Role and limits of inhibition in an excitatory burst generator

Explaining levels of synchrony and neuron phases

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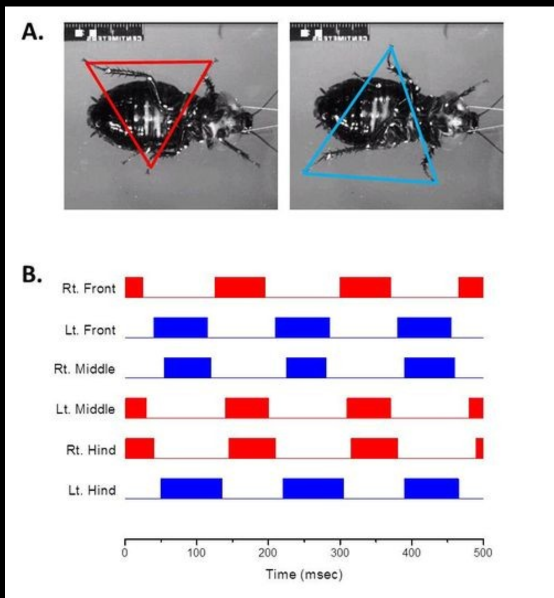
The other people who make it happen

- Experiments at Seattle Children's Research Inst. Center for Integrative Brain Research:
  - Tatiana Dashevskiy
  - Alfredo J. Garcia III
  - Jan-Marino Ramirez
- University of Washington Applied Math
  - Eric Shea-Brown
  - Joshua Mendoza
- NSF Grant #1122106, Boeing fellowship, Big Data Training Grant

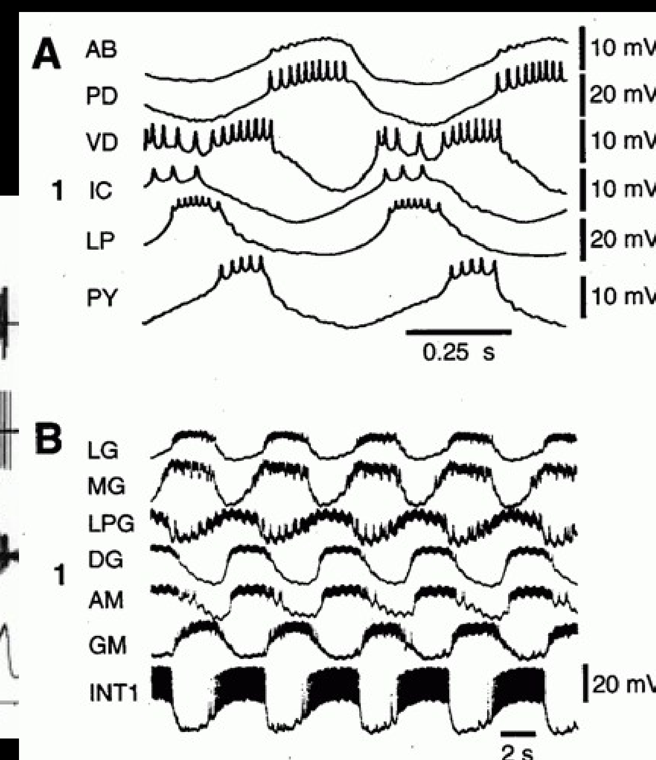
Many (semi-)autonomous activities are rhythmic



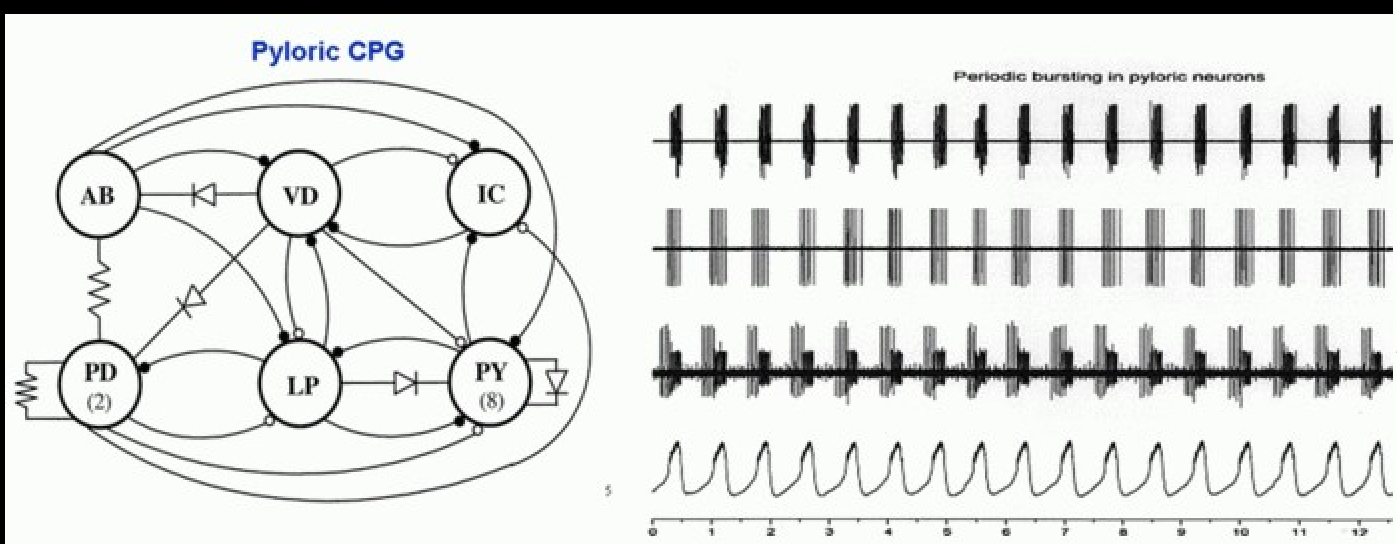
Locomotion
Ritzmann & Zill (2013)

Also:
- Chewing
- Whisking
- **Breathing**

Consensus view: **CPGs** which generate the patterns that can be controlled



Stomatogastric ganglion
Selverston (2008), Miller & Heinzel

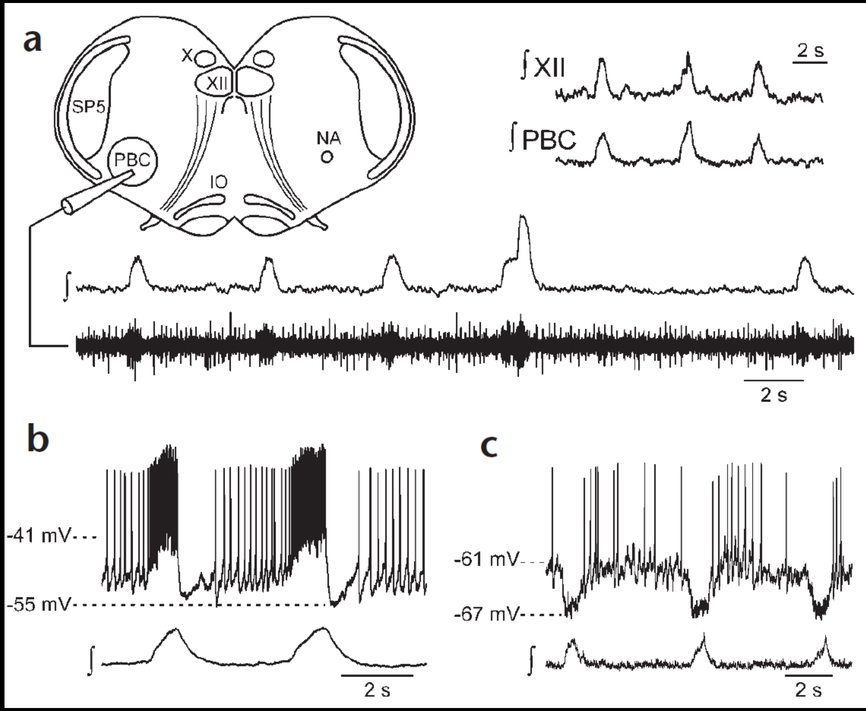


Breathing: an important rhythm Where does it come from?

