Estimation of Neural Connections from Multiple Spike Trains

Graph Structure Inference with Nuisance Inputs

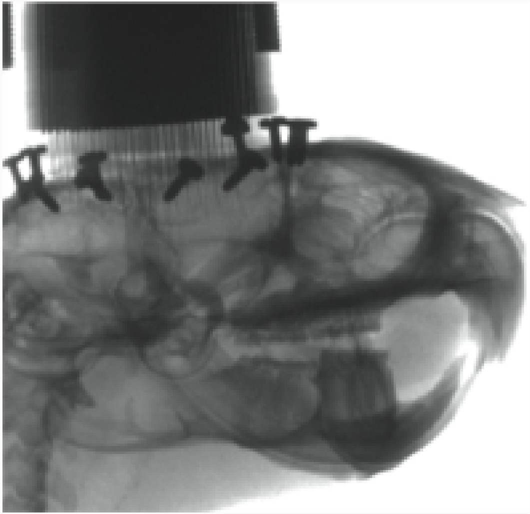
Noboru Murata

June 19, 2023

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

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)

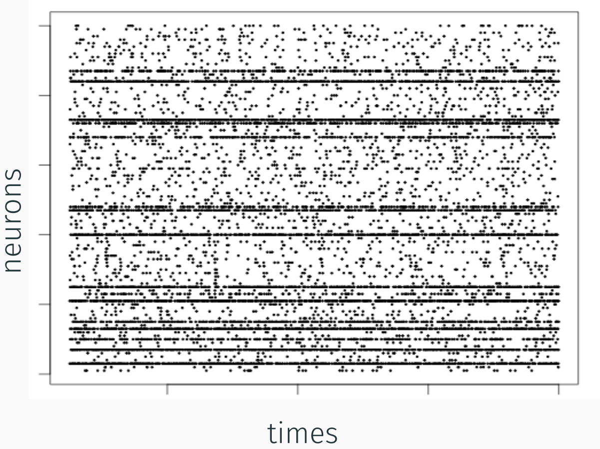


by courtesy of Dr. Tatsuno at University of Lethbridge

activities of individual neurons

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

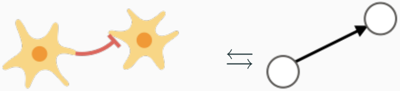
multi-variate point process

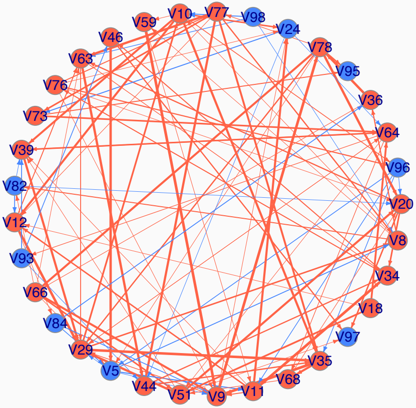


rearranged as binary sequence indicating states of neurons

- 0: resting
- 1: firing

multi-variate binary time series contains information of neural interactions





mathematical representation – directed graph

- node: neuron
- edge: synaptic connection

Objective

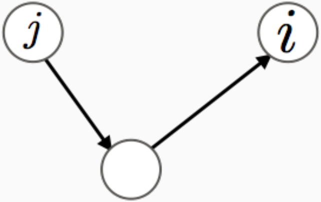
estimate weights of edges from binary time series at nodes typical methods for analysis

- 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
  - dynamical systems
- influence from unobserved neurons
- directed excitatory/inhibitory connections

correlation coefficient: statistics for analyzing relation of two random variables

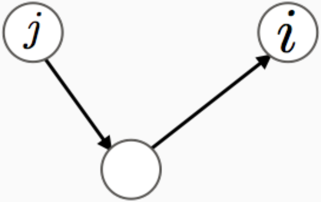
connections



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

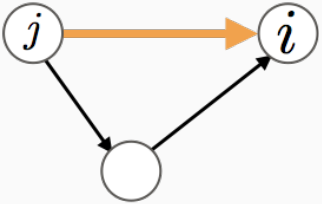
correlation coefficient: statistics for analyzing relation of two random variables

