DIPLOMA THESIS

Czech Technical University
in Prague

Faculty of Electrical Engineering
Department of Cybernetics

Acidbase Model Implementation for Interactive Simulator

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DIPLOMA THESIS ASSIGNMENT

Student: Bc. Petr M a c h e k

Study programme: Biomedical Engineering and Informatics

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Title of Diploma Thesis: Acidbase Model Implementation for Interactive Simulator

Guidelines:

1. Implement complex model of the whole-body acidbase published by [1].
2. Extend the model by basic body regulations (at least breathing regulation and kidneys).
3. Compare this approach to the one used in Physiomodel, discuss the improvement.
4. Discuss possibilities for interactive simulator web frontend.
5. Implement interactive simulator of acidbase balance.

Bibliography/Sources:

[1] Wolf, M. B., & DeLand, E. C. (2011). A mathematical model of blood-interstitial acid-base balance: application to dilution acidosis and acid-base status. Journal of applied physiology, 110(4), 988-1002.
[2] John A. Kellum, Paul Wg Elbers: Stewart´s Textbook of Acid-Base. Lulu.com 2009.

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Prague, December 12, 2015

Author statement for undergraduate thesis

I declare that the presented work was developed independently and that I have listed all sources of information within it in accordance with the methodical instructions for observing the ethical principles in the preparation of university theses.

Prague, date …… …….

signature

Annotation

The Diploma Thesis deals with an implementation of a mathematical model of blood-interstitial acid-base balance in Modelica language. The model is implemented using two methods – an equation-based approach using the mathematical equations directly and a component-based approach with the use of Chemical library. The model is extended by basic body regulation system in form of respiration and kidneys. There is also implemented an extended model with the addition of a cell compartment. The thesis compares the approach to the acid-base balance of the blood-interstitial model and more complex Physiomodel. It also discusses the possibilities of the usage of the implemented model for an interactive simulator.

Keywords

mathematical model; acid-base balance; regulation; acid-base disorders; respiratory regulation; metabolic regulation; Modelica; Chemical library; Physiolibrary; Physiomodel

Anotace

Diplomová práce se zabývá implementací matematického modelu acidobazické rovnováhy krve a intesticia v jazyce Modelica. Tento model byl implementován pomocí dvou různých metod – přístupu založeného na přímém využití matematických rovnic popisujících model a přístupu založeného na využití předdefinovaných bloků z knihovny s názvem Chemical. Model byl dále rozšířen o základní regulační principy dýchání a vylučování ledvin. Dále byl implementován model, který k modelu původnímu přidává další kompártment reprezentující buněčnou hmotu. Práce srovnává přístupy k acidobazické rovnováze implementovaného modelu a modelu s názvem Physiomodel. Zároveň diskutuje možnosti dalšího využití implementovaného modelu pro interaktivní simulátor.

Klíčová slova

matematický model, acidobazická rovnováha, regulace, acidobazické poruchy, respirační regulace, metabolická regulace, Modelica, knihovna Chemical, Physiolibrary, Physiomodel

Content

1 Introduction

For prediction of steady-state changes in blood acid-base chemistry, we need to know the physicochemical properties of the blood such as ion distribution and water distribution between the body parts. Understanding of the acid-base balance needs a complex insight into the physiological processes in human body. We need to consider the distribution of water, protein, electrolytes and other solutes in the body fluids. For this reason, mathematical models were developed. We took a model of M. B. Wolf and E. C. DeLand from 2011 of blood-interstitial acid-base balance, which combines the knowledge of the traditional Siggaard-Andersen approach and more recent approach of Stewart and its application to blood and blood-interstitial fluid by Wooten. [1]

More models were recently created. A model of dynamics of whole body fluid movements[2], but it did not involve the simulations of acid-base balance[3]. A mathematical model of whole-body O_2 and CO_2 transport with a representation of the acid-base chemistry of the blood, interstitium, and cells was developed[4], but it did not include the shifts of ions and water between the compartments[5]. To simulate the changes of acid-base balance due to the crystalloid infusions, another model was developed[6]. Another model for an acid-base balance of erythrocytes was developed, but it was made only for the erythrocytes in a solution of certain composition[7]. All the models were specific for certain conditions and thus their use was limited. The advantage of Wolf's model is its generality which allows us usage of the model in a wide range of conditions.[8]

The model was implemented and verified using VisSim as the simulation tool. VisSim is block-based language developed by Visual Solutions. Implementing more complex mathematical equations using block-based language is complicated and the result might be difficult to decipher for the uninformed reader. [9]

To make the model easier to understand and read, we reimplemented it in the Modelica language. Modelica is freely available, object-oriented modern language build on acausal

[1] Wolf and DeLand, 'A Mathematical Model of Blood-Interstitial Acid-Base Balance'.
[2] Gyenge et al., 'Transport of Fluid and Solutes in the Body I. Formulation of a Mathematical Model'; Gyenge et al., 'Transport of Fluid and Solutes in the Body. II. Model Validation and Implications'; Chapple et al., 'A Model of Human Microvascular Exchange'.
[3] Wolf, 'Whole Body Acid-Base and Fluid-Electrolyte Balance'.
[4] Andreassen and Rees, 'Mathematical Models of Oxygen and Carbon Dioxide Storage and Transport'.
[5] Wolf, 'Whole Body Acid-Base and Fluid-Electrolyte Balance'.
[6] Omron and Omron, 'A Physicochemical Model of Crystalloid Infusion on Acid-Base Status'.
[7] Raftos, Bulliman, and Kuchel, 'Evaluation of an Electrochemical Model of Erythrocyte pH Buffering Using 31P Nuclear Magnetic Resonance Data.'
[8] Wolf and DeLand, 'A Mathematical Model of Blood-Interstitial Acid-Base Balance'; Wolf, 'Whole Body Acid-Base and Fluid-Electrolyte Balance'.
[9] Wolf and DeLand, 'A Mathematical Model of Blood-Interstitial Acid-Base Balance'; Wolf, 'Whole Body Acid-Base and Fluid-Electrolyte Balance'.

modeling with mathematical equations. In Modelica, we do not have to construct equations using various blocks (e.g. constants, gains, etc.). The next advantage is the acausality of the language, which means we do not have to deduce the procedure of calculation. It is done by the compiler.

1.1 Theory of acids and bases

The first theory of acids and bases comes from late 19th century from Swedish chemist Svante Arrhenius called after him Arrhenius theory. When dissolved in an aqueous solution, Arrhenius acid cleaves a hydrogen cation (proton) and thus increases the H^+ concentration. An Arrhenius base is a substance that while dissolved in the water cleaves a hydroxide anion and thus increases the OH^- concentration in a solution.

$$HA \rightarrow H^+ + A^- \tag{1}$$

$$BOH \rightarrow B^+ + OH^- \tag{2}$$

This theory is most general and has some limitations. There are some substances, which increases the OH^- concentration in water but do not contain any OH group they could cleave off. In an aqueous solution, the OH^- concentration increases but it happens thanks to the OH^- residue from the water itself. [10]

The limitation of the hydroxide group or the need for water as a solvent removes the Brønsted-Lowry theory, which defines an acid as a donor of hydrogen cation while basis is an acceptor of hydrogen cation. While the acid dissociates in water, it increases the H^+ concentration and base increases the OH^- concentration by taking protons from water. [11]

$$HA + H_2O \leftrightarrow A^- + H_3O^+ \tag{3}$$

$$B + H_2O \leftrightarrow HB^+ + OH^- \tag{4}$$

This way a conjugate pair of acid (HA or HB^+) and base (A^- or B) is formed. The equilibrium between the conjugate pairs will be established. When the equilibrium is established depends on the strength of the acid or the base. The indicator of the strength of an acid or base is dissociation constant. The dissociation constant for an acid is

$$K_A = \frac{[A^-][H^+]}{[HA]} \tag{5}$$

while for a base

$$K_B = \frac{[HB^+][OH^-]}{[B]}. \tag{6}$$

[10] 'Acid/Base Basics'; 'Acids and Bases | Chemistry'.
[11] 'Acid/Base Basics'; 'Acids and Bases | Chemistry'.

The dissociation constant can have values in a wide range so we usually use the *pK* value which is a negative decadic logarithm of the dissociation constant:

$$pK = -\log_{10}(K). \tag{7}$$

The stronger the acid (or the base) is, the more dissociates in the water. Hence strong acids (or bases) have higher dissociation constant a thus lower the *pK* value. Strong acid (or base) is usually labeled the acid (or base) that fully dissociates in the water solution (the concentration of the other part of the conjugate pair is negligible). [12]

Similarly, as the *pK* value is a negative decadic logarithm of the dissociation constant, the *pH* value is a negative decadic logarithm of the H^+ ion concentration in a solution.

$$pH = -\log_{10}\left[H^+\right] \tag{8}$$

For the high concentration of substances (e.g. H^+, OH^-) in the solution, the effective concentration of the ions is somehow lower than the real concentration. This is caused by interaction between the ions of opposite charge. The associate into neutral pairs (e.g. H^+Cl^-). This effective concentration is called activity. We should be calculating the *pH* value using the activity instead of the concentration to be exact. In practice, for the calculation of *pH* value, we usually stick with the concentration of hydrogen ions instead of their activity, because the difference for the non-extreme *pH* values is negligible. In the human body, the *pH* values are close to neutral *pH* (in extreme 6.5 – 8) hence we can use the concentration of hydrogen ions with sufficient accuracy of the results. [13]

While we are talking here about the H^+ concentration in the water solution we should mention, that in reality, the free hydrogen cations in the water does not exist. Even if the hydrogen cation has an only single unit of positive charge, it is a bare nucleon (proton) and thus it has high charge density. Hence it is strongly attracted to any molecule with an excess of negative charge. The proton will be attracted by the lone electron pair of the H_2O molecule. The bond is created thanks to the sharing of an electron between the oxygen and the proton. The result is the creation of hydronium ion H_3O^+. [14]

$$H^+ + H_2O \rightarrow H_3O^+ \tag{9}$$

1.2 Acid-base balance in a human body

Acid-base homeostasis in a human body is very important. The *pH* is maintained in a narrow range (7.4 ±0.04 for blood, the cellular environment is more acidic ca. 7.0 – 7.2). To

[12] 'Acids and Bases | Chemistry'.
[13] 'The pH Scale'; McNamara and Worthley, 'Acid-Base Balance'.
[14] 'The pH Scale'.

keep the *pH* values in this narrow range, a number of the mechanisms is needed. Different systems work on different time scales. [15]

1.2.1 Importance in medicine

The narrow *pH* range is kept due to the importance of certain hydrogen cations concentrations in many biological processes. It is essential for a cell metabolism and transmembrane transport. The difference in *pH* might cause different protein conformations due to reaction with hydrogen ions. Proteins are an essential part of many structures in the cells and their functionality depends on their certain conformation. Enzymes are *pH* sensitive as well. The imbalance in ion distribution caused by acid-base imbalances might cause changes in bone density and muscle wasting. [16]

Acid-base homeostasis influences transmission of oxygen as well. Not only by the respiratory regulation, but it influences the dissociation curves which are important for the mechanism of diffusion of oxygen from the blood to the tissues. This effect is important especially for acute alkalosis because it decreases the release of oxygen from blood into the tissues. Even if the oxygen saturation of blood is high, tissues can suffer by the insufficiency of the oxygen. The changes of *pH* value also influence the contractile force of the heart. Greater effect has the acidosis with depression of the contractile force. [17]

1.2.2 Acute response

Chemical buffer systems deal with acute changes in the H^+ concentration. The reaction is in the matter of milliseconds[18]. In different parts of the body, we meet with different buffer systems. The most significant buffers for blood are the bicarbonate system and hemoglobin, for intracellular fluid, it is the proteins and phosphates and for extracellular fluid the bicarbonate system. The chemical buffers are composed of the conjugate pairs of acids and basis. [19]

For bicarbonate buffer, it is weak carbonic acid and the bicarbonate anion as a base.

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+ \tag{10}$$

[15] Nečas and spol., *Obecná Patologická Fyziologie*; Hamm, Nakhoul, and Hering-Smith, 'Acid-Base Homeostasis'.
[16] Nečas and spol., *Obecná Patologická Fyziologie*; Hamm, Nakhoul, and Hering-Smith, 'Acid-Base Homeostasis'.
[17] Nečas and spol., *Obecná Patologická Fyziologie*; Mitchell, Wildenthal, and Johnson, 'The Effects of Acid-Base Disturbances on Cardiovascular and Pulmonary Function'.
[18] Nečas and spol., *Obecná Patologická Fyziologie*.
[19] '7. Acidobazická Rovnováha • Funkce Buněk a Lidského Těla'.

