Human Body Drug Distribution

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EXECUTIVE SUMMARY

A human body simulator that mathematically models the concentration levels of a drug in the blood and in 23 tissues was developed. The model consists of over 1,100 simultaneous ordinary differential equations and two-hundred parameters. Case studies were performed which compared the model to experimentally obtained drug concentration data for two different drugs and showed that the model could reproduce experimental results extremely well.

Developing a human body model is critical to the pharmaceutical industry where $70 billion is spent every year on research and development of new drugs. This money is mostly used for in vitro and in vivo testing of large numbers of compounds with potential medical applications, most of which are later found to be unsuitable for further development. A human body simulator should refine this process by allowing pharmaceutical companies to screen more compounds using simulations as opposed to expensive lab testing. Additional applications include allowing doctors to make customized, optimized dosages for each of their patients that produce the exact desired effects of a drug.

Although sophisticated drug distribution models are available commercially, the model developed here is a significant advancement in models currently discussed in academic literature and thus can serve as a stepping stone for future work. The model includes the latest theory about the most critical organs in the body, a novel distribution system that integrates each body system at the level of the capillary, and a method to account for differences in concentration along spatial dimensions inside each tissue within the body.

To make the model truly predictive, two important elements should be developed in the future. Firstly, the model should be able to predict all the parameters of the drug which will affect its behavior inside the body. Currently, parameters are obtained from literature when possible and estimated when necessary. Secondly, the model should account for variations between persons. In order to do this, the predictive algorithms for estimating the parameters would need to consider genetics, body type, and other factors. Developing a mathematical model of the human body is a prerequisite for these other developments and thus was the focus of our work.

INTRODUCTION

The purpose of this project is to create a mathematical model of the human body with the intention of describing how a drug or chemical moves through the body with time. The model could improve human health, from helping a doctor to optimize patient doses, to streamlining the early stages of pharmaceutical research. Consider the following costs: American consumers spend over $200 billion on pharmaceuticals every year and American pharmaceutical companies spent nearly $70 billion in research and development in 2008 alone. A mathematical model of the body could greatly reduce costs for either party while providing greater insight into how the body works in both theory and practice.

BACKGROUND

Pharmacokinetics, a branch of pharmacology, is the study of the movement and fate of an externally administered substance within the body. Previous work in this field of study tends to be focused in one of two areas. The first area focuses on developing an overall mathematical model of the human body. This area of study would answer such questions as, what are the governing equations of the blood and heart that describe their impact on the flow of a drug in the body. The second area of study of pharmacokinetics focuses on a particular feature of the human body and attempts to describe this feature's impact on overall drug kinetics. Such a study might focus on how carrier mediated transport inside of the liver tissue is affected by the charge of the drug. Where the first area of study focuses on the whole body, the second takes a particular organ or component and attempts to describe it in great detail. This work will focus on the first area of study, or, developing an overall model of the human body.

Overall pharmacokinetic models tend to be physiologically based, and this is the tradition in which this work will continue. Physiologically based models should strive to incorporate as much

known anatomical, physiological, and chemical knowledge while accurately describing the movement of a drug or chemical throughout the body. The study of pharmacokinetics typically centers on what is called the "**A.D.M.E**" processes. That is: **A**bsorption, **D**istribution, **M**etabolism, and **E**xcretion. Absorption is the study of how, once a drug is ingested, it moves from the stomach to the blood stream. Distribution is the study of how the blood stream carries a drug throughout the body. Metabolism is the study of how a drug is degraded within the body and Excretion is the study of how a drug is exited from the body.

Each of the A.D.M.E. processes typically centers on a few organs. Absorption occurs in the stomach and small intestine for oral absorption of a drug and the skin for transdermal methods. Metabolism occurs mostly in the liver, though there can be variations. Excretion occurs through either the bladder or the colon. Distribution, mentioned last, is arguably more complex. Distribution involves the heart where blood from the systemic organs meets to move through the lungs and back out to the rest of the body. It also involves the movement of the drug, now in solution with blood, through the complex system of arteries and capillaries that make up the human circulatory system where the drug can potentially interact with many different sites and tissues within the body before finally returning to the heart within the venous system. The specific goal of this work then is to *develop an accurate overall physiologically based pharmacokinetic model that advances the level of anatomic and physiological detail of other models*.

THEORY

The theory will describe the anatomical and physiological basis for the governing equations for each of the A.D.M.E. components used within the model as well as any assumptions that were made in the development of these governing equations into their form used within the model.

Before examining each of the A.D.M.E. components individually, consider the overall structure of the model:

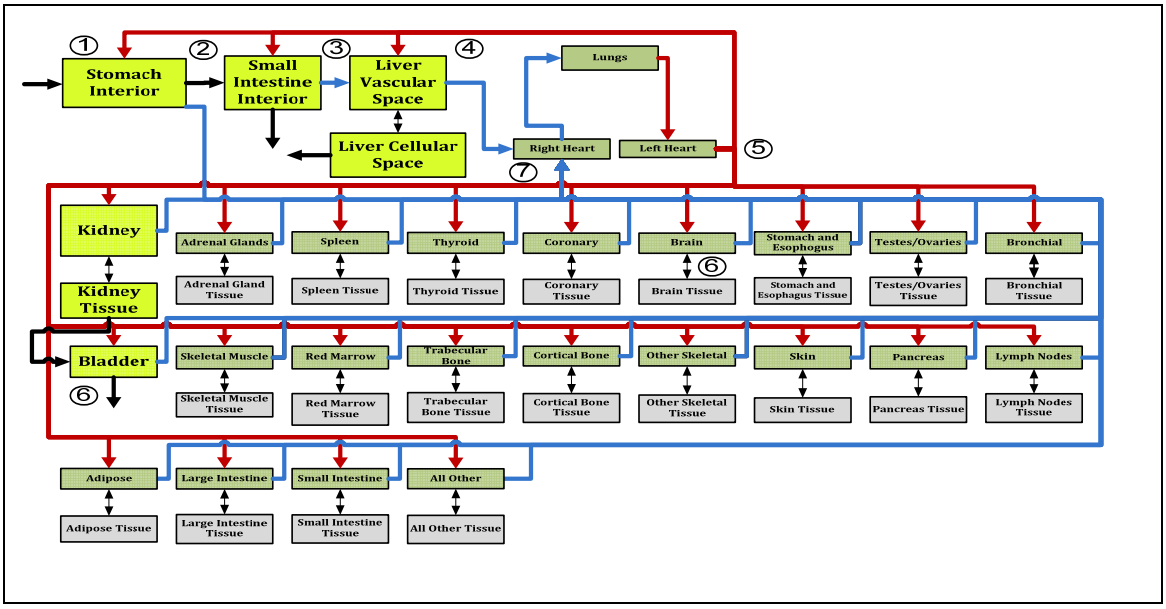

Figure 1: Flow Diagram for Overall Model

The sections highlighted in yellow represent the key organs in our absorption, metabolism, and excretion models with the rest collectively representing the distribution or circulatory system. At (1) a given mass of drug enters the stomach interior. (2) The drug enters the small intestine, becoming absorbed by the lining of the small intestine into the blood stream. (3) Blood moves from the small intestine into the liver, where it can either be metabolized in the cellular space of the liver or (4) goes to the heart, being diluted by joining other veins and mixing. (5) Blood moves from the pulmonary system to the entire body in the red arteries and then (6) moves to the capillary system and interacts with the tissue in various parts of the body. The drug that is transported to the kidney or liver may be excreted or metabolized. (7) The blood returns through the blue venous system back to the heart.

It should be noted that the model presented focuses on orally administered drugs and excludes drugs administered by transdermal, intravenous, and suppository methods. This was done because oral administration is by far the most common and practical method of drug distribution. Furthermore, any attempt to describe the body mathematically in a given time frame

must limit the scope of the problem in some way. The architecture of the model developed allows one to easily add other methods of administration if desired.

ABSORPTION

The goal of the Absorption component of the overall A.D.M.E. model is to describe the way an orally administered drug enters the blood stream. In order to do this, two organs must be described: the stomach and the small intestine.

THE STOMACH

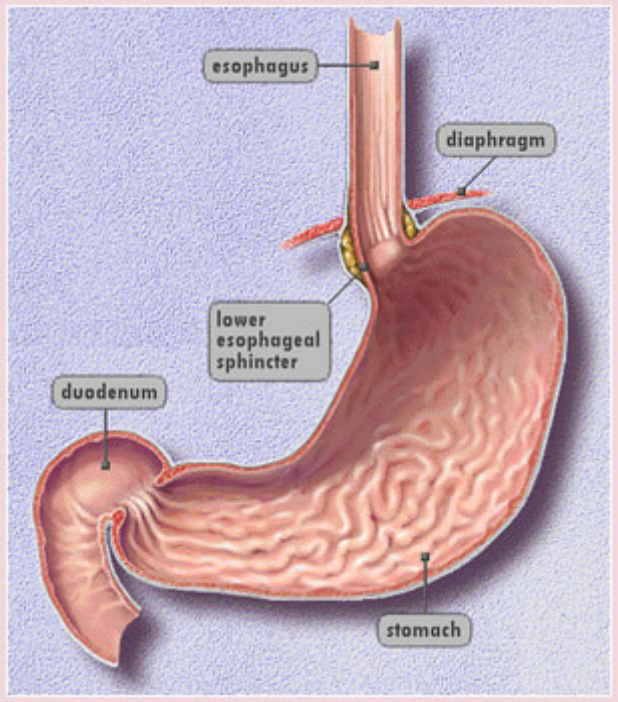

Figure 2: Anatomy of Stomach

An orally ingested drug first interacts with the body by entering the stomach. When food enters the stomach, mechanical and chemical digestion begins. Mechanical digestion occurs in the stomach due to churning. Churning, or the compression and expansion of the stomach, also mixes the gastric acid with the food in order to encourage chemical digestion. This mixing effect allows for a well-stirred assumption to be made when modeling the stomach. A second important aspect of the stomach related to its modeling is that the flow rate from the stomach into the small intestine is not constant but is related to the amount of food within the stomach. This issue is addressed later.

It is assumed that the gastric acid does not interfere with the drug except to help dissolve it. It is also assumed that the stomach behaves as a continually-stirred tank and that the drug behaves as an impulse input. This means that at time (t=0) the full dose of the drug enters the stomach, and that the concentration maximum in the stomach occurs at t=0.

It is well documented in literature that the rate of change of mass in the stomach depends on whether the mass in the stomach is solid or liquid[i]. Solid masses follow a linear curve, while liquid masses follow an exponential curve.

