BENG 221: Problem Solving Project

Mathematical Model for Carbon Monoxide Diffusion in Man

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Introduction

Carbon monoxide (CO) is an odorless, colorless gas that is found in combustion fumes, such as those produced by automobiles, burning charcoal and wood, and heating systems. CO can build up in enclosed spaces and lead to acute to chronic poisoning, or even death, if humans and animals are exposed to the gas for an extended period of time. Every year, more than 400 Americans die from unintentional CO poisoning, roughly 20,000 visit the emergency room and more than 4,000 are hospitalized[1]. CO is so lethal because when inhaled, it binds to hemoglobin, which is the principal oxygen carrier in blood, and produces carboxyhemoglobin. The formation of this compound reduces the oxygen-carrying capacity of hemoglobin and inhibits the transport and delivery of oxygen to the body.

The affinity between hemoglobin and CO is about 230 times stronger than the affinity between hemoglobin and oxygen, which further restricts oxygen supply[2]. Hemoglobin is a tetramer with four binding sites, and when CO binds one of these sites, it increases the affinity for oxygen at the remaining sites. This causes hemoglobin to retain bound oxygen that would otherwise be delivered to the body, leading to hypoxic tissue injury[3].

Problem statement: We designed a mathematical model for the uptake of CO to investigate the diffusive nature of CO into the bloodstream and calculate the time required for CO to reach lethal levels in an adult male.

Model

The model we chose is one of gas exchange between the lungs and the pulmonary capillaries based on a comprehensive model in literature[1]. The pulmonary capillaries are modeled as a rectangular prism, with alveoli on either side. The comprehensive model considers three dimensions, with x as the distance from one alveolus, y as the distance along the capillary, and z as the direction perpendicular to both x and y. Time (t) is measured from when a given element enters the capillary.

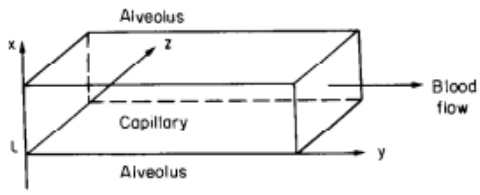

Fig. 1. The co-ordinate system.

The comprehensive model takes blood flow into account, but assumes that blood is homogeneous with each element flowing at the same velocity. The kinetics of the reactions of hemoglobin binding to oxygen and CO in the blood are given below:

$$Hb + O_2 \underset{k_{-1}}{\overset{k_1}{\leftrightarrow}} HbO_2$$

$$Hb + CO \underset{k_{-2}}{\overset{k_2}{\leftrightarrow}} HbCO$$

Average values are used for the rate constants. The concentrations of the species are denoted as follows: [O_2] as c_1, [CO] as c_2, [Hb] as c_3, [HbO_2] as c_4, and [HbCO] as c_5. The mass balance over the capillary is shown below:

$$\frac{d}{dt}\int_V c_i \, dV + \int_S \vec{J_i} \cdot \vec{n} \, dS + \int_V r_i \, dV = 0$$

In this equation, V is the control volume, c_i is the concentration of species i, $\vec{J_i}$ is the flux vector of species i, $\vec{n}$ is the normal vector to the surface, and r_i is the rate of generation of species i.

Applying the divergence theorem to the second term results in:

$$\int_V \left(\frac{dc_i}{dt} + \vec{u} \cdot \vec{\nabla} c_i + \vec{\nabla} \cdot \vec{J_i} + r_i\right) dV = 0$$

A new term, $\vec{u}$, represents the velocity of blood, which flows in the y direction. Since V is arbitrary, the integral can be removed. Applying Fick's Law ($\vec{J_i} = -D_i \vec{\nabla} c_i$) results in:

$$\frac{\partial c_i}{\partial t} + u\frac{\partial c_i}{\partial y} - D_i \nabla^2 c_i + r_i = 0$$

