Carbon Monoxide Diffusion Across Human Placenta

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All numerical experiments conducted in this project can be found here.

1 Introduction

Maternal smoking during pregnancy is a well-recognized risk factor that significantly impacts fetal development and health. Cigarette smoke contains carbon monoxide (CO), which is a harmful gas that readily crosses the placental barrier and preferentially binds to fetal hemoglobin over oxygen (O_2), forming carboxyhemoglobin (HbCO) (Figure 1). Carboxyhemoglobin (HbCO) is formed when CO binds with hemoglobin in the blood. Hemoglobin is a protein, (the first protein ever determined by human), in red blood cells responsible for transporting oxygen, and its affinity for CO is 250 times higher than for oxygen, which is why CO exposure can severely impact oxygen transport in the blood. This will leads to reduce the oxygen-carrying capacity of fetal blood and decreases fetal oxygen concentration, which can lead to various developmental issues and health problems in the fetus.

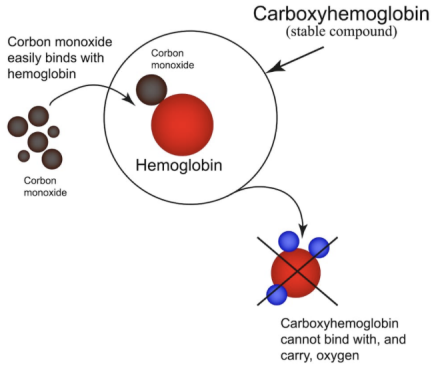


Figure 1: Hemoglobin, Oxygen, and Carbon Monoxide

The placenta is an organ that connects mother and fetus (Figure 2), it plays a crucial role in the exchange of nutrients, gases, and waste between the mother and fetus. It ensures that maternal and fetal blood streams remain separate while allowing selective substances to diffuse between them [4]. Understanding the dynamics of CO diffusion within the placenta in the context of maternal smoking, can give us knowledge about CO concentration in mother's blood, fetal blood, and placenta tissue.

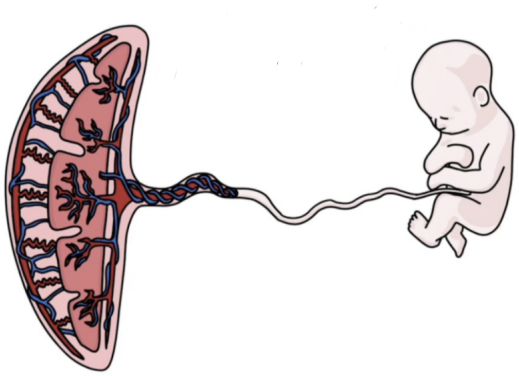


Figure 2: Placenta(Left), Fetus(Right)

Previous mathematical models, such as the cylinder structured model of placental circulation discussed by Heilmann (1979) [2] and the ODE model by Hill (1977)[3], provide us some insights into placental blood flow and gas exchange. However, these models do not fully address the geometry of the placenta, and also not the CO concentration in the entire placental domain, especially not considering the different physiological variations.

The primary aim of this study is to develop an spatial-temporal model to simulate the diffusion of CO across the entire placenta under conditions of increased maternal CO levels due to smoking. This model will build upon existing models [2], by adding an additional layer to simulate the fetal blood vessel. And also incorporate the ODE model discussed in [3].

