

MEMORANDUM

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MATHEMATICAL ANALYSIS
AND DIGITAL SIMULATION OF THE
RESPIRATORY CONTROL SYSTEM

Fred S. Grodins, M.D., June Buell and Alex J. Bart

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The **RAND** *Corporation*
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PREFACE

This Memorandum describes a mathematical model of the human respiratory control system. It was supported in part by the National Institutes of Health under the following grants: GM-09608-04; 4-K6-HE 14, 187; and 5-ROI-HE 01626.

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ABSTRACT

This Memorandum expresses the basic material balance relationships for the lung-blood-tissue gas transport and exchange system in a set of differential-difference equations containing a number of dependent time delays. Additional equations define the chemical details of transport and acid-base buffering, concentration equilibria, and blood flow behavior. Finally, a control function is included defining the dependence of ventilation upon CSF (H^+), and arterial (H^+) and P_{O_2} at the carotid chemoreceptors. A Fortran program was written for convenient digital simulation of the responses of the system to a wide variety of forcings, including CO_2 inhalation, hypoxia at sea level, altitude hypoxia, and metabolic disturbances in acid-base balance. Both dynamic and steady-state behavior of the model were reasonably realistic.

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MATHEMATICAL ANALYSIS AND DIGITAL SIMULATION OF THE RESPIRATORY CONTROL SYSTEM

1. INTRODUCTION

Although recognition of the basic "closed-loop" nature of the respiratory control system was certainly implicit in the writings of Haldane and Priestley [1], the first explicit quantitative formulation was made by Gray in 1945 [2]. His algebraic model was restricted to the steady-state responses of the system to CO_2 inhalation, arterial anoxemia, and metabolic disturbances in acid-base balance. The first dynamic analysis of this system appeared in 1954 [3], and although it represented a step forward in considering dynamics, it also represented a step backward in that it could accept only a single forcing, i.e., CO_2 inhalation. It also represented an oversimplified treatment that nevertheless led to nonlinear differential equations. At the time of its formulation, the state of the computer art was relatively primitive, and exploration of a more general and realistic model was not practical.

With the development of large computing facilities, interest in the realistic dynamic analysis of complex multivariate biological control systems has increased rapidly [4]. Beginning with Defares, Derkson, and Duyff in 1960 [5], the original dynamic model of the respiratory system has been refined and extended by several workers using both analog and digital simulation [6-9]. The present analysis represents a further step in this continuing study. The model has been made sufficiently general to accommodate a variety of forcings (CO_2 inhalation, hypoxia at sea level or at altitude, metabolic disturbances in acid-base balance, or combinations thereof). It treats the chemical buffering and gas transport systems in reasonable detail, including both Haldane and Bohr effects, and it

recognizes the presence of many transport delays that are themselves dependent variables. It permits convenient exploration of a variety of possible control functions, including the role of cerebrospinal fluid (CSF) hydrogen ion concentration, and of O_2 - CO_2 interaction at the peripheral chemoreceptors. Some of these features, particularly the buffer equations and the many dependent time delays, introduce formidable computational difficulties, which have been overcome in the digital simulation herein described.

2. GENERAL DESCRIPTION OF THE SYSTEM

We consider two major components, a controlled system ('plant' or 'process'), and a controlling system (controller).

2.1. Controlled System

The 'plant' comprises three major compartments (lung, brain, tissue) connected by the circulating blood (Fig. 1). The brain compartment is separated from a cerebrospinal fluid reservoir by a membrane of restricted permeability. The events of the respiratory cycle are ignored and the lungs regarded as a box of constant volume, uniform content, and zero dead space ventilated by a continuous unidirectional stream of gas. If the alveolar RQ differs from unity, as it generally will, the rates of flow of inspired and expired gas will differ. We assume that alveolar gas tensions, $P_{A(CO_2)}$, $P_{A(O_2)}$, and $P_{A(N_2)}$ are equal at every instant to those in expired air and arterial blood leaving the lung. The total oxygen content of this arterial blood, $C_{a(O_2)}$, will be the sum of physically dissolved and chemically combined (i.e., oxyhemoglobin) components. The former varies linearly with $P_{a(O_2)}$, whereas the latter is a complex function of both $P_{a(O_2)}$ and arterial blood pH (oxygen dissociation curve including Bohr effect [10]). Similarly, the total CO_2 content of

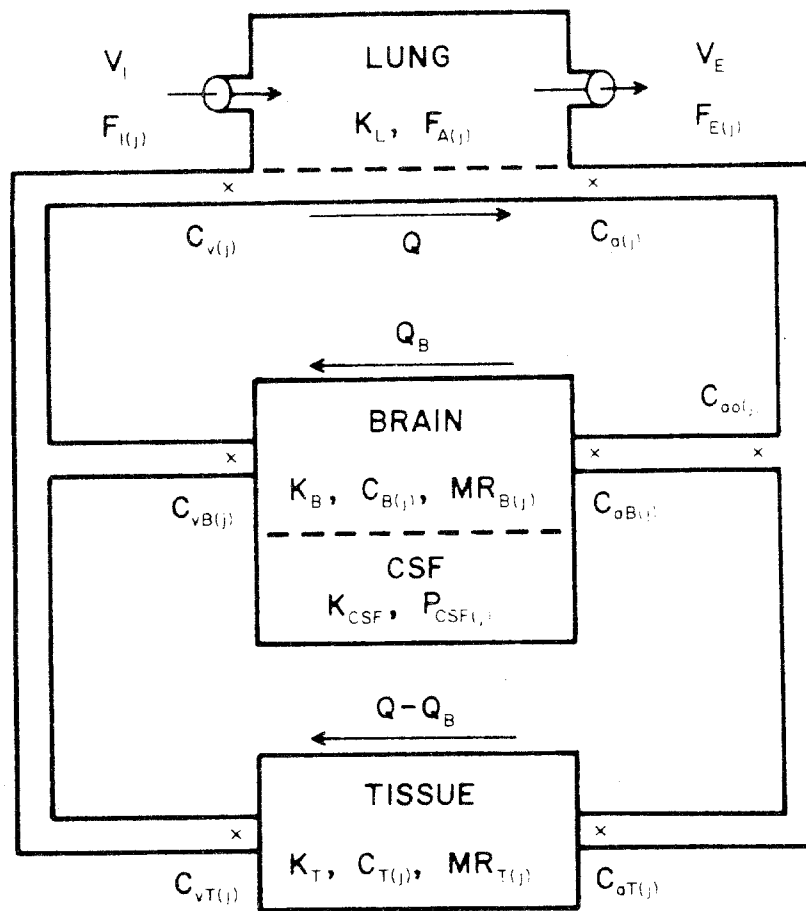


Fig. 1—The controlled system.

(Symbols defined in App. A.)

this blood, $C_a(\text{CO}_2)$, will comprise both physically dissolved and chemically combined components, the former varying linearly with $P_a(\text{CO}_2)$ and the latter being a complex implicit function of $P_a(\text{CO}_2)$, the standard bicarbonate content, $(\text{BHC}\text{O}_3)_b$, the total hemoglobin and oxyhemoglobin contents (Hb , HbO_2), and the plasma protein content (CO_2 absorption curve including Haldane effect [10]). Carbamate is not explicitly treated as a separate entity. The pH of this blood will depend upon its $P_a(\text{CO}_2)$ and bicarbonate content as defined by the Henderson-Hasselbalch equation. Only physically dissolved nitrogen will be present.

After a transport delay, which depends upon vascular volume and blood flow rate, this arterial blood arrives at the brain or tissue compartment. We regard the gas tensions in each of these reservoirs as uniform and equal to those in exiting venous blood. Oxygen is removed from and CO_2 is added to each reservoir at a constant rate set by metabolism. The oxygen and nitrogen contents of these reservoirs are taken to include only physically dissolved gas, but the total CO_2 content will include a bicarbonate component in accordance with the CO_2 absorption curve for that reservoir. No Haldane effect is attributed to the reservoirs' CO_2 buffers. Although we assume reservoir-venous blood equality for CO_2 tension, the bicarbonate and hydrogen-ion concentrations will not necessarily be the same. We do not attempt to treat this "effective impermeability" in any rigorous physico-chemical fashion [11], but simply reserve the right to restrict the movement of certain chemical species between the reservoirs and the blood. In this way, for example, we can simulate the limited availability of brain and CSF bicarbonate for buffering strong acid introduced into the blood, a feature of the "blood-brain barrier."

The brain compartment communicates with a cerebrospinal fluid reservoir via a membrane permeable to respiratory gases only. The latter diffuse across this membrane at rates proportional to their tension gradients. The entire gradient occurs across the membrane, the reservoir concentrations being regarded as uniform. The CSF reservoir differs from the brain compartment in containing no protein capable of buffering carbonic acid. For our purposes we regard it simply as a solution of sodium bicarbonate whose bicarbonate content thus remains constant at all CO_2 tensions above 10 mm Hg [10].

Venous blood leaving the brain combines with that leaving the tissue after appropriate time delays to form mixed venous blood, which after another delay, enters the lung to complete the circle of the gas transport and exchange process. Total cardiac output as well as the local blood flow to the brain are known to vary as functions of arterial CO_2 and oxygen tensions [12-16]. Since circulatory transport delays are functions of blood flow rates, these delays become dependent variables as $P_a(\text{CO}_2)$ and $P_a(\text{O}_2)$ change in response to such forcings as CO_2 inhalation or hypoxia. These delays are treated as pure dead times, which implies a square blood flow front with no intravascular "smearing."

2.2. Controlling System

This includes receptor elements that monitor concentrations of certain chemical species at particular locations, afferent nerves that transmit this information to the central nervous system, the neural centers themselves, motor nerves to the respiratory muscles, the muscles themselves, and finally the thorax-lung pump which they drive. As in our original model as well as those that have followed it, we shall not attempt to describe this system in terms of the details of its components but instead will go directly from chemical

concentrations at receptor sites as the inputs to ventilation as the output. In so doing, we shall assign no dynamic elements to this system, thus implying that any delays associated with it are negligibly short compared to those of the "plant." This is certainly true of the neural components and probably of the mechanical elements as well.

3. EQUATIONS OF THE SYSTEM

Using symbols and units defined in App. A and "normal" parameter values given in App. B, we first write material balance equations for CO_2 , O_2 , and N_2 for each of the three compartments, lung, brain, and tissue:

$$\dot{F}_A(\text{CO}_2) = \frac{1}{K_L} \left[V_I F_I(\text{CO}_2) - V_E F_A(\text{CO}_2) + \left(\frac{863}{B-47} \right) Q (C_v(\text{CO}_2) - C_a(\text{CO}_2)) \right] \quad (1.1)$$

$$\dot{F}_A(\text{O}_2) = \frac{1}{K_L} \left[V_I F_I(\text{O}_2) - V_E F_A(\text{O}_2) + \left(\frac{863}{B-47} \right) Q (C_v(\text{O}_2) - C_a(\text{O}_2)) \right] \quad (1.2)$$

$$\dot{F}_A(\text{N}_2) = \frac{1}{K_L} \left[V_I F_I(\text{N}_2) - V_E F_A(\text{N}_2) + \left(\frac{863}{B-47} \right) Q (C_v(\text{N}_2) - C_a(\text{N}_2)) \right] \quad (1.3)$$

$$\dot{C}_B(\text{CO}_2) = \frac{1}{K_B} \left[MR_B(\text{CO}_2) + Q_B (C_{aB}(\text{CO}_2) - C_{vB}(\text{CO}_2)) - D_{\text{CO}_2} (P_B(\text{CO}_2) - P_{\text{CSF}}(\text{CO}_2)) \right] \quad (1.4)$$

$$\dot{C}_B(\text{O}_2) = \frac{1}{K_B} \left[-MR_B(\text{O}_2) + Q_B (C_{aB}(\text{O}_2) - C_{vB}(\text{O}_2)) - D_{\text{O}_2} (P_B(\text{O}_2) - P_{\text{CSF}}(\text{O}_2)) \right] \quad (1.5)$$

$$\dot{C}_B(\text{N}_2) = \frac{1}{K_B} \left[Q_B (C_{aB}(\text{N}_2) - C_{vB}(\text{N}_2)) - D_{\text{N}_2} (P_B(\text{N}_2) - P_{\text{CSF}}(\text{N}_2)) \right] \quad (1.6)$$

$$\dot{C}_T(\text{CO}_2) = \frac{1}{K_T} \left[MR_T(\text{CO}_2) + (Q - Q_B) (C_{aT}(\text{CO}_2) - C_{vT}(\text{CO}_2)) \right] \quad (1.7)$$

$$\dot{C}_T(\text{O}_2) = \frac{1}{K_T} \left[-MR_T(\text{O}_2) + (Q - Q_B) (C_{aT}(\text{O}_2) - C_{vT}(\text{O}_2)) \right] \quad (1.8)$$

$$\dot{C}_T(\text{N}_2) = \frac{1}{K_T} \left[(Q - Q_B) (C_{aT}(\text{N}_2) - C_{vT}(\text{N}_2)) \right] \quad (1.9)$$

