

# Strong Ion Calculator – A Practical Bedside Application of Modern Quantitative Acid-Base Physiology

P. LLOYD

Anaesthetic Department, Hawke's Bay Regional Hospital, Hastings, NEW ZEALAND

---

## ABSTRACT

**Objective:** *To review acid-base balance by considering the physical effects of ions in solution and describe the use of a calculator to derive the strong ion difference and  $A_{\text{tot}}$  and strong ion gap.*

**Data sources:** *A review of articles reporting on the use of strong ion difference and  $A_{\text{tot}}$  in the interpretation of acid base balance.*

**Summary of review:** *Tremendous progress has been made in the last decade in our understanding of acid-base physiology. We now have a quantitative understanding of the mechanisms underlying the acidity of an aqueous solution. We can now predict the acidity given information about the concentration of the various ion-forming species within it. We can predict changes in acid-base status caused by disturbance of these factors, and finally, we can detect unmeasured anions with greater sensitivity than was previously possible with the anion gap, using either arterial or venous blood sampling. Acid-base interpretation has ceased to be an intuitive and arcane art. Much of it is now an exact computation that can be automated and incorporated into an online hospital laboratory information system.*

**Conclusions:** *All diseases and all therapies can affect a patient's acid-base status only through the final common pathway of one or more of the three independent factors. With Constable's equations we can now accurately predict the acidity of plasma. When there is a discrepancy between the observed and predicted acidity we can deduce the net concentration of unmeasured ions to account for the difference. (Critical Care and Resuscitation 2004; 6: 285-294)*

**Key words:** Strong ions, acid-base balance, strong ion difference, strong ion gap

---

*"All truth passes through three stages: first, it is ridiculed; second, it is violently opposed; and third, it is accepted as self-evident". Arthur Schopenhauer*

Acid-base physiology has recently undergone a revolution.<sup>1</sup> The old gods are gone. There is a new way to see the world and it takes some adjustment. For example, we no longer believe that acid-base physiology begins and ends solely with the Henderson-Hasselbalch equation.

Indeed it could be argued that our understanding of the processes underlying acid-base physiology has been hampered by using a distorted measure of acidity in the form of pH, which is no less complicated than the logarithm to the base 10 of the reciprocal of the hydrogen ion activity measured in moles per litre. Because of this, the form of the mathematical equations describing aqueous solutions becomes unnecessarily complicated.<sup>2,3</sup> How do you add two numbers using logs?

---

Correspondence to: Dr P. Lloyd, Anaesthetic Department, Hawke's Bay Regional Hospital, Hastings, New Zealand (e-mail: peter.lloyd@hawkesbaydhb.govt.nz)

At the time Hasselbalch put the "Hassel" into the Henderson equation (1916), the SI system of units was not established in medical practice, which is a pity because the acidity of physiological solutions (with the exception of gastric acid) rarely falls outside the range of 10 - 100 nmol/L extracellularly, and is somewhat more acidic intracellularly. Typical values are 40 nmol/L for arterial blood and 160 nmol/L inside cells. It is unnecessary to complicate the measurement of acidity by using such a misleading, nonlinear and unintuitive unit as pH.

It was known for many years that there was a link between the ionic species and acid-base physiology. It was also known that various physico-chemical relationships are obeyed, such as the requirement that all physiological solutions must be electrically neutral: that is the sum of the cations must be balanced by the sum of the anions.<sup>4</sup>

However, it was the insight of Peter Stewart in 1978 that enabled him to separate three independent factors from the many other dependent factors.<sup>5</sup> Independent factors are defined as those that influence the system but are not influenced by it. Stewart then created a system of simultaneous equations whose solution, the Stewart equation, related the acidity of plasma to the three independent factors.<sup>6</sup>

The major drawback is that the Stewart equation is a fourth-order polynomial of the form  $ax^4 + bx^3 + cx^2 + dx + e = 0$ . Such an equation cannot be solved with simple pocket calculators or spreadsheet formulas, which meant that Stewart's work could not be conveniently applied at the bedside.<sup>7</sup>

The other problem is that Stewart did not have accurate measures of several physiological constants for humans, so he was forced to estimate. Both problems were solved by Peter Constable. By excluding gastric juices whose hydrogen ion concentration is very high (in the millimole per litre range), and by ignoring species whose concentrations are in the micromolar and nanomolar range when writing the electroneutrality equation, Constable was able to reduce Stewart's equation to a simple quadratic equation,<sup>8</sup> the simplified strong ion equation, which is readily solved with any calculator that can add, subtract, multiply, divide and take square roots.

This equation is mathematically equivalent to Stewart's polynomial equation outside of gastric fluids, and when the protein and phosphate concentrations are zero it reduces to the Henderson equation (and its logarithmic form reduces to the Henderson-Hasselbalch equation), thereby creating a link with the great platform that our understanding of acid-base physiology had depended on for nearly a century.

Constable went on to experimentally determine the

normal values of relevant constants and parameters for several mammalian species, including man.<sup>9,10</sup> More importantly, he developed the concept of strong ion gap,<sup>10</sup> that had been originally proposed by Figge, Mydosh and Fencl.<sup>11</sup> This is an exercise in accounting for electric charge, in which unmeasured ionic species are identified by their influence on acidity, in the same way that a metal detector can find buried treasure because of the effect of certain metals on the magnetic field.

As a direct result of Constable's work it has been possible to create a calculator that accepts measured parameters such as the concentration of electrolytes, proteins and the blood gas measurements (pH and  $PCO_2$ ) and displays graphically the value of the independent factors, the predicted acidity, the measured acidity and the net concentration of unmeasured ions. This paper describes the development of the strong ion calculator.