2 Existing Model

2.1 ODE Model for CO Exchange Between Fetus and Mother [3]

The reaction model for carbon monoxide (CO) exchange between the mother and fetus as described by Hill et al. (1977)[3] is involving numerous constants and variables that influence its dynamics. Before delving into the model, we first define and describe these constants and variables to fully grasp the underlying mechanisms:

Symbol	Description	Type
$[HbCO]_m$	Maternal carboxyhemoglobin concentration	Variable
$[HbCO]_f$	Fetal carboxyhemoglobin concentration	Variable
cap_m	Maternal blood oxygen capacity	0.168
vol_m	Maternal blood volume	5000
cap_f	Fetal blood oxygen capacity	0.208
vol_f	Fetal blood volume	400
$\dot{V}_{CO_m}$	Maternal endogenous CO production rate	0.0153
$\dot{V}_{CO_f}$	Fetal endogenous CO production rate	0.0006
D_{LCO}	Lung diffusing capacity for CO	23
D_{PCO}	Placental diffusing capacity for CO	1.5
$\dot{V}_A$	Alveolar ventilation rate	6000
$P_{L_{CO}}$	Inspired Concentration of CO	Variable
$(P_{O2}/HbO_2)_L$	Ratio in lung capillaries	1.029
$(P_{O2}/HbO_2)_m$	Ratio in maternal placental capillaries	0.5609
$(P_{O2}/HbO_2)_f$	Ratio in fetal placental capillaries	0.4128
M_m	Maternal affinity for CO relative to O2	223
M_f	Fetal affinity for CO relative to O2	181

Table 1: Constants and Variables in Equations (1) and (2), used in Section 2.1.1. Values are taken from [3].

In the table outlined above, the highlighted variable $P_{L_{\text{CO}}}$ is the key parameter that we will change to simulate different scenarios within Hill's reaction model, providing us information on how different conditions affect this reaction. The ODE model described by Hill's is as follows:

$$\begin{aligned}\frac{d[HbCO]_m}{dt} =& \frac{100}{\text{cap}_m \text{vol}_m}\left(\dot{V}_{CO_m} + \frac{D_{LCO}P_{CO}}{1+\frac{713D_{LCO}}{\dot{V}_A}}\right) \\ &- D_{PCO}\left[P_{TCO} - \frac{(P_{O2}/HbO_2)_L[HbCO]_m}{M_m}\right] \\ &- D_{PCO}\left[\frac{(P_{O2}/HbO_2)_m[HbCO]_m}{M_m} - \frac{(P_{O2}/HbO_2)_f[HbCO]_f}{M_f}\right]\end{aligned} \tag{1}$$

$$\frac{d[HbCO]_f}{dt} = \frac{100}{\text{cap}_f \text{vol}_f}\left(\dot{V}_{CO_f} + D_{PCO}\left[P_{CO} - \frac{(P_{O2}/HbO_2)_m[HbCO]_m}{M_m}\right]\right) - D_{PCO}\left(\frac{(P_{O2}/HbO_2)_f[HbCO]_f}{M_f}\right) \tag{2}$$

After some simplification, we can rewrite (1) and(2) as

$$\frac{dy_1}{dt} = a_{11}y_1 + a_{12}y_2 + f_1, \tag{3}$$

$$\frac{dy_2}{dt} = a_{21}y_1 + a_{22}y_2 + f_2. \tag{4}$$

where:

$$\begin{aligned}
y_1 &= [HbCO]_m, \quad y_2 = [HbCO]_f, \\
a_{11} &= -\frac{D_{LCO}(P_{O2}/HbO_2)_L}{(1 + 713D_{LCO}/\dot{V}_A)\text{cap}_m \text{vol}_m M_m} + D_{PCO}, \\
a_{12} &= \frac{D_{PCO}(P_{O2}/HbO_2)_f}{\text{cap}_m M_m}, \\
f_1 &= \frac{\dot{V}_{CO_m} + D_{LCO}P_{L_{CO}}/(1 + 713D_{LCO}/\dot{V}_A)}{\text{cap}_m \text{vol}_m}. \\
a_{21} &= \frac{D_{PCO}(P_{O2}/HbO_2)_m}{\text{cap}_f M_m}, \\
a_{22} &= -\frac{D_{PCO}(P_{O2}/HbO_2)_f}{\text{cap}_f \text{vol}_f M_f}, \\
f_2 &= \frac{\dot{V}_{CO_f}}{\text{cap}_f \text{vol}_f}.
\end{aligned}$$

In this model, V_{COm} represents the volume rate of CO that is being metabolized in the maternal system, and D_{CO} denotes the rate at which CO diffuses through the placental membrane, dependent on the difference in partial pressures between alveolar and blood (maternal side) and between maternal and fetal blood. This equation reflects the dynamics of CO binding with hemoglobin to form carboxyhemoglobin (HbCO), thereby affecting the oxygenation of both maternal and fetal blood.

