Calculation of physiological acid-base parameters in multicompartment systems with application to human blood

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Wooten, E. Wrenn. Calculation of physiological acid-base parameters in multicompartment systems with application to human blood. J Appl Physiol 95: 2333–2344, 2003. First published August 15, 2003; 10.1152/japplphysiol.00560.2003.—A general formalism for calculating parameters describing physiological acid-base balance in single compartments is extended to multicompartment systems and demonstrated for the multicompartment example of human whole blood. Expressions for total titratable base, strong ion difference, change in total titratable base, change in strong ion difference, and change in Van Slyke standard bicarbonate are derived, giving calculated values in agreement with experimental data. The equations for multicompartment systems are found to have the same mathematical interrelationships as those for single compartments, and the relationship of the present formalism to the traditional form of the Van Slyke equation is also demonstrated. The multicompartment model brings the strong ion difference theory to the same quantitative level as the base excess method.

base excess; strong ion difference; Van Slyke equation; Stewart theory; use of proton balance to calculate BE as the change in common formalism and that BE and the change in SID (ΔSID) are numerically the same for plasma, provided that the concentrations of plasma noncarbonate buffers remain constant (43, 57). When this condition is not met, plasma ΔCB and plasma ΔSID differ by an added constant. If, however, the reference state is chosen to coincide with the new (abnormal) noncarbonate buffer concentrations, the equivalence of BE and ΔSID is restored (57).

A complete quantitative description of the acid-base status of an organism requires that both intra- and extracellular effects in multiple compartments be taken into consideration (47). To this end, Siggaard-Andersen (46–48) defined BE for plasma, erythrocyte fluid, whole blood, and extracellular fluid. In contrast, the published applications of Stewart’s SID theory thus far (e.g., see Refs. 1, 7, 20, 26, 39, 42) have been confined to plasma because no corresponding extent theory for multicompartment systems, such as whole blood or extracellular fluid, exists.

In the following, the formalism used to derive expressions for CB and SID in the single-compartment case of plasma (57) is extended to systems with multiple compartments. General equations for CB, SID, ΔCB, and ΔSID are obtained for multicompartment systems and applied to the specific example of human whole blood, after the relevant model for the single compartment of human erythrocyte fluid is derived. These equations give results approximating experimentally determined values. The formulas for multicompartment systems are shown to have the same mathematical interrelationships as those demonstrated previously for single compartments (57), and the relationship between the form of the expressions derived here and the form of the Van Slyke equation traditionally used to calculate BE is also demonstrated. SID theory for multicompartment systems is thus shown to be precise to the same level of approximation as the traditional equations used for BE (33, 47–49), thereby


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brining SID theory to the same quantitative level as
THE BE method.


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Single-compartment systems. Previously, it was shown that the master equation approach developed by Guenther (21) could be adapted to obtain expressions for the two acid-base parameters, CB and SID. In a
general notational form, the acid-base concentration
parameters \( P(\chi) \) in a single aqueous compartment \( \chi \) can be written as

\[
P(\chi) = C_\chi + \sum_n C_n(\chi) \tilde{\xi}_n(\chi) - D_\chi
\]

where \( \chi \) refers, for example, to plasma (\( \chi = P \)) or
erthrocyte fluid (\( \chi = E \)); \( P(\chi) \) represents either \( C_B(\chi) \)
or \( S_I(\chi) \) in compartment \( \chi \). Similarly, \( \tilde{\xi}_n \) is the aver-
age value per molecule of some physical property of
noncarbonate buffer species \( n \) (21, 57). In the case of
base excess, \( \tilde{\xi}_n \) is the average number of proton binding
sites per molecule, \( \tilde{e}_n(\chi) \). In SID theory, \( \tilde{\xi}_n(\chi) \) is the
opposite of the average charge per molecule of species
\( n \), \( \tilde{\xi}_n(\chi) \). The calculation of \( \tilde{\xi}_n(\chi) \) in terms of condi-
tional molar equilibrium constants and \( H^+ \) concen-
tration ([\( H^+ \)]) has been described in Ref. 57. \( C_\chi \) is the
equilibrium concentration of proton acceptor sites of
carbonate species (also equaling the opposite of the
charge concentration of carbonate species), \( C_n(\chi) \) is the
analytical concentration of noncarbonate buffer species
\( n \), and \( D_\chi \) is the difference between aqueous free proton
and free hydroxyl ion concentrations, all in compart-
ment \( \chi \) (57).

Following the convention used before (57), and first
advocated by Constable (6), terms that are small under
physiological conditions are neglected to get

\[
P(\chi) = [\text{HCO}_3^\text{\_}P] + \sum_n C_n(\chi) \tilde{\xi}_n(\chi)
\]

where \( [\text{HCO}_3^\text{\_}P] \) is the concentration of bicarbonate in
compartment \( \chi \). Because of the linearity of these ex-
pressions over the physiological pH range from 6.8 to
7.8 (47, 57), an approximate straight line form of \( P(\chi) \)
can be derived as (57)

\[
P(\chi) = [\text{HCO}_3^\text{\_}P] + \left( \sum_n C_n(\chi) \frac{\partial \tilde{\xi}_n}{\partial pH} \right) \text{pH}(\chi)
+ \sum_n C_n(\chi) \tilde{\xi}_{\text{min}(n)} - \sum_n C_n(\chi) b_n
\]

Here \( \tilde{\xi}_{\text{min}(n)}(\chi) \) represents either \( \tilde{\xi}_{\text{max}(n)}(\chi) \), the maximum
number of proton acceptor sites on species \( n \) for BE, or
\( \tilde{\xi}_{\text{min}(n)}(\chi) \), the opposite of the minimum possible charge
on species \( n \) for SID. \( b_n \) is a constant for species \( n \) and
at a given pH can be computed from Eqs. 2 and 3 to be

\[
b_n = \frac{\partial \tilde{\xi}_n}{\partial pH} \text{pH}(\chi) - \tilde{\xi}_n(\chi) + \tilde{\xi}_{\text{min}(n)}
\]

It is also worth noting

\[
\frac{\partial \tilde{\xi}_n}{\partial pH} = -\frac{\partial \tilde{\xi}_n}{\partial pH}
\]

as this relationship links the BE and SID theories (57).

An additional relevant relationship obtained from the
results of Ref. 57 is

\[
\tilde{z}_{\text{max}(n)}(\chi) = \tilde{\xi}_{\text{max}(n)}(\chi) + \tilde{\xi}_{\text{min}(n)}
\]

which provides the specific relationship between \( C_B \)
and SID as obtained previously (57)

\[
C_B(\chi) = S_I(\chi) + \sum_n C_n(\chi) \tilde{\xi}_{\text{max}(n)}
\]

where \( \tilde{\xi}_{\text{max}(n)} \) is the maximum possible charge of
species \( n \).

