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.

Table of contents

Front Matter 5

Thesis committee . . . 5

1 Specific Aims 6

1.1 Aim 1: An experiment simulation testbed for prototyping closed-loop optogenetic control experiments . . . 7

1.2 Aim 2: Enabling bidirectional actuation through the application of model-predictive control . . . 7

1.3 Aim 3: Applying CLOC to control latent population dynamics . . . 7

2 Background 8

2.1 Innovation . . . 8

3 Aim 1 9

3.1 Rationale . . . 9

3.2 Approach . . . 9

3.2.1 Subaim 1 . . . 9

3.2.2 Subaim 2 . . . 10

3.2.3 Subaim 3 . . . 10

4 Aim 2 12

4.1 Rationale . . . 12

4.2 Approach . . . 12

4.2.1 Subaim 1 . . . 12

4.2.2 Subaim 2 . . . 13

4.2.3 Subaim 3 . . . 13

5 Aim 3 15

5.1 Rationale . . . 15

5.2 Approach . . . 15

5.2.1 Subaim 1 . . . 15

5.2.2 Subaim 2 . . . 16

5.2.3 Subaim 3 . . . 16

6 Timeline 18

References 19

Front Matter

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1 Specific Aims

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 direct 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.

1.1 Aim 1: An experiment simulation testbed for prototyping closed-loop optogenetic control experiments

1.2 Aim 2: Enabling bidirectional actuation through the application of model-predictive control

1.3 Aim 3: Applying CLOC to control latent population dynamics

2 Background

A bunch of background info

2.1 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.

3.2.2 Subaim 2

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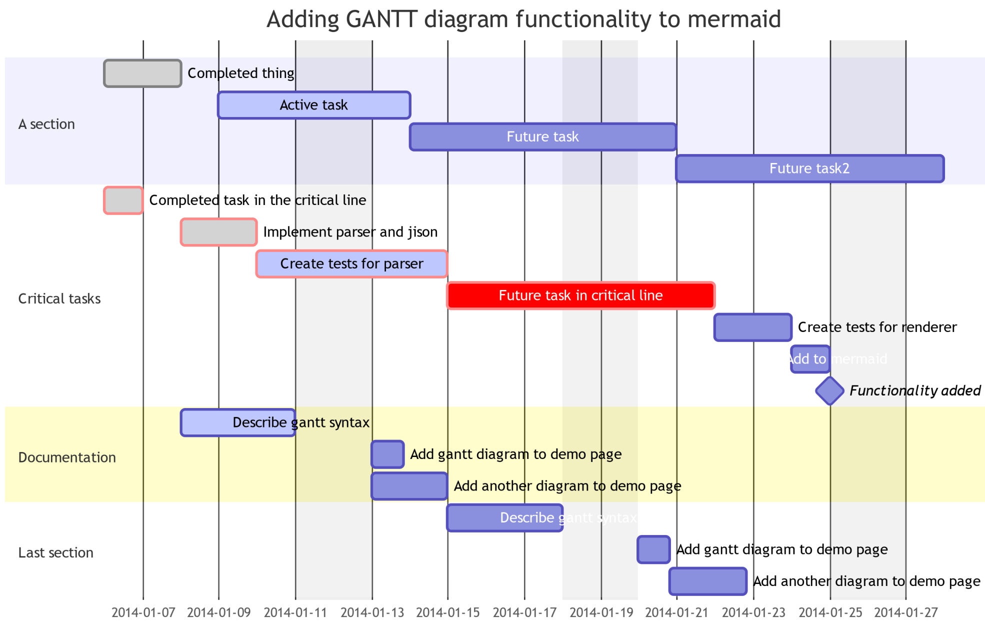
6 Timeline

See here for help.