The bicarbonate buffer system is open. The body can actively change both of its parts. The amount of H_2CO_3 is bound with the P_{CO2} and thus with the respiration while the HCO_3^- can be controlled by the kidneys. [20]

Thanks to the branched structure of proteins with a number of side chains, they can bound or cleave off the hydrogen cations. The hemoglobin system is important for dealing with the CO_2 production of metabolism. The carbon dioxide diffuses to the erythrocytes where thanks to carbon anhydrase can quickly form the carbonic acid, which dissociates into hydrogen cation and bicarbonate anion. Most of the bicarbonates leave the erythrocytes thanks to chloride shift (Hamburger effect) while anion of bicarbonate is exchanged for chloride anion to maintain the electroneutrality. Deoxygenated hemoglobin can bind the H^+ much more effectively that the oxygenated one and thus helps with the buffering of the products of metabolism. In lungs, the P_{CO2} is lower than in the body so the carbonic acid breaks into the water and carbon dioxide, which is breath out. The hydrogen cation is provided by the hemoglobin, where it was bound earlier. [21]

1.2.3 Long-term response

The other systems need longer time to properly react on the acid-based imbalances. The second fastest system helping with the balance is the shift of species between the buffer systems of blood and interstitium (tens of minutes). The intracellular buffers, as well as the bone mass, can response in few hours. The respiratory system can manipulate with the P_{CO2} and thus adjust the level of bicarbonates. Maximum efficiency occurs after 6 – 12 hours. The slowest system is the kidneys. They can adapt the excretion of acids (or bases) with a maximum effect after 3 – 5 days. [22]

1.3 Approaches to the acid-base balance

There are two main approaches to the description of blood acid-base chemistry. The classical approach of Ole Siggaard-Andersen is based on experimentally-determined nomograms[23]. Nomograms graphically describe the *pH* as a function of hemoglobin concentration, the pressure of carbon dioxide and base excess (*BE*). Base excess is the amount of milliequivalents of a strong acid (or base) that is needed to titrate one liter of blood to reach

[20] Nečas and spol., *Obecná Patologická Fyziologie*; Mitchell, Wildenthal, and Johnson, 'The Effects of Acid-Base Disturbances on Cardiovascular and Pulmonary Function'.
[21] '7. Acidobazická Rovnováha • Funkce Buněk a Lidského Těla'; Nečas and spol., *Obecná Patologická Fyziologie*.
[22] Koeppen, 'The Kidney and Acid-Base Regulation'; Nečas and spol., *Obecná Patologická Fyziologie*.
[23] Morgan, 'The Stewart Approach – One Clinician's Perspective'.

the normal *pH* (7.4). *BE* is derived from the Buffer Base (*BB*), which is the sum of bicarbonates and the non-bicarbonate buffers (*Buf*).

$$BB = \left[HCO_3^-\right] + \left[Buf^-\right] \tag{11}$$

The problem with *BB* was the dependency on the hemoglobin concentration (since it is one of the non-bicarbonate buffers), which makes it difficult to compare *BB* values for different patients. To avoid the dependency on the hemoglobin concentration the *BE* was defined as a difference between the *BB* at the given *pH* value and the value of normal buffer base (*NBB*), which is the value at of *BB* at *pH* 7.4.

$$BE = BB - NBB \tag{12}$$

Since both the values (*BB* and *NBB*) are dependent on the hemoglobin, the dependency is eliminated. The weak point of this approach is the need of standard conditions to be accurate. It does not deal with different plasma protein concentrations or ion balance. [24]

The second widespread approach is the approach of Stewart. It deals with the limitation of the need for normal plasma proteins (or plasmatic buffers generally). He mathematically deduces that *pH* is a function of P_{CO2}, *SID* (Strong Ion Difference) and concentration of total buffers. The total buffer is the sum of both conjugate pairs of the non-bicarbonate buffers.

$$Buf_{TOT} = \left[Buf\right] + \left[HBuf\right] \tag{13}$$

SID is the difference of fully dissociated cations and anions:

$$SID = \left[Na^+\right] + \left[K^+\right] + \left[Mg^{2+}\right] + \left[Ca^{2+}\right] - \left[Cl^-\right]. \tag{14}$$

The pressure of carbon dioxide is an indicator of the respiratory state while *SID* and Buf_{TOT} reflect the metabolic disorders. This approach offers better insight into the acid-base disturbances, but it considers only plasma and thus ignores the buffering capacity of hemoglobin (which is more significant than the capacity of plasmatic proteins). [25]

The two approaches are not in contradiction. Each is defined for different conditions. The first one is defined for blood with the same plasma proteins while the second is defined for plasma only, but is more general. Despite its limitations both approaches are commonly used in clinical praxis. There are more precise models of the acid-based balances, but they are not received well by clinicians due to their complexity. [26]

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[24] Kofranek, Matousek, and Andrlik, 'Border Flux Balance Approach towards Modelling Acid-Base Chemistry and Blood Gases Transport'; Ježek and Kofránek, 'Modern and Traditional Acid-Base Approaches Combined'; Morgan, 'The Stewart Approach – One Clinician's Perspective'.

[25] Kofranek, Matousek, and Andrlik, 'Border Flux Balance Approach towards Modelling Acid-Base Chemistry and Blood Gases Transport'; Ježek and Kofránek, 'Modern and Traditional Acid-Base Approaches Combined'; Morgan, 'The Stewart Approach – One Clinician's Perspective'.

[26] Ježek and Kofránek, 'Modern and Traditional Acid-Base Approaches Combined'; Kofranek, Matousek, and Andrlik, 'Border Flux Balance Approach towards Modelling Acid-Base Chemistry and Blood Gases Transport'.

1.4 Regulation

The human body produces ca. 20 000 mmol of carbon dioxide, which with the connection with body fluids (water) creates weak carbonic acid, and ca. 60 – 70 mmol of strong acids. The production of the acids in metabolism has to be in balance with their elimination from the body. The elimination of carbon dioxide is a task for respiration system while the elimination of strong acids provides kidneys. In the normal state, the intake and expenditure of the acids are in balance. The disturbances in the balance of CO_2 lead to respiratory disorders of acid-base balance – respiratory acidosis or respiratory alkalosis. Imbalance in the strong acids leads to the metabolic disturbances of acid-base balance – metabolic acidosis or metabolic alkalosis. [27]

The first to response to the acid-base imbalance are the buffer systems. The bicarbonate system provides a connection between the CO_2 and H^+ as shows figure 1. Thanks to this connection, kidneys can react on the imbalance of carbon dioxide and the respiratory system can compensate the strong acid disorders.

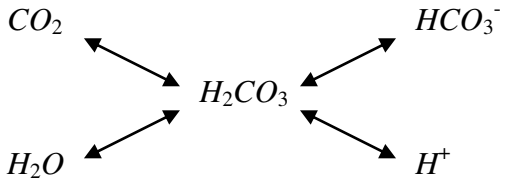

Figure 1: The relation between the hydrogen ions and carbon dioxide.

Besides the bicarbonate buffers, there are other non-bicarbonate buffers which we usually denote as *Buf* and their conjugate acid as *HBuf*. The relation between the *Buf* and *HBuf* shows figure 2.

[27] Nečas and spol., *Obecná Patologická Fyziologie*; Engliš, 'Smíšené Poruchy Acidobazického Metabolismu'.

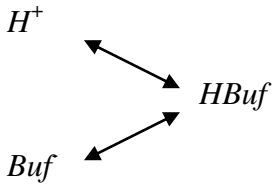

Figure 2: The relation between the non-bicarbonate buffer and hydrogen cation.

Combining both types of the buffer we receive an idea of the whole buffer system of the human body as shows figure 3. [28]

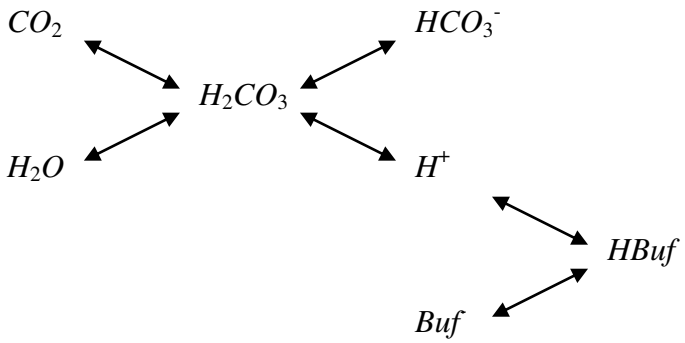

Figure 3: The representation of the buffer system of human body.

The buffer systems can help us with the fast response on the acute acid-base disorders but they can not fully compensate the disturbance and restore the physiological *pH* value. To fully compensate the acid-base disorder, we need to adjust the level of bicarbonates to restore the ideal level of H^+ concentration. There are two ways of influencing the level of HCO_3^-. The respiratory system can change the level of carbon dioxide and thus shift the balance of bicarbonate buffer (increase in the carbon dioxide pressure leads to increasing of bicarbonates while a decrease of P_{CO2} lowers the HCO_3^- see fig. 3). Kidneys can also manipulate with the level of bicarbonates. For every ion of a strong acid which is excluded by the kidneys, one ion of HCO_3^- is added to the body. Thus if we have a problem with the respiration (imbalance in carbon dioxide), kidneys can compensate the disorder – metabolic compensation of respiration

[28] Engliš, 'Smíšené Poruchy Acidobazického Metabolismu'; Nečas and spol., *Obecná Patologická Fyziologie*.

disorder; and if the imbalance in strong acids occurs, the respiratory system helps to compensate this disorder – respiratory response on a metabolic disorder. [29]

1.4.1 Metabolic acidosis

Metabolic acidosis is a disorder primary caused by an increase in hydrogen ion concentration. The acute redundancy of H^+ is compensated by the buffer systems. This causes a decrease in the *BB* (*BE* goes to negative values) and a slight decrease in *pH*. At the beginning, the level of carbon dioxide does not change, but as the disorder persists, the ventilation starts to increase. This will lower the carbon dioxide in the blood, which leads to the shift in the balance of bicarbonates (carbonic acid disintegrates into water and carbon dioxide, which leads to recombination of hydrogen ion and bicarbonate to carbonic acid and thus lowering the bicarbonates and increase of *pH*). Fully compensated metabolic acidosis is characteristic by low *BB* (negative *BE* – primary disorder) with low P_{CO2} value (caused by the regulation response) while the *pH* value is standard. [30]

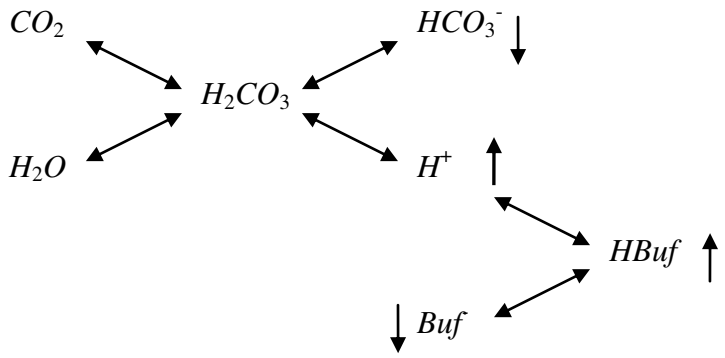

Figure 4: Non-compensated metabolic acidosis. The increase of the hydrogen ions causes consumption of bicarbonate and non-bicarbonate buffers. The respiration keeps constant CO_2 level.

[29] Koeppen, 'The Kidney and Acid-Base Regulation'; Hamm, Nakhoul, and Hering-Smith, 'Acid-Base Homeostasis'; Nečas and spol., *Obecná Patologická Fyziologie*.
[30] McNamara and Worthley, 'Acid-Base Balance'; Nečas and spol., *Obecná Patologická Fyziologie*.

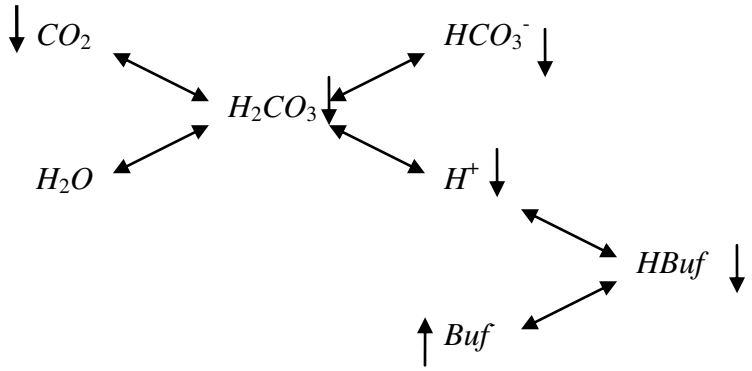

Figure 5: Fully compensated metabolic acidosis. The response of ventilation lowers the carbon dioxide level which shifts the balance of bicarbonates left and thus lowers the H^+ back to standard level.

1.4.2 Metabolic alkalosis

Metabolic alkalosis is caused by negative balance of strong acids in the system. This causes the increased *BB* and *BE* values. The buffer systems react by releasing the hydrogen ions to balance the *pH* value. Respiration keeps constant carbon dioxide level, but with the persistent disturbance, the ventilation lowers. The increased pressure of carbon dioxide shifts the balance of bicarbonate buffer system increasing the hydrogen ion concentration back to normal. The result of the respiratory compensation of metabolic alkalosis is increased P_{CO2} and *BE* (which is the primary problem). [31]

[31] McNamara and Worthley, 'Acid-Base Balance'; Nečas and spol., *Obecná Patologická Fyziologie*.

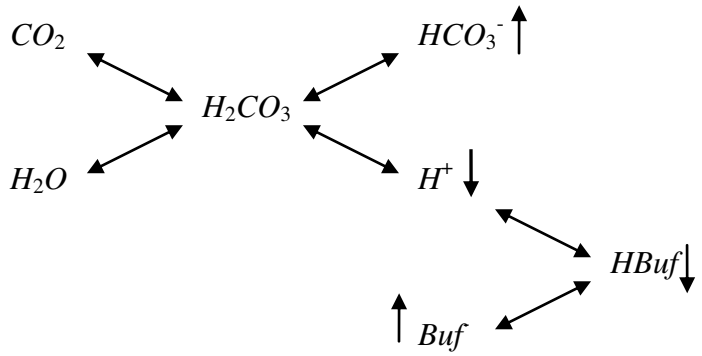

Figure 6: Non-compensated metabolic alkalosis. The decrease in the H^+ leads to releasing it from the buffers and shifts the balance of bicarbonate buffer system right increasing the hydrogen ions and bicarbonates. The CO_2 is kept constant due to ventilation.

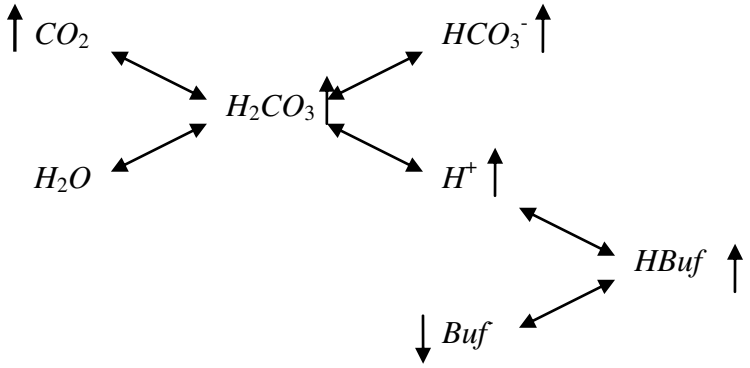

Figure 7: Fully compensated metabolic alkalosis. Increase in CO_2 shifts the bicarbonates balance further right increasing the hydrogen ion concentration. It bounds back to the non-bicarbonate buffers. The physiological *pH* is restored.

1.4.3 Respiratory acidosis

The cause of the respiratory acidosis is retention of carbon dioxide in the blood. Acute hypercapnia leads to increased dissociation of carbonic acid and thus increased hydrogen ion concentration. They are bound to non-bicarbonate buffers. Some of the newly created bicarbonates shift from plasma to interstitium which leads to a slight decrease in *BB* and *BE*. If the imbalance persists, kidneys start to excrete strong acids associated with equimolar intake of bicarbonates. The increase in bicarbonates shifts the bicarbonate buffer balance in advance of

carbonic acid and thus lowers the H^+. The result of fully compensated respiratory disturbance is high P_{CO2} and slightly increased *BE* with standard *pH*. [32]

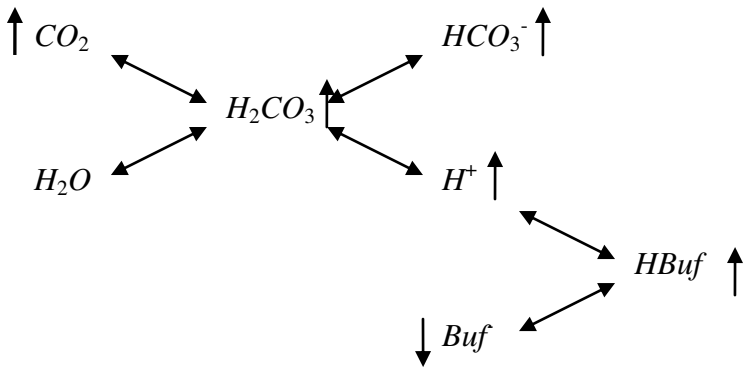

Figure 8: Non-compensated respiratory acidosis. Retention of carbon dioxide increases the carbon acid concentration which dissociates to bicarbonate anion and hydrogen ion. Non-bicarbonate buffers bound the redundant H^+ lowering the *pH*.

