EMERGING CHALLENGES IN MULTISCALE MODELING IN BIOLOGY

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1. Introduction

With growing computer power, novel diagnostic and therapeutic medical technologies, coupled with an increasing knowledge of pathophysiology from gene to organ systems, it is increasingly practical to apply multi-scale patient-specific modeling based on proven disease mechanisms to guide and predict the response to therapy in many aspects of medicine. This is an exciting and relatively new approach, for which efficient methods and computational tools are of the utmost importance. This session will address multi-scale modeling activities that are focused on crossing levels from proteins, cells, tissues, organs, up to the system level.

There are several significant motivations for multi-scale modeling in physiology. First, the need to model at multiple levels – spatially and temporally – becomes clear by simply considering physiology: organisms consist of organs, which are made of different tissues; these tissues are made up of sets of specialized cells interacting with each other. Within the cells complex biochemical processes regulate cell metabolism and short and long term behavior, all taking place on the underlying protein kinetics and gene expressions. Hence, a strong interconnection exists between all levels: normal function at a given level depends on the underlying synergy of sublevels – but also on higher levels, such as feedback via neural and hormonal mechanisms.

Multi-scale patient-specific modeling is an emerging frontier in computational biology and possibly the future of medicine. Just recently, NIH posted a new Funding Opportunity Announcement "Predictive Multiscale Models of the Physiome in Health and Disease", for which the first submission round closed in January 2008. A number of workshops and panel recommendations have also recognized and addressed the importance and the difficulties in interpreting experimental results that are cross-scale in space, time and state. The Multi-Scale Modeling (MSM) consortium, along with the participation of the Interagency Modeling and Analysis Group (IMAG) of a consortium of federal agencies aims to promote the development and exchange of tools, models, data and standards for the multi-scale modeling community.

2. Session summary

2.1. *Papers*

This session includes an invited talk, four reviewed oral presentations, two additional accepted papers and a tutorial. The studies presented include work on the merging of models that operate at different time-scales, semi-automatic generation of meshes at the (sub-)cellular level, multi-scale models of blood vessel growth, an efficient multi-scale approach to simulate small to macro-molecular processes, a comparison of finite element analysis at different scales, and combining continuum and discrete models applied to large biomolecules.

Our invited speaker **Peter Hunter** will talk about multi-scale, patient-specific modeling of lower limb mechanics. Such a biophysically detailed model of the human musculoskeletal system will aid diagnostic evaluation and surgical treatment.

Sachse *et al* describe an experimental/image processing method to obtain input for computational models at the subcellular-cellular scale – specifically spatial information on structures such as ryanodine receptors and the sarcolemma – to build geometrical models for computational models of cardiac excitation-contraction coupling. These models are important in studying the signaling cascade that transduces transmembrane depolarization to cellular mechanics. Gaining better insight in excitation-contraction is critical to understanding the healthy and diseased heart.

Neal *et al* present a novel case study of the integration of two different and independent multi-scale cardiovascular system models by making use of a "semantic simulation" framework. The two models are multi-scale in space and time. One of the challenges was to accomplish the integration of the different time-scales the two models operate on. The framework makes use of established ontology for anatomy and physiology to reason on and define relationships between the two models. Multi-scale modelers will be interested in the approaches and insights obtained from the combination of these specific models, and the informatics community will be interested in the conclusions about how models should be represented.

Voelz *et al* present a new multi-scale method that combines all-atom molecular dynamics with coarse-grained sampling. Two levels of physiology are encompassed: the atomic scale of protein side chains and small molecules, and the scale of macromolecular complexes. Their work takes an important step towards realistic modeling of a critical biological process such as the synthesis of proteins at the ribosome exit tunnel, and seems feasible to be applied to even larger systems.

