Modeling of Physiological Acid-Base Equilibria in Single and Multiple Compartments

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ESTAIC 2009

September 24, 2009

Modeling Physiological Acid-Base

We want as simple a model as possible but which still gives meaningful information.

We want the input and output of the model to be parameters which are easy to measure and understand.

Modeling Physiological Acid-Base

Equilibrium Thermodynamics-

It turns out that one can apply the condition of chemical equilibrium in physiological acid-base and obtain theoretical results which approximate measured parameters even though the system is not at true equilibrium.

Modeling Physiological Acid-Base

The exact theory of acid-base equilibria has been known for over half a century, but our ability to apply the theory in physiology has been limited by:

1. Sufficiently accessible computational power

2. Sufficient input data for the models

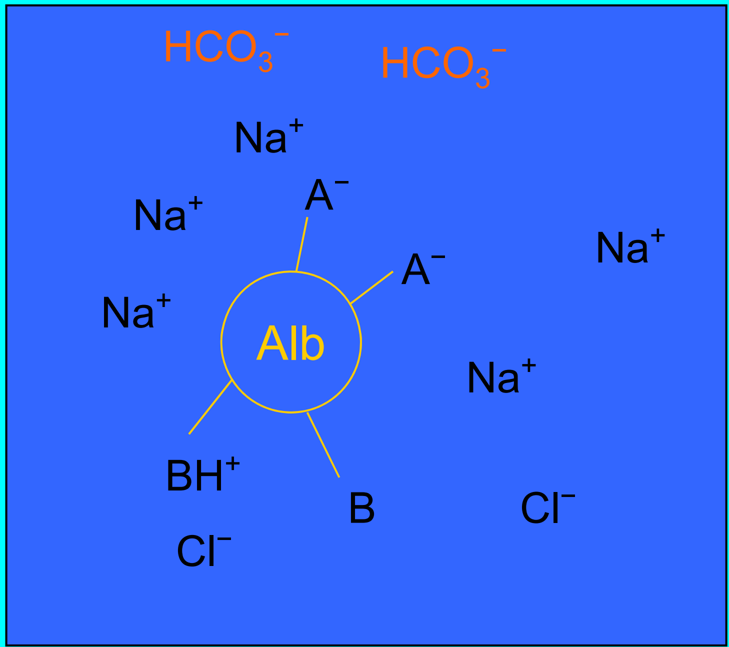
Acid-Base Parameters

Total Titratable Acid (C_H) = Total Net Concentration of Donatable Protons Over the pH Range of Interest

Total Titratable Base (C_B) = Total Net Concentration of Proton Acceptor Sites Over the pH Range of Interest

Total Titratable Charge = Strong Ion Difference (SID) = Sum of Cation Charge Concentration – Anion Charge Concentration for Ions Not Participating In Proton Transfer Reactions Over the pH Range of Interest

Total titratable base and strong ion difference are most often used because they are directly related to the metabolic component of an acid-base disorder.



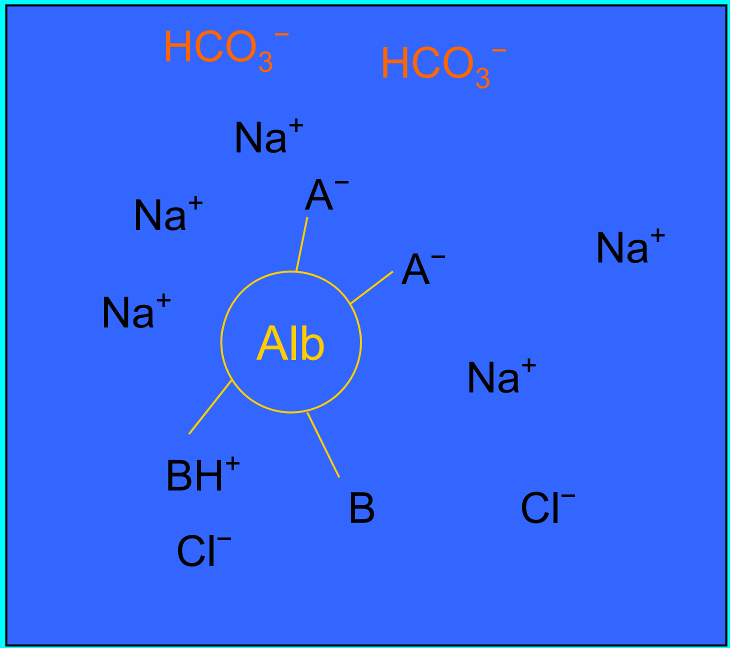
C_H	C_B	SID
3	5	3

$C_H = 2\ HCO_3^- + BH^+ = 3$

$C_B = 2\ HCO_3^- + 2\ A^- + B = 5$

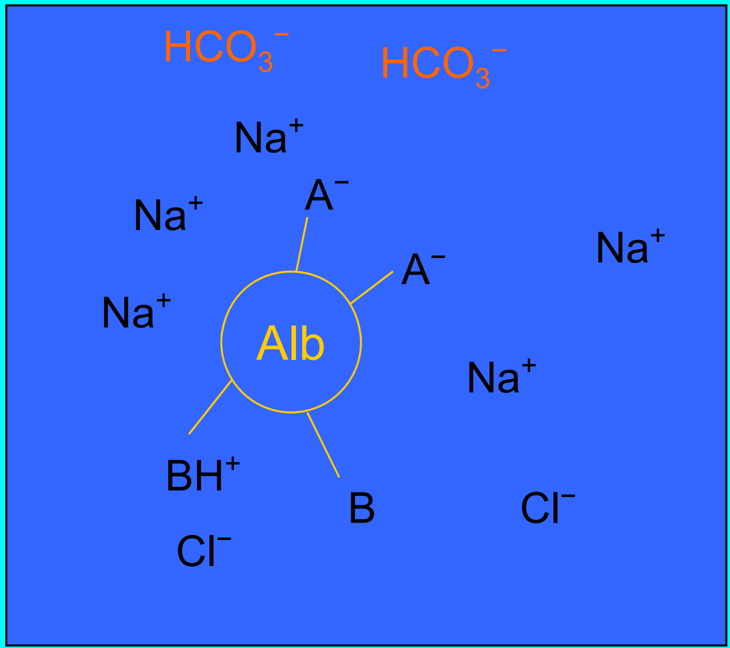
$SID = 5\ Na^+ - 2\ Cl^- = -(BH^+ - 2\ A^- - 2\ HCO_3^-) = 3$

