Using dynamics to constrain the connectivity of a neuronal population: a case study in the respiratory brainstem

Jonathan Rubin
Department of Mathematics
University of Pittsburgh

IPAM Workshop:
Mathematical Approaches for Connectome Analysis
February 12-16, 2024

PROJECT GOAL:

to determine how inspiratory bursts are generated (rhythm generation: RG) and shaped (pattern formation: PF) in the respiratory brainstem

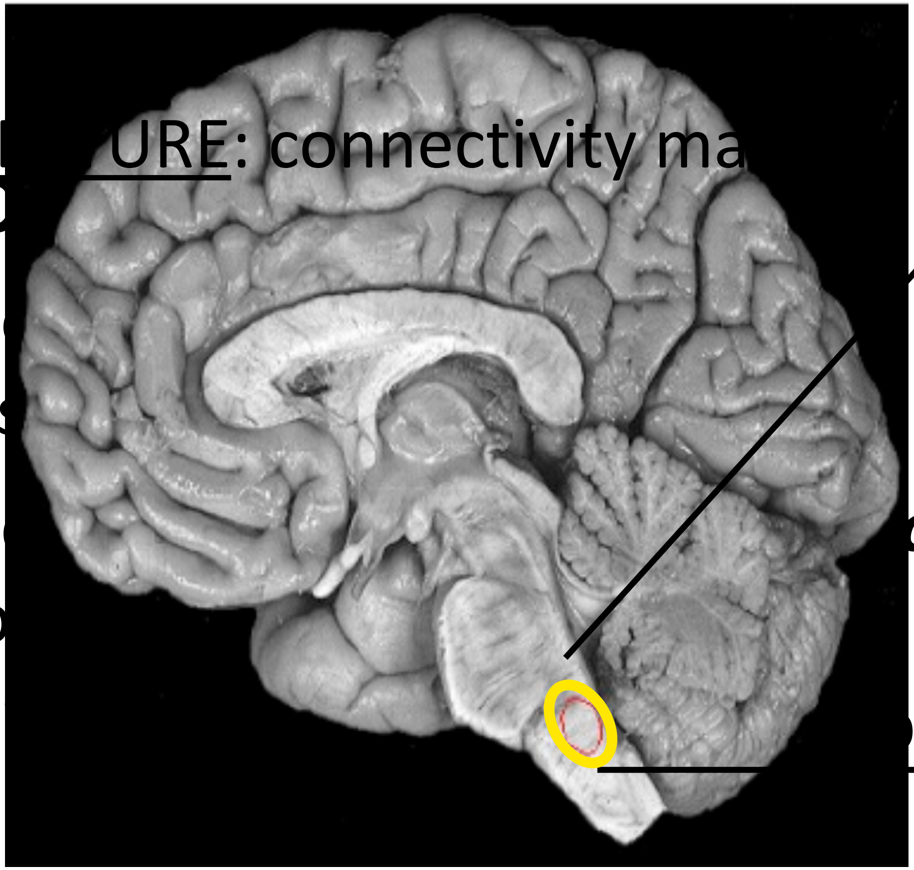
CONJ URE: connectivity ma

SUBGO

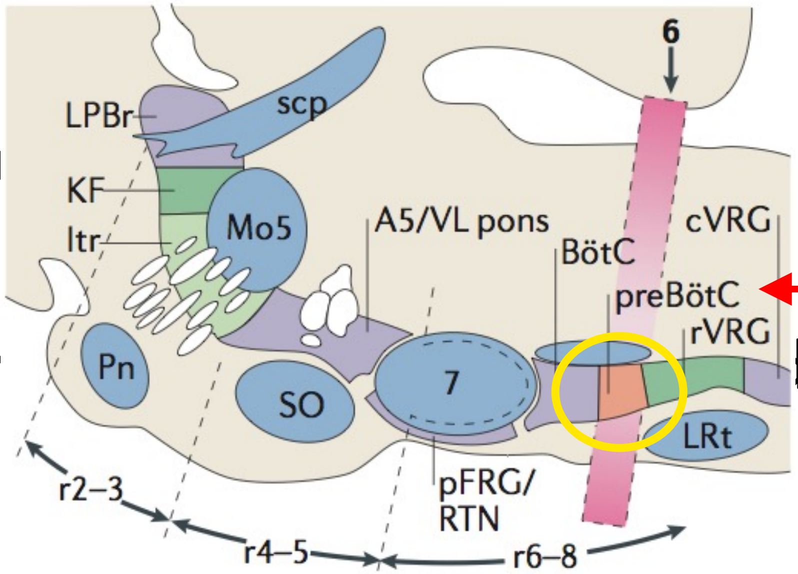
(1) to vari biophysical factors

(2) to ***ctom*** l weight distrib

(3) to lete



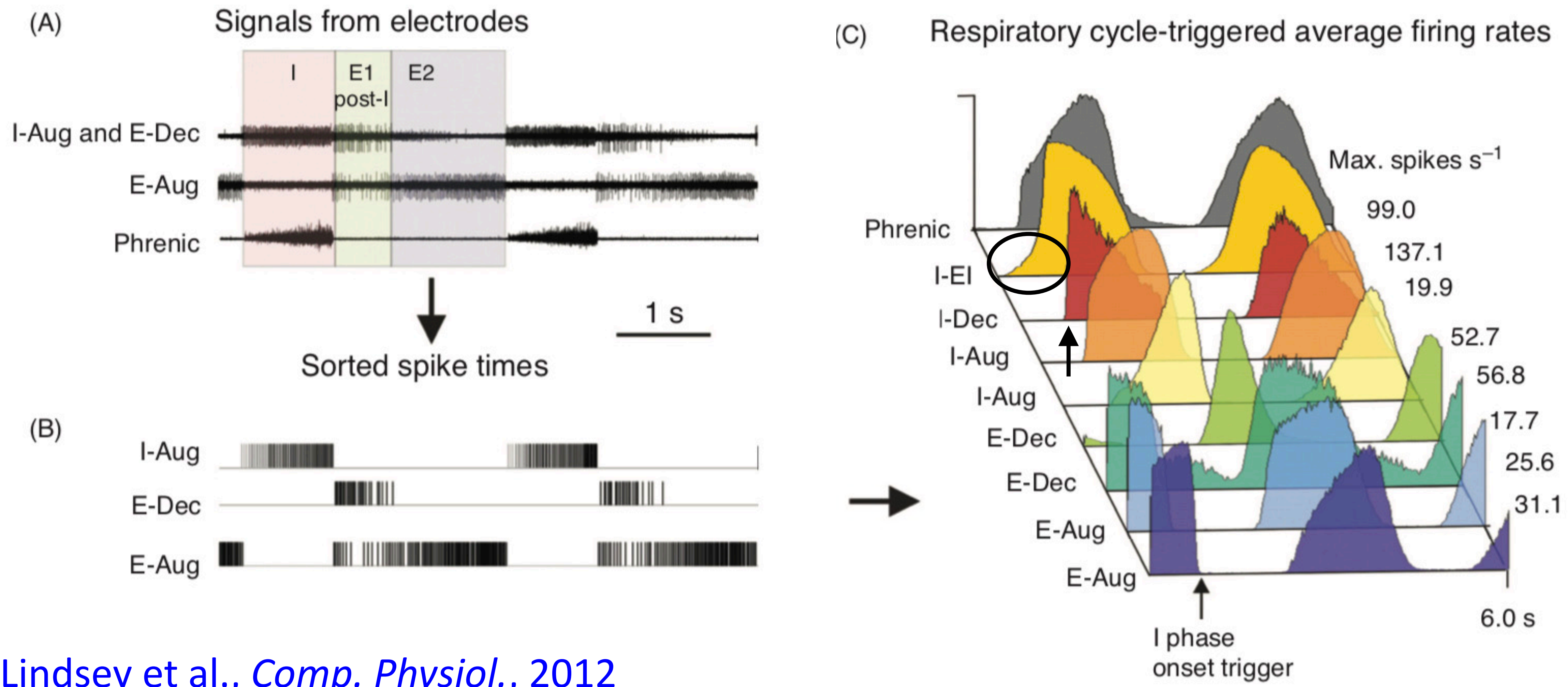
pre-Bötzinger Complex (preBötC)



Feldman and Del Negro, *NRN*, 2006

EXPERIMENTALLY OBSERVED PHENOMENA

1) 3-phase respiratory rhythms

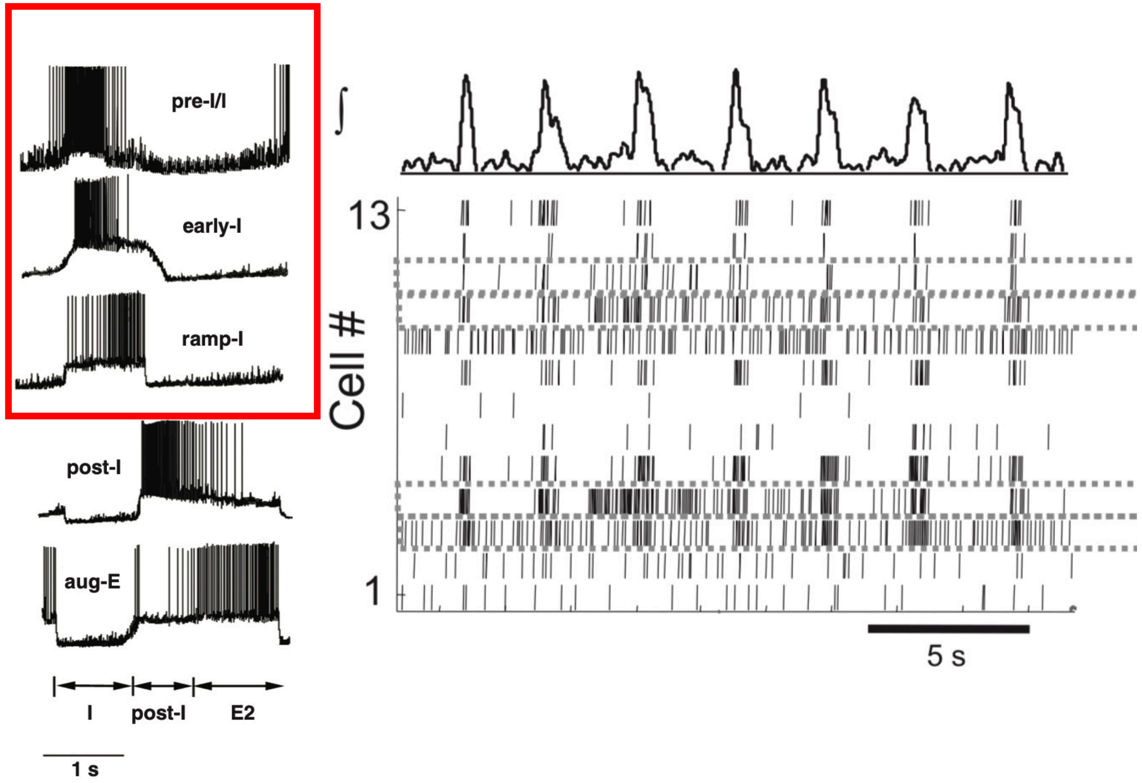


Lindsey et al., *Comp. Physiol.*, 2012

EXPERIMENTALLY OBSERVED PHENOMENA

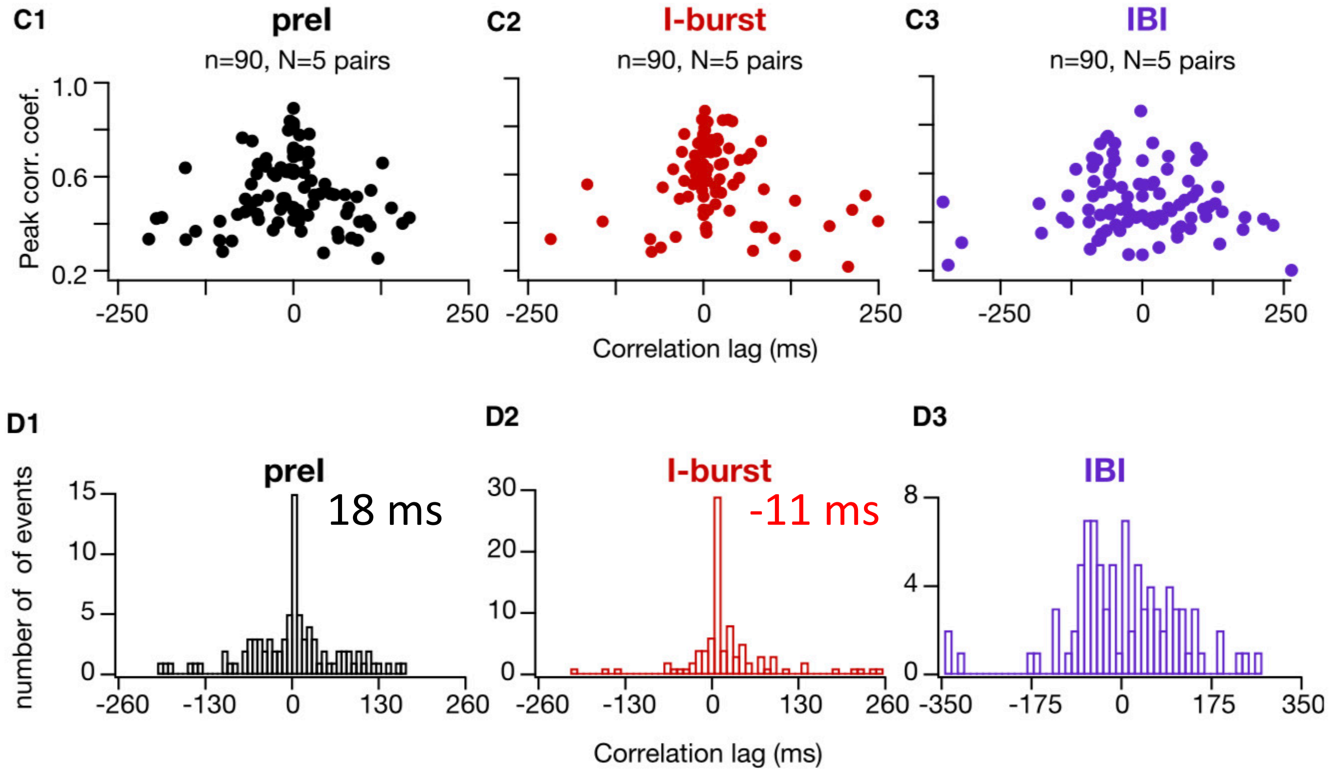
2) inspiratory dynamics: from scattered pre-I activity to synchronized I burst

early spikes transition to burst :



