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Integrative Physiology in Modelica

by

**Marek Mateják**

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Chemical library, Physiolibrary and Physiomodel – a Modelica support for integration of hybrid ordinary differential equations of physical chemistry, thermodynamics and hydraulics into one model of human physiology

(Dissertation thesis)

Supervisor: Doc. MUDr. Jiří Kofránek, CSc.

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Motto:

“Science is a method for deciding whether what we choose to believe has a basis in the laws of nature or not.”

Marcia McNutt

# Introduction

This works will show that it is possible to implement very complex mathematical description of physiology. It will show that it is much better to have one more detailed dynamical model with physical-based equations than plenty of simplified models with rough mathematical approximations. It will show that more detailed model must not bring more and more unknown parameters.

If we describe some system in physics, there can be many equations, however with only a few well-known constants. For example, an intracellular aerobic metabolism of glucose, lactate and fatty acids to produce defined amount of Acetyl-Coenzyme A. The simple version must have some unknown parameters, from which will be calculated the ratios between the intakes of the substances by the metabolism. The values of these parameters are not easy to estimate and measure. However, for the more detailed complex model it is possible to create whole metabolic pathways and calculate the molar flows from well-known and described chemical reactions. Yes, finally there is an option to calculate the parameter of simplified model from the complex one. But the question is: why to do this? As has been told the computer is fast enough and there is always better to extent or modify the complex detailed physical based model than some of its approximation.

The theory is one thing and the reality other. For some reason people love the simple models, because they are simple. They do not believe in the robust tools designed for building, checking, optimizing and simulating of the huge models. They do not believe in huge models, because until today it was typically a very unreadable set of assignments full of mistakes. And that is the reason why, the readability and the error-resistance of the complex models is the main goal of this thesis. All described physiology (with exception of the section 0) is with this aspect implemented by the author in [Modelica](https://www.modelica.org/) using best practices and features described in section 2. In the section 3 is shown, that each physical law is represented by the author as one equation in the code hidden behind the library component. Using this [Physiolibrary](http://www.physiolibrary.org/) and [Chemical](https://github.com/MarekMatejak/Chemical/releases) library there is by author of this thesis reimplemented and extended the huge model [HumMod](http://hummod.org/) 1.6, the biggest integrative physiological model of the year 2012. During reimplementation there was done more than thirty corrections by author of this dissertation thesis, as described in the last subsections about each main subsystem of [Physiomodel](http://www.physiomodel.org/) (sections: 4.1.5, 4.2.6, 4.3.9, 4.4.6, 4.5.5, 4.6.6, 4.7.3 and 4.8.1). The biggest extension is the new gases transport and acid-base model as described in sections 4.4.1, 4.5 and 6.1. In the section 4 is shown that also each part of the model is a component, which can be used and parametrized as many times as is necessary. Even more, all these components can be created hierarchically by diagrams as an analogy with electrical circuits. This graphical representation has the exact mathematical meaning with the physical laws in the lowest level of the hierarchy. Do not be confused, the talking about physiology in the section 4, similar as in each physiological books, are really descriptions of the running mathematical model behind in the specific hierarchical level. This is a result of the last generation of object-oriented equation-based software tools, which allows to exactly map almost each physiological terminology through the physics to the mathematics.

## Models From Mississippi

One of the first integrative mathematical models of human physiology was designed by (Guyton, et al., 1972). This model was integrates the most necessary relations to describe essential hypertension. Because this pathology include cardiovascular circulation, renal functions, Renin-Angiotensin-Aldosterone-System (RAAS), vasopressin and fluid balances, the model was quite complex to describe state of patient in period of minutes, days and months. It was compared and partially fitted to dog nephrectomy experiments. The model well describe also the regulation of cardiovascular system connected with extended water volume, which is caused by kidney function failure. It can give an answer to the increased blood flow in acute phase and the increase of blood pressure in chronic phase after hormonal inducted vasoconstriction (Guyton, 1991; Guyton and CE Coleman, 1973).

The power of integration was very strong and this model becomes the base of the next developments. Guyton and coworkers saw the interactions between regulations at different time scales and they can elegantly describe long term pathological processes. Guyton’s Textbook of Medical Physiology becomes the bestseller translated into at least 15 languages. And it is still upgraded even today with new editions in memorial.

The development of the model continued by more detailed cardio-vascular and body fluids regulations (Guyton, 1981; Guyton and CE Coleman, 1973; Guyton, et al., 1975). In 1983 Thomas G. Coleman, the Guyton’s coworker, published the model called “Human” (Coleman and Randall, 1983). This model becomes more interactive, based on the standard medical situations and cure by physicians. The user can simulate the cardiac failure, the renal failure or hemorrhage. And he can interact during simulation as setting infusion, transfusion, artificial ventilation, some selected drugs or/and dialysis. This model becomes the virtual simulator designed for teaching medical students. Even the interface was very simple, the teacher and the student can very well examine the state (described by physiological quantities as blood pressure, heart rate, ventilation rate, and so on) and cure them. The model was also reimplemented to [web version](http://placid.skidmore.edu/human/index.php) by Roy D. Meyers, Leo D. Geoffrion and Chris L. Doherty.

The usage of the model becomes more than only description of development of hypertension. They start to examine the microcirculation of tissues, the more detailed function of kidney connected with complex homeostasis, the ventilation and other. The scientific level of Mississippi University of Medical Center grows up also in one hand with NASA cooperation on interesting physiological researches such as in the project Digital Astronaut (Summers and Coleman, 2002). Estimation and validation of experiments in microgravity or in artificial environments are still one of the goals of the model. Even there was many type of simulations, there was only one model describing one organism at different setting and at different conditions.

In year 2005 was released the next version, called “Quantitative Circulatory Physiology” ([QCP](https://www.umc.edu/education/schools/medicine/basic_science/physiology_and_biophysics/core_facilities(physiology)/free_qcp_software_download.aspx)) (Abram, et al., 2007). These model continues in the style of the Human. Dr. Coleman extracts the parameter sets from the model. This allows to create a patient using separate file with parameters. Even there are more than one thousand parameters of the setting, the most of them can be copied or scaled.

The next improved versions was called “Digital Human” or “Quantitative Human Physiology” ([QHP](https://www.umc.edu/uploadedFiles/UMCedu/Content/Education/Schools/Medicine/Basic_Science/Physiology_and_Biophysics/Facilities/Modeling_Workshop/QHP07PreviewVersion.zip)) (Hester, et al., 2008). This model separate even the equations from the compiled executable file. Dr. Coleman define the new xml-based language of physiology formalization. Using these tags there is possible to implement the set of differential equations and implicit equations. To read these xml-files we designed the xsl-template for Mozilla browser called [QHPView](http://patf-biokyb.lf1.cuni.cz/wiki/projekty/qhp2007), which allows to read the equation in more human readable style. Also the graphical user interface was implemented using specific xml-language, what allows to design the application just by editing of these files. This mode has more than four thousand variables defined mostly as real [physical quantities](https://en.wikipedia.org/wiki/Physical_quantity). This model was in year 2010 renamed to “[HumMod](http://hummod.org/)” (Hester, et al., 2011; Hester, et al., 2011). Having more than 4500 physical quantities definitions belongs the HumMod to the biggest model of the complex human physiology.

## Formalization of Physiology

The building of mathematical models is tightly connected with the formalization process. The advantage of formalized description of examined reality using mathematical relations is that the deduction of behavior of examined objects can be done by solving the equations. The equations does not need to be solved manually, because typically it is the work for computers. These solution of differential equations simulate the behavior of the real object during period of time. It is called **computer simulation**.

One of the first formalized mathematical model in physiology was simplified model of neuron in 1943 by (McCulloch and Pitts, 1943). Five years later in 1948 was invented the compartmental approach for pharmacology by (Sheppard, 1948). Then model of excitable neural membrane was published by (Hodgkin and Huxley, 1952). In 1954 was designed also two compartmental models of respiration homeostasis by (Grodins, et al., 1954). In sixties with development of first computers became more complex models such as fist complex blood gases transport model (Grodins, et al., 1967) or regulation of blood circulation with body fluid balance (Coleman, et al., 1967). In seventies started to be published the complex models such as the mentioned Guyton’s models from Mississippi (Guyton, et al., 1972) or the models of homeostasis and body fluid balance by (Ikeda, et al., 1979). Personal computers in eighties and nineties makes from mathematical modeling one of the standard methods in physiological research. Nowadays physiological formalization have a new dimension thanks to international project [PHYSIOME](http://www.physiome.org/), which is the successor of the famous project [GENOME](http://web.ornl.gov/sci/techresources/Human_Genome/index.shtml). The goals of the project Physiome and the European project part called Virtual Physiology Human - [VPH](http://physiomeproject.org/about/the-virtual-physiological-human) is the formalized description of physiological functions. The basis are computers models of the physiological parts of the body (Bassingthwaighte, 2000).

Practical usage of these formalized model is todays concentrated to education using smart robotic simulators to emulate real situations in critical care medicine, such as mannequins from [Leardal](http://www.laerdal.com/us/) Company or [METIMan](http://www.caehealthcare.com/patient-simulators/metiman) from CAE Healthcare. There are also a huge set of educational interactive software based on physiological models starting from [HumMod](http://hummod.org/), our [Physiological Atlas](http://www.physiome.cz/atlas/) or our Virtual Patient. The new perspectives of the usage of the complex physiological models could be hardware-in-loop devices for automatic monitoring and curing of patients, improving product-life-cycle management of pharmacological drugs as simulated testing before clinical trials. Absolute futuristic vision includes the usage of the model for personalized medicine. The simulation of the selected patient is not possible today because of lack of methods to effectively set all the parameters of the complex model. However, leaving default values or simple scaling with type of pathological problem, height, sex, age, surface of skin or height is many time sufficient to observe the main implemented physiological principles even for the particular object.

## Goals – integrative model(s) in Modelica

Until this age there was a lot of options how to simulate a mathematical model using computers. Starting with analog or hybrid computers and finishing with todays sophisticated software for numerical solving of differential equations.

The woks will deal with two hypothesis:

**Hypothesis 1:**

***Modelica®, as the last generation of sophisticated industry tools designed for dynamical simulation of huge complex systems and machines, is suitable for exact formalization of integrative human physiology.***

**Hypothesis 2:**

***Mathematical formalizations of practical physiological knowledge about one organism is possible to integrate into one complex physiological model.***

If we want to take a physiology as science, we need to exactly describe the principles by the laws of nature.

If you need to create some mathematical equation without physical background, then you are just describing the data. Without the physical description are the data more valuable than their interpolation or worse – extrapolation functions. These measured relation between variables is valid only at the same conditions. And here is the main problem of the non-physical physiological researches. How to specify these conditions? Fortunately, because of homeostasis there can be assumed that many values are in normal ranges. However, not all unmeasured variables must be always in their mean values. And it can be hard to select the objects, to achieve the isolated conditions and to measure all connected independent variables. Going deeper in one hand with physical bases of processes it becomes more and more simplified. The parts of the physiological pathways can be already well described in physical level or at least there are known the significant connection between elementary processes. And in circle of research iterations the experiments can be more focused only on the unknown elementary interactions, which is today typically very specific research about one type of molecule. Going back to the top level the work could be finished by describing of the first experiment - the idea of the beginning of investigation, which is many times lost or hidden as almost useless example of usage comparing with potential of the results. This process is called an integration.

Nowadays are the base principles of physiology already described. These descriptions can be built on only a few physical laws as described in section 3. For exact definition of the physics behind it is no need for long chapters in books, conversely a mathematical equation is more than thousands word.

Kittnar, Otomar, and Mikuláš Mlček. *Atlas fyziologických regulací*. Grada Publishing as, 2009.

Modelica® is definitely the last generation of computer equation-based object-oriented language for physical modeling as is described in section 2. It contains all necessary support for exact definition of elementary physical laws as shown in my implementation of Physiolibrary (section 3) and also the support for robust integration of complex systems as shown in my implementation of a complex model of physiology – Physiomodel, which is described in section 4. By creating these two software extensions of Modelica environments I want to demonstrate the positive answer of the hypothetical question above.

* rovnice - skupiny rovnic - konektory - rovnake deje s parametrizaci

Imagine the power to develop complex physical human health simulation just by dragging, dropping and connecting of small amount of components from prepared library to schemes. Schemes such as electrical circuits with connectors independent of direction of calculation. And each of this scheme can be used many times in many other schemes with different values of parameters for each usage as tissues, cells, organelles, receptors, macromolecules are understood.

# Methods

## Physical principles

Generalization of physical laws leads to similar principles between many physical domains. Motivation is not only to have similar mathematical expressions, but also to use prepared methodology from one domain to another. For example an electrical circuit diagrams can be generalized for chemical, osmotic, hydraulic or other non-electrical systems. To do this, it is necessary to find analogies in physical quantities and physical laws. With only two quantities can be described the state of subsystems at interfaces. One of this variable is flow in term of [Kirchhoff’s law](https://en.wikipedia.org/wiki/Kirchhoff%27s_circuit_laws), i.e., the sum of connected flows is zero at each place in scheme. The second has to be non-flow in the meaning that it has the same value in each connected side. The flows are usually changes of some quantity in time such as volumetric flow, molar flow, heat flow, electric current, magnetic flux or mechanical force. The non-flows should be some effort such as pressure, electrochemical potential, temperature, electric potential, magnetic potential or space position. The most of physical laws from mentioned physical domains can be represented using equations with mentioned flow and non-flow physical quantities, for example the hydraulic resistance, diffusion, thermal conduction, Ohm’s law etc.

### International system of units

As a result of the very long tradition in medicine the values are still represented in “medical” units instead of physical units of international standard ([SI](https://en.wikipedia.org/wiki/International_System_of_Units)). Even in the last medical devices are still used mmHg, calories, degrees of Celsius and many others. The problem is that this units are more connected with type of their measurement than they usability in calculations with physical laws. However, almost always exist the simple recalculation between “medical” and physical SI units. In Modelica is a consensus that the running simulation is always in SI-units and recalculation from/to “medical” units can be done only before starting or after finishing of the simulation.

Table 1, Selected non-SI units

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Unit conversion table | | | | |
|  | 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 |
|  | x litreSTP | = | 0.044031617\*x | mol |
|  | x litreSATP | = | 0.040339548\*x | mol |
|  | x litreNIST | = | 0.041571200\*x | mol |
|  | x iu of Erythropoietin | = | ? | mol/m3 |

Energy in medicine and chemistry has been observed for very long period of time. 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. However, 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 millimeters the pressure unit is called millimeter 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 1eq, for example, has 1mol 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.

For gases, it is common to measure the amount as volume, which for specific measurement conditions is equivalent to the number of molecules. The International Union of Pure and Applied Chemistry ([IUPAC](http://www.iupac.org/)) set this standard condition for temperature and pressure ([STP](https://en.wikipedia.org/wiki/Standard_conditions_for_temperature_and_pressure)) precisely at 0°C and 100kPa. But other standards exist. For example, SATP is measured at 25°C and 100kPa, or the standard measurement condition at the National Institute of Standards and Technology ([NIST](http://webbook.nist.gov/chemistry/)), which is 20°C and 101.325kPa.

Chemical substances can be quantified many ways, typically as amount of substance in moles which after multiplication by Avogadro constant (6.02214129(27)×1023 mol−1) gives the number of substance particles. The amount of pure substance can be expressed from its molar mass, because each atom has known and recorded its molar mass in table of elements usually in unit Dalton (gram per one mole). However, each substance has different molar mass and as a result the conversion from mass to moles is always dependent on type (composition) of substance.

In physiology are wildly used also the units for direct-unmeasurable substances. Such small concentrations as 10-12 moles per liter are almost impossible to measure directly and only the indirect measurements with immunoreactions or biological effects are known. But the effect of some substances at these small concentration could be so crucial that they need to be somehow calculated in physiological models. Most of these substances are called hormones, but some could be also enzymes (renin) or cytokines (erythropoietin). Pharmacological [international units](http://www.who.int/biologicals/expert_committee/en/) of this substances are define as ratios to some extracted and purified standardized sample which has also unknown molar concentration, but known and well described biological effect. As a result the pharmacological international unit of substances have not many times any equivalent in SI units, but it need to be used in physiological calculations as they are. The danger of usage of these units is huge especially in pathologies, because their biological activity is many times species dependent and is usually defined within a “normal” population. For example the diabetes mellitus type 2 is present an insulin resistance, so the biological activity of the same amount of insulin for these individuals is totally different as in healthy one.

### Redundant physical quantities

Some standardization should be done also with definitions of physical quantities. For example each two variables in the reciprocal relation, connected only with trivial equation a=1/b, the handling of both does not bring any additional information to the model, because their physical meaning is the same. Even the zero-infinity numerical problem can be very easily solved by selecting variables like the smallest representable floating point number or like the highest representable floating point number which are typically far enough from tolerance limits even for very long simulations.

These couples of reciprocal quantities are derivable from almost each physiological parameter such as hydraulic conductance - hydraulic resistance, hydraulic compliance - hydraulic elasticity, frequency – period time, solubility – volatility, dissociation coefficient – association coefficient etc. To simplify this situation is better to select only one of each couple and build the physiological and chemical laws above as usually in physics which helps a lot with elimination of redundancies inside shared interfaces.

Bad practice is also to use unitless logarithm or other non-unit, non-physical variables in interfaces. Even if user has a good documentation how to convert this values. Values should have always the analogy in physical quantity, which are more user-friendly and more intuitive for next development.

### Conservation laws

The next step of physiology formalization is identification of physiological systems as physical systems. Based on interactions with environment there are [closed](https://en.wikipedia.org/wiki/Closed_system) and [open](https://en.wikipedia.org/wiki/Open_system_(systems_theory)) systems. The example of open system is oxygen transport, where is non-zero flow of oxygen from environment to body. In closed system are not interactions with environment. For example the chemical system of elementary particle in all its forms and in all places in the body without its exchange with environment is the closed system for the particle.

The [laws of conservations](https://en.wikipedia.org/wiki/Conservation_law) apply to closed systems. Energy, mass, amount of substance nor electric charge cannot be created from nothing. In dynamic models it is very intuitive, because there is a rule that input flow to one component is always output flow from another components etc. However, in steady-state calculation (section 3.3) must this system equation be written explicitly, which is not many times so intuitive. Because in steady-state are flows from/to components equal to zero.

## Modelica Principles

Modelica is an object-oriented, equation based computer language, which is standardized and maintained by Modelica Association ([www.modelica.org](http://www.modelica.org)). The non-proprietary standard of this language is supported by many other projects, companies and organizations. As a result there are available many environments for this language. For example [Dymola](http://www.3ds.com/products-services/catia/products/dymola/latest-release/), [OpenModelica](https://openmodelica.org/), SimulationX, JModelica, CATIA Systems, CyModelica, MapleSim or Wolfram SystemModeler.

My Modelica extensions called [Chemical](https://github.com/MarekMatejak/Chemical) (section 3.4), [Physiolibrary](https://github.com/MarekMatejak/Physiolibrary) (section 3) and [Physiomodel](https://github.com/physiology/Physiomodel) (section 4) should be running in all these environment, which support the [Modelica standard 3.3](https://www.modelica.org/documents/ModelicaSpec33.pdf) and [Modelica Standard Library 3.2.1](https://github.com/modelica/Modelica).

### Floating point numbers

From mathematical point of view the domain of real numbers has infinity members. How it is possible that it could be representable by finite small number of bites, i.e., 32 or 64 ones and zeros? The answer is by approximations. There must be always some limits of precisions, some tolerances. [Floating point](https://en.wikipedia.org/wiki/Floating_point) numbers are represented by scientific notation with mantissa (a) and exponent (b) as a\*10b. Both mantissa and exponent are represented by fixed number of bites. At single-precision floating point format there is one bit for sign, 8 bits for exponent and 23 bits for mantissa. This representation gives smallest number as 10-127, biggest number as 10127 and eps (the biggest number such as 1.0 + eps = 1.0) <10-6. This 32-bit precision is sufficient for the most common cases, but for specific calculations better precision exist. The 64-bit called as double-precision floating-point format has 11 for exponent (with theoretical range from 10-1027 to 101027) and 52 bits for mantissa (with eps<10-15).

Even the ranges and precisions are limited, the floating points calculations brings for user another traps. First of all is expressing equality of real numbers. For example, what does it means, if we say that x is equal to zero such as condition x==0? If the number x is set to zero by user and it does not change by calculation its value really remain zero, but if it is calculated it is always calculated with some precision. It means that the test of equality have sense only inside this tolerance range. If we have set tolerance to 10-3 then we should be satisfied with numbers greater than -0.001 and less than 0.001. Otherwise the solver may reach the limits of number representations and/or does not reach the equality any more.

The user tolerance definition for elementary mathematical operations are not needed, but it is necessary for iterative numerical methods. The most common are numerical solving of differential equation (such as Euler method, DASSL and other) or numerical solving of non-linear equations by iterative approximations (such as Newton method). At first look it seems that it is needed the tolerance for each tested variable in error condition of that algorithms. But this could be handled only by one relative tolerance and scaling of the variables. For this scaling Modelica uses the attribute ‘nominal’, which could be included in every real variable.

### Object-oriented programming

[Object oriented programming](https://en.wikipedia.org/wiki/Object-oriented_programming) is one of the greatest step in computer science. The programing of huge applications and systems becomes more simplified with re-using and extending of already defined [objects](https://en.wikipedia.org/wiki/Object_(computer_science)). Idea of an object as definition is very intuitive, because it copies the human language and thinking. Each defined term is an object, which can have more occurrences. Occurrence of object definition in the next code is named an [instance](https://en.wikipedia.org/wiki/Instance_(computer_science)).

Each object can have properties. The property could be primitive variable as number, text, true/false value or also an object. This can create hierarchical decomposition from one system as one object to its subsystems as more and more detailed definitions of the owner parts. Especially in physiology are these patterns everywhere. Having object for chemical reaction, chemical substance, organelle, membrane channel, cell, membrane, tissue or physiological system it is possible to compose new detailed objects as huge models of physiology using already described objects just by choosing the right parameters of these new instances.

It is not necessary to make decomposition of problem from up to down or vice versa, because object-oriented thinking just support to start everywhere. There is only one condition for effective object-oriented programing: *The minimization of object number at the same time as the minimization of instance number to describe the same system by the same rules*. This process is already used in mathematic or physical science, where the whole science can be exactly build from small number of base rules by finite minimized number of definitions.

These idea is hidden also in medicine books, where many principles or object are generalized and finally can be applied to many parts of the body systems. For example, one family of membrane receptors can be used in many pathways and can interact with many effectors.

The computer language principle is easy. As minimal example we define two objects: class B and class A. Class B has only one parameter p, which can have in each instances of B different value. Class A as an example of class composition contains two instances of class B, first with parameter set at 1 and second with parameter set at value 2.

class B "Definition of class B"

  parameter Real p "Real number parameter";

end B;

class A "Definition of class A"

  B b1(p=1) "First instance of class B";

  B b2(p=2) "Second instance of class B";

  B bArray[100](each p=3) "Array of one hundered instances of class B";

end A;

It is a good practice to write names of classes starting with capital letter and name of instances starting with lower case. The object-oriented pattern include any combination of parameters, variables and instances inside class definition. Other more sophisticated rules of object-oriented programing in Modelica could be described as a modification of this principle. The instances, variables and parameters can be hidden or publish outside the class just using the prefix ‘private’, ’protected’ and ‘public’, which gives useful restriction for next users called [encapsulation](https://en.wikipedia.org/wiki/Encapsulation_(object-oriented_programming)).

