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A mathematical model of pulmonary gas exchange under inflammatory stress

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Abstract

During a severe local or systemic inflammatory response, immune mediators target lung tissue. This process may lead to acute lung injury and impaired diffusion of gas molecules. Although several mathematical models of gas exchange have been described, none simulate acute lung injury following inflammatory stress. In view of recent laboratory and clinical progress in the understanding of the pathophysiology of acute lung injury, such a mathematical model would be useful. We first derived a partial differential equations model of gas exchange on a small physiological unit of the lung (325 alveoli), which we refer to as a respiratory unit (RU). We next developed a simple model of the acute inflammatory response and implemented its effects within a RU, creating a single RU model. Linking multiple RUs with various ventilation/perfusion ratios and taking into account pulmonary venous blood remixing yielded our lung-scale model. Using the lung-scale model, we explored the predicted effects of inflammation on ventilation/perfusion distribution and the resulting pulmonary venous partial pressure oxygen level during systemic inflammatory stresses. This model represents a first step towards the development of anatomically faithful models of gas exchange and ventilation under a broad range of local and systemic inflammatory stimuli resulting in acute lung injury, such as infection and mechanical strain of lung tissue.

Keywords

Acute inflammation; Acute Lung Injury; Immunology; Lung Edema

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Introduction

There is a substantial literature on mathematical models of gas exchange, that have focused on different aspects of the process of gas transfer and distribution between ambient air and blood, including distribution of ventilation, transport between alveolar air space and pulmonary capillaries, red blood cell rheology, hemoglobin dynamics and acid-base physiology (Ben-Tal, 2006). These models span different anatomical scales and have generally been useful to study airflow distribution, deposition of particulate drugs in airways, lung mechanics and shunt physiology.

New imaging techniques (Moller et al., 2002; Tawhai et al., 2003), cell-type identification tools (Olson et al., 2002) and high-throughput methods are providing a unique opportunity to construct and calibrate increasingly complex and realistic models that integrate the large body of existing knowledge with these newer data and provide modeling tools with significant translation impact into the understanding, and modification of, human disease. In the realm of critical care medicine, acute lung injury (ALI) is an inflammatory process that can be triggered by chemical, infectious or traumatic stimuli. ALI typically requires mechanical ventilatory support, is morbid and the most frequent manifestation of multisystem organ dysfunction, the leading cause of death in the ICU (Rubenfeld et al., 2007). ALI also has long-term consequences in those who survive the acute illness. Substantial public and corporate resources are devoted to prevent and treat ALI. There are also good animal models of ALI (Delclaux et al., 1997) and its pathophysiology is increasingly well understood (Ware, 2006).

To our knowledge, existing modeling efforts have not attempted to describe the progression of ALI following a local or systemic inflammatory stimulus. We therefore describe such an attempt, where the direct effects of inflammatory mediators on lung tissue are modeled, along with their impact on lung volumes, lung water content and gas exchange ability. This is the first step in constructing a truly multiscale representation of gas exchange under inflammatory stress, with an explicit representation of the time evolution of ventilation-perfusion inequalities under such conditions, thus linking cell and tissue level inflammation, physical and physiological alveolar phenomena at the mesoscale, to global gas exchange at the scale of the whole organ. Because this study is the first step in constructing such a framework, the process of model development is described in considerable detail, and the simulations presented do not explore the full flexibility of the model.

Methods

Overview

In order to explore the lung during an inflammatory response we modeled gas exchange and the inflammatory response within a small portion of the lung. We consider the local dynamics on a respiratory unit (RU), which consists of 25 alveoli and the capillaries surrounding them (Guyton et al., 2000). We constructed a model of gas exchange within a RU consisting of partial differential equations for oxygen, oxyhemoglobin, carbon dioxide, and bicarbonate. Figure 1 illustrates the interactions included within the single RU model.

A RU consists of three compartments, the alveolar air space, lung tissue and capillary blood. There are variables expressing the partial pressure of oxygen (PO_2) and carbon dioxide (PCO_2) in all three compartments, while oxyhemoglobin (HB_4) and bicarbonate (HCO_3^-) are only in the blood. We model the following biological processes, diffusion of oxygen and carbon dioxide, hemoglobin uptake of oxygen, and enzymatic reactions governing carbon dioxide and bicarbonate levels. We assume diffusion occurs across two distinct barriers within the RU, the blood/tissue and tissue/alveolar air space barriers. Tidal breathing

regulates alveolar gas pressures of oxygen and carbon dioxide within the alveolar space. Following the development of the gas exchange subsystem of the model, we incorporate a response to an inflammatory stimulus, the inflammation subsystem, leading to the development of ALI. This additional subsystem consists of equations for neutrophils and tumor necrosis factor (TNF), a canonical pro-inflammatory cytokine, in both the blood and tissue compartment. This immune subsystem has fewer details than other inflammation models (Chow et al., 2005; Daun et al., 2008), but has an explicit spatial domain.

The RU is modeled as a one-dimensional spatial domain along the length of the capillary with a uniform grid. Therefore, gas molecules in the blood and tissue and HB_4 and HCO_3^- in the blood all vary in time and space. We assume alveolar air space to be well mixed. Under this assumption, variables in this compartment are functions of time only. Space along the compartment is modeled as N units of equal length and variables are modeled on each unit. Therefore, the variable names are oxygen/carbon dioxide in blood on unit i , PO_{2Bi}/PCO_{2Bi} , in the tissue on unit i , PO_{2Ti}/PCO_{2Ti} , and in the alveolar air space, PO_{2A}/PCO_{2A} . Oxyhemoglobin and bicarbonate on unit i , are HB_{4i} and HCO_{3p}^- respectively. After developing the gas exchange subsystem, we will derive the immune variables based on their known interactions and effects on gas exchange.

Diffusion

Diffusion, the exchange of molecules and cells across both the alveolar air space/tissue and tissue/blood barriers, is the only form of interaction between the compartments. Previous models for gas exchange depict diffusion as movement from the alveolar space to the blood across a tissue barrier (Ben-Tal, 2006; Hahn et al., 1993; Hill et al., 1973; Keener et al., 1998). However, we consider lung tissue as a compartment, not merely a barrier. We have chosen this approach to better reflect the impact of tissue volume changes caused by inflammation on gas exchange between air and blood. In order to properly model the effects of inflammation, we derive terms for diffusion driven by PO_2 and PCO_2 gradients across each barrier, tissue/blood and air/tissue.

Gas diffusion across the tissue/blood and tissue/air barriers is described in Equations (1)–(3).

Detailed descriptions of the gas exchange parameters are in Table 1. The $\sigma_j^{O_2}$ parameters scale partial pressure to molar concentration, for example, $[O_2]_j = \sigma_j^{O_2} PO_{2j}$ in compartment j . The parameters expressing overall diffusion rates from compartments j to and from k are of

the form $D_{jk}^{O_2}$. The volumes of each compartment blood, tissue, and alveolar air space are represented by V_{B0} , V_{T0} , and V_{A0} , respectively. In order to derive these terms we initially considered the number of oxygen molecules diffusion across the barrier on each unit, which is a dependent on the partial pressure gradient between compartments. For example,

$D_{TB}^{O_2}(PO_{2Bi} - PO_{2Ti})/N$ expresses the number of oxygen molecules diffusing from tissue to blood per second on the i^{th} unit of space. The diffusion rate is assumed to be the same on

each spatial unit. Therefore the rate on a given unit is $D_{jk}^{O_2}/N$. To calculate the change in partial pressure due to diffusion across the barrier on each compartment we divided the number of oxygen molecules which are diffusing by volume on the spatial unit (i.e. V_{B0}/N) and σ for their respective compartments. The resulting expression are the first terms of Equations (1) and (2).

$$\frac{dPO_{2Bi}}{dt} = \frac{D_{TB}^{O_2}(PO_{2Ti} - PO_{2Bi})}{\sigma_B^{O_2} V_{B0}} \quad (1)$$

$$\frac{dPO_{2Ti}}{dt} = \frac{D_{TB}^{O_2}(PO_{2Bi} - PO_{2Ti})}{\sigma_T^{O_2} V_{T0}} + \frac{D_{TA}^{O_2}(PO_{2A} - PO_{2Ti})}{\sigma_T^{O_2} V_{T0}} \quad (2)$$

$$\frac{dPO_{2A}}{dt} = \frac{D_{TA}^{O_2}}{\sigma_A^{O_2} V_{A0} N} \sum_{i=1}^N (PO_{2Ti} - PO_{2A}) \quad (3)$$

