**Annual Report for Period:** 08/2006 - 07/2007 **Submitted on:** 07/19/2007
**Principal Investigator:** Bassingthwaighte, James B. **Award ID:** 0506477
**Organization:** U of Washington
**Title:**
MSM: Adaptive Multi-Scale Model Simulation, Reduction and Integration for Cardiac Muscle Physiology

## Project Participants

**Senior Personnel**

**Name:** Bassingthwaighte, James
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**

**Name:** Chizeck, Howard
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**

**Name:** Atlas, Les
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**

**Name:** Qian, Hong
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**

**Post-doc**

**Name:** Carlson, Brian
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**
Mechanical aspects of cardiovascular systems modeling.
Supported by NHLBI Training Grant.

**Graduate Student**

**Name:** Hawley, Stephen
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**
Working on PhD research with investigators. Topics include: systems and control theory for multiscale systems, and anamoly detection. Supported by grant.

**Undergraduate Student**

**Name:** Nicholson, Micah
**Worked for more than 160 Hours:** No
**Contribution to Project:**
Developed website versions of models of components of cardiovascular and respiratory system. Supported on REU-MARC fellowship.
His work finished in September 2006.

**Technician, Programmer**

**Name:** Neal, Max
**Worked for more than 160 Hours:** Yes
**Contribution to Project:**
Worked on model development and software tasks.

**Other Participant**

**Research Experience for Undergraduates**

## Organizational Partners

**Pacific Northwest National Laboratory**
PNNL tested and evaluated models or respiratory system developed by project.
We developed simplifed models of 3D respiratory mechanics --working to fit this to their data.

**University of California-San Diego**
Work with Dr. Andrew McCulloch, UCSD Dept. of Bioengineering. We supplied boundary conditions for finite element models of the heart.

**Medical College of Wisconsin**
Developed and exchanged cellular level models for cardiac metabolism.

## Other Collaborators or Contacts

Marco Cabrerra -- Case Western Reserve University: Joint work on metabolic modeling.

James Glazier -- Univ. Indiana: Planning for multiscale conference.

Daniel Beard -- Medical College WI: Metabolic modeling.

Other projects in Multiscale Modeling Consortium.

## Activities and Findings

**Research and Education Activities:**
Research Activities are in three areas:
(1) Circulatory Systems Model Formulation and Development.
(2) Theory and algorithms for multiscale system decomposition, aggregation and control.
(3) Theory and algorithms for detection of model anomalies.

Educational Activities include:
(4) Development of material used in graduate Bioengineering course.
(5) Student research participation.

In collaboration with other IMAG/MSM projects, a set of modeling standards is being developed and is evolving on the IMAG website. In building large scale models in a modular fashion, a common ontology is essential so that the names of variables and parameters are consistent from one module to another. This joint effort seeks to establish such standards.

**Findings:**
Major findings for the above activities:

(1) New models which provide clinical prediction of cardiac output upon blood loss.

(2) New results regarding state space decomposition of multiscale systems (for both linear and nonlinear cases). Preliminary results (examples) of control at multiple levels of complexity.
(3) Work has focused on the Empirical Mode Decomposition (EMD) algorithm. An understanding (in theoretical terms) of what this popular 'ad hoc' algorithm actually does has been obtained, along with mathematical results describing its properties.
(4) Methods of multiscale system decomposition based upon the EMD have been developed.

**Training and Development:**

Stephen Hawley (PhD candidate, EE) has developed skills in control theory, applied mathematics, physiological modeling and signal detection.

Max Neal (formerly technician, now in PhD program in BioInformatics) developed skills in physiological modeling and optimization. He was motivated to enter a graduate program to further his edeucation.

Micah Nicholson obtained experience in a research setting. He is currently an undergraduate Bioengineering major at Vanderbilt.

Brian Carlson (post-doctoral research fellow) has joined the project. He is working on improving the resolution of the cardiovascular systems models and defining microvascular control mechanisms.

The investigators have learned from each other, in this highly multidisciplinary project.

