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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 relatively young branch of physiology, which describes complex connected mechanisms and regulations of physiological systems in all levels (from molecular, cellular, tissue and organs to the level of whole body). And because each physiological knowledge becomes from examination and comparison of functionality of living organisms and nature, also basis of integrative physiology should be experiments and data, from which is possible to generalize the mathematical relations. Therefore, dissertation thesis in 4th section formalize the reproducible experiment, which can be described by physiological model (pg. 40-44). This model is as good as many real experiments it can describe. It is theoretically and practically shown, that the models is possible to integrate in the way that the resulting model is at least as good as all the models before integration. Typically this integration means finding new theory, which describes all desired phenomena. Its identification with real experiments in particular settings gives the model, which describes these desired experiment in the given precision.

This integrative approach based on physics is not the total novelty. Even the thought that whole complex human physiology is possible to integrate into one complex model is long years available in the development in University of Mississippi Center, where Arthur C. Guyton et al. bring the idea of connecting physiological knowledge together using exact mathematical notations. One of their first model, which starts this integrative physiological development was model of cardiovascular system with integrated volume, hormonal and neural regulations (Guyton, et al., 1972). The model was built from data of simplified cardiac function (Guyton, 1965); perfusion of lungs, kidneys and skeletal muscles; neural and hormonal regulations; body fluid balance; and very simplified transport of oxygen. The model simulates the relations between regulation of blood circulation, blood pressure and volume and pathophysiological mechanisms, which lead to essential chronic hypertension. For validation of the model behavior Guyton et al. proposed also experiments based on nephrectomy in dogs, which had a good fit with the model simulation (Guyton, et al., 1972). The model was continuously being extended and improved with more and more data and experiments, which it can simulate. This way was created the versions 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 a model "HumMod" (Hester, et al., 2010; Hester, et al., 2011). In the long term the integration of accessible physiological knowledge is one of the main goal of the Department of Physiology and Biophysics in Arthur C. Guyton Research Center of University of Mississippi Medical Centre. The team of this theoretical physiology is composed with researchers with overlap in mathematical, chemical, physical and physiological education. The result of their long years work is one complex integrative model of human physiology. The model called HumMod in version 1.6 is freely accessible for next academic development under GPL license.

In our opinion the subsystem of ***acid-base homeostasis and blood gases transport*** is one of the weakest part of the model. Very simplified calculation of blood acid-base, which does not use any non-bicarbonate acid-base buffer, need to be replaced by more complex calculation of pH regulations connected with transport of oxygen (O2) and carbon dioxide (CO2). The model from Mississippi for example does not bind the CO2 into hemoglobin (Bauer and Schröder, 1972); does not release the Bohr’s protons (Bohr, et al., 1904) and does not calculate any titration properties of non-bicarbonate weak acids. It is known that the acid-base status of blood is determined by strong ions difference (Stewart, 1981), bicarbonate (i.e. HCO3- created by hydration of CO2: CO2 + H2O <-> HCO3- + H+) (Henderson, 1908), plasma buffers such as plasmatic proteins (Figge, et al., 1992), phosphates and very significantly also by hemoglobin (Antonini, et al., 1963) inside red blood cells. While most of these acid-base buffers binds hydrogen ions (H+) independently on state of other substances the hemoglobin is different. The hemoglobin change the quaternary form A by binding of oxygen (Monod, et al., 1965), what could change also the other binding properties for H+ and also for CO2. There exit at least five different models of oxygen dissociation from hemoglobin: allosteric model (Eaton, et al., 2007; Monod, et al., 1965), Adair four-step oxygenation (Adair, 1925), Hill’s model (Hill, 1913), approximation using hyperbolic tangents (Siggaard-Andersen and Siggaard-Andersen, 1990) or other polynomial approximations (Severinghaus, 1979). The oxygen dissociation curve (ODC) of each of these model describes well the oxygen saturation (sO2) dependently on partial oxygen pressure (pO2) at fixed normal condition of temperature, pH, CO2, DPG, and other factors. However, only the allosteric and Adair approach is based on physical description of chemical processes. Other three models are only mathematical approximations of measured data, what does not matter until the model need to be extended with more ligands. Some of these complicated empirical extensions with effects of CO2 and pH by shift of ODC to the left or to the right are available (Dash and Bassingthwaighte, 2010; Rees and Andreassen, 2005; Severinghaus, 1979; Siggaard-Andersen and Siggaard-Andersen, 1990). However they fail, when the value of CO2 and pH is out of normal in the same time. The processes are in nonlinear relations, so 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 give the state of the binding of other ligands, whose saturation is also dependent on the other ligands. Therefore, the model is better to build upon physical and chemical theories, which are giving more answers for more questions than only mathematical approximation of one variable.

