

Overview

Intended audience

- **systems neuroscientists** interested in making more rigorous conclusions in circuit ID problems
- **experimental neuroscientists** looking for guidance on evaluating required intervention to answer circuit hypothesis questions

Goal

- Provide a practical conceptual framework for applying closed-loop to circuit identification problems
 - What's the value of closed-loop?
 - What can i say about causal connections given the experiments i'm doing?
 - How do I design an intervention which improves the strength of hypothesis testing?

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Introduction

Why? - Estimating causal interactions in the brain

- understanding relationship between structure and function
 - for basic science
 - and for discovering new therapies
 - optimize therapeutic targets for existing approaches

How? - Causal methods for network discovery from time-series

- Challenges faced when estimating network connectivity
 - [...]
- measures of dependence
 - correlation (granger causality, cross-correlation)
 - info theoretic (transfer entropy)
- role of conditioning
 - bivariate v.s. multivariate approaches
- (*statistical testing*)
 - need for group effect and post-hoc tests
 - issue of multiple comparisons
 - in the end we were leaning on IDTxl for this... may be appropriate to leave this out of scope
- (*perspective on role, limitations of granger causality in neuro*)
 - are some of these limitations alleviated by intervention? *
- *cite J.Runge*

Interventions in neuro

- (walkthrough from passive, open-loop, closed-loop with historic examples)
 - **passive** detect seizure from EEG
 - **open-loop** Penfield discovers spatial map of senses by electrical stimulation
 - **lesion studies** in neuro
 - disadvantages of lesioning
 - **closed-loop** Hodgkin, Huxley discover the role of ion channels in generating action potentials through voltage clamp
 - What is closed-loop control?
 - Responsive and per-sample feedback control in neuro
 - Comparison to standard neuro system identification procedures (stim, lesions)
 - Stanley, Rozell prior work in closed-loop opto

Role of interventions in causal inference

- core idea is that "stronger" interventions lead to "higher inferential power"
 - may mean identifying circuits with less data
 - but may also mean distinguishing circuits which may have been "observationally equivalent" under weaker interventions
- **Highlight that the impact of interventions may generalize across any particular choice of inference algorithm**
- intervention types

Multiple complementary perspectives (representations) of the same underlying network structure:

- The circuit view
 - $(A) \rightarrow (B) \leftrightarrow (C)$
- The dynamical system view

$$\begin{cases} x' = Ax + Bu \\ y = Cx + \eta \end{cases}$$

- The connectivity (adjacency matrix) view

$$\underbrace{\begin{bmatrix} \dot{x}_A \\ \dot{x}_B \\ \dot{x}_C \end{bmatrix}}_{\dot{x}} = \underbrace{\begin{bmatrix} w_{AA} & w_{AB} & w_{AC} \\ w_{BA} & w_{BB} & w_{BC} \\ w_{CA} & w_{CB} & w_{CC} \end{bmatrix}}_A \underbrace{\begin{bmatrix} x_A \\ x_B \\ x_C \end{bmatrix}}_x$$

- why consider multiple perspectives

Reachability

- concept of **binary reachability** as a "best case scenario" for identification.
 - binary reachability describes which pairs of nodes we expect to have any correlation
 - can be used to predict "equivalence classes", i.e. circuits which may be indistinguishable under certain interventions
 - how binary reachability is computed
 - [...equations here...]
- **graded reachability** can help predict the influence of parameter values (e.g. edge weights, time-constants) on identifiability
 - quantifies impact of inputs, noise on outputs
 - easiest to describe/understand in linear-gaussian setting
 - [...equations here...]

 **Figure:** illustrate reachability 

Understanding identification through derived properties of circuits (reachability rules)

 more appropriate for methods section? 

