5-2019

Investigation of optimal dosing strategies for Ertapenem for varying BMI using mathematical modeling

Bethany Jewett

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An Honors thesis presented to the faculty of the

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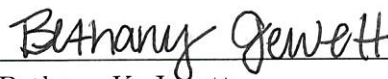
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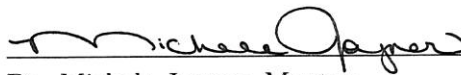
for a Bachelor of Science in Mathematics

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by

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April 2019

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Abstract

Previous research suggests that the efficacy of Ertapenem, a carbapenem antibiotic administered intravenously, is related to a patient's body mass index. Using an existing physiologically based pharmacokinetic (PBPK) model for Ertapenem, we constructed a least squares inverse problem to determine an optimal dose for males with varying body weights and heights. The criteria for an optimal dose was based upon pharmacokinetic and pharmacodynamic (PK/PD) parameters calculated for a male with a body height of 175 cm and a weight of 72 kg. We also adjusted dosing intervals to ensure that effective concentration of drug between doses was the same for all males regardless of BMI.

Contents

1 Introduction

Antibiotic resistance continues to be a major public health concern. A patient may become infected by antibiotic resistant bacteria in two ways: by being exposed to a strain of bacteria that is already resistant (usually in a hospital setting) or by receiving ineffective treatment. It is estimated that there are at least 2 million cases of antibiotic resistant infections that cause at least 23,000 deaths in the United States each year [5].

One measure to prevent the development of resistant strains is by giving patients a dose that sufficiently inhibits bacterial growth. If the bacteria causing the infection are able to multiply, then they have the potential to produce mutants that either require a higher concentration of antibiotic to be killed or are completely resistant to that antibiotic at any concentration [16, 24]. Thus, it is crucial that a patient receives a large enough dose such that these mutations can be prevented.

However, as the dose of an antibiotic increases, so does the possibility of a patient experiencing adverse effects [2, 23]. For example, higher doses are more likely to kill the micro flora in a patient's bowels making them susceptible to C. difficile-associated disease (CDAD)[23]. Moreover, at high enough concentrations, antibiotics can become toxic, causing organ failure or lowering an individual's seizure threshold [2, 3, 27].

The effective concentration of an antibiotic in a person is not only dependent on the dose they receive, but also certain physiological features which can impact the kinematics of the drug. In particular, body weight, BMI, age, and gender have all been shown to sometimes be relevant factors [18, 19]. Nevertheless, investigating this potential variability is not always feasible without sufficient evidence as performing clinical trials on a large enough population is both expensive and time-consuming. Fortunately, mathematical modeling based on well-established pharmacological principles can provide insight on how a particular dose might impact different demographics without putting any subjects at risk. This

strategy can also be used to make suggestions on what dose might be appropriate for a certain class of individuals.

1.1   Pharmacokinetics and Pharmacodynamics

Pharmacology is divided into two primary branches: pharmacokinetics and pharmacodynamics. Pharmacokinetics (PK) is the study of how a drug travels through the body; whereas, pharmacodynamics (PD) is the study of how a drug interacts with the body [25]. When determining antibiotic doses, it should be noted that only the free concentration of the drug is considered to be medicinally effective [6, 23]. The free concentration of a drug is defined as the portion of the drug in the blood that is not bound to plasma proteins [25]. Using PK concepts, one can determine how the amount of free concentration in the blood changes after the initial dose. This information defines a curve modeling free concentration over time (for an example, see Figure 2 in Section 2). The characteristics of this curve are considered to be related to PD concepts – positive or adverse affects, and antimicrobial activity [6].

In particular, there are 2 main attributes of these curves that indicate an antibiotic's efficacy: the peak free concentration ($C_{Bf_{max}}$) and the area underneath the free concentration curve (AUC). Both of these values are dependent on the rate of absorption and considered to be indicators of toxicity [23, 25]. These values, along with the minimum inhibitory concentration (MIC) for a particular bacteria, all serve as components of the three primary PK/PD parameters considered to determine whether an antibiotic will be effective against a particular bacteria [6, 23, 25]. Which PK/PD parameter to use is determined by the assumed mechanism of action of an antibiotic [6].

For certain antibiotics, like Aminoglycosides and Flouroquinolones, the concentration of the antibiotic directly correlates with bacteria eradication [23, 25]. These antibiotics are

referred to as concentration-dependent and their key parameter is the ratio of the peak free concentration and the MIC value of the bacteria of interest ($C_{Bf_{max}}/MIC$) [6, 15, 23]. Antibiotics are classified as time-dependent if bacterial eradication does not increase with higher concentrations above the MIC. Instead, the efficacy of these antibiotics is dependent on the length of time that the concentration is above the MIC (ex. β-lactams). Because of this, the key metric for time-dependent antibiotics is the percentage of time above the MIC. ($\%T > MIC$)[6, 15, 23]. Some antibiotics are considered to be both concentration-dependent and time-dependent – both the concentration and the length of time the are good predictors of efficacy [6, 15, 23]. To account for both of these dependencies, the parameter for these antibiotics (ex.Vancomycin) is the area underneath the curve over the minimum inhibitory concentration (AUC/MIC) [6, 15, 23]. Notably, once the parameter value for a specific bacteria and antibiotic is achieved, the antibiotic is not considered to be more effective at higher doses [6, 23].

1.2   Ertapenem

Effective against both gram-positive and gram-negative bacteria, Ertapenem is approved by the FDA to treat complicated intrabdominal infections, skin and structure infections, and urinary tract infections, as well as community acquired pneumonia, and uncomplicated pelvic infections [7]. The current dosing guidelines state that adults without renal impairment should be given a 1 gram dose intravenously for 3-14 days depending on the infection [10].

The efficacy of a dose of Ertapenem, like other β-lactams, is considered to be time-dependent. Ertapenem is considered to be effective at eradicating a particular bacteria when the free concentration is above the bacteria's MIC value for 40% of the dosing interval [15]. The kinematics of Ertapenem, modeled by Joyner et. al and described further in the

subsequent section, suggests that a good portion of the drug is stored in the fat affecting the amount of free concentration available to stop the infection [11, 12] .