D_i is the diffusion coefficient of component i. Applying the law of mass action to the kinetic reactions gives:

$$\begin{aligned} r_1 &= k_1 c_1 c_3 - k_{-1} c_4 \\ r_2 &= k_2 c_2 c_3 - k_{-2} c_5 \\ r_3 &= r_1 + r_2 \\ r_4 &= -r_1 \\ r_5 &= -r_2 \end{aligned}$$

Substituting the above rate equations results in the final model:

$$\frac{\partial c_1}{\partial t} + u\frac{\partial c_1}{\partial y} = -k_1 c_1 c_3 + k_{-1} c_4 + D_1 \nabla^2 c_1$$

$$\frac{\partial c_2}{\partial t} + u\frac{\partial c_2}{\partial y} = -k_2 c_2 c_3 + k_{-2} c_5 + D_2 \nabla^2 c_2$$

$$\frac{\partial c_3}{\partial t} + u\frac{\partial c_3}{\partial y} = -k_1 c_1 c_3 + k_{-1} c_4 - k_2 c_2 c_3 + k_{-2} c_5 + D_3 \nabla^2 c_3$$

$$\frac{\partial c_4}{\partial t} + u\frac{\partial c_4}{\partial y} = k_1 c_1 c_3 - k_{-1} c_4 + D_4 \nabla^2 c_4$$

$$\frac{\partial c_5}{\partial t} + u\frac{\partial c_5}{\partial y} = k_2 c_2 c_3 - k_{-2} c_5 + D_5 \nabla^2 c_5$$

The final model involves five coupled differential equations in three dimensions, the solution of which is beyond the scope of this class. Therefore, further assumptions were made to formulate a more accessible model.

Assumptions and Simplifications

In order to simplify the problem, only the concentration of free CO in the blood was modeled. This reduced the problem to a single PDE. In addition, the flow of blood was neglected, which reduced the problem to one dimension (the rectangular shape of the original model created symmetry along the z-axis). Finally, hemoglobin was assumed to bind irreversibly to CO. The release of CO from carboxyhemoglobin (HbCO) is dependent on the concentration of HbCO, which is not being tracked in the simplified model. The simplified model along with the final diffusion equation is shown below:

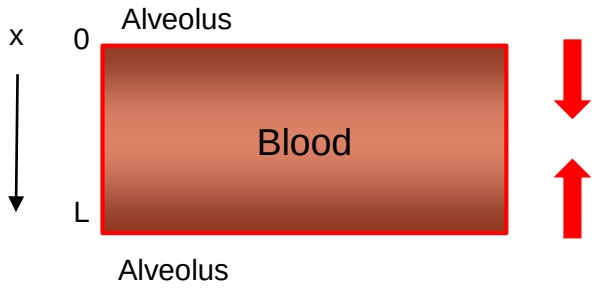

Figure 2: Simplified model for diffusion of CO through a pulmonary capillary of length L

$$\frac{\partial u(x,t)}{\partial t} = D\frac{\partial^2 u(x,t)}{\partial x^2} - k u(x,t) c_{Hb} \qquad \text{Equation 1}$$

with boundary conditions:

$$u(0,t) = C_0 \qquad \text{Equation 2}$$

$$u(L,t) = C_0 \qquad \text{Equation 3}$$

and initial conditions:

$$u(x,0) = g(x) = \begin{cases} C_0, & x = 0 \\ 0, & 0 < x < L \\ C_0, & x = L \end{cases} \qquad \text{Equation 4}$$

The final equation is a non-homogeneous partial differential equation that can be solved using both analytical and numerical methods.

Solving the Model

The simplified model (Equations 1-4) is solved by adding a particular solution to a homogeneous solution:

$$u(x,t) = u_H(x,t) + u_P(x)$$

The particular solution is the steady state of the system, which occurs when time approaches infinity:

$$u_P(x) = \lim_{t\to\infty} u(x,t)$$

$$\lim_{t\to\infty} \frac{\partial u(x,t)}{\partial t} = 0 = D\frac{d^2u_P(x)}{dx^2} - ku_P(x)c_{Hb}$$

Subtracting the particular solution, including boundary conditions, from the original PDE results in the homogeneous solution:

$$u_H(x,t) = u(x,t) - u_P(x)$$

The final set of equations and boundary conditions are displayed in Table 1:

