Multiscale Model of the Vagal Outflow to the Heart

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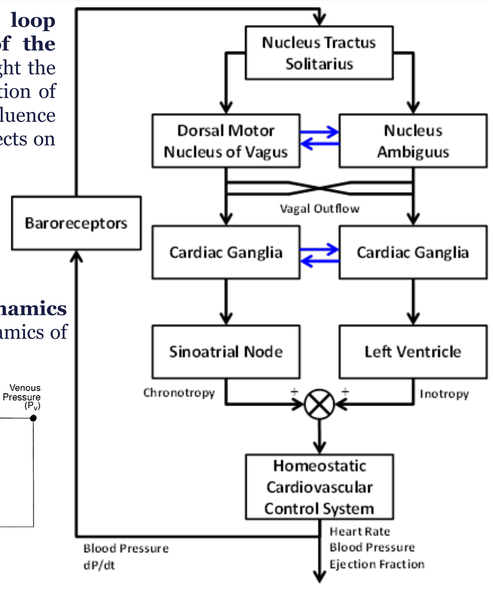
Abstract

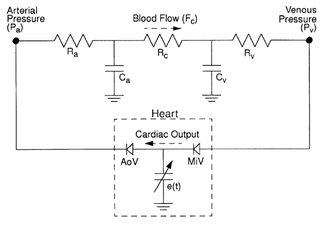
Vagal control of the heart has seen renewed interest due to the now well-recognized potential of manipulating cardiac vagal activity for novel therapeutic opportunities in treating heart disease. Recent anatomical and physiological evidence shows that vagal cardiac control is multimodal at both pre- and post-ganglionic neuronal levels. Coordination between multiple modes of control (e.g., of heart rate, ventricular contractility, etc) is essential for heart health. Disruption of such coordination is a hallmark of heart failure and arrhythmias, for example. Studies thus far have largely focused on the physiological effects of the vagus on heart rate without delving into the underlying neural networks, where insights are likely to yield targets for fine-grained manipulation of vagal activity to treat heart disease. Our project is aimed at addressing this unmet need by focusing on the central neuronal as well as cardiac ganglionic circuits driving chrono-, dromo- and iono- tropism. We will pursue an integrated multiscale modeling strategy that combines fine-grained anatomical tracing of control circuits and high-throughput transcriptional analysis of single neurons identified based on circuit connectivity, with computational modeling of the multiscale closed loop vagal cardiac control. These involve hemodynamics, brainstem neuronal networks, and cardiac ganglionic circuits involved in the coordinated inotropic and chronotropic control of the heart. We will develop detailed electrophysiological models of neuronal excitability in nucleus ambiguus (NA) and dorsal motor nucleus (DMV), as well as the targeted cardiac ganglia, and incorporate the transcriptional changes identified from coronary artery ligation experiments in these models. We hypothesize that coordination and integration of the control of rate and contractility occurring at the level of the NA/DMV and the level of the cardiac ganglia are the basis for cardioprotective vagal cardiac outflows.

Overall Concept

Structure of the closed loop model of vagal control of the heart. The blue arrows highlight the potential multi-level co-ordination of the neuronal functions that influence vagal outflow as well as the effects on the heart.

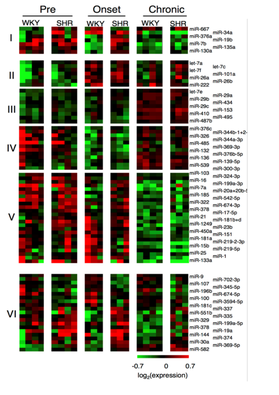


Schematic of the hemodynamics model accounting for the dynamics of heart and peripheral vessels.

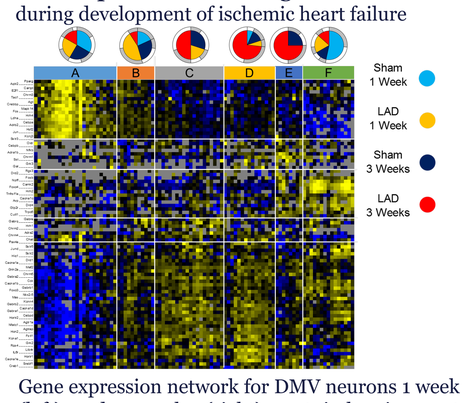


Data Collection Examples[1,6]

