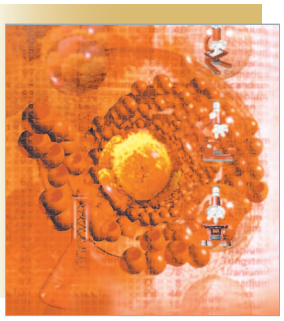

Multiscale Modeling of Biomedical, Biological, and Behavioral Systems (Part 1)

Understanding the Body from Atoms to Cells to Tissues to Organs to Populations

BY RONALD J. WHITE, GRACE C. Y. PENG, AND SEMAHAT S. DEMIR

Mathematical and computational modeling provide a natural infrastructure for systematically bringing together the wealth of data and knowledge obtained from biological, physiological, and clinical research. Furthermore, the power of this infrastructure is the ability for the model to simulate pathophysiology and predict how, when, and in whom diseases will develop. Historically, the majority of models in biology and physiology are created to understand a particular process or phenomenon by putting together known biological constructs, using modeling to fill in the gaps of the unknown, creating new hypotheses, and redesigning the models based on experimental outcomes and measures. These models are often used to supplement research efforts focused on specific biological questions and domain areas to provide new insights in understanding data.

As biological research has progressed and more and more information is collected with the development of new technology, researchers are increasingly interested in understanding the data from a systems perspective. This perspective pushes researchers to move beyond their specific questions to examine more general biological processes and systems that influence their domains of interest. From the engineering standpoint, these general processes and systems bring additional considerations for the boundary conditions or constitutive equations originally set for the local domain of interest. These other processes or systems may operate in different length or time scales, resulting in a very a complex system. Models are now becoming a necessary tool to drive, rather than merely supplement, biomedical research to better understand the human body as a complex system. However, modeling biological and physiological systems brings about many challenges that are not encountered in modeling classical engineering systems.

In 2003, the National Institutes of Health (NIH) held two seminal meetings to address the challenges associated with biological and physiological modeling. The first meeting, held in April 2003, resulted in the creation of the Interagency Modeling and Analysis Group (IMAG, http://www.nibib.nih.gov/Research/MultiScaleModeling/IMAG). The convening of IMAG helped the then newly formed (in 2000) National Institute of Biomedical Imaging and Bioengineering (NIBIB) determine its role in promoting modeling and analysis research. In the same year, on 6–7 November 2003, the trans-NIH Biomedical Information Science and Technology Initiative (BISTI) consortium (also formed in 2000) held its inaugural BISTI symposium with the larger biomedical community titled, "Digital Biology: The Emerging Paradigm." In this meeting, IMAG representatives helped to organize the quantitative biology session, which addressed the challenges associated with biological modeling. In both meetings, IMAG and NIH recognized that the biomedical modeling community was poised to tackle the problem of modeling systems across the biological continuum and, thus, to face the major problem of linking the multiple biological scales (e.g., atomic, molecular, molecular complexes, subcellular, cellular, multicell systems, tissue, organ, multiorgan systems, organism, population, and behavior) that operate in most of the biological world. In addition, these meetings reflected a strong desire among modelers to resolve the technical and sociological challenges associated with multidisciplinary partnerships necessary for this type of multiscale modeling (MSM).

IMAG responded to the feedback from these and other meetings and in 2004 released the Interagency Opportunities in MSM in Biomedical, Biological, and Behavioral Systems Solicitation (http://www.nibib.nih.gov/Research/MultiScaleModeling). This initiative encouraged researchers to develop new methods to link biological scales and address critical technical challenges associated with MSM in biomedical, biological, and behavioral systems. A further goal of this initiative was to form a MSM community to develop methods to effectively share models. After the interagency review panels in 2005, the IMAG representatives from NIH, National Science Foundation (NSF), Department of Energy (DOE), and National Aeronautics and Space Administration (NASA) made 24 awards, covering a range of scientific research areas, diseases, biological scales, software development, modeling methods, and computational tools (http://www.nibib.nih.gov/Research/MultiScaleModeling/ListName). These 24 projects formed the initial core discussions and workshops for the MSM consortium (www.imagwiki.org/mediawiki).

