**COMPLEX MODEL OF BLOOD ACID-BASE BALANCE**

Jiří Kofránek

Laboratory of Biocybernetics, Department of Pathological Physiology, First Faculty of Medicine, Charles University in Prague.  
e-mail: kofranek@email.com

**Annotation**

Originally, the classic Siggaard-Andersen nomogram, widely used in clinical practice for the assessment of acid-base balance, experimentally obtained at 38°C with the precondition of normal plasma protein concentrations. However, a nomogram is used in clinical practice to calculate from the data measured in blood samples tempered at 37°C. We made a simulation recalculating of the baseline experimental data to 37°C and set a new nomogram for 37°C. Compared with the original nomogram, there are no significant deviations, if BE does not deviate by more than 10 mmol/l; the results are, however, different with the deviations exceeding 15 mmol/l. We suggested an algorithm and a program, which enables calculation of BE from pH and pCO2 according to the original as well as adjusted normograms. However, the data, having been a base of the normogram, count with normal plasma protein concentrations. At these conditions, BE corresponds to SID changes based on Siggaard-Andersen nomogram, adjusted to 37°C. Thus, BE was not only defined in the dependence on haemoglobin concentrations, but also on plasma protein and phosphate concentrations. Furthermore, we combined Figge and Fencl plasma acid-base balance model with the data on the organism, enabling realisation of the pathogenesis of acid-base balance disturbances, which is in accordance with our earlier publication of the balance approach to the interpretation of acid-base balance.


**Key words**

Acid-base balance, formalised description, simulation model, blood gases, educational simulators

1. Introduction

Acid-base balance in the organism is controlled by two balances – carbon dioxide flow balance (respiration control) and strong acid production/excretion balance (regulation of acidification processes in the kidney). Both flows are connected via buffer systems. The balance disturbances result in pH changes in blood liquids. Drifts in the chemical balances of buffer systems, transport of substances between the buffer systems, H+/Na+ H+/K+ exchange between the cell and the interstitial liquid (and, in a long-term scale, washing out NaHCO3, KHCO3 and, later, CaCO3 and CaHPO4 from the bone mineral mass in chronic acidemia) are only suppressive mechanisms in acid-base disturbances. The basic regulation organs, able to control acid-base balance (by their effect on CO2 and H+/HCO3 flows) include the respiratory system and kidney.

From the clinical point of view, the arterial blood buffer system is an important indicator of the status of acid-base balance. CO2 retention or depletion during the change of carbon dioxide balance as well as H+/HCO3 retention or depletion during the changes of strong acid production/excretion balance develop into the drift of the chemical balance in bicarbonate and non-bicarbonate buffer systems.

Labelling the total concentration of non-bicarbonate bases [Buf] – which, in fact, are the buffer bases of plasma proteins and phosphates (and haemoglobin concentrations in the whole blood) – then the total concentration of non-bicarbonate buffer bases forms the Buffer Base (BB) value:

\[ BB = [HCO_3^-] + [Buf] \]

2. Classical approach of the “Danish School” for the assessment of acid-base disturbances

The variations in pCO2 result in pH changes; If the titration curve of pCO2 and pH changes is plotted in the semi-logarithmic scale, these titration curves verge on lines in the range of life-compatible pH values. This precondition was a base of blood acid-base balance tests introduced in the first half of 1950s by Paul Astrup. At that time, there were no electrodes which enable direct measurement of plasma pCO2. There were, however, relatively accurate methods of pH measurement. Astrup’s method of pCO2 analysis (1956) was based on the following procedure: first, blood pH was measured, then, the sample was automatically equilibrated by O2/CO2 mixture with accurately set pCO2. The blood sample was equilibrated with a high pCO2 gas mixture and the equilibration was followed by measuring pH. Then, the blood was equilibrated with a mixture with low carbon dioxide partial pressure and the equilibration was followed by another pH measurement. The points obtained were plotted into a semi-logarithmic graph to create a line, used to read out pCO2 according to baseline pH (see Fig. 1).

The Buffer Base concept made by Singer and Hastings (1948) was further improved by Siggaard-Andersen in (1960,1962), who introduced the difference of Buffer Base and its normal value - Normal Buffer Base (NBB) - as a clinically relevant factor:

\[ BE = BB - NBB \]

At normal circumstances, BE values (for blood samples with any haemoglobin concentrations) are zero. They are changed during a buffer reaction with strong acid or base added.
Siggaard-Andersen used the equilibrium titration curves to determine BB and BE. He added defined amounts of strong acids or bases to blood samples with various haematocrit concentrations, changing their BE. Then, the samples were titrated and the results were plotted in log PCO2/pH coordinates. The titration curves (being lines in the semi-logarithmic coordinates) of the blood samples with various haematocrit and the same BE always crossed in the same points (see Fig. 2). Similarly, the titration curves of the samples with various haematocrit concentrations (and various BE), but with the same BB crossed in the same points, too.

Thus, a nomogram with BE and BB curves with semi-logarithmic coordinates was obtained; the curves enabled the determination of BE and BB in the samples having been tested.

