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A Physiologically-Based Pharmacokinetic Model for the Antibiotic Levofloxacin

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ABSTRACT

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Levofloxacin is in a class of antibiotics known as fluoroquinolones, which treat infections by killing the bacteria that cause them. A physiologically-based pharmacokinetic (PBPK) model was developed to investigate the uptake, distribution, and elimination of Levofloxacin after a single dose. PBPK modeling uses parameters such as body weight, blood flow rates, partition coefficients, organ volumes, and several other parameters in order to model the distribution of a particular drug throughout the body. Levofloxacin is only moderately bound in human blood plasma, and, thus, for the purposes of this paper, linear bonding is incorporated into the model because the free or unbound portion of the drug is the only portion that is considered to be medicinally effective. Parameter estimation is then used to estimate the two unknown parameters given clinical data from literature on the total concentration of Levofloxacin in the blood over time. Once an adequate model is generated, the effects of varying Body Mass Index are tested for the absorption and distribution of Levofloxacin throughout the body.

ACKNOWLEDGMENTS

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1 Introduction

As described in Reference [19], pharmacokinetics is the study of the effect the body has on drugs. This branch of science focuses on answering the questions of how a particular drug enters the body, where the drug goes once it is inside the body, and how the body gets rid of the drug. Associated with the study of pharmacokinetics is the acronym ADME. The 'A' stands for absorption, the 'D' stands for distribution, the 'M' stands for metabolism, and the 'E' stands for excretion. Thus, the acronym ADME lists the different phases a drug goes through when being administered to an individual. The absorption of a drug is how the drug enters the body. There are various methods for how a particular drug enters the body. These methods include oral administration, intravenous administration, intraperitoneal administration, intramuscular administration, and inhalation administration. The most common route for drug administration is the oral method. Again, the 'D' in ADME stands for distribution, which is where the drug goes in the body once it has been administered to a patient. This includes how a particular drug is distributed throughout the body and what portion of the drug is considered to be bound or unbound. The 'M' stands for metabolism. Metabolism is how the body chemically modifies a particular drug. This process often takes place in the liver but can occur elsewhere, such as the lungs or gut. There are different enzymes that metabolize different drugs. For instance, the enzyme Cytochrome 1A2 metabolizes caffeine, and the enzyme Cytochrome E1 metabolizes alcohol. These enzymes metabolize these drugs in a variety of processes. These processes are oxidation, hydrolysis, and hydroxylation. The 'E' in ADME stands for excretion, which is the irreversible removal of a particular drug from the

body. Most drugs are excreted by the kidney through the urine, but drugs can also be excreted in the feces through the hepatic-biliary-liver system or in the sweat [19].

Physiologically-based pharmacokinetic (PBPK) modeling is a type of modeling that examines and predicts the absorption, distribution, metabolism, and excretion of a particular drug through the use of mathematical models. In order to use PBPK modeling, compartments that will be used in the model for the particular drug must be established. The common compartments used among various different types of drugs for PBPK modeling are the blood, kidney, gut, fat or adipose tissue, other tissues, metabolism, urine, and feces [19]. The compartments that should be used in the PBPK model for a drug are dependent upon the effects the drug has on various organs and tissues, how it is administrated and excreted, and what one is hoping to model. To better explain, take for instance the drug ertapenem. As explained in Reference [7], this drug is administered intravenously, or through the blood, and then distributed to various organs throughout the body. As a result, blood must be one of the compartments used in the model for this particular drug. Another aspect of the drug that must be taken into consideration when creating a model for a particular drug is determining what an individual is hoping to find out about the drug. For example, again using the drug ertapenem, one could hope to discover the effect that body mass index (BMI) has on the distribution of the drug as done by Whitney Forbes in her thesis [7]. Because BMI deals with adipose tissue or fat, this compartment must be a part of the model as this is what is being studied. The method of excretion for a particular drug must also be taken into account when creating the PBPK model. Again using ertapenem, it is metabolized in the kidney and gut and

then excreted in the urine and feces respectively. Thus, the kidney and gut must also be compartments in the PBPK model [7]. Since these are the compartments needed for this particular study, all other tissues are then lumped together in a compartment labeled other tissues. Again, the compartments are established for a particular drug based on which organs the drug affects the most, how the drug is administered and excreted, and what one is hoping to study. These are the basics behind the development of the PBPK model. The mathematics involved in the model will be explained in the following sections.

Once the compartments have been established, how the drug is broken down or activated must be taken into account. This is a key step in determining the mathematical equations. To begin, one must examine the different portions of the drug, specifically the bound and unbound concentrations of the drug. The bound concentration of the drug is the portion of the drug that stays in the blood until it is released in a linear or non-linear way. The unbound, or free, concentration of the drug is the portion of the drug that is considered to be medicinally effective [7].

For the purposes of this paper, PBPK modeling will be used to examine the drug Levofloxacin. Levofloxacin is in a class of antibiotics known as fluoroquinolones, which treat infections by killing the bacteria that cause them [13]. Levofloxacin was approved for use in the United States in 1996 [4]. The chemical structure of Levofloxacin is shown in Figure 1 below [14]. This particular drug can be used for a variety of purposes with regards to different types of infections. These various types of infections include pneumonia, chronic bronchitis, skin infections, urinary tract infections, sinus infections, prostate infections, and kidney infections [13]. As

explained in Reference [6], this particular drug can also be used to prevent anthrax infections for individuals who have been exposed to its germs in the air. The length of time this particular drug is taken is dependent upon the type and severity of the infection. However, no matter the length of time, it is important to finish the prescription and not simply stop taking the antibiotic when an individual believes he or she is better [5, 21]. In the following sections, we will derive the PBPK model for Levofloxacin.

