Development of an Ozone Inhalation Model

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Abstract

The goal of this project was to develop a mathematical dosimetry model that simulates the inhalation and deposition of ozone through the respiratory tract. The model is based upon a transport-diffusion partial differential equation which describes the flow of ozone through the respiratory tract and the diffusion of ozone in the air. The dosimetry model also encompasses the flux of ozone into the tissue giving total concentrations of ozone deposited in the lung. The model was solved using the Crank-Nicolson implicit scheme. Within our model, we split the domain into multiple compartments which mimic the different generations of the lungs. This required conservation of mass to be incorporated. The results generated by the dosimetry model were then linked with data regarding neurons called C-fibers, which are located in the bottom of the lungs. When exposed to ozone, C-fibers react and cause physiological changes such as frequency and depth of breathing. These are results of the body trying to counter the harmful effects of ozone inhalation. Incorporating this aspect to the inhalation model helps depict a more realistic cycle of ozone uptake.

Acknowledgements

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Contents

Chapter 1

Introduction

The EPA is currently working on a project which looks into the overarching effects of ozone on the body. Their project is broken down into several smaller projects. We worked in conjunction with the EPA on the first two parts of their project. The first thing we did on the first part of the project was look into the anatomy of the lungs. The lungs are comprised of 23 generations where generation 0 is the trachea. Located in the bottom of the lungs are neurons called C-fibers. C-fibers react in the presence of ozone and cause a change in both breathing rate and tidal volume and a measurable change in the Ca^{2+} ion [2]. The EPA wants to use this reaction to develop a model of the neural response which would recalculate the new breathing properties then feed back into the dosimetry model thus creating a cyclical model.

We worked mainly on the development of the ozone dosimetry model. In the model, we wish to accurately depict the propagation and absorption of ozone throughout the lungs so that it may be linked with the C-fiber data. In [1] the uptake of formaldehyde was modeled by

$$\begin{aligned} \frac{\partial C_a}{\partial t} + U\frac{\partial C_a}{\partial z} &= D_a\frac{\partial^2 C_a}{\partial z^2} - \frac{2}{R}J_R \\ -\frac{\partial C_t}{\partial t} + D_t\frac{\partial^2 C_t}{\partial r^2} &= K_f C_t + \frac{(V_{max}/V_t)C_t}{K_m + C_t} \end{aligned}$$

with variables defined as follows

C_a	vapor concentration in air	C_t	vapor concentration in the tissue
U	advection speed	z	axial direction through the airways
D_a	diffusivity of vapor in air (cm^2/s)	D_t	diffusivity of vapor in tissue (cm^2/s)
R	airway radius	r	tissue depth
K_f	First-order elimination constant (1/s)	K_m	Michaelis - Menten parameter (mg/m^3)
V_{max}	Michaelis - Menten parameter (mg/s)	V_t	tissue volume (m^3)

We adapted their model to our particular problem. Since ozone is a highly reactive compound, we assume that it reacts instantaneously and that it could never possibly saturate the tissue. From these assumptions we drop two terms in the second equation: the very first term and the Michaelis

- Menten term. Our set of equations then becomes:

$$\frac{\partial C_a}{\partial t} + U\frac{\partial C_a}{\partial z} = D_a\frac{\partial^2 C_a}{\partial z^2} - \frac{2}{R}J_R \tag{1.1}$$

$$D_t\frac{\partial^2 C_t}{\partial r^2} = K_f C_t \tag{1.2}$$

To better understand what is happening in equation (1.1), we then broke our first equation down into smaller components. The advection equation is given by:

$$\frac{\partial C_a}{\partial t} + U\frac{\partial C_a}{\partial z} = 0$$

This describes how ozone propagates through the lung airways. The diffusion equation is given by:

$$\frac{\partial C_a}{\partial t} = D_a\frac{\partial^2 C_a}{\partial z^2}$$

This describes how ozone diffuses through the air in the respiratory tract. It is also clear that $-\frac{2}{R}J_R$ describes how ozone is being removed from the first equation. So this flux term relates how much ozone is being absorbed into the tissue surrounding the airways. Using the equation (1.2), we can find an explicit expression for J_R which relates how ozone is being absorbed by the tissue, and thus allow us to compute solely with the first equation. A simple derivation gives that $J_R = \frac{k_t k_g}{k_g + k_t}C_a$ where k_t and k_g are mass transfer coefficients [*See appendix*].

Chapter 2

Methods

2.1 Dosimetry: Advection Diffusion Equation

The equation used for the ozone dosimetry model is simply given by the following:

$$u_t + Cu_x = Du_{xx} - \tilde{\alpha}u \tag{2.1}$$

where C is the advection velocity coefficient, D is the diffusivity coefficient, and $\tilde{\alpha}$ is a flux coefficient. To begin, the Crank-Nicolson method was used to solve the equation (2.1) in with zero boundaries conditions. The general form of the Crank-Nicolson is:

$$\frac{u_j^{n+1} - u_j^n}{\Delta t} = \frac{1}{2}\left[F_j^{n+1}\left(u, x, t, \frac{\partial u}{\partial x}, \frac{\partial^2 u}{\partial x^2}\right) + F_j^n\left(u, x, t, \frac{\partial u}{\partial x}, \frac{\partial^2 u}{\partial x^2}\right)\right]$$ †

Crank-Nicolson employs the trapezoidal rule in time and a centered difference in space. It is an implicit scheme which means we must algebraicly solve for our solution. This allows for our solution to be unconditionally stable which allows us to choose any step sizes. Having unconditional stability prevents the solution from blowing up based on step sizes.

