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Physiologically-Based Pharmacokinetic Model for Ertapenem

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A Physiologically-Based Pharmacokinetic Model for Ertapenem

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ABSTRACT

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Ertapenem is a carbapenem used to treat a wide range of bacterial infections. What sets ertapenem apart from other carbapenems is its longer half-life which implies it need only be administered once daily. We developed a physiologically-based pharmacokinetic model for the distribution of ertapenem within the body. In the model, parameters such as human body weight and height, age, organ volumes, blood flow rates, and partition coefficients of particular tissues are used to examine the absorption, distribution, metabolism, and excretion of ertapenem. The total and free blood concentrations found were then compared to experimental data. We then examined the sensitivity of the total concentration in the blood to body weight, body height, and age. This analysis allows the possibility of the model being used as a basis for understanding how differing health conditions might alter the concentration of ertapenem in the body and hence dosage may need to be adjusted.

DEDICATION

I dedicate this work to my mamaw, Doris McKeehan.

I miss you and I love you.

ACKNOWLEDGMENTS

I would like to acknowledge my thesis advisor, Dr. Michele Joyner. She has been amazing to work with and I could not have asked for anyone better. This is the first in-depth mathematical research I have done so I was very inexperienced. She gave me the guidance and support I needed to be successful. I especially would like to thank her and Dr. Ariel Cintron-Arias for pushing me to give an oral presentation at the Joint Mathematics Meetings. I would also like to acknowledge the entire Department of Mathematics and Statistics. I have been part of the department for 6 years now and they are like family. They have helped me grow not just academically but as a person too. I could not have chosen a better department to be a student.

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1 INTRODUCTION

Ertapenem is an antibiotic in the carbapenem family which is used to treat a wide range of antibacterial infections. What sets ertapenem apart from the other carbapenems is its longer half-life so it only needs to be administered once daily. We built a mathematical model which shows the concentration of ertapenem as it travels throughout the body. This project was a result of discussions with East Tennessee State University's Quillen College of Medicine and their interest in determining how much the concentration of ertapenem varied based on body mass index, BMI, in healthy and unhealthy individuals. We used data from from a study for healthy young adults to fit our model [8].

This problem is of interest because every antibiotic has a minimum inhibitory concentration, MIC, level. If the concentration of the antibiotic falls below its MIC level, the patient may become at risk for developing antibiotic resistance. By studying the concentration of ertapenem throughout the body based on a patient's BMI, it might be possible to determine if a patient could possibly need a smaller or larger dose depending on if he or she is average weight, underweight, overweight, or obese.

A preliminary model was developed by Manning, et. al. in [7]. We took this original model and expanded it to examine the free blood concentration levels which is most important when examining the effectiveness of an antibiotic.

In order to model the distribution of ertapenem throughout the body, we built a physiologically-based pharmacokinetic (PBPK) model. PBPK models use physiological and drug specific constants and parameters [3]. Pharmacokinetics is the study of the effects the body has on the absorption, distribution, metabolism, and excretion of

a drug, also known as ADME. In the following section, we discuss the PBPK model derivation for a 1 g dose of ertapenem administered intravenously once daily.

2 MODEL DERIVATION

Figure 1 is a basic schematic of our model. The drug is administered intravenously such that it goes straight into the blood stream. From the blood stream, it is distributed throughout the body. The specific compartments we chose to look at are the adipose, kidneys, and gut and then the rest of the body is grouped in the "other tissues" compartment. We chose to specifically look at the adipose because we wanted to research how a person's BMI affects the concentration of the drug throughout the body, the kidneys because 80% of ertapenem is excreted through the urine, and the gut because 10% of ertapenem is excreted through the feces [8]. Most PBPK models also include metabolism. We chose to exclude metabolism from our model because ertapenem is metabolized mostly in the kidneys [9]. After the drug flows through a particular compartment, it then returns to the blood stream and the distribution process is repeated. To build our basic model, we only considered a 24 hour period since ertapenem is to be administered once daily. Our ODE system calculates the change in concentration of the drug in each compartment over time ($\frac{dC_{tissue}}{dt}$). Table 1 lists the equations which make up our ODE system.

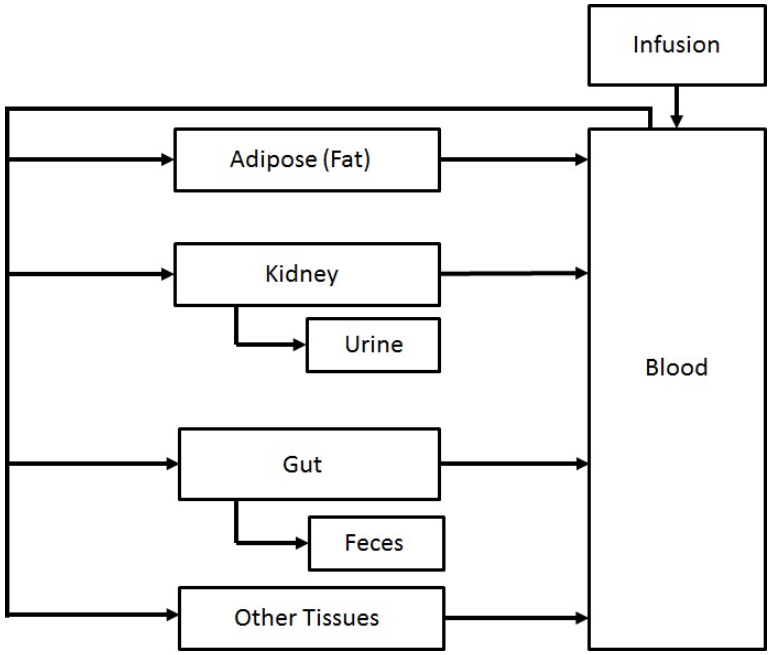

Figure 1: Model Schematic

Table 1: ODE System

Adipose	$\frac{dC_F}{dt} = \frac{Q_F\left(C_{Bf} - \frac{C_F}{P_F}\right)}{V_F}$
Kidneys	$\frac{dC_K}{dt} = \frac{Q_K\left(C_{Bf} - \frac{C_K}{P_K}\right) - k_U C_K}{V_K}$
Gut	$\frac{dC_G}{dt} = \frac{Q_G\left(C_{Bf} - \frac{C_G}{P_G}\right) - k_F C_G}{V_G}$
Other Tissues	$\frac{dC_{OT}}{dt} = \frac{Q_{OT}\left(C_{Bf} - \frac{C_{OT}}{P_{OT}}\right)}{V_{OT}}$
Blood	$\frac{dC_{Bl}}{dt} = \frac{Q_F\frac{C_F}{P_F} + Q_K\frac{C_K}{P_K} + Q_G\frac{C_G}{P_G} + Q_{OT}\frac{C_{OT}}{P_{OT}} + R_I - Q_{Total}C_{Bf}}{V_{Bl}}$
Urine	$\frac{dC_{Urine}}{dt} = \frac{k_U C_K}{V_K}$
Feces	$\frac{dC_{Feces}}{dt} = \frac{k_F C_G}{V_G}$

Ertapenem is highly bound to human plasma proteins. Only the free, unbound, portion of the drug actually saturates the tissues and can be excreted. Since only the free, or unbound, concentration of the drug is considered to be medicinally effective, we chose to look at both the total concentration and the free concentration in the blood. Also, the free concentration is the part of the concentration which can effectively be taken up by the tissues. This is also why we modeled the concentration in the tissues using the free concentration. The free concentration in the blood, C_{Bf}, is calculated from the total concentration in the blood using the equation

$$C_{Bf} = \frac{C_{Bl} - B_m - K_d + \sqrt{(B_m + K_d - C_{Bl})^2 + 4(K_d \cdot C_{Bl})}}{2}.$$

This equation for free concentration and the estimation for B_m and K_d are explained in detail in the next chapter.

The change in the amount of drug in a compartment at time t is represented by

$$\frac{dA_{tissue}}{dt} = Q_{tissue}\left(C_{Bf} - \frac{C_{tissue}}{P_{tissue}}\right).$$

In our model, the amount of ertapenem in a compartment is measured in grams. The amount of drug in a particular compartment can also be represented as the concentration in the compartment ($\frac{g}{mL}$) multiplied by the compartment's volume (mL). That is,

$$A_{tissue} = C_{tissue} \cdot V_{tissue}.$$

Therefore, at time t the change in concentration is

$$\begin{aligned}\frac{dC_{tissue}}{dt} &= \frac{d\frac{A_{tissue}}{V_{tissue}}}{dt} \\ &= \frac{1}{V_{tissue}} \cdot \frac{dA_{tissue}}{dt} \\ &= \frac{Q_{tissue}\left(C_{Bf} - \frac{C_{tissue}}{P_{tissue}}\right)}{V_{tissue}}.\end{aligned}$$

Figure 2 is the same schematic as before but this one includes a break down of all the mass balance equations in the ODE system. Each tissue compartment has a concentration coming in and a concentration going out. The kidney and gut compartments also have the portion of concentration being excreted.

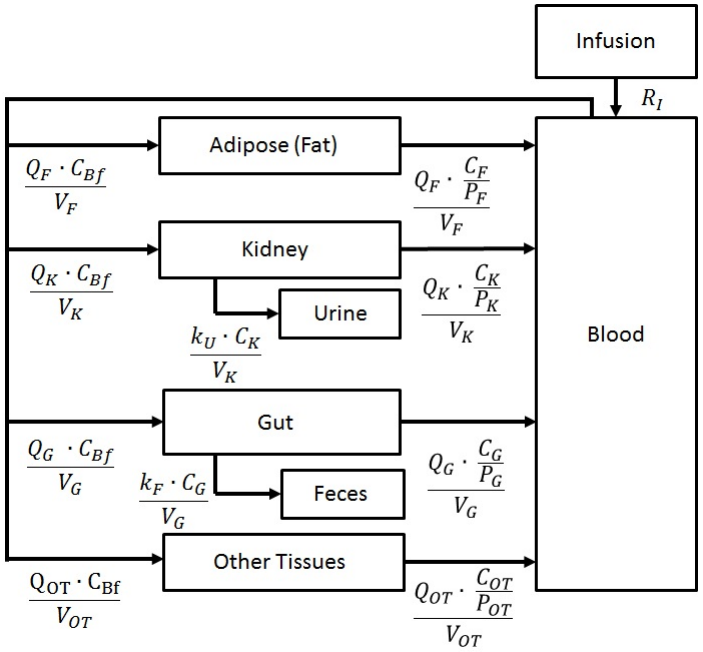

Figure 2: Model Schematic with Mass Balance Equations

As illustrated in Table 2, each of the Q_i terms represent the blood flow for the given tissue compartment, C_i represents the concentration, V_i represents the volume, P_i represents the partition coefficient, k_i represents the clearance rate, and R_I is the rate of infusion. The rate of infusion is given by

$$R_I = \begin{cases} \frac{D}{T_I} & \text{if } t \leq T_I \\ \\ 0 & \text{if } t > T_I. \end{cases}$$

where D is the dosage, 1 g, and T_I is the length of time of infusion, 30 minutes. All of these terms are constants except C_i and R_I. The blood flow rates and tissue volumes are strictly physiological, the partition coefficients are physiological and drug specific, and the clearance rates are drug specific.

Table 2: Definitions of Model Variables and Parameters

Symbol	Description	Units
C_i	Concentration of ertapenem in tissue i	$\frac{g}{mL}$
A_{Urine}	Amount of ertapenem in urine	g
A_{Feces}	Amount of ertapenem in feces	g
V_i	Volume of tissue i	mL
Q_i	Blood flow rate in tissue i	$\frac{mL}{hr}$
t	Time	hr
P_i	Tissue:blood partition coefficient for tissue i	$unitless$
BW	Body Weight	kg
BH	Body Height	m
AGE	Age	$years$
R_I	Rate of Infusion	$\frac{g}{hr}$
D	Dosage	g
T_I	Length of time of infusion	hr
k_U	Urine clearance constant	$\frac{mL}{hour}$
k_F	Feces clearance constant	$\frac{mL}{hour}$

In reference [4], the total blood flow rate was calculated based on body weight

using

$$Q_{Total} = 60 \cdot (235 \cdot BW)^{0.71} .$$

Each of the blood flow rates for the tissue compartments were calculated based on their fraction of the total blood flow rate. In order to determine the fraction of the total blood flow rate for the "other tissues" compartment, we subtracted the sum of the fraction of total blood flow for the adipose, kidney, and gut compartments from the total blood flow. The fraction of the total blood flow rate for the adipose tissue, kidneys, and gut were found in references [2] and [10],

$$\begin{aligned} Q_F &= 0.052 \cdot Q_{Total} \\ Q_K &= 0.19 \cdot Q_{Total} \\ Q_G &= 0.17 \cdot Q_{Total} \\ Q_{OT} &= Q_{Total} - (Q_F + Q_K + Q_G) \end{aligned}$$

The volume of the blood and the individual tissue compartments was calculated based on body weight, body height, and age. The volume for the "other tissues" compartment was calculated by subtracting the sum of the volumes for the blood, adipose, kidneys, and gut from the body weight in grams. We were able to do so because we assumed $BW = Volume \cdot \frac{1kg}{1L}$ since the densities of most soft tissues have

a value between 0.95 and 1.05 [5]. In references [6], [10], and [13], we have equations

$$\begin{aligned} V_{Bl} &= \frac{13.1 \cdot BH \cdot 100 + 18.05 \cdot BW - 480}{0.5723} \\ V_F &= (1.36 \cdot \frac{BW}{BH} - 42) \cdot 1000 \\ V_K &= 2 \cdot (5.04 + 2.53 \cdot AGE + 1.31 \cdot BW + 1.36 \cdot BH \cdot 100 - 255.7) \\ V_G &= (0.0171 \cdot BW) \cdot 1000 \\ V_{OT} &= BW \cdot 1000 - (V_{Bl} + V_F + V_K + V_G) \end{aligned}$$

The partition coefficients for the individual tissue compartments represent the tissue's solubility. They determine the portion of concentration that can flow from each tissue back into the blood. For example, $P_F = 1.946845001$ means 1 mL of adipose tissue can hold 1.946845001 times as much ertapenem as 1 mL of blood. The equation we used to estimate the partition coefficients includes both physiological and drug specific parameters.

$$P_t = \frac{[S_o \cdot N_t] + [(S_w \cdot 0.7P_t) + (S_o \cdot 0.3P_t)] + [S_w \cdot W_t]}{[S_o \cdot N_b] + [(S_w \cdot 0.7P_b) + (S_o \cdot 0.3P_b)] + [S_w \cdot W_b]}$$

where S_w is the solubility of the chemical in water and S_o is the solubility of the chemical in n-octanol [12]. N_t, P_t, and W_t are the fraction of tissue volume that is neutral lipids, phospholipids, and water, respectively; whereas, N_b, P_b, and W_b are the fraction of blood volume that is neutral lipids, phospholipids, and water. For ertapenem, $S_w = 0.069230349\frac{mol}{m^3}$ and $S_o = K_{ow} \cdot S_w$ where $K_{ow} = 1.66$ is the solubility of ertapenem in n-octanol:water [14]. Thus, using the equation, we calculated the

following:

$$\begin{aligned} P_F &= 1.946845001 \\ P_K &= 1.047008099 \\ P_G &= 0.896409391 \\ P_{OT} &= 1.012441852 \end{aligned}$$

The clearance rates for the kidneys and the gut are represented by k_U and k_F. Both of these parameters are drug specific. We needed to estimate both parameters such that the excretion of ertapenem through the urine was approximately 80% and through the feces was approximately 10%. This estimation will be discussed in the next chapter.

