**Charles University in Prague**

**First Faculty of Medicine**

Degree program: Human Physiology and Pathophysiology

Field of study: Biomedicine



Integrative Physiology in Modelica

by

**Marek Mateják**

Subtitle:

Physiolibrary and Physiomodel – a new Modelica support for hybrid ordinary differential physics of human physiology

(Dissertation thesis)

Supervisor: Doc. MUDr. Jiří Kofránek, CSc.

Praha, 2015

**Prohlášení:**

Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem řádně uvedl a citoval všechny použité prameny a literaturu. Současně prohlašuji, že práce nebyla využita k získání jiného nebo stejného titulu

Souhlasím s trvalým uložením elektronické verze mé práce v databázi systému meziuniverzitního projektu Theses.cz za účelem soustavné kontroly podobnosti kvalifikačních prací.

V Praze, 01.05.2015

Marek Mateják

Podpis

Identification record:

MATEJÁK, MAREK. Integrative Physiology in Modelica*.* Prague, 2015. Počet stran, počet příloh. Dissertation thesis. Charles University in Prague, First Faculty of Medicine, Institute of Pathological Physiology. Supervisor Doc. MUDr. Jiří Kofránek CSc.

Content

[1 Introduction 5](#_Toc415924153)

[1.1 State of the art 5](#_Toc415924154)

[1.2 Models by Tom G. Coleman 6](#_Toc415924155)

[1.3 Goals of this work 6](#_Toc415924156)

[2 Methods 8](#_Toc415924157)

[2.1 Physical principles 8](#_Toc415924158)

[2.2 Modelica Principles 10](#_Toc415924159)

[3 Physiolibrary 13](#_Toc415924160)

[3.1 Types 16](#_Toc415924161)

[3.2 Blocks 16](#_Toc415924162)

[3.3 Steady states 17](#_Toc415924163)

[3.4 Chemical domain 18](#_Toc415924164)

[3.5 Osmotic domain 23](#_Toc415924165)

[3.6 Thermal domain 25](#_Toc415924166)

[3.7 Hydraulic domain 27](#_Toc415924167)

[3.8 Population domain 28](#_Toc415924168)

[4 Physiomodel 30](#_Toc415924169)

[4.1 Cardiovascular system 30](#_Toc415924170)

[4.2 Body Water 35](#_Toc415924171)

[4.3 Hormones 39](#_Toc415924172)

[4.4 Electrolytes and Acid-Base 42](#_Toc415924173)

[4.5 Blood Gases 46](#_Toc415924174)

[4.6 Nutrients and Metabolism 48](#_Toc415924175)

[4.7 Thermoregulation 52](#_Toc415924176)

[4.8 Neural Regulations 53](#_Toc415924177)

[5 Discussion 56](#_Toc415924178)

[5.1 Physiological expandability 56](#_Toc415924179)

[5.2 Expandability in field of physical chemistry 57](#_Toc415924180)

[5.3 Computer Science expandability 59](#_Toc415924181)

[5.4 Mathematical expandability 61](#_Toc415924182)

[5.5 (In)Consistency 61](#_Toc415924183)

[6 Conclusion 62](#_Toc415924184)

[7 References 62](#_Toc415924185)

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

There is no necessary to simplify the deterministic mathematical description of physiology, because the computer power is today fast enough to calculate even a million of equation in real time simulation. Always is better to have more detailed dynamical model with physical-based equations than a simplified one with strange mathematical approximations. Why? Even very smart people think, that more detailed model must bring more and more unknown parameters. It is not true! 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 5) is with this aspect implemented by the author in Modelica 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 there is by author of this thesis reimplemented and extended the huge model HumMod 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 (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 5.1. 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.

## State of the art

d) literární úvod a přehled dané problematiky,

The simulation of integrative physiology has a connected history with development of computers and computer languages for numerical mathematics. One of the

EAI 690 (1973-1982)

Fortran

Matlab

Wolfram Mathematica

Dymola

OpenModelica

Physiome

CellML

SBML

JSim

## Models by Tom G. Coleman

Guyton

Human

QCP

Digital Human

Quantitative Human Physiology

HumMod

## Goals of this work

e) vymezení cílů práce, včetně stanovení hypotéz;

Hypothesis: **Are the last generation of sophisticated industry tools designed for dynamical simulation of huge complex systems and machines suitable for exact formalization of integrative human physiology?**

Physiology formalization

Integrative physiology

General physical principles

Exact science

* + Fyziologický model je možné rozširovať tak, že rozšírenie je minimálne tak dobré ako pôvodný model.
  + Matematickú formalizáciu a integráciu praktických fyziologických znalostí o jednom organizme je možné implementovať do jedného komplexného fyziologického modelu.

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.

Modelica:

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 law, 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, concentration, temperature, electric potential, magnetic potential or space position. The most of physical laws from mentioned physical domains can be represented with 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). 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. So 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.

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.

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 |

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) set this standard condition for temperature and pressure (STP) 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), 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. But each molecule or atom has its mass usually expressed by unit Dalton (gram per one mol) as molar mass or molar weight of substance. The problem is that each substance has different molar mass and as a result the conversion from mass to moles is always dependent on type 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 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.

### 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 and open 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 metabolism of elementary particle, which is in constant amount inside the body.

The laws of conservations 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 non-written rule to calculate with input flow from one component as output flow to another etc. But in steady state calculation (section 3.3) must this system equation be written explicitly, which is not many times so intuitive.

## 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 causes is supported by many other projects, companies and organizations. As a result there are available many environments for this language. For example Dymola, OpenModelica, JModelica, CATIA Systems, CyModelica, MapleSim or Wolfram SystemModeler.

My Modelica extensions called Physiolibrary (section 3) and Physiomodel (section 4) should be running in all these environment, which support the Modelica standard 3.2 or higher and Modelica Standard Library 3.2.1 or higher.

### 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 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 computer 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. 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.

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 by many effectors.

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;

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.

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. For example inheritance from defined classes can be also implemented to have base classes as instances. 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.

Modeling using graphical diagrams takes an analogy of textual representation. Usually is definition of each class accessible as an icon in the left side of environment called ‘Package Browser’. This classes 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 definition. 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’. But be careful, because double click to any class in ‘Package Browser’ 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 variables). The Modelica compilers 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++ 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”.

# Physiolibrary

The main result of this work is Physiolibrary, the Modelica library for Physiology. The whole section 3 is description of this library, which is the base for Physiomodel described in section 4.

Because of Modelica principles, there is possible with relative small amount of physical types describe basic rules of selected physical domains. At first I was implemented in Modelica the complex models such as Guyton’s ‘Overall Circulation’ [1, 2], Ikeda’s ‘Body Fluids’ [3, 4], Siggaard’s ‘Oxygen status algorithm’ [5, 6], ‘Quantitative Human Physiology’ [3] and finally Coleman’s ‘HumMod’ model [7]. Man can say that reimplementation of models does not bring a new knowledge, but I 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 [8, 9] and second is about modeling of oxygen, carbon dioxide and hydrogen ions binding on hemoglobin [10]. 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.

