

# ESTIMATION OF NEURAL CONNECTIONS FROM MULTIPLE SPIKE TRAINS

GRAPH STRUCTURE INFERENCE WITH NUISANCE INPUTS

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<https://noboru-murata.github.io/>

Introduction

Problem Formulation

Numerical Examples

- synthetic data analysis

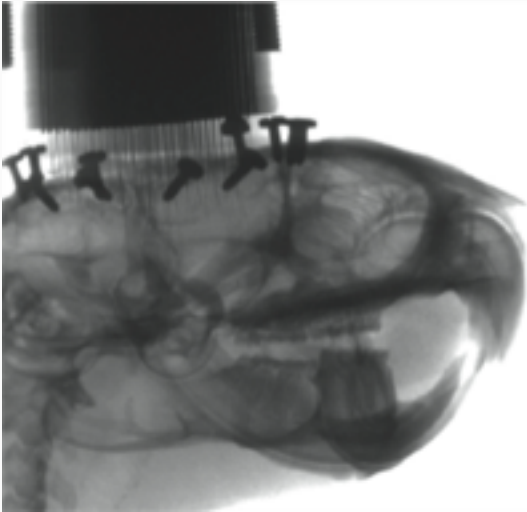
- real data analysis

Conclusion

# INTRODUCTION

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- estimating neural connections
  - understand functions of biological systems
  - investigate learning/adaptation mechanisms
- typical methods for measuring brain activities
  - fMRI (functional magnetic resonance imaging)
  - MEG (magnetoencephalography)
  - EEG (electroencephalography)
  - TPE (two-photon excitation microscopy)
  - multi-electrode recording
- different resolutions in
  - time (oxygen consumption - neuron firing)
  - space (brain mapping - synaptic connections)

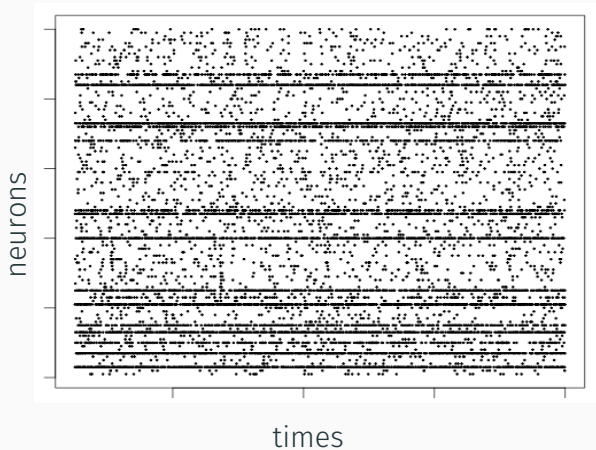


*by courtesy of Dr. Tatsuno at University of Lethbridge*

activities of individual neurons

- multiple neurons  
(tens - hundreds)
- long term measurement  
(several hours - several days)