Table 2. The Original PDE and the Particular/Homogeneous Equations

	Differential Equation	Lower B.C.	Upper B.C.
Original Equation	$\frac{\partial u(x,t)}{\partial t} = D\frac{\partial^2 u(x,t)}{\partial x^2} - ku(x,t)c_{Hb}$	$u(0,t) = C_0$	$u(L,t) = C_0$
Particular Equation	$0 = D\frac{d^2u_P(x)}{dx^2} - ku_P(x)c_{Hb}$	$u_P(0) = C_0$	$u_P(L) = C_0$
Homogeneous Equation	$\frac{\partial u_H(x,t)}{\partial t} = D\frac{\partial^2 u_H(x,t)}{\partial x^2}$	$u_H(0,t) = 0$	$u_H(L,t) = 0$

The particular equation is a linear second-order ordinary differential equation. The solution is obtained by substituting $u_P(x) = Ae^{\lambda x}$, and solving for the eigenvalues:

$$0 = D\lambda^2 - kc_{Hb}$$

$$\lambda = \pm\sqrt{\frac{kc_{Hb}}{D}}$$

A new constant, $\alpha = \sqrt{kc_{Hb}/D}$ was introduced to simplify the solution to the ODE:

$$u_P(x) = c_1e^{\alpha x} + c_2e^{-\alpha x}$$

Solving for the boundary conditions for the particular equation, listed in Table 1, the constants were found:

$$u_P(0) = c_1 + c_2 = C_0$$

$$u_P(L) = c_1 e^{\alpha L} + c_2 e^{-\alpha L} = C_0$$

$$c_1 = \frac{C_0}{1 + e^{\alpha L}}$$

$$c_2 = \frac{C_0 e^{\alpha L}}{1 + e^{\alpha L}}$$

Plugging in the constants results in the final particular solution:

$$u_P(x) = \frac{C_0}{1+e^{\alpha L}}\left(e^{\alpha x} + e^{\alpha(L-x)}\right) \qquad \text{Equation 5}$$

The homogenous PDE can be solved using separation of variables:

$$u_H(x,t) = G(t)\phi(x)$$

Substituting this new definition into the homogeneous PDE and rearranging results in one time-dependent equation and one space dependent equation:

$$\frac{\frac{d^2\phi(x)}{dx^2}}{\phi(x)} = \frac{1}{D}\frac{\frac{dG(t)}{dt}}{G(t)} = -\lambda$$

$$\frac{dG(t)}{dt} = -\lambda D G(t)$$

$$\frac{d^2\phi(x)}{dx^2} = -\lambda\,\phi(x)$$

The time-dependent equation can be solved as a linear first-order ODE:

$$G(t) = G_0 e^{-\lambda D t}$$

The space-dependent equation can be solved as a linear second-order ODE:

$$\phi(x) = A\sin\left(\sqrt{\lambda}x\right) + B\cos\left(\sqrt{\lambda}x\right)$$

Applying the boundary condition, $u_H(0,t) = 0$, gives that $B = 0$:

$$A\sin(0) + B\cos(0) = B = 0$$

Applying the boundary condition, $u_H(L,t) = 0$, gives the possible solutions for λ:

$$A\sin(\lambda L) = 0$$

$$\sqrt{\lambda} = \frac{n\pi x}{L}$$

Using the principle of superposition, the final solution to the homogeneous equation is the weighted sum of all possible solutions:

$$u_H(x,t) = \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi x}{L}\right) \mathrm{e}^{-\mathrm{D}\left(\frac{\mathrm{n}\pi}{\mathrm{L}}\right)^2 t} \qquad \text{Equation 6}$$

The solution to the original PDE is the sum of the particular solution (Equation 5) and the homogeneous solution (Equation 6) and the particular solution:

$$u(x,t) = \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi x}{L}\right) \mathrm{e}^{-\mathrm{D}\left(\frac{\mathrm{n}\pi}{\mathrm{L}}\right)^2 t} + \frac{C_0}{1+e^{\alpha L}}\left(e^{\alpha x} + e^{\alpha(L-x)}\right)$$

