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## Analysis of Mathematical Models of the Human Lung

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Thesis

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University.

by

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Master of Science

Director: Angela M Reynolds, Assistant Professor  
Department of Mathematics and Applied Mathematics

Virginia Commonwealth University  
Richmond, Virginia  
December 2013

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## **Abstract**

### **THESIS**

By Racheal L Cooper, Master of Science.

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Director: Angela M Reynolds, Assistant Professor, Department of Mathematics and Applied Mathematics.

The processes of lung ventilation and perfusion, diffusion, and gas transport make up the system of breathing and tissue oxygenation. Here, we present several mathematical formulations of the essential processes that contribute to breathing. These models aid in our understanding and analysis of this complex system and can be used to form treatments for patients on ventilators. With the right analysis and treatment options, patients can be helped and money can be saved. We conclude with the formulation of a mathematical model for the exchange of gasses in the body based on basic reaction kinetics.

## **Chapter One: Biological Background of Gas Exchange**

Breathing is an essential bodily process that ensures the survival of humans. The organ system responsible for this process is the respiratory system, shown in Figure (1.1). To begin the process, air enters through the oral cavity or nasal vestibule and moves through the nasal cavity due to compression of the diaphragm. First, after entering the nose, the air is warmed and large particulates are filtered from the air via nose hairs. Then, the air moves into the pharynx and through the trachea. Afterwards, it enters the bronchi and moves down into an alveolus where it diffuses into the blood in the capillary beds. Here, gasses are exchanged from the air of the alveolus to the blood and vice versus. Oxygen diffuses into the blood, attaching to the hemoglobin present in red blood cells. Carbon dioxide diffuses out of the blood, where it is dissolved as bicarbonate, and back into the air of the alveolus where it is expelled by the depression of the diaphragm and back out through the nose.

Due to the large surface area of the epithelial cells of the alveoli, which is approximated to be about 70-85 square meters of surface area per unit time for gas exchange over about 300 million alveoli in the human lung, making the lung an effective organ for oxygen distribution and carbon dioxide removal. Around 70 to 140 mL of blood are able to come in contact with lung tissue to pick up oxygen and provide oxygen to all cells in the body [3].

In this work, we will discuss a mathematical model for the processes involved in breathing: diffusion, gas exchange and transport, and the process of ventilation. Then we will introduce a specific model of mechanical ventilation and develop a model of gas transport that account for the competitive binding of the important molecules to hemoglobin.

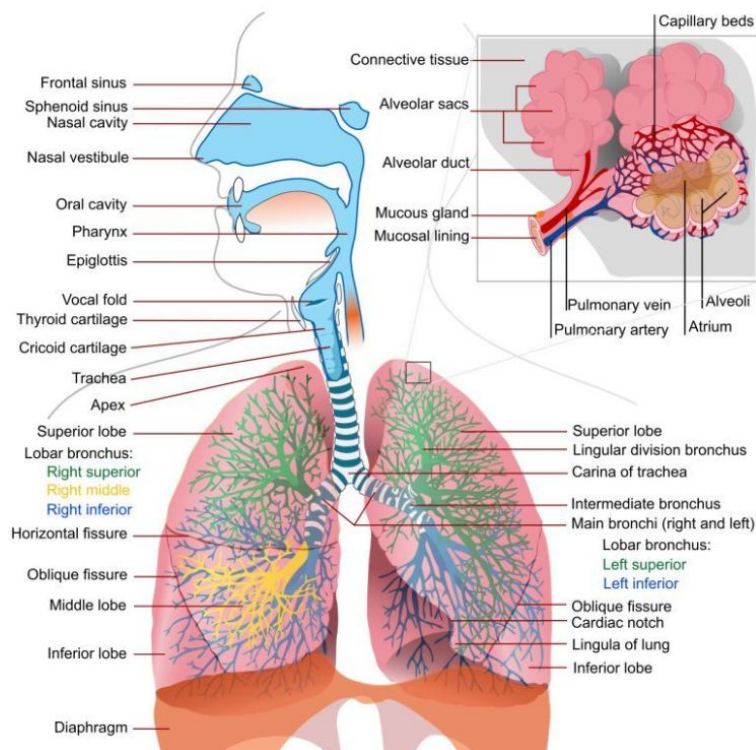


Figure 1.1: This diagram shows the important parts of the Respiratory System that are involved in oxygenating the blood. Also, a single alveolus is highlighted and the specific parts of the lung that are involved directly in exchanging gasses with the blood are shown [7].

## **Chapter Two: Mathematical Background of Gas Exchange**

We will examine mathematical models of the process involved in breathing. Mathematical models of physiological process are useful to help researchers understand the underlying dynamics of the process and analyze different outcomes of such processes. It is also useful to have a mathematical model that can give information about the system in cases where diseases affecting these processes are being studied. If a model can be used in place of a human patient to help understand how a disease progresses, people can be helped and money can be saved.

Specifically, when a patient has lung problems, intervention with a ventilator may be required in order to keep their oxygen saturation at appropriate levels. However, there is evidence that this forcing of air into the lungs can cause damage, trigger the inflammatory response, and lead to chronic medical problems for the patient in the future. Understanding lung dynamics will allow better protocols for mechanical ventilation of hospital patients.

In this chapter, we will analyze models presented in [3] for diffusion, oxygen and carbon dioxide uptake by the blood, and ventilation and perfusion.

### **2.1 Diffusion**

The process of diffusion is the main facilitator for the transfer of oxygen to the blood and carbon dioxide out of the blood and back into the alveoli air sacs. This process relies on concentration differences between where the essential gasses are and where they need to be.

Specifically, the process of diffusion works to move things from the side of some type of barrier with a higher concentration, to the other side where the concentration is lower.

To model diffusion mathematically, we consider the partial pressure of the gas in question, modeled using the ideal gas law as

$$PV = nkT \quad (2.1)$$

where  $P$  is the pressure of the gas being modeled,  $V$  is the volume,  $n$  is the number of gas molecules present,  $k$  is the Boltzmann's constant, and  $T$  is the temperature of the gas in Kelvin. However, this can be simplified using the equation  $c = n/V$  for the concentration of an ideal gas. Also, if we divide and multiply the equation through by Avogadro's number,  $N_A$  in order to express concentration in a more biologically relevant unit, moles per volume, we obtain

$$P = CRT \quad (2.2)$$

where  $C = c/N_A$  and  $R = kN_A$  (the universal gas constant).

In addition to these equations, we can further model the partial pressure of gasses using pressure  $P_i$  for gas  $i$  and constant  $x_i$  that represents the mole fraction of gas  $i$  in the mixture by

$$P_i = x_i P \quad (2.3)$$

where  $P$  is the pressure of the mixture. Therefore, to find the total pressure of the mix, we simply sum the partial pressures of each gas in the mixture.

In regards to diffusion, when each gas comes into contact with a liquid (such as the blood in the capillary beds in the lungs), steady state is reached and the partial pressure,  $P_i$



can be related to concentration of gas  $i$ ,  $c_i$ , as stated by

$$c_i = \sigma_i P_i \quad (2.4)$$

where  $\sigma_i$  is the solubility of gas  $i$ . If we divide through by  $\sigma_i$  and consider  $U_i$  to be the steady state concentration, we obtain a ratio that relates the partial pressure of gas  $s$  to the concentration at steady state of gas  $i$ . Specifically,  $P_i = U_i / \sigma_i$ .