Table 2, Physical connectors in my Physiolibrary compared with electrical connector of Modelica Standard Library

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Connector:** | | **flow variable** | | **non-flow variable** | |
|  | Chemical | molar flow | [mol.s-1] | concentration | [mol.m-3] |
|  | Hydraulic | volumetric flow | [m3.s-1] | pressure | [Pa] |
|  | Thermal | heat flow | [W] | temperature | [K] |
|  | Osmotic | volumetric flow | [m3.s-1] | osmolarity | [mol.m-3] |
| **C:\Users\marek\AppData\Local\Microsoft\Windows\INetCache\Content.Word\PopulationPorts.png** | Population | change of population | [s-1] | size of population | [1] |
|  | Electrical | electric current | [A] | electric potential | [V] |

Each connector in Physiolibrary define 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 concentration 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 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 flow | not exist | Molarity |
| 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 |
| C:\Users\marek\AppData\Local\Microsoft\Windows\INetCache\Content.Word\osmoticMembrane.png  Semipermeable membrane | osmoticCell  Osmotic cell | not exist | not exist | Osmolarity |
| 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. But 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). They 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, which still does not have physical explanation. 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 and which one 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

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 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 really 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 changes and 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

As was mentioned above, the chemical components can be connected by connectors composed by the substance molar concentration and molar flow of substance. Because both molar flow [mol.s-1] and molar concentration [mol.m-3] are connected in the connector with one substance and solution volume [m3], it logically leads to component, which accumulates the substance. These mathematical relations between concentration and solute flow are expressed by Equation 3 and Equation 4.

|  |  |
| --- | --- |
|  | Equation 3, Substance |
|  | Equation 4, Concentration |

This is the main block for chemical domain, called **Substance**. It can be used for different places of accumulation or/and for different substances. For example we can have many instances of this component in our model for different types of chemical substances in one place as in one chemical test-tube experiment and we can connect these instances with chemical reactions. Or we can have the same substances separated by any type of membranes as is typical in the body. Or we can do any combination of these substance-space divisions. There aren’t even any restrictions for type of substance, it can be electron, proton, atom, group of atoms, electrolytes, group of electrolytes, structural form of molecule, molecule, family of molecules, molecular complexes…

Physical chemistry can explain the heat consumed or liberated during chemical reaction, dissolution, phase transition or any molar changes using molar energies [J.mol-1]. At defined temperature and pressure has each substance an internal heat energy called *enthalpy* dH. For example the heat absorbed by chemical reaction is the difference of products enthalpies and reactants enthalpies, called *enthalpy of reaction*. From the enthalpies can be calculated not only heat flow to environment as Equation 5, but also the coefficient shifts caused by change of temperature as Equation 6 – called Van’t Hoff’s equation. Tabulated coefficients CT0 at fixed temperature T0 can be recalculated using gas constant R ≈ 8.314 J.K‑1.mol‑1, enthalpy of the process dH and current temperature T. The result is current coefficient CT at temperature T.

|  |  |
| --- | --- |
|  | Equation 5, Heat Flow |
|  | Equation 6, Van’t Hoff |

Van’t Hoff’s equation can be used for many coefficients such as dissociation constant, Henry’s constant, etc. The notation of subscript T in variables will mean in this section the temperature dependence, which can be solved using Equation 6.

Component of **chemical reaction** as Equation 7 is combined from definition of dissociation constant *KT* and reaction forward rate coefficient *kf,T* [s-1]. Because dissociation constant describes the equilibrium, the equation with zero reaction rate must be the same as *KT* definition: “*KT* is equal to the ratio between products and reactants concentrations”. Backward rate coefficient *kb,T* [s-1] is not explicitly needed, because it must be the same as *kf,T/KT*. So the Equation 7 can be read as “Current reaction flow [mol.s-1] per defined volume [m3] of solution is a difference between forward reaction rate and backward reaction rate”. The symbol *Ri(t)* means i-th reactant concentration [mol.m-3] at time t with stoichiometry *ri*. The symbol *Pj(t)* means j-th product concentration [mol.m-3] with stoichiometry *pj*. The specific calculations with charged particles in water need also to define activity coefficient for reactants and products named as γ, which are typically set default to one. The relation calculates also irreversible reaction just with setting the dissociation constant close to infinity or close to zero as suggested in section [Floating point numbers](#_Floating_point_numbers).

|  |  |
| --- | --- |
|  | Equation 7, Reaction |

The chemical reactions can consume (endothermic) and produce (exothermic) heat. As mentioned above, the amount of heat energy absorbed by reaction is called reaction enthalpy *dH* [J.mol-1]. For exothermic reaction is enthalpy negative. Current flow of heat energy [W] from reaction can be calculated using Equation 5. And using a heat connector in chemical reaction component there is together with heat flow connected the current temperature *T* [K] of solution. This current temperature *T* can change the dissociation constant *KT0*[[1]](#footnote-1) defined for temperature *T0* to value of *KT* using Equation 6.

Sometimes it is necessary to have an unlimited **source** of substance from huge environment. This can be represented just by prescribed concentration during simulation. Or for gaseous substance it can be defined by partial pressure at temperature *T*, which can be recalculated to molar concentration using ideal gas equation as Equation 8, where *R* is gas constant.

|  |  |
| --- | --- |
|  | Equation 8, Ideal Gas |

If the definition of physiological partial pressure is connected with standard conditions at temperature 0°C as usual, then the temperature T is always 273.15 K and the gaseous concentration is proportional to this physiological partial pressure. However, this physiological partial pressure is defined very unhappy because the real physical partial pressure of the ideal gas can be different because of different temperature.

Not only chemical reactions are strongly connected with heat transfers. Production of heat can be measured during condensation or during dissolution of gases in liquids. The equilibrium of **gas dissolution** can be driven by Henry’s law. It is typical for oxygen and carbon dioxide lungs exchange between particles located in air and the same chemical particles free dissolved in liquid. This relation (Equation 9 at zero flow) says that concentration [mol.m‑3] of freely dissolved gas particles in liquid is in equilibrium proportional to their concentration [mol.m-3] in gas above liquid. The ratio coefficient *kHT* [1] is known as Henry’s constant with different value for different gases and different solvents. For linear dynamic of the process it is added a dissolving rate coefficient *kdiss,T* [s‑1], which determines the speed of change from liquid dissolved state to gaseous state and does not affect the equilibrium. The current concentrations [mol.m-3] of selected gas is named in gaseous state as *AGas(t)* and in liquid-dissolved state as *ALiquid(t)*. Current volume of liquid solution is expressed as *volume(t)* [m3].

|  |  |
| --- | --- |
|  | Equation 9, Henry’s law |

The amount of heat liberated during dissolution [J.s-1] is calculated by Equation 5, where enthalpy of dissolution is tabulated constant dependent on selected gas and solvent. As in chemical reaction here is also applicable the Van’t Hoff’s law to shifting equilibrium ratio at different temperatures, expressed by Equation 6. The shift of Henry’s coefficient caused by higher temperature extract the dissolved gas from liquid.

Because the Henry’s coefficient of the solute can be different for different solvents, the law should be applicable also for equilibrium between two different liquids. The system of different liquid solvents should equilibrate at hypothetical gaseous concentration. This hypothetical gaseous concentration is in medical literature typically expressed as partial pressure. As a result, those pressure gradients are more usable than concentration gradients. Because there are equilibrated partial pressures, which not always have the same meaning as equality of concentrations. To have general component for **diffusion** of one substance (Equation 10) we need to fulfill the rule of equality of hypothetical gas concentrations as *In(t)/kHIn,T = Out(t)/kHOut,T* at zero flow, where *In(t)* and *Out(t)* are concentrations of substance at each side of the membrane and *kH* are Henry’s coefficients. Dynamically, the speed of diffusion flow [mol.s-1] is parametrized by permeability *PT* [m3.s-1], which is specific for selected substance and is proportionally dependent on the area of membrane, number of pores/opened passive channels or reciprocal value of membrane thickness.

|  |  |
| --- | --- |
|  | Equation 10, Diffusion |

At typical situation is on both side of the membrane the same solvent with the same *kH* and *dH*, which means zero heat flow and one as Henry’s coefficients ratio at each temperature.

The passive transport on **membrane** is not driven only by simple diffusion. Electrically charged particles are transported with much stronger power as Brown’s motion does. The power of electricity is so strong, that the chemical concentration [mol.m-3] of all positive and all negative charges is almost the same, which give us the rule of electroneutrality. With sufficient precision we can say that at each place at each time in the body is the same number of positive and negative charges. There is also needed to calculate with electroneutral transfers through membranes using Equation 11, where the sum of all electrical charges[[2]](#footnote-2) of transported particles is taken as zero.

|  |  |
| --- | --- |
|  | Equation 11, Electroneutrality |

The membrane steady state is described as Donnan’s equilibrium for passively transported particles [11]. The ratio coefficient for each cation is (1+a(t)) and the ratio coefficient for each anion is (1-a(t)). As a result the variable a(t) can be calculated to reach Equation 11 and Equation 12 at each time t. Because typically is water on the both side of membrane, there can be each Henry’s coefficients ratio kHi set to one. This means, that the same dissolving properties on both side of membrane. Such as in diffusion, the transport speed is driven by membrane permeability parameter Pi [m3.s] for each substance i, where Ini is its concentration [mol.m3] at first side and Outi is its concentration [mol.m3] on the other side of the membrane.

|  |  |
| --- | --- |
|  | Equation 12, Membrane |

If there is water on both side of the membrane the ratio of Henry’s coefficients is one for each temperature and heat transfer is zero.

