Introduction

Modern neuroscientists aim to study the combined activity of large populations of neurons across many regions of the brain simultaneously. The current state of the art in electrophysiology has researchers manually insert one or two electrode probes into the brain to gather data about neuron activity. This is prone to human error and does not scale well. My goal with this project is to make multi-probe electrophysiology experiments repeatable and efficient.

Researchers who want to use electrophysiology to study multiple brain regions simultaneously face three big challenges. First, researchers must locate target brain regions on a coordinate system (for mice see [1] and for rats see [2]) and accurately place probes at these precise locations. Second, while moving probes above the brain, researchers must plan routes that avoid collisions with other probes and the rig. Third, researchers must insert probes into the brain without breaking them. Together, these challenges mean each insertion is a slow and time-consuming process where success depends on the expertise of the researcher. My goal is to automate probe movements and insertions to reduce human error and enable experiments to scale up to large numbers of probes. Building on my lab's existing targeting software Pinpoint [3] and with funding from my 2023 Mary Gates Research Scholarship, I developed software to control manipulator hardware and conduct semi-autonomous single-probe electrophysiology (Fig. 1). This grant will provide funding for three further aims to reach complete automation. Aim 1: accurately and repeatably move probes to target coordinates; Aim 2: manage probe movements to avoid collisions; Aim 3: insert probes through the brain surface without breaking them.

Aim 1: Accurate and Repeatable Probe Placement

From other work, we know that human error and brain-brain variability introduce a 400-micron standard deviation in targeting brain regions [4]. I will reduce human error and make

probe positioning more accurate by collaborating with researchers at the Allen Institute to integrate computer-vision-based probe tracking with robotically controlled probe manipulators. My work in the past two years has been to develop a communication interface between manipulator hardware from various companies and the automation platform. Before, researchers had to manually identify where probes were in 3D space, which was prone to human error. The automation platform can automatically calibrate the position of probes and repeatably make positioning movements with submicrometer precision by using the computer vision probe tracking system in tandem with my manipulator hardware interface. Additionally, cameras can identify blood vessels to avoid and landmarks on the skull to calibrate positioning with. Together, this improves target accuracy, reliability, and safety.

Aim 2: Efficient and Collision-free Navigation of Multiple Probes

When multiple probes are used in an experiment, set-up times and collision risks are increased making it imperative that probe movements are carefully choreographed. I will utilize navigational algorithms backed by data from the computer vision probe tracking system to generate movement paths for the probes to take that avoid collisions with each other and the rig. While the probes are moving, cameras can visually check for potential collisions and safely update the route of a probe to avoid them. The automation platform can move multiple probes in parallel, reducing the time it takes to move to insertions as compared to the current serial process. This will enable experiments to scale to multiple probes efficiently.

Aim 3: Safe Insertions into the Brain

I will develop algorithms to autonomously insert probes into the brain while detecting failed attempts and collaborate with manipulator company Sensapex to develop an electrophysiology rig to support automated insertions. I will collaborate with researchers at the

Allen Institute to develop new methods that will allow their computer vision probe tracking system to detect when probes are at risk of breaking during insertion, stopping the process before damage occurs. Previous studies have established the best insertion speeds and driving patterns to reduce tissue damage and increase the signal-to-noise ratio of collected data [5]. The automation platform will enforce these practices to improve the safety of the subject and the quality of the data collected. For the tracking system to work well, the cameras used need to be well placed on the experiment rig, and all probes need to be in view. Traditional electrophysiology rigs use free-form setups that make it unnecessarily challenging to reliably track equipment, making automation difficult to support. I will collaborate with Sensapex to develop enhancements to their multi-probe rig platform (Fig. 2) to mount several manipulators and cameras together at once. This rig will impose constraints on equipment setup, enabling proper tracking of probes and ultimately safer insertions into the brain with automation.

