Guest Editorial
Special Issue on Medical Imaging and Image Computing in Computational Physiology

I. INTRODUCTION

ACCORDING to the STEP research roadmap [1] the virtual physiological human (VPH) is a methodological and technological framework that, once established, will enable the investigation of the human body as a single complex system. Underlying the VPH concept, the International Union for Physiological Sciences (IUPS) has been sponsoring the IUPS Physiome Project for more than a decade [2], [3]. This is a worldwide public domain effort to provide a computational framework for understanding human physiology. It aims at developing integrative models at all levels of biological organization, from genes to the whole organisms via gene regulatory networks, protein pathways, integrative cell functions, and tissue and whole organ structure/function relations. Such an approach aims at transforming current practice in medicine and underpins a new era of computational medicine [4].

In this context, medical imaging and image computing play, and will continue to play, an increasingly important role as they provide systems and methods to image, quantify and fuse both structural and functional information about the human being *in vivo*. These two broad research areas include the transformation of generic computational models to represent specific subjects, thus paving the way for personalized computational models [5]. Individualization of generic computational models through imaging can be realized in three complementary directions: 1) definition of the subject-specific computational domain (anatomy) and related subdomains (tissue types); 2) definition of boundary and initial conditions from (dynamic and/or functional) imaging; and 3) characterization of structural and functional tissue properties. In addition, imaging also plays a pivotal role in the evaluation and validation of such models both in humans and in animal models, and in the translation of models to the clinical setting with both diagnostic and therapeutic applications. In this specific context, molecular, biological, and pre-clinical imaging render additional data and understanding of basic structure and function in molecules, cells, tissues and animal models that may be transferred to human physiology where appropriate.

The applications of image-based VPH/Physiome models in basic and clinical domains are vast. Broadly speaking, they promise to become new virtual imaging techniques. Effectively more, often non-observable, parameters will be imaged *in silico* based on the integration of observable but sometimes sparse and inconsistent multimodal images and physiological measurements. Computational models will serve to engender interpretation of the measurements in a way compliant with the underlying biophysical, biochemical or biological laws of the physiological or pathophysiological processes under investigation. Ultimately, such investigative tools and systems will help our understanding of disease processes, the natural history of disease evolution, and the influence on the course of a disease of pharmacological and/or interventional therapeutic procedures. Cross-fertilization between imaging and modeling goes beyond interpretation of measurements in a way consistent with physiology. Image-based patient-specific modeling, combined with models of medical devices and pharmacological therapies, opens the way to predictive imaging whereby one will be able to understand, plan and optimize such interventions *in silico*.

II. SPECIAL ISSUE CONTENT

This special issue received 19 manuscripts from which 11 were accepted after a thorough assessment by three to four reviewers each. Additionally, a twelfth paper fitting the special issue was included from the accepted pool of regular submissions after consultation with the authors.

Although not by intention, and yet perhaps not so surprisingly, most of these papers are focused on various aspects of the cardiovascular system across various physiological processes and observational scales. Although progress has been made in Physiome research across virtually all organ systems [6]–[15], the cardiovascular system is perhaps the most developed, with the Cardiac Physiome Project being the first one to take off [16]. Virtually all of these papers report on multi-group research collaborations, showing the cross-disciplinary and international nature of this research endeavor.

The first set of papers deals with image-based anatomical models and atlases of various structures at an exquisite level of detail. Aslanidi *et al.* [17] present an experimental technique based on stained micro computed tomography (CT) images to construct very detailed atrial models of the canine heart. The proposed technique is able to image the Bachmann's bundle, the atrioventricular node, the pulmonary arteries and veins with clear inter-tissue contrast. In the paper by Zhao *et al.* [18], the authors outline a suite of image processing tools that have been used to construct a high-resolution image-based model of 3-D atrial anatomy, which incorporates realistic surface geometry and myofiber architecture. In Hoogendoorn *et al.* [19], the authors present a detailed atlas and spatio-temporal statistical model of the human heart based on a large population of $3D + \text{time}$ multi-slice computed tomography sequences, along with the framework for construction of the atlas. The paper by Sebastian *et al.* [20] proposes a model of the cardiac conduction system (CCS) based on structural information derived from stained calf tissue. The CCS model is based on L-systems grammars and is personalized based on a combination of subject-specific landmarks and population specific structural

statistics. The paper by Goyal *et al.* [21] develops a novel method to reconstruct 3-D coronary vasculature from cryomicrotome images, comprised of two distinct sets of data—from fluorescent microsphere beads and coronary vasculature.

