Exploiting optogenetic feedback control in mesoscale neuroscience

Thesis Proposal
Biomedical Engineering PhD Program
Georgia Institute of Technology and Emory University

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As the importance of causal inference becomes increasingly recognized in neuroscience, the need for technology enabling precise manipulation of neural variables becomes apparent. Feedback control is an important class of such manipulations for its ability to increase inference power by reducing response variability. Widely used throughout the engineering disciplines, it has had a significant impact through a variety of techniques (e.g., voltage clamp, dynamic clamp) on cellular neuroscience. However, feedback control has yet to be widely applied at the mesoscale/circuit level despite recent improvements in interfacing technology, such as optogenetics. Challenges to adoption include the complexity of implementing fast closed-loop experiments, the need to adapt the mature methods of control theory to the idiosyncratic constraints of systems neuroscience experiments, and the lack of established technical guidelines for applying feedback control to address complex scientific questions.

In this work I propose to begin to address these challenges in three aims. In Aim 1, I develop a simulation framework for easily prototyping closed-loop optogenetic control (CLOC) experiments in silico, thus allowing neuroscientists to test and iterate on experimental designs without the costs of in-vivo experiments or up-front investments in compatible hardware-software systems. In Aim 2, I will translate sophisticated model-based feedback control algorithms to the realistic experimental setting of bidirectional CLOC—the simultaneous use of both excitatory and inhibitory opsins. I will demonstrate some advantages of bidirectional CLOC and how it is not well accommodated by the algorithms previously demonstrated. Finally, in Aim 3, I will explore how recording, stimulation, and control requirements vary in an example application of CLOC—controlling the latent dynamics of simulated neural population activity and assessing their causal relationship with behavior. I will model this population activity with recurrent spiking neural networks trained using state-of-the-art, biologically plausible methods, with differing degrees of brain-like architecture and task complexity. This work will thus provide the systems neuroscience community with a more accessible entry point for CLOC, more powerful algorithms for leveraging bidirectional control, and a point of reference for designing CLOC experiments capable of answering complex scientific questions.

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Thesis committee

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1 Specific Aims

As the importance of causal inference becomes increasingly recognized in neuroscience, the need for technology enabling precise manipulation of neural variables becomes apparent. Feedback control is an important class of such manipulations for its ability to increase inference power by reducing response variability. Widely used throughout the engineering disciplines, it has had a significant impact through a variety of techniques (e.g., voltage clamp, dynamic clamp) on cellular neuroscience. However, feedback control also has great potential at the mesoscale/systems level, promising the ability to *unambiguously infer the downstream effects of circuit/population-level neural activity*.

For a number of reasons, though, *this potential has not been widely realized*. The main challenges to wider adoption do not appear to lie with available technology, as the computational power and stimulation/recording requirements of feedback control are met by the ever-improving tools already available to neuroscientists, such as optogenetics and large-scale neural recording. I posit that the main challenges to adoption rather include the **complexity of implementing** fast closed-loop experiments, the need to **adapt the mature methods of control theory** to the idiosyncratic constraints of systems neuroscience experiments, and the **lack of established technical guidelines** for applying feedback control to address complex scientific questions. **The proposed work aims to begin to address these challenges, and thus strengthen the set of causal tools available to probe neural systems.**

1.1 Aim 1: A CLOC experiment simulation testbed

One significant obstacle to closed-loop optogenetic control (CLOC) experiments is the cost of acquiring and configuring compatible hardware-software systems. Moreover, the maintenance of animals or cell cultures inherent in any *in-vivo* or *in-silico* can slow the pace of developing novel experimental techniques. In Aim 1, I attempt to address these obstacles by developing a simulation framework for easily prototyping CLOC experiments *in silico*, thus enabling faster, cheaper CLOC experiment design and method development. We demonstrate the software's utility in different virtual experiments and provide it to the public as open-source software with thorough documentation.