Morrow et al. (Matthew, et al., 1977; Morrow, et al., 1976) show that CO2 carboxylate the amino-terminals of all four subunits of hemoglobin tetramer. The different affinity for oxygenated and deoxygenated forms cause at the first look the competitive relation between CO2 and O2. However, the bounds are not competitive, because each ligand is binding on the different sides. So both CO2 and O2 can be bound on the same time on each subunit. Thanks to hemoglobin the blood is available to transfer 25% more CO2. About 10-11% of this CO2 is transported directly bonded as carb-amino terminal of hemoglobin subunit (Bauer and Schröder, 1972) and the rest is the result of pH change caused by binding of Bohr’s protons (i.e. increasing blood capacity for bicarbonate).

In this way the hemoglobin can smartly remain the pH between arterial and venous blood. For example in tissues, where the amount of H+ is increasing by CO2 in form of HCO3-, the hemoglobin during releasing of oxygen regulates the pH by binding of H+ (the deoxygenated forms has higher affinity to Bohr’s protons) (Bohr, et al., 1904; Siggaard-Andersen, 1971). There are more than ten bounding sites in hemoglobin A tetramer for Bohr protons. These sites changes affinity for H+ during change of shape of the molecule caused by binding or releasing of oxygen. The most of them are amino acid side chains located in 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 only with 2 fictive sides to calculate during (de)oxygenation the relative shift, which at normal conditions is approximately one H+ per two O2 (Antonini, et al., 1965).

As each chemical reaction also the binding ligands to hemoglobin are 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 temperature is known (Reeves, 1980; Weber and Campbell, 2011; Weber, et al., 2014). Using theory of physical chemistry should be possible to calculate the enthalpy of chemical reactions not only to shift of dissociation coefficients but also to calculate the amount of heat consumed or released by reaction.

The next weakness of the model HumMod 1.6 is the form of implementation. Although the source code separates "physiological definitions", they are not equations in the mathematical meaning but only assignments, when the value, which calculated from some expression, is stored to the selected variable. Whole model HumMod is implemented as „causal“, which in the prescribed sequence calculates the unknown variables from the expressions of known variables using the algorithm. This is not a formulation of equations, but only the implementation of algorithm (i.e. causal implementation). However, in complicated models often exist situations, where the equations are not possible to reach only by simple sequence of assignments. And for the numerical solution it is necessary to select an iterative method – HumMod for these cases has a construct of implicit equations. The huge weakness of HumMod 1.6 implementation is also the redundancy of the 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 use them by reference with selected setting instead of copying the contents of functions and objects in many places. The language, in which is HumMod 1.6 implemented, suffers by lack of modern computer language constructs, which could simplify the readability and visual verification of the implementation. The original source code is divided into hundreds of files, so it is not surprise than the research and development teams of complex physiological models in the project Physiome (Bassingthwaighte, 2000; Hunter, et al., 2002) rather use and extends the older and simpler models.

The ideal language for implementation of complex physical systems is Modelica ([www.modelica.org](http://www.modelica.org)). The equations can be formulated in Modelica without manual algebraic manipulations (“acausal” implementation). This language allows also for represent 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 as Ohm’s law and is represented by typical icon of rectangle in electrical circuits. Once the object with his icon is defined, it can be used with different setting as many times as necessary. This object-oriented approach allows for define also hierarchical components, which are composed from many other connected components. Almost each model can be implemented only by graphical diagrams having a relatively small set of domain-specific physical laws (called first principles) implemented as Modelica libraries. The physical connections of Modelica components bring the visual verification, which is readable also by non-Modelica users. This approach brings to the industry the very powerful tool for communication between programmer, developer and researcher.

As a result the Modelica is already used in many industrial applications (from automotive and aircraft industry to construction of robots, design of power plants). Nowadays exists a number of commercial and noncommercial (for example OpenModelica) Modelica environments, which can support building and simulation of the models in this language. Nowadays the libraries in Modelica mainly represent electrical, mechanical or magnetic domains. However, the Modelica language is general enough to define also libraries in chemical, thermal, hydraulic or population domains of physiology, which before this work did not exist. For example there should be possible from components of these libraries to implement the component for microcirculation, which is a hydraulic resistance in cardiovascular system. These component can be affected by many inputs caused local vasoconstriction or vasodilation. Using this object in different places of cardiovascular diagrams for different tissues with different setting the local microcirculation can react to all known local factors with prescribed sensitivity. So the question is: Is it possible to formalize the first principles in physiology to create compact Modelica library, from which should be possible to implement the HumMod 1.6 model and also 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

