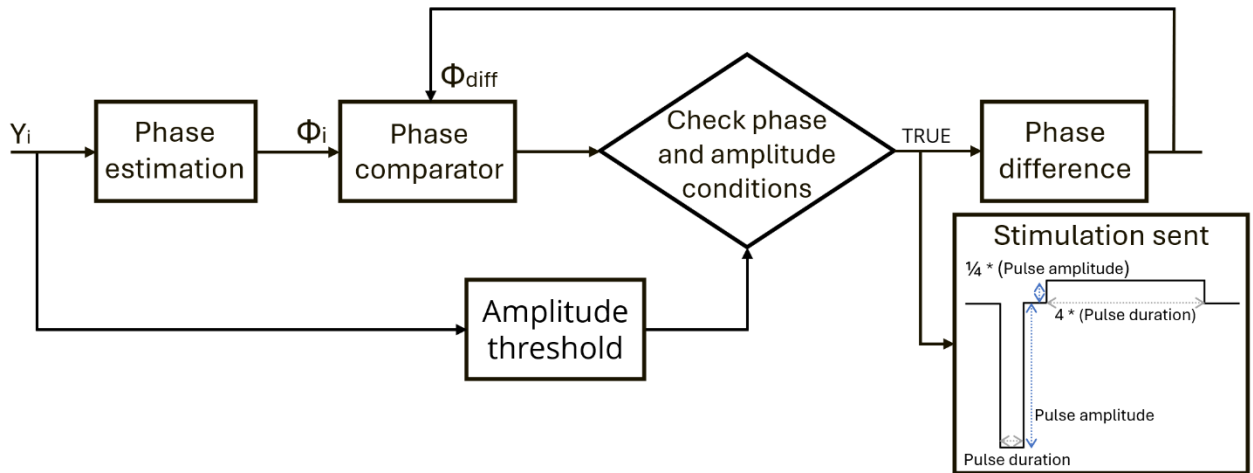


Fig. 6. 2 Block diagram for the phase-locked loop phase-specific stimulation design. Amplitude and estimated phase (Φ_i) of an incoming filtered sample were used to determine if a stimulation command is sent. The difference in the target phase and estimated phase of stimulation (Φ_{diff}) after delivery is used to adjust the triggering phase that determined the timing of stimulation.

Session	Peak β Frequency (Hz)	Thresholds (μV)	Mean Triggering Phase	Impedances (kΩ)
ST1	26	58	25	1-1.2
ST2	17	73	73	1-1.2

Table 6. 1 Parameters used for beta phase-triggered stimulation during saline benchtop experiments.

expected fluctuations in beta frequency, a window containing the most recent estimated oscillation periods was continually updated when an oscillation cycle was completed. If both the phase and amplitude conditions have been met, the device sent a stimulation command to deliver a single stimulation pulse. The BIC system only delivers asymmetric, biphasic, charge-balanced with a ratio of 4, stimulation pulses. The shape of the stimulation waveform delivered by the BIC is also depicted in Fig. 6.2. For the experiments demonstrating this design, detailed below, we delivered a stimulus with an initial phase of 250 μ s and 1 mA. Additional parameters used to inform beta phase-triggered stimulation for these experiments are further detailed in Table 6.1. When stimulation occurred, the triggering phase was updated using the difference between a set target phase value and the estimated phase of stimulation onset. The target phase is a flexible, user-defined parameter that can be set to time stimulation delivery during a specific phase range of interest. With the PLL design, we take advantage of this dynamic adaptation to enable timing corrections and account for system delays and mistimed stimulation delivery.

6.2 Verification of OMNI-BIC with the NeuroTest platform

6.2.1 Establishing feasibility in saline

Utilizing the NeuroTest benchtop (NTB) environment capable of simulating in vivo conditions to evaluate this second implementation of beta phase-triggered stimulation, saline experiments were performed to assess the PLL phase-specific stimulation design and stimulation artifact mitigation methods described above to provide beta phase-triggered stimulation during the depolarizing phase of beta. Two 2x8 ECoG paddles with Platinum-Iridium circular contacts set in a silicone substrate were used for benchtop evaluations. Each contact had a 2.4 mm diameter with neighboring contacts separated by 10 mm from center-to-center in both vertical and horizontal

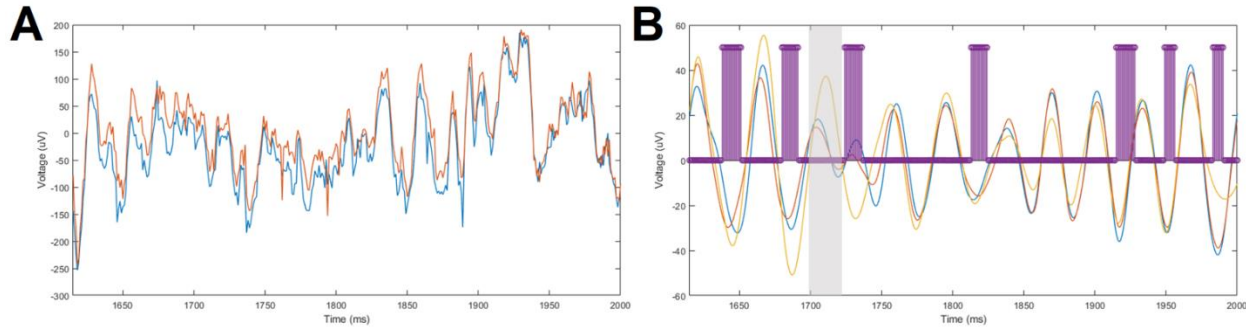


Fig. 6. 3 Recordings from saline benchtop evaluation experiments. A) Time-synchronized data obtained from separate recording-only sessions capturing the same segment of electrophysiology playback into saline. Synchronicity between the two recordings establishes repeatability and consistency across multiple benchtop recordings. B) Time-synchronized filtered data obtained from both recording-only sessions (blue and orange) and a session of beta phase-triggered stimulation (yellow) with observed stimulation activity (purple). Filtered oscillations are obtained from the same segment of electrophysiology playback depicted in A). This segment of beta phase-triggered stimulation indicates a limitation of the predictive nature of the PLL design to accommodate for the system latency. Satisfaction of the amplitude and phase conditions assumes a valid incoming beta oscillation target. The shaded oscillation demonstrates a scenario where criteria were satisfied and a stimulation response was triggered, but it was not a proper target for stimulation. However, these additional stimulation pulses are not hazardous and occur occasionally throughout evaluations.

directions. These paddles were connected to the BIC for recording and stimulation and placed in a saline tank with impedances ranging from 1-1.2 k Ω . Two horizontally adjacent contacts near the center of an ECoG paddle were selected for bipolar stimulation while the farthest contact from the stimulation pair was designated as the reference electrode. Resting state electrophysiology recordings, previously collected in a separate internal CorTec preclinical study with the BIC, were injected into a saline tank via the NTB. Files containing this data were read by the NTB, which then played back the neural data into saline and provided the neural input for the BIC system. Prior to delivering beta phase-triggered stimulation with the BIC, 5-minute recording-only sessions where the BIC sensed data injected into the saline tank by the NTB were performed. Offline power spectral density analyses of these 5-minute “resting state” recordings were used to determine distinct peaks within the beta frequency range, which were used as the center frequency for the IIR bandpass filter. After initializing the proper filter coefficients, the resulting filter was applied to the same 5-minute “resting state” recording to determine the amplitude threshold.

