SPECIFIC AIMS

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease resulting from a complex process where various prenatal or postnatal factors that affect preterm neonates interfere with lower respiratory tract development, leading to a severe, lifelong disease [1]. BPD is likely caused by two sets of conditions. In some scenarios, resuscitation at childbirth and aggressive mechanical ventilator use may cause the neonate to develop BPD. In other cases, BPD develops when the neonate is born during the canalicular (from the 17th to 26th week of gestation) or saccular (from the 27th to 36th week of gestation) stage of development. The underdeveloped structures, unthinned interstitium, and lack of surfactant production can lead to BPD [1].

As most severe cases of BPD occur in extremely preterm (EPT) and very preterm (VPT) infants, current treatment efforts focus on the prevention of BPD development, mainly prenatal prevention and minimal intubation. Use of maternal progesterone and surgical closure of the cervix with cerclage are well-known measures to prevent premature births [2]. Non-invasive respiratory ventilation strategies such as nasal continuous positive airway pressure (NCPAP) and high flow nasal cannulas (HFNCs) have also been developed to avoid risk of aggressive mechanical ventilation [3].

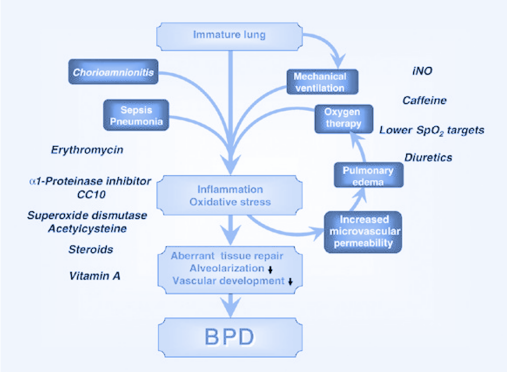

Figure 1. Current known causes and possible preventive measures of BPD.[5]

Although certain substances may decrease the chance of BPD development (Figure 1), the current gap in pathogenesis explains the lack of effective and satisfactory prevention and therapeutic approaches. If developed, BPD will lead to future complications such as higher risks for respiratory tract infections and asthma-like symptoms in preterm infants with BPD than preterm infants without BPD [4]. To fill this unmet need, this proposal aims to pioneer maturity prevention and approaches to reduce the risk of BPD development.

Specific Aim 1 will be to create a computational model simulating normal lung conditions and to verify that it is accurate. We seek to: (a) Reduce lung anatomy to “respiratory units" with discrete compartments (listed in sub-aim b); (b) Develop differential equations in MATLAB to govern the diffusion of oxygen over time from alveolar space, to alveolar capillary tissue, to pulmonary blood; (c) Verify that the model’s predicted steady state matches real-life expectations of normal respiration.

Objective: The model of the normal lung will serve as a control group and lay out conditions to be perturbed when simulating BPD conditions.

Specific Aim 2 will be to modify the computational model to simulate BPD conditions and compare it to normal lung conditions. We aim to: (a) Introduce inflammation and hemoglobin activity to the model to characterize the behavior of oxygen diffusion under BPD conditions. (b) Define the partial pressure of oxygen (PO_2) based on the volume of the compartment, the diffusion rate of oxygen across the compartments, and the concentration of oxygen per unit of pressure.

Objective: This model will be used to characterize BPD behavior in comparison to normal lung behavior and will then be used to observe the effects of therapeutics on BPD behavior.

Specific Aim 3 will be to test potential treatments of BPD using model parameters. We will: (a) Alter parameters to simulate three potential treatments for BPD: caffeine, vitamin A, and nitric oxide and (b) Compare treatment oxygen levels against those produced by the inflammation model.

Objective: The developed model will be used to evaluate the effectiveness of the aforementioned factors in preventing the onset of and treating BPD.

PROJECT SUMMARY

The goal of this project is to develop preventative approaches that reduce the risk of bronchopulmonary dysplasia (BPD) development. Generally, the approach for BPD treatment consists of therapeutics that treat symptoms after its onset. Furthermore, aggressive ventilator usage is currently used for BPD treatment, which can cause further damage to the lung tissues. In contrast to treatment after onset, this project takes a different strategy that involves preventing the development of BPD through use of treatments such as caffeine, vitamin A, and nitric oxide. The three substances (caffeine, vitamin A, and nitric oxide) have shown to reduce free radicals, a type of reactive oxidative species (ROS), in cells. Since ROS are one of the main causes of inflammation onset and blood vessel dysfunction, caffeine, vitamin A, and nitric oxide would therefore reduce the amount of ROS in the cells, preventing inflammation. By inhibiting and preventing the onset of initial airway inflammation, we predict that BPD will not occur. Successful completion of these proof-of-principle experiments will provide a foundation for BPD prevention.

PROJECT NARRATIVE

Each year, more than 28,000 babies in the United States are born extremely preterm (< 28 weeks gestation), increasing the risk for multiple morbidities such as bronchopulmonary dysplasia (BPD), an inflammatory condition caused by damage to delicate lung tissues primarily due to aggressive ventilator usage. This proposal takes a new approach towards preventing the onset of BPD through nonaggressive measures that seek to reduce inflammation.

Research Strategy

Significance

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that significantly increases the amount of inflammation in the patients' lung tissue [1]. Since this disease is largely caused by aggressive mechanical ventilator use on neonates with fragile or underdeveloped lungs, this disease mostly affects the premature neonatal population [1]. In fact, 10,000 to 15,000 newborns, or 67% of premature neonates, develop BPD in the United States every year [6,7]. The development of BPD often leads to future complications such as higher risks for respiratory tract infections and asthma-like symptoms [4]. Not only does BPD development affect the patients, but it also puts a burden on the families. The average cost of one day of hospitalization for a BPD patient is $3470 while the cost for a non-BPD patient is only $2575 (35% increase) [8]. These higher prices are largely impacted by the demand for more intense use of resources to treat BPD. Furthermore, rehospitalization rates for BPD neonates are 25.1% while non-BPD patients are just 16.2%. Lastly, the average length of hospitalization directly after birth is 103 days for BPD patients while non-BPD patients stay just 66.5 days. The 55% increase in length of stay is largely caused by additional comorbidities and complications [8]. These increased costs and length of hospital stays place a large burden on both the patients and their families.

Although BPD is a prevalent condition, there are currently few ways to prevent and treat this condition. Most treatments today focus on preventing premature birth [2]. For example, the use of maternal progesterone or surgical closure of the cervix is sometimes used in attempts to prevent premature birth. After birth, decreased use of intubation is also sometimes used to lessen the risk of BPD [2]. However, these measures may not always be possible especially when other health concerns are taken into consideration. Furthermore, there are currently no other treatments available for preventing BPD in premature neonates after birth apart from less mechanical ventilator use. Thus, the use of preventative factors such as caffeine, vitamin A, and nitric oxide is an effective regimen for BPD prevention and treatment [5].

With our proposed computational model which simulates the partial pressure of oxygen in alveoli capillary tissue, alveolar space, and pulmonary blood under different conditions, we will be able to better understand treatments for neonates at high risk of BPD. By looking into the effects each of these factors plays in decreasing inflammation in the lungs or preventing BPD, we will better understand which treatment may be best and guide clinicians to determine dosage for patients.

Innovation

Most mathematical models of partial pressure of oxygen in tissue, alveoli, and blood have been able to effectively observe how oxygen levels change over time [9]. However, they have not been able to model the effects of various factors such as caffeine, vitamin A, and nitric oxide. We will incorporate doses of caffeine, vitamin A, and nitric oxide into our model to evaluate the effectiveness of these factors in BPD treatment. Currently, no model has been applied to discover the effect of factors on BPD patients' oxygen levels. A model that can effectively simulate the effects of caffeine, vitamin A, and nitric oxide on BPD patients' oxygen levels would serve as a tool to evaluate treatment options for patients.

In our preliminary work, we have created an elementary mathematical model that shows oxygen partial pressure in patients' alveoli, tissue, and blood and simulates the effects of caffeine, vitamin A, and nitric oxide. Through future comparisons to actual patient oxygen partial pressure data, we hope to validate our model.

Background and Preliminary Results

We expect our mathematical model to simulate the partial pressure of oxygen in alveoli, tissue, and blood over time. From our model, we can see the control case **(Figure 1)** showing the partial pressure of oxygen in three compartments over time: alveoli, tissue, and blood. The partial pressures change rapidly initially but stabilize at a steady-state pressure. Using parameters from literature and assumptions, we can see that the partial pressures stabilize at around 97 mmHg at around 0.13 seconds.