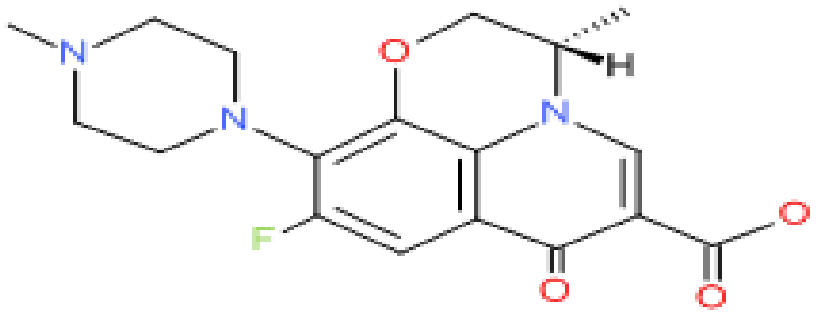

Figure 1: Levofloxacin Chemical Structure [14]

2 Model

For the purposes of this paper, we assume Levofloxacin is administered intravenously, which means it goes directly to into the bloodstream. From the blood stream, the drug is then distributed throughout the body and enters the various compartments representing portions on the body. The overall goal of the research conducted on Levofloxacin is to see how the drug is effected by body mass index, BMI. Therefore, compartments were chosen in which the effect of altering the BMI could be seen. The

compartments for our PBPK model of Levofloxacin will be the blood, adipose tissue (fat), the gut, the kidney, and other tissues, which consists of the rest of the body. The blood compartment was chosen for the model because the drug is administered intravenously, which is directly into the blood stream. The adipose compartment was chosen because the effects of BMI on the distribution of the drug will be examined. The kidney and gut were chosen due to the fact that they represent the routes of excretion for Levofloxacin. Lastly, the other tissues compartment because it encompasses all of the other tissues. After the drug travels through a particular compartment, it returns to the blood stream, and the process is repeated. Levofloxacin is administered daily, and, thus a 24 hour period is used in our model, with the dose for Levofloxacin being 750 mg [9]. The schematic for our model is given in Figure 2 below.

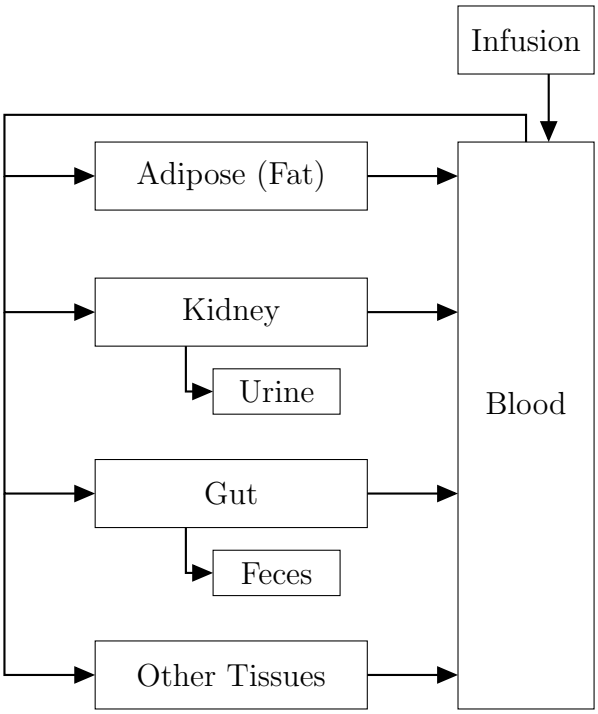

Figure 2: Schematic Representation of the Compartment Model [7]

The rate of infusion for a particular drug is the rate at which the drug is administered. Thus, for Levofloxacin, the rate of infusion, denoted R_I, is given by the following:

$$R_I = \begin{cases} 0 & \text{if } t > 1.5 \\ \\ \frac{D}{1.5} & \text{if } 0 < t < 1.5. \end{cases} . \tag{1}$$

Levofloxacin is administered over a 90 minute period. In the above equation, $t > 1.5$ stands for when the time exceeds 90 minutes, as $t = 1$ is one hour and, thus, $t = 1.5$ is 90 minutes [5]. When the time exceeds 90 minutes, the drug is no longer being

administered. Thus, the rate of infusion is 0. When the time is less than 90 minutes, the rate of infusion is $\frac{D}{T_I}$, where D is the dosage of 750 mg and T_I is the length of time for the infusion.

For each drug, there is a free or unbound concentration in the blood and a bound concentration of the drug in the blood [7]. The total concentration of the drug in the blood can then be given by the following equation:

$$C_{Bl} = C_{Bf} + C_{Bound},$$

where C_{Bl}, C_{Bf}, and C_{Bound} stand for the total concentration of the drug in the blood, the free concentration of the drug in the blood, and the bound concentration of the drug in the blood, respectively.

Levofloxacin has been found to range from 24-38% bound; therefore, it is only moderately bound to serum proteins [4]. It is important to remember why it is that the free portion of the drug must be calculated. The free or unbound portion of a particular drug is the part of the drug that is medicinally effective as it saturates the tissues and can be excreted [8]. The bound portion remains in the blood bound to the plasma [7]. Levofloxacin is 24-38% bound, so, for the purposes of this paper, when finding an equation for the bound portion of the drug, we will use an approximate percentage of 30%. Hence, the equation for the bound concentration of the drug is

$$C_{Bound} = 0.30 * C_{Bl}.$$

In order to rewrite the equation for the total concentration of the drug in the blood, the above equation can be substituted for the bound concentration of the

blood to produce the following equation

$$C_{Bl} = C_{Bf} + 0.30 * C_{Bl}.$$

If the above equation for the total concentration is then manipulated to solve for the free concentration, we have the following:

$$C_{Bf} = C_{Bl} - 0.30 * C_{Bl} = 0.70 * C_{Bl}. \tag{2}$$

In order to calculate the the concentration of the drug in each compartment, the volumes of the various compartments must also be calculated. We assume all of the subjects were male with the average measurements for height (BH) and weight (BW). The values used for the BH and BW are assumed to be 1.75 meters and 72 kilograms, respectively [20]. The subjects' height and weight were then used to calculate the volumes of the various compartments used in the model. The equations for the volumes compartment are given by the following equations:

$$\begin{aligned} V_{Bl} &= \frac{13.1(BH*100)+18.05(BW)-480}{0.5723} \\ V_K &= 15.4 + 2.04(BW) + 51.8(BH)^2 \\ V_F &= \frac{PBF}{100} * \frac{\frac{BW}{10^9}}{0.923} * 1000 \\ V_G &= 0.0171 * (BW) * 1000, \end{aligned}$$

$$\begin{aligned} \text{PBF} = {} & 785.58 - (563.95 * f(\text{Age})) - (27.12 * \text{Sex}) - \\ & (1199.65 * f(\text{BMI})) + (461.04 * f(\text{BMI})^2) + \\ & (63.08 * f(\text{BMI}) * \text{Sex}) + (822.11 * f(\text{BMI}) * f(\text{Age}) - \\ & (25.31 * f(\text{BMI})^2 * \text{Sex}) - (295.51 * f(BMI)^2 * f(\text{Age})) \end{aligned}$$