Physiological pH is determined by the simultaneous
solution of any of the expressions for \( P(\chi) \) and the
Henderson-Hasselbalch equation in a given compart-
ment \( \chi \).

\[
\text{pH}(\chi) = pK' + \log \frac{[\text{HCO}_3^\text{\_}P]}{\text{PCO}_2(\chi)}
\]

where, for human plasma, \( pK' = 6.103 \) and \( S \) is the
equilibrium constant between aqueous dissolved \( \text{CO}_2 \)
and \( \text{CO}_2 \) in the gas phase, and equals 0.0306 at 37°C
when \( [H^+] \) is in moles per liter, [\( \text{HCO}_3^\text{\_} \)]\(_P\) is in milli-
moles per liter, and \( \text{PCO}_2 \) is in Torr (4).

Multicompartment systems. For a multicompartment
system \( M \) with single subcompartments separated by
semipermeable membranes, the acid-base parameter
\( P(M) \) for the system can be expressed as a linear
combination of the parameter values \( P(\chi) \) in the
various single subcompartments \( \chi \) (28, 37, 47), assuming
that sufficient time has elapsed after a perturbation to
reach a new steady state (47)

\[
P(M) = \sum_\chi \phi(\chi) P(\chi)
\]

noting that for the volume fractions \( \phi(\chi) \)

\[
\sum_\chi \phi(\chi) = 1
\]

It follows that for constant volume fractions

\[
\Delta P(M) = \sum_\chi \phi(\chi) \Delta P(\chi)
\]

where \( \Delta \) denotes a change. The derivation of explicit
expressions for \( \Delta P(\chi) \) has been described in detail previ-
ously (57). The corresponding expression to Eq. 7 is
then obtained as

\[
C_B(M) = S_I(M) + \sum_\chi \sum_n \phi(\chi) C_n(\chi) \tilde{\xi}_{\text{max}(n)}
\]

and from this relation follows, similar to the result for
a single compartment (57)

\[
\Delta C_B(M) = \Delta S_I(M) + \sum_\chi \sum_n \phi(\chi) \tilde{\xi}_{\text{max}(n)} \Delta C_n(\chi)
\]

One of the issues encountered in multicompartment
systems is that variables such as \( \text{pH}(\chi) \) are often only
experimentally available for a single compartment. For
example, in routine clinical work, the plasma values
\( \text{pH}(P) \) and \( [\text{HCO}_3^\text{\_}]_P \) in equilibrium with the erythro-


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cyte phase and interstitial fluid are the variables typically measured, with the other pH(χ) and [HCO₃]ᵋψ seldom being obtained directly. It is therefore necessary to calculate the concentrations of species in one compartment from those in another. Fortunately, for many species of interest, concentrations can be calculated across the relevant membrane via the Nernst equation (12, 28, 40, 47)

\[ Δψ(χ) = -\frac{RT}{cF} \ln r_m(χ) = -\frac{RT}{cF} \ln \left( \frac{[H^+]_χ}{[H^+]_ψ} \right) \]

where \( Δψ(χ) \) is the membrane potential between compartment χ and the plasma compartment in volts, \( R \) is the gas constant (8.3144 J/mol·K), \( T \) is absolute temperature, \( c \) is the charge on the species under consideration, \( F \) is Faraday’s constant (96,485 Coulomb/mol), and \( r_m(χ) \) is the Donnan ratio for a given species \( m \) between compartment χ and plasma.

**Application to whole blood.** As a specific example of a multicompartment system, human whole blood (\( M = B \)) is considered. Whole blood is made up of contributions from the two single compartments of plasma (\( χ = P \)) and erythrocyte fluid (\( χ = E \)). This definition, together with Eq. 10, yields from Eq. 9 that

\[ P(B) = [1 - \phi(E)]P(P) + \phi(E)P(E) \]

\( \phi(E) \) can be equated with the hematocrit (47, 48). The Nernst equation (Eq. 14) can be used to calculate the erythrocyte pH and [HCO₃]ᵋψ from the corresponding plasma concentrations to calculate P(E). It follows from Eq. 11 that

\[ ΔP(B) = [1 - \phi(E)]ΔP(P) + \phi(E)ΔP(E) \]

under the assumption of constant hematocrit.

As an alternative to using the Nernst equation to calculate erythrocyte pH and [HCO₃]ᵋψ, other approaches specific to the determination of intraerythrocyte concentration have also been employed (47, 48). For example, in the case of the carbonate system equilibration line (the equation for \( C_B \) plotted as \( [HCO_3]_P \) vs. pH at constant \( C_B \)), as well as the equation relating pH and BE, as the Van Slyke equation (48). Because the latter is usually called the Van Slyke equation (33, 49), this is the convention that will be used here, and the former will be referred to as the CO₂ equilibration curve (47, 48).

It is instructive at this point to consider the relationship of the present model to the traditional form of the Van Slyke equation for whole blood, a recent version of which is given by Siggaard-Andersen and Fogh-Andersen (49) as

\[ BE(B) = \frac{1 - \frac{C_{HB}(B)}{C_{HB}^o}}{\frac{C_{HB}(E)}{C_{HB}^o}} \frac{Δ[HCO_3]_P}{\beta'(B)ΔpH(P))} \]

where \( BE(B) \) is the BE of whole blood, \( C_{HB}(B) \) is the hemoglobin concentration of whole blood, and \( Δ[HCO_3]_P \) and \( ΔpH(P) \) are the changes in the plasma bicarbonate concentration and in the plasma pH, respectively. \( C_{HB}^o \) is a constant, which depends on the erythrocyte fluid hemoglobin concentration \( C_{HB}(E) \) and the bicarbonate Donnan ratio \( r(E) \), both of which are assumed to have constant normal values (48), according to

\[ C_{HB}^o = \frac{C_{HB}(E)}{[1 - r(E)]} \]

Because Siggaard-Andersen and coworkers (48, 49) defined hemoglobin concentrations and buffer values in terms of the oxyhemoglobin monomer, a value for \( C_{HB}^o \) of 43 mM is obtained on substituting the appropriate human normal values, including a value for \( r(E) \) of 0.51. In some earlier references, a value of 0.57 was used, giving a \( C_{HB}^o \) of 48 mM (47). \( \beta'(B) \), an effective buffer value for whole blood (48), is the slope of the CO₂ equilibration curve for whole blood in a \( [HCO_3]_P \) vs. pH(P) coordinate system at constant non-carbonate buffer concentration and constant total titratable base (47, 48). \( \beta'(B) \) is calculated via (49)

\[ \beta'(B) = C_{HB}(B) \cdot \beta_{HB} + \beta(P) \]

where \( \beta_{HB} \) is the apparent molar buffer value of the oxyhemoglobin monomer in whole blood and is assigned a value of 2.3 in humans (49). \( \beta(P) \), with a default value of 7.7 mM in humans (49), is the buffer value of plasma computed from (49)

\[ \beta(P) = \sum_i C_i\beta_i \]
The \( \beta_i \) are the true molar buffer values of the noncarbonate buffers in plasma (including albumin, inorganic phosphate, and globulins) with concentrations \( C_i(P) \).

