Modeling Nonlinear Dynamics of the Mammalian Respiratory Central Pattern Generator Using the Hindmarsh-Rose Model of a Neuron

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Introduction

Central Pattern Generators (CPGs) are networks of neurons that fire rhythmically even in the absence of periodic stimuli, regulating things like breathing and heartbeats.

- through a complex series of physiological interactions, these networks fire impulses at different rates to produce different modalities of behavior (e.g. walking vs running)

Mammalian respiration is a 3-step process, and can be controlled and have different modalities.

- **Half-Center Oscillators (HCOs)** are the baseline of a mammalian respiratory CPG
- we can model mammalian respiration using 3 connected systems of neurons: the PreBötzinger Complex (Pre-BötC), Postinspiratory Complex (PiCo), Retrotrapezoid Nucleus / Parafacial Respiratory Group (RTN/pFRG)[1]

We use the **Hindmarsh-Rose (HR) neuron** to model both a HCO and a CPG, and it qualitatively explains neuronal bursting using three coupled differential equations[2].

- HR models a single neuron in the pond snail *Lymnaea*, which bursts upon receiving a stimulus
- the model is qualitative; it uses dimensionless units and does not give actual voltages and an accurate time scale

Hindmarsh-Rose Neuron Modeling

The Hindmarsh-Rose (HR) Neuron is modeled using a set of **three differential equations**, where x is membrane potential, y is ion transport rate, and z is the adaptation current.

$$\frac{dx}{dt} = y + (bx^2) - (ax^3) - z + I \tag{1}$$

$$\frac{dy}{dt} = c - (dx^2) - y \tag{2}$$

$$\frac{dz}{dt} = r(s(x - x_R) - z) \tag{3}$$

When coupling HR Neurons, we modeled two-way inhibitory connections using a sigmoidal function

$$S(x_i) = \frac{1}{1 + e^{-k(x_i - \Theta_{syn})}} \tag{4}$$

Where x_i is the neuron with id i. To inhibit a neuron, the equation (1) is modified to be

$$\frac{dx}{dt} = y + bx^2 - ax^3 - z + I - \sum_{i \in n}^{n} g(x - V_{syn})\,S(x_i) \tag{5}$$

Where n is the set of inhibitory neurons acting on the specific HR neuron.

We propose a differential equation modeling m, the modulation variable between two HR neurons, where t_1 and t_2 is the last inhibition period of the neurons and κ is the synchronization constant. Let $S(x_i) = S(x_i)\,m$.

