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Autoreferát disertační práce

Reunified description of acid-base physiology and chemistry of blood plasma

Znovusjednocení popisu acidobazické fyziologie a chemie krevní plazmy

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Content

List of abbreviations

A_{tot}	Total concentration of non-bicarbonate buffers (called weak acid in original formulation of Stewart)
$[A^-]$	Negative charge of buffers described, either just albumin or whole plasma, in this resume, it often means their average normal charge (in average normal concentration)
AG	Anion Gap, i.e. [Na+] + [K+] – [Cl-] – [HCO3-], used to see increased levels of so called unmeasured anions; it should be corrected for the level of albumin
BB	Buffer base, negative charge on plasmatic buffers, also called SID effective
BE	Base excess, increase or decrease of BB/C_B concentration to the situation at pH =7.4 and pCO_2 = 40 Torr
β	Buffer value of non-bicarbonate buffers, i.e. slope of their titration curve
C_B	Total titratable base. One of the *invariant* measures of acid-base status, it does not change with variation in pCO_2
C_H	Total titratable acid. One of the *invariant* measures of acid-base status. However, it changes with pCO_2 and thus is not suitable for physiology
C_i	Total concentration of each buffer substance
K_A, pK_A	Dissociation constant of mass-action equation; $pK_A = - \log_{10}(K_A)$
SIG	Strong ion gap, currently best measure of concentration of so called „unmeasured anions“; difference between measured (apparent) SID and BB

Abstrakt

Tato dizertace se zabývá důležitým problémem biomedicínské acidobazické teorie, kde existují dva zdánlivě neslučitelné způsoby popisu acidobazického stavu krevní plazmy, zatímco popisovaná fyziologie a chemie evidentně musí být pouze jedna. Tyto dva způsoby popisu se nazývají klasický přístup, který je založený především na práci Ole Siggaard-Andersena, a moderní přístup, který je založen na práci Petra Stewarta a jeho následovníků. Zdroje, ze kterých vycházím, jsou troje. Prvním zdrojem jsou obecně přijímané základní koncepty acidobazické chemie a fyziologie. Druhým zdrojem je elegantní formalizmus popisu acidobazických dějů v roztocích komplexního složení vytvořený Guentherem. Úvodní část dizertace je založena na těchto dvou východiscích, na nich pak staví detailní analýza podpořená použitím jednoduchých počítačových modelů. Výsledkem je formální popis několika složitějších koncepcí, včetně titračních křivek proteinů, chování bikarbonátu a proteinových pufrů ve společném roztoku, vztahu mezi nábojem silných iontů a nábojem proteinových pufrů a neostré hranice mezi silnými ionty a ionty pufrů ve fyziologii. Následuje porovnání různých modelů albuminu jakožto hlavního bílkovinného pufru krevní plazmy. Některé teoretické koncepce této práce, jako například pH - pK_A kriterium jsou validovány chováním těchto modelů. Třetím východiskem této práce je detailní znalost formulace obou přístupů. Následující část dizertace staví jak na této znalosti, tak na výsledcích obecné teorie rozvinuté v první části. Předložené porovnání obou přístupů je nejdetailnějším a nejdůkladnějším, jaké kdy bylo publikováno, alespoň pokud je mi známo. Je osvětleno několik fundamentálních slabin moderního přístupu, některé z nich jsou, zdá se, poprvé podrobeny vážné diskusi. Je odvozena transformace mezi rovnicemi a proměnnými obou přístupů, explicitní forma transformačních vztahů je původním příspěvkem k teorii. Existence transformace ukazuje, že žádný z přístupů neobsahuje informaci, která by v druhém přístupu chyběla. Na základě tohoto porovnání je navrhnut znovusjednocený popis, který by jak kombinoval silné stránky obou přístupů, tak eliminoval slabiny. Větší část je převzata z klasického přístupu, kde se několik klíčových konceptů jeví být lépe zakotvených buď v klinických potřebách, nebo v experimentu. Závěrem je demonstrováno využití získaného vhledu při tvorbě výukových acidobazických simulátorů, což bylo i původním cílem práce.

Klíčová slova: Acidobazická chemie, acidobazická fyziologie, Stewartova teorie, moderní přístup, přístup využívající silné ionty, klasický přístup, počítačové modelování, albumin, titrační křivky, rozdíl silných iontů, SID, přebytek bazí, base exces, BE, hypoproteinemická alkalóza.

