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MODEL OF CIRCULATORY, BLOOD GASES TRANSPORT AND ACID-BASE FOR MEDICAL SIMULATORS AND INTENSIVE CARE CLINICAL AID SYSTEM

Doctoral Thesis

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This thesis is dedicated to Johan, without whom it could have never been completed.

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The author declares authorship of a major part of the simulator design, described in chapter "Model visualization for medical simulators" and supervision over the development. The author acknowledges Bc. David Polák for the marvelous implementation and other co-authors of our first applications (Jan Šilar, Arnošt Mládek, David Polák and Jiří Kofránek) for their contributions. Not the least, the graphical team (Veronika Sýkorová, Martin Brož, Klára Ulčová) are to be acknowledged for their graphical work.

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Annotation

Integrative mathematical models in medicine have basically three purposes: to test the consistency of contemporary physiological understanding, to built demonstrative educational simulators and to predict patient-specific outcome using clinical aid systems. Presented thesis covers all three topics.

The proper blood circulation is a necessary, but not sufficient condition to ensure proper cell metabolism. It is therefore required to include also the respiration, gas transfer and acid-base balance into the consideration. Contemporary complex integrative models do not sufficiently include the acid-base balance and even dedicated acid-base models are not considering bodily compensations in dynamics.

Thus, we present an extendable mathematical proof-of-concept model of the circulatory system, coupled with oxygen and carbon dioxide transfer, with dynamic respiratory control and metabolic acid-base compensatory and correction mechanism. The ion balance and metabolism effects and osmotic water balance are optionally included as well. The general methodology for development of integrative physiological model is then formulated.

The model, validated by published clinical observations, enables better understanding of relations among circulation, respiration, blood gases transfer, ion composition and volume homeostasis. However, to make use of the model in education and to enable collaboration with clinicians, accessible simulators are required. Therefore, a technology for rapid development of web-based educational simulators has been developed and a set of educational simulators have been drafted.

Only under the precondition that clinicians will fully understand the model mechanics and its limitations, the model could be used to gain deeper insight into the individual patient state, predict his future state and virtually test the interventions using a clinical aid system, which would reduce mistakes and iatrogenic damages. Model usage for an intensive care unit aid system is proposed, largest obstacles are identified and further work is suggested.

Keywords: *Model, physiology, homeostasis, circulation, acid-base, simulator*

Anotace

Integrativní matematické modely v medicíně mají v zásadě tři účely: testovat konzistentnost současného fyziologického porozumění, vytvářet demonstrační vzdělávací simulátory a předpovídat specifické výsledky zdravotních stavů pacienta za pomoci systémů, které zkvalitní a zjednoduší zdravotní péči. Prezentovaná práce pokrývá všechny tři zmiňované účely.

Správný krevní oběh je nutnou, ale nikoli postačující podmínkou pro zajištění správného buněčného metabolismu. Proto je nezbytné zahrnout do úvah taktéž dýchání, přenos plynu a acidobazickou rovnováhu. Současné komplexní integrativní modely dostatečně nezahrnují acidobazickou rovnováhu a dokonce ani samostatné acidobazické modely neberou v úvahu dynamiku tělesných kompenzací.

Proto představujeme rozšířený model matematického pilotního modelu oběhového systému spolu s přenosem kyslíku a oxidu uhličitého s dynamickou regulací dýchacích cest a kompenzačním a korekčním mechanismem metabolické kyseliny. Taktéž zahrnujeme účinky iontové rovnováhy a metabolismu a osmotické vodní rovnováhy. V práci navrhujeme základní metodiku vývoje integrativního fyziologického modelu.

Model, ověřený zveřejněnými klinickými pozorováními, umožňuje lepší pochopení vztahů mezi oběhem, respirací, přenosem krevních plynů, složením iontů a objemovou homeostázou. K tomu, aby byl model využíván ve vzdělávání a umožněna spolupráce s lékaři jsou ovšem taktéž zapotřebí vhodné simulátory. Proto jsme vyvinuli technologii pro rychlý vývoj webových vzdělávacích simulátorů a současně navrhli sadu několika vzdělávacích simulátorů.

Pouze za předpokladu, že dosáhneme plného porozumění modelům a jejich omezením ze strany lékařů, může být model využíván pro získání hlubšího pohledu na stav pacienta, předpovídat jeho budoucí stav a prakticky testovat intervence v systému klinické pomoci. Použití modelu pro potřeby intenzivní péče o pacienty je navrženo, ale vyžaduje širší rozpracování této problematiky.

Klíčová slova: *Model, fyziologie, homeostáze, cirkulace, acidobáze, simulátor*

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Glossary

BE - base excess - a concentration of strong acid required to normalize the pH to 7.4 at pCO2 40 torr (5.3 kPa), Unless specifically stated, we consider it to be the same as BEox

BEox - base excess for fully oxygenated blood

FMI - Functional mockup interface is a standardized definition of API function, which allows communication with the model

FMU - Functional mockup unit is a package (a zip compressed folder) which implements FMI standard, i.e. a model saved in shareable format..

ICU - intensive care unit

ISF - interstitial fluid

pCO2 - partial pressure of the carbon dioxide

pO2 - partial pressure of the oxygen

SBE - standard base excess - recalculated as if the concentration of the hemoglobin was 5.3 g/dl (around one third of normal) as a compensation for interstitial fluids.

SID - strong ion difference

UA - unmeasured anions. Consists of anions of organic acids (including the lactate), sulfates, ketone bodies and phosphates.

1 Introduction

"Ten physiologists ignorant of mathematics will get precisely as far as one physiologist ignorant of mathematics, and no further."

(Wiener 1948)

1.1 Motivation

The assessment and management of a patient in a critical condition is an urgently important mission. According to a survey, acid-base equilibrium is the most complicated and hardest to understand topic in nephrology (Jhaveri et al. 2013) and, at the same time, it is considered as a basis for understanding nephrology (Leehey and Daugirdas 2016). Our preliminary microsurvey among specialists at the General University Hospital in Prague, conducted in early stages of this project, also indicated doubts in homeostasis knowledge among the intensive care unit (ICU) physicians.

Engineers develop dependency models (white box). The reality is however too complex to grasp as a whole. Therefore, medical doctors tend to use experience (black box) models. Our motivation is to explain the dependencies by developing educational aids. These aids, based on mathematical models, help medical students and doctors compare their judgement and better understand the often qualitatively contradicting processes.

The presented thesis is a foundation towards intensive care clinical aid system, built upon a mathematical model of circulation, fluid resuscitation and bodily homeostasis. The clinical aid aims at reducing iatrogenic damage (e.g. overcompensation of acid-base disturbance), avoid potential mistakes and better predict future states.

1.2 Structure of the dissertation

The main chapter is dedicated to the development of a set of physiological components and models. This chapter is divided into subsystems, where physiological background as well as the contemporary models are discussed separately. Particular subsystems are then integrated together and validated.

Next two chapters discuss the methodology of constructing large physiological models based on the author's experience and possible use of the physiological model as an clinical aid system. The obstacles as well as proposed approaches are described there.

The following chapter Model visualisation for medical simulators deals with a method of visualisation of complex models in the form of interactive web-based simulators. The results of this chapter include a set of simulators based on the Physiological model. The simulators are accessible (and runnable) at http://physiome.cz/apps/jezek/.

Due to the large span of topics, the state of the art is discussed in each chapter separately.

1.3 Circulation alone is not enough

Even though an enormous effort has been put into the study of human circulation, dealing with circulation alone is a huge simplification. The primary objective is to transfer blood gases and nutrients to the cells as well as metabolical waste from the cells. But circulation alone does not ensure proper cell metabolism - the maximal cell oxygen consumption depends on both maximal respiration and maximal circulation flows at once (Wagner 2011), therefore the circulation is not the only predictor.

Managing the circulation should not only involve the blood, but also the blood gases, oxygen (O_2) and carbon dioxide (CO_2), because tissue respiration is not only about lung respiration and circulating gases, but is also heavily influenced by acid-base and ion balance. The most important complication of tissue hypoperfusion is local acidemia caused by local hypercapnia and, in extreme cases, by local lactate acidosis (Kamel and Halperin 2016). Circulation is also sensitive to change of vascular volume and thus the volume is carefully regulated by osmotic balance and a number of other mechanisms. Therefore, to correctly evaluate the patient state and future prognosis, an integrative model covering all these parts together is inevitable.

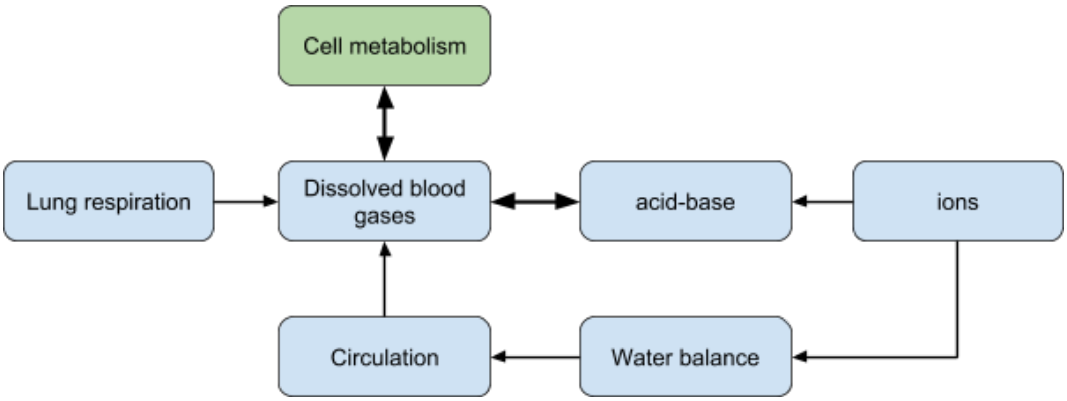


Figure 1: Basic schematics of the systems, ensuring a proper cell metabolism. In addition, all the systems have their own regulation mechanisms

1.4 The static assessment of homeostasis is not enough

All contemporary acid-base computation models (Siggaard-Andersen and Siggaard-Andersen 1990; Rees and Andreassen 2005; Wolf 2013) are assessing the steady state only. At the bedside, the dynamics are usually assessed using compensation diagrams

(e.g. (Engliš 1972)) or so-called Boston or Copenhagen rules (Severinghaus 1993; Wooten 2010). However, multiple disorders and compensations can occur simultaneously and the iatrogenic interventions can act even against own bodily compensations.

Not all the information provided by the ICU measurements are fully exploited. The acid-base markers could be used to gather deeper understanding of the inner pathophysiological processes, especially when a time-series is measured.

The presented research aims at developing a dynamic full-body model of circulatory, respiration, gas transport and acid-base balance to investigate the dynamics and to uncover the underlying pathogenesis and predict further progress.

1.5 A model is not enough

> *If the difficulty of a physiological problem is mathematical in essence, ten physiologists ignorant of mathematics will get precisely as far as one physiologist ignorant of mathematics, and no further. If a physiologist who knows no mathematics works together with a mathematician who knows no physiology, the one will be unable to state his problem in terms that the other can manipulate, and the second will be unable to put the answers in any form that the first can understand.*
>
> *(Wiener 1948)*

In such cases, a multidisciplinary cooperation is essential for fruitful results. To establish collaboration with clinicians, it is necessary to let the models be understood. Mutual understanding is a crucial precondition for any close cooperation. For the implementation of clinical aid systems, it is necessary to understand the complex models, how they were simplified and what are their limitations - it can not be done the other way around.

For such complex tasks a mathematical model alone is not satisfactory to grasp all the concepts and relations. Instead, a demonstration tool is required. Therefore we have prepared a system for rapid development of visual model simulators, making the model accessible via web-based application to users without technical background or expensive modeling tools. The simulation tool enables us to change model parameters and instantly observe the outputs. The model behavior could then be examined, learned from or opposed by a wide audience of medical students and professionals.

1.6 Dissertation goals

1. Prepare an extensible modeling platform for description of circulation, blood-gases, acid-base and water balance and develop a proof-of-concept model integrating all mentioned areas, able to describe and prognose the patient in critical state. The model should be based on contemporary quantitative knowledge of the aforementioned systems and allowed to make some compromises between complexity and practical usability.
   a. Development of complex models is a long-term, conceptual work. Mciodern modeling tools allow endless possibilities to build more elaborate and robust constructions. For fulfillment of the main goal and to ease further extensions, it is beneficial to follow a set of rules. As a partial goal, a methodology for complex physiological model development and extension should be formulated.
   b. The design and adoption of the clinical aid system is a lasting process, connected with a number of issues. Another partial goal is to draft the model usage for a clinical aid system.
2. To answer the concerns posed in the preceding section, a secondary goal is to design a technology for visualisation of the model for demonstrative and explanatory purposes.
   a. Partial goal is to develop a proof-of-concept set simulators, demonstrating the acid-base and electrolyte disorders.

2 The physiological model

"All models are wrong but some are useful"

(Box 1979)

In the motivation, we mentioned, how the acid-base is connected to the circulation and the overall state of the patient. Acid-base balance defines the homeostasis, which is a common environment for the whole organism. By understanding acid-base, and especially how and why it changes, we hope to predict the overall patient state and to ensure a preferred outcome.

Classic physiology textbooks (e.g. (Hall 2010; Silverthorn 2018)) offer deep insight into the physiology, but provide only qualitative knowledge. Many of the principles are already followed in the clinic, but it is hard to consider them all at once. That is where large computational models could be useful. Some of these phenomena, although already covered in the textbooks, have never been properly investigated and quantified (Wolkenhauer 2014). In order to predict the future patient state, we have to construct quantitative models, which differ from patient to patient and in time can even change for the same patient (Лищук et al. 2016, 2017).

Large integrative models do usually play a different role than specific, "small" models (Carson and Cobelli 2014). First of all, they are not intended to be identified on a specific patient, because the complexity and the number of unknowns would simply not allow it. Instead, they serve as a specific form of insight, a compendium of knowledge, where we test our hypotheses (Kofránek et al. 2017). If such models fit the data, or at least the trends, then the knowledge may be considered complete. If not, it suggests missing knowledge. Even the contemporary most advanced models do not exactly fit the data (Kurtz et al. 2018).

In a human body (and physiology as a whole), everything is interconnected and complex. We must simplify greatly, taking care to retain the main principles driving the physiological processes. Following the golden statement "All models are wrong but some are useful" (Box 1979), it is therefore crucial to define areas, where our models can be of some use.

Therefore, the aim of this chapter is to specify model requirements and use-cases. Based on the requirements, particular model components are developed and validated against expectations. The sub-components are integrated and the resulting model is simulated according to the use-cases and validated against literature data.

2.1 Model requirements and assumptions

The primary objective of the physiological model is to mimic physiological reactions of a patient in critical conditions.

The primary use-case of the model is a demonstration tool to gain a deeper understanding of the physiological and pathophysiological processes taking place during hypoperfusion, acid-base compensation and homeostasis maintenance. A secondary use-case of such a model is a ground for a future clinical aid system, as discussed later. The model should be simplified as much as possible. We always assume an ideal patient in a supine position, without any physical activity and with a basal metabolism, which is a standard in ICU.

Time scale

The first required simplification is to limit our timescale. The target time spans, in which the models should be used is in a range of minutes to days, that is from approximately a half an hour to one week. Any processes, which occur faster are simulated as time-instant and all processes, which take longer (such as vascular remodelling) are neglected. The selected time range should however fit within a normal intensive care unit hospitalization timeframe.

Fast changes can usually be described using first principles physics, and their complexity and uncertainty rises with time.

A human body acts like a non-linear chaotic system, where small changes in any observable state may lead to completely different outcomes. Therefore, the time scale is a serious limitation especially for a clinical aid system. For explanatory educational models, this requirement is not as strict, but the possible variances from the model results should be emphasized.

This requirement thus prefers the simplification of continuous beat-to-beat heart operation and breath-to-breath respiration to minute averages. The pulsatile mode creates fast modes (changes within Hertz, with required sampling frequency of at least 10 Hz), which are in contrast to slow bodily regulations (minutes to hours, i.e. 10^{-3} Hz).

Circulation

The basic circulation model must be included to be able to simulate different perfusion rates, blood mixing, intravenous infusions etc. In fact, the acid-base and blood gases should act as an extension of the circulation model of various complexities.

This would enable extending virtually any circulatory model with blood-gases and acid-base, considering the effects of various tissues perfusion. Extensions by mechanical circulatory support systems, applying infusions etc. are also possible.

Circulating blood gases and ions

The blood gases, as well as ions, should be dissolved in the circulating blood medium.

This allows blood mixing from variously perfused tissue and lung parts, leading to an “apparent shunt” (as observed by Pauley (Paulev and Siggaard-Andersen 2004)). Every tissue hypoperfusion is accompanied with hypercapnic acidosis due to locally higher pCO_2 in the tissue and venous outflow. The severity of which may be investigated only by including

the circulation models into consideration. In extreme cases of low tissue pO_2, the cellular O_2 consumption is limited, followed by an increase of lactate production (Wagner 2011).

Acid-base disturbances

The model must consider the acid-base balance, which is normally regulated in a narrow range. The acid-base status has an important effect on a hemoglobin saturation curve, which greatly affects the blood gases transfer to the tissues, is also crucial for the correct function of the whole organism.

Additionally, the model should physiologically correct the acid-base disorders and predict the acid-base compensations during the time. Namely the respiratory disorders, caused by either obstructed or artificial ventilation, inspired CO_2, pathological shunts, uneven lung perfusion and other reasons, eventually leading to respiratory alkalosis or respiratory acidosis. Metabolic disorders include hyperchloremic, dilution or organic acid induced acidosis and hypochloremic, hypoalbuminemic or contraction alkalosis.

All mentioned disorders shall be modelled in acute and compensated state and with physiological dynamics in between.

Blood-volume and osmolarity

The model must incorporate dynamic volume changes between blood and extracellular fluid based on osmolarity. This would allow simulations of a volume therapy (e.g. by different solutions such as Gelofusine, saline, Ringer lactate, Ringer acetate, dextrose, mannitol etc.)

Potential usage as a basis for an intensive care unit clinical aid system

Since one of the intended uses of the model is to serve as a clinical aid system, it should be eventually identified on a particular patient, therefore it is important to consider the identifiability of the model. This puts limitations on the number of at-once identified parameters, because the computation complexity of naive identification rises exponentially with the number of parameters.

Validity

Quantitative physiological models are used for understanding, classification (identification of an unobservable variable) and prediction. The description of the physiology is however often only qualitative. The validity of the model can be quantitative, or structural.

Quantitative validity is an extent to which the model fits the data. The model should be valid in comparison to clinically accepted standards. The exact difference in value is not as important as the trends and reactions; that is, that a reaction to a particular phenomena is already contained within the model. Using mean data to fit nonlinear systems exactly is generally impossible and therefore only approximate mean fit is presented. Exact fitting on individual patients should be a topic of a future work.

The sometimes neglected structural validity is a marker of model credibility as it enables better understanding and therefore therefore should be also considered.

Extensibility

Preparation of such a model is an ongoing task, with a number of foreseen additions and corrections, as the particular requirements and use-cases of the model grow. The modeling framework should therefore allow easy extensibility. This is facilitated by using first-order principles (incl. mass and energy conservation laws, electroneutrality assumption etc.) where appropriate and, if possible, by maintaining the structural validity of the model.

Complexity

Computational complexity is the amount of resources a machine needs to calculate the results and has to be considered for both the educational use, where quick response is necessary and for clinical aid, where the identification requires many runs of the model. Large complexity could also lead to numerical problems and thus yield false results.

Structural complexity is also an important issue - we have to avoid building an unnecessarily complex model, which would preclude the user from understanding the true principles. Under structural complexity we understand a number of orders (states) and non-linearities. Unnecessary complexity also makes the identification harder. All parts included in the model should therefore be kept from being too unnecessarily complex.

2.2 Integrative physiological models

Guyton's model and its successors - the flagship of the integrative physiology

Guyton's model (Guyton et al. 1972) is a landmark in the field of integrative physiology. This model, presented as a famous diagram (Figure 2) changed the way physiology was perceived. The model, originally aimed at long-term regulation of body fluids, has been further extended to various usages from educational simulators to NASA investigations. This model was already implemented on a digital computer in the FORTRAN language.

The paper (Guyton et al. 1972) summed many of Guyton's previous models and findings into one large-scale model, taking into account autonomic and heart rate controls, antidiuretic, angiotensin and aldosteron hormones, tissue fluids and electrolyte balances, kidney dynamics, vascular stress relaxation and more, which at first glance seemed to be unrelated. This model allowed to study effects of particular systems on overall regulation and unlocking the dependencies could still be a valuable help for a today's physician (Magder 2012). To describe the model as a whole, one needs access to the whole monograph (Guyton et al. 1973). Due to the rising popularity of personal computers, several user simulators were developed, which were intended for physiology students (Coleman and Randall 1983). Guyton and his collaborators have improved upon this model since its inception in milestone publications which followed in 1986/88 and 1992.

The simulators changed their name throughout the time - started as Human (Coleman and Randall 1983), then with increasing ambitions QCP (Quantitative Circulatory Physiology), QHP (Quantitative Human Physiology) and as of current, HumMod (Human Model) (Hester et al. 2011). The first models have been made available as FORTRAN code, which made the underlying dependencies hard to understand. Following updates from 1986, 1988 and 92 were also published in FORTRAN. These models from the ancient time of computer simulation and modeling were mostly focused for research and for reasoning of physiological phenomena.

Anyway, since the publishing of HumMod, the model and simulator pathways were split, which means that it is possible to change the model without changing the simulator and vice-versa. Moreover, we can take the model alone and reimplement it in other languages (Jiří Kofránek et al. March 20-22 2011; Kofránek 2013; Matejak and Kofranek 2015). Allegedly, the Hummod developers recently reimplemented Hummod into the Modelica language for better maintenance (R. Hester, personal communication, August 2018)

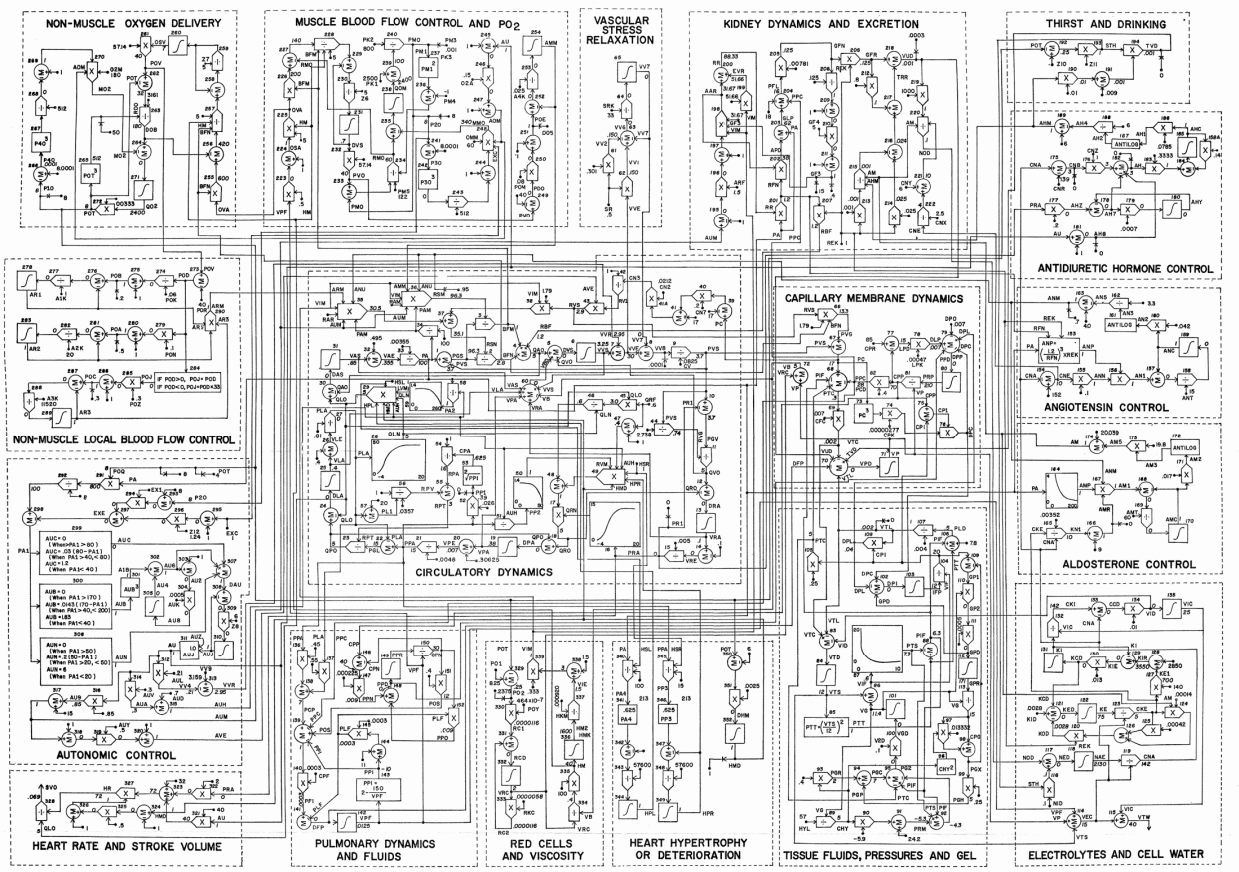


Figure 2: It is almost obligatory in a literature related to integrative physiological modeling to show the original Gyuton's overall regulation (Guyton et al. 1972) schema. However this drawing contains errors, "graphical typos", which were first corrected by Kofranek et al. (Kofránek and Rusz 2010)

Various other enhancements emerged based on this model. One for all - the Guyton's model is non-pulsatile, computing with mean pressures only. Werner et al (Werner et al. 2002) enhanced the model with a pulsatile circulatory core, leaving the other systems almost intact. However, although Gyuton's model has been validated many times against experimental data, it still fails the validation in particular cases, e. g. in Moss et al. (Moss et al. 2012) we can find examples, when it does not fit the expected experimental results. In our recent collaboration project we found out, that the model is not in correspondence with the salt-induced hypertension measurements data, one of the model's aims (Kurtz et al. 2018). Ironically, Guyton's model shaped generations of physiologists and changed the way we look at the kidney regulation of blood pressure which has already been criticized before (Henderson et al. 2010; Beard 2013, 2017).

Ikeda – regulation of body fluids

Ikeda et al (Ikeda et al. 1979) presented a nice complement to the Guyton model. Intended as a model of body-fluid regulation disorders, such as edema, dehydration or acid-base disorders, the model incorporates circulation, respiration, renal function and intra- and extra-cellular spaces and contains over 200 variables. As a nonstandard feature, the blocks of renal function and respiration are combined, so that acid-base disturbances could be studied over a wide range of time-scales.

However, the kidney acid-base balance is only based on the standard bicarbonate concentration and overall the model does not maintain the electroneutrality principle (as described in e. g. (Kofranek et al. 2007)). Similarly to Guyton's model, it is described as a network of interconnected analog adders, multipliers, and linear and nonlinear gain functions. This model receives some public attention even now, the most recent one being its implementation in the Berkeley-Madonna solver (Fontecave-Jallon and Thomas 2015).

Golem and Physiomodel – focus on acid-base

The Golem model (Kofránek et al. 2001) arises from the models of Ikeda and Guyton. It is based on the formulation of "the relationship of homeostasis of the internal environment (acid/base and electrolyte equilibrium, of transport of blood gases, of osmotic and volume homeostasis), respiration, circulation and kidneys including the regulatory influence of relevant hormones and the influence of some therapeutic procedures." However, although including a detailed acid-base compensation and ion status, the model still remains quite simplistic, containing only 39 non-linear differential equations. The circulation, for instance, is represented only in a steady state. More importantly, the acid-base calculations are not connected to ions, proteins and volume homeostasis at all. The complicated model implementation in Simulink effectively prevents any extension. Physiomodel (Matejak and Kofranek 2015), on the contrary, is a very complex model, based on the HumMod (Hester et al. 2011). The HumMod, aka the "best, most complete, mathematical model of human physiology ever created." (HC Simulation 2016) has been implemented into Modelica (Kofránek 2013) and notably extended in the field of acid-base (Guyton's originally did not

have acidbase, CO_2 transport and respiratory regulation). But this model, as a whole, is unsuitable for use as a clinical aid model. Given the model size, the isolation of a particular mechanism is unnecessarily complex. On the contrary, some parts are not elaborate enough (e.g. acid-base compensation).

Pneuma – cardio-pulmonary interaction

Pneuma (Fan and Khoo 2002) is a large integrative physiological model and its later extensions are aimed at cardio-pulmonary interaction and related regulations. Currently in version 3.0, however the acid-base balance is not addressed at all. It is implemented in simulink as a set of adders, multipliers and function blocks. For better clarity, we have also reimplemented the model into the Modelica, as a basis for future educational simulators (Bundil 2014).