$$\frac{dm}{dt} = e^{-\alpha(t_1 - t_2)} - \gamma \tag{6}$$

$$\gamma = e^{\alpha\kappa} \tag{7}$$

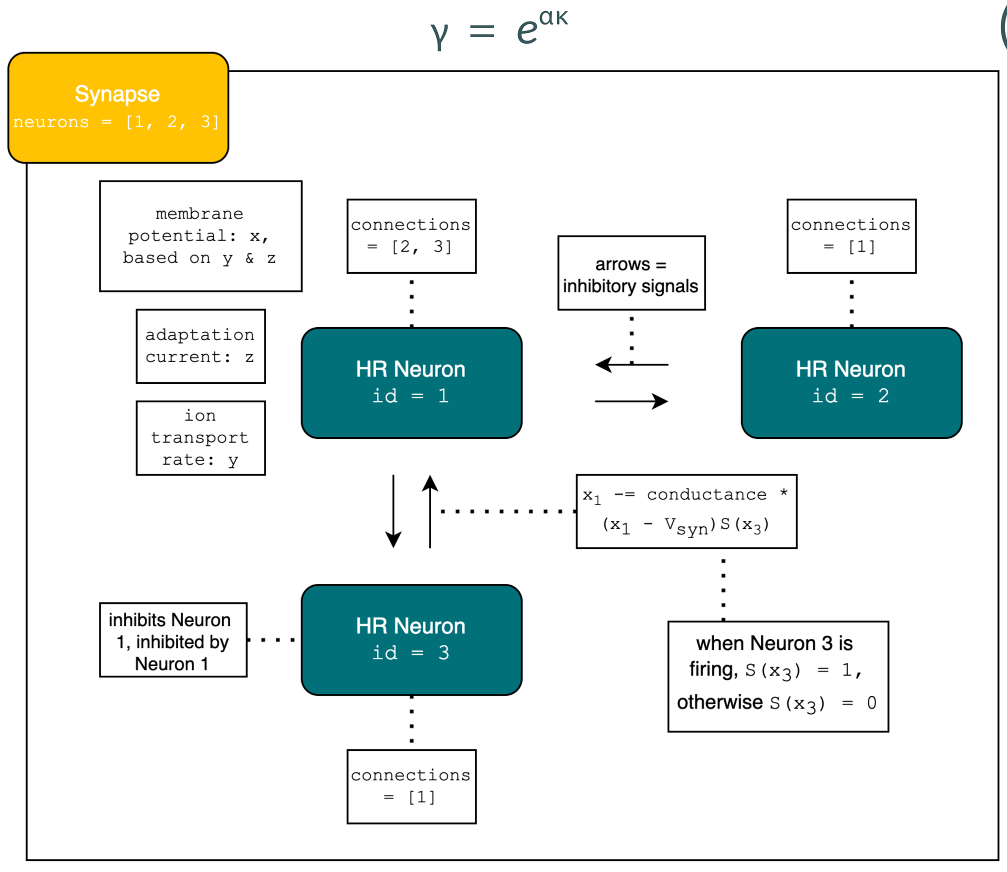

Figure 1: Modular Neural Network
How the modular neural network is constructed and implemented in our code

Hindmarsh-Rose & CPG Results

The HR model first produced aperiodic, or chaotic, activity at an injected current level (I) of approximately 3.15.

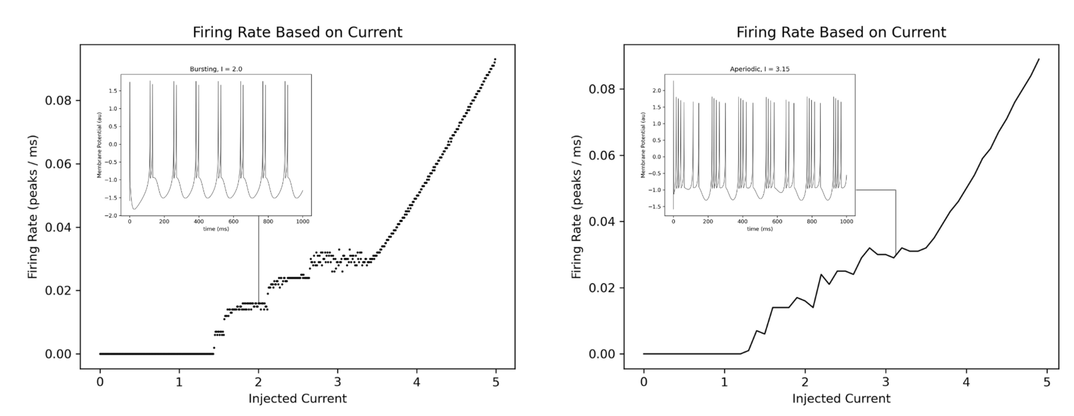

Figure 2: Firing Rate Based on Injected Current
The firing rate exhibits plateaus for the quiescent, spiking, bursting, and aperiodic regions, in order from left to right

Interspike Intervals (ISIs) of HR neurons are characteristic of a bifurcation diagram and produce chaotic behavior.