2.2 Discretization of Single Domain

First we discretize equation (2.1):

$$\frac{u_j^{n+1} - u_j^n}{\Delta t} =$$

$$\frac{1}{2}D\left[\left(\frac{u_{j+1}^{n+1} - 2u_j^{n+1} + u_{j-1}^{n+1}}{\Delta x^2}\right) + \left(\frac{u_{j+1}^n - 2u_j^n + u_{j-1}^n}{\Delta x^2}\right)\right]$$

$$-\frac{1}{2}C\left[\left(\frac{u_{j+1}^{n+1} - u_{j-1}^{n+1}}{2\Delta x}\right) + \left(\frac{u_{j+1}^n - u_{j-1}^n}{2\Delta x}\right)\right]$$

† u_j^n: The subscript is the spatial index and the superscript is the temporal index

$$-\frac{1}{2}\tilde{\alpha}\left[u_j^{n+1}+u_j^n\right]$$

We let $\gamma = \frac{1}{2}D\frac{\Delta t}{\Delta x^2}$, $\lambda = \frac{1}{4}C\frac{\Delta t}{\Delta x}$, and $\alpha = \Delta t\tilde{\alpha}$ then substitute and expand to get

$$\begin{aligned} u_j^{n+1}-u_j^n &= \gamma u_{j+1}^{n+1} - 2\gamma u_j^{n+1} + \gamma u_{j-1}^{n+1} \\ &+ \gamma u_{j+1}^{n} - 2\gamma u_j^{n} + \gamma u_{j-1}^{n} \\ &- \lambda u_{j+1}^{n+1} + \lambda u_{j-1}^{n+1} \\ &- \lambda u_{j+1}^{n} + \lambda u_{j-1}^{n} \\ &- \frac{1}{2}\alpha u_j^{n+1} - \frac{1}{2}\alpha u_j^n \end{aligned}$$

Next, we move the forward time components to the left-hand side and the current time components to the right-hand side and factor

$$(-\gamma-\lambda)\,u_{j-1}^{n+1} + \left(1+2\gamma+\frac{1}{2}\alpha\right)u_j^{n+1} + (\lambda-\gamma)\,u_{j+1}^{n+1} \tag{2.2}$$

$$= (\gamma+\lambda)\,u_{j-1}^{n} + \left(1-2\gamma-\frac{1}{2}\alpha\right)u_j^{n} + (\gamma-\lambda)\,u_{j+1}^{n} \tag{2.3}$$

Lastly, we place the coefficients into tridiagonal matrices

$$\mathrm{A} = \begin{bmatrix} 1+2\gamma+\frac{1}{2}\alpha & \lambda-\gamma & 0 & \cdots & 0 \\ -\gamma-\lambda & 1+2\gamma+\frac{1}{2}\alpha & \lambda-\gamma & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & \ddots & -\gamma-\lambda & 1+2\gamma+\frac{1}{2}\alpha & \lambda-\gamma \\ 0 & \cdots & 0 & -\gamma-\lambda & 1+2\gamma+\frac{1}{2}\alpha \end{bmatrix}$$

$$\mathrm{B} = \begin{bmatrix} 1-2\gamma-\frac{1}{2}\alpha & \gamma-\lambda & 0 & \cdots & 0 \\ \gamma+\lambda & 1-2\gamma-\frac{1}{2}\alpha & \gamma-\lambda & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & \ddots & \gamma+\lambda & 1-2\gamma-\frac{1}{2}\alpha & \gamma-\lambda \\ 0 & \cdots & 0 & \gamma+\lambda & 1-2\gamma-\frac{1}{2}\alpha \end{bmatrix}$$

This gives us [‡]

$$A\mathbf{u}^{n+1} = B\mathbf{u}^n$$

We then wish to solve for $\mathbf{u}^{n+1}$ to get our solution

$$\mathbf{u}^{n+1} = A^{-1} \cdot B\mathbf{u}^n \tag{2.4}$$

Note that A is never singular because the diagonal entries are always constant and never zero based upon the nonzero choices of Δx and Δt. Brute force calculation of the inverse of a matrix is very computationally expensive. We used the Thomas Algorithm to compute the inverse of the tridiagonal matrix [*See appendix*]. Initially, we establish values for Δx and Δt along with values of C, D, and α. Then we choose a duration to compute.

2.3 Multiple Domain: Internal Boundary Problems

We wish to numerically solve equation (2.1) but with the domain split into separate compartments. The split domain encompasses the possibility of having different values for the diffusivity coefficients, advection constants, and flux terms. The flux term is noticeably different between generations as it goes like $frac2RJ_R$ and it is easy to see R varies between generations. To combat this situation, we chose to implement an averaging technique over the internal domain boundary in order to maintain continuity. The continuity condition for our physical model is required to maintain conservation of mass. For simplicity we consider the case where there are only two compartments and generalize our findings for more compartments.

2.3.1 Discretization of Multiple Domain at an Internal Boundary

Discretizing of the two domain problem is demonstrated as follows, where the diffusivity constants and flux terms are averaged:

$$\frac{u_j^{n+1} - u_j^n}{\Delta t} =$$

$$\frac{1}{2}D_1\left[\frac{1}{2}\left(\frac{u_{j+1}^{n+1} - 2u_j^{n+1} + u_{j-1}^{n+1}}{\Delta x_1^2}\right) + \frac{1}{2}\left(\frac{u_{j+1}^{n} - 2u_j^{n} + u_{j-1}^{n}}{\Delta x_1^2}\right)\right]$$

$$+ \frac{1}{2}D_2\left[\frac{1}{2}\left(\frac{u_{j+1}^{n+1} - 2u_j^{n+1} + u_{j-1}^{n+1}}{\Delta x_2^2}\right) + \frac{1}{2}\left(\frac{u_{j+1}^{n} - 2u_j^{n} + u_{j-1}^{n}}{\Delta x_2^2}\right)\right]$$

$$- r_1C_1\left[\frac{1}{2}\left(\frac{u_{j+1}^{n+1} - u_{j-1}^{n+1}}{2\Delta x_1}\right) + \frac{1}{2}\left(\frac{u_{j+1}^{n} - u_{j-1}^{n}}{2\Delta x_1}\right)\right]$$

[‡]Boldface indicates a vector

$$- r_2 C_2 \left[\frac{1}{2} \left(\frac{u_{j+1}^{n+1} - u_{j-1}^{n+1}}{2\Delta x_2} \right) + \frac{1}{2} \left(\frac{u_{j+1}^{n} - u_{j-1}^{n}}{2\Delta x_2} \right) \right]$$

$$- \frac{1}{4}\tilde{\alpha_1} \left[u_j^{n+1} + u_j^n \right] - \frac{1}{4}\tilde{\alpha_2} \left[u_j^{n+1} + u_j^n \right]$$

where r_1 and r_2 are as calculated below to minimize the error in crossing the partition.

