Closed-loop identifiability in neural circuits

Abstract

The necessity of intervention (e.g. stimulation, lesion experiments) in inferring cause has long been understood in neuroscience. Recent work has highlighted the importance of a causal perspective in answering questions about network structure and function[1][2][3]. It is increasingly clear that recording from more of the brain and using sophisticated inference approaches is necessary but not sufficient to understand how the brain functions[4]. Indeed, it has been shown that open-loop stimulation and single-site lesioning experiments may also be insufficient [5][6][7][8]. In tandem, the advent of optogenetics has facilitated increasingly precise and useful forms of intervention including closed-loop control[9] - a form of stimulation which adapts inputs in response to measured activity and which shows promise in overcoming limitations of other interventions.

However, the potential of closed-loop stimulation for network inference has not yet been achieved. A major challenge remains in integrating established techniques from control theory, causal inferences, and design of experiments in neuroscience. It is not yet clear how best to design the particulars of closed-loop control to leverage the increased inferential power granted by these approaches.

Here, we attempt to lay out these complementary ideas from causal inference and control theory in a unified description, with the goal of discovering how and where closed-loop interventions are best applied. In support of this aim, we demonstrate the performance of standard network inference procedures in simulated spiking networks under passive, open-loop and closed-loop conditions. This investigation reveals general principles of how intervention interacts with circuit structure to shape the pattern of dependence across groups. In particular, we demonstrate a unique capacity of feedback control to distinguish competing circuit hypotheses by disrupting connections which would otherwise result in equivalent patterns of correlation.

This work continues the conversation around seeking causal answers to questions of how the brain functions and how best to use the tools at our disposal. We hope it aids those designing experiments in choosing how and where to apply stimulation in order to efficiently distinguish between competing hypotheses.

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1. Pearl, J. (2009). Causality. Cambridge university press. ↩
2. "Advancing functional connectivity research from association to causation" Reid et al. - Discusses concept of multiple circuit hypotheses being compatible with an observed pattern of correlation. Details a framework for understanding how methods may narrow the space of plausible hypotheses ↩
3. "Quasi-experimental causality in neuroscience and behavioral research" Marinescu et al. - argues for use of instrumental variables to make causal statements even in observational settings ↩
4. "Systematic errors in connectivity inferred from activity in strongly recurrent networks" Das & Fiete - demonstrates irreducible bias in connectivity estimates from highly-connected networks observed in passive settings. Suppresive open-loop stimulation was shown to reduce this bias ↩
5. "The promise and perils of causal circuit manipulations " Wolff, Olveczky - discusses acute v.s. chronic and disruptive v.s. physiological perturbations. Also mentions the promise of closed-loop control in this respect. ↩
6. "Inferring causal connectivity from pairwise recordings and optogenetics" *(preprint)* Lepperød et al. - discusses practical issues in inferring connectivity from stimulation which may provide common input to many neurons. Highly biased connectivity estimates can be greatly improved by applying instrumental variables. ↩

7. "Could a Neuroscientist Understand a Microprocessor?" Jonas & Kording - demonstrates the insufficiency of single-site lesioning and other common analysis techniques in neuroscience in reverse engineering the ground-truth structure of an aritificial neural network. ↩ ↩
8. Systematic Perturbation of an Artificial Neural Network: A Step Towards Quantifying Causal Contributions in The Brain - building on [7:1], this paper demonstrates the necessity of multi-site (rather than single-site) lesions in understanding the structure of artificial neural networks. ↩
9. "Closed-loop and Activity-Guided Optogenetic Control" Grosenick, Marshel, Deisseroth - reviews the motivation and methods for closed-loop optogenetic control for basic science and therapeutic applications ↩