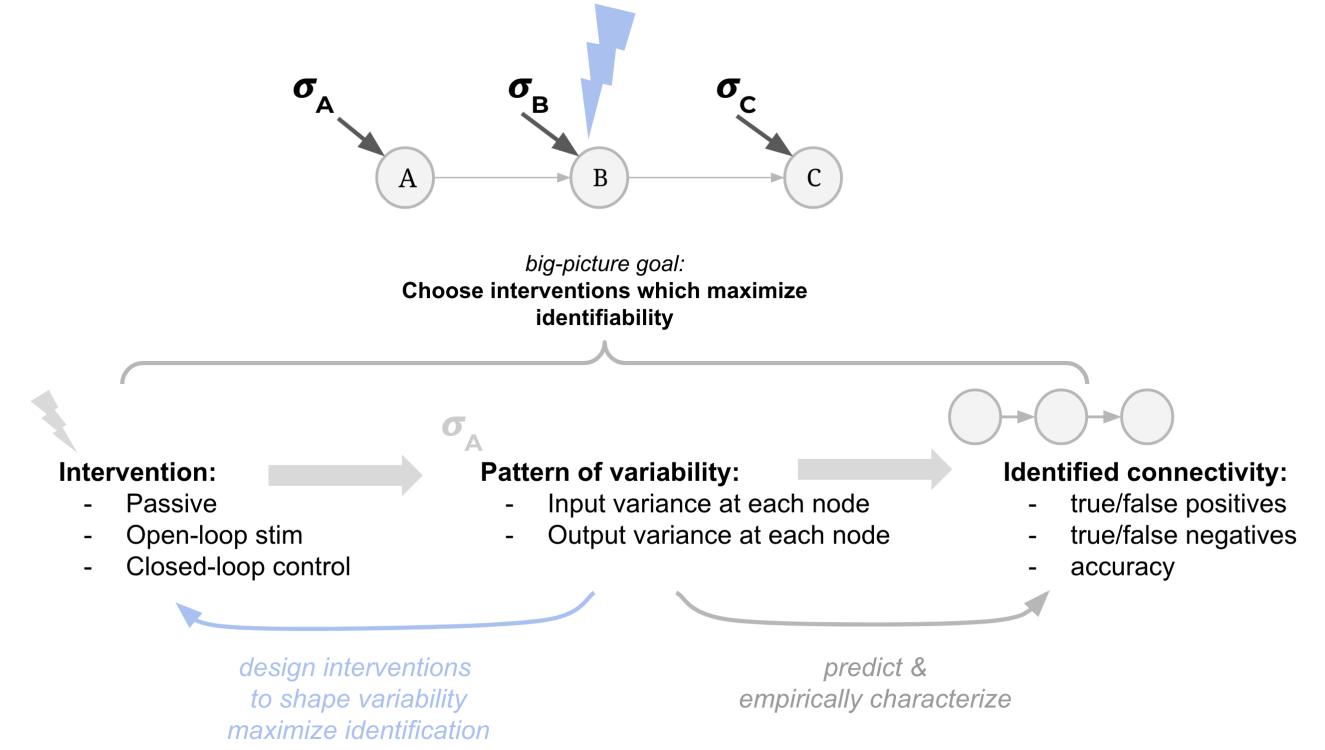
- connect **binary reachability** to classes of ambiguity
 - a pair of networks are ambiguous (given some intervention) if they are in the same markov equivalence class
 - ambiguity x intervention leads to the following classes
 - passively unambiguous
 - open-loop unambiguous
 - (single-site) closed-loop unambiguous



Figure DEMO: Applying CLINC to distinguish a pair of circuits (walkthrough)

- 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 $i \rightarrow j$ relative to in the output of node j

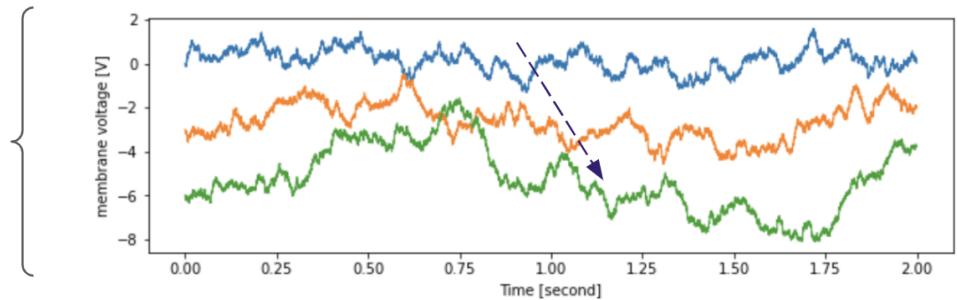
- for true, direct connections this quantity increasing means a (true positive) connection will be identified more easily (with high certainty, requiring less data)
- for false or indirect connections, this quantity increasing means a false positive connection is more likely to be identified
- as a result we want to maximize IDSNR for true links, and minimize it for false/indirect links



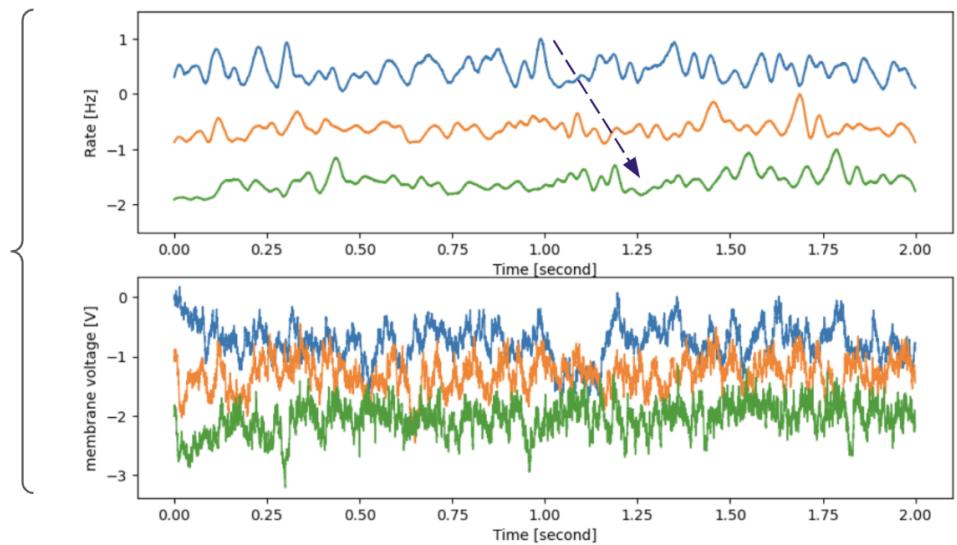
Methods

Network simulations

Gaussian network
(delayed interactions)