3 PARAMETER ESTIMATION

In chapter 2, we mentioned a few parameters which needed to be estimated. In this chapter, we will discuss those parameters and the methods used to estimate them.

3.1 Splitting the Blood Compartment

Every antibiotic has a minimum inhibitory concentration, MIC, level. If the concentration of the drug in the blood falls below its MIC level, the patient becomes at risk of developing antibiotic resistant bacteria. Since only the free concentration of the drug is considered to be medicinally effective, we decided to look at both the total and free concentration of ertapenem in the blood. In order to do so, we had to determine how much of the total concentration was free and how much was bound. Ertapenem is highly bound to human plasma proteins. In healthy young adults, the binding decreases as the total concentration in the blood increases. It is approximately 95% bound when the total concentration in the blood is less than $0.0001\frac{g}{mL}$ but decreases to 85% bound when the concentration reaches $0.0003\frac{g}{mL}$ [8]. The total concentration in the blood is given by

$$Total = Free + Bound.$$

In our model, we denoted the total concentration in the blood by C_{Bl}, the free concentration by C_{Bf}, and the bound concentration by C_{Bound}. The bound concentration in the blood can be modeled using a nonlinear Michaelis-Menten equation

$$C_{Bound} = \frac{B_m C_{Bf}}{K_d + C_{Bf}}$$

where B_m is the blood receptor content and K_d is the dissociation constant [11]. By substituting the equation for the bound concentration into the equation for the total concentration, we have

$$C_{Bl} = C_{Bf} + \frac{B_m C_{Bf}}{K_d + C_{Bf}}. \tag{1}$$

This allowed us to study the total and free concentrations without directly calculating the bound concentration. By simple algebraic manipulation and the quadratic formula, we were able to obtain the following equation for the free concentration

$$C_{Bf} = \frac{C_{Bl} - B_m - K_d + \sqrt{(B_m + K_d - C_{Bl})^2 + 4K_d C_{Bl}}}{2}. \tag{2}$$

This equation gives the free concentration in terms of C_{Bl}, B_m, and K_d.

After obtaining the equation for the free concentration in the blood, we had to determine a way to estimate B_m and K_d. We found clinical data that gave both the total and free concentrations in the blood at corresponding times after infusion. The data values are listed in Table 3 and can be seen in Figure 3. We were able to use this data and equation (1) to estimate B_m and K_d.

Table 3: Clinical Data for the Total and Free Concentrations in the Blood [9]

Time (hours)	Total Concentration ($\frac{mcg}{mL}$)	Free Concentration ($\frac{mcg}{mL}$)
0.1	96.5402	6.4626
0.25	160.2984	15.4753
4	50.5676	2.7021
6	30.4746	1.5832
8	20.5561	1.0984
12	10.4683	0.4221
18	3.6985	0.145

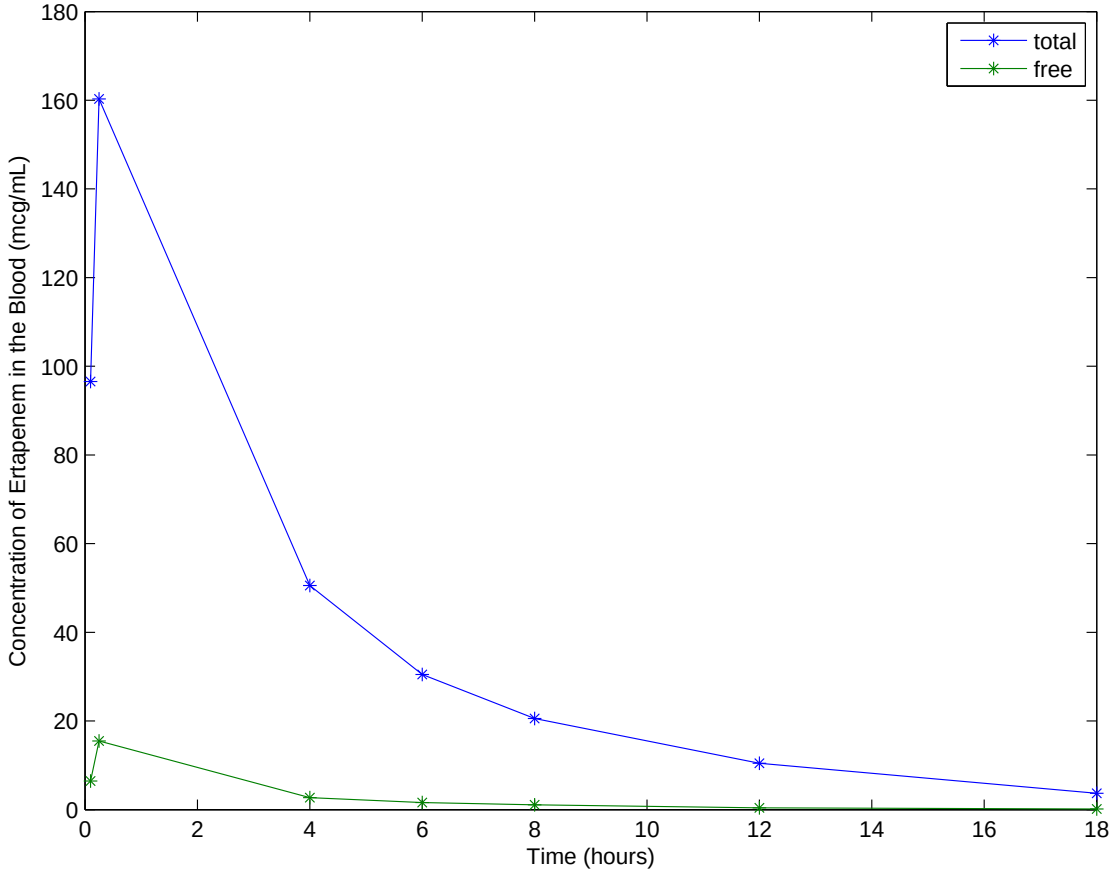

Figure 3: Clinical Data for the Total and Free Concentrations in the Blood

The values of C_{Bl} and C_{Bf} are from clinical data [9]. In Matlab, we used $fminsearch$, a built-in Matlab optimization algorithm, in order to estimate the values of B_m and K_d such that the cost function

$$J(B_m,\ K_d) = \sum (C_{Bl,data} - C_{Bl,pred}(B_m,\ K_d))^2 + \sum (C_{Bf,data} - C_{Bf,pred}(B_m,\ K_d))^2$$

is minimized where $C_{Bl,pred}(B_m,\ K_d)$ is the value of C_{Bl} using equation (1) and $C_{Bf,pred}(B_m,\ K_d)$ is the value of C_{Bf} using equation (2) with given values of B_m and K_d. We started with an initial guess and obtained optimal values of $B_m =$

$259.7319\frac{mcg}{mL}$ and $K_d = 12.2480\frac{mcg}{mL}$ with the cost function minimized to $J = 7.6216\ \left(\frac{mcg}{mL}\right)^2$. In some cases standard error and confidence intervals are used, but we have chosen to use point estimates in this paper. Figure 4 shows the approximation using equation (1) with the optimal values for B_m and K_d against the clinical data for the total concentration in the blood. Figure 5 shows the same for the free concentration in the blood.

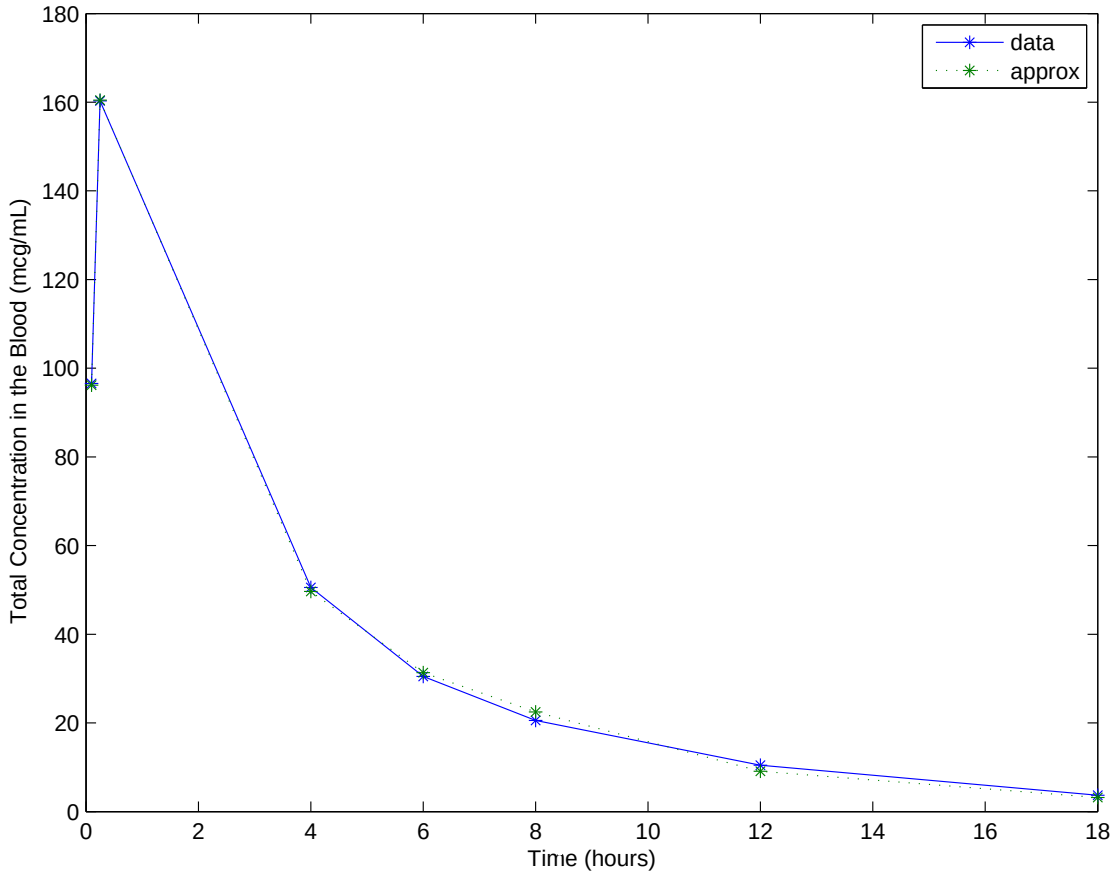

Figure 4: Clinical Data vs Estimated Values for the Total Concentration in the Blood

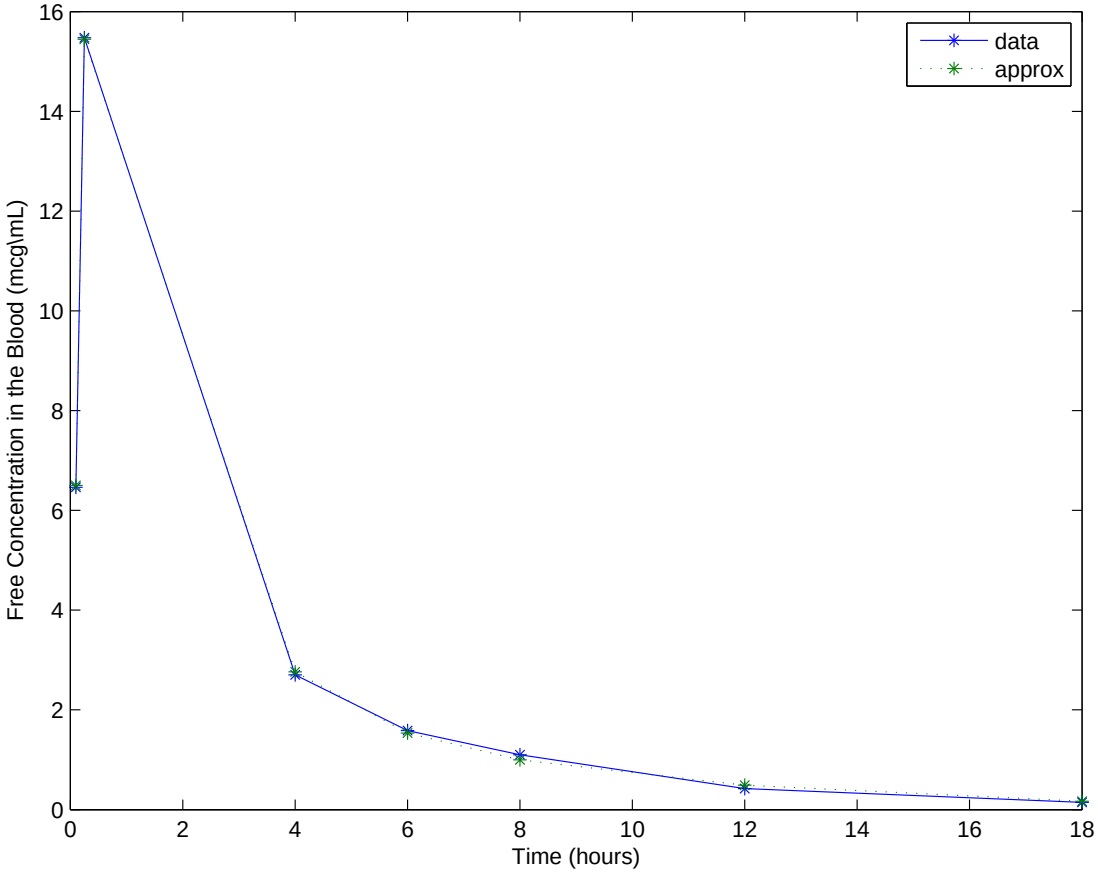

Figure 5: Clinical Data vs Estimated Values for the Free Concentration in the Blood

3.2 Estimating k_U and k_F

We used the equations

$$\begin{aligned} \frac{dC_{Urine}}{dt} &= \frac{k_U C_K}{V_K} \\ \frac{dC_{Feces}}{dt} &= \frac{k_F C_G}{V_G} \end{aligned}$$

to describe the excretion of ertapenem in the urine and feces. The parameters k_U and k_F are the clearance rates for the kidneys and the gut in $\frac{mL}{hour}$ and are drug specific.