Therefore, when air with partial pressure  $P_g$  of a gas  $g$  (such as oxygen or carbon dioxide) comes into contact with a liquid (such as the blood) that also contains gas  $g$  dissolved as some partial pressure  $P'_g$ , if  $P_g > P'_g$ , the gas diffuses into the liquid, and if  $P_g < P'_g$ , the gas diffuses out to the air. In other words, if the pressure in the liquid relates to the pressure in the air by  $\frac{U'_g}{\sigma_g} \neq P_g$ , the gas molecules will flow in the direction that achieves  $P_g = \frac{U'_g}{\sigma_g}$ .

A simple model of diffusion assumes that flow is linearly proportional to the difference in partial pressure across the membrane separating the gas and liquid, and it gives rise to

$$q = D_s \left( P_g - \frac{U_i}{\sigma_i} \right) \quad (2.5)$$

where  $q$  is the flux per unit area of gas,  $D_s$  is the surface diffusion constant, and all other parameters are defined as before. It is important to notice that the sign of the flux is positive when gas  $g$  is flowing into the dissolved state and negative otherwise. For example, the sign of  $q$  would be positive when oxygen is dissolving into the blood to be dispersed throughout the body and negative when carbon dioxide is being removed from the blood to be expelled from the body through breathing out. This model of diffusion will be added into another model that accounts for blood flow and the change in concentrations of oxygen and carbon dioxide in the blood.

## 2.2 Capillary-Alveolar Transport

Capillaries located close to the alveoli of the lung carry the blood close to the airspace so that oxygen can be diffused in and saturate hemoglobin and carbon dioxide can diffuse out. We can model this exchange mathematically. To do so, consider a cross-section of a capillary in the lung that has initial point  $x = 0$  and terminal point  $x = L$  that is positioned next to an alveolus. The capillary has cross-sectional area equal to the constant  $A$  and a perimeter  $p$ , and blood flows through the capillary from the initial to the terminal point, outside of which no diffusion is occurring. The value of the integral

$$A \int_0^L U(x, t) dx \quad (2.6)$$

represents the total amount of dissolved gas in the capillary at a given time, where  $U$  is the concentration of some gas dissolved in the blood and is distributed uniformly across the cross-section of the capillary. We also assume that the partial pressure of the gas,  $P_g$ , in the alveolar space is constant.

We know from physics that mass is conserved, so the value of

$$\frac{d}{dt} \left( A \int_0^L U(x, t) dx \right) = Av(0)U(0, t) + p \int_0^L q(x, t) dt - Av(L)U(L, t), \quad (2.7)$$

where  $v(x)$  is the velocity of the fluid at position  $x$  in the capillary and  $q$ , is the flux of gas along the capillary assuming that diffusion in the direction along the length  $L$  contributes less to overall diffusion than the diffusion that happens into and out of the capillary wall. The first term,  $Av(0)U(0, t)$  represents the movement into the capillary at the initial position  $x = 0$  at velocity  $v(0)$  and the third term,  $-Av(L)U(L, t)$ , represents movement out of the capillary at the end position  $x = L$  at velocity  $v(L)$ . The second term,  $p \int_0^L q(x, t) dt$ , represents the change in flux for along the perimeter of the capillary of length  $L$ .

Differentiating with respect to  $x$  gives the conservation law

$$U_t + (vU)_x = \frac{pq}{A}. \quad (2.8)$$

Assuming that flow is constant along the capillary and using the equation for flux obtained in the previous section, we have

$$\begin{aligned} U_t + vU_x &= \frac{p}{A} \left( D_s \left( P_g - \frac{U}{\sigma} \right) \right) \\ &= \frac{pD_s P_g}{A} - \frac{pD_s U}{A\sigma} \\ &= D_m P_g \sigma - D_m U \\ &= D_m (P_g \sigma - U) \end{aligned}$$

where  $D_m = \xi \left( \frac{D_s}{\sigma} \right)$  and  $\xi$  is the ratio of surface  $p$  to volume  $A$ . Notice that the units on the parameter  $D_m$  is the membrane exchange rate, the inverse of a time constant.

If we consider the system independent of time, we can discuss the steady state of the first-order linear differential equation

$$v \frac{dU}{dx} = D_m (P_g \sigma - U). \quad (2.9)$$

Biologically, we expect the rate of change of the concentration of dissolved gas in the blood at steady state to be inversely proportional to the fluid velocity. If we fix the concentration of the dissolved gas at the initial point of the capillary ( $x = 0$ ) to the constant  $U_0$ , we can solve equation (2.9) and obtain a decaying exponential given by

$$U(x) = \sigma P_g + (U_0 - \sigma P_g) e^{-\frac{D_m x}{v}}.$$

The total flux along the capillary is the sum of all individual flux  $q$  within the capillary of length  $L$  with parameter  $p$ . Mathematically, that is  $Q = p \int_0^L q dx$ . When in steady state, the total amount of dissolved gas is not changing so we can assume that equation (2.8) is equal to zero and thus,

$$Q = A(v(L)U(L,t) - v(0)U(0,t)) = vA(U(L) - U_0) \quad (2.10)$$

since we are in steady state and we assume a constant velocity. Using the solution to the linear equation, we obtain

$$Q = vA(U(L) - U_0) = vA \left( (\sigma P_g + (U_0 - \sigma P_g)e^{-\frac{D_m L}{v}}) - U_0 \right) \quad (2.11)$$

$$= vA\sigma(P_g - P_0)(1 - e^{-\frac{D_m L}{v}}) \quad (2.12)$$

where the partial pressure  $P_0$  at the left boundary condition  $x = 0$  is related to the initial gas concentration  $U_0$  by the ratio  $\sigma = U_0/P_0$ , as seen in section 2.1.1.

Notice that, as the total length of the capillary goes to infinity, the total flux  $Q$  approaches  $vA\sigma(P_g - P_0)$ . We can conclude from that that no matter how long the capillary is, the concentration of dissolved gas always approaches a constant.

In addition, the left of Figure (2.1) shows data obtained on the diffusion of important gasses as it flows from the arterial end to the venous end of a capillary that lies adjacent to an alveolus. As expected, the partial pressure of carbon dioxide decreases as blood is brought across the alveolus. The partial pressure of carbon dioxide in the alveolus is lower than the partial pressure in the blood, causing the movement into the alveolus. The partial pressure of the gas in the blood then decreases until it reaches approximately 40 mm Hg.