To solve for the constant A_n, the initial condition (Equation 4) is applied to the above solution. The entire equation is then multiplied by $\sin(m\pi x/L)$, where m is an arbitrary integer, and the result is integrated over the length of the capillary:

$$\int_0^L g(x)\sin\left(\frac{m\pi x}{L}\right)dx = \int_0^L \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi x}{L}\right)\sin\left(\frac{m\pi x}{L}\right)dx + \int_0^L \frac{C_0}{1+e^{\alpha L}}\left(e^{\alpha x} + e^{\alpha(L-x)}\right)\sin\left(\frac{m\pi x}{L}\right)dx$$

Using the orthogonal properties of the Fourier sine series, the equation can be simplified:

$$\int_0^L g(x)\sin\left(\frac{m\pi x}{L}\right)dx = \frac{A_m L}{2} + \int_0^L \frac{C_0}{1+e^{\alpha L}}\left(e^{\alpha x} + e^{\alpha(L-x)}\right)\sin\left(\frac{m\pi x}{L}\right)dx$$

Since the initial condition is zero everywhere except at the bounds, and the sine term is zero at the bounds, the left side of the equation becomes 0:

$$0 = \frac{A_m L}{2} + \int_0^L \frac{C_0}{1+e^{\alpha L}}\left(e^{\alpha x} + e^{\alpha(L-x)}\right)\sin\left(\frac{m\pi x}{L}\right)dx$$

The equation can be rearranged to solve for A_m, and the integral can be solved using integration by parts:

$$A_m = -\frac{2C_0}{L(1+e^{\alpha L})}\int_0^L \left(e^{\alpha x} + e^{\alpha(L-x)}\right)\sin\left(\frac{m\pi x}{L}\right)dx$$

$$A_n = -\frac{2C_0}{\alpha^2 L^2 + n^2\pi^2}\left(n\pi + e^{\alpha L}(-n\pi\cos(n\pi) + \alpha L\sin(n\pi))\right)$$

The final solution for the non-homogeneous PDE is Equation 7:

$$u(x,t) = \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi x}{L}\right) \mathrm{e}^{-\mathrm{D}\left(\frac{\mathrm{n}\pi}{\mathrm{L}}\right)^2 t} + \frac{C_0}{1+e^{\alpha L}}\left(e^{\alpha x} + e^{\alpha(L-x)}\right) \quad \text{Equation 7}$$

where:

$$\alpha = \sqrt{kc_{Hb}/D}$$

$$A_n = -\frac{2C_0}{\alpha^2 L^2 + n^2\pi^2}\left(n\pi + e^{\alpha L}(-n\pi\cos(n\pi) + \alpha L\sin(n\pi))\right)$$

Numerical Solution, Validation, and Observations

Table 2. Values for Constants

Constant	Description	Value
D	Diffusion Coefficient of CO[4]	$1.3 * 10^{-5}\ \frac{cm^2}{s}$
L	Width of a capillary[4]	$8 * 10^{-4} cm$
C_{Hb}	Concentration of Hemoglobin[6]	$2.3 * 10^{-3}\ \frac{mol}{L}$
k	Rate constant of CO binding to Hemoglobin[3]	$2 * 10^{5}\ \frac{L}{mol * s}$
C_0	Concentration of CO in fresh air[5]	$2.9 * 10^{-6}\ \frac{mol}{L}$
CO_{high}	Concentration of CO at lethal levels[5]	$4.1 * 10^{-5}\ \frac{mol}{L}$

Using the final solution to the non-homogeneous PDE (Equation 7), three-dimensional plots were constructed in order to illustrate how the blood stream concentration of CO changes with time and space under normal levels. The analytical solution, plotted using the first 5 and 50 terms of the infinite series, can be seen in Figure 3. Under these conditions, the CO concentration is highest at the interface between the capillary and the alveoli (boundary conditions). The concentration decreases as the distance from the edges increases, and reaches a minimum at the center. In both graphs, a similar steady-state profile is reached almost immediately after the start of the simulation. The main difference between the two plots is the

modeling of the initial condition, which is much better approximated with 50 terms than 5 terms.