where V_{Bl}, V_K, V_F, and V_G stand for the volume of the blood, volume of the kidney, volume of the fat, and volume of the gut, respectively. The equations for V_{Bl} and V_K were found in reference [18], the equation for V_G was found in reference [16], and the equations for V_F and PBF were found in reference [15]. Here, it is important to note that PBF stands for percent body fat, which is used to find the volume of the fat compartment as shown in the above equations. For the purposes of this paper, the sex = 0, indicating a male, and the age = 40, indicating 40 years of age. The volume of the other tissues compartment is calculated by taking a fraction of the total body weight that is not included in the other compartments, i.e. the blood, adipose, kidney, or gut. Thus, an equation for the body weight (BW) must be found. According to the International Life Sciences Institute [10], the density of most soft tissues falls between 0.95 and 1.05. There are only a few tissues with densities outside the range from 0.9 to 1.1. Thus, in order to formulate an equation for BW, it must first be assumed that the total volume of the body is equal to the body weight. In order to change the units for BW, the following equation can be used:

$$BW = Volume * \frac{1kg}{1L} * \frac{1L}{10^3 mL} [7].$$

Thus, as stated above, the equation for the volume of the other tissues compartment (V_{OT}) can now be constructed:

$$V_{OT} = BW * 1000 - (V_{Bl} + V_F + V_K + V_G).$$

Another important aspect of the mathematical model is the flow rate, denoted Q. It is of the utmost importance as the rate at which the drug flows through the various compartments in the body must be known in order to make the model work.

The total flow rate in the body can be calculated using the body weight (BW). The equation for the total flow rate in the body is the following:

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

Because the compartments are a percentage of the total body, it is also true that the flow rates for the various compartments are percentages of the flow rate for the total body. The different flow rates for the various compartments are listed in Table 1, which were found in References [2] and [16]:

Table 1: Flow Rates

Parameter	Value	Reference
Q_{Total}	$235 * (BW)^{0.71} * 60$	[2]
Q_F	$0.052 * Q_{Total}$	[16]
Q_K	$0.19 * Q_{Total}$	[16]
Q_G	$0.17 * Q_{Total}$	[16]
Q_{OT}	$Q_{Total} - (Q_F + QK + Q_G)$	[16]

Note that, in Table 1, Q_{OT} is defined as a fraction of Q_{Total} that is not in the adipose, kidney, or gut compartments. For the purposes of this paper, the venous-equilibrium model was used for the various tissue compartments. Through this model, one is able to conclude that the drug is able to reach an equilibrium concentration between the tissue and the blood in the amount of time it takes the blood to perfuse the tissue [7]. From this, one is able to then conclude that the concentration of Levofloxacin leaving the compartment in the venous blood is at equilibrium with the concentration of Levofloxacin in the compartment. Thus, a partition coefficient for

the equilibrium in the various tissues muse be introduced. This equilibrium partition coefficient will be represented as P_i, where i represents the various tissues represented by the compartments.

Various partition coefficients are needed for this mathematical model to work and be successful. The partition coefficients in the model represent the tissue's solubility. These coefficients are then able to let one know the percentage of the concentration of the drug that can flow from the various tissue compartments back to the blood. To better understand exactly what the partition coefficients stand for and their importance, consider the following example: If the partition coefficient for the kidney is $P_K = 1.5135$, then $1mL$ of kidney tissue can hold 1.5135 times as much Levofloxacin as $1mL$ of blood [7]. "The partition coefficients vary for each drug, and, thus, were calculated using an algorithm first introduced by Poulin and Krishman," [17]. This algorithm uses partition coefficient data that is based on n-octanol:water. The equation used in the algorithm uses both drug specific and physiological parameters to produce the following equation for the partition coefficient of the various tissues:

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

In the above equation, S_o and S_w are the solubility of the drug in n-octanol and water, respectively. Next, P_t, W_t, and N_t are the fractions of the tissue's volume that are phospholipids, water, and neutral lipids, respectively. On the other hand, P_b, W_b, and N_b are the fractions of the blood volume that are phospholipids, water, and neutral

lipids, respectively. The S_o and S_w values are drug specific, and, thus, had to be found in literature. For Levofloxacin, $S_w = 1.44 mol/m^3$ [1]. The S_o values was not available, and, thus, had to be calculated using the following equation:

$$S_o = K_{ow} * S_w.$$

In this equation, K_{ow} is the octanol-water partition coefficient. It is also important to note that $logP$ is equivalent to the K_{ow}, as the $logP$ value is what is reported in the literature [11]. It was found that $logP = K_{ow} = 4.3$ [22]. In this algorithm, the partition coefficient for the other tissues compartment was calculated as the muscle:blood partition coefficient. The following partition coefficients for the various compartments were calculated through the algorithm mentioned above and are listed in Table 2.

Table 2: Partition Coefficients

Parameter	Value
P_F	4.96
P_K	1.16
P_G	0.91
P_{OT}	1.12

A set of differential equations representing the change in concentration of the drug in each compartment over time ($\frac{dC_{tissue}}{dt}$) was constructed. This set of differential equations is referred to as the ODE System and is given in Equation (3).

$$
\begin{aligned}
V_F \frac{dC_F}{dt} &= Q_F(C_{Bf} - \frac{C_F}{P_F}) \\
V_K \frac{dC_K}{dt} &= Q_K(C_{Bf} - \frac{C_K}{P_K}) - k_U C_K \\
V_G \frac{dC_G}{dt} &= Q_G(C_{Bf} - \frac{C_G}{P_G}) - k_F C_G \\
V_{OT} \frac{dC_{OT}}{dt} &= Q_{OT}(C_{Bf} - \frac{C_{OT}}{P_{OT}}) \\
V_{OT} \frac{dC_{OT}}{dt} &= Q_{OT}(C_{Bf} - \frac{C_{OT}}{P_{OT}}) \\
V_{Bl} \frac{dC_{Bl}}{dt} &= Q_F C \frac{C_F}{P_F} + Q_K \frac{C_K}{P_K} + Q_G \frac{C_G}{P_G} + Q_{OT} \frac{C_{OT}}{P_{OT}} - Q_{Total} C_{Bf} + R_I \\
\frac{dA_U}{dt} &= k_U C_K \\
\frac{dA_F}{dt} &= k_F C_G
\end{aligned}
\tag{3}
$$

In the above equations, C_{Bf} and R_I are given in Equations (2) and (1), respectively. We assume that prior to infusion, there were no traces of Levofloxacin in the body. Thus, all initial conditions for the model are zero. A summary of variables and parameters for the model is given in Table 3 below.