Similarly for the right of Figure (2.1), which shows the partial pressure of oxygen in the blood versus the partial pressure in the alveolus. When entering the lung, there is very

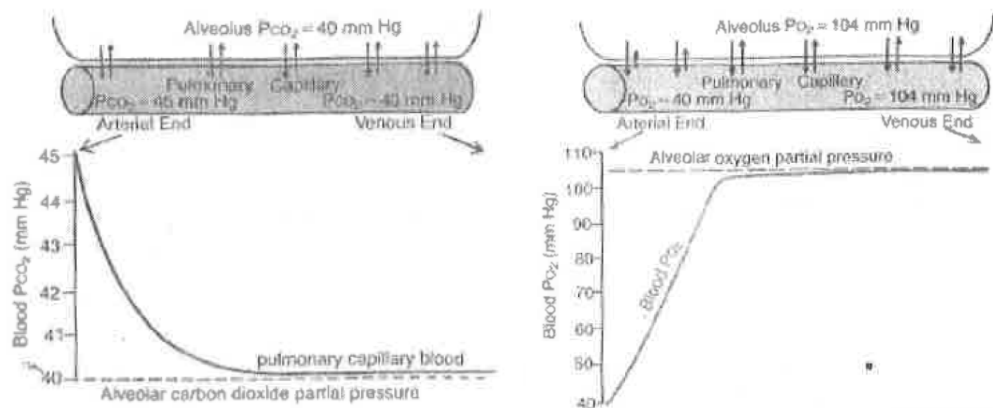


Figure 2.1: Gas exchange across the barriers in the lungs is shown for carbon dioxide (left) and oxygen (right). [3]

little oxygen in the blood and therefore the partial pressure is low. In the air of the alveolus, the partial pressure is higher, driving the oxygen into the capillary and increasing its partial pressure of oxygen in the blood. The curve shown indicates that this partial pressure increase fairly linearly until it reaches approximately 104 mm Hg, approximately the partial pressure of oxygen in the air of the alveolus. A model of these dynamics after discussing the specifics of gas exchange, which are ignored in the previously discussed model [4].

### 2.3 Removal and Uptake of Gasses

Blood moves from the arteries the the veins through the lungs, as discussed in the previous section. Here we will analyze the specifics of oxygen is dissolved into the blood from the air of an alveolus to be distributed though out the body and how carbon dioxide is removed from the blood to be expelled from the body. Not only does the structure of the alveoli and the location of the capillaries ensure the proper movement of gasses, the structure of the blood also play an important part in this process. The hemoglobin present in the red blood cells of vertebrates is the essential component that allows for this exchange. Figure (2.2)

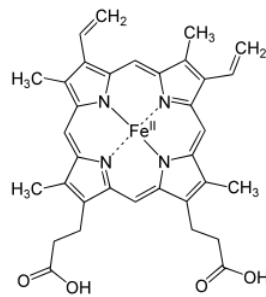


Figure 2.2: The molecular structure of unbound hemoglobin [3].

shows the structure of unbound hemoglobin that is present in the blood and Figure (2.3) shows a the structure of hemoglobin bound to  $O_2$  and  $CO_2$ .

Oxygen is bound to hemoglobin (Hb) molecules, where the reaction is represented by



where the forward and backward reactions happen at rates  $k_1$  and  $k_{-1}$ , respectively. The structure of hemoglobin is given in Figure (2.2) where there are four globin polypeptide chains and four heme groups that bind oxygen. There is a ferrous ion in the interior of each heme that can bind one oxygen molecule, and therefore each Hb can carry 4 oxygen molecules. This is indicated in the previous reaction. The structure of Hb bound to oxygen, as shown in Figure 2.3, is known as oxyhemoglobin.

The partial pressure of oxygen in the blood has been experimentally determined for various hemoglobin saturation levels, as shown in Figure (2.4). We see that in the pulmonary capillaries of the lung, hemoglobin is close to 100% saturated with partial pressure around 100mmHg. However, the percentage saturation of hemoglobin decreases as the red blood cells leave the lungs, due to the fact that oxygen is removed to satisfy the oxygen requirement of cells in the body. The average partial pressure of the resting system is 40mmHg where hemoglobin is saturated at around 75%. When the partial pressure of oxygen in the tissue

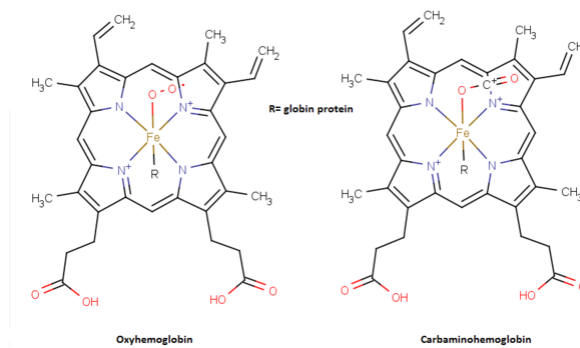
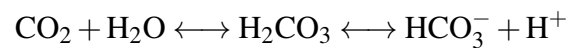


Figure 2.3: The molecular structure of hemoglobin bound to oxygen (left) and carbon dioxide (right) [3].

get close to or lower than this pressure, oxygen will move into the cells.

The binding and transport of carbon dioxide in the blood is more complicated. Carbon dioxide dissolves in the blood by being converted to bicarbonate via the reaction



where the first forward and backward reactions happen at rates  $k_2$  and  $k_{-2}$ , respectively, and the second happens at rates  $k_3$  and  $k_{-3}$ . For our purposes, the intermediate molecule  $\text{H}_2\text{CO}_3$  is ignored since the reaction  $\text{H}_2\text{CO}_3 \longleftrightarrow \text{HCO}_3^- + \text{H}^+$  is fast and can be ignored in the model we will discuss

Levels of  $\text{CO}_2$  higher than  $\text{O}_2$  in the tissues of the body cause this reaction to shift to the right into the red blood cells. The process causes a chloride shift, as shown on the left of Figure (2.5). The diffusion down the charge gradient of the negatively charged  $\text{HCO}_3^-$  ions into the red blood cells cause the red blood cell to become more positive and requires something to balance out the charge in the blood.

The red blood cells then move back to the lungs, carrying the carbon dioxide that is to be expelled from the body causing a reverse chloride shift, as seen on the right side of Figure

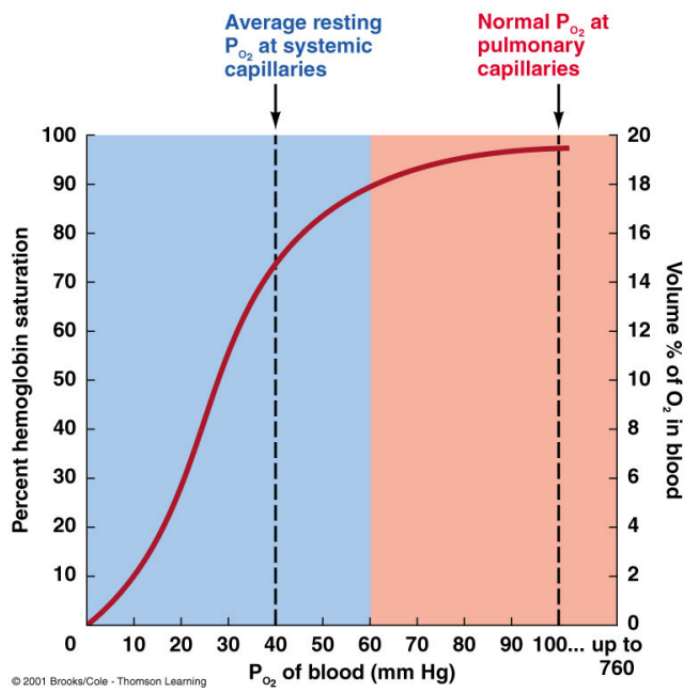


Figure 2.4: This figure shows saturation curve of hemoglobin bound to oxygen as it passes from the body to the lungs [6].