The balance (or diffusion) equations for the CSF subcompartment are written in terms of gas tensions:

$$\dot{P}_{\text{CSF}(\text{CO}_2)} = \left(D_{\text{CO}_2} / K_{\text{CSF}}^{k\alpha} \text{CSF}(\text{CO}_2) \right) \left(P_{\text{B}(\text{CO}_2)} - P_{\text{CSF}(\text{CO}_2)} \right) \quad (1.10)$$

$$\dot{P}_{\text{CSF}(\text{O}_2)} = \left(D_{\text{O}_2} / K_{\text{CSF}}^{k\alpha} \text{CSF}(\text{O}_2) \right) \left(P_{\text{B}(\text{O}_2)} - P_{\text{CSF}(\text{O}_2)} \right) \quad (1.11)$$

$$\dot{P}_{\text{CSF}(\text{N}_2)} = \left(D_{\text{N}_2} / K_{\text{CSF}}^{k\alpha} \text{CSF}(\text{N}_2) \right) \left(P_{\text{B}(\text{N}_2)} - P_{\text{CSF}(\text{N}_2)} \right) \quad (1.12)$$

By adding Eqs. (1.1)-(1.3), noting that the volumetric fractions of CO_2 , O_2 , and N_2 must add to one in both inspired and alveolar air, and that the sum, $\dot{F}_{\text{A}(\text{CO}_2)} + \dot{F}_{\text{A}(\text{O}_2)} + \dot{F}_{\text{A}(\text{N}_2)}$, must equal zero since the lung volume is constant, we can express V_E in terms of V_I :

$$V_E = V_I + \left(\frac{863}{B-47} \right) Q \left[\left(C_{\text{v}(\text{CO}_2)} - C_{\text{a}(\text{CO}_2)} \right) + \left(C_{\text{v}(\text{O}_2)} - C_{\text{a}(\text{O}_2)} \right) + \left(C_{\text{v}(\text{N}_2)} - C_{\text{a}(\text{N}_2)} \right) \right] \quad (2.1)$$

We now define alveolar-arterial concentration equilibria for CO_2 , O_2 , and N_2 . For CO_2 :

$$\begin{aligned} C_{\text{a}(\text{CO}_2)} &= (\text{BHCO}_3)_b + 0.375 \left[(\text{Hb}) - C_{\text{a}(\text{HbO}_2)} \right] - \left[0.16 + 2.3(\text{Hb}) \right] \\ &\quad \left[\log \left(\frac{C_{\text{a}(\text{CO}_2)}^{-k\alpha_{\text{CO}_2}} (B-47)^{F_{\text{A}(\text{CO}_2)}}}{0.01(B-47)^{F_{\text{A}(\text{CO}_2)}}} \right) - 0.14 \right] \\ &\quad + k\alpha_{\text{CO}_2} (B-47)^{F_{\text{A}(\text{CO}_2)}} \end{aligned} \quad (3.1)$$

For O_2 :

$$C_{\text{a}(\text{O}_2)} = k\alpha_{\text{O}_2} (B-47)^{F_{\text{A}(\text{O}_2)}} + C_{\text{a}(\text{HbO}_2)}, \quad (3.2)$$

where

$$C_{a(HbO_2)} = (Hb) \left[1 - \exp(-S(B-47)F_{A(O_2)}) \right]^2, \quad (3.3)$$

$$S = 0.44921(pH_a) - 0.10098 (pH_a)^2 + 0.0066815 (pH_a)^3 - 0.454, \quad (3.4)$$

$$pH_a = 9 - \log C_{a(H^+)}, \quad (3.5)$$

and

$$C_{a(H^+)} = K' \left[\frac{k_{\alpha CO_2}^{(B-47)F_{A(CO_2)}}}{C_{a(CO_2)}^{-k_{\alpha CO_2}^{(B-47)F_{A(CO_2)}}}} \right] \quad (3.6)$$

Thus Eq. (3.1) is the CO_2 buffer equation including the Haldane effect [2, 10], and Eq. (3.3) is the O_2 dissociation curve including the Bohr effect. Equations (3.3) and (3.4) were fitted empirically to standard data on human blood [17].

For N_2 , we have simply:

$$C_{a(N_2)} = k_{\alpha N_2}^{(B-47)F_{A(N_2)}}. \quad (3.7)$$

We next define venous blood-brain equilibria for CO_2 , O_2 , and N_2 in terms of gas tensions. For CO_2 :

$$C_{B(CO_2)} = (BHCO_3)_B - 0.62 \left[\log \left(\frac{C_{B(CO_2)}^{-k_{\alpha B(CO_2)}P_{B(CO_2)}}}{0.01 P_{B(CO_2)}} \right) - 0.14 \right] \\ + k_{\alpha B(CO_2)}P_{B(CO_2)}, \quad (4.1)$$

and

$$C_{vB}(\text{CO}_2) = (\text{BHC}_3)_b + 0.375 \left[(\text{Hb}) - C_{vB}(\text{HbO}_2) \right] - \left[0.16 + 2.3(\text{Hb}) \right] \\ \left[\log \left(\frac{C_{vB}(\text{CO}_2)^{-k_{a\text{CO}_2} P_B(\text{CO}_2)}}{0.01 P_B(\text{CO}_2)} \right) - 0.14 \right] + k_{a\text{CO}_2} P_B(\text{CO}_2). \quad (4.2)$$

Equation (4.1) is a modified CO_2 buffer relation for brain with the Hb and HbO_2 effects removed, and Eq. (4.2) is the same form as Eq. (3.1). For O_2 :

$$C_{vB}(\text{O}_2) = \frac{\alpha_{\text{O}_2}}{\alpha_{B(\text{O}_2)}} C_{B(\text{O}_2)} + C_{vB}(\text{HbO}_2), \quad (4.3)$$

where as before

$$C_{vB}(\text{HbO}_2) = (\text{Hb}) \left[1 - \exp \left(-S(C_{B(\text{O}_2)} / k_{a_{B(\text{O}_2)}}) \right) \right]^2; \\ C_{B(\text{O}_2)} = k_{a_{B(\text{O}_2)}} P_{B(\text{O}_2)}, \quad (4.4)$$

$$S = 0.44921(\text{pH}_{vB}) - 0.10098(\text{pH}_{vB})^2 + 0.0066815(\text{pH}_{vB})^3 - 0.454, \quad (4.5)$$

$$\text{pH}_{vB} = 9 - \log C_{vB}(\text{H}^+), \quad (4.6)$$

and

$$C_{vB}(\text{H}^+) = K' \left[\frac{k_{a\text{CO}_2} P_B(\text{CO}_2)}{C_{vB}(\text{CO}_2)^{-k_{a\text{CO}_2} P_B(\text{CO}_2)}} \right]. \quad (4.7)$$

Equations similar to (4.6) and (4.7) with C_{vB} replaced by C_B will yield $C_{B(\text{H}^+)}$ and pH_B .

For N_2 , we have simply:

$$C_{vB(N_2)} = \frac{\alpha_{N_2}}{\alpha_{B(N_2)}} C_{B(N_2)};$$

$$C_{B(N_2)} = k_{aB(N_2)} P_{B(N_2)} \quad (4.8)$$

An exactly analogous set of equations with values for the tissue reservoir (subscript T) and tissue venous blood (subscript vT) substituted for those of the brain and brain venous blood is used to define venous-tissue equilibria for CO_2 , O_2 , and N_2 . We will not bother to rewrite them but simply reserve the equation numbers [Eqs. (5.1)-(5.8)] to designate them.

We note here that the hydrogen-ion concentration in CSF, which we will need as an input to the controller, is given by:

$$C_{CSF(H^+)} = K' \left[\frac{k_{aCSF(CO_2)} P_{CSF(CO_2)}}{(BHCO_3)_{CSF}} \right], \quad (6.1)$$

and

$$pH_{CSF} = 9 - \log C_{CSF(H^+)}. \quad (6.2)$$

We next define the dependence of cardiac output and brain blood flow on arterial CO_2 and O_2 tensions using information from the literature [12-16] and assigning an arbitrary first-order lag to the responses. For cardiac output, we have:

$$\dot{Q} = (f_Q - Q)/r_1, \quad (7.1)$$

where

$$f_Q = Q_N + \Delta Q_{(O_2)} + \Delta Q_{(CO_2)}. \quad (7.2)$$

For $X \equiv (B-47)F_{A(O_2)} = P_a(O_2)$, and $X < 104$, we have:

$$\Delta Q_{(O_2)} = 9.6651 - 0.2885X + (2.9241E-3)X^2 - (1.0033E-5)X^3 \quad (7.3)^*$$

And for $X \geq 104$:

$$\Delta Q_{(O_2)} = 0. \quad (7.4)$$

For $Y \equiv (B-47)F_{A(CO_2)} = P_a(CO_2)$, and $40 \leq Y \leq 60$,

$$\Delta Q_{(CO_2)} = 0.3(Y - 40), \quad (7.5)$$

And for all other values of Y ,

$$\Delta Q_{(CO_2)} = 0. \quad (7.6)$$

For brain blood flow, we have:

$$\dot{Q}_B = (f_{Q_B} - Q_B)/r_2, \quad (7.7)$$

where

$$f_{Q_B} = Q_{BN} + \Delta Q_{B(O_2)} + \Delta Q_{B(CO_2)}. \quad (7.8)$$

*"Floating point" notation, i.e.: $E - n \equiv \times 10^{-n}$, in this and subsequent equations.

For $X < 104$:

$$\begin{aligned} \Delta Q_B(O_2) = & 2.785 - 0.1323X + (2.6032E-3)X^2 \\ & - (2.324E-5)X^3 + (7.6559E-8)X^4, \end{aligned} \quad (7.9)$$

And for $X \geq 104$:

$$\Delta Q_B(O_2) = 0. \quad (7.10)$$

For $Y < 38$:

$$\begin{aligned} \Delta Q_B(CO_2) = & (2.323E-2) - (3.1073E-2)Y \\ & + (8.0163E-4)Y^2 \end{aligned} \quad (7.11)$$

For $38 \leq Y \leq 44$:

$$\Delta Q_B(CO_2) = 0, \quad (7.12)$$

And for $Y > 44$:

$$\begin{aligned} \Delta Q_B(CO_2) = & -15.58 + 0.7607Y - (1.2947E-2)Y^2 \\ & + (9.3918E-5)Y^3 - (2.1748E-7)Y^4. \end{aligned} \quad (7.13)$$

In each case, the polynomials in X or Y represent empirical fits to data taken from the literature, data admittedly incomplete in several details.