References

1. L. Fenno, O. Yizhar, K. Deisseroth, The development and application of optogenetics. *Annual Review of Neuroscience*. **34**, 389–412 (2011).
2. J. S. Wiegert, M. Mahn, M. Prigge, Y. Printz, O. Yizhar, Silencing Neurons: Tools, Applications, and Experimental Constraints. *Neuron*. **95**, 504–529 (2017).
3. S. Sridharan, M. A. Gajowa, M. B. Ogando, U. K. Jagadisan, L. Abdeladim, M. Sadahiro, H. A. Bounds, W. D. Hendricks, T. S. Turney, I. Tayler, K. Gopakumar, I. A. Oldenburg, S. G. Brohawn, H. Adesnik, High-performance microbial opsins for spatially and temporally precise perturbations of large neuronal networks. *Neuron*. **110**, 1139–1155.e6 (2022).
4. J. Vierock, S. Rodriguez-Rozada, A. Dieter, F. Pieper, R. Sims, F. Tenedini, A. C. F. Bergs, I. Bendifallah, F. Zhou, N. Zeitzschel, J. Ahlbeck, S. Augustin, K. Sauter, E. Papagiakoumou, A. Gottschalk, P. Soba, V. Emiliani, A. K. Engel, P. Hegemann, J. S. Wiegert, BiPOLES is an optogenetic tool developed for bidirectional dual-color control of neurons. *Nature Communications*. **12**, 1–20 (2021).
5. H. Adesnik, L. Abdeladim, Probing neural codes with two-photon holographic optogenetics. *Nat Neurosci*. **24**, 1356–1366 (2021).
6. G. Faini, C. Molinier, C. Telliez, C. Tourain, B. C. Forget, E. Ronzitti, V. Emiliani, Ultrafast Light Targeting for High-Throughput Precise Control of Neuronal Networks. *bioRxiv*, 2021.06.14.448315 (2021).
7. B. L. Roth, DREADDs for Neuroscientists. *Neuron*. **89**, 683–694 (2016).
8. D. Eriksson, A. Schneider, A. Thirumalai, M. Alyahyay, B. de la Crompe, K. Sharma, P. Ruther, I. Diester, Multichannel optogenetics combined with laminar recordings for ultra-controlled neuronal interrogation. *Nat Commun*. **13**, 985 (2022).
9. N. A. Steinmetz, C. Aydin, A. Lebedeva, M. Okun, M. Pachitariu, M. Bauza, M. Beau, J. Bhagat, C. Böhm, M. Broux, S. Chen, J. Colonell, R. J. Gardner, B. Karsh, F. Kloosterman, D. Kostadinov, C. Mora-Lopez, J. O'Callaghan, J. Park, J. Putzeys, B. Sauerbrei, R. J. J. van Daal, A. Z. Vollan, S. Wang, M. Welkenhuysen, Z. Ye, J. T. Dudman, B. Dutta, A. W. Hantman, K. D. Harris, A. K. Lee, E. I. Moser, J. O'Keefe, A. Renart, K. Svoboda, M. Häusser, S. Haesler, M. Carandini, T. D. Harris, Neuropixels 2.0: A miniaturized high-density probe for stable, long-term brain recordings. *Science*. **372** (2021), doi:10.1126/science.abf4588.

10. J. H. Siegle, A. C. López, Y. A. Patel, K. Abramov, S. Ohayon, J. Voigts, Open Ephys: an open-source, plugin-based platform for multichannel electrophysiology. *J. Neural Eng.* **14**, 045003 (2017).

11. P. Gutruf, J. A. Rogers, Implantable, wireless device platforms for neuroscience research. *Current Opinion in Neurobiology*. **50**, 42–49 (2018).

12. W. Göbel, F. Helmchen, In Vivo Calcium Imaging of Neural Network Function. *Physiology*. **22**, 358–365 (2007).

13. T. Knöpfel, C. Song, Optical voltage imaging in neurons: moving from technology development to practical tool. *Nat Rev Neurosci*. **20**, 719–727 (2019).

14. K. Svoboda, R. Yasuda, Principles of Two-Photon Excitation Microscopy and Its Applications to Neuroscience. *Neuron*. **50**, 823–839 (2006).

