Whole body acid-base and fluid-electrolyte balance: a mathematical model

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Wolf MB. Whole body acid-base and fluid-electrolyte balance: a mathematical model. Am J Physiol Renal Physiol 305: F1118–F1131, 2013. First published July 24, 2013; doi:10.1152/ajprenal.00195.2013.—A cellular compartment was added to our previous mathematical model of steady-state acid-base and fluid-electrolyte chemistry to gain further understanding and aid diagnosis of complex disorders involving cellular involvement in critically ill patients. An important hypothesis to be validated was that the thermodynamic, standard free-energy of cellular H⁺ and Na⁺ pumps remained constant under all conditions. In addition, a hydrostatic-osmotic pressure balance was assumed to describe fluid exchange between plasma and interstitial fluid, including incorporation of compliance curves of vascular and interstitialial spaces. The description of the cellular compartment was validated by close comparison of measured and model-predicted cellular pH and electrolyte changes in vitro and in vivo. The new description of plasma-interstitial fluid exchange was validated using measured changes in fluid volumes after isoosmotic and hyperosmotic fluid infusions of NaCl and NaHCO₃. The validated model was used to explain the role of cells in the mechanism of saline or dilutional acidosis and acid-base effects of acidic or basic fluid infusions and the acid-base disorder due to potassium depletion. A module was created that would allow users, who do not possess the software, to determine, for free, the results of fluid infusions and urinary losses of water and solutes to the whole body.

A TRUE UNDERSTANDING OF THE physiological effects of disease processes and attendant fluid infusions and losses requires consideration of the distribution of water, protein, electrolytes, and electrically neutral solutes among all the body fluids. Many simple analytical solutions to subsets of this physicochemical problem have been used since the time of Henderson (22), but they have yielded only limited understanding. Recently, Wolf and DeLand (39) developed a model of the steady-state water and electrolyte exchanges between interstitial fluid (I), plasma (P), and erythrocytes (E). They showed (38) that their model could be used along with laboratory blood-chemistry values to predict both the abnormal fluid and electrolyte distribution and acid-base status in critically ill patients. However, the lack of a cellular compartment limited this tool to the study of disease processes lacking significant osmolarity changes. Another shortcoming was an incomplete description of the forces moving water between plasma and interstitial fluid.

Hence, the aims of the present study were to expand and modify the previous IPE model (39) by 1) adding a parenchymal cell compartment, 2) incorporating a more explicit description of the forces leading to plasma-interstitial water distribution, 3) providing much more extensive validation of both water and electrolyte distribution, and 4) examining the predictions of the model relative to understanding dilution (saline) acidosis, effects of infusion of acidic, and basic solutions and to explore the role of potassium, a primary intracellular ion, in acid-base balance.

Glossary

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>Concentration of nonbicarbonate buffers in plasma, meq/l P</td>
</tr>
<tr>
<td>Alb</td>
<td>Serum albumin, g/dl P</td>
</tr>
<tr>
<td>BE</td>
<td>Base excess, meq/l</td>
</tr>
<tr>
<td>CIPE</td>
<td>Cell (C), interstitial (I), plasma (P), erythrocyte (E) model</td>
</tr>
<tr>
<td>DMO</td>
<td>5-dimethylloxazolidine-2,4-dione</td>
</tr>
<tr>
<td>E</td>
<td>Electrical potential</td>
</tr>
<tr>
<td>EC</td>
<td>Extracellular</td>
</tr>
<tr>
<td>F</td>
<td>Faraday constant</td>
</tr>
<tr>
<td>F&lt;sub&gt;cell&lt;/sub&gt;</td>
<td>Ratio of large-vessel to whole body hematocrit</td>
</tr>
<tr>
<td>Gl</td>
<td>Serum globulins</td>
</tr>
<tr>
<td>H</td>
<td>Height, m</td>
</tr>
<tr>
<td>Hct</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>Im</td>
<td>Impermeable species, mmol/l W</td>
</tr>
<tr>
<td>J</td>
<td>Compartment designation</td>
</tr>
<tr>
<td>LBM</td>
<td>Lean body mass, kg</td>
</tr>
<tr>
<td>NIC</td>
<td>Nicotine</td>
</tr>
<tr>
<td>O</td>
<td>Osmolarity, mosmol/l W</td>
</tr>
<tr>
<td>P</td>
<td>Gas partial pressure, mmHg</td>
</tr>
<tr>
<td>Pr</td>
<td>Hydrostatic pressure, mmHg</td>
</tr>
<tr>
<td>R × T</td>
<td>Gas constant times temperature, mmHg/(mosmol/l W)</td>
</tr>
<tr>
<td>SID</td>
<td>Strong ion difference, meq/l</td>
</tr>
<tr>
<td>TBW</td>
<td>Total body water, liters</td>
</tr>
<tr>
<td>[T&lt;sub&gt;pro&lt;/sub&gt;]&lt;sub&gt;0&lt;/sub&gt;</td>
<td>Total plasma protein concentration, g/dl P</td>
</tr>
<tr>
<td>V</td>
<td>Volume, liters</td>
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<tr>
<td>Wt</td>
<td>Weight, kg</td>
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<td>XA</td>
<td>Refers to plasma unmeasured ions, meq/l P</td>
</tr>
<tr>
<td>Z</td>
<td>Electrical valence, meq/mmol</td>
</tr>
<tr>
<td>K&lt;sub&gt;0&lt;/sub&gt;</td>
<td>Equilibrium constant</td>
</tr>
<tr>
<td>k</td>
<td>constant</td>
</tr>
<tr>
<td>l</td>
<td>Liters of fluid (l P stands for liters of plasma; l W stands for liters of water)</td>
</tr>
<tr>
<td>r</td>
<td>Ratio of concentrations</td>
</tr>
<tr>
<td>s</td>
<td>Stands for substance or species</td>
</tr>
<tr>
<td>Δ</td>
<td>Change from control state</td>
</tr>
<tr>
<td>Ω</td>
<td>Osmotic pressure, mmHg</td>
</tr>
<tr>
<td>φ</td>
<td>Osmotic coefficient</td>
</tr>
<tr>
<td>σ</td>
<td>Osmotic reflection coefficient</td>
</tr>
<tr>
<td>[s]</td>
<td>Concentration of substance s in compartment J, mM</td>
</tr>
</tbody>
</table>

Subscripts and Superscripts

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Reference state</td>
</tr>
</tbody>
</table>
Assumptions. The steady-state, three-compartment, interstitial (I), plasma (P), erythrocyte (E) model that Wolf and DeLand developed previously (39) was based on the original steady-state, whole body fluid, and electrolyte model of DeLand and Bradham (12). In addition to the three compartments listed above, they included a fourth compartment, cells (C). Hence, like their model, the present CIPE model includes four homogeneous compartments (assumption 1). At this time, the volumes of slowly equilibrating fluids, such as transcellular, are lumped into that of cells. However, the solute concentrations in the cellular compartment are those of skeletal muscle (assumption 2) since the cellular mass of this tissue is clearly the largest in the body and the concentrations of its cellular ionic constituents are most often measured.

Each compartment is electrically neutral. Hence the mass of cations is constrained to equal the mass of anions in each compartment. This law of electroneutrality in a solution is an accepted physical fact. Another accepted fundamental principle in the model is mass balance. With the use of the terminology of Stewart (34), total model masses of "strong" ions, such as Na\(^+\), K\(^+\), and Cl\(^-\) ions that do not associate chemically with H\(^+\), are conserved. These masses constitute "independent" variables that are unchanged, except when solutes are added by infusions or lost by renal excretion. Similarly, the total volume of water is conserved. In contrast, the total masses of "weak" ions such as H\(^+\) and HCO\(_3\)\(^-\) are not conserved (27); hence, they are "dependent" variables in the model and change as a consequence of conditions explored.

Figure 1 shows a diagram of these four compartments and some of the chemical species they contain. As seen, H\(_2\)O, CO\(_2\), and Cl\(^-\) are assumed to have an equilibrium-based distribution among these compartments (assumption 3). K\(^+\) is also assumed to have an equilibrium distribution, but for only three compartments, since it is effectively impermeable to erythrocytes as found by Raftos et al. (31) (assumption 4). This assumption differs from that of DeLand and Bradham (12), who simulated Na\(^+\) and K\(^+\) distribution across erythrocyte and cellular membranes using a constant, standard-free-energy pump. In contrast, our previously validated IPE model (39) used the erythrocyte model of Raftos et al. (31) who found that besides K\(^+\), Na\(^+\) was also effectively impermeable to this membrane (assumption 5). Na\(^+\) and other small ions not shown, such as Ca\(^2+\), Mg\(^2+\), Pi\(^-\), and lac\(^-\), distribute at equilibrium across the I-P microvascular membrane, with the latter two also entering erythrocytes.

