# Estimation of Neural Connections from Multiple Spike Trains

## graph structure inference with nuisance inputs

Noboru Murata

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

Introduction

Problem Formulation

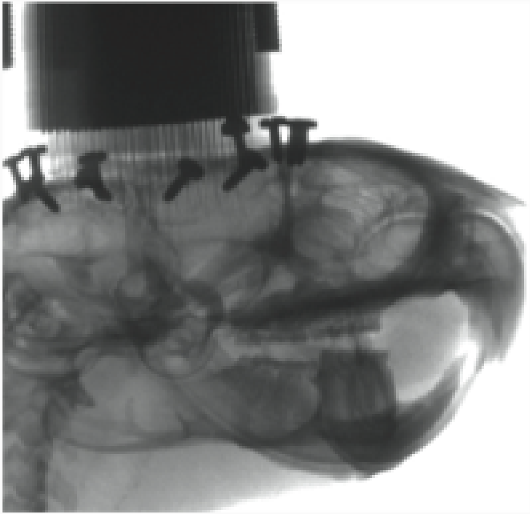
Numerical Examples

- synthetic data analysis
- real data analysis

Conclusion

# Introduction

- 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)

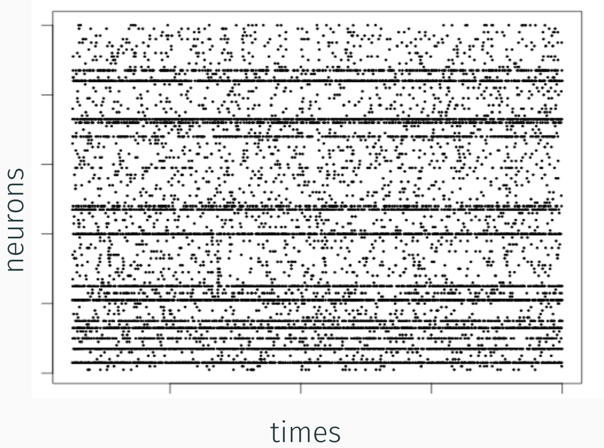


*by courtesy of Dr. Tatsuno at University of Lethbridge*

activities of individual neurons

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

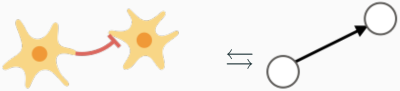
multi-variate stochastic process

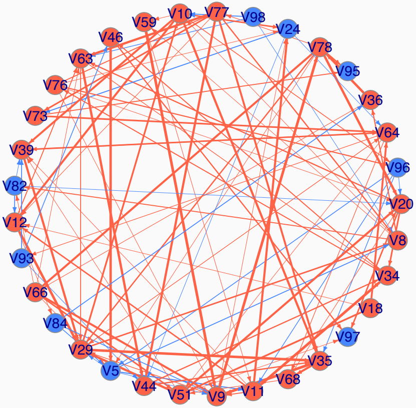



rearranged as binary sequence indicating states of neurons

- 0: resting
- 1: firing

multi-variate binary time series contains information of neural interactions






mathematical representation – directed graph

- node: neuron
- edge: synaptic connection

**Objective**

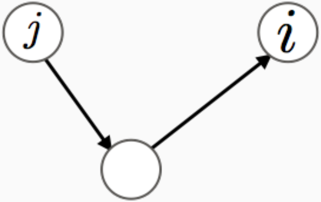
estimate weights of edges from binary time series at nodes typical methods for analysis

- 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

connections




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

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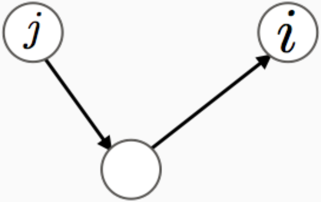


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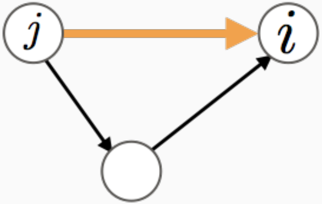


- spurious relation appears

correlation coefficient: statistics for analyzing relation of two random variables

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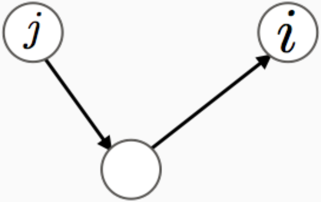


