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Formalization of Integrative Physiology

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Abstract

New information technologies bring with them new possibilities for defining and simulating complex physical systems. A huge amount of progress was made in this field with the Modelica language standard, developed by the worldwide nonprofit Modelica Association. Using the Modelica language specification, new chemical, hydraulic, thermal and population components for human physiology were designed for the implementation of the physiological principles in this thesis. Similarly to the electrical circuits already implemented in the Modelica Standard Library, it is also possible to connect the components of these libraries to the diagrams and, in this way, define more complex components of physiological systems. Using this kind of implementation, this thesis presents an extension and improvement of the HumMod version 1.6 model, developed at the University of Mississippi Medical Center (Jackson, MS), which has more than 5,000 variables. As a result of the use of graphical diagrams, our implementation is more expandable and more modifiable at each point. The precise rules of connections lead to fewer implementation errors. In addition, the visual verification of the model is achieved, because the physiological connections of diagrams are self-describing, which allows them to be directly examined and presented in the form in which they are implemented.

A new acid-base model for blood gas transport was here designed and integrated. This extension of HumMod 1.6 was more appropriate for describing the status of blood during oxygen and carbon dioxide transport, even during respiratory or metabolic acid-base disorders. The presented theory of multiple ligands binding to hemoglobin A is used to describe the equilibrium of oxygenation, carboxylation and oxygen-linked (de)protonation. This integrative approach not only shifts the oxygen-hemoglobin dissociation curve, it can also be used to calculate the carbon dioxide saturation and changes of linked protonation, which are significant for maintaining the pH of blood during blood gas exchange.

As a language for this complex physiological integrations, Modelica can be used—with new proposed physiological libraries behind it—thanks to the already established commercial and noncommercial support.

Abstrakt

Nové informační technologie přinášejí možnosti jak exaktně popsat a simulovat komplexní fyzikální systémy. Pokrok v tomto směru umožnila standardizace jazyka Modelica neziskovou celosvětovou asociací firem, univerzit a jednotlivců Modelica Association. Standard jazyka umožnil v této disertaci vytvořit chemické, hydraulické, tepelné a populační komponenty pro základní principy fyziologie člověka. Tyto nové Modelikové knihovny byly nazvány PHYSIOLIBRARY a CHEMICAL. Jejich základní komponenty je možné v Modelice graficky propojovat a tak vytvářet komplexnější komponenty fyziologických systémů, obdobně jako se v Modelice vytvářejí modely elektronických obvodů ze základních prvků elektronických komponent. Disertace ukazuje, jak lze obdobným způsobem vytvořit i tak komplexní modely jakým je model integrativní fyziologie člověka HumMod 1.6 který má více než 5000 proměnných. A nejen to, tyto modely je potom možné velmi intuitivně modifikovat a rozšiřovat. Disertační práce tak model amerických autorů HumMod 1.6 (www.hummod.org) nejen implementovala, ale i rozšířila o vlastnosti krve a hemoglobinu, které původní model neměl. Při reimplementaci modelu bylo odhaleno (a americkým autorům reportováno) 30 logických, matematických a fyziologických chyb, na které se při důkladné analýze modelu narazilo.

Byl vytvořen a integrován nový model acidobazické rovnováhy a transportu krevních plynů. Toto rozšíření modelu HumMod mnohem věrohodněji popisuje stav acidobazické rovnováhy krve a přenosu krevních plynů i v respiračních a metabolických acidobazických poruchách. Díky integračnímu přístupu byl také navržen nový pohled na přenos krevních plynů pomocí hemoglobinu A. Tento integrační model dokáže popsat nejen disociační křivku hemoglobinu pro kyslík, ale i pro oxid uhličitý a dokonce i pro kyslíkem propojené vodíkové ionty, které se významně podílejí na udržování pH v krve při výměně krevních plynů.

Prakticky i teoreticky pomocí exaktních definic je v práci ukázáno, že integrace nových poznatků do jednoho komplexního modelu lidské fyziologie je možná a přínosná. Jeho jazykem by mohla být právě Modelica s novými, prací vytvořenými, knihovnami fyziologických komponent díky podpoře velkého množství komerčních i nekomerčních nástrojů.

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# Introduction

Integrative physiology is a relatively young branch of physiology that describes the complex connected mechanisms and regulations of physiological systems at all levels (from molecular, cellular, tissue and organs to a level that encompasses the entire body). Physiological knowledge arises from examination and comparisons of the functionality of living organisms and nature; however, the basis of integrative physiology should also include experiments and data that can be used to generalize mathematical relations. Therefore, the fourth section of this dissertation thesis formalizes the reproducible experiment, which can be described using the physiological model (pg. 40-44). This model is useful for describing many real experiments. It is theoretically and practically shown that the model can be integrated in a way that the resulting model is at least as good as all the models available prior to integration. Typically, this integration means finding a new theory that can describe all the desired phenomena. Its identification with real experiments in particular gives rise to the new model that describes the desired experiment with the required precision.