Initialization of the amplitude threshold and additional variables, including a target phase and initial triggering phase, for various components of our control algorithm were set in a JSON file which was read in via our custom research application. The research platform was evaluated by performing beta phase-triggered stimulation with this benchtop setup for 1 hour. Stimulation was delivered by the BIC to target the depolarizing phase of the filtered beta wave, identified as the region between the negative zero-crossing (defined here as 180 degrees) and the minimum of an oscillation (defined here as 270 degrees). The target phase of the PLL design was set to 210 degrees to maximize stimulation delivery during the depolarizing phase while accounting for possible timing delays of stimulation. Time-series outcomes of these benchtop evaluations are shown in Fig. 6.3.

6.2.2 Analysis of beta phase-triggered stimulation performance

Data were analyzed offline with a custom MATLAB script to characterize the outcomes of the beta phase-triggered stimulation from the playback of preclinical electrophysiology in saline and clinical demonstrations. Files created during beta phase-triggered stimulation contained raw and processed electrophysiology recordings in addition to stimulation and phase values for individual samples. Samples indicating stimulation onset were identified and their corresponding phases were used to create a polar histogram. Polar histogram plots were used to visualize stimulation phase distribution during the benchtop assessment and clinical demonstration. Additionally, we defined three metrics to characterize system performance while executing beta phase-triggered stimulation: stimulation response rate (SRR), how well the system responded to target oscillations; stimulation hit rate (SHR), the percentage of all stimulation landing during the target phase range; and successful stimulation response rate (SSRR), how well the system delivered beta phase-triggered stimulation. These metrics were calculated using Eq. 1-3 respectively, where s_{total} is the total number of stimulation responses observed, s_{target} is the total number of stimulation pulses delivered during the target phase region, and N_{beta} is the total number of target beta waves detected.

$$SRR = \frac{s_{total}}{N_{beta}} \quad (6.3)$$

$$SHR = \frac{S_{target}}{S_{total}} \quad (6.2)$$

$$SSRR = \frac{S_{target}}{N_{beta}} \quad (6.3)$$

Prior work with OMNI-BIC has identified that due to the wireless nature of the BIC's communication, exceptions can occur during BIC-operated stimulation. These exceptions can affect stimulation output, yielding missed stimulation. Calculations of the defined metrics above do include oscillations affected by these exceptions when quantifying N_{beta} . To better understand the effect of encountered exceptions during stimulation, we report miss rates. While it may be possible for missed stimulation to occur aside from exceptions, no such instances were observed in these recordings.

6.2.2 Outcomes from saline benchtop evaluation

We evaluated beta phase-triggered stimulation performance during injection of neural signals into saline. The injected datasets each had distinct peak frequencies within the beta frequency range. Saline-Test 1 (ST1) had a beta peak at 26 Hz and Saline-Test 2 (ST2) had a beta peak at 17 Hz. Recordings for each session were characterized and outcome metrics, using the filtered beta activity logged by the BIC, of the beta phase-triggered stimulation paradigm for saline benchtop demonstrations are shown in Table 6.2. The phase distributions of delivered stimulation pulses relative to the phase of the filtered beta signal are visualized in Fig. 6.4.

Despite having two different peak frequencies, stimulation outcomes from both saline sessions yielded a significant portion of stimulation pulses being delivered during the depolarizing phase of beta oscillations. The mean phase angle for stimulation was determined to be 210.43 ± 22.46 degrees for ST1 and 209.94 ± 21.21 degrees for ST2. The mean phase angle for both sessions aligns with the target phase of 210 degrees set for the PLL.

Session	Stim Response Rate %	Stim Hit Rate %	Successful Stim Response Rate %	Miss Rate %
ST1	97.53	94.76	94.25	1.94
ST2	97.96	95.37	94.94	1.59

Table 6. 2 Outcome metrics of beta phase-triggered stimulation from saline demonstrations