Table 3: Definitions of Model Variables and Parameters

Symbol	**Description**	**Units**
C_i	Concentration of Levofloxacin in tissue i	mcg/mL
C_{Bf}	Concentration of free Levofloxacin in the blood i	mcg/mL
A_U	Amount of Levofloxacin in urine	mcg
A_F	Amount of Levofloxacin in feces	mcg
V_i	Volume of tissue i	mL
Q_i	Flow Rate in tissue i	mL/hr
t	Time	hr
P_i	Blood partition coefficient of tissue i	dimensionless
BW	Body Weight	kg
BH	Body Height	m
R_I	Rate of Infusion	mcg/hr
D	Dose	mcg
T_I	Length of Infusion	hr
k_U	First-order rate constant of urine excretion	mL/hr
k_F	First-order rate constant of feces excretion	mL/hr

3 Parameter Estimation

There are two unknown parameters, k_U (first-order rate constant of urine excretion) and k_F (first-order rate constant of feces excretion), which are estimated in this section. For Levofloxacin, clinical data was found for the total concentration of the drug in the blood at corresponding time points. This data was then extracted using an extraction program in Matlab, known as GRABIT, which extracts data from a file image [3]. The clinical data found in Reference [12] is given in Table 4:

Table 4: Clinical Data for the Total Concentration of Levofloxacin [12]

Time (t_j) (hr)	Total Concentration ($C_{Bl}(t_j) \equiv y_j$) (mcg/mL)
1.07	8.44
1.64	11.28
2.16	8.19
3.15	7.07
4.06	6.47
5.14	5.75
6.14	5.29
8.04	4.40
12.03	3.02
24.02	1.04
30.01	0.46
36.01	0.28

It important to note that the data given in Reference [12] is based on 36 hours since the time of infusion, even though we are primarily analyzing the total concentration of the drug over a 24 hour time period because Levofloxacin is administered once

a day. However, in hopes of obtaining more accurate results, all of the data points given in the literature were implemented into our program in Matlab.

The goal of parameter estimation is to find parameter values for the unknown parameters such that the model is a good approximation of the measured concentrations in the blood and the measured excretion. Both the data in Table 4 and the fact that 80 percent of Levofloxacin is excreted in the urine within a 24-hour period are used to estimate k_U and k_F. In order to estimate these values, an inverse problem was implemented. In the inverse problem, J is our cost function,

$$J(q) = \sum_{j=1}^{N} \left(\frac{\hat{y}_{1j} - C_{Bl}(t, \mathbf{q})}{C_{Bl}(t, \mathbf{q})} \right)^2 + \left(\frac{0.8 - A_U(24, q)}{A_U(24, q)} \right)^2. \tag{4}$$

For a specific value of k_U and k_F, the cost function calculates the difference between both the blood concentrations and urine excretions given by our model versus the data. These are then summed up for the values at each time step. The goal is to minimize this function in order to match the model output with the data found in literature as closely as possible using a program called *fminsearch*, which is a Matlab built in program. The function *fminsearch* uses a Nelder-Mead algorithm to choose new parameter values based on the calculated value of J. Once a certain criteria is met, the program outputs the optimal values for the parameters, which in this case are k_U and k_F. These values can then be used in the model. Once the cost function is minimized, one is able to assert that the model output matches the clinical data as closely as possible.

4 Results

After parameter estimation, the results are ready to be analyzed. Figure 3 below illustrates our model for the total concentration of the drug in the blood over a 24 hour period. We are interested in how our blood concentration levels match up to the data. We are also interested in our urine excretion with regards to it matching the data listed in Table 2.

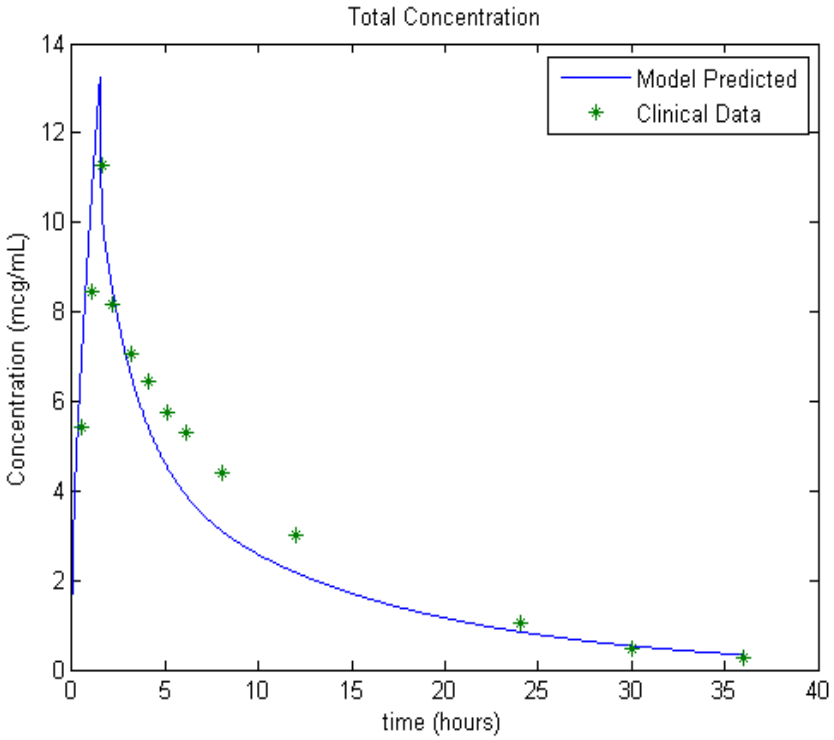

Figure 3: Total Concentration

From the graph, one can the see that the peak point for the clinical data and our model data match up fairly well. The ending values for the total concentration from our model data also matches up fairly well with the ending values for the clinical

data. The final concentrations of the graph are of concern because this is the area in which the minimum inhibitory concentration level becomes important. The minimum inhibitory concentration (MIC) level is the level at which, if the concentration of the drug in the blood falls below this level, the patient becomes susceptible to developing antibiotic resistance [7].The area under the curve is also of concern as it indicates the effectiveness of the antibiotic. If the area under the concentration curve is too high or the peak is too high, then the patient may be susceptible to experiencing toxic side effects [7]. Thus, the MIC level is important to both know and monitor. Each antibiotic has a MIC level, which differs depending on the bacteria that the antibiotic is trying to kill. Hence, when analyzing the results, the data that would be associated with the MIC level is the area that many are concerned with. The main issue in matching the clinical data to our model data lies in the middle portion of the graph. While one might not be as concerned with this portion of the graph as they are with the end portion of the graph that deals with the MIC level, it is still important to match the data as closely as possible for more accurate results. When calculating the partition coefficients, it was observed that altering these coefficients led to quite significant changes in the model and graph. After further research, it was found that the equations used to calculate the various partition coefficients offer a great starting place; however, further analyzing and manipulating these values may fix the middle portion of the graph. The algorithm used to predict these parameters may not produce results as accurate as those needed for the model to fairly accurately mimic the clinical data. It becomes even more evident that the issue lies in the middle portion of the graph when looking at Table 3, which shows the relative error between

the clinical data and the model data. From this, one is able to see that there is quite a bit of difference in the clinical data and the model data, which again, means, further manipulations, calculations, and reformulations need to be conducted.