This integrative approach based on physics is not entirely new. The idea that the entire complex human physiology can be integrated into one complex model has long since been in development at the University of Mississippi Medical Center, where Arthur C. Guyton et al. developed the idea of connecting physiological knowledge using exact mathematical notations. One of their first models, which began this integrative physiological development, was a model of the cardiovascular system with integrated volume, hormonal and neural regulations (Guyton et al., 1972). The model was built from data of simplified cardiac functions (Guyton, 1965); perfusion of lungs, kidneys and skeletal muscles; neural and hormonal regulations, body fluid balance and the simplified transport of oxygen. The model simulates the relations between the regulation of blood circulation, blood pressure and volume, as well as the pathophysiological mechanisms that lead to chronic hypertension. For validation of the model’s behavior, Guyton et al. also proposed experiments based on nephrectomy in dogs, which showed good fit with their model’s simulation (Guyton et al., 1972). The model has continuously been extended and improved with ever more data and experiments. In this way, versions of the model called "Human" (Coleman and Randall, 1983), "Quantitative Circulation Physiology - QCP" (Abram et al., 2007), "Digital Human", "Quantitative Human Physiology - QHP" (Hester et al., 2008) and finally, the "HumMod" model (Hester et al., 2010, 2011) have been developed.

In the long-term, the integration of accessible physiological knowledge is one of the main goals of the Department of Physiology and Biophysics at the Arthur C. Guyton Research Center at the University of Mississippi Medical Centre. The team researching this theoretical physiology is composed of researchers with knowledge that overlap in mathematical, chemical, physical and physiological fields. The result of their years of work is a complex integrative model of human physiology. The model, called HumMod in version 1.6, is freely accessible for continued academic development under a GPL license.

In our opinion, the subsystem of ***acid-base homeostasis and blood gases transport*** is one of the weakest parts of the model HumMod 1.6. An extremely simplified calculation of blood acid-base, which does not use any form of non-bicarbonate acid-base buffer, needs to be replaced by a more complex calculation of pH regulations connected with the transport of oxygen (O2) and carbon dioxide (CO2). The Mississippi University model does not, for example, bind CO2 to hemoglobin (Bauer and Schröder, 1972); it also does not release Bohr’s protons (Bohr et al., 1904) and does not calculate any titration properties for non-bicarbonate weak acids. It is known that the acid-base status of blood is determined by strong ion differences (Stewart, 1981), bicarbonate (i.e., HCO3- created by the hydration of CO2: CO2 + H2O <-> HCO3- + H+) (Henderson, 1908), plasma buffers such as plasmatic proteins (Figge, et al., 1992), phosphates and significantly, also by hemoglobin (Antonini, et al., 1963) inside red blood cells. While most of these acid-base buffers bind hydrogen ions (H+) independently onto the state of other substances, hemoglobin is different. Hemoglobin changes the quaternary form through the binding of oxygen (Monod, et al., 1965), which could also change other binding properties for H+ and for CO2. There exist at least five different models of oxygen hemoglobin saturation: the allosteric model (Eaton, et al., 2007; Monod, et al., 1965), Adair’s four-step oxygenation (Adair, 1925), Hill’s model (Hill, 1913), approximation using hyperbolic tangents (Siggaard-Andersen and Siggaard-Andersen, 1990) and other polynomial approximations (Severinghaus, 1979). The oxygen dissociation curve (ODC) of each of these models describes oxygen saturation (sO2) as dependent on partial oxygen pressure (pO2) at a fixed and normal conditions in terms of temperature, pH, CO2, DPG and other factors. However, only the allosteric and Adair approach is based on the physical description of chemical processes. The other three models are only mathematical approximations of measured data, which does not matter until the model needs to be extended with more ligands. There are already published some of these complicated empirical extensions pertaining to shift of ODC to the left or to the right caused by effects of CO2 and pH (Dash and Bassingthwaighte, 2010; Rees and Andreassen, 2005; Severinghaus, 1979; Siggaard-Andersen and Siggaard-Andersen, 1990). However, these extensions fail when the value of CO2 and pH is outside the norm at the same time. The O2, CO2 and H+ equilibrium on hemoglobin exists in non-linear relations; therefore, the effect of CO2 on sO2 is significantly dependent on pH and vice versa (Siggaard-Andersen, 1971). In addition, none of the extended approximations can provide the state of the binding of these ligands. Therefore, the model will be better if it is built from physical and chemical theories that will provide answers to more questions, instead of relying only on the mathematical approximation of one variable.

Morrow et al. and Matthew et al. (Matthew, et al., 1977; Morrow, et al., 1976) showed that CO2 carboxylates the amino-terminal of each subunits of hemoglobin tetramer. The different affinity for oxygenated and deoxygenated forms causes at first glance a competitive relation between CO2 and O2. However, the chemical bonds are not competitive, because each ligand binds on different sides of the hemoglobin subunit. Thus, both CO2 and O2 can be bound at the same time on each subunit. Thanks to hemoglobin, blood is available to transfer 25% more CO2. Roughly 10-11% of this CO2 is transported directly bonded as a carb-amino terminal of a hemoglobin subunit (Bauer and Schröder, 1972); the rest is the result of pH change caused by the binding of Bohr’s protons (i.e., an increased blood capacity for bicarbonates).

In this way, hemoglobin can preserve the pH between arterial and venous blood. For example, in tissues, where the amount of H+ is increased by CO2 in the form of HCO3-, hemoglobin – during the release of oxygen – regulates pH by binding H+ (the deoxygenated forms has higher affinity for Bohr’s protons) (Bohr et al., 1904; Siggaard-Andersen, 1971). There are more than ten bounding sites in a hemoglobin A tetramer for Bohr protons. These sites change affinity for H+ during a change in shape of the hemoglobin molecule, caused by the binding or releasing of oxygen. Most of these are amino acid side chains located in the beta-cleft (the place between beta subunits) (Perutz et al., 1980; Zheng et al., 2013). However, it is possible to simplify these Bohr’s sides as having only two fictive sides (Antonini et al., 1965).