Interested readers are invited to download the latest version from <http://homepage.mac.com/peterlloyd1/>. At the time of writing it is at Version 7.7. Macros should be disabled as they are unnecessary for the working of the calculator.

### Theoretical background - three independent factors

Several species exist in plasma and other aqueous physiological solutions. Under physiological conditions they divide fairly neatly into strong ions and weak electrolyte solutions. The strong ions by definition are > 99% dissociated throughout the physiological range of acidity.

Sodium, potassium, calcium, magnesium, chloride, sulphate and lactate are examples of strong ions. They carry a permanent, immutable electric charge when in solution. They do not participate in proton transfer reactions.<sup>3</sup> In respect of acid-base physiology, it is only the difference in the ionic charge (in mEq/L) carried by the strong cations and the strong anions that matters. This is the strong ion difference (SID); its normal value is approximately 35 mEq/L, and is roughly the  $[Na^+] - [Cl^-]$ . SID is the first of Stewart's independent factors.

Weak electrolyte solutions are the physiological buffers, and they are much less than 99% dissociated, but the degree of dissociation is in dynamic equilibrium with the prevailing acidity of the solution. Weak electrolytes are either volatile (carbonic acid and bicarbonate ion) or nonvolatile (protein and phosphate).

The nonvolatile buffers present in highest concentration in plasma in order are albumin, other plasma proteins ("globulins"), and phosphate; they are all weak acids. In order to develop Stewart's polynomial equation (and Constable's simplified strong ion equation- v.inf), it was necessary to model the proteins

and phosphates as if they were a mono-valent weak acid with a dissociation constant,  $K_a$  of 80 nmol/L (pKa of 7.1) and a concentration  $A_{tot}$ . This idealisation of a complex situation causes small deviations in the observed and predicted behaviour of physiological solutions.  $A_{tot}$  is the second independent factor. The dissociation of any weak electrolyte solution is described by the law of mass action for that reaction. The one describing the solution of  $CO_2$  and subsequent dissociation of carbonic acid to bicarbonate and hydrogen ions is the Henderson equation, whose logarithmic form is the Henderson-Hasselbalch equation.

Ultimately the volatile buffers are in equilibrium with  $PCO_2$ , which is classified as an independent factor because at equilibrium the  $PaCO_2$  is determined by the balance between the whole-body rate of production of  $CO_2$  and the alveolar ventilation rate.  $PCO_2$  is the third independent factor. Proteins and phosphate are the important nonvolatile buffers. Of the proteins, albumin normally carries three quarters of the electric charge.

The idealisation of the several weak acids as one is unnecessary for calculation of the strong ion gap. Instead, each of the weak acid equilibria, governed by its own dissociation constant, can be separately modelled. For this reason the strong ion gap concept is a particularly powerful application of quantitative acid-base physiology, and is robust in the sense that it makes no assumptions about the albumin to globulin ratio or the relative phosphate concentration.

Although Stewart modelled protein and phosphate as if they were one monovalent weak acid, Constable has introduced a more sophisticated model that assigns a fixed charge plus a variable charge to both proteins and phosphate.<sup>10</sup> The fixed charge component is included with the strong ions. Only the variable charge is included with the weak acids. This more sophisticated model better fits the data. What we now know is that all diseases and all therapies can affect the acid-base status of the patient only via the three independent factors. For example, administration of hydrochloric acid or sodium hydroxide causes acidosis or alkalosis respectively not because we administered hydrogen or hydroxyl ions respectively, but because we gave a strong anion (as in HCl) or strong cation (as in NaOH) unopposed by a strong ion of opposite charge, and therefore we affected the SID. Other diseases affect the  $PCO_2$ ; others the protein or phosphate concentration.

### Simplified strong ion equation

A physiological solution at equilibrium is described by the following equations:

- The law of conservation of mass
- The law of conservation of electric charge
- Henry's law
- The law of mass action for the carbonic acid-bicarbonate equilibrium (Henderson-Hasselbalch equation)
- The law of mass action for the nonvolatile buffer equilibria

The simultaneous solution<sup>8</sup> of these five equations gives Constable's simplified strong ion equation (SSIE). In full, it is shown below, where  $aH^+$  is the acidity,  $K'_1$  is the apparent dissociation constant for the carbonic acid-bicarbonate equilibrium,  $S_{CO_2}$  is the solubility coefficient of  $CO_2$  and  $K_a$  is the apparent dissociation constant for the idealised weak acid, all at 37°C. Although it looks complicated, close inspection shows the SSIE contains only the three independent factors identified by Stewart ( $PCO_2$ , SID and  $A_{tot}$ ) and the relevant physiological constants. In words the simplified strong ion equation says, "acidity is a function of  $PCO_2$ , total weak acid concentration ( $A_{tot}$ ), and SID". It computes the acidity given the values of the three independent factors.

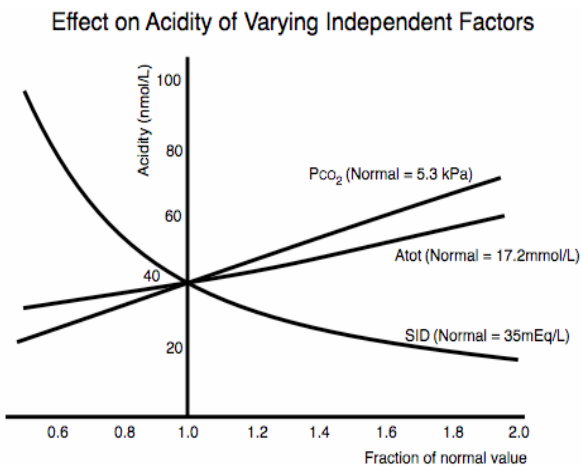
Acidity or hydrogen ion activity is what is measured by a pH meter and expressed on a linear scale, usually nmol/L. It is related to the hydrogen ion concentration by the activity coefficient whose value varies non-linearly with the acidity, temperature and ionic concentration of other species. When discussing acid-base physiology it is important to be clear that it is the acidity that is measured by a pH meter, not the hydrogen ion concentration and that acidity is the exact counterpart of pH but expressed on a linear scale.

