Editorial: TBME Letters Special Section on Multiscale Biomedical Signal and Image Modeling and Analysis

I. Third Series of Papers

THE present issue is a third part dedicated to the topic of *Multiscale Biomedical Signal and Image Modeling and Analysis* of a Special Issue of the IEEE TRANSACTION ON BIOMEDICAL ENGINEERING—Letters Session dedicated to *Multiscale Analysis*. The Editorials of the previous parts are reported in [1] and [2].

No doubt that biomedical signals processing and physiological modeling have been characterized in the last decades by a strict connection not only inside research fields but also at the clinical level. In order to really validate the parameters that are obtained after a more or less complicated signal processing procedure, it is necessary to insert these parameters inside a complicated model design for analysis to characterize them to describe relevant physiological functions. The characteristic response and analysis of models need to be validated through experimental analysis, which in most of the cases make use of processing of biomedical signals and images. This integration procedure between signal/image processing and physiological modeling is simply the first step toward a plurality of other integrative processes. In [3], the so-called MMM-paradigm has been mentioned along this research area, and the main issue was that multivariate (i.e., using more signals or channels of the same organ or biological structure), multiorgan (i.e., integrating the information among different organs or structures) and multiscale (i.e., connecting the information obtained at different scales: from genes, to proteins, to cells, etc., to the entire bodily compartment) was considered a relevant approach to improve physiological and clinical knowledge. More than that, it is now considered a fundamental step to put into practice the modern concept of "personalized medicine." The concept of "multiscale" does not simply mean to be able to process the information at the various different scales (including also the relatively "newcomer" scales obtained employing computational genomics, proteomics, and metabolomics), but to be able to correctly integrate the information across the scales that requires well-dedicated competences and training. Still, the problem of this approach is even more difficult due to the fact that there is not simply the need to correlate "geometrical scales" (from the gene level up to the organ level which, by the way, require a wide and different variety of approaches and algorithms to be applied) but even temporal scales that constitute another tough problem to be afforded in a comprehensive way.

As remarked in [2], a great merit of this conceptual approach and strategic plan is due to the *Physiome Project,* at the beginning of 2000 [4], as well as to the *Virtual Physiological Human (VPH) Project* of EU inside ICT for Health [5], [6] where the ultimate pragmatic goal would be to put at disposal to the scientists worldwide a large database in which the repositories are contained of all the information which could be obtained at the different scale levels, from gene to the entire organism, in a clear holistic view of human body: a kind of Library of Alexandria in which all the human knowledge is contained together with the various routines of signal/image processing and the most used models (electrical, mechanical, metabolic, and hybrid ones) to verify the experimental data.

II. Special Section Contents

There are 11 very interesting contributions published in this special section.

The paper by Carmena *et al*. studies the problem of cross-frequency coupling, i.e., how it is possible to calculate the phase among different signal sources in a multivariate approach. Through a novel method called multivariate phase coupling estimation (PCE), authors demonstrate that the phase estimation is better measured with PCE in respect to the more traditional bivariate methods, by reaching a higher statistical significance and for detecting direct and indirect couplings. This seems a relevant achievement in the application of multiscale brain networks.

The paper by Liang *et al*. presents an adaptive multiscale entropy (AME) measures in which the scales are adaptively derived directly from the data by virtue of recently developed multivariate empirical mode decomposition. The authors show computer simulations to verify the effectiveness of AME for analysis of the highly nonstationary data, and analyze local field potentials collected from the visual cortex of macaque monkey to demonstrate the usefulness of their AME approach to reveal the underlying dynamics in complex neural data.

It is well understood that cardiac fiber architecture plays an important role in the study of mechanical and electrical properties of the ventricles of the human heart. Diffusion tensor imaging (DTI) is predominantly used to image this architecture but is limited by its spatial resolution. Inherent to DTI is the fact that measurements are integral properties and, hence, may not provide the true orientation of fibers. Yuemin *et al*. investigate this assumption based on modeling of three different virtual cardiac fiber structures, simulating their corresponding DTI measurements based on Monte Carlo methods, and evaluating measurements across multiple observation scales.

The paper by Sermesant *et al*. approaches the problem of motion and contractility estimation from cine magnetic resonance (MR) images of the heart. An electromechanical model

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of cardiac wall motion has been developed by authors and the model results have been compared with the experimental data obtained on subjects with myocardial infarction or dilated myocardiopathy. Through the adjoint method, cardiac contractility is estimated by minimizing the error between model and experimental data on a few regions of the heart, suggesting this approach to better "personalize" patient diagnostic evaluation.

The paper by Bauer *et al*. suggests a method for a quantitative evaluation of brain tumor growing, based upon a multiscale, multisource model that simulates its growth from the cellular level up to biomechanical level, by accounting cell proliferation and tissue deformation. Different registration procedures are carried out on the data by comparing an atlas of healthy subjects with pathological patient images. This method finds important applications for the detection of tumor progression and its related prognosis.