Abstract

This thesis addresses an important problem of biomedical acid-base theory, where there are two apparently contradictory ways of describing the acid-base status of blood plasma, while the underlying physiology and chemistry obviously has to be only one. The two descriptions are called the traditional approach, based mainly on the work of Ole Siggaard-Andersen and the modern approach, based on the work of Peter Stewart and his followers. This work has three starting points. First are generally accepted basic concepts of acid-base chemistry and physiology. Second is an elegant formalism to the description of acid-base phenomena in complex solutions developed by Guenther. First part of this thesis builds on these two starting points, which serve as a basis for a detailed analysis augmented by the use of simple computer modelling. This results in formal description of several more advanced concepts, including the titration curves of proteins, behaviour of bicarbonate and protein buffers in single solution, relationship between strong ion charge and protein buffer charge and fuzzy division between strong ions and buffer ions in physiology. The modeling work then proceeds to comparing various models of albumin, principal protein buffer of blood plasma. Theoretical concepts of this work, such as pH-pK_A criterion are validated by the behaviour of these models. Third starting point is the detailed knowledge of the formulations of both approaches. Second part of this thesis builds on the results of the general theory developed in the first part; the presented comparison of the two approaches is the most detailed and comprehensive so far, at least to my knowledge. Several fundamental weaknesses of the modern approach are uncovered; some of them seem to be seriously discussed for the first time. The transformation between the two approaches is derived; the explicit form of the transformation relationships is an original contribution. The existence of the transformation shows that neither approach contains extra information to the other one. Out of this comparison, reunited description is suggested, combining the strengths of both approaches and eliminating the weak points. More is taken from the traditional approach, where several key concepts appear more rooted either in clinical needs or in experiment. The thesis concludes by showing the use of the gained insight in building educational acid-base simulators, which was the original purpose of this work.

Keywords: acid-base chemistry, acid-base physiology, Stewart theory, modern approach, strong ion approach, traditional approach, computer modelling, albumin, titration curve, strong ion difference, SID, base excess, BE, hypoproteinemic alkalosis

Introduction

In the past two decades, acid-base chemistry and its description in the context of human medicine have been divided into two opposing approaches: So called traditional approach, based on the work that Ole Siggaard-Andersen, Peter Astrup and others advanced in the 1960's and 70's (1), (2), (3), and the so called modern approach, conceived by Peter Stewart mainly in early 1980's (4), (5). Followers of Stewart's approach have seen their view as a "revolution in our understanding" of acid-base (6), providing "a unique insight into the pathophysiology of acid-base derangements'' (7) and describing true causal mechanism by which acid-base disorders develop (7). These researchers also claimed that the traditional approach has missed one important determinant of acid-base status, called total concentration of weak acid (A_{tot}), (8). This parameter has been shown to depend mainly on the concentration of albumin and associated with significant acid base disturbances (9), (10). However, Ole Siggaard-Andersen and others have maintained very skeptical look at the modern approach, countering with the statement that Stewart's approach "is anachronistic and the terminology misleading, confusing anions and cations with acids and bases." (11)

In this situation, I have become part of a research team, lead by my supervisor dr. Kofranek. Our group has been interested in building large scale computer models of internal environment and of acid-base physiology and later also smaller scale educational simulators. Given my deep interest in acid-base chemistry, I was naturally drawn into trying to figure out how the two approaches fit together and how well do elements of each theory describe the underlying acid-base physiology, which obviously has to be only one. Meanwhile, common links between the approaches gradually started to be published (12), (13), a process to which I have contributed as well (14). My work was needed in our computer modelling, but in the end, it also gave results that can be used directly in the clinical practice.

Both approaches use pCO_2 as a measure of respiratory disturbances. However, so called metabolic disturbances are characterized by a parameter called *BE* in the traditional approach, the same disturbances are characterized by so called strong ion difference (*SID*) in the modern approach. Both parameters change by a same amount when strong acid or base is added to the solution during the process of titration, i.e. $\Delta SID = \Delta BE = [H^+]_{Add} - [OH^-]_{Add}$. Change of pH can be plotted against this change (i.e. the amount of base or acid added),

resulting in a titration curve, whose shape is specific of each complex buffer. The third parameter, specific for the modern approach, is the aforementioned total concentration of weak acid (i.e. non-bicarbonate buffer) A_{tot}.

Hypothesis and goals

Given the fact that there is only one acid-base chemistry and the system of its regulation in organism also has to be only one, the two differing systems of description should have at least some common features based on the unique underlying reality.

The goal of this thesis was to find these common features, preferably in the form of a transformation between the variables and equations of the traditional and modern approach. It was possible that one of the approaches will turn out to be a more complete or detailed description. Another possibility was that both approaches are equally detailed, but the information is structured differently.

Once I have managed to derive this transformation in detail, another goal became possible – to suggest a reunified description based on the detailed analysis of the relationship between various parameters, judging strengths and weaknesses of each approach, especially in relation to the general theory and its consequences.

Finally, the goal was also to use the insight gained in this theoretical work for designing educational acid-base simulators.

Methods

This work was based on well established knowledge of general acid-base chemistry, acid-base physiology, calculus and mathematical modelling. An important source was also the relatively new formalism of Guenther, which was introduced to the acid-base physiology by

Wooten (12). The formalism provides ideal theoretical framework for a detailed description of complex acid-base solutions, such as those encountered in biology.

The work that has been done is mostly analytical or deductive, amender with the use of simple computer models needed to plot the accompanying graphs. These models were implemented in Microsoft Excel 2007, Wolfram Mathematica 8.0 and Modelica / Dymola, resulting graphs were plotted mostly in Microsoft Excel, 3D graphs in Wolfram Mathematica. No underlying data were needed, as both theories have already been shown to fit experimental data; the disagreement is in the level of interpretation of known facts rather than data precision.

