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# Introduction

## Imagine

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.

## State of the art

Fortran

Matlab

Wolfram Mathematica

Dymola

OpenModelica

Guyton1972

QCP

Digital Human

QHP

HumMod

Physiome

CellML

SBML

JSim

## Goals of this work

Physiology formalization

Integrative physiology

General physical principles

Exact science

# 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

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

Pressure units in medicine are also mainly based on historical measurements. For many years blood pressure was measured by the mercury sphygmomanometer, where the pressure is represented by the change of mercury hydrostatic column height. And because the scale of units on the column is in 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.

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 |
|  | pH = x | … | [H3O+] = 10-pH+3 | mol/m3 |
|  | x iu of Erythropoietin | = | ? | mol/m3 |

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.

The worst situation with physical unit is with physical quantity called pH, which determines the acidity of solution. The value of pH equals to minus decimal logarithm of hydrogen ion activity by definition. But the hydrogen ion activity in water solution has a meaning of hydronium ion concentration in non-SI unit “mol/l”. To correct this physical unit is necessary to shift the value to “mol/m3” (“mmol/l”). Similar situations can be observed with using of pK (minus decimal logarithm of dissociation constant for acid-base reactions), where in addition the physical unit is dependent on number of products and number of reactants.

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 model. 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. As example are chemical reactions which always reach equilibrium such as acid-base reactions or oxygen binding to hemoglobin. Or the elementary particles which are in steady state at 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 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, that 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.

### Floating point numbers

From mathematical point of view has the domain of real numbers infinity members. How it is possible, than 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 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 values 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.

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 only two instances of class B, first with parameter set at 1 and second with parameter set at value 2.

class B "Definition of class B"

  parameter Real p "Real number parameter";

end B;

class A "Definition of class A"

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

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

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

end A;

It is a good practice to write names of classes starting with capital letter and name of instances starting with lower case. The object-oriented pattern include any combination of parameters, variables and instances inside class definition. Other more sophisticated rules of object-oriented programing in Modelica could be described as a modification of this principle. 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.

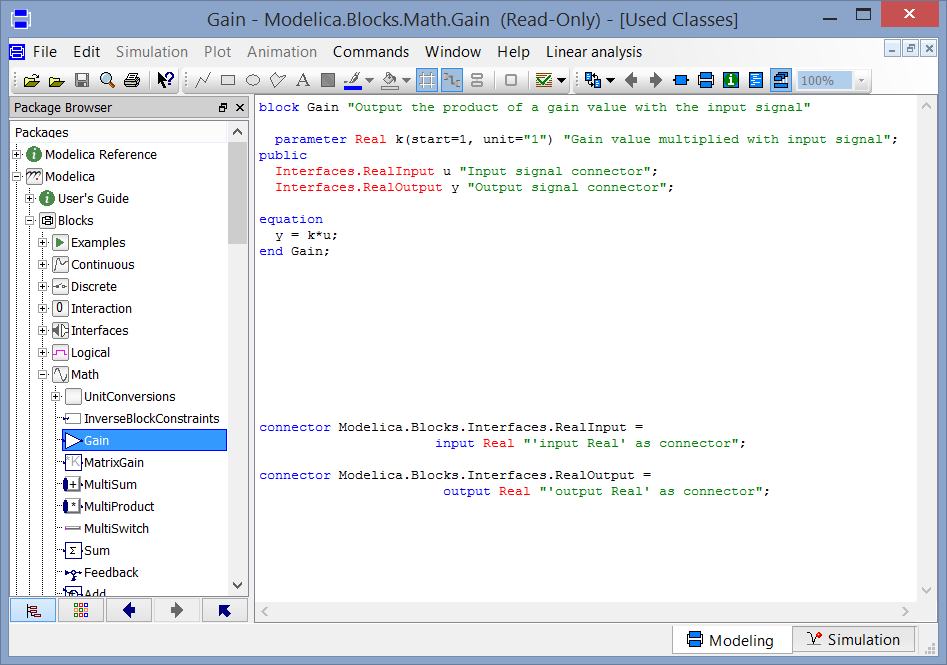


Figure 1, Standardized definition of class Gain inside Modelica Standard Library (MSL).