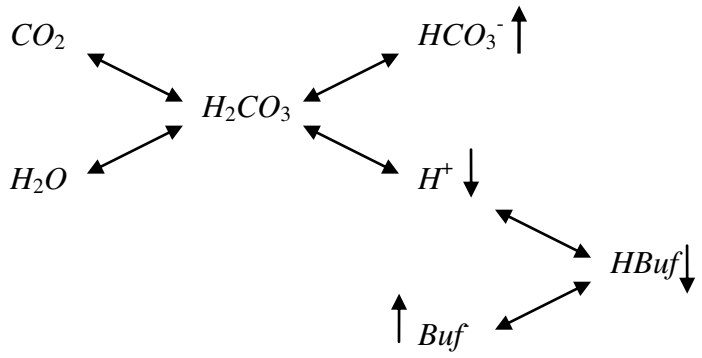

Figure 9: Fully compensated respiratory acidosis. Increased HCO_3^- consumes H^+ lowering their concentration, which leads to releasing hydrogen ions from non-bicarbonate buffers and restoring physiological *pH* level.

[32] McNamara and Worthley, 'Acid-Base Balance'; Nečas and spol., *Obecná Patologická Fyziologie*; Koeppen, 'The Kidney and Acid-Base Regulation'.

1.4.4 Respiratory alkalosis

Respiratory alkalosis is caused by depletion of carbon dioxide (hypocapnia). Lowering the carbon dioxide shifts the balance of bicarbonate buffer system to the left creating more carbonic acid which is linked with a decrease of bicarbonates and hydrogen ions. The hydrogen cation depletion is partially compensated by the non-bicarbonate buffers, which releases the H^+. The persistent respiratory disorder is compensated by reduced excretion of strong acids by the kidneys, which leads to a cumulation of hydrogen ions. The result of metabolic regulation of respiratory alkalosis is low P_{CO2}, and a slight decrease in *BB* and *BE* while *pH* is normal. [33]

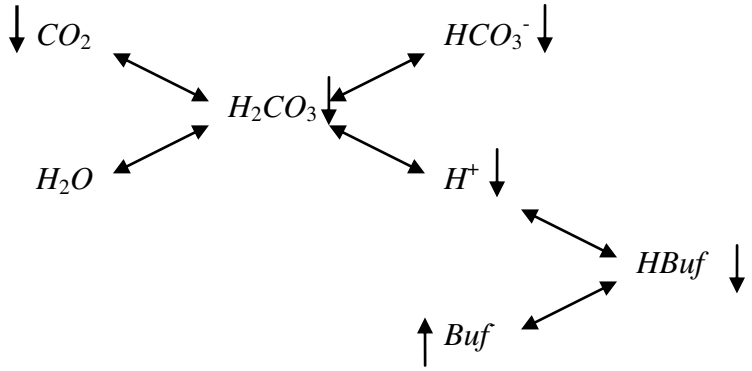

Figure 10: Non-compensated respiratory alkalosis. The decrease of carbon dioxide shifts the balance of bicarbonates in advance of carbonic acid lowering the hydrogen ions. The H^+ deficit is partially compensated by the non-bicarbonate buffers.

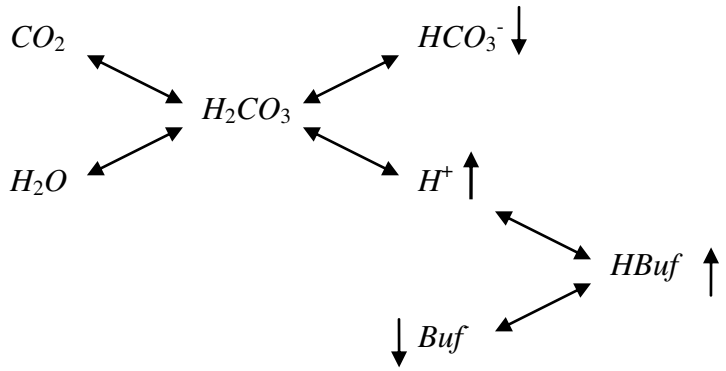

Figure 11: Fully compensated respiratory alkalosis. Retention hydrogen ions cause a decrease in bicarbonate anions and shifts the balance of non-bicarbonate buffers in advance of conjugate acids.

[33] McNamara and Worthley, 'Acid-Base Balance'; Nečas and spol., *Obecná Patologická Fyziologie*; Koeppen, 'The Kidney and Acid-Base Regulation'.

2 IPE model

2.1 Theoretical background

For predictions of acid-base disorders, we need an insight into the character of the imbalance. Mathematical models can greatly help us with such tasks. The models have been created since the begging of the computer history. Most of the models had their limitations since they neglected some parts of the complex acid-base balance system. Combining the approaches to the acid-base balance M. B. Wolf and E. C. DeLand created a blood-interstitial acid-base balance model. [34]

The main idea of the interstitial-plasma-erythrocyte (IPE) model is to compute concentrations of characteristic ions in each of those parts. This can be done using a number of assumptions.

- Each of the three fluids is considered homogeneous.
- Each part attains to electroneutrality.
- In each compartment, there is the same osmolarity.

The system is in equilibrium with the gas CO_2. It means it is an open system to the carbon and carbonates are not conserved. The other species and water volumes are considered conserved. The electroneutrality and the same osmolarity is reached by movements of mobile species and water across the membranes separating the compartments. [35]

The major permeant ion passing through erythrocyte membrane, separating erythrocytes and the plasma, is Cl^-. Its distribution is in equilibrium described by Donnan ratio between erythrocytes concentration and plasma concentration. The permeant ions across the capillary membrane between interstitial fluid and plasma are Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^- and phosphates. Their equilibrium distribution is as well described by the Donnan ratio. The H^+ cations can pass through all membranes. The concentration values of bicarbonates are intended by the P_{CO2} and the concentration of H^+. The H^+ concentration is connected with the pH value, hence the carbonates and bicarbonates are related to the pH. The partial pressure of carbon dioxide is considered to be the same for all compartments, but its solubility for each part is different. [36]

Besides the permeant ions, there are impermeant particles in each of the three compartments. In the case of the erythrocytes, there are charged macromolecules of hemoglobin, the metabolites DPG, ATP and GSH and small ions Na^+ and K^+. The impermeant molecules in plasma and interstitium are the serum albumin. Each of the three compartments

[34] Wolf and DeLand, 'A Mathematical Model of Blood-Interstitial Acid-Base Balance'; Wolf, 'Whole Body Acid-Base and Fluid-Electrolyte Balance'.
[35] Wolf and DeLand, 'A Mathematical Model of Blood-Interstitial Acid-Base Balance'.
[36] Ibid.

also contains unidentified species. The mass and charge of these unidentified species are adjusted to reach the reference state of the model. The ions of weak acids and the macromolecules (metabolites, hemoglobin, albumin) can bind or release the H^+ cations depending on their concentrations (*pH*). Therefore interaction with H^+ changes the charge of the molecules hence we use the *pH*-dependent charges for these species. [37]

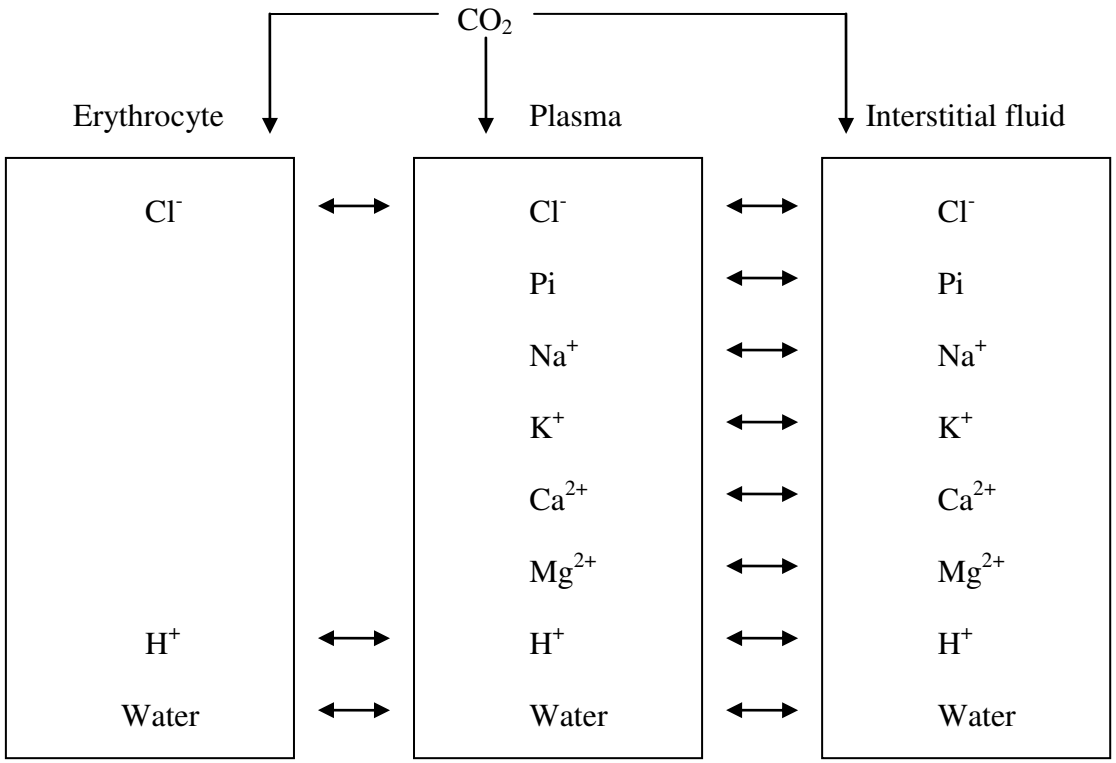

Figure 12: Diagram of the mobile species of the IPE model. The pressure of the carbon dioxide is same for all compartments but the solubility differs. The rest of species in each compartment is considered immobile.

One of our assumptions is the equilibrium distribution of all mobile species across all the membranes. This means the IPE model can not simulate a system with arterial blood since it is not in equilibrium with the interstitial fluid. Hence we will use the physiological values of venous blood and we have to keep in mind that in IPE model we work only with the venous blood. To simulate arterial blood we need only PE model.

[37] Ibid.

2.2 Mathematical background

To be able to compose the model, we have to express the assumption we made earlier mathematically. For each issue, we construct a set of equations. Here we take a closer look at the equations of the IPE model.

2.2.1 Electroneutrality

Each ion in the solution has an electrical valence Z which describes its charge. We can get the total charge of one species using the relation

$$Z \times N = \delta \tag{15}$$

where Z is the valence of the ion, N is the molar amount of the ion and δ is the total charge of the species. If the sum of the total charges for each species is zero, the solution is electric neutral. The electroneutrality is solved for each solution (compartment) separately. This means all the ions are in the same volume of solvent V. Hence we can use their concentration C in the equation of electroneutrality instead of the molar amount as shows the following relations.

$$\sum \delta = 0 \tag{16}$$

$$\sum (Z \times N) = 0 \tag{17}$$

$$\sum \left(Z \times \frac{N}{V} \right) = 0 \tag{18}$$

$$\sum (Z \times C) = 0 \tag{19}$$

Using the formula (19), we can construct the equations of electroneutrality for each of the three compartments. Since the interstitium and plasma has the same composition of the species (the concentrations are not the same), the equations of electroneutrality has the same form

$$\begin{aligned} &C_{Na} + C_K + 2C_{Ca} + 2C_{Mg} - C_{Cl} - C_{HCO_3} - 2C_{CO_3} + Z_{Pi} \times C_{Pi} \\ &+ Z_{Alb} \times C_{Alb} + Z_{im} \times C_{im} = 0. \end{aligned} \tag{20}$$

In the equation (20) the *Pi* is the combined form of the two forms of phosphates important in the physiological range of pH, *Alb* is the serum albumin and *im* represents the impermeable species. In the case of erythrocytes, the equation has following form [38]

$$\begin{aligned} &C_{Na} + C_K - C_{Cl} - C_{HCO_3} - 2C_{CO_3} + Z_{Hb} \times C_{Hb} + Z_{DPG} \times C_{DPG} \\ &+ Z_{ATP} \times C_{ATP} + Z_{GSH} \times C_{GSH} + Z_{im} \times C_{im} = 0. \end{aligned} \tag{21}$$

[38] Ibid.

