

# A MATHEMATICAL MODEL OF THE CHEMISTRY OF THE EXTERNAL RESPIRATORY SYSTEM

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## 1. Description of the model

The purpose of this paper is to summarize the mathematical aspects of our more complete study of this subject [1].

From the physiological data available and the working of the respiratory system as outlined in the foregoing reference, we set up a mathematical model to represent the more important of the known interrelated physiological functions and chemical reactions involved in the human respiratory system.

Figure 1 is a schematic illustration of the system and demonstrates the relationship of the inputs and outputs of the mathematical model to the actual system. The  $a$  and  $v$  in the figure refer to the amounts of the input "elements" or "building blocks" coming to the lungs in unit time from venous blood and from the air. The  $x$  refer to the amounts of the resulting numerous molecular species produced in the arterial blood and in the air of the lung sacs when equilibrium is reached and as determined by the solution of the mathematical model. At the present stage outputs of the tissue cells are introduced into the model in terms of the composition of the venous blood.

The model was constructed to provide an accounting for the mass of all the elements involved. Having available the equilibrium constants for the molecules formed, it was possible to establish the thermodynamics of the system within the model. In order to illustrate our approach, we have extracted a small piece of our respiratory model. Let us for simplicity set aside most of the substances found in the blood plasma compartment except for the carbon dioxide dissolved in water. As shown in table I this will result in the forming of chemical species such as  $H_2O$ ,  $OH^-$ ,  $H^+$ ,  $CO_2$ ,  $HCO_3^-$ . We suppose everything is held at constant temperature and pressure and that sufficient time has elapsed for the mixture to settle down. Our problem is to predict the equilibrium distribution.

To build up the chemical equilibrium model we first distinguished the dif-

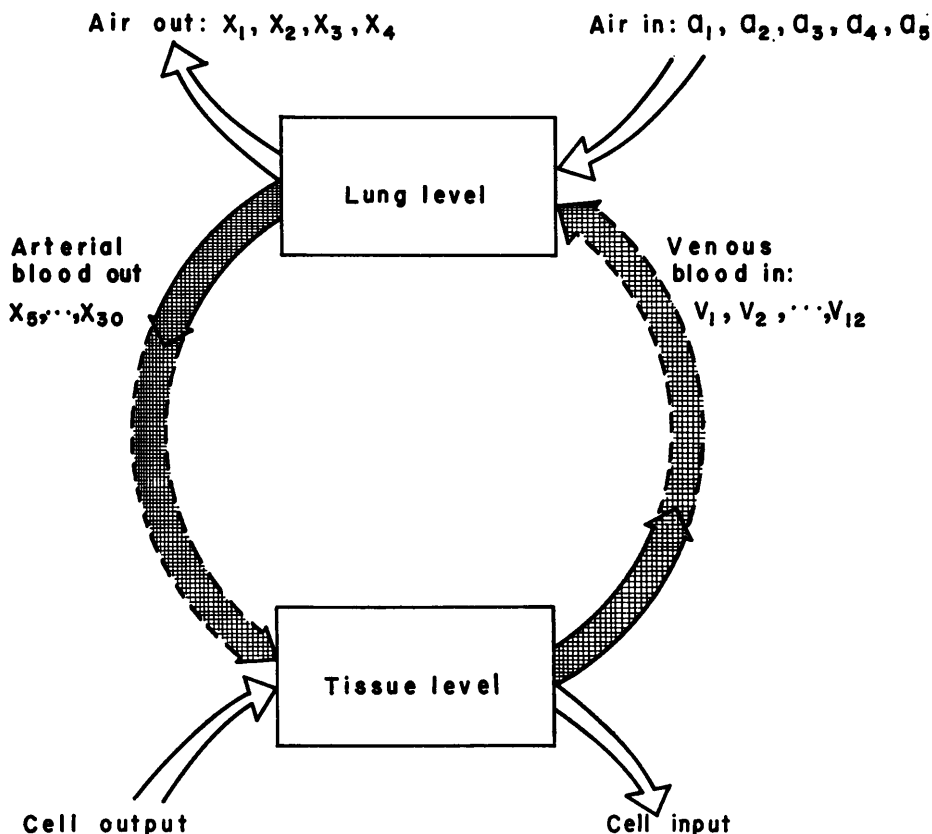


FIGURE 1

The relationship of the inputs and outputs of model I to the respiratory system.

ferent molecule types by giving a formula by which they could be formed from more elementary elements. A simple example of this is  $H_2O$  which indicates that water can be formed from two atoms of hydrogen and one of oxygen. Actually we could use any building blocks we please to build up the molecular types. Since organic molecules are very complex, we found it more convenient to use groups of atoms as our building blocks. In our model we used  $H^+$ ,  $OH^-$ , and  $CO_2$ . Thus, water is composed of one unit of  $H^+$  and one unit of  $OH^-$ , indicated by the position of the entries in the  $H_2O$  column of table I, while  $HCO_3^-$  is formed from one unit of  $OH^-$  and one unit of  $CO_2$  as shown by the position of the units in the  $HCO_3^-$  column.

To determine the unknown quantities of these molecules,  $x_i$ , in the equilibrium mixture we first expressed the chemical law of mass balance. In words, this law says that the total amount of each type of building block placed initially in the mixture is equal to the amounts used to form the various species in the mixture.

TABLE I  
A SIMPLE CHEMICAL MODEL

Building Blocks (Atoms)	Molecules in Mixture				
	H <sub>2</sub> O	H <sup>+</sup>	OH <sup>-</sup>	CO <sub>2</sub>	HCO <sub>3</sub> <sup>-</sup>
H <sup>+</sup>	1	1			
OH <sup>-</sup>	1		1		1
CO <sub>2</sub>				1	1
	Quantities in Mixture				
	X <sub>H<sub>2</sub>O</sub>	X <sub>H<sup>+</sup></sub>	X <sub>OH<sup>-</sup></sub>	X <sub>CO<sub>2</sub></sub>	X <sub>HCO<sub>3</sub><sup>-</sup></sub>
Mass Balance Relations					
Input H <sup>+</sup>	=	X <sub>H<sub>2</sub>O</sub>	+	X <sub>H<sup>+</sup></sub>	
Input OH <sup>-</sup>	=	X <sub>H<sub>2</sub>O</sub>		+	X <sub>OH<sup>-</sup></sub>
Input CO <sub>2</sub>	=			X <sub>CO<sub>2</sub></sub>	+ X <sub>HCO<sub>3</sub><sup>-</sup></sub>

The equations expressing each of these relations are shown in the bottom half of table I and are formed from the top half by multiplying  $x_i$  by the corresponding entries in any row and summing.