Equation 19 can also be derived from the present formalism. As shown previously (57), the assumption of constant noncarbonate buffer concentrations from Eq. 3 for a given compartment gives

\[
\Delta P(x) = \Delta[HCO_3^-]_x + \beta(x)\Delta pH(x)
\]

(23)

where

\[
\beta(x) = \sum_n C_n(x) \frac{\partial \delta \xi_n}{\partial pH}
\]

(24)

analogous to Eq. 22. \( \delta \xi_n/\partial pH \) is the molar buffer value of species \( n \), assumed to be constant over the physiological pH range, and \( \beta(x) \) is the buffer value of the noncarbonate buffer contribution in compartment \( x \) (57). Substituting Eq. 23 into Eq. 11 gives

\[
\Delta P(M) = \sum_x \phi(x) \{\Delta[HCO_3^-]_x + \beta(x)\Delta pH(x)\}
\]

(25)

under the assumption of constant hematocrit. This equation can be recast in terms of plasma concentrations \([HCO_3^-]_P\) and \( \text{pH}(P) \) in equilibrium with the other compartments (true plasma) to give

\[
\Delta P(M) = \Delta[HCO_3^-]_P \left[ \sum_x \phi(x) r_c(x) \right]
+ \Delta pH(P) \left[ \sum_x \phi(x) \beta(x) \frac{\partial pH(x)}{\partial pH(P)} \right]
\]

(26)

where \( r_c(x) \) is the bicarbonate Donnan ratio between compartment \( x \) and plasma and is assumed to have a constant value. By factoring out the term in \( r_c(x) \), Eq. 26 can then be written in the form

\[
\Delta P(M) = \left[ \sum_x \phi(x) r_c(x) \right] \Delta[HCO_3^-]_P + \beta'(M)\Delta pH(P)
\]

(27)

with

\[
\beta'(M) = \frac{\sum_x \phi(x) \beta(x) \frac{\partial pH(x)}{\partial pH(P)}}{\sum_x \phi(x) r_c(x)}
\]

(28)

\( \beta'(M) \), the effective buffer value of system \( M \), is the slope of the \( \text{CO}_2 \) equilibration curve for system \( M \) in a \([HCO_3^-]_P \) vs. \( \text{pH}(P) \) coordinate system at constant noncarbonate buffer concentration and constant \( C_B \) (47, 48). Equation 27 represents a general multicompartment form of the Van Slyke equation.

For the specific example of whole blood, Eq. 27 can be rewritten by using Eqs. 10 and 17 as

\[
\Delta P(B) = \{1 - [1 - r_c(E)]\phi(E)\} \{\Delta[HCO_3^-]_P
+ \beta'(B)\Delta pH(P)\}
\]

(29)

Likewise, substituting Eqs. 10, 17, and 18 into Eq. 28 and rearranging gives

\[
\Delta P(M) = \left[ \sum_x \phi(x) r_c(x) \right] \Delta VSSB(P) = \Delta VSSB(M)
\]

(36)

where \( \Delta VSSB(P) \) is the VSSB of plasma in equilibrium with the other compartments of system \( M \), and \( \Delta VSSB(M) \) is the VSSB of \( M \). The \( \Delta VSSB(P) \) for system \( M \) will be numerically different from the VSSB of plasma for separated plasma, since in the former case of system \( M \) this concentration represents the VSSB of plasma in equilibrium with the other single compartments (true plasma) and therefore will have a steeper \( \text{CO}_2 \) equilibration than with separated plasma (11).

Use of the above information regarding multicompartment systems together with Eq. 13 implies that, in general, as found in the single compartment case (57)

\[
\Delta C_M = \Delta \text{SID} = \Delta \text{VSSB}
\]

(37)
In the case of constant noncarbonate buffer concentrations \( \Delta C_n(x) = 0 \), however
\[
\Delta C_B(M) = \Delta S_{DB}(M) = \Delta V_{SSB}(M) \tag{38}
\]
but at the same time, it is also straightforward to deduce that if the reference state is chosen to include the new (abnormal) concentrations \( C_n(x) \), then in general
\[
\Delta C_B(M) = \Delta S_{DB}(M) = \Delta V_{SSB'}(M) \tag{39}
\]
where the primes refer to the new reference state (57).

**METHODS**

Calculations using the mathematical models derived in **THEORY** were carried out for human whole blood in a manner similar to that described previously for human plasma (57). Computation of acid-base parameters was performed by using Microsoft Excel 2002 running on a Compaq Presario 8000Z computer equipped with an AMD Athlon XP 1.733-GHz processor. pH was stepped in 0.01 increments to calculate the variables \( \tilde{z}_n(x) \), \( C_n(x) \), \( \Delta C_n(M) \), \( \Delta S_{DB}(M) \), \( \tilde{S}_{DB}(x) \), \( \tilde{S}_{DM}(x) \), \( \tilde{S}_{BD}(M) \), and \( \tilde{S}_{BB}(M) \) as well as to generate graphs of these same variables vs. pH. \( \Delta z_n(x) \) vs. pH was calculated by taking the tangent to the \( \tilde{z}_n(x) \) vs. \( pH \) curves (57). \( \beta(x) \) was calculated from Eq. 24, and \( \beta(M) \) was calculated by taking the tangent to the \( P(M) \) curve when carbonate species concentrations are set to 0.0 mM. All calculations were carried out at 37°C, except where otherwise noted. In a departure from previous work (57), no correction for ionic strength was performed, given the small changes produced in the final calculated values (57). In addition, following the approach of Sigggaard-Andersen (47), no correction for osmotic effects was explicitly included.

All protein amino acids, the heme moieties of hemoglobin, and the carboxyl group of 2,3-diphospho-D-glycerate (DPG) were assumed to behave as independent monoprotic acids (15, 16, 29, 30, 57). Inorganic phosphate was treated as a triprotic acid, and the two phosphates of DPG were assumed to behave as independent monoprotic acids.