The concentrations of Na\(^+\) and H\(^+\) in the cellular compartment are assumed to be at steady state, not equilibrium (assumption 6), because these ions are actively extruded through an energy-consuming pump, as originally suggested by DeLand and Bradham (12). Furthermore, the thermodynamic standard-free energy of each of these pumps is assumed to be constant in the face of varying conditions (assumption 7), which is similar to their assumption. This assumption will be explored in detail in the present study. H\(^+\) is assumed to follow equilibrium conditions in the other compartments (assumption 8) as we verified previously (39). The concentration of HCO\(_3\)\(^-\) in each compartment (shown for compartment I) is determined by the Henderson-Hasselbalch equilibrium relation using compartment concentrations of dissolved CO\(_2\) and H\(^+\) as we described previously (39). Although CO\(_2\) is assumed to be freely diffusible throughout the model fluid compartments, its water-dissolved concentrations are different because of different CO\(_2\) solubilities in each compartment.

The equilibrium distributions of H\(_2\)O across P-E and C-I membranes are based on equality of osmotic pressures (osmolarities) across each membrane (assumption 8) as described previously (39). Equal osmolarities in the I and P compartments was assumed in our previous study (39); however, in the present study, H\(_2\)O equilibrium across the I-P membrane is based on the Starling osmotic-hydrostatic, pressure-balance equation as used by Gyenge et al. (19) previously (assumption 9; see below).

Impermeable metabolites and the electrically charged protein, hemoglobin (Hb), exist in erythrocytes. As described in detail previously (39), the metabolites, DPG, ATP, and GSH interact with Hb, with the equations of these equilibrium reactions and their pK values simulated as Raftos et al. (31). Also from Raftos et al., the erythrocyte [H\(^+\)]-dependent reactions with Hb are simulated empirically, as described previously, by an algebraic, pH-dependent, Hb electrical-charge equation (assumptions 10). The [Hb]-dependent osmotic coefficient is also simulated empirically, as previously, by an algebraic equation (assumption 11). Albumin (Alb\(^-\)) and impermeable globulins (Gl\(^-\)) exist in plasma. The pH-dependent, algebraic, electrical-charge equation for albumin used previously (39) is from Figge (16). The charge on globulin is not considered important (assumptions 12). Only albumin exists in interstitial fluid. Due to a general lack of information, assumption 13 is that the initial interstitial albumin concentration is 50% of that in plasma but that this albumin is excluded from 50% of the interstitial space, which gives an osmotic pressure value similar to Gyenge et al. (19). Water movement into or out of this space changes the fractional excluded volume.

At this time, the new cellular compartment (see below) simply contains Na\(^+\), K\(^+\), Cl\(^-\), and H\(^+\); HCO\(_3\)\(^-\) is produced from CO\(_2\) and

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**METHODS**

*Mathematical Model*

*Assumptions.*
H$_2$O as in other compartments. A single impermeable species exists which is labeled Pro$^+$ in Fig. 1. However, besides protein, this species implicitly consists of ions, such as Ca$^{2+}$, Mg$^{2+}$, etc. that are at least partially bound to protein. This impermeable species interacts chemically with H$^+$ as described by a pKa of 6.5. This value was chosen because it is the effective value for histidine side chains on imidazole groups of myoglobin, a major protein in skeletal muscle. These details could change later if more detailed experimental data becomes available.

**Model equations.** In the following equations, superscripts refer to compartments and subscripts to species. Molar concentration of species “i” in water (W) volume of compartment “J” is written as $[i]_W$. The electroneutrality. In each compartment, J, for cations (+) and anions (−),

$$\sum Z_i^+ \times [+]_W - \sum Z_i^- \times [-]_W = 0$$

(1)

where $\Sigma$ is sum, Z is electrical valence (i.e., +1 for Na$^+$ and −1 for Cl$^-$, etc.), and $[\cdot]_W$ is ion molar concentration in mmol/lW. Electrical valence for albumin in plasma and interstitial compartments and for hemoglobin in erythrocytes are empirical algebraic equation given previously (39).

**Osmotic equilibrium.** Osmotic equilibrium across erythrocyte (E) and cell (C) membranes requires that,

$$\Omega^E = \Omega^C = \Omega^I$$

(2)

where O is osmolarity, defined for all solutes (s) in compartment J as,

$$\Omega^J = \sum \phi_s \times [s]_W$$

(3)

and $\phi$ is the osmotic coefficient for each solute. Following Raftos et al. (31), the values of $\phi$ for small charged solutes and uncharged solutes are 0.93 and 1.0, respectively, in each compartment. For impermeable solutes other than hemoglobin, a value of 1.0 was assumed for lack of better information. For hemoglobin, $\phi$ was determined by the algebraic equation of Raftos et al. given previously (39).

**Mass conservation (balance).** Mass balance for solutes such as, Na$^+$, K$^+$, and Cl$^-$ and for water requires that,

$$\sum V_s^J \times [s]_W = M_s$$

(4)

where V is volume in liters and M is mass of each solute in mmol. A solute may exist in from one to all four compartments. There is no mass conservation for ions, such as H$^+$ and HCO$_3^-$.

**Ions at equilibrium (Gibbs-Donnan).** Cl$^-$ is at equilibrium across all four compartment boundaries. Hence, if a mobile cation, such as K$^+$, is also at equilibrium between any two compartments, say 1 and 2, then,

$$\frac{[\text{Cl}^-]^1}{[\text{Cl}^-]^2} = \frac{[\text{K}^+]^2}{[\text{K}^+]^1}$$

(5)

This equation applies to all ions across the P-I microvascular membrane, except that the compartment numbers on the right-hand side are reversed if the ion is negatively charged. The other exception is that if the ion has a valence of 2, such as Ca$^{2+}$, then these latter terms are squared. From the assumption of equilibrium distribution of K$^+$ across the C-I membrane, then this equation holds there also. The thermodynamic derivation for this equilibrium relation is given in APPENDIX A.

**Ions at steady state.** Across the C-I membrane, the distributions of Na$^+$ and H$^+$ are moved away from an equilibrium state by active forces (Fig. 1). Hence, these distributions are classified as steady state. Deland and Bradham (12) showed that the steady-state pump energies for these ions could each be thermodynamically characterized by a constant determined from standard-state ion concentrations; however, they formulated their equations in terms of the Gibbs free-energy approach. Furthermore, they assumed that these constants did not change when perturbations were applied to the model. In the equivalent approach used in the current study, these ion distributions can be characterized (see APPENDIX A) by Donnan-like relations,

$$\frac{[\text{Cl}^-]^1}{[\text{Cl}^-]^2} = k_{Na} \times \frac{[\text{Na}^+]^2}{[\text{Na}^+]^1}$$

(6)

$$\frac{[\text{Cl}^-]^1}{[\text{Cl}^-]^2} = k_{H} \times \frac{[\text{H}^+]^2}{[\text{H}^+]^1}$$

(7)

The values of these two constants (Table 2) are determined from the standard-state ion concentrations in Table 1 and are unchanged thereafter. It is important to note that in the present study, the K$^+$ ratio can be substituted for the Cl$^-$ ratio, except that the K$^+$ ratio is inverted. Since the Cl$^-$ concentration ratio appears in Eqs. 5–7, equations can be derived relating any two of these four ions.

**Acid-base relations.** 1) Bicarbonate (Henderson-Hasselbach). In each compartment, J, following the approach of Raftos et al. (31),

$$[\text{HCO}_3^-]^J = S_{\text{CO}_2} P_{\text{CO}_2} \times 10^{(p\text{H}_2O-p\text{K})}$$

(8)

where S is solubility, P is partial pressure, and K is the equilibrium constant for the reaction. P$\text{CO}_2$ is the same throughout the fluid compartments. The value of pK for this reaction was assumed to be 6.1 in each compartment. Values of S are given in Table 1.

2) Metabolite and protein reactions. In compartment E, the metabolites, DPG, GSH, ATP and the protein, Hb, interact with H$^+$ such that their valence (Z) values are pH dependent. As described previously (39), following Raftos et al. (31), in general for species s,

$$Z_s = z_0 + z_1 \times \frac{b_1}{1 + b_1} + \frac{b_2}{1 + b_2}$$

(9)

where $z_0$ and $z_1$ are constants and $b_1 = 10^{(p\text{H}_2O-p\text{K})}$ and $b_2 = 10^{(p\text{H}_2O-p\text{K})}$. A similar equation described the pH-dependent Z values for albumin, except the value of plasma pH, was used. All the constant values were given previously (39).

In the new cell compartment, the buffering reaction of the impermeable species was treated similarly with $z_0 = 0$, $b_1 = 0$, $p\text{K}_1 = 6.5$, and $z_1$ equal to the charge value in Table 1.

