Physiolibrary - Modelica library for Physiology

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Abstract

Physiolibrary is a free open-source Modelica library designed for modeling human physiology. It is accessible on the Modelica Libraries web page at https://www.modelica.org/libraries. This library contains basic physical laws governing human physiology, usable for cardiovascular circulation, metabolic processes, nutrient distribution, thermoregulation, gases transport, electrolyte regulation, water distribution, hormonal regulation and pharmacological regulation.

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1 Introduction

Our laboratory have a long tradition building physiological libraries, starting with the Matlab/Simulink environment [1]. The origin of this Modelica Physiolibrary was in the first version of our HumMod Golem Edition model implementation [2-4], where it was called HumMod.Library. As the successors of Guyton's Medical Physiology School write, the original HumMod model [5] is “The best, most complete, mathematical model of human physiology ever created” [6].

We are also developing many types of smaller physiological models for use in medical education [7-9], so it was essential to separate this library from our HumMod Modelica implementation. This separation improves the quality of the next HumMod release and provides a useful Modelica library to modelers in this bioscience.

The library contains only carefully-chosen elementary physiological laws, which are the basis of more complex physiological processes. For example from only two type of blocks (Chemical.ChemicalReaction and Chemical.Substance) it is possible to compose the allosteric transitions [10] or the Michaelis-Menten equation.

2 Physiology

Physiology is a very progressive discipline, that examines how the living body works. And it is no surprise that all processes in the human body are driven by physical laws of nature. The great challenge is to marry old empirical experiments with the “new” physical principles. Many teams and projects in the word deal with this formalization of physiology, for example: Physiome[11], SBML[12], EuroPhysiome[13], VPH[14], CellML[15] etc. It is our hope that this library helps this unflagging effort of physiologists to exactly describe the processes.

2.1 Display units in physiology

Energy in medicine and chemistry has a very long tradition. One must not be confused by its different units and definitions. The researcher must be aware of multiple definitions of calorie, such as the international calorie, the 15° C calorie, the thermal calorie or the Calorie with a capital "C". The origin of this unit is in the thermal energy needed to heat one gram of water by one degree Celsius. But because the measurement conditions may differ, these alternative definitions are necessary. In physiology it is recommended to use only international calorie as defined in Table 1. The flow of heat/energy is usually calculated in kcal/min, but in physics this is called power and is expressed in the SI unit watts.

Pressure units in medicine are also mainly based on historical measurements. For many years blood pressure was measured by the mercury sphygmomanometer, where the pressure is represented by the change of mercury hydrostatic column height. And because the scale of units on the column is in millimetres the pressure unit is called millimetre of mercury 'mmHg'. There also exists a very small difference between this unit and torrs. It is caused again by variance in measurement conditions.

Many physiological processes are based on electrical principles in the human body. The main cause of this is that each cell has a nonconductive membrane with molecular structures called channels, through which the fluxes of electrolytes can be precisely regulated. Even more, the cells use energy from metabolism to retain a small electric potential between inside and outside. This view leads to a unit called equivalents or "Eq". A charge of 1 Eq, for example, has 1 mol of sodium cations (Na^+). The fluxes of electrically charged ions can be in mEq/min, but in physics the SI unit ampere is more generally used.

Another strange unit describing the amount of substance is the osmol ("Osm"), which has the same value as the mol, but which highlights the property that this substance cannot cross the membrane together with the flux of its solvent.

Unit conversion table (for Modelica environment display-unit setting)			
x kcal	=	4186.8*x	J
x kcal/min	=	69.78*x	W
x mmHg	=	133.322387415*x	Pa
x degC	=	273.15 + x	K
x mEq	=	96.4853365*x	C
x mEq/min	=	1.60808894*x	A
x mOsm	=	0.001*x	mol

Table 1, chosen Non-SI units in physiology

2.2 Chemical domains in physiology

In physiology books, chapters about chemical substances are organized by their types. The main reason for this is that each substance in the human body is regulated in a different way. For example the regulation of sodium is different from the regulation of potassium, and from the regulation of glucose, and so on. This view leads to the idea of having separate models of each substance. The origin of different flows and regulations is the (cellular) membrane. Water and solutions can cross it in different directions at the same time. Crossings occur for different reasons: water is driven mostly by osmotic gradients, electrolytes are driven by charge to reach Donnan's equilibrium, and some solutes can even be actively transported against their concentration or electrical gradients. And all this is specifically driven from the higher levels by neural and hormonal responses.

In Physiolibrary flows and fluxes of solutes are supported mostly by the Chemical package. All parts inside this Physiolibrary.Chemical package use the connector ConcentrationFlow, which defines the molar concentration and molar flow/flux rate of one solute. This is the supporting infrastructure for modeling membrane diffusion, accumulations of substances, reversal chemical reactions, Henry's law of gas solubility, dilution with additional solvent flow, membrane reabsorbtion, chemical degradation and physiological clearance.

For usage examples, please open the Chemical.Examples package.

2.3 Hydraulic domain in physiology

The main usage of the hydraulic domain in human physiology is modeling of the cardio-vascular system. And because there are no extreme thermodynamic conditions, the system can be really simple —it is only necessary to model conditions for incompressible water, at normal liquid-water temperatures and with relative pressure 5-20kPa. This boring thermodynamic state leads to the very simple blocks of hydraulic resistance, hydrostatic pressure, volumetric flow, inertia and finally the ideal block of blood accumulation called ElasticBalloon.

2.4 Thermal domain in physiology

For the human body to function optimally, it is critical to hold the core temperature at 35–39° C. A fever of 41° C for more than a short period of time causes brain damage. If the core temperature falls below 10° C, the heart stops. As in the hydraulic domain, the thermal domain is simplified to these conditions.