Results

Both approaches include same description of bicarbonate buffering. Thus, the key to the transformation between the two approaches is the description of all other buffers that are lumped under the name non-bicarbonate buffers. Here, the description of the traditional approach is so called van Slyke equation for plasma

$$BE = \Delta \mathrm{HCO_3^-} + \beta * \Delta \mathrm{pH} \tag{1.1}$$

, where BE is the base excess and β is the buffer capacity of non-bicarbonate buffers. The system is described by three equations in the modern approach.

$$A_{tot} = [HA] + [A^-] \tag{1.2}$$

$$K_A = \frac{[H^+] * [A^-]}{[HA]} \tag{1.3}$$

$$SID = [A^-] + [HCO_3^-] \tag{1.4}$$

, where [HA] and [A^-] are the concentrations of acid and base form of non-bicarbonate buffer and K_A is the apparent dissociation constant of lumped non-bicarbonate system. As is shown in the thesis (and various previous works, including the article of Matousek et al (14)), β can be calculated from the parameters of the modern approach as

$$\beta = A_{tot} * \frac{2.303 * K_A * 10^{-7.4}}{(10^{-7.4} + K_A)^2} \tag{1.5}$$

Another important relationship between the two approaches that was derived is

$$\Delta SID = BE + \Delta A_{tot} * \frac{K_A}{10^{-7.4} + K_A} \tag{1.6}$$

This relationship was already pointed out in words by Siggaard-Andersen and Fogh-Andersen (11).

Finally, when β is taken as third parameter of the traditional approach (it is naturally included information, but not considered as important as A_{tot} of the modern approach), transformation can be derived between these two parameters of the traditional approach (BE, β) and two parameters of the modern approach (SID, A_{tot}).

$$BE = SID - [HCO_3^-]_N - A_{tot} * \frac{K_A}{10^{-pHn} + K_A} \tag{1.7}$$

$$\beta = A_{tot} * \frac{2.303 * K_A * 10^{-pHn}}{(10^{-pHn} + K_A)^2} \tag{1.8}$$

$$SID = BE + [HCO_3^-]_N + \beta * \frac{K_A + 10^{-pHn}}{2.303 * 10^{-pHn}} \tag{1.9}$$

$$A_{tot} = \beta * \frac{(K_A + 10^{-pHn})^2}{2.303 * K_A * 10^{-pHn}} \tag{1.10}$$

, where pHn is normal physiological pH = 7.4, representing point where linearization is generally performed. When we substitute in the values of K_A derived by Matousek et al. (14) these relationships take following form

$$BE = SID - 24.4 - 0.8\, A_{tot} \tag{1.11}$$

$$\beta = 0.36\, A_{tot} \tag{1.12}$$

$$SID = BE + 24.4 + 2.22\, \beta \tag{1.13}$$

$$A_{tot} = 2.77\, \beta \tag{1.14}$$

To my knowledge, my thesis is the first publication to derive these transformation relationships in their explicit form. Similar (more complex) relationships are also derived for a case where total titratable base/buffer base (C_B/ *BB*), a parameter used in definition of *BE,* is not equal to *SID*. This is actually quite common in protein buffers and as such, it constitutes a more correct description of the system. Up to 1999, the two have been considered equal. It was Wooten (12) who first pointed at the fact that a more correct relation is

$$SID = BB - \sum_i C_i * \bar{z}_{\max(i)} \tag{1.15}$$

In this formula, C_i is a total concentration of each protein (or other) buffer and $\bar{z}_{\max(i)}$ is maximum charge of its amino-acid buffer residues.

As can be seen from formulas (1.12) and (1.14), values of β and A_{tot} are directly proportional. They are also proportional to the concentration of plasmatic buffer, most importantly albumin.