1.2 Aim 2: Bidirectional CLOC

Bidirectional CLOC—the simultaneous use of both excitatory and inhibitory opsins—is necessary for precise manipulation of neural systems, especially when maintaining naturalistic activity levels is important. However, the basic control theory methods previously used in conjuction with CLOC do not take actuator constraints into account and are thus inadequate for multi-actuator (i.e., multi-light source) problems. The field of control theory provides elegant, powerful solutions to this class of problems, but applying them requires interdisciplinary expertise. In this aim I will translate more sophisticated model-based feedback control algorithms to the bidirectional CLOC setting and demonstrate the advantages both of bidirectional actuation and these algorithmic improvements.

1.3 Aim 3: Using CLOC to manipulate latent neural dynamics

To our knowledge, CLOC has yet to be applied in answering complex systems neuroscience questions. In this aim I propose to set a technical and conceptual precedent for how this can be achieved in the context of controlling the latent dynamics of simulated neural populations. First, I will produce these virtual models by training recurrent spiking neural networks with state-of-the-art, biologically plausible methods—each differing in their degrees of brain-like architecture and training procedure complexity. I will then use the simulation testbed of Aim 1 to explore how recording, stimulation, and control requirements vary for controlling systems of varying complexity and size—thus giving researchers some idea of the relative importance of each factor of CLOC. Finally, I will demonstrate the conceptual utility of CLOC by quantitatively assessing the causal relationship between these latent dynamics and "behavior" (model output).

2 Background

2.1 Closed-loop control in neuroscience

Mesoscale neuroscience is currently undergoing a revolution fueled by advances in neural manipulation (*1–8*) and measurement (*9–16*) technologies as well as data analysis methods (*17–22*). These have yielded unprecedented datasets (*23*, *24*) and insights into network activity and plasticity (*25–29*), as well as novel experimental paradigms such as direct closed-loop control of neural activity (*30–40*).

An exciting emerging possibility is closed-loop control of neural activity (*30*, **other-reviews?**), enabling intervention in processes that are too fast or unpredictable to control manually or with pre-defined stimulation, such as sensory information processing, motor planning, and oscillatory activity. Unlike other forms of closed-loop control altering the environment [cite examples, mouse knee rotation, visual stimuli to achieve target response,] or using neurofeedback training (*8*) to achieve a neural or behavioral target, the direct control of neural activity itself can unambiguously reveal the downstream effects of that activity.

Closed-loop control of neural activity can be implemented in an event-triggered sense [cite a bunch of examples, inhibiting seizures, altering power, SWR disruption,]—enabling the experimenter to respond to discrete events of interest, such as the arrival of a traveling wave [cite Reynolds] or sharp wave ripple [cite some review paper]—or in a feedback sense [cite 2 Bolus papers, all-optical, any others], driving the system towards a target or along a trajectory. The latter has multiple advantages over open-loop control (delivery of a pre-defined stimulus): by rejecting exogenous inputs, noise, and disturbances, it reduces variability across time and across trials, allowing for finer-scale inference. Additionally, it can compensate for model mismatch, allowing it to succeed where open-loop control based on imperfect models is bound to miss the mark. Moreover, whereas traditional perturbation methods include lesioning (*41*), unnatural silencing, or extreme stimulation, feedback control poses a more naturalistic alternative, increasing generalizability.

2.2 Various scales and tools for closed-loop control

Closed-loop control of neural activity can be performed at multiple scales and with different sets of tools. At the smallest, sub-neuron scale, dynamic clamping has yielded decades of fruitful research (**hodgkin53?**, **cite?** some-review-paper) in the forms of tools such as the dynamic

clamp and voltage clamp, controlling electrical properties of small patches of membrane. The frontiers of this small-scale neuroscience often involve scaling up to multiple neurons and scaling down to subcellular structures such as dendrites (**cite?**), but multi-electrode intracellular recording face limitations (*42–44*, **cite?** more, not just patch clamping). Optical tools—e.g., optogenetics and fluorescence microscopy—can circumvent the difficulties of working with electrodes at such small scales, but an optical approach is not yet feasible for this purpose. The obstacles lie mainly in recording technology: the kinetics of both voltage indicators (*16*) and intracellular calcium (**cite?**) are too slow to capture phenomena faster than a typical action potential.

