Simbios Multiscale Strategy Statement

Background

Simbios is a National Center for Biomedical Computation focusing on physics-based simulation of biological structure. Its mission is dual: (1) to perform high quality research in simulation, and (2) to disseminate tools, models and trajectories relevant to physics-based simulation. Driving Biological Problems drive Simbios's research agenda and provide focus for the efforts in tool building. The driving biological problems and the associated seed projects and collaborations of Simbios span a wide range of length scales, from molecules (protein folding, RNA dynamics and myosin dynamics) to cells (cardiac tissue engineering, determinants of cell shape) to organs (neuromuscular dynamics and cardiovascular dynamics). Each of these biomedical problem areas is linked tightly to experimental efforts that generate data against which the results of simulations are compared. While each of these problems may have a fundamental or dominant scale, it is reasonable to ask under what circumstances it is necessary for these problems to consider multiple scales or "multiscale" for success. In principle, all biomedical problems are multiscale, since they have an atomic basis but also have measurable properties at the scale of cells, tissues, organs and organisms.

The goal of this document is to outline some of the key issues for multiscale modeling at Simbios, and to make explicit our strategy of deciding when a multiscale modeling effort is warranted.

The Multiscale Opportunity

What is multiscale simulation? Of course, there can be many definitions, but in general we are referring to simulation technologies that include information about multiple length scales. From a software engineering perspective, there are many ways that multiple scales can be treated. Ayton, Noid and Voth published a classification method focused on molecular multiscale methods, basically distinguishing the *serial scheme* (parameters for the coarse grained model are developed from an atomic model) and the *parallel scheme* (the coarse and atomistic models can interact or run concurrently). Our description below makes a similar distinction but we added clarification of the various possible flavors of the *parallel scheme* (b., c. and d.).

a. Having entirely separate simulations that are linked "manually" by an investigator who uses the results of one to inform the various modeling choices in another. For example, one could use all-atom simulations to calculate parameters for a separate coarse-grained model.

b. Having loosely coupled simulations (operationally separate codes) which are largely independent, but which exchange key parameters intermittently in order to create better models, informed by the other simulations. For example, linking atomistic and coarse-grained models such that parameters for the coarse grained simulation are context dependent and calculated "on the fly."

c. Having tightly coupled simulations (operationally separate codes), which are similar to the previous scenario, but for which there is qualitatively much higher bandwidth between the simulations, so that they should not be considered "largely independent" but instead could be called "tightly linked."

d. Having a single simulation (in a single designed code) in which multiple scales are treated within the same code. For example, one could have a simulation which concurrently has parts which are in all-atom detail and parts in some coarse grained detail, ideally with dynamic inter-conversion between the all-atom/coarse grained boundaries.

In all cases, the key point is that there is some communication between the scales, in order to produce more accurate or faster simulations. This communication can take many forms. There can be an active communication link during the simulation or the focus might be on increasing the physiologically realism of the model by incorporating more accurate boundary conditions, derived from a smaller scale.

There is much interest in multiscale simulation in biology and medicine for many reasons. First, the fundamental observation that all living systems operate at multiple scales makes it seem attractive to capture these scales in order best to capture the dynamics of structure at the most natural levels. One could argue that in biological systems, the dynamic nature of structures at all scales makes it difficult to accurately model systems without communication between multiple scales. Second, it is clear that structural dynamics at smaller length scales creates emergent properties at the larger scales that are important for accurate simulations. Sometimes, changes in dynamics at one scale will change the fundamental parameters of a simulation at another scale. Failure to recognize the evolution of these parameters can limit the accuracy of the simulations. Third, most current simulations are not multiscale, and there is a general belief that the introduction of methods for multiscale modeling will markedly improve current capabilities.

Because of the great interest in and challenges associated with multiscale modeling, there has been substantial activity in this area. The Interagency Modeling and Analysis Group (IMAG), which started as a joint effort between the NIH and the NSF and later expanded to include other funding agencies, embarked upon a collaborative grant program entitled "Multi-Scale Modeling Initiative" which is specifically focused on multiscale modeling. This program has made 24 awards in 2005, which range broadly in their focus both on biological problems and simulation technologies and are listed in Appendix A. As a result of the Multi-Scale Modeling Initiative, several other initiatives have been released and IMAG now hosts the Multiscale Modeling Consortium of investigators to further interact and explore questions in this field. In addition, there are several laboratories that have specifically taken on the multiscale challenge, including Klaus Shulten (creating coarse-grain techniques for large molecular ensembles), Greg

Voth (creating coarse-grain techniques for molecular structures), Andrew McCammon (linking Quantum and classical mechanics), and others.