This is of particular importance as Ertapenem is a broad spectrum antibiotic so its misuse has the potential to cause the development of multi-drug resistant bacteria [14]. In a retrospective study of the use of Ertapenem in a Singapore Hospital from 2006-2008, it was found that although Ertapenem was administered according to the current guidelines, there were still reported incidents of patients who had been treated with Ertapenem developing carbapenem resistant bacteria. The recommendations of this study was for doctors to continue to prescribe Ertapenem judiciously and to administer an adequate dose [17].

1.3 Mathematical Model

The kinetics of Ertapenem have been modeled by Joyner et. al using a physiologically based pharmacokinetic (PBPK) model [12]. A PBPK model divides the body into compartments and models the changing concentration of a drug in each compartment by system of differential equations. More specifically, these models utilize the volume of each compartment and their respective flow rates by accounting for physiological traits like weight, height, and gender [25]. These models can be useful in identifying a physiological factor that might impact the efficacy of a drug in a class of individuals. Joyner et. al's full model for males is defined in equation (5) and is described below. [12]. The mathematical model includes a compartment for the blood (Bl), the kidneys (K), the fat (F), the gut (G), and other tissues (OT). The model also accounts for the amount of the drug excreted in the urine (u) and the feces (f) separately.

The volumes of the compartments used in the model, with exception of V_{OT} ,were calculated using the following equations found in the literature [20, 22] :

$$V_{Bl} = \frac{13.1(BH)(100) + 18.05(BW) - 480}{0.5723}$$

$$V_K = 15.4 + 2.04(BW) + 51.8(BH)^2$$

$$V_F = \frac{\frac{\%BF}{100}(BW)}{0.923} \tag{1}$$

$$V_G = 0.0171(BW)(1000)$$

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

To account for the differences in BMI, sex (0 for males; 1 for females), and age, the percent Body Fat ($\%BF$) used to determine the volume of the fat compartment was calculated using the following equation [8]:

$$\%BF = -96.07 + (76.91 \log_{10}(BMI)) + (6.65 \log_{10}(Age)) + (11.40 Sex) \tag{2}$$

Notably, the model accounts for both the concentration of Ertapenem that is bounded in the albumin and is unbounded [11, 13, 21]. This relationship is described in the following equations:

$$C_{Bl} = C_{Bf} + C_{Bound} \tag{3}$$

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

The full model is included below and a summary of the variables is included in Figure 1:

$$V_F \frac{dC_F}{dt} = Q_F \left(\alpha C_{Bf} - \frac{C_F}{P_F} \right)$$

$$V_K \frac{dC_K}{dt} = Q_K \left(\alpha C_{Bf} - \frac{C_K}{P_K} - k_u C_K \right)$$

$$V_G \frac{dC_G}{dt} = Q_G \left(\alpha C_{Bf} - \frac{C_G}{P_G} - k_f C_G \right)$$

$$V_{OT} \frac{dC_{OT}}{dt} = Q_{OT} \left(\alpha C_{Bf} - \frac{C_{OT}}{P_{OT}} \right) \tag{5}$$

$$V_{Bl} \frac{dC_{Bl}}{dt} = Q_F \frac{C_F}{P_F} + Q_K \frac{C_K}{P_K} + Q_G \frac{C_G}{P_G} + Q_{OT} \frac{C_{OT}}{P_{OT}} - \alpha Q_{Total} C_{Bf} + R_I$$

$$\frac{dA_u}{dt} = k_u C_K$$

$$\frac{dA_f}{dt} = k_f C_K$$

with the rate of infusion being defined as

$$R_I = \begin{cases} \frac{D}{T_I}, & 0 \le t \le T_I \\ 1, & t > T_I \end{cases} \tag{6}$$

and the body's total flow rate is calculated by body weight using the following equation [26]:

$$Q_{Total} = 235(BW)^{0.71}(60). \tag{7}$$

10

Symbol	Description	Units
C_i	Concentration of ertapenem in tissue i	mcg/mL
C_{Bf}	Concentration of free ertapenem in the blood	mcg/mL
A_u	Amount of ertapenem in urine	mcg
A_f	Amount of ertapenem 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
α	Infusion Coefficient	dimensionless
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
B_m	Blood receptor constant	mcg/mL
K_d	Dissociation constant	mcg/mL

Figure 1: Summary of variables from Joyner et. al [12]

1.4   Impact of BMI and Gender

The mathematical model described in the previous section was used to investigate the impact of Body Mass Index (BMI) and gender on the efficacy of Ertapenem. When simulating this model for various BMIs, it was found that BMI *did* directly impact the profile of the concentration curve. Notably, those with a higher BMI had a smaller AUC and a lower maximum free concentration compared with those with an optimal BMI. Conversely, those with lower BMI had a larger free AUC and a higher peak free concentration. These results suggest that those with a lower BMI might be at risk for developing adverse reactions to Ertapenem and those with a higher BMI might be at risk for not having enough concentration to be appropriately effective [12]. They also found that gender had an impact as well. It was found that the free concentrations for females spanned a larger range of values

than for males. It was also found that BMI impacted the half-life of the drug for males, but less so females [12].

1.5   Present Work

The current paper is motivated by the previous work done by Joyner et al. [12]. The objective of this research is to determine if an optimal dose can be determined for different classes of BMI for males. For the purposes of this paper, we define an optimal dose to be one that maximizes bacterial inhibition while minimizing the chances of toxicity or adverse side effects. Because of this, we focus on optimizing the peak free concentration (C_{Bfmax}), the area under the concentration curve (AUC), and the time that the concentration is above the minimum inhibitory concentration (MIC).