LIF spiking network
(delayed interactions)



`small_circuit_scripts/circuit_functions/delayed_gaussian_network.py`

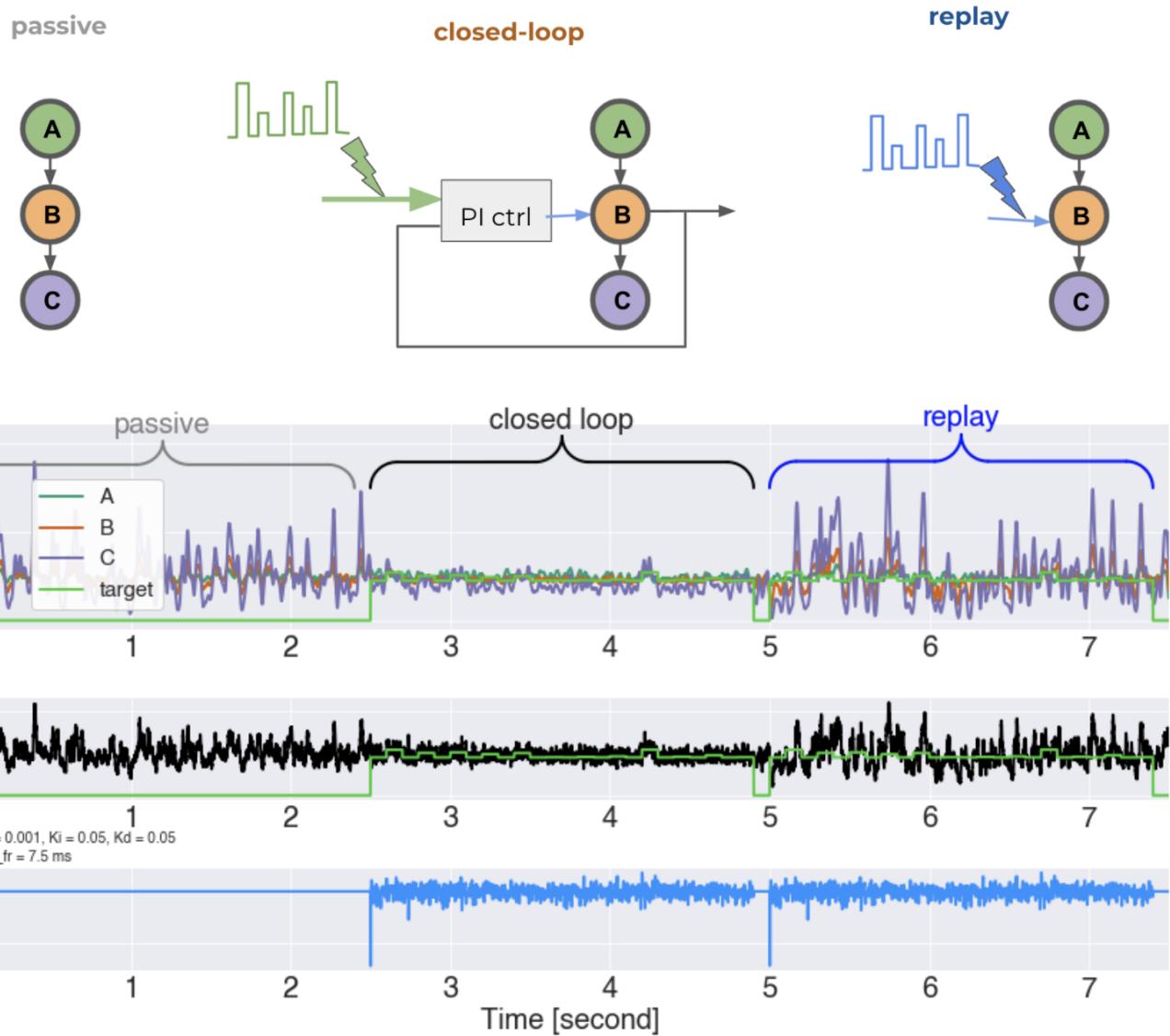
Figure GAUSSIAN: Gaussian and spiking networks simulated in Brian2

- all networks built on [Brian2](#) spiking neural network simulator
- (delayed) linear-gaussian network
 - required custom functionality to implement
 - [\[brian_delayed_gaussian\] repository](#)
 - allows us to understand impact of variability in simplest setting
- spiking network
 - includes additional difficulties associated with estimation based on spiking observations, nonlinearities

