Granger Causality Network Reconstruction of Neuronal Systems

Yanyang Xiao
Corporator: Yaoyu Zhang, Zhiqin Xu
Advisor: David Cai, Douglas Zhou

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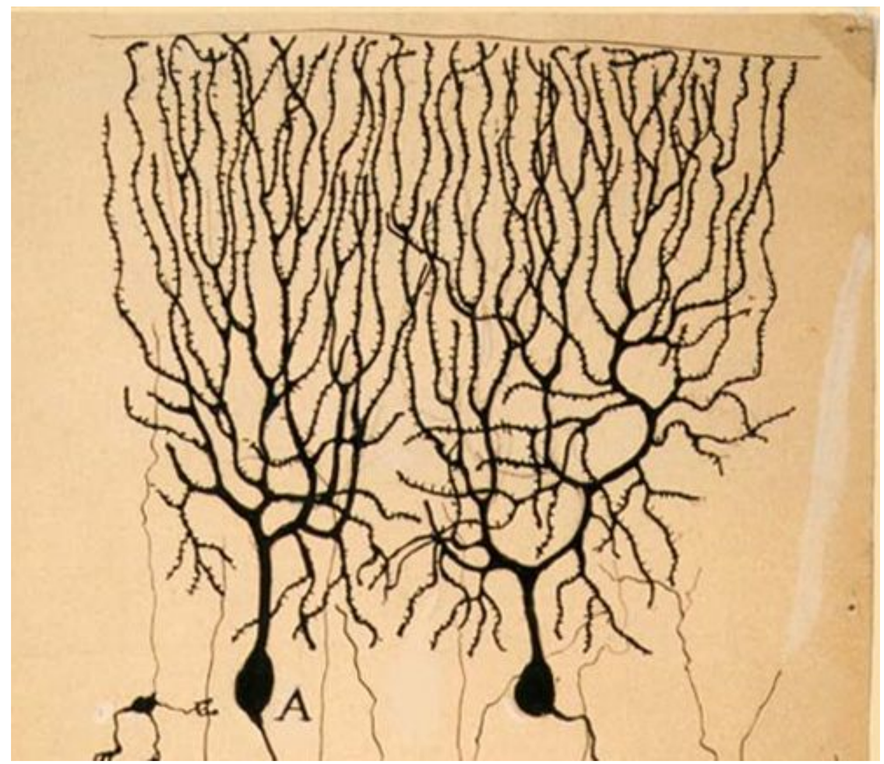
Background

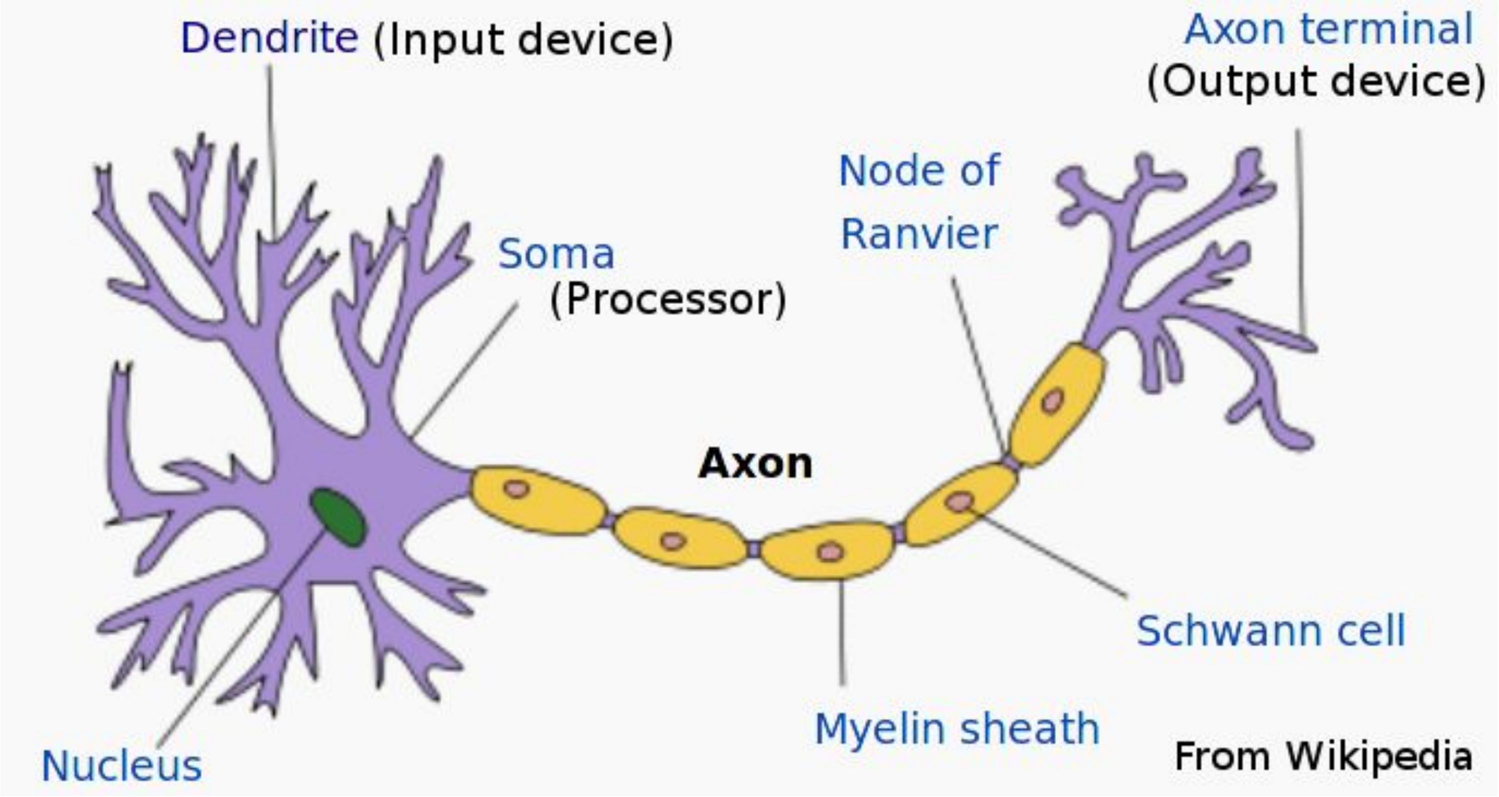
- The big problem: Neuronal network structure?
  - The network structure of nervous system plays a central role in its function.
- Challenges
  - 10^4 cells per mm^3
  - Scale of μm
  - 10^4 synaptics per cell
- Methods:
  - Functional connectivity
  - Tracer



Background

- Granger Causality is widely applied in this area
- fMRI, BOLD, LFP, Spike trains etc
  - M. Ding, Y. Chen, S.L. Bressler (2006) Granger causality: basic theory and application to neuroscience. In Handbook of Time Series Analysis, ed. B. Schelter, M. Winterhalder, and J. Timmer, Wiley-VCH Verlage, 2006: 451-474
  - ??? List more usage example?
- But without any theory support !

Properties of Neuron



- membranes are insulator with ion-channels
- solution and cytoplasm are conductor -- full of ions

Hodgkin–Huxley Model (HH)

- Based on physics, a detailed neuron model can be writen down.

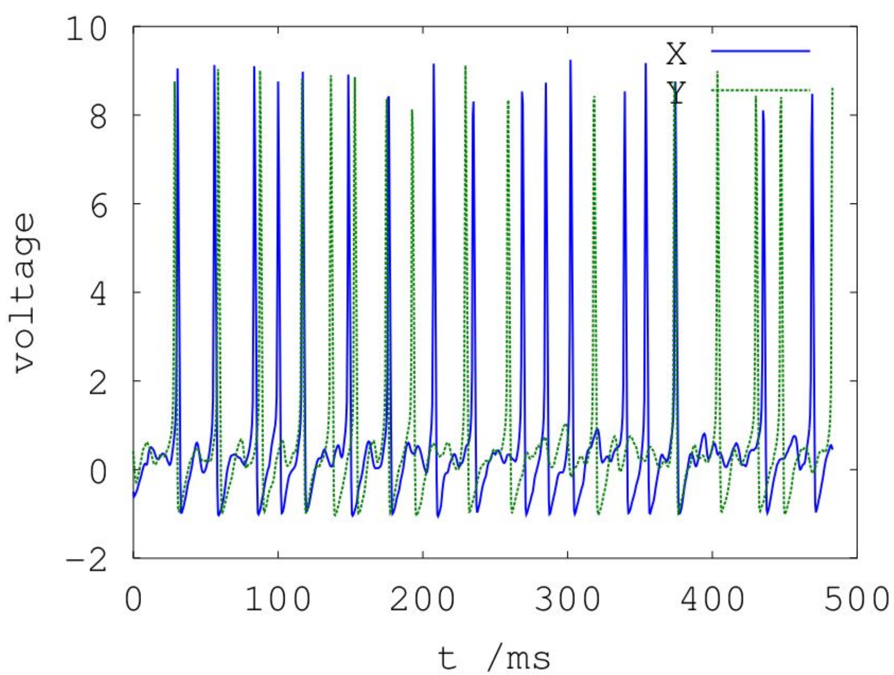
nonlinear terms

$$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + \bar{g}_K n^4 (V_m - V_K) + \bar{g}_{Na} m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l)$$

$$\frac{dn}{dt} = \alpha_n (1-n) - \beta_n n$$

$$\frac{dm}{dt} = \alpha_m (1-m) - \beta_m m$$

$$\frac{dh}{dt} = \alpha_h (1-h) - \beta_h h$$



$$I_i^{input} = I_i^E + I_i^I$$

$$I_i^E = G_i^E (V_i - V_G^E)$$

$$I_i^I = G_i^I (V_i - V_G^I)$$

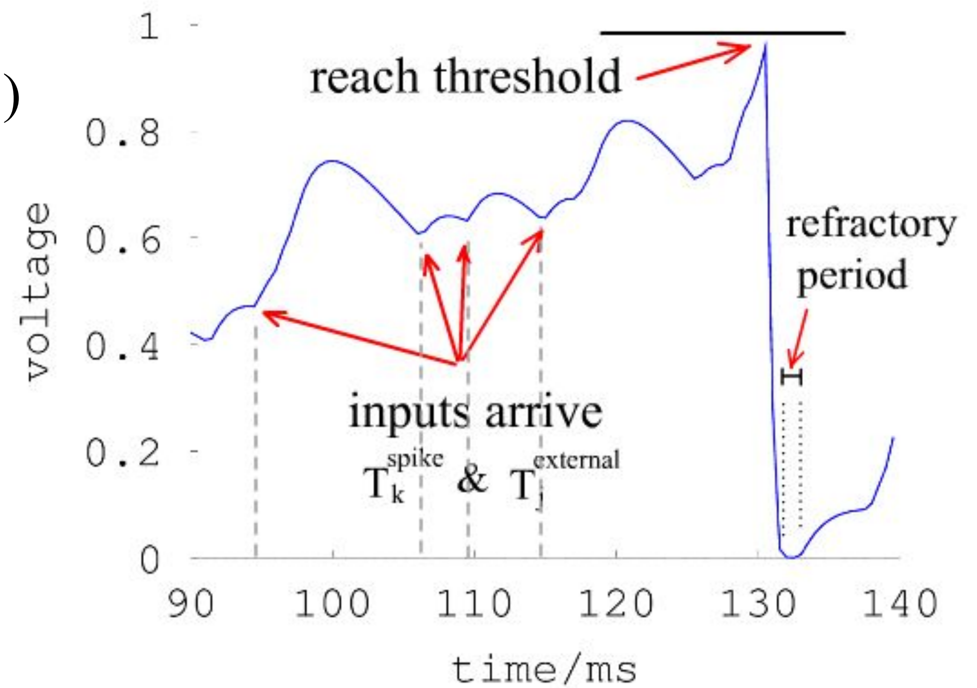
Leaky Integrate-And-Fire Model (I&F)