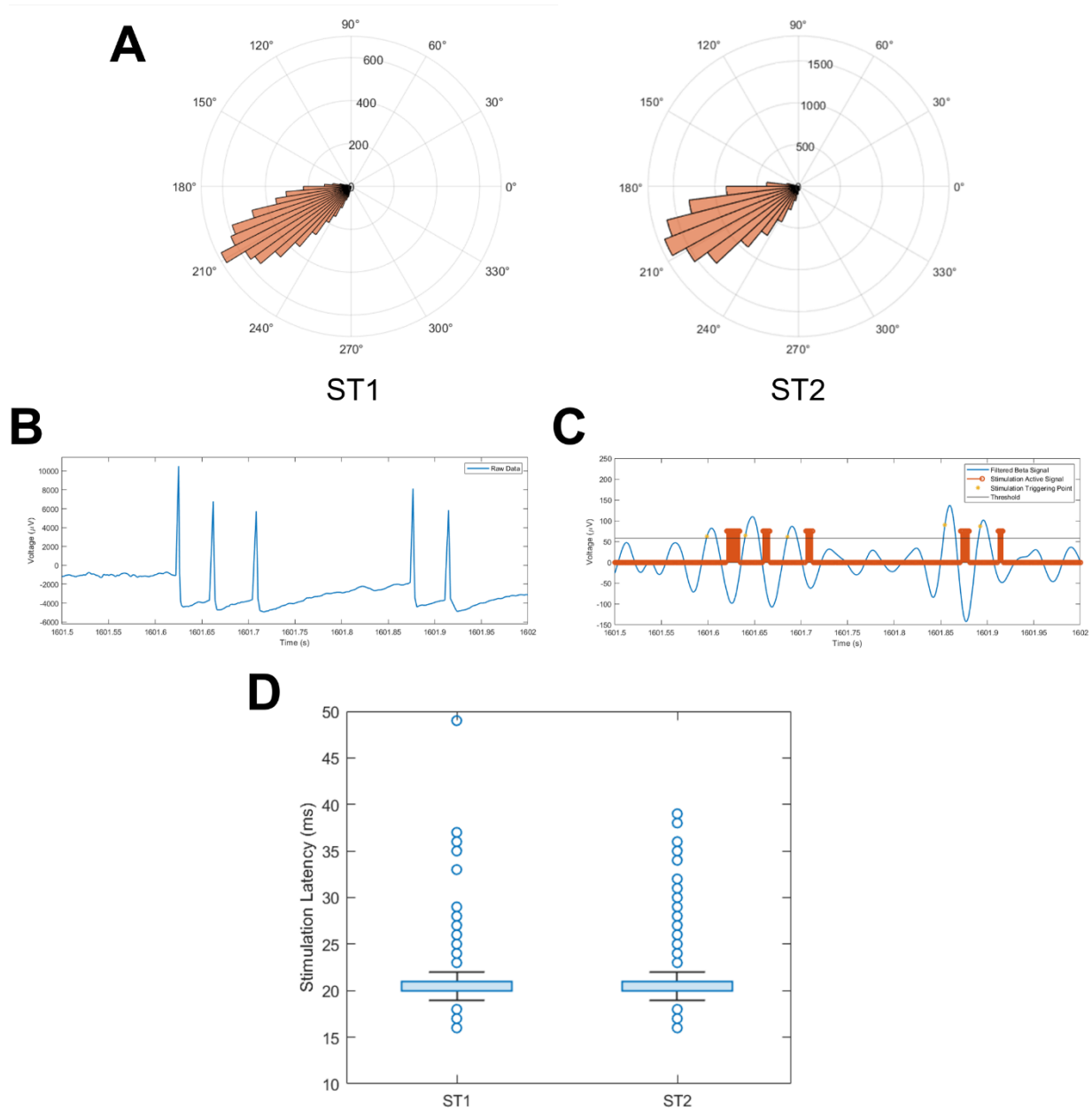


Fig. 6. 4 Outcomes from benchtop demonstrations of phase-triggered stimulation with the BIC device. A) Polar histograms of the phase angle at which stimulation occurred along the filtered beta signal while playing back preclinical ECoG data. B) Time series plot of raw recorded signals in a benchtop experiment with observed stimulation artifact and playback of previously recorded electrophysiology (collected from CorTec BIC devices in ovine models) injected into the saline tank. C) Time series plot of filtered beta activity and stimulation timing synchronized with (B). Samples that satisfy the phase and amplitude conditions of the implemented phase-locked loop design are denoted in yellow and indicate when a stimulation command is initiated. D) Boxplots of latencies between initiation of a stimulation command and stimulation delivery across the beta phase-triggered stimulation sessions.

Saline assessments also observed timeout exceptions, which affected beta phase-triggered stimulation delivery. Throughout the 1-hour stimulation sessions, ST1 missed 1.94% while ST2 missed 1.59% of valid oscillations.

6.2.3 Discussion

In this work, we addressed some of the vulnerabilities in the first iteration of development and evaluation with the OMNI-BIC, specifically with regards to beta phase-triggered stimulation. Via the OMNI-BIC, we implemented components to create a customized pipeline that enabled the BIC to robustly identify beta oscillations of interest and to appropriately time stimulation delivery. We then evaluated the system and algorithm’s ability to target the depolarizing phase of beta frequency oscillations in real-time within saline benchtop experiments with clinically relevant electrophysiology.

Previous applications of phase-triggered stimulation in the clinical space [18], [163], [167], [168] have similarly developed real-time processing and control policies to timely deliver stimulation. However, these applications of phase-triggered stimulation targeted lower-frequency oscillations, such as theta (4-7 Hz) and alpha (8-14 Hz) frequency bands. The systems presented in these applications, though maximizing the accuracy of phase estimations through various approaches, have more tolerance with timing constraints, considering the longer wavelengths of interest. Phase-triggered stimulation has been used to target specific phases of cortical beta oscillations within non-human primates [22]. However, this preclinical work utilized research-grade systems and connector solutions to record and stimulate from implanted electrodes, factors that may limit therapeutic investigation and potential translational impact. Along with the current state of fully implantable systems, which do not have the features to support the necessary time domain analysis for temporally driven paradigms, the BIC supplements the device landscape by providing a new set of tools within investigational research. The efforts presented here demonstrate the capabilities of the BIC platform to realize algorithms that are not currently feasible with other investigational devices. Furthermore, this system streamlines future therapeutic investigation of timing specificity and, to a certain degree, provides the necessary processing capacity achieved by bulkier research-grade systems. Although there is a tether required to power and operate the device, previous work

with the BIC has also presented miniaturization of the separate PC [119] to facilitate mobility during device use, potentially mirroring freedom of movement as seen with fully implantable neurostimulators.

The design used to execute beta phase-triggered stimulation in benchtop experiments observed robust delivery of stimulation during the desired depolarizing phase range ($> 80\%$), despite varying target frequencies across the beta frequency band. Additionally, the phase distribution was clustered around the initialized target phase of 210 degrees for all sessions, as seen with the narrow spreads depicted by the polar histograms in Fig. 6.4A and B. Initial evaluation with the BIC in Section 4.3.2 showed an approximate 22 ms latency between when a stimulation command is sent and when stimulation is observed- a significant hurdle considering the period of a high-beta 30 Hz oscillation is only 33.3 ms. Mean latencies across saline demonstrations (ST1: 20.61 ± 2.65 ms; ST2: 20.75 ± 2.43 ms) is consistent with this previous report of stimulation latency.

Although our additional signal processing components did not introduce significant timing delays, use of a PLL design accommodated for such timing concerns. By dynamically adapting the timing of triggered stimulation, the BIC system addresses not only potential time delays, but also adjusts stimulation delivery for a wide range of frequencies. Our signal processing pipeline also demonstrated the ability to simultaneously record and stimulate while maintaining adaptive stimulation performance. The stimulation artifact mitigation technique employed here minimized distortion from stimulation artifact whereas additional software components allowed recovery from residual stimulation effects. Customization of these parameters for these signal processing components enable case-specific tuning to ensure extraction of activity of interest.

6.3 Evaluation of beta phase-triggered stimulation in vivo

6.3.1 Transitioning from benchtop to in vivo

After confirming successful saline benchtop outcomes with the beta phase-triggered stimulation paradigm using the BIC, we demonstrated the delivery of the paradigm in human patients. While experiments with the NeuroTest platform were representative of an in vivo environment, we must recognize the heterogenous and complex nature of the true electrode-tissue interface that isn't

captured in a benchtop testbed. In evaluating the adaptive paradigm via in vivo testing, there is more thorough evaluation of its design and better characterization of real-world performance.

6.3.2 Patient overview

Two patients with epilepsy undergoing seizure monitoring at Harborview Medical Center were approached for their consent to participate in a closed-loop stimulation study approved by the University of Washington Institutional Review Board. The patients, referred to as Clinical Subject 1 (CS1) and Clinical Subject 2 (CS2), were implanted with sEEG electrodes as part of standard clinical monitoring procedures. Electrode locations were selected for clinical monitoring purposes and varied between subjects. Additional patient information and relevant paradigm parameters are detailed in Table 6.3. Electrode placement for each subject are shown in Fig. 6.5.

6.3.3 Experimental protocol

At the patient’s bedside, the BIC system accessed a subset of the implanted sEEG electrodes through externalized extensions with clinical touch-proof connections. The subset of electrodes to interface with the BIC device was selected after image reconstruction identified a cortical motor region of interest and a diagnostic sweep identified contacts with cortical connectivity. An evoked potential sweep was performed to narrow down electrodes within the selected subset for use in sensing and stimulation. Electrodes comprising the stimulation configuration that elicited CCEP activity were identified for stimulation in beta phase-triggered stimulation. An sEEG contact that observed CCEP from the stimulation electrodes was appointed as the sensing electrode for the adaptive stimulation paradigm. All recording and stimulating sEEG electrodes reported impedances under 1 k Ω .