However, for equilibrium, classical chemistry tells us another law must also be satisfied, the law of mass action. There are various ways to express this law. One way is to state that the so-called free energy of the system will "run down hill" until a minimum is reached. Now the function  $z$  which measures the free energy of the system has the simple form

$$(1) \quad z = x_{\text{H}_2\text{O}} \bar{F}_{\text{H}_2\text{O}} + x_{\text{H}^+} \bar{F}_{\text{H}^+} + x_{\text{OH}^-} \bar{F}_{\text{OH}^-} + x_{\text{CO}_2} \bar{F}_{\text{CO}_2} + x_{\text{HCO}_3^-} \bar{F}_{\text{HCO}_3^-}$$

where

$$(2) \quad \bar{F}_{\text{H}_2\text{O}} = c_{\text{H}_2\text{O}} + \log \frac{x_{\text{H}_2\text{O}}}{\sum x_i},$$

and so forth. The values of the constants such as  $c_{\text{H}_2\text{O}}$  can be found in chemical tables. All logs are natural logarithms.

The chemical equilibrium model in general can be expressed mathematically as follows: Let  $i = 1, \dots, m$  represent  $m$  different types of "building blocks" that can be used to generate  $j = (1, \dots, n)$  different possible types of species (molecules, ions). Let  $b_i$  be the number of each type of building block introduced into the mixture and let  $x_j \geq 0$  be the number of each species present.

The law of mass balance asserts

$$(3) \quad b_i = \sum_{j=1}^n a_{ij} x_j \quad i = 1, \dots, m,$$

where  $a_{ij}$  is the number of type  $i$  present in each unit of species  $j$  (the law of combining proportions).

According to Gibbs the total free energy of the system is given by

$$(4) \quad F(X) = \sum_{j=1}^n x_j \left( c_j + \log \frac{x_j}{\bar{x}} \right)$$

where

$$(5) \quad \bar{x} = \sum_{j=1}^n x_j, \quad X = (x_1, \dots, x_n)$$

and the equilibrium of the mixture takes place when the total free energy of the system is at minimum. Therefore, the mathematical problem consists of finding  $\min F(X)$  subject to the mass balance constraints and  $x_j \geq 0$ .

To solve this problem, the classical approach is to apply the method of Lagrange multipliers. It can be shown that this leads to a set of  $n - m$  conditions that must be satisfied by the values of  $x_j$ . These are known as the law of mass action. These conditions combined with the  $m$  equations for mass balance yield a system of  $n$  equations in  $n$  unknowns. Unfortunately, this system is a mixed system involving  $m$  equations linear in  $x_j$  and  $n - m$  equations linear in the logs of  $x_j$  and  $\bar{x}$ . Convergence properties of this mixed system do not appear to be well understood. On the other hand, it has been shown that  $F(X)$  is convex and it is possible to solve this problem by a sequence of quadratic approximations to this function; see [2] and also [3]. We have taken this approach in this study.

The model which we actually used, however, involved an extension of these techniques to a chemical system involving several phases. In particular we were interested in determining the equilibrium between three parts separated by membranes. In this case it was necessary to introduce a special charge equation and to rewrite the free energy equation in the more general form

$$(6) \quad F(X) = \sum_{\text{I}} x_j \left( c_j + \log \frac{x_j}{\bar{x}_{\text{I}}} \right) + \sum_{\text{II}} x_j \left( c_j + \log \frac{x_j}{\bar{x}_{\text{II}}} \right) \\ + \sum_{\text{III}} x_j \left( c_j + \log \frac{x_j}{\bar{x}_{\text{III}}} \right),$$

where  $\bar{x}_{\text{I}}$ ,  $\bar{x}_{\text{II}}$ ,  $\bar{x}_{\text{III}}$  are the total number of molecules, expressed in moles, in each of the parts and the summations are restricted to the species belonging to each part.

Because this formulation of the chemical equilibrium problem leads to a compact representation of the theory and provides a more direct technique for solution, we have added a section at the end of the paper reviewing the relationship of this approach to the usual one found in chemical texts.

The actual performing of the minimization for a full-scale physiological system is a very sizable problem. In fact, we think the human respiratory system represents the largest simultaneous multiphase chemical system whose solution was ever attempted on electronic computers. We explored the use of both digital and analog computers for this purpose. An important characteristic of the analog simulation is that the entire analog system is interconnected in just the