- Simplified neuron electrophysiology model.
- Easy to understand, easy to compute, easy to analyze (compared to Hodgkin–Huxley model)

nonlinear terms

$$\begin{cases} \dfrac{dV(t)}{dt} = -G_L\left(V(t)-\varepsilon_L\right) - G(t)\left(V(t)-\varepsilon_E\right) \\ \dfrac{dG(t)}{dt} = -\dfrac{G(t)}{\sigma} + S\sum_l \delta\left(t-T_l\right) \end{cases}$$

Input from other neurons and external input.

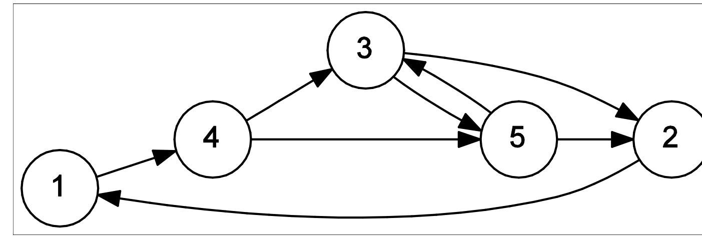


From Single Neuron to Neuronal Network

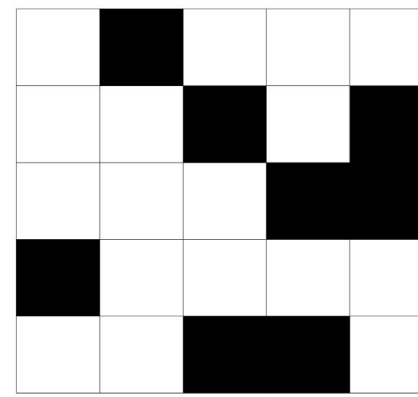
$$\begin{cases} \dfrac{dV_i(t)}{dt} = -G^L\left(V_i(t)-\varepsilon^E\right) - G_i^E(t)\left(V_i(t)-\varepsilon^E\right) \\[2ex] \dfrac{dG_i^E(t)}{dt} = -\dfrac{G_i^E(t)}{\sigma} + \sum\limits_{\substack{j=1 \\ j\neq i}}^{p} \sum\limits_{l} S_{ij}\,\delta\left(t-T_{jl}^S\right) + F_i \sum\limits_{l} \delta\left(t-T_{il}^F\right) \end{cases}$$

Input from other neurons

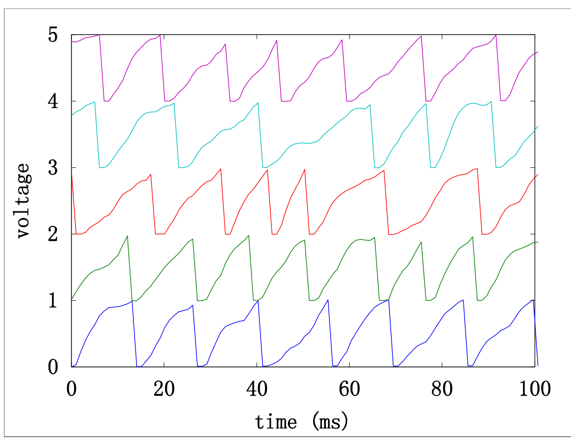
external input



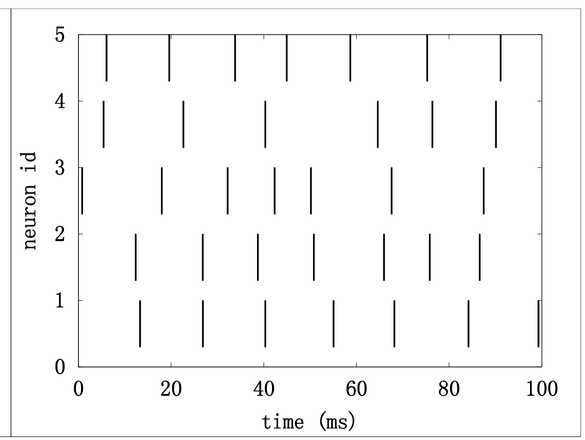
a network



Adjacency matrix of above network



Voltage trace



Spike Train

Q: Can we recover the network from the voltage trace or spike train data?

Granger Causality (GC)

- Idea: Causality <=> prediction improvement
  - N. Wiener (1956). The theory of prediction.
- Granger Causality <=> linear prediction improvement
  - C. W. J. Granger (1969). Investigating causal relations by econometric models and cross-spectral methods
  - Auto-regression of Xt using different variables:

$$x_t = \sum_{j=1}^{\infty} a_j^* x_{t-j} + \epsilon_t^*$$

$$x_t = \sum_{j=1}^{\infty} a_j x_{t-j} + \boxed{\sum_{j=1}^{\infty} b_j y_{t-j}} + \epsilon_t$$

Define GC: $$F_{y \to x} = \ln \frac{\mathrm{var}(\epsilon_t^*)}{\mathrm{var}(\epsilon_t)}$$

Multivariable GC

GC from Y to X conditional on Z (z_t can be a vector):

$$x_t = \sum_{j=1}^{\infty} a_j^* x_{t-j} + \sum_{j=1}^{\infty} c_j^* z_{t-j} + \varepsilon_t^*$$

$$x_t = \sum_{j=1}^{\infty} a_j x_{t-j} \boxed{+ \sum_{j=1}^{\infty} b_j y_{t-j}} + \sum_{j=1}^{\infty} c_j z_{t-j} + \varepsilon_t$$

Define GC: $$F_{y\to x|z} = \ln \frac{\operatorname{var} \varepsilon_t^*}{\operatorname{var} \varepsilon_t}$$

$$F_{y\to x|z} = 0 \;\Leftrightarrow\; \operatorname{var} \varepsilon_t^* = \operatorname{var} \varepsilon_t \;\Leftrightarrow\; b_j = 0 \;\forall j \ge 1$$

Basic Properties of GC

- GC is meaningful for stationary time series only.
- The prediction errors $(\varepsilon_t, \varepsilon_t^*)$ are white noise

$$\mathrm{cov}(\varepsilon_t, \varepsilon_{t-j}) \quad \forall j \in \mathbf{Z}, j \neq 0$$

- Change the scale of data does not change GC:

$$u_t = c_u x_t, v_t = c_v y_t \qquad \Rightarrow \qquad F_{u \to v} = F_{x \to y}, F_{v \to u} = F_{y \to x}$$

- Invertible Causal filter does not change GC:

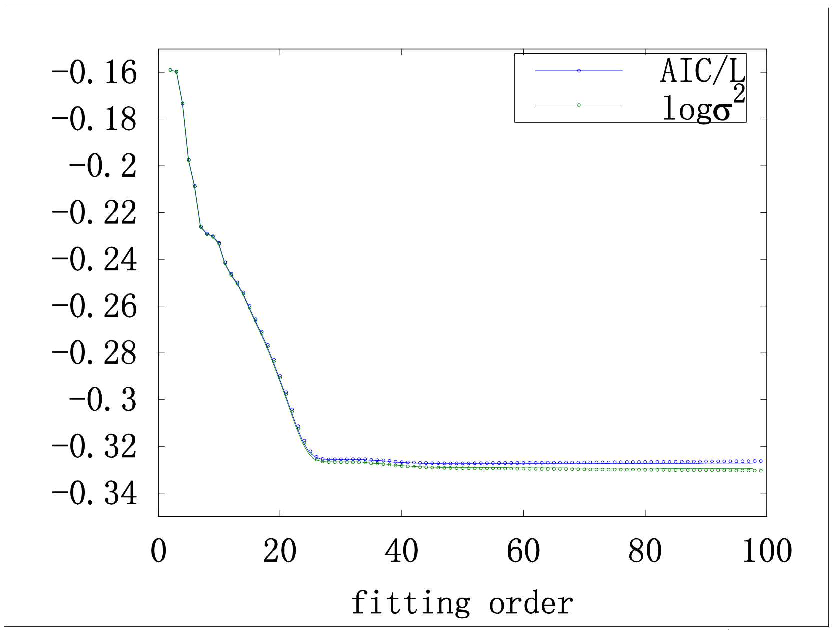
$$u_t = \sum_{j=0} c_j x_{t-j}, v_t = \sum_{j=0} d_j y_{t-j} \quad c_0 \neq 0, d_0 \neq 0$$

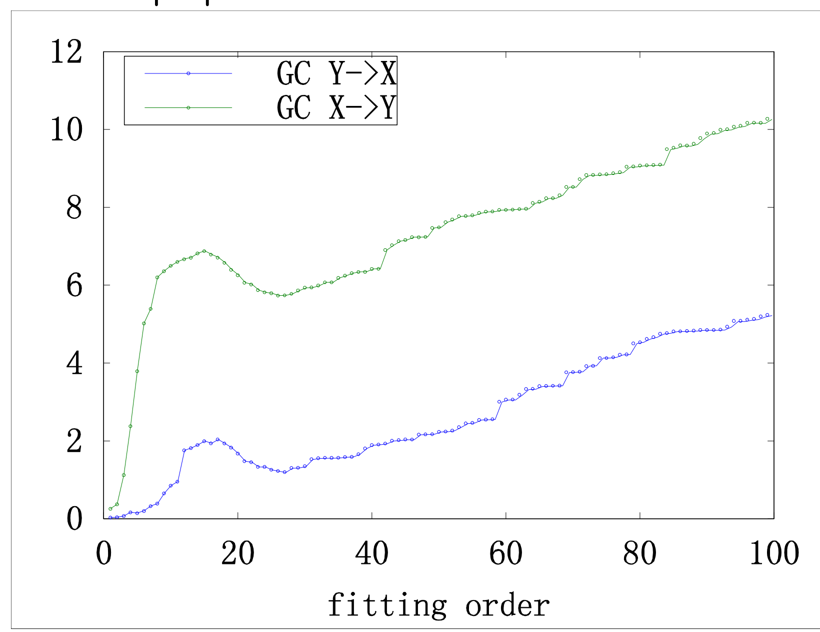
$$\Rightarrow \qquad F_{u \to v} = F_{x \to y}, F_{v \to u} = F_{y \to x}$$