As with each chemical reaction, the binding of ligands to hemoglobin are also dependent on temperature (Atha and Ackers, 1974; Chipperfield et al., 1967; Weber and Campbell, 2011; Weber et al., 2014). For example, the shift of ODC caused by different temperatures is a known factor (Reeves, 1980; Weber and Campbell, 2011; Weber et al., 2014). Using theories of physical chemistry, it should be possible to calculate the enthalpy of chemical reactions, not only to shift dissociation coefficients, but also to calculate the amount of heat consumed or released by a reaction.

Another weakness of the HumMod 1.6 model is its form of implementation. Although the source code separates "physiological definitions", they are not equations in a mathematical sense, but only assignments where the value, calculated from some expression, is stored to the selected variable. The entire HumMod model is implemented as “causal“, which in the prescribed sequence calculates the unknown variables from the expressions of known variables using an algorithm. This does not constitute a formulation of equations, but simply the implementation of an algorithm (i.e., causal implementation). However, in complicated models, situations often exist where the equations are not able to reach physical relations through only a simple sequence of assignments. Furthermore, for a numerical solution, it is necessary to select an iterative method; for these cases, the HumMod provides a construct of implicit equations.

The significant weakness of the HumMod 1.6 model’s implementation is also the redundancy of the physical relations. The implementation of physical laws is repeated in the model as many times as they are used. The base rule in informatics is to define the functions and objects once and to use them by referencing selected settings, instead of copying the contents of functions and objects in many places. The language, in which HumMod 1.6 is implemented suffers a lack of modern computer language constructs that can simplify the readability and visual verification of the implementation. The original source code is divided into hundreds of files; as such, it is not surprising than the research and development teams of complex physiological models in the Physiome Project (Bassingthwaighte, 2000; Hunter, et al., 2002) rather use and extend older and simpler models.

The ideal language for the implementation of complex physical systems is Modelica ([www.modelica.org](http://www.modelica.org)). Equations can be formulated in Modelica without manual algebraic manipulations (“acausal” implementation). This language also allows for representing the usage of objects by graphical icons, which refer to the definition with exact physical relations (<http://book.xogeny.com>). For example, the electrical resistor is defined according to Ohm’s law and is represented by a typical rectangle icon inside electrical circuits. Once the object with its icon has been defined, it can be used with different settings and as many times as necessary. This object-oriented approach also allows for defining hierarchical components that are composed from many other connected components. Almost each model can be implemented only by graphical diagrams that have a relatively small set of domain-specific physical laws (called first principles), implemented as Modelica libraries. The physical connections of Modelica components provide visual verification, which is readable also by non-Modelica users. This approach brings to the industry a very powerful tool for communication between programmer, developer and researcher.

As a result, Modelica is already being used in many industrial applications (from the automotive and aircraft industry to the construction of robots and the design of power plants). Nowadays, there exist a number of commercial and non-commercial (for example OpenModelica) Modelica environments that can support the building and simulation of models in this language. The libraries in Modelica today primarily represent electrical, mechanical or magnetic domains. However, the Modelica language is generally enough for also defining libraries in chemical, thermal, as well as in hydraulic or population domains of physiology, which prior to this work did not exist. For example, it should be possible from the components of these libraries to implement the component for microcirculation, which is hydraulic resistance within the cardiovascular system. These components can be affected by many inputs, causing local vasoconstriction or vasodilation. Using this object in different locations of cardiovascular diagrams for different tissues with different settings, local microcirculation can react to all known local factors with a prescribed sensitivity. The question that arises as a result is: is it possible to formalize the first principles in physiology to create a compact Modelica library, from which it should be possible to implement the HumMod 1.6 model, as well as the more detailed chemical processes during blood gases transport?

# Aims of the work

Hypothesis 1 (formalization):

*Modelica®, as the most recent generation of object-oriented equation-based computer language designed for the dynamic simulation of large complex physical systems and machines, is suitable for exact formalization of integrative human physiology.*

Hypothesis 2 (integrative):

*Mathematical formalizations of physiological knowledge about one organism can be integrated using graphical hierarchical physical diagrams into one complex physiological model, which will simulate all integrated physiological experiments.*

The formalization hypothesis comes from the observation that Modelica can very elegantly describe even very complex physical model of machines. Language Modelica is so general that the user can define his own physical units, physical quantities, physical relations, components of physical diagrams and also their connections. However, the robust compact support for physiology requires to formalize the first principles - physical laws, which are behind almost all physiological processes. For these purposes will be analyzed and decomposed the model HumMod 1.6 from Mississippi, because it is assumed as the most complete accessible model of human integrative physiology (<http://hummod.org>). Then the model HumMod 1.6 should be possible to re-implement and extend using combinations of almost only these physical laws. The Modelica implementation of the model using graphical diagrams will provide the visual verification of the model also by physiological community (non-Modelica users), what brings incredible feedbacks for next improvement and development of the model. So the goal of the thesis is to create the new libraries as part of Modelica environment, which will be usable also for many other models. This new libraries will contains general fixed, valid and verified set of components usable for very intuitive use in graphical diagrams.

