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A Software Framework for Integrative Physiological Model Simulation

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Abstract

Emergence of systems biology motivated more comprehensive and integrative approaches for modeling physiological processes. Presented study proposes a software framework to integrate multilevel and multiscale models for physiological processes. The aim of the study is to provide the interfacing mechanisms to facilitate the integration of models from multiple research groups increasing the ability to construct complex simulations of physiological models. In this paper, high level design of the proposed system, integration of physiological models and the architecture to modularize the integration are presented. As the proposed system targets a multiscale and multilevel integration of mathematical models, complex diseases or physiological processes effecting many organs or organ systems, like diabetes, are within in the application areas. Besides enhancing the model development processes; the presented study will accelerate the development, analysis and testing of integration approaches for multiscale and multilevel physiological models.

1. Introduction

Emergence of systems biology provided a comprehensive and integrative perspective to examine the structure and function at the cellular and organism levels instead of focusing on the isolated parts [6, 14]. However the challenge of building medical simulations where multiscale and multilevel physiological processes are developed together is often too great for any individual group since expertise from different fields is required. Therefore it is necessary to have frameworks where various models can be integrated leading to new simulation models from independently developed models. The present study addresses this challenge and proposes a software framework to integrate mathematical models of physiological processes ranging from intra cellular level up to organ, organ system and organism levels. Specifically; the aim is to facilitate the integration of multiscale and multilevel models of physiological processes in a modular framework. To achieve this task, instead of building the architecture based on the domain specific components such as anatomical and physiological information; we are focusing on the application enforced functionality, *integration of information*.

Mathematical models for the physiological processes represent the regulation, control and modification of a physiological variable which has an effect on defining the current state of the whole system [7]. A change in a physiological variable has a direct or indirect effect on processes determining other physiological variables. In other words, every physiological variable carries an information which needs to be accessed, used, modified or integrated by other variables. Therefore integration of physiological processes is conceptualized by the transfer, access or sharing of information among the models representing the processes, and will be referred as *information flow* throughout the paper.

In the proposed framework, models to be integrated are decoupled by separating the mechanisms of information flow from the information itself. Information flow architecture, which is a crucial part for the model integration is the focus for this paper.

In addition to the integration of various physiological processes, the software will also enable using different integration algorithms and approaches with the interfacing mechanism. Therefore developers will have control on what to integrate as well as on how to do the integration. With these attributes, the framework will provide a user friendly, plug-and-play type environment where both individual models of physiological processes and different integration approaches can be used.

In the next Section (Section 2), studies that are using integrative approaches and their attributes which motivated the proposed architecture are summarized. The rest of the presentation for the framework will be based on a case sce-

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nario using a circulatory system model [3] coupled with an IV drug model and its effects on a target organ [20]. In Section 3 details of the problem and the conceptualization of the system for integrating physiological processes is discussed. High level design of the proposed solution and overview about the system components are presented in Section 4. Design of the information flow idea, being the focus of this paper is discussed in Section 5 accompanied with the implications on the case scenario. Implementation details for the current status of the project are given in Section 6 to show how the components, which are not discussed in detail in this paper are integrated with the information flow mechanism.

2. Background

Integrating multilevel physiological processes requires both structural and functional hierarchical information for the contributing models. The hierarchical structure of the anatomy represents the organization starting from DNA sequences, RNA and protein, protein-protein interactions and protein-DNA interactions, to cells, tissues, organs, organ systems to the whole organism [6]. Modularity concept is also expanded for functionality in biological systems [10]. Importance of modularization is realized more as the multiscale modeling came into consideration for integrative physiology studies as modularization simplifies multiscale modeling [15]. Therefore in the proposed software framework, anatomical and physiological knowledge is defined using a modular, systematic representation.

One of the successful studies in cell level modeling, with an integrative approach, is the BioSPICE Project, which provides a framework for modeling, simulating intra and inter-cell processes. BioSPICE project also provides an integrative software environment that enables access to different computational biological tools [11].

Physiome Project [3], has a database of physiological models with different scale and levels. With the hierarchy of models from cell level to organ level, the project aims to analyse integrative biological function models and test the hypothesis using mathematical models [12]. JSIM [1], which is a Java-based system, is used to simulate the models in Physiome model repository. Although the models to be simulated vary from cellular level to organ and system level, they can only be simulated independently.