Figure 1 shows the relationship of the acidity to the three independent factors. In the case of  $PCO_2$  and  $A_{tot}$ , the relationship is fairly linear. In the case of SID it is reciprocal.

### Why acidity changes - the Gamblegram

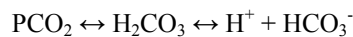
Dr. J. L. Gamble was a physiologist based at the Johns Hopkins university school of medicine. The eponymous gamblegram has two bars, one depicting the concentration of cations, the other anions (figure 2).

$$a_{H^+} = \frac{K'_1 S_{CO_2} P_{CO_2} + K_a [A_{tot}] - K_a [SID^+]}{2[SID^+]} + \frac{SQRT((K'_1 S_{CO_2} P_{CO_2} + K_a [SID^+] + K_a [A_{tot}])^2 - 4K_a^2 [SID^+][A_{tot}])}{2[SID^+]}$$

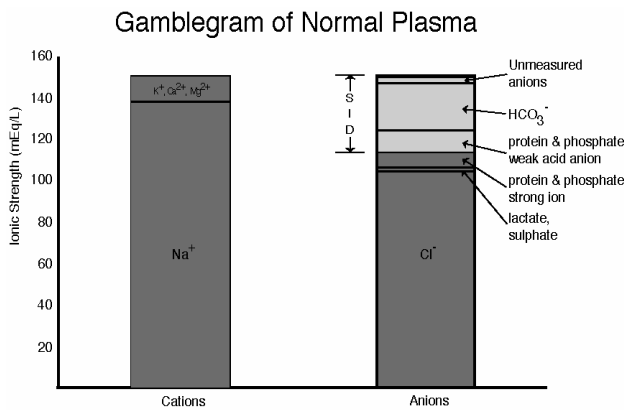


**Figure 1.** The effect on acidity of varying the three independent factors

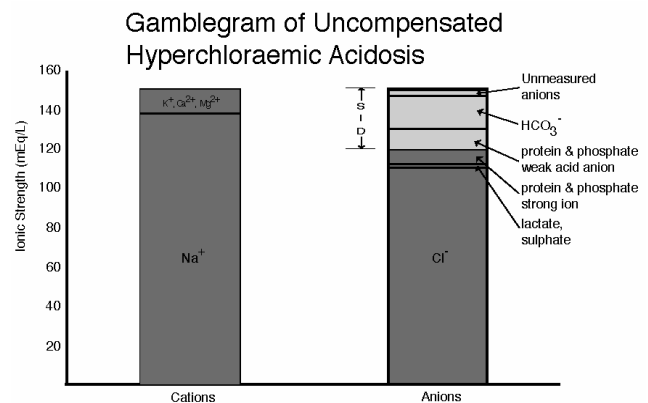
will buffer with bicarbonate, proteins and phosphate. The  $PCO_2$  will transiently rise, but because the whole-body production of  $CO_2$  is unchanged the  $PCO_2$  must return to normal. No sodium was given so the sodium concentration remains constant, but the chloride concentration has increased. The SID (roughly  $[Na^+] - [Cl^-]$ ) has decreased which means that the weak acids must shift their equilibrium position and reduce their weak acid anion concentration. Let's look at the carbonic acid-bicarbonate equilibrium.



At the new equilibrium this must continue to obey the law of mass action. If the bicarbonate concentration decreases and the  $PCO_2$  stays the same the acidity must increase. A similar argument applies to the protein and phosphate buffers whose overall concentration does not change but whose degree of dissociation shifts.



**Figure 2.** Gamblegram of normal plasma



**Figure 3.** Hyperchloeraemic acidosis without respiratory compensation

The crucial thing to understand is that the strong ions are fully dissociated throughout the physiological range of acidity: they are immutable. Just as a fluid changes its shape to conform to the shape of its container, the weak acid anions belonging to the various weak acid equilibria (bicarbonate, proteins, phosphate) must change their equilibrium concentrations to conform to the space available (the SID). Otherwise the solution would violate the requirement that at equilibrium the cations are opposed by an equal concentration of anions.

Remember that under physiological conditions the concentrations of hydrogen and hydroxyl ions are in the nanomolar range, one millionth the scale of the diagram and therefore invisible.

**Why acidity changes: hyperchloeraemic acidosis**

Space permits only one example. Starting with normal plasma and a patient undergoing controlled ventilation, we add sufficient concentrated hydrochloric acid to increase the patient's chloride concentration by 5 mEq/L. The immediate effect is that the hydrogen ions

So to summarise, administration of hydrochloric acid caused an increase in the chloride concentration and a decrease in the SID. The weak acids shifted their equilibrium position, causing the acidity to increase and the bicarbonate concentration to decrease (figure 3). Note that hydrogen ions and bicarbonate ions are entirely passive in this process: their concentration is ultimately determined by the SID,  $PCO_2$  and  $A_{tot}$ . Hydrogen and bicarbonate ions are dependent factors. Understanding this is the key to understanding acid-base physiology.