Let $\gamma_1 = \frac{1}{2} D_1 \frac{\Delta t}{\Delta x_1^2}$, $\gamma_2 = \frac{1}{2} D_2 \frac{\Delta t}{\Delta x_2^2}$, $\lambda_1 = \frac{1}{4} C_1 \frac{\Delta t}{\Delta x_1}$, $\lambda_2 = \frac{1}{4} C_2 \frac{\Delta t}{\Delta x_2}$, $\alpha_1 = \Delta t \tilde{\alpha_1}$, and $\alpha_2 = \Delta t \tilde{\alpha_2}$ then substitute, expand, and factor to get

$$\left(-\frac{1}{2}\gamma_1 - \frac{1}{2}\gamma_2 - \lambda_1 r_1 - \lambda_2 r_2 \right) u_{j-1}^{n+1} + \left(1 + \gamma_1 + \gamma_2 + \frac{1}{4}\gamma_1 + \frac{1}{4}\gamma_2 + \frac{1}{4}\alpha_1 + \frac{1}{4}\alpha_2 \right) u_j^{n+1}$$

$$+ \left(-\frac{1}{2}\gamma_1 - \frac{1}{2}\gamma_2 + \lambda_1 r_1 + \lambda_2 r_2 \right) u_{j+1}^{n+1}$$

$$= \left(\frac{1}{2}\gamma_1 + \frac{1}{2}\gamma_2 + \lambda_1 r_1 + \lambda_2 r_2 \right) u_{j-1}^{n}$$

$$+ \left(1 - \gamma_1 - \gamma_2 - \frac{1}{4}\gamma_1 - \frac{1}{4}\gamma_2 - \frac{1}{4}\alpha_1 - \frac{1}{4}\alpha_2 \right) u_j^n + \left(\frac{1}{2}\gamma_1 + \frac{1}{2}\gamma_2 - \lambda_1 r_1 - \lambda_2 r_2 \right) u_{j+1}^n$$

Again, we place the coefficients into tridiagonal matrices and solve for the $\mathbf{u}^{n+1}$ as in equation (2.4).

Optimization of Smoothing Coefficients

We wish to minimize the total error from propagating our solution across the internal boundaries in our domain by finding optimal ratios to multiply the advection terms across the partition by. We start by defining the discretization of u_x at a partition in our domain as $\tilde{u_x}$ given by

$$u_x \approx \tilde{u_x} = A \left[\frac{u_{j+1} - u_j}{\Delta x_2} \right] + B \left[\frac{u_j - u_{j-1}}{\Delta x_1} \right]$$

Then we use Taylor Series to approximate

$$\begin{aligned} u_{j+1} &\approx u_j + \Delta x_2 u_j' + \frac{1}{2}\Delta x_2^2 u_j'' + O(\Delta x_2^3) \\ u_{j-1} &\approx u_j - \Delta x_1 u_j' + \frac{1}{2}\Delta x_1^2 u_j'' + O(\Delta x_1^3) \end{aligned}$$

Plugging in the Taylor approximations we obtain

$$\begin{aligned}
\tilde{u_x} &= A\left[\frac{u_j + \Delta x_2 u_j' + \frac{1}{2}\Delta x_2^2 u_j'' + O(\Delta x_2^3) - u_j}{\Delta x_2}\right] + B\left[\frac{u_j - u_j + \Delta x_1 u_j' - \frac{1}{2}\Delta x_1^2 u_j'' + O(\Delta x_1^3)}{\Delta x_1}\right] \\
&= A\left[u_j' + \frac{1}{2}\Delta x_2 u_j'' + O(\Delta x_2^2)\right] + B\left[u_j' - \frac{1}{2}\Delta x_1 u_j'' + O(\Delta x_1^2)\right] \\
&= Au_j' + \frac{1}{2}A\Delta x_2 u_j'' + O(\Delta x_2^2) + Bu_j' - \frac{1}{2}B\Delta x_1 u_j'' + O(\Delta x_1^2) \\
&= (A+B)u_j' + \frac{1}{2}(A\Delta x_2 - B\Delta x_1)u_j'' + O(\Delta x_2^2) + O(\Delta x_1^2)
\end{aligned}$$

To minimize the error we need to minimize $u_x - \tilde{u_x}$. Noting that $u_x = u_j'$ gives

$$u_x - \tilde{u_x} = u_j' - (A+B)u_j' - \frac{1}{2}(A\Delta x_2 - B\Delta x_1)u_j'' + O(\Delta x_2^2) + O(\Delta x_1^2)$$

To minimize the above equation we need that $A + B = 1$ and $A\Delta x_2 - B\Delta x_1 = 0$
Solving for A and B we obtain:

$$A = \frac{\Delta x_1}{\Delta x_1 + \Delta x_2} \quad \text{and} \quad B = \frac{\Delta x_2}{\Delta x_1 + \Delta x_2}$$

Thus, by using these ratios, we minimize oscillations from crossing across partitions.

2.4 Non-Uniform Boundary Conditions

We break our boundary conditions into two distinct cases: the inhale and the exhale.

2.4.1 Inhale

We assume that all O_3 which reaches the last generation or bottom of the lungs is absorbed into the tissue. This implies a no flux condition on the -right-hand side. The left hand side of our system models the trachea and therefore should have an inhalation of ozone. We assume that the ozone inhaled in has already passed through the nasal cavity. We assume that our system is inhaling a set concentration of O_3, say C_0 on the LHS. This means that we need an extra vector for the initial inhaled O_3 so we take our system

$$A\mathbf{u}^{n+1} = B\mathbf{u}^n$$

and see from our general scheme above that the u_{j-1} terms have coefficients of $-\lambda - \gamma$ and $\lambda + \gamma$ for forward and current time respectively. Thus we add:

$$(-\lambda - \gamma)\begin{bmatrix} C_0 \\ \vdots \\ 0 \end{bmatrix} + A\mathbf{u}^{n+1} = (\lambda + \gamma)\begin{bmatrix} C_0 \\ \vdots \\ 0 \end{bmatrix} + B\mathbf{u}^n$$

The no flux boundary condition on the RHS implies that $\left.\frac{\partial u}{\partial x}\right|_{x=L} = 0$. Discretizing this gives $\frac{u_{j+1}-u_j}{\Delta x} = 0 \implies u_{j+1} = u_j$.

