Using Pharmacokinetics to Model Drug Delivery of Acetaminophen and Assess Effectiveness of Recommended Dosages for Typical and Atypical Liver Function

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1 Motivation/Purpose for the Simulation

In this project, we are modeling the rate of absorption of acetaminophen, also known as paracetamol, into the gastrointestinal (GI) tract and the bloodstream. The model is used to demonstrate the differences in the amount of acetaminophen present at steady-state for individuals with typical liver function and acute liver failure under normal usage. From this information, we hope to make conclusions about the recommended drug dosage for those impacted by liver (hepatic) conditions.

Acetaminophen is a common pain relief medication used in many drugs (i.e. Tylenol) that can be purchased over the counter. Due to the ease of accessibility of acetaminophen as well as its prevalence in many drugs, accidental overdose can occur as a result of incorrect dosage patterns, coupling multiple medications with acetaminophen together, and taking too large of a dosage at a time. The incorrect ingestion of acetaminophen has been shown to result in approximately 45.7% of cases of acute liver failure in North America and 65.4% in the UK [1]. Thus, the recommended dosage of acetaminophen has evolved over time, reducing from a maximum of 4000 mg to 3000 mg within 24 hours [2]. The aim of this reduction was to increase the safety of users and prevent accidental incidences of liver toxicity. However, this recommendation has been generalized to the entire population without consideration for liver function.

We believe that a distinction between recommended dosages for those with normal liver function and atypical liver function (i.e. acute liver failure) would be beneficial for human health and safety. Using first-order differential equations, we model the pharmacokinetics of drug dosages in the GI tract and bloodstream [3]. When a patient has a liver malfunction, it can take longer to metabolize drugs into the bloodstream. We will quantify these metabolism changes using past research to reveal the impact of acute liver failure on the steady-state mass of acetaminophen present in the blood with the currently recommended usage patterns.

2 Relevant Physiology and Anatomy

The main physiological pathway of acetaminophen consists of oral ingestion of the drug and transmission of the drug from the esophagus to the stomach, the small intestine, the liver, and finally the bloodstream (see Figure 1).

The primary mode of drug transport from the GI tract to the bloodstream for acetaminophen is passive diffusion [5], which occurs from the interior of the small intestine into the capillaries of the stomach and small intestine [4]. The diffusion rate is dependent on many factors such as the molecule's lipid solubility, size, degree of ionization, and the area of the absorptive surface. Since the surface of the cell membrane is a lipid, lipid-soluble drugs diffuse faster across cell membranes. Furthermore, smaller molecules tend to penetrate membranes faster than larger molecules.

Passive diffusion occurs from a region of high concentration to a region of low concentration to enter the bloodstream. As the concentration of the drug in the bloodstream increases over time, this concentration gradient will decrease. However, once the drug is metabolized by the cells, the concentration of the bloodstream will decrease, thus creating a larger concentration gradient between the small intestine and the bloodstream [6]. In our simulation, the rate at which the drug enters the GI tract is represented by

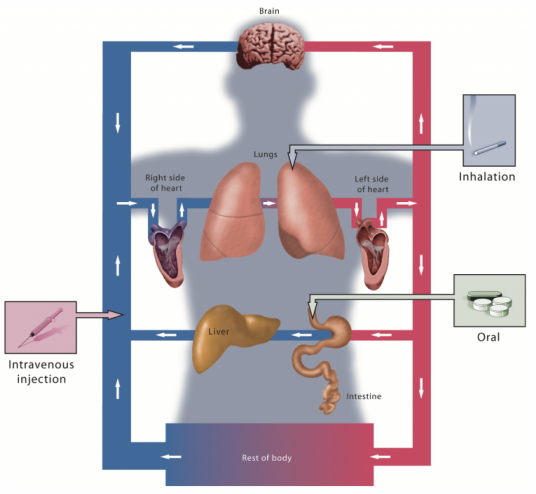

Figure 1: Methods of drug administration into the body, with the arterial system represented in red and venous in blue [4].

the parameter alpha (α), and the rate at which the drug leaves the GI tract and enters the bloodstream is accounted for by the parameter beta (β).