As expected, we see that the partial pressure of oxygen in alveoli decreases as oxygen diffuses into the tissue then blood. This resulted in an increase in partial pressure of oxygen in tissue and blood as the graph approached steady-state as shown in **Figures 2-4**. The development of BPD is characterized by inflammation in the lungs leading to a decrease in partial pressure of oxygen in the blood. This is effectively shown in our model by the decrease in the steady-state value of oxygen partial pressure in all three compartments when inflammation was added to the model. At nonzero levels of inflammation, the partial pressure of oxygen dropped below 97 mmHg-- 94 mmHg for our simulated low-risk BPD patients **(Figures 5-7)** and 77 mmHg for our high-risk BPD patients **(Figures 8-10)**.

When therapeutics were added to the model, we expected to see an increase in oxygen partial pressure for all three compartments, which was exactly what we observed. We simulated applying caffeine, nitric oxide, and vitamin A treatments to high-risk BPD patients. Caffeine was a relatively ineffective but still beneficial treatment, raising steady state oxygen partial pressure levels from 77 mmHg to 80 mmHg **(Figures 11-13)**. Nitric oxide was a slightly better treatment, raising the oxygen partial pressure to 84 mmHg **(Figures 14-16)**. Vitamin A was an extremely effective treatment, resulting in an oxygen partial pressure of 100 mmHg **(Figures 17-19)**.

Approach

Specific Aim 1: Create a computational model simulating normal lung conditions and verify that it is accurate.

Sub-aims:

Before any development of treatment for lung inflammation can be made, we must first construct a physiologically faithful computational model of a healthy lung. We can later alter the model's parameters to simulate inflammation. Designing and validating the computational model involves the following sub-aims: (a) Reduce lung anatomy to "respiratory units" with discrete compartments (listed in sub-aim b) and simplified geometry; (b) Develop differential equations to govern the diffusion of oxygen over time from alveolar space, to alveolar capillary tissue, to pulmonary blood; (c) Transcribe these equations into MATLAB code for plotting and observation of rate of oxygen diffusion and steady-state; (d) Verify that the computational model's predicted steady state matches real-life expectations of normal respiration.

Rationale:

Our computational model of the healthy lung is based on the equations derived in the journal article "A mathematical model of pulmonary gas exchange under inflammatory stress" by Angela Reynolds et al [9]. By dividing the lung into geometrically-simplified respiratory units, we simplify diffusion from a three-dimensional complication into several one-dimensional slivers that can easily be implemented in the computational model using Fick's law of diffusion. This segmentation is based on the assumption that gas does not mix well in alveolar capillary tissue and pulmonary bloodstream,

meaning each alveolus-tissue-blood sliver can potentially have a different partial pressure of oxygen. Segmentation in the model becomes important for BPD patients with issues in ventilation or perfusion as different portions of the lung and thus different respiratory units experience unequal oxygen supply from alveoli and unequal oxygen diffusion capacity. To calculate the total oxygen diffused from alveoli to pulmonary blood, the partial pressure of oxygen in each one-dimensional sliver is averaged for each compartment.

For our purpose of simulating normal lung conditions, we assume each one-dimensional sliver has equal oxygen supply and diffusion capacity (i.e., no issues with ventilation or perfusion). To implement Fick's law for oxygen diffusion from alveolar space to capillary tissue, and from capillary tissue to bloodstream, we applied experimentally determined oxygen diffusion rate constants for the alveolus-tissue and tissue-blood barriers as well as a conversion factor to calculate the concentration gradient of oxygen across these barriers based on the difference between partial pressure of oxygen between two compartments [9]. Our implementation of Fick's law also accounts for the volume of each compartment, with alveolar volume four-times the tissue volume, and twenty-five-times the blood volume, derived from the normal human physiological range [9].

Protocol:

To implement our Fick's law differential equations in a computational model, we created a MATLAB function to take initial partial pressure of oxygen in the alveolus, tissue, and blood compartments as inputs and track the level of partial pressure of oxygen in these compartments over a 0.3-second timespan. Initial partial pressures were determined as: 100 mmHg in the alveolus, based on oxygen content of inspired air; 70 mmHg in tissue, the midpoint between alveolus and blood due to residual oxygen from previous inspiration; and 40 mmHg in blood based on average pulmonary artery levels [10]. MATLAB's built-in differential equation solver ode23 was used to calculate partial pressure of oxygen over time.

The partial pressure of oxygen in the pulmonary bloodstream achieved in steady-state is one of the most important - if not the most important - parameter to determine health outcomes of BPD patients. We find that in the normal lung, blood oxygen levels rise to nearly 100 mmHg, as expected in normal respiration [10]. With our MATLAB function, we can also test hypoxic conditions by decreasing alveolar partial pressure of oxygen. We can also modulate the constants to simulate lung damage, weakness, and inflammation in BPD patients, which will be expanded on in Specific Aim 2.

Alternative Strategies:

Our computational model primarily considers temporal effects of oxygen diffusion, but we could give greater consideration to spatial effects by introducing more differential equations to quantify gas mixing between one-dimensional slivers. Furthermore, if we want to design a more complete picture of respiration, we could introduce a set of differential equations analogous to the oxygen diffusion equations for carbon dioxide.

Potential Pitfalls:

The primary potential pitfall of our simplified computational model of the normal lung is that it ignores sources of oxygen outside of inspiration and ignores all oxygen sinks, including cell metabolism. Total oxygen in the lung remains constant in our model, but this does not occur in real lungs; our model effectively over-reports pulmonary blood oxygen levels. Furthermore, as mentioned in the alternative strategies section, because our model reduces three dimensions to one dimension, we lose consideration of spatial effects that would make oxygen diffusion slower; diffusion occurs slightly too quickly in our model, which would result in steady-state being reached too quickly.

Specific Aim 2: Modify the computational model to simulate BPD conditions and compare to normal lung conditions.

Sub-aims:

In order to meet the objective of characterizing BPD behavior and evaluating the effectiveness of various therapeutics to treat the disease, we must establish and verify a BPD model that accurately characterizes oxygen levels in alveoli, tissue, and blood under the effects of BPD. To accomplish the outlined goals, we must: (a) modify the model from specific aim 1 to simulate BPD conditions, specifically altering the level of inflammation across alveoli in order to characterize the behavior of oxygen diffusion under BPD conditions, (b) define the quantities relevant to this model, focusing on the partial pressure of oxygen (PO_2) based on the volume of the compartment (V), the diffusion rate of oxygen across the compartments (D), and the concentration of oxygen per unit of pressure (σ).

Rationale:

Once we constructed the basic model to measure PO_2 in the three different compartments - alveoli, tissue, and blood - we needed to modify the model from specific aim 1 to include a factor of inflammation. In this model, we use an inflammation factor, z_i, which we can alter to change various levels of inflammatory conditions. It is implemented in the model through its effect on the volume of the compartment, V_{Bz}. Specifically, the volume of the blood compartment is inversely related to inflammation, as the vasoconstriction due to inflammation reduces the amount of blood and oxygen that can be held. Thus, with the alteration, we can characterize the behavior of partial pressure of oxygen (PO_2) and fully bound hemoglobin (Hb_4) under BPD conditions. Additionally, we can compare the partial pressure of oxygen in the alveoli, tissue, and blood between the normal and BPD conditions based on given values. This includes compartment volumes, the diffusion rate of oxygen across the compartments, and the concentration of oxygen per unit of pressure in each of the compartments. The paper only provided initial values of PO_2 in the alveoli and blood, so we provided an estimate for the initial value of PO_2 in tissue.

Protocol:

We implemented the model in MATLAB. With initialized values of 100 mmHg for PO_2 in the alveoli, 70 mmHg for PO_2 in the tissue, 40 mmHg for PO_2 in the blood, and 1.7×10^{-3} M for Hb_4. We used an ode23 solver to determine the PO_2 in the alveoli, blood, and tissue compartments over a 1 second time period. The ode23 solver utilized the equations we modified to include inflammation in order to output a graph of the PO_2 vs time, thus allowing us to trace when and where the PO_2 diffused between compartments. We compared the BPD condition to the normal lung condition by changing the z_i value from 0 (normal lung condition with no inflammation) to an assumed value of 20 (low risk BPD) and 0 to an assumed value of 100 (high risk BPD).

Alternative Strategies:

We used an inflammation factor to alter the volume of the compartment, but inflammation could have affected the other values that we assumed to be constants. We could have manually changed the constants to measure their effect on the partial pressure of oxygen in the alveoli, tissue, blood, and hemoglobin. However, this strategy would have been inefficient, and we were able to establish a model that functionally makes sense. Rather than trying to validate specific values for all the variables we are testing, we are only looking to establish a cause-effect relationship to determine the broader effects of inflammation of PO_2.

Potential Pitfalls:

We utilized a simplified model of the oxygen diffusion across the alveoli, tissue, and blood, implementing only one-directional flow between each of the compartments. Real-world specific interactions between all parts of the respiratory and circulatory system are much more complicated than we present and, thus, our model is not entirely mathematically accurate. Our model would include more variables that reflect the various ways that oxygen may dissipate before it reaches the blood and binds to hemoglobin. However, for our purposes of establishing a relationship between inflammation and oxygen availability to different systems in the body, our model is successful.

