Lansoprazole

One of the most popular stomach reflux medicine prescribed in the world

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Summary

Introduction: Lansoprazole is a Proton Pump Inhibitor (PPI) used for the treatment of acid reflux. Ages are shown to have influence on how the medicine work in humans' metabolism. An appropriate dose and when to take the medicine should be predicted for optimal effectiveness.
Method: A mathematical model is built up and simulated in a Python program with the given information (eg. Peak plasma concentration) based on Eurler's method. A number of graphs showing the changes in the mass of Lansoprazole in GI tract and blood are created with varying inputs of doses and time intervals between uses. Based on the original model, a new one is made to visualize how food influences the bioavailability of Lansoprazole.
Result and conclusion: The results of this model are only applied to patients without any other medical problems. Although many factors are not counted, the model do show how the amount of LFDT changes in humans plasma over time, which resembles the real graph plotted by realistic adminstration approximately 80%. Moreover, the infants (2–3 months old) have higher exposure to LFDT than adults, and the elderly should not use the medicine for longer than prescription to prevent bone fractures.

Contents

List of variables

t: Time (hours)

$M_{\text{GI}}(t)$: The mass of Lansoprazole in GI tract at time t (mg)

$M_{\text{Blood}}(t)$: The mass of Lansoprazole in bloodstream at time t (mg)

Δt: The change in time (hours)

ΔM_{GI}: The change in the mass of Lansoprazole in GI tract (mg)

ΔM_{Blood}: The change in the mass of Lansoprazole in bloodstream (mg)

$V_{\text{GI}}(t)$: The volume of contents in GI tract (10 L)

$V_{\text{Blood}}(t)$: The volume of blood in human body (4.5L)

d_1: The diffusion rate of Lansoprazole from GI tract to bloodstream (L/hour)

d_2: The elimination rate of Lansoprazole from bloodstream (L/hour)

k_1: Coefficient for t_{max} in plasma ($0 < k_1 < 1$)

k_2: Coefficient for $t_{half-life}$ in plasma ($k_2 > 1$)

Chapter 1

Introduction

Nowadays, the world keeps changing; people are completely immerged into work. Therefore, they do not have enough time for home-cooked meals, and the most available alternative is fast food. According to a paper published by National Center for Health Statistics, between 2013 and 2016, 36.6% of American adults consumed fast food on a given day [1]. Fast food is well-known for its high content of fat, which causes the lower esophageal sphincter to relax and to allow food to move up back to the esophagus. This situation is commonly named *"Acid Reflux"*.
Lansoprazole is Protons Pump Inhibitor (PPI). This helps reduce the long-lasting production of acid in the stomach and relieve the symptoms of acid reflux after a few days to weeks (depending on the seriousness of the patients). Due to its direct relationship to GI tract, it is necessary to predict the effect of food consumption on the bioavailability of Lansoprazole, so that a right dose is prescribed for the optimal result.
The purpose of this report is to determine the changes in concentration of Lansoprazole in blood over time. Interest will focus on the peak plasma level and the amount of time to reach that state with and without the consumption of food.
The calculations required for this will be explained and assembled in a Python program. Several graphs will plot out the wanted information. Even though this program is a large simplification of reality, leaving many disturbance factors (e.g. the thickness of absorption membrane and other medical usage) unnoted, the outcome of the program resembles the actual changes of amount of Lansoprazole Fast Disintegrating Tablet 30mg (LFDT) in humans body. After varying the input data, including doses and time intervals between usage, an ideal prescription will be deduced and discussed.
In this report, a systematical build-up of the mass determination of Lansoprazole will be done. First, in Chapter 2, the theory behind the mathematic model will be explained. Unkown constants of the model will be evaluated in chapter 3 with a simplified equation, followed by the validation of them in a complete interaction model in chapter 4. The stability on small and large time scale will also be tested in this chapter. The chapter 5 shows how ages influence the action of LFDT in our body. Chapter 6 will draw a conclusion for the result of this report.

Chapter 2

Mathematical model design

As mentioned in the Introduction, the graphs of mass of Lansoprazole in humans body versus time are plotted out based on a mathematical model. In this chapter, a step by step procedure of buiding up this system of equations are presented. Firstly, Section 2.1 presents the theory of Lansoprazole pathway in humans body. Secondly, Section 2.2 shows the theory behind the equation for the changes in mass of Lansoprazole in GI tract. Finally, the equation for the changes in mass of Lansoprazole in bloodstream is dedrived in section 2.3.

2.1 The pathway of Lansoprazole in humans body

Lansoprazole Fast Disintegrating Tablet (LFDT) is consumed orally. It passes through Esophagus, Stomach and Intestines (Small Intestin and Large Intestine) where it is diffused into the blood stream.
Lansoprazole is transformed into two active species which inhibit acid secretion by (H+,K+)-ATPase within the parietal cell canaliculus, but are not present in the systemic circulation [2].
LFDT is fully eliminated from the body. A study with 14C labelled lansoprazole indicated that approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the faeces [3].