However, to simulate the CO diffusion pattern, the concentration of HbCO in its current form isn't suitable for direct modeling. This is because HbCO (carboxyhemoglobin) is too large to diffuse across the placenta; only CO (carbon monoxide)

can diffuse. Therefore, we convert the HbCO concentration into CO concentration in mmHg using the following relation given in [1]

$$\text{PCO} = \frac{[\text{COHb}] \times \text{PO}_2}{[\text{O}_2\text{Hb}] \times M},$$

where:

- [HbCO] is the carboxyhemoglobin concentration given as a percentage of total hemoglobin.
- PO_2 is the partial pressure of oxygen in mmHg.
- $[\text{HbO}_2]$ is the oxyhemoglobin concentration, also given as a percentage saturation of hemoglobin.
- M is the equilibrium constant, which is 218 in this context.

For example, assuming [HBCO] = 10% and $[\text{HbO}_2]$is set to be around 87.5%, with a typical arterial oxygen pressure (PO_2) around 90 mmHg, the PCO is calculated as:

$$\text{PCO} = \frac{10 \times 90}{87.5 \times 218} = 0.046 \text{ mmHg}$$

With this relation, we can conduct our first numerical experiment using this ode model.

2.1.1 Numerical Experiment

In this simulation, we model a 24-hour period, consisting of 16 hours of exposure to an inspired concentration of 50 parts per million (ppm) carbon monoxide, equivalent to approximately 1 and a half packs of cigarettes per day, followed by an 8-hour washout period during sleep where no CO is contained in the environment.

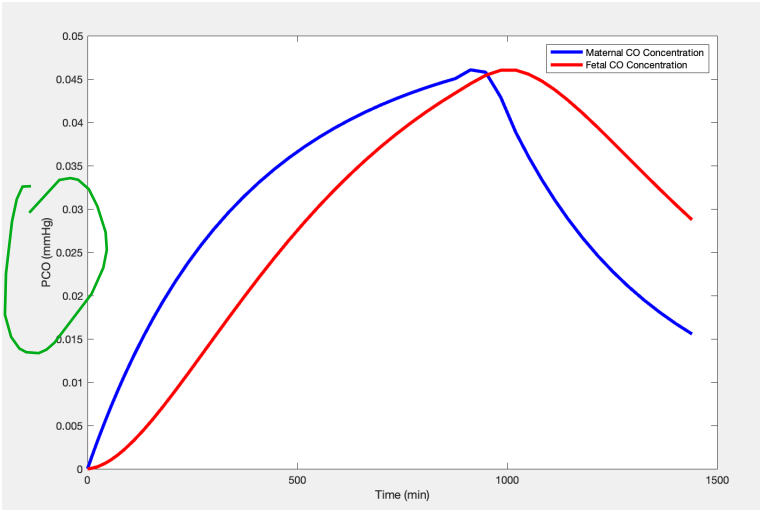


Figure 3: CO concentrations over time, with maternal concentrations shown in blue and fetal concentrations in red.

From the plotted results (Figure 3), it is observed that the carboxyhemoglobin concentration in the fetal blood can exceed that of the maternal blood, and the concentration decrease occurs over a much slower time scale in the fetus compared to the mother.

2.2 PDE Cylindrical Diffusion Model[2]

This mathematical model is based on a cylindrical geometry representing the placenta tissue and Maternal blood vessel, where diffusion of substances such as O_2 diffuse across two different sections (Figure 4).