Siggaard-Andersen used this procedure to find experimentally the dependence of hydrogen ion [H+] concentrations or pH on pCO2 and haemoglobin (Hb) concentrations; the results obtained were used to create clinically applicable nomograms expressing the following dependence:

\[ [H^+] = \text{function (pCO}_2,\text{BE, Hb)} \]

In the assessment of acid-base disturbances by BE and pCO2, it should be taken into consideration that the increase or the fall in CO2 affects neither the total concentration of the buffer bases (BB) nor BE. The increase results in the increase in carbonic acid concentration, dissociating into bicarbonate and hydrogen ions, which are, however, completely bound to non-carbonate buffer bases [Buf]; the increase in bicarbonate concentrations therefore corresponds with the same fall in non-bicarbonate buffers with the total [HCO3-]+[Buf] concentrations and, thus, BB as well as BE remaining practically unchanged. BB and BE are therefore considered pCO2 independent. This applies for plasma exactly but not exactly for the whole blood – pCO2 affects haemoglobin oxygenation. However, as deoxygenated haemoglobin has higher affinity to protons than oxygenated haemoglobin (the oxygenated blood therefore contains virtually higher non-bicarbonate buffer concentrations), the total concentration of buffer bases BB also depends on haemoglobin oxygen saturation (susceptible by pCO2).

Hence, to make acid-base balance models, it is beneficial to define standardised Buffer Base oxy-value (BBox) as BB, potentially found in the blood sample with full oxygen saturation of oxyhaemoglobin (i.e. full 100% oxygen saturation of haemoglobin). Similarly, the standardised Base Excess oxy-value (BBox) is defined as BE measured in the blood sample with full oxygen saturation of oxyhaemoglobin (Kofranek, 1980). Thus, BBox is really pCO2 – independent.

It is necessary to say that the independence of pCO2 and BBox does not apply for “in vivo” whole blood completely, as the increase in pCO2 is connected with higher increase of bicarbonates in plasma compared with that in the interstitium; thus, part of the bicarbonates is transported into the interstitial liquid during the increase in pCO2 (with a mild fall in BBox in acute pCO2 increase).

BB and BE (or BBox and BBox) change after addition of a strong acid (or strong base) or bicarbonates to the blood sample. Addition of one millimol of a strong acid to one litre of blood results in BB fall by one millimol; addition of one millimol of bicarbonates (or withdrawal of one millimol of hydrogen ions by a reaction with a strong base) results in BB and BE (BBox and BBox) increase by one millimol.

The variations in dissolved CO2 plasma concentrations (expressed as pCO2) and BE therefore characterise carbon dioxide flow balance and the variation in strong acid production/excretion balance, respectively. Thus, pCO2 and BE characterise the respiratory and metabolic parts of acid-base balance, respectively.
To use pH, pCO₂, and BE in clinical practice for the diagnosis of acid-base balance, so called compensation diagrams were created, expressing the effect of adaptation responses of the respiratory and renal systems to acid-base disturbances (Dell and Winters, 1970, Goldberg et al., 1973, Siggaard-Andersen, 1974, Grogono et al., 1976).

Siggaard-Andersen nomogram (expressed in the form of approximate equations) became a base for algorithm assessment in a number of laboratory automatons for the measurement of acid-base balance. A certain problem was that the experimental measurements for the construction of Siggaard-Andersen nomogram were carried out at 38°C. Modern devices for the measurement of acid-base balance (allowing direct measurement of pCO₂, pH and pO₂) usually give data for samples adjusted to 37°C.

However, a more serious problem was that the titration done to create an experimental nomogram was carried out with blood with normal plasma protein concentrations (72 g/l). If the plasma protein concentrations are lower (which is not rare in critically ill patients), the points on the nomogram are shifted and all the clinical counts derived from this nomogram are incorrect.

Later, Siggaard-Andersen published certain corrections, considering various plasma protein concentrations (Siggaard-Andersen, 1977, Siggaard-Andersen et al. 1985, Siggaard-Andersen, Fogh-Andersen, 1995); however, they were not included into clinical practice properly.

3. Steward’s “modern” approach

The abovementioned inaccuracies of the classical approach to the assessment of acid-base balance resulted in the attempt to find new methods of the description and assessment of blood acid-base balance in 1980s. The most used method was Stewart´s one (1983), improved later for clinical practice by Fencl et al. (1989, 1993, 2000).

Unlike Siggaard-Andersen’s method, Stewart’s description is limited to plasma only; however, it enables accurate description of hypo- and hyperalbuminaemia, dilute acidosis as well as concentration alkalosis. Stewart’s calculations are based on the combination of physical-chemical equations. The original Stewart’s calculations are based on simple preconditions:

1. The equation for water must apply:

\[ [H^+] \times [OH^-] = K_w \]

2. The constancy of the sum of weak acid concentrations (Buf), and their dissociated buffer bases (Buf):

\[ [Buf] + [HBuf] = [Buf_{TOT}] \]

3. Dissociation balance of non-bicarbonate buffer system:

\[ [Buf] \times [H^+] = K_{buf} \times [HBuf] \]

4. Dissociation balance of bicarbonate buffer:

\[ [H^+] \times [HCO_3^-] = M \times pCO_2 \]

5. Dissociation balance between bicarbonate and carbonate:

\[ [H^+] \times [CO_3^{2-}] = N \times [HCO_3^-] \]

6. Electroneutrality:

\[ SID + [H^+] - [CO_3^{2-}] - [Buf] - [HCO_3^-] - [OH^-] = 0 \]

with SID meaning the value of “strong ion difference” (residual anion) – defined as the difference between the concentrations of fully dissociated anions and cation (expressed in mEq/l). Practically, the value can be found out by the following equation:

\[ SID = [Na^+] + [K^+] + [Mg^{2+}] + [Ca^{2+}] - [Cl^-] \]