**Outreach Activities:**

Course on modeling principles and techniques is to be given September 8-15, 2007 at the University of Washington.

## Journal Publications

Bassingthwaighte JB, Chizeck HJ, Atlas LE, and Qian H., "Multiscale modeling of cardiac cellular interactions. In: The Communicative Cardiac Cell.", Ann. New York Acad. Sci. 1047:, edited by Sideman S, Beyar R, and Landesberg A. 2005, pp 395-424., p. 395-424, vol. 1047, (2005). Published,

Bassingthwaighte JB, Chizeck HJ, and Atlas LE., "Strategies and tactics in multiscale modeling of cell-to-organ systems.", Proc IEEE, p. 819-831, vol. 94, (2006). Published,

Neal ML and Bassingthwaighte JB., "Subject-specific models for the estimation of cardiac output and blood volume during hemorrhage.", Cardiovascular Engineering, p. , vol. , ( ). Accepted,

Kerckhoffs R, Cole M, Sachse F, Healy S, Neal M, Jones G, Bassingthwaighte JB, and McCulloch A., "From myocyte to torso: Spatially and temporally multi-scale simulation of cardiac injury.", Medicine Meets Virtual Reality, p. 49, vol. 14, (2006). Published,

Neal M, Bassingthwaighte JB, Kerckhoffs R, McCulloch A, Sachse F, Cole M, and Jones G., "Hemodynamics of hemorrhage simulated with an open-loop cardiopulmonary model.", Medicine Meets Virtual Reality, p. 58, vol. 14, (2006). Published,

Bassingthwaighte, JB, "A practical extension of hydrodynamic theory of porous transport for hydrophilic solutes", MICROCIRCULATION, p. 111, vol. 13, (2006). Published, 10.1080/1073968050046638

Musters MWJM, Bassingthwaighte JB, van Riel NAW, and van der Vusse GJ., "Computational evidence for protein-mediated fatty acid transport across the sarcolemma.", Biochem J, p. 669, vol. 393, (2006). Published,

Bassingthwaighte JB, Raymond GR, Ploger JD, Schwartz LM, and Bukowski TR., "GENTEX, a general multiscale model for in vivo tissue exchanges and intraorgan metabolism.", Phil Trans Roy Soc A: Mathematical, Physical and Engineering Sciences, p. 1423, vol. 364, (2006). Published,

Dash RK, Li Z, and Bassingthwaighte JB, "Simultaneous blood-tissue exchange of oxygen, carbon dioxide, bicarbonate, and hydrogen ion.", Ann Biomed Eng, p. 1129, vol. 34, (2006). Published,

Rubin DR, Grossman D, Neal ML, Cook DL, Bassingthwaighte JB, and Musen M., "Ontology-based representation of simulation models of physiology.", Amer Med Informatics Assoc 2006 Symposium Proc, p. 664, vol. , (2006). Published,

Kerckhoffs RCP, Neal ML, Gu Q, Bassingthwaighte JB, Omens JH, and McCulloch AD., "Coupling of a 3D finite element model of cardiac ventricular mechanics to lumped systems models of the systemic and pulmonary circulation.", Ann Biomed Eng, p. 1, vol. 35, (2007). Published,

Smith NA, Crampin EJ, Niederer SA, Bassingthwaighte JB, and Beard DA, "Computational biology of the cardiac myocyte: proposed standards for the physiome.", J Exper Biol, p. 1576, vol. 210, (2007). Published,

Hawley S, Atlas LE and Chizeck HJ, "Some Properties of an Empirical Mode Type Signal Decomposition Algorithm", IEEE Signal Processing Letters, p. , vol. , (2007). Submitted,

## Books or Other One-time Publications

## Web/Internet Site

**URL(s):**

www.physiome.org

**Description:**

The site contains the collection of models and modules used in the constrcution of the multiscale models, and contains the large mutiscale models themselves. Each is described, has the equations defined and can be run on the website.

## Other Specific Products

## Contributions

**Contributions within Discipline:**

This project has extended the ability to model physiological systems having multiple scales of resolution in real time, allowing for the potential use of these models in diagnosis and treatment.