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.

TODO: An action sequence figure 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.

### Connections

Each library class has some possibilities to connect their instance each together. In the case of restricted classes called ‘block’ (as ‘Gain’ on Fig1) 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.

TODO: An action sequence figure 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

# 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’ [Guyton1972], Ikeda’s ‘Body Fluids’ [Ikeda], Siggaard’s ‘Oxygen saturation algorithm’ [OSA], ‘Quantitative Human Physiology’ [QHP] and finally Coleman’s ‘HumMod’ model [HumMod]. 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 [Kulhanek] and second is about modeling of oxygen, carbon dioxide and hydrogen ions binding on hemoglobin [Matejak]. 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 3, 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 3), where the components can be connected using appropriate connector definition. As seen in Table 4, 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 4 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 4, 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.

TODO: Figure – the trap of cubic interpolation

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 |

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 Fig X , because in case of constant input x it is always y(ln(2)/k) = x + (y(0)-x)/2.

TODO: Figure of exponential adaptation.

## 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 2 and Equation 3.

|  |  |
| --- | --- |
|  | Equation 2 |
|  | Equation 3 |

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 this 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 4, but also the coefficient shifts caused by change of temperature as Equation 5 – 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 4 |
|  | Equation 5 |

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 5.

Component of **chemical reaction** as Equation 6 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 6 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 α, 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 6 |

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 4. And having 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 5.

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 7, where *R* is gas constant.

|  |  |
| --- | --- |
|  | Equation 7 |

If the definition of 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 partial pressure independently of current temperature of the system.

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 8 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 are 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 8 |

The amount of heat liberated during dissolution [J.s-1] is calculated by Equation 4, where enthalpy of dissolution is tabulated constant dependent on selected gas and solvent. And also here is applicable the Van’t Hoff’s law for shifting equilibrium ratio to different temperatures, expressed by Equation 5, where 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 generally are equilibrated partial pressures, which have not always the same meaning as equality of concentrations. To have general component for **diffusion** of one substance (Equation 9) we need to fulfil 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 9 |

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, what 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 10, where the sum of all electrical charges[[2]](#footnote-2) of transported particles is taken as zero.

|  |  |
| --- | --- |
|  | Equation 10 |

The membrane steady state is described as Donnan’s equilibrium for passively transported particles. 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 10 and Equation 11 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 mean the same dissolving properties on both side of membrane. Such as in duffusion, 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 11 |

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 this acids can occur in protonated or deprotonated 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 model 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 defines 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 12 |

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. 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 13.

|  |  |
| --- | --- |
|  | Equation 13 |
|  | Equation 14 |

An analogy of stream calculation is in medicine used the **clearance** terminology for extracting substance from the body such as extraction by kidneys, liver, enzymatic processes and so on. For defined substance are measured *Clearance* parameter as amount of solution flow, which is fully cleared from the substance. In contrast with stream, there is not volumetric loss of solution.

Man 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 15). 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 is take 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 15 |

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).

The chemical elements in nephron tubules can be reabsorbed from the primary urine back to the body. This complex processes can be approximated by Equation 15, 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 15 |

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 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. 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 16. And the specific osmolarity for each membrane *m* is expressed in Equation 17 as the concentration (*osmolaritym*) of all substances, which can’t cross this membrane *m* in the same speed as in the solution does.

|  |  |
| --- | --- |
|  | Equation 16 |
|  | Equation 17 |

If a user does not specify the number of membranes, then only one will be used (*m=1*). This setting generate 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 18. 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 18 |
|  | Equation 19 |

The pressure on both sides is composed with hydraulic and osmotic part, Equation 19. 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* are almost equilibrated with interstitial pressure called *pressurefiltrate* in Equation 20. Both pressures are in the meaning of Equation 19. 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 21. 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 22).

|  |  |
| --- | --- |
|  | Equation 20 |
|  | Equation 21 |
|  | Equation 22 |

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 15 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 15 |

Typically is the fraction *fract* approximated from flows of osmoles through membrane and/or from number of opened water channels.