An initial resting state recording was performed with the BIC. The recording was then processed to identify peaks within the beta frequency band. The frequency and amplitude threshold for the beta phase-triggered stimulation paradigm was selected to ensure triggered stimulation responses. After the stimulation parameters for the paradigm were set, low-frequency stimulation was first delivered to determine a baseline state for CCEPs. Beta phase-triggered stimulation was delivered for 5 minutes and followed by another set of low-frequency CCEP stimulation to obtain a post-stimulation state.

6.3.3 Performance of beta phase-triggered stimulation

Outcomes from clinical beta phase-triggered stimulation were obtained following Chapter 4.6.2. Resting state analyses identified beta frequency peaks at 20 Hz for Clinical Subject 1 (CS1) and 22 Hz for Clinical Subject 2 (CS2). Beta phase-triggered stimulation was delivered continuously for the entire 5-minute period. The mean phase angle for stimulation was 209.83 ± 32.70 degrees for CS1 and 210.03 ± 36.08 degrees for CS2. Phase distributions and outcome metrics of delivered stimulation pulses for both clinical participants are visualized in Fig. 6.6A and Table 6.4. A segment of beta phase-triggered stimulation is also shown in Fig. 6.6B.

Timeout exceptions were also observed during clinical beta phase-triggered stimulation delivery. Missed stimulation was higher for clinical subjects in comparison to benchtop sessions. CS1 missed 6.89% while CS2 missed 6.13% of valid targets.

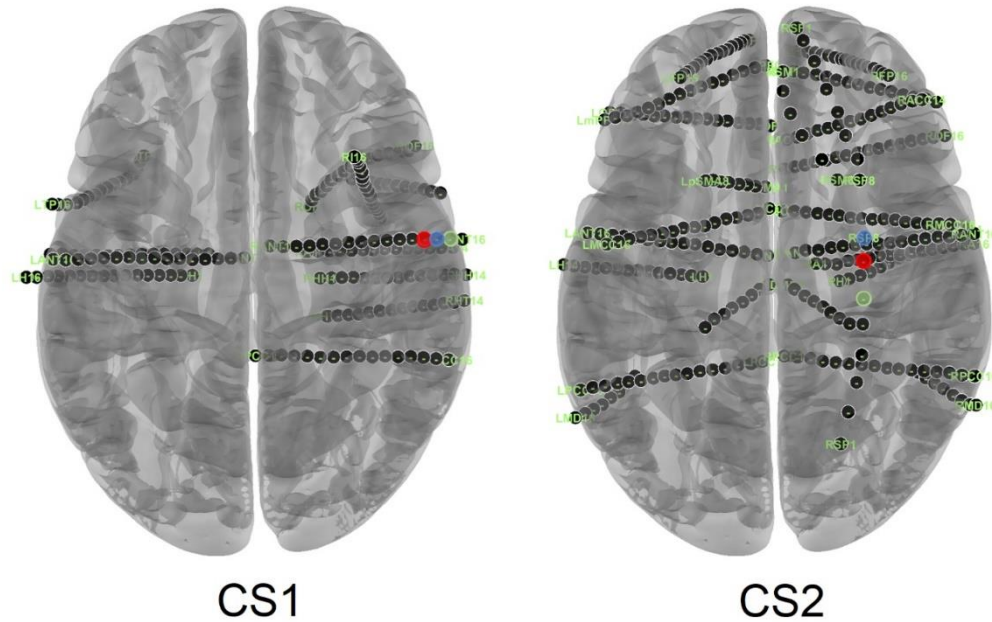


Fig. 6. 5 Electrode localization for CS1 (left) and CS2 (right). Electrodes used for sensing beta activity are shaded in green. The cathode and anode used for beta phase-triggered stimulation are shaded in red and blue, respectively. Implanted electrodes selected for beta phase-triggered stimulation with CS1 are intraparenchymal while identified electrodes for CS2 are placed over the surface of the cortex.

Subject	Peak β Frequency (Hz)	Thresholds (μ V)	Mean Triggering Phase	Impedances (k Ω)	Electrodes Region
CS1	20	10	68	0.9-1	Right precentral gyrus
CS2	22	15	44	0.9-1	Right cerebral cortex

Table 6. 3 Parameters used for beta phase-triggered stimulation with patients in the EMU.