Modelica language brings an analogy of these classical textual representation using graphical diagrams. Usually is definition of each class accessible as an icon in the left side of environment called ‘Package Browser’. These classes in could be as simple as elementary mathematical operation in Figure 1 or very complex classes, which could be hierarchically composed from other classes.

Figure 1, Standardized definition of class Gain inside Modelica Standard Library (MSL).

To make an instance from any class in ‘Package Browser’ it is necessary to have opened your class in diagram mode and drag&drop the selected class. Usually it is not possible to modify integrated library classes, so at first it is necessary to create ‘new Model’ (using menu command: File > New > Model) with unique name ‘MyClass’. Any class instance could be added to ‘MyClass’ just by drag&drop of icons from ‘Package Browser’. One must be careful, because double click to any class in ‘Package Browser’ can causes switch of class definitions.

Figure 2, Action sequence of inserting class instance

The restricted class called ‘model’ without connectors could be flattened, translated and simulated with all its instance trees. It is because they have section ‘equation’, where are defined all equations and connections between instances, which are needed to calculate whole behavior (defined by the same number of equation as the number of unknowns). The [Open Modelica Compiler](https://www.ida.liu.se/labs/pelab/modelica/OpenModelica/OpenModelicaDevelopersCourse/resources/slides/4-OMC%20Compiler-overview-slides.pdf) in first step translate this model structures into flat model, where the same equation and algorithm are extracted but not using object-oriented class definitions. This step can be done fully automatic and can generate huge amount of code comparing with original object-oriented representation. Then the compiler automatically translate this flattened model into lower level computer language such as [C/C++](https://cs.wikipedia.org/wiki/C%2B%2B) is. This code is running as typical computer program with inputs such as initial setting and outputs such as results of simulation during simulation time interval.

### Connections

Each library class has some possibilities to connect their instance each together. In the case of restricted classes called ‘block’ (as ‘Gain’ on Figure 1) they are only causal connectors, which can be ‘input’ or ‘output’ variables. The restricted class called ‘connector’ is here used only as a substitution of elementary type for real number (‘Real’) with causality direction prefix. After inserting any block instance to ‘MyClass’ there will be visible all input and output connectors. Connections of this type of connectors are intuitive – each output can be connected to many inputs with the meaning, that connected variables will have always the same value.

Figure 3, Action sequence of connecting connectors

Because the complex parts of model could have many inputs and outputs it exists in Modelica a special class called ‘expandable connector’. This connector does not have explicitly defined list of variables neither their causal direction, because it can be automatically generated from connections. For example if we connect a connector ‘c’ to this expandable connector named ‘busConnector’ as variable ‘busConnector.c3’ it automatically create an implicit definition from ‘c’ connector. This is designed only for huge models, sending values from one branch to another branch of instances. Usually it has not sense to use expandable connectors for models, where instances at top level are composed only from elementary classes.

What allows to create models like electrical circuits is a connector defined by two variables: nonflow and flow. The flow variable has prefix ‘flow’. It is possible to connect any number of connector instances of one definition together. These connections generated expected rules of circuits, where connected nonflows are equal, and the sum of connected flows is zero.

The best practice is to use negative flow values for outflowing from the component and positive for inflowing to the component.

### Conditional inputs

The Modelica library for physiology can be designed to have minimal number of components, which are necessary to describe any processes inside the human body. Thanks to support of steady state interfaces, there are the same components for dynamic and for equilibrium calculation. The conditional Modelica principle is used also for switch between parameter and input to the block. These inputs are called conditional inputs and they are in the same pattern as some components from MSL, for example as the component “Modelica.Analog.Basic.Resistor”.

# Building Modelica Libraries

The main result of this work is “[Physiolibrary](http://www.physiolibrary.org/)”, the Modelica library for physiology, and general Modelica library for electrochemical processes called “[Chemical](https://www.modelica.org/libraries)”. The whole section 3 is description of these libraries, which are the base for [Physiomodel](http://www.physiomodel.org/) described in section 4.

Table 2, Physical connectors in Physiolibrary and in Chemical library compared with electrical connector of Modelica Standard Library

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Connector: | | Non-flow variable |  | Flow variable |  |
| C:\Users\marek\AppData\Local\Microsoft\Windows\INetCache\Content.Word\ChemicalPorts.png | Substance | electrochemical potential | [J.mol-1] | molar flow | [mol.s-1] |
|  | Hydraulic | pressure | [Pa] | volumetric flow | [m3.s-1] |
|  | Thermal | temperature | [K] | heat flow | [W] |
| C:\Users\marek\AppData\Local\Microsoft\Windows\INetCache\Content.Word\PopulationPorts.png | Population | size of population | [1] | change of population | [s-1] |
|  | Electrical | electric potential | [V] | electric current | [A] |

Because of Modelica principles, there is possible with relative small amount of physical types describe basic rules of selected physical domains. At first we were implemented in Modelica the complex models such as Guyton’s ‘Overall Circulation’ (Guyton, et al., 1972; Kofránek, et al., 2009), Ikeda’s ‘Body Fluids’ (Ikeda, et al., 1979; Mateják and Kofránek, 2010), Siggaard’s ‘Oxygen status algorithm’ (Mateják, et al., 2012; Siggaard-Andersen and Siggaard-Andersen, 1990), ‘Quantitative Human Physiology’ (Mateják and Kofránek, 2010) and finally Coleman’s ‘[HumMod](http://hummod.org/)’ model (Mateják and Kofránek, 2011). Man can say that reimplementation of models does not bring a new knowledge, but we hope that this is not right and my methodology will be useful also for researchers designing their own theories and also for integration of models together. As a proof, that new theories can be based on physical laws already implemented in Physiolibrary, we presented some our models in physiological articles. First one is about modeling of pulsatile circulations (Kulhánek, et al., 2014; Kulhánek, et al., 2014) and second is about modeling of oxygen, carbon dioxide and hydrogen ions binding on hemoglobin (Mateják, et al., 2015). The integration of models also works well because of object-oriented programing with well-defined interfaces using physical SI units, physical quantities, physical connectors and physical laws. The main result of this integration of mentioned models is Physiomodel.

Each other connector of Physiolibrary or Chemical library belongs to one physical domain (see

Table 2), where the components can be connected using appropriate connector definition. As seen in Table 3, the most of the components have analogy throughout the domains. For example the resistor in electrical circuits have an analogy in chemical domain as diffusion, because the molar flow of substance is driven by electrochemical potential gradient in the same way as electric current is driven by voltage gradient. To define this mathematical analogies in Table 3 are selected the symbols ***e*** like effort for connector non-flow variables and symbols ***f*** like flow for connector flow variables. If there are more connectors in component, they are differentiated by index.

Table 3, Analogies of selected Physiolibrary and Chemical components based on connectors from Table 3 with electrical components of Modelica Standard Library

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Resistance** | **Accumulation** | **Stream** | **Inertia** | **Effort source** |
| *f1=G\*(e1 ‑ e2)*  *f1+f2=0* | *a=C\*e* | *f1+f2=0* | *f1+f2=0* | **e = E** |
| G..conductance | C..capacitance | F..stream flow | L..intertia | E..effort |
| C:\Users\marek\AppData\Local\Microsoft\Windows\INetCache\Content.Word\chemicalDiffusion.png  Chemical diffusion | substance  Chemical substance | Solution stream | not exist | MoleFraction |
| C:\Users\marek\AppData\Local\Microsoft\Windows\INetCache\Content.Word\hydraulicConductor.png  Hydraulic resistance | elasticVessel  Elastic vessel | not exist | Inertia | Pressure |
| C:\Users\marek\AppData\Local\Microsoft\Windows\INetCache\Content.Word\thermalConductor.png  Heat convection | heat  Heat accumulation | Heated mass flow | not exist | Temperature |
| not exist | Population | Growth, Differentiation | not exist | not exist |
| resistor  Electrical resistor | ec  Electrical capacitor | not exist | Inductor | Voltage |

## Types

The most of variables in mathematical models are real numbers and really they can be defined only using elementary type ‘Real’. So why the Physiolibrary need so many elementary types for the real numbers? Even the ‘Real’ is a simple type, which represents the number as described in section [Floating point numbers](#_Floating_point_numbers), in Modelica it can have the attributes, which differentiate the meaning of values. This meaning is for user-friendly using of the library components. With help of these attributes the Modelica environments can:

* find incompatible physical quantities in connections or equations
* recalculate the physical units in dialogs or in outputs
* assert the simulation when the values are not in their domain of definition
* increase the precision of results and speed up the calculations

The check of physical quantities is very useful especially for simple input/output connectors, which are in Physiolibrary specified for each type in package ‘Types.RealIO’. Using this typed connectors instead of simple RealInput/RealOutput there can be generated warning or even an error every time when user try to connect for example output connector of pressure value with input connector expecting volume value.

Setting parameters using dialogs during implementation of model can be really simplified by correct specification of physical units. Some environment can recalculate many non-SI units into expected SI units inside models, but they need to know at which SI unit is the value (see section [International system of units](#_International_system_of)). For the dialog setting of just one value into the model are prepared constants for each type in package ‘Types.Constants’. But if user use any Physiolibrary type for his parameter or variable all this unit recalculations should be also automatically recognized.

The min/max assertion are not always set as default debug feature for environments, but if they are then they could recognize bad results such as negative volumes, negative masses, temperatures less than 0 K. In correct physical models these values should not be reached, but user has always an options to implement any equation which he want. And because the correctness of each model can’t be decided automatically, any warning or assertion could be very useful.

Because of compatibility of all Modelica libraries and models they should be all values calculated in SI units. This rule generate strange dimension of some values. For example the SI unit for volume is cubic meter, but in the body compartments are at volumes of milliliters. So the numbers used for calculation will be million times smaller than the physiologist normally use. However, it does not matter, because these types in Physiolibrary have defined ‘nominal’ attribute, which move back the tolerance level from SI units to the typical values used in physiology.

## Blocks

The reason why Physiolibrary defines blocks is because they are missing in the Modelica Standard Library 3.2 (MSL). The blocks of Physiolibrary are graphical implementation of simple mathematical operation such as reciprocity, power etc. and also more complex blocks for interpolation of value by cubic function. Even this type of interpolation does not seem very physical it is needed for implementation of empirical dependencies, whose physical explanation lies beyond the scope of the model. The interpolation could be implemented different ways. The linear MSL look-up table approximates the value between known points by linear segments, which generates after derivation discontinuities. To solve this problem we selected a cubic **spline** interpolation curve, which has also continuous first derivations. The curve is defined by set of points with coordination x, y and slope. Approximated value v (coordinate y) is calculated from u (coordinate x), where point (u,v) lies on the curve. At first is selected a segment of curve, which is defined by nearest curve points. During initialization has each segment prepared coefficient a,b,c,d of cubic equation ax3+bx2+cx+d=y to reach these definition points at defined coordinates and slopes. But man must be careful with using this cubic splines, because in some cases the segment can be the non-injective function. In the other words, inverse calculation of x from y can have more solutions. Which one of the solutions is used could be dependent on guest/previous value. My recommendation is always to draw this curve before it is used in model and modify the slopes to minimize the non-injective segments.

Figure 4, Non-invertible segment of cubic interpolation caused by wild slope differences

### Factors

Special pattern used in Physiolibrary are factors. This idea is used in many physiological models, where are relative multiplication effects. At normal conditions are this effect at value one, when it want to increase the resulting value two-times its value is two, when it decrease the resulting value to half its value is 0.5. The resulting value can be affected by many effect, because at normal conditions the multiplication of ones is one. The graphical block for factor has always one input on top for unaffected value and one output on bottom for resulting value, which is calculated as the effect multiplied by the unaffected value. Calculation of effect differentiates the factors. In the package ‘Blocks.Factors’ are not only linearly o cubic interpolated from some left-located input, there are also factors, which could quickly or slowly adapt the effect in time to the left-located input. This adaptation is called ‘**lag**’ and the simple mathematical filter defined by Equation 1:

|  |  |
| --- | --- |
|  | Equation 1, Lag |

Where t is time, x is an input, y is an output as adapted value and k is a parameter. The meaning of parameter k could be solved from the hypothetical situation, when x is constant during simulation and y has another initial value as x. Solution of this simplification as simple differential equation of one unknown function y shows that the halftime of y adaptation to x value is exactly ln(2)/k as illustrated in Figure 5, because in case of constant input x it is always y(ln(2)/k) = x + (y(0)-x)/2.

Figure 5, Lag in specific setting as exponential adaptation to constant value

## Steady states

Each integrator is implemented in Physiolibrary 2.3 using [steady-state](https://en.wikipedia.org/wiki/Steady_state) interface. It gives a support for changing the convergent system of differential equation to system without derivations with direct calculation of the fixed converging state. This feature is not designed for non-convergent systems, such as oscillating or divergent. Even the periodical processes in physiology are common such as heart beating, breathing, pericardial cycle or menstrual cycle, they can be implemented as convergent system. The convergent system does not have a typical oscillating behavior, but the oscillation is usually simplified to the mean values and the frequencies (frequency is reciprocal period time). Surprisingly, for the most of variables this huge simplification does not change the impact to the other processes calculated also in mean values. Other situation is if we want to see the specific current points in the oscillating period. This kind of calculation brings huge complexity of additional processes, which can be in the convergent system neglected. For example if we calculate with convergent blood circulation, we can successively use mean pressures and mean blood flows with only two types of equation for elastic vessels and hydraulic resistor. But if we want to calculate the values of pressure and blood flow continuously beat-by-beat then it must be used many other physical laws for precise dynamic calculation such as opening and closing of valves, inertia of mass flow, pressure waves with reflections in 3D net of vessels, fluid convection model inside the vessels and many others, which completely disappear during complete time period of the process. Sometimes are also this dynamical effects necessary to calculate, but for long-term simulation of typical healthy patient in typical conditions they could be eliminated without loss of generality.

Having a convergent system of differential equation the point of convergence can be calculated by setting derivations to zero. This static time-independent situation is called steady-state. Typically it can be used for very quick processes, which converge in much shorter time as time of simulation. Solving these processes dynamically using differential equation leads to stiff-equations, which caused many problems in numerical solutions. Avoiding these very slow numerical calculations with uncertain results it is much better to calculate steady-state (equilibrium) immediately.

The main problem with definition of steady-state is, that the swapping of branches of Equation 2 can generate dependent equations. Especially in case of changing from dynamic state to steady state. For each dependent equation there should be added one additional equation. These additional equations typically describe the state of the system such as Conservation laws or the environment conditions.

|  |  |
| --- | --- |
|  | Equation 2, Steady State |

For example the chemical equilibrium is steady-state in chemical domain. The chemical reaction can be so fast, that for long-term simulation is always reached dissociation constant with sufficient precision. So the dynamic of reaching chemical equilibrium is not necessary to calculate in the model. One solution is to implement the system only as equilibrium. But the physical reality is the same as for models, where the dynamic is necessary. So much better is to implement the process with possibility to select the option for dynamic or steady state calculation by parameter before simulation. This implementation can be used for both short-term and for long-term simulations.

Steady-state not always means zero flows. For example the steady state of cardiovascular system is the state of non-zero mean cardiac output typically around 5 liters per minute. However the total derivations, which increase or decrease the mean volume inside vessels remains zero as defined by steady state. Constant mean vessel volumes lead to constant mean pressures, driven only by hydraulic resistances. And the systemic or pulmonary circulation at steady state can be really calculated as systemic or pulmonary resistance without any dynamic adaptations caused by spillover of blood volume.

## Chemical domain

The chemical connector gives the molar flow “∂nA” of the substance A. The [amount of the substance](https://en.wikipedia.org/wiki/Amount_of_substance) “nA” can be expressed by integration of this molar flows as shown in Equation 3. In equilibrium is the change of the substance “∂nA” zero and the amount of the substance “nA” remains constant.

|  |  |
| --- | --- |
|  | Equation 3, **Amount of the substance** |

From the amount of the substance “nA” can be expressed its [mole fraction](https://en.wikipedia.org/wiki/Mole_fraction) “xA”, [molar concentration](https://en.wikipedia.org/wiki/Molar_concentration) “cA” or [molality](https://en.wikipedia.org/wiki/Molality) “bA” in the solution. If the amount of all particles in the solution is “nT”, the volume of the whole solution is “VT” and the mass of the solvent is “mS” then the relation between mole fraction, concentration and molarity is the Equation 4.

|  |  |
| --- | --- |
|  | Equation 4, **Mole fraction** of the substance |

*For example the one liter of typical blood plasma, such as presented by (Raftos, et al., 1990), has total number of particles “nT” about 51.8 mol and it contains the water as solvent in mass of 0.93 kg. The mole fraction of water is about 0.995 mol/mol and the mole fraction of the chloride of the molar concentration 100 mmol/L is 0.00193 mol/mol.*

*In the cell is the situation different. For example in the red cells by (Raftos, et al., 1990) is the total number of particles “nT” about 38.7 mole per liter and the mass of water is only 0.69 kg per liter of intracellular fluid. However this values gives the same mole fraction of water as in plasma (0.995 mol/mol). The mole fraction of chloride, which molar concentration in erythrocyte is around 50 mol/L, is 0.0013 mol/mol.*

The current theory of physical chemistry need a correction coefficient between different ways of measurement of the substance in solution. This correction is called [activity coefficient](https://en.wikipedia.org/wiki/Activity_coefficient) . For the ideal substance it is 1. However, it can varies for electrolytes as predicted by Debey-Huckel (Debye and Huckel, 1923), Davies, Robinson-Strokes (Stokes and Robinson, 1948) and others. As a reason there should be inserted an activity of the substance “” instead of its mole fraction to the equation of the chemical potential.

|  |  |
| --- | --- |
|  | Equation 5, **Activity** of the substance |

Each chemical process want to equilibrate the [electrochemical potentials](https://en.wikipedia.org/wiki/Electrochemical_potential) of the substances. The electrochemical potential (Equation 6) is describing the free Gibbs energy of one mole of the substance in the solution at defined conditions. This definition is the base equation of the physical chemistry (Mortimer, 2008).

|  |  |
| --- | --- |
|  | Equation 6, **Electrochemical potential** |
|  | Equation 7, Chemical potential |

Where T is temperature of the solution, φ is electric potential of the solution, R is gas constant (8.314), is the number of charge of ion (0 is the substance is not an ion), F is faraday constant and is the chemical potential of the pure substance.

Typical chemical solution has the electric potential equal to zero (φ=0), so the electrochemical potential is the same as chemical potential (Mortimer, 2008). Also for all chemical processes in one homogenous chemical solution can be the electrical part of electrochemical potential neglected, because it is algebraically eliminated (it is the same in both side of electrochemical equality for each chemical substance). After removing electrical part of electrochemical potential only the chemical potential remains. However, for processes between different solutions it must be present. As a result a nonzero electric potentials between solutions can be presented.

### Chemical substance transports

The most intuitive equilibrium of electrochemical potentials is the equilibrating by diffusion to reach one homogenous mixture with the same activities of all substances in all places.

A little complicated is to imagine the equilibrium of uncharged substances through semipermeable membrane. The electric part of the potential is zero, because the substance has zero charge (z=0). So, there are equilibrating only chemical parts of the potential on both sides of the membrane. Because it is the same substance on both sides the equilibrium of both pressure and chemical potential is reached if the activities are the same in the both sides of membrane. This equilibration of permeable particles is usually called an [osmosis](https://en.wikipedia.org/wiki/Osmosis). And it is a reason why the water has the same mole fraction in plasma as in intracellular fluids of erythrocytes. Dual view of the same calculation can be sometimes simplified by impermeable particles, because the more impermeable particles causes the lower mole fraction of each permeable substance. In some cases the mathematical simplification “ln(1-x) ≈ x” can be used – e.g. for such small x as mole fraction of plasmatic proteins on capillary membranes, where ln(xPermeants) = ln(1‑xImpermeants) ≈ xImpermeants. In this case it seems like equilibration of osmolarities (molar concentration of impermeable substances), but in reality it is the equilibration of electrochemical potentials for each permeable substance as expressed in Equation 8, where must be extended with pressure dependence of its [state of matter](https://en.wikipedia.org/wiki/State_of_matter) as we do with constant molar volume Vm,A in case of incompressible substances.

|  |  |
| --- | --- |
|  | Equation 8, **Osmotic pressure** gradient across the membrane for uncharged incompressible permeable substance A |

The other equilibrium on red cell membrane is reached for chloride. The chloride can freely cross the membrane through membrane channel called chloride-shift. In contrast with electroneutral water the chloride has a charge number -1, what takes the membrane potential into the equation of its equilibrium. If we reorder this relation we get directly the [Nernst membrane potential](https://en.wikipedia.org/wiki/Resting_potential) equation as a relation between the ratio of chloride inside and outside the red cells.

|  |  |
| --- | --- |
|  | Equation 9, Algebraic derivation of **Nernst equilibrium** of passive ion transport on membrane from equality of electrochemical potentials |

*And really there are Donnan’s equilibrium on the red cells membrane, which generates the Donnan’s ratio about 0.5 for each permeable anion of charge -1 (Raftos, et al., 1990). And this ratio reflects the measurable electric potential about -12 mV (Gedde and Huestis, 1997). For chloride it seems that we can assume almost the same activity coefficients of the same substance on both side of the membrane, because ratio of activities is the same as Donnan’s ratio of concentrations.*

### The chemical substance formations

In all these kind of equilibrating of substance transport we worked with the same substance in the same phase and in the same solvent. This makes the equilibrium independent of the base chemical potentials of the pure substance (), because on both side of the equation was the same value. However if the chemical process create the new substance or change its phase then the is changed to the new substance. This process we called the formation of the substance A. And if there are carefully selected the reference substances, from which are the substances formed (e.g. H2(gas), O2(gas), N2(gas), C(graphite), Na(solid) and so on), then we can measure the relative (to these reference substances; marked by the degree symbol “°”) formation energies of the whole formation process to describe for any new formed substance in the chemical system by Equation 10.

|  |  |
| --- | --- |
|  | Equation 10, **Chemical potential of the pure substance** |

Where T is temperature, is [free Gibbs energy of formation](https://en.wikipedia.org/wiki/List_of_standard_Gibbs_free_energies_of_formation) of the substance A (relative to selected reference substances), is [free formation enthalpy](https://en.wikipedia.org/wiki/Standard_enthalpy_of_formation) (heat energy consumed by the formation) of the substance A (relative to selected reference substances) and is free formation entropy (the function of changed microstates by the formation) of the substance A (relative to selected reference substances). The relation between enthalpy H, entropy S and [Gibbs energy](https://en.wikipedia.org/wiki/Gibbs_free_energy) G (G = H - T\*S) is a main relation of chemical thermodynamics (Mortimer, 2008). Typically are the formation enthalpy and formation Gibbs energy tabulated value at T0 = 25°C and pressure p0 = 100 kPa.

This description molar Gibbs energies of the substances is a duality to description of the [equilibrium coefficient](https://en.wikipedia.org/wiki/Equilibrium_constant) of the chemical processes. For example the dissociation constant of chemical reaction A<->B in solution without electric potential, defined as K=[B]/[A] has a relation to the Gibbs energy of the reaction. If we set A as reference substance () then . This is also the result of the equilibrium of the chemical potentials, which defines the free Gibbs energy of the reaction :

|  |  |
| --- | --- |
|  | Equation 11, Algebraic derivation of free **Gibbs energy of the reaction** from its dissociation coefficient |

Using of free Gibbs energies instead of dissociation constants is much better, because it automatically fulfils the [principle of detailed balance](https://en.wikipedia.org/wiki/Detailed_balance). This fundamental principle can be also translated as follows: The product of dissociation constants must be equal to 1 for each closed chemical cycle (closed system of the reactions, which ends with the same substances, phases, enthalpies and entropies as it starts). This relation of dissociation constants is definitely not as intuitive as the thermodynamic meaning: The free Gibbs energy of each closed chemical cycle is 0, which means that isolated system does not consume or produce new energy. Mathematically said: The logarithm of 1 is 0.