Even the model HumMod 1.6 contains thousands of physical relations, it still calculate the processes in very simplified way. Almost each part of the model can be improved and implemented in more detail. Because our laboratory has a long tradition in calculation of acid-base homeostasis and blood gases transport (Kofránek, 2009; Mateják, et al., 2015; Matousek, et al., 2011) the work will be focused on extension of the model this particular way to improve calculation of blood pH, O2 and CO2 content in blood. As was said in introduction, the simulation of blood in HumMod 1.6 can not even calculate with non-bicarbonate acidbase buffers, and it does not calculate even with binding of CO2 or H+ to hemoglobin. These processes are so significant, that the HumMod 1.6 has a problem to calculate the total content of CO2 even in normal condition. So it is not surprise that the simulation results are different from observation of blood status at different conditions (Siggaard-Andersen, 1971; Siggaard-Andersen, et al., 1972; Siggaard-Andersen and Salling, 1971; Siggaard-Andersen, et al., 1972). To fix these discrepancies there should be implemented titration properties of plasmatic proteins (Figge, et al., 1992), phosphates and erythrocytes. It was found, that the most significant role plays the erythrocytes, because they are connected with blood plasma with chloride shift (membrane channel “Band 3”, which passively exchange one HCO3- for one Cl- in both directions). Not only by providing the carbonic anhydrase for Henderson-Hasselbalch reaction (CO2 + H2O <-> HCO3- + H+), but also by very sophisticated properties of hemoglobin. And only the integration approach can show that the major word in acid-base balance during blood gases transport has the allosteric binding of multiple ligands (O2, CO2 and H+) to hemoglobin. This work should take into account all these processes, and finally it should describe all these properties of hemoglobin A (HbA)[[1]](#footnote-1), which are until today described only separately (it did not exist any integrated model, which describes all these nontrivially connected phenomena):

1. Oxygen Dissociation Curve for HbA (Severinghaus, 1979)
2. Carboxylation of oxygenated and deoxygenated HbA at different pH (Bauer and Schröder, 1972; Matthew, et al., 1977)
3. Releasing H+ during oxygenation of HbA (Siggaard-Andersen, 1971)
4. The change of dissociations at different temperatures (Reeves, 1980; Weber, et al., 2014)

So the next goal is to propose new multiple-ligands allosteric theory to describe all these experiments, which plays significant role in acid-base status of blood during blood gases transport.

The building of complex integrated model has an implicit assumption that the resulting relations will be at least as good as the models, which are describing each phenomena separately. This is very important for integration physiology, because the complex model must converge in each phase of development into better description of simulated reality. This assumption is the main meaning of the second (integrative) hypothesis. The improvement of the model by integration is not certain and it must be taken care in each phase of development to fulfil the good fit with all described experiments. For this reason there exists still a discussion, whether is better to use small simple or huge complex models (Gavaghan, et al., 2006). However, if there is really possible always to build better integrative theory, which will describe all selected experiments in given precision, then this work should present the methods of physiological knowledge integration, which must be applied during each phase of development of complex integrative model. Because the development can go forward only using these rules, which prevent losing any integrated knowledge. At this point of view if the huge complex integrative physiological model is not as good as small simple physiological model, they can be integrated together and the result must be better than both of them.

As a goal of the thesis is to demonstrate the usage of formalized rules of integrative physiology, which are married with real observations and physiological experiments. The new integrated and validated theories should be finally implemented using hierarchical graphical diagrams to allow visual verification of the connected physiological principles. The simulation results must be always in good agreements with accumulated real data set.

# Materials and methods

The work is based on exact definitions, which must have unique meaning. Because only this way there can be build the integrative theory of human physiology, which is representable by computer simulation. The most of the exact formalization methods can be used from physics, where the mathematical relations have a long history.

The meaning of variables can be exactly defined using ***physical quantities and physical units.*** Physical quantities such as pressure, temperature, volume, mass, … are internationally accepted terms, which are very suitable for description of parameters and variables of the physiological models. Usually they are anatomically located in the body, which can separates they meaning for particular physiological systems, organs, tissues, fluids, cells or organelles. Unfortunately the values of the same physical quantity in the same location is not unique, because it can be represent in different physical units. This is critical for computer simulation, where the values can be shared between many integrated relations. However in physics is this problem already solved by definition of International System of Units (SI). This work fully accept this SI-units without any exceptions. Even if some values are extremely small (e.g. 1 ml = 10-6 m3) and some values are very unusual in physiology and medicine (e.g. Kelvin for temperature or charge of ions in Coulomb).

All ***physical definitions and relations*** between variables are formulated always for SI-units, which really simplify the usage of physics behind physiological principles. The properties of ***Modelica*** language such as mentioned automatic algebraic solver of the set of mathematical equations bring to the integrative physiology new light. The complex model in the Modelica is an input for compiler, which is developed by independent teams of mathematicians and programmers to maximize the class of numerically resolvable mathematical problems (Engelson, et al., 1999; Mattson, et al., 1997). So the user usually must not manually solve the mathematical expressions to implement algorithm of calculation, which was the hardest part of integrative computational physiology until today. The implementation of the integrative model starts to be so close to the physiological theory, that the researcher can be focused almost only on building the theories. However, the exact theory, which is representable by computer simulation must be mathematically well defined using the correct rules of building base Modelica components and their connections for the specific first principles of the physiology.