Determine the fitting order in the regression

- Akaike information criterion (AIC)
  - p-variable, fitting order m, data length L, variance of residual Σ

$$AIC/L = 2p^2 m/L + \ln|\Sigma| + C$$





GC is estimated with bias $E\left(\hat{F}_{y\to x}\right) = \frac{m}{L} + F_{y\to x}$

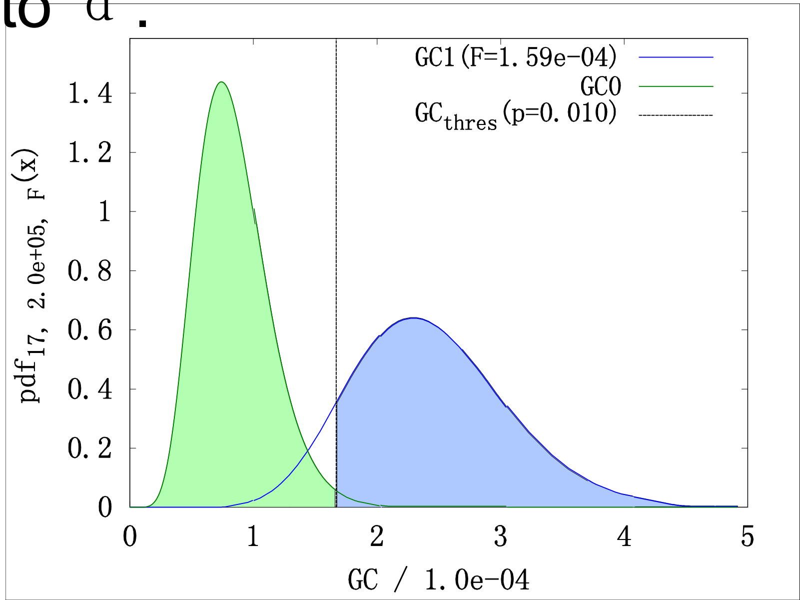
Significance Test of GC

- Significance Test: Null hypothesis: $F_{y \to x} = 0$
  - For data length L, fitting order M

$$L\hat{F}_{y \to x} \overset{a}{\sim} \chi^2_M$$

  - Set a acceptable probability of Type I error (α), compare the p value of $\hat{F}_{y \to x}$ to α .
- Confidence interval:

$$L\hat{F}_{y \to x} \overset{a}{\sim} \chi^2_M \left(LF_{y \to x} \right)$$



GC of Nonlinear System?

- Example: $\operatorname{var}\varepsilon_t = 1, \operatorname{var}\eta_t = 0.7, \operatorname{cov}(\varepsilon_t, \eta_t) = 0.4$

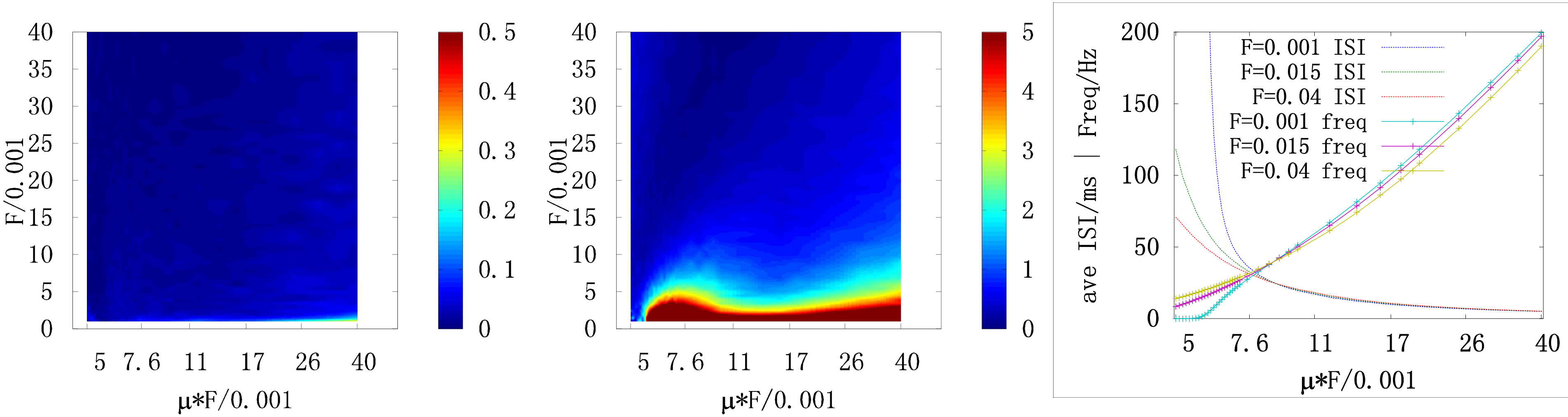
$$\begin{cases} X_t = 0.9X_{t-1} - 0.5X_{t-2} + \varepsilon_t \\ Y_t = 0.8Y_{t-1} - 0.5Y_{t-2} + 0.16X_{t-1} - 0.2X_{t-2} + \eta_t \end{cases}$$

$$\begin{cases} F_{X\to Y} \approx 0.053 \\ F_{Y\to X} = 0 \end{cases}$$ correct

$$Z_t = X_t^{\ 5} \quad \begin{cases} F_{Z\to Y} \approx 0.007 \\ F_{Y\to Z} \approx 0.017 \end{cases} \qquad Z_t = X_t^{\ 2} \quad \begin{cases} F_{Z\to Y} = 0.000 \\ F_{Y\to Z} = 0.000 \end{cases}$$ wrong

Not surprising ---- So how about neuronal network?

Apply Granger Causality to Hodgkin–Huxley model

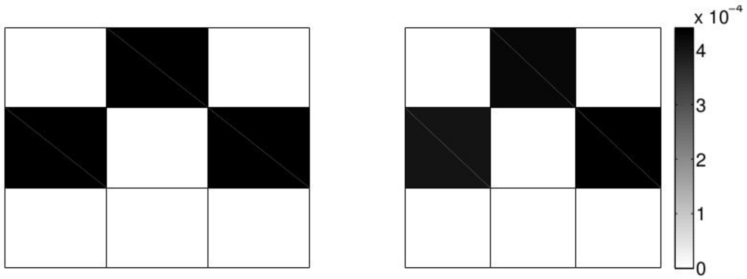


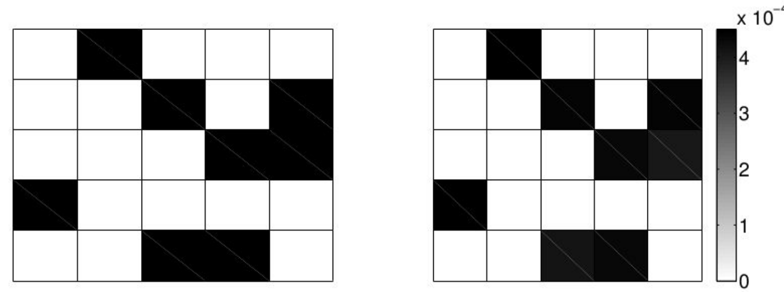
2 neuron, different dynamical regime.

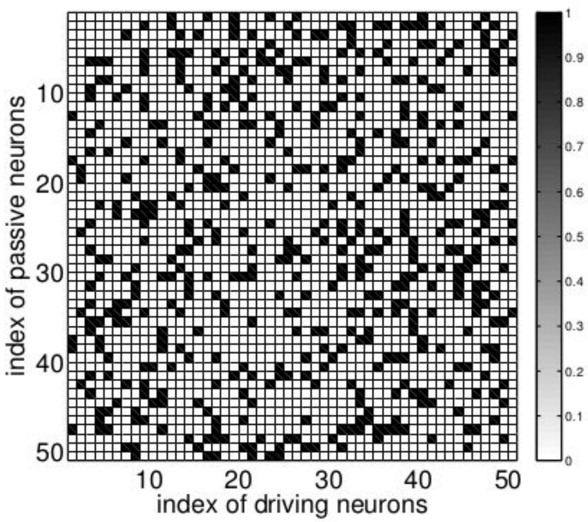
It's work !

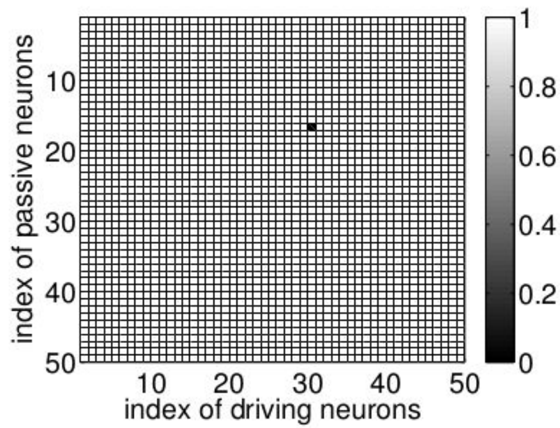
Apply Granger Causality to Hodgkin–Huxley model

