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?

Table of Contents

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
- *( 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) → (B) ↔ (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)

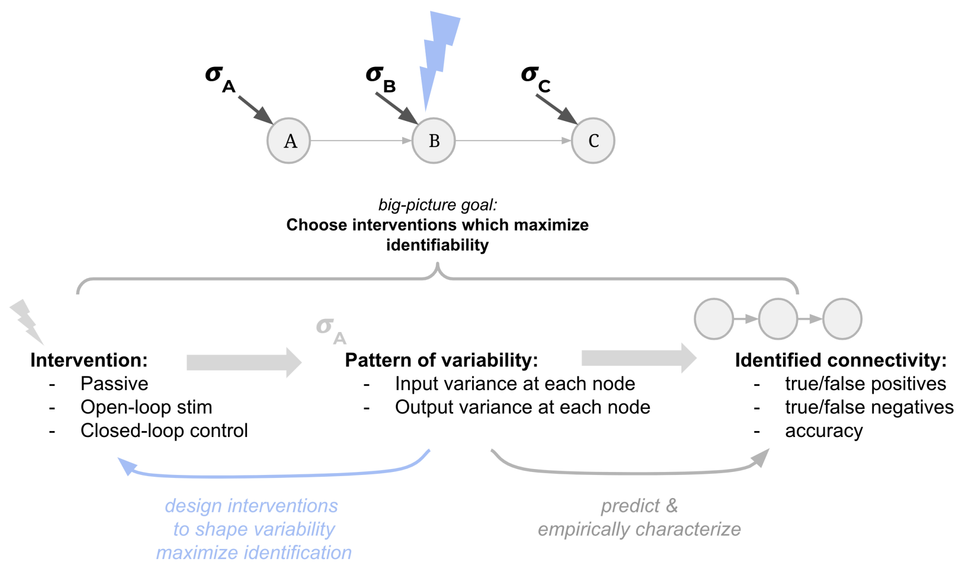
- [ ] ✂️ `more appropriate for methods section?` ✂️

- 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 $i \to j$ 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

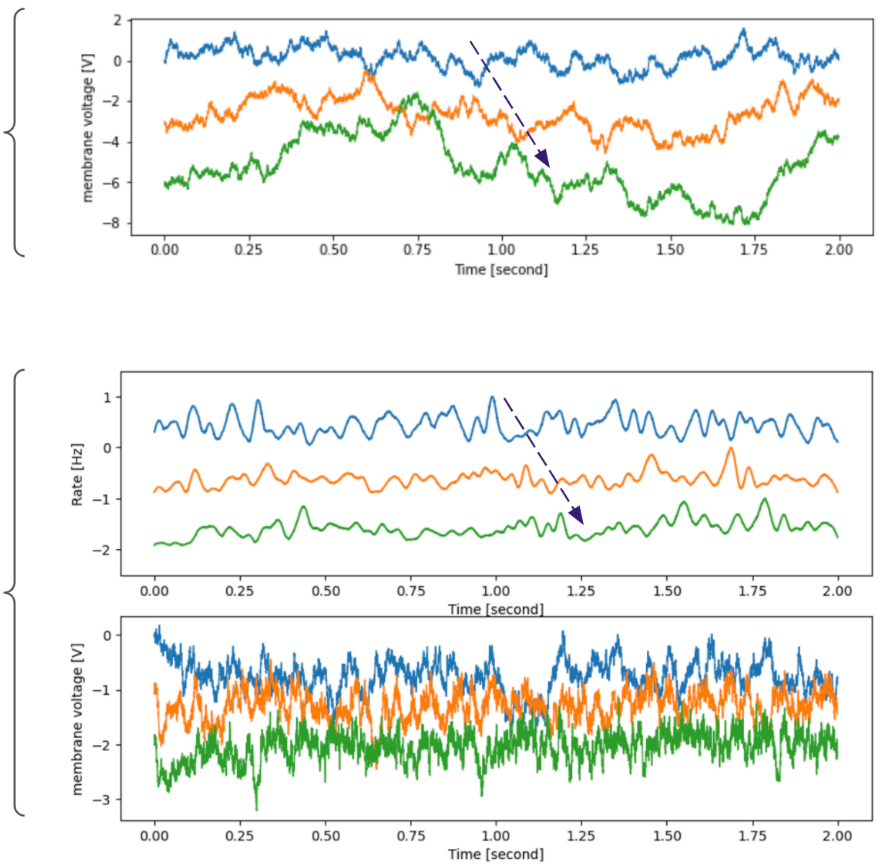


Methods

Network simulations

Gaussian network
(delayed interactions)