The elementary physical laws can be in Modelica represented as library component, from which as from the building blocks can be built whole complex model. The main principle of this implementation of the model as hierarchical graphical diagram is represented in Modelica language construct called ***physical connector***. This connector as an analogy from electrical circuits connections has pair of variables – flow and nonflow (e.g. electric current and electric potential). Each component can have as many connectors as needed, typically two or one. When the flow is not accumulated in the component the sum of all flow variables in each component’s connector is zero at each time (i.e. what is going inside by some connectors is going outside by other connectors). The connection between components using physical connector also does not lost or add any flow to the system, what automatically fulfil the physical idea, that there cannot be created (or loss) any energy, mass, amount of substance or any elementary particle from/to nothing. Only places, where can be generated, accumulated or transformed new flows are the components. So the connections of physical connectors generate always only simple equalities of nonflow variables and mentioned physical junction law for flows. This approach is so general that in Modelica already exist electrical components such as resistor, capacitor, inductor (Mattsson, et al., 1998); thermal components such as thermal conductance and thermal capacitor (Elmqvist, et al., 2003); or mechanical components such as spring or dumper (Engelson, et al., 1999).

However, the implementation of the theory into Modelica is only the second step of the complex integrative physiological model development. The first step is to integrate the theories, which describes the experiments. The methods for the integration was formalized in section 4. The reproducible ***real experiment*** is defined as a sampled function, which transform the setting to the outputs. This transformation is done by the real measurement of the data after experiment at defined setting. In physiology is typical that the mean values of the concentrations, temperatures, flows, pH etc. remain constant at normal optimal conditions – called homeostasis. These typical values of conditions and physiological variables are named as ***default setting***. Using default setting rapidly simplify the usage of the model, because there is not needed to set all parameters before each experiment, only the selected significant parameters, that are not in normal values can define the setting of the model or experiment. The model is also a function defined as set of hybrid ordinary differential equations. If all measured data of the experiment are close enough to simulated results then it can be said, that the model ***describes*** the experiment. Having exactly defined this relation the comparison of the model can be easily formalized as model A is ***at least as good as*** model B if and only if all experiments described by model B can be described by model A. However not all models are comparable, because there can exist an experiment E described only by A and experiment F described only by B. This is the typical situation in the repositories of physiological models such as in project Physiome (www.physiome.org), where each model can simulate different processes. However this work wants to open new horizons of physiological modeling, so it formalize the ***integration***, which said that for each pair of incomparable models it must always exist a model, which is at least as good as both these models. Using this approach the development of the huge complex integrative model of the human physiology can always converge to the more precise description of the real processes in the human body.

# Results

The results of this thesis can be divided into two groups: the new Modelica libraries ([www.physiolibrary.org](http://www.physiolibrary.org)) as implemented carefully selected first principles of physiological processes for building physiological models; and the complex model of human physiology ([www.physiomodel.org](http://www.physiomodel.org)), which extends HumMod 1.6 with new model of acid-base and blood gases transport.

Table 1, Used physical connectors, new connectors proposed in thesis are shown in italics.

|  |  |  |  |
| --- | --- | --- | --- |
| Connector | | Nonflow | Flow[[2]](#footnote-2) |
|  | Electrical | electric potential | electrical current |
|  | Thermal | Temperature | flow of heat |
| C:\Users\marek\AppData\Local\Microsoft\Windows\INetCache\Content.Word\ChemicalPorts.png | *Chemical* | *electrochemical potential* | *molar flow* |
|  | *Hydraulic* | *pressure* | *volumetric flow* |
| C:\Users\marek\AppData\Local\Microsoft\Windows\INetCache\Content.Word\PopulationPorts.png | *Population* | *size of population* | *change of population* |

Even the new Modelica libraries for physiology are mentioned first in the thesis, because the complex model is built above them, in the process of development was firstly implemented the complex model HumMod 1.6 in Modelica. Then the analysis of elementary processes leads to the general patterns, which was repeated in many places. And after this robust decomposition starts to be visible elementary physical laws, which are in original model totally hidden after flattened list of assignments of expression composed from particular variables. These carefully extracted ***first principles*** from hydraulic and thermal domain (Mateják, 2014a) was extended in this thesis with new chemical principles, which are much usable than the chemical principles of HumMod 1.6 – for example because the concentration or osmolarity is not always the same in chemical equilibrium in contrast with electrochemical potential. The relatively small compact set of components can be used for huge set of physiological models, what makes from these free open-source libraries called “***Physiolibrary***“ and the “***Chemical***” library the useful tool for academic or commercial development of physiological models in Modelica. The components from the libraries can be connected using connectors from Table 1.

The Physiolibrary components (Mateják, 2014b) above these physical connectors are the implementations of the selected first principles of physiology. From these first principles (these library components) can be derived almost any physiological process. Some of them are presented as analogy with components of electrical circuits. For example the resistance is defined as Ohm’s law, accumulation is a simple differential equation of integration of flow, and inertia is an effort as answer to change of flow. However most of components such as chemical reactions, ideal radiator or change of population per member are so domain specific, that there does not exist any analogy between electrical, chemical, hydraulic, thermal or population domain (Mateják, et al., 2014). Each of the component has a graphical icon, which represents its usage in the model defined by graphical diagrams called also circuits. After the user translate the model defined as a diagram of these components, there are automatically generated the mathematical equations, which are hidden behind the connections and the components. The main purpose of using graphical covering of the mathematical relations is to achieve visual verification, readability, reusability, reduce the number of errors, and allows the intuitive reorganization or extension of the model (Mateják, et al., 2008).