**THE STRONG ION CALCULATOR**

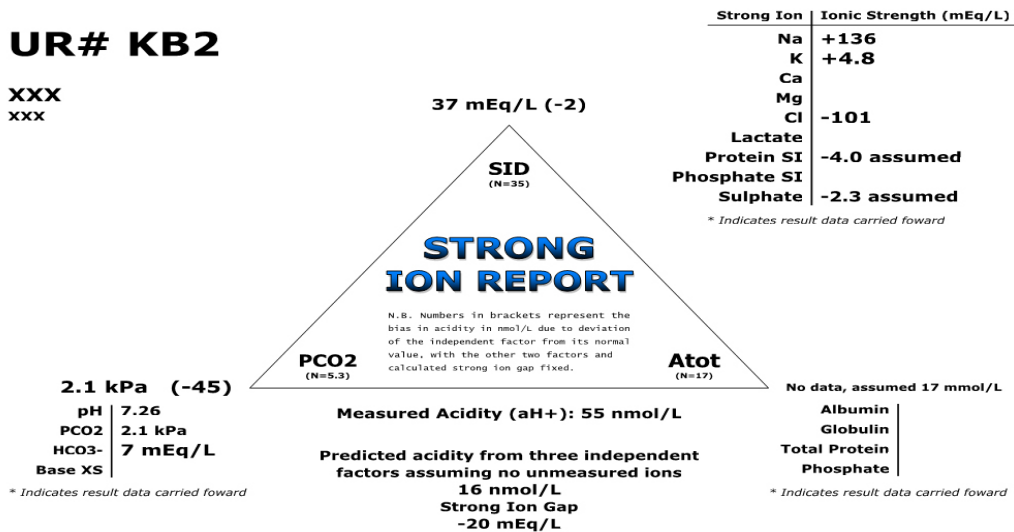
**Description**

This is a tool that applies our quantitative understanding of the relationship between the independent factors and acidity. A simple version is available for download, but a more sophisticated version has been

built into the Hawke’s Bay hospital’s online laboratory information system. This automatically fetches all the relevant parameters from the laboratory database, and, as long as the minimal data set is available, a strong ion report is generated and can be printed, both at the touch of a button. The minimum information required by the strong ion calculator is [Na], [K], [Cl], pH and PCO<sub>2</sub> (in either mmHg or kPa). However, missing data will adversely affect the accuracy of the calculation, so it is recommended that a complete suite of tests is performed for a patient on admission to the ICU. Subsequent tests

are performed as required by the clinical situation. The case illustrated in Figure 4 is a sick diabetic from Kerry Brandis’ online textbook.<sup>12</sup>

The salient features are as follows. Because there are three independent factors, each is placed at the apex of a triangle. This helps the user avoid the “can’t see the wood for the trees” phenomenon. Nearby are tabulated the individual results that contributed to the calculation of each independent factor. Beneath the triangle is the measured acidity (in nmol/L). This is compared with the expected acidity, based on the three independent para-



OVERALL SEVERE ACIDAEMIA FOR ARTERIAL BLOOD (55 nmol/L). SEVERE RESPIRATORY ALKALOSIS BIASES ACIDITY BY -45 nmol/L. MEASURED STRONG ION DIFFERENCE NORMAL. DEVIATION FROM 35mEq/L BIASES ACIDITY BY -2 nmol/L. LACTATE UNMEASURED. LARGE NET CONCENTRATION OF UNMEASURED ANIONS (SIG = -20 mEq/L).

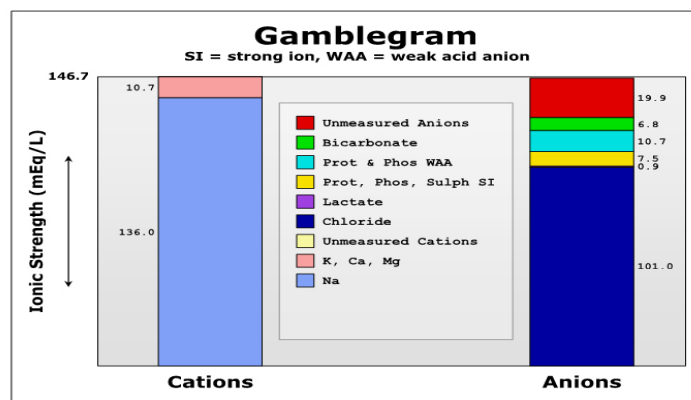


Figure 4. Strong ion calculator graphical report

meters, and using Constable's strong ion gap equation, the net concentration of unmeasured ions is displayed as strong ion gap (SIG).

Finally, the SIG is added to the measured SID, and this composite SID is used together with the  $PCO_2$  and  $A_{tot}$  to calculate the contribution of each factor individually to the total acid-base situation. The acidity is calculated with each independent factor as it is and again with each independent factor in turn returned to its normal value. The difference is the bias in acidity, and it is displayed in brackets after the value for the factor. A positive bias occurs, for example, with an increase in  $PCO_2$  or reduction in SID; a negative bias occurs with a decrease in  $PCO_2$  or protein concentration or an increase in SID. Thus we have two measures of the severity of disturbance of an independent parameter: the difference between its value and its normal value, and the bias in acidity caused by that deviation in the current clinical context. Beneath this is a printed report box and the gamblegram for the patient.

#### Derivations

The details are complicated because the calculator must be able to cope with all combinations of missing data, as long as the minimum data set is provided.