We now express the arterial concentrations of CO_2 , O_2 , and N_2 at the entrance of the brain, and of the tissue reservoirs—in terms of their concentrations in arterial blood leaving the lungs at an appropriate time in the past, i.e., at "lag time" $(t - \tau)$, where τ is the blood transport delay:

$$C_{aB}(CO_2)(t) = C_a(CO_2)(t-\tau_{aB}) \quad (8.1)$$

$$C_{aB}(O_2)(t) = C_a(O_2)(t-\tau_{aB}) \quad (8.2)$$

$$C_{aB}(N_2)(t) = C_a(N_2)(t-\tau_{aB}) \quad (8.3)$$

$$C_{aT}(CO_2)(t) = C_a(CO_2)(t-\tau_{aT}) \quad (8.4)$$

$$C_{aT}(O_2)(t) = C_a(O_2)(t-\tau_{aT}) \quad (8.5)$$

$$C_{aT}(N_2)(t) = C_a(N_2)(t-\tau_{aT}) \quad (8.6)$$

and in similar fashion, we express the mixed venous concentrations entering the lung in terms of concentrations in venous blood leaving the brain and tissue reservoirs at appropriate lag times:

$$C_v(CO_2)(t) = \frac{1}{Q} \left[Q_B(C_{vB}(CO_2)(t-\tau_{vB})) + (Q-Q_B)(C_{vT}(CO_2)(t-\tau_{vT})) \right] \quad (8.7)$$

$$C_v(O_2)(t) = \frac{1}{Q} \left[Q_B(C_{vB}(O_2)(t-\tau_{vB})) + (Q-Q_B)(C_{vT}(O_2)(t-\tau_{vT})) \right] \quad (8.8)$$

$$C_v(N_2)(t) = \frac{1}{Q} \left[Q_B(C_{vB}(N_2)(t-\tau_{vB})) + (Q-Q_B)(C_{vT}(N_2)(t-\tau_{vT})) \right] \quad (8.9)$$

The variables defined by Eqs. (8.1)-(8.9) will be called "lag variables" for convenience.

Finally we note that the transport delays are not constant but vary with blood flow rates as defined below:

$$\tau_{aB} = \frac{1.062}{\frac{1}{\tau_{aB} - \tau_{aB}(1)} \int_{t-\tau_{aB}}^{t-\tau_{aB}(1)} Q \, dt} + \frac{0.015}{t} \int_{t-\tau_{aB}(1)}^t Q_B \, dt \quad (8.10)$$

$$\tau_{aT} = \frac{1.062}{\frac{1}{\tau_{aT} - \tau_{aT}(1)} \int_{t-\tau_{aT}}^{t-\tau_{aT}(1)} Q \, dt} + \frac{0.735}{t} \int_{t-\tau_{aT}(1)}^t (Q - Q_B) \, dt \quad (8.11)$$

$$\tau_{vB} = \frac{0.06}{\frac{1}{\tau_{vB} - \tau_{vB}(1)} \int_{t-\tau_{vB}}^{t-\tau_{vB}(1)} Q_B \, dt} + \frac{0.188}{t} \int_{t-\tau_{vB}(1)}^t Q \, dt \quad (8.12)$$

$$\tau_{vT} = \frac{2.94}{\frac{1}{\tau_{vT} - \tau_{vT}(1)} \int_{t-\tau_{vT}}^{t-\tau_{vT}(1)} (Q - Q_B) \, dt} + \frac{0.188}{t} \int_{t-\tau_{vT}(1)}^t Q \, dt \quad (8.13)$$

$$\tau_{ao} = \frac{1.062}{\frac{1}{\tau_{ao} - \tau_{ao}(1)} \int_{t-\tau_{ao}}^{t-\tau_{ao}(1)} Q \, dt} + \frac{0.008}{t} \int_{t-\tau_{ao}(1)}^t Q_B \, dt \quad (8.14)$$

The last value, τ_{ao} , which does not appear in Eqs. (8.1)-(8.9), is the lung-to-carotid body delay and will be used in the controller function. In each equation, the numerator represents the volume of the appropriate vascular segment through which blood flows at the appropriate "past-average rate" defined by the denominator.

We have now written all of the relationships required to define the open-loop operation of the isolated "plant." To close the loops, it remains to write a controller function. A major purpose of our simulation is to explore the implications of a variety of such functions, and so far we have looked at two:

$$V_I = 1.1 C_{B(H^+)} + 1.31 P_{B(CO_2)} + TERM - V_{I(1)}, \quad (9.1)$$

and

$$V_I = 1.138 C_{CSF(H^+)} + 1.154 C_{a(H^+)}(t - \tau_{ao}) + TERM - V_{I(2)} \quad (9.2)$$

$$TERM = (23.6E-9) \left[104 - (B-47) F_{A(O_2)}(t - \tau_{ao}) \right]^{4.9}$$

$$\text{for } (B-47) F_{A(O_2)}(t - \tau_{ao}) < 104, \quad (9.3)$$

$$TERM = 0 \quad \text{for } (B-47) F_{A(O_2)}(t - \tau_{ao}) \geq 104, \quad (9.4)$$

and $V_{I(n)}$ are constants so adjusted that $P_{A(CO_2)} \approx 40.0$ at rest, breathing air at sea level (standard control point). Equation (9.1) is similar to that used in our earlier model, whereas Eq. (9.2) incorporates recent findings on the roles of CSF and peripheral receptors [18-21]. Neither includes an O_2 - CO_2 interaction term, but this as well as a variety of other possibilities can easily be introduced.

4. SOLUTION OF SYSTEM EQUATIONS BY DIGITAL COMPUTER

The equations were programmed for solution on IBM 7044 and CDC 3400 digital computers. For this purpose, the basic material balance equations [Eqs. (1.1)-(1.9)] were rewritten as differential-difference equations with variable time delays, using the appropriate

interrelationship equations developed above:

$$\begin{aligned} \dot{F}_{A(CO_2)} = \frac{1}{K_L} \left[V_I F_{I(CO_2)} - V_E F_{A(CO_2)} + \left(\frac{863}{B-47} \right) (Q_B C_{vB(CO_2)} (t - \tau_{vB}) \right. \\ \left. + (Q - Q_B) C_{vT(CO_2)} (t - \tau_{vT}) - Q C_{a(CO_2)}) \right] \end{aligned} \quad (10.1)$$

$$\begin{aligned} \dot{F}_{A(O_2)} = \frac{1}{K_L} \left[V_I F_{I(O_2)} - V_E F_{A(O_2)} + \left(\frac{863}{B-47} \right) (Q_B C_{vB(O_2)} (t - \tau_{vB}) \right. \\ \left. + (Q - Q_B) C_{vT(O_2)} (t - \tau_{vT}) - Q (k_{O_2} (B-47) F_{A(O_2)} + C_{a(HbO_2)})) \right] \end{aligned} \quad (10.2)$$

$$\begin{aligned} \dot{F}_{A(N_2)} = \frac{1}{K_L} \left[V_I F_{I(N_2)} - V_E F_{A(N_2)} + \left(\frac{863}{B-47} \right) (Q_B C_{vB(N_2)} (t - \tau_{vB}) \right. \\ \left. + (Q - Q_B) C_{vT(N_2)} (t - \tau_{vT}) - Q (k_{N_2} (B-47) F_{A(N_2)})) \right] \end{aligned} \quad (10.3)$$

$$\begin{aligned} \dot{C}_{B(CO_2)} = \frac{1}{K_B} \left[M R_{B(CO_2)} + Q_B (C_{a(CO_2)} (t - \tau_{aB}) - C_{vB(CO_2)}) \right. \\ \left. - D_{CO_2} (P_{B(CO_2)} - P_{CSF(CO_2)}) \right] \end{aligned} \quad (10.4)$$

$$\begin{aligned} \dot{C}_{B(O_2)} = \frac{1}{K_B} \left[-M R_{B(O_2)} + Q_B \left((k_{O_2} (B-47) F_{A(O_2)} + C_{a(HbO_2)}) (t - \tau_{aB}) \right. \right. \\ \left. \left. - \left(\frac{\alpha_{O_2}}{\alpha_{B(O_2)}} \right) C_{B(O_2)} - C_{vB(HbO_2)}) - D_{O_2} (P_{B(O_2)} - P_{CSF(O_2)}) \right] \end{aligned} \quad (10.5)$$

$$\begin{aligned} \dot{C}_{B(N_2)} = \frac{1}{K_B} & \left[Q_B \left(k \alpha_{N_2}^{(B-47)} F_{A(N_2)} (t - \tau_{aB}) - \left(\frac{\alpha_{N_2}}{\alpha_{B(N_2)}} \right) C_{B(N_2)} \right) \right. \\ & \left. - D_{N_2} \left(P_{B(N_2)} - P_{CSF(N_2)} \right) \right] \end{aligned} \quad (10.6)$$

$$\dot{C}_{T(CO_2)} = \frac{1}{K_T} \left[MR_T(CO_2) + (Q - Q_B) \left(C_a(CO_2) (t - \tau_{aB}) - C_{vT}(CO_2) \right) \right] \quad (10.7)$$

$$\begin{aligned} \dot{C}_{T(O_2)} = \frac{1}{K_T} & \left[-MR_T(O_2) + (Q - Q_B) \left\{ \left(k \alpha_{O_2}^{(B-47)} F_{A(O_2)} + C_{a(HbO_2)} \right) (t - \tau_{aT}) \right. \right. \\ & \left. \left. - \left(\frac{\alpha_{O_2}}{\alpha_{T(O_2)}} \right) C_{T(O_2)} - C_{vT}(HbO_2) \right\} \right] \end{aligned} \quad (10.8)$$

$$\begin{aligned} \dot{C}_{T(N_2)} = ((Q - Q_B) / K_T) & \left[\left(k \alpha_{N_2}^{(B-47)} F_{A(N_2)} \right) (t - \tau_{aT}) \right. \\ & \left. - \left(\frac{\alpha_{N_2}}{\alpha_{T(N_2)}} \right) C_{T(N_2)} \right] \end{aligned} \quad (10.9)$$

Equation (2.1) defining V_E in terms of V_I was also rewritten to incorporate the appropriate lag times:

$$\begin{aligned} V_E = V_I + \left(\frac{863}{B-47} \right) & \left(Q_B \left[\left(C_{vB}(CO_2) + C_{vB}(O_2) + C_{vB}(N_2) \right) (t - \tau_{vB}) \right] \right. \\ & + (Q - Q_B) \left[\left(C_{vT}(CO_2) + \left(\frac{\alpha_{O_2}}{\alpha_{T(O_2)}} \right) C_{T(O_2)} + C_{vT}(HbO_2) + \right. \right. \\ & \left. \left. + \left(\frac{\alpha_{N_2}}{\alpha_{T(N_2)}} \right) C_{T(N_2)} \right) (t - \tau_{vT}) \right] \\ & \left. - Q \left[C_a(CO_2) + k \alpha_{O_2}^{(B-47)} F_{A(O_2)} + C_{a(HbO_2)} + k \alpha_{N_2}^{(B-47)} F_{A(N_2)} \right] \right) \end{aligned} \quad (11.1)$$

Methods for the numerical integration of such differential-difference equations with several time lags have been considered in detail elsewhere [22-24]. Here we shall only point out certain special features of the present program that deserve comment.