TABLE II  
MODEL I: THE EXTERNAL RESPIRATORY SYSTEM

Input Elements (moles)		Output Composition by Molecular Species																					
		I. Air Out					II. Arterial Plasma					III. Red Cells											
Element	Source		O <sub>2</sub>	CO <sub>2</sub>	N <sub>2</sub>	H <sub>2</sub> O	OH-	Cl-	N <sub>2</sub>	H <sup>+</sup>	OH-	Cl-	K <sup>+</sup>	H <sub>2</sub> O	HCO <sub>2</sub>	H <sub>2</sub> CO <sub>2</sub>	CO <sub>2</sub>	HBI-	HBO <sub>2</sub>	HP <sub>r</sub> -			
	Air	Ve-nous Blood	$x_1$	$x_2$	$x_3$	$x_4$	$x_5$	$x_6$	$x_7$	$x_8$	$x_9$	$x_{10}$	$x_{11}$	$x_{12}$	$x_{13}$	$x_{14}$	$x_{15}$	$x_{16}$	$x_{17}$	$x_{18}$	$x_{19}$	$x_{20}$	
O <sub>2</sub>	$a_1$	$b_1$	1																				
CO <sub>2</sub>	$a_2$	$b_2$		1																			
N <sub>2</sub>	$a_3$	$b_3$	1																				
H <sup>+</sup>	$a_4$	$b_4$			1																		
OH-	$a_5$	$b_5$				1																	
Cl-	$a_6 = 0$	$b_6$					1																
Na <sup>+</sup>	$a_7 = 0$	$b_7$						1															
K <sup>+</sup>	$a_8 = 0$	$b_8$							1														
HBI-	$a_9 = 0$	$b_9$								1													
HP <sub>r</sub> -	$a_{10} = 0$	$b_{10}$									1												
HP <sub>r</sub> -	$a_{11} = 0$	$b_{11}$										1											
Charge $z$	$a_{12} = 0$	$b_{12} = 0$																					
Free-energy values $c_j$	$c_1$	$c_2$	$c_3$	$c_4$	$c_5$	$c_6$	$c_7$	$c_8$	$c_9$	$c_{10}$	$c_{11}$	$c_{12}$	$c_{13}$	$c_{14}$	$c_{15}$	$c_{16}$	$c_{17}$	$c_{18}$	$c_{19}$	$c_{20}$	$c_{21}$	$c_{22}$	

way hypothesized for the body. This enabled us to see at a glance how a change in the dial setting for any chemical species was immediately reflected throughout the analog system. One can imagine how such a simulator device with more subsystems could give a medical student at the controls a feel for the effect of this or that change on the functioning of the human body.

Having built these computational tools, we were now in position to get around a fundamental difficulty that confronts physiologists. Usually equilibrium constants for reactions dealing with blood chemistry *in vivo* are based on standard blood plasma solutions. This is because it had been difficult to assess the interactions of the many competing substances in the mixture. However, our procedure allows us to build up a rigorous model based on as many individual components as we please. Such a model, if it could be constructed, would have the advantage that it could predict reactions that are far from normal with regard to blood and environment.

The format of the model we used for validation is shown in table II, in which  $HP_p^-$  = miscellaneous protein in plasma,  $HBl = 1/4$  hemoglobin molecule,  $HP_r^-$  = miscellaneous protein in red cells, and all values  $c_j = 0$  except  $c_1 = -10.89$ ;  $c_2 = -7.69$ ;  $c_3 = -11.49$ ;  $c_{12} = c_{24} = -39.23$ ;  $c_4 = -36.44$ ;  $c_{13} = c_{25} = -21.20$ ;  $c_{29} = -16.23$ ; and  $c_{15} = c_{27} = 6.25$ .

Although this model appears to be complex, the important thing to notice is that it is just an expansion of the simple format described earlier. The inputs from lung sacs and venous blood are entered here in the same manner. The output  $x$ , or amounts of the species in the three compartments lungs, plasma, and red cells, appear on the right of the figure when a solution for equilibrium is obtained. It is noteworthy that most of the important respiration phenomena

TABLE III

## INPUTS FOR THE RESPIRATION SYSTEM MODEL

Taken from [4].  $B_l$  denotes  $1/4$  reduced hemoglobin molecule, mol. wt. 16,500; symbols  $P_p$  and  $P_r$  represent miscellaneous protein in plasma and red blood cells, respectively.

Element	From Lung-sac Air (moles per 0.031 moles air)	From Mixed-venous Blood (moles per liter)	Total
O <sub>2</sub>	$a_1 = 6.4872 \times 10^{-3}$	$v_1 = 6.83 \times 10^{-3}$	$b_1 = 1.33172 \times 10^{-2}$
CO <sub>2</sub>	$a_2 = 9.27 \times 10^{-6}$	$v_2 = 2.27 \times 10^{-2}$	$b_2 = 2.270927 \times 10^{-2}$
N <sub>2</sub>	$a_3 = 2.44176 \times 10^{-2}$	$v_3 = 4.37 \times 10^{-4}$	$b_3 = 2.48546 \times 10^{-2}$
H <sup>+</sup>	$a_4 = 0$	$v_4 = 46.7$	$b_4 = 46.70$
OH <sup>-</sup>	$a_5 = 0$	$v_5 = 46.71973$	$b_5 = 46.71973$
Cl <sup>-</sup>	$a_6 = 0$	$v_6 = 0.0814$	$b_6 = 0.0814$
Na <sup>+</sup>	$a_7 = 0$	$v_7 = 0.08092$	$b_7 = 0.08092$
K <sup>+</sup>	$a_8 = 0$	$v_8 = 0.050$	$b_8 = 0.050$
HBl <sup>-</sup>	$a_9 = 0$	$v_9 = 9.09 \times 10^{-3}$	$b_9 = 9.09 \times 10^{-3}$
HP <sub>p</sub> <sup>-</sup>	$a_{10} = 0$	$v_{10} = 8.80 \times 10^{-3}$	$b_{10} = 8.80 \times 10^{-3}$
HP <sub>r</sub> <sup>-</sup>	$a_{11} = 0$	$v_{11} = 1.19 \times 10^{-2}$	$b_{11} = 1.19 \times 10^{-2}$
Charge $z$	$a_{12} = 0$	$v_{12} = 0$	$b_{12} = 0$

can be described in detail and rigorously interrelated on one page by the use of this format. We believe that this compact organization of a large part of the theory is by itself an important contribution.

As a test we have actually calculated the  $x$ , using this model and inputs from the venous blood and lungs of an average resting adult male (see table III), and compared them with observed values. The thirty outputs listed in the third column of table IV are the amounts of the lung gases and chemical species of the arterial blood as calculated by the machine. In the next column the actual observed values from physiological tables are shown for the same species.

The representative values listed in the last column were obtained from [4], p. 272 and p. 52, where they are reported as being observed averages except in the case of dissolved blood gases, which are reported as "synthesized" and "derived from basic assumptions and factors and constants."