#### $A_{tot}$ calculation

Albumin, like other proteins, is a string of amino acids with an N-terminal at one end and a C-terminal at the other. In theory,<sup>14,15</sup> with MRI-based determination of the dissociation constant of every amino acid along the chain, we could determine the acid-base behavior of albumin as a whole. In practice albumin is but one protein among several in plasma; the rest are collectively called "globulins". For this reason, it is more practical to determine experimentally the overall acid-base behavior of albumin and the plasma proteins. This is precisely what was done by Peter Constable.<sup>10</sup> He showed that proteins have some permanent charge (typically about -4mEq/L) due to acidic residues whose dissociation constants are far higher than the range of acidity seen under physiological conditions. The rest of the charge on proteins is variable and is therefore in dynamic equilibrium with the overall acidity (figure 5). In normal arterial plasma it is about -10 mEq/L. Constable determined that plasma  $A_{tot}$  can be modelled as a monovalent acid with a dissociation constant of 80 nmol/L and a normal concentration of 17.2 mmol/L. The mean albumin, globulin and phosphate concentrations in Constable's study were 45.5g/L, 31.4 g/L and 1.2mmol/L, respectively.<sup>10</sup>

Sigaard-Andersen has shown that albumin, globulins and phosphate normally buffer in the proportions 73%, 22% and 5% respectively.<sup>16</sup> Based on the fact that the

normal  $A_{tot}$  is 17.2 mmol/L and albumin and globulin contribute buffering in the ratio  $(.73/.22)/(45.5/31.4) = 2.28991$  by mass, and phosphate is 2 mmol/L of buffer per mmol/L concentration:

#### 1. Albumin + total protein measured

Let x be the  $A_{tot}$  mmol per gram of globulin

$$17.2 = 2.28991 * x * 45.5 + x * 31.4 + 2.4$$

$$A_{tot} = 0.262733 * [\text{albumin}] + 0.0906257 * [\text{globulin}] + 2 * [\text{phosphate}]$$

#### 2. Albumin only measured

$$17.2 = 45.5 * x + 2.4$$

$$A_{tot} = 0.325275 * [\text{albumin}] + 2 * [\text{phosphate}]$$

#### 3. Total protein only measured

$$17.2 = 76.9 * x + 2.4$$

$$A_{tot} = 0.192458 * [\text{total protein}] + 2 * [\text{phosphate}]$$

#### 4. Neither total protein nor albumin measured

$A_{tot}$  defaults to  $14.8 + 2 * [\text{phosphate}]$ . If phosphate also was not measured its value defaults to 1.2 mmol/L, so in conclusion the default  $A_{tot}$  is 17.2 mmol/L if nothing was measured. Note that the spurious precision of the decimals is an artifact of long division, and the calculator rounds off its results appropriately before displaying them.

#### Phosphate

Phosphoric acid dissociates to dihydrogen phosphate, then monohydrogen phosphate, then phosphate. At physiological acidity, dihydrogen phosphate exists in equilibrium with monohydrogen phosphate. The concentrations of the parent acid or pure phosphate ion are effectively zero. At 37°C the  $K_a$  for the dihydrogen phosphate  $\leftrightarrow$  monohydrogen phosphate equilibrium is 219 nmol/L.<sup>14</sup>

Some buffer ions have real behavior that deviates from ideal, necessitating the use of ionic strength rather than concentration.<sup>17</sup> In the area of acid-base physiology, four ions deviate significantly from ideal: monohydrogen phosphate, calcium, magnesium and sulphate. For each of these ions, their behavior is as if they each have an ionic charge of three, not two. The other ions with a charge of +1 or -1 behave as expected.

First it is necessary to state two equations for a generalised acid: the law of mass action (1) and the law of conservation of mass (2)

$$K_a = aH^+ * [A^-] / [HA] \quad (1)$$

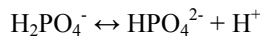
$$[HA] + [A^-] = [A_{tot}] \quad (2)$$

where  $aH^+$  is the acidity measured with a pH meter and expressed on a linear scale, and  $K_a$  is the apparent dissociation constant for the reaction.

Combining (1) and (2) and rearranging, we get

$$[A^-] = [A_{tot}]/(1+aH^+/K_a) \quad (3)$$

For the dihydrogen phosphate to monohydrogen phosphate reaction, we get:



$H_2PO_4^-$  is the acid and has a charge of -1mEq/mmol,  $HPO_4^{2-}$  is the weak acid anion and has an ionic strength of -3mEq/mmol.

Since all phosphate in plasma is either dihydrogen phosphate or monohydrogen phosphate, we write:

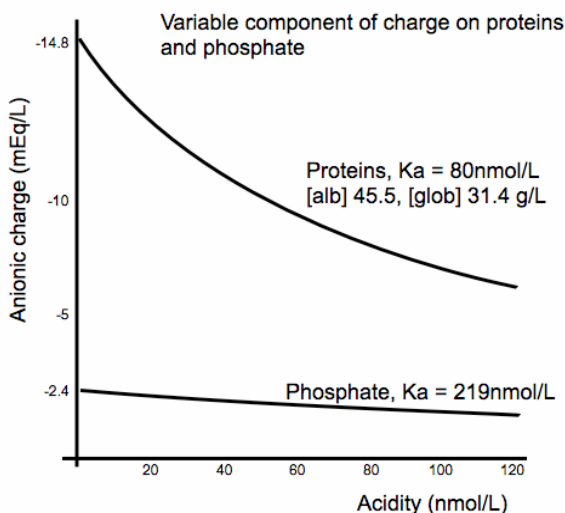
$$[H_2PO_4^-] + [HPO_4^{2-}] = [\text{phosphate}]$$

Substituting, and using 3 for the ionic strength of monohydrogen phosphate, we get