**Pressure equilibrium across the P-I membrane.** The Starling principle is used to describe the steady-state pressure balance across the microvascular membrane (19). Hence,

$$p_{\text{Pr}} - p_{\text{Pr}0} = \sigma_{\text{sm}} \times (\Pi_{\text{P}} - \Pi_{\text{I}}) - 19.3 \times \sigma_{\text{sm}} \times (O_2 - O_2) = 0$$

(10)

where $\Pi$ and $\Pi_{\text{P}}$ stand for capillary (microvascular) hydrostatic and plasma colloid-osmotic pressures, respectively. $\sigma_{\text{sm}}$ and $\sigma_{\text{sm}0}$ are the osmotic reflection coefficients for large and small molecules, respectively, across the microvascular wall (Table 2). The 19.3 mmHg/(mosmol/lW) constant is for a temperature of 37°C. A positive value for $p_{\text{Pr}}$ pushes fluid out of plasma whereas a positive $\Pi_{\text{P}}$ or $\Pi_{\text{I}}$ pulls fluid into plasma. All pressures are in mmHg.

1) Hydrostatic pressure. Following the approach of Gyenge et al. (19), microvascular hydrostatic pressure ($p_{\text{Pr}}$) is a linear function of blood volume. However, it is convenient to relate it to the change in blood volume from its reference state ($\Delta V_{\text{B}}$), hence,

$$p_{\text{Pr}} - p_{\text{Pr}0} = k_{\text{B}} \times \frac{\Delta V_{\text{B}}}{V_{\text{B}0}}$$

(11)

where $k_{\text{B}}$ is a constant and superscript 0 refers to the standard-state value (Table 1).

Gyenge et al. (20) described intermittent hydrostatic pressure ($p_{\text{Pr}1}$) as a three-phase, piecewise-linear function of interstitial volume. The phases were: dehydration, moderate hydration (mh) and overhydration.
### Table 1. Standard-state data

<table>
<thead>
<tr>
<th>Compartment: Solute or Quantity (units)</th>
<th>Venous Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erythrocyte (E)</td>
</tr>
<tr>
<td>V, l</td>
<td>1.44</td>
</tr>
<tr>
<td>Blood volume,* l</td>
<td></td>
</tr>
<tr>
<td>II, mmHg</td>
<td>120</td>
</tr>
<tr>
<td>Albumin, g/dlW or g/dlV</td>
<td>4.31</td>
</tr>
<tr>
<td>Total plasma protein, g/dlV</td>
<td>7.04†</td>
</tr>
<tr>
<td>[Na⁺]†</td>
<td>13.7</td>
</tr>
<tr>
<td>[K⁺]†</td>
<td>136</td>
</tr>
<tr>
<td>[Cl⁻]†</td>
<td>73.2</td>
</tr>
<tr>
<td>pH</td>
<td>7.19</td>
</tr>
<tr>
<td>[HCO₃⁻]†</td>
<td>20</td>
</tr>
<tr>
<td>Pr (mono- and divalent)†</td>
<td>0.92</td>
</tr>
<tr>
<td>Ca²⁺ + Mg²⁺</td>
<td>3,3</td>
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<tr>
<td>Lactate⁻</td>
<td>1.06</td>
</tr>
<tr>
<td>Hb (tetramer), b mM</td>
<td>5.3</td>
</tr>
<tr>
<td>DPG, b mM</td>
<td>4.4</td>
</tr>
<tr>
<td>ATP, b mM</td>
<td>1.8</td>
</tr>
<tr>
<td>GSH, b mM</td>
<td>2.2</td>
</tr>
<tr>
<td>Fractional H₂O content, a ml/l</td>
<td>0.73</td>
</tr>
<tr>
<td>CO₂ solubility, mM/mmHg</td>
<td>0.026</td>
</tr>
<tr>
<td>Hct, %</td>
<td>43.9†</td>
</tr>
<tr>
<td>Osmolarity, mosmol/lW</td>
<td>288.9</td>
</tr>
<tr>
<td>Impermeables, mmol/lW</td>
<td>16.8</td>
</tr>
<tr>
<td>Charge on impermeables, mEq/lW or mEq/mosmol⁻</td>
<td>-3.25†</td>
</tr>
<tr>
<td>Uncharged permeables (urea and glucose), mmol/lW</td>
<td>10.6</td>
</tr>
<tr>
<td>Hydrostatic-pressure difference (Pr⁺ – Pr⁻), mmHg</td>
<td>0.097*</td>
</tr>
</tbody>
</table>

See GLOSSARY for definitions. *From Boer et al. (6) as corrected for fractional water content in P and E compartments. †From O’Kell and Elliot (28). ‡Similar to Gyenge et al. (19). ‡‡From Raftos et al. (31). #From Wolf and Deland (39). #†Values determined to make model compartment volumes and other unknowns equal to selected standard-state values. #Cell units only.

(oh). Following their approach, but only considering the last two phases for the present study,

\[
P_r^1 - P_r^{i0} = k_l^{1-ur} \frac{\Delta V_l}{V_l^{i0}}, \quad \Delta V_l = \Delta V_l^{i0} \leq k_l^{1-ur} \quad (12)
\]

where \(k_l^{1-ur}\) and \(P_r^{1-ur}\) are the fractional change in volume and the pressure at which the transition between the two phases occurs. The constants in Eq. 12 (Table 2) were determined from experimental data (see RESULTS).

2) Osmotic pressure. Colloid osmotic pressures (II) for plasma and interstitial proteins were determined from the polynomial equations given by Ahlqvist (2). For plasma, that contains both albumin and globulins.

### Table 2. Model constants

<table>
<thead>
<tr>
<th>Constant</th>
<th>Units</th>
<th>Eq. No</th>
<th>Value (Ref.)</th>
</tr>
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<tbody>
<tr>
<td>(k_{sc})</td>
<td>7</td>
<td>368 (Table 1)</td>
<td>17.5 (15)</td>
</tr>
<tr>
<td>(k_{st})</td>
<td>8</td>
<td>10 (Table 1)</td>
<td></td>
</tr>
<tr>
<td>(k_{ch})</td>
<td>mmHg</td>
<td>11</td>
<td>93*</td>
</tr>
<tr>
<td>(k_{ch})</td>
<td>mmHg</td>
<td>12</td>
<td>0.097*</td>
</tr>
<tr>
<td>(P_{ch})</td>
<td>mmHg</td>
<td>12</td>
<td>9*</td>
</tr>
<tr>
<td>(\sigma_{sh})</td>
<td>mmHg</td>
<td>12</td>
<td>8.3*</td>
</tr>
<tr>
<td>(\sigma_{sm})</td>
<td>9</td>
<td>0.99 (19)</td>
<td></td>
</tr>
<tr>
<td>(\sigma_{sm})</td>
<td>9</td>
<td>0.5 (36)</td>
<td></td>
</tr>
</tbody>
</table>

See GLOSSARY for definitions. *Determined experimentally (see RESULTS).
The values of the constants (k) in the various equations are shown in Table 2.

MODEL SOLUTION. The model has seven constrained equations, electroneutrality for each of the four compartments, as described by Eq. 1, osmotic equilibrium across E and C membranes, as described by Eq. 2 and the pressure-equilibrium equation across the P-I membrane, as described by Eq. 10. These relations were simulated using the VisSim computer program (Visual Solutions, Westford, MA) by attaching appropriate CONSTRAINT blocks in the simulation as described previously (39). VisSim allows unknowns to be specified by attaching UNKNOWN blocks. For a valid solution satisfying these seven constraints, seven unknowns are specified. For the standard-state solution, the seven unknowns are those described above (Table 1). The values given in Table 1 are those found by VisSim using a Newton-Raphson approach to this complex optimization problem.

When electrolytes and water are added to the model to simulate experimental infusion protocols, appropriate electrolyte masses and water volume are incremented and the model equations solved again. For such nonstandard-state solutions, seven new, nonstandard-state unknowns are specified. Those chosen were as follows: VCW, VPW, VW, [Cl−]EW, [Cl−]PW, [Cl−]EW, and pHW. All the other variables in the model are determined in VisSim from these seven values.

To simulate some experiments where plasma concentration values were measured, these concentration values were fixed in the model solution by constraining the appropriate model variables to these measured values. The additional constraints allowed specification of a like number of additional unknowns. These unknowns were usually masses of the constrained electrolytes. Hence, if [Na+]p were measured, for example, and then constrained in the model, the new unknown would be the total mass of Na+.

MODEL VARIABLES. Model variables were as follows: [Na+], [K+], [Cl−], [H+], [HCO3−], [Cl−], [CO2], and urea, glucose in all compartments; [Hb], [GSH−], [ATP−], [DPG−] in erythrocytes; [Pi−] and [lact−] in L, P, and E compartments; Ca2+, Mg2+, and albumin in L and P compartments; and Pro− (Im−) in C and E compartments.

