

## Independence of Variables in Stewart's Model of the Acid-Base Chemistry of the Blood Plasma

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**Abstract:** Several approaches have been taken to modelling of the acid-base chemistry of blood. The Stewart approach includes three independent variables (SID,  $PCO_2$ ,  $A_{tot}$ ), which are postulated to completely describe causal mechanisms behind changes in acid-base status. This paper explores this postulate, simulating typical clinical examples using an online modeling tool. For changes in alveolar ventilation, production of strong acid, and selective removal of non-charged protein buffers, this postulate is true. However for non-selective protein buffer removal SID and  $A_{tot}$  cannot be seen as independent. The paper discusses the implication of this on diagnosis of acid-base disturbances in patients with abnormal protein concentration.

**Keywords:** Acid base chemistry, computer simulation, computer experiment, equilibrium, model approximation, physiological models, physiology, state variables

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### 1. INTRODUCTION

Several approaches have been taken to modelling of the acid-base chemistry of blood. Broadly, these can be classified into those of Siggaard-Andersen (1974, 1977) and colleagues and those seen as more 'modern', i.e. those of Stewart (1983) and other authors (Figge et al., 1991; Constable, 2000; Fencl et al. 2000). The Stewart approach has been seen by some authors as a revolution in ability to understand the true nature of an acid-base disturbance (Constable, 2003). This is largely due to the modelling formulation adopted by Stewart, where reaction equations are represented by mass balance and mass action equations, and 3 variables are selected as 'independent variables'. These three independent variables are partial pressure of carbon dioxide  $pCO_2$ , total concentration of plasma weak acid  $A_{tot}$  and strong ion difference SID. Their independence has meant two things: first, that values of these three variables can be used to solve all Stewart's equations describing acid-base chemistry of plasma; and second, their independence has been ascribed to fact that they themselves do change as a result of different (independent) physiological mechanisms: Changes of alveolar ventilation affect the carbon dioxide level ( $pCO_2$ ), disturbances of strong ion levels affect SID and changes of total plasma buffer level (mainly protein, especially albumin) affect  $A_{tot}$ . These physiological mechanisms are seen as independent causes of acid-base disturbances.

This article explores the ability of Stewart's three independent variables to describe some typical clinical disorders resulting in acid-base disturbances, i.e. changes in alveolar ventilation, the onset of anaerobic metabolism and the loss of plasma protein during for example acute nephrotic syndrome, burn trauma or sepsis. It illustrates situations where Stewart's assumptions of independence are valid and more importantly, where they may be questioned.

### 2. STEWART'S MODEL OF ACID BASE CHEMISTRY OF PLASMA

Figure 1 illustrates Stewart's model of the acid-base chemistry of plasma. It includes mass action equations describing reaction equilibria of the dissociation of water, the non-bicarbonate buffer, the bicarbonate buffer and the carbonate buffer, although it is usual to omit the equations representing water and carbonate (Constable, 1997). The model also includes mass balance equations keeping track of the total non-bicarbonate buffer (weak acid), and a single equation describing electrical neutrality in the plasma. The sum of strong cations minus the sum of strong anions – so called strong ion difference – has to equal the negative charge of the buffers. Since the buffers in Stewart's model are only negatively charged in their base form ( $A^-$  and bicarbonate), this means that SID equals concentration of  $A^-$  and of bicarbonate.

$$SID = HCO_3^- + A^- \quad (1)$$

Equation 1 is practically equal to the line 6 of figure 1 (the original Stewart model), since all the omitted terms are negligible and do not change the numerical solution (Constable, 1997). The model assumes a single non-bicarbonate buffer (equation) lumping all protein buffers and phosphate in the plasma.

Fig. 1

Reaction Equations	Mathematical Representation
$H^+ + OH^- \rightleftharpoons H_2O$	$[H^+] \cdot [OH^-] = K_w$
$H^+ + A^- \rightleftharpoons HA$	$[H^+] \cdot [A^-] = K_A \cdot [HA]$
$H^+ + HCO_3^- \rightleftharpoons H_2O + CO_2$	$[H^+] \cdot [HCO_3^-] = K_c \cdot pCO_2$
$H^+ + CO_3^{2-} \rightleftharpoons HCO_3^-$	$[H^+] \cdot [CO_3^{2-}] = K_3 \cdot [HCO_3^-]$
	$[A^-] + [HA] = [A_{tot}]$
	$[SID] + [H^+] - [HCO_3^-] - [A^-] - [CO_3^{2-}] - [OH^-] = 0$

Fig. 1. Stewart's model of plasma acid base chemistry, including reaction and mathematical equations: Equations playing a significant role are shown in black. In the electroneutrality equation, terms that are several orders lower in magnitude than the rest can be omitted, and are shown in gray. Equation constants have the following values:  $K_w = 4.4e-14$  (eq/L)<sup>2</sup>,  $K_A = 3 \cdot 10^{-7}$  (eq/L),  $K_c = 2.46 \cdot 10^{-11}$  (Eq/L)<sup>2</sup>/mmHg,  $K_3 = 6 \cdot 10^{-11}$  Eq/L.