The values in parentheses are "fixed values" in the sense that they can occur only in the compartment indicated and do not explicitly enter into chemical reactions as represented in this model. They should be exactly equal to the values in the last column. Differences in these two sets of values are an indication of the precision inherent in the computational procedure. The values in compartment I are given in mole fraction to be comparable to the more familiar volume-percent.

It will be seen that the agreement between the values from the model in column three and the observed values in column four is quite satisfactory in most cases.

Comments should be made about some of the calculated and observed values in table IV to put them in their proper perspective:

1) The values are listed in order for compartments I, II, and III: lung sacs, blood plasma, and red cells, respectively.

2) The values for lung sacs are given in mole fraction to be more easily comparable to the familiar volume-percent standard. All other values are given in terms of moles per volume produced.

3) The mechanism of breathing with its complex intermittent flow, mixing, and diffusion effects has been approximated in this initial study. The total volume and composition of atmospheric air per liter of blood was not provided by the source data. However, the air inputs,  $a_1, \dots, a_6$ , can be determined from the standard composition of atmospheric air at sea level and the known composition of lung sac air and the incremental changes of the gaseous elements of venous and arterial blood. The values of  $a_1, \dots, a_6$  shown in table III were established in this manner.

Several other techniques may be used for approximating the breathing mechanism. For example, the set of input elements  $a_1, \dots, a_6$ , may be established as representing a large excess volume of air having the observed composition of the gases of the pulmonary alveoli of a normal resting male. The assumption introduced by this procedure is that the concentration of gases in the alveoli of resting individuals does not change significantly during the breathing cycle. Alterna-

TABLE IV

COMPARISON OF VALUES OBTAINED FROM MODEL I AND OBSERVED BLOOD VALUES

Species	Quantity	Value from Model (moles/vol. produced)	Observed Value (moles/vol. existing)
Compartment I. Lung-sac Air			
O <sub>2</sub>	$x_1/\bar{x}$	0.1355	0.1315
CO <sub>2</sub>	$x_2/\bar{x}$	0.0547	0.0526
N <sub>2</sub>	$x_3/\bar{x}$	0.751	0.754
H <sub>2</sub> O	$x_4/\bar{x}$	0.0611	0.0611
Compartment II. Plasma			
O <sub>2</sub>	$x_5$	$7.33 \times 10^{-5}$	$6.34 \times 10^{-5}$
CO <sub>2</sub>	$x_6$	$7.26 \times 10^{-4}$	$6.96 \times 10^{-4}$
N <sub>2</sub>	$x_7$	$2.23 \times 10^{-4}$	$2.16 \times 10^{-4}$
H <sup>+</sup>	$x_8$	$2.20 \times 10^{-8}$	$2.104 \times 10^{-8}$
OH <sup>-</sup>	$x_9$	$3.49 \times 10^{-7}$	$3.578 \times 10^{-7}$
Cl <sup>-</sup>	$x_{10}$	$5.80 \times 10^{-2}$	$5.7 \times 10^{-2}$
Na <sup>+</sup>	$x_{11}$	$(8.092 \times 10^{-2})$	$8.092 \times 10^{-2}$
H <sub>2</sub> O	$x_{12}$	28.859	28.71
HCO <sub>3</sub> <sup>-</sup>	$x_{13}$	$1.406 \times 10^{-2}$	$1.375 \times 10^{-2}$
H <sub>2</sub> CO <sub>3</sub>	$x_{14}$	$6.62 \times 10^{-21}$	Not reported
CO <sub>3</sub> <sup>=</sup>	$x_{15}$	$2.22 \times 10^{-5}$	Not reported
HP <sub>p,i</sub> <sup>-</sup>	$x_{16}$	$(8.80 \times 10^{-3})$	$8.80 \times 10^{-3}$
Compartment III. Red Cells			
O <sub>2</sub>	$x_{17}$	$4.53 \times 10^{-5}$	$6.43 \times 10^{-5}$
CO <sub>2</sub>	$x_{18}$	$4.49 \times 10^{-4}$	$4.73 \times 10^{-4}$
N <sub>2</sub>	$x_{19}$	$1.38 \times 10^{-4}$	$2.20 \times 10^{-4}$
H <sup>+</sup>	$x_{20}$	$2.088 \times 10^{-8}$	$2.093 \times 10^{-8}$
OH <sup>-</sup>	$x_{21}$	$1.406 \times 10^{-7}$	$1.416 \times 10^{-7}$
Cl <sup>-</sup>	$x_{22}$	$2.34 \times 10^{-2}$	$2.4 \times 10^{-2}$
K <sup>+</sup>	$x_{23}$	$(5.0 \times 10^{-2})$	$5.0 \times 10^{-2}$
H <sub>2</sub> O	$x_{24}$	17.84	18.00
HCO <sub>3</sub> <sup>-</sup>	$x_{25}$	$5.67 \times 10^{-3}$	$5.987 \times 10^{-3}$
H <sub>2</sub> CO <sub>3</sub>	$x_{26}$	$4.09 \times 10^{-21}$	Not reported
CO <sub>3</sub> <sup>=</sup>	$x_{27}$	$5.84 \times 10^{-5}$	Not reported
HbI <sup>-</sup>	$x_{28}$	$3.107 \times 10^{-4}$	$3.636 \times 10^{-4}$
HbIO <sub>2</sub> <sup>=</sup>	$x_{29}$	$8.78 \times 10^{-3}$	$8.7264 \times 10^{-3}$
HP <sub>r</sub> <sup>-</sup>	$x_{30}$	$(1.19 \times 10^{-2})$	$1.19 \times 10^{-2}$
Total moles			
Compartment I		0.0326879	Respiration Quotient (CO <sub>2</sub> out)/(O <sub>2</sub> in) = 0.86 Percent hemoglobin saturation = 96.6
Compartment II		29.021472	
Compartment III		17.9401779	
Compartment II + III		46.9616499	

tively, the computer can be programmed to sample the concentrations of O<sub>2</sub> and CO<sub>2</sub> in either the arterial blood or sac air compartments and to calculate by a series of iterations the amount of atmospheric air of given composition required to make these lung or blood values correspond to previously established



standards. All of these techniques have been used and are satisfactory for representing the breathing mechanism within their limitations. These devices avoid the necessity, at this early stage, of combining a physical model of breathing with the present chemical model of the respiratory system.

