Editorial: Special Issue on Multiscale Modeling and Analysis in Computational Biology and Medicine—Part-1

I. Scope of the Special Issue

COMPUTATIONAL modeling and analysis in biology and medicine have received major attention in recent years. The interdisciplinary efforts developed so far aimed at elucidating structures and functions of living systems with major challenges in computational modeling and analysis to understand, analyze, and predict the complex mechanisms of biological systems. Continued research investigations in computational biology and physiology have addressed important issues across many applications spanning from molecular dynamics, biological signaling pathways, cellular biology and communication, tissue mechanobiology, organ function and performance, systemic autoregulation, all the way up to lifestyle and environmental influences, and behavioral responses.

Researchers are now beginning to address the grand challenge of multiscale computational modeling and analysis: effectively capturing biological and physiological interdependencies and interactions across multiple observational scales—not only in time and space, but also in terms of multi-biophysical and biochemical processes– and doing so in a computationally efficient manner. The development of many such models involves the design of multimodal data acquisition instrumentation and systems capable of measuring and monitoring structural and functional properties *in vivo*, with increased spatiotemporal resolution, and in a minimally invasive manner.

Over the last few years, the research work is being extended not only to further improve the basic understanding of biological and physiological models but also to explore translational biomedical research. For example, multiscale multiphysics modeling approaches are now paving the way to better understand the mechanisms of disease and its treatment, thus helping to establish diagnostic biomarkers, physiology-based patient selection criteria, and more principled strategies for choosing, personalizing, and optimizing therapeutic options. Multiscale computational modeling promises to become a fundamental contributor to future biomedical sciences and technologies, and personalized predictive healthcare.

This IEEE TBME Letters Special Issue on *Multiscale Modeling and Analysis for Computational Biology and Medicine* solicited short manuscripts of novel methodologies with high potential impact and early breakthroughs. Topical coverage of the special issue includes the study of multiscale systems in biology and human physiology. Submissions were encouraged in translational biomedical research and applications to medicine. Where appropriate, contributions were welcome when making use of open modeling standards, public databases, open access infrastructures, and open source modeling frameworks in this arena. No specific organ or biological subsystems were targeted and industrial contributions in technology development and translation to the environment or clinical practice, as well as enhancement or discovery of new functional knowledge were also welcome.

II. Special Issue Papers

The papers in this special issue demonstrate some of the most exciting developments in multiscale modeling and analysis in computational biology and medicine across all levels of time, scale, and organ systems.

Our call for papers for the special issue received an overwhelming response with 243 submitted manuscripts. As 22 papers are being published in Part-1, additional papers will be published in a forthcoming Part-2 of the Special Issue.

As per organ systems, ten papers correspond to cardiovascular system, four to nervous system, two to muscular-skeletal system, two to respiratory system, one to endocrine system, one to special sense organs (namely hearing), and, finally, two papers with applications in oncology and embryology. All in all, the collection of papers in this issue nicely covers all scales from genes, to intracellular processes, intercellular communication, tissue models all the way up to organ scales and system models.

Some of the manuscripts presented in this collection refer to novel imaging sequences for multiresolution imaging or provide multiscale models of biology, physiology, biophysics, or biochemistry; some papers tackle specific computational issues associated with such models; others provide domain-specific modeling of physiological or pathophysiological processes related to insulin secretion, organogenesis and tumor genesis, and auto regulation among others. Papers in this issue have relevance for key disease processes like atherosclerosis, diabetes, cardiac ischemia, atrial tachycardia, stroke, hearing impairment, oncology, etc.

The first ten letters are connected to the cardiovascular system, viz. to the modeling and analysis of electrical propagation in the heart and vascular fluid dynamics.

Censi *et al.* provide a graph-theoretical multiscale analysis of the correlation structure of gene expression induced in heart tissue by atrial fibrillation. The influence of disease increases the general connectivity of the gene regulation network, and the proposed analysis provides both a general appreciation of

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regulation network connectivity and the sketching of a biological interpretation of the studied disease.