2.2 The change in mass of LFDT in GI tract over time

In humans body, LFDT is passively diffused from the GI tract with high concentration of LFDT at first to the blood stream with lower concentration. Therefore, the diffusion rate d_1 relates to the changes in mass of LFDT in GI tract. The value of d_1 is determined in the next chapter:

$$\Delta M_{GI} = M_{GI}(t + \Delta t) - M_{GI}(t) = -d_1 \Delta t (\frac{M_{GI}(t)}{V_{GI}} - \frac{M_{Blood}(t)}{V_{Blood}})$$

$$\Leftrightarrow \Delta M_{GI} = -d_1 \Delta t(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) \tag{2.1}$$

Then, the balance equation 2.1 is divided by Δ_t:

$$\frac{\Delta M_{GI}}{\Delta t} = -d_1(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5})$$

And the limit for Δt to zero is taken:

$$\lim_{\Delta t \to 0} \frac{\Delta M_{GI}}{\Delta t} = \lim_{\Delta t \to 0} -d_1(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5})$$

$$\Leftrightarrow \frac{dM_{GI}}{dt} = -d_1(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) \tag{2.2}$$

2.3 The change in mass of LFDT in bloodstream over time

Beside the diffusion rate d_1, the mass of LFDT in bloodstream also depends on the elimination rate d_2 of LFDT from bloodstream. The value of d_2 is determined in the next chapter:

$$\Delta M_{Blood} = M_{Blood}(t + \Delta t) - M_{Blood}(t) = -d_1 \Delta t(\frac{M_{GI}(t)}{V_{GI}} - \frac{M_{Blood}(t)}{V_{Blood}}) - d_2 \frac{M_{Blood}(t)}{V_{Blood}}$$

$$\Leftrightarrow \Delta M_{Blood} = -d_1 \Delta t(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) - d_2 \frac{M_{Blood}(t)}{4.5} \tag{2.3}$$

Then, the balance equation 2.3 is divided by Δ_t:

$$\frac{\Delta M_{Blood}}{\Delta t} = -d_1(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) - d_2 \frac{M_{Blood}(t)}{4.5}$$

And the limit for Δt to zero is taken:

$$\lim_{\Delta t \to 0} \frac{\Delta M_{Blood}}{\Delta t} = \lim_{\Delta t \to 0} -d_1(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) - d_2 \frac{M_{Blood}(t)}{4.5}$$

$$\Leftrightarrow \frac{dM_{Blood}}{dt} = -d_1(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) - d_2 \frac{M_{Blood}(t)}{4.5} \tag{2.4}$$

To conclude, LFDT is consumed orally and diffused from GI tract to bloodstream. A mathematical model is built up from its passive diffusion principle:

$$\begin{cases} \dfrac{dM_{GI}}{dt} &= -d_1(\dfrac{M_{GI}(t)}{10} - \dfrac{M_{Blood}(t)}{4.5}), & M_{GI}(0) = 30 \\ \dfrac{dM_{Blood}}{dt} &= d_1(\dfrac{M_{GI}(t)}{10} - \dfrac{M_{Blood}(t)}{4.5}) - d_2 \frac{M_{Blood}(t)}{4.5}, & M_{Blood}(0) = 0. \end{cases} \tag{2.5}$$

Chapter 3

Determination of diffusion rate d_1 and elimination rate d_2

In Chapter 2, a couple of differential equations for the change in mass of LFDT in humans body are built up. However, diffusion rate d_1 and elimination rate d_2 are still unknown. Their value ranges are discussed respectively in section 3.2 and section 3.3. The stability of the model is checked in section 3.1. Finally, in section 3.4, the combination of d_1 and d_2 is validated.
(For an example of Python programs used in this chapter, see Appendix A)

3.1 The stability of the mass of LFDT in bloodstream model

In the estimation of d_1 and d_2 , only the simplified equation 2.4 is used, and dM_{MGI} is assumed to be constant, 30 mg (a tablet of LFDT). The equation $\frac{dM_{Blood}}{dt} = 0$ is solved to give the equilibrium point:

$$M_{blood}equi. = \frac{13.5d_1}{d_1 + d_2} \tag{3.1}$$

Because both d_1 and d_2 are positive, this equilirium point is also positive. Moreover, when the mass of LFDT in bloodstream is half of the equilibrium value, $\frac{dM_{Blood}}{dt}$ is positive; when the mass of LFDT in bloodstream is twice of the equilibrium value, $\frac{dM_{Blood}}{dt}$ is negative. This leads to the fact that this equilibrium point is stable.

