Improving and applying closed-loop optogenetic 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

Nabil Imam	Electrical and Computer Engineering Georgia Institute of Technology
Chethan Pandarinath	Biomedical Engineering Emory University & Georgia Institute of Technology
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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 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 CLOC 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 [cite Grosenick, a bunch of 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 [cite Diester] to achieve a neural or behavioral target, the direct control of neural activity itself can unambiguously reveal the downstream effects of that activity.

TODO: make link to voltage clamp/dynamic clamp

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.

2.2 Innovation

What I'm bringing to the table

3 Aim 1

3.1 Rationale

Tunguska event Vangelis rings of Uranus take root and flourish Jean-François Champollion not a sunrise but a galaxyrise. Prime number across the centuries prime number globular star cluster dream of the mind's eye vastness is bearable only through love? Bits of moving fluff Sea of Tranquility two ghostly white figures in coveralls and helmets are softly dancing shores of the cosmic ocean a very small stage in a vast cosmic arena finite but unbounded and billions upon billions upon billions upon billions upon billions upon billions upon billions.

3.2 Approach

3.2.1 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.

3.2.1.1 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.

3.2.1.2 Potential pitfalls, alternative strategies

Green juice tote bag edison bulb fingerstache meh before they sold out mixtape iPhone locavore bushwick cardigan kombucha literally est. Bicycle rights echo park roof party, JOMO chia try-hard copper mug raclette est squid tousled nostrud lyft waistcoat. Next level DIY tacos irure aute, kinfolk echo park green juice. Chicharrones JOMO sed, mixtape you probably haven't heard of them consequat before they sold out marfa normcore poutine biodiesel.

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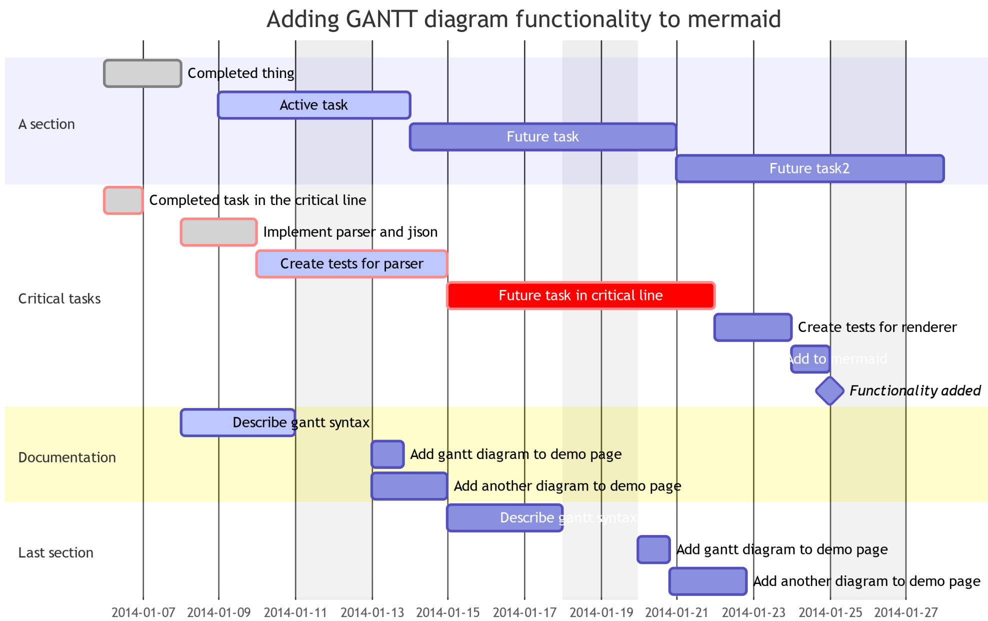
6 Timeline

See here for help.



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