Kromě komplexních modelů fyziologie z Mississippi University jako je HumMod (Hester, et al., 2011) dnes existují celé repositáře implementovaných modelů. Většina daného výzkumu byla financována z mezinárodního projektu Physiome (Bassingthwaighte, 2000; Hunter, et al., 2002; Hunter, et al., 2006). Modely jsou rozděleny do úzkých oblastí fyziologie, kterých se týkají. Například pro modely srdce tak vznikl dokonce samostatný podprojekt Cardiome (Bassingthwaighte, 1997). V Evropě se projekt EuroPhysiome (Fenner, et al., 2008) oficiálně nazývá Virtual Physiology Human - VPH (Díaz-Zuccarini, et al., 2014; Hunter and Viceconte, 2009). Cíle projektu jsou však stejné a dokonce i účast je celosvětová. Na formalizaci fyziologie jsou vyvíjeny počítačové jazyky System Biology Markup Language - SBML a Cellular Markup Language - CellML (Smith, et al., 2013). A to i přesto, že Evropa financuje zároveň projekty určené pro vývoj univerzálního modelovacího jazyka Modelica a nástrojů s ním spojených (75 Mill. € v letech 2007-2015 přes ITEA2 projekty EUROSYSLIB, MODELISAR, OPENPROD, and MODRIO). Technicky i prakticky jazyk Modelica daleko převyšuje možnosti nejen jazyků SBML, zda CellML, ale dokonce i užívaných komerčních nástrojů. Pro udržení kroku tak například firma MATHWORKS (US) přichází s Modelice velmi podobným systémem Simscape v programovém prostředí Matlab, avšak s obrovskou nevýhodou, že zápis modelu není standardizovaný a tím je nepřenosný mezi jinými prostředími. Mezinárodní firmy jako Dassault Systemes, Wolfram nebo MAPLESOFT zvolili opačnou strategii a jejich komerční produkty již jazyk Modelica podporují natolik, že je ho možné propojovat s dalšími softwarovými možnostmi jako jsou CAD[[3]](#footnote-3) systémy nebo jiné optimalizační a matematické nástavby. Jazyk Modelica je tak úspěšný, že se dnes dostává na první příčky v simulačních prostředích v automobilovém i energetickém průmyslu. Z akademického hlediska je však podstatné, že vedle komerčních nástrojů se začínají prosazovat i nekomerční volně šiřitelné nástroje jazyka Modelica jako je OpenModelica, ve kterém je naše knihovna Physiolibrary testována a plně podporována. Dokonce naše implementace modelu HumMod Golem Edition slouží jako jeden z testů pro sledování efektivity překladače OpenModelica (Kofránek, et al., 2011).

Udržovat velké množství navzájem nepropojitelných modelů je mnohem jednodušší, než modely spolu integrovat v jeden velký komplexní celek. Opačný postup, tj. vytvoření specifických konkrétních modelů pro konkrétní vstupy a výstupy z jednoho velkého komplexního modelu by však mělo být teoreticky plně automatizovatelné. Tento silný potenciál velkých komplexních modelů však zůstává skrytý do doby, než bude možné modely navzájem integrovat a formalizovat pomocí hierarchických (objektově-orientovaných) jazyků s pevně specifikovaným na rovnicích založeným (equation based) významem. Právě Modelica přináší dané možnosti - např. možnosti skládat fyzikální zákony v tak komplexní celky jako jsou fyziologické systémy. Modelica je však jen jakási robustní nadstavba nad matematikou hybridních diferenciálních rovnic, kterými je daný systém popsatelný. Bez ohledu na jazyk zápisu nadále zůstává tou nejpodstatnější prací integrativní fyziologie nacházení nových teorií, které budou schopny komplexně vysvětlit pozorované děje. Děje, které například nastávají v krvi při průchodu kapilár plicních sklípcích nebo při průchodu kapilár v jednotlivých tkáních.

Integrace komplexního přenosu krevních plynů s HbA musí zastřešovat všechny tři nelineární provázané procesy jako je vazba kyslíku, oxidu uhličitého a Bohrových protonů. I přesto, že separátně jsou tyto procesy dobře známé, tak až tato disertační práce jako první přináší teorii vázání všech tří ligandů do kapilár plicních alveol nebo při průchodu kapilár v jednotlivých tkáních (O2, CO2, H+) s HbA. Využívá přitom zásadně fyzikálních vztahů chemického equilibria na hemoglobinu, kde jednotlivé ligandy jsou mezi sebou alostericky propojeny.

Dnes nejuznávanějšími modely vazby kyslíku na hemoglobin jsou modely (Eaton, et al., 2007), které vycházejí s původního alosterického Monod-Wyman-Changeux (MWC) modelu (Monod, et al., 1965). Avšak tyto modely vysvětlují pouze vázání kyslíku při pevně daných podmínkách a nevysvětlují doprovodné změny vázání CO2 nebo H+. Model v práci je sice založen na starším Adairově principu postupného vázání O2 na tetramer ve čtyřech krocích, avšak vysvětluje zároveň i dané doprovodné děje. A to do takové míry, že je možné z modelu přesně vyjádřit množství konkrétní formy HbA určené formami podjednotek (tím, zda jsou na ni dané ligandy navázané nebo ne).