Plugging this into our scheme gives:

$$\begin{aligned}
u_t &= Du_{xx} - Cu_x - \tilde{\alpha}u \\
\frac{u_j^{n+1} - u_j^n}{\Delta t} &= \frac{1}{2}D\left[\frac{u_{j+1}^{n+1} - 2u_j^{n+1} + u_{j-1}^{n+1}}{\Delta x^2} + \frac{u_{j+1}^n - 2u_j^n + u_{j-1}^n}{\Delta x^2}\right] \\
&- \frac{1}{2}C\left[\frac{u_{j+1}^{n+1} - u_{j-1}^{n+1}}{2\Delta x} + \frac{u_{j+1}^n + u_{j-1}^n}{2\Delta x}\right] \\
&- \frac{1}{2}\tilde{\alpha}\left[u_j^{n+1} + u_j^n\right]
\end{aligned}$$

plugging in $u_{j+1} = u_j$ gives

$$\begin{aligned}
\frac{u_j^{n+1} - u_j^n}{\Delta t} &= \frac{1}{2}D\left[\frac{u_j^{n+1} - 2u_j^{n+1} + u_{j-1}^{n+1}}{\Delta x^2} + \frac{u_j^n - 2u_j^n + u_{j-1}^n}{\Delta x^2}\right] \\
&- \frac{1}{2}C\left[\frac{u_j^{n+1} - u_{j-1}^{n+1}}{2\Delta x} + \frac{u_j^n + u_{j-1}^n}{2\Delta x}\right] \\
&- \frac{1}{2}\tilde{\alpha}\left[u_j^{n+1} + u_j^n\right]
\end{aligned}$$

Letting $\gamma = \frac{1}{2}\frac{D\Delta t}{\Delta x^2}$, $\alpha = \Delta t\tilde{\alpha}$ and $\lambda = \frac{1}{4}\frac{C\Delta t}{\Delta x}$ implies

$$\begin{aligned}
\implies u_j^{n+1} - u_j^n &= -\gamma u_j^{n+1} + \gamma u_{j-1}^{n+1} - \gamma u_j^n - \gamma u_{j-1}^n - \lambda u_j^{n+1} \\
&\quad + \lambda u_{j-1}^{n+1} - \lambda u_j^n - \lambda u_{j-1}^n - \frac{1}{2}\alpha u_j^{n+1} - \frac{1}{2}\alpha u_j^n
\end{aligned}$$

Rearranging terms to separate the different time steps yields:

$$\left(1 + \gamma + \lambda + \frac{1}{2}\alpha\right)u_j^{n+1} + (-\gamma - \lambda)\,u_{j-1}^n = \left(1 - \gamma - \lambda - \frac{1}{2}\alpha\right)u_j^n + (\gamma + \lambda)\,u_{j-1}^n$$

Thus in our matrix, the last entry of the diagonal of the current time matrix should be $\left(1 - \gamma - \lambda - \frac{1}{2}\alpha\right)$ and on the forward time matrix $\left(1 + \gamma + \lambda + \frac{1}{2}\alpha\right)$.

2.4.2 Exhale

We maintain the no flux on the right hand side, but now we are no longer inhaling the constant ozone concentration, C_0, on the left hand boundary. Now we impose a no flux condition to the LHS to simulate O_3 leaving the respiratory tract. We need $\left.\frac{\partial u}{\partial x}\right|_{x=0} = 0 \implies \frac{u_j - u_{j-1}}{\Delta x} = 0 \implies u_j = u_{j-1}$ at $x = 0$. Using our general scheme :

$$\begin{aligned}
\frac{u_j^{n+1} - u_j^n}{\Delta t} &= \frac{1}{2} D \left[\frac{u_{j+1}^{n+1} - 2u_j^{n+1} + u_{j-1}^{n+1}}{\Delta x^2} + \frac{u_{j+1}^n - 2u_j^n + u_{j-1}^n}{\Delta x^2} \right] \\
&- \frac{1}{2} C \left[\frac{u_{j+1}^{n+1} - u_{j-1}^{n+1}}{2\Delta x} + \frac{u_{j+1}^n + u_{j-1}^n}{2\Delta x} \right] \\
&- \frac{1}{2} \tilde{\alpha} \left[u_j^{n+1} + u_j^n \right]
\end{aligned}$$

Plugging in the condition $u_{j-1} = u_j$ gives

$$\begin{aligned}
\frac{u_j^{n+1} - u_j^n}{\Delta t} &= \frac{1}{2} D \left[\frac{u_{j+1}^{n+1} - 2u_j^{n+1} + u_j^{n+1}}{\Delta x^2} + \frac{u_{j+1}^n - 2u_j^n + u_j^n}{\Delta x^2} \right] \\
&- \frac{1}{2} C \left[\frac{u_{j+1}^{n+1} - u_j^{n+1}}{2\Delta x} + \frac{u_{j+1}^n + u_j^n}{2\Delta x} \right] \\
&- \frac{1}{2} \tilde{\alpha} \left[u_j^{n+1} + u_j^n \right]
\end{aligned}$$

Using the same substitutions as above yields

$$u_j^{n+1} - u_j^n = \gamma u_{j+1}^{n+1} - \gamma u_j^n + \gamma u_{j+1}^n - \gamma u_j^n - \lambda u_{j+1}^{n+1} + \lambda u_j^{n+1} - \lambda u_{j+1}^n - \lambda u_j^n - \frac{1}{2}\alpha u_j^{n+1} - \frac{1}{2}\alpha u_j^n$$