For liquids:
$$\frac{dM_s}{dt} = -k_s \cdot M_s \quad \textbf{(1)}$$

For solids:
$$\frac{dM_s}{dt} = -k_s \quad \textbf{(2)}$$

$\mathbf{k_s}$ is a rate transfer constant and $\mathbf{M_s}$ is the amount of drug in the stomach at a given time.

The flow rate of the drug from the stomach, F, is also important to know because this is the input to the small intestine. As was mentioned earlier, the flow rate of the stomach behaves as a function of the amount of drug in the stomach.

$$F = k \cdot M_s \quad \textbf{(3)}$$

Using equations two, three, and four to solve for the flow rate of the stomach with respect to time yields the following equations for liquids and solids respectively, where M_{s0} is the mass in the stomach at time=0.

For liquids: $$F = k \cdot M_{s0} e^{-k_s \cdot t} \quad (4)$$

For solids: $$F = k \cdot (M_{s0} - k_s \cdot t) \quad (5)$$

It is also important to know the concentration of the drug in the stomach at any time. Because the tank is well mixed and has only an outflow, the concentration in the stomach is constant with respect to time. Equation 7 represents the concentration of the drug in the stomach where DOSE is the dose of the drug and ρ the density of the food mixture.

$$C = \frac{DOSE}{M_{s0}/\rho} \quad (6)$$

SMALL INTESTINE

The small intestine is the main site where drug absorption occurs. The small intestine for humans is approximately seven meters long with an average diameter of 2.5-3 cm. Because the small intestine is essentially a long tube, it is modeled as a plug flow reactor. The derivation of our model equation is shown below. Starting with a general equation for a non-steady state plug flow reactor, we have:

$$\frac{\partial C_i}{\partial t} = -\frac{1}{r} \cdot \frac{\partial}{\partial r}\left[\left(-D_e \cdot \frac{\partial C_i}{\partial r} \cdot r\right) + U_r \cdot C_i \cdot r\right] - \frac{\partial}{\partial z}\left[\left(-D_e \cdot \frac{\partial C_i}{\partial z}\right) + U_z \cdot C_i\right] - r_i \quad (7)$$

Where D_e is the effective diffusivity, U_r and U_z are the superficial velocity in the radial and axial directions respectively, and r_i is the rate of absorption from the small intestine into the systemic circulation. This general mass balance includes both radial and

axial convective and diffusive flux terms. It is assumed that the variation in concentration in the radial direction is negligible, and that only the axial variations are important.

$$-\frac{1}{r}\cdot\frac{\partial}{\partial r}\left[\left(-D_e\cdot\frac{\partial C_i}{\partial r}\cdot r\right)+U_r\cdot C_i\cdot r\right]=0 \quad (8)$$

It is also assumed that the diffusive flux term is negligible compared to the convective flux term.

$$\left(-D_e\cdot\frac{\partial C_i}{\partial z}\right)=0 \quad (9)$$

This leaves the equation below, where the superficial velocity is dependent on whether the food is liquid or solid and can be described by equations five or six divided by the cross-sectional area and the density of the small intestine. Because it is constant with respect to the axial direction, it can be removed from the derivative.

$$\frac{\partial C_i}{\partial t}=-\frac{\partial}{\partial z}\left[U_z\cdot C_i\right]-r_i=-U_z\cdot\frac{\partial C_i}{\partial z}-r_i \quad (10)$$

It can be shown for many drugs that the rate of absorption through the small intestine into the systemic circulation can be modeled as a first order absorption, or:

$$r_i=k_a\cdot C_i \quad (11)$$

where k_a is an absorption rate constant. It assumes that the concentration of the drug on the outside of the gut wall is negligible, or, that the drug on the outside of the gut wall is very quickly removed and passed to the liver. This yields our final equation modeling the small intestine:

— — **(12)**

Initial concentrations of and the concentration at the inlet must be specified in order to make this equation well-posed.

If the drug is not absorbed by the time it reaches the final z, it enters the colon and is subsequently excreted as waste. It is of little interest to track the rate of change of the amount of drug through the colon because it has no effect on the amount of drug available to the systemic organs.

It is important to know how much of the drug is absorbed through the gut wall. The mass of drug absorbed through the gut wall can be described by equation 10, below, for any time interval.

$$Abs(t) = \int_0^L A \cdot k_a \cdot \Delta C \cdot dz \quad \textbf{(13)}$$

DISTRIBUTION

The goal of the Distribution component of the overall A.D.M.E. model is to describe the way an orally administered drug moves through the blood system. In order to do this, three areas need to be discussed: the heart, blood transit times, and the capillary system.

HEART

The heart is central to the human circulatory system and a simplified diagram of the way the heart interacts with the rest of the body is given below.

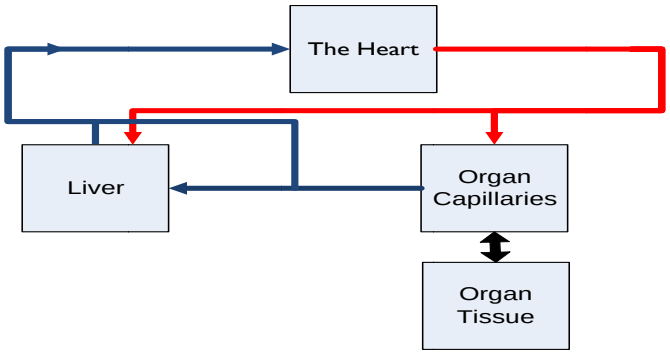

Figure 3: Flow Chart Illustrating the Heart's Relationship to Overall Circulation

In a closed circulatory system, blood exits the heart through the aorta and moves through the arterial system of the body where it will eventually move into the capillary system of body organs and interact with the tissue. The blood then moves out of the tissue capillaries, some passing through the liver, and returning to the heart to begin again. The overall concentration of drug inside the blood is required for most equations used in the model and the heart was chosen as the site for which to track this concentration. We began with a simple mass balance on the heart:

$$\frac{dM_{Heart}}{dt} = F_{liver} + F_{veins} - F_{arteries} \qquad (14)$$

Where M_{heart} is the total mass of drug inside the heart, F_{liver} is the flow rate of drug from the liver, F_{veins} is the flow rate of drug from all other veins, and $F_{arteries}$ is the flow rate out of the heart through the arterial system. For use in the model, a more concise formula was developed where the change in concentration inside the heart is simply the sum of the change in concentration from entrance to exit for each of the capillaries in the body, divided by the volume of the heart. This just means that if drug enters a capillary but does not exit, it will reduce the concentration of drug.

$$\frac{\boldsymbol{dC_H}}{\boldsymbol{dt}} = \frac{\sum \boldsymbol{Q_i \Delta Cap_i}}{\boldsymbol{V_h}} \quad \textbf{(15)}$$

Where Q_i is the flow rate to a given capillary, $\boldsymbol{\Delta Cap_i}$ is difference in concentration between the entrance and exit of a given capillary, and V_h is the volume of the heart. Different transit times to different body systems were also incorporated numerically into the model.

TRANSIT TIMES

An important question in modeling the circulatory system is: How do we account for the fact that blood moves from the heart to the different organ systems at different speeds? That is, it may take longer for a single volume element of blood to move from the heart to the toe and back than it will for a similar element of blood to move to the kidney and back. Since it is of specific important to the oral absorption model developed here, calculations were performed on the transit times for the movement of blood from the hepatic portal vein, through the inferior vena cava, and finally to the heart. Due to the high flow rate of blood through these veins (about 2000-3000$\frac{cm^3}{min}$) and small volumes of these veins (about 20 cm^3), transit times are very small, less than a second.

The way other transit times were handled was by incorporating some of the work done by Legget et al. These researches injected trace radioactive elements into a human and tracked the time it took for the radioactive elements to appear in different organ systems inside the body. From this work,

we included in our model the transit time from the right heart to the left heart (about 8 seconds) and used the estimated transit time to the extremities as the basis for all our organ systems (about 3 seconds). The way this method works in the code is in the calculations of drug concentration for the heart, values are used for previous time elements, depending upon the specific transit times for different tissues.[ii] In summary, the transit times we focused on were from the liver to the heart (assumed instantaneous), transit time from the right heart to the left heart (8 seconds), and finally from the heart to the rest of the body and back (3 seconds each way). More work could be done in developing different transit times for different organ systems in the body to increase physiological realism. Our goal was simply to include basic theory into the code with the ability to improve detail depending on the focus of future work or the discovery of more information.

CAPILLARIES

All of the organ systems inside the body are integrated with one another through the blood system and are described at the level of the capillary. Below is a schematic showing how the capillary system interacts with the entire body.

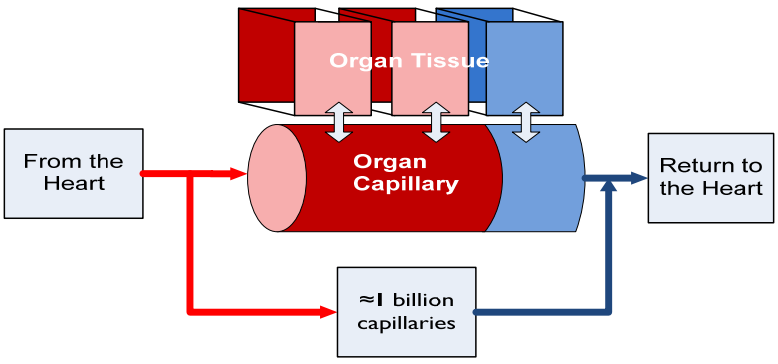

Figure 4: Diagram of Micro level Capillary and Tissue System

Essentially, blood can enter a single capillary in a given organ, moves through the capillary exchanging drug with the tissue, and then returns to the heart. The capillaries within an organ or

tissue system were considered to be uniform. Differences, however, were accounted for between capillaries of different tissues, and this is especially true for the liver and kidney. The equation describing the change in concentration of a capillary is given below:

$$\frac{\partial C_v}{\partial t} = -v\frac{\partial C_v}{\partial z} - k(C_v - C_t) \quad \textbf{(16)}$$

Where is the concentration of drug inside the capillary, is the velocity of blood through the capillary, k is the constant describing the rate of drug transfer between the capillary and the tissue, and is the concentration of drug inside the tissue. The rate of concentration change inside of the tissue is simply the mass transfer term from the previous equation:

$$\frac{\partial C_t}{\partial t} = k(C_v - C_t) \quad \textbf{(17)}$$

With the equations describing the heart, these equations model the concentration of drug in the different capillaries and tissues throughout the body and integrate them into a unified simulation.

