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A Software Framework for Multiscale and Multilevel Physiological Model Integration and Simulation

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Abstract— **Emergence of systems biology motivated more comprehensive and integrative approaches for modeling physiological processes. In this paper, the design of a software framework for facilitating the integration of multilevel and multiscale physiological processes is presented. To build such an integrative environment, a layered design is proposed, where the structural and functional information is separated from the information flow and integration mechanism. Interfacing mechanisms are proposed to handle the integration of multilevel and multiscale processes. Integration of the processes and the information flow among the processes is modularized to use the anatomical and physiological information. The aim of the proposed design is to enhance the model development processes; but more importantly to accelerate the development, analysis and testing of integration approaches for multiscale and multilevel physiological models.**

I. 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 [1], [2]. However, transferring of models and extending them by integrating with other models from various research projects requires an object oriented and modular approach, which is not an easy task [3]. Therefore it is necessary to have frameworks where various models can be easily integrated with a plug-and-play type, user friendly interface. 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 such a modular, plug-and-play type framework, a novel approach is adopted to conceptualize the physiological processes and their integration.

Mathematical models for 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 [4]. 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.

The most challenging part in multiscale modeling of biological systems is the interpretation of the information [5]. The presented framework approaches this issue by decoupling models to be integrated by separating the mechanisms of information flow from the information itself. Model developers will benefit from the modularization of the information flow and integration mechanism, as the software will also enable using different integration algorithms and approaches independent of the models. Therefore developers will have control on what to integrate as well as on how to do the integration.

II. Background

Modeling and simulation of complex physical systems have been extensively studied outside the biology domain. There are tools and languages, such as, Modelica [6], Matlab Simulink [7] and Ptolemy [8] that provide creation and simulation of mathematical models for physical systems as well as integration of submodels.

With the emergence of systems biology, development of modeling and simulation tools for this domain increased, such as, SCIRun [9] and Systems Biology Toolbox for Matlab [10]. SCIRun is a general purpose problem solving environment for physical and biological systems and uses a data-flow architecture to integrate the steps of preparing, executing, and visualizing simulations. The Systems Biology Toolbox for Matlab provides an extensible environment for modeling, simulation, importing SBML (Systems Biology Markup Language) models and analysis tools.

Digital Human Project introduces the ideas for development of a "functional" visible human and determines the importance of multilevel and multiscale modeling starting from system down to molecule level [11].

Another project, focusing on the 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 is the Physiome Project [12], [13]. With the hierarchy of models in the repository from cell level to organ level, the project aims to analyse integrative biological function models and test the hypothesis using mathematical models [14]. JSIM [15], which is a Java-based system, is used to simulate the models in Physiome model repository. SAPHIR, which is a modular and interactive

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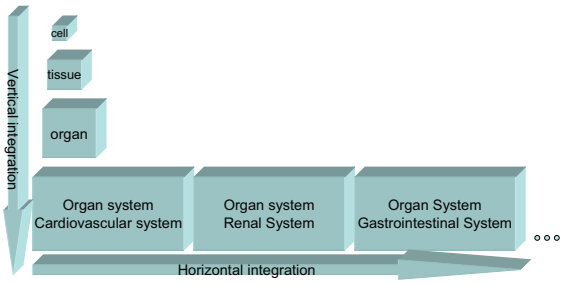

Fig. 1. Horizontal and Vertical Integration: Models to be integrated vary from inter cellular level up to organ system level. Based on the level of the detail of the models to be integrated, two different integration approaches are defined, *horizontal* or *vertical*.

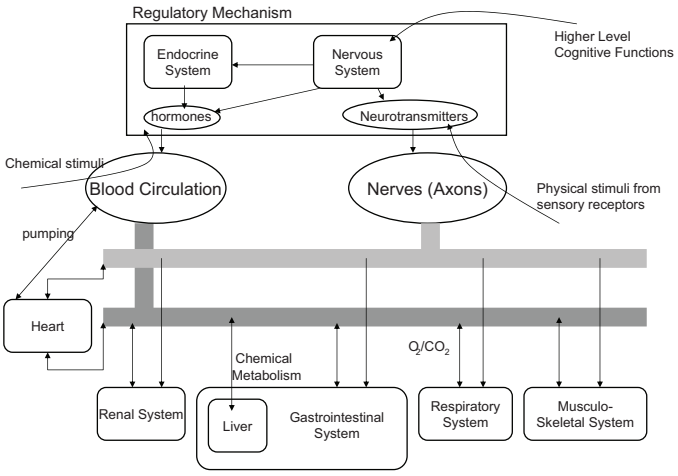

Fig. 2. Information Flow: Circulatory and nervous systems are the main medium for information flow. Information is carried through these systems by the use of physiological variables and is modified, integrated and used by physiological processes.