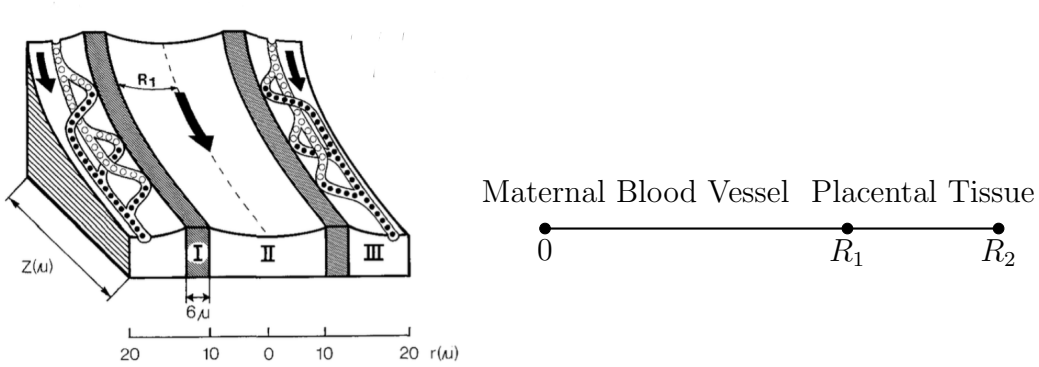


Figure 4: Simulated Domain: 0-R1 represents the half of region II (Maternal Blood Vessel), R1-R2 represents region I (Placental Tissue)

The concentration of the selected substances is modeled with the following partial differential equations:

$$\frac{\partial C_1}{\partial t} = D_1 \left(\frac{\partial^2 C_1}{\partial r^2} + \frac{1}{r} \frac{\partial C_1}{\partial r} \right), \qquad r \in [0, R_1] \tag{5}$$

$$\frac{\partial C_2}{\partial t} = D_2 \left(\frac{\partial^2 C_2}{\partial r^2} + \frac{1}{r} \frac{\partial C_2}{\partial r} \right), \qquad r \in [R_1, R_2] \tag{6}$$

In the equations above, C_1 and C_2 represent the concentrations of the substances in two different regions of the placental cylinder, with C_1 being in the left region $[0, R_1]$ and C_2 in the right region $[R_1, R_2]$. The terms D_1 and D_2 are the diffusion coefficients in blood and tissue.

At the interface $r = R_1$ between the two regions, the continuity of flux and concentration is maintained:

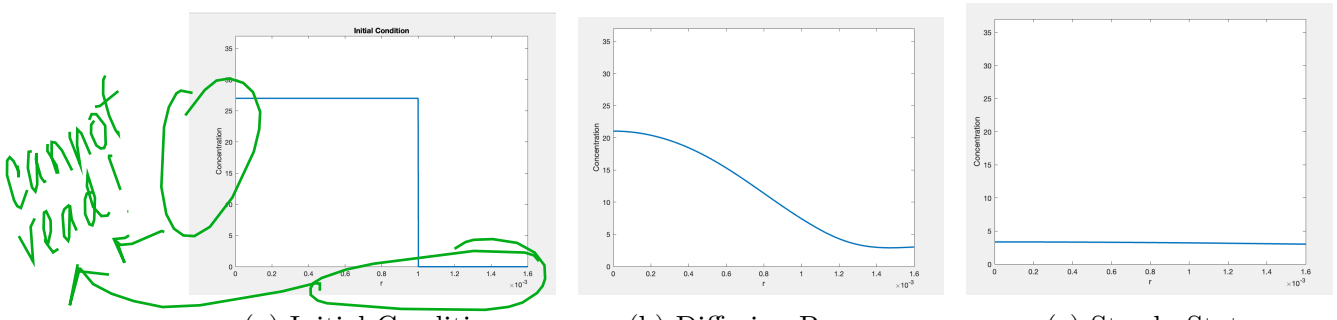
$$D_1 \left. \frac{\partial C_1}{\partial r} \right|_{r=R_1} = D_2 \left. \frac{\partial C_2}{\partial r} \right|_{r=R_1}, \tag{7}$$

$$C_1 = C_2 \text{ at } r = R_1. \tag{8}$$

This ensure that there is no buildup or sudden drop in concentration at the boundary between the two cylindrical regions, allowing for a smooth transition of diffusion across the interface, and more importantly, ensures the mass conservation.