Carroll & Ramirez, *J. Neurophys.*, 2013

pairwise cross-correlations tighten:



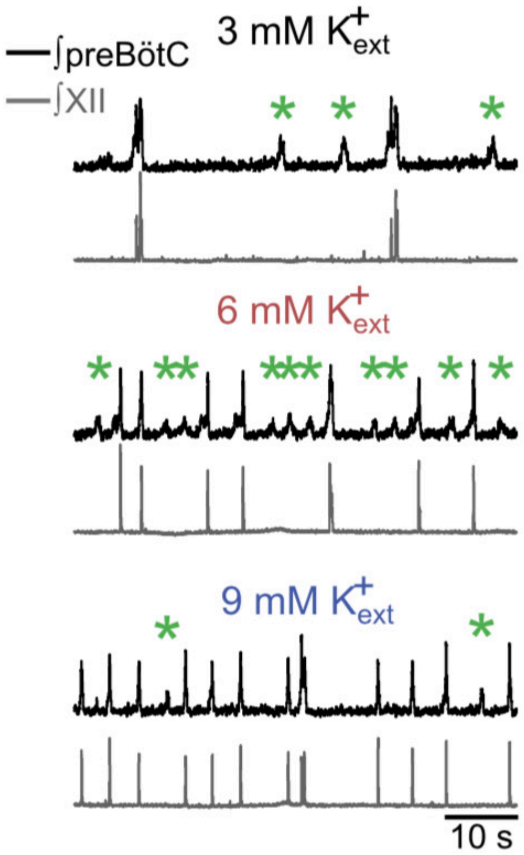
Ashhad & Feldman, *Neuron*, 2020

EXPERIMENTALLY OBSERVED PHENOMENA

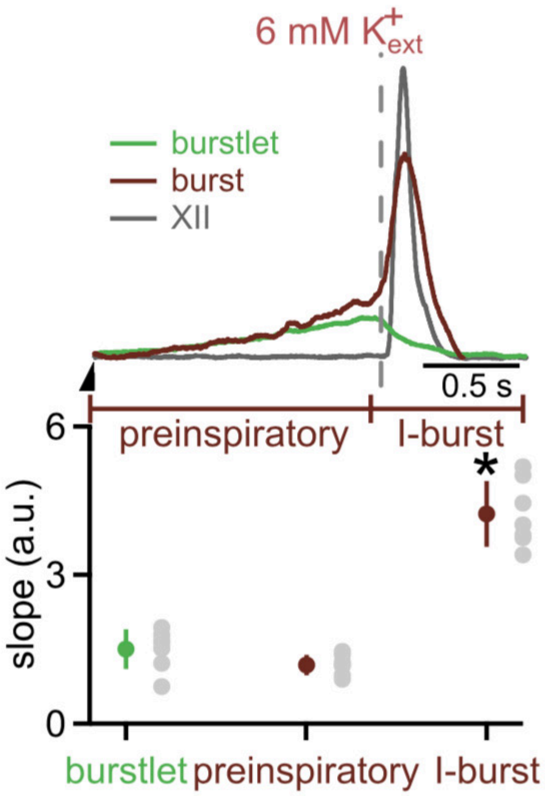
Kam et al., *J. Neurosci* (x2), 2013

3) transition can be prolonged or can even fail: *burstlets*

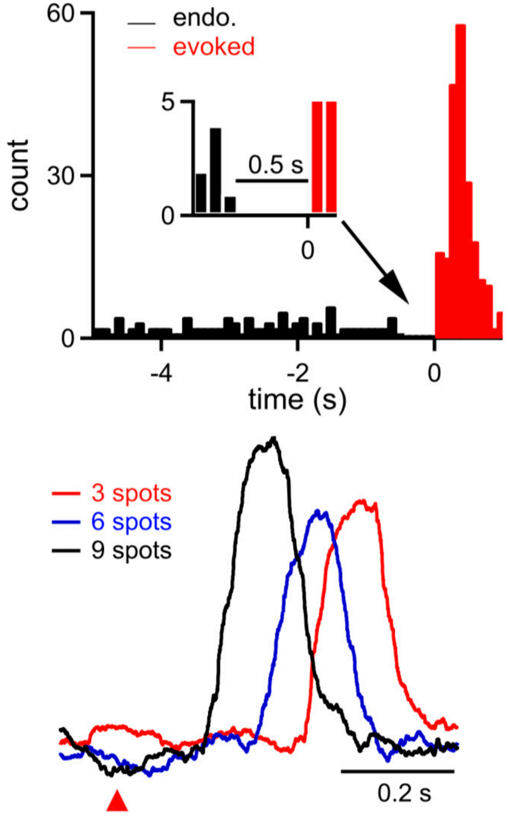
bursts & burstlets; only bursts drive muscles



initially, burstlets and bursts look the same



delay from initiation to burst can be long and variable

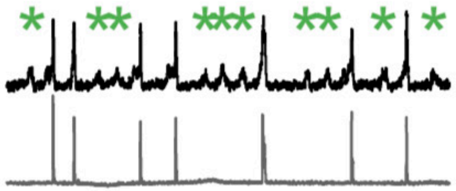


PAUSE

1) 3-phase respiratory rhythms

2) inspiratory dynamics: from scattered pre-I activity to synchronized I burst

3) transition can be prolonged or can even fail: ***burstlets***

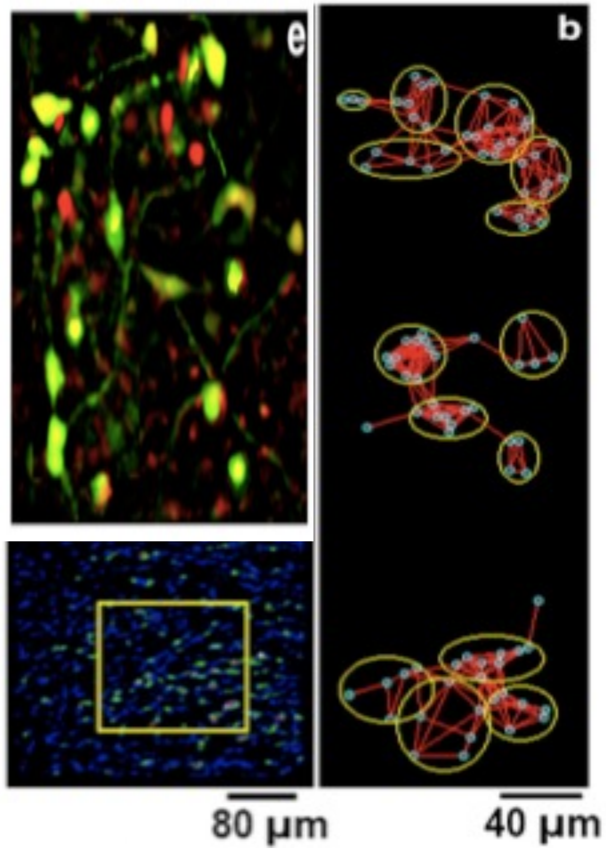


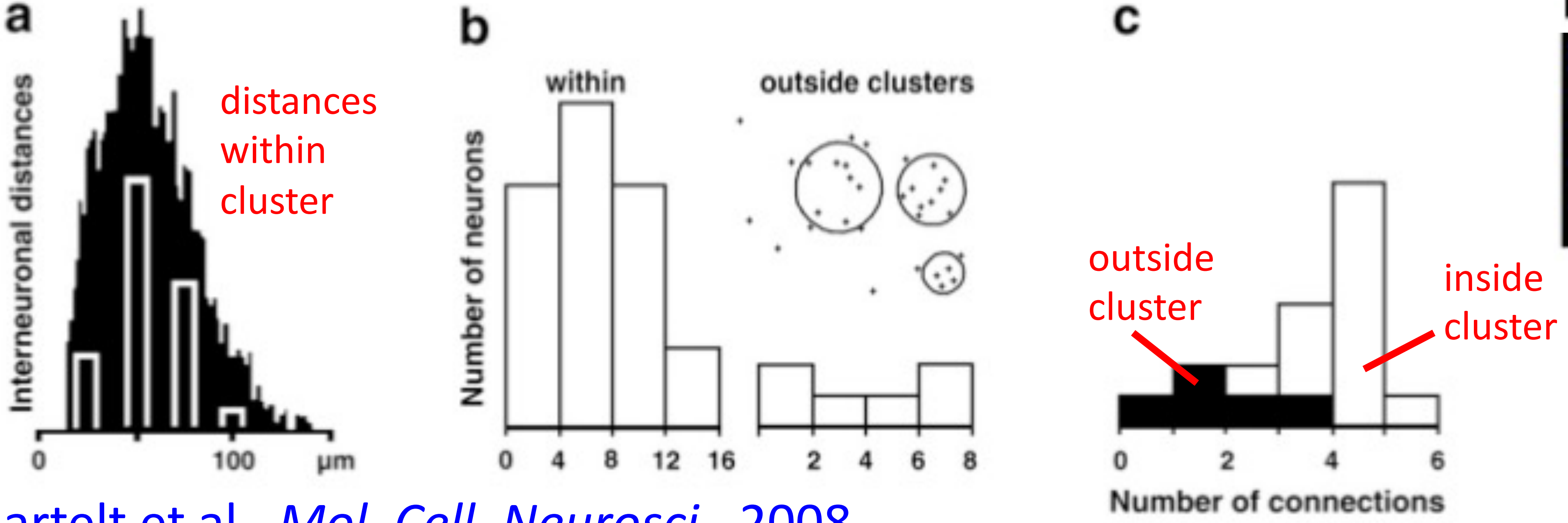
A model that reproduces and explains the mechanisms behind these key observations would be a triumph.

EXPERIMENTALLY OBSERVED PHENOMENA

4) preBötC is a caveman network (in organotypic culture)

- slice preparations (organotypic culture)
- ~90% of neurons in local clusters (*right b*; *below a*)
- cluster size distribution characterized (*below b*)
- dense intra-cluster connections (*below c - open*)
- sparse inter-cluster links (*below c - filled*)

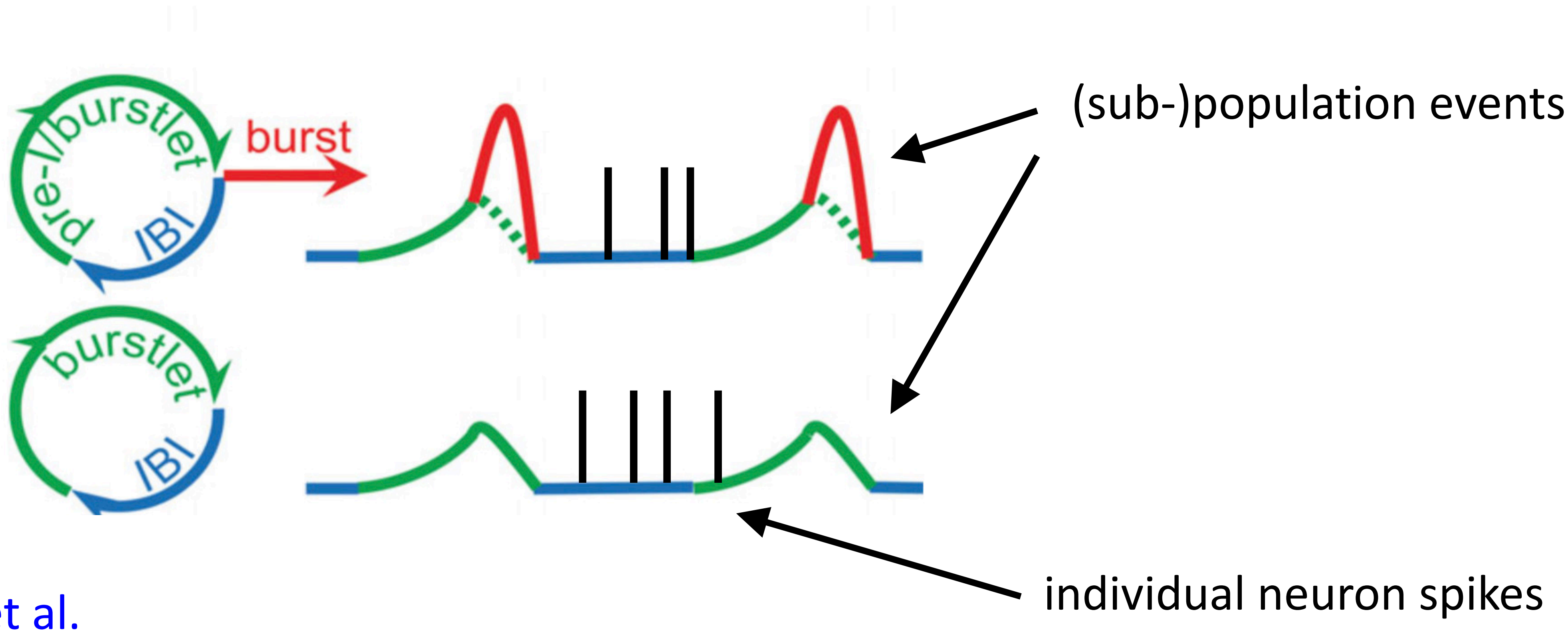




Hartelt et al., *Mol. Cell. Neurosci.*, 2008

EXPERIMENTALLY OBSERVED PHENOMENA - SUMMARY

Each respiratory cycle is driven by an inspiratory event generated by a (caveman?) network of neurons in the preBötC that initiates as a burstlet and may, after some delay, transition into a functional burst.