From literature, we knew approximately 80% of ertapenem is excreted in the urine and approximately 10% in the feces. Thus, since they are drug specific, we were able to estimate k_U and k_F by choosing values such that the amount of ertapenem, $A_{urine} = C_{urine} \cdot V_K$, in the urine after 24 hours was approximately $0.8g$ (80% of a $1g$ dose) and the amount in the feces was approximately $0.1g$ (10% of a $1g$ dose). Doing so, we found the values $k_U = 55,000\frac{mL}{hour}$ and $k_F = 8,000\frac{mL}{hour}$ which gave us 79.63% excreted in the urine and 18.24% excreted in the feces after 24 hours. Although more than 10% was excreted in the feces, the model did not incorporate metabolism. We believe that if the model included metabolism, then we could have further reduced the error in the feces output. However, as is, the model for total blood concentration matches the data in the literature well (see Figure 6 in chapter 4).

3.3 Estimation for the Model During Infusion

We had difficulties getting the peak of the total and free concentrations in the blood in our model to match that of the clinical data. This was due to the model excreting the drug too quickly. Since this is a model, it does not automatically know that a drug will not be immediately excreted within the 30 minute infusion time. To control this, rather than having the proportion of the free concentration be partially determined by the amount of drug excreted, we set the excretion in the urine and the feces equal to zero during the infusion (first 30 minutes) and estimated the proportion of the free concentration being distributed throughout the body. We did so by calculating an inverse problem. In the model, during infusion, instead of assuming the outflow from the blood compartment was the entire free portion of the

drug, we instead assumed that the outflow from the blood to the tissue compartments was αC_{Bf} where α was the parameter we were estimating. In Matlab, we used the fminsearch optimization algorithm again to estimate α such that the cost function, in equation (2), was minimized. For the inverse problem, we used

$$J(\alpha) = \sum (C_{Bl,data} - C_{Bl,pred}(\alpha))^2 + \sum (C_{Bf,data} - C_{Bf,pred}(\alpha))^2. \tag{3}$$

We started with an initial guess and obtained an optimal value of $\alpha = 0.2789$ with the cost function minimized to $J = 52.7576 \ \left(\frac{mcg}{mL}\right)^2$.

After estimating all of the parameters from this chapter, we were able to complete our basic model for a young adult male with average weight and height. Having a complete basic model meant we could start performing simulations. We ran simulations for males and females who are underweight, average weight, overweight, and obese for both a one day, 24 hour, period and a 3 day, 72 hour, period. The details of these simulations are the topic of the next chapter.

4 SIMULATIONS

We compared our model based on a young adult male with average body weight and height, age 32 years weighing 72 kg (159 lbs) and a height of 1.778 m (70 in), to clinical data [1] [15]. When compared to the clinical data, the total concentration in the blood for our model had an error of 4.22% (Figure 6) and the free concentration had an error of 2.12% (Figure 7). After building this basic model, we then used it to run simulations by varying the parameters body weight and body height.

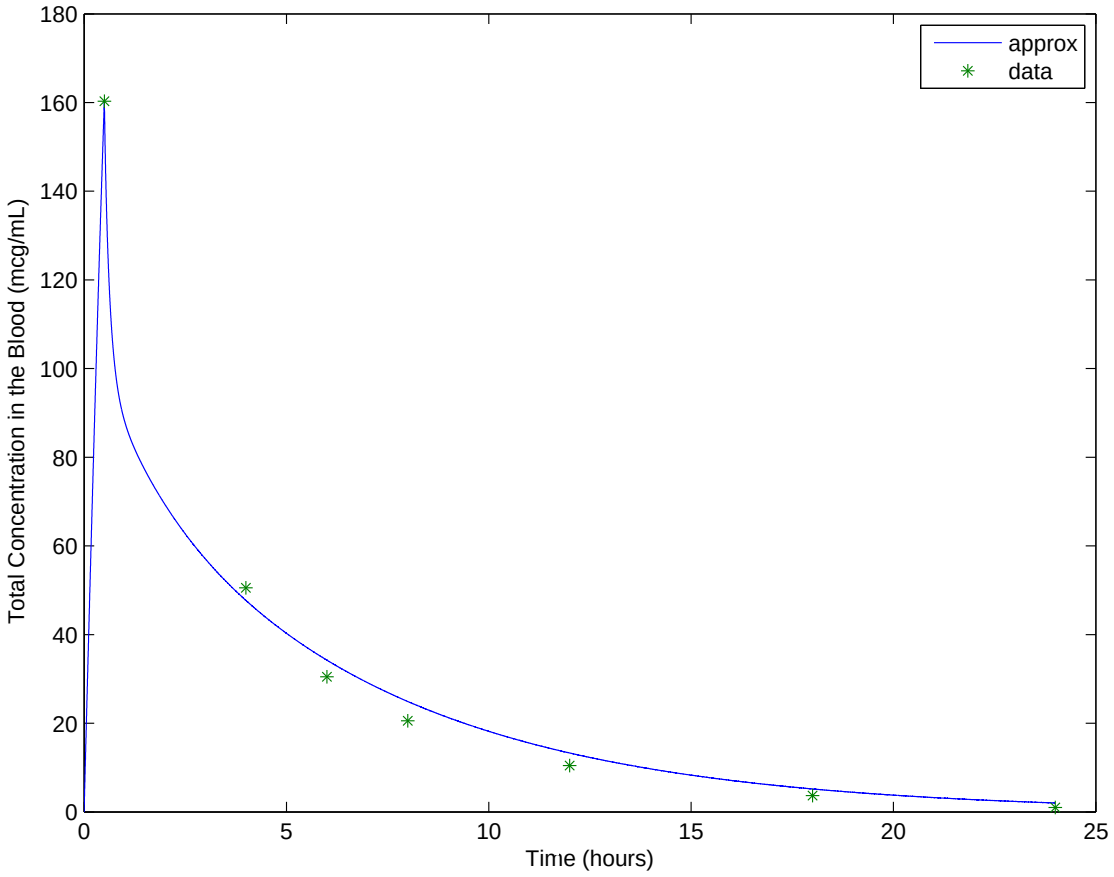

Figure 6: Total Concentration in the Blood

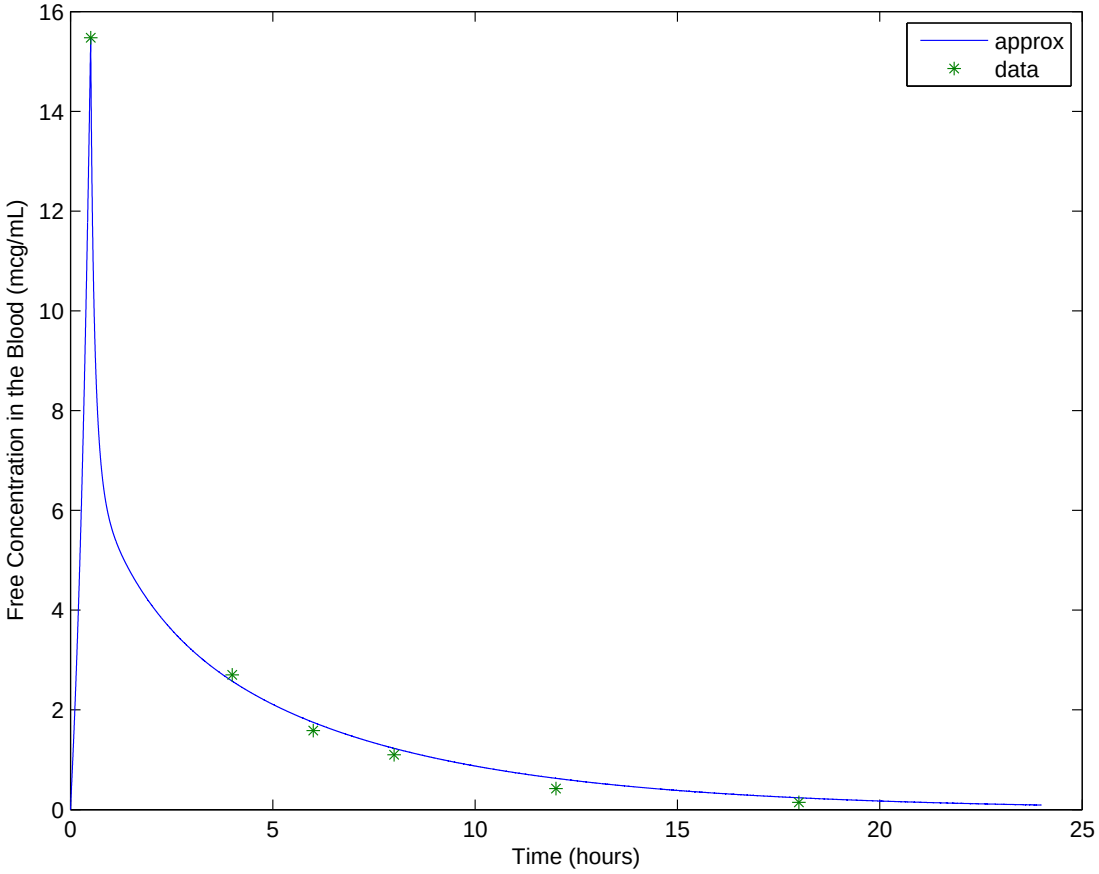

Figure 7: Free Concentration in the Blood

4.1 Male BMI

In order to study the effects of BMI on the concentration of ertapenem throughout the body, we took our basic model for a young male of average weight and height and changed only the weight to show the difference in the concentration based upon BMI classification of a young adult male of average height. In Table 4, the weights used corresponding to underweight, average weight, overweight, and obese are listed.

Table 4: Weights (Males) [15]

Weight Description	Numerical Weight (kg)
Underweight	55
Average Weight	72
Overweight	85
Obese	106

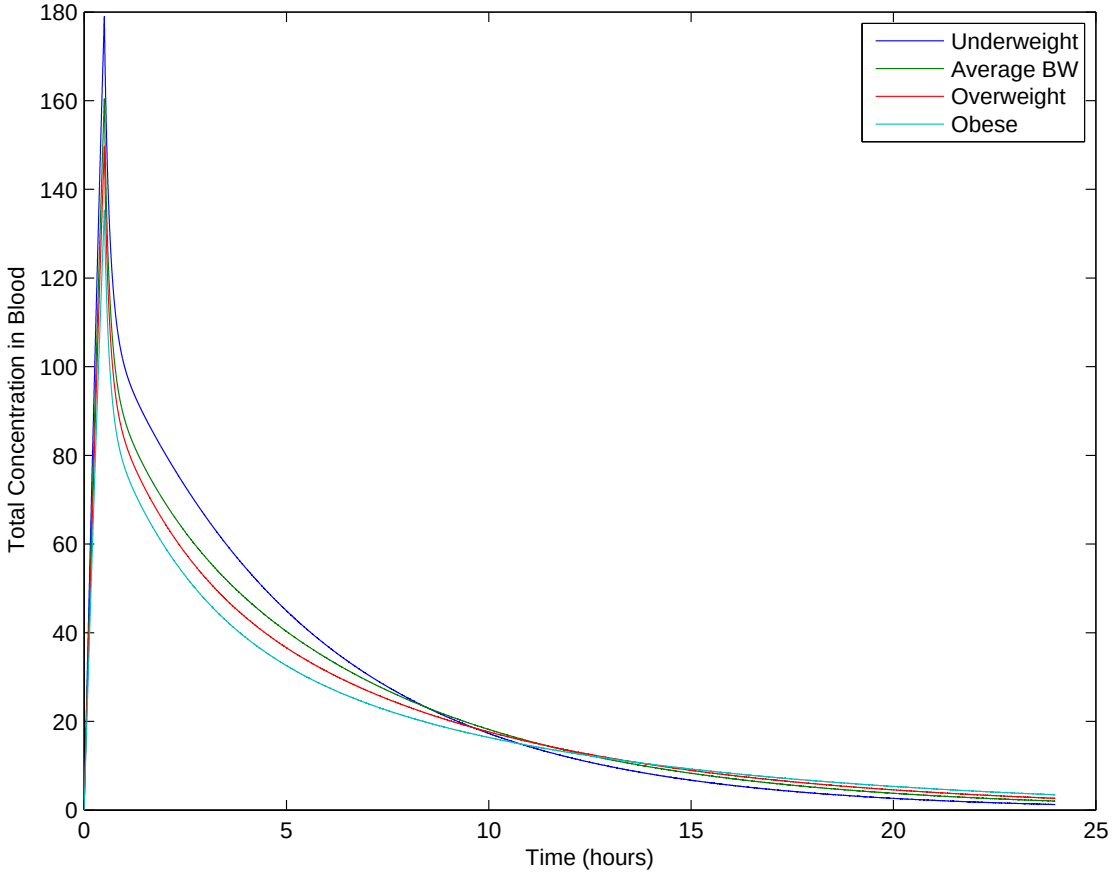

Figure 8: Total Concentration in the Blood (Male BMI)

Figure 8 shows a comparison of the total concentration in the blood based on BMI. Between hours 0.5 and approximately 10, the total concentration in the blood

is lowest for obese. After that, the total concentration in the blood is highest for obese. The concentration for underweight is the exact opposite. More important than the total concentration in the blood though is the free concentration which can be seen in Figure 9 below.