## Thermal domain

It is not surprise that in thermal domain is accumulated the heat energy as in Equation 23. 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 24). 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 23 |
|  | Equation 24 |

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 4 and Equation 5). 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 25. 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 25 |

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 13 and Equation 26 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 26 |

Temperature T means the temperature at the origin of the mass flow, which could be a problem if the mas flow change the direction (streamMassFlow<0). In this situation must be smoothly changed the temperature source to the second connector of the component.

Typically the microcirculation is so effective, than 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 the heated liquid and the maximal heat to environment can be limited by equilibrium of temperatures of outflowing liquid and the environment around radiator as Equation 27. If it is assumed that all heat energy of the inflowing liquid is divided only to heat energy transferred to the environment and the heat energy of the outflowing liquid then it leads to Equation 28. And really the amount of transferred heat to the environment is proportional to the overflow 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 27 |
|  | Equation 28 |

In the body can blood transfer about 5% more heat from working muscles to lungs than is calculated by Equation 28, because of endothermic behavior of hemoglobin deoxygenation [odkaz na moj clanok]. This additional heat is not accumulated to mass as temperature change. It is released by chemical reaction during changing the form of molecules as described in above sections as chemical enthalpy. The chemical enthalpy take place also during sweating, when the water change phase from liquid to gas. This process effectively cool 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 29 and Equation 30. 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. If the volume decreases bellow V0 the walls lost their tension then they do not generate the positive pressure inside. The result is the same pressure inside as outside the vessel. At very small volume called VCollaps starts the vessel generate the negative sucking pressure, which should be the mathematical prevention not to reach 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 difference between external pressures at the middle between zero volume and VCollaps.

|  |  |
| --- | --- |
|  | Equation 29 |
|  | Equation 30 |

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. That gives small pressure depth to the accounting of inspiration and expiration periods.

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 31 |

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 32. 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 32 |

Typically is selected one point 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.

For hydraulic valves is designed 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*.

Ideal valve

|  |  |
| --- | --- |
|  | Equation 35 |
|  |  |

Switching state

Forward/ backward flow

Forward conductance/ backward resistance

|  |  |
| --- | --- |
|  | Equation 34 |
|  | Equation 35 |

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.

Modelica implementation

Inertia

|  |  |
| --- | --- |
|  | Equation 36 |

Pump

Generation of volumetric flow

heart

Elastic membrane

Cavity in cavity

Ventilation

|  |  |
| --- | --- |
|  | Equation 33 |

## Population domain

Bla bla

## Steady states

(Non-)oscilating system

Der = 0,

Chemical equilibrium,

Law of delailed balance

Hydraulical equilibrium

# Physiomodel

## Cardiovascular system

### Heart

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) [1, 2] and end systolic volume (ESV) [3]. The HR and heart contractility [4] can be influenced by nervus vagus [5], epinephrine [6] or angiotensin II [7]. The most common descriptions are pressure-volume relations [8] as in famous A-V fistula experiments [9] or filling pressure experiments [10] or less invasive exercise experiments [11].

The HR is typically generated in sinoatrial node. The conduction of signal is measured and described by electrocardiograms [12, 13]. Autonomous nerves control heart rate [14, 15] for example as a response of baroreflexes [16, 17].

There is some evidence of non-steady state behavior of end diastolic volume, because the stroke volume is dependent on heart rate [18, 19].

### Blood flow

The blood flow through blood vessels depends on blood viscosity [20]. Viscosity of blood is strongly dependent on the hematocrit [21-23], 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 transported. Optimal hematocrit for oxygen transport between this two conditions was experimentally measured as 40-60% in the most tissues [24, 25].

### Vasoconstriction

Vascular smooth muscle tone is regulated [26, 27] with many influences. 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.

In pulmonary circulation is vasoconstriction driven mainly by vascular redox O2 sensor, what is resulting into perfusion-ventilation matching to optimize the oxygen transport from lung alveolus to blood [28].

