Editorial: TBME Letters Special Issue on Multiscale Modeling and Analysis in Computational Biology and Medicine—Part-2

I. Second Series of Papers

As announced in the previous special issue (IEEE Transactions on Biomedical Engineering (TBME) Letters, vol. 58, no. 10, Part 1), we are pleased to present Part-2 of the IEEE TBME Letters Special Issue on Multiscale Modeling and Analysis in Computational Biology and Medicine. It complements Part-1 by introducing other meritorious research work in progress where computational modeling and analysis is the key focus for better understanding of complex mechanisms and systems in biology and physiology. These contributions highlight the dynamics observed in this field where much remains to be done. The challenging problems crossing and bridging multiple scales, from genes to organs, are addressed under systems biology and physiological systems also provide future directions of research investigations in the 21st century.

The roots of the tremendous modeling efforts all over the world can be found as interdisciplinary research in archived publications as early as the middle of 20th century when Macy Conferences were organized with scholars from various disciplines in New York by the initiative of W. McCulloch and the J. Macy, Jr., Foundation from 1946 to 1953 (http://www.asc-cybernetics.org/foundations/history/MacySummary.htm). These conferences promoted interdisciplinary research in system biology and cybernetics that laid the foundation of cognitive sciences. Norbert Wiener, a mathematician and founder of cybernetics, took a leadership role in Macy Conferences exploring system theory to deal with a large spectrum of applications, including living bodies. Another major cybernetics initiative was led by William Ross Ashby, a psychiatrist, and Heinz von Foerster, a biophysicist. They introduced pioneering concepts for system evolution, morphogenesis, energy and matter exchanges, and equilibrium states utilizing information theory in studies related to system biology and cybernetics. More recently, as pointed out in the Editorial of Part-1, the Physiome project initiated by Bassingthwaighte and others, the Interagency Modeling and Analysis Group (IMAG) Multiscale Modeling initiatives, and the Virtual Physiological Human initiative by the European Community led to several research programs throughout the world. These two volumes of the TBME Special Issue on Multiscale Modeling and Analysis for Computational Biology and Medicine is a modest contribution to this significant and fast growing interdisciplinary research area. Our previous editorial referred to several review papers [1]–[11] published recently in other journals such as Proceedings of the IEEE, *Annals of Biomedical Engineering*, *Philosophical Transactions of the Royal Society A*, IEEE Reviews in Biomedical Engineering, *special issues of the IEEE EMBS Magazine*, etc., where the readers can find the recent progression in research. This Special Issue of IEEE TBME Letters provides the current state of the art and addresses fast emerging and fascinating issues in modeling of complex biological systems and characterization of physiological processes with a potential impact of improving medical diagnoses and treatment.

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II. Special Issue Contents

Most of the 21 papers in this Part-2 of the Special Issue are addressing complex mechanisms and computational modeling involved in biological systems, from gene and protein levels to organs.

The first set of papers deals with nervous and vascular systems. Pelegri *et al.* present a study on axon kinematics when a traumatic strain is applied and the role played by the glial matrix. The transition of axonal behavior between low and high stretch levels is modeled and simulated within neural tissue. Marquering *et al.* apply multiscale decomposition of flow patterns in an aneurysm phantom in order to better apprehend and quantify the mixture of complex features observed by means of several modalities. Gao *et al.* propose a strategy for quantifying interstitial cells of Cajal (ICC) networks by developing two metrics based on network density and connectivity. They use the single normal equation simulation to analyze the physiological effects of ICC depletion at various physical scales. Kapela and Tsoukias have integrated vascular cells into a multicellular model of the vascular wall accounting for spatial heterogeneity in calcium signaling and nonuniform deformations of a vessel segment. Such an approach allows investigating the mechanisms involved in altered vasoreactivity. Tomaso *et al.* report a multiscale (in space and time) model of atherosclerotic plaque formation based on transport and chemical interactions pointing out the relation between plaque growth and mean blood low-density lipoproteins. The second paper presented by Fotiadis *et al.* describes a platform capable, from patient-specific 3-D datasets, to provide blood flow cues. Wall shear stress distribution is modeled during the plaque progression through real-time simulations in grid environments.