Combining these two equations, the result is the fourth degree algebraic equation, enabling calculation of hydrogen ion concentrations in dependence on SID, the total concentration of weak acids and their buffer bases [Buf_{TOT}] and pCO₂ (the dependent variable is underlined in the equation, independent variations and constants are in bold and italic, respectively):

\[ [H^+]^4 + (SID + K_{buf}) \times [H^+]^3 + (K_{buf} \times (SID - Buf_{TOT})) \times pCO_2 \times [H^+]^2 - (K_{buf} \times (K'w + M \times pCO_2)) \times N \times M \times pCO_2 \times [H^+] - K'w \times N \times M \times pCO_2 = 0 \]

Solving of the equation gives hydrogen ion concentration, depending on the respiratory part of acid-base balance – i.e. pCO₂ and, moreover, on the respiratory part of SID independent metabolic parameters as well as on the total concentration of non-bicarbonate bases and acids [Buf_{TOT}]:

\[ pH = function (pCO_2, SID, [Buf_{TOT}]) \]

The total concentration of non-bicarbonate bases [Buf_{TOT}] is related to the total plasma protein (albumin) concentration. More detailed studies consider the total phosphate concentrations, too. The results of these studies are relationships enabling (by means of a computer programme) calculation of pH (and other variables such as bicarbonate concentrations etc.) from pCO₂, SID, and total phosphate [Pi] and plasma albumin [Alb_{TOT}] concentrations (see, for example, Watson, 1999):

\[ pH = function (pCO_2, SID, [Alb_{TOT}], [Pi]) \]

One of the most detailed quantitative analyses of plasma acid-base balance (Figge, 2009) improving Figge-Fencl’s model (Figge et al. 1992) even corrects the effect of externally added citrate [Cit] in the plasma sample used for the laboratory test.

\[ pH = function (pCO_2, SID, [Alb_{TOT}], [Pi], [Cit]) \]

4. Benefits and drawbacks of Stewart’s approach

Mathematical relationships between the variables derived from the quantitative physical-chemical analysis enable calculation of dependent variables – pH, being a base for other dependent variables, i.e. bicarbonate concentrations – from independent variables (i.e. pCO₂, SID, albumin and phosphate concentrations or, as the case may be, concentrations of the citrate added to the plasma sample).

Stewart’s approach enables more detailed description of some of the pathophysiological conditions (the effect of hypo- and hyperalbuminaemia on acid-base balance, dilution acidosis or concentration alkalosis) and, at first site, gives the clinicians the feeling of better insight into the etiology of acid base disturbances. To determine “independent” variables, used for the calculation of other acid-base parameters, it is
necessary to do explicit measurements of phosphate, Na⁺, Cl⁻, HCO₃⁻ and other ion concentrations, which clinicians work in their diagnostic forethought with.

On the contrary, the drawbacks of Stewart’s theory include the fact that he works with plasma only. Moreover, some Stewart’s followers, fascinated by the possibility to calculate acid-base parameters - pH (and proper concentrations of bicarbonates, carbonates and non-bicarbonate acids) – from independent variables (pCO₂, SID, [Alb_{TOT}], [Pi]), often make objectively incorrect conclusions in their interpretation. In the calculation, the independence of baseline variables, particularly SID, is meant not in a causal but in a strictly mathematical meaning. This is, however, often forgotten in clinical-physiological practice, which often results in incorrect interpretation of the causality relationship between the causes of acid-base disturbances.

5. “Mathematical wizardry” of Stewart’s followers

A number of Stewart’s followers considered his mathematical relationships as “oracle” – incorrect causal relationships are deduced from substantially correct mathematical relationships. The causality of mathematical calculations (where independent variables are calculated from dependent ones) is confused with the causality of pathophysiological relationships.

For example, some authors deduct that one of the elementary causal relationships of acid-base disturbances are changes in SID concentrations. Sirker et al. (2001) even states that “the transport of hydrogen ions through membranes (via hydrogen channels) does not affect their actual concentration. Direct removal of H⁺ from one compartment can alter neither the value of any independent variable nor [H⁺] concentration... the equilibrium dissociation of water balances any fluctuations in [H⁺] concentrations and serves as an inexhaustible source or sink for H⁺ ions”.

There is no rational explanation for the opinion that SID (as a mathematical construct, not a physical-chemical characteristic) affects [H⁺] concentrations in a certain mechanistic way to keep electroneutrality – any buffer reaction is a shifted chemical balance only; thus, there is no way how they could affect the electroneutrality themselves (without membrane transport).

6. Are both approaches significantly different?

Excited debates lead by supporters of both theories in international journals (e.g. Dubin et al. 2007, Dubin 2007, Kaplan 2007, Kurz et al., 2008, Kelum 2009) might suggest that both theories are completely different and their applicability will be proved during the time. In fact, both theories are complementary. If similar conditions of their applicability are observed (i.e. they are used for plasma with normal albumin and phosphate concentrations only), the results are, in fact, identical. It is obvious that if one of the theories is used out of the area which it was proposed for, it fails and the other theory seems to be more accurate. For example, reduced protein concentrations do not correspond to the conditions determined experimentally for Siggaard-Andersen nomogram; if this nomogram is used for BE assessment in patients with hyperalbuminaemia, incorrect values are obtained. In this case, the use of Stewart’s method prevents incorrect diagnosis. On the other hand, Stewart does not calculate with the effect of such an important blood buffer - haemoglobin in erythrocytes. Stewart’s approach is applicable neither for the calculation of the amount of infusion solutions for the correction of the acid-base disturbance nor for the assessment of the grade of respiratory and renal compensation of the acid-base disturbance. During the bedside diagnostics it is advisable to consider both theories and to realise their benefits and limits (Kelum, 2005).

