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Systems Biology and Physiome Projects

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The emergence of systems biology as a result of the molecular revolution in biology and progress in genomic and proteomics is now beginning to affect medicine. The systems approaches are poised to revolutionize medicine as they have been revolutionizing biology, through their application to drug discovery and therapeutic applications including personalized medicine, introduction of novel diagnostic and surgical procedures, design and use of medical devices, and education and training. While the terms “systems biology,” “systems physiology,” and “systems medicine” are frequently used but not always defined, we will attempt to provide working definitions of these terms, and give examples of ongoing physiome projects.

1. Systems Biology, Systems Physiology, Systems Medicine and Physiome Projects

Systems biology can be defined as a field of study that takes into account complex interactions in biological systems at different scales of biological organization, from the molecular to cellular, organ, organism and even societal and ecosystem levels. Systems biology is characterized by its integrative nature which sets it apart from the mostly reductionist nature of molecular biology; it is also characterized by quantitative descriptions of biological processes, with a wide use of mathematical and computational techniques. Thus, important attributes of systems biology are development and application of predictive experiment-based mathematical and computational modeling, use of bioinformatics, combined with experimental studies (increasingly using high-throughput techniques). Consistent with such an understanding of systems biology, modeling techniques incorporate multiple spatial and temporal scales (multi-scale modeling). Just as physiology is a branch of biology, systems physiology is a branch of systems biology; it focuses on the function of interacting parts of the system at cell, tissue, organ and organ system scales, and is tightly coupled with structural anatomical information.

Systems medicine is a branch of systems biology dealing with applications to medical and clinical problems. Examples of systems medicine include application of systems biology to achieve a quantitative understanding of disease processes, to drug discovery, and to designing diagnostic tools. A subset of systems medicine that relies on individual patient’s data or a specific group of patients is the emerging subject of personalized medicine. A recent review on the subject of systems medicine provides numerous examples (Auffray et al., 2009). The relationships between different systems areas of study are illustrated in Figure 1. Very importantly, systems biological approaches rely heavily on experimental data spanning multiple spatial and temporal scales and different levels of biological organization, as shown on the right side of the figure.

The term *physiome*, from “physio-” (life) and “-ome” (whole), refers to the behavior/function of the whole biological system; it was introduced by James Bassingthwaighe (Bassingthwaighe, 1995; Bassingthwaighe et al., 1998). The biological system can be an organism, organ, tissue, a cell, a subcellular structure (e.g., mitochondria), or a physiological system (e.g., the immune system); thus, we refer to specific *physiomes* as the *cardiome*, the *epitheliome*, the *metabolome*, *bone physiome*, *angiogenesis physiome*, or *tumor physiome*.

Finally, the Physiome Project is a world-wide effort to achieve a quantitative and comprehensive description of various *physiomes*; *physiome* projects investigate specific *physiomes* e.g. the *cardiome* (a complete description of the heart including its anatomy, molecular, cellular and organ mechanics, electrophysiology, electro-mechanical coupling, and metabolic processes in health and disease), the *epitheliome*, the *metabolome*. New areas of research, especially as complex as systems biology and as ambitious as the Physiome Project, require new enabling infrastructure. Below, we will describe the emerging infrastructure for systems biology and the Physiome Project, and give examples of *physiome* projects.

Note that synthetic biology is another emerging area of biomedical science that will benefit from the infrastructure being established for the Physiome Project. The modules or “bricks” of genetic or mRNA sequence, being created as functional modules by the synthetic biology community, map nicely into the CellML1.1 modular approach of building complex models from simpler, modular components (Rouilly et al., 2007).