Values of the independent variables are  $pCO_2 = 5.3$  kPa,  $SID = 41.7$  meq/l and  $A_{tot} = 19$  meq/l in normal conditions (Stewart, 1983). Solving Stewart's equations (lines 1-6 of figure 1) for these values gives the values of the dependent variables:  $pH=7.40$ ;  $A^- = 16.8$  meq/l;  $HA = 2.2$  meq/l;  $HCO_3^- = 24.9$  meq/L, and  $CO_3^{2-} = 0.04$  meq/L.

One of Stewart's state variables is  $pCO_2$ , rather than total  $CO_2$  (in form of  $CO_2$ ,  $HCO_3^-$  and other). This variable is selected because the buffering system of bicarbonate behaves as an open system in the body, equilibrating back to a given  $pCO_2$  after any buffering has occurred.

### 3. INTERPRETATION OF CLINICAL SITUATIONS USING STEWART'S MODEL

This section describes the interpretation of physiological disorders using Stewart's model, these being changes in ventilation, the onset of anaerobic metabolism and the loss of plasma protein in two distinct ways during for example nephrotic syndrome, burn trauma or sepsis. These are explained both in terms of the reaction equations included in figure 1, and exemplified using an implementation of these reactions. This implementation is part of a broader atlas of physiological models available online to the reader at [www.physiome.cz/atlas/acidobaze/04/ Index.htm](http://www.physiome.cz/atlas/acidobaze/04/ Index.htm)

#### 3.1 Changes in Alveolar Ventilation

Changes in the acid-base status of plasma due to hyperventilation can be seen in figure 2a, with the direction in these changes shown by the bold arrows. Increased ventilation reduces  $CO_2$  levels (black arrow), which in turn causes reaction 1 to proceed to the right, bicarbonate and hydrogen ions reacting in equimolar amounts (gray arrows). Physiological  $H^+$  concentrations are in the nanomolar range meaning that the shift in reaction equation 1 to the right must be compensated by an equivalent shift in reaction equation 2 to the left (empty arrow). The result is that the sum of  $A^-$  and  $HCO_3^-$  is constant at the level of millimoles, i.e.  $SID$  stays constant. In addition the proportions of  $A^-$  relative to  $HA$  have changed but the total concentration  $A_{tot}$  remains constant. Changes in ventilation are therefore well described by Stewart's 3 independent variables: a changing  $pCO_2$ , with constant  $SID$  and  $A_{tot}$ .

Fig. 2a

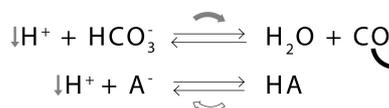


Fig. 2b

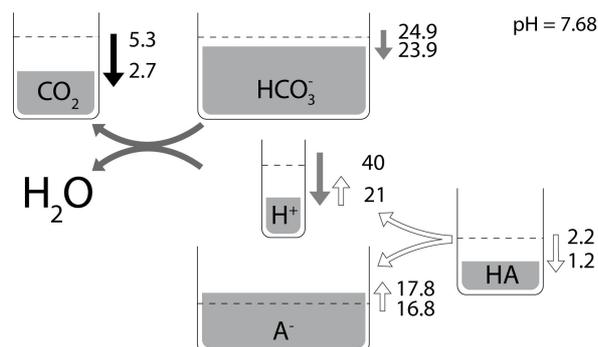


Fig. 2. Respiratory alkalosis: A typical situation is simulated whereby  $pCO_2$  changes from normal level of 5.3 to 2.7 kPa. Numbers represent before and after situations, and are given in meq/L, except for  $H^+$  (neq/L), and  $CO_2$ (kPa). Arrows represent the direction of change with black arrow representing  $CO_2$  disturbance, gray arrows the reaction of the bicarbonate system and empty arrows the reactions of non-bicarbonate buffers. Resulting pH corresponds to the after concentration of  $H^+$ .