The second set of papers focuses on personalized modeling of cardiac electrical activity or vascular flow dynamics. The paper by Krueger *et al.* [22] presents a chain of tools that is an important step towards the use of detailed atrial models for patient-specific AF diagnosis and ablation therapy planning and thus their clinical translation. Ho, Mithraratne and Hunter [23] present a numerical simulation of detailed cerebral venous flow. While ample attention has been given to arterial cerebral flow dynamics and 1-D, 2-D, and 3-D models have been reported in the literature, this work is the first one providing an anatomically accurate 3-D model of cerebral venous return flow. In the subsequent paper, Ho *et al.* [24] report on a 3-D model and a 0-D model for the flow analysis of trans-jugular intrahepatic portosystemic shunt (TIPS), which induces drastic flow alterations in the liver. The proposed model is useful towards a theoretical understanding of TIPS procedures as well as to develop patient-specific planning systems that trade-off the risks inherent to the procedure with the urgency of relieving the patient from the pain associated with portal hypertension.

The third category of papers deals with computational methods for simulating medical imagery and incorporate knowledge of imaging physics and physiology/biophysics. These papers are important as they enable the generation of gold-standard data for validating computational models and allow understanding of how physiology or biophysics affect image quality and appearance. The paper by Prakosa *et al.* [25] proposes a new approach for the generation of synthetic but visually realistic time series of cardiac images based on an electromechanical model of the heart and real clinical 3-D+time image sequences. Such databases of visually realistic images of controls and patients can be generated when the underlying cardiac motion and some biophysical parameters are known. Glatard *et al.* [26] present the virtual imaging platform (VIP), a platform accessible via the web to facilitate the sharing of object models and multimodality medical image simulators, and to provide access to distributed computing and storage resources. Such resources open exciting avenues for developing large databases of images with ground truth data to evaluate medical image analysis and modeling techniques.

Finally, the last two papers focus on models of virtual treatment of cerebral aneurysms and on assessing the quality of numerical meshes in cardiac simulations. The work by Morales *et al.* [27] present a method based on dynamic path planning to model the distribution of embolization coils in cerebral aneurysms. The virtual coiling technique reproduces the macroscopic behavior of inserted coils and properly captures the densities, shapes and coil distributions inside aneurysmal cavities. The method was used to assess local aneurysmal hemodynamics after coiling using computational fluid dynamics. Lamata *et al.* [28] explored various mesh quality criteria for cardiac simulations. They stressed that generic geometrical quality metrics have limited success in predicting stability, and an analysis of the simulation problem may be required for an optimal definition of quality.

III. FUTURE TRENDS AND CHALLENGES

This special issue confirms the important progress made in the area of the cardiovascular system in terms of patient specific modeling. It has also shown that there is ample space for further research within and beyond this organ system. In particular, we hope this special issue will help anticipate the challenges and opportunities in personalized modeling of other organ systems where personalization and image-based modeling have had more limited penetration so far.

Without pretending to survey this area exhaustively, a number of future trends and challenges are highlighted here:

1) Multiscale Structural and Functional Biomedical Imaging: Modeling progress is inherently tightly coupled to our ability to interpret new biomedical measurements and to gain new insights into basic biological and physiological mechanisms [29]. Clinical translation of models is limited by the ability to couple generic models to patient-specific data. Biomedical imaging, from nano- to macro-scales is one of the fundamental experimental and clinical tools to gain physiological understanding or personalized predictions. The last decades have witnessed an enormous development of imaging techniques across observational scales; more recently, a number of articles have started to recognize the importance of multiscale multimodal imaging in various application domains in both biology and medicine ([30]–[34] among many others). Other research avenues emphasize integrative image-based assessments of structure and function [35]–[37]. The challenge will now be to seamlessly integrate image information across micro-, meso-, and macro- scales and to build further detailed multi-scale anatomo-functional models.

2) Detailed Multiscale Anatomical Modeling Amenable for Physiological Modeling: The works of Hoogendoorn *et al.* [19], Sebastian *et al.* [20], Goyal *et al.* [21], and Aslanidi *et al.* [17] illustrate the value of different imaging modalities from micro to macro scales, to reconstruct various anatomical organ structures. Information across scales needs to be appropriately amalgamated both in terms of anatomy and physiology using computational models. In some cases, models can be informed from subject-specific imaging modalities but the work of Sebastian *et al.* [20], Krueger *et al.* [22], and Hoogendoorn *et al.* [19] also show how domain information can be used to produce generative models that fill in for missing individualized data by resourcing to generative rules based on anatomical or physiological knowledge further constrained by statistical information from relevant species or population data.

