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

- Interventions in neuro
    - lesion studies in neuro
        - disadvantages of lesioning
- 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
- **Causal methods for network discovery from time-series**
    - What challenges are faced when estimating network connectivity?
        - [...]
    - background building from granger causality towards more complex methods
        - highlight limitations with current approaches
    - *cite J.Runge*
- Interventions from the perspective of 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

Methods

Multiple complementary perspectives (represenations) 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

Interventions in causal identification

- intervention types
    - 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

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 🏞️

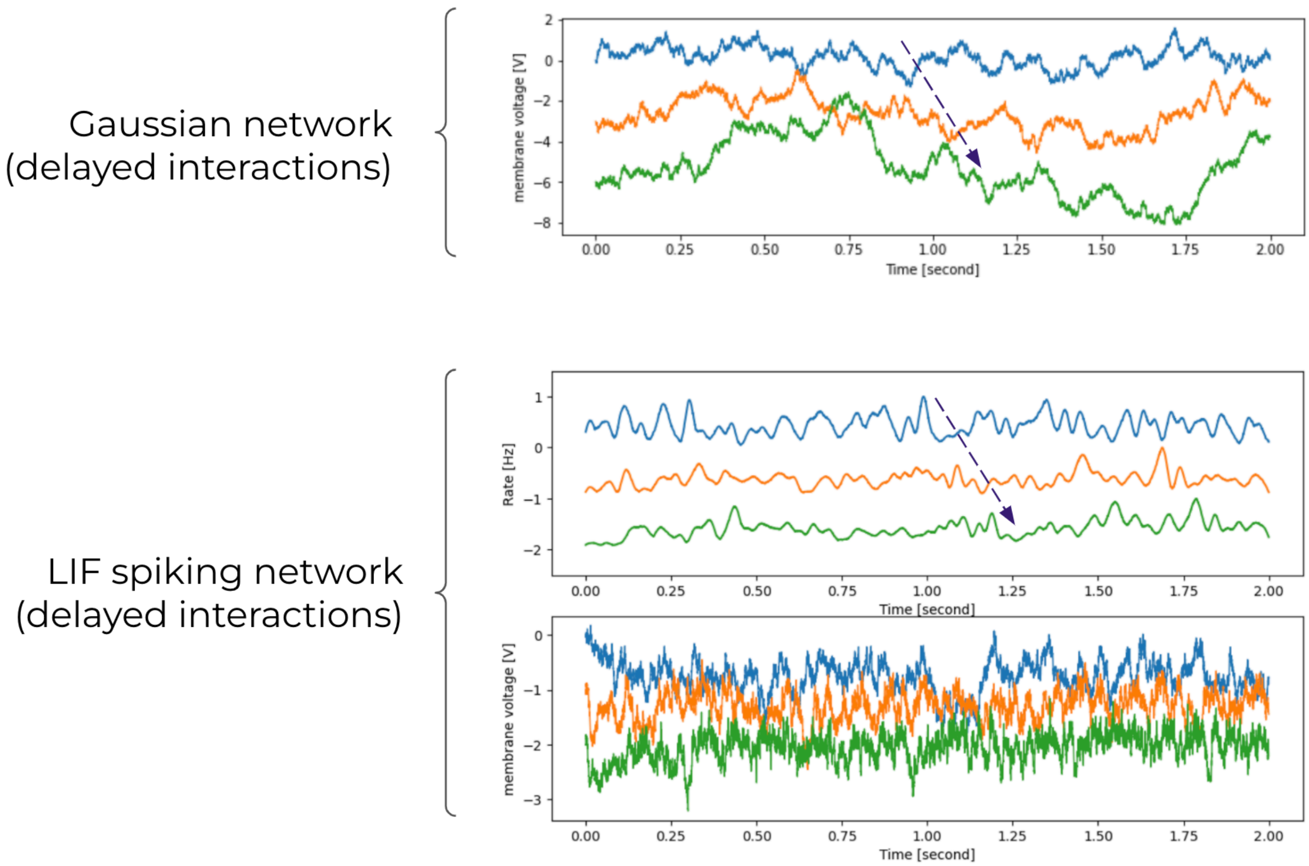
Understanding identification through derived properties of circuits (reachability rules)