Project Timeline

This project has two concurrent threads: developing automation software and building compatible electrophysiology rigs. I will use the Fall and Winter quarters to research and develop the automation platform then use the Spring quarter to test it with prospective labs and make improvements based on feedback (see Figure 3 for details). From SfN 2023, I have gathered a list of 30+ labs that are interested in using the automation platform, and I anticipate gathering more from this year's conference. In addition to researchers in my lab and our connection to the International Brain Lab, I will gather data on targeting accuracy, total experiment duration, and neuron yield in collected data. This data, matching the goals of my three aims, will allow me to evaluate the effectiveness of the automation platform and allow me to make improvements based on feedback from the researchers.

Expected Results and Impacts

I expect that with the automation platform handling manipulator movements, human error in multi-probe electrophysiology will be reduced, increasing the repeatability of brain-wide experiments. In addition to reducing the 400-micron standard deviation in probe placement, the computer vision system has broader oversight on the rig during insertion, allowing for the system to prevent probes from breaking during insertion. It would be a challenge for a researcher to keep track of and manage all moving parts through the restricted view of a microscope. With probe insertion speeds and patterns being enforced by the automation system, I also expect to see a higher neuron yield in the collected data as compared to manually inserted probes. Together, the automation platform will ensure the repeatability and reliability of multi-probe electrophysiology experiments.

More importantly, this platform will allow electrophysiology experiments to scale to the large number of probes required for brain-wide recordings, making simultaneous study of multiple regions of the brain viable. Based on historical data from manual electrophysiology experiments in my lab, we have found that it takes an average of 15 minutes to go from calibration to a probe's final target in the brain. This means an advanced eight-probe recording could take up to two hours to set up manually, increasing the stress on subjects during the experiment. Through the parallelization of historically serial tasks, the automation platform will make any electrophysiology experiment take the same amount of time as a single probe experiment and dramatically reduce the stress and workload on both the subject and researcher. Ultimately, this platform accelerates neuroscience research by making electrophysiology more reproducible and efficient, making it viable to plan and execute complex experiments that record activity in multiple regions of the brain to answer questions about our behavior.