Specific Aim 3: Test preventative factors for BPD development with the computational model to evaluate their effectiveness in preventing the onset of and treating BPD.

Sub-aims

With a complete and physiologically faithful computational model of a lung with inflamed conditions, the goal of this specific aim is (a) to proceed with altering the initial parameters in our inflamed model to simulate an inflamed lung receiving BPD preventative factors, and (b) to evaluate their effectiveness in preventing the development of and treating BPD. The preventative factors that will be introduced are caffeine, vitamin A, and nitric oxide.

Rationale

The modifications made in order to simulate the treatment of caffeine, vitamin A, and nitric oxide to an inflamed lung is based on multiple journals. However, because clinical trials of these preventative factors on human preterm infants would raise ethical concerns, the modifications will be based on animal models, specifically rat models. In preterm human infants, it has been noted that there is an observed association with elevated concentrations of oxygen and prolonged increase in blood chemokine, an inflammatory cytokine, concentrations [11]. Based on 6-day-old rat newborns, exposure to supraphysiologic O_2 resulted in an upregulation of chemokines and proinflammatory cytokines. The treatment of caffeine then effectively abolished any hyperoxia-mediated increase in chemokine and proinflammatory cytokine mRNA expression [11]. Thus, it can be inferred that caffeine decreases the pulmonary tissue expression of chemokines and leukocyte influx following hyperoxia from oxygen ventilator usage.

Vitamin A and its active metabolites have been found to be significant in promoting normal respiratory epithelial differentiation, growth, and anti-inflammation [12]. The Brown Norway rat model of airway hypersensitivity found that vitamin A influences gene expression in the inflammatory process through its involvement in the immune system and alleviation of oxidative stress. This is also reflected in premature babies, where administration of high vitamin A doses reduced the development of BPD from 85% in the control group to 45% in the treatment group [12]. Similar to that of vitamin A, nitric oxide is involved in the pathogenesis of inflammation [13]. Under normal conditions, nitric oxide has been proven to be useful for the treatment of inflammation as an anti-inflammatory [13].

Protocol

We once again implemented our model in MATLAB with further modifications made. Because the parameter z_i reflects the degree of inflammation in our lung model, z_i will be adjusted accordingly to reflect our treatments of caffeine, vitamin A, and nitric oxide. The initial parameter values set for PO_2 in the alveoli, PO_2 in the tissue, PO_2 in the blood, and Hb_4 are kept the same because these treatments do not affect these parameters. In this case, we chose the z_i values of caffeine, vitamin A, and nitric oxide to be 80, 10, and 50 respectively. Nitric oxide has a moderate degree of inflammation

because nitric oxide is linked to the immune response, but increasing its concentration may actually induce an inflammatory response, the opposite of our treatment intention [13]. Vitamin A and caffeine are both complementary and alternative medicines that work in chemoprevention associated with chronic inflammation such as BPD as observed in inflammatory conditions [14]. However, caffeine has the highest degree of inflammation because it is difficult to have specific effects on just the respiratory system. Vitamin A has the lowest degree of inflammation because it is considerably more involved in the anti-inflammatory pathway as aforementioned. This will then enable us to be able to compare the BPD condition to the BPD condition with treatment and to see the effects of these therapeutic treatments in the partial pressure of oxygen.

Alternative Strategies

We only chose to simulate three of the many preventative factors for BPD development shown in literature, but our model can definitely extend further by simulating additional factors. For example, additional preventative factors may include avoiding supraphysiologic O_2 exposure, using steroids such as hydrocortisone, and even administering extra surfactant in extreme premature cases of underdeveloped lungs [15]. It will be interesting to see the effects of these additional factors on our model and to evaluate their efficiency by comparing their results with the results from our initial simulation with caffeine, vitamin A, and nitric oxide.

Potential Pitfalls

The interactions between the inflammatory response and caffeine is significantly more complicated than what our model can represent, which will be one of the major limitations for our computational model. Our simulation for the degree of lung inflammation is controlled by a single variable denoted z_i, but the interactions between our simulated preventative factors and lung inflammation are much more complex. There are multiple factors and targets that can cause inflammation: from molecules such as chemokines, cytokines, leukocytes, free radicals, oxidative stress, down to gene expression and regulation. Thus, it is difficult to model the individual effects of each cause of inflammation and have it fully incorporated into our model.

Another limitation for our model is the lack of clinical trials in infants to further confirm the parameter values chosen for these treatments. As aforementioned, many numbers derived in our model are based on animal models. This is due to the fact that clinical trials on human preterm infants would raise ethical concerns and would be difficult to research and execute. However, we believe that this should not affect our model significantly, as it has been noted in the literature that early exposure to high oxygen concentrations results in progressive lung disease, which closely resembles BPD in premature infants [11].

Conclusion

Our computational model simulated the effects of therapeutic treatments on an inflamed lung to determine the most effective treatment for ameliorating respiratory inflammation. We recognize that our computational model has limitations, and future steps should include the consideration of spatial effects and other oxygen sources and sinks. Furthermore, we should consider that oxygen binding to proteins in blood or oxygen carriage in a chemically modified form will result in a non-uniform oxygen distribution. For our current purposes of creating a simpler model that still stays physiologically faithful to healthy and inflamed lungs, our model is successful as a proof of concept of the effects of various therapeutic treatments to reduce respiratory inflammation. As such, we will consider all three specific aims to be successful if the initial model, inflamed model, and model with therapy accurately reflect experimental findings. Future progress for renewal and revision would be implementing our model both in vitro and in vivo. In vitro modeling would include cell scaffolding to construct a 3D model of the lung and utilize optics to measure oxygen levels, and in vivo modeling would include preliminary studies in preterm infants in addition to the usage of lung data using pulse oximeters.

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Equation Table

Equation	Source
$\frac{dPO_{2Bi}}{dt} = \frac{D_{TB}^{O2}(PO_{2Ti} - PO_{2Bi})}{\sigma_B^{O2} V_{B0}}$	Literature [9] Equation 1
$\frac{dPO_{2Ti}}{dt} = \frac{D_{TB}^{O2}(PO_{2Bi} - PO_{2Ti})}{\sigma_T^{O2} V_{T0}} + \frac{D_{TA}^{O2}(PO_{2A} - PO_{2Ti})}{\sigma_T^{O2} V_{T0}}$	Literature [9] Equation 2
$\frac{dPO_{2A}}{dt} = \frac{D_{TA}^{O2}}{\sigma_A^{O2} V_{A0} N} \sum_{i=1}^{N} (PO_{2Ti} - PO_{2A})$	Literature [9] Equation 3
$V_B(\bar{z}_i) = \frac{V_{B0}}{1+m_{vtb}\bar{z}_i}$	Literature [9] Equation 31
$V_T(\bar{z}_i) = V_{T0} + V_{B0} - \frac{V_{B0}}{1+m_{vtb}\bar{z}_i} + V_{Amin0} - \frac{V_{Amin0}}{1+m_{vta}\bar{z}_i}$	Literature [9] Equation 32
$\frac{dPO_{2Bi}}{dt} = \frac{D_{TB}^{O2}(PO_{2Ti} - PO_{2Bi})}{\sigma_B^{O2} V_B(\bar{z}_i)} + \frac{m}{\sigma_B^{O2}}(k^- HB_{4i} - k^+(T_{Hb} - HB_{4i})PO_{2B}^m - v$ *$v\nabla_i PO_{2Bi}$ was eliminated since spatial effects are negligible in the one-dimensional model	Literature [9] Equation 35
$\frac{dHB_{4i}}{dt} = k^+(T_{Hb} - HB_{4i})PO_{2B}^m - k^- HB_{4i} - v\nabla_i HB_{4i}$ *$v\nabla_i HB_{4i}$ was eliminated since spatial effects are negligible in the one-dimensional model	Literature [9] Equation 36
$\frac{dPO_{2Ti}}{dt} = \frac{D_{TB}^{O2}(PO_{2Bi} - PO_{2Ti})}{\sigma_T^{O2} V_T(\bar{z}_i)} + \frac{D_{TA}^{O2}(PO_{2Ai} - PO_{2Ti})}{\sigma_T^{O2} V_T(\bar{z}_i)} + D_{O_2 T}\nabla_i^2 PO_{2Ti}$ *$D_{O_2 T}\nabla_i^2 PO_{2Ti}$ was eliminated since spatial effects are negligible in the one-dimensional model	Literature [9] Equation 41
$\frac{dPO_{2A}}{dt} = \frac{D_{TA}^{O2}}{\sigma_A^{O2} V_A(y,\bar{z}_i) N} \sum_{i=1}^{N} (PO_{2Ti} - PO_{2A})$	Literature [9] Equation 46
$V_A(y,\bar{z}_i) = V_{Amin}(\bar{z}_i) + y$ and $V_{Amin}(\bar{z}_i) = \frac{V_{Amin0}}{1+m_{vta}\bar{z}_i}$ *$V_{Amin0} = V_{A0}$, assumption: $y = 0$ Therefore: $V_{Amin}(\bar{z}_i) = \frac{V_{A0}}{1+m_{vta}\bar{z}_i}$	Literature [9] Equation 48