Separating the time steps as above gives:

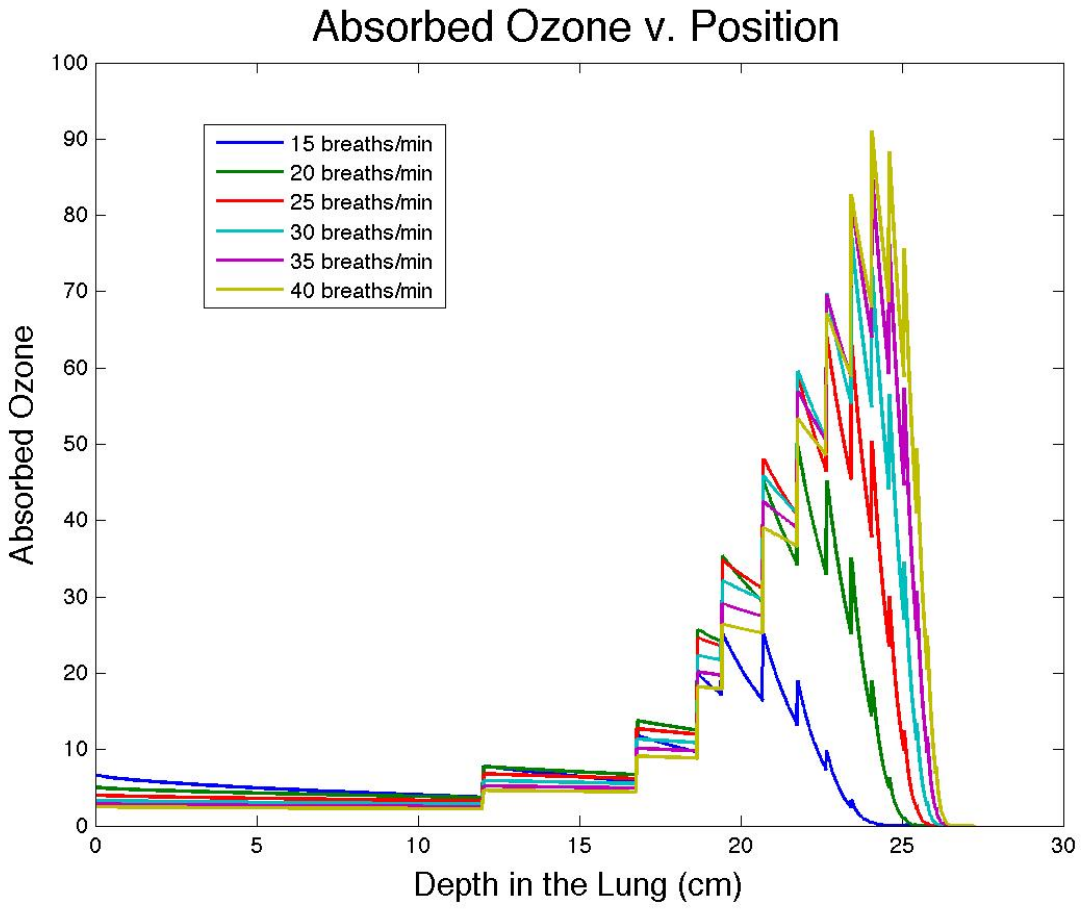
$$\left(1 + \gamma - \lambda + \frac{1}{2}\alpha\right) u_j^{n+1} + (-\gamma - \lambda)\, u_{j+1}^{n+1} = \left(1 - \gamma - \lambda - \frac{1}{2}\alpha\right) u_j^n + (\gamma - \lambda)\, u_{j+1}^n$$

Thus, the first entry of the diagonal on the forward time matrix becomes $\left(1 + \gamma - \lambda + \frac{1}{2}\alpha\right)$ and the first entry on the current time matrix becomes $\left(1 - \gamma + \lambda - \frac{1}{2}\alpha\right)$.

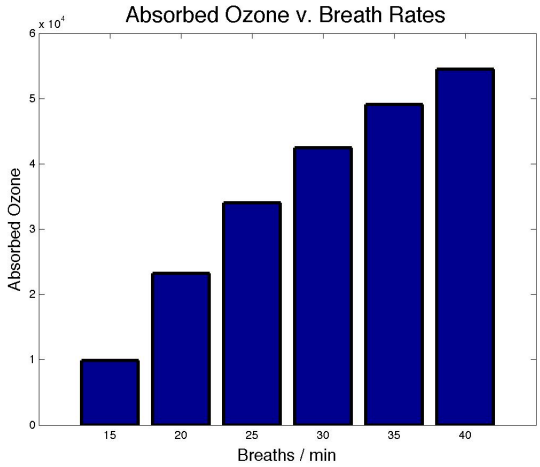
Chapter 3

Dosimetry Results

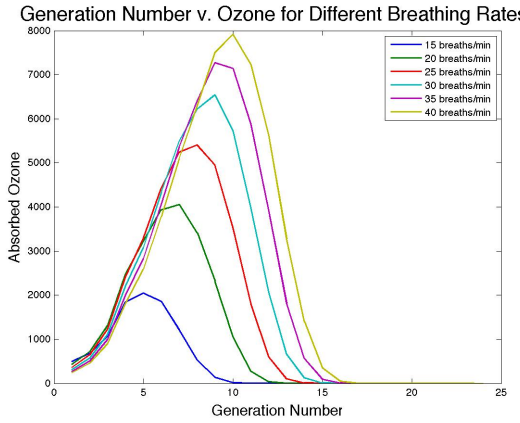
We ran our program using parameters for the human lung. As we did not include a section of our code to account for nasal scrubbing, which is the removing of toxins from the air through the use of hairs in the nasal passageways, we view the inhaled concentration of ozone as being the ozone that remains after nasal scrubbing. When we ran our data, we used the inhaled concentration $C_0 = 1$ and then looked into the patterns that formed for different breathing rates.