The first concerns the calculation of current values for $C_a(\text{CO}_2)$, $C_a(\text{HbO}_2)$, $C_{vB}(\text{CO}_2)$, $C_{vB}(\text{HbO}_2)$, $C_{vT}(\text{CO}_2)$, and $C_{vT}(\text{HbO}_2)$ to put into this system of equations. Special problems are involved here because of the interdependence of CO_2 content, oxyhemoglobin content, and pH, and because of the fact that the buffer equation cannot be solved explicitly for the desired variable. Let us examine the procedure used here. Starting with the current value of $F_A(\text{CO}_2)$ and a trial guess for $C_a(\text{CO}_2)$ (say $C_a(\text{CO}_2)(1)$), we calculate $C_a(\text{H}^+)(1)$ and $\text{pH}_a(1)$ from Eqs. (3.6) and (3.5). Putting this value of $\text{pH}_a(1)$ into Eq. (3.4) and using the current value of $F_A(\text{O}_2)$, we obtain $C_a(\text{HbO}_2)(1)$ from Eq. (3.3). Then using $C_a(\text{HbO}_2)$, we solve Eq. (3.1) for $C_a(\text{CO}_2)(2)$. We do this by a process of iterative guessing, putting $C_a(\text{CO}_2)(1)$ on the right hand side, calculating $C_a(\text{CO}_2)(2)$ on the left, comparing the two, adjusting $C_a(\text{CO}_2)(1)$ and repeating until the two agree within a predetermined limit of error. Now, using this new value for $C_a(\text{CO}_2)$, we repeat the entire process, recalculating pH_a , $C_a(\text{HbO}_2)$, and $C_a(\text{CO}_2)$ until we get a $C_a(\text{CO}_2)$ that satisfies Eq. (3.1) on the first trial. Going next to the brain, we solve Eq. (4.1) for $P_B(\text{CO}_2)$, using the current value of $C_B(\text{CO}_2)$. Again we use an iterative guessing procedure, but since HbO_2 is not involved here, it is unnecessary to include the pH and HbO_2 steps. Then using this value of $P_B(\text{CO}_2)$, the current value of $C_B(\text{O}_2)$, and an initial trial guess for $C_{vB}(\text{CO}_2)$, we apply the complete iterative procedure to Eqs. (4.2)-(4.7) to obtain current values for $C_{vB}(\text{CO}_2)$, $C_{vB}(\text{O}_2)$ and pH_{vB} . Finally, going to the tissue reservoir, we apply

the same technique to Eqs. (5.1)-(5.7) to obtain current values for $P_T(\text{CO}_2)$, $C_{VT}(\text{CO}_2)$, $C_{VT}(\text{O}_2)$, and pH_{VT} .

A second feature involves the storage and retrieval of the "lag variables" defined by Eqs. (8.1)-(8.9). Provision is made for storing in the computer previous values of these variables in a table, continuously updated, that extends an appropriate distance into the past, usually 0.5-1.5 minutes. After calculating current values for the lag times, an interpolation routine is used to retrieve the proper values of the lag variables for use in the next integration step. In early versions of the program, current rather than average blood flow values were used to calculate the required τ values, but in later versions, the correct average values were computed. To obtain these it was necessary to integrate the various blood flow-time functions "backwards" into the past, starting at current time and stopping when the value of the integral became equal to the appropriate vascular volume. This point defined the lower limit of the integration and hence the appropriate τ .

Finally, for convenience in future explorations and modifications, the programs have been written in the form of multiple subroutines, each of which can be altered more or less independently of the others. The latest version of our Fortran IV program includes approximately 500 statements.* A sample tabular output is provided in App. C, and graphs of the material will be discussed below.

5. RESULTS

The equations of the model and the corresponding digital simulations have evolved through several stages of increasing complexity. In the first version there was no CSF compartment, and τ values were

* Programs are available from the authors on request.

computed from current rather than "past-average" blood flows. The controller inputs were brain P_{CO_2} , brain (H^+) , and arterial P_{O_2} at the peripheral chemoreceptors. A variety of forcings were studied including: (a) CO_2 inhalation (1, 3, 5 percent) and recovery; (b) hypoxia at sea level (10, 8, 6 percent O_2) and recovery; and (c) altitude hypoxia (15,000, 18,000, 20,000 feet). With few exceptions, the solutions were stable, and the quasi-steady state values were close to those expected in the prototype (Table 1). It is noteworthy that a true steady state, if judged by the alveolar RQ calculated at each step, was not attained in 30 minutes for any of the forcings except perhaps 1 percent CO_2 . Transient behavior during CO_2 inhalation and recovery was similar in form to that of an earlier model [3]; an example is given in Fig. 2. However, it will be noted that the "on response" of ventilation is much faster in the present

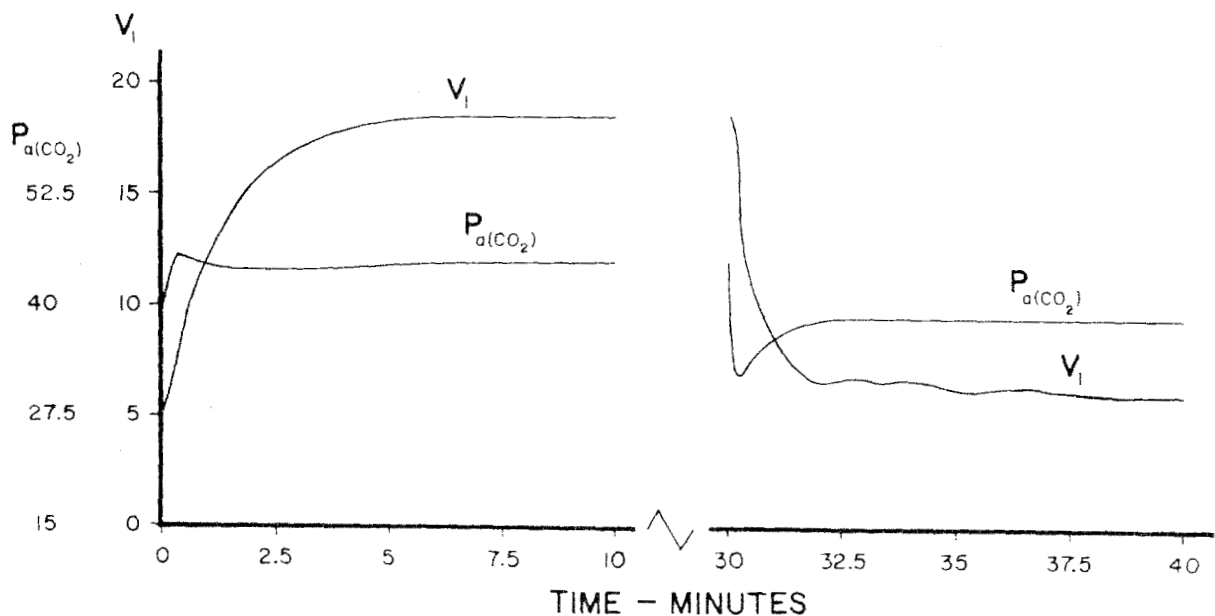


Fig. 2—Response of Version 1 to 5% CO_2 "pulse."

Pulse on at zero time, off at 30 min.

Table 1

STEADY STATE VALUES-VERSION 1

Variable*	Normal Control	CO ₂ Inhalation				Hypoxia at Sea Level			Hypoxia at Altitude		
		1% CO ₂	3% CO ₂	5% CO ₂		10% O ₂	8% O ₂	6% O ₂	15,000'	18,000'	20,000'
V _I	5.07	6.10	9.88	16.67		6.44	10.36	11.09	5.73	6.48	7.12
V _E	5.03	6.06	9.84	16.61		6.42	10.33	11.12	5.67	6.44	7.09
F _A (CO ₂)	.0557	.0563	.0585	.0665		.0473	.0405	.0316	.0948	.0994	.1020
F _A (O ₂)	.1480	.1585	.1783	.1913		.0505	.0405	.0311	.1069	.1052	.6945
F _A (N ₂)	.7963	.7852	.7632	.7422		.9021	.9190	.9372	.7982	.7954	.7933
P _A (CO ₂)	39.7	40.1	41.7	47.4		33.7	28.9	22.6	36.2	33.1	30.8
P _B (CO ₂)	50.2	50.7	52.6	55.9		40.0	34.8	26.2	43.0	39.2	36.4
P _T (CO ₂)	44.7	45.1	46.4	51.4		37.1	31.7	25.1	39.7	36.3	33.8
P _A (O ₂)	105.5	113.0	127.1	136.4		36.0	28.9	22.2	40.8	35.0	31.6
P _B (O ₂)	37.3	37.8	38.7	48.1		24.2	21.5	16.1	27.0	23.6	21.6
P _T (O ₂)	47.2	48.0	51.2	58.5		28.2	23.4	18.3	31.1	27.5	25.3
C _a (CO ₂)	.5748	.5768	.5846	.6118		.5551	.5285	.4857	.5672	.5517	.5393
C _B (CO ₂)	.6415	.6435	.6513	.6597		.6081	.5710	.5230	.6148	.5980	.5842
C _T (CO ₂)	.6094	.6111	.6160	.6363		.5816	.5532	.5112	.5939	.5773	.5643
C _a (HbO ₂)	.1976	.1983	.1991	.1993		.1430	.1262	.1080	.1525	.1409	.1332
C _{vB} (HbO ₂)	.1331	.1340	.1352	.1542		.0970	.0835	.0781	.1055	.0952	.0890

Table 1—continued

Variable*	Normal Control	CO ₂ Inhalation			Hypoxia at Sea Level			Hypoxia at Altitude		
		1% CO ₂	3% CO ₂	5% CO ₂	10% O ₂	8% O ₂	6% O ₂	15,000'	18,000'	20,000'
C _v T(HbO ₂)	.1585	.1598	.1642	.1718	.1147	.1012	.0848	.1222	.1130	.1067
C _B (O ₂)	.0012	.0012	.0012	.0015	.0008	.0007	.0005	.0008	.0007	.0007
C _T (O ₂)	.0015	.0015	.0016	.0018	.0009	.0007	.0006	.0010	.0009	.0008
C _B (N ₂)	.0097	.0096	.0093	.0091	.0110	.0012	.0115	.0052	.0045	.0041
C _T (N ₂)	.0097	.0096	.0093	.0091	.0110	.0112	.0114	.0052	.0045	.0041
pH _a	7.411	7.408	7.397	7.359	7.469	7.517	7.590	7.447	7.476	7.500
pH _B	7.354	7.350	7.340	7.318	7.429	7.468	7.556	7.406	7.435	7.458
pH _T	7.384	7.381	7.372	7.340	7.447	7.500	7.566	7.426	7.454	7.382
Q	6.00	6.04	6.52	8.22	8.60	9.51	10.59	8.08	8.72	9.15
Q _B	.750	.750	.750	1.04	1.08	1.17	1.37	1.05	1.08	1.12
Alveolar RQ	.875	.874	.872	.848	.952	1.02	1.10	.901	.935	.960
Time	∞	30	30	30	30	30	30	30	30	30

* See App. A for definition of symbols.

model, requiring only 3 minutes to reach the 80 percent level rather than the 12 minutes needed by the original version [3]. This difference has also been noted by others [5, 9] who have separated out a brain compartment from the single lumped tissue reservoir previously assumed [3]; it is directly related to the relative ratios of compartment volume to blood flow. Closer attention to the early details of the prototype response [19-21] has indicated that neither model is too faithful, for there appears to be an initial fast response of relatively modest magnitude followed by a much slower but larger component. Moreover, the ventilatory response lags considerably behind the change in jugular venous P_{CO_2} after the first minute [19]. These matters will be referred to again later. As expected, a short interval of periodic breathing occurred on sudden return to air after a prolonged period of hypoxia (Fig. 3). Figure 4 shows a phenomenon occasionally encountered, i.e., the sudden appearance of numerical instability in a previously stable solution in this case after 35 minutes at an altitude of 20,000 feet. Disappearance of this behavior on changing the integration step size confirms the suspicion that it is a computational and not a model instability.*

In the second stage of development, a CSF reservoir was added, but τ values were still computed from current blood flows. The controller inputs were now the CSF (H^+), and both arterial (H^+) and

*With single precision arithmetic, a step size of 0.01 minute was satisfactory on the CDC 3400 (48-bit word). On the IBM 7044 (36-bit word), a step size of 0.007812, i.e., $1/2^7$, was usually satisfactory, but occasionally a smaller one was required ($1/2^8$ or $1/2^9$).

