Inferring Microcircuit Connectivity Dynamics from Spike Data

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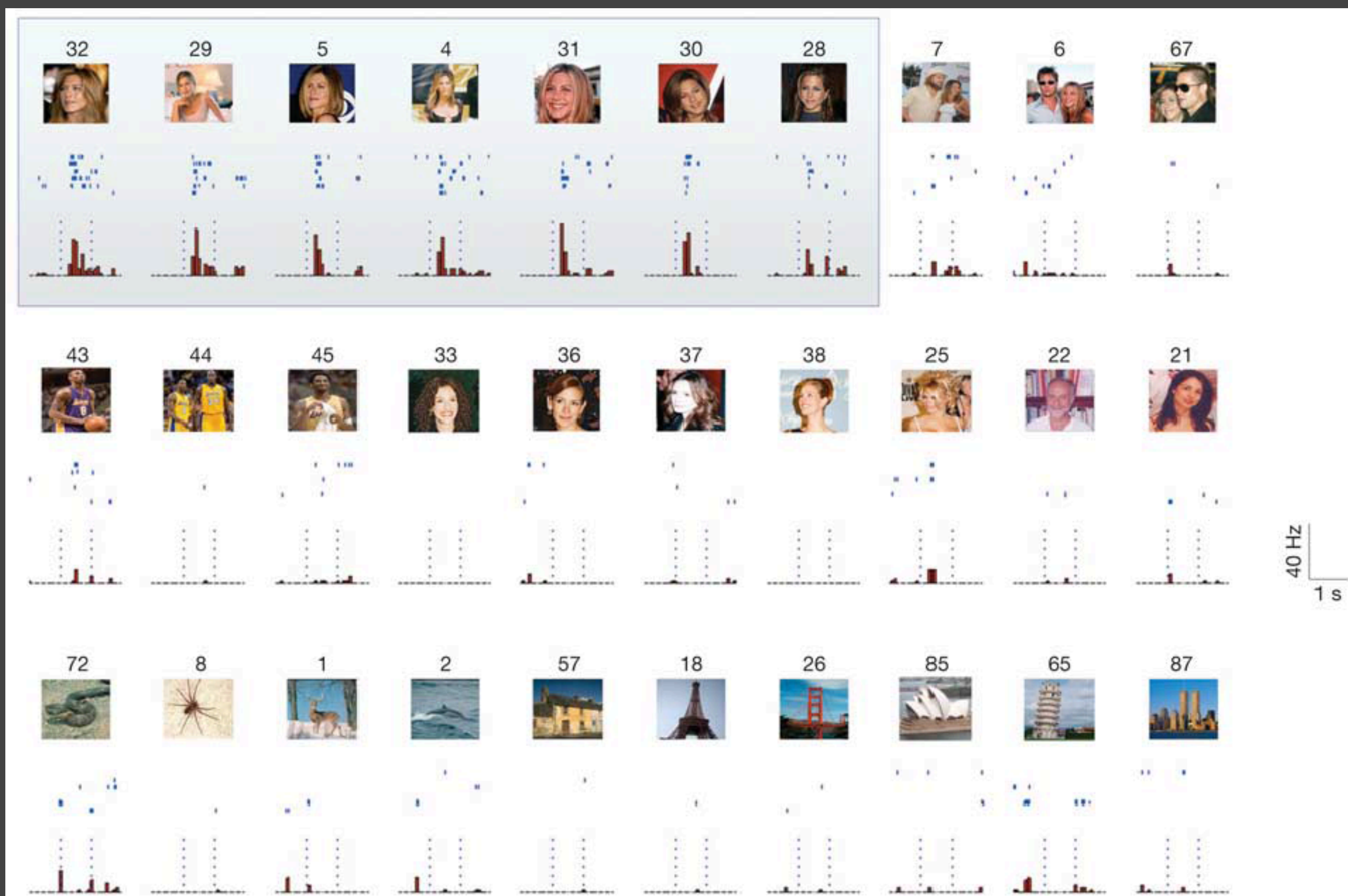
Theoretical Neuroscience Workshop, Janelia, September 26, 2016

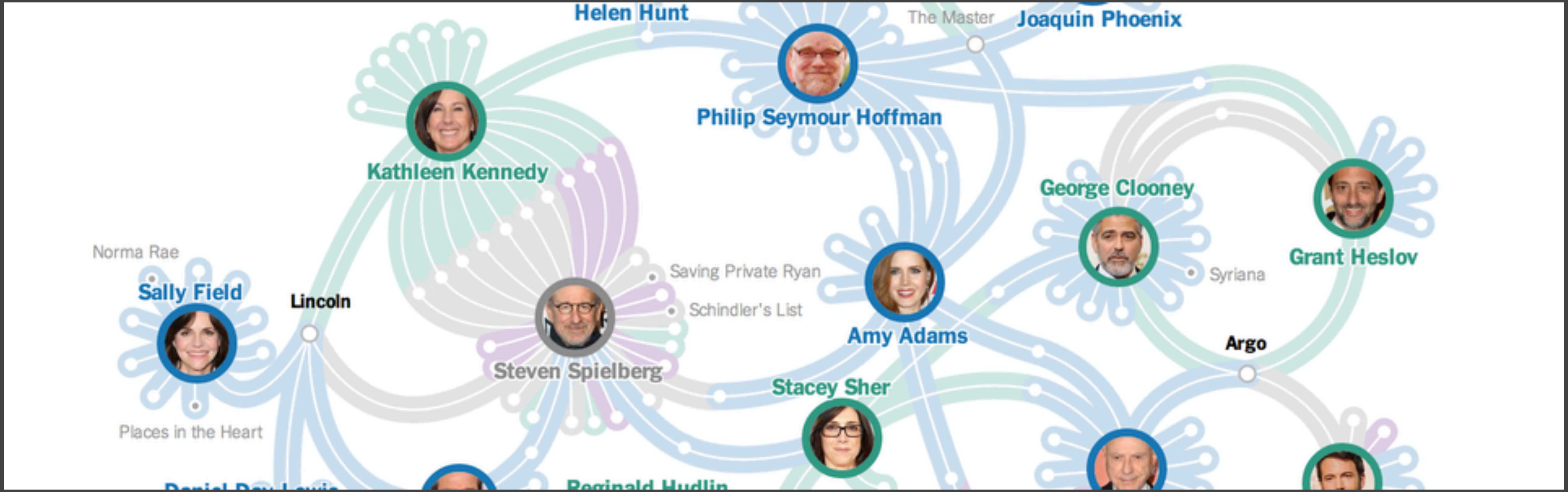
Classic System Neurophysiology



"Jennifer Aniston" cell in the left posterior hippocampus

Qian Quiroga et al (2005), Nature

The Importance of Connection



Outline

1. Motivations

2. A Biophysical Model of Ultra Precise Spike Transmission

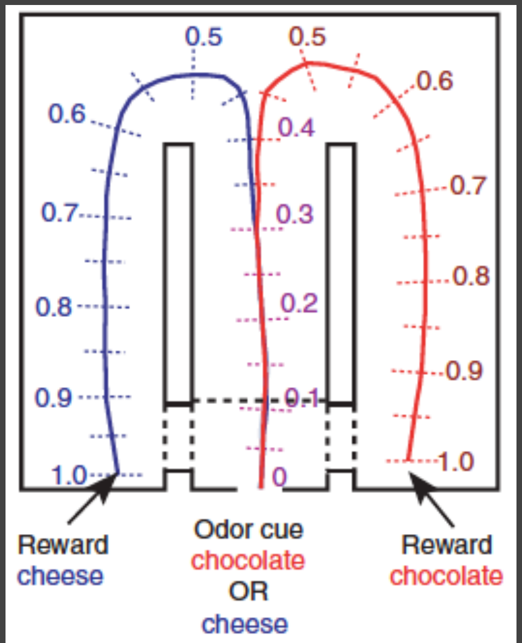
3. Nonparametric Statistics Synthesizes Biophysics

1. Motivations

Motivation: Inferring the Dynamic Organization of Neuronal Microcircuits during Behavior

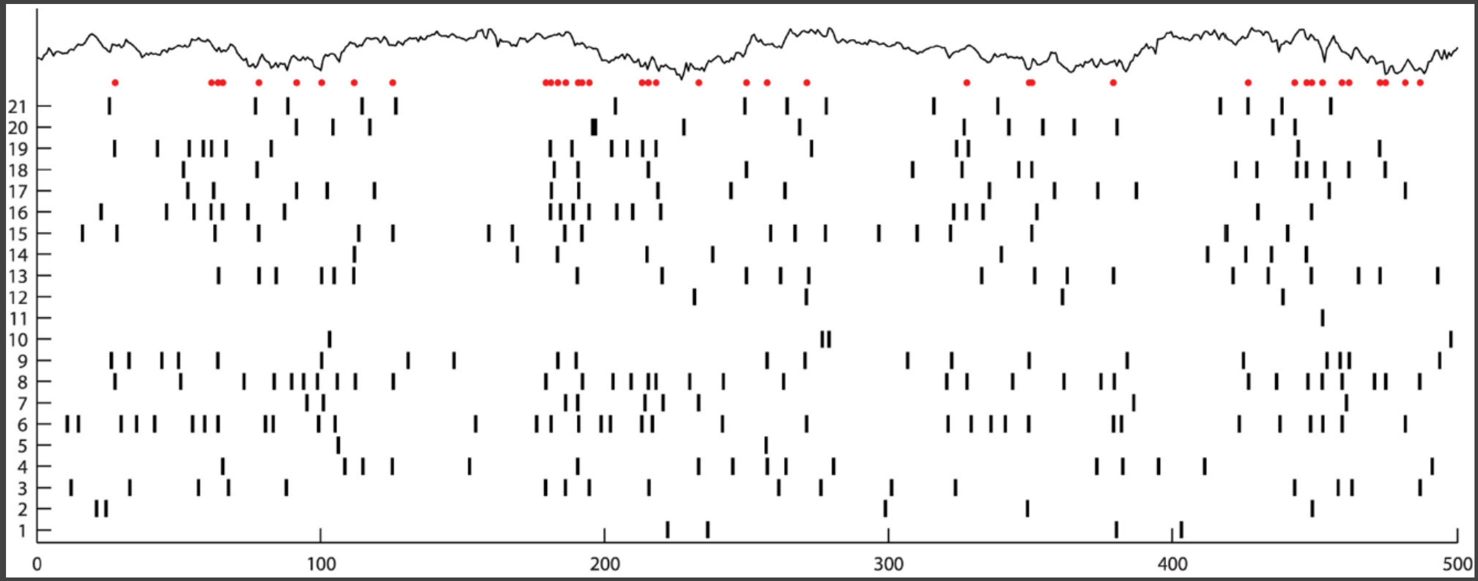
Decision task

Recording in the prefrontal cortex



Monosynaptic connections are detected and identified by looking at correlated spikes

Cell



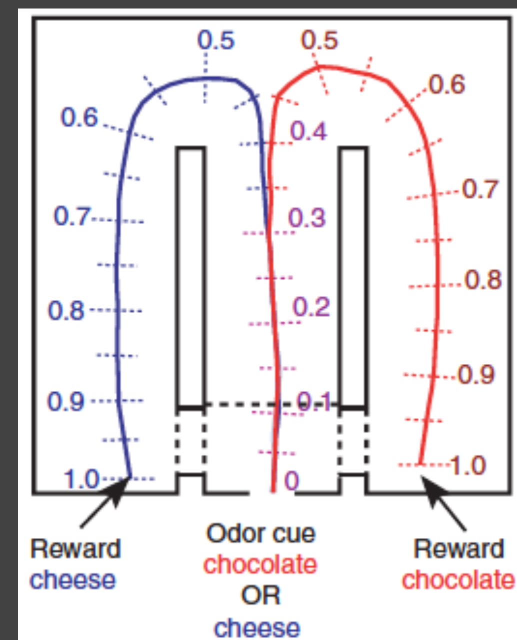
Time (ms)

Fujisawa et al (2008), Nat Neurosci

Motivation: Inferring the Dynamic Organization of Neuronal Microcircuits during Behavior

Decision task

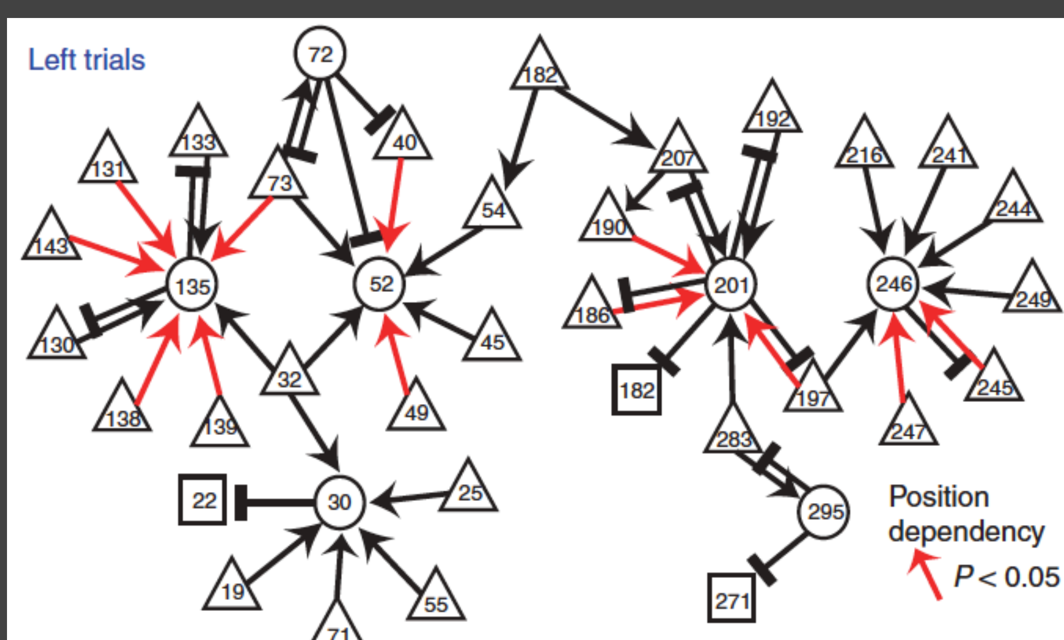
Recording in the prefrontal cortex

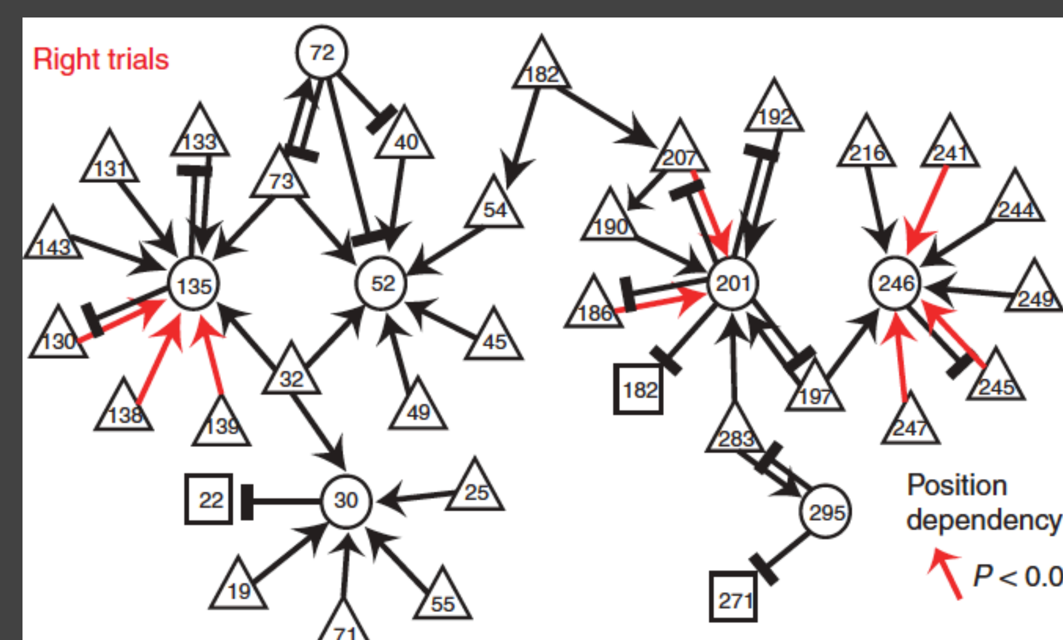


Excitatory connection

Inhibitory connection

Microcircuits are reconstructed based on spike correlation

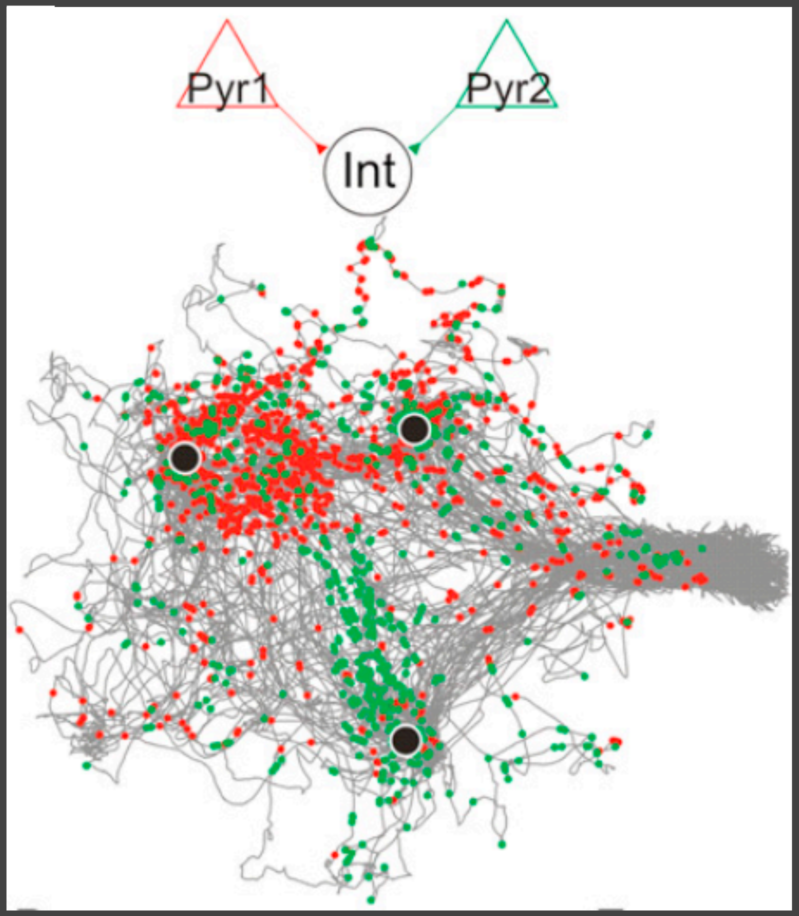




Fujisawa et al (2008), Nat Neurosci

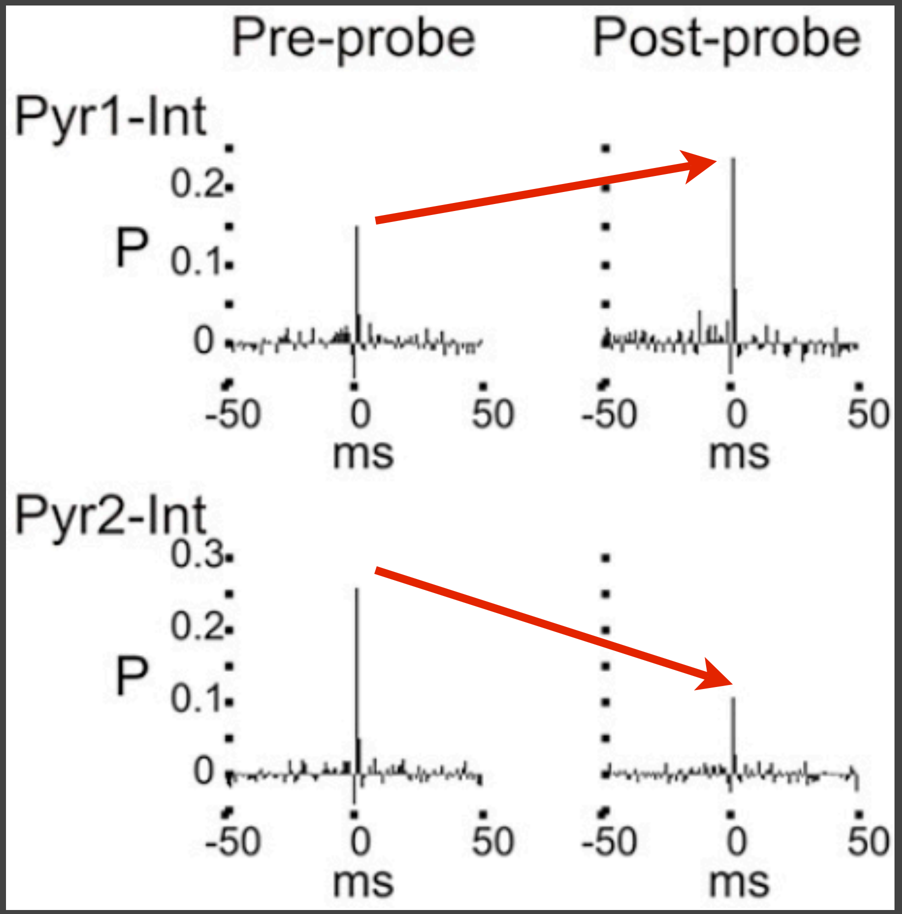
Motivation: Inferring the Dynamic Organization of Neuronal Microcircuits during Behavior

Spatial location of pairing events



Gray : Animal path
Color dots : Pairing events
Black dots : Goals
Pyr : Pyramidal cell
Int : Interneuron

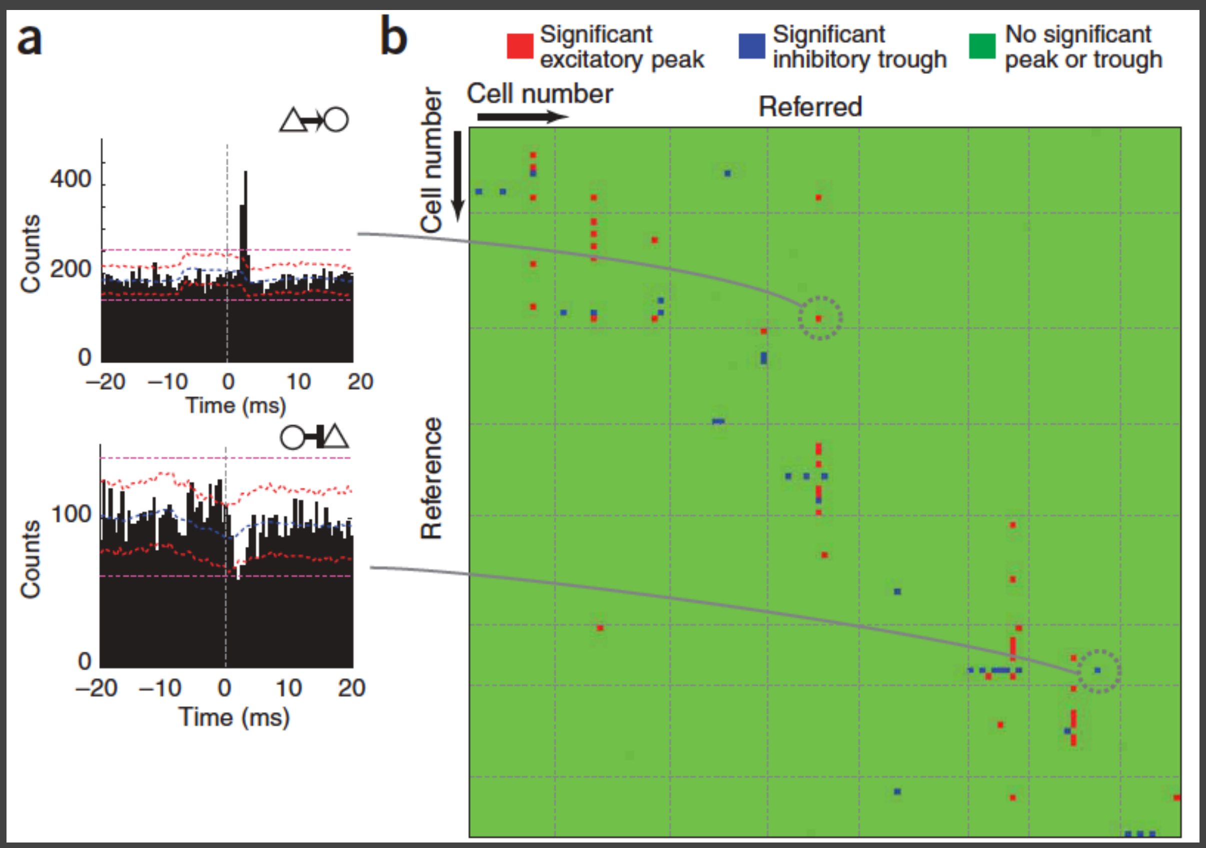
Plasticity from fine-time spike correlation