- the membrane potential of an HR neuron where its ion transport rate is exactly − 2.5 is varied using injected current
- at approximately $I =$ 3.15, both graphs are chaotic

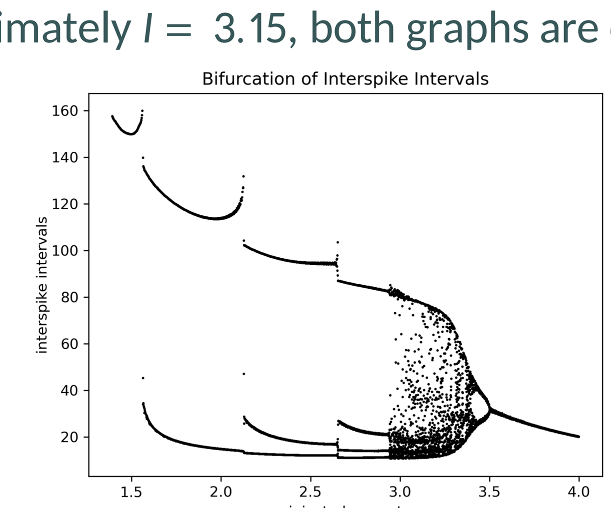

Figure 3: Bifurcation Diagram
The bursting behavior undergoes bifurcations as observed in the ISI with increasing current

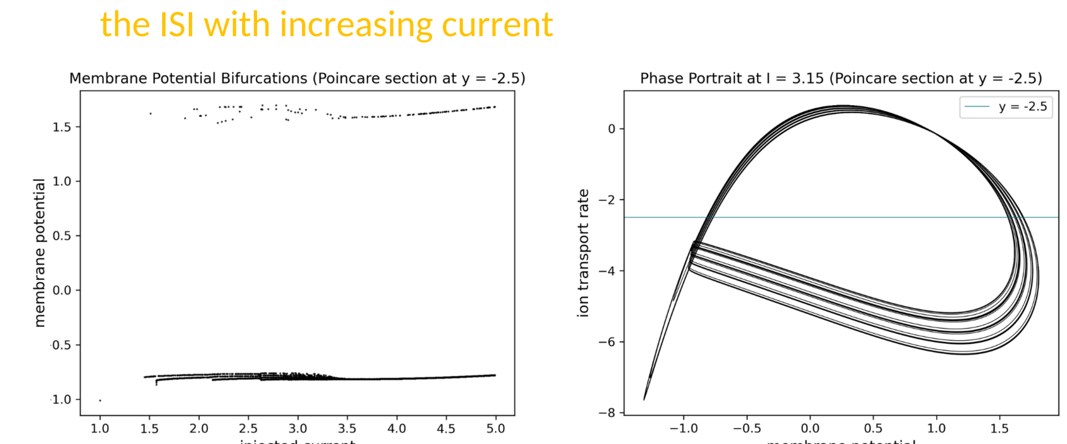

Figure 4: Bifurcation Diagram
The membrane potential undergoes bifurcations as observed in the area with y = 2.5, with increasing current

A HCO is modeled by coupling 2 HR neurons, producing periodic anti-phase behavior.

- we modeled a mammalian respiratory network using a system of three oscillator kernels, each represented by a single HR neuron