Andreasen and Rees – circulation and whole-body acidbase

Rees and Andreassen (Rees and Andreassen 2005) and (Andreassen and Rees 2005) presented a mathematical model based on the physicochemical description of the Siggaard-Andersen blood acid-base chemistry, including the interstitial fluids and tissue compartments. The effects of the circulatory system on pulmonary shunts is also included, but the tissues can not be separated and their perfusion observed alone. Wolf et al. (Wolf and Deland 2011b) claim, that the generality of the model is limited, because the "fundamental model parameter values were chosen to achieve this end". This could however be claimed for their model as well.

The acid-base chemistry is based on the calculation of a buffer base (BB) and compared to the SID and ion composition. The ions are however not included in the model and also the acid-base compensation is not predicted. In addition, due to the chosen modeling approach it might be problematic to extend the model modularly. Therefore this approach is not suitable as an universal basis for a potentially complex model of inner homeostasis.

Wolf – the complex model of acid-base equilibria

The physicochemical approach to acid-base (Stewart 1981) inspired Wolf and Deland to present a whole body acid-base and water balance model, including erythrocytes, plasma and interstitium, based on fundamental laws of physical chemistry (Wolf and Deland 2011b). This model has been further extended to take cells into account (Wolf 2013). This model is aimed solely at acid-base and water redistribution among the four compartments (erythrocyte, plasma, interstitium and cells) and is only the steady-state balance of the venous compartment, therefore no active bodily compensations are taken into account. The arterial values, namely arterial pCO_2 (normally used at the bedside as a respiratory disorder marker) are transformed into venous values. To make use of the model, we have also reimplemented this model in the Modelica language (as a supplement to (Ježek and Kofránek 2018)). This model is an impressive example of the power of first principles in biochemical modeling,

where the acid-base status is computed based on Donnan balance on the membrane and osmotic balance. However it also suffers from its principal drawbacks, such that some parts (usually those well-known) are modelled with great detail (e.g. calcium ionization, oncotic pressure), whereas some other (unknown or hard to measure) are just wild guesses (e.g. the concentration of interstitial albumin is hard-set at ⅓ of the plasmatic concentration, or the H+ concentration in cells is constantly set at 1/10 of the nominal concentration). Without any sensitivity analysis of the guessed parameters, the value of the model is at the very least questionable.

Other models

The list of integrative physiological models above is by far not complete, as a variety of other models exists, both large and small, built for particular or general usage, but those above were selected as significantly related to the specified requirements. A thorough overview of other respiratory and acid-base models could be found in (Mogensen 2011), a complex approach to multiscale integrative physiology is described in (Hunter and Nielsen 2005) and repositories of a number of physiological models are listed in (Kofránek and Ježek 2018b).

2.3 Development of the Human physiology model

Since none of the contemporary integrative models above fulfills the requirements, we have to construct a new model. This model is based on a number of simpler, already known models. Even the integration of already known models is a demanding task, because the models have been validated on different individuals (or datasets) and even slight difference on inputs may lead to large inconsistencies in the feedback loops. All values must therefore be carefully set and, if necessary, some of the parameters fine-tuned.

Conceptually, a single huge, complicated all-purpose model is not appropriate for all use cases. First, the complexity of such a model is high and unnecessary for simpler tasks, and secondary, limiting the complexity keeps the model and assumptions understandable and eases model debugging.

Instead of a huge black-box model, we prefer a combination of compatible components, tailored for the particular usage.

The human physiology model can be divided into the following components and described separately:

- The cardiovascular system has a lot of attention. Also identification of the (basic) circulation is an already solved problem, at least in theory.
- Blood-gases transport and acid-base are an undividable submodel, as majority of oxygen is bound to the hemoglobin in a competitive binding with carbon dioxide. Carbon dioxide dissolved in plasma dissociates to dissolved HCO_3^-, which affects the pH, which in turn affects the oxygen dissociation curve of hemoglobin.

- Respiration and a tissue metabolism is built on the two preceding models. The alveolar ventilation is regulated to ensure the required partial pressure of blood gases in the arterial segment. The tissue metabolism then consumes the O_2 and gives off the CO_2 to the bloodstream. Multiple tissues with different perfusion can be combined together. The metabolism of tissues is disturbed with low pO_2, resulting in move from an aerobic metabolism to anaerobic one, associated with production of lactate.
- The metabolic acid-base compensation is realized by the kidneys, which regulates the amount of expelled ions and HCO_3^- (thus, the lost BE) by NH_4^+ excretion and titratable acidity of the urine. Various phenomena (like vomiting and diarrhea and a number of others) lead to ion disturbances.
- The interstitial fluid provides a large (and sometimes neglected) buffer zone, which affects especially acute acid-base disturbances and fluid balance. Fluid balance is a dynamic domain, where the water flows between bodily compartments (most simplified between plasma and interstitium) driven by osmotic (and oncotic) gradient.

Unless indicated otherwise, we limit ourselves to a description of the implemented model, as the physiological function is better described in medical textbooks (Hall 2010; Lumb 2012; Kamel and Halperin 2016; Silbernagl and Despopoulos 2016; Silverthorn 2018).

2.4 Model implementation

The Modelica language (Fritzson and Engelson 1998) is a promising tool for authoring biomedical models (Kulhánek et al. 2014; Kofránek and Ježek 2015), 2018.

Modelica is an object-oriented equation based modeling language, aimed at physical modeling of complex systems. Most important, a computation causality of the model is inferred automatically at the compile time and does not have to be specified by the author. This principle, already exploited by other simulation tools (e.g. the Mathworks SimScape) allows for great component reusability and structural plausibility. A number of development tools, both proprietary and open-source, are available (see a list at the (Modelica Association 2017)),

We have published a number of articles about the usage of Modelica elsewhere and therefore would kindly redirect the curious reader to refer to published sources (e.g. (Bundil 2014; Doležalová 2014; Kalecký 2015; Ježek et al. 2017)). An attached paper Lumped models of the cardiovascular system of various complexity (Ježek et al. 2017) provides a quick introduction into the main principles of the Modelica language. In line with the modeling methodology described in our paper (Ježek et al. 2017), we continue using the Physiolibrary (Mateják et al. 2014), structuring model in visual levels and using inheritance to minify the repeating the code.

To keep the model easily composable, all components are based on the circulation model. The blood gases as well as solutes are circulating within the blood medium. The

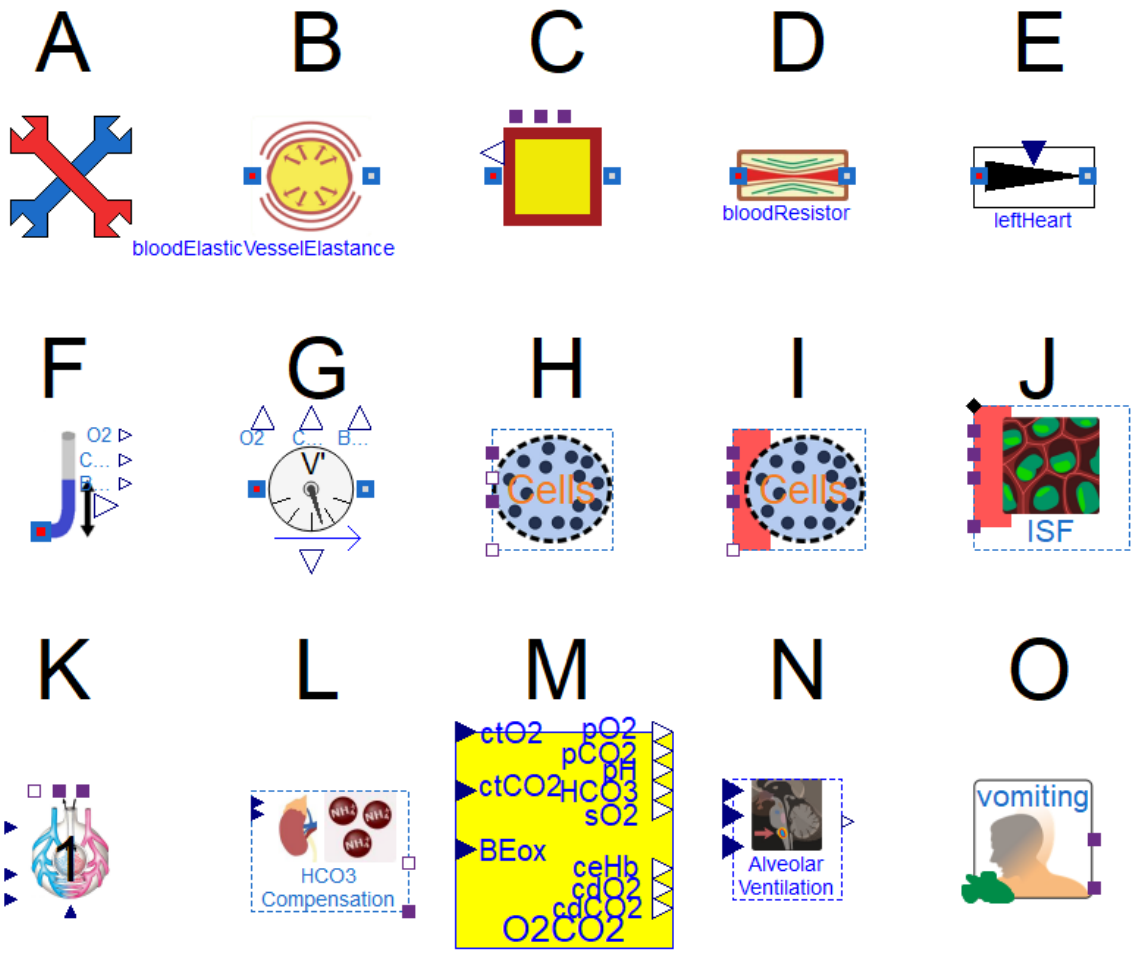


Figure 3: Icons of the main model components:

A: ModelSetting class, which allows to set parameters and conditions for the whole model.

B: Elastic compartment generate pressure based on its current volume. Contains dissolved blood gases and ions within its volume.

C: Constant volume contains dissolved blood gases and ions within its constantly-set volume.

D: Resistance creates resistance to the blood flow

E: Blood pump pumps blood.

F: Pressure sensor reads pressure and solutes from the bloodstream.

G: Flow sensor reads flow and solutes from the bloodstream.

H: Cells consume O_2 and produce CO_2 and optionally produces UA and consumes HCO_3^-

I: TissueCells extends the Cells with pO_2 calculation and possible lactate production)

J: Interstitial fluid

K: Lungs (here constituted from one compartment) try to maintain normal pO_2 and pCO_2.

L: Kidney metabolic compensations submodel produce HCO_3^- and consume UA and Cl

M: O_2CO_2 block calculates the pH, pO_2, pCO_2 and other variables from the state properties of the blood.

circulation provides a set of volume compartments, which contain dissolved solutes. Other systems are connected to those compartments and are exchanging solutes / fluids. The blood within the circulation is implemented using a joint connector of hydraulics and concentrations, merged using stream connectors. A special object BloodPort is able to extract the chemical (concentration) domains from the BloodPort back and forth (like a multiplexer), so we can connect the flow of solutes independently (further details in section Ions and Figure 7). All exchanges are designed to be electroneutral. The ions are specified separately in an enumerator and all components using the ions are independent on the actual number of ions. This provides an easy extendability by other ions.

Some advanced features of Modelica have been used, namely we often use class inheritance hierarchy for extending the model with new features. An outer ModelSettings class (Figure 3 A) has been used for configuring the model, e.g. turning features on and off and adjusting all important parameters from one class. A number of models could then be uniquely set only by parametrization (or redeclarization) of this component. Thus, we do not repeat the code and prevent inconsistencies and errors.

To meet different objectives with the same model, sometimes a very high detail is required and other times a low complexity is preferred. To reuse components, it is beneficial to have a possibility to switch features on and off for a particular case. The Modelica language provides a language construct for making the entire component conditional, based on some boolean parameter. The conditionality is solved at translation time, which makes the parameter fixed for the current simulation and therefore can not change between resimulations.

The model implementation follows the methodology recommendations specified in the following chapter Methodological approach to model development.

2.5 Cardiovascular models

It can be stated, that everything is related to circulation. Or at least at the first glance it seems to be so. Circulation has been in the spotlight since pioneer work of William Harvey in the beginning of the 17th century. Currently, there are many mathematical models of circulation, accompanied by a number of physical circulatory loops. The usage ranges from short educational observations to hardware-in-the-loop tests of mechanical circulatory supports. We understand the circulatory models as a lumped, dynamic description of circulation fluid. Steady-state models as well as the computational fluid dynamics analyses are not relevant to this work and are therefore omitted.

We can choose between two major approaches to the physical modeling of circulation. Pulsatile circulation deals with shorter time spans and a models' detailed flow. Our approach to implementation of pulsatile models of circulation has been thoroughly described in Lumped models of the cardiovascular system of various complexity (Ježek et al. 2017) (In attachment). The pulsatility may affect the blood distribution, particularly with circulatory support devices (Bělohlávek et al. 2012) .

A number of publications have been devoted to identification of pulsatile circulation (Mukkamala 2000; Hann et al. 2010; Pironet 2016; Kosta et al. 2017; Chase et al. 2018) and some systems have been directly aimed at invasive monitoring of cardiovascular functions (e.g. LiDCO, PiCCO or Vigileo). However, the required time scale of hours and days automatically rules out the pulsatile circulation.

Several non-pulsatile cardiovascular models have been considered, most of them having a similar 6-compartment structure. In detail, the Guyton-Coleman-Granger (Guyton et al. 1972) model, well known and well elaborated, with a number of extensions (e.g. extension to pulsatile circulation by Hernandez et al. (Hernández et al. 2011; Hernández-Ramırez et al. 2016)) or an approach by Lishchuk et al (Lishchouk 1991), who developed a clinical methodology based on non-invasive identification of non-pulsatile circulatory model (Burakovskiĭ 1982).

The circulation model is not the priority for the current research. Firstly, a number of circulatory models, both the continuous and the pulsatile flow, have already been designed and identified, for both education and clinical practice. The connection of our acid-base approach to the circulation demonstrates its abilities. For a long-term simulation, a simplest circulation model would be satisfying, for a detailed view, pulsatile models could be used instead. The acid-base and the metabolism however stays the same. Both ways, we can still construct shunt paths and put multiple tissues / lung sections in parallel and demonstrate different behaviour for an uneven flow through branches.

Since we aim for simplicity and in agreement with the requirements, we can omit all other circulation regulations, although they might play a vital role in both short-term and long-term time scales. These regulations will be substituted by calibration measurements in a clinical aid scenario, or may be added later (e.g. baroreflex, fluid regulation in kidneys), if such requirement arise for the educational applications.

The simplest circulation (see Figure 4 D) consists of two concentration compartments (volume, in which the solutes are dissolved) - one representing systemic veins (that is equilibrated with systemic tissues), and the other representing pulmonary veins (and systemic arteries, which holds the same concentrations of blood gases). The pulmonary veins compartment is modeled using fixed volume, in which the solutes (i.e. the blood gases and ions) are dissolved, whereas the venous compartment has the ability to change volume (and concentrate or dilute the solutes), when external volume is administered.

Implementation

The 6-compartmental Guyton's circulatory model has already been implemented in Modelica as an example in Physiolibrary (Mateják et al. 2014) (see Figure 4 A). For model construction we follow the methods described in our recent paper "Lumped models of the cardiovascular system of various complexity" (Ježek et al. 2017) (In attachment). We have extended it with blood gases transport (O_2 and CO_2) and transport of ions (Na, Cl, K, albumin) (Figure 4 B). Here, stream connectors are used (Franke et al. 2009) to facilitate the implementation within one model of the simple circulation model (contents of the elastic

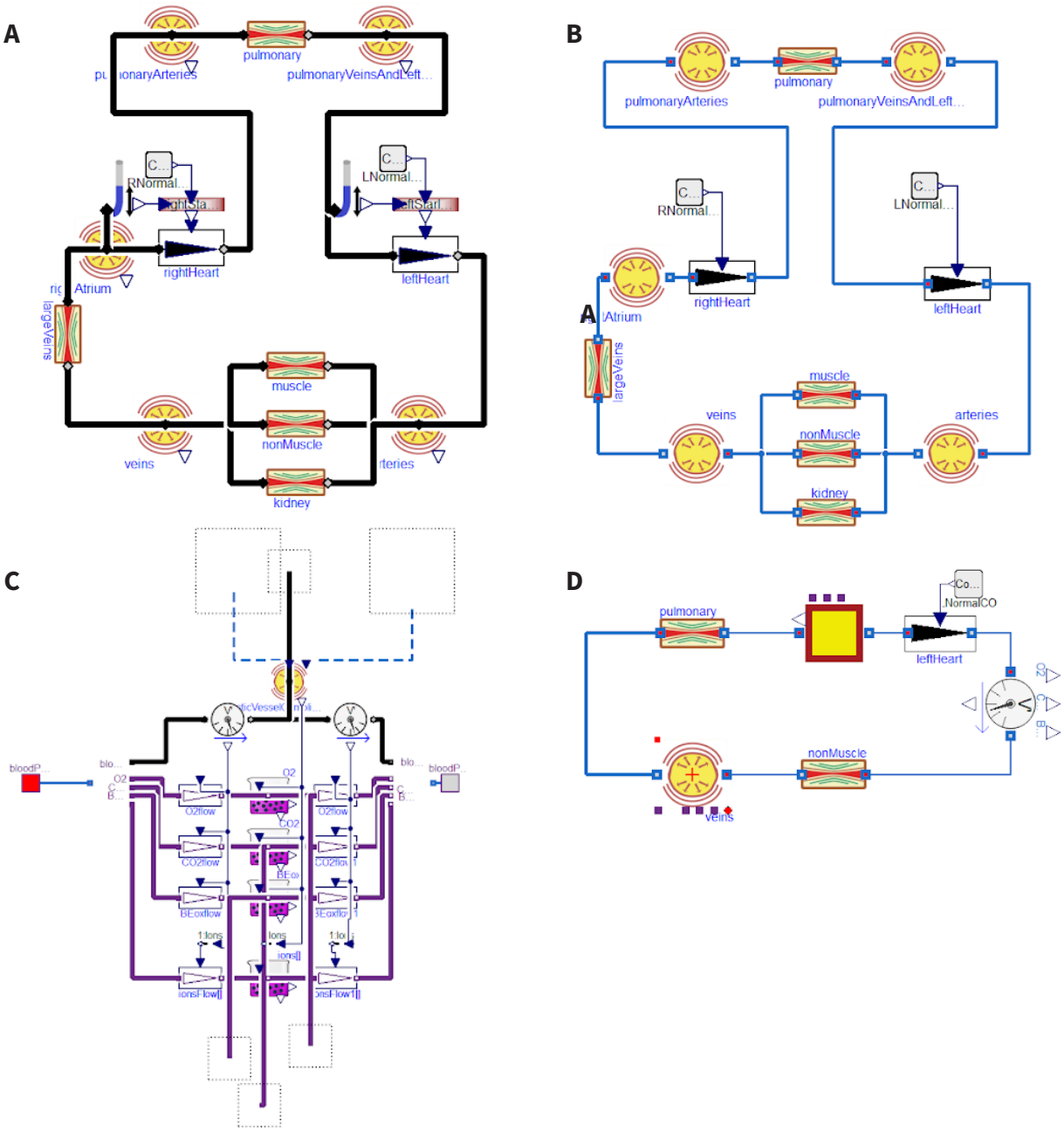


Figure 4:

A) Modelica implementation of cardiovascular system after the core of Gyuton's model (Guyton et al. 1972), as implemented in (Mateják et al. 2014). This model is intended for more detailed simulation of minute-flow circulation

B) An extension of the circulatory model with blood gases and ion transport

C) A detail of the extended elastic compartment, with the original elastic compartment and concentration compartments, representing blood gases and ion accumulation, and conditional inputs and outputs (dashed placeholders)

D) The simplest circulation consisting of a single pump and one elastic compartment, representing the systemic vein, whereas the second compartment (pulmonary veins, yellow rectangle) has fixed volume.

compartment are shown in Figure 4 C). The stream connectors ensure automatic mixing of concentrations at flow connections (e.g. multiple segments of lungs or tissues). A minimal model limits itself to a single elastic compartment and has been implemented using the same components (Figure 4 D). Generally, any other model from the set of pulsatile models published in (Ježek et al. 2017) could be used with minimal modifications.

2.6 Acid-base and blood gases models

Contemporary approach to bedside acid-base evaluation

Three approaches are used at the bedside acid-base assessment: the bicarbonate approach, the traditional, or Siggaard-Andersen's and the modern, or Stewart's approach. The first is based on concentration of HCO_3^-, the second on an artificial, non-physical metric Base Excess (BE) and the third on a strong ion difference (SID), a sum of strong ions in plasma. Each approach has a way how to understand the body state and take the bodily processes into account, however, the two latter are dominantly used in the clinical practice currently. The preferred clinical approach to acid-base chemistry remains controversial (Berend 2013).

Kimura et al. compared studies which claimed superiority of one or another approach, however the compared studies "shows inconsistent results on the comparison between the two approaches for diagnostic and prognostic performances. We found crucial limitations in those studies, which could lead to the reasons of the discrepancy" (Kimura et al. 2018).

Formalizations

Siggaard-Andersen quantitatively formalized his BE-pCO_2-pH nomogram to the famous Van-Slyke equation (Siggaard-Andersen 1977) and later extended it with detailed calculations of oxygen dissociation curves, total concentrations and partial pressures in (Siggaard-Andersen and Siggaard-Andersen 1990). The BE has been first introduced for blood in vitro, as the value in vivo has been slightly different due to the influence of extracellular fluids (Severinghaus 1993), which has been corrected by an introduction of a standard base excess (SBE). The SBE is basically a base excess if the hemoglobin concentration was 5 g/dL, which compensates for interstitial fluid, which is approximately 3 times the volume of plasma and contains no erythrocytes (in contrast to about 15 g/dL in blood). Today a newer computation is standardized (Berend 2018), but the principle holds.

Stewart's, or physicochemical approach (Stewart 1981) has been formalized also by other authors, who mostly just took a different approach to quantization of charged proteins and phosphates (Figge 27 October, 2013; Fencl et al. 2000).

Compensation

However, each of the three contemporarily used bedside approaches only quantifies the current state and thus needs to somehow take the bodily regulations into account. The bicarbonate approach uses so called Boston rules, as presented by Schwartz and Relman

(Schwartz and Relman 1963). The rules are sometimes updated or different values are used (Yartsev 2013). The Copenhagen rules, based on a standard base excess of Traditional Siggaard-Andersen's approach, have also a set of rules to a bedside assessment of acid-base compensation (MORGAN Senior et al. 2003).

Compensation has been covered by a number of authors, notably Schlichtig et al. (Schlichtig et al. 1998a, 1998b). Years before, a few authors (Albert et al. 1967; Engel et al. 1968; Dell and Winters 1970) presented the compensation of the SBE as functions of pCO_2 for chronic and acute respiratory or metabolic acidosis / alkalosis respectively. Siggaard-Andersen then incorporated the compensation into his nomogram (Siggaard-Andersen 1971). A number of authors also described compensation in Stewart's terms, e.g. (Morgan 2009; Story 2016). In the Czech clinical practice, a nomogram by Engliš (Engliš 1972) is traditionally used, which he adapted from results of Winters et al. (Winters et al. 1969). This approach could be enhanced by the computer program (Engliš et al. 2006).

However, to my knowledge, a complex model of dynamic acid-base compensation has not yet been presented. Even the "The best, most complete, mathematical model of human physiology ever created" (HC Simulation 2016) still does not have physiologically explicable acid-base compensation, namely is unable to compensate respiratory acidosis and inadequately compensates metabolic disorders (Mateják 2015).

The balance approach to the acid-base equilibrium

The balance approach to the acid-base equilibrium (Kofránek and Ježek 2018a) (Attached), preceded by the border-flux theory (Kofranek et al. 2007), warns about an uncritical adoption of Stewart's approach and extends this physicochemical approach with further relations and with Siggaard-Andersen's BE nomenclature. The balance approach aims to physiocochemically describe the pathogenesis of acid-base disruptions. The contemporary acid-base model concentrates on instant balance. The dynamic change is to our knowledge not considered. For common acid-base disturbances, we also propose introducing the dynamic regulatory mechanisms, such as kidneys, interstitial volume and cells contribution. The approach presented in this chapter follows the effort by formalising and quantifying the theory into a consistent mathematical model.

The main points of the balance approach (adapted from (Kofránek and Ježek 2018c)):

- All fluxes and reactions in a human body are electro-neutral. This might not be completely true for individual biochemical processes, but given cellular or tissue scale, this assumption is perfectly justified. Therefore, not only membrane fluxes, but also a metabolism of particular substance (e.g. albumin) must be accompanied by an accordingly charged ion (e.g. -12 mol H+ per mol albumin at normal pH). Similarly, HCO_3^- fluxes are always accompanied by charged ions (either symport or antiport) flux to maintain flux electroneutrality.
- the CO_2 / HCO_3^- buffer system is present everywhere in the organism and HCO_3^- has by several orders of magnitude higher concentrations than H+ (normal values of HCO_3^- are around 24 mmol/l, whereas H+ is logarithmically related to pH by -log([H+]) and thus

the H+ concentration at normal pH of 7.4 is approx. 40 nmol/l, which is around 0.15% of the HCO_3^- concentration). Therefore it is correct to assume that all H+ fluxes could be considered as inverted bicarbonate fluxes, i.e. generation of H+ results in consumption of HCO_3^- and vice versa, consumption of H+ could be viewed as a generation of HCO_3^-. Note, that a CO_2 molecule is released or utilized respectively, but this is negligible given the total flow of CO_2 through the organism.

- Buffer systems act as a reservoir of bicarbonates.
- Flux of protons and bicarbonates could be expressed in the BE and the SID interchangeably. As we demonstrated in (Ježek and Kofránek 2018) (in attachment), there exists a direct, quantifiable relationship between the BE and the SID. In fact, the BE could be used also as an indicator of an ion flow (mostly being a flow of HCO_3^- accompanied by a cation or an anion flow in the opposite direction). The BE depends on hemoglobin saturation and therefore we use the BEox instead, which is a value of the BE in fully saturated blood (see the appendix of Ježek and Kofránek (Ježek and Kofránek 2018)). The SID is, however, slightly dependent on pCO_2 in vivo due to a chloride-HCO_3^- exchange with the erythrocytes. Although this may be negligible, it is more convenient to use the truly independent BEox. To avoid confusion, the term BE would be used further in place of BEox, unless stated otherwise.
- Disbalance between production and consumption of particular matter does create a relative surplus (or shortage respectively) and could be viewed as an absolute flux in an otherwise balanced system (Figure 5).

The balance approach to acid-base equilibrium has not yet garnered much attention. In fact, it is a didactic extension and does not provide new diagnostic tools. This approach however allows us to:

- calculate the blood acid-base status, also with blood mixing
- calculate compensations in time
- describe a linkage of a metabolism, acid-base compensations to ion balance (e.g. the disputed hypoalbuminemic alkalosis) through the generation and consumption of the BE, that is a HCO_3^- ion.
- By using the BEox, the model could be extended with other ions (with BE-SID recalculation). Flows of HCO_3^- could then be viewed as flows of BEox - or as a change in the SID.

Implementation

The pH of blood depends on BEox (or SID), the concentrations of so-called weak ions (albumin, phosphate) and pCO_2 and slightly also on pO_2 (as the CO_2 competitively binds to hemoglobin as well, when not occupied by the oxygen). The dissolved CO_2 then mostly dissociates to HCO_3^-. We often need to recompute from total gas blood concentration to its partial pressure and back. For these calculations, we use the Siggaard-Andersen Oxygen Status algorithm (Siggaard-Andersen and Siggaard-Andersen 1990) (Figure 6).

