A deep learning approach to infer connectivity and neuronal dynamics from spike trains

Machine Learning and Optimization Seminar
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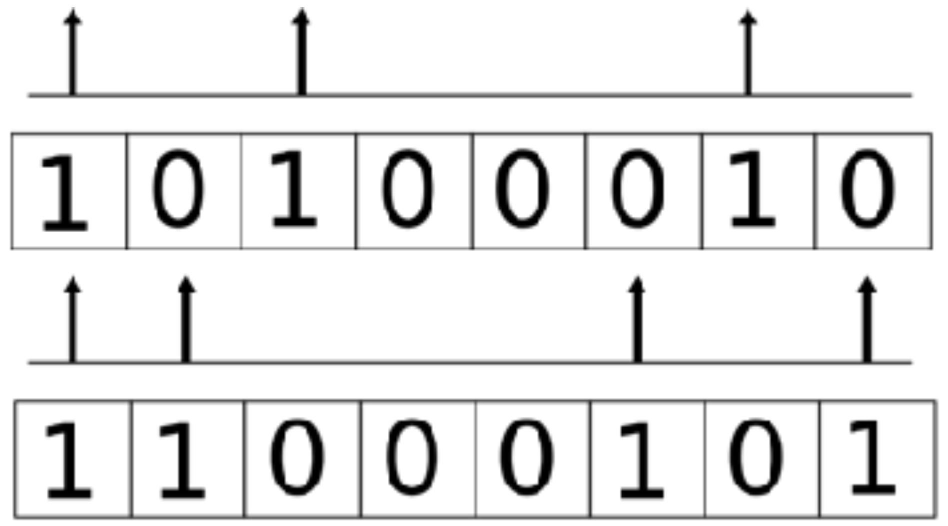
Spike-train cross-correlation function (CCF)

$$x(t) = \sum_i \delta\left(t - t_i^f\right)$$

$$y(t) = \sum_j \delta\left(t - t_j^f\right)$$



$$\rightarrow \quad c_{xy}(\tau) = \langle x(t)y(t+\tau)\rangle - \langle x(t)\rangle\langle y(t+\tau)\rangle,$$

where $\langle . \rangle$ is an ensemble average.

- How spike-trains are temporarily related;
- Provide information to infer connectivity;

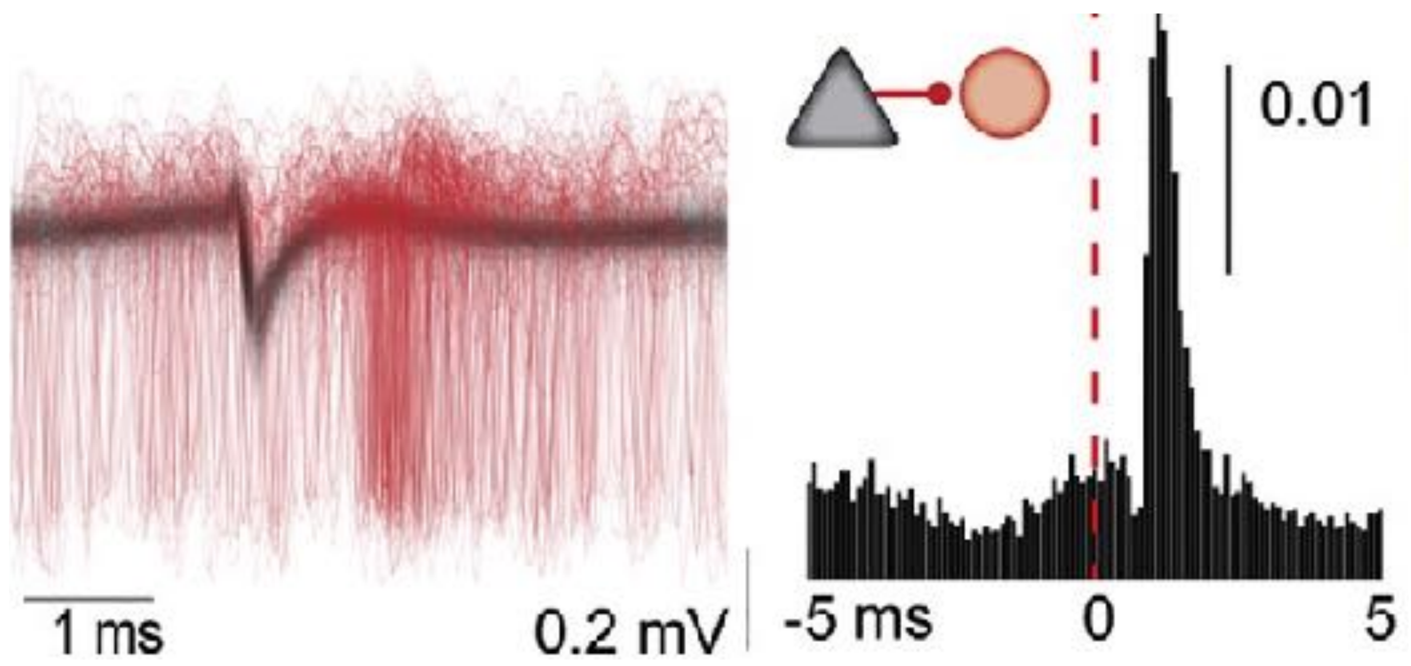
Spike-train cross-correlation functions (CCF) are very informative

- A **sharp peak within a few milliseconds** in the CCF indicates the presence of a connection.

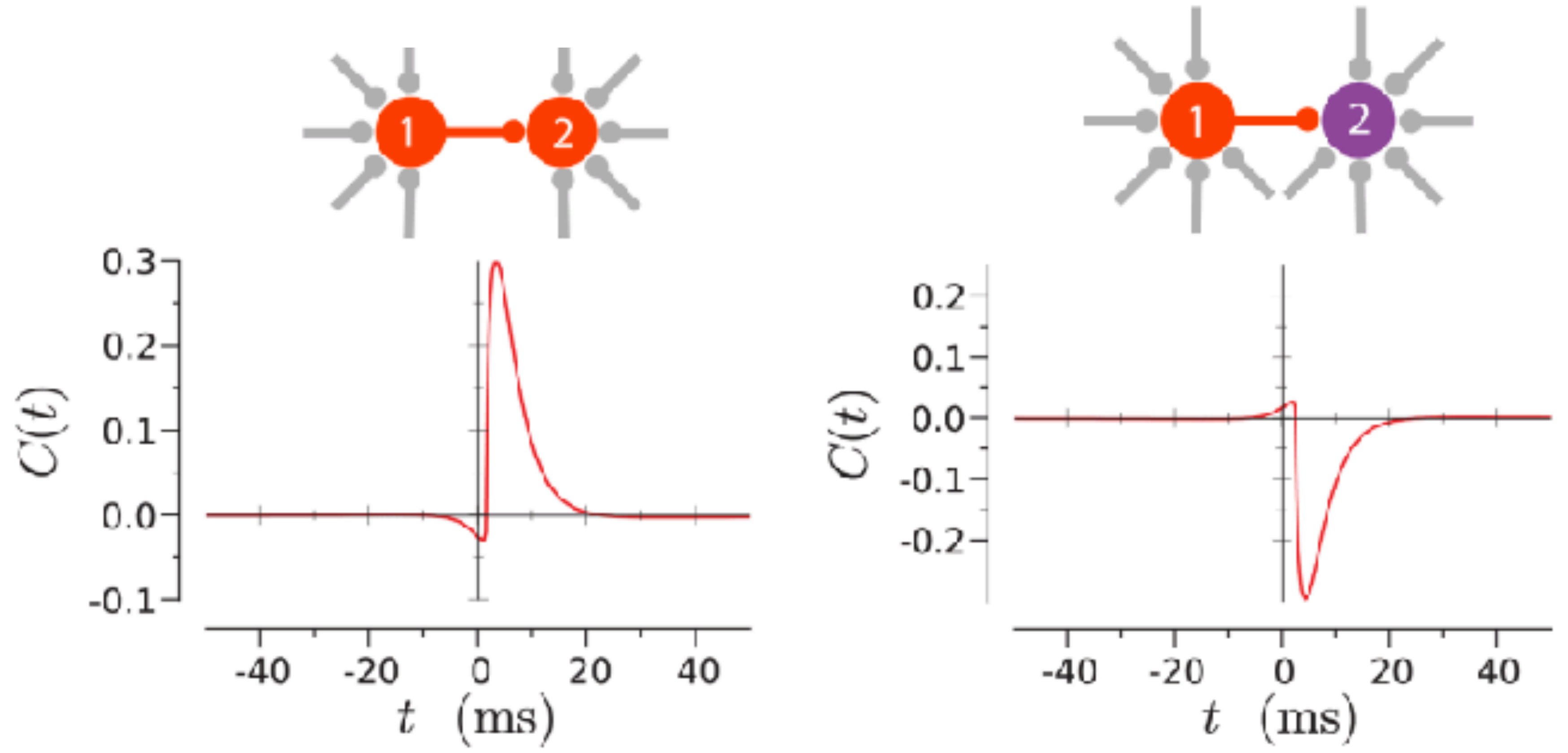
- **Synaptic properties** can be observed in the CCF.

in vivo multi-electrode extracelular recordings dorsal CA1 pyramidal layer

Cross-correlation



English et al., *Neuron* 96: 505–520 (2017)

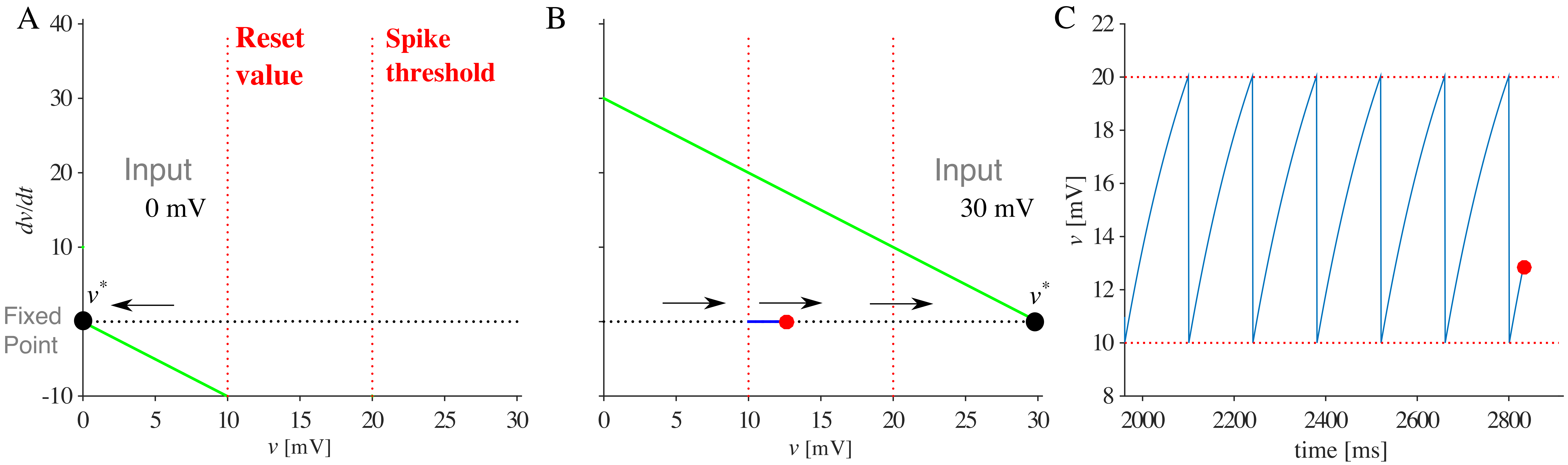


Ostojic et al., *J. Neurosci*. 29: 10234 –10253 (2009)

Neurons have a very rich individual neuronal dynamics.
Can CCF say something about **intrinsic dynamics**?

Dynamical systems

$$\tau_{\mathrm{m}} \dot{v} = f(v) + \text{input} + \text{update rule}$$



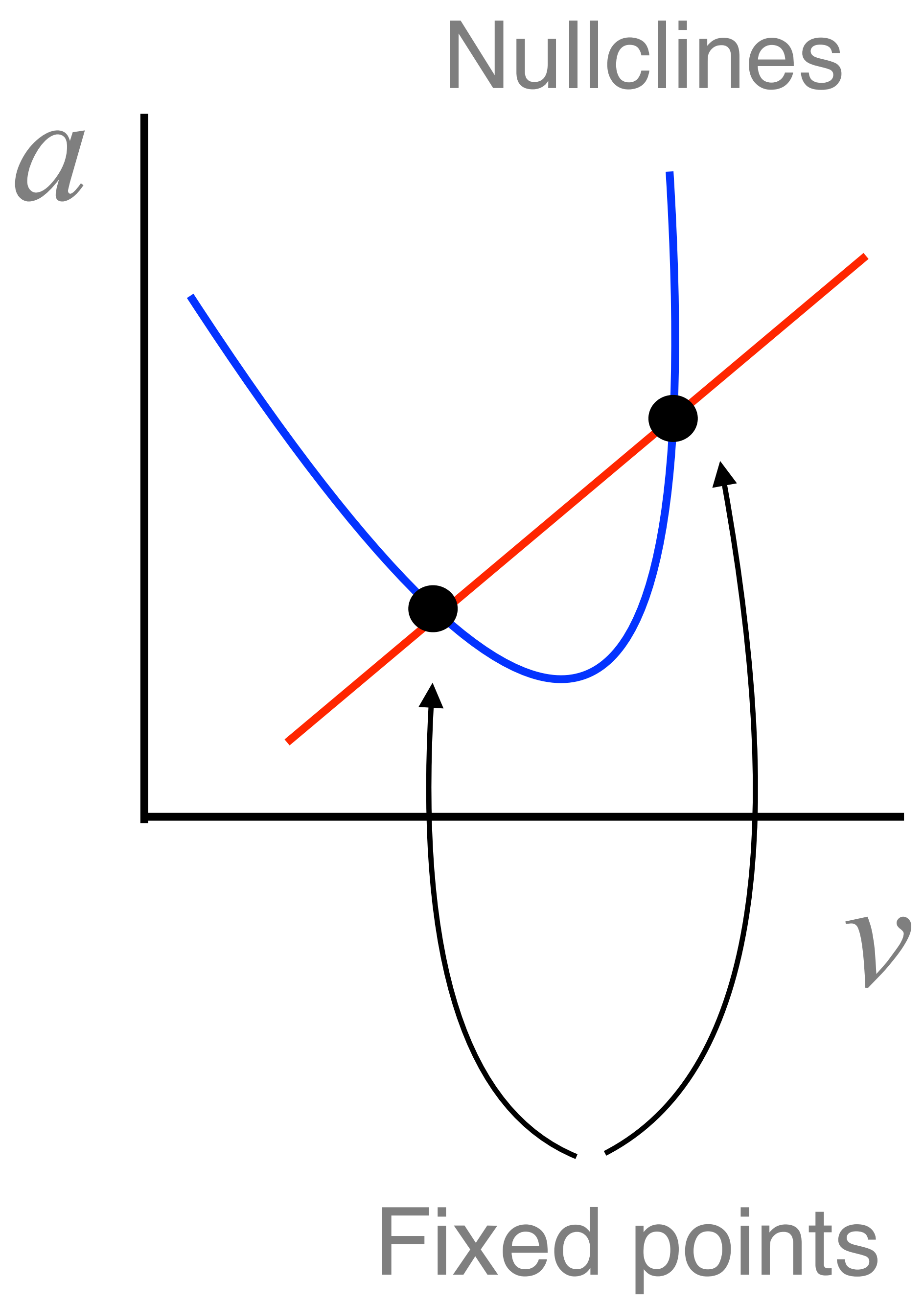
Nullcline!