connections



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

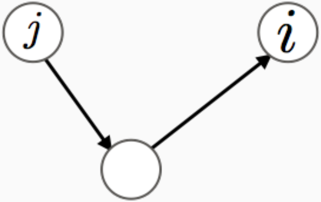
pseudo-correlation



- spurious relation appears

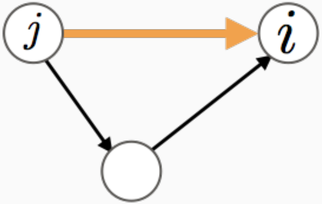
correlation coefficient: statistics for analyzing relation of two random variables

connections



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

pseudo-correlation

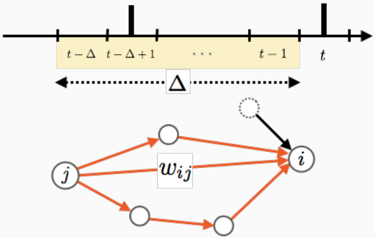


- spurious relation appears

Pseudo correlation

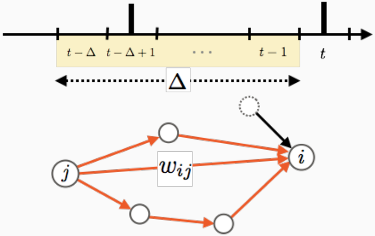
a common problem in complex network analysis

delayed correlation coefficient: statistics for analyzing time series

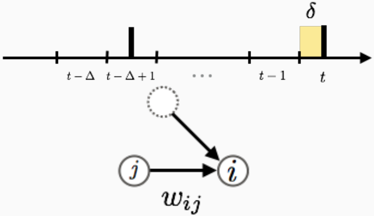


- appropriate intervals have to be considered
- information propagates multiple paths
- spurious relation appears

delayed correlation coefficient: statistics for analyzing time series

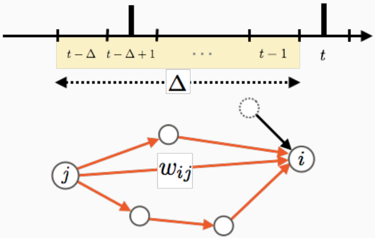


- appropriate intervals have to be considered
- information propagates multiple paths
- spurious relation appears

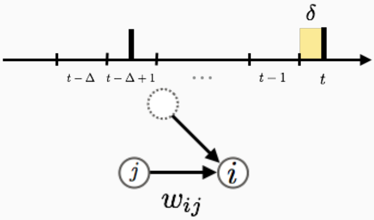


- consider short intervals?

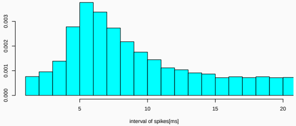
delayed correlation coefficient: statistics for analyzing time series



- 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 and dynamical systems
- influence from unobserved neurons
- directed excitatory/inhibitory connections

a mathematical framework for treating

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

Main contribution

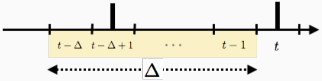
solve those problems with simple mathematical tricks

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_Δ
  - $U_i(t) \in \mathbb{R}$: 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

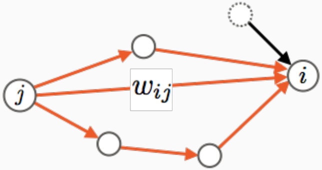
weighted sum of inputs from unobserved/observed neurons

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



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

λ_{ij} : pseudo connection including undirect paths

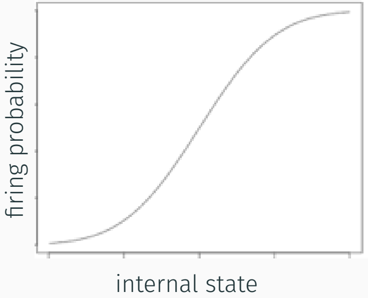


Remarks

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

stochastic dependency on internal state:

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



Assumption

- we assume a probit model, where Φ_{σ^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,

λ_{ij} : pseudo connection.

- neuron firing

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

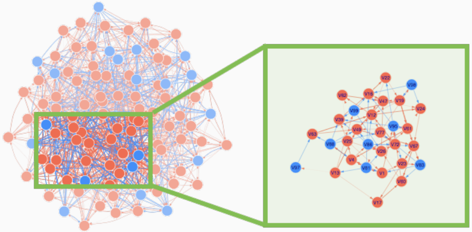
$$\phi_{\sigma^2}(z) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\Big(-\frac{z^2}{2\sigma^2}\Big),$$

Φ_{σ^2} : cdf of $\mathcal{N}(0, \sigma^2)$, integral of ϕ_{σ^2}.