- "Central pattern generator" in brainstem
  - Pre-Bötzinger complex (preBot) [Smith et al. 1991; Ramirez & Richter 1996; Rekling & Feldman 1998; Feldman et al. 2013]
  - Heterogeneous: bursters, tonic (periodic) spikers, and quiescent
  - Synchronized population bursts via excitation

Difference from usual CPGs:
- ~300 neurons... why so many?
- Recurrent E/I network (inh. up to 50% of cells in preBot [Hayes et al. 2012])

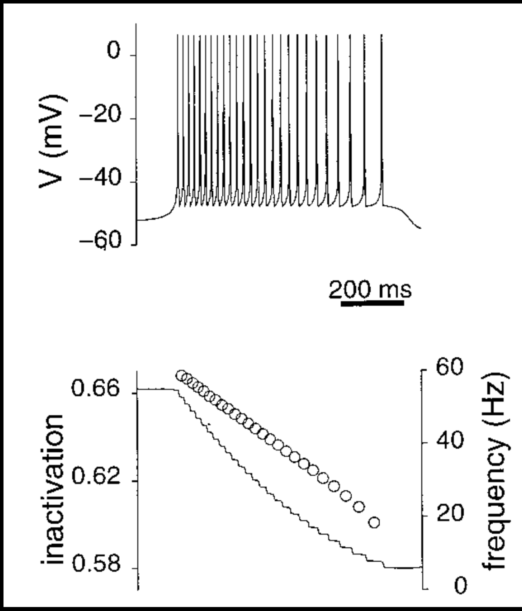
S Lieske, M Thoby-Brisson, P Telgkamp, and J-M Ramirez (2000)



inspiratory cell expiratory

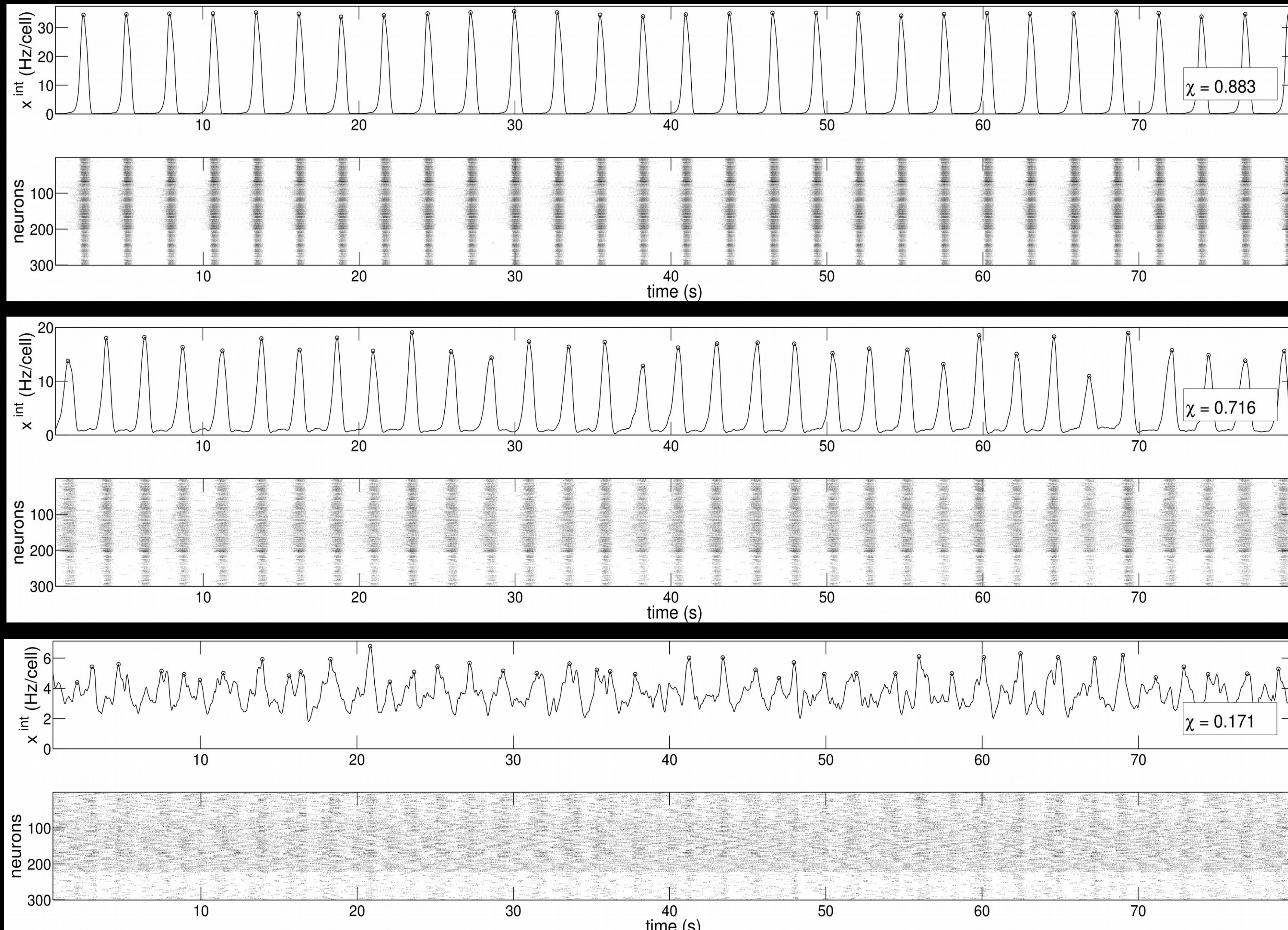
We model the effect of inhibitory cells in the population

- Heterogeneous neurons [Butera et al. 1999; see also Best et al. 2005; Rubin et al. 2009; Toporikova & Butera 2011; Park & Rubin 2013]
- Embedded in sparse network ($N=300$, $k=3$ – 6) [Gaiteri & Rubin 2011; Carroll & Ramirez 2013]
- Vary fraction of inhibitory cells p_I (≤ 0.5 [Hayes et al. 2012])
- Look for:
  - Effects on synchrony
  - Rhythm properties
  - Functional role for inhibition?