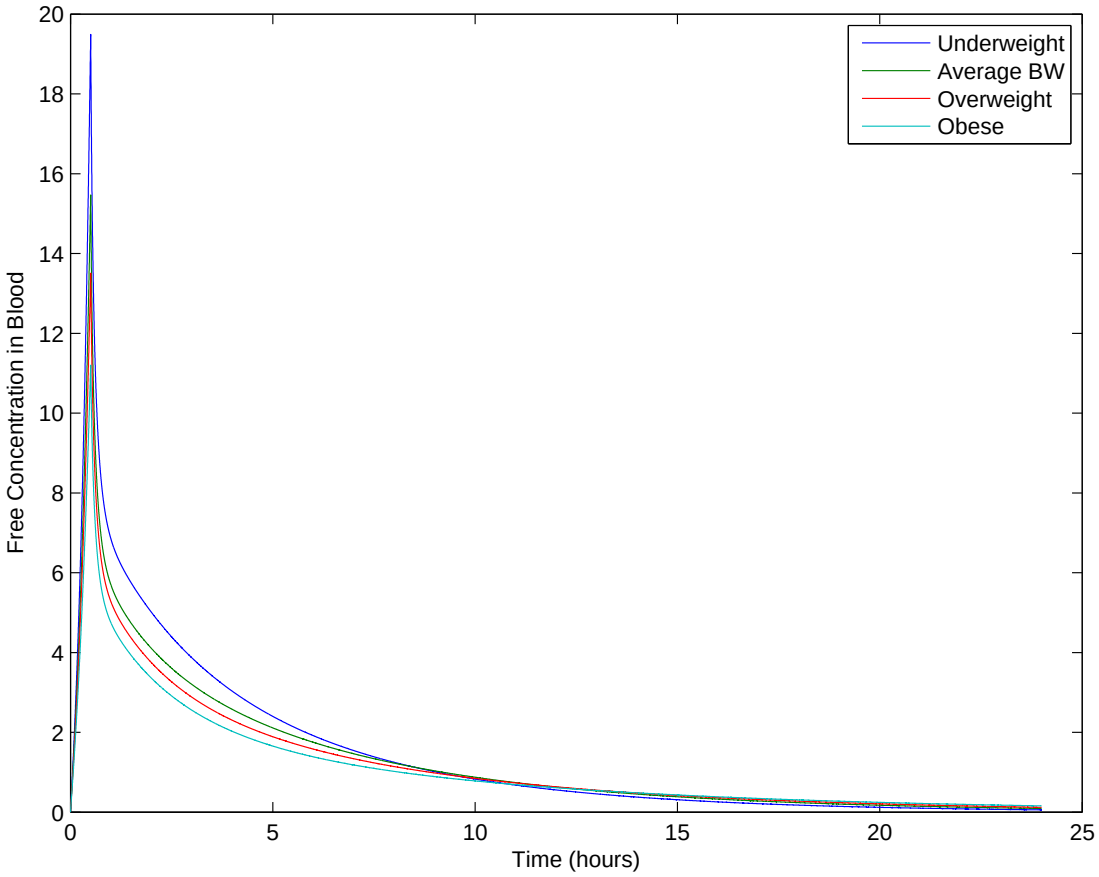

Figure 9: Free Concentration in the Blood (Male BMI)

The free concentration cannot fall below the MIC level so it is important to look at the lowest values of the concentration. This can be seen below in Figure 10 which is the same as Figure 9 but it only shows the concentration for hours 20 to 24.

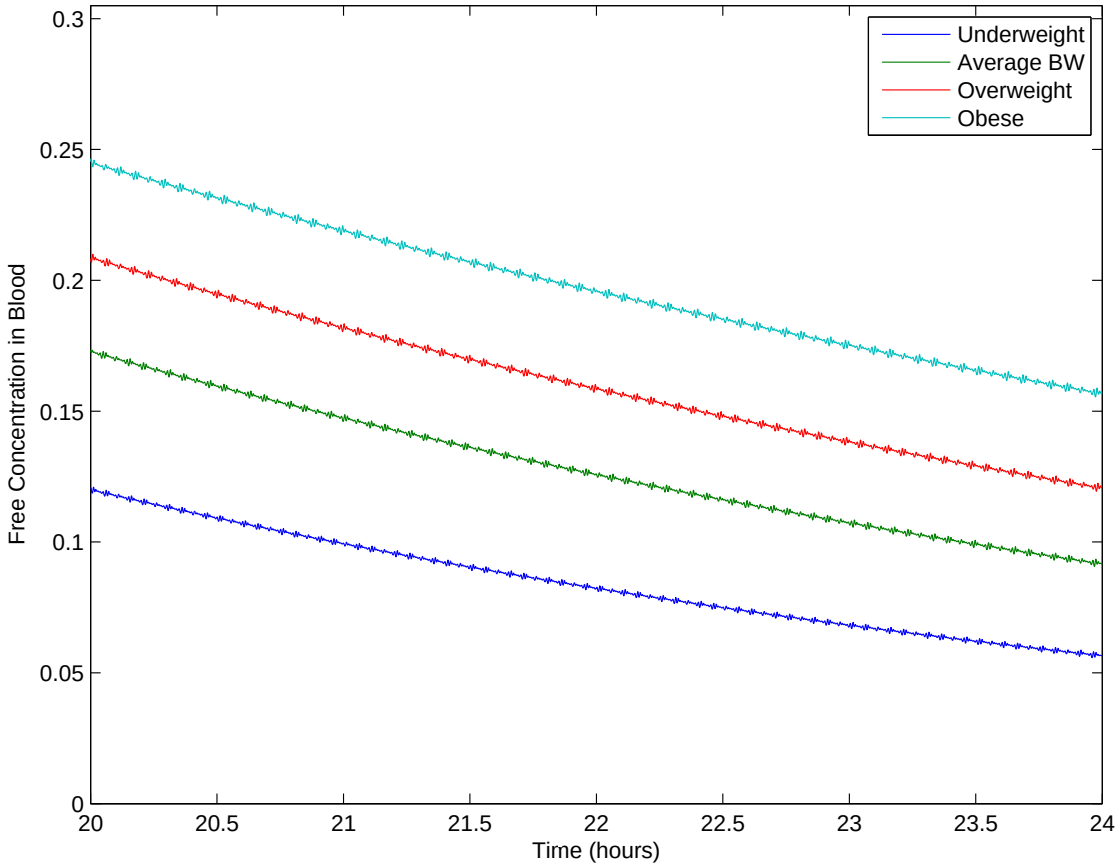

Figure 10: Free Concentration in the Blood for Hours 20 to 24(Male BMI)

In Figure 10, underweight males have the lowest concentration at approximately $0.0565\frac{mcg}{mL}$. The lowest concentration for average weight is approximately $0.0916\frac{mcg}{mL}$, overweight is approximately $0.1207\frac{mcg}{mL}$, and obese is approximately $0.1569\frac{mcg}{mL}$. Thus implying BMI does have an effect on concentration.

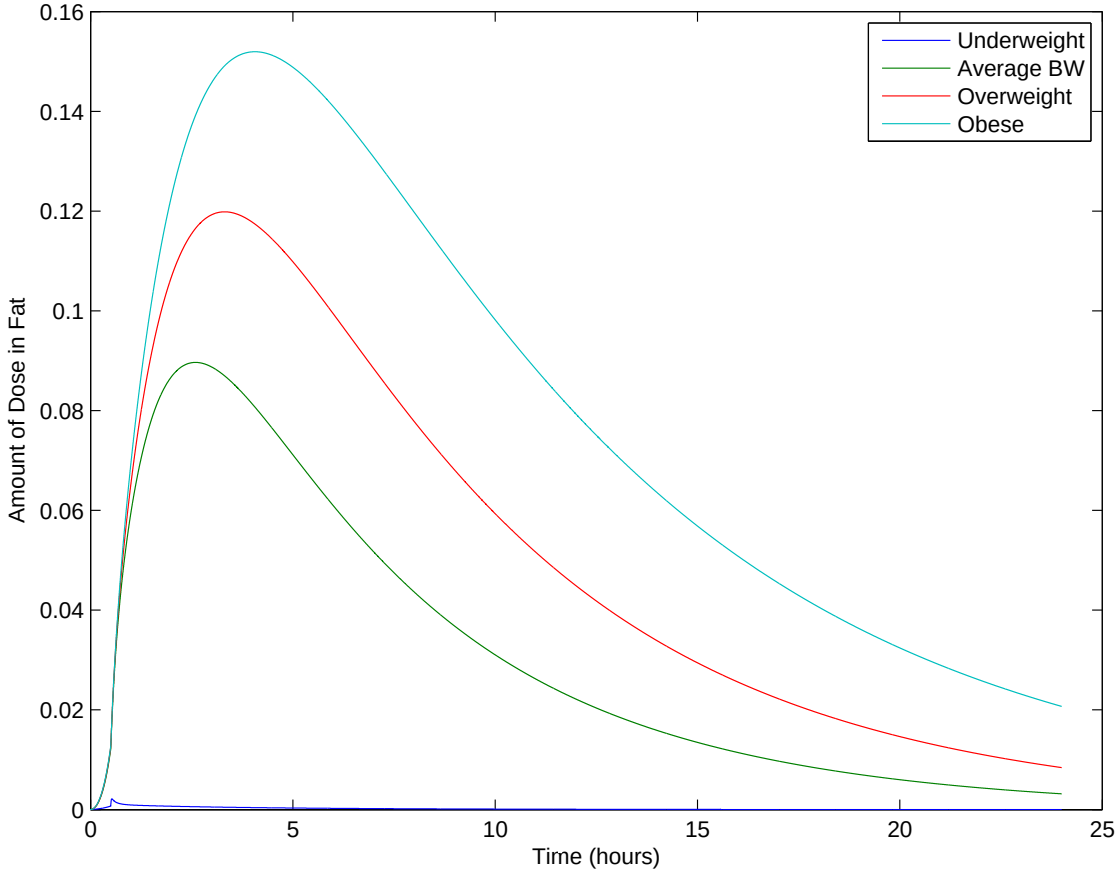

Figure 11: Amount of Dose in the Adipose Tissue (Male BMI)

Figure 11 is the amount of the 1 g dose in the adipose tissue, or fat tissue. The curve for underweight barely rises above zero which makes sense since an underweight person has less fatty tissue; therefore, there is less tissue volume for the drug to absorb. Applying the same theory, it makes sense that the amount of ertapenem in the adipose tissue is greatest in those who are obese because they have the most fatty tissue.

4.2 Female BMI

Just as we did for male BMI, we changed the weights to correspond to females who are underweight, average weight, overweight, and obese. The weights used can be found in Table 5. We kept the age at 32 years but changed the average weight to 61 kg (134 lbs) and height to 1.62 m (64 in) [1] [15]. We also had to change the equations used for the volumes of the tissues. In references [2], [6], [10], the equations for volume were

$$\begin{aligned} V_{Bl} &= \frac{35.5 \cdot BH \cdot 100 + 2.27 \cdot BW - 3382}{0.6178} \\ V_F &= (1.61\frac{BW}{BH} - 38.3) \cdot 1000 \\ V_K &= 2 \cdot (5.04 \cdot 2 + 2.53 \cdot AGE + 1.31 \cdot BW + 1.36 \cdot BH \cdot 100 - 255.7) \\ V_G &= (0.0171 \cdot BW) \cdot 1000 \\ V_{OT} &= BW \cdot 1000 - (V_B + V_F + V_K + V_G). \end{aligned}$$

Table 5: Weights (Females) [15]

Weight Description	Numerical Weight (kg)
Underweight	44
Average Weight	61
Overweight	72
Obese	99

The volumes for males are greater than the volumes for females in all the compartments except for the adipose tissue. Also note that all of the volumes for males and females increase as body weight increases except for the volume of the other tissues in females which actually decreases as body weight increases. This is due to the large

increases in the volume of the adipose tissue as body weight increases.