The accordance and differences of both approaches are as follows.

Both Stewart and Siggaard-Andersen use pCO₂ as a parameter describing the respiratory part of acid-base balance. According to the “Danish School”, the metabolic part is represented by BB or its deviation from the norm – BE. According to Stewart, the metabolic part is represented by SID as the difference of fully dissociated positively and negatively charged anions and cations – in the respect of keeping the principle of electroneutrality, it might seem at first sight that, numerically, SID is identical with plasma BB (Fig. 3).

SID = [HCO₃⁻] + [Buf⁻] = BB

But is it true really? Siggaard-Andersen (2006) states so. However, focused on the importance of non-bicarbonate bases, certain differences can be seen.

Plasma non-bicarbonate bases include phosphates and plasma proteins – particularly albumin (the effect of globulins on acid-base balance is insignificant). The albumin hydrogen ion can be bound to the following negatively charged amino acids (Figge, 2009): cysteine, glutamic and asparagine acid, tyrosine and carboxyl end of protein polymer. Labelling these binding sites as Alb⁻, the binding of hydrogen ions can neutralise the electric charge (as presumed in the classical Stewart’s theory):

Alb⁻ + H⁺ = HAlb

Hydrogen ions van, however, be bound to imidazol cores of histidine as well as to arginine, lysine and NH₂-end of an albumin molecule. Labelling these binding sites as Alb, then the binding of hydrogen ions results in the creation of positive charge:

![Fig. 3 SID and BB are nearly identical. The variations in SID and BB are completely identical: dSID=dBB.](image-url)
Alb + H⁺ = HAlb⁺

Labelling the total concentrations of non-bicarbonate bases by Stewart and Siggaard-Andersen as [Buf₁⁻] and [Buf₂⁻], respectively, a small difference can be observed (the concentrations are considered in miliequivalents):

\[
[Buf₁⁻] = [PO₄^{3-}] + [HPO₄^{2-}] + [H₂PO₄⁻] + [Alb] - [HAlb⁺]
\]

\[
[Buf₂⁻] = [PO₄^{3-}] + [HPO₄^{2-}] + [H₂PO₄⁻] + [Alb] + [Alb]
\]

The concentration of non-bicarbonate bases is a bit higher by Siggaard-Andersen, as the relationship [Alb]>[HAlb⁺] applies at physiological conditions. This obviously suggests the difference between normal SID (around 38 mmol/l) and normal plasma BB (stated as 41.7 mmol/l).

However, as it applies that the variation in [Alb] concentrations is related to the variation in [HAlb⁺] concentrations:

\[
d[Alb] = d[HAlb⁺]
\]

The variation in the concentrations of the non-bicarbonate bases by Siggaard-Andersen will be identical with that of non-bicarbonate bases by Stewart:

\[
d[Buf₁⁻] = d[Buf₂⁻]
\]

The variation in BB or BE is therefore the same as that of SID:

\[
dBB = dSID
\]

Thus, it would meaningful for clinical purposes to calculate normal SID for various plasma protein and phosphate concentrations: NSID=function ([Alb₂₀⁺], [Pi]), similarly as normal SID for various plasma protein and phosphate concentrations are considered in miliequivalents: (respectively, a small difference can be observed (the concentrations are considered in miliequivalents)).

However, the problem is that what circulates in the blood vessels is not plasma only, but plasma and erythrocytes. A more accurate quantitative analysis requires considering the whole blood and it is also necessary to re-evaluate and connect both the approaches.

The outcome of the connection will be the sufficiently quantified Figge-Fenc’s model of plasma (Figge, 2009) and experimental data for the whole blood, included in Siggaard-Andersen nomogram.

7. Formalisation of Siggaard-Andersen nomogram

The first step necessary for the realisation of this connection is to formalise Siggaard-Andersen nomogram.

The literature describes a number of equations which formalise Siggaard-Andersen nomogram with higher or lower accuracy (e.g. Siggaard-Andersen et al. 1988). Lang and Zander (2002) compared the accuracy of BE calculation in 7 approximations of various authors. The most accurate approximation was that of Van Slyk equation by Zander (1995). Surprisingly, it was, however, shown that the formalisation of Siggaard-Andersen nomogram from 1980, used in a lot of our models in the past, approximated Siggaard-Andersen nomogram with higher accuracy than the relationships having been published later (Fig. 4).