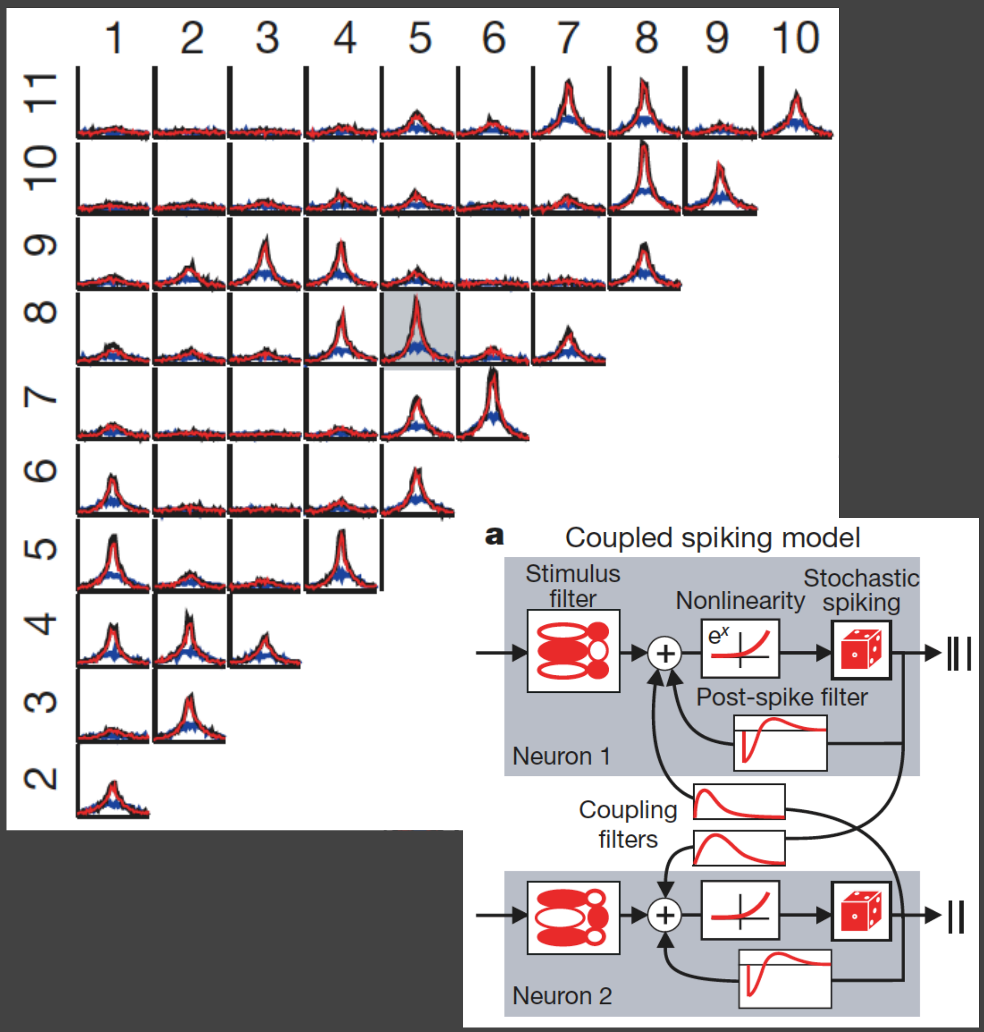
Dupret, O'Neil & Csicsvari (2013), Neuron

Standard Methods of Connectivity Inference

Pair-wise



Ensemble



Based on timescale separation

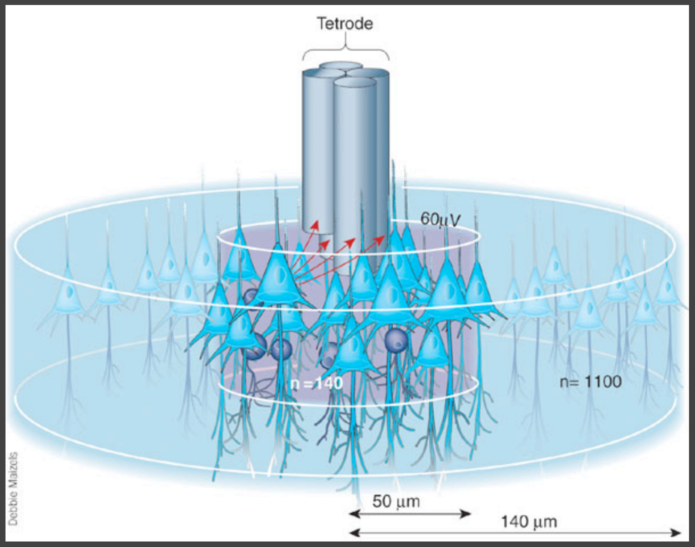
Based on multi-parameters fitting (GLM)

Both: Functional Connectivity + Millisecond Spike Correlation

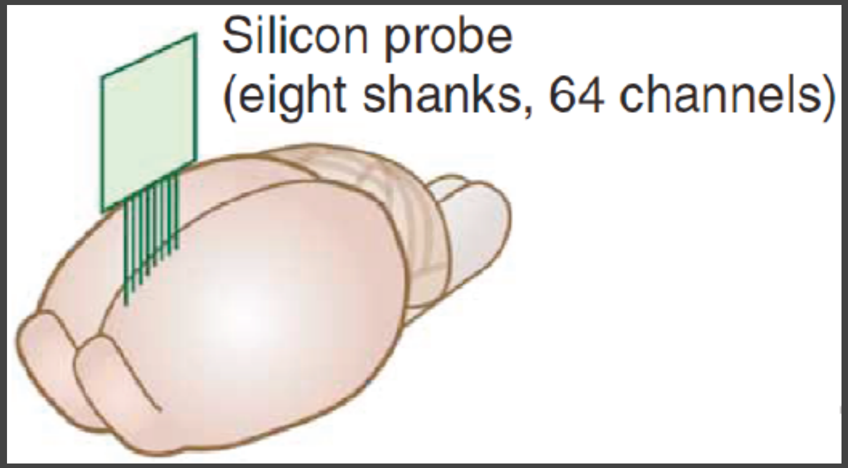
Fujisawa et al (2008), Nat Neurosci

Schneidman et al (2006), Nature
Pillow et al (2008), Nature

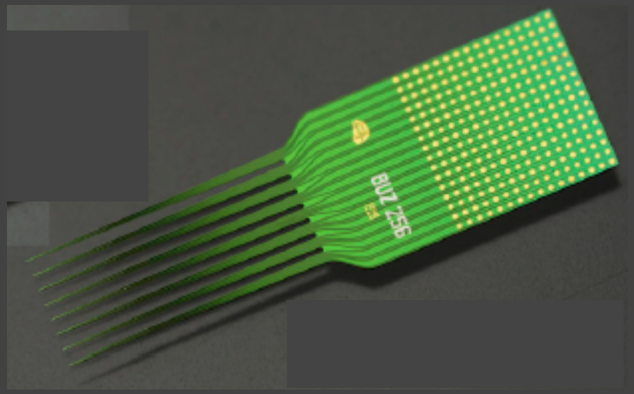
Large-Scale Recording of Neuronal Ensembles

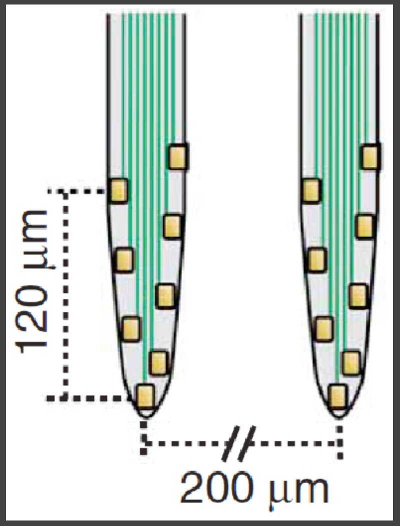


Only a local microcircuit can be recorded

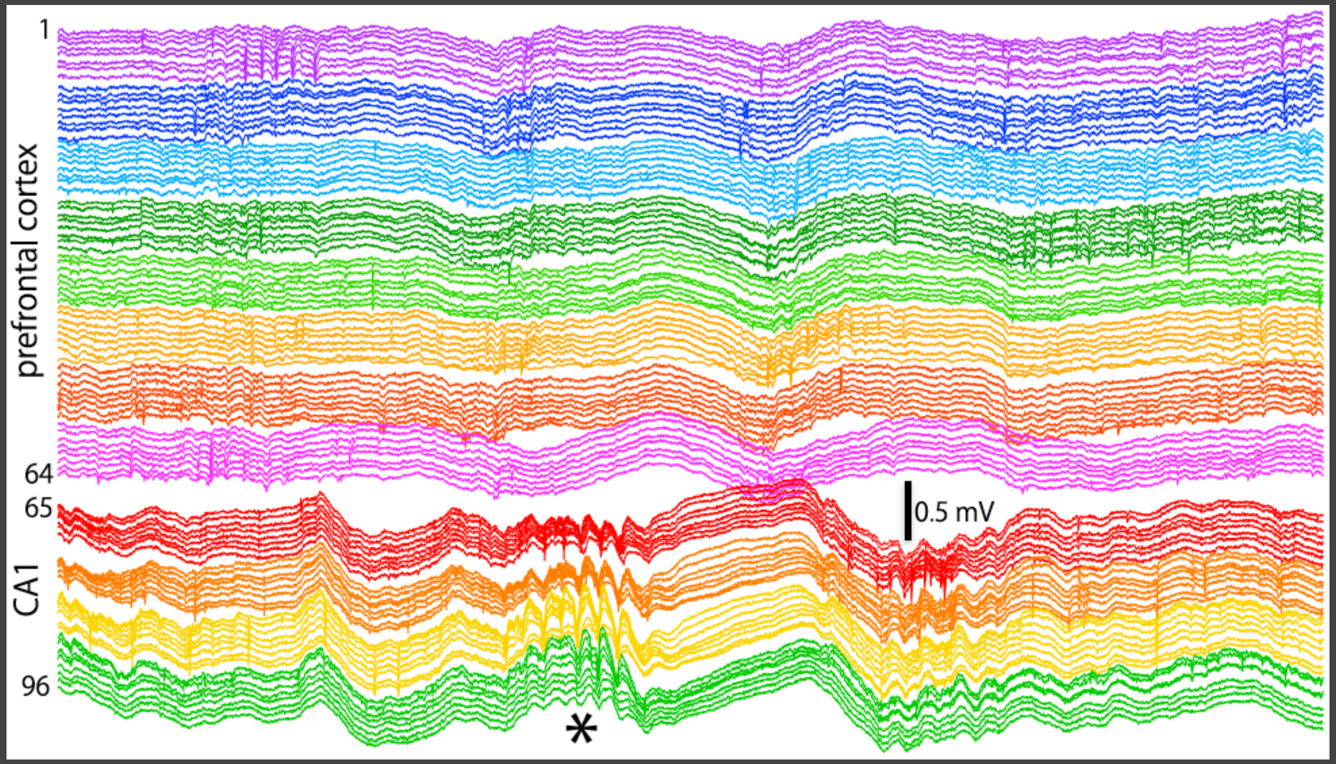


A high-density silicone probe is composed of 8 shanks





Each shank contains 8 electrodes

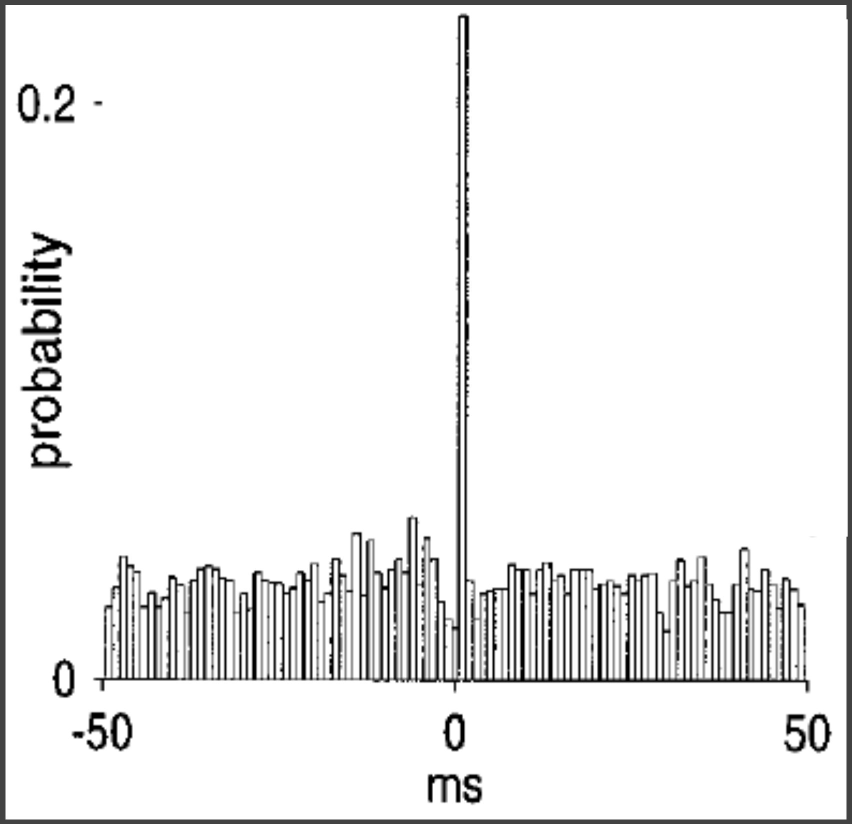


About hundred extracellular potentials can be recorded at the millisecond precision

Buzsáki (2004), Nat Neurosci
Buzsaki et al (2015), Neuron

Monosynaptic Identification from CCG

CA1 pyramidal layer in the behaving rat
Wire tetrodes and silicon probes

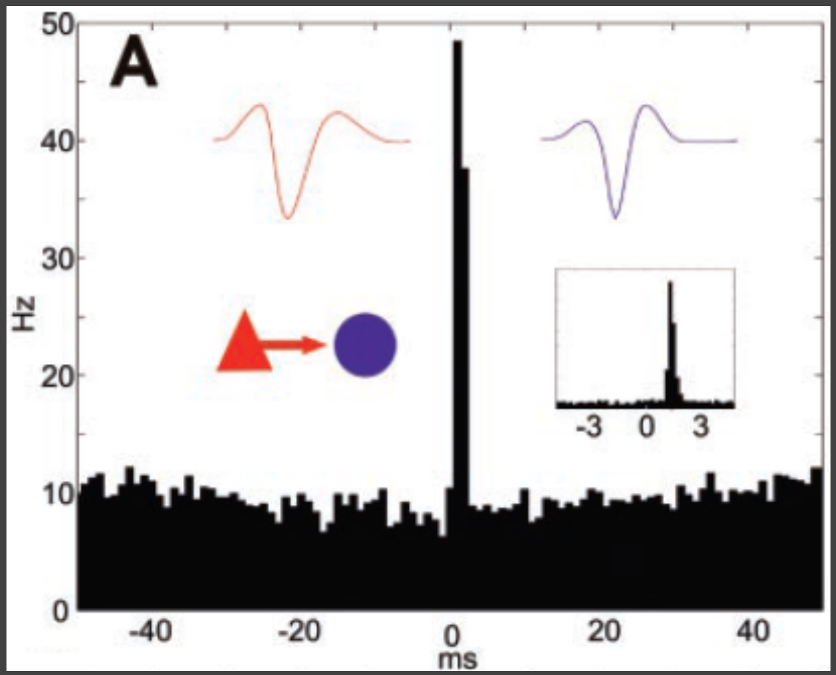


Excitatory connection
pyramidal => interneuron
(37/449)

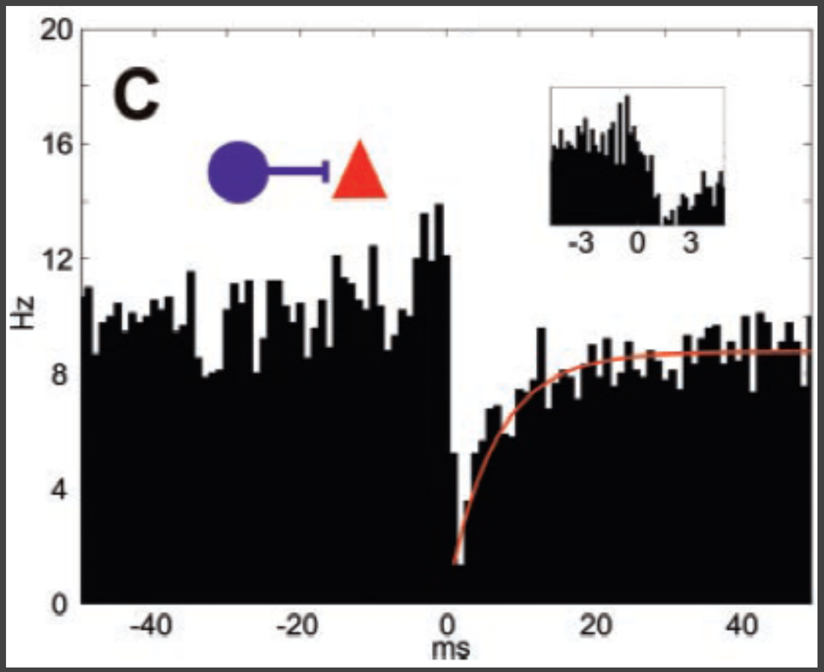
Csicsvari et al (1998), Neuron

Monosynaptic Identification from CCG

Prefontal cortex of the anesthetized rat
64-site 2-d silicone probe for high-density extracellular recording



Excitatory connection
pyramidal => interneuron
(58/56845)

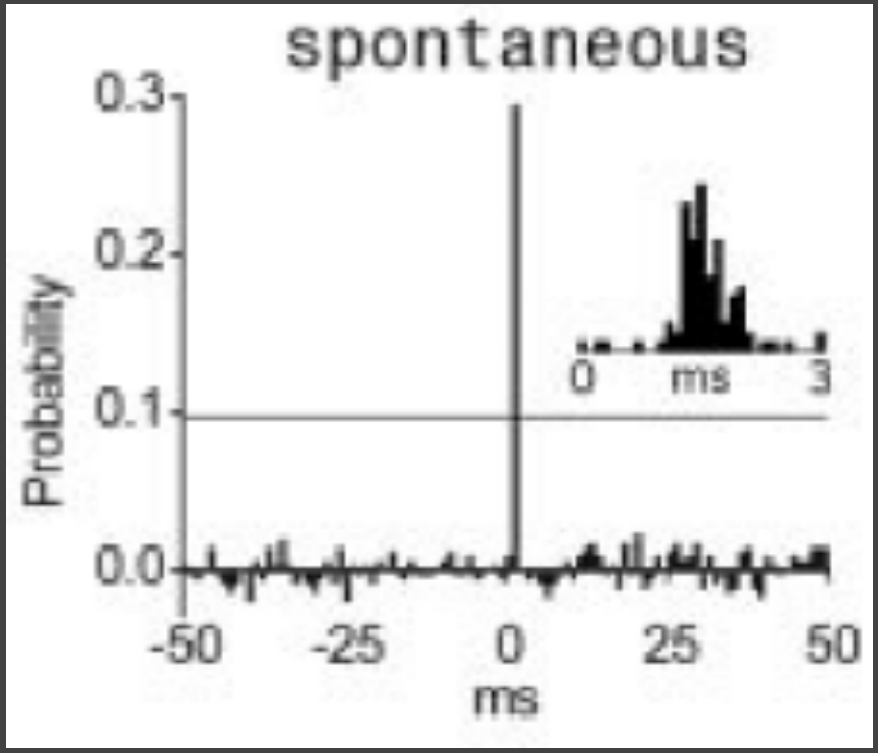


Inhibitory connection
interneuron => pyramidal
(21/56845)

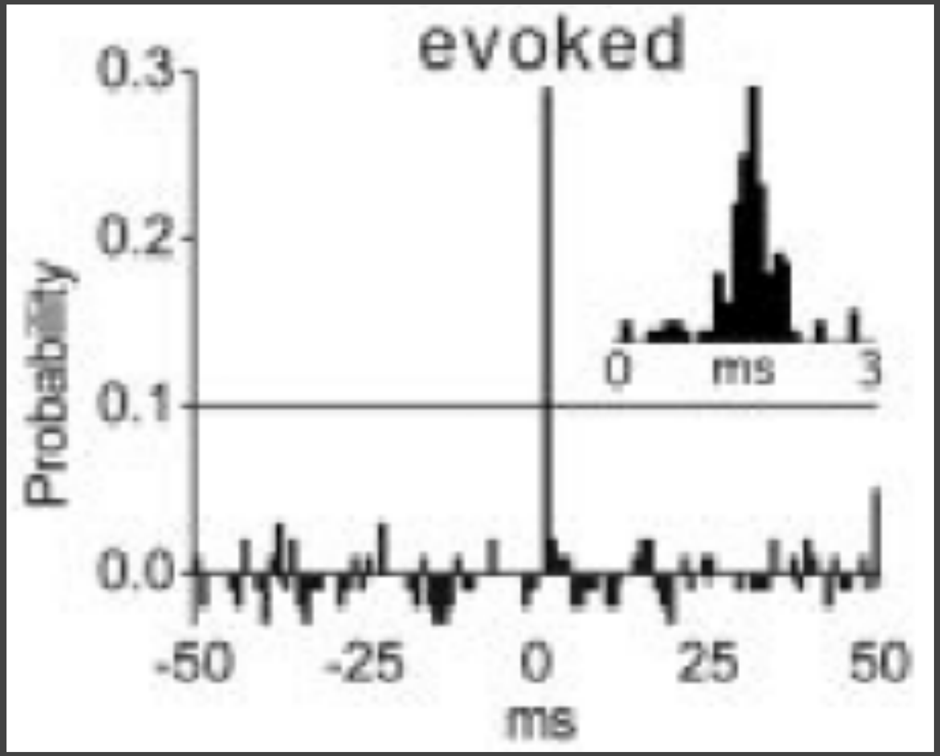
Barthó et al (2004), J Neurophysiol

Monosynaptic Identification from CCG

CA1 region of the hippocampus of the anesthetized rat
Paired extracellular-intracellular recording



Spontaneous presynaptic spikes
(pyramidal => interneuron)



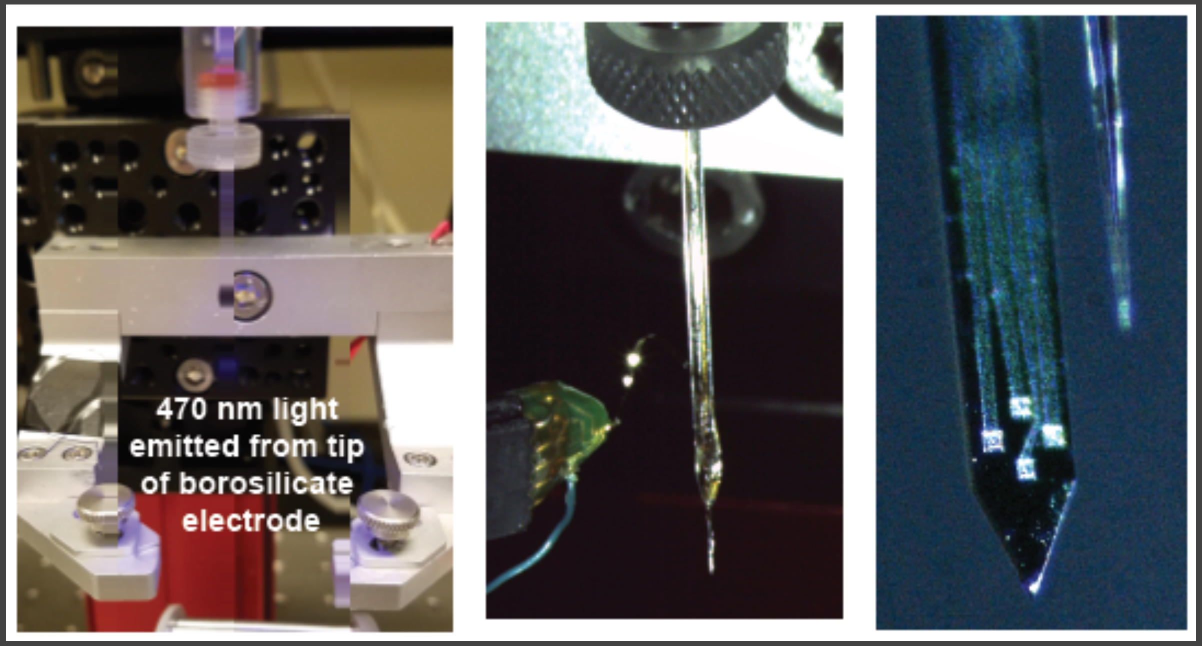
Intracellularly evoked presynaptic spikes

