A mathematical model of blood-interstitial acid-base balance: application to dilution acidosis and acid-base status

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Wolf MB, DeLand EC. A mathematical model of blood-interstitial acid-base balance: application to dilution acidosis and acid-base status. J Appl Physiol 110: 988–1002, 2011. First published January 6, 2011; doi:10.1152/japplphysiol.00514.2010.—We developed mathematical models that predict equilibrium distribution of water and electrolytes (proteins and simple ions), metabolites, and other species between plasma and erythrocyte fluids (blood) and interstitial fluid. The models use physicochemical principles of electroneutrality in a fluid compartment and osmotic equilibrium between compartments and transmembrane Donnan relationships for mobile species. Across the erythrocyte membrane, the significant mobile species Cl− is assumed to reach electrochemical equilibrium, whereas Na+ and K+ distributions are away from equilibrium because of the Na+/K+ pump, but movement from this steady state is restricted because of their effective short-term impermeability. Across the capillary membrane separating plasma and interstitial fluid, Na+, K+, Ca2+, Mg2+, Cl−, and H+ are mobile and establish Donnan equilibrium distribution ratios. In each compartment, attainment of equilibrium by carbonates, phosphates, proteins, and metabolites is determined by their reactions with H+. These relationships produce the recognized exchange of Cl− and bicarbonate across the erythrocyte membrane. The blood submodel was validated by its close predictions of in vitro experimental data, blood pH, pH-dependent ratio of H+, Cl−, and HCO3− concentrations in erythrocytes to that in plasma, and blood hematocrit. The blood-interstitial model was validated against available in vivo laboratory data from humans with respiratory acid-base disorders. Model predictions were used to gain understanding of the important acid-base disorder caused by addition of saline solutions. Blood model results were used as a basis for estimating errors in base excess predictions in blood by the traditional approach of Siggaard-Andersen (acid-base status) and more recent approaches by others using measured blood pH and Pco2 values. Blood-interstitial model predictions were also used as a basis for assessing prediction errors of extracellular acid-base status values, such as by the standard base excess approach. Hence, these new models can give considerable insight into the physicochemical mechanisms producing acid-base disorders and aid in their diagnoses.

base excess; standard base excess; acid-base disorders; dilution acidosis; Van Slyke equation; Siggaard-Andersen nomogram; Stewart approach

ANALYTICAL DESCRIPTIONS of the physicochemical properties of blood are required to predict steady-state changes in blood acid-base chemistry over a wide range of conditions. Such descriptions, using fundamental principles of electrochemical and osmotic equilibria, have been sought from the early decades of the 20th century (5, 17, 18, 41), but the use of these for understanding of human acid-base balance and its disorders was cumbersome. The more recent blood base excess (BE) approach by Siggaard-Andersen (35, 37, 38) and the plasma strong-ion difference (SID) approach of Stewart and adherents (2, 19, 39) and its application to blood and blood-interstitial fluid by Wooten (42, 44) have given more insight into understanding and diagnosing acid-base disorders, but each has limitations, leading to controversies about their accuracy and usefulness.

Development of computer technology and simulation languages has provided the means to gain greater insight into acid-base chemistry of complex body fluid systems. Early in the history of digital computers, DeLand and co-workers (3, 4) used principles of chemical equilibrium thermodynamics, as suggested earlier by Henderson (17), to formulate complex models for blood alone and for blood and interstitial and intracellular fluids in chemical communication. To account for ions not at equilibrium, such as Na+ and K+, a constant Gibbs free-energy parameter (the energy of the ion pump) was assigned to them. Hence, these mobile ions attained steady-state distributions across membranes, whereas other mobile ions distributed in a Donnan equilibrium. Another hallmark of DeLand’s models was the detailed description of the interactions of hemoglobin with O2 and H+. The solution to the equations in the DeLand models involved complex algorithms aimed at minimizing the total free energy of the chemical system. Understandably, the solution time was exceedingly long with the relatively slow computers of that day. Today, the availability and speed of personal computers greatly decrease the difficulty of solving these equations and allow for other approaches to determine equilibrium and steady states in biochemical systems.

A more recent effort was the much more simplified computer model of Raftos et al. (30), which used equilibrium principles to simulate the acid-base chemistry of erythrocytes suspended in a water-electrolyte environment of varying pH. Water could move across the erythrocyte membrane, along with Cl− and other anions, but the membrane was assumed to be effectively impermeable to other species, such as Na+ and K+. The latter ions are maintained away from equilibrium by the Na+/K+ pump phenomenon. An additional simplification was that the pH-dependent electrical charge for hemoglobin was described by only a three-parameter equation, instead of the 10 parameters used by DeLand (3). The model of Raftos et al. was able to accurately predict pH and hematocrit changes as measured by them in erythrocyte suspensions. Most recently, Rees and Andreassen (31) devised a computer model of blood chemistry that could accurately predict the results of the Siggaard-Andersen nomogram (35) over the physiological pH range; however, the generality of the model was limited, because fundamental model parameter values were chosen to achieve this end.
The present study takes the approach of Raftos et al. (30) for simulating the erythrocyte acid-base chemistry and exchanges across the erythrocyte membrane, but it also simulates plasma and interstitial compartments. Hence, the purposes of this study are to 1) describe and justify the blood and blood-interstitial models, 2) validate these models using experimental data on pH, electrolyte, and water distribution using a variety of experimental data in the literature, 3) use the clinical condition of saline acidosis to demonstrate the ability of the models to explain complex causes of acid-base disorders not easily understood using previous approaches, 4) demonstrate the ability of these models to predict clinical acid-base data where the only metabolic disturbance is gain or loss of HCl, as in the Siggaard-Andersen BE approach (35), and 5) use model predictions as a basis for estimating errors in prediction by other approaches in vitro and in vivo.

**Glossary**

- **\(A_{tot}\)**: Concentration of nonbicarbonate buffers in plasma (meq/l

- **AG**: Anion gap (meq/l

- **BE**: Base excess [blood (meq/l

- **C**: Concentration (g/l, mmol/l, meq/l

- **Hct**: Hematocrit

- **IPE**:Interstitial-plasma-erythrocyte compartments

- **K**: Equilibrium constant

- **l_{IPE}**: Liters in IPE

- **l_{I}**: Liters in compartment \(j\)

- **l_{p}**: Liters in plasma

- **M**: Mass, mmol

- **P**: Partial pressure (Torr

- **S**: Solubility (mmol·l \(^{-1}\)·Torr \(^{-1}\)

- **Sat**: Hemoglobin O2 saturation (%

- **SBE**: Standard base excess (meq/l

- **SID**: Strong ion difference (meq/l

- **SIG**: Strong ion gap (meq/l

- **V**: Volume (liters

- **Z**: Ionic valence (meq/mmol

- **a**: Arterial

- **f**: Fractional

- **im**: Impermeable species

- **oxy**: Fully oxygenated blood

- **pK**: -log \(_{10}\) (\(K\))

- **r**: Ion ratio

- **s**: Solute

- **v**: Venous

- **z_0, z_1, z_2**: Empirically determined coefficients

- **\(\Delta\)**: Change from reference state

- **\(\varepsilon\)**: Negligibly small number

- **\(\Phi\)**: Osmotic coefficient

**Subscripts and superscripts**

- **0**: Reference state

- **eff**: Effective

- **Alb**: Serum albumin

- **B**: Blood

- **E**: Erythrocytes

- **EW**: Erythrocyte water

- **Hb**: Hemoglobin

- **I**: Interstitial fluid

- **P**: Plasma

- **P_i**: Phosphate

- **PW**: Plasma water

- **W**: Water

**METHODS**

The basic electrochemical, interstitial-plasma-erythrocyte (IPE) model computes concentrations of a number of ionic species and fluid volumes in blood (plasma and erythrocytes) in equilibrium with a third buffering compartment, interstitial fluid. Each of the three fluids is considered a homogeneous compartment constrained to electroneutrality. A fundamental requirement governing solute and water distribution at equilibrium is that each compartment attains the same osmolality. The three compartments are in equilibrium with a gas phase of constant CO2 concentration. Hence, it is an open system where CO2 and, hence, carbonates are not conserved. Water volumes and masses of all other species, except H\(^+\), are conserved.

The major permeant (mobile) ion considered across the erythrocyte membrane is Cl\(^-\). Its equilibrium distribution is described by an electrical charge-dependent Donnan ratio between plasma and erythrocytes. H\(^+\) is also considered to be at electrochemical equilibrium.