It is possible to try further specification of our approximation.

\[
BE = \{1 - 0.0143 \times Alb \times 0.0304 \times pCO₂ \times 10^{pH - 7.4} - 24.26 \} \times \{9.5 + 1.63 \times Alb \} \times [pH - 7.4]
\]
On the contrary, models of plasma acid-base balance, e.g. Watson’s (Watson, 1999) or Figge-Fencl’s (Figge, 2009) nomogram is used for the assessment of measured nomograms without any correction. Moreover, this nomogram is used for identification of the models created for 37°C in a number of works (e.g. Reeves and Andreassen 2005).
The dependence of BE on haemoglobin concentrations at pH=7.3878 and pCO₂=41.862 torr according to the data from Sigaard-Andersen nomogram at 38°C (in fully oxygenated blood). At 37°C, these values correspond to the standard values of pH=7.4 and pCO₂=40 torr (see Fig. 11). According to the definition, BE at 37°C will be therefore zero in all cases. At 38°C, their BE will be different, depending on haemoglobin concentration (see Fig. 12).

To obtain a set of the values characterising the BE curve for Sigaard-Andersen nomogram corrected to 37°C, it is advisable to carry out simulation experiments with carbon dioxide blood titration in blood samples with various haemoglobin concentrations for each BE37°C in the condition of full oxygen saturation (see the calculation algorithm scheme in Fig. 13). Correction factor dBE38°C (depending on haemoglobin concentration and corresponding to BE zero value at 37°C) was always added to each BE37°C. This correction shift was a base for BE38°C:

\[ \text{BE}_{38^\circ C} = \text{BE}_{37^\circ C} + \text{dBE}_{38^\circ C} \]

A set of pH38°C was calculated from a set of BE38°C and pCO₂38°C by Sigaard-Andersen nomogram (by means of BEINV algorithm – see Fig. 7). pCO₂38°C and pH38°C were then re-calculated to the values corresponding to 37°C.

This procedure enabled obtaining the titration curves for 37°C. The intersections of the curves with the same BE37°C and various haematocrit characterise the BE curve of Sigaard-Andersen nomogram corrected to 37°C (see Fig. 14).
For new coordinates of BE curves, see Fig. 15 and 16. The calculation of new coordinates of BB (i.e. the coordinates where the curves – or lines in the semi-logarithmic scale – of blood samples with the same BB cut each other is simpler. In anaerobic heating (or cooling) must apply that:

\[ d[HCO_3^-] = d[Buf^-] + d[H^+] \]

as \( d[H^+] \ll d[HCO_3^-] \),

thus, it applies that \( d[HCO_3^-] = d[Buf^-] \), i.e. BB do not vary; thus:

\[ BB_{37°C} = BB_{38°C} \]

For new coordinates of BE curves, see Fig. 15 and 16.

The calculation of new coordinates of BB curves (i.e. the coordinates where the curves – or lines in the semi-logarithmic scale – of blood samples with the same BB cut each other is simpler. In anaerobic heating (or cooling) must apply that:

\[ d[HCO_3^-] = d[Buf^-] + d[H^+] \]

as \( d[H^+] \ll d[HCO_3^-] \),

thus, it applies that \( d[HCO_3^-] = d[Buf^-] \), i.e. BB do not vary; thus:

\[ BB_{37°C} = BB_{38°C} \]

For new coordinates of BE curves, see Fig. 15 and 16. The calculation of new coordinates of BB curves (i.e. the coordinates where the curves – or lines in the semi-logarithmic scale – of blood samples with the same BB cut each other is simpler. In anaerobic heating (or cooling) must apply that:

\[ d[HCO_3^-] = d[Buf^-] + d[H^+] \]

as \( d[H^+] \ll d[HCO_3^-] \),

thus, it applies that \( d[HCO_3^-] = d[Buf^-] \), i.e. BB do not vary; thus:

\[ BB_{37°C} = BB_{38°C} \]
Consequent dependence can be linearised by the following relationship (Fig. 17):

\[ dBE = 0.3 - 0.018 \text{cHb} \]

where cHb is haemoglobin concentration in g/100ml.

NBB\textsubscript{38°C} is calculated by the known, in clinical practice used, relationship (Siggaard-Andersen, 1960):

\[ \text{NBB}_{38°C} = 41.7 + 0.42 \text{cHb} \]

The substitution of NBB\textsubscript{37°C} results in a slightly different relationship:

\[ \text{NBB}_{37°C} = 42.0 + 0.402 \text{cHb} \]

BB\textsubscript{37°C} value will be calculated from BE\textsubscript{37°C} and haemoglobin concentration:

\[ \text{BB}_{37°C} = 42.0 + 0.402 \text{cHB} + \text{BE}_{37°C} \]

For the comparison of the curve Siggaard-Andersen nomograms for 37°C and 38°C, see Fig. 18 and Table 1.

In clinical laboratory practice, data (pH and pCO\textsubscript{2}) are measured at the standard temperature of 37°C; however,
they are assessed (BE calculation) by means of Siggaard-Andersen nomogram, created originally for 38°C. Thus, the comparison of the course of the titration curves according to the original and corrected Siggaard-Andersen nomogram (Fig. 19) is interesting in the view of clinical outcomes. It is obvious that noticeable deviations occur as late as with BE under 10 mmol/l and more significant ones at BE exceeding 15 mmol/l.

Table 1 Coordinates of BE and BB curves for original (37°C) and corrected (37°C) Siggaard-Andersen nomogram.

9. Erythrocytes and plasma
Now, Siggaard-Andersen nomogram is formalised for the same temperature, which detailed models of plasma acid-base balance, created by Stewart’s model, are identified for. These models (e.g. Figge 2009), anyhow considering the details of the effect of the dissociation constants of particular amino acids in an albumin molecule, entirely neglect the effect of such a substantial buffer as haemoglobin in erythrocytes. On the other hand, the drawback of the models based on experimental data derived from Siggaard-Andersen nomogram, is a precondition of normal plasma protein concentration.