Organ of Interest

Most drugs have organs or tissues in which it is desired that the drug be activated, bind with certain proteins, or interact with the tissues in a specific way. For example, the drug atenolol acts in the brain and treats hypertension. Another drug, Imatinib, is an anti-cancer drug that is to act on cancer cells. The model designates the region in which a drug is designed to act as an organ of interest, and it is assumed that once the drug reaches this region that it is instantly eliminated and that the concentration in the tissue of the organ of interest is always 0. This is accomplished by eliminating the C_t term in equation 16 and 17. The amount of drug that has entered the tissue or organ of interest can then by found by integrating along the length of the tissue for every time interval in a similar manner as was done with the small intestine.[iii]

METABOLISM

Metabolism, or the breakdown of the active form of a drug into inactive forms, can occur in many parts of the human body, yet metabolism by the liver typically accounts for the vast majority of drug elimination.[iv]

The drug initially arrives in the liver within venous blood from the gastrointestinal tract via the hepatic portal vein before moving to the heart. This gives the liver a crucial role in determining what percentage of a drug will be available to enter the blood stream for drugs that are orally absorbed and is known as the First Pass Metabolism effect. The liver also receives arterial blood from hepatic arteries and can metabolize the drug by this mechanism as well. This blood supply of the liver is illustrated in Figure 3 below. Drugs in the blood must make their way from the bulk blood flow to the smallest branches of flow

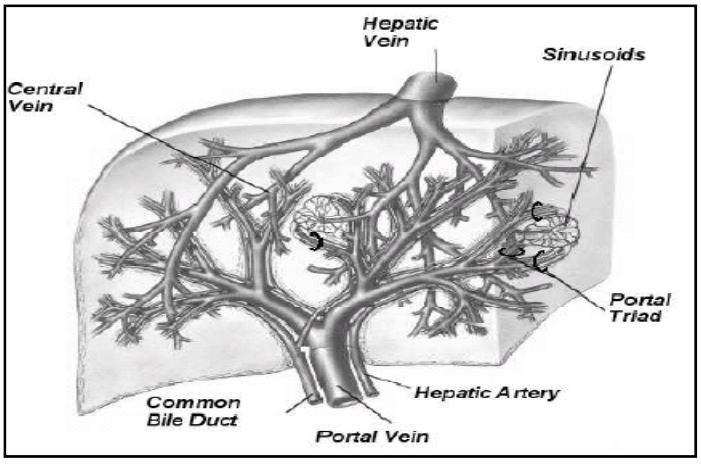

Figure 5: Diagram of blood flow in the liver

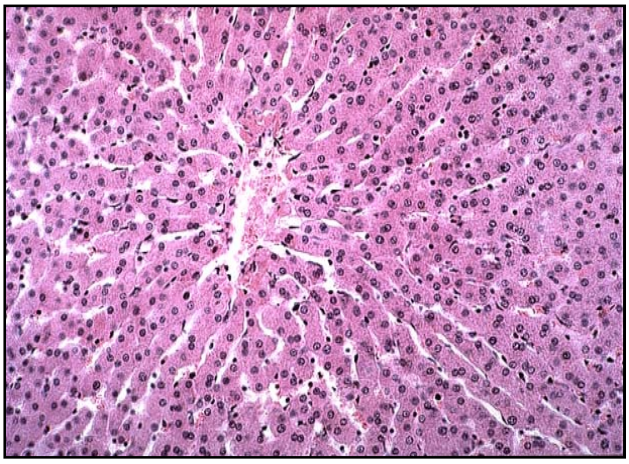

Figure 6: Liver Tissue

inside the liver, the sinusoids, which behave in much the same way as capillaries. Once in

the sinusoids a drug must then cross into the hepatocytic space. Hepatocytes are the primary functional cells of the liver, where metabolism actually occurs. The sinusoidal space and hepatocytic cells are shown in Figure 4 above where the red cells are the hepatocytes and the empty spaces are the sinusoids. Below is a diagram which illustrates the microstructure of the liver.

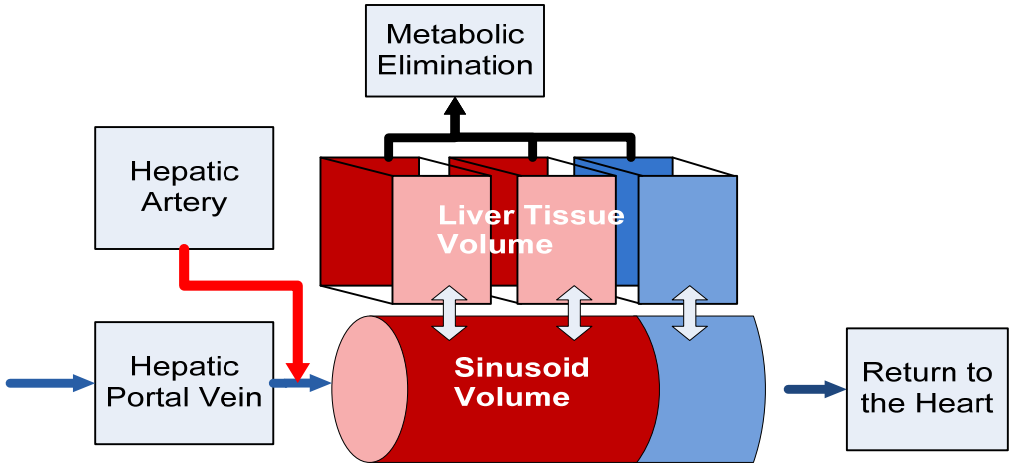

Figure 7: Diagram of Drug Movement At Micro Level in the liver

Based on these observations we implemented the convection dispersion model of the liver as proposed by Roberts and Anissimov[v]. This model divides the liver into two spaces: the vascular compartment embodied by the venous, arterial, and sinusoidal spaces inside the liver and the cellular spaces, which represent the hepatocytic cells. The equation which describes the liver vascular space is given below, which is the equation for a PFR for which radial terms have been neglected and with mass transfer terms relating to the liver cellular space.

$$V_{\mathrm{p}} \frac{\partial C_{\mathrm{P_p}}(z,t)}{\partial t} = V_{\mathrm{p}} D \frac{\partial^2 C_{\mathrm{P_p}}(z,t)}{\partial z^2} - V_{\mathrm{p}} v \frac{\partial C_{\mathrm{P_p}}(z,t)}{\partial z} - PS(fu_{\mathrm{p}} C_{\mathrm{P_p}}(z,t) - fu_{\mathrm{h}} C_{\mathrm{P_h}}(z,t)) \quad \textbf{(18)}$$

Where $\boldsymbol{V_p}$ is the volume of plasma inside of the vascular compartment, $\boldsymbol{C_{P_p}}$ is the concentration of drug inside of the blood in the vascular compartment, **D** is the diffusivity with the drug with respect to the boundary**, v** is the velocity of the plasma as it moves through the liver**, PS** is the permeability surface area product, $\boldsymbol{fu_p}$ is the unbound fraction of drug inside the plasma$\boldsymbol{fu_h}$**.** The second equation describes the concentration of drug inside the cellular space and is simultaneous with the first but is an ordinary differential equation.

$$V_{\mathrm{h}} \frac{\partial C_{\mathrm{P_h}}(z,t)}{\partial t} = PS(fu_{\mathrm{p}} C_{\mathrm{P_p}}(z,t) - fu_{\mathrm{h}} C_{\mathrm{P_h}}(z,t)) - CL_{\mathrm{int}} C_{\mathrm{P_h}}(z,t) \quad \textbf{(19)}$$

Where $\boldsymbol{V_h}$the volume of plasma inside the hepatocytic space**,** $\boldsymbol{C_{P_h}}$ is the concentration of drug inside the hepatocytic space**,** and $\boldsymbol{CL_{int}}$ is the intrinsic metabolic clearance of the hepatocytic cellular space. The value of the constants used in these equations will vary from drug to drug and from person to person and are necessary parameters of the model.

EXCRETION

The second major source of elimination of drugs throughout the body is the excretion of the drug in urine. The kidney receives blood from the renal artery which is a division of the abdominal aorta. This blood passes through the tissue of the kidney, is filtered, and passes to the inferior vena cava. Both the abdominal aorta and the inferior vena cava are highly

perfused regions, thus the concentration of drug entering the kidney will be a significant portion of the blood. The residue from filtration is then passed to the ureter where it joins the urine and is passed out of the body. An overview of the kidney anatomy is illustrated in Figure 8, and a schematic of the way this anatomy is captured at the level of the capillary is illustrated in Figure 9.

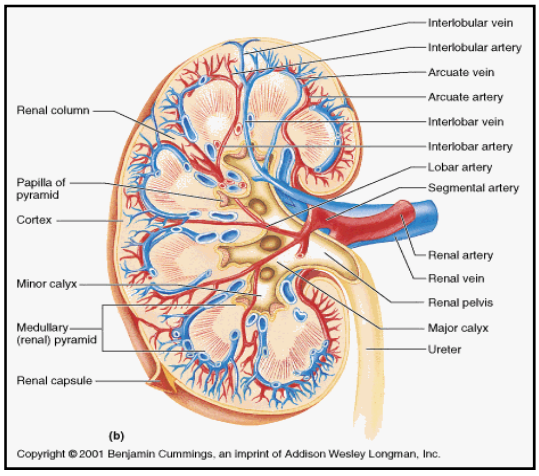

Figure 8: Kidney Anatomy

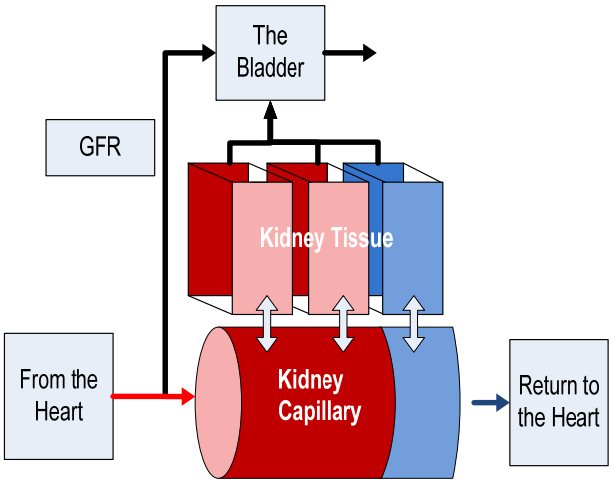

Figure 9: Drug movement at the micro level inside the kidney

From these observations our group proposed a model of the kidney that divides the kidney into three spaces, the kidney capillaries, the kidney tissue, and the urine as shown in Figure 5[vi]. The equations used to describe these regions are given below. First, the concentration in the capillary is similar to that of the small intestine, with a convective term and a mass transfer term interacting with the kidney tissue. The velocity is simply the flow rate of blood going to the capillary, minus what is sent through glomoremular filtration, divided by the area of the capillary.

$$\frac{\partial C_V}{\partial t} = \left(\frac{Q - GFR}{A_{cap}}\right)\frac{\partial C_v}{\partial z} - k_a(C_V - C_T) \quad \textbf{(20)}$$

Where is the concentration of drug inside the capillary, Q is the flow rate of blood through the capillary, is the cross sectional area of the capillary, GFR is the flow rate of glomoremular filtration, is the constant describing the rate of transfer between the capillary and the tissue, and is the concentration of drug inside the kidney tissue. Next is the equation describing the concentration of drug inside the kidney tissue. This is simply the mass transfer into the tissue from the capillary minus the mass transfer to the urine.

$$\frac{\partial C_T}{\partial t} = k_a(C_V - C_T) - k_u(C_T - C_U) \quad \textbf{(21)}$$

Where is the constant describing the rate of transfer between the tissue and the urine and is the concentration of drug inside the urine. Finally, we have the equation describing the urine concentration. The inside of the bladder is considered well mixed, and the equation describing the concentration is simply the sum of the mass transfer from all kidney tissues, the concentration inside the drug multiplied by the flow rate of glomoremular filtration, with the concentration inside the urine times the flow rate of urine exiting.

$$\frac{dC_u}{dt} = \left[\sum k_u(C_T - C_U)\right] + C_V GFR - Q_U C_U \quad \textbf{(22)}$$

Where is the average flow rate of urine. Together, these equations describe how the kidney eliminates a drug from the body.