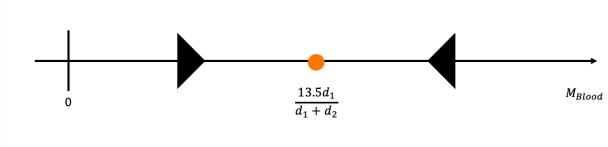

Figure 3.1: Phase line of the mass of LFDT in bloodstream M_{Blood}

3.2 Diffusion rate d_1

d_2 is assumed to be zero:

$$\frac{dM_{Blood}}{dt} = d_1(3 - \frac{M_{Blood}(t)}{4.5}), \quad M_{Blood}(0) = 0 \tag{3.2}$$

3.2.1 Analytical solving of simplified equation

The equation 3.2 is solved analytically:

$$\int \frac{1}{3 * 4.5 - M_{blood}} dM_{Blood} = \int \frac{d_1}{4.5} dt \Leftrightarrow -\ln(13.5 - M_{blood}) = \frac{d_1}{4.5} + c$$

The value of c is determined by plug-in of $M_{Blood}(0)$:

$$c = -\ln 13.5$$

$$\Rightarrow -\ln(13.5 - M_{blood}) = \frac{d_1}{4.5} - \ln 13.5 \tag{3.3}$$

3.2.2 d_1 value range

In reality, the amount of time for LFDT to reach its peak plasma concentration is from 1.5 hours to 2 hours [2]. However, in this simplified model, the concentration of LFDT in GI is kept constant over time, which leads to the fact that the mass of LFDT in bloodstream M_{Blood} reaches its equilibrium much earlier than expected. Hence, it is assumed to take M_{Blood} only k_1 times the real needed time to hit the peak ($k_1 < 1$). It is impossible to find the exact moment M_{Blood} reaches the equilibrium point of 13.5 mg (based on equation 3.1), it is assumed that the mass of LFDT in plasma is 13.45 mg at a moment between $1.5k_1$ and $2k_1$ hour. These given values are plugged into the equation 3.3, giving the value range of the diffusion rate d_1 from $\frac{12.5964}{k_1}$ to $\frac{16.79526}{k_1}$.
The smaller k_1 is, the faster the system reaches its equilibrium. Moreover, although the equilibrium is reached much faster than in reality, it is only possible to be approximately twice faster at maximum. Therefore, 0.5 is chosen to be the value of value of k_1. As a consequence, the maximum d_1 value is 33.5906 because it gives the smoothest graph when simulating in Python based on Euler's method.
With $d_1 = 33.5906$, the model 3.2 is simulated in Python with difference step-sizes $(0.1, \frac{0.1}{2}, \frac{0.1}{4}, \frac{0.1}{8})$:

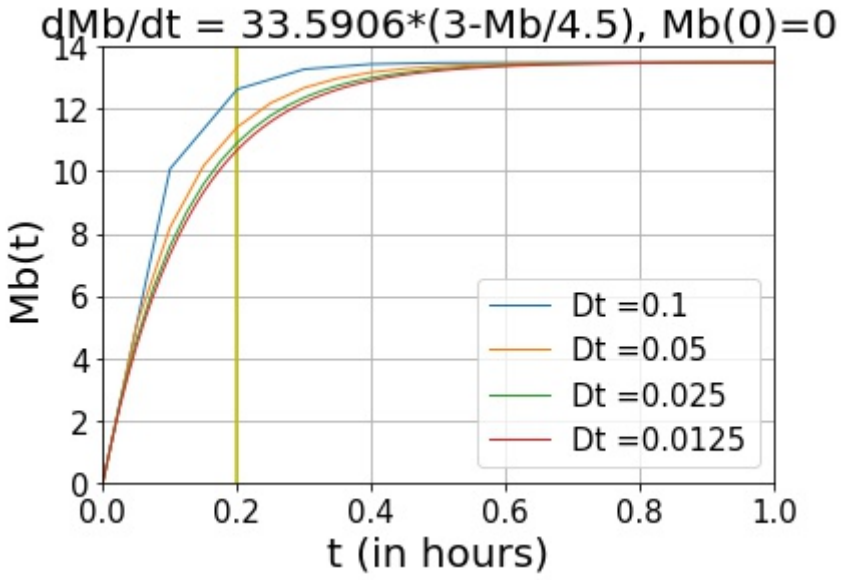

Figure 3.2: The mass of LFDT in bloodstream over time with different step-sizes Δt, $d_2 = 0$

In the figure 3.1, the largest differences in the value of M_{Blood} occur around 0.2 hours, so the step-sizes are very important to know the mass of LFDT in plasma at 0.2 hours. The goal for the absolute value of error is smaller than 0.03 mg; hence, smaller step-sizes (eg. $0.001, \frac{0.001}{2}, \frac{0.001}{4}$, etc) are simulated in Python program. Among those values of Δt, 0.001 is the largest number that fits the goal. With $\Delta t = 0.001$, the error is approximately -0.017 mg.

