Automating Multi-probe Electrophysiology Insertions for Simultaneous Multi-region Recordings

The brain is a complex network of interconnected regions, each playing a unique role in our cognition and behavior. A simple activity such as picking up your phone to check the time engages multiple regions of the brain simultaneously, including those responsible for visual processing, learning, motor control, and memory formation. Our current understanding of these intricate interactions is limited by the tools we use to study them. Electrophysiology is one of the tools our lab uses to study the brain. In this technique, high-density silicon probes are inserted into the brain to record the electrical signals from nearby neurons[i,ii]. These signals represent the brain's activity and provide valuable insights into its function. Because the brain functions as a network of connected regions[iii], we must study the isolated activity of neurons in one area in addition to the simultaneous activity of neurons from many brain regions together. Despite having intense training and expertise, neuroscientists can often accidentally miss their target region when inserting probes for electrophysiology[iv]. Past research has also shown that even expert researchers struggle to perform reproducible experiments when using more than one probe at once[iv]. In addition, experimenters sometimes rush certain aspects of the insertion to save time even though we know this can risk the quality of the data gathered[v]. These challenges are what my project aims to solve. In my project, I will develop an automated experiment platform that will make multi-probe electrophysiology efficient and reproducible while enforcing practices for gathering high-quality data.

My project aims to facilitate the collection of multi-regional electrophysiology datasets by leveraging automation and interactive software. Over the last year, with funding from my Spring – Summer 2023 Mary Gates Research Scholarship, I developed Ephys Link to facilitate communication between robotic manipulators employed in electrophysiology experiments and external software applications. Alongside Ephys Link, I developed Ephys Copilot, a software application built on top of Ephys Link, to execute single-probe electrophysiology insertions autonomously (fig. 1). My goal for the Spring through Autumn quarters of 2024 is to work with researchers at the Allen Institute to integrate the Allen Institute's camera-based probe-tracking technology[vi] into my existing automation platform to enable automated electrophysiology recordings without the need for experimenter management. Then, through our partnership with Sensapex, we will apply this automation stack to their new eight-manipulator electrophysiology rig (fig. 2), enabling efficient, reproducible, and data-rich simultaneous multi-region electrophysiology recordings. I will be spearheading the development of the new automation systems while also working in pair-coding sessions with my mentor to integrate my work into the broader electrophysiology software stack developed in our lab.

My project focuses on automation because achieving complete automation would help solve the problems with multi-probe electrophysiology insertions described earlier including making them more efficient and reproducible while enforcing practices that provide high-quality data. With automation, multiple probes can be inserted into the brain in parallel, speeding up the procedural steps of an experiment and reducing the time it takes to gather data. Additionally, since the process is tightly controlled by a computer, procedures can be repeated precisely, reducing human error. Finally, research has shown that inserting probes at high speeds into brain tissue can cause greater tissue damage and compromise the signal-to-noise ratio among other aspects of the electrophysiological recordings[v]. Often, electrophysiology experimenters may not abide by slower insertion speeds, and they will end up missing potential data. The use of automation can help enforce insertion speeds and procedures that minimize tissue damage and enhance recording quality.

The platforms that I am building on have already seen tremendous success: in the summer of 2023 I wrote descriptions of Ephys Link and Copilot in a paper recently accepted in eLife[vii], I helped organize and run two Allen Institute Neuropixels Workshops (June 2022 and 2023), and in November 2023 I presented my automation platform both as a poster at the Society for Neuroscience (SfN) conference and at the Brain Initiative "Tools, Tech, and Theory" event. Over the summer, I co-authored a paper with my mentor Dr. Daniel Birman on these electrophysiology planning and automation tools we created this past year. In our paper, I described in detail how the automation platform worked and how it can be used by labs. I also ran demos and tutorials of these tools during the Allen Institute Neuropixels Workshop held at UW twice. The Neuropixels Workshop sees researchers and labs from across the nation and the world come to learn about specific tools and techniques featured in the Steinmetz Lab. These tools and techniques include running automated electrophysiology experiments using the tools I developed. Finally, I accompanied the lab to SfN in D.C. and presented a poster detailing the automation platform, how labs can utilize it, and the kinds of new data and research it can facilitate. At SfN I also demonstrated these tools at the Brain Initiative "Tools, Tech, and Theory" event to broaden our reach of the platform. Based on our most recent usage stats we believe about 50 unique neuroscience labs are accessing our tools each week, a substantial portion of the neuroscience community. From my poster session and demo event, 32 new labs across the nation and internationally got in contact with me expressing interest in getting the automation platform into their labs. In addition to my development of the automation platform, I will also be onboarding these labs onto our platform and getting them started with automated electrophysiology experiments.