Figure 2b shows situation after  $pCO_2$  has approximately halved due to increased alveolar ventilation. Bicarbonate decreases and  $A^-$  increases by 1.0 meq/l, the increase in  $A^-$  being fuelled by an equivalent decrease in  $HA$ . Values of both  $SID$  and  $A_{tot}$  are represented graphically in the figure:  $SID$  is the sum of the cups containing  $HCO_3^-$  and  $A^-$ , while  $A_{tot}$  is the sum of cups containing  $A^-$  and  $HA$ .

### 3.2 Metabolic Production of Lactic Acid

Changes in the acid-base status of plasma due to increases in strong acid can be seen in figure 3a. Dissociation of strong acid produces  $H^+$  which is bound to either  $HCO_3^-$  or  $A^-$  causing both reactions to move to the right, maintaining  $H^+$  concentrations in the nanomolar range. The net reduction in the sum of  $HCO_3^-$  and  $A^-$  (i.e. SID) is equivalent to the amount of  $H^+$  added from the metabolism (at the millimolar level). Assuming adequate ventilation, the increased  $CO_2$  is removed, maintaining normal  $pCO_2$  levels. The proportions of  $A^-$  relative to HA have changed, but the total concentration  $A_{tot}$  remains constant. Adding strong acid produced in the metabolism is therefore well described by Stewart's 3 independent variables: a changing SID, with constant  $pCO_2$  and  $A_{tot}$ .

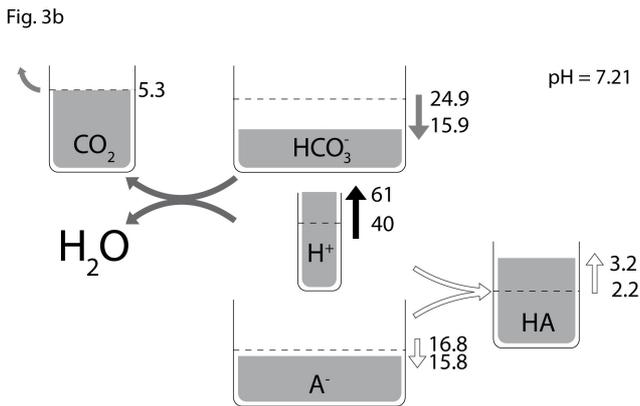
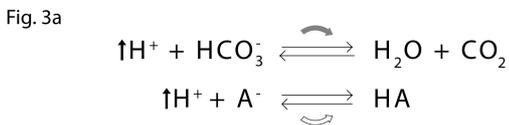


Fig. 3. Metabolic acidosis: A typical situation where 10 meq/L of strong acid is added and SID changes from normal level of 41.7 to 31.7 meq/l. All the numbers are in meq/L, except for  $H^+$ (neq/L), and  $CO_2$  (kPa). Black arrow represents original disturbance, gray arrows reactions of the bicarbonate system and empty arrows reactions of non-bicarbonate buffers. Resulting pH corresponds to the after concentration of  $H^+$ .

Figure 3b shows situation after addition of 10 meq/L (=10,000,000 neq/L) of acid. Both bicarbonate and  $A^-$  decrease, the decrease in  $A^-$  causing an equivalent increase in HA.  $pCO_2$  remains constant and pH changes accordingly to changes in  $HCO_3^-$ ,  $A^-$  and HA.

### 3.3 Protein changes with loss of the acidic form only

Stewart's model describes a decrease in  $A_{tot}$  with constant SID as a hypoproteinemic alkalosis. Such a situation arises when  $A_{tot}$  is reduced by loss of the acidic form of protein HA only. One of the pathological states where this could be implied is nephrotic syndrome (Kurtz et al, 2008). In nephrotic syndrome, plasma albumin is filtered into urine and lost. The albumin loss can be described as a loss of HA, whenever pH of urine is acidic enough (around 5.0), because albumin is known to be in its acidic form in such a low pH environment. Selective removal of the HA component of  $A_{tot}$  causes reaction 2 to proceed to the right,  $A^-$  and hydrogen ions reacting in equimolar amounts. The reaction replenishes lost HA from  $A^-$  at the cost of loss of hydrogen ion. Physiological  $H^+$  concentrations are in the nanomolar range meaning that the shift in reaction equation 2 to the right must be compensated by an equivalent shift in reaction equation 1 to the left – bicarbonate is formed from  $CO_2$ , with  $pCO_2$  returning to its original value due to the open system. The result is the sum of  $A^-$  and  $HCO_3^-$  being constant at the level of millimoles, i.e. constant SID. In addition, the proportion of  $A^-$  relative to HA changes and  $A_{tot}$  is reduced.