2.2.2 Osmotic equilibrium

The osmolarity O_x is the result of concentration C_x of the species multiplied by its osmotic coefficient ϕ_x.

$$O_x = C_x \times \phi_x \tag{22}$$

The total osmolarity O is the sum of osmolarities of each species O_x in the solution

$$O = \sum O_x \tag{23}$$

$$O = \sum \left(C_x \times \phi_x \right) \tag{24}$$

To reach the osmotic equilibrium, there has to be the same osmolarity on each side of the membrane and so the difference between the osmolarities has to be negligible.

$$O_1 = O_2 \tag{25}$$

The values of osmotic coefficient ϕ_x are in most cases equal to one. For Na^+, K^+, Cl^- and phosphates the value ϕ_x = 0.93. The osmotic coefficient for hemoglobin are experimentally measured and the results match the polynomial equation[39]

$$\phi_{Hb} = 1 + 0.115 \times C_{Hb} + 0.0256 \left(C_{Hb} \right)^2 . \tag{26}$$

Using the formula above (24), we can create equations for osmolarity in erythrocytes

$$\begin{aligned} O = {} & 0.93 \times C_{Na} + 0.93 \times C_K + 0.93 \times C_{Cl} + 0.93 \times C_{Pi} + \phi_{Hb} \times C_{Hb} \\ & + C_{DPG} + C_{ATP} + C_{GSH} + C_{HCO_3} + C_{CO_3} + C_{im} \end{aligned} \tag{27}$$

and for plasma and interstitium [40]

$$\begin{aligned} O = {} & 0.93 \times C_{Na} + 0.93 \times C_K + 0.93 \times C_{Cl} + 0.93 \times C_{Pi} + C_{Ca} \\ & + C_{Mg} + C_{Alb} + C_{HCO_3} + C_{CO_3} + C_{im} . \end{aligned} \tag{28}$$

2.2.3 Transmembrane transport

To reach the equilibrium, the permeant ions move through the membranes dividing the compartments. The equilibrium is known as the Donnan equilibrium distribution. For each permeant ion, we can express the ratio r of its distribution on the membrane.

$$\left(r \right)^z = \frac{C_1}{C_2} \tag{29}$$

C_1 and C_2 are the concentrations of a permeant species on one and the second side of the membrane. The power z of the ratio is the valence of the species (one for Na^+, two for Ca^{2+}

[39] Raftos, Bulliman, and Kuchel, 'Evaluation of an Electrochemical Model of Erythrocyte pH Buffering Using 31P Nuclear Magnetic Resonance Data.'
[40] Wolf and DeLand, 'A Mathematical Model of Blood-Interstitial Acid-Base Balance'.

etc.). If the ratio for one polarity of ions (for example cations) is *r* the ratio for the opposite polarity (anions in this case) is inverted. [41]

$$\frac{C_1^+}{C_2^+} = (r)^z = \frac{C_2^-}{C_1^-} \tag{30}$$

2.2.4 Carbonates concentration

The concentration of carbonates and bicarbonates in each compartment are determined using Henderson-Hasselbalch equation for bicarbonates:

$$C_{HCO_3} = S_{CO_2} \times P_{CO_2} \times 10^{pH-pK_{carb1}} \tag{31}$$

and for carbonates

$$C_{CO_3} = C_{HCO_3} \times 10^{pH-pK_{carb2}} \tag{32}$$

where *S* is the CO_2 solubility, P_{CO2} is the partial pressure of the carbon dioxide (which is the same for all compartments) and pK_{carb1} and pK_{carb2} are the first and second dissociation constants of carbonic acid. [42]

2.2.5 Charge of pH-dependent species

Some species in the solution are not fully dissociated. The level of their dissociation depends on the acidity of the solution. The charge of these species can be expressed using following equation

$$Z = z_0 + z_1 \times \frac{b_1}{1+b_1} + z_2 \times \frac{b_2}{1+b_2} \tag{33}$$

where

$$b_1 = 10^{pH-pK_1} \tag{34}$$

and

$$b_2 = 10^{ph-pK_2}. \tag{35}$$

The z_0, z_1, and z_2 are specific constants for the species. These equations are fitted to provide data similar to the experimental ones. The electrical charge of hemoglobin depends on besides the pH on the O_2 saturation. The equation above solves the charge of fully saturated hemoglobin, but in the venous blood, hemoglobin is lesser saturated. The charge can be expressed as

[41] Ibid.
[42] Ibid.; Raftos, Bulliman, and Kuchel, 'Evaluation of an Electrochemical Model of Erythrocyte pH Buffering Using 31P Nuclear Magnetic Resonance Data.'

$$Z = Z_{oxy} + 1.5 \times \frac{1 - fSat}{fSat} \tag{36}$$

Where Z_{oxy} is the charge of fully saturated hemoglobin, *fSat* is the fractional O_2 saturation and Z is the desired charge of partially saturated hemoglobin. [43]

Table 1: Coefficients for *pH*-dependent charges[44].

Solute	z_0	z_1	z_2
Hemoglobin	15.6	-23	-4
Albumin	-10.7	-16	0
DPG	-3	-1	-1
ATP	-3	-1	0
GSH	-1	-1	-1
phosphates	-1	-1	0

2.2.6 Mass and volume conservation

Since the system is closed for all species except the carbon, we have to obey the principle of mass conservation. Hence all species except the carbonates and bicarbonates follows the equation

$$V^E \times C^E + V^P \times C^P + V^I \times C^I = M \tag{37}$$

where V^E is the volume of water in erythrocytes, V^P volume of water in plasma and V^I volume of interstitial fluid. The concentrations C use the same superscript pattern and M is the total mass of the species. For the water, we can simplify this equation only for volumes

$$V^E + V^p + V^I = V \tag{38}$$

where V is the total volume of water in the system. [45]

2.3 Equation-based implementation

First, we need to define a standard state. For this state, we use values from the literature. The body should be in the standard state while there is nothing special happening. For this state, the majority of the values are given, but there are the unidentified species in each compartment. We do not know their concentration and their charge. These values have to be determined

[43] Wolf and DeLand, 'A Mathematical Model of Blood-Interstitial Acid-Base Balance'; Raftos, Bulliman, and Kuchel, 'Evaluation of an Electrochemical Model of Erythrocyte pH Buffering Using 31P Nuclear Magnetic Resonance Data.'
[44] Wolf and DeLand, 'A Mathematical Model of Blood-Interstitial Acid-Base Balance'.
[45] Ibid.

experimentally. The concentration and charge influences the distribution of other species hence we must adjust the unidentified species to fit the known values to the standard state. We will set the volume of blood and interstitial fluid and the partial pressure of carbon dioxide in the model.

Table 2: Reference state concentrations of species in the model[46]. The concentrations of unidentified species are acquired experimentally to reach the reference state.

Solute [mmol/l]	Erythrocytes	Plasma	Interstitium
Hemoglobin	5.3		
Albumin		0.65	0.19
DPG	4.4		
ATP	1.8		
GSH	2.2		
Na	10	141	142
K	99	4.2	4.14
Cl	55.3	104	118
Ca		2.3	2.2
Mg		0.8	0.75
Phosphates	0.67	1.16	1.2
Unidentified	24.9	6	6.36

Table 3: Other parameters[47]. The charges of unidentified species are acquired experimentally to reach the reference state.

Parameter	Erythrocytes	Plasma	Interstitium
P_{CO2} [torr]	46	46	46
Water [l]	1.606	2.632	10
Z_{im} [-]	-9.2	1.4	-5.3

For the future calculations, we will have to get some more values, which can be derived from the values mentioned above. The blood volume is divided into the volume of erythrocytes and volume of plasma. Using the volume for each compartment, we can calculate the mass of all species and thus their total mass.

The model is implemented using the Modelica language. This allows us to solve the model as a system of equations. It means we must have as many equations as there are unknowns. The purpose of this model is to solve the equilibrium distribution of the mobile

[46] Ibid.
[47] Ibid.

species across the compartments. Hence the concentrations of the mobile ions are the unknowns. Water can pass through all the membranes as well, so the volumes of water in each of the three compartments are the next unknowns. Since the system is open for the carbon dioxide, the concentration of bicarbonates in each compartment is unknown as well.

The Cl^- can pass through all membranes, hence we need to calculate its concentrations in all three compartments which give us three unknowns. The rest of the mobile species (Na^+, K^+, Ca^+, Mg^+, and phosphates) moves only between the plasma and interstitial fluid. That gives us ten more unknowns. Water volumes of each compartment leave us three more unknowns and the HCO_3^- concentration in erythrocytes, plasma, and interstitial fluid are the next three. It gives us a total of nineteen unknowns.

To solve this system we need nineteen independent equations. We will use the mass conservation principle, the assumption of electroneutrality and osmotic equilibrium and the Donnan equilibrium distribution. All the six mobile ions mentioned above are conserved. It gives us six equations for their mass conservation. In the whole system, the total volume of water is constant, which gives use one more equation for volume conservation. The electroneutrality for all three compartments gives us three more equations and two more for the osmotic equilibrium between them. Last seven equations we need are for the Donnan equilibrium distribution of mobile species. There is one for the plasma-erythrocyte movement since there are only two mobile species (Cl^- and H^+) and six for the plasma-interstitium movement (besides the last mentioned two there are Na^+, K^+, Ca^+, Mg^+, and phosphates). This gives us a total of nineteen equations needed to calculate our unknowns.

Table 4: Main unknowns and equations in the IPE model.

Unknown	Quantity	Equations	Quantity
Cl- concentration	3	Mass conservation	6
Other mobile ions	10	Volume conservation	1
Water volumes	3	Electroneutrality	3
HCO3- concentration	3	Osmotic equilibrium	2
		Donnan distribution	7
Total	19	Total	19

The rest of variables can be derived from the distribution of the ions in each compartment. The value of pH is derived using the HCO_3^- concentration and P_{CO2} value (which is constant for the whole model), carbonates can be calculated using the pH and HCO_3^- concentration. The pH-dependent charges are computed using pH and the change in concentrations of immobile species is calculated using the volumes of water in each compartment.

2.3.1 Model functionality

The IPE model a steady state model. Its goal is to solve the distribution of species in equilibrium under different circumstances. Modelica solves the steady state at the beginning of the simulation, hence we do not see any changes in results while all parameters are constant. Using other simulating tools (e.g. VisSim as for the original implementation) we can see changing variables during simulation when there are no changes in parameters. This does not mean the model is dynamic, it is the only result of solving complex mathematical tasks like algebraic loops. Modelica solves the consistent initial state, while block-based models solve the transient during simulation. The algebraic loop is a case when the output of operation affects its input. We can illustrate simple algebraic loop on figure 13. This loop has a simple solution but usually, we use some mathematical algorithm. One of the possibilities is using the iteration while we use an initial estimate, compute the result, which we use for computing a more precise result in next step etc. unit we have a result with sufficient accuracy. In the real human body, the equilibrium between blood and interstitial fluid occurs in tens of minutes[48].

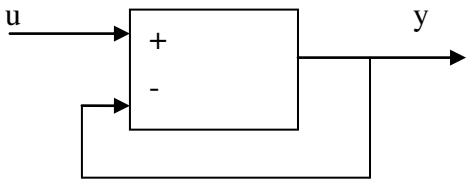

Figure 13: Example of a simple algebraic loop.

First, we have to set all parameters to reach the reference state. This is done by manipulating with the concentration and charge of unidentified species in each compartment. We had to set the right concentrations to match the overall osmolarity of the system. Important was a number of unidentified species in each compartment to balance the water distribution. Since the system is open only for the carbonates, we had to adjust the charge of unidentified species which helped us to reach the reference level of the bicarbonates thanks to the assumption of electroneutrality.

With the help of IPE model, we can simulate respiratory disturbances by changing the P_{CO2}. The P_{CO2} parameter is part of in the Henderson-Hasselbalch equation (31) where appears together with the HCO_3 concentration and pH. Since the system is closed, the overall amount of ions is constant. We can not change the concentration of HCO_3 for given P_{CO2}, because of electroneutrality. This means only change in pH is possible. This causes the change of pH-

[48] Nečas and spol., *Obecná Patologická Fyziologie*.

dependent charges so the carbonates concentration eventually changes along with the distribution of other mobile species. We might also want to know what the actual P_{CO2} level for certain *pH* is. For this case, we can simply set the *pH* value. The result will be the same as in the previous case. There is no difference between setting the P_{CO2} leaving the *pH* to compute or vice versa setting the *pH* and leaving the P_{CO2} variable.

We can also simulate the metabolic disorders by adding (or subtracting) certain species into the system. For this reason, we have the *X* variables (*XCl* for Cl^- etc.). We might want to observe what happens when we add some acid into the system. We can use e.g. 200 mmol of *HCl*. It is strong acid thus it will fully dissociate. Most of the H^+ cations will react with bicarbonates creating carbonic acid which will disassemble to water and carbon dioxide. While not compensated, the carbon dioxide will be breath out. The amount of water is negligible (ca. 3.6 ml). The result will be (besides increased chlorine) decreased the level of bicarbonates and lowered *pH* value due to slightly increased the level of H^+ cations (ca. 32 nmol/l). The model is not conserved for the H^+ cations. This means we do not have to add them along with the chlorine while adding the *HCl*. We simply add 200 mmol of Cl^-. Adding the ions will change the balance of electrical charge. To keep the system in neutrality, we need to subtract other anions, which will be the bicarbonates, because the system is open for them. As the Henderson-Hasselbalch equation (31) states the decrease in bicarbonates (while the P_{CO2} level is fixed) leads to decrease in the *pH*. Knowing the *pH* value, we know also the H^+ concentration.

2.4 Component-based implementation

For modeling physiological processes in the human body, a special library called Physiolibrary was developed. It is a free open-source Modelica library containing basic physical laws governing human physiology. The Physiolibrary is divided into set of domains, each solving certain issues (thermal, hydraulic etc.) Each domain contains components describing the laws of a single theme of physics. Hence we can use it for modeling cardiovascular circulation, thermoregulation, water distribution, electrochemical processes etc. [49]

For chemical and osmotic domains, the Physiolibrary recommends using another library called Chemical. This library is based on equilibrating the electrochemical potentials of the substances, following the modern theories of physical chemistry. It dynamically solves the chemical equilibration of a homogeneous chemical solution with fully thermodynamic states, supported also through thermal, mechanical, electrical and fluid components of Modelica Standard Library. For the implementation, we used Chemical library version 1.1.0. [50]

[49] Mateják et al., 'Physiolibrary -Modelica Library for Physiology'; 'Physiolibrary'.
[50] Matejak et al., 'Free Modelica Library for Chemical and Electrochemical Processes'; 'MarekMatejak/Chemical'.

Each of the three compartments of IPE model is considered a homogeneous solution. We need to create one solution for erythrocytes, plasma, and interstitial fluid. In the Chemical library, we use a component called *Solution*. This component represents chemical solution as a homogeneous mixture of the substances. We must fill this solution with the species it contains. For each chemical substance in the compartment, we have to create one component called *Substance*. There are common species contained in each of the three compartments. These are the dissolved carbon dioxide, water, bicarbonates and carbonates, phosphates, and the small ions of Na^+, K^+, and Cl^- as well as H^+. There are also special species for each compartment: the metabolites and hemoglobin for erythrocytes and albumin and Ca^{2+} and Mg^{2+} ions for plasma and interstitial fluid. The mobile species can pass through the membrane dividing the neighbor compartments. These species moves through special canals in the membranes. For each species, we can simulate such canal using the *Membrane* component. The dissolved carbon dioxide and water react to form weak carbonic acid. This acid dissociates depending on the concentration of H^+. In the first stage, it creates H^+ and HCO_3^-. This reaction can be simulated by the *Reaction* component connecting the substrates on the one side and the products on the other side. Similarly, we can write down dissociation of $HCO3^-$ into H^+ and CO_3^{2-} and balance between two main forms of phosphates in the physiological *pH* ($H_2PO_4^-$ and HPO_4^{2-}). For the rest species with *pH*-dependent charge, we will set the fixed value for the standard *pH*.