Protocols for experimental validation studies and model simulation. IN VITRO RAT-DIAPHRAGM STUDIES (TO VALIDATE CELL BUFFERING PROPERTIES). Adler et al. (1) incubated a group of intact rat diaphragms in a Krebs-Ringer bicarbonate solution at 37°C, over a range of bath PCO2 values, while maintaining bath HCO3− concentration relatively constant (respiratory disturbance) and in another group, to a range of bath HCO3− concentrations while maintaining PCO2 relatively constant (metabolic disturbance). For each disturbance, both bath and cell pHs were measured at each individual condition; cell pH (pHf), was measured using both 5,5-dimethyloxazolidine-2,4-dione (DMO), a weak acid, and nicotine (NIC), a weak base. The reasoning was that mean pHf would lie somewhere between the DMO and NIC values.

Model simulation of the rat diaphragm experiments was achieved by keeping model V constant and constraining interstitial ion concentrations to the bath-buffer values (simulated large-volume bath). For respiratory disturbances, model PCO2 and pHf were constrained to the measured values at each condition. Hence, the interstitial fluid of the model approximated the bathing fluid. Then, the model was solved for the values of pHf and other variables consistent with these constraints. For metabolic conditions, pHf and [HCO3−] were constrained to measured values at each condition and PCO2 and Cl− mass were designated as unknowns, the latter to simulate acid addition or deficit (see DISCUSSION). Then, the model was solved to obtain the value of pHf and other variables consistent with the measurements at each condition. Clearly, these experiments did not mimic in vivo conditions, since extracellular K+ concentrations change markedly in vivo during acid-base disturbances (18), see below.

IN VIVO STUDIES (TO VALIDATE CELL BUFFERING PROPERTIES). 1) Respiratory and metabolic (infusions of HCl or NaHCO3) disturbances. There have been studies in humans, dogs and rats where both pHf and pHf (DMO) were measured. Manfredi (26) measured arterial PCO2, pH, and pHf in five healthy, awake human subjects under control conditions, during respiratory alkalosis (3 h of voluntary hyperventilation) and respiratory alkalosis (3 h of 7% CO2 breathing). Manfredi calculated pHf by adding 0.02 to the arterial-blood values. Waddell and Butler (35) used four anesthetized and nephrectomized dogs, individually subjected to serial periods of respiratory and/or metabolic disturbances. Brown and Goot (8) used 10 similarly prepared dogs where 20 mmol/kg of 1 M NaHCO3 or 5 mmol/kg of 0.3 M HCl were infused. Irvine and Dow (23) made measurements in 24 rats. The first group of eight were sham-operated controls, the second group were nephrectomized, and the last group were given NH4Cl by stomach tube 24 h after the operation. Measurements were made 48 h after the operation.

In the model simulation of these studies and ones to follow, model PCO2 was constrained to the measured value of venous blood. If only arterial values were given, they were corrected to venous by multiplying by 1.15, the ratio of normal venous to arterial values. For HCl infusion, the model mass of Cl− was increased appropriately. For NaHCO3 infusion, the mass of Na+ was incremented. See DISCUSSION for the rationale of this approach.

2) Metabolic acid-base consequences due to K+ and Cl− depletion (to validate ion-pump assumptions). Grantham and Schloerb (18) measured pHf and pHf (DMO) along with plasma and muscle electrolytes in dogs. Five animals were maintained on a low K+ diet for 18 days, but NaHCO3 was added to the diet and drinking water. Six additional dogs were dietary-Cl− depleted for 22 days, and five of these were further Cl− depleted by 4 days of gastric drainage. They also included data for control experiments from a previous study. Plasma and muscle electrolytes were measured at the end of each experiment.

Simulation of these experiments was first, have the VisSim program constrain model values to experimental-control mean values of [Na+]p, [K+]p, [Cl−]p, pHf, and pHf (normally, dependent variables) and designate the whole body masses of Na+, K+, and Cl−, and the value of [XA−]p (the net concentration of unmeasured ions) as unknowns to be determined by the program. For this control condition, the other model variables that were compared with experimental values were [Na+]p, [K+]p, [Cl−]p, pHf, and pHf (normally, dependent variables). Although not experimentally measured, the control values of Vf and Vc were recorded to compare with subsequent perturbations. Next, the constrained variables, above, were set to the measured K+ -depletion values and the model solved to obtain new cellular ion concentrations and pHf, new values of Vf and Vc and altered values of ionic masses and [XA−]p. This latter procedure was then repeated for the K− and Cl− depletion experiments.

CIPE VOLUME DISTRIBUTION MEASUREMENTS (TO VALIDATE PLASMA-INTERSTITIAL, FLUID-BALANCE ASSUMPTIONS). A major shortcoming of our previous IPE model (39) was that the model-predicted changes in compartmental volumes were never fully validated. To address this fault, the volume predictions were compared with the measurements of Bradham et al. (7) and Dörr et al. (14) in anesthetized, nephrectomized and splenectomized dogs and those of Onarheim (30), Bradham et al. (7) and Dörr et al. (14) measured hematocrit (Hct), the volume of erythrocytes (Vf) using 51Cr-tagged cells, plasma volume (Vp) calculated from Vf and Hct values using an assumed Fcav value of 0.88 (ratio of large-vessel to whole body hematocrit), extracellular water (VECW) using 14C-sucrose or 35S, and the volume of other cells (VC) calculated as the difference between total body water (TW), measured with H3OH, and VECW. These measurements were made for a sham infusion (n = 7) before and after infusion of either 20 ml/kg of isotonic (0.154 M) NaCl solution (n = 5), 10 ml/kg of 0.892 M NaCl (n = 5), or 10 ml/kg of...
0.892 M NaHCO₃ (N = 5), except Dörr et al. (7) only infused NaHCO₃ (n = 9). Onarheim (13) used three groups (6 animals each) of anesthetized and nephrectomized Wistar rats. The first group served as controls, the second group was infused with 100 ml/kg of Ringer’s-acetate (R-ac) solution, and the third group was given 10 ml/kg of 1.2 M (7%) NaCl. Measurements made in each group were Hct, VP using ¹²⁵I-albumin, VₑCW using ⁵¹Cr-EDTA, and plasma electrolyte concentrations among others.

Model simulation of these infusions was by incrementing the total volume of water and masses of ions according to the volume infused and composition of each solution. For the R-ac infusion simulation, the acetate was not added since it is metabolized by the time of the steady-state measurement period (starting 2 h postinfusion).

RESULTS

Validation

The first step in the validation process was to determine if the buffering characteristics of the cell compartment approximated that of experimental data.

In vitro rat-diaphragm studies. As seen in Fig. 2, Adler (1) found that for either a respiratory (top) or metabolic (bottom) disturbance, cell pH (pHₑ) increased monotonically with bath (extracellular) pH (pHₑ) using either DMO (open circles) or NIC (filled circles) for pHₑ measurements. However, the DMO data were up to 0.5 pH units larger than the NIC data.

Model predictions are shown by the solid lines in both panels of Fig. 2, top and bottom. These lines are almost straight, but curve slightly upward at increasing pHₑ. The model results tend to be closer to the DMO data at high pHₑ, whereas they are closer to the NIC data at low pHₑ. These results follow the trend of the experimental data, but with a slightly greater slope.

Heisler and Piiper (21) determined the slope of the [HCO₃⁻]/[H⁺] curve in rat-diaphragm experiments over a 1–40% CO₂ range. They found a mean value of 67 meq/(pH kgH₂O), with an SD value of 10–11. The model-predicted result of 59 meq/(pH kgH₂O) is quite comparable. Burton (9) gives values of from 54 to 116 meq/(pH kgH₂O) in skeletal muscle of various animals.

As seen in Fig. 2, over the physiological range of pHₑ values, model predictions lie between the DMO and NIC measurements as might be expected for mean pHₑ values. The only additional assumptions made in the model to obtain these results were that pHₑ = 6.9 under our standard conditions and that histidine (pKₐ = 6.5) was the primary cell-buffering species (see Discussion).

In vivo studies. RESPIRATORY AND METABOLIC DISTURBANCES. Changes in pHₑ, as related to interstitial-pH (pHᵢ) changes, are shown in Fig. 3 for both respiratory (top) and metabolic (bottom) disturbances. The filled symbols in Fig. 3, top, show the mean values and SD bars for the respiratory disturbances in three studies: Manfredi (26), circles; Brown and Goot (8), Waddell and Butler (35), and Grantham and Schloerb (18) and on rats by Irvine and Dow (23). Top: data for respiratory acid-base disturbances. Bottom: data for metabolic acid-base disturbances.
line (Fig. 3, top) shows the human-model results for a range of \( \text{PCO}_2 \) values.