After entering the bloodstream, the drug will pass through the portal vein into the liver. The first-pass effect occurs, as the liver will induce extensive metabolism of the drug. From there, the drug exits through the venous system and enters the systemic circulation, which distributes the drug to the body's tissues [7]. Notably, distribution is not uniform for each tissue. Rather, it depends on the differences in blood perfusion between the systemic circulation and the tissue, tissue binding, regional pH, and the permeability of the cell membranes. Additionally, the rate at which the drug enters the tissue is dependent on factors including blood flow to the tissue and tissue mass. When the rate of flow of the drug into the tissue is the same as the rate of flow out of the tissue, the tissue is deemed to have reached a distribution equilibrium. Reaching this equilibrium demonstrates drug delivery to the tissue. A quicker equilibrium can be reached if there is a high level of vascularization between the blood and tissue.

Once the drug enters the cells, one of the main courses of action is the inhibiting of the COX pathway [8]. The exact mechanism of acetaminophen's action still remains unclear. However, the main mechanism is its inhibition of the COX pathway which leads to its analgesic (pain-relieving) and antipyretic (fever-reducing) properties. It has been theorized that acetaminophen inhibits a splice variant of the COX-1 enzyme, but this has not been confirmed in humans.

After distribution, the drug leaves the cells and re-enters the bloodstream, eventually accumulating in the liver. In the liver, acetaminophen is converted into pharmacologically inactive glucuronide and sulfate as well as oxidized into a reactive metabolite NAPQI (N-acetyl-p-benzoquinone imine). Although only 5-10% of the drug is broken down into NAPQI, this highly reactive molecule leads to acetaminophen-induced hepatotoxicity. Roughly 5% of the initial dose of acetaminophen that entered the body is excreted unchanged [9]. Finally, post leaving the liver, most of the glucuronide and sulfate metabolites get transported to the kidneys from the bloodstream. After arriving in the kidneys, these metabolites are excreted.

The rate of excretion from the body is directly proportional to the rate at which the liver functions to prepare the drug for excretion. When a hepatic injury is present, this entire process (first-pass and second-pass) takes longer, leading to a greater accumulation and longer half-life of acetaminophen in the blood. Thus, in our model, α is dependent on liver function and excretion rates.

3 General Components of the System and Mathematical Model

Before discussing the model, there are several important parameters to outline. Namely, α and β, which are the metabolisms in the bloodstream and GI tract, respectively. These values are calculated from the half-life in the bloodstream and GI tract as shown in Equations 1 and 2.

$$\alpha = \frac{ln(2)}{half\_life\_bloodstream} \tag{1}$$

Drug metabolism in the bloodstream [10].

$$\beta = \frac{ln(2)}{half\_life\_gi\_tract} \tag{2}$$

Drug metabolism in the GI tract [10].

To compile the Simulink system necessary for the demonstration of our model, we used several components seen in Figure 2.

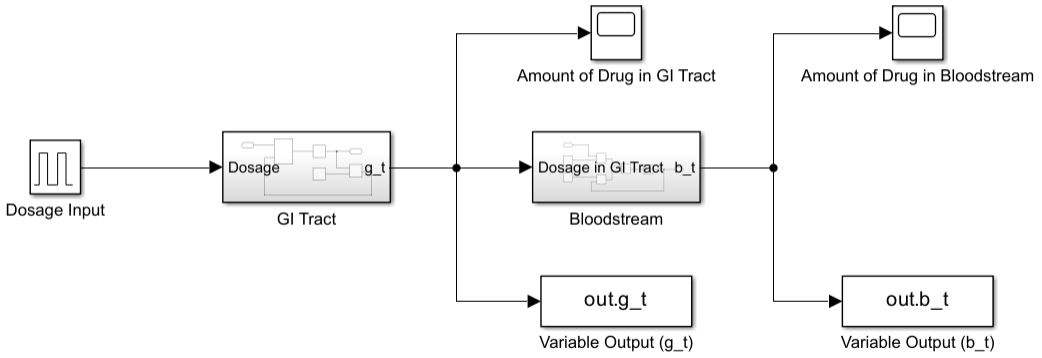

Figure 2: Drug administration model completed in Simulink. Demonstrates the amount of drug in the GI tract and bloodstream over time given initial parameters including dosage amount and frequency.