C_B = SID + maximum possible charge = SID + 2



Normal

C_H	C_B	SID
3	5	3

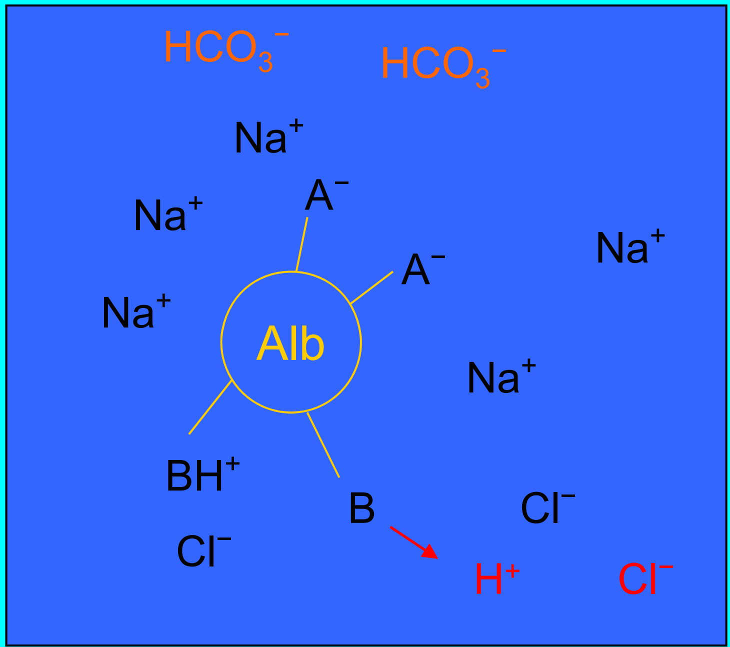


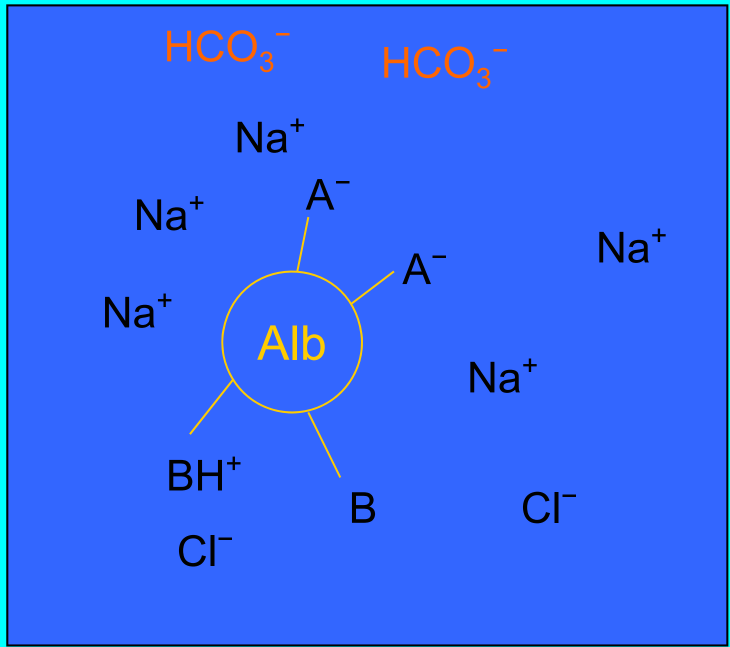
Normal

C_H	C_B	SID
3	5	3

+ 1 HCl

Abnormal

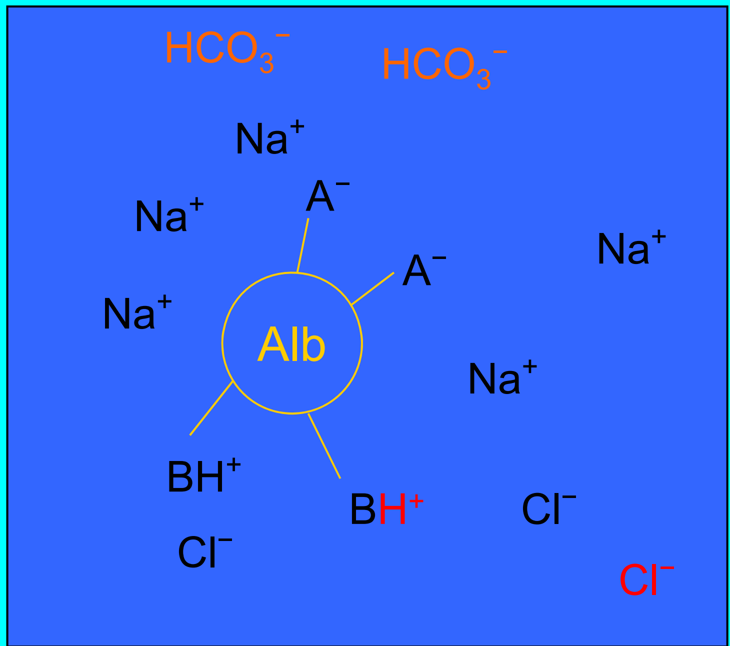




Normal

C_H	C_B	SID
3	5	3

+ 1 HCl



Abnormal

C_H	C_B	SID
4	4	2
ΔC_H	ΔC_B	ΔSID
+1	-1	-1

Wooten, E.W. Analytic calculation of physiological acid-base parameters in plasma. *J. Appl. Physiol.* 86: 326-334, 1999.
(Corrigenda. *J. Appl. Physiol.* 86: June 1999, following table of contents).

Wooten EW. Calculation of physiological acid-base parameters in multicompartment systems with application to human blood. *J Appl Physiol* 95: 2333-2344, 2003.

Formal Calculation

$$P(\chi) = C_{\bar{\xi}}(\chi) + \sum_n \mathrm{C}_n(\chi)\bar{\xi}_n(\chi) - \mathrm{D}_{\bar{\xi}}(\chi)$$

$$\mathrm{C_H}(\chi) = 2[\mathrm{H_2CO_3}^*]_\chi + [\mathrm{HCO_3}^-]_\chi + \sum_n \mathrm{C}_n(\chi)\bar{n}_n(\chi) + \mathrm{D}_\chi$$

$$\mathrm{C_B}(\chi) = [\mathrm{HCO_3}^-]_\chi + 2[\mathrm{CO_3}^{2-}]_\chi + \sum_n \mathrm{C}_n(\chi)\bar{e}_n(\chi) - \mathrm{D}_\chi$$

$$\mathrm{SID}(\chi) = [\mathrm{HCO_3}^-]_\chi + 2[\mathrm{CO_3}^{2-}]_\chi - \sum_n \mathrm{C}_n(\chi)\bar{z}_n(\chi) - \mathrm{D}_\chi$$

$$\mathrm{D}_\chi = [\mathrm{H}^+]_\chi - [\mathrm{OH}^-]_\chi$$

Formal Calculation

$$\bar{n}_n(\chi) = \sum_{j(n)=0}^{\bar{n}_{\max(n)}} j(n) \cdot \alpha_{j(n)}(\chi)$$

$$\bar{e}_n(\chi) = \bar{n}_{\max(n)} - \bar{n}_n(\chi)$$

$$\bar{z}_n(\chi) = \bar{z}_{\max(n)} - \bar{e}_n(\chi)$$

Formal Calculation

$$\alpha_{j(n)}(\chi) = \frac{[\mathrm{H}^+]_{\chi}^{j(n)} \prod_{\ell(n)=0}^{\bar{n}_{\max(n)}-j(n)} K_{\ell(n)}}{\sum_{j(n)=0}^{\bar{n}_{\max(n)}} [\mathrm{H}^+]_{\chi}^{j(n)} \prod_{\ell(n)=0}^{\bar{n}_{\max(n)}-j(n)} K_{\ell(n)}}$$

$$K_0 = 1$$

Formal Calculation

$$[\mathrm{H}^+]_\chi = 10^{-\mathrm{pH}(\chi)}$$ obtained from measured pH

Effective equilibrium constant K may be obtained experimentally or theoretically with

$$\frac{\partial K_{\ell(n)}}{\partial \mathrm{pH}(\chi)} = 0 \quad \text{or} \quad K_{\ell(n)} = f(\mathrm{pH})$$

Formal Calculation

$$K' = \frac{[H^+]_\chi \; [HCO_3^{\,-}]_\chi}{S \bullet P_{CO_2}(\chi)}$$

$$K_2 = \frac{[H^+]_\chi \; [CO_3^{\,2-}]_\chi}{[HCO_3^{\,-}]_\chi}$$

Approximate Relationships

$$P(\chi) \approx [\mathrm{HCO_3}^-]_\chi + \sum_n \mathrm{C}_n(\chi)\left(\frac{\partial \bar{\xi}_n}{\partial \mathrm{pH}}\mathrm{pH}(\chi) + \kappa_{\bar{\xi}_n}\right)$$

$$\mathrm{C_B}(\chi) \approx [\mathrm{HCO_3}^-]_\chi + \sum_n \mathrm{C}_n(\chi)\left(\frac{\partial \bar{e}_n}{\partial \mathrm{pH}}\mathrm{pH}(\chi) + \kappa_{\bar{e}_n}\right)$$

$$\mathrm{SID}(\chi) \approx [\mathrm{HCO_3}^-]_\chi - \sum_n \mathrm{C}_n(\chi)\left(\frac{\partial \bar{z}_n}{\partial \mathrm{pH}}\mathrm{pH}(\chi) + \kappa_{\bar{z}_n}\right)$$

$$\beta(\chi) = \sum_n \mathrm{C}_n(\chi)\frac{\partial \bar{\xi}_n}{\partial \mathrm{pH}}$$