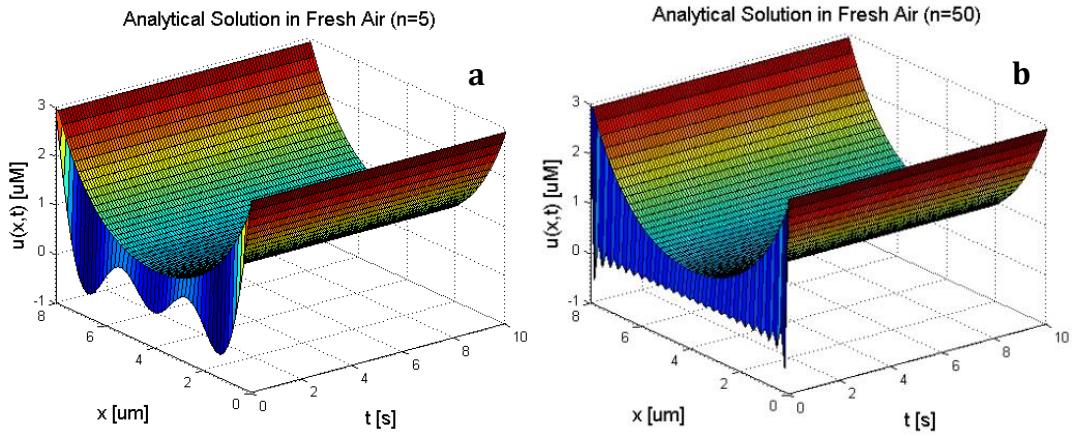

Figure 3: Surface plots of the analytical solution using (a) the first 5 terms and (b) the first 50 terms of the infinite series at normal CO levels.

In order to assess the validity of the analytical solution, an additional surface plot was created using instead the first 500 terms of the infinite series and compared to the Matlab PDEPE solution under the same conditions. The resulting plots are found in Figure 4. The results for each solution were virtually identical.

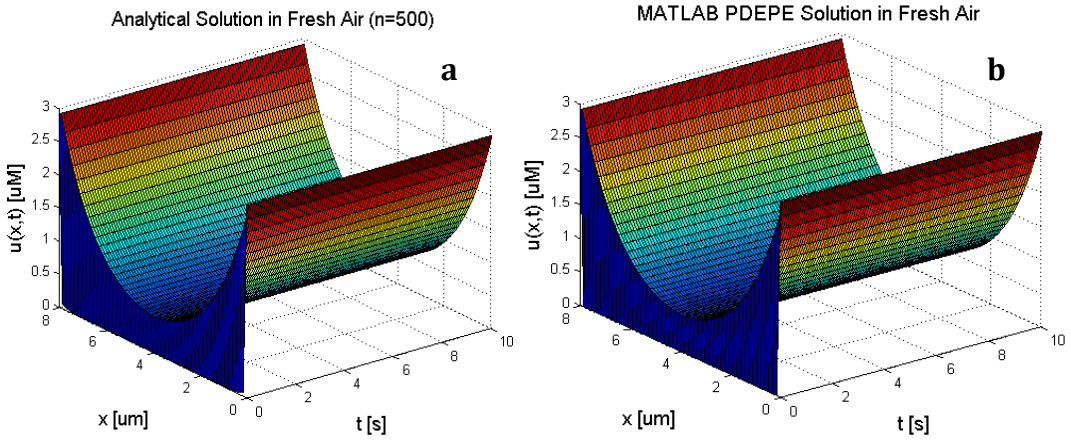

Figure 4: Surface plots at normal CO level of (a) the analytical solution using the first 500 terms of the infinite series and (b) using the Matlab PDEPE solution

The most surprising result of the simulations was that the steady-state concentration profile was achieved almost immediately. In order to obtain a more accurate understanding of this phenomenon, the concentration at the center of the capillary was analyzed at a much smaller timescale. Figure 5a shows how the concentration of free CO at the center of the capillary reaches steady-state after the first 0.04 seconds of diffusing into the capillary. Figure 5b shows the surface plot of this phenomenon.