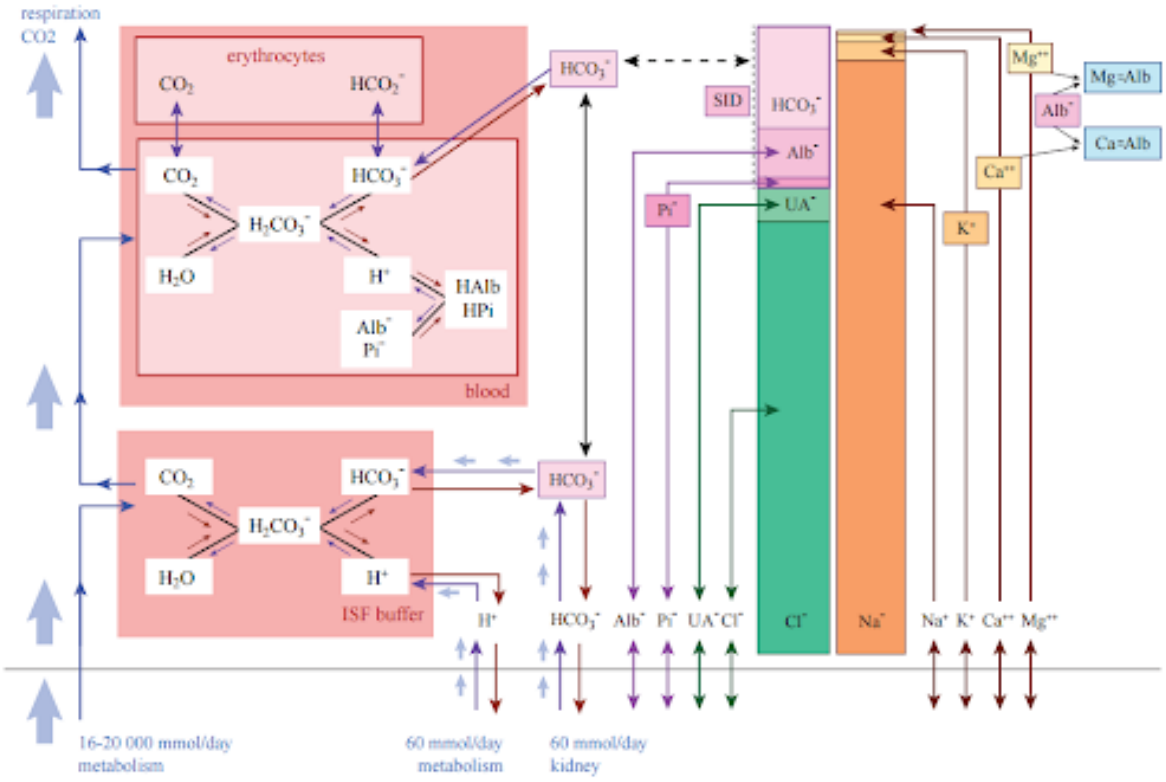


Figure 5: The interconnection of acid–base and ion balance. All transfers of ions to or from extracellular fluid (ECF) are in sum electroneutral. Consequently, the flows of H^+ and HCO_3^- to or from ECF are always accompanied by the flow of other ions, balancing the electroneutrality. H^+ ions from metabolic production of strong acids are immediately bound by the bicarbonate buffer, reducing the bicarbonate levels. In normal physiological conditions such depleted bicarbonates are balanced by bicarbonate production in kidneys during urine acidification. Metabolic disturbances of the acid–base balance lead to a shift in the balance of bicarbonate and simultaneously to a corresponding change of the ion composition of ECF. Respiratory disturbances alter the level of CO_2 in blood and subsequently in interstitial fluid, followed by a change of CO_2 level in buffer systems, resulting in a pH shift.

2.7 Ions

Given our requirements, the model should be extendable by various ions.

The main state variables must be independent of each other. From experience, basic physical quantities are especially suitable. Thus, for an acid-base description we chose the total oxygen concentration (tO_2, mol/m^3), the total carbon dioxide concentration (tCO_2, mol/m^3) and a base excess for fully oxygenated blood (BEox, mol/m^3).

For the current phase of this study, the ions only include concentrations of Na, Cl, Albumin and organic acids (or unmeasured anions, UA). Additional solutes could be added later, however these four are necessary to describe the most important phenomena. The lactate is considered to be included in within the UA.

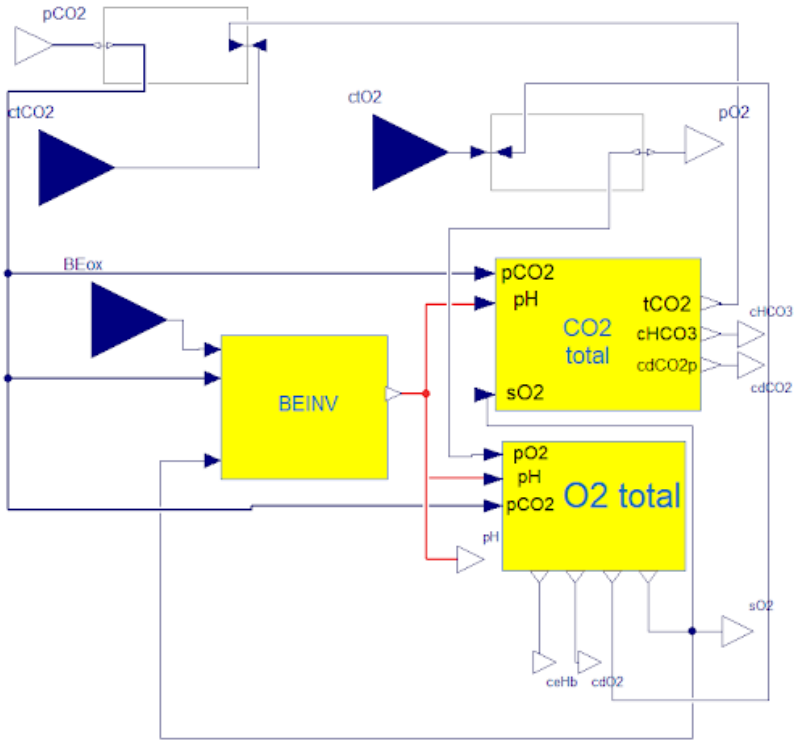


Figure 6: A Modelica implementation of acid-base calculations. The original Siggaard-Andersen algorithms are hidden inside the yellow boxes. For our usage, the inputs (the filled blue triangles) and outputs (the stroked white triangles) to the algorithms (the total O_2 to pO_2 and the total CO_2 to pCO_2) are inverted (the top of the image).

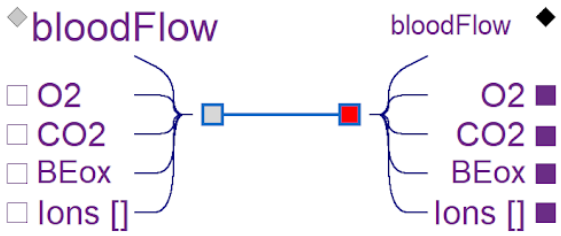
However, it is important to note, that from one point of view, the BEox state variable is redundant as it could be inferred from the ion concentrations. Using Stewart's SID (e.g., the calculations used in (Moviat et al. 2003)), which can be obtained from the ion concentrations, and our SID to the BE recalculations (Ježek and Kofránek 2018), we can obtain another value for the BE, which might not be exactly the same as the one defined by the BEox state variable. Thus, the BE might seem obsolete. However, from the experience with the Physiomodel, it is not advised to use ions as state variables for acid-base calculations, since small changes in the amount of any of the ions lead to a huge acid-base disturbances and computational instability of the model. Therefore, a redundant metric was introduced to stabilize the acidbase and make it independent of the ions. Given the measurement precision of the particular ions, it is justified to use the BE instead (Agrafiotis et al. 2018.)

Omitting K^+, Ca^{2+} and Mg^{2+} then underestimates the UA and osmolarity. This is not an issue in educational aids, but must be considered for a potential clinical use. In addition, the UA are not measured (from definition) and therefore are calculated from the measured solutes and pH – similarly to the BE.

Implementation

The ion transfer, as well as the transfer of the blood gases and BEox, has been integrated within the blood stream connector by AcidBaseBalance.Interfaces.BloodPort_in_Extension (Figure 7). Chemical domains from Physiolibrary are used for the concentration dimensions. All the ions are enumerated in the AcidBaseBalance.Ions.IonsEnum and could therefore be easily extended. However, note, that each additional ion would proportionally increase the complexity. This implementation allows us to both mix blood flows and deal with the individual ions at once.

A



B

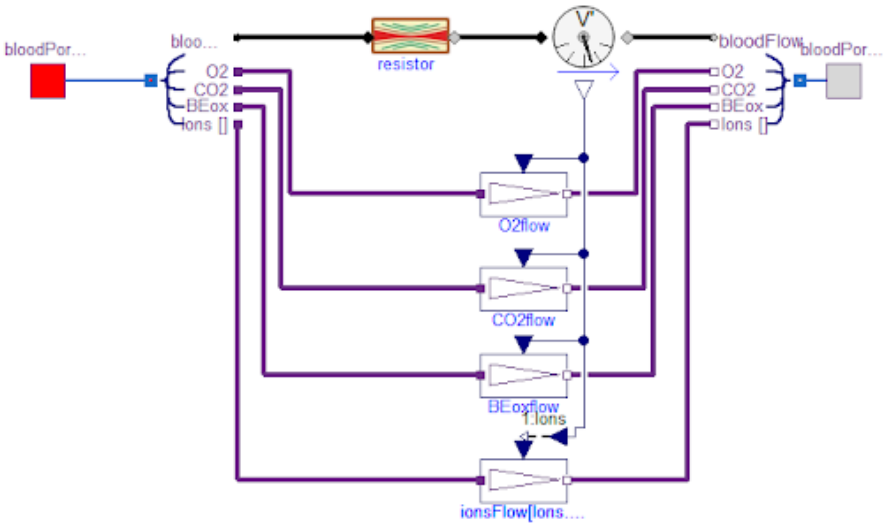


Figure 7:

A) BloodPort_out_extension combined bloodFlow, a pressure-flow connector, with chemical connectors transferring blood gases, BEox and an array of ions into a single BloodPort connector. This connector could be then expanded again to single connectors.

B) The usage of BloodPort in the BloodResistor component - the blood flow is limited by the resistor and the individual concentrations are moved according to the flow rate of the blood.

2.8 Interstitial fluid

The ISF is a reservoir of blood gases, HCO_3^- and other ions and separates the cells from the circulating blood. For modeling purposes, however, we decided to have ISF and tissue cells as separated compartments. Changes in plasma composition and / or blood gases concentrations affect the concentrations in the ISF, which leads to a shift of the particular ions. Since the HCO_3^- could move as any other ion, it leads to a flow of the BE.

Blood gases and ion storage

The concentration gradient moves solutes along its direction. The flow through the capillary membrane must maintain electroneutrality and we assume it quickly reaches the Donnan equilibrium.

However, for O_2, the concentration gradient is the difference in concentrations of dissolved O_2, not the total O_2 transported in blood. Only a minor part of the O_2 is actually dissolved and most of it is bound to hemoglobin. In the ISF, on the other hand, no hemoglobin is present and therefore the ISF O_2 concentration is equilibrated with the blood dissolved O_2.

The CO_2 is also partially bound to hemoglobin, but the majority is dissociated into HCO_3^- in both blood and ISF. At lower oxygen saturations, CO_2 is also bound to the hemoglobin

For charged substances (HCO_3^-, Cl etc), the other important force in addition to concentration gradient, is the electrostatic force. In accordance with the border flux theory assumptions, we maintain all ion fluxes charge neutral and also all compartments must maintain electroneutrality. For uneven capillary ion permeabilities, the ions are then forced to converge to a Donnan equilibrium (Donnan 1924). The most important non-permeant solute is the albumin, concentration of which in the ISF is set arbitrarily at ⅓ of the plasmatic concentration (consistently with (Andreassen and Rees 2005; Wolf and Deland 2011b; Silbernagl and Despopoulos 2016)).

For model initialization, the initial concentration of solutes in the ISF is set based on the static Donnan equilibrium of plasmatic concentration.

Water balance

In addition, the osmotic force moves water in the osmotic gradient until the osmotic equilibrium is found. Osmotic forces are driven especially by impermeable solutes, such as albumin. Osmolarity is computed as a sum of all ions and HCO_3^-. To maintain a stable ISF initial volume, we have to compensate the simplifications (oncotic pressure, hydrostatic pressure, fixed ratio of plasma-isf albumin concentration, omitting important ions, omitting a lympha flow etc.) by adding a total of 9.5 mmol (approx. 0.95 mmol/l) of impermeable solutes to the ISF. For longer simulation times (> 10h) the fluid balance between ISF and plasma is marginal compared to excretion and regulation mechanisms, which are not implemented. The water balance is thus an optional feature for short-term demonstrations.

Implementation

The schematics of the implementation is shown in Figure 8. The dissolved O_2 and CO_2 have to be calculated from the total amounts, because what actually drives the membrane transfer are the dissolved gases, not the total concentration. To properly set the initial ion concentration, the Donnan equilibrium is solved at initialization (the green block) and the total amount of O_2, CO_2, HCO_3^- and ion concentrations are set accordingly. Then all ion flows follow the Donnan balance. Because of the variable charge of the albumin, the concentrations have to be recalculated to charges (the yellow blocks). The water transfer control is optional.

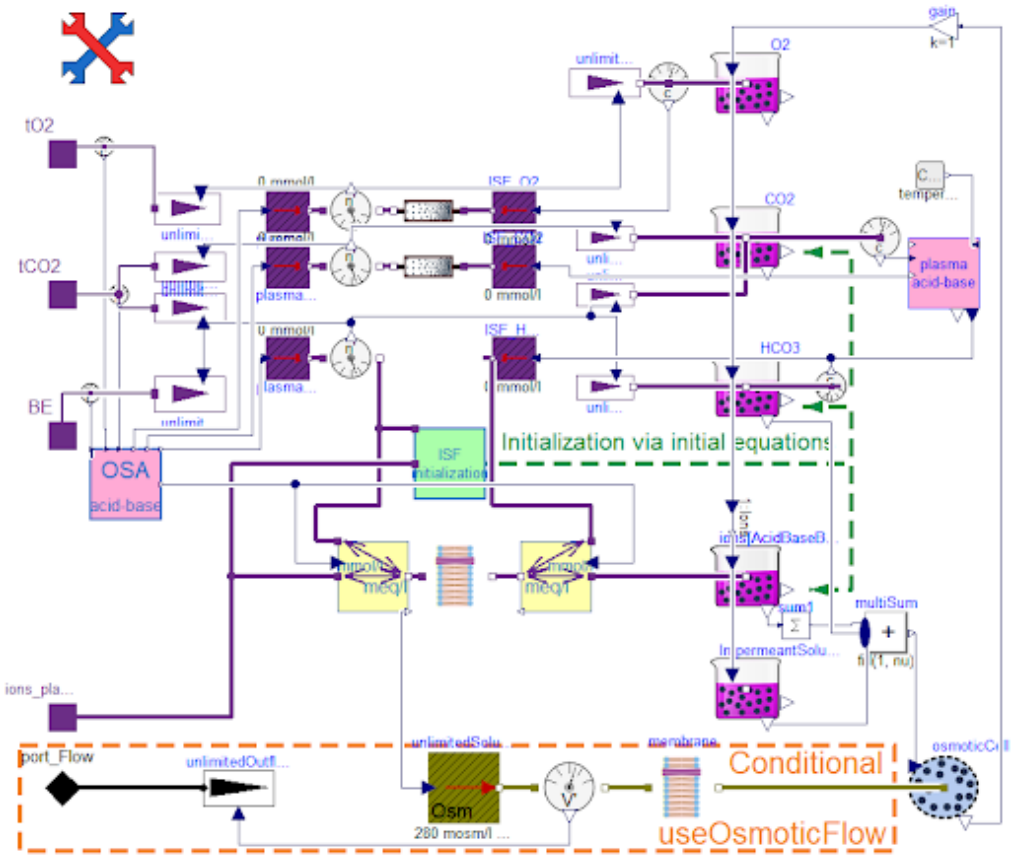


Figure 8: Schematics of the interstitial fluid component

2.9 Tissues

Under the term tissues we understand the respiration and metabolic contributions of the cells. The cells consume around 11 mmol/min of O_2 and, given the respiratory quotient of 85% for a normal Western diet, produce around 9.4 mmol/min of CO_2. Apart from oxygen

requirements, cells also produce around 60 mmol/day of organic acids, which, under an assumption of organic acid charge 1 eq/mol, requires 60 mmol/day of HCO_3^-.

Hypoxemia and lactate acidosis

The gas transport resistance is comprised of the capillary membrane and the tissue depth.. "The normal average end capillary pO_2 is about 5.0 kPa (37.6 mmHg), with a considerable variation among different tissues. The average pO_2 difference between erythrocytes and mitochondria is about 3.4 kPa (25.5)"(Siggaard-Andersen et al. 1995) The diffusiobility has been calculated from these information about the gradient.

When the oxygen partial pressure in cells drops under 0.1 kPa then the cells are not able to fully support their metabolism by O_2 and start producing lactate (which is otherwise further metabolised using the O_2) in in a process which is termed an anaerobic metabolism (Siggaard-Andersen et al. 1995). To maintain electroneutrality, an H+ ion is produced along each $lactate^-$, leading to a so-called lactate acidosis.

As pointed out by Rogers (Robergs et al. 2004), the term lactate acidosis oversimplifies the real processes (the lactate- is developed from pyruvate-, thus no H+ ion production. The pyruvate- is however derived from neutral glucose, thus the H+ is already produced in hydrolysis and we should not refer to it as lactic acidosis), but it has already established itself in the common nomenclature..

As the lactate is produced, it must be metabolised in the liver or excreted by the kidneys and, due to the electroneutrality principle, it costs exactly same amount of H+ ions as were produced together with the lactate. Therefore, the lactate acidosis is only a transient disbalance between the production and catabolism.

We consider the lactate production to be linearly proportional to the oxygen concentration, at least up to a breaking point (Figure 9). This is an arguable simplification, however in reality we may never know precisely which part of the tissues are suffering from hypoxemia. A further investigation would be required to refine the relationship.

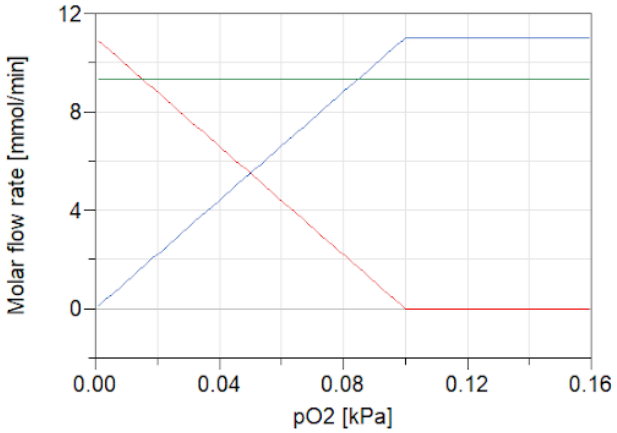


Figure 9: Consumption of O_2 (blue), production of CO_2 (green) and production of lactate in dependence of partial pressure of the O_2.

The carbon dioxide production remains unchanged, although in reality the respiration quotient would be slightly different.

Implementation

The acid-base status on the membrane is inherited and shared with the ISF membrane calculations (Figure 10 B).

When the effects of a limited flow are not the objective, we advise to use a simplified model (Figure 10 A). This simplification avoids the need to solve the whole acid-base status which is a computationally intensive requirement for calculating the pO_2 membrane. The simplest tissue metabolism produces a fixed amount of O_2, which is set to 11 mmol/min and a slightly less amount of CO_2 (by the respiration quotient, which is 85% by default).

The production of UA and consumption of HCO_3^- is optional.

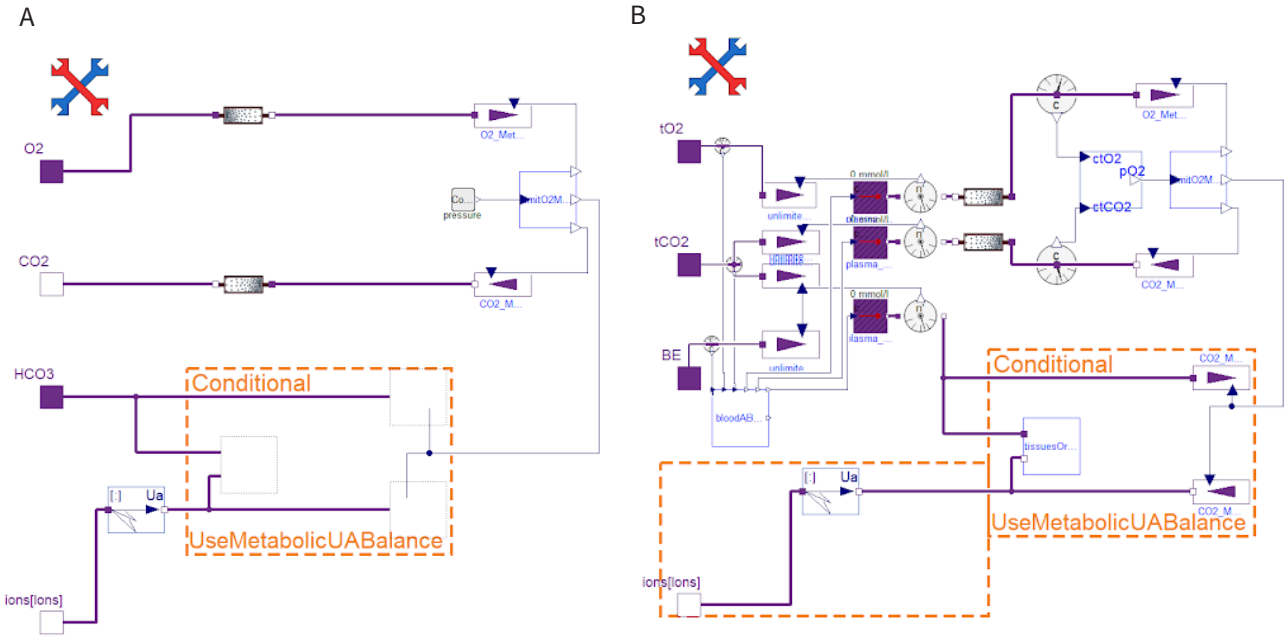


Figure 10: Simple cells (A) only remove a constant flow of O_2 and add a constant flow of CO_2. Both cells can conditionally produce UA (and therefore consume an according amount of HCO_3^-). But the TissueCells (B) can lower their oxygen consumption in exchange for lactate production

2.10 Respiration

Here, a substantially simplified model of the respiratory system is used. In fact, we deal with only a part of the respiratory system, starting from alveoli. Airways, respiratory mechanics and gas mixing are not a part of the current model. Our respiratory model starts with alveolar ventilation, i.e. the gas volume flow rate which flows through the alveoli, which is normally a function of breath volume, frequency and dead space volume. However, with identifiability, low computational complexity and timescale requirements in mind, we decided to keep the model as straightforward as possible.

More detailed modeling is done elsewhere, for example in the Pneuma model (Fan and Khoo 2002), which we have already implemented in Modelica and Physiolibrary (Bundil 2014) and which could extend the presented model in the future, if such a requirement arises. Another candidate is the respiratory and perfusion model presented in (Mogensen 2011).

The implemented gas transfer in lungs follows a basic assumption, that the alveolar blood gas partial pressure equilibrates to the partial pressure of the gas in the blood leaving the lungs.

In addition, not all blood flows through the appropriately ventilated alveolus. Some alveoli might be poorly perfused and / or poorly ventilated, which leads to apparent shunts, impairing the lungs function (Paulev and Siggaard-Andersen 2004). To simulate the various possible perfusion and ventilation modes (one of the requirements), the lung component is doubled and parallelised. The two compartments can then describe a range of ventilation-perfusion disbalances (Rees et al. 2010).

However, the gases concentration in the alveolus depends on alveolar ventilation. The appropriate alveolar ventilation regulation depends on arterial pO_2, pCO_2 and pH. The reaction to pCO_2 is almost instant. The reaction to pH is however delayed, because the chemoreceptors are behind the hemo-encephalitic barrier, where the transfer of the HCO_3^- (or H+) along the concentration gradient is substantially limited (Ainslie and Duffin 2009). A simple steady-state behavioral model of the alveolar ventilation regulation is taken from Ikeda's large integrative model (Ikeda et al. 1979), in which the alveolar ventilation control model from Cunningham was adapted (Cunningham et al. 1961). This model however shows the regulation in equilibrium, therefore we have slowed the reaction sensitivity to pH using the first order integrative delay to match the 6 - 12 hours delay in respiratory adaptation observed in a clinical practice (Siggaard-Andersen 1971) and adapted the constants to fit the compensation diagram. More detailed models are available, e.g. Larraza et al. (Larraza et al. 2014) presents a successor of Rees and Andreasen's model, with an integrated respiratory control model by Duffin (Duffin 2005).

Implementation

The lungs share a common base with a common interface (LungsBase), which uses total O_2 and CO_2 and BEox interfaces and venous O_2 and CO_2 concentrations, alveolar ventilation and a blood flow as inputs. Inside the lung compartments there are hidden acid-base calculations, which keep the arterial partial pressures of O_2 and CO_2 at the same values as the alveolar partial pressures. The difference in the concentrations creates the molar flow rate of the gases through the chemical interfaces. To simulate different ventilation and perfusion, the lung calculations are doubled and parallelized (LungsTwoCompartment).

The alveolar ventilation input is normally regulated by the Alveolar ventilation block (Figure 3 K), which takes the arterial pO_2, pCO_2, pH and basal alveolar ventilations as inputs and gives the alveolar ventilation volume flow rate as the only output. The regulation

could be turned off by setting the UseRespiratoryCompensation to false, in which case the unregulated basal alveolar ventilation would be used instead.

2.11 Kidneys

A number of researchers devoted their lifetime to study the kidney function and its effect on acid-base. The kidneys regulate the acid-base balance in multiple ways. For our usage, we took the simple formulation of the acid-base compensation function by excretion of NH_4^+ and varying the urine pH. This simplification should be satisfactory for acid-base compensations (Koeppen 2009). Interestingly, even the most complex physiology model to date (i.e. the HumMod (HC Simulation 2016)) does not have the titratable acidity compensation implemented.

We reimplemented both of these compensations, improve them and couple them together to quantify the amount of produced bicarbonate.

Titratable acidity of the urine

First, the kidneys excrete so called titratable acidity into the urine, while maintaining bounded urine pH to prevent kidney stones (Halperin et al. 2006). The model of urine acidification is based on Ikeda (Ikeda et al. 1979), with an added integrator feedback to slow the compensatory reaction to 2-3 days (Figure 11). The inputs are arterial pH, an aldosterone modifier and urine pH.

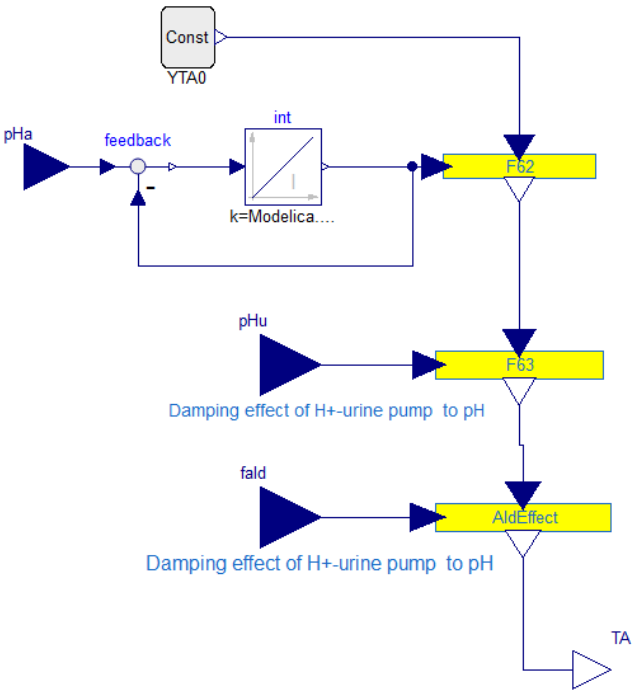


Figure 11: Titratable acidity is based on functions of Ikeda (Ikeda et al. 1979), extended by the integration delay.

Ammonium excretion

The second major contributor is the ammonium excretion (Figure 12). The basic mechanics of ammonium excretion are taken from Hummod (Hester et al. 2011), version 1.6, and related Physiomodel (Matejak and Kofranek 2015) and are in line with contemporary understanding.

However, these models do not correspond in the case of respiratory acidosis, where the compensatory nomogram from Siggaard-Anderson, as reproduced by the oxygen status algorithm (Siggaard-Andersen and Siggaard-Andersen 1990; Siggaard-Andersen 1997), as well as the nomogram used in the Czech clinics at the bedside (Engliš 1972) predict an incomplete pH compensation (see FigSAOSANomogram). The Hummod, on the contrary, compensates the pH fully.

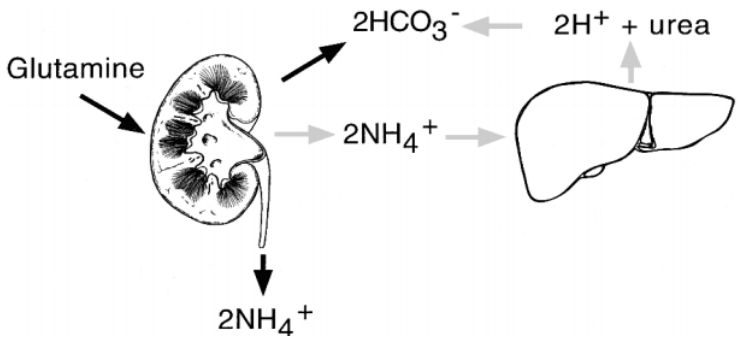


Figure 12: HCO_3^- production by excretion of NH_4^+, obtained by breaking the glutamine. Image from (Koeppen 1998)

Limit of HCO_3^- absorption during respiratory acidosis

It is supposed, that the NH3 production has an upper limit – e.g. Tannen and Hamid (Tannen and Hamid 1985) show a limitation in the HCO_3^- resorption rate, which would affect the NH3 excretion. However, Halperin and Kamel (Halperin et al. 2010) oppose this view and state, that there is no threshold for HCO_3^- resorption, unless the effective arterial blood volume is not expanded (e.g. by Na). Which is supposedly the case of the HCO_3^- reabsorption measurements, as there were done by using the $NaHCO_3^-$ infusions.