Diffusion across the tissue/air barrier is more complex because the alveolar air space compartment is assumed to be well mixed while the tissue compartment is not. As in above derivation, $D_{TA}^{O_2}(PO_{2Ti} - PO_{2A})/N$ is the number of molecules that will diffuse from air to tissue per second on each spatial unit. In the tissue compartment the derivation is the same as above. This term is multiplied by -1 , since it appears in the tissue equation and we divided by V_{T0}/N and $\sigma_T^{O_2}$, in order to calculate the change in PO_{2Ti} . This then simplifies to the second term of Equation (2). For the change in partial pressure for the air compartment one sums $D_{TA}^{O_2}(PO_{2Ti} - PO_{2A})/N$ over all units to account for exchange with each unit of the tissue and then divides by the volume of alveolar airspace, V_{A0} , and $\sigma_A^{O_2}$ obtaining Equation (3).

Blood/O₂

As blood traverses the capillary through a RU, oxygen diffuses into the blood and reacts with hemoglobin. Rather than accounting for the full dynamics of all four oxygen binding sites on hemoglobin tetramers, we consider hemoglobin as being either partially saturated (HB_m) or fully saturated (HB_4), where m is a Hill factor derived empirically from the oxyhemoglobin dissociation curve (Keener et al., 1998). We refer to HB_m as unsaturated hemoglobin. Oxygen binds to HB_m to form HB_4 at the rate k^+ and it detaches at the rate k^- from HB_4 , to return to HB_m . The reaction between unsaturated and saturated hemoglobin and oxygen is modeled by Equations (4)–(6).

$$\frac{d}{dt} HB_m = -k^+ HB_m PO_{2B}^m + k^- HB_4 \quad (4)$$

$$\frac{d}{dt} HB_4 = k^+ HB_m PO_{2B}^m - k^- HB_4 \quad (5)$$

$$\frac{d}{dt} PO_{2B} = m \frac{-k^+ HB_m PO_{2B}^m + k^- HB_4}{\sigma_B^{O_2}} \quad (6)$$

Total concentration hemoglobin, T_{HB} , is conserved. Thus, HB_m can be replaced with $T_{HB} - HB_4$ and equations (4)–(6) reduce to equations (7) and (8).

$$\frac{d}{dt}HB_4 = k^+(T_{HB} - HB_4)PO_{2B}^m - k^-HB_4 \quad (7)$$

$$\frac{d}{dt}PO_{2B} = m \frac{-k^+(T_{HB} - HB_4)PO_{2B}^m + k^-HB_4}{\sigma_B^{O_2}} \quad (8)$$

The temporal dynamics are much faster than the spatial dynamics. Therefore, we assume quasi steady state for the saturated hemoglobin when determining parameter values. This is necessary to develop an equation for percent saturation of hemoglobin that is dependent on PO_{2B} only. We find that percent saturation of hemoglobin is an increasing sigmoid function of the partial pressure of oxygen, $(PO_{2B}^m + (1 - m/4)R_H) / (PO_{2B}^m + R_H)$. Using the data for this curve we find that $m=3.6$ and $R_H = k^-/k^+ = 177916$ ((Guyton et al., 2000). Incorporating flow of these molecules in the blood and the diffusion terms described earlier yields Equations (9)–(10). The speed of blood (cm/s) is represented by v_0 . This subsystem now includes both the spatial and temporal dynamics for O_2 in the blood. Equations (11) and (12) are the discretized version of (9) and (10), where ∇_i is the discrete approximation to the first derivative.

$$\frac{\partial}{\partial t}HB_4 = k^+(T_{HB} - HB_4)PO_{2B}^m - k^-HB_4 - v_0 \frac{\partial}{\partial x}HB_4 \quad (9)$$

$$\frac{\partial}{\partial t}PO_{2B} = m \frac{k^-HB_4 - k^+(T_{HB} - HB_4)PO_{2B}^m}{\sigma_B^{O_2}} - v_0 \frac{\partial}{\partial x}PO_{2B} \quad (10)$$

$$\frac{dHB_{4i}}{dt} = k^+(T_H - HB_{4i})PO_{2B}^m - k^-HB_{4i} - v_0 \nabla_i HB_{4i} \quad (11)$$

$$\frac{dPO_{2Bi}}{dt} = m \frac{k^-HB_{4i} - k^+(T_H - HB_{4i})PO_{2B}^m}{\sigma_B^{O_2}} - v_0 \nabla_i PO_{2Bi} \quad (12)$$

Blood/ CO_2

As dissolved CO_2 and bicarbonate traverses the RU, bicarbonate releases CO_2 into the blood stream. This occurs by a catalyzed enzymatic reaction in which bicarbonate is the substrate. The reverse reaction is of the same type, however, with CO_2 as the substrate (Bidani et al., 1988). These reactions are modeled by the first two terms of Equations (13)–(14).

These terms are Michaelis-Menten type where the k_{cat} parameters represent the maximum rate of the catalytic reaction and k_m is the Michaelis constant, the level of the substrate for

which the reaction occurs at half k_{cat} . The variable is PCO_2 , hence the substrate in terms of the equation variables is $\sigma_B^C PCO_{2B}$, the concentration of CO_2 . Finally, we incorporate blood flow and diffusion between tissue and blood in this subsystem as done previously for O_2 in the blood. The CO_2 /bicarbonate subsystem in the blood including temporal and spatial dynamics is described by Equations (13) and (14). Equations (15) and (16) are the discretized form of this subsystem.

$$\frac{\partial}{\partial t} HCO_3^- = k_{catCB} \frac{\sigma_B^C PCO_{2B}}{k_{mCB} + \sigma_B^C PCO_{2B}} - k_{catHC} \frac{HCO_3^-}{k_{mHC} + HCO_3^-} - v_0 \frac{\partial}{\partial x} HCO_3^- \quad (13)$$

$$\frac{\partial}{\partial t} PCO_{2B} = \frac{1}{\sigma_B^C} \left(k_{catHC} \frac{HCO_3^-}{k_{mHC} + HCO_3^-} - k_{catCB} \frac{\sigma_B^C PCO_{2B}}{k_{mCB} + \sigma_B^C PCO_{2B}} \right) - v_0 \frac{\partial}{\partial x} PCO_{2B} \quad (14)$$

$$\frac{dHCO_{3i}^-}{dt} = k_{catCB} \frac{\sigma_B^C PCO_{2Bi}}{k_{mCB} + \sigma_B^C PCO_{2Bi}} - k_{catHC} \frac{HCO_{3i}^-}{k_{mHC} + HCO_{3i}^-} - v_0 \nabla_i HCO_{3i}^- \quad (15)$$

$$\frac{dPCO_{2Bi}}{dt} = \frac{1}{\sigma_B^C} \left(k_{catHC} \frac{HCO_{3i}^-}{k_{mHC} + HCO_{3i}^-} - k_{catCB} \frac{\sigma_B^C PCO_{2Bi}}{k_{mCB} + \sigma_B^C PCO_{2Bi}} \right) - v_0 \nabla_i PCO_{2Bi} \quad (16)$$

Tissue/ O_2 & CO_2

Within tissue, the only interaction modeled other than the diffusion between compartments is the diffusion of gas molecules along the tissue, expressed by the reaction-diffusion Equations (17)–(18), where ∇_i^2 is the discrete approximation to the second derivative.

$$\frac{dPO_{2Ti}}{dt} = \frac{D_{TB}^{O_2}(PO_{2Bi} - PO_{2Ti})}{\sigma_T^{O_2} V_{T0}} + \frac{D_{TA}^{O_2}(PO_{2A} - PO_{2Ti})}{\sigma_T^{O_2} V_{T0}} + D_{O_2T} \nabla_i^2 PO_{2Ti} \quad (17)$$

$$\frac{dPCO_{2Ti}}{dt} = \frac{D_{TB}^C(PCO_{2Bi} - PCO_{2Ti})}{\sigma_T^C V_{T0}} + \frac{D_{TA}^C(PCO_{2A} - PCO_{2Ti})}{\sigma_T^C V_{T0}} + D_{CT} \nabla_i^2 PCO_{2Ti} \quad (18)$$