- 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
-

- 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

Network simulations



small_circuit_scripts/circuit_functions/delayed_gaussian_network.py

Figure GAUSSIAN: Gaussian and spiking networks simulated in Brian2

- built on Brian2 spiking neural network simulator
- (delayed) linear-gaussian network
    - required custom functionality to implement
        - [brian_delayed_gaussian] repository
- spiking network

Extracting circuit estimates

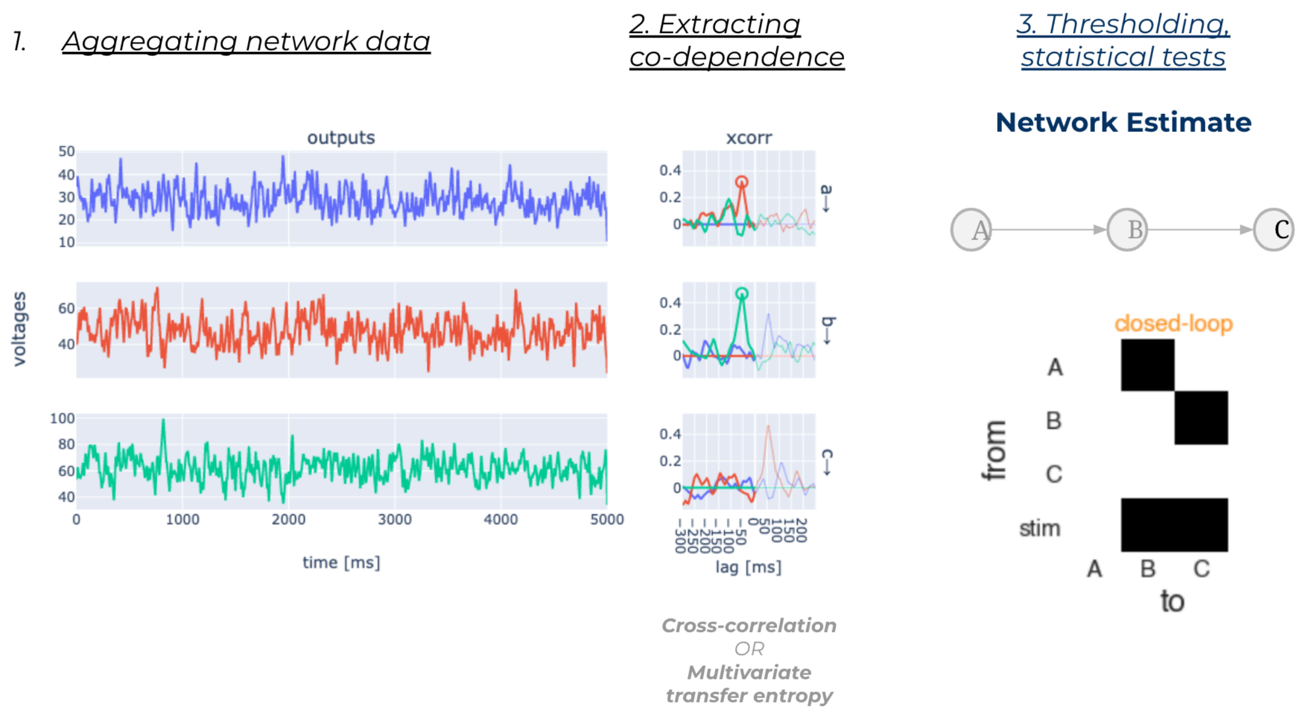


Figure PIPELINE: Process of detecting connections in a network model

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

Results

🏞️

Figure DEMO: Applying CLINC to distinguish a pair of circuits (case-study)

- explanation using binary reachability rules
    - consider postponing until we introduce intervention?
    - i.e. have one figure that walks through both reachability and impact of intervention
- *(e.g. Advancing functional connectivity research from association to causation, Combining multiple functional connectivity methods to improve causal inferences)*

[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

Extracting circuit estimates

- *(see methods for xcorr, muTE)*

Quantifying successful identification

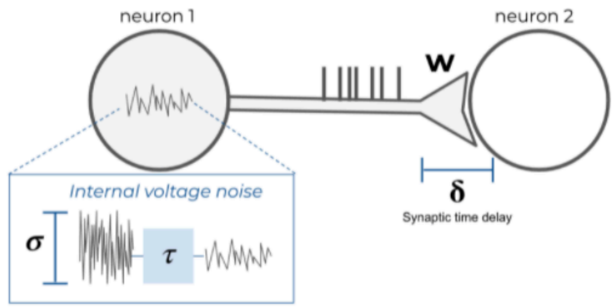
- binary "classification" metrics
    - accuracy, F1 score (Wang & Shanechi 2019)
    - AUC (Pastore)
    - Jaccard index (Lepage, Ching, and Kramer 2013)
    - true/false positives, true/false negatives
- graded metrics (*not a core focus here*)
    - distance between identified connection strength 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 (?)*