For higher NH_4^+ production rate, the demand for HCO_3^- reabsorption is also increased. We hypothesize, that the concentration of the bicarbonate competitively affects the NH_4^+-H pump in proximal tubule (which is the same pump, acting competitively - compare fig 1-9 and fig 1-14 in (Halperin et al. 2010)), therefore competitively sensitive to plasmatic HCO_3^- concentration.

Therefore, high concentration of HCO_3^- effectively slows the transfer of NH_4^+. As a result, the respiratory acidosis is not fully compensated due to the high HCO_3^- concentration, but respiratory alkalosis is compensated to normal pH.

This is in accordance with observations, that during a chronic respiratory acidosis the

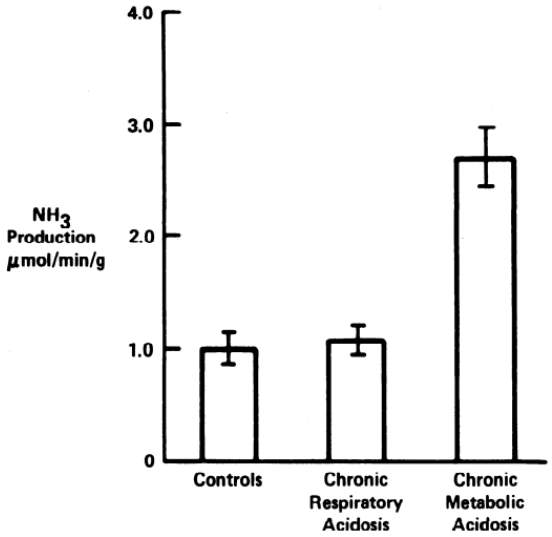


Figure 13: During metabolic acidosis the NH3 production rises, however during chronic respiratory acidosis the NH3 production rate is not substantially elevated over the baseline level.

"FIG. 1. NH3 production by isolated kidney perfused at pH 7.4 from normal rats and those with chronic respiratory acidosis (10% CO_2) and chronic metabolic acidosis (1.5% NH&l) of 3 days duration. Metabolic acidosis results in adaptive increase in renal NH3 production, but no difference in capacity to produce NH3 is apparent with chronic respiratory acidosis." Image and quotation from (Rodriguez-Nichols et al. 1984).

ammonium production rate of the NH_4^+ is not elevated above normal, unlike the metabolic acidosis. (Rodriguez-Nichols et al. 1984; Tannen and Hamid 1985) (see Figure 13).

To our knowledge, this effect has not been thoroughly studied nor quantified, however the phenomena is hidden in the observed acid-base compensatory diagrams, e.g. by Siggaard-Andersen (Siggaard-Andersen 1971) and its later application (Siggaard-Andersen and Siggaard-Andersen 1990). The respiratory acidosis maximal compensation curve presents the resorption rate limitation, under which the kidneys are unable to generate more HCO_3^-, than is produced by the metabolism and therefore the compensation stops.

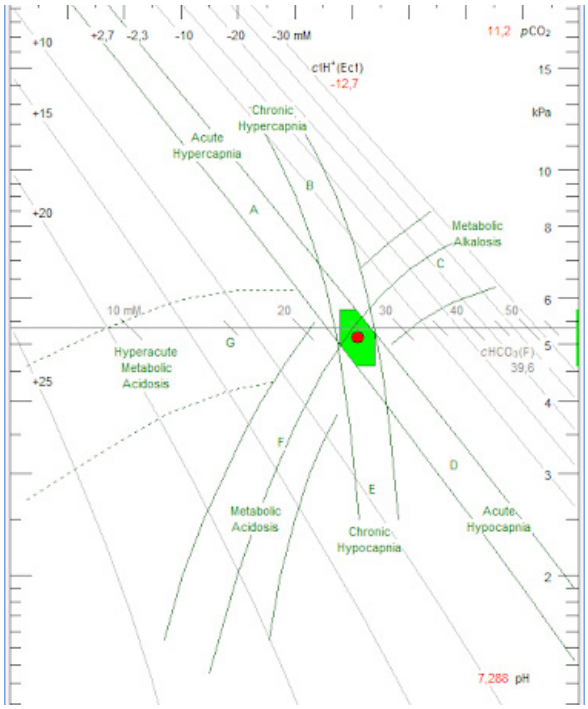
We have fitted the chronic respiratory acidosis area from the compensation nomogram (Figure 14 A) into a mean curve (Figure 14 B), where the maximum HCO_3^-, at which the kidneys are unable to produce more than the basal metabolism flow is described as a function of the pH. The four parameter symmetrical sigmoideal function (Equation 1) with the parameters in table 1 is used to fit the data (Figure 14)

1 $$maxHCO3limitation = A + (B - A)/(1 + (pH/C)^D)$$

A	B	C	D
-122.029	46.16094	7.565033	89.04176

Table 1: Parameter values of Equation 1

A



B

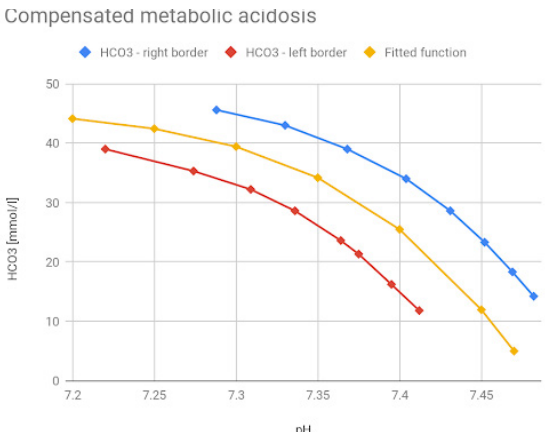


Figure 14:

A) A compensatory nomogram - screenshot from the Siggaard-Andersen's Oxygen Status Algorithm (Siggaard-Andersen 1997). ctH+ (concentration of titratable H+) is equal to -BE, respectively -SBE in current case.

B) The limiter of ammonium excretion is a function of pH and bicarbonate concentration.

When the limiter is applied as a hard maximal bound, it leads to numerical problems by generating a large number of state events, called chattering. The problem lies in the way the events are handled by the Modelica runtime. Therefore, we applied smooth limiting by using an exponential rational function:

$$dhco3 = kh \cdot (HCO3_{actual} - maxHCO3limitation)$$

$$HCO3limit = \frac{e^{dhco3}}{1 + e^{dhco3}}$$

$$y = u \cdot (1 - HCO3limit)$$

where kh is an arbitral smoothing constant (kh = 1000), u is a HCO_3^- production molar flow rate input and y the limited HCO_3^- production output. The characteristics are shown in a Figure 15.

This is only a behavioral estimation though, the limiter would probably have a slightly different response to maintain balance. The other kidney compensations, including the titratable acidity, have been left untouched, although in fact they collaborate with each other. A deep physicochemical understanding of this process is however still missing.

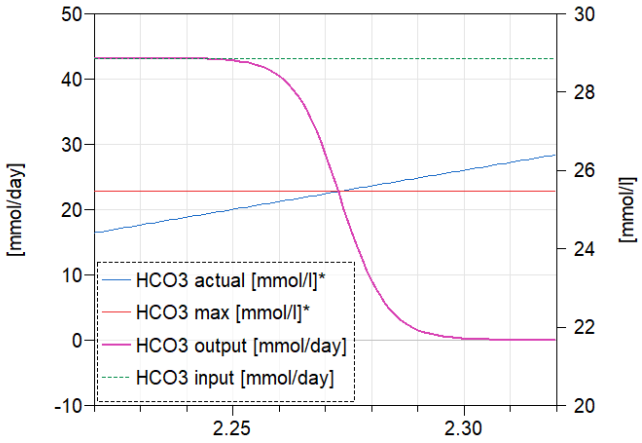


Figure 15: HCO_3^- production limiter

Long-term compensation of chronic change in metabolism rate

Another discrepancy of the NH_4^+ excretion model based solely on the Hummod is in the non-normal metabolism rate. In such cases, the NH_4^+ compensation manages to match the amount of excreted NH_4^+, but not to neutralize the pH difference. In fact, it would maintain a non-zero BE (see the characteristic in Figure 16 B). The modified model also slowly changes the normal metabolic flow rate (with an anti-windup protection limiter at 200% of the normal metabolic flow rate). The original long-term proximal tubule compensation had to be overridden, because two integrative regulations in series produce oscillations - see Figure 16.

Electroneutrality considerations - the excretion of chloride and organic anions

To maintain the electroneutrality, the produced bicarbonate must be accompanied by a produced cation or an excreted anion. Normally, the amount of co-transferred HCO_3^- must balance the amount of metabolically produced UA (anions of organic acids, sulfates and phosphates). When the UA are in a low concentration or not available at all, some other anion, mostly the omnipresent Cl, is excreted instead.

This limitation is implemented using a quadratic limiter function

$$UAMaxRate = (\frac{UA}{k})^2 \ for\, UA > 0,\ else\, 0$$

where the k has been arbitrarily set to 1000. The missing flow rate is then filled by the flow of the chloride ion. Resulting characteristics could be seen in Figure 17.

Although the true mechanics are much more complex, this approach provides a robust solution without the need for detailed ion regulation.

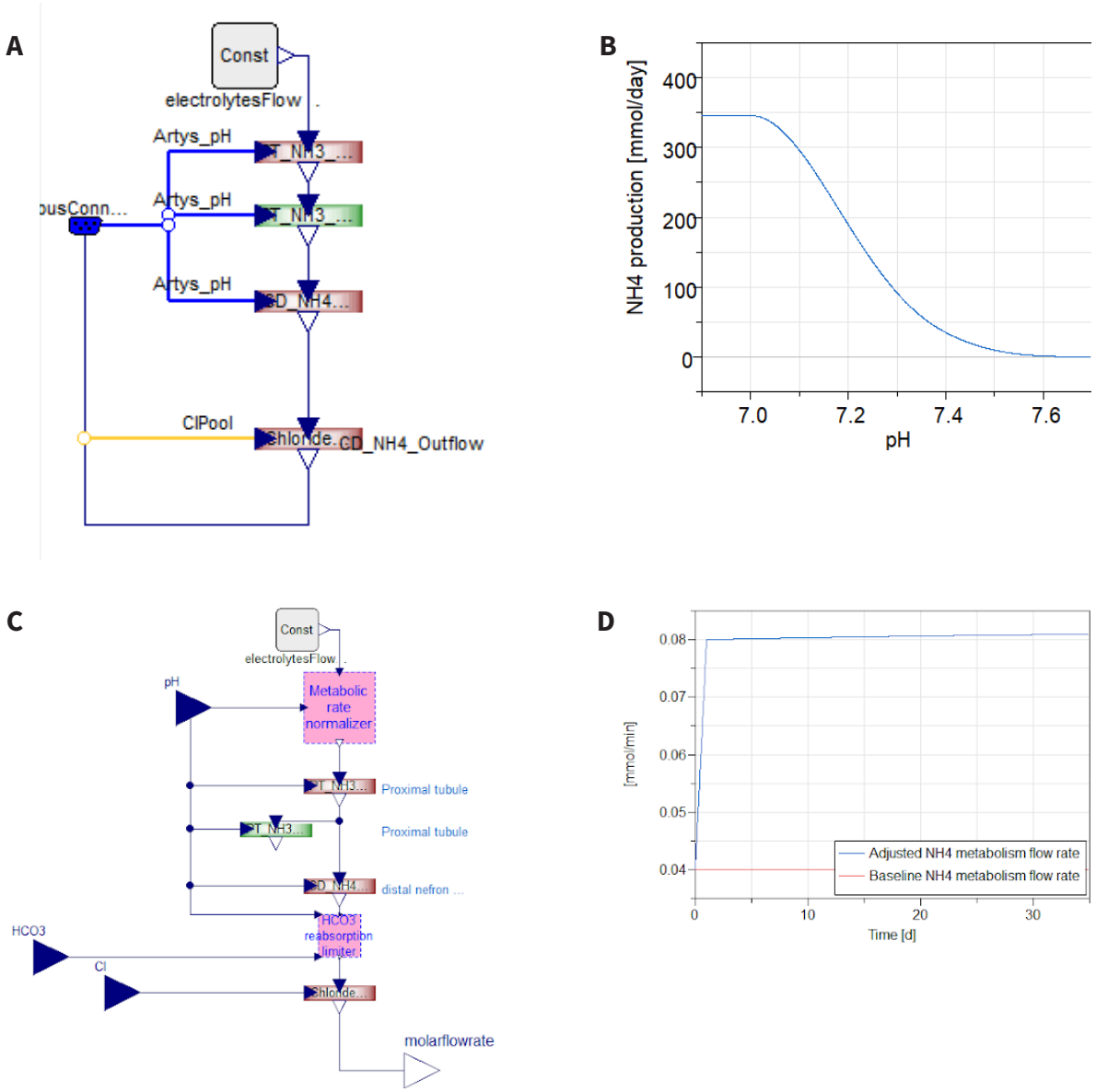


Figure 16: The original model (A) from Physiomodel and its characteristics (B). This means, that for a chronically increased metabolism, the system would never fully compensate. The modified model has a metabolic production baseline modification and a HCO_3^- limiter (C). Rise of the metabolic production baseline is limited by 1000 at 200% (D).

Implementation

The implementation is shown in the Figure 18. Given the bicarbonate concentration and pH inputs and BEox and ions array interface, the KidneyMetabolicCompensation component produces a flow of HCO_3^- and consumes UA (and a chloride ion, given the circumstances).

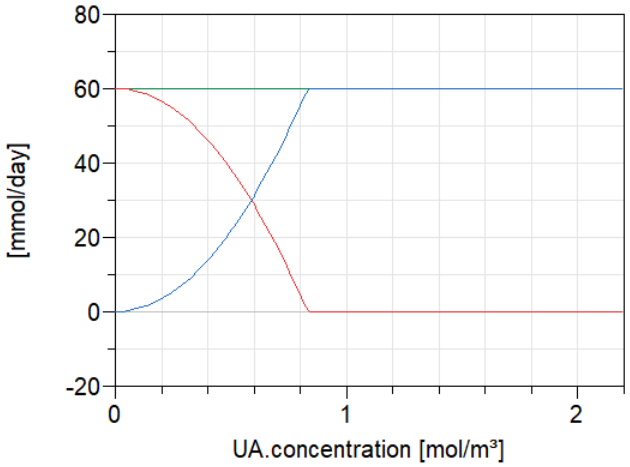


Figure 17: To maintain the electroneutrality, the bicarbonate production flow (green) is accompanied by excretion of organic acids (blue), if there are enough of them. The chloride ions are used in case of low UA concentrations.

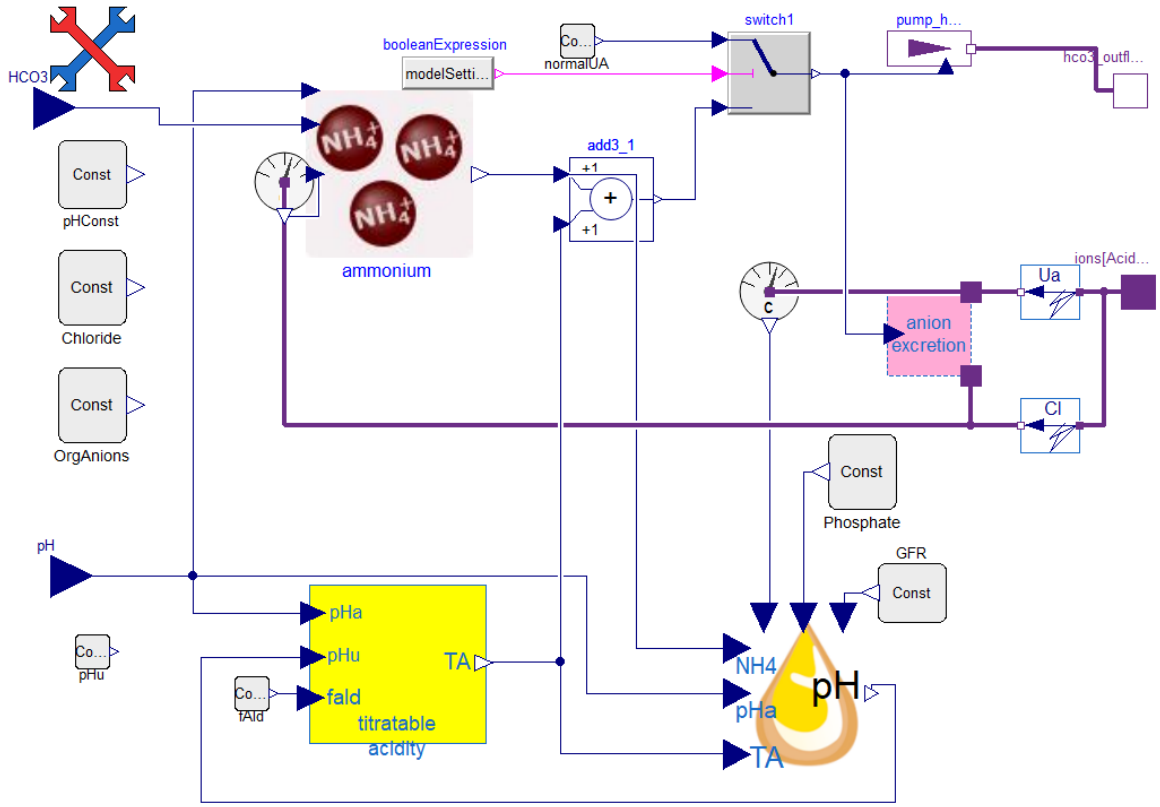


Figure 18: the schematics of the kidney regulation. The HCO_3^- produced by ammonium excretion and titratable acidity sum together and have to be counterweighted by the anion excretion.

2.12 Maneuvers, interventions and events

The body is seldom left by itself. Instead, it undergoes a number of interventions, including medication, fluid and solutes administration and bodily maneuvers. For the current stage of the model, the pharmacokinetics nor pharmacodynamics are considered. The only implemented event is vomiting (Figure 19), which is a sample cause for metabolic alkalosis.

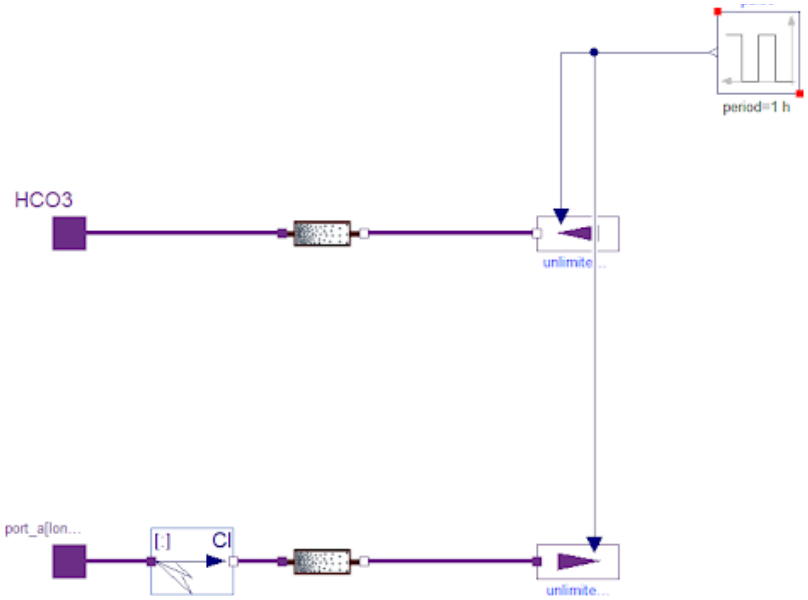


Figure 19: The inner schema of the model (right) describe the outflow of chloride ions and the apparent generation of HCO_3^-.

2.13 Model integration, verification and validation

The circulation serves as a base to which other components are connected. First we have to set the initial conditions step by step. Initial conditions, which are too far from the steady-state solution would prevent the numerical solver from finding a solution. Also, the initial transients would trigger the compensational mechanisms (a shift of HCO_3^- from interstitium, integration of respiratory and kidney responses), which would take a long time to disappear. Initial conditions should be therefore set iteratively from the simplest to more complex models.

First of all, we start with the circulation model and extend it with blood gases. Then we set the alveolar ventilation (with disabled regulation), so the pCO_2 would be set at 5.3 kPa. Then the steady values of O_2 and CO_2 arterial and venous concentrations are to be set as the initial values. Then we connect the tissues (with disabled osmotic shifts), so they may act as a buffering solution and shift the BE, if connected into an unstable environment. Then we can enable the osmotic shifts and adjust the impermeant solutes concentration to keep the ISF volume constant. This iterative procedure assures consistent initial conditions, which are not too far from a steady state.

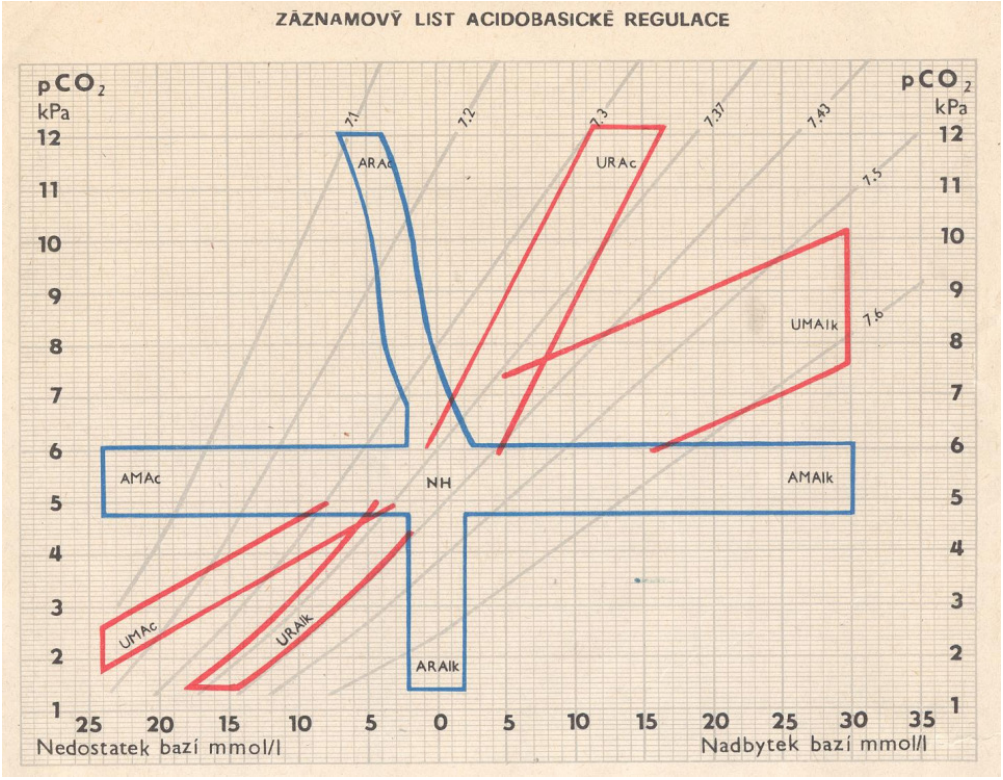


Figure 20: A record sheet for a bed-side assesment of acid-base disorders (Engliš 1972). X axis - a base excess (right positive, left negative), NH - normal values, ARAc - Acute Respiratory Acidosis, ARAlk - Acute Respiratory alkalosis, AMAc - Acute metabolic Acidosis, AMAlk - Acute metabolic alkalosis, URAc - chronic Respiratory Acidosis, UMAlk - chronic metabolic alkalosis, UMAc - chronic metabolic Acidosis, URAlk - chronic Respiratory alkalosis. The image reproduced from (Vymětal Undated).

Verification

Verification (a process of assessing the implementation of the model against the conceptual model (Carson 2002)) has basically two parts: first the actual implementation and second making sure the results of numerical simulation are not compromised by numerical errors. The numerics can be checked by running the model at by order of magnitude lower tolerance (and/or the result sampling frequency) and comparing against each other. If there is some visible discrepancy, the numerical issues probably take place. Decrease the tolerance (that is increase the precision) and repeat the process.

Validation

Validation (a process of checking the model against the physical data (Carson 2002)) is performed by comparing the model outputs to the data from literature. For a normal state we considered the physiological values from general medical textbooks ((Hall 2010; Lumb 2012; Kamel and Halperin 2016)). Although the general methodology advises validation of

individual components, we rarely have data from separated organs. Thus, only the individual components are normally verified and then the whole model is validated.

For acute states of acid-base disorders and their compensations, we are comparing the results with the nomograms used in clinical praxis. Particularly, we are aware of two: the Siggaard-Andersens compensation nomogram and the compensation nomogram by Engliš (Engliš 1972), used in the Czech clinical practice.

The compensatory nomogram by Engliš has been put together in 1972 (Engliš 1972) as a compilation of described compensations (Kildeberg 1963, 1964; Brackett et al. 1965; Eichenholz 1965; Albert et al. 1967; Winters 1967). Since then, it has found its way into the Czechoslovakian clinical praxis in mass-printed record sheets for bed-side assessing acid-base balance and compensations during time (see Figure 20).The parts of the nomogram has been already known In the western world (Winters et al. 1969) and Engliš put them all together into one nomogram. Because we used the Siggaard-Andersen's nomogram for behavioral identification of the compensatory limitation during chronic respiratory acidosis, we primarily use the Engliš nomogram for the validation.

2.14 Model results

Normal state

The complete model (class AcidBaseBalance.Results.CompleteModel in the model package) presents both respiratory and metabolic compensations, respiratory and metabolic production and ion and water balance between plasma and interstitium. The model is shown in Figure 21 A. This model was run for a month under normal conditions and with no interventions. The results are presented in Figure 21 B-E and are within normal physiological bounds.

Impaired lung ventilation or perfusion

The distribution of lung ventilation is important for proper function. The alveoli which are under-ventilated, but normally perfused affect the overall lung function, by forming an apparent shunt (as observed by Pauley (Paulev and Siggaard-Andersen 2004)). Therefore, the body normally avoids perfusion of the impaired alveoli by increasing their resistance. If a large portion of the lungs is affected, it results in increased pulmonary resistance, pulmonary hypertension and eventually cor pulmonale (Menashe et al. 1965). The long-term regulation is however not a part of the model.

For demonstration purposes (and for an identification of the "apparent shunt"), it is enough to divide the lungs into two compartments, and divide the perfusion and ventilation between them. The alveolar ventilation is set constant at 4.61 l/min and no regulatory effects are employed, therefore the kidneys and ISF blocks are missing.

