Closed-Loop Identifiability in Neural Circuits

true

,

Abstract

!!!! Todo 3/16: - Mention basic science applications of CL control - Maybe more forecasting idea of shaping correlations? (don't want reader to be surprised by structure of paper's argument)

The necessity of intervention in inferring cause has long been understood in neuroscience. Recent work has highlighted the limitations of passive observation and single-site lesion studies in accurately recovering causal circuit structure. The advent of optogenetics has facilitated increasingly precise forms of intervention including closed-loop control which may help eliminate confounding influences. However, it is not yet clear how best to apply closed-loop control to leverage this increased inferential power. In this paper, we use tools from causal inference, control theory, and neuroscience to show when and how closed-loop interventions can more effectively reveal causal relationships. `We also examine the performance of standard network inference procedures in simulated spiking networks under passive, open-loop and closed-loop conditions.` 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[1]. Our results build toward a practical framework to improve design of neuroscience experiments to answer causal questions about neural circuits.

Introduction

Estimating causal interactions in the brain

!!!! - 70% done

[1] may end up discussing quantitative advantages such as bidirectional variance (and correlation) control. If that's a strong focus in the results, should be talked about more in the abstract also

!!!! Todo 3/16: - "We first propose…" paragraph (could build out or move or change focus away from the 'framework') - think about condensing and/or moving "Inferring causal interactions from time series" subsection - Maybe add half a paragraph or so in the discussion about how causal inference tools can help above correlation analysis (e.g., PC algorithm)

Many hypotheses about neural circuits are phrased in terms of causal relationships: "will changes in activity to this region of the brain produce corresponding changes in another region?" Understanding these causal relationships is critical to both scientific understanding and to developing effective therapeutic interventions, which require knowledge of how potential therapies will impact brain activity and patient outcomes.

A range of mathematical and practical challenges make it difficult to determine these causal relationships. In studies that rely only observational data, it is often impossible to determine whether observed patterns of activity are caused by known and controlled inputs, or whether they are instead spurious connections generated by recurrent activity, indirect relationships, or unobserved "confounders." It is generally understood that moving from experiments involving passive observation to more complex levels of intervention allows experimenters to better tackle challenges to circuit identification. However, while chemical and surgical lesion experiments have historically been employed to remove the influence of possible confounds, they are likely to dramatically disrupt circuits from their typical functions, making conclusions about underlying causal structure drawn from these experiments unlikely to hold in naturalistic settings (Chicharro and Ledberg 2012). *Closed-loop* interventions […] ==“Adam-to-Do” (2022): short description of closed-loop in neuro, maybe drawing from text in this collapsable:==

Proposal text to draw from:

For decades, engineers have used feedback control to actuate a system based on measured activity to reduce variability, compensate for imperfect measurements, drive systems to desired set points, and decouple connected systems […]

There is an increasing interest in using approaches from closed-loop control for neural stimulation to both study complex neural circuits and treat neurologic disorders. Recently, a growing community is developing and applying closed-loop stimulation strategies at the cellular and circuit level (Miranda-Dominguez, Gonia, and Netoff 2010; Santaniello, Burns, et al. 2011; Ching et al. 2013; Iolov, Ditlevsen, and Longtin 2014; Nandi, Kafashan, and Ching 2016; Bolus et al. 2018) to understand the brain (Packer et al. 2015) as well as treat disorders (Santaniello, Fiengo, et al. 2011; Paz et al. 2013; Ehrens, Sritharan, and Sarma 2015; Choi et al. 2016; Yang and Shanechi 2016; Kozák and Berényi 2017; Sorokin et al. 2017) The advent of optogenetic stimulation has accelerated the potential for effective closed-loop stimulation by providing actuation strategies that can be more precisely targeted and have minimal recording artifacts compared to conventional microelectrode stimulation (Grosenick, Marshel,

and Deisseroth 2015)

Most applications of closed-loop control to neuroscience to date have used "activity-guided / responsive / triggered stimulation" wherein a predesigned stimulus is delivered in response to a detected event. For example, in (Krook-Magnuson et al. 2013) the authors detect seizure activity from spiking and local field potential features to trigger a pulse-train of inhibitory optogenetic stimulation which interrupts the seizure. While this is an effective approach for many applications, these types of closed-loop experiments should be distinguished from closed-loop with ongoing feedback such as dynamic clamp. In these feedback control approaches parameters of stimulation are adjusted on much faster timescales in response to measured activity. For dynamic clamp experiments, this low-latency ongoing feedback control allows experimenters to deliver currents which mimic virtual ion channels which would be implausible with triggered predesigned stimulation. These approaches provide additional precision in being able to drive activity patterns, but also come with increased algorithmic and hardware demands. For the rest of this document, we will use "closed-loop control" or "feedback control" to refer to this second, more specific class of approaches.

While many such new actuation and measurement tools have recently become available for neural systems, we require the development of principled algorithmic tools for designing feedback controllers to use these neural interfaces. Our collaborators have previously demonstrated successful closed-loop optogenetic control (CLOC) in-vitro (Newman et al. 2015) and in-vivo (Bolus et al. 2018) to track naturalistic, time-varying trajectories of firing rate.

