Sparsity and inhibition in the pre-Bötzinger complex can explain levels of synchrony and the presence of expiratory neurons

Kameron Decker Harris[1], Tatiana Dashevskiy[2], Alfredo J. Garcia III[2], Eric T. Shea-Brown[1], Jan-Marino Ramirez[2]

[1] Applied Mathematics, Univ. of Washington, Seattle, WA; [2] Ctr. for Integrative Brain Res., Seattle Children's Res. Inst., Seattle, WA

Introduction

The **pre-Bötzinger complex (preBot)** is an area of the brainstem identified as the core **central pattern generator for respiration**, in particular inspiration. Rhythmic bursts of neuronal activity drive downstream motoneurons to generate breaths. Under synaptic isolation there are **silent**, **tonic spiking**, and **bursting** neurons.

We study network synchronization in a heterogeneous population of cells, to examine combined effects of:
- **Inhibition**. Not essential for rhythm generation in preBot but shapes the pattern, giving rise to expiratory neurons in preBot.
- **Sparsity of connections**. Adds heterogeneity and burst variability.

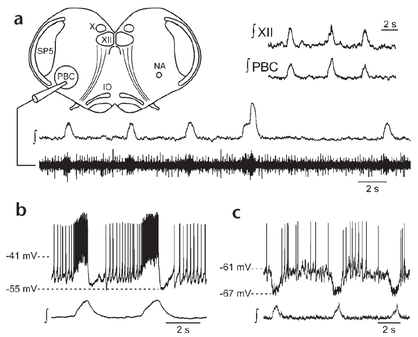


Image credit: Lieske et al. (2000)

Model description

Individual neurons are modeled following the persistent sodium (square-wave) burster model of Butera, Rinzel, & Smith (1999). Cells are made intrinsically **bursting**, **tonic spiking**, or **quiescent** by adjusting the leak conductance g_L.

$$\dot{V} = -\left(I_{\text{app}} + I_{\text{L}} + I_{\text{Na}} + I_{\text{K}} + I_{\text{Nap}} + I_{\text{syn}}\right)/C_m$$
$$\dot{h} = \left(h_\infty(V) - h\right)/\tau_h(V)$$
$$\dot{n} = \left(n_\infty(V) - n\right)/\tau_n(V)$$
$$I_{\text{L}} = g_{\text{L}}(V - E_{\text{L}})$$
$$I_{\text{Na}} = g_{\text{Na}} m_\infty^3 (1-n)(V - E_{\text{Na}})$$
$$I_{\text{K}} = g_{\text{K}} n^4 (V - E_{\text{K}})$$
$$I_{\text{Nap}} = g_{\text{Nap}} m_{\text{p},\infty} h (V - E_{\text{Na}})$$
$$I_{\text{syn},i} = (V_i - E_{\text{syn}}) \sum_{j:j\to i} g_{ij} s_{ij}$$
$$\dot{s}_{ij} = \left((1 - s_{ij}) m_\infty(V_j) - s_{ij}\right)/\tau_{\text{syn}}$$
$$m_\infty(V_j) = \frac{1}{1 + \exp\left((V_j - E_{\text{syn}})/\sigma_{\text{syn}}\right)}$$

Network configuration

We model the preBot with a heterogeneous (degree and neuron type) network of 300 neurons.

The network is generated via:

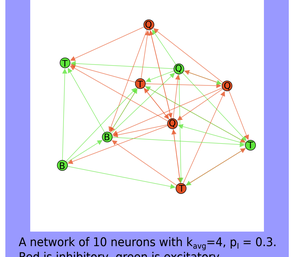
1. Add directed edges uniformly at random with probability $(k_{avg}/2)/(N-1)$. The **average total degree (in- plus out-degree) is then k_{avg}**.

2. Assign neuron types bursting, tonic spiking, or bursting with respective probabilities 0.25, 0.45, 0.3.

3. Assign neurons as **inhibitory with probability p_I**.

We vary the following network parameters to see their effect on network rhythm generation: p_I, k_{avg}, excitatory and inhibitory synaptic conductances g_E and g_I