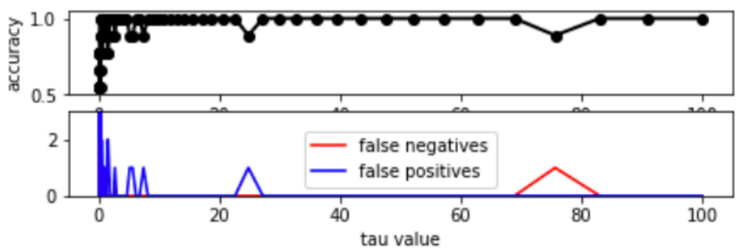
Impact of node, network parameters

- **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

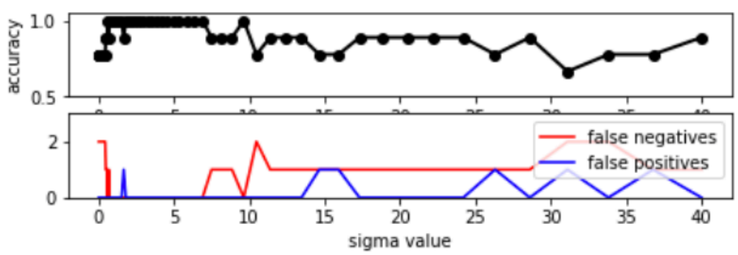
- delay δ increases time-separability of sources
  - at $\delta = 0$ limit, connections are harder to distinguish
    - especially direct v.s. indirect
- noise σ has a "location specific" impact describe by IDSNR transfer function
  - generally, high noise "upstream" of a connection increases the strength 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

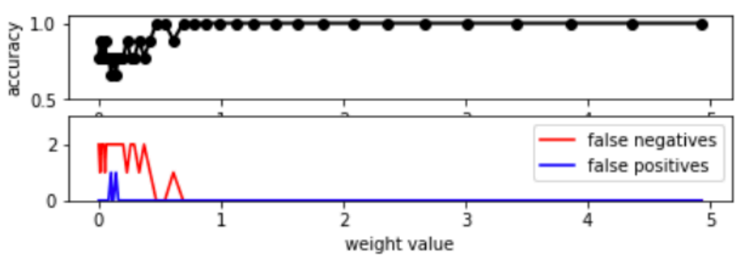




Tau:
Time-constant of internal noise
effective noise amplitude seems to increase with low tau



