

A. Specific Aims

Our broad goal is to serve as a resource of expertise in methodology and technology for modeling and analysis of physiological processes, which include circulatory mass transport and exchange, metabolic reactions, and more importantly in the post-genomic era, large-scale integrations of molecular, cellular, and physiological systems. Within this broad goal are four main endeavors that serve as specific aims of this proposal:

Aim 1. To develop new modeling technologies that enhance the capability of investigators to form and analyze quantitative hypotheses, and to design and interpret experiments.

This overall aim is the subject of the projects detailed in Section D.I. The specific techniques include: (1) providing a Java-based simulation environment, JSIM, that will run on a variety of platforms (Windows, Unix), extending our Unix-based interface (XSIM) to a significantly larger user community with enhanced overall utility—JSIM will support a wider range of model types and modeling methodologies, model and data exchange via the internet, and a variety of new visualization capabilities; (2) developing a generic approach to the simulation of transport in complex geometries such as capillary networks; (3) implementing new approaches to modeling stochastic processes in transport and exchange such as occur with ionic channels or in systems with sparse numbers of protein or signalling molecules; (4) implementing optimization-based metabolic network analysis, introducing thermodynamic constraints; and (5) integrating JSIM with a XML-based markup language, Cell Systems Modeling Language (CSML).

Aim 2. To research, develop, and implement new models applicable to research in the fields of circulatory mass transport, transcapillary and transmembrane transport, and metabolic reactions.

This aim is the object of projects in Section D.II. The three groups of specific modeling target areas are: (A) Whole Organ Transport, including continuing the development of the general, nonlinear blood-tissue exchange model, reconstructing whole vascular networks using 3-dimensional Voronoi tessellation, estimating flow from the kinetics of permeating contrast agents, modeling hemoglobin gas exchange in lung and tissues, and modeling water fluxes during tracer and osmotic exchanges; (B) Cellular Metabolism and Control, including six projects on cardiac muscle metabolism using biochemical circuit theory, energy balance, excitation-contraction coupling, oxidative phosphorylation, TCA cycle kinetics and fatty acid metabolism, and ATP regulation by cross-bridge dynamics; and (C) Integration of Cell and Molecular Processes, including motor proteins and muscle contraction, electrodiffusion and ionic exchanges, stochastic ionic channel behavior, and stochastic activation dynamics of T-cells.

Aim 3. To serve the research community in the use of modeling technology and simulation analysis by providing appropriate models, instruction, and consultation.

This goal is to support the collaborative projects in Section D.III. No funding is requested for Aim 3 studies as they are supported by funds available to the various collaborating principal investigators. While we continue to support long term collaboration with nuclear medicine and imaging groups that are using positron emission tomography, and biomedical

researchers using high resolution tracer techniques to study membrane transport processes and metabolism, new collaborations have been established in cardiac biomechanics, cellular signalling, and energetics. This specific aim is also furthered by the core project D.IV.C on Dissemination and Training.

Aim 4. To provide computational and administrative support for the Resource; to provide for oversight of the Resource by advisory and user committees; and to provide dissemination of the expertise and methodologies developed by the Resource so that it will be useful to the scientific community at large. This Aim is to be achieved through the methods described in Section D.IV and includes two subcontracts to collaborating investigators at McGill and Vanderbilt.

B. Background and Significance

The primary role of this Resource Facility is to provide tools to researchers for modeling integrated physiological systems. With ever increasing complexity, these tools become more difficult to apply to practical problems. Thus, in addition to developing state-of-the-art technologies, we are compelled to make the tools as simple to implement as possible, and to provide education and tutorial services to the community.

When the Resource Facility was established, our initial focus was on blood-tissue exchange of solutes and water with considerable emphasis on the nature of the heterogeneity of blood flow and its effects on the estimates of transport parameters rather than on the metabolic transformations. We now provide methods for analyzing increasingly detailed molecular transport and metabolic processes in increasingly realistic anatomical settings. The breadth of biophysical sub-systems incorporated the modeling analysis has gradually increased as we have integrated various phenomena from basic transport and metabolism to energetics, to excitation-contraction coupling and cardiac biomechanics. The result of this broad integration is that we have coupled our expertise in transport physiology with growing expertise in molecular and cellular systems. This expertise comes with the recruitment of new core and collaborating faculty with diverse but highly quantitative backgrounds. They bring enthusiasm, intelligence, and vision via their deep involvement in the Resource and its programs.

We propose to develop tools for the study of regulation in biochemical reactions, metabolic networks, biofluid and transport processes, and, in general, systems physiology. Integrating representations of previously isolated systems into correctly functioning virtual or computational organisms is the great hope of modern systems biology. How do we combine multifaceted knowledge in the forms of both experimental observations and theoretical models? The common thread that holds physical and engineering sciences together—mathematical modeling—is what we find to be the most promising approach. Our Resource Facility has been at the forefront of mathematical modeling in physiology, now recognized as a central component of the Physiome Project, for the past quarter century. This strength and past experience will enable us to play a leading role in the next five years, developing new tools and exploring novel methods for integrative biology leading to new computational approaches to biomedicine.