LIF spiking network
(delayed interactions)



small_circuit_scripts/circuit_functions/delayed_gaussian_network.py

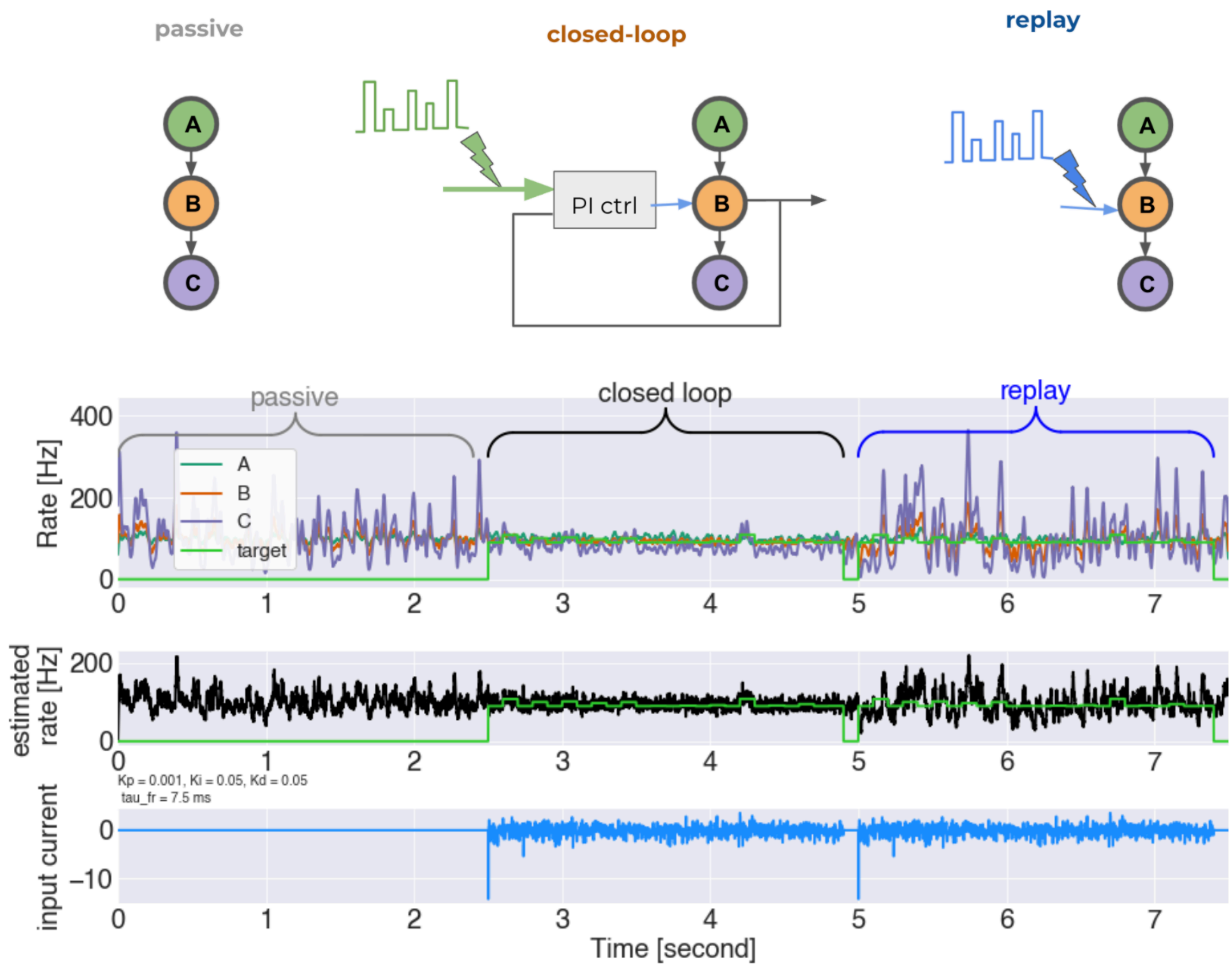
Figure GAUSSIAN: Gaussian and spiking networks simulated in Brian2

- 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 stregnth
        - gain
        - bandwidth
    - controller delay
- additional stimulation factors (open- & closed-loop)
  ↪️ click to expand
    - **stimulus location**
        - single-site
        - multi-site
        - location relative to features of network
            - in-degree/out-degree
            - upstream/downstream of hypothesized connection
    - stimulus intensity
        - expected mean output rate
        - frequency content