Kam, Feldman et al.

PROJECT GOAL:

to determine how inspiratory bursts are generated (rhythm generation: RG) and shaped (pattern formation: PF) in the respiratory brainstem

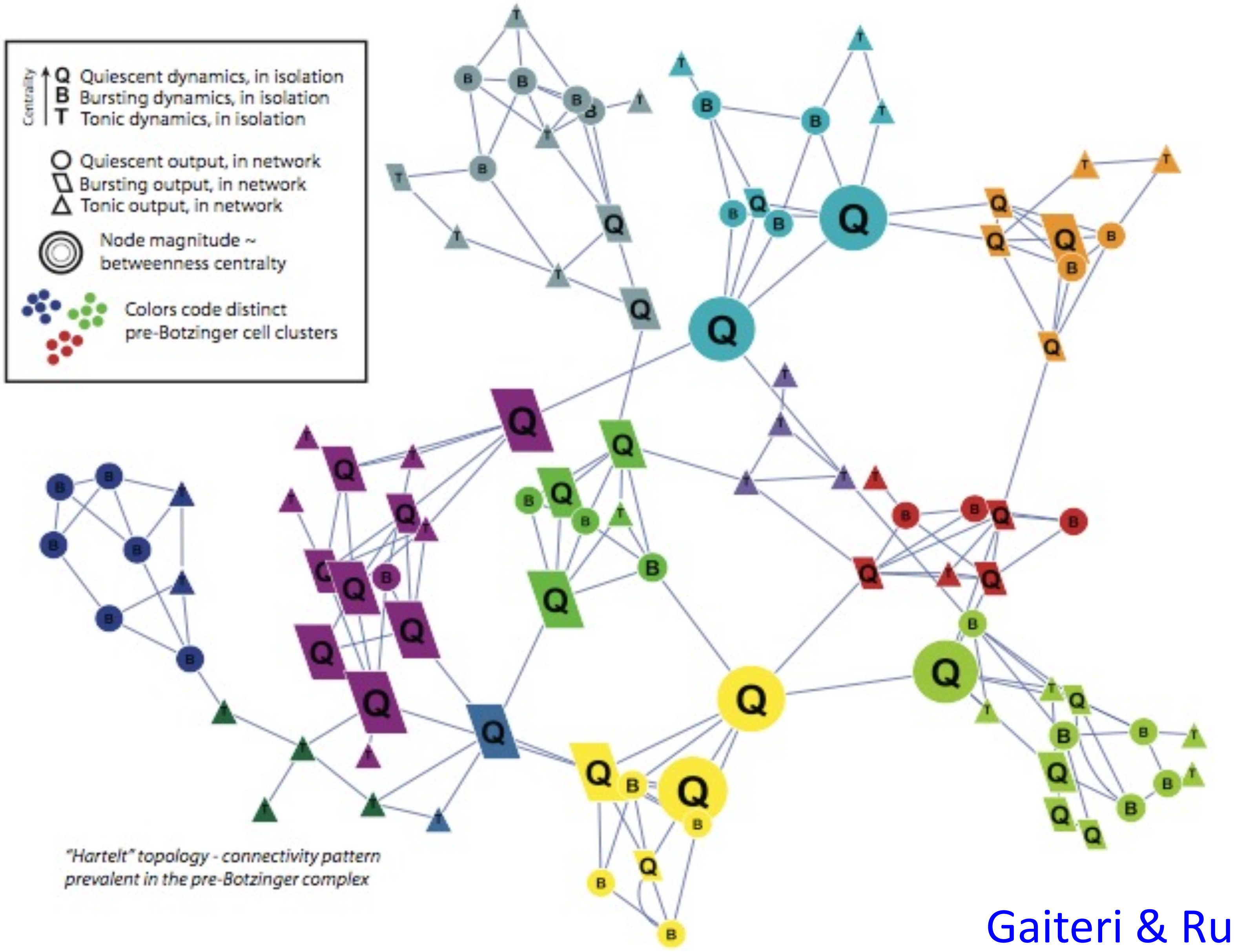
OUTLINE FROM HERE ON

1) Gaiteri & Rubin – caveman fails
2) Phillips & Rubin – biophysical model of the burstlet → burst transition
3) Ashhad & Feldman – focus on connectivity (with IF neurons)
4) MSBP – a new framework to fully focus on connectivity

NOT IN THIS TALK

1) cool models for how individual neurons can produce ramping activity
2) applying maximum entropy models to fMRI data for SZ vs. HC subjects

(1) Computational model preBötC networks with HH dynamics



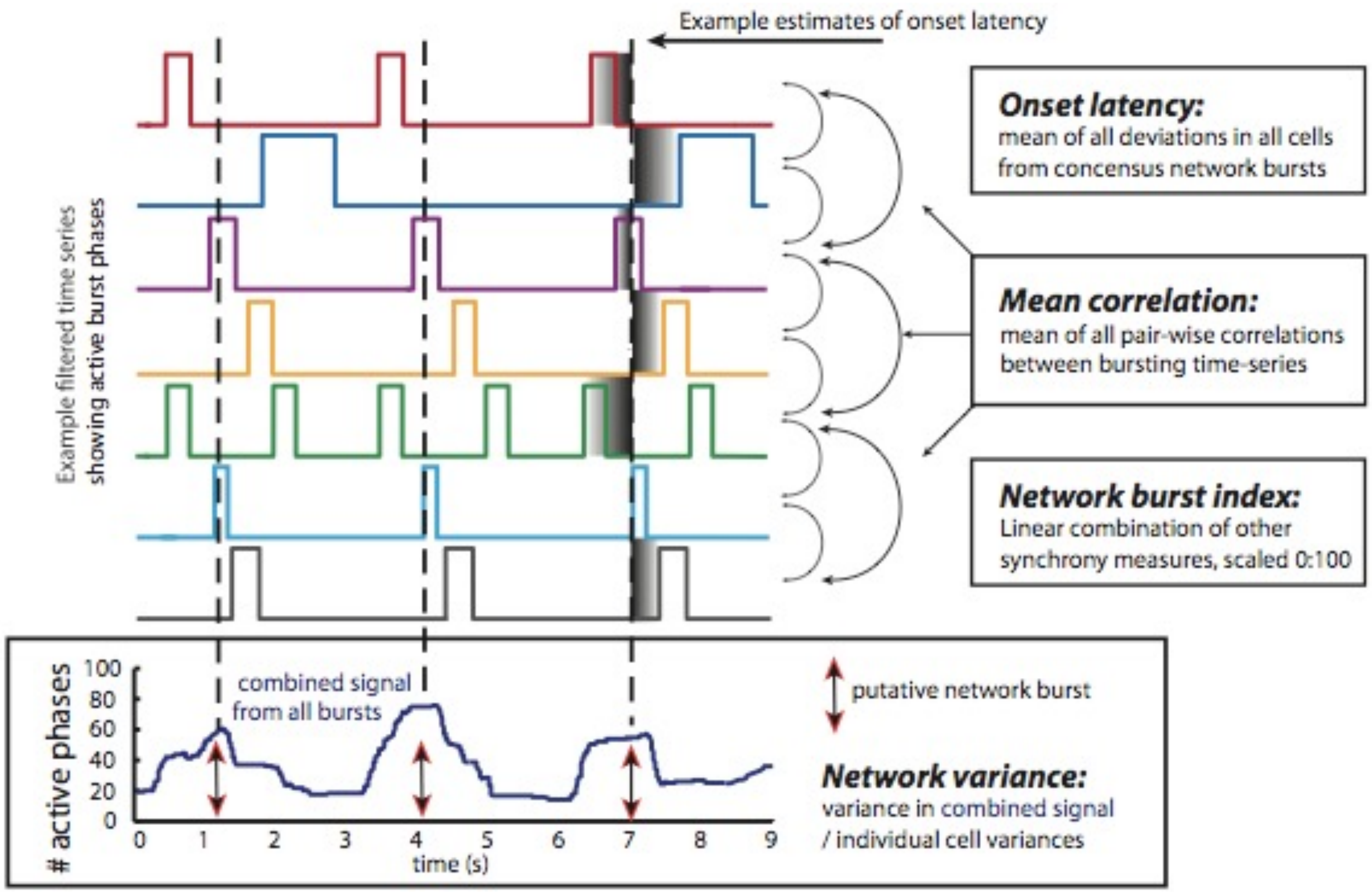
- network built using Hartelt et al.'s statistics
- Q: How can this synchronize?? (David?)
- colors code clusters
- sizes code betweenness centrality
- Idea: Maybe specific dynamics at key places in network promotes synchronization
- letters code intrinsic dynamics
- shapes code dynamics in coupled network

Gaiteri & Rubin, *Front. Comp. Neuro.*, 2011

Simulation and analysis of ongoing emergent dynamics

filter each neuron's output and score each network's burst synchrony

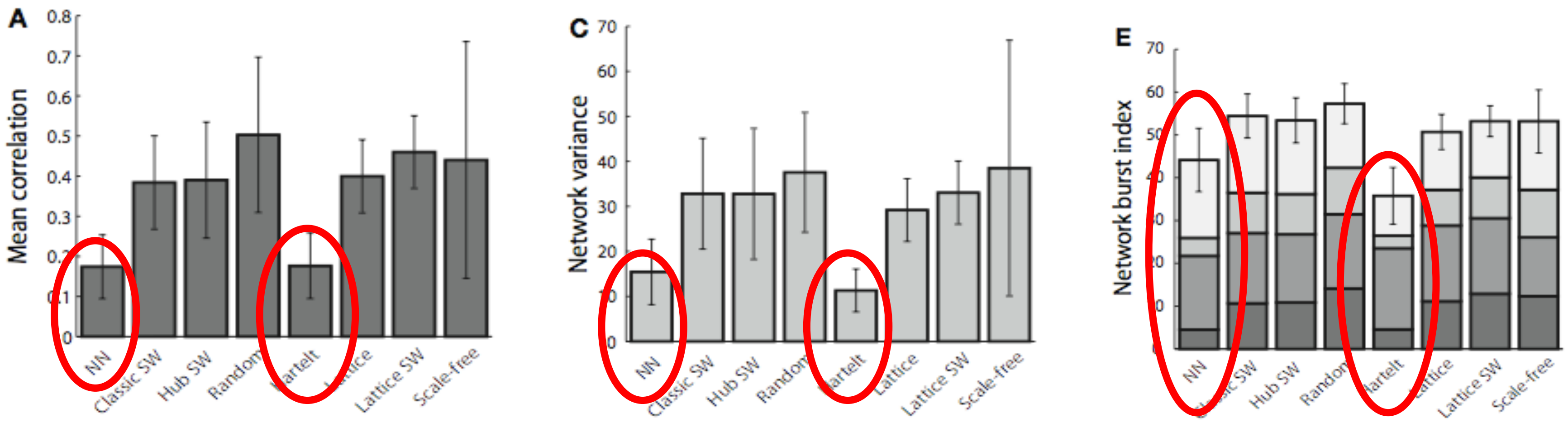
NBI = mean correlation + network variance + # bursting + (1/onset latency)



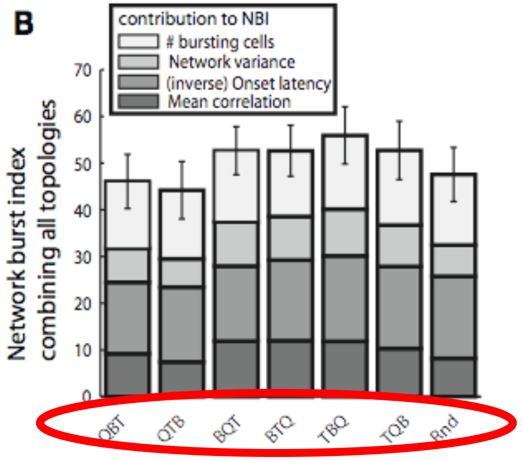
Results: network burst synchrony vs. network topology

(1) all network burst synchrony measures vary significantly w/topology

(2) correlation/variance and overall NBI: ***NN and Hartelt perform worst***



(3) special dynamics at hubs does not help



Gaiteri & Rubin, *Frontiers Comp. Neuro.*, 2011

Why does the Hartelt network fail?