Hence, the equilibrium distributions of Cl\(^-\) and H\(^+\) are related. The permeant ions across the capillary membrane separating plasma and interstitial fluid are the cations Na\(^+\), K\(^+\), Ca\(^{2+}\), Mg\(^{2+}\), H\(^+\) and the anions Cl\(^-\), H\(_2\)PO\(_4\)\(^-\), and HPO\(_4\)\(^2-\). They are described by appropriate Donnan ratios across this membrane. Bicarbonate and carbonate concentrations in each compartment are determined from compartment pH and PCO2 values (PCO2 assumed equal in all compartments) and the Henderson-Hasselbalch equation (pK assumed equal in all compartments). Hence, the equilibrium distribution of bicarbonate is related to that of Cl\(^-\).

Following the approach of Raftos et al. (30), identified, impermeable ions inside the erythrocyte are the charged macromolecule hemoglobin, the metabolites 2,3-diphosphoglycerate (DPG), ATP, and GSH, and the small ions Na\(^+\) and K\(^+\). There is an additional unidentified, impermeable ion, the mass and charge of which are adjusted to help match the model normal state to the reference state of the system (see below). The identified, impermeant ion in plasma and interstitial fluid is serum albumin; there are unidentified, impermeant anions in these compartments, as well, and the masses and charges of these anions are also adjusted to match the model concentrations to the concentrations in the reference (normal) state. The pH-dependent charges of the identified, impermeable ions, other than Na\(^+\) and K\(^+\), are determined using the approach of Raftos et al. (30), as described below. Binding of ions such as Cl\(^-\) and Ca\(^{2+}\) to these macromolecules is not considered.

When model predictions were compared with experimental data from experiments on blood in vitro, the interstitial compartment was excluded from the model and 1 liter of blood was the reference state. The blood model solution was for equilibration in a period \(1\ h\) after the perturbation (30). Almost always, the experimental conditions were for fully oxygenated arterial blood. In contrast, for comparisons in vivo, the model blood was converted to venous, because it is venous blood that is in equilibrium with the interstitial fluid. Venous blood is obtained by changing arterial PCO2 (PaCO2) to venous PCO2 (PvCO2) and modifying the charge on hemoglobin (see below) for the reduced O2 saturation value in venous blood. The latter model is based on 5 liters of blood and 10 liters of interstitial fluid for direct comparison of model predictions of acid-base status with those of Siggaard-Andersen (38) and Wooten (42, 44).

The models directly predict chemical variables such as pH and ions concentrations in the various compartments; however, many studies report derived variables, such as BE of blood, standard BE (SBE) for extracellular fluid, or SID of plasma as computed from measured quantities, as in Eqs. 14–17. These quantities are often used to diagnose the acid-base disorder. We will show how the model can be used in similar diagnostic procedures and compare our results with those in the literature.
Model Equations

In the following equations, $C_s^F$ represents concentration (mmol/l) of solute $s$ in compartment or fluid $J$. This concentration can be expressed in liters of erythrocytes (E), plasma (P), interstitial fluid (I), or water (W) in each of these compartments. Hence, $C_{PW}^s$ represents the concentration of Na$^+$ in plasma water (mmol/l$_{PW}$). Since the volume of interstitial fluid (V$I$) is considered to be all water, I denotes the water content of this volume.

Electroneutrality in each compartment. Each ion in the model has an electrical valence (Z), which has a magnitude and an electrical sign. For electroneutrality in a compartment, the algebraic sum of the products of Z and C of all ions in the compartment must equal $\epsilon$, a negligibly small number. For the following equations, it is most convenient to express volumes (V) in terms of liters of water. Hence, for plasma, for example, concentrations are in millimoles per liter of plasma water. For ions where Z = 1, only the concentration part of the term is included. Hence, for plasma water (ignoring superscripts)

$$C_{Na} + C_K + 2 \times C_{Ca} + 2 \times C_{Mg} - C_{Cl} - C_{HCO_3} - 2 \times C_{CO_3} + Z_{Pi} \times C_{Pi} + Z_{im} \times C_{im} = \epsilon$$

where $Pi$ is the combined form of the two forms of phosphate important in the physiological pH range. Alb is serum albumin, and im is an impermeable species. The effects of serum globulins on acid-base balance were assumed to be negligible following the conclusion of Figge et al. (11). The equation for interstitial fluid is the same as Eq. 1, except the concentrations are in millimoles per liter of interstitial fluid.

The equation for erythrocytes is

$$C_{Na} + C_K - C_{Cl} - C_{HCO_3} - 2 \times C_{CO_3} + Z_{Hb} \times C_{Hb} + Z_{DPG} \times C_{DPG} + Z_{ATP} \times C_{ATP} + Z_{GSH} \times C_{GSH} + Z_{im} \times C_{im} = \epsilon$$

where concentrations are in millimoles per liter of erythrocyte water.

Osmotic equilibrium. At equilibrium, the sum of the difference (\(\Delta\)) in osmolalities for each species across the erythrocyte and capillary membranes is negligibly close to zero. The $\Delta$ values are consistently expressed as the concentration in one compartment minus the concentration in the adjacent compartment for species present in adjacent compartments. The osmolality contributed by each species is the product of the osmotic coefficient (\(\phi\)) and its concentration (mmol/l$_W$). Hence, across the erythrocyte membrane (superscripts omitted)

$$\phi_{Na} \times \Delta C_{Na} + \phi_{K} \times \Delta C_{K} + \phi_{Pi} \times \Delta C_{Pi} + \phi_{GSH} \times \Delta C_{GSH} + \phi_{im} \times \Delta C_{im}$$

and

$$\phi_{ATP} \times \Delta C_{ATP} + \phi_{HCO_3} \times \Delta C_{HCO_3} + \phi_{CO_3} \times \Delta C_{CO_3} + \phi_{Hb} \times \Delta C_{Hb}$$

where $\phi_{Hb}$ is 1.05, across the capillary membrane, and the ratio of albumin concentrations across the capillary membrane is assumed constant.

The $\phi$ values for all species other than hemoglobin are given in Table 1. For this species, Raftos et al. (30) fit their experimental observations with the polymer equation used in the present study

$$\phi_{Hb} = 1 + 0.115 \times (C_{Hb}^{PW}) + 0.0256 \times (C_{Hb}^{PW})^2$$

Transmembrane transport. Permeant ions reach Donnan equilibrium distributions (41) across the two membranes. Hence, across the capillary membrane

$$\frac{C_{Cl}^W}{C_{Cl}^E} = \frac{C_{Pi}^W}{C_{Pi}^E} = \frac{C_{HCO_3}^W}{C_{HCO_3}^E} = \frac{C_{CO_3}^W}{C_{CO_3}^E}$$

where $\frac{C_{Cl}^W}{C_{Cl}^E}$ is the Donnan concentration ratio for anions (mmol/l$_W$ divided by mmol/l$_E$) and $Z_{dp}$ is the electrical charge per molecule for the combined two forms of phosphate. For Cl$^-$, across the erythrocyte membrane, Eq. 5 reduces to the concentration ratio for Cl$^-$ (mmol/l$_W$ divided by mmol/l$_E$), which is equal to the inverse of that for H$^+$, since both distributions are dependent on electrical forces, as described by Raftos et al. (30).

Table 1. Reference-state data

<table>
<thead>
<tr>
<th>Fluid: Compartment</th>
<th>Arterial Blood</th>
<th>Venous Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erythrocyte</td>
<td>Plasma</td>
</tr>
<tr>
<td>Solute or quantity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (tetramer), mmol/l</td>
<td>5.3</td>
<td>0.65</td>
</tr>
<tr>
<td>Albumin (43 g/l), mmol/l</td>
<td>4.4</td>
<td>1</td>
</tr>
<tr>
<td>ATP, mmol/l</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>GSH, mmol/l</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Na, mmol/l</td>
<td>10</td>
<td>140</td>
</tr>
<tr>
<td>K, mmol/l</td>
<td>99</td>
<td>4.1</td>
</tr>
<tr>
<td>Cl, mmol/l</td>
<td>53.8</td>
<td>105</td>
</tr>
<tr>
<td>Ca, mmol/l</td>
<td>*</td>
<td>2.3</td>
</tr>
<tr>
<td>Mg, mmol/l</td>
<td>+</td>
<td>0.8</td>
</tr>
<tr>
<td>P, (mono- and divalent), mmol/l</td>
<td>0.67</td>
<td>1.16</td>
</tr>
<tr>
<td>Pco2, Torr</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>pH</td>
<td>7.22</td>
<td>7.4</td>
</tr>
<tr>
<td>HCO3, mmol/l</td>
<td>13.6</td>
<td>24.2</td>
</tr>
<tr>
<td>Hemoglobin O2 saturation, %</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>Fractional water content</td>
<td>0.73</td>
<td>0.94</td>
</tr>
<tr>
<td>Hct, %</td>
<td>44</td>
<td>282</td>
</tr>
<tr>
<td>Osmolality, mosmol/lw</td>
<td>20.2</td>
<td>0</td>
</tr>
<tr>
<td>Charge on impermeable solutes, meq/l</td>
<td>-9.2</td>
<td>-5.3</td>
</tr>
<tr>
<td>Uncharged permeable solutes, mmol/l</td>
<td>4.7</td>
<td>6</td>
</tr>
</tbody>
</table>