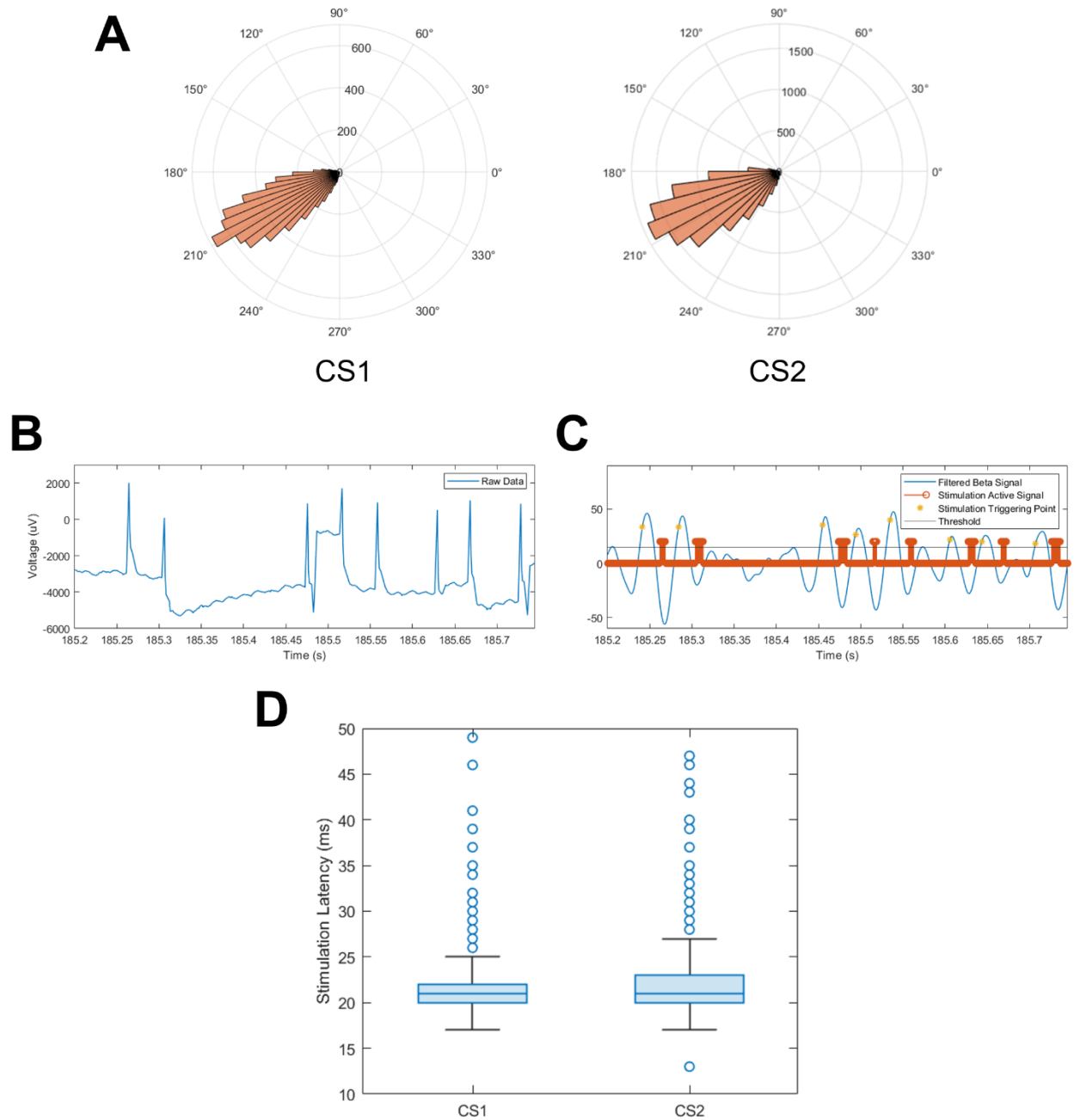


Fig. 6. 6 Outcomes from clinical demonstrations of beta phase-triggered stimulation in the EMU. A) Polar histograms of the phase angle at which stimulation occurred along the filtered beta signal while recording sEEG activity. B) Time series plot of raw recorded signals during the 5-min beta phase-triggered stimulation session. C) Time series plot of filtered beta activity and stimulation timing synchronized with (B). Samples that satisfy the phase and amplitude conditions of the implemented phase-locked loop design are denoted in yellow and indicate when a stimulation command was initiated by the BIC device. D) Boxplots of latencies between initiation of a stimulation command and stimulation delivery across both clinical beta phase-triggered stimulation sessions.

Subject	Stim Response Rate %	Stim Hit Rate %	Successful Stim Response Rate %	Miss Rate %
CS1	93.10	89.17	83.02	6.89
CS2	93.87	86.94	81.61	6.13

Table 6. 4 Performance metrics from beta phase-triggered stimulation sessions in the EMU.

6.3.4 Discussion

Following robust saline benchtop outcomes, we assessed the feasibility of the beta phase-triggered stimulation paradigm with the BIC, the adaptive stimulation paradigm implemented within OMNI-BIC was performed with patients at the bedside. Following the same protocol outlined in Chapter 4.6.1 and 4.6.2 for identifying stimulation parameters for the paradigm and analyzing outcomes from the in vivo demonstrations, similar phase-specific delivery of stimulation was observed.

While we observe robust beta phase-triggered stimulation in both saline and clinical conditions, there is a drop in performance when transitioning to the in vivo environment. One contributor to this discrepancy is the initialization of parameters for the beta phase-triggered stimulation paradigm using preliminary resting state recordings. Natural fluctuations in neural activity may make certain initializations suboptimal when delivering adaptive stimulation for a longer timescale, a factor that is not accounted for within benchtop recordings. Given the timing sensitivity of this paradigm, more responsive approaches to updating certain parameters of the PLL design may be needed to preserve beta phase-triggered stimulation performance. Though we adjust for fluctuations temporally by updating the triggering phase of the PLL, other aspects of the paradigm design, such as the amplitude threshold, may need to be intermittently updated.

In addition to the dynamic nature of oscillations, factors with respect to the platform may also be responsible for the observed difference in performance. The average stimulation latencies between benchtop and the EMU, depicted in 6.3D and 6.5D, respectively, were similar. However, there is a larger range in stimulation latencies observed in experiments performed in the EMU. The range of stimulation latencies from benchtop experiments is about 3 ms while that of clinical experiments is approximately 10 ms. This increased range between stimulation command initiation and stimulation delivery understandably yields increases in mistimed stimulation, while also affecting timing corrections made during beta phase-triggered stimulation. Furthermore, we must

consider the impact of exceptions. Exceptions with the BIC system have been previously documented [121] and are typical when performing stimulation with the device. As stimulation commands are initiated via OMNI-BIC, exceptions thrown by the BIC device interfere with the execution of those commands, yielding delayed or no stimulation responses. These exceptions are indicative of system states where stimulation cannot be delivered when requested. Increases in the percentage of exceptions affecting stimulation commands between saline and clinical experiments point to exceptions as being another contributing aspect to this performance difference. Given how consistent these measures are within a collection setting, it is reasonable to attribute the influence of the data collection environment on the performance of beta phase-triggered stimulation. The presence of clinical equipment and the noise introduced can potentially affect wireless communication protocols used for time-critical operations with the BIC. This highlights the potential sensitivity of the BIC device and how external environments may influence operation. Our clinical setup also utilized externalized sEEG leads with custom connections that can further introduce noise. In a case where the BIC is fully implanted within a patient, we would expect the platform to perform more robustly as external factors will likely have a less significant impact on stability during operation.

Another caveat to consider is the predictive approach of the PLL design to execute phase-triggered stimulation. The weakness of this design manifests with notable changes in beta activity and is exemplified when: 1) cases where beta oscillations sufficiently larger than the amplitude threshold do not trigger a stimulation response and 2) occasions where additional stimulation is delivered in response to oscillations that seemingly satisfy target criteria, but are not the proper targets to respond with stimulation. Particularly, they raise a concern about how this may affect the ability to deliver beta phase-triggered stimulation consistently. In narrowing down these specific instances, we see that such events occur due to suboptimal criteria during beta phase-triggered stimulation. For example, the triggering phase may be set earlier such that the amplitude of the specific sample does not yet satisfy the amplitude threshold. By the time a sample of an oscillation does start to satisfy the amplitude condition, the phase of that and subsequent samples is past satisfying the phase condition. This can be further influenced by our phase estimation method, as potential errors in estimation can introduce further shifts in the phase. The conditions to trigger

stimulation created by these suboptimal criteria can pose limitations of the integrity of beta phase-triggered stimulation performance. And while the methods employed here are sufficient and translated to robust depolarizing beta phase-triggered stimulation in the presented demonstrations, modifications to the current approach can be incorporated to improve the responsiveness of this adaptive algorithm. Revisiting how phase shifts are determined to better reduce phase estimation variance and implementing dynamic amplitude thresholds with fluctuating activity can minimize the likelihood of similar events occurring in the future.

One key limitation to consider with respect to our implemented algorithm design emerges during operation at higher stimulation amplitudes. With the BIC system, recovery from stimulation artifact at high stimulation amplitudes yields exponentially decaying offset curves, significantly impacting filtered oscillations of interest. The artifact recovery period observed in these demonstrations follows an exponential trend, however, aspects of our signal processing pipeline minimize the effect of this offset. Stimulation amplitudes higher than those employed here may observe higher frequency drift, potentially overwhelming the effect of the implemented components discussed here. One potential approach to overcome this hardware limitation is through the integration of more specialized filters or signal processing techniques to better target these offsets and provide more robust recognition of underlying oscillations. We anticipate that with the OMNI-BIC, development of such components can be readily incorporated into the current design to enable adaptive stimulation experiments at higher amplitudes.

Another consideration to account for is the extension of the presented design to additional frequency bands. While the demonstrations targeted beta frequency oscillations, we can expect this design to be immediately applicable for lower frequency activity, including theta and alpha frequency bands. However, this algorithm could not be extended for higher frequencies, such as in the higher gamma frequency band. With the identified system delays of the BIC, the current design would not be able to perform phase-triggered stimulation with oscillations above 30 Hz. Possible communication drops during operation can further impact the current design's abilities for use with higher frequency bands. To accommodate for higher frequency oscillations, design changes within the OMNI-BIC could be implemented, by utilizing longer history windows to determine if conditions have been met to trigger stimulation.

