Modeling and analysis of autonomic circuits underlying closed-loop cardiovascular control to identify key contributors to individual variability

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Cardiovascular diseases are the leading cause of death in the United States. Recently, there has been increasing recognition of the importance of neural regulation in heart health and disease. The purpose of this neural regulation of the cardiovascular system is to maintain blood flow and blood pressure, which is done by regulating variables such as heart rate. An emerging therapeutic for cardiovascular diseases known as vagus nerve stimulation seeks to exploit our understanding of the effects of neural regulation on heart function. However, a significant barrier to its clinical use is identifying individuals who will benefit most from treatment due to the significant underlying variability in patient heart function and neural regulation. Computational modeling augments experimental methods to further our understanding of closed-loop cardiovascular control and provides a means to identify drivers and biomarkers of inter-individual heterogeneity. The objective of this dissertation is to *develop closed-loop computational models of cardiac control to identify sources of phenotypic variability at cellular-level and organism-level scales affecting neural activity and cardiac physiology*.

Towards this goal we have developed a library of single-neuron electrophysiology models from single-cell transcriptomic data to bridge the gap between gene expression heterogeneity and electrophysiological function variability. From 104 unique gene expression combinations identified from the transcriptomic data, the model predictions reproduced the two experimentally observed neuronal firing behaviors. Post-hoc analysis also showed that model-predicted parameters were correlated with relative gene expression.

To explore inter-individual heterogeneity at the organismal level, we extended an existing closed-loop cardiovascular control model to include the heart's "little brain", the intrinsic cardiac nervous system. Inclusion of a representation of the intrinsic cardiac nervous system is necessary for modeling the response to vagus nerve stimulation. Validation of this model based on hemodynamic responses to vagus nerve stimulation and heart rate responses to deep breathing is shown. This model was then used to test alternative scenarios of nerve fiber activation in vagus nerve stimulation. We found that preferential sensory nerve fiber activation accounts for experimentally observed heart rate responses. This model provides the basis for the work presented in the subsequent chapters.

Next, we apply the model to explore neural adaptation to compensate for myocardial infarction using *in silico* patient cohorts to quantify inter-individual variability. We use the *in silico* patient cohorts to represent alternative scenarios of neural adaptation that occur from pre- to post-infarct to compensate for loss of cardiac function. By identifying similarities between cardiac autonomic

regulation in individuals who are better able to adapt after a heart attack, we suggest possible neural pathways to target for therapeutic intervention.

A complementary approach to using *in silico* patient cohorts for exploring inter-individual variability is to develop patient-specific models. We extended our previously developed closed-loop cardiovascular system model to include respiratory regulation. We developed a pipeline to calibrate the models to hemodynamic and respiratory data from patients in response to various inhaled oxygen and carbon dioxide concentrations.

We have developed computational models of cardiovascular regulation for identifying contributors to variability in heart function. Starting from models of electrophysiological heterogeneity in cardiac neurons to systems physiology models used for analysis of population variability, these models serve as an integrative framework for using disparate, multiscale molecular, anatomical, and physiological datasets for developing predictive tools for hypothesis testing and generation.