- Case of bigger network







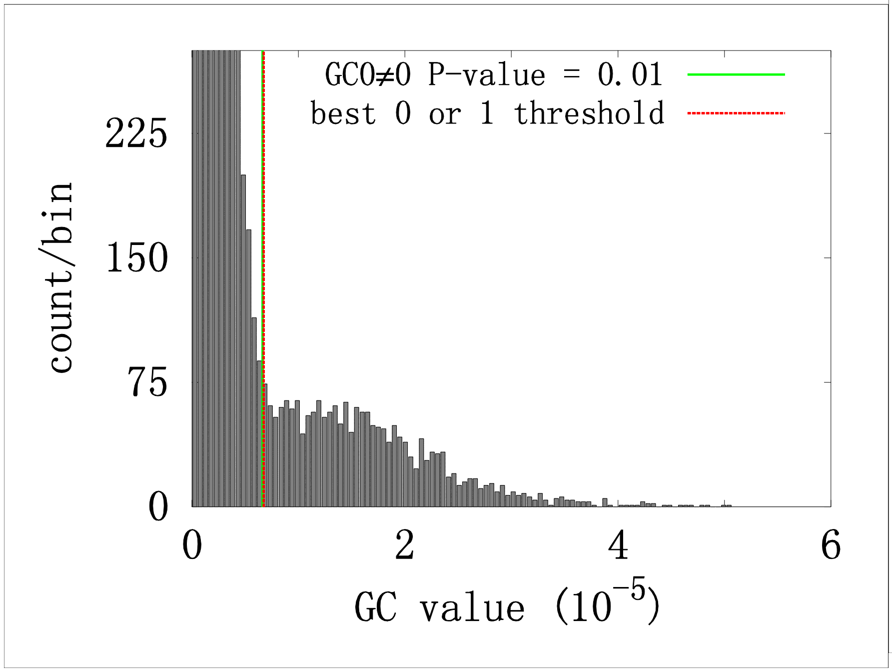


1000 neuron case (10% connection) also have >98% correctness

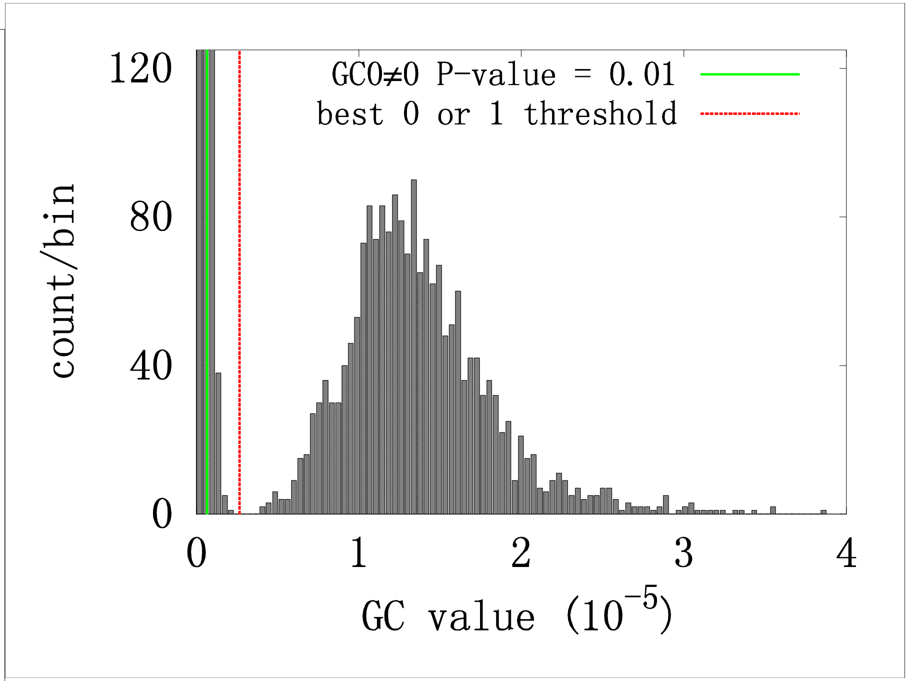
Work for both voltage data and spike train data!

Apply Granger Causality to Integrate-And-Fire Model

100 neuron, 20% sparseness, EPSP=0.5mV



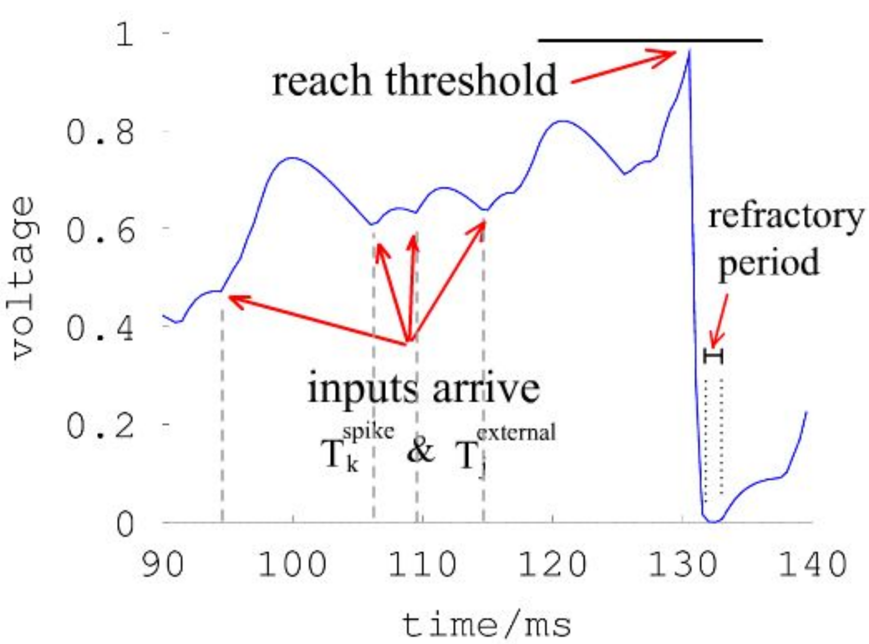
T=10^3 sec, 86% edges correct.

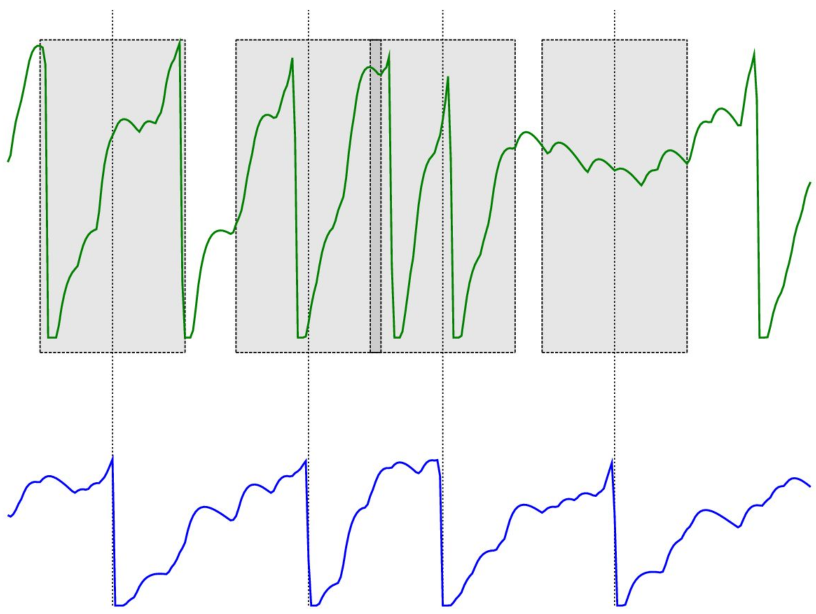


T=10^4 sec, 100% edges correct.

Point of view of Spike-triggered average

- Every pulse cause a voltage jump in postsynaptic neuron
  - Spike-triggered average could be used to capture the jump.

