Physiomodel – An Integrative Physiology in Modelica

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***Abstract*— Physiomodel (http://www.physiomodel.org) is our reimplementation and extension of an integrative physiological model called HumMod 1.6 (http://www.hummod.org) using our Physiolibrary (http://www.physiolibrary.org). The computer language Modelica is well-suited to exactly formalize integrative physiology. Modelica is an equation-based, and object-oriented language for hybrid ordinary differential equations (http://www.modelica.org). Almost every physiological term can be defined as a class in this language and can be instantiated as many times as it occurs in the body. Each class has a graphical icon for use in diagrams. These diagrams are self-describing; the Modelica code generated from them is the full representation of the underlying mathematical model. Special Modelica constructs of physical connectors from Physiolibrary allow us to create diagrams that are analogies of electrical circuits with Kirchhoff's laws. As electric currents and electric potentials are connected in electrical domain, so are molar flows and concentrations in the chemical domain; volumetric flows and pressures in the hydraulic domain; flows of heat energy and temperatures in the thermal domain; and changes and amounts of members in the population domain.**

I. Inteoduction

Times are changing. Mathematical modeling will no longer require manual numerical solving or the manual algebraic solving of sets of equations. They can be solved automatically by sophisticated algorithms and tools such as Modelica compilers and solvers. So the equations can be written in their natural form, just as they appear in physics textbooks. This gives the user a comfortable environment to build the theories and physiological models in very short time. This comfort also guarantees less errors and more physical consistency. Even better, the connection of these equation- based principles with object-oriented principles makes Modelica [1] a great language for the huge systems that are typical in integrative physiology. Encapsulating physical laws gives useful tools even to users who are not familiar with advanced computer science, physics, or mathematics behind the simulation.

Modelica users can still define the model with functions, but we found that almost everything is better defined as equations without solving the assignments manually. It is also possible to write all the equations in the model into one class. This model will run if all inputs and parameters are known. However, typically there are a lot of equations with the same meaning. For example, the hydraulic resistance equation can be used for different blood vessels or for whole parts of the cardiovascular system. Or the function of specific membrane receptors can play a role in cells, tissues or organs in the same model. If we do not use an object-oriented approach then we have to rewrite all these equations for each usage. The much better way to build complex physiological models is to use components from a library; a library such as our Physiolibrary [2, 3]. Libraries define the basic physical equations of elementary processes. These components are general for many models, so they are tested and debugged across many models in many Modelica environments. The user can also add his own components to the model. These components are typically more complex than the elementary laws of Physiolibrary. For example, our general component for microcirculation is used for each tissue as a part of Physiomodel. This component's parameters can enable or set the combinations of different vasoconstriction and vasodilation reactions.

One could say that reimplemening the models does not bring new knowledge, but we hope that our methodology will be useful for researchers devising their own theories, and also in integrating models together. As smaller examples that new theories can be based on physical laws already implemented in Physiolibrary, we presented a model of pulsatile circulations [4, 5]; and a model of oxygen, carbon dioxide and hydrogen ions binding on hemoglobin [6].

We began our Modelica implementation of the big model with complex models such as Guyton's 'Overall Circulation' [7], Siggaard's 'Oxygen status algorithm' [8], 'Quantitative Human Physiology' and finally Coleman's 'HumMod' model [9]. The integration of these complex models works well because of an object-oriented programing paradigm, combined with well-defined interfaces using physical SI units, physical quantities, physical connectors and physical laws. And the result of integrating the aforementioned models in Modelica using the Physiolibrary is the Physiomodel.

II. Physiolibrary

With Physiolibrary as a free Modelica library we won in library awards at the 10th International Modelica Conference 2014. It is free for commercial and non-commercial purposes under Modelica License 2.0. It is a good alternative platform for student's works or theses as we recognized when teaching bioengineer's classes.

A Types of real numbers

The 'Real', a simple type in Modelica which represents the real number, can have attributes which differentiate the meaning of its values. With the help of these attributes Modelica environments can be more user-friendly, because they can:

- find ***incompatible physical quantities*** in connections or equations
- recalculate the ***physical units*** in dialogs or in outputs
- increase the ***precision*** of results and speed up the calculations

Using physical quantities the compiler generates a warning or even an error every time a user tries to, for example, use pressure in a place where the model expects volume.

Setting parameters using dialogs during the implementation of model can be greatly simplified by specifying the physical units. Some Modelica environments can recalculate many non-SI units into expected SI units inside models. So, if the user uses any Physiolibrary type for his parameter or his variable then these automatic unit recalculations are available.