Table 5: Comparison between Data and Model for Total Concentration

Clinical Data (mcg/mL)	Model Data (mcg/mL)	Relative Error (%)
5.44	6.92	27.24
8.44	10.75	27.27
11.28	10.04	11.02
8.19	8.52	4.07
7.07	6.62	6.40
6.47	5.45	15.65
5.75	4.50	21.68
5.29	3.89	26.40
4.40	3.11	29.22
3.02	2.17	28.12
1.04	0.85	18.06
0.46	0.53	16.12
0.28	0.34	18.73

We are also interested in the urine excretion. The clinical data and our model data match very well as seen in Figure 4. The urine excretion for the clinical date is 80% and the urine excretion for the model is 80.21%. Thus, for the urine excretion, the data matches up very nice. The percent relative error in point estimates for the urine is 0.2680%.

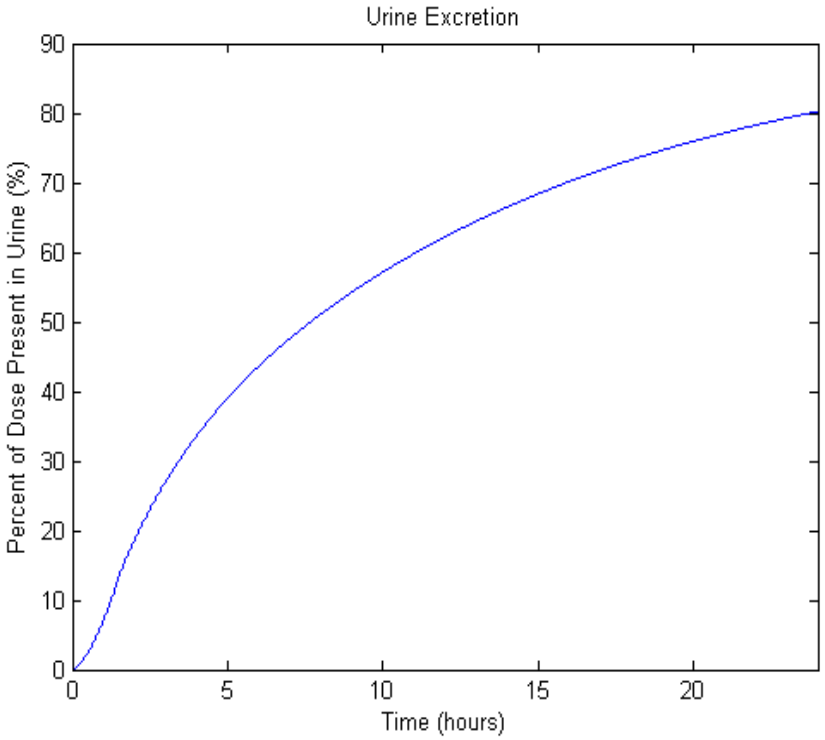

Figure 4: Urine Excretion

Using the inverse problem discussed in the parameter estimation section, we were able to find the following values for k_U and k_F:

$$k_U = 1.2924\, ml/hr \text{ and } k_F = 0.1160\, mL/hr.$$

These were the optimal values for k_U and k_F that were used to generate the above graph for total concentration.

5 Sensitivity Analysis and Revised Inverse Problem

After obtaining the results of the parameter estimation and looking at the total concentration graph, it was concluded that a sensitivity analysis should be conducted in order to obtain better results. There was some doubt surrounding the equation for calculating the partition coefficients, and, thus we decided to conduct a sensitivity analysis to test the effects of the partition coefficients. A sensitivity analysis is used to see how the variables change with respect to the parameters. It allows us to see which parameters most affect the given variables, and, thus, which parameters need to be the most precise. In other words, the sensitivity analysis was done in order to see if the partition coefficient had an effect on the output generated through our model. In order to do this, a system of differential equations was generated by taking the partial derivative of the variables with respect to the parameters. The ODE system used for the sensitivity analysis consisted of 49 differential equations. The partial derivatives of the original 10 equations that were used in our original ODE system for our PBPK model where taken with respect to k_U, k_F, P_F, P_K, P_G, and P_{OT}. Instead of listing all 49 equations here, one set of partial differential equations will be discussed, i.e. the equations with respect to P_F. Recall, P_F is the partition coefficient for the fat compartment. Again, the original equations were are given in Equation (3). Those equations with respect to P_F are as follows:

$$\frac{d}{dt}\frac{dC_F}{dP_F} = \frac{Q_f}{V_F}\frac{dC_{Bf}}{dP_F} - \frac{Q_F}{V_F}\frac{P_F\frac{dC_F}{dP_F} - C_F}{P_F^2}$$

$$\frac{d}{dt}\frac{dC_K}{dP_F} = \frac{Q_K}{V_K}\frac{dC_{BF}}{dP_F} - \frac{Q_K}{V_K} * \frac{1}{P_K}\frac{dC_{BF}}{dP_F} - \frac{1}{V_K} * k_U\frac{dC_K}{dP_F}$$

$$\frac{d}{dt}\frac{dC_B}{dP_F} = \frac{Q_G}{V_B}\frac{dC_{BF}}{dP_F} - \frac{Q_G}{V_G} * \frac{1}{P_G}\frac{dC_G}{dP_F}$$

$$\frac{d}{dt}\frac{dC_{OT}}{dP_F} = \frac{Q_{OT}}{V_{OT}}\frac{dC_{BF}}{dP_F} - \frac{Q_{OT}}{V_{OT}} * \frac{1}{P_{OT}}\frac{dC_{OT}}{dP_F}$$

$$\frac{d}{dt}\frac{C_{Bl}}{dP_F} = \frac{Q_F}{V_B} * \frac{1}{P_F}\frac{P_F\frac{dC_F}{dP_F} - C_F}{P_F^2} + \frac{Q_K}{V_B} * \frac{1}{P_K}\frac{dC_K}{dP_F} + \frac{Q_G}{V_B} * \frac{1}{P_B}\frac{dC_G}{dP_F} + \frac{Q_{OT}}{V_B} * \frac{1}{P_{OT}}\frac{dC_{OT}}{dP_F} - \frac{Q_{Total}}{V_B} * \frac{dC_{BF}}{dP_F}$$

$$\frac{d}{dt}\frac{dA_U}{dP_F} = K_U\frac{dC_K}{dP_F}$$

$$\frac{d}{dt}\frac{dA_F}{dP_F} = k_F\frac{dC_G}{dP_F}$$

In order to determine which parameter has the greatest effect on the variables, we calculated the relative sensitivity in the usual manner by using the modified L_2 norm, which is the following:

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

This equation allows us to normalize the sensitivity. The results of the given sensitivity analysis are indicated in Figure 5.

