The Virtual Physiological Rat Project

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Welcome to The Virtual Physiological Rat Newsletter

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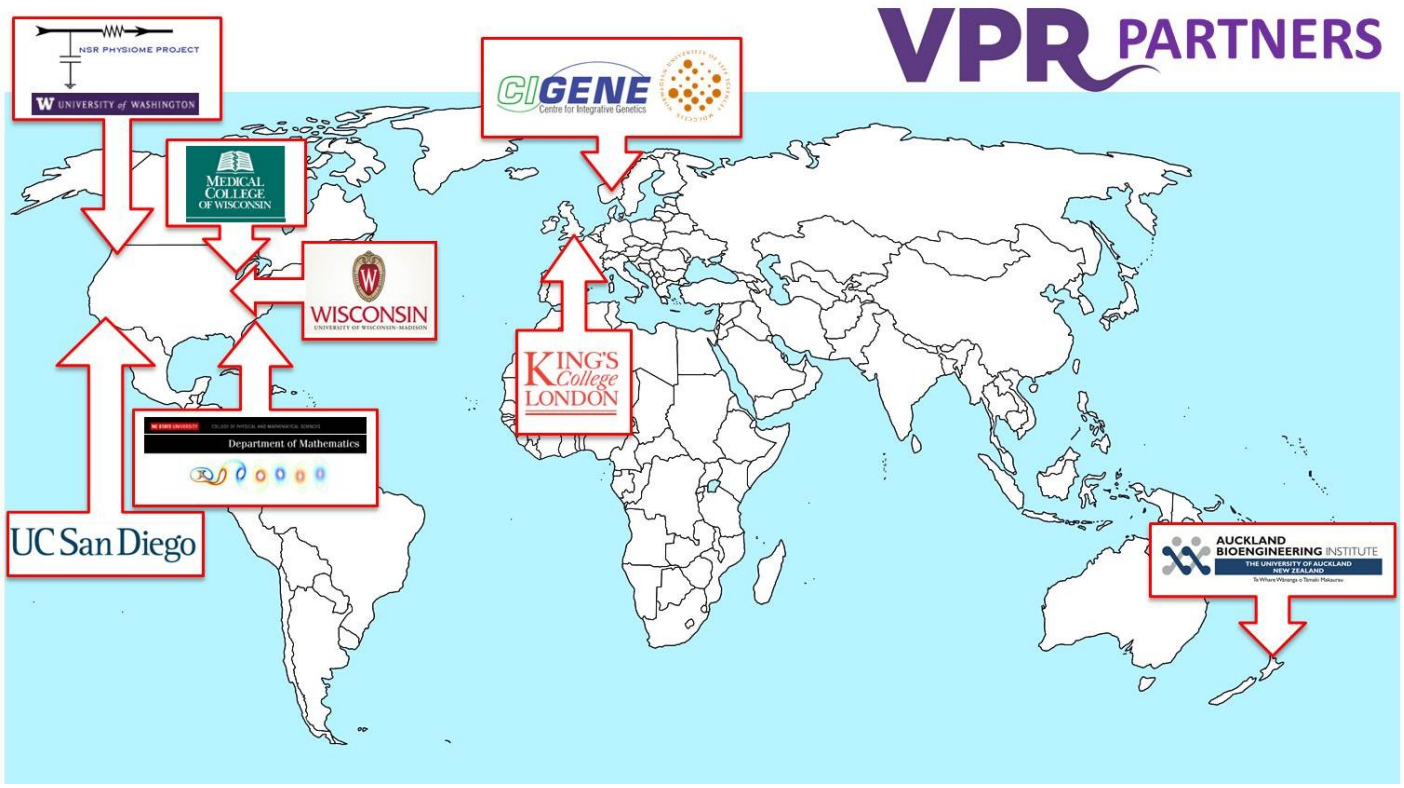
Welcome to the inaugural newsletter for the Virtual Physiological Rat Project.

The VPR project is coordinated at the Medical College of Wisconsin (MCW), with six additional partner institutions, identified in the map below. Partners in the United States (MCW, University of Wisconsin-Madison, University of Washington-Seattle, North Carolina State, University of California-San Diego) and across the world (University of Auckland, Norwegian University of Life Sciences, King's College of London) are working together to identify and validate how multiple genes and environmental factors interact to determine physiological function. This quarterly newsletter will 1) highlight, on a rotating basis, each of the six projects, 2) highlight new publications, 3) provide links to new resources, including software, computational models, data sets, and animal models, and 4) introduce the people behind the VPR.



Click here for the VPR website

VPR History

The Virtual Physiological Rat (VPR) project is an international collaboration, supported by NIH grant P50-GM094503, working to analyze, interpret, simulate, and ultimately predict physiological function in health and disease. Using laboratory rats—or more specifically, a variety of specialized strains of rat—as research models, the project is charged with determining: (1.) how clinically important metrics of mammalian physiology (e.g., blood pressure) are regulated; (2.) when and why physiological regulation leads to unhealthy states (e.g., hypertension), and (3.) how physiological and pathophysiological function emerge from the interaction of molecular-, cellular-, tissue-, and organ-level processes in an organism. In short, following successes in molecular genetics over recent decades, our goal is to "put Humpty Dumpty back together again"[1].