Relationship of C_B to SID

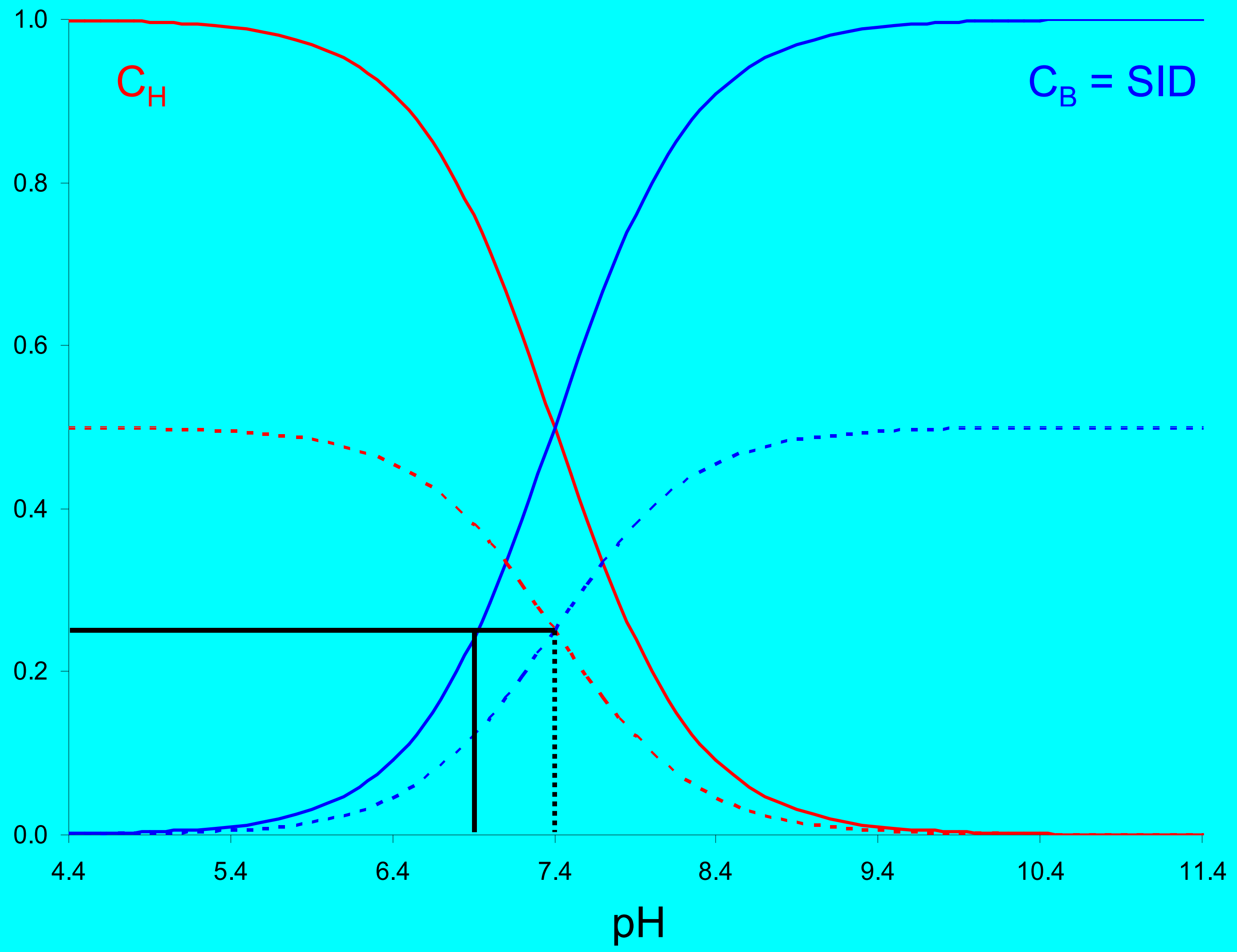
$$\frac{\partial \bar{e}_n}{\partial \mathrm{pH}} = -\frac{\partial \bar{z}_n}{\partial \mathrm{pH}}$$

$$\mathrm{C_B}(\chi) = \mathrm{SID}(\chi) + \sum_n \mathrm{C}_n(\chi)\,\bar{z}_{\max(n)}$$

$$\Delta\mathrm{C_B}(\chi) = \Delta\mathrm{SID}(\chi) + \sum_n \bar{z}_{\max(n)}\,\Delta\mathrm{C}_n(\chi)$$

For constant non-carbonate buffer concentration, $\Delta \mathrm{C}_n = 0$ mM:

$$\Delta\mathrm{C_B}(\chi) = \Delta\mathrm{SID}(\chi) = \text{Base Excess}$$



Patient A

$C_n = 1$

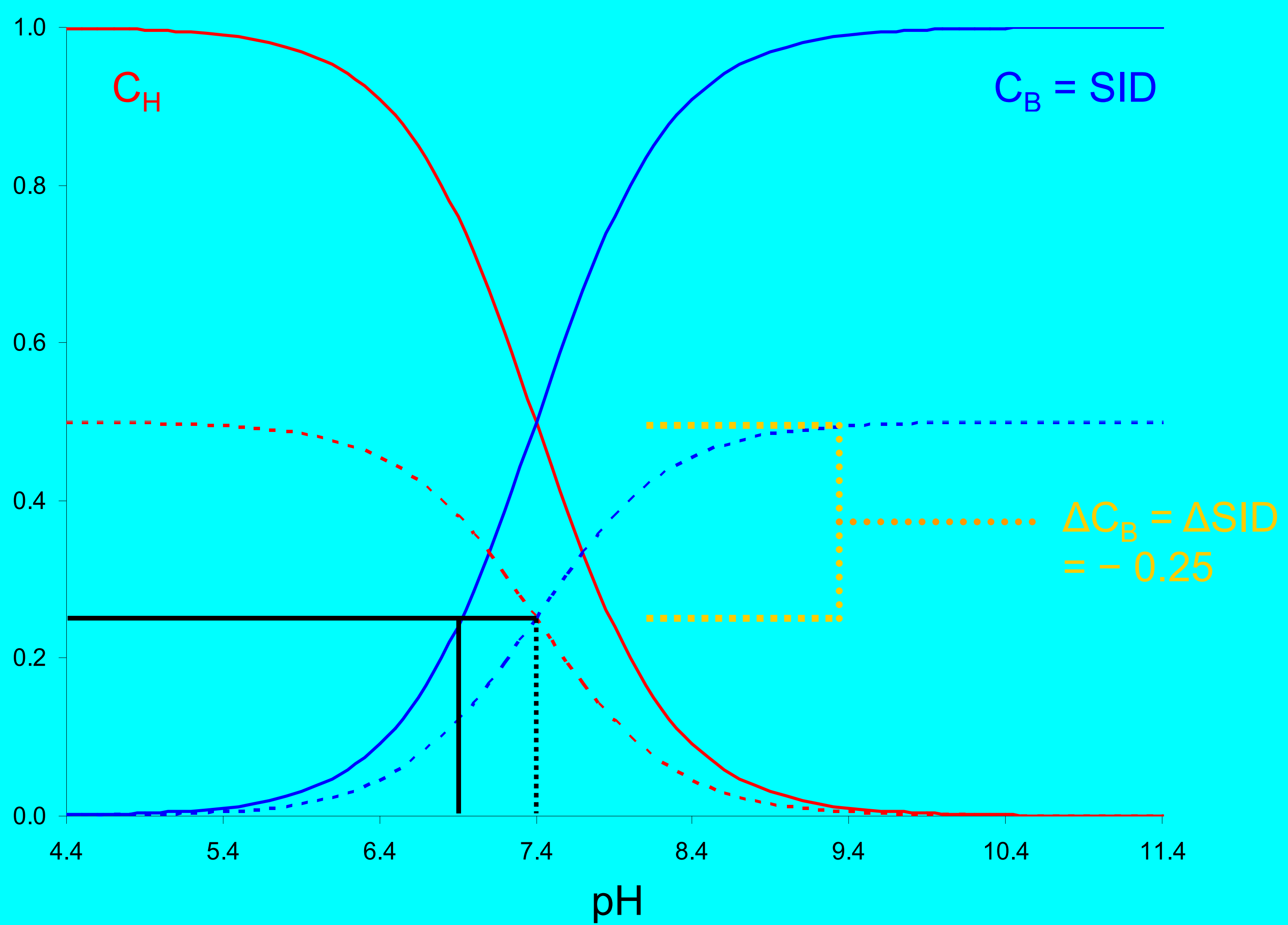
Patient A′

$C_n = 0.5$

$$HA \rightleftarrows H^+ + A^-$$

$$C_B = C_n \frac{K}{[H^+] + K}$$

$$C_H = C_n \frac{[H^+]}{[H^+] + K}$$



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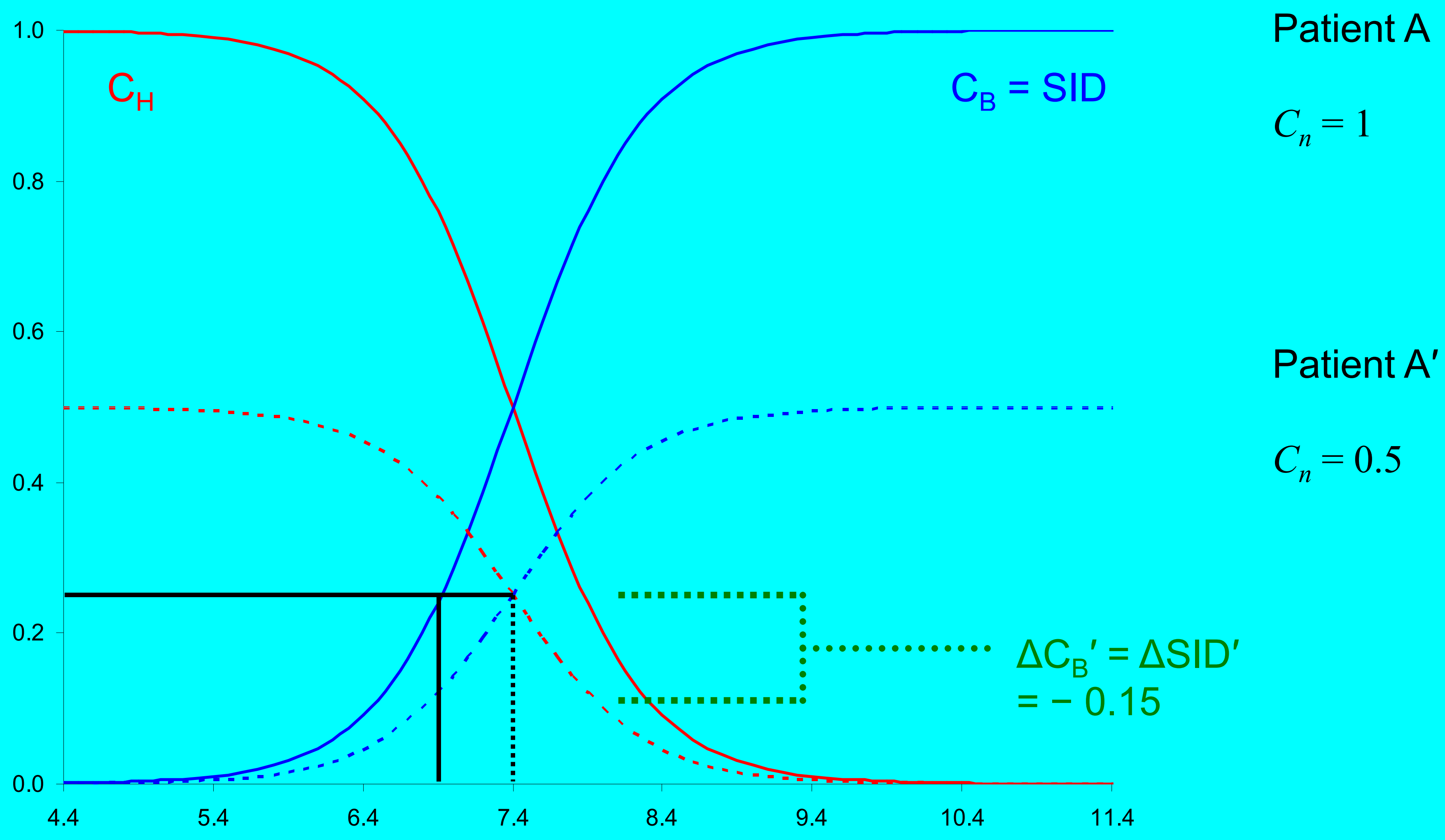

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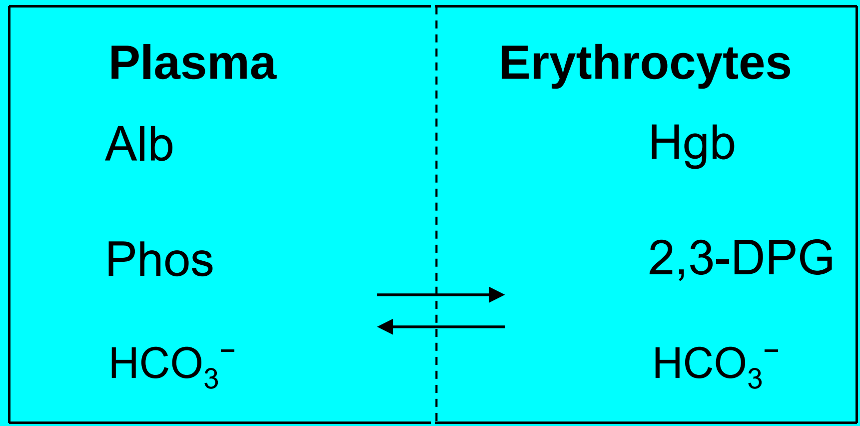
$$C_B = C_n \frac{K}{[H^+] + K}$$

$$C_H = C_n \frac{[H^+]}{[H^+] + K}$$

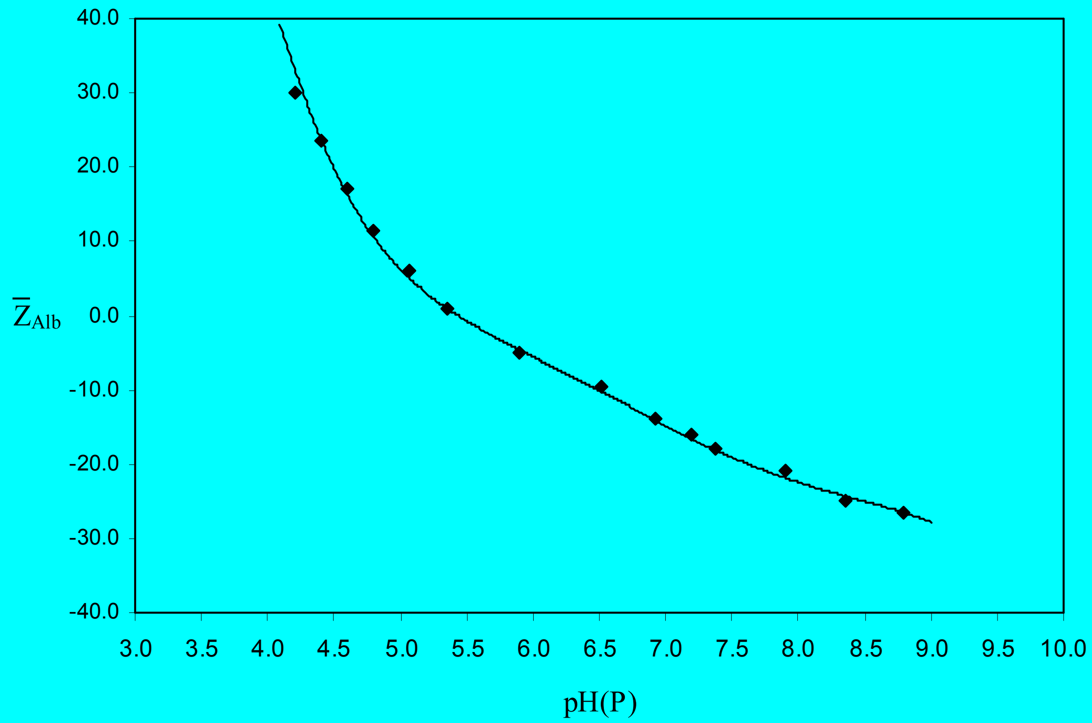
Multicompartment Systems



$$P(M) = \sum_{\chi} \phi(\chi) P(\chi)$$

$$\Delta\psi(\chi) = -\frac{RT}{cF} \ln r_m(\chi) = -\frac{RT}{cF} \ln \frac{[\mathrm{H}^+]_\chi}{[\mathrm{H}^+]_\mathrm{P}} = -\frac{RT}{cF} \ln \frac{[\mathrm{HCO_3}^-]_\chi}{[\mathrm{HCO_3}^-]_\mathrm{P}}$$