The model AcidBaseBalance.Results.ImpairedLungVentilation is shown in Figure 22. The model has been modified to simulate a ventilation ratio from 1:1 (50%:50%) to 1:10

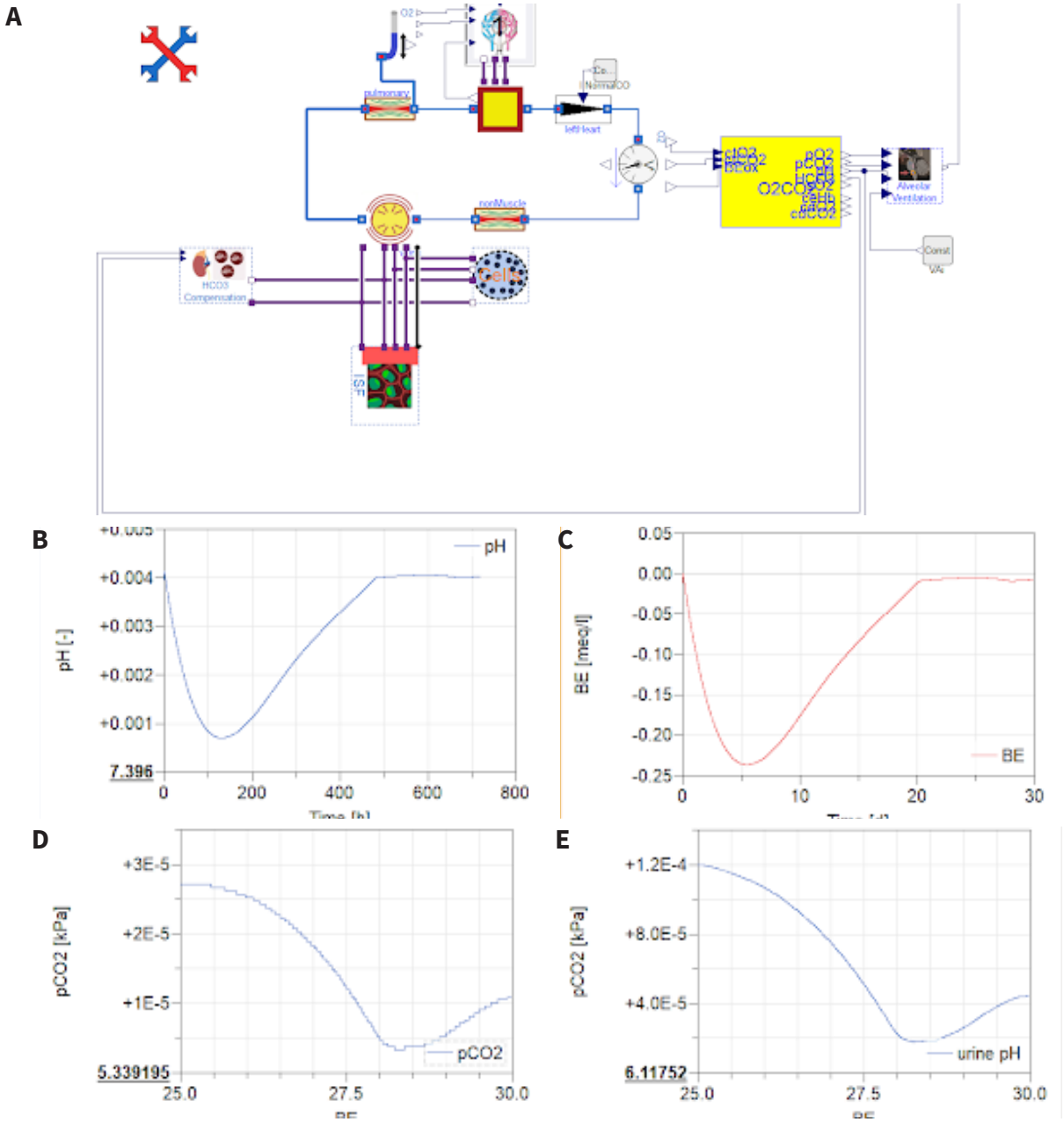


Figure 21: The complete model schematics (A) during normal conditions (B – E) The model shows some transients at start, which are however clinically irrelevant

(91%:9%) after one hour and to change the perfusion in the same ratio after another hour.

The results are shown in the Figure 23 and demonstrate the crippling effect of uneven ventilation on lung performance. When the circulation is modified accordingly, the lung function returns to normal. The exact results could not be validated, but the general response fulfills the expectations. This model has an accompanied web simulator, discussed later.

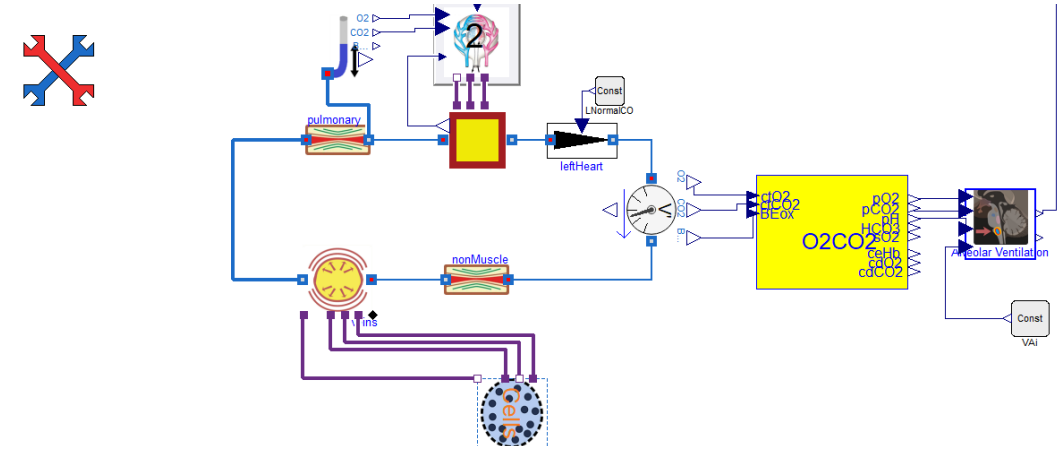


Figure 22: The model demonstrating impaired lung ventilation. Note the usage of the double lungs.

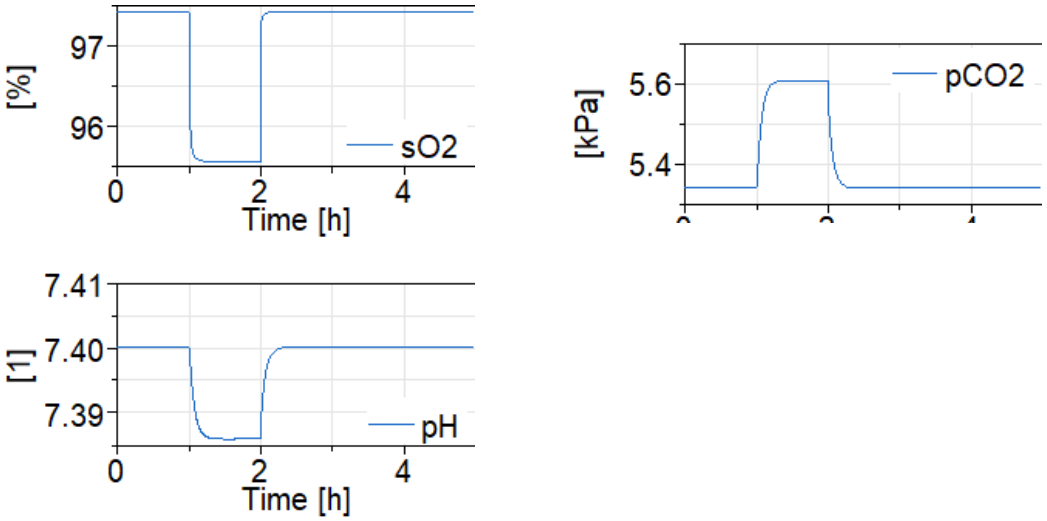


Figure 23: The uneven ventilation after one hour results in reduction of a lung ability to properly saturate blood with oxygen and extract CO_2

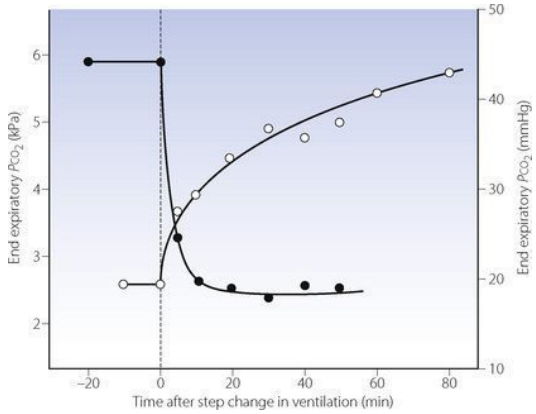
Asymmetric reaction to step in alveolar ventilation

It has been observed (Lumb 2012), that a sharp step from higher to lower ventilation causes a slower reaction in arterial pCO_2 than the opposite step from lower to higher ventilation. We demonstrate the ability of the model to reproduce that behavior. This effect is caused by the accumulation of the CO_2 in the interstitium, which is therefore crucial to be included in this model. Then we had to experimentally adjust the oxygen consumption (7.5 mmol/min) to get the similar result as described in literature (Figure 24)

The perfusion effect

During low tissue perfusion the CO_2 produced by the tissues is less flowed away, resulting in higher pCO_2. This leads to an acidic environment, which could lead to a protein

A



B

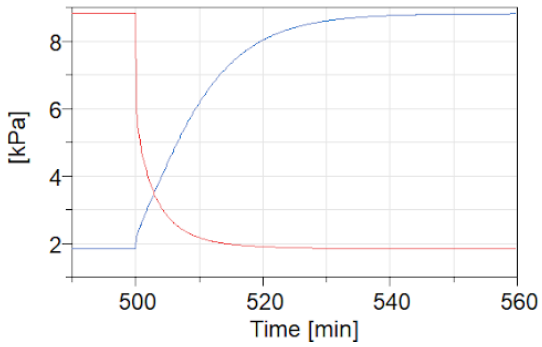


Figure 24:

A) A change in respiration on end tidal CO_2 effect. The step from 14 to 3.3 L/min causes slower reaction than the opposite step from 3.3 to 14 L/min. The difference is in the ISF volume, which contains the HCO_3^-, which is produced by the metabolism. This change in dynamics is then governed by its size and could be useful for guessing the size of the ISF. The total metabolism rate could be given by VA and end tidal pCO_2, but those changes say something also about the volumes. The image reproduced from (Lumb 2012), figure 10.11

B) Reproduced result

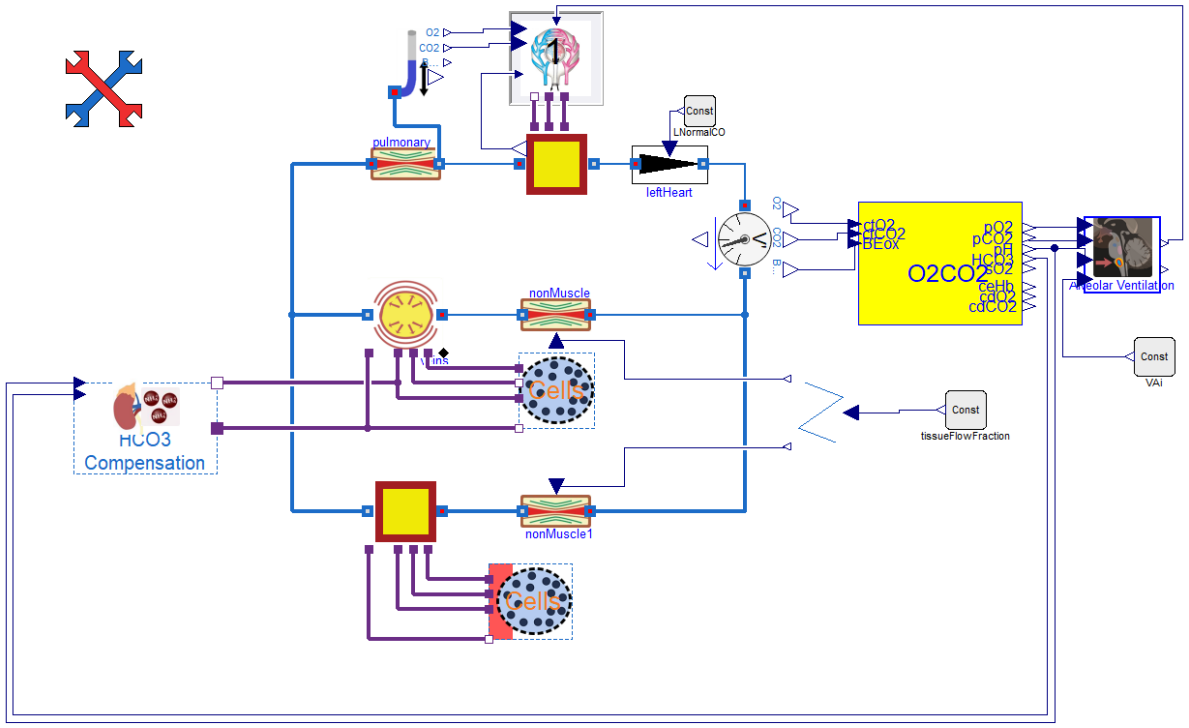


Figure 25: The model used for simulation of the tissue hypoperfusion

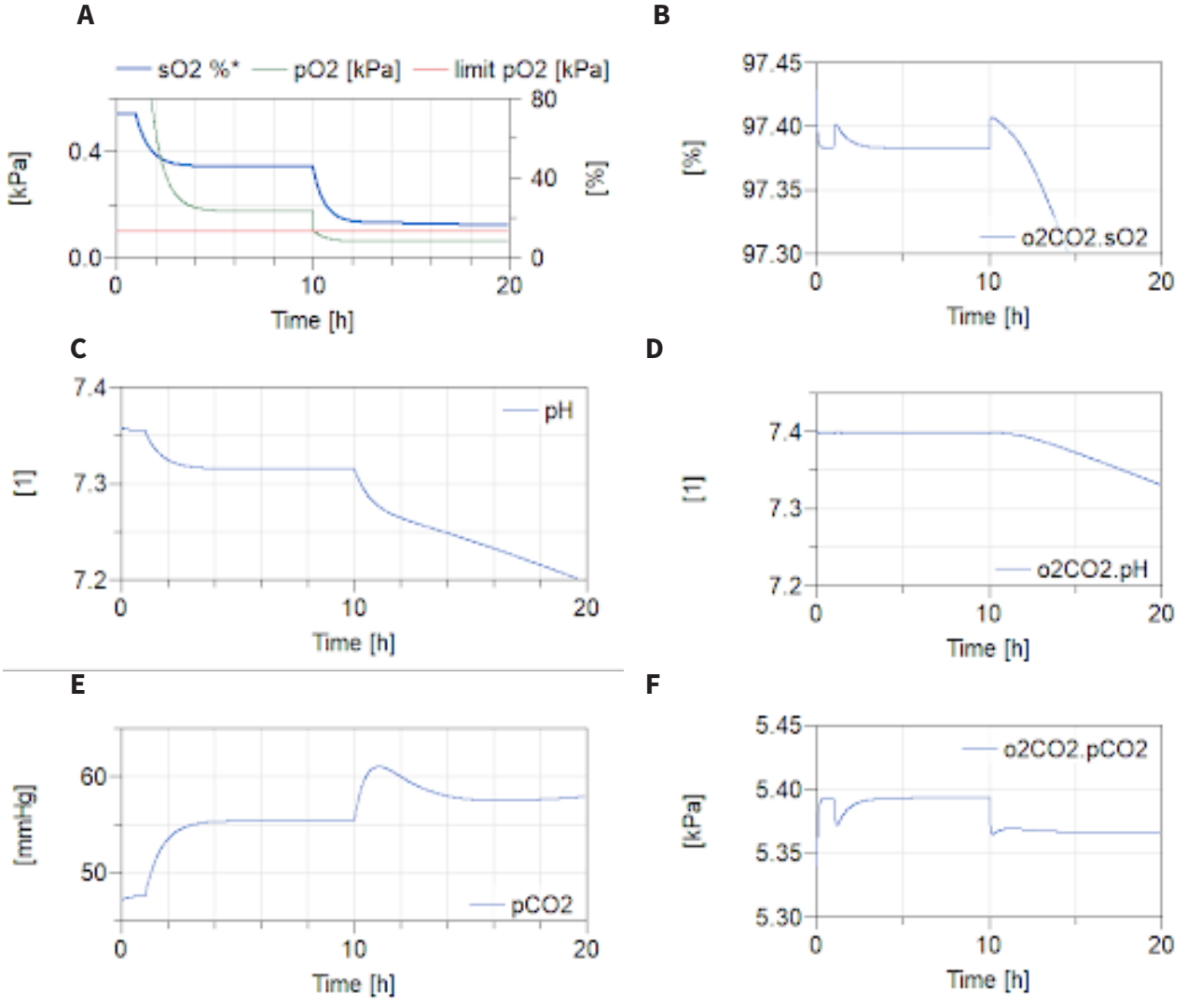


Figure 26: After 1 day for model stabilization, the perfusion of a small part of tissues has been limited by 50% after one hour and by 90% at 10 hours. During mild hypoperfusion, only the local tissues are affected (left - A, C, E). But since severe hypoperfusion, where the pO_2 drops below the critical level (A) associated with lactate production, the hypoperfusion of the 1% of the tissues severely affects the whole organism (BDF).

dysfunction due to the altered conformation (Graham et al. 1997). This phenomena demonstrates the necessity of using the the acid-base model together with the circulation.

We can demonstrate two cases - in the first case the local acidosis emerges only due to the concentration of CO_2 in underperfunded tissue, and in the second case, the hypoxemia leads to lactate acidosis.

The model is shown in Figure 25. It includes kidneys, but the metabolic and respiration compensations are turned off. The secondary parallel tissue has a 1% nominal cardiac output and a 1% nominal respiratory metabolism. To observe both cases, the perfusion has

been limited by 50% (to 0.5% of the nominal flow) after one hour and by 90% (to 0.1%) after 10 hours to unleash the lactic acidosis. The results are in line with the expectations, that the local acidosis is not well observable in the whole system, until the emergence of lactic acidosis (Figure 26). Note, that the tissues show values for venous blood.

Respiratory acidosis

Respiratory acidosis is caused by an inadequate alveolar ventilation, usually by an bronchial obstruction or alveolar damage. Experimentally, it has been achieved by increasing the fraction of CO_2 in the inspired air. The respiratory centrum then immediately reacts with a higher respiratory rate, but fails to correct completely. The respiratory acidosis is then compensated in the kidneys by the increase of BE.

For this simulation we use adjusted Complete model from the Figure 21 A. We allow for one day to let the model come to a rest. After 1 day we set the $FiCO_2$ to 7%, with both respiratory and metabolic compensations. The results are in the Figure 27. It can be seen, that the sharp rise of the pCO_2 is accompanied by a small sudden fall in the BE. This is a response of the interstitium, where the accumulated HCO_3^- is getting exchanged for Cl and with Na ions. The acute response (BE -2, pCO_2 8 kPa) is in accordance with the Engliš nomogram and general accordance of other measurements (Brackett et al. 1965; Ellingsen et al. 1987).

The metabolic compensatory reaction increases the BE to 6, which helps to stabilize but does not fully compensate the pH. The postulated explanation is that the concentration of HCO_3^- exceeds the maximal HCO_3^- resorption concentration rate and the HCO_3^- production is thus limited (Figure 27 E and F). The observed compensated pH is in compliance with both the Engliš and Siggaard-Andersen compensatory nomograms and with generally observed compensation time of 3-5 days (Hall 2010; Silverthorn 2018).

It has been observed (Tannen and Ross 1979; Tannen and Hamid 1985), that during the respiratory acidosis, the pH of the urine is reduced by about 0.1 of pH, which is reproduced in Figure 27 G. It is caused by the rise of NH_4^+ production (Figure 27 H).

Respiratory alkalosis

Alkalosis has mostly iatrogenic causes, a mild alkalosis is well tolerated, but a severe alkalosis (with pH over 7.65) is a major complication with around 80% mortality (Ronco et al. 2009).

The respiratory alkalosis may be caused by pathological stimulation of respiratory center or iatrogenic by inadequate artificial ventilation. For this simulation we use the adjusted Complete model from the Figure 21 A. After letting the model maintain steady-state for 1 day, we simulate the respiratory alkalosis by setting alveolar hyperventilation to 200% of norm for 9 days. The results are presented in Figure 28.

The sudden drop in plasmatic pCO_2 (and bicarbonates) in plasma leads to a shift of HCO_3^- (and ions) from the ISF to plasma (or from plasma to the ISF respectively), thus changing the BE and the SID. This has not been observed in compensatory nomograms, although the SBE is much less affected and still well within the bounds of Siggaard-Andersen's nomogram (Figure 28 B).

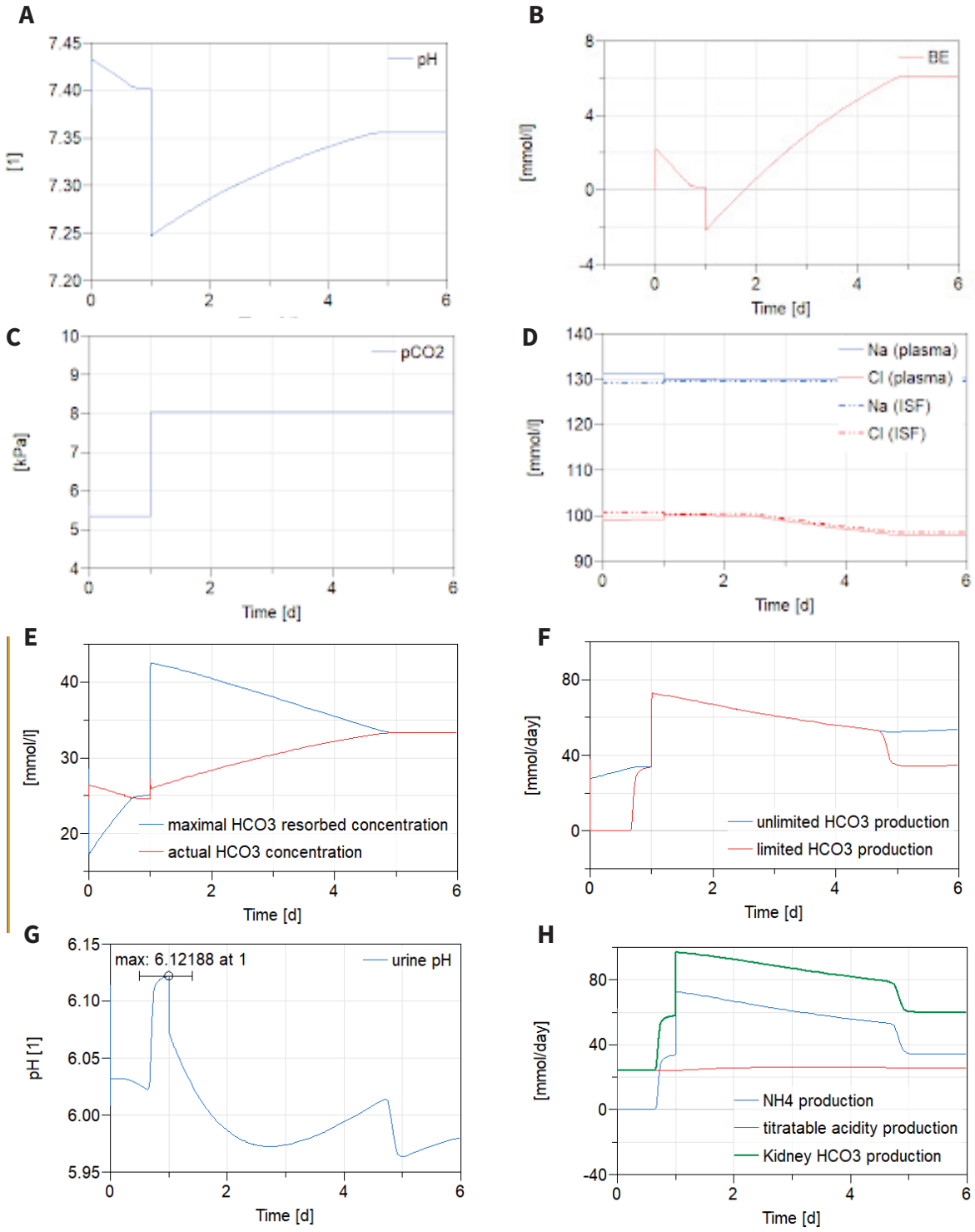


Figure 27: After 1 day for reaching steady-state, the fraction of inspired CO_2 has been increased to 7% which results in immediate pCO_2 rise (C) and respiratory acidemia (A). The drop in the BE is caused by a shift of HCO_3^- from ISF, together with other ions exchange (D). The HCO_3^- resorption limiter acts at the end of metabolic compensations (E, F, H). urine pH reacts acidically (G).

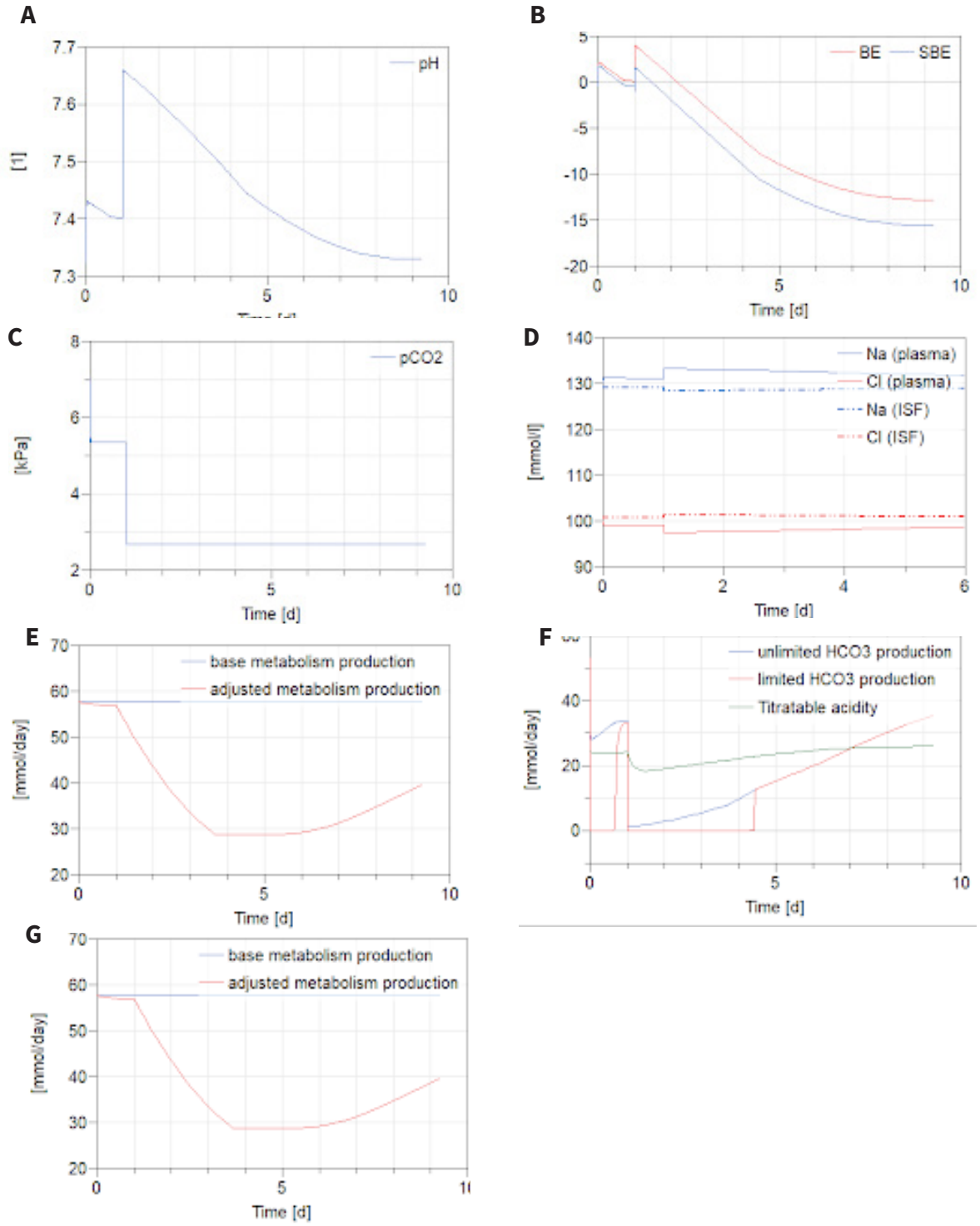


Figure 28: After 1 day to reach a steady-state, the alveolar ventilation has been increased to twice the norm, which decreases the pCO_2 and develops severe respiratory alkalemia (A, C). The rise in the BE is associated with an electroneutral shift of HCO_3^- together with other ions between the ISF and plasma (B, D). The HCO_3^- limiter inhibits the HCO_3^- resorption (E, F). The pH overcompensation is an artefact caused by the integrator windup (G).

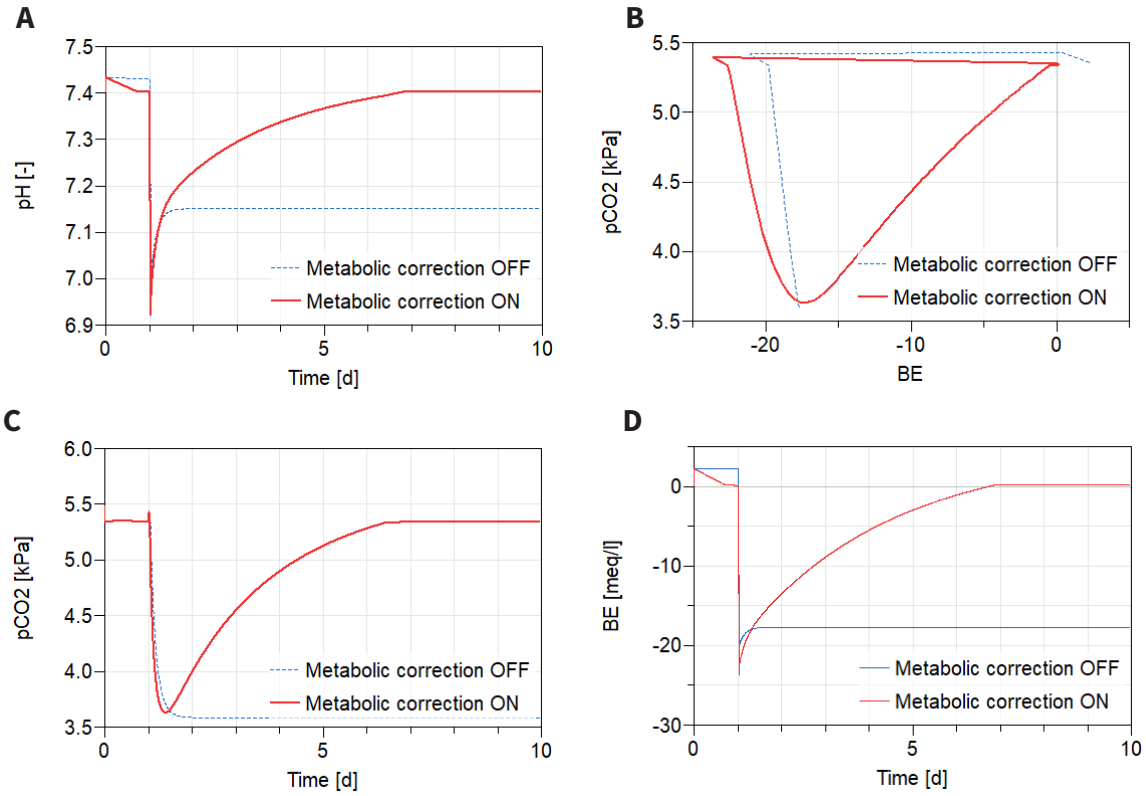


Figure 29: After 1 day to reach a steady-state, 250 mmol of UA is produced, together with depletion of an equimolar amount of HCO_3^-. That results in severe metabolic acidemia (A, B), which is compensated by respiration in about 12 hours (A, C), If the metabolic correction is not impaired, it corrects the BE within a couple of days (A, B, C). The response follows well the clinical observations in the Engliš nomogram (D).