Values were taken or derived from Dill et al. (5), Fencl et al. (10), Fogh-Andersen and Siggaard-Andersen (13), Funder and Wieth (14), Nagaki and Teraoka (27), Raftos et al. (30), and Wooten (42). DPG, 2,3-diphosphoglycerate; Hct, hematocrit. *Erythrocyte Ca and Mg are assumed to be totally bound.
Mass and volume conservation. Each of the conserved solutes (s) obeys a mass-conservation relation

$$V_{EW}^s C_{s EW} + V_{PW}^s C_{s PW} + V^s I_s^s = M_s$$

where $M$ is the mass (mmol) of solute.

For water

$$V_{EW}^w + V_{PW}^w + V^w I_w^w = V^w$$

where $V^w$ is the total volume of water in the system. The constant total masses of solutes (Eq. 6) and volume of water (Eq. 7) are determined from the reference-state values in Table 1.

For impermeable solutes in the erythrocyte compartment, such as hemoglobin

$$C_{s HB}^s = M_{s HB}^s V_{EW}^s$$

where the constant mass of hemoglobin in the reference state (super- script 0) is determined from the values in Table 1. Other impermeable species in all compartments are described by relations similar to Eq. 8. Hence, these solute concentrations change as water shifts between compartments.

Carbonates and pH-dependent charge species. Following Raftos et al. (30), carbonate concentrations in each compartment are determined using the Henderson-Hasselbalch equation. Hence, for plasma, for example

$$C_{s CO_3}^P = S_{s CO_2}^P \times P_{s CO_2}^P \times 10^{\rho s - pK_{s carbonate}}$$

and

$$C_{s CO_3}^P = C_{s HCO_3}^P \times 10^{\rho s - pK_{s carbonate}}$$

where $S$ is CO$_2$ solubility and $pK_{s carbonate}$ and $pK_{s carbonate}$ are the first and second dissociation constants of carbonic acid. The $\rho$S and $S$ values at 37°C are shown in Tables 2 and 3. These $pK$ values and the $P_{CO_2}$ value are assumed to be the same for the other two compartments. The appropriate pH in Eq. 9 is that for plasma in chemical communication with erythrocytes, designated blood pH (pH$_b$).

For solutes with pH-dependent charges, such as hemoglobin, serum albumin, and our representation of the two principal forms of phosphate (Table 2), the variable charge can be described (30) as

$$Z_i = z_0 + \frac{b_1}{1 + b_{1}} + z_2 \frac{b_2}{1 + b_2}, \quad b_1 = 10^{\rho s - pK_1}$$

and

$$b_2 = 10^{\rho s - pK_2}$$

where $z_0$, $z_1$, $z_2$, $pK_1$, and $pK_2$ are constants to be determined that provide a good fit to experimental data (Table 2).

The electrical charge on hemoglobin described in Table 2 is for 100% O$_2$-saturated blood. For lower saturation values, as in venous blood, the charge becomes less negative. To achieve the reference-state value for venous blood pH (Table 1), we found that the charge on hemoglobin (tetramer) can be written as

$$Z_{HB}^{s'} = Z_{HB}^{s'} + 1.5 \times (1 - f_{Sat})$$

where $Z_{HB}^{s'}$ is the pH-dependent charge from Table 2 and $f_{Sat}$ is the fractional O$_2$ saturation. The form of Eq. 11 was suggested by the data of Gros et al. (15) over the physiological range, and the value of 1.5 is similar to their value of 1.8.

Compartment volumes. Often plasma and erythrocyte compartment volumes are expressed as liters of solution, such as liters of plasma, rather than liters of plasma water. To account for the volumes not occupied by water, we define the fractional volume of water as $V_{PW}^w / V_{PW}^w$ and $V_{EW}^w / V_{EW}^w$. Then the volumes of solids in these two compartments are $V_{PS} = V_P \times (1 - f_{PW})$ and $V_{ES} = V_E \times (1 - f_{EW})$, and the fractional hematocrit (IH) is

$$f_{IH} = \frac{V_{EW}^s + V_{ES}^s}{V_{PW}^s + V_{PS}^s + V_{EW}^s + V_{ES}^s}$$

Model Solution

Programming language. The VisSim (version 7) programming language (Visual Solutions, Westford, MA) was selected, partly because it has a built-in optimization algorithm (Newton-Raphson) that can find the unknown values of selected variables subject to imposed constraints. VisSim is a block-oriented language. Mathematical operations are coded by dragging function boxes from a menu onto the computer screen. Box connectors are dragged from one box to another to designate the information flow. As a simple example, Fig. 1 shows a VisSim diagram for implementing part of the plasma electrochemical equilibrium constraint of Eq. 1. A summer block sums the ionic concentrations of Na$^+$, K$^+$, HCO$_3^-$, and Cl$^-$ in plasma water (PW) using appropriate signs for their valences. Na$^+$ and K$^+$ concentrations are taken from outputs of other computations (e.g., Eq. 13), but Cl$^-$ concentration in plasma water is denoted as an unknown value to be found by connecting it to the output terminal of an unknown block. The input to this block is an initial guess, 100 mm/$l_{PW}$, taken from a constant block. HCO$_3^-$ concentration is computed from the Henderson-Hasselbalch equation (Eq. 9) using a power block, a constant-multiplexer block for CO$_2$ solubility multiplying PCO$_2$, and a multiplier block. The ionic contribution of serum albumin (Alb) is its concentration in plasma water times its valence Z$_{Alb}$, as computed from connecting both variables to a multiplier block and then connecting its output to the summer block. The latter variables are outputs from other computations. The remaining terms in Eq. 1 are incorporated similarly. To force the summation to be close to zero, the output of the summer block is connected to a constraint block. The VisSim program finds values for the unknown variables that satisfy the various constraints (see above). Numerous other mathematical and engineering-type function blocks, including integration blocks for solving differential equations, are available. Hence, VisSim allows these blocks to be symbolically connected to simulate the various equations in our model. VisSim translates
these connections into a digital “C” code, leading to a solution of the model equations.

Method of solution of model equations. The model equations were constructed in VisSim. The constraints of electroneutrality (Eqs. 1 and 2) and osmotic equilibrium (Eq. 3) were implemented by forming the equations and feeding their sums into constraint blocks similar to Fig. 1. For the three compartments, there are a total of five constraints. Hence, we are allowed to choose five unknown variables and designate them as such by connecting them to unknown blocks. Those chosen were $C^{\text{PW}}$, $V^{\text{PW}}$, $V^{\text{I}}$, $C^{\text{PW}}$, and the $C^-$ Donnan ratio ($r^\text{PW}$) of plasma water to interstitial fluid. Running the program produces values of these variables that simultaneously bring the values of the plasma water to interstitial fluid. Running the program produces values for venous plasma bicarbonate concentration is calculated from the Henderson-Hasselbalch equation (Eq. 9).

Wooten (43) recently developed a more general equation for BE, derived from the change in effective SID in blood ($\Delta\text{SID}_{\text{bl}}$). The concept of SID was originally suggested by Stewart (39). He proposed that a primary determinant of pH in a fluid compartment was the net ionic concentration of “strong cations,” such as $Na^+$, and “strong anions,” such as $Cl^-$. Strong refers to ions that are totally dissociated in solution; their dissociation is not pH-dependent. For example, in our plasma compartment

$$\text{SID} = C_{Na} + C_k + 2 \times C_{Ca} + 2 \times C_{Mg} - C_{Cl} \quad (15)$$

where concentrations are in millimoles per liter of plasma. This SID value is usually denoted SID$_{\text{mn}}$, because the concentrations in plasma are commonly measured.