- hypothesis 1: wrong dynamics – Butera model is out of date

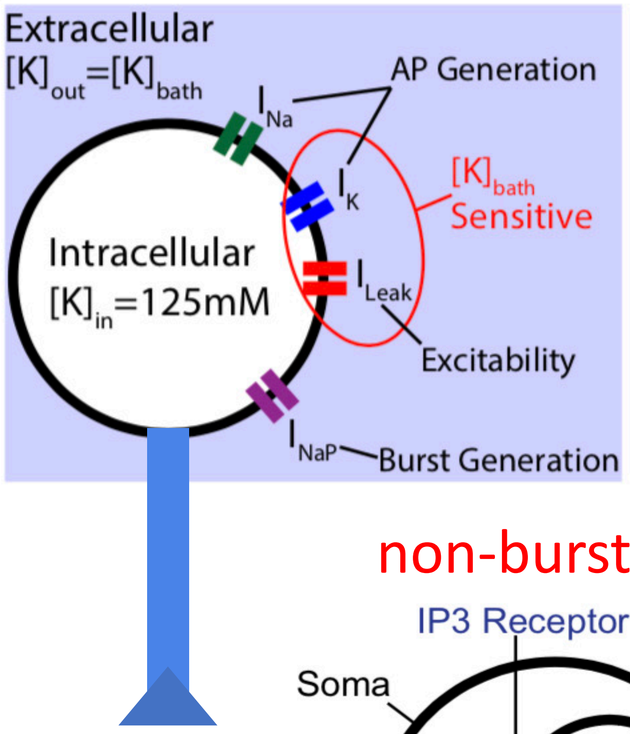
  cf. Rubin et al., *PNAS,* 2009; Toporikova & Butera, *JCNS*, 2011; Jasinski et al., *EJN*, 2013; Park & Rubin, *JCNS*, 2013; Song et al., *eNeuro*, 2015; Phillips et al., *eLife*, 2019 & 2022

- hypothesis 2: wrong architecture – results based on culture do not reflect true connection pattern

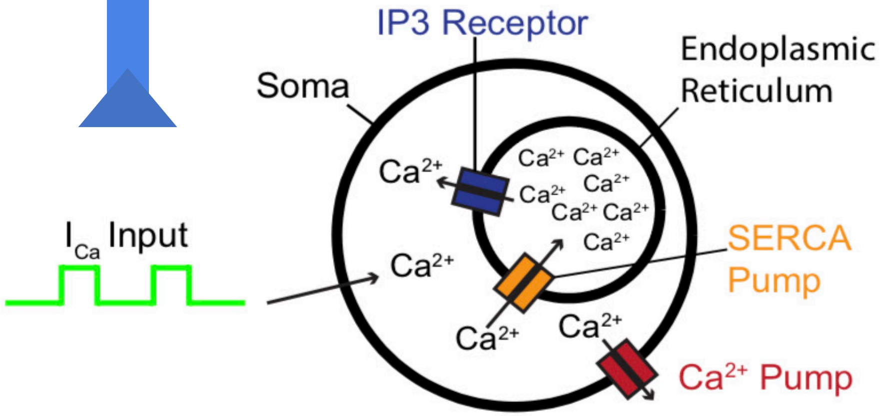
(2) Results with updated dynamics and 2 sub-population network

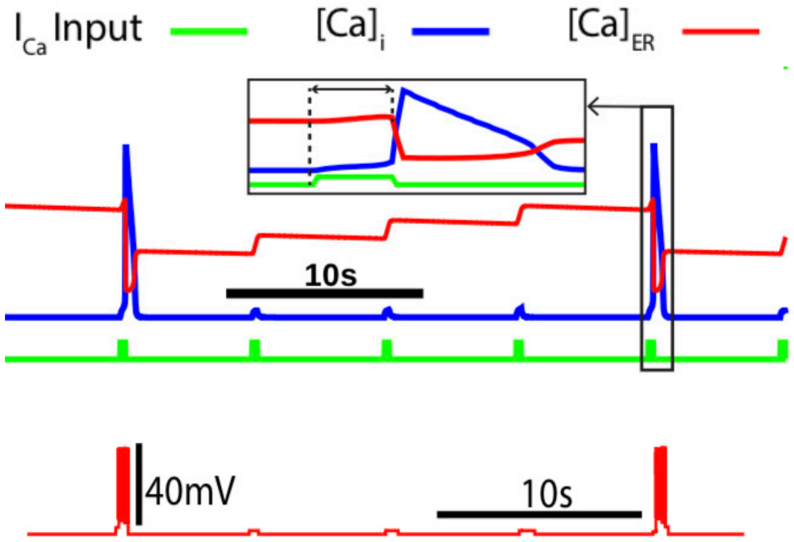
Phillips & Rubin, *eLife*, 2022

rhythm generator

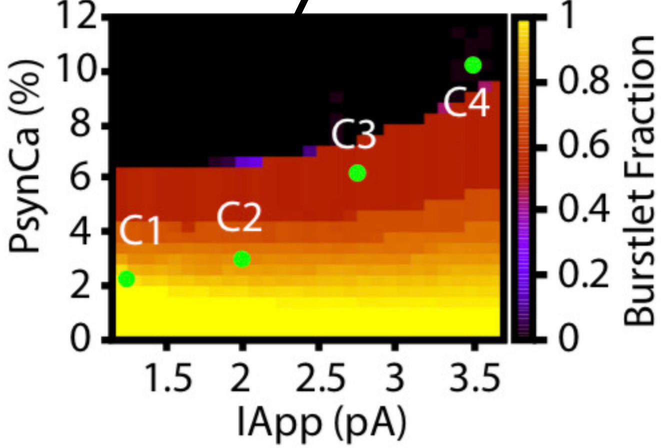


non-burster



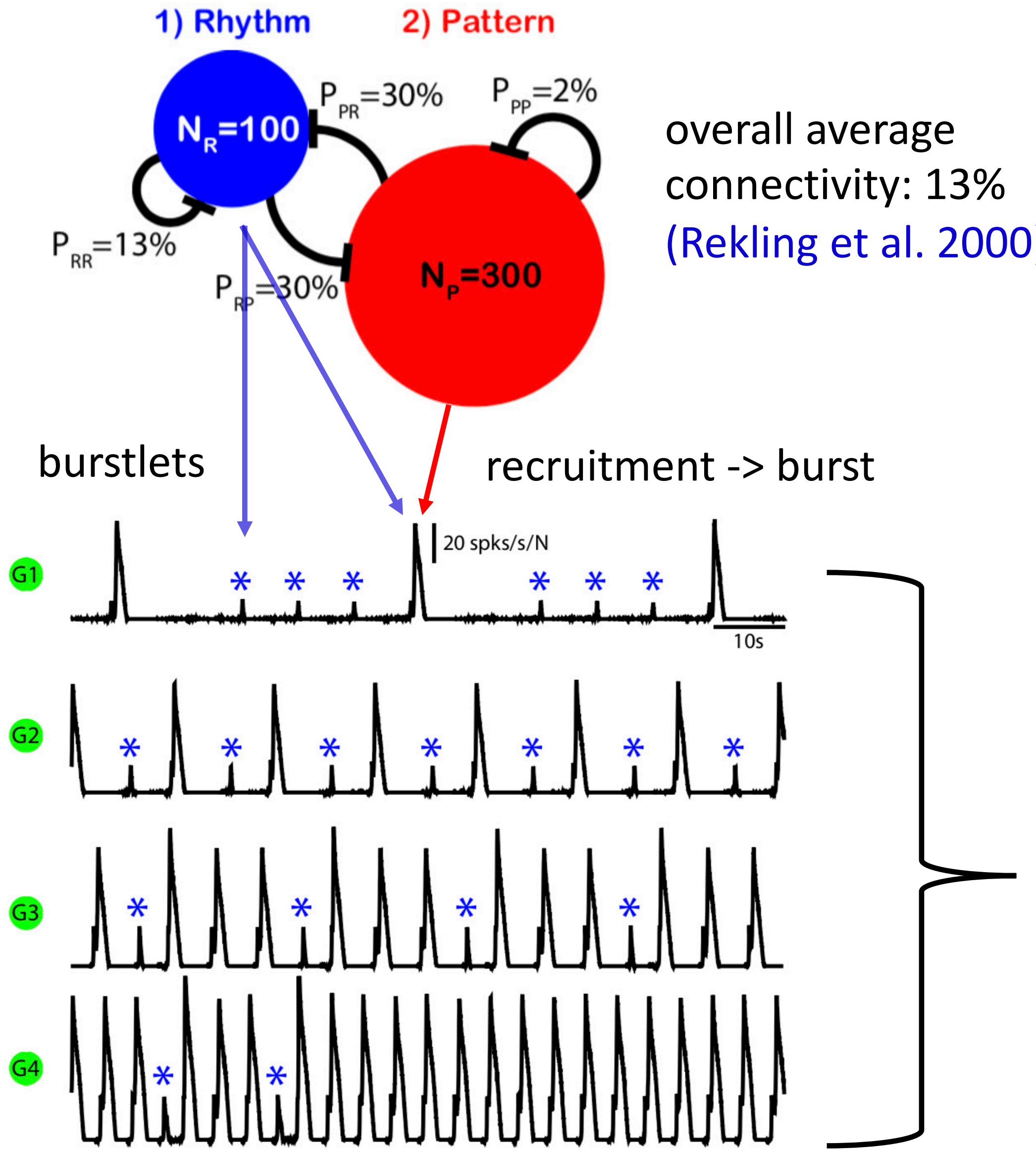


complete
entrainment
(BF=0)

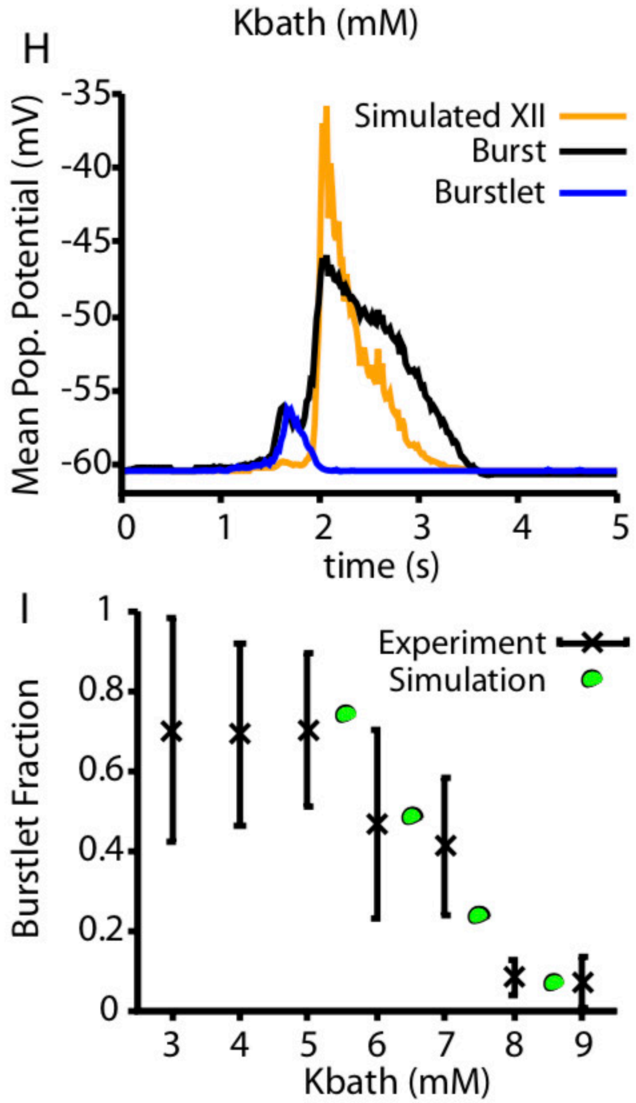


From 2 neurons to 2 subpops: matches data!