The sophisticated calculation should be used for macromolecules, because they can reach many structural and chemical forms. For example, each protein is composed by amino acids and some of these acids can occur in protonated or deprotonated[[3]](#footnote-3) forms, which changes the electric charge of whole protein. This average charge relation with pH is called titration curve. And there is not only hydrogen ions, which are binding into macromolecule. It is impossible to calculate exactly each form of the molecule and each reactions between them, but using the law of detailed balance it is possible to calculate equilibrium only from the list of defined independent reactions on macromolecule. The principle was for example used by famous Monod-Wyman-Changeux (MWC) model [12] of allosteric transition. The idea is to select and define the specific form of macromolecule, which will take a role in other processes. For example quaternal structural changes. In case of allostery, the form is selected as unliganted one and there is only a structural change of this form as chemical reaction between deoxygenated relaxed form of hemoglobin and deoxygenated tense form of hemoglobin. The components called **chemical speciation** does not implicitly define any reaction, but it only calculate the fraction of specific forms from each group. In the case of MWC model is group defined by structural composition, for example all oxygenated or deoxygenated forms in tense state.

The group is modeled as the set of independent reactions, which take place on independent sides of macromolecule of selected state. The results of these reactions are fractions between selected state of the sides and all possible states of the sides. From these fractions can be easily defined the fraction of the specific form just by multiplication them together.

|  |  |
| --- | --- |
|  | Equation 13, Speciation |

Concentration of macromolecule specific form named as specificFormConc(t) is calculated as a fraction in group with concentration named as groupConc(t). These specific form concentrations can be used for specific chemical reactions, which are defining for example the structural changes. Problem of the calculation is that there is condition of equilibrium and it does not reflect the dynamic changes. But for the most of cases are reactions fast enough to reach the defined equilibriums on the macromolecules. Using this calculation of chemical speciation can extend the Adair’s model of hemoglobin binding with hydrogen ions and carbon dioxide and calculate not only oxygen saturation, but also the titration shifts and the saturation of carbon dioxide [10]. And it can be generally used for any equilibrated chemical system of macromolecules.

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 *soluteFlow* is here the volumetric flow of whole solution *streamFlow* multiplied by *concentration* in the origin of stream in Equation 14.

|  |  |
| --- | --- |
|  | Equation 14, Stream |
|  | Equation 15, 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. In contrast with stream, there is not volumetric 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 16). 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 volume takes place, then the concentration fall down to half after time expressed as parameter *HalfTime*. In condition of the constant solution volume it could be rewritten also to clearance calculation as Clearance = volume\*ln(2)/HalfTime.

|  |  |
| --- | --- |
|  | Equation 16, 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).

Chemical substances in nephron tubules can be reabsorbed from the primary urine back to the body. This complex processes can be approximated by Equation 17, where the molar flow of reabsorbed substance is expressed with threshold called MaxReab. This maximal reabsorption is typically caused by saturation and busyness of membrane channels, which does not allow higher reabsorption than MaxReab. For example the glucose is fully reabsorbed by kidney nephrons (Base=1) when the input flow to tubules does not reach the threshold (MaxReab).

|  |  |
| --- | --- |
|  | Equation 17, Reabsorption |

If the speed of reabsorption is not fast enough to continuously reabsorb all inflowing molar flow of substance, then it is necessary to set Base parameter to other value as one and calculates with effectiveness of reabsorption processes.

## Osmotic domain

In the osmotic domain is accumulated a volume, in contrast with chemical domain, where it is accumulated molar amount of substance. So the flow variable inside the osmotic connector is volumetric flow of solution, not molar flow of solute. The non-flow variable is osmolarity, which has physical units as molar concentration (mmol/L of impermeable particles). Because there can be connected more types of semipermeable membranes with one accumulated volume, different osmolarity must be expressed for each of these membranes. For example the blood plasma is directly connected with:

1. capillary membrane, where the colloid osmolarity is expressed as the concentration of plasmatic proteins
2. cellular membrane, where the osmolarity is calculated also from all impermeable substances which can freely cross capillary membrane

As a reason the **accumulation** component called *OsmoticCell* has the array of osmotic connectors specified by semipermeable membranes. The volumetric flows called *volumeFlowm* from each connector are integrated into one *volume* as in Equation 18. And the specific osmolarity for each membrane *m* is expressed in Equation 19 as the concentration (*osmolaritym*) of all substances, which can’t cross this membrane *m* in the same speed as in the solution does.

|  |  |
| --- | --- |
|  | Equation 18, Osmotic Cell |
|  | Equation 19, Osmolarity |

If a user does not specify the number of membranes, then only one will be used (*m=1*). This setting generates only one connector with one osmolarity and the volumetric flow.

Calculation of amount of impermeable substances inside is not part of the OsmoticCell. Usually it can be implemented using chemical Substance components as accumulation of chemical substance.

The transport through the **semipermeable membrane** is driven by pressure gradient as in Equation 20. At steady state are pressures equilibrated for example by diluting of impermeable solutes or by volume-generated hydraulic pressure inside elastic membrane. Dynamically is the speed of equilibration determined by parameter permeability *Perm*.

|  |  |
| --- | --- |
|  | Equation 20, Permeability |
|  | Equation 21, Osmotic Pressure |

The pressure on both sides is composed with hydraulic and osmotic part, Equation 21. While the hydraulic pressure push the flux to the other side of the membrane, the osmotic pressure suck the flux from the opposite side of the membrane. As a reason the osmotic part must have negative sign in the equation. The recalculation of osmotic pressure from osmolarity is approximated by Mortinner using temperature *T* [K] and gas constants R ≈ 8.314 m3.Pa.K‑1.mol‑1.

Because of the properties of capillary microcirculation, the outflowing blood pressure *pressureo* is almost equilibrated with interstitial pressure called *pressurefiltrate* in Equation 22. Both pressures are in the meaning of Equation 21. This ideal situation of equilibrium leads to simplified calculation of **ideal filtration** on capillary membrane. The molar overflow [mol.s-1] of impermeable substances is the same in the inflow (subscript *i*) and in the outflow (subscript *o*) of the capillary net as expressed by Equation 23. And finally the volumetric flux (*filtrationFlow* [m3.s-1]) of filtrate through capillary membrane is the same as the difference between the volumetric flows inflowing and outflowing from capillary net (Equation 24).

|  |  |
| --- | --- |
|  | Equation 22, Ideal Filtration |
|  | Equation 23, Molar Flow |
|  | Equation 24, Volume Flow |

The component *IdealOverflowFiltration* has two osmotic connectors. Typical usage is to connect first connector to circulated liquid inside and second to the environment around the circulation segment. For example, in capillary microcirculation of tissue the first connector is connected to blood osmolarity in input of the capillary net and the second connector is connected to tissue interstitial osmolarity. The absolute value of flow in both connectors is the volume flux through capillary membrane. Blood flow through capillaries is a parameter or input signal to this component such as temperature or hydraulic pressures on both sides of capillary membrane.

Not always is the filtration ideal. Especially in kidney it is not possible to have the final urine in the same osmolarity as the kidney medulla is. The glomerular filtration is much higher than the inflowing urine to the bladder. The difference of this volumetric flows is the total reabsorbed flow by the kidneys. This total flow can be divided into parts of nephrons, where Equation 25 can be used. If the minimal flow through tubule (*OutflowMin*) is not set, then the reabsorption is the fraction (*fract*) of inflowing volume to the tubule called as *inflow*.

|  |  |
| --- | --- |
|  | Equation 25, Reabsorption |

The fraction *fract* can be approximated from number of opened water channels and/or from active transport of osmoles through membrane.