-> Also add citation to [**?**]

Despite the promise of these closed-loop strategies for identifying causal relations in neural circuits, however, it is not yet fully understood *when* more complex intervention strategies can provide additional inferential power, or *how* these experiments should be optimally designed. In this paper we demonstrate when and how closed-loop interventions can reveal the causal structure governing neural circuits. Drawing from ideas in causal inference (Pearl 2009) (Maathuis and Nandy 2016) [**?**], we describe the classes of models that can be distinguished by a given set of input-output experiments, and what experiments are necessary to uniquely determine specific causal relationships.

We first propose a mathematical framework that describes how open- and closed-loop interventions impact observable qualities of neural circuits. Using this framework, experimentalists propose a set of candidate hypotheses describing the potential causal structure of the circuit under study, and then select a series of interventions that best allows them to distinguish between these hypotheses. Using both simple controlled models and in silico models of spiking networks, we explore factors that govern the efficacy of these types of interventions. Guided by the results of this exploration, we present a set of recommendations that can guide the design of open- and closed-loop experiments to better uncover the

causal structure underlying neural circuits.

Inferring causal interactions from time series. A number of strategies have been proposed to detect causal relationships between observed variables. Wiener-Granger (or predictive) causality states that a variable X "Granger-causes" Y if X contains information relevant to Y that is not contained in Y itself or any other variable [**?**]. This concept has traditionally been operationalized with vector autoregressive models [**?**]; the requirement that *all* potentially causative variables be considered makes these notions of dependence susceptible to unobserved confounders [**?**].

Our work initially focuses on measures of directional interaction that are based on lagged correlations [**?**]. These metrics look at the correlation of time series collected from pairs of nodes at various lags and detect peaks at negative time lags. Such peaks could indicate the presence of a direct causal relationship – but they could also stem from indirect causal links or hidden confounders [**?**]. In these bivariate correlation methods, it is thus necessary to consider patterns of correlation between many pairs of nodes in order to differentiate between direct, indirect, and confounding relationships [**?**]. This distinguishes these strategies from some multivariate methods that "control" for the effects of potential confounders. While cross-correlation-based measures are generally limited to detecting linear functional relationships between nodes, their computational feasibility makes them a frequent metric of choice in experimental neuroscience work [**?**] [**?**] [**?**].

Other techniques detect directional interaction stemming from more general or complex relationships. Information-theoretic methods, which use information-based measures to assess the reduction in entropy knowledge of one variable provides about another, are closely related to Granger causality [**?**] [**?**]. The *transfer entropy* $T_{X\to Y}(t) = I(Y_t\colon X_{<t} \mid Y_{<t})$ extends this notion to time series by measuring the amount of information present in Y_t that is not contained in the past of either X or Y (denoted $X_{<t}$ and $Y_{<t}$) [**?**]. Using transfer entropy as a measure of causal interaction requires accounting for potential confounding variables; the *conditional transfer entropy* $T_{X\to Y|Z}(t) = I(Y_t\colon X_{<t} \mid Y_{<t}, Z_{<t})$ conditions on the past of other variables to account for their potential confounding influence [**?**, Sec. 4.2.3]. Conditional transfer entropy can thus be interpreted as the amount of information present in Y that is not contained in the past of X, the past of Y, or the past of other variables Z.

To quantify the strength of causal interactions, information-theoretic and transfer-entropy-based methods typically require knowledge of the ground truth causal relationships that exist [**?**] or an ability to perturb the system [**?**] [**?**]. In practice, these quantities are typically interpreted as "information transfer," and a variety of estimation strategies and methods to automatically select the conditioning set (i.e., the variables and time lags that should be conditioned on) are used (e.g., [**?**]). Multivariate conditional transfer entropy approaches using various variable selection schemes can differentiate between direct interactions, indirect interactions, and common

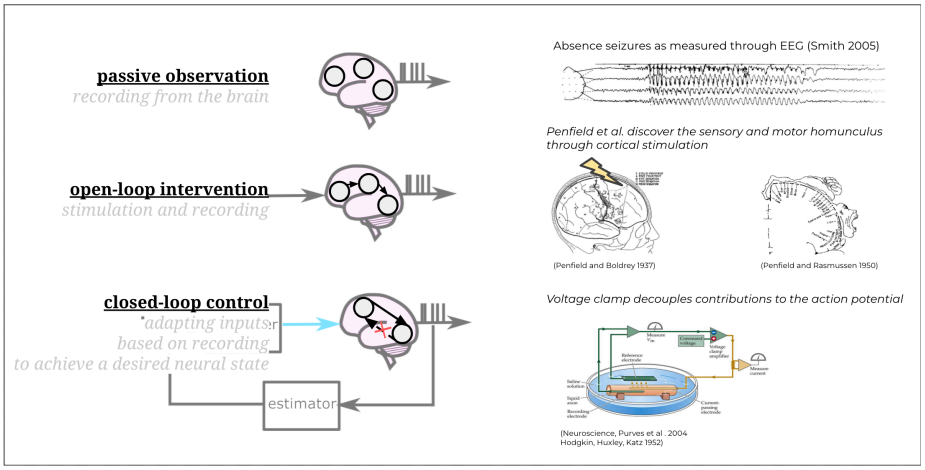
causes, but their results depend on choices such as the binning strategies used to discretize continuous signals, the specific statistical tests used, and the estimator used to compute transfer entropy [**?**]. `[If we end up making the jump to IDTxl in our results: In our empirical results using transfer-entropy-based notions of directional influence we use the IDTxl toolbox \cite{wollstadt2019idtxl}.]` However, despite their mathematical differences, previous work has found that cross-correlation-based metrics and information-based metrics tend to produce qualitatively similar results, with similar patterns of true and false positives [**?**].