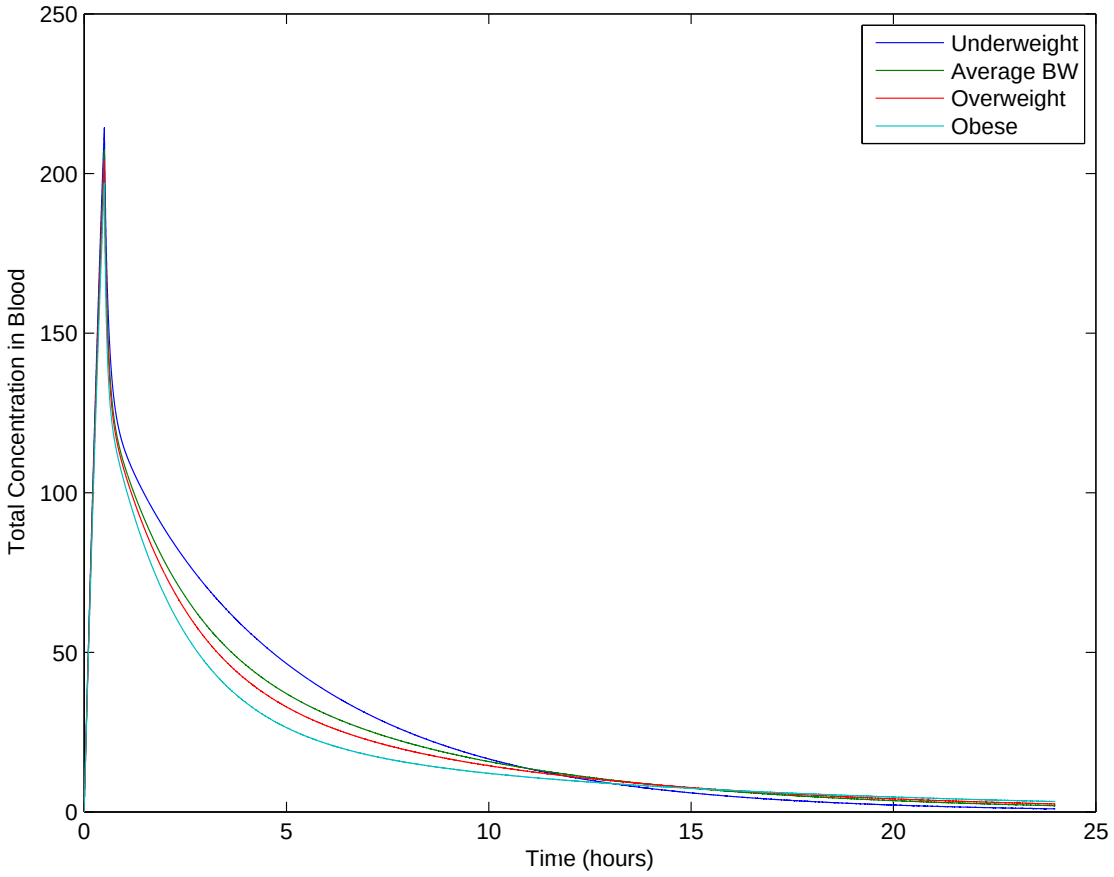

Figure 12: Total Concentration in the Blood (Female BMI)

Figure 12 shows the total concentration of ertapenem in the blood. Just like the total concentration in the blood for males, underweight females starts out having the highest concentration and obese females the lowest. However, instead of switching at approximately hour 10, the switch occurs at approximately hour 13. This difference will affect the other compartments as well.

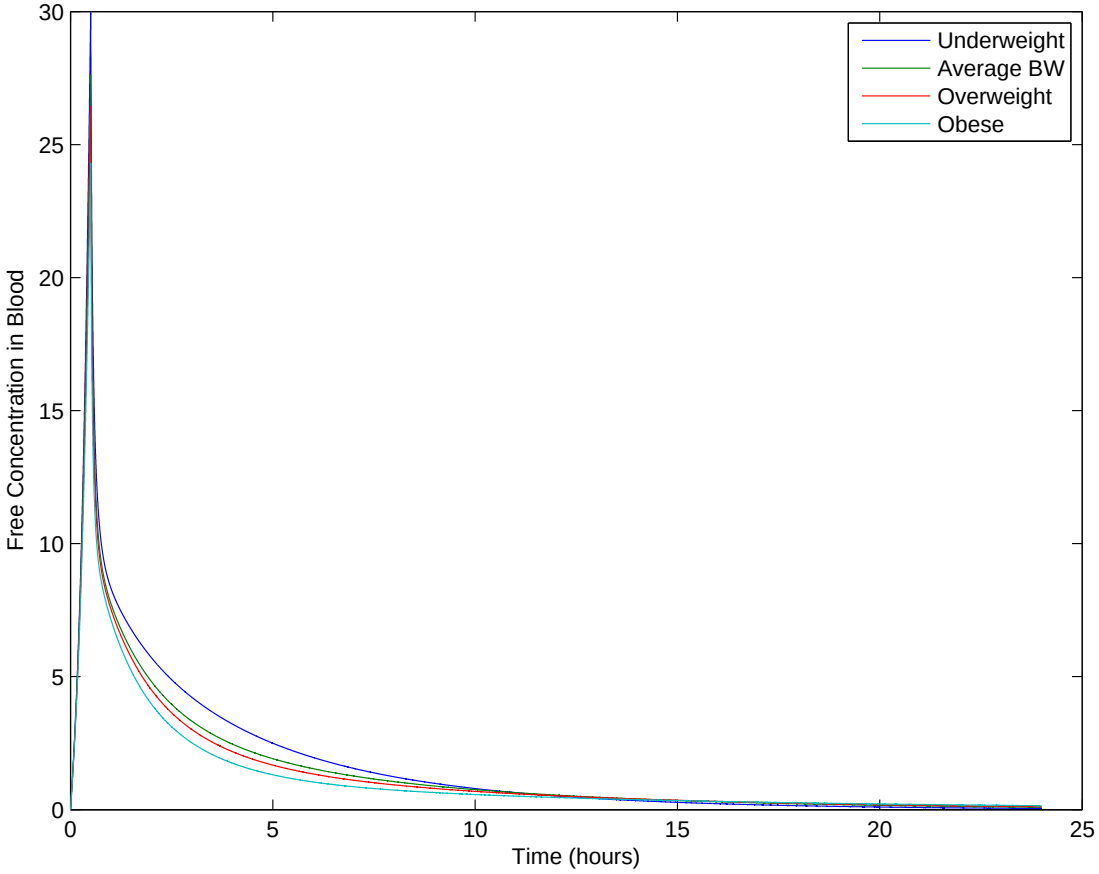

Figure 13: Free Concentration in the Blood (Female BMI)

The peak for the free concentration in the blood for underweight males was at approximately $19.4899\frac{mcg}{mL}$. However, for the females it is higher at approximately $29.9616\frac{mcg}{mL}$. The peak for average weight males was approximately $15.4687\frac{mcg}{mL}$ and for average weight females it was $27.6066\frac{mcg}{mL}$. Overweight males had a peak at $13.5064\frac{mcg}{mL}$ and overweight females had a peak at $26.4586\frac{mcg}{mL}$. Obese males and females had the lowest peaks at $11.2016\frac{mcg}{mL}$ for males and $24.2995\frac{mcg}{mL}$ for females.

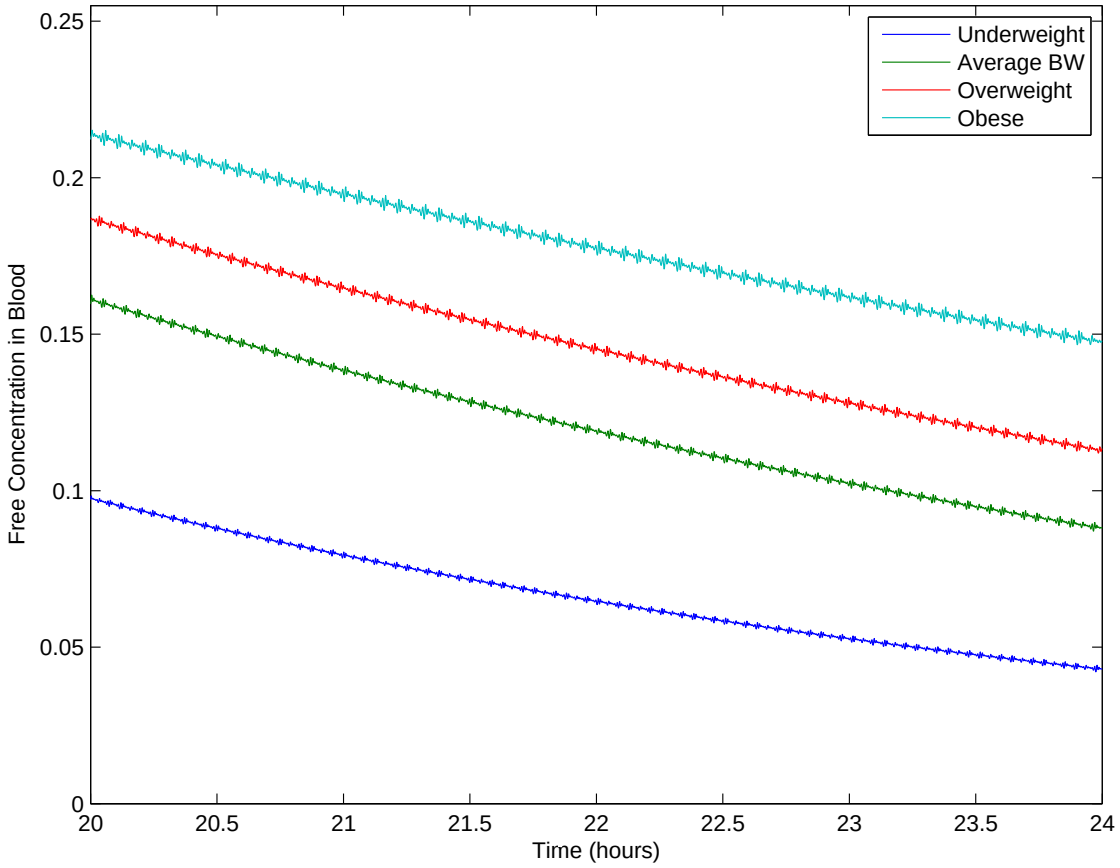

Figure 14: Free Concentration in the Blood Hours 20 to 24 (Female BMI)

By looking at Figure 14, you can see the minimum concentration for underweight females is approximately $0.0430\frac{mcg}{mL}$, average weight is approximately $0.0880\frac{mcg}{mL}$, overweight is approximately $0.1134\frac{mcg}{mL}$, and obese is approximately $0.1478\frac{mcg}{mL}$. So for underweight, average weight, overweight, and obese females, the peak concentrations are higher but the minimum concentrations are lower compared to underweight, average weight, overweight, and obese males.

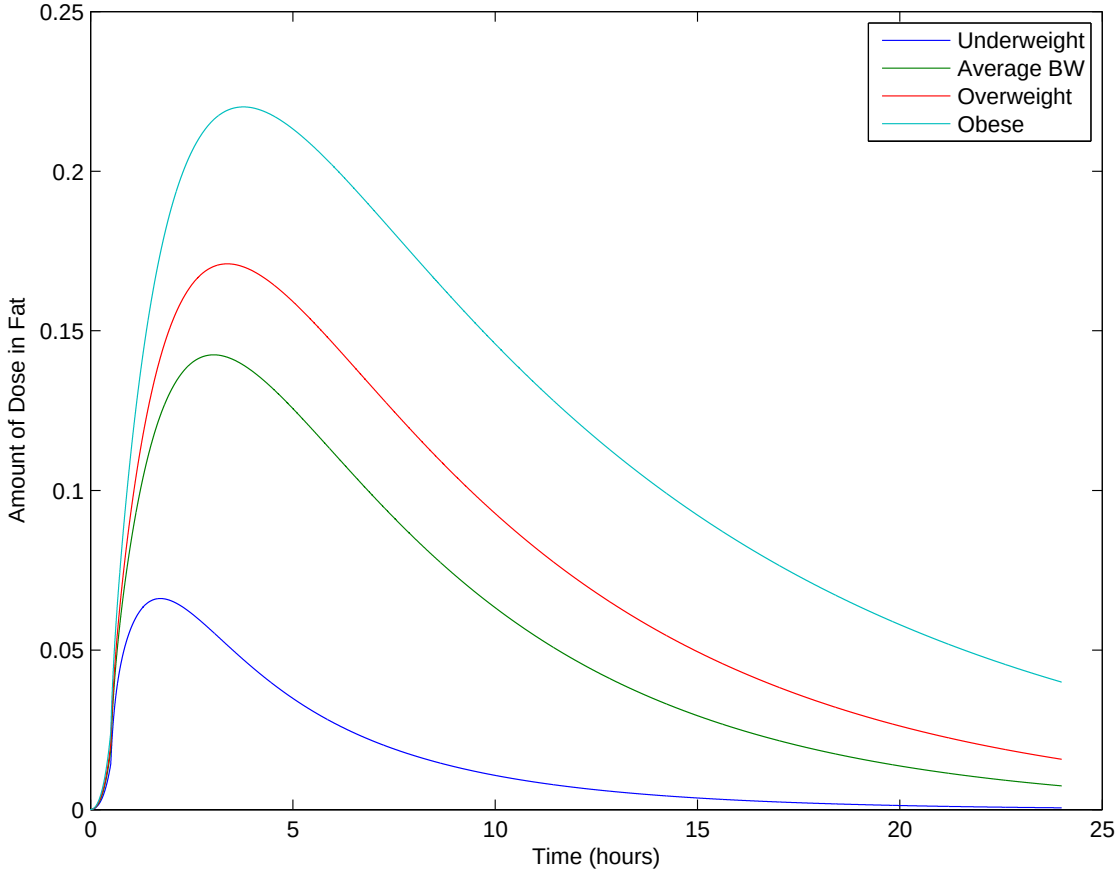

Figure 15: Amount of Dose in the Adipose Tissue (Female BMI)

When looking at the peak for the amount of ertapenem in the adipose tissue, the amount is approximately 0.0022 *mcg* for underweight males, 0.0897 *mcg* for average weight males, 0.1199 *mcg* for overweight males, and 0.1520 *mcg* for obese males. However, the peaks for the females are higher at approximately 0.0661 *mcg* for underweight, 0.1425 *mcg* for average weight, 0.1710 *mcg* for overweight, and 0.2201 *mcg* for obese. As for the minimum amounts, the minimum for males is approximately 0.0000 *mcg* for underweight, 0.0032 *mcg* for average weight, 0.0084 *mcg* for overweight, and 0.0207 *mcg* for obese. Again, the amounts for the females are higher

with minimums at approximately 0.0010 mcg for underweight, 0.0074 mcg for average weight, 0.0158 mcg for overweight, and 0.0399 mcg for obese. The increased amount of ertapenem in the adipose tissue of females is due to the larger volume of adipose tissue. A greater amount staying in the adipose tissue causes the concentration in the blood to be lower has shown above.

4.3 Male BMI - 3 days

The next step we took was studying the concentration when a patient receives a 1 g dose of ertapenem every 24 hours over a period of three days. We used the exact same equations but instead of ending after 24 hours, the model repeats the process for two more days. The only difference is at the beginning of the second and third day. Instead of starting with 0 g of ertapenem at the time of infusion, the model starts out with the concentration of drug still in the body from the previous dose.

As mentioned before, an antibiotic must stay above its MIC level to prevent the risk of a patient developing antibiotic resistant bacteria, but it is also dangerous if the concentration stays too high for too long. Such an event can be toxic to the patient. Figure 16 shows the total concentration in the blood over the three day period and Figure 17 shows the free concentration.