As shown in the example of the simple reaction A<->B the free Gibbs energy of the reaction () is the difference between free Gibbs energies of product and substrate (). This rule is called Hess’ law and can be used for any chemical process with any number of substances with any stoichiometric coefficients “v”. If we use the positive-negative stoichiometric coefficient notations (e.g. vB=2, vA=-3 for reaction 3 A <-> 2 B) we can extend the equilibrium to any number of reactants and products:

|  |  |
| --- | --- |
|  | Equation 12, **Hess’s law** in the equilibrium of chemical reaction 0<->v1A1 + v2A2 +… |

*For example the equilibrium of Henderson-Hasselbalch reaction H2O + CO2 <-> HCO3- + H+ in red cells at 37°C can be calculated from* [*tabulated*](http://www.update.uu.se/~jolkkonen/pdf/CRC_TD.pdf) *formation energies (shifted from 25°C to 37°C) of substances as ,* ***,*** *, as reaction free Gibbs energy . So the negative decimal logarithm of the dissociation constant is pK=6.3. However, the bicarbonate is an anion, so it must be corrected by activity coefficient to reach its physiologically measured intracellular concentration of 11.6 mmol/L (xHCO3=3e-4, aHCO3=1.9e-4) at pH=7.2=-log10(aH+) (aH+=6.31e-8), where the mole fraction of the free dissolved carbon dioxide xCO2=aCO2=3.22e-5 and mole fraction of water xH2O=aH2O=0.995 as data presented by Raftos et al. (Raftos, et al., 1990). The same pattern with the same activity coefficient of bicarbonate can be applied to blood plasma to reach typical concentration of bicarbonate 24 mmol/L at pH=7.4 and at the same mole fraction of carbon dioxide xCO2=aCO2=3.22e-5.*

In our example we calculated with free dissolved gas in liquid. Gases such as carbon dioxide or oxygen are equilibrated in lungs between their gaseous and aqueous state of matter. The equilibrium of this process is in physical chemistry described as Henry’s law. And thanks to this fixed linear dependence between gaseous and aqueous form it is possible to exchange the meaning of partial pressures of the gases with their concentration of free dissolved form. The relation between mole fraction xA,g and partial pressure pA of the substance A in gas of total pressure pT is xA,g=pA/pT. And Henry’s coefficient can be defined as kH = xA,l / xA,g , where xA,l is a mole fraction of free dissolved substance A in liquid. Also this coefficient can be rewritten to Gibbs energy of the chemical process:

|  |  |
| --- | --- |
|  | Equation 13, Algebraic derivation of free Gibbs energy of the gas dissolution in liquid from its Henry’s coefficient |

*The main problem with these parameters is, that they are shifted from mole fraction to molality in water such as in NIST (U.S. Department of Commerce, National Institute of Standard and Technology) tables. So if we use the value from* [*NIST*](http://webbook.nist.gov/chemistry/)*, e.g. 0.034 mol/kg/bar for CO2 it should be recalculated to mole fraction units using water molar mass 0.018 kg/mol as kH=0.034\*0.018. And the calculation of mole fraction of free dissolved CO2 at pCO2=40 mmHg in blood is xCO2=0.034\*0.018\*40/760=3.22e-5. The molar concentration in erythrocytes can be expressed by multiplication of the total amount of substances 38.7 mol in one liter of intracellular fluid and the resulted value 1.24 mmol/L is in good agreement with* [*Siggaard’s data*](http://siggaard-andersen.dk/OsaTextbook.htm) *(Siggaard-Andersen and Siggaard-Andersen, 1990).*

### Change of phase of the substance

The change of phase is in physiology is mainly connected with evaporation of water in lungs or as sweat in skin. In chemical equation it means also the equilibration of chemical potentials of the water in liquid phase and in gaseous phase.

|  |  |
| --- | --- |
|  | Equation 14, Algebraic derivation of equilibrium of water evaporation |

The free formation enthalpy of liquid water is [-285.8 kJ/mol](http://www.update.uu.se/~jolkkonen/pdf/CRC_TD.pdf) and of gaseous water is  [-241.8 kJ/mol](http://www.update.uu.se/~jolkkonen/pdf/CRC_TD.pdf). The free formation Gibbs energy of liquid water is [-237.1 kJ/mol](http://www.update.uu.se/~jolkkonen/pdf/CRC_TD.pdf) and of gaseous water [-228.6 kJ/mol](http://www.update.uu.se/~jolkkonen/pdf/CRC_TD.pdf) at 25°C and 100kPa. From these values can be expressed free entropy of formation as -163.14 J/mol/K for liquid water and -44.27 J/mol/K for gaseous water at 25°C and 100kPa using Equation 15. As a result of almost constant enthalpy and entropy of formation, it can be recalculated the free Gibbs energy of vaporization to temperature T at pressure 100kPa.

|  |  |
| --- | --- |
|  | Equation 15, Water evaporation molar energies |

*The free Gibbs energy of vaporization is -44030+118.867\*T and the vapor pressure of water is xH2O\*exp((-44030/T+118.867)/8.314) bar. Using this relation for pure water at the body temperature of 310 K (37°C) and normal atmospheric pressure of 100kPa we get the vapor pressure 6.22 kPa (47.2mmHg) at equilibrium of the vaporization process. This value is close to the observation of* [*6.28 kPa (47.7mmHg)*](http://www.thunderscientific.com/tech_info/reflibrary/its90formulas.pdf)*.*

### Stream, degradation and clearance

The chemical substance can be transported together with solution. The component modeling volumetric flow of solution is called **stream**. Typically it is stream used with air transport of oxygen or carbon dioxide during ventilation and for transportation of substances using blood circulation. The calculated molar flow of entrained substance named as ∂*nA* is here the molar flow of whole solution ∂*n* multiplied by mole fraction *xA* in the origin of stream as Equation 16.

|  |  |
| --- | --- |
|  | Equation 16, Stream |
|  | Equation 17, Clearance |

An analogy of stream calculation is in medicine the **clearance**, which is used for calculation of extracting substance from the body such as kidneys excretion, liver metabolism, enzymatic processes and so on. For defined substance the *Clearance* parameter are measured as amount of solution flow, which is fully cleared from the substance. Because we use the mole fraction instead of molar concentration we need to convert mole fraction to molar concentration using mole density of the solution *ρm* [mol.m-3], which is the total amount of the substances per volume unit. In contrast with stream, there is not loss of solution.

One must be careful, because clearance is not only one possible way of removing substances from the body. For some cases there is also passive **degradation** of molecules in whole solution volume (Equation 18). In contrast with clearance, it is dependent of distribution space of substance. If there is no other change of substance and only degradation in the constant amount of solution *n* takes place, then the concentration fall down to half after time expressed as parameter *HalfTime*. In condition of the constant solution amount it could be rewritten also to clearance calculation as Clearance = (n/*ρm*)\*ln(2)/HalfTime.

|  |  |
| --- | --- |
|  | Equation 18, Degradation |

The simplest chemical components for chemical substances are just putting a prescribed number as molar flow of substance, called **Pump**. This molar flow is usually calculated by user defined schemes, for example using normal flow as parameter affected by factors as described in section [Blocks](#_Blocks).

### Macromolecule equilibria

The macromolecules in physiology are very common, e.g. proteins, DNA, RNA... These molecules are typically polymers composed from only small amount of basis as amino acids for proteins or nucleotides for DNA. By polymerization of these bases it is created one strand, where not only the order of the basis are critical for next functions. Also the whole space conformation with all type of presented bounds determine the function of the macromolecule. From the chemical point of view there are a many distinguishable forms of the macromolecule. For example the side chains of some amino acids can be presented as base or conjugate acids form, some can be presented even in acid or conjugate base form at the typical cellular or interstitial pH. Fortunately the reactions with ligands can be independent on different sites in macromolecules, which really simplify the calculation of equilibrium. The mole fraction of the specific state “sQ” (defined by selected quaternary conformation “Q” and by state of each independent site “i” at equilibrium), is calculated by Equation 19. The equation can be read as the probability of the selected form in quaternary conformation (xsQ) is the probability of quaternary conformation (xQ) multiplied by probability of each selected site form in the quaternary conformation (xi/xQ).

|  |  |
| --- | --- |
|  | Equation 19, Speciation |

As a result of these general equation for equilibrium of the macromolecule there can be easily expressed changes between quaternary conformations. For example the allosteric effect on hemoglobin can be described by tensed and relaxed conformation of hemoglobin tetramer molecule, where the binding of oxygen is in each conformation independent. However the affinity of oxygen in tensed conformation is much higher than in relaxed conformation. This simplification as firstly presented by Monod-Wyman-Changeux model in 1965 (Monod, et al., 1965) is the basis of all allosteric regulations.

Our research above these allosteric effects can even extend the model with many possible quaternary states and with many ligands. I designed the mathematical description of the hemoglobin model including oxygenation, carboxylation, Bohr’s effects and heat balance. The coauthor Stanislav Matoušek makes the review and scientific language support of paper. The coauthor Tomáš Kulhánek makes the identification of the parameters of the model to fit experimental data. And as shown in the following paper, the model describe the interconnection of all phenomena, which are nonlinearly joined together. And therefore is not possible to describe it separately as independent processes.

## Thermal domain

It is not surprise that in thermal domain is accumulated the heat energy as in Equation 20. From **accumulated heat** can be calculated temperature [K] using properties of materials such as their specific heat [J.kg-1.K-1] and mass [kg] (Equation 21). Because in human physiology is temperature regulated to 37°C (=310.15 K), the relative heat is shifted to this value. The negative value of heat has the meaning of missing heat to 37°C and the positive value of relative heat means heat excess and higher temperature.

|  |  |
| --- | --- |
|  | Equation 20, Heat |
|  | Equation 21, Temperature |

The connectors in heat domains use temperature [K] as non-flow and heat flow [J.s-1] in the meaning of change of heat energy. The connector is inherited from the package Thermal.HeatTransfer of Modelica Standard Library (MSL 3.2.1), which makes a compatibility with all standard thermal components of that package.

**Heat conduction** is driven by temperature gradient as shown in Equation 22. Heat is transferred from warmer to colder environment until the temperature is equilibrated. The speed of conduction is determined by parameter Cond, which can be expressed also as reciprocal value of heat resistance.

|  |  |
| --- | --- |
|  | Equation 22, Conduction |

Heat is transported also together with mass. Each loss of mass will decrease the absolute heat, but it does not change the temperature. The situation is an analogy of substance molar flow, when the whole solution is outflowing. Also the equations Equation 16 and Equation 23 are similar, but the meaning of variables are different. The **heat stream** is based of mass flow [kg.s‑1] not molar flow and there is not molar fraction, but “concentration of heat energy” expressed as multiplication of temperature [K] with specific heat of the mass [J.kg-1.K-1].

|  |  |
| --- | --- |
|  | Equation 23, Heat change by water evaporation |

Typically the microcirculation is so effective, that the outgoing blood from capillary nets has the same temperature as the tissue around capillaries. The principle of heat transfer from blood to tissue is like **ideal radiator**, because in the radiator is also overflowing of the heated liquid. Specific heat [J.kg-1.K-1] of this liquid is named as *SpecificHeat*. Amount of transferred heat to the environment is proportional to the flow of the liquid inside the radiator called *massFlow* [kg.s‑1]*.* Maximal heat flow to environment can be limited by equilibrium of temperatures of outflowing liquid and the environment around radiator as Equation 24. Equation 25 says that all heat energy of the inflowing liquid (Ti\*SpecificHeat) is divided only to heat energy transferred to the environment (heatFlowToEnv/massFlow) and the heat energy of the outflowing liquid (To\*SpecificHeat).

|  |  |
| --- | --- |
|  | Equation 24, Ideal Radiator |
|  | Equation 25, Heat Flow |

However, the blood can transfer about 5% more heat from working muscles to lungs than is calculated by Equation 25, because of endothermic behavior of hemoglobin deoxygenation (Mateják, et al., 2015). This additional heat is not accumulated to mass as temperature changes. It is released by chemical reaction during changing the form of molecules as described in above sections as chemical enthalpy. This kind of chemical enthalpy take place also during sweating, when the water change phase from liquid to gas. This process effectively cools the skin down even if the environment temperature is higher than temperature of skin.

## Hydraulic domain

The modeling of cardiovascular system is based on hydraulic principles, where volume [m3] in **elastic vessels** generates pressure [Pa] and the pressure pushes the blood flow [m3.s‑1] through the circulation. The main component of accumulation of volume is called ElasticVessel and is described with Equation 26 and Equation 27. As a result of elastic properties of blood vessels, there is an increase of the pressure together with increase of the volume inside this component. This proportional dependence is set by parameter Compliance [m3.Pa‑1], which is the property of the wall of the blood vessel. For example the compliance is bigger for systemic veins, where the same additional volume does not increase the pressure as much as in systemic arteries. The walls do not generate the positive pressure inside, when the volume decreases bellow V0 and they lose their tension. The result is the same pressure inside as outside the vessel.

|  |  |
| --- | --- |
|  | Equation 26, Volume |
|  | Equation 27, ElasticVessel |

Fortunately, typical working state of elastic vessels at each places during each phase in heart period is at the first branch, where volume>V0. The second additional branch solves critical situations, which could appear for example after massive hemorrhage. The external pressure around vessels PExt are typically set to zero with exception of a local bandage or an intrathorax pressure. The negative intrathorax pressure around ‑500 Pa is a result of respiration quotient. Inside the lungs are more oxygen sucked by hemoglobin than carbon dioxide released from blood, what means the lack of molecules inside properly working alveoli. That gives small pressure debt to the intrathorax extravascular pressure accounting during whole respiration period.

The volumetric flow through segment of vessel is driven by pressure gradient. This component is called **Conductor** or hydraulic resistor. Flow goes from higher to lower pressure. Its value is determined with conductance Cond [m3.s‑1.Pa‑1], which can be expressed with reciprocal value as hydraulic resistance [Pa.s.m‑3].

|  |  |
| --- | --- |
|  | Equation 28, Conductance |

The conductance is dependent on current radius of the vessel. Vasoconstriction and vasodilation changes the radius, so it changes the conductance. Higher conductance means the higher flow for the same pressure gradient.

Pressure in liquid is also generated by gravity. The hydrostatic pressure is dependent on depth below the surface, on density of the liquid and on gravitational acceleration. For example pressure of one atmosphere is on the bottom of 0.76 m high column of mercury or on the bottom of about 10 m high column of water. This phenomenon caused the additional blood pressure in the lower parts of the circulation and lower blood pressure in the upper parts as expressed by Equation 29. The classical formula (gravity\*density\*height) is here extended with pumping effect (*pumpE*), which significantly helps to break the **hydrostatic column** with vein’s valves.

|  |  |
| --- | --- |
|  | Equation 29, Hydrostatic pressure gradient |

Typically, one point is selected for the circulation (e.g. heart aortic valve). Height below this point is positive. Height above this point is negative. Change of orthostatic position of the body during standing or lying is represented by changing the heights of computed vessels. Gravitational acceleration (*gravity*) in the earth surface is always set to 9.8 [m.s‑1]. The pumping effect is changing with movements of legs, because the segments of leg veins between valves can push the blood up only when the leg’s skeletal muscles are periodically contracting and relaxing.

**Ideal valve** is designed hydraulic component as conductor, but with different resistance for each flow direction. Forward flow has high conductance (low resistance) *Gon* and backward flow has low conductance (high resistance) *Goff*. Second branch of Equation 30 is valid during opened phase (pressure gradient > 0) and otherwise if the valve is closed the first branch takes place instead. At the break point defined by pressure gradient 0 are valid both branches with zero.

|  |  |
| --- | --- |
|  | Equation 30, Valve |

The backward conductance is typically very small - there can be generated small volumetric flow in case of closed valve. However, this flow can be so small, that it could be described by swelling of valve membrane without any direct connection between liquids on both sides.

The resistance of mass to any change in motion is called **inertia**. The volumetric flow has the tendency to continue forward and as a result will the volumetric flow continuously react to the change of pressures. The other view to the Equation 31 is generating pressure proportionally to the change of the flow. The higher parameter Inertance [Pa.m‑3.s2] means the higher pressure gradient answer to the same change of volumetric flow.

|  |  |
| --- | --- |
|  | Equation 31, Inertia |

The inertance of fluid in vessel segment can be expressed as density\*length/cross-sectional area. Typically the inertia is the most important in aorta, where in each heart cycle starts and stops the blood flow from left ventricle.

## Population domain

The models in physiology need to count also the organisms, cells, viruses, bacteria, etc. As in predator-prey model do there is also an accumulation of members of the **populations**, which can reproduce or die. Even though all the calculations are in real numbers as Equation 32, the results can be rounded to the integers quite easy. However the number of cells is typically very high and this approximation with floating point numbers can count any huge amount of members.

|  |  |
| --- | --- |
|  | Equation 32, Population |

The number of members is called *population(t)*. The increase or decrease of the members is called *populationChange(t).* As population is usually selected one type of cells. For example red cells, which are produced by erythropoiesis in bone marrow. Even more, as population can be implemented also only one phase of the cell maturation, differentiation or reproduction, where exist the properties differentiating these cell from others.

Reproduction, mortality and stream are represented by the same equation. The main idea is proportional dependence of population change on population size as expressed Equation 33.

|  |  |
| --- | --- |
|  | Equation 33, Change |

The parameter *changePerPopulationMember* can be recalculated from lifetime or half-life, where *lifetime = ln(2)\*half-life* and *changePerPopulationMember = 1/lifetime*. Even this conditions and behavior is very simplified it can show the main trends of dynamic and can fit the steady states of the system.

# Physiomodel

Diagram 1, Physiomodel subsystems, top-level diagram implementation

## Cardiovascular system

Cardiovascular system is decomposed into heart, pulmonary circulation and systemic circulation as implemented in Diagram 2. These components are connected using Physiolibrary hydraulic connectors, where pressure and volumetric flow is hidden behind the black line connections. Both pulmonary and systemic circulation have during steady state the same behavior as simple hydraulic resistor. The heart has during steady-state the behavior of continuous hydraulic pump. However during dynamical middle-term simulation is the situation more complex and blood volumes can dynamically spillover between blood vessels changing the current blood pressure and blood flows. The heart pumping is more complexly described in subsection Heart and both dynamical circulations are in detail described in the subsection Circulation using tissue arterioles, capillary and venules of the subsection Microcirculation.

Because the blood volume and hematocrit strongly influents both blood pressure and blood flow in all places of cardiovascular system, their implementation is also inside the Diagram 2, called red cells and blood properties. These components, which are calculating the amount of red cells, the volume of blood, hematocrit, blood viscosity effect on hydraulic conductance etc., are described in subsection Blood.

Diagram 2, Cardiovascular system, the black line in top-right represents the pressure and blood flow in the end of pulmonary veins, bottom-right black line in the start of aorta, bottom-left in the end of systemic veins and top-left in the start of pulmonary arteries.

### Heart

The model of blood pumping by heart consists from models of heart atriums, ventricles, sinoatrial node, atrial pressure receptors and atriopeptin. Heart component has four hydraulic connectors, where are connected the veins and the arteries. From systemic veins is blood transferred directly into the right atrium, from which the right ventricle is filled. The right ventricle is ejected into pulmonary arteries using connector in the left bottom corner of heart icon (see on Diagram 2). After oxygenation in lungs blood goes to the left atrium and left ventricle, from which is ejected into aorta (Diagram 2). The pathological state of mixing deoxygenated with oxygenated blood, when the foramen ovale is opened, is not implemented yet. So during steady state is the flow in connector of veins the same as the flow in connector of arteries for both half of the heart.

The sino-atrial node calculate the heart rate and it will be described together with low pressure receptors in section about autonomic neural activity. Atriopeptin as hormone produced by heart in answer to blood pressure inside heart atriums will be described in section about hormones.

Because the long-term heart activity can be modeled using mean values of pressures and flows, there must not be solved beat by beat. Instead of dynamic periodical values it is calculated precisely in values, which are arithmetical average of the flow or pressure during each heart period, called mean variables or mean values. At this conditions can be the heart atrium implemented using simple elastic vessel of Physiolibrary defined by Equation 26 and Equation 27 and represented by yellow circles on Diagram 3.

Diagram 3, Heart, deoxygenated (oxygenated) blood goes from systemic (pulmonary) veins to pulmonary (systemic) arteries through right (left) heart atrium and right (left) ventricle

The heart ventricle as implemented in Diagram 4 has two hydraulic connectors, which represents the area before input valve and the area after output valve. Through this area it is going some blood flow and also it is here generated some pressure as usual in hydraulic connector. Flow going to the arteries is called cardiac output. Cardiac output (CO) as a mean blood flow from heart ventricle is heart rate (HR) multiplied by stroke volume (SV), where stroke volume is difference of end diastolic volume (EDV) (Carter, et al., 1998; Gaasch, et al., 1975) and end systolic volume (ESV) (NODA, et al., 1993). The most common descriptions are pressure-volume relations (Sagawa, et al., 1988) as in A-V fistula experiments (Guyton and Sagawa, 1961) or filling pressure experiments (SUGA and SAGAWA, 1974) or less invasive exercise experiments (Little and Cheng, 1993).

This model is not solving the situation of very short time for good filling of the ventricle. However, using Physiolibrary there is possible to make the beat-by-beat implementations as we describe in articles (Kulhánek, et al., 2014; Kulhánek, et al., 2014). These publications show the opening and closing valves (Equation 30), which simulate the current pressure and flow during diastolic filling and systolic ejection of ventricles. Even more there is also integrated the blood flow inertia (Equation 31), which has a significant role on shape of blood flow and pressure (e.g. generating Dicrotic Notch) during these short-term events.

Diagram 4, Heart Ventricle, the block diastole is calculating the end diastolic volume from mean filling pressure, the block systole is calculating the end systolic volume from mean arterial pressure and contractility, which is a function of the beta receptors activity.

### Circulation

In pulmonary circulation is blood flowing through pulmonary arteries, capillaries and veins. All of these is represented in Diagram 5 by the elastic vessel (Equation 26 and Equation 27) and hydraulic resistor (Equation 28). A special block is used for calculation of perfusion of ventilated alveoli based on total blood flow through pulmonary capillaries called lungBloodFlow.

Diagram 5, Pulmonary Circulation

The local regulation of vasoconstriction and vasodilation in lungs (Archer and Michelakis, 2002) is not implemented, but can be easily inserted in the next versions.

In systemic circulation the blood flow from systemic arteries (Roach and Burton, 1957) is divided into branches for different tissues. In the upper part of Diagram 6 are the coronary (micro)circulation through heart, the next are all other peripheral organs except of splanchnic circulation, and the splanchnic circulation, where is the blood from gastro-intestinal tract mixed with blood from hepatic arteries. The lower part of Diagram 6 represent the sequestered blood in the lower parts of the body caused by hydrostatic gravitation effect (Equation 29). Characteristics of sequestering blood in leg vessels are measured with many orthostatic experiments (Bevegärd and Lodin, 1962; Bock, et al., 1930; Henry and Gauer, 1950; Mayerson, et al., 1939; OCHSNER, et al., 1951; Pollack and Wood, 1949; Thompson, et al., 1928). And together with function of blood pumping effect (using vein valves during contraction and relaxation of surrounding skeletal muscle) it answers the question why is so uncomfortable log-term staying at one place without motion in contrast with long-term walking (Armstrong, et al., 1985; LAUGHLIN, 1987; Laughlin and Armstrong, 1983).