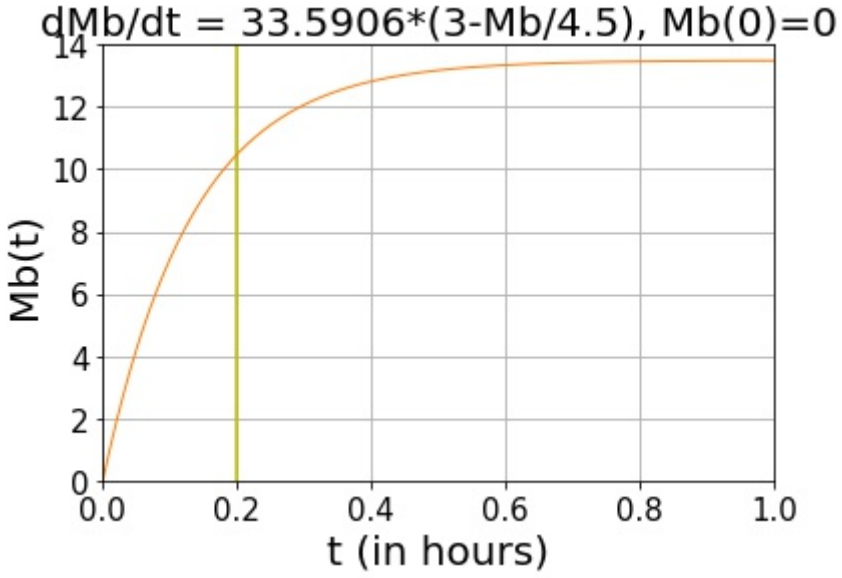

Figure 3.3: The mass of LFDT in bloodstream over time with $\Delta t = 0.001$, $d_2 = 0$

3.3 Elimination rate d_2

d_1 is assumed to be zero, and the mass of LFDT in plasma at $t = 0$ is the equilibrium point of model 3.2, $M_{Blood} = 13.5$:

$$\frac{dM_{Blood}}{dt} = -d_2 \frac{M_{Blood}(t)}{4.5}, \quad M_{Blood}(0) = 13.5 \tag{3.4}$$

3.3.1 Analytical solving of simplified equation

The equation 3.4 is solved analytically:

$$4.5 \int \frac{1}{M_{blood}} dM_{Blood} = -d2 \int dt \Leftrightarrow 4.5 \ln (M_{Blood}) = -d_2 t + c$$

The value of c is determined by plug-in of $M_{Blood}(0)$:

$$c = 4.5 \ln 13.5$$

$$\Rightarrow 4.5 \ln (M_{Blood}) = -d_2 t + 4.5 \ln 13.5 \tag{3.5}$$

3.3.2 d_2 value range

In reality, the half-life of LFDT in plasma is 1.5 ($\pm$1) hours [2]. However, the concentration of LFDT in GI tract is kept constant over time, $M_G I = 30$, so the amount of time for LFDT to reduce by half should be longer than in reality, between $0.5k_2$ and $2.5k_2$ ($k_2 > 1$). These values of k_2 are plugged into the equation 3.5 to get the value range for d_2, from $\frac{1.2477}{k_2}$ to $\frac{6.2383}{k_2}$.
The larger k_2 is, the slower the original mass of LFDT in plasma reduces by half. In a normal person's metabolism, a reasonable k_2 value is 2. As a result, the maximum d_2 value is 3.11915 because it gives the smoothest graph when simulating in Python based on Euler's method.
With $d_2 = 3.11915$, the model 3.4 is simulated in Python difference step-sizes ($0.1, \frac{0.1}{2}, \frac{0.1}{4}, \frac{0.1}{8}$):

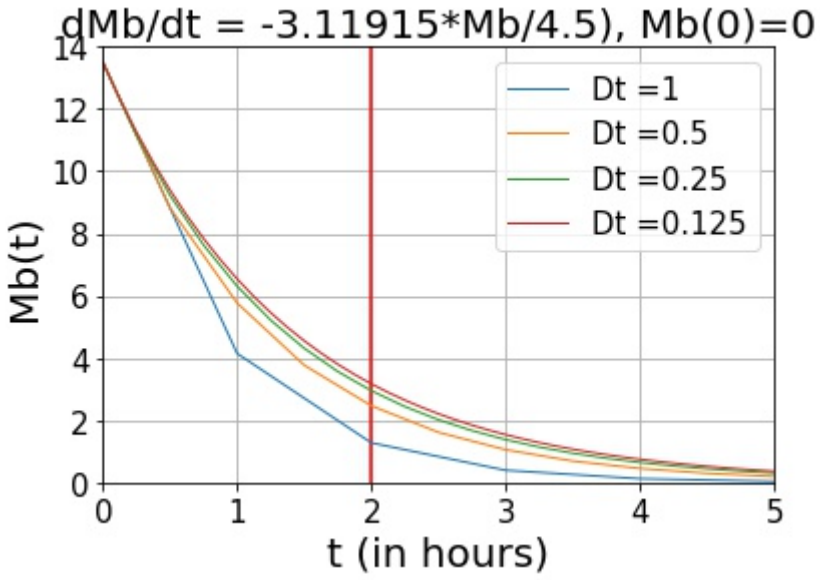

Figure 3.4: The mass of LFDT in bloodstream over time with different step-sizes Δt, $d_1 = 0$

In the figure 3.3, the largest differences in the value of M_{Blood} occur around 2 hours, so the step-sizes are very important to know the mass of LFDT in plasma at 2 hours. Then the model is simulated with step-sizes of 0.001 and 0.002 to calculate the error of $\Delta t = 0.001$, which fits the goal for error with d_1, E $= 1.6 * 10^{-3}$. This error is small enough for the system.