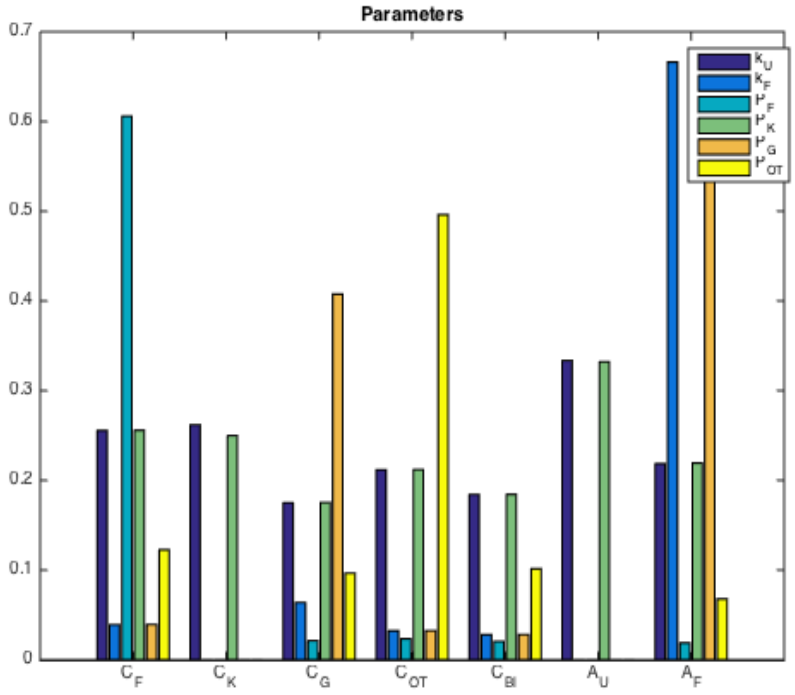

Figure 5: Sensitivity Analysis Results

From the above graph, we are able to easily conclude that the partition coefficients have an effect on the model across the board. For this reason, it is easily concluded that the partition coefficients do need to be accurate in order for our model to fit the data.

After concluding that the partition coefficients do have an effect on the model, a revised inverse problem was used to find the optimal values for k_U, k_F, P_F, P_K, P_G, and P_{OT}. In order to do this, we conducted a revised inverse problem. Again, we used *fminsearch* to estimate the values for k_U, k_F, P_F, P_K, P_G, and P_{OT}. In other words, we now choose $q = [k_U, k_F, P_F, P_K, P_G, P_{OT}]$ in Equation (4).

The following table shows the old partition coefficients used in the previous inverse problem and the new ones generated through the revised inverse problem.

Table 6: Old vs New Partition Coefficients

Old	New
$P_F = 4.96$	$P_F = 1.04$
$P_K = 1.16$	$P_K = 3.03$
$P_G = 0.91$	$P_G = 1.00$
$P_{OT} = 1.12$	$P_{OT} = 1.65$

The first model using the original partition coefficients is given in Figure 3. The second model using the optimal values for the partition coefficients is given in Figure 6.

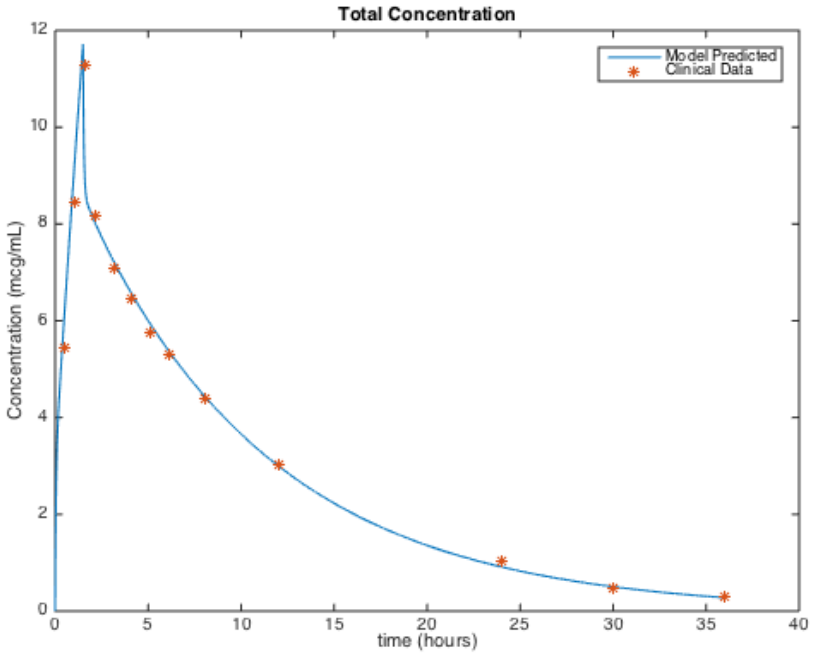

Figure 6: Model with New Partition Coefficients

Thus, it can be concluded that the new values found for the partition coefficients through the revised inverse problem generate a much better model that fits the data.

6 BMI Variation Study

It was speculated that Body Mass Index (BMI) would have an effect on the distribution of the drug throughout the body. Using our model, we were able to test the distribution of Levofloxacin throughout the body in individuals who are considered under weight, normal weight, over weight, obese, and extremely obese. In order to do this, it is first important to know the calculation for BMI.

$$BMI = \frac{BW}{(BH)^2}$$

where BW is measured in kilograms and BM is meters. Using this equation, we were able to test the affects of varying BMI on the distribution of Levofloxacin throughout the body. So, in order to do this, we fixed the body height at 177.8 centimeters, which is equivalent to 5 feet and 9 inches. We were then able to vary the body weight by setting of values for BMI that were indicative of a particular BMI category. Table 7 lists the ranges for the values of a $5'9"$ individual given different body weights. Using the different ranges for BMI for the different categories, we were able to vary the BW within these ranges in order to see the distribution of the drug throughout the body.