For human plasma, it was assumed that albumin and inorganic phosphate were sufficient to account for all of the noncarbonate buffer activity (15, 16, 55, 57), and simulations of acid-base balance used the human albumin and inorganic phosphate dissociation constants given by Figge et al. (15). Bicarbonate concentrations were derived from the Henderson-Hasselbalch equation (Eq. 8) together with plasma pH and PCO2 (4). The effective equilibrium constants for human albumin, phosphate, and carbonate at 37°C are given in Table 1.

For human erythrocyte fluid, a slightly different approach was required because no complete theoretical or experimental equilibria constant data under erythrocyte physiological conditions could be found. The calculation was carried out for oxygenated blood, and it was assumed, in accordance with the work of Sigggaard-Andersen (47) and Reeves (38), that the noncarbonate buffer species of human oxygenated erythrocyte fluid are primarily oxyhemoglobin and free DPG. For the equilibrium constants of the \( \alpha \) and \( \beta \) chains in the human oxyhemoglobin tetramer, effective \( pK_a \) values calculated from a modified Tanford-Kirkwood theory were available at 25°C and an ionic strength of 0.10 M from the work of Matthew et al. (30). A similar publication, again by Matthew et al. (29), provided the effective \( pK_a \) of free DPG at 25°C and ionic strength 0.10 M. At the same time, more recent experimental \( pK_a \) data for the solvent of the solvent-accessible histidine imidazole groups of human carbon monoxymyoglobin were available from a study by Fang et al. (13) at 29°C in 0.1 M HEPES buffer plus 0.1 M chloride. These experimental values were used for the solvent-accessible histidine imidazole groups instead of the theoretical values determined from the modified Tanford-Kirkwood theory (30). \( \beta \)-Histamine (\( \beta \)-His)\(^{57} \) and \( \beta \)-His\(^{15} \), considered nontitratable by Matthew et al. (30), were found to be titratable even from Fig. 10 of Fang et al. (13).

The effective oxyhemoglobin proton dissociation constants \( K_e \) were then corrected to 37°C by employing the van’t Hoff relation (3, 9)
\[
\ln \frac{K_e}{K_1} = -\frac{\Delta H^o}{R} \left( \frac{1}{T_z} - \frac{1}{T_1} \right) \tag{40}
\]
where \( \Delta H^o \) is the standard enthalpy of ionization for the ionizable groups of human hemoglobin, all of which were assumed to have the same \( \Delta H^o \), in accordance with the findings of Stadie and Martin (51). The \( \Delta H^o \) was calculated by changing the enthalpy in 1 cal/mol increments to minimize the function
\[
S^2 = \sum \left( \tilde{z}_{n(E)} - \tilde{z}_{n(E)b} \right)^2 \tag{41}
\]
where \( \tilde{z}_{n(E)b} \) is the theoretically calculated average charges of the hemoglobin tetramer, and \( \tilde{z}_{n(E)} \) is the experimentally determined oxyhemoglobin values for \( k = 31 \) experimental pH data points at 37°C obtained from the data of Raftos et al. (36). The numerical values for the data points, originally presented in graphical form in Fig. 4 of Ref. 36, were provided courtesy of Dr. J. Raftos. These values were then corrected for the small contribution from a PCO2 of 0.25 Torr under the experimental conditions of that study (36) by calculating the bicarbonate contribution from PCO2 and pH by using Eq. 8, then adding this to the experimental value to give \( \tilde{z}_{n(E)b} \). The minimum \( S^2 \) of 1.3 thus obtained provided a \( \Delta H^o \) of 10.6 kcal/mol (44.5 kJ/mol).

Based on work by Reeves (38), the order of magnitude of the standard enthalpy of ionization for DPG was assumed to be \(-1\) kcal/mol and thus not expected to cause a significant temperature dependence; therefore, these values were left uncorrected for temperature. The uncorrected human oxyhemoglobin and DPG effective \( pK_a \) values are also listed in Table 1.

Values for pH(E) were obtained from Eq. 14 and the plasma pH(P), under the assumption of a membrane potential of \(-13.0\) mV (47, 48). [HCO\(_3\)]\(_p\) was calculated from Eq. 17, together with [HCO\(_3\)]\(_b\) and pH(P). Whole blood acid-base parameters were calculated by using the above models for human plasma and erythrocyte fluid, which were then incorporated into Eqs. 15 and 16, assuming a constant hematocrit of 44% (4). For calculation of [HCO\(_3\)]\(_b\), using Eqs. 19 and 32, a value of 43 mM was used for CMB\(_b\).

Numerical values for the comparison experimental data for human oxyhemoglobin at 25°C were obtained from Table 1 of Ref. 41 and assumed to be free of carbonate. The comparison numerical data for human oxyhemoglobin at 37°C were obtained from Raftos et al. (36) as discussed above. The numerical values for the experimentally derived titration curves of whole blood at PCO2 = 28.7 Torr, 40.0 Torr, and 66.0 Torr were read directly from Fig. 10 of Ref. 47.

The designations “normal plasma” and “normal erythrocyte fluid” used in the DISCUSSION, tables, and figures refer to the normal human values pH(P) = 7.40, [HCO\(_3\)]\(_p\) = 24.25 mM, PCO2(P) = 40.0 Torr, pH(E) = 7.19, [HCO\(_3\)]\(_b\) = 12.49 mM, and the concentrations of noncarbonate buffer species.
Table 1. \( pK \) and equilibrium constant values for carbonate and noncarbonate buffers of human oxygenated whole blood