Renal blood flow need to estimate optimal glomerular filtration pressure [29, 30] and to preventing washout of kidney medulla concentrations. This can be driven by local mechanoreceptor-myogenic pattern [31, 32], baroreflex-like patterns [33], angiotensin II [34] or tubuloglomerular feedback [35, 36].

Splanchnic circulation deliver all blood from gastro-intestinal tract to liver by portal vein [37]. In liver is the hepatic blood flow determined by portal vein and hepatic artery blood flow. Normal hepatic blood flow can vary from 970 to 2370 ml/min [38] in dependence on gastro intestinal blood flow. Portal blood volume and pressure is known in typical or in changed histamine concentration [39] or catecholamine concentration [40, 41]. The splanchnic circulation is a blood reservoir during hemorrhage or blood volume infusion with hormonal or neural regulation [42, 43].

[Maass-Moreno1992,Bradley1953,Bradley1952,Mitzner1974,Laine1979]

- effect of norepinephrine [Greenway1985,Laut1987]

- effect of histamine [Greenway1973]

Brain blood flow [Kety1948]

### Vessels Compliance

The compliance of systemic arteries is constant around normal working conditions [Roach1957].

Systemic veins [Shigemi1994,Echt1974,Gauer1956]

### Muscle pump effect

[Armstrong1985,Laughlin1987,Laughlin1983]

### Sequestered volume

[Ochsner1951,Mayerson1939,Bevegard1962,Pollack1949,Block1930,Henry1950,Thomson1928]

### Blood Volume regulations

- hypoproteinemia [Manning1990,Manning1983]

### Autoregulation of circulation

- CO on CO2 [Davidson1986]

- ,Hogan1990,Lash1987,Malo1984,Marshall1995,Metting1989,Metting1988,Weber2000,Borgström1975,Whalen1974,Frisbee2000,Berg1997,Burattini1994,POHOST1976,Archer1996,Goodman1978,Granger1976,Granger1969,Harder1996,Harder1996,Marshall1988,Frisbee2000,Kunert1996,Prewitt1976,Kuwahira1993]

RAAS and other regulations .. see hormones, nerves and drugs

## Osmolarity and Water distribution

The model of water (Fig1) 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. Chosen distribution of body water (41 l) between compartments is written in Table V.



Table VI, 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 |

Typical mean water flows between all compartments are listed in Table VII as described in many studies [44-47]. In gastrointestinal tract are absorbed, in each torso 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. Outflow of water to urine is modeled by kidney.

Table VIII,Typical steady-state water flows between compartments [ml/min]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | plasma | UT | MT | LT | Total |
| 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

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* by Eq1, where *R* is gas constant and *T* is temperature.

We can assume, that average molar mass of globulins is 34.5 kDa and molar mass of albumin is 66.5 kDa. And also that the mass of albumins is about 60% of total plasmatic protein mass.

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

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

The model of proteins (Fig2) has four main compartments: blood plasma, upper torso interstitium, middle torso interstitium and lower torso interstitium. Normal concentrations at interstitial compartments are listed in table Table X. Normal proteins synthesis and degradation of 10 mg/min can be changed with deviation of their colloid pressure or plasmatic concentration. Movement between compartments is caused by capillary membrane concentration gradient or lymph flow from interstitium to blood as implemented in scheme of Fig2. And special changes of plasmatic concentration could be done by intravenous therapy, hemorrhage or pathological states, when proteins enter the peritoneum space or primary urine filtrate.

Table XI, Typical protein concentrations in interstitium [mmol/l]

|  |  |  |
| --- | --- | --- |
| Upper torso | Middle torso | Lower torso |
| 0.6 | 0.48 | 0.4 |



### Gastro intestinal water absorption

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 Fig1.



Because in original HumMod 1.6.1 model is the mean absorption from GILumen calculated by coefficient of osmotic gradient Absorption [ml/min] = 140 \* (0.286 [osm/l] - 0.253 [osm/l]), the pressure-gradient osmotic permeability (cond) of library membrane block has to be derived to have the same flow at the same settings. We know that the volumetric flow in this block is calculated by equation Eq1, so the recalculated parameter cond to value 0.14/(8.314\*310.15) [ml/(Pa.min)].