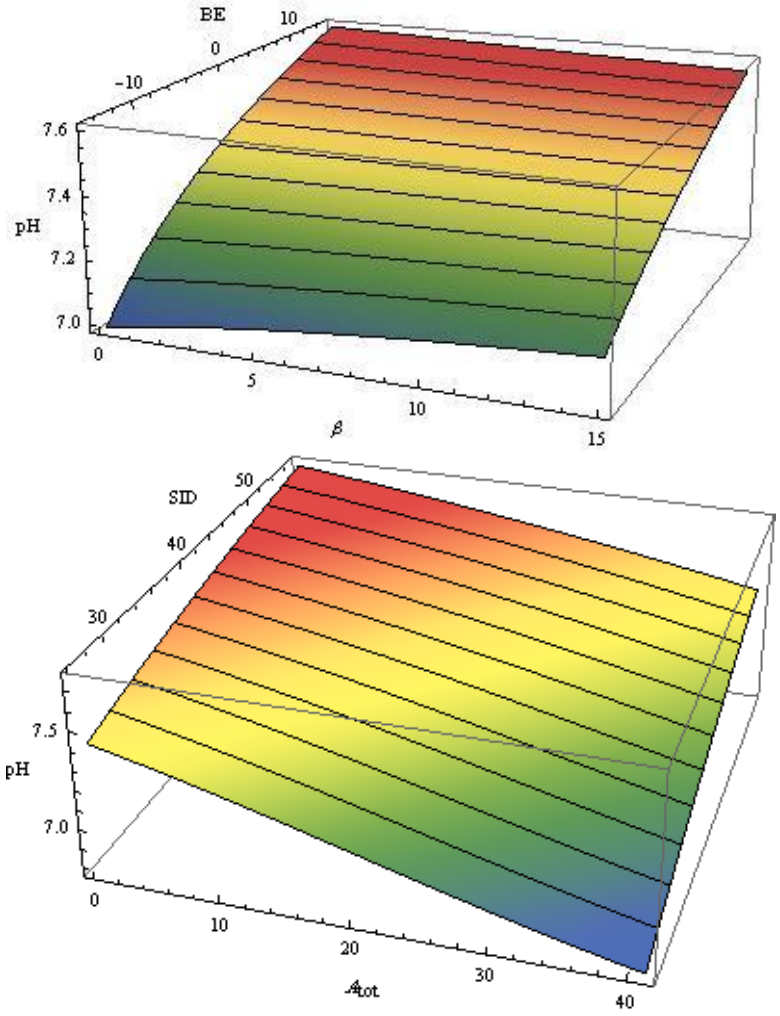

Figure 1: *3D plot illustrating a relationship between* β*, BE and pH (upper graph) and* A_{tot}*, SID and pH (lower graph).* pCO_2 *is kept constant, equal to 40 mmHg. Upper graph shows that pH varies mainly with BE.* β *also plays role, but around BE = 0, no or very small relationship between pH and* β *is seen. On the contrary, there is always a large negative relationship between* A_{tot} *and pH. Since both* A_{tot} *and* β *are directly proportional to the concentration of albumin, the large change of pH observed in the modern approach cannot be considered inherent property of albumin. The changes are explained by different ways of varying the concentration of albumin (either keeping SID or BE constant during the process).*

When only the concentration of albumin is measured, this relationship can be lumped and expressed as

$$A_{tot} = 0.47 * C_{W,Alb} \qquad \beta = 0.17 * C_{W,Alb} \tag{1.16}$$

, where $C_{W,Alb}$ is concentration of albumin in g/l.

Given the direct proportionality between albumin concentration, A_{tot} and β, it might be interesting to ask, why significant acid-base disturbances (called hypoproteinemic alkalosis and hyperproteinemic acidosis) are associated with changes of albumin concentration only in the modern approach. The answer might be surprising at first. These changes are only seen, when concentration of albumin is varied while SID is kept constant. The changes are much different when albumin concentration is varied while BE is kept constant. When BE is close to zero, these changes are also almost non-existent. This can be seen on figure 1.

Thus the concepts of hypoproteinemic alkalosis and hyperproteinemic acidosis, supposedly missed by the traditional approach, can only be considered artifacts of the choice of the coordinates. This thesis seems to be the first work to explicitly point at this fact.

Based on the theory developed in the first part of the thesis, the work identifies several fundamental weaknesses of the modern approach. First one is the single K_A description of protein buffering that the modern approach uses. Protein can be understood as a series of buffer amino acid residues with differing dissociation constants (K_A's). When these K_A's are regarded as random numbers, the resulting titration buffer curve is generally much closer to straight line than to a curve of a single K_A buffer. Titration curves of three random proteins of 10 pK_A's (range 5-9) as compared to a single K_A buffer can be seen at figures 2 and 3.

Second weakness of the modern approach is Stewart's notion of independent and dependent variables. Stewart posits that 3 independent variables (pCO_2, *SID* and A_{tot}) are the causative agents of all acid-base changes and the changes of all other variables are only secondary. This notion is flawed and has been criticized by other authors before, including Kurtz (15) and Wooten (16). However, there is a special feature that Stewart's independent variables have: They behave as *invariants* during acid-base equilibrations and hydrogen ion redistributions. Third weakness of the modern approach is its lack of compensation diagrams.