Alveolar O_2 and CO_2

An average healthy human breathes about 15 times a minute with an inspiration:expiration time ratio of 1:3. We assumed a total tidal breath of 500 ml, with 150 ml of dead space ventilation, yielding an effective alveolar ventilation of 350 ml per breath, with residual total alveolar volume at the end of expiration 2300 ml (Guyton et al., 2000). This corresponds to an influx of 2.92×10^{-5} ml of new gas per RU per breath, termed V_{C0} and referred to as alveolar ventilation, and an end expiration (residual) volume of 1.92×10^{-4} ml per RU (V_{Amin0}). In order to develop equations for the changes in partial pressures of O_2 and CO_2 in

alveolar gas, we first derive equations for the change in alveolar volume on a RU, Equations (19)–(21).

$$sh(t) = \frac{1}{1 + e^{-\sigma(t_{in} - \text{mod}(t, t_{in} + t_{out}))}} \quad (19)$$

$$\dot{y} = \frac{V_{CO} sh(t)}{\tau_1} - \frac{y}{\tau_2} \quad (20)$$

$$V_{A0}(y) = V_{Amin0} + y \quad (21)$$

Equation (19) is a smooth heavy side function that is approximately one during inspiration and zero during expiration. The length of inspiration is $t_{in}=1$ second and length of expiration is $t_{out}=3$ seconds. The parameter σ controls the abruptness of the function's switch from one to zero. For our calculations we set σ to 20. The variable y in Equation (20) is a measure of the alveolar volume change. During inspiration there is growth in y and it decays during expiration. The τ 's are chosen such that in t_{in} seconds y reaches V_{CO} and decays to zero in t_{out} seconds. Therefore, the equation of alveolar air volume, Equation (21), is V_{Amin0} at end of expiration and $V_{Amin0}+V_{CO}$ at the end of inspiration.

We are now ready to model the change in alveolar air space partial pressures of O_2 and CO_2 . We will refer to the partial pressure of the O_2 and CO_2 in the air as PO_{2air} and PCO_{2air} respectively. Under normal conditions, where we are assuming that optimality between the screening effect and alveolar size has been achieved, PO_{2air} is 150 mmHg and PCO_{2air} is 0 mmHg (Guyton et al., 2000). In order to properly model the changes in partial pressure, we track the changes in number of molecules and convert to a partial pressure change as we did with diffusion between compartments. The number of oxygen molecules in the alveolar space is the concentration of O_2 times the volume in the alveolar space, $V_{A0}[O_2]$. During inspiration the change in number of molecules due to breathing, not diffusion, is Equation (22). This equation simplifies to Equation (23) when we assume that there is no change in outside air concentration. Dividing Equation (23) through by σ_A we derive the differential equation for the partial pressure for oxygen in the alveolar air space, Equation (24).

$$\frac{d}{dt}(V_{A0}(y)[O_2]) = \frac{d}{dt}(V_{A0}(y)[O_2]_{air}(t)) \quad (22)$$

$$\frac{d}{dt}[O_2] = ([O_2]_{air}(t) - [O_2])R \quad (23)$$

$$\text{with } R = \frac{\frac{d}{dt} V_{A0}(y)}{V_{A0}(y)}$$

$$\frac{d}{dt}PO_{2A} = R(PO_{2air} - PO_{2A}) \quad (24)$$

During expiration we assume that the air within the RU is well mixed; therefore all expired air has the same concentration. With this assumption there is no change in concentration and therefore pressure during expiration. Including diffusion, we model changes in alveolar PO_2 during breathing by Equation (25). The equation for CO_2 has the same form.

$$\frac{dPO_{2A}}{dt} = \frac{D_{TA}^{O_2}}{\sigma_A^{O_2} V_{A0}(y)N} \sum_{i=1}^N (PO_{2Ti} - PO_{2A}) + \begin{cases} \text{Inspiration} & R(PO_{2air} - PO_{2A}) \\ \text{Expiration.} & 0 \end{cases} \quad (25)$$

The immune subsystem

We use a simple model of the inflammatory response which includes TNF and neutrophils (Abraham, 2003; Pallister et al., 2002). TNF activates circulating neutrophils in the blood. Once activated, neutrophils can “diffuse” into lung tissue by transendothelial migration, where inflammatory factors cause stickiness of the endothelial surface such that activated neutrophils attach to endothelium and marginate into tissue locally (Petri et al., 2008). Activated neutrophils in both the blood and tissue produce TNF. TNF diffuses between the tissue and blood barrier by passive diffusion (Pappenheimer et al., 1951). Also, since inflammation is function of many factors not included in this model that could sustain inflammatory effects after the levels of TNF and activated neutrophils have dropped, we incorporate into our model a differential equation for inflammation. Inflammation’s growth is dependent on TNF levels. However, it decays at a slower rate than TNF.

We model these biological interactions with Equations (26)–(30). This subsystem consists of equations for TNF in the blood, TNF_B , and activated neutrophils on each unit of the blood, NA_{Bi} , and for both TNF and activated neutrophils on each unit of the tissue compartment, TNF_i and NA_i . Note that unlike other variables in this subsystem TNF_B is not a function of space, since it is well mixed in the blood. The inflammation variable is a function of space and time. It is a measure of the local tissue inflammation and is represented by z_i .

$$\frac{dTNF_B}{dt} = -\mu_{TB} TNF_B - \alpha N_0 \frac{TNF_B^2}{k_{tn}^2 + TNF_B^2} + \frac{\sum_{i=1}^N r_p(z_i)(TNF_i - TNF_B)}{NV_{B0}} + \gamma_B \frac{L}{N} \sum_{i=1}^N NA_{Bi} \quad (26)$$

$$\frac{dNA_{Bi}}{dt} = -\mu_{NB} NA_{Bi} + \beta N_0 \frac{TNF_B^2}{k_{tn}^2 + TNF_B^2} - \frac{r_v(z_i) NA_{Bi}}{V_{B0}} - v_0 \nabla_i NA_{Bi} \quad (27)$$

$$\frac{dTNF_i}{dt} = -\mu_T TNF_i + \frac{r_p(z_i)(TNF_B - TNF_i)}{V_{T0}} + \gamma_T NA_i + D_T \nabla_i^2 TNF_i \quad (28)$$

$$\frac{dNA_i}{dt} = -\mu_N NA_i + \frac{r_v(z_i)NA_{Bi}}{V_{T0}} - \chi \nabla_i (NA_i \nabla_i TNF_i) \quad (29)$$

$$\frac{dz_i}{dt} = -\mu_z z_i + \frac{k_{zg} TNF_i^2}{k_{zg}^2 + TNF_i^2} (1 - z_i) \quad (30)$$

$$r_p(x) = m_p x + b$$

$$r_v(x) = \frac{k_v x^2}{k^2 + x^2}$$

The first term of all equations models decay of the variable. The second term of Equation (27) models the activation of resting neutrophils by TNF in the blood. This reaction is modeled by a Hill type equation with an exponent of two. This nonlinearity models the need for multiple TNF molecules to bring about the activation of a neutrophil. A similar term appears as the second term of the TNF_B equation, Equation (26), to model the consumption of TNF during this process. The third term in Equations (26)–(27) and the second terms of Equations (28)–(29) model diffusion. These terms do not have the same form because the mechanisms by which neutrophils and TNF diffuse during an inflammatory response are different.

Increasing local inflammation promotes activated neutrophils diffusion, however these effects saturate for higher levels of inflammation, hence there is a maximum rate for the diffusion of neutrophils. Due to these properties of neutrophil diffusion we model this with a hill type function, $r_v(z_i)$. Note that resting neutrophils are assumed not to diffuse; therefore, there is no activation of neutrophils within the tissue. Once an activated neutrophil diffuses into to the tissue we assume that it does not diffuse back into the blood.