As was mentioned these libraries was separated from the complex physiological model in the final phase of the development. This work began with the reimplementation of the original Guyton model from 1972 into the Modelica (Mateják, et al., 2009). One year later, was implemented also the QHP model into Modelica (Mateják and Kofránek, 2010). This model was one of the main results of our successful national project, “E-Golem: medical learning simulator of human physiological functions as a background of e-learning teaching of critical care medicine” (2006–2009, MSM/2C, 2C06031). The next model implemented into Modelica was HumMod 1.6 (Mateják and Kofránek, 2011). Having achieved this implementation, it became very easy to extend the model with new acid-base theories, or new blood gas transport and cardiovascular details. Thus, in 2012, I implemented into the model Siggaard-Andersen’s new blood oxygen status model (Siggaard-Andersen and Siggaard-Andersen, 1990). The model was able to simulate the support of artificial ventilation, for example, and even extravascular oxygenation (Mateják, et al., 2012). These and many other inputs, such as infusions, dialyses, transfusions and hemorrhages, were designed for educational simulations, as part of the project entitled “Virtual patient – Simulator for medical education” (2011–2014, MPO/FR, FR-TI3/869). In the same manner of educational simulation, different scenarios of acid-base and respiratory disorders—for example, ketoacidosis (Mateják, 2013)—were also tested in the model, into which the new acid-base calculations had already been implemented, as a result of electroneutrality, along with calculations for each significant chemical substance. Furthermore, there was designed the general principle of ***allosteric equilibria***, which could be used, for example, to calculate the hemoglobin model with three ligands: oxygen, carbon dioxide and hydrogen ions (Mateják, 2015b; Mateják, et al., 2015a). As shown in the thesis, all these physiological descriptions can be easily integrated into a single model, which was named “***Physiomodel***”. The detail structure of this model is described in thesis in section 5.

The development of the ***multiligands allosteric hemoglobin model*** passes also different setbacks. The praxis shows, that it is not good idea to extend the models, which are based on mathematical approximations such as Hill’s, Siggaard’s, or Severinghauss’ model. These extensions fail in description of more reconnected phenomena, which needed to be integrated together. In our case they was oxygen saturation of hemoglobin (Severinghaus, 1979), carboxylation of hemoglobin (Bauer and Schröder, 1972) and Bohr’s protons binding to hemoglobin (Siggaard-Andersen, 1971) at variable values of pH and levels of O2 a CO2. However, if the model has physical bases of elementary chemical reactions with particular ligands (Mateják, et al., 2015) then the model ready to extensions even with other ligands such as chloride, 2,3-diphosphoglycerate or other organic phosphates. Even more, our model describes chemical bounds, accumulations and releasing of particular molecules (Figure 1), what enables its simple integrations to the complex physiological models. 

Figure 1, Comparison of measured data (circles) of hemoglobin oxygenation (Severinghaus, 1979), carboxylation (Bauer and Schröder, 1972), Bohr’s titration (Siggaard-Andersen, 1971) and Bohr’s effect (Naeraa, et al., 1963) with simulation outputs (lines) of the presented integrative hemoglobin model (Mateják, et al., 2015).

In Modelica this model of hemoglobin binding can be represented only using four library components: *chemical substance* (representing specific forms of whole tetramer and also of independent sides in macromolecule at selected conformation); *chemical reaction* (representing each particular reaction of binding ligands); *chemical speciation* (for calculation of the whole tetramer concentration from the concentrations of it’s independent selected sides); and *chemical solution* (representing extensive and intensive properties of the chemical solution, where all processes take place). These components from the proposed Chemical library are ones of the small amount of the building blocks of chemical domain, which can be connected using chemical connectors (Table 1).

Similarly as chemical domain based on physical chemistry, also the hydraulic domain is composed from small numbers of components, from which is possible to create the most of models of cardiovascular system (Kulhánek, et al., 2014). These models are represented using Physiolibrary and describes in various details the pulsating blood circulation. Unfortunately none of these pulsatile model was fully integrated with Physiomodel, because the Physiomodel has many regulations, which are designed primary to non-pulsatile long-term simulations. However there integration must be somehow possible.

The question of complex physiological models is whether it makes sense to build the “monsters” with thousands of equations and variables. Even in the thesis is theoretically proven, that the integration of any models must exist (section 4, ***integration theorem***), their finding in the level of first principles can be extremely difficult. However, having the complex model of accumulated physiological knowledge formalized in computer language could bring many benefits and the new approaches to integrative physiology.