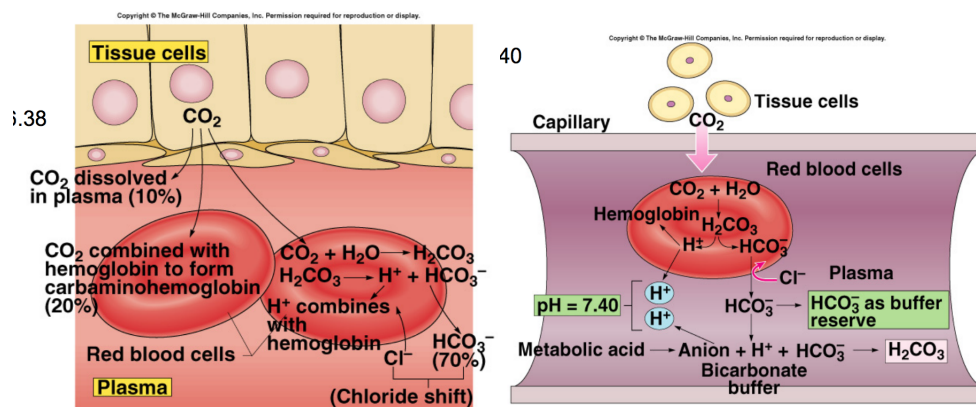


Figure 2.5: This figure shows a schematic of carbon dioxide dissolving into bicarbonate the blood to be transferred to the lungs via the cardiovascular system (left) and the process by which oxygen binds to hemoglobin to be transferred via the cardiovascular system to the body (right). (Citation)



(2.5). In the following sections, we discuss models of gas exchange for these two gasses and we will later incorporate them into a model of carbon dioxide exchange that accounts for its competitive binding with oxygen on hemoglobin.

### 2.3.1 Mathematical Model of Oxygen Exchange

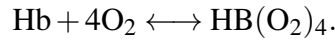
Mathematically modeling the exchange of these gasses requires conservation equations, as derived above, for each of the important gasses involved. First, we model oxygen exchange by considering the concentrations of oxygen ( $O_2$ ), hemoglobin (Hb), and oxygen bound hemoglobin ( $Hb(O_2)_4$ ) denoted  $[O_2]$ ,  $[Hb]$ , and  $[Hb(O_2)_4]$ , respectively. For simplicity, we set  $W = [O_2]$ ,  $Y = [Hb(O_2)_4]$ , and  $Z = [Hb]$ , and let  $D_{O_2}$  denote the oxygen exchange rate constant. The equations for this system are

$$v \frac{dW}{dx} = D_{O_2}(\sigma_{O_2} P_{O_2} - W) + 4k_{-1}Y - 4k_1ZW^4 \quad (2.14)$$

$$v \frac{dY}{dx} = k_1ZW^4 - k_{-1}Y \quad (2.15)$$

$$v \frac{dZ}{dx} = k_{-1}Y - k_1ZW^4. \quad (2.16)$$

These equations are based on the reaction equation stated previously



The first equation models the change in concentration of oxygen where the first term is derived in the previous section. The second term accounts for the increase in oxygen concentration at a rate of  $k_{-1}$  when the bond between hemoglobin and each of the four oxygen molecules breaks and the third term accounts for the decrease in oxygen concentration at a rate of  $k_1$  when four oxygen molecules bond to unbound hemoglobin. The second equation models the change in concentration of bound hemoglobin where the first term, the

additive inverse of the third term in equation (2.15), is contributing to the increase of bound hemoglobin concentration by a rate of  $k_1$ . The second term accounts for the decrease in bound hemoglobin concentration at a rate of  $k_{-1}$  due to it the bonds being broken. The third equation accounts for the change in concentration of unbound hemoglobin where the first term, the additive inverse of the second term in equation (2.16), contributes to the increase in unbound hemoglobin concentration at a rate of  $k_{-1}$  by the same dynamics. The second term accounts for the decrease in concentration of unbound hemoglobin at a rate of  $k_1$  due to its binding with four oxygen molecules.

Since we assume that no hemoglobin is introduced or removed from the system, we take  $Z + Y = Z_0$  and eliminate the last equation by adding equations (2.15) and (2.16), we obtain

$$v \frac{d}{dx}(W + 4Y) = D_{O_2}(\sigma_{O_2} P_{O_2} - W). \quad (2.17)$$

Physiologically, the uptake of oxygen by hemoglobin in the red bloods cells happens quickly compared to the other dynamics so we can assume a quasi-steady state on  $Y$  giving us

$$Y = \frac{Z_0 W^4}{K + W^4} \quad (2.18)$$

where  $K = \frac{k_{-2}}{k_2}$ .

We obtain a final equation for the change in concentration of oxygen and bound hemoglobin by substituting (2.19) into (2.18) and obtaining

$$v \frac{d}{dx}(W + \frac{4Z_0 W^4}{K + W^4}) = D_{O_2}(\sigma_{O_2} P_{O_2} - W).$$

The function  $f(W) = \frac{W^4}{K + W^4}$  is known as the oxygen saturation for hemoglobin and we

can simplify the equation into

$$v \frac{d}{dx} (W + 4Z_0 f(W)) = D_{O_2} (\sigma_{O_2} P_{O_2} - W). \quad (2.19)$$

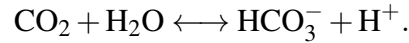
### 2.3.2 Mathematical Model of Carbon Dioxide Exchange

Finally, we model carbon dioxide exchange by considering the concentrations of carbon dioxide ( $CO_2$ ) and bicarbonate ( $HCO_3^-$ ), denoted  $[CO_2]$  and  $[HCO_3^-]$ , respectively. For simplicity, we set  $U = [CO_2]$  and  $V = [HCO_3^-]$ , we assume that the system is in steady state, and that diffusion within the capillaries is nonexistent. The equations for this system are

$$v \frac{dU}{dx} = D_{CO_2} (\sigma_{CO_2} P_{CO_2} - U) + k_{-2} MV - k_2 U \quad (2.20)$$

$$v \frac{dV}{dx} = k_2 U - k_{-2} MV \quad (2.21)$$

where  $D_{CO_2}$  is the exchange rate, similar to above and  $M = [H^+]$ . These equations are based on the reaction equation



The first equation models the change in concentration of carbon dioxide due to diffusion. The first term in (2.1) accounts for the influx of carbon dioxide when it's diffusing into the system and the removal when it's diffusing out. The second term accounts for the change in concentration of carbon dioxide when bicarbonate encounters a hydrogen ion. When this happens, it converts into carbon dioxide and water, as seen in the reaction schematic above, increasing the concentration of carbon dioxide in the system at a rate  $k_{-2}$ . The third term accounts for the decrease in carbon dioxide concentration at a rate of  $k_2$  due to its contact with water which occurs after the chloride shift happens. The second equation models

the change in concentration of bicarbonate where the first term, the additive inverse of the second term in equation (2.22), accounts for the increase in concentration of bicarbonate at a rate of  $k_2$  due to the same dynamics. The last term accounts for the decrease in bicarbonate concentration at a rate of  $k_{-2}$  when it encounter a hydrogen ion and binds.

