

# The Physico-chemical Theory of Acid-Base Balance

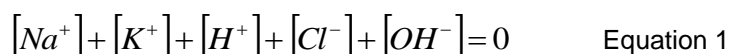
As for most fields of science, there are competing arguments, or debates, regarding key concepts and interpretations of data. The field of acid-base chemistry is a notable example of this. I have decided to include this topic within this textbook because it reveals the dynamic nature of science, the important quest in science to challenge anything and everything, and the potential cost of knowledge if this challenge does not adhere to the rules of the scientific method. The added benefit of this content is that it reinforces the importance of multiple competing cations to the binding of base negative charges.

In 1981, the late **Peter Stewart** (Figure 1), a Canadian physiologist working in the U.S., proposed a new method for estimating and explaining blood acid-base balance. Peter argued that the traditional academic explanation of acid-base balance, which was based on the **Henderson-Hasselbalch equation** and related conjugate acid-base view of proton release and buffering, was in error due to its inability to account for the balance of charge. Peter based his approach at quantifying acid-base disturbances on the principle of **electro-chemical neutrality**, where the net charge of the positively and negatively charged components in solution must equal zero.



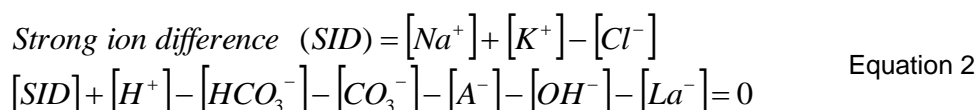
**Figure 1.** photograph of Peter Stewart, who died of complications from heart failure in 1993.

Such an expression can be presented mathematically, as done in Equation 1 for the main ionic elements of body fluid sodium ( $\text{Na}^+$ ), potassium ( $\text{K}^+$ ), chloride ( $\text{Cl}^-$ ), hydroxyl ( $\text{OH}^-$ ) groups and protons ( $\text{H}^+$ ).



Now, Equation 1 would be easy to apply and solve, but there are additional charged molecules in body fluids besides ions and cations. Such added charged components are proteins, and metabolites such as lactate ( $\text{La}^-$ ) and bicarbonate ( $\text{HCO}_3^-$ ). To add more complexity, bicarbonate is also influenced by blood  $\text{PCO}_2$ . Thus, components need to be included that account for proteins, lactate and the **bicarbonate- $\text{CO}_2$ -ventilation system**.

To improve on Equation 1, as a component of the total calculations needed to account for this electrochemical neutrality approach, it can be re-expressed as Equation 2, showing the entity known as the **strong ion difference**.



Equation 2 is not used to solve for  $[\text{H}^+]$  as there are other equations that include some of these variables that also need simultaneous computation. These additional

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equations are presented in Equations 3 to 8, with equation 8 being the final fourth order polynomial for solving the  $[H^+]$ .

$$K_A = 3.0 \times 10^{-7}; K_w (37^\circ C) = 4.4 \times 10^{-14}; K_c = 2.46 \times 10^{-11}; K_3 = 1.66 \times 10^{-12} \quad \text{Equation 3}$$

$$a = [SID] + K_A \quad \text{Equation 4}$$

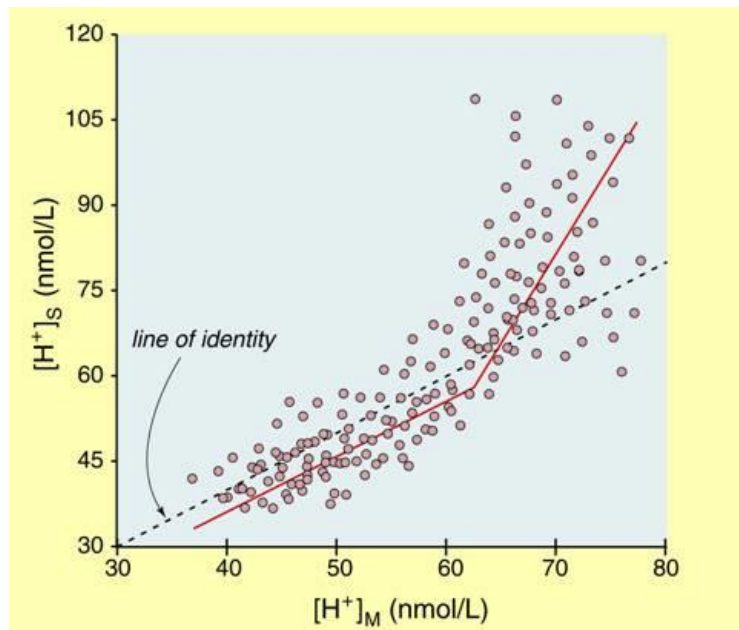
$$b = K_A ([SID] - [A_{TOT}]) - (K_c \times PCO_2 \times K_w) \quad \text{Equation 5}$$