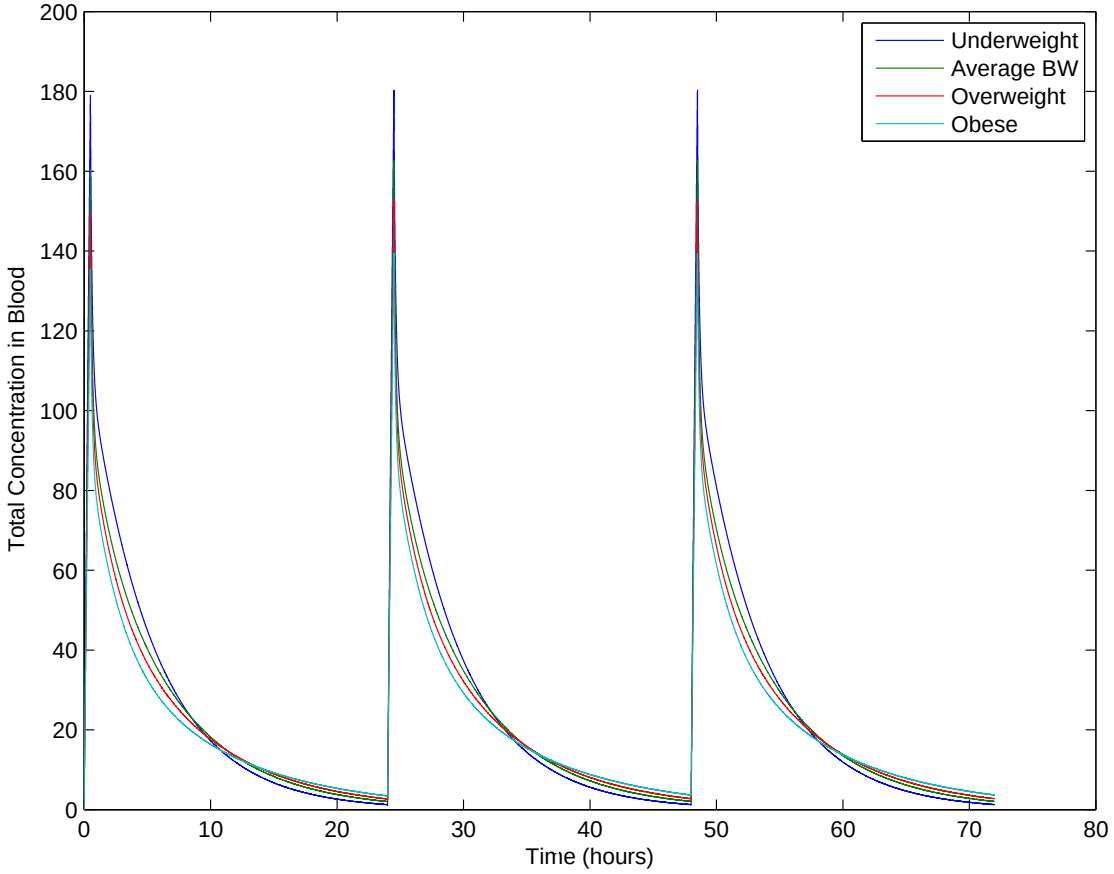

Figure 16: Total Concentration in the Blood (Male BMI - 3 Days)

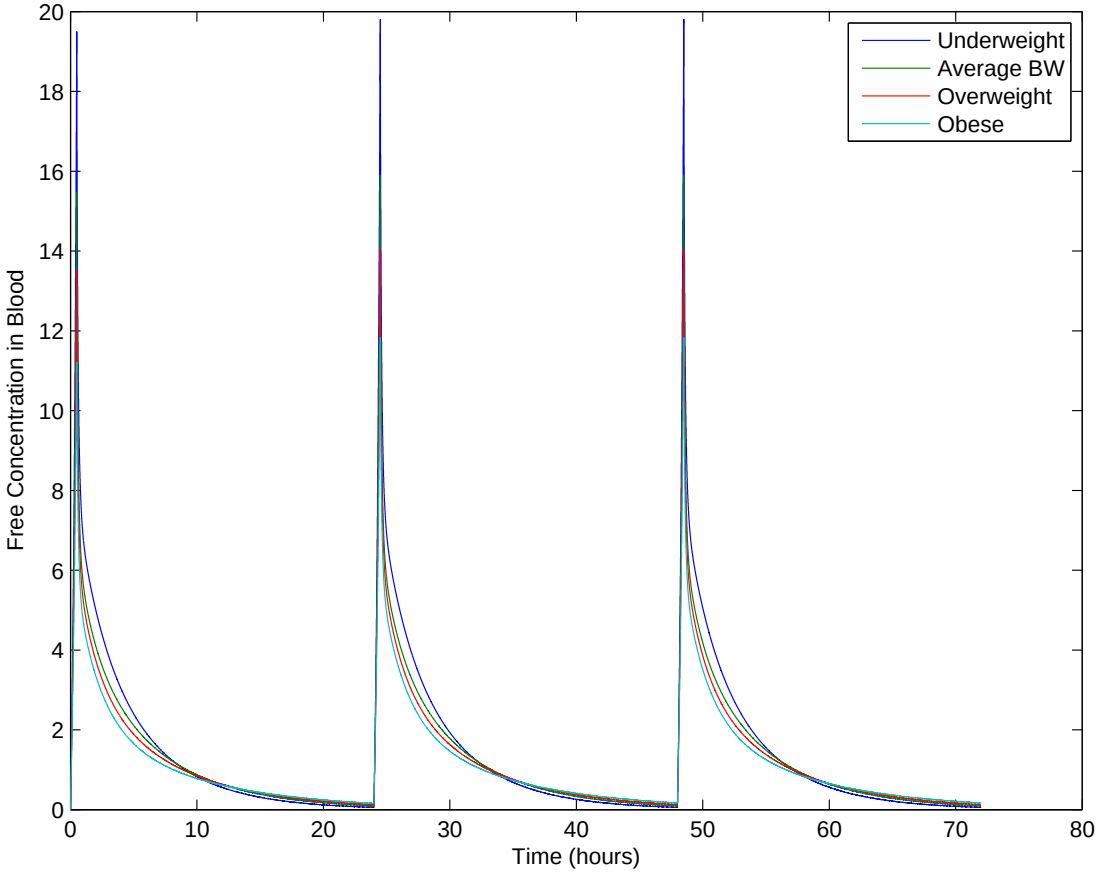

Figure 17: Free Concentration in the Blood (Male BMI - 3 Days)

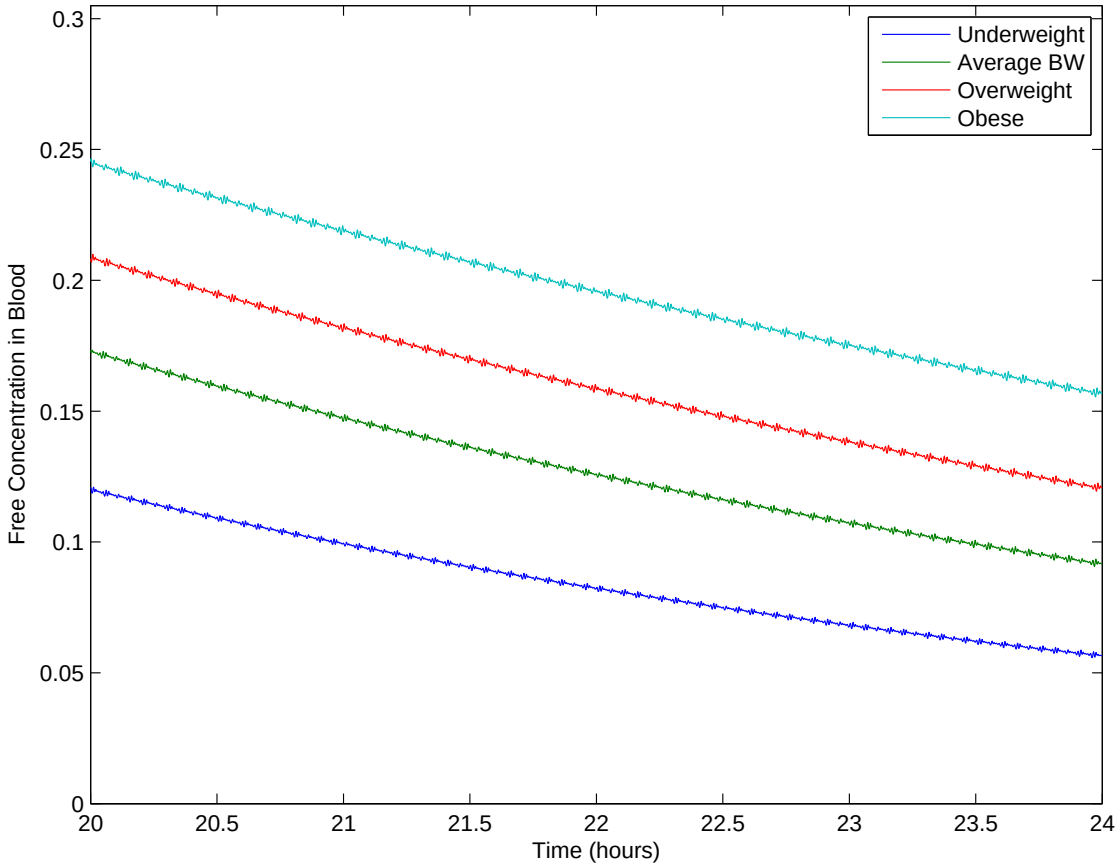

Figure 18: Free Concentration in the Blood Hours 20 to 24 (Male BMI - 3 Days)

Figure 18 above shows the free concentration in the blood over the last four hours of day one and Figure 19 below shows the free concentration in the blood over the last four hours on the third day. For hours 20 to 24, the free concentration in the blood for underweight starts at approximately $0.1205\frac{mcg}{mL}$ and ends at approximately $0.0565\frac{mcg}{mL}$. The values for hours 68 to 72 are approximately $0.1209\frac{mcg}{mL}$ at hour 68 and $0.0572\frac{mcg}{mL}$ at hour 72. For average weight over the hours 20 to 24, the free concentration starts at approximately $0.1733\frac{mcg}{mL}$ and ends at approximately $0.0916\frac{mcg}{mL}$. The values are approximately $0.1757\frac{mcg}{mL}$ for hour 68 and $0.0934\frac{mcg}{mL}$ for hour 72. For overweight

over the hours 20 to 24, the free concentration starts at approximately $0.2083\frac{mcg}{mL}$ and ends at approximately $0.0.1207\frac{mcg}{mL}$. However, for hours 68 to 72, the concentration starts at approximately $0.2143\frac{mcg}{mL}$ and ends at approximately $0.1248\frac{mcg}{mL}$. The difference between hours 20 to 24 and 68 to 72 are greatest for obese. For hours 20 to 24, the concentration starts at approximately $0.2453\frac{mcg}{mL}$ and ends at approximately $0.1569\frac{mcg}{mL}$, and for hours 68 to 72, the concentration starts at approximately $0.2606\frac{mcg}{mL}$ and ends at approximately $0.1670\frac{mcg}{mL}$. As weight increases, the difference between the concentration at hour 24 and 72 increases.

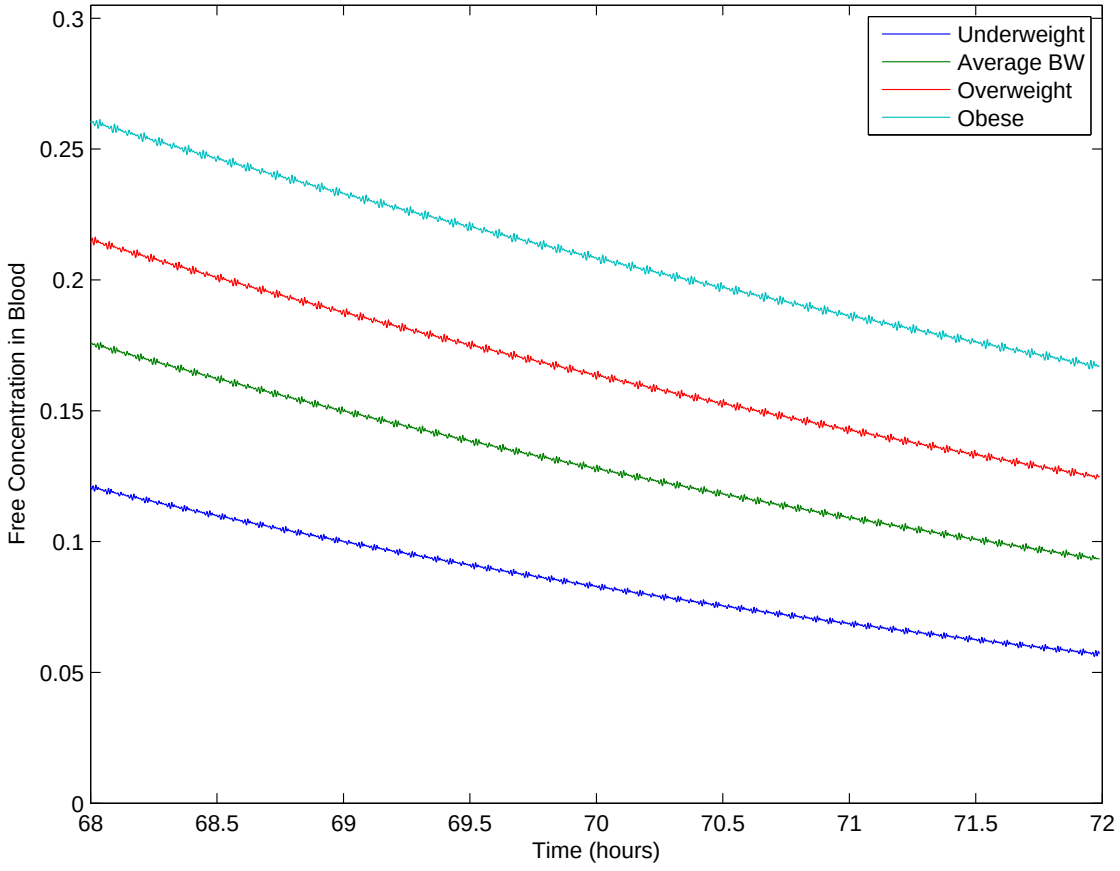

Figure 19: Free Concentration in the Blood Hours 68 to 72 (Male BMI - 3 Days)