After flowing through tissues goes blood into systemic veins, which zero-pressure-volume is driven by venoconstriction. The venoconstriction is driven by sympathetic neural answer as part of baroreflex (ECHT, et al., 1974; GAUER, et al., 1956; Shigemi, et al., 1994). The last phenomenon in systemic veins in place of entering intrathorax cavity can be collapsing of the veins. This is caused by small negative intrathorax pressure, which can suck all volume from vein at the place of diaphragm and restrict the blood flow as collapsing vessels do if there is not enough blood volume.

Diagram 6, Systemic Circulation

Peripheral circulation part is composed with eight type of tissues: bone, neural, adipose, skeletal and respiratory muscle, renal, skin and the rest. These organs are implemented by the same class of microcirculation with different parametrical setting. The exception from general microcirculation is the renal circulation of kidneys (Diagram 10). These is very specific, because the blood flow after renal arcuate artery and afferent arterioles access the glomerular capillaries net. After the glomeruli and efferent arterioles is blood divided again to the capillary net of vasa recta or interlobular capillary net. The differences of renal circulation are significant, because the renal blood flow is typically around 20 % of cardiac output.

Diagram 7, Peripheral Circulation

Splanchnic circulation deliver all blood from gastro-intestinal tract to liver by portal vein (Bradley, et al., 1953). In liver is the hepatic blood flow determined by portal vein and hepatic artery blood flow. Normal hepatic blood flow can vary from 1 to 2.5 l/min (BRADLEY, et al., 1952) in dependence on gastro intestinal blood flow. The splanchnic circulation can have a function of blood reservoir during hemorrhage or during blood infusion (Greenway and Lister, 1974; Maass-Moreno and Rothe, 1992).

Diagram 8, Splanchnic Circulation

### Microcirculation

The blood flow through blood vessels depends on blood viscosity (Whittaker and Winton, 1933), as shown by upper factor of Diagram 9. Bellow this factor is the vasodilation/vasoconstriction effect of anesthesia, then effect of angiotensin 2, vasopressin and catecholamines. The catecholamines such as epinephrine or norepinephrine freely dissolved in extracellular fluids are described in section Hormones and their effect on alpha receptors are calculated as variable AlphaPool\_Effect. The alpha receptors can be also stimulated by sympathetic neural activity (GangliaGeneral\_NA) or inhibited using alpha blockers (AlphaBlocade\_Effect) as will be described in section about Neural Activity. Next factor is for skeletal muscles, where a metaboreflex dilates the arterioles to bring more oxygen and nutrients into working tissue. The next factor is an adaptation on long-term low hypoxic condition by angiogenesis, where new branches between arterioles and venules caused lower resistance for blood flow. The partial pressure of oxygen can have also acute effect on vasodilation (or local vasoconstriction in lungs). However in brain must be calculated also the effect of carbon dioxide (Kety and Schmidt, 1948), which increases the blood conductance in situation when it must be washed out or decreases the blood conductance when it must be accumulated to eliminate the local rapid pH changes. The local metabolic demand for oxygen is also one of the factors of vascular resistance. The last one is the embolism, where the perceptual part of tissue circulation can be blocked by an embolus, which can be blood clot, gas bubble or any solid blockage of blood stream.

Diagram 9, Microcirculation

An exception of microcirculation is the renal circulation of kidneys, where only the efferent interlobar part is driven by some of mentioned factors. The strictly regulated renal blood flow by both afferent and efferent arterioles (Diagram 10) needs to set optimal filtration pressure (Manning, 1987; Manning, 1990) and to prevent washout of kidney medulla concentrations. This can be driven by number of working nephrons, tubule-glomerular-feedback (Ito and Carretero, 1990; Moore and Casellas, 1990), baroreflex-like patterns (Skarlatos, et al., 1993), local mechanoreceptor-myogenic pattern (Aukland, 1989; Drummond, et al., 2008) and by efferent interlobar microcirculation (Heyeraas and Aukland, 1987).

Diagram 10, Renal (Micro-) Circulation of Kidneys

The hydraulic resistance (reciprocal value of conductance) is regulated by cross-sectional area of vessels. The higher cross-area the faster can be the blood stream at the same pressure gradient. Radius of this area is a function of circumference, which is determined by current length of vascular smooth muscle around. The vascular smooth muscle tone is regulated with many influences described as factors above (Mellander and Bjornberg, 1992; Shigemi, et al., 1994). The vasoconstriction causes increasing of resistance and pressure together with decreasing blood flow. The vasodilation has opposite effects. This kind of vascular regulations is specific for each tissues, where can be disabled or enabled any of the factors or it can be set to different sensibility for different tissues.

### Blood properties

Blood volume is calculated as plasma volume plus volume of red cells. The blood plasma volume is calculated by Water subsystem, but the amount of red cells is integrated inside Cardiovascular subsystem with component of Diagram 11. Using population components from Physiolibrary (Equation 32 and Equation 33) is implemented increasing of erythrocytes by erythropoiesis or transfusion and decreasing of erythrocytes by their natural mortality or by hemorrhage. The rate of erythropoiesis is determined by concentration of erythropoietin, which is modeled in section about Hormones.

Diagram 11, Red Cells

The last additional component of cardiovascular system is block with general blood properties such as total blood volume, hematocrit, viscosity or viscosity conductance effect. Viscosity of blood is strongly dependent on the hematocrit (Begg and Hearns, 1966; Schrier, et al., 1970; Stone, et al., 1968), so the higher number of red cells the less ability for blood to move. But if there are more red cells with hemoglobin, then the more oxygen can be connected to hemoglobin. As a result optimal hematocrit for oxygen transport between this two conditions is experimentally measured as 40-60% in the most tissues (Fan, et al., 1980; Jan and Chien, 1977).

Figure 6, Viscosity Conductance Effect on Hematocrit with measured data of Fan et al. (Fan, et al., 1980)

### Comparison with HumMod v1.6

The cardiovascular system has many differences between Physiomodel and HumMod 1.6 with very similar results of the simulations.

In our Physiomodel is the accumulation of blood volume in systemic veins implemented with the same component (Equation 27, ElasticVessel) as in other places of circulation. And the total blood volume is calculated as the sum of these compartments. The original HumMod v1.6 is calculating integration of total blood volume instead of systemic venous blood volume, which is calculated as the rest of the blood volume from all other places in the body. These reformulations leads to the same steady state equations, so during normal situation when the blood volume remains constant the simulation results are the same. Also after stabilization and equilibration to the new blood volume must be reached the same results. However, our component based solution has better properties in dynamical situation, where the fast blood changes can be apply to the specific parts of the circulation with local dynamical responses. The cross checking in Physiomodel is done using the conservation law of blood volume with known changes of total blood volume. The change of sum of blood volume of all circulation components must be the same as the external changes from/to circulation. These tests uncovers also the non-correctly defined changes of blood volume of heart ventricles and their connections with end systolic pressures, which are also corrected in Physiomodel in contrast with HumMod 1.6.

Because each circulation component must be connected in the circuit diagrams, all blood flows are correctly defined by these diagrams in Physiomodel. The original textual representation of HumMod has not any type of connection checking, so there is very easy to forget to connect for example blood flow from splanchnic circulation to the systemic veins. In Modelica diagrams it is visible if some physical connectors are not connected. So the user see the blood outflow from component unconnected. Even to make flows from/to the environment he should use the specific component such as flow pumps or fixed pressure source.

In the graphical diagrams are the connections very illustrative. Finding the all equations of blood flows in original HumMod and effort to understand of these equations must lead also to very similar illustrations. If these illustrations has a mathematical meaning behind as in Modelica then is the understanding and upgrading of the model very easy. In this diagram is for example immediately evident that the coronary circulation in the HumMod is accessing the systemic veins as other peripheral blood flows. The Physiomodel changes this to more anatomic precise idea that coronary circulation ends directly in the right atrium. As a result it was recalculated the resistance parameter of coronary vessels to new pressure gradient (between aorta and right atrium) to reach the same coronary blood flow.

There are still some small disproportions of cardiovascular system in both models. For example the changing of pulmonary blood flows through ventilated alveoli is not connected in circulation circuit. The total pulmonary circulation in these versions is independent of this process, which in reality must be interconnected. Also the renal blood flow through vasa recta in not correctly connected in cardiovascular system. All of these parts can be upgraded in the next version of the models.

## Body Water

The model of water (Diagram 12) such as the model of extracellular proteins is divided into eight main compartments: blood plasma (plasma), red blood cells (RBC), interstitial (IST) / intracellular (ICF) water of upper torso (UT), middle torso (MT) and lower torso (LT). These compartments are connected with chemical connectors, which support also the osmotic processes. Selected distribution of body water (41L for 70kg man) between compartments is written in Table IV. From these values can be expressed also the total interstitial, extracellular or intracellular volume used for simplified pharmacokinetic calculations.

Table IV, Typical steady-state water volume of compartments [L]

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Plasma | RBC | UT\_IST | UT\_ICF | MT\_IST | MT\_ICF | LT\_IST | LT\_ICF |
| 3.0 | 1.6 | 2.3 | 5.0 | 5.7 | 12.5 | 3.4 | 7.5 |

Diagram 12, Water Subsystem

Selected mean water flows between all compartments are listed in Table V as examined in many studies (Eisenhoffer, et al., 1994; Engeset, et al., 1973; Henriksen, 1985; Xie, et al., 1995). The steady state of Table V causes the sum of each row and each column to be zero. Rows has the meaning of flow description and columns means the places. The places into which comes the water if the value is positive. Or the places from which becomes the water if the value is negative. For example in the first line is the water absorbed from diet in gastrointestinal tract - it comes from the environment (ENV) and goes into the blood plasma (Plasma). In each torso it is metabolically produced and also excreted by sweating or by vaporization. Flows such as hemorrhage, transfusion, intravenous drip, to peritoneum, to lungs edema are zero at normal condition. Excretion to urine is modeled by kidney component.

Table V, Selected steady-state water flows between compartments [ml/min]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Plasma | UT | MT | LT | ENV |
| From diet | 1.4 |  |  |  | -1.4 |
| Across capillaries | -3.01 | 0.38 | 1.23 | 1.40 |  |
| Lymph | 2.41 | -0.32 | -0.75 | -1.34 |  |
| From metabolism |  | 0.06 | 0.11 | 0.06 | -0.23 |
| Evaporation |  | -0.12 | -0.59 | -0.12 | 0.83 |
| Urination | -0.8 |  |  |  | 0.8 |

### Extracellular proteins

Water distribution between cardiovascular and interstitial space is married with colloid osmotic pressures, what leads to calculation of extracellular proteins of the same compartments as described in previous section. Usually are proteins calculated at mass units, but our implementation calculate their amount of substance, because the mole fractions plays the role in osmotic equilibrium (Equation 8). The molar mass of albumin is 66.5 kDa. And the mass of albumins is about 60% of total plasmatic protein mass. The rest of significant colloid proteins are globulins. The typical molar amount of plasmatic proteins as presented in Table VI. The general way how to recalculate the mass-molar units can be joining an osmotic pressure equation as mass function (Ahlqvist, 2003; Manning, 1987) with Equation 8, where the molar volume of water is around 0.018 L/kg.

Table VI, Typical plasma proteins concentrations

|  |  |  |
| --- | --- | --- |
| Total | Albumin | Globulins |
| 1.44 mmol/L | 0.63 mmol/L | 0.81 mmol/L |
| 28 µmol/mol | 12 µmol/mol | 16 µmol/mol |

As was mentioned, the model of proteins (Diagram 13) has four main compartments: blood plasma, upper torso interstitial space, middle torso interstitial space and lower torso interstitial space. Normal concentrations at interstitial compartments are listed in Table VII. Normal mean proteins synthesis is the same as protein degradation. Their current values can be changed with deviation of their plasmatic concentration. Movement between compartments is caused by capillary membrane concentration gradient or by lymph flow (Mayerson, et al., 1960) from interstitial space to blood as implemented in scheme of Diagram 13. And special changes of plasmatic concentration can be done by intravenous therapy, hemorrhage or pathological states. Pathological states such as proteins entering the peritoneum space or breaking glomerular membrane as filtration to primary urine.

Table VII, Typical protein concentrations in interstitium

|  |  |  |
| --- | --- | --- |
| Upper torso | Middle torso | Lower torso |
| 0.6 mmol/L | 0.48 mmol/L | 0.4 mmol/L |
| 28 µmol/mol | 28 µmol/mol | 28 µmol/mol |

Diagram 13, Subsystem of Extracellular Proteins

### Gastro intestinal water absorption

As presented in Table VTable IV, the mean water in diet should be about 2 l/day, which is the sum of water in food and drinks. Firstly is water accumulated in gastro intestinal lumen (GILumen). From the lumen can water cross the cellular membrane of gastrointestinal cells (OsmBody\_CellWall) using aquaporines to equilibrate its extracellular and intracellular mole fractions (Diagram 14).

Diagram 14, Water Absorption in Gastro-Intestinal Tract

The absorption of water from gastrointestinal lumen into the intestinal cells is here driven only by osmotic forces. The typical mean intake of 2 L/day is caused by mean osmotic pressure gradient of 25 kPa at temperature of 37°C. From these assumptions can easily express the permeability parameter as 0.08 L/(kPa.day).

### Upper/Middle/Lower torso water

Flow between plasma and interstitium is determined by colloid osmolarity on the capillary walls. Another way is the one directional lymph flow from interstitium to blood plasma (Eisenhoffer, et al., 1994; Engeset, et al., 1973; Henriksen, 1985), as presented in Table V. These flows can be influenced by the internal pressure in tissues caused by its volume and skin as examined by Gyuton (Guyton, 1965) or Xie (Xie, et al., 1995). Water crossing the capillary wall is driven by hydrostatic-[oncotic](https://en.wikipedia.org/wiki/Oncotic_pressure) pressure gradients as expressed by Equation 8.

Table VIII, Amount of substances per liter of fluids

|  |  |  |  |
| --- | --- | --- | --- |
| Substance | UT | MT | LT |
| IST - Total | 21.96 mol | 17.57 mol | 14.64 mol |
| IST - Water | 21.85 mol | 17.48 mol | 14.57 mol |
| IST - Electrolytes | 0.10 mol | 0.08 mol | 0.06 mol |
| IST - Urea | 2.3 mmol | 1.9 mmol | 1.5 mmol |
| IST - Glucose | 2.3 mmol | 1.9 mmol | 1.5 mmol |
| ICF - Total | 39.05 mol | 39.05 mol | 39.05 mol |
| ICF - Water | 38.86 mol | 38.86 mol | 38.86 mol |
| ICF – Electrolytes | 0.15 mol | 0.15 mol | 0.15 mol |
| ICF - Urea | 4.1 mmol | 4.1 mmol | 4.1 mmol |

However the flow of water between interstitium and cells is determined by its model fraction equilibrium. In cellular membrane the proteins osmolarity plays the minor role, because their concentration is only about 1 mol/L. Here in extracellular space is total amount of substances divided into water, electrolytes, urea, glucose and other solutes. And in intracellular space are water, electrolytes, urea and other solutes. The small total amount of solution in interstitial fluid is caused with huge molecules, which take the most of solution volume (60-74%) by their small amount (less than 10 mmol/L).

Diagram 15, Water exchanges for Upper, Middle or Lower Torso

### Kidney water excretion

In kidney is water delivered by blood to the glomerulus, where is blood plasma filtrated to glomerular filtrate (GFR). Most of this filtrate is reabsorbed in nephron parts: proximal tubule (PT), loop of Henle (LH), distal tubule (DT) and collecting ducts (CD) and the rest is accumulated in bladder as urine.

Table IX, Typical average steady-state flows through nephron [ml/min]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| GFR | to LH | to DT | to CD | to Bladder |
| 120 ml/min | 57 ml/min | 41 ml/min | 4.6 ml/min | 0.8 ml/min |

Diagram 16, Water excretion by kidney nephrons

Proximal tubule:

Glomerular filtrate in glomerulus has the same pressure as blood in glomerulus and this pressure push it into nephrons. Reabsorption fraction in proximal tubule is determined only with sodium reabsorption of proximal tubule.

Loop of Henle:

Only the short coronary nephrons contains the aquaporin channels inside loop of Henle, which makes here the water reabsorption fraction only 37% of sodium reabsorption fraction (Gottschalk and Mylle, 1959; Nielsen, et al., 2000).

Distal tubule:

Outflow of filtrate to collecting duct is determined by outflow of sodium, where it is dependent on ADH nephron concentration as was described in studies of Khokhar et al. and Atherton et al. (Atherton, et al., 1971; Khokhar, et al., 1976).

Collecting duct:

In collecting duct are the number of active aquaporin channels driven by ADH and it proportionally means the volumetric flow rate of reabsorbed water by collecting duct tubules (Jamison and Lacy, 1972; Jamison, et al., 1971). Changing the activity of aquaporin channels is modeled by integration of inactive channels driven by ADH concentration as simulating the process of their intracellular vesicular storage. There is the minimal water outflow to urine, which is determined by sodium outflow to urine and medulla osmolarity.

### Hydrostatic spillover

Orthostatic position play also a role in water transports. The hydrostatic pressure component can be calculated using Equation 29. Together with hydrodynamic blood pressure and osmotic pressure components it forms the pressure gradient on capillary walls of tissues. The values of blood hydrostatic pressure and interstitium hydrostatic pressure are different in stand up possition. They are caused by different height of compact liquid columns, which are generating the pressure. The blood vessels are mostly compact and open tubes, where the highest place determine the hydrostatic pressure of the places below. And these hydrostatic pressure component can be calculated only from the height difference. While the interstitial space can be more hydrostatically independent, which means that the weight of the tissue water can be hanged using system of cavity membranes, what generated a smaller heights of hydrostatic columns. In lower torso veins are during motions of leg skeletal muscle enabled the pumping effect of the same basis as the heart pumping. The reason is the availability of vein valves, between which are accumulated some volume of blood from lower parts during skeletal muscle relaxation and ejected to upper parts of systemic veins during skeletal muscle contraction. This pumping effect are not only reducing of hydrostatic pressure, but also actively increases the blood flow of systemic veins during walking, running or cycling.

### Relational comparison with HumMod 1.6.1

The main differences between HumMod and Physiomodel water calculation is that Physiomodel is more physical based, but with almost the same results.

It means that for example the osmosis is calculated by equilibrium of chemical potentials as in textbooks of physical chemistry (Mortimer, 2008). The impermeable proteins of plasma and interstitial fluid are in Physiomodel recalculated to molar amounts. These molar amounts was selected by mass amounts of HumMod to reach the same normal values of osmotic pressures on capillary membrane. The oncotic pressure is calculated in both models from these proteins, which cannot freely cross the capillary membrane. Their molar concentrations in Table VI, Typical plasma proteins concentrationTable VI and in Table VII are consistent with both the physical osmotic pressure calculation and with their original mass concentration (Ahlqvist, 2003), where the ratio between mass and molar concentration is the average molar mass of these proteins.

In textual representation is easy to misuse the variable in the place of another one. As a result the equations can be totally wrong, which is immediately seen in simulation results, or worse if the both variables has the similar values then all seems to be all right until the specific setting is applied. This is the case of regional capillary blood pressure in HumMod 1.6. If the patient is lying on the bed all this regional pressure are the same. If he stand up the hydrostatic pressures changes with different heights differences from heart (Equation 29). As a result there will be higher regional capillary pressure in lower torso and lower regional capillary pressure in upper torso. The Physiomodel calculate with that, but in HumMod 1.6 is this tissue capillary pressure gradients calculated always only from upper torso capillaries pressure also in middle or in lower torso.

In Physiomodel it is also improved the relation of losing water by vaporization in respiratory pathways. In HumMod 1.6 is assumed that all water in expired air becomes from vaporization. However, there can be significant humidity of the inspired air. The Physiomodel just insert this humidity to slow down the expiration of the water in hot humid environment.

The last differences of the Physiomodel with the HumMod 1.6 is the behavior of the tissue water in initial state and during steady state. For example the lymph flow of upper torso was too slow to deliver the same amount of water from upper torso interstitial space as the amount of water crossing the capillaries membranes at the same time and in the same place. So the interstitial water of the upper torso is slowly increasing from the beginning of the simulation to some pathophysiological values. To prevent this instability of the model we recalculate the permeability coefficient of the upper capillaries to meet the steady state of these flows. As a result there are initial steady state of interstitial water in Physiomodel.

## Hormones

### Anti-Diuretic Hormone (ADH, Vasopressin)

Arginine vasopressin known as antidiuretic hormone (ADH) has molecular weight of 1084 Dalton. ADH as a hypothalamic neurohormone is synthesized in the cell bodies of magnocellular neurons of paraventricular and supraoptic nucleui and it is intracellulary transported to the lower side of these neurons in posterior pituitary.

Diagram 17, Vasopressin

The model (Diagram 17) accumulates the amount of this hormone in four places: in the cell bodies of magnocellular neurons (Slow Mass), from where need to be transported to the posterior pituitary part of the cells; in the posterior pituitary side of neurons (Fast Mass), where ADH is prepared for secretion into blood; in the whole body extracellular fluid (ECF); and in the kidney tissue, where it plays the role in water reabsorption. The normal long-time amounts of ADH in these compartments are listed in Table 10, but during the regulation the concentrations can be increased of the hundreds or thousands times (Lankford, et al., 1991). The normal long-term mean rate of synthesis, secretion and degradation should be the same at steady-state. But the secretion as a short-time process can reach much higher changes. The effect of various changes and concentrations was demonstrated in dosage experiments (Atherton, et al., 1971). The internal secretion is determined by osmoreceptors and pituitary activity. Osmoreceptors are the cells in anterior hypothalamus near the supraoptic nuclei. When the osmolarity increase the osmoreceptors shrink and they send a neural signal to release ADH (Young, et al., 1977). Other possibility to regulate ADH secretion is cardiovascular centrum reflexes (Erwald and Wiechel, 1978).

Table 10, Selected long-term steady state amounts of vasopressin

|  |  |  |  |
| --- | --- | --- | --- |
| Slow Mass | Fast Mass | ECF | Kidney Medulla |
| 15.7 nmol | 2.95 nmol | 0.028 nmol | 0.000 057 nmol |

The vasopressin inside cells is modeled using instances of chemical Substance class, the intracellular vesicular mole fraction is 1 because ADH is transported as pure substance by vesicles down the cell. The degradation is divided into liver, kidney and other tissue blood clearance. To reach the mean constant level of ADH the sum of all long-term mean losses must be the same as the long-term mean synthesis and secretion. The loss of ADH in these organs as an enzymatic degradation in liver, kidney and other tissue is dependent on blood flow.

A typical concentration in blood plasma and extracellular fluid is in order of ng/l, pg/ml, pmol/l or mIU/l. Increase of concentration causes the water reabsorption in kidney (Lankford, et al., 1991).

### Atriopeptin

The secretion of atrium natriuretic peptide (ANP) is driven by mean blood pressure in both atria. These pressures are relative to pericardium pressure around noted with suffix ‘\_TMP’ in Diagram 18. There is an adaptation of secretion to current pressures with half time about fifteen minutes makes from ANP the middle-term regulator of blood pressure and blood volume (Conte, et al., 1992; METZLER, et al., 1986; Mizelle, et al., 1990; Nicholls and Richards, 1987; Renkin and Tucker, 1996; Weidmann, et al., 1986; Yandle, et al., 1986).

