Abstract

The formalization of integrative physiology in the level of computer simulation is presented. For integrative purposes each physiological variable is exactly defined as physical quantity with physical unit. The relations between these variables are deduced from the selected physical laws called first principles. The number of these principles was minimalized such as axioms in mathematics or fundamental equations in physics. The presented set of first principles is compact enough to describe the largest model of integrative physiology in year 2012. For example using the base principles from physical chemistry, it should be possible to formalize all known chemical and electrochemical processes. All selected first principles are formalized with respect to integration into complex physiological systems. The methods of integration use mathematical logic with comparison of physiological models based on compliance with physiological experiments. The integration methods are defined to always improve the model to eliminate stagnation of development of new complex theories.

The results of this thesis are mathematical relations, using which should be possible to interpret the physiological knowledge, which is based on physical and chemical processes. All variables and parameters have physical meaning, what allows for accurate physical integrating their relations together. The physical meaning of parameter is critical also for next development of theories, where the known values of parameters can be recalculated to new theories or scaled to be patient invariant. The scaling of parameters to height, body weight, skin surface and so on make them almost independent of patient, what brings possibility to define individual patient only with a small set of parameters.

The known physiological processes and systems was formalized using the first principles. The new approach was designed based on graphical schemes, which exactly define the complex model. These schemes are self-describing and allows for flexible rearranging the model. Even more, the computer code is automatically generated from these schemes, what allows the computer simulation of the formalized physiological systems. The created support of these kind of implementation of new physiological theories was tested on implementation of the best, most complied mathematical model of human physiology of the year 2012, on new integrative acid-base theory and on new development of integrative model of hemoglobin allosteric equilibrium. The new integrative acid-base model with blood gas transport extends the most complied model. It improves of stability of the whole model and it is more sufficiently describes the status of blood during oxygen and carbon dioxide transport even during respiratory or metabolic acid-base disorders.

Methodology is set, that after each integration, reduction and extension of the model, it must be at least as good as all preceding theories and models. The language of this complex physiological theory could be Modelica with physiological libraries behind, because it already has a huge commercial and noncommercial support.

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Dedication

This thesis is dedicated to Dr. Tom G. Coleman, professor emeritus in University of Mississippi Medical Centre, who inspired me the most with his complex work on field of integrative physiology in level of computer simulation and from whose work I have established my view of integrative physiology formalization.

# Introduction

Having detailed computer simulation, which can predict the behavior of the system is a dream of many scientist. However, in the world of physics many predictions are already possible. Even in chemistry in year 2013 M. Karplus, M. Levitt and A. Warshell won the Nobel Prize for the development of multiscale models for complex chemical systems, which predicts the chemical reaction properties even for complex molecules. So why this kind of computer prediction should not be possible in complex physiology? What need to be done to reach that goal?

I have a strong belief, that for this purposes the physiological processes must be formalized in the meaning of physical generalization and mathematical integration. Formalization in the level of exact physical description should be the step in the right direction, because the physics generalize the processes in the nature. However, the human physiology is very complex and it must be described with respect to this complexity. So the effective and exact integration of the physiological knowledge could be the clue to the *in silico* predictions.

There are already many observations of relations between physical quantities in physiology. Many of them are statistically significant. However the statistical approximation is not enough if there are connected more than two variables. For this reason the blind nonphysical relations should be more studied and described using physical processes. The building mathematical relations between variables in physiology must be represented by designing the theory based on first physical principles. As a result from base principles the relation even between more than two variables can be easily deduced. The mathematical deduction can strongly maintain the consistence of the theory without being in dispute with other parts of the theory. However, these theoretical relations must always fit the observations. If they does not fit the measurements, the theory must be rearranged.

The implementation of exactly formalized theory is named a model. Thanks to mathematical relations it should be possible to implement the formalized theory into almost any computer language, even to the list of few types of computer processor instructions. However there are huge difference in effectiveness and readability of these implementation, which are critical for verification of the model. Having the last generation of computer language designed for implementation of complex physical models the step from theory to model is minimalized and the work can be more focused on to the formalization of theory than on implementation of theory to computer language. Thanks to this new approach in computer science the complex integrative physiological theory has almost the same meaning as the complex integrative model.

The formalization of integrative physiology can be understand as finding the base principles from physics and to define the methods how to integrate these base principles together into one complex model of human physiology. This approach already started in Mississippi in sixties 19th century. This work follow up to this development from University of Mississippi Medical Centre by finding better base principles, finding better way to implement the model and finally by extending the model with better principles of chemical processes such as presented in hemoglobin model with three different ligands.

In the beginning of this work was reimplementation of different physiological models to Matlab/Simulink (Mathworks corp., U.S.). This approach was very time-consuming with only a consistency-verification purposes. The models in Simulink were not simplified and not self-describing. Even more, these models was unable to easy extended or modified. That was the reason why we go away from causal simulation tools and we starts to look for new possibilities how to formalize the physiological model for computer simulation (Mateják, et al., 2008). The solution for our criteria of computer language was achieved by Modelica language, where I easily implemented original Guyton model from year 1972 (Mateják, et al., 2009). One year later I implemented to Modelica the model QHP (Mateják and Kofránek, 2010). This model was one of the main result of our very successful national project „e-Golem: mediacal learning simulator of human physiological functions as a backgound of e-learning teaching of critical care medicine“ (2006-2009, MSM/2C, 2C06031). The next model, I implemented in Modelica, was HumMod 1.6 (Mateják and Kofránek, 2011). This implementation has an automatic comparison of output values with original model, so it can describe all experiments for which was designed the original one. Having our implementation it starts to be very easy to extend the model with new acid-base theory, blood gases transport or new cardiovascular details. So, in year 2012 I implemented into the model the new blood oxygen status model of Siggaard-Andersona (Siggaard-Andersen and Siggaard-Andersen, 1990). The Model was able to simulate for example the support of artificial ventilation or even extravascular oxygenation (Mateják, et al., 2012). These and many other inputs such as infusions, dialyses, transfusions or hemorrhage was designed for educational simulations in project „Virtual patient - Simulator for medical education“ (2011-2014, MPO/FR, FR-TI3/869). In the same manner of educational simulation was in the model tested also different scenarios of acid-base and respiratory disorders, for example the ketoacidosis (Mateják, 2013), where was already implemented the new calculation of acid-base as a result of electroneutrality with calculation of each significant chemical substance. One of my significant result of this work was separating of the main principles from the model into the Modelica library called Physiolibrary (Mateják, et al., 2014). This library won the free Modelica library awards at 10th International Modelica Conference in year 2014 in Lund, Sweden. Having for example these base principles for hydraulic calculation of cardiovascular system, we was implemented and identified the more detailed cardiovascular models (Kulhánek, et al., 2014). Working on the physical chemistry theory behind physiology I formalized the first principles of electrochemical processes in year 2015. Using these chemical formalizations it is possible to implement almost each equilibrium from physical chemistry. And more, I designed also the general principle of allosteric equilibria, which was 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 the one model, which I named Physiomodel.