An alternative is to estimate SID from the remaining “weak” ionic species, which should equal –SID$_{\text{mn}}$, but its magnitude is usually less because of unmeasured (unidentified) anions in plasma. Hence, for plasma, identified ions are predominantly carbonates, phosphates (P), and serum albumin. Hence

$$\text{SID} = - (-C_{\text{HCO}_3} - 2 \times C_{\text{CO}_3} + Z_{\text{Pi}} \times C_{\text{Pi}} + Z_{\text{Ab}} \times C_{\text{Ab}}) \quad (16)$$

where the negative sign before the expression in parentheses makes this SID value numerically positive. The SID value determined from Eq. 16 requires calculation of $Z_{\text{Pi}}$ and $Z_{\text{Ab}}$ from empirically determined formulas such as that of Figge et al. (11). It is usually referred to as the effective SID (SID$_{\text{eq}}$). The total electrical charge of the latter phosphate and albumin terms is often referred to as $\lambda_{\text{net}}$ (positive sign).

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From the approach of Wooten (44, an expression for the effective SID of blood or of the IPE system from which BE or SBE(IPE) could be determined as the change from normal was derived. Hence

\[
\text{SID (IPE)} = \left[ 1 - \left( 1 - \frac{fH}{V^B + V^I} \right) \times fH \times \frac{V^B}{V^B + V^I} \right] \times \frac{C_{PbCO}_3}{V^I} \\
+ \left( 1 - fH \times \frac{V^B}{V^B + V^I} \right) \times \left[ C_{Pb}^p \times \left( 8 \times \text{pH}^B - 41 \right) \right] + C_{Pb}^p \times \left( 0.3 \times \text{pH}^B - 0.4 \right) + C_{Hb}^p \times \frac{V^B}{V^B + V^I} \times \left( 10.2 \times \text{pH}^B - 73.6 \right) + C_{DPG}^p \times fH \times \frac{V^B}{V^B + V^I} \times \left( 0.7 \times \text{pH}^B - 0.5 \right)
\]

(17)

where \( \frac{fH}{V^B + V^I} \) is the ratio of bicarbonate concentrations in erythrocytes to that in plasma, expressed as milliequivalents per liter of erythrocytes per milliequivalents per liter of plasma. BE is determined from the change in SID (ASID) when \( V^I = 0 \), whereas setting the volume ratio to one-third allows for SBE to be determined for the IPE system. When using Eq. 17, we use Wooten’s values: hematocrit is 44% (\( fH = 0.44 \)), the concentrations of albumin and phosphate in plasma are 0.66 and 1.16 mmol/l, respectively, and erythrocyte hemoglobin and DPG concentrations are 5.3 and 6 mmol/l, respectively.

When making BE predictions with our blood model, we assume that blood BE is determined as the amount (meq/l) of blood of acid (HCl) that needs to be added or subtracted from the model reference state to achieve the subject’s measured pHB at the measured PaCO2. The simulation procedure is to set \( P_{ACO}_2 \) to the measured value, \( pHB \) to the desired value. Only \( M_{Cl} = 1 \) is used, and any constraint block to force model \( pH^B \) to the desired value. Only \( M_{Cl} \) is changed, because H⁺ is not conserved in the model. Model solution produces the value of BE between 

\[ 0, \text{ whereas setting the volume} \]

where \( M_{Cl} = 1 \) is an unknown, and use a constraint block to force model \( pH^B \) to the desired value. Only \( M_{Cl} \) is changed, because H⁺ is not conserved in the model. Model solution produces the value of BE (\( -\Delta M_{Cl} \)) required to achieve these conditions. The same procedure is used to estimate SBE when the IPE fluid system is considered, except SBE is expressed as milliequivalents per liter in PBE.

RESULTS

Reference State

For the blood model solution to closely predict the arterial blood values in Table 1, it was necessary to adjust the mass and/or charge on the unidentified, impermeant species in the plasma and erythrocyte compartments. The first adjustment procedure was to only consider blood by setting \( V^I = 0 \). Then only three constraints remained, since interstitial electroneutrality and osmotic equilibrium no longer applied, and the two unknowns pertaining to the interstitial compartment were no longer part of the solution. The three values specified to achieve the desired reference solution are \( M_{im}^E \), \( Z_{im}^E \), and \( Z_{im}^p \). Although the latter values affected the values of all variables, requiring a trial-and-error procedure, blood hematocrit, erythrocyte-to-plasma Donnan ratio, and blood pH, respectively, were most sensitive to individual manipulation. When the values found for these impermeant species (Table 1) were used, the model solution matched the concentration and volume data for arterial blood. Permeable, uncharged solutes were set to equal concentrations (per \( I_{lv} \)) in each compartment, so as to obtain a normal osmolality of 282 mosmol/l. Resulting \( HCO_3^\) concentrations and erythrocyte pH are as shown.

For the full IPE model, the volume of the arterial blood model was increased to 5 l by multiplying volumes and masses by a factor of 5. Next, the interstitial compartment was added, and venous conditions of 46 Torr \( P_{ACO}_2 \) and 75% O2 saturation were set. Then \( M_{im}^E \) and \( Z_{im}^E \) values were adjusted (Table 1) to achieve \( V^I = 10 l \) and keep venous blood pH at the selected normal reference value of 7.37 shown in Table 1. There was no attempt later to arbitrarily change these parameter values to match any given situation.

Validation of Blood Model

Blood pH-dependent variables. In a number of studies, \( P_{CO}_2 \) was changed and/or acid or base was added to blood, and the concentrations of various species were determined. The first of these studies is that of Funder and Wieth (14). To test the hypothesis that the distributions of \( Cl^- \) and \( H^+ \) between plasma and erythrocytes are at a Donnan equilibrium, they performed a number of short-term (\(<1 h \) of equilibration) acid-base experiments on fully oxygenated human blood at 38°C. The first series altered \( P_{CO}_2 \), and the second series added HCl or NaOH, each adjusted to maintain plasma \( Na^+ \) concentration nearly constant. Figure 2 shows their measured data for the relationship between erythrocyte and blood pH values (\( pH^E \) and \( pH^B \), respectively). Their data for the two types of disturbances were intermixed; apparently, the type of disturbance did not affect the results. Their data are close to linear over the physiological range but show a distinct downward concavity at very high \( pH^B \) values. We use the notation of Siggaard-Andersen (35) in Fig. 2. Hence, addition of base to blood produces a BE equivalent to the milliequivalents per liter of base added, and addition of acid produces a BE with a negative value.

Model predictions for the primary \( P_{ACO}_2 \) change data (BE = 0) are shown in Fig. 2. Addition of HCl to the model or addition of NaOH (subtraction of HCl) did not change these predictions. The model predictions, based on a Donnan distribution for \( H^+ \), closely follow the data of Funder and Wieth (14), thereby confirming their hypothesis. Also shown in Fig. 2 is an approximation suggested by Siggaard-Andersen (37) that is similar to the model predictions and the data of Funder and Wieth. In contrast, the prediction from the study by Purcell et al. (29),
determined over a small blood pH range (7.36–7.43), produces large errors when used over the entire physiological range.

Funder and Wieth (14) also determined the ratio of Cl$^{-}$/H$^{+}$ concentration (rcl, in meq/lW) in erythrocytes to plasma under the same conditions as the experimental data in Fig. 2. In Fig. 3, these data are shown as we measured them off their graphical plot. Also shown are data we measured from the graphical plots of Dill et al. (5) and Hastings et al. (16) from venous blood of normal men. All experimental data sets show a similar trend. Model predictions, generated as described for the pH$^B$ data, are shown for BE values from −15 to 15 meq/lB. The model predictions, again, are largely independent of BE values and are approximately linear over the pH$^B$ physiological range. These predictions are quite similar to the experimental results over this range. Close comparison of model prediction and experimental results, again, substantiate the validity of the assumption of a Donnan distribution for Cl$^{-}$/H$^{+}$ across the erythrocyte membrane.

Dill et al. (5) and Hastings et al. (16) also measured the HCO$_3^-$ concentration ratio (rHCO$_3^-$) in their experiments. Concentrations were in milliequivalents per liter of water in each fluid. Their experimental values are shown in Fig. 4. Henderson et al. (18) also measured rHCO$_3^-$, but they only reported values from their fit to these data (Fig. 4). All experimental data sets show similar linear trends but are somewhat more scattered than the rCl data of Fig. 3. The corresponding model predictions (BE = 0), again, are almost linear. Predictions for the other BE values are quite similar. These predictions show the same trend as the experimental data but lie below them. This discrepancy is caused by our use of bicarbonate pK values (Table 2) and CO$_2$ solubilities (Table 3) in plasma and erythrocytes in the model that were different from those used in these studies to calculate HCO$_3^-$ concentrations from pH$^B$ values when the Henderson-Hasselbalch equation was used. It is clear from Figs. 3 and 4 that rHCO$_3^-$ is proportional, but not necessarily equal, to the Donnan ratio, rCl. Also shown in Fig. 4 is the model prediction of the HCO$_3^-$ concentration ratio when the concentrations are expressed per liter of volume in the two compartments. It is somewhat different from the relation suggested by Siggaard-Andersen (37) and used by Wooten (43, 44), which may lead to errors when it is used to predict acid-base status in patients.