TNF diffusion also increases as inflamed endothelium becomes more porous to all small molecules (Aird, 2005). We assume this dependence to be linear and is model with the function $r_p(z_i)$. Diffusion for both TNF and activated neutrophils are modeled as with the gas molecules with the $r_v(z_i)$ or $r_p(z_i)$ taking the role of the diffusion constant.

The final term in Equation (26) expresses the production of TNF by activated neutrophils.

This sum is an numerical estimate for the integral $\gamma_B \int_0^L NA_B(x, t) dx$. This integral accounts for TNF produced by the activated neutrophils throughout the entire blood compartment. We denote the length of the capillary with L . The last term of Equation (27) is flow of neutrophils in the blood. The last term of the Equation (28), represents chemotaxis of tissue neutrophils towards TNF. The last final two terms of the tissue TNF equation (29) are production of TNF from neutrophils and diffusion of TNF within the tissue compartment, respectively.

We model local inflammation with Equation (30), which consists of two terms, growth and decay. The growth of inflammation is dependent on the local TNF. We model this dependence using a Hill type function. This nonlinearity is used since there must be substantial levels of TNF in the tissue to trigger inflammatory changes and the growth rate of inflammation saturates. Note that the inflammation variable has a maximum value of one, which corresponds to tissue being severely inflamed.

Single RU model: Effects of inflammation on gas exchange

During an inflammatory response, there is swelling of the tissue layer caused by capillary leak. In terms of the classic Starling description of inter-compartmental fluid shifts (Guyton et al., 2000), the overall permeability of the capillary to water and osmotically active molecules is increased. As a result, the increased tissue volume encroaches on both alveolar and capillary volumes. Our model does not explicitly include Starling mechanisms to drive intercompartmental fluid shifts. Rather, we use a simpler phenomenological description where volumes are directly impacted by the average local intensity of inflammation. Specifically, we replace, V_{B0} , V_{T0} , V_{Amin0} , V_{C0} and v_0 with V_B , V_T , V_{Amin} , V_C and v respectively, where V_B , V_T , V_{Amin} and V_C are functions of the average of the local

inflammation variables, $\bar{z}_i = \frac{1}{N} \sum_i^N z_i$. V_B a sigmoidal function that decreases as $\bar{z}_i$ increases and has maximum V_{B0} , Equation (31). V_{Amin} is a similar shaped function, but with a maximum of V_{Amin0} , and it tracks the minimum of the alveolar air space (volume at the end expiration), Equation (33). As $\bar{z}_i$ increases the amount volume lost from the blood and alveolar air space is added to the volume of the tissue yielding Equation (32). Note the parameters are set such that $m_{vta} > m_{vtb}$, since swelling tissue expands more readily into the more compliant alveolar air space than into the blood compartment. In this model as the compartment volumes change we maintain a constant blood flow. Therefore, velocity of blood is a function of the blood volume and it is determined by $v = v_0 V_{B0}/V_B$.

Inflammation increases lung stiffness reducing the lung's ability to generate a tidal volume (decrease of V_C). We modeled this change in V_C with a sigmoidal function of inflammation, as we did with compartmental volumes, where maximal alveolar ventilation is V_{C0} . The parameter m_c determines the effectiveness of inflammation to reduce V_C , see Equation (34).

$$V_B(\bar{z}_i) = \frac{V_{B0}}{1 + m_{vtb}\bar{z}_i} \quad (31)$$

$$V_T(\bar{z}_i) = V_{T0} + V_{B0} - \frac{V_{B0}}{1 + m_{vtb}\bar{z}_i} + V_{Amin0} - \frac{V_{Amin0}}{1 + m_{vta}\bar{z}_i} \quad (32)$$

$$V_{Amin}(\bar{z}_i) = \frac{V_{Amin0}}{1 + m_{vta}\bar{z}_i} \quad (33)$$

$$V_C(\bar{z}_i) = \frac{V_{C0}}{1 + m_c\bar{z}_i} \quad (34)$$

Taking into account these changes due to inflammation, we have the final form of our model, Equations (35)–(48).

BLOOD EQUATIONS

$$\frac{dPO_{2Bi}}{dt} = \frac{D_{TB}^{O_2}(PO_{2Ti} - PO_{2Bi})}{\sigma_B^{O_2} V_B(\bar{z}_i)} + \frac{m}{\sigma_B^{O_2}} (k^- HB_{4i} - k^+(T_{Hb} - HB_{4i})PO_{2B}^m) - v\nabla_i PO_{2Bi} \quad (35)$$

$$\frac{dHB_{4i}}{dt} = k^+(T_{Hb} - HB_{4i})PO_{2B}^m - k^- HB_{4i} - v\nabla_i HB_{4i} \quad (36)$$

With $k^- = R_H k^+$

$$\frac{dPCO_{2Bi}}{dt} = \frac{D_{TB}^C(PCO_{2Ti} - PCO_{2Bi})}{\sigma_B^C V_B(\bar{z}_i)} + \frac{1}{\sigma_B^C} \left(k_{catHC} \frac{HCO_{3i}^-}{k_{mHC} + HCO_{3i}^-} - k_{catCB} \frac{\sigma_B^C PCO_{2Bi}}{k_{mCB} + \sigma_B^C PCO_{2Bi}} \right) \quad (37)$$

$$\frac{dHCO_{3i}^-}{dt} = k_{catCB} \frac{\sigma_B^C PCO_{2Bi}}{k_{mCB} + \sigma_B^C PCO_{2Bi}} - k_{catHC} \frac{HCO_{3i}^-}{k_{mHC} + HCO_{3i}^-} - v\nabla_i HCO_{3i}^- \quad (38)$$

$$\frac{dT_{NF}_B}{dt} = -\mu_{TB} T_{NF}_B - \alpha N_0 \frac{T_{NF}_B^2}{k_{In} + T_{NF}_B^2} + \frac{\sum_{i=1}^N r_p(\bar{z}_i)(T_{NF}_i - T_{NF}_B)}{NV_B(\bar{z}_i)} + \gamma_B \frac{L}{N} \sum_{i=1}^N NA_{Bi} \quad (39)$$

$$\frac{dNA_{Bi}}{dt} = -\mu_{NB} NA_{Bi} + \beta N_0 \frac{T_{NF}_B^2}{k_{In} + T_{NF}_B^2} - \frac{r_v(\bar{z}_i) NA_{Bi}}{V_B(\bar{z}_i)} - v\nabla_i NA_{Bi} \quad (40)$$

$$V_B(\bar{z}_i) = \frac{V_{B0}}{1 + m_{vib} \bar{z}_i}$$

TISSUE EQUATIONS

$$\frac{dPO_{2Ti}}{dt} = \frac{D_{TB}^{O_2}(PO_{2Bi} - PO_{2Ti})}{\sigma_T^{O_2} V_T(\bar{z}_i)} + \frac{D_{TA}^{O_2}(PO_{2A} - PO_{2Ti})}{\sigma_T^{O_2} V_T(\bar{z}_i)} + D_{O_2T} \nabla_i^2 PO_{2Ti} \quad (41)$$

$$\frac{dPCO_{2Ti}}{dt} = \frac{D_{TB}^C(PCO_{2Bi} - PCO_{2Ti})}{\sigma_T^C V_T(\bar{z}_i)} + \frac{D_{TA}^C(PCO_{2A} - PCO_{2Ti})}{\sigma_T^C V_T(\bar{z}_i)} + D_{CT} \nabla_i^2 PCO_{2Ti} \quad (42)$$

$$\frac{dT_{NF_i}}{dt} = -\mu_T T_{NF_i} + \frac{r_p(z_i)(T_{NF_B} - T_{NF_i})}{V_T(\bar{z}_i)} + \gamma_B N A_i + D_T \nabla_i^2 T_{NF_i} \quad (43)$$

$$\frac{dN A_i}{dt} = -\mu_N N A_i + \frac{r_v(z_i) N A_{Bi}}{V_T(\bar{z}_i)} - \chi \nabla_i (N A_i \nabla_i T_{NF_i}) \quad (44)$$

$$\frac{dz_i}{dt} = -\mu_z z_i + \frac{k_{zg}(T_{NF_i} + T_{NF_B})^2}{k_{tz}^2 (T_{NF_i} + T_{NF_B})^2} (1 - z_i) \quad (45)$$

$$V_T(\bar{z}_i) = V_{T0} + V_{B0} - \frac{V_{B0}}{1 + m_{vfb} \bar{z}_i} + V_{Amin0} - \frac{V_{Amin0}}{1 + m_{vfa} \bar{z}_i}$$