The "Dosage Input" block is a pulse generator that uses the initial dosage parameter to simulate ingestion of the drug into one's body. The "GI Tract" subsystem block takes in this input and outputs the amount of drug in the GI tract at time t. The output, $g(t)$, is sent to the MATLAB workspace by the "Variable Output (g_t)" to workspace block and visualized using a scope by the "Amount of Drug in GI Tract" block. After the output of the GI tract is calculated, it is sent to the "Bloodstream" subsystem block. This subsystem calculates the amount of drug in the bloodstream at time t, $b(t)$, which is outputted similarly to the MATLAB workspace and visualized in a scope by blocks "Variable Output (b_t)" and "Amount of Drug in Bloodstream", respectively.

Diving into the subsystems, we will first look at the GI tract as described by Equation 3 and shown in Figure 3.

$$\frac{dg}{dt} = f(t) - \beta g(t) \tag{3}$$

The first-order differential equation to model drug amount in GI tract [3].

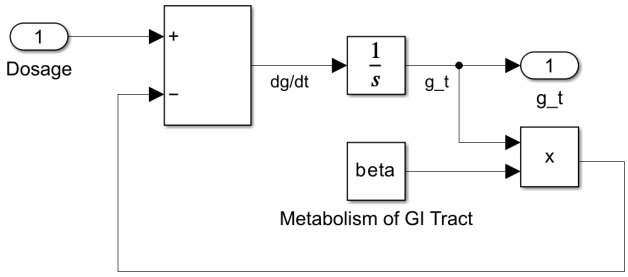

Figure 3: GI tract subsystem block representing Equation 3.

The GI tract subsystem takes the dosage input value and, using Equation 3, calculates a $\frac{dg}{dt}$ which is integrated to find $g(t)$. The $\frac{dg}{dt}$ is calculated using a subtraction block of $f(t)$ and $\beta g(t)$. $f(t)$ is the initial dosage input. $\beta g(t)$ is obtained by using a product block of the constant input β from the MATLAB workspace and $g(t)$ obtained from the integral block of $\frac{dg}{dt}$. The output $g(t)$ is sent to the main model for visualization, transmission to the MATLAB workspace, and implementation in the bloodstream subsystem.

Next, we look at the bloodstream subsystem which is created from Equation 4 and pictured in Figure 4.

$$\frac{db}{dt} = \beta g(t) - \alpha b(t) \tag{4}$$

The first-order differential equation to model drug amount in bloodstream [3].

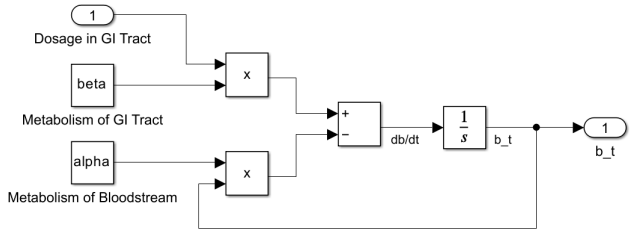

Figure 4: Bloodstream subsystem block representing Equation 4.