It is well known that blood hematocrit varies with pH$^B$ (18), although this water shift between plasma and erythrocytes is usually ignored in studies of the acid-base status of blood (35). As shown in Fig. 5 by the experimental data from normal men from Henderson et al. (18), this effect could be important in severe acid-base disorders. Because hematocrit values vary when the concentrations are expressed per liter of volume in the two compartments.
considerably between studies, it was necessary to scale the experimental data for their two studies (18, 35) to our model reference-state value of 44% at pH\textsubscript{B} 7.4. The model predictions closely follow the scaled experimental data. This result supports the assumption that plasma and erythrocytes are in osmotic equilibrium.

**Prediction of blood pH changes due to acid or base additions.** Siggaard-Andersen (35) measured pH\textsubscript{B} changes after subjecting oxygenated blood (blood hemoglobin concentration of 15.1 g/100 ml) to changes in PCO\textsubscript{2} (BE = 0) and adding acid (−BE values) or base (+BE values). He used these data to derive a nomogram from which BE could be predicted. The acid-base status (traditional approach to acid-base analysis) consisted of P\textsubscript{ACO}, pH\textsubscript{B}, and BE values. Hematocrit (blood hemoglobin concentration) was a fourth variable sometimes considered. Figure 6 shows our representation of his experimental data and model predictions plotted with the axes he originally proposed, although one might expect that they would be reversed, as pH\textsubscript{B} is the dependent variable. His experimental data (mean from 3 samples) for BE = 0, −15, and 15 meq/l\textsubscript{B} are shown on the P\textsubscript{ACO}-pH\textsubscript{B} plot. Model predictions of pH\textsubscript{B}, using these same BE and P\textsubscript{ACO} values, are also shown. To determine these model predictions, our assumption was that his BE values were equivalent to loss or addition of HCl. Model pH\textsubscript{B} predictions are very close to the experimental data, except for the BE = −15 meq/l\textsubscript{B} curve, which deviates somewhat from the measured data, but only at low P\textsubscript{ACO} values.

The Siggaard-Andersen nomogram (35) was based on experimental data shown in Fig. 6. He assumed that the basic blood CO\textsubscript{2} equilibration (absorption) curve was a straight line passing through the 40 Torr PCO\textsubscript{2}-pH\textsubscript{B} 7.4 point and close to the other two points (BE = 0 data). For other BE values, the straight lines were assumed to parallel the BE = 0 line and pass through the appropriate BE value on the BE curve shown in Fig. 6. His BE curve was calculated using a number of assumptions, but our model predictions were quite close. Hence, the BE for a blood sample can be determined by drawing a straight line through the measured PCO\textsubscript{2}-pH\textsubscript{B} point parallel to the BE = 0 line and determining the BE value at which the sample line intersects the BE curve. A modification is that the slopes of these lines shift slightly with changes in blood hemoglobin concentration. As described below, a more modern approach is to use the more accurate Van Slyke equation (Eq. 14) for these BE estimations.

**Prediction of blood pH changes due to saline addition.** Morgan et al. (26) added various crystalloid solutions to normal, fully oxygenated human blood at constant, normal P\textsubscript{ACO}. Determined from measured blood pH, P\textsubscript{ACO}, and hemoglobin concentration data were the changes in BE using the Siggaard-Andersen traditional approach (Van Slyke equation, Eq. 14) and the effective SID of plasma (Eq. 16) using empirically derived, pH-dependent charge effects for albumin and phosphate similar to that of Figge et al. (11). We obtained the numerical BE and hemoglobin data from Dr. T. J. Morgan and used it (with his permission) to determine pH\textsubscript{B} values for 150 mM saline addition. The procedure was to simultaneously solve Eqs. 9 and 14 with VisSim, using his hemoglobin data, specifying pH\textsubscript{B} as the unknown, and constraining BE to the measured value. Since P\textsubscript{ACO} values were not explicitly known, we first found the value (42.2 Torr) that would give the normal pH\textsubscript{B} value (7.383) at his normal hemoglobin concentration (5.53 mM). This P\textsubscript{ACO} value was assumed to apply for the rest of the experimental data. Model simulation of saline addition was to increase M\textsubscript{Na} and M\textsubscript{Cl} by 150 mmol/l of solution added. Hence, dilution of 1 liter of blood with 1 liter of NaCl solution would cause a fall to 0.5 of blood hemoglobin concentration relative to normal and add 150 mmol to the masses of these ions. The result is a pH\textsubscript{B} drop to 7.22. Figure 7 shows the changes in pH\textsubscript{B} for serial additions of 150 mM NaCl. The experimental results show an increasing acidemia with saline additions.
Acid-Base Disorders

Application of Blood Model to Diagnose Saline-Induced Acid-Base Disorders

We can use the blood model to predict (diagnose) the nature and amount of the fluid addition in a saline-acidosis disorder. In this case, we need additional information other than just pH and Pco₂. To determine the volume of water added and the added masses of Na⁺ and Cl⁻, we designate these three quantities as unknowns in the simulation. Then, besides constraining pH to the predicted value in the example cited above, we also need to constrain plasma concentrations of Na⁺ and Cl⁻ to measured values. From the simulation results described above, these are 147 and 130 meq/l, respectively, the assumed measured values. Running the simulation resulted in predicted additions of 1 liter of water and 150 meq of Na⁺ and of Cl⁻, the correct values. This example shows how this program could be used at the bedside to diagnose disorders in critically ill patients. However, it is likely that these patients have more than one disorder and that interstitial fluid contributions must also be considered (see below).

Application of Arterial Blood Model to Acid-Base Status Predictions (Diagnosis)

Since derivation of the Siggaard-Andersen nomogram, a number of simple, analytical expressions have been derived to provide more accurate descriptions of BE curves. Two of these are the Van Slyke equation (Eq. 14) derived by Siggaard-Andersen (37) and an equation (Eq. 17) derived from the change in blood SID by Wooten (42). Figure 8 shows the difference between their predictions and those from the model for simulated acid and base additions producing a range of pHB values, but at a constant normal PaCO₂. For the model implementation, first, PaCO₂ was set to 40 Torr. Then pHB was constrained to a value in the graph (e.g., 7.0) by subtracting 7.0 from the computed pHB value using an adder block and connecting this block to a constraint block. The output of an unknown block, designated the change in Cl⁻ mass (ΔMCl⁻), was added to reference-state MCl⁻. Then the simulation program automatically determined the unknown value of BE (−ΔMCl⁻) consistent with pHB 7.0. All these equation predictions, as well as the model prediction, pass through the BE = 0 value at pHB 7.4. The Van Slyke equation is close to the model predictions for higher pHB values, but it overestimates model BE substantially at lower pHB values. In contrast, the Wooten equation is similar to model predictions at lower pHB values, but it overestimates these predictions at higher pHB values.

For more specific comparisons, we used a number of clinical situations from Siggaard-Andersen. He used his nomogram (35) to estimate BE from pHB, PₐCO₂, and hematocrit data (34, 37) for various clinical abnormalities. The implicit assumption is that erythrocyte hemoglobin concentration is constant and that hematocrit is proportional to blood hemoglobin concentration. Table 4 shows BE predictions from these data by Siggaard-Andersen using his nomogram, the Van Slyke equation (Eq. 14), the equation derived by Wooten (Eq. 17), and our model. For model implementation, PaCO₂ was set to the value indicated in Table 4, and pHB was constrained to the value in

![Fig. 8. Differences between BE estimates using different algebraic equations and blood model predictions for metabolic acid-base disorders of blood. Van Slyke equation (37) (Eq. 14) and Wooten’s equation (42, 44) (Eq. 17) are shown.](image-url)