There are four calculated values, enclosed in parentheses, which are fixed because these species have no freedom to vary in the present model. These four calculated values should, therefore, be exactly equal to the corresponding observed values except for machine and code errors.

The greatest difficulty in validating the model arose in connection with the representation of acidity and the concentrations of  $H^+$  and  $OH^-$ . The observed values of acidity in blood are obtained and reported in terms of pH, an empirical measure. The values calculated by the model appeared to be low in  $H^+$  concentration until we applied the correction to the observed pH values as suggested by the literature [5]. After this correction was made the observed values fell nicely in line with the values calculated by the machine.

It is of interest to observe the respiration quotient,  $(CO_2 \text{ out})/(O_2 \text{ in})$ . The calculated value is 0.86, a value well within the range for resting individuals.

## 2. A review of certain chemical thermodynamic concepts

Since the relationship between our formulation of the model and the usual procedure of expressing a series of chemical reactions and their equilibrium constants is not readily apparent, we have added the following discussion of these thermodynamic concepts. Suppose a compartment contains various species such as  $H_2O$ ,  $OH^-$ ,  $H^+$ ,  $CO_2$ , and  $HCO_3^-$ , when  $CO_2$  is dissolved in the solution. The amounts of these various constituents depend on the total amounts of water and carbon dioxide originally "dumped" into the compartment, but their relative concentrations to each other satisfy certain conditions that are independent of the input amounts. In general the concentrations (or activities) of the species at equilibrium have the property that, independent of the input quantities, one or more ratios of products of concentration among them have fixed values. These nonlinear conditions are called mass-action relationships.

For example, if we let  $\bar{x}$  denote the total number of molecules in the mixture, so that

$$(7) \quad \bar{x} = x_{H_2O} + x_{OH^-} + x_H + x_{CO_2} + x_{HCO_3^-},$$

where  $x_{H_2O}$  = the number of nonionized water molecules,  $x_{OH^-}$  = the number of ions of  $OH^-$ , and so forth, and define

$$(8) \quad N_{H_2O} = \frac{x_{H_2O}}{\bar{x}}, \quad N_{OH^-} = \frac{x_{OH^-}}{\bar{x}},$$

and so forth, to be the concentrations of these species in the mixture, then the mass-action law states that

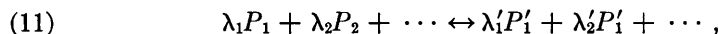
$$(9) \quad \frac{N_{H_2O}}{(N_{OH^-})(N_{H^+})} = K_1,$$

where  $K_1$  has a fixed value (at constant temperature and pressure), called the equilibrium constant for the reaction  $\text{H}^+ + \text{OH}^- \leftrightarrow \text{H}_2\text{O}$ . Even if no  $\text{CO}_2$  were present, or if a salt were added to the mixture, this same relationship would hold despite the fact that the individual concentrations forming the above ratios could be changing drastically. Another mass-action relationship that holds among the concentrations, independent of the amounts of inputs, is

$$(10) \quad \frac{(N_{\text{HCO}_3^-})(N_{\text{H}^+})}{(N_{\text{CO}_2})(N_{\text{H}_2\text{O}})} = K_2,$$

where  $K_2$  is the equilibrium constant for the reaction  $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{HCO}_3^- + \text{H}^+$ . The conventional method for determining the equilibrium composition is to find the values of the five unknown  $x_j$  that satisfy five equations, two of which are nonlinear and are the two mass-action conditions given above, while the remaining three are linear and express the mass balance in relation to the original inputs, as illustrated earlier in table I. However, as noted earlier in this paper, we have found it more convenient to bypass the mass-action relationships by finding the equilibrium composition through direct minimization of the free-energy function subject only to the mass-balance conditions. We wish now to demonstrate the mathematical equivalence of these two methods.

In general for a chemical reaction represented by



the corresponding mass-action relationship is

$$(12) \quad K = \frac{(N'_1)^{\lambda'_1} (N'_2)^{\lambda'_2} \cdots}{(N_1)^{\lambda_1} (N_2)^{\lambda_2} \cdots},$$

where the  $P_j$  are the reactant species, the  $P'_j$  are the product species, the  $\lambda_j$  and  $\lambda'_j$  are the corresponding numbers of moles of each species,  $K$  is the equilibrium constant, and the  $N_j$  and  $N'_j$  are the concentrations of the constituents  $P_j$  and  $P'_j$ . We may also state the mass-action law in logarithmic form by taking logarithms of both sides. Thus,

$$(13) \quad \log K = (\lambda'_1 \log N'_1 + \lambda'_2 \log N'_2 + \cdots) \\ - (\lambda \log N_1 + \lambda_2 \log N_2 + \cdots).$$

It is important to note that a chemical-reaction equation, denoted by (11), is simply a relation among the column vectors  $\bar{P}_j$  of input elements  $a_{ij}$  associated with each species  $P_j$ . Thus if we denote  $\bar{P}_j = (a_{1j}, a_{2j}, \cdots, a_{mj})$ , we have, corresponding to (11),

$$(14) \quad \lambda_1 \bar{P}_1 + \lambda_2 \bar{P}_2 + \cdots = \lambda'_1 \bar{P}'_1 + \lambda'_2 \bar{P}'_2 + \cdots.$$

This is easily seen from an example. Suppose  $\text{H}^+$  and  $\text{OH}^-$  are considered input elements forming species  $\text{H}^+$ ,  $\text{OH}^-$ , and  $\text{H}_2\text{O}$ . We form table V, where the entry  $a_{ij}$  in row  $i$  and column  $j$  is the quantity of the input element  $i$  found in the species  $j$ . It is clear that the chemical reaction  $\text{H}^+ + \text{OH}^- \leftrightarrow \text{H}_2\text{O}$  is simply a statement about the corresponding column vectors in table V, namely,

