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MULTISCALE MODELING AND SIMULATION SESSION: FROM MOLECULES TO CELLS TO ORGANISMS

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1. Session Background and Motivation

Today's biology and biomedical research is increasing inundated with data, based in part on improved instrumentation and techniques that automate the data capture and storage. Genomics and proteomics efforts are producing data at an increasing rate, the data are more of a descriptive nature and do not provide information on functional and structural integration and interactions of the parts. Improved microscopy and imaging, along with other types of instrumentation, are also producing data on components of larger living system. But to better understand human physiology and to allow for predictive capabilities of disease prevention and treatment it is crucial to develop multiscale models and simulation systems that can operate at and across various scales, across the length scale from nanometers for molecules to meters for human bodies, as well as across time scale from nano-seconds for molecular interactions to minutes, hours and years for human life. For example, new experimental techniques are able to observe the cellular dynamics and the localization of intracellular proteins at the same time. A multiscale modeling approach incorporating molecular and cellular mechanisms is needed to explain these data.

A number of workshops and panel recommendations have recently recognized and addressed the importance and the difficulties in interpreting experimental results that are cross-scale in space, time and state. The multiscale modeling consortium, along with the participation of the Interagency Modeling and Analysis Group (IMAG) of a number of federal agencies that include the National Institutes of Health (NIH), National Science Foundation (NSF), National Aviation and Space Agency (NASA), Department of Energy, (DOE), Department of Defense (DoD) and the United States Department of Agriculture (USDA), aims to promote the development and exchange of tools, models, data and standards for the MultiScale Modeling (MSM) community. The NSF blue ribbon panel recognizes that Simulation Based Engineering Science (SBES) [1] applied to the multiscale study of biological systems and clinical medicine, or simulation based medicine, may bring us closer to the realization of P4 medicine (predictive, preventative, personalized, and participatory). The June 2005 President's Information Technology Advisory Committee (PITAC) report on computational science [2] and the 2005 National Research Council report [3], both specifically recommended increased and sustained support for infrastructure development to meet the computational challenges ahead.

2. Session Summary

This session includes an invited talk, six reviewed oral presentation, three additional accepted papers, and an associated tutorial. We structured the session to include work at various levels (molecular, cellular, tissue, organ, and whole body) and across these levels. The presentations reflect a variety of approaches, from molecular dynamics, numerical analysis, mesh generation, Markov Chain modeling, and use of ontologies. The variety of approaches will continue developing and will bring together new data types and models. This will result in a better understanding of the relationship between scales of biology, and ultimately will enhance biological understanding. The area of multiscale modeling is rich indeed, and will provide challenges for years to come.

The invited talk by **Kamm *et al*.** discusses the role that "mechanical signaling" plays in regulating biological function in health and disease. His approach considers how forces are transmitted through the various load-bearing structures within the cell and how these forces act to create conformational change in critical signaling proteins or protein complexes. He considers a hierarchical structure of transmission of stress across the membrane, and uses a variety of simulation methods (molecular dynamics, to Brownian dynamics to finite element methods) to predict the distribution of stress and their consequences. Experimental data on specific systems (models that focus on

forces acting through the focal adhesion complex and transmitted throughout the actin cytoskeleton) are used as input or to validate the computational models.

Two papers focus on either predicting protein structure or identifying functional sites in proteins. **Glazer *et al.*** describe an approach to help identify function of the increasing number of solved protein structure with unknown function, produced by the structural genomics initiative. In particular they combine molecular dynamics simulation (to produce a variety of snapshots of the protein) along with their previously described machine-learning algorithm FEATURE can provide an improvement in the recognition of functional sites in proteins. Treating the molecules as dynamic entities improves the ability of structure-based function prediction methods to annotate possible function sites.

Li and Goddard a novel method to predict transmembrane proteins structures in a heuristic fashion. They focus on the G protein – coupled receptors (GPCRs) system, which is important since it mediates the sense of vision, smell, taste and pain, and they are involved in cell recognition and communication processes. The authors developed a first principles methods for predicting structures and functions of GPCR and apply these methods to two receptor systems. Their approach is to model the entire GPCR with molecular dynamics and then use this model of the receptor to design a target ligand.

