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BME-143

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Final Project Writeup

Introduction

For this project, I focused on developing a pharmacokinetic model for Rifampin, a common antibiotic used to treat tuberculosis. Since Rifampin is usually taken orally and works in the lungs where the tuberculosis bacterium primarily resides, the pharmacokinetic model would have to account for the drug circulating in the blood and reaching various tissues in the body before reaching its site of action. Therefore, a physiologically based pharmacokinetic(PBPK) model would be the best approach to the issue of vasculature, as it considers the different drug distributions in other tissues of the body. I have chosen to implement the model from Lyons et al.(2013), a PBPK model of Rifampin in mice. In this project, I aim to implement the model from Lyons et al. by exploring additional metrics not addressed in the original article. In addition, I will change the model's dosing to an intravenous(IV) dose method to better understand the differences between oral and injected doses.

Methods

Core Model Implementation

I intend to fully implement the methodology in Lyons et al. with a few changes that better suit the model implementation. I will not perform the Monte Carlo simulation of the parameter values, as the methodology is not well defined. This exclusion also extends to the sensitivity analysis, so I will not reproduce Figure 7A. Instead, I will attempt to generate the median change of Rifampin drug concentrations over time using the median parameter values in Tables 1 and 2 of the article. This change will allow me to develop all the figures in the article except for Figure 7A, the sensitivity analysis, and the percentile-based values from Figures 3-6.

To implement the model from Lyons et al., I used a MATLAB app, SimBiology, designed for PK/PD modeling. In the first phase of the model, I used graphical design to draw and implement the model diagram with additional elements that will allow SimBiology to recognize the drug in each compartment and record the reactions occurring between the different compartments; these functions are all automatically incorporated into the SimBiology code and are returned as ODEs. Most of the parameters will come directly from the paper without any changes. Tissue volume and blood flow must be calculated using their fractional values and the body weight in kg. All the calculations are in the Excel sheet attached to the final submission. Blood/plasma partition is not explicitly stated in the article; however, based on the follow-up paper from Lyons et al.(2015), its value is 0.9.

Compartments will remain the same in this model. Although initially in kg, the volume will be set to liters(L) since we assume the tissue's 1kg/L density.

The dose will be represented in mg, the multiple of the drug dose, and the body weight in kilograms. To help generate Figures 2-7B, the drug will have five different dose variants:

10mg/kg, 15mg/kg, 20mg/kg, and 40mg/kg for a single bolus dose and 10mg/kg for three doses every 24 hours. For all doses, the start time will be 0 hours.

Species are compartment elements, and the Rifampin concentration will be the only element we will observe in a 120-hour timeframe. All initial concentrations of the Rifampin in each compartment will be set to zero. Figures 3-7 show that the drug plasma concentration will be derived from the venous drug concentration over the blood-to-plasma partition. However, we will also look at the drug concentration in the lung, liver, and kidney compartments to recreate Figure 4 from Lyons et al. Given that our dose is in mg and our volume is in L, the model will use mg/m as the concentration unit. Lyons et al. report the concentration as µg/g for tissues and µg/mL for plasma. However, given the 1kg/L assumption, all these concentration units should be in a 1:1 conversion with each other.

The ODEs for the amount in mg of the drug in each compartment are found in the appendix. I will not implement the ODEs directly into the model. Instead, I will use them to interpret the kinetics occurring within each compartment. Therefore, I will break them into distinct reactions that will serve as the nodes of change between the different species of drugs.

Variations in the 50%± muscle/blood partition factor(PM) will be included and tested separately at a 10mg/kg dose to help recreate Figure 7B.

For Figure 2 and Table 3 recreation, we will use the non-compartmental analysis(NCA) and Observables features in the SimBiology model analyzer to calculate AUC, tmax, Cmax, and t1/2.

Perturbations in the model

The first perturbation will investigate the sensitive parameters in this model. We already did the PM through Figure 7B. Therefore, we will use the variants function to perform the same 50%± change in clearance rate (CL) and absorption rate (ka). However, Bioavailability (Fa) is the drug's bioavailability, or the percentage amount taken in, and as such, it can never be less than 1. Therefore, Fa will be varied at 0.5 and 0.25.

The second perturbation in this model will be looking at how this drug can be changed from oral to IV injectable. As such, we will keep the same 10mg/kg dose, both single and multiple, to see how the injectable dose has changed the dose-response in the plasma liver, kidney, and lung. We will also investigate the AUC, Cmax, tmax, and t1/2 in plasma for the single dose. The other single doses will not be recorded since 10mg/kg is sufficient to see the change.

Results and Discussion

Model Validation

We can make a few observations by comparing the model-generated Figures and those from Lyons et al.

- The AUC in Figure 2 of Lyons et al. saturates at a similar value and time to that of the recreated Figure 2. Both AUC responses seem to saturate at around 50 hours.

- Based on the results of the recreated Figure 2, Figure 3-7, and the NCA parameters in Table 1, we can conclude that the drug plasma concentration results for the 10mg/kg single dose match relatively well with those of Lyons et al. median plasma value.
- We may also conclude that the 10mg/kg dose response for lungs, liver, and kidneys in the recreated Figure 4 also matches the median dose result from Lyons et al. Figure 4.
- The recreated Figures 3 and 6 also confirm that the 15mg/kg, 20mg/kg, and 40mg/kg single doses match the median response in Lyons et al. in their corresponding figures.
- Finally, Figure 7 results closely match its Lyons et al. counterpart, Figure 7B.

Overall, the model results indicate that the model was successfully implemented for the median parameter values and displayed similar non-compartmental analysis results.