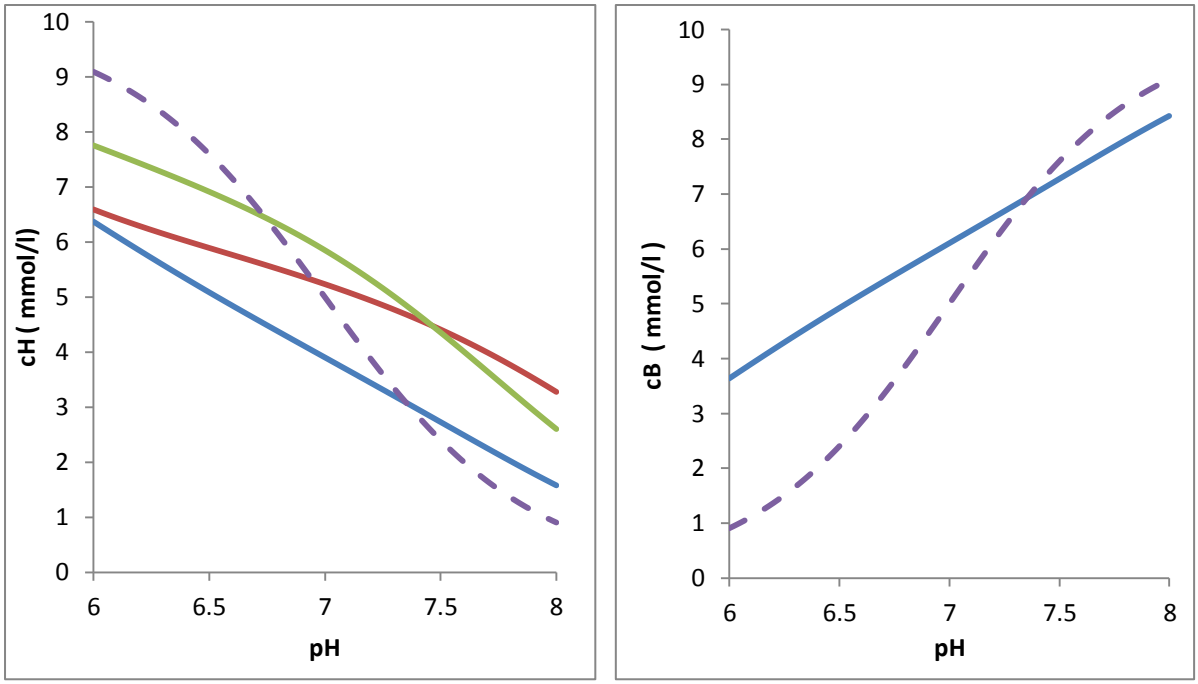

Figure 2 and 3: *Left: Titration curves of three random protein buffers (with 10 buffer residues) compared to a titration curve of single K_A buffer (dashed line). Although the lines of random protein buffers can be slightly curved, they never produce bending typical for a single K_A buffer. Plotted as pH against total titratable acid (C_H). Right: Protein no 1, can be approximated by a straight line much better than by single K_A curve. Plotted as pH against total titratable base (C_B) (mirror plot).*

Fourth weakness is the difficulty in identifying the key parameters, K_A of single buffer system and normal value of A_{tot} (or the value of A_{tot} per gram of albumin). Various methods have been used in trying to determine these parameters. The method that seems to provide the best fit was used by Matousek et al (14). It reverses the equation (1.5) and the equation for negative charge of non bicarbonate buffers

$$[A^-] = A_{tot} * \frac{K_A}{10^{-pHn} + K_A} \tag{1.17}$$

When these two equations are reversed, we get following expressions

$$A_{tot} = \frac{2.303 * [A^-]^2}{2.303[A^-] - \beta} \tag{1.18}$$

$$K_A = \frac{10^{-pH} * (2.303[A^-] - \beta)}{\beta} \tag{1.19}$$

Both β (slope of titration curve) and [A^-] (charge) can be measured, although the measurement of charge is more difficult. In the case of albumin, these relationships give much better fit to Figge-Fencl reference model than the parameters determined by Staempfli and Constable (17), as can be seen in figure 4.