Table 4. Comparison of blood-BE prediction methods

<table>
<thead>
<tr>
<th>Cases</th>
<th>Blood Dataa</th>
<th>BE, meq/lb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arterial Pco₂, Torr</td>
<td>pHB</td>
</tr>
<tr>
<td>Chronic pulmonary arterial insufficiency</td>
<td>82</td>
<td>7.34</td>
</tr>
<tr>
<td>Diabetic coma</td>
<td>24.5</td>
<td>7.21</td>
</tr>
<tr>
<td>After severe exercise</td>
<td>36</td>
<td>7.22</td>
</tr>
<tr>
<td>Acute pneumothorax</td>
<td>41</td>
<td>7.37</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29.3</td>
<td>7.75</td>
</tr>
<tr>
<td>+Respiratory insufficiency</td>
<td>64</td>
<td>7.48</td>
</tr>
<tr>
<td>Acute hypercapnia</td>
<td>100</td>
<td>7.09</td>
</tr>
<tr>
<td>Acute hypercapnia</td>
<td>16</td>
<td>7.7</td>
</tr>
<tr>
<td>Chronic hypercapnia</td>
<td>80</td>
<td>7.3</td>
</tr>
<tr>
<td>Chronic hypercapnia</td>
<td>25</td>
<td>7.44</td>
</tr>
<tr>
<td>Acute base deficit</td>
<td>30</td>
<td>6.9</td>
</tr>
<tr>
<td>Chronic base deficit</td>
<td>10</td>
<td>7.15</td>
</tr>
<tr>
<td>Chronic BE</td>
<td>55</td>
<td>7.6</td>
</tr>
</tbody>
</table>

BE, base excess. aCases and data from Siggaard-Andersen (34, 37). bEstimated by Siggaard-Andersen from his nomogram (35). cFrom Van Slyke equation (Eq. 14). dFrom Wooten equation (Eq. 17), with V⁰ = 0. Value is assumed, because it was not given.
Table 4, as described above. When hematocrit was different from our reference-state value, the desired value was achieved by using a constraint block in the same manner as for constraining pH$_B$, except the unknown value was a guess of the initial hematocrit of the subject before the acid-base perturbation took place. Usually, the model-predicted unknown value was within a few hematocrit percentage points of the final hematocrit.

In general, use of these approximate methods produced BE values similar to model predictions. Differences were generally <3 meq/l$_B$. Hematocrit changes over the normal range did not change model predictions substantially; the assumption of normal hematocrit in the last seven cases produced errors of less than ±2 meq/l$_B$ for the largest changes in BE. Hence, if the only acid-base disturbance is gain or loss of acid and base, the combination of Pa$_{CO2}$ and pHB changes are such that BE is less than about ±30 meq/l$_B$ and the other restrictions enumerated by Siggaard-Andersen (35) are not violated, various simple methods of estimating BE in blood are sufficiently accurate, and the model is not required. However, we could not have come to this conclusion without using the model.

Validation of the IPE Model

Validation is more difficult and less exact for the IPE model than for the blood model for a number of reasons. 1) Experiments in humans often involve giving fluids of various kinds to compensate for renal losses. 2) Obtaining steady-state conditions is always an issue because of consideration for human tolerance and safety. 3) The contribution of muscle and other parenchymal cells to the response to acid-base stress is an open question. 4) The extent of the acid-base stress is necessarily restricted. These considerations limit the experimental data available and cloud interpretation from human experiments where acid or base is given. Hence, use of such data awaits further model development to include a parenchymal cell compartment. However, there are numerous human studies where Pa$_{CO2}$ was varied acutely and acid-base data were measured.

The first set of available data is from Brackett et al. (1), who measured a whole body CO$_2$ titration curve in normal men for elevated Pa$_{CO2}$ values. After 60 min of equilibration at baseline conditions, the subjects were first exposed to 7% CO$_2$ for 40–90 min and then to 10% CO$_2$ for as long as they could tolerate this level (up to ~30 min). pH$_B$, Pa$_{CO2}$, and some plasma electrolytes were measured during the baseline period and in the transient and steady-state periods after each step in CO$_2$ inhalation. Figure 9 shows the experimentally measured H$^+$ concentration data of Brackett et al. for their normal and high Pa$_{CO2}$ values with corresponding SE bars. Also shown in this range are similar data from Elkinton et al. (8) for normal men exposed to ~7.5% CO$_2$ for 21–30 min and from Manfredi (22) for normal men exposed to 7% CO$_2$ for 3 h. Model predictions over the entire pH range (SBE = 0) are almost linear and pass through these measured data points.

In addition to the latter respiratory acidosis data, Elkinton et al. (8) and Manfredi (22) had their subjects voluntarily hyperventilate (30 min and 3 h, respectively) to reduce Pa$_{CO2}$ and cause a respiratory alkalosis. As seen in Fig. 9, their results and those of similar additional studies by Eldridge and Salzer (7) and Tomashefski et al. (40) lie well below model predictions of the SBE = 0 curve. As shown by the model predictions for acid or base additions equivalent to ~15 or 15 meq/l$_{IPE}$, voluntary hyperventilation apparently caused a metabolic acidosis, in addition to the respiratory alkalosis. However, consecutive measurements over a 4-h period in passively hyperventilated, anesthetized, surgical patients by Papadoulis and Keats (28) showed a similar result. Hence, it is unclear if the metabolic acidosis is caused by the increased work of hyperventilatory breathing or another mechanism.

Application of IPE Model to Diagnose Saline-Addition Acid-Base Disorders

The same simulation experiment done with the blood model can be done with the IPE model. In this case, 5 liters of the same saline solution (equal to the initial blood volume) are added to the model. The result is that pH$_B$ drops to 7.27, a lesser change than that noted above because of the additional buffering of the interstitial fluid. Model SBE$_{IPE}$ was only ~6.8 meq/l$_{IPE}$, as calculated from the 136 meq of Cl$^-$ subtracted to return model pH$_B$ to 7.37 (venous blood) and the now 20 liters of volume in the model. If the original Stewart approach (39) were used for analysis, the appropriate SID could be a weighted value for the combined plasma-interstitial fluids and $A_{int}$ would have to take into consideration the contribution of the interstitial fluid.

Model diagnosis of this disorder in a patient would proceed similarly as described above for blood. Hence, pH$_B$ and plasma concentrations of Na$^+$ and Cl$^-$ would be constrained to measured values. As noted above, the unknowns would be the added volume of water and the added masses of Na$^+$ and Cl$^-$. Model solution returns the values of 5 liters of water added and 750 meq of Na$^+$ and Cl$^-$ added to this patient, hence, the diagnosis of the disorder. Diagnosis of a combined disorder of acid gain or loss and saline addition could be similarly determined.
Schlichtig et al. (33) characterized acid-base disturbances in terms of SBE to study compensation in humans. Using data from the studies cited above and others, they determined SBE using the Van Slyke equation (37) modified with a hemoglobin concentration reduced to one-third of the blood value to account for interstitial dilution of the hemoglobin effect, as suggested by Sigggaard-Andersen (38). For acute respiratory disturbances, they concluded that SBE = 0, statistically, over the PaCO₂ range of 10–100 Torr, although their data showed a preponderance of negative values at less than ~30 Torr PaCO₂.

Recently, using a modification of his ΔBE formulation for blood (42), Wooten (44) proposed a formula (Eq. 17) for calculating SBE for the IPE fluid system. Using data of Brackett et al. (1) and Eldridge et al. (7), we compared these predictions with the model prediction for acute respiratory acidosis and alkalosis, respectively. Table 5 shows the results.

As seen for respiratory acidosis, all approaches make similar predictions of SBE values near zero, as found by Schlichtig et al. using the Van Slyke equation. In contrast, for respiratory alkalosis, Wooten’s equation and the model predictions were statistically, over ΔPaCO₂ range of 20–100 Torr, where SBE was determined from the Van Slyke equation and Δ refers to change from the normal 40-Torr value. From these data, we used our IPE model to predict pHB at the extreme ends, as shown in Table 5. Then estimates of SBE were determined in the other approaches using these pHB values. All approaches predicted similar values, but our model predicts a slope of ~0.44, rather than 0.4 found using the Van Slyke or Wooten equation.

Table 5. Comparison of SBE predictions in acute and chronic respiratory acidosis and alkalosis

<table>
<thead>
<tr>
<th>Respiratory Disorder</th>
<th>Arterial PaCO₂, Torr</th>
<th>pHB</th>
<th>SBE, meq/lHWE</th>
<th>A</th>
<th>B</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute acidosisa</td>
<td>78</td>
<td>7.17</td>
<td>~0.5</td>
<td>~0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute alkalosisa</td>
<td>19</td>
<td>7.61</td>
<td>~2.4</td>
<td>~4.7</td>
<td>~4.7</td>
<td></td>
</tr>
<tr>
<td>Chronic acidosisa</td>
<td>100</td>
<td>7.32</td>
<td>22.8</td>
<td>25.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic alkalosisa</td>
<td>20</td>
<td>7.48</td>
<td>9.6</td>
<td>10.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IPE, interstitial-plasma-erythrocyte; SBE, standard BE. aFrom Van Slyke equation (Eq. 14), with hemoglobin (monomer) concentration = 3 mmol/lHWE.