modeling environment, uses core models for blood pressure regulation and fluid homeostasis. The project aims to provide a grid environment for integrating models for renal system [16].

III. Method

The physiology can be generalized as processes controlling and regulating the important properties of the human system [17]. These properties, such as the state of stability, are defined to be the relative constancy of a wide range of variables (blood pressure, blood glucose level, body temperature etc.) controlled by physiological processes. Physiological processes starting from the inter and intra cellular levels up to organ system level, can be modeled as the functionalities of the anatomical components in these different levels.

In the presented study integration of physiological processes are grouped into two basic groups based on the scale and level of the anatomical and physiological structure that the processes take place (Figure 1). *Vertical Integration* refers to the integration of physiological processes via variables which carry information from different hierarchical levels of anatomical and physiological structures. *Horizontal Integration* is the type of integration that uses the modularity for the biological components within the same level. Organs in a specific organ system or set of organs in different organ systems communicate in a horizontal organization through the circulatory and nervous systems (Figure 2).

As an illustrative example, consider the oxygen transportation in the body. Oxygen enters the circulatory system through the lungs in respiratory system and transported through the circulation to the rest of the body. Calculating the oxygen concentration in liver in the gastrointestinal system requires communication of these two systems, or more specifically lungs and liver through circulation. Mathematical models representing physiological processes in both organs will share and manipulate the information about the oxygen concentration in the blood stream provided by a physiological variable. In order to handle this communication, mathematical models will use the connection information provided by the physiological and anatomical structures.

At the structural level, the nature of the horizontal interaction between the different components in complex biological systems is well-structured. The inputs and outputs of the organs are well-defined and limited to: i) electrochemical signals transmitted through the nervous system, ii) hormones and other material transmitted through the circulatory system, iii) mechanical interaction with environment and neighboring structures, and iv) material transport through the surfaces, which is significant only in limited cases, such as, skin, lungs, and gastrointestinal tract.

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 be thought of as a point to point communication mechanism where the information in the form of electrical signals are transmitted (Figure 2). Once the information is disseminated among the processes, individual models representing the processes integrate the available information.

IV. High Level Design of the System

As seen in Figure 3, 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 from the functionality, has an advantage for reusability and extendability of the framework. Since the representation of the structural information is independent of the information flow and integration mechanism, a change in the functional layer, *link layer* would not have an effect on the *anatomical* or *physiological layer*. Moreover the developers will be getting advantage of a higher level of reuse, which is an important advantage of using ontology based architecture [18].

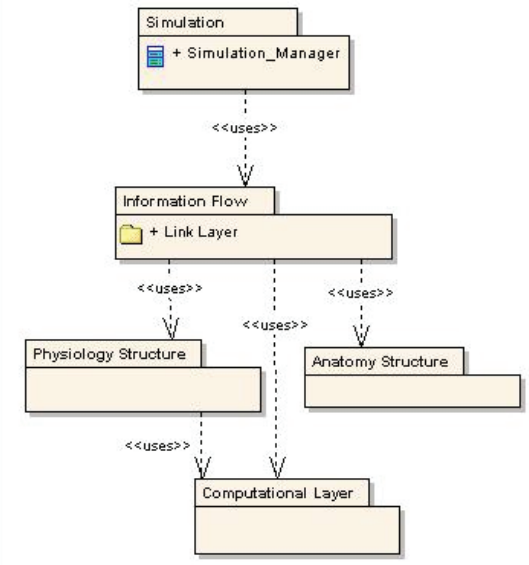

Fig. 3. High level design of the system: Structural and functional information is separated. Information flow and integration mechanisms are also modularized and separated from the structural and functional information. Application specific functionality, uses the domain specific layers to perform the simulation.