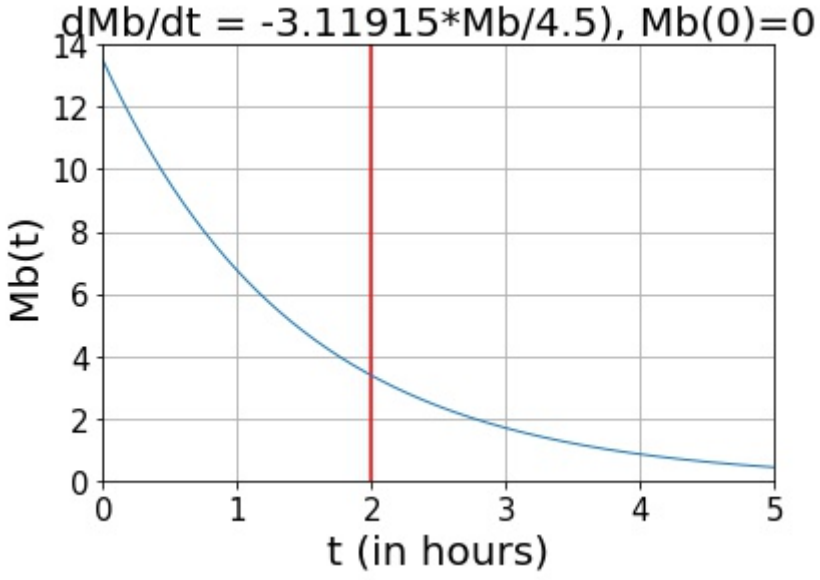

Figure 3.5: The mass of LFDT in bloodstream over time with $\Delta t = 0.001$, $d_1 = 0$

3.4 Validation of d_1 and d_2 in simplified model

The complete simplified model for the mass of Lansoprazole in bloodstream over time is:

$$\frac{dM_{Blood}}{dt} = 33.5906(3 - \frac{M_{Blood}(t)}{4.5}) - 3.11915\frac{M_{Blood}(t)}{4.5}, \quad M_{Blood}(0) = 0 \tag{3.6}$$

This model is simulated in a Python program with different step-sizes, giving the following graphs:

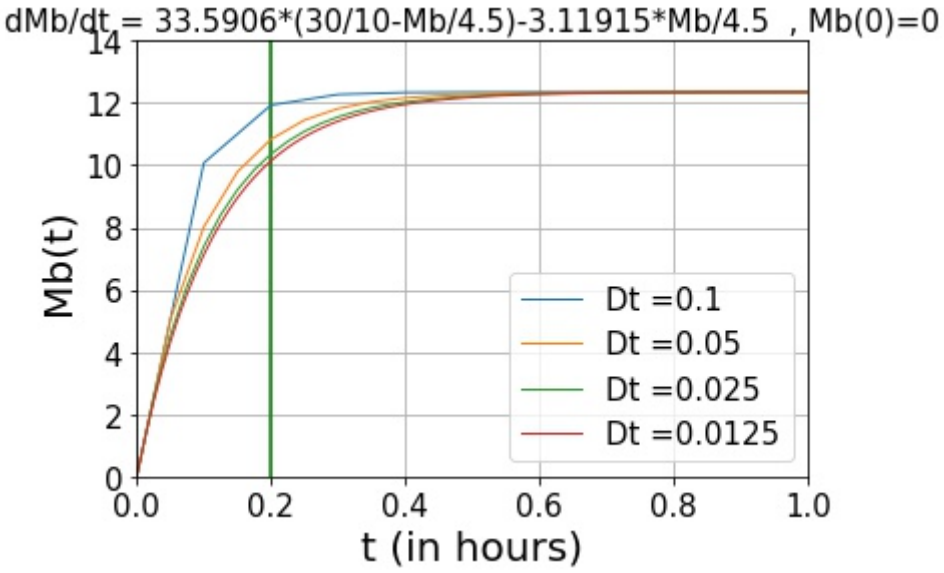

Figure 3.6: The mass of LFDT in bloodstream over time with different stepsizes Δt

The figure above shows that the moment when M_{Blood} hits the peak is about 0.75 hours, which fits the value of k_1. Moreover, it can be seen that at t = 0.2, there are the largest differences among the values of M_{Blood}. Therefore, the model is stimulated again with the step-sizes 0.001 and 0.002 to calculate the error of M_{Blood} at t = 0.2 and check whether $\Delta t = 0.001$ is small enough for the system. The error is -0.01619, which has absolute value smaller than 0.03. Then $\Delta t = 0.001$ fits the model.