Avg degree = 6, $g_E = g_I = 2.0$ nS

Increasing inhibition

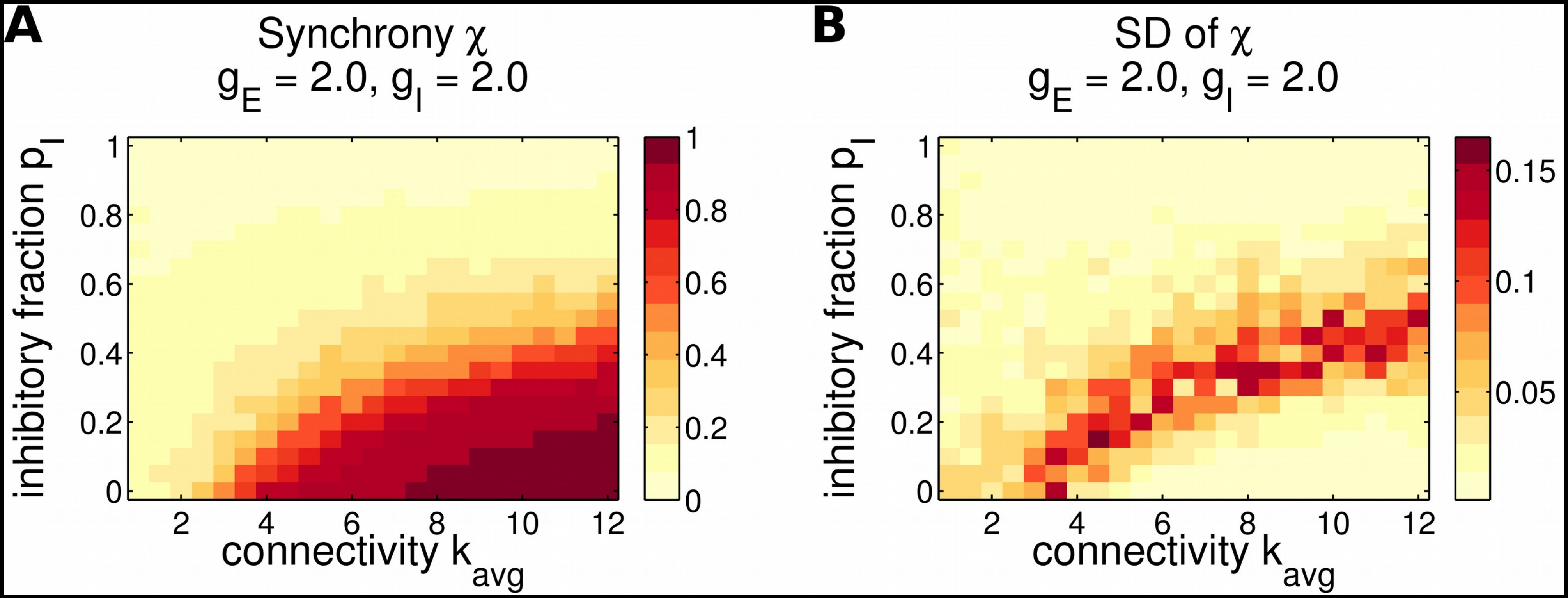


Sparsity & inhibition both degrade the rhythm – (E/I balance)

- Synchronous network oscillation from excitatory interactions
- Stronger with more/stronger connections
- Same effect changing g_E / g_I... E/I balance what matters

