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Design of a framework for modeling, integration and simulation of physiological models☆

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ABSTRACT

Multiscale modeling and integration of physiological models carry challenges due to the complex nature of physiological processes. High coupling within and among scales present a significant challenge in constructing and integrating multiscale physiological models. In order to deal with such challenges in a systematic way, there is a significant need for an information technology framework together with related analytical and computational tools that will facilitate integration of models and simulations of complex biological systems. Physiological Model Simulation, Integration and Modeling Framework (Phy-SIM) is an information technology framework providing the tools to facilitate development, integration and simulation of integrated models of human physiology. Phy-SIM brings software level solutions to the challenges raised by the complex nature of physiological systems. The aim of Phy-SIM, and this paper is to lay some foundation with the new approaches such as *information flow* and *modular* representation of the physiological models. The ultimate goal is to enhance the development of both the models and the integration approaches of multiscale physiological processes and thus this paper focuses on the design approaches that would achieve such a goal.

1. Introduction

Emergence of systems biology provided a comprehensive and integrative perspective to examine the structure and function at the cellular and organism levels of complex biological systems instead of focusing on the isolated parts [1]. However due to the complex nature of the physiological systems, development, integration of multiscale models and linking the layers stand as one of the challenges for the model developers [2]. In order to increase the effectiveness of multiscale integration of physiological processes, it is obvious that information technology approaches are required.

Physiological Model Simulation, Integration and Modeling Framework, Phy-SIM, is an information technology framework with related analytical and computational tools that facilitates development, integration and simulation of physiological models. Besides providing tools to develop physiological models, the strongest feature of the framework is providing the environment to aid the development of integration approaches. Since the problem of multiscale integration of physiological models, is itself an open research area, frameworks such as Phy-SIM providing tools to enhance the process is very critical.

A module is a structurally and functionally meaningful part of a system that can be separated from other

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components. Modularity is advantageous for model storing, sharing and reproducibility [3]. Although modularity is a desirable feature for the definition of physiological models, it is not usually properly implemented [4].

Modularity in living organisms is studied from an evolutionary perspective and it is stated that, modular architectures with functional separation are more robust and amenable to design and adaptation. In evolution, modularity brings an advantage to modifications in modules without changing intrinsic behaviors and so providing high reusability [5]. Evolution in nature is actually not so different than evolution in software environments. Reusability, easy extension/modification are desirable attributes in software life-cycles as well. Therefore in addition to the structural modularity in anatomy, importance of the protocols and hierarchy in functionality for biological systems should also be considered when developing models of physiological processes as they simplify modeling, abstraction and enable robustness [6]. Based on these realizations, Phy-SIM proposes two levels of modularity, *structural modularity* and *functional modularity*, which are new perspectives toward multilevel and multiscale integration of physiological processes. The proposed mechanism of functional modularity through the information flow approach is a novel contribution to the physiological model development domain. Integration of physiological processes is conceptualized by the transfer, access or sharing of information among the models representing the processes, and is defined as *information flow* by the authors. Structural modularity on the other hand is observable in the anatomical and physiological organization of the human body. Phy-SIM uses the ontological representation of the anatomical and physiological information to achieve structural modularity.

The heuristic guidelines in software engineering design principles aim for low coupling and high cohesion [7]. For the domains such as physiological system models, where the domain problem itself is inherently coupled and tangled, software engineering principles are very crucial. Therefore we adapt the similar design approaches in software engineering to make the problem more manageable for model developers by reducing the effects of high coupling in multiscale physiological models. As detailed in Section 4, layered design to achieve high modularity and the mediator design pattern are used to manage the communication among highly integrated modules. This way Phy-SIM achieves a software level improvement in the coupled nature of physiological models. The details of the proposed software level solutions for the multiscale physiological model integration and the sample use scenarios to show how these design decisions improve the model development process will be the focus of this paper.

2. Background

Integrative physiology following the emergence of systems biology is perceived to be central for better interpretation of physiological data starting from organ or system level down to genomic and proteomic data through the integration of these different levels of models [8]. In recent years, several big initiatives that try to create environments for researchers from various disciplines to achieve a collaborative environment and develop tools for integrative physiology research were launched. Digital Human Project introduces the idea of development of a “functional” visible human and emphasizes the importance of multilevel and multiscale modeling starting from system down to molecule level [9]. Physiome Project aims to build a database of physiological models with different scale and levels. Currently, models in this project are accessible through a web interface and some are supported with computer models [10]. Virtual Physiological Human Network of Excellence (VPH) aims to support research for developing tools, standards, models and simulations of the human body [11].

As the modeling efforts accelerated, the standards for storing and sharing mathematical models became very important especially for the cellular level data and models. CellML and SBML (Systems Biology Markup Language) are the most widely used standards storing and sharing of model descriptions. CellML is used for mathematical descriptions of cell functions. SBML defines an XML-based mark-up language standard for describing biochemical reaction networks models. Besides these domain specific standards, some physiological models are represented using MML (Mathematical Modeling Language).

Parallel to the modeling efforts, development of tools and software frameworks for integrative physiology studies have also gained attention. Physiome Project provides tools to enable integration with quantitative descriptions of relations among models and parameter sets to identify these relations. JSIM [12], which is a Java-based system, is used to simulate the models in Physiome model repository [13]. In [14], a new approach from a semantic simulation framework, SemSim, is presented for the integration of multiscale models of cardiac circulation. In this study the focus is on the integration of cross-platform models and translating procedural simulation code to a procedural code.

3. Objectives and barriers in multiscale physiological model integration domain—a software perspective

Phy-SIM aims to achieve the following in the domain of multiscale physiological model development and simulation:

1. Separation of structure from function: by the adopted modular design, definitions of mathematical models, anatomy and physiology are separated from the integration mechanism. The functional modularity is also achieved by defining protocols separately to handle information flow and integration which helps to deal with the highly coupled physiological models (detailed in Section 4.1.2).
2. Anatomical and physiological annotations: building complex models out of individual, multiscale models would be a challenging process. The challenge would increase as more collaborative efforts, share models developed by various institutions/experts. In order to integrate the models, there should be more metadata available for the models. Phy-SIM proposes an ontology based design for representing anatomical and physiological information associated with the mathematical models of physiological processes.