Tento teoretický nadhled na equilibrium na makromolekule, které podléhá chemickému principu detailní rovnováhy, je možné zobecnit a tak jsme vytvořili komponentu chemické speciace jako jeden ze základních principů chemické domény. Pomocí dané komponenty je možné implementovat model makromolekuly s libovolným množstvím ligandů, které se vážou nezávisle na konkrétní kvarterní strukturní formu makromolekuly. Kvarterní formy makromolekuly je přitom možné také libovolně na sebe provázat pomocí chemických reakcí. Komponenta tedy umožňuje velmi přehledně zapisovat libovolné alosterické procesy s libovolným množstvím ligandů.

Zápis pomocí grafických schémat přitom může ukrývat i množství informací, které jsou automaticky odvozeny z jednotlivých zapojeni. Například každá chemická reakce má svou entalpii, tj. teplo, které zkonzumuje jeden stechiometrický mol reaktantů při přeměně na jeden stechiometrický mol produktů. Pokud je tato entalpie záporná mluvíme o exotermní reakci, pokud je kladná mluvíme o reakci endotermické. Ze základních principů termodynamiky plyne, že pokud je chemická reakce reverzibilní, tak teplo, které v jednom směru zkonzumuje, musí v opačném směru vypustit. Ukazuje se, že vázání O2 na HbA je reakce endotermická (tj. teplo vyzařuje) a tedy naopak odvázaný O2 v metabolicky aktivních tkáních navazuje teplo, které takto přenáší do plic (Mateják, et al., 2015; Weber and Campbell, 2011; Weber, et al., 2014). Tím přispívá náš model i zlepšení výpočtu termoregulace.

# Conclusions

Jednoznačným závěrem je, že fyziologické modely člověka je možné integrovat do jednoho komplexního modelu, který by měl popisovat všechny experimenty původních modelů. Toto tvrzení práce dokazuje teoreticky pomocí exaktně definovaných pojmů a zároveň ukazuje příklad integrace nového přístupu formalizovaného popisu acidobazické rovnováhy a přenosu krevních plynů s velkým komplexním modelem HumMod 1.6.

Nový prací vypracovaný přístup k modelování acidobazické rovnováhy založený na komplexní znalosti všech elektrolytů, signifikantních zásad a kyselin bere v úvahu titrační křivky daných acidobazickou pufrů. Z totálních koncentrací všech těchto chemických látek tak určí kyselost roztoku (pH) tak, aby platila elektroneutralita roztoku a chemické equilibrium na každé acidobazické reakci. A to jak v plazmě, tak v intersticiální tekutině, tak i v buňkách. Jedinou výjimkou v našem integrovaném komplexním modelu je hemoglobin, jehož titrační křivka se mění s množstvím navázaného O2 i CO2. Právě vlastnosti hemoglobinu přímo určují stav krve při přenosu krevních plynů. Ukázalo se, že je možné využitím chemické detailní rovnováhy (Alberty, 2004) vysvětlit vzájemné propojení afinit O2, CO2 a H+ a vysvětlit tak přenosové vlastnosti hemoglobinu A při všech možných kombinacích fyziologických a patofyziologických hodnot pO2, pCO2 a pH, které mohou nastat při přenosu krevních plynů i během respiračních nebo metabolických acidobazických poruch. Navíc integrační přístup pomocí jednotlivých chemických reakcí na konkrétních místech na makromolekule umožňuje sledovat i tepelné vlivy a exotermické-endotermické vlastnosti. Tím bylo možné náš model rozšířit i o vlivy vázání tepla jednotlivými reakcemi. Potvrdilo se i pozorování, že hemoglobin je schopen přenést asi 5% vyprodukovaného tepla z metabolicky aktivní tkáně do plic aniž tento typ přenosu tepla měl vliv na změnu teploty krve (Mateják, et al., 2015).

Úkolem integrativní fyziologie není vytvářet nové matematické rovnice, naopak využívat aktuální fyzikální vztahy na popis fyziologických systémů. Práce ukazuje, že aproximaci dat křivkami nelze rozvíjet dalšími aproximacemi, protože takový přístup by znamenal identifikovat n-dimenzionální funkce s nefyzikálními parametry, což by vyžadovalo kn naměřených bodů, kde k je počet bodů v jedné dimenzi. Například pokud by postačovalo 100 bodů pro každý experiment nad hemoglobinem měřící vliv jedné veličiny na druhou veličinu (tj. například pro křivky sO2(pO2), sCO2(pH), ΔBH+(pH)), tak počet bodů na podobně přesnou identifikaci trojrozměrné aproximace ([sO2, sCO2, ΔBH+] = f(pO2, pCO2, pH)) by musel být 1003=106. Tento počet by navíc exponenciálně narůstal s každým novým ligandem, nemluvě o tom, že parametry daných funkcí by neměly žádný fyzikální význam, takže jejich hodnoty by nebylo možné využít v dalším vývoji. Proto by měly být nefyzikální aproximace použity pouze v krajním případě a to pouze k určení vztahu mezi dvěma veličinami. K propojeným závislostem je již potřeba přistupovat jinak - přes fyzikální a chemické vztahy, které umožňují pracovat na rozdíl od daných aproximací s libovolným počtem rovnic / proměnných. Práce se proto nezabývá metodami identifikace množství nefyzikálních parametrů z komplexních experimentů. Naopak předpokládá, že všechny parametry nebo aproximace vztahů mezi dvojicemi veličin jsou přímým výsledkem konkrétních měření.