Although this is a linear system with the explicit solution, we can gain insight into the dynamics by approximating the solution with a singular perturbation technique, which will prove useful in gaining insight into the previous model. First, we add the two equations together and obtain

$$v \frac{d}{dx}(U + V) = D_{\text{CO}_2}(\sigma_{\text{CO}_2} P_{\text{CO}_2} - U) \quad (2.22)$$

and then we assume state on the concentration of bicarbonate over the length of the capillary. This assumption leads to

$$V = \frac{k_2 U}{k_{-2} M}. \quad (2.23)$$

Now if we assume that  $M$ , the concentration of hydrogen ions is constant and substitute equation (2.25) into equation (2.24), we obtain

$$v \frac{d}{dx} \left( U + \frac{k_2}{k_{-2}} U \right) = D_{\text{CO}_2}(\sigma_{\text{CO}_2} P_{\text{CO}_2} - U)$$

or equivalently,

$$v \left( 1 + \frac{k_2}{k_{-2}} \right) \frac{dU}{dx} = D_{\text{CO}_2}(\sigma_{\text{CO}_2} P_{\text{CO}_2} - U) \quad (2.24)$$

Notice that this equation has the same form as equation (2.10), and therefore we can calculate the total flux  $Q$ . First we must impose the conditions  $U = U_0 = \sigma_{\text{CO}_2} P_0$  and

$V = V_0 = \frac{k_2}{k_{-2}}U_0$ . Therefore, the total flux is given as

$$Q = v\left(1 + \frac{k_2}{k_{-2}}\right)\sigma_{\text{CO}_2}(P_0 - P_{\text{CO}_2})\left(1 - e^{-\frac{D_{\text{CO}_2}L}{v(1+k_2/k_{-2})}}\right). \quad (2.25)$$

Notice that as the exponent of the exponential goes to infinity, the flux approaches the value  $v\left(1 + \frac{k_2}{k_{-2}}\right)\sigma_{\text{CO}_2}(P_0 - P_{\text{CO}_2})$  which is a factor of  $\left(1 + \frac{k_2}{k_{-2}}\right)$  larger than it was in equation (2.13). This tells us that this when this reaction occurs, the flow rate is increased by a factor of  $\left(1 + \frac{k_2}{k_{-2}}\right)$ .

## 2.4 Ventilation and Perfusion

The process of breathing is mediated by ventilation of the alveoli when air is inspired and perfusion of the capillaries with blood. A combination of these things controls the amount of gas in the lungs that gets dissolved into the blood [4]. The ventilation-perfusion ratio  $\dot{V}/Q$  is used to determine the gas content of the lungs and blood, where  $\dot{V}$  is the flow rate of air in the lungs and  $Q$  is the volume flow rate of blood into and out of the capillaries. Normally, around 500 mL of air is inspired per breath and only about 350 mL participates in gas exchange. Therefore, with about 15 breaths per minute, the volume flow rate of air into the lungs is around  $\dot{V} = 5250$  mL/minute. Cardiac output is about 70 mL of blood per beat, and therefore, with about 72 beats per minute, the approximate value of the flow rate of blood is around  $Q = 5000$  mL/min.

The flow of gas in the lung can be modeled by the equation

$$\dot{V}(c_i - c_a) \quad (2.26)$$

where  $c_i$  and  $c_a$  are the concentrations of gas in inspired and alveolar air, respectively.

Similarly, in the blood, the flow of gas into the blood can be modeled by

$$Q(c_L - c_0) \quad (2.27)$$

where  $c_0$  and  $c_L$  are capillary gas concentrations in and out of the blood, respectively.

Therefore, the ventilation-perfusion ratio is given by

$$\frac{\dot{V}}{Q} = \frac{c_L - c_0}{c_i - c_a} \quad (2.28)$$

In the next chapter, we discuss a detailed mathematical model of ventilation.

### A Mathematical Model of Lung Ventilation

Steimle et al., 2011 models ventilation of a healthy human lung by considering a lung divided into horizontal layers where the number of alveoli in each layer  $i$  is modeled by

$$N_{A,i} = \frac{N_A}{N_{Layers}}; \quad i = [1 : N_{Layers}] \quad (3.1)$$

where the total number of alveoli is denoted  $N_A$  and the total number of layers is denoted  $N_{Layers}$ . For each layer  $i$ , the smaller numbers represent the most non-dependent, or furthest to the front of the torso, layer of the lung. The left image of figure (3.1) shows a schematic of this.

Also, let  $P_{CW}$ ,  $P_{Hydro}$ ,  $P_{Mus}$ , and  $P_{EA}$  denote chest wall pressure, hydrostatic pressure, pressure exerted by the muscles during breathing, and extraalveolar pressure respectively. The pressure exerted by the muscles during breathing for each layer  $i$  of the lung can be

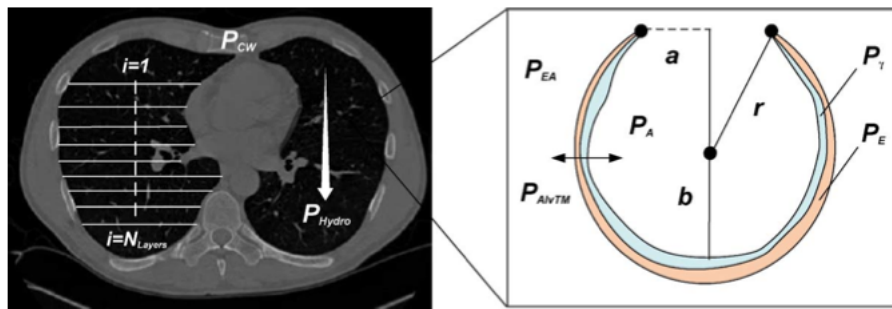


Figure 3.1: This figure shows a diagram of the layers of the lung, as discussed in this model (left) and a schematic of how parameters are defined in a single, spherical alveolus.

modeled by

$$P_{EA,i} = P_{CW} + P_{Hydro,i} = P_{Mus} \quad (3.2)$$

We can calculate  $P_{Hydro,i}$  by the sum

$$P_{Hydro,i} = \sum_{j=1}^{i-1} \rho_{Lung,j} \cdot g \cdot t_j \quad (3.3)$$

where  $\rho_{Lung,j}$  denotes the density of lung layer  $j$ ,  $g$  denotes the gravitational acceleration, and  $t_j$  denotes the thickness of lung layer  $j$ .

The difference between extraalveolar and alveolar pressure, which is called the alveolar transmural pressure, is denoted  $P_{AlvTM,i}$  and is modeled by

$$P_{AlvTM,i} = P_A - P_{EA,i}. \quad (3.4)$$

This can also be modeled in terms of pressure due to lung tissue elasticity, denoted  $P_{E,i}$ , and the pressure due to surface tension, denoted  $P_{\gamma,i}$ . The equation for this is given by

$$P_{AlvTM,i} = P_{E,i} + P_{\gamma,i} \quad (3.5)$$

Combining equations (3.2), (3.4), and (3.5) leads to the following model for alveolar pressure,  $P_A$

$$P_A = P_{\gamma,i} + P_{E,i} + P_{CW} + P_{Hydro,i} \quad (3.6)$$



We can also model the total volume of air in the lungs, denoted  $V_{Air}$  as

$$V_{Air} = V_{AD} + \sum_{i=1}^{N_{Layers}} (N_{A,i} \cdot V + A, i) \quad (3.7)$$

where  $V_{AD}$  and  $V_{A,i}$  denote anatomical deadspace and the volume of alveolus  $i$ , respectively.