The MSM consortium has been very active in disseminating information through wiki discussions, annual meetings, and virtual presentations. It was through the MSM consortium that we solicited the articles that are published in the March–April

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and the May–June 2009 special issues of *IEEE Engineering in Medicine and Biology Magazine*. This first group of articles focuses on modeling at the microscale end of the biological continuum, whereas the second group of articles (in the May–June issue) focuses on modeling at the macroscale end of the biological continuum, covering tissues, organs, and behavior.

In this issue, the first article by Qutub et al. provides a nice overview of the current state of computational models of angiogenesis. The authors describe molecular level and cell level models and how they are integrated to form multiscale models for predicting the mechanisms of angiogenesis. The second article by Pivkin et al. describes a multiscale model, from the atomistic to the cell level, of blood flow and clot formation. The authors present a new simulation incorporating the effects of red blood cells on the platelet dynamics. The third article by Beyer and Meyer-Hermann presents a new agent-based method to model of cell–cell interactions while allowing the internal dynamics of the cells to change. This type of multiscale model would allow investigators to examine the impact of the cellular properties on tissue organization. The fourth article by Lu et al. presents a multiscale model of subcellular components to better elucidate the structure and function of heart muscle cells. The fifth paper by Taufer et al. explores multiple computational scales applied to molecular docking models. The last article by Ortoleva et al. presents a nanoscale approach that integrates atomistic and molecular scales. The authors use this approach to examine a variety of applications, from alternative biofuels to therapeutic drug delivery systems for medicine.

We wish to thank all the authors for their contributions to these two special issues. We are very grateful to Dr. John Enderle, the previous editor-in-chief who first invited IMAG to work on these special issues on 7 November 2003 during the Digital Biology Symposium and who waited so patiently for us to fund the projects, form the MSM consortium, and see these projects come to fruition. We owe a particular debt of gratitude to Dr. Semahat Demir, IMAG member and editorial board member of the magazine for her support of these special issues. We also express our appreciation to Dr. Michael Neuman for taking over the magazine's reins and bringing these special issues to realization.

Ronald J. White is a senior fellow at Universities Space Research Association in Houston, Texas, and is serving as the Senior Scientist for Policy and Processes for National Aeronautics and Space Administration (NASA)'s Human Research Program. He is a full member of the International Academy of Astronautics (IAA) and a member of its Board of Trustees. His previous positions include associate director of the National Space Biomedical Research Institute, Professor at Baylor College of Medicine, Chief Scientist of the Life Sciences Division at NASA Headquarters, Research Professor of Physiology at the Uniformed Services University of the Health Sciences, senior scientist and manager of Biomedical Research, Analysis, and Planning at General Electric Company, professor of mathematics and director of honors at the University of Louisiana at Lafayette. A specialist in space life sciences and biomedical research, he has served as NASA program scientist for the following spacelab missions: Spacelab Life Sciences 1 (SLS-1), International Microgravity Laboratory 1 (IML-1), and the U.S. component of the German Spacelab Mission D-2.

Grace C. Y. Peng received her B.S. degree in electrical engineering from the University of Illinois, her M.S. and Ph.D. degrees in biomedical engineering from Northwestern University. She has served as faculty at Catholic University of America and Johns Hopkins University. She is a program director in the National Institute of Biomedical Imaging and Bioengineering (NIBIB) at the National Institutes of Health. In 2003, she created and began coordinating the Interagency Modeling and Analysis Group (IMAG), which now consists of program officers from eight government agencies of the United States and Canada. She is interested in promoting the development of intelligent tools and reusable models, and integrating these approaches in engineering systems and multiscale physiological problems.

Semahat S. Demir received her B.S. degree (EE) from Istanbul Technical University, M.S. degree (BME) from Bosphorous University, and a second M.S. degree and a Ph.D. degree (ECE) from Rice University, and BME postdoctoral training at Johns Hopkins University. She is a fellow of the American Institute of Medical and Biological Engineering (AIMBE). She is the program director for biomedical engineering at NSF. Before joining NSF, she worked in academia (USA and Turkey) and in industry (Germany and Turkey). Her expertise is computational modeling of bioelectricity in cardiac cells and bursting neurons. She developed simulation-based teaching and learning resources including interactive cell modeling resource, iCell.

Address for Correspondence: Grace C. Y. Peng, National Institute of Biomedical Imaging and Bioengineering, 6707 Democracy Blvd., Suite 200, MSC 5469, Bethesda, MD 20892 USA. E-mail: penggr@mail.nih.gov.