Our results establish the feasibility in utilizing the BIC and OMNI-BIC platform to successfully deliver beta phase-triggered stimulation. The ability to design and deliver phase-triggered stimulation is particularly notable, given the lack of available clinical systems to deliver this subcategory of adaptive stimulation [169], [170]. Additionally, this work is the first demonstration of the BIC system recording and stimulating with clinical patients, indicating the potential of these tools to support broader novel, time-dependent stimulation designs, to improve therapeutic efficacy of neuromodulation, and to aid in the investigation of the mechanisms underlying disease-affected networks and their treatment through stimulation.

6.4 Assessing short-term neuroplasticity outcomes

6.4.1 Patient overview

Data collection performed from one of the patients, specifically CS2, approached in Section 6.3.1 is described in the following sections. For additional information regarding this subject, refer to Section 6.3.2.

6.4.2 Experimental protocol

For these stimulation experiments, additional low-frequency stimulation CCEP experiments were conducted before and after beta phase-triggered stimulation was delivered to determine if the adaptive stimulation paradigm induced any short-term modulation in CCEP activity. A timeline for assessing short-term neuroplasticity modulation with BIC-delivered beta phase-triggered stimulation is detailed in Fig. 6.7.

To prioritize the ability to determine if any neuroplasticity modulation could be observed, the TDT system was used for CCEP data collection. This aimed to minimize ambiguities when analyzing the CCEP data post-hoc. Stimulation parameters for CCEP experiments were 1 Hz frequency, 200 μ s pulse width, and 4 mA stimulation amplitude. Polarity reversals were randomly performed throughout stimulation to minimize the effect of entrainment, and a total of 100 pulses were delivered for each CCEP session.

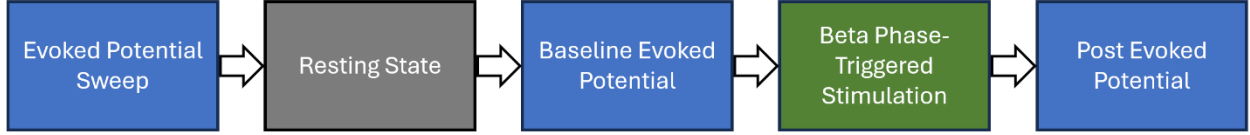


Fig. 6. 7 Sequence of data collection experiments to evaluate the short-term neuroplasticity effects observed with beta phase-triggered stimulation, as measured by CCEP activity.

6.4.3 Characterization of CCEP outcomes

Recordings obtained from CCEP collection were segmented into 1 s epochs, based on the timing of stimulation artifact, and divided into pre- and post-beta phase-triggered stimulation conditions. The segmented data was further grouped based on the polarity of stimulation contacts, denoted as Polarity 1 and Polarity 2, within each condition. This additional subdivision was done in order to determine if modulation of CCEP components was due to stimulation configuration, rather than from the adaptive stimulation paradigm. CCEP trials were then averaged without additional signal processing to minimize possible distortion of CCEP components. An equal number of CCEP trials between each permutation of condition and stimulation polarity were used to comprise these averages. With this pipeline, a total of six CCEP averages were obtained: pre-Polarity 1, pre-Polarity 2, post-Polarity 1, post-Polarity 2, pre-All Trials, post-All Trials.

CCEP components were identified by comparing oscillatory activity between CCEP averages across different polarity configurations. Any activity that inverted between the two polarities were eliminated, as only artifacts reverse when performing a polarity reversal and are not considered consistent neural activity. Remaining oscillatory components were then qualitatively assessed for consistent modulation between the pre- and post-stimulation conditions. While there were numerous oscillatory components comprising the evoked response, only a select subset of components observed to experience consistent modulation were used to assess connectivity changes. To assess the degree of modulation of the identified CCEP components, changes in the components' amplitudes, within their respective stimulation polarity configurations, were compared between the pre- and post-beta phase-triggered stimulation states. In addition to characterizing amplitude changes from the average CCEP responses, statistical tests to assess the nature of distributions between the before and after states were performed. Two-sample Kolmogorov-Smirnov tests were used to further determine if the before and after distributions of

trials were distinct. This statistical test was used to clarify if any observed amplitude modulation in the CCEP components could be due to alternative factors, such as high variation in trial distributions, in lieu of connectivity changes from adaptive stimulation.

6.4.4 Short-term neuroplasticity outcomes

CCEP outcomes collected with the TDT system identified distinct oscillations in the CCEP response that were believed to be electrophysiological up to 500 ms post-stimulation. Further inspection of these oscillatory components focused on CCEP components evoked within the first

