Simbios Summary

Simbios is a National Center for Biomedical Computing (NCBC). The NCBC program is part of the NIH Roadmap for Medical Research, and the National Center was established in response to RFA-RM-04-003 (http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-04-003.html). It is led by Russ Altman (Departments of Genetics, Medicine, Bioengineering & Computer Science), Scott Delp (Departments of Bioengineering and Mechanical Engineering), and Vijay Pande (Departments of Chemistry, Structural Biology, & Computer Science) of Stanford University. It is focused on physics-based simulation of biological structures.

Physics-based simulation provides a powerful framework for understanding biological form and function and helps biomedical researchers understand the physical constraints on biological systems as they engineer novel drugs, drug delivery systems, synthetic tissues, medical devices, and surgical interventions. Although individual investigators have made elegant contributions to physics-based modeling in biomedicine, the field is fragmented. Modeling applications are typically limited to a single physical scale, and individual investigators frequently must create their own software. These conditions create a major barrier to advancing simulation capabilities. The National Center for Physics-Based **Sim**ulation of **Bio**logical **S**tructures (Simbios) is working to integrate the field and accelerate future research.

Simbios is developing and disseminating open-source simulation software that addresses both developer and user needs:

- Simbody – a multibody dynamics package written by experienced professionals that enables advanced modeling of the geometry and physics of biological systems
- OpenSim – a musculoskeletal modeling and dynamics simulations software package built on top of Simbody
- OpenMM – a software library and application that provides accelerated molecular dynamics simulations on high-performance computer architectures, particularly graphics processor units or GPUs

To ensure utility and accuracy, the software and training material are being developed and tested in close collaboration with biomedical scientists.

Our repository for software and documentation, http://simtk.org, provides the necessary infrastructure for software development, testing, dissemination, and discussion for any hosted projects, and specifically for Simbios software.

Our driving biological problems currently focus on neuroprosthetics dynamics and drug target dynamics. Past driving biological problems include RNA folding, protein folding, myosin dynamics, neuromuscular dynamics, and cardiovascular mechanics.

We provide multiple ways to interact with Simtk.org and use the Simbios software, thus serving users with different levels of computational sophistication, from clinicians to modelers to computational scientists.

CORE 1: BIOCOMPUTATION RESEARCH

The scope of our Center is broad enough to encompass many biomedical research domains, and yet is focused in its mission to use physical and mathematical modeling to create accurate simulations of biological structure and function.

Our simulation tools enable biomedical scientists to develop and share accurate models and simulations of biological structures—from molecules to organisms. SIMBODY—which includes high performance algorithms for performing matrix operations, generating and integrating equations of motion, performing linear and nonlinear optimization, and modeling contact between bodies—provides an excellent foundation for developers. SIMBODY has enabled the development of powerful graphics-based applications, such as OPENSIM for simulations of human biomechanics and MACROMOLECULEBUILDER (previously known as RNABUILDER) for simulating coarse-grained models of large complexes of RNAs and proteins. We have also developed OPENMM, a tool for both developers and end-users interested in high-performance, customizable molecular mechanics. Through these software tools, we have enabled thousands of researchers to do rigorous, high-performance physics-based simulations.

CORE 2: DRIVING BIOLOGICAL PROBLEMS

We developed criteria for the selection of our Driving Biological Problems (DBPs). The criteria below drove our choice of our initial DBPs (individually or in aggregate) and will drive our choice of problems throughout the life of the Center.

- *Canonical*: Results should be guaranteed to have broad applicability.
- *Cover a range of scales*: Each DBP should cover some range of scales.
- *Physics-based*: Expressed by analyzing geometry and physics of the biological system.
- *Data rich*: Rich experimental data providing constraints that drive and validate models.
- *World-class, engaged experimentalists*
- *Collectively cover a broad area of biophysical modeling*
- *Have important implications for disease*

Our DBPs satisfy these criteria and are briefly reviewed here. These DBPs are at different stages of maturity. We encourage collaboration in each of these DBP areas, including DBPs that have graduated and are no longer actively funded by Simbios. Multiscale capabilities are encouraged from the onset, since these features cannot simply be added later.

NEUROPROSTHETICS DYNAMICS (INTRODUCED FALL 2010)

The long-term goal of this project is to develop arm prostheses for amputees that can be directly controlled by the brain. Achieving this goal requires decoding motor intention from recordings of brain activity during complex movement patterns. Towards that end, this project seeks to 1) establish a freely moving animal model to directly measure the context-dependency of motor cortical activity and 2) develop computer-vision algorithms and biomechanical models to automatically determine body and limb orientations during free movement over long periods of time.

Drug Target Dynamics (introduced Fall 2010)

This project is developing physics-based methods to improve drug-docking and the modeling of unexpected drug-target interactions. Specifically, it seeks to understand how physical simulations can improve docking for G-protein coupled receptor proteins (GPCRs), which constitute approximately 50% of all drug targets.

RNA Folding (introduced Fall 2004)

This project represents a macromolecule-scale study of the process of folding. Although the primary scale of the RNA work is at the atomic level, certain computations are too expensive to perform atomistically; thus, the project requires coarse-grain representations for which we have provided several options, including a 1 ball per base representation, a 5 balls/base representation as well an internal coordinate representation using multibody dynamics.