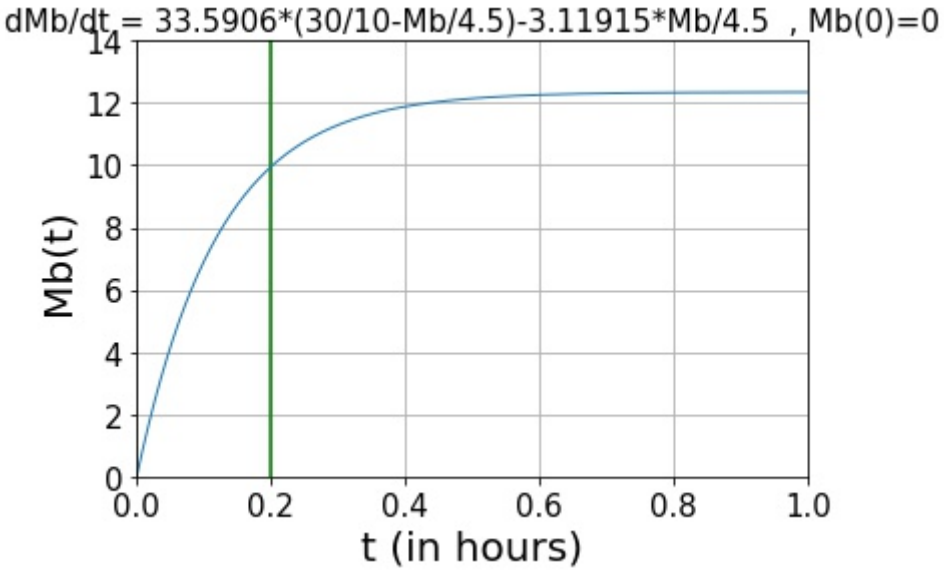

Figure 3.7: The mass of LFDT in bloodstream over time with $\Delta t = 0.001$

In summary, the simplified model for the mass of LFDT in bloodstream over time has a stable equilibrium point. Also, based on it, the value of d_1 and d_2 are estimated, respectively 33.5906 and 3.11915. A reasonable step-size for the model is $\Delta t = 0.001$.

Chapter 4

Interaction system of the mass of LFDT in GI tract and in bloodstream

In the previous chapter, the diffusion rate d_1 and the elimination rate d_2 are estimated based on the simplified model of M_{Blood} with an assumption that the mass of LFDT in GI tract is constantly 30 mg. Therefore, in section 4.1 of this chapter, those values are validated once again in the whole interaction system of M_{GI} and M_{Blood}, followed by the evaluation of the stability of the model in section 4.2. The chapter ends with the simulation of the model on larger time scale in section **??**. (For an example of Python programs used in this chapter, see Appendix B)

4.1 Validation of d_1 and d_2 in interaction system

The complete model for the interaction system of M_{GI} and M_{Blood} is:

$$\begin{cases} \frac{dM_{GI}}{dt} = -33.5906(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}), & M_{GI}(0) = 30 \\ \frac{dM_{Blood}}{dt} = 33.5906(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) - 3.11915\frac{M_{Blood}(t)}{4.5}, & M_{Blood}(0) = 0. \end{cases} \tag{4.1}$$

The complete model is simulated in a Python program with $\Delta t = 0.001$ giving the following graph:

In figure 4.1 , M_{Blood} hits the peak at t = 0.3, which is much earlier than in reality, 1.5–2 hours. Also, the maximum mass of LFDT in plasma is about 8 mg, making the peak plasma concentration of LFDT be 1.7 mg/L. This concentration is 1.7 times higher than the realistic average level of 1 mg/L [4].
The reason for this mismatch is the value of d_1. In reality, the maximum mass of LFDT in bloodstream is only 4.5 mg, while in the section 3.2, equilibrium point (13.5 mg) of

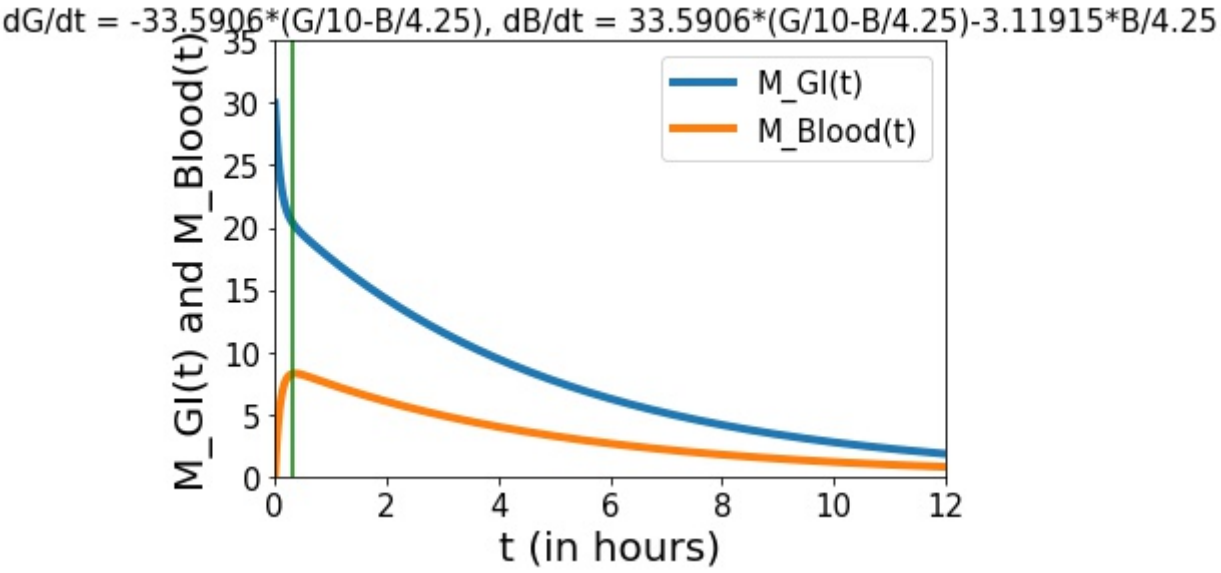

Figure 4.1: The mass of LFDT in GI tract and bloodstream over time with $\Delta t = 0.001$