Fyzikální veličiny a fyzikální zákony jsou definovány příliš elementární a univerzální. Ve fyziologii je běžné, že i fyziologický jev, který se vysvětluje jedním pojmem, je ve skutečnosti násobné využití několika fyzikálních veličin ve více fyzikálních dějích. Právě propojení pojmů z fyziky a z fyzikální chemie s pojmy fyziologie je krok správným směrem, protože jedině tak je možné využívat připraven aparát z těchto exaktně rozvinutých věd. To, že na první pohled dané komponenty navržené v práci vypadají primitivně a intuitivně je obrovským úspěchem toho, že se dané propojení vydařilo a nabídlo tak silný a univerzální aparát v podobě softwarových knihoven na hierarchické definování komplexních fyziologických modelů. Tyto Modelikové knihovny Physiolibrary a Chemical jsou publikovány jako výsledek této práce pod [Modelica Licencí 2](https://www.modelica.org/licenses/ModelicaLicense2) pod Univerzitou Karlovou, což znamená, že je může využít každý na vlastní riziko pro nekomerční i komerční účely.

Na rozdíl od daných knihoven, které již získaly svou téměř finální podobu, tak komplexní integrační model člověka je teprve jakýmsi prvním nástřelem. Zdaleka nepopisuje dopodrobna všechny známé jevy ve fyziologii. Physiomodel vyžaduje ještě velké množství úsilí, aby byl schopen vysvětlit další a další patofyziologické stavy. Avšak jak teoreticky ukazuje práce, tak jeho další vývoj je možný až do takové míry, že bude schopen dávat odpovědi i na velmi komplexní a propojené fyziologické problémy. Akumulace znalostí do jedné rozsáhlé teorie uchopitelné jak pro počítač[[4]](#footnote-4), tak pro člověka[[5]](#footnote-5), má obrovský potenciál, který dosud nebyl možný.

# References

Adair, G.S. The hemoglobin system VI. The oxygen dissociation curve of hemoglobin. *J. Biol. Chem.* 1925;63(2):529-545.

Antonini, E.*, et al.* Studies on the relations between molecular and functional properties of hemoglobin IV. The Bohr effect in human hemoglobin measured by proton binding. *J. Biol. Chem.* 1963;238(9):2950-2957.

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

Bauer, C. and Schröder, E. Carbamino compounds of haemoglobin in human adult and foetal blood. *J. Physiol.* 1972;227(2):457-471.

Eaton, W.A.*, et al.* Evolution of allosteric models for hemoglobin. *IUBMB Life* 2007;59(8‐9):586-599.

Figge, J., Mydosh, T. and Fencl, V. Serum proteins and acid-base equilibria: a follow-up. *J Lab Clin Med* 1992;120(5):713-719.

Henderson, L.J. Concerning the relationship between the strength of acids and their capacity to preserve neutrality. *American Journal of Physiology--Legacy Content* 1908;21(2):173-179.

Hill, A.V. The combinations of haemoglobin with oxygen and with carbon monoxide. I. *Biochem. J.* 1913;7(5):471.

Hunter, P., Robbins, P. and Noble, D. The IUPS human physiome project. *Pflügers Archiv* 2002;445(1):1-9.

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

Kofránek, J., Mateják, M. and Privitzer, P. HumMod - large scale physiological model in Modelica. In, *8th. International Modelica Conference*. Dresden, Germany; 2011.

Mateják, M. Physiolibrary - fyziológia v Modelice. In, *Medsoft 2014*. 2014.

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

Matousek, S., Handy, J. and Rees, S.E. Acid–base chemistry of plasma: consolidation of the traditional and modern approaches from a mathematical and clinical perspective. *Journal of clinical monitoring and computing* 2011;25(1):57-70.

Matthew, J.B.*, et al.* Quantitative determination of carbamino adducts of alpha and beta chains in human adult hemoglobin in presence and absence of carbon monoxide and 2, 3-diphosphoglycerate. *J. Biol. Chem.* 1977;252(7):2234-2244.