The paper by Spencer *et al*. investigates cultures of cortical neurons grown spontaneously on a multielectrode array environment. In particular, the processing of the neuron spikes provides significant parameters related to connectivity and synchrony. Through a proper model, it is possible to capture the evolution of the structural/functional properties of the neurons using a complex network approach that takes into account the multiple time scales of the overall system. That allows to determine the important ordered sequences of synchronization in the network.

Jaume *et al*. approach the problem of deciphering the brain circuitry using imaging of a mouse brain, obtained at a large scale level, integrated with manually tracing of the connections between neurons. Hence, this operation of creating a graph of the brain circuitry is called connectome. This structure could have a noticeable impact on the understanding of neuro-degenerative diseases such as Alzheimer's disease. Even if considerably smaller than a human brain, a mouse brain already exhibits one billion connections and manually tracing the connectome of a mouse brain can only be achieved partially. The objective of this paper is to scale up the tracing by using automated image segmentation and a parallel computing approach designed for domain experts. The design decisions are explained by using a parallel approach and some results are presented and discussed for the achievement of segmentation of the vasculature and the cell nuclei, which have been obtained without any manual intervention.

The paper by Garbe *et al*. introduces us into the important field of measuring morphological alterations in tissues in chronic muscular diseases in an animal study (mice). Inherited Duchenne muscular dystrophy mice were considered: tissue slices were analyzed by combining second harmonic generation microscopy with multiphoton *XYZ* image stacks and several measurements were done on cells as well as observations on myofibrils or sarcomeres. The boundary-tensor approach, properly adapted, allows to obtain in a quicker and automatic way the morphometric data. That would allow to develop a clinical image database for the diagnosis and follow-up of specific morphological alterations in chronic muscular diseases.

The paper by Fain *et al*. studies how it is possible to develop a kinetic model *in vivo* using MR in the brain, by using hyperpolarized ^{13}C-labeled pyruvate studies. They demonstrate that, using a simultaneous acquisition of ^{1}H and ^{13}C with contrast agent injection, they are able to improve the accuracy of the model by efficiently separating extracellular by intracellular ^{13}C kinetics. Through this approach a better estimation is fulfilled for the segmentation process of the involved brain areas in connectivity studies.

Filipovic *et al*. present a multiscale approach to compute the transport of circular and elliptical particles in 2-D laminar flow. The method aims at improving the understanding of particle transport mechanics in circulatory systems, thereby facilitating the design of nanoparticles to be used for drug delivery in cancer prevention and pain management. Analysis across different length scales is performed by coupling a macroscopic model based on finite-element analysis and a mesoscopic model using dissipative particle dynamics methods. Suitable simulations emphasize that the proposed multiscale approach might find wide applications in the modeling aspects of micro/nano particle motion when designing advanced drug delivery systems.

The paper by *Kim et al*. presents an in-silico evaluation method of glucose control model protocols for critically ill patients with hyperglycemia. The authors use a virtual patient model of the critically ill patient with hyperglycemia and evaluate comparatively the clinic glucose control protocols in a computational environment. They conclude that the in-silico simulation method using a virtual patient model could be useful for predicting hypoglycemic incidence of novel glucose control protocols for critically ill patients, prior to clinical trials.

III. Future Trends and Challenges

As mentioned previously in Section I, the overall vision of developing multiscale models and resources that can allow to dynamically and adaptively interact among different levels within an organ or subsystems as well among all subsystems imposes an incredible challenge to data analysis and networking. The massive computational and interactive infrastructure support would allow to obtain a comprehensive environment where it is possible to navigate passing through different scales (i.e., from nanoscale, to microscale, to milliscale, and upward) by fusing electrical characteristics with mechanical properties of fibers and tissues and hence to better investigate their overall pathophysiological behaviors [7], [8].

Another challenging issue in developing multiscale computational models is how to compute suggestive parameters of complexity inside a communicating network [9]: there, it does not seem important how big is the network itself but rather how connectivity properties are involved or are structuring, for example, in a developing living process. In most of the cases, a decreasing in the values of complexity parameters or the degree of connectivity is correlated to pathological events (like, for example, in central or autonomic nervous systems) [10].

The task of the researcher will be the more difficult job to use properly this large amount of information, as well as its "basic software" of processing/modeling, starting from a (possibly) original biological idea and fulfilling the expected results of "integrative physiology and personalized medicine" [11], [12].

Certainly, we are quite far to reach this ambitious ultimate goal but, on the other hand, many research groups are working in multiscale modeling and biomedical signal processing, with the objective to demonstrate that a great plus of information

might be obtained through this integration process toward the improvement of diagnostic procedures, drug designing, and therapeutic interventions [13]–[15].

We would like to 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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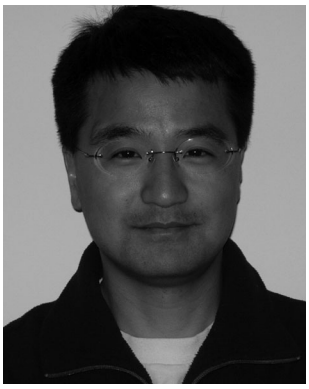

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