Anatomical layer uses an ontological representation of the structural information. Foundational Model of Anatomy (FMA), is used to represent the taxonomy and part-whole relations for the anatomical information [19]. Ontological representation of the anatomical information is defined in *anatomical layer* and is independent from all other layers.

In order to have a modular representation of physiological processes and variables, a high level representation is used in *physiological layer*. Physiological variables are defined based on their qualitative, quantitative and temporal attributes. In addition to the variable attributes, physiological variables also aggregates the mathematical representation of the physiological process which modifies the variable itself.

Mathematical representations of the physiological processes are modularized in *computational layer*. Mathematical models are defined based on the models of computation. Models of computation are classified according to the ways they deal with concurrency and time concepts, as: *continuous time models, discrete time models* and *discrete event models*. Mathematical models in this layer are independent of any other components in the higher layers. Thus any dependency among physiological variables are not reflected to this layer, making it easier to develop mathematical models.

Link layer handles the flow of information and integration of the information uses the anatomical and physiological representations from the lower levels (See Section IV-A). 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.

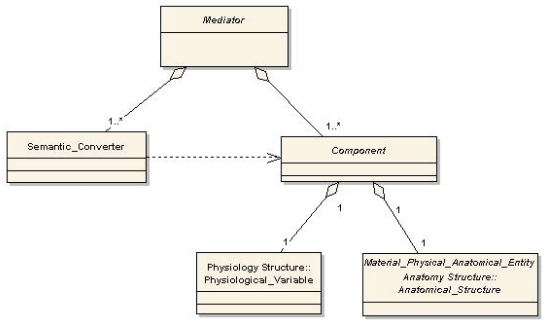

Fig. 4. Link Layer Design: This layer is responsible for the modularization of information flow and integration mechanisms.

A. Link Layer

As stated in Section I, a novel approach is presented by separating the information integration from the information itself. *Link layer* achieves separation by modularizing the functionality for information flow and integration of physiological models. Physiological information represented with the physiological variables and associated anatomical structure information are encapsulated within software units called *components* (Figure 4). Processes aggregated by the physiological variables impose dependencies among physiological variables due to the mathematical representations. For instance, calculating the cardiac output in a cardiopulmonary mechanics model requires the value for the blood flow across the aortic valve. The semantics of this type of dependency in the *link layer* would require a horizontal connection among the corresponding components, a basic input/output relationship. For another illustrative example, consider the case where cellular level response models for the change in heart rate are to be integrated with the organ level cardiovascular system model. In this *vertical integration* case, the developer should implement a multiscale model integration approach among these components.

Dependencies among physiological variables carry an important role for the simulation besides the computation of the models, as the simulation will perform a sequential run of individual models. Therefore, the dependencies among physiological variables should be represented at the *link layer*, where it will be transparent to the *simulation layer* as well as the *physiological layer*. On the other hand, defining these dependencies within the *components* will increase the tangling among components, which will make it harder to reuse, modify extend the models. Considering these constraints, presented design proposes separate units where the dependencies and various integration mechanisms can be modeled and the components can be interfaced using these units. In other words, these software units, *semantic converter*s, will represent the semantics of the dependencies among components and will increase the modularity of the whole system. Based on the types of integration and dependencies among processes, following types of *semantic converter*s are introduced:

- Horizontal Semantic Converter: Implements the seman-

tics for *horizontal integration* by encapsulating dependencies among models which are at the same structural and functional level.
- Vertical Semantic Converter: Implements the semantics for *vertical integration*. In order to manage vertical integration, link layer uses hierarchical information from anatomical ontology together with corresponding variable from physiological ontology. Multiscale and multilevel integration approaches will be implemented within *vertical semantic converter*s.

Mediator behaves as a control unit for the network composed of components and semantic converters. Performing validity checks on the integrated models to avoid algebraic loops, compilation of the whole model to build an order of execution to be passed to the *simulation layer* are the responsibilities of the *mediator*.

All the software components mentioned above, compose the structure to represent the network for the information flow, where *components* correspond to the nodes and *semantic converters* are the links. Any type of information flow mechanism can be built with this structure where multiscale and multilevel models can be integrated to represent a detailed model.

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. A detailed example is presented for the information flow trough circulatory system in the next section (Section V).