Yu *et al.* model spatiotemporal calcium dynamics due to calcium flux via the sarcolemma and buffering inside, which play a critical role in studying excitation-contraction coupling in both normal and diseased cardiac myocytes. A subcellular model, containing several realistic transverse tubules (t-tubules), is incorporated and assumed to reside at different locations relative to the cell membrane. Calcium concentration calculated from whole-cell modeling is adopted as part of the boundary constraint in the subcellular model. Preliminary simulations show that calcium dynamics in rodent ventricular myocytes is tightly regulated by the t-tubule ultrastructure and calcium flux via the sarcolemma.

Zhang *et al.* developed computational models of the human atria and torso to study the relationship between P-wave morphology and the origins of the focal excitations leading to atrial arrhythmias. Simulations showed that the proposed method was practical and could predict the atrial focal locations with 85% accuracy.

Pashaei *et al*. introduce a modeling methodology coupling the cardiac conduction system (CCS) to cardiac myocytes through a model of Purkinje–Ventricular Junctions (PVJs). A one-manifold implementation of the fast marching method based on Eikonal-type equations is used for modeling heart electrophysiology, which facilitates the multiscale 1-D–3-D coupling at very low computational costs. Given the realistic activation sequences produced by such method, this work can have impact on optimizing cardiac rhythm management therapies.

Wilhelms *et al*. developed multiscale computer simulations of cardiac ischemia using realistic models of human ventricles. These were useful in understanding of the mechanisms responsible for the shifts of the ST segment following coronary artery occlusion, which often leads to lethal ventricular arrhythmias or heart failure. Transmembrane voltage distributions in the heart and corresponding body surface potentials were computed with varying transmural extent of the ischemic region at different ischemia stages. Some of the simulated ischemia cases were "electrically silent", i.e., they could hardly be identified in the 12-lead ECG, thus demonstrating the power of predictive models.

Reumann *et al*. shift the focus of the special issue toward efficient computational paradigms. Efficiently solving multiscale and multiphysics models, supporting research into translational medical science, will require sophisticated hybrid high performance programming models. This work shows that such hybrid models perform favorably when compared to simpler strategies. Examples are given in the context of computational cardiology. The authors hypothesize that faster than real-time multiscale cardiac simulations can be achieved on these systems shortly.

Humeau *et al*. make the observation that regulatory processes of the cardiovascular system (CVS) involve systemic interactions and interdependencies across multiple scales. For the CVS analysis, different multiscale studies have been proposed, mostly performed on heart rate variability signals (HRV) reflecting the central CVS; only few were dedicated to data from the peripheral CVS, such as laser Doppler flowmetry (LDF) signals. This work presents a multiscale entropy analysis of LDF signals that shows a marked distinct behavior from one of the HRVs and whose origin the authors hypothesize to be dominated by cardiac activity.

Ho *et al*. developed a model of intracranial aneurysms (IAs) in modeling the physics at the molecular, cellular, blood vessel and organ levels occurring over time scales ranging from seconds to years. Comprehensive mathematical modeling of Ias, therefore, requires the description and integration of events across length and time scales that span many orders of magnitude. A computational framework is presented illustrating the combination of three models operating at different length and time scales: 1) shear stress induced nitric oxide production; 2) smooth muscle cell apoptosis; and 3) fluid-structure-growth modeling.

Wu *et al*. proposed a new diagnostic parameter based on dynamic pulse wave velocity (PWV) for assessing the degree of atherosclerosis for the aged and diabetic populations. This manuscript reports on a method for analyzing the measurements of a newly developed acquisition system with multiscale entropy. Large-scale multiscale entropy index (MEILS) was chosen as the assessment parameter. MEILS PWV could not only differentiate the adult and elderly control groups from two stages of diabetic patients, but could also better reflect the impact of age and blood sugar control on the progression of atherosclerosis.

The analysis of follow-up data from patients suffering from heart failure is a difficult task, due to the complex and multifactorial nature of this pathology. Le Rolle *et al*., present a coupled model, integrating a pulsatile heart into a model of the short to long-term regulations of the cardiovascular system. An interface method is proposed to couple these models, which present significantly different time scales. Results from a sensitivity analysis of the original and integrated models are proposed, with simulations reproducing the main effects of the short and long-term responses of an acute decompensated heart failure episode on a patient undergoing cardiac resynchronization therapy.

There are two contributions in the muscular-skeletal system depicted in this special issue.