### Upper/Middle/Lower torso water

Flow between plasma and interstitium is determined by colloid osmolarity of extracellular proteins. Through the capillaries wall is distributed the water to or from the interstitium. Another way is the one directional lymph flow from interstitium to blood plasma [45-47], as presented in Table XII. These flows can be influenced by the internal pressure in tissues caused by its volume and skin as examined by Gyuton [48] or Xie [44]. Water crowing the capillary wall is driven by hydrostatic-colloid pressure gradients, where the pressure elements are for each torso listed in table ?.

Table XIII, Typical pressures at capillary walls [kPa]

|  |  |  |  |
| --- | --- | --- | --- |
|  | Upper | Middle | Lower |
| blood hydrostatic | 2.2 kPa | 2.2 kPa | 3.1 kPa |
| blood coloid | 3.7 kPa | 3.7 kPa | 3.7 kPa |
| interstitium hydrostatic | -0.6 kPa | -0.6 kPa | -0.6 kPa |
| interstitium coloid | 1.6 kPa | 1.2 kPa | 1 kPa |
| total gradient | 0.7 kPa | 0.3 kPa | 1.0 kPa |
| Permeability [ml/(kPa.min)] | 0.54 | 4.1 | 1.4 |
| capillary wall filtrate | 0.38 ml/min | 1.23 ml/min | 1.40 ml/min |

Table XIV, Typical osmolarities of substances [mosm/l]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | electrolytes | Urea | glucose | Unknown |
| ECF | 250 | 6 | 6 | 24 |
| ICF | 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 interstitium and in cells (typically 285 mosm/l).



### Kidney

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

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



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 in 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 [49, 50].

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. [51, 52].

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 [53, 54]. 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.

## Hormones

### Vasopressin

Arginine vasopressin known as antidiuretic hormone (ADH) has molecular weight of 1084 Dalton and one international unit of ADH was measured to be 2.5ug [55]. 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.



Figure 2

The model (Fig1) 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 reabsorbtion. The normal amounts of ADH in these compartments are listed in table Tab1. The normal mean rate of synthesis, secretion and degradation is 3.2 ng/min (49.2 pmol/s) [56], where the 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. Other possibility to regulate ADH secretion is cardiovascular centrum reflexes.

Table 16

|  |  |  |  |
| --- | --- | --- | --- |
| Slow Mass | Fast Mass | ECF | Medulla |
| 17 ug | 3.2 ug | 0.03 ug | 6.2e-5 ug |
| 15.7 nmol | 2.95 nmol | 0.028 nmol | 5.7e-5 nmol |
| 6.8 IU | 1.28 IU | 0.012 IU | 2.5e-5 IU |

Even the vasopressin inside cells is modeled using instances of chemical Substance class, the 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 clearance.

Table 17

|  |  |  |
| --- | --- | --- |
| Liver degradation | Kidney degradation | Other degradation |
| 0.98 ng/min | 1.46 ng/min | 0.8 ng/min |
| 0.9 pmol/min | 1.35 pmol/min | 0.74 pmol/min |
| 0.39 mIU/min | 0.58 mIU/min | 0.32 mIU/min |

Clearance of ADH is divided into liver, kidney and other tissue [57]. To reach the mean constant level of ADH the sum of these changes from Tab2 must be the same as mean secretion during normal mean blood flow through liver (1.15 L/min), kidney (1.24 L/min) and other tissue (0.4 L/min), which are equivalents of clearances from table Tab3.

Table 18

|  |  |  |
| --- | --- | --- |
| Liver clearance | Kidney clearance | Other tissue clearance |
| 0.58 l/min | 0.73 l/min | 0.4 l/min |

A typical mean concentration in extracellular fluid is 2 ng/l, 1.8 pmol/l or 0.8 mIU/l [58]. Increasing of concentration will increase the water reabsorption in kidney.