Phosphate charge

$$\begin{aligned} &= -3*[\text{monohydrogen phosphate}] \\ &\quad -1*[\text{dihydrogen phosphate}] \\ &= -[\text{phosphate}] (3/(1+aH^+/K_a) \\ &\quad + 1 (1-1/(1+aH^+/K_a))) \\ &= -([\text{phosphate}] + 2*[\text{phosphate}]/(1+aH^+/K_a)). \end{aligned}$$

So the fixed phosphate charge is -1 mEq/mmol and the variable charge is  $-2/(1+aH^+/K_a)$  mEq/mmol (figure 5)



**Figure 5.** The variable charge on proteins and phosphate in normal plasma. The additional permanent charge (-1.2 mEq/L for phosphate, -4 mEq/L for proteins) is not depicted here

*Strong ion difference*

The strong ion calculator takes the concentrations of the measured strong electrolytes (and in the case of calcium and magnesium converts the concentration into ionic strength). The only strong ion that is not routinely available for analysis in modern medical laboratories is sulphate. Its concentration can increase greatly in renal failure. Most papers have assumed a concentration of 0.75 mmol/L, giving it an ionic strength of -2.25 mEq/L.

The fixed (strong) anionic charges on proteins and phosphate are calculated, depending on what has been measured. If nothing was measured the calculator assumes a normal value. The equations were derived as follows. Constable measured the fixed charge on proteins (-4 mEq/L).<sup>10</sup> This, together with the concentrations of albumin and globulin in Constable's study allows us to discover the amount of charge per gram of globulin and albumin.

The charge on albumin per gram was calculated as 2.28991 times the charge on globulin (this is based on the relative buffer charge), because no direct data is available:

1. Both albumin and total protein measured

$$\begin{aligned} \text{SID} = & [Na^+] + [K^+] + 3*[Ca^{2+}] + 3*[Mg^{2+}] \\ & - [Cl^-] - [lactate^-] \\ & - 0.0683456*[albumin] - 0.0298464*[globulin] \\ & - [phosphate] - 3*[sulphate] \end{aligned}$$

2. Albumin only measured (the factor 0.090 comes directly from Constable<sup>10</sup>)

$$\begin{aligned} \text{SID} = & [Na^+] + [K^+] + 3*[Ca^{2+}] + 3*[Mg^{2+}] \\ & - [Cl^-] - [lactate^-] \\ & - 0.090*[albumin] - [phosphate] - 3*[sulphate] \end{aligned}$$

3. Total protein only measured (the factor 0.052 comes directly from Constable<sup>10</sup>):

$$\begin{aligned} \text{SID} = & [Na^+] + [K^+] + 3*[Ca^{2+}] + 3*[Mg^{2+}] \\ & - [Cl^-] - [lactate^-] \\ & - 0.052*[total protein] - [phosphate] - 3*[sulphate] \end{aligned}$$

4. Neither albumin nor total protein measured

$$\begin{aligned} \text{SID} = & [Na^+] + [K^+] + 3*[Ca^{2+}] + 3*[Mg^{2+}] \\ & - [Cl^-] - [lactate^-] \\ & - 4 - [phosphate] - 3*[sulphate] \end{aligned}$$

*Strong ion gap*

The strong ion calculator uses the general result that  $[A^-] = ([HA] + [A^-])/(1+aH^+/K_a)$ . So if both the acidity

and the total concentration ([HA] + [A<sup>-</sup>]) of each of the weak acid species are known, the concentration of each species' anion can be calculated. This can now be fed into the electroneutrality equation:

$$\left( \begin{array}{l} \text{Measured Strong Cations} + \\ \text{Unmeasured Strong Cations} \end{array} \right) = \left( \begin{array}{l} \text{Measured Strong Anions} + \\ \text{Unmeasured Strong Anions} + \\ \text{[Bicarbonate]} + \\ \text{[Albumin Weak Acid Anion]} + \\ \text{[Globulins Weak Acid Anion]} + \\ \text{[Phosphate Weak Acid Anion]} \end{array} \right) \quad (4)$$

$$\text{We define strong ion gap (SIG) = [Unmeasured strong cations]} - [\text{Unmeasured strong anions}] \quad (5)$$

Combining equations 4 and 5 and rearranging gives us the strong ion gap equation 6, which gives the net concentration of unmeasured strong ions. Its normal value is zero. A negative SIG signifies net unmeasured anions. A positive SIG is uncommon, and if severe it most likely represents paraproteinaemia<sup>13</sup>, because the abnormal proteins carry less negative charge than would be expected from their concentration. In practice, a SIG more than 5 mEq/L or less than -5 mEq/L is significant.

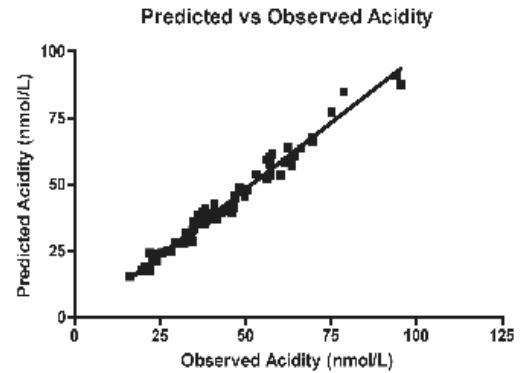
$$\text{SIG} = \left( \begin{array}{l} \text{[Bicarbonate]} + \\ \text{[Albumin Weak Acid Anion]} + \\ \text{[Globulin Weak Acid Anion]} + \\ \text{[Phosphate Weak Acid Anion]} \end{array} \right) - \text{SID} \quad (6)$$