The next three Letters relate to cardiovascular and electrophysiological systems. Dux-Santoy *et al.* have modeled the multiscale effects of an antiarrhythmic drug, the dofetilide, and more precisely its impact on the specialized cardiac conduction system. The construction of a ventricular model based on L-systems is proposed by Sebastian *et al.* This model includes the main

elements of the conduction system, anatomical and physiological constraints, and statistical priors to mirror stochastic variability. Pop *et al.* describe a simple two-variable macroscopic model to derive the propagation of stimulated action potential replicating the *in vivo* electroanatomical mapping protocol applied on animals. Scar and fiber directions are estimated through diffusion-weighted MRI. Relevant examples of simulations are given for noninducible and macroreentrant ventricular tachycardia. Two other papers of this series also focus on electrical activities. The approach proposed by Laforet *et al.* aims at a better understanding of the relation between cellular action potential generation, propagation over the uterine tissue, and the surface electrohysterogram by plugging the in-depth model into a volume conductor model. This work in progress introduces new insights for prediction of labor and preterm delivery. Du *et al.* have analyzed the role of calcium in gastrointestinal motility through a 2-D model. An innovative approach is described in modeling of multiple mechanisms involved in the tension–extension process.

The third part of this issue gathers contributions on modeling interactions among different biological levels related to other physiological systems. Raimondi *et al.* described cartilage growth, a major issue for tissue engineering *in vitro*. They report a PDE microscale–macroscale model capable to integrate perfusion flow, nutrient, etc., and to render tissue growth in realistic scaffold geometries. The mechanisms appearing at the cartilage–bone interface in the onset and the installation of osteoarthritis are examined by Shim *et al.* They design a multiscale model based on open-source ontologies developed in the Physiome project with cellular, micro, and macro levels. The remodeling process of fibered structures is examined by Saez *et al.* It relies on a von Mises statistical distribution accounting for the dispersion of the fibrils. Then, controlling the change in the orientation of fibrils by external stimuli is shown. Kong *et al.* present a large-scale initiative on glioblastoma which makes use of the new nuclear phenotypic data available in the Cancer Genome Atlas project. They point out the clinical and biological interests to in-silico data. The last three letters in this section investigate issues related to protein and pharmacodynamic interactions. Androulakis *et al.* model the pulsatile secretion of glucocorticoids and their pharmacodynamics effect. The model allows investigating the difference in transcriptional responses to different types of exposure, pulsatile or constant, and the implication of ultradian rhythms in glucocorticoid secretion patterns in disease. Dewey *et al.* present a multiscale modeling approach to development of new therapeutic drugs. They provide basic views on space- and time-scales and propose new paradigms to deal with the inherent complexity they bring. The characterization of the time dynamics of a thyroid hormone is the objective of Orsi *et al.* They report a linear time-invariant model which, when matched to experimental data, leads to comprehend the links between velocity of hormone conversion and internalization with system mass. A new model for the reconstruction of gene networks is proposed by Qiu *et al.* that qualitatively behaves like the Hill kinetics but using the same mathematical representation for both activation and inhibition. Their work leads to new biological hypotheses on repressing protein synthesis in gene knockout experiments.

In addition, two Letters in this issue are oriented toward information and communication technologies in multiscale modeling. The first one, by Chatziioannou *et al.*, argues for the pivotal role of ontologies in biology. They propose a graph theoretical approach in their paper exemplified on pancreatic cancer and a T-cell acute lymphoblastic leukemia gene set integrating Resnik semantic similarity matrix. Chang *et al.* emphasize the importance of model reusability, sharing, and storage. They present a study on how multiscale modeling and simulation can be improved using the Modeling Markup Language (MML) framework, an open source protocol.

III. Future Trends and Challenges

Understandingly, the future expectations from computational modeling in diagnosis, treatment, and even prognosis of physiological and behavioral diseases are very high. Although in many clinical situations today, computational models are being used in patient-specific procedures (such as computer-assisted intervention in cardiodefibrillators and stents, etc.); the potential applications of biophysiological models cover a very large spectrum of clinical issues for better health care. A new generation of medical technologies and drugs could be derived from optimization of simulated model responses for specific care delivery for a given patient or a group of patients leading to "personalized medicine." A significant challenge toward this objective is to develop reliable computational models and tools that can provide an effective optimal balance between the generalized physiological knowledge and patient-specific data to accurately simulate and predict patient's behavior and response. There is still a long way to go, and improvements in healthcare may be not so easily and immediately achievable for "personalized medicine." There are many reasons for that from practical problems to fundamental issues. Some of the major challenges are briefly summarized next.