Perturbations

By varying the three additional parameters, we can make a few observations:

- By varying the ka, we see in Figure 8 that a higher ka correlates with the reaction reaching the maximum concentration faster. This aligns with the logic that having a higher absorption rate would mean the drug is absorbed into the plasma much more quickly.
- By varying the clearance rate, we observe in Figure 9 that the drug retained in the system increases the lower the CL is. This follows the logic that the lower the drug is eliminated from the system through the excretory system, the more of the drug remains in the system.
- In both cases, we see a lower bioavailability rate correlated to a lower maximum concentration of the drug in plasma. This follows the logic that we will get a smaller response by decreasing the amount of drug that enters the system.

However, let's compare all four sensitivity parameters. We notice that the maximum drug concentration in plasma will directly correlate with Fa and ka and inversely with CL and PM. PM and, secondly, Fa appear to have a greater impact on the 10mg/k dose, as seen in Figures 7 and 10. These results directly correlate with the sensitivity analysis in Figure 7A by Lyons et al.

In the second perturbation set, Figures 10 and 12 show that the drug immediately enters the blood and spreads much faster into the system, peaking almost instantly. We see in Table 1 that the Cmax and tmax of the drug in plasma change as the drug absorption in the body is no longer reliable on the gut, which absorbs the drug and sends it to the liver before it spreads in the veins. This latter part may be why the liver drug concentration is tamer than the other compartments. We get a much faster and stronger response by removing the intermediary steps. However, we also notice in Table 1 and Figure 11 that t1/2 in and AUC remain within range of the regular bolus response, indicating that no matter the injection route, the drug will retain its half-life, and the amount of drug in the bloodstream through time is still the same.