For individuals who are underweight, concerning the distribution of Levofloxacin throughout the body, it was concluded that there was less of the drug in the fat and more in the blood initially as seen in Figure 7. This was expected as an

Table 7: BMI Ranges for Different BW

Body Type	BMI Range
Under Weight	under 18.5
Normal Weight	18.5 - 24.9
Over Weight	25 - 29.9
Obesity	30 - 39.9
Extreme Obesity	40 and over

individual who is underweight will have less body fat to store the drug. Because of this, we see an initial peek in our model that is above the model for an individual of normal weight. At the end of the model, the levels of Levofloxacin for an individual who is underweight fell below the levels of an individual of normal weight. Again, this was expected as Levofloxacin is in the body for a shorter amount of time and is flowing out faster as a result of there being less fat in the body.

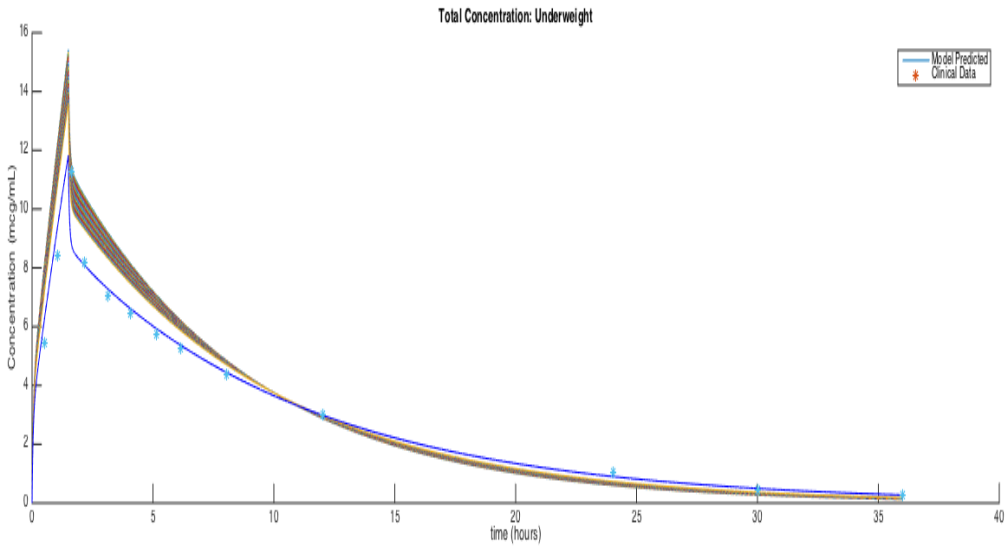

Figure 7: Total Excretion for Underweight Individual

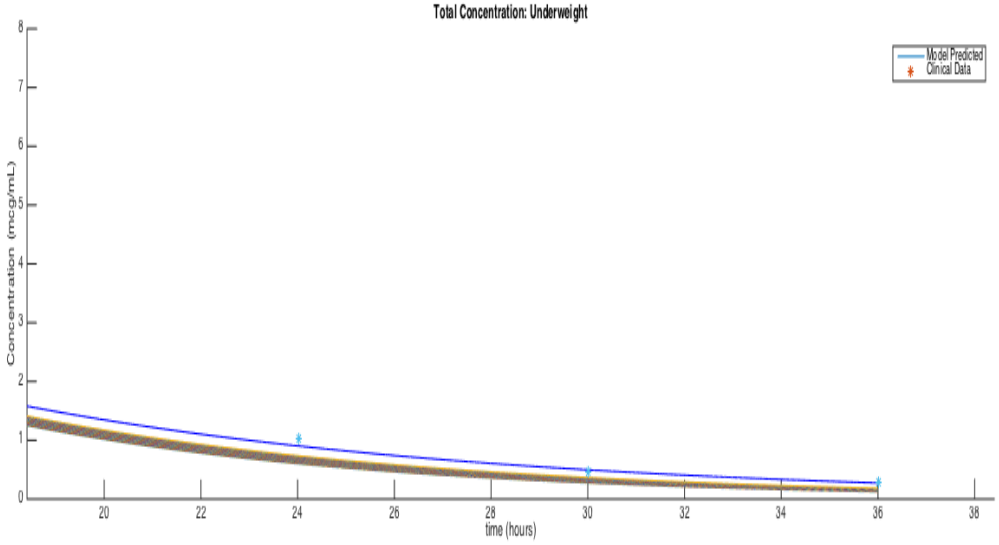

Figure 8: Data and Model in Figure 7 is shown from 18 to 36 hours

The explanation given for the variance in the model for an individual who is underweight versus an individual who is of normal weight is shown in the above figures. The dark blue line is the model for an individual of normal weight that is simply being used for comparison. Figure 8 zooms in on the final concentrations of Figure 7. The trend seen at the end of the dosage may be problematic, because it may cause the concentration to stay below the MIC level for longer than desired, which could potentially lead to the development of resistant bacteria.

For individuals who are considered overweight, it was concluded that there was more of the drug in the fat and less in the blood initially as seen in Figure 9. This was expected as an individual who is overweight will have more body fat to store the drug. Because of this, we will not see an initial peek in our new model that is above the original model for an individual of normal weight. At the end of the model, the

levels of Levofloxacin for an individual who is overweight lie above the levels of an individual of normal weight. Again, this was expected as Levofloxacin is in the body for a longer amount of time and is flowing out slower as a result of there being more fat in the body. The results for total concentration of Levofloxacin in the blood for an individual who is considered to be overweight are given in Figure 9.