Constants and Variables Table

Parameter	Value	Description	Source
PO_{2Ti}	95 mmHg	Partial pressure of oxygen in alveoli capillary tissue	Assumption: Midpoint between alveolus and pulmonary artery
PO_{2Bi}	40 mmHg	Partial pressure of oxygen in pulmonary artery	Literature [9,10]
PO_{2A}	150 mmHg	Partial pressure of oxygen in alveolar space	Literature [9]
PO_{2B}^{m}	95 mmHg	Partial pressure of oxygen in pulmonary bloodstream given m-level saturation of Hb	Literature [9]
D_{TB}^{O2}	$6.7 * 10^{-12}$L/s	Rate constant for the diffusion of oxygen between tissue and blood.	Literature [9]
D_{TA}^{O2}	$2.4 * 10^{-12}$L/s	Rate constant for the diffusion of oxygen between tissue and air.	Literature [9]
σ_{A}^{O2}	$5.2 * 10^{-6}$ M/mmHg	$[O_2] = \sigma_{A}^{O2} PO_2$ in the tissue	Literature [9]
σ_{B}^{O2}	$1.2 * 10^{-6}$ M/mmHg	$[O_2] = \sigma_{B}^{O2} PO_2$ in the blood	Literature [9]
σ_{T}^{O2}	$1.2 * 10^{-6}$ M/mmHg	$[O_2] = \sigma_{T}^{O2} PO_2$ in the tissue	Literature [9]
V_{B0}	$7.5 * 10^{-9}$L	Blood volume: blood volume in the capillaries of a RU under normal conditions.	Literature [9]
V_{T0}	$4.2 * 10^{-8}$L	Tissue Volume: tissue volume in a RU under normal conditions.	Literature [9]
V_{Amin0}	$1.9 * 10^{-7}$L	Minimum of the alveolar air space: volume of the alveolar air space in a RU at the end of expiration under normal conditions.	Literature [9]
N	$1.2 * 10^{-7}$	Number of respiratory units in the lung.	Literature [9]
m_{vta}	1	Hill Constant, sets the level of inflammation which causes tissue swelling into the tissue compartment to reach half its maximum.	Literature [9]

		mvta>mvtb, since swelling tissue expands more readily into alveolar air space.	
m_{vtb}	0.4	Hill Constant, sets the level of inflammation which causes tissue swelling into the blood compartment to reach half its maximum compartment to reach half its maximum.	Literature [9]
m	3.6	Number of oxygen molecules needed to bind to Hb_m in order to form Hb_4.	Literature [9]
k^+	$5 * 10^{-4} \frac{1}{s}$	Rate at which m oxygen molecules bind to Hb_m to form Hb_4.	Literature [9]
k^-	$9\frac{1}{s}$	Rate at which m oxygen molecules unbind Hb_4 to form Hb_m	Literature [9]
HB_{4i}	$1.7 * 10^{-3}$M	Arterial concentration of saturated hemoglobin	Literature [9]
T_{HB}	$1.7 * 10^{-3}$M	Concentration of total hemoglobin, Hb_4 + Hb_m	Literature [9]
$\bar{z}_i$	Variable	Index of average global inflammation in the lung. In this R21, ranges from 0 (no inflammation) to 100 (severe inflammation)	Literature [9]

Figures

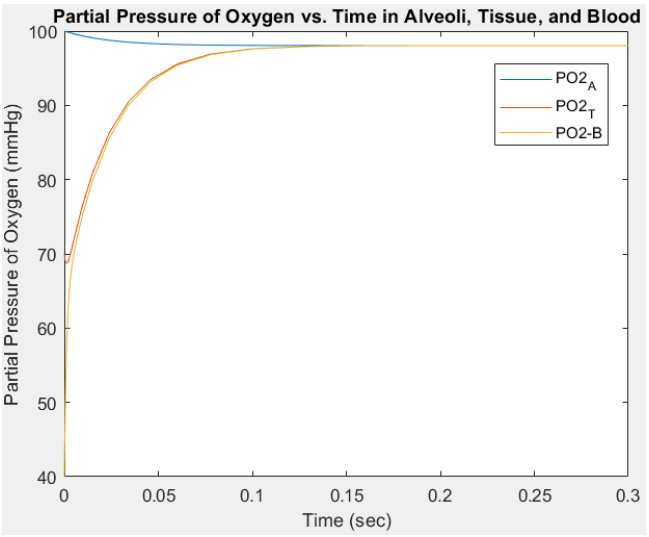

Figure 1. Basic computational model. No inflammation, no influence of hemoglobin. Diffusion takes place inside a one-dimensional silver containing three compartments: alveolar space, alveolar capillary tissue, and pulmonary blood.

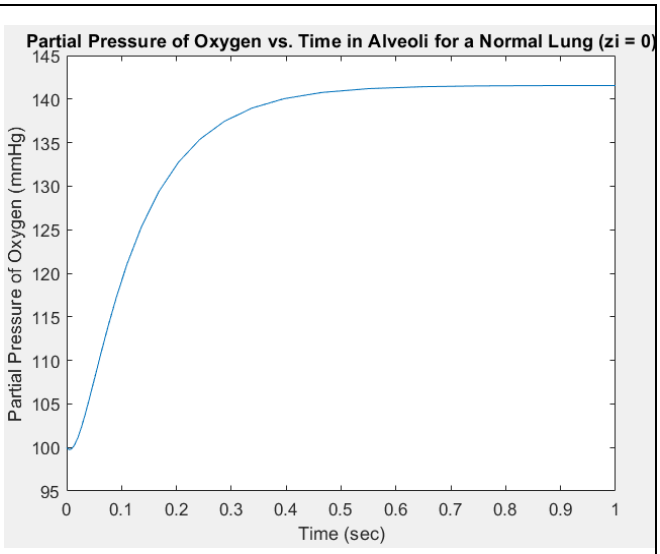

Figure 2. Computational model altered to account for hemoglobin activity and inflammation (z_i = 0 meaning no inflammation, severity increases as z_i increases). For Figures 2-4, steady-state PO_2 in each compartment is greater than initial PO_2 values because the initial presence of Hb_4 causes oxygen release into the system.

Alveolar PO_2, z_i = 0.

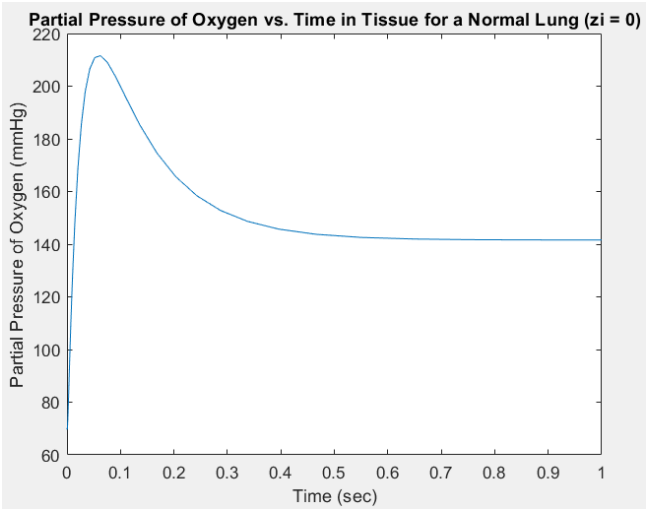

Figure 3. Tissue PO_2, zi = 0.

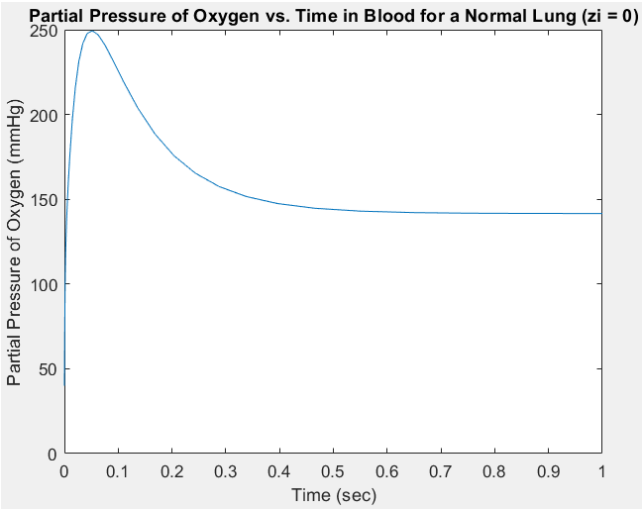

Figure 4. Blood PO_2, z_i = 0.