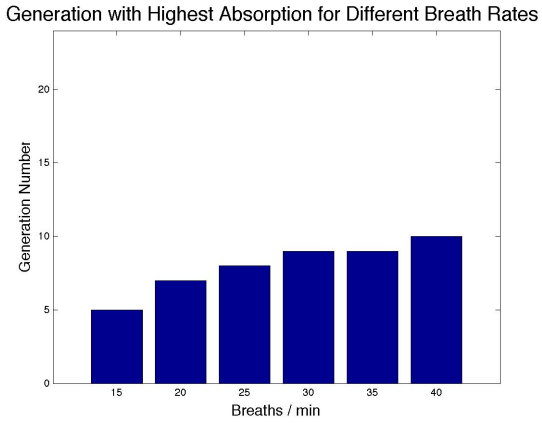


This figure depicts where ozone is absorbed in the lungs for different breathing rates. For reference, 15 breaths per minute is a resting breathing rate, like that of a person sitting still, while 40 breaths per minute corresponds to someone exercising vigorously. It is clear that our model predicts that the faster a human breaths, that the deeper the ozone penetrates into the lungs and that more ozone is absorbed. The spikes that are seen relate to the fact that as ozone moves from one generation to the next, the radius of the airway get smaller, which increases the amount of ozone absorbed as the flux into out of the system is inversely proportional to the radius of each generation. As ozone continues through the generation, it is absorbed.

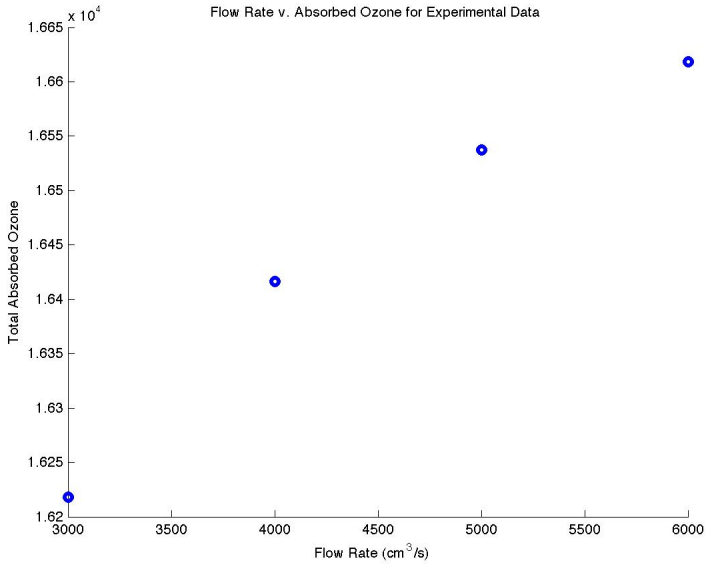


This depicts the total amount of ozone inhaled by the lungs for each breathing rate.

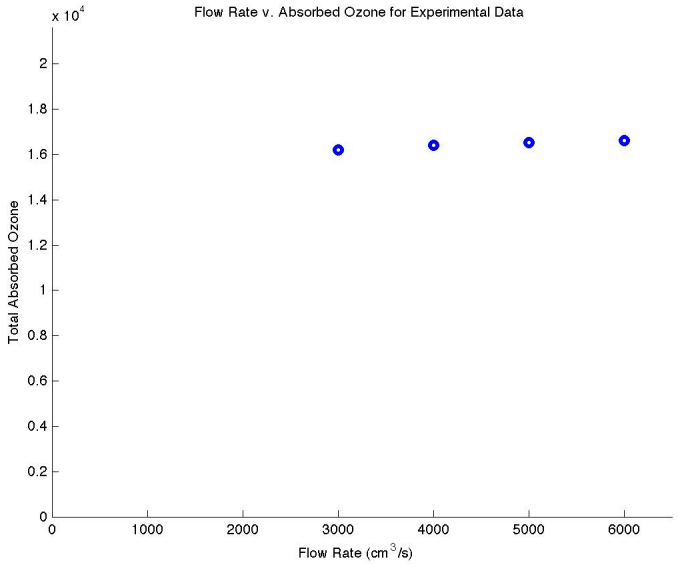




We also ran our code with parameters given to us by another member of the EPA who developed an experiment meant to mimic the lining of the lungs. In his experiment, he used a tube with different sized compartments. It consists of six compartments that are 4 cm long with a radius of 1.03 cm. Between each of these compartments is a smaller compartment of .7 cm in length and .79 cm in radius. He lined the tube with a fluid similar to the lining of the lungs. Using this data, we ran our code to compare to his results. We tried to recreate one of his plots by running our code for the same duration of time and using the same flow rates.



These plots are our recreation of his plot. Since we assume the tissue depth in the lung is infinitely thick, we do not include the possibility for the saturation of tissue. However, the experimentalist's results clearly reflected that his imitation fluid experienced some saturation.



Chapter 4

C-Fibers

C-Fibers are neurons located in the lower part of the lungs and are responsible for combating the damaging effects of ozone inhalation. C-Fibers generate neurological signals which create physiological changes to the respiratory system. These changes include rapid breathing patterns and decrease in tidal volume. The dosimetry results allow us to move to a C-Fiber response model. From literature, [2], we know ozone activates hTRPA1-HEK cells and what response is given by dosage and duration of exposure. Depicted in *Figure 6.1*, we see the response curve for one concentration over time on the left and the maximum responses over all time for multiple concentrations on the right.

