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# A combined model of respiratory drive and acid-base status

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**Abstract:** Control of respiration has previously been investigated, and models have been built to explain different aspects of respiration. Models of respiratory drive have been limited in terms of the description of acid-base relations in blood. The purpose of this study is to explore the consequences of adding an acid-base model of the whole body to a respiratory drive model. We built a model that combines a compartment model of acid-base relations of the whole body, and a model of respiratory drive. We explored which effect the buffering capacity of full blood compared to only plasma has on respiratory drive, and we investigated which consequences the addition of body compartments has on the dynamic behavior of the model. The addition of a whole blood model results in only small differences in respiratory drive over the physiological range. Adding compartment volumes for blood, tissue and interstitial fluid results in a changed dynamic behavior when the system is exposed to a typical physiological change. In conclusion, it is not necessary to include the buffering capacity of whole blood compared to plasma in a model of this kind. A compartment model seems to give a better understanding of the dynamics of change in respiration.

*Keywords:* Physiological model, Circulatory and respiratory systems

## 1. INTRODUCTION

It is widely accepted that the respiratory drive to breath is constituted of a central drive, a peripheral drive and a drive dependent on state of the patient. This is known as the "Oxford model". Duffin (2005)
The central drive originates from the central chemoreceptors in the medulla oblongata, and is triggered by hydrogen ion concentration ($[H^+]$). It is not yet fully understood if the central chemoreceptors react to the intra- or extracellular environment, see Nattie (1999), but it is assumed that the $[H^+]$ in medullary cerebrospinal fluid (CSF) is a good estimate of the chemoreceptor $[H^+]$. Duffin (2005)
The peripheral drive originates from the peripheral chemoreceptors in the aortic and carotid bodies which are sensitive to $[H^+]$ and modulated by the partial pressure of oxygen ($PO_2$) in arterial blood. Duffin (2005)

A model of respiratory drive as the sum of central, peripheral and wakefulness drive has been presented by Duffin (2005). In this model the central drive is dependent on a threshold to breath and chemoreceptor sensitivity to $[H^+]$. Likewise, the peripheral drive has a threshold and a sensitivity to $[H^+]$ that is dependent on $PO_2$. Duffin's model is capable of simulating changes in minute ventilation ($\dot{V}$). This model of changes in $\dot{V}$ can be extended by the use of empirical equations obtained from rebreathing experiments, which divide $\dot{V}$ into the respective breathing frequency (f) and tidal volume ($V_T$), Duffin et al. (2000).

The combined models of Duffin represent the state of the art in terms of models of chemoreceptor control of respiration. Despite this, it can be argued that the representation of acid-base chemistry included in these models is lacking, being based only on models of plasma chemistry and ignoring both the erythrocyte fraction of blood and the acid-base chemistry of other body stores including interstitial fluid and tissues, Farhi and Rahn (1960).

Recently, models have been formulated of both the acid-base chemistry of whole blood, Rees and Andreassen (2005), and a dynamic model of whole body $O_2$- and $CO_2$-transport including the acid-base chemistry of interstitial fluid and tissue, Andreassen and Rees (2005). The model does not however include a representation of respiratory drive.

The purpose of this study is to explore the consequences of greater complexity to the models of respiratory drive formulated by Duffin. These models are extended to include the models of acid base chemistry formulated by

Andreassen and Rees (2005). In doing so this article explores the consequences of including acid-base chemistry and compartmental stores representing the erythrocyte fraction of blood, interstitial fluid and tissues.

## 2. METHOD

### *2.1 Model formulations*

A mathematical model was built combining the models of chemoreceptor control of ventilation (Duffin et al. (2000), Duffin (2005)) with those of acid-base chemistry (Andreassen and Rees (2005), Rees and Andreassen (2005)) using MatLab R2008a. This model contains four model elements: acid-base relations, cerebrospinal fluid (CSF), respiratory drive, and a calculation of $V_T$ and f, as illustrated in figure 1. These are now described in turn.

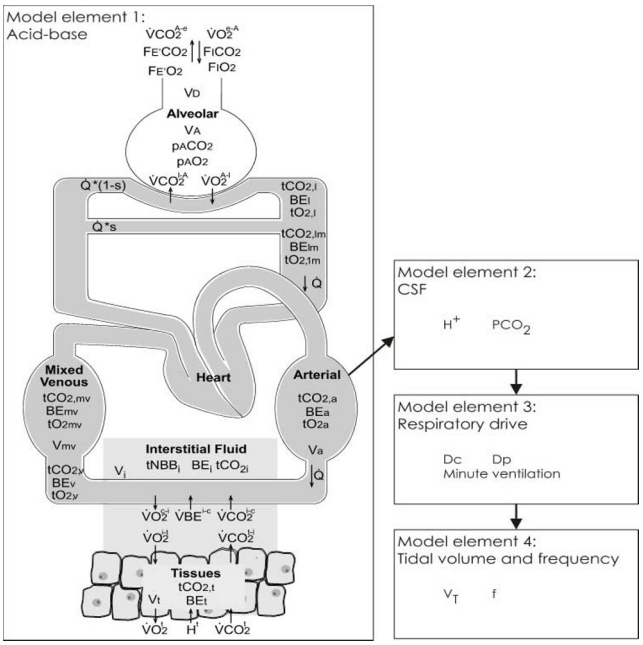


Fig. 1. An overview of the four elements of the combined model of respiratory drive and acid-base relations in the whole body.

