Modeling brainstem neuronal networks that drive breathing

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Infection in newborn infants can contribute to respiratory dysfunction. **However** inflammation doesn't disrupt breathing as severely after approximately 12 months of age.

Why?

> *Likely answer: The resiliency of respiratory control is weaker and more vulnerable to stress. Or more simply, the biophysical properties of cells generating the drive to breathe are different == developmental immaturity.*

What's different?

> *Much harder to answer: we don't entirely know*

Pragmatic problem

We want to resolve the physiological consequences of developmental changes in the brain happening near birth, focusing on the brainstem circuits that generate rhythmic motor output associated with breathing.

Julia and Neural ODEs

I think there's two things that may prove interesting in the space of neural ODEs and Julia-esque solutions to scientific computing.

1. Universal differential equations might be leveraged as a (more) data-driven approach to development of conductance-based models of neurons. Augmenting models with neural nets might tighten the relationship between real-world data and in silico simulation.
2. There's also a **problem of language**. Domain-specific languages for generating efficient machine code simulation of biologically-inspired models of neurons and neural networks is nothing new in neuroscience, but there's obvious trade-offs going on between composability, portability, architecture support and model flexibility.

Experimental strategy

High-throughput single-cell transcriptomics

Microdissect tissue samples from the brainstem of newborn mice at different stages of development (e.g. late embryonic period → early postnatal ages → juvenile ages). Dissociate tissue samples and sort isolated single cells into a microwell plate for RNAseq. Resulting transcriptomic data hopefully resolves the underlying trajectory of changes in gene expression occuring within cellular subpopulations (e.g. using pseudotime ordering, RNA velocity, or both).

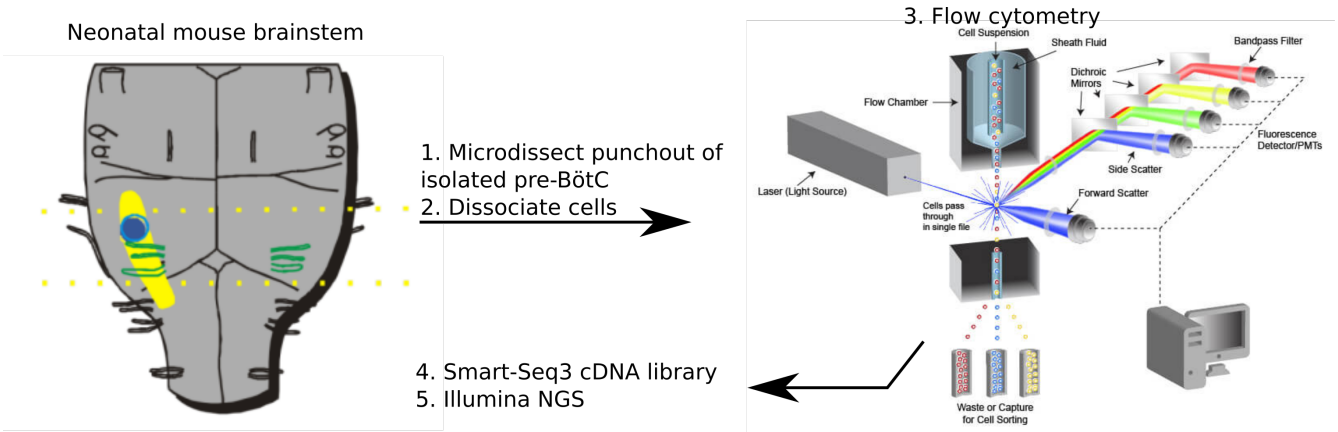


Figure 1. Next-gen sequencing workflow

Annotate single-cell data with physiological data using PatchSeq

PatchSeq involves recording intracellular voltage and subsequently aspirating the cell's cytosol in order to capture mRNA for later cDNA library generation. Therefore a physiological readout of behavior (voltage/current recording) gets paired with the transcriptomic profile of a specific cell. These data points compliment the superset of transcriptomic data described in the preceding section.