Similar synaptic transmission probability

Marshall et al (2002), J Neurosci

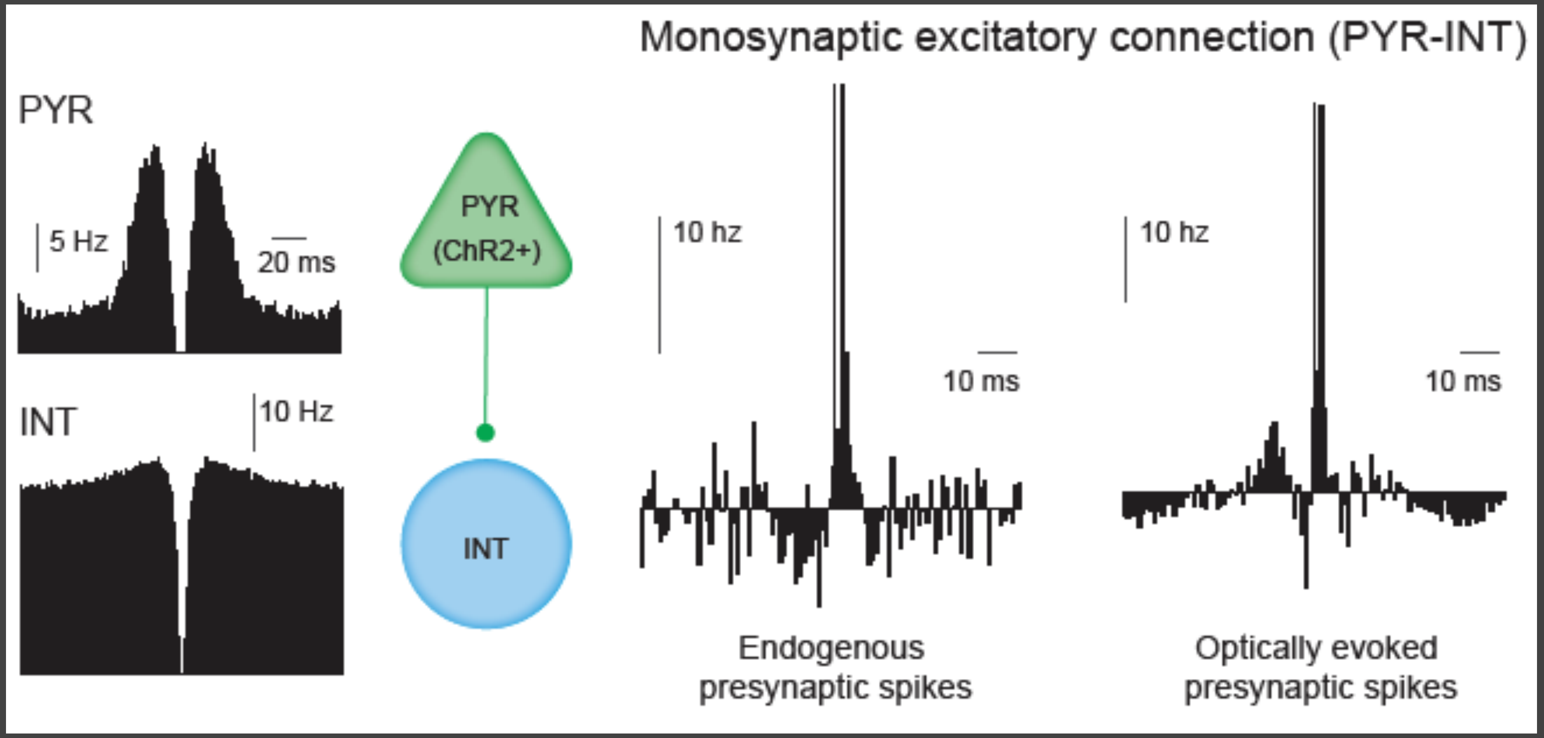
Monosynaptic Identification from CCG

Monosynaptic connection in hippocampus CA1
from pyramidal neuron to interneuron



uLED stimulation of CA1 pyramidal neurons in CaMKII:ChR2 transgenic mice (optogenetics)

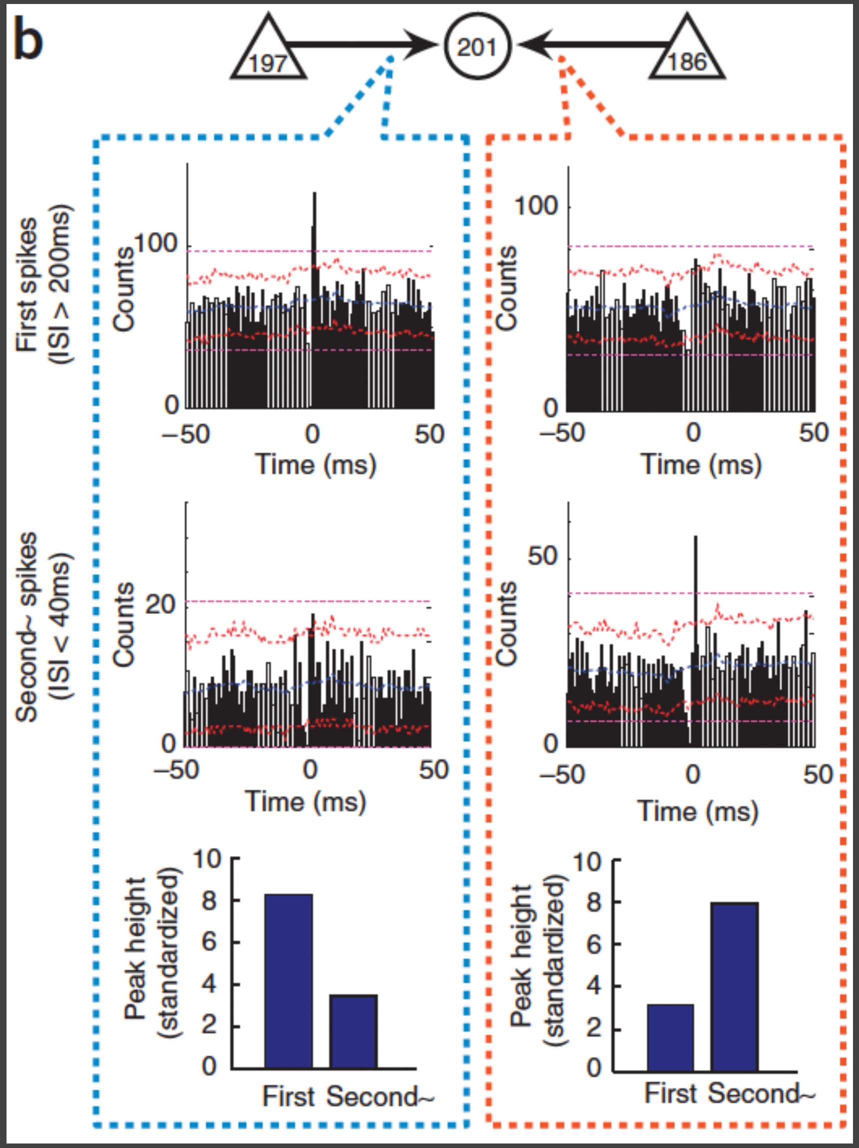
Spike recording in interneuron with silicon probe



English et al (2016), IPAN

Monosynaptic Identification from CCG

Medial prefrontal cortex of the behaving rat
Extracellular recording (64-site silicone probe)

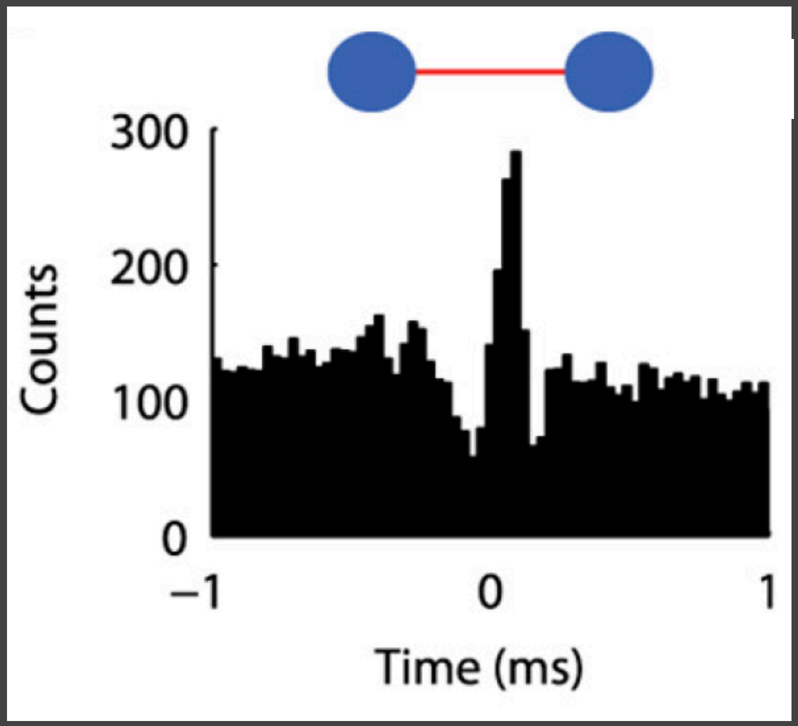


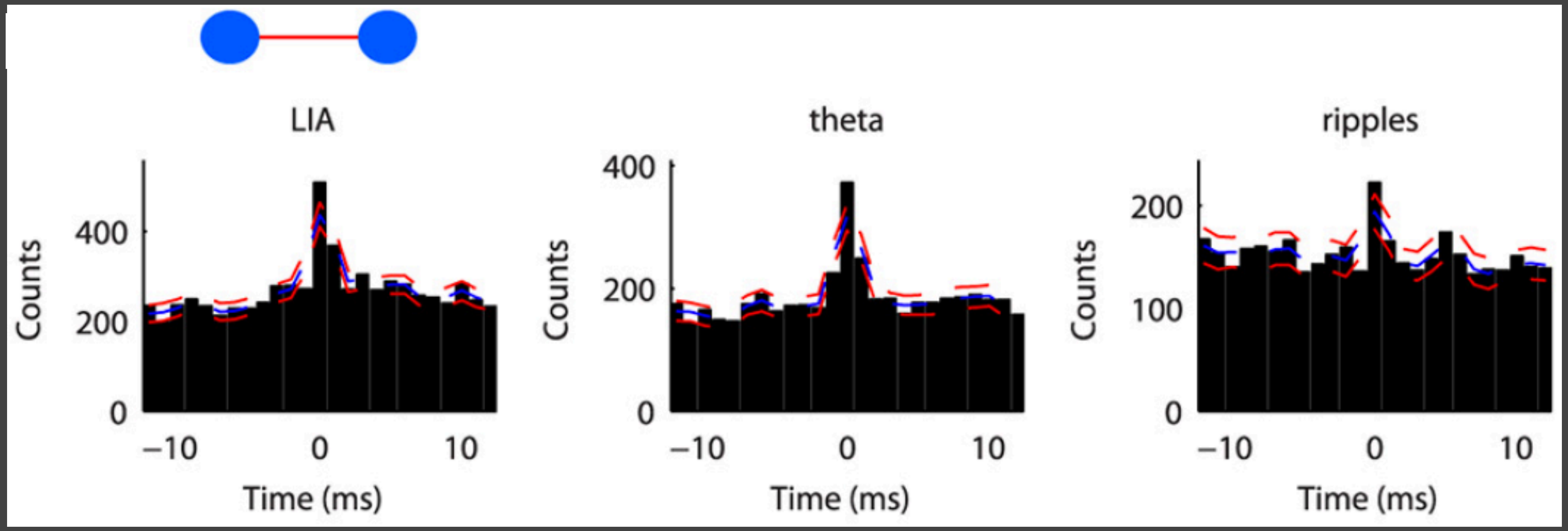
Putative spike transmission efficacy depends on the firing pattern of the presynaptic neuron

Fujisawa et al (2008), Nat Neurosci

Ultra Fine-Temporal Spike Correlation

CA1 and CA3 of the behaving rat
Extracellular recording (64-site silicone probe)





Submillisecond correlation

Precise correlation can be robust to network state

Diba et al (2014), J Neurosci

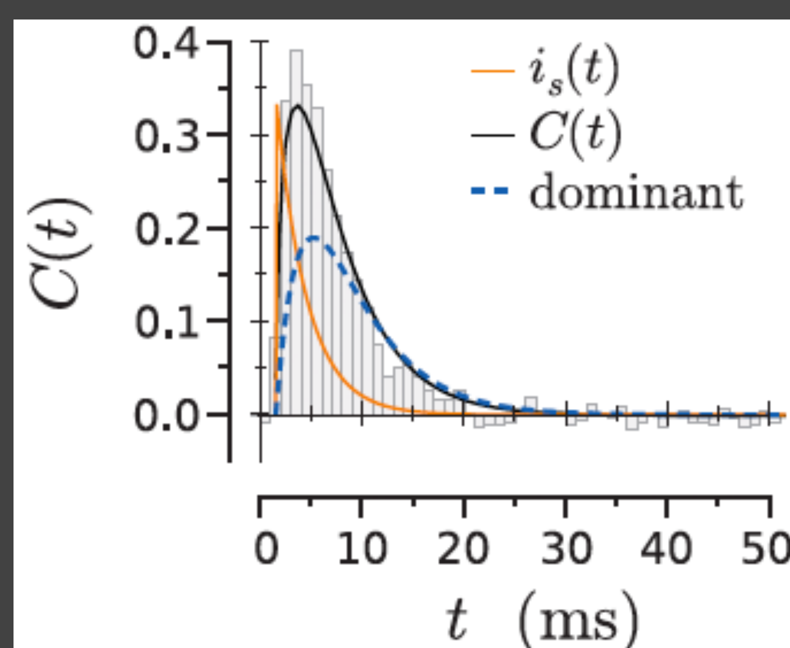
Modeling Study

10234 • The Journal of Neuroscience, August 19, 2009 • 29(33):10234–10253

Behavioral/Systems/Cognitive

How Connectivity, Background Activity, and Synaptic Properties Shape the Cross-Correlation between Spike Trains

Srdjan Ostojic,[1,2] Nicolas Brunel,[3] and Vincent Hakim[2]
[1]Institut des Systemes Complexes Paris Ile-de-France and [2]Laboratoire de Physique Statistique, Centre National de la Recherche Scientifique, Université Pierre et Marie Curie, Université Paris-Diderot, Ecole Normale Supérieure, 75005 Paris, France, and [3]Laboratoire de Neurophysique et Physiologie, Centre National de la Recherche Scientifique, Unité Mixte de Recherche 8119, Université Paris Descartes, 75006 Paris, France

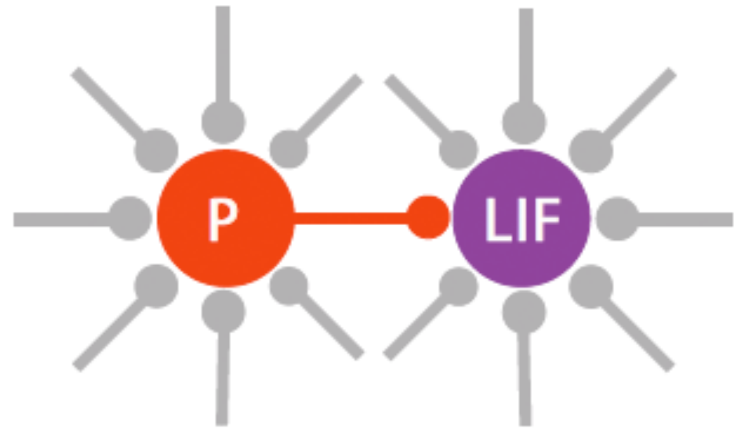


Cross-correlogram between Poisson and LIF neurons

Modeling Study

Excitatory synapse
Decay time constant = 3 ms

Poisson neuron



Leaky Integrate-and-Fire neuron
Membrane time constant : 10 ms
Refractory period: 0 ms

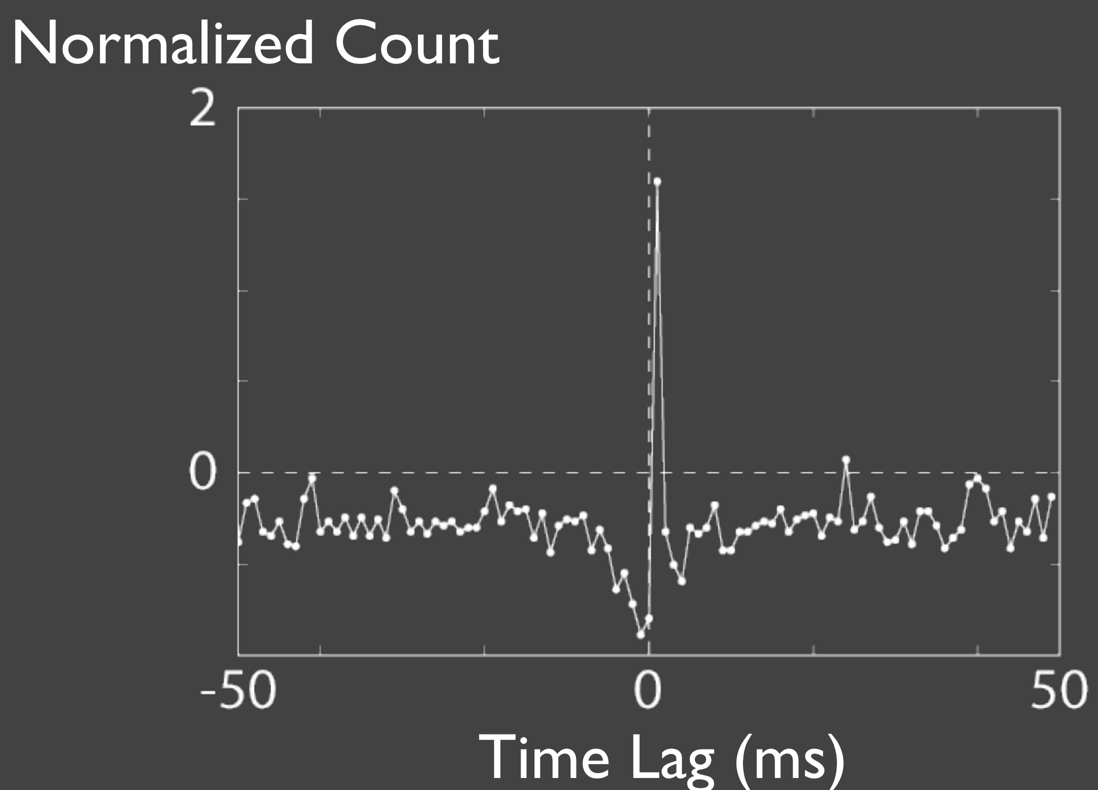
Background network synaptic input :
White noise (fast)

Ostojic, Brunel & Hakim (2009), J Neurosci

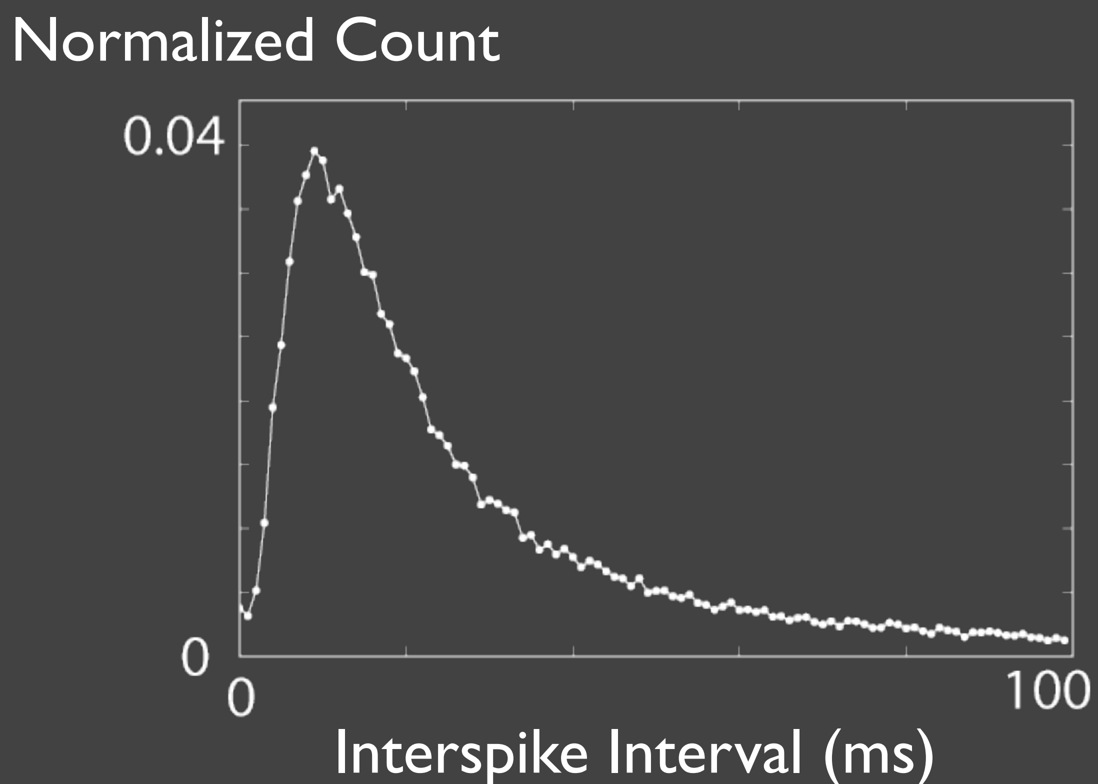
Constraints of the Model

Data

Ultra precise spike transmission



Gamma distribution



Shige's data (Fujisawa et al, 2008)

Constraints of the Model

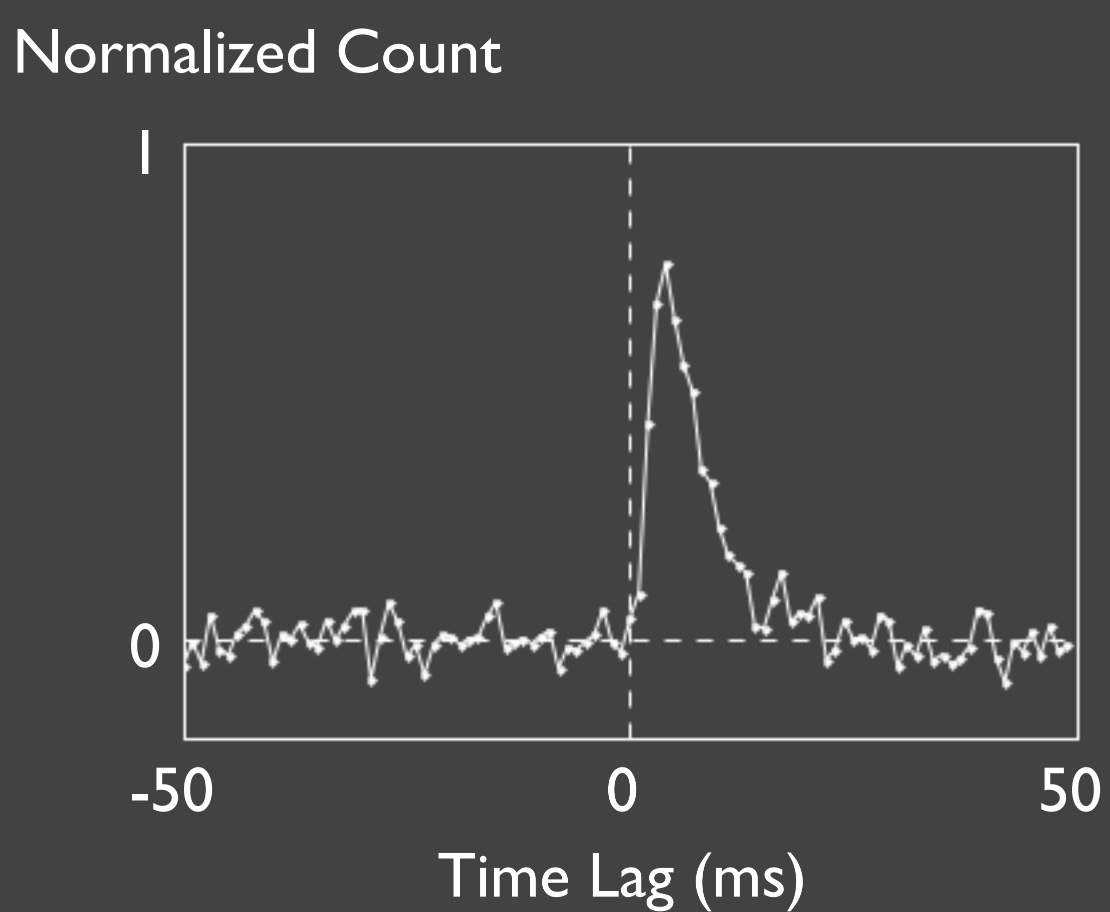
	Cell 1	Cell 2
Cell 1	Auto-Correlogram$_1$	Cross-Correlogram$_{12}$
Cell 2	Cross-Correlogram$_{12}$	Auto-Correlogram$_2$