$$\tau_{\mathrm{m}} \dot{v} = -v + \text{input} + \text{update rule} = 0$$

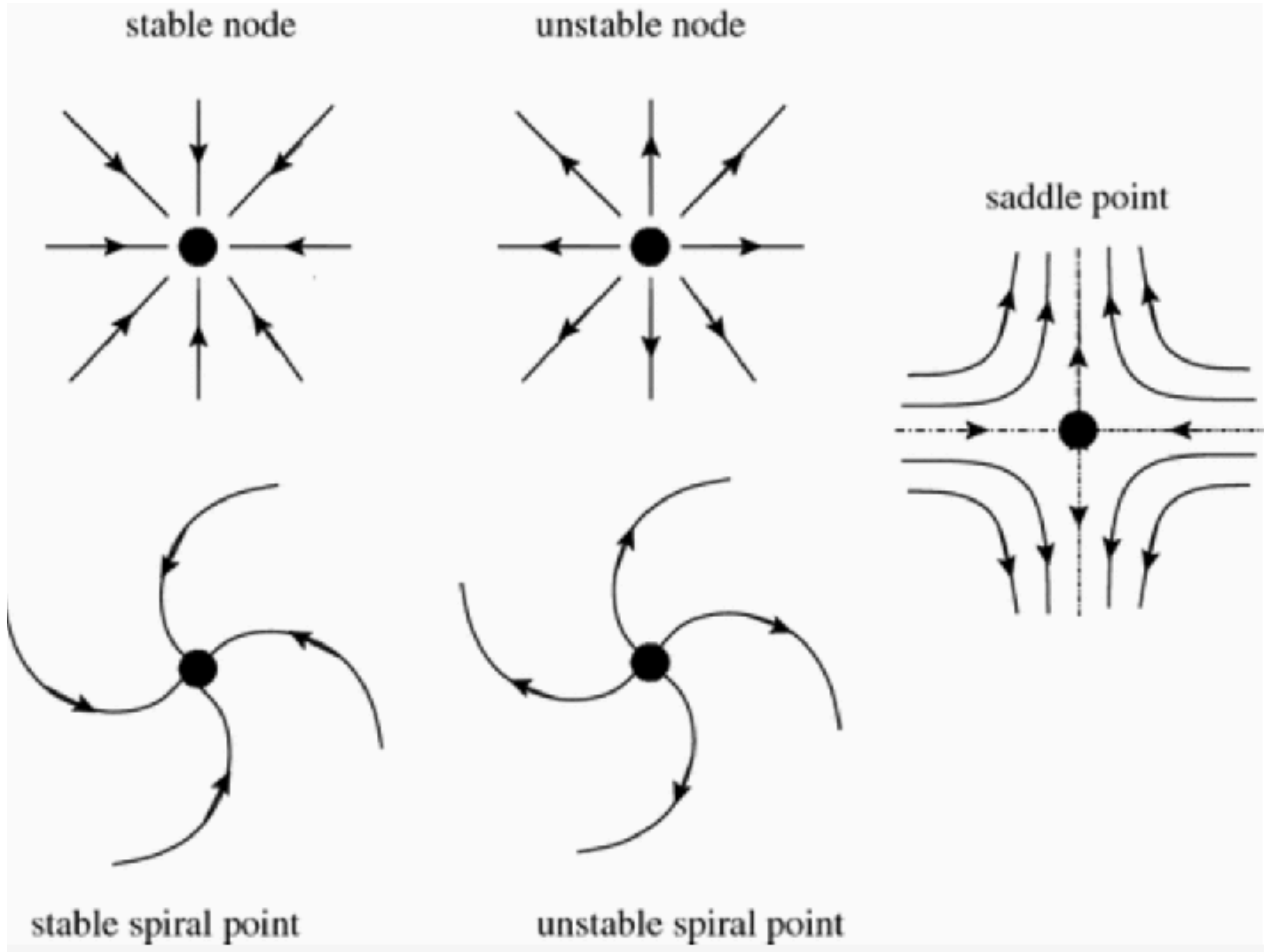
Dynamical systems

$$\tau_v \dot{v} = v^2 - a + RI \quad = 0$$

$$\tau_a \dot{a} = a + v \quad = 0$$



Fixed points can attract or repel trajectories!

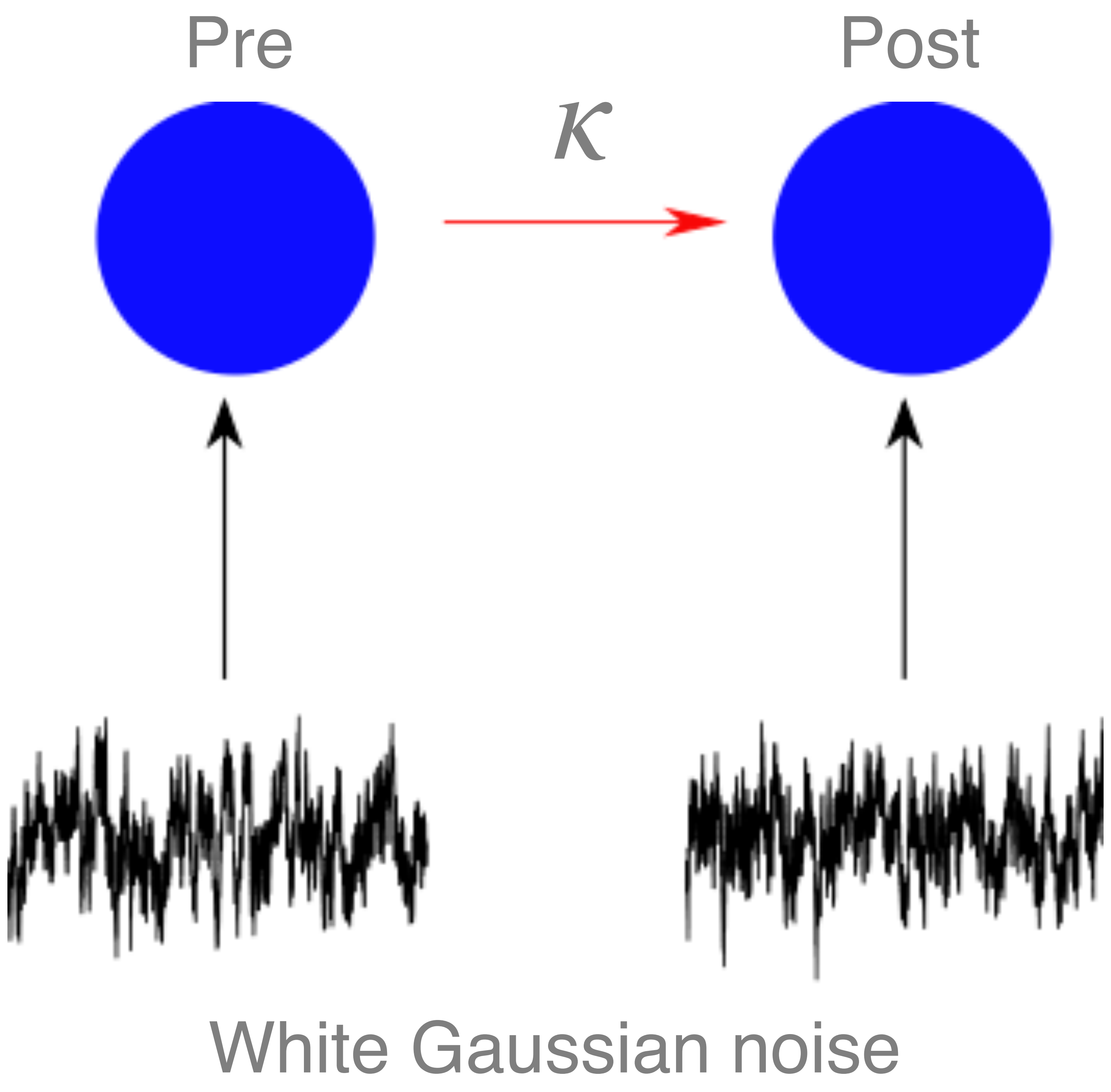


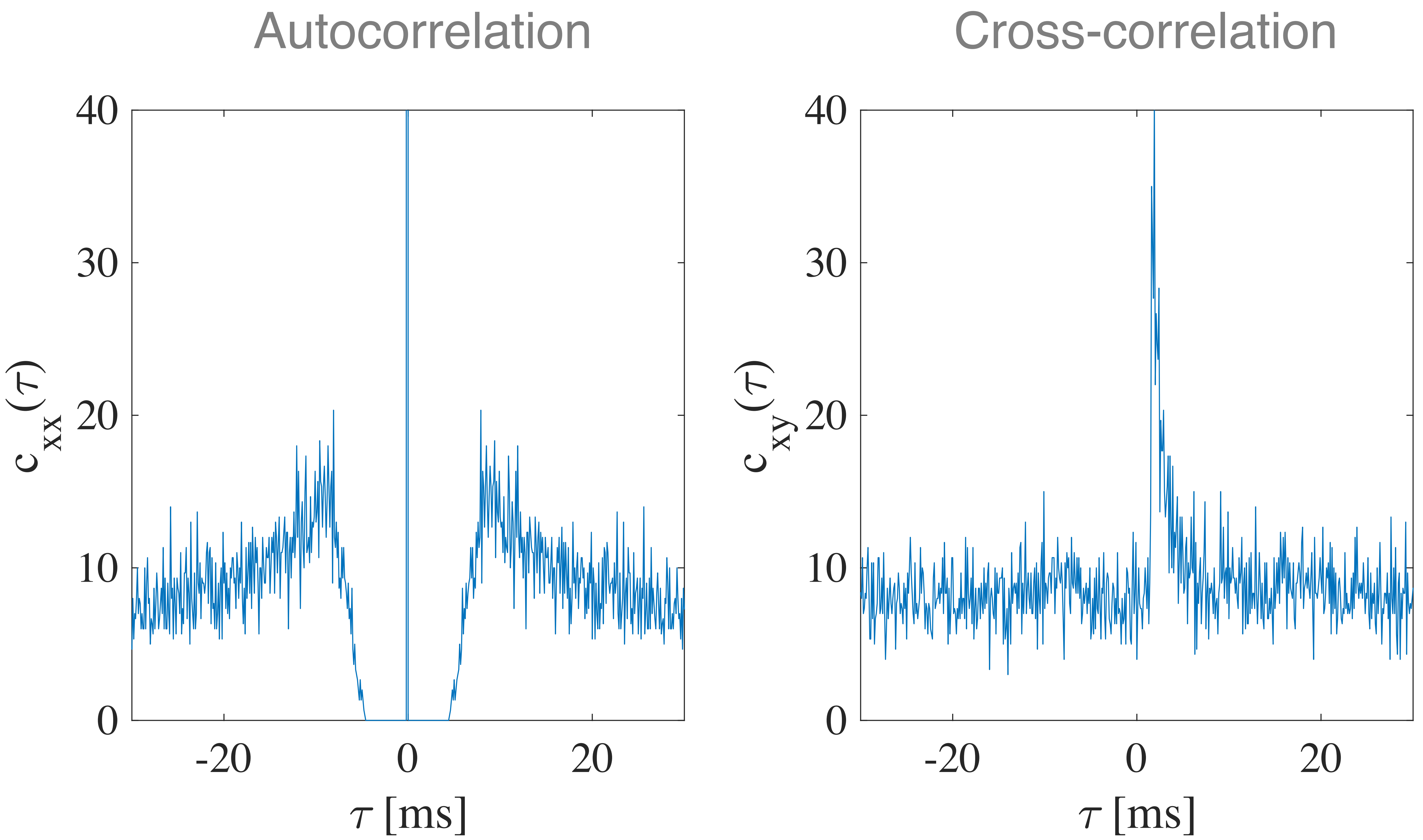
Stauffer D., Stanley H.E., Lesne A. (2017)

Preliminaries

- Two neurons are coupled in an ultra-precise monosynaptic model:

Platkiewicz *et al*. *J Comput Neurosci* **49,** 131–157 (2021)





Are they model dependent?

- We will be working with models where nonlinearities $f(v)$ change:

$$C\dot{v} = f(v) + I$$

How these mechanisms connect to biophysics

Depending on parameters, ionic currents can flexibly create multiple nonlinearities which are reflected on c_{xy}

I_{NaP}+I_{h} model

$$C\frac{dV}{dt} = -I_L - I_h - I_{Nap} + I_{app} + I_{in}(t)$$

$$I_L = G_L\left(V - E_L\right)$$

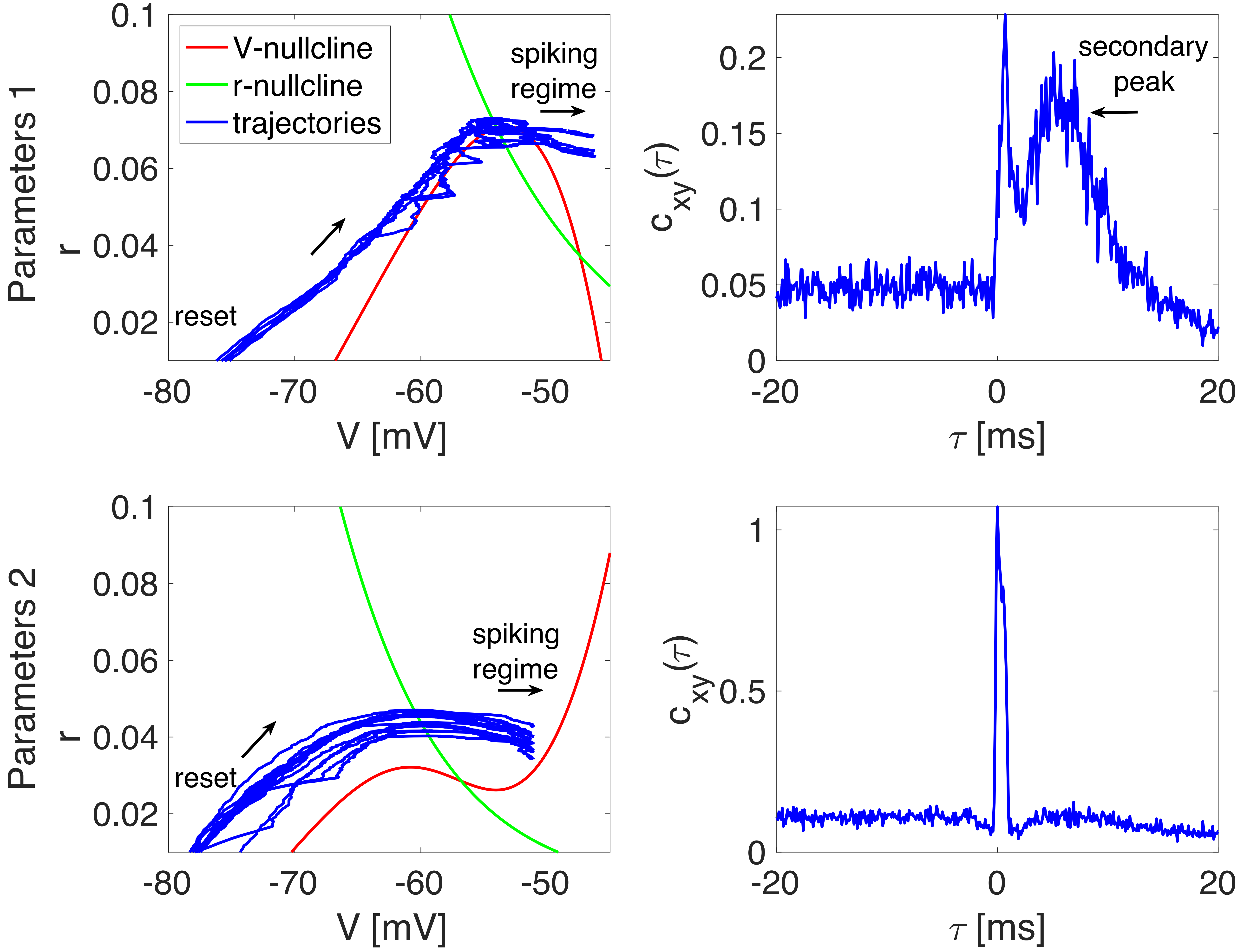
$$I_h = G_h r\left(V - E_h\right)$$

$$I_{Nap} = G_p p_\infty(V)\left(V - E_{Na}\right)$$

$$x\ (= r, p)$$

$$\frac{dx}{dt} = \frac{x_\infty(V) - x}{\tau_x(V)}$$

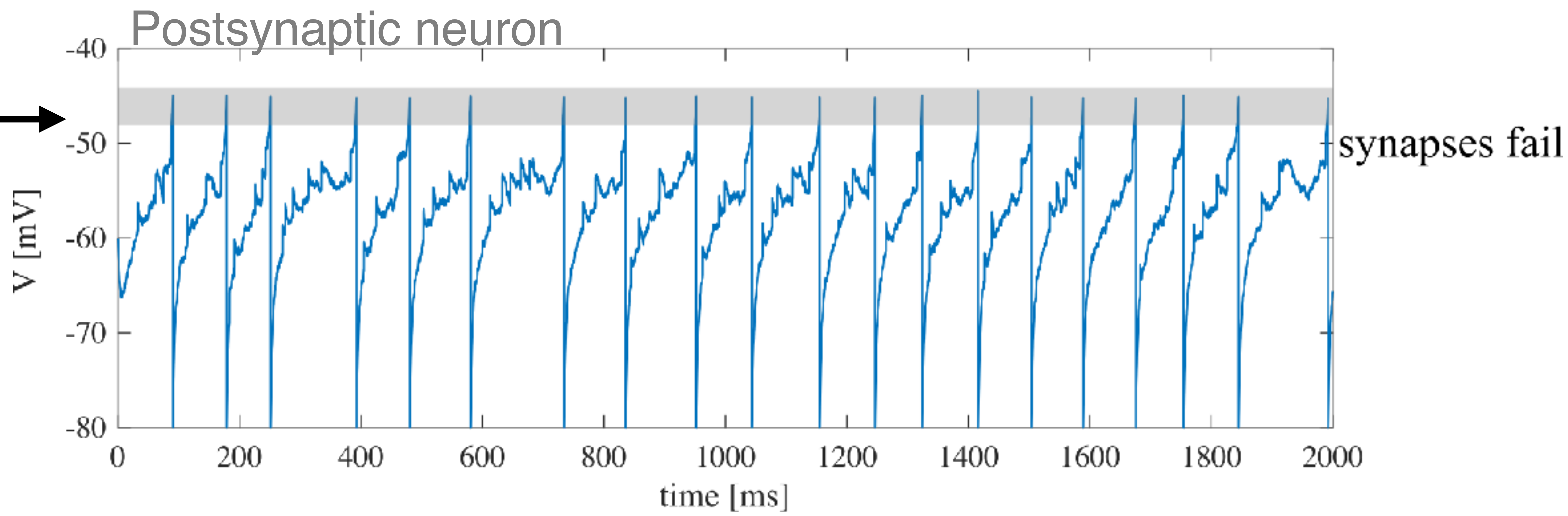
Rotstein H.G., *J. Comput. Neurosci*. 43: 243–271 (2017)