Implementing interventions

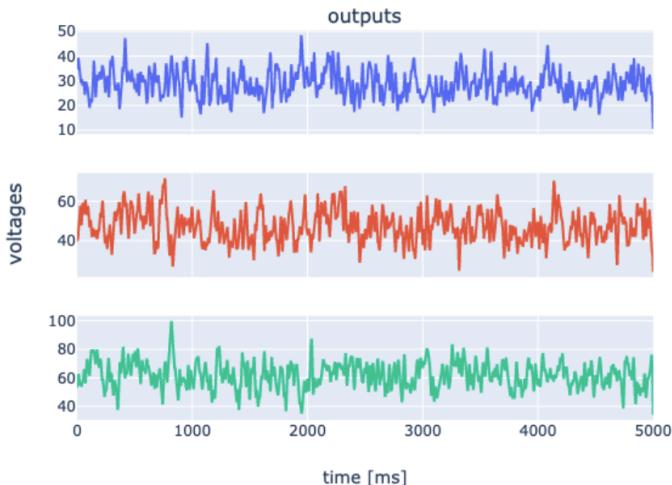
- passive observation
- open-loop stimulation
 - simulated as direct current injection
 - but uniform across a population
 - (see [Kyle Johnsen's cleosim toolbox](#) for more detailed simulation of stimulation)
- closed-loop stimulation
 - approaches for control

- going with "model-free" PID control of output rates
- comparison to randomization in traditional experiment design
- controller strength
 - gain
 - bandwidth
- controller delay
- additional stimulation factors (open- & closed-loop)
 - ▶ click to expand

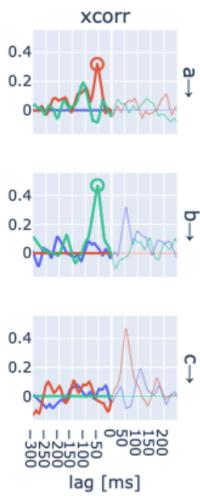


Extracting circuit estimates

1. Aggregating network data

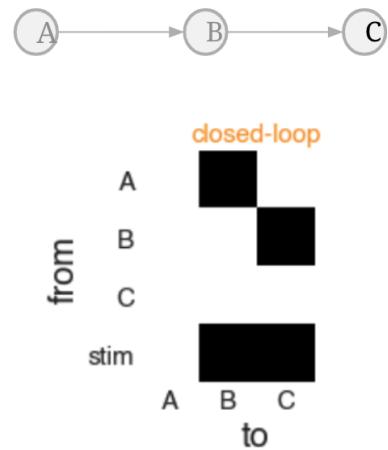


2. Extracting co-dependence



3. Thresholding, statistical tests

Network Estimate



*Cross-correlation
OR
Multivariate transfer entropy*

Figure PIPELINE: Process of detecting connections in a network model

Outputs of network

- spikes from populations of neurons

lagged cross-correlation

- connection to / equivalence with Granger Causality (GC)
 - review of GC in neuro
 - requisite assumptions
 - limitations of GC
- xcorr features
 - peak-SNR
 - prominence
 - time of peak
- window of time-lags considered for direct connections
 - some multiple of expected synaptic delay

multivariate transfer entropy (muTE)

- advantages above usual GC approach

statistical testing

- for muTE, handled by IDTxl

- includes appropriate multiple-comparison testing

Quantifying successful identification

- binary "classification" metrics
 - accuracy, F1 score (Wang & Shafechi 2019)
 - AUC (Pastore)
 - Jaccard index (Lepage, Ching, and Kramer 2013)
 - true/false positives, true/false negatives
- graded metrics (*not a core focus here*)
 - distance between identified connection strength and ground-truth
 - MSE (Lepperod et al. 2018)
 - error in output reconstruction
- *relevant "negative control" for comparison (?)*
 - identified connectivity for random network?
 - some shuffled data-surrogate procedure?
- *relevant "positive control" for comparison (?)*

Results

[Binary Sim.] - Characterizing circuit-pair ambiguity through binary reachability properties

- proportion of each ambiguity class as a function of circuit size
 - possibly weight proportions by observed frequency of triplet motifs
- Figure:** ambiguity class by circuit size
- SCOPE: cut?

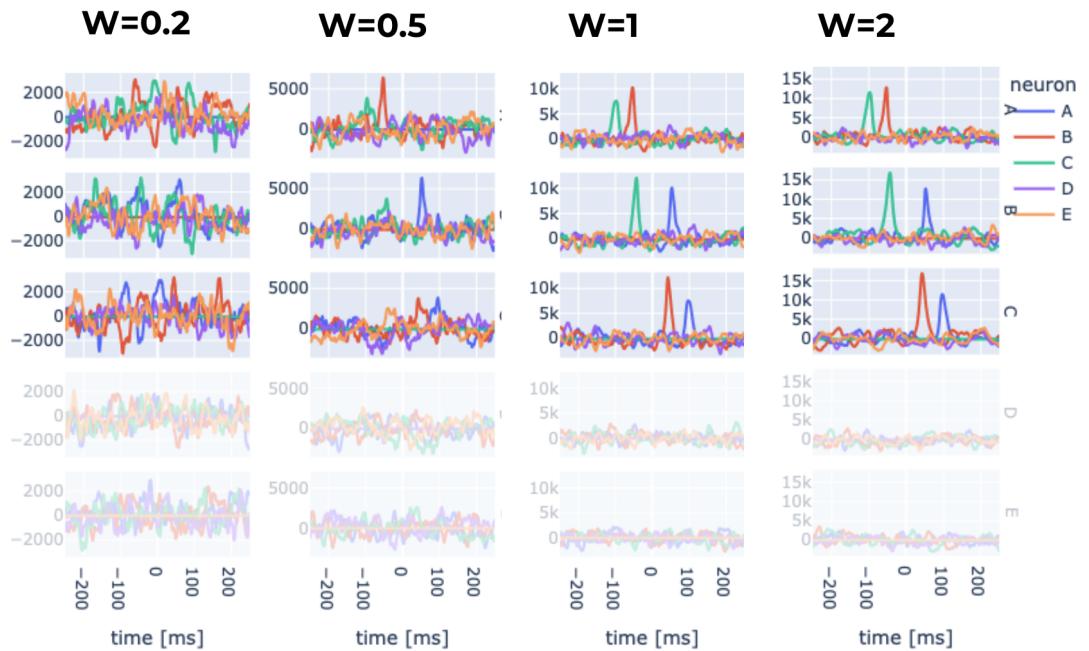
Characterization of network estimation performance - Impact of node, network parameters