3) From Image Databases to Human Development and Disease Progression Models: The image analysis community has developed advanced techniques for building computational atlases of various organ systems [38]–[42]. More specifically, recent emphasis has been placed in terms of modeling human development [43]–[45] and disease progression [46]–[49] thus creating highly detailed spatio-temporal atlases. One of the challenges is to underpin current phenotypic generative models with biophysical and physiological principles (e.g., [50]).

4) Linking Anatomically Accurate Biophysical Models to Omics Data: VPH/Physiome models are *sensu stricto* multi-scale models that link subcellular and cellular processes with

tissue, organ and system levels. Some recent papers have started to recognize the need to link up omics scales with tissue and organ scales [51], [52] in a spatially resolved fashion. Future research will seek to inform, with omics data, anatomically and physiologically accurate multiscale models and gain insights into their relative role in health and disease.

5) Image-Based Estimation of Patient-Specific In Vivo Tissue Properties: Measurement techniques, which are not primarily designed to produce images, such as electroencephalography (EEG), electrocardiography (EKG), and others, but which produce data susceptible to be represented as maps (i.e., containing positional information), can be seen as forms of medical imaging. Estimation of tissue properties or model parameters from state-of-the-art medical imagery or anatomically localized multidimensional signals is fundamental for model personalization and clinical applications [53]. To this end, new data assimilation techniques are emerging [54]–[61] some of which account for modeling and measuring uncertainties [62].

6) Noninvasive Imaging of Physiological Properties Through Biophysical Modeling: Closely connected to the previous challenge, the combination of imaging and personalized modeling enables virtual imaging techniques, viz. imaging of nondirectly measurable physiological information. Examples of such techniques are cardiac electrophysiology [63], [64], vascular flows in aneurysms [65]–[67] and stenosis [68], [69], cardiac and coronary hemodynamics [70], [71], bone mechanical stresses and remodeling [72], among others.

7) Image-Based and Patient-Specific Virtual Treatment Modeling for Interventional Planning: The work by Morales *et al.* [27] showed how the combination of device modeling and virtual deployment, in addition to patient-specific image-based anatomical modeling, can help to carry out patient-specific treatment plans and assess alternative therapeutic strategies. Although a number of such approaches have already been introduced in the literature [73]–[79], further research efforts will be invested in modeling devices and interventions as well as the interplay between the devices and relevant biological processes [80]–[84].

8) Integration and Fusion of Multimodal Imaging and Multidimensional Physiological Signals for Model Personalization: The distinction between imaging and multidimensional signals becomes less and less essential in the context of biophysical and physiological model personalization and, indeed, from a clinical point of view both approaches provide complementary information of individuals. Physiological signals, particularly those obtained through seamless sensing through wearable or home monitoring [85]–[88] and those obtained through invasive interventional sensors [89]–[92] can provide essential information to personalized models [93]. The former, contribute relevant information on the biorhythms, lifestyle or environmental factors from patients while the latter provide information on the immediate physiological response to specific therapeutic actions thus enabling therapy optimization during delivery.

9) Image-Based Modeling Frameworks and Standards: As the paradigm behind the Physiome and the VPH gains widespread acceptance in the scientific domain, there is an urgent requirement to demonstrate its translational value into the clinics and its adoption by industry. Focusing in the specific area of image-based modeling, a number of toolkits[1] have been developed to facilitate the task of building both patient-specific image-based models [15], [94]–[96] and for clinical prototyping of image-based modeling tools [77]. Such image-based modeling frameworks are complementary to the various simulation tools available within the VPH Toolkit [97]–[99] and, in some cases, are part of it. Additionally, a number of markup language standards are being developed [100]–[102] that will be crucial for addressing some of the challenges associated with multiscale and multiphysics coupling of multimodal data and computational models. Specifically, new modeling frameworks and standards will have to address measurement and model uncertainties [103] and their propagation to predictions thereof.

All in all, there are many opportunities for advanced biomedical imaging and biomedical image computing research in relationship with integrative physiological modeling. Our community will undoubtedly contribute to and witness a research expansion in terms of new methodologies and image-enabled physiological insights in the years to come.

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[1]A number of image-based modelling frameworks supporting complementary or specialized functionality have been developed over the last few years: cmGUI (http://www.physiomeproject.org), GIMIAS (http://www.gimias.org), MedINRIA (med.inria.fr), SCIRun (http://www.scirun.org), MAF (http://www.openmaf.org), Slicer (http://www.slicer.org), etc. Interoperability efforts have taken place within the CTK Consortium (http://www.commontk.org).

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