Cell 1 : Presynaptic
Cell 2 : Postsynaptic

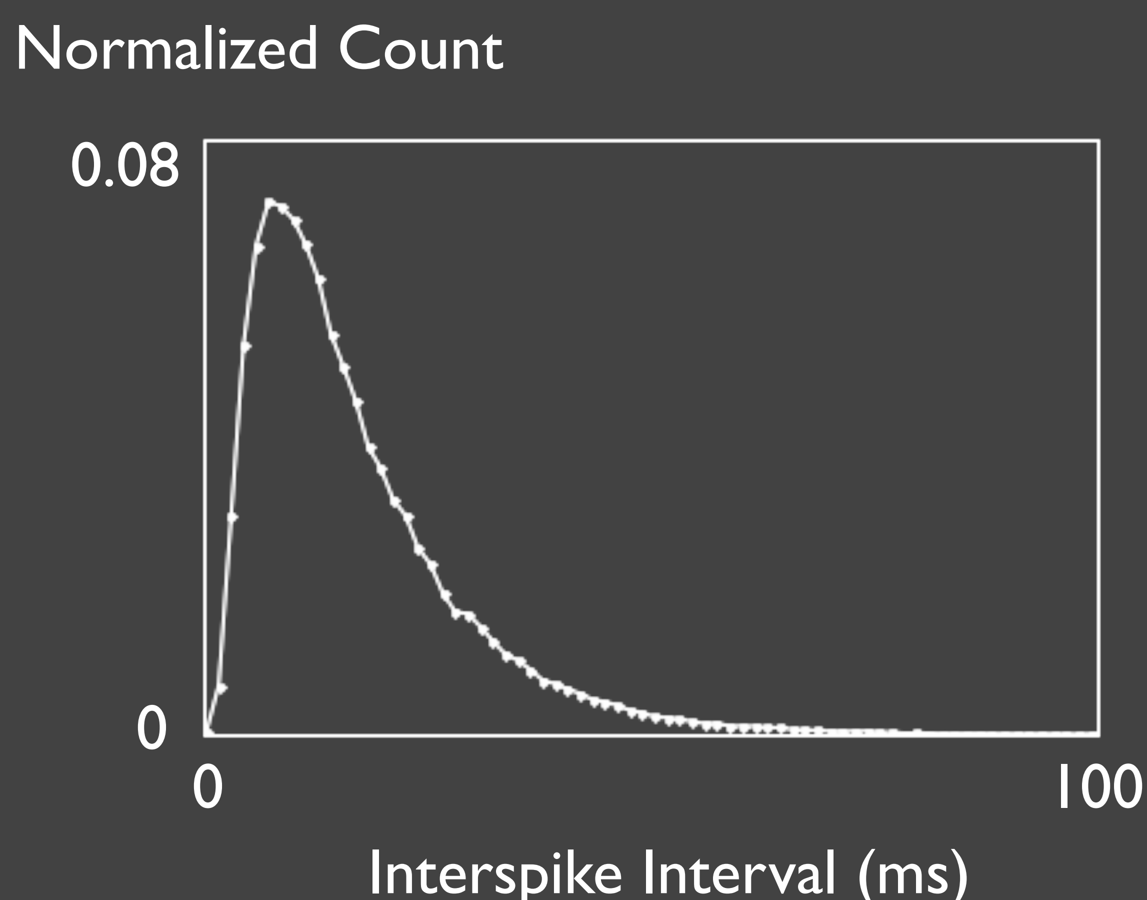
Unsatisfactory Fit

Model

Not ultra-precise spike transmission



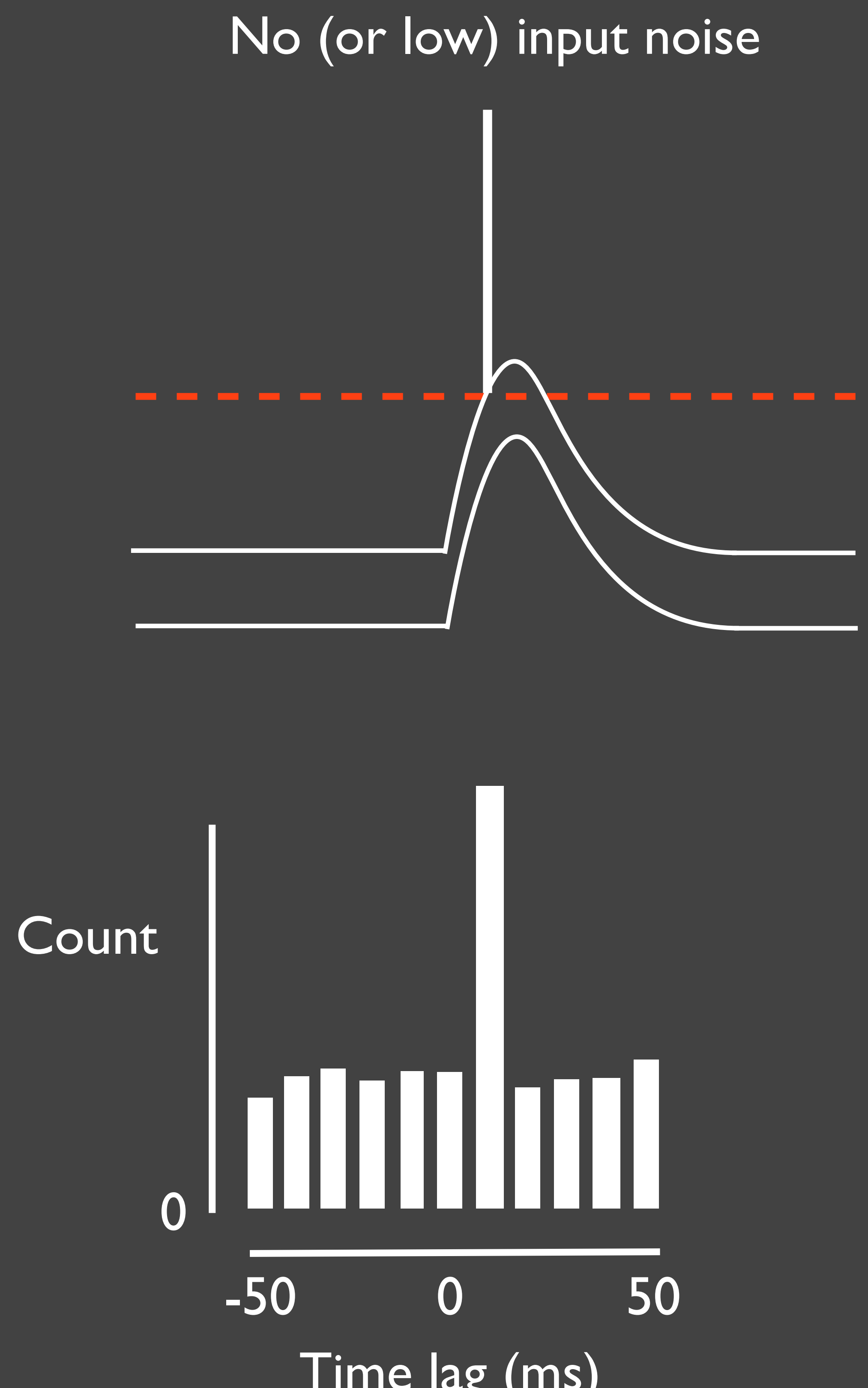
Gamma distribution



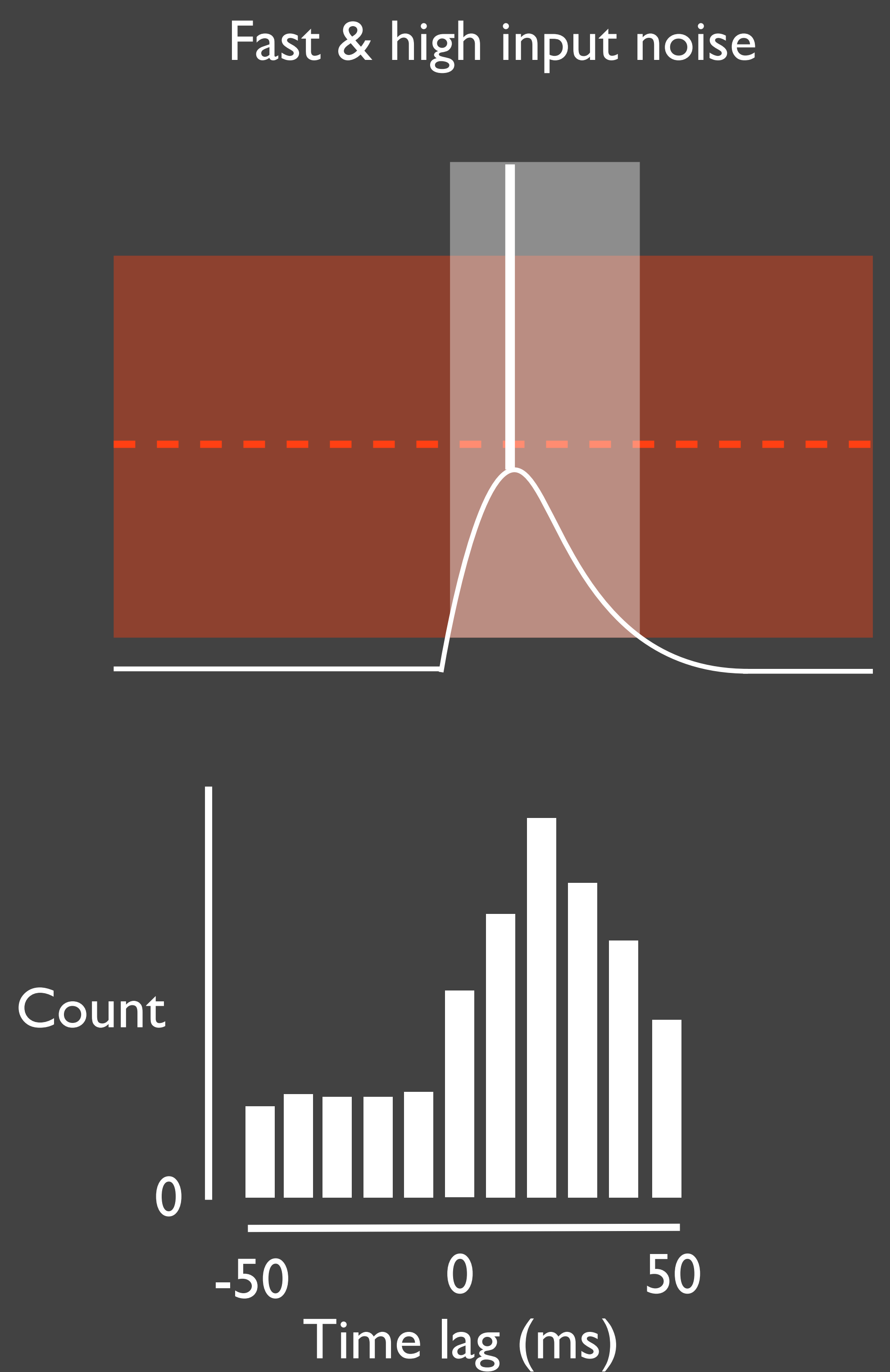
Ostojic, Brunel & Hakim (2009), J Neurosci
Ostojic (2011), J Neurophysiol

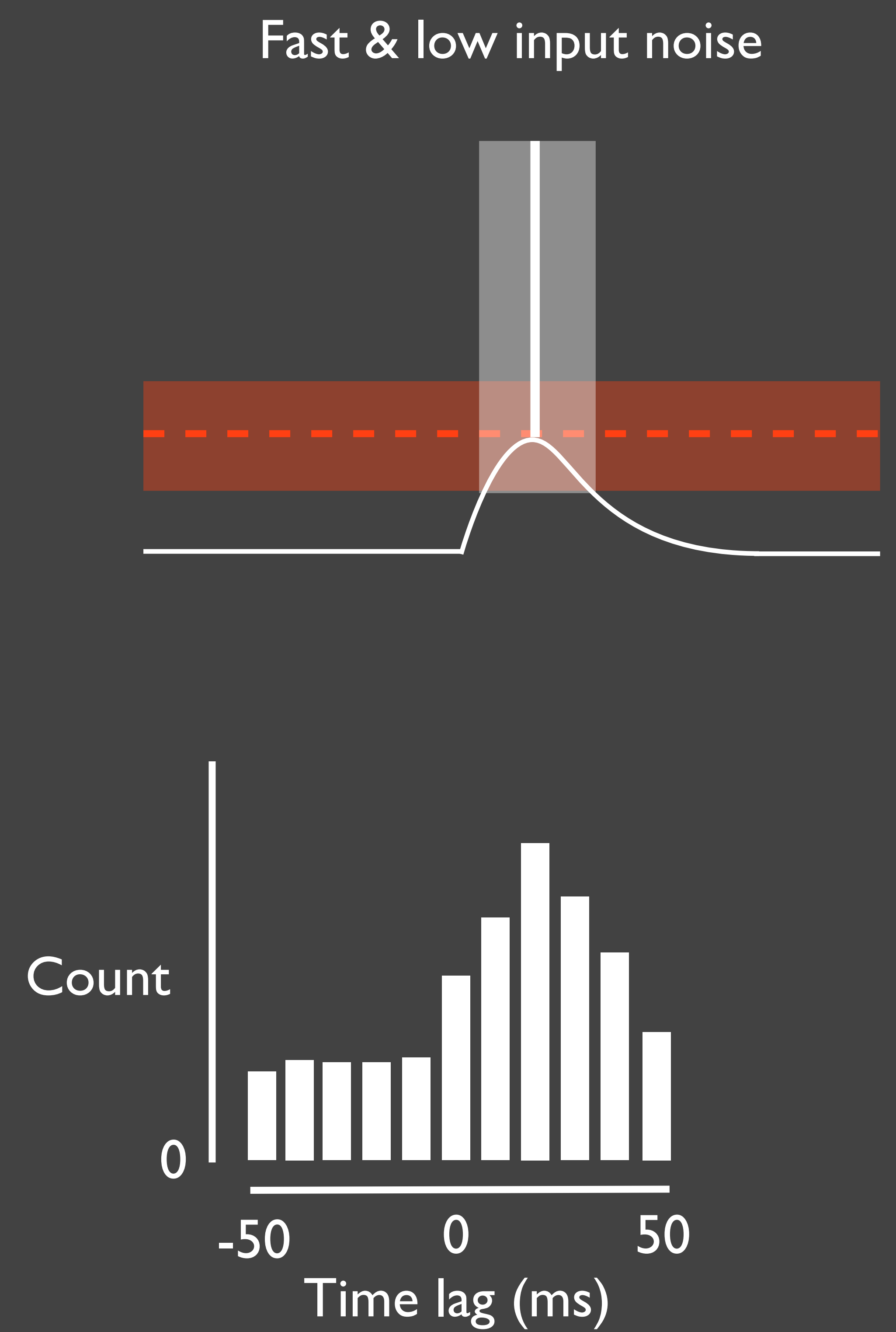
2. A Biophysical Model of Ultra Precise Spike Transmission

A Feel for the Problem

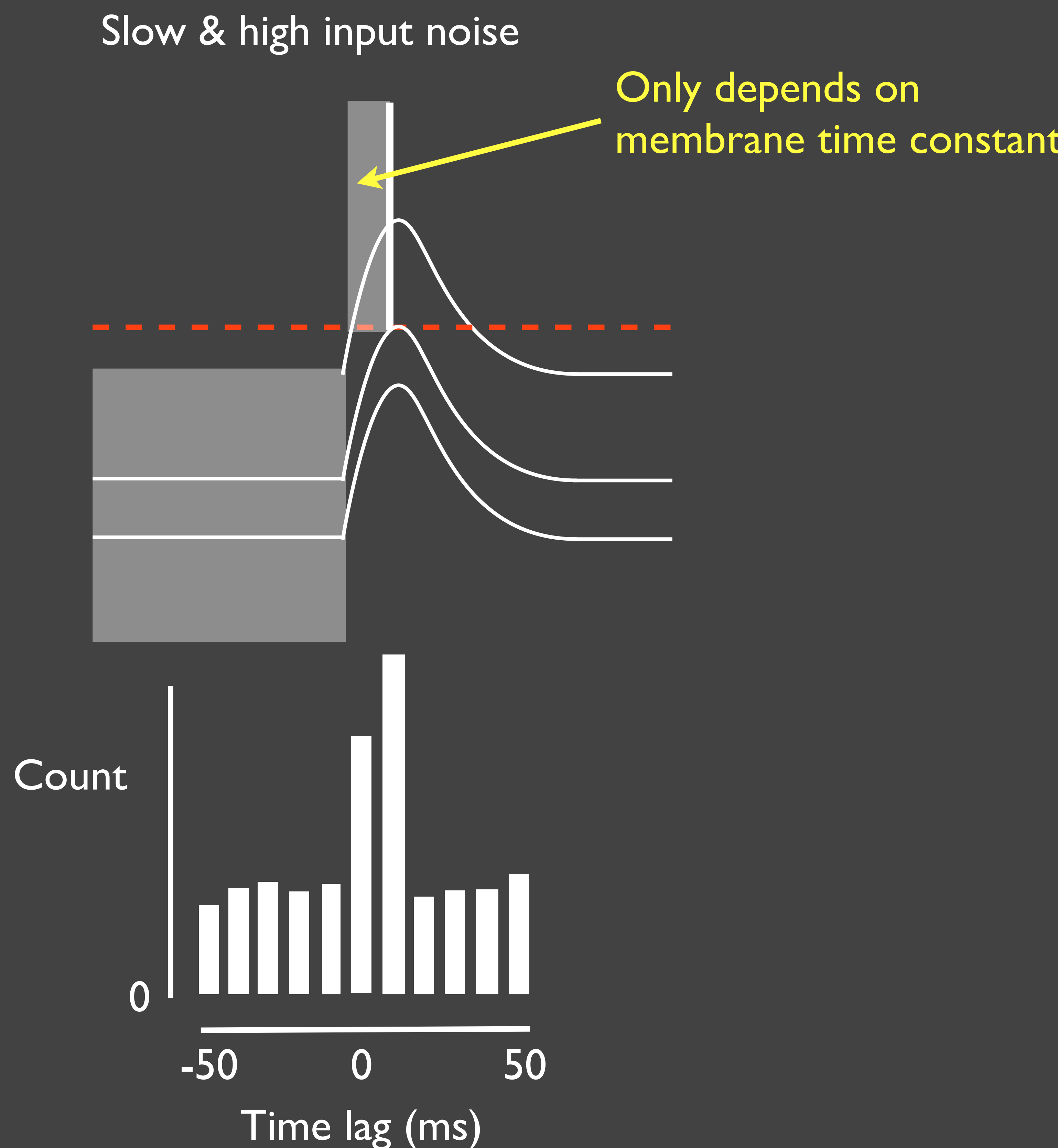


A Feel for the Problem





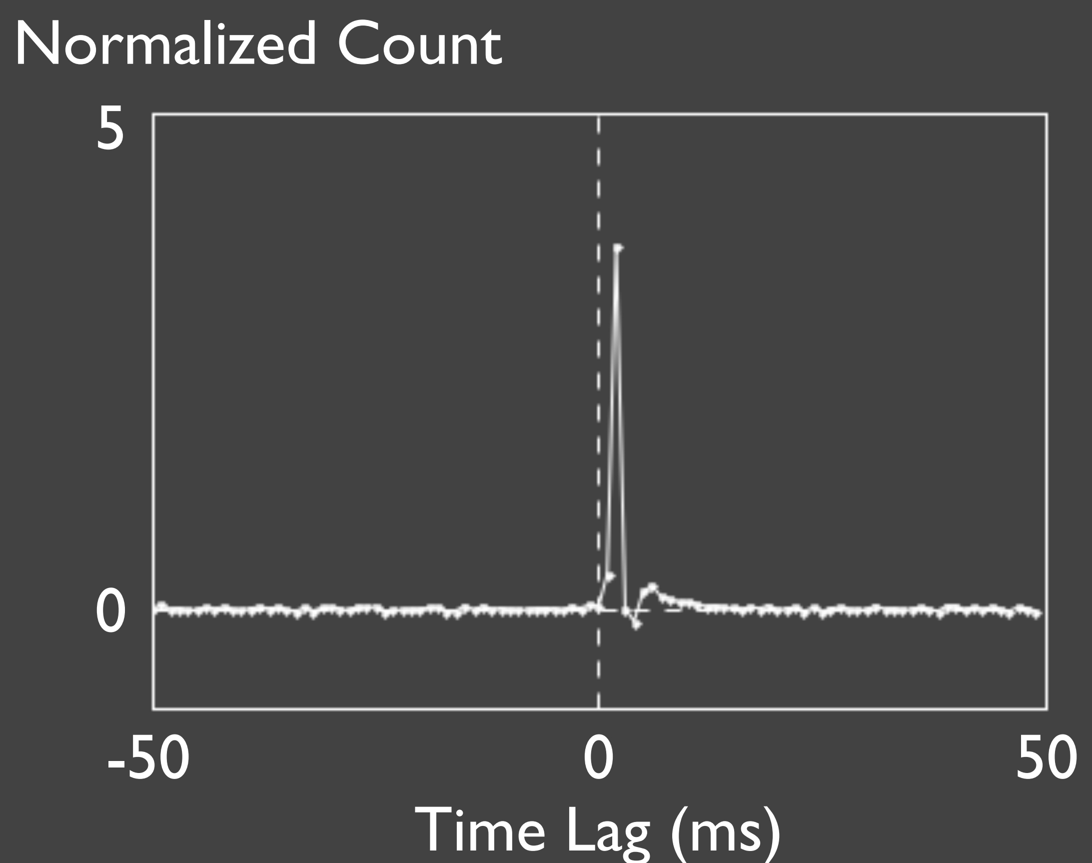
A Feel for the Problem



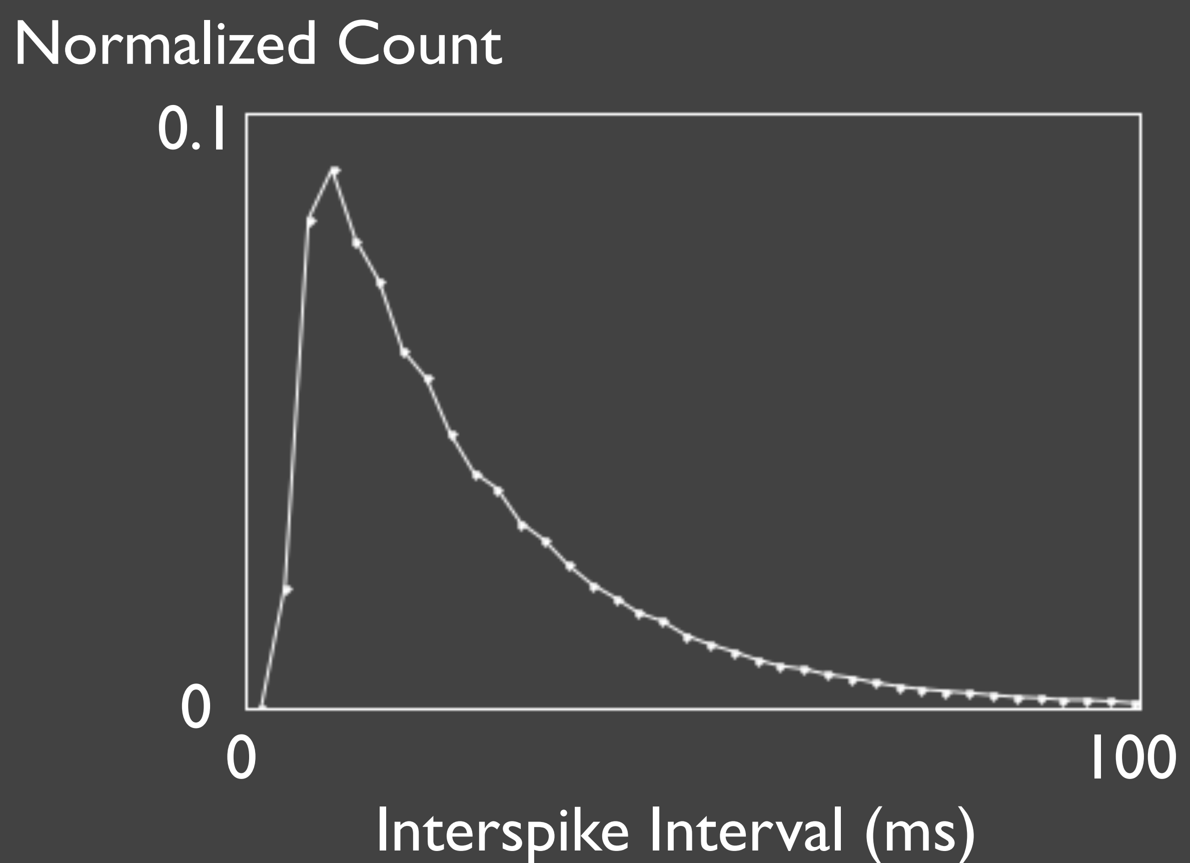
Low Input Variability at Spike Initiation Timescale Meets the Constraints