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

Morrow, J.*, et al.* Carbon 13 resonances of 13CO2 carbamino adducts of alpha and beta chains in human adult hemoglobin. *J. Biol. Chem.* 1976;251(2):477-484.

Reeves, R.B. The effect of temperature on the oxygen equilibrium curve of human blood. *Respir. Physiol.* 1980;42(3):317-328.

Severinghaus, J.W. Simple, accurate equations for human blood O2 dissociation computations. *J. Appl. Physiol.* 1979;46(3):599-602.

Siggaard-Andersen, O. Oxygen-Linked Hydrogen Ion Binding of Human Hemoglobin. Effects of Carbon Dioxide and 2, 3-Diphosphoglycerate I. Studies on Erythrolysate. *Scand. J. Clin. Lab. Invest.* 1971;27(4):351-360.

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

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

Weber, R.E., Fago, A. and Campbell, K.L. Enthalpic partitioning of the reduced temperature sensitivity of O2 binding in bovine hemoglobin. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology* 2014.

Publikace Autora, které jsou podkladem disertace

1. s impact faktorem (uvést hodnotu IF)
2. Mateják Marek, Kulhánek Tomáš, Matoušek Stanislav. Adair-based hemoglobin equilibrium with oxygen, carbon dioxide and hydrogen ion activity. Scandinavian Journal of Clinical and Laboratory Investigation, **IF: 2.009**, ISSN: 0036-5513 (print), 1502-7686 (electronic).
3. T. Kulhánek, J. Kofránek, and M. Mateják. Modeling of short-term mechanism of arterial pressure control in the cardiovascular system: Object oriented and acausal approach. Computers in Biology and Medicine, Received 15 May 2014, Accepted 22 August 2014, Available online 1 September 2014.<http://dx.doi.org/10.1016/j.compbiomed.2014.08.025>, **IF: 1.475**, ISSN: 0010-4825

b) bez IF

1. T. Kulhanek, M. Matejak, J. Silar, and J. Kofranek. Parameter estimation of complex mathematical models of human physiology using remote simulation distributed in scientific cloud. In Biomedical and Health Informatics (BHI), 2014 IEEE EMBS International Conference on, pages 712–715, June 2014.
2. Marek Mateják, Tomáš Kulhánek, Jan Šilar, Pavol Privitzer, Filip Ježek, Jiří Kofránek: [Physiolibrary -Modelica library for Physiology](http://www.researchgate.net/publication/259892318_Physiolibrary_-Modelica_library_for_Physiology), In Conference Proceeding, 10th International Modelica Conference 2014, March 12, 2014 ([1st price](http://patf-biokyb.lf1.cuni.cz/wiki/_media/modelicafreelibraryaward2014.pdf))
3. Tomáš Kulhánek, Marek Mateják, Jan Šilar, Jiří Kofránek: Identifikace fyziologických systémů, sborník příspěvků MEDSOFT 2014, ISSN 1803-8115, 148-153
4. Marek Mateják: Physiolibrary - fyziológia v Modelice, sborník příspěvků MEDSOFT 2014, ISSN 1803-8115, 165-172
5. Filip Ježek, Anna Doležalová, Marek Mateják: Vývoj modelu pro výukovou aplikaci ECMO, sborník příspěvků MEDSOFT 2014, ISSN 1803-8115, 82-89
6. Mateják,M.: Krvné plyny, acidobáza a hemoglobín. 19. Konferencia Slovenských a Českých Patofyziológov, Lekárska fakulta MU Brno, 5.-6. září 2013, GRIFTART s.r.o. Brno, ISBN 978-80-905337-3-8
7. Mateják, Marek: Simulovanie ketoacidózy. In MEDSOFT 2013, (Milena Ziethamlová Ed.) Praha: Agentura Action M, Praha, str.140-150, ISSN 1803-8115.
8. Mateják, Marek, Nedvědová, Barbora, Doležaloví, Anna, Kofránek, Jiří, Kulhánek, Tomáš: Model ECMO oxygenátoru. In MEDSOFT 2012, (Milena Ziethamlová Ed.) Praha: Agentura Action M, Praha, str. 205-214, ISSN 1803-8115.
9. Jiří Kofránek, Marek Mateják, Pavol Privitzer: HumMod - large scale physiological model in Modelica. 8th International Modelica Conference 2011, Dresden.
10. Marek Mateják, Jiří Kofránek: HUMMOD - GOLEM EDITION - ROZSÁHLÝ MODEL FYZIOLOGICKÝCH SYSTÉMŮ. In Medsoft 2011
11. Jiří Kofránek: KOMPLEXNÍ MODELY FYZIOLOGICKÝCH SYSTÉMŮ JAKO TEORETICKÝ PODKLAD PRO VÝUKOVÉ SIMULÁTORY. In Medsoft 2011
12. Filip Ježek, Marek Mateják, Pavol Privitzer: Simulace tlakových a průtokových křivek u různě velikých pacientů s pulsatilní srdeční podporou. In Medsoft 2011
13. Mateják,M., Kofránek,J.: Quantitative human physiology – rozsiahly model fyziologických regulácií ako podklad pre lekársky výukový simulátor. 18. Konferencia Slovenských a Českých Patofyziológov, Lekárska fakulta UPJŠ Košice, 9.-10. september 2010, (Roman Beňačka Ed.), Equilibria s.r.o. Košice
14. Privitzer,P., Mateják,M., Šilar,J., Tribula,M., Kofránek,J.: Od modelu k simulátoru v internetovom prehliadači. 18. Konferencia Slovenských a Českých Patofyziológov, Lekárska fakulta UPJŠ Košice, 9.-10. september 2010, (Roman Beňačka Ed.), Equilibria s.r.o. Košice
15. Marek Mateják, Jiří Kofránek: Rozsáhlý model fyziologických regulací v modelice. MEDSOFT 2010. Praha: Agentura Action M, Praha 2010, str. 66-80. ISSN 1803-81115
16. Jiří Kofránek, Matoušek Stanislav, Marek Mateják: Modelování acidobazické rovnováhy. MEDSOFT 2010. Praha: Agentura Action M, Praha 2010, str. 66-80. ISSN 1803-81115
17. Jiří Kofránek, Marek Mateják: Electrophysiology in Modelica, Introduction to large models: Quantitative Human Physiology; Modeling Multiscale Cardiovascular and Respiratory System Dynamics, Physiome Project – National Simulation Project. August 23-27,2010, N140 William H.Foege Building, Univesity of Washington, Seattle, WA 98195; <http://www.physiome.org/Course/Session_1/index.html>
18. Jiří Kofránek, Marek Mateják, Pavol Privitzer: Dřinu strojům – moderní softwarové nástroje pro tvorbu simulačního jádra výukových programů, MEFANET 2009, 3. Konference lékařských fakult ČR a SR s mezinárodní účastí na téma e-learning a zdravotnická informatika ve výuce lékařských oborů, Masarykova Univezita, Brno, 2009, ISBN 978-80-7392-118-7
19. Jiří Kofránek, Marek Mateják, Pavol Privitzer: Kreativní propojení objektových technológií pro tvorbu výukových biomedicínkých simulátorů. **OBJEKTY 2009**,