## multi-variate point process



rearranged as binary sequence  
indicating states of neurons

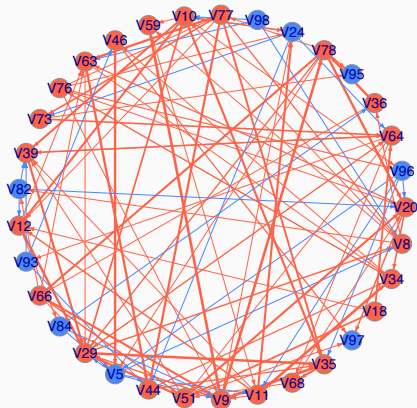
- 0: resting
- 1: firing

multi-variate binary time series  
contains information of neural  
interactions



mathematical representation –  
directed graph

- node: neuron
- edge: synaptic connection



## Objective

estimate weights of edges from binary  
time series at nodes

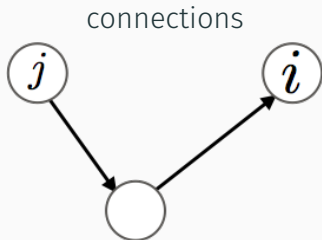
## typical methods for analysis

- pair-wise:
  - cross-correlation  
(e.g. Wilson and McNaughton 1994)
  - joint peri-stimulus time histogram (e.g. Ito and Tsuji 2000)
- graph-based:
  - sparse inverse covariance matrix (e.g. Friedman, Hastie, and Tibshirani 2008)
  - digraph Laplacian (e.g. Noda et al. 2014)
- higher-order:
  - information geometric measure (e.g. Nakahara and Amari 2002; Tatsuno, Fellous, and Amari 2009)
  - Granger causality (e.g. Kim et al. 2011)



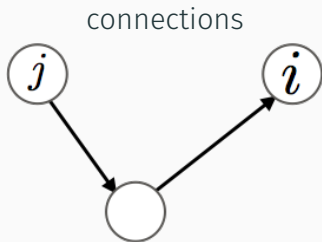
- pseudo correlation caused by higher-order effects
- influence from unobserved neurons
- directed excitatory/inhibitory connections

correlation coefficient: statistics for analyzing relation of two random variables

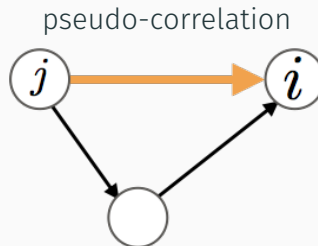


- no direct relation exists
- two nodes are connected with the same node

correlation coefficient: statistics for analyzing relation of two random variables

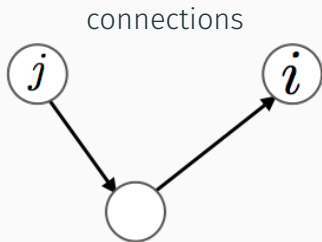


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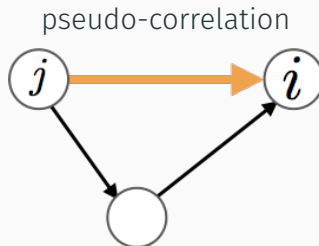


- spurious relation appears

correlation coefficient: statistics for analyzing relation of two random variables



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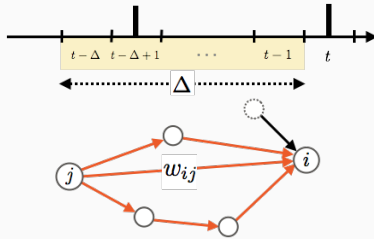


- spurious relation appears

## Pseudo correlation

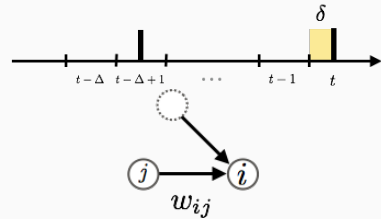
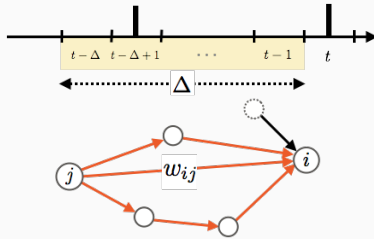
a common problem in complex network analysis

delayed correlation coefficient: statistics for analyzing time series



- appropriate intervals have to be considered
- information propagates multiple paths
- spurious relation appears

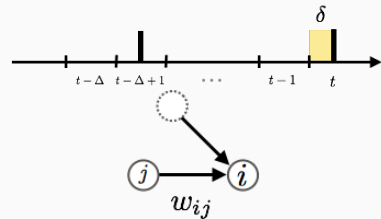
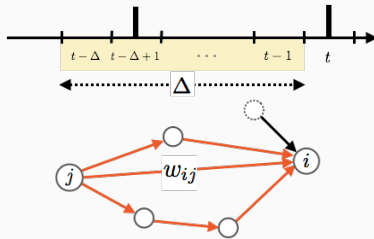
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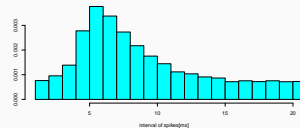
- consider short intervals?

delayed correlation coefficient: statistics for analyzing time series



- appropriate intervals have to be considered
- information propagates multiple paths
- spurious relation appears

- consider short intervals?