First step

- remove nuisance input B and estimate pseudo connection λ

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



Theorem

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

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

where f_Y is the pdf of Y and

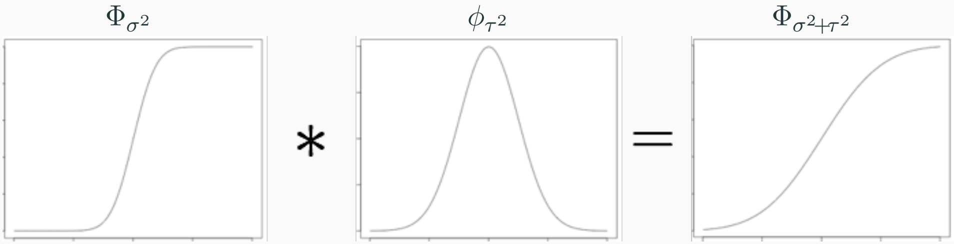
$$\begin{aligned} f_Y^-(x) &= f_Y(\mathbb{E}[Y]-x), \\ h &= g * f_Y^- . \end{aligned}$$

A special case is discussed in Hyvärinen 2002.

Corollary

If function g is Φ_{σ^2} and random variable X is constant value x, and probability density function f_Y is Gaussian with mean $\mathbb{E}[Y]$ and variance τ^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 $X_j[t_\Delta]=1$,

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

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

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

- let us apply the corollary for calculating conditional expectation

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

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

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

- for binary random variables, the following holds

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

- therefore, we obtain

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

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

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

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

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

Assumption

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

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

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

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 we 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

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

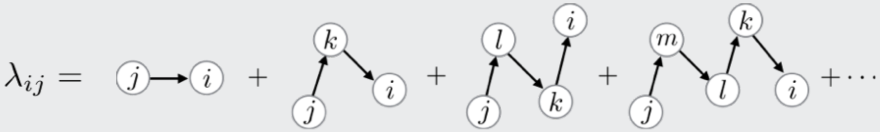
- empirical estimates of conditional probability

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

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

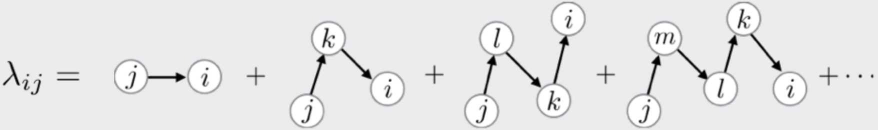
Second step

- decompose pseudo connections λ with direct connections w



Second step

- decompose pseudo connections λ with direct connections w



- consider an expansion with appropriate δ, δ' (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_δ

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

- we obtain an expansion of λ as

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

- 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 θ and w:

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

- relation between θ and w:

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

Assumption

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

- relation between θ and w:

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

Assumption

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

- calculate θ 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
  - inhibitory neurons - negative connections only

Third step

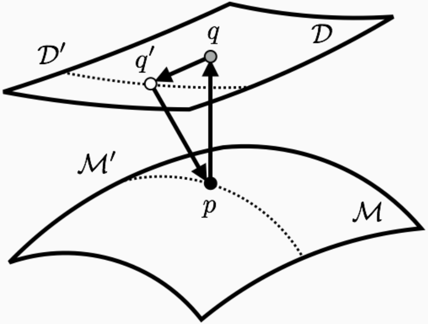
- estimate types of neurons consistent with data:
    - excitatory neurons - positive connections only
    - inhibitory neurons - negative connections only

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

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

Third step

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



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:

- factorial model in data manifold
- Gibbs sampling

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**

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

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

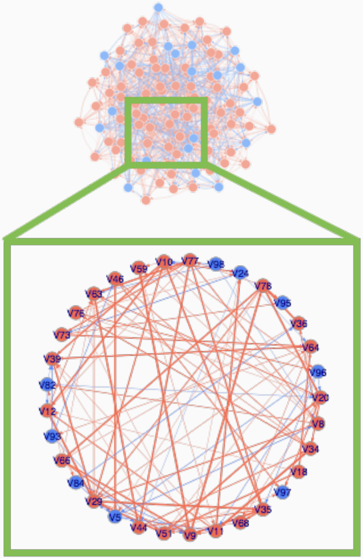
    $\mathrm{diag}(\boldsymbol{\Theta}^{(\tau+1)}) \leftarrow 0$ ▷ *update diagonal elements*