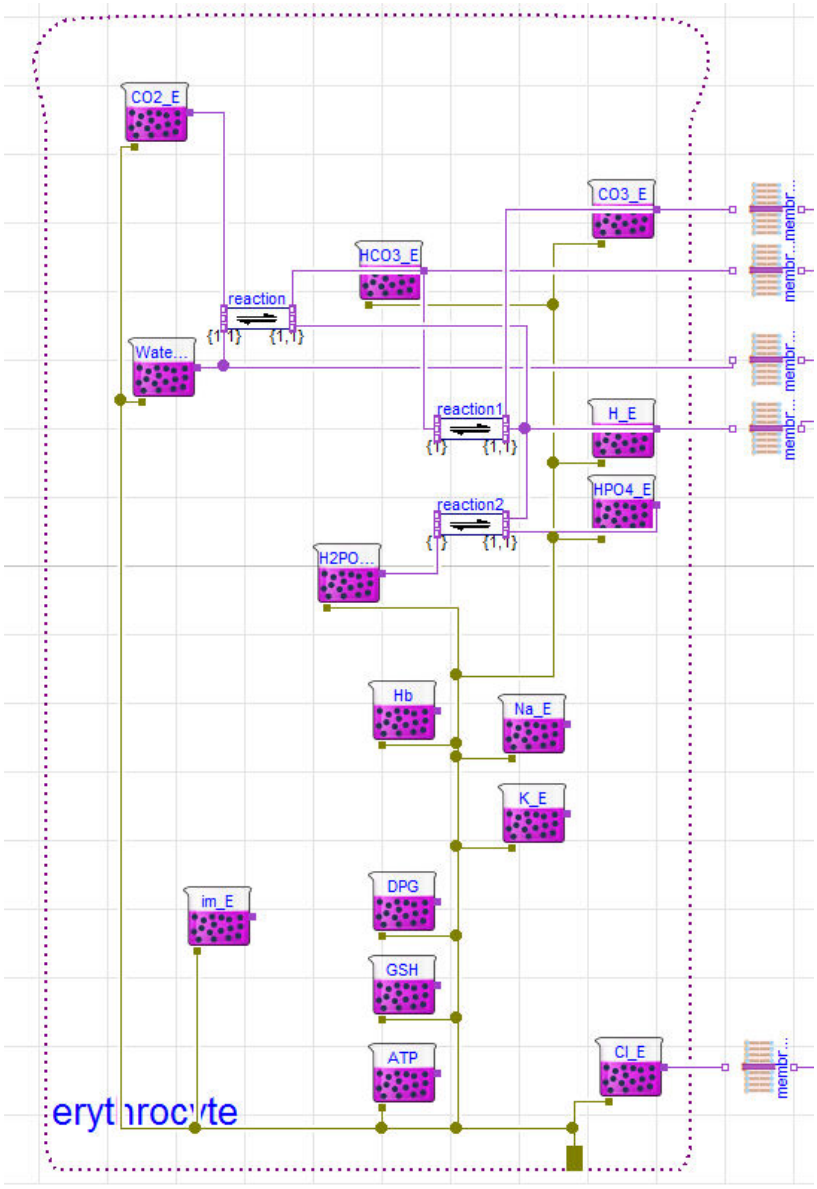

Figure 14: Construction of erythrocyte compartment using Chemical library. We can see all the substances contained in the solution. The mobile species are able to pass through the membrane.

2.5 Results

2.5.1 Equation-based model

For the model validation, we used the same experiments as are discussed in the results part of Wolf's article[51]. Measurements are usually performed on arterial blood, but with the IPE model, we can simulate the venous blood (because it is steady state model). To be able to repeat the experiments made by Wolf, we had to create a model of arterial blood. Arterial blood is not

[51] Wolf and DeLand, 'A Mathematical Model of Blood-Interstitial Acid-Base Balance'.

in equilibrium with the interstitial fluid so we had to remove the whole interstitial part. For validation of our implementation, we created a model named *blood*.

The first experiment we reproduced was the dependency of the *pH* of erythrocytes for a range of plasma *pH*. The relation between the *pH* of blood plasma and the *pH* of erythrocytes seems to be almost linear. To validate this relation in our implementation of the model, we used the model called *blood*. We set variable *pH* of plasma and observed the influence on the erythrocyte *pH*. The result was almost linear with the *pH* in erythrocytes rising slower than the *pH* in plasma as expected. The following figure 15 compares results of our implementation using Modelica (the red curve) and the results of original implementation. As we can see, the red curve closely follows the black one which shows the results of model implemented using VisSim.

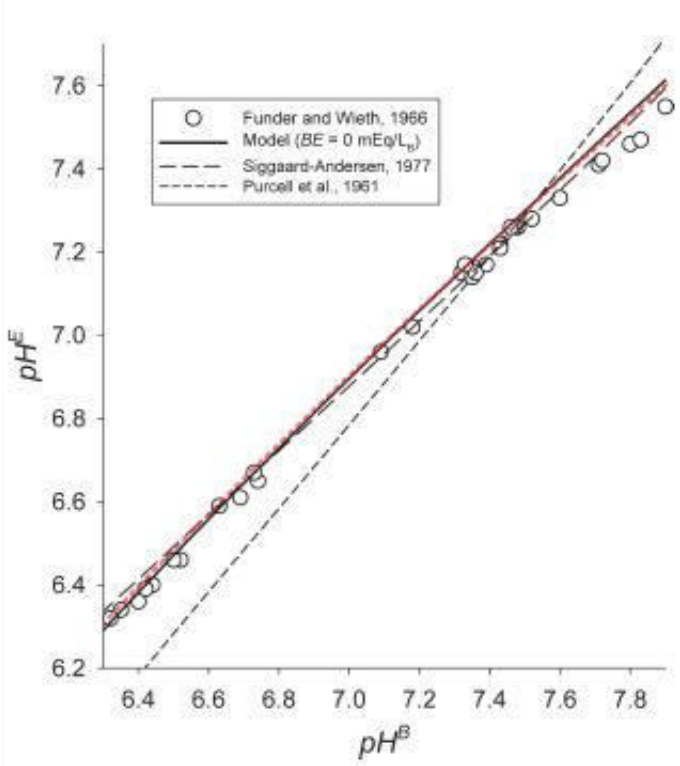

Figure 15: Dependency of the *pH* value in erythrocytes on the *pH* of plasma. The red curve shows results of our implementation in comparison with the black curve as a result of VisSim implementation.

The next experiments show the Donnan equilibrium distribution in different values of *pH* in the model. Since all the mobile ions reach this state, we can illustrate the distribution using the Cl^-. We will define the *rCl* as a ratio of Cl^- concentrations of erythrocytes relative to plasma. This experiment was performed on the arterial blood so we again used the *blood* model and observed the chloride distribution ratio across the range of *pH*. Figure 16 shows the results

of our model in red with comparison with other experiments from the original implementation. We can observe similar trends. The values in the physiological range are quite similar but our curve is a little bit steeper for very low *pH*.

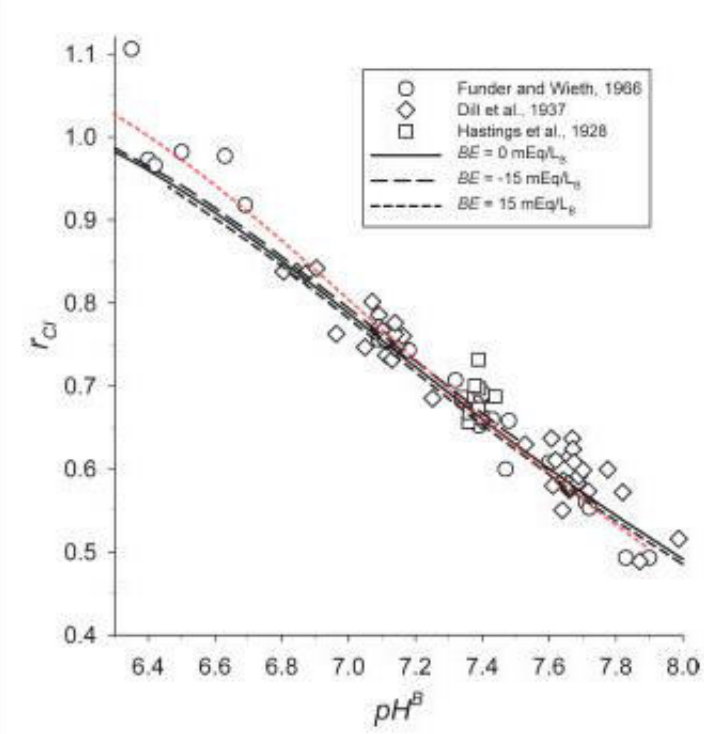

Figure 16: Donnan ratio for equilibrium distribution of Cl^- concentrations in erythrocytes water relative to plasma water for various *pH* values. The red curve shows results of our implementation of the model, while the black curve shows the original results.

As the figure 16 shows, the distribution of ions changes in various *pH* values. To balance these changes, the water shifts as well. We can illustrate this water shifts using the hematocrit. This is the ratio of erythrocytes volume in the blood. As the water shifts, this ratio changes as well. Figure 17 shows the change in hematocrit. The red curve for our results is little steeper as suggests the results of the previous experiment with the ions distributions. This experiment was done for the arterial blood[52] again so we used the *blood* model. This difference between the original and our implementation for last two experiments might be caused by additional uncharged permeable solutes contained in erythrocytes and plasma[53]. For lack of information about their distribution, we had to make them immobile or ignore them. This causes a difference in osmilarity of the two compartments and thus changes the water distribution slightly. The shifted water balance changes concentrations of the ions and thus their ratio as well as overall volume of the compartments which affects the hematocrit.

[52] Ibid.
[53] Ibid.

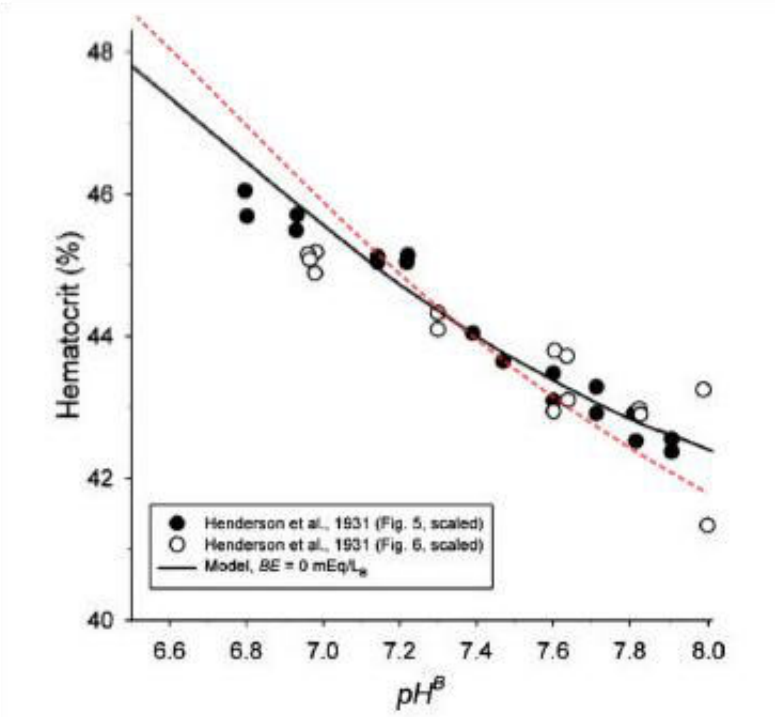

Figure 17: Changes in hematocrit in various *pH* values. The red curve shows results of the model implemented in Modelica.

With the changes of *pH*, there has to be another change. Since our model is conserved for all species besides the carbonates, we have to adjust their concentrations by changing the pressure of carbon dioxide. In the human body, the dependency is reversed. This means with the change of P_{CO2}, there is a change of *pH* in the system. This way we can simulate uncompensated respiratory disturbances. Following figure (18) shows the change of P_{CO2} with the change of plasma *pH*. The relationship between the pressure of carbon dioxide and *pH* value is influenced by the amount of bases (or acids) in the body. To measure the amount of bases in a body, we use *BE*. Keeping *BE* constant during the *pH* changes require possibility to change the amount of acids (or bases) in the system. To keep the *BE* constant, we opened the system for chlorides. This experiment was made for arterial blood[54], so we had to use the *blood* model.

[54] Ibid.

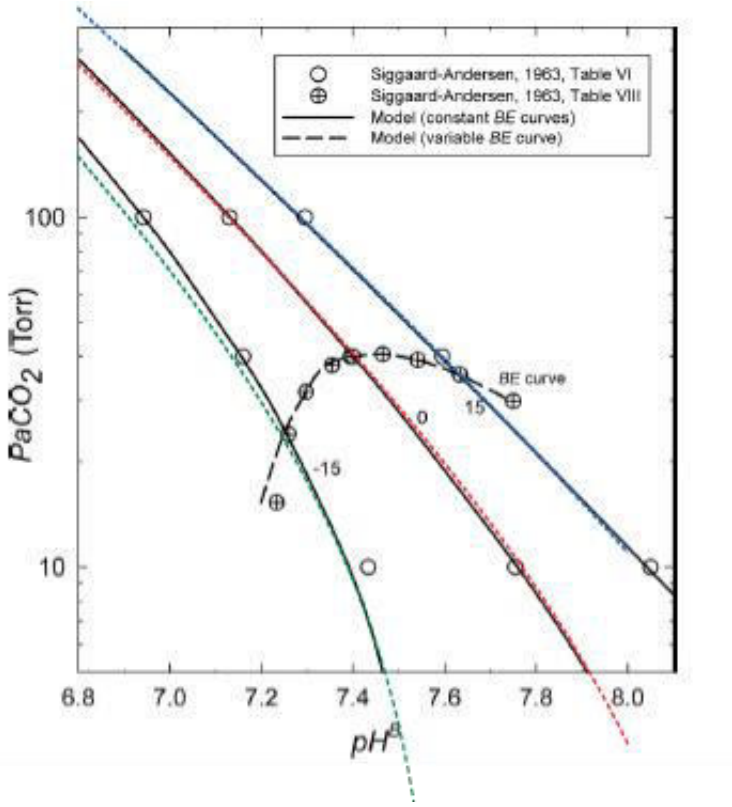

Figure 18: Changes in P_{CO2} for a range of *pH* values. The black curves represent results of the original implementation. Blue curve shows the result of our implementation for *BE* of 15 mEq/l, red for *BE* 0 mEq/l and green for *BE* -15 mEq/l.

To validate the IPE model, not only the PE (blood) model, Wolf made a similar experiment. He observed a relation between *pH* of plasma and pressure of carbon dioxide for different values of *SBE*. *SBE* value is analogical to *BE* value, but for calculating *SBE* we use only one-third of hemoglobin concentration we use for calculating *BE*. Figure 19 shows the results of Wolf's implementation of IPE model in VisSim in black while the results of our implementation are in color. Our results for *SBE* 0 and 15 mEq/l follows results of the original VisSim implementation. For the *SBE* -15 mEq/l, the results differ slightly with growing deviation for low values of carbon dioxide pressure in all three cases. The difference might be caused by the use of venous blood in our case (because of the steady state model) but in the results of Wolf he works with Pa_{CO2} instead of P_{CO2}, which represents the pressure of carbon dioxide in arterial blood. For this experiment, we used models called *Exp_PCO2_SBE0*, *Exp_PCO2_SBE15*, and *Exp_PCO2_SBEminus15*.