2.2.1 Numerical Experiment

In the following numerical experiment, we simulate the diffusion of oxygen across the two regions: the maternal blood vessel and the placental tissue, as previously described in Section 2.2. The initial conditions are set with a constant oxygen concentration within the mother's blood and zero concentration in the placental tissue (Figure 5a). Over time, we see the simulation reveals that the oxygen concentration gradually equilibrates between these two regions (Figure 5b), eventually reaching a steady state (Figure 5c), as expected.



(a) Initial Condition (b) Diffusing Process (c) Steady State

Figure 5: Oxygen Diffusion Across the Placenta

3 Cooperated Model

The PDE model described in Section 2.2 only accounts for two regions within the placenta: the maternal blood vessel and the placental tissue. However, to better understand the carbon monoxide concentration dynamics in both the mother and the fetus, we have expanded this model by adding a third region (Figure 6). This additional region represents the fetal blood circulation. By modifying the original model to include this third region, we can more accurately simulate and analyze the diffusion of CO from maternal blood, through the placental tissue, and into the fetal bloodstream, thereby providing a more knowledge about the dynamics of the CO concentration in different region.

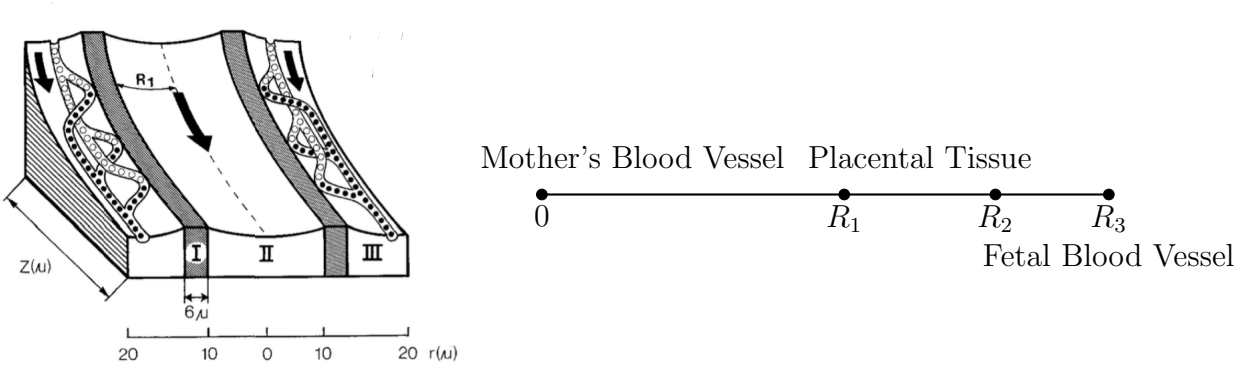


Figure 6: Simulated Domain: 0-R1 represents the half of region II (Maternal Blood Vessel), R1-R2 represents region I (Placental Tissue), R2-R3 represents region III (Fetal Blood Vessel).