Subthreshold vs. near-action potential voltages

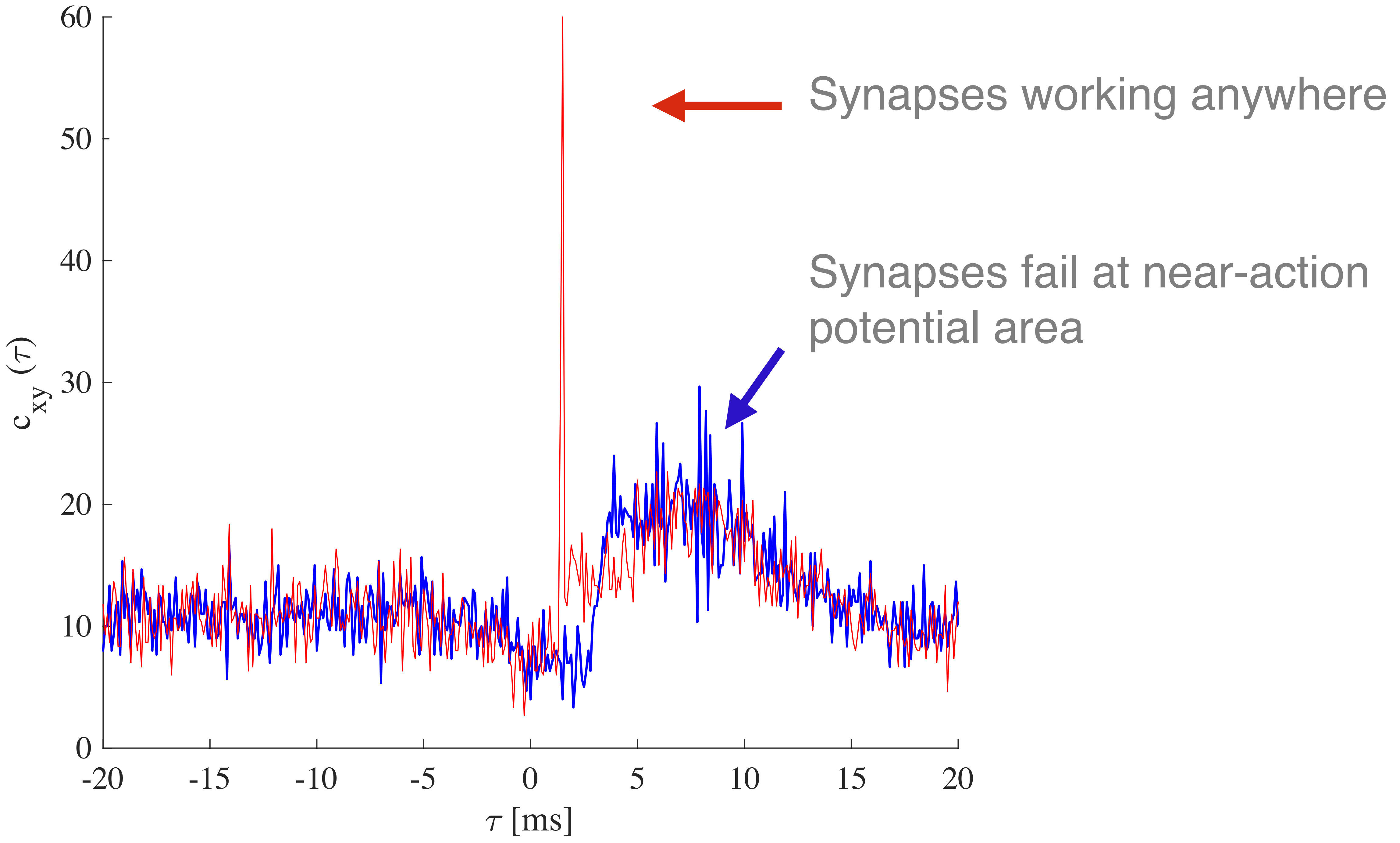
membrane potential at
near-action potential voltages

membrane potential at
subthreshold voltages

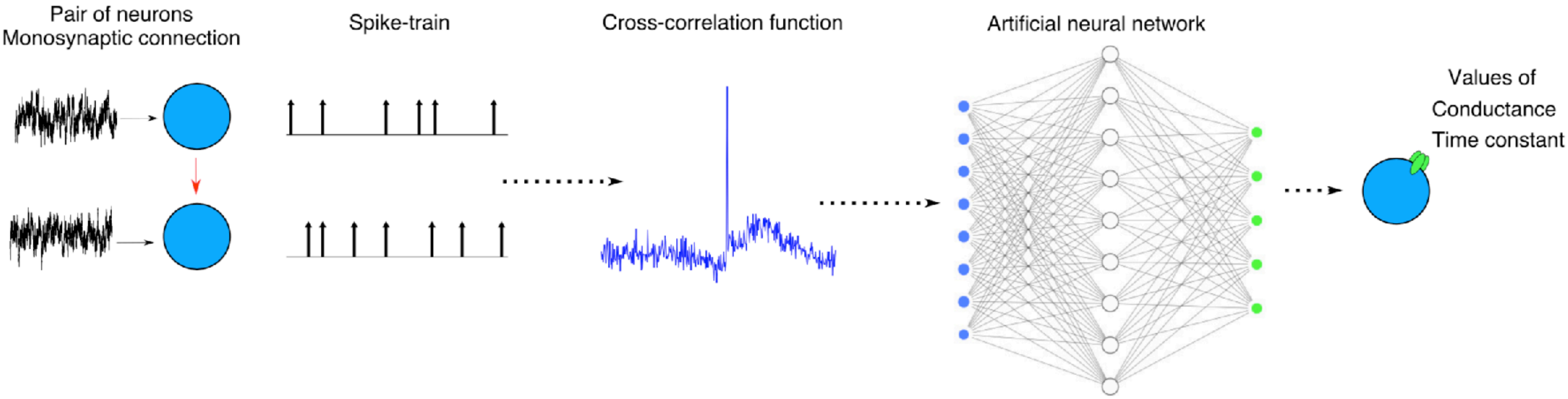


Removing events arriving at
near-action potential voltages:

Only second peak shows up!

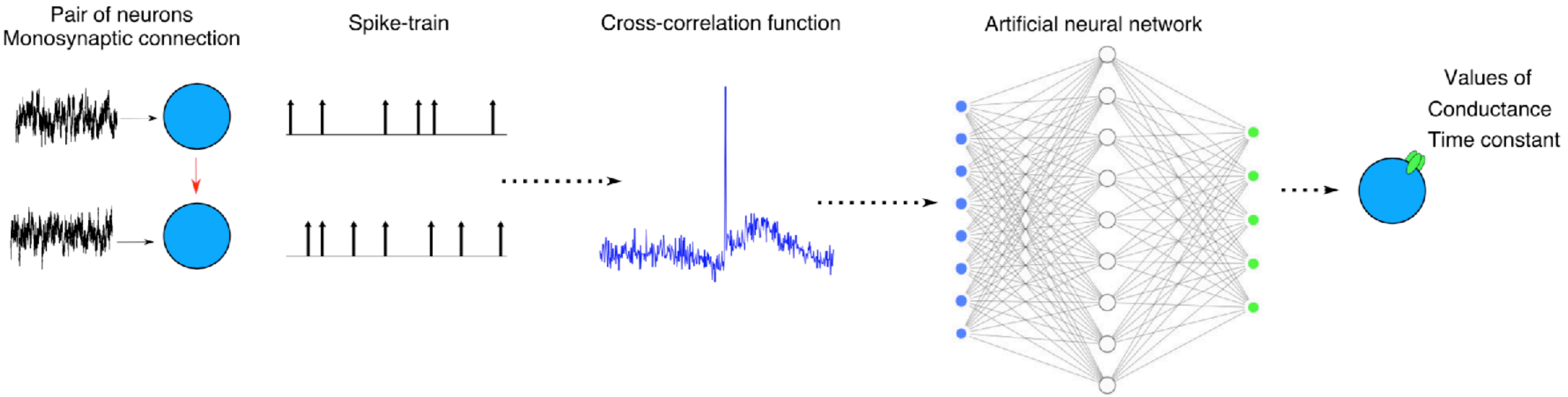


Can we use these signatures?



to what extent can **CCFs** be used to capture **intrinsic neuronal dynamics**?

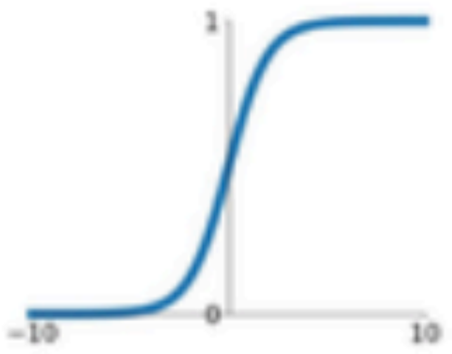
parameters of ionic currents such as **conductance** and **time constant**?



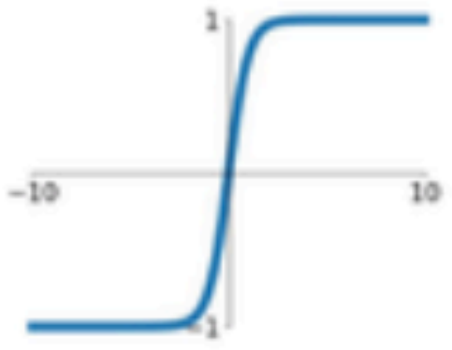
<u>We vary:</u>

- Activation functions

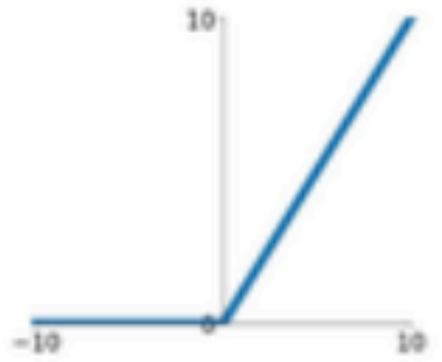
Sigmoid
$\sigma(x) = \frac{1}{1+e^{-x}}$



tanh
$\tanh(x)$



ReLU
$\max(0, x)$



<u>Training procedure:</u>

- Training:validation is 80:20
- Backpropagation algorithm;
- Stochastic gradient descent;
- Cross-entropy loss function;

$$\mathcal{L} = -\frac{1}{m}\sum_{i=1}^{m} y_i \log(\hat{y}_i),$$

<u>We measure:</u>

$$\text{Precision} = \frac{TP}{TP+FP}.$$

$$\text{Recall} = \frac{TP}{TP+FN}.$$

$$\text{F1}-\text{score} = \frac{2 \times (\text{Precision} \times \text{Recall})}{\text{Precision} + \text{Recall}}.$$

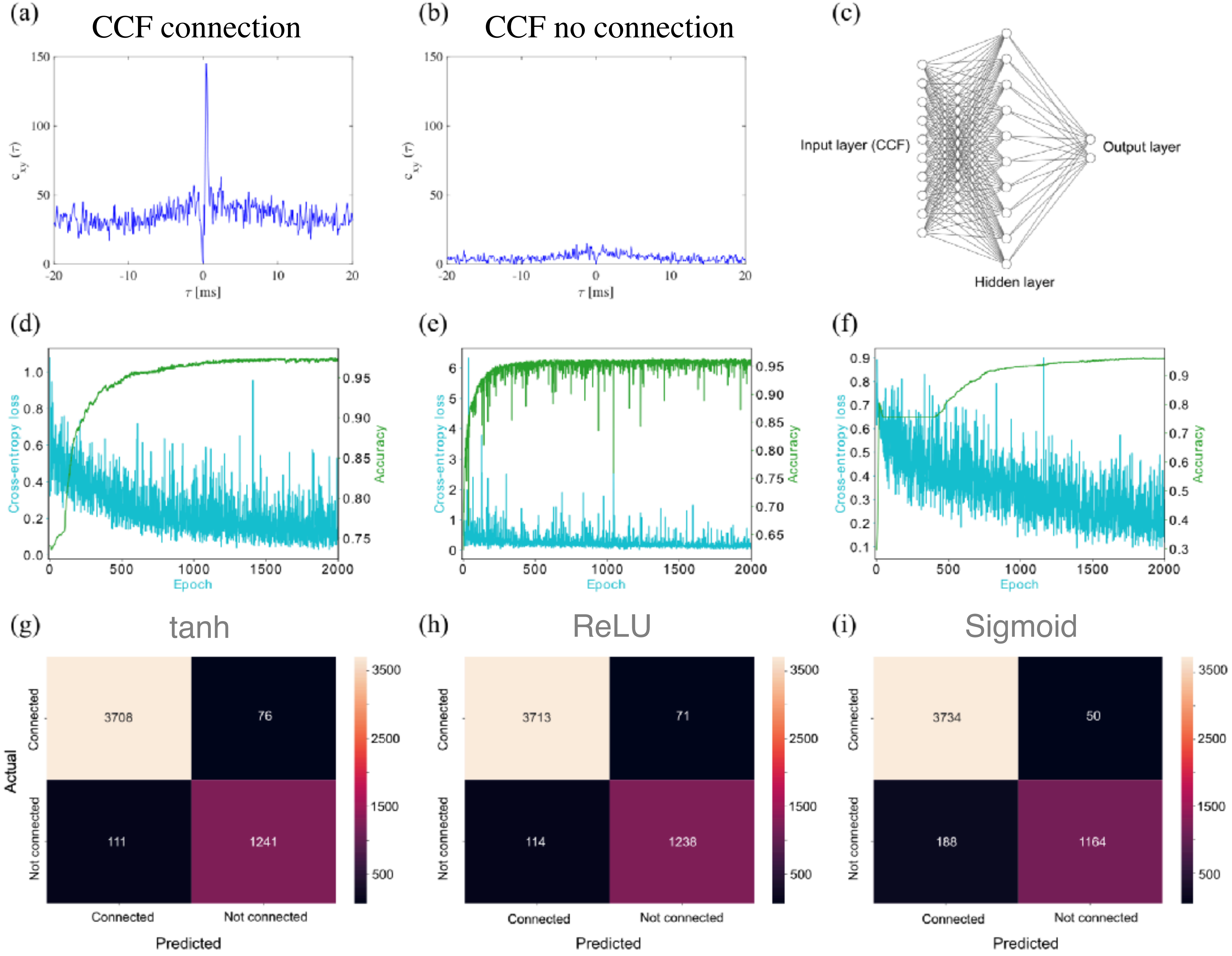
$$MCC = \frac{(TP \times TN - FP \times FN)}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}}.$$

Monosynaptic connections from experimental data

(Sam McKenzie - University of New Mexico)