My previous Mary Gates Research Scholarship award allowed me to focus my time and energy on my research project without the distraction of seeking out other part-time jobs or internships. Receiving the Mary Gates Research Scholarship award twice in my undergraduate research career, along with my publication and conference presentations, will clearly demonstrate to graduate schools and industry positions that I am well-prepared for a career in research tool development. At UW, I am pursuing my computer science education with a focus on research, driven by the desire to solve problems and create innovations that benefit the community, not just generate revenue. My involvement in the electrophysiology automation project has allowed me to contribute to the neuroscience community and understand the dynamics of the research world. My research scholarship experience has been instrumental in shaping my educational journey including graduate school and my future career in the computer science industry.

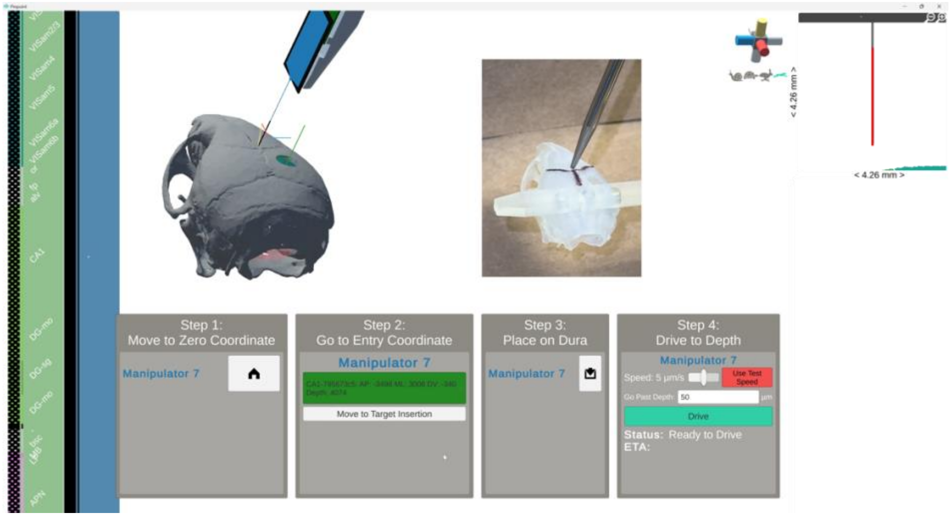

Figure 1: Single probe automation with Ephys Copilot. On the left is a virtual skull and an electrode probe. On the right is a camera view of a 3D-printed skull and probe in real life. Once the scientist has selected their target region (as denoted by the green line going into the virtual skull), Ephys Copilot will compute a trajectory and drive the real-life probe to the target location with sub-micron precision. Note how this current process requires scientists to intervene at key steps such as during calibration and Dura penetration. The goal of my project is to eliminate these impedances and enable automated multi-probe automation with camera imaging.

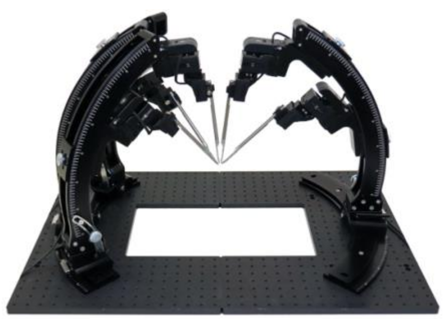

Figure 2: Sensapex eight-probe electrophysiology rig. In this image, the silver sticks in the center are the probes and they are attached to the manipulators. Manipulators are mounted on metal rig parts arranged in a ring on a base plate. This image features five probes for clarity, but more rings can be attached to form a circle of manipulators. My software will be responsible for driving these probes and running the experiments without the need for experimenter management.

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[iii] Mante, V., Sussillo, D., Shenoy, K. V., & Newsome, W. T. (2013). Context-dependent computation by recurrent dynamics in prefrontal cortex. *nature*, *503*(7474), 78-84.

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[v] Fiáth, R., Márton, A. L., Mátyás, F., Pinke, D., Márton, G., Tóth, K., & Ulbert, I. (2019). Slow insertion of silicon probes improves the quality of acute neuronal recordings. *Scientific Reports*, *9*(1), 111.

[vi] Allen Institute, Parallax (2023), GitHub Repository, https://github.com/AllenNeuralDynamics/parallax

[vii] Birman, D., Yang, K. J., West, S. J., Karsh, B., Browning, Y., International Brain Laboratory, ... & Steinmetz, N. A. (2023). Pinpoint: trajectory planning for multi-probe electrophysiology and injections in an interactive web-based 3D environment. *bioRxiv*, 2023-07.