- spike intervals are random

a mathematical framework for treating

- pseudo correlation caused by higher-order effects
- influence from unobserved neurons
- directed excitatory/inhibitory connections



a mathematical framework for treating

- pseudo correlation caused by higher-order effects
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- directed excitatory/inhibitory connections

### Main contribution

solve those problems with simple mathematical tricks

## PROBLEM FORMULATION

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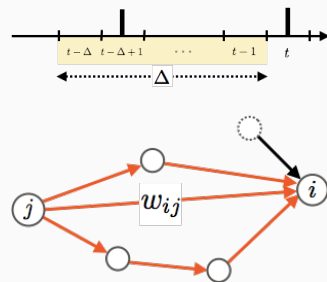
- indices
  - $i \in \{1, 2, \dots, N\}$ : index of neurons
  - $t \in \{1, 2, \dots, T\}$ : discrete time of measurement
  - $t_\Delta = [t - \Delta, \dots, t - 1]$ :  
interval for delayed correlation
- states
  - $X_i(t) \in \{0, 1\}$ : state of neuron  $i$  at time  $t$
  - $X_i[t_\Delta] \in \{0, 1\}$ : state of neuron  $i$  in interval  $t_\Delta$
  - $U_i(t) \in \mathbb{R}$ : internal state of neuron  $i$  at time  $t$
- connections
  - $w_{ij} \in \mathbb{R}$ : synaptic connection from neuron  $j$  to neuron  $i$
  - $\lambda_{ij} \in \mathbb{R}$ : pseudo connection from neuron  $j$  to neuron  $i$

weighted sum of inputs from unobserved/observed neurons

$$U_i(t) = B_i(t) + \sum_{j=1}^N \lambda_{ij} X_j[t_\Delta],$$

$B_i(t)$  : nuisance inputs from unobserved neurons

$\lambda_{ij}$  : **pseudo connection** including undirect paths



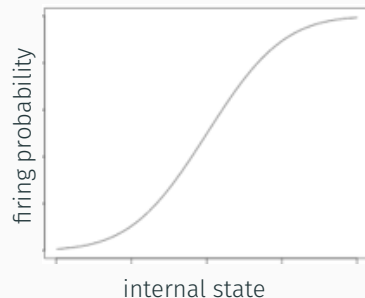
## Remarks

- signal from neuron  $j$  has several paths
- $\lambda_{ij}$  includes direct and undirect connections

stochastic dependency on internal state:

$$\Pr(X_i(t) = 1) = \Phi_{\sigma^2}(U_i(t)),$$

$$\Phi_{\sigma^2} : \text{cdf of } \mathcal{N}(0, \sigma^2).$$



### Assumption

- we assume a probit model, where  $\Phi_{\sigma^2}$  is the integral of

$$\phi_{\sigma^2}(z) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{z^2}{2\sigma^2}\right)$$

- internal state

$$U_i(t) = B_i(t) + \sum_{j=1}^N \lambda_{ij} X_j[t_\Delta],$$

$B_i(t)$  : nuisance inputs,

$\lambda_{ij}$  : pseudo connection.