V. Case Scenario and Results

A case scenario is used to present the proposed solution for the problem of handling information flow among physiological processes and horizontal integration of the information. In the presented case, concentration of an intravenous drug is the information to be carried through the circulatory system. Cardiopulmonary mechanics model from the Physiome Project Model repository [13] 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 intravenous 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].

Models defined in Mathematical Modeling Language (MML) are preprocessed 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. In the presented case, information flow is managed by the circulatory system modeled with the cardiopulmonary mechanics which is composed of 182 *component*s each of which correspond to a physiological variable.

Cardiopulmonary mechanics model constitutes as the intrinsic model for the circulatory system. Model determining the concentration of the intravenous drug corresponds to the extrinsic model. Therefore, components in the intravenous drug model integrates the information from the cardiopulmonary mechanics model and transports the information about the concentration of the injected drug to the circulatory system. These two models are integrated over the cardiac output variable which is defined as an intrinsic component having a constant value in the information flow mechanism.

By horizontally integrating the cardiopulmonary mechanics model with the intravenous drug model, we were able to see the effect of change in cardiac output on the drug concentration in the blood stream. The integration mechanism replaces the constant representation of one variable in intravenous drug model with the regulated variable in cardiopulmonary mechanics model. If the intravenous drug model were to be simulated as is, the cardiac output variable will be a constant and its regulations, changes will not be considered.

Figure 5, shows the part of the framework where the integration of the cardiopulmonary mechanics and the intravenous drug model is performed. The first step in this process is to build the medium for the flow of information, intrinsic components 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 as an *extrinsic* model. Third step is to show how the information flow mechanism can be used to access the variables in the circulatory system. In Figure 5, the third model loaded is an extension of the intravenous 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 the 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. Once the required information is collected from the user, *Mediator* compiles the models, performs the integration, and passes the required information to the simulation step. Simulation is then performed based on the compiled model and the user defined parameters such as simulation start and end times.

VI. Conclusion

Presented framework will provide a development environment where multilevel and multiscale physiological models can be integrated and simulated. The ultimate goal is to enhance the development of both the physiological

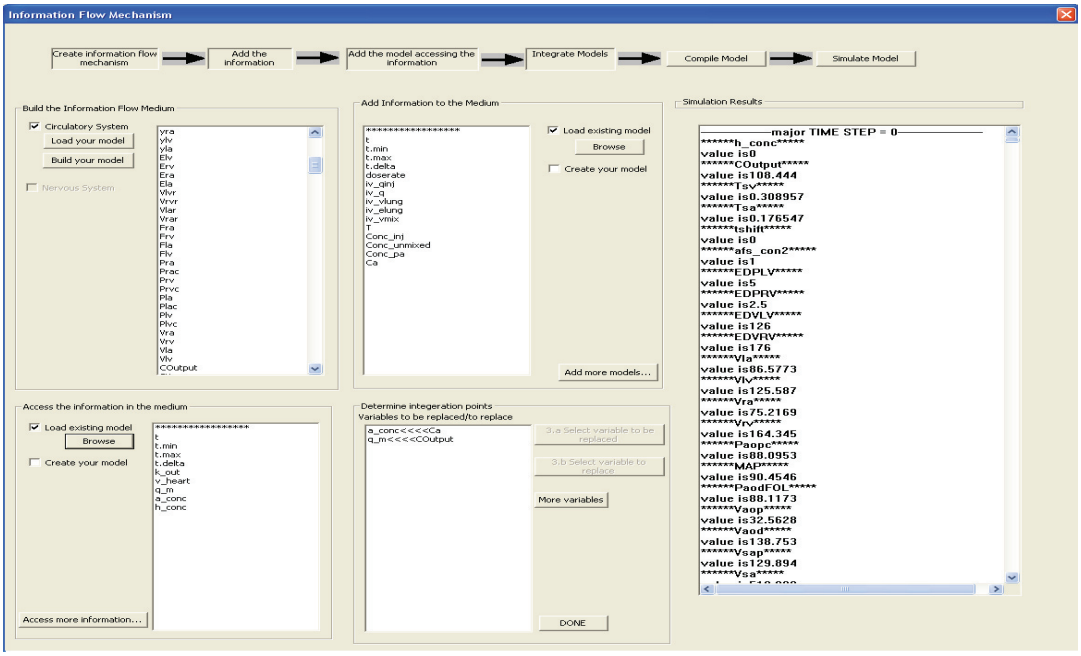

Fig. 5. UI Screen shot: This part of the application directs the user to perform an integrated model. In this case, the information is carried through circulatory system and new information is integrated with drug injection.

models and the integrative approaches. Major components of the system are complete, and 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. With the proposed framework, model development for such complex diseases will accelerate together with the integrative approaches for multiscale models.