2   Determining optimal PK/PD parameters

Since the concentration values for a male receiving a 1g/day dose with the body height of 175 cm and body weight of 72 kg (hereafter referred to as the typical male) provided in the pamphlet distributed by Merck & co., received FDA approval, we assume that those values are optimal [10]. Moreover, since these values were used by Joyner et. al to fit their PBPK model, we assume that the attributes of the model's concentration curves for a male with the body height of 175 cm and body weight of 72 kg are also optimal [12]. We first simulated the PBPK model for one 1 gram dose for the typical male using Matlab. Because we were only interested in determining an optimal dose based upon BMI, we kept age constant at 39 years. We also assumed there was no Ertapenem in the system initially so we set all of our initial conditions of our model to be zero.
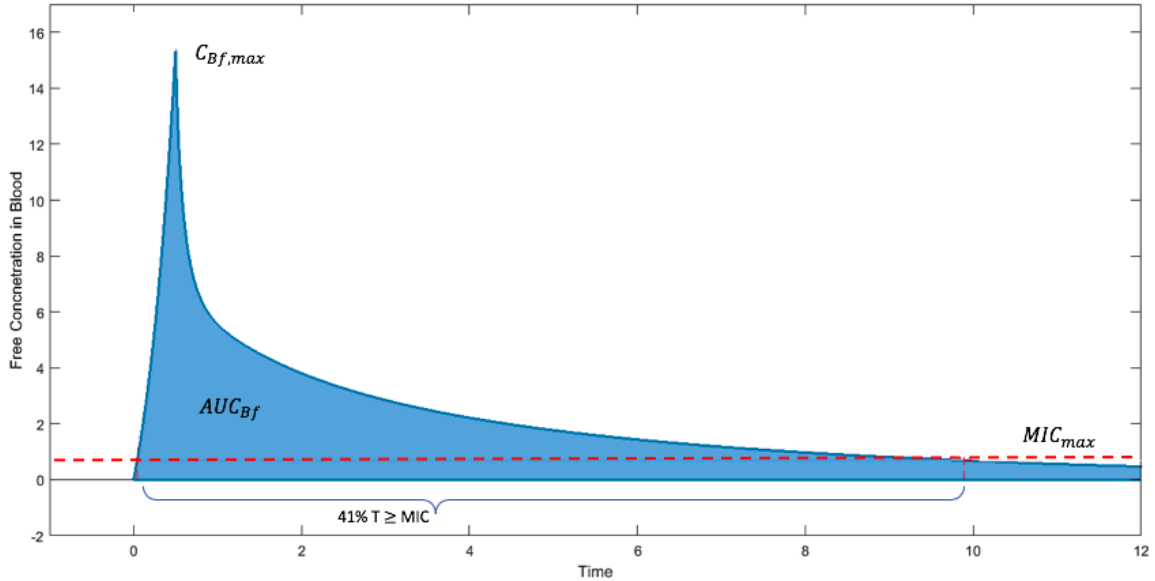
Figure 2: This figure is the free concentration in the blood across time for a typical male from 0-12 hours. The AUC is the area shaded in light blue, $C_{Bf,max}$ is the max concentration value, and MIC_{max} is depicted with a red-dotted line.

Figure 2 shows the quantities of interest for this study. $C_{Bf_{max}}$ is shown as the peak concentration, occurring after the initial infusion time. To determine this value, we used the Matlab function `max` and found for the typical male, the value is approximately $15.3\frac{mcg}{mL}$ [**MATLAB:2017b**]. The area under the concentration curve AUC is shown in Figure 2's shaded blue region. In order to calculate this, we needed to integrate C_{Bf} across the dosing interval (0 to 24 hours). We estimated the integral by using the Matlab function `trapz` which numerically approximates this integral using the trapezoidal rule [**MATLAB:2017b**]. The trapezoidal rule calculates an estimate for area by first splitting the independent variable into partitions and evaluating the function at these partitions. These values are then used to construct trapezoids so that when the areas of all of these trapezoids are added together they produce an estimate for the overall area underneath

13

the curve [9]. We found that for typical male the AUC_{0-24} to be $2.8 \times 10^4 \frac{mcg}{mL}$.

Instead of optimizing dose for a particular bacteria, we decided to use the largest possible MIC value that 1 g dose for a typical male would be effective against. We denote this value as MIC_{max} and is represented in Figure 2 with a red dashed line. To calculate this, we leverage the fact that Ertapenem is considered to be effective against a particular bacteria when the free concentration in the blood is above the bacteria's minimum inhibitory concentration for more than 40% of the dosing interval [15].

In an effort to be conservative, we defined MIC_{max} to be the maximum value that the free concentration is greater than or equal to for 41% of the dosing interval. To calculate this value, we simulated the model for a typical male and found the minimum free concentration in the 59th percentile. This method to find MIC_{max} satisfies the above definition as the simulated free concentration values in the 59th percentile correspond to the highest free concentration for 41% of the time interval.

Thus, we consider the free concentration of $0.6872 \frac{(g)}{(mL)}$ to be our optimal value for MIC_{max}. Note, for the typical male this value is the same after each additional dose as well. This is because in the model for a typical male there is not any Ertapenem leftover in the system for a 1 g dose after 24 hours. We summarize the values of interest for the optimization problem in Table 1.

Table 1: Rounded Parameter values used in cost function, $J(D; BW, BH)$, to optimize dosage.

Parameter	Model value	Units
$C_{Bf_{max}}$	15.3	$\frac{(mcg)}{(mL)}$
AUC_{0-24}	$2.8e+04$	$\frac{(mcg)}{(mL)}t$
MIC_{max}	0.6872	$\frac{(mcg)}{(mL)}$

3 Optimizing dose

3.1 Inverse Problem

To determine an optimal dose, we constructed a least squares inverse problem using the calculated values of $C_{Bf_{max}}$, AUC_{Bf}, and MIC_{max} from the typical male as our true data against which we would like to optimize. More specifically, we are assuming that the optimal dose D will on an individual's body weight (BW) and body height (BH); therefore, we constructed the cost function, $J(D; BW, BH)$ in Equation (8), to compare these optimal values with the model outputs for different dosages D for a given body weight (BW) and body height (BH). Since the values of $C_{Bf_{max}}$, AUC_{Bf}, and MIC_{max} are all different orders of magnitude, we built our cost function to compare the relative error between the optimal values and the model output, i.e. a weighted cost function with the weights as the given data as follows:

$$
\begin{aligned}
J(D; BW, BH) = & \frac{\left(C_{Bf_{max}} - C_{Bf_{max,pred}}(D; BW, BH)\right)^2}{C_{Bf_{max}}} \\
& + \frac{(AUC_{Bf} - AUC_{Bf,pred}(D; BW, BH))^2}{AUC_{Bf}} \\
& + \frac{(MIC_{max} - MIC_{max,pred}(D; BW, BH))^2}{MIC_{max}}
\end{aligned}
\tag{8}
$$