<table>
<thead>
<tr>
<th>Species</th>
<th>( pK )</th>
<th>Species</th>
<th>( pK )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td></td>
<td>Hemoglobin (cont.)</td>
<td></td>
</tr>
<tr>
<td>Cysteine</td>
<td>8.50</td>
<td>( \beta ) Tyr35</td>
<td>11.00</td>
</tr>
<tr>
<td>Aspartic acid and glutamic acid (98)</td>
<td>4.00</td>
<td>( \beta ) Tyr130</td>
<td>10.31</td>
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<td>Tyrosine (18)</td>
<td>9.60</td>
<td>( \beta ) Tyr145</td>
<td>10.71</td>
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<td>Arginine and lysine (77)</td>
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<td>( \alpha ) Lys7</td>
<td>11.70</td>
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<td>Histidine#1</td>
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<td>( \alpha ) Lys11</td>
<td>10.75</td>
</tr>
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<td>10.75</td>
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<td>( \alpha ) Lys56</td>
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<td>6.75</td>
<td>( \alpha ) Lys90</td>
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<td>6.36</td>
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<td>10.99</td>
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<td>( \alpha ) Lys127</td>
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<td>6.17</td>
<td>( \beta ) Lys8</td>
<td>10.57</td>
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<td>6.73</td>
<td>( \beta ) Lys17</td>
<td>11.52</td>
</tr>
<tr>
<td>Histidine#13</td>
<td>5.82</td>
<td>( \beta ) Lys59</td>
<td>10.48</td>
</tr>
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<td>Histidine#14</td>
<td>7.3</td>
<td>( \beta ) Lys61</td>
<td>10.65</td>
</tr>
<tr>
<td>Histidine#15</td>
<td>5.2</td>
<td>( \beta ) Lys65</td>
<td>10.65</td>
</tr>
<tr>
<td>Histidine#16</td>
<td>7.3</td>
<td>( \beta ) Lys66</td>
<td>11.02</td>
</tr>
<tr>
<td>NH(_2)-terminal</td>
<td>8.00</td>
<td>( \beta ) Lys82</td>
<td>9.40</td>
</tr>
<tr>
<td>COOH-terminal</td>
<td>3.10</td>
<td>( \beta ) Lys95</td>
<td>10.75</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \alpha ) Asp6</td>
<td>2.91</td>
<td>( \beta ) Lys120</td>
<td>10.58</td>
</tr>
<tr>
<td>( \alpha ) Asp47</td>
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<td>( \beta ) Lys132</td>
<td>11.86</td>
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<td>( \beta ) Lys144</td>
<td>10.54</td>
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<tr>
<td>( \alpha ) Asp74</td>
<td>2.99</td>
<td>( \alpha ) Arg31</td>
<td>13.55</td>
</tr>
<tr>
<td>( \alpha ) Asp75</td>
<td>3.86</td>
<td>( \alpha ) Arg92</td>
<td>12.21</td>
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<td>( \alpha ) Asp95</td>
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<td>13.72</td>
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<td>( \alpha ) Asp94</td>
<td>4.21</td>
<td>( \beta ) Arg40</td>
<td>12.69</td>
</tr>
<tr>
<td>( \alpha ) Asp126</td>
<td>2.69</td>
<td>( \beta ) Arg104</td>
<td>12.52</td>
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<tr>
<td>( \beta ) Asp21</td>
<td>3.92</td>
<td>( \alpha ) His20</td>
<td>7.06</td>
</tr>
<tr>
<td>( \beta ) Asp47</td>
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<td>6.09</td>
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<td>6.30</td>
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<tr>
<td>( \beta ) Asp94</td>
<td>2.98</td>
<td>( \alpha ) His112</td>
<td>7.48</td>
</tr>
<tr>
<td>( \beta ) Asp99</td>
<td>4.29</td>
<td>( \beta ) His2</td>
<td>6.41</td>
</tr>
<tr>
<td>( \alpha ) Glu23</td>
<td>4.15</td>
<td>( \beta ) His77</td>
<td>7.73</td>
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<td>( \alpha ) Glu27</td>
<td>2.34</td>
<td>( \beta ) His97</td>
<td>7.66</td>
</tr>
<tr>
<td>( \alpha ) Glu30</td>
<td>2.79</td>
<td>( \beta ) His116</td>
<td>6.26</td>
</tr>
<tr>
<td>( \alpha ) Glu116</td>
<td>4.24</td>
<td>( \beta ) His117</td>
<td>6.42</td>
</tr>
<tr>
<td>( \beta ) Glu6</td>
<td>4.51</td>
<td>( \beta ) His143</td>
<td>5.73</td>
</tr>
<tr>
<td>( \alpha ) Glu7</td>
<td>3.08</td>
<td>( \beta ) His146</td>
<td>6.47</td>
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<tr>
<td>( \beta ) Glu22</td>
<td>3.22</td>
<td>( \alpha ) Val1</td>
<td>7.30</td>
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<tr>
<td>( \beta ) Glu26</td>
<td>2.39</td>
<td>( \beta ) Val1</td>
<td>6.80</td>
</tr>
<tr>
<td>( \beta ) Glu43</td>
<td>4.34</td>
<td>2,3-Diphosphoglycerate</td>
<td></td>
</tr>
<tr>
<td>( \beta ) Glu90</td>
<td>4.49</td>
<td>Carboxyl</td>
<td>( pK_C = 4.58 )</td>
</tr>
<tr>
<td>( \beta ) Glu101</td>
<td>3.35</td>
<td>Phosphate#1</td>
<td>( pK_1 = 3.19 )</td>
</tr>
<tr>
<td>( \beta ) Glu121</td>
<td>2.73</td>
<td>Phosphate#2</td>
<td>( pK_2 = 6.69 )</td>
</tr>
<tr>
<td>( \alpha ) Arg141</td>
<td>2.19</td>
<td>( \beta ) His116</td>
<td>6.26</td>
</tr>
<tr>
<td>( \alpha ) His146</td>
<td>3.55</td>
<td>( \beta ) His117</td>
<td>6.42</td>
</tr>
<tr>
<td>( \alpha ) heme1</td>
<td>3.98</td>
<td>Inorganic phosphate</td>
<td>( pK_1 = 1.91 )</td>
</tr>
<tr>
<td>( \alpha ) heme2</td>
<td>3.46</td>
<td>( H_3PO_4 )</td>
<td>( pK_1 = 2.66 )</td>
</tr>
<tr>
<td>( \beta ) heme1</td>
<td>3.81</td>
<td>( H_2PO_4^- )</td>
<td>( pK_2 = 6.66 )</td>
</tr>
<tr>
<td>( \beta ) heme2</td>
<td>4.04</td>
<td>( HPO_4^{2-} )</td>
<td>( pK_3 = 11.78 )</td>
</tr>
<tr>
<td>( \beta ) Cys93</td>
<td>10.24</td>
<td>Carbonate</td>
<td>( S = 0.0306 )</td>
</tr>
<tr>
<td>( \alpha ) Tyr24</td>
<td>10.55</td>
<td>( PCO_2 )</td>
<td>( pK^F = 6.103 )</td>
</tr>
</tbody>
</table>

Solvent-accessible histidine imidazole values for oxyhemoglobin are at 29°C (13). The remaining oxyhemoglobin (30) and 2,3-diphosphoglycerate (DPG) (29) values are at 25°C, and the albumin (15), inorganic phosphate (15), and carbonate (4) values are at 37°C. Numbers in parentheses under albumin indicate number of amino acid residues present in the protein.
Table 2. Single-compartment concentrations and physical constants for the noncarbonate buffers of normal human oxygenated whole blood

<table>
<thead>
<tr>
<th>Species</th>
<th>$C_i(x)_i$, mM</th>
<th>$\bar{e}_{\max i}$</th>
<th>$\bar{e}_{\min i}$</th>
<th>$\bar{e}_{\max i}$</th>
<th>$b_n$</th>
<th>$\delta_{\bar{e}}/\delta pH$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>0.66</td>
<td>212</td>
<td>-118</td>
<td>94</td>
<td>159</td>
<td>8.0</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>5.3</td>
<td>162</td>
<td>-76</td>
<td>86</td>
<td>147.5</td>
<td>10.2</td>
</tr>
<tr>
<td>DPG</td>
<td>6.0</td>
<td>5.0</td>
<td>-5.0</td>
<td>5.0</td>
<td>5.4</td>
<td>0.70</td>
</tr>
<tr>
<td>Inorganic phosphate</td>
<td>1.16</td>
<td>3</td>
<td>-3</td>
<td>0</td>
<td>3.4</td>
<td>0.30</td>
</tr>
</tbody>
</table>

See Single-compartment systems for definitions.