It should be noted that the commonness of loss of the HA form of the protein in nephrotic syndrome (or in any other disorder – see section 3.4) could be questioned. While there are examples of patients with nephrotic syndrome hypoproteinemia and metabolic alkalosis described in literature (McAuliffe et al., 1986), the most common pH seen in this group of patients is within physiological limits (Brenner, DuBose et al., 2004). This is in agreement with filtering of albumin into urine in both HA and  $A^-$  forms.  $A^-$  form is only converted into HA in renal distal tubuli and collecting ducts, where  $H^+$  ions are actively secreted into the tubular lumen and bind with the  $A^-$  to convert it into HA. Due the availability of albumin as an extra urinary buffer system, the luminal pH decreases slowly and the secretion of  $H^+$  tends to proceed in excess to the body's need (Steinmetz et al., 1971; Steinmetz, 1986) and can thus cause a tendency to alkalosis. However, this secretion is soon readjusted, HA and  $A^-$  are lost in proportion (section 3.4), and pH returns to normal.

Primary changes in HA, whilst potentially uncommon, are therefore well described by Stewart's 3 independent variables: a changing  $A_{tot}$ , with constant SID and  $pCO_2$ .

Fig. 4a

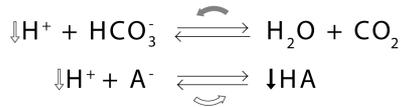


Fig. 4b

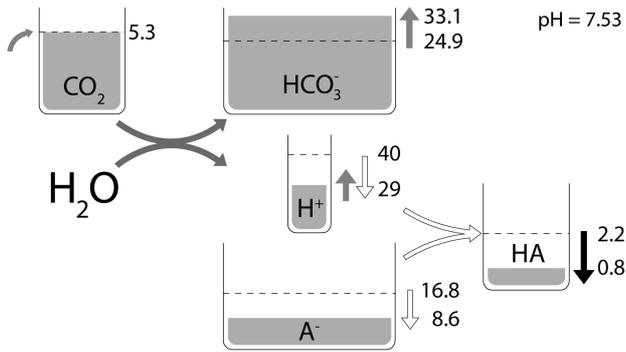


Fig. 4. Loss of the acidic form of protein: We simulate a situation of loss of 9.5 meq/L of HA, this loss actually exceeding the original concentration of HA. All values are in meq/L, except for H<sup>+</sup> (neq/L), and CO<sub>2</sub> (kPa). Black arrow represents original disturbance, empty arrows reactions of non-bicarbonate buffers and gray arrows reactions of the bicarbonate system. Resulting pH corresponds to the after concentration of H<sup>+</sup>.

Figure 4 illustrates an example of HA loss. A<sub>tot</sub> is reduced by 9.5, as seen by both reduction in A<sup>-</sup> and HA. The reduction in A<sup>-</sup> of 8.2 meq/L is equivalent to the increase in bicarbonate, giving constant SID. pCO<sub>2</sub> remains constant.

### 3.4 Protein changes with loss of both acid and base form

Disorders such as sepsis or burn trauma are associated with increased permeability of capillary membranes in damaged areas, causing both forms of protein buffers (HA and A<sup>-</sup>) to be lost. Changes in the acid-base status of plasma due to these disorders might therefore be represented as removal of the HA and A<sup>-</sup> in the proportion seen in plasma, as illustrated in figure 5. Removal of HA and A<sup>-</sup> in proportion causes no disturbance of the equilibrium of reaction 2, and as a consequence no change in the equilibrium of reaction 1. A<sup>-</sup> is, however reduced, but at constant values of HCO<sub>3</sub><sup>-</sup>, meaning that the net concentration of A<sup>-</sup> and HCO<sub>3</sub><sup>-</sup>, i.e. SID, is reduced.

It should be noted that patients with burns and sepsis often present with metabolic changes of pH ranging from acidosis to normal pH and even alkalosis. This has been ascribed to the production of metabolic acids like lactate due to the

underlying disorders (section 3.2) as well as the infusion therapy. However, in both of these disorders and in most of the other causes of protein loss, the underlying mechanism (generally filtration) gives no reason to believe that HA is lost alone and not in the current proportion to A<sup>-</sup>, whatever the proportion of these forms in plasma is.