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

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

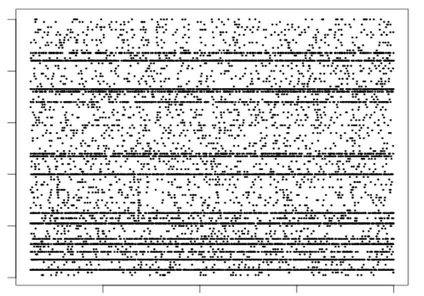
Output: $\hat{W}(\boldsymbol{z})$

Numerical Examples

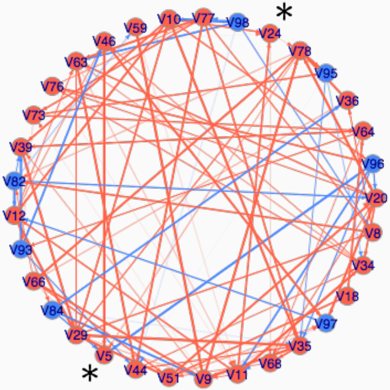


Izhikevich's neuron model (Izhikevich 2003)

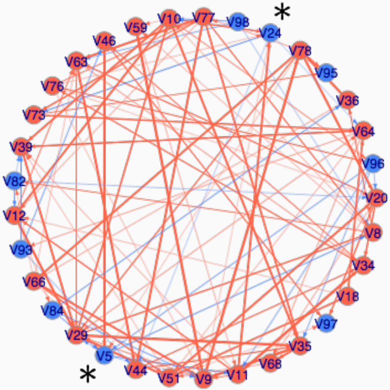
- $N = 33$ out of 100 neurons
- excitatory:inhibitory = 80%:20%
- $w_{ij} \sim \mathrm{Unif}[-10, 10]$
- $\#\{w_{\cdot j}\} \leq 10$