Table 2 gives in Table 2. “Normal whole blood” likewise refers to the corresponding human multicomponent model with a constant hematocrit of 44%.

Finally, although Eq. 2 provides exact expressions for $C_B(M)$ and SID(M), the linear forms obtained from Eq. 3 are more easily manipulated. These were substituted into Eq. 15, which after rearrangement of the bicarbonate term in a manner similar to that used to for Eq. 29 gave

$$P(B) = \{ 1 - [1 - r_i(E)]\phi(E)|HCO_3^-|B + [1 - \phi(E)] \}$$

$$\left\{ \sum_i C_i(P)\frac{\delta \tilde{e}_i}{\delta pH} \right\} \pH(P) + \sum_i C_i(P)\bar{e}_{\min i} - \sum_j C_j(P)b_j \phi(E)$$

$$\left\{ \sum_j C_j(E)\frac{\delta \tilde{e}_j}{\delta pH} \right\} \pH(E) + \sum_j C_j(E)\bar{e}_{\min j} - \sum_j C_j(E)b_j \right\}$$

where the index $i$ extends over the plasma and the index $j$ over the erythrocyte noncarbonate buffers. To obtain explicit numerical forms, the values in Table 2 were then substituted into Eq. 42. Equation 31 was employed to obtain the hemoglobin term as a function of $C_{Hb}(B)$. The approximation that the bicarbonate Donnan ratio is a constant at $r_i(E) \approx 0.51$ over the physiological pH range was also used, as well as that

$$\pH(E) = \pH(P) - 0.21$$

also found to be a good approximation over the physiological range, giving explicit linear forms for $C_{Hb}(B)$ and SID(B) as functions of $\pH(P)$.

$$C_{Hb}(B) = [1 - 0.49\phi(E)|HCO_3^-|B + [1 - \phi(E)]|C_{Ab}(B)|[8.0 \pH(P) + 53] + C_{Plas}(P)|0.30 \pH(P) - 0.4]$$

$$+ C_{Hb}(B)|10.2[\pH(P) - 0.21] + 14.5] + \phi(E)C_{DPG}(E)|0.70\pH(P) - 0.21] - 0.4]$$

$$SID(B) = [1 - 0.49\phi(E)|HCO_3^-|B + [1 - \phi(E)]|C_{Ab}(B)|[8.0 \pH(P) - 41] + C_{Plas}(P)|0.30 \pH(P) - 0.4]$$

$$+ C_{Hb}(B)|10.2[\pH(P) - 0.21] - 71.5] + \phi(E)C_{DPG}(E)|0.70\pH(P) - 0.21] - 0.4]$$

RESULTS

Theoretical titration curves for human oxyhemoglobin with corresponding experimental data from Rollemo et al. at 25°C (41) and from Raftos et al. at 37°C (36) are shown in Fig. 1. Theoretical titration curves for human whole blood at $P_{CO_2} = 28.7$, 40, and 66 Torr are shown in Fig. 2 together with experimental data obtained by Sigggaard-Andersen (45, 47). In keeping with the practice of graphing the equations for $C_B$ and SID in a $[HCO_3^-]_P$ vs. $\pH(P)$ coordinate system as advocated by Davenport (11), Fig. 3 shows such plots illustrated for human whole blood and plasma. To compare the traditional Van Slyke equation (Eq. 19) with that derived from $\pH$ and effective conditional molar equilibrium constants (Eq. 32), a graph of human whole blood $[HCO_3^-]_P$, vs. $\pH(P)$ is provided in Fig. 4, together with the corresponding curve obtained from the more complete Eqs. 2 and 15 at constant $P(B)$.

Various calculated parameter values are compared with the results of experimental data and other models in Table 3. Calculated values are under normal conditions as defined in METHODS.

The derivation of the explicit linear forms for $P(M)$ as described in METHODS gave the following results from Eq. 42

$$C_{Hb}(B) = [1 - 0.49\phi(E)|HCO_3^-|B + [1 - \phi(E)]|C_{Ab}(B)|[8.0 \pH(P) + 53] + C_{Plas}(P)|0.30 \pH(P) - 0.4]$$

$$+ C_{Hb}(B)|10.2[\pH(P) - 0.21] + 14.5] + \phi(E)C_{DPG}(E)|0.70\pH(P) - 0.21] - 0.4]$$

The extent to which these expressions approximate the results from Eqs. 2 and 15 is demonstrated in Fig. 5 for human whole blood and plasma. To calculate the variables for plasma, $\phi(E)$ and $C_{Hb}(B)$ are both set to zero.

Also note that, in these explicit linear forms, the hemoglobin concentration is expressed as the concentration of tetramer.

DISCUSSION

The accuracy of the single and multicompartment models can be assessed by how well they predict experimentally accessible parameters. In general, agree-
obtained by Stadie and Martin (51). A
here of 10.6 kcal/mol is similar to the 10 kcal/mol
° C (36). The
from Raftos et al. at 37
° C (38) at 25
° pH), however, is similar to the 0.69 published by
Reeves (38) at 25
° C. Still, it is striking how well the theory predicts the
experimental titration curves for human oxyhemoglobin shown in Fig. 1, given the number of assumptions inherent in the calculation. Dedicated calculations of the effective pKₐ of hemoglobin and DPG under erythrocyte physiological temperature and ionic strength conditions would most likely give better agreement, and the need for more accurate effective pKₐ may stimulate further research in this area.

Despite the mild discrepancies in the erythrocyte portion of the model, the experimental titration curves (45, 47) for human whole blood shown in Fig. 2 are

![Fig. 2. Change in total titratable base (ΔC₉) vs. plasma pH [pH(P)] titration curves for human whole blood at 37°C and variable PCO₂. Theoretical curves and experimentally derived values from Ref. 47 at PCO₂ = 28.7 (●), 40.0 (○), and 66.0 (●) Torr are shown.](image)

Fig. 2. Change in total titratable base (ΔC₉) vs. plasma pH [pH(P)] titration curves for human whole blood at 37°C and variable PCO₂. Theoretical curves and experimentally derived values from Ref. 47 at PCO₂ = 28.7 (●), 40.0 (○), and 66.0 (●) Torr are shown.