Guo reports on a work designed to investigate the modal characteristics of the human spine. A 3-D finite element model of the spine was used to extract resonant frequencies and modal modes. The vibration configurations of the lumbar spine can explore the motion mechanism of different lumbar components under whole body vibration and make us to understand the vibration- induced spine diseases. The findings in this study will be helpful to understand injuries related to the spine in regard to clinical treatment, ergonomic design, and development of mechanical production toward human spine safety.

Isaacson *et al*. point to the fact that although survival rates of warfighters in recent conflicts are among the highest in military history, those who have sustained proximal limb amputations may pose additional rehabilitation concerns. Traditional prosthetic limbs may not provide adequate function for returning to an active lifestyle. Osseo integration has emerged as an acknowledged treatment for those with limited residual limb length and those with skin side-effects associated with a socket. Electrically induced osseous integration has been proposed as an option

for expediting periprosthetic fixation; preliminary studies demonstrated its feasibility enhancing current prosthetics with a functional cathode. To assure safe and effective electrical fields that are conducive for osseous induction and osseous integration, the authors developed multiscale modeling approaches to simulate the expected electric metrics at the bone-implant interface. This translational computational biological process has supported biomedical electrode design, implant placement, and experiments to date have demonstrated the clinical feasibility of electrically induced osseous integration.

Four papers tackle in a multiscale fashion problems related to the nervous system.

Chen and Calhoun present a new approach to blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI), which is a widely used method for brain mapping. BOLD fMRI signal detection is based on an intravoxel dephasing mechanism. This model involves bulk nuclear spin precession in a BOLD-induced inhomogeneous magnetic field within a millimeter-resolution voxel, that is, BOLD signal formation spans a huge spatial scale range from angstrom to millimeter. In this letter, a computational model for multiresolution BOLD fMRI simulation is presented, which consists of partitioning the nuclear spin pool into spin packets at a mesoscopic scale and calculating multiresolution voxel signals by grouping spin packets at a macroscopic scale range. Under a small angle approximation, it was found that the BOLD signal intensity is related to its phase counterpart (or BOLD fieldmap) across two spatial resolution levels.

Even though neuronal cellular volume dynamics has been linked to cell apoptosis and intrinsic optical signals, there is no quantitative model for describing neuronal volume dynamics on the millisecond time scale. Lee *et al*. introduce a multiphysics neuron model where the cell volume is a time-varying variable and multiple physical principles are combined to build governing equations. Using this model, the authors analyzed neuronal volume responses during excitation, which elucidated the variety of optical signals observed experimentally across the literature. This multiscale analysis of the multiphysics model will provide not only a novel quantitative elucidation of physiologically important phenomena related with cellular volume dynamics but also a chance for further studies such as the interesting possibility of inferring the balance of ion flux from plateau volume changes.

Buldu *et al*. propose a new methodology to evaluate the balance between segregation and integration in functional brain networks by using singular value decomposition (SVD) techniques. By means of magnetoencephalography (MEG), they obtain the brain activity of a control group of nineteen individuals during a memory task. Subsequently, node-to-node correlations were projected into a complex network, which is analyzed from the perspective of its modular structure encoded in the contribution matrix. In this way, the authors were able to study the role that nodes play inside/outside its community and to identify connector and local hubs.

The letter by Bouteiller *et al*., the last one focused on the neurovascular system, reports on an integrative model of the nervous system. One of the fundamental characteristics of the brain is its hierarchical organization. Scales in both space and time that must be considered when integrating across hierarchies of the nervous system are sufficiently great as to have impeded the development of routine multilevel modeling methodologies. The authors have tackled the problem of how changes at the level of kinetic parameters of a receptor-channel model are translated into changes in the temporal firing pattern of a single neuron, and ultimately, changes in the spatiotemporal activity of a network of neurons. They demonstrate a powerful methodology that can be applied to understand the effects of a given local process within multiple hierarchical levels of the nervous system.

Two letters were contributed in the area of the respiratory system.

Di Marzio *et al*. introduce a combined mechanical and optical model of the lungs. A multiscale, multiphysics model generates synthetic images of alveolar compression under spherical indentation at the visceral pleura of inflated lung. A mechanical model connects the millimeter scale of an indenter tip to the behavior of alveoli, walls, and membrane at the micrometer scale. A finite-difference model of optical coherence tomography (OCT) generates the resulting images. The complete computational model will have impact in the evaluation of new imaging systems, and as gold-standards for algorithms for obtaining quantitative data on deformation. Among the potential biomedical applications, a better understanding of recruitment of alveoli during inflation of a lung, obtained through a combination of models and imaging could lead to improvements in noninvasive treatment of atelectasis.