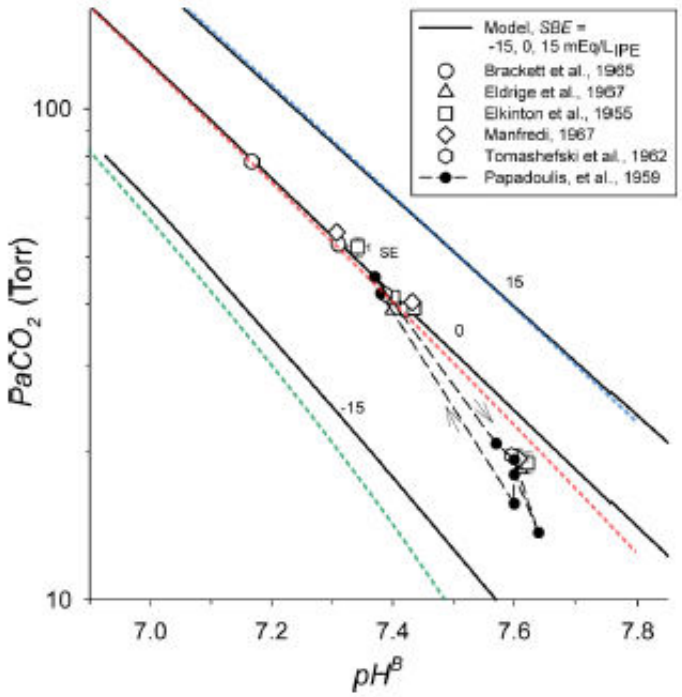

Figure 19: Relation between a pressure of carbon dioxide and plasma *pH*. Black curves show results of original implementation. Color curves show the result of our implementation. Blue represent *SBE* 15 mEq/l, red *SBE* 0 mEq/l and green *SBE* -15 mEq/l.

2.5.2 Component-based model

We implemented a model which comprises all principles and assumptions of Wolf and DeLand[55]. We had to make some adjustments to cover the way the Chemical library is constructed. We calculated the concentration of dissolved carbon dioxide instead of setting the pressure of its gaseous form. For the dissociation of the carbonates and phosphates, we created a reaction with H^+. The only way to observe *pH* is using the H^+ concentration. For the rest of the species with the *pH*-dependent, we use the reference charge (the charge they have in the standard state) because we are not able to make such simple dissociation reaction for them.

With this model, we were not able to reach the equilibrium with physiological values for neither pH nor the concentration of some species. The H^+ concentration for each compartment shows figure 20.

[55] Ibid.

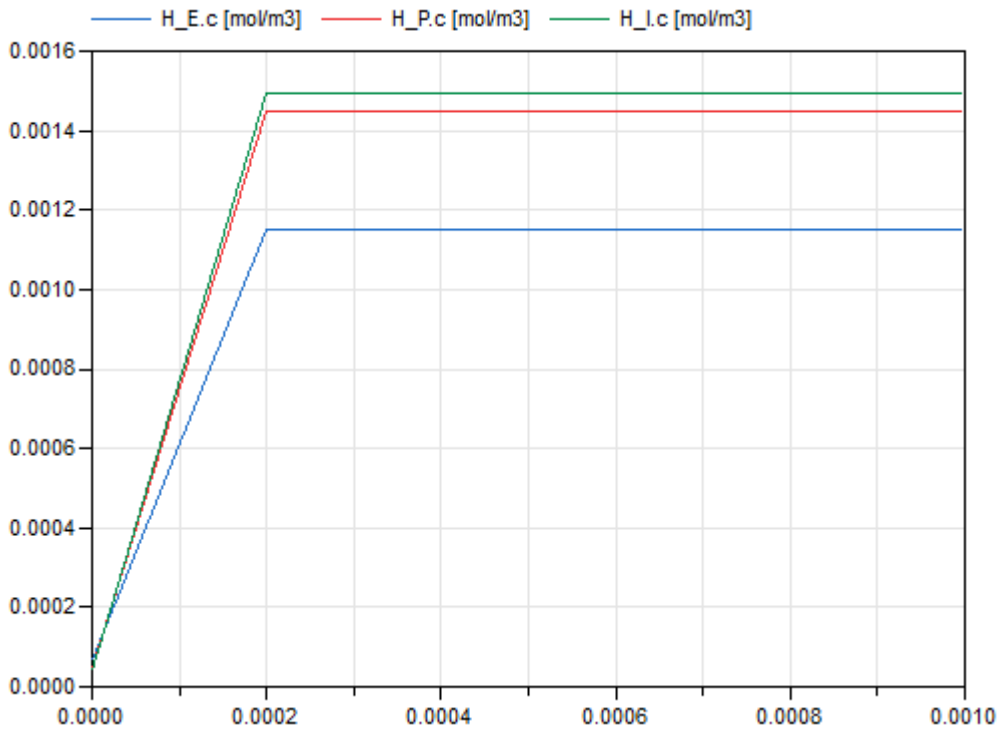

Figure 20: Concentration of H^+ cations in the component-based model for the IPE compartments. These H^+ concentrations correspond to ca. *pH* 3.

The assumption of electroneutrality in each compartment was violated. There was an overall charge of each solution in thousands of coulombs. The assumption of Donnan ratio for all mobile species across a membrane was not satisfied either. We were not able to correct these issues like in the equation based model because the charge or amount of unidentified species did not affect the ionic distribution. The change in charges of the *pH*-dependent species did not affect the overall distribution of the mobile species either; it changes only the overall charge of the solution. We tried not to use the reactions in the solutions. We set the physiological values for each species instead. The results were similar except the H^+ concentrations. The H^+ cations were allowed only to pass from one compartment to another, but their concentrations were diminishing as shows following figure (21).

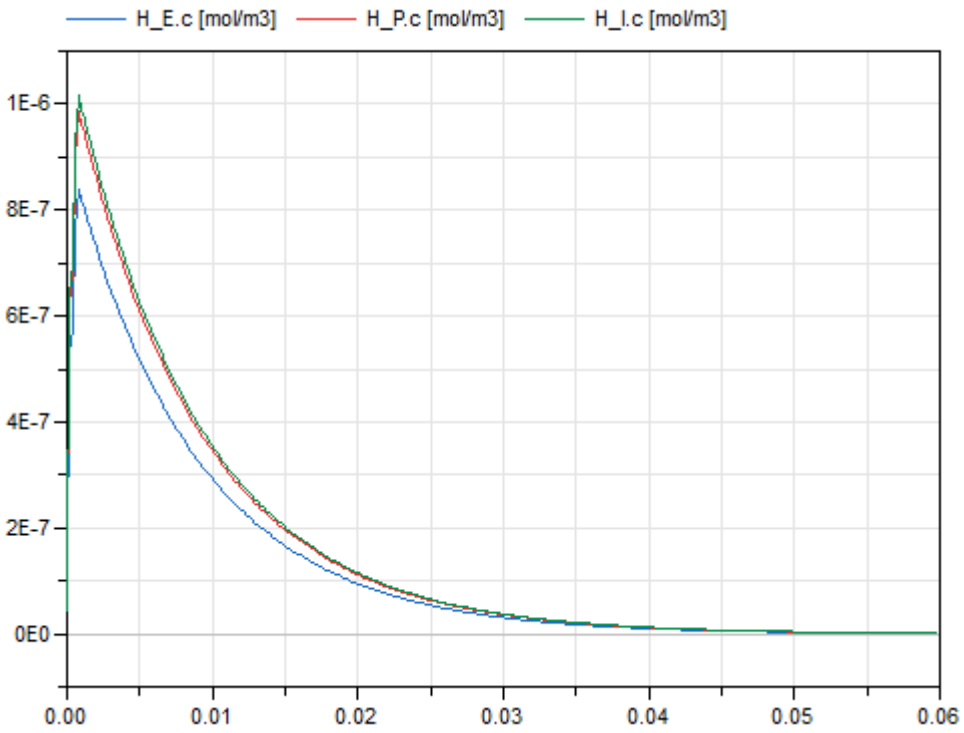

Figure 21: Concentration of H^+ cations for IPE compartments with the reaction disabled. The cations are allowed only to switch between the compartments but their concentration diminishes in all compartments.

2.6 Discussion

The equation based IPE model works well. We can use it to simulate various situations in a human body. We can change the concentration of the species in the system. This way we can observe what happens when there is low (or high) level of certain substance (e.g. chlorine, sodium etc.). We can set a combination of these irregularities. We have implemented parameters which change the overall amount of some species (Cl^-, Na^+, K^+, Ca^+, Mg^+, and water) in the model, so we can observe the effect of the addition of a certain amount of a substance to the system. This can help us to simulate metabolic disorders in the human body. We can also make changes in the pressure of carbon dioxide which simulate the respiratory problems.

Since the Modelica language is acausal, we can make the changes mentioned above and observe the changes of *pH* or we can make the *pH* parameter which we can manipulate with and one of the parameters mentioned above make a variable. This way we can see exactly how much of a substance is needed to get a certain value of *pH*.

The main advantage of Wolf's approach is its generality, which makes it useable for a wide range of cases. We can manipulate with a number of parameters to adapt to a lot of scenarios. Despite the many possibilities of utilization of the model, its mathematical apparatus

is not complicated. While implemented using Modelica, it is transparent and nicely explains the laws of acid-base balance.

Some of the limitations of Wolf's model comes from his assumptions. All the compartments of his model are considered homogeneous. In the human body, this is not true. The blood runs through many different organs. The following equilibration of the arterial blood in the tissue depends on its flow and an amount of carbon dioxide produced in that tissue. Hence the resultant equilibrium of the venous blood may differ for different body parts. This means we can not solve problems of individual organs but the body as a whole. The model is also a steady state model and thus we can observe only a result of a process, not the process itself.

In the component-based IPE model, we were not able to reach the electroneutral state in the compartments. This violates one of the basic assumptions we made. We also could not use the changes of charge with the changes of *pH*. The only way to observe *pH* is via H^+ concentration. We also could not reach the physiological value of the H^+ concentration. This might be caused by the reactions we used for the dissociation of carbonates and phosphates. While we set all the reactions aside and observed the concentration (and amount) of the H^+ concentrations, it was not conserved and was declining to zero. The concentration stabilized after removing the possibility of passing through the membrane. With the change of an amount of a mobile species its equilibrium distribution changes as well, but we lack the physiological values of some species. The Chemical library seems to work with physical chemistry using strict laws of physics thermodynamics and chemical relations while the IPE model uses simplifications (*pH*-dependent charge instead of reactions, simple osmotic equations etc.) and does not go in such deep as the Chemical library. We found the Chemical library inappropriate for the implementation of the IPE model of M. B. Wolf and E. C. DeLand.

The Physiomodel is a component-based model of the whole human body. Because its complexity, it is divided into several submodels, which shares some variables. The Physiomodel deals with a much wide range of physiological processes and thus it is divided into many partial models, each dealing with a specific area of interest. Physiomodel separately deals with the electrolytes, ventilation and gas exchange, proteins and water distribution. The IPE model focuses on the acid-base balance and does not care about other physiological processes in such depth as the Physiomodel. The influence of ventilation is narrowed to P_{CO2} deals only with erythrocyte, plasma and interstitial fluid *pH* and takes all fluid as one homogeneous compartment. The approach of Physiomodel to the acid-base balance is not compatible with the model of Wolf and DeLand and their assumptions.

The equation based model simulates the physiological processes in a human body as we expected and we can use it for various experiments. This can help us understand the basic acid-base balance of our system and use it for some predictions. The block-based model implemented using the Chemical library does not work so well. We are not able to obtain

physiological values of some species in the system and its functionality is not as intuitive as the equation based model where we can plainly see cause and effect of each change we made.

2.7 CIPE model

We have also implemented the CIPE (cells – interstitial fluid – plasma – erythrocytes) model. This extends the IPE model adding the buffering cellular compartment which should compensate some of the previous IPE model limitations. [56]

The CIPE model follows the same assumptions as the IPE model with some changes. We added a cellular compartment which is homogeneous like the other ones. For this cell compartment, we use the data of skeletal muscle cells. These cells make the largest mass of a human body and they are also often used for data gathering. The H^+ and Na^+ are not in equilibrium in the cell compartment like the other species. It is caused by the active pump so their distribution is adjusted using a coefficient which does not change for various conditions. We also use a more explicit description of the forces leading to water distribution across the microvascular membrane separating plasma and interstitial fluid. We do not use the equality of osmotic pressure like for E-P and C-I membranes. The water distribution between interstitial fluid and plasma is based on the Starling osmotic-hydrostatic pressure-balance. [57]

2.7.1 Mathematical Background

We use the same principles as in the IPE model with few additional equations for the P-I water balance and for the distribution of Na^+ and H^+ across the cell membrane. The distribution of hydrogen and sodium are similar to other species, but the ratio is adjusted by a coefficient as following equations (39, 40) describes [58]

$$\frac{C_{Cl}^{I}}{C_{Cl}^{C}} = k_{Na}\frac{C_{Na}^{C}}{C_{Na}^{I}}, \tag{39}$$

$$\frac{C_{Cl}^{I}}{C_{Cl}^{C}} = k_{H}\frac{C_{H}^{C}}{C_{H}^{I}} \tag{40}$$

where $kNa = 368$ and $kH = 10$.

Pressure equilibrium across the microvascular P-I membrane uses the starling principle as the equation (41) describes:

$$\mathrm{Pr}^{B} - \mathrm{Pr}^{I} - \sigma_{lm} \times (\Pi^{P} - \Pi^{I}) - 19.3 \times \sigma_{sm} \times (O^{P} - O^{I}) = 0. \tag{41}$$

[56] Wolf, 'Whole Body Acid-Base and Fluid-Electrolyte Balance'.
[57] Ibid.
[58] Ibid.