15. A. Kazemipour, O. Novak, D. Flickinger, J. S. Marvin, A. S. Abdelfattah, J. King, P. M. Borden, J. J. Kim, S. H. Al-Abdullatif, P. E. Deal, E. W. Miller, E. R. Schreiter, S. Druckmann, K. Svoboda, L. L. Looger, K. Podgorski, Kilohertz frame-rate two-photon tomography. *Nature Methods*. **16**, 778–786 (2019).

16. J. Wu, Y. Liang, S. Chen, C. L. Hsu, M. Chavarha, S. W. Evans, D. Shi, M. Z. Lin, K. K. Tsia, N. Ji, Kilohertz two-photon fluorescence microscopy imaging of neural activity in vivo. *Nature Methods*. **17**, 287–290 (2020).

17. L. van der Maaten, G. Hinton, Visualizing Data using t-SNE. *Journal of Machine Learning Research*. **9**, 2579–2605 (2008).

18. G. J. Berman, D. M. Choi, W. Bialek, J. W. Shaevitz, Mapping the stereotyped behaviour of freely moving fruit flies. *Journal of The Royal Society Interface*. **11**, 20140672 (2014).

19. A. Mathis, P. Mamidanna, K. M. Cury, T. Abe, V. N. Murthy, M. W. Mathis, M. Bethge, DeepLabCut: markerless pose estimation of user-defined body parts with deep learning. *Nat Neurosci*. **21**, 1281–1289 (2018).

20. O. G. Sani, H. Abbaspourazad, Y. T. Wong, B. Pesaran, M. M. Shanechi, Modeling behaviorally relevant neural dynamics enabled by preferential subspace identification. *Nature Neuroscience*. **24**, 140–149 (2021).

21. O. Sporns, Graph theory methods: applications in brain networks. *Dialogues in Clinical Neuroscience*. **20**, 111–121 (2018).

22. S. Schneider, J. H. Lee, M. W. Mathis, Learnable latent embeddings for joint behavioral and neural analysis (2022), doi:10.48550/arXiv.2204.00673.

23. L. K. Scheffer, C. S. Xu, M. Januszewski, Z. Lu, S. Takemura, K. J. Hayworth, G. B. Huang, K. Shinomiya, J. Maitlin-Shepard, S. Berg, J. Clements, P. M. Hubbard, W. T. Katz, L. Umayam, T. Zhao, D. Ackerman, T. Blakely, J. Bogovic, T. Dolafi, D. Kainmueller, T. Kawase, K. A. Khairy, L. Leavitt, P. H. Li, L. Lindsey, N. Neubarth, D. J. Olbris, H. Otsuna, E. T. Trautman, M. Ito, A. S. Bates, J. Goldammer, T. Wolff, R. Svirskas, P. Schlegel, E. Neace, C. J. Knecht, C. X. Alvarado, D. A. Bailey, S. Ballinger, J. A. Borycz, B. S. Canino, N. Cheatham, M. Cook, M. Dreher, O. Duclos, B. Eubanks, K. Fairbanks, S. Finley, N. Forknall, A. Francis, G. P. Hopkins, E. M. Joyce, S. Kim, N. A. Kirk, J. Kovalyak, S. A. Lauchie, A. Lohff, C. Maldonado, E. A. Manley, S. McLin, C. Mooney, M. Ndama, O. Ogundeyi, N. Okeoma, C. Ordish, N. Padilla, C. M. Patrick, T. Paterson, E. E. Phillips, E. M. Phillips, N. Rampally, C. Ribeiro, M. K. Robertson, J. T. Rymer, S. M. Ryan, M. Sammons, A. K. Scott, A. L. Scott, A. Shinomiya, C. Smith, K. Smith, N. L. Smith, M. A. Sobeski, A. Suleiman, J. Swift, S. Takemura, I. Talebi, D. Tarnogorska, E. Tenshaw, T. Tokhi, J. J. Walsh, T. Yang, J. A. Horne, F. Li, R. Parekh, P. K. Rivlin, V. Jayaraman, M. Costa, G. S. Jefferis, K. Ito, S. Saalfeld, R. George, I. A. Meinertzhagen, G. M. Rubin, H. F. Hess, V. Jain, S. M. Plaza, A connectome and analysis of the adult Drosophila central brain. *eLife*. **9**, e57443 (2020).