Extracting circuit estimates

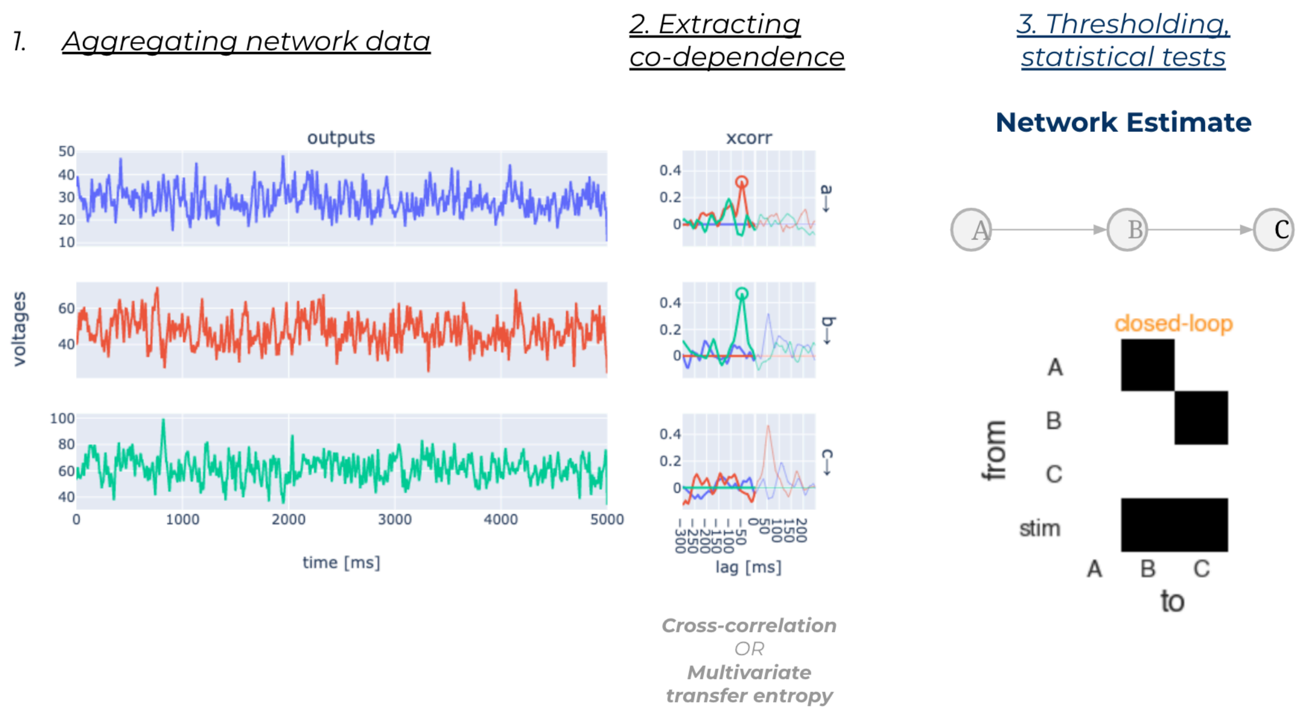


Figure PIPELINE: Process of detecting connections in a network model

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 & Shanechi 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

  - **parameters**
    - synaptic (edge) weights - w
    - synaptic (edge) delay - δ
    - time-constants - τ
    - node noise - σ
  - **expected results**
    - weight increases xcorr peaks
    - τ blurs xcorr peak in time
    - delay δ increases time-separability of sources
      - at $\delta = 0$ limit, connections are harder to distinguish
        - especially direct v.s. indirect
    - noise σ has a "location specific" impact describe by IDSNR transfer function
      - generally, high noise "upstream" of a connection increases the strength of a hypothesized connection
        - as long as any path is present between $i \rightarrow\rightarrow j$
      - high noise "downstream" of a connection, but impinging on the output node competes with / blurs / corrupts
      - **The location-dependent impact of noise on connection identifiability may be one key way in which different forms of intervention**