Interventions in neuroscience & causal inference

!!!! - 70% done

!!!! Todo - Get language more precise and effective *(see writing_tasks)*

Data collected from experimental settings can provide more inferential power than observational data alone. For example, consider an experimentalist who is considering multiple causal hypotheses for two nodes under study, x and y: the hypothesis that x is driving y, the hypothesis that y is driving x, or the hypothesis that the two variables are being independently driven by a hidden confounder. Observational data revealing that x and y produce correlated time-series data is equally consistent with each of these three causal hypotheses, providing the experimentalist with no inferential power. Experimentally manipulating x and observing the output of y, however, allows the scientist to begin to establish which causal interaction pattern is at work. Consistent with intuition from neuroscience literature, a rich theoretical literature has described the central role of interventions in inferring causal structure from data [**?**, **?**].



> **Figure INTRO:** Examples of the roles interventions have played in neuroscience. (A) *Passive observation* does not involve stimulating the brain. In this example, passive observational data is used to identify patients suffering

from absence seizures. (B) *Open-loop stimulation* involves recording activity in the brain after perturbing a region with a known input signal. Using systematic *open-loop stimulation experiments*, Penfield uncovered the spatial organization of how senses and movement are mapped in the cortex [**?**] [**?**]. (C) *Closed-loop control* uses feedback control to precisely specify activity in certain brain regions regardless of activity in other regions. Using closed-loop control, ==todo-Adam== [**?**].

The inferential power of interventions is depends on *where* stimulation is applied: interventions on some portions of a system may provide more information about the system's causal structure than interventions in other areas. And interventions are also more valuable when they more effectively set the state of the system: "perfect" closed-loop control, which completely severs a node's activity from its inputs, are often more informative than "soft" interventions that only partially control a part of the system [**?**].

In experimental neuroscience settings, experimenters are faced with deciding between interventions that differ in both location and effectiveness. For example, stimulation can often only be applied to certain regions of the brain. And while experimenters may be able to exactly manipulate activity in some parts of the brain using closed-loop control, in other locations it may only be possible to apply weaker forms of intervention that perturb a region but do not manipulate its activity exactly to a desired state. In Section [X], we compare the effectiveness of open-loop, closed-loop, and partially-effective closed-loop control.

Although algorithms designed to choose optimal interventions are often designed for simple models with strong assumptions,[2] they provide intuition that can aid practitioners seeking to design real-world experiments that provide as much scientific insight as possible.[3] Importantly, the informativeness of interventions is often independent of the algorithm used to infer causal connections, meaning that certain interventions can reveal portions of a circuit's causal structure that would be impossible for *any* algorithm to infer from only observational data [**?**] ==(<- Matt to Adam: make sure this citation is in the right place)==. We similarly expect the results we demonstrate in this paper to both inform experimentalists and open avenues for further research.

Representations & reachability

!!!! - 60% done

!!!! todo - Rewrite X=XW+E as vector version - Describe what 'reachability' is *(see writing_tasks)*

[2] These assumptions are typically on properties such as the types of functional relationships that exist in circuits, the visibility and structure of confounding relationships, and noise statistics.

[3] if citations needed here, could start by looking for a good high-level reference in either [**?**] or [**?**]. (Both of these papers are pretty technical, so likely wouln't be great citations on their own.)

Different mathematical representations of circuits can elucidate different connectivity properties. For example, consider the circuit $A \to B \leftarrow C$. This circuit can be modeled by the dynamical system

$$\begin{cases} \dot{x}_A &= f_A(e_A) \\ \dot{x}_B &= f_B(x_A, x_C, e_B) \\ \dot{x}_C &= f_C(e_C), \end{cases}$$

where e_A, e_B, and e_C represent exogenous inputs that are inputs from other variables and each other[4].

When the system is linear we can use matrix notation to describe the impact of each node on the others:[5]

$$x_{t+1} = Wx_t + e_t,$$

where $x_t \in \mathbb{R}^p$ denotes the state of each of the p nodes at time t, and $e_t \in \mathbb{R}^p$ denotes the instantiation of each node's (independent and identically-distributed) private noise variance at time t.

!!!! - TODO Adam, write out the dynamical system version of this

where W represents the *adjacency matrix*

$$W = \begin{bmatrix} w_{AA} & w_{AB} & w_{AC} \\ w_{BA} & w_{BB} & w_{BC} \\ w_{CA} & w_{CB} & w_{CC} \end{bmatrix}.$$

In the circuit $A \to B \leftarrow C$, we would have $w_{AB} \neq 0$ and $w_{CB} \neq 0$.

The adjacency matrix captures directional first-order connections in the circuit: w_{ij}, for example, describes how activity in x_j changes in response to activity in x_i.

Our goal is to reason about the relationship between underlying causal structure (which we want to understand) and the correlation or information shared by pairs of nodes in the circuit (which we can observe). Quantities based on the adjacency matrix and weighted reachability matrix bridge this gap, connecting the causal structure of a circuit to the correlation structure its nodes will produce.