Training

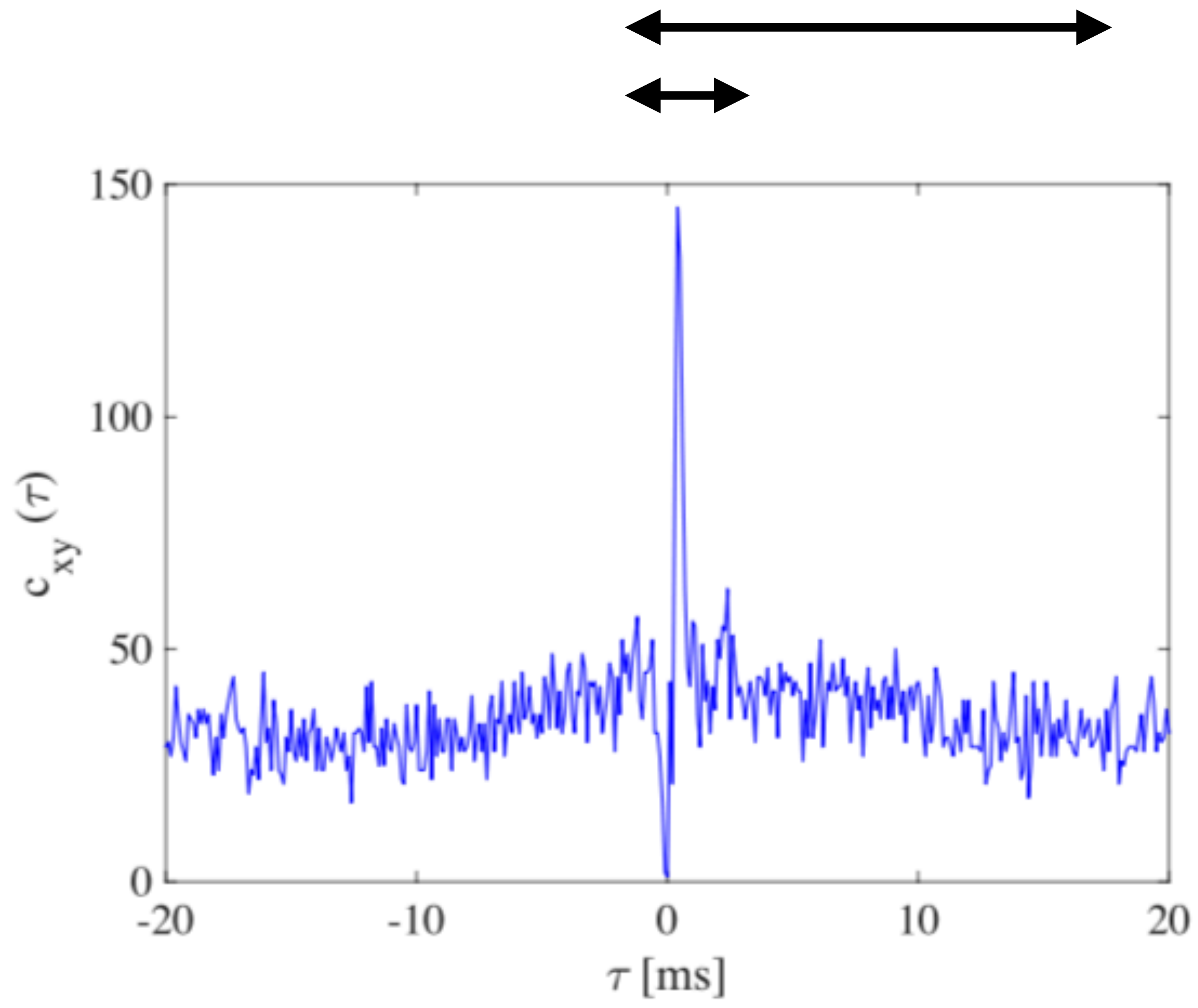
Confusion matrices



high classification accuracy

Activation function	Connection	Precision	Recall	F1-score	MCC
tanh	No	0.97	0.98	0.97	0.903
	Yes	0.94	0.92	0.93	
ReLU	No	0.97	0.99	0.98	0.914
	Yes	0.97	0.91	0.94	
Sigmoid	No	0.95	0.99	0.97	0.88
	Yes	0.96	0.86	0.91	

Using information from longer lags change doesn't change results

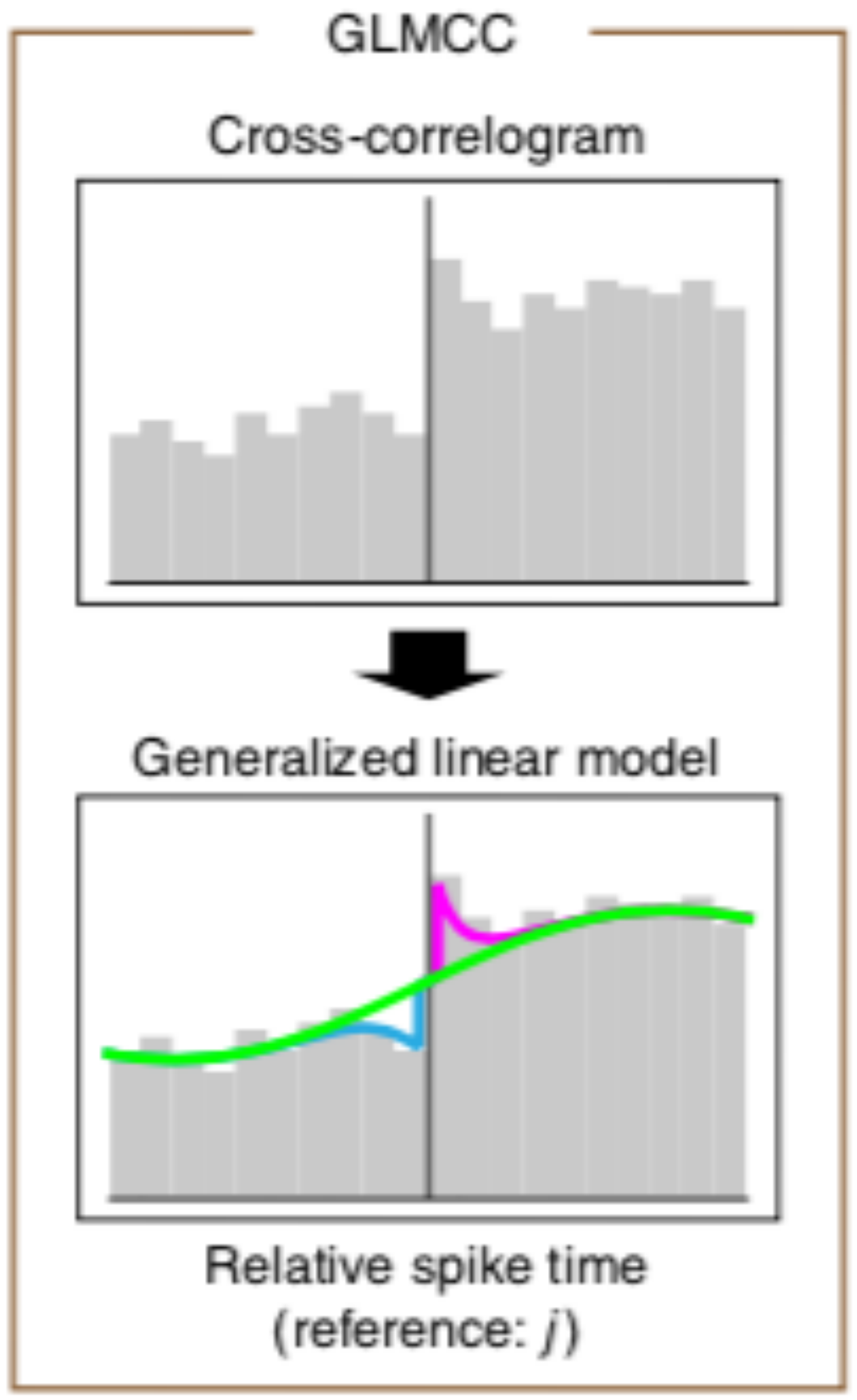


F1-scores and MCCs are slightly lower

Only around 1st peak

Activation function	Connection	Precision	Recall	F1-score	MCC
tanh	No	0.94	0.96	0.95	0.813
	Yes	0.88	0.84	0.86	
ReLU	No	0.99	0.95	0.97	0.881
	Yes	0.87	0.97	0.91	
Sigmoid	No	0.92	0.98	0.95	0.795
	Yes	0.92	0.77	0.84	

This is how it has been done



Kobayashi et al., *Nat Commun.*, 10:4468 (2019)

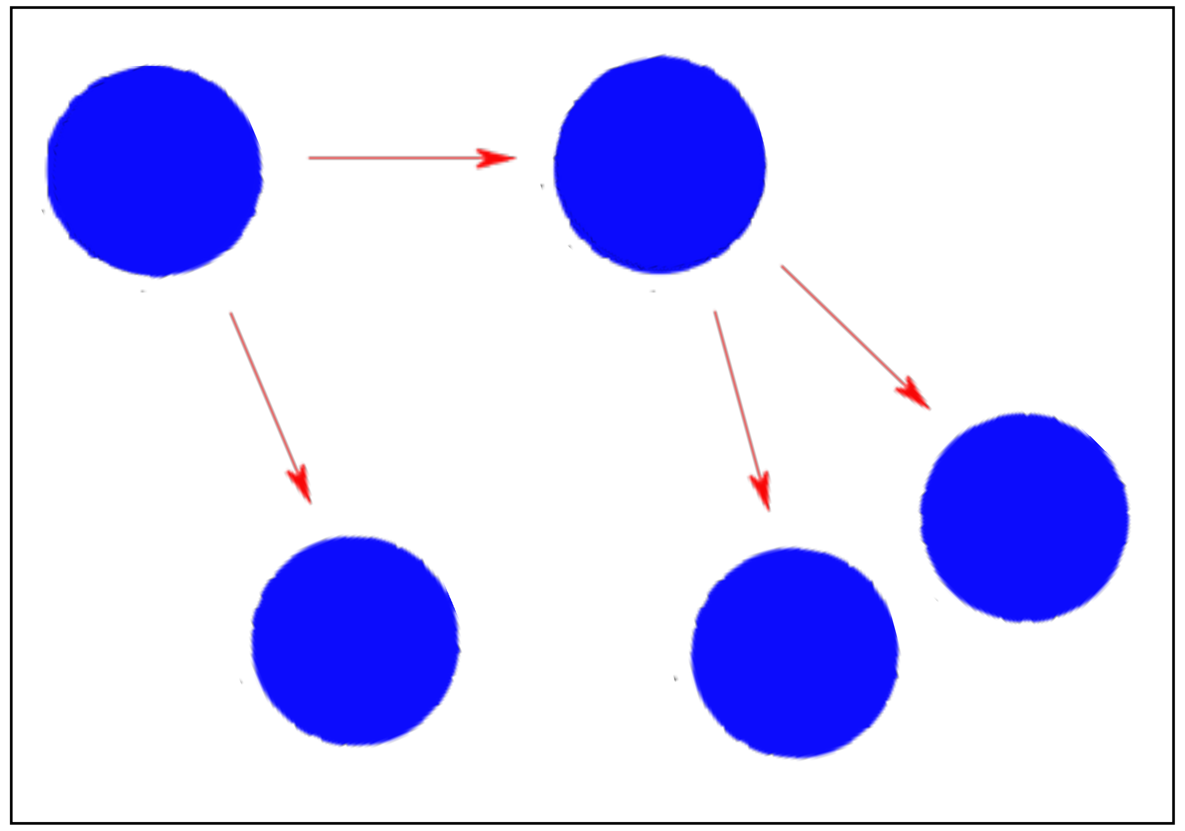
Or others that rely on a single lag…

Artificial neural networks: what about time constants and conductance values?

Generation of synthetic data

- Database with 25,000 CCFs

Random arrangements of a 5x5 network (always monosynapses)



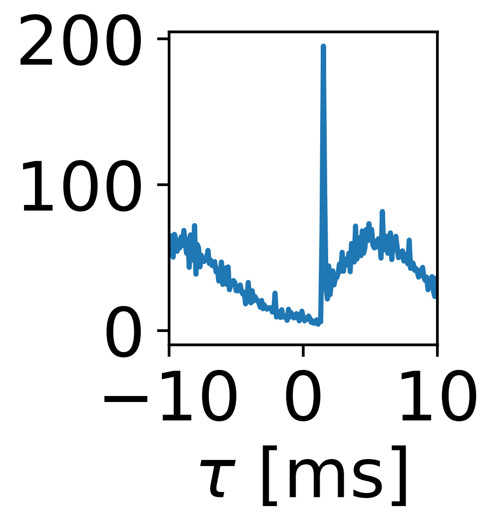
- Each CCF 100 trials per network

G_h in the range [1.5,5.5]

τ_h in the range [40,200]

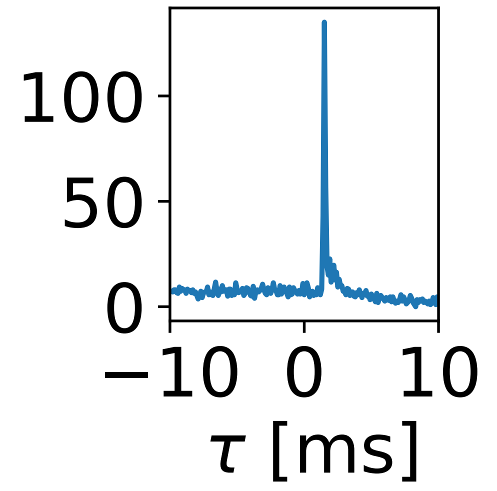
- Labelling process:

Connection where Ih with Gh = 1.5



: 1

Connection where Ih with Gh = 3.5

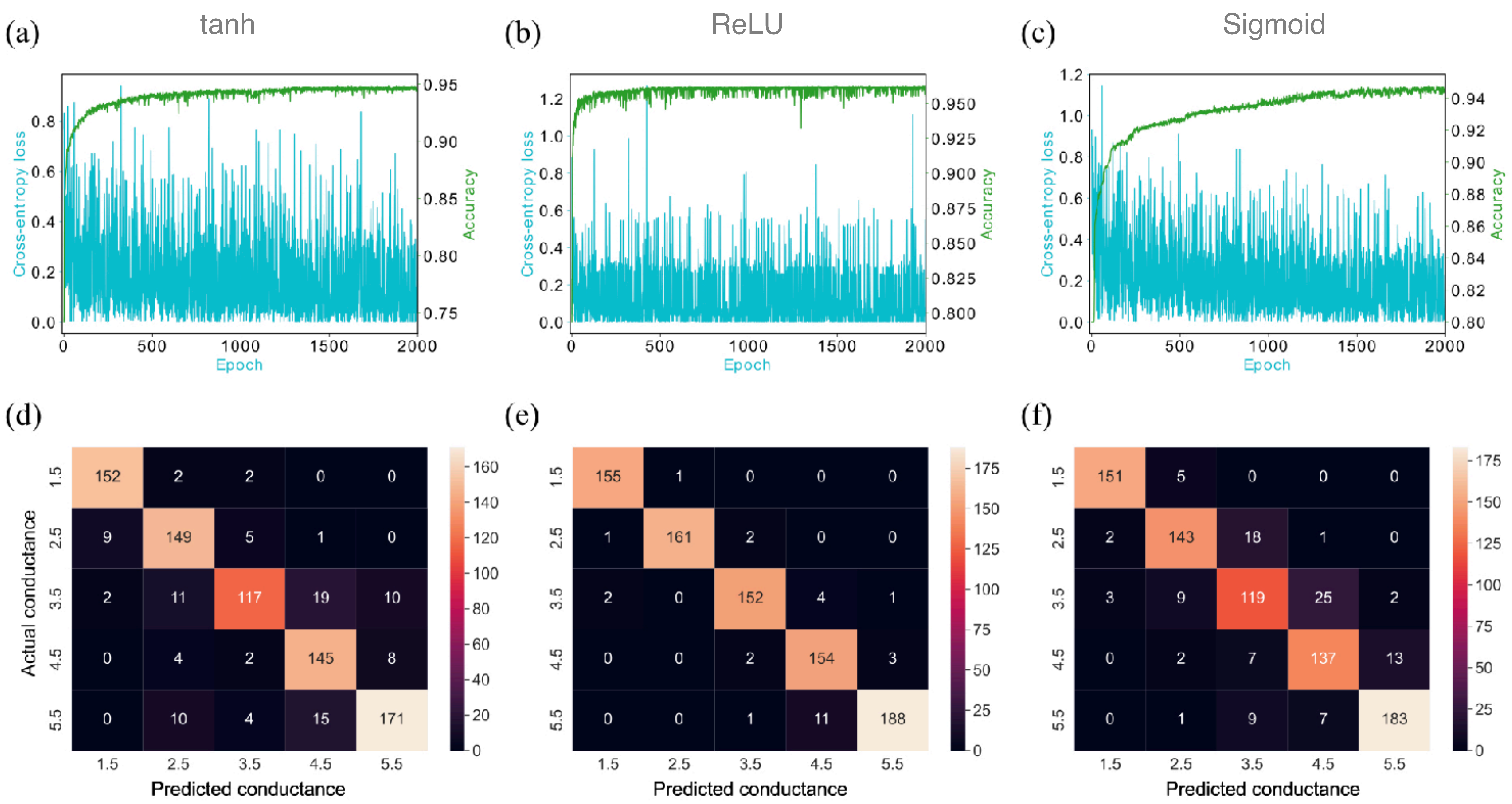


: 2

All other cases

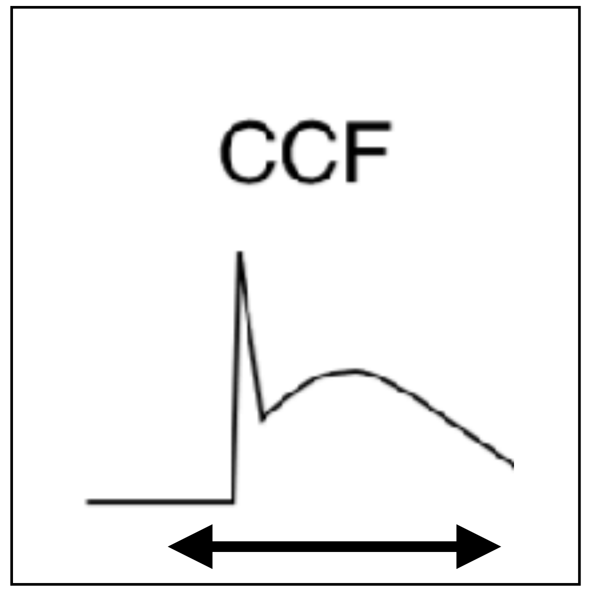
: 0

Conductances and time constants are classified with high accuracy;

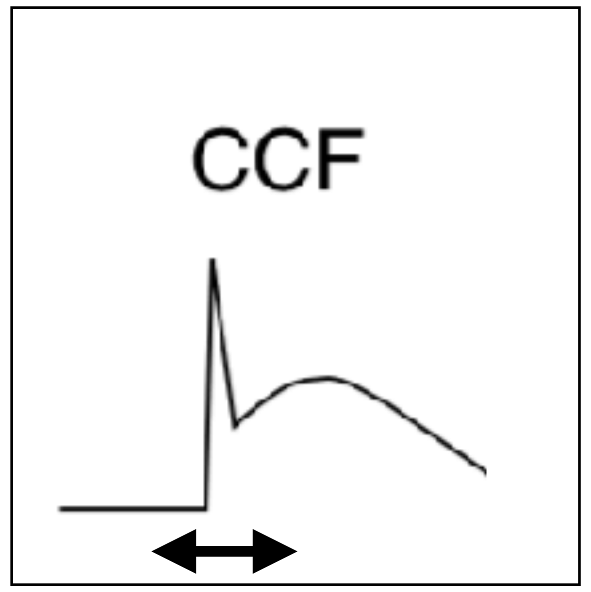


ReLU is more reliable.