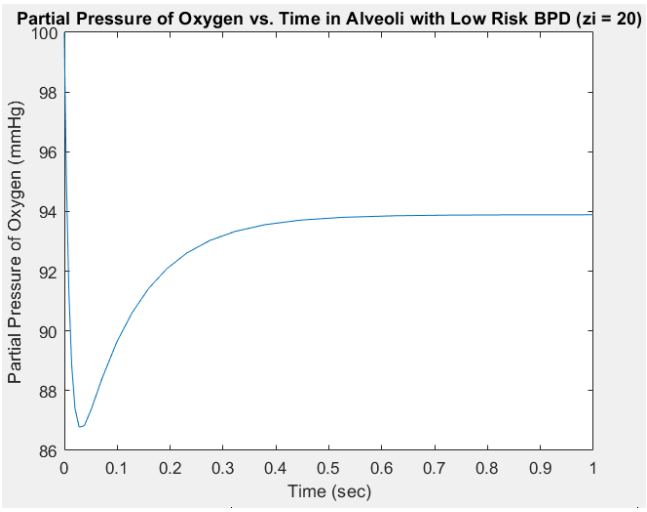

Figure 5. Inflammation index z_i increased to 20. Alveolar oxygen quickly diffuses into the other chambers, but increases as steady state approaches as oxygen levels equilibrate. This will become a trend for all other figures.

Additionally, steady-state PO_2 levels in each compartment decrease with increasing inflammation, demonstrating that inflammation impairs oxygen diffusion from alveoli to tissue to blood.

Alveolar PO_2, $z_i = 20$.

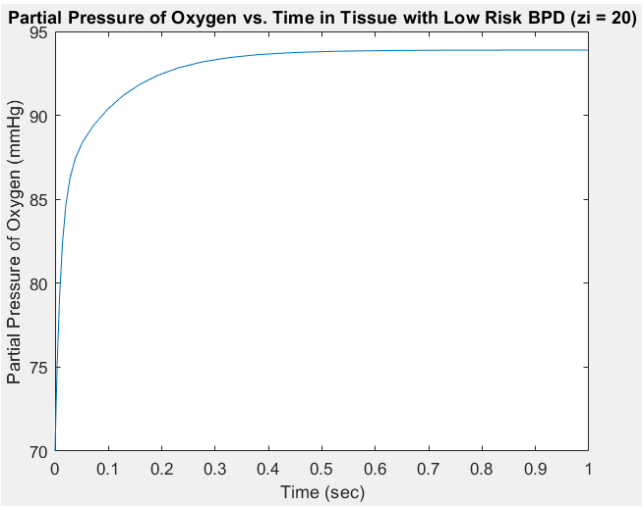

Figure 6. With $z_i > 0$, it becomes apparent that diffusion of oxygen through tissue is more impaired than diffusion of oxygen into the bloodstream. This likely occurs because tissue is the compartment that best retains fluid intake caused by inflammation.

Tissue PO_2, $z_i = 20$.

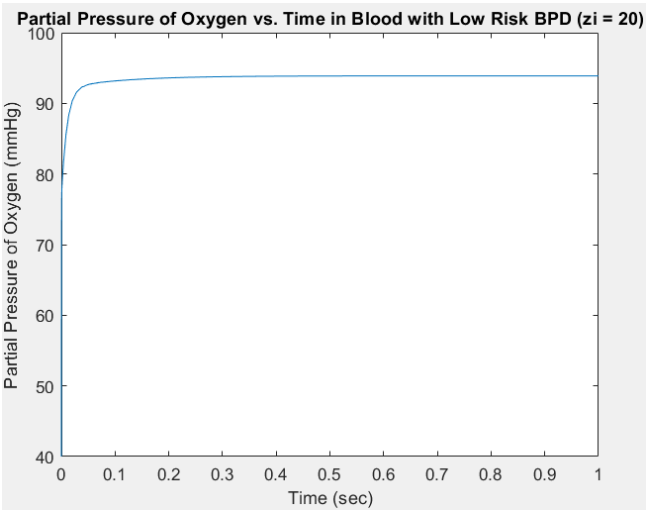

Figure 7. Blood PO_2, $z_i = 20$.

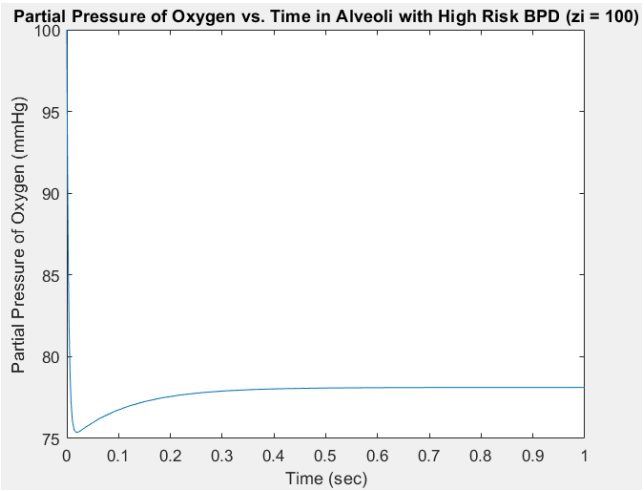

Figure 8. Inflammation index z_i increased to 100. Same trends as before with previous graphs, but even greater impairment of oxygen diffusion between compartments. There is a lower steady-state PO_2 for all compartments.

Alveolar PO_2, $z_i = 100$.

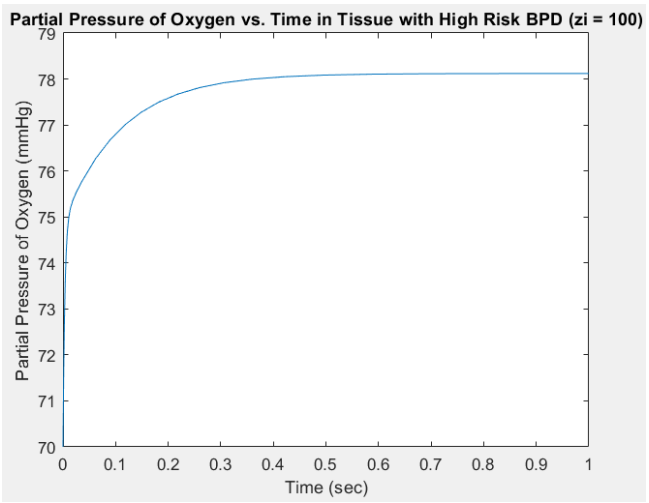

Figure 9. Tissue PO_2, z_i = 100.

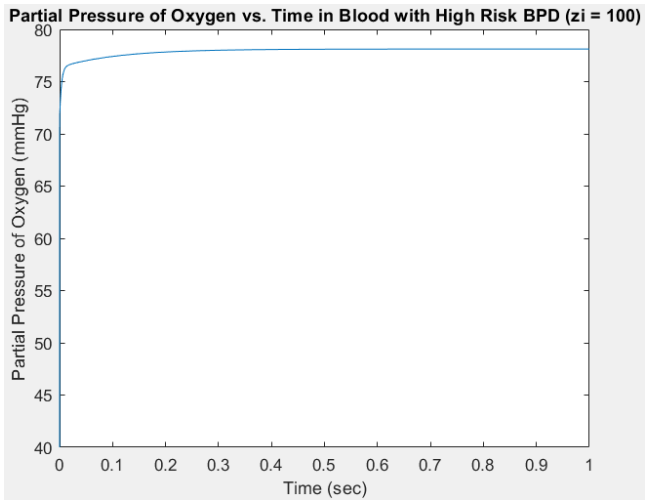

Figure 10. Blood PO_2, z_i = 100.

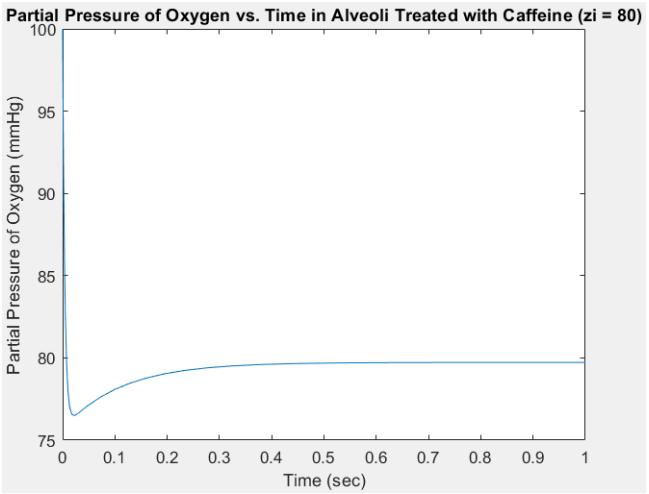

Figure 11. According to literature, caffeine is a fairly ineffective treatment for BPD; we simulate treating a high-risk BDP patient with caffeine by reducing z_i from 100 to 80.