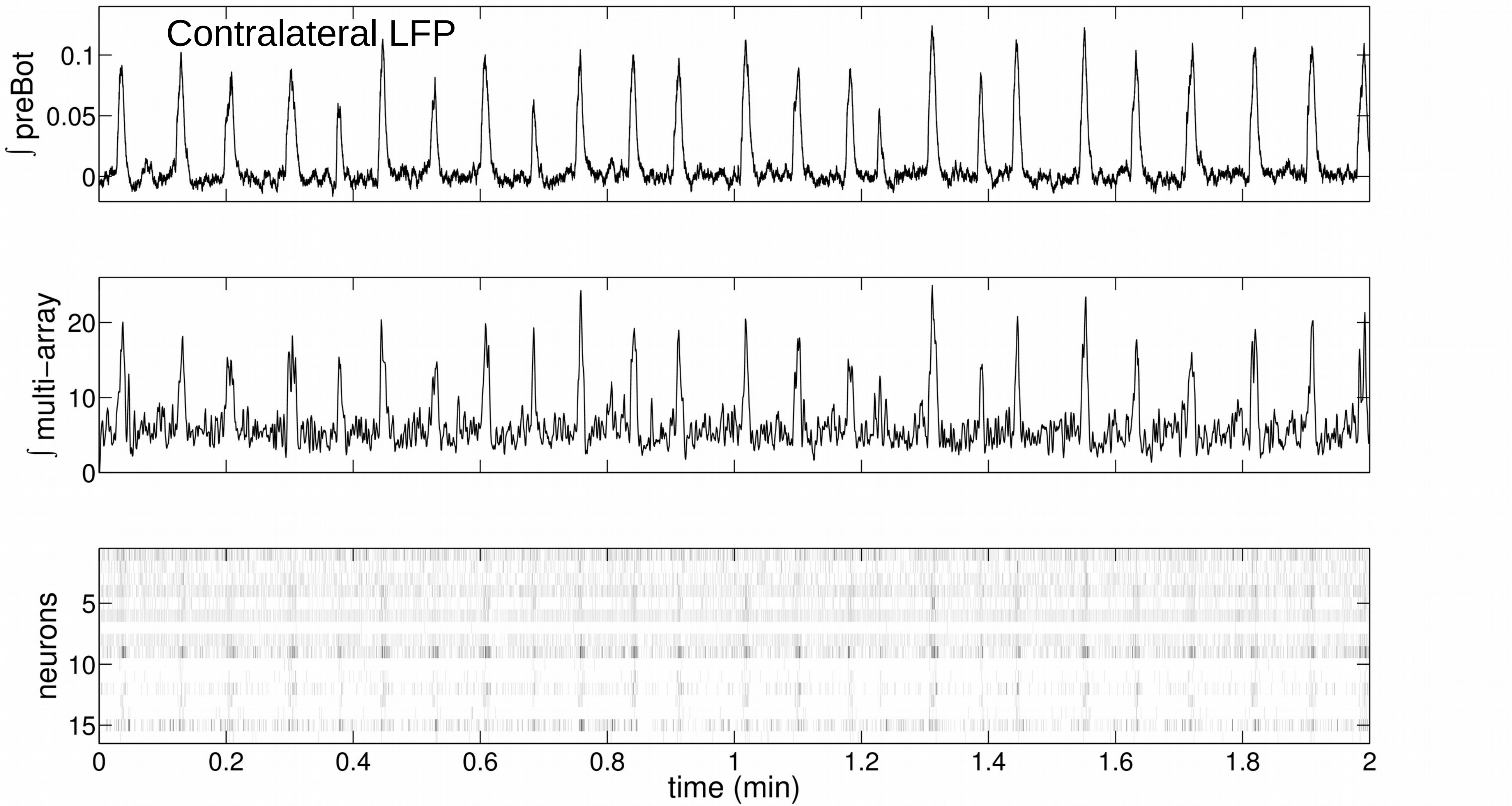
Autocorrelation measure

Variance across network realizations



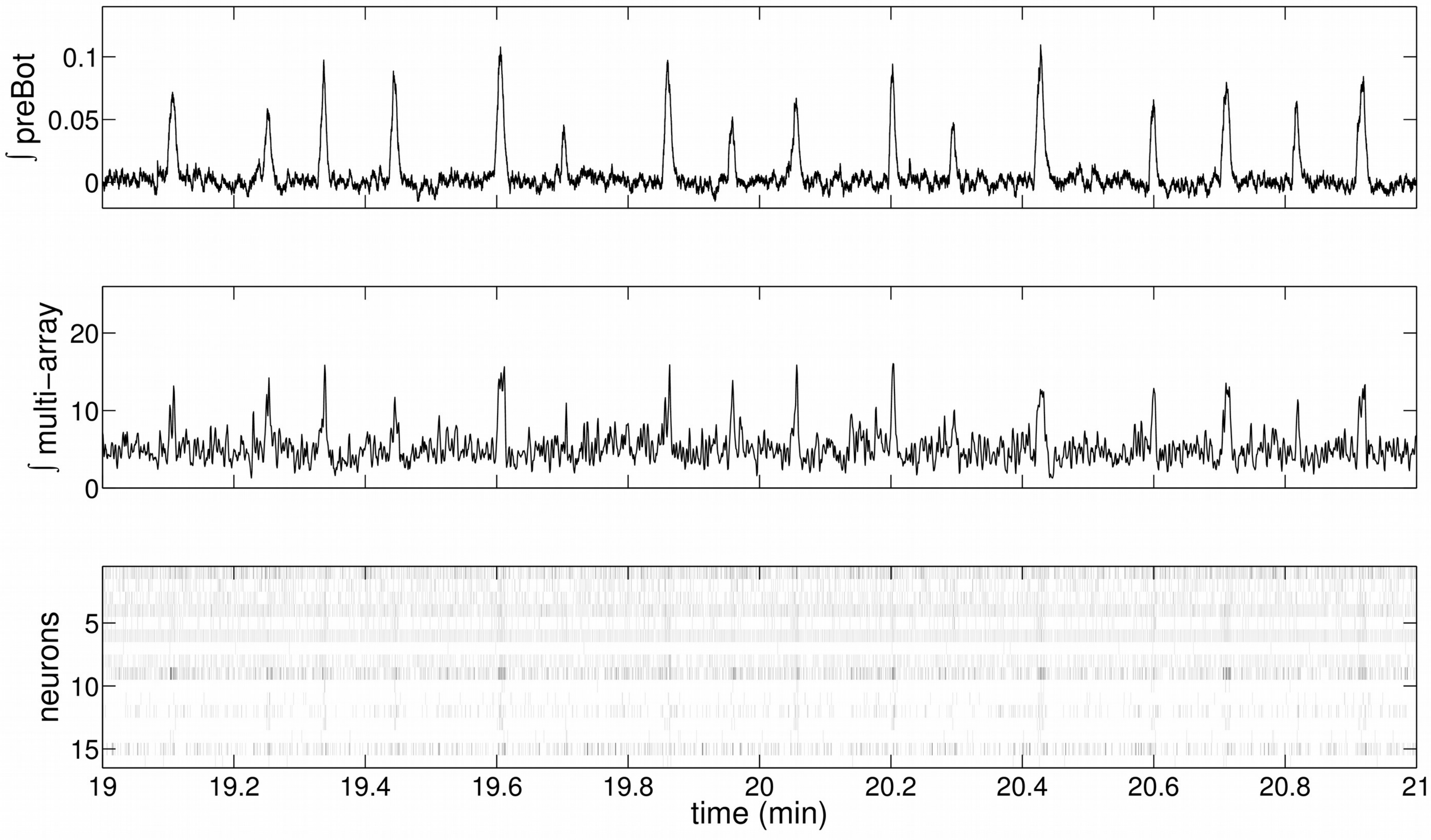
Experiments confirm E/I balance determines synchrony

Control: χ=0.56



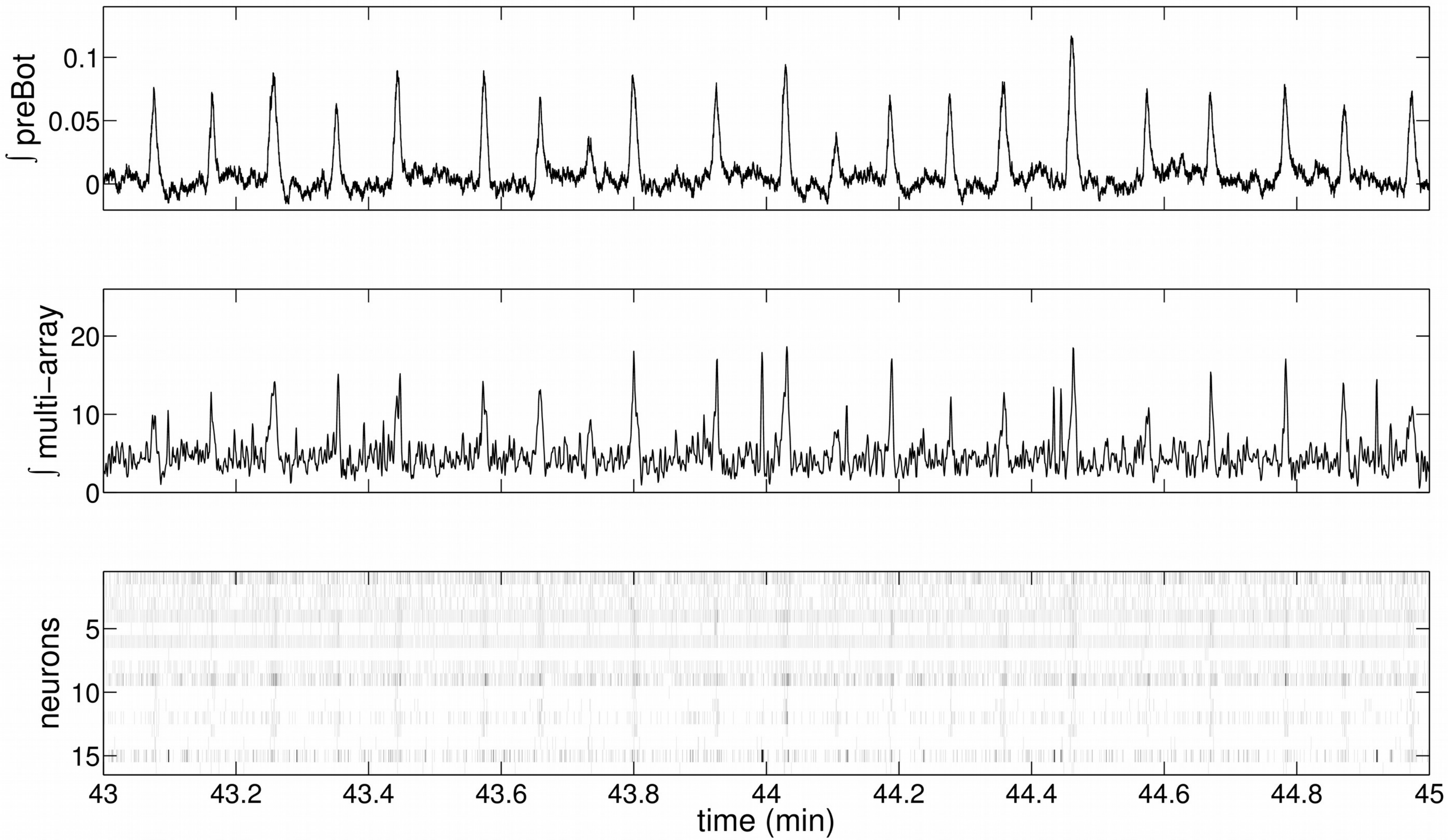
Experiments confirm E/I balance determines synchrony