To ensure the compatibility of all Modelica libraries and models all values must be calculated in SI units during the simulation. This rule can generate strange dimensions for some values. For example, the SI unit for volume is cubic meter, but body compartments are typically measured in milliliters. So the numbers used for calculation will be a million times smaller than the physiologist normally uses. However, this does not matter, because for these types Physiolibrary defines a 'nominal' attribute, which translates the tolerance level from SI units back to the typical nominal values used in physiology.

B Connectors and Components

Each connector in Physiolibrary defines one physical domain (see Table 1). As seen in Table 2, most of the components have analogies throughout the domains. For example, the resistor in electrical circuits has an analogy in the chemical domain as diffusion, because the molar flow of a substance is driven by the concentration gradient in the same way an electric current is driven by the voltage gradient.

To define the mathematical analogies in Table 2 we use the symbols e for effort (for connector nonflow variables) and f for flow (for connector flow variables). If there are more connectors in a component, they are differentiated by index.

Unfortunately many elementary components in Physiolibrary do not have analogies through these domains. The special definitions in Physiolibrary include, for example, the components for chemical reaction, for hydrostatic pressure, for Henry's solubility of gas in liquid, for Donnan's equilibrium of electrolytes on membrane etc.

For each connection of n connectors the Modelica compiler will automatically generate one equation as an analogy of Kirchhoff's current law for flow variables of the connectors and *n-1* equations as equalities between nonflow variables of the connectors.

Connector:		flow variable	nonflow variable
	Chemical	molar flow [mol.s^{-1}]	concentration [mol.m^{-3}]
	Hydraulic	volumetric flow [m^3.s^{-1}]	pressure [Pa]
	Thermal	heat flow [W]	temperature [K]
	Osmotic	volumetric flow [m^3.s^{-1}]	osmolarity [mol.m^{-3}]
	Population	change [s^{-1}]	size [1]
	Electrical	electric current [A]	electric potential [V]

Table 1, Physical connectors in my Physiolibrary compared with electrical connector in the Modelica Standard Library

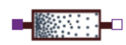
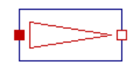
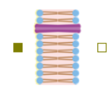
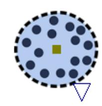
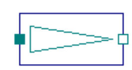
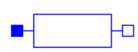
Resistance	Accumulation	Stream
$f_1=G^*(e_1 - e_2)$ $f_1+f_2=0$	$\int f = a$ $a=C^*e$	$f_1 = \begin{cases} F\,e_1, & F \ge 0 \\ F\,e_2, & F < 0 \end{cases}$ $f_1+f_2=0$
G..conductance	C..capacitance	F..stream flow
 Chemical diffusion	 Substance	 Solution flow
 Hydraulic resistance	 Elastic vessel	not applicable
 Heat convection	 Heat	 Heated mass flow
 Semipermeable membrane	 Osmotic cell	not applicable
not applicable	 Population	 Growth, Differentiation
 Electrical resistor	 Electrical capacitor	not applicable

Table 2, Analogies of selected Physiolibrary components based on connectors from Table 1 compared with electrical components in the Modelica Standard Library

The Kirchhoff's law simply says that there is not loss of flows between connected connectors, when each negative flow of the connector comes from its component and each positive flow comes into its component.

III. Physiomodel

The model Hummod, as well as its predecessor – Quantitative Human Physiology (QHP) model, is distributed in its source form as open source (the model and the simulator are available to the public at the website http://hummod.org). The model HumMod (verion 1.6) structure is written in a special XML language and incorporates 991 files located in 149 directories. Thanks to this fact, the model equations and their relationships are comprehensible with difficulty, and many research teams therefore prefer to use older and more simpler models of complex physiological regulations.

Using PHYSIOLIBRARY, we reimplemented, modified and extended HumMod model into Modelica language. The implementation of HumMod in Modelica creates a transparent and legible model structure and therefore offers easier model modifications. The new model – PHYSIOMODEL is richly hierarchically structured, easily modifiable, and "self-documenting". Modelica allows much clearer than other simulation environments, to express the physiological nature of the modeled reality. During reimplementation, HumMod into Modelica language was found more than 30 logical, mathematical or physiological mistakes, which was reported back to the authors. Because of graphical schemes, our implementation is more error-proof. New acid-base model with blood gas transport was here designed and integrated. This extensions of HumMod are more sufficiently describing the status of blood during oxygen and carbon dioxide transport even during respiratory or metabolic acid-base disorders.Each part of human physiology is part of one integrated whole. As a result, only one model of integrative human physiology can represent all known processes of the human body. This model can be almost automatically simplified in various aspects. A specific part of the model can be selected for simulation. The model or its specific part can address the various types of measured data of research. In addition, the consistence of modeled relations are more strongly achieved in comparison with the separated models.