The directional k^{th}-order connections in the circuit are similarly described by the matrix W^k, so the *weighted reachability matrix*

$$\widetilde{W} = \sum_{k=0}^{\infty} W^k$$

[4]the most important property of e for the math to work, i believe, is that they're random variables independent of each other. This is not true in general if E is capturing input from common sources, other nodes in the network. I think to solve this, we'll need to have an endogenous independent noise term and an externally applied (potentially common) stimulus term.

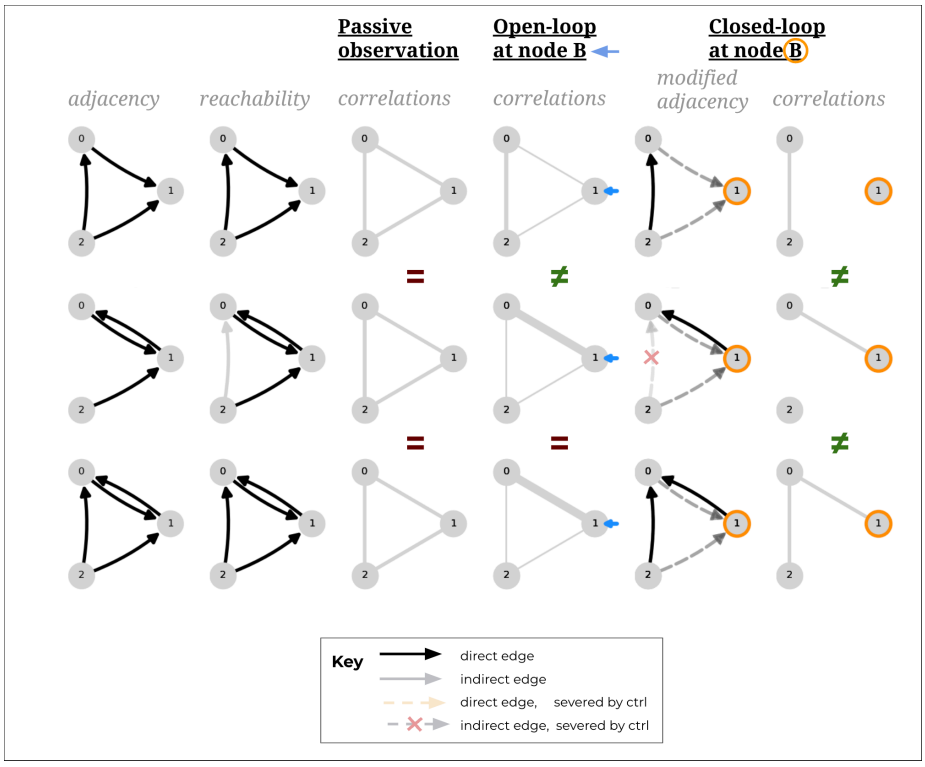
[5]have to be careful with this. this almost looks like a dynamical system, but isn't. In simulation we're doing something like an SCM, where the circuit is sorted topologically then computed sequentially. have to resolve / compare these implementations

describes the total impact – through both first-order (direct) connections and higher-order (indirect) connections – of each node on the others. Whether node j is "reachable" (Skiena 2011) from node i by a direct or indirect connection is thus indicated by $\widetilde{W}_{ij} \neq 0$, with the magnitude of $\widetilde{W}_{ij}$ indicating sensitive node j is to a change in node i.

This notion of reachability, encoded by the pattern of nonzero entries in $\widetilde{W}$, allows us to determine when two nodes will be correlated (or more generally, contain information about each other). Moreover, as we will describe in Sections [REF] and [REF], quantities derived from these representations can also be used to describe the impact of open- and closed-loop interventions on circuit behavior, allowing us to quantitatively explore the impact of these interventions on the identifiability of circuits.

!!!! - 70% done

!!!! todo - Talk about what 'reachability' means (total direct+indirect impact) - [Matt:] Rewrite first paragraph to not use notation (place this box before any theory/notation sections) - [Matt:] Set expectation here that we're talking about linear Gaussian circuits



> **Figure DEMO *(box format)*: Applying CLINC to distinguish a pair of circuits** > > Consider the three-node identification problem shown in the figure above, in which the experimenter has identified three hypotheses for

the causal structure of the circuit. These circuit hypotheses, shown as directed graphs in column 1, can each also be represented by an adjacency matrix of the form **??**: for example, circuit A is represented by an adjacency matrix in which w_{01}, w_{20}, and $w_{21} \neq 0$. Note that hypotheses A and C have direct connections between nodes 0 and 2; while hypothesis B does not have a direct connection between these nodes, computing the weighted reachability matrix $\widetilde{W}$ in circuit B an *indirect* connection exists through the path $2 \rightarrow 1 \rightarrow 0$ (illustrated in gray in column 2). $>>$ Because there are direct or indirect connections between each pair of nodes, passive observation of each hypothesized circuit would reveal that each pair of nodes is correlated (column 3). These three hypotheses are therefore difficult to distinguish[6] for an experimentalist who performs only passive observation, but can be distinguished through stimulation. $>>$ Column 4 shows the impact on observed correlations of performing *open-loop* control on node 1. In hypothesis A, node 1 is not a driver of other nodes, so open-loop stimulation at this site will not increase the correlation between the signal observed at node 1 and other nodes. The path from node 1 to 0 in hypotheses B and C, meanwhile, causes the open-loop stimulation at node 1 to *increase* the observed correlation between nodes 1 and 0. An experimenter can thus distinguish between hypothesis A and the other two hypotheses by appling open-loop control and observing the resulting pattern of correlations (column 4). However, this pattern of open-loop stimulation would not allow the experimenter to distinguish between hypotheses B and C. $>>$ *Closed-loop* control (columns 5 and 6) can provide the experimenter with even more inferential power. Column 5 shows the resulting adjacency matrix when this closed-loop control is applied to node 1. In each hypothesis, the impact of this closed-loop control is to remove the impact of other nodes on node 1, because when perfect closed-loop is applied the activity of node 1 is completely independent of other nodes. (These severed connections are depicted in column 5 by dashed lines.) In hypothesis B, this also results in the elimation of the indirect connection from node 2 to node 1. The application of closed-loop control at node 1 thus results in a different observed correlation structure in each of the three circuit hypotheses (column 6). This means that the experimenter can therefore distinguish between these circuit hypotheses by applying closed-loop control – a task not possible with passive observation or open-loop control.