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

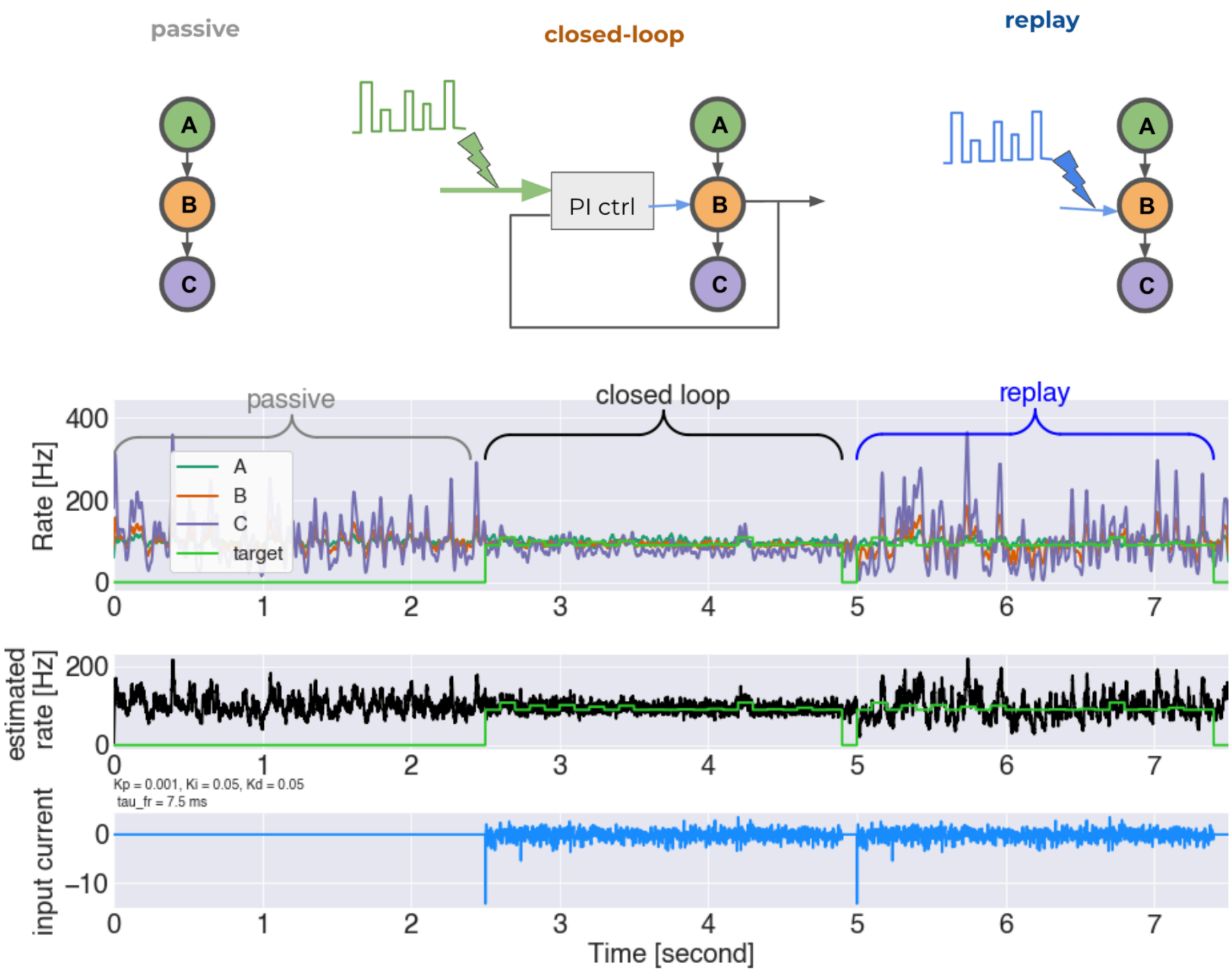
- *(e.g. Identification of excitatory-inhibitory links and network topology in large-scale neuronal assemblies from multi-electrode recordings)*
- comparison to predicted IDSNR
- **impact of circuit structure**
- degree of nodes
    - in/out-degree
    - of source - i
    - of target - j

- presence of indirect correlations
- presence of feedback loops
- # of circuits in equivalence class

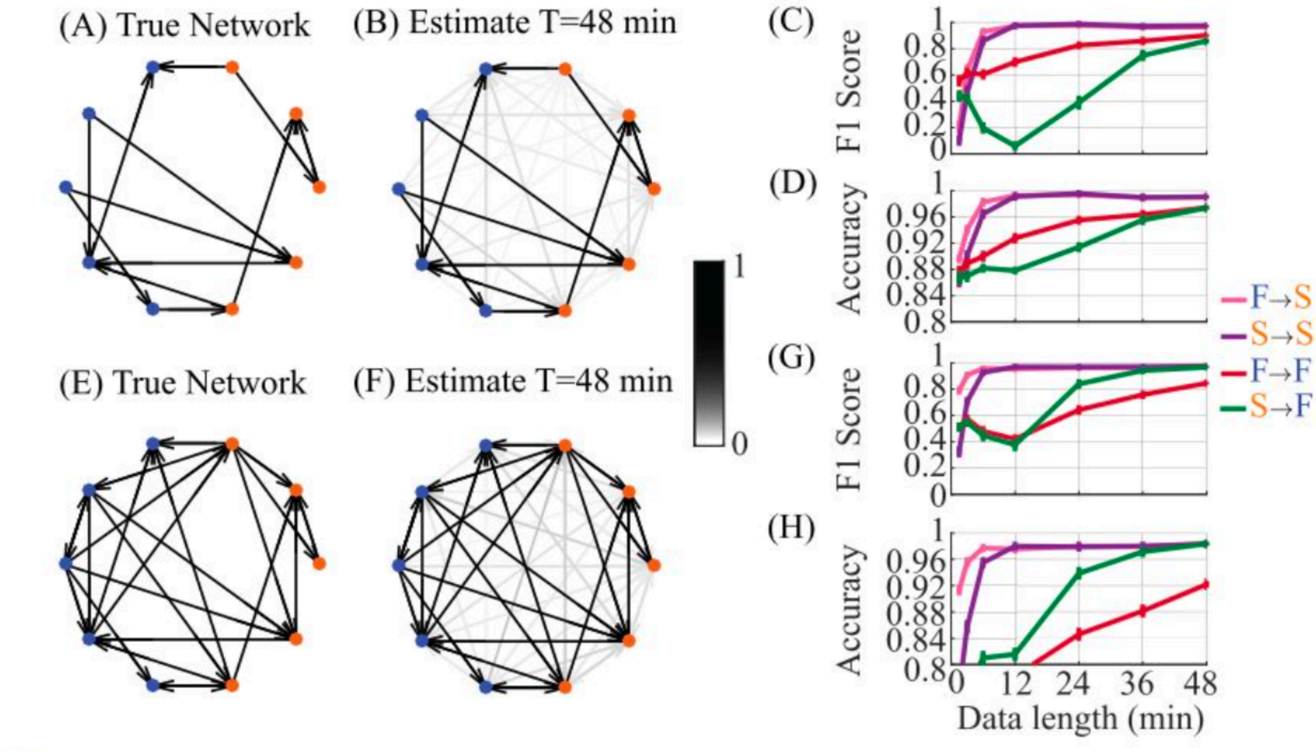
Figure MOTIF: Interaction of network structure and intervention location on identifiability