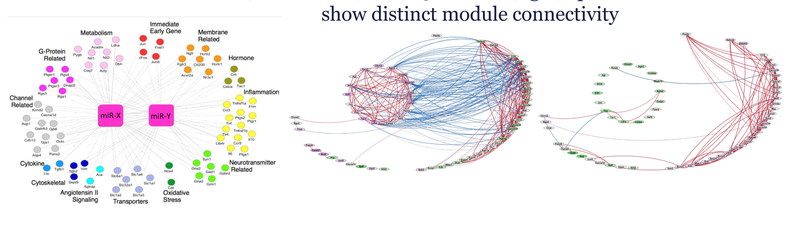
microRNA from NTS during development of hypertension



Gene expression from single DMV neurons during development of ischemic heart failure



Gene expression network for DMV neurons 1 week (left) and 3 weeks (right) post ischemia onset show distinct module connectivity

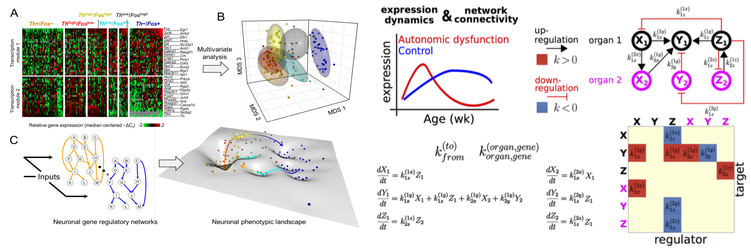


From Neuronal Gene Expression to Cardiac Physiology

Gene Networks and Dynamic Expression[1,2,5]

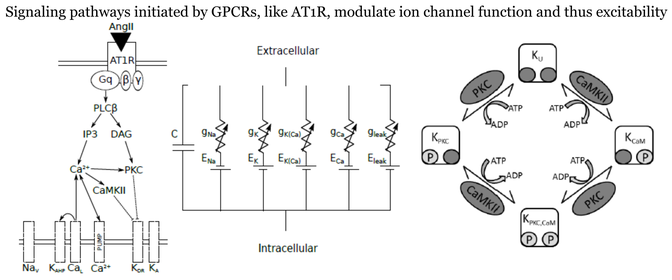
Example gene expression from NTS that defines neuronal response phenotype to hypertensive challenge

Modeling of gene expression dynamics using ODE's based on real data collected during the development of hypertension

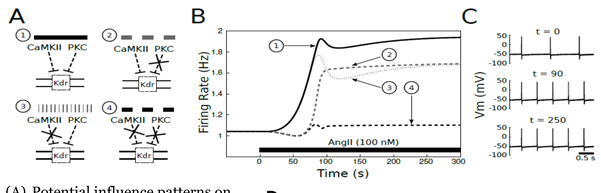


Signaling Pathways Ion Channel Function[3]

Signaling pathways initiated by GPCRs, like AT1R, modulate ion channel function and thus excitability

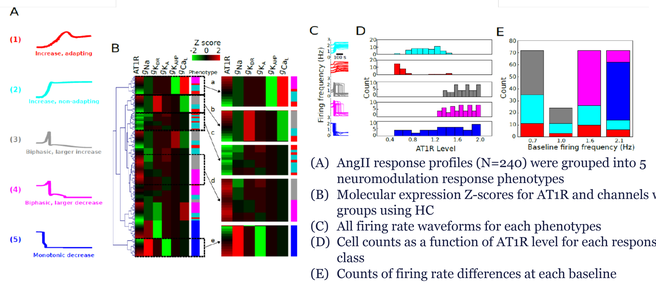


Relating Gene Expression to Electrophysiology[3,4]



(A) Potential influence patterns on ion channel function
(B) Resulting firing rate related to AngII levels over varying exposure times
(C) Simulated spike patterns
(D) Separatrix for potential firing frequencies for varying AngII levels and exposure times

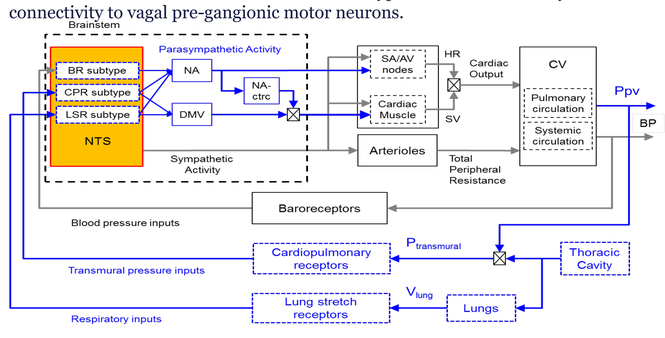
Gene Networks Drive Functional Phenotypes[4]