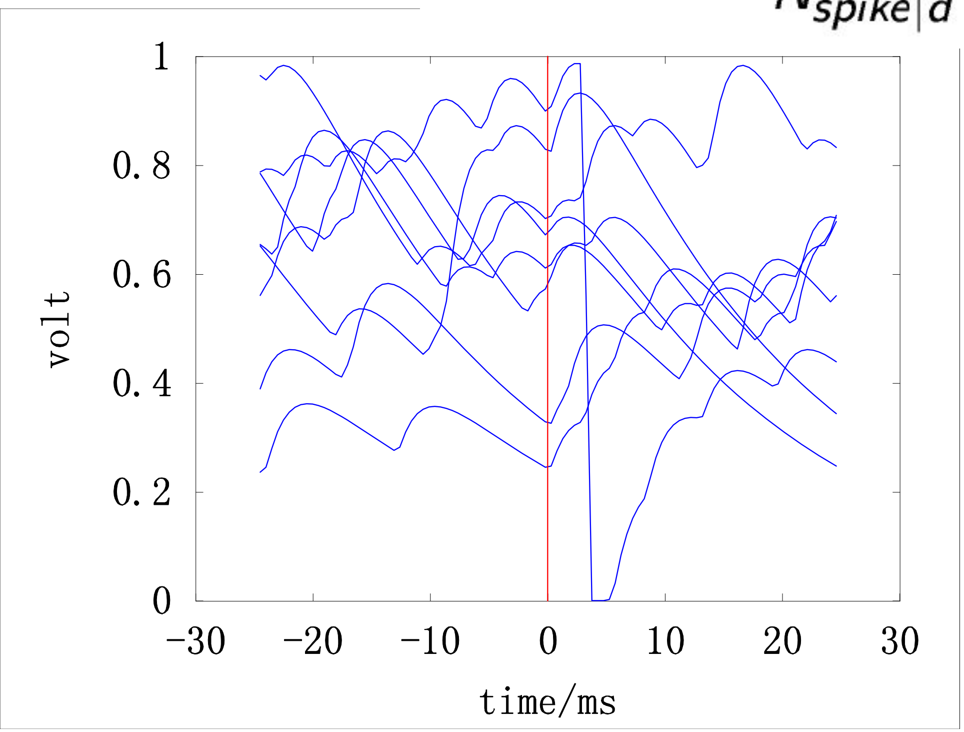


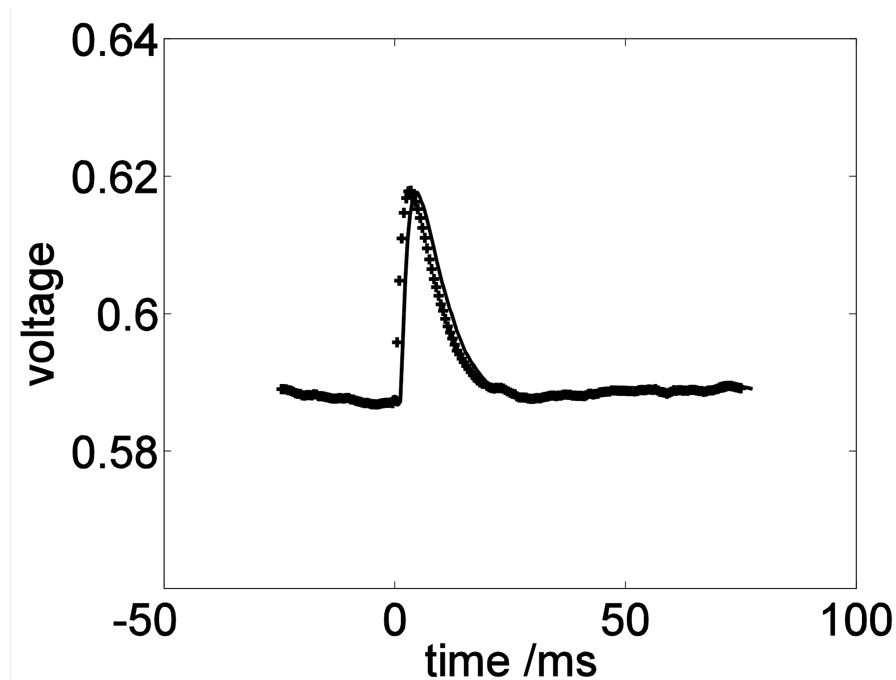


Point of view of Spike-triggered average

- Define spike-triggered value

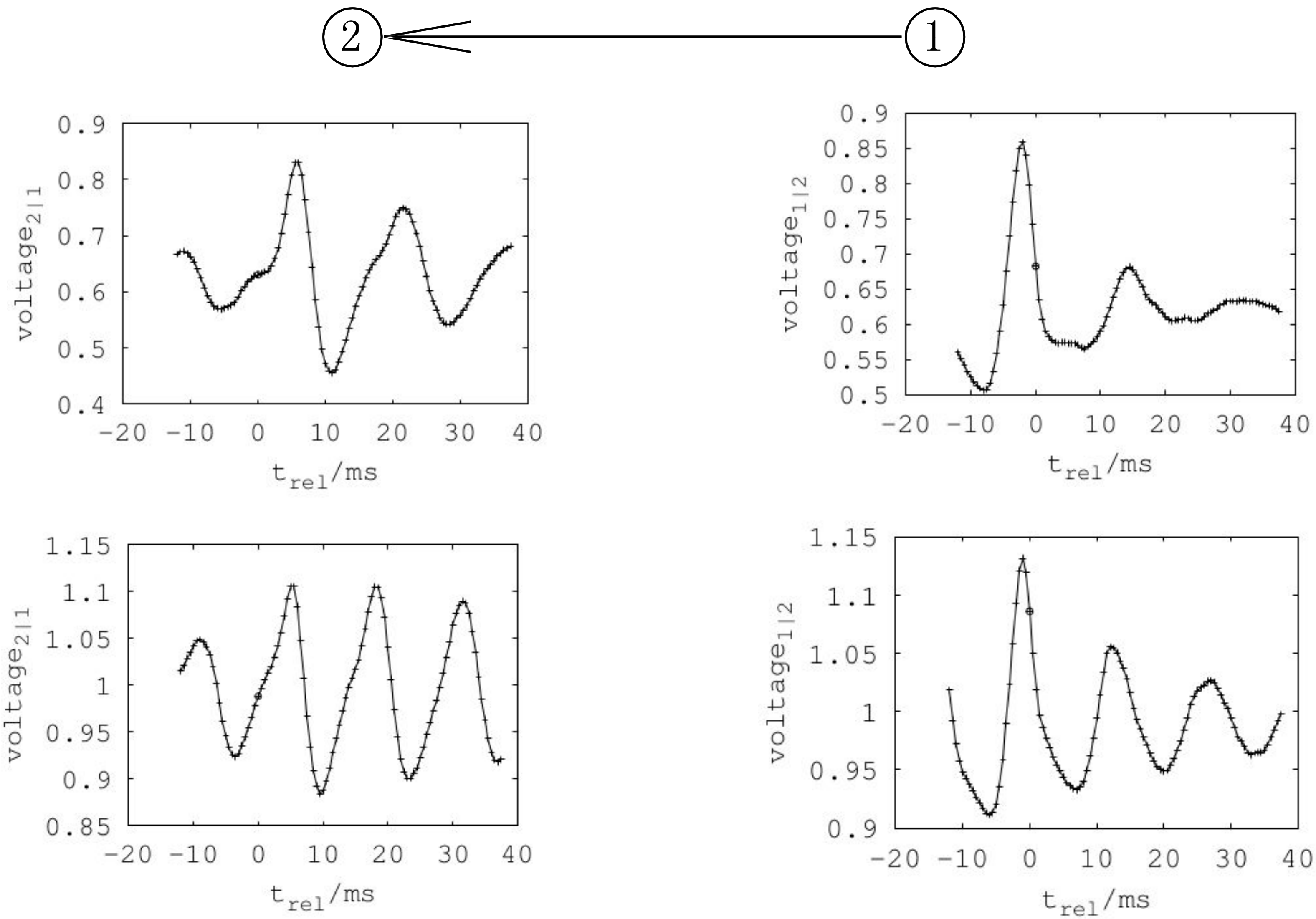
$$V_{p|d}(t_{rel}) \triangleq \frac{1}{N_{spike|d}} \sum_{k=1}^{N_{spike|d}} V_p(T_{k|d} + t_{rel}).$$



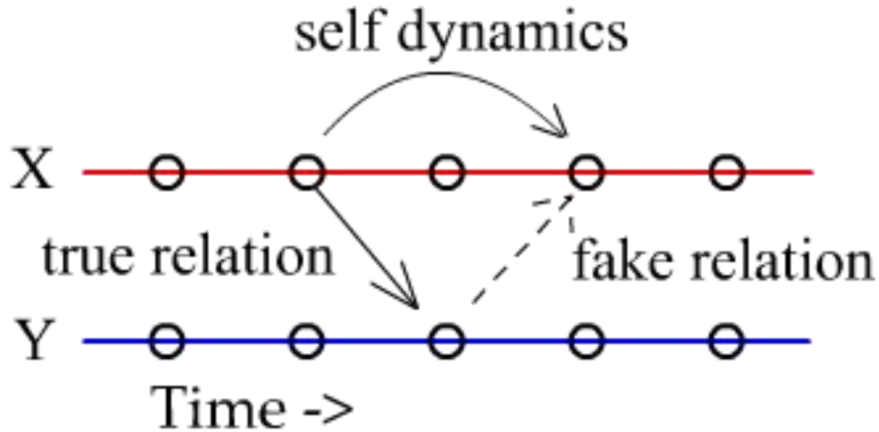


Looks good

Spike-triggered average could failed to reveal causal relationship



Problem of spike-triggered average



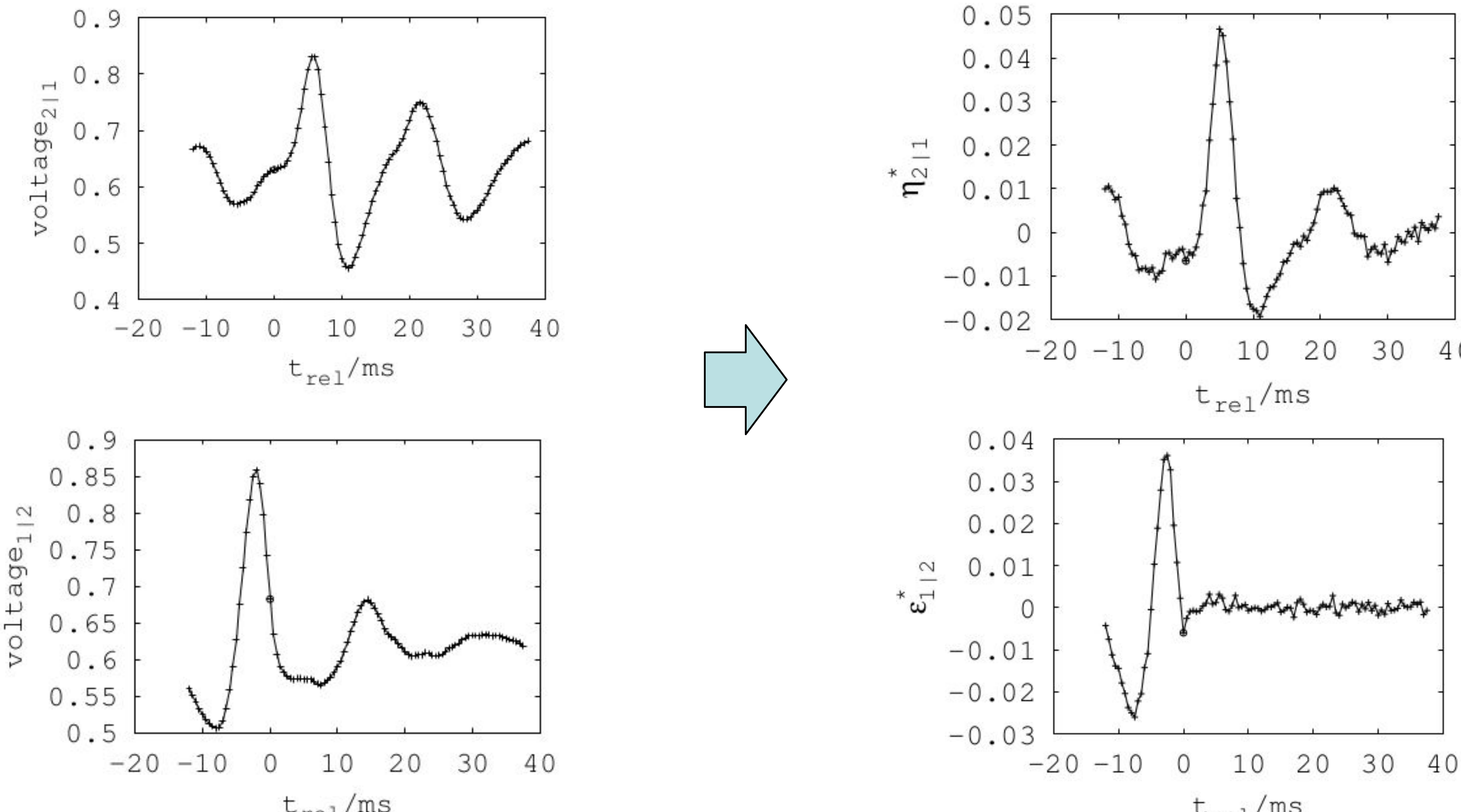
- Solution: eliminate effect of self dynamics
- -> Do autoregression first

$$\begin{cases} x_t = \sum_{j=1}^{\infty} \tilde{a}_j x_{t-j} + \varepsilon_t^* \\ y_t = \sum_{j=1}^{\infty} \tilde{d}_j y_{t-j} + \eta_t^* \end{cases}$$

- Then analyze causal relations between ε_t^* and η_t^*

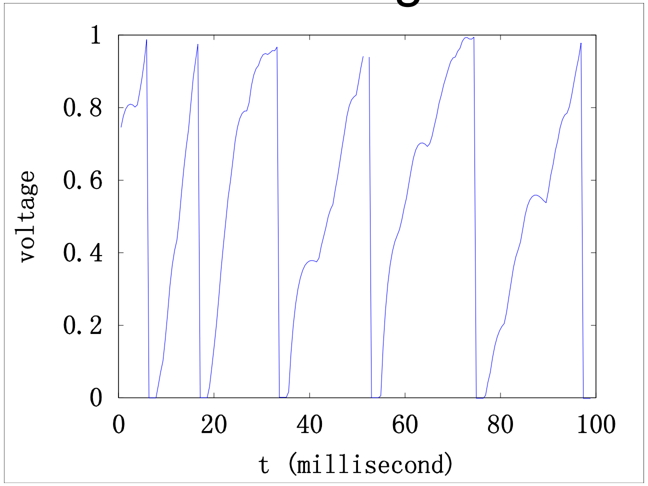
Spike-triggered average of residual

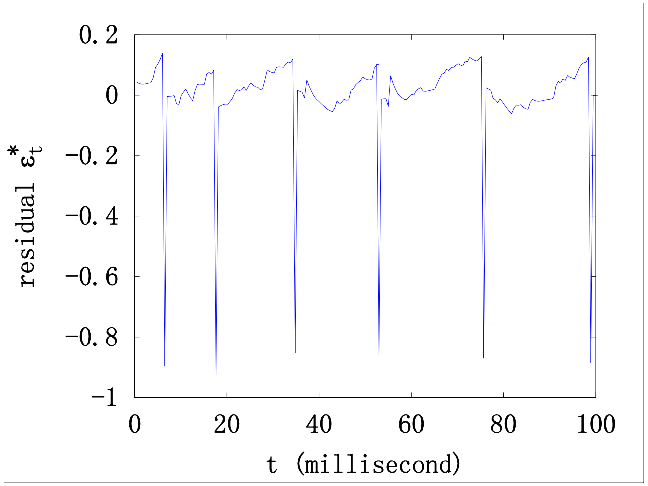
- It's now work!