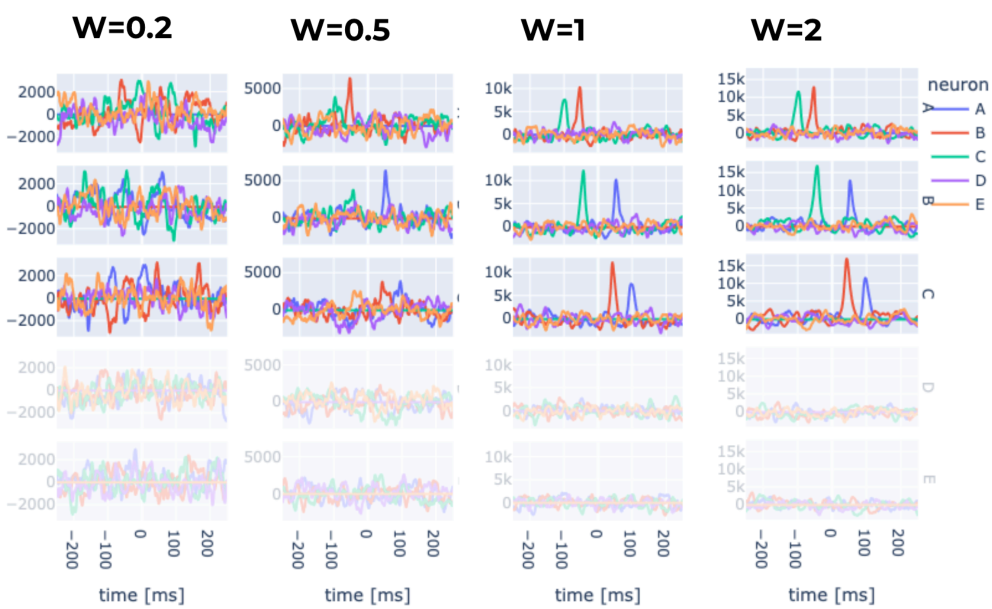
impact circuit estimates

- **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)

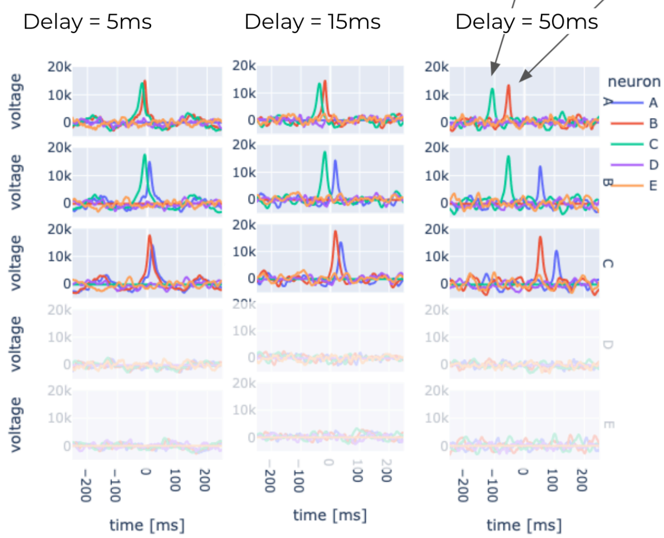


Impact of delay: (A→B→C)

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

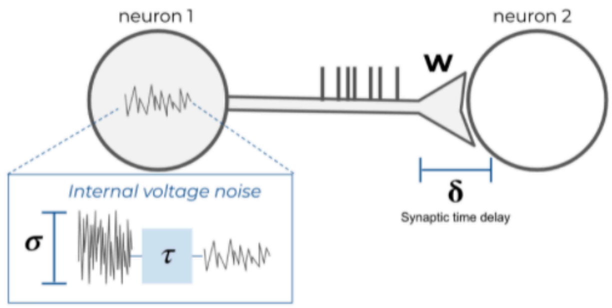
A→→C, indirect link

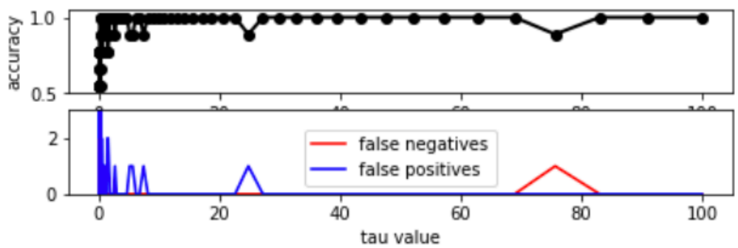
A→B, direct causal link



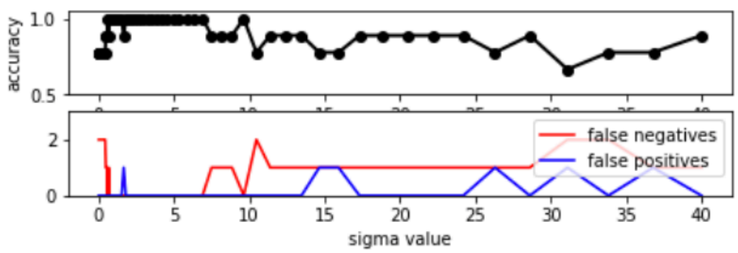
Increasing delay
increases separation between
direct / monosynaptic
connections
and **indirect** / polysynaptic
connections