The aim of this work is to connect both approaches into one model, potentially usable as a subsystem of the complex model of homeostasis in the organism with the possibility to simulate complex osmotic, ion, volume and acid-base disturbances.

First, using the experimental data from Siggaard-Andersen nomogram, the titration curves of plasma and erythrocytes should be separated – the result should be a model of the buffer behaviour of erythrocytes, connected with the detailed model of plasma acid-base balance, created by Stewart’s approach, regarding various plasma protein and phosphate concentrations.

Siggaard-Andersen verified experimentally that the curves of plasma and blood samples with various haematocrit and the same BE cut each other in one point on the BE curve (see Fig. 2). Similarly, the curves of blood samples with the same BB cut each other in one point on the BB curve. It raises a question, why the BB and BE titration curves cut each other in the same points on Siggaard-Andersen nomogram?

To reply this question, it is necessary to realise that blood titration with carbon dioxide results in the increase in bicarbonate concentrations in plasma and erythrocytes during the increase in \( p_{CO_2} \).

Regarding the plasma itself by Stewart – then, during plasma titration with carbon dioxide, the sum of bicarbonates and all non-bicarbonate buffer bases, forming \( BB_p \) and \( SID \), are unchanged (Fig. 20) – \( SID \) and \( p_{CO_2} \) are therefore mutually independent variables, which, together with another independent variable, plasma protein concentration, determines the value of the dependent variable – pH.

This basic Stewart’s canon does not apply in blood (see Fig. 21) – in the titration with carbon dioxide, plasma SID, corresponding (with the abovementioned objections) with \( BB_p \), varies. The increase in \( p_{CO_2} \) causes the increase in \( BB_p \) (and SID), whereas the decrease in \( p_{CO_2} \) causes the decrease in \( BB_p \). As the erythrocyte has more non-bicarbonate bases (particularly due to haemoglobin) than plasma, and the dissociation reaction of carbonic acid is more shifted to the right, there is a higher increase in bicarbonate concentrations in erythrocytes than in plasma. Bicarbonates are transported into plasma by the concentration gradient (by exchange for chloride ions). Thus, the increase in \( CO_2 \) concentrations is associated with the decrease or increase in BB concentrations in erythrocytes or plasma, respectively.

Blood titration with carbon dioxide helps achieve \( p_{CO_2} \) at which BB concentrations in erythrocytes and plasma equilibrate (BB in erythrocytes than in plasma. Bicarbonates are transported into plasma by the concentration gradient (by exchange for chloride ions). Thus, the increase in \( CO_2 \) concentrations is associated with the decrease or increase in BB concentrations in erythrocytes or plasma, respectively.

Regarding the plasma itself by Stewart – then, during plasma titration with carbon dioxide, the sum of bicarbonates and all non-bicarbonate buffer bases, forming \( BB_p \) and \( SID \), are unchanged (Fig. 20) – \( SID \) and \( p_{CO_2} \) are therefore mutually independent variables, which, together with another independent variable, plasma protein concentration, determines the value of the dependent variable – pH.

This basic Stewart’s canon does not apply in blood (see Fig. 21) – in the titration with carbon dioxide, plasma SID, corresponding (with the abovementioned objections) with \( BB_p \), varies. The increase in \( p_{CO_2} \) causes the increase in \( BB_p \) (and SID), whereas the decrease in \( p_{CO_2} \) causes the decrease in \( BB_p \). As the erythrocyte has more non-bicarbonate bases (particularly due to haemoglobin) than plasma, and the dissociation reaction of carbonic acid is more shifted to the right, there is a higher increase in bicarbonate concentrations in erythrocytes than in plasma. Bicarbonates are transported into plasma by the concentration gradient (by exchange for chloride ions). Thus, the increase in \( CO_2 \) concentrations is associated with the decrease or increase in BB concentrations in erythrocytes or plasma, respectively.

Blood titration with carbon dioxide helps achieve \( p_{CO_2} \) at which BB concentrations in erythrocytes and plasma equilibrate (BB in erythrocytes than in plasma. Bicarbonates are transported into plasma by the concentration gradient (by exchange for chloride ions). Thus, the increase in \( CO_2 \) concentrations is associated with the decrease or increase in BB concentrations in erythrocytes or plasma, respectively.
The BE curve can also be interpreted in other way. Regarding the fact that BE is the difference between BB and normal proper NBB for the given haemoglobin concentration, then the precondition of the equality of BE in plasma and erythrocytes means:

\[ \text{BB}_e - \text{NBB}_e = \text{BB}_p - \text{NBB}_p \]

This can be specified:

\[ \text{BB}_e - \text{BB}_p = \text{NBB}_e - \text{NBB}_p = \text{constant} \]

This means that the BE curve can be interpreted as the geometric site of the points (i.e. pCO\(_2\) and pH values) with a constant difference between BB in erythrocytes and plasma, which equals the difference between the proper values in erythrocytes and plasma (pCO\(_2\)=40 torr and plasma pH=7.4).

If the equation NBB\(_{\text{pCO}_2}\) = 41.7 + 0.42 cHb applies (Siggaard-Andersen, 1962), then haemoglobin concentration in erythrocytes cHb = 33.34 g/100ml is NBB\(_{\text{pCO}_2}\)=0.42×33.34 =14 mmol/l (according to our correction of Siggaard-Andersen nomogram, this value was 0.402×33.34 =13.4 mmol/l for 37°C).