Therefore, we have revised the previous model in Section 2.2 to include the third region representing the fetal blood circulation. The new model is as follows

$$\begin{aligned}
\frac{\partial C_1}{\partial t} &= D_1 \left(\frac{\partial^2 C_1}{\partial r^2} + \frac{1}{r} \frac{\partial C_1}{\partial r} \right), && r \in [0, R_1] \\
\frac{\partial C_2}{\partial t} &= D_2 \left(\frac{\partial^2 C_2}{\partial r^2} + \frac{1}{r} \frac{\partial C_2}{\partial r} \right), && r \in [R_1, R_2] \\
\frac{\partial C_3}{\partial t} &= D_1 \left(\frac{\partial^2 C_3}{\partial r^2} + \frac{1}{r} \frac{\partial C_3}{\partial r} \right), && r \in [R_2, R_3]
\end{aligned}$$

This formulation captures the diffusion of CO in three distinct zones: maternal blood (Region 1), placental tissue (Region 2), and fetal blood (Region 3). The coefficients D_1 represent the diffusion coefficients in the maternal and fetal blood, and D_2 for the placental tissue. The interface conditions are defined as

$$D_1 \left. \frac{\partial C_1}{\partial r} \right|_{r=R_1} = D_2 \left. \frac{\partial C_2}{\partial r} \right|_{r=R_1}, \quad D_2 \left. \frac{\partial C_2}{\partial r} \right|_{r=R_2} = D_1 \left. \frac{\partial C_3}{\partial r} \right|_{r=R_2}$$
$$C_1 = C_2 \text{ at } r = R_1, \quad C_2 = C_3 \text{ at } r = R_2.$$

Similarly as in Section 2.2, These conditions ensure continuity of flux and concentration at the interfaces between regions, which ensures the mass and energy conservation.

Building upon the existing framework, we next integrate our modified model with the previously described ODE model referenced in Section 2.1, by introducing a time-dependent boundary conditions for our PDE model as follows

$$C(0,t) = C_{\mathrm{CO}_m}(t),$$

and

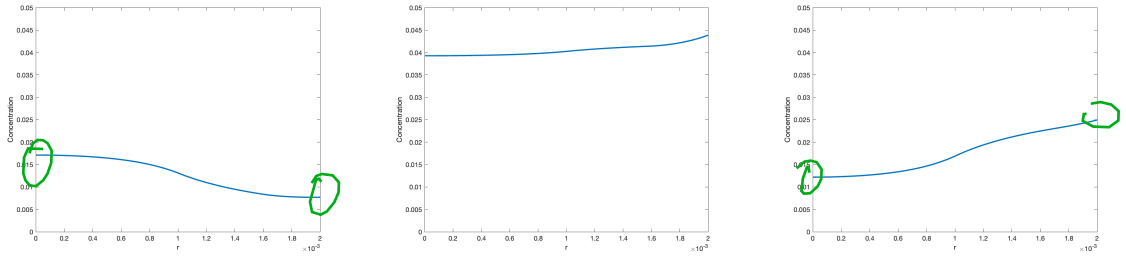
$$C(R_3,t) = C_{\mathrm{CO}_f}(t),$$

where $C_{\mathrm{CO}_m}(t)$ and $C_{\mathrm{CO}_f}(t)$ represent the concentrations of carbon monoxide, measured in mmHg, as a function of time t obtained form the ODE model in Section 2.1 which tracks CO levels over time in both the maternal and fetal bloodstreams. By coupling these dynamic boundary conditions with our spatial model, we can now perform the simulation that counts temporal and spatial variations in CO concentration across the maternal blood stream to placental tissue to fetal bloodstream.

4 Numerical Result

4.0.1 Simulation 1

We perform the following simulations under the same settings described in Section 2.1.1, simulating a 24-hour period. This period includes a 16-hour daytime during which the mother is exposed to a CO concentration of 50 ppm, equivalent to approximately one and a half packs of cigarettes, followed by an 8-hour sleeping period. From the results (Figure 10), we observe that initially, the CO concentration on the mother's side is higher than on the fetal side (Figure 7a). However, after reaching the peak concentration (Figure 7b), the CO levels in both the fetus and the placental tissue rise. At the end of the 24-hour period (Figure 7c), the residual concentration of CO in the fetal blood and placental tissue remains higher than in the maternal blood, indicating a significant retention of CO in fetal blood.