… but only if information beyond the first peak is provided



Activation function	G_h	Precision	Recall	F1-score	MCC
G_h variation					
tanh	No connection	0.96	1.0	0.98	0.849
	1.5	0.98	0.78	0.87	
	2.5	0.88	0.75	0.81	
	3.5	0.87	0.68	0.76	
	4.5	0.83	0.70	0.76	
	5.5	0.86	0.86	0.86	
ReLU	No connection	0.95	1.0	0.98	0.876
	1.5	1.0	0.8	0.89	
	2.5	1.0	0.81	0.89	
	3.5	0.99	0.80	0.89	
	4.5	0.95	0.79	0.86	
	5.5	0.99	0.76	0.86	
Sigmoid	No connection	0.96	1.0	0.98	0.856
	1.5	0.94	0.76	0.84	
	2.5	0.90	0.72	0.80	
	3.5	0.89	0.70	0.78	
	4.5	0.88	0.70	0.78	
	5.5	0.88	0.95	0.91	
τ_h variation					
Activation function	**τ_h**	**Precision**	**Recall**	**F1-score**	**MCC**
tanh	No connection	0.95	1.0	0.97	0.803
	40	0.86	0.76	0.81	
	80	0.82	0.66	0.73	
	120	0.83	0.67	0.74	
	160	0.93	0.60	0.73	
	200	0.94	0.67	0.78	
ReLU	No connection	0.95	1.0	0.97	0.829
	40	0.97	0.74	0.84	
	80	0.92	0.70	0.79	
	120	0.96	0.66	0.78	
	160	0.96	0.70	0.81	
	200	0.98	0.78	0.81	
Sigmoid	No connection	0.95	1.0	0.97	0.784
	40	0.79	0.76	0.77	
	80	0.81	0.61	0.70	
	120	0.78	0.60	0.68	
	160	0.91	0.60	0.72	
	200	0.92	0.65	0.76	



Activation function	G_h	Precision	Recall	F1-score	MCC
G_h variation					
tanh	No connection	0.95	1.0	0.98	0.704
	1.5	0.82	0.48	0.61	
	2.5	0.56	0.67	0.61	
	3.5	0.57	0.42	0.48	
	4.5	0.77	0.36	0.50	
	5.5	0.62	0.63	0.63	
ReLU	No connection	0.95	1.0	0.98	0.792
	1.5	0.89	0.76	0.82	
	2.5	0.82	0.69	0.75	
	3.5	0.73	0.58	0.65	
	4.5	0.80	0.58	0.68	
	5.5	0.84	0.66	0.74	
Sigmoid	No connection	0.95	1.0	0.98	0.746
	1.5	0.87	0.67	0.75	
	2.5	0.71	0.64	0.68	
	3.5	0.60	0.52	0.56	
	4.5	0.71	0.53	0.61	
	5.5	0.75	0.55	0.64	
τ_h variation					
Activation function	**τ_h**	**Precision**	**Recall**	**F1-score**	**MCC**
tanh	No connection	0.95	1.0	0.97	0.634
	40	0.55	0.63	0.59	
	80	0.45	0.20	0.27	
	120	0.44	0.47	0.46	
	160	0.57	0.37	0.45	
	200	0.67	0.38	0.49	
ReLU	No connection	0.94	1.0	0.97	0.659
	40	0.67	0.71	0.69	
	80	0.70	0.32	0.44	
	120	0.44	0.33	0.38	
	160	0.72	0.34	0.46	
	200	0.50	0.54	0.52	
Sigmoid	No connection	0.94	1.0	0.97	0.623
	40	0.68	0.62	0.65	
	80	0.43	0.35	0.38	
	120	0.42	0.36	0.39	
	160	0.42	0.32	0.36	
	200	0.66	0.33	0.44	

Can we use CCFs?

CCFs are essentially linear metrics

Channel dynamics is not linear!

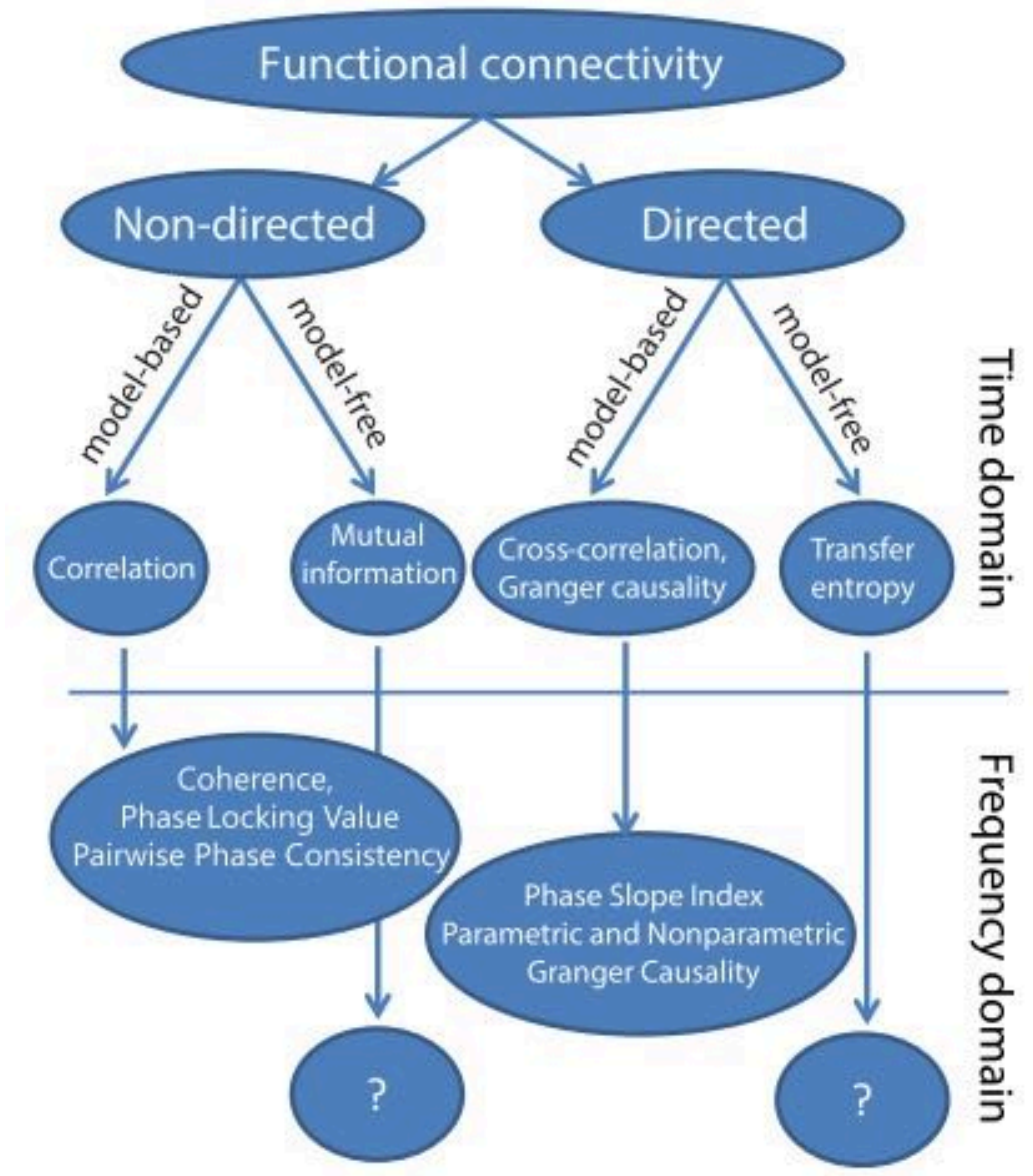
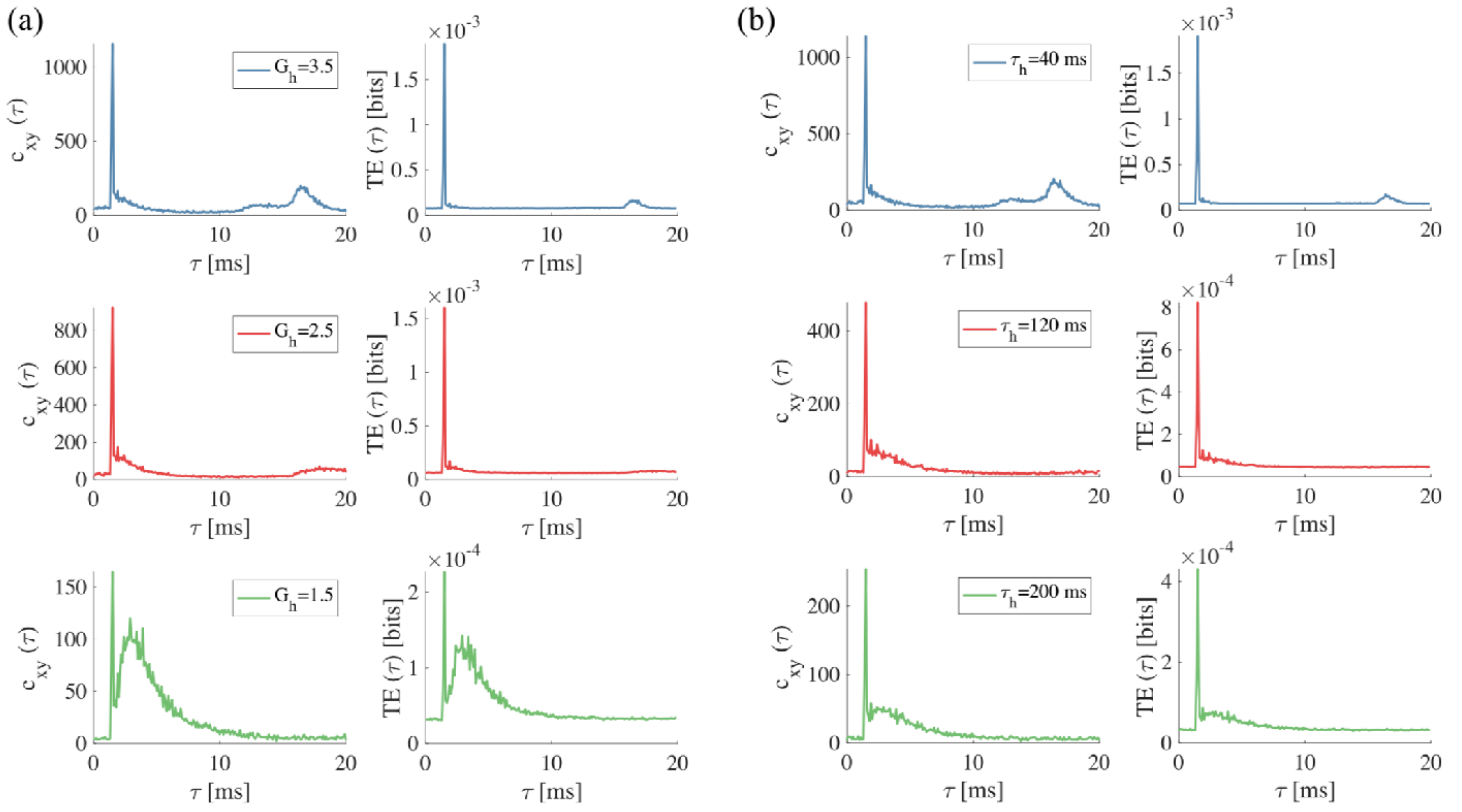


FIGURE 1 | A taxonomy of popular methods for quantifying functional connectivity.

Bastos and Schoffelen, *Front Syst Neurosci 9:*175 (2016).

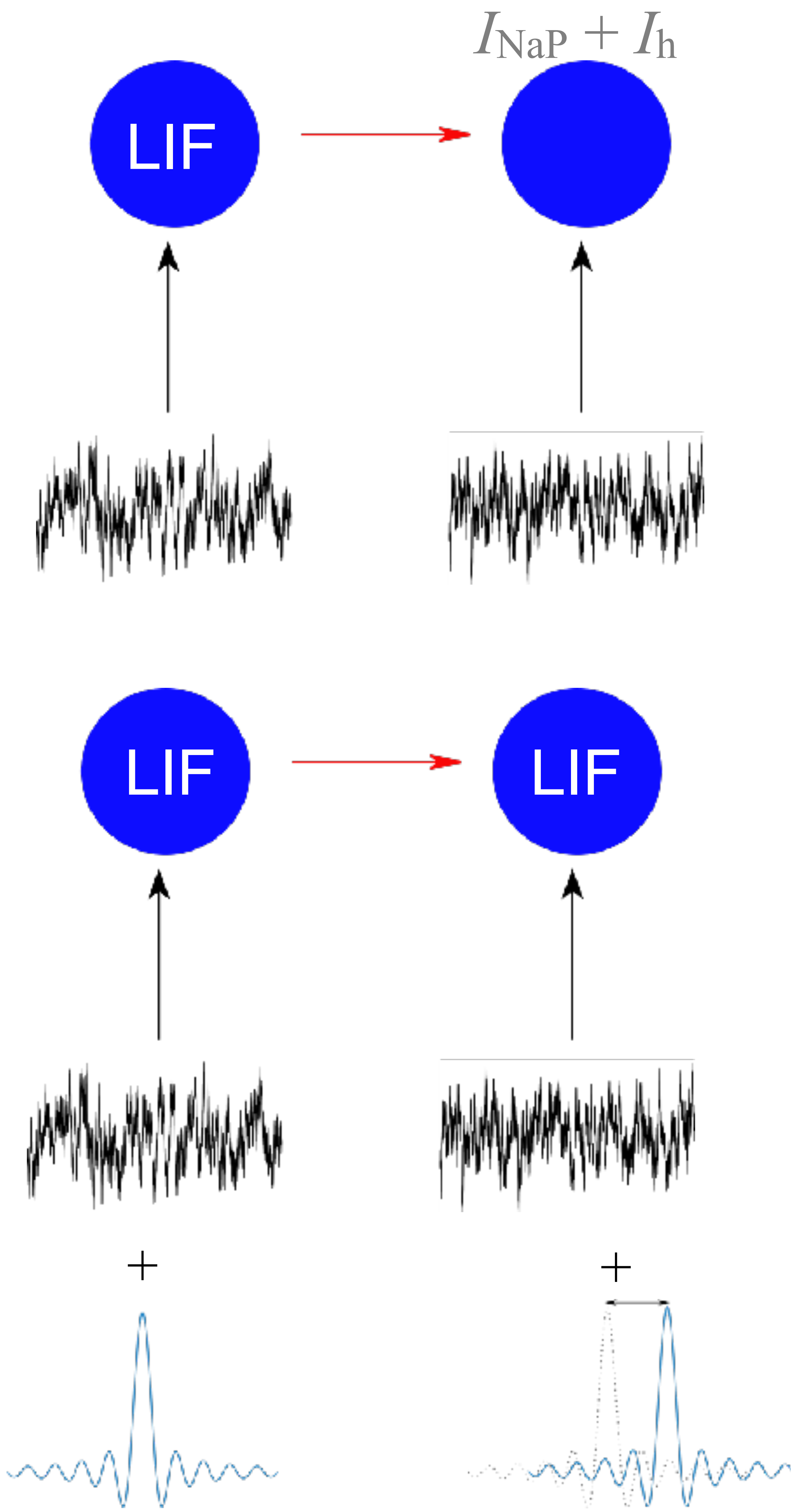


- Similar **variety** of data in TEs is and CCFs,
- Variety is the only input necessary for a **supervised training algorithm.**