- gaussian network simulation
 - ▶ click to expand
- spiking network simulation
 - all gaussian params, plus ...
 - spiking nonlinearity
 - gain
 - bias
 - spiking threshold

Impact of weight

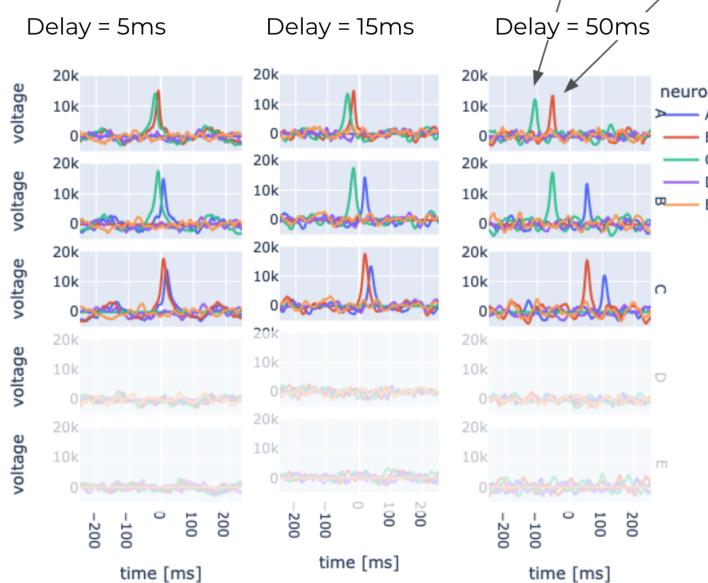
(delay = 50ms,
tau=5ms,
sigma=250)

*Increasing weight increases SNR
(of True and False positives - direct & indirect)*



Impact of delay: (A \rightarrow B \rightarrow C)

(weight=2,
tau=5ms,
sigma=250)

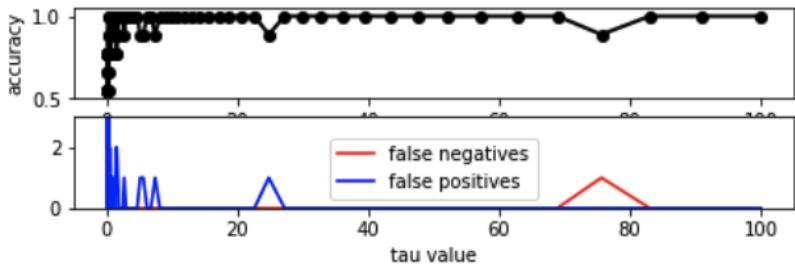
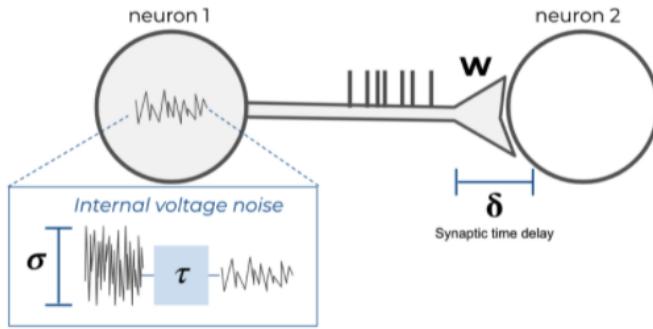