Diagram 18, Atrium Natriuretic Peptide

### Catecholamines (Epinephrine; Norepinephrine)

The model of catecholamine accumulation, secretion and clearance are very simple. Driven by sympathetic neural activity is secreted in adrenal gland. Than it is accumulated in extracellular space and continuously degraded with clearance, which at long-term steady state causes the same mean degradation as the mean secretion for the long-term average of concentration. This model is observed also by experiment of 60-minutes continuous intravenous epinephrine infusion, where different nominal rates causes different steady-state plasma epinephrine concentrations (Clutter, et al., 1980).

Diagram 19, Catecholamines model is composed with model of Epinephrine and Nonepineprhine

The effect of catecholamine in alpha or in beta receptors on the effector organs is expressed as decimal logarithm of the concentration. This effect is combined with sympathetic neural activity on the receptors and can be blocked by alpha- or beta- blockers.

### Erythropoietin (EPO)

The erythropoietin (EPO) secretion is driven by partial oxygen pressure in kidneys (BAUER, 1993) (Goldberg and Schneider, 1994; Jacobson, et al., 1957; Pagel, et al., 1988; Porter and Goldberg, 1993). In contrast with previous hormones the distribution space of EPO is not whole extracellular fluid, but only about 40% of them (Miller, et al., 1982; Reissmann, et al., 1965). The mean degradation must be the same as the mean secretion during typical mean concentration in steady-state.

The role of erythropoietin is connected with erythropoiesis in the bone marrow (Jacobson, et al., 1957; Roush, 1995; Winearls, et al., 1986).

### Insulin and glucagon

Insulin is one of the most studies hormone. His molar mass is 5.808 kDa. First standard international unit of insulin was in year 1958 (Standardization and Organization, 1958), the last discontinued definition from year 1986 has improved to 38.46 µg/IU (Standardization and Organization, 1987). Using this definition it is possible to estimate the conversion such as 6.621pmol/IU.

The insulin pharmacokinetic and pharmacodynamics obeys the same principle as the model of glucose-insulin homeostasis by Guyton et al. (Guyton, et al., 1978). Insulin is synthetized and stored in beta-cells and its secretion is driven primary by glucose and secondary by keto-acids (Imai, et al., 2008; Rutter and Hill, 2006). Portal and peripheral vein insulin has different concentration (Blackard and Nelson, 1970), because insulin is transported just after secretion by portal vein to liver. Absorbance and clearance was measured by many infusion experiments (Dobson, et al., 1967; DOEDEN and RIZZA, 1987; GINSBERG, et al., 1973).

Problems with insufficient insulin secretion results in type 1 diabetes mellitus and the receptor insensibility leads to type 2 diabetes mellitus (George, et al., 2004; Prager, et al., 1987; Summers, et al., 1997), where many differences between normal and obese individuals has been observed (Prager, et al., 1986). Insulin has the significant effects to glucose absorption by cells of liver (Iwanishi, et al., 2000; Previs, et al., 2000; Rother, et al., 1998), where is glucose stored and release to/from glycogen (glycogenesis, glycogenolysis), created from amino-acids (gluconeogenesis) or transformed to fats (lipogenesis) (Guyton, et al., 1978; Miles, et al., 1995; Prager, et al., 1986). The similar effect to glucose absorption and storage as glycogen is modeled in skeletal muscle tissue. The insulin also helps the fatty acids to be stored in adipose tissue as modeled in lipid submodel of metabolism fraction.

Against to this storage effect of Insulin goes glucagon, which helps to increase the glucose and fatty acids concentration in the extracellular space. But the dependence of secretion of glucagon is on the insulin concentration (and of course the glucose concentration) makes from it the secondary regulator of blood glucose concentration.

### Leptin

Leptin is secreted by adipose tissue as a signal from accumulated lipids (JÉQuier, 2002). But the idea to cure obesity with leptin fails on leptin resistance joined with obesity (Myers Jr, et al., 2010) (Friedman-Einat, et al., 2003). The clearance of leptin is primarily by kidney (Cumin, et al., 1996). It has multiple effects on higher metabolic centers (Mantzoros, et al., 2011; Wong, et al., 2004), which is modeled mainly by influencing of diet composition and the amount of eaten food as a result of changed taste by leptin concentration.

### Renin-angiotensin-aldosterone system

The secretion of renin in kidney is driven by tubulo-glomerular feedback (TGF) (Braam, et al., 1993; Seeliger, et al., 1999) and adrenergic receptors (Almgård and Ljungqvist, 1975; WINER, et al., 1969). The clearance is primarily by liver (Christlieb, et al., 1968). Renin is an enzyme, which converts angiotensinogen into angiotensin I. This conversion obeys Michaelis-Menton dynamics, which makes linear dependence between the amount of renin and the rate of conversion (Goldblatt, et al., 1953). The same dynamic is observed in lungs with angiotensin converting enzyme (ACE), where is angiotensin I transformed into angiotensin II. In optimal regulation conditions it gives the linear dependence between renin concentration and angiotensin II concentration (Claassen, et al., 2013).

### Thyroid hormones

The main purpose of thyroid hormones in our model is to maintain basal metabolism in connection with long-term thermoregulation (Edelman, 1974). The concentrations, secretions and clearance of thyroid hormones are well known because of relative easy measurement of iodine radioactive isotopes (HAYS, 1993; Chopra, 1976; Larsen, 1972; Nicoloff, et al., 1972). During cold months increasing of triiodothyronine (T3) (Hesslink, et al., 1992) increase the basal metabolism (Osiba, 1957) what improve the heat regulation in cold conditions. The impulse for the production and secretion of T3 and thyroxine (T4) is thyrothropin (TSH) (Jackson, 1982). And the secretion of TSH is driven by thermoreceptors and it is directly suppressed by T3 (Gross and Pitt-Rivers, 1953; Hesslink, et al., 1992; SURKS and LIFSCHITZ, 1977; SURKS and OPPENHEIMER, 1976). The clearance of TSH is much quicker than clearance of T3 or T4  (Ridgway, et al., 1974), as a result its concentration can be directly estimated from the secretion, which is determined by current thyroxines concentrations and temeprature.

### Comparison with HumMod 1.6

There are also some small corrections of hormonal equations in Physiomodel, but the mean levels of hormones are finally almost the same as in HumMod 1.6. Solving for example the mish-mash of physical units or the confusion of a variable.

The clear vision of modeling all organic chemical substances was to calculate the amount of their molecules. This is the idea of using molar units. The amount of substance in moles multiplied by Avogadro constant has the meaning of the number of particles. However, today even the Avogadro constant is approximated and as a decimal number it has only first eight from twenty-tree digits exactly determined. It means, that the precision of counting the particles of solution is limited and we exactly do not know to measure and to work with very small molar concentrations (such as piko- or fento- moles per liter). Unfortunately these very small concentrations are biologically significant for some hormones, enzymes or cytokines. Instead of physical units there must be used some pharmacokinetic units (u or iu – international unit defined by [WHO](http://www.who.int/biologicals/reference_preparations/en/)), which are defined by the solution extract as a result of described purification. In Physiomodel is this situation solved using redefinition of Physiolibrary, where all moles are switched to international units of the specific hormone, enzyme or cytokine. This redefined library components must be used for each block calculating with the connected substance. For example if we want to create the chemical reaction of this ‘unmeasurable’ hormone with his receptor then also the concentration and amount of receptors must be in the same international units as the hormone is. Hormones, enzymes or cytokines with already known conversion should be used in their physical amount of substance better than international units.

It is not surprise that the physical units can be a source of many mistakes in the models, especially for hormones, where the unusual prefixes as micro-, nano-, piko-, fento- are used together with more alternatives how to express the concentrations such as molar concentration, mass concentration, molar fraction, mass fraction or international units. For example in HumMod 1.6 are this unit mish-mash with thyroid hormones, where the concentration if one hundred times higher because switch ‘ug/ml’ for ‘ug/dl’ – compared with data of (CHOPRA, et al., 1975). Using Physiolibrary in some user-friendly Modelica environments there are automatic support to recalculation SI units into non-SI units, including different prefixes. Using this automated physical unit support for inputs and outputs of simulation there is the modeling process becomes more error-free in the field of unit conversions.

The other example of change of variable names in HumMod 1.6 is in intracellular renin fluxes calculations. Instead of the flux from free renin synthesis to renin granules, there is the same variable used as intake and outtake of the renin granules. So the renin granules has the same concentration during each time in each simulation experiment even if rapid secretion occurs. Using the diagram modeling of Physiolibrary it is very clear, from which or to which compartment are the flows of renin. And the probability of this kind of mistake decreases because the connections are visually self-descriptive.

The change of physical units can hide the more contextual errors. For example the change of vasopressin by blood clearance in circulating blood through tissue must be less or equal than the amount of vasopressin inflowing by blood to this tissue. And because here are in the flow multiplied coefficient hidden the recalculation from milliliters to liters, there the value higher than one is hidden by dividing of thousand. This confusion is visible in other tissue clearance of vasopressin in HumMod 1.6 and in Physiomodel it is resolved by selecting full clearance in this type of tissue, which generates only a little lower degradation of vasopressin.

## Electrolytes and Acid-Base

### Acid-base

The acid-base balance calculation is based on electroneutrality. In plasma, in extracellular and in intracellular fluid it is calculated summary of charges of strong ions, which do not significantly change their charge at pH from 5 to 9. This is called strong ion difference (**SID**) (Stewart, 1981). As an analogy of SID can be used the variable anion gap (**AG**), which is the same as SID with charge of bicarbonates (AG = SID – [HCO3-]), where are also not included the amounts and properties of other non-bicarbonates acid-base puffers. The acid-base buffers (HCO3-and other weak ions) are calculated as the **negative** summary charge concentration at normal conditions (prefix N) called normal strong ion difference (**NSID**). The **normal conditions** are defined as **plasma pH=7.4, full oxygen saturation, CO2 partial pressure 40mmHg and temperature 37°C**. The NSID describes the potential of acid-base buffers. It has in normal condition the same value as SID. In situation of higher value of NSID than SID (for example there is an excess of strong acids) is the arterial pH<7.4 during normal state of respiration at 37°C. And if NSID<SID then pH>7.4 (for example excess of strong bases) during normal state of respiration at 37°C. Both SID and NSID can be calculated in plasma (suffix P) and inside erythrocytes (suffix E). The titration of one liter of blood to reach the normal conditions need to use the same amount of strong acid as the differences between SID and NSID in plasma and in erythrocytes (Mateják, 2013): expressed as **BEox** = Hct\*(SIDE-NSIDE)+(1-Hct)\*(SIDP-NSIDP), where Hct is the hematocrit and BEox is the base excess of oxygenated blood as defined by (Kofránek, 2009; Kofranek, et al., 2007). This measurable amount of titrant can be expressed also as negative value called titratable hydrogen ions of oxygenated blood (**cTHox** = ‑BEox) used by Siggaard with Van-Slyke equation (Siggaard-Andersen, 2005). The BEox and cTHox are independent of blood gases (CO2, HCO3-, O2), which makes from them a perfect candidates for describing metabolic part of acid-base disorders. The respiratory problems or additional regulations of acid-base disorders should be seen immediately from arterial blood partial pressure of CO2, which should be normally regulated by respiration to 40mmHg.

Diagram 20, Acid-Base Subsystem

The acid-base equilibrium is connected with all charged substances by electroneutrality. The charges of substances are calculated in physical unit called equivalent (**eq**) or miliequivalent (1 meq = 0.001 eq). The positive value means positive charge, negative means negative charge. From definition the one **equivalent** is the charge of one mol of protons, which is the same as one mol of sodium cations Na+ or the same as half mole of calcium cations Ca2+. The typical SIDP is composed with Na+, K+, Cl-, SO42-, Lactate‑ and the typical NSIDP is calculated as a negative sum of normal bicarbonate HCO3-, albumin, phosphates and globulins charges at hypothetical pH=7.4 and temperature 37°C. In erythrocytes the SIDE is typically sum of charges of K+, Cl-, Na+, Mg2+ and SO42-. The NSIDE is the negative sum of charges of HCO3-, hemoglobin, phosphates such as 2,3-DPG, ATP, ADP and GSH at hypothetical plasma pH=7.4, full oxygen saturation of hemoglobin and temperature 37°C. Other electrolytes and buffers are neglected because of their small concentration and/or small charge. This calculation in Physiomodel is similar as calculation of Raftos et al. (Raftos, et al., 1990), Wolf et al. (Wolf, 2013; Wolf and DeLand, 2011).

Diagram 21, Acid Buffers (Normal Strong Ions Difference)

The calculation of charge of the weak ions (weak acids) is dependent on pH, because they are each time equilibrated such as chemical reactions in Table 11. First schematic reaction is called Henderson-Hasselbalch equation and is usually used to calculate the carbonic acid dissociation to bicarbonate, many times connected also with CO2 dissolution in water (Equation 13) and CO2 hydration to H2CO3 accelerated by carbonic anhydrase inside red cells. The acid-base equilibrium can be calculated as Equation 11, where the dissociation constant K can be defined using negative decimal logarithm as pK = ‑log10(K).

Table 11, Scheme of acid-base reactions

|  |  |  |
| --- | --- | --- |
| Group of acid | Type of reaction | Example of acids |
| Monoprotic | HA ↔ A- + H+ | HCl, -COOH, some protein side chains |
| Diprotic | H2A ↔ HA- + H+ ↔ A2- + 2H+ | H2SO4, H2CO3 |
| Polyprotic | HnA ↔ Hn-1A- + H+ ↔ … | H3PO4 |
| Brønsted | AH+ ↔ AH + H+ | NH4+, -NH3+, some protein side chains |

Table 12, Dissociation constants (pK) of selected acid-base reactions

|  |  |  |
| --- | --- | --- |
| Chemical reaction | pK | Temperature of pK |
| CO2(aq) + H2O ↔ H+ + HCO3- | 6.103 | 37°C |
| HCO3- ↔ H+ + CO32- | 10.329 | 25°C |
| AcAc ↔ H+ + AcAc- | 3.6 | 37°C |
| β-Hb ↔ H+ + β-Hb- | 4.7 | 37°C |
| HSO4- ↔ H+ + SO42- | 1.99 | 25°C |
| H3PO4 ↔ H+ + H2PO4- | 1.91 | 37°C |
| H2PO4- ↔ H+ + HPO42- | 6.66 | 37°C |
| HPO42- ↔ H+ + PO43- | 11.78 | 37°C |
| NH­4+ ↔ H+ + NH­3 | 9.25 | 25°C |

### Kidney acid-base regulation

In the kidney is pH regulated with excretion of titratable hydrogen ions H+ and with ammonium ions NH4+. In contrast with H+ of weak acids, the protons connected into NH4+ remains more bounded than separated as H+ and NH3 at pH is lower than 9.2. Which is the typical situation, because urine pH can vary between 4.6 and 8. To connect the flowing acidity of urine (pHu) with flow of all charged substances is used electroneutrality. The total molar flow of each substance is described in following subsections, but not always the charge of substance in urine remains the same as in extracellular fluid. This is caused by different pH. For example during acidic conditions (more H+, lower pH) of urine the H+ is joining the organic acids and phosphates (H2PO4-). And during more basic conditions (less H+, higher pH) of urine the H+ leaves from phosphates (HPO42-) or even some H+ can be separated also from NH4+ , HCO3-. These electrolytes as HPO42-, PO43-­, CO32- or C2O42- can react with calcium Ca2+ to create solid salts crystals known as the kidney stones. The charge of each substance is calculated using its scheme of chemical reaction (Table 11) in equilibrium of Equation 11 using dissociation constants from Table 12.

### Sodium

The sodium (Na+) concentration is modelled in extracellular space to reach typical value from 140 to 150 mmol/L. Intake of sodium is from diet by gastro-intestinal tract, outtake to urine is regulated by kidney and outtake by sweating is expressed as sweat glands (Diagram 22). Other mechanisms to change the sodium mass (often together with change of fluids volume) are modeled as dialysis, intravenous drip, transfusion or hemorrhage.

Diagram 22, Sodium in extracellular fluid

Diagram 23, Kidney excterion of sodium

In the kidney are the sodium cations filtered by glomerulus to primary urine of nephrone. In each part of nephrone the sodium is actively reabsorbed into the kidney medulla (Diagram 23). And together with sodium is reabsorbed also the water expect the collecting duct and the Henle’s loops of juxtamedullary nephrons, where are missing the aquaporines. After glomerular filtration is the sodium reabsorbed in proximal tubule, loop of Henle, distal tubule and finally in collecting duct. The reabsorption is driven by aldosterone, atrial natriuretic peptide and angiotensine 2. Reabsorbed sodium is accumulated inside kidney medulla, where it is the secondary determinator of osmolarity. The first is urea. From kidney medulla is washed out by vasa recta blood flow, where the equilibrium between tubular reabsorption and vasa recta outflow set the high intramedullary sodium concentration.

Diagram 24, Sodium excretion by sweat gland

The backward reabsorption of sodium from excreted sweat is driven by aldosterone. When the amount of excreted water by sweat glands is high all sodium from sweat is not reabsorbed and it remains as salts in surface of skin.

### Potassium

The most of potassium (K+) is stored inside cells, so the potassium model must be composed at least with two compartments – intracellular and extracellular (Diagram 25). The intake is mainly from gastro-intestinal tract and main outtake goes through kidney nephrons to urine. The potassium flow through cellular membrane is regulated by Nernst potential, by aldosterone and by glucose intake to the cells. Also the kidney excretion and sweating potassium amount is affected by number of channels, which expression is affected by aldosterone.

Diagram 25, Potassium of intracellular and extracellular fluid

Diagram 26, Cellular membrane potassium transport

Diagram 27, Kidney potassium excretion

### Phosphates and Sulfates

The sulfates (SO42-) and phosphates (H­PO42-, H­2PO4-) are accumulated in extracellular fluid. Intake is from diet and unregulated outtake to urine just undergoes the Donnan’s equilibrium at glomerular membrane (Equation 9).

### Comparison with HumMod 1.6

Acid-base in Physiomodel is totally different as in HumMod 1.6. The new calculation uses the original electrolytes models of strong ions. However, the pH is calculated from electroneutrality equation applied on significant weak ions as phosphates, proteins and carbonic acid. Charge of these weak ions is dependent on pH known as titration curve, so the idea is to find the value of pH, which generates sufficient charges of the weak ions at electroneutrality with the rest of solution. The state variables are the total amounts of substances, which in the case of weak ions includes all their protonated and deprotonated forms. For example the inorganic extracellular phosphates means H3PO4, H2PO4-, HPO42- and PO43- form. The total amount is independent of pH, but the total charge on the phosphates is pH dependent. The same idea of calculation can be done also for total amount of albumin, globulins, hemoglobin or carbon dioxide. For example if we assume some constant total concentrations of all weak acids in blood plasma then we can talk about titration curve of the plasma as a function of SID on pH. However this function is dependent on the type and total concentrations of weak acids, so all charged solutes in solution must be included in calculation. This makes our acid-base model in Physiomodel better than acid-base calculation of HumMod 1.6, because there was not calculation of weak ions charges except bicarbonate. And what is worse, the inorganic phosphate is calculated as a strong ion, which does not change the form with the change of pH.

The same style of the acid-base model is applied also to urine in Physiomodel. The acidity of urine was not calculated in HumMod 1.6, but because there are all necessary data the acidity of the primary urine is calculated from the electroneutrality of all the outflowing substances. In future can be this calculation used for example for the modeling of kidney stones or for more precise functions of membrane channels in nephrons.

During simulation of metabolic acidosis as ketoacidosis (Mateják, 2013) we found that the original pH regulation is so strong that there is excreted even the non-existing chloride from the body. This confusion leads even to negative chloride concentrations. To prevent this confusion we add in Physiomodel the stopper function, which start to stop the chloride excretion if his extracellular concentration fall below 50 mmol/L. Today we do not have the exact data for this pathological function, but the insufficiency of chloride during acidosis are the known phenomenon (Levitin, et al., 1958). However in conscious patients is this situation solved with the salty taste.

## Blood Gases

To support metabolism of each cell there must be delivered oxygen (O2). And carbon dioxide (CO2) must be transported out of the body. Both called blood gases are critical for life. The blood gases transport starts by lungs ventilation to reach optimal alveolar partial pressures of carbon dioxide (pCO2) and oxygen (pO2). These pressures play roles in gases dissolving in blood. However, the total amount of transported gases is dependent also on blood flow, binding properties of hemoglobin, temperature and hydrogen ion activity. The blood is delivered so close to cells by tissue microcirculation that no other active delivery is needed and only diffusion take place here.

Diagram 28, Gases Subsystem

The submodels of gases transport are: ventilation, where is calculated the air flow, water vapor dilution, temperatures and pressures effect; oxygen transport; carbon dioxide transport; and acid-base as hydrogen ion activity calculations.

### Ventilation

Natural ventilation is driven mainly by neural reflexes. Their sensors are central chemoreceptors, which answer to change of intracellular pH; peripheral chemoreceptors located in arterial sinus and aorta detecting changes blood gases and receptors of skeletal muscle metaboreflex. Whole afferent path of respiratory reflexes are in the model summarized into one normalized value called TotalDrive, from which is in efferent part calculated the respiratory rate and normalized respiratory center motoric nerve activity.

From the lungs properties are then calculated current tidal volume (for example 450 ml at body conditions - temperature of 37°C and 100% humidity) and current dead space volume (for example 150ml at body conditions). Because the temperature and humidity in lungs differs from surrounding air environment, the alveolar ventilation is recalculated to the inspired air conditions in submodel called alveolarVentilation.

Diagram 29, Regulation of Ventilation

### Oxygen

Content of air oxygen in earth atmosphere is typically 21% with atmospheric pressure 101325 Pa, which give its partial pressure in air around 21 kPa. But the amount of oxygen molecules are still dependent on temperature driven by [ideal gas](https://en.wikipedia.org/wiki/Ideal_gas_law) equation. For example in 0°C (273.15 K) dry air is molar concentration of oxygen 9.2 mmol/l, while in 40°C dry air is oxygen molar concentration only 8.1 mmol/l at the same oxygen partial pressure of 21 kPa.

In respiratory paths are air heated to body temperature and diluted by water. Volume of inspired air is changed, which is reflected in variable AlveolarVentilation recalculated to inspired air conditions. Once the air is transported to the alveolus, the exchange take place. Oxygen dissolve in blood plasma and chemically bound the hemoglobin molecules inside red cells. Dissolving of oxygen in water is driven by Henry’s law (Equation 13), where also take place the body temperature.

Diagram 30, Oxygen

### Hemoglobin

Hemoglobin allosterically binds oxygen, carbon dioxide and hydrogen ions, what makes cross‑dependences between concentrations of all three substances in blood (Mateják, et al., 2015).

The most common hemoglobin in adults is hemoglobin A. As protein tetramer is symmetrically composed with four subunits: two alpha and two beta. In the middle of each subunit is heme with central ferritin atom (Fe2+), where the oxygen molecule is bounded. Bounding of oxygen (oxygenation) caused small change of shape of heme, which increase the probability of relaxed space conformation of whole tetramer. Otherwise, the tensed conformation is more common for fully deoxygenated tetramer. The binding of CO2 into terminal ‑NH2 group of each subunit is known as carboxylation and it is competitive with H+ binding in the same place to form –NH3+. These reactions has also different dissociation constants in tensed and in relaxed conformation. In beta-cleft are also more than ten other amino acid side chains, which are binding H+ (Bohr’s protons) with different dissociation constants in relaxed and tensed state. In normal condition is the release of two oxygen molecules connected with binding of one H+ and vice versa.

