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ONTOLOGY BASED DESIGN FOR INTEGRATIVE SIMULATION OF HUMAN PHYSIOLOGY

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ABSTRACT

Mathematical modeling of physiological processes of human body has been studied in all levels from cell up to organs and organ systems. Although the initial idea for working on individual models of human physiology was to have a better understanding of the whole mechanism, not enough integrative approaches have been developed yet. To build an integrative framework for physiological processes, the first step should be defining anatomical structure of human body. For the integration of the mathematical models, which represent physiological processes at different levels, horizontal and vertical connection of the anatomical structure is required. In this paper we present the high level design of an application programming interface, which aims to provide integration of multilevel physiological models through an ontology based framework.

1. INTRODUCTION AND BACKGROUND

Considering the human body as a complex system , the problem of modeling and simulating it can be divided into subproblems of modeling the anatomical or physiolocial components at different levels.

Starting from early 1960's with heart models [12], building mathematical models for different levels and scales of human physiology has been an area of interest to multidisciplinary research. Although, extensive studies have been conducted ever since, within the scope of medical simulation and mathematical modeling of biological systems at different levels for human body ; the ultimate goal of this process has been neglected and little has been done in the name of integrating them to model the whole system [8]. In this paper, we present a high level design of a programming interface for integrating mathematical models of physiological processes at different levels to better understand the complete system. We designed an ontology based architecture, capturing the anatomical structure of human body, to enhance the integration of physiological models.

When we look at the efforts to build models for different levels of human body, we see that there are very advanced studies in the cell level, such as modeling of gene networks [3] and complex signaling pathways [2]. Similarly higher levels of modeling for organs and organ systems have been studied intensely. Especially there are detailed models for heart, lung and cardiovascular system. Multiscale modeling approaches for heart and lung introduces the idea of model integration. In the study presented by Winslow *et.al.* [18], model for the electrical physiology of heart integrates sub models from cell to organ level. Similarly, mathematical modeling for lungs requires integration of multiple coupled subsystems, such as conducting airways, respiratory airways, pulmonary capillaries and pulmonary vasculature [5].

While individual models for different levels of human body are being developed, the need for more collaborative and integrative approaches in mathematical modeling of physiological research is realized with *Integrative Physiology* and *Integrative Biology*. One of the successful studies in cell level modeling, contributing to the area of Integrative Biology, 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 [7].

Integrative Physiology 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 [5]. Physiome Project, realizing the importance of Integrative Physiology, 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. Physiome Project also provides tools to enable integration with quantitative descriptions of relations among models and parameter sets to identify these relations.

We argue that, to achieve a more complete understanding of the complex system, which is the human body as a whole, an integrative environment for both anatomical and physiological models is required. Following the Gestalt theory, saying that "the whole is something else than the sum of its parts, because summing up is a meaningless procedure, whereas the whole-part relationship is meaningful" [11]; we realize that the framework enabling integration of these models should be built on a systematic representation of domain knowledge. Therefore we propose a programming interface, which is built on top of an anatomical ontology based architecture, to enable integration of multilevel and multiscale physiological models.

In this paper we will define the problem and its components for building such a programming interface and describe our approach for designing this framework with a focus on the ontology based architecture. In the next section, we will identify the problem, then determine the domain and application specific components. Section 3 gives the details of the high level design of the domain specific components with a focus on the ontology based architecture. Section 4 summarizes the advantages of the proposed method and what we promise with our framework.

2. PROBLEM DEFINITION AND METHODOLOGY

In order to build an application programming interface for integrating different models of human physiology as part of multiscale simulations, we first divide our problem into domain specific and application specific components. Domain specific components are determined based on the structural and functional requirements for modeling physilogical processes of human body. These components are:

- Anatomical structure
- Physiological structure
- Models of Computation
- Information Flow Interface

Having defined these components, information flow interface will handle the model interconnections and integrations using the physiological and anatomical structure.