A \rightarrow C, indirect link

A \rightarrow B, direct causal link

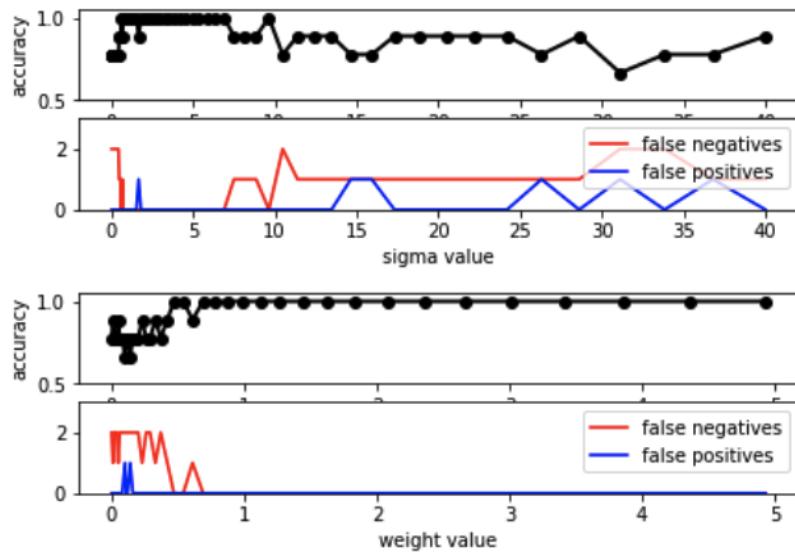
Increasing delay
increases separation between
direct / monosynaptic
connections
and **indirect** / polysynaptic
connections

This is good for telling apart
direct vs indirect causes,
especially in the passive
observation setting



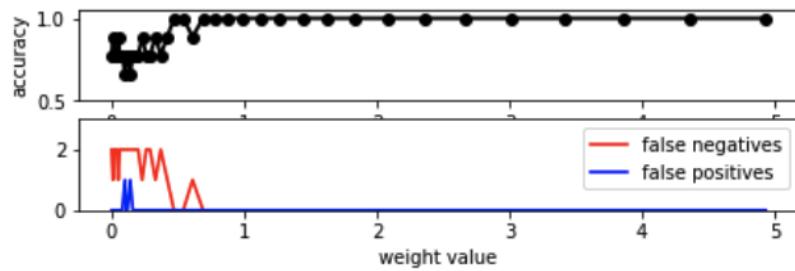
Tau:

Time-constant of internal noise
effective noise amplitude seems to increase with low tau



Sigma:

Std dev. of internal noise for neurons



Weight:

Connection strength,
Change in downstream voltage after and upstream spike

Figure PROPS: impact of intrinsic network properties on identifiability

- (e.g. Identification of excitatory-inhibitory links and network topology in large-scale neuronal assemblies from multi-electrode recordings)
- comparison to predicted IDSNR



Figure PREDICT: Comparing predicted and empirical identification performance

- layout: scatterplot and curve fit of empirical vs predicted accuracy (false positives, false negatives)
 - segmented by circuit type?

