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

SUBGOALS:

(1) to elucidate the contributions of various ion currents and other biophysical factors to inspiratory bursting
(2) to determine the preBötC connectome (connection pattern and weight distribution)
(3) to integrate (1) & (2) into a complete theory

CONJECTURE: connectivity matters!

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:

pairwise cross-correlations tighten:

Carroll & Ramirez, *J. Neurophys.*, 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

---

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

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 $\rightarrow$ 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
Computational model preBötC networks with HH dynamics

• network built using Hartelt et al. statistics
• colors code clusters
• shapes code dynamics
• sizes code betweenness centrality
• letters code intrinsic dynamics
• networks synchronize

Q: How can this synchronize??

Idea: Maybe specific dynamics at key places in network promotes synchronization

Simulation and analysis of ongoing emergent dynamics

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

\[ \text{NBI} = \text{mean correlation} + \text{network variance} + \# \text{ bursting} + \frac{1}{\text{onset latency}} \]
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

Why does the Hartelt network fail?

• hypothesis 1: wrong dynamics – Butera model is out of date


• hypothesis 2: wrong architecture – results based on culture do not reflect true connection pattern
(2) Results with updated dynamics and 2 sub-population network

rhythm generator

Phillips & Rubin, *eLife*, 2022

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

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

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

- 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)

Tryba et al., *J. Neurosci.*, 2003
start with monotone MSBP

mathematically:

\[ s_i(t) \in \{0, 1, w \geq 1\} \]

\[ s_i(t + 1) = \max \{H(\sum_{j \rightarrow i} e_{ij} s_j(t) - k_1); wH(\sum_{j \rightarrow i} e_{ij} s_j(t) - k_2); s_i(t)\} \]

where \( j \rightarrow i \) denotes a directed edge from \( j \) to \( i \) in the graph

graphically:
Is MSBP helpful?

**Result 1:** 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:*

Density of vertices at the first state

Density of vertices at the second state
how can we use this? back to holographic experiments:

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

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

3) Simulations

\[ p_c(n): 50\% \quad \rightarrow \quad n = |V| \]

Kam et al. (2013) *J Neurosci*

Wang et al. (2014) *eLife*
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 \(\{\text{graphs, } k_1, \text{ and } w\}\) such that constraints hold.
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 preBötzinger complex (*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