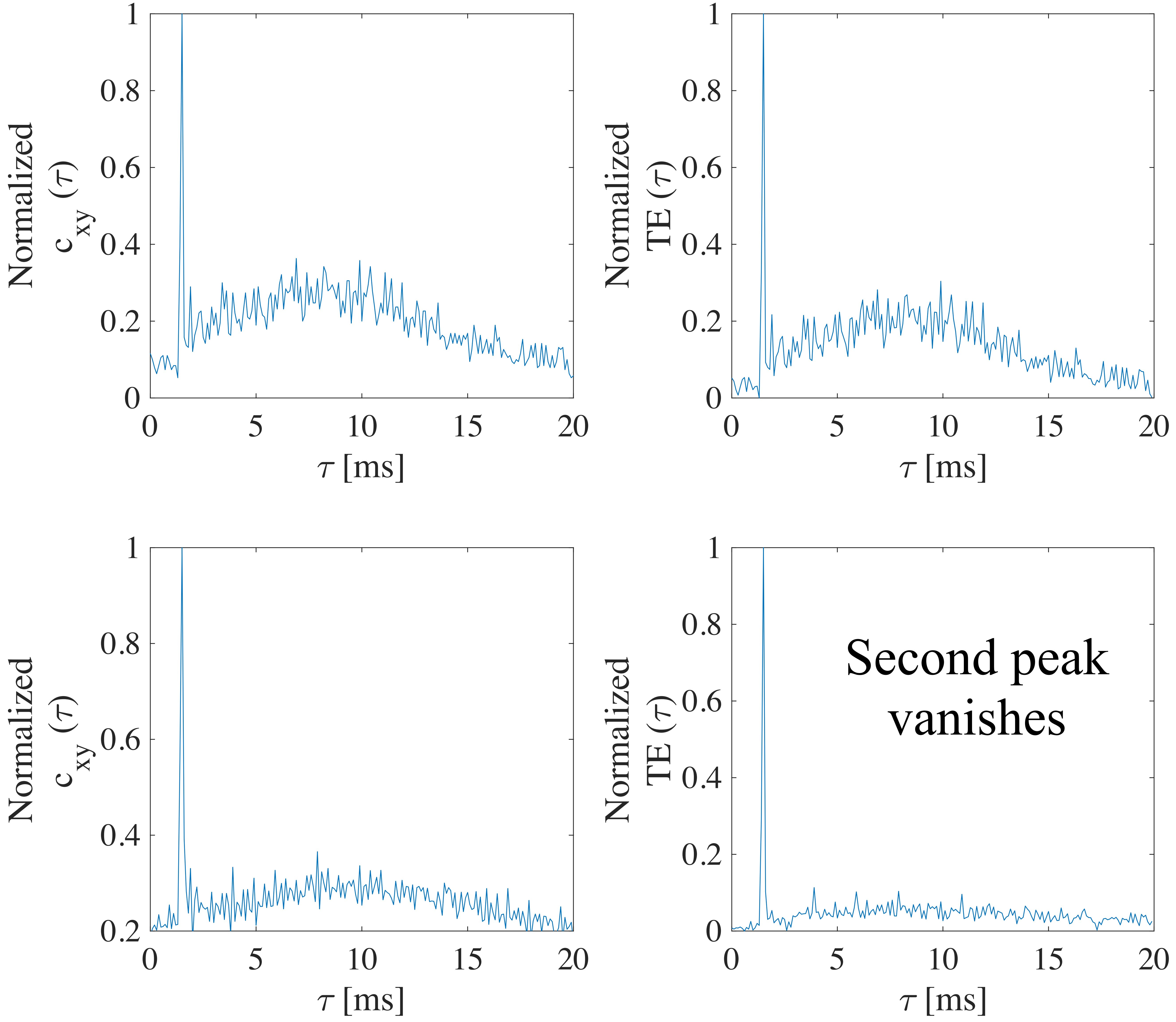
Confounding factors

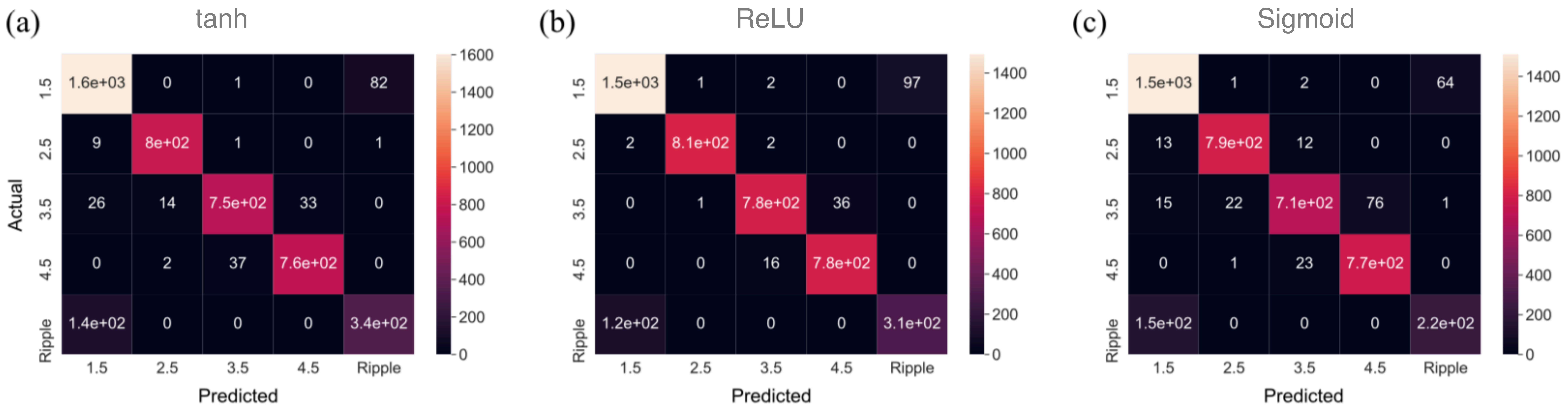
Correlation and Causality

Correlation but no Causality



Second peak persists in transfer entropy





G_h variation					
Activation function	G_h	**Precision**	**Recall**	**F1-score**	**MCC**
tanh	No connection	0.93	0.99	0.96	0.791
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	3.5	0.95	0.75	0.84	
	4.5	0.96	0.76	0.85	
	Ripple	0.48	0.34	0.40	
ReLU	No connection	0.93	0.99	0.96	0.789
	1.5	0.92	0.75	0.83	
	2.5	1.0	0.81	0.89	
	3.5	0.98	0.79	0.87	
	4.5	0.96	0.78	0.86	
	Ripple	0.49	0.31	0.38	
Sigmoid	No connection	0.92	0.99	0.96	0.777
	1.5	0.90	0.76	0.82	
	2.5	0.97	0.79	0.87	
	3.5	0.95	0.71	0.81	
	4.5	0.91	0.77	0.84	
	Ripple	0.50	0.22	0.31	

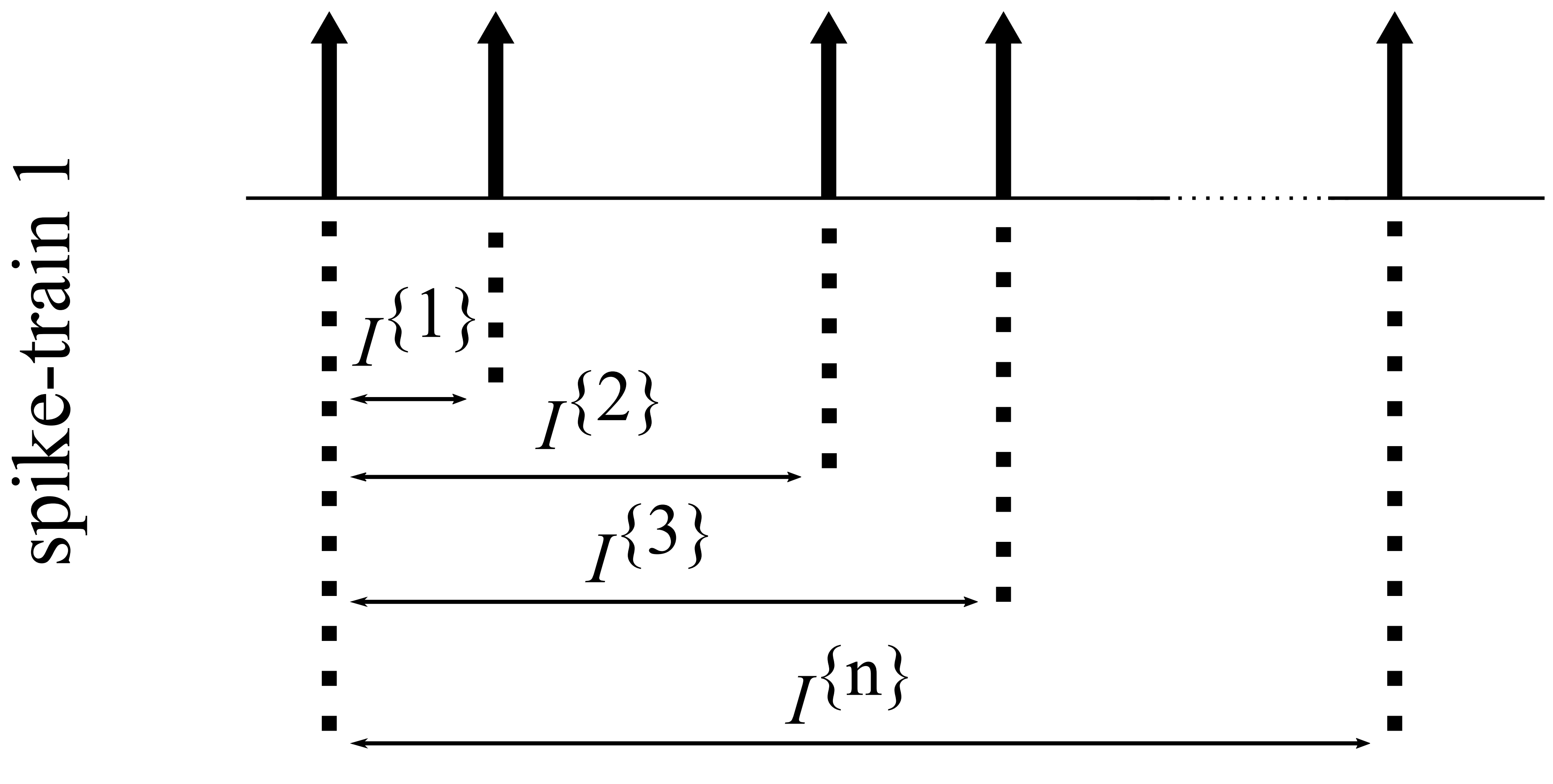
Confounding factors lower the accuracy

But how one could improve the classification without TE?

Connection between interval statistics and spike-train statistics

- Perkel , Gerstein, and Moore. *Biophys. J.*, 7(4):419–440, 1967.