Phillips & Rubin, *eLife*, 2022



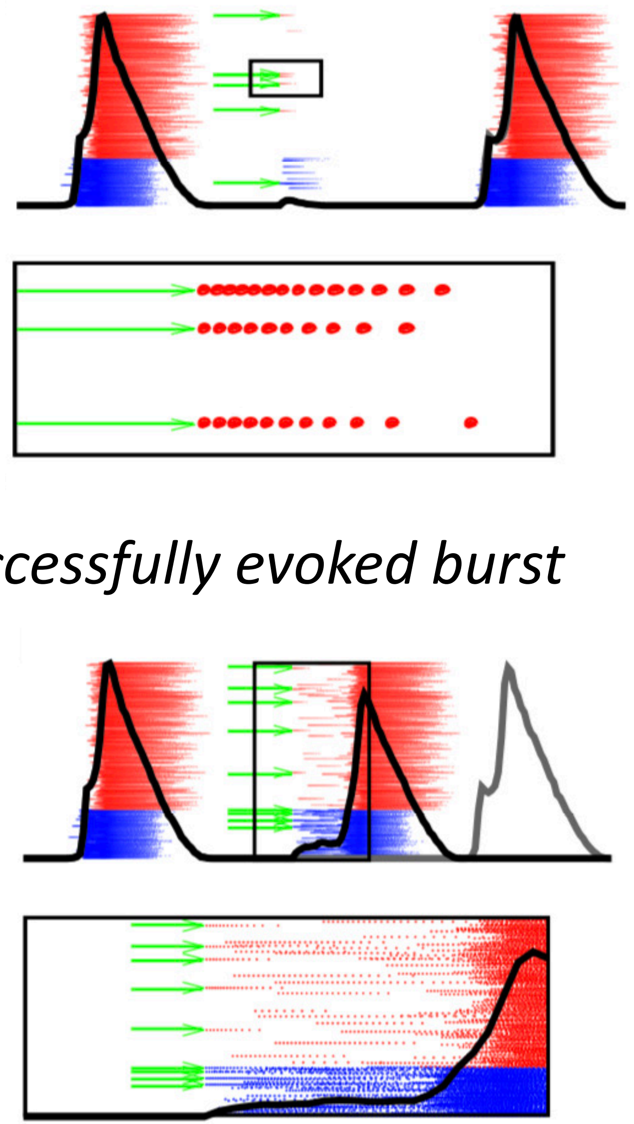
overall average connectivity: 13%
(Rekling et al. 2000)



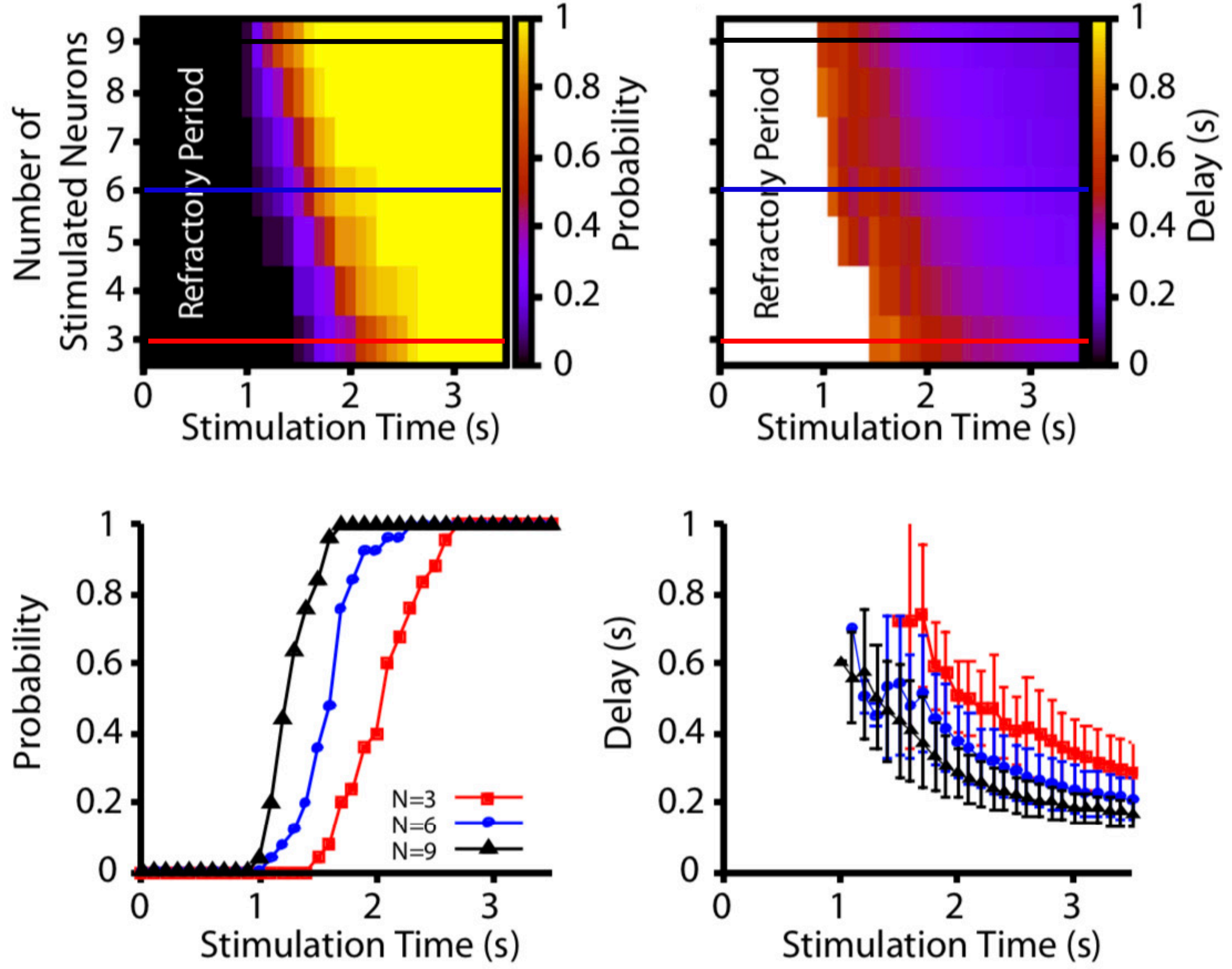
2-subpop network also matches holographic uncaging experiments

failure to evoke burst

successfully evoked burst

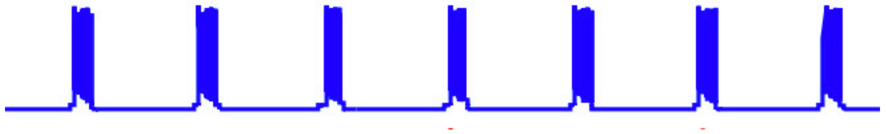


summary:

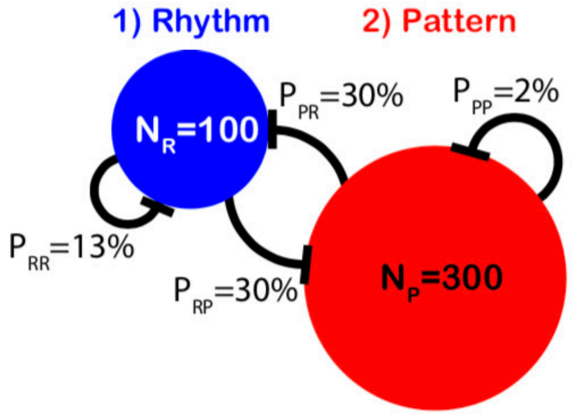


Recipe for burstlets+bursts

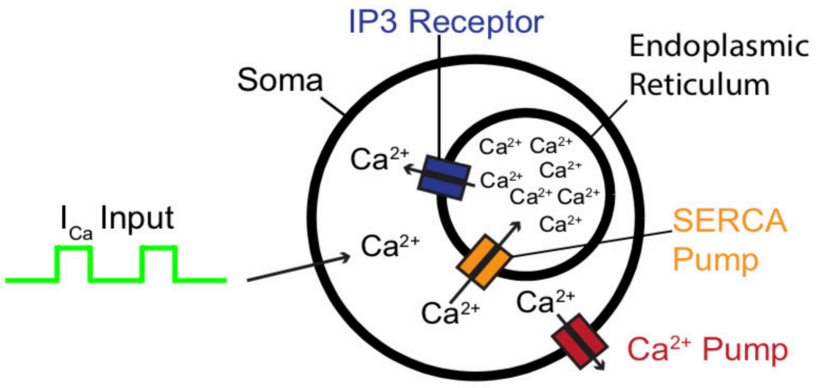
- RG subpopulation bursting



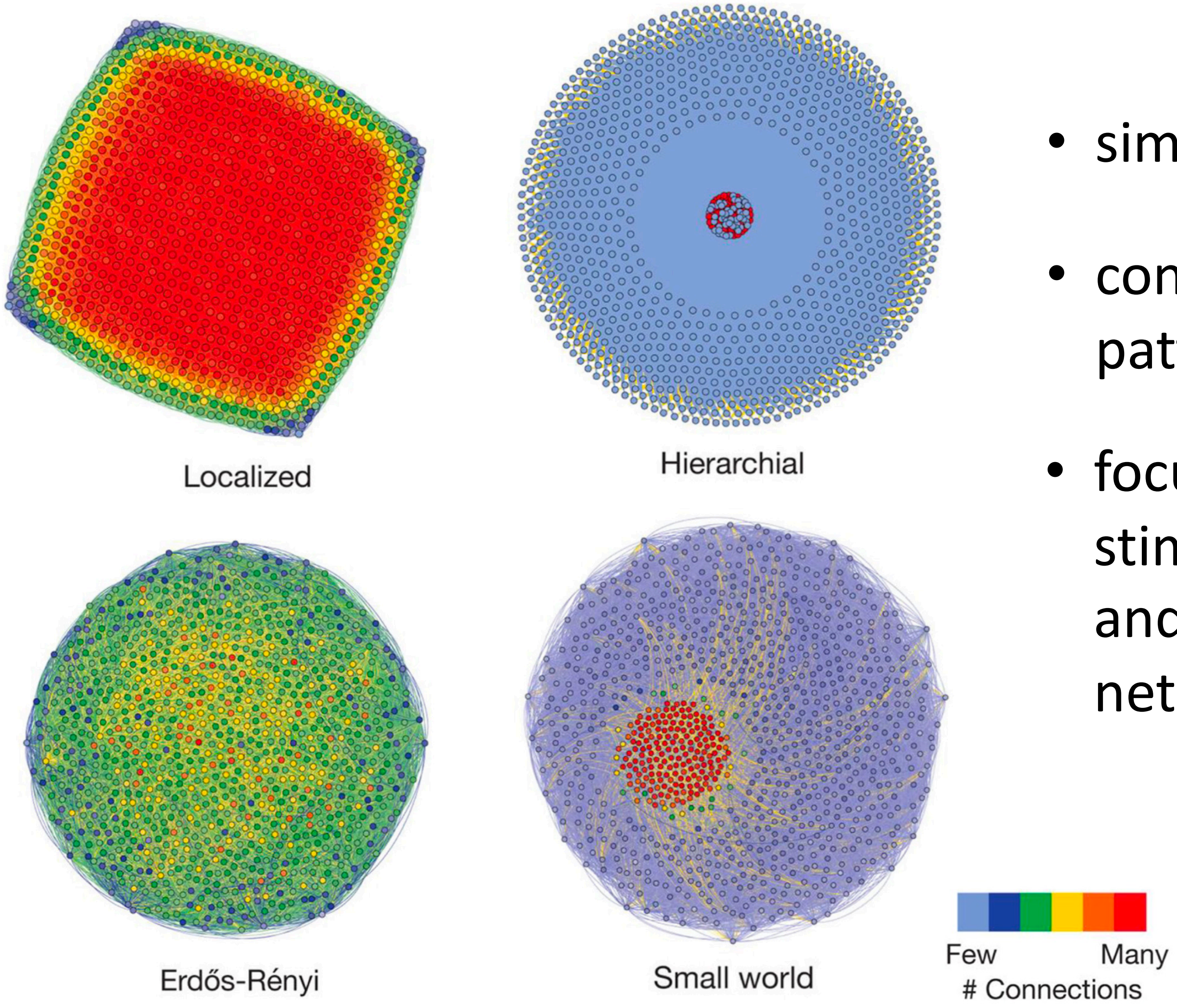
- synaptic coupling within and between RG and PF subpopulations