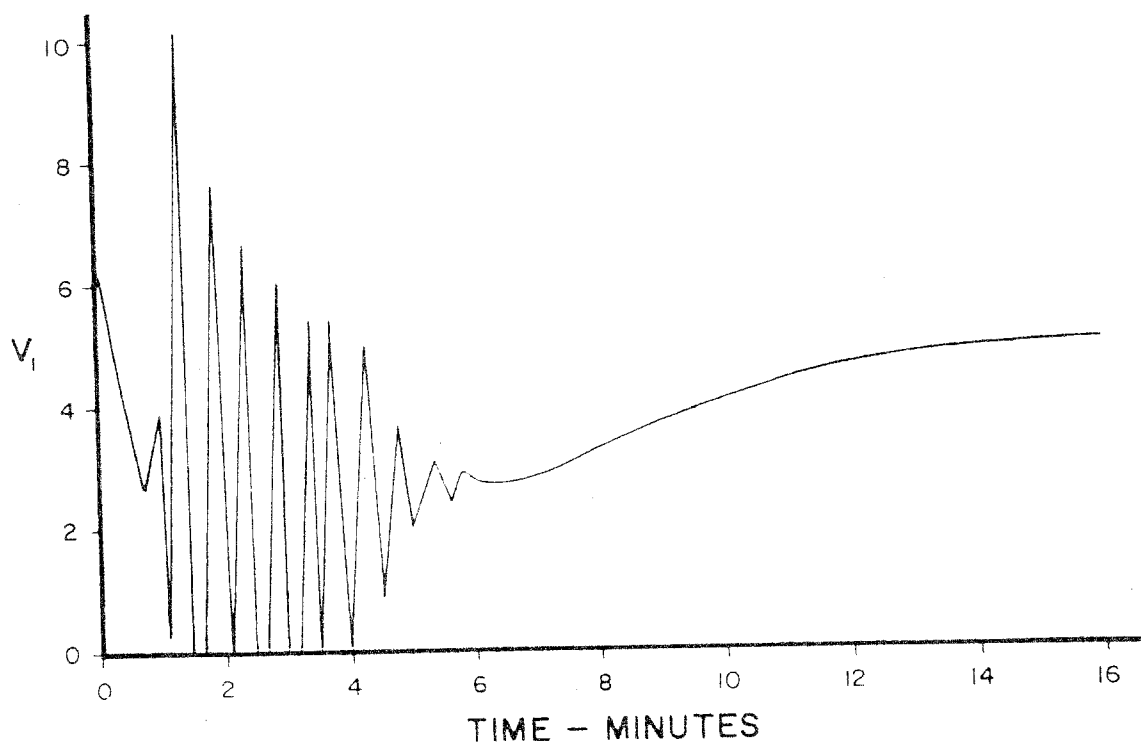


Fig. 3—Periodic breathing on recovery from hypoxia (30 min on 10% O_2 , Version 1). Value $F_{I(O_2)}$ changed exponentially from 0.10 to 0.21 during first min.

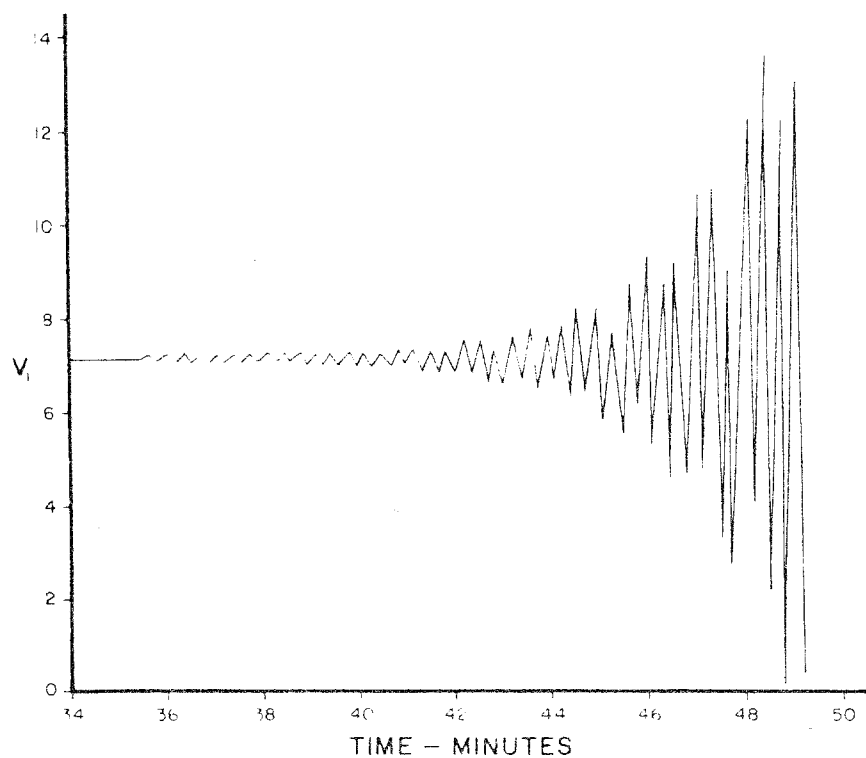


Fig. 4—Sudden appearance of numerical instability after 35 min at 20,000 ft. Version 1.

P_{O_2} at the peripheral chemoreceptors, a control scheme similar to that suggested by Lambertsen [19], and compatible with the recent work of Mitchell, et al. [18]. This control function should introduce both fast and slow components into the CO_2 response, and should also permit a preliminary study of responses to metabolic acidosis. Figure 5 shows the behavior of ventilation, CSF (H^+), and arterial (lung exit) (H^+) during and following a 30 minute "pulse" of 5 percent CO_2 in inspired air. The similarity of the "on transient" to the behavior observed in dogs by Lambertsen [19] is apparent. In contrast with Version 1, ventilation once more requires 12 minutes to reach 80 percent of its total response, but in contrast with our original

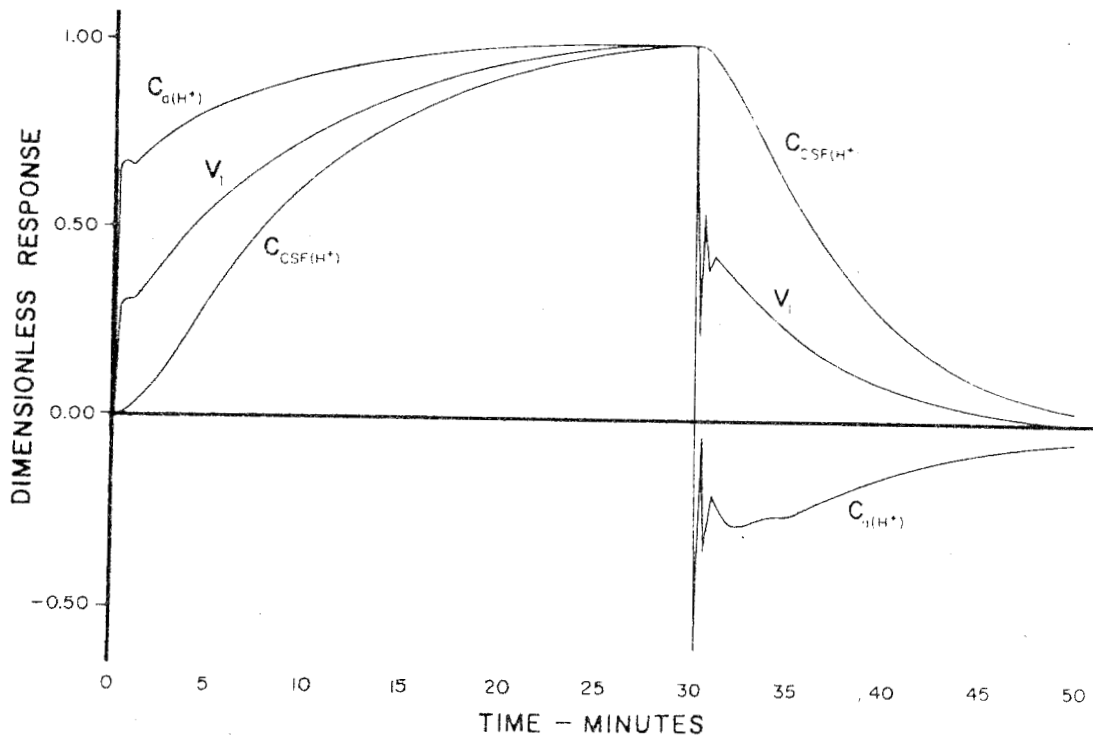


Fig. 2—Response of Version 1 to 5% CO_2 "pulse."
Pulse on at zero time, off at 30 min.

model [3] and in agreement with recent observations [19-21], we now also have an initial rapid component so that about 30 percent of the response occurs within one minute. The exact relationship between the three curves in Fig. 5 can be altered by changing the relative weightings assigned to peripheral and CSF (H^+) receptors. Although the entire time course of the response to metabolic acidosis was obtained, the transient portion is not really very relevant, for the forcing was introduced in a highly artificial manner, i.e., a step change in $(BHCO_3)_B$ and $(BHCO_3)_T$ at zero time while keeping $(BHCO_3)_B$ and $(BHCO_3)_{CSF}$ constant. However, it is of interest that a stable solution was obtained and that the steady state values shown in Table 2 are quite realistic [2]. Thus, the same reduction in arterial pH produced by 5 percent CO_2 inhalation on the one hand, and by metabolic acidosis on the other was associated with a ventilation ratio of 3.66 in the former and only 1.25 in the latter. Whereas CO_2 inhalation produced hypercapnia and increased (H^+) throughout the body, the increase in (H^+) in metabolic acidosis was confined to the blood and "not-brain" tissue, while the (H^+) of brain and CSF actually fell. Thus the general qualitative and quantitative behavior of the model seems quite reasonable under these conditions.

The major modification introduced into the third version of the model was the use of correct "past-average" blood flow values to compute current values for the time lags. This did not produce any significant difference in the response to a 5 percent CO_2 pulse. The computer generated graph of Fig. 6 includes the time course of brain (or internal jugular) (H^+) which is identical with that of brain P_{CO_2} on this non-dimensional plot, and this leads the ventilatory response after the first minute of the "on" transient, in agreement with experimental observations noted previously [25].

Table 2

STEADY STATE VALUES—VERSION 2

Variable*	Normal Control	Metabolic Acidosis	5% CO ₂
V _I	5.37	6.71	19.66
V _E	5.33	6.67	19.62
F _A (CO ₂)	.0526	.0421	.0644
F _A (O ₂)	.1514	.1632	.1941
F _A (N ₂)	.7959	.7947	.7415
P _A (CO ₂)	37.5	30.0	45.9
P _B (CO ₂)	47.8	43.4	55.3
P _{CSF} (CO ₂)	47.8	43.4	55.2
P _T (CO ₂)	42.3	34.5	50.1
P _A (O ₂)	108.0	116.3	138.4
P _B (O ₂)	36.5	32.4	45.0
P _{CSF} (O ₂)	36.2	32.1	44.6
P _T (O ₂)	46.7	50.6	57.0
C _a (CO ₂)	.5629	.3966	.6048
C _B (CO ₂)	.6396	.6185	.6718
C _{CSF} (CO ₂)	.6172	.6142	.6222
C _{vB} (CO ₂)	.6309	.4855	.6588
C _T (CO ₂)	.6130	.4212	.6500
C _{vT} (CO ₂)	.5975	.4300	.6314
C _a (HbO ₂)	.1981	.1982	.1994
C _{vB} (HbO ₂)	.1324	.1120	.1483
C _{vT} (HbO ₂)	.1592	.1608	.1705
pH _a	7.427	7.370	7.368
pH _B	7.375	7.404	7.331

Table 2—continued

Variable*	Normal Control	Metabolic Acidosis	5% CO ₂
pH _{CSF}	7.344	7.386	7.281
pH _{VB}	7.369	7.293	7.322
pH _T	7.412	7.334	7.361
pH _{VT}	7.401	7.344	7.348
Q	6.00	6.00	7.77
Q _B	.736	.562	.926
Alveolar RQ	.875	.875	.874
Time	∞	77	49

* See App. A for definition of symbols.