In addition to domain specific requirements, we have to consider the requirements enforced at the application level, such as visualization and simulation. However in this paper we will focus on the domain specific components.

2.1 Anatomical Structure

The first step in building this integrative environment for such a complex structure, is to define an underlying ontology representing the human anatomy with descriptive, modular part-whole relations. We used the "Foundational Model of Anatomy (FMA)" [17, 16, 14], to achieve this step. FMA is composed of parts to cover class inclusion relationships (Anatomical Ontology), constitutive relations, spatial relationships (*Anatomical Structural Abstraction*), transformational relationships (*Anatomical transformation abstraction*) and metaknowledge for the human body. We adopted the abstraction mechanism proposed by anatomical ontology and anatomical structural abstraction components, which together provide the sufficient and necessary information for conceptualizing the hierarchical structure of the human body and its parts [17].

2.2 Physiological Structure

The second step is to define the physiological models in a systemic way similar to anatomy. To achieve this step, we need a physiological ontology which will enable integrating qualitative and quantitative functional knowledge. There are ongoing projects like *Foundational Model of Physiology* [4], to build an ontology for human physiology. However there is not any available complete physiological ontology yet.

Until a robust and well defined ontology for physiology becomes available, we decided to define a high level abstraction for the human physiology to conceptualize the mechanism. We can generalize the physiology as processes controlling and regulating the important properties of the human system [1]. The state of stability, homeostasis, is defined to be the relative constancy of a wide range of physiological variables. Therefore we have designed our physiological structure on the basis of physiological variables and their stability.

2.3 Models of Computation

The technological improvements (such as, MRI, CT, ECG and EKG) helping to gather physiological data, increased the interest in the applied mathematical modeling in human physiology. As a result of this interdisciplinary effort, physiological processes causing changes in the values of physiological variables such as change of blood pressure, blood temperature, blood glucose levels, concentration of many chemicals can be mathematically modeled.

Models of computation can be thought of as design patterns in object oriented paradigm, which will behave as the core of the solution [10]. Based on this analogy, we can classify the models of computation according to the ways they deal with concurrency and time concepts.

Physiological processes are distributed models. Although mathematical models describing these processes can both be represented with lumped parameter approximations or as distributed models; most of the time lumped parameter models are preferred [9] such as models for the cardiovascular system. For example using the Windkessel model, which is a lumped parameter model, the whole human cardiovascular system can be modeled [15, p.138].

Having this observation, the next issue is classifying models based on different time and concurrency approaches . We have adopted below models from Ptolemy Project [10] to define the following models of computation for describing physiological processes in human body:

- Continuous Time Models: The change of a physiological variable is defined with differential equations in these type of models.
- Discrete Time Models: These are the models which describe the change of a physiological variable with algebraic equations.
- Discrete Events: These are the models, which occur with a specific time stamp during a time course. They do not necessarily contain any mathematical computation, but they effect a physiological variable.

We need to define an interface to handle the integration of different models of computation, which will manage this through the flow of information.

2.4 Information Flow

Mathematically, as described in Section 2.3, physiological processes are distributed processes, which requires connec-