The alveolus is assumed to be spherical, for simplification, and thus the volume of a section of the alveolus with height  $b$  from the opening and radius  $r$  is given by

$$V_{A,i} = \frac{1}{3} \pi \cdot b_i^2 (2r_i - b_i). \quad (3.8)$$

This formula is given as formula (4.40) in (Citation, Schaums Formulas and Tables). Similarly, the surface area,  $S_A$ , of a spherical alveolus can be calculated by

$$S_{A,i} = 2\pi \cdot r_i b_i = \pi(b_i^2 + a^2) \quad (3.9)$$

where  $a$  is the length of the opening of the alveolus. This constant is, for simplification, assumed to be constant and the same for all alveolus. We can isolate the constant  $r$  from equation (3.9), as follows

$$r_i = \frac{a^2 + b_i^2}{2b_i} \quad (3.10)$$

Last, we define total lung capacity,  $V_{TLC} = V_{AMax} + V_{AD}$ , we can calculate the total lung,  $V_{AMax}$  volume by

$$V_{AMax} = \frac{V_{TLC} - V_{AD}}{N_A}. \quad (3.11)$$

Recall that  $N_A$  is the total number of alveoli. Here we are assuming that all alveoli in the

lungs are the same size.

The formula for pressure exerted by the chest wall,  $P_{CW}$ , is stated in (citation, ventilation paper) by

$$P_{CW} = 0.071 \text{ kPa} - \ln \left( \frac{95\%}{(V_{Air}/V_{TLC}) - 22\%} - 1 \right) \cdot 0.58 \text{ kPa} \quad (3.12)$$

Also, (citation) discusses a model for  $P_\gamma$ , the pressure due to surface tension given by

$$S_{0new,i} = \begin{cases} S_{A,i}, & \text{if } 1 < S_{r,i} \\ S_{0,i}, & \text{if } S_{Meta} \leq S_{r,i} \leq 1 \\ S_{A,i}/S_{Meta}, & \text{if } S_{r,i} < S_{Meta} \end{cases} \quad (3.13)$$

where  $S_A$  and  $S_0$  are the alveolar surface areas where the latter is surface area before compression. The variable  $S_0$  controls hysteresis and will be updated per breath cycle to give the proper amount of hysteresis each time. The variable  $S_{Meta}$  denotes the point where relative surface area of the lung reaches the minimal surface tension. The variable that controls the location of the jumps on the interval  $(1, S_{Meta})$ ,  $S_{r,i}$  is the relative alveolar surface area, and is

$$S_{r,i} = \frac{S_{A,i}}{S_{0,i}}, \quad (3.14)$$

the ratio of total surface area to surface area before compression of each partition  $i$  of the alveolus.

In simulations, the value  $S_{Meta} = 61.7\%$  is used and the surface tension can be calculated

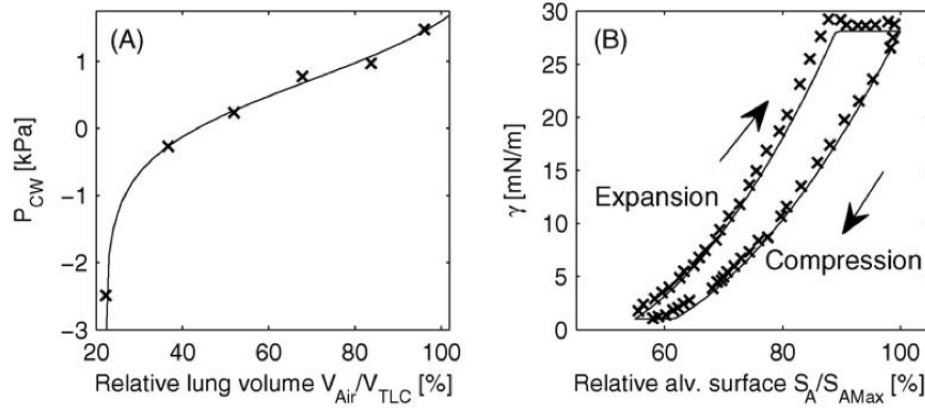


Figure 3.2: This figure shows results from the model presented in Steimle et al., 2011. On the left, we have a plot of chest wall pressure versus relative lung volume and on the right, surface tension versus relative alveolar surface [5].

using the following polynomial

$$\gamma_i = 98.9 \text{ nM/m} \cdot s_{r,i}^2 - 89 \text{ mN/m} \cdot s_{r,i} + 18.3 \text{ mN/m} \quad (3.15)$$

where  $s_{r,i}$  is defined in equation (3.14).

The pressure due to surface tension can be calculated as a function of alveolar surface area using the following Laplace equation

$$p_{\gamma,i} = \frac{2 \cdot \gamma_i}{r_i} \quad (3.16)$$

where  $\gamma_i$  and  $r_i$  is the surface tension and radius at layer  $i$ , respectively.

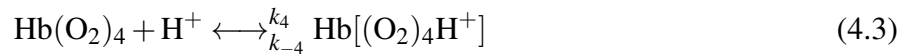
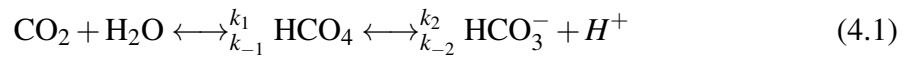
Figure (3.2) shows the results of these equations. On the left, relative lung volume is plotted versus the pressure in the chest wall. We see that as the lung volume increases, the pressure in the chest wall also increases. On the right, relative alveolar surface is plotted versus the surface tension during expansion and compression of the lung. During expansion, as the surface volume is increased, the surface tension also increases up to around 28 mN/m

where it remains constant until compression begins, during which it decreases as relative alveolar surface area decreases.

### A Mathematical Model of Gas Dynamics in the Body

We change our focus to a mathematical model of how carbon dioxide and oxygen change in the body. After leaving the lungs, most hemoglobin is saturated with enough oxygen to satisfy the oxygen requirement of the body. However, there are some states in which hydrogen ions bind with hemoglobin in some forms, which can decrease the oxygen saturation of the blood. This model will analyze how the presence of hemoglobin bound to a single hydrogen ion and saturated hemoglobin bound to a hydrogen ion affect the overall oxygen saturation of blood.

Consider the reactions that account for the interactions between the major compounds involved in the transport of oxygen and carbon dioxide throughout the body.



Notice that because the reaction occurring at a rate  $k_1$  happens quickly, it is ignored in the system. The first two reactions are exactly the same as we have seen previously. The last two equations account for the binding of hemoglobin to other molecules present in the blood. In the third equation, when hemoglobin saturated with oxygen encounters a hydrogen ion, it will bind (or be unbound) at a rate of  $k_4$  ( $k_{-4}$ ). Also, unbound hemoglobin can bind

(or be unbound) to hydrogen ions at a rate of  $k_5$  ( $k_{-5}$ ).

Using traditional reaction kinetics, these reactions can be turned into a system of ordinary differential equations were we ignore the spatial dynamics of the system and consider only how the concentrations of each molecule is changing over time in the body after it leave the lungs. The beginning of simulations for this model will be set at the time frame in which blood is leaving the lungs and the end of simulations will be set at a the time right before returning to the lungs. Therefore, blood hemoglobin will be saturated with oxygen at the beginning. The total time in simulations will be about one minute, the time it takes for blood to fully circulate around the body [3].