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

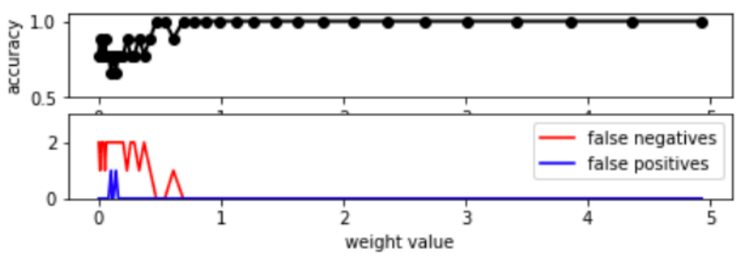




Tau:
Time-constant of internal noise
effective noise amplitude seems to increase with low tau



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

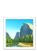


Figure PREDICT: Comparing predicted and emprical

identification performance

- layout: scatterplot and curve fit of emprical 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

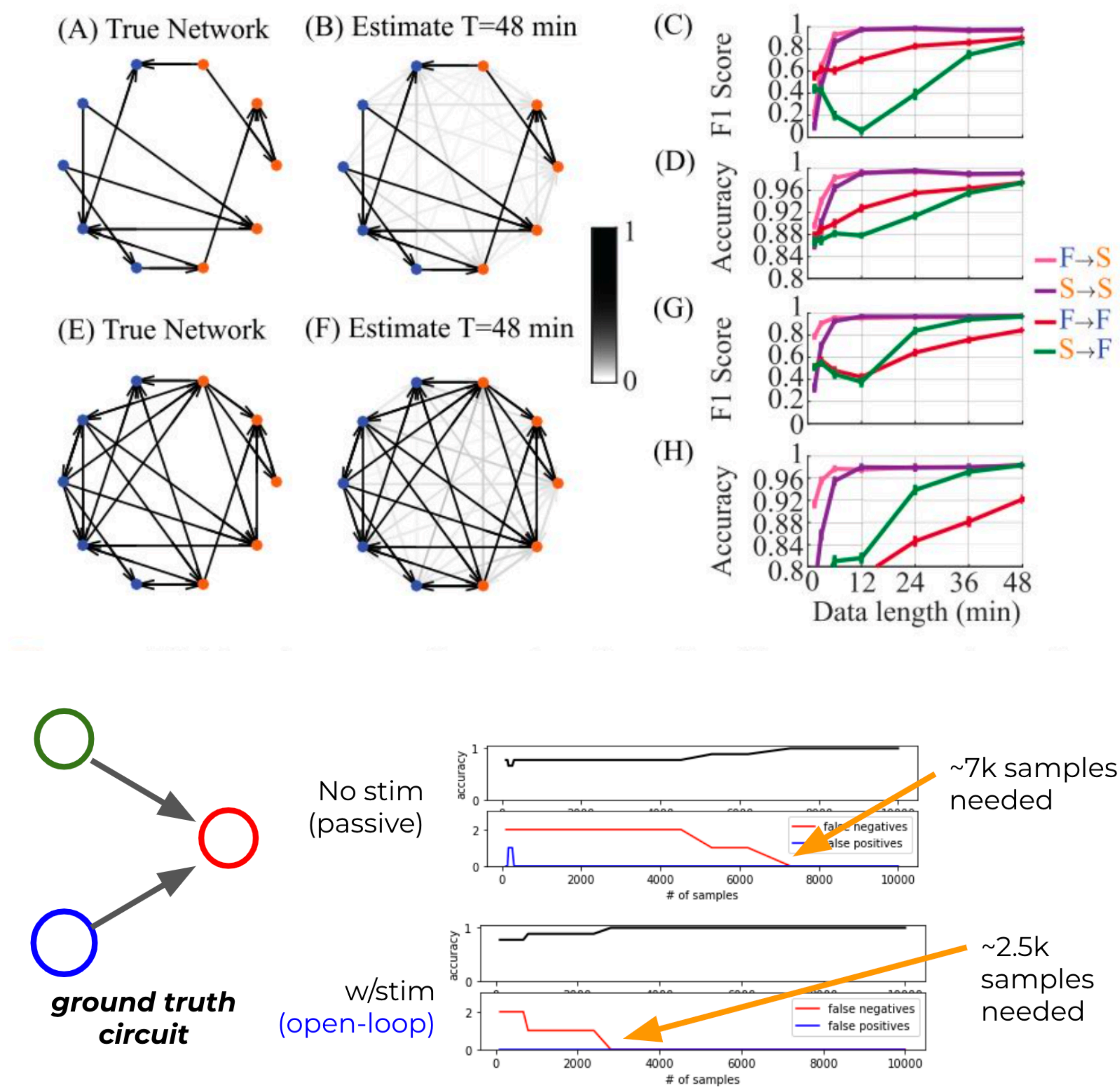