Siggaard-Andersen used the mixture of O\(_2\) - CO\(_2\) for blood titration with fully oxygen-saturated blood – in fact, the BE curves are those for fully oxygenated blood – i.e. the abovementioned standardised oxyvalues of Base Excess – BBe (Kofránek, 1980). BE or BB exert a linear increase in haemoglobin oxygen desaturation:

\[ \text{BE} = \text{BE}_{\text{ox}} + 0.2 \text{cHb} (1-\text{sO}_2) \]

where cHb is haemoglobin concentration [g/100ml] and sO\(_2\) is haemoglobin oxygen saturation (Siggaard-Andersen 1988).

10. Separation of plasma and erythrocyte titration curves on Siggaard-Andersen nomogram

It is recommended to test if it is possible to make a model of blood acid-base balance from the experimental data on Siggaard-Andersen nomogram as a combination of the models of plasma and erythrocyte titration curves (Fig 22). The titration curves (plotted as lines in the semi-logarithmic scale) can be read out directly from the nomogram. The titration curves of erythrocytes can be obtained from the nomogram as follows: chose the blood concentration of haemoglobin 33.34 g/100 ml, which is the value with haematocrit having the value of one. The titration curve of this “virtual blood” with carbon dioxide follows pH variations (measured on the outer side of the erythrocyte) during pCO\(_2\) changes. The titration curve of the blood with a given haemoglobin and, thus, haematocrit concentrations cHb in (g/100ml blood).

\[ \text{Hk}=\text{cHb}/33.34 \]

(supposing the normal haemoglobin concentration in erythrocytes 33.34 g/100ml) will lie between the titration curves of plasma and erythrocytes in the semi-logarithmic coordinates log\(_10\) (pCO\(_2\)) – pH. It will cut the curves for plasma and erythrocytes in a point of the BE curve. As non-bicarbonate buffers (haemoglobin and phosphates) have a higher buffer capacity in erythrocytes than those in plasma (plasma proteins and phosphates), and non-bicarbonate bases in erythrocytes bind more hydrogen ions than those in plasma during blood titration with increasing concentrations of carbon dioxide, the concentration of bicarbonates increases more significantly in the erythrocyte than in plasma. The consequence is the transfer of bicarbonates between the erythrocyte and plasma (accompanied with a counter chloride transport). Labelling the amount of bicarbonates in 1 litre, transferred from erythrocytes into plasma during blood titration with carbon dioxide: mHCO\(_3\)ep [mmol/l], then the variations in plasma BE and BB is:

\[ \text{dBB}_p = \text{dBE}_p = \text{mHCO}_3\text{ep}/(1-\text{Hk}) \]

The corresponding variation of BE in erythrocytes is:

\[ \text{dBB}_e = \text{dBE}_e = \text{mHCO}_3\text{ep}/\text{Hk} \]

Choosing, for example, haemoglobin concentration 15 g/100 ml (and haematocrit concentration 15/33.34=0.4449) for the transfer of 1mmol of bicarbonate, there will be an increase and decrease in plasma and erythrocyte BE as well as BB concentrations by 1/(1-0.4449)=1.8015 mmol/l and by 1/0.4449=2.2477 mmol/l, respectively. There will be left and right shifts on plasma and erythrocyte titration curves (see Fig. 23), respectively – their intersection corresponds with the point on the titration curve with haemoglobin concentration 15 g/100 ml, in which 1 ml of bicarbonates were transferred from erythrocytes into plasma during the increase of pCO\(_2\) from the baseline value of 40 tor. As seen in Figure 23, this intersection lies on the titration curve with haemoglobin concentration 15 g/100 ml, modelled according to the data in Siggaard-Andersen nomogram (by means of the abovementioned function BEINV). Similarly, this curve includes the intersections of the left and right s of plasma and erythrocyte curves after the transfer of 2 and 1 mmol of bicarbonates from erythrocytes into plasma (during pCO\(_2\) increase) and from plasma into erythrocytes (during pCO\(_2\) increase), respectively.

Figures 24 and 25 show the results of the modelling of the titration curves for blood titration with carbon dioxide at BE -10 mmol/l and 10 mmol/l. Fig. 26 shows the results of the modelling of blood titration with carbon dioxide in the range of BE -20 to 20 mmol/l.
It has been shown that the titration curves of plasma, erythrocytes and blood with haemoglobin concentration 15 g/100 ml with BE=0 mmol/l. The plasma and erythrocyte curves cut each other in point (1) and on Base Excess in point BE=0, respectively. The transfer of bicarbonates from erythrocytes into plasma during blood titration with carbon dioxide shifts the plasma and erythrocyte curves to the right and to the left (with the increase and decrease in plasma and erythrocyte BE and BB values, respectively). The curves cut each other in points (2) and (3) on the titration curve with haemoglobin concentration 15g/100 ml. The decrease in pCO₂ causes the transfer of bicarbonates from plasma to erythrocytes with following decrease in plasma BE and BB, which results in the right shift of the titration curve and increase in erythrocyte BB with the left shift of erythrocyte curve. The curves cut each other on the blood titration curve (in point 4) with haemoglobin concentration 15 g/100 ml, modelled by the data in Siggaard-Andersen nomogram. This suggests that the titration curves can be modelled by the intersections of the shifts on plasma and erythrocyte titration curves.