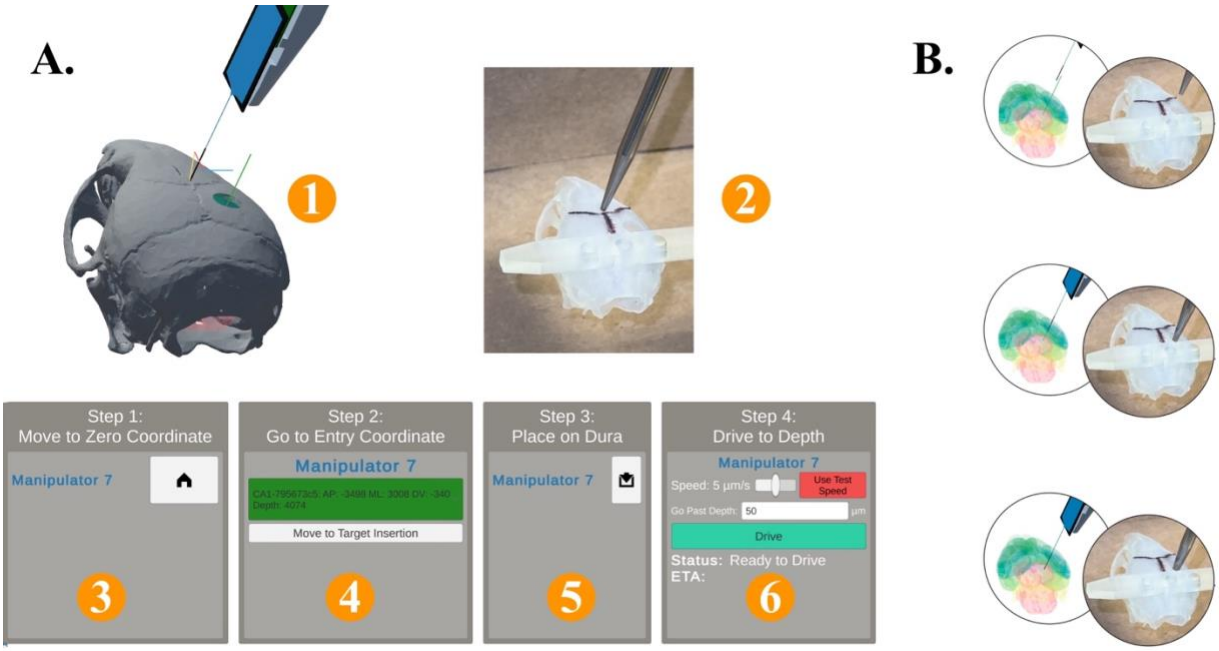

Figure 1: Single probe electrophysiology automation system. (A) 1) a virtual skull and an electrode probe. 2) a camera view of a 3D-printed skull and probe in real life moving in sync with the virtual ones. 3) A button for researchers to identify when their probe position has been (manually) calibrated to the skull landmark at Bregma. With automation, this step can be removed since computer vision will be used to detect when probes are calibrated. 4) Researchers can select a target region to move probes to once they are calibrated. The automation platform will compute a collision-free trajectory and drive the real-life probe to the target location. 5) In the semi-automated platform, researchers must pierce the brain surface manually. The completely automated platform will perform this step autonomously while ensuring probes do not bend or break. 6) Drive the probes to the target depth. (B) These images show the insertion process. As the real probe (right) is inserted into the 3D-printed skull, we can see the virtual probe (left) following and showing in real time where the probe is inside the brain.

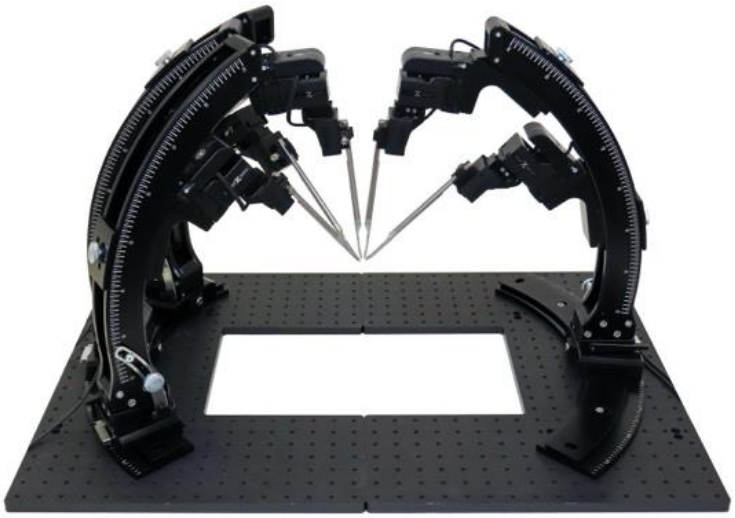

Figure 2: Sensapex multi-probe electrophysiology rig. The silver sticks in the center are probes attached to the manipulators. Manipulators are mounted on metal arms arranged in a ring on a base plate. This image features five probes for clarity, but more arms can be attached to form a circle of manipulators and multiple probes can be mounted on each arm as well. Aim 3 will work to develop additional components such as camera mounts to support automation. Camera mounts will ensure that the computer vision-based probe tracking system has a consistent placement on the rig. The arms mount system ensures that when the rig is opened to move subjects in place, the equipment can be moved back into the same position afterward.

	Fall Quarter	Winter Quarter	Spring Quarter
Research	Aims software development: iterate computer vision probe tracking system with Allen Institute, develop probe routing algorithm, and develop safe insertion system.		Evaluate the platform with prospective laboratories and IBL and iterate on feedback.
	Sensapex multi-probe rig development.		Help laboratories acquire and set up rigs for automation.
Conferences	SfN 2024: Present on current automation platform, meet with Sensapex to develop multi-probe rig.		
Meetings	Lab meetings, Sensapex multi-probe rig system, and Allen Institute computer vision probe tracking system.		Prospective labs to set up and test.

Figure 3: Project timeline. Fall and Winter quarters will be used to develop aims while Spring quarter is for sharing it with prospective labs, evaluating its performance, and making improvements based on feedback.

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