the simplified model is used for the calculation. If the mass of LFDT in plasma reaches maximum value of 4.5 mg at $1.5k_1$ ($M_{Blood}(1.5k_1) = 4.5$), the value of the diffusion rate d_1 turns into $\frac{1.2163}{k_1}$. If k_2 is constant and k_1 decreases, the maximum value ofM_{Blood} increases and t_{max} decreases (1).
The value of k_2 is not the reason for mistake in the system 4.1, because no mater how much LDFT is available at t = 0, the value of d_2 is always $\frac{6.2383}{k_2}$. If k_1 is constant and k_2 increases, both the maximum value of$M_{Blood}$and t_{max} increase(2).
Based on point (1) and (2), the value of k_1 and k_2 are modified, so that the graph of M_{Blood} versus t for the built-up model matches the one in reality most. Consequently, k_1 and k_2 are respectively 0.45 and 2.11, making d_1 and d_2 become respectively 2.7029 and 2.9565. Although the part of graph after hitting the peak is not exactly the same as in reality, it makes sense because this system ignores many other factors in real metabolism.

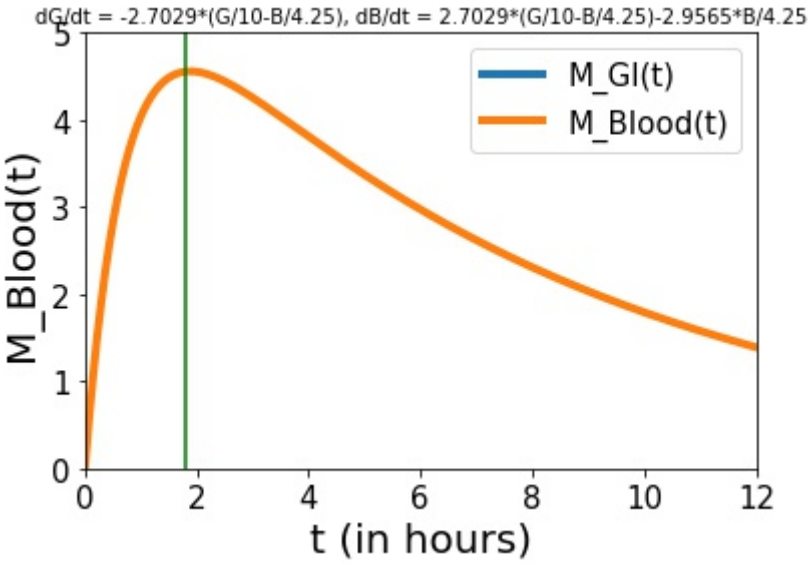

Figure 4.2: The mass of LFDT in bloodstream over time, $\Delta t = 0.001$

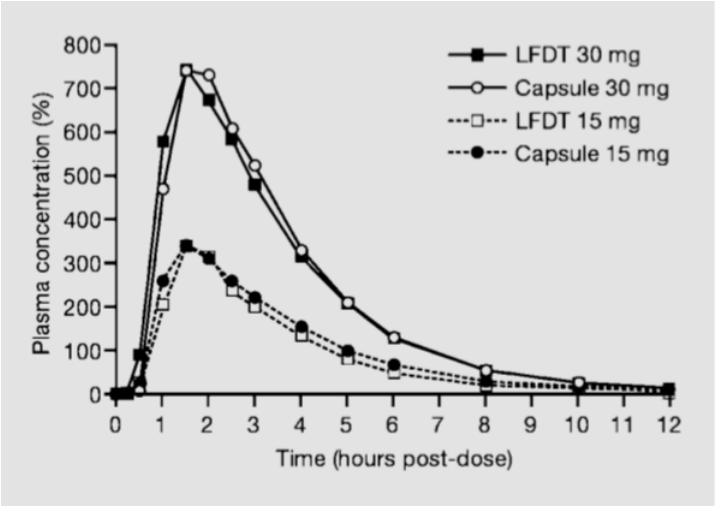

Figure 4.3: Comparison of mean lansoprazole plasma concentration time profiles between LFDT and lansoprazole capsule at 15- and 30-mg doses [4]

4.2 The stability of the interaction system model

The final model for the interaction system between the mass of Lansoprazole in GI tract and in bloodstream is:

$$\begin{cases} \dfrac{dM_{GI}}{dt} &= -2.7029\left(\dfrac{M_{GI}(t)}{10} - \dfrac{M_{Blood}(t)}{4.5}\right) \\ \dfrac{dM_{Blood}}{dt} &= 2.7029\left(\dfrac{M_{GI}(t)}{10} - \dfrac{M_{Blood}(t)}{4.5}\right) - 2.9565\dfrac{M_{Blood}(t)}{4.5}. \end{cases} \tag{4.2}$$