After four days, the alkalosis is compensated, which is well in the said time-frame of 3-5 days (Hall 2010; Silverthorn 2018). Interestingly, the kidney's main HCO_3^- excretion mechanism (NH_4^+) is limited and therefore HCO_3^- is not produced, which compensated the alkalosis. The speed of HCO_3^- generation (and thus of the compensation) is mostly given by the body metabolism rate, (Figure 28 E, F).

The pH overshoot is caused by integral windup in the kidney response delay (Figure 28 G). This shall be mitigated by a proper physicochemical kidney model.

Although we observe fall in tissue pO_2, it is still far from the limit, where the lactic acid is produced. However, the lactate production during alkalemia plays a role in its compensation (Eldridge and Salzer 1967). This effect is not properly incorporated.

Metabolic acidosis

Metabolic acidosis is mostly caused by a disbalance between faster production of organic anions (associated with HCO_3^- depletion) and slower metabolic degradation (associated with HCO_3^- production). Acute metabolic acidemia may be caused by e.g. tissue hypoperfusion followed by lactate production.

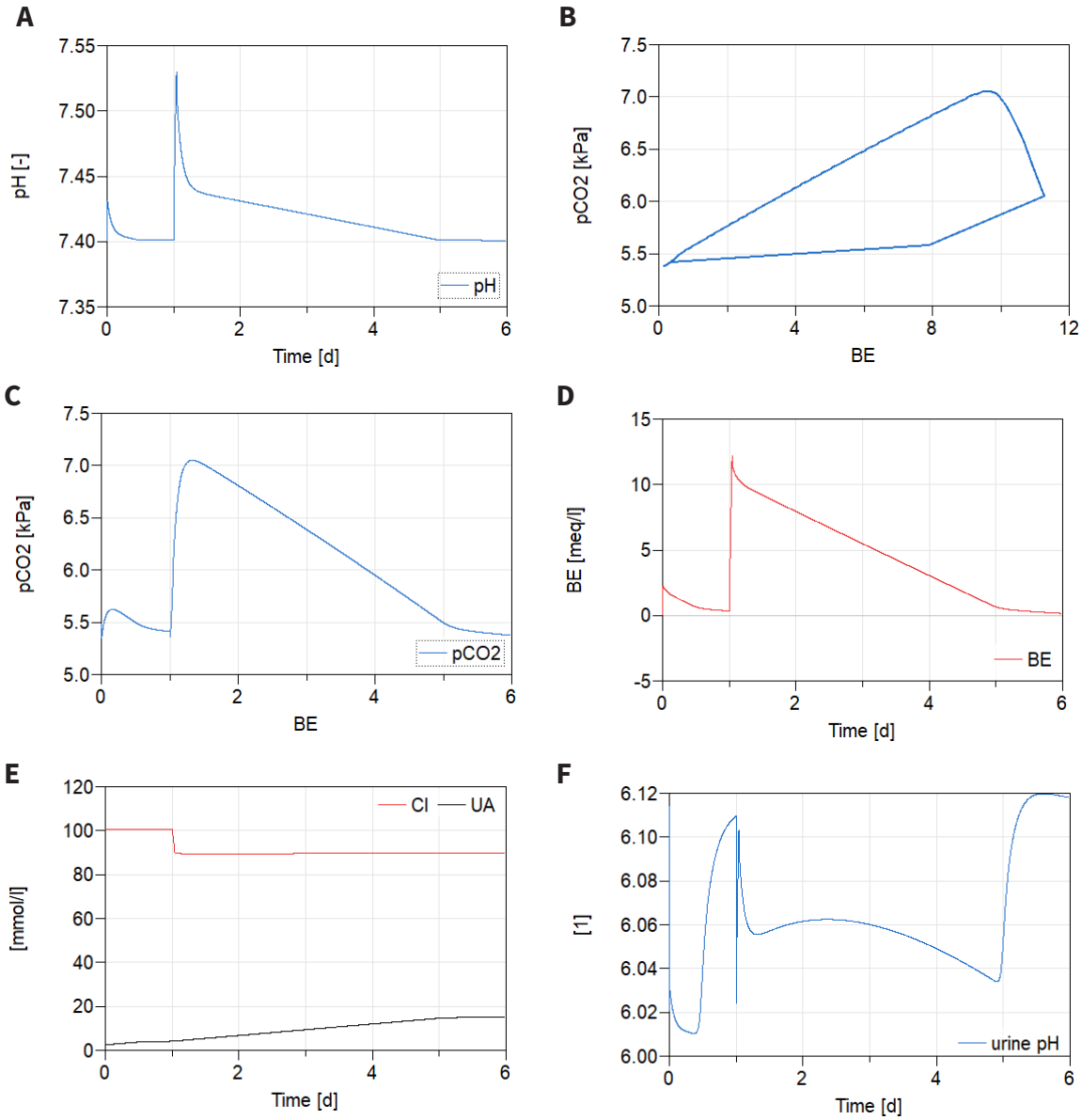


Figure 30: After 1 day to settle the steady-state, severe vomiting occurs, resulting in loss of 150 mmol of chloride and production of an equimolar amount of H+. Severe metabolic alkalosis follows (A). The respiration quickly compensates the pH in around 6 hours (A, C), followed by metabolic correction, which corrects the pH in 5 days. The response is well within the Engliš clinical observation nomogram (D). The metabolic correction limits UA excretion, rising its level and compensating thus the missing Cl in the SID (E). The HCO_3^- resorption limiter limits the NH_4^+ excretion, resulting in paradoxical urine acidification (F).

Again, we use the adjusted Complete model (Figure 21 A). After one day to settle the transients, we simulated a sudden rise in metabolic production by 10,000% for one hour (250 mmol in total) with respiratory compensation and for both the fixed and regulated metabolic correction. The respiratory compensation reacts by hyperventilation (Figure 29)

within a day. If the metabolic correction is enabled (not impaired), the kidney corrects the BE within 6 days to normal.

The acute reaction and chronic compensations are in agreement with the Engliš diagram.

Metabolic alkalosis

Metabolic alkalosis is mostly caused by a disbalance between a slower metabolic degradation (associated with HCO_3^- production) and a faster production of organic anions (associated with HCO_3^- depletion). In our experiment, metabolic alkalosis has been induced by repeated heavy vomiting, which forces the organism to produce substitute stomach acid and thus deplete Cl- and produce HCO_3^- (for each H+ spent with each Cl-).

We have simulated heavy vomiting, with a loss of 150 mmol of HCl in one hour. This produces a severe alkalemia, which is however quickly compensated by hypoventilation (Figure 30 A-C). Then the kidney metabolic correction develops and corrects the missing chloride by UA, respectively by holding back its excretion, so the UA rises (Figure 30 E). The acute and chronic course is well within the bounds of the Engliš nomogram (Figure 30 D). The whole metabolic correction takes around 4 days, which is supported by an experience from clinical praxis. Due to a limitation of NH_4^+ excretion, we can observe the paradoxical acidification of urine (Figure 30 F).

2.15 Discussion

We presented a physiological model of respiration and acid-base homeostasis, with circulation as its basis. The approach to modeling acid-base follows the principles sketched in the balance approach to acid-base equilibrium (Kofranek et al. 2007; Kofránek and Ježek 2018c). The model is able to dynamically simulate a number of circulatory, perfushion, respiratory and metabolic disorders and is validated by comparison to clinical data and to compensatory nomograms.

The ratios of lung ventilations and tissue perfusion and some other parameters are just arbitrary mathematical constructs, which can however describe the measured data and therefore are subjects for identification on individual patients. Kamel and Halperin (Kamel and Halperin 2016) suggested measuring both brachial and central venous Astrup measurements. Thus, we know the distribution of the blood - if the peripheral venous blood is more acidic than the central venous, then the flow to the peripherals is decreased.

In a way, the model resembles a generalized concept of a whole-body transport by Andreassen and Rees (Andreassen and Rees 2005), but it is built upon HCO_3^- balance (the BE) and including the ion balance. This extension was made possible by employing the balance approach to acid-base, which allows to decouple the ions from acid-base calculations. The ions tend to be problematic, and their exact mechanism is often unknown. When required, the ions could be re-coupled again into the acid-base consideration by the presented BE-SID

recalculation (Ježek and Kofránek 2018). On the other hand, in our current implementation it adds a degree of freedom, where the BE is in a way redundant information to the full ion composition. For future extensions, the consistency of the ion composition and the BE has to be treated carefully.

The presented model is accessible as an open-source project under MIT licence at https://github.com/filip-jezek/NewBloodyMary. The model has been built and tested in the Dymola 2019 by Dassault Systémes, but should be compatible with all Modelica editors. However, the latest OpenModelica 1.12 does not even manage to open the model due to an unknown bug.

Limitations

A number of phenomena are not integrated within the current model, as it is a strong belief of the author, that these may have smaller influence on the model than common measurement uncertainties. Namely, the Cl to HCO_3^- exchange between erythrocyte and plasma due to change of pCO_2, as quantified in Ježek and also by other authors (O'Neill and Robbins 2017; Ježek and Kofránek 2018). This so-called Hamburger shift affects the venous SID in contrast to lower-pCO_2 arterial environment. The SID is then not an independent property. However, within normal differences between arterial and venous pCO_2 (which is where this shift might be of importance), the difference is small enough to be neglected in comparison to other necessary simplifications (see the fig. 3B in (Ježek and Kofránek 2018)).

The minimal circulation model is demonstrative only and could be extended to virtually any complexity. Pulsatile models, however, have little usability with such long-regulations as acid-base compensations. The circulation has been also avoided due to complex cardiovascular regulations. If required to be done precisely, one would end with Guyton's model - at least. Thus, the circulation is planned to be corrected from patients data, as the identification of the cardiovascular system already receives lot of attention. Similarly, the fluid balance is a complex process, which can however be simplified for short term patient-specific identification.

The Respiration module of the current model considers the alveolar ventilation only. The inspired gas concentrations are however different from the alveolar concentrations, mostly due to mixing with dead space. For usage in the clinic, the respiratory extension is inevitable. Useful respiratory models could be found in e.g. (Mogensen 2011; Ben-Tal and Tawhai 2013) or the Pneuma model (Fan and Khoo 2002), which we have previously implemented in Modelica (Bundil 2014)

Some common ions are missing from the model completely - especially phosphates, a buffer with a minimal importance, Ca^{2+}, Mg^{2+} and K^+ ions. The idea was to start with a proof-of-concept approach, as any ion could be very easily added just by expanding the ion enumerator.

Ion disbalances (diarrhea acidosis, vomiting alkalosis, hyperphosphatemic acidosis, hypoalbuminemic alkalosis) are not described exactly due to missing ion balance. That

is an independent regulation and stabilization of all ions. This is however connected to detailed water balance. Therefore, substantial contribution to the future model extension lies in properly modeling the kidney, as most of the regulations are kidney-related. Once the bodily outflows are regulated, one also has to consider the stabilization of the inputs - such as the digestive system, periodical infusions etc. This however by far extends the scope of this thesis.

Cells, a largest fluid compartment, are not incorporated into the buffering considerations and water balance at all. Despite that they may play some role, especially in water balance, they usually actively hold their inner homeostasis and their effect can be described only very vaguely. Thus, it is a common approach (e.g. initial versions of the Wolf model (Wolf and Deland 2011b)) to omit the cells compartment completely in acid-base models.

Nevertheless, the presented model is capable of describing pathogenesis of a range of acid-base disorders.

Computational complexity

The complete model contains more than 1800 equations, out of which over 1200 are alias variables (a different name for the same variable, e.g. connector joints etc.) and 580 are true time-varying variables.

Large integrative physiological models are usually numerically hard to solve. One of the reasons is they tend to be very stiff - some flows in the organism are very slow (e.g. an inflow of organic acids in mmoles per day), others are extremely fast (ions transfers on membrane), which require particular attention of the numerical solver. In addition, physiological models in general are naturally non-linear, but acid-base is an extreme variant - with the exponential dependency of pH on H+, where very low difference in the H+ value (in order of 10^{-7}) makes changes in orders of units of pH.

The development was executed on a four-core i7-3610QM @ 2.30GHz CPU with 32GB RAM, running Windows 10 Enterprise, build 1803. The computation of a reference model (MetabolicAlkalosis scenario, time 5 000 000s, 5000 output intervals in Dymola 2019 using the generally preferred DASSL algorithm) took 120s. Almost 6 years newer machine (six-core AMD Ryzen 5 2600 @ 3.4 GHz, 16GB RAM) required 109s for the same scenario. This low margin is due the single-thread nature of the model computation, i.e. the Modelica models are not very well suited for parallelization and therefore only one processor core is effectively utilized. Setting experimental support for multi-thread simulation (command Advanced. ParallelizeCode = true) in Dymola 2019 resulted in even slower computation speed (145s and 136s, respectively).

Thus, newer machines with more cores and parallel threads do not provide any significant acceleration and, vice-versa, the computation also runs similarly on older and not as powerful machines. There is an ongoing research on parallelization of co-simulation FMUs (which are employed for the model visualization, see below), but the problem is not yet satisfactorily solved (e.g. (Saidi et al. 2016)).

The model usage for clinical aid would include a number of model runs for the identification, which could pose an obstacle. Identification methods however scale well with parallelization using e.g. genetic algorithms (Cantu-Paz 1999). To reduce the computational burden, the parts of the model which are not required to simulate a particular task, shall therefore be disconnected. This also helps to better identify the model's behaviour.

From our analysis of the computational complexity of the model, most of the computational effort is produced by sub-optimal implementation of Siggaard-Andersen's acid-base calculations (the o2co2 block, calculating pH, pO_2, pCO_2, sO_2 out of total O_2 and CO_2 and BEox), which is an exact replica of the algorithms used in the Oxygen Status Algorithm application (Siggaard-Andersen and Siggaard-Andersen 1990). If the computational complexity was a major issue, one can simplify the model by e.g. substituting the BE-pH calculation by the method we proposed in (Ježek and Kofránek 2018), together with the oxygen dissociation curve in Dash et al. (Dash et al. 2016). However the computation speed proved to be just sufficient for smooth visualization on a modern consumer-level hardware.

3 Methodological approach to model development

"Modeling is an art."

Based on experience, the author proposes the following general methodology for development of quantitative physiological models. We will illustrate the examples in the Modelica language and the presented model, but it is meant as a general methodology also for other equation-based modeling languages (e.g., SimScape) and other physiological models.

1. Modeling is an art of simplification - the most precise model would otherwise be an exact copy of the system. Therefore, it is essential to correctly identify the most important features of the system (or, in other words, most influential on the output) within the defined conditions. Therefore, we have to determine first the normal operating conditions, under which we observe the system. Then, we need to define meaningful requirements of the model, such as time scale, observed outputs.

2. Draft the general model structure and define the interfaces between the components. The model structure shall maintain the structural validity of the physical object if possible. The structural validity assures good understandability and allows for easy extensibility.

   For the currently presented model, the structural validity means also having the circulation, which drags ions and gases as the core part of the model. Other parts are then connected either via circulation elements, or its communication points - capillary membranes, alveoli etc. Current modeling tools, such as employed Modelica, are capable of this abstraction.

   The best practice is always to use SI units for all models, but they often happen to be impractical, especially in physiology. E.g., the blood flow unit of m^3/s yields incredible small values, whereas a unit of l/min is much more convenient. Therefore, Modelica offers a feature called display units, which allow to show the recalculated derived unit for the input of parameters and for presentation of results, although a different unit is used for the calculations.

   In the presented model, most of all variables and all interfaces, have been set to correctly represent their true physical unit. Physiolibrary extends the set of units, already defined in the Modelica Standard Library (MSL) by units specifically used in physiology.

   The physiolibrary is based on SI units with recalculations to more commonly used units and interfaces of common domains.

3. Draft model subsystems, describe what could affect their behavior (inputs) and how they can affect the surrounding components (outputs). Then, model mechanics and relationships should be designed, based on system knowledge or observed behaviour.

Start from simplest models to gain understanding of the relations and prevent errors. Use only the absolutely necessary components to fulfil the requirements. Additional complexity is unnecessary, as it harms both computational complexity and comprehension of the system and it has even been stated, that the complexity may harm accuracy of prediction (Green and Armstrong 2015)(Sun et al. 2016).

Prefer the behavioral description first, if such data are available, unless full understanding of the behavior based on the first principle physicochemical processes is available.

We used a similar combination of physicochemical and behavioral modeling in our previous paper (Ježek and Kofránek 2018). The crude behavioral description may then be expanded and described properly, if such requirement arises. Detailed physicochemical description has the advantage of deeper understanding and often enables to integrate more dependencies and enables to consider natural bounds and relations, not only the bounds of measured data.

Use inheritance to prepare the component to be superseded by other component with a different time scale or precision, as described in (Ježek et al. 2017). E.g. simple circulation could be extended by a pulsatile one, a simple vessel could be extended by a branching subsystem etc.

We advise to maintain the structural validity of each subcomponent as well.

4. Validate the subcomponents on available data (time course, steady state) against the objectives. Build (and maintain) a dedicated test bed for each subsystem (unit tests), where other components are substituted with dummy parts (mock components). These test cases could be run automatically later to ensure some change did not impair the proper functionality of the component (regression testing). Integrate the subcomponents into the main model, use dummy submodels to guess initial values if necessary.

   Make sure the subcomponents in the final model have a comparable level of detail, precision and validity, unless it is a part of objectives or requirements (e.g. in our case, the Donnan equilibrium between the ISF and plasma in contrast to ignoring the effect of cells is justified only by the requirement of electroneutrality)

   A high level of accuracy of one component must not contrasts with crude simplification of the phenomena in any other part. It's not worth counting grains of sand, when you throw in several bricks. E.g. the Wolf model (Wolf and Deland 2011a, 2011b; Wolf 2013, 2015) shows an extraordinary level of detail in virtually all aspects, including ionization of Ca2+ and Mg2+, whereas the albumin concentration in the ISF, a driving force behind the oncotic pressure and Donnan equilibrium is set as one third of a plasmatic level.

5. Iterate to fit other phenomena and datasets, revisit behaviorally described / simplified models and add required complexity. Have doubts to include particular phenomena? Build a model to test the assumptions of negligibility.

6. The test dataset might not be satisfactory. Prepare interactive visualization of the objective behavior and share with the experts in the field to get expert feedback. This methodology is described in the chapter Model visualization for medical simulators.

4 Discussion of model usage for the intensive care clinical aid system

"If it was easy, it would have been already done."

It is a long and thorny path from the idea to the clinical aid system. The aim of this chapter is to discuss the intended use of the model.

The motivation of the thesis is to provide clinicians with a visual aid to support their decision. The idea is to have a patient's virtual copy, a model, identified by a number of measurements, where we could see the hidden states and partially predict the future. The role of mathematical models in a clinical practice is further discussed from the viewpoint of a ventilator aid system in Rees at al. (Rees 2011). Such aids are already in use, e.g. (Burakovskiĭ 1982) or are being constructed (Spadaro et al. 2018) or considered (Bighamian 2017). Rees and Karbing summed special consideration regarding the use of a ventilator model as a clinical aid system in (Rees and Karbing 2016).

It might be objected, that under the condition of fully understanding of the physiological mechanics (e.g. by using the developed simulators described below) and maximal attention, the output of the model might be guessed without a need of a clinical system. The clinical system aims to ease the work of a clinician and to avoid mistakes, especially in critical circumstances, not substituting a clinician.

The adoption and agreement is crucial for clinical benefits. The medical staff, their understanding and opinions about the system should not be ignored in the process. We hope, that the developed demonstrational simulators would ease the recognition of the benefits of such a system.

The model has been developed with the purpose of possible identification in mind. That means a minimal amount of parameters, that could vary among individuals. The problem lies especially in individual parameter identification. The naive computational complexity for identification of independent parameters is $(O) = 2^n$, where the n is the number of the parameters. The identification becomes practically infeasible with the number of parameters higher than 6 or 7. The safe number of simultaneously identified parameters is around 6. The proposed approach therefore lies in tearing the system into identifiable components, using predefined parameters set for given diagnosis.

For clinical use, a minimal model can be constructed, where the model has a minimal complexity (and a number of parameters) to allow unique identification. Such a model is aimed specifically at fitting the data, structural validity and extensibility are of a minor

concern. To reduce the number of parameters, some parameters could be, with a help of a sensitivity analysis, considered as constants, some of them could be fixed as constants, whereas some other could be grouped and chosen from a pre-set group of constants for the selected diagnosis.

Models with a smaller number of parameters are not necessarily worse than higher-parameter-number models, the contrary might be a way - Holmes and Lumens (Holmes and Lumens 2018) suggest, that “reducing rather than increasing model complexity may be the key to realizing the promise of patient-specific modeling for clinical applications” .

We do not present a minimal model per se, but a basis for one, which could be further reduced and optimized.

4.1 Data acquisition

Another problem is online data acquisition. Some hospital information systems already store data from laboratory examinations (in particular blood examinations, such as ions and acid-base status), but the data from patient monitors (especially about circulation status) are normally not stored anywhere. The same holds for data from connected support machines (ECMO, ventilator, drug dispensers) etc. Some machines do provide a possibility to export data for investigative purposes. However the storage frequency is often limited, leaving us with trends or mean minute values. Some of the devices do not support this functionality at all.

From the author experience, this is the biggest obstacle in considering a model-based decision system into a clinical environment. To address this issue, we have investigated the possibility of an optical acquisition system (Tošner 2017), which however proved too complicated even for research purposes. A cooperation with the device manufacturer seems therefore unavoidable.

4.2 Identification

Identification of a complex non-linear systems is a challenging task. The task itself is generally NP complete. It can be solved heuristically by the generation of a random model population with random parameters and then optimizing the population (Chen and Zhou 2015; Kofránek et al. 2017) and find the best candidate by e.g. genetic algorithms. Pruett and Hester (Pruett and Hester 2016) suggested constructing surrogate models from a population of complex models to drastically reduce the model complexity for the specified objective.

The subsystems are measured at different time scales - e.g. the circulation could be measured continuously hundreds of times per second, whereas the acid-base and plasma composition is routinely measured once or twice per day. The model could be then torn into several parts and identified individually. Actually, the presented model is especially suitable for it, as some systems are not directly dependent on others. Circulation could be identified

alone (Burakovskiĭ et al. 1980; Gesenhues et al. 2017) and similarly, we can identify the gases out of the data from the ventilation machine (Spadaro et al. 2018) and response to fluid therapy (Bighamian et al. 2016). The acid-base compensations could be guessed either from the kidney output (i.e. the urine) and more importantly, the time course of blood and urine composition. Having several time points would enable to identify the hidden states (ISF, cells, level of compensations) and to better predict the prognosis. The precise method of identification is however subject to further investigation.

4.3 Interventions and medication

Any external interventions have to be especially addressed for the future clinical aid system. The pharmacokinetics and pharmakodynamics are not part of this thesis and they have to be elaborated before the model could be used for a clinical scenario. Administration of medicaments is frequent in critically ill patients and its effects can not be simply omitted. Sometimes the effect could be easily assessed from measured values (e.g. diuretics), in another cases it would require detailed analysis. It would be beneficial to include a prognosis of effects of the most common medicaments into the model to see the impact before an actual medication.

Other possible interventions and events (e.g. a change of position, nourishment, diarrhea, unplanned iatrogenic interventions etc) must be carefully considered before clinical adoption.

4.4 Conclusions

The presented model is intended as a basis for a clinical aid system, further elaborations and optimization are however required, especially in the areas of pharmacology, data acquisition and identification.

Accessible simulators are necessary to understand the importance and abilities of such a tool and could be therefore helpful in its adoption.

5 Model visualization for medical simulators

"I hear and I forget. I see and I remember. I do and I understand." Xunzi

The models are becoming a means of communicating knowledge about the system and can be used to evaluate hypotheses about system's functiouhn.

However, models can become too complex for easy comprehension and equations alone are sometimes not enough to understand the system's behavior as a whole. The end user thus needs to run and adjust the model to gain an appropriate understanding about its function. Our use-case of models is aimed at interactive demonstrational and educational tools.

In physiological modeling, a number of modeling tools are used - e.g. Mathworks Matlab/Simulink, CellML, JSim, OpenModelica etc - and each one requires an installation and at least some familiarization with the tool to be able to run the models. Some tools even require a (very expensive) commercial licence. To overcome this, a standalone simulator is required, preferably without a need of installing anything. Web-based technologies do offer a convenient solution (Kofránek et al. 2009b) and allow the simulator applications to be accessed as simply as the rest of the contemporary world-wide web.

However, development of a simulator is often a demanding task. Some effort has been put into development of web-based simulators, e.g. the proprietary Modelica.university (Tiller and Winkler 2017) or the Bodylight framework (Ježek et al. 2013) based on the discontinued (Smith 2015) Microsoft Silverlight.

Some researchers (e.g. (Zhang 2001; Kulhánek et al. 2013; Christ and Thews 2016) and a number of others) aimed at a client-server simulation. Such a solution relies on a server which performs the computation and a client only receives the resulting data. Based on the user input, the client asks for a new set of data. The second possible approach is fully client-side, in which the client is responsible for both the computation and user interaction (see Figure 31).

The client-side concept is initially more demanding task, as the whole calculation has to be performed in a web-enabled language, i.e. JavaScript, it however offers some advantages. Especially for educational purposes, the server does not have to bear entire classroom's worth of computation at the same time.The requirement of smooth visualization, including continuous simulation graphing, movement of animated components and prompt interaction therefore prefers the client-side approach. Although the usage of a modern cloud technologies with scalable computational power and decentralized geographical location would reduce the client-server lag to satisfying levels, the price of the infrastructure and development is substantially higher and scales sharply with any new user. Of course, very

computationally demanding simulators are not meant to be client-simulated, but those are out of scope of the discussed physiological models.

As of 2018, no open web-based simulator platform capable of running complex equation-based models exists.