n-ordered interspike intervals

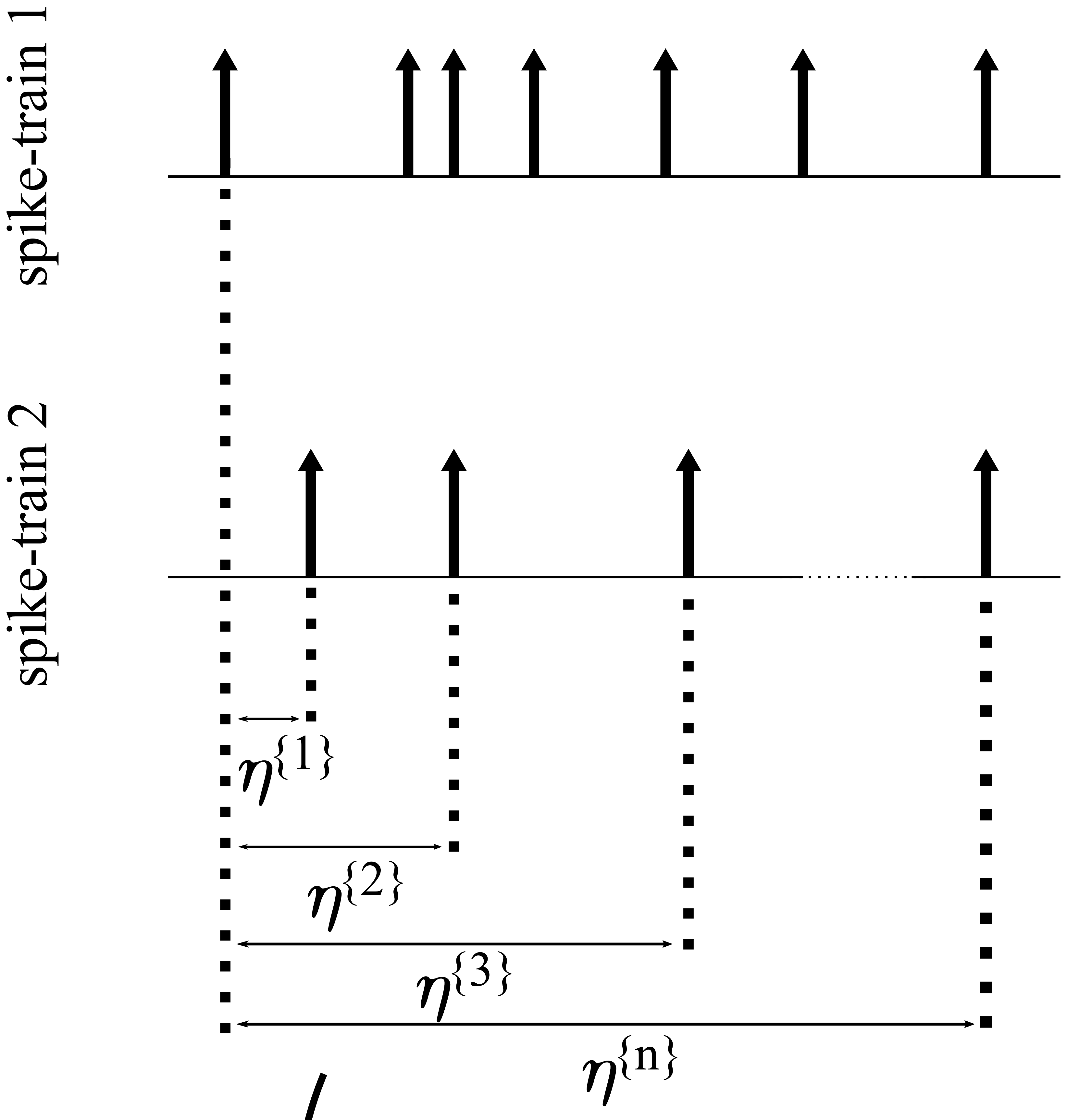


Connected to

Autocorrelation function

$$c_{xx}(\tau) \approx I^1 + I^2 + \ldots I^n$$

n-ordered cross-spike intervals

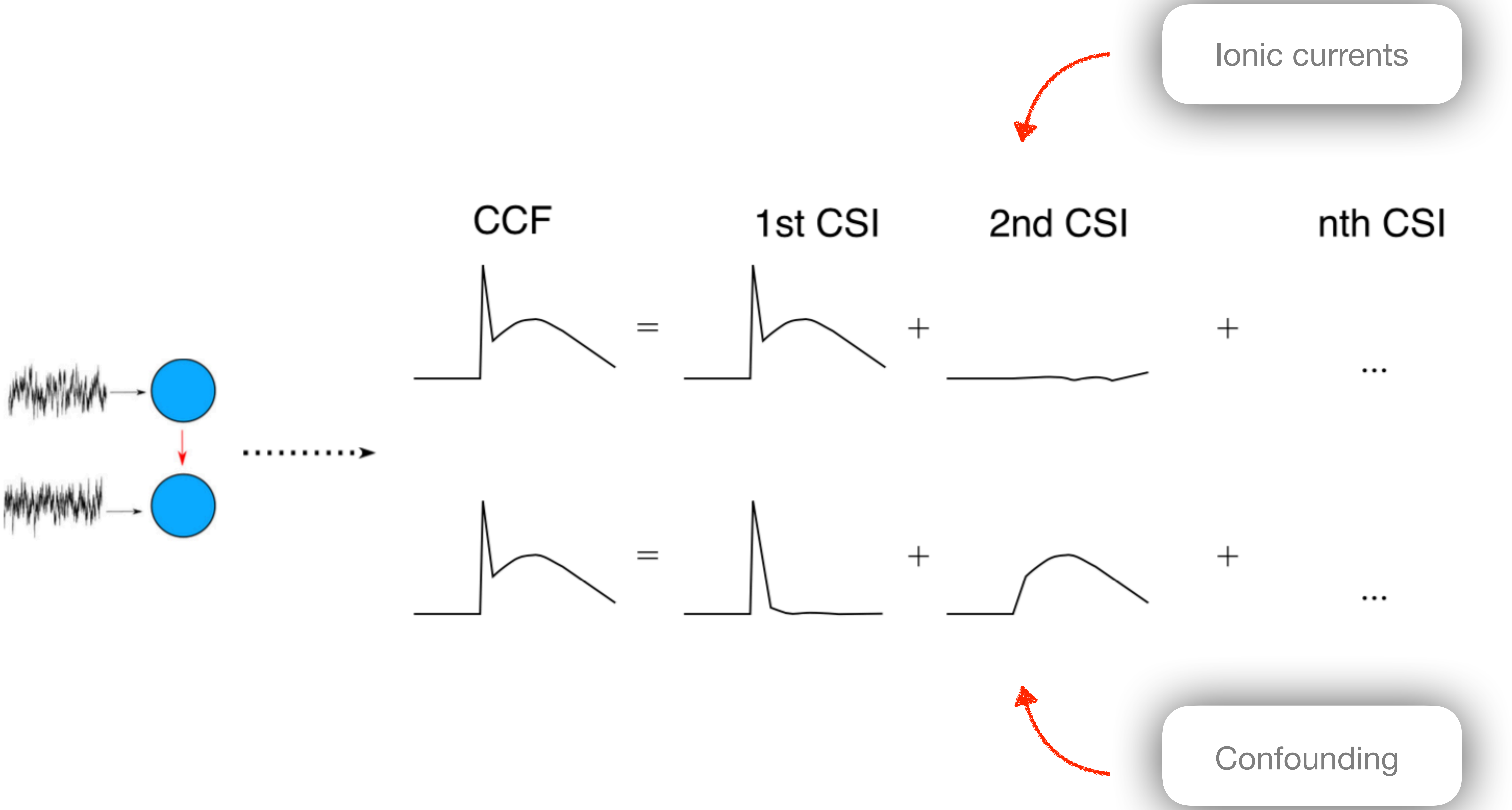


Connected to

Cross-correlation function

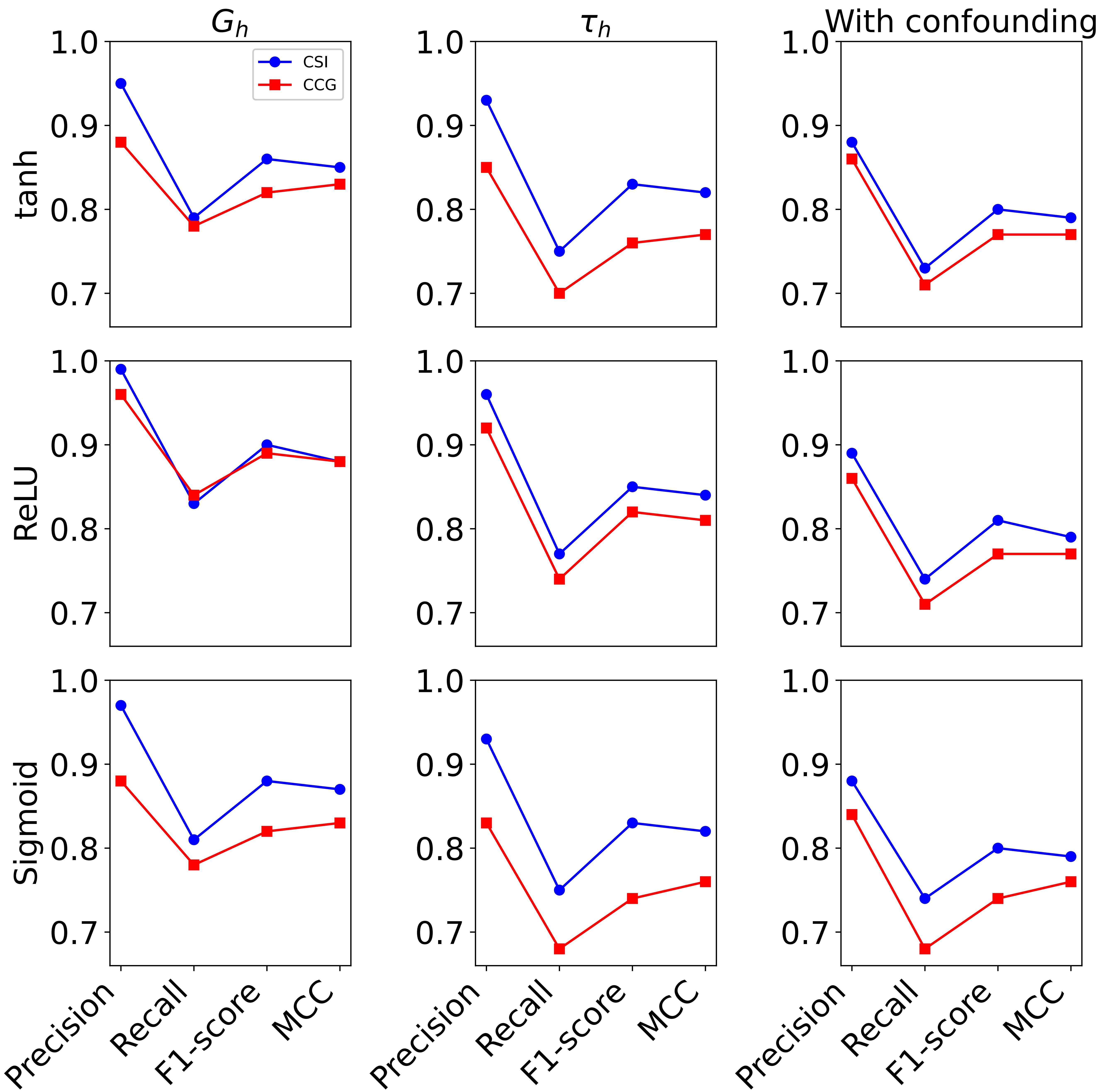
$$c_{xy}(\tau) \approx \eta^1 + \eta^2 + \ldots \eta^n$$

Connection between interval statistics and spike-train statistics

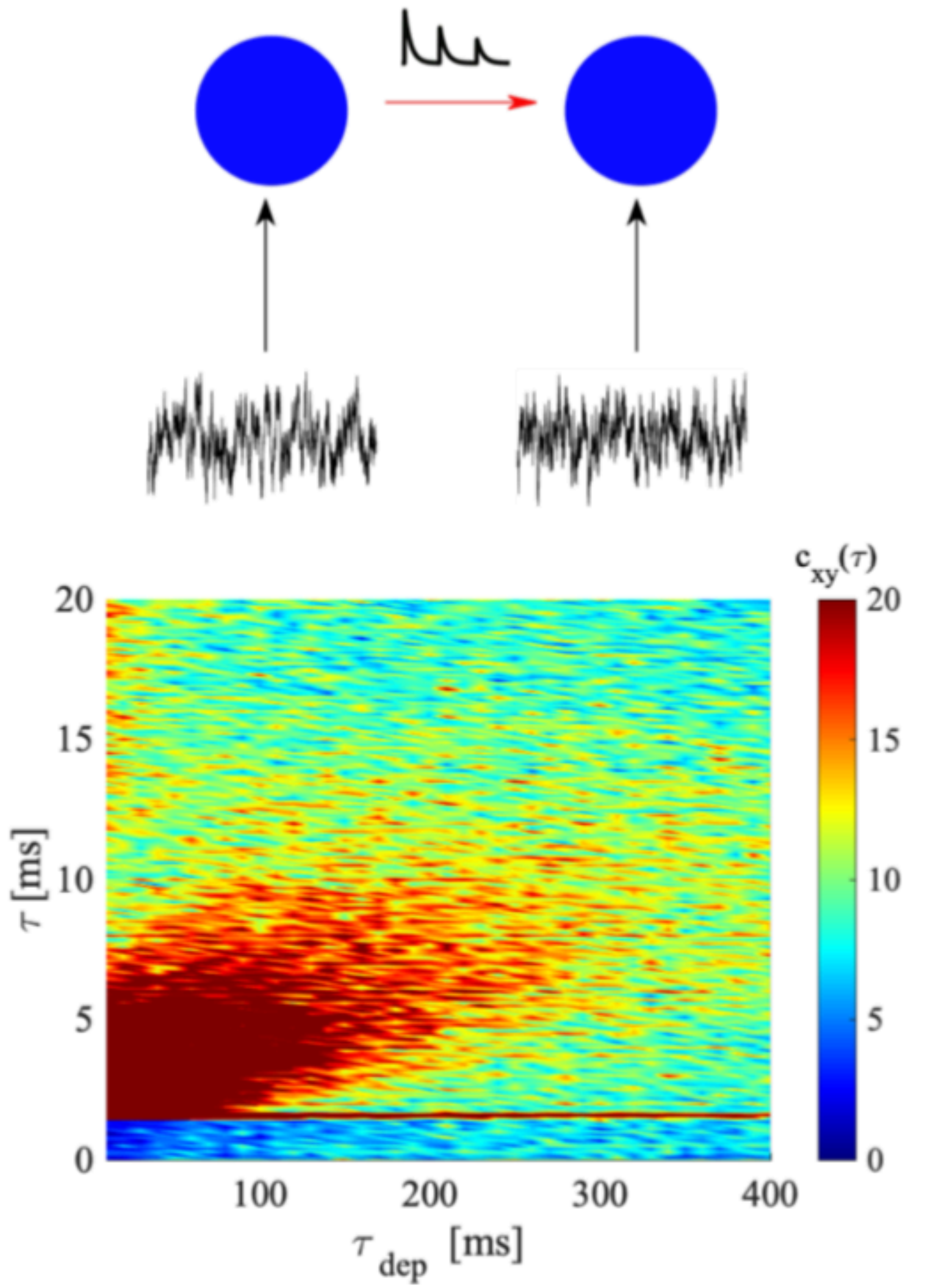


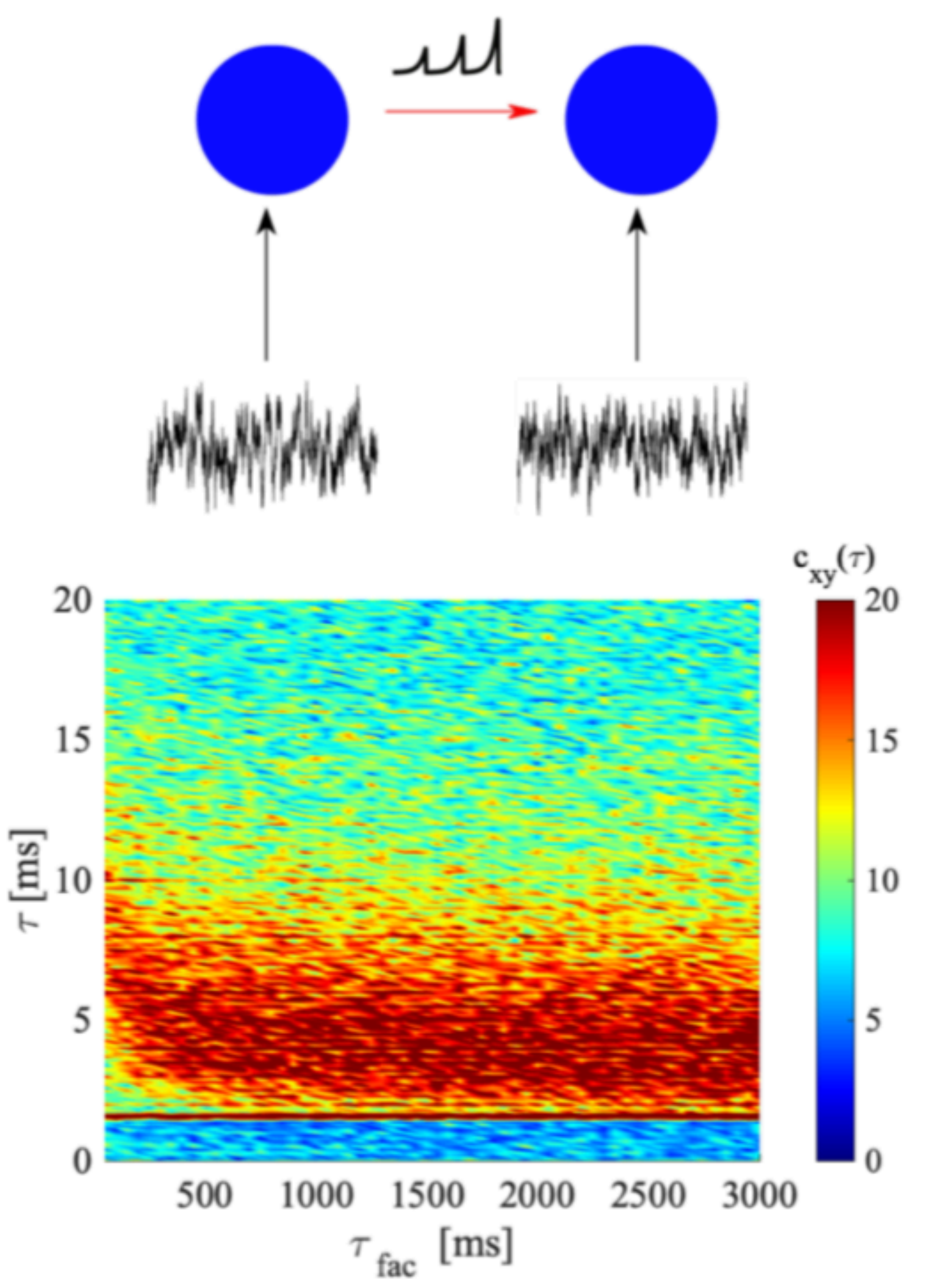
CSIs vs. CCFs

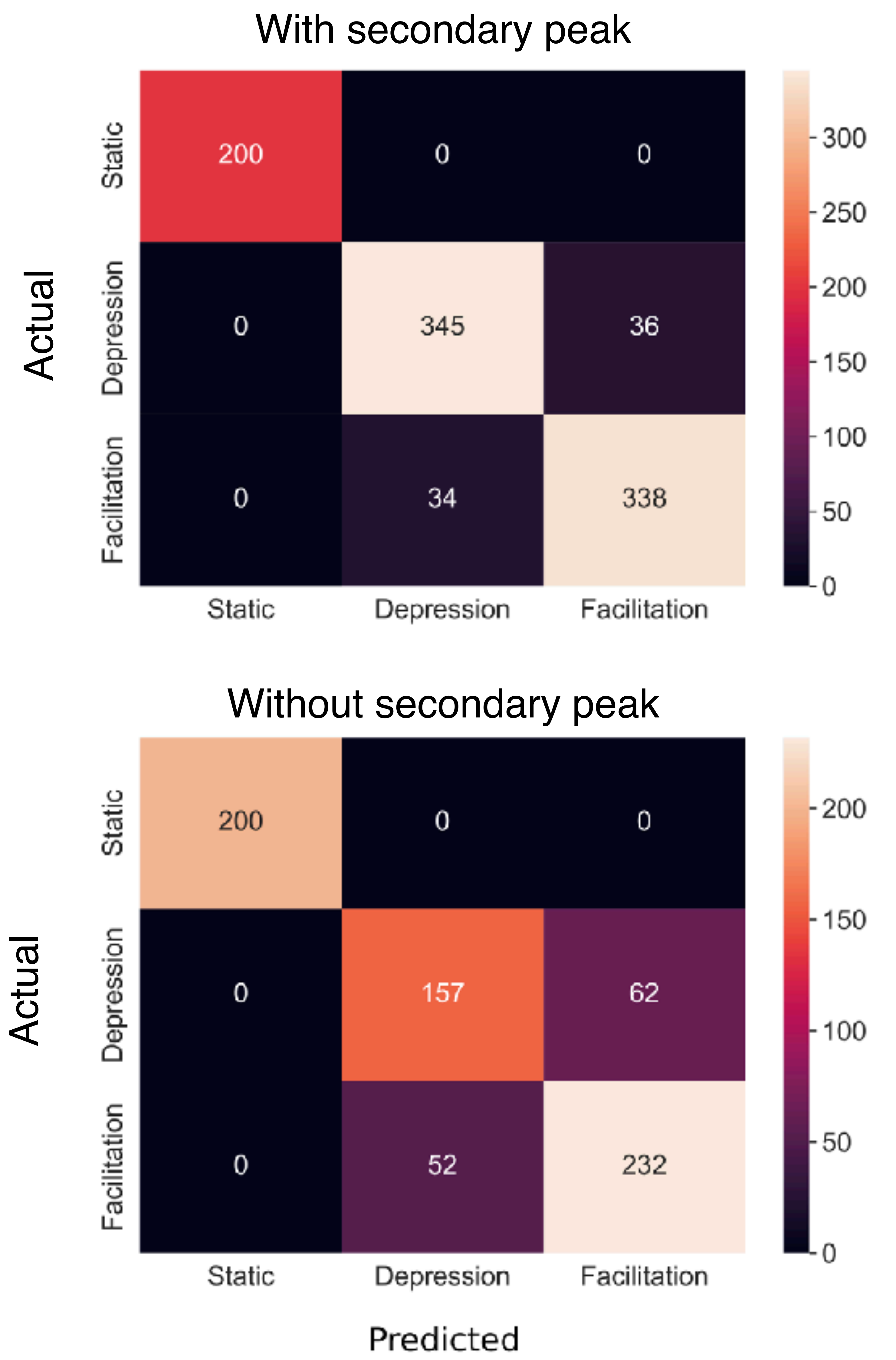
- Classification improves!
- Even with confounding factors