Relation of Spike-triggered Average and GC

- Observation
  - Residual of voltage likes delta function





- Spike-triggered Value and covariance:

$$\begin{aligned}\eta^*_{p|d}(t_{rel}) &= \frac{1}{N_{spike|d}} \sum_{t=1}^{L} \eta^*_p(t) \cdot S_d(t - t_{rel}) \\ &\approx \frac{L}{N_{spike|d}} \frac{1}{h_d} \mathrm{E}\left(\eta^*_p(t)\epsilon^*_d(t - t_{rel})\right)\end{aligned}$$

Relation of Spike-triggered Average and GC

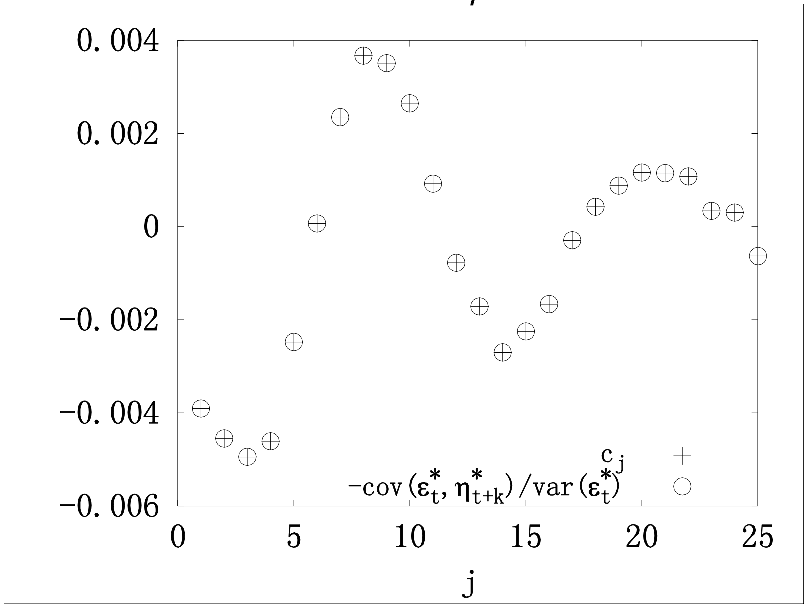
- Property of GC

$$x_t = \sum_{j=1}^{\infty} a_j^* x_{t-j} + \varepsilon_t^*, \quad y_t = \sum_{j=1}^{\infty} d_j^* y_{t-j} + \eta_t^* \quad \Rightarrow \quad \begin{aligned} F_{\varepsilon^* \to \eta^*} &= F_{x \to y} \\ F_{\eta^* \to \varepsilon^*} &= F_{y \to x} \end{aligned}$$

- Asymptotics for c_j small

$$\eta_t^* + \sum_{j=1}^{\infty} \tilde{d}_j \eta_{t-j}^* + \sum_{j=1}^{\infty} \tilde{c}_j \epsilon_{t-j}^* = \eta_t$$

$$\tilde{c}_j \approx -\mathrm{E}(\epsilon_t^* \eta_{t+j}^*)/\mathrm{var}(\epsilon_t^*) \quad \forall j \geq 1$$



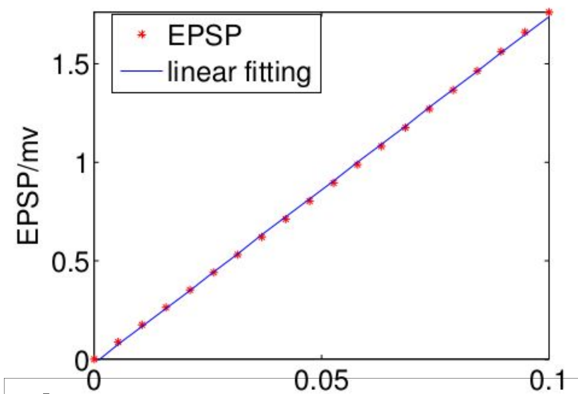
$$F_{x \to y} \approx \frac{\mathrm{var}(\epsilon_t)}{\mathrm{var}(\eta_t)} \sum_{j=1}^{\infty} \tilde{c}_j^2 \approx \frac{(h_d \cdot \Delta t \cdot \nu_x)^2}{\mathrm{var}(\eta_t)\mathrm{var}(\epsilon_t^*)} \sum_{t_{rel}>0} \eta_{y|x}^*(t_{rel})^2$$

Prediction From Above Relation

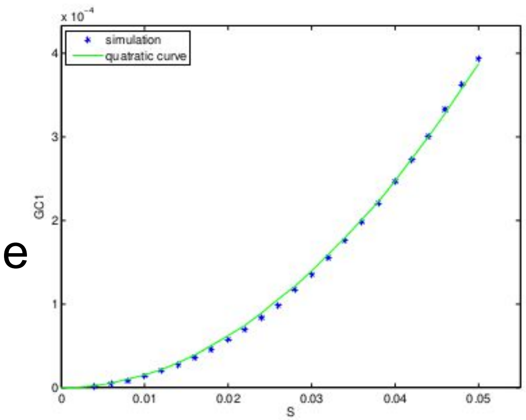
- EPSP proportional to Coupling strength

$$GC \propto (\text{Coupling strength})^2$$

2 neuron,
1 edge



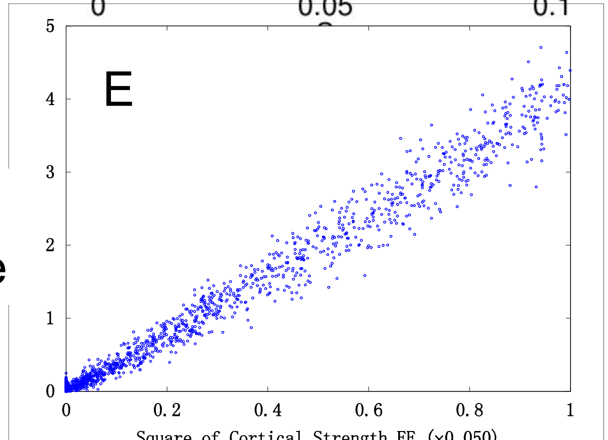
GC
value



S

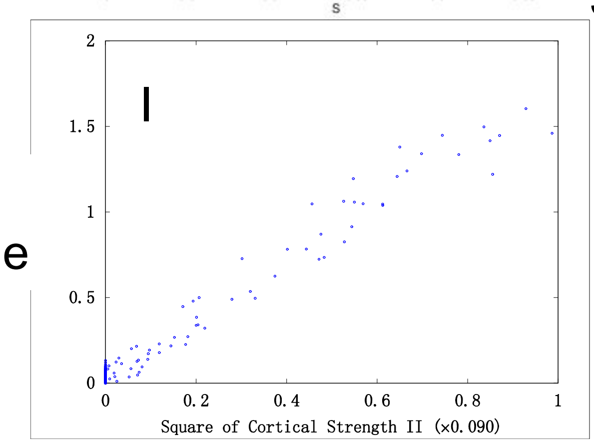
100 Neuron,
9900 edges in
total at most.

GC
value



S^2

GC
value



S^2

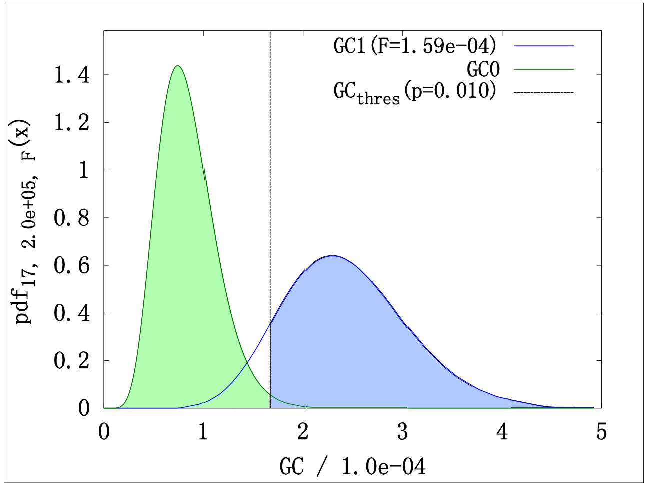
Minimum data length for a good network reconstruction

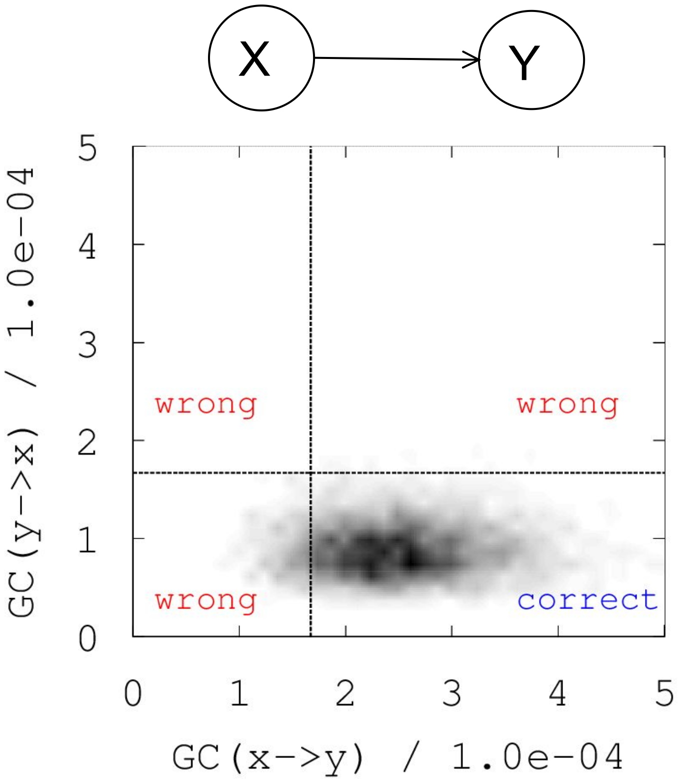
- Define correct probability

$$p_{\text{correct}} = \int_0^{F_{thres}} \rho_{m,L,F0}(F)\,\mathrm{d}F\left(1 - \int_0^{F_{thres}} \rho_{m,L,F1}(F)\,\mathrm{d}F\right),$$