DNQX @ 0.7 μM: χ=0.43



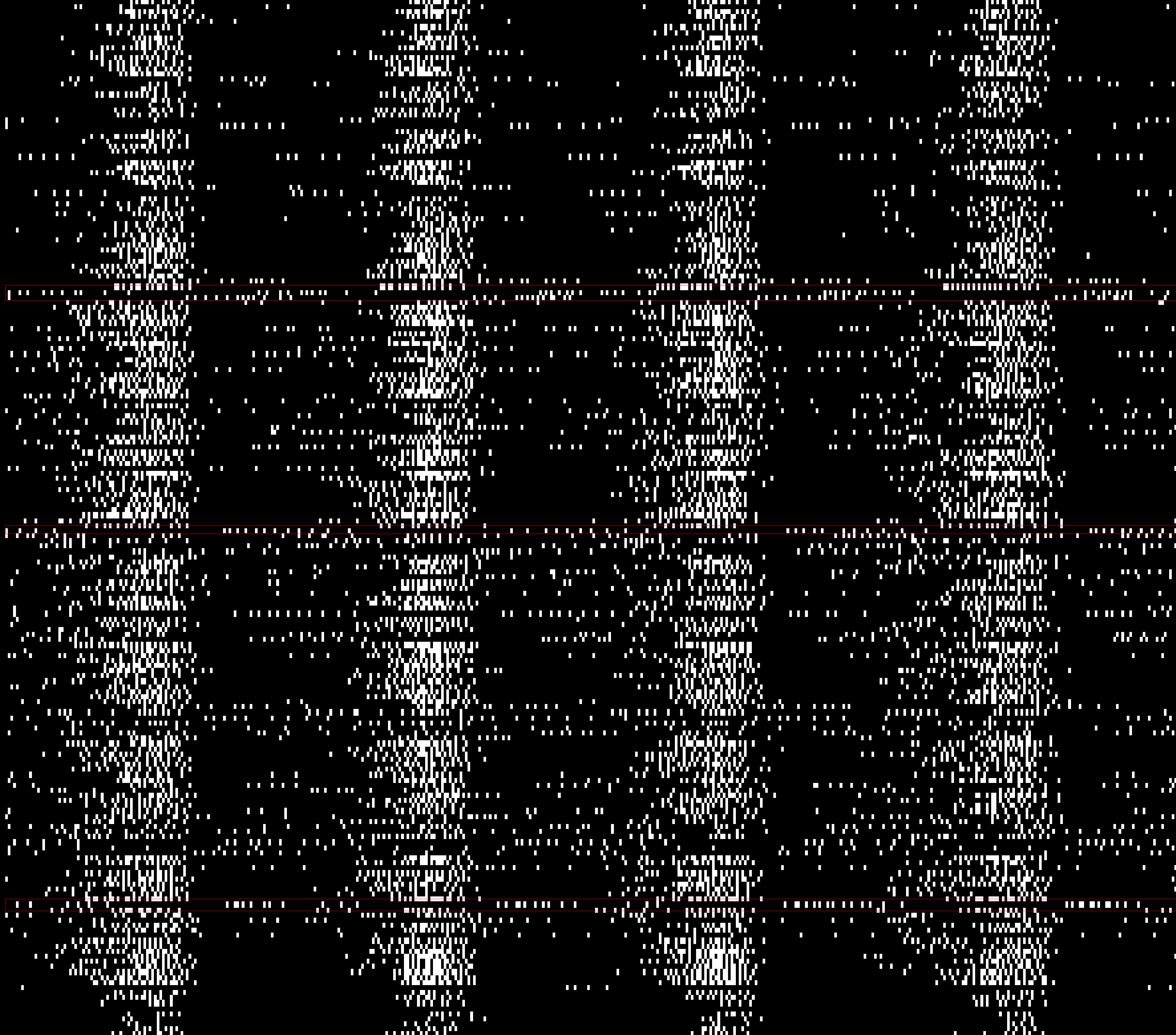
Experiments confirm E/I balance determines synchrony