Human Albumin Charge vs. pH
(Figge-Fencl Model)

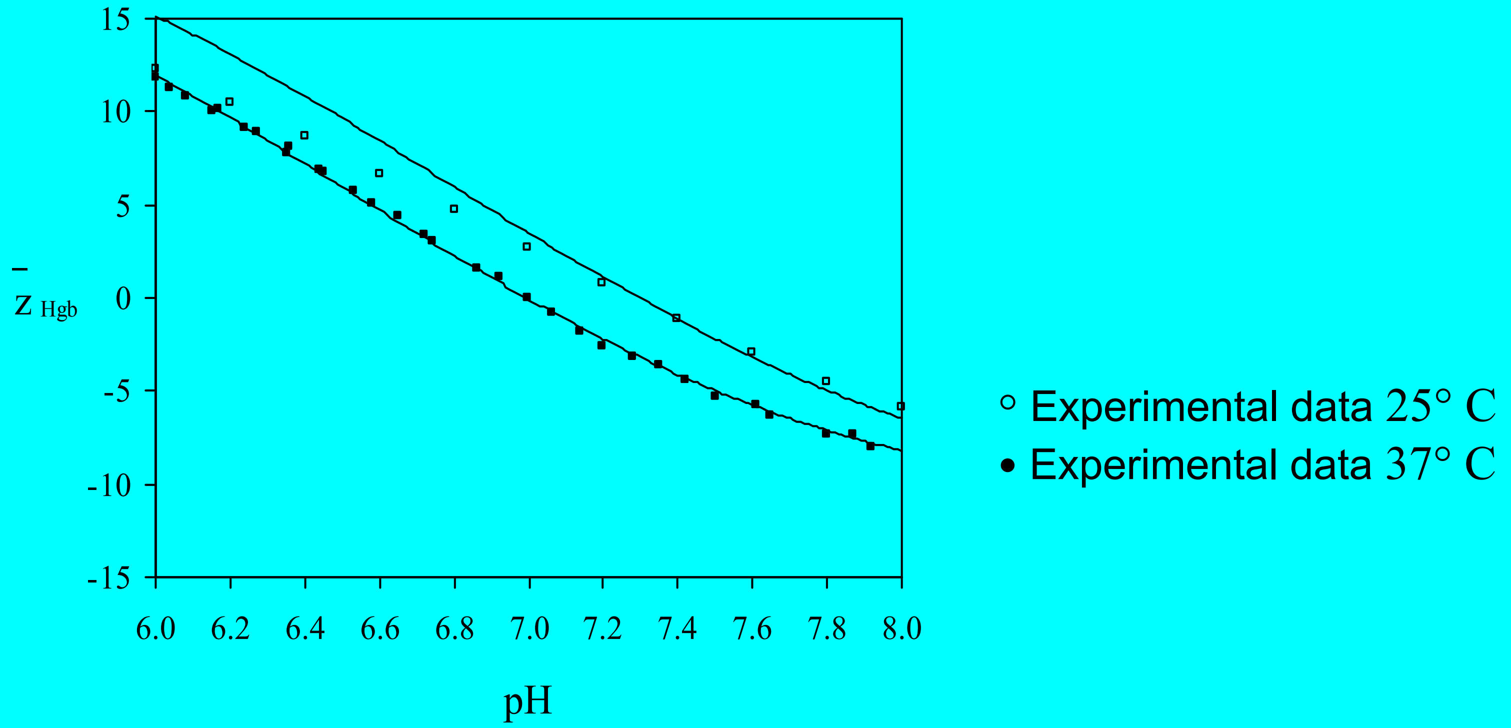


- 37° C

Figge J. The Figge-Fencl Quantitative Acid-Base Model of Human Acid-Base Physiology. 22 December, 2007. http://www.figge-fencl.org

Includes pH dependent pKa for histidines from conformational transition

Human Oxyhemoglobin Charge vs. pH



Wooten EW. Calculation of physiological acid-base parameters in multicompartment systems with application to human blood. *J Appl Physiol* 95: 2333-2344, 2003.

Total Titratable Base for Human Whole Blood

$$C_B(B) = \{1 - 0.49\phi_B(E)\}[HCO_3^-]_P$$

$$+ \{1 - \phi_B(E)\}\{C_{Alb}(P)\left(8.0\,pH(P) + 53\right) + C_{Phos}(P)\left(0.30\,pH(P) - 0.4\right)\}$$

$$+ C_{Hgb}(B)\{10.2\,pH(P) + 12.4\} + \phi_B(E)C_{DPG}(E)\{0.70\,pH(P) - 0.5\}$$

All concentrations in mM

Strong Ion Difference for Human Whole Blood

$$\mathrm{SID(B)} = \{1 - 0.49\phi_B(\mathrm{E})\}[\mathrm{HCO_3}^-]_\mathrm{P}$$

$$+\{1-\phi_B(\mathrm{E})\}\{C_{Alb}(\mathrm{P})(8.0\,\mathrm{pH(P)} - 41) + C_{Phos}(\mathrm{P})(0.30\,\mathrm{pH(P)} - 0.4)\}$$

$$+C_{Hgb}(\mathrm{B})\{10.2\ \mathrm{pH(P)} - 73.6\} + \phi_B(\mathrm{E})C_{DPG}(\mathrm{E})\{0.70\ \mathrm{pH(P)} - 0.5\}$$