Qutub *et al* describe a multi-scale model of vessel growth, which encompasses five different models (blood flow, oxygen transport, growth factor distribution and signaling, cell sensing, cell movement and proliferation), which operate on different time and spatial scales. They address issues regarding the integration of these models and an interesting feature is the coupling with an experimental database, which facilitates the comparison between model and experimental results on one side, and the prescription of initial and boundary conditions on the other.

Two other papers were accepted to the session as part of the final publication of the meeting.

Cheng *et al* developed adaptive finite element methods to calculate electrostatic interactions and ligand binding rate constants for large biomolecules. They combined continuum modeling with discrete methods to efficiently model both diffusion and Brownian dynamics.

Eswaran *et al* developed micro-finite element and larger-scale continuum finite element models of the vertebral body, and assessed when micro-FE modeling might be necessary. It is a promising tool for understanding and predicting clinical fracture risk.

2.2. *Tutorial*

The tutorial is to address two interrelated topics: 1) an exemplary problem, multi-scale modeling applied to cardiac electromechanics of the failing heart and 2) generic problems associated with and the necessity for model sharing.

Cardiac electromechanics

In an integrated model of the failing heart it is necessary to integrate electrophysiological and contractile function at the intracellular level since heart failure is associated with dysregulation of intracellular excitation-contraction coupling mechanisms. But heart failure is also a tissue level problem with fibrosis and conduction abnormalities, an organ level problem (dilatation and hypertrophy), a circulatory system problem (increased plasma volume and peripheral resistance), and a systemic syndrome with shortness of breath and fatique. We and others have developed multi-scale three-dimensional models of ventricular electromechanics that integrate from molecular to cellular, tissue, organ and system scales. These models are multi-scale in that they simultaneously solve molecular and cellular systems ODE models, tissue-scale constitutive models, organ-scale finite-element models of action potential propagation and stress equilibrium, subject to dynamic boundary conditions generated by circulatory-system scale lumped-parameter models of hemodynamics and ventricular-vascular coupling. They are also functionally integrated in that they simultaneously solve electrophysiological and mechanical models (i.e. excitation-contraction coupling) and include feedback across physical scales (e.g. from baro-reflex to adrenergic receptor signaling) and between functions (e.g. mechanoelectric feedback).

Model sharing

The open sharing of models is critical to the advancement of the science. Reproducibility is ostensibly the goal of publication of scientific research, but the diligence exhibited by scientists in describing their experimental methods and procedures and approaches to analyses is not paralleled when it comes to modeling.

Rarely are models as fully and clearly defined as was accomplished by Hodgkin and Huxley (1952): every figure can be reproduced from their equations and parameters. Reasons for inadequacy in journal articles include the complexity of matching the written report to the computational code, the reluctance of journals to accept long detailed articles, and the additional labor required for putting code, manuals, descriptions, tutorials, test cases, solutions, etc, in good form, all of which are beyond the minimal effort required to produce the research result. There are also the issues of reluctance to reveal the details, like secret ingredients in a recipe, or to provide the latest and best science to one's competitors. While it is more difficult to present technically complicated models to a broad user community than it is to provide simplified conceptual models. It is more important to make the difficult ones available for workers to explore, understand and build upon. "On the shoulders of giants…". What's more, the funding agencies, scientific societies, and journal editors are beginning to require full disclosure: It won't be just "Publish or Perish" but "Disseminate usable products (models, techniques, data) or Perish! It is an oligation accompanying federal and foundation funding to make our world better.

3. Acknowledgements

The session organizers would like to thank the set of reviewers for their efforts in evaluating the papers that were submitted. The first special session on multi-scale modeling was held in 1999, with a session on Computer Modeling in Physiology: From Cell to Tissue. The second session was held last year (Multiscale Modeling and Simulation: from Molecules to Cells to Organisms). Last year we hoped that it would not be another 8 years before the richness of this area would be seen again at the Pacific Symposium on Biocomputing, so we also acknowledge the assistance of many individuals who helped support the notion of holding this third session on multi-scale modeling.

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