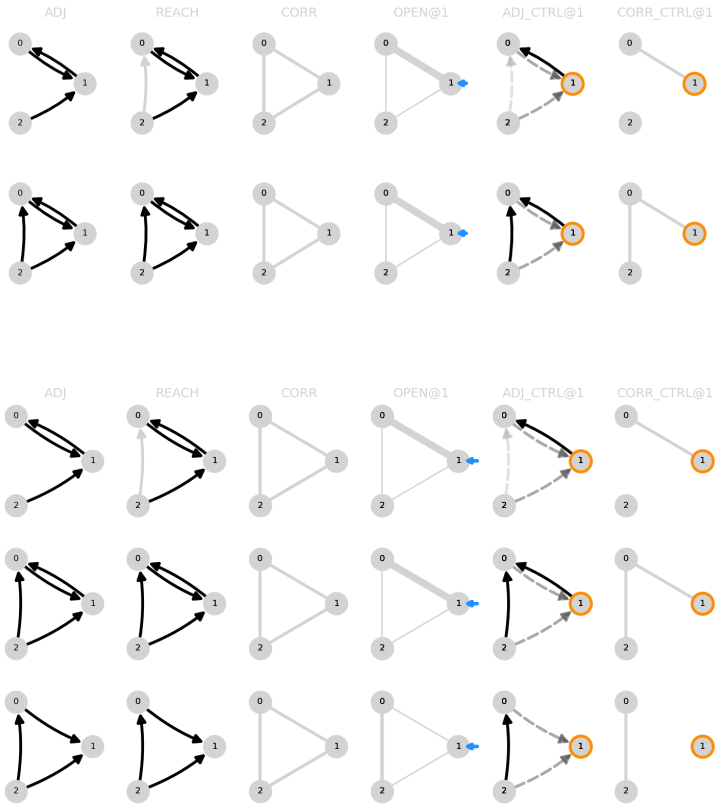
figure to do items for "Adam-to-Do" (2022)

- ☐ "Adam-to-Do" (2022) - change labels at top from "B" to "1"
- ☐ "Adam-to-Do" (2022) - add (A) (B) (C) labels to each row
- ☐ "Adam-to-Do" (2022) - in legend, change in/direct "edge" to in/direct "connection"
- ☐ "Adam-to-Do" (2022) - in legend, orange dashed arrow to dark gray

–

[6] saying "difficult to distinguish" instead of "indistinguishable" here since the magnitudes of the correlations could also be informative with different assumptions

2,3 circuit versions, straight from code



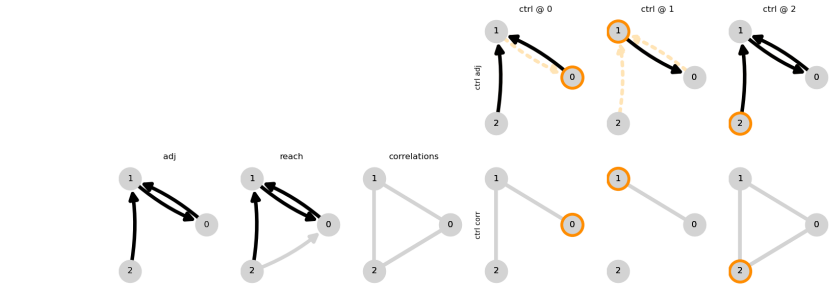
> 3 circuit walkthrough, walkthrough will all intervention locations might be appropriate for the supplement

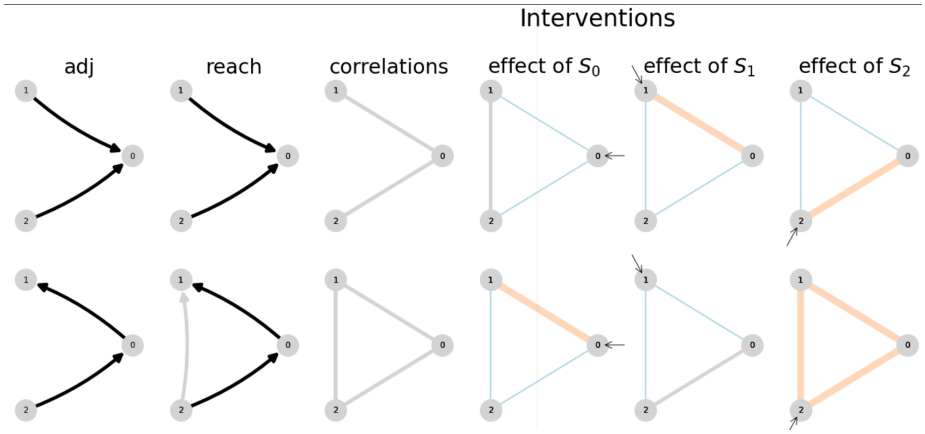
to do items

- ☐ find and include frequent circuit (curto + motif)
- ☐ wrap circuits we want in `example_circuits.py`
- ☐ alt method of displaying indirect paths?
  - https://networkx.org/documentation/stable/reference/algorithms/generated/networkx.algorithms.s