ALVEOLAR AIR SPACE EQUATIONS

$$\frac{dPO_{2A}}{dt} = \frac{D_{TA}^{O_2}}{\sigma_A^{O_2} V_A(y, \bar{z}_i) N} \sum_{i=1}^N (PO_{2Ti} - PO_{2A}) + \left\{ \begin{array}{ll} \text{Inspiration} & R(PO_{2air} - PO_{2A}) \\ \text{Expiration} & 0 \end{array} \right\} \quad (46)$$

$$\frac{dPCO_{2A}}{dt} = \frac{D_{TA}^C}{\sigma_A^C V_A(y, \bar{z}_i) N} \sum_{i=1}^N (PCO_{2Ti} - PCO_{2A}) + \left\{ \begin{array}{ll} \text{Inspiration} & R(PCO_{2air} - PCO_{2A}) \\ \text{Expiration} & 0 \end{array} \right\} \quad (47)$$

$$y' = \frac{V_C(\bar{z}_i) sh(t)}{\tau_1} - \frac{y}{\tau_2} \quad (48)$$

$$\begin{aligned} V_A(y, \bar{z}_i) &= V_{Amin}(\bar{z}_i) + y \\ V_{Amin}(\bar{z}_i) &= \frac{V_{Amin0}}{1 + m_{vfa} \bar{z}_i} \\ V_C(\bar{z}_i) &= \frac{V_{C0}}{1 + m_c \bar{z}_i} \\ sh(t) &= \frac{1}{1 + e^{-\sigma(t_{in} - \text{mod}(t_{in} + t_{out}))}} \\ R &= \frac{\frac{d}{dt} V_A(y, \bar{z}_i)}{V_A(y, \bar{z}_i)} \end{aligned}$$

DIFFUSION FUNCTIONS

$$\begin{aligned} r_p(x) &= m_p x + b \\ r_v(x) &= \frac{k_v x^2}{k^2 + x^2} \end{aligned}$$

Explanations of parameter values for the gas exchange and immune subsystems are given in Table 1 and 2, respectively. Most gas exchange parameters are experimentally well characterized. Remaining parameters were chosen to reproduce known biological behaviors of model subsystems. Parameterization of the gas exchange subsystem was such that hemoglobin and oxygen dynamics stabilize in the first third of the capillary while bicarbonate and carbon dioxide reactions stabilize in the first tenth of the capillary (Guyton et al., 2000). For the immune subsystem parameters were estimated, such that there is bistability between fixed points representing health and non-recovery (Day et al., 2006; Reynolds et al., 2006).

Lung-scale model

We next linked the output of multiple RUs under various physiological conditions by the method depicted in Figure 2. We assumed that initial compartmental volumes were uniform across RUs. Therefore, all blood variable concentrations at the arterial end and initial compartmental volumes, V_{T0} , V_{B0} , and V_{A0} , are the same on each RU. We introduced heterogeneity by ranging ventilation/perfusion ratios from 0.31 to 1.15, following a truncated normal distribution $N\sim(0.73, 0.04)$ (Neumann et al., 2001). This was achieved by ranging scaled alveolar ventilation from 150 ml and 550 ml using $N\sim(350 \text{ ml}, 10^4 \text{ ml}^2)$, while holding perfusion constant (480 ml/breath cycle). For convenience, we refer to the scaled volume, which are the individual RU volumes scaled by the number of alveoli.

At the venous end, mixing of the blood exiting the RUs is accounted for by the system of ODEs, Equations (49)–(52). Equations (49) and (50), include the dynamics between hemoglobin and oxygen. Initial conditions for PO_{2B} are calculated by averaging venous blood PO_2 level from each RU. Initial HB_4 concentration is calculated by determining the percent saturation of pooled blood. Equations (51) and (52) include the dynamics between carbon dioxide and bicarbonate. The initial condition for PCO_{2B} and HCO_3^- are calculated, as with PO_{2B} , by averaging over the venous blood PCO_2 and HCO_3^- level from each RU. The system is simulated to steady state, yielding mixed PO_2 , HB_4 , PCO_2 , and HCO_3^- of the multiscale lung-scale model.

$$\frac{dPO_{2B}}{dt} = \frac{m}{\sigma_B^{O_2}} \left(k^- HB_4 - k^+ (T_H - HB_4) PO_{2B}^m \right) \quad (49)$$

$$\frac{dHB_4}{dt} = k^+ (T_H - HB_4) PO_{2B}^m - k^- HB_4 \quad (50)$$

$$\frac{dPCO_{2B}}{dt} = + \frac{1}{\sigma_B^C} \left(k_{catHC} \frac{HCO_3^-}{k_{mHC} + HCO_3^-} - k_{catCB} \frac{\sigma_B^C PCO_{2B}}{k_{mCB} + \sigma_B^C PCO_{2B}} \right) \quad (51)$$

$$\frac{dHCO_3^-}{dt} = k_{catCB} \frac{\sigma_B^C PCO_{2B}}{k_{mCB} + \sigma_B^C PCO_{2B}} - k_{catHC} \frac{HCO_3^-}{k_{mHC} + HCO_3^-} \quad (52)$$

Models were developed using XPPAUT (Ermentrout, 2002). Grid implementation of the code was performed using MATLAB® (The MathWorks, Natick, MA) on the computational resources of PittGrid (www.pittgrid.pitt.edu).

Implementing shunting

In severely inflamed alveoli, fluid accumulates in air space and surfactant production is compromised, resulting in increased surface tension in the alveolar wall, leading to alveolar closure. Thus, supply of fresh alveolar air to the tissue is eliminated. In animal models of inflammatory lung injury, shunting has been shown to increase from less than 5% at baseline to more than 50% with injury (Neumann et al., 2001). In order to model this effect, the diffusion rate between the air and tissue compartments is set to zero when scaled alveolar ventilation falls below 40% of V_{CO} (scaled 140 ml). All other dynamics remain the same and the alveolar air space no longer participates in the RU dynamics. We refer to this critical value as the alveolar closure threshold.

Results

Gas exchange during tidal breathing

Simulations of the model in the absence of inflammation give results similar to those observed experimentally (Guyton et al., 2000). PO_2 in the blood increases from 40 mmHg at the pulmonary arterial end (PO_{2B0}) to 101.7 mmHg at the pulmonary venous end (PO_{2B20}) as blood crosses the capillary, which is similar to the levels seen in the tissue compartment (Figure 3A, B). HB_4 becomes saturated in the first third of the capillary, Figure 3C. The oscillations arise in Figure 3A, B, C due to varying PO_2 in the alveolar air space during breathing. PO_2 in alveolar air space oscillates between 96.2 and 101.7 mmHg during the four-second breath cycle, see Figure 3D.

Blood PCO_2 drops from 45 to 40.7 mmHg as the blood transverses the capillary, see Figure 4A. Enzymatic reactions between bicarbonate and CO_2 stabilize in the first few space units (Figure 4C). PCO_2 in the alveolar space oscillates between 40.70 and 43.16 mmHg, similar oscillations occur in the tissue, see Figure 4B, D. The oscillations of PCO_2 in the tissue occur over the entire length of the tissue unlike those of PO_2 in the tissue. This is due to the higher diffusion coefficient for carbon dioxide in the tissue. Carbon dioxide decreases during inspiration, since inspired air has a PCO_2 of zero.

The immune subsystem

The immune subsystem is bistable between health and non-recovery (sustained inflammation). In health, TNF_i , TNF_B , NA_i , NA_{Bi} and z_i return to zero in all compartments. For sustained inflammation, corresponding to an outcome of death, these variables evolve to a persistently elevated value. Given an initial dose of TNF_B below 2.23 this subsystem will resolve itself to health and above this level the system will not recover (Eichacker et al., 1991). In our model, inflammation can also be triggered by initializing one of the other immune variables above its threshold for survival (simulations not shown).