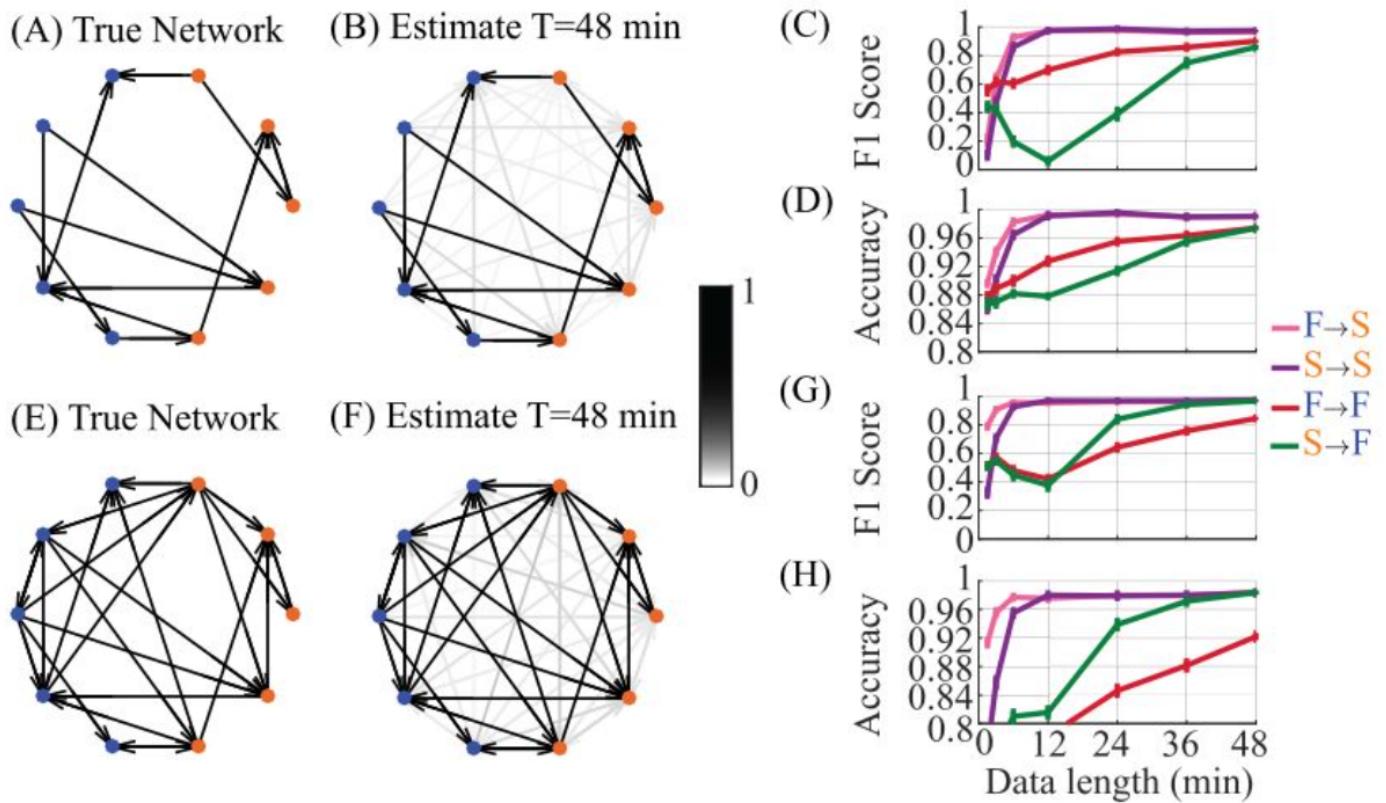
- could be part of figures above

Impact of intervention



Figure DISAMBIG: Stronger intervention facilitates disambiguating equivalent hypotheses

- like a quantitative version of [binary proportion figure](#)
- in example: shows a dataset with many correlations, multiple plausible circuit hypotheses
- patterns of correlation become more specific with increasing intervention strength
- in aggregate: focuses on reduced bias, higher accuracy for "infinite" data limit
- closed-loop > open-loop > passive



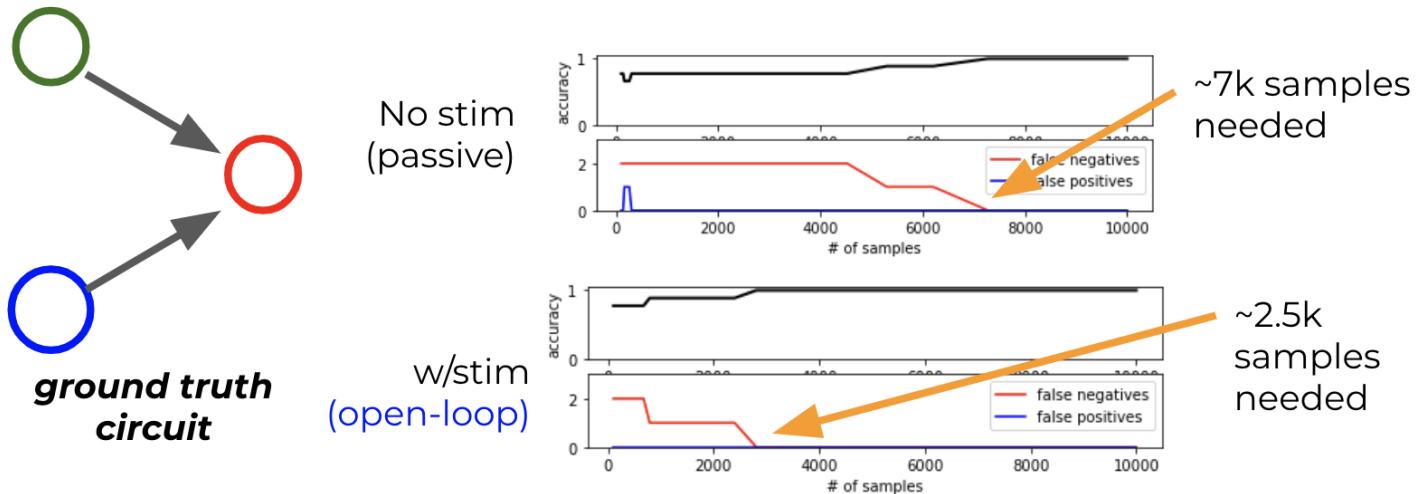


Figure DATA: Analysis of simulated circuits suggest stronger intervention facilitates identification with less data