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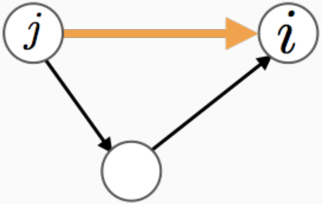


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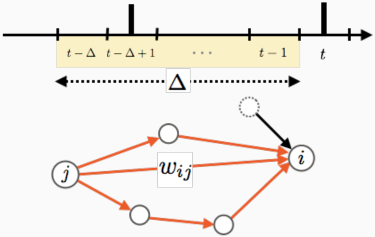
**Pseudo correlation**

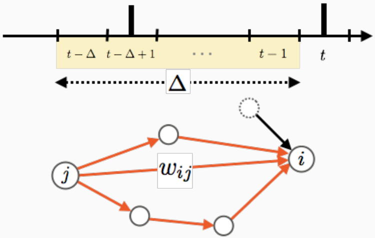
a common problem in complex network analysis

delayed correlation coefficient: statistics for analyzing time series




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

delayed correlation coefficient: statistics for analyzing time series

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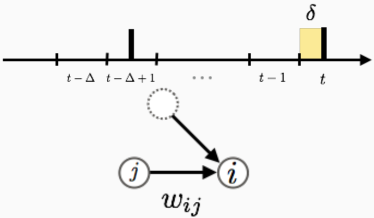
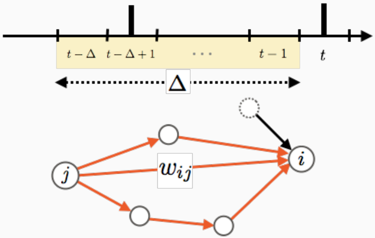



- consider short intervals?

delayed correlation coefficient: statistics for analyzing time series

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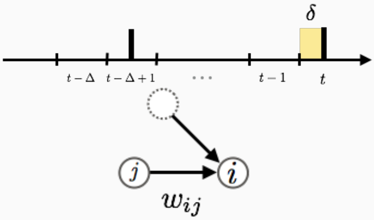


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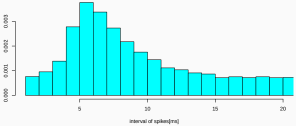


- spike intervals are random

a mathematical framework for treating

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

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**Main contribution**

solve those problems with simple mathematical tricks

# Problem Formulation

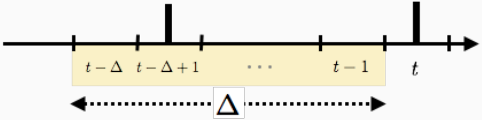
- indeces
  - $i \in \{1, 2, \ldots, N\}$: index of neurons
  - $t \in \{1, 2, \ldots, T\}$: discrete time of measurement
  - $t_\Delta = [t - \Delta, \ldots, t - 1]$:
    interval for delayed correlation
- states
  - $X_i(t) \in \{0, 1\}$: state of neuron $i$ at time $t$
  - $X_i[t_\Delta] \in \{0, 1\}$: 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 $i$

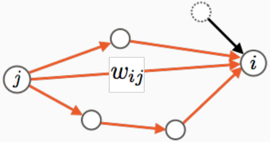
weighted sum of inputs from unobserved/observed neurons:

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

$B_i(t)$ : 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

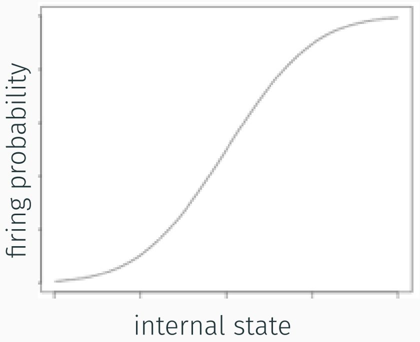
stochastic dependency on internal state:

$$\Pr\big(X_i(t) = 1\big) = \Phi_{\sigma^2}\big(U_i(t)\big),$$
$$\Phi_{\sigma^2} : \text{cdf of } \mathcal{N}(0, \sigma^2).$$

**Model assumption**

- we assume a probit model
- $\Phi_{\sigma^2}$ 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:

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

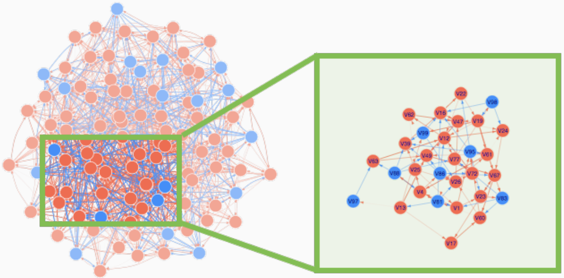
$$\phi_{\sigma^2}(z) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{z^2}{2\sigma^2}\right),$$

$\Phi_{\sigma^2}$ : 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*

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

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

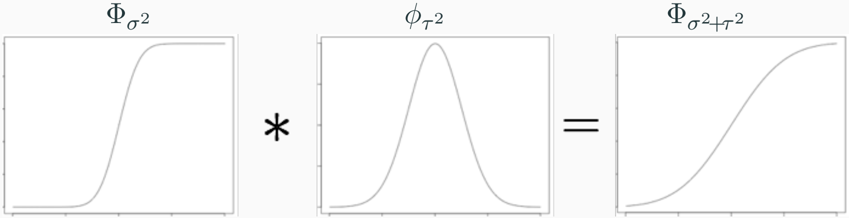
$$\begin{aligned} f_Y^-(x) &= f_Y(\mathbb{E}[Y]-x), \\ h &= g * f_Y^-. \end{aligned}$$

A special case is discussed in Hyvärinen 2002.

### Corollary

*If the 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*

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



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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apply the corollary for calculating conditional expectation:

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

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:

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

holds, therefore, obtain:

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

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

$$
\begin{aligned}
U_i(t \mid X_j[t_\Delta]{=}1) &= \lambda_{ij} + C_{ij}(t \mid X_j[t_\Delta]{=}1), \\
U_i(t \mid X_j[t_\Delta]{=}0) &= \phantom{\lambda_{ij} +{}} C_{ij}(t \mid X_j[t_\Delta]{=}0).
\end{aligned}
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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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## Assumption

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

then obtain:

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

estimator of pseudo connection:

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

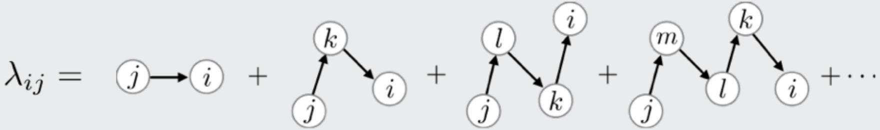
empirical estimates of conditional probability:

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

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

## Second step

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



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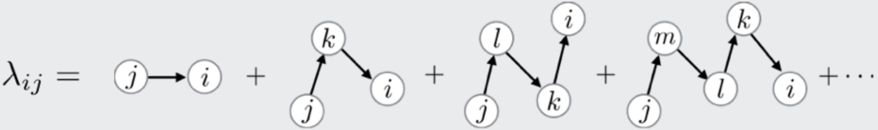


consider an expansion with appropriate $\delta, \delta'$ (delay time)

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

introducing a virtual probability with an appropriate interval $t_\delta$

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

obtain an expansion of $\lambda$ as:

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

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this expression gives a simple matrix form:

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

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

relation between $\theta$ and $w$:

$$\begin{aligned}\theta_{ij} &= \Pr(X_i(t)=1 \mid X_j[t_\delta]=1) && \triangleright \text{ use expectation form}\\ &= \mathbb{E}\big[\Phi_{\sigma^2}(w_{ij} + C'_{ij})\big] && \triangleright\ t_\delta \text{ is small enough}\\ &= \Phi_{\rho^2}\big(w_{ij} + \mathbb{E}[C'_{ij}]\big) && \triangleright \text{ by the corollary}\end{aligned}$$

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▷ use expectation form

▷ $t_\delta$ is small enough

▷ by the corollary

**Assumption**

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

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\end{aligned}
$$

**Assumption**

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

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

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

### Third step

estimate types of neurons consistent with data:

- excitatory neurons - positive connections only
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treated as hidden variables $\boldsymbol{z} \in \{0, 1\}^N$:

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

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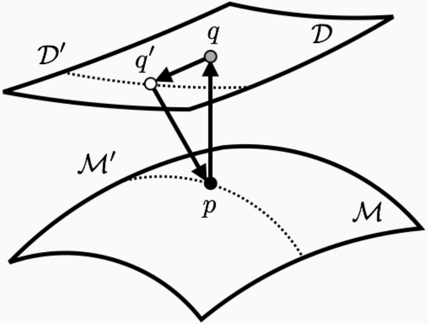



treated as hidden variables $\boldsymbol{z} \in \{0, 1\}^N$:

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

use em algorithm (Amari 1995)

with approximations:

## Proposed Algorithm:

Input: $\Lambda, \bar{C}, \boldsymbol{z}$

**function** ESTIMATEW($\Lambda, \bar{C}, \boldsymbol{z}$)

  Initialization: $\Theta^{(1)} \leftarrow [0,1]^{N\times N}$, $\Lambda^{(1)} \leftarrow \Lambda$

  **for** $\tau \leftarrow 1, T$ **do**

    $W^{(\tau+1)} \leftarrow \Lambda^{(\tau)}(I - \Theta^{(\tau)})$

    **for** $i \leftarrow 1, N$ **do**

      **for** $j \leftarrow 1, N$ **do**

$$[\hat{W}(\boldsymbol{z})^{(\tau+1)}]_{ij} \leftarrow \begin{cases} z_j[W^{(\tau+1)}]_{ij}, & [W^{(\tau+1)}]_{ij} > 0 \\ (1 - z_j)[W^{(\tau+1)}]_{ij}, & [W^{(\tau+1)}]_{ij} < 0 \end{cases}$$

      **end for**

    **end for**

    $\left[\Theta^{(\tau+1)}\right]_{ij} \leftarrow \Phi_1\left([\hat{W}(\boldsymbol{z})^{(\tau+1)}]_{ij} + \bar{C}_{ij}\right)$

    $\mathrm{diag}(\boldsymbol{\Theta}^{(\tau+1)}) \leftarrow 0$ ▷ update diagonal elements

    $\Lambda^{(\tau+1)} \leftarrow \Lambda^{(\tau)}$

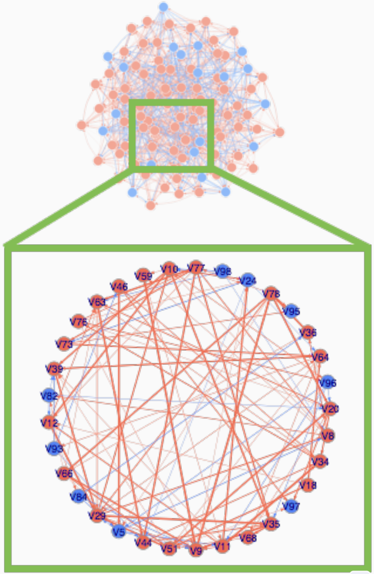
    $\mathrm{diag}\left(\Lambda^{(\tau+1)}\right) \leftarrow \mathrm{diag}\left(\Lambda^{(\tau)}\Theta^{(\tau+1)}\right)$ ▷ update diagonal elements

  **end for**

**end function**

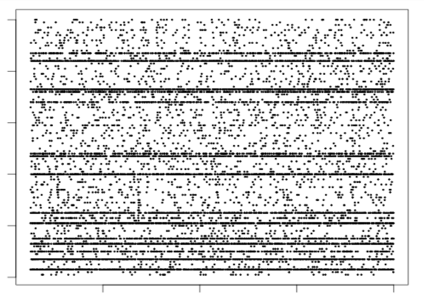
Output: $\hat{W}(\boldsymbol{z})$

# Numerical Examples

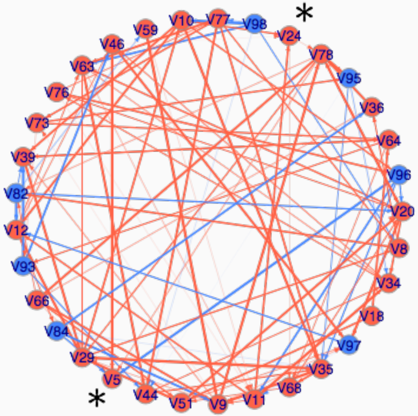



Izhikevich's neuron model (Izhikevich 2003)