- calcium-induced calcium release



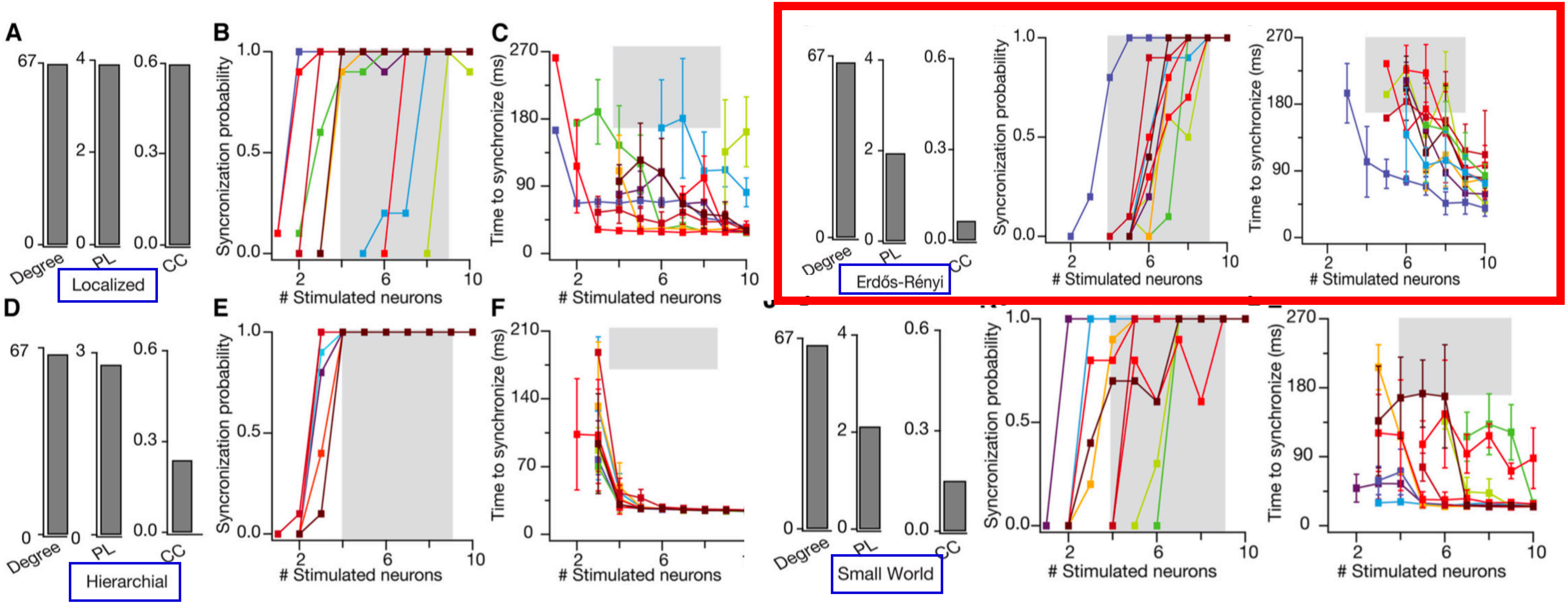
(3) Focus on network alone: *architecture for synchronized bursting?*



- simple LIF neurons at nodes (vs. HH)
- consider 4 different connection patterns
- focus on holographic experiments: stimulate 1-10 neurons initially and observe subsequent induced network activity

Ashhad et al., *J. Neurosci.*, 2023

Results: only ER networks with log-normal weight distribution match experiments on induced burst (or burstlet) generation



Ashhad et al., *J. Neurosci.*, 2023

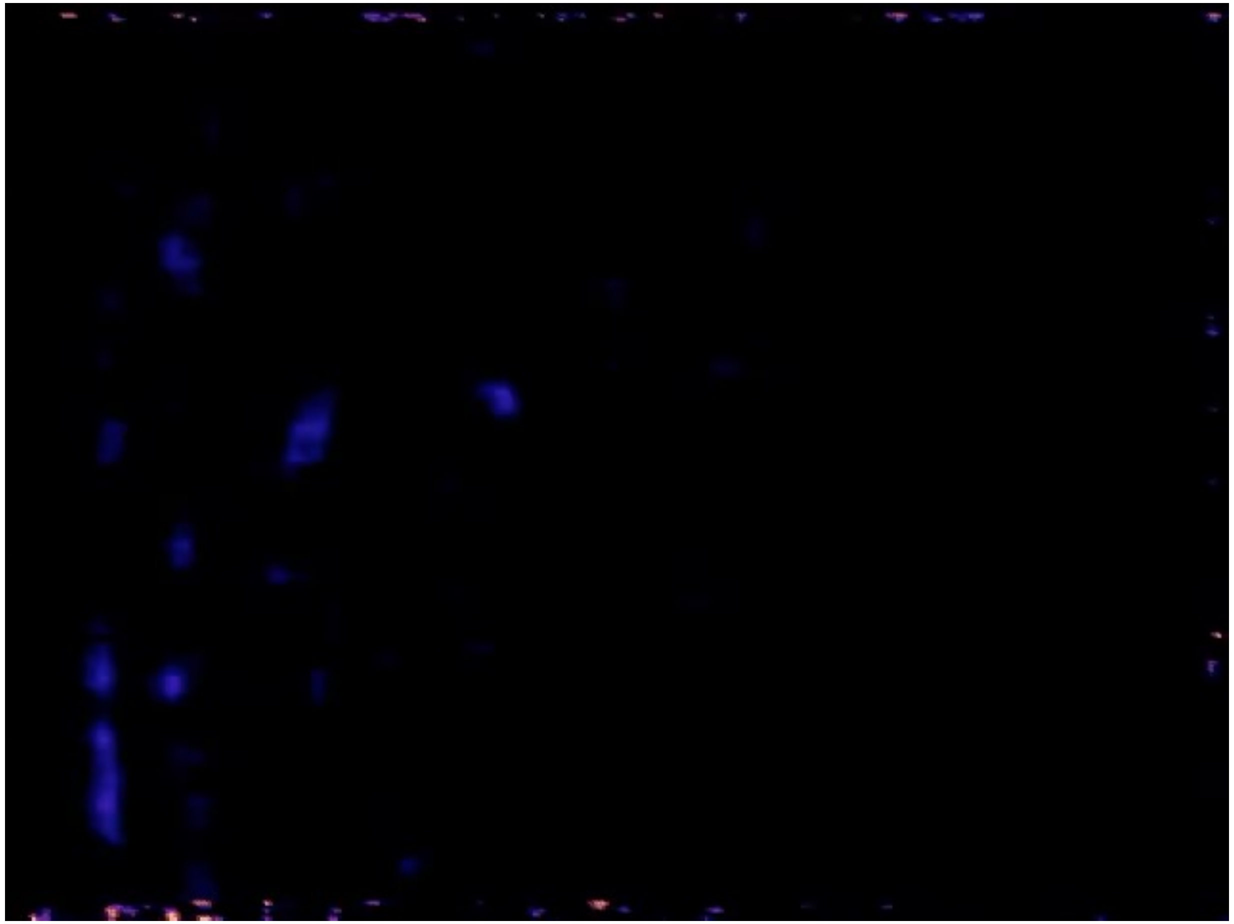
***Prediction*: preBötC network has ER architecture with log-normal synaptic weight distribution**

***However*: Phillips & Rubin network captures uncaging experiments without log-normal synaptic weights, using two populations with different random connection probabilities**

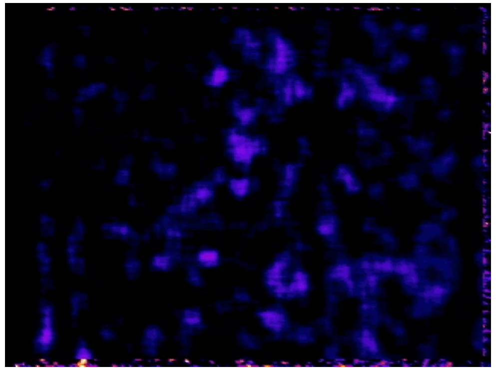
***Idea*: Try to develop a framework where we can use mathematical analysis to go beyond simulation results**

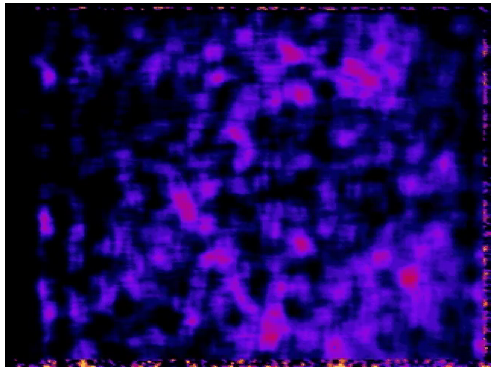
recall: EXPERIMENTALLY OBSERVED PHENOMENA

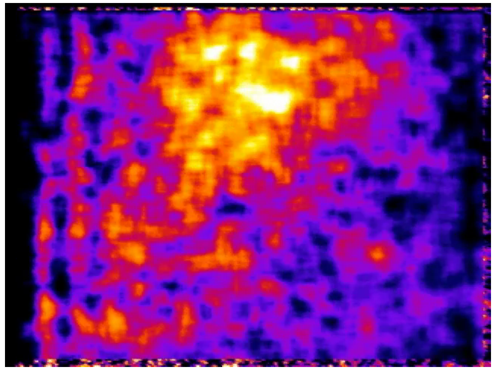
2) inspiratory dynamics: from scattered pre-I activity to synchronized I burst



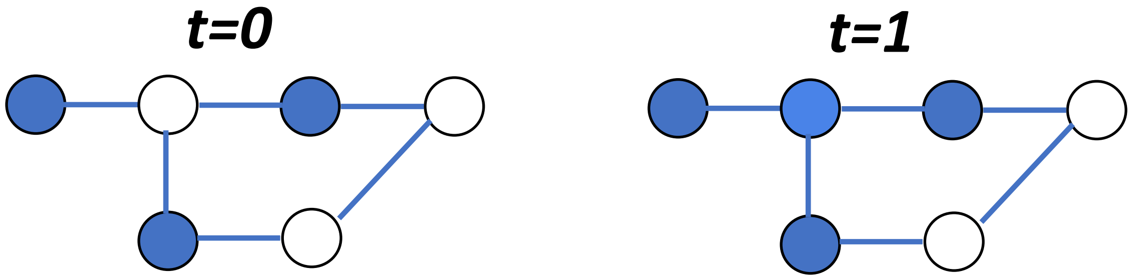
Jeffrey C. Smith, NIH (retired)







bootstrap percolation



- Consider a graph $G = (V,E)$
- For each $v_i \in V$, assign a state $s_i \in \{0,1\}$ where we call *0* "inactive" and *1* "active"
- Impose discrete time dynamics with a *k-threshold update rule* and *monotonicity*:

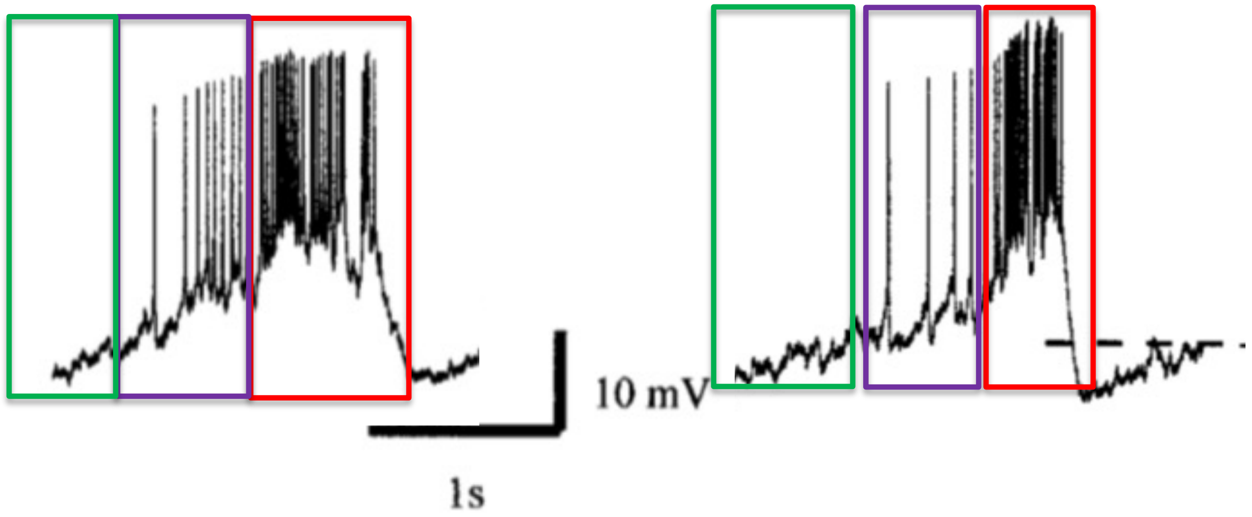
$$s_i(t+1) = \max\left\{X_i(t),\ H\left(\sum_{j=1}^{n} e_{ij} s_j(t) - (k+\epsilon)\right)\right\},\quad 0<\epsilon<1$$

where

$$e_{ij} = \begin{cases} 1, & \exists \text{ connection between } v_i \text{ and } v_j \\ 0, & \text{else} \end{cases}$$

Chalupa et al. (1979), van Enter (1987), Schonmann (1992), Holroyd (2003), Kozma et al. (2004, 2005), Balogh et al. (2006, 2012), Janson et al. (2016) } find $p_c(G,k,n)$

respiratory network version: multi-state bootstrap percolation (MSBP)



Tryba et al., *J. Neurosci.*, 2003

- three states & two thresholds: (k_1, k_2)

  0: inactive

  1: weakly active (sporadic activity) – node sends output of ***strength 1***

  2: fully active (bursting) – node sends output of ***strength w > 1***

- *G = (V,E)*: *directed* graph (*digraph*)