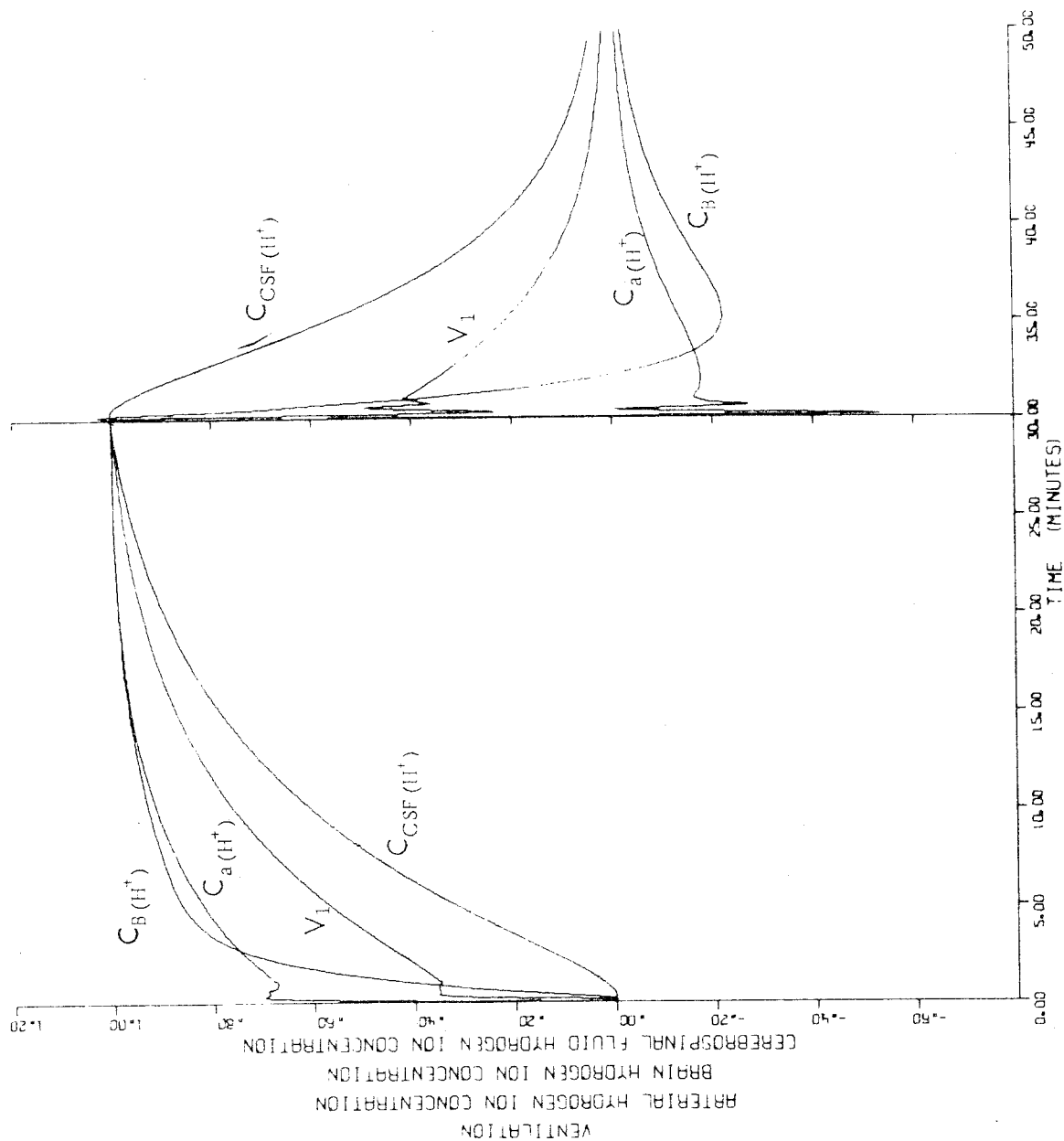


Fig. 6—Computer generated plot of Version 3 response to 5% CO₂ pulse. Pulse on at zero time, off at 30 min. Non-dimensional ordinate scale.

Early details of the "on" and "off" transients appear in the expanded time scale graphs of Fig. 7. The response to a 30 minute "pulse" of 10 percent oxygen with subsequent return to air is shown in Figs. 8-10. Prominent features are the ventilation overshoot during the "on" transient (Fig. 8), and the prolonged interval of periodic breathing during recovery (Fig. 10). This periodicity persists longer than it did in Version 1 (Fig. 3), but in the latter, return to air was accomplished gradually over one minute whereas in the present example it was instantaneous. Also nicely illustrated is the sequence: $P_{A(O_2)}$ fall-delay-ventilation rise- $P_{A(CO_2)}$ and $C_a(H^+)$ fall at the start of hypoxia (Fig. 8), as well as the sequence: $P_{A(O_2)}$ rise-delay-ventilation fall- $P_{A(CO_2)}$ and $C_a(H^+)$ rise at the start of recovery (Fig. 9).

6. DISCUSSION

A major purpose of the present study was to provide a sufficiently detailed mathematical description and digital simulation of the "plant" so that a significantly wide variety of forcings and control hypotheses could be explored. This has been accomplished to some extent, the plant description taking the form of a set of differential-difference equations, incorporating a number of dependent time-delays, which express the basic material balance relationships of the system. Additional equations are required to define the chemical details of gas transport and acid-base buffering mechanisms, concentration equilibria in various parts of the system, and the dependence of blood flow rates upon CO_2 and O_2 concentrations. Finally, a control loop manipulating pulmonary ventilation according to any one of a variety of possible schemes can be included. The model is sufficiently general to accept many sorts of forcings, e.g., CO_2 inhalation, hypoxia at sea level or at altitude, metabolic

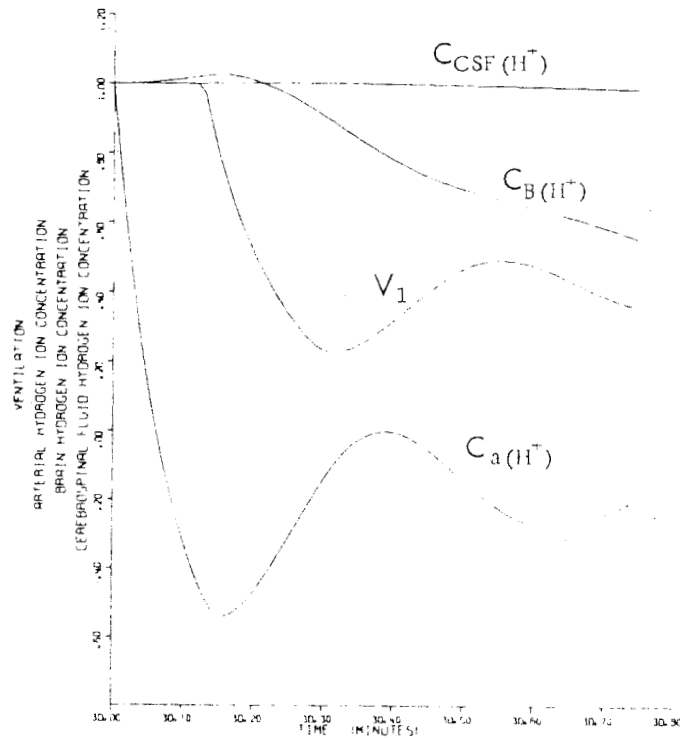
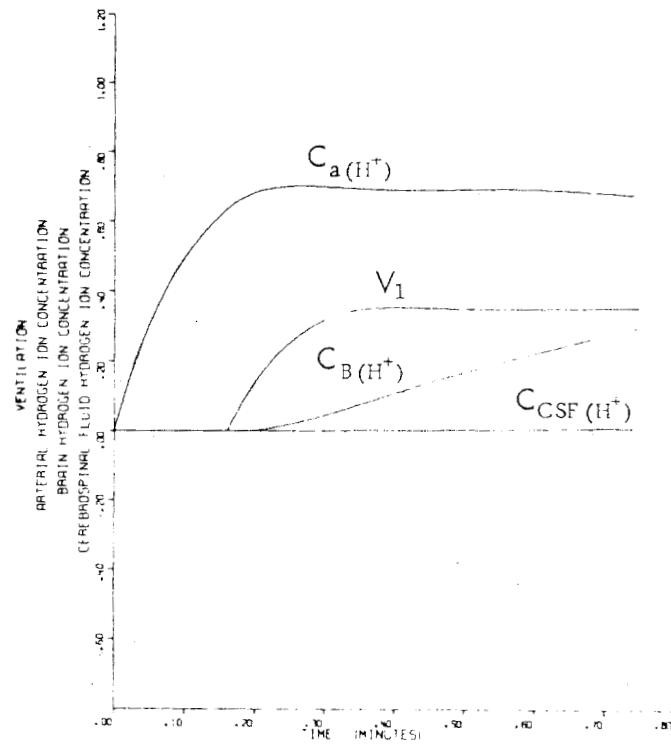


Fig. 7—Expanded time scale plots of Fig. 6 for intervals 0.00–0.75 min and 30.00–30.75 min to show early details of on and off transients. Non-dimensional ordinate scales.

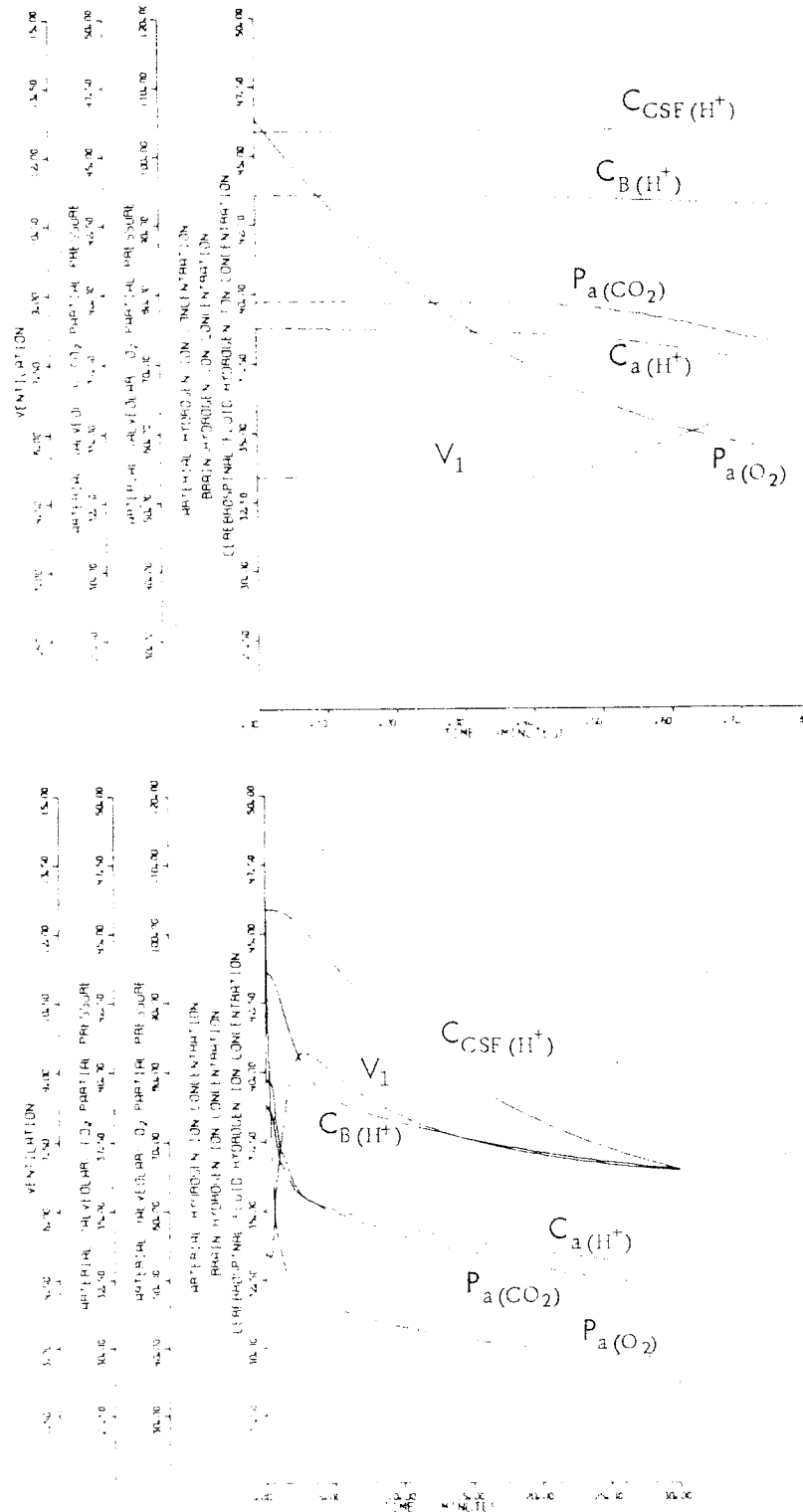


Fig. 8—Computer plots of response of Version 3 to step input of 10% O₂. Expanded time scale plot above shows early detail.