- neuron firing

$$\Pr(X_i(t) = 1) = \Phi_{\sigma^2}(U_i(t)),$$

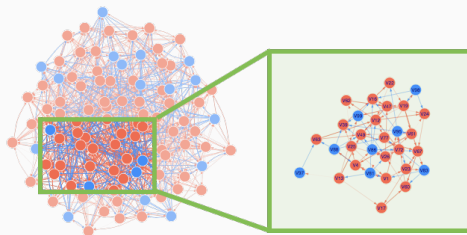
$$\phi_{\sigma^2}(z) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{z^2}{2\sigma^2}\right),$$

$\Phi_{\sigma^2}$  : cdf of  $\mathcal{N}(0, \sigma^2)$ , integral of  $\phi_{\sigma^2}$ .

## First step

- remove nuisance input  $B$  and estimate pseudo connection  $\lambda$

$$U_i(t) = B_i(t) + \sum_{j=1}^N \lambda_{ij} X_j[t_{\Delta}].$$



## Theorem

Let  $X$  and  $Y$  be independent random variables. For any function  $g$ , we have

$$\mathbb{E}[g(X + Y)] = \mathbb{E}[h(X + \mathbb{E}[Y])],$$

where  $f_Y$  is the pdf of  $Y$  and

$$f_Y^-(x) = f_Y(\mathbb{E}[Y] - x),$$

$$h = g * f_Y^-.$$

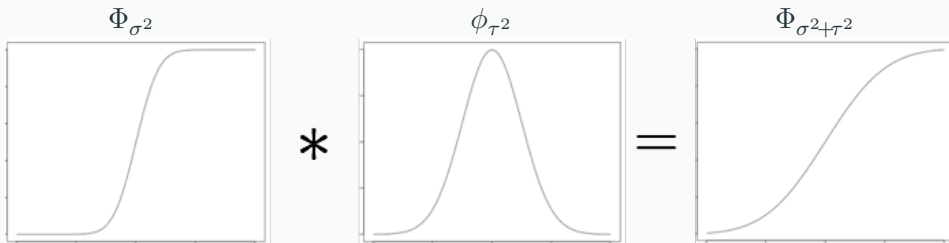
A special case is discussed in Hyvärinen 2002.



## Corollary

If function  $g$  is  $\Phi_{\sigma^2}$  and random variable  $X$  is constant value  $x$ , and probability density function  $f_Y$  is Gaussian with mean  $\mathbb{E}[Y]$  and variance  $\tau^2$ , we have

$$\mathbb{E}[\Phi_{\sigma^2}(x + Y)] = \Phi_{\sigma^2 + \tau^2}(x + \mathbb{E}[Y]).$$



- consider the case of  $X_j[t_\Delta]=1$ ,

$$\begin{aligned} U_i(t \mid X_j[t_\Delta]=1) &= B_i(t) + \lambda_{ij}X_j[t_\Delta] + \sum_{k \neq j} \lambda_{ik}X_k[t_\Delta] \\ &= \lambda_{ij} + C_{ij}(t \mid X_j[t_\Delta]=1). \end{aligned}$$

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- let us apply the corollary for calculating conditional expectation

$$\begin{aligned} \mathbb{E}[X_i(t) \mid X_j[t_\Delta]=1] &= \mathbb{E}[\Phi_{\sigma^2}(U_i(t \mid X_j[t_\Delta]=1))] \\ &= \mathbb{E}[\Phi_{\sigma^2}(\lambda_{ij} + C_{ij}(t \mid X_j[t_\Delta]=1))] \\ &= \Phi_{\rho^2}(\lambda_{ij} + \bar{C}_{ij}), \end{aligned}$$

where we assume  $C_{ij} \sim \mathcal{N}(\bar{C}_{ij}, \tau^2)$  and  $\rho^2 = \sigma^2 + \tau^2$ .