Figure DATA: Analysis of simulated circuits suggest stronger intervention facilitates identification with less data

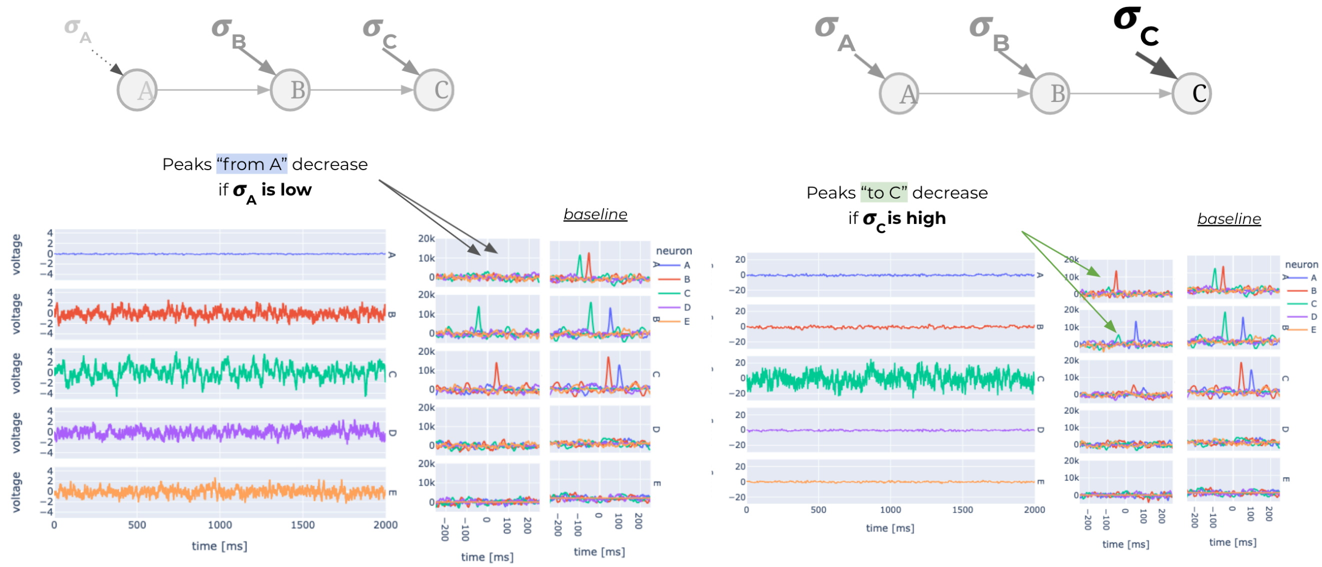
- *metric:* # of samples required to reach accuracy threshold
- closed-loop > open-loop > passive

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

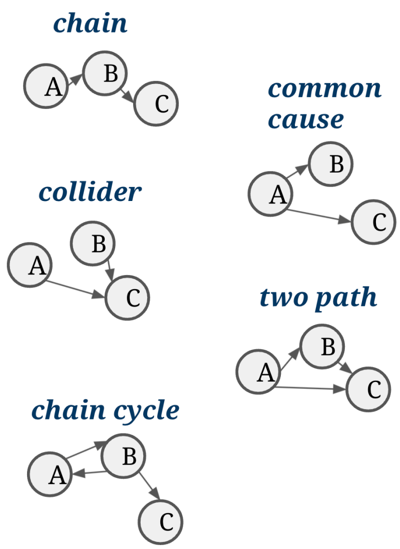
Impact of (relative) sigma

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



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

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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