Model

Ultra-precise spike transmission



Gamma-like distribution

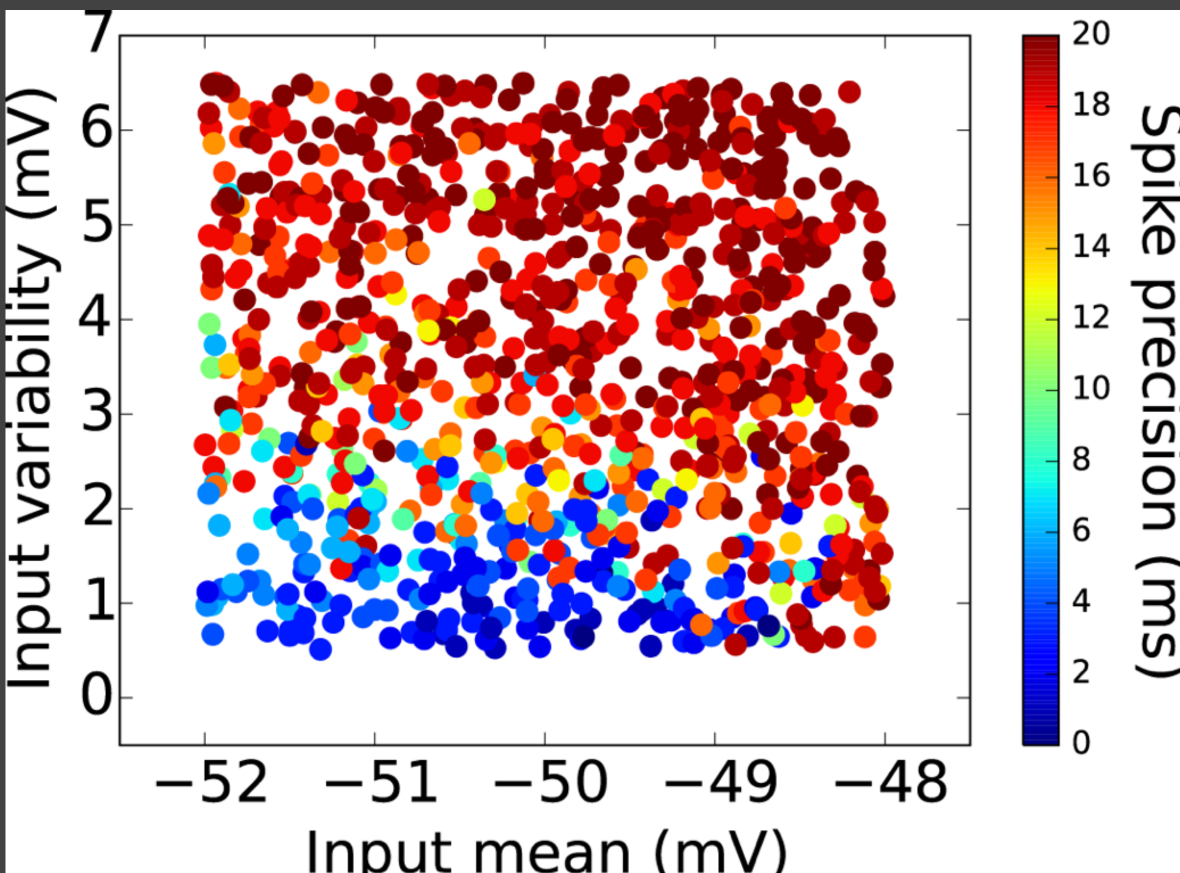


Platkiewicz, Watson, Buzsáki & Amarasingham (in prep)

Low Input Variability at Spike Initiation Timescale Meets the Constraints

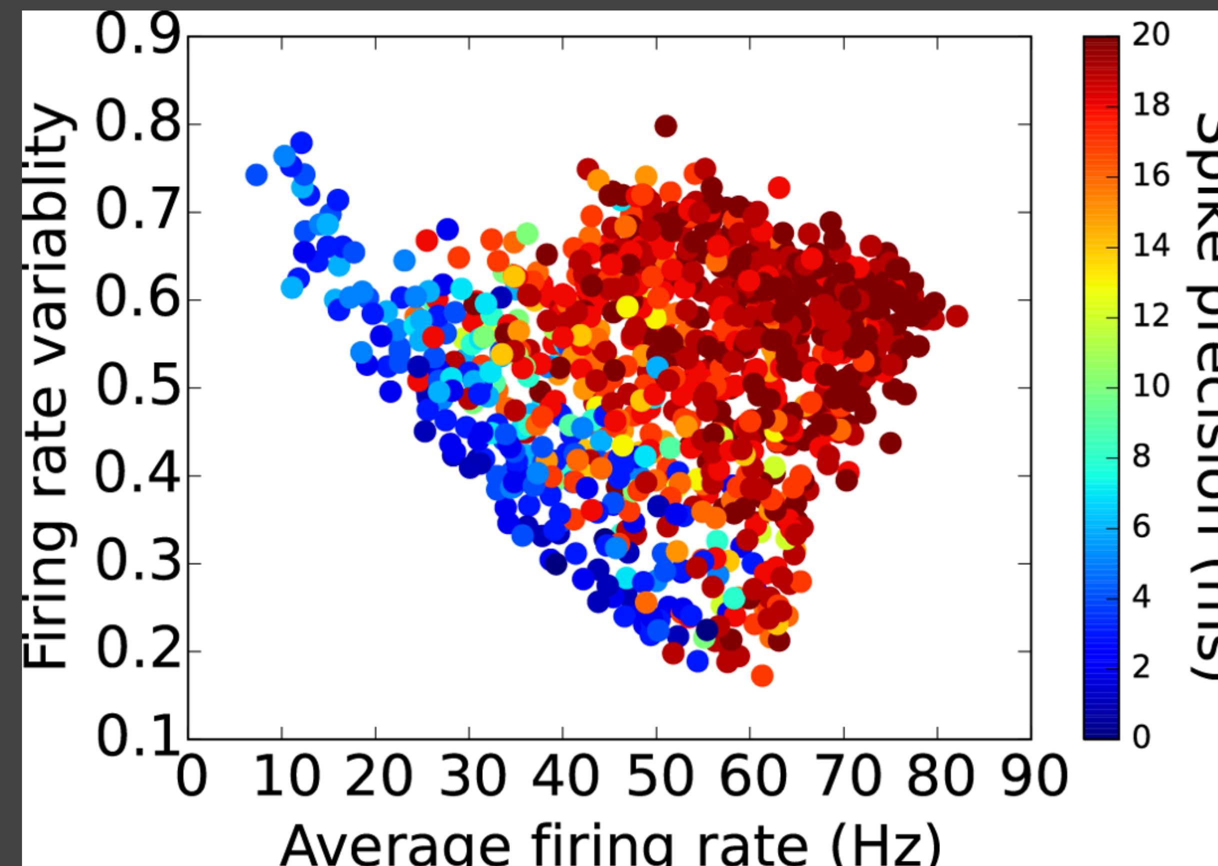
Model

Standard-deviation

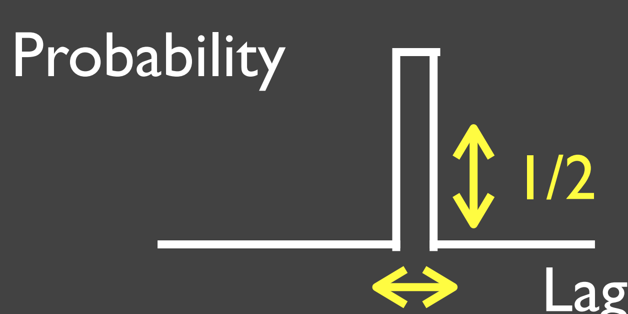


Mapping onto statistical input parameters

CV = Standard-deviation/mean



Mapping onto statistical output parameters

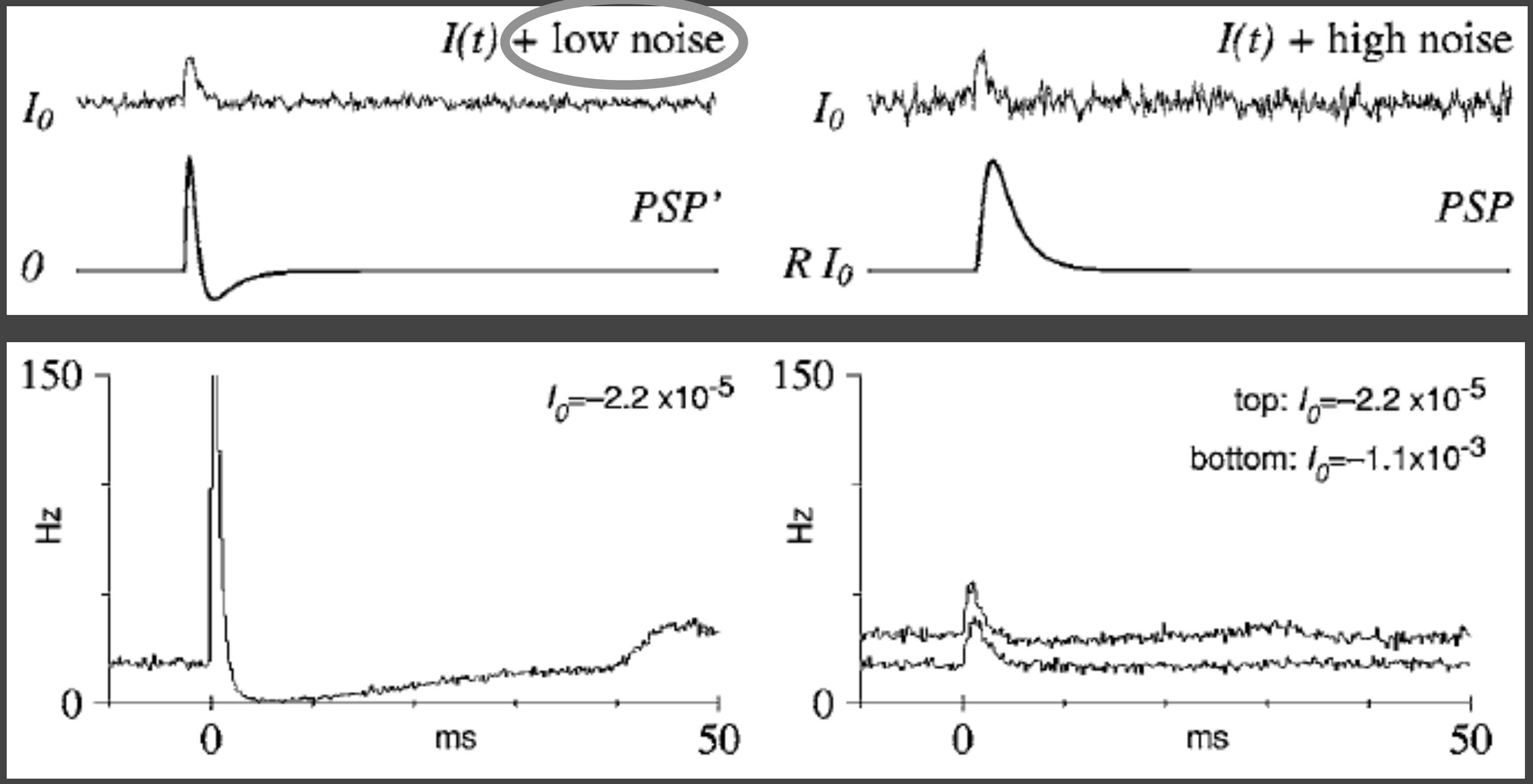


Spike precision

Platkiewicz, Watson, Buzsáki & Amarasingham (in prep)

Stochastic Phenomenon: Instantaneous Response to PSP Derivative

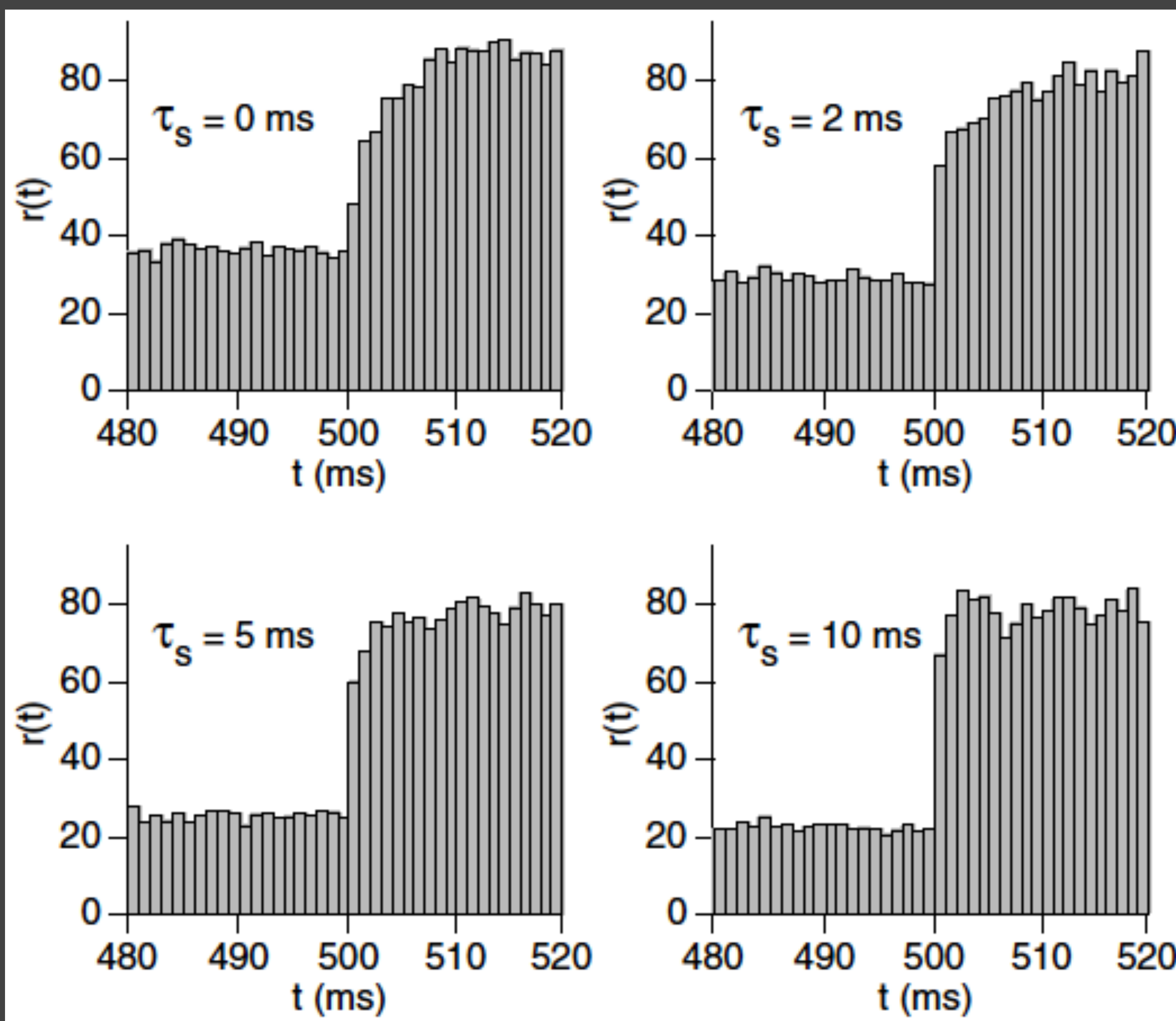
Response of a Leaky Integrate-and-Fire neuron
driven by white noise to a synaptic input



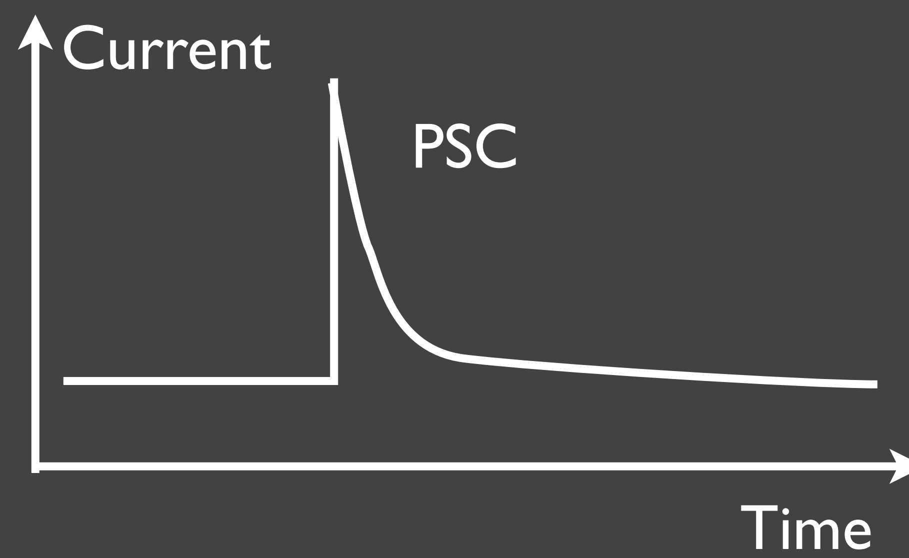
Herrmann & Gerstner (2001, 2002), J Comput Neurosci
Fetz & Gustafsson (1983), J Physiol

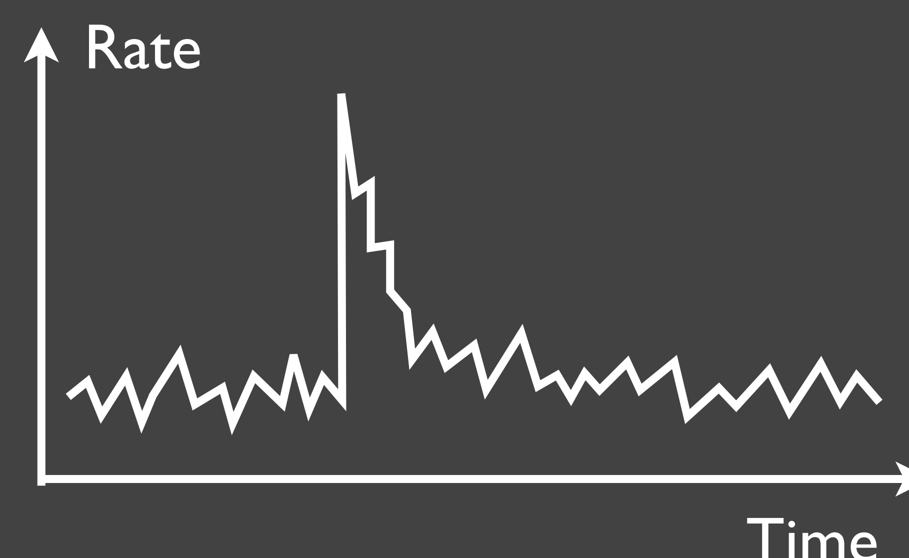
Stochastic Phenomenon: Instantaneous Response to Input Transient

Response of a Leaky Integrate-and-Fire neuron driven by colored noise to a step



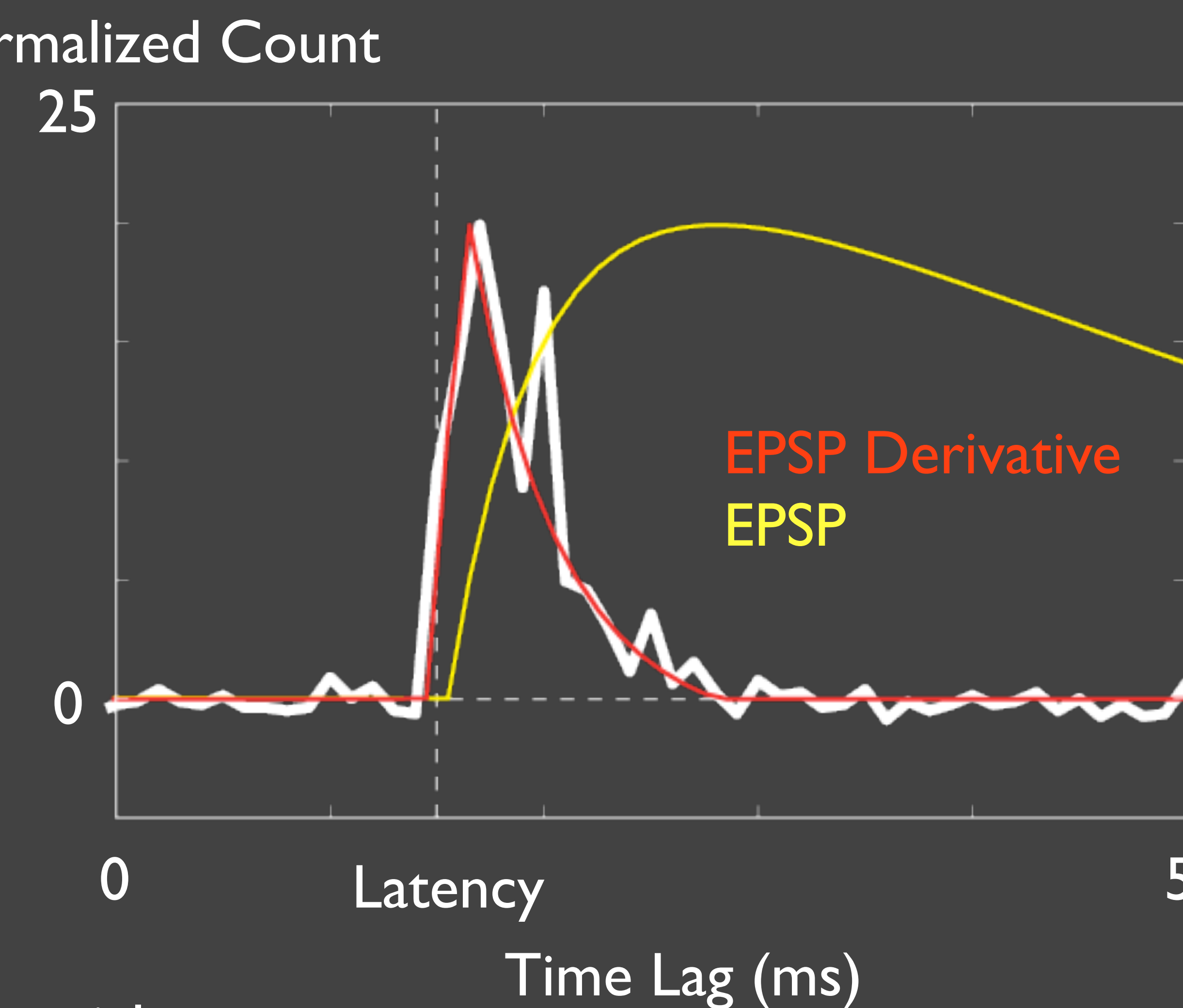
τ_m = 10 ms
τ_s : Synaptic timescale
r : Firing rate
t : Time





Brunel, Chance, Fourcaud & Abbott (2001), PRL
Tchumatchenko, Malyshev, Wolf, Volgushev (2011), J Neurosci