## Thermal domain

It is not surprise that in thermal domain is accumulated the heat energy as in Equation 26. 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 27). 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 26, Heat |
|  | Equation 27, 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. These variables are compatible also with Van’t Hoff’s equations (Equation 5 and Equation 6). As a reason the same thermal connector can be used for endothermic or exothermic chemical reaction, for changing environments with different solubilities (components for gas dissolution and for membrane) or for partial pressure recalculation using ideal gas equation. Even more, the connector is designed to be compatible with all standard Modelica library Thermal.HeatTransfer components.

**Heat conduction** is driven by temperature gradient as shown in Equation 28. 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 28, 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 14 and Equation 29 are similar, but the meaning of variables are different. The **heat stream** is based of mass flow [kg.s‑1] not volumetric flow and there is not molar concentration, but concentration of heat energy expressed as multiplication of temperature [K] with specific heat of the mass [J.kg-1.K-1].

|  |  |
| --- | --- |
|  | Equation 29, Stream |

Temperature T means the temperature at the origin of the mass flow, which could be a problem if the mass flow change the direction (massFlow<0). In this situation the temperature source must be smoothly changed to the second connector of the component. If the substance is changed from liquid to gaseous state (evaporation), then the non-zero vaporization heat of substance must be included.

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. And the maximal heat flow to environment can be limited by equilibrium of temperatures of outflowing liquid and the environment around radiator as Equation 30. Equation 31 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). And really the amount of transferred heat to the environment is proportional to the flow of the liquid inside the radiator called *massFlow* [kg.s‑1]*.* The specific heat [J.kg-1.K-1] of this liquid is named *SpecificHeat*.

|  |  |
| --- | --- |
|  | Equation 30, Ideal Radiator |
|  | Equation 31, Heat Flow |

However, the blood can transfer about 5% more heat from working muscles to lungs than is calculated by Equation 31, because of endothermic behavior of hemoglobin deoxygenation [10]. 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 32 and Equation 33. 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. At very small volume called VCollaps, the vessel starts to generate negative sucking pressure, which should be the mathematical prevention of unwanted negative volumes inside. But in classical numerical software this solution can easily fail on the tolerance for volume, because the volume near the zero starts to generate too huge pressure changes with too small volume changes. As a result parameter *A* is selected more for numerical stability as for fitting real behavior during collapsing condition. A good choice could be for example to achieve the limiting difference between external pressures at the middle between zero volume and VCollaps.

|  |  |
| --- | --- |
|  | Equation 32, Volume |
|  | Equation 33, 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. And the third branch solves only the situation, when something sucks the blood volume. 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 mean 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 34, 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 35. The classical formula (gravity\*density\*height) is here extended with pumping effect (*pumpE*), which significantly helps to break the **hydrostatic column** with valves inside the veins.

|  |  |
| --- | --- |
|  | Equation 35, Hydrostatic |

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 they are compressing with muscle abound.

**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*. Opening pressure gradient can be moved from zero to non-zero value called Pknee. Second branch of Equation 36 is valid During opened phase (pressure gradient > Pknee) and if the valve is closed the first branch takes place instead. At the break point defined by pressure gradient Pknee are valid both branches with flow of Goff\*Pknee.

|  |  |
| --- | --- |
|  | Equation 36, Valve |

Typical setting is selecting the knee point (volumetric flow Pknee\*Goff at pressure Pknee) very close to origin (Pknee=0), what simplifies the equation to forward and backward resistor. Even the backward conductance is very small, there can be generated small volumetric flow in case of closed valve. But 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 37 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 37, 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 heart.

## 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 38, 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 38, 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 39.

|  |  |
| --- | --- |
|  | Equation 39, 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 circulation 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 at the start of aorta, bottom-left at the end of systemic veins and top-left at 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 secretion. 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 calculated beat by beat. Instead of current values at defined second 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 32 and Equation 33 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 is going some blood flow and also 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) [13, 14] and end systolic volume (ESV) [15]. The most common descriptions are pressure-volume relations [16] as in A-V fistula experiments [17] or filling pressure experiments [18] or less invasive exercise experiments [19].

This model is not solving the situation of very short time for good filling of the ventricle. Especially during tachycardia there is an evidence of the dependence of stroke volume on heart rate [20, 21], which could be well described using dynamic beat-by-beat implementation. Using Physiolibrary there is possible to make the beat-by-beat implementations as we describe in articles [8, 9]. These publications show the opening and closing valves (Equation 36), 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 37), which has a significant role on shape of functions (generating Dicrotic Notch, ..) during these short-time events. But the switch of time scale to shorter times opens more questions, which we have not answered in these articles. For example the shape of pressure function in different places of circulation is more caused of pressure pulse wave than the filling blood volume of the vessel [22]. These waves are moving much faster than blood and they can even be reflected to the opposite way of blood flow. In continuous flow calculations are these waves eliminated, because they wave characteristic caused the equality of positive and negative areas under and below the mean pressure [23].

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 32 and Equation 33) and hydraulic resistor (Equation 34). 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 [24] is not implemented, but can be easily inserted in the next versions.

In systemic circulation the blood flow is after elastic vessel component for systemic arteries [25] divided into branches for different tissues. In the upper part of Diagram 6 are the instances of 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 inside the liver. The lower part of Diagram 6 represent the sequestered blood in the lower parts of the body caused by hydrostatic gravitation effect (Equation 35). Characteristics of sequestering blood in leg vessels are measured with many orthostatic experiments [26-32]. 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 [33-35].

After flowing through tissues goes blood into systemic veins, which zero-pressure-volume is driven by venoconstriction driven by sympathetic neural answer as part of baroreflex [36-38]. 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 when 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 8). 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 [39]. 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 [40] in dependence on gastro intestinal blood flow. Portal blood volume and pressure is known in typical or in changed histamine concentration [41], catecholamine concentration (sympathetic activity) [42, 43]. The splanchnic circulation can have a function of blood reservoir during hemorrhage or during blood infusion [44, 45].

Diagram 8, Splanchnic Circulation

### Microcirculation

The blood flow through blood vessels depends on blood viscosity [46], 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 [47], 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 8) needs to set optimal filtration pressure [48, 49] and to prevent washout of kidney medulla concentrations. This can be driven by number of working nephrons, tubule-glomerular-feedback [50, 51], baroreflex-like patterns [52], local mechanoreceptor-myogenic pattern [53, 54] and by efferent interlobar microcirculation [55].

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 [38, 56]. 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 38 and Equation 39) 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 calculation of general blood properties such as total blood volume, hematocrit, viscosity or viscosity conductance effect. Viscosity of blood is strongly dependent on the hematocrit [57-59], so the higher number of red cells the less ability for blood to move. But if there are more red cells with hemoglobin, the more oxygen can be connected to hemoglobin. Optimal hematocrit for oxygen transport between this two conditions was experimentally measured as 40-60% in the most tissues [60, 61].

Figure 6, Viscosity Conductance Effect on Hematocrit with measured data of Fan et al. [60]

### 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 33, 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 of 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 it is thrown an error if some physical connectors are not connected. So the user cannot leave the blood outflow from component unconnected. And if he want to make flows from/to the environment he must use the specific component such as flow pumps or pressure pumps.

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 osmotic connectors because an osmolality is the main force of transferring the water in the body. 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 [62-65]. 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, into which comes the water if the value is positive or from which becomes the water if the value is negative, for example the blood plasma (PLASMA) or the environment (ENV). The water is absorbed from diet in gastrointestinal tract. 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 |
| through capilaries | -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 |
| to urine | -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 molar concentration *c* plays the role in osmotic pressure *p* as Equation 21. 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 [48, 66] with our Equation 21.

Table VI, Typical plasma proteins concentrations [mmol/l]

|  |  |  |
| --- | --- | --- |
| Total | Albumin | Globulins |
| 1.44 | 0.63 | 0.81 |

As was mentioned, the model of proteins (Figure 3) 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 colloid pressure or plasmatic concentration. Movement between compartments is caused by capillary membrane concentration gradient or by lymph flow [67] 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 [mmol/l]

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

Diagram 13, Subsystem of Extracellular Proteins

### Gastro intestinal water absorption

As presented in Table 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), where it has the mean osmolarity about 253 mosm/l. This osmolarity is composed mostly with sodium with anions (160 mosm/l), dietary fiber (43 mosm/l) and potassium with anions (50 mosm/l). Water is sucked by gastrointestinal cells, where is the mean osmolarity about 286 mosm/l called OsmBody\_CellWall in 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 osmolarity gradient of 9 mosm/L on cell membranes, which is the same as mean osmotic pressure gradient of 25 kPa at temperature of 37°C. From these assumptions can easily express the permeability parameter of Equation 20 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 [63-65], 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 [68] or Xie [62]. Water crossing the capillary wall is driven by hydrostatic-colloid pressure gradients as expressed by Equation 20.