In the field of systems and control engineering, this project is developing techniques that are applicable for the control of systems that have both macro- and nanoscale components. This is an unsolved need of the developing field of nanoengineering.

This project has also enhanced understanding of the Empirical Mode Decomposition signal detection algorithm (which is being used here to determine when model scales need to be changed, so as to maintain fidelity).

**Contributions to Other Disciplines:**

The signal processing, systems and control, and modeling methods of this work are applicable to many fields other than physiology, biology and bioengineering.

**Contributions to Human Resource Development:**

This work is supporting one PhD student, it has motivated the work of a second PhD student and a post-doctoral fellow, and has involved one undergraduate researcher.

**Contributions to Resources for Research and Education:**

Materials developed with the support of this project have been used in two graduate courses and two undergraduate classes at the University of Washington. In addition, some software developed in this project will be used in an NHLBI Summer Modeling Course (September 2007).

**Contributions Beyond Science and Engineering:**

## Special Requirements

**Special reporting requirements:** None
**Change in Objectives or Scope:** None
**Unobligated funds:** $ 0.00

**Animal, Human Subjects, Biohazards:** None

**Categories for which nothing is reported:**

Any Book
Any Product
Contributions: To Any Beyond Science and Engineering

Project Title: MSM: Adaptive Multi-Scale Model Simulation, Reduction and Integration for Cardiac Muscle Physiology
PI: James Bassingthwaighte
Awardee: University of Washington
Award Number: 0506477
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**Report for Grant Year Ending August 2007**

## 1. EMPIRICAL MODE DECOMPOSITION:

We have applied an Empirical Mode Decomposition (EMD)-type method to the analysis of outputs of multiscale cardiovascular models to detect changes in the underlying model. Such changes are fundamentally time-varying so the resulting signals are likely to lack the stationary property required of other signal analysis methods. This method of analysis reveals both changes in instantaneous frequency and long term trends allowing one to construct an efficient detection algorithm based on the signal components. We have modified the existing EMD method, changing it slightly so that it is amenable to mathematical analysis of its properties and performance (#14).

The empirical mode decomposition (EMD) is an algorithmic method of signal decomposition that produces a representation of the signal as a sum of components derived from the data. As these components are derived from the data, rather than a previously chosen set of functions, the method is adaptive and local. The adaptivity and locality make it a suitable method for the analysis of complex, nonstationary signals.

We have recently begun to study the use of the EMD for scale separation of the state space of multiscale models. The goal of this work is to produce a scale separated hierarchy of subsystems. Such a hierarchy has two advantages. First it is amenable to simulation using a multistep numerical integration algorithm, such algorithms are much more efficient than single-step algorithms and versions of these are in use in computationally demanding areas like molecular dynamics. These multistep algorithms require a means of partitioning the differential equation into fast and slow parts. Our EMD based method will allow for the automation of this partitioning. Second the hierarchical model allows one to investigate model reduction at each time-scale independently, potentially eliminating time-scale information that is of little use to the researcher's present goal.

## 2. Cardiovascular and Respiratory System Modeling

### A. Work on Modeling Methods and Standards

Our first paper from the MSM IMAG effort was a general description of our methods and philosophy of approach (#1 in the publication list). The general idea was to develop models for practical implementation, i.e. computable in practical time for the purpose. This necessitated posing the question of (a) how to reduce model complexity without losing fidelity in its required behavior, (b) developing methods of detection of inconsistencies in the model solutions during runs, (c) finding effective methods of correcting discerned deficiencies, and (d) re-reducing the model complexity with modified corrected modules providing the correct behavior.

The paper by Anderson and Bassingthwaighte (#11) presents two reductionist maneuvers illustrating that even simple models are reduced at the cost of losses in robustness and fidelity to the original equations. Other examples of explicit steps of reduction are being worked out for muscle contraction, for diffusion approximation, for biochemical reactions, and for convection-permeation algorithms.