true



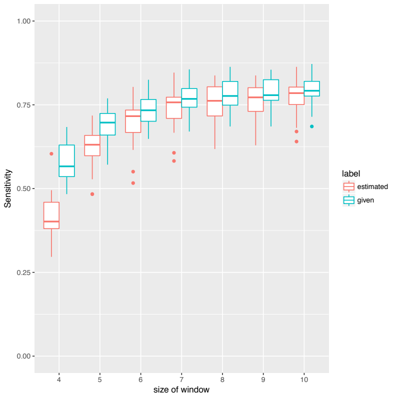
estimated



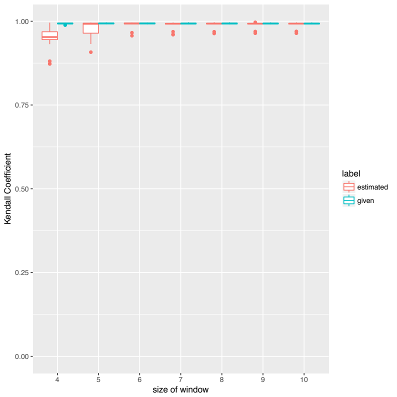
remarks

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

sensitivity



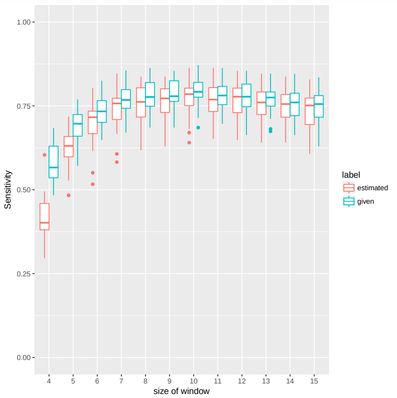
Kendall coefficient



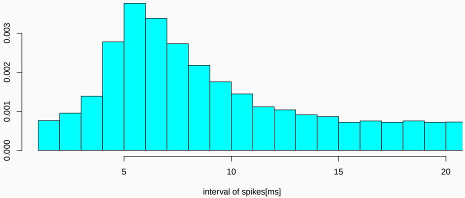
remarks

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

sensitivity



spike interval

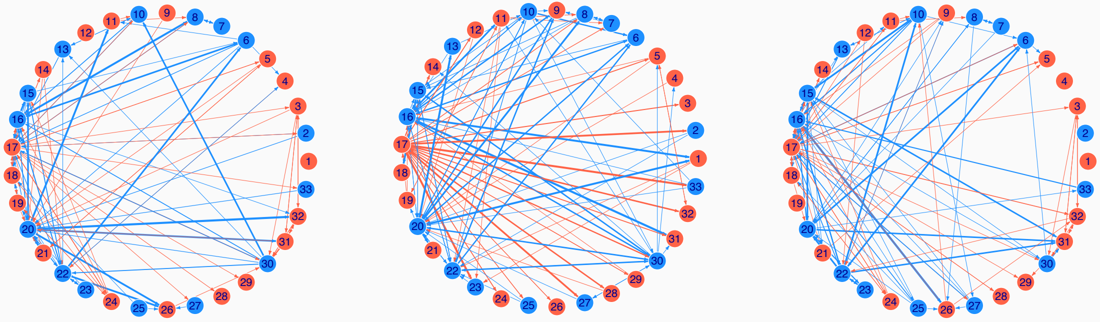


remark

- 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

Amari, Shun-ichi (Jan. 1995). "The EM Algorithm and Information Geometry in Neural Network Learning." In: *Neural Computation* 7.1, pp. 13–18. DOI: 10.1162/neco.1995.7.1.13.

Friedman, Jerome, Trevor Hastie, and Robert Tibshirani (July 2008). "Sparse inverse covariance estimation with the graphical lasso." In: *Biostatistics* 9.3, pp. 432–441. DOI: 10.1093/biostatistics/kxm045.

Hyvärinen, Aapo (Aug. 6, 2002). "Gaussian moments for noisy independent component analysis." In: *IEEE Signal Processing Letters* 6 (6), pp. 145–147. DOI: 10.1109/97.763148.

Ito, Hiroyuki and Satoshi Tsuji (Jan. 2000). "Model Dependence in Quantification of Spike Interdependence by Joint Peri-Stimulus Time Histogram." In: *Neural Computation* 12.1, pp. 195–217. DOI: 10.1162/089976600300015952.

Izhikevich, Eugene M. (Nov. 2003). "Simple model of spiking neurons." In: *IEEE Transactions on Neural Networks* 14 (6), pp. 1569–1572. DOI: 10.1109/TNN.2003.820440.

Kim, Sanggyun et al. (Mar. 24, 2011). "A Granger Causality Measure for Point Process Models of Ensemble Neural Spiking Activity." In: *PLoS Computational Biology* 7.3. DOI: 10.1371/journal.pcbi.1001110.

Nakahara, Hiroyuki and Shun-ichi Amari (Oct. 2002). "Information-Geometric Measure for Neural Spikes." In: *Neural Computation* 14.10, pp. 2269–2316. DOI: 10.1162/08997660260293238.

Noda, Atsushi et al. (July 2014). "Intrinsic Graph Structure Estimation Using Graph Laplacian." In: *Neural Computation* 26.7, pp. 1455–1483. DOI: 10.1162/NECO_a_00603.

Tatsuno, Masami, Jean-Marc Fellous, and Shun-ichi Amari (Aug. 2009). "Information-Geometric Measures as Robust Estimators of Connection Strengths and External Inputs." In: *Neural Computation* 21.8, pp. 2309–2335. DOI: 10.1162/neco.2009.04-08-748.

Tatsuno, Masami, Peter Lipa, and Bruce L. McNaughton (Oct. 18, 2006). "Methodological Considerations on the Use of Template Matching to Study Long-Lasting Memory Trace Replay." In: *The Journal of Neuroscience* 26 (42), pp. 10727–10742. DOI: 10.1523/JNEUROSCI.3317-06.2006. PMID: 17050712.

Wilson, Matthew A. and Bruce L. McNaughton (July 29, 1994). "Reactivation of Hippocampal Ensemble Memories During Sleep." In: *Science* 265 (5172), pp. 676–679. DOI: 10.1126/science.8036517. PMID: 8036517.