TABLE V  
EXAMPLE OF CHEMICAL-REACTION EQUATION AS A RELATION  
AMONG COLUMN VECTORS  $\bar{F}_j$

Input Element	Species		
	H <sup>+</sup>	OH <sup>-</sup>	H <sub>2</sub> O
H <sup>+</sup>	1	0	1
OH <sup>-</sup>	0	1	1

$$(15) \quad \begin{bmatrix} 1 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \end{bmatrix} = \begin{bmatrix} 1 \\ 1 \end{bmatrix}.$$

We shall now show that the mass-action law holds for the values of  $x_j$  that minimize

$$(16) \quad F(X) = \sum_{j=1}^n x_j \bar{F}_j,$$

where in particular  $\bar{F}_j$  is given by

$$(17) \quad \bar{F}_j = RT \left( c_j + \log \frac{x_j}{\bar{x}} \right).$$

As noted earlier, this expression for  $\bar{F}_j$  is essentially an approximation for dilute solutions and ideal gases of the more general expression (18) below. It will be assumed unless otherwise stated that

$$(18) \quad \bar{F}_j = RT(c_j + \log a_j),$$

where each  $a_j$ , the "activity," is some function of the concentration  $x_j/\bar{x}$ ; that is to say,  $a_j$  (and hence  $\bar{F}_j$ , the free energy per mole of the  $j$ th constituent) remains unchanged if all quantities  $x_j$  are increased proportionally. We now establish the following mathematical theorem:

**THEOREM.** *If for every  $j$ ,  $\bar{F}_j = \bar{F}_j(x_j/\bar{x})$  is a function of  $x_j/\bar{x}$  only, then*

$$(19) \quad \frac{\partial F}{\partial x_j} = \bar{F}_j, \quad j = 1, \dots, n.$$

Because of (19),  $\bar{F}_j$  is commonly called the partial molar free energy of the  $j$ th constituent. To prove this relation note first that the free energy  $F(X)$  is a homogeneous function of degree one in the variables  $(x_1, \dots, x_n)$ , and for any homogeneous functions of degree one it is generally true that

$$(20) \quad F(X) \equiv \sum_{j=1}^n x_j \frac{\partial F}{\partial x_j}.$$

This relationship (20) is known as Euler's theorem for homogeneous forms of the first degree. In words, it says that total free energy can be determined as if  $\partial F/\partial x_j$  is the contribution of the  $j$ th constituent per mole.

The foregoing theorem is easy to prove. We shall establish it as follows. From (18), the assumed homogeneity of degree zero for  $\bar{F}_j$ , for all  $t$ , we have

$$(21) \quad tF(x_1, \dots, x_n) \equiv F(tx_1, \dots, tx_n).$$

Hence, taking the partial derivative of both sides with respect to  $t$ , we obtain

$$(22) \quad F(x_1, \dots, x_n) \equiv \sum_{j=1}^n \frac{\partial F(tx_1, \dots, tx_n)}{\partial (tx_j)} x_j.$$

Setting  $t = 1$  yields (20).

To establish (19) we now assume that  $F(X)$  is given by (16), where  $\bar{F}_j = \bar{F}_j(x_j/\bar{x})$ , and take the partial derivative of  $F(X)$  with respect to  $x_j$ . This yields

$$(23) \quad \frac{\partial F}{\partial x_j} = \bar{F}_j + \sum_{k=1}^n x_k \frac{\partial \bar{F}_k}{\partial \bar{x}}, \quad j = 1, \dots, n,$$

where we have replaced  $\partial \bar{F}_k / \partial x_j$  by  $\partial \bar{F}_k / \partial \bar{x}$  since  $\partial \bar{x} / \partial x_k = 1$ . We now show that the summation term vanishes. Multiplying both sides by  $x_j$  and summing on  $j$  yields, by relations (20) and (16),

$$(24) \quad 0 = (x_1 + x_2 + \dots + x_n) \left( \sum_{k=1}^n x_k \frac{\partial \bar{F}_k}{\partial \bar{x}} \right).$$

Since  $x_j \geq 0$ , and  $\sum_{j=1}^n x_j > 0$ , the second factor of the product must vanish and (19) follows from (23).

Having established that  $\bar{F}_j = \partial F / \partial x_j$ , let us turn to the main problem of minimizing the free-energy function  $F(X)$  subject to mass-balance constraints

$$(25) \quad \phi_i(X) = \sum_{j=1}^n a_{ij}x_j - b_i = 0, \quad i = 1, \dots, m.$$

We now review the Lagrange method for minimizing a general function  $F(X)$  subject to  $m$  general constraints,  $\phi_i(X) = 0$ , and later specialize the functions  $\phi_i$ . The first step is to assign unknown multipliers  $\pi_i$  to the functions  $\phi_i(X)$  and seek the unconstrained minimum of the function

$$(26) \quad G(X) = F(X) - \pi_1\phi_1(X) - \pi_2\phi_2(X) \dots - \pi_m\phi_m(X).$$

If for some choice of  $\pi_i$ , the point  $X = X^0$  where the minimum of  $G(X)$  occurs happens to satisfy the constraints  $\phi_i(X^0) = 0$ , then this unconstrained minimum point  $X^0$  for  $G(X)$  is the constrained minimum point for  $F(X)$ . To see this, note that  $\min G(X) = G(X^0) = F(X^0)$ , and that for all other  $X$  that satisfy  $\phi_i(X) = 0$  we have  $F(X) \geq F(X^0)$  because  $F(X) = G(X) \geq \min G(X) = F(X^0)$ . When  $F(X)$  possesses partial derivatives and assumes its minimum at some interior point of the domain of definition, it can be shown that such multipliers always exist. We now specialize  $\phi_i(X)$  to be linear as given by (25). In this case we may rewrite  $G(X)$  by collecting all terms with common  $x_j$ , obtaining