In the VPR Project, computer simulation is the vehicle for integrating biophysical processes into consistent representations of biological function for developing and representing hypotheses, for interpreting observations, and for designing experiments. By integrating models representing major system components into combined simulation, we obtain insight into how low-level molecular processes influence high-level phenotypes. For example, decades of work have lead to the ability to capture the mechanical and electrical operation of the heart at high levels of fidelity. Similarly, we are beginning to understand how energy metabolism – which transduces the chemical free energy to drive cardiac mechanics and electrophysiology– operates in health and in certain disease states. It remains an open question if and how a disruption of normal metabolism can impact cardiac function. Moreover, a practical understanding of how metabolic function in the cardiomyocyte can influence cardiovascular health requires a functional synthesis of the operation of the heart, the vasculature, the autonomic system, and the kidney. Putting Humpty Dumpty back together again is indeed a task for all of the King's horses and all of the King's men.

Realization of the grand nature of this challenge led to the call for an international "Physiome Project", initiated by James Bassingthwaighte, Peter Hunter, and Denis Noble. Their efforts led to the launch of the IUPS Physiome Project and laid the foundation for the European Commission's Virtual Physiological Human (VPH) Programme, and the NIH-sponsored VPR Project. As in the VPH Programme, progress in the VPR Project depends not only on capturing physiological function in appropriate and effective mathematical models, but also on representing and sharing data, models, and related knowledge in a common framework. Software development and model and data dissemination work under the VPR is carried out in collaboration with the VPH and the broader Physiome community. Our focus on the rat as a research model allows us to take advantage of a tremendous legacy of published data and to conduct critical new experiments to deliver a suite of representative models and data sets unprecedented in its coherence and depth.

Current VPR research is focused primarily on cellular metabolism, cardiac mechanics and electrophysiology, vascular biology, renal function, and whole-body cardiovascular function and transport. The six projects (Cardiovascular Dynamics, Whole-Body Function, Heart, Kidney, Genetics & Novel Rat Strains) are led by investigators at seven institutions as described in the welcome statement.

Further reading: Beard et al., (2012) Multiscale modeling and data integration in the Virtual Physiological Rat Project. *Ann Biomed Eng* 40:2365-78.

[1] Noble, D., *The music of life: biology beyond the genome*. 2006, Oxford; New York: Oxford University Press, xiii, 153 p

Meet the people behind the VPR

In future issues, this spot will be used to feature trainees, including students, postdocs, and summer trainees. The VPR includes a diverse group of researchers with backgrounds in physiology, molecular biology, computational modeling, and engineering. The stories behind how each trainee became involved in this project are quite interesting! Stay tuned to meet each trainee!

For this inaugural issue, we would like to give thanks to the whole VPR group for a very successful first year. The photo below was taken at the first annual VPR External Advisory Board meeting, held at Discovery World in Milwaukee, WI on July 26-27, 2012. More than fifty attendees spent two exciting days discussing each project with both oral and poster presentations by the lead investigators and many students and fellows.

Creative ideas and positive feedback were provided by our four External Advisory Board members: Gregory Fink (Pharmacology & Toxicology, Michigan State University), William Jusko (Pharmaceutical Sciences, SUNY Buffalo), Joseph Nadeau (Institute for Systems Biology), and Aleksander Popel (Biomedical Engineering, Johns Hopkins University).

Virtual Physiological Rat project group photo taken at Discovery World at Pier Wisconsin on Milwaukee's lakefront, July 23, 2012.

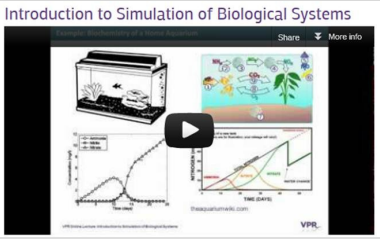
VPR Outreach, Education & Dissemination

Video Tutorials, Meetings, Webinars, and more

The VPR Outreach and Dissemination team is hard at work preparing educational materials and making resources available to the scientific community. All software, models and data sets developed as part of the VPR project are available through the RESOURCE section of the website.

Educational materials include VIDEO TUTORIALS, announcements for events, and access to webinars. For a career perspective, we are preparing materials and biographies to demonstrate the diverse backgrounds of the VPR team.

Training programs for undergraduates, graduate students, postdoctoral fellows, and the broader scientific community are available. Announcements for summer programs, workshops, and course offerings are posted on the VPR website.



PUBLICATION CORNER

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3. Bugenhagen SM, Beard DA. Specification, construction, and extract reduction of state transition system models of biochemical processes. *J Chem Phys*. 137(15): 154108, 2012.

4. Olufsen MS, Hill NA, Vaughan GA, Sainsbury C, Johnson M. Simulation of rarefaction: impact on blood pressure in the systemic and pulmonary large and small arteries. *J Fluid Mech*. 705:280-305, 2012.

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Please visit www.virtualrat.org/publications for more publications.

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