Figures

Recreated Figures/Tables from Lyons et al. vs Figures from the article

Figure 1: Model Diagram

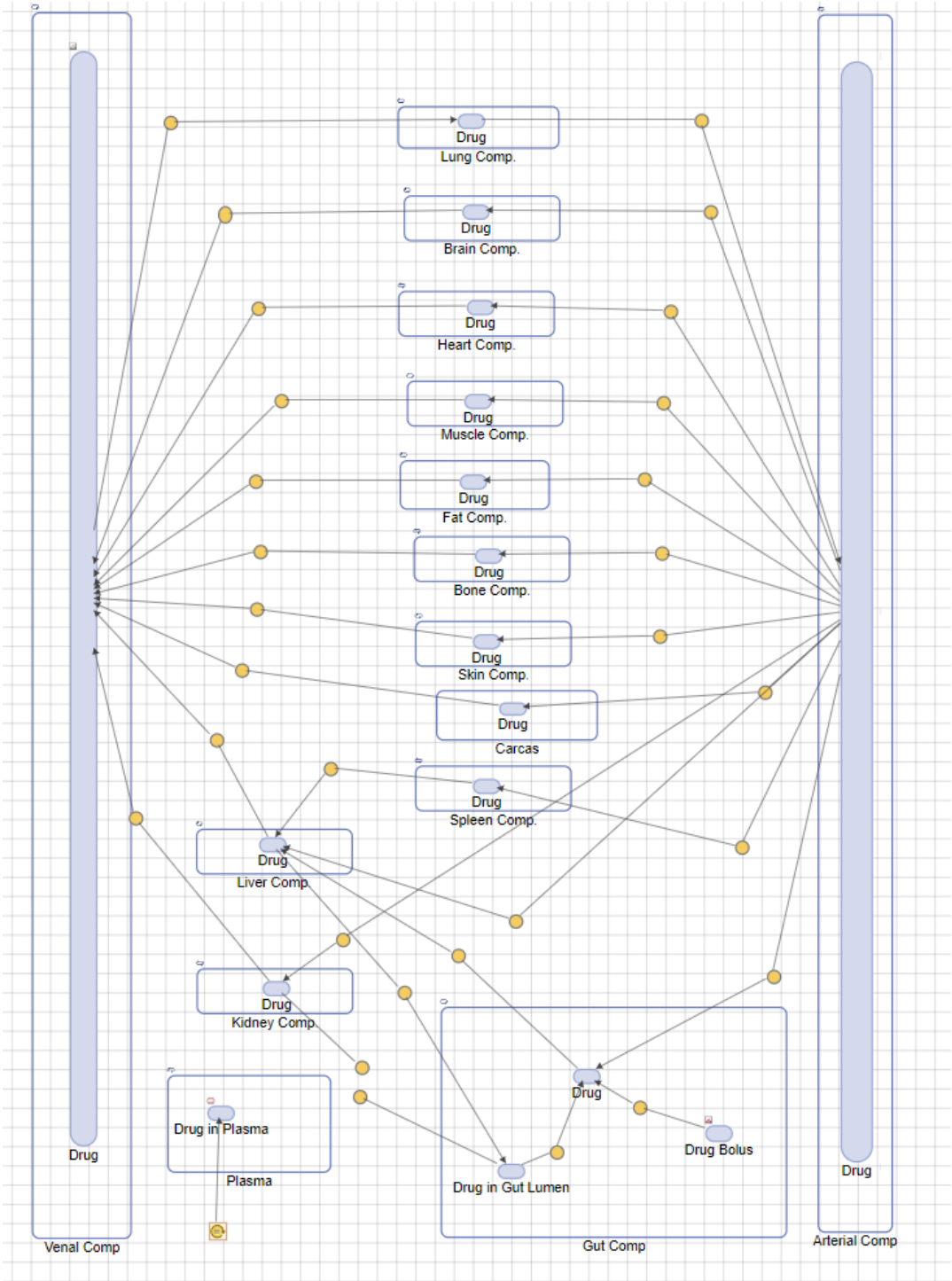


Figure 2: 10mg/kg single oral dose AUC over time

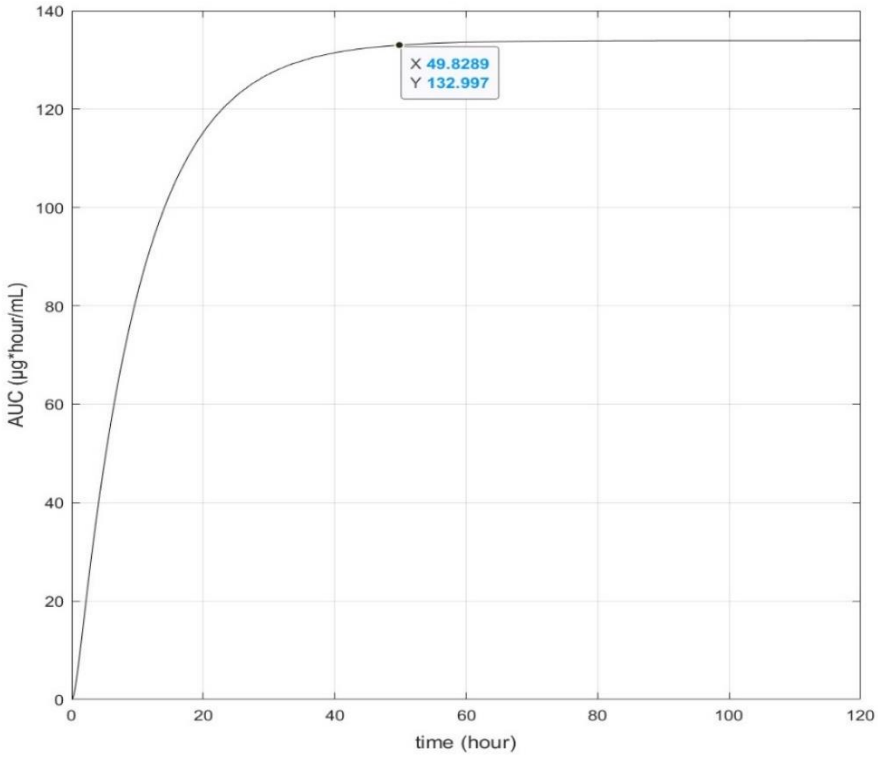


Figure 3: 10mg/mL and 15mg/kg oral bolus dose Rifampin concentrations in mouse plasma

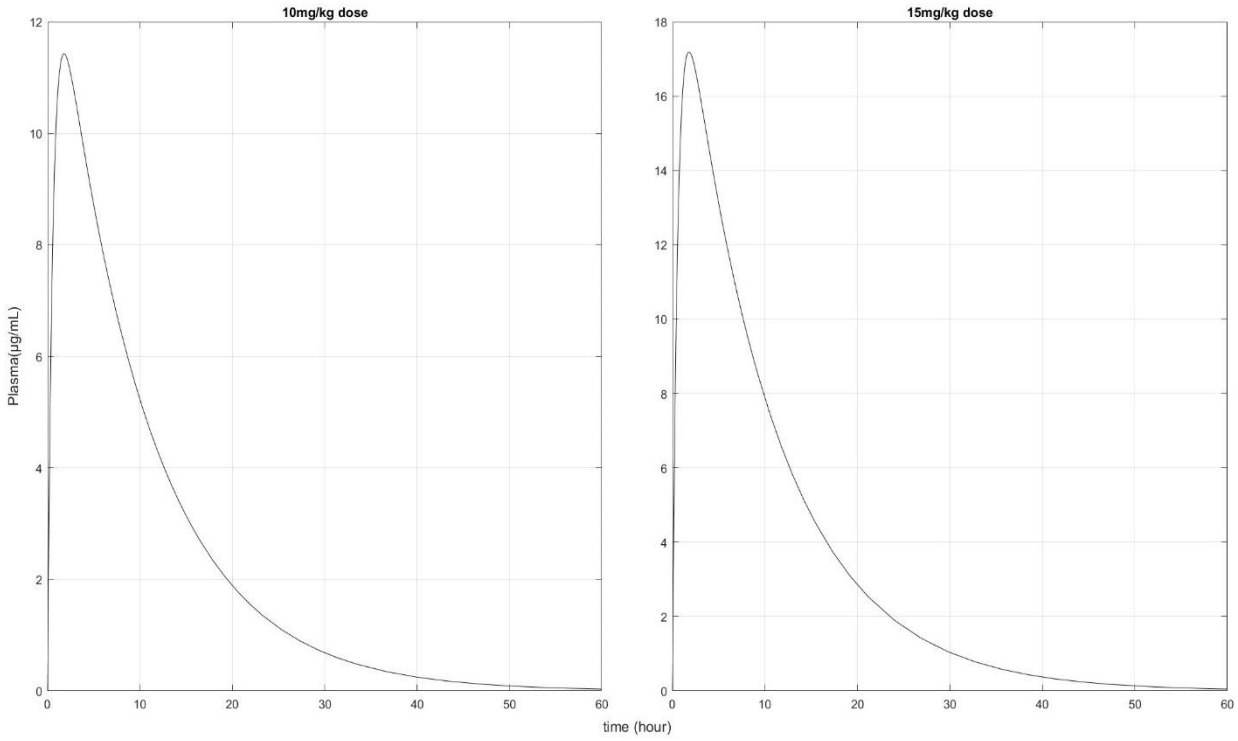


Figure 4: 10mg/mL oral bolus dose Rifampin concentrations in mouse plasma, lung, liver, and kidney