### Renin

Renin is an enzyme for conversion of Angiotensinogen to Angiotensin I. From Michaelis-Menton equation (Eq1) is known, that the rate of enzymatic chemical reaction *v* is linearly proportional to the enzyme molar concentration *E* at defined substrate concentration *S*. So instead the extremely small molar concentration it is wildly used Goldblatt unit (GU) of Renin , which is equal to the reaction flow rate of one ng of AngiotensinI from one mg of Angiotensinogen per one hour (1 ng AI/h).

Molecular mass of Renin is 48 kDa [59], normal plasma concentration are written in table Tab2. We use the conversion between renin activity GU and international unit as 11.2 uIU/GU and assumption that 1000 IU are equal 0.6 mg of renin as proposed Simon et al [60]. Problem is, that the renin activity (GU) change with many other factors like acidity [61] or bounding of renin with other molecules. That means problem with GU definition, which may differs from research to research. Therefore the GU unit is more like unit for angiotensin I synthesis rate, not the right unit for renin amount.

Table 19

|  |  |  |
| --- | --- | --- |
| Lower limit | Upper limit | Normal |
| 290 GU/L | 5700 GU/L | 2000 GU/L |
| 3.3 IU/L | 63.8 IU/L | 22.4 IU/L |
| 2 ug/L | 38.3 ug/l | 13.4 ug/L |
| 0.04 nmol/l | 0.8 nmol/l | 0.28 nmol/L |

(<http://europepmc.org/abstract/MED/2856717>)

Because molar mass of Angiotensingen is 56.8 kDa and molar mass of Angiotensin 1 is 0.9 kDa.

### Insulin

Model of insulin obeys the same principle as the model of glucose-insulin homeostasis by Guyton et al. [62]. Insulin is synthetized and stored in beta-cells and its secretion is driven by glucose and keto-acids [63, 64]. Portal and peripheral vein insulin has different concentration [65], because insulin is transported just after secretion by portal vein to liver. Absorbance and clearance was measured by many infusion experiments [66-68].

The effects are parts of liver metabolism, glucose, keto-acid and lipid submodels [62, 69, 70], where the details of receptor binding are also described [71-73].

Problems with insufficient insulin secretion results in type 1 diabetes mellitus and with receptor resistance lead to type 2 diabetes mellitus [74-76], where many differences between normal and obese individuals should be included [70].

*Insulin is one of the most studies hormone. First standard international unit of insulin from year 1958 has 41.67ug/IU (*[*http://whqlibdoc.who.int/trs/WHO\_TRS\_172.pdf*](http://whqlibdoc.who.int/trs/WHO_TRS_172.pdf)*, page 10), the last discontinued definition from year 1986 has 38.46ug/IU (*[*http://whqlibdoc.who.int/trs/WHO\_TRS\_760\_(part1).pdf?ua=1*](http://whqlibdoc.who.int/trs/WHO_TRS_760_(part1).pdf?ua=1)*, page 26). Using molar mass of 5808 Da it is possible to write also conversion such as 6.621pmol/IU.*



### Glucagon

Model of

### Leptin

Model of

### Thyroid hormones

The main purpose of thyroid hormones in our model is to maintain long-term thermoregulation [77]. The concentrations, secretions and clearance of thyroid hormones are well known because of relative easy measurement of iodine radioactive isotopes [78-81]. During cold months increasing of triiodothyronine (T3) [82] increase the basal metabolism [83] what improve the heat regulation in cold conditions. The impulse for the production and secretion of T3 and thyroxine (T4) is thyrothropin (TSH) [84]. And the secretion of TSH is driven by thermoreceptors and it is directly suppressed by T3 [82, 85-87]. The clearance of TSH is much quicker than clearance of T3 or T4  [88], as a result its concentration can be directly estimated from the secretion as implemented in FigX.



## Electrolytes and Acid-Base

### Acid-base

The blood acid-base balance calculation is based on electroneutrality. In plasma 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). From acid-base buffers (weak ions) is also calculated the summary charge concentration at normal conditions (prefix N) called normal strong ion difference (NSID), where the normal conditions defined as plasma pH=7.4, full oxygen saturation, CO2 partial pressure of 40mmHg and temperature of 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 will use the amount of strong acid equal to Hct\*(SIDE-NSIDE)+(1-Hct)\*(SIDP-NSIDP). This measurable amount of titrant can be called also base excess of oxygenated blood (BEox) or as negative titratable hydrogen ions of oxygenated blood (-cTHox) used by Siggaard with Van-Slyke equation.