Note, when a dose, D, produces a small value for J, this indicates that this dose produces a $C_{Bf_{max}}$, AUC_{Bf}, and MIC_{max} that are close to the values for the typical male. To calculate the dose that produces the smallest possible J and thus minimizes the relative error the most, we used the built in Matlab function `fminsearch`. This function utilizes a Nelder-Mead algorithm which is an iterative procedure that estimates parameters based upon an initial guess. The algorithm works by using estimated parameter values and evaluating the cost or error that these values produce. If an estimated parameter

15

value produces a lower error than the previous estimate, the algorithm will make its next estimate in the same direction, otherwise the algorithm will pivot and estimate a parameter in another direction. This process is continued until the difference in the error values converge to a certain threshold. For our investigation, we chose an initial guess for D to by 1g and used a threshold of 10^{-6} [1].

Note in the above procedure that D is the only parameter being varied. Thus, to obtain an optimal dose based on BMI, we repeated the steps above 196 times using 14 different body heights ranging from 160 to 193 cm and 14 different body weights ranging from 56.7 to 115.7 kg. BMI was calculated after the optimization using its formal definition [4]:

$$BMI = \frac{BW}{BH^2}. \tag{9}$$

The range of values used were chosen such that they spanned BMIs considered to be underweight to severely obese. The criteria for these classifications is recorded in Table 2 and the BMIs (rounded) considered in the study are shown in Figure 3 and our shaded according to their classification.

Table 2: BMI with Classification [4]

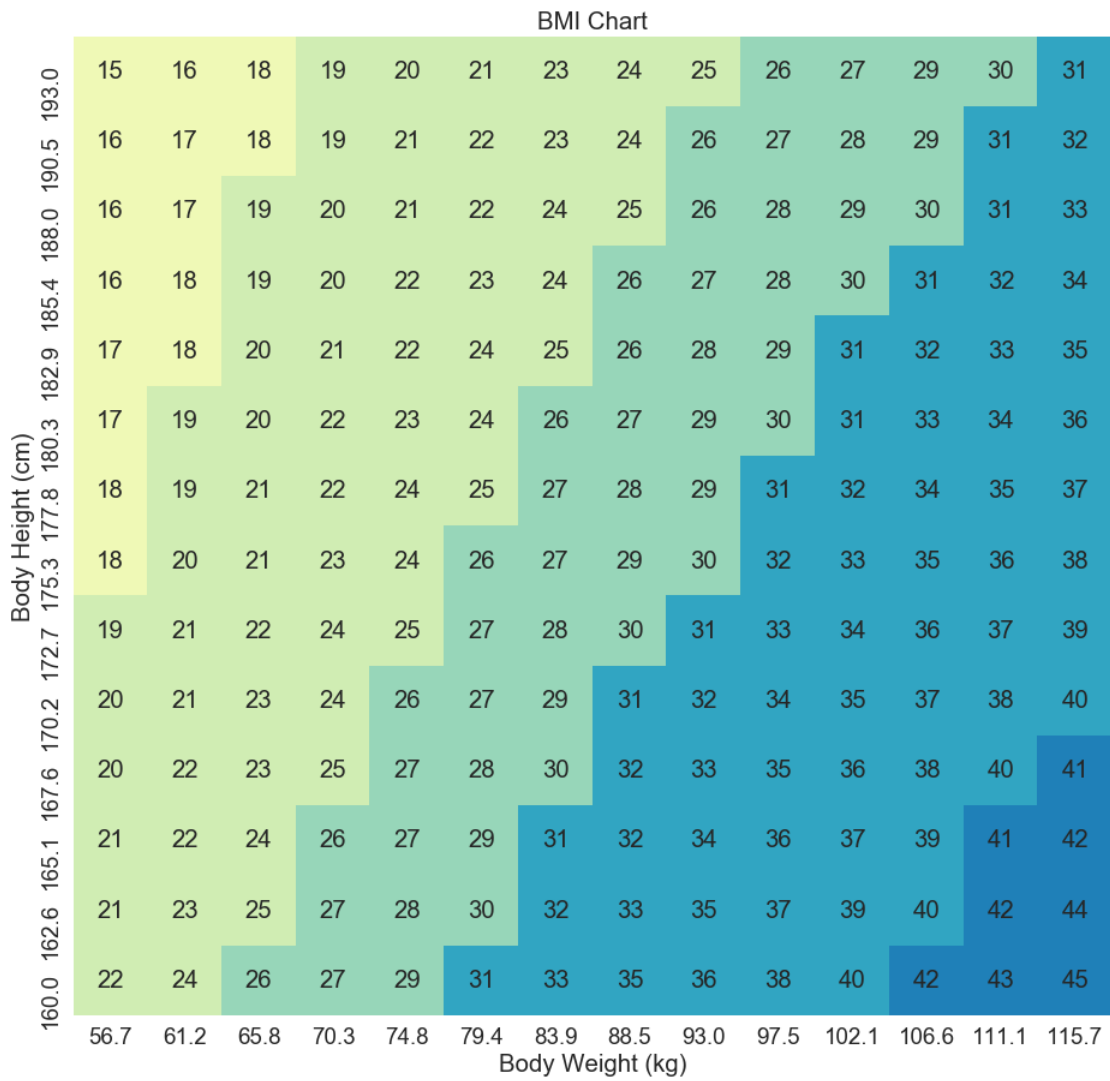| Classification	BMI
Underweight	<18.5
Healthy	18.5-25
Overweight	25.1-30
Obese	30.1-40
Severely Obese	40.1-50

Figure 3: BMI chart of height-weight combinations considered in optimization. BMIs are rounded to the nearest whole number and shaded according to the classification recorded in Table 2.

