Raynor Cerebellum Project Statement of Work
Batista Lab

Overview.

As a strategy that we hope will enable dramatic improvements in neuromodulation therapies in humans, we will use Rhesus monkeys to develop “smart neuromodulation” of the motor cortex via microstimulation in the thalamus, particularly the cerebellar-recipient zone. Such a system will enable us to explore a prosthetic system that ultimately can augment or replace the function of a damaged cerebellum in human patients. We will take advantage of unique technologies available for monkey research to explore the options for target areas and stimulation parameters more thoroughly and flexibly than can be done in patients. Our goal is to help doctors know precisely where to position electrodes and how to program stimulation patterns that will benefit their patients the most. Our animal work follows humane practices as articulated by the National Institutes of Health, overseen by a full-time veterinary staff, and as approved by the University of Pittsburgh’s Animal Care and Use Committee.

Procedures.

We will implant a custom hardware platform that will enable us to insert multielectrode arrays into primary motor cortex, premotor cortex, and motor thalamus. With this platform, we will execute our work in three parts: mapping of neural and behavioral responses to microstimulation (open-loop), modeling of the response to stimulation, and finally, influencing behavior via closed-loop modulation of neural state.

First, we will map how electric stimulation in motor thalamus influences neural population activity in motor cortex. In each experimental session, we will acutely advance a 32-channel Plexon V-probe into motor thalamus. We will build a thorough map, but of particular interest

will be the region that receives inputs from the cerebellum and projects to the motor cortex. We also will place multiple 384-channel Neuropixel probes in motor and premotor cortex to monitor neural population activity. With this set of probes implanted, we will electrically stimulate each electrode on the thalamus probe, looking for extended effects on motor cortex activity. We will also monitor any impacts of microstimulation on motor behavior. Each day will test a different region of motor thalamus to develop a general stimulation map of motor thalamus.

Second, we will extend and refine this thalamus stimulation map. We will explore the effects of different stimulation parameters on motor cortex population activity. These parameters for each of the 32 stimulation channels in the thalamus will include stimulation duration, amplitude, frequency, and temporal patterning. Going beyond these single-channel parameters, we will also test how stimulation on multiple electrodes combine together to influence cortical activity. This will combinatorially increase the possible stimulation parameter space, so part of this work will involve building a predictive model of thalamic stimulation effects. We hope to build off of Yuki Minai's, Matt Smith's and Byron Yu's work on corticocortical stimulation modeling with MiSO, expanding the model to thalamic stimulation. We also hope to integrate with Maryam Shanechi's AI-based approaches to efficiently explore stimulation parameter space.

Third, with this model, we will test the thalamic stimulation in "closed-loop", where we choose stimulation parameters to drive the motor cortex to a desired neural state, by reading out its current state and choosing how to stimulate to attain the desired state. This will require not just a good model of how thalamus stimulation affects motor cortex, but also development of real-time algorithms for using recorded neural activity to pick appropriate stimulation parameters. The MiSO framework is crucial for this endeavor.

Rationale.

Monkeys have distinct advantages for a study like ours. First, we have complete flexibility where we can place our electrodes. In contrast, in patients, clinical need drives electrode placement. Second, we can collect extensive data sets - months of recordings with hundreds of tests run per day. Data of this scale could be needed to map the terrain and explore all the possibilities. Third, our animals are not enduring neurological conditions. This means that we can get a system working that influences arm movements in an able-bodied individual, and have an understanding of what the target is for a therapy. We plan to proceed in partnership and in close coordination with the clinical teams. We hope that our approaches will be guided by their needs.