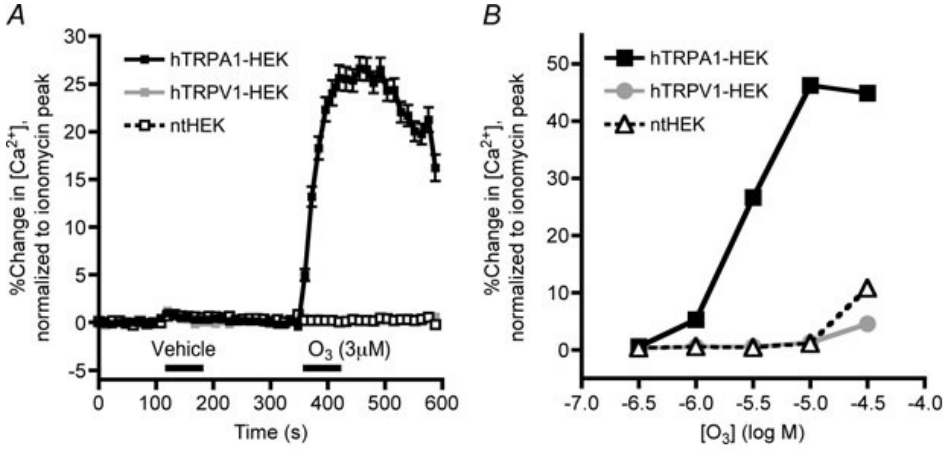
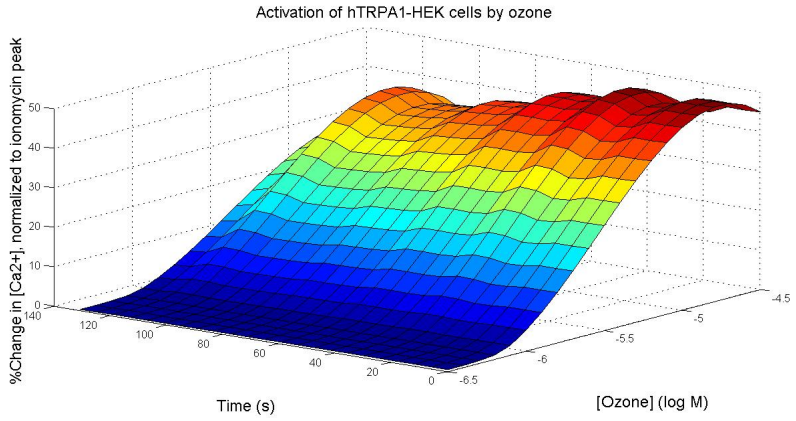


Figure 6.1 **Activation of hTRPA1-HEK cells by ozone**: Left: Mean ± S.E.M. Ca^{2+} responses of hTRPA1-HEK (black line, n=447), hTRPV1-HEK (gray line, n=188) and ntHEK cells (broken line, n=389) to vehicle and ozone (3 μM). Drugs were applied for 60 s (black line). Right: Dose-response relationships of Ca^{2+} responses of hTRPA1-HEK (black squares), hTRPV1-HEK(gray circles) and ntHEK cells (open triangles) to ozone (300 nM to 30 μM) (data comprise > 188 cells). Data represent the maximum response during the 60 s agonist treatment taken from mean cell response versus time curves (note that the S.E.M. is contained within symbol).

We combined the data in *Figure 6.1* to generate a surface which takes ozone concentration and time as inputs and outputs the change in the Ca^{2+} ion.



The data given by the right curve in *Figure 6.1* was smoothed by an interpolation polynomial.

We developed a hypothesis about how the C-Fibers would respond in vivo to ozone. The hypothesis assumes that the C-Fibers located in each generation would respond to the total amount of ozone absorbed in that generation per breath. The response would give a maximum percent change in the Ca^{2+} ion and this maximum response would be compared to each of the maximum responses in the proceeding breaths. Concisely, a set of global maximums are developed from the local maximum responses developed in each generation for each breath. These global maximums determine the overall C-Fiber response for the body. However, there is little or no experimental data to bolster this hypothesis. Using this hypothesis, we developed two C-Fiber response curves.

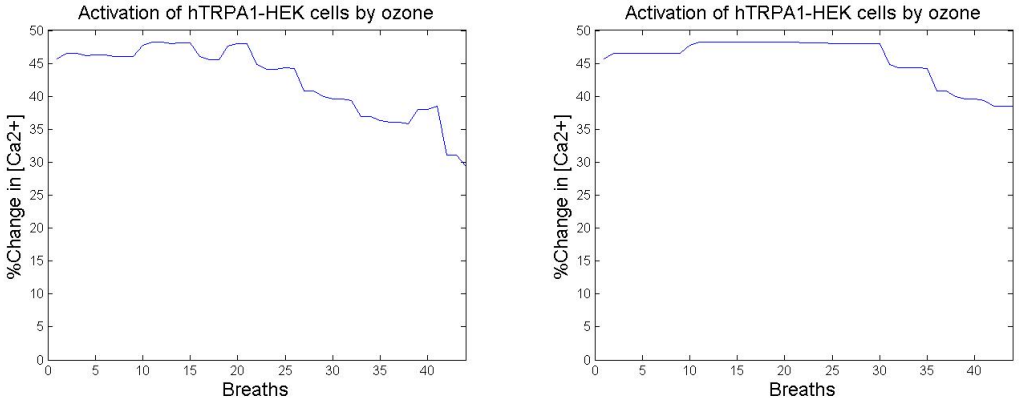


Figure 6.2 The left response curve is a single initial dose of (3 μM) O_3 over 44 breaths. The right response curve is 10 consecutive doses of (3 μM) O_3 over 44 breaths starting at breath 1. The data generated by these curves give information to the body so that it can make physiological changes such as shallow, rapid breaths. This gives a relation between the dosimetry model data and the neural response model which is still yet to be developed.

Chapter 5

Further Developments

Currently, we have developed code that will run the dosimetry model with internal boundaries and various external boundary conditions for any given lung parameters. With quick substitutions for the human lung parameters (i.e. radius, number of generations, length of each generation) our code can run the same transport-diffusion model for any other animal, as is evidenced by our running data for the EPA's experiment. This is beneficial when experimental data is gathered using animals such as rats or monkeys.

With the work completed on the dosimetry model and C-fiber data, the EPA will development a third part of the full model. The third component of the model pertains to the body's physiological reaction to the damaging effects of ozone. The response generated by the C-fibers causes the body to increase breathing rates and decrease tidal volume. The EPA aims to use the C-fiber data to create a neurological response model which will recalculate the parameters of breathing given an ozone dosage. From there the dosimetry model can be rerun with the new breathing properties and circulated for long term exposures.