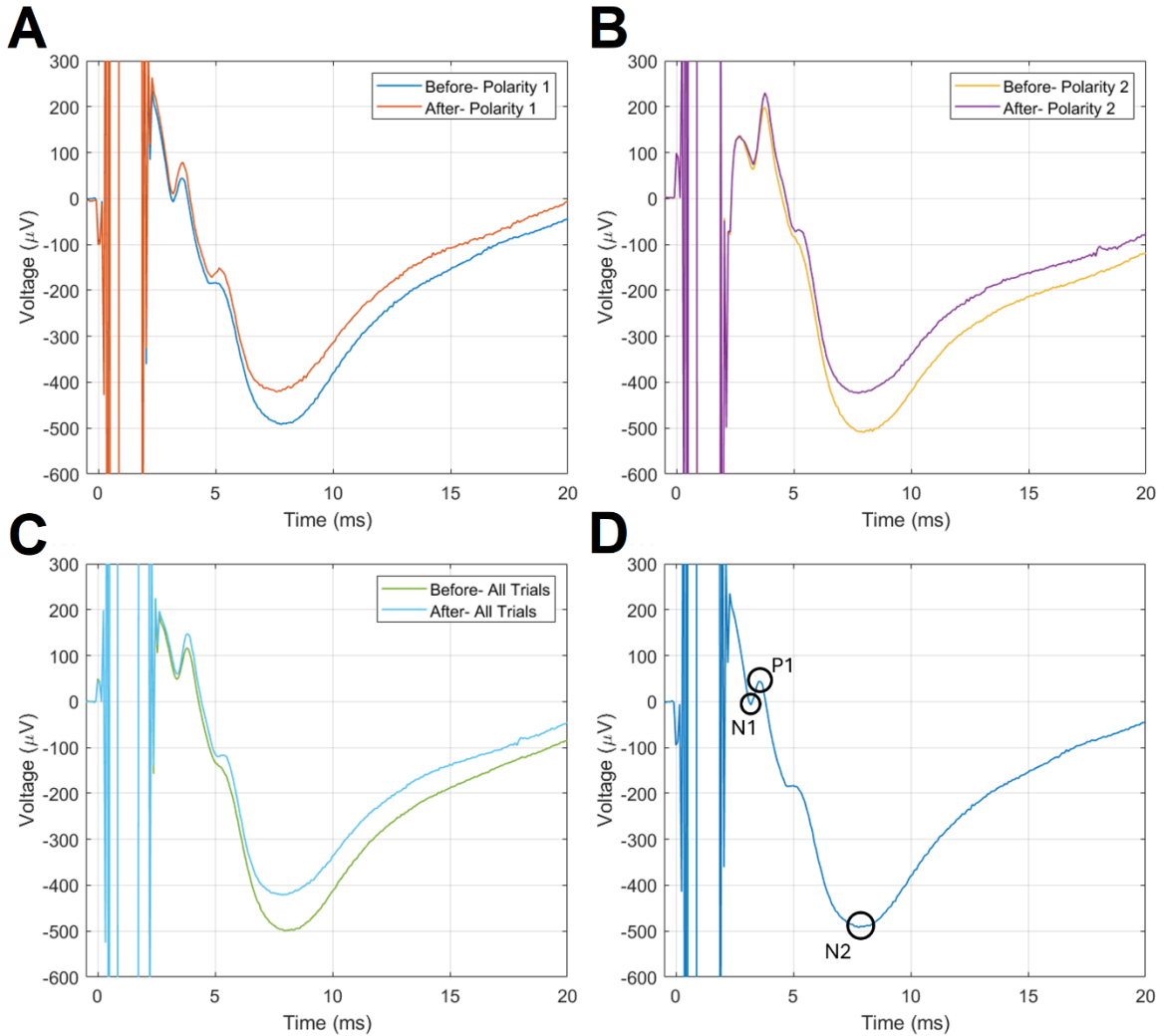


Fig. 6. 8 Raw averages of CCEP activity collected with the TDT system before and after beta phase-triggered stimulation. Zooming into the first 30 ms following stimulation identified early-latency CCEP components demonstrating amplitude modulation between before and after stimulation conditions within the A) original polarity, B) reverse polarity, and C) across all trials. D) Oscillatory components, denoted as N1, P1, and N2 are highlighted on one of the CCEP averages obtained from A).

Stimulation Configuration	N1	P1	N2
Polarity 1	0.3584	0.0171*	0.0021*
Polarity 2	0.2408	0.0317*	p < 0.001*
All Trials	0.2606	0.1930	p < 0.001*

Table 6. 5 Statistical results from comparing before and after beta phase-triggered stimulation distributions of the amplitudes of identified oscillatory components of CCEP activity in Fig. 6.8. Asterisks identify p-values that indicate significant differences between distributions of pre- and post-stimulation states.

20 ms following stimulation. A negative peak at approximately 3.2 ms, a positive peak around 3.7 ms, and another negative peak about 8 ms following stimulation, were identified and labelled as N1, P1, and N2, as shown in Fig. 6.8A-D. These components were analyzed to determine potential corticocortical connectivity effects from beta phase-triggered stimulation.

When comparing pre- and post-stimulation states, N1 and N2 components both observed a decrease in magnitude, while the P1 component observed an enhancement. Amplitude changes and statistical outcomes from the two-sample Kolmogorov-Smirnov test are shown in Table 6.5. Results from the two-sample Kolmogorov-Smirnov tests indicated significant differences for the P1 and N2 components between before and after beta phase-triggered stimulation conditions. It should be noted that statistical outcomes observed for the All Trials condition clarified that polarity configuration could have an influence on identifying notable amplitude modulation of CCEP components.

6.4.5 Discussion and future directions

In conjunction with the feasibility work performed in Chapter 6.3, this Section evaluated the potential for the investigational platform to execute beta phase-triggered stimulation and induce neuroplasticity effects with this adaptive stimulation paradigm in vivo. Using an established research-grade electrophysiology system to minimize ambiguity, we captured CCEP activity, the identified biomarker of interest, and were able to characterize notable connectivity changes following adaptive stimulation delivery via amplitude modulation of early-latency CCEP components. The work presented in this Chapter establishes the groundwork towards facilitating

clinical characterization of the relationship between corticocortical connectivity and phase of cortical oscillations via the BIC system.

While we observed CCEP modulation, we must acknowledge considerations when interpreting these reported outcomes. First, we are unable to distinguish whether this modulation is specifically due to the timing of stimulation delivery, or the presence of stimulation overall. While prior work has demonstrated that non-phase specific stimulation did not yield any notable modulation of CCEP activity [22], there has also been reports of repetitive stimulation inducing excitability changes in CCEPs [152]. It is important to note that the conditions under which stimulation was delivered, such as total stimulation duration, may be alternative variables contributing to these outcomes. Nonetheless, future work ascertaining the explicit impact of stimulation timing with the proposed platform will contribute towards further characterization of the relationship between phase and neuroplasticity mechanisms.

Secondly, although the underlying mechanism behind the observed modulatory effects is not a focus of this work, it's important to highlight how the simultaneous enhancement and depression of CCEP activity from depolarizing beta phase-specific stimulation diverges from reported findings with this adaptive stimulation paradigm. One preclinical study explored the relationship between stimulation along particular phases of cortical beta oscillations and corticocortical connectivity outcomes, characterizing a distinct, bidirectional plasticity effect following hyperpolarizing and depolarizing phase stimulation [22]. However, differences in CCEP outcomes between that study and this work may vary due to differences in the time course of beta phase-triggered stimulation applied, considering that the duration of neuromodulation impacts characteristics of neuroplasticity effects [89], [171], [172]. However, it's crucial to consider that oscillatory components comprising CCEPs can be reflective of different circuitry and capture unique dynamics, thus consistent potentiation or depression across all oscillatory components may not be plausible. This nuance may reflect the need for patient-specific characterization and tuning prior to determining how best to drive desired connectivity outcomes.

Ultimately, outcomes from this work demonstrate the capacity for the OMNI-BIC and BIC platform to drive neuroplasticity effects using stimulation approaches. Considering the exploratory

nature of the presented findings, future efforts will be required to elucidate upon the presented considerations. To better characterize the influence of stimulation timing on inducing neuroplasticity effects, additional experiments should focus on performing beta phase-triggered stimulation targeting both the depolarizing and hyperpolarizing phases of beta oscillations to replicate the preclinical work done in Zanos et al. [22]. Modifications to the implemented paradigm design in Chapter 6.1 can be readily made to easily enable this exploration into the effect of phase specificity. Furthermore, as the therapeutic effects of plasticity modulation were not examined in this work, additional investigation would be needed to characterize behavioral changes from driving such plasticity changes. Considering the crucial role of neuroplasticity in facilitating functional improvements, such mechanisms capable of driving cortical reorganization have promising implications for promoting recovery from neural injury, including stroke.

6.5 Conclusions

Building on the previous development and verification efforts, we presented a more robust design for implementing depolarizing beta phase-triggered stimulation via OMNI-BIC. We observed consistent stimulation delivery during the target phase region in both saline and in vivo experiments, establishing the feasibility of the paradigm. In addition to verifying beta phase-triggered stimulation, we determined if the implemented paradigm could induce plasticity effects via modulation of CCEP components. In comparing between pre- and post-stimulation states, we observed significant modulation of components. While additional investigation is needed to better characterize the nature of this modulation and its implication towards behavioral outcomes, the presented work in this chapter provides a preliminary demonstration of the proposed platform to facilitate neuroplasticity-inducing neuromodulation research.