Escape Noise Model



Cross-Correlogram

Escape function

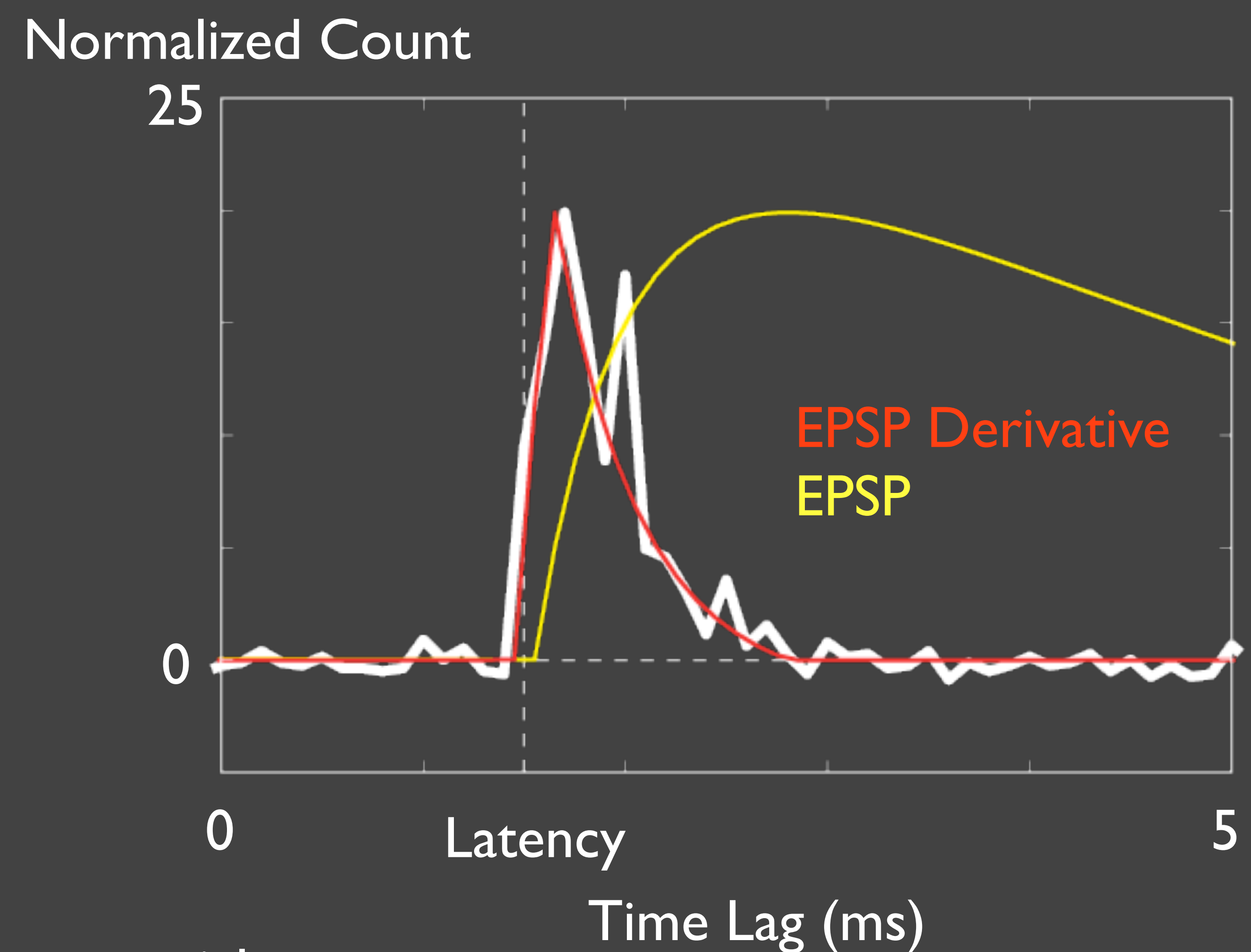
Spike-triggered average membrane potential

Postsynaptic potential

$$\mathrm{CCG} \approx F\left(V_m + PSP, \frac{d}{dt}[V_m + PSP]\right)$$

Platkiewicz, Watson, Buzsáki & Amarasingham (in prep)

Escape Noise Model



Cross-Correlogram

Escape function

Spike-triggered average membrane potential

Postsynaptic potential

$$\mathrm{CCG} \approx F\big(V_m + PSP, \frac{d}{dt}[V_m + PSP]\big)$$

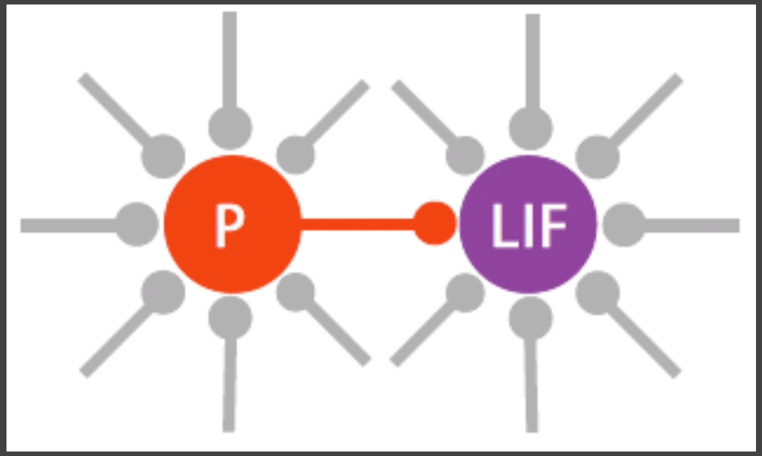
$$\mathrm{CCG} \approx F\big(V_m, \dot{V}_m\big) + \partial_x F(V_m, \dot{V}_m) \cdot PSP + \partial_y F(V_m, \dot{V}_m) \cdot \frac{d}{dt} PSP$$

Platkiewicz, Watson, Buzsáki & Amarasingham (in prep)

Low Input Variability at Spike Initiation Timescale Meets the Constraints

Excitatory synapse
Decay time constant = 3 ms

Poisson neuron



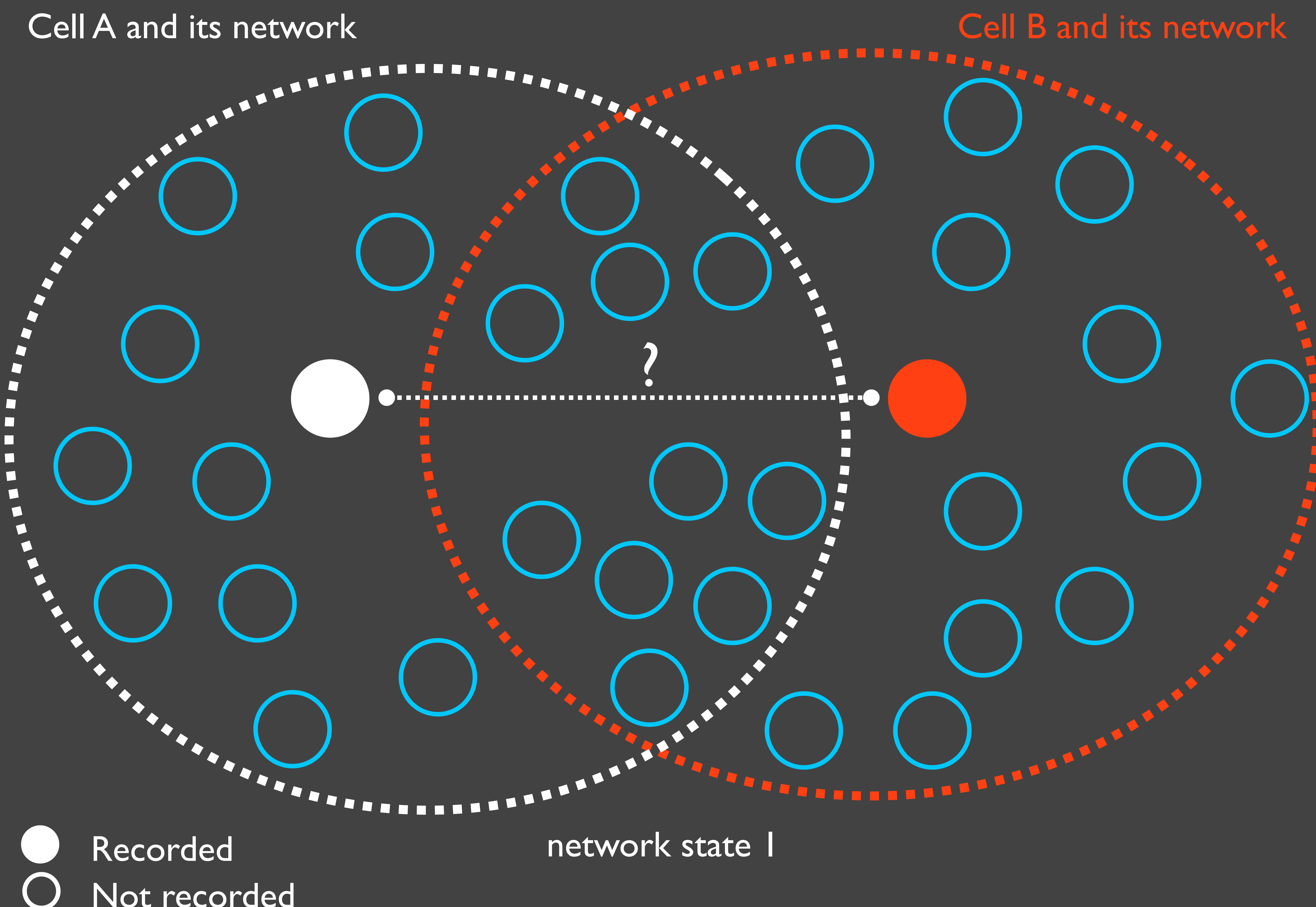
Leaky Integrate-and-Fire neuron
Membrane time constant : 10 ms
Refractory period: 0 ms

Background network synaptic input :
fast noise with low variability
or slow noise

Platkiewicz, Watson, Buzsáki & Amarasingham (in prep)

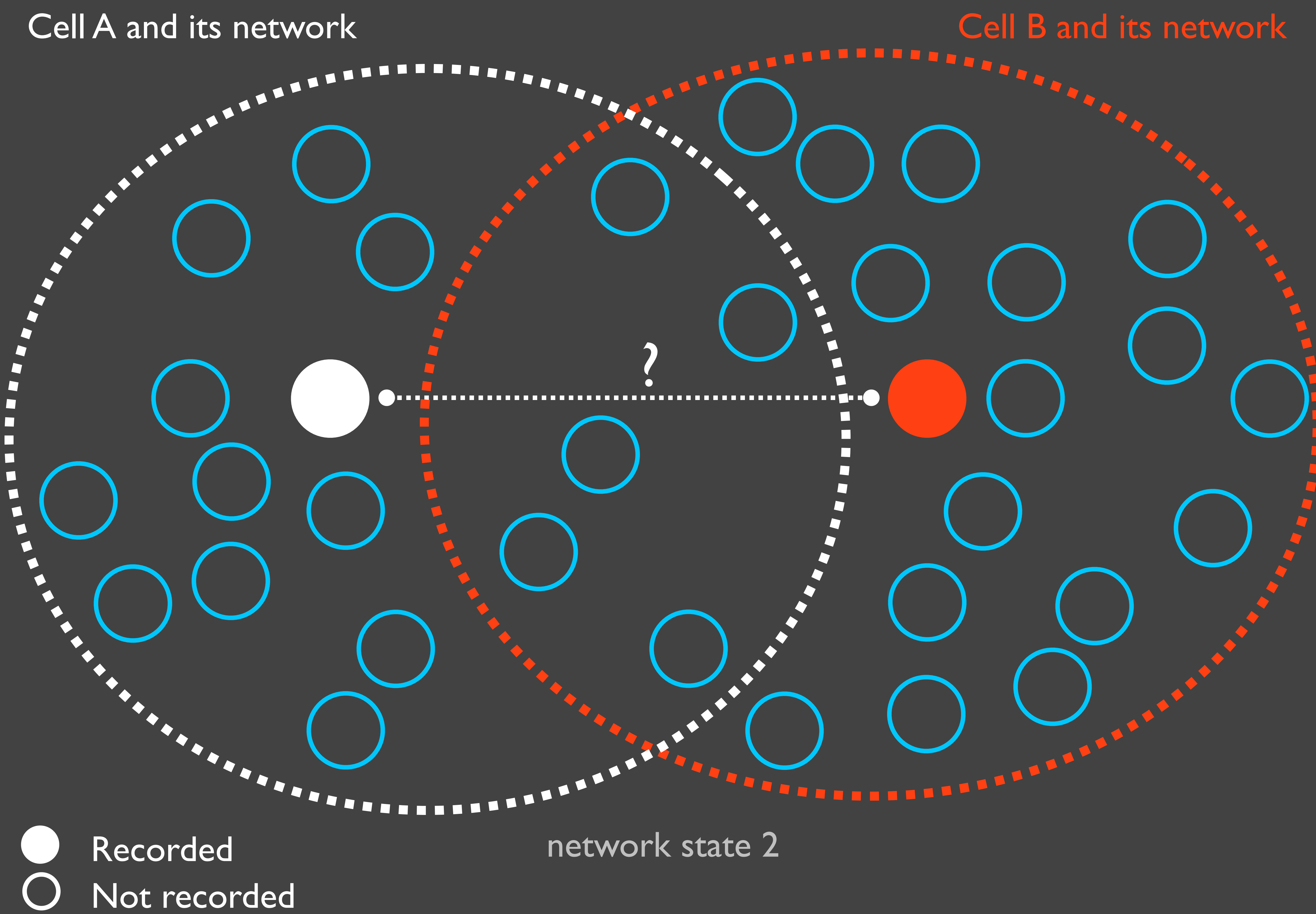
4. Nonparametric Statistics Synthesizes Biophysics

The Jitter Idea



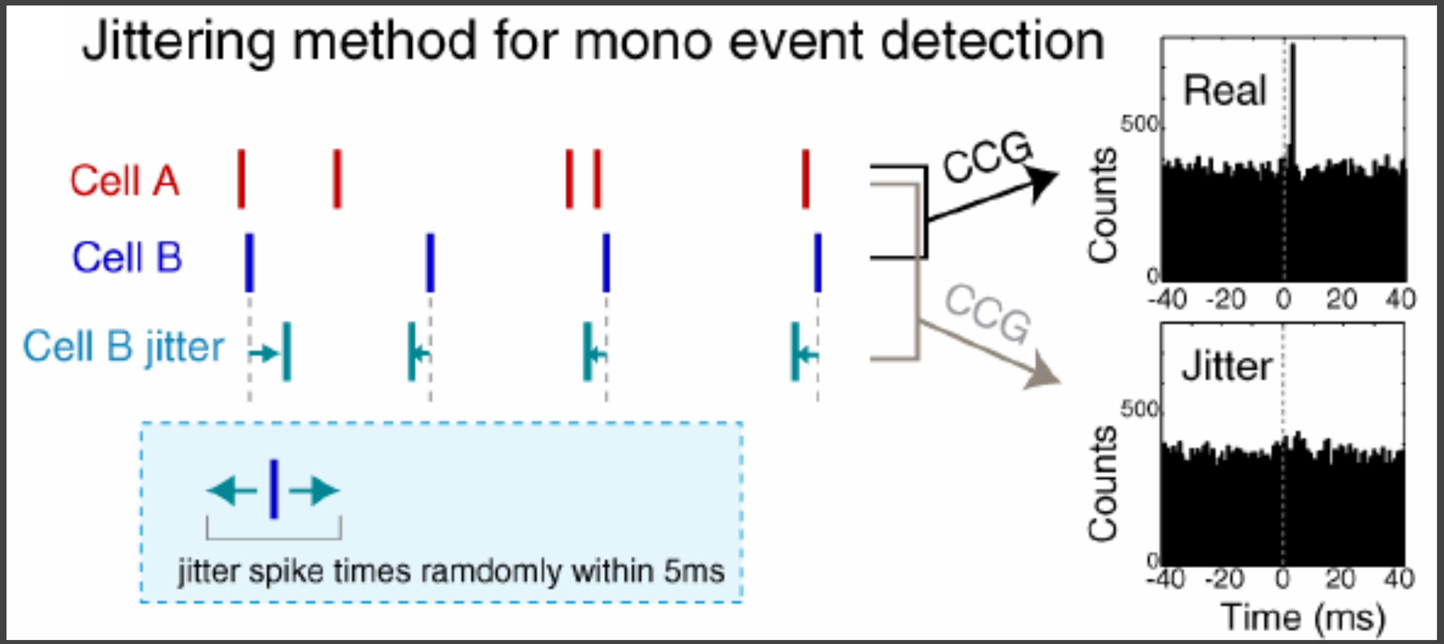
network state 1

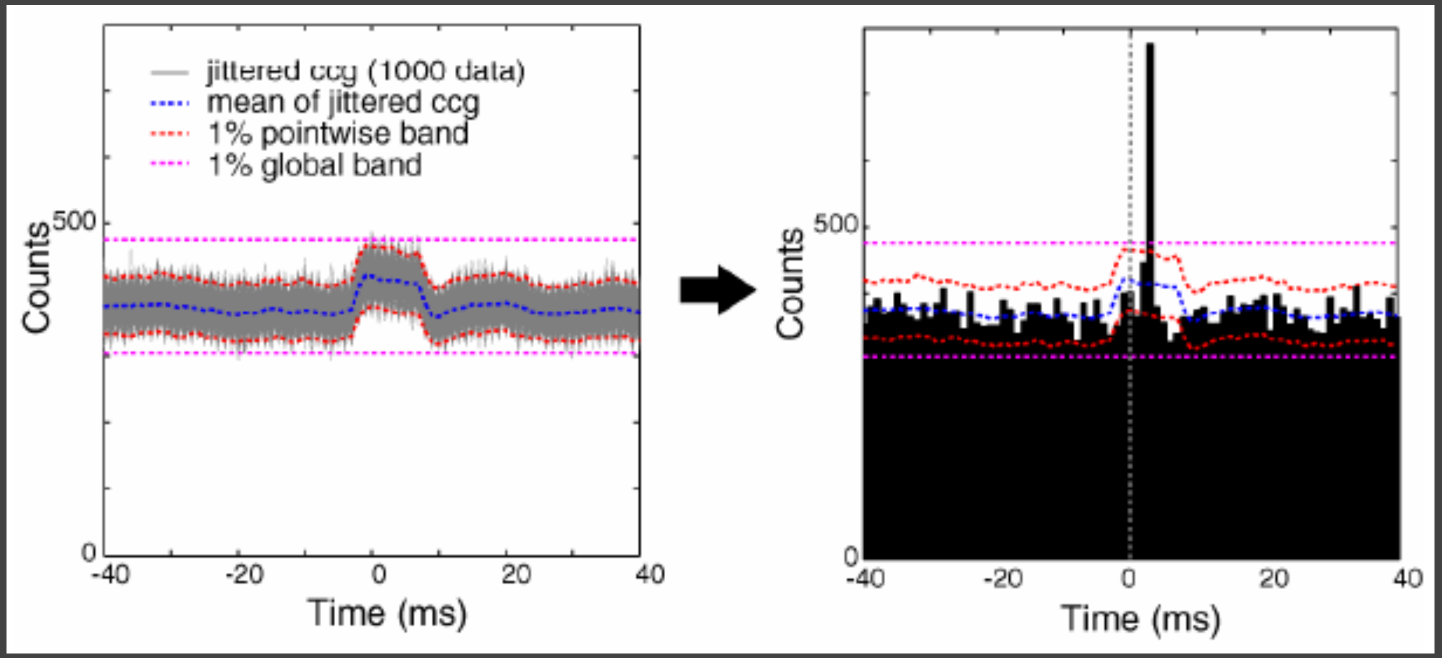
The Jitter Idea



Connectivity Inference and Estimation

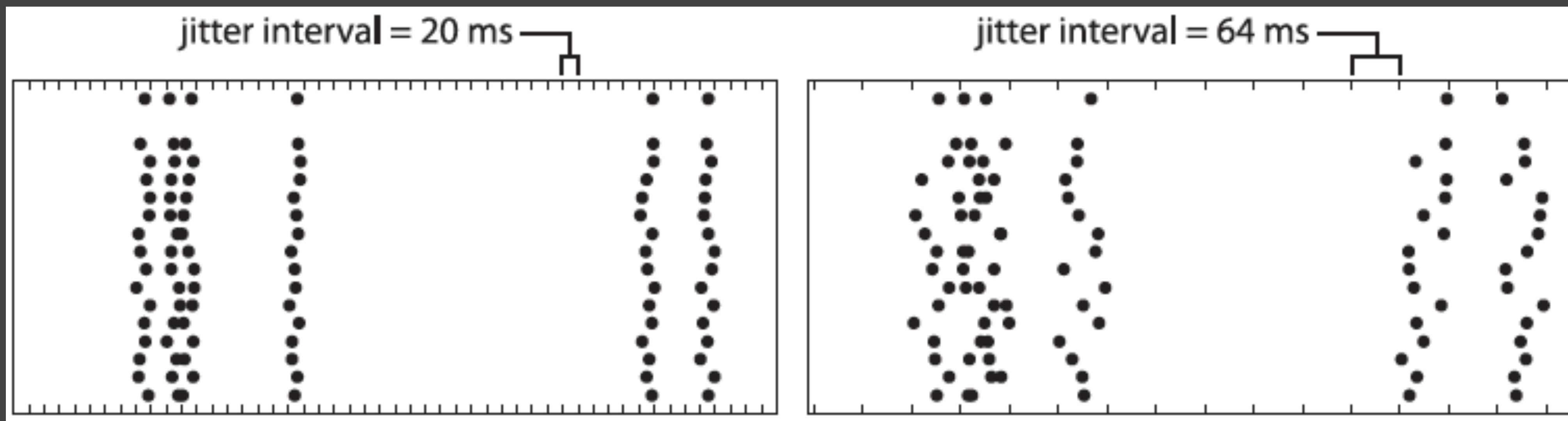
Monosynapse : pair that show excess co-firing at short-latencies
(compared to the jitter baseline)

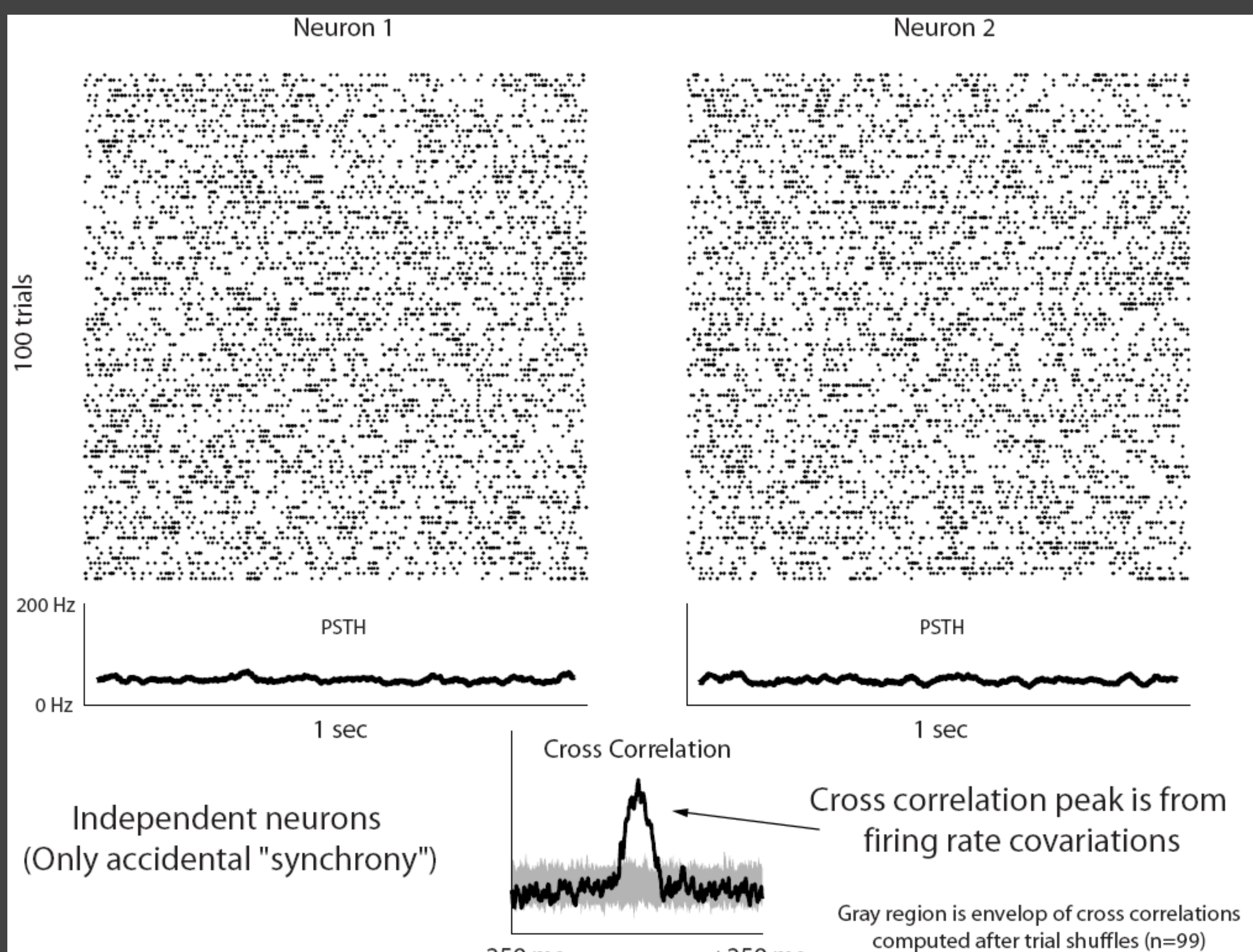




Fujisawa et al (2008), Nat Neurosci
Amarasingham et al (2012), J Neurophysiol

Connectivity Inference and Estimation





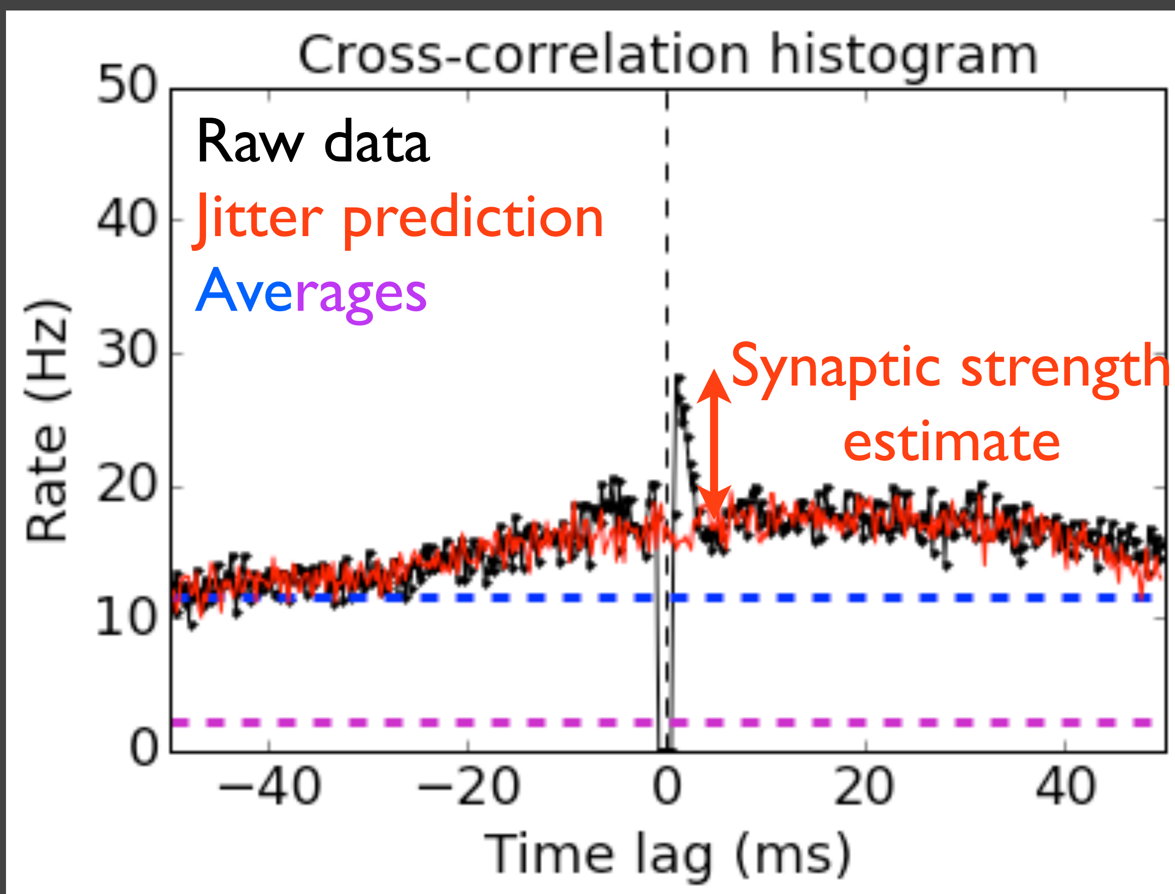
The jitter method tests the null hypothesis that the (co-)firing rate is modulated at a given timescale.