Appendices

Appendix A

Flux Term Derivation

Our model is given by

$$\begin{aligned} \frac{\partial C_a}{\partial t} + U\frac{\partial C_a}{\partial z} &= D_a\frac{\partial^2 C_a}{\partial z^2} - \frac{2}{R}J_R \\ D_t\frac{\partial^2 C_t}{\partial r^2} &= K_f C_t \end{aligned}$$

where the flux term J_R couples the two equations together. An expression for J_R can be derived explicitly. According to [1] the air-tissue interface is linked by $C_{a:t}$ and $C_{t:a}$, where the first is the concentration on the air side of the air-tissue interface, and the second is on the tissue side. They are related by $C_{t:a} = P_{t:a}C_{a:t}$, where $P_{t:a}$ is a partition coefficient. It is given that $J_R = k_g(C_a - C_{a:t})$, where k_g is a mass transfer coefficient. J_R is also given by $J_R = k_t C_{a:t} + k_i$, where both k_t and k_i are mass transfer coefficients. However, we assume steady-state transport of ozone, so $k_i \to 0$. We also know that $C_{a:t} = \frac{k_g}{k_g + k_t}C_a$.

We now work with our second equation:

$$D_t\frac{\partial^2 C_t}{\partial r^2} = K_f C_t$$

With boundary conditions

$$C_t(0) = C_{t:a} = P_{t:a}C_{a:t}$$

and

$$C_t(L) = 0$$

Where L is the tissue depth. The first assumption comes from the the fact that the concentration of ozone has to be continuous across the air-tissue interface and the second comes from assuming that ozone never diffuses all the way through the tissue since it is so highly reactive. For simplicity, we assume $L \to \infty$ and therefore $\lim_{x\to\infty} C_t(x) = 0$

We know that we can make this assumption from a simple mathematical proof that the depth of tissue does not affect the total concentration in the tissue. We know that the total concentration in tissue at some given time is given by $C_t = \int_0^L C_t dr$. If the total concentration does not depend on L, then we need that $\frac{d}{dL}C_t = \frac{d}{dL}\int_0^L C_t dr = 0$. By the Fundamental Theorem of Calculus we have that $\frac{d}{dL}\int_0^L C_t dr = C_t(L)$. But from our assumption that $C_t(L) = 0$, i.e. that the concentration of ozone at the end of the tissue is zero. We have that the total length of tissue L does not matter.

We proceed and solve

$$D_t\frac{\partial^2 C_t}{\partial r^2} = K_f C_t$$

From ODE theory, we know that the answer is

$$C_t(r) = Ae^{\sqrt{\frac{K_f}{D_t}}r} + Be^{-\sqrt{\frac{K_f}{D_t}}r}$$

Taking a derivative yields

$$\frac{\partial C_t}{\partial r} = \sqrt{\frac{K_f}{D_t}}Ae^{\sqrt{\frac{K_f}{D_t}}r} - \sqrt{\frac{K_f}{D_t}}Be^{-\sqrt{\frac{K_f}{D_t}}r}$$

Letting $\gamma = \sqrt{\frac{K_f}{D_t}}$ gives

$$C_t(r) = Ae^{\gamma r} + Be^{-\gamma r}$$

$$\frac{\partial C_t}{\partial r} = \gamma Ae^{\gamma r} - \gamma Be^{-\gamma r}$$

Using the B.C. $\lim_{x\to\infty} C_t(x) = 0$

$$\begin{aligned} 0 &= \lim_{x\to\infty} Ae^{\gamma x} + Be^{-\gamma x} \implies \\ 0 &= \lim_{x\to\infty} Ae^{\gamma x} \end{aligned}$$

Since $\lim_{x\to\infty} e^{\gamma x}$ is non-zero this implies that $A = 0$ therefore using the B.C. $C_t(0) = P_{t:a}C_{a:t}$ gives

$$P_{t:a}C_{a:t} = B$$

Hence:

$$C_t = P_{t:a}C_{a:t}e^{-\sqrt{\frac{K_f}{D_t}}r}$$

Setting our two J_R equations equal and plugging in our B we obtain k_t:

$$\begin{aligned} J_R = k_t C_{a:t} &= D_t \gamma P_{t:a} C_{a:t} \\ k_t &= \sqrt{D_t K_f} P_{t:a} \end{aligned}$$

Thus,

$$J_R = \frac{k_t k_g}{k_g + k_t} C_a$$

Appendix B

Thomas Algorithm

The Thomas algorithm, also known as the tridiagonal matrix algorithm (TDMA), is used to solve tridiagonal matrix equations with $O(n)$ operations rather than $O(n^3)$ operations using Gaussian elimination.

Matlab code*:

```
function x = thomasAlgo3(a,b,c,d)
% a, b, c are the column vectors for the compressed tridiagonal matrix,
% d is the right vector
n = length(b); % n is the number of rows

% Modify the first-row coefficients
c(1) = c(1) / b(1);    % Division by zero risk.
d(1) = d(1) / b(1);    % Division by zero would imply a singular matrix.

for i = 2:n
    id = 1 / (b(i) - c(i-1) * a(i));  % Division by zero risk.
    c(i) = c(i)* id;                % Last value calculated is redundant.
    d(i) = (d(i) - d(i-1) * a(i)) * id;
end

% Now back substitute.
x(n) = d(n);
for i = n-1:-1:1
    x(i) = d(i) - c(i) * x(i + 1);
end
```

*http://wikipedia.org/wiki/Thomas_algorithm

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[2] *Ozone activates airwaiy nerves via the selective stimulation of TRPA1 ion channels* Taylor-Clark, Thomas E. and Undem, Bradley J. The Journal of Physiology. 2010. Pages 423-433. Accessed June 15, 2011.

[3] *Morphometry of the Human Lung* Ewald R. Weibel. 1963.

[4] *Dosimetry Modeling of Inhaled Formaldehyde: The Human Respiratory Tract* John H. Overton, Joulia S. Kimbell, and Frederick J. Miller. Toxicological Sciences **64**, pages 122-134. 2001. Received 26 March 2001; accepted 4 August 2001.

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