3.2   Results

Using our cost function $J(D; BW, BH)$, we calculated an optimal dose for each height weight combination. The results of this optimization are depicted in Figure 4. While there is a positive relationship between BMI and the optimized dose, this relationship is not as clear as the relationship between body weight and the optimized dose. The results of the optimization indicate that the relationship between a male's body weight and optimized dose is approximately linear. Thus, although BMI does appear to be a significant factor in predicting optimal dose, our results suggests that dosing according to body weight should be sufficient.
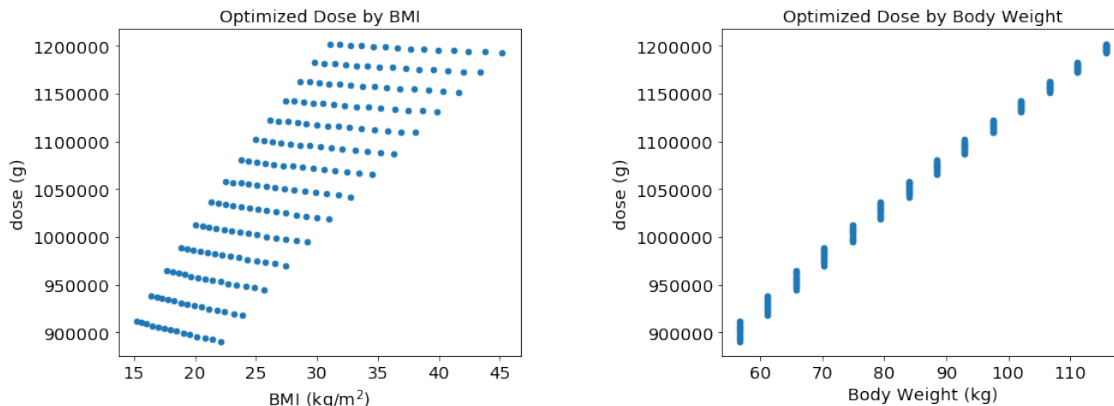

Figure 4: Optimal dose values obtained from $J(D; BW; BH)$ for varying BMI (right) and for varying Body weight (left)

To evaluate the effectiveness of our optimization on maximizing the efficacy of Ertapenem, we simulated the model with each height weight combination with their respective optimal dose and calculated their $C_{Bf_{max}}$ and AUC values (Figure 5 & 6).
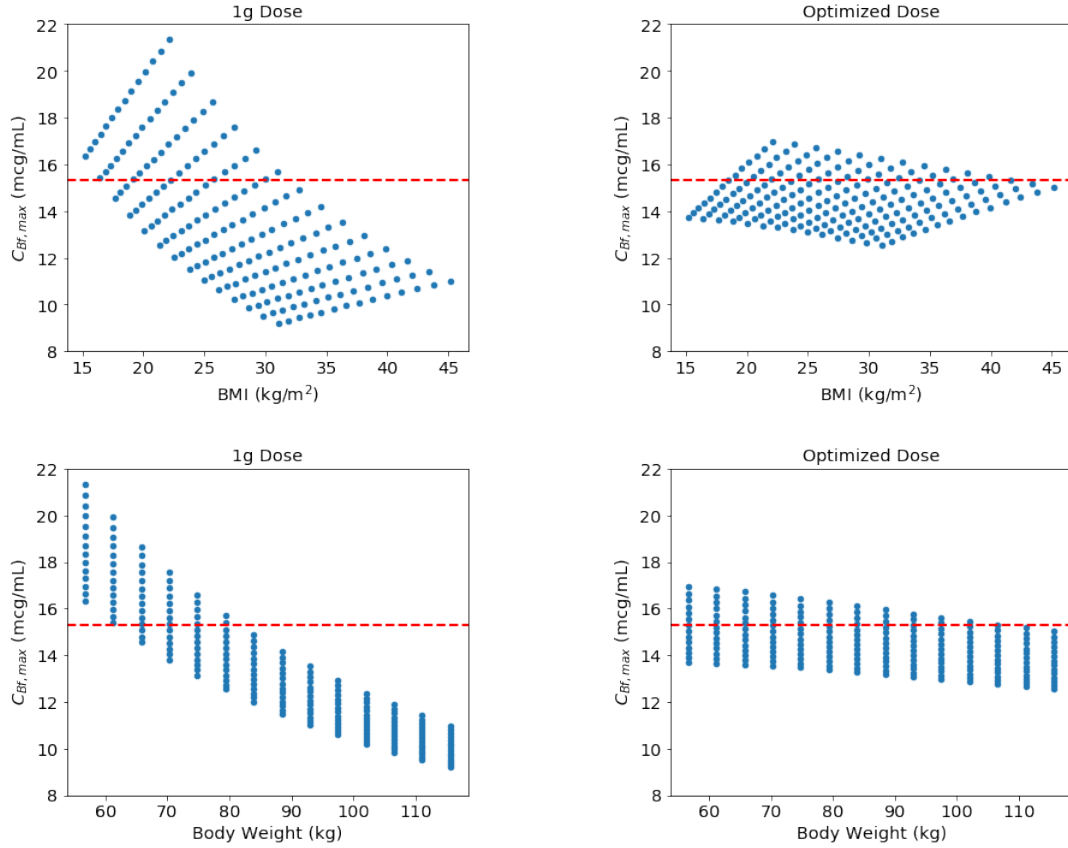
Figure 5: Maximum free concentration grouped by BMI and body weight. The red dashed line represents the maximum free concentration of a typical male after a 1 g dose. On the left, are the maximum free concentrations with the normal 1 gram dose. On the right are the maximum free concentration values obtained from simulating the model with the optimized dose.