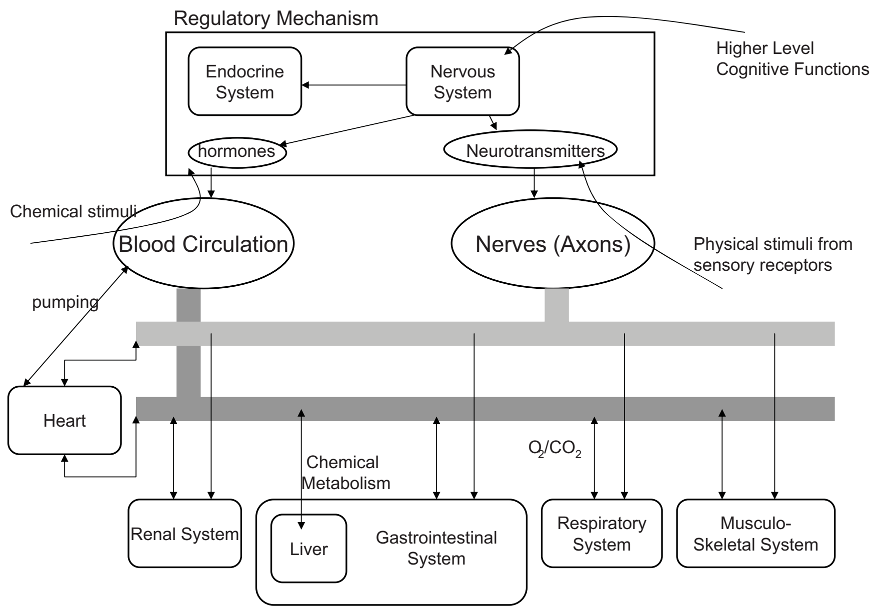

Figure 1: Communication among organs and organ systems with nervous and circulatory systems, showing the requirement for a horizontal connection among anatomical structures.

tion of multiple models. Physiologically, the information encapsulated with physiological variables are distributed to the body by nervous and circulatory systems as in Figure 1.

In Figure 1, we see that organs in a specific organ system or set of organs in different organ systems communicate in a *horizontal* organization through circulatory and nervous system. For example, oxygen enters the circulatory system through the lungs in respiratory system. Calculating the oxygen concentration in liver in the gastrointestinal system, requires communication of these two systems, or more specifically lungs and liver. Mathematical models representing physiological processes in both organs, will share and manipulate the information about the oxygen concentration in blood 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.

For some cases, the level of integration may be limited to a single organ or organ part. For example, in Figure 2 we see the abstraction of mathematical models used to describe the physiology of heart. Heart physiology is dependent on electrical activity, mechanical behavior and chemical dynamics. Although all of these models describe different physiological processes, they are coupled together to describe the heart physiology altogether. Moreover modeling a single physiological processes, such as electrical model of heart, requires a hierarchical approach starting from cell to the whole organ[18]. Therefore integration of such multilevel models, requires a hierarchical, *vertical*, connectivity information.

Based on the connectivity requirements presented with Figure 1 and Figure 2, we identify two types inter-connections for both nervous and circulatory system to handle the information flow among physiological processes at different granularities:

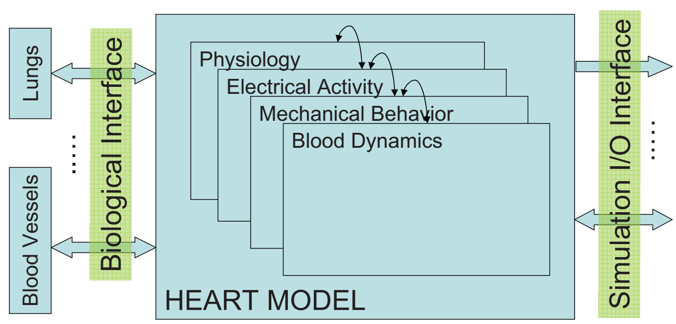

Figure 2: Physiological models of heart. These models are coupled to explain the whole physiology of heart. In order to represent a complete physiology of heart, the models should communicate based on vertical connection among anatomical structures.

- Horizontal connection: Information flow among organs, organ systems require this type of connection information among anatomical entities.
- Vertical connection: Information flow within an organ or an organ part uses vertical connectivity information among anatomical entities.