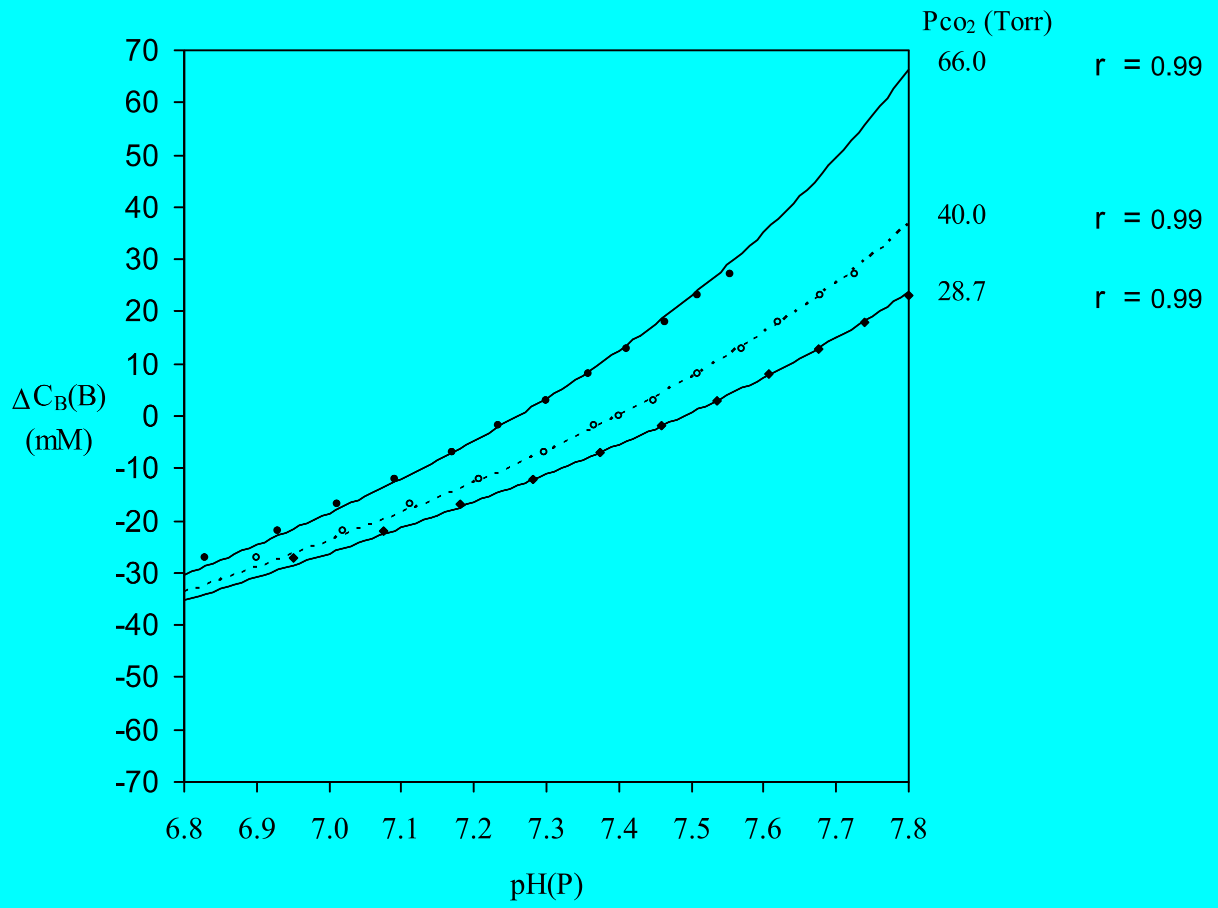
All concentrations in mM

Model for Human Whole Blood at pH(P) = 7.4

Parameter	Model	Previous Values
SID(B)	44	47.9
β(B)	29	26, 28

All concentrations in mM

Base Excess vs. pH(P) for Human Whole Blood *in vitro*



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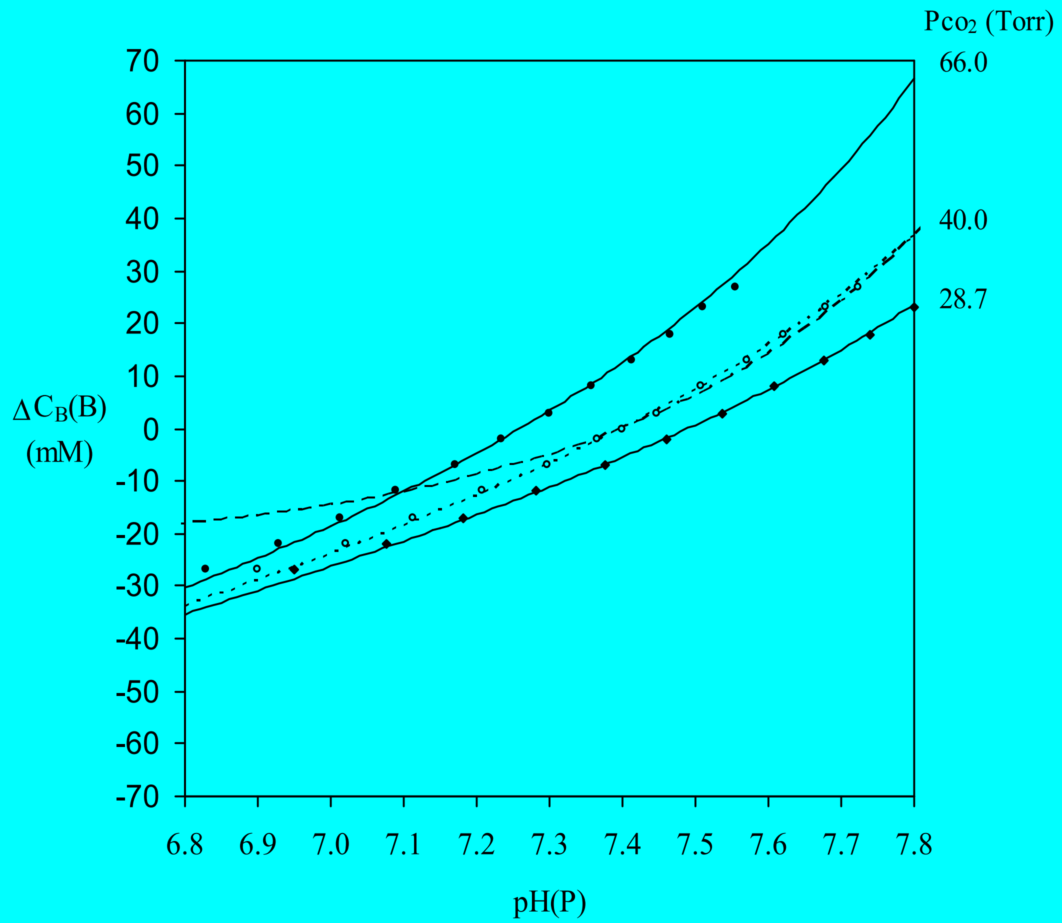
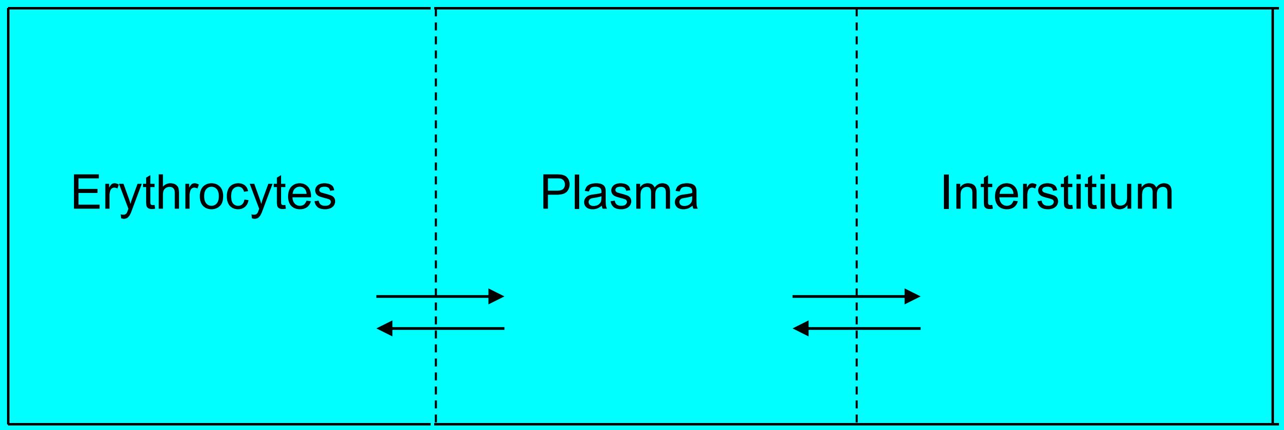


Bicarbonate alone (- - - - - -) at P_{CO_2} 40.0 Torr

Acid-Base Parameters for Human “Extracellular Fluid”= *IPE* System:



Proton distribution across these three compartments persists for several hours arguing that intracellular buffering is a slower process

The interstitium is a very complicated heterogeneous mix of collagen and proteoglycans in a gel for which assumption of aqueous behavior may be invalid

Acid-Base Parameters for Human “Extracellular Fluid”:

$$P(IPE) = \sum_{\chi} \phi_{IPE}(\chi) P(\chi)$$

Acid-Base Parameters for Human "Extracellular Fluid":

$$P(IPE) = \sum_{\chi} \phi_{IPE}(\chi) P(\chi)$$

The Siggaard-Andersen Approximation:

$$P(\mathrm{I}) \approx P(\mathrm{P})$$

$$P(IPE) = \frac{\lambda \phi_B(\mathrm{E}) V_B}{V_{IPE}} P(\mathrm{E}) + \frac{\left(V_{IPE} - \lambda \phi_B(\mathrm{E}) V_B\right)}{V_{IPE}} P(\mathrm{P})$$