The bloodstream subsystem takes the dosage in the GI tract, $g(t)$, from the previous subsystem and, using Equation 4, calculates a $\frac{db}{dt}$ which is integrated to find $b(t)$. $\frac{db}{dt}$ is computed by using a subtraction block of $\beta g(t)$ and $\alpha b(t)$. $\beta g(t)$ is obtained by using a product block of the constant input β from the MATLAB workspace and $g(t)$ obtained from GI tract subsystem depicted in Figure 3. $\alpha b(t)$ is obtained by using a product block of the constant input α from the MATLAB workspace and $b(t)$ obtained from the integral block of $\frac{db}{dt}$. The output $b(t)$ is sent to the main system for visualization and transmission to the MATLAB workspace.

4 Simulation Results for Healthy Physiology and Liver Failure Conditions

Numerous assumptions must be made in order to produce our model. First, we assume steady-state conditions, meaning that the amount of drug deposited into the small intestine is equal to the amount of drug that diffuses into the bloodstream (no loss of drug in the GI tract). The initial dosage is assumed to be the recommended dosage of Tylenol, which is 2 500 mg tablets taken every 6 hours [2]. Additionally, we assume the initial dose (1000 mg) is entirely ingested and present in the small intestine within 60 seconds. As a result, to enable the dosage to be input in a pulse generator, we multiply it by 60 and adjust the generator pulse width $((\frac{\frac{1}{pulse\_period}}{60}) * 100)$ to account for the appropriate time conversions.

To calculate bloodstream content outputs in a healthy physiology and liver failure condition, we adjust specific parameters. The normal half-life for acetaminophen in the bloodstream was found to be 3 hours. When analyzing patients with hepatotoxicity, the half-life increases up to 6.4 hours [11]. Altering this value impacts the α metabolism used in the model. Half-life in the GI tract was set to a constant 2.5 hours [11] throughout both conditions. An example of the parameters.m MATLAB file is shown in Figure 7 in the Appendix (Section 5). Figures 5 and 6 compare the steady-state amount of acetaminophen found in patients with normal liver function, and those with hepatotoxicity after repeated consumption of the recommended dosage over 48 hours. These figures were generated using the code from Figure 8 in the Appendix (Section 5).

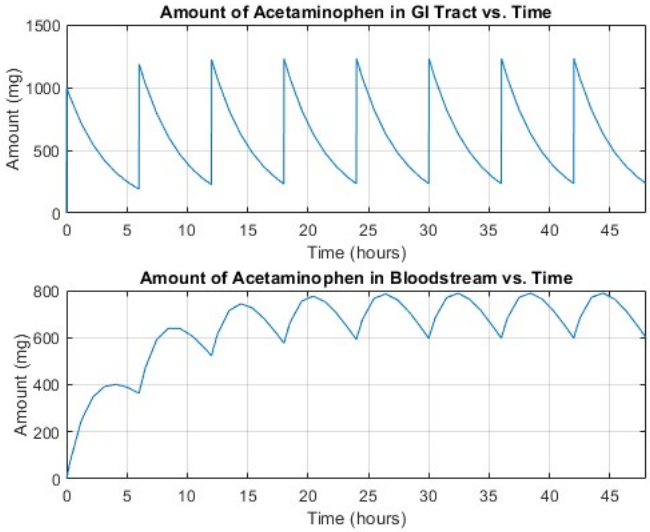

Figure 5: Mass of acetaminophen in the GI tract and bloodstream for normal liver function.

Here, we can see that the steady-state mass of acetaminophen in the bloodstream after repeated use ranges between approximately 600 and 800 mg. Currently, this is seen as a safe range to remain in and effective dosage to alleviate the conditions acetaminophen aims to ease (pain, fever). However, as we can see in 6, subjects with liver failure are subject to a larger steady-state amount of acetaminophen in the bloodstream.