A high level model for cardiovascular -respiratory responses to physiological interventions has just been accepted (#12) and is the lead in a series of papers on integrated modeling. The reported model was designed for real time detection and prediction in the Intensive Care Unit, a setting in which the modularity and adaptability are required.

Other studies completed essential component modules at the molecular and transport levels (#2 on porous transport, #3 on endothelial transport, #5 on capillary permeability, #6 and #10 on gas exchange).

GENTEX (#4) is a very large organ level model that can be run as a compartmental model or a mutlipath, model allowing for the observed flow heterogeneity in imagiing studies and for a sequences of intracellular reactions, expanding in full state up to 110,000 differential equations in execution. This is highly integrated multicellular, multiscale model extending from transporters (competitive and non-competitve, but approximating complex transporters such as for fatty acid (#3)) and enzymatic biochemical reactions, binding to mobile and immobile proteins, to spatially heterogeneous flows, tracer deposition densities, and reactions. It allows descriptions of selected regions of interest for imaging analysis (especially valuable for PET and NMR). A feature of the computational realization is that modules not being used are not computed, for example, if the permeability for a solute entering the cell is zero, the transport and intracellular equations are not executed.

A particular success has been in reducing the complexity of the models of oxygen transport from blood (where it attaches 99% to hemoglobin) into tissue (where in heart and skeletal muscle it attaches to and usually saturates myoglobin binding sites), and in the model by Dash (#6) accounts for the influences of CO2, pH, temperature and 2,3-DPG on the binding. The use of a concentration-dependent Hill coefficient approximation for instantaneous binding allows rapid computation for gradients along the capillary while using a slightly reduced permeability of the red blood cells (RBC) to account for the kinetics of binding and release from (hemoglobin Hb). A version of this for pulmonary alveolar-blood exchange is in progress (#10).

SPECIFIC SCIENTIFIC COLLABORATIONS WITHIN THE MSM IMAG GROUP:

Biochemical systems kinetic models provide the basis for understanding the dependence of local intramyocardial regional blood flows and contractile energy use, and will position models like GENTEX to be used in describing the relationships between the spread of electrical activation and contractile performance and local flow. The collaboration with McCulloch and Kerckhoffs (#8) provides the linkage between the 3D heart models of the San Diego group and our 1D circulatory mechanics models (#12).

The collaboration with Beard at the Med Coll Wisc is strengthened by his recruitment of Ranjan Dash, formerly with us and then with Marco Cabrera, and is represented in a paper in press (#13). This liaison is developing further as we put up their models on our Physiome website (www.physiome.org) and develop new applications of network models.

Collaboration with the Cabrera/Saidel group at CWRU has been at the discussion level over the past few years. Bassingthwaighte is on the advisory board for their MIMS (Modeling in Metabolic Systems) program, and we have a commonality of interest in metabolism in contractile muscle, but not yet a coauthored publication nor the joint development or use of models.

EFFORTS IN DEVELOPING STANDARDS AND MODELING DATABASES

The development of a set of modeling standards is currently being pursued in Working Group 10, chaired by Bassingthwaighte, with the plan being to have a first draft agreement this summer. (See IMAG WG10 Discussion). A preliminary publication stemming from the first set drafted by Jim Bassingthwaighte, Nicolas Smith and Dan Beard in Nov 2006 has been published (#9), but needs improvements that are currently being undertaken.

In building large scale models in a modular fashion a common ontology is essential so that the names of variables and parameters are consistent from one module to another. The principles are expressed by Rubin et al (#7) as a type of Bioinformatics; this approach emerges from prior use of the ontology of the Visible Human Project supported by NLM. We are taking next steps in this at the University of Washington in collaboration with James Brinkley at UW. The idea is to use the ontology as a database not only of names but of composition, material properties and other features of physiological or pathological importance. His system is now effective in linking a pair of computational models into a single composite model; it uses an ontology to reconcile variable and parameter names, and allows the use of synonyms.