### Carbon dioxide

The most of carbon dioxide is transported by blood from tissues to lungs as bicarbonate (HCO3-). Even only small amount is bounded to hemoglobin, it makes also significant part of transported CO2 (about 23%), because of connection with oxygen binding. As written in previous section, the change of hemoglobin conformation changes also the binding properties of CO2.

The HCO3- is a salt of carbonic acid (H2CO3). It significantly affects the acid-base as mentioned in section 4.4.1. The hydration of free dissolved CO2 to H2CO3 in blood is enzymatically accelerated by carbonic anhydrases inside the red cells, from which is the HCO3- transported to plasma in exchange for chloride ion Cl- using hamburger shift channels to reach Donnan equilibrium (Equation 9).

### Comparison with HumMod 1.6

The main idea of blood gases transport subsystem is the same in both models composed with exchange in lungs, systemic arteries, exchange in tissues, and through systemic veins back to lungs. The difference is in calculations of total amount of gases in blood from their partial pressure and vice versa. The Physiomodel uses more precise calculation based on Siggaard-Andersen’s OSA (Oxygen Status Algorithm)(Siggaard-Andersen and Siggaard-Andersen, 1990). This calculation of hemoglobin oxygen saturation is dependent on pH, DPG, temperature and carbon dioxide. Also the recalculation between carbon dioxide partial pressure and carbon dioxide content in blood is from OSA in Physiomodel. This divide the total amount of carbon dioxide in blood into free dissolved carbon dioxide in plasma and in erythrocytes, into bicarbonate in plasma, and into bicarbonate and carboxylated hemoglobin amino-terminals in erythrocytes. This calculations are better as the simplified calculations of HumMod 1.6, where is the carbon dioxide calculated only as one bicarbonate concentration for whole blood independently on hematocrit or on oxygen saturation.

## Nutrients and Metabolism

Almost all mechanical energy of human body is taken from food, metabolized into small high energy compounds such as ATP, which is used by muscles, by membrane channels or by vesicular transports. The body can metabolize three groups of organic compounds: sacharides, proteins and lipids. After eating them they are absorbed in form of base nutrients such as glucose, lactate, amino acids, fatty acids, triglycerides or keto acids. The regulation of uptake, usage, storage, release or transformation of these nutrients is done mainly by hormones as leptin, insulin, glucagon and thyroxine.

Diagram 31, Nutrients and metabolism subsystem

### Cellular metabolism

The base nutrients can be changed in cellular cytosol by glycolysis or lipolysis into acetyl coenzyme A, which is used directly by mitochondrial citric acid cycle to produce high energy electrons (bound to NADH or FADH), which helps to throw the hydronium ions (H3O+ noted as H+) into the mitochondrial intermembrane space. And finally, to equilibrate the electrochemical potentials the hydronium ions has to go back to the mitochondrial matrix through the ATP synthase. The new synthetized ATP is exchanged for ADP and one phosphate across mitochondrial membranes using electroneutral symporter mechanism.

The ratio between using of the base nutrients can differs with type of cell (Randle, 1986). For example the heart muscle prefers lactate more than other organs, neural tissue prefers glucose and keto acids and it does not use any fatty acids or triglycerides (Owen, et al., 1967). The amino acids can be metabolized only by liver or in kidney tubules(Hannaford, et al., 1982), because only there can be eliminated the toxic ammonia (NH4+).

### Liver metabolism

To support good function of all cells it is necessary to have balanced extracellular concentrations of the base nutrients, even if the food is monotone and does not explicitly contains all type of these nutrients in sufficient ratios. The transforming processes from one base nutrients to another take place in livers known as gluconeogenesis(Wahren and Ekberg, 2007), ketogenesis(McGarry and Foster, 1976) or lipogenesis(Kotani, et al., 2004). Gluconeogenesis creates new glucose from amino acids, ketogenesis creates keto acids from lipids and lipogenesis can create triglycerides from glucose or amino acids.

The base nutrients can be also stored as lipids in adipose tissue or as glycogen in liver or in muscles. Stored lipids are long-time reservoir of energy in contrast with glucose stored as glycogen, which can be used much faster(Chiasson, et al., 1976). Process of storing glucose into glycogen granules is known as glycogenesis and reversal process of releasing glucose from glycogen is known as glycogenolysis (Diagram 32).

Diagram 32, Liver transformations of base nutrients

### Lipids

The lipids are transported from gastro-intestinal tract by lymph to blood plasma using chylomicrons. Chylomicrons contains mainly triglycerides, which are hydrolyzed into fatty acids. The fatty acids can be stored into lipid deposits or used for metabolic purposes of cells.

In the wall of capillaries of adipose tissue or muscles is expressed the enzyme lipoprotein lipase, which transform the triglycerides of chylomicrons into fatty acids and glycerol. These fatty acids can very easy cross the cellular membrane and be stored in adipose tissues or used as fuel for energy metabolism. Only the small amount of free fatty acids is transported by cardiovascular system typically connected to albumin. However, the turnover of them is extremely fast: each 2 or 3 minutes is half of these free fatty acids used for energy metabolism and replaced by new fatty acids from lipid deposits (Frayn, 2002).

Diagram 33, Transformation between Triglycerides, Free Fatty Acids and Lipid Deposits

### Proteins, amino-acids and urea

Almost all proteins from diet are absorbed as amino-acids. There are only 20 types of amino acids and 10 of them are essential. The essential amino acids cannot be synthetized in human body, so they must be part of the food. The primary role of amino acids is to build new proteins, but they can be also used as fuel for metabolism. The degradation of amino acids (deamination) take place almost entirely in liver hepatocytes, because only there can be transformed the toxic byproduct NH4+ into urea. The other place for deamination is in kidney nephrone tubular cell, from which is NH4+ excreted directly to urine as one of very efficient mechanism of H+ excretion without decreasing the urine pH. The deamination of amino acids in liver will prepare new glucose or triglycerides as source of energy for other cells. The new synthetized urea diffuse into the blood and take primary role in high kidney medulla osmolarity, which is necessary for water balance (Sands, 1999).

### Keto-acids

Keto acids are not the primary fuel for metabolism, but in some critical situations they can temporary substitute the missing of main nutrients especially for neural tissue. During ketoacidosis there are elevated levels of acetylacetate and beta-hydroxybutyrate. Both keto-acids are synthetized in liver from acetyl coenzyme A, which is created mainly from free fatty acids, acetic acid or ethanol (McGarry and Foster, 1976). They can be metabolized in various tissues, but the speed of degradation is limited with speed of mitochondrial metabolism. So if the production is higher than these limits, they can caused metabolic acidosis accompanied with elevated renal excretion of them (Angielski and Lukowicz, 1978; Mateják, 2013).



Figure 7, Keto acids

### Comparison with HumMod 1.6

The nutrients metabolism in Physiomodel has only small differences from HumMod 1.6 such as correcting units, stabilizing shape of approximated curves or setting of optimal diet for very long simulations.

For example the physical unit of glucose consumed during anaerobic metabolism by the tissue is in HumMod 1.6 expressed in mg/min and this value is assigned by mistake into variable in cal/min. In Modelica an user is not approved to connect incompatible physical quantity or physical units without conversion. So it should automatically prevent this type of error in Physiomodel, because glucose is here always represented by ‘amount of substance’ and ‘molar flows’ as physical quantities using ‘moles’ and ‘moles per second’ as SI-units. These units are used in each place of the Physiomodel – in chemical reactions, in glucose transports or in glucose storage.

Some approximation of effects use the cubic interpolation splines to express the empirical dependences. Using of these splines is quite easy: The user set only a few points of the x-y graph between the dependent variables. For example for the definition of the linear line only one point is enough, for more nonlinear functions are used typically two or three points. These points contains the value of x-axe, the value of y-axe and the value of slope. And the slope is the biggest problem, because it determines the shape of the function between two points. If the slope is two sharp then a small fluctuation could happened. It means that the shape of the function can leave the interval defined by y-coordinates of the points. In this situation the function loses its invertibility and it could be inconsistent also for some type of non-linear solvers such as “Newton solver”. So if it is not necessary then it is better to avoid this fluctuation by correcting of the nearest slope to the more comfort value or by adding more definition points. In HumMod 1.6 these fluctuations can be observed for example in mass effect of the glycogen to glycogenesis in liver, or in glucagon effect to ketogenesis in liver. These situations are solved in Physiomodel rotating the slope of the middle point to slightly more horizontal direction as shown in Figure 8 and Figure 9.

Figure 8, LM\_Metabolism.Glycogenesis.GlycogenMassEffect

Figure 9, LM\_Metabolism.KetoAcids.GlucagonEffect

For Physiomodel was prepared the optimal diet for the default setting (for 75kg man with metabolic rate of 2500kcal/day). There was selected to be 2000kcal of carbohydrates, 300kcal of proteins and 200kcal of fats in diet per each day. In long term simulation with this diet is the adipose tissue stabilized at 3.6 kg as 5% of body mass - typical for healthy state with normal secretion of leptin.

## Thermoregulation

### Heat

The human body works best at core temperature around 37°C. All chemical processes are dependent on temperature (Equation 6). If the temperature rise up the proteins structures become unstable. Even, actually the gene expression of 394 from 12,600 investigated genes are upregulated or downregulated after 20 minutes exposure of 43°C as examined Sonna et al. (Sonna, et al., 2002). At higher temperature there are expressed more heat shock proteins and at lower temperature there are expressed more cold shock proteins (Katschinski, 2004). Both can change the cellular processes, helps with protein refolding and if the situation get worst they can start also the cellular apoptosis. Also the cellular membrane processes are affected. So the regulation of body temperature is very important. The main mechanism how to regulate body temperature is by regulation of skin blood flow (Hardy and Soderstrom, 1938; Hsieh, et al., 1965; Kamon and Belding, 1968) (Equation 24) and of course the amount of clothes by feeling of warm or cold. There is also long-term (in periods of months) regulation of heat by thyroid hormones (Osiba, 1957), which increase or decrease the speed of basal metabolism as the source of heat in each cell. Short-term heat production is typically based on working muscles (Saltin and Hermansen, 1966) or by shivering (Florez-Duquet and McDonald, 1998). The efficiency of skeletal muscle is about 30%, so the significant part of consumed energy is released as heat during motion. It is assumed for heat transfer of any microcirculation, that temperature of outgoing blood is the same as temperature of tissue (Equation 24), so the blood flow directly determine the amount of transferred heat between body core and tissue. Typically the heat is conducted from warmer place to colder, but the heat can be also transferred by chemical processes as evaporation against the temperature gradient.

### Evaporation

The significant loss of heat is connected with evaporation of water (Equation 23) in upper respiratory pathways during air inspiration (Brebbia, et al., 1957). The cold dry air from environment is here heated to body temperature and fully saturated with water. Water is also evaporated directly from the surface of skin. In contrast with water loss by respiration the function of sweat glands can be regulated (Dodt and Zotterman, 1952; HENSEL, 1953; Piwonka and Robinson, 1967; Sato, 1977; Wyndham, et al., 1966). The regulation of sweating set the amount of water excreted by skin. During higher physical activity this evaporated water bound the heat as enthalpy of vaporization, which is more effective in dry, warm and windy environment. Howeve, it works even if the environment temperature is higher than body temperature. So, there must be adequate water intake by drinking to prevent dehydration.

### Comparison with HumMod 1.6

Thermoregulation has only one small difference between Physiomodel and HumMod 1.6 - in fatigue of sweat glands. The usage of fuel in sweat glands is in Physiomodel dependent on current rate of sweating water, not on the constant default base value of this rate as in HumMod 1.6.

## Neural Regulations

The integrative model of human physiology contains also the main neural regulations, because the autonomic nerves drive directly the base processes such as vasoconstriction of blood vessels, heart rate, heart contractility (SUGA, et al., 1976), kidney functions, secretions of hormones, respiration, sweating etc. The inputs to the autonomic neural reflexes are from specialized cells, which are measuring the current state of the system: baroreceptors (carotid sinus, aorta, heart atria), osmoreceptors (hypothalamus), chemoreceptors (carotid sinus, aorta, medulla oblongata) or thermoreceptors (skin). In these cells are starting the neural impulses, which are used for the calculation of the final answer. There are two autonomic pathways: sympathetic and parasympathetic. If the signal reach the end of the last neuron in pathway, the noradrenaline is typically released for sympathetic and acetylcholine is released typically for parasympathetic stimulation. The synapse receptors of the effector cells are typically muscarinic in parasympathetic and adrenergic in sympathetic pathways. There are two groups of adrenergic receptors: alpha and beta. Both adrenergic receptor groups react on epinephrine and on norepinephrine. As a result the model of the alpha/beta receptors can be dependent on sympathetic stimuli together with extracellular concentration of these catecholamines, other agonists (e.g. desglymidodrine) or antagonists (alpha/beta blockers). The model of alpha receptors can be used in many places such as for the model of microcirculation, which is used for many tissues with different parametrical setting.

The autonomic regulations just correct the functions of cells, tissues and organs. In many cases they are not necessary for life. They can even be removes by surgery (vagotomy, endoscopic thoracic sympathectomy). However, the quality of life rapidly decreases, because the loss of regulations decrease the limits where the body works properly. For example the loss of regulation of heart rate is critical in increased physical activity, when is needed higher cardiac output to support oxygen transport to muscles. And without the external innervation the heart (Bootsma, et al., 1994; Warner and Cox, 1962) is still beating using autonomic oscillations of sino-atrial node cells, without the useful information (Xenopoulos and Applegate, 1994) about muscle metabolism, about current blood status, and about blood pressures (Ferguson, et al., 1985; Takeshita, et al., 1979).

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| Neural pathway | Receptors | Effectors |
| Baroreflex | carotid sinus artery and atrial baroreceptors | heart, vasoconstriction/vasodilation |
| Metaboreflex | skeletal muscle chemoreceptors | heart, vasoconstriction/vasodilation |
| Termoregulation | skin termoreceptors, core termoreceptors | vasoconstriction/vasodilation of skin vessels, sweating |
| Respiration reflexes | central chemoreceptors, peripheral chemoreceptors,  skeletal muscle pH | respiration rate, tidal volume |
| Drive of kidney function | atrial low pressure receptors | proximal tubule sodium reabsorption |

### Comparison with HumMod 1.6

In Physiomodel is shifted the reaction of central chemoreceptors to new more precise value of their intracellular pH=7.08 (Kintner, et al., 2000) as a result of detailed tissues respiratory quotients based on metabolic consumption of base nutrients. The details of this shift connected is described in section 6.1.

The next difference is correction of the shape of oxygen effect in the same central chemoreceptors, where the change between Physiomodel and HumMod curves are ploted in Figure 10.

Figure 10, Correction of oxygen effect on central chemoreceptors.

# Theory of Model Development

The integrative model of human physiology is a representation of the physiological theory. As each natural science also the physiology must be based on real experiments and logic. The model of physiological functions must be proven with measurements. And the huge power of deduction between proven models can be used to prove new facts or identify the questionable situations. All is believed to be deterministic and there cannot be any mathematical controversy.

The following exact logical definitions and theorems just say, that it is possible to develop by *integration, reduction* and *extension* from previous models the model, which must be *at least as good as* the previous models. Robustness (the ‘at least as good as’ operator) of the model must take into account all *real experiments* behind the models (the ‘be described’ operator) and the dimensions and size of *image* of the model (number and type of results). This comparison of the models can be defined by comparison of all their real experiments. Integration of new knowledge can be done without losing of any potential of the model to solve the previously described real experimental data. The extension of the image of the model with new physiological definitions of new variables should be also mentioned as improvement. In the other side the extension with new unnecessary parameters and with new inputs is unwanted, because it brings correlations and problems with unique identification to individual objects. As a reason the reduction of *domain* (number and type of parameters) will be also exactly defined to get the model at least as good as the original one. As a result of these rules of development the better model should describe more data with more outputs and less parameters. Having each time the logical proof that the new version of the model is better than the previous version then the new version must be always better than each model in its history.

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| 1. **Real Experiment** |  |
| ***Real experiment*** *R*in [domain of definition](https://en.wikipedia.org/wiki/Domain_of_a_function) *D* giving data in [image domain](https://en.wikipedia.org/wiki/Image_(mathematics)) *I*, where for each setting ***s*** is the run of the experiment giving measurable data *R(s)*. | |
|  | |

Each experiments must be [reproducible](https://en.wikipedia.org/wiki/Deterministic_system) with the same output at the same setting without any other assumed conditions. Ranges and type of these setting values determine the domain of definition. For example if we have only a parameter *s1*, which can reach the values from 0 to 1, then the domain of the experiment is one-dimensional interval <0,1>. Similarly must be handled the outputs, for example as values from -10 to 10 having image as one-dimensional interval <‑10,10>. Typically is the setting constant during the experiment and the data as measured outputs can varies during the experiment.

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| 1. **Default Setting** |  |
| ***Default setting*** are fixed values in domain *D*, which represent the selected state as set of parameters and inputs for all experiments. | |
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Default setting must be consistent, which could be achieved by measuring all these values for one individual object, at well-defined conditions in the fixed time. This snapshot of all values is typically used for parameters, which can be ignored or neglected in experiments to reduce the complexity and dimension of domain *D*. This is very comfortable, because using default setting can be designed experiments just with a few parameters, which directly determines the outputs. Default setting should be selected to represent the normal state of normal patient in normal conditions to achieve the reasonable normal data even for long-term experiment *R(D,I)*. If it is not really necessary, the default values should not be changed during development.

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| 1. **Model** |  |
| ***Theoretical model*** *M* in [domain](https://en.wikipedia.org/wiki/Domain_of_a_function) *D* giving data in [image](https://en.wikipedia.org/wiki/Image_(mathematics)) *I*, where for each setting *s* is the simulation of the model *M* giving the simulation outputs *M(s)*. | |
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Model is always an approximation of the reality. Even if we use the fundamental physical relations, we should not be sure that it exactly match the reality. There is the same assumption as in real experiment definition: the unique results for each parameters of the model (reproducibility). In the other words all necessary settings should be known before both real and theoretical experiment. For this reason the parameters and inputs are usually defined as physical quantities with physical units. Also the model setting *s* typically remains constant during the simulation and the outputs can varies in time. This dynamical behavior is caused by differential equation, which can dynamically react on prescribed changes of the setting. Each model *M*in domain *D* should give the reasonable results for the default values . However this condition is not part of definition, it is just a very practical thing.

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| 1. Experiment **is described** by model |  |
| Experiment *R* ***is described*** by model *M* in domain with precision *P* using [metric](https://en.wikipedia.org/wiki/Metric_space) *dIR* of image *IR* if and only if the image of the experiment *IR* is subset of the image of the model *IM* and the distance between data and simulation for each setting is less than *P*. | |
|  | |

Figure 11, Definition domains of model and experiment and the position of partial settings

The setting *s={sRM, sR}* becomes from the design of experiments. The model can reduce the setting only to the main information necessary to determine the right behavior at each cases (as setting *sRM*). The comparison of the measured data with the result of the simulation could be done different ways. Always it must be used some error calculation called metric, which gives the information how similar are the curves. There can be used any mathematical [norm](https://en.wikipedia.org/wiki/Norm_(mathematics)). Having points in specific time there can be used e.g. sum of square distances between simulation and measured points. The value of precision *P* must be selected appropriate to selected metric and precision of measurements. The ideal value of precision P is 0.5% for Euclidean norm. However this precision is too hard for the most of physiological measurements, so even 10% error is tolerated by Physiomodel today.

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| 1. **Model Comparison** |  |
| Model M1 ***is at least as good as*** M2 if and only if it can describe all experiments, which can be described by M2. | |
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Almost each debate about different models of the same thing is about recognition, which model is better. This definition cannot compare all models, because there can be some situations when the second model is better than the first one even if in other situation is the best the first one. So this operator “be at least as good as” can be applied if all real experiments described by “worse” model are described also by “better” model. From the “is described” operator this new operator inherited the very useful properties: . So the better model has the number of output variables at least as big as worse model. The equality of the models occurs when M1(D1,I1) P M2(D2,I2) and M2(D2,I2) P M1(D1,I1). In this situation the direct result is the equality of images (I1=I2) and the same set of experiments, which are described by both models. The other property of the operator ‘at least as good as’ is the transitivity, which means that if and then . This transitive relation is a result from definitions of both “be described” relations as , which is the definition of “be at least as good as” operator between M1 and M3. Having transitive "is at least as great as" operator for model comparison is critical for development, because if the new version is at least as good as the last version of the model during each time of development then the new version must be also at least as good as all versions in the history of the development.

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| 1. **Incomparable Models** |  |
| Model M1 ***is incomparable*** with M2 if and only if M1 is not at least as good as M2 (precision P) and M2 is not at least as good as M1  (precision P). | |
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Negation of this relation between two models must give one of the models at least as good as the other model. In other words if the models are not incomparable then they are comparable. The incomparable operator is commutative, so if then .

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| 1. **Integration** |  |
| MAB is an ***integration*** of two models MA and MB­ in precision P if and only if MAB describes all data, which are described using the model MA or the model MB | |
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Having models for different type of experiments, there must be an option how to merge them together in one model, which will describe all these experiments. This integration is the most problematic stage of development, because for each process there must be selected only one relation even if it is described in both models different way. The new integrated model must be usually re-implemented to new theory, which describe both kind of experiments. If there is not possible to fine smooth mathematical relation for both groups of behavior then it can be always implemented as “if-then-else-” solution. The existence of conditional integration is the proof of Integration Theorem, which says that there must exist some integration for each two models.

Integration Theorem:

For example if we have two models of aortic valve: one for opened valve and second for closed valve then we can integrate them together using condition of opening and closing valve. If the integration is based on improved physical theories then the final model could get much higher potential for solving even much complicated experiments than the original experiments of both integrated models. This integration phenomen we observed when we has integrated for example the new physical chemistry theory with HumMod 1.6. The original HumMod 1.6 is based on equilibration of molar concentration and osmolarity. However using this old relations there was not possible to describe the equilibrium on erythrocyte membrane. Using new physical theory we solve not only that problem – we bring to the model the solution all electrochemical processes, which are based on new physical chemistry relations, as written in section 3.4.

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| 1. **Reduction** |  |
| *Mr*is a ***reduction*** of the model *M* in precision *P* to new domain Dr if and only if its domain *Dr* is subset of the domain *D* and *Mr* describes all experiments described by the original model *M* in the same image. | |
|  | |

The model after reduction of domain is at least as good as the original model. The image remains the same. The domain is reduced typically by removing correlated parameters or making parameters more invariant to have the same default values during all experiments (parameters become constants). Making values more invariant has in physiology long tradition – typically as scaling values per weight, skin surface, height, age, sex, and so on.

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| 1. **Extension** |  |
| *Me*is an ***extension*** of the model *M* if and only if the original image *I* is subset of the extended image *Ie* and *Me* describes all data described of the original model *M* in the extended image *Ie* with precision *P*. | |
|  | |

The model after extension of image is at least as good as the original model, because only the image was extended . The domain and the experiments remains the same.

Development using these rules of integration, image extension and domain reduction gives always the next version of the model consistent with all previously integrated knowledge. However, there is necessary to collect knowledge of integrated real experiments and their measured data to know exactly the limits of the current version of the model. These references to scientific research are inseparable part of the complex model.

# Discussion

The integrative description of human physiology using Modelica opens the new possibilities of scientific examination and interconnection of physiology with many scientific disciplines. One must realize that under the physiological description is always some chemical, hydraulic, thermal, osmotic or population based domains. And the laws of these physical domains can be exactly described by mathematical equations. As has been shown, the whole human physiology can be described as huge set of these mathematical equations. Without the object-orienting equation-based approach of computer science it should not be possible that easy create, extent, modify or understand such huge mathematical models.