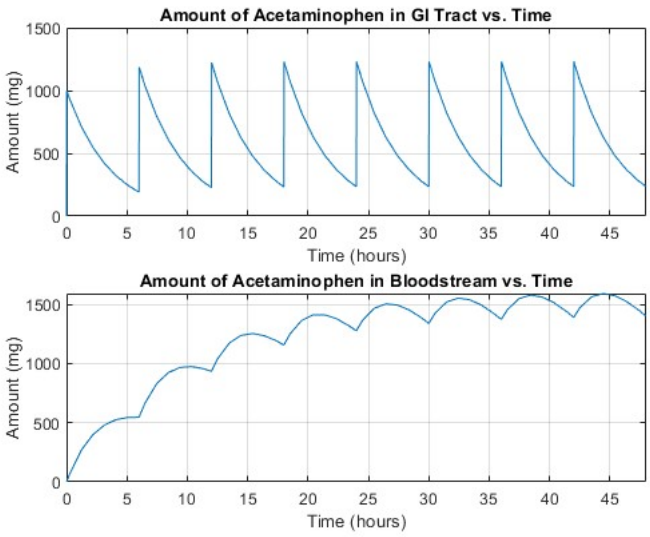

Figure 6: Mass of acetaminophen in the GI tract and bloodstream for abnormal liver function.

The mass present in the blood is shown to range between approximately 1400 and 1600 mg. As a result of the increased half-life of subjects with liver failure, the drug remains in the bloodstream longer and exists at a higher mass in the blood. Additionally, a steady-state amount of drug in the bloodstream takes longer to achieve.

5 Conclusion

Therefore, as demonstrated by our simulation, we can see that patients with liver failure are delivering an inappropriate amount of acetaminophen to their system despite taking the recommended dosage. The increased dosage depicted above may result in even further damage to the liver, making this issue compounding. Thus, we believe our initial claim that individuals with atypical liver function should be subjected to different dosage recommendations than those with typical liver function is confirmed. We can use this model to further investigate appropriate dosage patterns for this patient population.

The model could be improved through increased complexity. Specifically, the model's assumptions may result in a significant difference in the output compared to what occurs in actual physiology. Performing analysis to understand if these assumptions can increase in complexity may help the model generalize better and be more accurate.

Finally, our simulation has other potential uses. For example, it could be used to help determine personalized dosage patterns for individuals if provided their half-life in the bloodstream. While this may be an unrealistic measure to be provided, we believe that this value may be able to be predicted based on measures of liver function. Even more, the model can be altered to demonstrate the delivery of other drugs. This may be important for drugs with greater toxicity, as it can be used to determine dosage patterns that will avoid any risk of a lethal dosage. Finally, adjustment of the GI tract absorption may also provide insight into the impact of GI health on oral drug delivery.

References

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Appendix

```
% filename: parameters.m

% dosage of ingestion, acetaminophen, in mg
dosage_amount = 1000;

% adjust dosage for input into system
initial_dosage = dosage_amount*60;

% pulse period to determine frequency of dosage ingestion, in hours
pulse_period = 6;

% pulse width adjusts dosage to represent, in % of pulse period
pulse_width = ((1/pulse_period)/60)*100;

% total time window to view drug in system, in hours
total_time = 48;

% drug half-life of acetaminophen in the bloodstream/GI tract, in hours
half_life_bloodstream = 3;
half_life_gi_tract = 2.5;

% the metabolism of the drug in the bloodstream, in 1/hours
alpha = log(2)/half_life_bloodstream;

% the metabolism of the drug in the GI tract, in 1/hours
beta = log(2)/half_life_gi_tract;
```

Figure 7: MATLAB code of parameters for model.

```
% filename: plot_graphs.m

% from Simulink
% g_t = amount of drug in the GI tract at time t, in mg
% b_t = amount of drug in the bloodstream at time t, in mg

figure;
subplot(2,1,1);
plot(out.tout, out.g_t)
xlim([0,total_time])
title("Amount of Acetaminophen in GI Tract vs. Time")
xlabel("Time (hours)")
ylabel("Amount (mg)")
grid on;

subplot(2,1,2);
plot(out.tout, out.b_t)
xlim([0,total_time])
title("Amount of Acetaminophen in Bloodstream vs. Time")
xlabel("Time (hours)")
ylabel("Amount (mg)")
grid on;
```

Figure 8: MATLAB code of plots made from model outputs.