2. Computational Methodologies for Systems Biology and Physiome Projects

All physiological systems are associated with the interactions of multiple physical processes, not least because tissues grow and adapt to their continually changing environments. These ‘multi-physics’ systems are also multi-scale: processes at the cell and tissue scales are linked intimately with molecular events at the gene and protein levels. One example can be seen in the study of cerebral aneurysms, as illustrated in Figure 2. Alterations of flow in the cerebral blood vessels induce a pressure and shear response that, via numerous cellular signaling pathways, produces a change in the composition of the tissue (primarily collagen, elastin and smooth muscle). The resulting change in the mechanical properties of the tissue is reflected in the wall mechanics and hence aneurysm shape. This shape then influences the flow solutions.

To understand and quantify these complex multi-scale and multi-physics processes, the *physiome* modeling community are currently developing three model encoding standards: SBML¹ (for 0D+time biochemical pathways), CellML² (for 0D+time biophysical models) and FieldML³ (for n-dimensional spatial fields). The standards define how models are structured, how the mathematical equations are encoded and how units are defined. They typically use XML as the means of serialization. Two major model repositories have been developed—Biomodels⁴ (primarily SBML pathways models) and the CellML⁵ repository. The SBML and CellML groups are now working together to produce common metadata standards, based on ontologies, for annotating the models with biological and biophysical information. These metadata standards are needed both for checking the biological and biophysical correctness of models but also to ease the process of combining models into composite models (e.g. combining electrophysiological models with calcium transport models, myofilament mechanics models and signal transduction models) and for using the cell models in tissue level simulations. Another metadata standard under development by the SBML and CellML

¹www.sbml.org

²www.cellml.org

³www.fieldml.org

⁴www.biomodels.org

⁵www.cellml.org/models

communities is SED-ML for encoding the numerical algorithms and associated parameters for running a model simulation.

Establishing these standards and model repositories has been an important step in achieving a robust foundation for the modeling community – particularly when the curated models are available at the time of publication, as is increasingly the case. The next goal for this work is to develop data standards and improved databases for model parameter sets, including the ability to record the provenance of parameters. Parameter sets can be stored in CellML files (for example) but there are currently no mechanisms for annotating the experimental origin of these parameters and their dependence on species, temperature, pH, etc, is often obscure. Having the models and data available in standardized formats with clearly stated dependencies will improve the utility of models and facilitate the creation of workflows that can generate model results from parameter sets and input data in order to compare model predictions with experimental data in an automated fashion. The goal here is to greatly improve the reusability of models and clarify their limitations.

The general strategy adopted by the community developing the modeling standards is as follows:

1. Develop markup languages (MLs) for encoding models, including metadata, and data.
2. Develop application programming interfaces (APIs) based on the MLs.
3. Develop libraries of open source tools that can read and write the ML encoded files.
4. Develop data and model repositories based on MLs.
5. Implement work flows that enable model results to be demonstrably reproduced.

A software framework is also being developed by the Physiome Project, based on the markup languages and model repositories, to solve the equations for these multi-scale, multi-physics processes. The framework is open source and based on internationally collaborative efforts. For example, some components of this framework are:

1. **OpenCell** (www.cellml.org/tools/opencell) is the open source code for running CellML models.
2. **Cmgui** (www.cmiss.org/cmgui) is the open source code for rendering FieldML files.
Zinc (www.cmiss.org/cmgui/zinc) provides the open source framework for building user interfaces.
3. **OpenCMISS** (www.cmiss.org/openCMISS) is being developed as the open source computational code for solving the equations representing the physical laws – e.g. (for the example in Fig. 2) Navier-Stokes equations for the flow, large deformation elasticity equations for the arterial wall mechanics, reaction-diffusion equations for transmural signaling. It is designed to handle the nonlinear, anisotropic and inhomogenous material properties characteristic of soft biological tissues. OpenCMISS has interfaces to both CellML and FieldML. The 3D geometry and other spatial input fields used in OpenCMISS are read from FieldML files. The mechanical constitutive laws and signaling pathway models are encoded in CellML. OpenCMISS uses MPI for distributed memory parallel programming.