Ročník konference, Hradec Králové, 5.-6.11.2009, (Pavel Kříž Ed.), Gaudeamus, Hradec Králové, s. 1-21. ISBN 978-80-7435-009-2

1. Jiří Kofránek, Pavol Privitzer, Marek Mateják, Martin Tribula: Akauzální modelování – nový přístup pro tvorbu simulačních her. MEDSOFT 2009. (Milena Zeithamlová Ed.) Praha: Agentura Action M, Praha 2008, str. 31-37. ISBN 978-80-904326-0-4
2. Jiří Kofránek, Marek Mateják, Pavol Privitzer: Causal or acausal modeling: labour for humans or labour for machines. In Technical Conmputing Prague 2008, 16th Annual Conference Proceedings. (Cleve Moler, Aleš Procházka, Robert bartko, Martin Folin, Jan Houška, Petr Byron Eds). Humusoft s.r.o., Prague, 2008, ISBN 978-80-7080-692-0. CD ROM, str. 1-16, [Online] http://www2.humusoft.cz/kofranek/058\_Kofranek.pdf.
3. Marek Mateják, Jiří Kofránek, Jan Rusz: Akauzální „vzkřísení“ Guytonova diagramu. MEDSOFT 2009. (Milena Zeithamlová Ed.) Praha: Agentura Action M, Praha 2008, str. 105-120. ISBN 978-80-904326-0-4
4. Jiří Kofránek, Jan Rusz, Marek Mateják: From Guyton’s graphic diagram to multimedia simulators for teaching physiology. (Resurection of Guyton’s Chart for educational purpose) **Proceedings of the Jackson Cardiovascular-Renal Meeting 2008**. (Stephanie Lucas Ed,), CD ROM, 11. pp.
5. Marek Mateják, Jiří Kofránek: [Modelica vs. blokovo-orientované jazyky matematického modelovania.](http://patf-biokyb.lf1.cuni.cz/wiki/_media/modelica_vs.pdf?id=nase_publikace&cache=cache) In **OBJEKTY 2008** (Žilina SR): Žilinská Univerzita, 20.-21.11.2008, (Jan Janech Ed.), Edis, Žilina, s. 79-94. ISBN 978-80-8070-923-3
6. Marek Mateják: SVK 9/ Jazyky pre fyziologické modelovanie
7. Kofránek Jiří, Andrlík Michal, Mateják Marek, Matoušek Stanislav, Privitzer Pavol, Stodulka Petr, Tribula Martin, Vacek Ondřej: Škola (multimediální simulační) hrou: využití multimediálních aplikací a simulačních modelů ve výuce patologické fyziologie, Sborník 17. Konference českých a slovenských patofyziologů, 11-12. září 2008, ISBN 978-80-254-0863-6, CD ROM příloha