With the emergence of systems biology, development of modeling and simulation tools for this domain increased, such as, SCIRun [5] and Systems Biology Toolbox for Matlab [19]. Although SCIRun is a general purpose problem solving environment for physical and biological systems, it does not provide a simulation and modeling framework. It uses a data-flow architecture to integrate the steps of preparing, executing, and visualizing simulations of physical and

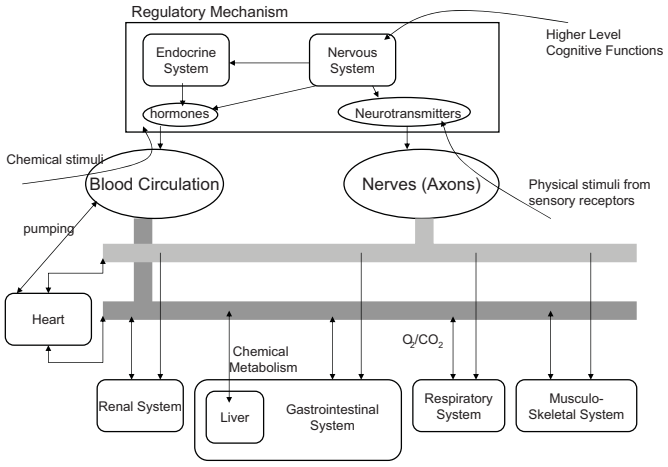

Figure 1. Information flow among physiological processes through circulatory and nervous systems.

biological systems. The Systems Biology Toolbox for Matlab provides an extensible environment for modeling, simulation, importing SBML (Systems Biology Markup Language) models and analysis tools.

Modeling and simulation of complex physical systems have been extensively studied outside the biology domain. There are tools and languages, such as, Modelica [4], Matlab Simulink [2] and Ptolemy [9] that provide creation and simulation of mathematical models for physical systems as well as integration of submodels. However none of these tools or languages are designed for the specific domain of biological systems.

3. Problem Specification

Every physiological property (blood pressure, blood glucose level, body temperature etc.) is associated with an anatomical structure; and the mechanism that controls, modifies and regulates is represented with a physiological process [8]. Circulatory and nervous systems are the mechanisms that manage the flow of information among the processes and physiological properties. The flow of information in the circulatory system can be thought of as a broadcasting mechanism, where information in the form of physiological variables are transported in the blood stream. On the other hand, the nervous system can thought as a point-to-point communication mechanism where the information in the form of electrical signals are transmitted (See Figure 1). Once the information is disseminated among the processes, individual models representing the processes integrate the available information.

A case scenario is used to present the proposed solu-

tion for the problem of handling information flow among physiological processes and integration of the information. In the presented case, concentration of an intravenous(IV) drug is the information to be carried through the circulatory system. Cardiopulmonary mechanics model from the Physiome Project Model repository [3] is used to model the circulatory system. The cardiopulmonary mechanics model is composed of a four-chamber varying-elastance heart, pericardium, systemic circulation, pulmonary circulation, coronary circulation, baroreceptors, and airway mechanics. Model for the IV drug represents the changes in the concentration of the injected drug in the injection site, vascular mixing, concentration in the arterial tree and concentration at the target organ [20].

4. High Level Design of the System

As seen in Figure 2, a layered design separating the structural and functional information from the information flow mechanism is proposed. The dependency among the layers are in one direction keeping the coupling among separate layers low. The design decision for separating the anatomical and physiological ontology and functionality, has an advantage for the reusability and extendability of the framework. The developers will be getting advantage of a higher level of reuse, which is an important advantage of using ontology based architecture [21].

Mathematical models are used to represent the dynamics of the physiological attributes. Mathematical representation of any processes is independent of the physiological variable that it controls, regulates or modifies. However every biological process depends on the mathematical model as it has different concurrency and time constraints. While some processes occur at discrete time steps and can be described by algebraic equations, some processes span a continuous time frame and can be described with differential equations. On the other hand some processes may not show a regular behavior, and can occur at specific times. Models of computation can be thought of as design patterns in object oriented paradigm, which will behave as the core of the solution [13]. Based on this analogy, the models of computation are modularized in *Computational Layer* and are classified according to the ways they deal with concurrency and time concepts, as: *Continuous Time Models*, *Discrete Time Models*, *Discrete Event Models*.