1. Both albumin and total protein measured  
 $\text{SIG} = [\text{bicarbonate}] + 0.0262733 * [\text{albumin}] / (1 + a\text{H}^+ / 80) + 0.0906257 * [\text{globulin}] / (1 + a\text{H}^+ / 80) + 2 * [\text{phosphate}] / (1 + a\text{H}^+ / 219) - \text{SID}$
2. Albumin only measured  
 $\text{SIG} = [\text{bicarbonate}] + 0.325275 * [\text{albumin}] / (1 + a\text{H}^+ / 80) + 2 * [\text{phosphate}] / (1 + a\text{H}^+ / 219) - \text{SID}$
3. Total protein only measured  
 $\text{SIG} = [\text{bicarbonate}] + 0.192458 * [\text{total protein}] / (1 + a\text{H}^+ / 80) + 2 * [\text{phosphate}] / (1 + a\text{H}^+ / 219) - \text{SID}$
4. Neither albumin nor total protein were measured  
 Defaults to first equation with assumed normal albumin and globulin concentrations.

*Performance*

The strong ion calculator was tested against a reference laboratory data set.<sup>14</sup> These subjects were different from those whose data were used to develop the calculator. First the observed acidity was plotted against predicted acidity (Figure 6), together with a

linear regression.



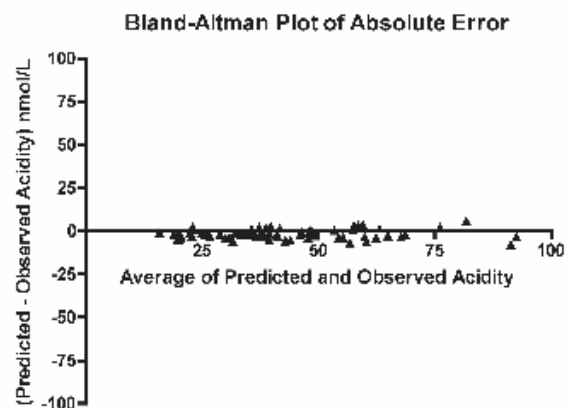
**Figure 6.** Performance of strong ion calculator: predicted vs. observed acidity for a reference laboratory data set. The slope is 0.9989 and R<sup>2</sup> is 0.9766

Another method to assess the performance of the calculator is to use a Bland-Altman plot,<sup>18,19,20</sup> (Figure 7). In this case the strong ion calculator had a bias of -1.8 nmol/L and a precision of 2.7nmol/L (compared with a normal arterial plasma acidity of 40 nmol/L).

*Precision*

One concern that has been expressed about the quantitative approach to acid-base physiology is that the measurement of SID (and to a lesser extent A<sub>tot</sub>) depends on multiple measurements, each of which is subject to its own laboratory error, and that calculations such as predicted acidity or SIG will suffer so badly from the cumulative error that they will be useless.

Whilst it is possible to calculate exactly the standard deviation of a sum (because variances add), it is not possible to do this for more complex calculations such as the simplified strong ion equation or the strong ion gap equation. In this case it is necessary to determine the standard deviation experimentally by performing a Monte Carlo simulation.



**Figure 7.** Bland-Altman plot of (predicted - observed) vs. (average of predicted and observed) acidity in a reference laboratory data set.

Using a computer<sup>21</sup> and appropriate software<sup>22</sup> an array of 4 million virtual patients was created to test the variability of derived parameters given laboratory imprecision. Each patient parameter, such as [sodium], was simulated as a normally-distributed variable with the standard deviation corresponding to the precision obtained in my laboratory's quality control activities (Mr. J. Greenwood, Charge Technologist (Biochemistry Laboratory), Hawke's Bay Regional Hospital, Personal communication). The standard deviation of the calculated acidity and SIG in this array was 2 nmol/L and 0.03mEq/L respectively. The small laboratory error allows us to use quantitative analysis of acid-base in individual patients.

#### Comparison with traditional acid-base analysis

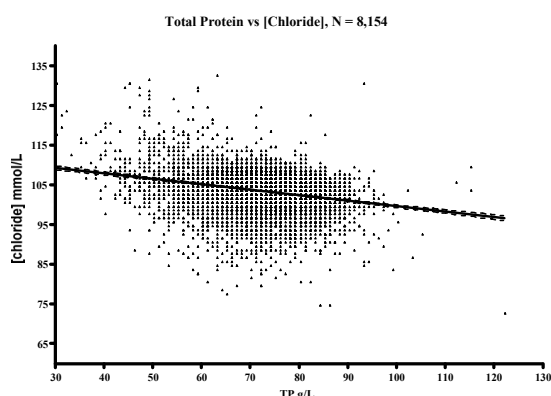
Strong ion analysis is performed on intact, non-haemolysed whole blood. The pH and ion electrodes are in physical contact with plasma. Plasma must simultaneously satisfy all the physicochemical equations discussed earlier, therefore strong ion analysis is appropriately done on plasma and no attempt is made to extrapolate its results to the intracellular compartment or the whole body.

Base excess is calculated on whole blood using the Van Slyke equation<sup>7</sup>

$$BE = \{[HCO_3^-] - 24.4 + (2.3*[Hb] + 7.7)*(pH - 7.4)\}*(1 - 0.023*[Hb])$$

where bicarbonate is calculated from plasma with the Henderson-Hasselbalch equation (i.e. from pH and PCO<sub>2</sub>), and [Hb] is in mmol/L.

The normal renal response to chronic hypoproteinaemia is to retain chloride. Proteins are weak acids. The primary hypoproteinaemic alkalosis is compensated by a strong ion acidosis, Figure 8.