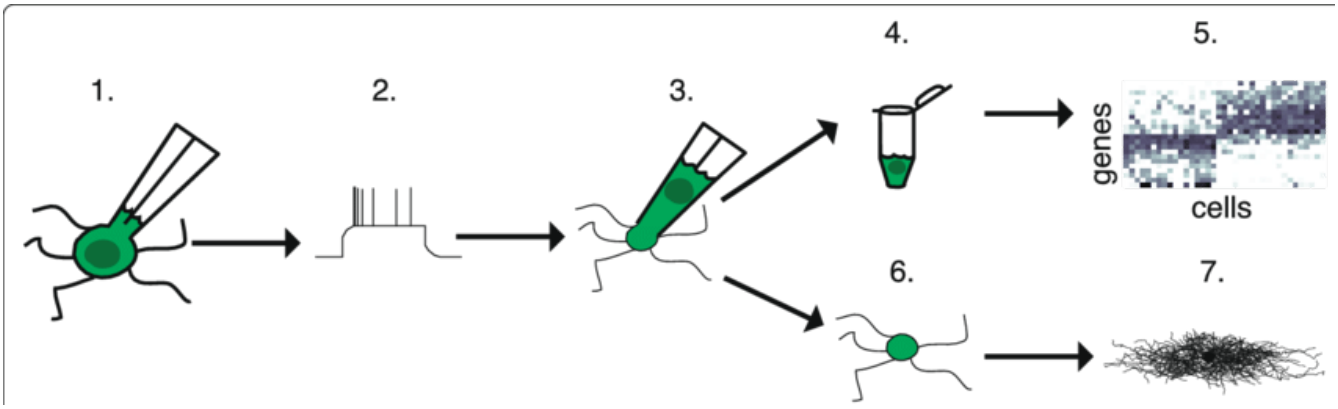


Figure 2. PatchSeq workflow (Cadwell et al. 2017)

Model neurons and fit to real data

Build a detailed yet flexible Hodgkin-Huxley model that consists of things we know about (e.g. known prominent membrane currents) and neural nets to account for things we may not have considered or can't easily model (e.g. unmeasurable distally located currents, stochasticity of activity, other signaling pathways). Fit such a model *directly* to experimental recordings of spontaneous respiratory neuron activity. Ideas for structure of the model discussed in Model Ideas below.

Light field microscopy for whole network data

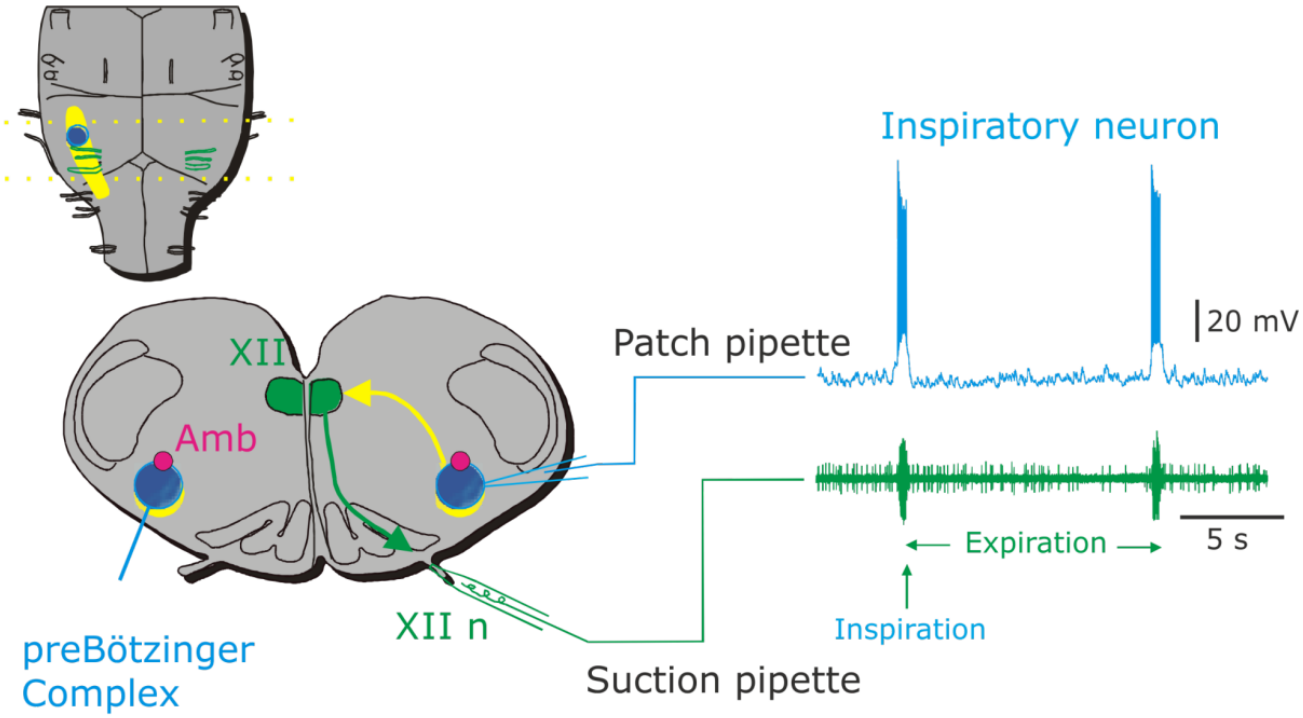
Light field microscopy can be used to take time-lapse recordings of calcium activated fluorescence within a volume of the brain, providing a proxy for cellular level spiking activity within an observed population. A stretch goal would be to pair this with post-hoc *in situ* sequencing or hybridization assays (we have core facilities for this), and compare against network simulations.