$$(27) \quad G(X) = F(X) - \sum (\pi \bar{P}_j)x_j + \pi b,$$

where  $\pi = (\pi_1, \pi_2, \dots, \pi_m)$  is a row vector,  $\bar{P}_j = (a_{1j}, a_{2j}, \dots, a_{mj})$  is the column vector of coefficients associated with species  $j$  defined earlier, and  $b = (b_1, b_2, \dots, b_m)$  is the column vector of constants. The coefficient of  $x_j$  is the constant  $\pi \bar{P}_j$  and depends on the choice of  $\pi$ . At an unconstrained minimum of  $G(X)$ ,  $X$  satisfies

$$(28) \quad \frac{\partial F}{\partial x_j} - (\pi \bar{P}_j) = 0$$

for any choice of  $\pi$ . Also for any given chemical reaction (11) we may multiply the corresponding vector relation (14) by  $\pi$ , obtaining

$$(29) \quad \lambda_1(\pi \bar{P}_1) + \lambda_2(\pi \bar{P}_2) + \cdots = \lambda'_1(\pi \bar{P}'_1) + \lambda'_2(\pi \bar{P}'_2) + \cdots,$$

which holds for any choice of  $\pi$ . Thus, substituting  $\partial F/\partial x_j = \pi \bar{P}_j$ , we have

$$(30) \quad \lambda_1 \frac{\partial F}{\partial x_1} + \lambda_2 \frac{\partial F}{\partial x_2} + \cdots = \lambda'_1 \frac{\partial F}{\partial x'_1} + \lambda'_2 \frac{\partial F}{\partial x'_2} + \cdots,$$

which holds for the  $X$  that minimizes  $G(X)$  for any choice of  $\pi$ . Since  $F$  has a special form (16) that satisfies  $\partial F/\partial x_j = \bar{F}_j$ , we also have, for any such  $X$ ,

$$(31) \quad \lambda_1 \bar{F}_1 + \lambda_2 \bar{F}_2 + \cdots = \lambda'_1 \bar{F}'_1 + \lambda'_2 \bar{F}'_2 + \cdots.$$

If we further set

$$(32) \quad \bar{F}_j = RT(c_j + \log a_j),$$

then upon substitution, rearranging of terms, and dropping of the common factor  $RT$ , we get the relationship

$$(33) \quad (\lambda'_1 c'_1 + \lambda'_2 c'_2 + \cdots) - (\lambda_1 c_1 + \lambda_2 c_2 + \cdots) \\ = (\lambda'_1 \log \alpha'_1 + \lambda'_2 \log \alpha'_2 + \cdots) - (\lambda_1 \log \alpha_1 + \lambda_2 \log \alpha_2 + \cdots)$$

for all  $X$  that minimize  $G(X)$  for any choice of  $\pi$ . In particular, for that  $\pi$  that yields  $X = X^0$  satisfying the mass balances  $\phi_i(X) = 0$  and thereby minimizing the free energy  $F(X)$ , this same relationship must hold. But this holds even if we start out with a different set of  $b_i$  values since the expression is independent of  $b_i$ . If we define

$$(34) \quad \log K = (\lambda'_1 c'_1 + \lambda'_2 c'_2 \cdots) - (\lambda_1 c_1 + \lambda_2 c_2 \cdots),$$

then (33) establishes the mass-action law in logarithmic form and in terms of activities. If the activities are given by  $a_j = x_j/\bar{x}$ , then this is the same as the mass-action law stated earlier in equation (13). If

$$(35) \quad a_j = \gamma_j \frac{x_j}{\bar{x}},$$

where  $\gamma_j$  is some constant, this also yields the mass-action law stated earlier with an adjusted value for  $\log K$ . In this manner, the  $c_j$  values from the free-energy function can be used to define the equilibrium constants, and conversely as shown below.

### 3. Determining $c_j$ values from equilibrium constants

As was noted earlier, the equilibrium constants for many common reactions are tabulated in physical-chemical tables.

We wish to discuss how to adjust the  $c_j$  values so that the equilibrium constants

are directly applicable to the model. To be precise, we note that for those  $x$  that satisfy the mass balances, the expression for  $F(X)$  may be replaced by

$$(36) \quad F(X) = \sum_{j=1}^n x_j \left( \bar{c}_j + \log \frac{x_j}{\bar{x}} \right) - \sum_{i=1}^m k_i b_i,$$

where the  $k_i$  are constants and the  $\bar{c}_j$  bear a direct relationship to the equilibrium constants. The numbers  $k_i$  were selected so that when multiplied by the  $i$ th mass-balance equation and the  $m$  equations summed and subtracted from  $F(X)$ ,  $m$  of the new coefficients of the  $x_j$ , denoted  $\bar{c}_j$ , would vanish. In place of the original function  $F(X)$  the function

$$(37) \quad G(X) = \sum_{j=1}^n x_j \left( \bar{c}_j + \log \frac{x_j}{\bar{x}} \right)$$

was minimized subject to the mass-balance constraints. Since the two functions differ by a constant,  $\sum_{i=1}^m k_i b_i$ , the value of  $X = X^0$  that minimizes  $F(X)$  also minimizes  $G(X)$ .

Any  $m$  of the  $\bar{c}_j$  can be made to vanish by suitably choosing the  $k_i$  values, provided that the square array of coefficients  $[a_{ij}]$  associated with these  $j$  is nonsingular, that is, provided that their determinant  $\neq 0$ .

For model I the  $\bar{c}_j$  values associated with species  $H^+$  and  $OH^-$  in compartment II, among others, were made to vanish

$$(38) \quad \bar{c}_{H^+} = \bar{c}_{OH^-} = 0.$$

Now the equilibrium constant for water does not depend on whether we use  $c_j$  or  $\bar{c}_j$  values for its definition in (34), its value being the same since it must yield the same right member of (33). Hence, for compartment II species,

$$(39) \quad \log K_{H_2O} = \bar{c}_{H_2O} - \bar{c}_{H^+} - \bar{c}_{OH^-} = \bar{c}_{H_2O}.$$

In other words, the value of  $\bar{c}_{12} = c_{H_2O}$  can be directly obtained from the equilibrium constant for water. In the next section the entire set of  $n - m$  remaining  $\bar{c}_j$  values is evaluated in this manner from equilibrium constants.