In the equation (41) *Pr* stands for a hydrostatic pressure, *Π* for the osmotic pressure and *O* is the osmolarity. The superscript *B* stands for blood while *I* and *P* are interstitial fluid and plasma, respectively. The σ_{lm} and σ_{sm} and are the osmotic reflection coefficients for large and small molecules, respectively. The constant 19.3 takes this value for the temperature of 37°C. The hydrostatic pressure of blood shows the equation (42).

$$\mathrm{Pr}^{B} - \mathrm{Pr}^{B0} = 17.5 \times \frac{\Delta V^{B}}{V^{B}} \tag{42}$$

where the difference in of hydrostatic blood pressure is proportional to the relative change in volume. For the hydrostatic pressure of interstitial fluid apply similar equations (43, 44).

$$\mathrm{Pr}^{I} - \mathrm{Pr}^{I0} = 93 \times \frac{\Delta V^{I}}{V^{I0}} \text{ for } \frac{\Delta V^{I}}{V^{I0}} \leq 0.097 \tag{43}$$

$$\mathrm{Pr}^{I} - \mathrm{Pr}^{I0} = 9 + 8.3 \times \frac{\Delta V^{I}}{V^{I0}} \text{ for } \frac{\Delta V^{I}}{V^{I0}} > 0.097 \tag{44}$$

For the standard state is the hydrostatic pressure between interstitial fluid and blood fixed as shows equation (45).

$$\mathrm{Pr}B0 - \mathrm{Pr}I0 = 17.3 \tag{45}$$

Plasma contains next to albumin some other proteins so its osmotic pressure counts with albumins (*Alb*) and total plasma protein (*Tpro*)

$$\begin{aligned} \Pi^{P} &= C^{P}_{Alb} \times \left[2.8 + 0.18 \times T_{pro} + 0.012 \times \left(T_{pro}\right)^{2}\right] + \\ &\left(T_{pro} - C^{P}_{Alb}\right) \times \left[0.9 + 0.12 \times T_{pro} + 0.004 \times \left(T_{pro}\right)^{2}\right] \end{aligned} \tag{46}$$

Since interstitial fluid contains the only albumin, we can simplify the previous equation (46) to the form of (47) [59]

$$\Pi^{I} = C^{I}_{Alb} \times \left[2.8 + 0.18 \times C^{I}_{Alb} + 0.012 \times \left(C^{I}_{Alb}\right)^{2}\right] \tag{47}$$

2.7.2 Results

For validation of the CIPE model, we made an experiment with the dependence of the cell *pH* on the *pH* in interstitial fluid. We simulated a respiratory acid-base imbalance with the variable P_{CO2} value and a metabolic disorder by adding or subtracting Na^{+} ions. The comparison of VisSim model predictions and our implementation in Modelica shows following figure (22). For both cases, the results follow the results of original implementation.

[59] Ibid.

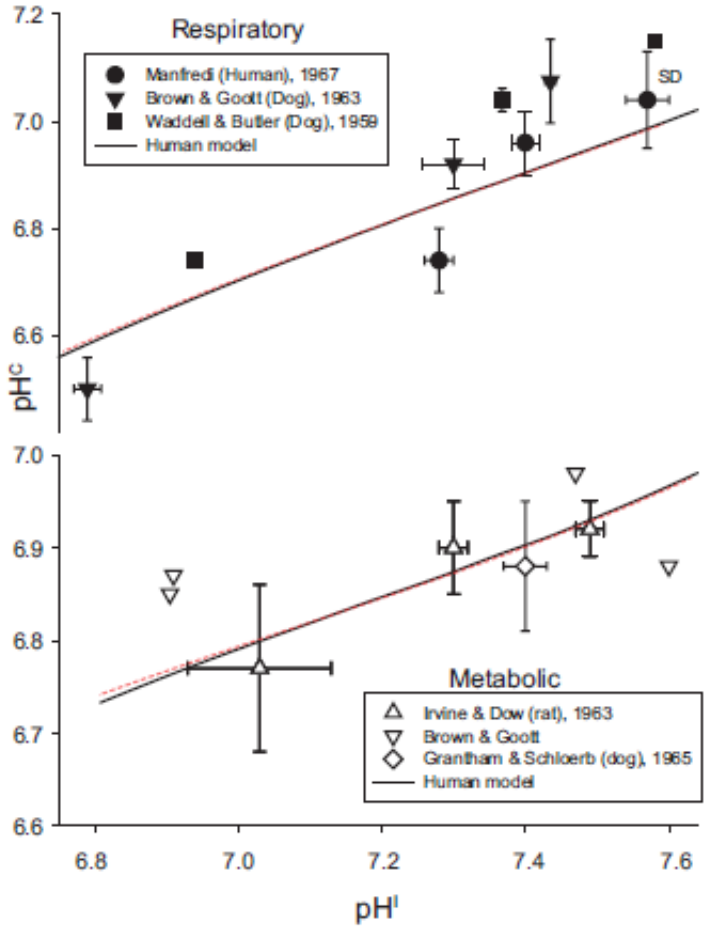

Figure 22: Changes in cell *pH* caused by variable interstitial *pH*. Red curves are made by our implementation of the model in Modelica, while the black curves are made by Wolf's implementation. The top chart shows the imbalance caused by the respiratory disorder, bottom chart is for metabolic disorders.

2.7.3 Discussion

We implemented the CIPE model as an extension to the IPE model which lacks the cellular compartment. The cellular compartment is an important buffering system. We followed the description of the CIPE model. The implementation of CIPE model by Wolf in VisSim works differently. He is observing changes of total water volumes and total ions (Na^+, Cl^-, K^+ and unidentified anions) which are not consistent with our implementation. We work with laws of mass and volume conservation as described by Wolf. The results of experiments we were able to reproduce are similar with the results of original results, but with our implementation, we were not able to repeat all the experiments made by Wolf.

Since the IPE model lacks the important buffering system of the cell compartment, the results of the CIPE model should be more precise. But the implementation of Wolf in VisSim differs from our implementation using Modelica, we were not able to reliably verify the

precision of our implementation and thus the validity results. The CIPE model also specifies the water shift across the microvascular (P-I) membrane, which should improve the water volumes prediction. The downside of this specification is a discontinuous progress of the pressure of the interstitial fluid, what causes step changes in the volumes of plasma and interstitial fluid as shows figure 23. This might cause inaccuracy around the point of the step change.

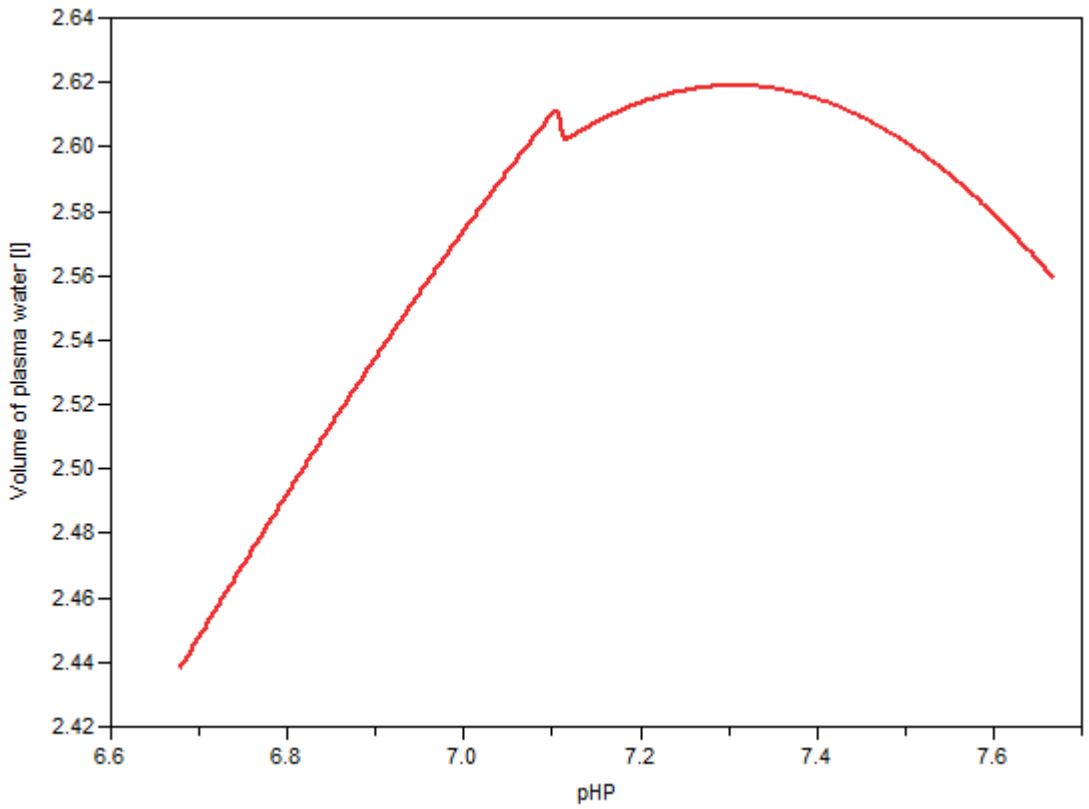

Figure 23: Volume of plasmatic water for a variable *pH* value of plasma. We can see the step change caused by the discontinuous progress of the hydrostatic pressure of interstitial fluid.

3 IPE model regulation

The acid-base disorders have two main reasons. One is the disturbance in the production and elimination of carbon dioxide, for which is the respiration responsible. The second reason is the disturbance in the gains and losses of strong acids. To keep the balance, kidneys have to control the elimination of ions. While some problem occurs, the first is the response of the buffer system. This helps to keep *pH* in close range for acute problems. If the problem persists, the body tries to adapt the situation and next regulation systems come to play. If the respiratory disorder persists, it must be compensated by the shift of strong ions balance, hence we call it metabolic regulation. The prolonged imbalance in strong ions must be compensated by the weak carbonic acid and thus by the respiratory system. [60]

While we have two different ways of response depending on the nature of the disorder, we have to make two models each for one kind of the disturbance. One model deals with the respiratory problems using metabolic regulation. The second model can simulate metabolic imbalances which are compensated via respiration.

Both these regulation systems react to prolonged disturbances. It means the systems need some time to reach its maximal efficiency. For the respiratory response, it is six to twelve hours, while the metabolic response needs three to five days[61]. The IPE model is a steady state model so it does not deal with the time scale of a process. The results reflect only the steady state. Even if the simulation is dynamic due to the regulation, it does not reflect the dynamics of a real system. We can only compare the results after stabilization of the values.

To regulate an acid-base imbalance, we need to invoke a change in certain variables. In mathematics, the change is represented by a derivation. This means that to invoke the change in a certain variable, we will use its derivation. As a control mechanism, we will use the difference (*dpH*) of the required (*pH*0) and the current *pH* value.

$$dpH = pH0 - pH \tag{48}$$

The mean of the respiratory regulation is the change of carbon dioxide pressure. To simulate this type of regulation, we set the derivation of P_{CO2} ($\delta(P_{CO2})$) equal to the *dpH*.

$$\delta(P_{CO2}) = -dpH \tag{49}$$

The negative value of *dpH* is caused by the need of the decrease in P_{CO2} value for metabolic acidosis ($dpH > 0$) and vice versa. As the *dpH* value is closing to zero, the change of P_{CO2} value becomes slower. Theoretically, the *dpH* would never reach the zero, but it will soon reach close enough. The illustration of this process shows the figure 24. For the metabolic regulation, we used the derivation of variable *X*, which represents the universal base. Since we need to add the

[60] McNamara and Worthley, 'Acid-Base Balance'; Nečas and spol., *Obecná Patologická Fyziologie*.
[61] Nečas and spol., *Obecná Patologická Fyziologie*.

base to regulate the respiratory acidosis ($dpH > 0$) we will use a positive sign in this equation (50).

$$\delta(X) = dpH \tag{50}$$

3.1 Metabolic regulation

Metabolic regulation is a response to the respiratory disorders, and so the deviation of the pressure of carbon dioxide from the standard state. We set the (pathological) value of P_{CO2} and a parameter for standard pH value (e.g. $pH0 = 7.37$). To balance the pH, we have to change the concentration of ions. We are balancing the pH of plasma. For the ion balance, we use a variable X [mEq]. This variable is a substitute of strong ions, which we would have to adjust, to compensate the respiratory disturbance. For the pH balance, the adding of acid is equivalent to subtracting a base and vice versa. This means, if the X value is positive, the system needs more base (cations) or less acid (Cl^-). The negative value of X is equivalent to a gain of acids or loss of bases.

Since we use the universal variable, it does not influence the distribution of the mobile species, thus the result of this simulation is not really in the steady state. The X is not mobile so it stays in plasma, while most of the plasma ions are mobile. We can manually set amount of other species (e.g. Cl^- or Na^+) to substitute the universal species X. To simulate the steady state situation, we would have to choose one species, which compensates the shift of P_{CO2}.

3.2 Respiratory regulation

The human body compensates the long-term ionic imbalances thanks to the respiratory system. The strong acids are substituted by the weak carbonic acid, which amount depends on the amount of carbon dioxide in the solution and thus on the pressure of it in the lungs. Hyperventilation lowers the P_{CO2} in alveoli, while hypoventilation increases its value. We can add (or subtract) amount of ions to the system and observe how the respiration adapts.

3.3 Results

To demonstrate the results of regulations of acid-base disorders we use a compensatory diagram. This diagram shows connections between P_{CO2}, pH with addition information about BE or bicarbonates – values usually observed in clinical praxis. It is divided into areas with typical values of the parameters for acid-base disorders. We can simulate certain disorder and observe how the regulation system deals with it. The arrows show how the regulation system

reacts on disturbances in acid-base balance. It starts with a dot, which represents the acute state of acid-base disturbance (which we induced). The point shows how the system reacts on the prolonged disturbance.

The results of the regulation of metabolic disorders show figure 25. The green arrows represent the regulation of occurred disturbance. For the metabolic acidosis we added Cl^- (150 mmol and 250 mmol). The uncompensated metabolic acidosis causes drops in *pH*. The respiration system reacts by increasing the ventilation and thus lowering the P_{CO2}. Metabolic alkalosis caused by adding Na^+ (150 mmol and 250 mmol) was compensated by hypoventilation to raise the P_{CO2}. The *BE* value (equivalent for H^+ excess or deficit but with opposite sign) changes only slightly.

Respiratory problems were simulating by directly manipulating with the P_{CO2}. In figure 24, they are represented by red arrows. For respiratory acidosis we raised the pressure of carbon dioxide while to induce the respiratory alkalosis, we lowered the P_{CO2} value. To balance the *pH*, the model had to adjust a number of acids or bases in the system, what is a cause of the significant *BE* (or H^+ excess or deficit) changes for metabolic regulation.

The *BE* value (or H^+ excess or deficit) was slightly different for our experiments. This is caused by using the venous blood while the compensating diagrams are usually constructed using data for arterial blood. The arterial blood is not in equilibrium with interstitial fluid so the distribution of mobile species is different. For the metabolic regulation, we also use the universal variable which does not influence the distribution of other species like the specific ions would. This causes more inaccuracy.

For illustration, we show the process of respiratory regulation of metabolic alkalosis caused by adding 250 mmol of Na^+. Figure 24 shows the rise of P_{CO2} as a reaction on increased *pH* value. We show the dynamics of the regulation, but we have to keep in mind, it does not represent the real process of respiration response of the human body.