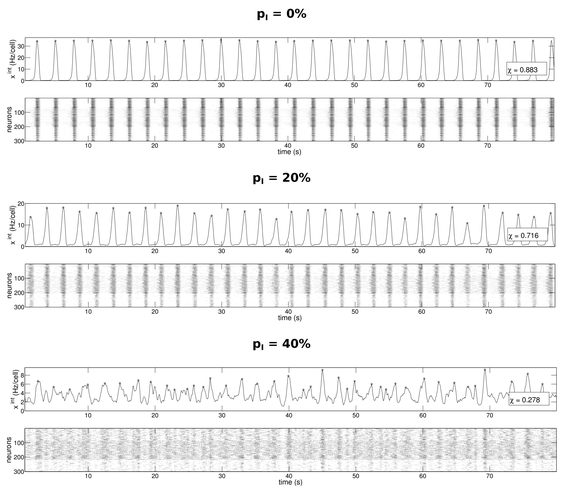
Visualizing network construction



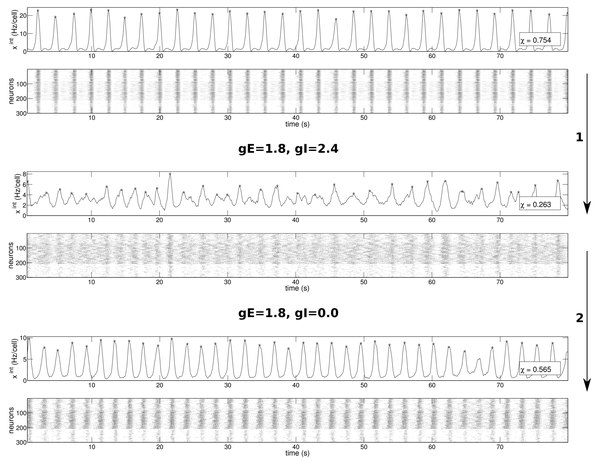
A network of 10 neurons with k_{avg}=4, p_I = 0.3. Red is inhibitory, green is excitatory.

Model ouput exhibits burst variability similar to slice preparations

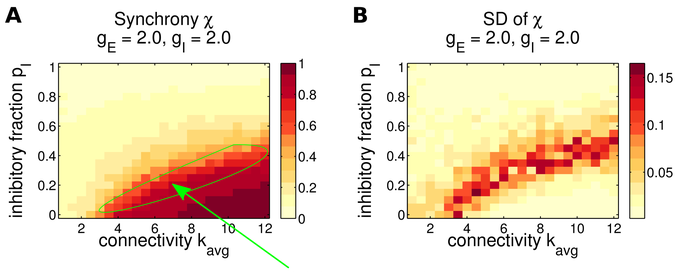
THIS COLUMN: Fix k_{avg}=6, g_E=g_I=2.0. Increasing the fraction of cells which are inhibitory (p_I) adds variability until the rhythm is destroyed.



THIS COLUMN: Similar to the slice experiments (right), fix k_{avg}=6, p_I=20% and lower the synaptic conductances to mimic the effects of excitation and inhibition blockers. Blocking excitation degrades the rhythm, which is recovered by blocking inhibition.



Inihbition and sparsity weaken the rhythm



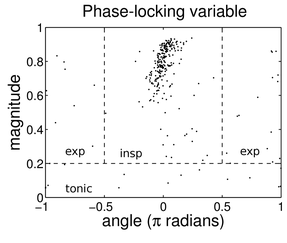
Variability overved in real networks suggests network is near the "edge of stability". This could facilitate control of rhythm.

We measure the synchrony of a population with the **autocorrelation synchrony measure χ** of Golomb (2007) defined by:

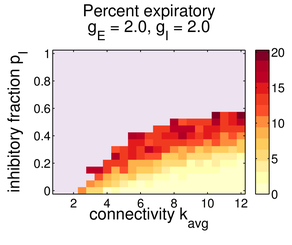
$$\chi^2 = \frac{\sigma_V^2}{\frac{1}{N}\sum_{i=1}^N \sigma_{V_i}^2} \qquad \sigma_V^2 = \left\langle \left[\frac{1}{N}\sum_{i=1}^N V_i(t)\right]^2 \right\rangle_t - \left[\left\langle \frac{1}{N}\sum_{i=1}^N V_i(t)\right\rangle_t\right]^2$$
$$\sigma_{V_i}^2 = \left\langle [V_i(t)]^2 \right\rangle_t - \left[\langle V_i(t)\rangle_t\right]^2 .$$

LEFT: Synchrony parameter χ as a function of the network parameters. **A**, the average χ over realizations of the networks, plotted versus the amount of connections k_{avg} and the fraction of nodes which are inhibitory p_I. **B**, the standard deviation of χ over realizations. Higher standard deviation indicates that the synchrony is not reliable for different networks with those parameters. The area of highest standard deviation occurs at the boundary of low and high synchrony.

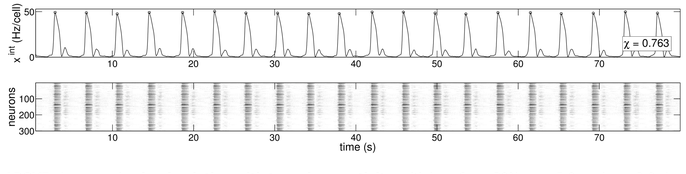
Inhibition creates an expiratory population in even unstructured networks



Neuron phase-locking variables for k_{avg} = 6, p_I = 20%. Each variable is a complex number z_i with $0 \le |z_i| \le 1$. The magnitude $|z_i|$ is plotted against angle arg z_i. These are **used to define inspiratory, expiratory, and tonic neurons** via the labeled regions separated by the dashed lines.