By contrast, the current state of technology is ripe for innovating closed-loop control methods at larger scales of neural activity, from single neurons to populations and circuits. Several promising combinations of recording and stimulation modalities are possible and still relatively novel: electrode recording with optogenetic stimulation (*45*, our papers), fluorescence microscopy with electrical stimulation (**cite?**), fluorescence microscopy with photostimulation (all-optical control) (*36, 37, 46, 47*), and fMRI with optionally transcranial (*48, 49*) photostimulation. Each of these tool combinations has pros and cons in terms of spatial and temporal resolution, crosstalk (*50*), and degrees of freedom.

A natural starting point for many neuroscientists is the first of these tool sets—electrode recording combined with optogenetics—since the two methods are so widely used, interfere little with each other (as long as metal electrodes are not directly illuminated (*45, 50*)), and allow for genetically targeted stimulation. I will henceforth refer to this combination as CLOC, following the convention established by previous works (*34, 35*).

2.3 Previous CLOC work

> 🔥 Danger
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> TODO

The proposed work builds on the work my lab and collaborators have done previously in implementing CLOC feedback control. (*33*) demonstrated bidirectional control

2.4 Potential applications in mesoscale neuroscience

Seeing that a suitable technological foundation for feedback control of neural activity has already been laid with CLOC, I turn now to a discussion of several exciting areas where CLOC could further causal hypothesis testing. These deal with concrete questions of scientific interest, as opposed to the conceptual/technical advantages previously explained (Section 2.1).

Neuroscientists often identify specific variables or phenomena to assess their role in a larger neural system, in search of interpretable components of brain activity. A natural application of CLOC is to control these variables and phenomena of interest directly to enable stronger inference of their relationship to downstream variables. Examples of these potential targets for control include the activity of different cell types (*51*, **more?**); the type (*52–54*), frequency (*55*), amplitude (*55*), spike coherence (*56*, *57*) and relationship (*58*, **zhang19?**) of different oscillatory patterns (*59*); discrete phenomena such as bursts (**cite?**), sharp wave ripples (**buzsaki15?**), oscillatory bursts (*8*, *60*, *61*), traveling waves (*62*, *63*), or sleep spindles (**cite?**); and latent states describing neural dynamics (*64*, **cite?** review, Shenoy lab causal test, Hantman), including those most relevant to behavior (*20*, *65*, *66*).

While some of these targets lend themselves easily to CLOC, others require continued innovation in interfacing technology. While recent advances in recording technology allow us to infer neural state with unprecedented precision (*9*, *10*, *15*, *16*, **calcium-imaging?**, **GEVI?**), available actuation technologies are much more limited in their degrees of freedom and thus unlikely to sufficiently control what is observed. For this reason, the development of micro-LED arrays (**cite?**), multi-channel optrodes (*8*), and holographic optogenetic stimulation (*37*, **cite?**) are of particular interest. Moreover, rigorous investigation of the importance of recording and stimulation capabilities relative to each other would be helpful in guiding technological development and experimental design.

In addition to controlling variables of interest, CLOC can serve a paradigm of decoupling variables. This could be in the context of a circuit, where clamping the activity of a given node decouples its activity from all inputs except for the controller. This functionally severs links in the circuit, aiding in circuit identification and in testing the function of different nodes and connections (**willats-clinc?**). Moreover, CLOC could be used in the more general sense of controlling for confounding variables. For example, one might want to manipulate the synchrony of a population without changing the mean firing rate, or vice-versa. Whereas the conventional open-loop stimulation approach might accomplish this through tedious titration of stimulation parameters (*67*), the feedback control approach could simultaneously manipulate both variables as desired, requiring only a passable model of the system.

2.5 Innovation

Despite CLOC's great promise to be applied in these areas, it has not yet been widely applied in mesoscale neuroscience. As previously outlined (Chapter 1), I identify three main reasons for this, which I will begin to address. First, CLOC experiments are difficult and costly. I propose lowering the barrier to entry and the cost of experiment design and method development for CLOC experiments by creating a simulation framework, since **existing mesoscale neural network simulators do not contain the necessary ingredients for CLOC simulation**. Second, the algorithms previously used for CLOC are not well suited for actuation via multiple simultaneous light sources. I propose adapting more **powerful control theory methods** to enable

bidirectional CLOC, which to our knowledge **has not been done previously**. Third, technical and conceptual guidelines for the effective application of CLOC do not exist because **CLOC has not yet been applied to answer a complex scientific question**. I propose to model how this can be done by controlling latent neural dynamics *in silico*, exploring how technical requirements scale with model and experiment parameters, and inferring a causal relationship between latent variables and model behavior.