For the purposes of the model, we assume that all reverse reactions happen at rate  $k_{-i}$  for each forward rate  $k_i$ . The reaction that happens at rate  $k_1$  is ignored, as we assume that the reaction that  $k_1 \gg 0$ . We collapse this into a single rate constants  $k$  and  $k_-$ . We also assume that water is readily available in the human body. The equations are given by

$$\frac{dX}{dt} = 4k_{-3}M - 4k_3X^4A - \alpha \quad (4.5)$$

$$\frac{dY}{dt} = k_-ZH - kY + \beta \quad (4.6)$$

$$\frac{dZ}{dt} = kY - k_-ZH \quad (4.7)$$

$$\frac{dM}{dt} = k_3AX^4 - k_{-3}M - k_4MH + k_{-4}D \quad (4.8)$$

$$\frac{dH}{dt} = kY - k_-HZ - k_4HM + k_{-4}D - k_5HA + k_{-5}B \quad (4.9)$$

$$\frac{dA}{dt} = k_{-3}M - k_3AX^4 - k_5AH + k_{-5}B \quad (4.10)$$

$$\frac{dB}{dt} = k_5AH - k_{-5}B \quad (4.11)$$

$$\frac{dD}{dt} = k_4MH - k_{-4}D \quad (4.12)$$

$$(4.13)$$

where  $X = [\text{O}_2]$ ,  $Y = [\text{CO}_2]$ ,  $Z = [\text{HCO}_3^-]$ ,  $M = [\text{Hb}(\text{O}_2)_4]$ ,  $H = [\text{H}^+]$ ,  $A = [\text{Hb}]$ ,  $B = [\text{Hb}(\text{H}^+)]$ , and  $D = [\text{Hb}((\text{O}_2)(\text{H}^+))]$ .

We consider the system in the body well mixed, and therefore, consider the time dependent system as a whole instead of relative to gas exchange over the capillary beds. The initial conditions of the model will rely on the saturation of hemoglobin, which is given by the function  $S = \frac{M}{M+A+B+D}$ . At the beginning, we expect hemoglobin to be 97% saturated with oxygen, we want  $S \approx 0.97$ . Also, we expect the concentration of carbon dioxide to be small but nonzero.

The parameters from the model are adapted from [8] and the model is fit with  $\alpha = \beta = 0$  such that steady state remains close to the initial conditions. For this model, the initial conditions are

$$X(0) = 104$$

$$Y(0) = 40$$

$$Z(0) = .024$$

$$M(0) = .00186$$

$$H(0) = .000000004$$

$$A(0) = .000113$$

$$B(0) = .000113$$

$$D(0) = .000113$$

where the first are partial pressures obtained from literature that specifically match Figure (2.1). For the last six initial condition, we rely on the knowledge that the total concentration of hemoglobin is  $0.0022M$  and force the sum  $M + A + B + D = 0.002 M$ . Last, the initial

condition for hydrogen ions is set to the pH of blood, which is around  $10^{-7.4}$ .

After the parameters are modified, the parameters  $\alpha$  and  $\beta$  are changed to  $\alpha = 1$  and  $\beta = 0.15$ , which lead to the decrease in partial pressure of oxygen and increase in partial pressure of carbon dioxide, as expected when blood is circulated throughout the body. Figure (4.1) shows the change in partial pressure of oxygen and carbon dioxide over the 60 second period it takes for blood to circulate through the body. On the left, we see that the partial pressure of oxygen starts at around 104 mm Hg and after circulation when the blood reenters the lungs, it is at around 40 mmHg, which matches up with Figure (2.1).

The saturation of hemoglobin, modeled by the ration of fully bound hemoglobin to the sum of all states of hemoglobin is shown in Figure (4.2). We see that it is initially saturated at about 97% and when the blood reenters the lungs, it's saturated at around 70%, as expected from Figure (2.4).

To further analyze the model, we consider the situation where hemoglobin can only bind with oxygen, as in the original simulation. That is, we set  $B(0) = D(0) = 0$  and change  $A(0) = 0.00034$  to keep the sum of total hemoglobin the same and consider the saturation function  $S' = \frac{M}{M+A}$ .

The change in partial pressure of oxygen and carbon dioxide result in very similar curves to before, however the saturation curve is changed slightly. We see in Figure (4.3) that the saturation changes at about the same rate but, with the altered initial conditions, it's slightly higher.

#### 4.1 Conclusions

The gas exchange process, driven by diffusion and the binding of oxygen to hemoglobin molecules, is a complex system that can be modeled mathematically. With these mathematical models, it is possible to study the underlying dynamics of the system to better understand