PLANS FOR THE COMING YEAR

One goal is the development, coordinated with the ontologic developments, of a set of

terminology for physiologic modeling. Beginning with "Terminology for Physiological Transport, Exchange and Reaction" by Bassingthwaighte and an international committee (Am J Physiol 250: H539-H545, 1986), we are working to update this by extending it into electrophysiology, metabolism and into respiratory physiology. (Respiratory terminology was formalized in the'50s and is incompatible with standard usage in physics, chemistry and the rest of biology.)

Our database of Models (www.physiome.org/Models) has been much extended in the past year. Over 150 models are now available for download. Most of these can be run over the web using Wikis, so the potential users can explore them on a whim to determine their behavior and utility. Model tutorials are being set up with the support of a Training Grant from NHLBI (T15 HL088516 PI: JBB) and courses are being offered in modeling for cardiovascular and respiratory investigators twice a yeaar starting this September 8-14. We expect to put up about 50 models in the coming year as we have a backlog of research models that need documentation, explanation and tutorial exposition in order to make them palatable for more general usage.

Methods of model reduction and optimization is a continuing prime target. We intend to compile a set of models with two or three levels of reduction and to publish descriptions of the benefits and costs of various reductions.

Our original plan for the modeling, described above in the first paragraph on Cardiovascular and Respiratory modeling, is not guaranteed to work. While the Empirical Mode Decomposition method of detection of change does work, it is not obvious how to generalize it into a method that distinguishes physiological change from model inadequacy. Nor is it obvious how to infer how, when a model is found to be inadequate to describe a current physiological state, how to go back down to the particular fundamental modules (cellular level where the responses really occur) in order to re-parameterize the reduced form models. We need to develop alternative detection methods, to compare the messages coming from them, in flight, so to speak, just as Boeing uses four sensors for feedback on critical controllers in airplanes, and to interpret the messages and effect improvement by correcting the deviant modules. Going back down the reduction cascade is a one-to-many problem, and the objective is to return to re-parameterize as few basic modules as possible. If we fail at this difficult set of task, we still have the whole multiscale system of course, but the cost is longer computation times and a loss of utility.

Publications over the previous year (Overlaps with those in press last year)

REFEREED PUBLICATIONS:

1. Bassingthwaighte JB, Chizeck HJ, and Atlas LE. Strategies and tactics in multiscale modeling of cell-to-organ systems. Proc IEEE 94: 819-831, 2006.

2. Bassingthwaighte JB. A practical extension of hydrodynamic theory of porous transport for hydrophilic solutes. Microcirculation 13: 111-118, 2006.

3. Musters MWJM, Bassingthwaighte JB, van Riel NAW, and van der Vusse GJ. Computational evidence for protein-mediated fat ty acid transport across the sarcolemma. Biochem J 393: 669-678, 2006.

4. Bassingthwaighte JB, Raymond GR, Ploger JD, Schwartz LM, and Bukowski TR. GENTEX, a general multiscale model for [ital ic] in vivo [plain] tissue exchanges and intraorgan metabolism. Phil Trans Roy Soc A: Mathematical, Physical and Engineering Sciences 364(1843): 1423-1442, 2006.

5. Bassingthwaighte JB. Capillary Permeability. edited by Akay M. New York: Encyclopedia of Biomedical Engineering, John Wiley and Sons, Inc, 2006.

6. Dash RK, Li Z, and Bassingthwaighte JB. Simultaneous blood-tissue exchange of oxygen, carbon dioxide, bicarbonate, and hydrogen ion. Ann Biomed Eng 34: 1129-1148, 2006.

7. Rubin DR, Grossman D, Neal ML, Cook DL, Bassingthwaighte JB, and Musen M. Ontology-based representation of simulation models of physiology. Amer Med Informatics Assoc 2006 Symposium Proc 664-668, 2006.

8. Kerckhoffs RCP, Neal ML, Gu Q, Bassingthwaighte JB, Omens JH, and McCulloch AD. Coupling of a 3D finite element model of cardiac ventricular mechanics to lumped systems models of the systemic and pulmonary circulation. Ann Biomed Eng 35: 1-18, 2007.