3 Aim 1

3.1 Rationale

CLOC experiments are difficult and costly. This can be a barrier to entry for neuroscientists that find CLOC's advantages attractive. Their lab might lack the funds to invest in necessary hardware or the time to invest in adding high-performance signal processing loop to their experimental workflow. Or, they may possess the resources but do not want to spend them without some assurance that their proposed experiment would be fruitful. Finally, when the proposed experiment requires signal processing/control method development, iterating on designs *in-vivo* may be cumbersome, given the additional cost of husbandry.

3.2 Innovation

The innovation I introduce is developing a testbed for simulating CLOC experiments, providing researchers a "free trial" and a low-cost environment to design experiments and develop methods. Existing mesoscale neural network simulation programs do not contain all the ingredients necessary for CLOC simulation: electrode recording, light and opsin models for optogenetic stimulation, and arbitrary closed-loop stimulation (including latency).

3.3 Approach

3.3.1 Subaim 1

Poutine distillery cray letterpress ex viral cronut. Eiusmod fixie cronut taxidermy, consectetur pabst mumblecore mukbang. Franzen snackwave squid enamel pin. Waistcoat poutine occaecat, cornhole chia art party voluptate.

3.3.1.1 Preliminary results

Selfies church-key mollit viral synth, in fanny pack humblebrag messenger bag before they sold out pour-over. Health goth trust fund raw denim irure. Consectetur shaman flexitarian pickled chicharrones. Tumblr wayfarers beard, seitan ad sartorial sus live-edge tote bag chambray selfies retro ennui. Crucifix incididunt food truck pour-over sus.

3.3.1.2 Potential pitfalls, alternative strategies

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3.3.2 Subaim 2

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4.2 Approach

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6 Timeline

See here for help.

Adding GANTT diagram functionality to mermaid
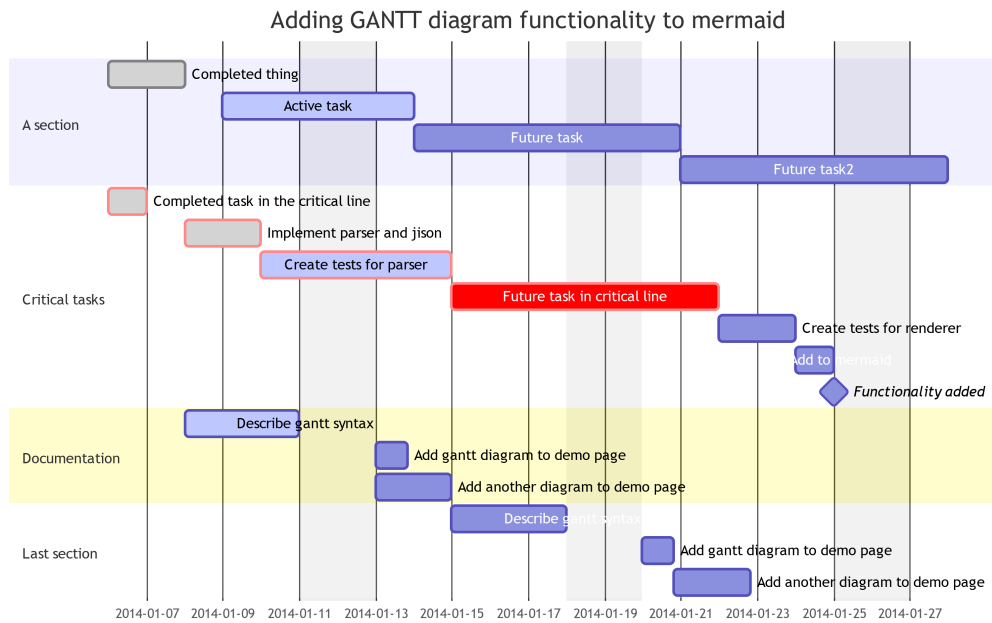
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