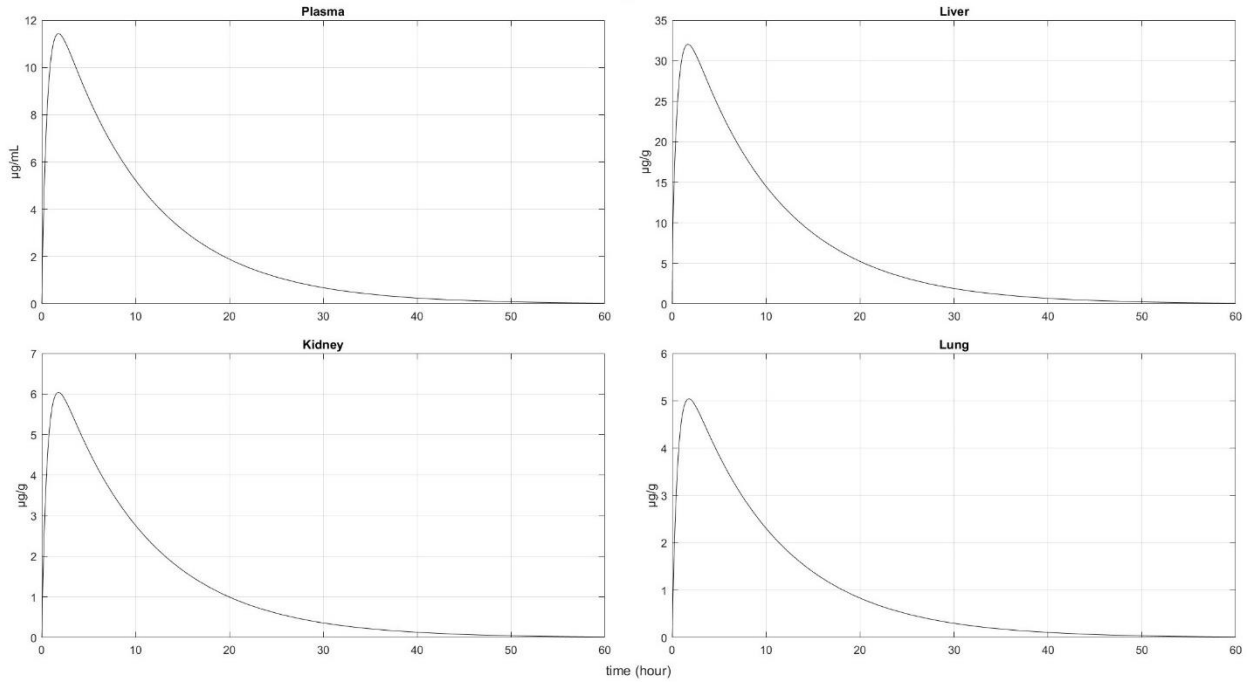


Figure 5: 10mg/mL repeated oral bolus dose Rifampin concentrations in mouse plasma and liver

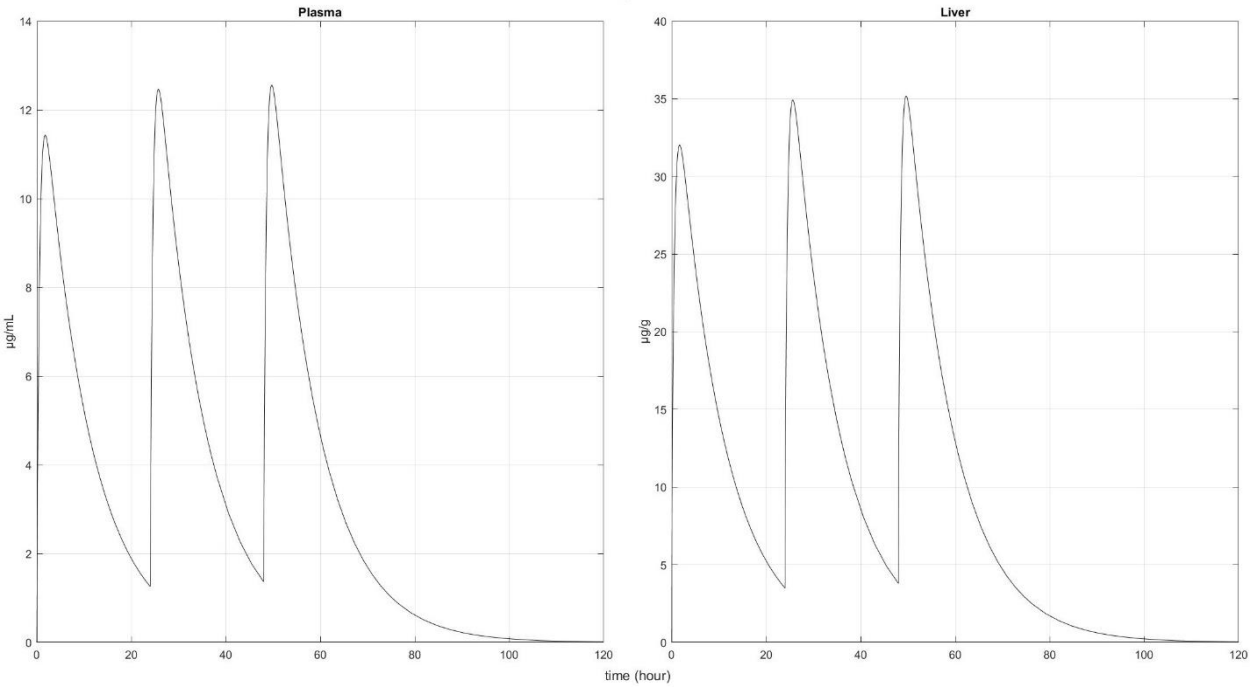


Figure 6: 10mg/mL, 20mg/kg, and 40mg/kg oral bolus dose Rifampin concentrations in mouse plasma