COMPARTMENTAL MODEL

The compartmental model used as a comparison is one done by Lawrence X. Yu and Gordon L. Amidon. The stomach, small intestine, and colon are considered as well-stirred regions with first order inputs and outputs. The small intestine is broken into 7 compartments. The rest of the body

is broken into three compartments based on blood perfusion, with the central compartment, the most highly perfused compartment, having an elimination term. For more information concerning their model, readers are referred to their paper which was included with this report.

METHODS

METHOD OF LINES

The partial differential equations used to describe the small intestine, liver, kidneys, and capillaries were solved by using a finite difference grid using the method of lines. See table 3 below. The element (j) is the time element, increasing as one moves to the right and element (i) is the length element increasing as one moves down representing increasing depth of length inside of the organ in question.

Table 1: Finite Difference Grid

i , j	i , j+1	i , j+2	i, N
i+1, j			
i+2, j			
M, j			M, N

The method of lines allows us to eliminate one of the variables in question, in this case length, by creating a separate *ordinary* differential equation for each length element inside the liver. The user can define the total length of any organ, how discrete each element of z is, and from this our program will create the appropriate number of simultaneous equations and solve them. For example concerning the small intestine, if we want the length to be 10 cm and dz to be 0.1 cm, our program will create 100 simultaneous equations and solve each one at a given time before moving

to the next time element and solving for each length. This gives our program flexibility in that it can solve an arbitrary number of simultaneous ordinary/partial differential equations.

The steps taken in using the method of lines for the small intestine is shown below. First, a backwards difference method is used to discretize the spatial variable. Then, a system of ODE's are given according to how many equations are needed. This process is summarized below.

1) *Discretize spatial variable*

$$\frac{\partial C_j(t)}{\partial t} = f_j = -U_z(t) \cdot \frac{C_j - C_{j-1}}{dz} - k_a \cdot C_i \tag{23}$$

2) *Apply the boundary condition and solve the system described below.*

$$C_1(t) = f_1 = C_D$$

$$\frac{\partial C_2(t)}{\partial t} = f_2 = -U(t) \cdot \frac{C_2 - C_1}{dz} - k_a \cdot C_2$$

$$\frac{\partial C_N(t)}{\partial t} = f_N = -U(t) \cdot \frac{C_N - C_{N-1}}{dz} - k_a \cdot C_N$$

4TH ORDER RUNGE KUTTA METHOD

It was mentioned previously that our program is capable of generating an arbitrary number of simultaneous ordinary differential equations. These systems are solved using the 4th Order Runge Kutta method. Given a differential equation of the form:

Which related to a function of form:

$$y = g(t, y) \text{ with a derivative}$$

Then given the initial conditions of g(t,y) we can estimate the next value of y in time by:

$$y_{t+1} = y_t + \frac{h}{6}(k_1 + k_2 + k_3 + k_4)$$

Where collectively the different values of k are an estimation of the slope of our function.

The values of k are calculated by the following equations:

$$k_1 = f(t_{n,}\, y_n)$$

$$k_2 = f(t_n + \frac{h}{2}, y_n + \frac{1}{2}hk_1)$$

$$k_3 = f(t_n + \frac{h}{2}, y_n + \frac{1}{2}hk_2)$$

$$k_4 = f(t_n + \frac{h}{2}, y_n + \frac{1}{2}hk_3)$$

It is important to recognize that when solving a system, every ODE will have its own k values and that the k values are a function of every variable affecting a given ODE.

The above equations are used for a function of only two variables, t, and y. The 4th Order Runge Kutta method is capable of solving any number of simultaneous ordinary differential equations and is the method used in our model.

RESULTS

STOMACH

The figure below contains sample results of the mass in the stomach after the consumption of a 500 g liquid drink. Because the food was liquid, the mass in the stomach decreases exponentially, and is entirely empty in about two hours.

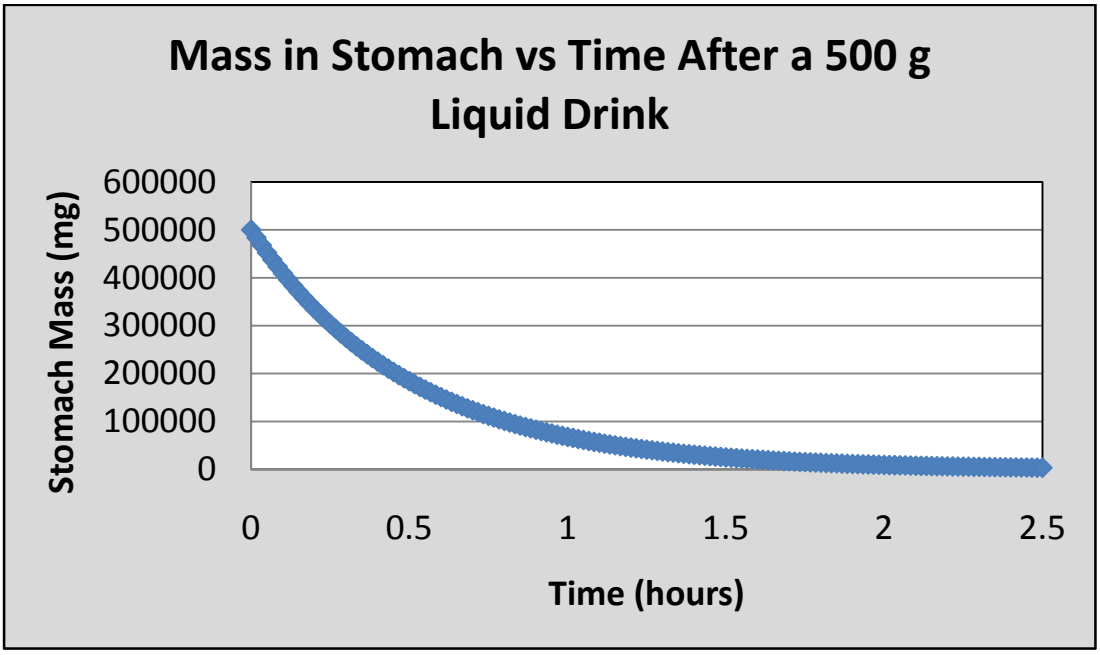

Figure 10: Sample Stomach Results

SMALL INTESTINE

The figure below contains sample results for the small intestine in both 3-D and 2-D graphs. In the 3-D graph it can be seen that the concentration decreases in the small intestine along its length and along the time dimension. It may seem unintuitive of why the concentration at a given length would change with respect to time if the input concentration from the stomach were constant. The reason is because the flow rate is constantly changing. As

time goes on, the flow rate is much slower, and as a result, it is taking longer for the drug to pass through the small intestine and more of it is being absorbed at earlier lengths.

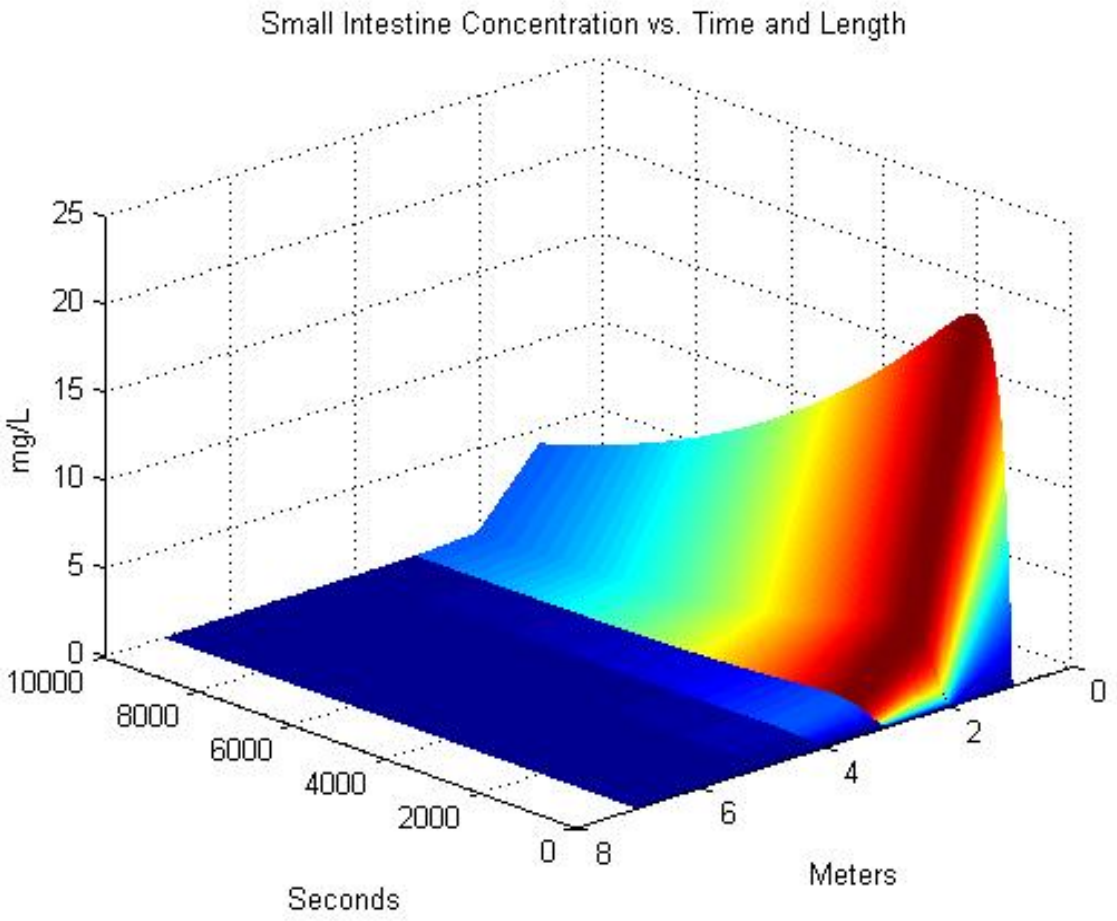

Figure 11: 3D Graph of Concentration in the Small Intestine vs. Time and Length

The same trends can be seen in the 2-D graphs where the concentration vs. time for different lengths of the small intestine was graphed, and the concentration vs. distance for different times was graphed. Again, the concentration decreases along the length and time dimension.