24. A. L. Juavinett, G. Bekheet, A. K. Churchland, Chronically implanted Neuropixels probes enable high-yield recordings in freely moving mice. *eLife*. **8**, e47188 (2019).

25. E. R. Oby, M. D. Golub, J. A. Hennig, A. D. Degenhart, E. C. Tyler-Kabara, B. M. Yu, S. M. Chase, A. P. Batista, New neural activity patterns emerge with long-term learning. *Proceedings of the National Academy of Sciences*. **116**, 15210–15215 (2019).

26. Y. Yang, S. Qiao, O. G. Sani, J. I. Sedillo, B. Ferrentino, B. Pesaran, M. M. Shanechi, Modelling and prediction of the dynamic responses of large-scale brain networks during direct electrical stimulation. *Nature Biomedical Engineering*. **5**, 324–345 (2021).

27. B. R. Cowley, A. C. Snyder, K. Acar, R. C. Williamson, B. M. Yu, M. A. Smith, Slow Drift of Neural Activity as a Signature of Impulsivity in Macaque Visual and Prefrontal Cortex. *Neuron*. **108**, 551–567.e8 (2020).

28. L. Avitan, C. Stringer, Not so spontaneous: Multi-dimensional representations of behaviors and context in sensory areas. *Neuron* (2022), doi:10.1016/j.neuron.2022.06.019.

29. M. Jazayeri, S. Ostojic, Interpreting neural computations by examining intrinsic and embedding dimensionality of neural activity. *Current Opinion in Neurobiology*. **70**, 113–120 (2021).

30. L. Grosenick, J. H. Marshel, K. Deisseroth, Review Closed-Loop and Activity-Guided Optogenetic Control. *Neuron*. **86**, 106–139 (2015).

31. A. Kumar, I. Vlachos, A. Aertsen, C. Boucsein, Challenges of understanding brain function by selective modulation of neuronal subpopulations. *Trends in Neurosciences*. **36**, 579–586 (2013).

32. S. M. Potter, A. El Hady, E. E. Fetz, Closed-loop neuroscience and neuroengineering. *Frontiers in Neural Circuits*. **0**, 115 (2014).

33. J. P. Newman, M. F. Fong, D. C. Millard, C. J. Whitmire, G. B. Stanley, S. M. Potter, Optogenetic feedback control of neural activity. *eLife* (2015), doi:10.7554/eLife.07192.

34. M. F. Bolus, A. A. Willats, C. J. Whitmire, C. J. Rozell, G. B. Stanley, Design strategies for dynamic closed-loop optogenetic neurocontrol in vivo. *Journal of Neural Engineering*. **15**, 026011 (2018).

35. M. F. Bolus, A. A. Willats, C. J. Rozell, G. B. Stanley, *Journal of neural engineering*, in press, doi:10.1101/2020.06.25.171785.

36. V. Emiliani, A. E. Cohen, K. Deisseroth, M. Häusser, All-optical interrogation of neural circuits. *Journal of Neuroscience*. **35**, 13917–13926 (2015).

37. Z. Zhang, L. E. Russell, A. M. Packer, O. M. Gauld, M. Häusser, Closed-loop all-optical interrogation of neural circuits in vivo. *Nature Methods*. **15**, 1037–1040 (2018).

38. E. Krook-Magnuson, C. Armstrong, M. Oijala, I. Soltesz, On-demand optogenetic control of spontaneous seizures in temporal lobe epilepsy. *Nature Communications*. **4**, 1–8 (2013).

39. A. Witt, A. Palmigiano, A. Neef, A. El Hady, F. Wolf, D. Battaglia, Controlling the oscillation phase through precisely timed closed-loop optogenetic stimulation: a computational study. *Frontiers in Neural Circuits*. **7**, 1–17 (2013).

40. S. Dutta, E. Ackermann, C. Kemere, Analysis of an open source, closed-loop, realtime system for hippocampal sharp-wave ripple disruption. *Journal of Neural Engineering*. **16**, 016009 (2019).