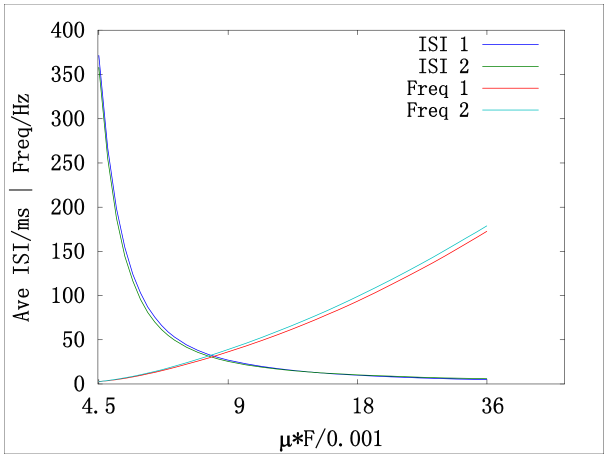
- false positive error rate=0.01, p_{correct}=90%, fitting order m

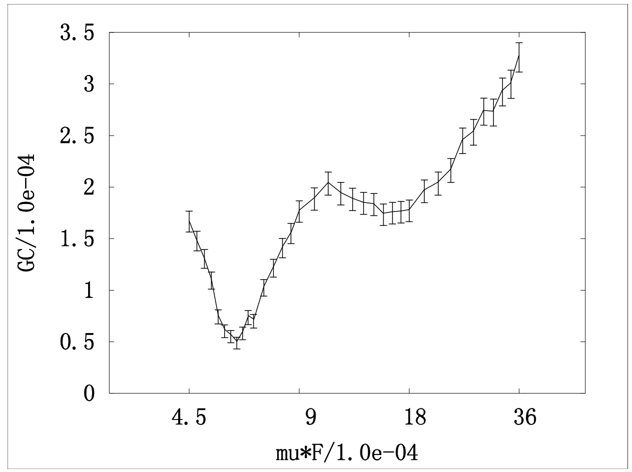
$$T_{\min} \approx \frac{10.00}{F_{\text{true}}}\left(1.153 + \frac{\sqrt{m-0.513}}{1.917}\right)\Delta t$$

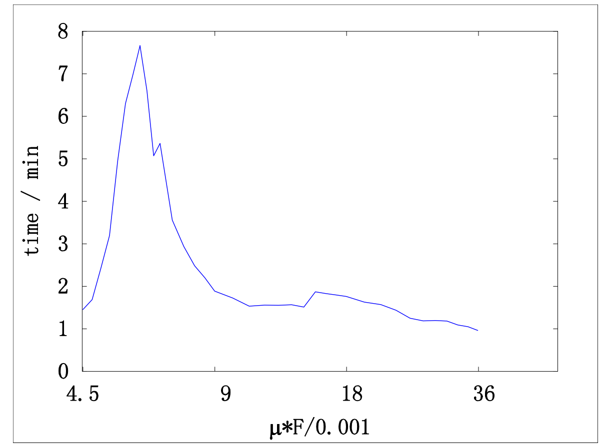


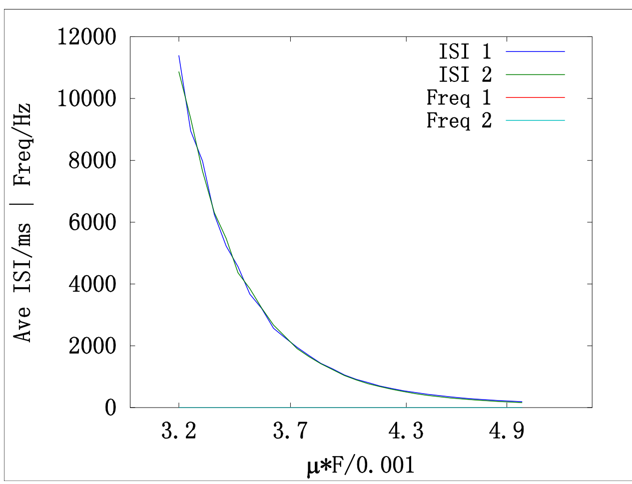


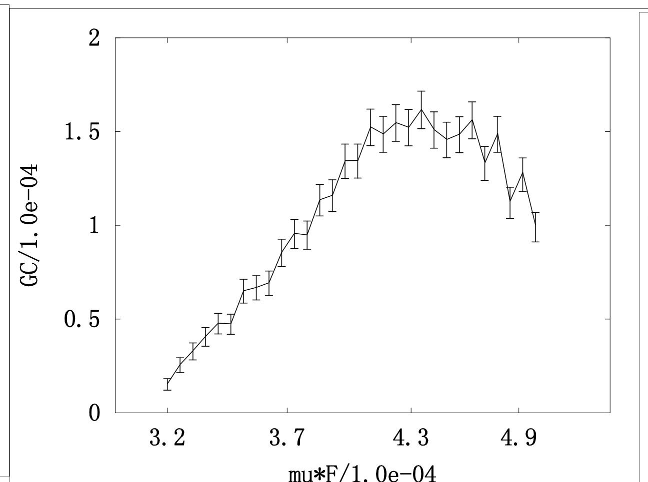
Minimum data length for a good network reconstruction

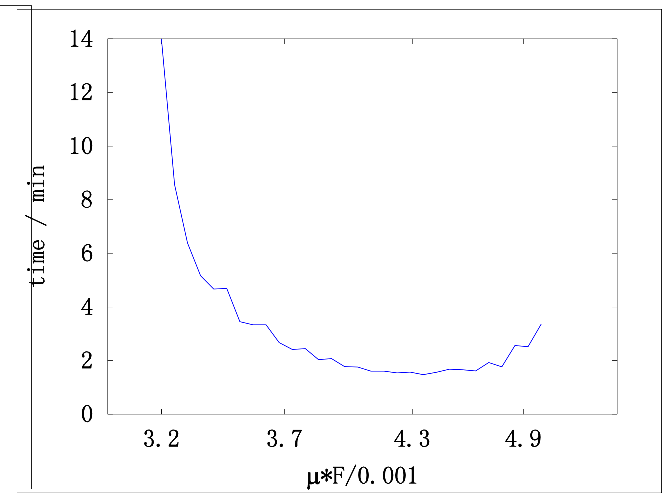












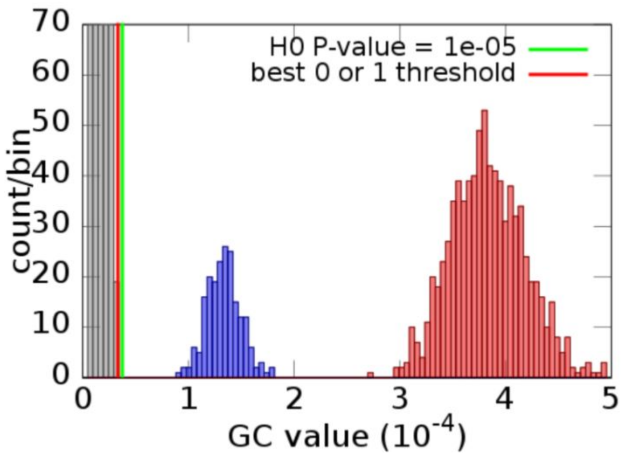
Firing interval v.s. total input strength

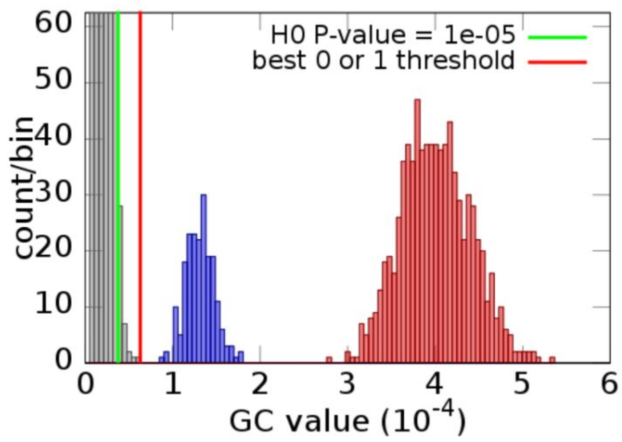
GC v.s. total input strength

Minimum time v.s. total input strength

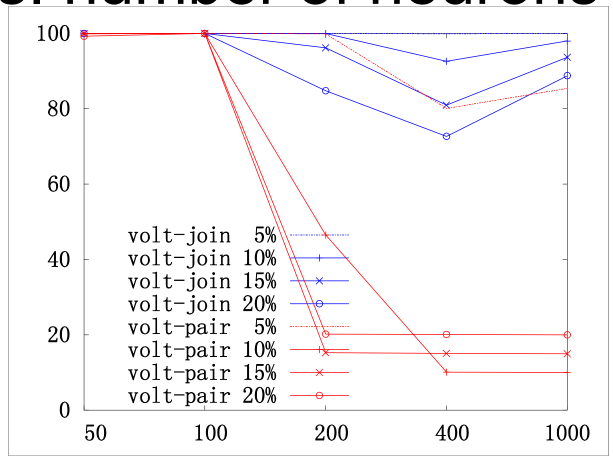
GC of sub network

- Pairwise GC v.s. joint-regression GC
  - 80 Excitatory neuron, 20 Inhibitory neuron