Alveolar PO_2, z_i = 80.

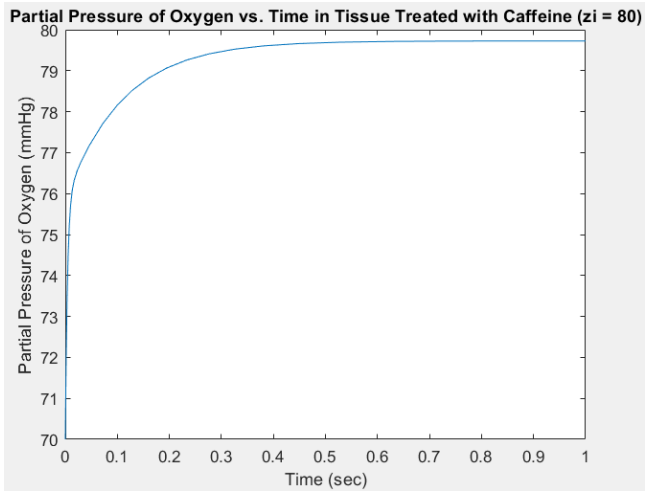

Figure 12. Tissue PO_2, z_i = 80. Caffeine treatment.

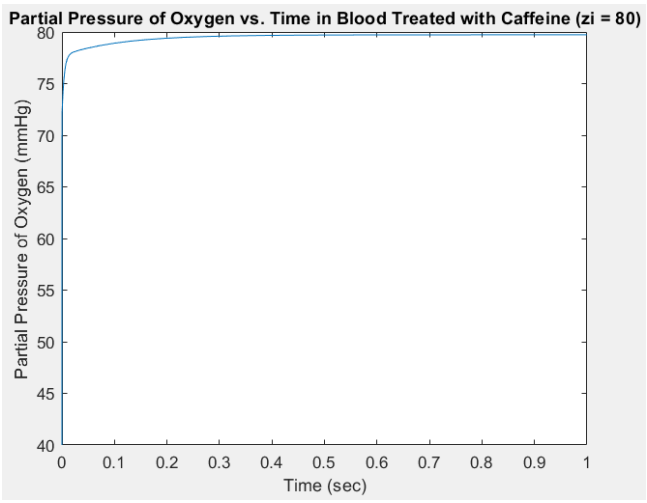

Figure 13. Blood PO_2, z_i = 80. Caffeine treatment.

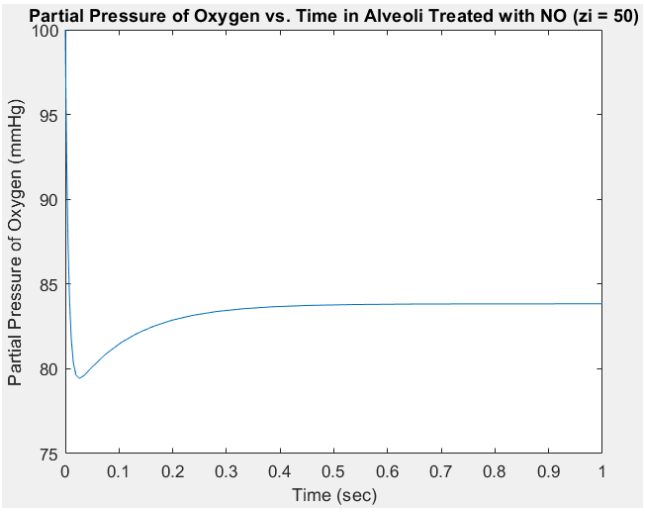

Figure 14. According to literature, nitric oxide (NO) is a slightly better treatment for BPD; we simulate treating a high-risk BDP patient with NO by reducing z_i from 100 to 50.

Alveolar PO_2, z_i = 50.

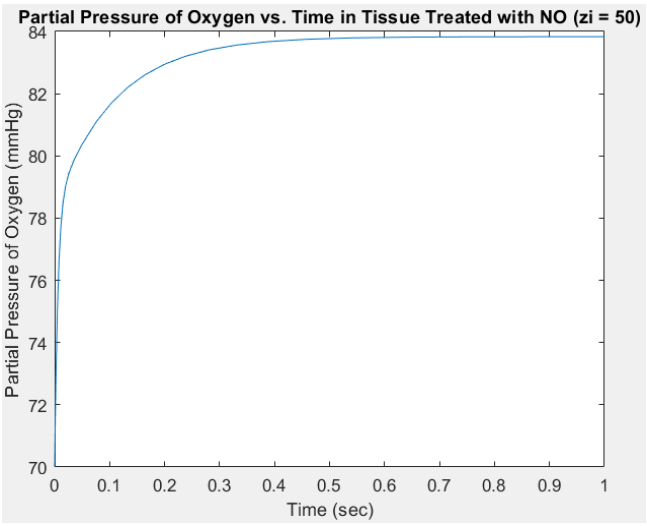

Figure 15. Tissue PO_2, z_i = 50. Nitric oxide treatment.

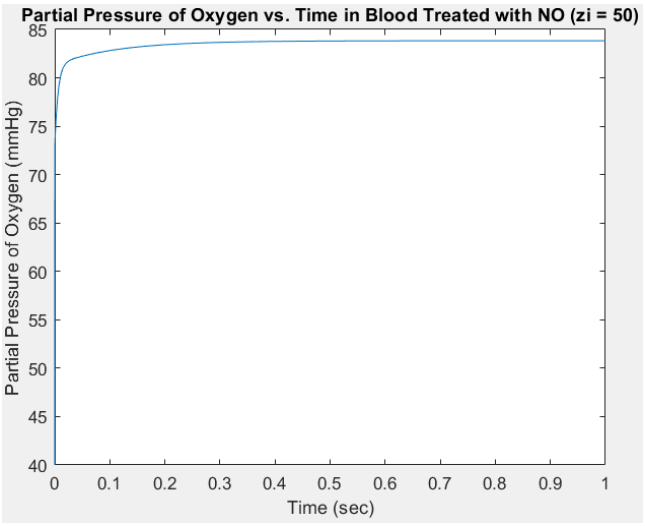

Figure 16. Blood PO_2, z_i = 50. Nitric oxide treatment.

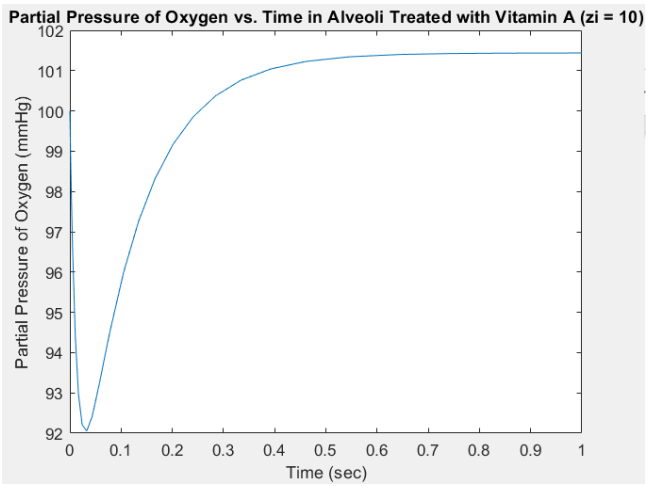

Figure 17. According to literature, vitamin A is a highly effective anti-inflammatory treatment; we simulate treating a high-risk BPD patient by reducing z_i from 100 to 10.

Alveolar PO_2, z_i = 10.

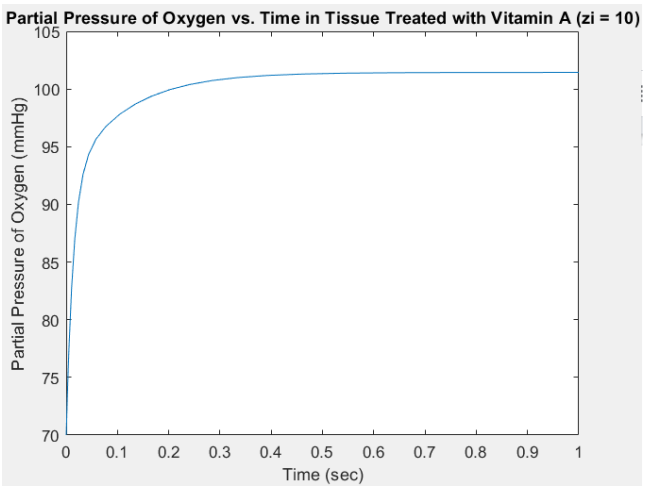

Figure 18. Tissue PO_2, z_i = 10. Vitamin A treatment.