The Physiomodel and HumMod are built upon huge physiological knowledge. The model incorporates more than six hundred references of the original research papers (cited on https://www.zotero.org/groups/physiomodel). Most of them are measurements of specific parts or the parameters of the original model HumMod. However we extended this database with more research papers, which we also integrated in Physiomodel. These references are very useful, because each new version of the model must be consistent with all these carefully selected data.

Physiomodel can be broken down as in general physiological textbooks, where the main chapters are about circulation, respiration, acid-base regulations, electrolytes, water balance, metabolism and diet, the neural system, and thermoregulation. In this top-level diagram, the inputs and outputs of these physiological systems are grouped and distributed using the Modelica expandable connector, which ultimately contains more than three hundred variables generated from current connections.

As an example of Physiomodel components, we present here the body water system (Fig. 2) and its torso water components (Fig. 3). Both these classes are built upon the osmotic domain of Physiolibrary using elementary components with osmotic connectors (Table 1). Namely we use the *OsmoticCell component* to represent volume accumulation as blood plasma, interstitial fluids and intracellular fluids; **t***he osmotic membrane component (Membrane***)** to represent the capillary and cellular membrane permeability of water; and *volumetric flow source components (SolventFlux)* which represent the inflows or outflows of water from other subsystem of Physiomodel as might be caused by hemorrhage, transfusion, intravenous drip, sweating, evaporation or water synthesis by metabolism.

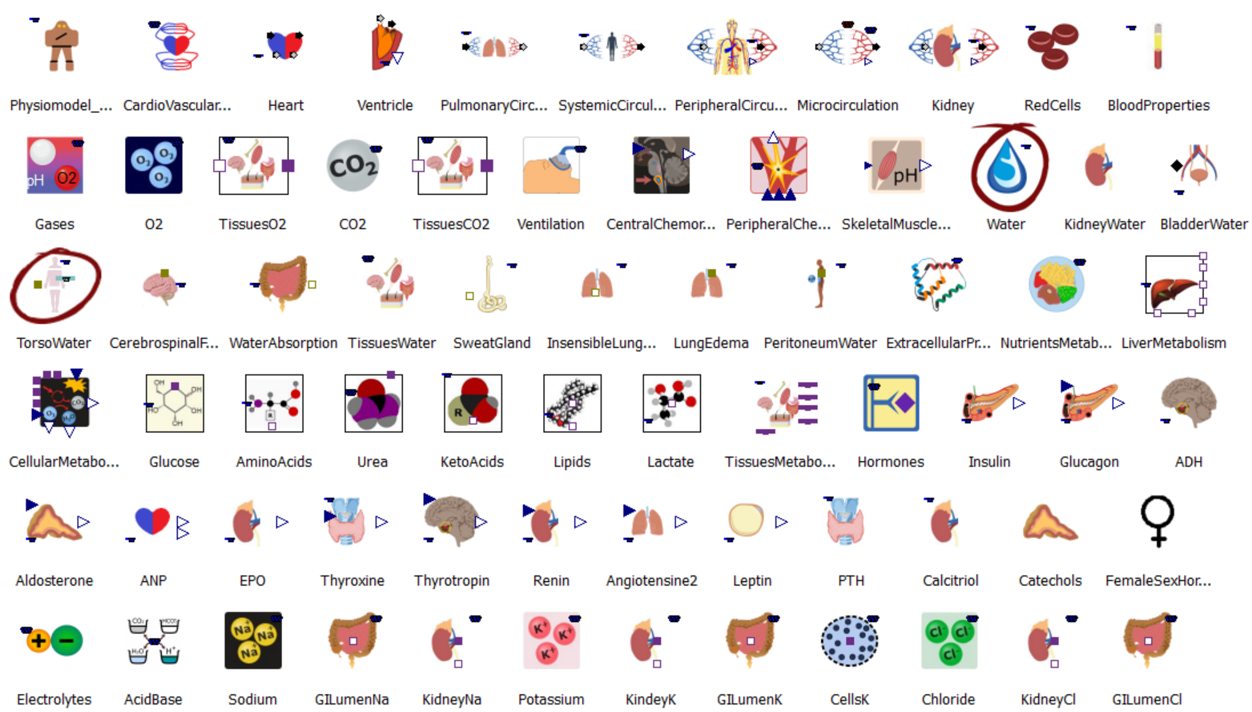


Figure 1, Selected Physiomodel classes. The hierarchical structure of the model is created by using their instances in the definition of other classes. For example the overall model is the first class and it is composed from classes: CardioVascularSystem, Gases, Water, ExtracellularProteins, NutrientsMetabolism, Nerves, Heats, Setup and Status. The components of Physiolibrary are used in the lowest levels of this Physiomodel hierarchy. Marked classes are defined by diagrams in Fig. 2 and Fig. 3.