DNQX @ 0.7 μM, PTX @ 20 μM: χ=0.50

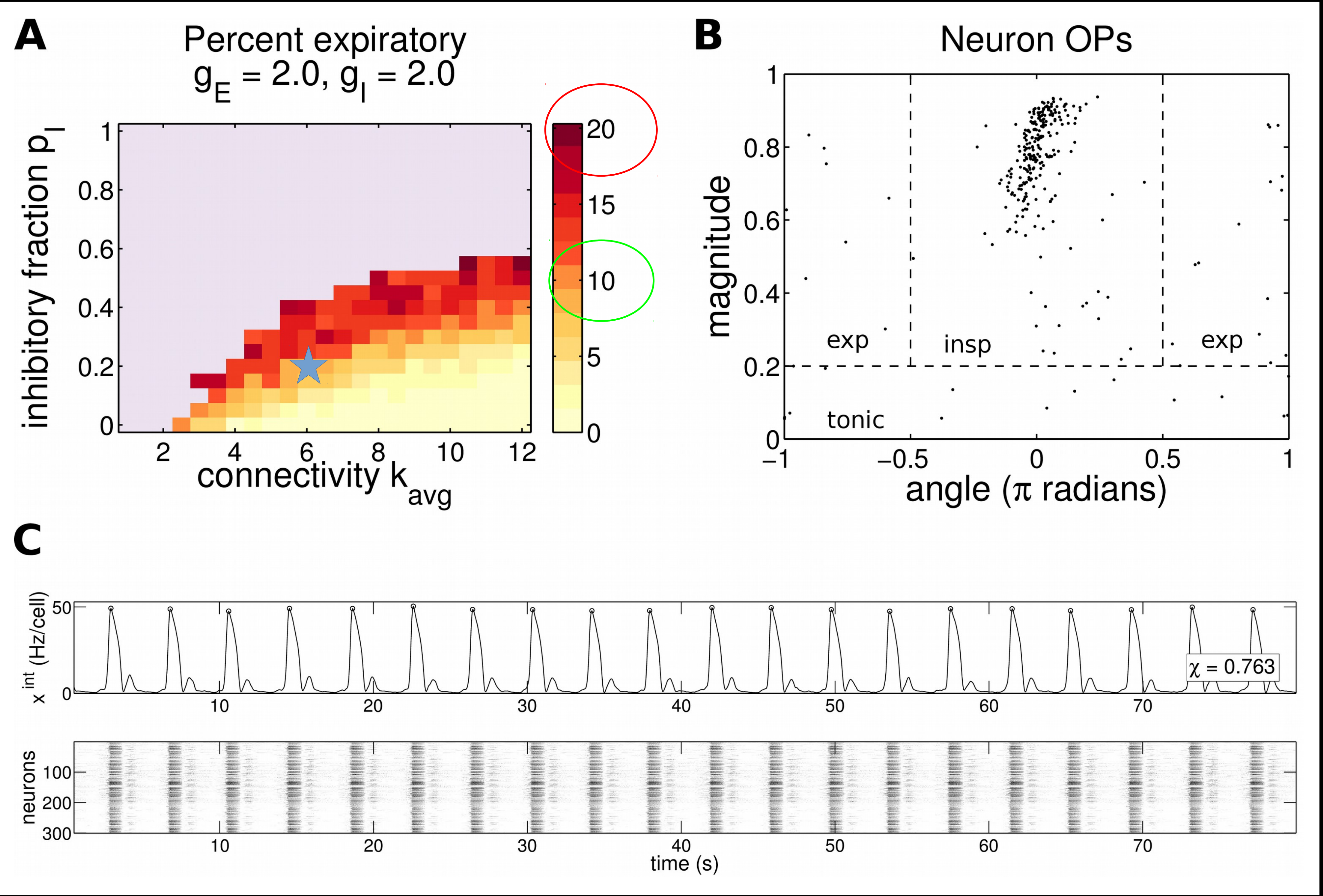


In model, with p_I=0.2

Expiratory cells



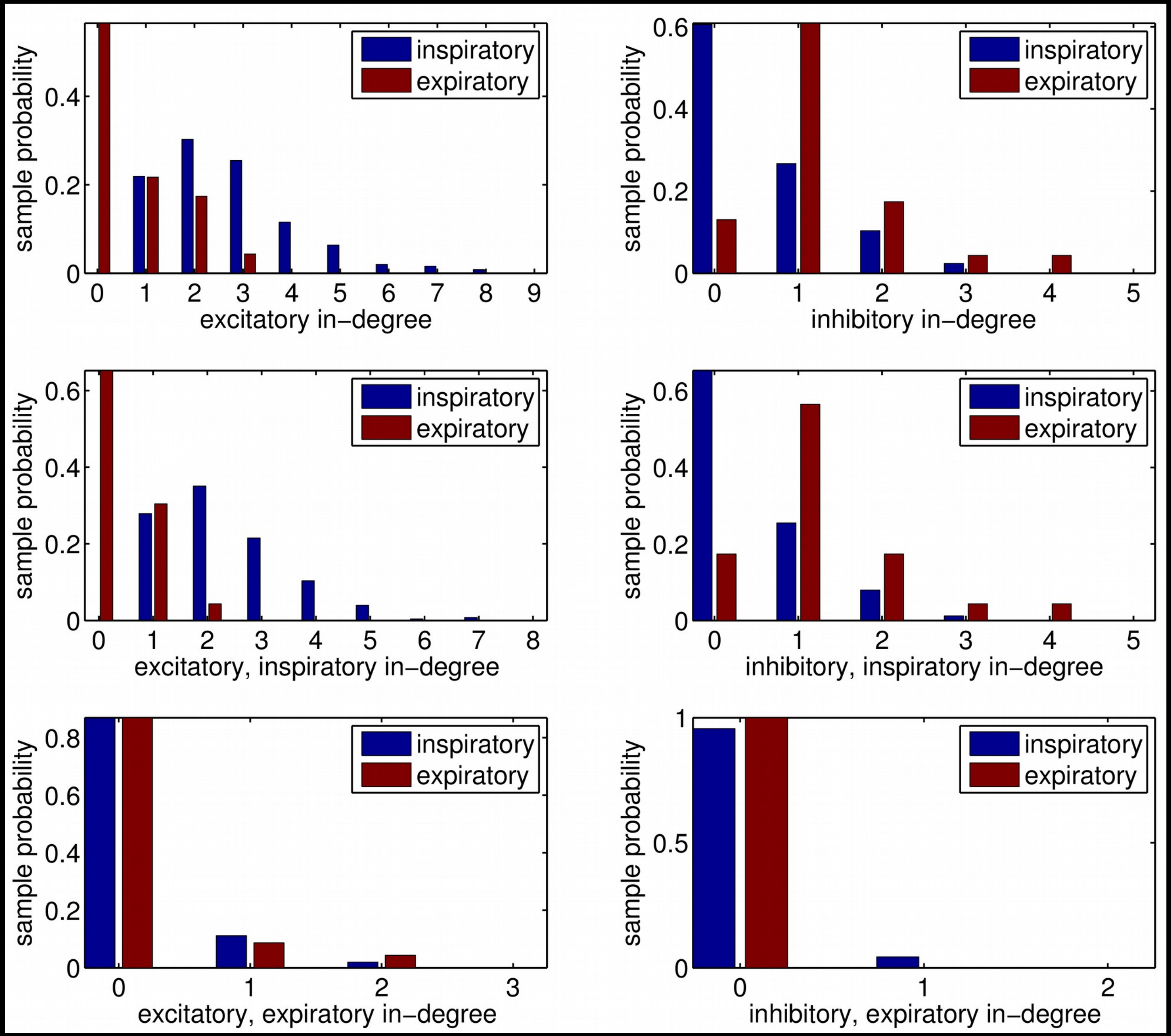
Expiratory neurons arise from inhibition



Inputs determine phase

Overall degrees:

Degrees labeled by phase:



- **Expiratory** neurons receive **less excitation**, preferentially **from other expiratory**
- **Expiratory** neurons receive **more inhibition**, preferentially **from inspiratory**
- Inspiratory is reverse

“Phases as spins” model reproduces synchrony phase diagram

Phases align/anti-align based on excitatory/inhibitory inputs

Makes sense with “binary”-like bursting neurons

We construct a spin-type model that includes both effects:

$$H = -\sum_{i<j} A_{ij}^{(\mathrm{E})}\sigma_i\sigma_j + \alpha\sum_{i<j} A_{ij}^{(\mathrm{I})}\sigma_i\sigma_j$$

Mean field theory works on tree-like graphs: sparse ER

[Dembo & Montanari 2010]

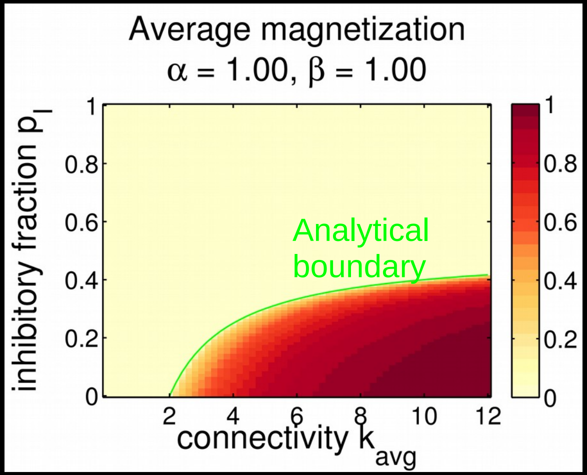
MF synchronization

$$\bar{m} = \sum_k P(k)\tanh\left(\beta(1 - p_I - \alpha p_I)k\bar{m}\right)$$

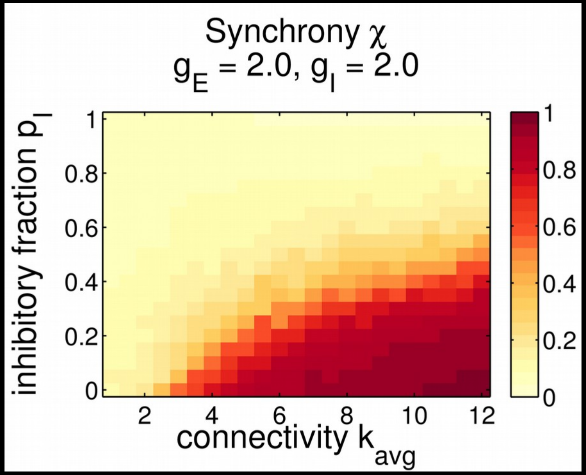
Implicit equation for amount of synchronization

Yields phase boundary:

$$p_I < \frac{1}{1+\alpha}\left(1 - \frac{1}{\beta k_{\mathrm{avg}}}\right)$$



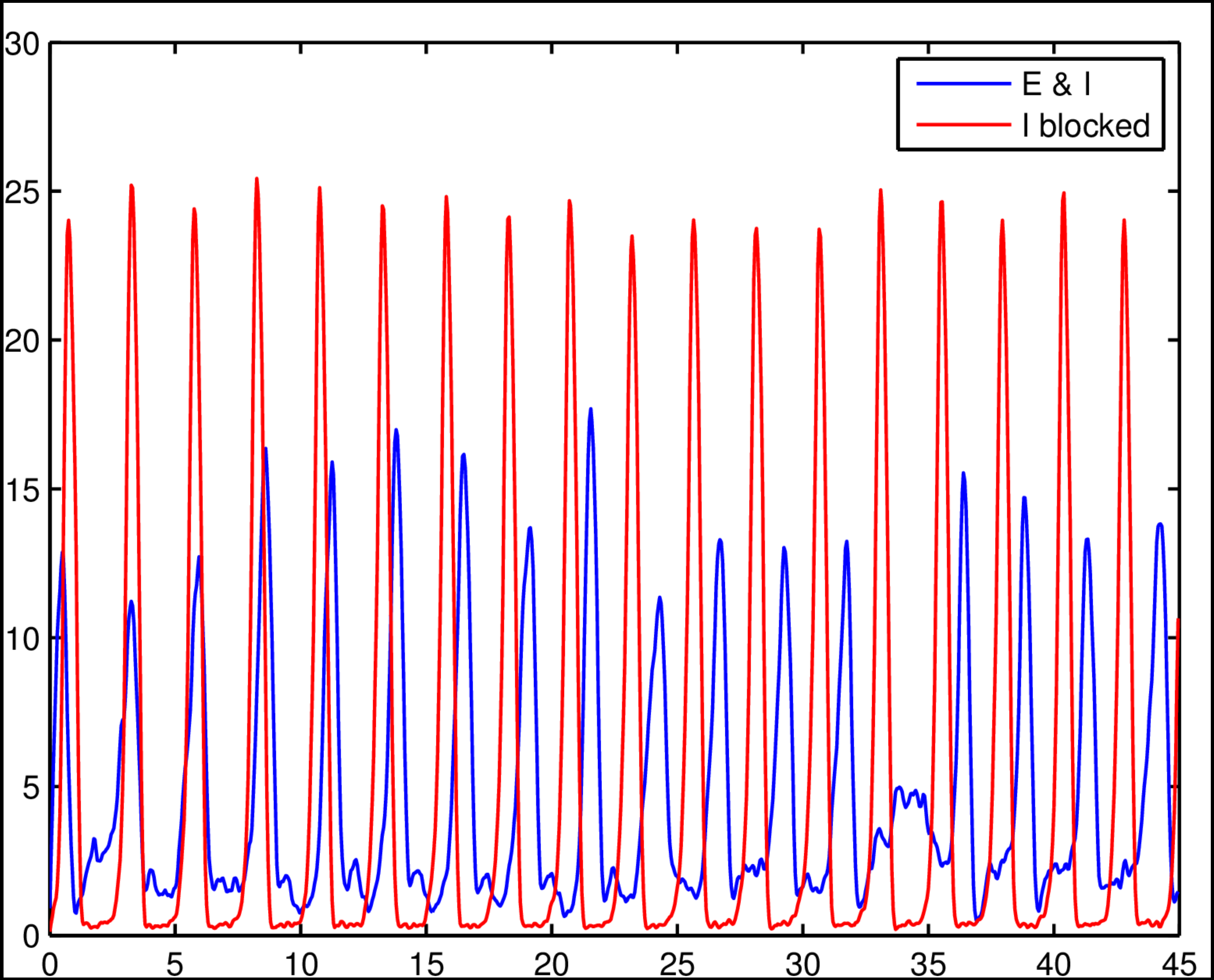
versus



So what good is inhibition?

- Diversity of cell types: expiratory cells
- Shapes the rhythm – broader than w/o
- A control knob?
  - Sherman et al. (2015) deactivate rhythm w/ strong optogenetic input to Gly2 cells in vivo
  - Has not worked with pulse input to model... can get sharpening as found
- Gain control [e.g., Azim]
  - So far, do not see evidence of the effect in model
- More dynamic range? (have to test)

Example: inhibit I population sharpens



Thank you!

- My dissertation committee and collaborators:
  - Eric Shea-Brown, Ioana Dumitriu, Nino Ramirez, Stefan Mihalas, Adrienne Fairhall
  - Tatiana Dashevskiy, Tatiana Anderson, Afredo Garcia, Aguan Wei, Joshua Mendoza
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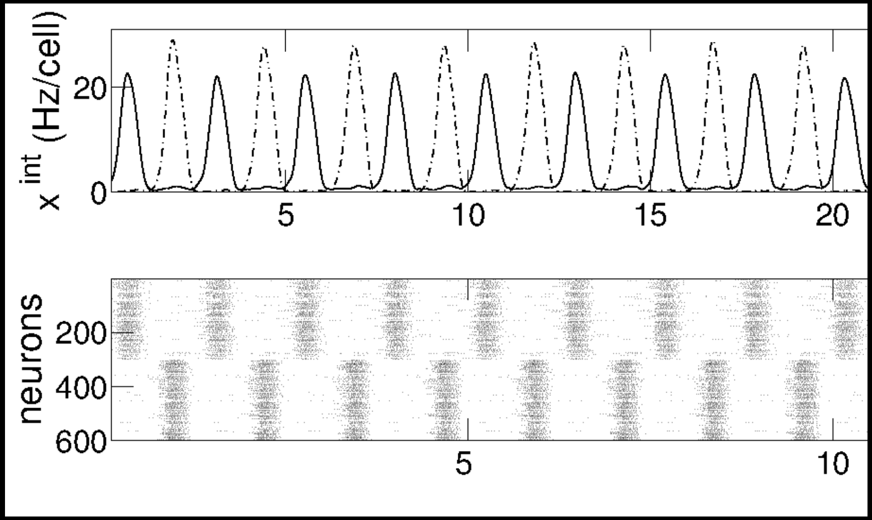
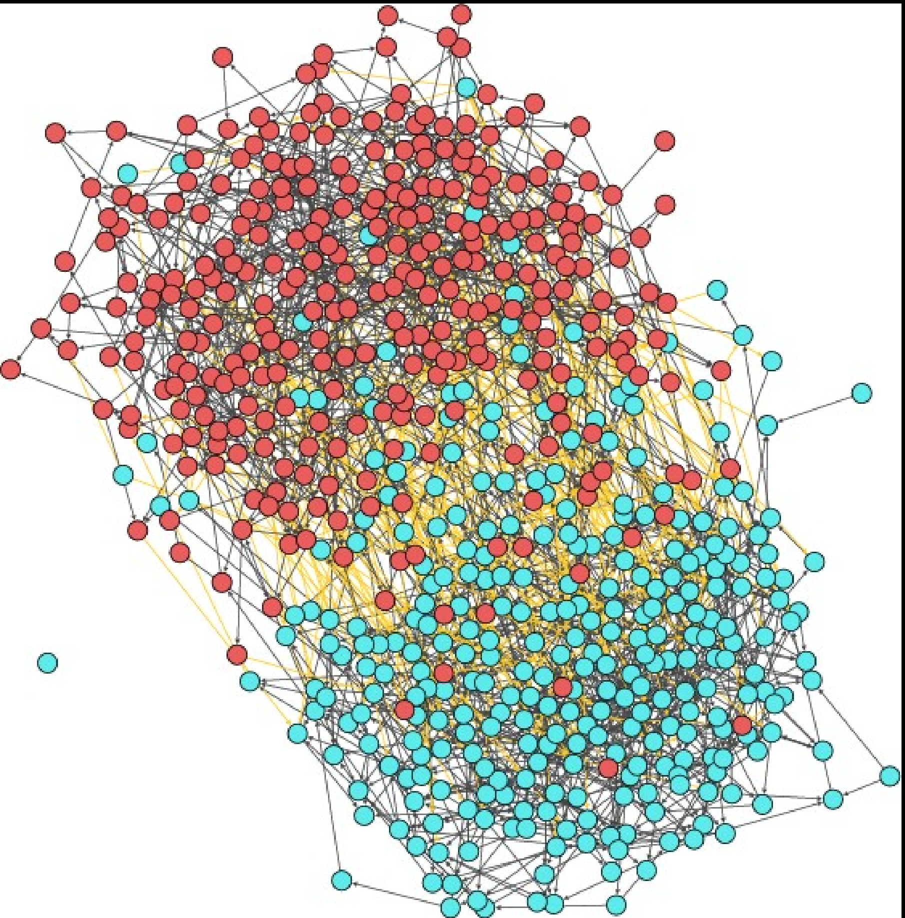
- NSF Grant #1122106, Boeing fellowship, Big Data Training Grant
- Computational neuroscience and Applied Mathematics communities at UW

How to get 50% expiratory neurons?