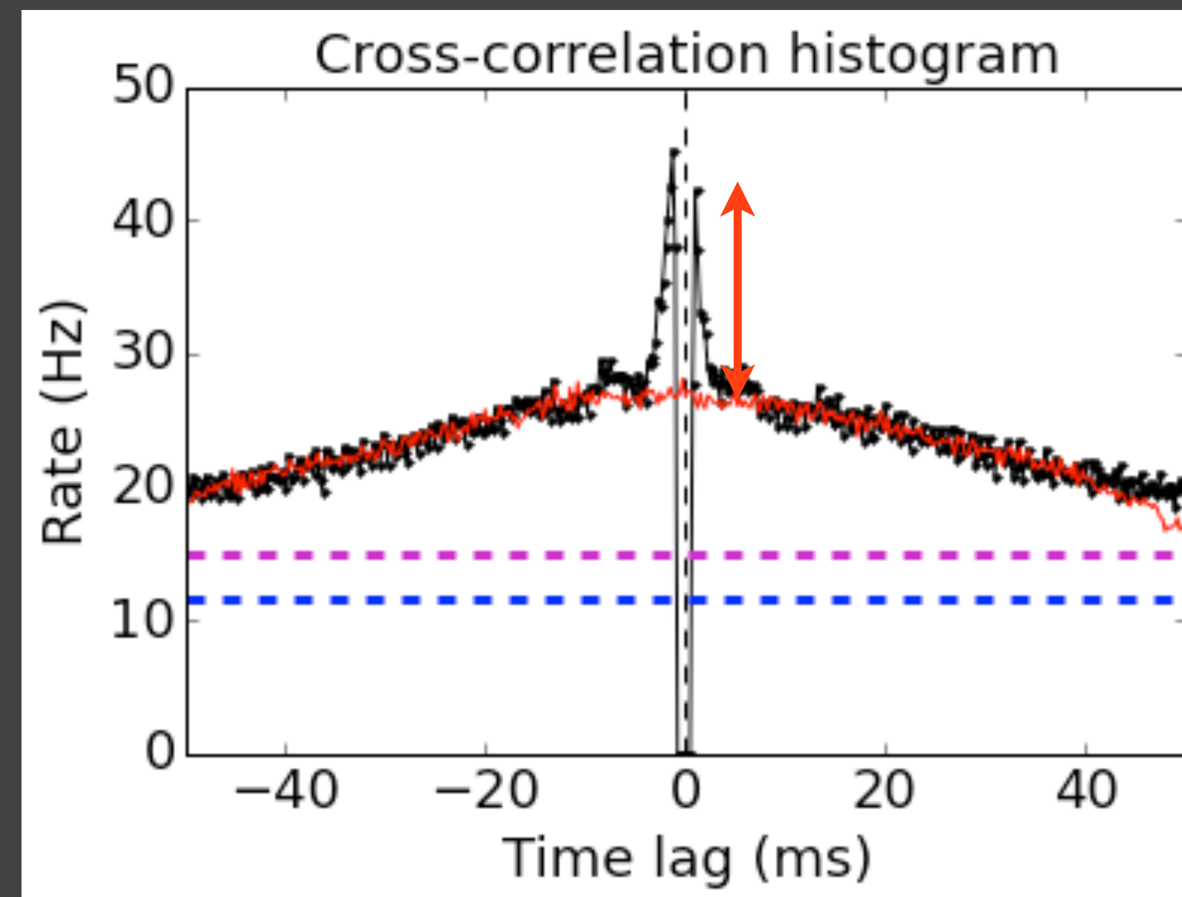
Null : there is no direct connection, but background network modulation.

Brody (1999), Neural Comp
Amarasingham et al (2012), J Neurophysiol

Jitter Applied to Real Data

Multiunit electrode
CA1 pyramidal to CA1 interneuron

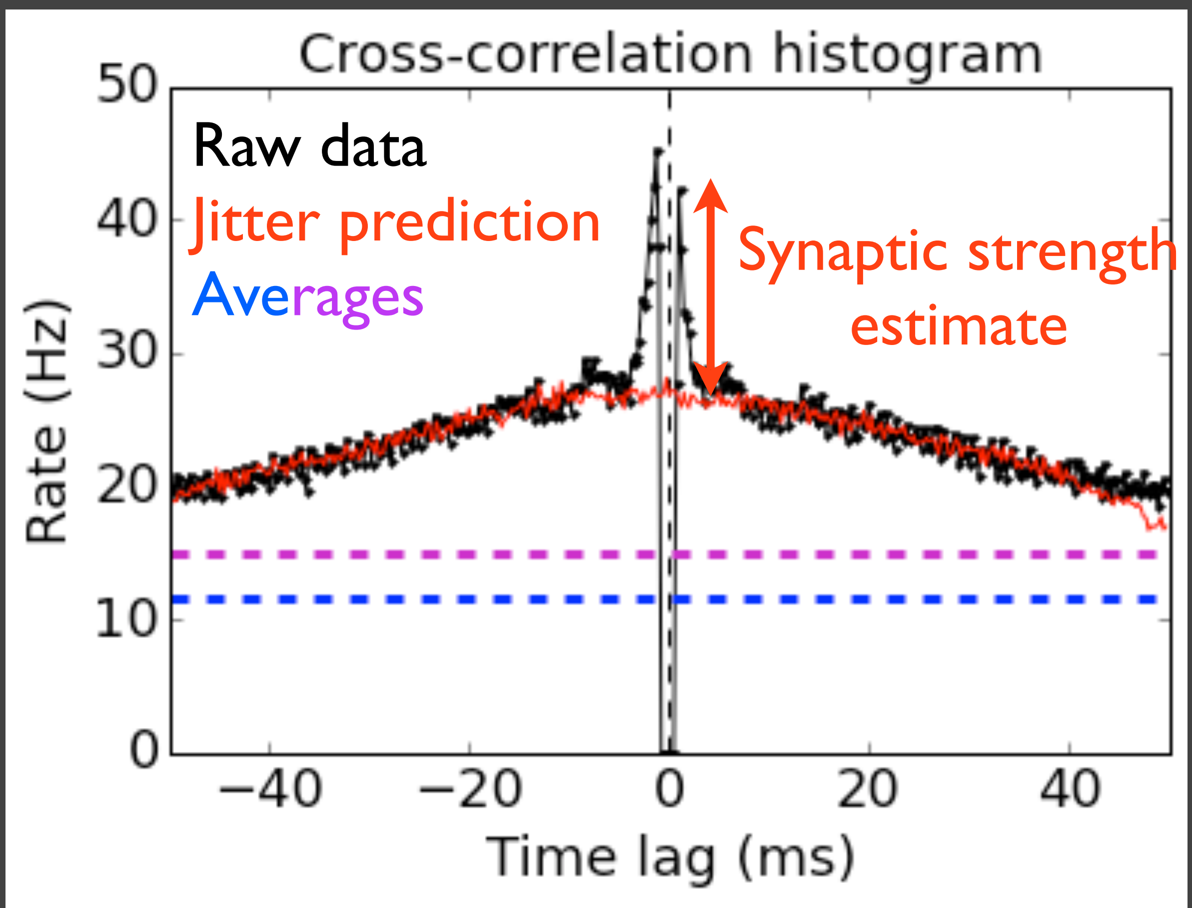


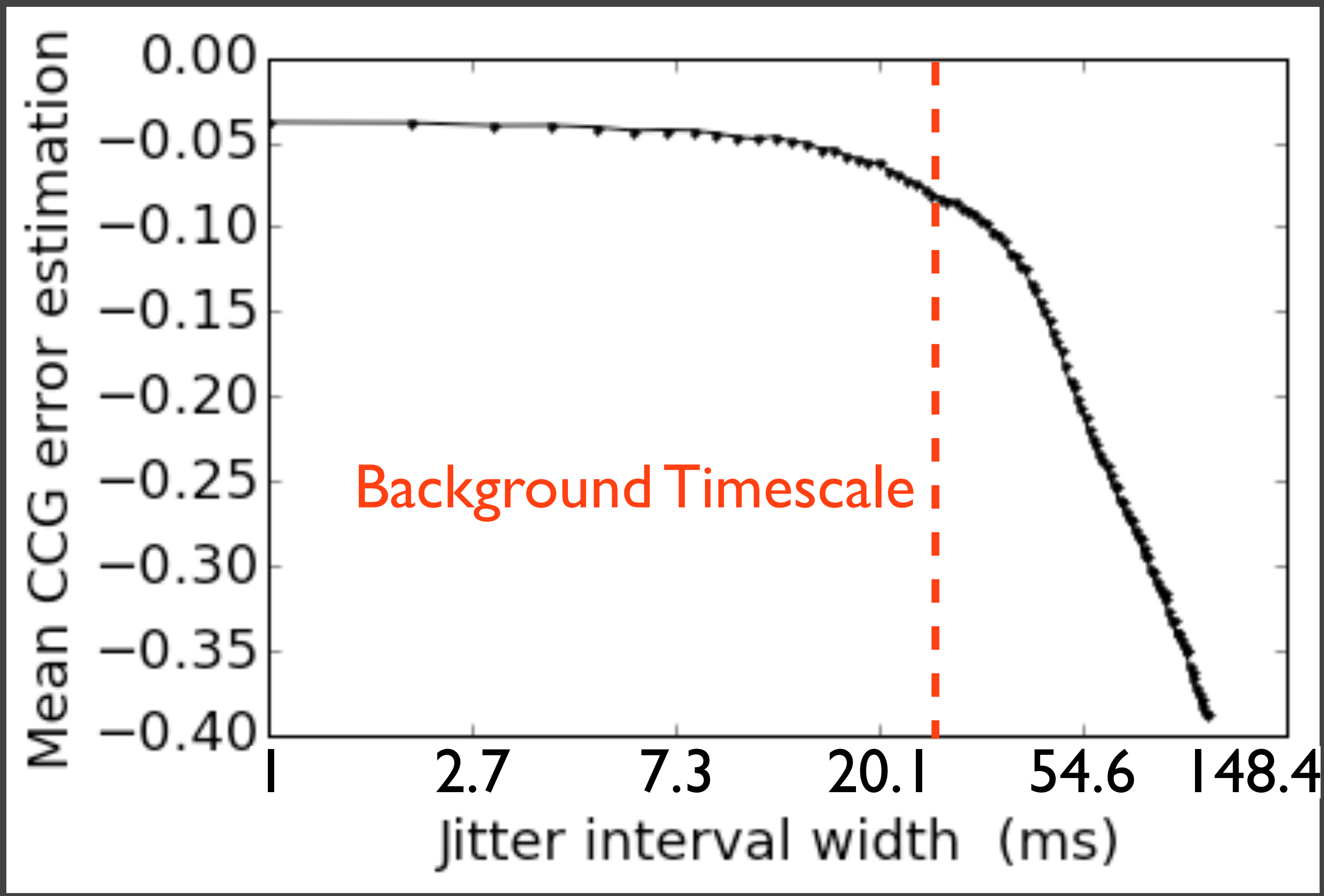


Dan English's data

Background Timescale Estimation

Multiunit electrode
CA1 pyramidal to CA1 interneuron

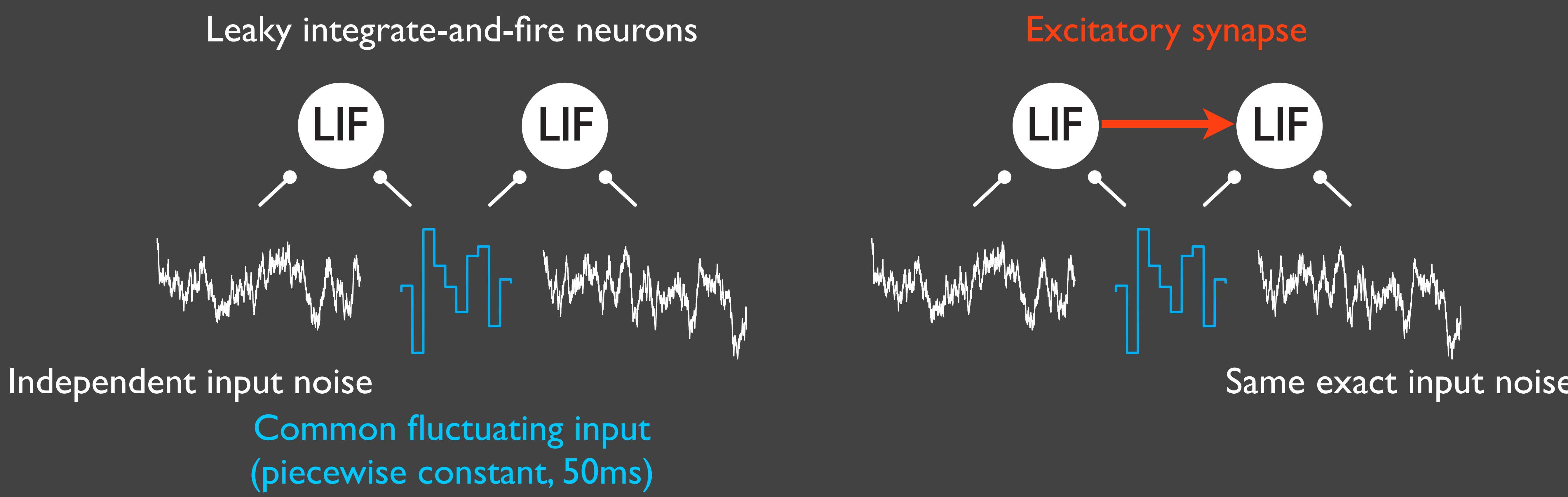




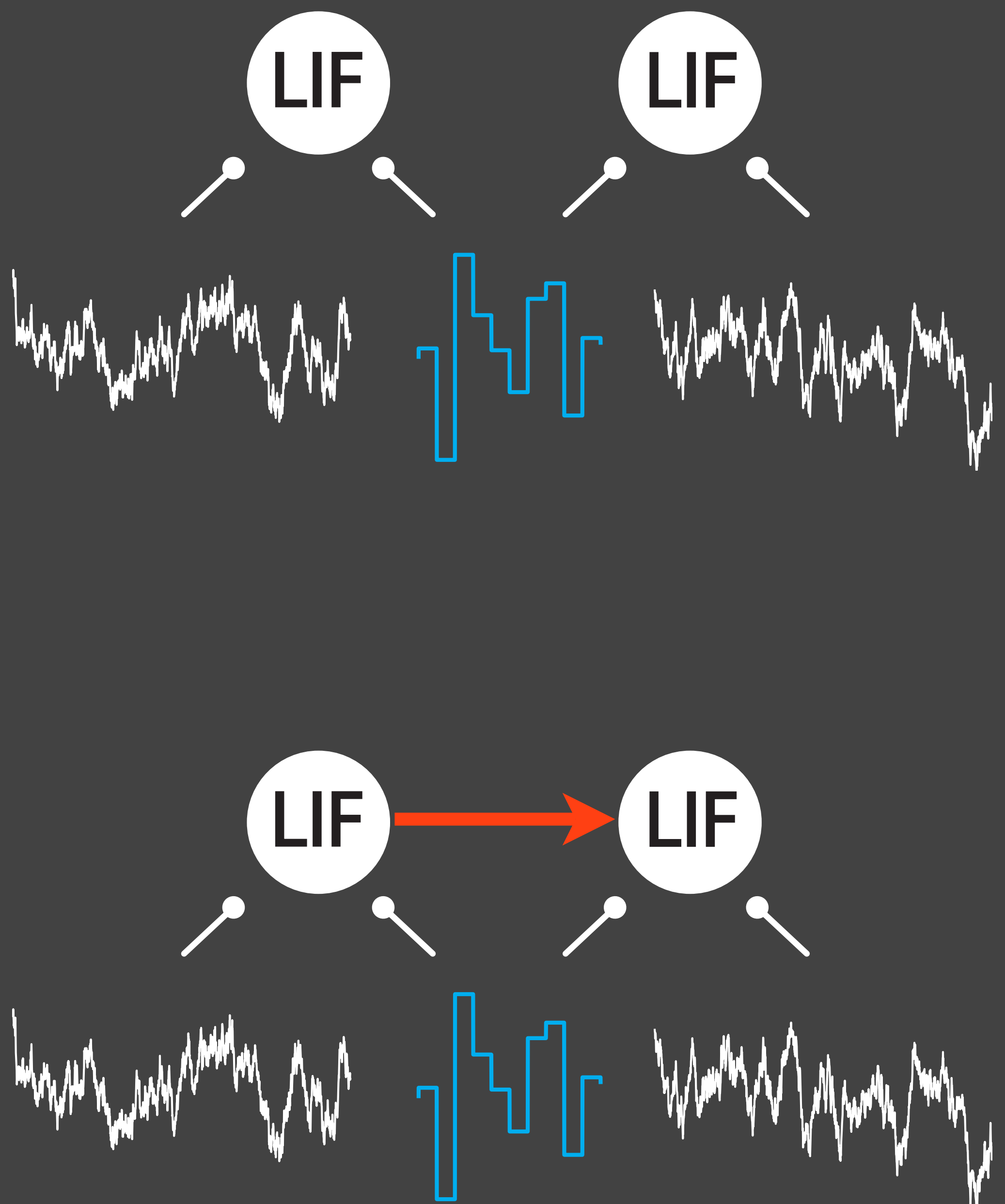
Estimation of the background timescale
by test inversion