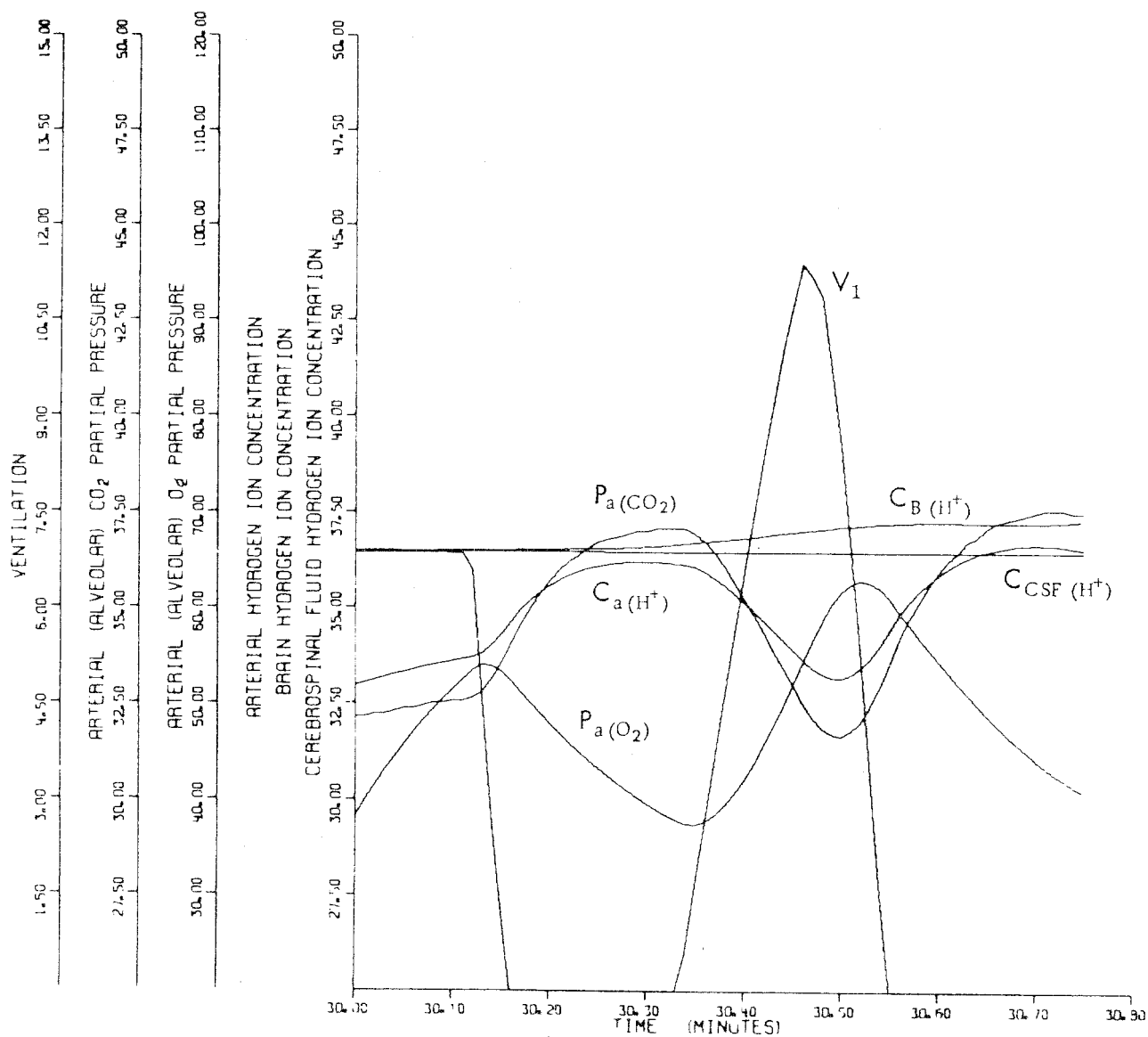


Fig. 9—Computer plot of behavior of Version 3 during first 0.75 min following instantaneous return to air after 30 min on 10% O₂.

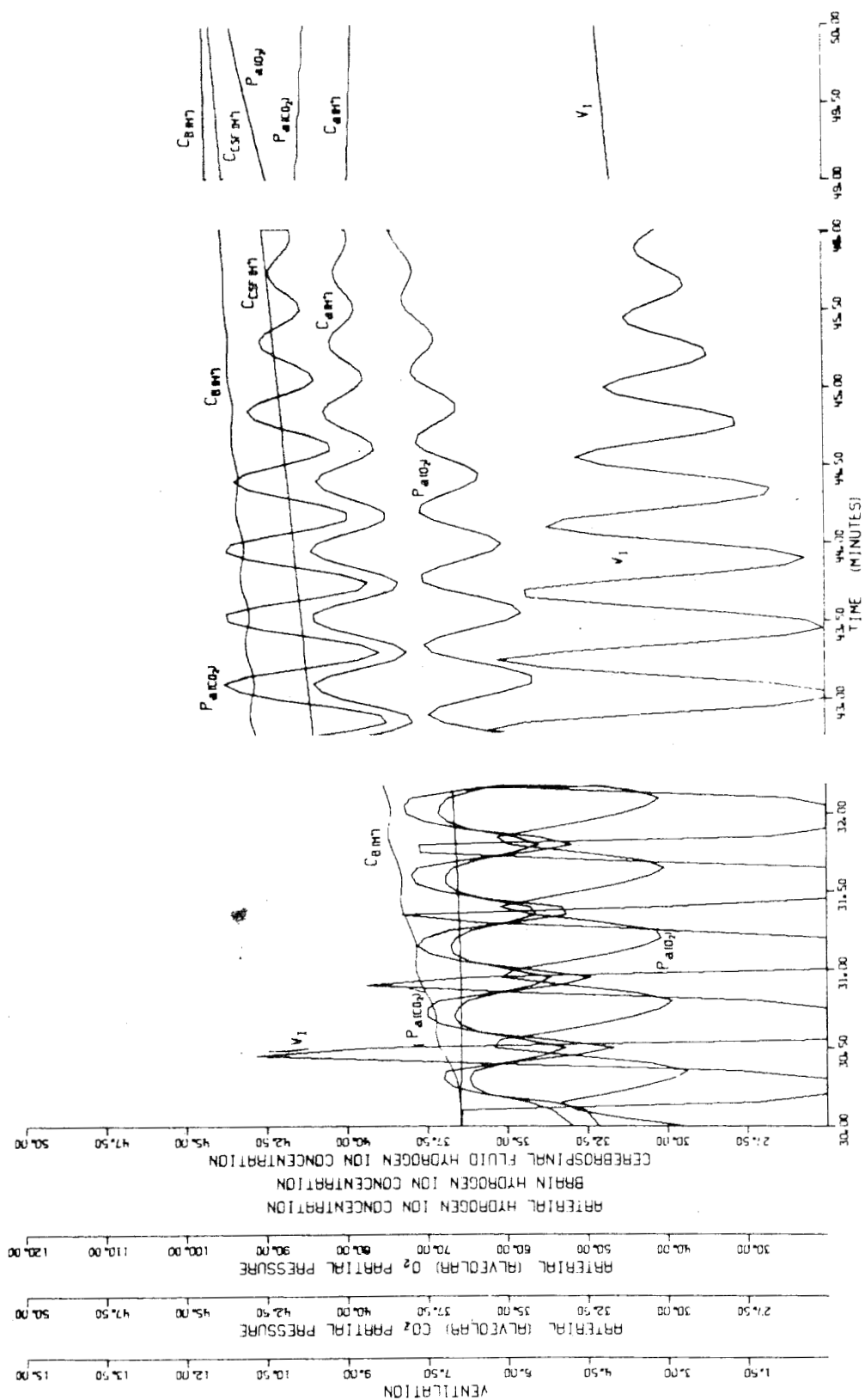


Fig. 10—Continuation of Fig. 9 with compressed time scale to show subsequent course of recovery from hypoxia.

acidosis and alkalosis, or any combinations thereof, and any arbitrary time course can be assigned to them. Concentrations of a variety of chemical species are available at several different locations for use in possible control functions. Extension of the model to include any number of additional distinct tissue compartments is simple in principle, as in the inclusion of other inhaled agents such as anesthetics.

Solution of this system of nonlinear equations would be completely impractical without computer assistance. The digital computer is particularly suited for large multivariate systems incorporating time delays, although the storage requirements for retaining the past histories of many variables may get uncomfortably large. To our knowledge, this is the first time that a set of differential-difference equations whose time delays themselves are dependent variables has been solved by digital techniques [22]. The latest version of our program requires about one minute of machine time (CDC 3400) for every four minutes of experimental simulation.

Indicative of the importance of dynamic simulation is the fact that many recent contributions to our understanding of the "chemical control" of ventilation have been based upon the study of dynamic transients in an attempt to separate peripheral (fast) from central (slow) components [19-21]. Such studies led Lambertsen [19] to suggest a dual sensing mechanism for the ventilatory response to CO_2 , one receptor responding directly to arterial (H^+) and the other to the (H^+) of an appropriate central fluid, perhaps CSF. This suggestion fits in very well with the results of Dejours' "two breath CO_2 test" before and after chemoreceptor denervation [20, 21] as well as with other observations indicating the existence of superficial medullary receptors sensitive to CSF (H^+) [18]. A control scheme

of this sort incorporated into our model closely reproduced Lambertsen's observations. In both experiment and model (Fig. 6), arterial P_{CO_2} (or (H^+)) changed most rapidly, followed in order by brain venous P_{CO_2} (or (H^+)), ventilation, and finally CSF P_{CO_2} (or (H^+)). It is not essential to this scheme that the central receptors be superficial and exposed directly to "bulk CSF," for they could lie somewhat deeper within the medulla in accordance with the classical view and the recent studies of Pappenheimer, et al. [25], responding to the (H^+) of the appropriate local central fluid. It is essential, however, that there be a separate arterial receptor for (H^+) else the results of chemoceptor denervation could not be accounted for [20, 21].

Dejours [20], and Bouverot, et al. [21], have also used a "two breath O_2 test" to study the peripheral (fast) response to 100 percent O_2 . They noted the difficulty of assessing the mechanism of the ventilatory response to long lasting pure oxygen inhalation because of the operation of many other factors involving the gas transport systems. Such factors are taken into account in the present model, and prolonged administration of 100 percent O_2 in Version 1 resulted in a mild hyperventilation associated with arterial hypocapnia and alkalemia together with brain and venous hypercapnia and increased (H^+) [26]. The initial depression of ventilation observed by Dejours was not reproduced, for we have not yet rewritten our control function to include an " O_2 threshold" as high as 200 mm Hg. We are confident that this modification together with an appropriate interaction term involving arterial (H^+) and P_{O_2} at the carotid chemoceptors will permit Version 3 of our model to reproduce Dejours' CO_2 and O_2 results in detail.