- PreBot & Botzinger complexes (inspiration + active expiration)
- **Add structure to network**





2-block stochastic block model

Work with undergraduate Joshua Mendoza

Synchrony measure

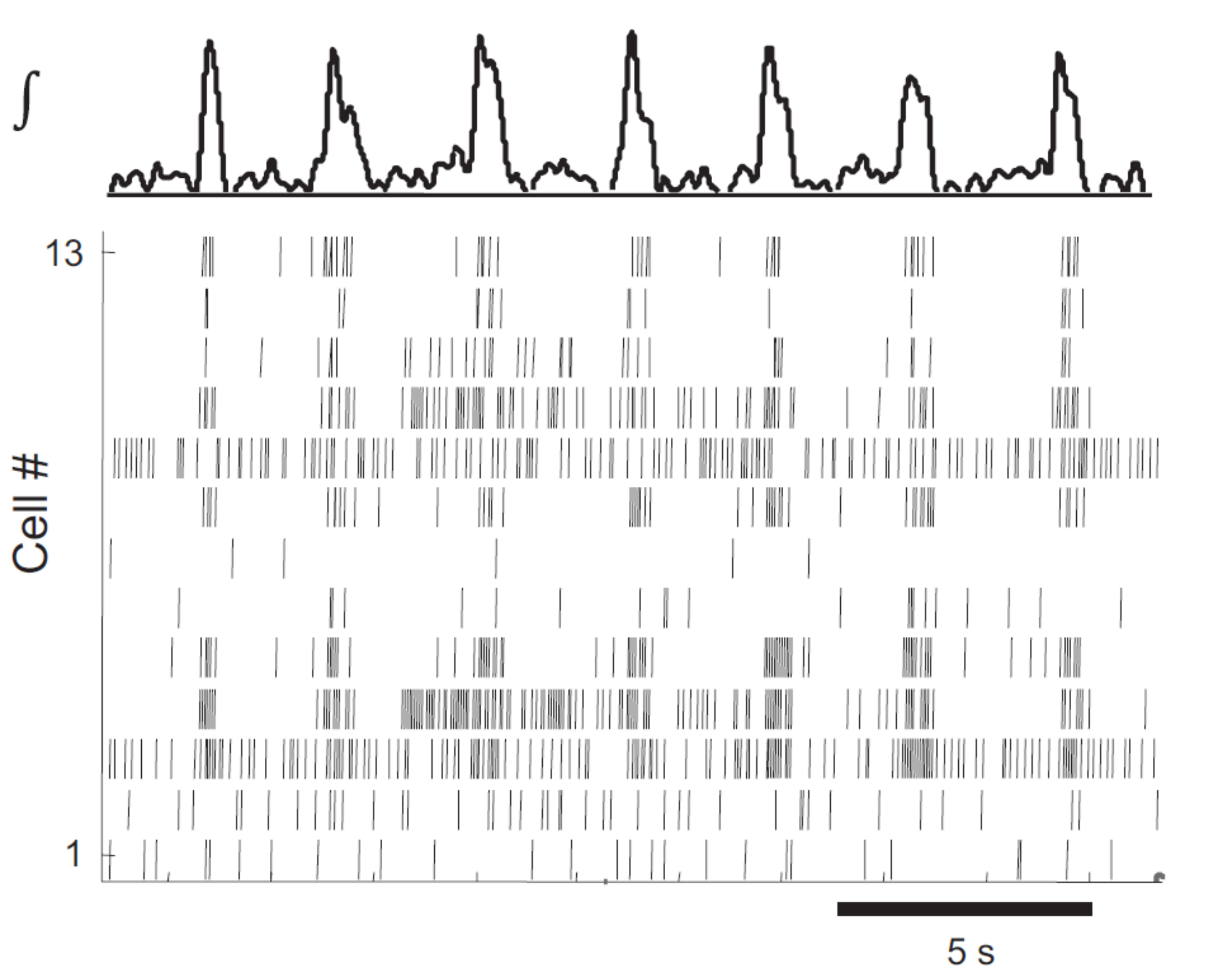
$$\chi = \left(\frac{\langle \bar{x}^{\mathrm{filt}}(t)^2 \rangle_t - \langle \bar{x}^{\mathrm{filt}}(t) \rangle_t^2}{\frac{1}{N} \sum_{i=1}^{N} \left[\langle x_i^{\mathrm{filt}}(t)^2 \rangle_t - \langle x_i^{\mathrm{filt}}(t) \rangle_t^2 \right]} \right)^{1/2}$$

Square root of ratio of

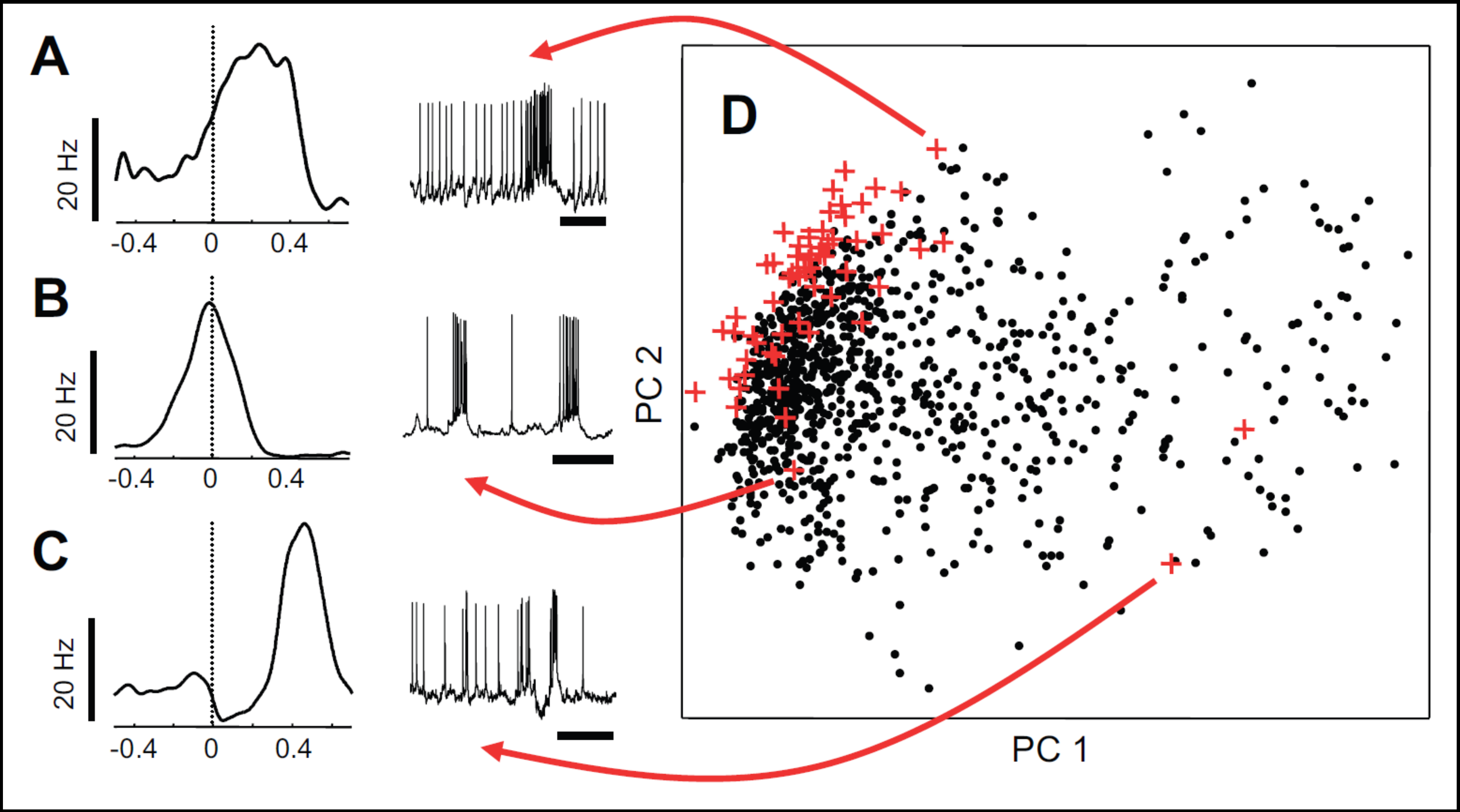
- MS deviations of pop average to
- pop average of MS deviations

Stochastic assembly

Cycle-cycle role of individual neurons is variable



Carroll, Viemari, Ramirez. J Neurophysiol (2013).



Red dots = intracellular recordings
Black dots = multielectrode

Carroll, Viemari, Ramirez. J Neurophysiol (2013).