The small intestine graphs suggest that no drug enters the colon. This is actually entirely dependent upon the length used for the small intestine, ka, and the flow rate coming from

the stomach. For these sample results, a large value of ka was used, which resulted in nearly all of the drug being absorbed through the gut wall.

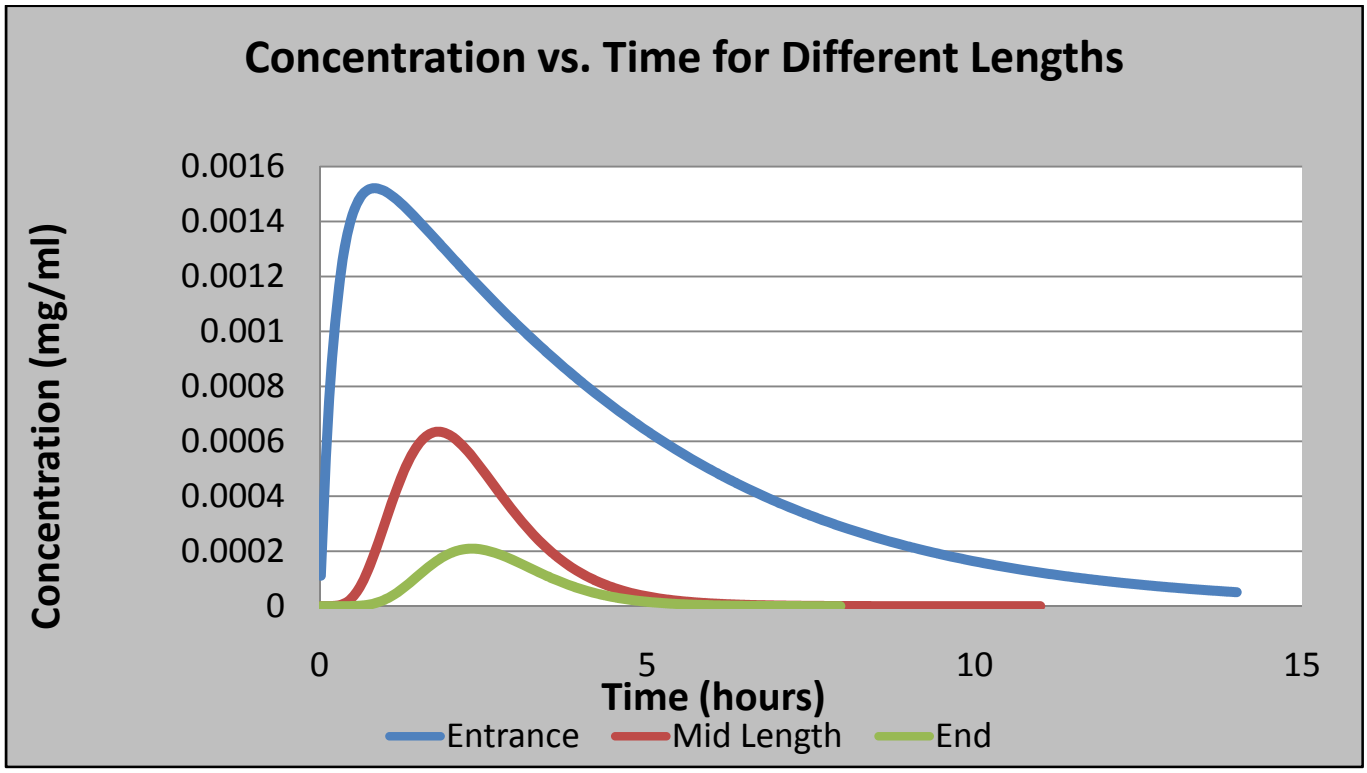

Figure 12: Concentration vs. Time for Different Small Intestine Lengths

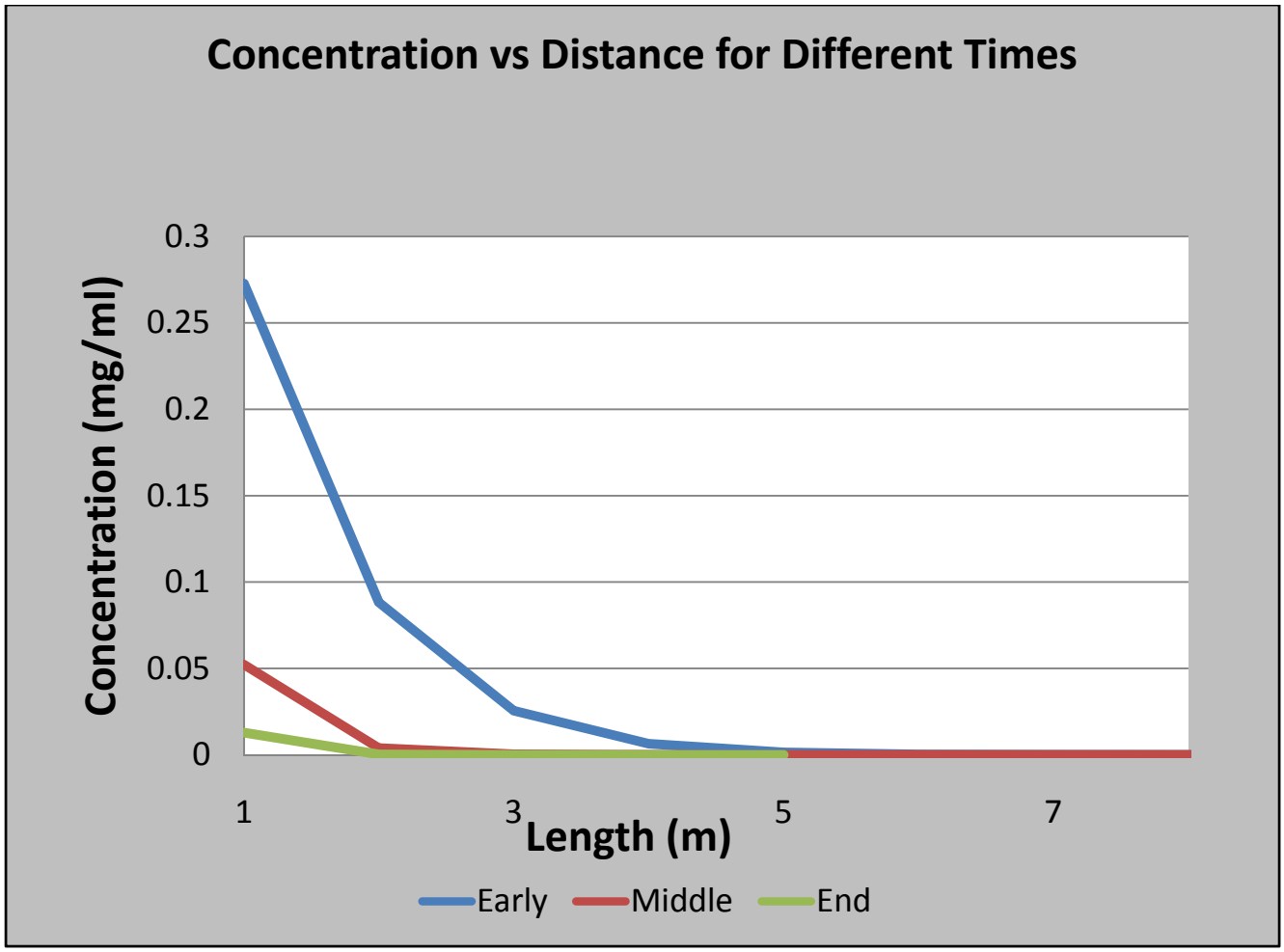

Figure 13: Concentration vs. Distance in the Small Intestine for Different Times

HEART

The blood concentration is assumed to be the same as the concentration found in the heart after mixing occurs. The following graph contains the concentration of the drug Cefuroxime in the blood with respect to time. The concentration initially increases until the rate of absorption of the drug equals the rate of elimination of the drug from the blood. This drug experienced a single peak, unlike other drugs which experience two peaks as will be seen in the case studies.

The double peak is an interesting phenomenon and should be discussed briefly. The first peak occurs when the rate of absorption of the drug equals the rate of elimination of the drug and the rate at which the drug enters the tissues. After the first peak, the blood concentration begins to decrease due to the rate of elimination and the rate of the drug entering the tissue being greater than the rate of absorption. This occurs until the drug gradient across the capillaries into the tissue reverses, which causes the drug in the tissues to reenter the capillary system. At this point, for a brief time, the drug concentration in the blood again begins to increase. Finally, the rate of elimination of the drug becomes dominant and the blood concentration decreases to zero over time. This phenomenon will be seen in the case study results and also can be seen in the capillary and urine results.