As expected, when we simulate our model with the optimized doses, there is less variation in the maximum free concentration ($C_{Bf_{max}}$) than when using a 1g dose for everyone (Figure 5). Moreover, the simulated values of $C_{Bf_{max}}$ are closer to the $C_{Bf_{max}}$ of the typical male when grouped by BMI or body weight. Instead of a spread in the peak concentration from approximately 8 $\frac{mcg}{mL}$ to 22 $\frac{mcg}{mL}$ (a spread of 14 $\frac{mcg}{mL}$), the range has been reduced to a

spread from approximately 12-18 $\frac{mcg}{mL}$ (a spread of only 8 $\frac{mcg}{mL}$). Similarly, the AUC values calculated using the optimal dosages are much closer to the AUC values for a typical male (Figure 6). In this case, we were able to reduce the spread to almost a negligible difference when compared to the typical male.
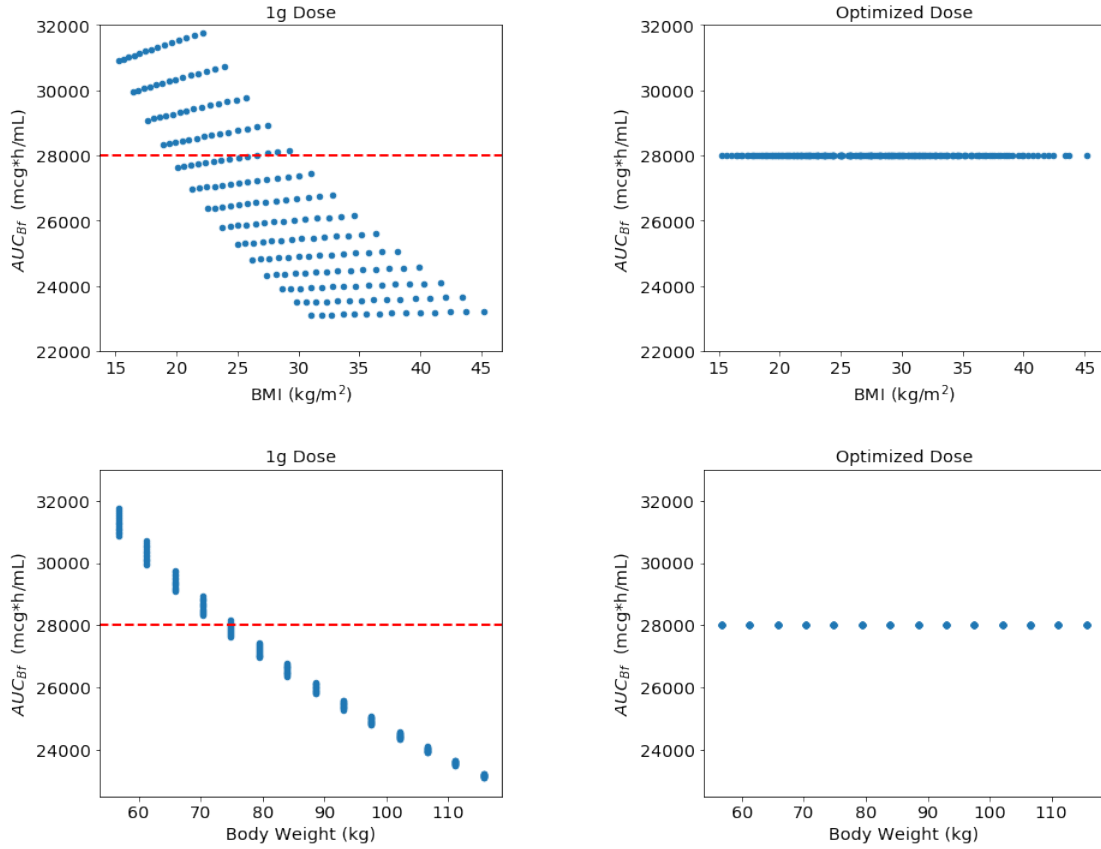

Figure 6: Area underneath the concentration curve grouped by BMI and body weight. The red dashed line represents the AUC of a typical male after a 1 g dose. On the left, are the AUC values with the normal 1 gram dose. On the right are the AUC values obtained from simulating the model with the optimized dose.

We were also interested in the impact that using the optimal dose had on the MIC_{max}. Using our optimal dosages, we had a greater number of height-weight combinations with

MIC_{max} values at or above the value of the typical male (Figure 6). However, we still had that some of our simulations had MIC_{max} values below the value for the typical male (Figure 6). Recall, that if a value falls below, there is a higher probability of an individual developing resistant bacteria.
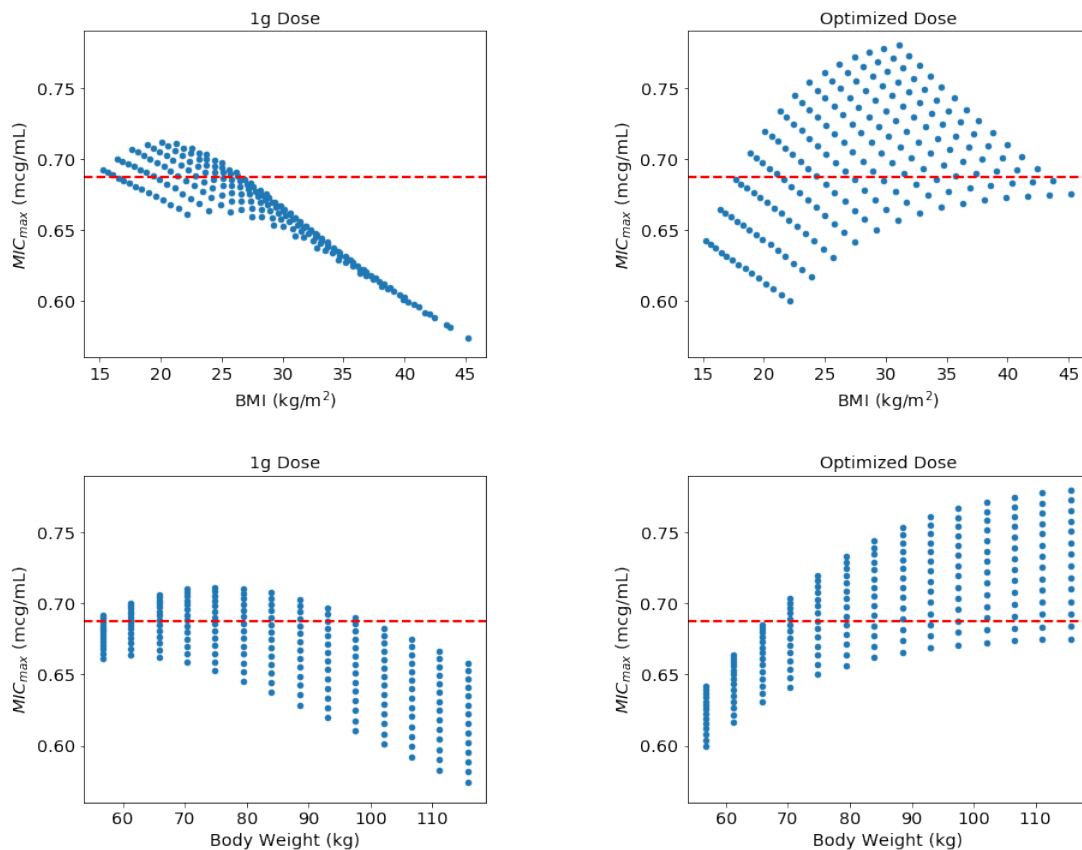