Theoretical curves and experimentally derived values from Ref. 47 at PCO₂ = 28.7 (●), 40.0 (○), and 66.0 (●) Torr are shown.

A summary of theoretical values obtained for various different parameters is presented in Table 3, where these values are also compared with previously published data. A few comments are in order regarding specific values, as well as some of the features of Figs. 1–5.

Results for the plasma single compartment using the present formalism have been given previously (57), and the extent to which this model and others like it reproduce experimental data has been discussed by several authors (15, 55, 57). It has been shown that the model produces excellent agreement with experimental data for human plasma, even when the plasma globulin component is neglected; for example, the SID values of 39 mM from Ref. 57 and the SID of 40.4 mM from Ref. 9 agree well with the value determined by Singer and Hastings (50) of 41.7 mM. This is despite the apparent disagreement between the buffer value β(P) = 5.7 mM obtained from the present model and the β(P) = 7.7 mM published by Siggaard-Andersen (47, 49).

Although probably the weakest portion of the model currently, the theory for the erythrocyte compartment nonetheless produces values commensurate with previously published data, although returning values were slightly higher than those published for the charge on the human oxyhemoglobin tetramer (e.g., −2.10 vs. −2.54) and slightly lower for the tetramer molar buffer value (e.g., 10.2 vs. 10.8). Similarly, the theoretical charge on DPG of −4.6 is lower than the −4.1 given in Table 3. The molar buffer value (∂δ[C₉]/∂pH), however, is similar to the 0.69 published by Reeves (38) at 25°C but lower than the 1.0 obtained from Raftos et al. at 37°C (36). The ΔH° determined here of 10.6 kcal/mol is similar to the 10 kcal/mol obtained by Stadie and Martin (51). A ΔH° of 9 kcal/mol was found by Antonini et al. (2) for the alkaline groups and −1.5 kcal/mol for the acid groups of human hemoglobin. The validity of the approximation of Stadie and Martin that all ionizable groups of hemoglobin have the same standard enthalpy of ionization probably lies in the fact that, over the physiological pH range, groups with pKₐ outside the physiological pH range largely have a fixed charge, and therefore the overall molecular charge is relatively insensitive to small temperature-induced changes in the effective pKₐ of these groups. Although the agreement of the model with the data from Rollema et al. (41) at 25°C is seen to be moderately good over the physiological range, the agreement at low pH is not as impressive.

![Fig. 3. Plasma HCO₃⁻ concentration ([HCO₃⁻]ₚ) vs. pH(P) graphs for human whole blood (a) and plasma (b), indicated by solid lines. The normal physiological state is indicated by the arrow at pH(P) = 7.40, where the solid lines intersect. A dotted line is shown for an acid-base disturbance of whole blood at a metabolic component (a’) in a patient with pH(P) = 7.16 and [HCO₃⁻]ₚ = 25.60 mM. The arrow at pH(P) = 7.16 also indicates where this line crosses that for plasma. All lines have normal noncarbonate buffer concentrations. To obtain ΔP = ΔC₉ = change in strong ion difference (ΔSID) = change in Van Slyke standard bicarbonate for a given body fluid (ΔVSSB), any of the lines is traced back to pH(P) = 7.40 to get the corresponding [HCO₃⁻]ₚ. Then 24.25 mM is subtracted from this result to obtain ΔVSSB[P] for that body fluid. This value is then scaled by the appropriate distribution function as indicated in Eq. 36 to obtain the body fluid parameter, giving ΔP(P) = 0.0 mM and ΔP(B) = −5.3 mM.](image)

Fig. 3. Plasma HCO₃⁻ concentration ([HCO₃⁻]ₚ) vs. pH(P) graphs for human whole blood (a) and plasma (b), indicated by solid lines. The normal physiological state is indicated by the arrow at pH(P) = 7.40, where the solid lines intersect. A dotted line is shown for an acid-base disturbance of whole blood at a metabolic component (a’) in a patient with pH(P) = 7.16 and [HCO₃⁻]ₚ = 25.60 mM. The arrow at pH(P) = 7.16 also indicates where this line crosses that for plasma. All lines have normal noncarbonate buffer concentrations. To obtain ΔP = ΔC₉ = change in strong ion difference (ΔSID) = change in Van Slyke standard bicarbonate for a given body fluid (ΔVSSB), any of the lines is traced back to pH(P) = 7.40 to get the corresponding [HCO₃⁻]ₚ. Then 24.25 mM is subtracted from this result to obtain ΔVSSB[P] for that body fluid. This value is then scaled by the appropriate distribution function as indicated in Eq. 36 to obtain the body fluid parameter, giving ΔP(P) = 0.0 mM and ΔP(B) = −5.3 mM.

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faithfully reproduced by the theory for three different Pco2 values. The normal values calculated for SID in human plasma, erythrocyte fluid, and whole blood also agree reasonably well with those obtained by direct calculation (Table 3). Additionally, the titration curves for Cbi(B) and SID(B) are shown to be well approximated, to within 1 mM over the physiological range, by the linear forms of Eqs. 44 and 45. This is also the case for Cbi(P) and SID(P), as previously demonstrated (57). These results place confidence in the ability of the present formalism to predict the acid-base behavior of the multicompartment physiological system human whole blood. It bears mentioning, however, that acid-base parameters may be different in different species (6, 9), requiring a separate analysis for each.

In addition to reproducing the experimental human whole blood titration curves, the model also reproduces the traditional Van Slyke equation. Furthermore, the relationship of the present formalism to that of Siggaard-Andersen (47–49) has been demonstrated, providing Eq. 27 as a general multicompartment form of the Van Slyke equation. Figure 4 compares the values for [HCO3]p in human whole blood calculated with the traditional Van Slyke equation (Eq. 19) by using the parameters of Siggaard-Andersen and Fogh-Andersen (49) with that calculated by using the Van Slyke expression determined with the present model (Eq. 32). The [HCO3]p vs. pH curve calculated for whole blood with the complete expression (Eqs. 2 and 15) is also shown. Exact agreement between the approximate values of Eqs. 19 and 32 is present, and these deviate significantly from the values calculated with the more complete expression only at low pH(P). This deviation is a consequence, as discussed before by Siggaard-Andersen (47), of the pH dependence of parameters such as the Donnan ratio for bicarbonate and the buffer values of the noncarbonate species, which are assumed to have constant values in the approximate formulas (47). It is also a reflection of the use of Eq. 18 for the pH distribution in the derivation of the tradi-