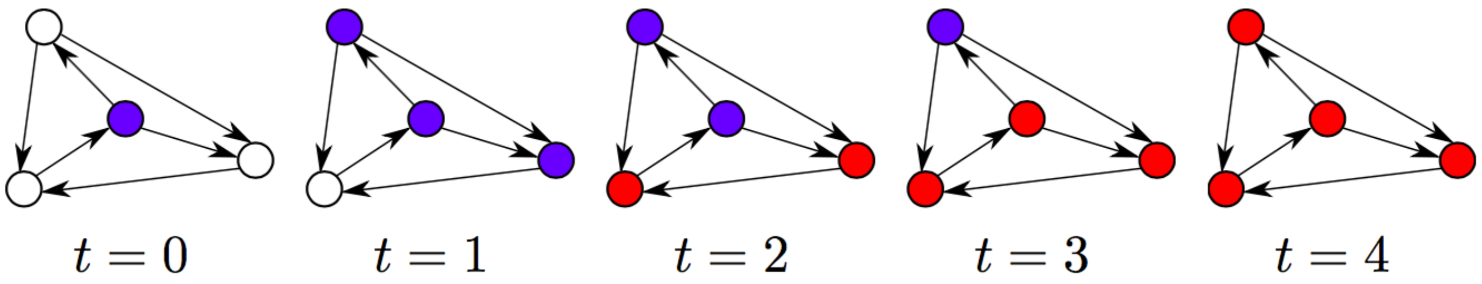
start with monotone MSBP

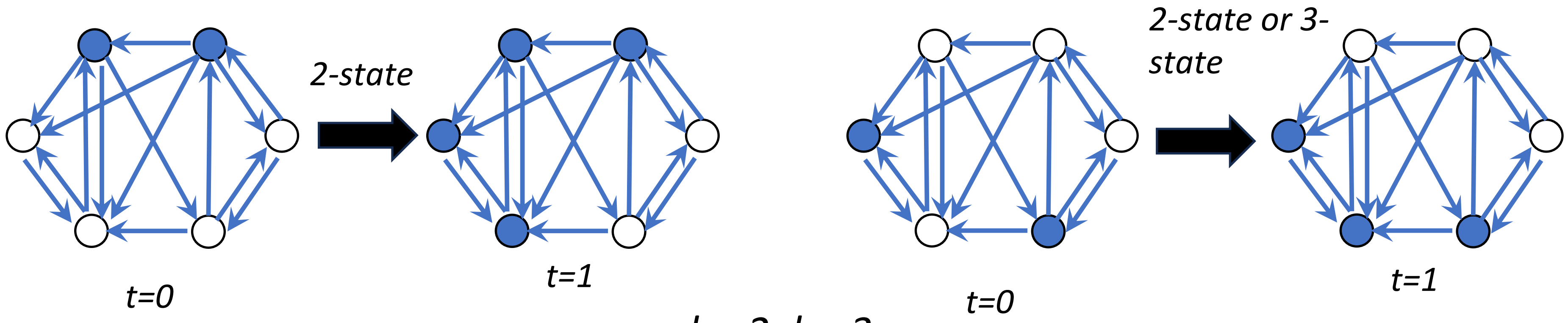
mathematically:

$$\begin{cases} s_i(t) \in \{0, 1, w \geq 1\} \\ s_i(t+1) = \max\{H(\sum_{j\to i} e_{ij}s_j(t) - k_1); wH(\sum_{j\to i} e_{ij}s_j(t) - k_2); s_i(t)\} \end{cases}$$

where $j \to i$ denotes a directed edge from j to i in the graph

graphically:



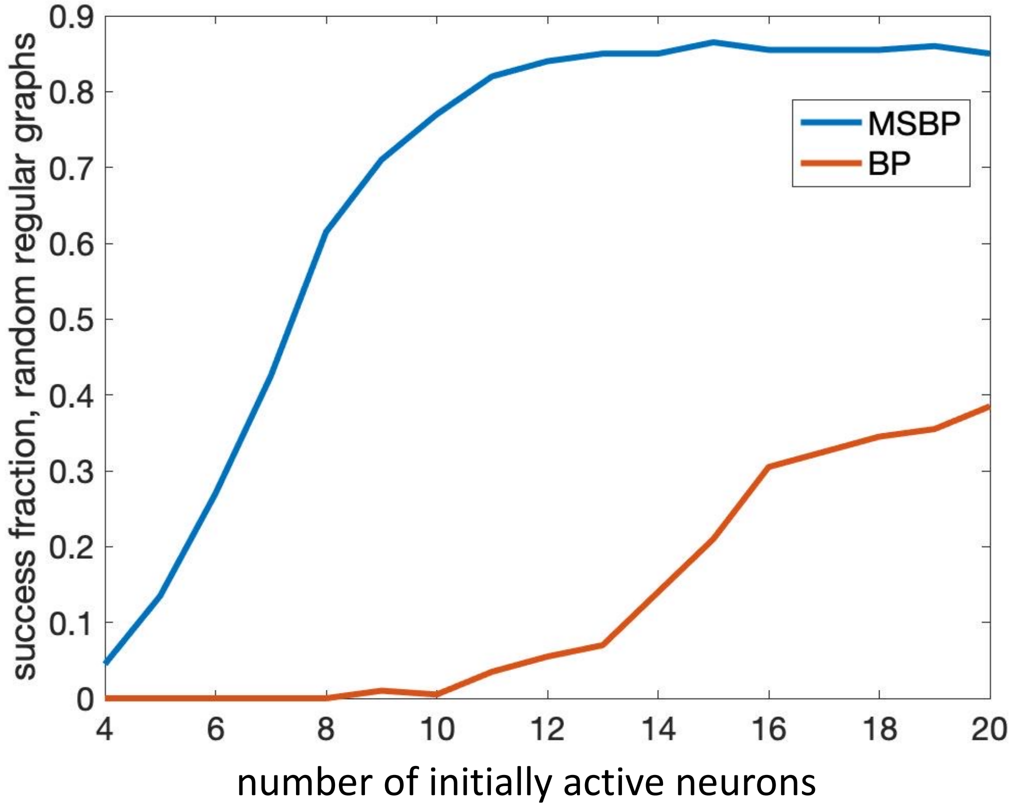


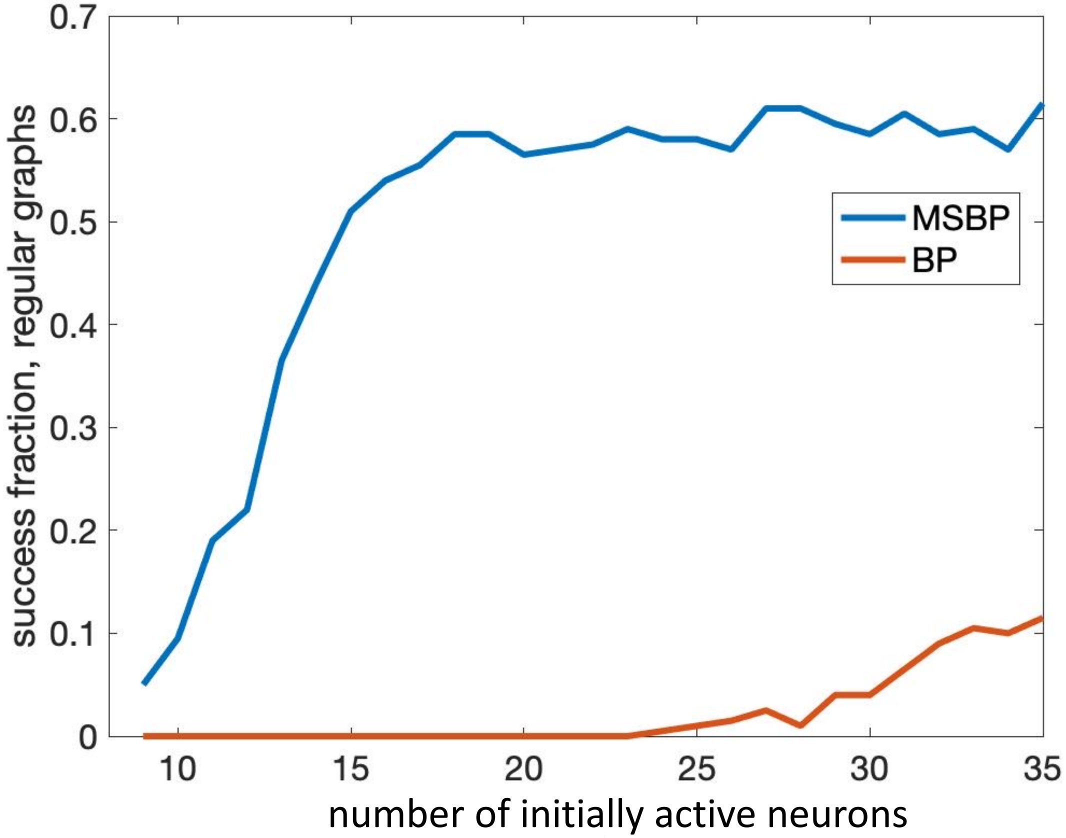
k_1=2, k_2=3

Is MSBP helpful?

<u>Result 1</u>: *MSBP is (in some parameter regimes, on some graphs) different from BP – Take-away:* ***bursting matters! & MSBP may be (at least mathematically) interesting***

2 examples with different (k_1, k_2, w)