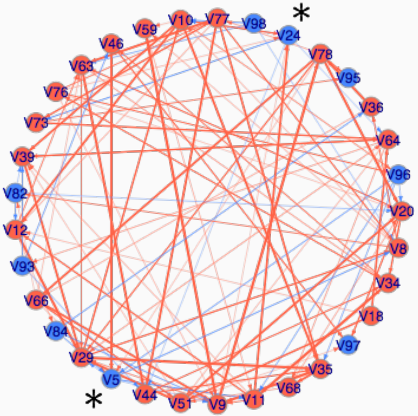
- $N = 33$ out of $100$ neurons
- excitatory:inhibitory = 80\
- $w_{ij} \sim \texttt{Unif}[-10, 10]$
- $\#\{w_{\cdot i}\} \leq 10$



true



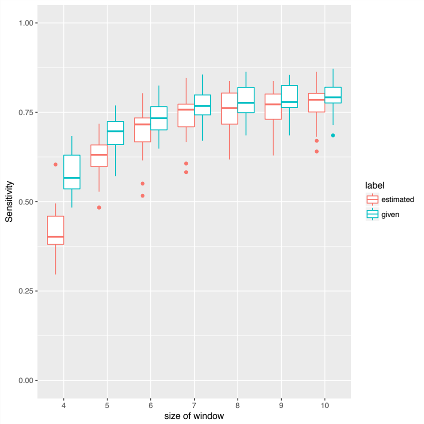

estimated



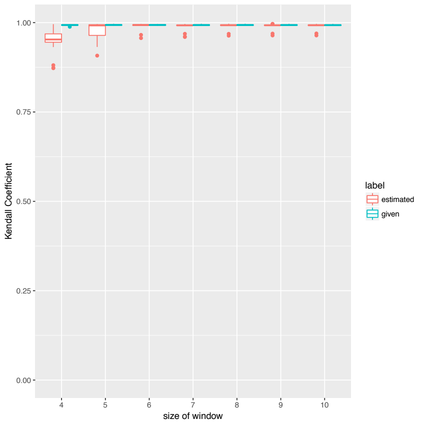

## remarks

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

sensitivity



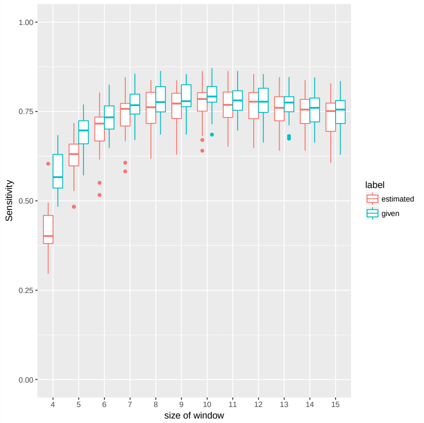

Kendall coefficient



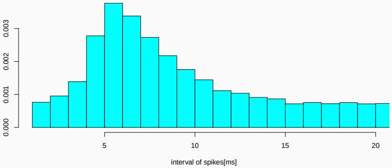

## remarks

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

sensitivity




spike interval

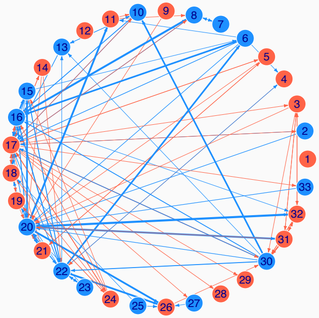



**remark**

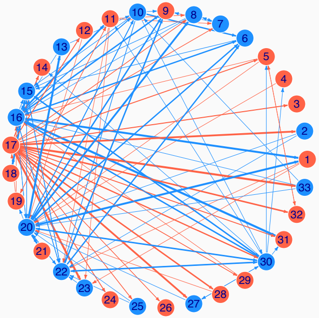
- sensitivity is affected by choice of correlation interval memory trace replay: (Wilson and McNaughton 1994; Tatsuno, Lipa, and McNaughton 2006)

- purpose: examine the hyposesis "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

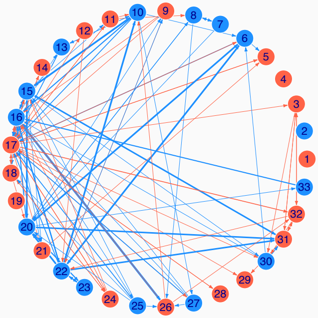
pre-task




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

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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