For example, in relation to the problem mentioned above of modeling cerebral aneurysms, the modeling language CellML allows individual signaling pathways to be modeled and checked in OpenCell then combined into signaling networks that link shear stress signals on endothelial cells to the production of collagen, elastin and smooth muscle in the arterial wall. The mass and orientation of these arterial wall constituents is then coupled via mixture theory to the

constitutive laws of large deformation elasticity theory. The signal transduction pathways that control smooth muscle cells and fibroblasts are modeled in CellML as systems of ordinary differential equations and nonlinear algebraic equations describing the signaling networks. The shear stress acting on the endothelial cells provides the input to this signaling network and the output is linked via mixture theory to the constitutive laws used in openCMISS for solving the tissue mechanics.

Bioinformatics is another enabling methodology for systems biology and physiome projects. The term bioinformatics was first introduced to mean the application of information technology to the field of molecular biology. However, the term has evolved and its limits have been expanding to now include not only computer analysis of genomic and proteomic information, but also analysis of complex signaling and metabolic pathways, protein-protein, protein-DNA interactions, and analysis of various anatomical images and biological signals (e.g., EKG). Thus, more generally bioinformatics can be viewed as a methodology to generate hypotheses and derive scientific knowledge from computer analysis of complex biological experimental data. Medical informatics is both a branch of bioinformatics dealing with human patients data, and a process of managing medical information for more general non-scientific purposes. Bioinformatics is a major enabling methodology for systems biology and physiome projects. Bioinformatics will continue to evolve as new areas of application emerge; e.g., future applications of bioinformatics are likely to include analysis of computational models stored in model repositories.

3. Examples of Physiome Projects by System and by Disease

Below are several examples of physiome-type projects where significant progress has been achieved in integrating experiment-based computational models at multiple scales.

- **Cardiovascular system**

Current physiome models of the heart include the mechanics of the ventricular wall, based on large deformation elasticity theory (Nash and Hunter, 2001), the reaction-diffusion processes governing the propagation of waves of electrical excitation (Hunter et al., 2003), the fluid mechanics of ventricular blood flow (Nordsletten et al., 2007) and the perfusion of myocardial tissue through the coronary blood vessels (Lee et al., 2009). The reaction-diffusion models in particular link down to ion channel mechanisms, where they can exploit the 40 years of work by Denis Noble and colleagues on modeling cardiac cell electrophysiology (Nickerson and Hunter, 2006). Examples of current applications are in drug discovery, the diagnosis of coronary artery disease and the design of implanted cardiac devices.

- **Respiratory system.** Current physiome models of the lungs include transport processes in the conducting airways (Tawhai and Hunter, 2004) and gas exchange in the respiratory airways (Tawhai et al., 2004), blood flow in the pulmonary vasculature (Burrowes et al., 2008) and soft tissue mechanics (Tawhai et al., 2008). Applications to the diagnosis and treatment of COPD and emphysema are being developed.
- **Gastrointestinal system:** Reaction-diffusion models of the electrical activity in the gastrointestinal system are being developed that link to the interstitial cells of Cajal (Pullan et al., 2004).
- **Musculoskeletal system:** Physiome models of the bones, muscles, tendons, ligaments and cartilage of the musculo-skeletal system are being developed for applications in patella articulation (Fernandez and Hunter, 2005), the treatment of cerebral palsy (Fernandez and Ho et al, 2005) and muscle activation (Fernandez and Buist et al, 2005). See also Cristofolini et al., 1996, 2006.