- for binary random variables, the following holds

$$\mathbb{E}[X_i(t) \mid X_j[t_\Delta]=1] = \Pr(X_i(t)=1 \mid X_j[t_\Delta]=1).$$

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- therefore, we obtain

$$\begin{aligned} \Phi_{\rho^2}(\lambda_{ij} + \bar{C}_{ij}) &= \Pr(X_i(t) = 1 \mid X_j[t_\Delta]=1), \\ \Leftrightarrow \lambda_{ij} + \bar{C}_{ij} &= \rho \cdot \Phi_1^{-1}(\Pr(X_i(t)=1 \mid X_j[t_\Delta]=1)). \end{aligned}$$

- consider the both cases of  $X_j[t_\Delta] = 1$  and  $X_j[t_\Delta] = 0$ ,

$$U_i(t \mid X_j[t_\Delta] = 1) = \lambda_{ij} + C_{ij}(t \mid X_j[t_\Delta] = 1),$$

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## Assumption

$$C_{ij}(t \mid X_j[t_\Delta] = 1), C_{ij}(t \mid X_j[t_\Delta] = 0) \sim \mathcal{N}(\bar{C}_{ij}, \tau^2)$$

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- then we obtain

$$\lambda_{ij} + \bar{C}_{ij} = \rho \cdot \Phi_1^{-1}(\Pr(X_i(t) = 1 \mid X_j[t_\Delta] = 1)),$$

$$\bar{C}_{ij} = \rho \cdot \Phi_1^{-1}(\Pr(X_i(t) = 1 \mid X_j[t_\Delta] = 0)).$$



- estimator of pseudo connection

$$\lambda_{ij} = \rho \left\{ \Phi_1^{-1} \left( \Pr(X_i(t)=1 \mid X_j[t_\Delta]=1) \right) - \Phi_1^{-1} \left( \Pr(X_i(t)=1 \mid X_j[t_\Delta]=0) \right) \right\}.$$

- empirical estimates of conditional probability

$$\Pr(X_i(t)=1 \mid X_j[t_\Delta]=1) = \frac{1}{Z} \sum_t X_i(t \mid X_j[t_\Delta]=1),$$

$$\Pr(X_i(t)=1 \mid X_j[t_\Delta]=0) = \frac{1}{Z'} \sum_t X_i(t \mid X_j[t_\Delta]=0).$$

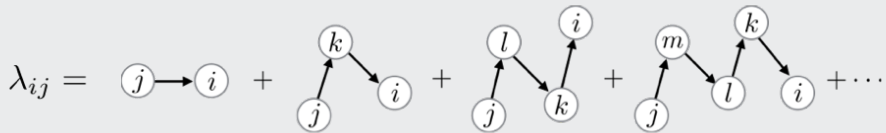
## Second step

- decompose pseudo connections  $\lambda$  with direct connections  $w$

$$\lambda_{ij} = \begin{array}{c} \textcircled{j} \longrightarrow \textcircled{i} \end{array} + \begin{array}{c} \textcircled{k} \\ \nearrow \searrow \\ \textcircled{j} \quad \textcircled{i} \end{array} + \begin{array}{c} \textcircled{l} \quad \textcircled{i} \\ \nearrow \quad \nearrow \\ \textcircled{j} \quad \textcircled{k} \end{array} + \begin{array}{c} \textcircled{m} \quad \textcircled{k} \\ \nearrow \quad \nearrow \searrow \\ \textcircled{j} \quad \textcircled{l} \quad \textcircled{i} \end{array} + \dots$$

## Second step

- decompose pseudo connections  $\lambda$  with direct connections  $w$



- consider an expansion with appropriate  $\delta, \delta'$  (delay time)

$$\begin{aligned} \lambda_{ij} &= w_{ij} \\ &+ \sum_k w_{ik} \Pr(X_k(t-\delta)=1 \mid X_j(t-\delta')=1) \\ &+ (\text{higher order terms}). \end{aligned}$$