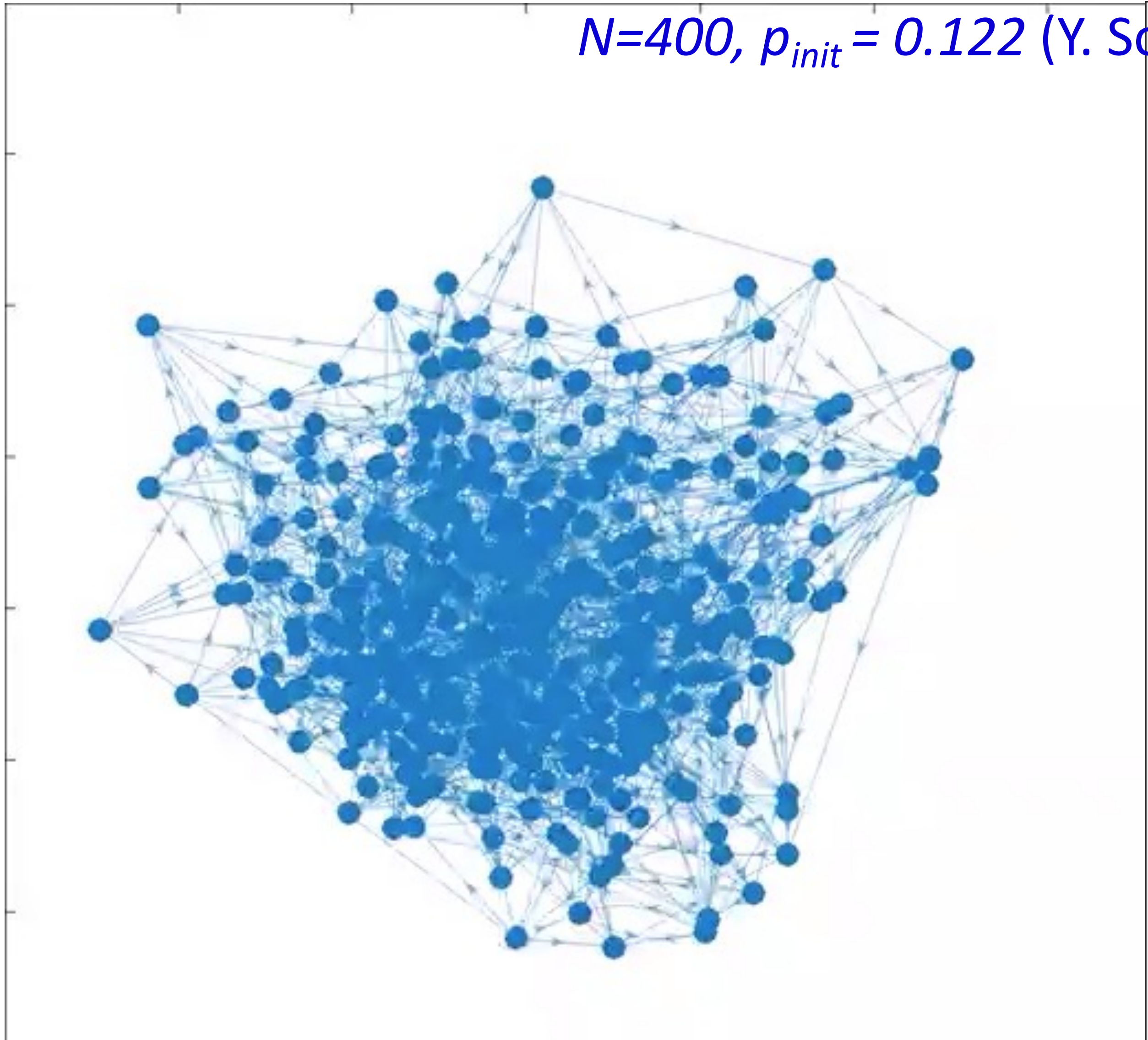


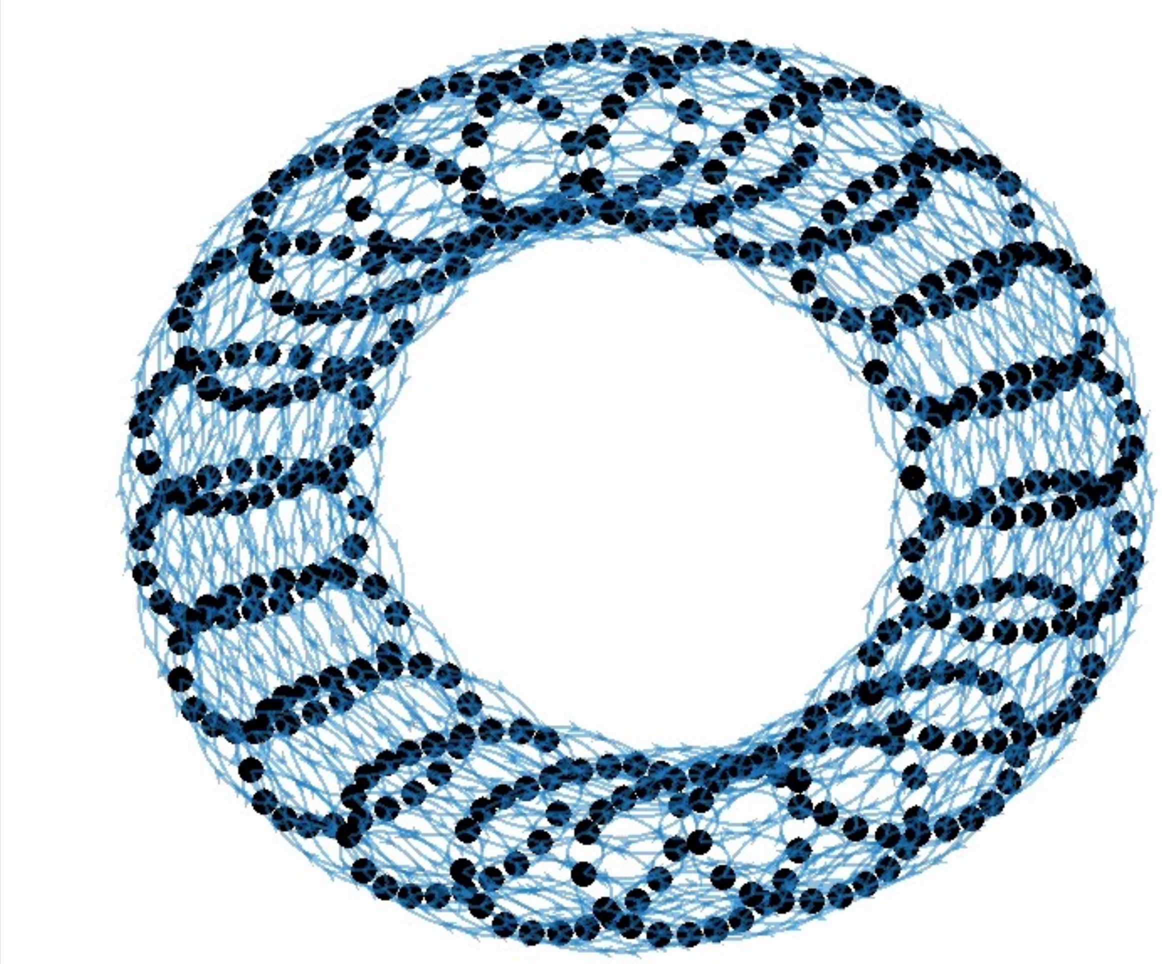


Result 2: Global architecture can affect many properties of MSBP

dynamic examples: MSBP on random regular digraph and on torus

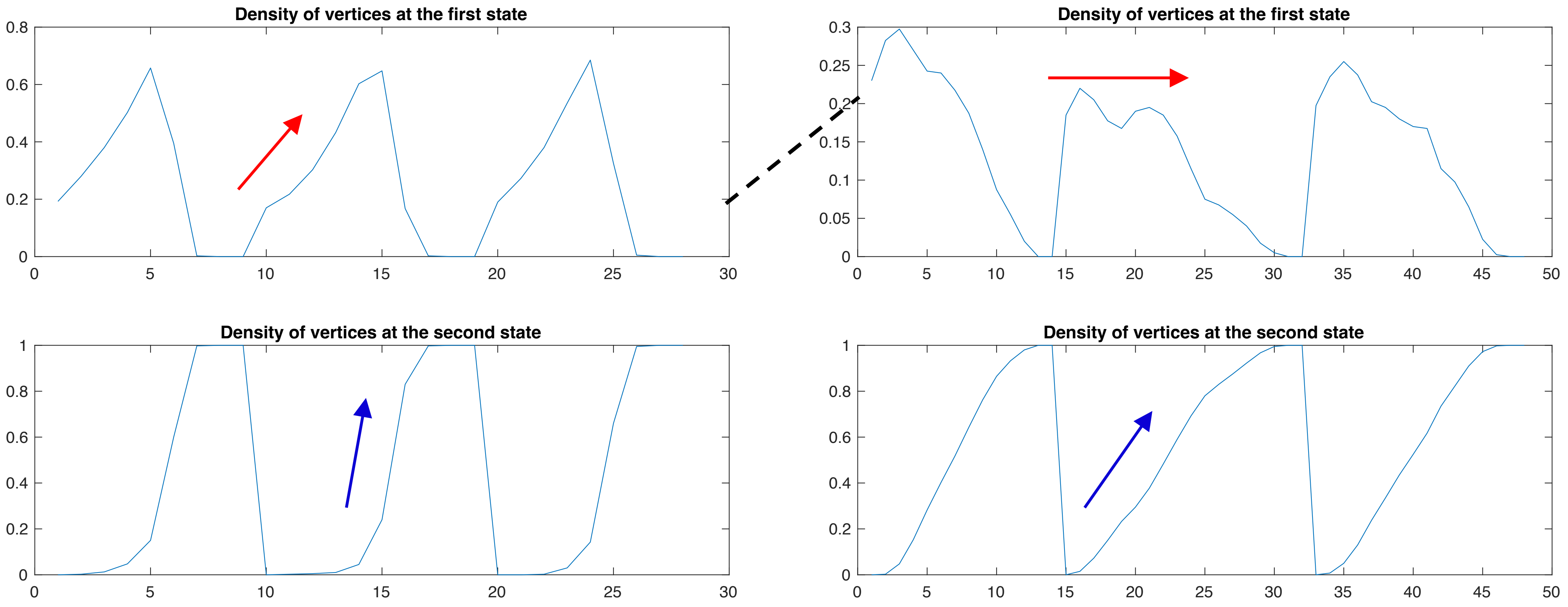
N=400, p_{init} = 0.122 (Y. Sokolov, unpublished)





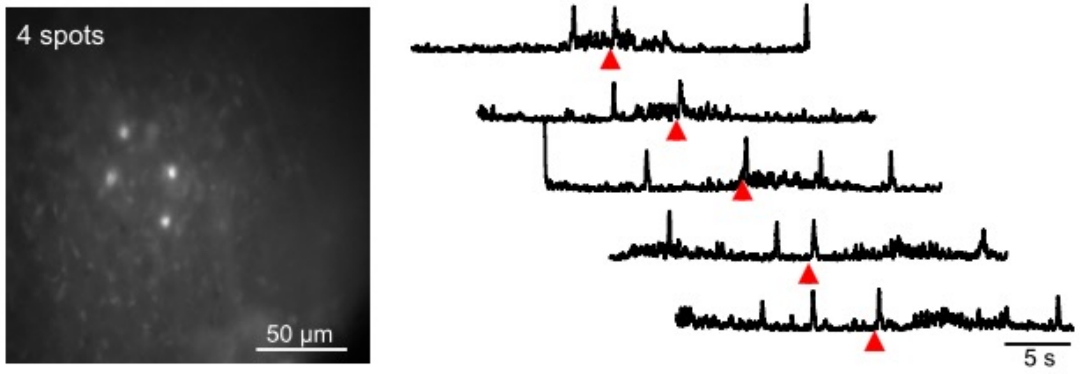
Result 2: Global architecture can affect many properties of MSBP

random regular digraph: *torus:*



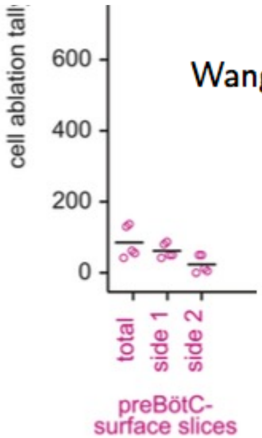
how can we use this? back to holographic experiments:

1) Simultaneous excitation of 4-9 neurons can initiate bursts



Kam et al. (2013) *J Neurosci*

2) Rhythm stops after the ablations of $\sim 15\%$ (85 ± 20) of Dbx1 preBötC neurons

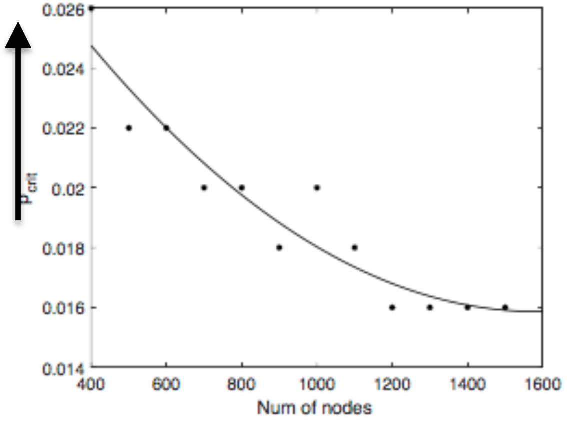


Wang et al. (2014) eLife

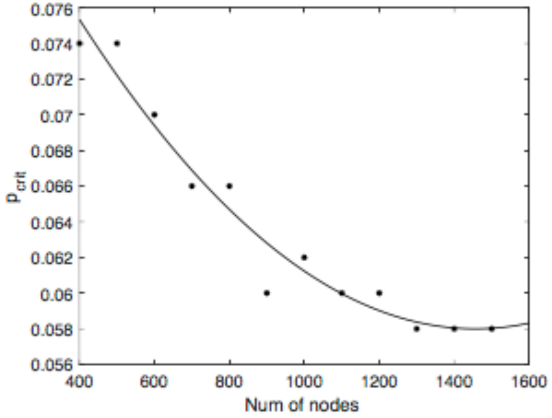
3) Simulations

$p_c(n)$: 50% success

$n = |V|$



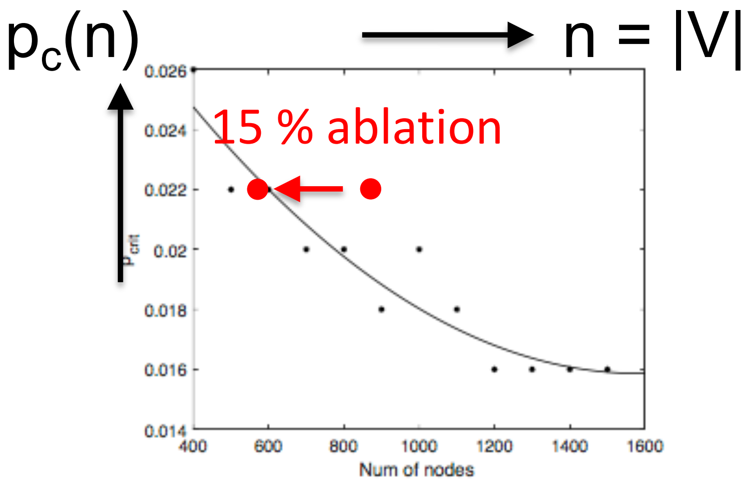
Lattice + Gaussian edges



$G_{Z_N^2, p_d}$

a possible approach (in progress...)

- For given graph and MSBP (k_1, k_2, w) parameters, mean field model gives estimate for $p_c(n)$ for any n (decreases as n increases)
- Size of respiratory network, n^*, has been estimated ($n^* \approx 500$)
- Experiments from previous slide constrain $p_c(n)$.
- Other experiments (Kam et al., 2013) also show that $k_2 \approx (3/2)k_1$.
- Thus, predict that network is among those {graphs, k_1, and w} such that constraints hold.



Lattice + Gaussian edges

SUMMARY

(1) to elucidate the contributions of various ion currents and other biophysical factors to inspiratory bursting

CICR is a likely mechanism to convert burstlets into bursts

(other results support roles for I_{NaP}, I_{CAN} & other factors)

(2) to determine the preBötC ***connectome*** (connection pattern and weight distribution)

it's unlikely to be a caveman network

more likely: 2 coupled sub-networks, weight distribution may matter

MSBP may help – at least will allow for rapid exploration, deriving constraints

(3) to integrate (1) & (2) into a complete theory

dynamics at nodes matter for capturing dynamics of network

SUNY Upstate Medical: Chris Gaiteri
Seattle Children's Research: Ryan Phillips
NIH (emeritus): Jeff Smith

Greg Constantine
Amin Rahimian
Sabrina Streipert