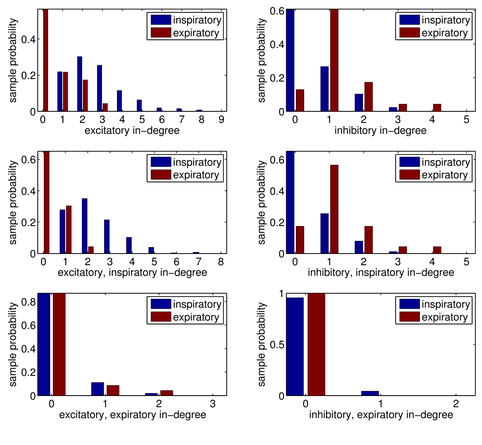


Expiratory (out-of-phase from the main rhythm) neurons as a function of network parameters k_{avg} and p_I. The **fraction of expiratory neurons increases as the connectivity becomes weaker or more inhibition is added**. The blue indicates where we cannot accurately determine burst peaks, when χ < 0.25.

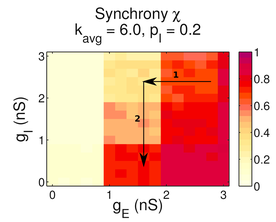


ABOVE: An example of **a simulation with two-phase activity**, with k_{avg}=6, p_I=30%, g_E = 5.0, and g_I = 2.0. A minority of neurons produce a reliable, small bump after every burst aligned near 0.7π, so it is more of a post-inspiratory or pre-expiratory burst. This activity occurs rarely.

BELOW: Model expiratory cells receive different inputs than inspiratory cells. These results are for k_{avg} = 6, p_I = 20%. There were 251 inspiratory, 23 expiratory, 15 tonic, and 11 silent cells. Expiratory cells receive less excitatory and more inhibitory connections than inspiratory cells and preferentially receive excitatory input from other expiratory cells (middle and bottom left). Also, inhibitory input tends to come from inspiratory cells rather than other expiratory cells (middle and bottom right).This shows that expiratory cells' in-neighborhood consists of other excitatory, expiratory cells and/or inhibitory, inspiratory cells.

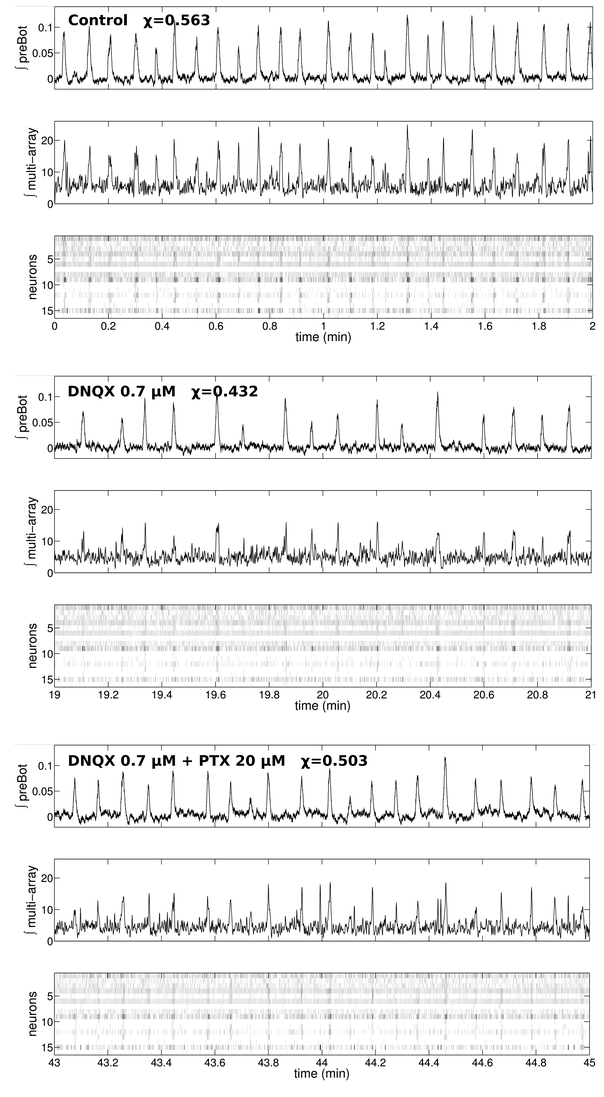


Experiments support partial synchrony mediated by E/I balance



We compared effects predicted by the **model (heatmap, left)** to **experiments (traces, below)** in mouse preBot-containing slice preparation. In experiments, we apply DNQX, an excitation blocker followed by DNQX plus picrotoxin (PTX), which blocks inhibition.

Lowered excitation degrades the rhythm, which is restored when inhibition is blocked.



Conclusions & future directions

- Network heterogeneity (sparsity and cell-type) and inhibition explain variability in preBot rhythm
- The preBot can only generate one rhythm despite presence of expiratory cells
- Model variability that matches real networks is near the edge of stability, which may facilitate control
- We are conducting further experiments where we quantify the level of variability with combinations of DNQX and PTX to create another "heat map" like those of χ for the model
- We are studying the same effects in a model of the preBot and Botzinger complexes to study multiple rhythms

Bibliography
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