The Virtual Physiological Rat Project

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Welcome to The Virtual Physiological Rat Newsletter

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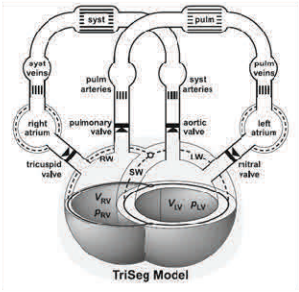
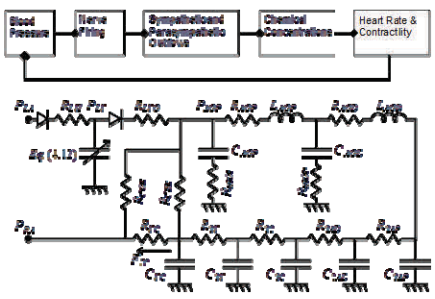
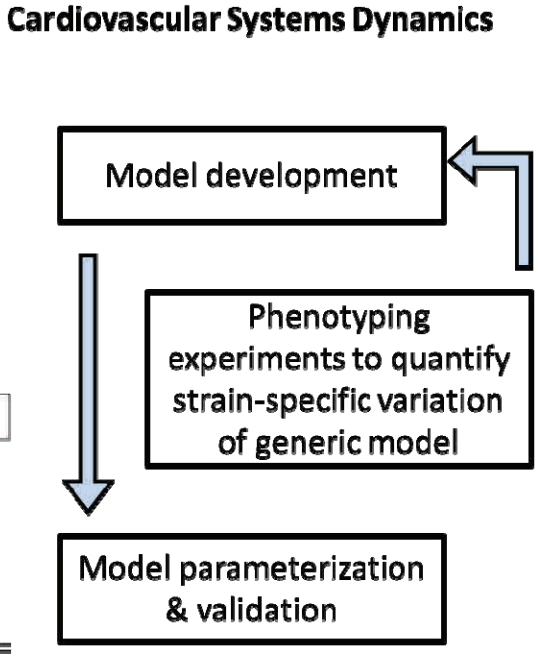
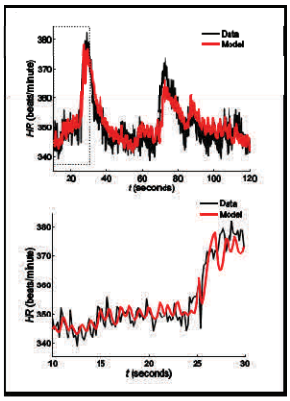
VPR Project 1 Overview: **Cardiovascular Systems Dynamics**

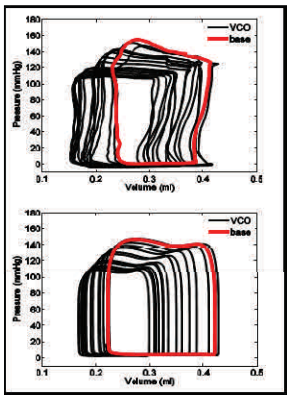
A comprehensive understanding of complex cardiovascular disease requires the ability to look at the system as a whole. Within this project, the modeling efforts begin with the circulatory system and uses a lumped parameter network model to account for viscous, elastic, and inertial forces within the system. Simulations of the baroreflex system, the myogenic response in resistance arteries, and closed-loop cardiovascular dynamics are being used to uncover strain and stressor related differences in model parameters. Phenotyping experiments are being run on different strains, under different conditions, to identify and test strain-specific versions of the generic model. The generic cardiovascular model is then parameterized and validated using the experimental data collected on the various strains.