Four papers present models of cardiac cell function and structure, or organ behavior. **Deremigio *et al.*** presents a Markov Chain model for coupled intracellular Ca^{2+} channel modeling. This specific approach uses a Kronecker structure representation for the Ca^{2+} release site models. The authors show that the Kronecker structured representation can take advantage of a number of off-the-shelf solvers. The paper provides benchmarks using numerical iterative solution techniques and shows that convergence can be much faster than the traditional methods of Monte Carlo simulation.

Rice *et al*. explore widely used approach to computational modeling of the cardiac muscle contraction (global feedback on Ca^{2+} binding affinity). The results suggest that this approach produces hysteresis in the steady-state force-Ca^{2+} responses when sufficient positive feedback is employed to replicate the steep Ca^{2+} sensitivity found in real muscle. The resulting hysteresis is quite pronounced and disagrees with experimental characterizations in cardiac muscle that generally show little if any hysteresis. This result will impact future modeling in this area.

Lumens *et al*. present a lumped model (CircAdapt model) of the closed-loop cardiovascular system that includes ventricular interaction. Direct ventricular interaction via the interventricular septum plays an important role in ventricular hemodynamics and mechanics. The authors describe the model and the inclusion of septum geometry. They then compare their model output with

experimental data. They are able to realistically represent the left ventricle right ventricle interaction through the septum. This allows the authors to claim the broader applicability of physiological application of the CircAdapt model.

Sachse *et al*. describe an approach to develop anatomical models of the cardiac cell, with input the confocal imaging of living ventricular myocytes with sub-micrometer resolution. The method includes generation of dense triangular surface meshes representing the sub-cellular structures (transverse tubular systems). The modeling approach can be applied to computational studies of the cell and sub-cellular physical behavior and physiology and is more broadly applicable to cardiac function associated with changes in anatomy or protein distribution.

Three other papers were accepted to the session as part of the final publication of the meeting. The paper by **Agarwal and Roychowdhury** introduce concepts from electronic circuit design, namely automated nonlinear phase macromodel extraction techniques, to model circadian rhythm in both mammalian and Drosophila systems. It has been shown that such "PPV" (Perturbation Projection Vector) phase macromodels are able to accurately capture the gamut of phase/frequency related dynamics of oscillators. These techniques provide fast/accurate simulations of oscillator systems, predicting synchronization and resetting in circadian rhythms via injection locking cued by light inputs. In addition, PPV waveforms provide direct insight into the effect of light on phases of the oscillating rhythms.

The paper by **Gennari *et al*.** describes an approach to merge computational models of sub-systems into larger integrated models. The approach is illustrated by combining three independently-coded models of overlapping parts of the cardiovascular regulatory system. They demonstrate approach to annotating these models with ontologies that enables the merging of the three models into a multi-scale model that can answer questions beyond the scope of any single model.

Finally, a paper by **Rader and Harrell** present a method of classifying protein structures based on a simple model of the protein's dynamics, using correlation analysis of mode shapes as the guideline of protein classification. The approach is based on a Gaussian Network Model (GNM). The method is based on a coarse-grained model, where each protein residue is represented by a single point (at the residue's alpha-carbon), and residue centers within 7 angstroms are connect by a harmonic potential. The proteins are classified based on similarity of the low frequency eigenvectors of the model's harmonic interaction matrix.

Acknowledgments

The session organizers would like to thank the set of reviewers for their efforts in evaluating the many papers that were submitted. We also acknowledge the assistance of many individuals who helped support the notion of holding a special session on Multiscale Modeling. The previous special session in this area was held in 1999, with a session on Computer Modeling in Physiology: From Cell to Tissue. We felt it was time to re-engage the participants of this symposium with a broader set of modern biological and biomedical challenges. We hope that it will not be another 8 years before the richness of this area is seen again at the Pacific Symposium on Biocomputing.

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