The mean experimental data (open symbols) with SD bars in Fig. 3, bottom, show similar changes as above but produced by metabolic acid-base disturbances. The upward-triangle data are from Irvine and Dow (23), the downward-triangle data are from individual experiments by Brown and Goott (8), and the open-diamond data point represents the mean of controls by Grantham and Schloerb (18). These data show that the changes in \( \text{pH}^C \) (DMO) and \( \text{pH}^I \) parallel each other just as in the respiratory disturbances (Fig. 3, top) but with a greater slope than for the respiratory disturbances (note \( \text{pH}^C \) scale change). The slightly upward-curved, solid line (Fig. 3, bottom) shows the results from the model where Na\(^+\) was added from control state to simulate metabolic alkalosis and where \( \text{Cl}^- \) was added from control state to simulate metabolic acidosis (see DISCUSSION). As in the in vitro studies (Fig. 2), the model results closely mimic the experimental data trend.

**ACID-BASE CONSEQUENCES OF K\(^+\) AND CL\(^-\) DEPLETION.** Table 3 shows the experimental results and model predictions for the K\(^+\) and \( \text{Cl}^- \) depletion experiments of Grantham and Schloerb (18). Table 3, top, shows the experimental measurements in plasma and the matching model-constraint values (italics) for each of the three groups. As seen, under the conditions of these experiments, K\(^+\) depletion alone or with added \( \text{Cl}^- \) depletion resulted in measured decreases in control \( [\text{K}^+]^P \) and \( [\text{Cl}^-]^P \) and decreases in interstitial \( [\text{H}^+]^I \) ([\( \text{H}^+]^I \)). The decreases in \( [\text{H}^+]^I \) were consistent with an extracellular metabolic alkalosis since \( \text{PCO}_2 \) increased from control.

Table 3, top middle, shows corresponding experimental measurements for muscle electrolytes for the three conditions along with model predictions (italics). The model \( [\text{K}^+]^C \) and \( [\text{Na}^+]^C \) control predictions are very close to the control measurements, even though there was no attempt to directly match them with these experimental data. For both K\(^+\) depletion alone \( s\) or with added gastric drainage, measured \( [\text{Na}^+]^C \) more than doubled, compared with control, whereas \( [\text{K}^+]^C \) greatly decreased. However, there was no significant difference between these measurements under these conditions. However, in contrast to the extracellular metabolic alkalosis, there was a cellular acidosis in both conditions. Hence, extracellular and cellular acid-base states may go in opposite directions when conditions such as K\(^+\) depletion occur. The model predicted these quantitative changes reasonably well, considering the large SD values of the measurements.

Table 3, bottom middle, shows ionic-concentration ratios derived from experimental data. These experimental data prompted Grantham and Schloerb (18) to suggest that there is a fixed relationship between the transcellular concentration ratios of \( \text{H}^+ \) and K\(^+\). In all three cases, the measurements suggest a value near 10, the value used in the model. Unfortunately, there is no way to derive statistics for this relationship from just the mean and SD values given by Grantham and Schloerb. However, they used another approach (see Fig. 4, Model (change from control))

<table>
<thead>
<tr>
<th>Species</th>
<th>Control (n = 11)</th>
<th>Human Model</th>
<th>K(^+) Depletion (n = 11)</th>
<th>Human Model</th>
<th>K(^+) Depletion and Gastric Drainage (n = 5)</th>
<th>Human Model</th>
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<tr>
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<td><strong>Venous Plasma</strong></td>
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<tr>
<td></td>
<td>([\text{Na}^+]^P, \text{mEq/l})</td>
<td>146 ± 5.6</td>
<td>146</td>
<td>152 ± 2.7</td>
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<td>147</td>
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<td></td>
<td>([\text{K}^+]^P, \text{mEq/l})</td>
<td>4.3 ± 0.3</td>
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<td>2.2 ± 0.3</td>
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<td></td>
<td>([\text{Cl}^-]^P, \text{mEq/l})</td>
<td>105 ± 4</td>
<td>97 ± 5</td>
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<td>88 ± 8.9</td>
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<td></td>
<td>(\text{PCO}_2, \text{mmHg})</td>
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<td>48.2 ± 5.3</td>
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<td>49.3</td>
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<td>([\text{H}^+]^I, \text{nM})</td>
<td>40 ± 0.8†</td>
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<td>32 ± 0.7</td>
<td>32</td>
<td>31</td>
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<td></td>
<td><strong>Muscle-Cell Water (model (k_{Na} = 368))</strong></td>
<td>14.5 ± 10.3</td>
<td>13.3</td>
<td>30.8 ± 15.2*</td>
<td>24.2</td>
<td>32 ± 23.5*</td>
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<tr>
<td></td>
<td>([\text{K}^+]^P, \text{mEq/lw})</td>
<td>151 ± 10.3</td>
<td>125 ± 15.6*</td>
<td>129</td>
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<td>([\text{H}^+]^I, \text{nM})</td>
<td>133 ± 7</td>
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<td><strong>Concentration ratios</strong></td>
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<td>11</td>
<td>8.42</td>
<td>10</td>
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<td></td>
<td>([\text{H}^+]^I \div [\text{K}^+]^I)</td>
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<td>368</td>
<td>280</td>
<td>368</td>
<td>230</td>
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<td></td>
<td><strong>Model (change from control)</strong></td>
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<tr>
<td></td>
<td>(\text{Na}^+, \text{mEq/kg})</td>
<td>9.8</td>
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<tr>
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<td>(\text{K}^+, \text{mEq/kg})</td>
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<td>(\text{Cl}^-, \text{mEq/kg})</td>
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<td>(\text{XA}^-, \text{mEq/l})</td>
<td>2.7</td>
<td>3.8</td>
<td>2.7</td>
<td>3.8</td>
<td>2.7</td>
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<td>(\Delta V^I \text{(l)})</td>
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<td>2.2</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>(\Delta V^I \text{(l)})</td>
<td>-2.5</td>
<td>-1.2</td>
<td>-2.5</td>
<td>-1.2</td>
<td>-2.5</td>
</tr>
</tbody>
</table>

Statistical values are means ± SD. See glossary for definitions. *For either \(\text{Na}^+\) or \(\text{K}^+\), not statistically significant from each other, \(P > 0.05\).
Figure 4. Large graph shows experimental data for the H⁺ concentration ratio (gradient) across the cell membrane plotted against the transcellular K⁺ gradient from Grantham and Schloerb (18), open circles, and Schloerb and Grantham (32), open triangles. The slope of the regression line passing through the origin is 9.95 ± 0.33 SE. Inset graph shows experimental data (open triangles) from Schloerb and Grantham (32) for the transcellular Na⁺ gradient plotted against the corresponding K⁺ gradient. The slope of the regression line through the origin is 444 ± 50 SE.

The bottom section of Table 3 shows the model-predicted changes in ion masses and [X\(^+\)]\(^P\) required for the model to predict the plasma-concentration values in these conditions for a 70-kg man. For K⁺ depletion, the major changes are a large increase from control of 9.8 meq/kg in Na⁺ mass and a similarly large decrease in K⁺ mass, the latter predominantly from cells. The predicted increase in Cl⁻ mass relative to control would suggest an increase in extracellular [Cl⁻], but measured [Cl⁻]\(^P\) actually decreased. The reason for this latter observation, as shown by the model, was the large shift of water from cells (negative ΔV\(^C\)) that accompanied the cellular K⁺ loss shown in Table 3. From the model, the most important change brought about by gastric drainage was net loss of Cl⁻ compared with control, leading to a further decrease in [Cl⁻]\(^P\).

Figure 4 shows concentration ratios of Table 3 plotted for individual experiments. The larger graph shows plots of the data from Grantham and Schloerb (18), open circles, for the K⁺ depletion experiments alone and with accompanying Cl⁻ depletion, whereas the data from Schloerb and Grantham (32), open triangles, show data for added gastric Cl⁻ depletion. The regression line shows the statistical relationship between the transcellular H⁺ and K⁺ ratios for a wide range of values. The slope value of 9.95 ± 0.33 SE is clearly not different from the constant value of 10 assumed in the present study (see DISCUSSION). Figure 4, inset, shows Na⁺ and K⁺ concentration-ratio data from Schloerb and Grantham (32). The slope of the relationship is 444 ± 50 SE. The large scatter in the data prevents a strong assertion that this value remains constant over a wide range of conditions. However, the value is not statistically different from the \(k_{Na}\) value of 368 assumed in the model.

Since the exact value of \(k_{Na}\) is questionable, it is interesting to look at the effect of changes in this value on model results. Hence, Table 4 shows the same experimental data as Table 3, other than plasma values and concentration ratios, but with \(k_{Na}\) set to either 280 or 230, the experimental values of Table 3 for K⁺ depletion or K⁺ and Cl⁻ depletion, respectively. To simulate these changes, the model standard-[Na⁺]\(^C\) value was increased in proportion to the decrease in \(k_{Na}\) (see Eq. 6). Hence, it was also necessary to increase the mass of Na⁺ in the model. Then, the new values of the seven unknowns were determined, as above, to establish the new standard state. Finally, the three sets of experimental conditions were each simulated in the model and the new results obtained as before. These new values are shown in Table 4. As seen, other than the expected increases in [Na⁺]\(^C\) for the three conditions, the results and their trends are quite similar to those in Table 3. Hence, the model is fairly insensitive to changes in \(k_{Na}\). It is clear, however, that this procedure is not a true sensitivity analysis of this parameter because a \(k_{Na}\) change necessitated re-solving the model to find the new values of the seven unknown parameters of the standard state.