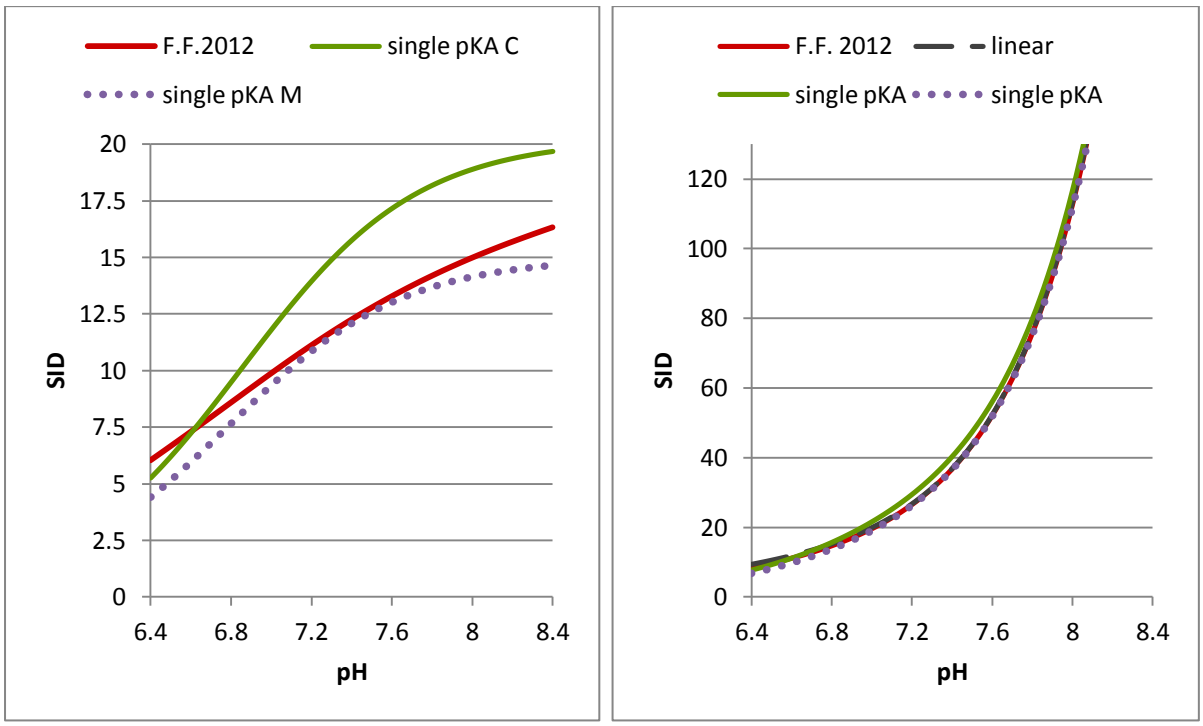

Figure 4 and 5: *Comparison of single pK_A (or K_A) models of albumin, with parameters determined by Matousek et al (marked M)* (14), *Staempfli and Constable* (17) *(marked C) to the reference model of Figge-Fencl (marked F.F. 2012). Left graph shows that around pH = 7.4, Matousek's parameters give the best fit to the reference model, which is a consequence of calculus theory (Taylor series). When both models are plotted together with the open bicarbonate buffer, bad fit of Staempfli's parameters becomes covered by dominant buffering effect of open bicarbonate buffer.*

While charge of a single protein can be measured, although with difficulties, total charge of all plasmatic buffers (also denoted as [A^-] is a highly problematic quantity. Most commonly, it is simply estimated from the equation (1.4), which can be rearranged to isolate [A^-].

$$[A^-] = SID - [HCO_3^-] = BB - [HCO_3^-] \qquad (1.20)$$

However, values of both *SID* and *BB* are only partially resulting of measurement. Partially, they are a matter of consensus. Various reasons for this imprecision are discussed in the

thesis, including unmeasured anions, small difference of large numbers, variation of strong ion binding to albumin and other proteins with pH, difficult to measure charge of globulins (in case of using *BB*) and lack of consensus on including the amino-acid residues behaving like strong ions, but being bound to proteins (in the thesis, charge due to these residues is referred to as internal SID, *iSID*). All of these factors result in lack of consensus on what should normal values of $[A^-]$ be (i.e. in normal concentration of buffers and/or strong ions), which results in various values of determined K_A and normal A_{tot}.

The analysis of the common links and of the weak and strong points of each approach provides a good starting point to suggesting a reunified description. The discussion starts by pointing at the fact that SID is not the only choice for an *invariant*, other ones include C_H, C_B/BB, BE and concentration of titratable hydrogen ion ctH^+ (recently suggested by Siggaard-Andersen as a replacement of BE). Each of these quantities is an interval measure of acid and base content in the solution. Similarly, A_{tot} is not the only *invariant* measure of buffer concentration, alternative measure is β. Out of these options, C_H does not behave as an invariant in the presence of open bicarbonate buffer and is discarded. Similar reason means that ctH^+ is a misleading parameter, because despite its name, it is derived from C_B/BB. SID and C_B/BB can be used, but their use requires knowledge of total concentration of buffer, if one wants to differentiate between their changes due to buffering and their changes due to different buffer concentration (14).

Thus BE and β, coming from the traditional approach, are identified as the best choice of *invariant* measures to the acid-base status of blood plasma. Beside these, bicarbonate and especially standard bicarbonate can be considered satisfactory for most of clinical practice. However, in the auxiliary parameters, such as those used for determination of unmeasured anions, modern approach performs better. Strong ion gap (SIG) (18), (19) or corrected AG (20) should be used in clinical practice, especially when hypoalbuminemia is present. Furthermore, values of major electrolytes, such as $[Na^+]$ and $[Cl^-]$ (and possibly also inorganic *SID*, but properly understood) can be used to aid diagnosis, since their values are in relation with acid-base parameters due to the mutual dependence, especially in the kidney regulator.