In order to have a modular representation of physiological processes and variables, a high level ontology is developed. Physiological processes are defined based on their qualitative, quantitative and temporal attributes. The systematic representation of the physiological information is modularized in *Physiological Layer*.

Anatomical associations of the processes are defined with the hierarchy represented through the anatomical ontology. Foundational Model of Anatomy, FMA [16, 17, 18], is used to represent the taxonomy and part-whole relations for the anatomical information. Ontological representation of the anatomical information is defined in *Anatomical Layer* and is independent from all other layers.

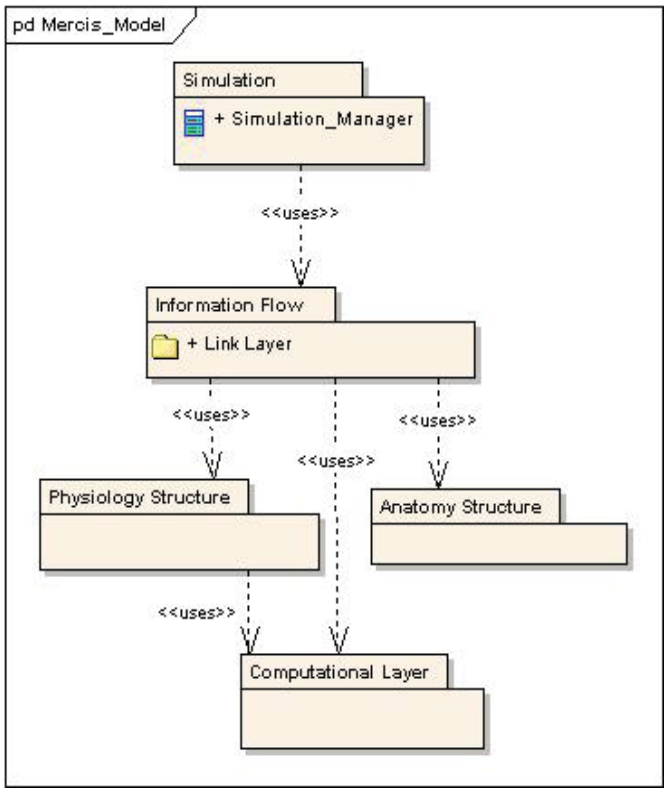

Figure 2. High Level Design

In the architecture shown in Figure 2,link layer handles the flow of information and integration of the information uses the anatomical and physiological information from the lower levels (See Section 5). Simulation of the integrated models is managed by the *Simulation Layer*, behaving as an application layer. In the following section details for the *Link Layer* is given within the realm of information flow and information integration.

5. Information Flow

Link Layer which sits on top of the physiological and anatomical layers, is designed as in Figure 3. Structural and functional information is encapsulated in *Component*s, which correspond to a single physiological variable and a corresponding model. A number of components come together to represent a physiological process. In the presented sample models, cardiopulmonary mechanics is composed of 182 *component*s each of which correspond to a physiological property with a mathematical model. The depen-

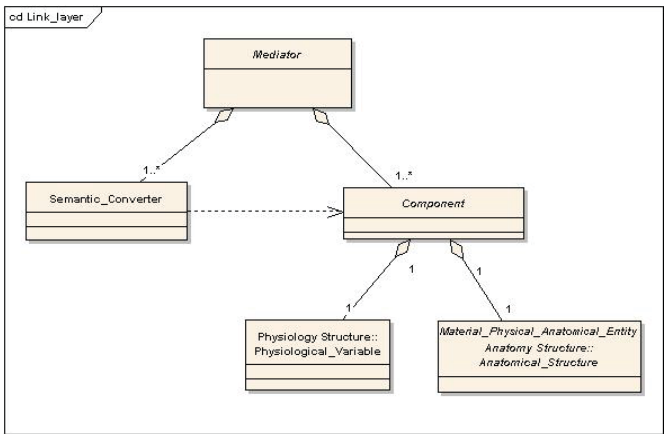

Figure 3. Design for the layer responsible of the information flow among the individual physiological models.

dency among physiological variables are defined through *Semantic Converters*. These units decouple physiological variables by encapsulating the semantics of the dependency. In the case of the cardiopulmonary mechanics model, mathematical model regulating the cardiac output depends on the values of the flow through the aortic valve which depends on other variables. Such dependencies among variables are also used to determine the simulation order. Therefore the semantics of the dependency among the *Components* is defined in the *Semantic converter*s and is used by the *Mediator* to pass to the upper layer, *Simulation Layer*.