Figure 7: Maximum MIC value for 196 body height weight simulations grouped by BMI and body weight. On the left are the model outputs using the normal 1 g dose. On the right are the model outputs using the optimal doses. The red dashed line indicates the MIC_{max} for the typical male.

4   Adjusting dosing intervals

4.1   Methods

When using the new dosage obtained from minimizing our cost function, the differences between the typical male and the model outputs for the different height-weight combinations of the peak free concentrations and area underneath the concentration curves decreased significantly (Figure 5 & 6). However, there was still some variation between the maximum MIC values (Figure 7). To mitigate this, we adjusted the length of the dosing intervals such that the free concentration was the typical male's MIC_{max} value for 41% of the time. To find this length of time for each height and weight combination, we first simulated the model using the optimal dose and then determined the the amount of time the free concentration was above the MIC_{max} value for the typical male. We then divided this time by 0.41 to get the length of our dosing interval.

4.2   Results

The adjusted length of dosing intervals are shown in Figure 8. Interestingly, based upon Figure 8, it appears that BMI is a better indicator of how much the dosing interval might need to adjusted more so than body weight. For instance, examining Figure 8, we see that given a BMI of kg/m^2, the patient should be given Ertapenem every 22.5 hours instead of 24 hours. We note that the adjusted dosing interval did not vary greatly from the typical 24 hour dosing period; however, even this small change makes a change in the overall effectiveness of the antibiotic as discussed below.
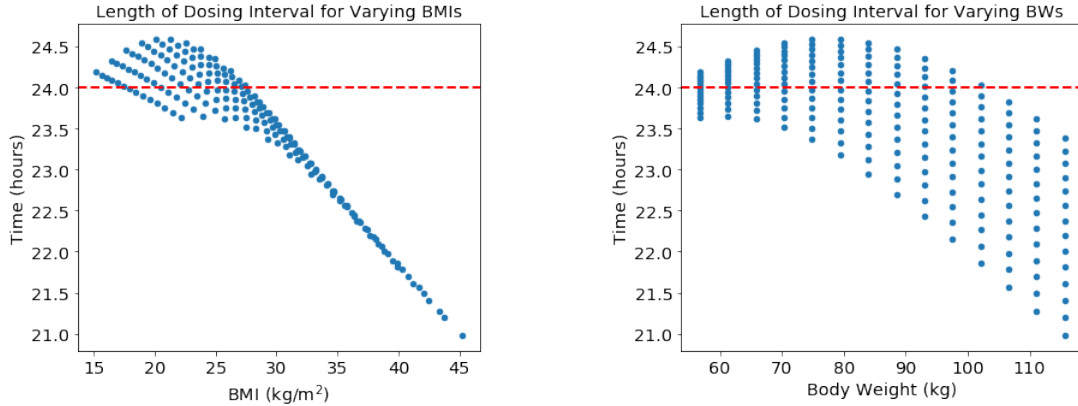
Figure 8: Length of dosing interval by BMI (left) and body weight (right). The red dashed line represents the dosing interval for the typical male.

Similar to our evaluation of the optimal doses, we considered the impact that these adjusted doing times would have on the $C_{Bf_{max}}$ and the AUC_{Bf}. Since the time of the next dose dose not impact the first peak free concentration, $C_{Bf_{max_1}}$, we examined the peak free concentration on day 7, denoted $C_{Bf_{max_7}}$, as this concentration would increase if there were concentrations of Ertapenem leftover in the model after each day. To do this, we simulated one day of the model assuming that there was no Ertapenem initially in the system for a fixed height and weight. We then used the concentration values from the previous day as our initial conditions for the next day. We repeated this process for 7 days for all 196 combinations.