$$c = K_A (K_c \times PCO_2 \times K_w) + (K_3 \times K_c \times PCO_2) \quad \text{Equation 6}$$

$$d = (K_A \times K_3 \times K_c \times PCO_2) \quad \text{Equation 7}$$

$$0 = [H^+]^4 + a[H^+]^3 + b[H^+]^2 - c[H^+] - d \quad \text{Equation 8}$$

By treating  $[H^+]$  as the only unknown of Equation 8, computation can occur to solve for  $[H^+]$  and hence pH. To do this accurately, precise values for all other variables of Equations 3 to 8 need to be known. While this sounds straight forward in theory, the inability to acquire accurate values for  $[A_{TOT}]$  and venous  $PCO_2$  (when applying to venous blood) limits application of this approach. Furthermore, there is no way to accurately apply this approach to intracellular **acid-base balance**, especially for excitable cells that oppose electrochemical neutrality through the generation and maintenance of the membrane potential.



**Figure 2.** Data from research from Kowalchuk and Schueermann (1993) of the error associated with using the Stewart approach to calculate blood pH. Note the marked skewed computation of pH below a pH value of 6.26 (65 nmol/L). Adapted from Kowalchuk JM, Schueermann BW. *Can J Physiol Pharmacol.* 1993;72:818-826.

Research that has attempted to validate the Stewart approach by comparing computed to measured blood pH has proven unsupportive of the accuracy and validity of Equations 3 to 8. For example, researchers have reported a correlation coefficient for measured and calculated blood pH of only 0.81 (Figure 2), indicating that the Stewart approach only explained 66% of the variability in measured blood pH. Added concern was raised, as also shown in Figure 2, with a consistent under prediction of the  $[H^+]$

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(over prediction of pH) between pH 7.5 to 6.63. Of added concern is the skewed distribution of the data (greater error) above a  $[H^+]$  of 65 nmol/L (pH<6.26) involving a reversal to an over prediction of the  $[H^+]$ . Unfortunately, the premature death of Peter Stewart in 1993 from complications from heart failure was a loss in and of itself, but it also largely muted the needed critical reflection of competing explanations of metabolic acidosis; the “Stewart approach” vs. the “Henderson Hasselbalch” approach, vs. an alternate, perhaps combined, explanation. Today, the field of acid-base physiology and the conglomerate of acid-base physiologists still remain far from united on the cause and explanation of metabolic acidosis!

## Glossary Words

**Peter Stewart** was a Canadian physiologist who proposed a method of computing and understanding changes in acid-base balance based on physico-chemical principles.

**Henderson-Hasselbalch equation** expresses the components of pH, the pKa, and the ratio of free base to acid concentrations for an acid-base pair.

**electro-chemical neutrality** is the principle based on the retention of neutral charge that has to be maintained despite changes in the production or removal of metabolites of positive or negative charge.

**bicarbonate-CO<sub>2</sub>-ventilation system** is the proton buffering system comprising blood bicarbonate ( $HCO_3^-$ ), carbon dioxide ( $CO_2$ ) and pulmonary ventilation.

**strong ion difference** is the electrochemical (mEq/L) difference between the sum of sodium and potassium ( $Na^+ + K^+$ ) minus chloride ( $Cl^-$ ).

**acid-base balance** refers to the net status of the components known to influence the pH of body fluids.