This is most likely due to the high value of the diffusivity constant ($1.3 * 10^{-5} cm^2/s = 0.13\ m^2/s$), and the high value of the rate constant ($2 * 10^5\ M^{-1}s^{-1}$). Combined, this means that the carbon dioxide rapidly diffuses into the bloodstream, but is quickly bound to the hemoglobin in the bloodstream.

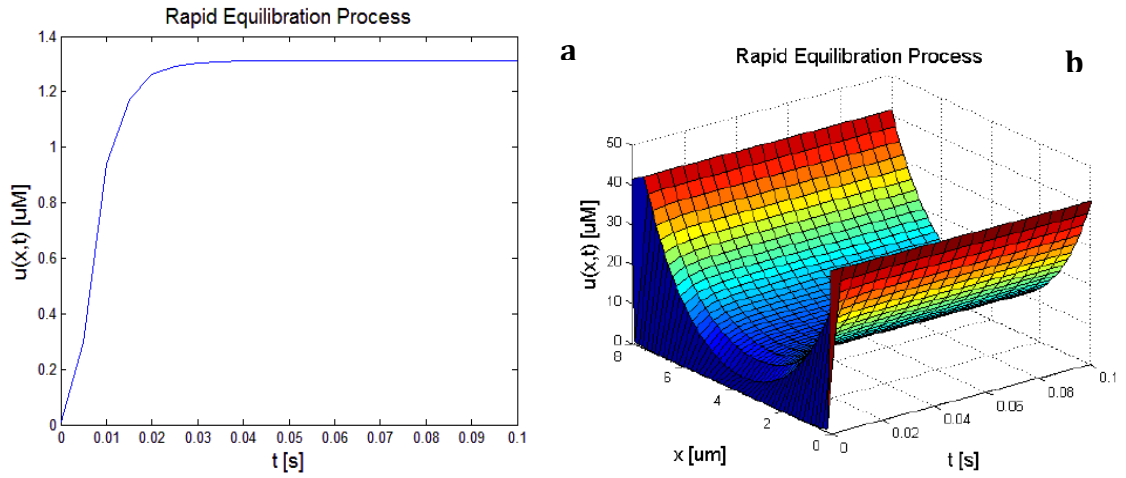

Figure 5: A plot of (a) the centerline concentration of CO from $t = 0$ to $t = 0.1$ seconds and (b) the surface plot of the shorter timescale

After looking at the analytical solution, it became apparent that the general shape of the concentration profile was controlled by $\alpha = \sqrt{kc_{Hb}/D}$, and the timescale was controlled by just the diffusion coefficient. Although it has units of cm^{-1}, α bears a resemblance to dimension-less numbers such as the Sherwood number (the ratio of convective mass transfer coefficient to conductive mass transfer coefficient). In this case, α is the ratio between the rate of CO uptake by hemoglobin, and the diffusion of CO into the blood. A high value of α, as seen in Figure 6a, represents a faster reaction rate than diffusion. A low value of α, as seen in Figure 6b, represents a faster diffusion rate than reaction rate. The low value of α results in a solution that has a shallower concentration profile, because CO does not bind as quickly to hemoglobin. The high value of α results in almost no free CO in the bloodstream, since it is bound to the hemoglobin so quickly.