Walters *et al*. address one of the key challenges for computational fluid dynamics (CFD) simulations of human lung airflow, namely, the sheer size and complexity of the complete, multiscale geometry of the bronchopulmonary tree. Since 3-D CFD simulations of the full airway tree are currently intractable, this letter explores a recently proposed method for closing the CFD model by application of physiologically correct boundary conditions at truncated outlets. A realistic, reduced geometry model of the lung airway based on CT data has been constructed up to generation 18, including extrathoracic bronchi and bronchiole regions. Results indicate that the new method yields reasonable results for pressure drop through the airway, at a small fraction of the cost of fully resolved simulations.

Cobelli *et al*. contributed a letter in the area of endocrine system. Insulin secretion from pancreatic beta-cells is a fundamental physiological process, and its impairment plays a pivotal role in the development of diabetes. Mathematical modeling of insulin secretion has a long history, both on the level of the entire body and on the cellular and subcellular scale. However, little direct communication between these disparate scales has been included in mathematical models so far. Recently, a minimal model of the incretin effect, by which the gut hormone GLP-1 enhances insulin secretion, was proposed. To understand how this model couples to cellular events, a previously published mechanistic model of insulin secretion was used, and it was shown mathematically that induction of glucose-competence in beta-cells by GLP-1 can underline derivative control by GLP-1.

Gan and Zhang devote their letter to one of the special sense organs, viz. the ear. A finite element (FE) model of the human

ear including the ear canal, middle ear, and spiral cochlea was constructed from histological sections of human temporal bone. Multiphysics analysis of the acoustics, structure, and fluid coupling in the ear was conducted in the model. The viscoelastic material behavior was applied to the middle ear soft tissues based on dynamic measurements of tissues. This comprehensive ear model provides a novel computational tool to visualize and compute the implantable hearing devices and surgical procedures.

The last two letters present research applied to oncology and embryology.

There is a renewed interest in tumor genesis provoked by glycolysis and prosurvival autophagy following the mitochondrial permeability transition during cell death. In the first paper, Cho *et al*., investigate such mitochondrial dysfunction by developing a multiscale model that integrates the dynamic behaviors of essential oncogenic proteins, cells, and their microenvironment. By means of a number of simulation studies, the authors conclude that the cellular mitochondrial status is critical in triggering tumor genesis during the cell death process, particularly under harsh microenvironments.

In the second letter, Brodland offers a multiscale biochemical-mechanical framework that integrates genetic networks, cell mechanics, and whole-embryo mechanics. The author identifies components of the framework for which quantitative descriptions are currently available, and use the framework to gain insight into convergent extension and gastrulation—crucial tissue movements that occur in early-stage amphibian embryos.

III. Overall Perspective and Outlook

Part 1 of this special issue provides a really extensive picture of the-state-of-the-art in multiscale computational model spanning various organ systems, multiphenomena modeling at multiple spatiotemporal observational scales.

The presented bulk of work provides new insights into fundamental physiological mechanisms while others are closer to clinical translation or to support the development of medical devices and implants. Various organ systems have been tackled as well as specific dynamic processes in oncology and embryology.

Through the work reported in this thematic issue, we hope that IEEE TBME has contributed to the substantial international effort going on in Europe, America, and Asia [16] under the heading of International Physiome or Virtual Physiological Human projects [1], [2], [6], [7], [13], [14], [19], [23]..

The most recent visions of these initiatives, to which this special issue contributes, have been reported in the recent vision paper by a large cadre of experts in [15] and entail not only modeling strategies but also educational [21], data and databases [12], [27], modeling standards and repositories [9], [22], [26], and modeling tools [5], [8], [10], [17], [18], [25], among others.

Other related special issues have appeared over the last few years also contributing, at large, to this endeavor [3], [4], [10], [11], [18], [20], [28], [29] (Parts 1 and 2), [24]. Additionally, a number of other focused special issues are underway reveling the various angles and topical nature of this initiative. They also demonstrate the hope and promise that multiscale modeling and simulation bear for one day transforming the way that biomedical research and healthcare are carried out toward more holistic and integrative strategies.