Protein Folding (introduced Spring 2008)

This project investigates the folding kinetics of proteins and protein-protein complexes, through a coupled approach of detailed simulations validated and tested by experiment. A key aspect is the development of OpenMM (Open Molecular Mechanics), an extensible API for molecular mechanics. OpenMM is designed to operate with the tens of different Molecular Dynamics codes with overlapping functionality, each with their own user base and designed to take hardware acceleration into account, in particular computations on Graphic Processor Units (GPUs). An applications layer is also provided so end-users can directly take advantage of OpenMM's speed and flexibility in designing new forces and other simulation components.

Myosin Dynamics (introduced Fall 2004)

This project represents a scale that is one order of magnitude larger than RNA. Myosin represents the fundamental source of motive force in many living systems, and so its biological importance is high. It is fundamentally a physical problem: how does the cell turn the chemical energy of ATP into movement? The relevant scales for myosin range from Angstroms to nanometers. This project uses a range of experimental techniques. Myosin dynamics is important for understanding myopathies and the generation of motive force throughout organ systems.

Neuromuscular Dynamics (introduced Fall 2004)

The range of scales relevant to this problem is impressive: the precise physical properties of a muscle cell at the micron scale, all the way to the macroscopic forces generated by muscles on the scale of centimeters. Modeling of human motion is a biomechanical and physical problem. A primary application is in the planning of interventions to assist patients with abnormal movement dynamics, e.g., children with cerebral palsy, and adults with stroke and Parkinson's disease. Advances in imaging provide rich data sets for building and evaluating models.

Cardiovascular Dynamics (introduced Fall 2005)

This project represents scale from millimeters to meters, and focuses on the dynamics of fluid flow through the branching system of blood vessels in the human cardiovascular system. This DBP is important because the physics of fluid flow are markedly different than the physics of multibody dynamics used at the molecular and neuromuscular level.

Cores 3-6: Infrastructure, Training, Dissemination of Research Results & Administration

Infrastructure: Our plans for infrastructure include delivering software to the biomedical research community, via Simtk.org, and supporting its routine use across diverse biomedical research domains. We have established and maintain a hardware infrastructure that guarantees consistent and robust access to Simtk.org and encourage researchers to leverage the community and infrastructure that has been developed around the site. This infrastructure does not generally include computing power for user applications, which must be identified through separate mechanisms.

Training: A highlight of our training program is our distinguished postdoc program. We have also established a summer internship program through which San Francisco State University computer science students learn about biocomputation while assisting with the development of Simbios software. The third component of our program is to train individuals on using Simbios software. We achieve this through on-line documentation, as well as workshops and webinars.

Dissemination: The user community for Simtk.org and its software is diverse and large. Our dissemination activities include the following highlights:

- *Simtk.org*: where all software developed by or in active collaboration with Simbios is made available. The site is open to all individuals wishing to host software, data, and models related to biocomputation.
- *The Biomedical Computation Review*, a magazine to increase public awareness of the intersection of biomedicine and computation. It is available in print and on-line.
- Applications and associated algorithms and models are created under an open-source license consistent with free academic use and commercialization.

For information on administration, see http://simbios.stanford.edu/.

Opportunities for collaboration

1. **Extend the application of existing Simbios efforts in the same biological realm:** We are currently focusing on neuroprosthetics dynamics and drug target dynamics. In the past, we have studied RNA folding, protein folding, myosin dynamics, neuromuscular dynamics, and cardiovascular dynamics. We welcome collaborations in closely related areas where existing technologies can be directly tested with little modification.

2. **Adoption of our APIs:** We have released three APIs and welcome collaborations that utilize them. These collaborations could be at an algorithmic level or could focus on the use of the code to solve a particular biological problem. Our APIs include:

    - OpenMM – an API for molecular dynamics, designed to take hardware acceleration via Graphical Processor Units (GPUs) into account. We have incorporated this API into GROMACS, CHARMM, and TINKER, have developed an AMBER (Sander)-

compatible interface to this API, and are actively seeking collaborators to incorporate this API into a wide range of additional Molecular Dynamics (MD) codes.

- OpenSim – an API to simulate the movement of musculoskeletal structures. The API enables individuals to extend and customize the OpenSim application, including adding new components to a model, creating new types of probes to extract values from a simulation, and developing new types of analyses. We welcome collaborators who leverage this API to create new algorithms or workflows that help solve a particular biological problem.

- Simbody – a high-performance multibody dynamics API that delivers accuracy suitable for scientific and engineering applications with real-time interactive capabilities suitable for virtual worlds and games. We have used it for internal coordinate modeling of molecules and for coarse-grained models. Simbody has also been used for neuromuscular models of human gait and for robotics applications. We are actively seeking collaborators to incorporate this API into other applications, particularly those for biosimulation.

3. **Introduce new models and other data into the Simbios capabilities:** We are interested in sharing data and models produced by other groups, as part of a dissemination repository.

4. **Develop basic relevant algorithms.** We are interested in breakthroughs at the basic algorithmic level that will help facilitate faster or more accurate simulations at any scale, as well as multiscale simulations. We are also interested in algorithms that can be significantly accelerated using GPUs, which has become one of our focus areas for Molecular Dynamics.

5. **Provide applications that can be downloaded from Simtk.org**. We are interested in providing applications (using novel models, methods and algorithms) that end users (scientists and clinicians) can download from Simtk.org and use in their research.

6. **Develop ways to perform data mining and analysis of Simbios output.** We are interested in methods to analyze simulations, visualize them, and pull out useful new biomedical knowledge.

7. **Run experimental projects to be additional driving biological problems.** We are currently focusing on two biological application areas. We would welcome collaborations that introduce new biological areas, and extend and test code we developed for our previous application areas to new areas.