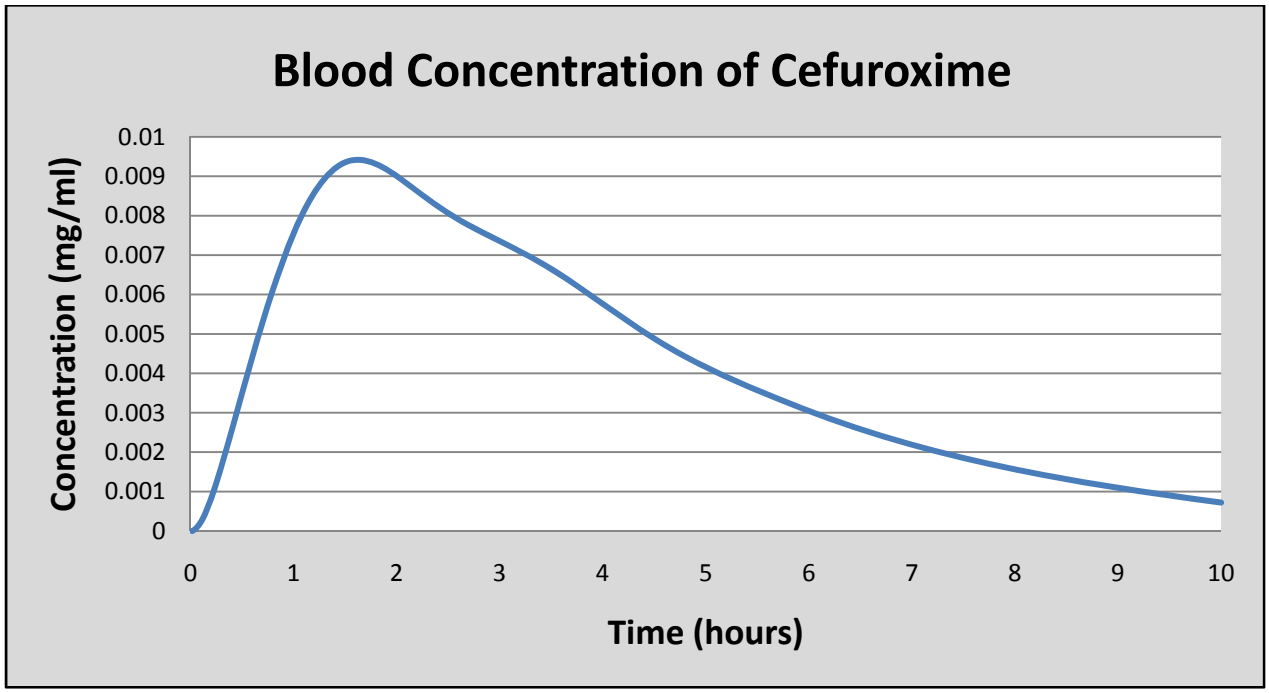

Figure 14: Concentration of Drug in the Blood with Time

CAPILLARIES

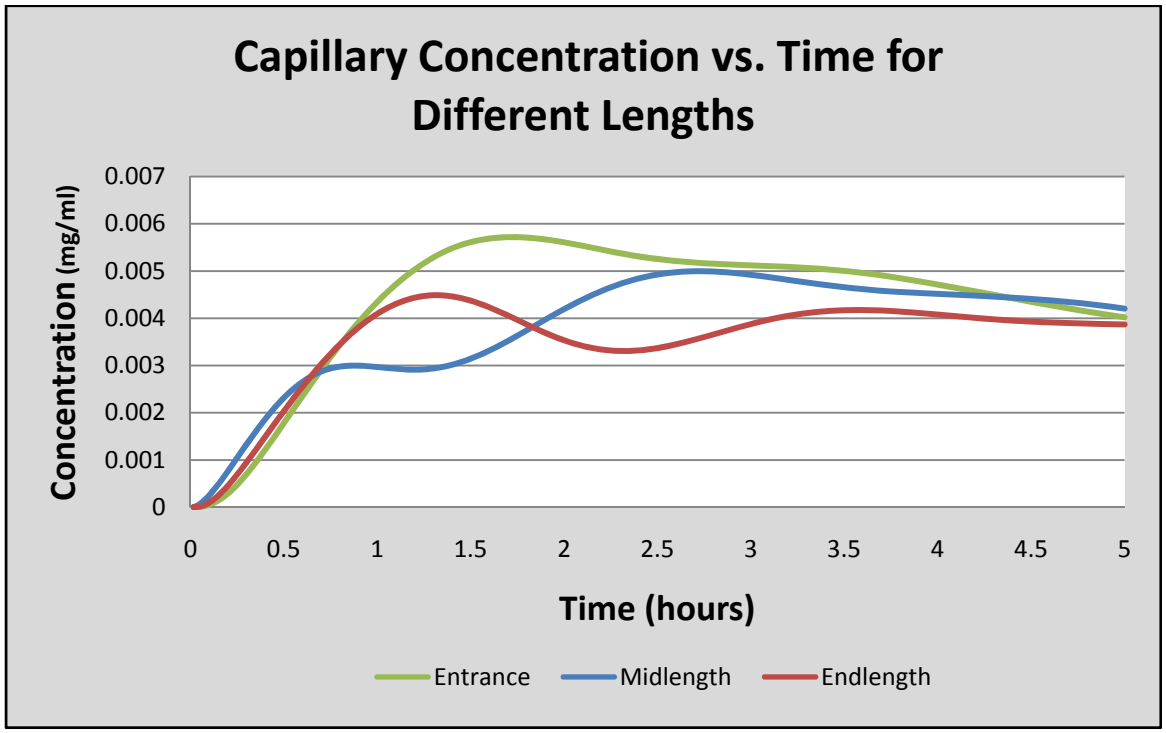

Figure 15: Concentration vs. Time for Different Lengths in a Capillary With Low Blood Velocity

The capillary results were some of the most interesting results obtained. The double peak effect can again be seen in these results. Interestingly, the first peak occurs for the entrance at the same time the stomach is emptying and absorption stops. The first peak occurs earlier for the midlength and endlength sections of the capillaries because as the rate of drug absorption decreases, the amount of drug entering the capillaries also decreases. The rate of transfer of drug from the capillaries to the tissues decreases more quickly at the entrance lengths and enters a pseudo equilibrium with the tissue regions. This delays the first peak for the entrance length. Eventually for all lengths, the concentration in the capillaries and tissue decreases slowly as it is metabolized in the liver and eliminated via the kidney.

METABOLISM: LIVER

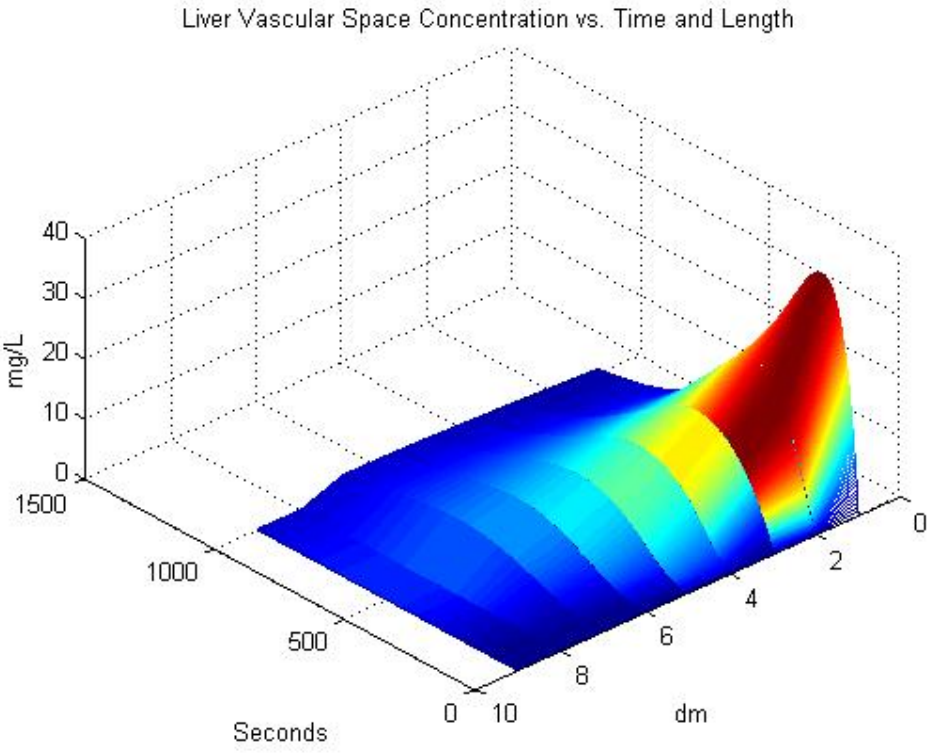

Figure 16: 3D Graph of Concentration in the Liver vs. Time and Length

The figure above contains a 3-D graph of sample results obtained for the liver. Due to the first pass metabolism effect, a large part of the dosage is eliminated in the liver; it can be seen that the exiting concentration is greater than zero, however, and this will pass to the heart to be mixed with the rest of the blood. As time increases and as the input concentration to the liver decreases, the drug becomes more fully metabolized until practically none enters the circulatory system.

EXCRETION

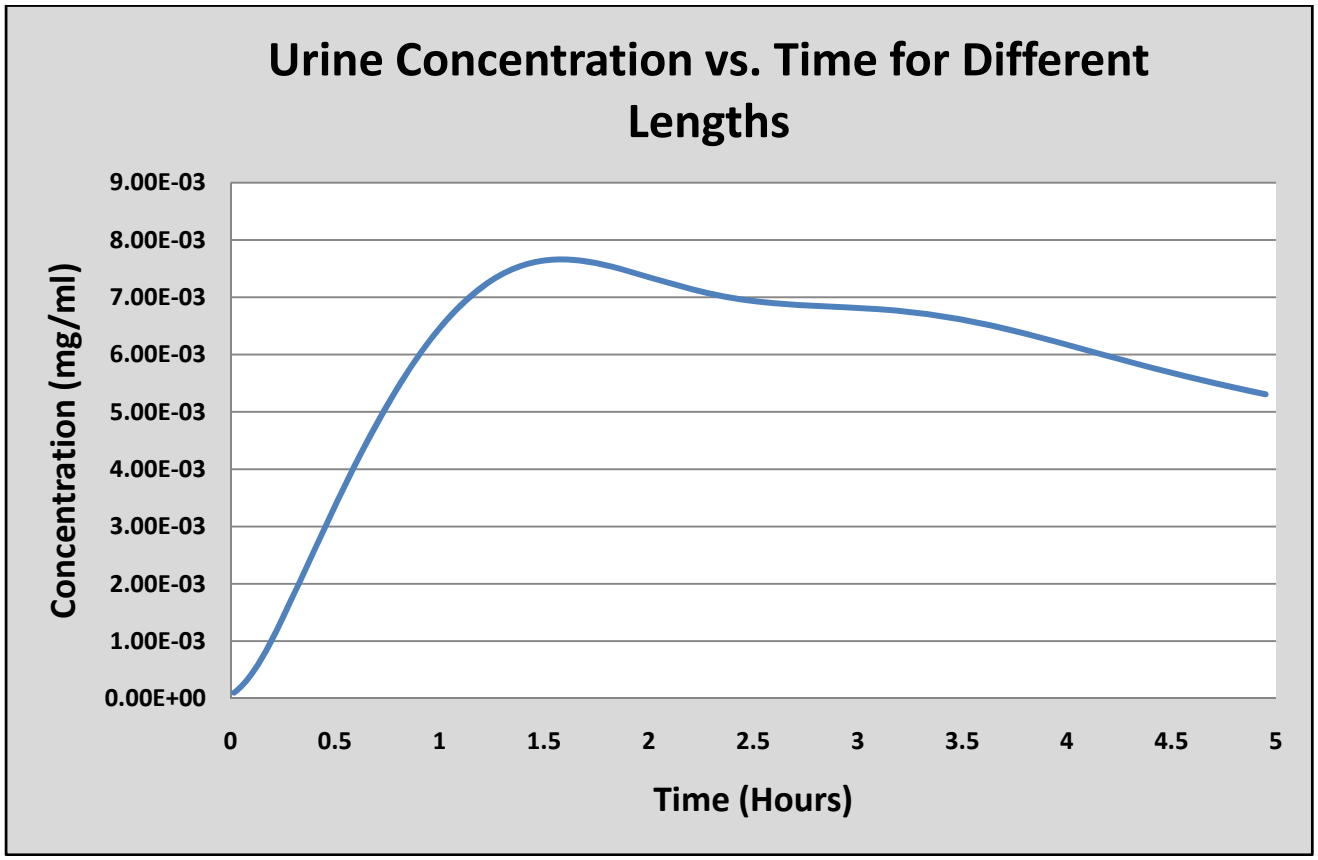

Figure 17: Concentration of Drug vs. Time inside the Bladder (urine)

The urine concentration is dependent on the amount of drug entering the bladder and the amount of drug being eliminated in the bladder. The amount of drug being eliminated in the bladder was modeled as being constant. After writing the code for the bladder, the authors have decided that it may be better to specify that every 3 or 4 hours the patient urinates and empties their bladder. This would change significantly the appearance of the above curve. Currently, because it is assumed that the urination rate is constant, the top peak results when the urination rate equals the absorption rate into the urine. In some ways, the behavior of the urine graph is similar to the behavior observed in the graphs of blood concentration. It is advised that future students look into a better way of modeling the bladder.