The second part of the validation process is to examine the comparison of volume changes experimentally measured and those predicted.

**CIPE volume-distribution measurements. ISOTONIC INFUSIONS.** The changes in fluid volumes due to infusions of 0.154 M NaCl by Bradham et al. (7) and Ringer’s acetate (R-ac) by Onarheim (30) are shown in Fig. 5. Figure 5, top, shows control data (hatched bars) from Bradham et al. no infusion was given. As seen, the mean percent changes for Hct, V\(^E\), V\(^P\), V\(^E_{CW}\), and V\(^C\) were not significantly different from sham preinfusion levels, considering the SD values shown. Figure 5, bottom, shows data on these same quantities after NaCl infusion (hatched bars) and R-ac infusion (light-gray bars) compared with preinfusion data. Infusion of either solution caused significant decreases in Hct and significant increases in V\(^P\) and V\(^E_{CW}\). As expected, NaCl infusion caused little change in erythrocyte and other -cell volumes because this concentration of NaCl is considered to be isotonic. Onarheim did not measure volumes of erythrocytes or other cells, but the model results below suggested that these volumes increased significantly, indicating that R-ac is not isotonic in the steady-state period ~2 h after the infusion because of acetate metabolism (see DISCUSSION).

Model predictions for the NaCl infusion (circles) are quite similar to the experimental data. However, this result is expected because the slope of the steep portion of the interstitial...
P-V curve was selected (Eq. 12) to match the measured change in $V^P$ (see DISCUSSION). Similarly, model results for the R-ac infusion (triangles) were very close to the experimental results. Again, this result was expected because the slope of the flat portion of the interstitial P-V curve was selected (Eq. 12) to match the measured change in $V^P$.

**Hyperosmotic Infusions.** Figure 6, top, shows the results (hatched bars) for infusion of 0.892 M NaCl by Bradham et al. (7). The experimental data show that this hyperosmotic infusion dehydrates cells, leading to large increases in $V^{ECW}$ and $V^P$. The consequences are a large decrease in Hct. Calculated interstitial volume (not shown) also increases. The model results (circles) somewhat overestimate the changes measured by Bradham et al. (7).

Figure 6, bottom, shows the experimental results for hyperosmotic infusions of NaHCO$_3$ by Bradham et al. (7), Dörr et al. (14), and Onarheim (30), black, light-grey, and hatched-bars, respectively. Results of these studies indicate cell dehydration and resultant increases in $V^{ECW}$ and $V^P$, leading to a decreased Hct. Again, Onarheim did not measure changes in cell volumes. Model results for these three infusions, circles, downward triangles, and squares, respectively, show better agreement with experimental results than for the NaCl infusion (Fig. 6, top).

The good comparison between experimental measurements and model predictions for these hyperosmotic infusions serve as validation for the model formulations related to fluid movement between the CIPE-model compartments.

**Physiological Findings Using the CIPE Model**

The validated model can be used to gain further understanding of some poorly understood phenomena in electrolyte and acid-base physiology.

**Table 4. Plasma and muscle, acid-base and electrolyte changes due to K$^+$ and Cl$^-$ depletion by Grantham and Schloerb (18) with altered model kNa values**

<table>
<thead>
<tr>
<th>Species</th>
<th>Control (n = 11)</th>
<th>Human Model</th>
<th>K$^+$ Depletion (n = 11)</th>
<th>Human Model</th>
<th>K$^+$ Depletion and Gastric Drainage (n = 5)</th>
<th>Human Model</th>
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<tbody>
<tr>
<td>[Na$^+$]$^\circ$, mEq/lw</td>
<td>14.5 ± 10.3</td>
<td>17.4</td>
<td>30.8 ± 15.2*</td>
<td>31.1</td>
<td>32 ± 23.5*</td>
<td>28.7</td>
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<tr>
<td>[K$^+$]$^\circ$, mEq/lw</td>
<td>151 ± 10.3</td>
<td>144</td>
<td>125 ± 15.6*</td>
<td>126</td>
<td>115 ± 6.7*</td>
<td>126</td>
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<td>[H$^+$]$^\circ$, mM</td>
<td>133 ± 7</td>
<td>133</td>
<td>166 ± 12</td>
<td>182</td>
<td>184 ± 14</td>
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**Muscle-Cell Water (model kNa = 280)**

<table>
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<tr>
<th>Species</th>
<th>Control (n = 11)</th>
<th>Human Model</th>
<th>K$^+$ Depletion (n = 11)</th>
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<th>K$^+$ Depletion and Gastric Drainage (n = 5)</th>
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<tr>
<td>Na$^+$, mEq/kg</td>
<td>14.5 ± 10.3</td>
<td>21.2</td>
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<td>-2.3</td>
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**Model (change from control)**

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<th>Species</th>
<th>Control (n = 11)</th>
<th>Human Model</th>
<th>K$^+$ Depletion (n = 11)</th>
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<tr>
<td>Na$^+$, mEq/kg</td>
<td>14.5 ± 10.3</td>
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Statistical values are means ± SD. See GLOSSARY for definitions. *‡For either Na$^+$ or K$^+$, not statistically significant difference from each other, $P > 0.05$.

**Dilutional-, saline-, hyperchloremic-acidosis.** There has been a fierce debate concerning the mechanism of the extracellular acidosis caused by addition of isotonic saline and other neutral fluids such as mannitol or some 'balanced'-salt solutions. The traditional, “bicarbonate-centered,” approach described by Lang and Zander (24) holds that the decrease in blood pH (pH$_B$) is “caused” by plasma-bicarbonate dilution with bicarbonate-poor fluids. These authors developed a three-compartment mathematical model of blood-interstitial bicarbonate exchange that predicts this dilution by bicarbonate-free fluids at constant PCO$_2$ (open system). However, an alternative approach, attributed to Stewart (34) and becoming more frequently used clinically, suggests that mainly changes in the plasma strong-ion (i.e., Na$^+$) difference (SID) and less so by weak-ion (i.e., serum albumin) effects ($A_{col}$) “cause” acid-base changes. Hence, changes in [HCO$_3^-$]$^P$ are a consequence of these changes. Recently, Doberer et al. (13) criticized the idea that changes in plasma SID is the mechanism producing the acidosis.

This author chooses to look at this controversy from his experience of modeling human fluid and electrolyte balance. In our recent study (39) using the blood (PE) model, infusion of 1 liter of isotonic saline (0.154 M) to 1 liter of blood produced a drop in pH$_B$ (acidosis) by almost 0.2 units. The cause of this acidosis was the combined effects of adding a 1-liter volume of H$_2$O and a 0.154 mol mass of NaCl. These additions initiated movements of water and electrolytes between plasma and erythrocytes and chemical reactions in both compartments that, together, led to the new steady state showing decreases in both pH$_B$ and [HCO$_3^-$]$^P$, along with other changes. Hence, changing a total mass or total volume (independent variables), or both, resulted in changes in all electrolyte concentration (dependent
variables) in both erythrocytes and plasma and a volume shift between these compartments. A decrease in plasma SID is just a consequence of this change in plasma-ion concentrations (function of dependent variables). Adding an interstitial compartment as did Lang and Zander (24) and a cellular compartment as in the present study does not change these concepts, only their complexity.

Adding 5 liters of 0.154 M NaCl to our IPE model in our previous study (39) resulted in a pHB drop of only ~0.1 units. Hence, the mechanisms of interstitial buffering came into play. However, there was no cell compartment present. In the present model that includes a cellular compartment, the same perturbation caused a drop of only ~0.05 units, much less than predicted by the IPE model. A model experiment was used to examine the reason (mechanism) for this change. First, the perturbation was 5 liters of water (~70 ml/kg) and second, it was 0.77 mol of NaCl (the amount in 5 liters of saline solution). With the use of just the water, there was a drop of 0.03 units, whereas using just the NaCl, caused a drop of 0.02 units. Hence, the additive-acidotic effects were caused by both water and NaCl additions. Since [Cl−]P increased as a result of the saline infusion, hyperchloremia was also produced. If we do the same experiment with isoosmotic (0.3 M) mannitol, the pH drop is larger, down by 0.07 units, but [Cl−]P is decreased (hypochloremia). With the use of just the mannitol, the drop was ~0.03 units. Hence, mannitol, by itself, has a greater acidotic effect than NaCl. This result may be because 0.3 M mannitol increases extracellular osmolarity by about 20 mosmol/lW; hence, it dehydrates cells in contrast to isotonic saline. In both cases, the model predicts an intracellular acido.