Table VIII, Typical osmolarities of substances on cellular membrane [mosm/l]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| CELLULAr membrane | electrolytes | Urea | glucose | other |
| ECF [mosm/L] | 250 | 6 | 6 | 24 |
| ICF [mosm/L] | 266 | 6 | 0 | 13 |

However the flow of water between interstitium and cells is determined by all substances. In cellular membrane the proteins osmolarity plays the minor role, because their concentration is only about 1 mosm/l. Here in extracellular space is osmolarity divided into electrolytes, urea, glucose and others solutes. And in intracellular space are electrolytes, urea and others solutes. Osmolarity in equilibrium must be the same in interstitial space and in cells (typically 285 mosm/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 the water reabsorption fraction only 37% of sodium reabsorption fraction [69, 70].

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. [71, 72].

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 [73, 74]. 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. Independently on aquaporin channels is calculated 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 35. Together with hydrodynamic blood pressure and osmotic pressure components it forms the pressure gradient on capillary walls of tissues. The mean hydrostatic pressure values for each torso are listed in Table VIII as part of the mean total pressure gradient of capillary walls. Comparing the values of blood hydrostatic pressure and interstitium hydrostatic pressure one can see the significant differences. 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 osmotic pressure is calculated by Equation 21 from physical chemistry. 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 osmotic pressure is calculates in both models only from these proteins, which cannot freely cross the capillary membrane. Their molar concentrations in Table VI and in Table VII are consistent with both the physical osmotic pressure calculation and with their original mass concentration, 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 35). 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. So 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 16) 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 nephron tissue, where it plays the role in water reabsorption. The normal long-time amounts of ADH in these compartments are listed in Table 11, but during the regulation the concentrations can be increased of the hundreds or thousands times [75]. 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 [71]. 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 [76]. Other possibility to regulate ADH secretion is cardiovascular centrum reflexes [77].

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 |

Even the vasopressin inside cells is modeled using instances of chemical Substance class, the intracellular concentrations here do not have sense because ADH is transported 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 [75].

### 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 [78-84].

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 [85].

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 [86] [87-90]. In contrast with previous hormones the distribution space of EPO is not whole extracellular fluid, but only about 40% of them [91, 92]. 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 [88, 93, 94].

### 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 [95], the last discontinued definition from year 1986 has improved to 38.46 µg/IU [96]. 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. [97]. Insulin is synthetized and stored in beta-cells and its secretion is driven primary by glucose and secondary by keto-acids [98, 99]. Portal and peripheral vein insulin has different concentration [100], because insulin is transported just after secretion by portal vein to liver. Absorbance and clearance was measured by many infusion experiments [101-103].

Problems with insufficient insulin secretion results in type 1 diabetes mellitus and the receptor insensibility leads to type 2 diabetes mellitus [104-106], where many differences between normal and obese individuals has been observed [107]. Insulin has the significant effects to glucose absorption by cells of liver [108-110], where is glucose stored and release to/from glycogen (glycogenesis, glycogenolysis), created from amino-acids (gluconeogenesis) or transformed to fats (lipogenesis) [97, 107, 111]. 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 [112]. But the idea to cure obesity with leptin fails on leptin resistance joined with obesity [113] [114]. The clearance of leptin is primarily by kidney [115]. It has multiple effects on higher metabolic centers [116, 117], 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) [118, 119] and adrenergic receptors [120, 121]. The clearance is primarily by liver [122]. 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 [123]. 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 [124].

### Thyroid hormones

The main purpose of thyroid hormones in our model is to maintain basal metabolism in connection with long-term thermoregulation [125]. The concentrations, secretions and clearance of thyroid hormones are well known because of relative easy measurement of iodine radioactive isotopes [126-129]. During cold months increasing of triiodothyronine (T3) [130] increase the basal metabolism [131] what improve the heat regulation in cold conditions. The impulse for the production and secretion of T3 and thyroxine (T4) is thyrothropin (TSH) [132]. And the secretion of TSH is driven by thermoreceptors and it is directly suppressed by T3 [130, 133-135]. The clearance of TSH is much quicker than clearance of T3 or T4  [136], 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), 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. For hormones, enzymes or cytokines with already known conversion between international unit and molar concentration it should be used molar concentration.

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 [137]. 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 somehow written the same variable as intake and outtake of the renin granules. So the renin granules has the same concentration during each time in each simulation experiment. 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 typo 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 charge concentration for strong ions, which do not significantly change their charge at pH from 5 to 9. This is called strong ion difference (**SID**) [138]. 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: expressed as **BEox** = Hct\*(SIDE-NSIDE)+(1-Hct)\*(SIDP-NSIDP), where Hct is the hematocrit and BEox is the base excess of oxygenated blood. 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 [139]. 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. [140], Wolf et al. [141, 142].

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 9) and CO2 hydration to H2CO3 accelerated by carbonic anhydrase inside red cells. The acid-base equilibrium can be calculated as steady-state of Equation 7, where the dissociation constant K can be defined using negative decimal logarithm as pK = ‑log10(K). But be careful with unit compatibilities in definitions of pH and pK, because in chemistry is typical concentration unit “mol.L-1” instead of physical SI-unit “mol.m-3” (mmol/L). The shift of tabulated dissociation constants from defined temperature is calculated using Equation 6.

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) ↔ 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 the equation of electroneutrality (Equation 11). 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, where 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 salts as HPO42-, PO43-­, CO32- or C2O42- can react with calcium Ca2+ to create the kidney stones. The charge of each substance is calculated using its scheme of chemical reaction (Table 11) in equilibrium of Equation 7 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 exterminator 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 12).

### 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 will generate sufficient the weak ions charges with the electroneutrality of the rest solution. The state variables are the total amounts of substances, which in the case of weak ions includes all their (de)protonated forms. For example the inorganic extracellular phosphates means H3PO4, H2PO4-, HPO42- and PO43-. The total amount of these phosphates is independent of pH, but the 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 charge 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 [143] 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 [144]. 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 transport are critical for life. It 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 gas equation (Equation 8). 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 9), 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 [10].

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 12).

Table 13, Carbon dioxide forms concentrations in blood at normal condition with 45% hematocrit

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Arterial plasma | Arterial RBC | Venous plasma | Venous RBC |
| Dissolved CO2 | 1.2 mmol/l | 1.2 mmol/l | 1.4 mmol/l | 1.4 mmol/l |
| HCO3- | 24.4 mmol/l | 13.1 mmol/l | 26.3 mmol/l | 13.2 mmol/l |
| Hb-CO2 |  | 2.4 mmol/l |  | 3.2 mmol/l |
| Total | 25.6 mmol/l | 16.7 mmol/l | 27.6 mmol/l | 17.6 mmol/l |
| Total blood | 21.6 mmol/l | | 23.1 mmol/l | |

### 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)[6]. 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: saccharides, 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 achieve the electroneutrality has to the hydronium ions go back to the mitochondrial matrix through the ATP synthase. The new synthetized ATP is exchanged for ADP and one phosphate using electroneutral symporter mechanism.

The ratio between using of the base nutrients can differs with type of cell [145]. 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 [146]. The amino acids can be metabolized only by liver or in kidney tubules[147], 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[148], ketogenesis[149] or lipogenesis[150]. 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[151]. Process of storing glucose into glycogen granules is known as glycogenesis and reversal process of releasing glucose from glycogen is known as glycogenolysis (Diagram 31).

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 [152].

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 [153].

### 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 [154]. 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 during elevated renal excretion of them [143, 155].