Case Studies

Atenolol

A case study was performed for two drugs in which the performance of our model was compared to a compartmental model and values obtained in literature. The first case study was done on a common drug that treats hypertension. The results of a case study done for a 100 mg dose are shown below.

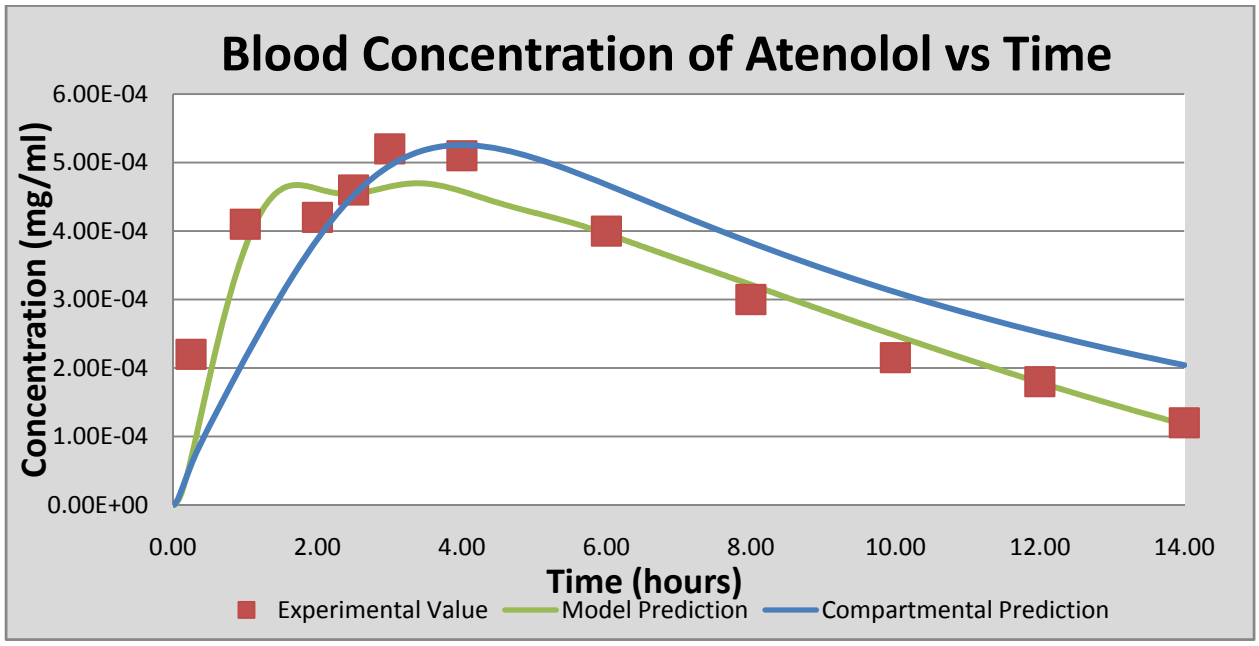

Figure 18: Comparison of Experimental Data and Model Predictions: Atenolol

Both results were obtained by manipulation of only two constants, the stomach constant K_s and the small intestine absorption constant K_a. All other parameters were estimated based on means previously discussed. As can be seen, the compartmental model had greater error in its predictions than did our model. Furthermore, the compartmental model lacked the sophistication needed to reproduce the double peak seen in both the literature values and in our model.

The compartmental model is also unable to track the amount of drug absorbed into the brain, the site where the drug acts. Our model predicted that 11.1% of the dose was absorbed into the brain.

In addition to comparing the model to experimental results of drug concentration in the blood, it is of interest how drug concentration changes with time inside the tissue of interest. For Atenolol, which treats hypertension, the intended tissue is the brain. Below are the results for the concentration of drug inside of the brain tissue for different tissue lengths.

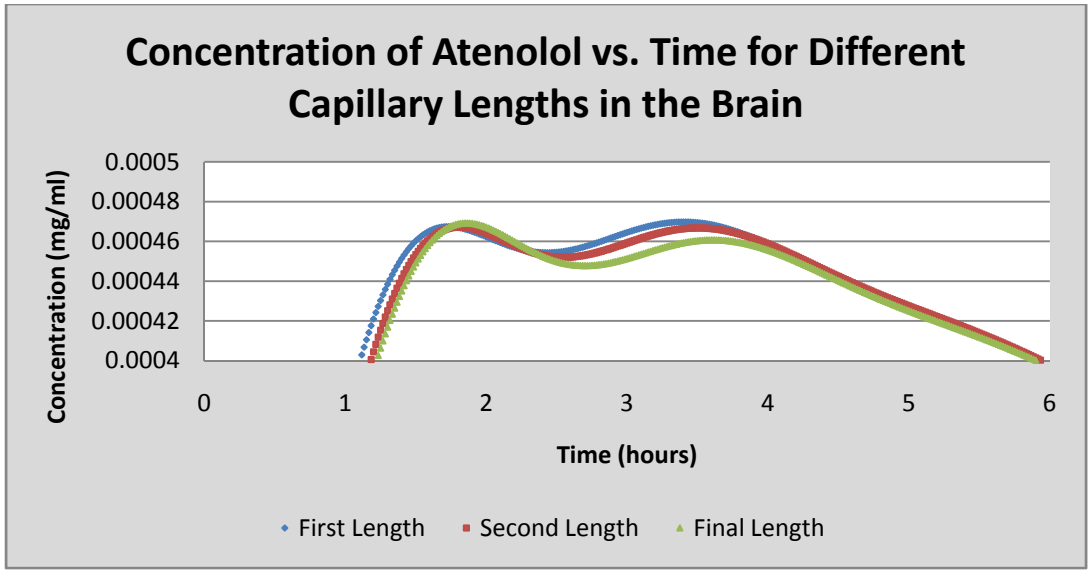

Figure 19: Concentration vs. Time for Different Capillary Lengths in Target Tissue: Atenolol

The dimensions of the graph were chosen to highlight the differences in concentration between different length elements inside the brain. At earlier times and lower concentrations as well as later times there is little differentiation between the lengths. We can see from this graph that the concentration for different length elements inside the brain is similar to the overall concentration in the blood. The double peak phenomenon is also seen. For example, at early times the initial length element has high concentrations, with eventually the middle and final lengths having greater concentration. Below are the results which describe the concentration of drug along tissue length for different times.

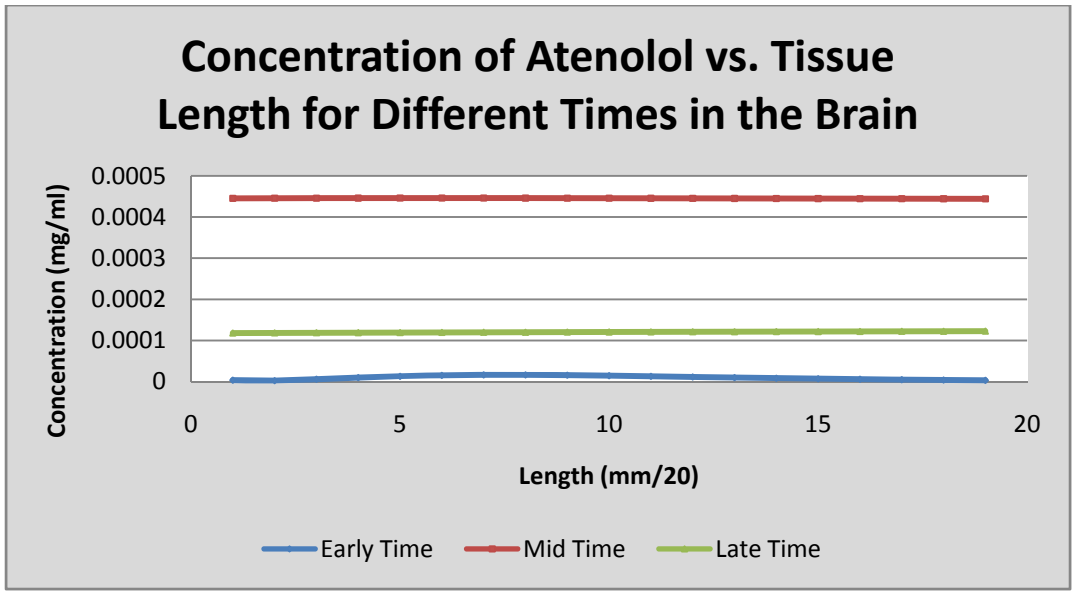

Figure 20: Concentration vs. Tissue Length for Different Times: Atenolol

For Atenolol in the brain, there is little variation with length. This is because it is a highly perfused tissue with high blood velocities inside the tissue. Tissues with lower blood flow rates will show greater variation along tissue length. Here we can also see that blood concentration begins low, increases, and then decreases again much as would be expected.

IMATINIB

A case study was also performed on the drug Imatinib, an anticancer agent. Although the compartmental model can make a good prediction for Imatinib in the blood, it is unable to do so in the tissues. This is because the compartmental model lumps together all tissues into two regions: well perfused tissues and lesser perfused tissues. As a result, tissue concentrations are rough and inaccurate estimates that do not correspond to actual tissue concentrations. Our model was able to predict accurately the concentration of Imatinib not only in the blood but also in the tissues. Below are the results comparing the model's prediction of blood concentration vs. time with experimental data as well as with the compartmental model.