DISCUSSION

To provide improved understanding of the causes of acid-base disorders and to aid in their diagnoses, we have formulated and validated mathematical models of blood and blood-interstitial acid-base chemistry. The blood model incorporates physicochemical factors leading to an equilibrium distribution of ions, water, and metabolites in the two fluids, plasma and erythrocytes, that constitute blood, and the blood-interstitial model uses the same factors and also applies them to the interstitial fluid in equilibrium with blood.

The blood model validated and used in this study was most closely associated with that of Raftos et al. (30), because the same equilibrium assumptions were used. However, Raftos et al. were more concerned with the response of erythrocytes to changes in their bathing medium. In contrast, our models were for the purpose of understanding and diagnosing the causes of acid-base disorders. However, the model of Raftos et al. and our model are predated by models of DeLand and associates (3, 4). They considered many more chemical species and the complex buffering reactions of hemoglobin and serum albumin, and they simulated a parenchymal cell compartment (4). They also computed steady states, as they allowed Na⁺ and K⁺ to move across cell boundaries as dictated by active pumps and passive processes. Even so, their free-energy-based approach gives solutions similar to that of our blood model (personal communication). However, the DeLand models were not initially designed for diagnosing acid-base disorders, in contrast to the long-term intent of our present model.

Model Assumptions

Two key features of the present models are the following assumptions: 1) a Donnan (electrochemical) equilibrium obtains for Cl⁻ and H⁺ across the erythrocyte membrane and the same obtains for these ions plus Ca²⁺, Mg²⁺, and phosphates across the capillary membrane separating plasma and interstitial fluid, and 2) osmotic equilibrium governs water distribution across both membranes. Similar to the model of Raftos et al. (30), Na⁺ and K⁺ were considered impermeable across the erythrocyte membrane, and bicarbonate concentrations in each compartment were derived from compartmental PCO₂, pH, and the Henderson-Hasselbalch equation. Similarly, we used an empirical approach to simulate the interactions of H⁺ with hemoglobin and serum albumin and the osmotic coefficient of hemoglobin. However, we also included the capability of simulating venous blood by varying the electrical charge on hemoglobin as hemoglobin O₂ saturation varied. This latter effect was necessary, because it is venous blood that is in equilibrium with interstitial fluid. One or more of these characteristics differentiate this model from recent approaches (31, 43, 44) used to characterize acid-base disturbances.

These key assumptions used in the present models were fundamental to an early study of electrolyte and water equilibria in blood by Van Slyke et al. (41) and were basically unchallenged in later studies (5, 18, 41). However, subsequent challenges to these assumptions led Funder and Wieth (14) to make more refined measurements of the distribution of Cl⁻ and H⁺ in blood after additions of acid-base-altering solutions. Their findings led to the conclusions that Cl⁻ and H⁺ distributions were each at electrochemical equilibrium across the
erythrocyte membrane and that water redistribution was as predicted from the osmotic equilibrium assumption.

**Blood Model Validation**

A fundamental requirement of the validity and usefulness of any compartmental acid-base model is its ability to accurately predict pH changes due to 1) changes in Pco2, 2) addition of acids or bases, 3) addition of other kinds of fluids, and 4) changes in parameters characteristic of physiological and clinical acid-base disturbances. The Stewart model (12) was shown to have some of these capabilities, but it only considered the plasma compartment. We have shown that the present blood model satisfies the first three conditions (Figs. 6 and 7) in the present study.

Further validation must come from a model’s ability to accurately predict electrolyte distributions and other data. Close comparison of our blood model results with experimental data in blood of Funder and Wieth (14) in Figs. 2 and 3 shows such predictions and provides validation of the Donnan distribution assumption. This assumption may be appropriate for human blood, but there may be exceptions for erythrocytes from other species. Also, close model predictions of the experimental data shown in Fig. 5 validate the osmotic equilibrium assumption, but inherent in the latter model predictions is the use of a nonlinear osmotic coefficient of hemoglobin (30). There has been considerable debate about the erythrocyte as a perfect osmometer, but the approach of Raftos et al. (30), including their empirical, osmotic coefficient for hemoglobin, produces close prediction of experimental results without the need to invoke additional mechanisms.

However, we can lift the osmotic equilibrium constraint in the model to see the result. Consider a case where PaCO2 = 10 Torr and BE = 15 meq/l due to a loss of 15 meq of HCl. The model predicts pHB = 8.04 and rCl = 0.48, with osmolality decreasing from 282 to 267 mosmol/l. Removing the constraint results in pHB = 8.03, rCl = 0.37, and erythrocyte and plasma osmolarieties of 210 and 292 mosmol/l, respectively. Hence, predictions of pHB and BE would be little affected, but predicted Cl− distribution would be significantly changed; the slope of the rCl vs. pHB relationship of Fig. 3 would go from 0.28 to 0.44, which would be quite different from the experimental data. Hence, this constraint has a significant effect on predicted electrolyte distribution. The effects of such constraints can be examined only by using models of the complexity described in this study.

The model closely predicted the trend of bicarbonate distribution data (Fig. 4), but the concentration ratio data lay somewhat below experimental measurements. Early studies (5, 18, 41) treated HCO3− as a permeable ion that distributed as Cl−. This assumption may be true, but in the present study and in the study of Raftos et al. (30), HCO3− concentrations were determined using the H+ concentration in each compartment and the Henderson-Hasselbalch equation. Since H+ concentration ratios are determined from Cl− concentration ratios, the proportionality of HCO3− concentration ratios follows. The model predicts lower values in Fig. 4, because assumptions for the pK and CO2 solubility values used in the model differ from those of various experimental studies that also derived HCO3− values using the Henderson-Hasselbalch equation.

An important consideration in the model validation process used to obtain the predictions in Figs. 2–7 is that model parameters were not altered to match any specific experimental measurement. Only in this way can the validity of model mechanisms and processes be fairly assessed. Hence, the parameter values used to obtain the reference state, such as total masses of permeable ions and compartmental masses of impermeable ions, remained constant. The only exceptions were gain or loss of the masses of Na+ and Cl− (i.e., saline addition) and the added volume of water necessary to simulate a given experiment.

**IPE Model Validation**

The blood model is appropriate for predicting the results of experiments with blood, but it is less accurate and informative when describing or diagnosing acid-base changes estimated from a subject’s blood sample. The IPE model is more appropriate for in vivo diagnoses. However, validation was less complete for the IPE model than for the blood model, because there is no acid-base disturbance that does not involve the unknown response of parenchymal cells, and their effect is not included in the present model. Also, accurate simulation of experiments on humans for chronic respiratory conditions and acid or base additions requires data on water and electrolyte intake and excretion that are most often not available. However, we did find that the model accurately predicted pHB values in acute respiratory alkalosis (Fig. 9). Wooten’s (44) findings were similar, in that the PaCO2-pHB data point pairs of Brackett et al. (1) were very close to his computed curve for SBE(IPE) = 0. We could not make model predictions of pHB for acute respiratory alkalosis, because there is a metabolic acidosis component (Fig. 9, Table 5), and its mechanism is not known. Increased ventilation is required to create the decrease in PaCO2 characteristic of this condition. Hence, lactate or other acid production may be the cause, but Eldridge and Salzer (7) did not measure substantial changes in this production.

**Application of Models to Understand Saline Dilution Effects**

Dilution of body fluids due to fluid retention in the body or fluid infusions is a very important cause of many acid-base disturbances in the clinic (6). The acidosis produced is often characterized as dilutional, saline, or hyperchloremic (26). An early mechanism proposed (21) to explain the cause of the acidosis is dilution of HCO3− concentration and the accompanying decrease in pH as predicted by the Henderson-Hasselbalch equation. However, this bicarbonate-centered explanation missed the point that the decrease in pH produces the decrease in HCO3− concentration, as the latter is normally determined from measured pH and this equation. In contrast, the more recent Stewart approach to explain dilutional acidosis as described by Morgan et al. (23) holds that HCO3− concentration and pH are dependent variables determined by the independent variables Pco2, SId, and weak acids (Aion). Since Stewart (39) developed his theory in plasma, the latter two variables are usually measured in plasma, whereas their independence is compromised if they are not determined in blood, as Wooten (42) did for SId.