In the Physiolibrary.Thermal package, the connector HeatConnector is composed of temperature and thermal flow. The main blocks are: Conductor, IdealRadiator and HeatAccumulation. The heat conductor conducts the heat from the source, such us muscles or metabolically active tissue, to its surrounding. IdealRadiator delivers heat to tissues by blood circulation. HeatAccumulation plays a role in accumulating thermal energy in each tissue mass driven by its heat capacity.

2.5 Osmotic domain in physiology

One of the basic phenomenon of biological systems is the osmotically-driven flow of water. This is always connected with semipermeable membranes. The different concentrations of impermeable solutes on both sides of the membrane causes the pressure at the concentrated side to rise[16]. This pressure difference is called osmotic pressure. Osmotic pressure

is linearly proportional to the concentration gradient of impermeable solutes. The osmolarity (osmotic concentration) is also one of the main indexes of human body balance, called homeostasis. Its value should not significantly deviate for a long period of time from a value of 285-295 mOsm/l.

In Physiolibrary the osmotic connector OsmoticFlowConnector is composed of the osmotic concentration and the volumetric flux of permeable liquid. The two main blocks are called Membrane and OsmoticCell. Here, inside the membrane blocks, it is of course possible to also define hydraulic pressure and temperatures effects on both sides of membrane.

2.6 Mixing domains in physiology

Some physical events take place between these domains. For these events, Physiolibrary includes an additional package called Mixed.

For example, the Mixed package contains the block for the ideal gas equation, which connects the molar and pressure connector. Another example is the block PartialPressure, which combines the ideal gas equation with Henry's law of gas solubility already implemented in the Chemical.GasSolubility block.

2.7 Types and units

The most common errors in HumMod Golem Edition were caused by using bad physical units. The main problem of medical research, articles, and experiments is using obscure units from medicine, pharmacology, biology and non-physics disciplines.

The Physiolibrary fulfills the Modelica ideal of using SI units as the main unit for each variable, and the previously described physiological units are also implemented as the displayUnits for each variable. Using these displayUnits the user sets and sees the "physiological" values. The implementation can also be joined to any unit-correct Modelica models and physical equations without crashing due to unit incompatibilities. The unit support of Physiolibrary is so strong that you even can chose the right unit-typed “input real”/”output real” from the library package Types.RealIO. As can be expected, only the non-specific packages States and Blocks in the Physiolibrary have variables without units.

2.8 States and equilibriums

We define an ***equilibrated system*** (ES) as a non-differential system derived from a differential system (DS) by using zero derivations and by adding additional system equations (ASE). The number of the ASE must be the same as the number of algebraically dependent equations in the non-differential system derived from DS by setting zero derivations. The ASE describes the system from the top view mostly such as the equations of mass conservation laws.

Using Physiolibrary an ES can be represented by simple modification of each model, using all the parts with the “der” operators from the States.State class. The purpose of this is to enable the user to easily switch from the original differential system to an ES. Do not worry, each differentiable class in Physiolibrary is defined with the States.State extension.

To define a model as an ES the user should extend it with partial model States.StateSystem and then define the ASE as the normalizedState vector. The model works still as before, until the Simulation parameter is switched to State.SimulationType.Equilibrated. After that it often changes to one big nonlinear strong component, but without solver stiff or convergence problems.

This style of system implementation also brings other benefits. To see these possibilities, you have to realize that ASE must be invariances in a dynamical simulation. This is really useful for debugging.

For example see the model States.Examples.SimpleReaction_Equilibrated, which implements the equilibrium of the closed system as a solution of two chemical substances with a simple reversible reaction between them.

It is always a big challenge to nicely solve initial values of differential system. However, it should be possible to solve the ES in initial phase. And this is the idea behind the States.SimulationTypes.InitSteadyState option.

2.9 File utilities—input/output manipulations

During the creation and debugging of huge integrated models it is necessary to easily define consistent input, output and test sets of all output variables for some subsystems. Let's imagine that we have a model composed only of subsystems that converge from some constant inputs to constant outputs. It should be possible to substitute each main subsystem for its chosen constant output values as parameters. Comparing the model with these parametric values and the original subsystem can show the wrong part of the simulation.

For example in the huge HumMod model it is necessary to debug smaller parts separately. These tools could be use, because HumMod is the type of constant-converged model. Each subsystem in the first level has the constant input values set for its

output variables. Simulating, for example, the cardiovascular subsystem is possible by creating the high-level system with the original cardiovascular subsystem, but with a constant metabolic, constant thermoregulation, constant hormonal, constant water, constant proteins, constant gases, constant electrolytes and constant status subsystem.

Because the number of output variables for each subsytem changes during development, it is a good idea to have only one list for each subsystem. And generating consistent sets to store, restore, compare initial and final values is possible by the same pattern as presented in the package Types.Example. In this package it is also possible to define a customized way to save and load the variables that connect subsystems together. For this purpose, one has to redeclare the package Types.Utilities with simple functions for reading and writing values, such as is done in the default package FileUtilities.

3 Conclusion

In our opinion the best way to understand this library is to download it from the Modelica web pages at www.modelica.org/libraries and examine the examples. We recommend examining the package Hydraulica.Examples, which provides an example of a simplified cardiovascular system; the package Chemical.Examples, which provides an example of allosteric hemoglobin oxygen binding; the package Osmotic.Examples, which simulates cell volume in hypertonic and hypotonic environments; and finally the package Thermal.Examples, which simulates the heating of circulated blood inside active muscles.

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