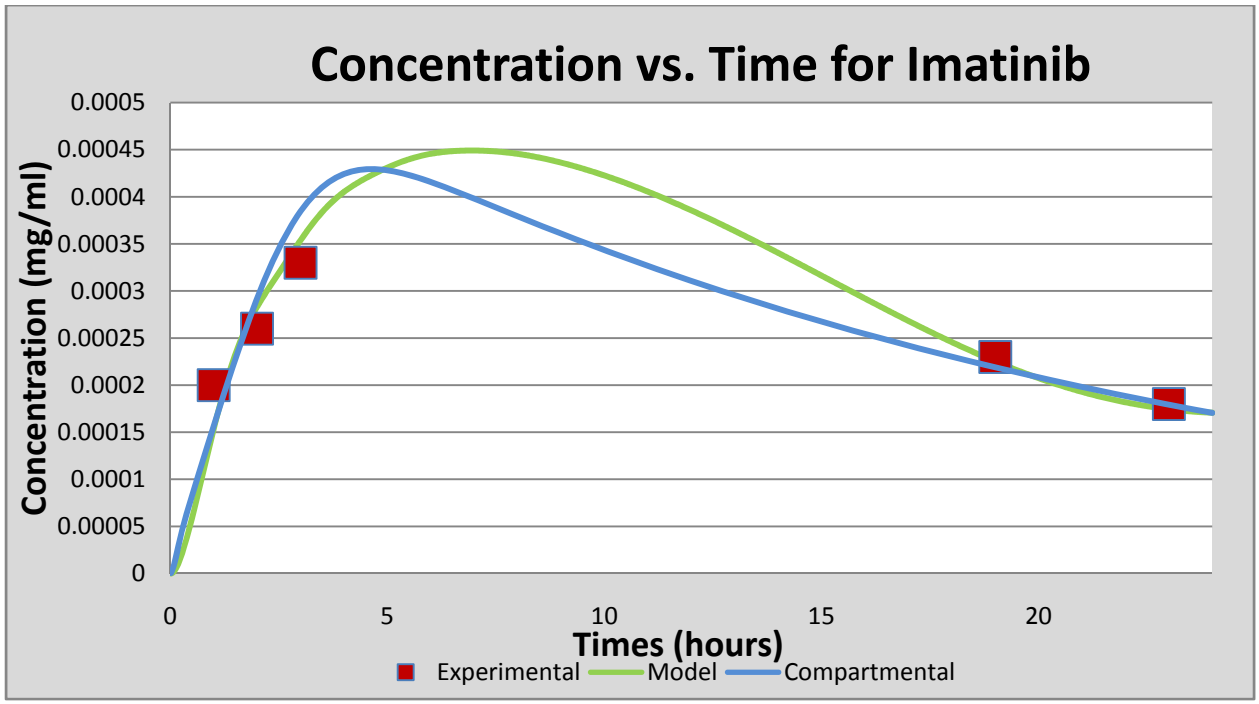

Figure 21: Comparison of Experimental Data and Model Predictions: Imatinib

As mentioned earlier, it is of interest how drug concentration changes with time inside the tissue of interest. For Imatinib, which treats cancer, the intended tissue is cancerous tissue. We assumed for our case study that the cancer was in the stomach and esophageal tissue. Below are the results for the concentration of drug inside of the brain tissue for different tissue lengths.

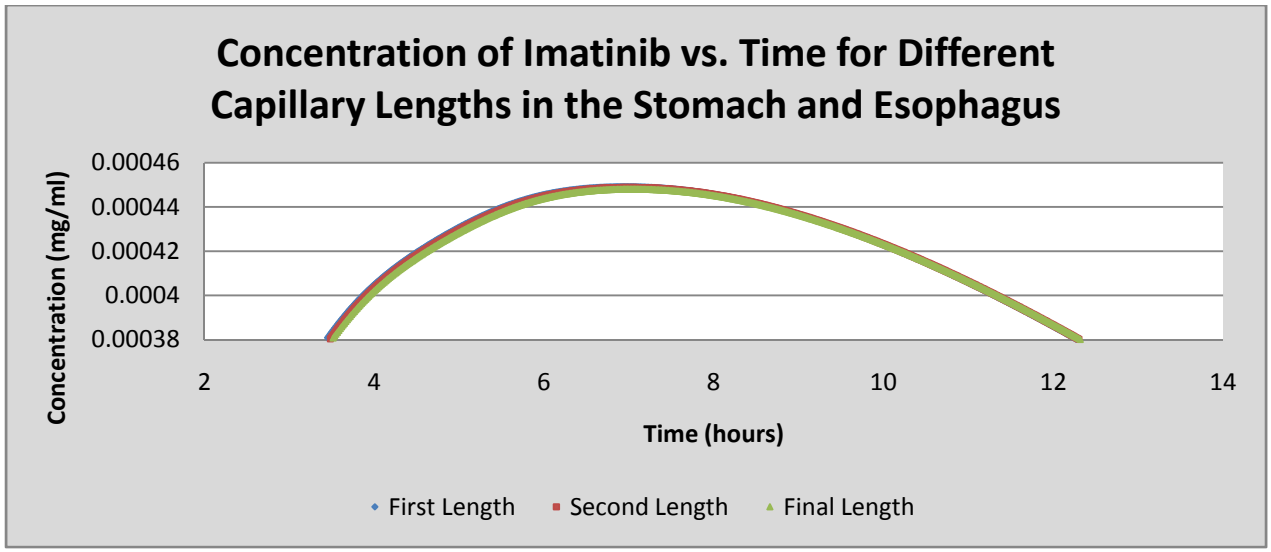

Figure 22: Concentration vs. Time for Different Lengths: Imatinib

The dimensions of the graph were chosen to highlight the differences in concentration between different length elements inside the stomach and esophagus. We can see from this graph that the concentration for different length elements inside the stomach and esophagus is still related to the overall concentration in the blood, with little differences between different length elements. The stomach and esophagus, like the brain, is a tissue with high volumes and velocities of blood flow and as such little variation along the length of the tissue is expected.

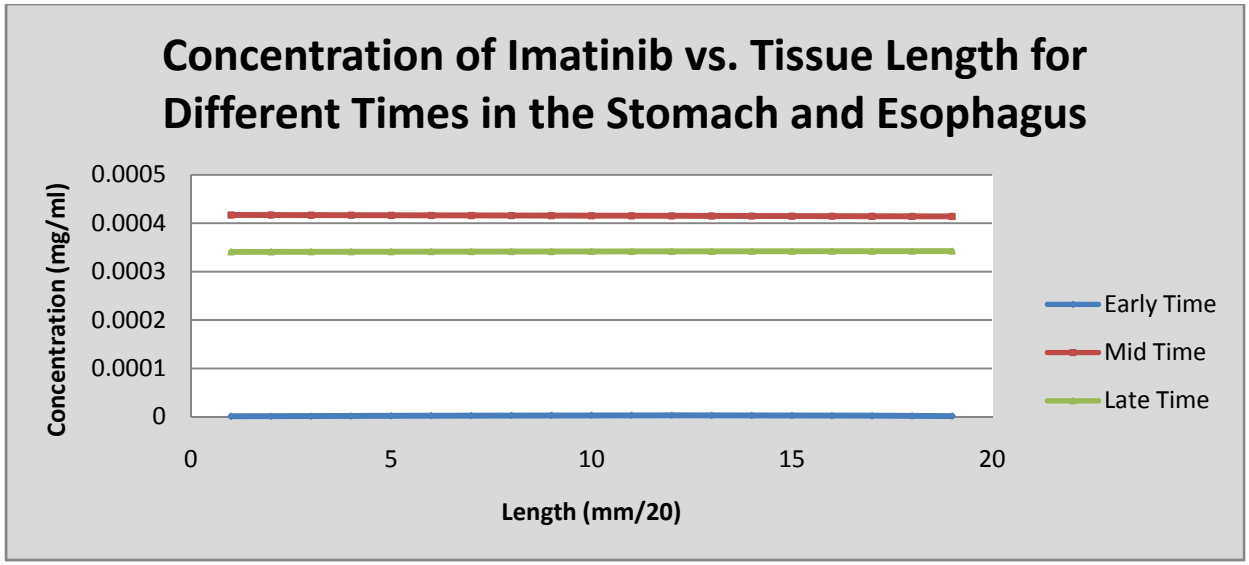

Figure 23: Concentration vs. Length for Different Times: Imatinib

Similar to our results for Atenolol, for Imatinib there is little variation with length. In addition, we see that the concentration in the stomach and esophageal tissue behaves much as expected. The concentration starts low throughout, increases, and then begins decreasing as the drug throughout the body is eliminated.

CONCLUSION

Future work should focus on predicting parameters and incorporating differences due to population variation. Improvements can also be made with the bladder model, as was discussed, or in distribution transit times. Parameter prediction would give the model true predictive power that would be able to simulate in vitro or in vivo data without using previous lab work in order to optimize parameters.

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[i] Jobling, Malcolm. "Mythical Models of Gastric Emptying and Implications for Food Consumption Studies." Environmental Biology of Fishes. 16: (1986): 1573-5133

[ii] In the current version of the Fortran model, transit times have been placed in comments or need to be reimplemented by future students. This was removed the last week of class in order to help debug certain issues in the code, and it simply never was reimplemented. It was found that transit times did not have a significant effect on the results; nonetheless, it would be little work for future students to reimplement this code, or even to improve upon the theory by using different times for different organ systems as opposed to a lumped assumption of 3 seconds for the organ and tissue systems.

[iii] The Fortran model behaves in the way described above, however, instead of specifying Ct as 0, equations 16 and 17 are rewritten to where they do not depend on C_t in an if-then loop. This allows for C_t to be calculated as if there were no drug in the tissue while actually keeping track of how much has entered the tissue. In order to find the total amount entered for the entire simulation, one should simply integrate the concentration over the volume of tissue at the final time element. This was done in an excel spreadsheet and was not included in the code due to time constraints in the last week.

[iv] Roberts, Michael. "A Dispersion Model of Hepatic Elimination." Journal of Pharmacokinetics and Biopharmaceutics 14(1985): 261-262.

[v] Roberts, Michael. "Model of Hepatic Elimination and Organ Distribution Kinetics with the Extended Convection Dispersion Model." Journal of Pharmacokinetics and Biopharmaceutics 27(1999): 343-363.

[vi] Sirianni, Gina. "Organ Clearance Concepts: New Perspectives on Old Principles." Journal of Pharmacokinetics and Biopharmaceutics 25(1997): 449-461.