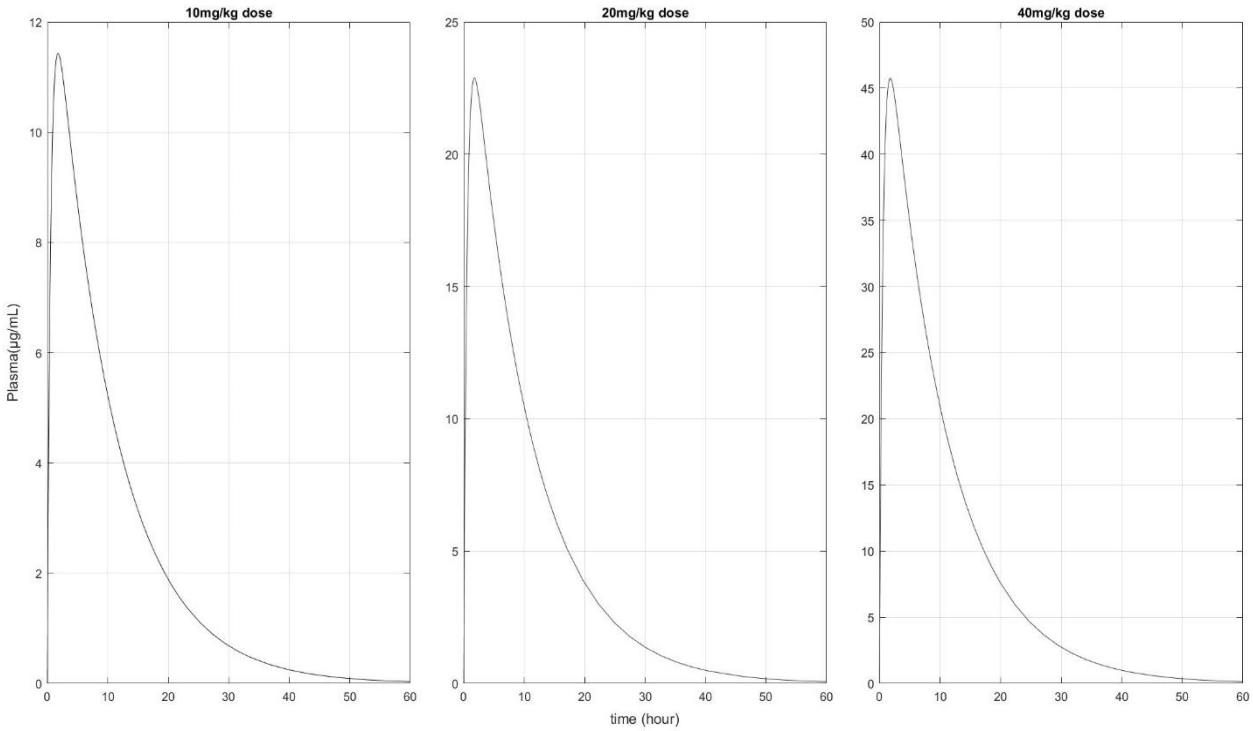
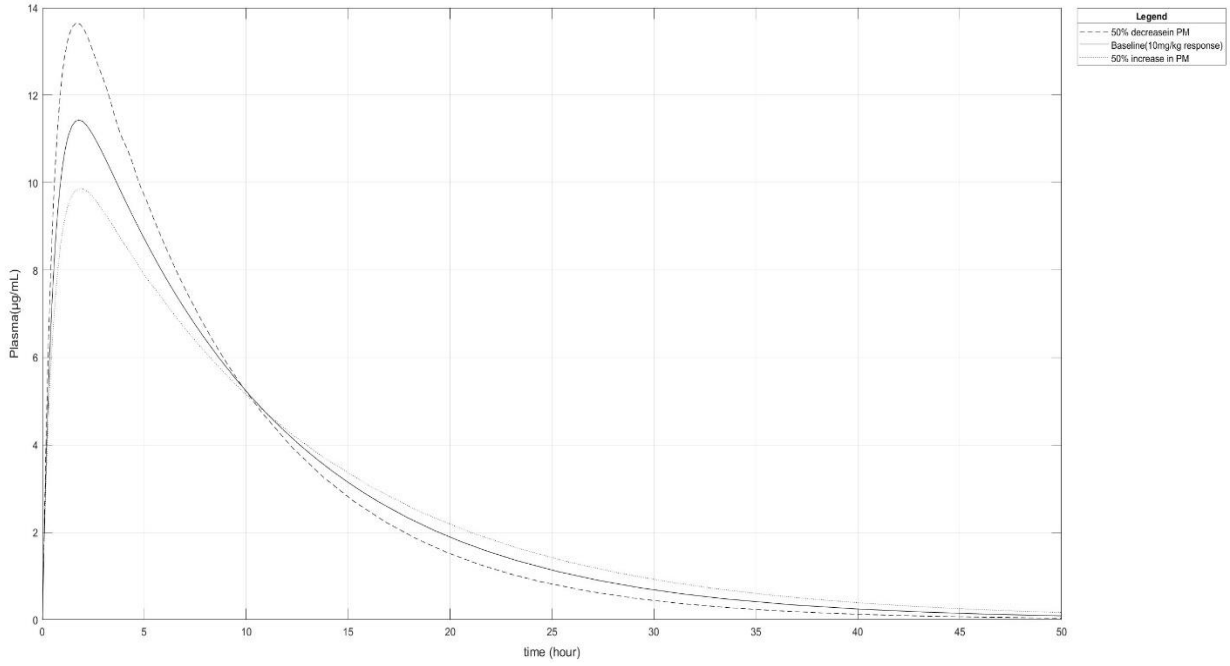