Using charges of strong electrolytes on SID side and charges of weak ions on NSID side of electroneutrality equation joins the acid-base submodel equilibrium with all charged substances.

The typical SIDP and NSIDP is 40 meq/l and typical SIDE and NSIDE is 30 meq/l. The typical SIDP is composed with Na (145), K(4), Cl (104), SO2(2mmol/l), Lactate(1) and the typical NSIDP is composed with bicarbonate (24.5), albumin(12.5meq/l), phosphates() and globilins(). In erythrocytes the SIDE is composed with K(102), Na(7.5), Mg(2mmol/l), Cl(68), SO2(1) and lactate (). The NSIDE is composed with bicarbonate(15), hemoglobin (21mmol/l), 2,3-DPG(5mmol/l), ATP(1.3mmol/l), ADP(0.2mmol/l), phosphates(). Other electrolytes and buffers are neglected because of their small concentration and/or small charge.



NormalSID is calculated from plasma and erythrocytes weak ions…



Intracellular pH is calculated only from intracellular potassium(151 mmol/L), bicarbonate(17-23 mmol/L), buffers(22-28 mmol/L) and lactate(1 mmol/L). Other cations (12 mmol/L) and anions (117 mmol/L) are assumed as constant. From electroneutrality can be calculated the current amount of bicarbonate as non-bicarbonate ions difference. And because the carbon dioxide partial pressure is also known, the acidity can be expressed from Hendersom-Hasselbalch EqX.

pH=7.2, pCO2 = 45mmHg – 60 mmHg:

HCO3=0.23\*(45\*101.325/760)\*10^(7.2-6.1)=0.386\*pCO2=17

HCO3=0.23\*(60\*101.325/760)\*10^(7.2-6.1)=23

## Gases

To support metabolism of each cell there must be delivered oxygen. And carbon dioxide 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 oxygen and carbon dioxide. These pressures play roles in gases dissolving in blood, but here is the total amount of transported gases dependent also on blood flow, binding properties of hemoglobin, temperature and hydrogen ion activity. In tissue microcirculation is blood delivered so close to cells that no other active delivery is needed and only diffusion take place here.



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 depends on many factors and are driven 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 of arterial blood pH and pO2 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 (typical 11 per minute) and normalized respiratory center motoric nerve activity.

From the lungs properties are then calculated current tidal volume (450 ml at body conditions - temperature of 37°C and 100% humidity) and current dead space volume (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.



### 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 Eq1, where P is partial pressure, R is gas constant and T is temperature in Kelvins. For example in 0 degC (273.15 K) dry air is molar concentration of oxygen 9.2 mmol/l, while in 40 degC 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, where also take place the body temperature.



### Carbon dioxide

Production 200ml/min (STP) [89] = 8.8 mmol/min.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | 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 |
| Carbamino | Neligible | 2.4 mmol/l | Neligible | 3.8 mmol/l |
| Total | 25.6 mmol/l | 16.7 mmol/l | 27.6 mmol/l | 18.4 mmol/l |

pCO2=40mmHg,pH=7.4,HCO3=24.5 mmol/l, aCO2= 0.231 (mmol/l)/kPa, pK=6.1 at 37degC

## Nutrients and Metabolism

Energy for human body is taken from food. The food is simplified to carbohydrates, proteins and fat. After eating are nutrients absorbed to body extracellular fluid. Nutrients can be also synthetized mostly by liver as gluconeogenesis, ketogenesis or lipogenesis .

exercise[90, 91]

lactate and pyruvate (hypoxia)[92, 93]

protein[94]

### Cellular metabolism

Kidney excretion

### Keto-acids

Kidney excretion

Brain metabolism[95]

## Thermoregulation

## Neural Reflexes

# Discussion

# Conclusion

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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)