No attempt was made in the construction of model I to determine the absolute  $c_j$  values as defined in terms of  $F_j^0$  values. All  $c_j$  values shown are the relative  $\bar{c}_j$  values as obtained from equilibrium constants.

#### 4. Determination of free-energy values

So far we have described the operation of the model in terms of the several compartments, the thermodynamics involved, the inputs, and the mass and charge conservation constraints. We shall now discuss the numerous chemical reactions involved, how they are represented in the model, and how the mass-action or partial-molal free-energy constraint operates (with the others) to yield an equilibrium solution. The mass-action equations describe the formation of the molecular species of columns  $x_1, \dots, x_{30}$  in the three compartments, I: Air Out, II: Arterial Plasma, and III: Red Cells, and relate similar species occurring in more than one compartment (see table II).

For example, the entry 1 in column 12, row 4, compartment II; the entry 1 in the same column, row 5, and the entry  $c_{12}$  in the bottom row together express the chemical equation,  $H^+ + OH^- \leftrightarrow H_2O$ , in the mass-action form,

$$(40) \quad \log \frac{[H^+]_{II}[OH^-]_{II}}{[H_2O]_{II}} = c_{12},$$

where  $c_{12} = \log K_w$ , and  $K_w$  is the ionization constant for water on the mole-fraction scale at 37° C. It was shown previously that constants such as  $c_{12}$  derived from equilibrium constants may be used in the model with the same results as if the individual  $F^0/(RT)$  values for each species were obtained from tables and used.

In a manner similar to that described for the water reactions, the other reactions involved are entered in the model. For the same species occurring in both compartments II and III, the assumption is made that their original energy coefficients  $c_j$  (not necessarily  $\bar{c}_j$  values) are the same in both compartments. This results, for example, in  $[O_2]_{II} = [O_2]_{III}$ . The other reactions and their  $c_j$  values are given in table VI. In this table the species are shown in square

TABLE VI  
REACTIONS AND FREE-ENERGY VALUES FOR MODEL I, 37°C

Column	Mass Action	$c_j = \log K$
(1)	$\log \frac{[O_2]_{II}}{[O_2]_{I}}$ or III	-10.89
(2)	$\log \frac{[CO_2]_{II}}{[CO_2]_{I}}$ or III	-7.69
(3)	$\log \frac{[N_2]_{II}}{[N_2]_{I}}$ or III	-11.49
(12)(24)	$\log \frac{[H^+]_{II}[OH^-]_{II}}{[H_2O]_{II}}$ or III or III or III	-39.23
(4)	$\log \frac{[H^+]_{II}[OH^-]_{II}}{[H_2O]_{I}}$ or III or III $= c_{12} + \log \frac{[H_2O]_{II}}{[H_2O]_{I}}$	-36.44
(13)(25)	$\log \frac{[CO_2]_{II}[OH^-]_{II}}{[HCO_3^-]_{II}}$ or III or III or III	-21.20
(29)	$\log \frac{[O_2]_{III}[HBI^-]_{III}}{[HBI O_2^-]_{III}}$ $= c_i + \log \frac{[O_2]_{I}[HBI^-]_{III}}{[HBI O_2^-]_{III}}$	-16.23
(14)(26)	$\log \frac{[CO_2]_{II}[H_2O]_{II}}{[H_2CO_3]_{II}}$ or III or III or III	0
(15)(27)	$\log \frac{[CO_2]_{II}[OH^-]_{II}}{[CO_3^{2-}]_{II}[H^+]_{II}}$ or III or III or III or III	6.25

brackets, indicating concentration in mole fraction. The  $c_j$  values were calculated from the  $K$  values shown in table VII all converted to the mole-fraction scale, and are the adjusted  $\bar{c}_j$  values referred to earlier. The values of  $c_j = 0$  for all the columns not listed in table VI.

It is important in applying these data to the model, that the  $K$  values from the literature all be converted to the same scale (that is, molar, molal, or mole fraction). Most  $K$  values are reported on the molal scale, some on the molar,

TABLE VII  
 EQUILIBRIUM CONSTANTS

Column	Equilibrium Constant	Reference
(1)	$K = 0.0232$	[6], p. 54
(2)	$K = 0.5672$	[7], p. 1092
(3)	$K = 0.0127$	[6], p. 54
(12)(24)	$\log_{10} K = -13.55$	[8], p. 152
(4)	$\log_{10} K = \log_{10} K_w + \log_{10} \frac{[\text{H}_2\text{O}]_{\text{II}}}{[\text{H}_2\text{O}]_{\text{I}}}$ or III $\log_{10} \frac{[\text{H}_2\text{O}]_{\text{II}}}{[\text{H}_2\text{O}]_{\text{I}}} = 1.21396$	[7], p. 1465
(13)(25)	$\log_{10} K = \log_{10} K_w - \log_{10} K_{1\text{H}_2\text{CO}_3}$ $\log_{10} K_{1\text{H}_2\text{CO}_3} = -6.09$	[4], p. 272
(29)	$\log_{10} K = -7.0486$	[6], p. 64
(14)(26)	$\log_{10} K = 0$	[8], p. 244
(15)(27)	$\log_{10} K = \log_{10} [\text{CO}_2]_{\text{II}}[\text{OH}^-]_{\text{II}}/[\text{HCO}_3^-]_{\text{II}}(K_{2\text{H}_2\text{CO}_3})$ $\log_{10} K_{2\text{H}_2\text{CO}_3} = -10.25$	[7], p. 1198

and in some cases, unfortunately, the scale is not indicated. All  $K$  values were converted to the mole-fraction scale for use in the model. It is also important that the  $K$  values are those for the temperature of interest (310.18 Kelvin in the model so far), or are converted to the value for  $K_{310.18}$  if the necessary thermodynamic data permit. At a later stage the appropriate thermodynamic functions can be introduced into the model, relating free energy to temperature and pressure, and perhaps to electrical and gravitational fields and to surface effects.

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