Table 3. Theoretically derived normal parameter values compared with previous published data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Present Study</th>
<th>Previous Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cbi(P)</td>
<td>101</td>
<td>39(57)</td>
</tr>
<tr>
<td>SID(P)</td>
<td>39</td>
<td>39(57), 41.7(50), 40.4(9)</td>
</tr>
<tr>
<td>Cbi(E)</td>
<td>507</td>
<td>—</td>
</tr>
<tr>
<td>SID(E)</td>
<td>51</td>
<td>55.7(50), 54.6(36), 52(19)</td>
</tr>
<tr>
<td>Cbi(B)</td>
<td>279</td>
<td>—</td>
</tr>
<tr>
<td>SID(B)</td>
<td>44</td>
<td>47.9(50)</td>
</tr>
<tr>
<td>β(P)</td>
<td>5.7</td>
<td>7.7(49)</td>
</tr>
<tr>
<td>β(E)</td>
<td>58</td>
<td>63(47)</td>
</tr>
<tr>
<td>β(B)</td>
<td>29</td>
<td>26(47)a, 28(54)</td>
</tr>
<tr>
<td>β(E)</td>
<td>9.5(2.4a)</td>
<td>2.34(47)</td>
</tr>
<tr>
<td>β(B)</td>
<td>29</td>
<td>29(47)</td>
</tr>
<tr>
<td>δCbi</td>
<td>0.3</td>
<td>0.98(15), 0.99(17)</td>
</tr>
<tr>
<td>δSID</td>
<td>0.72</td>
<td>0.31(49)</td>
</tr>
<tr>
<td>δSID</td>
<td>0.15</td>
<td>10.8(36)a, 11.2(51)a, 11.3(2)a</td>
</tr>
<tr>
<td>£Cbi</td>
<td>0.70</td>
<td>1.2(36), 1.2(38)</td>
</tr>
<tr>
<td>£SID</td>
<td>0.18</td>
<td>2.14(36), 2.14(38)</td>
</tr>
<tr>
<td>£SID</td>
<td>0.10</td>
<td>2.14(36), 2.14(38)</td>
</tr>
<tr>
<td>£SID</td>
<td>0.10</td>
<td>2.14(36), 2.14(38)</td>
</tr>
</tbody>
</table>

Values for concentration parameters are in mM. Numbers in parentheses are Refs. See text for definitions. aCalculated from Eq. 3, Section 2.2.5 of Ref. 47. bCorresponding values in Eqs. 21 and 33. See text for discussion. cDefined in terms of the hemoglobin monomer to agree with definition in Ref. 47. dEquivalent to the δ'ib term in Eq. 21. eDefined in terms of the hemoglobin tetramer.
tional form, as opposed to Eq. 14 in the more complete expression.

It also bears mentioning that the value of 7.7 mM used for $\beta(P)$ in Eq. 21, although similar to the effective value of 7.3 mM for $\beta'(P)$ derived via Eq. 34, should not actually be the same as the true buffer value for plasma in Eq. 22. Similarly, the $\beta(E)$ of 63 mM given in Ref. 48 should not give a $\beta'(E)$ of 2.3 according to Eq. 35. It is important to point out, however, that the expression quoted by Siggaard-Andersen in the form of Eq. 21 actually appears to be an empirical relationship, and it is thus possible that the appearance of the factor 7.7 mM is coincidental.

Figure 3 demonstrates the important point that, in a multicompartment system, a complete quantitative treatment of the metabolic component of an acid-base disturbance requires that one account for all of the nonvolatile excess acid or base, considering the relative contributions from each compartment. For example, suppose that a patient presents with pH(P) contributions from each compartment. For example, nonvolatile excess acid or base, considering the relative disturbance requires that one account for all of the multicompartment system, a complete quantitative expression quoted by Siggaard-Andersen in the form of Eq. 21

In contrast to Siggaard-Andersen’s approach to calculating BE, Stewart calculated SID as a variable in its own right. Based on this, Stewart considered the effect of noncarbonate buffer concentrations on SID, leading others to interpret hyper- or hypoproteinemic states as forms of acid-base disorders by examining $\Delta$SID, the corresponding variable to $\Delta$CB, as a deviation from its normal value (23, 31, 42). Siggaard-Andersen and co-workers (49) have rejected this notion. Although differences in noncarbonate buffer concentrations do enter into the calculation of BE via Eq. 21, this has the effect of producing $\Delta$CB and altering the slope, but not the normal physiological position, of the CO2 equilibrium curve (32, 49, 57). Because this approach produces small changes in the final calculated BE, the default values are commonly used independent of the actual noncarbonate buffer concentrations (11, 49).

Although the Stewart theory is often said to have an advantage over BE in that it claims to examine the only independent variables of acid-base physiology (24, 25, 52, 53), this contention has been challenged (5, 49, 56). However, the clear theoretical disadvantage that the Stewart approach has had relative to the BE method is that its previous formulations did not treat the complete acid-base disorder quantitatively, because only the plasma compartment was considered. The present treatment of multicompartment systems brings the SID theory to the same quantitative level, and within the same degree of precision, as the traditional BE theory. It is also worth noting that the more complete expressions simplify under certain limiting conditions to the Henderson-Hasselbalch equation, as shown by Constable (6), and to the Van Slyke equation, as shown in the present work.

The model presented here provides a unifying formalism for the BE and SID approaches, and provides flexibility in the quantitative description of acid-base disorders, by allowing calculation of the absolute quantities CB and SID for single compartments or systems with multiple compartments, including the examples of human plasma, erythrocytes, and whole blood demonstrated. Both exact expressions and linear approximations can be used for calculation. With the use of these equations, acid-base status can be assessed from the vantage point of both CB and SID, considering changes in noncarbonate buffer concentration either explicitly (Eq. 37) or implicitly (Eq. 39). Given an extant theory for calculating absolute values of acid-base parameters in the whole organism, factors involved in acid-base disturbances can be more fully explored.

In conclusion, the general formalism previously developed for calculating parameters describing physiological acid-base balance in single compartments has been extended to multicompartment systems. Together with the previously obtained model for human plasma, a model for the human erythrocyte single compartment was used to obtain expressions for the multicompartment case of human whole blood. Calculations using these equations produced values that approximate a wide range of experimental data, providing confidence.
in the model. The equations for multicompartment systems were found to have the same mathematical interrelationships as those for single compartments. The relationship of the present formalism to the traditional form of the Van Slyke equation was also demonstrated, and a general multicompartment form of the Van Slyke equation was given. With the multicompartment model, the SID theory is brought to the same quantitative level as the BE method.

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