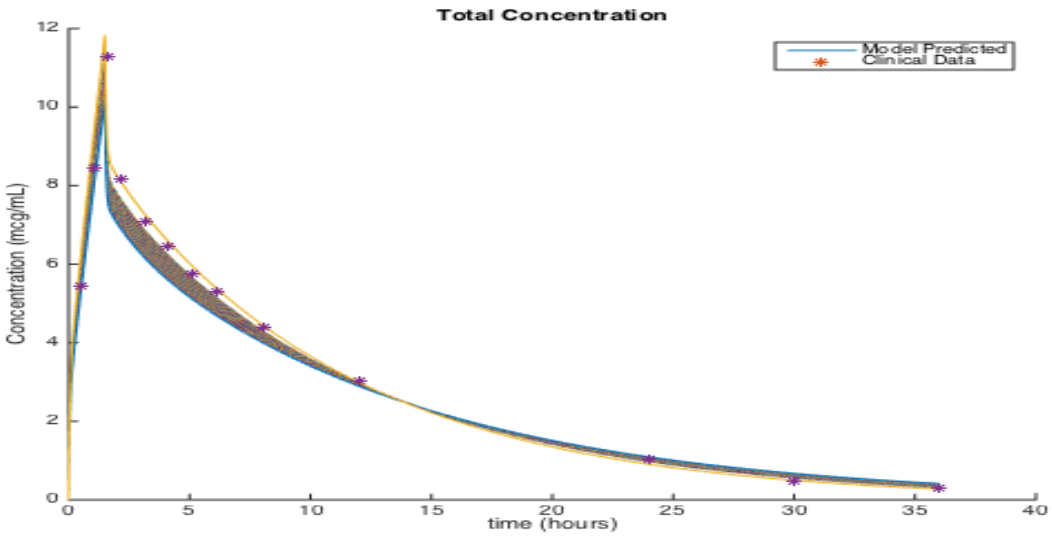

Figure 9: Total Excretion for Overweight Individual

For individuals who are considered to be obese and severely obese, the above explanation for an individual who is overweight can be used. However, the amount of fat in the body increases, and, thus, initially the body will have more fat to store the drug, so, the initial peek in the graph will continue to drop. Again, because of the increasing amount of fat in the body, the drug will flow out slower, and, thus, we see the levels at the end of the graph being below those for an individual of normal weight. The graphs for individuals who are obese or severely obese are given in Figures 10

and 11, respectively.

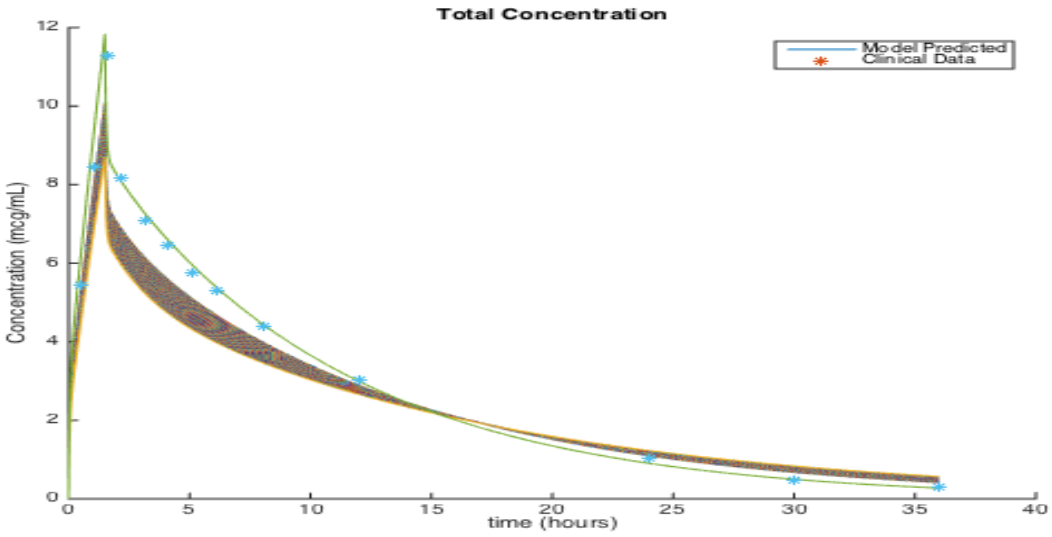

Figure 10: Total Excretion for Obese Individual

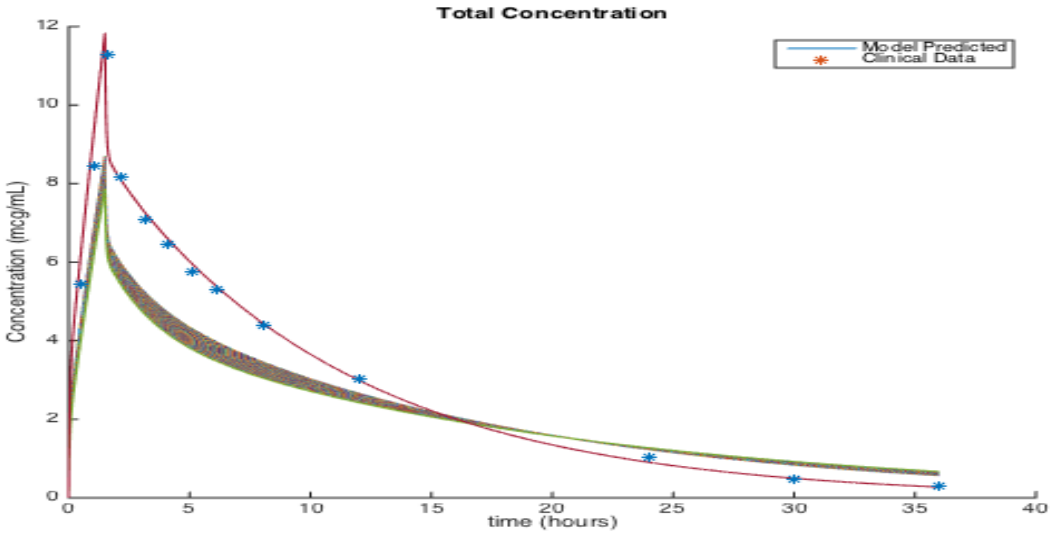

Figure 11: Total Excretion for Severely Obese Individual

7 Conclusions

The goal of this research was to develop a mathematical model to analyze the absorption and distribution of Levofloxacin throughout the body. In the initial model only values of k_U and k_F were estimated; however, estimating k_U, k_F and the partition coefficients produced a model with a better fit to the data. Using the new model, we were then able to test the effects of BMI on the distribution of the drug throughout the body. It was concluded that for individuals with a lower BMI who are considered underweight, there is an initial peek in the graph above the model for normal BMI due to the fact that there was initially more of Levofloxacin in the blood, because there was less fat to store the drug. Towards the end of the 36 hour period, the levels of Levofloxacin in the blood were below those for an individual with normal BMI because less of the drug was being stored in the fat, so it was flowing out faster. The opposite effects were seen in individuals who were overweight, obese, and severely obese, with the effects increasing as BMI increased. All in all, the model development proved to be very successful in showing how Levofloxacin is absorbed and distributed throughout the body and in testing the effects that BMI has on the distribution of the drug.

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