# Discussion

With exception of HumMod (Hester, et al., 2011) from University of Mississippi Medical Centre there exist whole repositories of the physiological models based on hybrid ordinary diferential equations. The most of these models was supported by international project Physiome (Bassingthwaighte, 2000; Hunter, et al., 2002; Hunter, et al., 2006). They are divided into specific areas of physiology. For example for the model of heart was established separate project called Cardiome (Bassingthwaighte, 1997). The branche of Physiome in Europe is called Virtual Physiology Human - VPH (Díaz-Zuccarini, et al., 2014; Hunter and Viceconte, 2009) or EuroPhysiome (Fenner, et al., 2008). The goals of the projects are the same – to formalize physiology in the level of computer simulation. To this formalization was even developed a special computer languages such as System Biology Markup Language – SBML and Cellular Markup Language - CellML (Smith, et al., 2013). However the language Modelica as language for modeling compoex physical systems is supported much better with know-how (International Modelica Conferences from year 2000; Modelica Association of unitersities, companies and individuals; standardization of the computer language; …) and also with foundation (e.g. research projects within Europe spend 75 Mill. € in the years 2007-2015 to further improve Modelica and Modelica related technology). Practicaly the language Modelica is not only better than mentioned SBML or CellML, but also then comertial tools. For this reason the Mathwork (Inc., USA) grounded system Simscape in environment MATLAB, which is very similar to Modelica with almost the same possibilities of hierarchical graphical diagram modeling. However, this notation is not standardized, so it is not supported in different environments or tools. Much better commertial strategy was established by companies such as Dassault Systemes (Inc., France), Wolfram (Inc. USA) or MAPLESOFT (Inc. USA), whose commercial products already support Modelica language with connection to additional software possibilities such as CAD[[3]](#footnote-3) systems, visualization tools, optimalizations or mathematical tools. The usage of the language Modelica in these environments are in the first places in automotive or energetic industry. From the academic point of view is important, that there are also noncommertial free accessible Modelica environments – for example OpenModelica, in which the Physiolibrary is already tested and supported. Even our implementation HumMod Golem Edition is used as a benchmark for testing and optimalization of OpenModelica compilers and solver (Kofránek, et al., 2011).

Maintain of huge amount of specific separated physiological models in repositories is incomparable easier than integrating them together into one compex model. The reverse way, i.e. generating specific small models for small number of inputs and outputs from one big complex model should be theoretically fully automatizable. However, this big potential of complex physiological models is not usable until the models will be effectively integrated. The language Modelica put the effectivity of integration and implementation of the complex system at the high level of reusability, readability and error-proofness. The Modelica is really the last generation of computer language, which combine object-oriented approach, code generation from hierarchical graphical diagrams, equation-based notation and many others very usefull properties. For this reason is the Modelica a perfect candidate of the language for integrative physiology. However, the most inmportant part of integration is not an implementation but developing the new theories, which can describe the observed phenomena. In this field the work integrate the HumMod 1.6 with new acid-base calculation and blood gases transport model. The new integrative acid-base theory was build upon titration properties of carbonic acid, inorganic phosphates, albumin, globulins and hemoglobin. The electroneutrality of in each body fluid is reached at calculated pH. However, the most complicated part was observed the hemoglobin, which acid-base buffering properties are dependent on the state of other ligands such as O2 or CO2. And reversely the dissociation of these blood gases are dependent on pH. Even more the bindings of O2 and CO2 are also cross-dependent. The processes such as oxygen dissociation, hemoglobin carboxylation and also Bohr’s proton binding are known for a long time. However our model is the first one, which interconnect them together into one integrative model, which can successfully describes all these observations (Figure 1). The huge advantage is, that the model use only the formulated chemical first principles, which opens the door for next extensions with binding of new ligands or other chemical processes on hemoglobin.

Nowadays the most common models of hemoglobin oxygen dissociation are an allosteric models (Eaton, et al., 2007), which comes from original Monod-Wyman-Changeux (MWC) approach (Monod, et al., 1965). Hoever these models describes only binding of oxygen at fixed conditions. They do not integrate accompanied binding or releasing of CO2 or H+. Our model is based on Adair’s approach of loading O2 in four step gradually for each subunit of hemoglobin tetramer molecule. These steps divide state of hemoglobin molecule into five groups (without oxygen, one bound oxygen,.. four bound oxygen). In each of these groups can be calculated the CO2 and H+ eqiulibrium at each of the four subunits. These new approach is called macromolecule equilibria or chemical speciation (pg. 39-40 in the thesis) and it is so general that it can be applied also to mentioned allosteric models, which calculates only oxygen binding. From the results is possible to express any concentration of any macromolecule form defined by state of modeled chemical bounds on its independent sites. This is possible, because in chemical equilibrium is always reached the detailed balance (Shiryaeva, 2010) as a result of thermodynamic energetic properties of chemical reactions. This detailed balance is the result of formulated chemical first principles from electrochemical potentials of the substance called also molar Gibb’s energy of the substance in the chemical solution.

The implementation using graphical diagrams can hide many other information, which can be directly and exactly derived and generated from connections of the used components. For example the heat energy of the chemical system, i.e. enthalpy, can be directly derived from the properties and from the amounts of substances. The implemented system this way reflects the real behavior, e.g. when during exothermic chemical reaction is increasing temperature of the solution. So there is no need to make the assumption of fixed temperature or fixed concentratios, because all variables are calculated in the same time to fulfil the dynamical physical differential equations of the simulated system. In our model is shown that binding of O2 to HbA is exothermic reaction (i.e. it releases heat) and reversely the releasing O2 in metabolically active tissue consume the same amount of heat (endothermic direction of the reaction). This way is the heat smartly exchanged between tissues and the core of the body (lungs) (Mateják, et al., 2015; Weber and Campbell, 2011; Weber, et al., 2014). Even it is only the 4-5% of produced heat, this processes can be integrated also into the calculation of thermoregulation in the model. This and many other possibilities to relatively simple extensions of the complex physiological model would be never established if the model was not constructed above the formalized first principles of the integrative physiology based on physics and physical chemistry.