- introduce a virtual probability with an appropriate interval  $t_\delta$

$$\theta_{ij} = \Pr(X_i(t)=1 \mid X_j[t_\delta]=1).$$

- we obtain an expansion of  $\lambda$  as

$$\lambda_{ij} = w_{ij} + \sum_k w_{ik} \theta_{kj} + \sum_{k,l} w_{ik} \theta_{kl} \theta_{lj} + \sum_{k,l,m} w_{ik} \theta_{kl} \theta_{lm} \theta_{mj} + \dots$$

- this expression gives a simple matrix form

$$\begin{aligned} \Lambda &= W(I + \Theta + \Theta^2 + \Theta^3 + \dots) && \triangleright \text{Neumann series} \\ &= W(I - \Theta)^{-1}, \end{aligned}$$

where  $W = (w_{ij})$  and  $\Theta = (\theta_{ij})$ .

- relation between  $\theta$  and  $w$ :

$$\begin{aligned}\theta_{ij} &= \Pr(X_i(t)=1 \mid X_j[t_\delta]=1) \\ &= \mathbb{E}[\Phi_{\sigma^2}(w_{ij} + C'_{ij})] \\ &= \Phi_{\rho^2}(w_{ij} + \mathbb{E}[C'_{ij}])\end{aligned}$$

- ▷ use expectation form
- ▷  $t_\delta$  is small enough
- ▷ by the corollary

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### Assumption

$$C'_{ij} \sim \mathcal{N}(\bar{C}_{ij}, \tau^2)$$

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- ▷ use expectation form
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- ▷ by the corollary

### Assumption

$$C'_{ij} \sim \mathcal{N}(\bar{C}_{ij}, \tau^2)$$

- calculate  $\theta$  by using  $w$  as

$$\begin{aligned}\theta_{ij} &= \Phi_{\rho^2}(w_{ij} + \bar{C}_{ij}), \\ \bar{C}_{ij} &= \rho \cdot \Phi_1^{-1}(\Pr(X_i(t)=1 \mid X_j[t_\Delta]=0)).\end{aligned}$$

### Third step

- estimate types of neurons consistent with data:
  - excitatory neurons - positive connections only
  - inhibitory neurons - negative connections only



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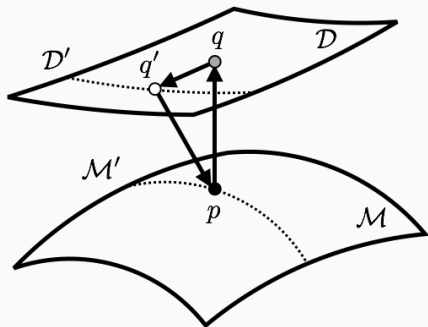
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treated as hidden variables  $\mathbf{z} \in \{0, 1\}^N$

$$\Pr(\text{Data} \mid W, \mathbf{z}) \Leftrightarrow \Pr(\mathbf{z} \mid \text{Data}, W)$$

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treated as hidden variables  $\mathbf{z} \in \{0, 1\}^N$

$$\Pr(\text{Data} \mid W, \mathbf{z}) \Leftrightarrow \Pr(\mathbf{z} \mid \text{Data}, W)$$

use em algorithm (Amari 1995)

with approximations:

- factorial model in data manifold
- Gibbs sampling

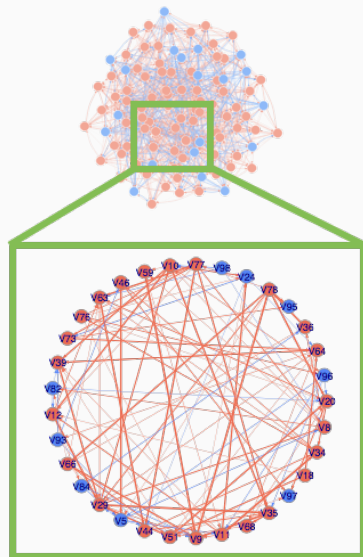
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1: Input:  $\Lambda, \bar{C}, \mathbf{z}$ 
2: function ESTIMATEW( $\Lambda, \bar{C}, \mathbf{z}$ )
3:   Initialization:  $\Theta^{(1)} \leftarrow [0, 1]^{N \times N}, \Lambda^{(1)} \leftarrow \Lambda$ 
4:   for  $\tau \leftarrow 1, T$  do
5:      $W^{(\tau+1)} \leftarrow \Lambda^{(\tau)}(I - \Theta^{(\tau)})$ 
6:     for  $i \leftarrow 1, N$  do
7:       for  $j \leftarrow 1, N$  do
8:          $[\hat{W}(\mathbf{z})^{(\tau+1)}]_{ij} \leftarrow \begin{cases} z_j [W^{(\tau+1)}]_{ij}, & [W^{(\tau+1)}]_{ij} > 0 \\ (1 - z_j) [W^{(\tau+1)}]_{ij}, & [W^{(\tau+1)}]_{ij} < 0 \end{cases}$ 
9:          $[\Theta^{(\tau+1)}]_{ij} \leftarrow \Phi_1([\hat{W}(\mathbf{z})^{(\tau+1)}]_{ij} + \bar{C}_{ij})$ 
10:         $\text{diag}(\Theta^{(\tau+1)}) \leftarrow 0$   $\triangleright$  update diagonal elements
11:         $\Lambda^{(\tau+1)} \leftarrow \Lambda^{(\tau)}$ 
12:         $\text{diag}(\Lambda^{(\tau+1)}) \leftarrow \text{diag}(\Lambda^{(\tau)} \Theta^{(\tau+1)})$   $\triangleright$  update diagonal elements
13: Output:  $\hat{W}(\mathbf{z})$ 

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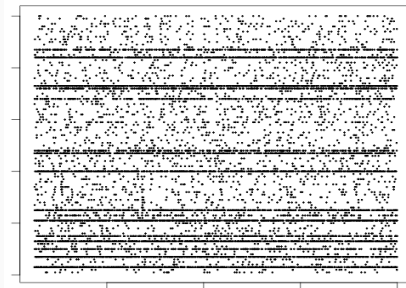
## NUMERICAL EXAMPLES

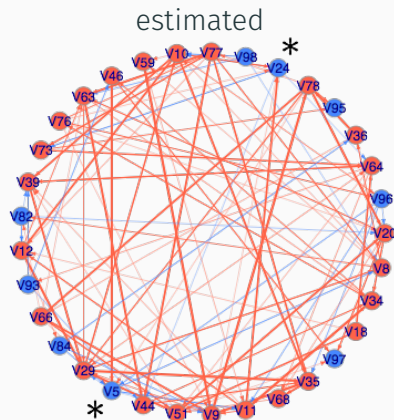
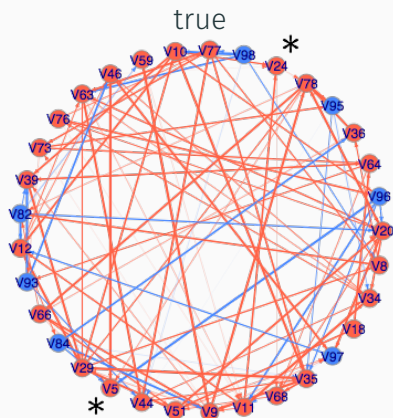
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Izhikevich's neuron model  
(Izhikevich 2003)

- $N = 33$  out of 100 neurons
- excitatory:inhibitory = 80%:20%
- $w_{ij} \sim \text{Unif}[-10, 10]$
- $\#\{w_{ij}\} \leq 10$