see also

more inspiration: - Combining multiple functional connectivity methods to improve causal inferences - Advancing functional connectivity research from association to causation - Fig1. of “Systematic errors in connectivity”





this figure does a great job of: - setting up a key - incrementally adding confounds - highlighting severed edges this figure does NOT - explicitly address mutliple hypotheses

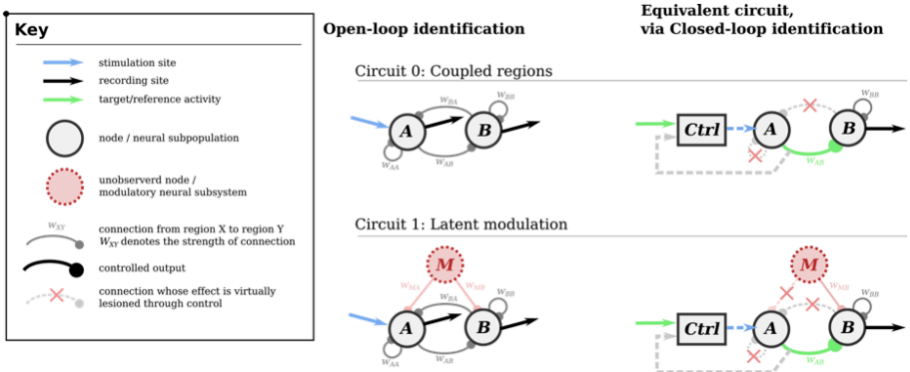


Figure 11: Closed-loop control compensates for inputs to a node in simple circuits: *The left column shows a simple circuit and recording and stimulation sites for an open-loop experiment. The right column shows the functional circuit which results from closed-loop control of the output of region A. Generally, assuming perfectly effective control, the impact of other inputs to a controlled node is nullified and therefore crossed off the functional circuit diagram.*

Figure 11: Closed-loop control compensates for inputs to a node in simple circuits: The left column shows a simple circuit and recording and

stimulation sites for an open-loop experiment. The right column shows the functional circuit which results from closed-loop control of the output of region A. Generally, assuming perfectly effective control, the impact of other inputs to a controlled node is nullified and therefore crossed off the functional circuit diagram.

this figure does a great job of: - using a minimal version of the key above - showing two competing hypotheses - (throughs latent / common modulation in for fun)

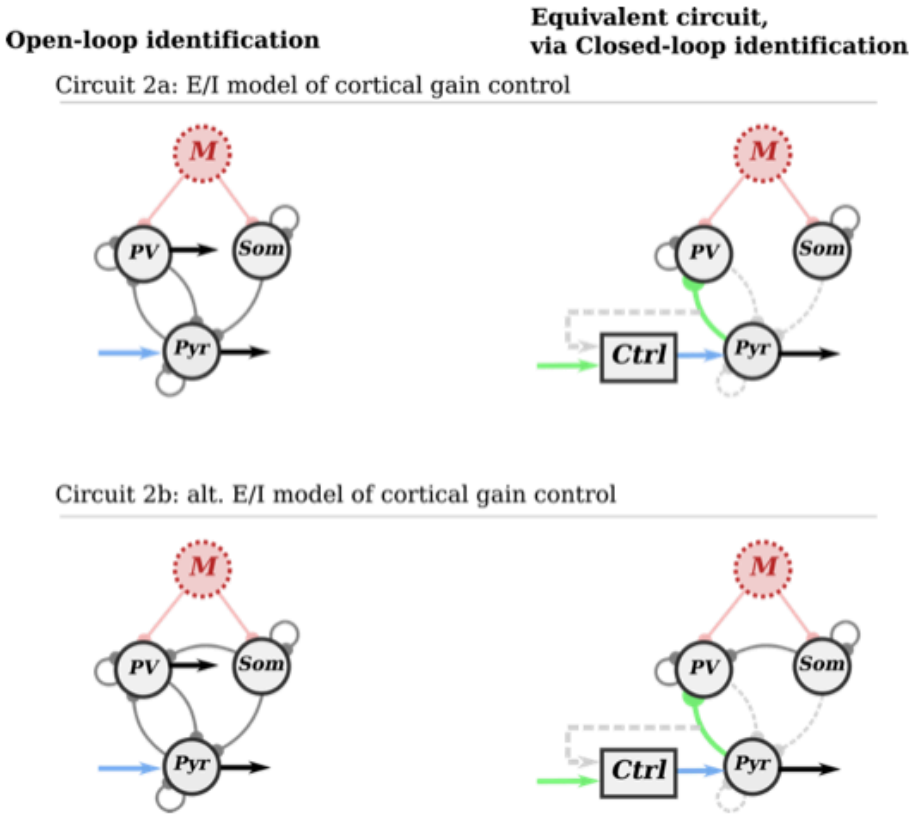


Figure 12: Closed-loop control allows for two circuit hypotheses to be distinguished. Two hypothesized circuits for the relationships between pyramidal (Pyr, excitatory), parvalbumin-positive (PV, inhibitory), and somatostain-expressing (Som, inhibitory) cells are shown in the two rows. Dashed lines in the right column represent connections whose effects are compensated for through closed-loop control of the Pyr node. By measuring correlations between recorded regions during closed-loop control it is possible to distinguish which hypothesized circuit better matches the data. Notably in the open-loop intervention, activity in all regions is correlated for both hypothesized circuits leading to ambiguity.