The aim of this work is to develop a client-side simulator technology, based on the chosen Modelica language and a simulator-producing toolchain. This technology has been named Bodylight.js

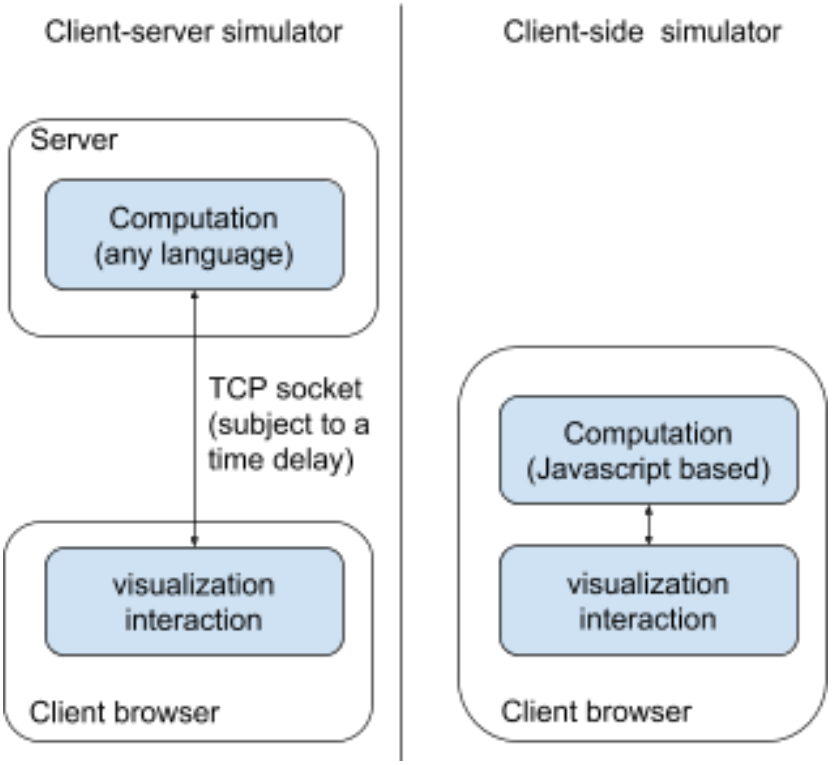


Figure 31: Client-server vs the client side approach

5.1 The Bodylight.js build process

The author has contributed to development of web-based simulators since 2012 (Ježek et al. 2012). After designing a set of simulators (a sample is shown on Figure 32), based on the custom Bodylight framework, built on a Microsoft Silverlight web technology (Ježek et al. 2013), the core Silverlight platform has been discontinued (Smith 2015). Lessons learned - do not rely on proprietary platforms. Thus, the effort has been recently restarted, and consequently the approach has been based on open standards:

- Modelica language for modeling (Fritzson and Engelson 1998)
- Functional Mockup Interface (FMI) for model simulation
- HTML5 + JavaScript for model presentation and interaction

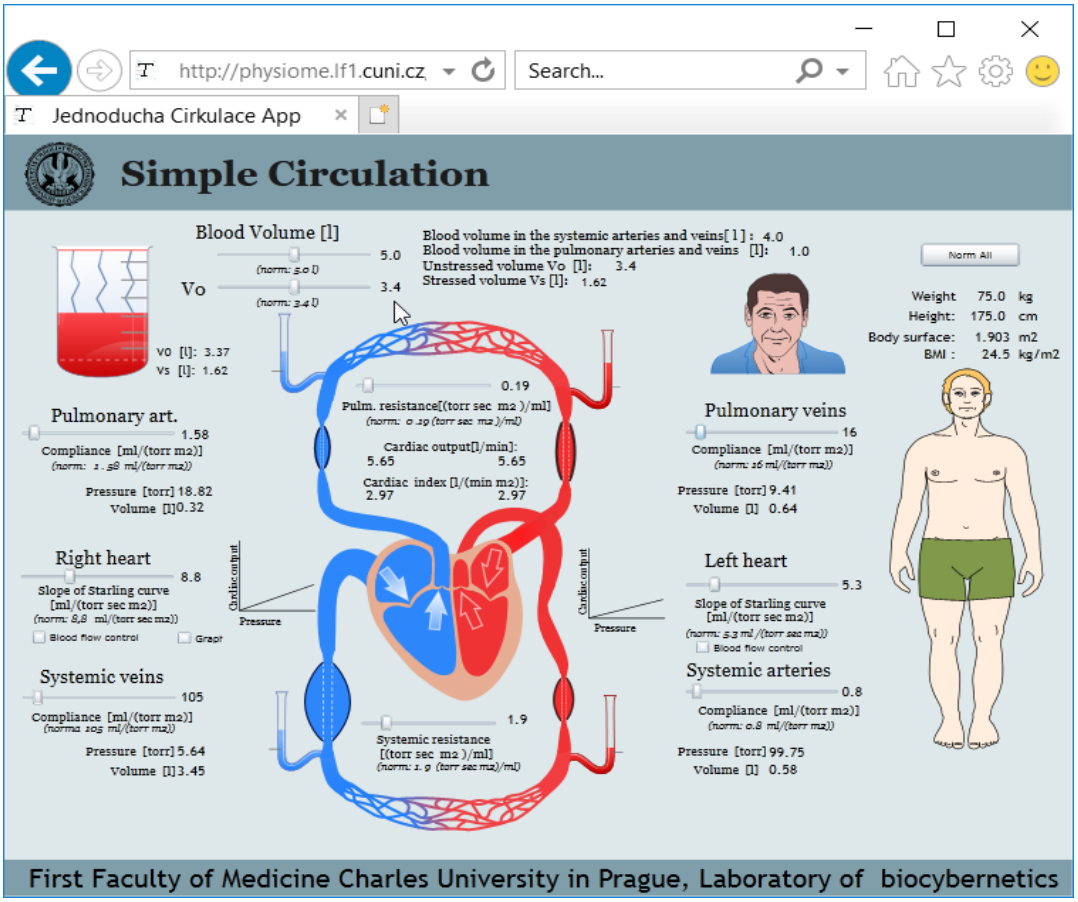


Figure 32: The simulator of simple circulation, built using the Silverlight technology (Tribula et al. 2013)

Driven by industrial needs to share and co-simulate models of various languages and tools, the Functional Mockup Interface (FMI) (Blochwitz et al. 2012) emerged as an open standard. Developed and maintained by the Modelica association (Lund, Sweden), it quickly gained wide support from tool vendors. As of September 2018, 110 tools are capable of either FMI export, import or both (Modelica Association 2017).

The FMI, currently in version 2.0, is a specification, separating the model description (in xml format) and functionality (as a compiled binary and optionally a source code) by exposing a defined set of functions as an interface. Packed in zip archive, this is then called the Functional Mockup Unit (FMU) for Model Exchange. The model files included in the FMU can be supplemented with a compiled solver (and optionally its source code) to enable simulation without an external solver (the FMU) for Co-simulation (Modelica Association 2014). The FMU options are visualized in Figure 33.

To receive results from the model, the solver must initialize the model, perform the time integration of the continuous part and solve the discrete time events. Standard Modelica compilation ends in an executable file, which already contains both the model and

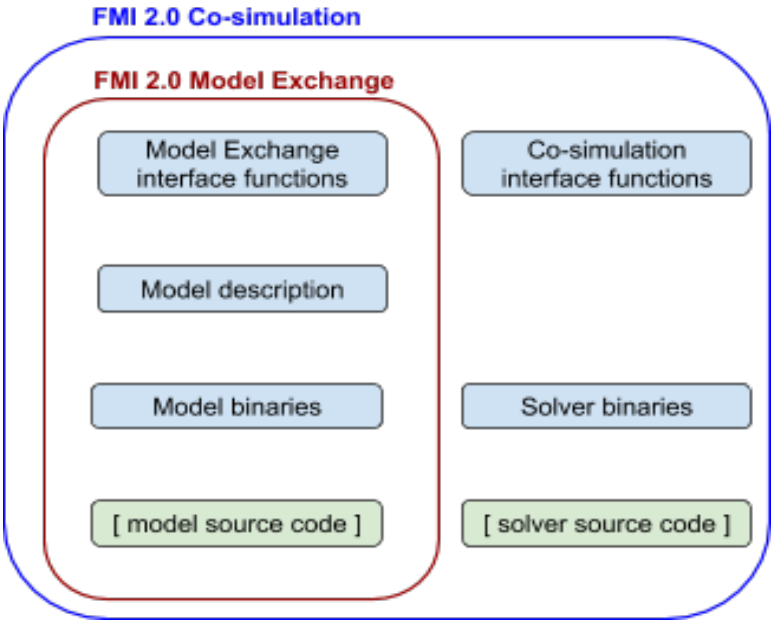


Figure 33: Content of FMU can vary, depending on usage (simplified).

the solver. In addition, the FMI for Co-simulation provides standard FMI functions, which offer a full control over the model simulation (make a next time step, set parameters, read variables, …) as required by the simulator. The advantage of using the FMI functions is the standardization, which ensures further compatibility of export from multiple tools and their future versions.

The task is to get the executable into JavaScript, so it can run in the browser. As shown in Figure 33, the FMU can contain the source code of both the model and the solver. The C code could be then translated to JavaScript using Emscripten (Zakai 2011). The Emscripten translation offers two targets: ASM.JS and WebAssembly (or WASM). Asm.js is a turing-complete subset of the JavaScript language, used as a compilation target. WebAssembly is the next evolution of the Asm.js approach It is designed to “Define a portable, size- and load-time-efficient binary format to serve as a compilation target which can be compiled to execute at native speed by taking advantage of common hardware capabilities available on a wide range of platforms, including mobile and IoT” (WebAssembly Working Group). The model compilation to a binary format effectively obfuscates the model code, so the method is suitable for proprietary or undisclosable models as well. The translated FMU code is then linked to the model controls (such as start, stop, parameters input etc), graphs and animated components in the web page using the FMI API functions.

Especially for educational purposes, the value or graphs alone is not enough. The simulators should provide rich content, including images and animations controlled by the model’s output. Thus, the animation components are designed and animated in Adobe Animate and then exported as an HTML component, exposing their animation timelines as Javascript functions, which are linked to the model. The animation timelines could be

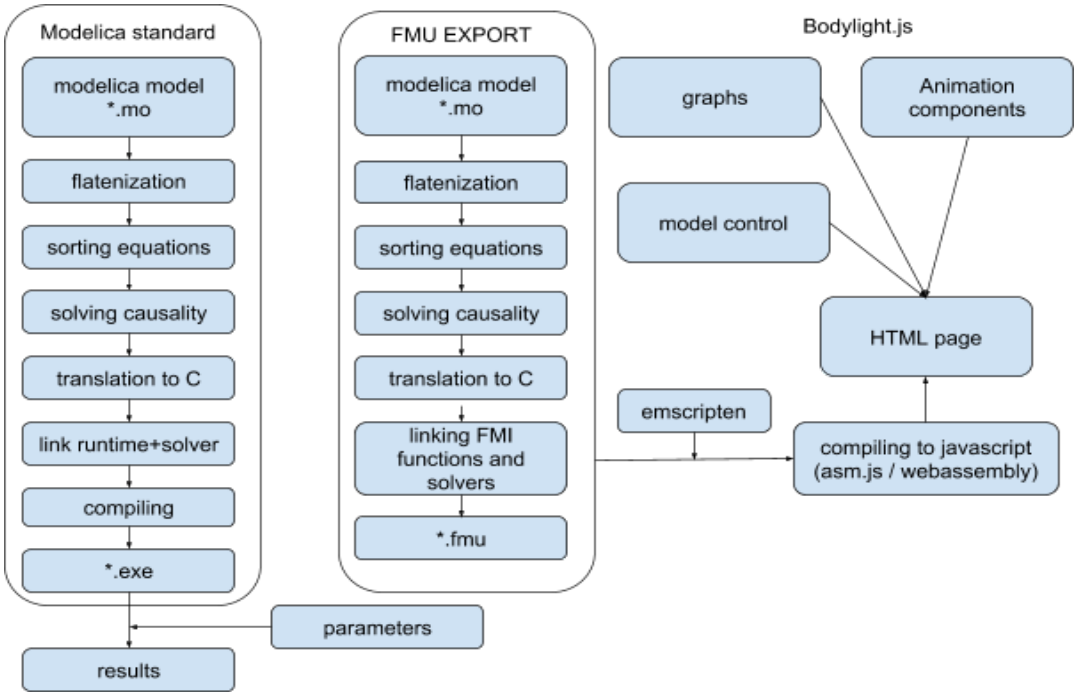


Figure 34: Comparison of the standard Modelica build process, compared to the FMU build process. The FMU is exported and the packaged sources are translated into the JavaScript to enable web-simulation.

nested, so it is possible to animate e.g. width and height of a component independently, but the animations have to be stackable, that is they are not truly independent. The whole web-simulator build process is visualised in Figure 34.

The model could be run in two modes - continuous simulation, when the model's time is synchronized with real-time (in the meaning of wall-clock time, not true real-time computing) at given ratio and so called "one shot", a simulation that runs instantaneously. The former is convenient for e. g. heart beat visualization, whereas the other for e. g. oxygen dissociation curve characteristics.

The interaction with the model is provided using classic components: a slider, an editable field and a button. The slider and a text-box can modify any non-fixed parameter from the model. In addition for continuous simulations, buttons can modify any discrete value (e.g. boolean), which can be traced in the Modelica code and reacted by an appropriate action (e.g. an intake of instant infusion).

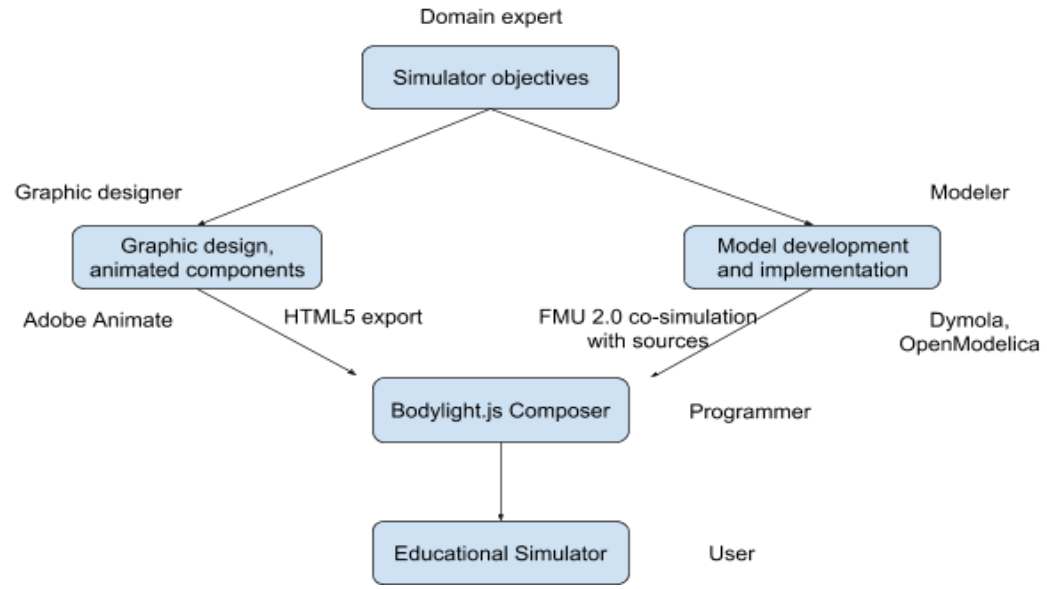


Figure 35: The development of an educational simulator requires collaboration of a number of specialists. The BodyLight composer substantially eases this process.

Figure 36: The Bodylight.js Composer allows to compose the simulator in the browser.

5.2 The Bodylight.js Composer

As illustrated by the Figure 35, the development of an educational simulator is a multi-disciplinary task (Kofránek et al. 2009a, 2009b):

- The domain expert (teacher) sets the simulator objectives and designs a simulation scenario
- The modeler develops and implements the mathematical model
- The graphic designer draws and animates the components and prepares the layout
- The integrator composes the simulator together.

In fact, the simulator composition could be simplified to a bare minimum - all inputs are already known and prepared, thus it is only necessary to interconnect the controls and graphical components with the model inputs and outputs. And that could be mostly automatized. Therefore, to make the simulator development more efficient, a special helper composer tool has been developed (Figure 36).

The composer allows to upload the FMU, manage the model settings, upload animations and other graphical components, insert graphs and HTML controls, and interconnect it all together and then export a standalone HTML5 web-page application, almost without any programming experience.

5.3 Implemented simulators

The usage of the model developed in the previous chapter is wide. Here we present only concepts of what might be useful for explaining the acid-base. Each use-case should be however validated and the simulator must have an appropriate UX design before use as an educational simulator.

All implemented simulators are accessible at http://physiome.cz/apps/jezek/ .

A proof of concept application

First, we have reimplemented the Simple Circulation application (Figure 37), implemented originally on the Silverlight platform (compare to Figure 32). The application looks very similar and has the same functionality.

Ion composition and properties of acid-base balance

The first, rather a demonstrative application, shows a composition of plasma ions, together with acid-base balance (Figure 38). Although a similar image can be found in numerous textbooks, the interactivity plays an important role in understanding the relations.

This application demonstrates the electroneutrality of the solution – by adding NaOH we are in fact adding Na^+ together with the HCO_3^-, as the OH^- instantly binds with CO_2 and

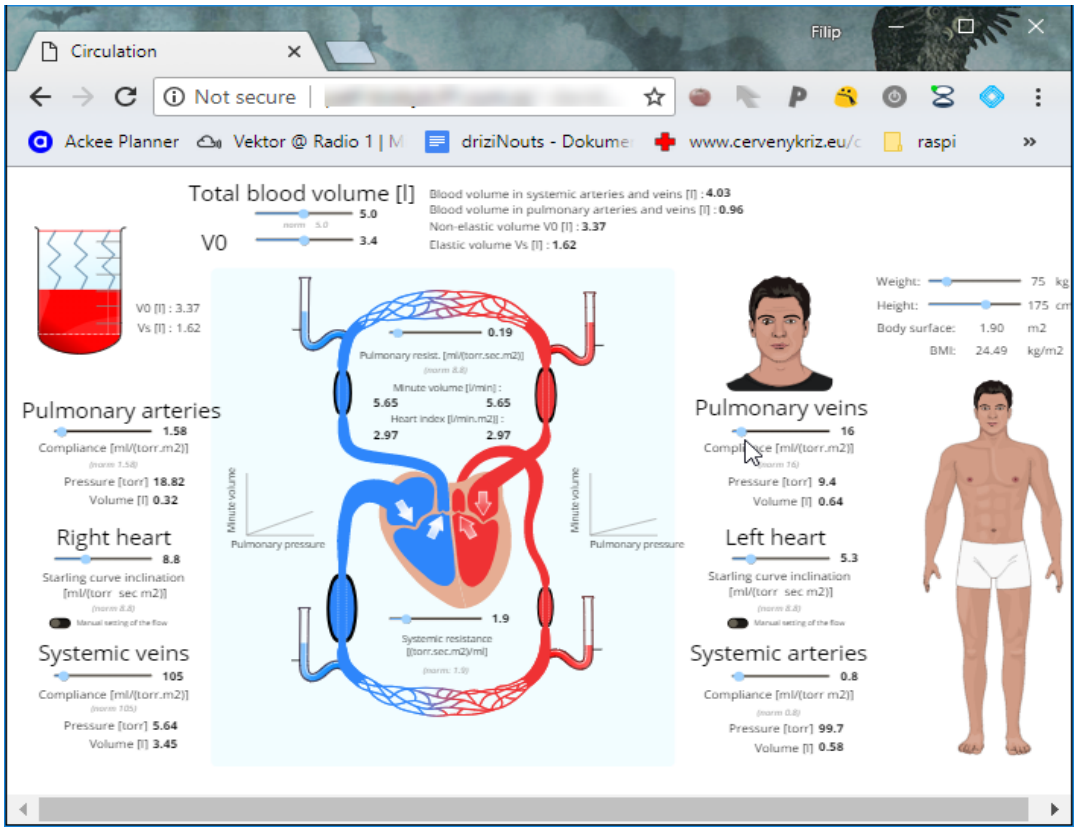


Figure 37: A proof of concept application was made to mimic the previous technology application (compare to Figure 32).

by adding HCl, the H^+ is instantly buffered by the HCO_3^- and CO_2 is released. Dilution and concentration affects the ion concentrations and thus the pH as well.

All clinically relevant markers (the BE, the SID) are present. The computation of the BE is based on the SID (see the attached paper (Ježek and Kofránek 2018) for detailed description). For the time being, all computations are made under the assumptions of full oxygen saturation.

The underlying model has been validated in Ježek et al. (Ježek and Kofránek 2018).

Oxygen dissociation curve

The hemoglobin ability to bind a dioxygen molecule shows a nonlinear sigmoideal-like characteristics and depends on a number of factors. The oxygen dissociation curve is usually shown as a relationship of oxygen saturation (sO_2) on partial oxygen pressure (pO_2). The characteristics may be shifted left (i.e. better binding ability of oxygen on hemoglobin) or right (i.e. worse binding ability) due to shift in pH, concentration of DPG and carbon monoxide, hemoglobin concentration, fetal hemoglobin fraction and temperature.

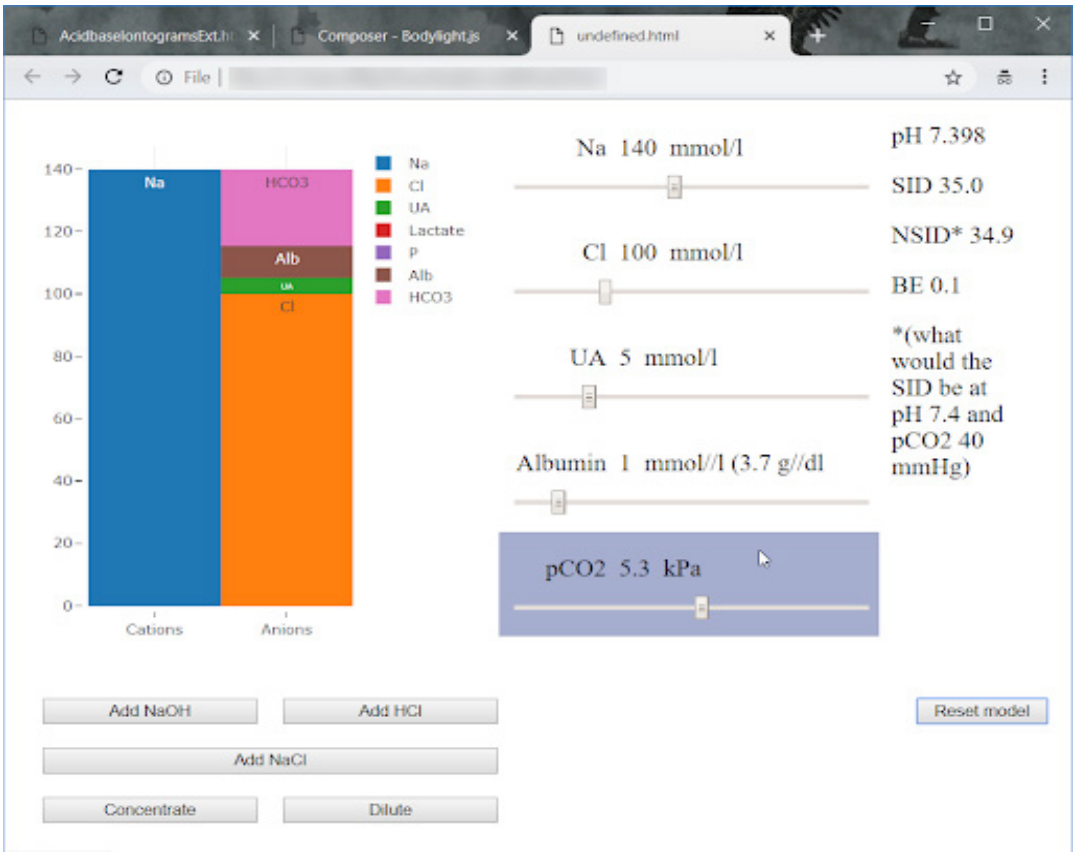


Figure 38: Plasma ion composition simulator concept

Many textbooks describe the shift qualitatively, we offer a quantization of all together to observe a mix of effects (Figure 39). The visualization is build on Siggaard-Andersen's OSA algorithm (Siggaard-Andersen and Siggaard-Andersen 1990), used as an acid-base core in the presented model.

Lung shunts, ventilation and perfusion

As described in section 2.10 Respiration, the ability of lungs to remove CO_2 from blood and supply the oxygen, is sensitive to shunts and uneven ventilation and perfusion. We have prepared an application to quantify these phenomena (Figure 40).

Tissue hypoperfusion and lactate acidosis

Connection of circulation, blood gases transfer and acid-base allows us to demonstrate effects of hypoperfusion-related local tissue hypercapnic acidosis and, eventually, lactic acidosis.

The model used is the same as described in the section The perfusion effect with the exception of the possibility to turn the metabolic compensation on and off.

Figure 39: Oxygen dissociation curve simulator concept

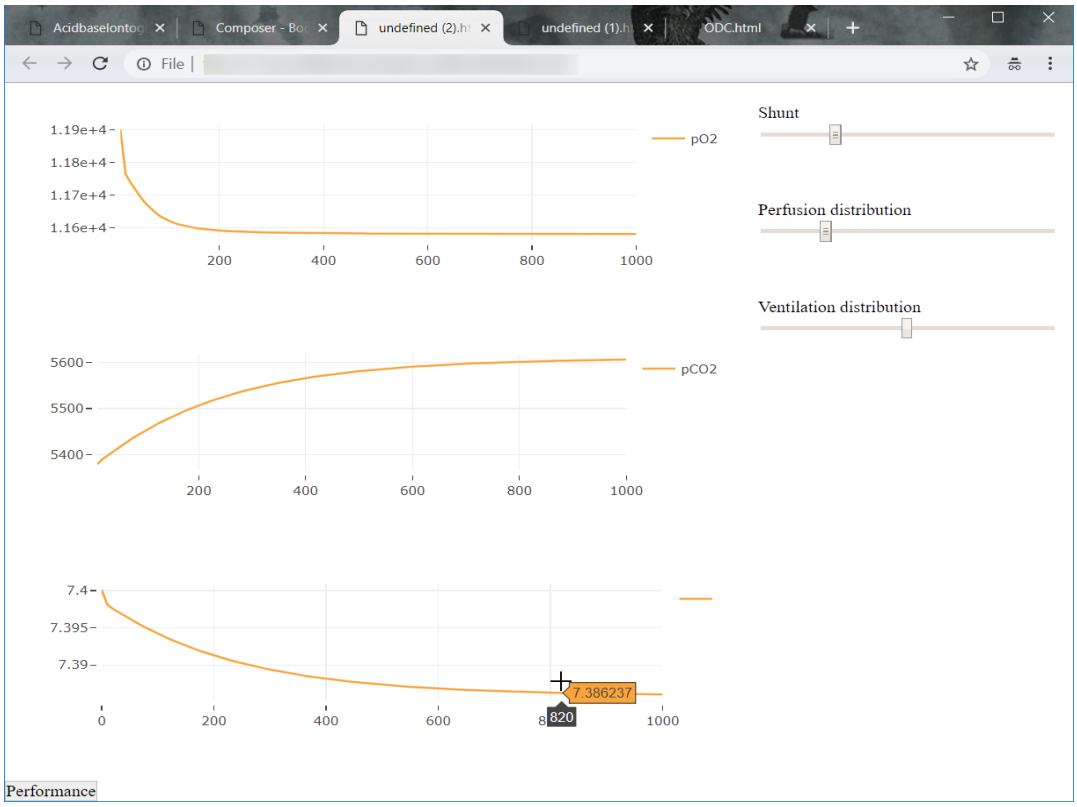


Figure 40: Concept for simulator of uneven lung ventilator and perfusion

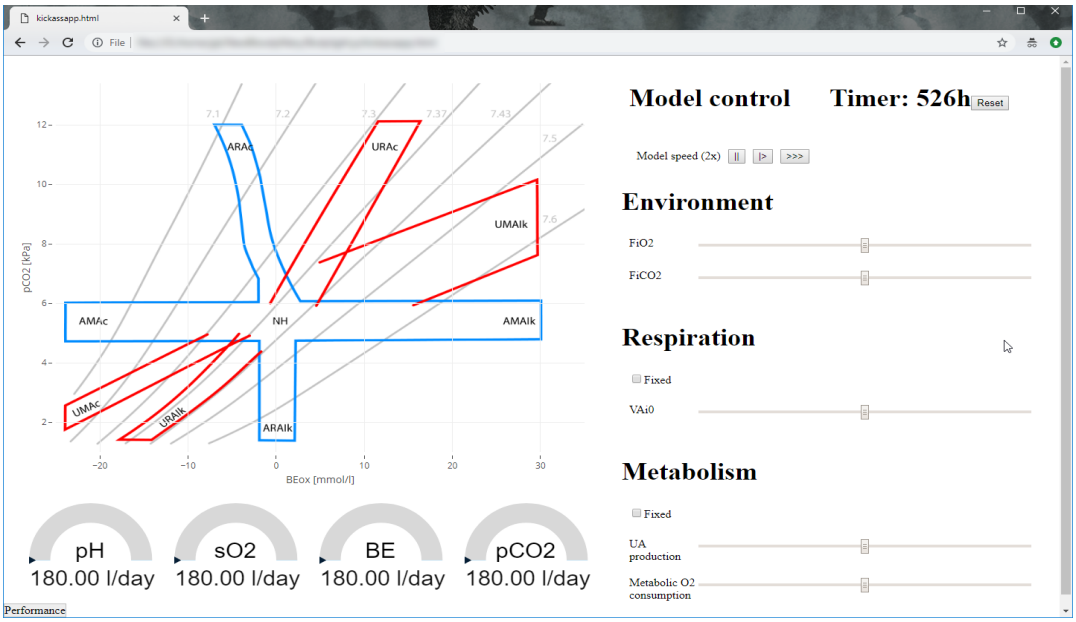


Figure 41: A concept for compensatory and correction responses.

5.4 Complex model simulator

The complex model simulator aims at demonstration of the compensatory and correction mechanism (Figure 41). The model response is compared to a compensatory nomogram. The user could adjust environmental parameters (fraction of inspired gases), metabolic rates and respiratory drive.

5.5 Other simulators

Aside from simulators designed in this thesis, a number of other simulators have been developed based on the described concept. They are all presented at http://physiome.cz/apps/ (see Figure 42).