**Blood model.** Morgan (26) found that the degree of acidosis caused by crystalloid infusions depended on the SId of the infusion solution. Solutions with SId = 0, such as isotonic
saline, caused the greatest acidifying effect, because they produced the largest decreases in plasma SID, even though plasma concentrations of Na\(^+\) and Cl\(^-\) may increase. For example, our blood model predictions for an infusion of isotonic saline that doubles blood volume are increases in Na\(^+\) and Cl\(^-\) concentrations of 7 and 25 meq/l\(\text{p}\), respectively, hence, a decrease in plasma SID of 18 meq/l\(\text{p}\). These changes are consistent with a hyperchloremic metabolic acidosis. However, it is not only SID that is changed. As observed by Morgan et al. (23, 26), A\(_{\text{tot}}\) is also diluted, but this dilution causes a metabolic alkalosis. For example, model prediction of pH\(\text{B}\) in the example noted above is 7.22, where A\(_{\text{tot}}\) was reduced from 14 to 5 meq/l\(\text{p}\). If just A\(_{\text{tot}}\) had been reduced to this level, pH\(\text{B}\) would have actually risen to 7.48. Hence, the competing effects of a metabolic acidosis caused by a decrease in SID and a metabolic alkalosis caused by a decrease in A\(_{\text{tot}}\) produce the final effect. In this example, the SID effect clearly predominated. The utility of our model is clearly evident in this analysis, because it gives quantitation to an otherwise largely qualitative analysis.

Another interesting insight from the blood model is that it is clearly the dilutional effect of the added volume (water) that causes the acidosis. Just adding the water in the example above reduces pH\(\text{B}\) to 7.16. Hence, NaCl addition, by itself, actually causes a metabolic alkalosis, as pH\(\text{B}\) increased to 7.48.

Therefore, the traditional approach can estimate the BE produced by addition of crystalloid solutions to blood but does not explain the cause of the acid-base disturbance. The Stewart approach gives qualitative insight into the cause of the disturbance from changes in plasma SID and A\(_{\text{tot}}\), but only a blood model, such as we have described in this study, can give not only qualitative insight, but can accurately predict quantitative effects. However, these predictions using the blood model are only valid in vitro.

**IPE model.** It is clear that accurate determination of the cause of acid-base disorders in a patient requires consideration of the buffering effect of the interstitial fluid as we described above by addition of a volume of saline equivalent to blood volume to the IPE system. As expected, the resulting pH\(\text{B}\) change was considerably less because of the buffering of the interstitial fluid. Dilution with just water or addition of just NaCl would give the same qualitative effects they produce in blood but different quantitative effects. Hence, it is important to use the more complete IPE model when diagnosing acid-base disorders and specifying fluid therapy for their treatment. Insight into the latter is not something that simple models (i.e., the Van Slyke equation) can provide.

**Application to Acid-Base Status Determination**

**Traditional approach.** We used the model to examine the assumptions behind construction of the Siggaard-Andersen (35) nomogram (Fig. 6) for predicting the acid-base status (traditional approach) of a subject’s blood from measurement of pH\(\text{B}\) and P\(_{\text{ACO}_2}\). We found that model-generated constant BE curves passed very near or through experimental measurements of Siggaard-Andersen from 10 to 100 Torr P\(_{\text{ACO}_2}\). Also, his variable BE curve measurements were closely predicted. These results confirm that the assumptions made by Siggaard-Andersen in construction of the nomogram would not produce large errors over this P\(_{\text{ACO}_2}\) range. However, it is clear from Fig. 6 that constant BE lines are not straight and that nomogram BE estimates for P\(_{\text{ACO}_2}\) values outside this range are increasingly inaccurate. Hence, other approaches could improve the accuracy of predictions.

Siggaard-Andersen (37) found that his algebraic Van Slyke equation gave BE predictions that varied less than ±3 meq/l\(\text{p}\) from nomogram predictions for his selected extreme cases of acid-base disorders. Hence, he deemed this approach an acceptable substitute. Using the model as a reference, we showed in Fig. 8 that considerable error could be incurred using the Van Slyke equation predictions at pH\(\text{B}\) < 7.0 or > 7.8. A much better prediction approach at pH\(\text{B}\) < 7.4 was from an equation derived by Wooten (42) for the SID of blood (see below). We showed in Table 4 that all these methods predicted BE values within ~3 meq/l\(\text{p}\) of each other for clinical scenarios suggested by Siggaard-Andersen (36, 37). We could not have come to these conclusions without the use of our blood model. Hence, an important use of a model is to give a reference basis for comparing the accuracy of various approaches.

The traditional approach of BE estimation was originally based (35) on the assumption that the acid-base disorders considered are solely due to a gain or loss of acid or base, although a more recent update (38) allows corrections for disorders caused by abnormal plasma phosphate or albumin concentrations. Even so, a common criticism (2) is that this approach does not fully explain the cause of more complex acid-base disorders. An early alternative proposed was the anion-gap approach, popularized by Emmett and Narins (9) in 1977 and still used widely. It predicts qualitative acid-base effects, but only due to the presence of unidentified organic ions, either added to plasma or present due to abnormal metabolic processes.

**Stewart approach (SID).** Stewart (39) in 1981 suggested a different approach to analyzing acid-base disorders. He proposed that the difference in the sum of plasma concentrations of “strong” cations, such as Na\(^+\), and anions, such as Cl\(^-\), that did not chemically associate with H\(^+\), called the SID, was an independent variable in an equation that could be solved for plasma H\(^+\) concentration. He derived this equation from the electroneutrality concept. Another independent variable in the Stewart approach was total charge on nonbicarbonate buffers (A\(_{\text{tot}}\)), namely, proteins and phosphate. Hence, acid-base status was defined as the value of plasma pH consistent with the values of P\(_{\text{CO}_2}\), plasma SID, and plasma A\(_{\text{tot}}\). The anion-gap approach is often used in conjunction with the Stewart approach, and a composite parameter, the strong-ion gap, has emerged to predict the amounts of unidentified ions in plasma (20, 25).

The applicability of Stewart’s approach (39) to understanding blood acid-base disorders is limited, because he did not indicate a way to apply his formulation to the multicompartment system that is blood. However, his unpublished work does give equations for a general Donnan equilibrium across a membrane. The classical Stewart approach (plasma only) has been widely used (2, 10, 20, 24, 32, 33) to try to explain acid-base abnormalities in blood with altered plasma protein concentrations and in body fluids of critically ill patients with hypoalbuminemia combined with other acid-base disturbances.
SID prediction using ion-equilibrium theory. The ion-equilibrium theory was devised (2) to unify various approaches; Wooten (42) used a single “master equation” to derive a linear algebraic equation for blood SID (Eq. 17). Blood BE is equivalent to changes from normal in the latter quantity. Importantly, this derivation allowed Stewart SID theory, centered on plasma, to be applicable to blood. This blood SID equation shows that its value can change due to changes in plasma concentrations of phosphate and serum albumin, blood concentration of hemoglobin, and erythrocyte DPG concentration. Hematocrit is also a potentially variable quantity in the equation, since we know that it changes with pH\text{B} (Fig. 5). Hence, changes in any of these quantities can produce acid-base disorders not attributable to simple acid-base additions or losses. This effect due to hypoalbuminemia, for example, is well characterized in the study of Fencl et al. (10) with critically ill patients. However, Wooten (42) never explored the accuracy of his predictions for changes in these quantities. In addition, the derivation assumed that pH\text{E} = pH\text{B} – 0.21, as found by Purcell et al. (29), and that the ratio of HCO\text{3}\^- concentration (expressed in I\text{E} or I\text{P}) in erythrocytes to that in plasma is constant. However, we showed in Fig. 2 that the approximation of Purcell et al. yielded considerable error when extrapolated beyond their limited pH measurement range. Also the results of Fig. 4 showed that this HCO\text{3}\^- ratio varied with pH\text{B}. Ignoring these effects leads to errors that should be evaluated.

In conclusion, we have produced mathematical models of physicochemical processes governing the equilibrium water volumes and concentrations of electrolytes and nonelectrolytes in blood and in blood in equilibrium with interstitial fluid. We have validated these models against extensive experimental data. The models can be used to improve our understanding of the factors leading to acid-base disorders, such as we showed for the effects of dilution with saline or water. Our models predicted BE and SBE values similar to those estimated using the traditional approach in ill patients, consistent with the limitations of that approach. This result further reinforces the validity of that approach. However, the traditional approach does not adequately explain the causes of complex disturbances in contrast to the new models described in this study. Hence, these new models represent ever-evolving tools giving more understanding to physicians who deal with acid-base disorders in critically ill patients.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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