Figure 7: 10mg/mL baseline plasma Rifampin concentration with a 50% increase and decrease in PM



Perturbation Responses

Figure 8: 10mg/mL baseline plasma Rifampin concentration with a 50% increase and decrease in absorption rate(ka)

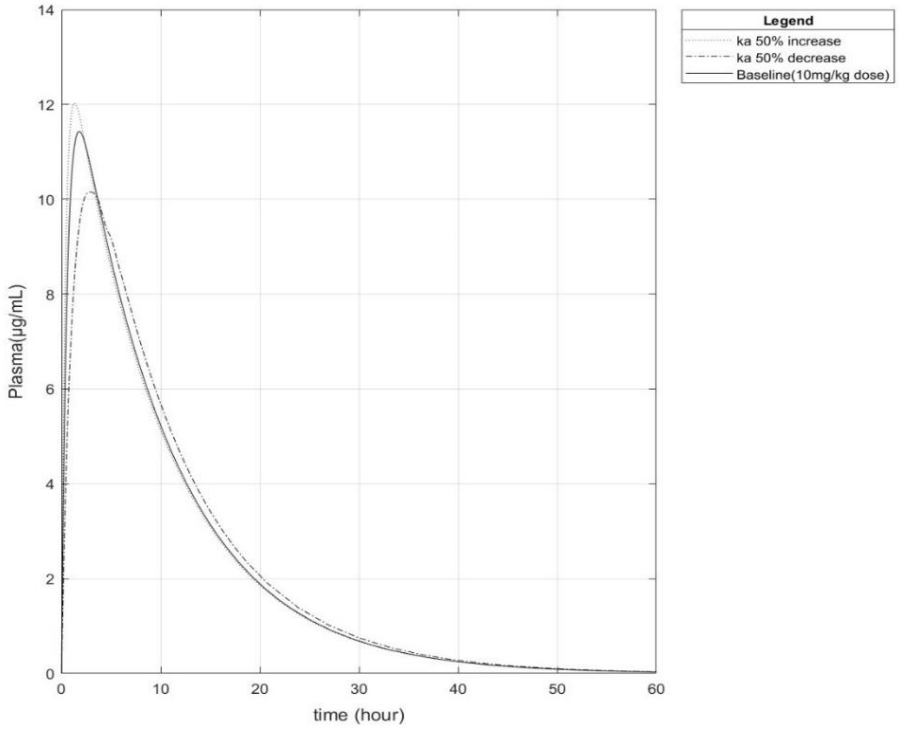


Figure 9: 10mg/mL baseline plasma Rifampin concentration with a 50% increase and decrease in clearance rate(CL)

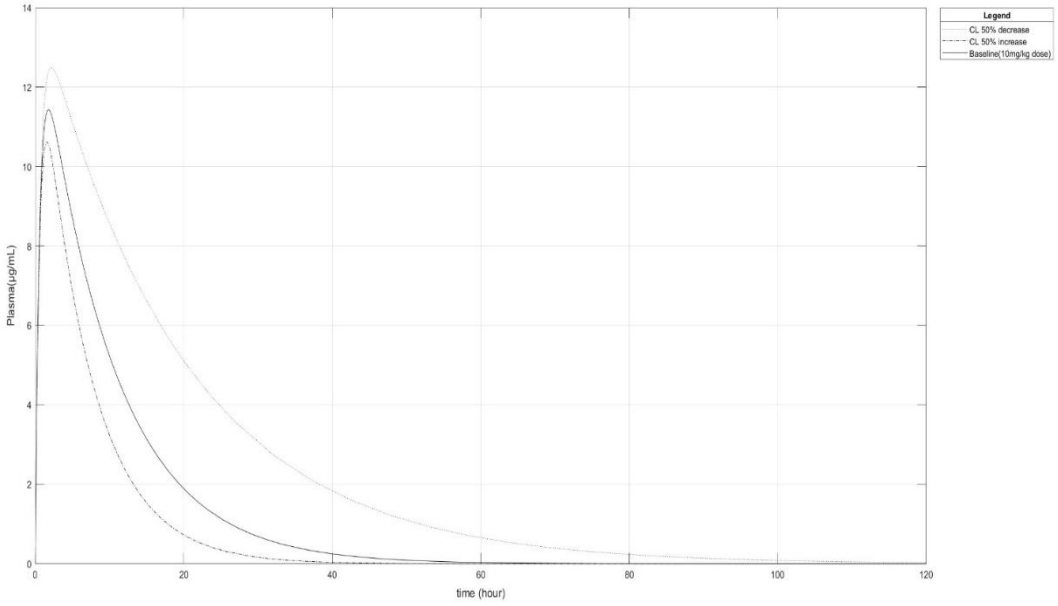
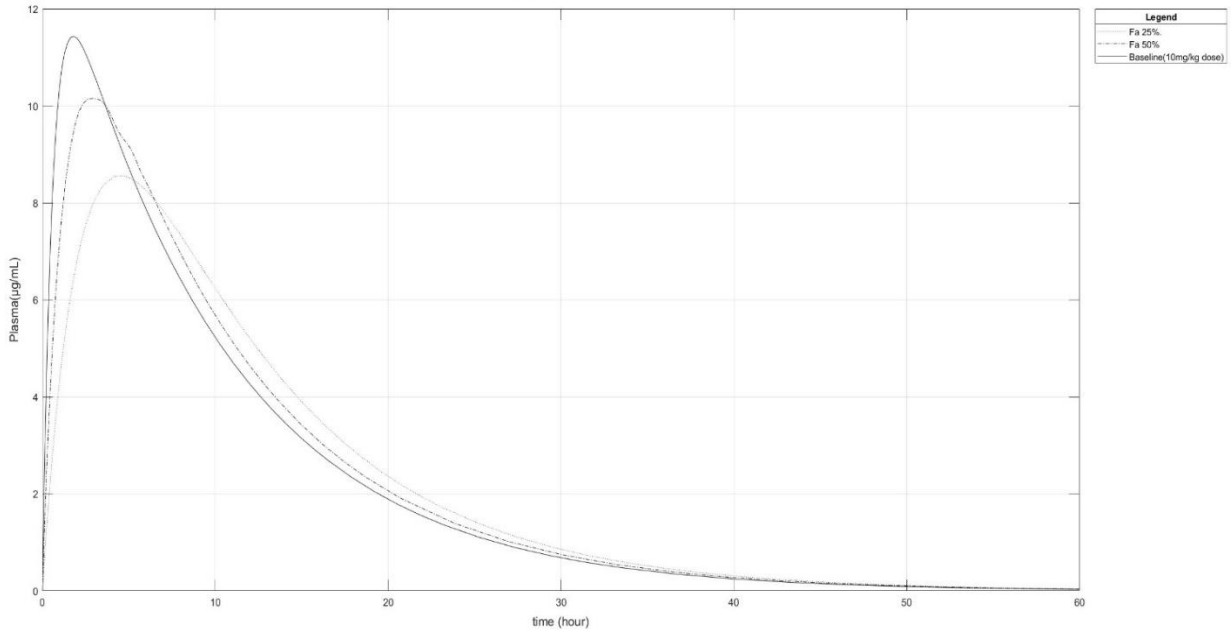