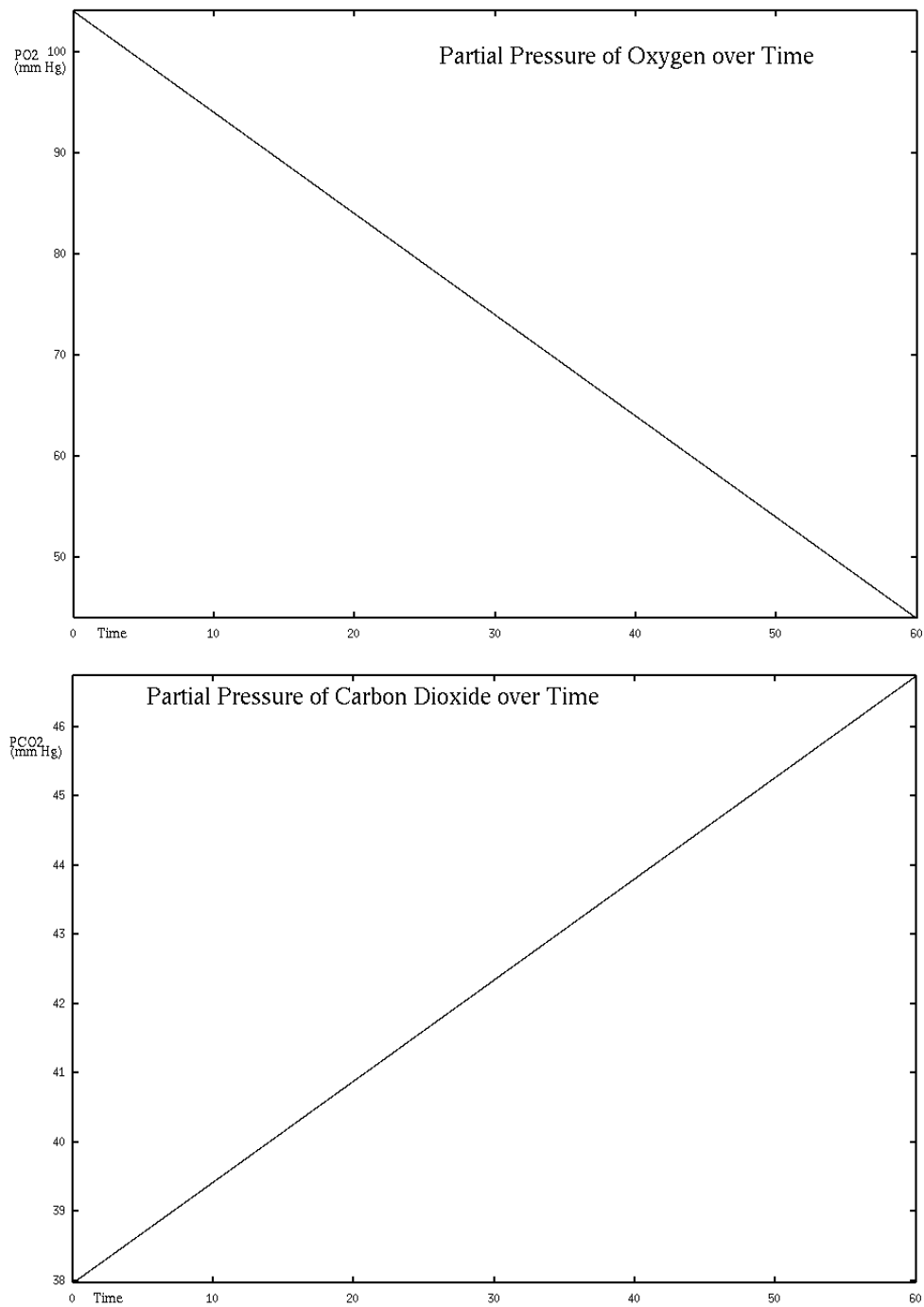


Figure 4.1: Model results for the partial pressure of oxygen (left) and carbon dioxide (right) after parameter fitting.

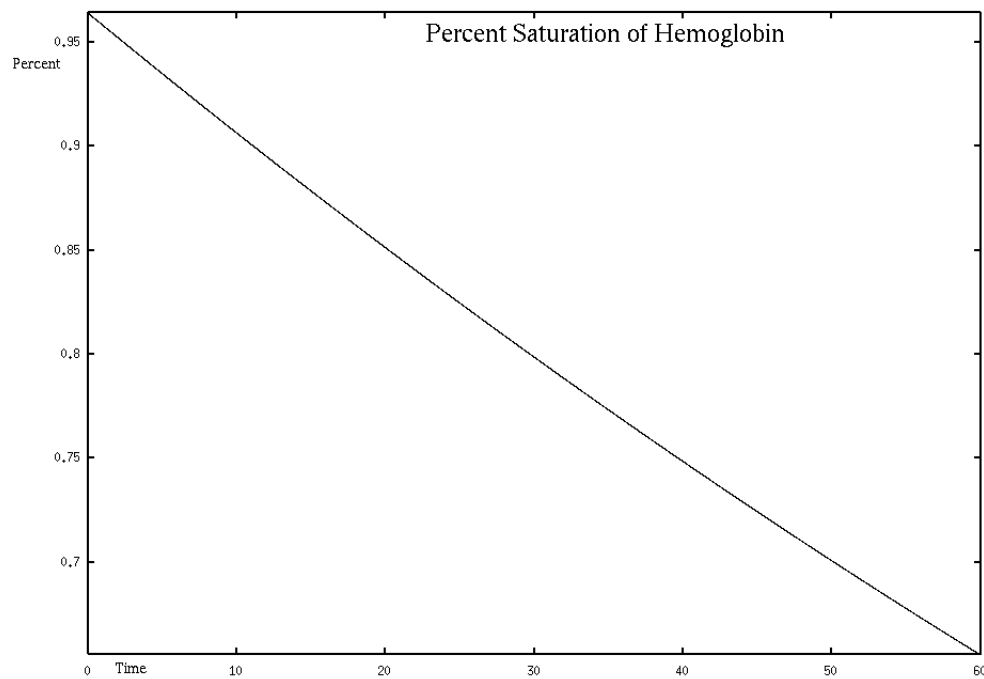


Figure 4.2: This figure shows the saturation curve for hemoglobin.

how interventions can be taken to help patients on ventilators. Further exploration of this topic is warranted to help millions of patients and save money.

The mathematical models presented here for the basis for creating and understanding more complex models of these interactions. The basics of diffusion, gas transport, capillary-alveolar interactions, and lung ventilation form the understanding of the simple dynamics, and can therefore be applied to large more complex models that account for larger systems and more interactions within those systems.

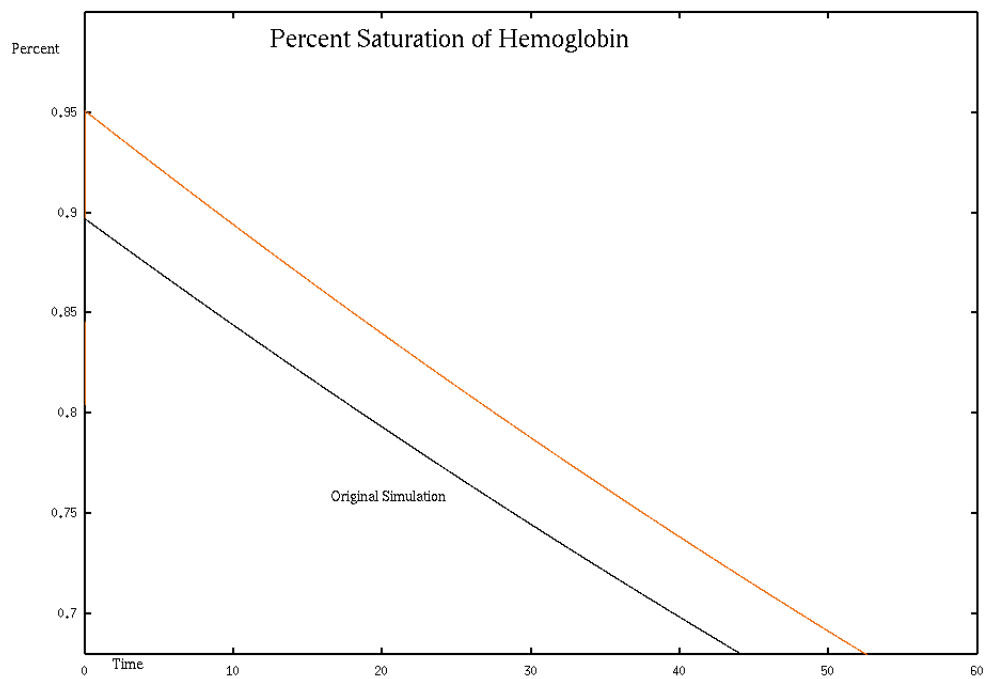


Figure 4.3: This figure compares the saturation curve for hemoglobin from the original simulation (above) to the simulation with initial conditions  $B(0) = D(0) = 0$  and  $A(0) = 0.00034$ . The figure shows the results where the bottom curve (black line) is the saturation curve from the original simulation and the top curve (red line) is the saturation curve under the altered initial conditions.

### **Vita**

Racheal Lindsey Cooper was born in Petersburg, Virginia. After obtaining a High School diploma at Prince George High School, she attended Old Dominion University in Norfolk, Virginia for two semesters. During this time she received the Virginia Governor's Scholarship and was a member of the Honor's College. Upon completing two semesters at this college, she transferred to Virginia Commonwealth University and began pursuing Mathematics. She was a STEM Scholar, was secretary and founding member of the VCU Mathematics Club and was a founding member of the the VCU branch of Pi My Epsilon. After obtaining her Bachelor's Degree from Virginia Commonwealth University, she continued at the institution to pursue Graduate School.

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