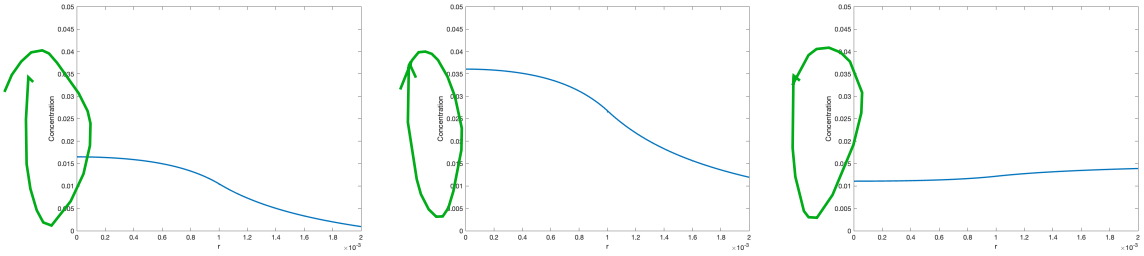
(a) 3 hours (b) 16 hours (c) 24 hours

Figure 7: CO Diffusion Across the Placental

4.0.2 Simulation 2

In this simulation, we implement a free boundary condition at R_3 to explore pure diffusion dynamics from the mother's side to the fetus, without considering physical factors that might enhance this diffusion process. Typically, setting a boundary condition at R_3 would account for the fetus's physical activities, such as variations in breathing rate, which could accelerate diffusion. However, by assuming a free boundary, we focus solely on passive diffusion from the maternal end. We observe that the CO concentration for entire 24 hours period at R_3 is significantly lower (Figure 8) than in the previous case (Section 4.0.1). This result suggests that the placental tissue may act as a barrier, slowing down or even preventing the diffusion of CO to the fetus.

good interpretation of results.



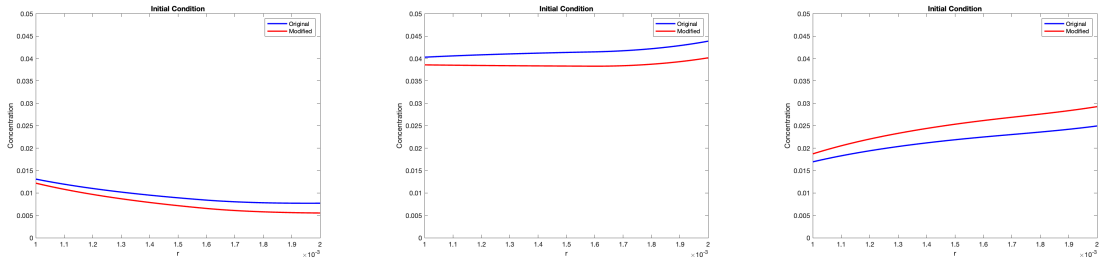
(a) 3 hour (b) 16 hours (c) 24 hours

Figure 8: CO Diffusion Across the Placental (Free Boundry Cndition)

4.0.3 Simulation 3

In this simulation, we consider a scenario where an individual resides at a higher altitude. Living at higher altitudes typically leads to an increase of HbO_2 and leads

to decreased $\frac{P_{O2}}{HbO_2}$ ratio. This increase occurs because the partial pressure of oxygen (P_{O2}) is lower at high altitudes, compelling the body to adapt by enhancing oxygen delivery to the tissues, reflected in higher hemoglobin saturation (HbO_2). Consequently, in our simulations, the red curves represent cases at higher altitudes, while the blue curves correspond to those in (Section 4.0.1). We observe that during periods of increased CO exposure, the red curves rise more slowly compared to the blue ones. However, during the decline phase, the decrease is also slower for the red curves, ultimately leaving a higher residue of CO at the end of the 24-hour period which is not initially expected.[1]