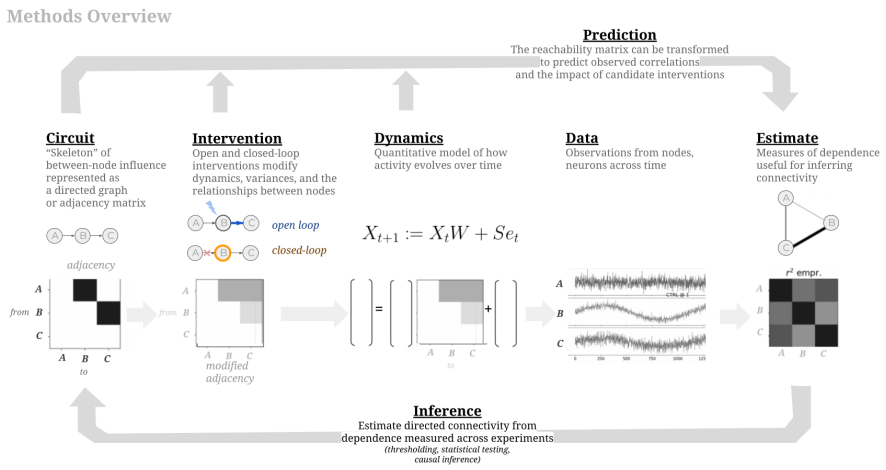
more notes

probably want - two circuits which look clearly different - ! but which have equivalent reachability - possibly with reciprocal connections - possssibly with common modulation

- do we need to reflect back from set of possible observations to consistent hypotheses?
  - mention markov equivalence classes explicitly?
- intuitive explanation using binary reachability rules
- *point to the rest of the paper as deepening and generalizing these ideas*
- *(example papers - Advancing functional connectivity research from association to causation, Combining multiple functional connectivity methods to improve causal inferences)*
- connect **graded reachability** to ID-SNR
  - IDSNR_{ij} measures the strength of signal related to the connection $i \to j$ relative to in the output of node j
  - for true, direct connections this quantity increasing means a (true positive) connection will be identified more easily (with high certainty, requiring less data)
  - for false or indirect connections, this quantity increasing means a false positive connection is more likely to be identified
  - as a result we want to maximize IDSNR for true links, and minimize it for false/indirect links

(see also `sketches_and_notation/walkthrough_EI_dissection.md`)

Theory / Prediction



> **Figure OVERVIEW: …**

Predicting correlation structure (theory)

A linear-Gaussian circuit can be described by 1) the variance of the gaussian private (independent) noise at each node, and 2) the weight of the linear relationships between each pair of connected nodes. Let $s \in \mathbb{R}^p$ denote the variance of each of the p nodes in the circuit, and $W \in \mathbb{R}^{p \times p}$ denote the matrix of connection strengths such that

$$W_{ij} = \text{strength of } i \to j \text{ connection.}$$

Note that $\left[(W^T)s\right]_j$ gives the variance at node j due to length-1 (direct) connections, and more generally, $\left[(W^T)^k s\right]_j$ gives the variance at node j due to length-k (indirect) connections. The *total* variance at node j is thus $\left[\sum_{k=0}^{\infty}(W^T)^k s\right]_j$.

Our goal is to connect private variances and connection strengths to observed pairwise correlations in the circuit. Defining $X \in \mathbb{R}^{p \times n}$ as the matrix of n observations of each node, we have[7]

$$\begin{aligned}\Sigma = \text{cov}(X) &= \mathbb{E}\left[XX^T\right] \\ &= (I - W^T)^{-1}\text{diag}(s)(I - W^T)^{-T} \\ &= \widetilde{W}\text{diag}(s)\widetilde{W}^T,\end{aligned}$$

[7]To see this, denote by $E \in \mathbb{R}^{p \times n}$ the matrix of n private noise observations for each node. Note that $X = W^T X + E$, so $X = E(I - W^T)^{-1}$. The covariance matrix $\Sigma = \text{cov}(X) = \mathbb{E}\left[XX^T\right]$ can then be written as $\Sigma = \mathbb{E}\left[(I - W^T)^{-1}EE^T(I - W^T)^{-1}\right] = (I - W^T)^{-1}\text{cov}(E)(I - W^T)^{-T} = (I - W^T)^{-1}\text{diag}(s)(I - W^T)^{-T}$.

where $\widetilde{W} = \sum_{k=0}^{\infty}(W)^k$ denotes the *weighted reachability matrix*, whose $(i,j)^{\text{th}}$ entry indicates the total influence of node i on node j through both direct and indirect connections.[8] That is, $\widetilde{W}_{ij}$ tells us how much variance at node j would result from injecting a unit of private variance at node i. We can equivalently write $\Sigma_{ij} = \sum_{k=1}^{p} \widetilde{W}_{ik}\widetilde{W}_{jk}s_k$.