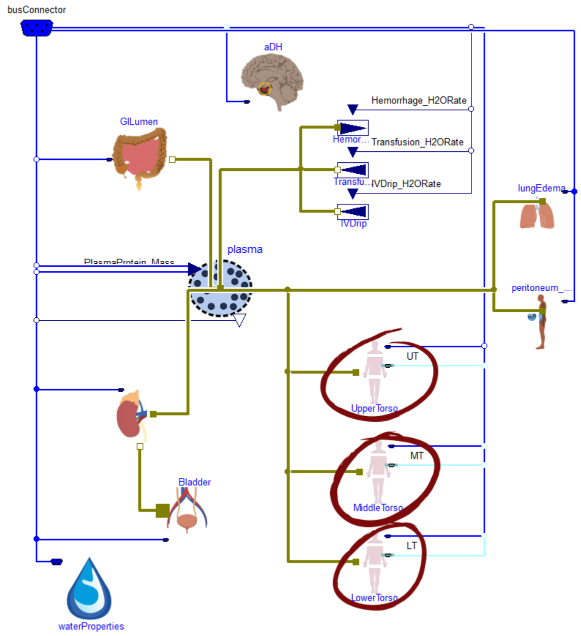


Figure 2, Water as one of the top Physiomodel components. Each thin blue line is a simple real value, each blue tick line is an expandable connector, each yellow line is a Kirchhoff's connection between osmotic connectors. Marked components are instances of TorsoWater defined as a diagram of Fig. 3. This class is parametrized here for three usages: upper, middle and lower torso.

The Physiomodel was used for our project "Virtual Patient" [10], where many theoretical scenarios can be simulated with a virtual environment like a computer game. For example, increasing the capillaries' permeability to water causes a pathological state, where the volume of blood plasma rapidly decreases, outflowing into slightly increasing interstitial fluid. Blood volume and blood viscosity changes result in small cardiac output and insufficient blood flow. The processes that regulate the circulations, gas transport, metabolism and acid-base try to compensate for this new state, but are insufficient. As the patient simulation goes into septic shock, the user can use the dynamic simulation to cure the "patient" by giving dynamical inputs to the model such as respiratory support, intravenous infusions and/or medication using different drug combinations.

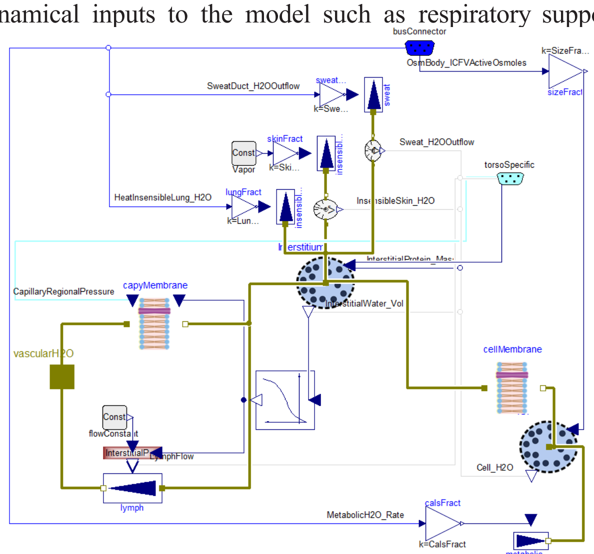


Figure 3, TorsoWater component used for UpperTorso, MidleTorso and LowerTorso instances in the Water component of Fig. 2. Each component is from Physiolibrary with a standardised and well-described meaning.

IV. Open source consortium

We believe that this never-ending development of HumMod and Physiomodel will continue, as we uncover and integrate principles from physiology, physical chemistry, computer science, physics and mathematics. To support this independent development of an open-source description of integrative physiology, we want to establish a non-profit organization together with a group from Jackson/Mississippi (authors of the original HumMod model). This organization would allow its members to utilize this model for commercial and grant projects. We are also open to new partners, new ideas and new cooperation. So if you are interesting in the development or usage of Physiomodel or Physiolibrary, please do not hesitate to contact us.

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