# Conclusions

This thesis theoretically proved that all physiological models (as hybrid ordinary differential equation) can be integrated into one complex model. However, the integration of the models often means to build new theories, what can be extremely difficult. The integration is much easier if the models are based on first principles, because these principles are already prepared for development. These first principles of physiology are here implemented as a small compact set of components (as free open-source Modelica libraries Physiolibrary and Chemical library) with only few types of physical connectors, where all connectors of the same type can be connected together in diagrams. Using these type of connections and components, the hierarchical graphical development of complex integrative physiological model was demonstrated on reimplementation of the model HumMod 1.6 from University of Mississippi, which was extended with new acid-base homeostasis and detailed blood gases transport. This resultig complex model is called Physiomodel.

The new approach of integrative acid-base modelling was developed. Until today nobody need to calculate each charged particle in each body fluids (such as blool plasma, erythrocytes intracellular fluid, interstitium, intracellular fluid of specific tissues), because for the estimation of acid-base disorders was selectd only rough markers such as pH, strong ions difference (SID), bicarbonate (HCO3-) or eventualy anion gap (AG). These markers are also the results of our model, but they are outputs, not inputs to the model. For example even HumMod 1.6 can calculate SID from the significant electrolytes, whose balance is detailly modeled by absorbtion, storage and regulated kidney excretions. The transport of CO2 was improved in the presented model in the thesis, so the calculation of bicarbonate better reflects the real processes such as Henreson-Hasselbalch equation, binding CO2 to hemoglobin or Haldane effect of hemoglobin. And what is the biggest improvement is the inclusion of the role of acid-base buffers to the model. The non-bicarbonate buffers such as albumin, globulins, phosphates and hemoglobin, because the level of these “weak acids” or “weak bases” very significantly shift the pH even in the same condition of SID and CO2. The pH is calculated from all these charged substances to reach the total electroneutrality in each body fluid. However the most complicated part is how to calculate the charge of the hemoglobin, because the state of H+ binding is dependent on both CO2 and O2.

As a result the new integrative model of O2, CO2, H+ and hemoglobin equilibrium was developed (Mateják, et al., 2015). This model can calculate together the binding of O2, CO2 and H+ into the hemoglobin in such detail, that it is even possible to express from the model a concentration of any selected form of hemoglobin tetramer defined by number of bound O2, CO2 and H+ at defined conditions. This is possible because the formalized first principles, fromwhich is the model exclusively composed, are based on physical chemistry. The thermodynamic equilibrium of closed chemical system in physical chemistry always achieves the chemical detailed balance, where the dissociation coefficients of each reactions are estimated from complex set of measurable data. Even more, also the enthalpies can be estimated from temperature dependences, what makes some chemical reactions exothermic and some reactions endothermic. The simulation using these data can show the comsuming heat during deoxygenation, carboxylation and during loading of Bohr’s protons; and releasing of heat during oxygenation, decarboxylation and during releasing of Bohr’s protons. Connecting this system to the thermoregulation of the HumMod 1.6 it was shown, that this way can be transported even 4-5% of produced heat from metabolically active tissue to the body core (lungs).

In physiology is typical to have a one term for complex process, regulation or even for whole physiological sytem. Thanks to hierarchical decomposition, these terms can be implemented as components of the entire model. Having graphical diagrams there is almost no need to write the source code, all can be “drawn” almost only using the already defined components. Because at the lowest level of hierarchical graphical diagrams are the selected first principles as mentioned components of Physiolibrary. Inside these components are manually written the physical laws, which are making the relations between the variables from connectors. For example in chemical domain this approach is tidly connected with the physical chemistry allowing to use all formalizations of this science. Having chemical processes defined through Gibbs energies and enthalpies, the most of parameters can be also in the level of formation energies of substances, which are well known and tabulated values even for some organic molecules. However, for unknown forms of molecules also these parameters can be recalculated from dissociation coefficients, solubility coefficients or other measured data. Independently of the complex model built above the libraries, also these libraries can be improved. For example if there will be available the theory to calculate these molecular energies from the structure of the molecule then the components can be improved with this calculation but the interface can remain the same, so the already implemented models will be still runnable even with this new hypothetical version of the chemical library.

In contrast with the libraries, which achieved their final look, the complex model called Physiomodel is only the frist demonstration of complex integrative model of human physiology. It does not describes in details all known physiological processes. It will cost a lot of effort to integrate more and more molecular processes and pathophysiological disorders. However as was shown this direction is not a dead end and theoretically the development in this way is possible and beneficial. As a result the model can brings many answers even for very complex and connected problems. These accumulation of physiological knowledge into so readable complex theory (as hierarchical graphical diagrams, which generates the code) in the level of computer simulation was not possible until today.

The Modelica libraries Physiolibrary 2.3.0 and Chemical 1.1.0-beta are publicated in Modelica libraries web pages ([www.modelica.org/libraries](http://www.modelica.org/libraries)) as a result of this work using a [Modelica License 2](https://www.modelica.org/licenses/ModelicaLicense2) under Charles University, what means that everybody can use them on own risk for comertial and noncomertial purposes.

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1. Hemoglobin A is 97% of total hemoglobin in adults. I tis a protein - tetramer composed from two alpha and two beta subunits coded by genes HbA1, HbA2 in 16th chromosome and HBB in 11th chromosome. In the middle of each four subunit is hem with one iron atom. [↑](#footnote-ref-1)
2. The flow incoming to the component has positive value. The flow outgoing from component is negative. [↑](#footnote-ref-2)
3. CAD – Computer Aided Drafting = počítačom podporované 2D alebo 3D technické kreslenie [↑](#footnote-ref-3)