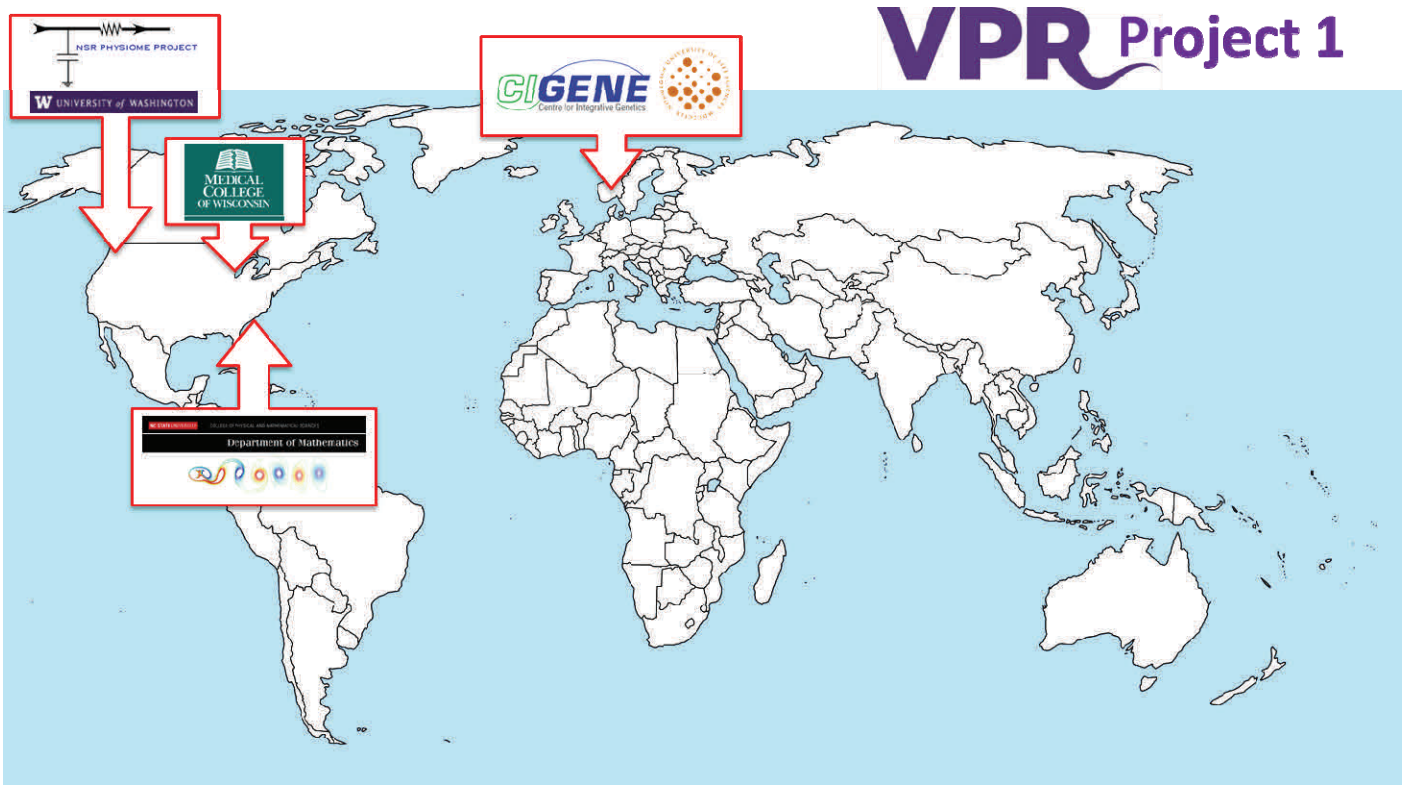




Click here for the VPR website

Project 1: Cardiovascular Systems Dynamics

Hypertension predisposes individuals for heart failure, stroke and kidney disease, and is therefore is a major source of morbidity and mortality. Its etiology remains enigmatic despite intense research efforts over many decades. By use of empirically well-constrained computer models describing the coupled function of the baroreceptor reflex, the mechanics of the circulatory system, renal function, and the renin-angiotensin system, we have demonstrated quantitatively that arterial stiffening seems sufficient to explain age-related emergence of hypertension (http://arxiv.org/abs/1305.0727). This work, which directly contradicts the major governing theories in the field, reveals how an emergent understanding of a physiological system can emerge from systems/computational analysis. Specifically, the empirically observed chronic changes in pulse pressure with age, and the impaired capacity of hypertensive individuals to regulate short-term changes in blood pressure, arise as emergent properties of the integrated system.



Cardiovascular Systems Dynamics: Project 1 primary sites include the Medical College of Wisconsin, University of Washington, North Carolina State University, and at the Norwegian University of Life Sciences.

Meet the people behind Project 1

Shivendra Tewari, PhD

I opted for a B.S. degree in Computer Science and a M.S. degree in Mathematics both from Jiwaji University, India. Then I joined the National Institute of Technology (NIT), Bhopal, and earned my Ph.D. in Applied Mathematics. I took several courses in Mathematical Biology for my pre-Ph.D. course work, which motivated me to study biological processes using mathematical modeling. In fact, I ended-up conducting my doctoral studies in Computational Neuroscience. As a doctoral student at NIT Bhopal and postdoctoral fellow at the Indian Statistical Institute Bangalore, I developed mathematical models for intra- and inter-cellular processes in the hippocampus. This work made me realize the importance of inter-connected cell-signaling networks at a higher level, i.e. at the systems level. However, this work primarily focused on mathematical modeling without any exposure to experimental data for model validation, which I quickly realized to be very important for realistic understanding of the biological process under study. At that point I learned of the Beard-Dash group, and also the VPR project, which works at an interface of theoretical and experimental approaches. This motivated me to join their research group as a postdoctoral position to further advance my academic career.