Chapter 7

Conclusion

The work in this dissertation presented development and evaluation efforts towards a promising solution to support advances in adaptive neuromodulation and its potential to improve upon current therapies for neural injury. Centered around the investigational CorTec BIC device, I have proposed an investigational research platform capable of facilitating clinical investigation of novel adaptive stimulation algorithms. Following its development, the platform was then assessed for its capability to support neuroplasticity research, ultimately culminating into a preliminary demonstration of using the proposed platform’s abilities to carry out neuroplasticity-inducing adaptive neurostimulation research. Below we will summarize the aims that guided these research endeavors and the significant outcomes from each objective.

7.1 Review of Aims

7.1.1 Aim #1: Develop and evaluate an investigational research platform capable of enabling exploration of adaptive stimulation

In Chapter 3, we identified the CorTec BIC as a device with unique features not currently available within the implantable neuromodulation device space. To enable customizable exploration of adaptive stimulation algorithm design, the aim was to develop an interface that would allow developers full access to the capabilities of the system. However, recognizing the lack of standardization in software design within the research space and how this can impede dissemination and extension efforts with the BIC device, we identified a preexisting software framework, OMNI, to inform the architecture design for interfacing with the BIC. In Chapter 4, we utilized the OMNI framework to develop the OMNI-BIC interface and demonstrated its versatility by implementing various functionalities, including open-loop and adaptive stimulation paradigms.

Chapter 4 also explored initial evaluation of the OMNI-BIC and BIC platform, assessing system performance within both a benchtop development environment and intraoperative in-human case.

Communication characterization from these evaluations demonstrated viability of the platform and benefits from implemented functionalities such as data loss interpolation. Furthermore, we were able to confirm the platform’s ability to execute a diverse array of stimulation paradigms. While there has yet to be use of the proposed platform in the true intended use case, these initial outcomes are indicators of a promising research tool equipped with common research functionalities and its capacity to realize custom capabilities.

In addition, Chapter 4 introduced the NeuroTest platform, a benchtop testing rig capable of neural playback and recording within a saline environment emulating the tissue-electrode interface, aiming to support evaluation initiatives for neuromodulation experiments. To demonstrate how this testbed can promote benchmarking and standardization in evaluation efforts, the NeuroTest was deployed to different sites and characterized. We determined that this testing environment was stable and exhibited similar characteristics despite testing unique electrophysiology systems for distinct applications, proving a useful tool for informing experimentalists prior to beginning in vivo experiments.

7.1.2 Aim #2: Characterize the platform’s ability to assess neuroplasticity changes

Utilizing the tools presented in Chapter 4, we assessed the platform’s ability to capture CCEP activity, an established biomarker of interest for characterizing neuroplasticity effects. To establish that the proposed platform is a comprehensive tool that can be applied to neuroplasticity research, we set to determine if the BIC is capable of reliably recording this measure.

In Chapter 5, we introduced the NeuroTest testbed’s ability to simulate CCEP experiments within saline and characterized sensing limitations of the BIC system under the presence of stimulation. These benchtop experiments revealed the principal signal processing challenge to resolve in order to identify CCEP activity. We subsequently identified signal processing methods to overcome the sensing challenges and tested the efficacy of these techniques on CCEP data collected with patients in the EMU and intraoperatively during clinical implantation of the BIC device. The processing techniques yielded mixed outcomes, suggesting a need for additional testing. However, this work elucidated the interpretation of these clinical outcomes and provided direction towards designing future evaluation efforts to improve the pipeline for collecting CCEP activity with the BIC system.

7.1.3 Aim #3 Assess the platform's ability to investigate a novel approach to modulating neuroplasticity outcomes

Finally, to assess the ability for the investigational platform to facilitate neuroplasticity research, we aimed to determine the capacity of the investigational platform to induce plasticity effects using adaptive stimulation methods. Motivated by the timing guidelines driving LTP and LTD effects, beta phase-triggered stimulation was identified as a paradigm of interest and implemented within OMNI-BIC.

We designed an algorithm incorporating signal processing components to mitigate the impact of stimulation artifact, extract underlying beta oscillations, and dynamically determine when to deliver stimulation. Following implementation, we verified the adaptive paradigm in saline via neural playback using the NeuroTest environment. With encouraging results from these benchtop assessments, we proceeded to deliver beta phase-triggered stimulation in patients staying at the EMU and assessed neuroplasticity changes by capturing CCEPs. Notable modulation in CCEP activity demonstrated the ability for the implemented paradigm to drive plasticity effects. While there needs to be continued efforts to assess how changes in connectivity influences reductions in impairment from neural injury, these preliminary findings demonstrate the potential for the platform to facilitate further research efforts investigating the role of plasticity in neural reorganization and improvements in functional outcomes.

7.2 Towards standardizing and benchmarking neurotechnologies

The efforts presented in this dissertation encompass multiple stages within a systems engineering life cycle, with a notable emphasis on the verification of various aspects of an investigational platform. These verification endeavors proved critical to not only establishing feasibility, but also navigating interpretation of in vivo outcomes, as done in Chapter 5. The evaluations performed throughout this work highlight the benefit of thorough characterization and the need to ensure some standard means to confirm the capabilities of a novel technology and assess performance. While there are diverse research thrusts throughout the neuromodulation field, it is likely that there is a lot of overlap in the systems and functionalities used towards realizing those applications. As demonstrated in Chapters 5 and 6, the fundamental stimulation capability posed similar

challenges in distinct uses of the BIC device. Incorporating standardized evaluation of novel neurotechnologies will result in raising confidence in their capabilities, facilitating scientific advances, and minimizing ineffective redundancies within the field.

7.3 Supporting efforts to evaluate the relationship between neuroplasticity and behavior

The significance of this work is that it serves as a building block for future research efforts aiming to characterize neuroplasticity mechanisms and how subsequent connectivity changes can influence functional outcomes from neural injury. This dissertation did not examine the scientific or clinical outcomes from plasticity modulation, but rather focused on the feasibility of the developed platform to achieve this effect. However, with recent in-human implantation of the BIC device, there is a unique opportunity to begin using the proposed platform and exploring the translational potential of neuroplasticity-inducing stimulation within the chronic stage of stroke. The customized stimulation capabilities of the proposed platform, alongside the pipelines identified for collecting CCEP activity, will be essential functionalities immediately applied to facilitate the investigation into the efficacy of neuroplasticity-inducing methods. Supplementing these functionalities with standard clinical metrics of behavior, alongside additional measures of connectivity like motor evoked potentials, will provide a rich dataset to illustrate the role of neural plasticity in realizing therapeutic outcomes. Such efforts describing the relationship between neuroplasticity and behavior will elucidate the nature of connectivity biomarkers and inform more intentional approaches towards inducing neuroplastic changes, culminating into rehabilitative interventions that could extend the typical window for functional recovery. And while the original motivation is within the scope of neural injury like stroke, such insights can have substantial therapeutic impact within the greater context of neurological disorders.

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