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 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 in Physiomodel is glucose 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 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. As the direct result of temperature dependent chemical reactions there is a change of the reaction rates and the dissociation constants (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. [156]. At higher temperature there are expressed more heat shock proteins and at lower temperature there are expressed more cold shock proteins [157]. 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 affected by partial pressures (Equation 8) and osmotic pressures (Equation 21) are dependent on temperatures. So the regulation of body temperature is very important. The main mechanism how to regulate body temperature is by regulation of skin blood flow [158-160] (Equation 30) and of course the amount of clothes by feeling of warm or cold. There is also long-time (in periods of months) regulation of heat by thyroid hormones [131], which increase or decrease the speed of basal metabolism as the source of heat in each cell. Short-time heat production is typically based on working muscles [161] or by shivering [162]. The efficiency of skeletal muscle is about 30%, so the significant part of consumed energy is released as heat during each motion. For heat transfer of any microcirculation it is assumed, that temperature of outgoing blood is the same as temperature of tissue (Equation 30), 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 29) in upper respiratory pathways during air inspiration [163]. 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 [164-168]. 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 even if the environment temperature is higher than body temperature. However, 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 [169], 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 [170, 171] is still beating using autonomic oscillations of sino-atrial node cells, without the useful information [172] about muscle metabolism, about current blood status, and about blood pressures [173, 174].

|  |  |  |
| --- | --- | --- |
| **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 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 5.1.

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.

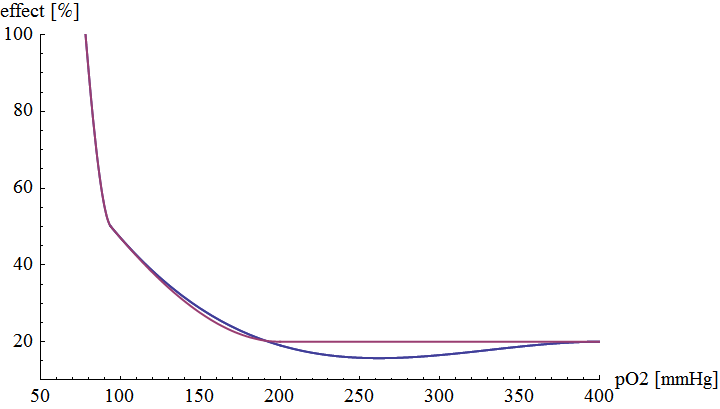


Figure 10, Correction of oxygen effect on central chemoreceptors.

# Discussion

h) diskuze metodických postupů a výsledků, včetně srovnání s literaturou;

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. A few of parameters are patient specific such as weights or volumes of the body, the organs or the tissues. 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 I implement the HumMod model in Modelica, I 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 I 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 (TENRR) 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 TENRR 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 many researches are more close to our new value, 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 higher 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 are all electrolytes and acid-base buffers as state variables 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 me that dissociation constant is not really the constant. It is dependent on temperature, so the Van’t Hoff’s law (Equation 6) 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 (Equation 5). And using the conditional thermal heat port it allows 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 is hidden by default, all instances of chemical reactions in the model remains the same and with the same setting and connections as before these thermal extensions.

Now I start the new approach which can calculate also the dissociation coefficient at defined temperature from thermodynamic properties of substrates and products of the reaction. The idea is to simplify the usage of chemical reaction component. The user will just select the type of all substrates and products and the dissociation coefficient will be automatically calculated. This is theoretically possible if there will be also a database of all modelled chemical substances with their relative enthalpies of formation (ΔfH) and entropies of formation (ΔfS). From these data can be expressed the Gibbs energy of formation (ΔfG) for the substance at temperature T as ΔfG = ΔfH - T\*ΔfS. The enthalpy of the reaction by Hess law is the sum of formation enthalpies of products minus the sum of formation enthalpies of substrates. Having Gibbs energies of all products and all substrates, the Gibbs energy of reaction (ΔrG) is also the result of Hess law. And the dissociation coefficient (K) of the reaction at temperature T is defined from the Gibbs energy of reaction as Equation 10, where R is the gas constant.

|  |  |
| --- | --- |
|  | Equation 10, Gibbs free energy of reaction |

Only one small problem is, that this thermodynamic theory of physical chemistry is valid in ideal gas conditions. However the chemical processes in the body are more like water solution of electrolytes. The adaptation to water condition can be simplified using activities instead of concentrations, where the activity is the concentration multiplied by activity coefficient. 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 as calculation of activity coefficients. And imagine the creation of metabolic pathways just by connecting substances with this new implementation of chemical reaction. User just select 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 forward reaction rates to start the simulation.

This kind of improvement guarantees also the more sophisticated rule of chemical systems called “Principle of 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 10.

Also the next chemical reaction parameter kf (forward rate coefficient) can be calculated using Gibbs energies. The idea is to use the transition state theory as Equation 10 for this calculation, where κ is proportional constant, kB is Boltzmann constant, h is Planck constant, R is gas constant, T is temperature, ΔfGs is the sum of Gibbs formation energies of substrates and ΔfGt is the Gibbs formation energy of transition state.

|  |  |
| --- | --- |
|  | Equation 10, Transition state theory |

The difference ΔrG‡ = ΔfGt ‑ ΔfGs is called activation energy of the reaction. However, this calculation still need to have ΔfGt or ΔrG‡ as parameter. This exchange of parameter kf for parameter ΔrG‡has sense only if it will be possible to attach the connection to the database of these values.

## Computer Science expandability

The Modelica language is still developing, so there is still possible to add some keywords or features, which improve the model definitions. My attempt of steady state implementations in Modelica shows, that there is problem with correct decomposition of the model designed in steady state mode. In dynamical mode, each decomposition into components must be locally balanced in current Modelica (version less or equals 3.3), which means the same number of equations as the number of unknown variables in each component. Each connector of two variables (flow and non-flow) is counted as one known and one unknown variable, even if the decision of which one will be known and which one will be unknown is dependent on usage. For example the resistor with two connectors will have two equations - Ohm’s law and Kirchhoff’s first law and two unknown - generated by two connectors. However in steady state mode, there are some equations dependent and instead of these equations there should be taken more general laws describing the system as a whole. These conservation laws of masses, energies, charges, number of elementary particles are global and they cannot be a part of only one component. It is against the primary Modelica rule about locally balanced model! My solution is to leave this very useful rule as it is and generate these conservation laws from additional setting of the model variables during translation of the model.

My proposal is to add the real type properties “totals” and “totalsCoef” as arrays in the same length for each real variable instance. If the user in the model properly set these properties for the accumulating states and for the flows between outside and inside then the conservation law can be automatically generated if needed. The weighted sum of all non-flow variables in the same conservation law[[4]](#footnote-4) can be used in generated equation with a new generated state variable describing the total amount of conservation law. The weighted sum of flow variables in the same conservation law[[5]](#footnote-5) will be a change of this new state variable. If there is not any flow then the system is closed and this change is zero. Weight of the value of the variable in these sums are coefficients from “totalsCoef” at the same position as the string in “totals” which determines the conservation law for the selected real variable. This string value as one element of the array “totals” can determine more levels of conservation laws, which are named by prefix of this value until some ‘.’ character. The shorter prefix the more general conservation law. The longer prefix means more specific conservation law as part of the general conservation laws defined by each its shorter prefix.

In the simplified flat situation of one conservation law and default totalsCoef={1}: The array of strings has only one element, which is non-empty string without ‘.’ characters. The name of total amount of the conservation law will be the same as the name written in “totals[1]” property, so the value of this total amount will be the same as the sum of all state variables with the same name in property “totals[1]”. During steady state are all these components switched to be in steady state (Equation 2), so that means no changes at all when the subsystem is closed (without external flows). If the steady state subsystem is open, then it is needed to reflect the changes only as changes of the total amount. Here can be used the same property “totals[1]” of all flow variables. The current change of total amount is the sum of all flow variables with the same “totals[1]” string in the model.