Efforts to expand the base of analytical and computational expertise in the biomedical sciences are increasingly important as scientific knowledge deepens and expands. While

molecular biology appears, on the surface, not to require much mathematics, an overwhelming amount of quantitative information is becoming available at the subcellular and molecular levels. Understanding phenomena at a more integrated level—that is, understanding cell dynamics, and organ and organism behavior—requires a mathematical framework. Thus, the development of the mathematical framework is an important thrust of core projects lead by Qian (D.I.C) and Beard (D.I.B and D.I.D). Also, the development of software that utilizes this framework is now of great importance; this is seen in particular in the projects in collaboration with the Cell Systems Initiative (CSI) at University of Washington in the coalescence of JSIM (our Java-based simulation analysis system) and CSML (an XML-based Cell System Modeling Language) in D.I.E, D.II.C.4, and D.III.A.3.

To balance our own rapid growth in scope, we continue to build up the program in collaboration with others. This is reflected in Sections D.II and D.III, devoted to specific projects which utilize our core technologies. While collaborative projects have always been important to the NSR, these projects receive an even greater emphasis now, as collaborative exchange becomes fundamentally necessary in all areas of modern biomedical research.

One example of this outreach and cooperation is our mutually beneficial collaboration with the Resource Facility for Population Kinetics (RFPK). Relating biophysical description to experimental data requires model fitting, i.e., optimization. While optimization technology has been developed by our Resource in the past, future development will be in the hands of the experts at the RFPK. Our users need to optimize large and noisy data sets acquired by positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI). The special-purpose techniques for fitting time-course data, with mixed statistical noise and cross correlations between parameters, that the RFPK has developed will benefit the rapidly growing user community in these imaging fields. There are capabilities provided by their new package, SPK (System for Population Kinetics), described in the letter of collaboration from Dr. Paolo Vicini, Director of RFPK. In turn, we provide them with JSIM and our kinetic models for applications in pharmacodynamic and pharmacokinetic studies.

There is a growing need for large-scale integrated formulations of systems and computer programs that can be shared by investigators for research and teaching. It is recognized that as molecular biologists retrain themselves to study integrated systems, and that as new investigators undertake their training, they need to obtain a hierarchical understanding of models progressing from the simplest to the complex. It has become clear that the role of crudely descriptive models is diminishing because their behavior, at some refined level of observation, is unrealistic. On the other hand, very complex models are not only time consuming to develop and run, but have historically been nearly impossible to make useful to investigators other than the model developers. Our development of JSIM is designed to aid as a teaching and training tool, as well as a model development tool. JSIM is immediately (within 10 minutes) useful to graduate and undergraduate students without prior familiarity with simulation. Some projects are designed explicitly to help guide the user community through from elementary knowledge to expert usage. While this is a part of all sections, three are targeted to this end: one on enzyme kinetic models, D.II.B.3 (Bassingthwaighte), and the two D.IV.D Dissemination projects, the Web Tutorial on Space-Distributed Whole Organ Models (Schwab) and the Transport Tutorial Development (Roselli).

We believe that an important role of this Resource is in training on local, national, and international levels. Our plans for this role are under the Dissemination and Training Core. We believe that our success as a Resource depends on developing the expertise among scientists who will lead programs independent from our Resource. At the same time, we plan to maintain leadership in our particular area of expertise and to be able to make continuing new contributions to our direct collaborators and to those who function totally independently.

Our nation needs a network of Resource Facilities, each with a targeted focus, in order to begin a coherent integrated effort toward the “Physiome Project” (Bassingthwaight, 1992, 1995, 2000; Kohl, Noble and Hunter, 2001). This endeavor, a successor to the Genome, Proteome, Morphome projects, is focused on how organisms actually function. The project magnitude vastly exceeds that of the Genome Project in the breadth of its scope and in its requirements for databasing and annotation, and for communication of observations and interpretations. Its underpinnings lie not only in the Genome and the Proteome but in the vast array of scarcely retrievable physiological information. The Physiome Project must be electronically based, for it is clear that retrieval of detailed information from the print literature is incomplete and slow. A major inhibition to the thorough understanding of physiology is the lack of sufficient means of integrating the information that is available into an understanding of the system’s behavior. For example within a cell, the complexity of the interactions is immense. The processes of binding, reaction, diffusion, transmembrane transport, competition, and regulation are all influenced by the local concentrations of substrates, metabolites, the pH and pCa, and the presence of agonists and antagonists at receptor sites. Add to this the down- or up-regulation of expression of proteins and the other processes of long term physiological regulation. Models representing such systems have not been developed beyond relatively primitive stages.

In our Resource we emphasize the assemblage of models that have general utility on their own and that should also serve as modules in yet more comprehensive model systems. XSIM, and now JSIM, the modeling tools, are vehicles for the display of the behavior of models by improved visualization techniques. Our group’s background expertise in fractal and chaotic non-linear dynamical systems helps in assessing behavior of these complex systems. Biological systems have no “set-points”; nevertheless, most of control system theory still applies. Temporal fluctuations are the norm; there is sometimes period doubling (“on the route to chaos”) or overt chaotic behavior.

We hope that this Resource will only be one of a set of Resource facilities collaborating on a subset of the Physiome Project. Since we cannot be master all of these interrelated fields within our own group and its affiliated groups at the University of Washington, we are engaged in collaborative projects (or subcontracts) which provide expertise directly bearing on our long-term goals. Our focus, centered as it is on cardiac function, will serve the Cardiome component of the Physiome Project. Even so, as our techniques and tools are well suited to studies of substrate and agonist (etc.) effects in many different organs, we would anticipate supplying strategies and computer code to investigators working on other organs or systems.