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. 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. Indeed, it has been shown that open-loop stimulation and single-site lesioning experiments may also be insufficient. In tandem, the advent of optogenetics has facilitated increasingly precise and useful forms of intervention including closed-loop control - 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.