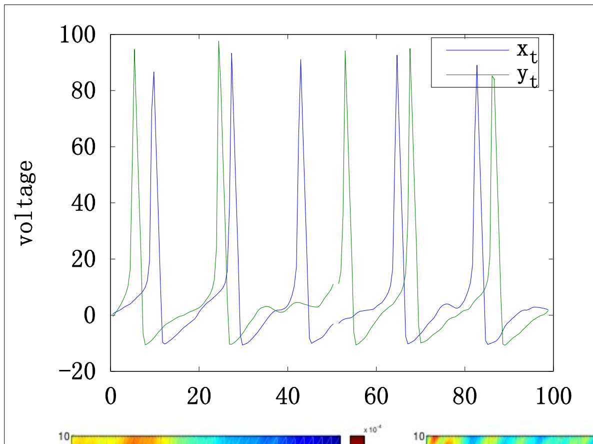


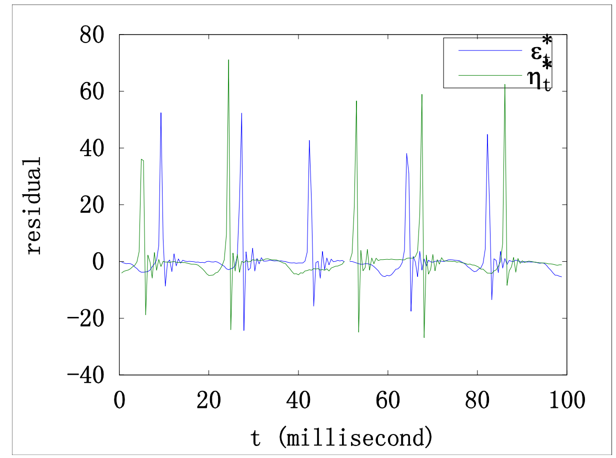
  - Correctness v.s. number of neurons and sparseness



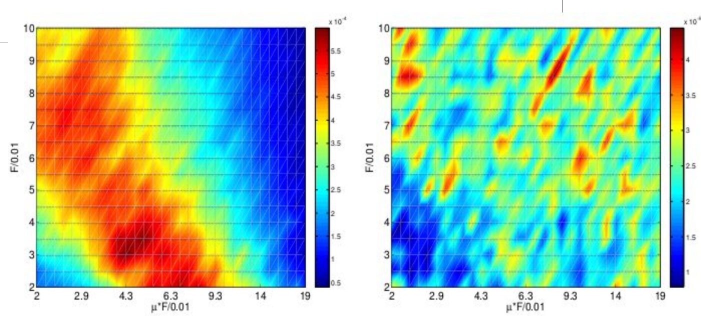
Results of HH

Typical Voltage trace and spike train

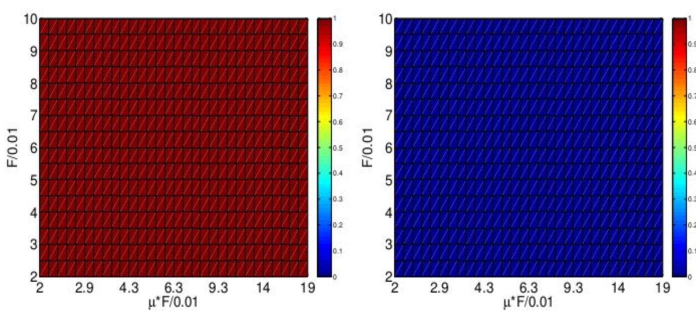


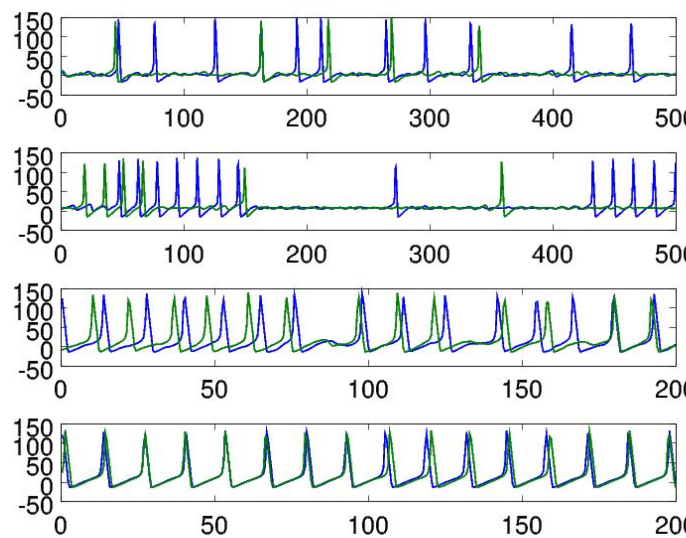


Parameter scan of GC

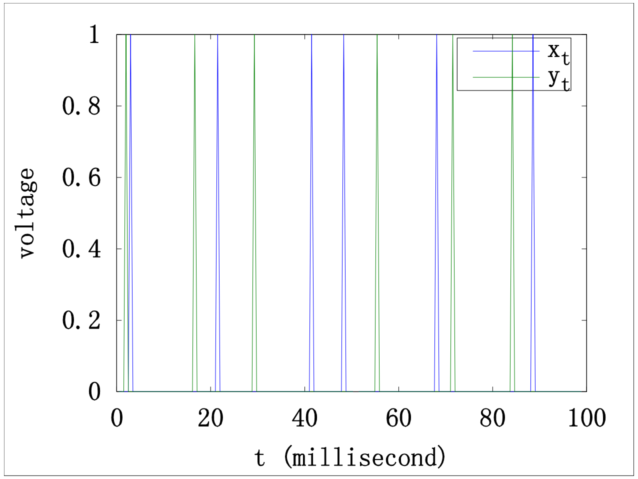


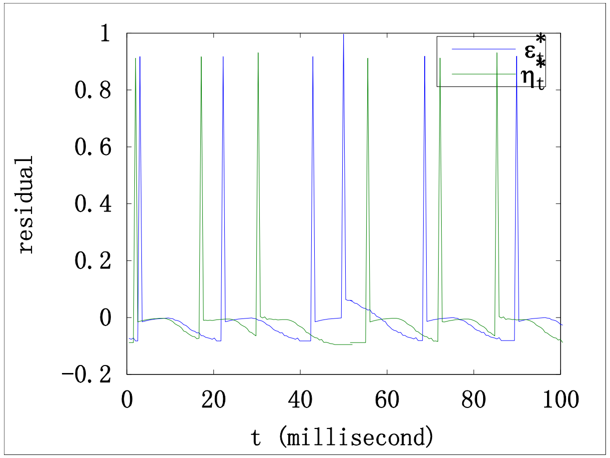
(a) GC"1" (b) GC"0"

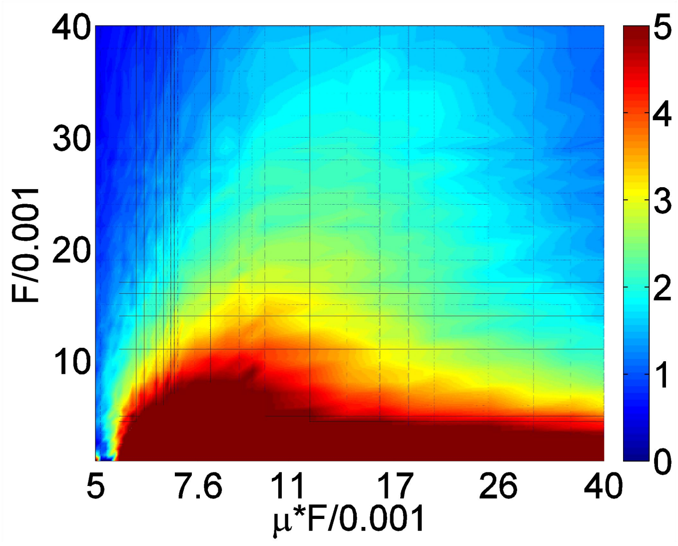


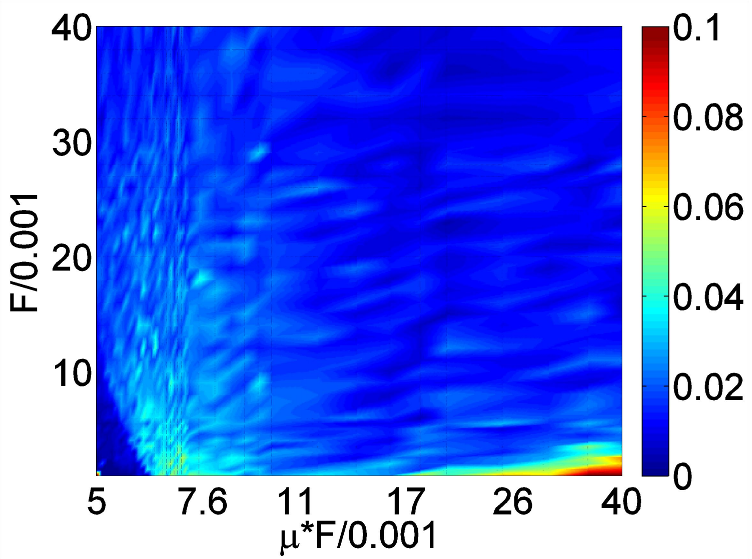


For spike train data









Partial directed coherence and GC

- Luiz A. BaccalaÂ, Koichi Sameshima, Partial directed coherence: a new concept in neural structure determination

$$\begin{bmatrix} x_1(n) \\ \vdots \\ x_N(n) \end{bmatrix} = \sum_{r=1}^{p} \mathbf{A}_r \begin{bmatrix} x_1(n-r) \\ \vdots \\ x_N(n-r) \end{bmatrix} + \begin{bmatrix} w_1(n) \\ \vdots \\ w_N(n) \end{bmatrix}$$

$$\mathbf{A}_r = \begin{bmatrix} a_{11}(r) & a_{12}(r) & \cdots & \cdots & a_{1N}(r) \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & a_{ij}(r) & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ a_{N1}(r) & \cdots & \cdots & \cdots & a_{NN}(r) \end{bmatrix}$$

$$\mathbf{H}(f) = \bar{\mathbf{A}}^{-1}(f) = (\mathbf{I} - \mathbf{A}(f))^{-1}$$

PDC: $\bar{\pi}_{ij}(f) \triangleq \dfrac{\bar{A}_{ij}(f)}{\sqrt{\bar{\mathbf{a}}_j^{\mathrm{H}}(f)\bar{\mathbf{a}}_j(f)}}$

$$GC(i \leftarrow j) \approx \frac{1}{2\pi}\int_{-\pi}^{\pi} \log\left(1 + \left|\bar{\pi}_{ij}(f)\right|^2\right) df$$

GC Limitation

- Common input
- Non-stationary data
  - trend;
  - contain pure periodic component
- Non-linear measurement: $\tilde{x}_t = f(x_t)$
  - Could lead to totally different result.
- Nonlinear system

Summary, Weakness and Further Possible Work

- Granger causality works well in Hodgkin–Huxley model (a highly nonlinear model) and I&F model.
  - That's because GC has eliminated the histroy affection of each time series, and approximate the spike-triggered value which captures information flow between neurons.

- Weakness:
  - 1. Needs very long data, typically 15 min of data.
  - Various limitations.
  - Not designed for neuron science.