Impact of intervention

- intervention types
    - passive observation
    - open-loop stimulation
    - closed-loop stimulation
        - 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



passive
closed-loop
replay
A
B
C
PI ctrl
passive
closed loop
replay
Rate [Hz]
target
estimated rate [Hz]
Kp = 0.001, Ki = 0.05, Kd = 0.05
tau_fr = 7.5 ms
input current
Time [second]



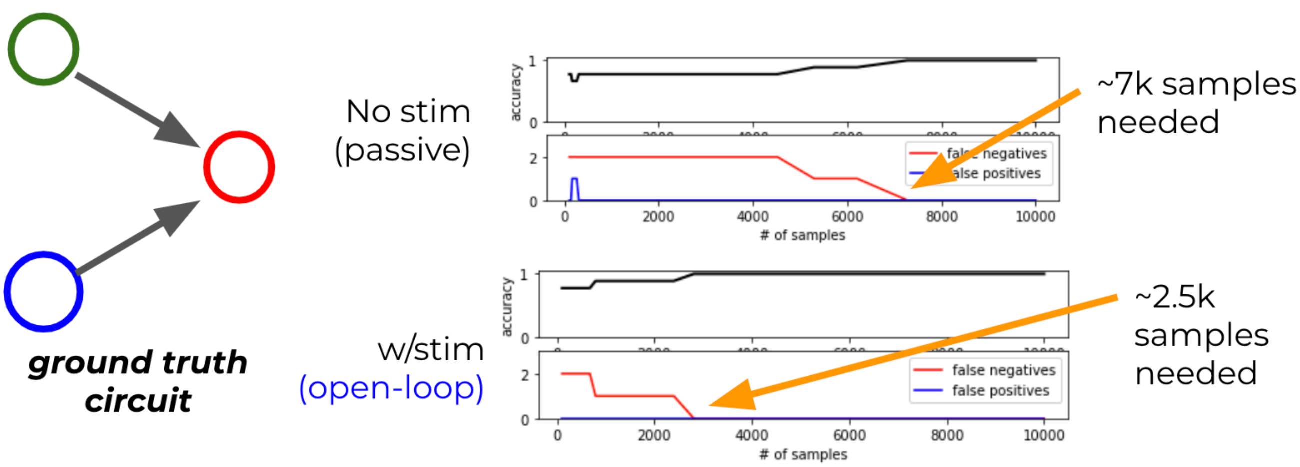


Figure DATA: Analysis of simulated circuits suggest stronger intervention facilitates identification with less data

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

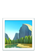


Figure PREDICT: Comparing predicted and emprical identification performance

- layout: scatterplot and curve fit of emprical vs predicted accuracy (false positives, false negatives)
    - segmented by circuit type?
- could be part of figures above

Figure DISAMBIG: Stronger intervention facilitates disambiguating equivalent hypotheses

- SCOPE: can this be combined with case-study walkthrough?
- 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

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