Figure 10: 10mg/mL baseline mouse plasma Rifampin concentration with a 50% increase and decrease in Bioavailability(Fa)



IV Dosing

Figure 11: 10mg/mL IV bolus dose Rifampin concentrations in mouse plasma, lung, liver, and kidney

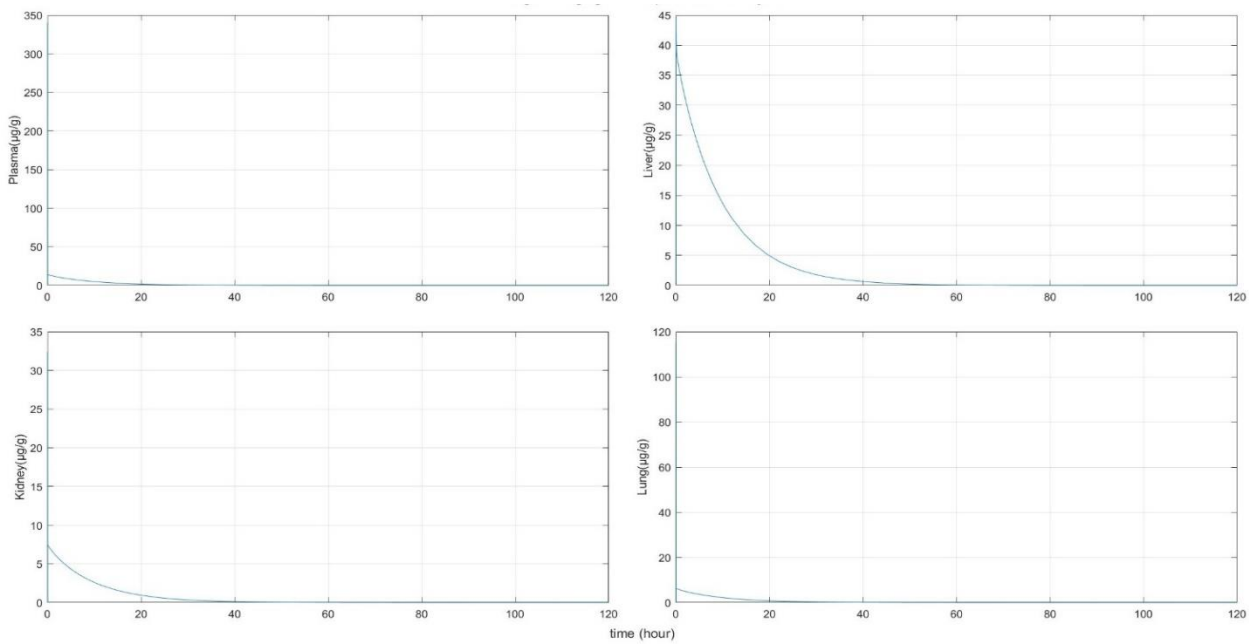


Figure 12: 10mg/kg single IV dose plasma concentration AUC over time

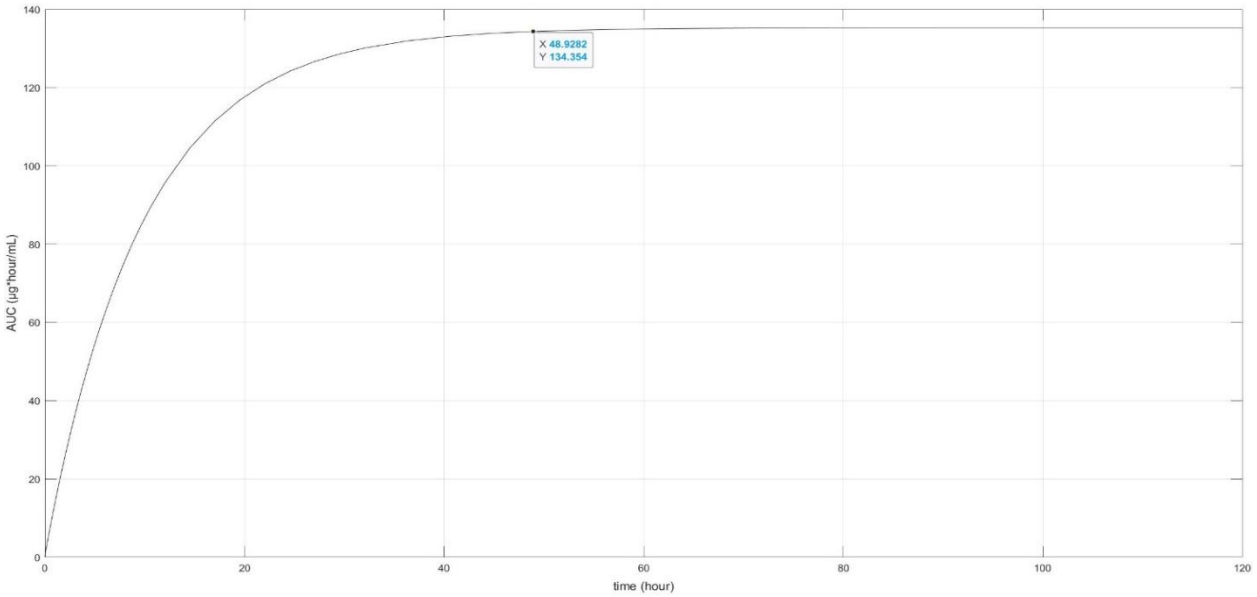


Figure 13: 10mg/mL repeated IV bolus dose Rifampin concentrations in mouse plasma and liver

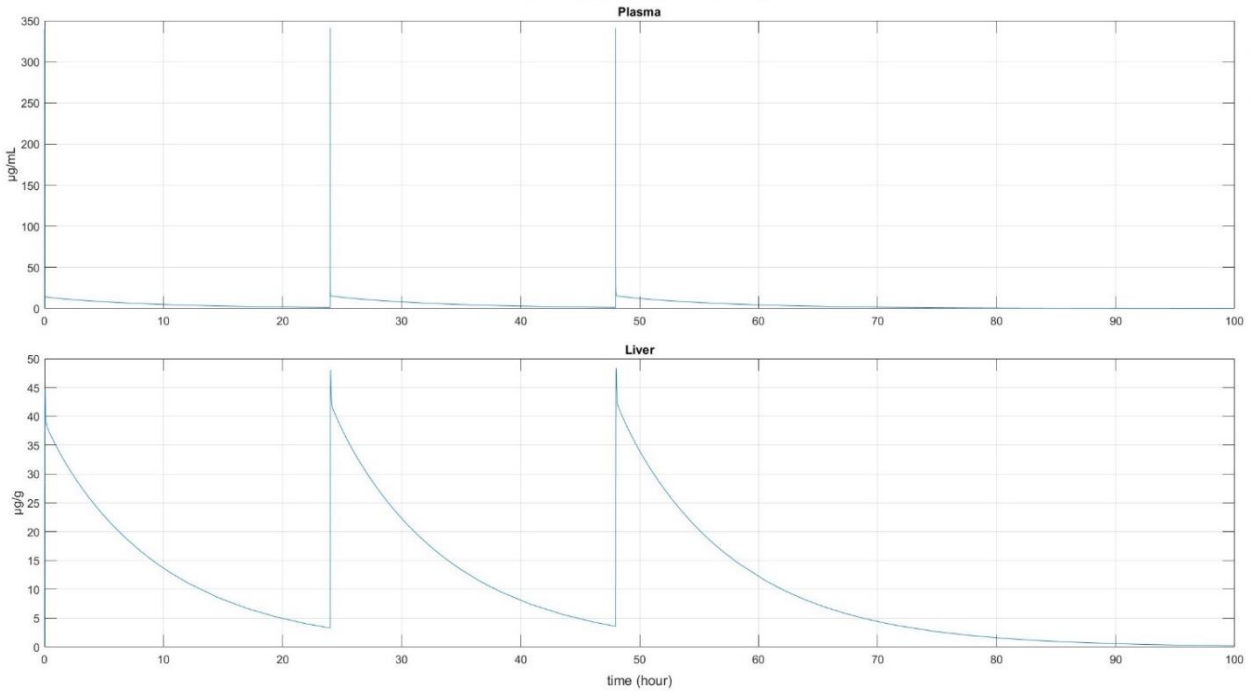


Table 1: Rifampin mouse plasma concentration NCA results from 10mg/kg oral dose from Lyons et al., the implemented model, and the 10mg/kg IV Rifampin dose

NCA Parameters(units)	Lyons et al.	Single Oral Rifampin dose	Single IV Rifampin dose
Cmax(µg/mL)	11.41	11.43421717	339.7893306
tmax(h)	1.78	1.800609769	0
half-life(t1/2) (h)	6.77	6.954410787	6.234112704
AUC(µg*h/mL)	132.9	133.9119122	135.2785852

Notes

I used ChatGPT to help me understand SimBiology's functions and interpret the ODEs generated by SimBiology.

The link to SimBiology and instructions for interpreting and installing the program are in this file's reference section.

The figures in this file are also included in the PowerPoint file attached to the final submission for better resolution.

References

1. Lyons, M. A., & Lenaerts, A. J. (2015). Computational pharmacokinetics/pharmacodynamics of rifampin in a mouse tuberculosis infection model. *Journal of Pharmacokinetics and Pharmacodynamics*, *42*(4), 375–389. https://doi.org/10.1007/s10928-015-9419-z
2. Lyons, M. A., Reisfeld, B., Yang, R. S. H., & Lenaerts, A. J. (2013). A Physiologically Based Pharmacokinetic Model of Rifampin in Mice. *Antimicrobial Agents and Chemotherapy*, *57*(4), 1763–1771. https://doi.org/10.1128/AAC.01567-12
3. https://www.mathworks.com/help/simbio/