**Figure 8.** Scatterplot of all laboratory results for a 3-month period in which both [total protein] and [chloride] were simultaneously measured. A linear regression with 95% confidence interval for the slope is included.

The chloride concentration increases 1.4 mmol/L for every 10 g/L reduction in [total protein]. When a patient is on or near the linear regression line, the base excess and the SIG agree closely. When not (and this happens frequently as can be seen), BE and SIG disagree. The main reason is that the base excess calculation is done with incomplete information. It has no knowledge of either the strong ions or the weak electrolyte concentrations: it looks only at the relationship between pH and PCO<sub>2</sub>.

The anion gap (AG) was an improvement on base excess because AG is calculated from [Na<sup>+</sup>], [K<sup>+</sup>], [Cl<sup>-</sup>], pH and PCO<sub>2</sub>. It is no coincidence that the anion gap ranges between 8 - 18 mmol/L and the total charge on proteins and phosphate is 17 mEq/L when these are normal. The SIG is more sensitive to the presence of unmeasured anions than is the AG because, in a patient with hypoproteinaemia, the concentration of unmeasured anions has to be very large before the AG reaches the threshold. Only quantitative strong ion analysis formally looks at all three independent factors simultaneously. The SIG is like an "anion gap on steroids".

Finally, the SIG will detect unmeasured anions in venous blood as well as arterial, which makes strong ion analysis a useful screening tool for poisoning or metabolic states in which there are unmeasured anions present in the blood.

#### Conclusion

All diseases and all therapies can affect a patient's acid-base status only through the final common pathway of one or more of the three independent factors. With Constable's equations we can now accurately predict the acidity of plasma. When there is a discrepancy between the observed and predicted acidity we can deduce the net concentration of unmeasured ions to account for the difference. We can also answer practical questions, such as "Is this patient's acidaemia appropriate for the degree of hypercapnia plus hyperchloraemia in the context of their concurrent hypoproteinaemia?" Such questions cannot be answered exactly with traditional methods.

Quantitative acid-base physiology has moved out of the academic realm and is now a practical tool for clinicians.

#### Acknowledgements

Thanks to Jim Greenwood, John Gush, Mike Kuzman and Dr Peter Constable for their help, expert-ise and advice. Mike Kuzman is the man to ask about implementing the strong ion calculator in your own hospital's online laboratory system and may be contacted by telephone (+64 6 8788109) or by e-mail (Mike.Kuzman@hawkesbaydhhb.govt.nz).

Received: 5 July 2004  
Accepted: 19 July 2004

## REFERENCES

1. Constable PD. Hyperchloremic acidosis: the classic example of strong ion acidosis. *Anesth Analg* 2003;96:919-22
2. Wooten EW. Calculation of physiological acid-base parameters in multicompartiment systems with application to human blood. *J Appl Physiol* 2003;95:2333-2344
3. Wooten EW. Analytic calculation of physiological acid-base parameters in plasma. *J Appl Physiol* 1999;86:326-334
4. Singer RB, Hastings AB. An improved clinical method for the estimation of disturbances in the acid-base balance of human blood. *Medicine (Baltimore)*; 1948;27:223-242
5. Stewart PA. Independent and dependent variables of acid-base control. *Respir. Physiol* 1978;33:9-26
6. Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* 1983;61:1444-1461
7. Morgan TJ. Standard base excess. *Australasian Anaesthesia* 2003, Pages 98-99
8. Constable PD. A simplified strong ion model for acid-base equilibria: application to horse plasma. *J Appl Physiol* 1997;83:297-311
9. Constable PD. Total weak acid concentration and effective dissociation constant of nonvolatile buffers in human plasma. *J Appl Physiol* 2001;91:1364-1371
10. Constable PD. Experimental determination of net protein charge and  $A_{tot}$  and  $K_a$  of nonvolatile buffers in human plasma. *J Appl Physiol* 2003;95:620-630
11. Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow-up. *J Lab Clin Invest* 1992;120:713-719
12. [http://www.qldanaesthesia.com/AcidBaseBook/AB9\\_6Case2.htm](http://www.qldanaesthesia.com/AcidBaseBook/AB9_6Case2.htm)
13. Fencl V, Leith DE. Stewart's quantitative acid-base chemistry: applications in biology and medicine. *Respir Physiol* 1993;91:1-16
14. Figge J, Rossing TH, Fencl V. The role of serum proteins in acid base equilibria, *J Lab Clin Med* 1991;117:453-67
15. Figge J, Mydosh T, Fencl V. Serum proteins and acid base equilibria: a follow-up, *J Lab Clin Med* 1992;120:713-719.
16. Sigaard-Andersen O, Rorth M, Strickland DAP. The buffer value of plasma, erythrocyte fluid and whole blood. In: Workshop on pH and Blood Gases, 1975. Washington DC: National Bureau of Standards, 1977, p11-19.
17. Biochemistry 221, Buffer Capacity, Ionic Strength, and Tables of pKa, [www.biochem.perdue.edu/~courses/undergrad/221/wwwboard/handouts/supplemental/buffer.pdf](http://www.biochem.perdue.edu/~courses/undergrad/221/wwwboard/handouts/supplemental/buffer.pdf)
18. Bland MJ, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;ii:307-310.
19. Bland MJ, Altman DG. Comparing methods of measurement: why plotting difference against standard method is misleading. *Lancet* 1995;346:1085-1087.
20. Myles, Paul S, Gin T. Statistical methods for anaesthesia and intensive care. Butterworth Heineman 2000, Reprinted 2001, Pages 90-91.
21. Macintosh PowerBook G4 1GHz with 1GB RAM
22. Mathematica 5.0.1.0, Copyright Wolfram Research, Inc 1988-2003