This work does not describe how to find, fit or estimate the huge number of all parameters of the model. Some parameters are patient specific such as weights or volumes of the body, the organs or the tissues. However, the most of parameters are properties of chemical substances, membranes, tissues and organs, which are typically not patient-specific and they are even invariant of other variables or parameters. In the other side, there are also interpolation curves, which very simplified empirical observations such as of the hormone effects or neural reflexes. In the next development these interpolations should be more complexly modeled by physical and chemical bases of the processes. For example the shifting of interpolation curve of hemoglobin saturation with oxygen as is implemented in HumMod 1.6 does not allow to examine this process together with binding of Bohr’s protons and with binding of carbon dioxide as in our model. And definitely does not show the transfer of heat using these chemical processes.

## Physiological expandability

After we implement the HumMod model in Modelica, we realized that improving of the model can be done without damages of the work done before. Comparing the resulting model with original one and the right consultation with measured data brings the better equations and more stable model in each improving step.

For example in original model is calculated production of carbon dioxide in each tissues with the same global respiration quotient (RQ). The flow of produced carbon dioxide was proportional to the flow of consumed oxygen and it was independent on type of tissues. There was already calculated the right flow of consumed oxygen with the right type and amount of consumed metabolites. And because we know, the respiration quotient for each of these metabolites we improve the amount of produced carbon dioxide per tissue. As a result there was higher production of CO2 in neural tissues, because neurons cannot metabolize fats (RQ=0.7) and their primary source of energy is glucose (RQ=1). Comparing the results of simulation before and after this modification, it was shown that the patient starts to hyperventilate. After short investigation was found, that this hyperventilation is caused by neural regulation of respiration. It was quite easy, because the total effect of neural respiratory regulation (TotalDrive) in normal situation should have the value one such as each other effect. Looking at diagram one can see the connected systems from which are the TotalDrive calculated. After examination of these few systems it is clear that it goes from central chemoreceptors, which are firing the impulses as answer to intracellular pH of these neural cells in brain. And logically there is a shift of intracellular pH of neurons (pHin) caused by higher production of CO2 than before. Let must be found if the new value of calculated pHin reflects better the reality. And really the measured value of pHin in physiological papers are more close to our new value (Kintner, et al., 2000), which was automatically calculated from the model acid-base equations of each intracellular environment. As a result there is necessary to shift the interpolation curve, which was estimated to lower values of pHin. These effect of central chemoreceptors must be shift to have normal value at normal pHin. After this correction the model can have the same or better neural respiratory regulations and the same or better normal state of other variables with more precise local status of tissues and blood. The better means, that all changed values must be consulted and compared with some research as in our cases the pHin was.

The other example of physiological expandability is adding the new acid-base module. At first we tried to calculate the blood acidity from base excess of oxygenated blood (BEox) using empirical Van Slyke equation such as Siggaard Anderson did with cTH=- BEox. And because the BEox was not calculated in original model it had to be somehow defined. The first idea was to create the state variable. There was some sources of acids or bases (mainly from metabolism) and some losses of acids and bases (mainly by kidney). The change of bases was the same as the change of BEox, the change of acids had a meaning of the negative change of BEox. However, this implementation failed in a few hours of simulation. The question was why, because these theory seems to be correct. After short examination of simulation results, one can see the lost electroneutrality of blood plasma. In the model are already integrated all main electrolytes and all main acid-base puffers, so there is possible each time to calculate the strong ions difference (SID) or the charge on acid-base puffers at calculated pH. As a result of electroneutrality, the sum of all these charges must be zero. And it was not. As a first generator of these problems was assumed to be the changes of BEox. And really if there is more properly connected all flows of electrolytes and flows of all organic acids with changes of BEox the stability of the model increase from hours to days or even months of simulation time. However it still failed because of electroneutrality. And that brought me the new idea: if in the model has all electrolytes and acid-base buffers as state variables, then the BEox is not state variable and it can be directly calculated from equation of electroneutrality as is described in section 4.4.1. After this improving of BEox the model starts to be stable for more than year of simulation time. And as a result of added equation, it never loses the electroneutrality again.

## Expandability in field of physical chemistry

The main problem with original model is, that the calculation is causal and very redundant. Almost all physical and chemical law as equation is repeated as many times as it occurs in the body. Using Modelica it brings the opportunity to define one law only in one place and use it just by reference to this place. It does not matter which variable is an output from the equation, because Modelica can do automatically the algebraic manipulation during compilation time.

For example only one component defines each chemical reactions. Improving of this component will be improved all chemical reactions in the model. My first implementation of chemical reaction has two main parameters: dissociation constant and reaction forward rate. At equilibrium all is calculated only from dissociation constant, because there is no speed of reaction. The next investigation of chemical bases told us that dissociation constant is not really the constant. It is dependent on temperature, so the Van’t Hoff’s law was added to this component with default setting at zero reaction enthalpy. In the other words, if the reaction enthalpy as parameter is not set by user in the specific occurrence then it has the same behavior as before. However it brings a possibility to define also non-zero enthalpy for reactions with equilibrium dependent on temperature. The investigation of the meaning of reaction enthalpy brings also another idea: to calculate the flow of heat energy from/to reaction. And using the conditional thermal heat port it allowed the chemical reaction to be a multidomain (chemical and thermal) component. So as in the chemical theory the positive reaction enthalpy means the endothermic reaction and the negative value of reaction enthalpy means the exothermic reaction. And because the heat port was hidden by default, all instances of chemical reactions in the model remained the same and with the same setting and connections as before these thermal extensions.

The next approach in the field of physical chemistry showed us, that we can calculate also the dissociation coefficient at defined temperature from thermodynamic properties of substrates and products of the reaction. The idea was to simplify the usage of chemical reaction component. The user just selects the type of all substrates and products and the dissociation coefficient is automatically calculated. This approach uses a database of chemical substances with their free enthalpies of formation (ΔfH) and free Gibbs energy of formation (ΔfG). The enthalpy of the reaction is the sum of formation enthalpies of products minus the sum of formation enthalpies of substrates ([Hess’s law](https://en.wikipedia.org/wiki/Hess%27s_law)). Having Gibbs energies of all products and all substrates, the Gibbs energy of reaction (ΔrG) is also the result of Hess’s law (Equation 11). And the dissociation coefficient (K) of the reaction at temperature T is defined from the Gibbs energy of reaction as Equation 34, where R is the gas constant.

|  |  |
| --- | --- |
|  | Equation 34, Gibbs free energy of reaction |

The chemical processes in the body are in water solution of electrolytes. The adaptation to water condition can be done activity coefficients. The water surrounds the charged particles and creates the solvation shells, which decrease the activity of the substance. This behavior is driven by Poisson-Boltzmann model, which can be simplified with Debie-Hückel theory. The creation of metabolic pathways should be really simple - just by connecting substances with this implementation of chemical reaction. User just selects the names of substances instead of strange values of dissociation coefficients for each reaction. And if these reactions are all in equilibrium there are even not needed the value of kinetic rate coefficients to start the simulation.

This kind of improvement guarantees also the more sophisticated rule of chemical systems called “[Principle of Detailed Balance](https://en.wikipedia.org/wiki/Detailed_balance)”. The “Principle of Detailed Balance” says that in closed equilibrated chemical system is reached equilibrium at each chemical reaction. As a reason of this law the product of dissociation constants in the chemical circles is equal to one. So if the user define the chemical system as chemical reactions in circle and he want to set all dissociation constants as parameters then he must always think about this dependences between them. However the new proposal based on Gibbs energies does not allow to brake this fundamental rule of chemical systems. For example having closed system of chemical reaction: A1<->A2, A2<->A3 and A3<->A1 after a long time, when the concentrations of A1, A2 and A3 are constant. The K12= A2/A1, K23= A2/A3 and K31= A3/A1 are dissociation constants of the reactions at temperature T. If the user wants to set the dissociation constants the following dependence must be verified by user: K123 = K12\* K23\* K31 = 1. However, if there the system is calculated from Gibbs energies of formation of each substance ΔfG1, ΔfG2 and ΔfG3 then this relation will be automatically fulfilled as relation 0 = (ΔfG2- ΔfG1) + (ΔfG3- ΔfG2) + (ΔfG1- ΔfG3) = ΔrG12 + ΔrG23 + ΔrG31 = ΔrG123. Because ΔrG = 0 if and only if K = 1 as say the Equation 34.

## Effort of Integrative Physiology

If we assume that the extension is made using the rule of integration and image extension then this theoretical view should confirm our hypothesis 1: “**For each physiological model it exists an extension, which is at least as well as the original model”**.

The practical situation is a little different, because the image extension is many times connected also with domain extension, which is not assumed as improvement of the model. In many places in Chemical library and Physiolibrary is this solved using “default” setting. It means, that the new parameters are designed to be unnecessary to use if the user directly does not want to use them. The user does not need to set them, because they have default value. The example is the kinetics coefficient of the chemical processes. It is set to be fast enough to equilibrate the process in very short time. The user, which is interested only to view the chemical equilibrium, just ignore the setting of this kinetics coefficient.

So if it is possible it is better to design the parameters already scaled and almost independent of other setting. For example the weights of organs and tissues can be represented by parameters defined as fractions to whole weight. This automatically scale the size of each organ when we set only one parameter – total weight of the individual patient. Also the default values solving switch between preselected genotypes or phenotypes can be considered as part of the model. This trick can decrease even a complex setting into one choose of the type of setting, what is considered as rapid improving of the model using theory above. Modelica was a great support to solve initial equations, where can be the relations between parameters implemented.

The formalization of models properties also partially answer our second hypothesis: “**Mathematical formalization and integration of practical physiological knowledge about one organism is possible to implement into one complex physiological model”**.

As an extension also the integration has the same problems whit increasing of the parameters and inputs of the model. Solving it using default values, scaled parameters or predefined datasets is not always a good idea. Mas should be sure, that during integration some redundant relation does not occurs in the model. This state is very dangerous and is not automatically detectable. The redundant equation or redundant variable is an alternative equation of something what is already presented in model. If this redundant variable is the state variable its change as a flow is calculated twice, but there must not be twice more flows. If the new whole subsystem is inserted to the model, which already calculate some part of that subsystem then the regulations and answers to the state of new subsystem will be mish-mash. The only one clear solution is to remove all duplicated variables and duplicated relations even if there are calculating the same thing different way. This way should be selected the trusted relations and eliminated the relations with lower credibility. As an example is making of our extension of acid-base model as described in sections 6.1, 4.4.1 and 4.4.2.

# Conclusion

The theory of integrative model development has been formalized (Section 5). Using these rules the [Physiomodel](http://www.physiomodel.org/) (Section 4) - huge integrative model of human physiology has been created in [Modelica](https://www.modelica.org/), a computer language standardized by [Modelica Association](https://www.modelica.org/association). The model is an extension and integration of model [HumMod](http://hummod.org/) 1.6 from Mississippi University of Medical Center. The Physiomodel integrates to the original HumMod model the new acid-base (Section 4.4.1, Section 4.4.6 and Section 6.1) and new blood gases transport approach (Section 4.5). As part of acid-base and gases transport model there has been developed the new general model of complex chemical equilibria on macromolecules – as demonstrated by O2-H+-CO2-HemoglobinA system (Section 4.5.3 and Section 3.4.5). The main results of this work are also the new Modelica libraries called [Physiolibrary](http://www.physiolibrary.org/) and [Chemical library](https://github.com/MarekMatejak/Chemical/releases) (Section 3), which are already integrated to open-source Modelica environment called [OpenModelica](https://openmodelica.org/).

The result of formalized theory of model development (Section 5) are the rules for comparison, reduction, extension and integration of the models. The comparison between models is based on real experiments, which can be described by models. The reduction here means elimination of correlated parameters. The extension means the addition of new relations with new variables to the model, which does not collide with the rest of model. And finally the integration means the development of new theory, which can describe all real experiments of previously separated models. The rules are designed to always reach the better model than the models, from which it comes from.

During the compilation of Physiomodel (Section 4) there was presented more than eight thousands variables. The most of these variables are generated from graphical connection, so the number of real physically distinguishable variables are about four-five thousands. There are also more than four thousands parameters. However each of them has default value and they are designed using reduction rule to be invariant of other parameters or variables. For example instead of parameter containing absolute weight of the tissue or organ there is a parameter containing fraction of total body weight for the tissue or organ. So it is easy to simulate the experiments, because it can be described only by few parameters and the rest remains as default values.

During implementation of HumMod we correct more than thirty mistakes in original implementation as described in subsection called “Comparison with HumMod 1.6” in appropriate position of description of whole model (4.1.5, 4.2.6, 4.3.9, 4.4.6, 4.5.5, 4.6.6, 4.7.3, 4.8.1). The most of this mistakes was caused by misused of non-SI units (e.g. mg/L instead of mg/dl) or by misusing of physical quantities (e.g. mass concentration instead of molar concentration). The other mistakes misuse the connection of variables (exchanging of variable names) or ignore the known facts (e.g. the charge of inorganic phosphates is dependent on pH). And some subsystems was designed just very simple to describe the physiological function, which we want to examine (e.g. synergy of blood gas binding to hemoglobin).

As has been shown in section about physical and Modelica backgrounds (Section 2), the principles can be implemented in high error-proof level. The correctly defined basis can generate error or warning almost each time when the user want to use the variable or the class in the questionable way. User can in Modelica design the predefined submodules with well-defined inputs, outputs, parameters and connectors. For next usage of these components it is almost not possible to mish-mash physical unit or physical quantity.

The object-oriented equation-based Modelica language allows us to create very robust support of integrative physiology based on physical principles (Section 3). Similar support was already implemented for technical sciences as libraries of electrical, magnetic, mechanical or thermal processes. However in physiology we need more sophisticated domains such as electrochemical (for chemical reactions, membrane transports, water evaporation, diffusion..) or hydraulic domain (for cardiovascular system). Making an analogy to existing systems was created the Physiolibrary 2.3 – a library for physiological processes, which was assumed by Modelica Association in Modelica Library Awards as the best free Modelica library in year 2014. Nowadays we released the general library for electrochemical processes called Chemical library, which is more general for electrochemical equilibration processes. This library is a by-product of our integration of membrane electrochemical equilibria based on Donnan’s electrolytes equilibrium and Nernst membrane potential in the field of physical chemistry described in section 3.4.

# References

Abram, S.R.*, et al.* Quantitative circulatory physiology: an integrative mathematical model of human physiology for medical education. *Advances in physiology education* 2007;31(2):202-210.

Ahlqvist, J. Plasma protein osmotic pressure equations for humans. *Journal of Applied Physiology* 2003;94(3):1288-1289.

Almgård, L. and Ljungqvist, A. Effect of circulating norepinephrine on the renin release from the denervated kidney. *Scandinavian journal of urology and nephrology* 1975;9(2):119-124.

Angielski, S. and Lukowicz, J. The role of the kidney in the removal of ketone bodies under different acid-base status of the rat. *The American Journal of Clinical Nutrition* 1978;31(9):1635-1641.

Archer, S. and Michelakis, E. The Mechanism(s) of Hypoxic Pulmonary Vasoconstriction: Potassium Channels, Redox O2 Sensors, and Controversies. 2002.

Armstrong, R., Vandenakker, C. and Laughlin, M. Muscle blood flow patterns during exercise in partially curarized rats. *Journal of Applied Physiology* 1985;58:698-701.

Atherton, J., Green, R. and Thomas, S. Influence of lysine-vasopressin dosage on the time course of changes in renal tissue and urinary composition in the conscious rat. *J. Physiol. (Lond.)* 1971;213(2):291-309.

Aukland, K. Myogenic mechanisms in the kidney. *Journal of hypertension. Supplement: official journal of the International Society of Hypertension* 1989;7(4):S71-76; discussion S77.

Bassingthwaighte, J.B. Strategies for the physiome project. *Annals of biomedical engineering* 2000;28(8):1043-1058.

BAUER, C. A WIDESPREAD OXYGEN SENSOR REVEALED. In.: C/O WILLIAMS & WILKINS, PO BOX 1496, BALTIMORE, MD 21203; 1993.

Begg, T. and Hearns, J. Components in blood viscosity. The relative contribution of haematocrit, plasma fibrinogen and other proteins. *Clinical science* 1966;31(1):87-93.

Bevegärd, S. and Lodin, A. Postural Circulatory Changes at Rest and during Exercise in five Patients with Congenital Absence of Valves in the Deep Veins of the Legs. *Acta Medica Scandinavica* 1962;172(1):21-29.

Blackard, W.G. and Nelson, N.C. Portal and Peripheral Vein Immunoreactive Insulin Concentrations Before and After Glucose Infusion. *Diabetes* 1970;19(5):302-306.

Bock, A.V., Dill, D.B. and Edwards, H.T. ON THE RELATION OF CHANGES IN BLOOD VELOCITY AND VOLUME FLOW OF BLOOD TO CHANGE OF POSTURE. *The Journal of Clinical Investigation* 1930;8(4):533-544.

Bootsma, M.*, et al.* Heart rate and heart rate variability as indexes of sympathovagal balance. *American Journal of Physiology* 1994;266:H1565-H1565.

Braam, B.*, et al.* Relevance of the tubuloglomerular feedback mechanism in pathophysiology. *Journal of the American Society of Nephrology* 1993;4(6):1257-1274.

BRADLEY, S.E., INGELFINGER, F.J. and BRADLEY, G.P. Hepatic Circulation in Cirrhosis of the Liver. *Circulation* 1952;5(3):419-429.

Bradley, S.E.*, et al.* The circulating splanchnic blood volume in dog and man. *Transactions of the Association of American Physicians* 1953;66:294-302.

Brebbia, D.R., Goldman, R.F. and Buskirk, E.R. Water Vapor Loss From the Respiratory Tract During Outdoor Exercise in the Cold. 1957.

Carter, Y.M.*, et al.* Diastolic properties, myocardial water content, and histologic condition of the rat left ventricle: effect of varied osmolarity of a coronary perfusate. *J Heart Lung Transplant* 1998;17(2):140-149.

Claassen, K.*, et al.* A detailed physiologically-based model to simulate the pharmacokinetics and hormonal pharmacodynamics of enalapril on the circulating endocrine renin-angiotensin-aldosterone system. *Frontiers in Physiology* 2013;4.

Clutter, W.E.*, et al.* Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. *The Journal of Clinical Investigation* 1980;66(1):94-101.

Coleman, T.*, et al.* Long-term regulation of the circulation. *Interrelationships with body fluid volumes, Physical Bases of Circulatory Transport: Regulation and Exchange, WB Saunders Co, Philadelphia* 1967.

Coleman, T.G. and Randall, J.E. A Comprehensive Physiological Model. *The Physiologist* 1983;26(1).

Conte, G.*, et al.* Role of inhibition of atrial natriuretic factor release in the down-regulation of salt excretion. *Kidney Int* 1992;42:673-680.

Cumin, F., Baum, H.P. and Levens, N. Leptin is cleared from the circulation primarily by the kidney. *Int J Obes Relat Metab Disord* 1996;20(12):1120-1126.

Debye, P. and Huckel, E. Theory of electrolytes, part 1. *Freezing point depression and cognate phenomena Phys. Zeits* 1923;24:185-206.

Dobson, H.L.*, et al.* Absorption of 131-I labeled modified insulin. *Metabolism* 1967;16(8):723-732.

Dodt, E. and Zotterman, Y. Mode of action of warm receptors. *Acta physiologica scandinavica* 1952;26(4):345-357.

DOEDEN, B. and RIZZA, R. Use of a Variable Insulin Infusion to Assess Insulin Action in Obesity: Defects in Both the Kinetics and Amplitude of Response. *The Journal of Clinical Endocrinology & Metabolism* 1987;64(5):902-908.

Drummond, H.A., Grifoni, S.C. and Jernigan, N.L. A new trick for an old dogma: ENaC proteins as mechanotransducers in vascular smooth muscle. *Physiology* 2008;23(1):23-31.

Edelman, I.S. Thyroid Thermogenesis. *New England Journal of Medicine* 1974;290(23):1303-1308.

ECHT, M.*, et al.* Effective Compliance of the Total Vascular Bed and the Intrathoracic Compartment Derived from Changes in Central Venous Pressure Induced by Volume Changes in Man. *Circulation Research* 1974;34(1):61-68.

Eisenhoffer, J., Lee, S. and Johnston, M. Pressure-flow relationships in isolated sheep prenodal lymphatic vessels. *American Journal of Physiology-Heart and Circulatory Physiology* 1994;36(3):H938.

Engeset, A.*, et al.* Studies on human peripheral lymph. I. Sampling method. *Lymphology* 1973;6(1):1-5.

Erwald, R. and Wiechel, K. Effect of vasopressin on central and splanchnic hemodynamics in awake man. *Acta chirurgica Scandinavica* 1978;144(6):347.

Fan, F.C.*, et al.* Effects of hematocrit variations on regional hemodynamics and oxygen transport in the dog. 1980.

Ferguson, D.W., Abboud, F.M. and Mark, A.L. Relative contribution of aortic and carotid baroreflexes to heart rate control in man during steady state and dynamic increases in arterial pressure. *The Journal of Clinical Investigation* 1985;76(6):2265-2274.

Florez-Duquet, M. and McDonald, R.B. Cold-induced thermoregulation and biological aging. *Physiological reviews* 1998;78(2):339-358.

Frayn, K. Adipose tissue as a buffer for daily lipid flux. *Diabetologia* 2002;45(9):1201-1210.

Friedman-Einat, M.*, et al.* Serum leptin activity in obese and lean patients. *Regulatory peptides* 2003;111(1):77-82.

Gaasch, W.H.*, et al.* Dynamic determinants of letf ventricular diastolic pressure-volume relations in man. *Circulation* 1975;51(2):317-323.

GAUER, O.H., HENRY, J.P. and SIEKER, H.O. Changes in Central Venous Pressure after Moderate Hemorrhage and Transfusion in Man. *Circulation Research* 1956;4(1):79-84.

Gedde, M.M. and Huestis, W.H. Membrane potential and human erythrocyte shape. *Biophys. J.* 1997;72(3):1220.

George, S.*, et al.* A family with severe insulin resistance and diabetes due to a mutation in AKT2. *Science* 2004;304(5675):1325-1328.

GINSBERG, S.*, et al.* Serum Insulin Levels Following Administration of Exogenous Insulin. *The Journal of Clinical Endocrinology & Metabolism* 1973;36(6):1175-1179.

Goldberg, M.A. and Schneider, T.J. Similarities between the oxygen-sensing mechanisms regulating the expression of vascular endothelial growth factor and erythropoietin. *Journal of Biological Chemistry* 1994;269(6):4355-4359.

Goldblatt, H., Lamfrom, H. and Haas, E. Physiological Properties of Renin and Hypertensin. 1953.

Gottschalk, C.W. and Mylle, M. Micropuncture study of the mammalian urinary concentrating mechanism: evidence for the countercurrent hypothesis. *American Journal of Physiology--Legacy Content* 1959;196(4):927-936.

Greenway, C.V. and Lister, G.E. Capacitance effects and blood reservoir function in the splanchnic vascular bed during non-hypotensive haemorrhage and blood volume expansion in anaesthetized cats. *J. Physiol. (Lond.)* 1974;237(2):279-294.

Grodins, F.S., Buell, J. and Bart, A.J. Mathematical analysis and digital simulation of the respiratory control system. In.: DTIC Document; 1967.

Grodins, F.S.*, et al.* Respiratory responses to CO2 inhalation. A theoretical study of a nonlinear biological regulator. *Journal of applied physiology* 1954;7(3):283-308.

