**Title:** Brainstem mechanisms of cardio-ventilatory coupling

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**Title of Grant:** MODELING BRAINSTEM INFLAMMATION'S ROLE IN SYSTEMIC DYSFUNCTION DURING SEPSIS

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**Abstract text:**

We are developing computational models of cardio-respiratory control to understand neural mechanisms of cardio-respiratory interaction and how these mechanisms are involved in the loss of cardio-respiratory variability during illness. Our cardio-respiratory model is a system of coupled ordinary differential equations that produce neuronal population activity of the brainstem respiratory central pattern generator (rCPG) as well as the heart rate, arterial blood pressure and the tidal volume of the lungs. We use statistical techniques to quantify the physiological output of rodents and humans and rigorously fit our computational model to reproduce this output. Inferring key parameters of the coupling between the rCPG and the cardiovascular system, that represent specific neuronal and physiological properties, allows us to model and draw conclusions about physiological mechanisms for cardio-respiratory control.

Our current research focuses on three independent pathways of the nervous system that induce structure in the variability of cardiovascular and respiratory output. In the model, we implement respiratory input to vascular tone by way of the sympathetic motor output controlling vasoconstriction, respiratory input to the heart rate by way of modulating the vagal tone to the heart, and cardiovascular input to the rCPG by way of the baroreflex activated inputs to the respiratory neurons.

The characteristics of the sympathetic and parasympathetic inputs of the cardiovascular system are calibrated against a dataset of human cardio-respiratory behavior during normal and slow deep breathing. Utilizing our computational model, we demonstrate mechanisms that support the hypothesis that rCPG input to the sympathetic nerve is responsible for the increase in blood pressure respiratory modulation as well as for the decrease in blood pressure observed during slow deep breathing.

Respiratory input to the heart and vasculature does not explain the partial synchronization between respiration and the beating of the heart characteristic to cardio-ventilatory coupling (CVC) which is the increased likelihood of a heartbeat to occur just before inspiration. Here, we utilize the model to demonstrate the hypothesis that CVC is an entrainment of the rCPG by pressure pulses which emerges due to baroreceptor input to the rCPG neurons. In an *in situ* rat preparation, perfusate pressure pulses that occur during expiration alter the firing rate of brainstem respiratory neurons and delay the time of the next inspiration onset. By implementing baroreflex inputs to a specific population of neurons in a model of the rodent rCPG, we capture the response of respiratory timing to baroreflex perturbations. We translated this mechanism to the closed loop model of human cardio-respiratory interaction. The blood pressure pulse that follows each heartbeat facilitates the activity of expiratory neurons and when occurring at the end of expiration slightly delays the expiration-to-inspiration phase transition. This baroreflex coupling of the rCPG to the blood pressure is fit to reproduce the distribution of heartbeats relative to the onset of inspiration. In this manner, the model suggests that the rCPG response to baroreflex from the beating of the heart induces partial entrainment of respiration by the heartbeat.

**Please use the 10 Simple Rules for Credible Models to describe your model**

**Rule 1 – Define context clearly**:

We are developing computational models of cardio-respiratory control to understand physiological mechanisms of cardiorespiratory interaction.

**Rule 2 – Use appropriate data:**

Appropriate data for the computational model are single-unit recordings from neurons generating the cardiorespiratory patterning and behavioral data including respiration, ECG, and blood pressure. These data were collected from rodents, patients, and volunteer participants.

**Rule 3 – Evaluate within context:**

Mechanisms are tested in reduced versions of our computational model before being implemented in the “full” closed-loop model of cardio-respiratory interaction. For example, we utilize data from experiments of baroreceptor stimulation in the *in situ* rat preparation. In these animals, the lungs are not functional, and a machine controls the perfusate pressure within the circulatory system. We generate hypotheses based on these data and then implement and evaluate them in a model of the *in situ* prep. Then such a proposed mechanism is propagated to a closed-loop model of human cardiorespiratory interactions and applied to explain some observations taken from human data. In this way our proposed mechanisms can be calibrated against rodent in one model and then validated against human data in another model.

**Rule 4 – List limitations explicitly:**

Our computational model of cardio-respiratory interaction is implemented at a relatively coarse level. It does not capture sophisticated neuronal or cardiac electrophysiology at the level of individual action potentials. However, we find that it is sufficient to model the firing rate of the relevant neuronal populations and the phase of the heartbeat as well as putative mechanism by which they interact to explain the observed interactions within and structure of variability in the respiratory and cardiovascular data.

**Rule 5 – Use version control.**

The development of our simulation platforms utilizes the Git version control software. We are hosting local repositories for development, and these local repositories are regularly synchronized with repositories hosted at GitLab,

**Rule 6 – Document adequately.**

Our computational experiments are documented with a laboratory-notebook style description of our iterative investigations. In our computational model, a simulation that represents some pharmacological manipulation or disease involves altering some biophysical parameters, such as the weight of a synaptic transmission from one neuronal population to another. When a simulation is performed to investigate such a manipulation, it becomes a specific version of our computational experiment (for example Trial 1). We record the biophysical manipulations that were performed to produce this instance of our computational experiment. If this proposed manipulation is somehow undesirable, a note is made to describe the failure mode, and usually some brief thoughts are included about why this proposed manipulation failed. It may be convenient to perform pairs or families of simulations in a single trial in order to represent for example a “control simulation” as well as a “drug simulation” or a “manipulation simulation”; these notes may compare the manipulation outcome across the family of simulations in that trial. Simulation trials are identified by a number and by the date on which this batch of trials were performed. In this way, simulation trials can be cross referenced, and their provenance traced. For example, the first simulation trial on August 1st could be based on the ninth simulation trial from June the 7th, which had a particularly desirable outcome. Perhaps after a series of dead ends, the tenth simulation trial on August 1st could be re-based to start over from the fifth simulation trial from June 10th, which had a desirable outcome using an alternate hypothesis.

**Rule 7 – Disseminate broadly.**

Models will be submitted to ModelDB at the time of publication or made publicly available on a widely used source code repository (for example GitHub or GitLab) as appropriate. The equations and formulae upon which our models are based will be sufficiently documented in publications to reproduce our simulations.

**Rule 8 – Get independent reviews.**

We have committed to two independent reviews. The evaluators will be a scientist and an engineer at CWRU who are knowledgeable of rhythmic biologic data and modeling but not directly involved in this project.

**Rule 9 – Test competing implementations.**

Our simulations are implemented by separate individuals in multiple simulation environments. Our research group uses MATLAB, python, C, C++, and Microsoft Excel for simulations. Our simulation outputs are the solutions to ordinary differential equations, and our different simulation platforms use different numerical solvers to produce these solutions.

**Rule 10 – Conform to standards.**

We complied with HIPAA data stewardship standards when handling human data.