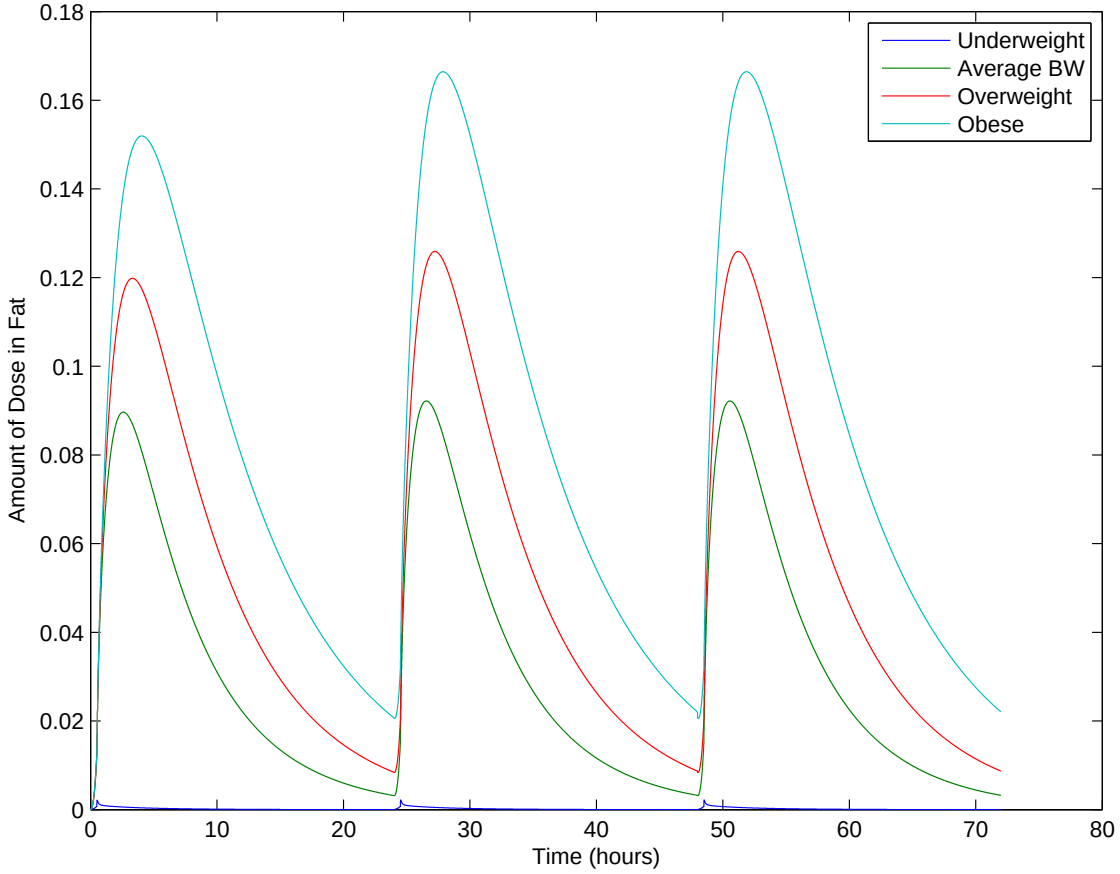

Figure 20: Amount of Dose in the Adipose Tissue (Male BMI - 3 Days)

The peaks right after infusion are higher on the second and third day, but the minimum amounts at the end of each 24 hour period are approximately the same.

4.4 Female BMI - 3 days

This is the same as the previous simulation but it is for females rather than males. It uses the changes described at the beginning of sections 4.2 and 4.3. Figure 21 shows the total concentration in the blood over the three day period and Figure 22 shows the free concentration.

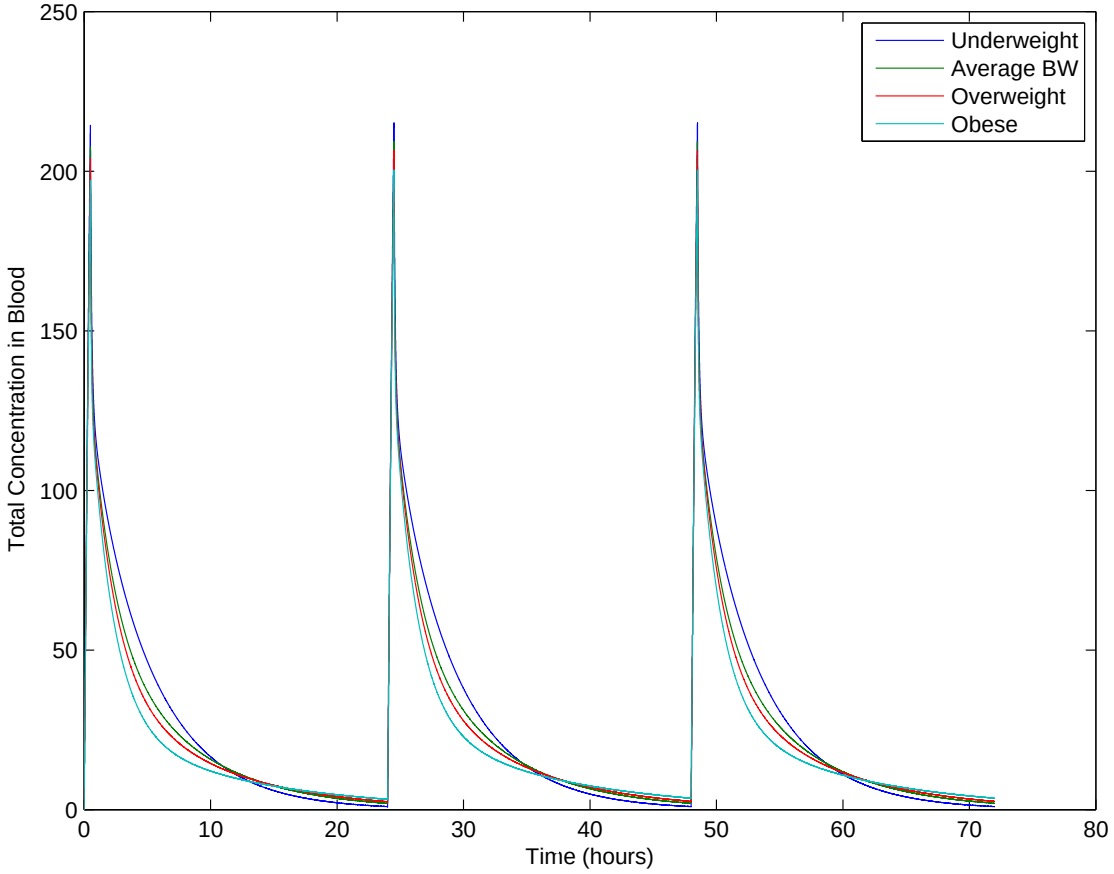

Figure 21: Total Concentration in the Blood (Female BMI - 3 Days)

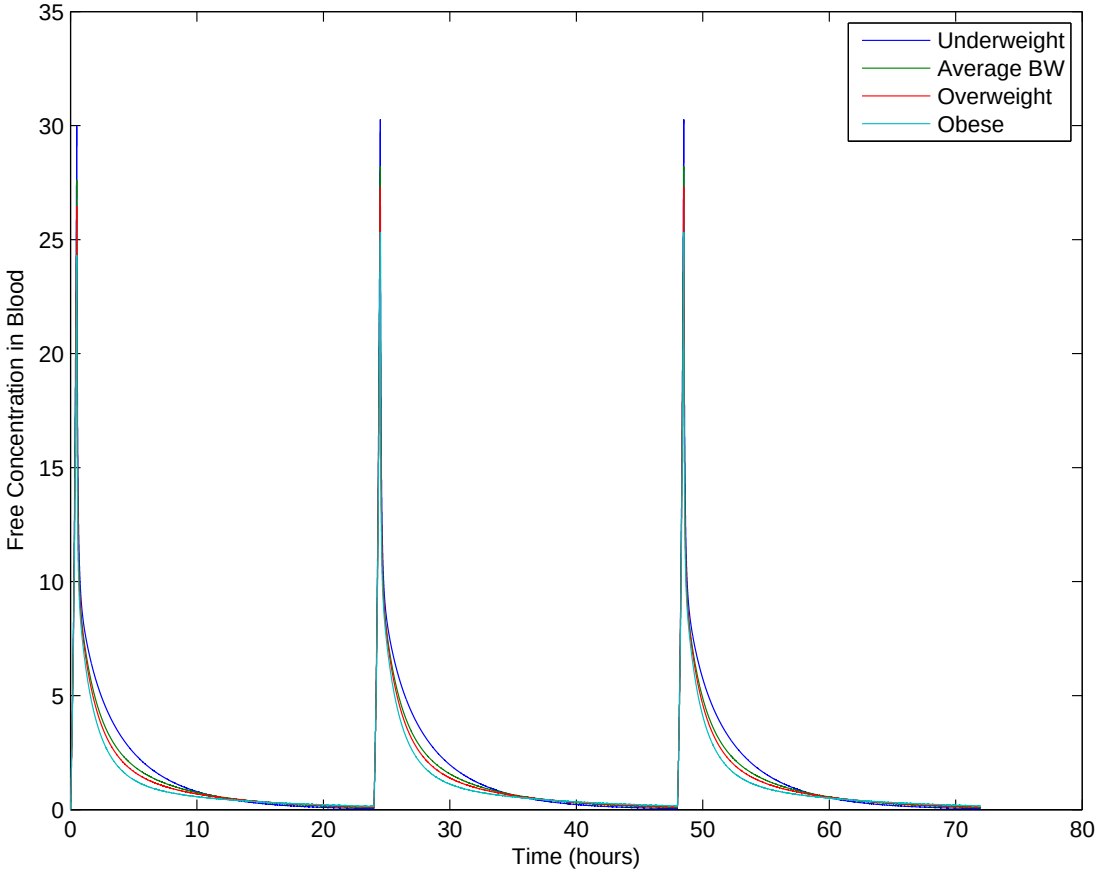

Figure 22: Free Concentration in the Blood (Female BMI - 3 Days)

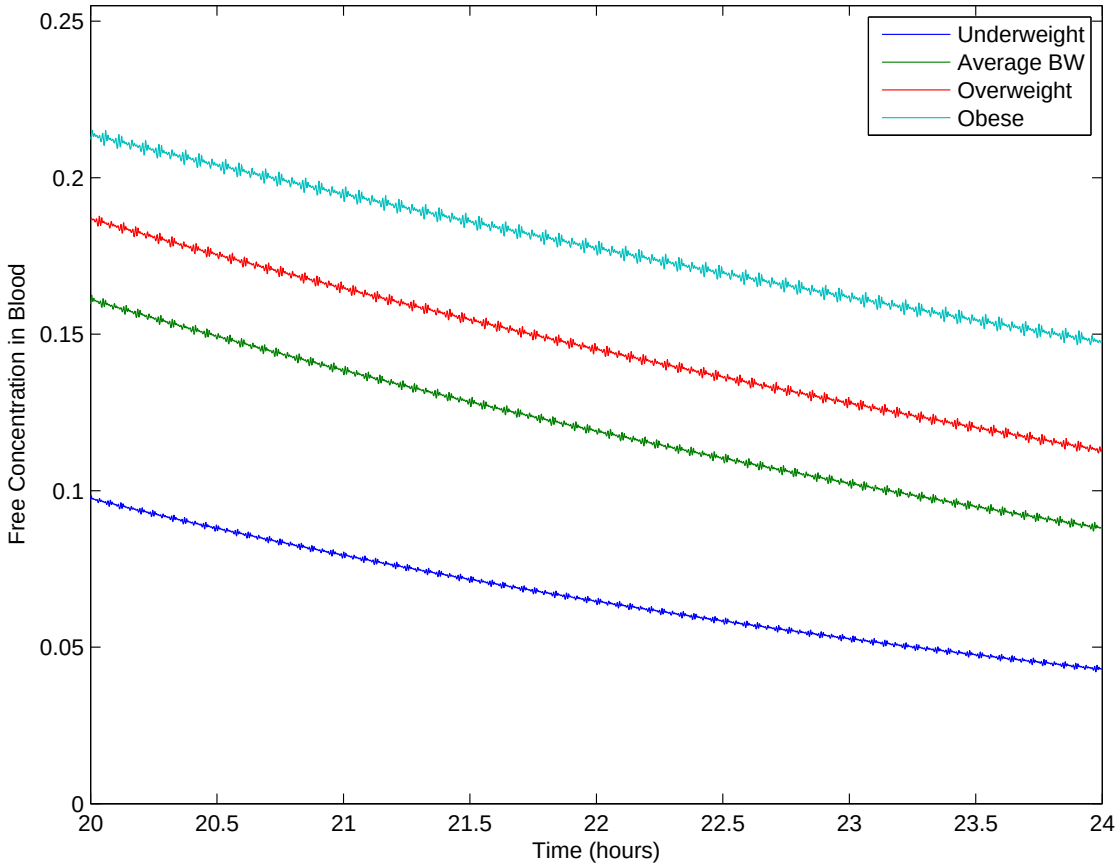

Figure 23: Free Concentration in the Blood Hours 20 to 24 (Female BMI - 3 Days)

Figure 23 above shows the free concentration in the blood over the last four hours of day one and Figure 24 below shows the free concentration in the blood over the last four hours on the third day. For hours 20 to 24, the free concentration in the blood for underweight starts at approximately $0.0971\frac{mcg}{mL}$ and ends at approximately $0.0430\frac{mcg}{mL}$. The values for hours 68 to 72 are approximately $0.0.0981\frac{mcg}{mL}$ at hour 68 and $0.0436\frac{mcg}{mL}$ at hour 72. For average weight over the hours 20 to 24, the free concentration starts at approximately $0.1597\frac{mcg}{mL}$ and ends at approximately $0.0880\frac{mcg}{mL}$. The values are approximately $0.1646\frac{mcg}{mL}$ for hour 68 and $0.0902\frac{mcg}{mL}$ for hour72. For overweight over

the hours 20 to 24, the free concentration starts at approximately $0.1868\frac{mcg}{mL}$ and ends at approximately $0.1134\frac{mcg}{mL}$. However, for hours 68 to 72, the concentration starts at approximately $0.1954\frac{mcg}{mL}$ and ends at approximately $0.1187\frac{mcg}{mL}$. The difference between hours 20 to 24 and 68 to 72 are greatest for obese. For hours 20 to 24, the concentration starts at approximately $0.2122\frac{mcg}{mL}$ and ends at approximately $0.1478\frac{mcg}{mL}$, and for hours 68 to 72, the concentration is higher starting at approximately $0.2351\frac{mcg}{mL}$ and ending at approximately $0.1639\frac{mcg}{mL}$. The amount of difference between hours 24 and 72 are higher for females, but the values of the concentrations are all slightly higher for males.