Gross, J. and Pitt-Rivers, R. 3: 5: 3′-Triiodothyronine. 2. Physiological activity. *Biochemical Journal* 1953;53(4):652.

Guyton, A.C. Interstitial fluid pressure: II. Pressure-volume curves of interstitial space. *Circulation research* 1965;16(5):452-460.

Guyton, A.C. The relationship of cardiac output and arterial pressure control. *Circulation* 1981;64(6):1079-1088.

Guyton, A.C. Blood pressure control--special role of the kidneys and body fluids. *Science* 1991;252(5014):1813-1816.

Guyton, A.C. and CE Coleman, T. Circulatory physiology: cardiac output and its regulation. 1973.

Guyton, A.C., Coleman, T.G. and Granger, H.J. Circulation: overall regulation. *Annual review of physiology* 1972;34(1):13-44.

Guyton, A.C. and Sagawa, K. Compensations of cardiac output and other circulatory functions in areflex dogs with large AV fistulas. *Am. J. Physiol* 1961;200:1157.

Guyton, A.C., Taylor, A.E. and Granger, H.J. Dynamics and control of the body fluids. Saunders; 1975.

Guyton, J.R.*, et al.* A Model of Glucose-insulin Homeostasis in Man that Incorporates the Heterogeneous Fast Pool Theory of Pancreatic Insulin Release. *Diabetes* 1978;27(10):1027-1042.

Hannaford, M.C.*, et al.* Protein wasting due to acidosis of prolonged fasting. 1982.

Hardy, J.D. and Soderstrom, G.F. Heat Loss from the Nude Body and Peripheral Blood Flow at Temperatures of 22°C. to 35°C.: Two Figures. *The Journal of Nutrition* 1938;16(5):493-510.

HAYS, M.T. Colonic excretion of iodide in normal human subjects. *Thyroid* 1993;3(1):31-35.

Henriksen, J.H. Estimation of lymphatic conductance: A model based on protein-kinetic studies and haemodynamic measurements in patients with cirrhosis of the liver and in pigs. *Scandinavian journal of clinical & laboratory investigation* 1985;45(2):123-130.

Henry, J.P. and Gauer, O.H. THE INFLUENCE OF TEMPERATURE UPON VENOUS PRESSURE IN THE FOOT. *The Journal of Clinical Investigation* 1950;29(7):855-861.

HENSEL, H. The time factor in thermoreceptor excitation. *Acta Physiologica Scandinavica* 1953;29(1):109-116.

Hesslink, R.L.*, et al.* Human cold air habituation is independent of thyroxine and thyrotropin. 1992.

Hester, R.L.*, et al.* HumMod: A Modeling Environment for the Simulation of Integrative Human Physiology. *Frontiers in physiology* 2011;2:12.

Hester, R.L., Coleman, T. and Summers, R. A multilevel open source integrative model of human physiology. *The FASEB Journal* 2008;22(1\_MeetingAbstracts):756.758.

Hester, R.L.*, et al.* Systems biology and integrative physiological modelling. *The Journal of physiology* 2011;589(5):1053-1060.

Heyeraas, K.J. and Aukland, K. Interlobular arterial resistance: Influence of renal arterial pressure and angiotensin II. *Kidney Int* 1987;31(6):1291-1298.

Hodgkin, A.L. and Huxley, A.F. A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of physiology* 1952;117(4):500-544.

Hsieh, A.C.L., Nagasaka, T. and Carlson, L.D. Effects of immersion of the hand in cold water on digital blood flow. 1965.

Chiasson, J.*, et al.* Differential sensitivity of glycogenolysis and gluconeogenesis to insulin infusions in dogs. *Diabetes* 1976;25(4):283-291.

Chopra, I.J. An assessment of daily production and significance of thyroidal secretion of 3, 3', 5'-triiodothyronine (reverse T3) in man. *The Journal of Clinical Investigation* 1976;58(1):32-40.

CHOPRA, I.J., HERSHMAN, J.M. and HORNABROOK, R.W. Serum Thyroid Hormone and Thyrotropin Levels in Subjects from Endemic Goiter Regions of New Guinea. *The Journal of Clinical Endocrinology & Metabolism* 1975;40(2):326-333.

Christlieb, A.R.*, et al.* Renin extraction by the human liver. *Experimental Biology and Medicine* 1968;128(3):821-823.

Ikeda, N.*, et al.* A model of overall regulation of body fluids. *Annals of biomedical engineering* 1979;7(2):135-166.

Imai, J.*, et al.* Regulation of Pancreatic β Cell Mass by Neuronal Signals from the Liver. *Science* 2008;322(5905):1250-1254.

Ito, S. and Carretero, O.A. An in vitro approach to the study of macula densa-mediated glomerular hemodynamics. *Kidney Int* 1990;38(6):1206-1210.

Iwanishi, M., Czech, M.P. and Cherniack, A.D. The Protein-tyrosine Kinase Fer Associates with Signaling Complexes Containing Insulin Receptor Substrate-1 and Phosphatidylinositol 3-Kinase. *Journal of Biological Chemistry* 2000;275(50):38995-39000.

Jackson, I.M.D. Thyrotropin-Releasing Hormone. *New England Journal of Medicine* 1982;306(3):145-155.

Jacobson, L.O.*, et al.* Role of the Kidney in Erythropoiesis. *Nature* 1957;179(4560):633-634.

Jamison, R. and Lacy, F.B. Evidence for urinary dilution by the collecting tubule. *Am. J. Physiol* 1972;223:898-902.

Jamison, R.L.*, et al.* A micropuncture study of collecting tubule function in rats with hereditary diabetes insipidus. *Journal of Clinical Investigation* 1971;50(11):2444.

Jan, K.M. and Chien, S. Effect of hematocrit variations on coronary hemodynamics and oxygen utilization. 1977.

JÉQuier, E. Leptin Signaling, Adiposity, and Energy Balance. *Annals of the New York Academy of Sciences* 2002;967(1):379-388.

Kamon, E. and Belding, H.S. Heat uptake and dermal conductance in forearm and hand when heated. 1968.

Katschinski, D.M. On heat and cells and proteins. *Physiology* 2004;19(1):11-15.

Kety, S.S. and Schmidt, C.F. THE EFFECTS OF ALTERED ARTERIAL TENSIONS OF CARBON DIOXIDE AND OXYGEN ON CEREBRAL BLOOD FLOW AND CEREBRAL OXYGEN CONSUMPTION OF NORMAL YOUNG MEN 1. *The Journal of Clinical Investigation* 1948;27(4):484-492.

Khokhar, A.*, et al.* Effect of vasopressin on plasma volume and renin release in man. *Clinical Science* 1976;50(Pt 5):415-424.

Kintner, D.*, et al.* 31P-MRS-based determination of brain intracellular and interstitial pH: its application to in vivo H+ compartmentation and cellular regulation during hypoxic/ischemic conditions. *Neurochemical research* 2000;25(9-10):1385-1396.

Kofránek, J. Complex model of blood acid-base balance. In: Ziethamlová, M., editor, *MEDSOFT 2009*. Creative Connections; 2009. p. 23-60.

Kofránek, J., Mateják, M. and Privitzer, P. Leaving toil to machines - building simulation kernel of educational software in modern software environments. In, *Mefanet 2009*. Masaryk University, Brno; 2009.

Kofranek, J., Matousek, S. and Andrlik, M. Border flux balance approach towards modelling acid-base chemistry and blood gases transport. In, *In: Proceedings of the 6th EUROSIM congress on modelling and simulation. Ljubljana: University of Ljubljana*. 2007. p. 1-9.

Kotani, K.*, et al.* GLUT4 glucose transporter deficiency increases hepatic lipid production and peripheral lipid utilization. *The Journal of clinical investigation* 2004;114(11):1666-1675.

Kulhánek, T., Kofránek, J. and Mateják, M. Modeling of short-term mechanism of arterial pressure control in the cardiovascular system: Object-oriented and acausal approach. *Computers in Biology and Medicine* 2014;54(0):137-144.

Kulhánek, T.*, et al.* Simple models of the cardiovascular system for educational and research purposes. *MEFANET Journal* 2014.

Lankford, S.P.*, et al.* Regulation of collecting duct water permeability independent of cAMP-mediated AVP response. *American Journal of Physiology-Renal Physiology* 1991;261(3):F554-F566.

Larsen, P.R. Direct immunoassay of triiodothyronine in human serum. *The Journal of Clinical Investigation* 1972;51(8):1939-1949.

LAUGHLIN, M.H. Skeletal muscle blood flow capacity: role of muscle pump in exercise hyperemia. *Am J Physiol* 1987;253:1004.

Laughlin, M.H. and Armstrong, R. Rat muscle blood flows as a function of time during prolonged slow treadmill exercise. *Am J Physiol Heart Circ Physiol* 1983;244:H814-H824.

Levitin, H., Branscome, W. and Epstein, F.H. The pathogenesis of hypochloremia in respiratory acidosis. *Journal of Clinical Investigation* 1958;37(12):1667.

Little, W.C. and Cheng, C.P. Effect of exercise on left ventricular-arterial coupling assessed in the pressure-volume plane. *AMERICAN JOURNAL OF PHYSIOLOGY* 1993;264:H1629-H1629.

Maass-Moreno, R. and Rothe, C.F. Contribution of the large hepatic veins to postsinusoidal vascular resistance. *Am J Physiol Gastrointest Liver Physiol* 1992;262:G14-G22.

Manning, R.D. Renal hemodynamic, fluid volume, and arterial pressure changes during hyperproteinemia. 1987.

Manning, R.D. Effects of hypoproteinemia on blood volume and arterial pressure of volume-loaded dogs. 1990.

Mantzoros, C.S.*, et al.* Leptin in human physiology and pathophysiology. 2011.

Mateják, M. Simulovanie ketoacidózy. *Medsoft* 2013:140-150.

Mateják, M. Simulovanie ketoacidózy. In, *Medsoft 2013*. 2013. p. 140-150.

Mateják, M. and Kofránek, J. Rozsáhlý model fyziologických regulací v Modelice. *Medsoft* 2010:126-146.

Mateják, M. and Kofránek, J. HumMod–Golem Edition–Rozsáhlý model fyziologických systémů. *Medsoft* 2011:182-196.

Mateják, M., Kulhánek, T. and Matoušek, S. Adair-based hemoglobin equilibrium with oxygen, carbon dioxide and hydrogen ion activity. *Scandinavian Journal of Clinical & Laboratory Investigation* 2015:1-8.

Mateják, M.*, et al.* Model ECMO oxygenátoru. *Medsoft* 2012:205-2014.

Mayerson, H.S., Sweeney, H.M. and Toth, L.A. THE INFLUENCE OF POSTURE ON CIRCULATION TIME. 1939.

Mayerson, H.S.*, et al.* Regional differences in capillary permeability. 1960.

McCulloch, W.S. and Pitts, W. A logical calculus of the ideas immanent in nervous activity. *The bulletin of mathematical biophysics* 1943;5(4):115-133.

McGarry, J.D. and Foster, D.W. Ketogenesis and its regulation. *Am J Med* 1976;61(1):9-13.

McGarry, J.D. and Foster, D.W. Ketogenesis and its regulation. *The American Journal of Medicine* 1976;61(1):9-13.

Mellander, S. and Bjornberg, J. Regulation of Vascular Smooth Muscle Tone and Capillary Pressure. 1992.

METZLER, C.H.*, et al.* Increased right or left atrial pressure stimulates release of atrial natriuretic peptides in conscious dogs. *Endocrinology* 1986;119(5):2396-2398.

Miles, P.D.*, et al.* Kinetics of insulin action in vivo: identification of rate-limiting steps. *Diabetes* 1995;44(8):947-953.

Miller, M.E., Cronkite, E.P. and Garcia, J.F. Plasma levels of immunoreactive erythropoietin after acute blood loss in man. *British journal of haematology* 1982;52(4):545-549.

Mizelle, H.L.*, et al.* Atrial natriuretic peptide induces sustained natriuresis in conscious dogs. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 1990;258(6):R1445-R1452.

Monod, J., Wyman, J. and Changeux, J.-P. On the nature of allosteric transitions: a plausible model. *J. Mol. Biol.* 1965;12(1):88-118.

Moore, L.C. and Casellas, D. Tubuloglomerular feedback dependence of autoregulation in rat juxtamedullary afferent arterioles. *Kidney Int* 1990;37(6):1402-1408.

Mortimer, R.G. 8 - The Thermodynamics of Electrical Systems. In: Mortimer, R.G., editor, *Physical Chemistry (Third Edition)*. Burlington: Academic Press; 2008. p. 297.

Mortimer, R.G. Physical Chemistry (Third Edition). In: Mortimer, R.G., editor. Burlington: Academic Press; 2008. p. 1-1385.

Myers Jr, M.G.*, et al.* Obesity and leptin resistance: distinguishing cause from effect. *Trends in Endocrinology & Metabolism* 2010;21(11):643-651.

Nicoloff, J.T.*, et al.* Simultaneous Measurement of Thyroxine and Triiodothyronine Peripheral Turnover Kinetics in Man. *The Journal of Clinical Investigation* 1972;51(3):473-483.

Nielsen, S.*, et al.* Key roles of renal aquaporins in water balance and water-balance disorders. *Physiology* 2000;15(3):136-143.

Nicholls, M. and Richards, A. Human studies with atrial natriuretic factor. *Endocrinology and metabolism clinics of North America* 1987;16(1):199-223.

NODA, T.*, et al.* Curvilinearity of LV end-systolic pressure-volume and dP/dt,-end-diastolic volume relations. 1993.

OCHSNER, A., COLP, R. and BURCH, G.E. Normal Blood Pressure in the Superficial Venous System of Man at Rest in the Supine Position. *Circulation* 1951;3(5):674-680.

Osiba, S. THE SEASONAL VARIATION OF BASAL METABOLISM AND ACTIVITY OF THYROID GLAND IN MAN. *The Japanese Journal of Physiology* 1957;7:355-365.

Owen, O.E.*, et al.* Brain Metabolism during Fasting\*. *The Journal of Clinical Investigation* 1967;46(10):1589-1595.

Pagel, H., Jelkmann, W. and Weiss, C. A comparison of the effects of renal artery constriction and anemia on the production of erythropoietin. *Pflugers Arch.* 1988;413(1):62-66.

Piwonka, R.W. and Robinson, S. Acclimatization of highly trained men to work in severe heat. 1967.

Pollack, A.A. and Wood, E.H. Venous Pressure in the Saphenous Vein at the Ankle in Man during Exercise and Changes in Posture. 1949.

Porter, D. and Goldberg, M. Regulation of erythropoietin production. *Experimental hematology* 1993;21(3):399-404.

Prager, R., Wallace, P. and Olefsky, J.M. In vivo kinetics of insulin action on peripheral glucose disposal and hepatic glucose output in normal and obese subjects. *The Journal of Clinical Investigation* 1986;78(2):472-481.

Prager, R., Wallace, P. and Olefsky, J.M. Hyperinsulinemia Does Not Compensate for Peripheral Insulin Resistance in Obesity. *Diabetes* 1987;36(3):327-334.

Previs, S.F.*, et al.* Contrasting effects of IRS-1 versus IRS-2 gene disruption on carbohydrate and lipid metabolism in vivo. *J Biol Chem* 2000;275(50):38990-38994.

Raftos, J.E., Bulliman, B.T. and Kuchel, P.W. Evaluation of an electrochemical model of erythrocyte pH buffering using 31P nuclear magnetic resonance data. *The Journal of general physiology* 1990;95(6):1183-1204.

Randle, P.J. Fuel selection in animals. *Biochemical Society Transactions* 1986;14(5):799.

Reissmann, K.R.*, et al.* Influence of disappearance rate and distribution space on plasma concentration of erythropoietin in normal rats. *J Lab Clin Med* 1965;65:967-975.

Renkin, E. and Tucker, V. Atrial Natriuretic Peptide as a Regulator of Transvascular Fluid Balance. *Physiology* 1996;11(3):138-143.

Ridgway, E.C., Weintraub, B.D. and Maloof, F. Metabolic Clearance and Production Rates of Human Thyrotropin. *The Journal of Clinical Investigation* 1974;53(3):895-903.

Roach, M.R. and Burton, A.C. THE REASON FOR THE SHAPE OF THE DISTENSIBILITY CURVES OF ARTERIES. *Canadian Journal of Biochemistry and Physiology* 1957;35(8):681-690.

Rother, K.I.*, et al.* Evidence That IRS-2 Phosphorylation Is Required for Insulin Action in Hepatocytes. *Journal of Biological Chemistry* 1998;273(28):17491-17497.

Roush, W. An "off switch" for red blood cells. *Science* 1995;268(5207):27-28.

Rutter, G.A. and Hill, E.V. Insulin Vesicle Release: Walk, Kiss, Pause … Then Run. 2006.

Sagawa, K.*, et al.* Cardiac contraction and the pressure-volume relationship. Oxford University Press New York; 1988.

Saltin, B. and Hermansen, L. Esophageal, rectal, and muscle temperature during exercise. 1966.

Sands, J.M. Urea Transport: It’s Not Just “Freely Diffusible” Anymore. 1999.

Sato, K. The physiology, pharmacology, and biochemistry of the eccrine sweat gland. In, *Reviews of Physiology, Biochemistry and Pharmacology, Volume 79*. Springer; 1977. p. 51-131.

Seeliger, E.*, et al.* Pressure-dependent renin release: effects of sodium intake and changes of total body sodium. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 1999;277(2):R548-R555.

Sheppard, C. The Theory of the Study of Transfers within a Multi‐Compartment System Using Isotopic Tracers. *Journal of Applied Physics* 1948;19(1):70-76.

Shigemi, K., Brunner, M.J. and Shoukas, A.A. -and -Adrenergic mechanisms in the control of vascular capacitance by the carotid sinus baroreflex system. *AMERICAN JOURNAL OF PHYSIOLOGY* 1994;267:H201-H201.

Schrier, R.W.*, et al.* Influence of hematocrit and colloid on whole blood viscosity during volume expansion. *Am. J. Physiol* 1970;218(346):77.

Siggaard-Andersen, O. Acid-base balance. *Encyclopedia of respiratory medicine* 2005:1-6.

Siggaard-Andersen, O. and Siggaard-Andersen, M. The oxygen status algorithm: a computer program for calculating and displaying pH and blood gas data. *Scand. J. Clin. Lab. Invest.* 1990;50(S203):29-45.

Skarlatos, S.*, et al.* Spontaneous pressure-flow relationships in renal circulation of conscious dogs. *Am J Physiol* 1993;264(5 Pt 2):H1517-1527.

Sonna, L.A.*, et al.* Invited review: effects of heat and cold stress on mammalian gene expression. *Journal of Applied Physiology* 2002;92(4):1725-1742.

Standardization, W.E.C.o.B. and Organization, W.H. WHO Expert Committee on Biological Standardization [meeting held in Geneva from 22 to 27 September 1958]: Twelfth report. 1958:10.

Standardization, W.E.C.o.B. and Organization, W.H. WHO Expert Committee on Biological Standardization: Thirty-seventh Report. 1987:26.

Stewart, P.A. How to understand acid-base: a quantitative acid-base primer for biology and medicine. Edward Arnold London; 1981.

Stokes, R.H. and Robinson, R.A. Ionic Hydration and Activity in Electrolyte Solutions. *J. Am. Chem. Soc.* 1948;70(5):1870-1878.

Stone, H., Thompson HK and Schmidt-Nielsen, K. Influence of erythrocytes on blood viscosity. 1968.

SUGA, H. and SAGAWA, K. Instantaneous Pressure-Volume Relationships and Their Ratio in the Excised, Supported Canine Left Ventricle. *Circulation Research* 1974;35(1):117-126.

SUGA, H., SAGAWA, K. and KOSTIUK, D.P. Controls of ventricular contractility assessed by pressure-volume ratio, Emax. *Cardiovascular Research* 1976;10(5):582-592.

Summers, R. and Coleman, T. Computer systems analysis of the cardiovascular mechanisms of reentry orthostasis in astronauts. In, *Computers in Cardiology, 2002*. IEEE; 2002. p. 521-524.

Summers, R.L.*, et al.* Theoretical analysis of the mechanisms of chronic hyperinsulinemia. *Computers in Biology and Medicine* 1997;27(3):249-256.

SURKS, M.I. and LIFSCHITZ, B.M. Biphasic Thyrotropin Suppression in Euthyroid and Hypothyroid Rats. *Endocrinology* 1977;101(3):769-775.

SURKS, M.I. and OPPENHEIMER, J.H. Incomplete Suppression of Thyrotropin Secretion after Single Injection of Large L-Triiodothyronine Doses into Hypothyroid Rats. *Endocrinology* 1976;99(6):1432-1441.

Takeshita, A.*, et al.* Effect of central venous pressure on arterial baroreflex control of heart rate. 1979.

Thompson, W.O., Thompson, P.K. and Dailey, M.E. THE EFFECT OF POSTURE UPON THE COMPOSITION AND VOLUME OF THE BLOOD IN MAN 1. *The Journal of Clinical Investigation* 1928;5(4):573-604.

Wahren, J. and Ekberg, K. Splanchnic regulation of glucose production. *Annu. Rev. Nutr.* 2007;27:329-345.

Warner, H.R. and Cox, A. A mathematical model of heart rate control by sympathetic and vagus efferent information. 1962.

Weidmann, P.*, et al.* Blood levels and renal effects of atrial natriuretic peptide in normal man. *Journal of Clinical Investigation* 1986;77(3):734.

Whittaker, S.R.F. and Winton, F.R. The apparent viscosity of blood flowing in the isolated hindlimb of the dog, and its variation with corpuscular concentration. *J. Physiol. (Lond.)* 1933;78(4):339-369.

Winearls, C.*, et al.* EFFECT OF HUMAN ERYTHROPOIETIN DERIVED FROM RECOMBINANT DNA ON THE ANAEMIA OF PATIENTS MAINTAINED BY CHRONIC HAEMODIALYSIS. *The Lancet* 1986;328(8517):1175-1178.

WINER, N.*, et al.* Adrenergic receptor mediation of renin secretion. *The Journal of Clinical Endocrinology & Metabolism* 1969;29(9):1168-1175.

Wolf, M.B. Whole body acid-base and fluid-electrolyte balance: a mathematical model. 2013.

Wolf, M.B. and DeLand, E.C. A mathematical model of blood-interstitial acid-base balance: application to dilution acidosis and acid-base status. *J. Appl. Physiol.* 2011;110(4):988-1002.

Wong, S.L.*, et al.* Leptin hormonal kinetics in the fed state: effects of adiposity, age, and gender on endogenous leptin production and clearance rates. *The Journal of Clinical Endocrinology & Metabolism* 2004;89(6):2672-2677.

Wyndham, C.H.*, et al.* Fatigue of the sweat gland response. 1966.

Xenopoulos, N.P. and Applegate, R.J. The effect of vagal stimulation on left ventricular systolic and diastolic performance. *American Journal of Physiology-Heart and Circulatory Physiology* 1994;35(6):H2167.

Xie, S.*, et al.* A model of human microvascular exchange. *Microvascular research* 1995;49(2):141-162.

Yandle, T.G.*, et al.* Metabolic clearance rate and plasma half life of alpha-human atrial natriuretic peptide in man. *Life Sci* 1986;38(20):1827-1833.

Young, D.B., Pan, Y. and Guyton, A.C. Control of extracellular sodium concentration by antidiuretic hormone-thirst feedback mechanism. *Am J Physiol* 1977;232(5).