*Model element 1: Acid-base* The acid-base model element consists of five compartments: lung alveoli, arterial blood, venous blood, interstitial fluid, and tissue cells as illustrated in figure 1, Andreassen and Rees (2005). Each of the blood compartments is represented as a set of chemical reactions describing transport of $CO_2$ and buffering of $H^+$ in the plasma, and the competitive binding of $H^+$, $O_2$ and $CO_2$ to haemoglobin in the red blood cells. The model is originally designed to calculate the effects of metabolic and respiratory perturbations, and both bicarbonate and non-bicarbonate buffers are included. The model does not include the compensation of the kidneys as this takes hours or days.
State variables for each compartment enables addition or subtraction of mass and calculation of all variables describing the compartment. The state variables for the lung alveoli are end-tidal fractions of $CO_2$ and $O_2$ ($FetCO_2$ and $FetO_2$). For arterial and venous blood they are total $CO_2$ concentration ($tCO_2$), base excess (BE), and total oxygen concentration ($tO_2$). The concentration of 2,3-diphosphoglycerate in blood (DPG), the oxygen carrying capacity of haemoglobin per liter blood (Hb), and the concentration of non-bicarbonate buffer in plasma (tNBBp) are assumed constant and equal in all blood compartments (DPG = 5 mmol/L, Hb = 9.3 mmol/L, tNBBp = 23.5 meq/L).
The transport of substrate between the compartments of the model is described by a number of equations, and the changes in state variables caused by the flow of substrates are described by differential equations.

*Model element 2: CSF* The model of Andreassen and Rees (2005) is extended as illustrated in figure 1 to include a compartment describing CSF. As for Duffin this is represented as a compartment without volume, and assumed to have instantaneous equilibration with arterial $PCO_2$. Duffin (2005) assumes that $PCO_2$ of CSF is approximately 6 Torr above arterial $PCO_2$, but since other studies based on the physiology of the medulla oblongata and it's surroundings suggest that $PCO_2$ of medullary CSF is only 2-3 Torr above arterial $PCO_2$, see Crawford and Severinghaus (1978), it is decided to assume that arterial and CSF $PCO_2$ are equal. CSF $H^+$ concentration is calculated as by Duffin (2005) using a model of the buffer reactions in CSF. This is represented as the model of Stewart for plasma as used by Duffin (2005), but modified to cater for the greatly reduced protein concentration in CSF in relation to plasma, as follows.

The modified Stewart model consists of six equations, and (1) to (4) are mass action equations:

$$[H^+] \cdot [OH^-] = K'_W \tag{1}$$

$$[H^+] \cdot [HCO_3^-] = K_C \cdot PCO_2 \tag{2}$$

$$[H^+] \cdot [CO_3^{2-}] = K_3 \cdot [HCO_3^-] \tag{3}$$

$$[P_i] = P_{i,Tot} \cdot \left\{ 2 - \frac{[H^+]}{K_2 + [H^+]} \right\} \tag{4}$$

where $K'_W$ is the ion product for water ($2.39 \cdot 10^{-14}$ $mol^2/L^2$), $K_C$ is the combination of equilibrium and solubility constants ($2.45 \cdot 10^{-11}$ $mol^2/L^2$/Torr), $K_3$ is the dissociation constant for carbonate ($1.16 \cdot 10^{-10}$ mol/L), $P_{i,Tot}$ is the concentration of phosphate in CSF ($0.61 \cdot 10^{-3}$ mol/L), and $K_2$ is the phosphoric acid dissociation constant ($2.19 \cdot 10^{-7}$ mol/L)

Equation (5) of the modified Stewart model describes serum albumin dissociation from the concentration of net charges on albumin ($[A^-]$), the fixed negative charge concentration with 21 fixed negative charges per mole of albumin ($[A^-_{Fixed}]$) which can be calculated as shown below, $[H^+]$, the concentration of histidine residues with 16 residues per mole of albumin ($[A_{H,Tot}]$) which can be calculated as shown below, and the histidine dissociation constant ($K_H$) which is $1.77 \cdot 10^{-7}$ mol/L. The concentration of albumin in CSF ([Alb]) is 1.25 g/dL, and 66,500 is the molecular weight of albumin.

$$\begin{aligned} [A^-] &= [A^-_{Fixed}] - \frac{[H^+] \cdot [A_{H,Tot}]}{K_H + [H^+]} \\ [A^-_{Fixed}] &= 21 \cdot [Alb] \cdot \frac{10}{66,500} \\ [A_{H,Tot}] &= 16 \cdot [Alb] \cdot \frac{10}{66,500} \end{aligned} \tag{5}$$