9. Smith NA, Crampin EJ, Niederer SA, Bassingthwaighte JB, and Beard DA. Computational biology of the cardiac myocyte: proposed standards for the physiome. J Exper Biol 210: 1576-1583, 2007.

IN PRESS.

10. Carlson BE, Anderson JC, Raymond GR, Dash RK, and Bassingthwaighte JB. Modeling oxygen and carbon dioxide transport and exchange in a closed loop circulatory system. Adv Exp Med and Biol: Int Soc Oxygen Transport to Tissue , 2007.

11. Anderson JC, Raymond GM, and Bassingthwaighte JB. Tracers in physiological systems modeling. Am J Nutrit (In press)

12. Neal ML and Bassingthwaighte JB. Subject-specific models for the estimation of cardiac output and blood volume during hemorrhage. Cardiovasc Engineering , 2007 (In press)

SUBMITTED AND IN PREPARATION FOR SUBMISSION THIS SUMMER

13. Qi F, Yang F, Wu F, Qian H, Kushmerick MJ, Bassingthwaighte JB, and Beard DA.

Role of the purine nucleotide cycle in muscle energy balance. Am J Physiol Heart Circ Physiol (submitted)

14. Hawley S, Atlas LE and Chizeck HJ. "Some Properties of an Empirical Mode Type Signal Decomposition Algorithm". (submitted to IEEE Signal Processing Letters, 2007)

15. Bassingthwaighte JB, Chizeck HJ, Hawley SD, Atlas, LE and Qian, H. Challenges for Signal Processing in the Physiome. IEEE Signal Processing (In preparation)

16. Bassingthwaighte JB and Qian H. Transport phenomena in the contracting heart: regional blood flow heterogeneity is driven by regional cellular demands. In: Control and Regulation of Transport Phenomena. Ann. New York Acad Sci, edited by Sideman S, Beyar R, and Landesberg A. 2008.(sub july07)

17. Yipintsoi T, Li Z, Kroll K, Feigl EO, and Bassingthwaighte JB. Redistribution of regional myocardial blood flow in dog hearts during catecholamine and adenosine infusion. Am J Physiol (submitted)

ABSTRACTS OR MEETING PRESENTATIONS:

1. Bassingthwaighte JB, Matuszkiewicz A, Krueger MB, Park JS, Raymond GM, Butterworth E, Neal M, and Hlastala M. The Physiome in Pharmacokinetics, Pharmacodynamics and Toxicology, 34. The Toxicologist CD--An Official Journal of the Society of Toxicology 90: 7, March, 2006.

2. Kerckhoffs R, Cole M, Sachse F, Healy S, Neal M, Jones G, Bassingthwaighte JB, and McCulloch A. From myocyte to torso: Spatially and temporally multi-scale simulation of cardiac injury. Modern Medicine Meets Virtual Reality 14: 49, 2006.

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4. Bassingthwaighte JB, Neal ML, Dash RK, Carlson BE, and Anderson JC. The Role of Hemoglobin in Respiratory Gas Exchanges. 34th Conf Int Soc Oxygen Transport to Tissue` 34: 41, 2006.

5. Bassingthwaighte JB. Balances in Cellular Metabolism and Energetics: Principles in Modeling. Mathematical Modeling in Nutrition and the Health Sciences Proc: 15, 2006.

6. Bassingthwaighte J. Capillarity, Regional Blood FLows, and Metabolism. Proc Eur Conf Microcirc SNE1, 2006.

7. Kerckhoffs RCP, Neal ML, Gu Q, Bassingthwaighte JB, Omens JH, and McCulloch

AD. Pulmonary artery constriction in a finite element model of cardiac mechanics in the circulation. Abstracts of the Biomedical Engineering Society Fall Meeting , 2006.

8. Kerckhoffs RCP, Neal ML, Bassingthwaighte JB, Omens JH, and McCulloch AD. Ventricular interaction quantified with a novel multi-scale cardiovascular model. 6th Internat Cong Indust and Appl Math Zurich , 2007.