Current work in multiscale modeling at Simbios

Simbios already has a number of projects that can be considered multiscale, by the definitions above. They are quickly reviewed here.

1. RNA dynamics. We have created the NAST program that uses a coarse grained (one ball per base) representation of RNA in order to create initial models. NAST uses a knowledge-based force-field for initial creation of the coarse grained RNA structure. In a second step, the coarse grained model is converted into a full atomic model so that it can be further refined using physics-based all-atom force fields. We have also created RNABuilder, which treats the kinematics at multiple levels of resolution, with bases and/or selected regions of molecules rigid and the remaining bonds free to rotate. The force-field is knowledge-based and applied to all bases, regardless of the level of resolution of the kinematics.

2. Myosin dynamics. We have created a rigid body representation of myosin in order to simulate the dynamic features of its walk along actin filaments. The individual full atomic structures have been made rigid in key “hinge” location, and all flexibility has been assigned to these hinges. The resulting great reduction in degrees of freedom allows us to retain molecular-level representation, but reduce the search space for dynamic hypotheses. (Similar efforts are underway with RNA using the Simbody code for articular multibody dynamics).

3. Protein dynamics. We have extended the Markov State Model formalism to include multiple scales in a novel way. What sets this scheme apart is the new way in which the different scales communicate: by constructing a transition matrix out of multiple scales, we can use the simpler models where sufficient and fill in with more detail where needed. For example, within this scheme, one can naturally combine all-atom explicit solvent, all-atom implicit solvent, coarse grained, and even simple mathematical models. A first, simple application of this was made in the simulation of the misfolding and oligomerization of Abeta monomers (implicated in Alzheimer's Disease), and we are working to more broadly include these methods in our MSMbuilder software.

4. Neuromuscular. We have developed models of human movement dynamics that simulate the physics of muscle force generation. The generation of muscle forces is driven by the interaction of actin and myosin on the scale of 1-10nm, whereas human movement occurs on the scale of meters. To bridge this gap, we use models that represent the change in force with alteration of actin-myosin overlap (i.e., the “force-length effect) with simple models that characterize the behavior of muscle.

5. Cardiovascular. We have developed multiscale fluid-structure interaction models of the vascular system to quantify flow and pressure wave propagation from the large arteries to the microcirculation. Our approach involves using "variational multiscale

methods" to couple reduced order models of the small blood vessels beyond the limits of image resolution to patient-specific models of large arteries. A second multiscale project involves creating 3D nano and microscale models of blood vessels from 3D Serial Block Face Scanning Electron Microscopy (SBFSEM) and Immunofluorescent Array Tomography (IAT) and using this to deduce continuum scale properties.

The Simbios Multiscale Strategy

Despite the efforts, enumerated above, in multiscale modeling, there remains a question about how vigorously Simbios should approach multiscale modeling technologies. Current efforts are opportunistic and there is no explicit strategy to focus on multiscale capabilities in the SimTK core. Having said that, it is important to recognize that the Simbody multibody mechanics code is inherently multiscale--it has a very general representation of structures as articulated rigid bodies, and the work on RNA, myosin and neuromuscular mechanics all take advantage (to different degrees) of the power of this general abstraction for physical structures.

More generally, the Simbios strategy for multiscale modeling is based on pragmatics, and is driven by the following principles.

1. Multiscale modeling should be driven by biomedical problems that require it. These may result from interactions at different length scales or time scales or both. The level of detail to be incorporated at each scale and between scales, as with all models, should be driven by the biomedical question. Modelers should make sure to engage biomedical and or clinical expertise accordingly. Some examples of biomedical problems requiring multiscale include:

* Slow/fast integrators where a walking model is linked to a knee deformation model in the study of the evolution of arthritis

* Quantum mechanics and molecular mechanics when there are quantum events (e.g. the isomerization of retinal in a the rhodopsin G-protein coupled receptor) that have important impact on mechanical constraints.

* Cardiac modeling where the response of vascular tissues to pressures and flows leads to changing constitutive properties over time.

* Links between systems biology and structural biology. The structural conformational changes of membrane-bound protein receptors may lead to changes in ion flux or other downstream signals that then affect cellular signaling systems that are simulated with reaction-diffusion schemes. For example, the opening of an ion channel for calcium that leads to a signaling cascade.