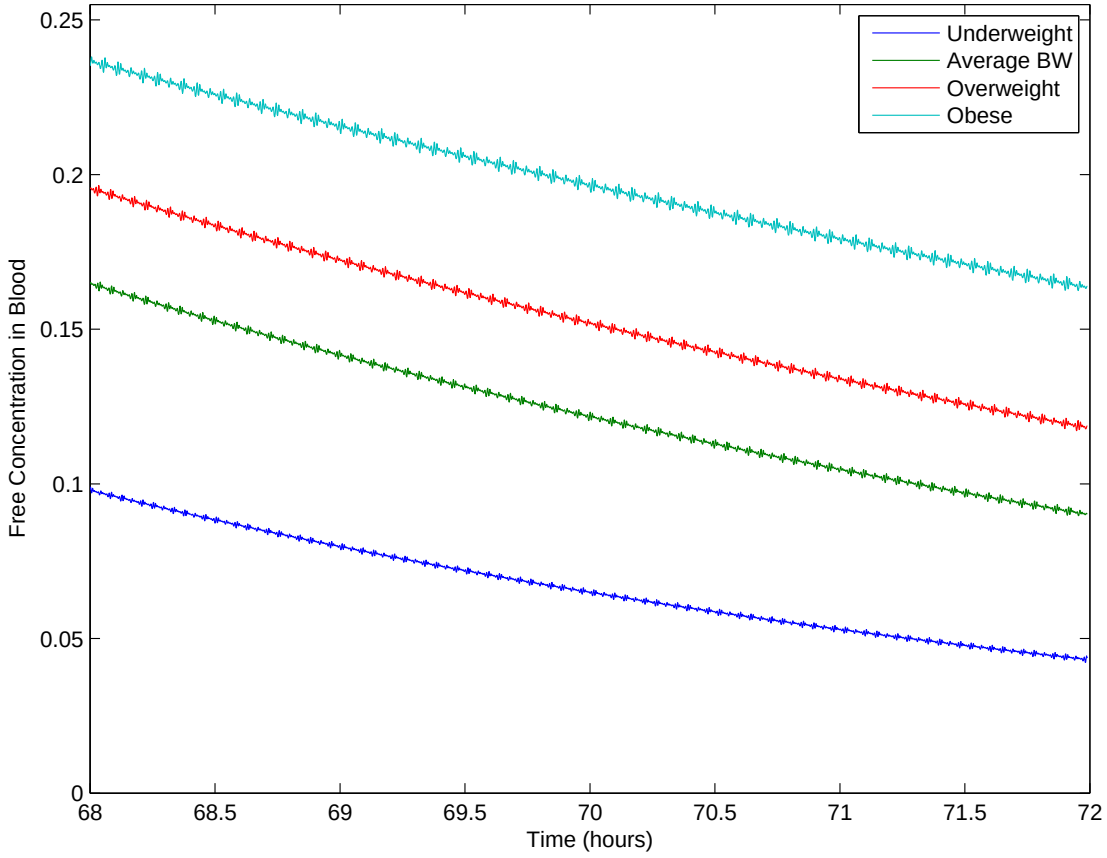

Figure 24: Free Concentration in the Blood Hours 68 to 72 (Female BMI - 3 Days)

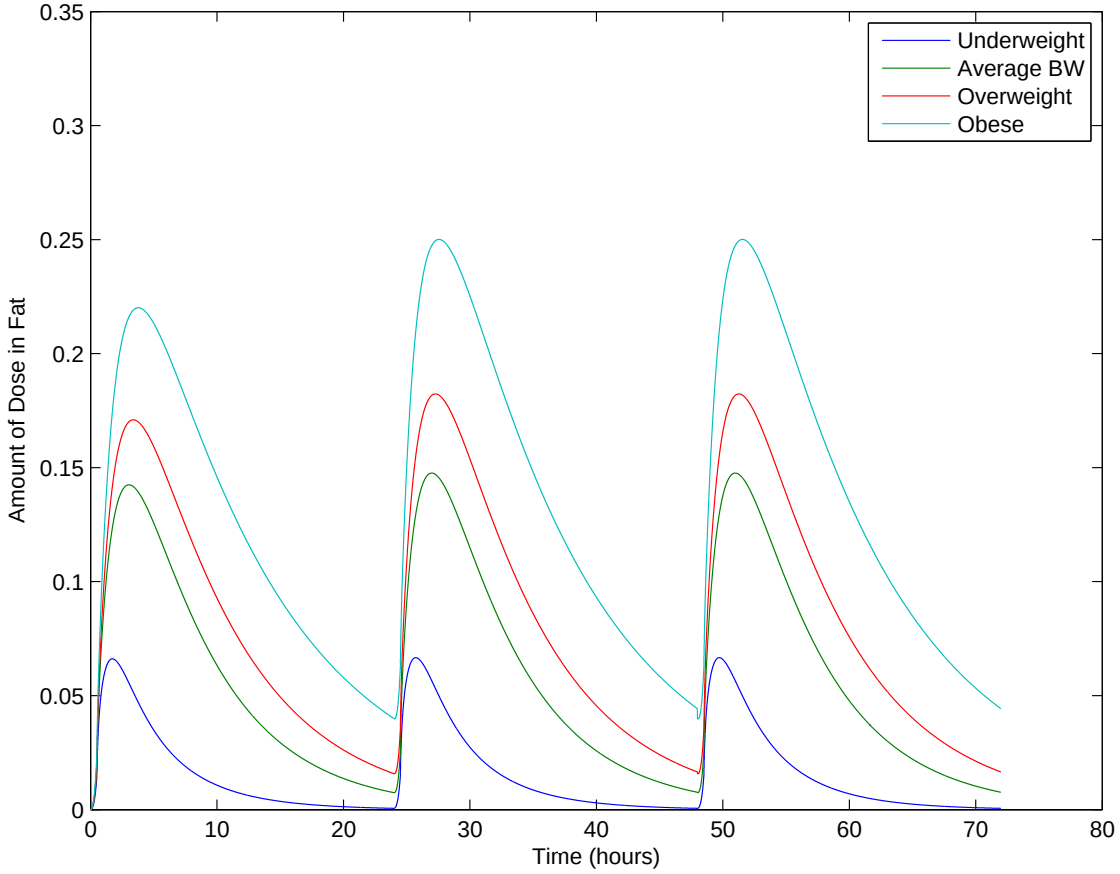

Figure 25: Amount of Dose in the Adipose Tissue (Female BMI - 3 Days)

Just as in the model for the males, the peaks right after infusion are higher on the second and third day, but the minimum amounts at the end of each 24 hour period are approximately the same.

5 SENSITIVITY ANALYSIS

PBPK models rely on physiological constants such as blood flow rates and tissue volumes. These constants also have terms they rely on. The blood flow rates for the individual tissue compartments were calculated as fractions of the total blood flow, but the total blood flow is calculated based on body weight. The individual tissue volumes depend on body height, body weight, and age. Specifically, the volume of the gut depends on body weight; the volume of the blood and adipose tissue depends on body height and weight; the volume of the kidneys depends on body height, body weight, and age; and the volume for the "other tissues" compartment depends on body weight and the volumes of the other compartments. PBPK models also rely on drug specific parameters such as the clearance rate of ertapenem through the kidneys and gut, k_U and k_F respectively. Therefore, we tested our basic model's sensitivity to the parameters body height, body weight, age, k_U, and k_F.

Sensitivity analysis allowed us to determine if slight changes in those parameters would have a large affect on the concentrations produced by our model. If a particular parameter is considered to be sensitive, it is crucial that the value used in the model is accurate in order for the model to be reliable. The sensitivity of a state variable to the parameters is determined by calculating $\frac{\partial C_{tissue}}{\partial q_j}$ for each state variable C_{tissue} and each parameter q_j where

$$C_{tissue} = \{C_F, C_K, C_G, C_{OT}, C_{Bl}\} \ \ and \ \ q = \{BH, BW, AGE, k_U, k_F\}.$$

To calculate the relative sensitivity which determines which parameter has the

most effect on each state variable, we used the modified L_2 norm

$$\left|\left|\frac{\partial C_{tissue}}{\partial q_j}\right|\right|_2 = \left[\frac{1}{t_f - t_0}\int_{t_0}^{t_f}\left(\frac{\partial C_{tissue}}{\partial q_j}\right)^2 dt\right]^{\frac{1}{2}} \frac{q_j}{maxC_{tissue}}$$

which normalizes the sensitivity values by removing the units. Figure 26 shows the relative sensitivities of body height, body weight, age, k_U, and k_F for the concentration of each compartment.

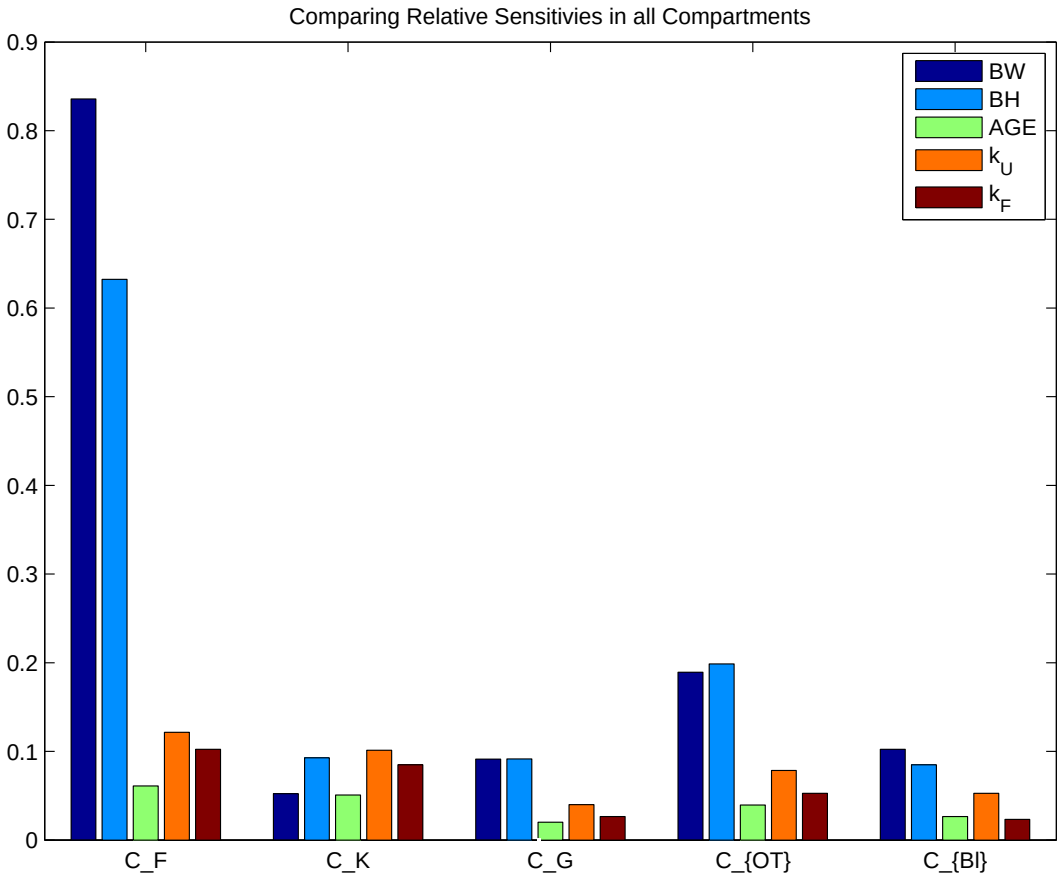

Figure 26: Relative Sensitivities

The adipose tissue compartment is most sensitive to body weight and height which is understandable considering a person's body weight and height extremely

effects the volume of the adipose tissue. Neither the kidney nor gut compartments are very sensitive to any of the parameters. The sensitivity for body weight and height is slightly raised for the "other tissues" compartment. This is because the volume and blood flow rate of the "other tissues" compartment is dependent on the volumes and blood flow rates of the other compartments. Therefore, since the adipose is so sharply sensitive to body weight and height, that sensitivity is passed on to the "other tissues" compartment.

6 CONCLUSIONS

We built a physiologically-based pharmacokinetic model for the antibiotic ertapenem. In order to do so, we had to use both physiological constants and drug specific parameters where some of the parameters had to be estimated. We were able to build a basic model that only has a 4.25% error when compared to clinical data. After completing the basic model, we were able to study the affects of body mass index and gender on the concentration of ertapenem throughout the body. We looked at one $1g$ dose over a 24 hour period and three $1g$ doses given every 24 hours over a 72 hour period for both males and females. We saw that the free concentration in the blood, which is the part that is considered to be medicinally effective, is higher for males than females and it is slightly higher in overweight and obese patients at the end of 72 hours when compared to the concentration at the end of 24 hours.

In the future, this model can be used to study the minimum inhibitory concentration level. It can also be expanded to study the effects health conditions may have on the concentration throughout the body. Health conditions which effect the renal system for example might change the concentration due to the drug not being able to be excreted through the feces properly.

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