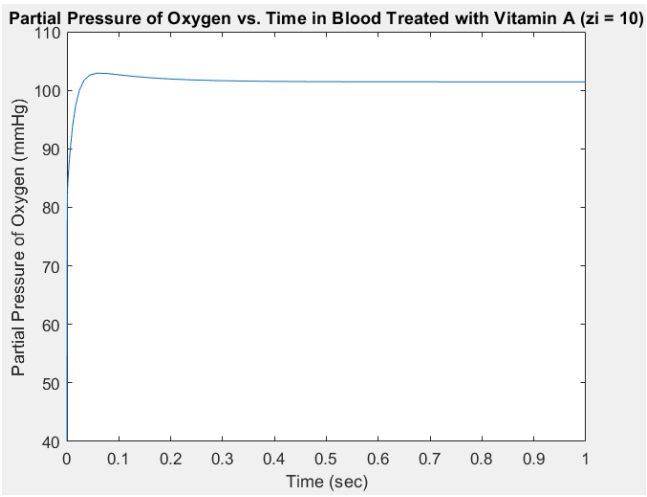

Figure 19. Blood PO_2, z_i = 10. Vitamin A treatment.

```
function wahoo = R21model()
clear all; close all;
wahoo = 100;

%Specific Aim 1
%direction of flow: alveolar -> tissue -> blood
PO2_A0 = 100;                           %initial alveolar PO2
PO2_T0 = 70;                            %initial tissue PO2
PO2_B0 = 40;                            %inital blood PO2

PO2_init = [PO2_A0 PO2_T0 PO2_B0];      %initialized PO2

tspan = [0, 0.3];
[t0, y0]  = ode23s(@fo, tspan, PO2_init); %ode23 solver
figure;
plot(t0,y0); %graph of PO2 in alveoli, tissue, and blood over 0.3 seconds
legend("PO2_A", "PO2_T", "PO2-B")
title("Partial Pressure of Oxygen vs. Time in Alveoli, Tissue, and Blood")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")

%Specific Aim 2
%zi = 0
HB4i = 1.7 * 10^(-3);                   %initial hemoglobin
PO2_init = [PO2_A0 PO2_T0 PO2_B0 HB4i]; %initialized PO2 + HB4
tspan = [0, 1];
[t1, y1] = ode23s(@f1, tspan, PO2_init); %ode23 solver
figure;
plot(t1,y1(:,1));                       %graph of PO2 in alveoli w/ zi = 0
title("Partial Pressure of Oxygen vs. Time in Alveoli for a Normal Lung (zi = 0)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
plot(t1,y1(:,2));                       %graph of PO2 in tissue w/ zi = 0
title("Partial Pressure of Oxygen vs. Time in Tissue for a Normal Lung (zi = 0)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
plot(t1,y1(:,3));                       %graph of PO2 in blood w/ zi = 0
title("Partial Pressure of Oxygen vs. Time in Blood for a Normal Lung (zi = 0)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")

%zi = 20
[t2, y2] = ode23s(@f2, tspan, PO2_init); %ode23 solver
figure;
plot(t2,y2(:,1));                       %graph of PO2 in alveoli w/ zi = 20
title("Partial Pressure of Oxygen vs. Time in Alveoli with Low Risk BPD (zi = 20)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
```

```
plot(t2,y2(:,2));                       %graph of PO2 in tissue w/ zi = 20
title("Partial Pressure of Oxygen vs. Time in Tissue with Low Risk BPD (zi = 20)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
plot(t2,y2(:,3));                       %graph of PO2 in blood w/ zi = 20
title("Partial Pressure of Oxygen vs. Time in Blood with Low Risk BPD (zi = 20)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")

%zi = 100
[t3, y3] = ode23s(@f3, tspan, PO2_init); %ode23 solver
figure;
plot(t3,y3(:,1));                       %graph of PO2 in alveoli w/ zi = 100
title("Partial Pressure of Oxygen vs. Time in Alveoli with High Risk BPD (zi = 100)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
plot(t3,y3(:,2));                       %graph of PO2 in tissue w/ zi = 100
title("Partial Pressure of Oxygen vs. Time in Tissue with High Risk BPD (zi = 100)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
plot(t3,y3(:,3));                       %graph of PO2 in blood w/ zi = 100
title("Partial Pressure of Oxygen vs. Time in Blood with High Risk BPD (zi = 100)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")

%Specific Aim 3
%Caffeine - zi = 80
[t4, y4] = ode23s(@f4, tspan, PO2_init); %ode23 solver
figure;
plot(t4,y4(:,1));                       %graph of PO2 in alveoli w/ zi = 80
plot(t4,y4(:,3));                       %graph of PO2 in blood w/ zi = 80
title("Partial Pressure of Oxygen vs. Time in Alveoli Treated with Caffeine (zi = 80)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
plot(t4,y4(:,2));                       %graph of PO2 in tissue w/ zi = 80
plot(t4,y4(:,3));                       %graph of PO2 in blood w/ zi = 80
title("Partial Pressure of Oxygen vs. Time in Tissue Treated with Caffeine (zi = 80)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
plot(t4,y4(:,3));                       %graph of PO2 in blood w/ zi = 80
title("Partial Pressure of Oxygen vs. Time in Blood Treated with Caffeine (zi = 80)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")

%Vitamin A - zi = 10
[t5, y5] = ode23s(@f5, tspan, PO2_init); %ode23 solver
```

```
figure;
plot(t5,y5(:,1));                       %graph of PO2 in alveoli w/ zi = 10
title("Partial Pressure of Oxygen vs. Time in Alveoli Treated with Vitamin A (zi = 10)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
plot(t5,y5(:,2));                       %graph of PO2 in tissue w/ zi = 10
title("Partial Pressure of Oxygen vs. Time in Tissue Treated with Vitamin A (zi = 10)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
plot(t5,y5(:,3));                       %graph of PO2 in blood w/ zi = 10
title("Partial Pressure of Oxygen vs. Time in Blood Treated with Vitamin A (zi = 10)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")

%Nitric Oxide - zi = 50
[t6, y6] = ode23s(@f6, tspan, PO2_init); %ode23 solver
figure;
plot(t6,y6(:,1));                       %graph of PO2 in alveoli w/ zi = 50
title("Partial Pressure of Oxygen vs. Time in Alveoli Treated with NO (zi = 50)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
plot(t6,y6(:,2));                       %graph of PO2 in tissue w/ zi = 50
title("Partial Pressure of Oxygen vs. Time in Tissue Treated with NO (zi = 50)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")
figure;
plot(t6,y6(:,3));                       %graph of PO2 in blood w/ zi = 50
title("Partial Pressure of Oxygen vs. Time in Blood Treated with NO (zi = 50)")
xlabel("Time (sec)")
ylabel("Partial Pressure of Oxygen (mmHg)")

function dydt = fo(t, y)     % specific aim 1
DO2_TB = 6.7 * 10^(-12);     % diffusion from tissue to blood
DO2_TA = 2.4 * 10^(-12);     % diffusion from tissue to alveoli