The dynamics of this subsystem determine the volumes of the compartments and the alveolar ventilation in the alveolar space during an inflammatory response. In Figure 5, we display the effects of inflammation on the compartmental volumes and alveolar ventilation: tissue swelling is accompanied by a corresponding reduction in other compartmental volumes. Figure 5 illustrates end-inspiratory volumes during an insult of insult ($TNF_B(0)=4$), the subsystem does not recover. Alveolar ventilation is reduced to 34.5 ml. The inset in Figure 5 is a zoomed view of the box in lower left corner of Figure 5, showing the expansion of the tissue compartment into the blood compartment. Velocity of the blood increases with

similar dynamics to those of the tissue volume with a maximum 0.297 cm/sec following the survivable challenge, and 0.400 cm/s following the lethal challenge.

Simulations of a single RU

Combining both the gas exchange and immune subsystems simulates the effects of inflammation on gas exchange. During a lethal insult ($TNF_B(0)=4$) PO_2 drops to 43.3 ml at the venous end, hemoglobin no longer saturates in the capillary, and PCO_2 also increases significantly to 41.1 mmHg at the venous end. A non-lethal response ($TNF_B(0)=2$) is accompanied by minimal changes in the gas exchange subsystem.

The model predicts an interesting phenomenon. Following a lethal inflammatory insult, hemoglobin will eventually fail to saturate as it traverses the capillary as PO_2 decreases (Figure 6). This is shown in the top curve (red) of Figure 6, which is the percent of total hemoglobin that is fully saturated, $100H_{B4}/T_{HB}$ versus time. More unexpected is the prediction that the percent of the capillary traversed before hemoglobin equilibrates with O_2 decreases with time as this equilibrium point moves further away from the full saturation.

Lung-scale model

The time evolution of the distribution of scaled RU volumes $N \sim (350 \text{ ml}, 10^4 \text{ ml}^2)$ for a lethal insult predicts that a significant proportion of RUs will reach the alveolar closing threshold within 12 hours and all are below closing volume by 24 hours (Figure 7). The overall structure of the distribution remains unchanged as the average decreases, but its variance decreases in time.

In Figure 8, we display predictions of pulmonary venous PO_2 of the lung-scale model, and of transients of single RU with minimum (150 ml), mean (350 ml) and maximum (550 ml) initial scaled alveolar ventilations. The lung-scale model transient is always below the transient with initial alveolar ventilation 350 ml due to mixing of the pulmonary blood in the proximal pulmonary veins, in accordance to experimental observations (Guyton et al., 2000). As we wished to evaluate the relative impact of changes in lung volumes and shunting on gas exchange, we also displayed the prediction of a model where shunting was not implemented, confirming the major role of shunting in the rapid deterioration of gas exchange during a lethal inflammatory stimulus (Neumann et al., 2001).

In Figure 9 we compare the effect of altering diffusion and shunting during inflammation. We plotted the transients for pulmonary venous PO_2 with shunting and diffusion both increased and decreased by fifty percent. For the increased shunting curve (blue) the alveolar closure scaled volume threshold was set to 70 ml and for the decreased shunting curve (red) it was set to 210 ml. As expected the lower closure causes more significant drops in PO_2 . Initial levels are even reduced, since with the lower threshold even in the absence of inflammation there are RUs in the distribution which have shunted. With the lower threshold the drops in PO_2 levels are consistent with the normal parameter set with no shunting until approximately 24 hours. When altering diffusion the across the barrier diffusion rate constants for all the gases and the immune variables were changed simultaneously and the normal closure threshold was used when implementing shunting. For the decreased diffusion (green) curve these rate constants were set to half their normal level and for the increased diffusion (gray) curve they were set to 1.5 their normal level. Decreased diffusion initially results in lower PO_2 levels than in the normal case. This is due to less oxygen diffusing into the blood. Overall we see that less diffusion leads to higher PO_2 levels, this is because of the decrease in the diffusion of neutrophils. Fewer neutrophils in the tissue causes less tissue swelling. More diffusion has the opposite effect due to the increased diffusion of

neutrophils. Therefore, even though the gas molecules diffuse more, the PO_2 level is significantly lower due to inflammation.

Discussion

Our model for gas exchange contains an immune subsystem and explicit lung tissue layer. This model therefore is used to simulate inflammation within a respiratory unit and determine the effect of inflammation on the ability for gas exchange to occur. A variety of stimuli can trigger inflammation, including infection and activated neutrophils (Delclaux et al., 1997; Domenici-Lombardo et al., 1995; Simons et al., 1987; Song et al., 2001). A mild inflammatory stimulus does not result in a significant change in partial pressure for either oxygen or carbon dioxide. Larger stimuli lead to a significant reduction in partial pressure of oxygen at the pulmonary venous end, and therefore systemic arterial circulation. This effect is driven by (1) impaired gas diffusion caused by tissue swelling, (2) closure of alveoli below a critical respiratory unit volume, and (3) oxygen remixing in the pulmonary veins.

Other mathematical models of the lung have concentrated on lung mechanics, pulmonary circulation, gas exchange with the tissue layer treated as a barrier, airway mechanics, and drug deposition in the tracheo-bronchial tree (Ben-Tal, 2006; Hahn et al., 1993; Hill et al., 1973; Liu et al., 1998; Menges et al., 2001). With the exception of mycobacterial granuloma formation modeling (Marino et al., 2004; Marino et al., 2007), attempts at mathematical simulation of lung injury have been sparse, although pulmonary immunity and injury are of immense clinical interest and relevance. Immune-mediated lung injury has typically only been approached with experimental models. These experiments include both insults from the blood and directly introduced into the lung in the form of lipopolysaccharide instillation, chemical injury, and pathogen deposition (Bergeron et al., 1998; Domenici-Lombardo et al., 1995). The model we present is the first to incorporate a tissue layer allowing the explicit stimulation of immune effector cells or molecular mediators, and their potential modulation for therapeutic purposes. Our formulation is also conducive to the introduction of varying amount of details at different scales of description, depending on the goals of simulations. For example, we included many details regarding molecular mechanisms of gas exchange, and fewer details on the local immune response. The formulation of the RU model is computationally intensive to simulate, owing to the spatial description and the wide range of time-scales involved. The fast time scale of tidal breathing compared to inflammatory dynamics supports temporal averaging of the fast dynamics over the breath cycle to develop a more computationally feasible model. Accordingly, we are developing an approximation to this model without an explicit breathing mechanism that captures the inflammatory effects on gas exchange. Once the numerical accuracy of this approximation is confirmed, we will have derived a computationally efficient model that allows multiple RUs under heterogeneous conditions seen in the lung to be linked using a physiologically reasonable implementation of diffusion (simulating extension of a process to neighboring RUs) and advection (simulating lymphatic transport of bacteria for example). Though our primary goal was to model pulmonary response to a systemic challenge, our model could capture different modes of local injury, once RUs are explicitly linked by a spatial formulation at that scale, potentially informed by existing structural models of experimental data (Burrowes et al., 2006; Swan et al., 2008). The introduction of more realistic heterogeneity in ventilation and perfusion, in ways that reflect interventions such as positive end-expiratory pressure or positional (prone) therapy is also of high relevance because these intervention specifically target patients that under inflammatory stress and because there is strong evidence that interventions themselves trigger inflammation (Slutsky et al., 2003). Viral infections, chemical pneumonitis and autoimmune lung disease are other ailments where gas exchange is exquisitely linked to pulmonary inflammation, and where a disease-specific, more detailed representation of the pulmonary immune response could be interface

with our model. We are particularly interested in the development of influenza-related acute pulmonary failure (Hancioglu, B. et al., 2007; Hancioglu et al., 2007), a hallmark of highly cytopathic strains (Kobasa et al., 2007).