We then found the peak free concentration over those 7 days ($C_{Bf_{max_7}}$) shown in Figure 9. Interestingly, although the change in the dosing time for a BMI between 15 and 30 is only approximately a half hour, this adjustment seems to keep the $C_{Bf_{max_7}}$ much closer to the $C_{Bf_{max}}$ value of a typical male.
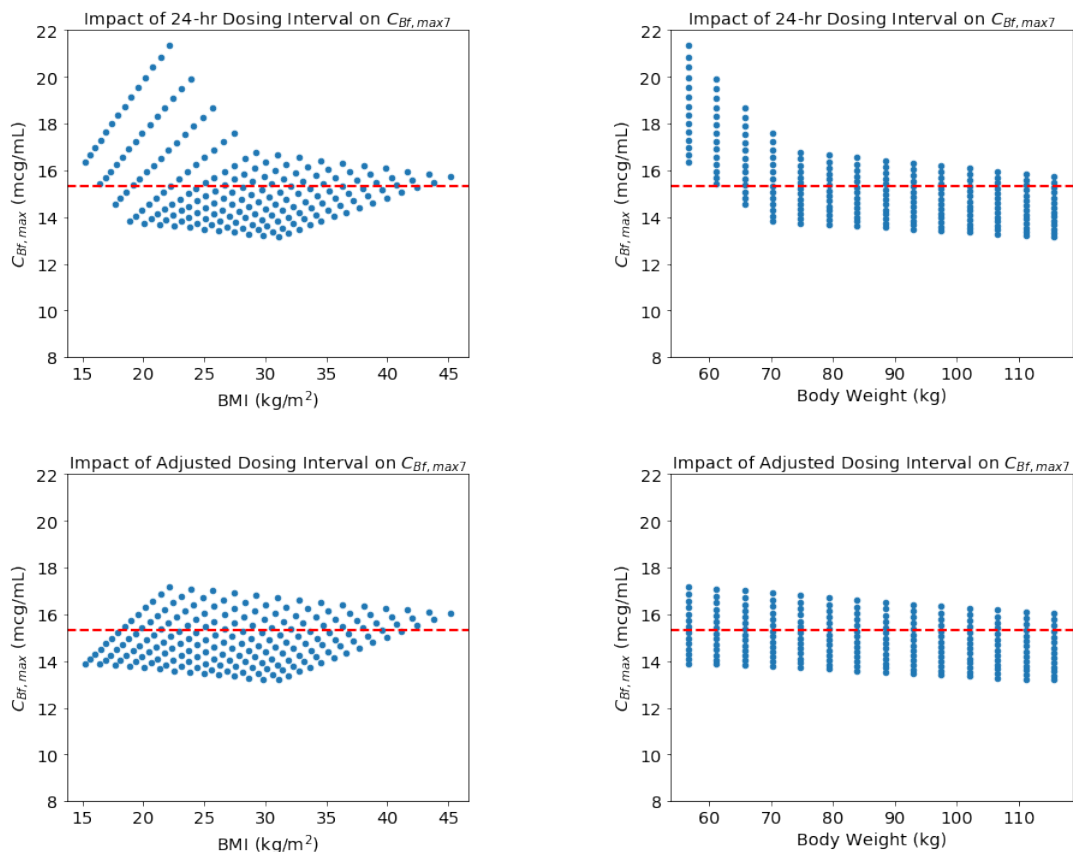
Figure 9: Maximum free concentration over 7 days. Top: maximum free concentration over a span of 7 days when doses are administered ever 24 hours. Bottom: maximum free concentration when doses are administered according to the adjusted dosing interval.

For examining the impact on the AUC_{Bf}, we calculated the AUC_{Bf} over the time of the initial dose, T_{I_1}, until the time immediately before the next dose, T_{I_2}. Figure 9 shows that the area underneath the free concentration curve over the the first adjusted dosing interval $(T_{I1} - T_{I2})$ does decrease slightly for a male with a BMI ≥ 30 (Figure 8). Although the AUC values from the adjusted dose vary more from the AUC of the typical male, these values are still more in line with the typical male assuming the standard dose of 1g every
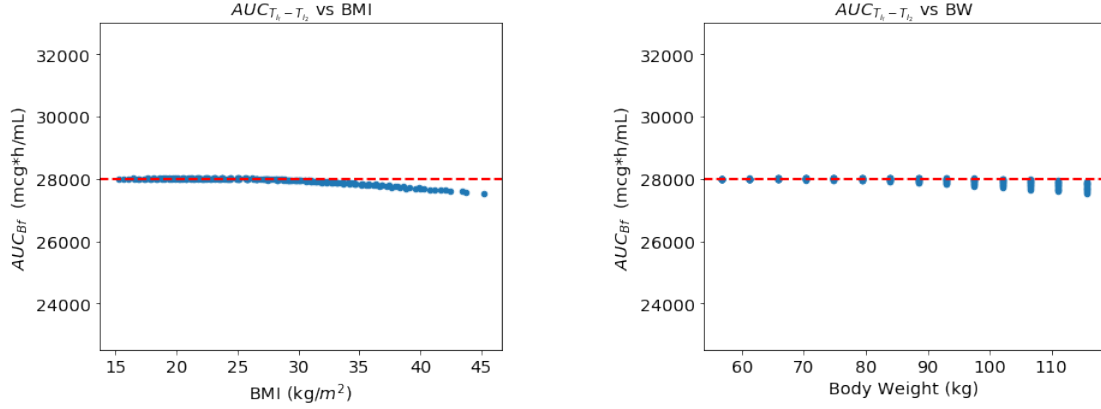
24 hours. (Figure 6).

Figure 10: Area under the concentration curves over the adjusted dosing interval for varying BMIs (Left) and for varying body weights (Right). The red dashed line represents the AUC of the typical male with a 1 g dose over 24 hours.

5   Conclusions

Creating dosing strategies for an antibiotic is a balancing act. Enough must be administered to ensure that the antibiotic will be able to effectively stop the infection without administering an amount that could be harmful to a patient. In this project, we optimized dose for males of varying heights and weights by comparing attributes of their free concentration profiles to those of a male with a body height of 175 cm and a weight of 72 kg. We also adjusted the dosing interval so that the MIC that the antibiotic is considered effective against is similar despite differences in height and weight.

Based on our results, we would recommend that the amount of Ertapenem prescribed to a patient should be based upon the their body weight and the time between doses should be based upon their BMI. This dosing strategy appears to minimize the variation in the $C_{Bf_{max}}$ and the AUC between the typical male and other males of varying body

25

weights and heights. This minimization could potentially prevent adverse reactions as both $C_{Bf_{max}}$ and the AUC can be used as indicators of toxicity. Moreover, this strategy focuses on optimizing the maximum MIC of the antibiotic to closely match the MIC_{max} of a typical male to ensure that bacterial inhibition would be similar across BMIs.

Although this paper focused on optimizing dose towards the maximum MIC value that a typical male is considered to be effective against, the methodology in this paper could be modified to optimize dose towards the MIC of a particular bacteria. More specifically, the dosing interval could be adjusted (as described in section 4.1) so that the free concentration remained above the MIC of interest for over 40% of the time for each body weight and height. The PBPK model used by Joyner et. al could then be simulated for these intervals to check that the concentrations of the antibiotic do not exceed a certain threshold.

That being said, there are still improvements that could be made to the proposed dosing recommendations. For example, previous research suggests that the kinematics of Ertapenem in females differs from that of males. To provide an exhaustive dosing recommendation, a similar methodology to the one recorded in this paper should be conducted for females. Further improvements could potentially be made by investigating optimizing the dose to account for age as well. Since proper dosing is one way to mitigate the threat of antibiotic resistant bacteria, we hope that this research might be used as motivation to further examine how Ertapenem is administered for different individuals.

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