Publikace autora bez vztahu k tématu disertace

1. s IF (uvést hodnotu IF)
2. Jiří Kofránek, Stanislav Matoušek, Jan Rusz, Petr Stodulka, Pavol Privitzer, Marek Mateják, Martin Tribula,: Atlas of physiology and pathophysiology - web-based multimedia teaching tool with simulation games. Computer Methods and Programs in Biomedicine 2011, **IF: 1.516**, ISSN: 0169-2607.
3. bez IF
4. Kulhánek T., Mateják M., Šilar J.,Privitzer P., Tribula M., Ježek F., Kofránek J.: Hybridní architektura pro webové simulátory. MEDSOFT 2013, str. 115-121, ISSN 1803-8115
5. Šilar J., Stavåker K., Mateják M., Privitzer P., Nagy J.: Modeling with Partial Differential Equations - Modelica Language Extension Proposal. OpenModelica Annual Workshop February 3, 2014
6. Kulhánek T.,Mateják M., Šilar J.,Privitzer P., Tribula M., Ježek F., Kofránek J.: RESTful web service to build loosely coupled web based simulation of human physiology: IEEE EMBC 2013, Osaka, Japan 3-7 July 2013, late breaking research poster, published in August 2013, Trans JSMBE, ONLINE ISSN: 1881-4379
7. Kulhánek T, Mateják M., Šilar J.,Privitzer P., Tribula M., Ježek F., Kofránek J. Hybrid architecture for web simulators of pathological physiology. EFMI STC 2013 Prague 17-19 April 2013. WS1 workshop.
8. Privitzer P., Šilar J., Kulhánek T., Mateják M., Kofránek J.:Simulation Applications in Medical Education. EFMI STC 2013 Prague 17-19 April 2013. WS1 workshop.
9. Ježek, Filip, Kroček, Tomáš, Mateják, Marek, Kofránek, Jiří: Zkušenosti z inovace výuky modelování a simulace na FEL ČVUT. In MEDSOFT 2012, (Milena Ziethamlová Ed.) Praha: Agentura Action M, Praha, str. 139-146, ISSN 1803-8115.
10. Jiří Kofránek, Pavol Privitzer, Marek Mateják, Stanislav Matoušek: Use of Web Multimedia Simulation in Biomedical Teaching, Worldcomp 2011, Las Vegas.
11. Martin Tribula, Marek Mateják, Pavol Privitzer: Webový simulátor ledvin. MEDSOFT 2010. Praha: Agentura Action M, Praha 2010, str. 201-210. ISSN 1803-81115
12. Jiří Kofránek, Pavol Privitzer, Marek Mateják, Ondřej Vacek, Martin Tribula, Jan Rusz: Schola ludus in modern garment: use of web multimedia simulation in biomedical teaching. Proceedings of the 7th IFAC Symposium on Modeling and Control in Biomedical Systems, Aalborg, Denmark, August 12-14, 2009, 425-430
13. Jiří Kofránek, Marek Mateják, Stanislav Matoušek, Pavol Privitzer, Martin Tribula, Ondřej Vacek: School as a (multimedia simulation) play: use of multimedia applications in teaching of pathological physiology. In MEFANET 2008. (Daniel Schwarz, Ladislav Dušek, Stanislav Štípek, Vladimír Mihál Eds.), Masarykova Univerzita, Brno, 2008, ISBN 978-80-7392-065-4, CD ROM, str. 1-26, [Online] http://www.mefanet.cz/res/file/articles/prispevek-mefanet-anglicky-kofranek.pdf
14. Kofránek Jiří, Mateják Marek, Matoušek Stanislav, Privitzer Pavol, Stodulka Petr, Tribula Martin, Vacek Ondřej, Hlaváček Josef: Škola (simulační) hrou. Sborník 17. Konference českých a slovenských patofyziologů, 11-12. září 2008, str.14
15. Kofránek Jiří, Privitzer Pavol, Stodulka Petr, Tribula Martin, Mateják Marek: Metodologie tvorby webových výukových simulátorů. Sborník 17. Konference českých a slovenských patofyziologů, 11-12. září 2008, str.19-20

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)
4. Uchopitelností pro počítač se myslí, že dokáže daný model numericky řešit - pro dané nastavení dokáže simulovat stav každé proměnné modelu v čase. [↑](#footnote-ref-4)
5. Uchopitelnost pro člověka znamená hierarchické schémata, které jsou velmi Intuitivní, je možné je libovolně přeskupovat a jejich komponenty jsou

   parametrizovatelné a mnohonásobně použitelné. [↑](#footnote-ref-5)