Respiratory neuroscience background

The predominate source of spontaneous activity that drives breathing movements orginates in a brainstem region called the pre-Bötzinger complex. This population of neurons dictates the timing of rhythmic inspiratory breathing, while other downstream pools of neurons transform excitatory output from the pre-Bötzinger complex into the coordinated activation of muscles necessary to inhale. The pre-Bötzinger complex can also modulate the *type* of inspiratory effort, producing longer lasting sigh-like activity, or more rapid gasping.

The network is a heterogenous mixture of neuronal populations, distinct classes/suites of ionic membrane currents, and that those properties affect their individual biophysical behavior. It is presumed that the net effect of these population-specific membrane properties is an **emergent network rhythmicity**, sometimes called a *group pacemaker*.

Finally, small groups of neurons embeddedd in the pre-Bötzinger can exert network-wide effects, operating in parallel to modulate breathing (adjusting respiratory frequency, duration of breath, etc).



Preface: Commentary on modeling is specific to how things are *in this particularly brain region*. There's a lot more to unpack about the state of the art more broadly in computational neuroscience.

Current general modeling strategies

Models of the pre-BötC incorporate terms for additional ionic membrane currents into Hodgkin-Huxley ODE systems. Whereas a textbook example of the Hodgkin-Huxley conductance model typically consists of a fast sodium current (I_{Na}) and delayed potassium current (I_K), models of periodically bursting neurons in the pre-BötC usually introduce additional putatively important membrane currents, such as persistent sodium current (I_{NaP}), calcium-activated currents (I_{CAN}), etc.

Topology may also be considered, with edges formed between nodes (neurons) based on presumed network architecture (e.g. small-world vs random network). In the simplest case, each HH neuron is a stand-in for the mean activity of a homogenous subpopulation of neurons. Therefore a handful of nodes will represent separate subpopulations interacting with each other. In other cases, many nodes are interconnected by varying degrees and the parameterization of each individual neuron is drawn from a distribution (e.g. normally distributed values for current magnitudes or weighting of synaptic connections).

Theoretical issues

Typically only one or two additional current types have been incorporated into pre-existing preBötC models. Model parameters are tuned within plausible value ranges to achieve a qualitatively acceptable result (e.g. periodic bursting). Minimalistic models may answer whether one current type *could* be sufficient to render spontaneous network rhythmicity, however the

phase plane trajectory of any particular current may be quite different with other actors absent from the system.

Decades of work in other brain areas shows that dendrites can filter, amplify, and modulate incoming synaptic potentials, but models of respiratory rhythm generation ignore morphology. Neurons are modeled as single comparment cells, disregarding voltage propagation along neuronal processes. However, dendritic morphology *can* and *has been* modeled in other subfields of neuroscience.

Practical issues

Electrophysiology is slow and tedious. mRNA degradation is also a problem. This means: Data is hard to come by and recording time must be kept to a minimum. Classical experiments using pharmacology (ion channel blockers) and current stimulus-response take too long—we want high quality mRNA and more data points if possible.

Originally the plan was to use massive (as in many) feature extraction or feed raw data through a deep learning model (e.g. LSTM-FCN). The problem there is more data is needed, and as far as I can tell, most deep learning models aren't optimized for high frequency data (we record at 20kHz; downsampling data below 8kHz begins to lose information).

Structure of the data

What types of information are available to us? * Voltage/current of individual neurons * Net motor activity (reflects total network output) * Morphology of individual neurons * Activity of neurons at the network level * Potentially spatial information (via in situ hybridization)

Model ideas

- Literature-informed approach
- Iterative build-up (i.e. we get more information as we go; hopefully inferring additional terms.
- Use motor output as a trigger for synaptic input simulation (potentially side-step the need for full/parallel simulation of the whole network)
- Use transcriptomic data to **validate** parameter fitting.
- Filter gene features in transcriptomic data for ionic membrane currents for candidates that are not included in the model.