In full hierarchical situation of one conservation law model and default totalsCoef: The array of strings has only one element. Because there are many criteria to divide the total amount defined by conservation laws in different levels, there must be an option how to hierarchically define the total amounts in the system. For example if we look at the oxygen in the body, we can use spatial hierarchy to tell, where the amount of oxygen is. So the total amount of oxygen in the body can be divided at first level into oxygen as gas in lungs, total oxygen in blood, total oxygen in extravascular space. And for example at the second level the total oxygen of blood can be divided into oxygen in plasma and oxygen inside red cells. At third level the total oxygen of red cells can be divided into free dissolved, bound into hemoglobin A and bound into fetal hemoglobin so on. And all oxygenated forms of hemoglobin will have the property “totals[1]” set to the same value, for example as totals = {“O2.blood.redCells.hemoglobin”}. The solver should have an option to select at which level will be calculated the steady state. If the all oxygen components can be in steady state, then steady state is selected at the top level. If there is a component, which is changing slowly enough to not be in steady state the next level must be assumed. In the situation where even the last level is not selected for steady state of for stable system the whole oxygen subsystem must be computed in typical dynamical mode.

One variable can be accounted in more conservation laws. For example the macromolecule with more bound ligands could be in conservation laws of all these ligands and of course in conservation law of the macromolecule. Because the elementary elements are stable in the body, there can be also done as many total amounts as many types of chemical elementary elements are in the body. Each molecule then will have the “totals[:]” array in the same length as many types of atoms it contains. For each atom can be specified how many times it occurs in the molecule in property “totalsCoef [:]”. For example if we want to define the total amount of carbon C and oxygen O atoms in the system, then the variables describing the molar amount (as state variable) and the molar flows (as flow variables) of molecule of carbon dioxide CO2 have the totals={“Carbon”,”Oxygen”} and totalsCoef ={1,2}.

## Mathematical expandability

The examination of physiological systems brings also ideas about mathematical calculations. Typical universal numerical solvers for ordinary differential equations must solve the problem from just the low level mathematical description behind. These description is typically only the set of differential equations plus the tolerance as limiting value of precision. However, if there is some more structural information of the model, the solver could be more robust, quicker and it allows to solve more tasks. The information about steady states of subsystems can be very useful for new generation of numerical solvers, which could solve the hard stiff mathematical problems very fast and without so many integrative steps as current ODE numerical solvers does.

My new proposal of the numerical ODE solver SSSS (Steady-State Stiff Solver) could operate more as physic or physiologist, because it could recognize the open or closed physical systems inside the model and resolve weather the parts are stable, equilibrated or in dynamical state. This solver will work with the subsystems designed for steady state calculations. User will specify the interval of time steps, where he wants to run the simulation. The very fast processes compared with these time steps should be calculated as steady states. The states of very slow processes (compared with selected time steps) are stable and they should not be significant in the results. Using this kind of numerical solver there should be possible to design the same model for very short-time simulations (as chemical reactions in picoseconds) and for very long-time simulation (as living of patient on some diet during years of simulation time). The equations behind the model will be the same, but the numerical calculation must be appropriate to the selected time window, during which the user wants to run the simulation. However, this automatic solver need additional information from user about the modeled systems. This new keywords must be integrated into the equation based computer language as described in the end of the following section.

## (In)Consistency

Common situation during robust deterministic investigation of physiological process is the overdetermined description. There are more relations than the number of the unknowns. However, to have well determined system with only one unique solution there must be the same number of independent equations as the number of unknowns. Even the quantum theory or the chaos theory is deterministic, so in the modern physics it must be exactly one solution each time for the well described physiological model. If the equations allows more than one solution then is something missing. This situation is very exciting, because it can bring the new physiological theories or new dependencies. These new equations must be consistent with the rest of model and also they must be proven by experiments. More frequent situation is, that during the study of the problem there are collected more equations than unknowns. This description of the model must be consistent, so the number of redundant equations must be the same as difference between the collected equations and unknowns. The redundant equation can be the dependent equation such as some linear combination of the rest of equations, a simplified approximation of the rest or an additional description of the more detailed part.

In theoretical medicine research the mathematical model exactly describes the physiological or pathophysiological processes. The goal is to be mathematically consistent with physical bases of the processes. Having detailed physical and chemical description of the same process from different point of view is possible to collect more equations than the number of unknown.

Some research generates the empirical mathematical relationships of observed data from measurements. It could help to estimate the behavior of the system. However, without having a theoretical model is hard to select all significant data to measure. For example the breath-hold during parabolic flights exercise experiment with measuring of blood pressure, cardiac output and many other values {TODO refenences to Hoffman}. They did not measure the intrathorax pressure, so the breath-hold effect on cardiovascular system as Valsalva’s maneuver remains unknown.

# Conclusion

j) souhrn (v českém i anglickém jazyce);

Výsledkom práce je podpora integratívnej fyziológie v moderných

# References

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

2. Guyton, A.C., T.G. Coleman, and H.J. Granger, *Circulation: overall regulation.* Annual Review of Physiology, 1972. **34**(1): p. 13-44.

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

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

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

6. Siggaard-Andersen, O. and M. Siggaard-Andersen, *The oxygen status algorithm: a computer program for calculating and displaying pH and blood gas data.* Scandinavian Journal of Clinical & Laboratory Investigation, 1990. **50**(S203): p. 29-45.

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

8. Kulhánek, T., J. Kofránek, and M. Mateják, *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): p. 137-144.

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

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

11. Donnan, F.G., *Theorie der Membrangleichgewichte und Membranpotentiale bei Vorhandensein von nicht dialysierenden Elektrolyten. Ein Beitrag zur physikalisch-chemischen Physiologie.* Zeitschrift für Elektrochemie und angewandte physikalische Chemie, 1911. **17**(14): p. 572-581.

12. Monod, J., J. Wyman, and J.-P. Changeux, *On the nature of allosteric transitions: a plausible model.* Journal of Molecular Biology, 1965. **12**(1): p. 88-118.

13. 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.* The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation, 1998. **17**(2): p. 140-149.

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

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

16. Sagawa, K., et al., *Cardiac contraction and the pressure-volume relationship*. Vol. 480. 1988: Oxford University Press New York.

17. Guyton, A.C. and K. Sagawa, *Compensations of cardiac output and other circulatory functions in areflex dogs with large AV fistulas.* The American journal of physiology, 1961. **200**: p. 1157.

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

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

20. ROSS, J., J.W. LINHART, and E. BRAUNWALD, *Effects of Changing Heart Rate in Man by Electrical Stimulation of the Right Atrium: Studies at Rest, during Exercise, and with Isoproterenol.* Circulation, 1965. **32**(4): p. 549-558.

21. Sugimoto, T., K. Sagawa, and A. Guyton, *Effect of tachycardia on cardiac output during normal and increased venous return*. Vol. 211. 1966. 288-292.

22. Yambe, T., et al., *Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI).* Biomedicine & Pharmacotherapy, 2004. **58, Supplement 1**(0): p. S95-S98.

23. Follansbee, P.S. and C. Frantz, *Wave Propagation in the Split Hopkinson Pressure Bar.* Journal of Engineering Materials and Technology, 1983. **105**(1): p. 61-66.

24. Archer, S. and E. Michelakis, *The Mechanism(s) of Hypoxic Pulmonary Vasoconstriction: Potassium Channels, Redox O2 Sensors, and Controversies*. Vol. 17. 2002. 131-137.

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

26. Bevegärd, S. and A. Lodin, *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): p. 21-29.

27. Bock, A.V., D.B. Dill, and H.T. Edwards, *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): p. 533-544.

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

29. Mayerson, H.S., H.M. Sweeney, and L.A. Toth, *THE INFLUENCE OF POSTURE ON CIRCULATION TIME*. Vol. 125. 1939. 481-485.

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

31. Pollack, A.A. and E.H. Wood, *Venous Pressure in the Saphenous Vein at the Ankle in Man during Exercise and Changes in Posture*. Vol. 1. 1949. 649-662.

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

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

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

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

36. 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): p. 61-68.

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

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

39. Bradley, S.E., et al., *The circulating splanchnic blood volume in dog and man.* Trans Assoc Am Physicians, 1953. **66**: p. 294-302.

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

41. Greenway, C. and G. Oshiro, *Effects of histamine on hepatic volume (outflow block) in anaesthetized dogs.* British journal of pharmacology, 1973. **47**(2): p. 282-290.

42. Greenway, C.V., K.L. Seaman, and I.R. Innes, *Norepinephrine on venous compliance and unstressed volume in cat liver*. Vol. 248. 1985. H468-H476.