3. ARCHITECTURE

We have mapped the domain specific components described in Section 2, to a software architecture and defined the following packages:

- Anatomy Structure: Maps the anatomical ontology to a software design

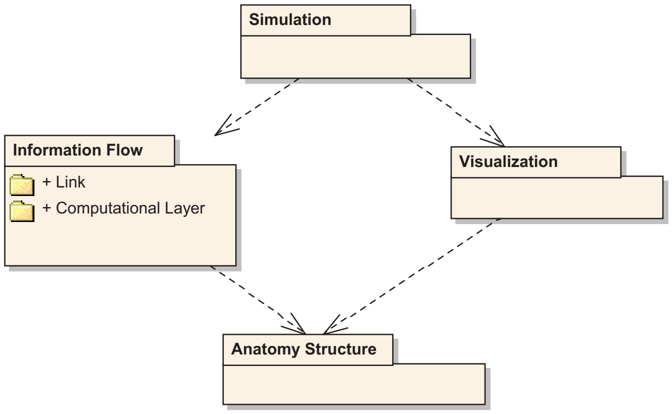

Figure 3: High level design of the programming interface. *Simulation* and *Visualization* are the application specific components; *Information Flow* and *Anatomy Structure* are the domain specific components. Application specific components depend on the domain specific components.

- Information Flow: Physiological structure, models of computation and the interface for flow of information among models are covered.

These are the components extracted from the domain of human anatomy and physiology. We also need to define the components responsible for handling the application functionality :

- Visualization
- Simulation

The packages are designed in a layered structure such that, the anatomical structure information provides the foundational information for the API. Both the domain and application functionalities are layered upon this foundation. Information flow layer and the visualization layer, which require structural information resides on top of *"Anatomy Structure"* layer. The top layer is the application specific simulation layer, depending only on the visualization and information flow layers as in Figure 3.

The ontological components, extracted from FMA, are defined in the *"Anatomy Structure"* package, and detailed design of this package will be explained in Section 3.1. The abstraction for the physiological ontology and the functionality imposed by the physiology domain is defined in the information flow package and explained in Section 3.2.

3.1 Ontology Based Architecture

FMA defines a canonical symbolic model accommodating an instantiated anatomy [16], which suits well with object oriented design paradigm. In order to map the ontology to a software architecture, we have used the implementation of FMA ontology with Protégé system [13].

In FMA, all anatomical entities are classified based on taxonomical and constitutional relationships. Taxonomical relations generalizes all the anatomical entities into three basic classes as *Anatomical Structure*, *Anatomical Set* and *Body Substance*. Constitutional relationships determine the anatomical entities' relationships with the macroscopic organizational unit, *Organ* [16]. FMA ontology categorizes the entities down to the cell level, introducing the smallest organization unit as *Cell*.

"Anatomical Structure" is the base class for all of the physical anatomical entities, except for the body substances such as blood or mucus, defined under the class *Body Substance*. Another abstraction level for the anatomical entity is introduced, to cover the sets of same class anatomical entities with *Body Set* class.

Based on these organizational principles we defined the high level design as in Figure 4.

Although one-to-one mapping from the FMA ontology to a software architecture is possible, defining more than 70,000 anatomical classes and their relations defeats the purpose of object oriented design. Therefore, we chose to prune the taxonomical tree at a level, where the classification is descriptive. As we are building an application interface, introducing new subclasses with new relations based on the scope of the application, is a valid and desired option. In Figure 4, we see the class diagram of the highest level entities, with a high abstraction degree. Nevertheless the attributes introduced at this level is sufficient and necessary for representing physiological models and their connectivity. In Table 1, we see a group of attributes, with the level of anatomy they have been introduced. In order to integrate multilevel mathematical models in the *"Information Flow"* package with the types of connections defined in Section 2.4, we need to have the horizontal and vertical connection information among anatomical entities. In Table 1, we can also see how the anatomical attributes are used for this connectivity information.

As seen from Figure 3, there is also a dependency between the *"Visualization"* package and the *"Anatomy Structure"* package. Spatial relationships among the anatomical entities are required to perform the visualization. The attributes such as "*attaches to*" and "*surrounded by*" , represent the spatial relations with other anatomical entities, that we can use for the visualization functionality (Table 1).

3.2 Information Flow Architecture

This layer defines the physiological structure in "*Link*" package and models of computation in "*Computational Layer* package to define the physiological processes in relation with anatomical and physiological structure as in Figure 5.