- **Immune System and Inflammation:** Significant advances have been made in physiome-type quantitative description of the immune system and inflammatory processes (Vodovotz et al., 2009; Vodovotz et al., 2008).
- **Cancer:** Cancer involves gradual pathological genetic and epigenetic changes in the cells leading to uncontrolled growth and gradually affecting the entire organism. Numerous approaches to modeling various aspects of cancer have been formulated at different scales, from signaling pathways involved in tumorigenesis to spatial and temporal patterns of tumor growth and angiogenesis (Anderson and Quaranta, 2008; Bearer et al., 2009; Deisboeck et al., 2009; Mac Gabhann and Popel, 2006; Macklin et al., 2009; Qutub et al., 2009; Zhang et al., 2009).
- **Angiogenesis:** The growth of new vessels from pre-existing microvasculature is central to many diseases, including cancer, age-related macular degeneration, myocardial and peripheral ischemic diseases, and rheumatoid arthritis. Over 70 diseases have been identified as angiogenesis dependent. Integrative modeling approaches are being developed at multiple scales for different disease applications (Chaplain et al., 2006; Mac Gabhann and Popel, 2008; Owen et al., 2009; Qutub et al., 2009; Peirce, 2008).

4. Applications and Future of Systems Biology and Medicine

Powerful systems approaches to biology and medicine and the increasing number and scope of physiome projects are already revolutionizing the field, by bringing new quantitative level of fundamental understanding of biological processes and by enhancing countless applications. The desire to look at a biological system as a whole, with the complexity of interactions among its components, is associated with significant challenges but will also bring enormous rewards.

The challenges include the creation of enabling mathematical, computational and experimental methodologies. Examples of the mathematical and computational methodologies adapted for the use in systems biology and physiome projects are multiscale and agent-based modeling; analysis of complex pathways and networks; creating efficient algorithms for solving multi-dimensional multi-physics equations; creating ontologies and markup languages for standard representation of computational models; designing computational models using modular structure with the ability of using the modules in multiple applications; creating platforms for integration of computational models developed by different researchers, laboratories and companies; creating repositories of computational models. It should be a requirement for good modeling practice to make data and models available at the time of publication in a form where others can reproduce the modeling results. The physiome infrastructure is being built to facilitate this.

Examples of experimental methodologies, in addition to those developed in the fields of genomics and proteomics, include molecular, cellular and tissue imaging whereby anatomical, physiological, and pathophysiological information can be obtained at multiple levels of biological organization; high-throughput microfluidic devices that enable high spatial and temporal resolution in mapping signaling and metabolic processes, even at a single cell level; and nano- and micro-sensors for obtaining in vivo data in animals and humans.

The rewards from the integration of novel computational and experimental techniques would be a new level of understanding of biology and the ability to design more efficient medical treatments. The applications include advances in drug discovery and therapeutic applications, better diagnostic tools, new and improved surgical procedures and medical devices. In the future one can imagine selecting computational modules dealing with a specific organ or disease from a repository of models, linking them to relevant genomic, proteomic, pathway, anatomical, and physiological and pathological data from repositories of experimental and

clinical data, and performing simulations to make functional predictions at different scales. Such predictions should be possible for individual patients, e.g., to design a surgical procedure or drug treatment, thus advancing the field of personalized medicine. Systems approaches will also have profound effects on education and training of biologists, engineers, and medical professionals. Educational paradigm will evolve to include quantitative and computer methodologies for all biology-based professions and the conceptual thinking and techniques for understanding the behavior of complex systems.

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Systems study of interacting parts

Experimental data

Figure 1.
Relationships between systems approaches in biology, physiology, and medicine and experimental data at different levels of biological organization.

Figure 2.

The major components involved in linking signaling pathways at the cell level to continuum mechanics at the tissue level. Large deformation soft tissue mechanics is used to solve for the shape of the aneurysm. 3D CFD within this arterial volume then gives pressure and shear stress acting on the endothelial cells lining the arterial wall. The endothelial cells respond via signaling pathways that communicate with the smooth muscle cells and fibroblasts to remodel the matrix of collagen and elastin that determines the mechanical properties of the tissue. The blood vessel wall is constantly adapting to the mechanical loads. The purpose of coupling these processes together is to better understand the factors that lead to cerebral aneurysms.