1. Project title: MODELING BRAINSTEM INFLAMMATION'S ROLE IN SYSTEMIC DYSFUNCTION DURING SEPSIS

2. A one/two sentence summary of the project topic with a hyperlink to more detailed information via the IMAG wiki.

- Sepsis occurs in million Americans yearly and kills up to 30% of these patients. Surviving sepsis depends on early detection and a biometric tracking susceptible patients is urgently needed. Our group is developing data-driven models for tracking and predicting a transition point from controlled systemic infection to sepsis.

3. Details regarding Model Credibility plan following the CPMS Ten Simple Rules (TSR) format.

Rule 1 – Define context clearly:

- Context of use: to establish data-driven models that utilize cardiorespiratory data recorded in Intensive Care Units to track patients over-time and predict recovery or onset of sepsis. The primary data for the Dynamic Bayesian Network and Dynamic Network Analyses (DyBN and DyNA, respectively) are molecular (cytokines). We are constructing DyBN and DyNA to identify molecular networks and interaction in the peripheral and central inflammatory response as well as their relationship to the recorded physiologic (systems-level) cardiorespiratory waveform data. Similarly, we are developing computational models of cardio-respiratory control to differentiate between healthy and septic subjects based on cardiorespiratory data. We are use machine learning approaches to teach the models to reproduce the physiologic outputs obtained from non-septic and septic human patients and from healthy and septic rodents.

Rule 2 – Use appropriate data:

- Appropriate data for the data-driven models (DyBN and DyNA) and the computational model are the waveform predictability index (NonLinear Complexity Index) and Cardiorespiratory Coupling index

- Appropriate data for DyBN and DyNA are the concentrations of cytokines as determined by Luminex. Expression levels will be verified by ELISA, which is more sensitive for the rodent.

- 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:

- Generally, our workflow begins with an observation that originates in some motor or otherwise behavioral data. From this observation, we make an inference: based on our general working hypothesis for the organization of the respiratory neuronal circuits and their cardiac interactions, a mechanism that supports this observation. This conceptual model for a mechanism is then implemented in our computational model and evaluated against the data that informed the development of the conceptual model.

- Proposed mechanisms are evaluated within the context of inter-participant or inter-animal variability. For example, if the strength of cardioventilatory coupling (the impact of a heartbeat on the subsequent inspiratory timing) within a cohort is observed to take on some distribution, can we use our computational mode to show how our proposed mechanism (in other words our conceptual model) explains the subject-to-subject variability. Moreover, we test whether this mechanism be tuned to fit individual participants rather than just qualitatively reproducing trends seen within group data.

- Some mechanisms may be 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.

- The quality and availability of data is always a limitation on the inferences that can be drawn from such data. But by utilizing rodents and patients, we can improve the power of our inferences through validation within and across these groups.

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, which is a professional software development and deployment platform (https://about.gitlab.com).

- We are also versioning our computational experiments based on the timeline of our iterative investigatory procedure. This versioning system refers to simulations that test specific hypotheses or evaluate model sensitivity. So, these "model versions" refer explicitly to some changes in biophysical quantities (see our response for Rule 6 – document adequately), which define "what is being simulated" rather than substantial changes to our simulation platforms.

Rule 6 – Document adequately.

- Our C++ source code is documented using the Doxygen documentation generator (http://www.doxygen.nl/).

- 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 "pathological 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.

- Our projects are regularly presented at the annual meetings of the Society for Neuroscience and the Organization for Computational Neuroscience. We will present at more domain-specific meetings such as the 17th International Conference on Complexity in Acute Illness (ICCAI) 2019, which will be held on Sept 26-27th 2019.

- Simulations are currently disseminated internally using a web-based graphical environment. This environment allows simulations to be performed with adjustments made to biophysical parameters in the graphical environment and displayed on-line over the web. This environment may be made public depending on the ongoing availability of our web resources.

Rule 8 – Get independent reviews.

- We have committed to two reviews; the first one occurred 'in house' on May 10th and the second one will also occur here in May 2020 evaluators will not be associated with 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.