Mediator is responsible for compiling the integrated models to handle mediation of information, results of which will be passed to the simulation layer to run the models. In order to have a serializable simulation order of components, the dependencies among components should be resolved. The *Mediator*, resolves the cyclic dependencies in the compilation process. Except for the algebraic loops, *Mediator* will resolve the cycles and create a sequential order of components using the dependencies defined by the *Semantic Converters*.

For the case of the circulatory system, information flow idea presented above is extended. Components that are part of the circulatory system are grouped as *Extrinsic* and *Intrinsic*. Intrinsic components correspond to the physiological variables and models that determine the mechanics of the flow of information, such as the cardiac output, flow of blood at the arterial tree, blood pressure, etc. Extrinsic components correspond to variables representing the information carried through the blood stream, using the intrinsic information. In the presented case, cardiopulmonary mechanics model constitutes as the intrinsic model. Model determining the concentration of the IV drug corresponds to the extrinsic model. Therefore, components in the IV drug model integrates the information from the cardiopulmonary mechanics model and transports the information about the concentration of the injected drug in to the circulatory system. These two models are integrated over the cardiac output variable which is defined as an intrinsic component. If the IV drug model were to be simulated as is, the cardiac output variable will be a constant and its regulations, changes will not be considered. By integrating the cardiopulmonary mechanics model with the IV drug model as an integration of intrinsic and extrinsic models, we were able to see the effect of change in cardiac output on the drug concentration in the blood stream.

Two types of integration schemes are used in the proposed system. The presented case of integration of information through the circulatory system, is an example of *horizontal* integration. Horizontal integration refers to the flow of information and integration among the physiological variables which have the same level anatomical structure associations. In the presented case scenario,the variables for the cardiac output in the IV drug model and the cardiopulmonary mechanics model were horizontally integrated. The integration mechanism replaces the constant representation of one variable in IV drug model with the regulated variable in cardiopulmonary mechanics model. Anatomical information associated with the physiological processes guide the integration process and determine the choice for the semantics of the integration. In the IV drug model, the cardiac output, defined as the blood flow through heart is an attribute associated with the heart. The variable to be integrated on the cardiopulmonary mechanics model is associated with an anatomical structure, the same structure in this case, which is in the same level in the anatomical ontology representation.

The other type of integration is the *vertical* integration. Multiscale and multilevel integration of physiological processes will be handled with this type of integration mechanisms. In the case of multilevel integration, the variables to be integrated are associated with anatomical structures having part-whole or parent-child relationships. Semantic converters will implement the vertical integration approaches. Aggregation and dispersion of the variables are the basic approaches proposed for implementing semantics of the vertical integration of multilevel models. For the case of the multiscale integration, the real challenge is at the computational side. There are two approaches to simulate multiscale models. The first approach is a brute force technique, and relies on simulation of all the individual (low level) subcomponents to aggregate and compute the high level behavior. This type of aggregation is naturally supported by the object-oriented design, which allows hierarchical construction. However there is a practical limitation of this approach, the computational cost. The second ap-

proach tries to reduce the computational complexity by relying on model reduction techniques. Since mathematical models for complex biological systems both contain linear and nonlinear models, an approach handling both of these systems should be adopted. Model reduction for large scale nonlinear dynamical systems is an open problem and is outside the scope of this paper.

6. Implementation Details

Current implementation of the proposed system uses models from the Physiome Project repository. Physiological processes in this repository systematically describes models from the literature using the Mathematical Modeling Language (MML). Presented system preprocesses MML models to create the library of mathematical models to be used by the physiological processes. MML files are parsed on line to create *Component*s with the physiological variables. On line parsing also creates *Semantic Converters* extracting the dependencies among the physiological variables from the model equations. Model developers can choose to associate these components with anatomical structures using the ontology representation in the framework.