3.2.1 Link Layer

The communication functionality of the human physiology crosscuts the structure imposed by the ontology. This increases the tangling among the anatomical entities described in Section 3.1. Therefore, we used the *Mediator Pattern* [6] and introduced an abstract *Mediator* to handle the flow of information (Figure 5). Based on the nature of the flow of information in nervous system or circulatory system, the behavior of corresponding mediator can change, however the idea of controlling the flow of information will be same for all. We decrease the degree of coupling among anatomical

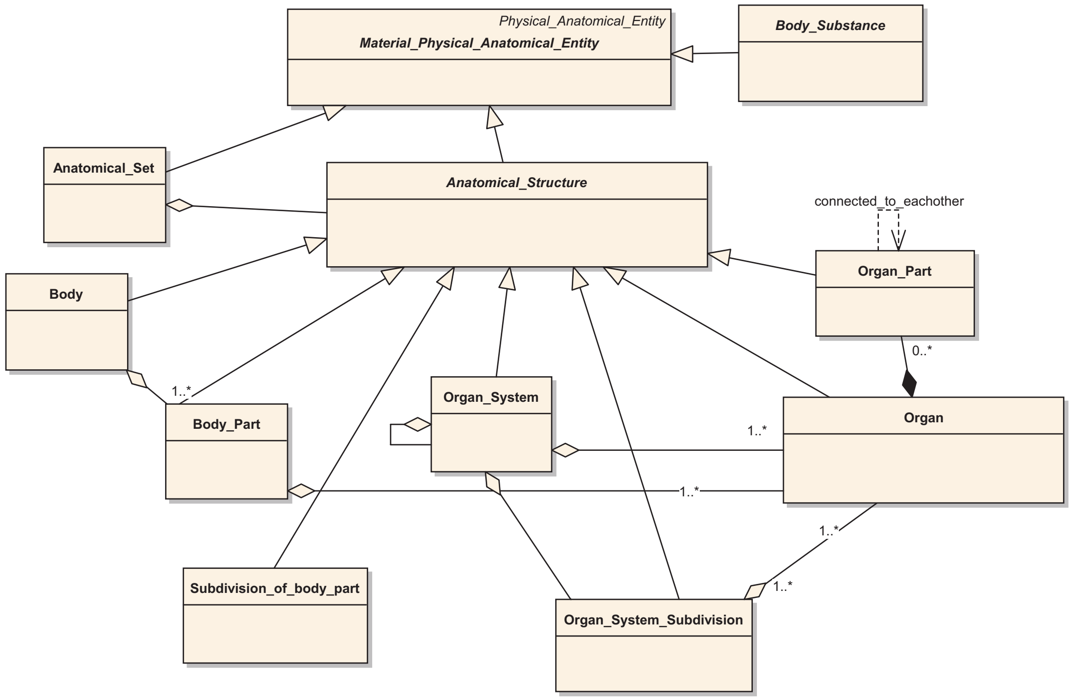

Figure 4: Mapping of FMA ontology to a high level object oriented design based on taxonomical and constitutional relationships. Taxonomical relationships are represented with "*is-a*" relation and constitutional relations are represented with "*aggregation*" relation.

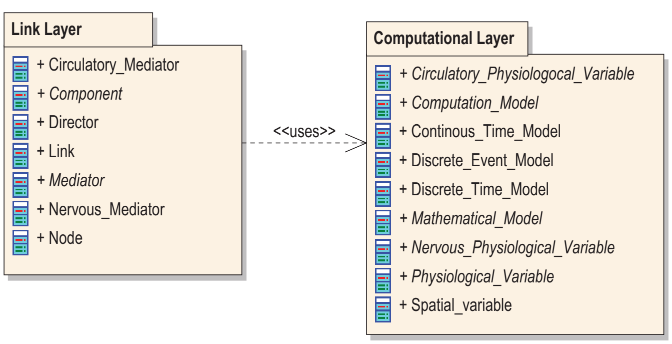

Figure 5: The high level design of *Information Flow* package. *Link Layer* is responsible for the physiological structure and the interface for the information flow. *Computational Layer* provides the models of computation required to build the physiological models.

structures by carrying the responsibility of horizontal or vertical connection of anatomical entities to the mediator. In other words, we encapsulate the integration process within the *Mediator*.