43. Lautt, W.W., C.V. Greenway, and D.J. Legare, *Effect of hepatic nerves, norepinephrine, angiotensin, and elevated central venous pressure on postsinusoidal resistance sites and intrahepatic pressures in cats.* Microvascular Research, 1987. **33**(1): p. 50-61.

44. Greenway, C.V. and G.E. Lister, *Capacitance effects and blood reservoir function in the splanchnic vascular bed during non-hypotensive haemorrhage and blood volume expansion in anaesthetized cats.* The Journal of Physiology, 1974. **237**(2): p. 279-294.

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

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

47. Kety, S.S. and C.F. Schmidt, *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): p. 484-492.

48. Manning, R.D., *Renal hemodynamic, fluid volume, and arterial pressure changes during hyperproteinemia*. Vol. 252. 1987. F403-F411.

49. Manning, R.D., *Effects of hypoproteinemia on blood volume and arterial pressure of volume-loaded dogs*. Vol. 259. 1990. H1317-H1324.

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

51. Ito, S. and O.A. Carretero, *An in vitro approach to the study of macula densa-mediated glomerular hemodynamics.* Kidney Int, 1990. **38**(6): p. 1206-10.

52. Skarlatos, S., et al., *Spontaneous pressure-flow relationships in renal circulation of conscious dogs.* Am J Physiol, 1993. **264**(5 Pt 2): p. H1517-27.

53. Aukland, K., *Myogenic mechanisms in the kidney.* Journal of hypertension. Supplement: official journal of the International Society of Hypertension, 1989. **7**(4): p. S71-6; discussion S77.

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

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

56. Mellander, S. and J. Bjornberg, *Regulation of Vascular Smooth Muscle Tone and Capillary Pressure*. Vol. 7. 1992. 113-119.

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

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

59. Stone, H., Thompson HK, and K. Schmidt-Nielsen, *Influence of erythrocytes on blood viscosity*. Vol. 214. 1968. 913-918.

60. Fan, F.C., et al., *Effects of hematocrit variations on regional hemodynamics and oxygen transport in the dog*. Vol. 238. 1980. H545-H522.

61. Jan, K.M. and S. Chien, *Effect of hematocrit variations on coronary hemodynamics and oxygen utilization*. Vol. 233. 1977. H106-H113.

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

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

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

65. 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): p. 123-130.

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

67. Mayerson, H.S., et al., *Regional differences in capillary permeability*. Vol. 198. 1960. 155-160.

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

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

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

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

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

73. 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): p. 2444.

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

75. 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): p. F554-F566.

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

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

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

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

80. 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): p. R1445-R1452.

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

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

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

84. 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): p. 1827-33.

85. 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): p. 94-101.

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

87. Goldberg, M.A. and T.J. Schneider, *Similarities between the oxygen-sensing mechanisms regulating the expression of vascular endothelial growth factor and erythropoietin.* Journal of Biological Chemistry, 1994. **269**(6): p. 4355-9.

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

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

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

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

92. 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**: p. 967-975.

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

94. 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): p. 1175-1178.

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

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

97. 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): p. 1027-1042.

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

99. Rutter, G.A. and E.V. Hill, *Insulin Vesicle Release: Walk, Kiss, Pause … Then Run*. Vol. 21. 2006. 189-196.

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

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

102. DOEDEN, B. and R. RIZZA, *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): p. 902-908.

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

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

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

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

107. Prager, R., P. Wallace, and J.M. Olefsky, *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): p. 472-481.

108. Iwanishi, M., M.P. Czech, and A.D. Cherniack, *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): p. 38995-39000.

109. 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): p. 38990-4.

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

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

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

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

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

115. Cumin, F., H.P. Baum, and N. Levens, *Leptin is cleared from the circulation primarily by the kidney.* International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity, 1996. **20**(12): p. 1120-1126.

116. Mantzoros, C.S., et al., *Leptin in human physiology and pathophysiology*. Vol. 301. 2011. E567-E584.

117. 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): p. 2672-2677.

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

119. 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): p. R548-R555.

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

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

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

123. Goldblatt, H., H. Lamfrom, and E. Haas, *Physiological Properties of Renin and Hypertensin*. Vol. 175. 1953. 75-83.

124. 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**.

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

126. 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): p. 32-40.

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

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

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

130. Hesslink, R.L., et al., *Human cold air habituation is independent of thyroxine and thyrotropin*. Vol. 72. 1992. 2134-2139.

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

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

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

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

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

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

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

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

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

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

141. Wolf, M.B., *Whole body acid-base and fluid-electrolyte balance: a mathematical model*. Vol. 305. 2013. F1118-F1131.

142. Wolf, M.B. and E.C. DeLand, *A mathematical model of blood-interstitial acid-base balance: application to dilution acidosis and acid-base status.* Journal of applied physiology, 2011. **110**(4): p. 988-1002.

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

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

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

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

147. Hannaford, M.C., et al., *Protein wasting due to acidosis of prolonged fasting*. Vol. 243. 1982. E251-E256.

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

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

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

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

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

153. Sands, J.M., *Urea Transport: It’s Not Just “Freely Diffusible” Anymore*. Vol. 14. 1999. 46-47.

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

155. Angielski, S. and J. Lukowicz, *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): p. 1635-41.

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

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

158. Hardy, J.D. and G.F. Soderstrom, *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): p. 493-510.

159. Hsieh, A.C.L., T. Nagasaka, and L.D. Carlson, *Effects of immersion of the hand in cold water on digital blood flow*. Vol. 20. 1965. 61-64.

160. Kamon, E. and H.S. Belding, *Heat uptake and dermal conductance in forearm and hand when heated*. Vol. 24. 1968. 277-281.

161. Saltin, B. and L. Hermansen, *Esophageal, rectal, and muscle temperature during exercise*. Vol. 21. 1966. 1757-1762.

162. Florez-Duquet, M. and R.B. McDonald, *Cold-induced thermoregulation and biological aging.* Physiol Rev, 1998. **78**(2): p. 339-58.

163. Brebbia, D.R., R.F. Goldman, and E.R. Buskirk, *Water Vapor Loss From the Respiratory Tract During Outdoor Exercise in the Cold*. Vol. 11. 1957. 219-222.

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

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

166. Piwonka, R.W. and S. Robinson, *Acclimatization of highly trained men to work in severe heat*. Vol. 22. 1967. 9-12.

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

168. Wyndham, C.H., et al., *Fatigue of the sweat gland response*. Vol. 21. 1966. 107-110.

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

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

171. Warner, H.R. and A. Cox, *A mathematical model of heart rate control by sympathetic and vagus efferent information*. Vol. 17. 1962. 349-355.

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

173. Ferguson, D.W., F.M. Abboud, and A.L. Mark, *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): p. 2265-2274.

174. Takeshita, A., et al., *Effect of central venous pressure on arterial baroreflex control of heart rate*. Vol. 236. 1979. H42-H47.

1. The value of dissociation constant at fixed temperature T0 as model parameter KT0 can be calculated from difference of tabulated Gibbs energies of products and reactants called Gibbs energy of reaction ΔG using relation KT0= exp(-ΔG/(R.T0)). [↑](#footnote-ref-1)
2. Electric charge of an atom can be expressed by number of missing or additional electrons. This elementary charge of protons or electrons can be recalculated to Coulomb using Faradays constant. Not all substances have fixed electrical charges, because for example the acid-base reactions or oxidation-reduction can change the average charge of the substances. [↑](#footnote-ref-2)
3. Deprotonated form (An-1) of the acid (HAn) is the same as conjugate base of the acid, which is created from acid by the removal of proton (H+). The charge *n* for amino acids is 0 or 1 at physiological conditions. [↑](#footnote-ref-3)
4. Non-flow variable is each variable without Modelica prefix ‘flow’. [↑](#footnote-ref-4)
5. Flow variable is each connector variable with Modelica prefix ‘flow’. Each non-flow variable of the same conservation law must be defined inside the same class, where the connector of the conservation law is defined. In steady state of the conservation law this connector flow should be divided into internal part which is zero and to the external part which non-zero value is a part of the change of the total amount. [↑](#footnote-ref-5)