Changes in HA and A<sup>-</sup> in proportion are therefore poorly described by Stewart's 3 independent variables with changes of both A<sub>tot</sub> and SID in conditions of constant pCO<sub>2</sub>.

Figure 5 illustrates a typical situation of A<sup>-</sup> and HA loss in proportion. A<sub>tot</sub> decreases by 9.5 meq/L, as seen by both reduction in A<sup>-</sup> and HA. The reduction in A<sup>-</sup> of 8.4 meq/L gives an equimolar reduction in SID. pCO<sub>2</sub> remains constant.

Fig. 5a

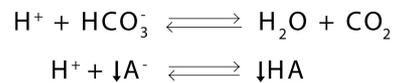


Fig. 5b

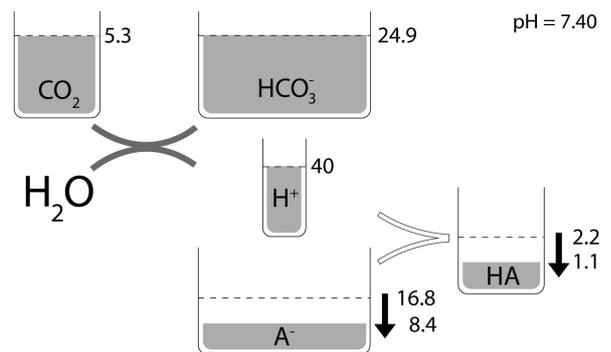


Fig. 5. Loss of both forms of protein: We simulate a typical situation of loss of 9.5 meq/L of HA and A<sup>-</sup> in proportion. All the numbers are in meq/L, except H<sup>+</sup> (neq/L), and CO<sub>2</sub> (kPa). Black arrows represent original disturbance. No compensatory buffering reactions occur. Resulting pH corresponds to the after concentration of H<sup>+</sup>.

## 4. DISCUSSION

There has been a considerable debate as to whether the modern or the traditional approach to modeling the acid-base status of plasma provides a better diagnosis of patients with acid-base disturbances (McAuliffe et al., 1986; Severinghaus, 1993; Siggaard-Andersen et al., 1995; Constable, 2000; Fencl et al., 2000; Dubin et al., 2007, Kurtz et al., 2008). One of the important improvements proposed by Stewart was the representation of three 'independent variables' (SID, A<sub>tot</sub>

and  $p\text{CO}_2$ ), values of which enable unique solution of all Stewart's equations describing acid-base chemistry of plasma. These variables have been postulated as an improvement in helping to distinguish between different causal mechanisms of changes in acid-base chemistry, such that if values of SID,  $A_{\text{tot}}$  and  $p\text{CO}_2$  are known then the complete causal mechanisms behind changes in acid-base status can be understood. This postulate relies upon the assumption that each independent variable is affected by different causal mechanisms. If the same causal effect changes more than one of the independent variables then the independent variables are no longer capable of complete separation of all causal mechanisms. This paper explores this postulate, simulating typical clinical examples and illustrating independence between the variables, or otherwise, in these examples.

In most of the examples described here the assumption of independence between the variables is true. These examples are changes in alveolar ventilation, production of strong acid, and changes in protein concentration in physiological situation where the non-charged part of protein buffers (HA) is selectively removed. However this is not always true, and in the situation where protein buffers are non-selectively removed, both SID and  $A_{\text{tot}}$  values change as a result without the need for a change in pH.

Lack of independence between these variables can lead to misdiagnosis. For example, some authors applying Stewart's model (Fencl et al., 2000) claim that patients with a low SID and low  $A_{\text{tot}}$  should be interpreted as having a low SID acidosis due to a primary electrolyte problem, combined with hypoalbuminemic alkalosis (low  $A_{\text{tot}}$ ) due to protein loss. These authors postulate that the combined effects of the acidosis and alkalosis lead to a normal value of pH. It can be seen from this analysis presented in this paper that this situation can be equally well described by loss of protein such that  $A^-$  and HA forms are lost in proportion. In this context, the electrolyte disturbance is secondary to the effects of  $A^-$  change on protein loss and  $A_{\text{tot}}$  and SID are not independent. Indeed, Siggaard-Andersen and colleagues have previously criticized the concept of alkalosis or acidosis as being caused by changes in total concentration of protein buffers, i.e. albumin, or in the case of whole blood, haemoglobin (1995).

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