(a) 3 hour (b) 16 hours (c) 24 hours

Figure 9: CO Diffusion Across the Placental

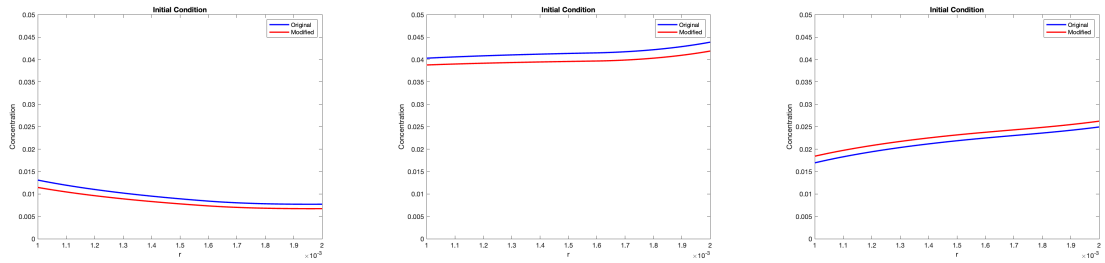
4.0.4 Simulation 4

In this simulation, we consider individuals with varying body weights, as body weight influences blood volume. For example, in pregnant mothers, the blood volume can increase significantly, approximately representing about 7% of their body weight.[2] To simulate this, we adjust the blood volume from 4L to 5L. In our results, the red curve, representing a blood volume of 5L, shows a slower rate of increase and decrease in CO concentration compared to the blue curve, which represents a 4L

[1]It is important to acknowledge that the current simulation, which only considers a 24-hour period with a fixed CO intake, may not fully represent the complex dynamics of CO exposure, particularly in high-altitude environments. To gain a more comprehensive understanding of this scenario, a longer-duration simulation with varying levels of CO exposure should be conducted. Additionally, incorporating changes in other physical parameters, such as varying activity levels or different environmental conditions, might provide more insights into the physiological impacts and adaptive responses to CO.

[2]This percentage is a general estimation and varies among individuals. During pregnancy, the increase in blood volume is particularly significant to support fetal development, often increasing by about 45%.

blood volume. Consequently, the simulation reveals that a larger blood volume leads to higher residual CO levels at the end of the 24-hour period.



(a) 3 hour (b) 16 hours (c) 24 hours

Figure 10: CO Diffusion Across the Placental

5 Conclusion

In conclusion, through the simulations conducted in this project, we have explored the carbon monoxide (CO) diffusion from maternal blood through placental tissue and into fetal blood. To achieve this, we constructed a partial differential equation (PDE) model in cylinder structure that simulates these diffusion processes. Our approach involved modifying the diffusion model described in [2] and integrating the ODE model discussed in [3] to create a comprehensive framework for analyzing CO diffusion under various physiological conditions.

Our findings has shown that with increased altitude or a larger maternal blood volume, the concentration of CO initially tends to be lower during the CO intake period. Interestingly, during the simulated washout period, which assumes no further CO exposure, the decline in concentration is slower in cases of higher altitude and increased blood volume. This results in a higher residual concentration of CO at the end of the 24-hour period than expected. To better understand these dynamics, a longer time simulation should be performed in order to better understand these scenarios. Additionally, I observe that the CO concentrations in mothers and babies can vary significantly depending on the simulation duration and CO exposure pattern. This variability indicates that it is no reasonable to predict fetal CO levels solely based on maternal blood measurements, especially without detailed information on CO exposure patterns. Instead, the CO concentration in the placenta tissue may offer a more accurate prediction of fetal CO levels compared to that in the mother's blood. However, measuring CO concentration directly in placental tissue

poses significant practical challenges. ✓

This work was great. Very thorough and thoughtful. I hope you enjoyed working on it!

In the future, make the graphs more readable.

References

[1] Ronald Coburn. The partial pressure of carbon monoxide in human tissues calculated using a parallel capillary-tissue cylinder model. *Journal of Applied Physiology*, 124, 01 2018.

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