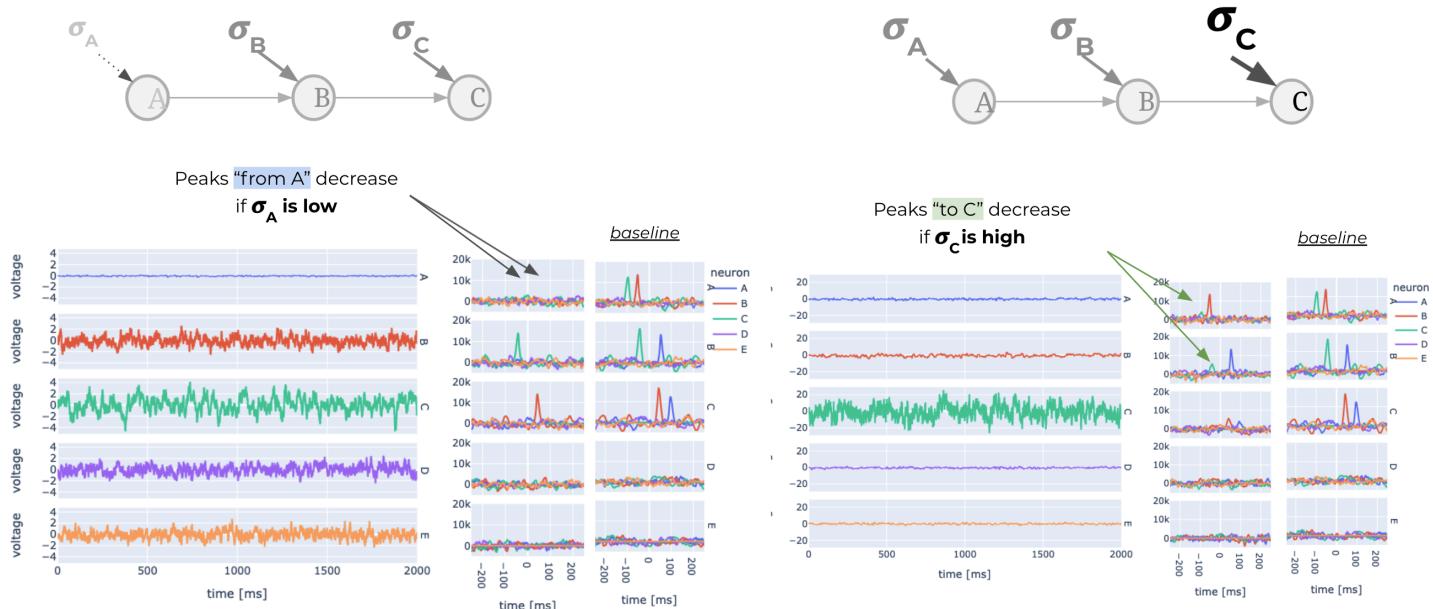
- metric: # of samples required to reach accuracy threshold
- closed-loop > open-loop > passive

impact of circuit structure

- degree of nodes
 - in/out-degree
 - of source - i
 - of target - j
- presence of indirect correlations
- presence of feedback loops
- # of circuits in equivalence class

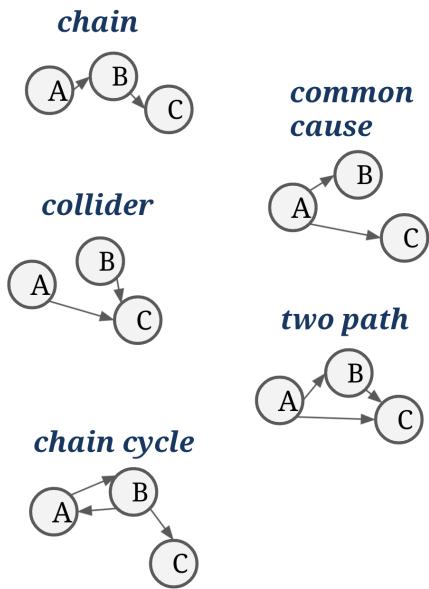
Impact of (relative) sigma

($W=3$, delay = 50ms, $\tau=5$ ms)



Sweep Circuit Type:

(for the most part, stim. Is applied at node B)



Circuit Type	Passive	Open -loop	Closed. -loop	across interventions	
chain	89.9%	91.2%	88.2%	89.8%	chain
common	86.7%	86.7%	84.5%	85.9%	common
collider	84.5%	86.7%	88.9%	86.7%	collider
two_path	77.8%	84.1%	76.2%	79.4%	two_path
chain_cycle	72.3%	73.6%	75.0%	73.6%	chain_cycle
across circuits	85.2%	87.0%	85.4%		
for each circuit type intervention with highest accuracy is bolded					

⚠ numbers in this figure are out-dated, likely not representative ⚠

Figure MOTIF: Interaction of network structure and intervention location on identifiability

Discussion

- Comparison to related work
 - comparison to work in ANNs
 - Kording, fakhar
 - comparison to Shanechi
 - comparison to Bassett "network controllability" view
- Limitations of evaluated interventions
 - quantifying the impact of imperfect / realistic control
 - barriers such as low spatial / temporal precision may prevent high-performing control
- Limitations of network extraction approach
 - limitations of bivariate xcorr
 - effect of design / hyperparameters
 - nonlinear TE estimators
 - time bin size
 - extraction from spiking, firing rates, LFP
- Limitations of **network simulation**
 - small number of nodes
 - simple neuron dynamics
 - didn't focus on intricate connectivity that has been observed
 - future work - apply to more complex Brian2 network models
 - assumed measurement from entire network
 - homogeneity in network parameters
 - understanding mediating effect of spike counts
- **Recommendations for designing network discovery experiments**
 - At the experiment-design phase, analyze competing hypotheses
 - through the lens of CLINC reachability / IDSNR
 - evaluate what can be distinguished under different interventions
 - A spectrum of interventions - pick the right tool for the job
 - stronger interventions generally come with cost
 - increased experiment complexity
 - depending on challenges, similarity of hypothesized circuits...
 - passive observation may be enough
 - or stronger interventions may be required
- Future work
 - tighter integration of knowledge of intervention into network estimation procedure
 - stimulus-conditional transfer entropy

Supplement

- organization of clinc-gen, clinc-analysis codebases