Acidity and basic crystalloid-solution infusions. ACIDIC SOLUTIONS. Acidic crystalloid infusions are usually HCl or NH4Cl, but use of these substances is not standard clinical practice. However, because of eating, drinking, and metabolism, body fluids often become acidic. Hence, model investigation into the effects of acidic infusions can give some insight into clinical metabolic acid-base disorders. Previously, the acid-base effects of such solutions were only evaluated with an approximated IPE model as by Siggaard-Andersen (33) or by Wooten (40). With the use of the more complete IPE model (39), infusing 1 liter of 0.3 M HCl into a normal 70 kg human drops pHB to <7. However, if we use the present CIPE model, pHB drops to only ~7.2. Obviously, cellular buffering plays a large role in determining pHB. It is interesting that in the model simulation of this infusion, only 0.3 mol of Cl− were added because it is not necessary to include H+ mass as an independent variable in the model; [H+] is a dependent variable (27). Osmolarity dropped

Fig. 5. Top: experimental data (hatched bars) for % change from preinfusion values for hematocrit (Hct) and volumes (V) of erythrocytes (E), plasma (P), extracellular water (ECW), and cell water (C) due to sham infusion by Bradham et al. (7). Bottom: experimental data for infusion of 20 ml/kg of 0.154 M NaCl by Bradham et al. (7), hatched bars; and 100 ml/kg of Ringer’s acetate (R-ac) by Onarheim (30), grey bars. Corresponding model predictions are shown by grey circles and triangles, respectively.

Fig. 6. Same as Fig. 4, except that the top is for an infusion of 10 ml/kg of 0.892 M NaCl by Bradham et al. (7) and the bottom is for infusion of 10 ml/kg of 0.892 M NaHCO3 by Bradham et al. (7), black bars, and Dörr et al. (14), grey bars. Hatched bars show experimental data for an infusion of 1.2 M NaHCO3 by Onarheim (30). Corresponding model predictions are shown by grey circles, triangles, and squares, respectively.
by $\sim 6$ mosmol/lW because of a decreased $[\text{HCO}_3^-]$. Hence, 0.3 M HCl appears to be a near-isotonic solution. However, to make it isotonic, the model requires a 0.56 M concentration, which produces a significant hyperchloremia.

**Basic Solutions.** Therapeutic, basic-crystalloid infusions typically contain NaHCO$_3$ as the principal buffer. However, sometimes it is replaced by organic species (e.g., acetate) which eventually are metabolized. These solutions are usually used to counteract clinical metabolic-acidosis conditions. Performing the same model experiment as above, but with the use of NaHCO$_3$ (0.3 mol of Na$^+$ added) instead of HCl, the finding is that pH$_{H^+}$ rises to $\sim 7.6$ when using the IPE model, but only to $\sim 7.5$ (+0.1 units) using the CIPE model, again showing the effect of cellular buffering. In this case, osmolarity increases $\sim 4$ mosmol/lW, due to the small increase in [HCO$_3^-$]. Hence, 0.3 M NaHCO$_3$ appears to be near isotonic since most of the HCO$_3^-$ added does not directly contribute to the osmolarity. However, to make it isotonic, the model requires a 0.19 M concentration (1.6%), which is somewhat greater than the 1.2–1.4% normally used in clinical situations. Addition of 1 liter of 0.19 M NaHCO$_3$ to the 70-kg model increases blood pH by 0.058 units.

**Hypertonic Saline.** To counteract brain edema, 3 or 5% NaCl solutions are often employed. The model was used to compare the effects of these two solutions on decreasing model cell volume and the detrimental acidifying effect. Adding 1 liter of a 3% or 5% solution to the model causes 6.2 or 11.2% decreases in cell volume, respectively, and 0.016 or 0.022 pH-unit drops, respectively, compared with standard values.

**Discussion**

The major aims of this study were to extend our previous IPE computer model (39) by adding a cellular compartment and to improve prediction of plasma-interstitial fluid exchange by simulating the changes in both hydrostatic and osmotic forces in these two compartments. In this way, the prediction accuracy of the model could be improved for both isotonic and nonisotonic infusions and for studying disease processes such as diabetes mellitus where significant body fluid osmolarity changes may occur. Even though the results in this study have shown that the validated CIPE model can accurately predict cellular acid-base changes, their electrolyte-changing consequences and the results of isotonic and hyperosmotic infusions, it is important to substantiate the new assumptions in this model.

**Cellular Compartment**

When simulating the cellular compartment, some major assumptions had to be made. 1) For Na$^+$ and H$^+$, rather than relying on some empirical relationship between intracellular and extracellular concentrations, a more mechanistic approach was chosen, similar to that of Deland and Bradham (12) (see APPENDIX A). It was assumed that a constant, thermodynamic-free-energy pump moved Na$^+$ and H$^+$ out of the cell so that the transcellular Na$^+$ and H$^+$ concentration ratios (gradients) were always fixed multiples of the transcellular Cl$^-$ (or K$^+$) gradient (see Eqs. 6 and 7); Cl$^-$ and K$^+$ were assumed to be passively distributed ions here.

The validity of the fixed relationship between H$^+$ and K$^+$ gradients across the cell membrane was established by the experimental metabolic-alkalosis results of Grantham and Schloerb (18) shown in Table 3 and Fig. 3. The value of 10 found for the relationship between H$^+$ and K$^+$ gradients is also similar to the value of $\sim 13$ found by Irvine and Dow (23) in rats during metabolic acidosis conditions. 2) For Na$^+$, a similar assumption was made as for H$^+$, except that the fixed value in the relationship was 368 as calculated from standard-state data (Table 1). The data in Table 3 and Fig. 3 give some degree of validity for this latter assumption but not as strongly as for H$^+$. The reason may be the difficulty in accurately measuring [Na$^+$]$^C$ as shown by the large SD values in Table 3. However, the results of Table 4 show that the model results are relatively insensitive to changes in this constant. 3) Cellular acid-base buffering was primarily by the histidine side chains of cellular proteins. Histidine has the greatest influence on protein buffering in the physiological range because of its average pK of $\sim 6.5$. The reasonably good agreement between the experimental data and model predictions from a number of studies (see Figs. 1 and 2) support the validity of the intent of this assumption. However, it is likely that a more complete description of intracellular protein buffering, if available, would be much more complex and the intent was to keep the cellular model simple at this point.

To achieve the standard-state cell volume (Table 1) required a value of 129 mmol/lW of impermeable cellular proteins (Table 1), one of the seven unknown quantities necessary to achieve the standard state. The electrical charge on these proteins (assumed to be attributable to histidine side chains) necessary to achieve a standard-state pH$_C$ of 6.9 was $\sim 1.52$ meq/mmol (another of the unknowns). These unknown values are not unique since they would change if intracellular ionic species such as Ca$^{2+}$ and Mg$^{2+}$ were included in the cellular compartment or if a more complete description of cellular-protein buffering was included.

**Water distribution across the microvascular membrane.** Previously, we used (39) the formulation of the model from Deland and Bradham (12) where exchange of substances between plasma and interstitial fluid was solely dependent upon differences in their molar concentrations, osmolarities in our case. The assumption in the present study is that the Starling principle (25) could describe forces affecting fluid distribution (Eq. 10). Hence, the algebraic sum of hydrostatic pressures, colloid osmotic pressures, and crystalloid osmotic pressure across the capillary membrane summed to zero in steady state. This assumption was used previously by Gyenge et al. (19) to describe dynamic exchanges of water between these compartments. However, their description required identification of the values of a number of rate constants, a procedure not necessary using the present approach.

Describing the forces distributing water between plasma and interstitial fluid in the present model was first done by describing the hydrostatic pressures generated in these fluids as being simply dependent on changes in vascular and interstitial volumes, respectively (Eqs. 10 and 11). Second, the osmotic pressures in both compartments were described by cubic functions of protein concentration (Eq. 12).

Validation of the present approach used to characterize plasma-interstitial water exchange comes principally from the close prediction of the measured volume changes due to
hyperosmotic fluids in Fig. 4. However, it is possible that the current normal-human model will not accurately predict fluid and electrolyte changes in some pathological situations, particularly ones where fluid absorption from the interstitial space could occur; examples are hemorrhage or severe vascular fluid loss due to cholera toxin. In these and similar situations, model assumptions and descriptions could be changed so that the resulting pathological model would then give accurate predictions. An example is the study of Chapple et al. (10) where the model parameters of the plasma-interstitial fluid-exchange equations were modified to simulate experimental results in nephrotics.

Model Development

The model developed and validated in this study and in our previous one (39) is not the first one to attempt to describe whole body acid-base and fluid balance. Early in the history of digital computers, DeLand and Bradham (12) developed a complex model that was a precursor to the present one. However, the clinical impact was slight because of the solution time required with the primitive computer technology of that time.