It has been shown that the titration curves modelled by means of the intersections of the shifts of plasma and erythrocyte titration curves (due to the transfer of bicarbonates between the erythrocyte and plasma) copy the titration curves modelled direct by Siggaard-Andersen nomogram with a sufficient accuracy.

It therefore means that the modelling of blood titration with carbon dioxide can be based on the combination of plasma and erythrocyte titration curves. The modelling of blood titration with varied plasma protein concentration can be based on the combination of plasma titration curve with various plasma protein concentrations (for which, however, Siggaard-Andersen nomogram does not apply) – for example by Figge-Fenchel’s model (Figge, 2009), and erythrocyte titration curve (obtained from the experimental data of Siggaard-Andersen nomogram, corrected to 37°C).

11. Connection of the erythrocyte model by Siggaard-Andersen nomogram, corrected to 37°C and Figge-Fenchel’s model of plasma

Fig. 27 shows erythrocyte titration curves with various BE by Siggaard-Andersen nomogram – the erythrocytes are modelled as blood with haemoglobin concentration 33.34 g/100ml (corresponding to the proper haematocrit value of 1). In the semi-logarithmic scale, these curves are lines with variable slopes (k) and offset (h), depending on BE concentrations in erythrocytes (BEᵃ).

\[
\log_{10}(pCO_2) = k \cdot pH + h
\]

\[
k = f(BE_\text{er})
\]

\[
h = g(BE_\text{er})
\]

Functions “f” and “g” are approximated by polynomic regression according to the data from Siggaard-Andersen nomogram, corrected to 37°C (see Fig. 28 and 29).
pH (pH of the outer side of erythrocytes), depending on PCO₂ and BE in erythrocytes (BE₀), is calculated by means of eryBEINV function; for its algorithm, see Fig. 30.

pH=eryBEINV(pCO₂, BE₀)

The erythrocyte model is connected with the plasma model. Figge-Fencl’s model (Figge, 2009), combined, in addition, with the effect of globulin concentrations (calculated by means of their “buffer value” by Siggaard-Andersen, 1995), was selected as a plasma model. BEINV function calculates blood pH in dependence on pCO₂, total phosphate (Pitot), albumin (Alb), globulin (Glob) and haemoglobin concentrations as well as on standardised oxyvalues BEox, (i.e. BE found in fully oxygenated blood), PCO₂ and haemoglobin oxygen saturation:

pH=eryBEINV(pCO₂, BE₀)

For the principle of the calculation and for the algorithm itself, see Fig. 31 and 32, respectively.

First, BE is calculated according to the grade of desaturation (from SO₂) and BEox. This value is considered initial for plasma and erythrocytes (BE). pH is calculated from pCO₂.
However, the plasma titration curve has a smaller slope than that for erythrocytes (see Fig. 31) and plasma pH (\(pH_{plasma}\)) is calculated according to plasma BE (BE\(_p\)); pH on the outer side of erythrocytes (\(pH_{erythrocytes}\)), calculated according to erythrocyte BE (BE\(_{er}\)), is different. Then, the transfer of bicarbonates between plasma and erythrocytes is calculated by iteration – the transfer causes variations in plasma BE\(_p\) and erythrocyte BE\(_{er}\) BEs – the ratio of BE variations in erythrocytes and plasma depend on haematocrit. The iteration converges to the final value in plasma calculated according to both erythrocyte and plasma BE\(_p\) (\(pH = pH_{plasma} = pH_{erythrocytes}\)).

The algorithm also calculates the normal SID (NSID) – i.e. the SID, in which pH=7.4 with the given haemoglobin, albumin and phosphate concentrations and PCO\(_2\)=40 torr.

There is a wider definition of BE in this model compared with classical Siggaard-Andersen’s nomogram interpretation – its normal value depends not only on haemoglobin concentrations but also on albumin, globulin and phosphate concentrations - like Siggaard-Andersen’s van Slyke equation (Siggaard-Andersen, 1977, 2006). Unlike in classical plasma models by Stewart and his followers, this model enables to demonstrate that the relationship between SID and pCO\(_2\) does not apply in the whole blood. The model (and the related formalised relationships) can be used in a number of clinical-physiological calculations.

For the model, including its source text and the description of all used mathematical relationships and algorithms, see www.physiome.cz/acidbase.

11. Conclusion

Siggaard-Andersen nomogram was recalculated from original 38°C to standard 37°C. The experimental data of Fige and Fencl’s model of plasma acid-base balance was combined with the data based on Siggaard-Andersen nomogram, corrected to 37°C. It was obtained a model of blood acid-base balance combining the plasma model with variable albumin, globulin and phosphate concentrations and connected with the erythrocyte model. The model is a core of an extent model of acid-base balance which enables the realisation of pathogenesis of acid-base disturbances in compliance with the balance approach to the interpretation of ABB disturbances, published earlier (Kofránek et al., 2007).

Acknowledgements

The work was supported by the project of National Programme of Research No. 2C06031, “e-Golem”, the development project of Ministry of Education, Youth and Sports C20/2008 and by Creative Connections s.r.o. company.

References


Corresponding author
 Jiří Kofránek, Laboratory of Biocybernetics, Department of Pathophysiology, U nemocnice 5, 128 53 Prague 2, Czech Republic, e-mail: kofranek@gmail.com.