Our model is limited in a number of ways. Although the characterization of physicochemical parameters describing local gas exchange is adequate, quantification of parameters characterizing pulmonary blood flow and alveolar ventilation, and our treatment of ventilation-perfusion heterogeneity, is quite insufficient. We achieved heterogeneity in ventilation-perfusion by allowing ventilation to vary, while keeping perfusion constant on each RU. This resulted in a range of ventilation-perfusion ratio which is typically less than that encountered experimentally (Alfaro et al., 2001; Maurenbrecher et al., 2001; Neumann et al., 2001). The likely impact of a wider range of ventilation-perfusion ratios would be to accelerate the deterioration of gas exchange impairment in mixed pulmonary venous blood. There is a growing body of data that could guide this development (Alfaro et al., 2001; Hoffman et al., 2004; Moller et al., 2002). We made no attempt to link alveolar gas content to inspired gas content. This would be of high relevance if inhalation modes of treatment or disease propagation are contemplated, especially with particulate agents (Sapoval et al., 2002; Weibel et al., 2005). Similarly, our treatment of lung tissue swelling could be greatly improved with a more detail treatment of local hydrostatic and oncotic pressures. This would be of relevance for serious simulations of positional therapy. Yet, there is a dearth of suitable datasets to properly triangulate many of the parameters on which to base such extensions. Such datasets would ideally contain information on local concentrations of relevant immune mediators, counts of activated immune cells and relative volume distributions of alveolar air space, capillary blood and lung tissue. We also assumed fixed boundary conditions for pulmonary arterial gas and acid-base status. Clearly, a closed loop model that included a metabolic component would be preferable, since, for example, decreased oxygen delivery may result in increased extraction and lower input oxygen partial pressures on the pulmonary arterial boundary. Accordingly, we would expect model predictions to be more optimistic than observations for extreme hypoxia. We also assumed an oxyhemoglobin dissociation curve that was independent of blood pH. Both of these simplifications could be addressed in extensions of our models. Interestingly, promising experimental techniques allow less invasive and repetitive measurement of ventilation-perfusion ratios (Rhodes et al., 1989; Roca et al., 1994), offering exciting new possibilities to compare prediction of multiscale organ physiology to experimental paradigms of acute lung injury.

In conclusion, we believe the model presented herein constitutes an important first step in the development of realistic simulations of pulmonary function under inflammatory stress, and of interventions aimed at improving gas exchange in this broadly relevant context. The model is generically multiscale and be improved in its physiologic accuracy and computational load.

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Figure 1. Model Schematic for a single RU

Interactions included within the single RU model. Resting neutrophils, activated neutrophils in the tissue and blood are represented by N_0 , NA , and NA_B , respectively. The subscript B on TNF designates blood TNF . Arrows across the barriers between the compartments represent diffusion. Black arrows represent upregulation. The green arrow between HB_4 and O_2 represents the binding and unbinding of O_2 to HB_4 . The white/blue arrow between CO_2 and HCO_3^- represents the enzymatic reactions between CO_2 and HCO_3^- . The red arrow represents the interactions between the immune and the gas exchange subsystems.

Figure 2. Model schematics for the linking of multiple RUs to create a lung-scale model

The first column represents concentrations and partial pressures entering the RU. These are the same on all RUs throughout the simulations. All compartmental volumes are uniformly distributed across the RUs. Initial levels used are given in Table 1. The initial alveolar ventilation on the RUs was determined by sampling a normal truncated distribution. Simulations were run for the various RUs and then a weighted average dependent on the distribution was taken of the blood variables values on exiting the RU. This weighted average is used as the initial condition for the ODE system that models venous mixing of the blood exiting the various RUs. The results of this mixing are the output of the full model, which are the variables in the left column.

Figure 3. Oxygen and saturated hemoglobin levels under normal conditions

A. PO_2 (mmHg) levels in blood. Zero on the x -axis represents the pulmonary arterial end of the capillary, while, moving right in space, 20 is the pulmonary venous end. The y -axis is time, therefore the columns represent the capillary PO_2 levels in a space unit as time progresses. **B.** PO_2 levels in the tissue. **C.** Saturated hemoglobin in the blood. **D.** Alveolar PO_2 levels with a four second breath cycle, one second inspiration and 3 seconds expiration.

Figure 4. Carbon Dioxide and Bicarbonate levels under normal conditions

A. PCO_2 (mmHg) levels in blood. Zero on the x -axis represents the pulmonary arterial end of the capillary, moving to the right is space along the capillary. The y -axis is time; columns represent PCO_2 levels on individual space units as time progresses. **B.** PCO_2 (mmHg) in the tissue. **C.** Bicarbonate in the blood. **D.** Alveolus PCO_2 levels with a four second breath cycle, one second inspiration and 3 second expiration.

Figure 5. Compartment volumes and alveolar ventilation during inflammation initiated in the blood

Initial levels of TNF in the blood (TNF_B) = 4. The model reaches a steady state where the immune variables remain elevated and lung volumes are impaired. Inset is an enlarged view of the box in the lower left corner of the large plot. This shows in more detail the swelling of the tissue compartment into the blood compartment as inflammation increases.

Figure 6. The effects of lethal inflammation on hemoglobin saturation

The bottom curve (blue) is the percent of the capillary traversed before oxygen equilibrates with hemoglobin versus time following the inflammatory insult (see text for details). The top curve (red) is the percent of the total hemoglobin that is fully saturated.

Figure 7. Distributions of alveolar ventilations at times 0, 12 and 24 hours following a lethal insult

Initially, 500 RUs are normally distributed between with scaled alveolar ventilation between 150 and 550 ml (mean = 350 ml) (black bars). After 12 hours the mean scaled volume has dropped to 127 ml (dark gray bars). At 24 hours the mean scaled alveolar ventilation average is 47 ml (pale grey bars). The dotted vertical line at 140 ml represents the scaled alveolar ventilation used as the alveolar closure threshold.

Figure 8. Dynamics of pulmonary venous O_2 following a lethal insult of TNF

Dashed lines represent dynamics of single RUs with minimum scaled alveolar ventilation, 150 ml (green), mean scaled alveolar ventilation, 350 ml (blue), and maximum scaled alveolar ventilation, 550 ml (red). Following redistribution of blood exiting RUs, the dynamic of pulmonary venous O_2 varies whether shunting is present or not, without shunting (black) and with shunting (grey).

Figure 9. Varying the diffusion constant and alveolar closure threshold during a lethal insult

For the diffusion curves the diffusion constants for all variables which diffuse was increased and decreased by fifty percent throughout the simulation. The alveolar closure threshold was increased and decreased by fifty percent for the shunting curves. This threshold was 70 ml for the increased shunting curve (blue) and 210 ml for the decreased shunting curve.

Table 1

Gas Exchange Parameters

Parameter	Value	Description	Comments	Source
L	$7\left(\frac{0.02\pi}{2}\right) = 0.22\text{cm}$	Length of RU along the capillary	Estimated by assuming that an individual alveolus diameter is 0.02 cm and that as the blood traverses the lung it is in contact with half of the circumference of seven alveoli.	(Guyton et al., 2000)
h	$\frac{L}{20} = 0.011\text{cm}$	Length of each unit of space along the capillary	We use 20 spatial units in our calculations.	
t_{in}	1 second	Length of inspiration	Total time for breathing cycle is assumed to be 4 seconds, 1.5 breaths per minute. The inhalation time is one forth of the total time.	
t_{out}	3 seconds	Length of expiration	See above comment for t_{in} .	
V_0	0.29 cm/sec	Speed of blood	We estimated the range for v_0 0.01788–0.4398 cm/sec, by assuming transient times for blood between 0.5 to 12.3 seconds with the capillary length calculated above. We took 0.75 seconds to be our transient time under normal conditions.	
PO_{2BO}	40 mmHg	Pulmonary arterial PO_2		(Guyton et al., 2000)
PCO_{2BO}	45 mmHg	Pulmonary arterial PCO_2		(Guyton et al., 2000)
PO_{2air}	150 mmHg	Air PO_2		(Guyton et al., 2000)
PCO_{2air}	0 mmHg	Air PCO_2		(Guyton et al., 2000)
iHB_4	1.7×10^{-3} M	Arterial concentration of saturated hemoglobin	Found by fitting our oxyhemoglobin curve such that hemoglobin is 50% saturated at a PO_2 of 27 mmHg and 99% saturated at a PO_2 of 100 mmHg and assuming PO_{2BO} is 40 mmHg	(Keener et al., 1998)
$iHCO_3^-$	2.4×10^{-2} M	Arterial concentration of bicarbonate.		(Guyton et al., 2000)
O_2 D_{TB}	6.7×10^{-12} L/s	Rate constant for the diffusion of oxygen between tissue and blood.		
O_2 D_{TA}	2.4×10^{-12} L/s	Rate constant for the diffusion of oxygen between tissue and air.		
CO_2 D_{TB}	8.5×10^{-11} L/s	Rate constant for the diffusion of carbon dioxide between tissue and blood.		
C D_{TA}	7.6×10^{-10} L/s	Rate constant for the diffusion of carbon dioxide between tissue and air.		