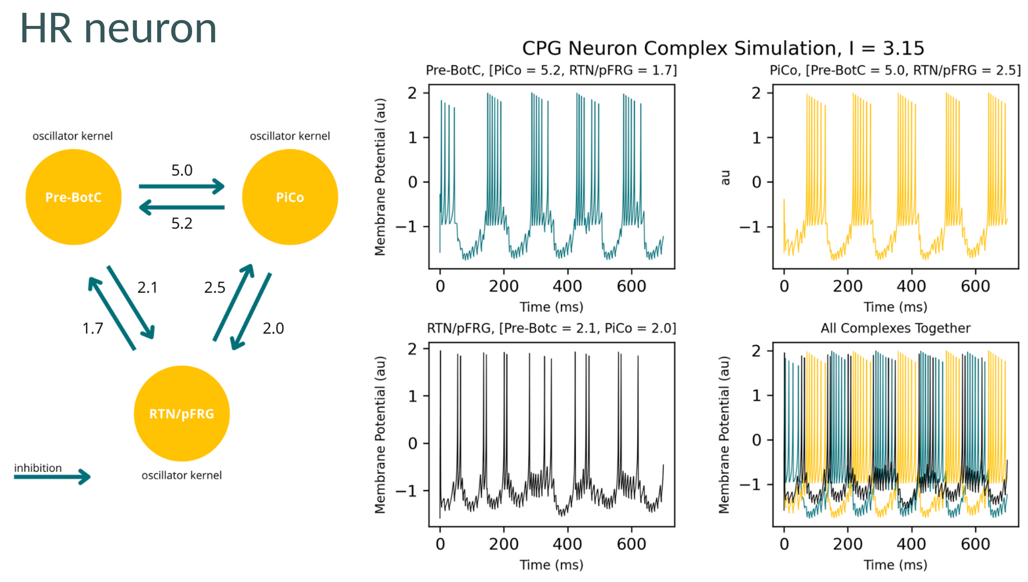

Figure 5: CPG Neuron Complex Simulation
The simulation for a central pattern generator using three mutually inhibitory Hindmarsh-Rose neurons

- there is chaos in both the period and firing rate of each complex, as well as the number of spikes in each burst
  - the three oscillator kernels remain triphasic, and never fire atthe same time

References

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Modulation Variable Results

Using our differential equation for m, we simulate two coupled HR neurons at different currents and observe synchrony.

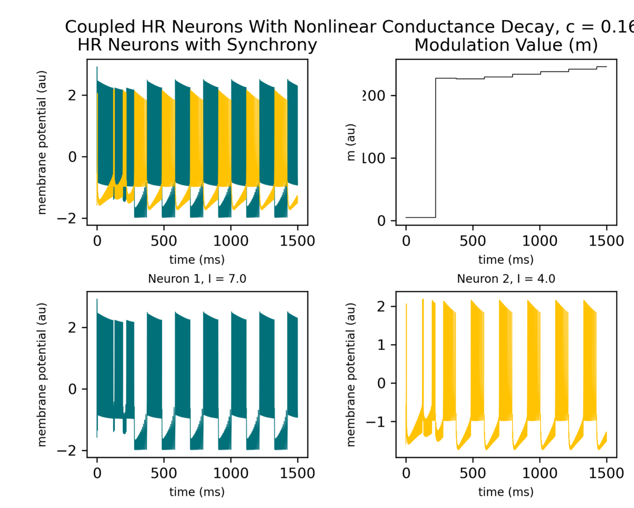

Figure 6: Coupled HR Neurons with Synchrony
2 HR neurons at currents of 7.0 and 4.0 with completely different bursting periods stabilize overtime due to changes in modulation value to Neuron 1

- varying κ allows us to create an offset between the two HR neurons

Discussions & Conclusions

The biological complexity of the CPG demands that we first create a simplified model to be able to build upon it in the future.

- theories argue that the different cranial areas involved in respiration don't have completely independent behavior
  - each segment primarily controls a single action, allowing us to simplify our exploration
- using three neurons, we developed a basis that is much more difficult to obtain using a more complex model
- we successfully simulated whether **external stimulation** is capable of consistently inducing the rhythmic firing behavior of CPGs
- stimulation of the initial neuron via an exogenous current led to **cyclical and sustained firing** by the rest of the neurons; we modeled a potentially functional CPG

The interspike interval fundamentally changed at different points of injected current: we believe these to be potentially indicative of different modalities of breathing.

- a region of injected current yielded inconsistent and aperiodic (chaotic) firing rates in a model of a singular neuron
- we hypothesize that the inhibitory connections between these neurons in a network act as a stabilizing mechanism, eliminating chaotic behavior

Potential conditions which we believe this research to potentially yield **therapeutics** for include apnea, Rett's Syndrome, and even potentially Sudden Infant Death Syndrome (SIDS).

- the pathologies of all these conditions all have one thing in common: respiratory arrest due to indeterminate causes
- a closed loop system detecting CPG failure and activating stimulation could be a potential treatment; our work provides a basis for such exploration in the future

The additional differential equation, indicated by the variable m, serves as a **dynamic synaptic weight**.

- it is distinct from the conductance variable, which is a physical property of the neuron
- m evolves over time to adapt the HCO to a certain frequency of firing
- allows us to change firing rhythm over time, like how neuromodulators alter the frequency of a CPG on a task-dependent basis

Figure 7: Github Repository & Additional Results

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