Integration of physiological models, requires considering the individual mathematical models as a whole to perform a multiscale simulation. Therefore, mathematical interpretation of the integrated models will be handled by the *Director* owned by a *Mediator* (Figure 5).

3.2.2 *Computational Layer*

This package defines the physiological ontology of the human body in the level of physiological variables. As we have pointed earlier in Section 2.2, there is currently no available physiological ontology. Therefore, we decided to abstract the physiological ontology to the level of physiological variables, according to the type of information flow they are involved in. These variables are:

- Circulatory Physiological Variables : These are the variables that are processed within the circulatory system, such as blood pressure, blood volume, oxygen concentration in blood.
- Nervous Physiological Variables: Physiological processes in the nervous system are generally transformed as a series of nerve impulses. These impulses, and thus the nervous physiological variables are in either chemical or electrical forms [1].
- Spatial Physiological Variables: Physical location of the anatomical entities have effects on most of the physiological processes. For example, boundary information of a heart muscle will be used for the mechanical models. Therefore these types of spatial variables will be used in combination with other types of variables.

In addition to these physiological variables, which are responsible for the flow of information among processes, we also need variables local to an organ or system. For example, in the nervous system, sensory organs will produce the chemical or electrical stimuli based on the change in another

Anatomical attribute	Level introduced	Used for
arterial supply	Anatomical strct.	Horizontal conn.
nerve supply	Anatomical strct.	Horizontal conn.
venous drainage	Anatomical strct.	Horizontal conn.
part/part of	Anatomical strct.	Vertical conn.
regional part/regional part of	Anatomical strct.	Vertical conn.
constitutional part/constitutional part of	Anatomical strct.	Vertical conn.
tributary/tributary of	Vein	Horizontal conn.
branch/branch of	Artery	Horizontal conn.
continuous with	Material physical Anatomical Entity	Horizontal conn. and Visualization
attaches to	Organ part	Vertical conn. and Visualization
surrounded by	Organ	Vertical conn. and Visualization
contained in	Organ	Vertical conn. and Visualization

Table 1: Some of the attributes that we have mapped to our design, which are defined in the ontology. To be able to handle the information flow among anatomical entities, we will use these variables in the Information Flow Layer. Some of the variables will be used by the Visualization layer as well.

sensed variable. The sensed variable will be local to the sensory organ and the information about the sensed variable will be carried with a nervous physiological variable. However, we still need to represent the sensing process and the transfer of information encapsulated from the local variable to the nervous physiological variable. For such local physiological variables, instances of *Physiological Variable* class will be used.

Another component of *Computation Layer* package is *Mathematical Model*. Based on the determined models of computation in Section 2.3, we defined the interfaces for *Continuous Time Models*, *Discrete Time Models* and *Discrete Event Models*.

4. CONCLUSION

In this paper, we present high level design of an application programming interface, to integrate the multilevel and multiscale mathematical models of physiological processes. The most important advantage of the proposed framework is the ontology based design, which enhances the integration process for different levels of physiological models. The integrative nature of the framework is introduced by the models of computation for physiological processes with an interface for the flow of information between these models. We also introduce a high level abstraction for the physiological ontology in order to modularize the physiological processes. With this approach, we are able to integrate models starting from inter-cell level up to organ and organ system level. In the future, when a detailed physiological ontology becomes available, we will integrate that ontology to our design to make our framework more flexible and descriptive. The proposed framework will ultimately contribute to better understanding of the whole system by adopting an Integrative Physiology approach.

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