SigO2_A = 5.2 * 10^(-6);     % concentration of O2
SigO2_B = 1.2 * 10^(-6);     % concentration of O2
SigO2_T = 1.2 * 10^(-6);     % concentration of O2
V_B0 = 7.5 * 10^(-9);        %
V_T0 = 4.2 * 10^(-8);        %
V_A0 = 1.9 * 10^(-7);        %
N = 1.2 * 10^(-7);           %

dydt = [
%alveolar
(DO2_TA / (SigO2_A*V_A0)) * (y(2) - y(1))
%tissue
(DO2_TB / (SigO2_T*V_T0)) * (y(3) - y(2)) + (DO2_TA / (SigO2_T*V_T0)) * (y(1) - y(2))
%blood
```

```
(DO2_TB / (SigO2_B*V_B0)) * (y(2) - y(3))
];

return;

function dydt = f1(t, y)    % specific aim 2 - zi = 0
DO2_TB = 6.7 * 10^(-12);
DO2_TA = 2.4 * 10^(-12);
SigO2_A = 5.2 * 10^(-6);
SigO2_B = 1.2 * 10^(-6);
SigO2_T = 1.2 * 10^(-6);
V_B0 = 7.5 * 10^(-9);
V_T0 = 4.2 * 10^(-8);
V_A0 = 1.9 * 10^(-7);
N = 1.2 * 10^(-7);

zi = 0;
mvta = 1;
mvtb = 0.4;
m = 3.6;
k_plus = 5 * 10^(-4);
k_minus = 9;
THb = 2.2 * 10^(-3);
PO2m_B = 95;
V_Bz = V_B0 / (1 + mvtb*zi);
V_Az = V_A0 / (1 + mvta*zi);
V_Tz = V_T0 + V_B0 - V_Bz + V_A0 - V_Az;

dydt = [
    %alveolar
    (DO2_TA / (SigO2_A*V_Az)) * (y(2) - y(1))
    %tissue
    (DO2_TB / (SigO2_T*V_Tz)) * (y(3) - y(2)) + (DO2_TA / (SigO2_T*V_T0)) * (y(1) - y(2))
    %blood
    (DO2_TB / (SigO2_B*V_Bz)) * (y(2) - y(3)) + (m/SigO2_B)*(k_minus*y(4) - k_plus*(THb-y↙
(4))*PO2m_B)
    %hemoglobin
    (k_plus*(THb - y(4))*(PO2m_B) - k_minus*y(4))
    ];

return;

function dydt = f2(t, y)     % specific aim 2 - zi = 20
DO2_TB = 6.7 * 10^(-12);
DO2_TA = 2.4 * 10^(-12);
SigO2_A = 5.2 * 10^(-6);
SigO2_B = 1.2 * 10^(-6);
SigO2_T = 1.2 * 10^(-6);
V_B0 = 7.5 * 10^(-9);
V_T0 = 4.2 * 10^(-8);
V_A0 = 1.9 * 10^(-7);
```

```
N = 1.2 * 10^(-7);

zi = 20;
mvta = 1;
mvtb = 0.4;
m = 3.6;
k_plus = 5 * 10^(-4);
k_minus = 9;
THb = 2.2 * 10^(-3);
PO2m_B = 95;
V_Bz = V_B0 / (1 + mvtb*zi);
V_Az = V_A0 / (1 + mvta*zi);
V_Tz = V_T0 + V_B0 - V_Bz + V_A0 - V_Az;

dydt = [
    %alveolar
    (DO2_TA / (SigO2_A*V_Az)) * (y(2) - y(1))
    %tissue
    (DO2_TB / (SigO2_T*V_Tz)) * (y(3) - y(2)) + (DO2_TA / (SigO2_T*V_T0)) * (y(1) - y(2))
    %blood
    (DO2_TB / (SigO2_B*V_Bz)) * (y(2) - y(3)) + (m/SigO2_B)*(k_minus*y(4) - k_plus*(THb-y↙
(4))*PO2m_B)
    %hemoglobin
    (k_plus*(THb - y(4))*(PO2m_B) - k_minus*y(4))
    ];

return;

function dydt = f3(t, y)      % specific aim 2 - zi = 100
DO2_TB = 6.7 * 10^(-12);
DO2_TA = 2.4 * 10^(-12);
SigO2_A = 5.2 * 10^(-6);
SigO2_B = 1.2 * 10^(-6);
SigO2_T = 1.2 * 10^(-6);
V_B0 = 7.5 * 10^(-9);
V_T0 = 4.2 * 10^(-8);
V_A0 = 1.9 * 10^(-7);
N = 1.2 * 10^(-7);

zi = 100;
mvta = 1;
mvtb = 0.4;
m = 3.6;
k_plus = 5 * 10^(-4);
k_minus = 9;
THb = 2.2 * 10^(-3);
PO2m_B = 95;
V_Bz = V_B0 / (1 + mvtb*zi);
V_Az = V_A0 / (1 + mvta*zi);
V_Tz = V_T0 + V_B0 - V_Bz + V_A0 - V_Az;
```

```
dydt = [
    %alveolar
    (DO2_TA / (SigO2_A*V_Az)) * (y(2) - y(1))
    %tissue
    (DO2_TB / (SigO2_T*V_Tz)) * (y(3) - y(2)) + (DO2_TA / (SigO2_T*V_T0)) * (y(1) - y(2))
    %blood
    (DO2_TB / (SigO2_B*V_Bz)) * (y(2) - y(3)) + (m/SigO2_B)*(k_minus*y(4) - k_plus*(THb-y↙
(4))*PO2m_B)
    %hemoglobin
    (k_plus*(THb - y(4))*(PO2m_B) - k_minus*y(4))
    ];

return;

function dydt = f4(t, y)      % specific aim 3 - zi = 80
DO2_TB = 6.7 * 10^(-12);
DO2_TA = 2.4 * 10^(-12);
SigO2_A = 5.2 * 10^(-6);
SigO2_B = 1.2 * 10^(-6);
SigO2_T = 1.2 * 10^(-6);
V_B0 = 7.5 * 10^(-9);
V_T0 = 4.2 * 10^(-8);
V_A0 = 1.9 * 10^(-7);
N = 1.2 * 10^(-7);

zi = 80;
mvta = 1;
mvtb = 0.4;
m = 3.6;
k_plus = 5 * 10^(-4);
k_minus = 9;
THb = 2.2 * 10^(-3);
PO2m_B = 95;
V_Bz = V_B0 / (1 + mvtb*zi);
V_Az = V_A0 / (1 + mvta*zi);
V_Tz = V_T0 + V_B0 - V_Bz + V_A0 - V_Az;

dydt = [
    %alveolar
    (DO2_TA / (SigO2_A*V_Az)) * (y(2) - y(1))
    %tissue
    (DO2_TB / (SigO2_T*V_Tz)) * (y(3) - y(2)) + (DO2_TA / (SigO2_T*V_T0)) * (y(1) - y(2))
    %blood
    (DO2_TB / (SigO2_B*V_Bz)) * (y(2) - y(3)) + (m/SigO2_B)*(k_minus*y(4) - k_plus*(THb-y↙
(4))*PO2m_B)
    %hemoglobin
    (k_plus*(THb - y(4))*(PO2m_B) - k_minus*y(4))
    ];

return;
```

```
function dydt = f5(t, y)      % specific aim 3 - zi = 10
DO2_TB = 6.7 * 10^(-12);
DO2_TA = 2.4 * 10^(-12);
SigO2_A = 5.2 * 10^(-6);
SigO2_B = 1.2 * 10^(-6);
SigO2_T = 1.2 * 10^(-6);
V_B0 = 7.5 * 10^(-9);
V_T0 = 4.2 * 10^(-8);
V_A0 = 1.9 * 10^(-7);
N = 1.2 * 10^(-7);

zi = 10;
mvta = 1;
mvtb = 0.4;
m = 3.6;
k_plus = 5 * 10^(-4);
k_minus = 9;
THb = 2.2 * 10^(-3);
PO2m_B = 95;
V_Bz = V_B0 / (1 + mvtb*zi);
V_Az = V_A0 / (1 + mvta*zi);
V_Tz = V_T0 + V_B0 - V_Bz + V_A0 - V_Az;

dydt = [
    %alveolar
    (DO2_TA / (SigO2_A*V_Az)) * (y(2) - y(1))
    %tissue
    (DO2_TB / (SigO2_T*V_Tz)) * (y(3) - y(2)) + (DO2_TA / (SigO2_T*V_T0)) * (y(1) - y(2))
    %blood
    (DO2_TB / (SigO2_B*V_Bz)) * (y(2) - y(3)) + (m/SigO2_B)*(k_minus*y(4) - k_plus*(THb-y↙
(4))*PO2m_B)
    %hemoglobin
    (k_plus*(THb - y(4))*(PO2m_B) - k_minus*y(4))
    ];

return;

function dydt = f6(t, y)      % specific aim 3 - zi = 50
DO2_TB = 6.7 * 10^(-12);
DO2_TA = 2.4 * 10^(-12);
SigO2_A = 5.2 * 10^(-6);
SigO2_B = 1.2 * 10^(-6);
SigO2_T = 1.2 * 10^(-6);
V_B0 = 7.5 * 10^(-9);
V_T0 = 4.2 * 10^(-8);
V_A0 = 1.9 * 10^(-7);
N = 1.2 * 10^(-7);

zi = 50;
mvta = 1;
mvtb = 0.4;
```

```
m = 3.6;
k_plus = 5 * 10^(-4);
k_minus = 9;
THb = 2.2 * 10^(-3);
PO2m_B = 95;
V_Bz = V_B0 / (1 + mvtb*zi);
V_Az = V_A0 / (1 + mvta*zi);
V_Tz = V_T0 + V_B0 - V_Bz + V_A0 - V_Az;

dydt = [
    %alveolar
    (DO2_TA / (SigO2_A*V_Az)) * (y(2) - y(1))
    %tissue
    (DO2_TB / (SigO2_T*V_Tz)) * (y(3) - y(2)) + (DO2_TA / (SigO2_T*V_T0)) * (y(1) - y(2))
    %blood
    (DO2_TB / (SigO2_B*V_Bz)) * (y(2) - y(3)) + (m/SigO2_B)*(k_minus*y(4) - k_plus*(THb-y↙
(4))*PO2m_B)
    %hemoglobin
    (k_plus*(THb - y(4))*(PO2m_B) - k_minus*y(4))
    ];

return;
```