REFERENCES

[1] A. Aderem, "Systems biology: Its practice and challenges," *Cell*, vol. 121, pp. 511–513, 2005.

[2] H. Kitano, "Systems biology: A brief overview," *Science*, vol. 295, pp. 1662–1664, 2002.

[3] D. Noble, "Modeling the heart–from genes to cells to the whole organ," *Science*, 2002.

[4] R. M. Berne and M. N. Levy, *Physiology*. Mosby, 1998.

[5] J. B. Bassingthwaighte and H. J. Chizeck, "The physiome projects and multiscale modeling," *IEEE Signal Processing Magazine*, 2008.

[6] "Modelica, a unified object-oriented language for physical systems modeling; language specification 2.0. the modelica association, http://www.modelica.org," 2002.

[7] "Mathworks Inc., Simulink, http://www.mathworks.com/products/simulink."

[8] J. T. Buck, S. Ha, E. A. Lee, and D. G. Messerschmitt, "Ptolemy: A framework for simulating and prototyping heterogeneous systems," *International Journal of Computer Simulation special issue on Simulation Software Development*, vol. 4, 1994.

[9] "SCIRun: A scientific computing problem solving environment. scientific computing and imaging institute (sci), http://software.sci.utah.edu/scirun.html," 2002.

[10] H. Schmidt and M. Jirstrand, "Systems biology toolbox for matlab: A computational platform for research in systems biology," *Bioinformatics Advance Access*, vol. 22, 2005.

[11] G. Higgins, B. Athey, J. Bassingthwaighte, J. Burgess, H. Champion, K. Cleary, P. Dev, J. Duncan, M. Hopmeier, D. Jenkins, C. Johnson, H. Kelly, R. Leitch, W. Lorensen, D. Metaxas, V. Spitzer, N. Vaidehi, K. Vosburgh, and R. Winslow, "Final report of the meeting "modeling & simulation in medicine: Towards an integrated framework"," *Computer Aided Surgery*, pp. 32–39, 2001.

[12] E. J. Crampin, M. Halstead, P. Hunter, P. Nielsen, D. Noble, N. Smith, and M. Tawhai, "Computational physiology and the physiome project," *Experimental Physiology*, vol. 89, pp. 1–26, 2003.

[13] "Physiome project, http://www.physiome.org/."

[14] P. J. Hunter and T. K. Borg, "Integration from proteins to organs: the physiome project," *Nature Reviews, Molecular Cell Biology*, 2003.

[15] "Jsim, http://www.physiome.org/jsim/."

[16] S. R. Thomas, E. Abdulhay, P. Baconnier, J. Fontecave, J. P. Françoise, F. Guillaud, P. Hannaert, A. Hernandez, V. Le Rolle, P. Maziere, F. Tahi, and F. Zehraoui, "Saphir - a multi-scale, multi-resolution modeling environment targeting blood pressure regulation and fluid homeostasis," in *Proceedings of the 29th Annual International Conference of the IEEE EMBS*, 2007, pp. 6648–6651.

[17] R. M. Berne and M. N. Levy, *Principles of Physiology*. Mosby, 2000.

[18] X. Wang, C. W. Chan, and H. Hamilton, "Design of knowledge-based systems with the ontology-domain-system approach," in *Proceedings of SEKE*, 2002, pp. 15–19.

[19] C. Rosse, J. L. V. Mejino, B. R. Modayur, R. M. Jakobovits, K. P. Hinshaw, and J. F. Brinkley, "Motivation and organizational principles for anatomical knowledge representation: The digital anatomist symbolic knowledge base," *Journal of the American Medical Informatics Association*, 1998.

[20] R. Upton, "A model of the first pass passage of drugs from i.v. injection site to the heart-parameter estimates for lignocaine in the sheep," *British Journal of Anasthesia*, 1996.