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1. Project Title: Multiscale Model of the Vagal Outflow to the Heart

2. The aim of this collaborative U01 project to develop a multiscale model of how heart is controlled by the brainstem.

3. Details regarding the Model Credibility plan
A. List of Planned Actions
These actions are in alignment with the CPMS Ten Simple Rules, as listed in the below table.

B. Information gained by each Credibility Action

a. The single cell data contains information on the balance of cellular functional states, that can be used to tune the proportions of various cell phenotypes in the model
b. Physiological data provides constraints on the overall circuit function to limit parameter ranges
c. Not all parameters are expected to have equal influence over the network dynamics. Global sensitivity analysis will rank the parameters with highest influence over cardiac function, in the face of simultaneous variations in all the parameters, to help prioritize the experiments for estimating the corresponding parameters
d. Implementing multiple alternative models tests different assumptions

C. Actions and Activities classified within the CPMS TSR framework

#	Ten Simple Rules	Planned and Ongoing Actions
1	Define context clearly	We are interested in studying vagal control of cardiac function through modeling the neuronal populations that constitute a multilevel closed loop control circuit. This model focuses on how such neuronal populations interact in the rat to modulate heart rate and contractility. Specific details in the manuscripts.
2	Use appropriate data	The data from which the model is built is collected under healthy conditions as well as with selected pathological states of hypertension and heart failure. We collect data comes from laser captured neurons from the hearts and brains of rats in both healthy and pathological states. The use of laser capture permits transcriptomic examination of anatomically specific and cell-type specific samples from a relevant in vivo context.
3	Evaluate within context	The model will be validated against physiological data sourced from the same rat models of

		hypertension and heart failure that the molecular data was derived from. All models are being evaluated using global sensitivity analysis. Parameters chosen for variation in the models are based on sensitivity analysis results and biological relevance.
4	List limitations explicitly	The limitations of each model were stated explicitly in the accompanying publications
5	User version control	Manual versioning for major changes to the model. Automatic version control is partly implemented using Dropbox for Business functionality to create a new version after each autosaving of the files.
6	Document adequately	Development process is not being documented prior to publication. However, institute-wide efforts are being made to introduce electronic laboratory notebooks that would improve model development documentation. The code is annotated to include relevant explanations to aid in understanding the model, when accompanied by the model equations and text from the associated manuscript.
7	Disseminate broadly	All model codes as well as code required to generate results shown in the manuscripts will continue to be provided as supplementary material with the respective publications. Model code on ModelDB is available for manuscript reviewers during peer-review. Model and data are disseminated via meetings. Manuscripts will continue to be published via open access.
8	Get independent reviews	So far, all the models were independently reproduced by laboratory colleagues not directly involved in the specific project. New members to the lab routinely review prior models as part of their initial training.
9	Test competing implementations	The initial model development is ongoing in MATLAB. Alternative implementations will be developed using NEURON as well as custom software in C++ from Drexel University colleagues.
10	Conform to standards	We conform to the best practice standards for ModelDB submission. Simulation workflows, data collection, data processing, data reporting conform to practices generally accepted by the process control engineering community.

D. Description of how the planned activities will lead to a credible model:

We are generating novel single neuron transcriptomic data sets from brainstem control circuits that will enable us to build multiscale models that incorporate gene regulatory networks

underlying adaptive changes in vagal control of cardiac function. By incorporating such data, and evaluating the model for critical parameters using global sensitivity analysis, and testing alternative assumptions for distributions of neuronal transcriptomic states, we will be able to develop confidence on why certain gene regulatory network mechanisms are consistent with observed data and others are not. Open dissemination of the results, model code and associated data sets, will enable independent evaluation by others.

E. Progress to-date and Plans for next reporting cycle (6 months). What has been achieved since last reporting?

We developed a new model of gene regulatory networks across organs based on gene expression time series data obtained from an animal model for human essential hypertension without a known genetic or environmental cause. We have also developed a preliminary circuit model of the closed loop control of cardiac function. Over the next project period, we will analyze the model to evaluate the relative contribution of various brainstem components to the maintenance of cardiovascular physiology during normal versus heart failure conditions.

4. Issues/concerns identified as critical or problematic to achieve the standard of credibility set by MSM Consortium

One issue is the lack of clear guidance on independent review. As there is no clear direction/consensus from the MSM Consortium, we have chosen to engage laboratory colleagues that are not otherwise involved in the project to start with the manuscript text, equations, parameter tables, and list of assumptions, to independently develop MATLAB code to attempt to reproduce the simulations and analyses. It would be helpful to obtain additional guidance on whether this sufficiently addresses the rule #8 in the above table.

5. What other factors, if any, contribute to credibility but cannot be reported within the TSR structure?

None so far.