(A) AngII response profiles (N=240) were grouped into 5 neuromodulation response phenotypes
(B) Molecular expression Z-scores for AT1R and channels were groups using HC
(C) All firing rate waveforms for each phenotypes
(D) Cell counts as a function of AT1R level for each response class
(E) Counts of firing rate differences at each baseline

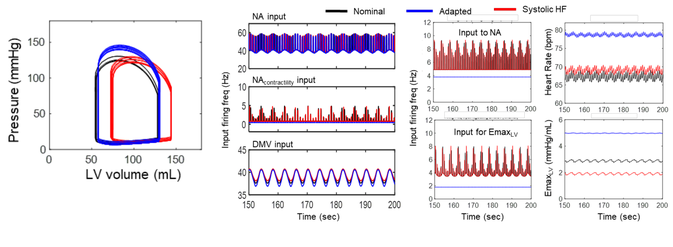
Neuronal Subtypes Drive Cardiac Control Outcomes

Model framework to account for neuronal sub-type in the NTS with assymetic connectivity to vagal pre-gangionic motor neurons.

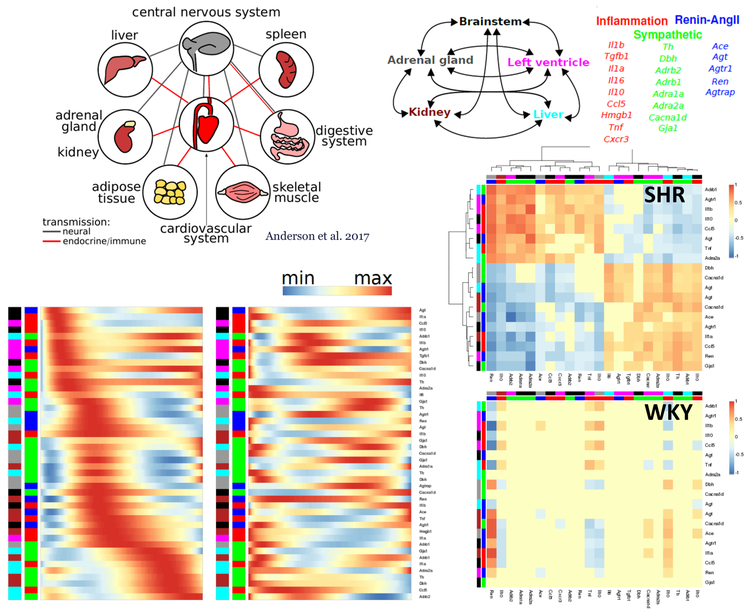


Adaptation of Neuronal Responds to Pathology

Modeling systolic HF and consequences of neuron-controller adaptation (NA-DMV only)



Organ - Organ Interactions Influence Cardiac Control[2]



Credible Practice of Modeling and Simulation

Define Context	We are interested in studying vagal control of cardiac function through modeling the neuronal populations that constitute this control loop. This model focuses on how such neuronal populations interact in the rat to modulate heart rate and contractility. 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.
Appropriate data	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.
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.
List Limitations	Models are translated between platforms to check validity when possible. New members to the lab routinely review prior models as part of their initial training.
Version Control	Version control is maintained manually, with documentation and provenace available upon request.
Documentation	Model code will continue to be made available via ModelDB with the accompaying README.
Dissemination	Model code on ModelDB available for manuscript reviewers during peer-review. Model freely available after publication. Model and data disseminated via meetings. Manuscript published in open-source journal.
Independent Review	Models are translated between platforms to check validity when possible. New members to the lab routinely review prior models as part of their initial training.
Test Implementations	The initial model development is ongoing. Alternative implementations will be developed using NEURON as well as custom software in C++ from Drexel University colleagues.
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.

References

1) Park J, Brureau A, Kernan K, Starks A, Gulati S, Ogunnaike B, Schwaber J, Vadigepalli R. Inputs drive cell phenotype variability. Genome Res. 2014 Jun;24(6):930-41.
2) Anderson WD, DeCicco D, Schwaber JS, Vadigepalli R. A data-driven modeling approach to identify disease-specific multi-organ networks driving physiological dysregulation. PLoS Comput Biol. 2017 Jul 21;13(7):e1005627.
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6) DeCicco D, Zhu H, Brureau A, Schwaber JS, Vadigepalli R. MicroRNA network changes in the brain stem underlie the development of hypertension. Physiol Genomics. 2015 Sep;47(9):388-99.

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