Many leading researchers have emphasized the need for sharing biological and physiological databases, which requires appropriate infrastructure (repositories), standardization (data encoding, ontologies, annotations, modeling languages), systems interoperability (anonymization, authentication procedures), legal and ethical rules, and so on [3]–[5], [7], [8]. The use of models and simulations in clinical practice is another major issue. The clinical usage of a model and simulation assumes that the models have been completely validated with high confidence and their operations are compatible with the clinical constraints that the physicians face. Such requirements could be better addressed by understanding the genotype–phenotype relations and their mapping onto the different space-time scales. There has to be a tradeoff here to find between fine physiological granularity (that can be simulated with the constantly increasing computer power at our disposal) and coarser outcome models (based on limited variables of significance for clinicians).

Furthermore, theoretical concerns on limited physiological knowledge and modeling methodologies must be considered as the most critical issues as they go well beyond model development and its reduction to clinical implementation [2]. Up to now, only small systems (with positive and negative loops over

various architectures) have been explored mathematically in terms of analytical properties (critical points, limit cycles, etc.). Even a system built with a few nonlinear differential equations may lead to severe complexities in multiscale environment. On one hand, links between scales, merging variables into more global ones while keeping a biological or physiological significance, impose complex situations. On the other hand, a mixture of slow and fast temporal processes operating simultaneously creates a difficult challenge to tackle in producing and analyzing complex physiological behavior: How to build enough flexible models capable to adaptation to the changing physiological interaction, environment, and architecture? For example, how to model the transition between healthy and pathological behaviors for a specific physiological process? As mentioned in Section I, such processes evolve with morphogenesis and self-organization and, of course, aging that alters the cellular responses. In addition, deterministic approaches have been favored in modeling but stochastic processes have to be considered in the formation of tissue organization and the evolution of functional behavior.

Technological issues are also of great significance and cannot be omitted. They impact modeling tasks in several ways. First, any attempt for modeling and simulation is confronted to the validation problem by collecting appropriate data and by fitting the required parameters under consideration. The datasets are provided by sensors (mainly, but not limited to, multidimensional signal and imaging sources) and have to be dealt with proper information processing. Sensing capabilities and processing methods will continue to evolve on their own but revisiting models when new advances are made is needed. Something that may not be effectively used at a given time could be utilized later for better results. A good example is new applications of medical imaging technologies with analysis of environmental and epidemiological information: What new insights can be brought when thousands of images per second could be accessible and analyzed with different geographical resources? Furthermore, many model variables are not observed simultaneously *in vivo*. The design of new multimodal instruments may be desirable in order to access simultaneously in the context of multiscale biological processes, reducing the errors caused by the registration problems over time and space. Data acquisitions over longer time scales with controlled groups under different environmental and epidemiological conditions need to be studied. Next, but certainly not the last, medical technologies are evolving very fast with short-term clinical applications and patient benefits while the development of models is still a slow process requiring years of research and validation. In other words, there should be parity in the development pace between advances brought by technologies and insights provided by models.

In summary, an in-depth understanding of living systems requires models due to the complexity to face. The foundations of such an integrated interdisciplinary enterprise are on the way. It calls for a coherent international effort [6] where interdisciplinary research among various areas related to biology, engineering and applied sciences, and medicine should be promoted with a seamless bridge between technology development and clinical implementation.

The Guest Editors would like to again acknowledge the constant support received from Dr. A. Dhawan, Senior Editor, and his team. We hope that these papers published in these IEEE TBME Letters on emerging technologies will be useful to researchers from all disciplines to allow them to contribute to new breakthroughs in this grand challenge of computation modeling in biology and medicine.

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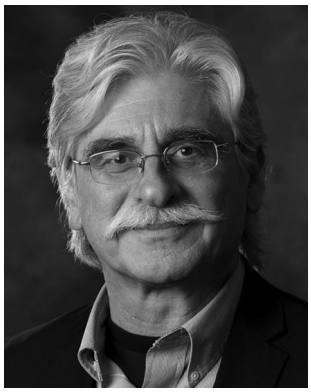

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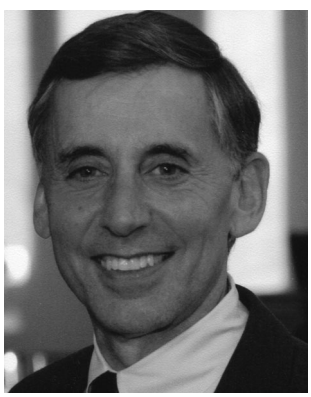

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