Although step or pulse inputs of gases are convenient and widely used forcings, the production of metabolic disturbances in acid-base balance is carried out in a variety of nonstandard ways ranging from intravenous injection of acid or alkali to prolonged ingestion of NH_4Cl or NaHCO_3 or diabetic accumulation of ketone bodies. The nature of the transient response is of course critically dependent upon the time course of the forcing function, and while it is possible to simulate a wide variety of these in the model, we have not yet carried out any such systematic exploration. Very recently, the primary role of the peripheral chemoreceptors in the ventilatory responses to metabolic acid-base disturbances as conceived by Mitchell, et al. [27], has been questioned by Fencel, Miller, and Pappenheimer [28], who found changes in CSF (H^+) deemed sufficient to account for the behavior of ventilation. There also seems to be disagreement as to whether chemoreceptor denervation abolishes ventilatory responses to metabolic acid-base disturbances [29, 30]. Although some of this disagreement may be more apparent than real and dependent upon such factors as the severity and duration of the disturbance, presence or absence of anesthesia, species difference, etc., it is apparent that much more work is needed here to define the details of material transport and buffering mechanisms in the brain as well as the location of the central chemoreceptors.

Despite some obvious defects, the present model thus seems to provide a useful dynamic summary and synthesis of much of our present understanding of lung-blood-tissue gas transport, acid-base buffering, and what is generally called the "chemical control of pulmonary ventilation." Although many of its features can also be found in other recent models [5-9], the present version is perhaps somewhat more complete and general. It can serve as a convenient base for

studying sensitivity to parameter variations, for exploring modified control modes, and for gradual expansion to include aspects so far neglected. With this in mind, the digital simulation program has been made flexible enough to allow convenient modification and expansion.

That both modification and expansion will be necessary is abundantly clear: Our treatment of tissue buffering and material exchange across the blood-brain barrier is at best only a very crude first approximation. As noted above, detailed knowledge of these matters is both important and lacking. The model does not account for the hyperpnea of exercise, and although we could easily introduce a term proportional to O_2 consumption into our control function to accomplish this [31], the "physiological isomorphism" of such a term still seems to be obscure [32]. Moreover, attempting to account for exercise hyperpnea in this way would make it painfully obvious that the model includes no really general description of the control of cardiac output and regional blood flow. Since the respiratory and cardiovascular systems are really part of a single gas transport system, close coupling between their control mechanisms might be expected, and it would seem that a real understanding of either requires an understanding of both [33].

Coupling between various physiological systems treated as a collection of nonlinear oscillators has been considered by Iberall and Cardon [34], and spectral analyses of skin temperature [34] and ventilation [34, 35] time series obtained from normal resting men have been carried out in efforts to identify significant frequencies. Four major periods appear, which Iberall suggests may be associated with a metabolic rate cycle (1-2 minutes), a vasomotor cycle (5-10 minutes), a tissue gas storage cycle (20-40 minutes), and a tissue heat storage cycle (2 hours). Our model includes tissue gas storages

with relatively long time constants, short lags in the response of cardiac output and brain blood flow, and a number of short blood transport delays. The latter are primarily responsible for the short period oscillations (about 0.5 minute) observed in the model during the early stages of recovery from hypoxia or CO₂ inhalation. It is certainly possible that tissue metabolic rate is normally periodic at rest as suggested by Iberall, and it is well known that capillary blood flow, at least in some vascular beds, is intermittent [36], but we have not yet included these possibilities in our model.

Finally, although the "chemorespiratory" physiologist interested primarily in the physics, chemistry, and control of lung-blood-tissue gas transport, buffering and exchange might be reasonably happy with this model, the "neurorespiratory" physiologist interested primarily in the intimate central neural mechanism of respiratory cycle generation will not be happy with it at all. Certainly there are no illuminating insights here for him! Perhaps this points out the most fruitful direction for further work both experimental and theoretical, providing we remember that "neural control" and "chemical control" are not mutually exclusive but are interrelated parts of a single mechanism.

Appendix A

SYMBOLS AND UNITS FOR EQUATIONS OF SYSTEM

A.1. EXPLANATION

A complete symbol has the general form, $A_{i,j}$, where A designates the class of variable (e.g., solubility coefficient, concentration, metabolic rate, etc.), i specifies the location (e.g., brain, blood at lung exit, etc.), and j identifies the chemical species (e.g., O_2 , CO_2 , H^+ , etc.). In certain cases, one or both subscripts are omitted (e.g., Q cardiac output; B barometric pressure).

A.2. TABLE OF SYMBOLS AND UNITS

Character	Subscripts		Definition	Units
	Location (i)	Species (j)		
a		gas	solubility coefficient for gas in blood	liter (STPD)/liter blood/atm, 37°C
	B	(gas)	for gas in brain	liter (STPD)/liter brain/atm, 37°C
	T	(gas)	for gas in tissue	liters (STPD)/liter tissue/atm, 37°C
	CSF	(gas)	for gas in cerebrospinal fluid	liters (STPD)/liter CSF/atm, 37°C
			barometric pressure	mm Hg
B ($BHCO_3$)			standard bicarbonate content	
	b		of blood	liters CO_2 (STPD)/liter blood, 37°C
	B		of brain	liters CO_2 (STPD)/liter brain, 37°C
	T		of tissue	liters CO_2 (STPD)/liter tissue, 37°C

Char- acter	Subscripts		Definition	Units
	Loca- tion (i)	Species (j)		
C	CSF		of cerebrospinal fluid	liters CO ₂ (STPD)/ liter CSF, 37°C
			concentration	
		(gas)	of gas	liters (STPD)
		(HbO ₂)	of oxyhemoglobin	liters O ₂ (STPD)
		(H ⁺)	of hydrogen ion	nanomoles
	a		in blood at lung exit	liter blood ⁻¹
	aB		in blood at brain entrance	liter blood ⁻¹
	aT		in blood at tissue entrance	liter blood ⁻¹
	B		in brain	liter brain ⁻¹
	CSF		in cerebrospinal fluid	liter CSF ⁻¹
	T		in tissue	liter tissue ⁻¹
	v		in blood at lung entrance	liter blood ⁻¹
	ao		in blood at carotid body	liter blood ⁻¹
	vB		in blood at brain exit	liter blood ⁻¹
	vT		in blood at tissue exit	liter blood ⁻¹
D		gas	diffusion coefficient for gas across "blood-brain" barrier	liters (STPD)/min/ mm Hg
F			volumetric fraction	dimensionless
		(gas)	of gas	
	A		in dry alveolar gas	
	E		in dry expired gas	
(Hb)	I		in dry inspired gas	
			blood oxygen capacity	liters (STPD)/liter blood
k			conversion factor	atm/mm Hg
K'			dissociation constant for carbonic acid	nanomoles/liter
			volume	liters
K	B		of brain	
	CSF		of cerebrospinal fluid	

Char- acter	Subscripts		Definition	Units
	Loca- tion (i)	Species (j)		
MR	T		of tissue	
	L		of alveoli	
		(CO ₂)	metabolic rate of carbon dioxide production	liters (STPD)/min
		(O ₂)	of oxygen consumption	
P	B		by brain	
	T		by tissue	
			tension or partial pressure	mm Hg
		(gas)	of gas	
pH	A		in alveoli	
	a		in blood at lung exit	
	B		in brain	
	CSF		in cerebrospinal fluid	
Q	I		in inspired air	
			pH	
	a		of blood at lung exit	
	vB		of blood at brain exit	
ΔQ	vT		of blood at tissue exit	
	CSF		of cerebrospinal fluid	
			blood flow	liters/min
			cardiac output	
r	B		cerebral	
	N		normal (resting)	
			change in blood flow	liters/min
			cardiac output	
t	B		cerebral	
		(CO ₂)	due to carbon dioxide	
		(O ₂)	due to oxygen	
			time constant	minutes
	1		for cardiac output response	
	2		for cerebral blood flow response	
			time	minutes

Char- acter	Subscripts		Definition	Units
	Loca- tion (i)	Species (j)		
T	aB	(1)	blood transport delay from lung to brain	minutes
	aT		from lung to tissue	
	vB		from brain to lung	
	vT		from tissue to lung	
	ao		from lung to carotid body	
V	i		in appropriate segment of total path	liters (BTPS)/min
	E		gas flow rate (alveolar) expiratory	
	I		inspiratory (i.e., ventilation)	

Appendix B

"NORMAL" PARAMETER VALUES*

α_{CO_2}	=	0.510**	k	=	0.00132
α_{O_2}	=	0.0240	K'	=	795
α_{N_2}	=	0.0130	K _B	=	1.000
B	=	760	K _{CSF}	=	0.100
(BHCO ₃) _b	=	0.5470	K _T	=	39.00
(BHCO ₃) _B	=	0.5850***	K _L	=	3.00
(BHCO ₃) _T	=	0.5850***	MR _B (CO ₂)	=	0.050
(BHCO ₃) _{CSF}	=	0.5850	MR _B (O ₂)	=	0.050
D _{CO₂}	=	81.99 × 10 ⁻⁷	MR _T (CO ₂)	=	0.182
D _{O₂}	=	4.361 × 10 ⁻⁷	MR _T (O ₂)	=	0.215
D _{N₂}	=	2.524 × 10 ⁻⁷	Q _N	=	6.000
F _I (CO ₂)	=	0.0000	Q _{BN}	=	0.750
F _I (O ₂)	=	0.2100	r ₁	=	0.100
F _I (N ₂)	=	0.7900	r ₂	=	0.100
(Hb)	=	0.2000			

*Some parameter values were assigned in writing the system equations, e.g., buffer slope and Haldane effect [Eq. (3.1)], vascular segment volumes [Eqs. (8.10)–(8.14)], controller gains [Eqs. (9.1)–(9.4)], etc.

**Although equations distinguish between α values for blood, brain, tissue, and CSF, they were all set equal in this initial exploration.

***These values now appear to be too high [37], and will require revision in future explorations.

Appendix C

SAMPLE OF COMPUTER TABULAR PRINT-OUT

TIME 0.0500	CO2	O2	N2	D E R I V A T I V E S	PCO2	PO2	ALV RQ PN2	0.8812 RQ (H+)	DIFF PH	-0.0057 HBO2
ALVEOLAR	0.0557	0.1388	0.8055	-0.0003	-0.1687	0.1690	39.7114	98.9683	574.3203	
ARTERIAL	0.5749	0.1999	0.0099				39.7114	98.9683	574.3203	38.7691
BRAIN	0.6503	0.0012	0.0097	0.0000	0.0000	-0.0000	50.2072	36.7730	568.1752	43.5849
TISSUE	0.6245	0.0015	0.0097	0.0000	0.0000	0.0000	44.6013	46.1382	567.6018	40.1557
CSF				0.0081	-0.0007	0.0250	50.1404	36.7779	568.0054	45.8715
V BRAIN	0.6413	0.1343	0.0097				50.2072	36.7730	568.1752	44.2284
V TISSUE	0.6091	0.1598	0.0097				44.6013	46.1382	567.6018	41.2193
TRANSPORT TIMES--AB			VB	VT	AT	AO **	VI	VE	Q	QB
	0.1970	0.1113	0.5913	0.3170	0.1877	5.0474	5.0091	6.0055	0.7505	0.2229
									0.0537	DERIVATIVES

46-

TIME 0.0600	CO2	O2	N2	D E R I V A T I V E S	PCO2	PO2	ALV RQ PN2	0.8850 RQ (H+)	DIFF PH	-0.0095 HBO2
ALVEOLAR	0.0557	0.1371	0.8072	-0.0004	-0.1695	0.1658	39.7090	97.7770	575.5140	
ARTERIAL	0.5750	0.1997	0.0099				39.7090	97.7770	575.5140	38.7642
BRAIN	0.6503	0.0012	0.0097	-0.0000	0.0001	-0.0000	50.2072	36.7840	568.1739	43.5849
TISSUE	0.6245	0.0015	0.0097	0.0000	0.0000	0.0000	44.6014	46.1476	567.6023	40.1557
CSF				0.0081	0.0008	0.0247	50.1404	36.7779	568.0057	45.8716
V BRAIN	0.6413	0.1343	0.0097				50.2072	36.7840	568.1739	44.2290
V TISSUE	0.6091	0.1598	0.0097				44.6014	46.1476	567.6023	41.2197
TRANSPORT TIMES--AB			VB	VT	AT	AC **	VI	VE	Q	QB
	0.1970	0.1113	0.5913	0.3170	0.1876	5.0475	5.0104	6.0079	0.7512	0.2524
									0.0859	DERIVATIVES

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