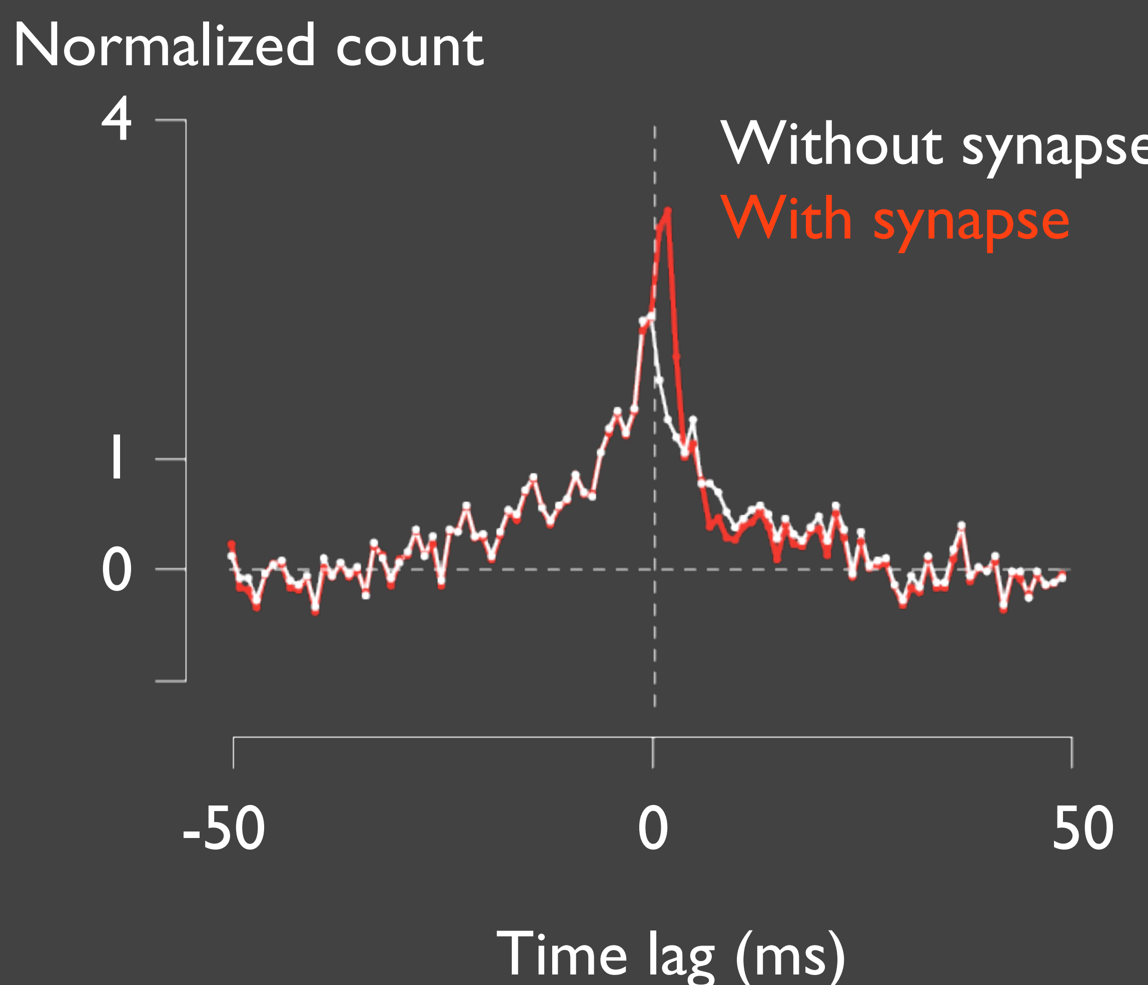
Dan English's data

A Simple Setup to Test the Jitter Method

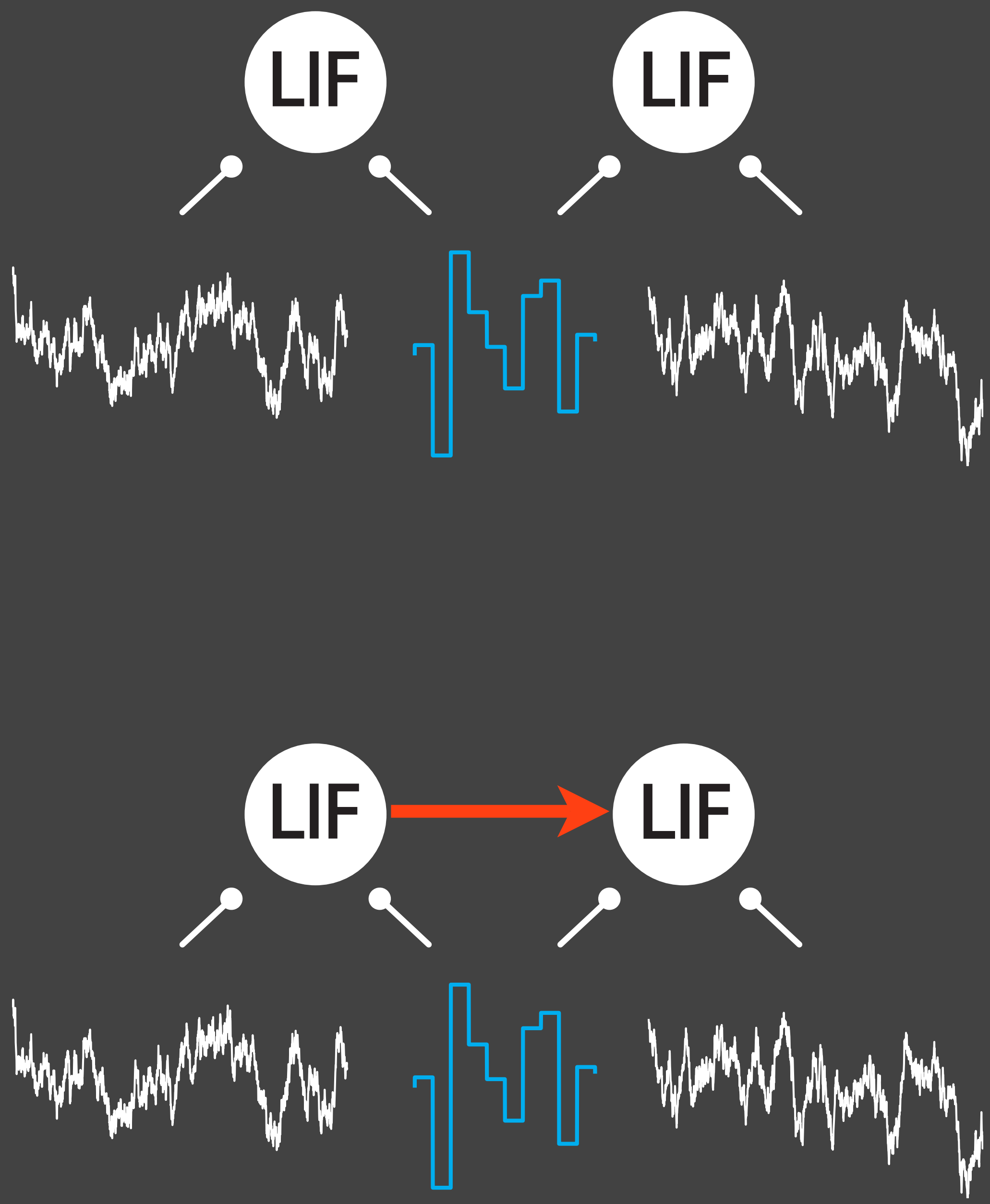


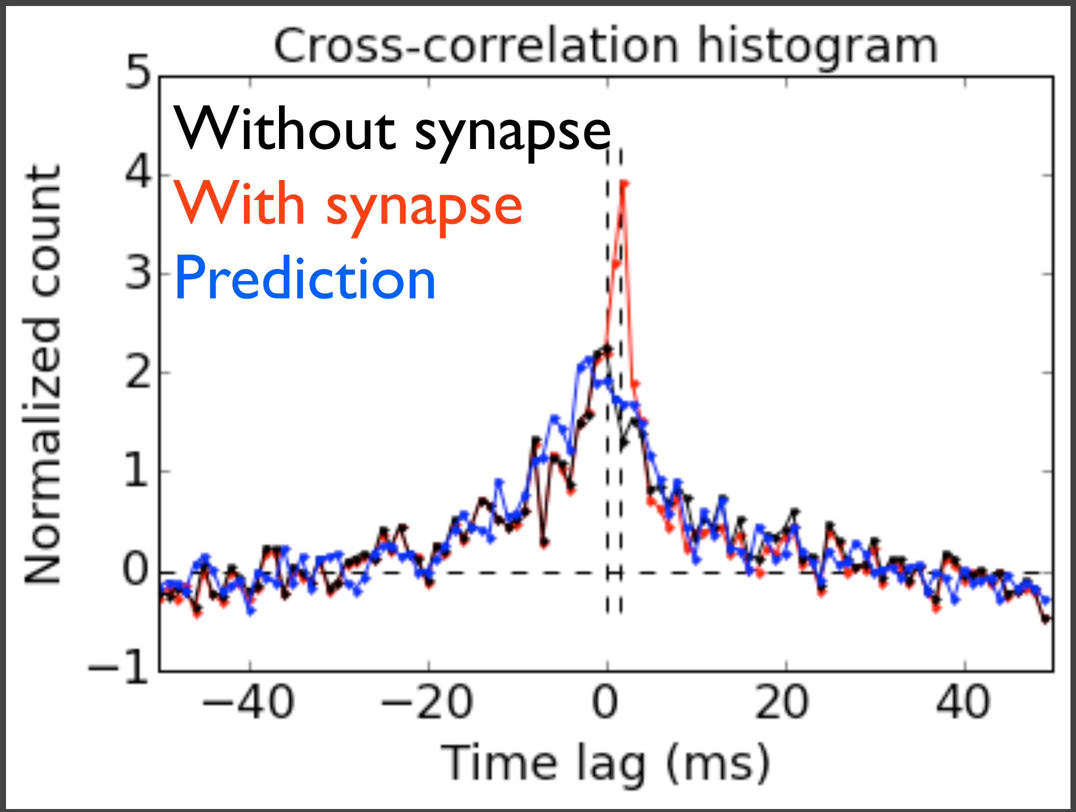
A Simple Setup to Test the Jitter Method



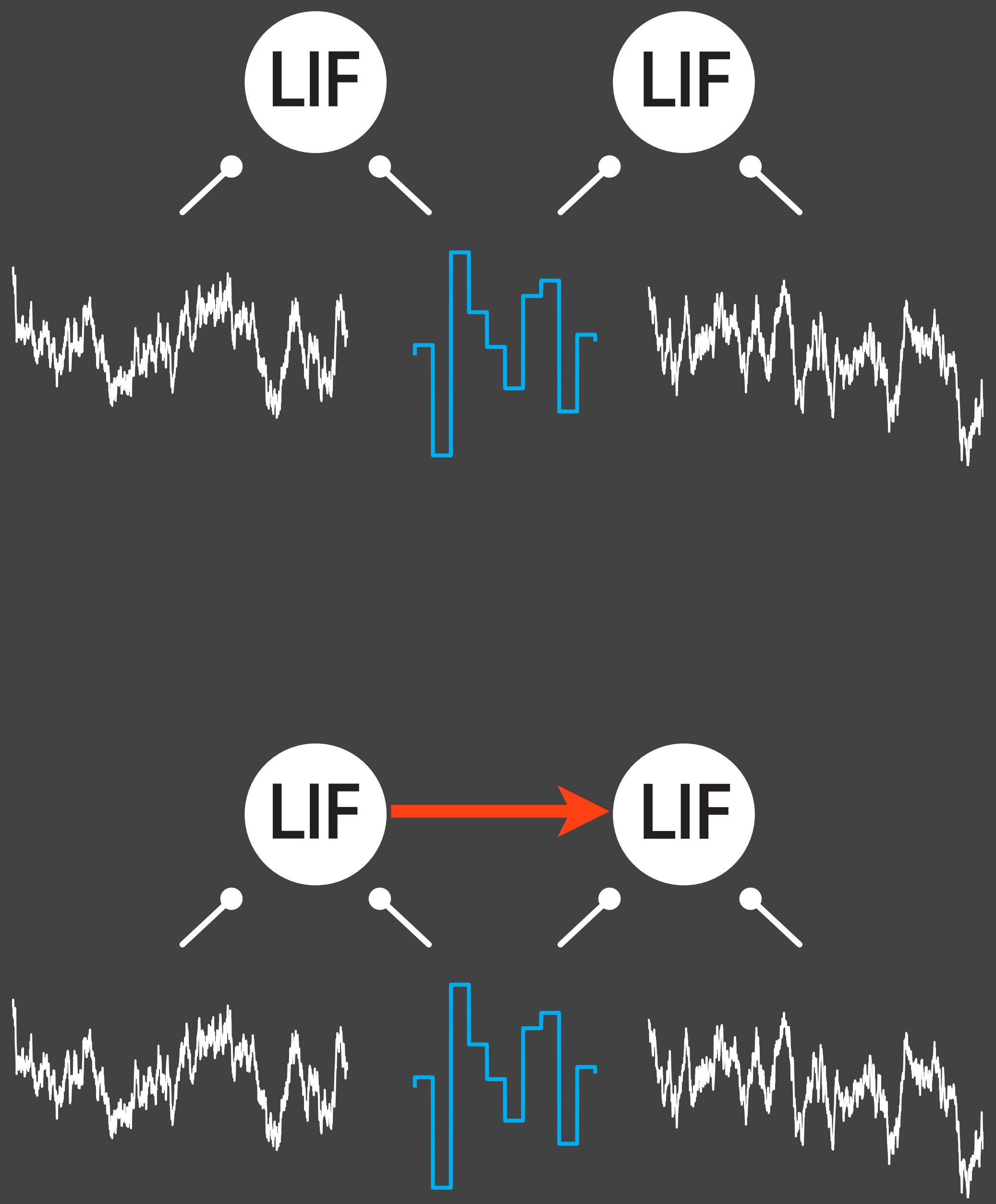


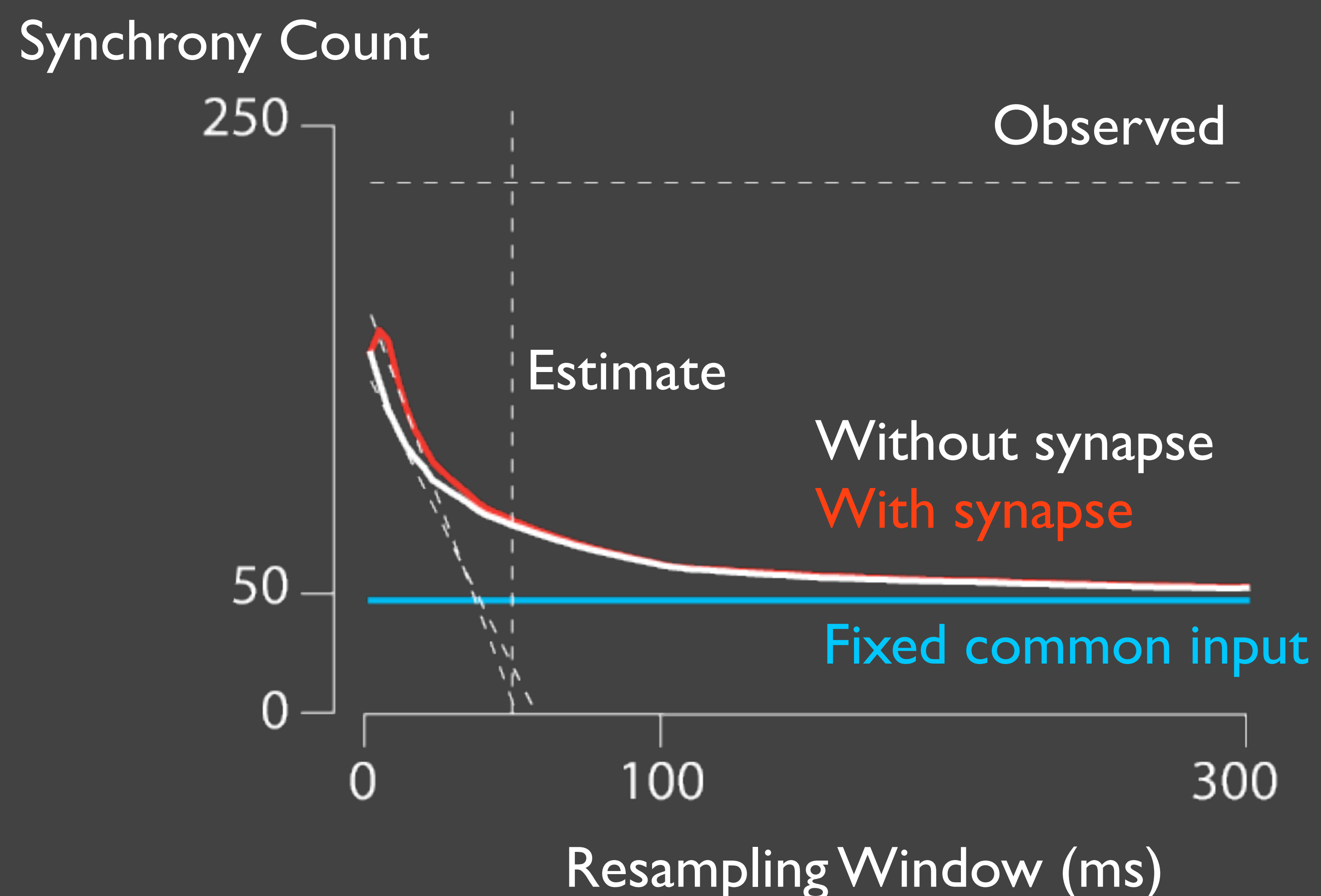
A Simple Setup to Test the Jitter Method



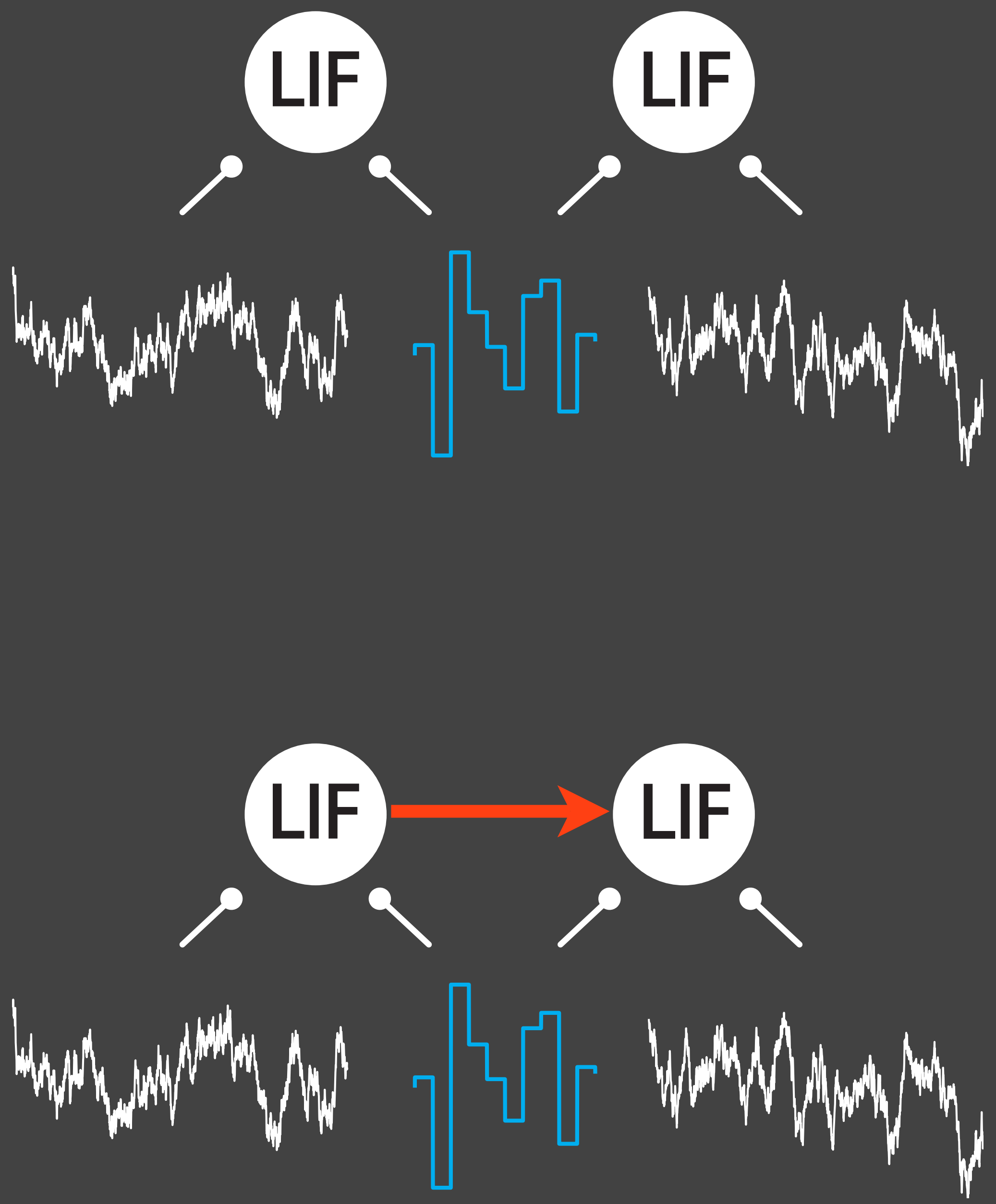


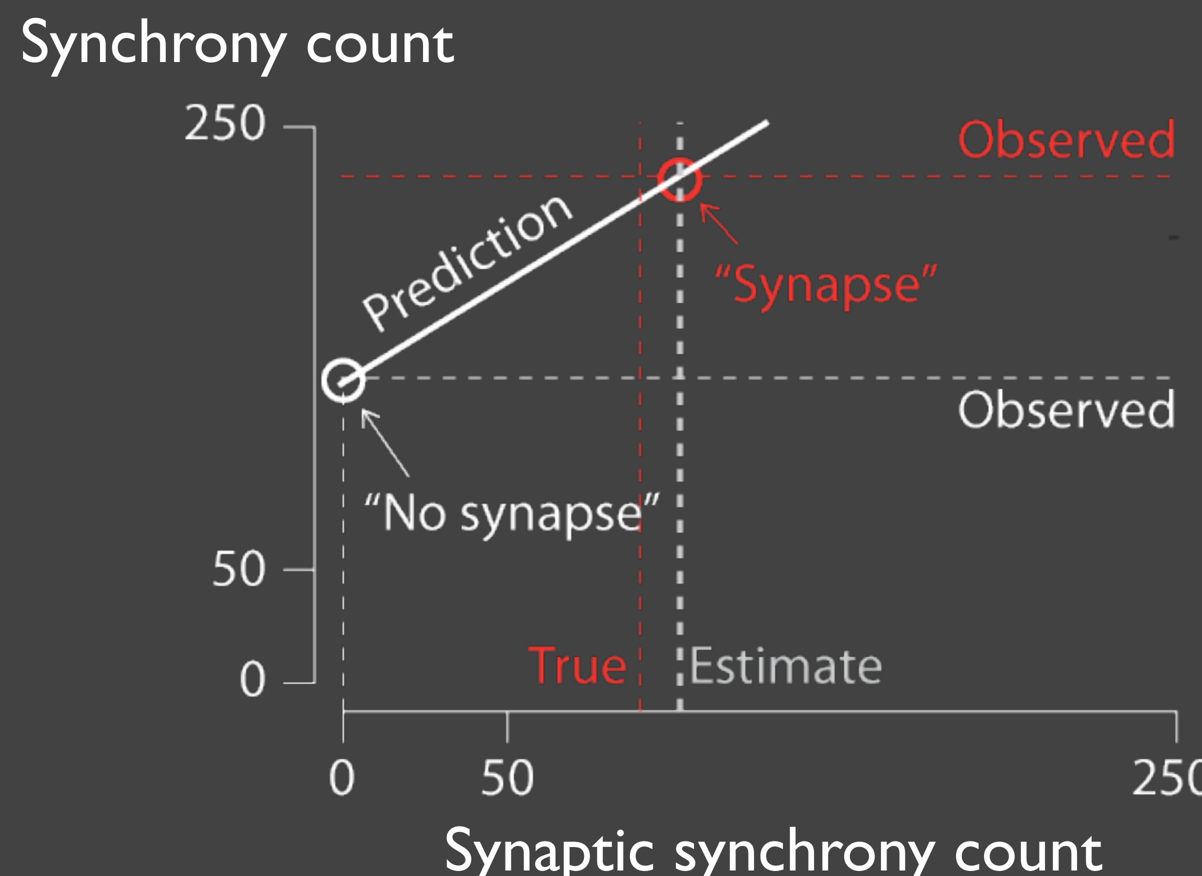
Estimating the Common Input Timescale

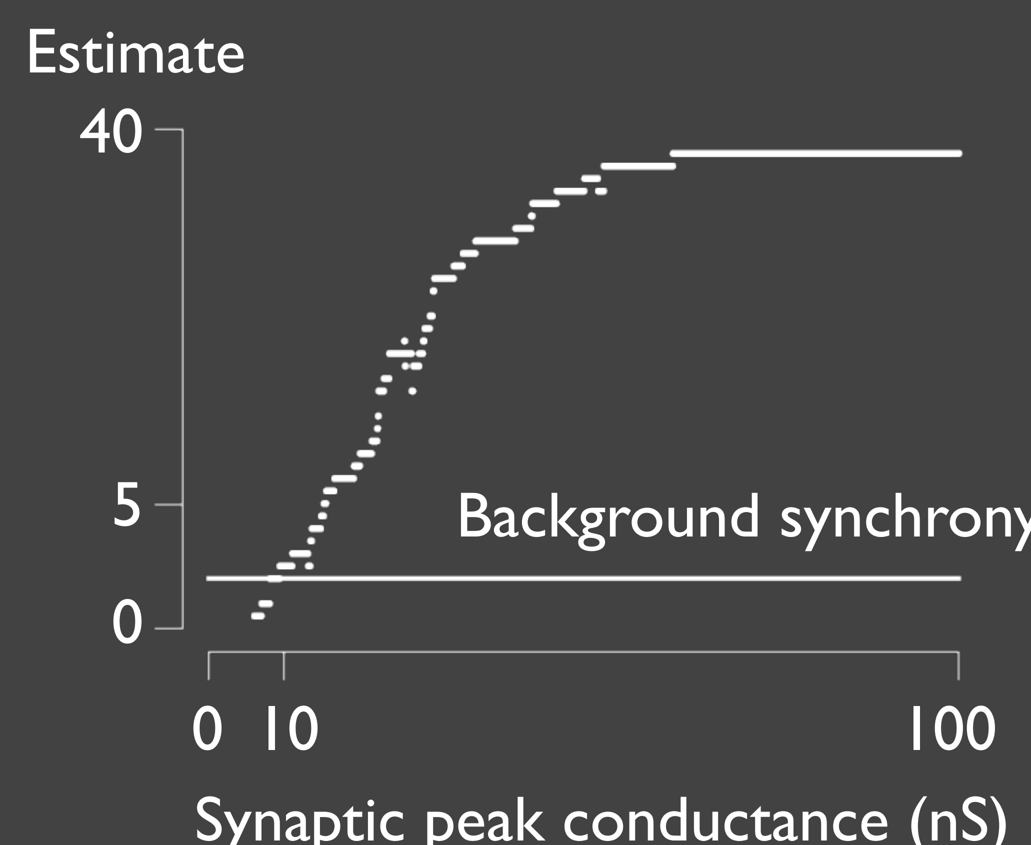




Estimating the Synaptic Strength





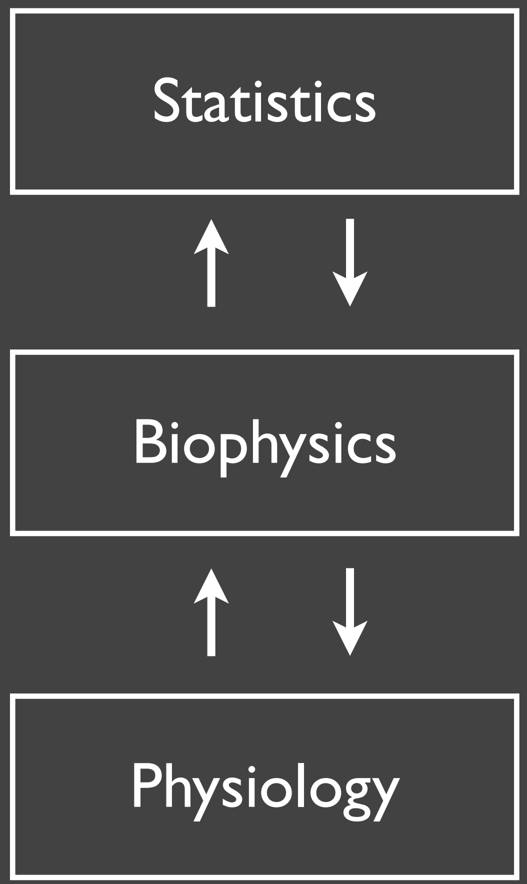


Conclusions

• It is possible to reproduce ultra-precise (< 3ms) monosynaptic spike transmission in a standard biophysical synaptic transmission model.

• It critically depends on the statistics/dynamics of the background modulation (low variability at spike initiation timescale).

• Nonparametric statistics is more appropriate for analyzing extracellular spike data. There is a direct, but not trivial, connection with biophysics.



Perspectives

- How brain state affects spike transmission and spike-time dependent plasticity?

- If we ablate a monosynapse, would the ultra peaky CCG remain? or, what is the cooperation between STDP and common input?

- What is the simplest way to validate our model *in vivo*?

- What is the most efficient way to experimentally distinguish a monosynapse from multiple converging synapses or common inputs? (using optogenetics)

- How does our conclusions affect the treatment of triplet interaction? microcircuit connectivity?

Thank you!

Acknowledgments

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