Parameter	Value	Description	Comments	Source
O_2 σ_B	1.2×10^{-6} M/mmHg	$[O_2] = \sigma_B^{O_2} PO_2$ in the blood.	Calculated from the solubility coefficient for oxygen in water.	(Guyton et al., 2000)
O_2 σ_T	1.2×10^{-6} M/mmHg	$[O_2] = \sigma_T^{O_2} PO_2$ in the tissue.	Calculated from the solubility coefficient for oxygen in water.	(Guyton et al., 2000)
O_2 σ_A	5.2×10^{-5} M/mmHg	$[O_2] = \sigma_A^{O_2} PO_2$ in the air.	Calculated from $nRT = PV$.	
σ_B^C	3.0×10^{-5} M/mmHg	$[CO_2] = \sigma_B^C PCO_2$ in the blood.	Calculated from the solubility coefficient for carbon dioxide in water.	(Guyton et al., 2000)
σ_T^C	3.0×10^{-5} M/mmHg	$[CO_2] = \sigma_T^C PCO_2$ in the tissue.	Calculated from the solubility coefficient for carbon dioxide in water.	(Guyton et al., 2000)
σ_A^C	5.2×10^{-5} M/mmHg	$[CO_2] = \sigma_A^C PCO_2$ in the air.	Calculated from $nRT = PV$.	
N_{ru}	1.2×10^7	Number of RU's in the lung.	Calculated assuming that there are 3×10^8 alveoli in the lung and that each RU consists of 25 alveoli.	(Guyton et al., 2000)
V_{h0}	$\frac{0.09}{N_{ru}} = 7.5 \times 10^{-9} L$	Blood volume: blood volume in the capillaries of a RU under normal conditions.	There is between 0.07–0.14L of blood in the lung capillaries. For our simulations, we assume under normal condition that the blood volume is 0.09L.	(Keener et al., 1998)
V_{T0}	$\frac{0.5}{N_{ru}} = 4.2 \times 10^{-8} L$	Tissue Volume: tissue volume in a RU under normal conditions.	Calculated assuming that there is 0.5L of tissue in the lung.	
V_{Amn0}	$\frac{2.3}{N_{ru}} = 1.9 \times 10^{-7} L$	Minimum of the alveolar air space: volume of the alveolar air space in a RU at the end of expiration under normal conditions.	Calculated assuming that the minimum volume in the lung is 2.3L.	(Guyton et al., 2000)
V_c	$\frac{0.35}{N_{ru}} = 2.9 \times 10^{-8} L$	Alveolar Ventilation: the volume inhaled into a RU during a breath under normal conditions.	Calculated assuming that alveolar ventilation for the whole lung was 0.35 L.	
$R_H = \frac{k^-}{k^+}$	1.8×10^5	Ratio of the reverse and forward reaction rates for the saturation of hemoglobin.	This ratio was found by fitting the oxyhemoglobin saturation curve as described for iHB_d .	
m	3.6	Number of oxygen molecules needed to bind to Hb_m in order to form Hb_d .	This parameter was found by fitting the oxyhemoglobin saturation curve as described for iHB_d .	
k^+	$5 \times 10^{-4}/s$	Rate at which m oxygen molecules bind to Hb_m to form Hb_d .	This parameter was chosen to ensure the hemoglobin and oxygen dynamics stabilize in first third of the capillary.	(Guyton et al., 2000)
T_{HB}	2.2×10^{-3} M	Concentration of total hemoglobin, $HB_d + HB_m$.		(Guyton et al., 2000)

Parameter	Value	Description	Comments	Source
k_{catCB}	$8.8 \times 10^5/s$	Maximum rate of the enzymatic reaction with CO_2 as the substrate.	Fit such that the carbon dioxide and bicarbonate dynamics stabilize in the first tenth of the capillary.	(Guyton et al., 2000)
k_{mCB}	0.01 M	Michaelis-Menten Constant, concentration where the reaction occurs at half the maximum rate, for the enzymatic reaction with CO_2 as the substrate.	See comment for k_{catCB} .	
k_{catHC}	$2.0 \times 10^5/s$	Maximum rate of the enzymatic reaction with HCO_3^- as the substrate.	See comment for k_{catCB} .	
k_{mHC}	0.02 M	Michaelis-Menten Constant, concentration where reaction occurs at half the maximum rate, for the enzymatic reaction with HCO_3^- as the substrate.	See comment for k_{catCB} .	
D_{O_2T}	$3.2 \times 10^{-5} \text{ cm}^2/s$	Oxygen diffusion constant in water.		(MacDougall et al., 1967)
D_{CT}	$6.5 \times 10^{-4} \text{ cm}^2/s$	The diffusion constant for diffusion of carbon dioxide within the tissue.	Diffusion of carbon dioxide is 20 times faster than that of oxygen.	(Guyton et al., 2000)
σ	20	This parameter determines the rise in $sh(t)$ our approximation to the Heaviside function.	Increasing this parameter sharpens the rise in $sh(t)$.	
τ_1	0.5 s	Time constant for inspiration.	Chosen so that V_{CO} is inhaled in t_{in} seconds.	
τ_2	0.7 s	Time constant for expiration.	Chosen so that V_{CO} is exhaled in t_{out} seconds.	

Table 2

Immune Subsystem Parameters

Parameter	Value	Description
μ_{TB}	1.8/s	Decay rate of TNF_B (blood).
α	8	Rate at which TNF_B is depleted during the activation of neutrophils.
N_0	1.2	Amount of resting neutrophils available for activation.
k_m	1	Hill Constant, the TNF_B level at where the activation of neutrophils occurs at half its maximum rate.
m_p	1×10^{-5}	Slope of the linear function of z modeling the change in the diffusion rate of TNF and TNF_B during an inflammatory response.
b	1×10^{-3}	y -intercept of the linear function of z modeling the change in the diffusion rate of TNF and TNF_B during an inflammatory response.
γ_B	3	Production rate of TNF_B from neutrophils in the blood
μ_{NB}	0.05/s	Decay rate of activated neutrophils in the blood.
β	12/s	Rate of at which neutrophils are activated by TNF .
k_v	1×10^{-4} /s	Maximum diffusion rate for activated neutrophils.
k	0.7	Hill Constant, the level of inflammation at where the diffusion of neutrophils occurs at half its maximum rate.
μ_T	1.8/s	Decay rate of TNF .
γ_T	3	Production rate of TNF from neutrophils in the tissue.
D_T	$1 \text{ cm}^2/\text{s}$	Diffusion constant for diffusion of TNF within the tissue.
μ_N	0.05/s	Decay rate of neutrophil within the tissue.
χ	1	Chemotaxis constant for neutrophils.
μ_z	0.01/s	Decay rate of inflammation.
k_{zg}	0.1/s	Growth rate of inflammation
k_{zg}	2	Hill Constant, the level of TNF at where growth of inflammation is half its maximum rate.
m_{th}	0.4	Hill Constant, sets the level of inflammation which causes tissue swelling into the blood compartment to reach half its maximum.
m_{td}	1	Hill Constant, sets the level of inflammation which causes tissue swelling into the tissue compartment to reach half its maximum. $m_{td} > m_{th}$, since swelling tissue expands more readily into alveolar air space.
m_c	10	Hill Constant, sets the level of inflammation which causes the alveolar ventilation to fall to half its maximum.