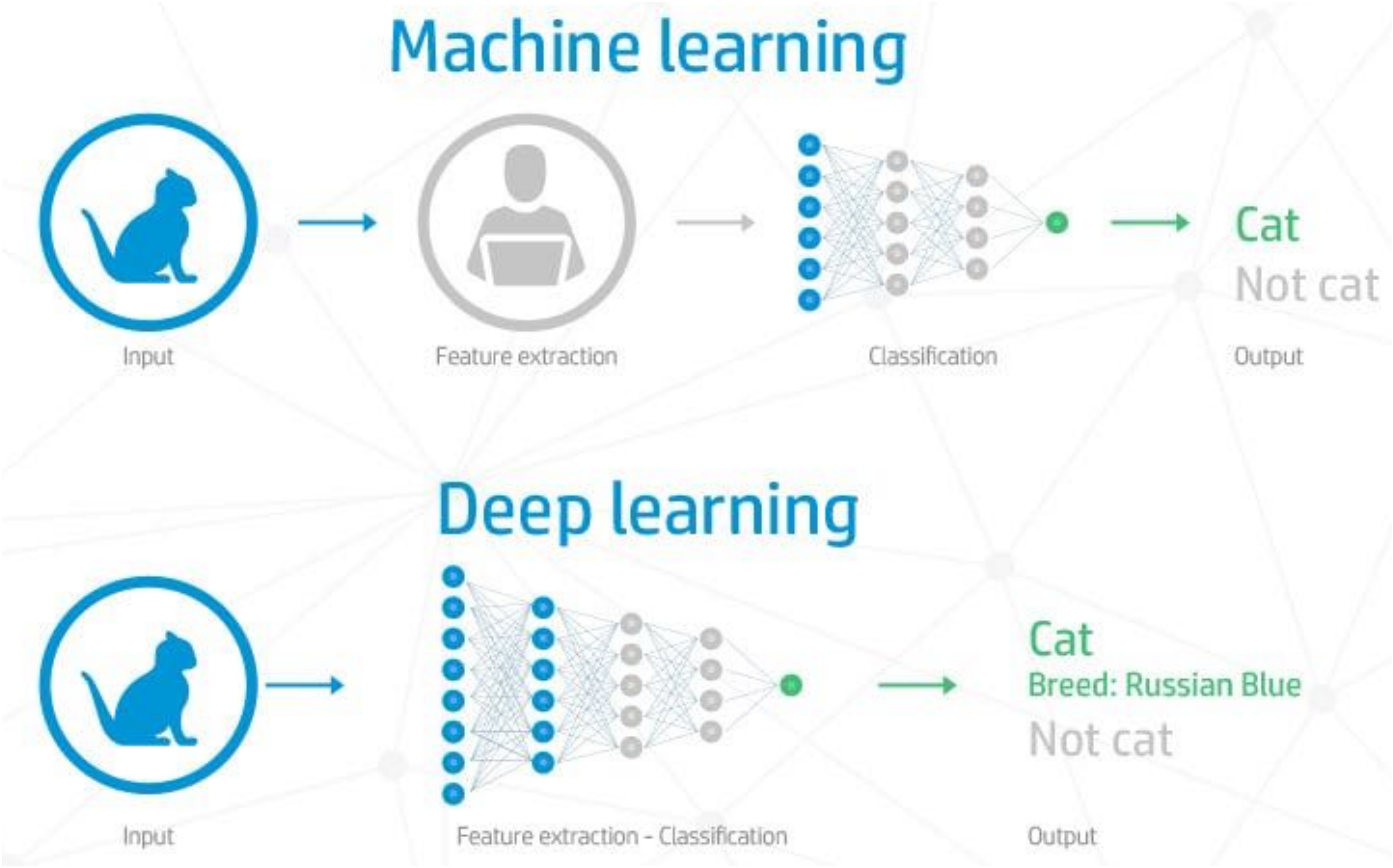
Short-term plasticity can be well classified if CCF includes intrinsic dynamics information



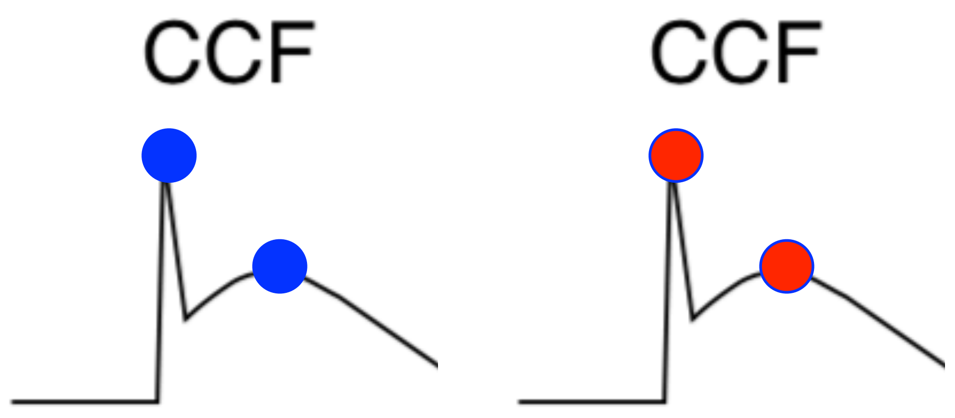




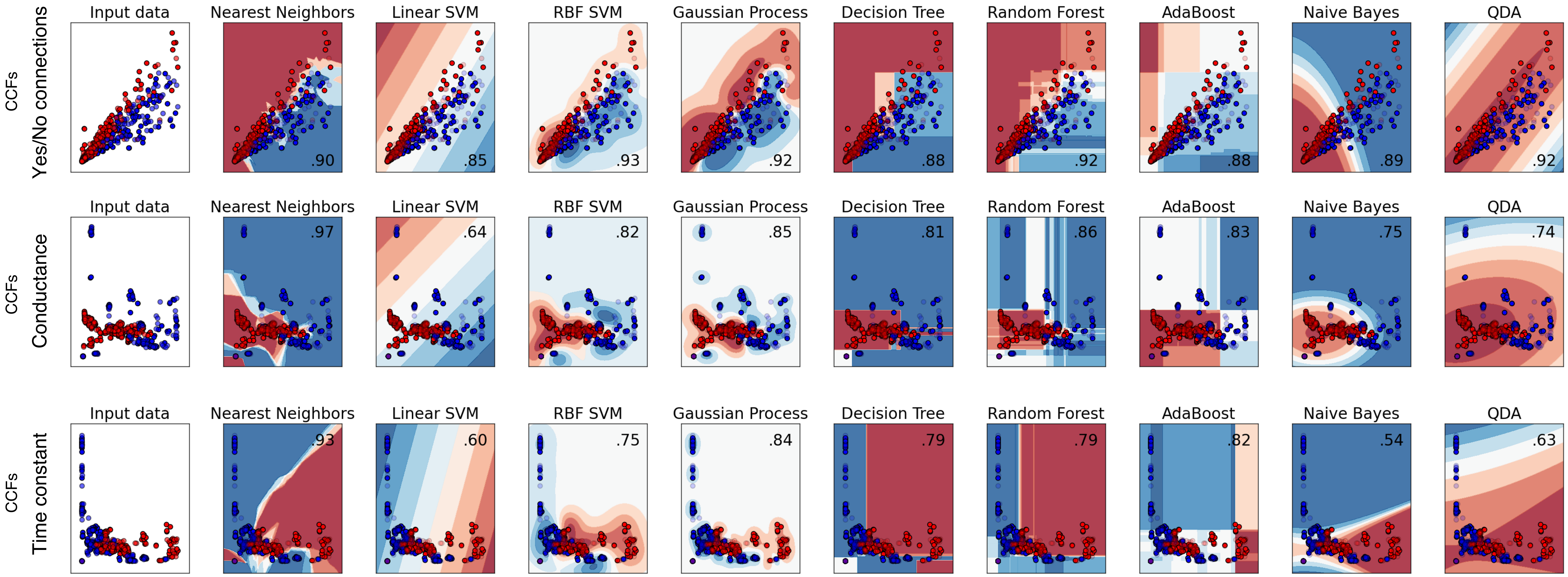
A comparison of several Machine Learning classifiers to distinguish biophysical features



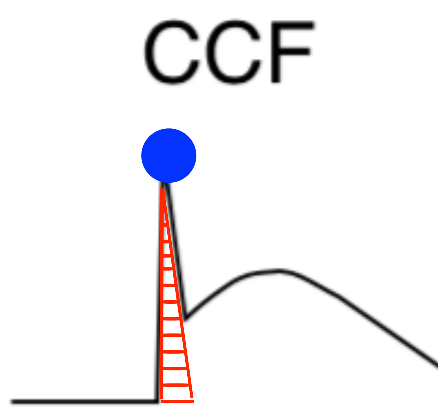
A comparison of several Machine Learning classifiers to distinguish biophysical features



Depending on the classifiers and purpose, two delays can be enough;



A comparison of several Machine Learning classifiers to distinguish biophysical features



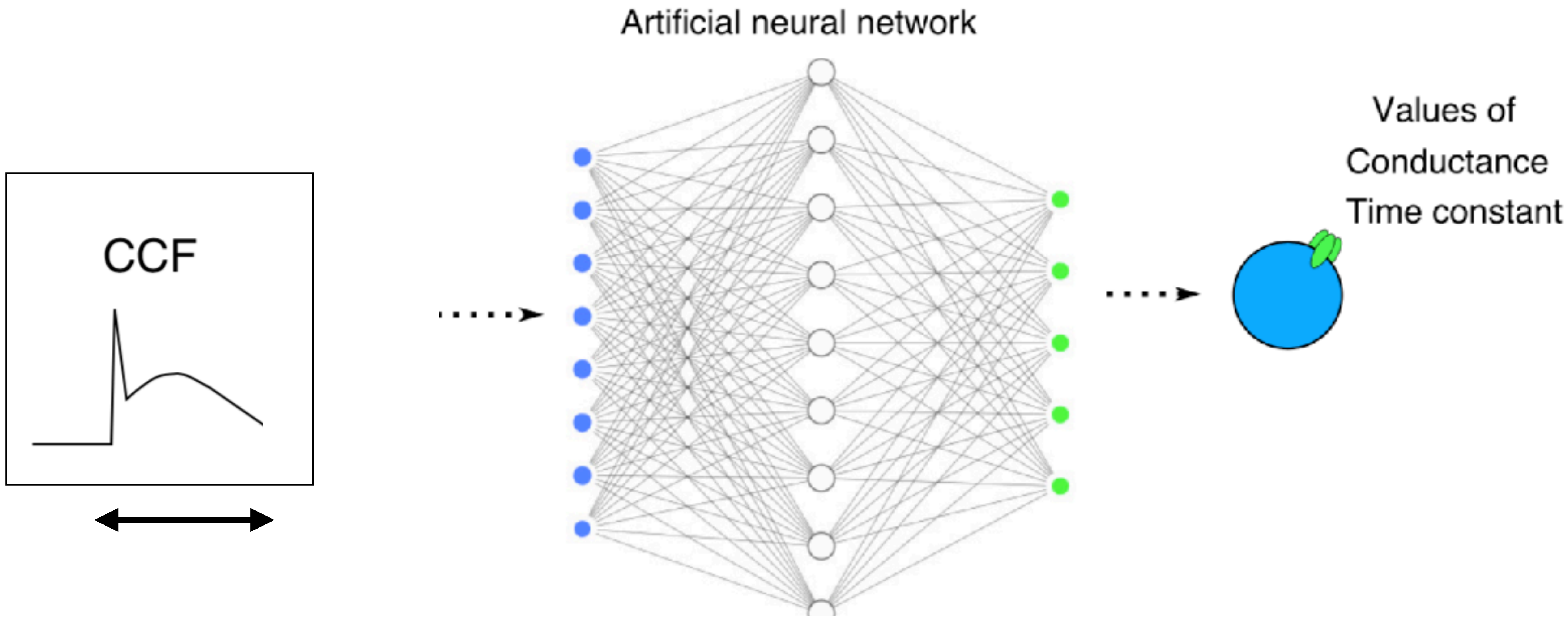
Features now are the first peak value and its area

Conclusions

Ionic properties can be extracted from CCFs

… only with information from lags beyond the first peak

Lags with **subthreshold dynamics**!!

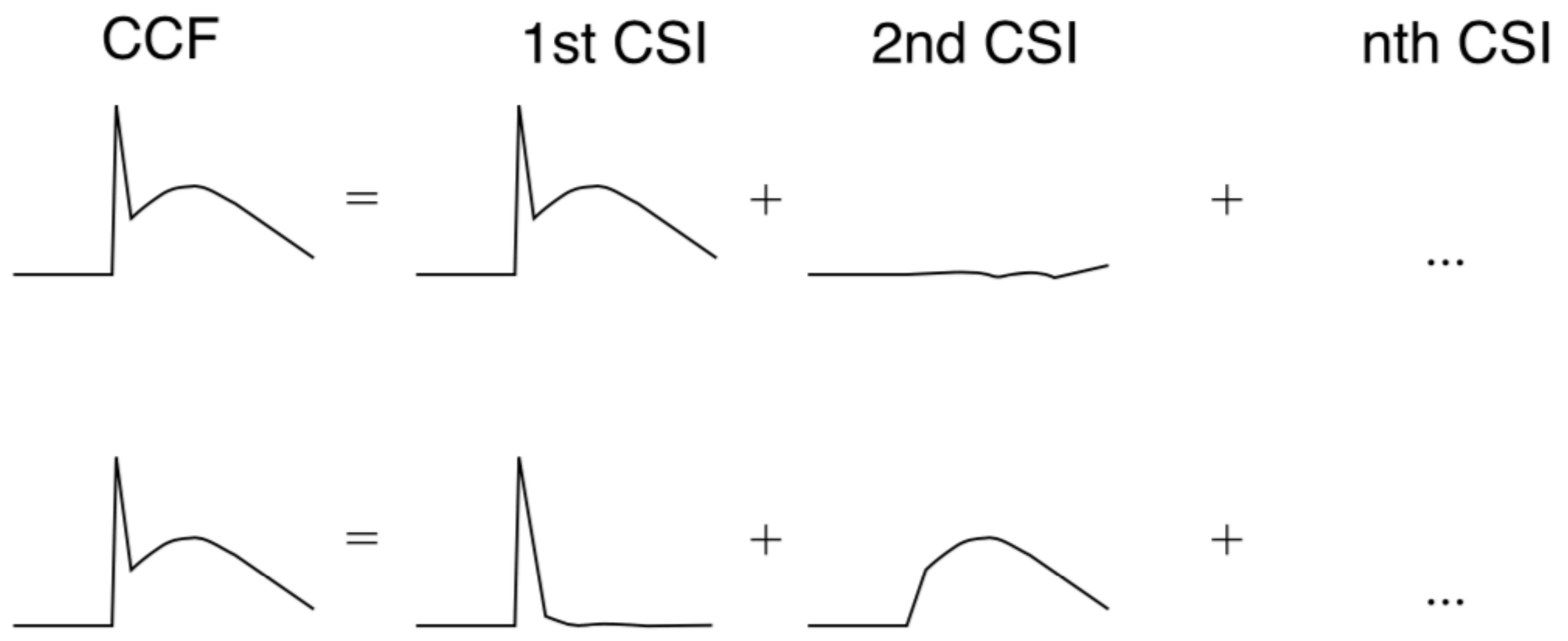


Conclusions

Our results do not require sophisticated information-theoretic metrics such as **transfer entropy**

… but suffer from confounding factors provided by background oscillations.

The cross-spike intervals is an alternative that improves the classification algorithms accuracy.



References

- Toyama, K., Kimura, M., & Tanaka, K., *46*(2), 191-201, 1981
- English, D. F., McKenzie, S., Evans, T., Kim, K., Yoon, E., & Buzsáki, G., *Neuron*, *96*(2), 505-520, 2017
- Platkiewicz, J., Saccomano, Z., McKenzie, S., English, D., & Amarasingham, A., *J Comput Neurosci*, *49*(2), 131-157, 2021
- Rotstein, H. G., *J Comput Neurosci*, *43*(3), 243-271, 2017
- Perkel, D. H., Gerstein, G. L., & Moore, G. P. *Biophys J*, *7*(4), 391-418, 1967
- Tsodyks, M., Pawelzik, K., & Markram, H., *Neural Computat*, *10*(4), 821-835, 1998
- McKenzie, S., Huszár, R., English, D. F., Kim, K., Christensen, F., Yoon, E., & Buzsáki, G., *Neuron*, *109*(6), 1040-1054, 2021

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Thank you very much!