Much more recent models by Bert and colleagues (10, 19, 20) have studied the dynamics of whole body fluid movements, have not included the simulation of acid-base balance. Recently, Andreasons and Rees (3) developed a whole body model, but it did not include water or individual ionic shifts among the body fluids. Their model was primarily used to examine the effects of respiratory disturbances on blood acid-base balance. Later, the Stewart approach was used by Omron and Omron (29) to formulate a simplified whole-body model that determined the change in acid-base status due to crystalloid infusions.

It should be emphasized that the latter set of models simulated the dynamics of fluid movement, whereas the present model just looks at steady-state changes. A major difference is that dynamic models introduce a whole new set of parameters (rate constants) the values of which are generally not known. Hence, they are found by parameter-estimation procedures that may require special computer programs and algorithms or just “brute force” trial and error procedures. Validity of these kinds of models requires extensive sensitivity analyses to ensure that the accuracy of the parameter values found are not adversely affected by noise in the experimental data used to determine these parameter values. In contrast, the intent of the present study was to formulate a steady-state model that could be used, eventually, for clinical situations where dynamics are not critically important. It is more likely in this kind of model that the values of important parameters are known or can be estimated more easily and with a reasonable accuracy. Hence, sensitivity analyses used for validation are less important in this nondynamic model.

As a consequence of these previous models, there was a need for a more complete description of whole body fluid and electrolyte balance that could be run rapidly on a desktop computer and that was extensively validated against experimental data. The whole-body (CIPE) model described in this study accurately predicts steady-state changes in fluid volumes, extracellular and cellular electrolytes, and acid-base variables due to fluid infusions of acids, bases and neutral solutions. This fully validated model is able to predict the cellular effects of such complex clinical perturbations as K+ and Cl− depletion and explain the acid-base changes due to infusions of neutral isotonic solutions and infusions of acidic or basic solutions.

As models become more complex and difficult to manipulate, they are less able and less likely to be used clinically. Hence, a module has been developed (see Appendix B) to allow users to simply determine the effects of fluid infusions and urinary losses on whole-body fluid and electrolyte (acid-base) balance. In addition, this new CIPE model will be incorporated into a diagnostic module in the same way as before for the IPE model (38). This latter step will allow accurate diagnostic, acid-base predictions in disease processes such as diabetic ketoacidosis, nephrotic syndrome and others where cellular volume is compromised. However, it is expected that to simulate some disease processes, the fundamental assumptions for the ‘normal’ model in the present study may have to be changed as others (10) have found necessary.

APPENDIX A

In the original whole-body model of DeLand and Bradham (12), a thermodynamic approach was used to describe the forces moving ions across membranes. As described by Wolf and DeLand (37), this approach defines the difference in free energy (Δμi) of an ionic species (i) between two solutions separated by a membrane as

$$\Delta \mu_i = R \times T \times \ln(r_i) + Z_i \times F \times \Delta E$$

(A1)

where R is the gas constant, T is absolute temperature, r is the ratio of mole-fraction concentrations between the solutions, Z is electrical valence, F is the Faraday constant, and ΔE is electrical potential difference across the membrane.

For an ion, such as Cl−, whose distribution across body-compartment membrane boundaries is taken to be passive (11), Δμi = 0 defines its equilibrium state across a membrane separating adjacent compartments. Hence, since Z = −1 for this ion, Eq. A1 becomes

$$\ln(r_{Cl}) = \frac{F}{R \times T} \times \Delta E$$

(A2)

Equation A2 can be used to determine the value of ΔE.

For a cation, such as Na+, that is also passively distributed across the microvascular membrane separating plasma and interstitial fluid,

$$\ln(r_{Na}) = -\ln(r_{Cl})$$

(A3)

which can be reduced to

$$r_{Na} \times r_{Cl} = 1$$

(A4)

which is the familiar Donnan relationship for a cation-anion pair across the microvascular membrane. Since K+ distribution across the cell membrane is close to that predicted by the Nerst equation (11), this simplifying assumption was made. Hence, Eq. A4 holds for the distribution of K+ and Cl− across the cellular membrane.

However, a similar relationship is not true for either H+ or Na+ across the cellular membrane because energy-requiring active pumps move these ions away from the Donnan equilibrium state. Hence, for H+ distribution across this membrane, using Eqs. A1 and A2,

$$\ln(r_{H} \times r_{Cl}) = \frac{\Delta \mu_{H}}{R \times T}$$

(A5)

where ΔμH, the energy of the transmembrane H+ pump, is not 0 and its value is assumed to remain constant. In this case, the distribution of H+ is not at equilibrium but is in a steady state. Equation A5 simplifies to,
Fig. B1. VisSim-Viewer screen shot for a simulated infusion of 10 ml/kg of 892 mM NaHCO₃ solution (case 2). Values of some of the important CIPE-model variables are shown. See APPENDIX B for details about obtaining this program module.

\[ r_{\text{H}} \times r_{\text{Cl}} = k_{\text{H}} \]  

which is the same as Eq. 7 when rearranged. Equation A6 could also have been written as,

\[ \frac{r_{\text{H}}}{r_{\text{K}}} = k_{\text{H}} \]  

because K⁺ is assumed to be at equilibrium across the cell membrane. Equation A7 suggests that the distributions of H⁺ and K⁺ across the cell membrane are linearly related at steady state, as shown by the data in Table 3.

APPENDIX B

VisSim simulation programs can be run by users who do not possess the program. The procedure is to sign up on the VisSim web site and then download the free version of VisSim Viewer program.

The CIPE model described in this study has been incorporated into an Infusion-Urinary loss module that can be run using the Viewer program. A user can specify the type of infusion (i.e., NaCl), its molarity and the volume of the infusate. Simultaneously, the volume and composition of urine can also be specified. The module will solve the model with these new conditions and display the values of important CIPE-model variables.

An example is shown in Fig. B1. It shows the results of infusing 0.7 l of 892 mM NaHCO₃ (case 2) to a normal 70-kg individual.

The module and instructions on its use can be obtained from this author upon request. It is the initial version (V 1.0) and will be updated depending upon user’s needs and suggestions.

APPENDIX C

Estimates of Normal Body-Compartment Volumes

Normal values (superscript 0) for the liters of plasma volume (Vp₀), erythrocyte volume (Vₑ₀), and the extracellular volume (Vₑ_), for adults were determined from the statistical regression equations of Boer (6); he calculated interstitial volume (Vᵢ₀) as the difference between Vₑ₀ and Vp₀. His anthropomorphic, gender-independent normal regressions were expressed in terms of lean body mass (LBM), derived from height (H), weight (W), and gender-dependent regressions for total-body water (Vᵢ₀), assuming that LBM is Vᵢ₀/0.73. Hence,

\[ V^{\text{TW0}}(\text{males}) = 0.297 \times Wt(\text{kg}) + 19.5 \times H(\text{m}) - 14 \]

or

\[ V^{\text{TW0}}(\text{females}) = 0.184 \times Wt(\text{kg}) + 34.5 \times H(\text{m}) - 35. \]

Boer (6) used ⁸²Br for determination of Vₑ₀, which even after correction for cell penetration, provides an upper limit because it also penetrates connective tissue and bone (4). Because a prime intent of the model was to predict the effects of crystalloid fluid infusions over a 2–3 h period, it was decided to assume that normal values were similar to the minimum values determined using ¹⁴C-sucrose (17). Hence, a correction factor of 0.755 was applied to the Vₑ₀ values estimated above. In the model, normal cell volume (Vᵢ₀) was taken as the difference between Vᵢ₀ and Vₑ₀, which is likely to be an overestimate due to ignoring the smaller amounts of fluids in connective tissue, etc.

To compare model results with experimental data in vivo, it was sometimes necessary to compute the venous large-vessel hematocrit (Hctᵥ) from the total-body hematocrit (Hctₚ). This value is determined from the relationship, 

\[ F_{\text{cell}} = \frac{Hct_{\text{p}}}{Hct_{\text{v}}} \]

F_{\text{cell}} is thought to be ~0.88 for adults over a wide hematocrit range, the value used in the model for normal adults.

ACKNOWLEDGMENTS

I acknowledge the late Dr. Edward DeLand of The RAND Corp. and University of California, Los Angeles (UCLA), mentor and friend, for invaluable insight into the modeling of fluid and electrolyte balance. He will be greatly missed. I also thank Dr. Gilbert Bradham of Medical University of South Carolina for help and friendship. I will always remember walking down the halls of the UCLA Medical Center with him in fear that I might drop one of the heavy boxes of IBM punch cards containing the code for the original RAND fluid and electrolyte model. Special thanks to Dr. James Maloney (UCLA) who made it possible to experimentally validate and extend the RAND fluid and electrolyte model and who helped me get a fellowship and provided a research home for me as I pursued my Ph.D. degree.
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