Total Titratable Base for Human Extracellular Fluid (*IPE*)

$$\mathrm{C_B}(IPE) = \left\{1 - \frac{\lambda\phi_B(\mathrm{E})V_B 0.49}{V_{IPE}}\right\}[\mathrm{HCO_3}^-]_\mathrm{P}$$

$$+\left(1 - \frac{\lambda\phi_B(\mathrm{E})V_B}{V_{IPE}}\right)\left\{\mathrm{C}_{Alb}(\mathrm{P})\left(8.0\,\mathrm{pH(P)} + 53\right) + \mathrm{C}_{Phos}(\mathrm{P})\left(0.30\,\mathrm{pH(P)} - 0.4\right)\right\}$$

$$+\frac{\lambda V_B}{V_{IPE}}\mathrm{C}_{Hgb}(\mathrm{B})\left\{10.2\,\mathrm{pH(P)} + 12.4\right\} + \frac{\lambda\phi_B(\mathrm{E})V_B}{V_{IPE}}\mathrm{C}_{DPG}(\mathrm{E})\left\{0.70\,\mathrm{pH(P)} - 0.5\right\}$$

All concentrations in mM

Total Titratable Base for Human Extracellular Fluid (*IPE*)

$$C_B(IPE) = \left(1 - 0.16\phi_B(E)\right)[HCO_3^-]_P$$

$$+\left(1 - 0.33\phi_B(E)\right)\left\{C_{Alb}(P)\left(8.0\,pH(P) + 53\right) + C_{Phos}(P)\left(0.30\,pH(P) - 0.4\right)\right\}$$

$$+0.33C_{Hgb}(B)\left\{10.2\ pH(P) + 12\right\} + 0.33\phi_B(E)C_{DPG}(E)\left\{0.70\,pH(P) - 0.5\right\}$$

All concentrations in mM

Strong Ion Difference for Human Extracellular Fluid (*IPE*)

$$\mathrm{SID}(IPE) = \left\{1 - \frac{\lambda \phi_B(\mathrm{E}) V_B 0.49}{V_{IPE}}\right\}[\mathrm{HCO_3}^-]_\mathrm{P}$$

$$+\left(1 - \frac{\lambda \phi_B(\mathrm{E}) V_B}{V_{IPE}}\right)\left\{\mathrm{C}_{Alb}(\mathrm{P})\left(8.0\ \mathrm{pH(P)} - 41\right) + \mathrm{C}_{Phos}(\mathrm{P})\left(0.30\ \mathrm{pH(P)} - 0.4\right)\right\}$$

$$+\frac{\lambda V_B}{V_{IPE}}\mathrm{C}_{Hgb}(\mathrm{B})\left\{10.2\ \mathrm{pH(P)} - 73.6\right\} + \frac{\lambda \phi_B(\mathrm{E}) V_B}{V_{IPE}}\mathrm{C}_{DPG}(\mathrm{E})\left\{0.70\ \mathrm{pH(P)} - 0.5\right\}$$

All concentrations in mM

Strong Ion Difference for Human Extracellular Fluid (*IPE*)

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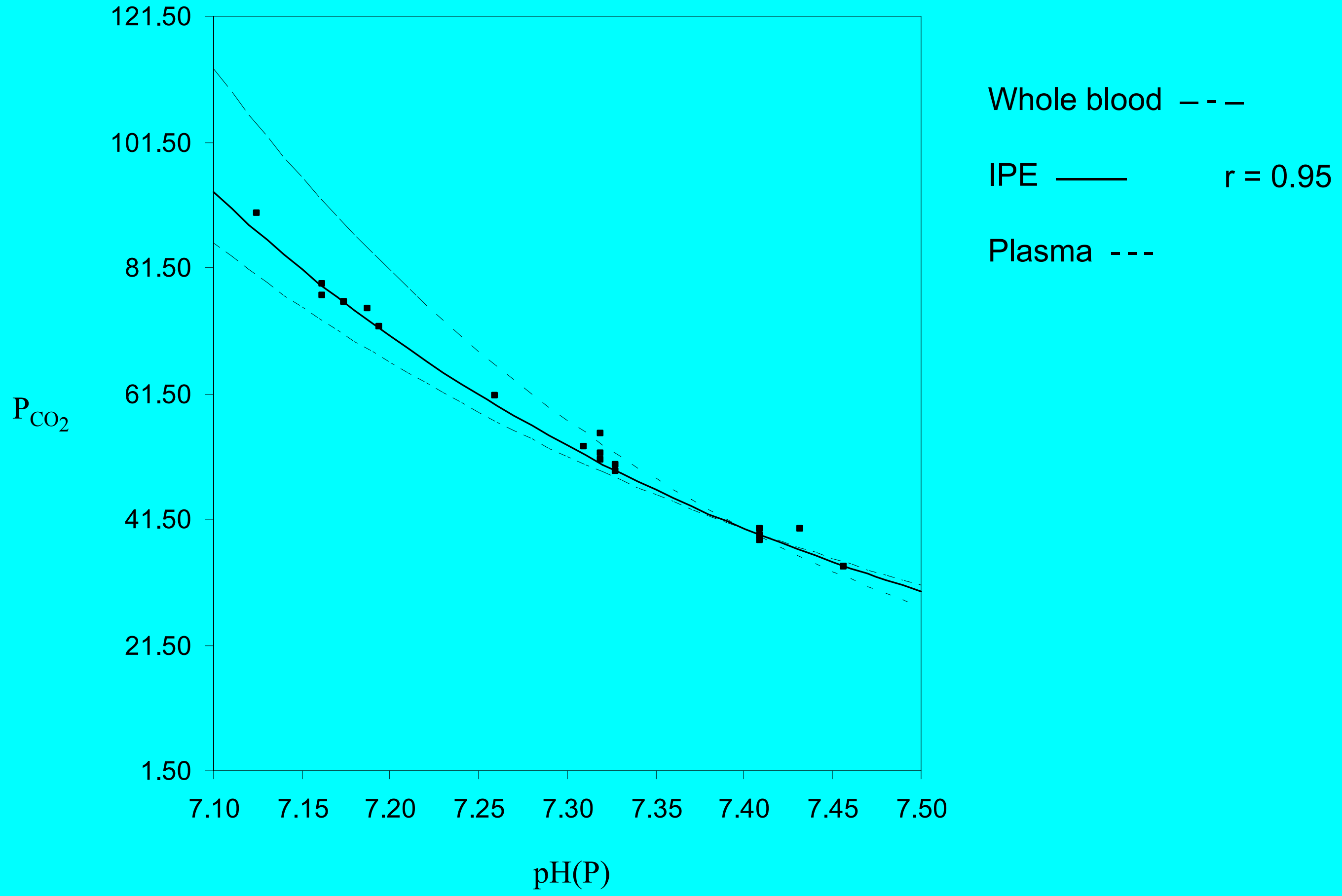
$$+ 0.33\mathrm{C}_{Hgb}(\mathrm{B})\left\{10.2\,\mathrm{pH(P)} - 73.6\right\} + 0.33\phi_B(\mathrm{E})\mathrm{C}_{DPG}(\mathrm{E})\left\{0.70\,\mathrm{pH(P)} - 0.5\right\}$$