Under passive observation, the squared correlation coefficient can thus be written as

$$\begin{aligned} r^2(i,j) &= \frac{\Sigma_{ij}}{\Sigma_{ii}\Sigma_{jj}} \\ &= \frac{\left(\sum_{k=1}^{p} \widetilde{W}_{ik}\widetilde{W}_{jk}s_k\right)^2}{\left(\sum_{k=1}^{p} \widetilde{W}_{ik}^2 s_k\right)\left(\sum_{k=1}^{p} \widetilde{W}_{jk}^2 s_k\right)}. \end{aligned}$$

This framework also allows us to predict the impact of open- and closed-loop control on the pairwise correlations we expect to observe. To model the application of open-loop control on node c, we add an arbitrary amount of private variance to s_c: $s_c \leftarrow s_c + s_c^{(OL)}$. To model the application of closed-loop control on node c, we first sever inputs to node c by setting $W_{k,c} = 0$ for $k = 1, \ldots p$, and then set the private variance of node c by setting s_c to any arbitrary value. Because c's inputs have been severed, this private noise will become exactly node c's output variance.

!!!! todo [Matt:] add table from `sketches_and_notation/intro-background/causal_vs_expt.md` and modify text above to match

!!!! todo - Some redundancy with simulation methods; cut and paste anything useful in 4.2 and put into 3.1 / 3.2

Simulation Methods

!!!! todo - reorganize / split sections

@ import "/section_content/methods0_simulations_interventions_estimates.md"

@ import "/section_content/methods2_hypothesis_entropy.md"

Results

!!!! - overall, 60% done

Impact of intervention on estimation performance

!!!! todo - comaprison signs in rows of DISAMBIG figure !!!! todo - merge from "box style" where entrire story is in caption, to having something in body of

[8] We can use $p-1$ as an upper limit on the sum $\widetilde{W} = \sum_{k=0}^{\infty} W^k$ when there are no recurrent connections.

results text !!!! todo - write “explain why CL is better” section, ? exile it to discussion section? !!!! todo - connect DISAMBIG caption to quantitative variance explanation section !!!! todo - collapse figvar - do we need to make shared input point here? or is discussion fine? !!!! todo - dR/dS needs to mention R as r^2 corr @ import “/section_content/results1_impact_of_intervention.md”

Notes from matt

- [super minor] First part of fig DISAMBIG: subsections (A) through (C) work really well
- [super minor] in caption for (D-F): “modifications to the passive correlation pattern” is a bit confusing in the context of open-loop intervention
- [super minor] also in caption for (D-F): really like “intervention-specific fingerprint” terminology. The last sentence of the (D-F) caption really hits the message home, possible to emphasize that this is the take-home message earlier?
- [narrative/organization] fig DISAMBIG feels really example-y, more like a proof of concept than ‘results.’ The writing in Sec 5.1.1 also has this flavor, like it could be in a methods section. (The plot in the top right feels much more results-ey.) Not necessarily a bad thing, maybe just a consideration for thinking about article vs perspective flavor.
- [missing] Section 5.1.2.1: what are the definitions of S_k, CoReach(i,j|S_k), and R_{ij}?
- [narrative] Section 5.1.2.1: the narrative here really works for me, but it’s a little unclear whether this is more of a ‘result’ or a ‘recipe’ – the figures here also feel more example/proof-of-concept-ey, and the math here helps ground things in
- [missing] discussion of partial closed-loop control?

Discussion

limitations

The examples explored in this work simplify several key features that may have relevant contributions to circuit identification in practical experiments. […]

`full observability`

results summary → summary of value closed-loop generally

Closed-loop control has the disadvantages of being more complex to implement and requires specialized real-time hardware and software, however it has been shown to have multifaceted usefulness in clinical and basic science applications. Here we focused on two advantages in particular; First, the capacity for functional lesioning which (reversibly) severs inputs to nodes and second, closed-loop control’s capacity to precisely shape variance across nodes. Both of these advantages facilitate opportunities for closed-loop intervention to reveal more circuit

structure than passive observation or even open-loop experiments.

summary of guidelines for experimentors

In studying the utility of various intervention for circuit inference we arrived at a few general guidelines which may assist experimental neuroscientists in designing the right intervention for the quesiton at hand. First, more ambiguous hypotheses sets require "stronger" interventions to distinguish. Open-loop intervention may be sufficient to determine directionality of functional relationships, but as larger numbers of similar hypotheses [...] closed-loop intervention reduces the hypothesis set more efficiently. Second, we find that dense networks with strong reciprocal connections tend to result in many equivalent circuit hypotheses, but that well-placed closed-loop control can disrupt loops and simplify correlation structure to be more identifiable.[9] Recurrent loops are a common feature of neural circuit, and represent key opportunities for successful closed-loop intervention. The same is true for circuits with strong indirect correlations

`hidden confounds`

"funnel out", future work → broad impact

`sequential experimental design`

see limitations_future_work.md

References

see pandoc pandoc-citations

Supplement

"Adam-to-Do." 2022.

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[9] this corroborates Ila Fiete's paper on bias as a function of recurrent network strength