In Figure 4, a prototype is presented to build the integrated system for the aforementioned system with the cardiopulmonary mechanics and the IV drug model. The first step is to build the medium for the flow of information, circulatory system. As stated in Section 5, models contributing to the mechanics of the circulatory system are modeled as *intrinsic* models. Having defined the intrinsic variables for the circulatory system, the second step is to add the extrinsic information to the model. Users can load the selected .mml file and add the information to the circulatory system by declaring the model as an *extrinsic* model. Third step is presented to show how the information flow mechanism can be used to access the variables in the circulatory system. In Figure 4, the third model loaded is the part of the IV drug model which calculates the effect of the drug at a target organ. This model accesses both the intrinsic variables, such as the blood flow and extrinsic variables like the drug concentration in the blood stream. Although the dependencies within a single model are extracted automatically by the parser, the points of integration for the loaded models should be user controlled. The last step handles the horizontal integration among the user defined integration points, which are the cardiac output and concentration of the drug in arterial system for the presented case. Having the required information to compile the model to prepare for the simulation, *Mediator* compiles the models, performs the integration, and passes the required information to the simulation step.

7. Conclusion

In addition to providing an integrative simulation environment for complex biological systems, the presented architecture will facilitate shared model development as well as data and model sharing among multiple research groups. Therefore the proposed framework will bring a new perspective with the multiscale, multilevel model integration approach.

Although major components of the system are complete, the development step is being pursued in the context of possible applications. As we are targeting a multiscale and multilevel integration of mathematical models, diseases or physiological processes effecting many organs or organ systems are within in the application areas. Diabetes, which has complications such as heart diseases, blindness, nerve damage and kidney damage, is one of the most interesting application areas, having effects on many organs and organ systems. Another complex process which presents an application area for the proposed framework is Orthostatic Tolerance. It is a very critical measure for astronauts or anyone who faces sudden gravitations changes and gravitational stress. Orthostatic tolerance is dependent on the degree of vasoconstriction and the magnitude of plasma volume, which in turn determines the tendency to faint when standing upright. This mechanism, having effects on circulatory system and nervous system is another very interesting application area to integrate different models in our software framework.

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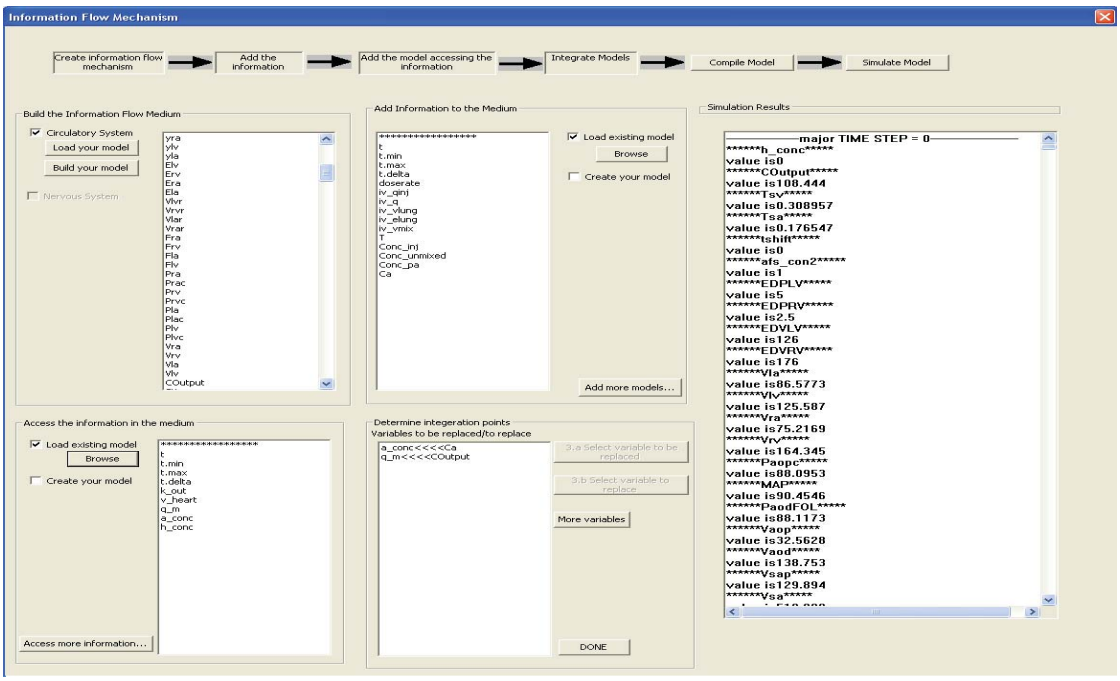

Figure 4. Prototype showing the integration of models to create the circulatory system's extrinsic and intrinsic components.

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