All concentrations in mM

Model for Human *IPE* at pH(P) = 7.4

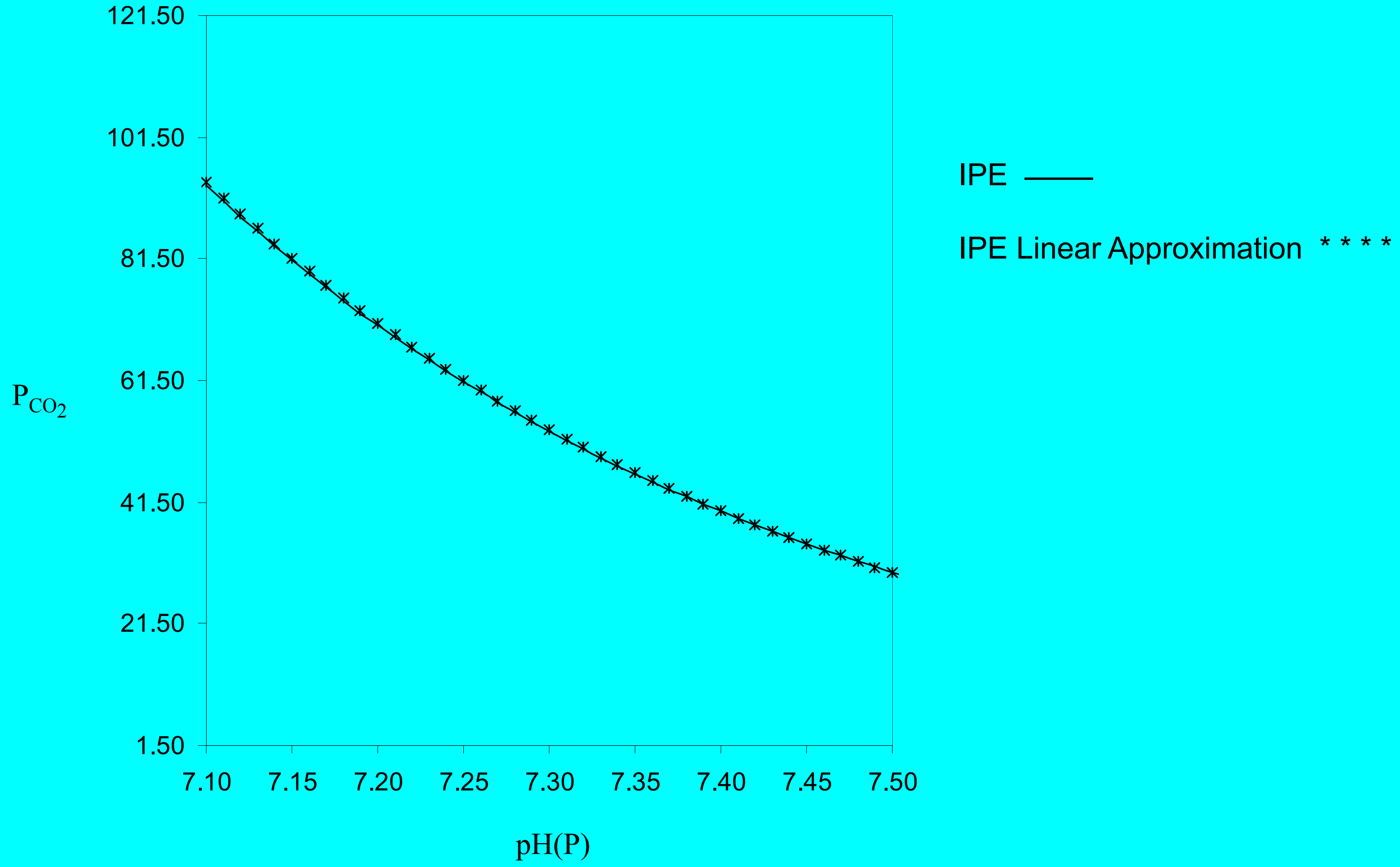
Parameter	Model	Previous Values
SID*(IPE)*	40	39.5
$\frac{\partial [HCO_3^-]_P}{\partial pH(P)}$	−12	−12, −16, −21

P_{CO_2}(P) vs. pH(P) for Humans *in vivo*



Experimental data points from **Brackett et al.** *New Engl J Med* 272: 6-12, 1965.

P_{CO_2}(P) vs. pH(P) for Humans *in vivo*



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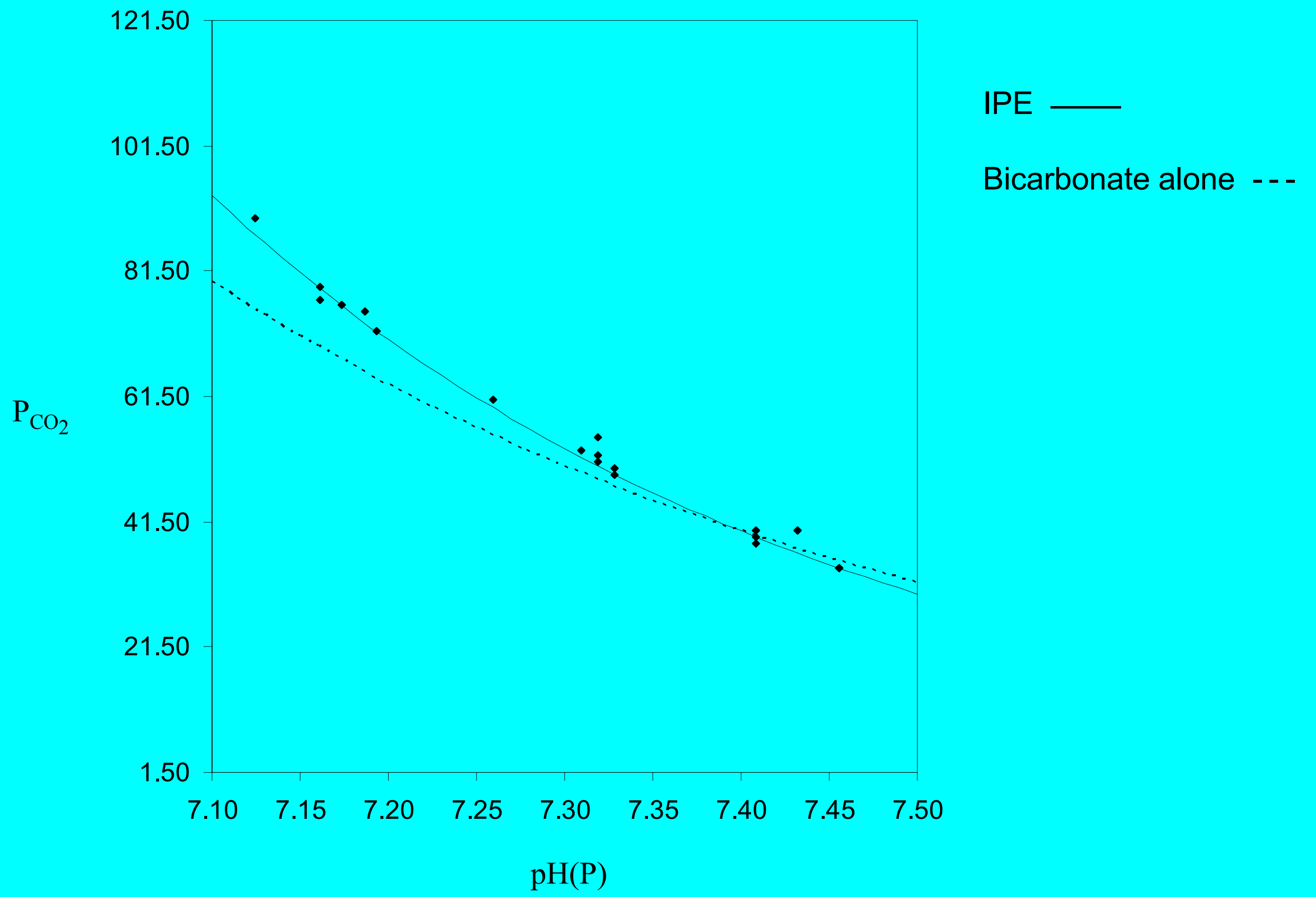
P_{CO_2}(P) vs. pH(P) for Humans *in vivo*



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For Constant Noncarbonate Buffer Concentration

$$\mathrm{BE(P)} = \Delta \mathrm{C_B}(P) = \Delta \mathrm{SID}(P)$$

$$\mathrm{BE(B)} = \Delta \mathrm{C_B}(B) = \Delta \mathrm{SID}(B)$$

$$\mathrm{BE(ECF)} = \Delta \mathrm{C_B}(IPE) = \Delta \mathrm{SID}(IPE)$$

$$\mathrm{BE(ECF)} = \text{Standard Base Excess}$$

$$\mathrm{SID}(IPE) = \text{Standard Strong Ion Difference}$$

Future work

Model the effects of chloride and calcium binding to albumin to get a more precise model for plasma and a better value for SIG

Include the effects of multicompartment systems in the evaluation of SIG

Explicitly incorporate the effects of specific interstitial proteins in the model

Do precise clinical comparisons between the plasma, blood, and IPE models

Acknowledgements

I thank Dr. Sunni Barnes of Baylor University for helpful advice regarding statistical analysis

Questions?

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