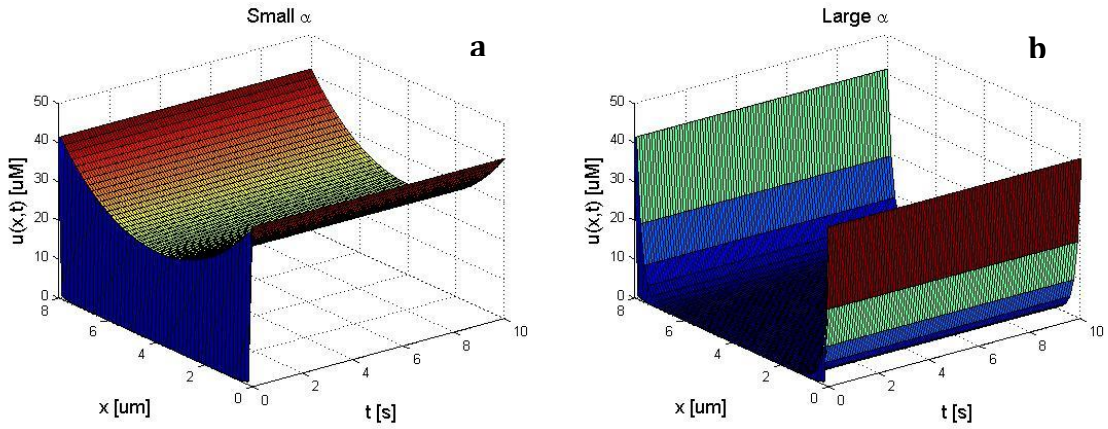

Figure 6: Surface plots at high carbon levels for (a) $\alpha = 0.5\ \alpha_0$ and (b)$\alpha = 5\ \alpha_0$, where α_0 is the value from literature.

Changing the diffusion coefficient while keeping α constant had the same effect as slowing down the timescale. This effect is seen in Figure 7. This is because the diffusion coefficient was only visible outside of α in the exponential decay part of the solution.

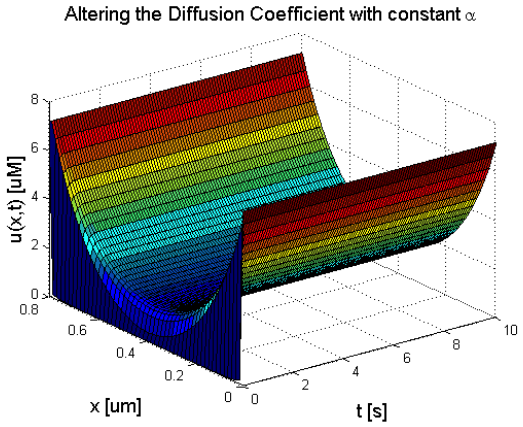

Figure 7: Surface plot of diffusion coefficient divided by 20 while keeping α constant

In order to better approximate realistic conditions, a cylindrical geometry was investigated. Using MATLAB's PDEPE function, the problem was easily converted from rectangular coordinates to cylindrical coordinates. Figure 8 shows the radial

concentration over time. As before, the steady state is achieved almost instantaneously.

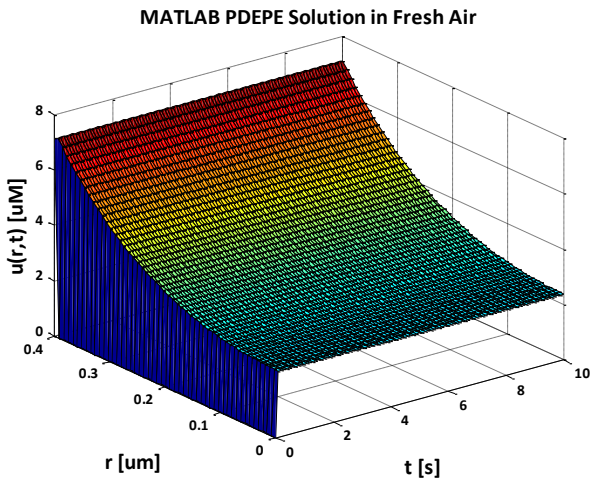

Figure 8: Matlab PDEPE solution for normal CO concentration using cylindrical coordinates

Because the purpose of this project was to study the dynamics of CO poisoning in man, a similar three-dimensional plot of the analytical solution was constructed using a CO concentration nearly 15 times higher than in normal atmospheric conditions. The result can be found in Figure 9. Despite the significant change in boundary condition values, the plot is just a rescaling of the original plot. The results from this solution are used later to determine the lifespan of a man in these conditions.