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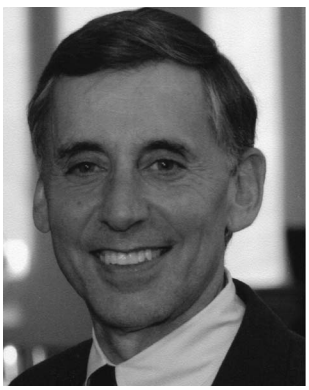
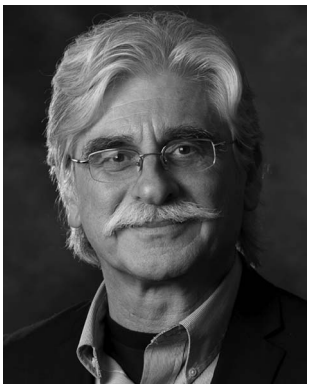


David Z. D'Argenio is Professor of biomedical engineering at the University of Southern California, and holder of the Chonette Chair of Biomedical Technology. Professor D'Argenio has been a member of the Biomedical Engineering Faculty at the USC, since 1979. He is a Fellow of the American Institute for Engineering in Medicine and Biology and of the American Association of Pharmaceutical Scientists. From 2003–2008, he served on the US FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. He has served as Chairman of the Department of Biomedical Engineering at the USC, from 1996–2003, and as the Associate Dean for Academic Affairs in the School of Engineering at the USC from, 1993–1996. Since 1985, he has codirected, with Prof. Vasilis Marmarelis, the Biomedical Modeling and Simulations Resource at USC, an NIH/NIBIB-supported center that develops and applies advanced modeling methods to biomedical systems. He currently serves on the Editor Boards of the *Journal of Pharmacokinetics and Pharmacodynamics* and *Computer Methods and Programs in Biomedicine*.



Vasilis Z. Marmarelis (M'79–SM'94–F'97) was born in Mytiline, Greece, on November 16, 1949. He received the Diploma in electrical and mechanical engineering from the National Technical University of Athens, in 1972, and the M.S. and Ph.D. degrees in engineering science (information science and bioinformation systems) from the California Institute of Technology, in 1973 and 1976, respectively.

He joined the Faculty of Biomedical and Electrical Engineering at the University of Southern California, in 1978, where he is currently Professor and Codirector of the Biomedical Simulations Resource, a research center dedicated to modeling/simulation studies of biomedical systems under NIH funding, since 1985. His main research interests are in the areas of nonlinear and nonstationary biomedical system modeling, with emphasis on multivariable systems (e.g., multiinput/multioutput modeling of neuronal ensembles) and closed-loop/nested-loop modeling (e.g., blood glucose regulation or cerebral flow autoregulation). Over the last 12 years, he has also developed and tested a novel technology for 3-D diagnostic imaging [Multimodal Ultrasound Tomography (MUT)], which is capable of noninvasive tissue characterization and lesion differentiation for the early detection of breast cancer and other clinical applications. He served as Chairman of the Biomedical Engineering Department from1990 to 1996. He is coauthor of the pioneering book titled *Analysis of Physiological Systems: The White Noise Approach* (New York: Plenum, 1978; Russian translation: Moscow, Mir Press, 1981; Chinese translation: Academy of Sciences Press, Beijing, 1990), editor of three research volumes on *Advanced Methods of Physiological System Modeling* (Plenum, 1987, 1989, 1994) and author of a recent monograph titled *Nonlinear Dynamic Modeling of Physiological Systems* (IEEE Press & Wiley Interscience, 2004). He has published more than 100 peer-reviewed papers and book chapters in the areas of biomedical system modeling and signal analysis.

Prof. Marmarelis is a Fellow of the American Institute for Medical and Biological Engineering.

Anushka Michailova received the Master's degree in physics and Ph.D. degree in molecular biology and genetics from the Sofia University, in 1996.

She is Associate Project Scientist in the Bioengineering Department at the University of California, San Diego (UCSD). She is Co-PI of the NBCR core project: *Structurally and Functionally Integrated Modeling of Cell and Organ Biophysics*. Her research focuses on using mathematical methods to model and better understand cardiac cells, delineating Ca^{2+} mediated signaling, excitation-contraction coupling, and energy metabolism.