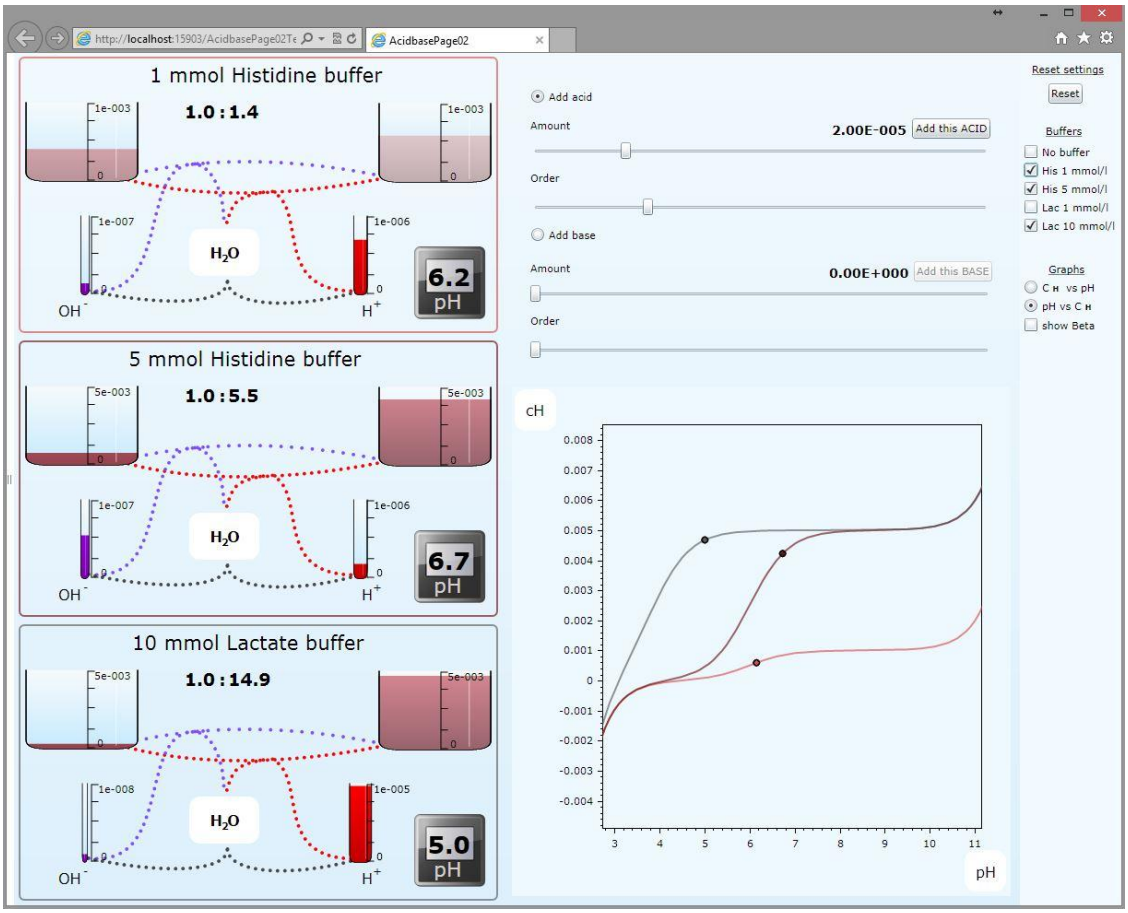

Figure 6: *The user interphase of an educational acid-base simulator built in our research group. The simulator can be used to explain properties of buffers.*

The insight gained while comparing the two approaches was used in design our new acid-base simulators, such as the one seen in figure 6

Discussion

While the use of the united theory in computer modeling was the primary focus, the process also gave results that can be directly used in clinical diagnostics and clinical practice. To my knowledge, several accomplishments of this work can be considered original contributions to the field of biomedical acid-base theory. First of all, this appears to be the most detailed and comprehensive comparison of the two approaches published so far, both between themselves with regard to the general formalism of Guenther. In comparing them, this work

is also the first one to publish explicit transformation relationships between the variables and equations of both approaches, including the transformation between *SID*, A_{tot}, *BE* and β.

By generating buffering curves of random pK_A proteins, the work also demonstrates that there is a theoretical reason, why the linear approximation to protein buffering curve generally performs better than single pK_A approximation. This is one of the weaknesses of the modern approach, which hasn't been given much discussion so far. Finally, the problem of identifiability of the modern approach parameters seems to be approached in a novel way.

Original contribution is also in the structure and design of the presented simulators.

Several articles comparing the two approaches have been published before this work. Schlichtig et al (21) were the first one to compare the clinical usefulness of both approaches, as well as showing parts of the mathematical link between them. Kellum authored a qualitative clinical review advising the clinicians to use both approaches in concert rather than contradiction (13). Some of the features of the relationship between the two approaches, covered here in formal mathematical notation (including the key relationship (3.32)), were also described in words by Siggaard-Andersen and Fogh-Andersen (11). These authors were also the first ones to point out that the concepts of hyperproteinemic acidosis and hypoproteinemic alkalosis depend on the choice of other independent variables (figure 1), although again only in words. Maybe due to the critical tone of the father of the traditional approach, his explanation never seemed to get much appreciation. Major breakthrough came, when Wooten (12) published a theoretical analysis that links both approaches together mathematically and placed them in the context of elegant Guenther's formalism (22). However, due to the limited space of a common physiology article, Wooten's review contains surpassingly condensed mathematical expressions, possibly yielding it inaccessible to most of interested readers.

The thesis builds on the work of Guenther, Wooten and Siggaard-Andersen. Larger format of the text makes it possible to properly introduce Guenther's ideas, which is done for the first time in physiologically relevant literature. The thesis shows that linearization makes more sense than single K_A approximation in case of protein buffers. Same ideas are illustrated while comparing different models of albumin. The thesis also builds on the article

of me and my co-authors, which compared both approaches both mathematically and clinically (14), describing how the parameters of the modern approach can be identified. My thesis brings this further by showing that the values of A_{tot} (per gram of albumin) and K_A critically depend on the normal value of *SID* (i.e. also the buffer charge), which is partially arbitrary. The lack of consensus over the value of *SID* means that there is not a unique way of identifying the values of A_{tot} and K_A.