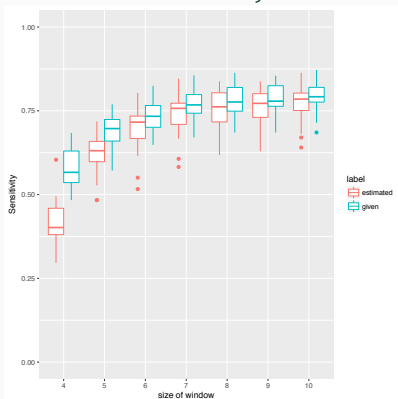




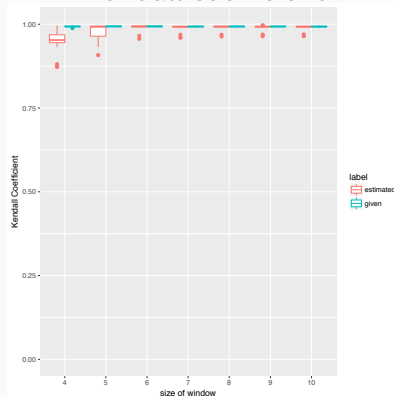
### remarks

- estimation is scale indeterminate
- inhibitory connections are difficult to estimate

## sensitivity



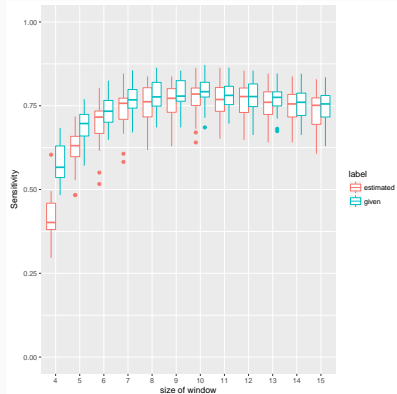
## Kendall coefficient



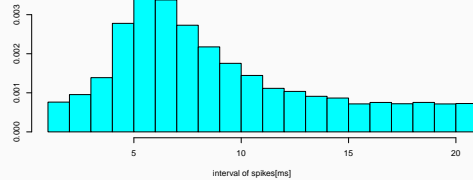
## remarks

- estimation accuracy gets better if neuron types are given
- order of weights %strength is estimated with sufficient accuracy

sensitivity



spike interval



## remark

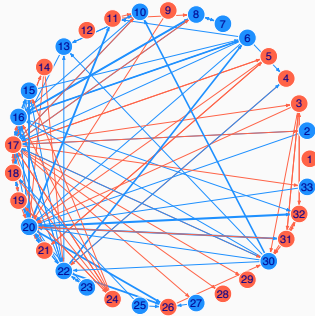
- sensitivity is affected by choice of correlation interval



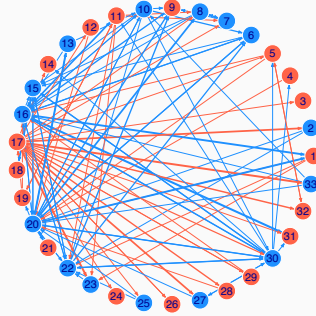
memory trace replay (Wilson and McNaughton 1994; Tatsuno, Lipa, and McNaughton 2006)

- purpose: examine the hypothesis “the replay of activity patterns during sleep plays an important role in the consolidation process of memory”
- measurements:
  - pre-task: activity of control
  - task: activity in learning stage
  - post-task: activity in non-REM stage

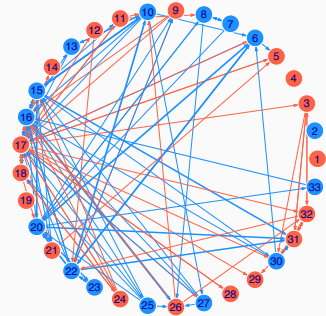
pre-task



task



post-task



### remarks

- some connections changed at task period are retained at post-task period (e.g. 8,11,12,20)
- result should be discussed from the viewpoint of biology

## CONCLUSION






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we consider an approach to solve the following problems



- pseudo correlation caused by higher-order effect
- influence from unobserved neurons
- directional excitatory/inhibitory connections

possible extension would be

- estimating the number of connections
- estimating activation functions of individual neurons
- applying other real-world data

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