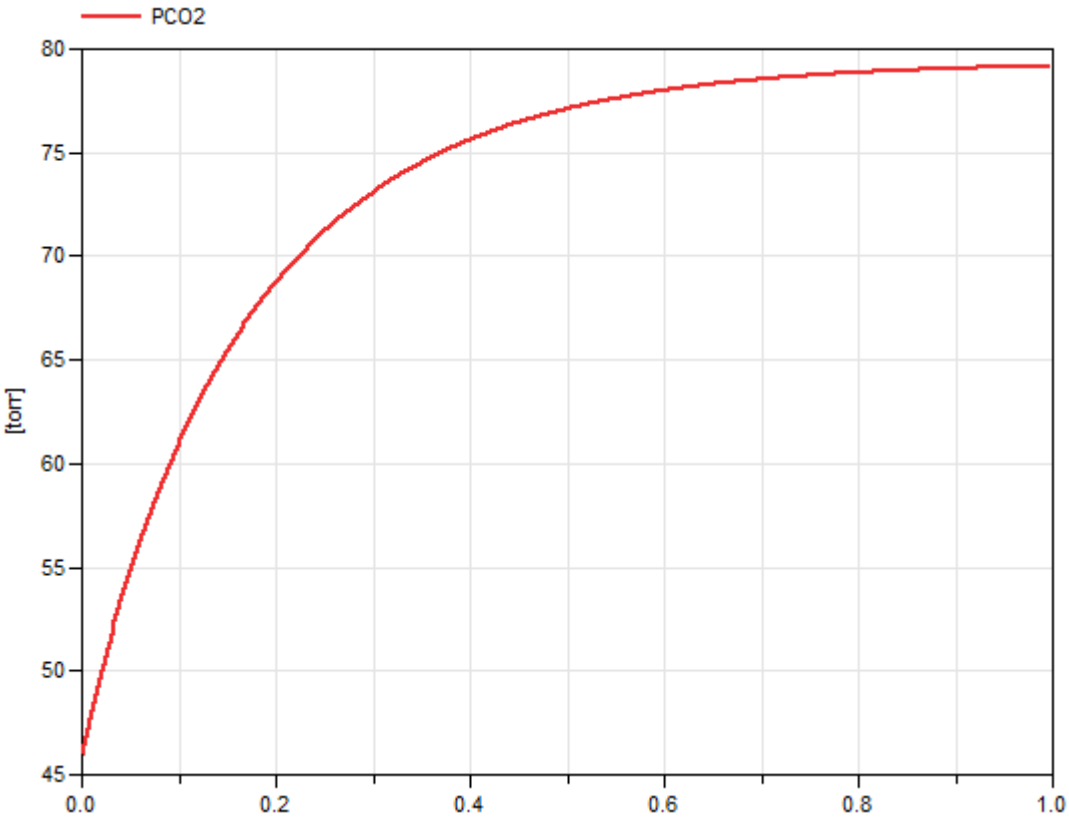

Figure 24: Dynamics of the respiratory response on metabolic alkalosis. The process does not correspond to the real process of respiration regulation.

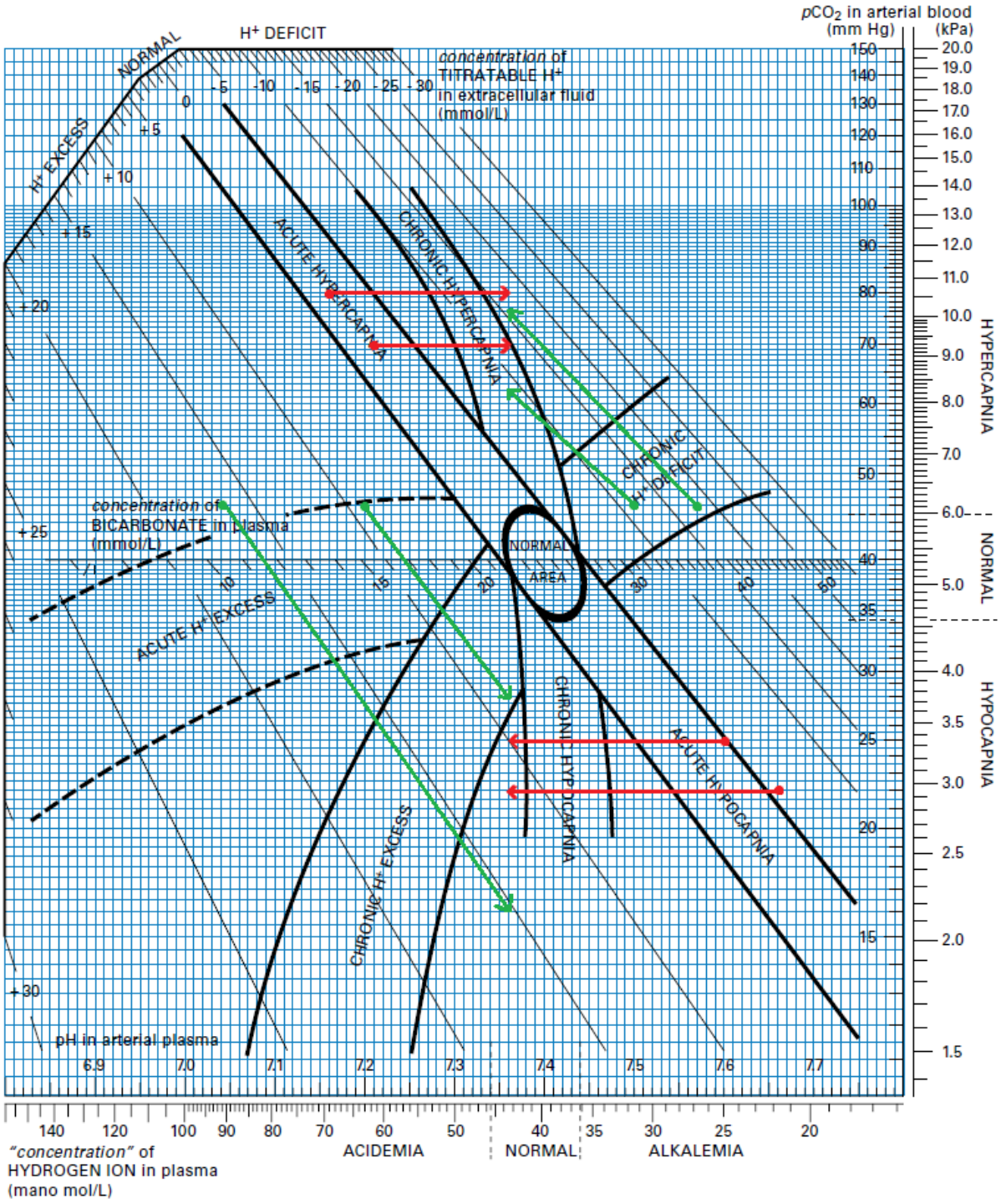

Figure 25: Compensating diagram of acid-base disturbances[62]. The arrows show results of the regulation process. The beginning state of the patient is represented by the dot and the fully compensated state shows the point. The red curves show regulation of respiratory disorders while the green shows regulation of metabolic disorders.

[62] 'Sa_sbd.png (PNG Obrázek, 766 × 915 Bodů)'.

4. Interactive simulator

The IPE model offers us a great insight into the mechanisms of the acid-base balance of the human body. The mathematical apparatus is easy to understand and covers most of the physiological principles. These properties make it a suitable tool for the educational purpose. We can simulate many acid-base disorders e.g. uncompensated metabolic or respiratory acidosis or alkalosis, compensated acid-base disorder, single or combined disorder etc. For every case, we have to choose the right model and modify adequate parameters. We can do this in one dose or we can continually modify the parameters in time. With this tool, we can follow the process of the equilibration and observe the dependencies. This can help with understanding the whole acid-base balance and thus help with the predictions of acid-base disorders. Figure 25 illustrates the experiment with the addition of chloride anions into the system and the reaction of plasma *pH*.

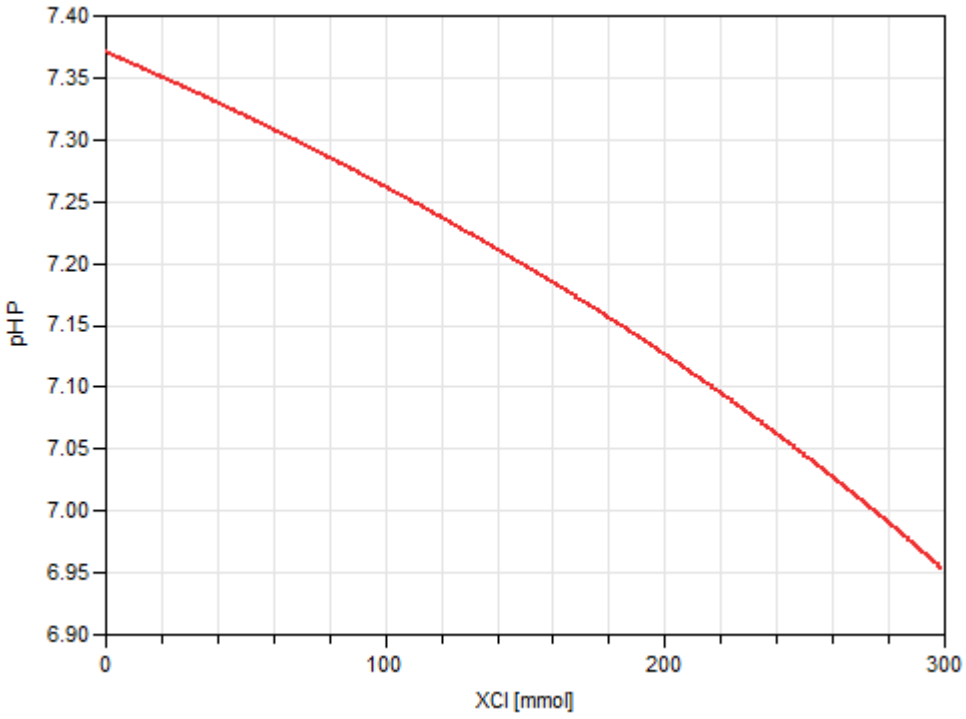

Figure 25: Example of dependency of plasma *pH* on the addition of chlorine into the system. While the dose of chlorides increases, the *pH* lowers.

For each model, we would make a short introduction to help the viewer clarify the modifiable parameters. To the results, we would add a commentary to explain the chain of processes that led to the certain result. We would enable display of most frequently observed quantities in the clinical praxis.

For more devoted users we would allow manipulating with more of the model's parameters (e.g. changing directly concentration of any species in the model) and add the possibility of display all the variables of the model in the results. This could help with the acid-base predictions in clinical praxis. The downside of the IPE model is the lack of dynamics. We need to keep in mind we simulate only the steady state and thus the result of the process. The dynamics of the process in not involved. We also need to keep in mind the time scale of the processes which we simulate and adapt to it.

We implemented three different models. One is only for erythrocytes and plasma, which can simulate the arterial blood, the second model is the IPE model, which simulates blood in equilibrium with interstitial fluid and the last model is the CIPE model which extends the IPE models adding the skeletal muscle cells as additional compartment. The user would be allowed to choose one of the three models depending on the experiments he intends to do.

For the technical reasons, we did not implement the interactive web simulator. We were not able to reach any eligible tools which would provide us a suitable interface for interconnection of the Modelica model and a web application.

5 Conclusion

We implemented three models of acid-base balance in Modelica language. The models were originally implemented and verified using VisSim, which is block-based language, while Modelica is based on solving set equations. One model is for blood only (erythrocytes and plasma) which can simulate the arterial blood. The second model is the IPE model, which is a model of venous blood which is in equilibrium with the interstitial fluid. The third model is the expansion of the IPE model adding fourth compartment – the cells. All models were verified by reproducing the experiments done earlier with the original implementation. With the first two models (PE and IPE) we were able to reproduce most of the experiments successfully. With the CIPE model, we were able to reproduce only some of the experiments done with original implementation. We gained access to the original implementation of the CIPE model in VisSim, but we found it was implemented differently than our model in Modelica. In the original implementation, Wolf used another approach than described in his article. His model calculated differences in total water volumes and ion amounts while we followed his article and worked with the mass and volume conservation laws.

The IPE model was also implemented using Chemical library. Chemical library is an analogy of Physiolibrary focused on chemical and electrochemical processes. The Modelica libraries are component-based tools, allowing us the construction of models using predefined blocks and linking them together. The results of this implementation were not satisfactory. We found Wolf's approach to superficial using some simplifications, while the Chemical library goes much deeper and thus is not compatible with Wolf's assumptions.

We also compared Wolf's approach to acid-base balance with the approach of Physiomodel. Physiomodel is a model of human physiology constructed in Modelica language with the use of the Physiolibrary. The Physiomodel is sectioned into many submodels. Each submodel deals with specific part of human physiology. The acid-base balance includes many different physiological processes. In Physiomodel, the acid-base balance is viewed in much wider context. The Wolf's approach is too focused on the acid-base balance and ion distribution hence he simplifies some other physiological processes. This makes the Wolf's IPE model too dedicated and not suitable as part of a complex model.

We extended the IPE model with basic respiratory and renal regulations. The respiratory regulation adjusts the pressure of carbon dioxide in the system to induce the physiological *pH*. The change of P_{CO2} simulates adjustments of ventilation. The metabolic regulation returns the *pH* values to the physiological range by retention or excretion of acids or bases. The regulation systems were validated using the compensation diagrams.

The most significant advantage of using Modelica instead of block-based modeling language is the readability of the model. Instead of hundreds or thousands of blocks linked together, we use a set of equations, which is solved by the Modelica solver. The disadvantage of this implementation is a possibility of initialization of the model. The model has to deal with complex mathematical operations (powers and logarithms) which result in a non-unique solution of the set of equations. We have to help the solver to choose the right solution by setting the values which should be the right ones. This might be complicated for extreme events when the balance is significantly shifted from the standard state.

The approach of Wolf to the acid-base balance is easy to understand. The implementation in Modelica is quite self-explanatory and gives us great insight into the chain of events during the acid-base imbalances. This could be used for education. The user would be able to observe many variables during various scenarios. To implement the interactive web simulator we did not get a suitable tool, which could provide us interface to link Modelica with a web application.

Appendix A: Models

Our implementations of the models are contained in a single package called *Models.mo*. This package contains the model PE model called *blood*. This model was used for verification of the experiments made with the arterial blood. The next part of the package is the equation based implementation of the IPE model. It is contained in *IPE_EquationBased* part. Here we can find a partial model called *Part*. The default setting is used in the model *Default*, which extends the partial model. Some experiments made with this model are contained here. They are named *Exp_*[indication of the experiment]. Here are also the models extended by the regulations – *respiratoryRegulation* and *metabolicRegulation*. The component-base implementation is contained in part called *IPE_ComponenetBased.* The implementation of the IPE model is called *Model*. There are also contained some experiments we tried to make with this component-based model. They are again named *Exp_*[indication of the experiment]. The last part called *CIPE* contains the extension of the IPE model by adding the cell compartment. The model is called *CIPE.*

For the component-based implementation of the IPE model was used the Chemical library. To run this implementation, we need to load the Chemical library into our Modelica editor. For this reason, we add the version of Chemical library used in the folder named *dependencies*.

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