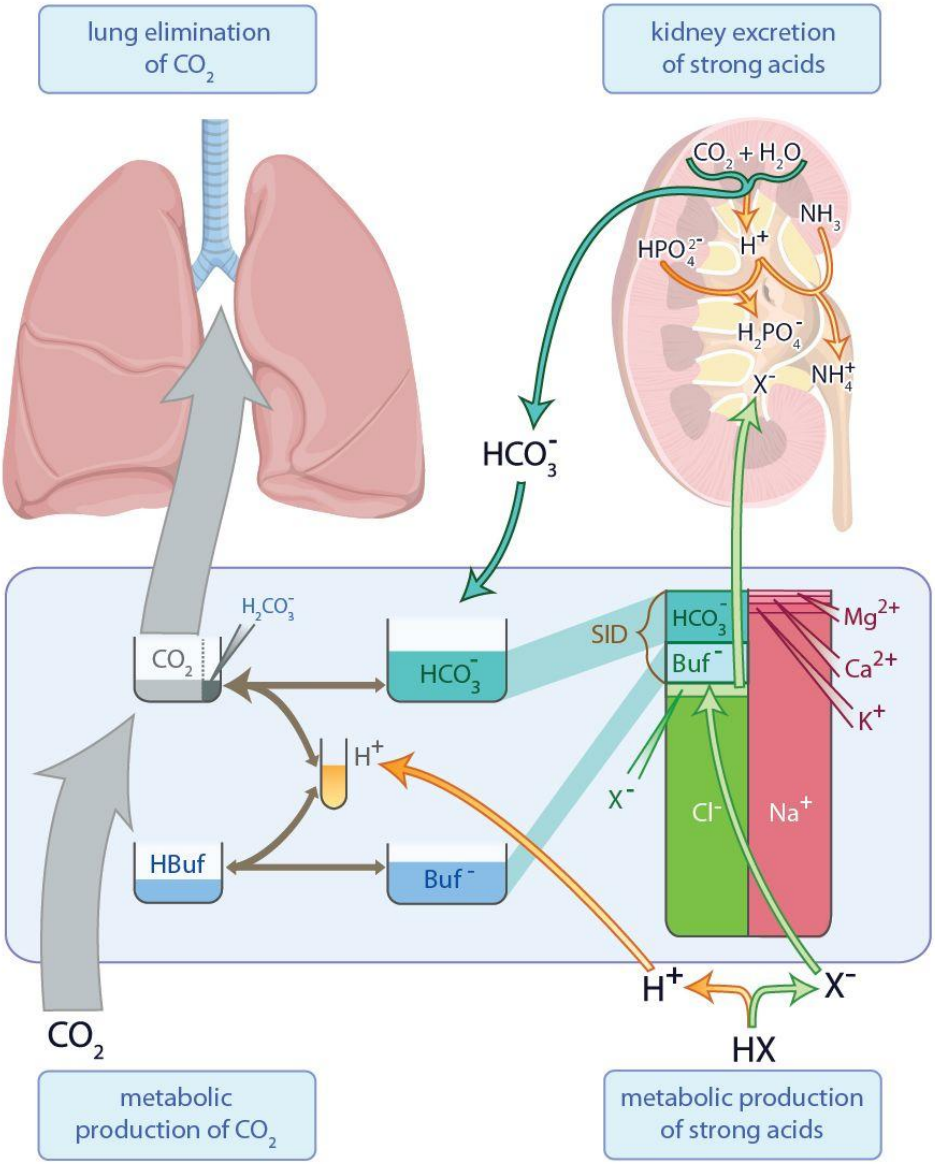

Figure 7: *Overall scheme of acid-base physiology of regulated coupled buffer reactions, all in equilibrium with the other ones, connected by electroneutrality to the strong ions. The scheme can also be used as possible graphical output of future acid-base simulator.*

The presented analysis shows that reunified description is not only possible, but also that it should, using pure rationality, contain much larger portions of the traditional approach than expected from some late opinions. But most importantly, the overall physiology of regulated coupled buffer reactions, all in equilibrium with the other ones, connected by electroneutrality to the strong ions, should be remembered. This is seen in figure 7.

Conclusion

Widespread use of computers and the development of formalized description of acid-base equilibria even in complex solutions give us new possibilities to understanding acid-base physiology and chemistry of physiological fluids. With this in mind, the two most used approaches to the description of acid-base status of plasma were compared, leading to the following conclusions: 1) Modern approach of Peter Stewart contains major weaknesses. 2) There is a mathematical transformation between the equations and variables of the traditional and the modern approach.

The existence of transformation does not mean that the information in each approach is structured equally well in sense of its direct clinical usefulness. However, it gives a framework for combining the strong parts of each approach and using them in concert. A rational choice for diagnostics of acid-base disturbances seems to be the combination of parameters pH, pCO_2, $[HCO_3^-]$, BE, β, SIG or AG corrected, $[Na^+]$ and $[Cl^-]$.

The field is complex, but not beyond grasp. Interactive computer models can be an effective teaching tool to understanding the interplay between various parameters.

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Publications of the author

I) Related to the thesis

A) In IF journals

1. Matousek, Stanislav, Handy, Jonathan, Rees, Stephen Edward. Acid–base chemistry of plasma: consolidation of the traditional and modern approaches from a mathematical and clinical perspective. *Journal of clinical monitoring and computing*, *25*(1), 57-70, 2011. **IF 0.71**

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B) Other publications

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