VPR aims at integrating molecular and cellular processes at the whole-organ and whole-body (or systems) levels to understand physiology and pathophysiology. Not only that, it also studies the effects of external stimuli (e.g., environment and diets) over the resulting phenotypes (e.g., hypertension). So far my role in VPR has been primarily in Project 1 (Simulations of Cardiovascular Systems Dynamics). I have been studying the effect of an important external stimulus (chronic hypoxia) giving rise to a specific phenotype (idiopathic pulmonary hypertension). We have successfully developed a mechanistic mathematical model of cardiac mechanics and blood circulation to quantitatively reproduce the experimental measurements that describe the chronic hypoxia-induced pulmonary vasculature remodeling. This work is being done in collaboration with Dr. Naomi Chesler at the University of Wisconsin – Madison, who provides the experimental data.

Apart from working on the cardiovascular systems modeling, I am also working with Dr. Dash on calcium handling in cardiac mitochondria and cardiomyocytes, associated with several pathologies (e.g., cardiac ischemia-reperfusion injury), which is complementary to the VPR Project, where I make use of my earlier research experience. Prior to joining the Beard-Dash research group, I was a theoretical electrophysiologist who was interested in designing and performing own electrophysiological experiments to understand transmembrane transport processes and their electrical activities, and how they influence cellular function under physiological and pathophysiological conditions. Under the support of Drs. Beard and Dash, I have got an opportunity to learn patch-clamping of not only cardiac cells, but also cardiac mitochondria and associated membranes, under the supervision of Dr. Kathleen Kinnally at the New York University. Upon returning to MCW, we will be performing patch-clamping experiments using mitoplasts, proteoliposomes and lipid-bilayers to measure membrane electrical activities in cardiac mitochondria.

Meet the people behind Project 1

Gary Raymond, MS

Gary, trained as an oceanographer, after working for NOAA and then in Oceanography at UW, has been in Bioengineering since 1988 working as a Scientific Programmer with Jim Bassingthwaighte and colleagues at the National Simulation Resource Facility. He has developed mathematical models of biological processes, mainly for transport through the circulation and for transmembrane transport and cellular metabolism, particularly as applied to the heart. Several of these models required accounting for the heterogeneity of regional blood flows in the heart by using multi-capillary models. The heterogeneity was a feature of branching arterial networks in general and near-neighbor regions were correlated in their flows. The spatial arrangements were fractal, with logarithmic falloff in correlation with distance between points. Tracer washout from the heart likewise showed logarithmic or power law form, another fractal.

Gary extended his expertise to time signal analysis and developed new methods of statistical analysis to handle fractal time series. Eleven of his papers and 7 abstracts are on this topic, and he is now recognized nationally as an expert.

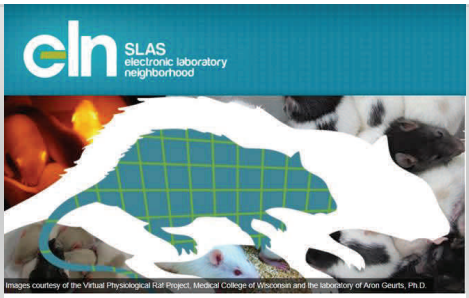
He contributed 8 papers to the oceanography literature, and since coming to Bioengineering 26 peer-reviewed papers and 28 abstracts of presentations at national meetings. His expertise and his highly developed sense for accuracy and reproducibility of scientific evidence has contributed to his skills in reviewing scientific papers submitted to a variety of journals. He recently received a letter from an editor saying that his review of a submitted paper was the best this editor had received in a decade.

Gary is the consultant for people around the world now, not only for fractals, but for JSim, our simulation analysis system designed for analyzing experimental data. He is by far the most expert person at coding the biological models, and is supported in part by the Virtual Physiological Rat program. He has the patience and the skill to spread his knowledge widely, and does so day after day to many students and to many professors.

VPR Outreach, Education & Dissemination

Recent News

The VPR has been featured in an article in SLAS Electronic Laboratory Neighborhood. Please check out "The Virtual Rat: Exploration of Complex Diseases Will Impact Drug Discovery, Development."



The Virtual Rat: Exploration of Complex Diseases Will Impact Drug Discovery, Development

PUBLICATION CORNER

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