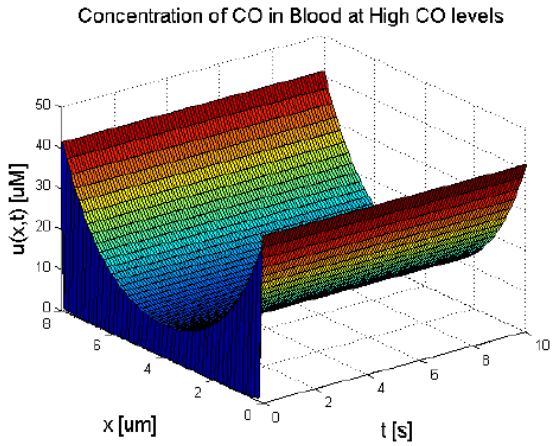

Figure 9: Surface plots of the analytical solution for high levels of CO concentration (a) showing normal time points and (b) showing rapid equilibration

When a person is exposed to high levels of CO, there is a particular time of exposure that can be tolerated before the person becomes lethally poisoned. The information

obtained from the analytical model was used to estimate this time of exposure. The rate law describing CO binding to hemoglobin, assuming irreversibility, is:

$$r = k[Hb][CO]_{mean}$$

Where: $r = \frac{[HbCO]}{t}$ and $[HbCO] = (\%HbCO)[Hb]$

For an adult male, having 70% of CO-bound hemoglobin leads to poisoning and subsequent death[2]. This information, along with the analytical solution, was used to estimate the exposure time, yielding a result of 17 seconds. This result matches the rapid equilibration process from our previous observations. As a means of comparison, the exposure time was also calculated using a widely-accepted reference model[7].

$$(\%HbCO) = 3(\%CO)T$$

$$T = \frac{(\%HbCO)}{3(\%CO)} = \frac{70\%}{3(0.1\%)} = 233.33\,\text{min} \sim 4\ hours$$

Limitations of the Analytical Model

Based on the surface plots obtained for the different scenarios under study, the concentration of CO reached a steady state value within the first 0.04 seconds. Intuitively, it is that this is not a realistic result. Comparison with the reference model confirms this presumption. It so follows that the setup of this model- the assumptions made, were the cause of such a large discrepancy. For instance, competition between CO and oxygen binding to hemoglobin is expected to have a large effect on the concentration of free CO and would therefore significantly alter the final solution. The effects of blood flow on CO transport through the body were neglected as well. It is expected that by taking these into account the time required for CO-bound hemoglobin to reach a lethal level will be much longer. Therefore, improvement on this model should aim to follow more realistic assumptions. Inclusion of the reversibility of CO binding to hemoglobin as well as multi-dimensional diffusion of CO are other improvements to consider.

Conclusions and Future Work

A simplified model of carbon monoxide diffusion through the lungs and its binding kinetics to hemoglobin was considered in this project. Using separation of variables and other mathematical tools, an analytical solution of the model was obtained along with plots showing the concentration of carbon monoxide as a function of space and time. Regardless of the specified boundary conditions, this model showed rapid equilibration of carbon monoxide concentration in the bloodstream. Comparison with a reference model confirmed that our results were far from accurate. This was

likely due to the assumptions made when establishing the model. Future studies should account for competition as well as cooperative binding, as this is expected to significantly change the solution. The effects of blood flow must also be incorporated into the set of PDEs. This analysis was performed considering only the x-direction, thereby, another means for improvement would be modeling multi-dimensional diffusion. Even with further analytical tools from this class, the original model with five coupled partial differential equations in three dimensions may not be solvable. However, a finite difference approximation could be used to solve this system and obtain more accurate results.

The core principles used for this project extend to other applications. For instance, a similar model may be derived to study oxygen diffusion from the lungs, and to the muscles. However, this particular project would need to also account for hemoglobin binding to 2,3-biphosphoglyceric acid, which plays a key role in oxygen transport in the body. In conclusion, this simplified model is adequate to understand the nature of diffusion of a gas into an enclosed space, but without taking into account multiple dimensions, non-homogeneous blood flow, and competitive binding.

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