5.6 Discussion

The presented technology allows to rapidly develop client-side interactive visual simulators. Thanks to the Bodylight.js Composer, the development of a simulator becomes quick and simple.

The simulators are usable on all current major web browsers, including Microsoft Edge, Mozilla Firefox, Google Chrome, MacOs Safari, iOS Safari (since iOS 11.4), Chrome for Android (since version 7.0). And any future browsers that have support for WASM (WebAssembly) and at least ECMAScript 2017 (JavaScript).

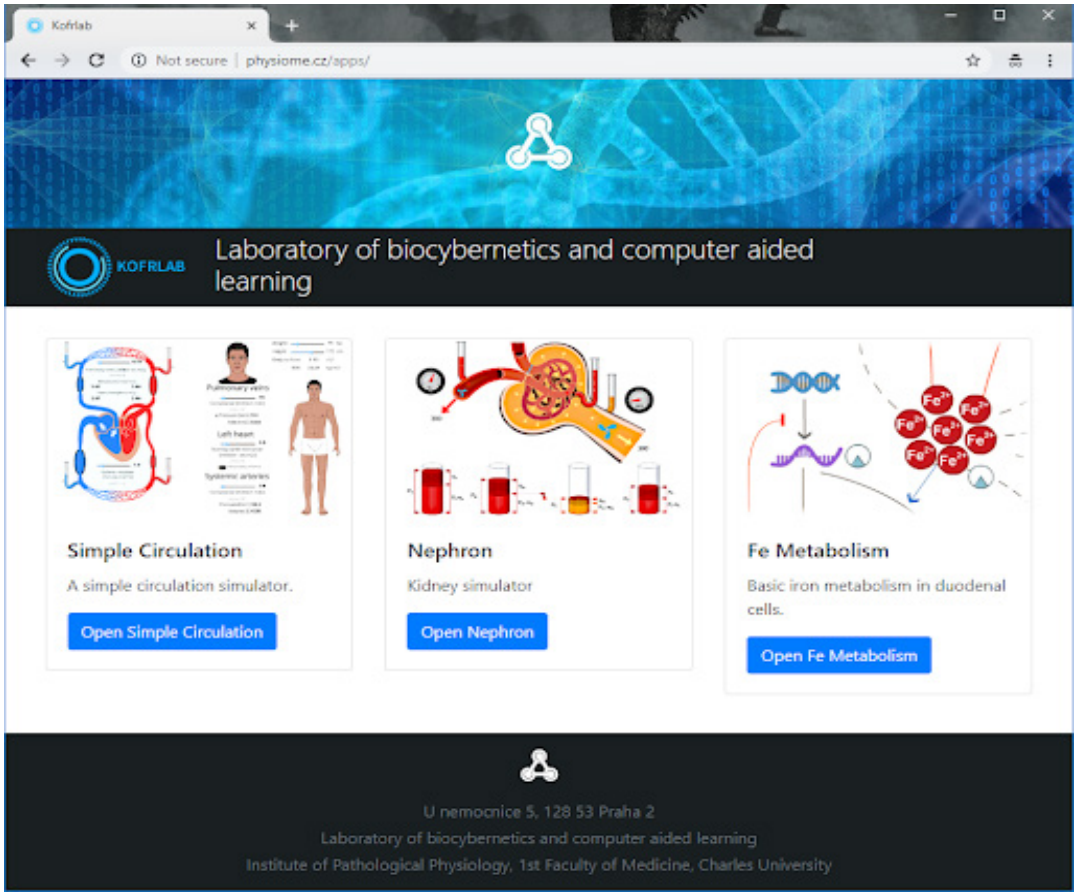


Figure 42: Contemporary educational applications developed using the Bodylight.JS technology (as of December of 2018)

Because commercial Modelica tool algorithms are proprietary, the toolchain is currently limited due to an expensive licence of the Dymola Source Code Export (currently provided by the Laboratory of Biocybernetics and Computer Aided Learning, Institute of Pathological, Physiology, 1st Faculty of Medicine, Charles University), which is required to export the FMU including the C++ source code and a CVODE solver. This could be,however, avoided in the future on condition OpenModelica upgrades their solver to anything better than the currently exported simple Euler solver, which provides unsatisfactory results for complex models. This is, however, beyond the scope of the current project.

Ironically, the performance of the model is not an issue in most use cases, its visualization however is more resource requiring. To find performance bottlenecks, a live performance statistics view is generated within the Bodylight.js Composer. A large number of animations and graphs substantially affects the resulting framerate, since they have to be redrawn each frame – compare the required times in Figure 43. The current free graphing libraries (currently we use the plotly.js graphing library) are too resource expensive (especially for multiple lines) and could be greatly optimized in the future.

Performance statistics	
Frame duration: 98ms (10.2 fps)	
unnamed (chart)	
setItem	18 ms
setItem	27 ms
setItem	16 ms
setItem	16 ms
setItem	16 ms
unnamed (chart)	
extendTrace	8 ms
AcidBaseBalanceVisualizationIontograms (MODEL)	
tick	68 us

Figure 43: Generated performance statistics from the Ion Composition Simulator. One model tick requires around 70 µs, whereas a simple graph requires by around three orders of magnitude more time.

The Bodylight.js composer is under continuous development, open to all types of collaboration. It is planned to release the tool to the public as a non-commercial open-source project.

Further development of the Bodylight.js would include a 3D animation and its connectivity to the model results. Thanks to open libraries, such as Babylon.js (@xtreemze et al.) one can have 3D objects animated similarly to 2D, for example a 3D pulsating heart, with details of valves opening and closing based on a model, that could be rotated and examined in function.

Also, a co-simulation of several models and switching between them is planned for future releases.

6 Summary and perspective

We have demonstrated a proof-of-concept model, able to dynamically simulate a number of ventilation, perfusion, acid-base and ion disorder pathologies, which brings together relations not quantitatively considered in contemporary models. The model proves, that the balance approach to acid-base may be handy for modeling the whole body homeostasis.

We hope, that the drafted educational applications will succeed in facilitating deeper understanding of the pathophysiological processes, and the proposed clinical aid system would eventually help the clinician to gain deeper insight into the patient's condition and to select the optimal therapeutic strategy.

6.1 Thesis achievements

All goals set in the section 1.6 Dissertation goals were met. Specifically, (1) the physiological model of the circulation, blood-gases, acid-base and water balance has been built and validated by comparison to clinical data from literature (see respective paragraph in chapter The physiological model). The model allows to observe the bodily compensation and correction dynamics. The developed platform is extendable and allows easy orientation and simple experiment setup. Thereby, the main goal of the thesis has been fulfilled.

The methodology of building extensible models has been described in part in (Ježek et al. 2017) and in the chapter Methodological approach to model development, which satisfies the first partial goal (1a).

Alongside the development of the physiological model, the relation between the two predominant approaches to the body acid-base has been found and quantified in (Ježek and Kofránek 2018). Furthermore, we hypothesized, implemented and tested the limitation in maximal HCO_3^- resorption during NH_4^+ excretion in kidneys, which ensured data fit of compensation of respiratory acidosis and, to our knowledge, does not principally contradict other data sets.

The possible usage of the developed model for a clinical aid system (goal 1b) has been discussed and most important further steps have been suggested in the chapter Discussion of model usage for intensive care clinical aid system and thereby the second partial goal fulfilled.

The model results have been visualised using the web-based simulators (goal 2a). In order to do that, the simulator-building toolchain and a method to build the client-side simulator based on the powerful modelica language has been designed, developed (chapter Model visualization for medical simulators) and published (Silar et al. 2019), which satisfies the secondary goal (2).

6.2 Future outline

For further understanding of the acid-base regulations, the kidney submodel should be extended with detailed ion excretion balances (which are currently neglected), proximal tubule adaptation (currently a rough integration-limiter control) and a thorough description of the NH_4^+ limitation (currently only a behavioral draft). From the measured behavior (both Siggaard-Andersen's and Engliš compensation nomograms), some limitation preventing full pH compensation, still exists. Whether the exact limitation mechanism is truly as proposed, is uncertain and a subject for further detailed investigation on physicochemical basis.

Detailed analysis of volume therapy (crystalloid and colloid infusions) and its validation would provide useful demonstrative tools for assessing a patient state and prognosis.

Especially for a clinical aid system, the model should be also extended by basic pharmacokinetics and pharmacodynamics. Although the model has been validated by data from literature, a thorough clinical validation is required before a clinical use. The development of the clinical aid system is a long term process. We recommend following the suggestions for clinical aid device development - especially keep on searching for the possibilities of online data acquisition.

Further development of the Bodylight.js Composer will provide accessible model visualization for demonstration and education. Most importantly, efforts should be focused on enabling suitable FMI export from at least one open-source tool. The designed technology for rapid development of interactive simulators has already been used for simulators used in medical education with great success and the paper describing its usage is currently under preparation.

Protein effect on acid-base balance

The protein level attracts a lot of attention, especially for being an important mortality predictor in critically ill patients (Herrmann et al. 1992). Hypoalbuminemic alkalosis is a disputed topic. But regarding its buffering effects on the acid-base status, it has only a minimal effect (Matoušek, Stanislav 2013; Ježek and Kofránek 2018) The balance approach to acidbase could explain cases of hypoalbuminemic acidosis better than the conventional approach.

McAuliffe (McAuliffe et al. 1986) claims, that a decrease of albumin by 1 g/dl produces an increase in an apparent base excess of 3.7 meq/liter. The study is however based only on 8 patients, mostly in acute conditions and the hypoalbuminemia is usually compensated by slight respiratory acidosis. Nicholson (Nicholson et al. 2000) discusses the plasma serum albumin level after albumin infusion during normal synthesis and catabolism and in critically ill patients, where he claims albumin transfer to interstitium, lower production and possible higher catabolism. It has been observed in vitro, that alkalosis caused by hypoalbuminemia does not change the SID (Rossing et al. 1986). If it is administered together with Na (or exchanged for Cl), it would change the SID, and keep the BE and pH constant. However in

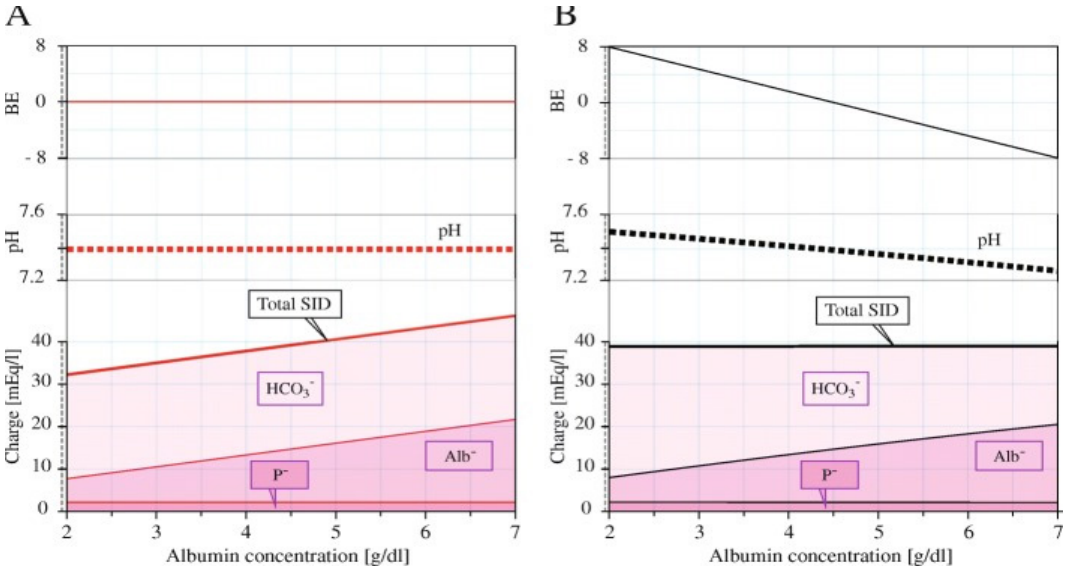


Figure 44: Change in the SID keeps the pH unchanged, maintaining the SID changes the BE and pH. Image from Ježek and Kofránek (Ježek and Kofránek 2018)

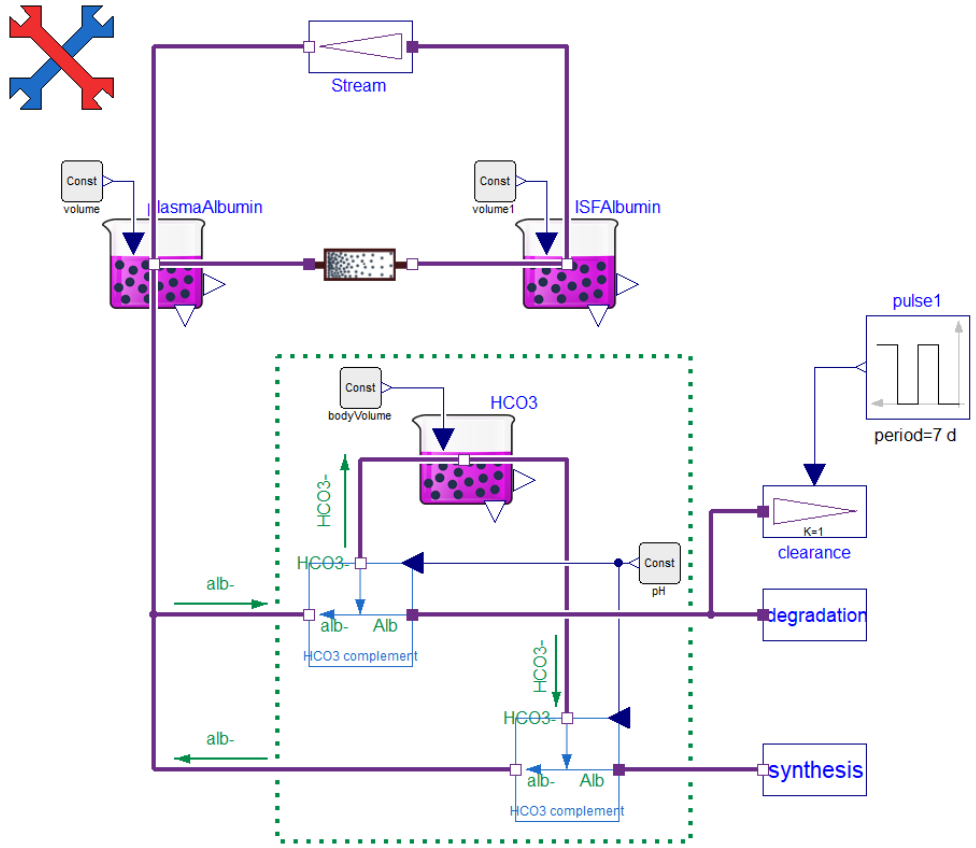


Figure 45: The draft of an unfinished model of albumin effect on acid–base balance

vivo we observe the contrary. Therefore the albumin has to be exchanged for HCO_3^-, which would keep the SID constant, but change the BE and the pH (Figure 44). Therefore, the question remains, how the constant SID is held.

We have prepared a stand-alone model to assess the case of albumin metabolism and its effect on acid-base balance (see Figure 45). The albumin is circulated between plasma (volume 3 liters out of 5 liters of blood volume) and the ISF (10 liters) by capillary leakage and back to plasma by a lymphatic flow (5 l/day). The conductance of the capillary leakage has been set at 1.5 ml/min, so that the concentration of the ISF is held at approximately 33% of the plasma concentration.

The albumin is produced and degraded depending on its concentration (the functions have been adopted from the Physiomodel (Matejak and Kofranek 2015)).

An albumin protein has a charge of around -18 meq/mol (Fencl et al. 2000) at normal pH of 7.4. Owing to the electroneutrality principle, the albumin must therefore be synthesised (and degraded) together with H+ ion. As viewed by the balance approach to acid-base, this

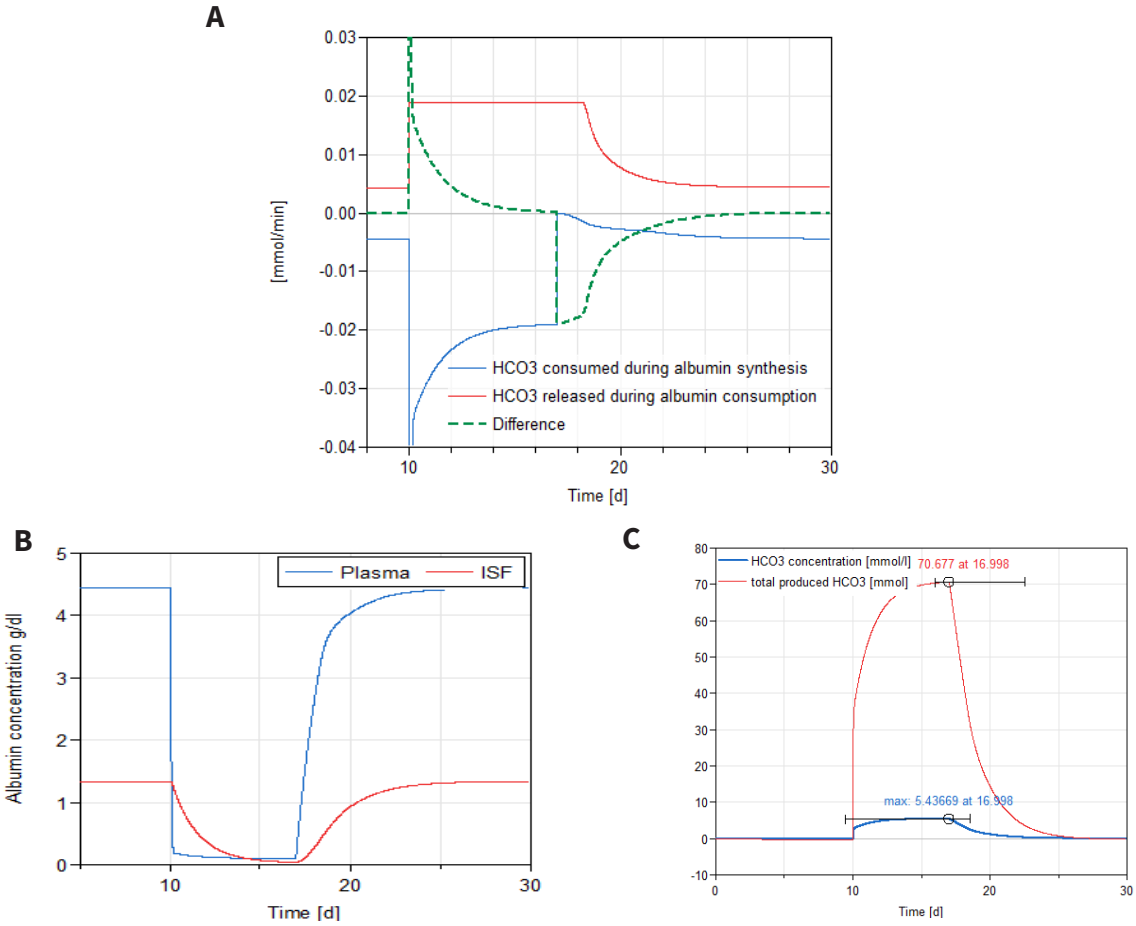


Figure 46: Balance of HCO_3^- production and catabolism during step in albumin consumption (A), the albumin concentration (B) and the balance of the HCO_3^-, or, in another words, change in BE (C).

equals the exact, but opposite amount of HCO_3^-. When the production and consumption are in balance, no additional HCO_3^- is produced or consumed. However, when disbalanced (e.g. after a surgery etc), the catabolic rate increases (Figure 46 A) and so does the HCO_3^-. The increased concentration of HCO_3^- (dissolved in both plasma and the ISF), corresponds to the rise of the BE.

We modeled an experimental setup with added clearance, simulating a sudden drop in plasma albumin concentration by an extremely increased catabolism (e.g. after a surgery) for 7 days, when the catabolism returns back to normal. The increased catabolism rate leads to a fast and extreme drop of plasma albumin concentration, followed by a slower drop in ISF albumin reserves. The disbalance in production and consumption leads to production of around 70 mmol of HCO_3^-, which, when diluted into body fluids (3 liters of plasma + 10 liters of interstitial fluid) leads to the BE increase to around 5.43, producing an alkalemia (Figure 46 B, C). With respiratory and uncompromised metabolic compensation the change in the BE would be however substantially smaller. Therefore, spontaneous hypoalbuminemic alkalosis can hardly produce serious alkalosis and is often only accompanying other acid-base disturbances in critically ill patients. Our results are in agreement with Ronco et al., who claims, that hypoproteinemic alkalosis may develop only during acute conditions (Ronco et al. 2009), otherwise it is compensated by kidneys.

Recent review by Levitt and Levitt (Levitt and Levitt 2016) claims, that lower plasma albumin levels result from a higher capillary permeability, however the (limited) measurements of albumin synthesis and the transcapillary escape rate cannot explain the plasma levels (Komáromi et al. 2016). Komáromi also observed an elevated post-surgery production rate (Komáromi et al. 2015). These observation would only contribute to the lower difference in albumin production and catabolism during hypoalbuminemia and therefore develop lower alkalemia.

Based on the presented model results and controversy regarding albumin, we decided not to include the albumin balance into the whole model for the sake of simplicity and stability.

This section demonstrated the methodology by drafting a simple model of protein balance and how it affects the acid-base balance. The model has to be evaluated against clinical data, however, to our best knowledge, the available data are not in the required time resolution to properly validate the theoretically defined dynamics and therefore a prospective clinical study should be planned. Only then the role of protein balance in the acid-base equilibrium could be properly assessed.

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8 List of author's publications

The author declares that, although uncommon, each publication has an equal contribution of all authors. Mostly because it was impossible to gather required signed statements of each author, as dictated by the directive for dissertation defence.

8.1 Publications related to the dissertation topic

Articles published in WoS impacted journals

1. **(Attached)** Kurtz TW, DiCarlo SE, Pravenec M, **Ježek** F, Šilar J, Kofránek J, et al. Testing Computer Models Predicting Human Responses to a High-Salt Diet. Hypertension. Lippincott Williams & WilkinsHagerstown, MD; 2018; Available: https://www.ahajournals.org/doi/abs/10.1161/HYPERTENSIONAHA.118.11552
   IF 6.823 (2017), Q1 (WoS), SJR 3.795, Q1 in Internal Medicine (Scimago), 1 WoS citation

2. **(Attached) Ježek** F, Kofránek J. Modern and traditional approaches combined into an effective gray-box mathematical model of full-blood acid-base. Theor Biol Med Model. 2018;15: 14 Available https://tbiomed.biomedcentral.com/articles/10.1186/s12976-018-0086-9
   IF 2.0, Q2 (WoS), SJR 0.783, Q1 in Modeling and simulation (Scimago)

3. **(Attached) Ježek** F, Kulhánek T, Kalecký K, Kofránek J. Lumped models of the cardiovascular system of various complexity. Biocybernetics and Biomedical Engineering. 2017;37: 666–678. Available: https://www.sciencedirect.com/science/article/abs/pii/S0208521617300268
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Articles published in peer-reviewed journals:

4. Šilar J, **Ježek** F, Kofránek J. PDEModelica1: a Modelica language extension for partial differential equations implemented in OpenModelica. International Journal of Modelling and Simulation. Taylor & Francis; 2018;38: 128–137. Available: https://www.tandfonline.com/doi/abs/10.1080/02286203.2017.1404417
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Other WoS indexed publications

5. **Ježek** F, Tribula M, Kulhánek T, Mateják M, Privitzer P, Šilar J, et al. Surviving sepsis--a 3D integrative educational simulator. Conf Proc IEEE Eng Med Biol Soc. 2015;2015: 3679–3682. Available: https://ieeexplore.ieee.org/abstract/document/7319191
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6 Google Scholar citations

8. **Ježek** F, Privitzer P, Mateják M, Macků D. Demonstration of the Risk of Fixed Ejection Volume in Ventricular Assist Devices in Small Patients Using Web Simulator. 5th European Conference of the International Federation for Medical and Biological Engineering. Springer Berlin Heidelberg; 2012. pp. 489–492. Available: https://link.springer.com/chapter/10.1007/978-3-642-23508-5_127
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Other publications

9. Silar J, **Ježek** F, Mládek A, Polák D, Kofránek J. Model visualization for e-learning, Kidney simulator for medical students. Proceedings of the 13th International Modelica Conference, Regensburg, Germany, March 4-6, 2019. Linköping University Electronic Press; 2019.
International peer-reviewed conference contribution (accepted)

10. Kofránek J, **Ježek** F. Modelica language – a promising tool for publishing and sharing biomedical models. Proceedings of the North American Modelica Conference. Linköping University Electronic Press; 2018.
International peer-reviewed conference contribution

11. Kofránek J, **Ježek** F. Acid-Base equilibrium modeling based on the balance concept. In: MEDSOFT 2018. Creative Connections s.r.o.; 2018. p. 49–68.
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12. Kofránek J, Kulhánek T, Mateják M, **Ježek** F, Šilar J. Integrative physiology in Modelica. In: Proceedings of the 12th International Modelica Conference, Prague, Czech Republic, May 15-17, 2017. Linköping University Electronic Press; 2017. p. 589–603.
International peer-reviewed conference contribution

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14. Matejak M, Tribula M, **Ježek** F, Kofranek J. Free Modelica Library for Chemical and Electrochemical Processes. Proceedings of the 11th International Modelica Conference, Versailles, France, September 21-23, 2015. Linköping University Electronic Press; 2015. pp. 359–366.
International peer-reviewed conference contribution
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International peer-reviewed conference contribution
31 Google Scholar Citations

16. Kofránek J, **Ježek** F. Использование языка Моделика для моделирования физиологических систем на примере модели гемодинамики (Using the Modelica language to simulate physiological systems on the example of a hemodynamic model). In: Laboratory of Biocybernetics, Charles University, Prague [Internet]. 25 Jun 2015. Available: http://www.creativeconnections.cz/modelicaexamples

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8.2 Publications unrelated to the dissertation topic

Articles published in peer-reviewed journals

25. Vojáček A, **Ježek** F. Modelica in Area of Thermodynamic and Energy Systems Applications with a Focus on ClaRa Library. TRANSACTIONS ON ELECTRICAL ENGINEERING. transoneleng.org; 2018;64: 59. Available: http://www.transoneleng.org/2018/20183c.pdf
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26. Macků D, Huňka P, **Ježek** F. ECMO AMBULANCE AND ADVANCED EMERGENCY MEDICAL SYSTEM. Lékař a technika - Clinician and Technology. ojs.cvut.cz; 2017;42: 14–16. Available https://ojs.cvut.cz/ojs/index.php/CTJ/article/download/4215/4069
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WoS indexed publications

27. Macku D, **Jezek** F, Hunka P. CAN WE GENERATE SYSTEMIC ARTERIAL HYPERTENSION BY PULSATILE LVAD IN OUR PATIENTS? [Internet]. International Journal of Artificial Organs. 72/74 via Friuli, 20135 Milan, Italy: Wichtig Editore; 2011. pp. 682–682. Available: https://apps.webofknowledge.com//full_record.do?product=UA&search_mode=OneClickSearch&qid=33&SID=C4pCHUBSYwOyFdo9yUO&page=1&doc=6
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Other publications

30. Fořtová A, **Ježek** F. VVER 1000 Pressurizer System and Control Modelling in Dymola. 2018 26th International Conference on Nuclear Engineering. American Society of Mechanical Engineers; 2018. pp. V009T16A017–V009T16A017.
International peer-reviewed conference contribution

31. MACKŮ, D., F. **JEŽEK** a P. HUŇKA. Chronic Non-Pulsatile Blood Flow in the Human

Body. In: Abstracts ASAIO 59th Annual Conference. 59th Annual Conference, Chicago, 2013-06-12/2013-06-15. Boca Raton: ASAIO, 2013. p. 21.
International peer-reviewed conference contribution

32. MACKŮ, D. a F. **JEŽEK**. Iatrogenic Arterial Hypertension Generated by the Pulsatile Left Ventricular Assist Device. In: Archives des Maladies du Cœur et des Vaisseaux - Pratique. 31èmes Journées de l'Hypertension Artérielle - 5th International Meeting of the French Society of Hypertension, Paris, 2011-12-15/2011-12-16. Paris: Elsevier, 2011. p. 131. ISSN 1261-694X.
International peer-reviewed conference contribution

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International peer-reviewed conference contribution

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9 Attachments

1. Kurtz TW, DiCarlo SE, Pravenec M, Ježek F, Šilar J, Kofránek J, et al. Testing Computer Models Predicting Human Responses to a High-Salt Diet. Hypertension. Lippincott Williams & WilkinsHagerstown, MD; 2018; Available: https://www.ahajournals.org/doi/abs/10.1161/HYPERTENSIONAHA.118.11552
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2. Ježek F, Kofránek J. Modern and traditional approaches combined into an effective gray-box mathematical model of full-blood acid-base. Theor Biol Med Model. 2018;15: 14 Available https://tbiomed.biomedcentral.com/articles/10.1186/s12976-018-0086-9
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