2. Multiscale modeling should not be pursued for its own sake. It is, almost by definition, much more difficult than single scale modeling. In addition, multiscale simulations may be less likely to be general purpose, since the detailed interaction of length and time scales may be peculiar to a particular biomedical domain. Before

deciding that a multiscale approach is required, considerable efforts should be expended trying to avoid it.

3. Multiscale modeling should include links to relevant experiments at all represented scales. A critical goal of Simbios is to ensure that simulations are always linked to experimental data. Thus, for a multiscale simulation to make sense, it must be informed by experimental data at all the modeled levels.

4. Because of the complexity of multiscale modeling and the need to drive it by the specific needs of a particular problem and its associated data sources, general purpose multiscale code does not seem to be a likely outcome. Instead, it seems more prudent to create robust single scale (length or time) codes that have appropriate hooks for linking to each other in the cases where multiscale simulation seems required.

APPENDIX

24 proposals funded by the Multi-Scale Modeling Initiative.

PI Name	*Proposal Title*	*Funding Agency*	*Program Officer/ Agency Contact*
Victor Barocas	Multi-Scale Mechanics of Bioengineered Tissues	NIH/NIBIB	F. Wang
James Bassingthwaighte	Adaptive Multi-Scale Model Simulation, Reduction and Integration for Cardiac Muscle Physiology	NSF/BES	S. Demir
Daniel Beard	Multi-Scale Modeling of the Heart in Metabolic Syndrome and Cardiovascular Disease	NIH/NIBIB	G. Peng
James Brasseur	Micro-Scale Transport as a Critical Link between Molecular-Scale Absorption and Macro-Scale Mixingin Gut Physiology and Function	NSF/CTS	M. Plesniak
Marco Cabrera	Time Course of Metabolic Adaptations during Loading and Unloading	NASA	R. White
David Cai	Collaborative Research: Cortical Processing across Multiple Time and Space Scales	NSF/DMS	T Russell
Yoonsuck Choe	Multi-Scale Imaging, Analysis, and Integration of Brain Networks	NIH/NINDS	Y. Liu
James Glazier	Multi-Scale Studies of Segmentation in Vertebrate Embryos	NIH/NIGMS	P. Lyster
Trent Guess	Dynamic Simulation of Joints Using Multi-Scale Modeling	NSF/CMS	K. Chong
Teresa Head-Gordon	Multi-Scale Models to Study How Spatial Organization of Cellular Components Influences Signaling	NIH/NIGMS	P. Lyster
Roger Kamm	Multi-Scale Analysis of Cellular Force Transmission and Biochemical Activation	NIH/NIGMS	P. Lyster
George Karniadakis	A Stochastic Molecular Dynamics Method for Multi-Scale Modeling of Blood Platelet Phenomena	NSF/DMS	T. Russell
Denise Kirschner	A Multi-Scale Approach for Understanding Antigen Presentation in Immunity	NIH/NLM and NIAID	V. Florance
Robert Kunz	Multi-Scale Human Respiratory System Simulations to Study the Health Effects of Aging, Disease and Inhaled Substances	NIH/NIEHS	D. Balshaw
Anthony Ladd	Multi-Scale Modeling of Chemical-to-Mechanical Energy Conversion in Actin-Based Motility	NSF/CTS	M. Plesniak
Ching-Long Lin	Multi-Scale Simulation of Gas Flow Distribution in the Human Lung	NIH/NIBIB	G. Peng
Ernst Georg Luebeck	Scales of Carcinogenesis: Cells, Crypts and Cancer	NIH/NCI	J. Couch
Andrew McCulloch	Multi-Scale Modeling of the Mouse Heart: From Genotype to Phenotype	NSF/BES	S. Demir
Peter Ortoleva	Intercellular Genomics of Subsurface Microbial Colonies	DOE/ASCR	G. Johnson
Niles Pierce	Coarse-Graining DNA Energy Landscapes for the Analysis of Hybridization Kinetics	NSF/DMS	T. Russell
Jay Schieber	CISE: Multi-Scale Modeling to Develop a Cyberinfrastructure for the Dynamics of Flexible and Stiff Entangled Macromolecules	NSF/OCI	M. Heller
Stanislav Shvartsman	Collaborative Research: Multi-Scale Analysis of Epithelial Patterning: Modeling and Experiments	NIH/NIGMS	P. Lyster
Michela Taufer	DAPLDS: A Dynamically Adaptive Protein-Ligand Docking System Based on Multi-Scale Modeling	NSF/OCI	M. Heller