4.2.1 Relationship among initial conditions, M_{GI} and M_{Blood}

In reality, no records show that Lansoprazole is diffused from bloodstream to GI tract. Therefore, under any circumstances, the initial condition of M_{GI} is at least $\frac{20}{9}$times greater than one of M_{Blood}, so that the concentration in GI tract is higher. Even if the mass in two environments are equal and both different from zero, the concentration in plasma is higher. Then, the medicine would diffuse to GI tract, which does not fit the reality. Due to this reason, the graph of M_{GI} is always monotonically decreasing; the graph of M_{GI} always has the upward peak. Moreover, both solutions are non-oscillating. This trend can be seen in the following examples:

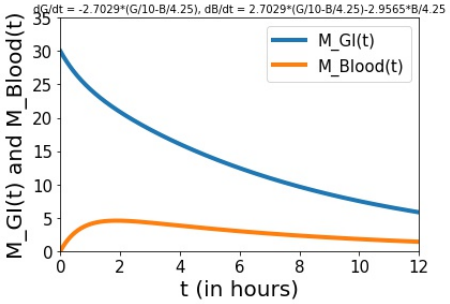

Figure 4.4: The mass of LFDT in bloodstream over time, $\Delta t = 0.001$
$M_{GI}(0) = 30; M_{Blood}(0) = 0$

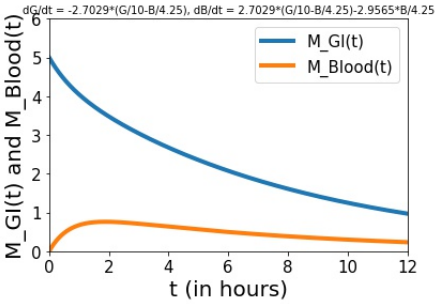

Figure 4.5: The mass of LFDT in bloodstream over time, $\Delta t = 0.001$
$M_{GI}(0) = 5; M_{Blood}(0) = 0$

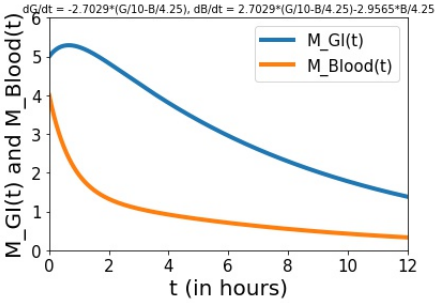

Figure 4.6: The mass of LFDT in bloodstream over time, $\Delta t = 0.001$
$M_{GI}(0) = 5; M_{Blood}(0) = 4$

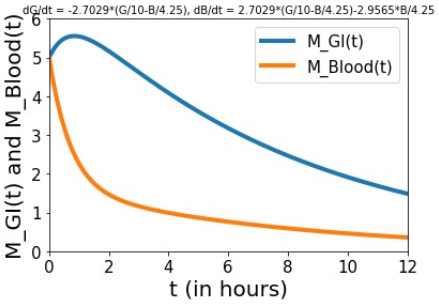

Figure 4.7: The mass of LFDT in bloodstream over time, $\Delta t = 0.001$
$M_{GI}(0) = 5; M_{Blood}(0) = 5$

4.2.2 Equilibrium point of interaction system

The equilibrium point of the system can be calculated analytically by solving the following set of equations:

$$\begin{cases} \dfrac{dM_{GI}}{dt} &= 0 \\ \dfrac{dM_{Blood}}{dt} &= 0 \end{cases} \Leftrightarrow \begin{cases} M_{GI} &= 0 \\ M_{Blood} &= 0 \end{cases} \tag{4.3}$$

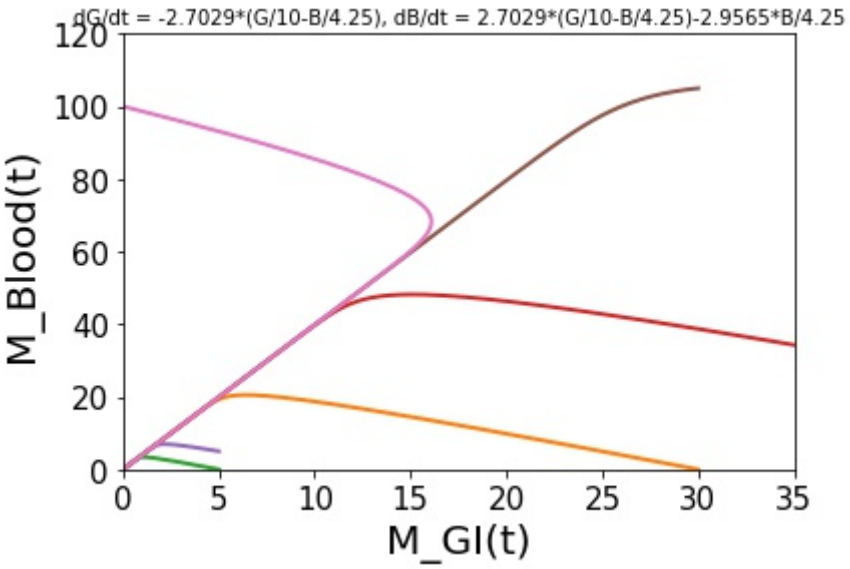

Figure 4.8: The mass of LFDT in GI tract versus in bloodstream,
$\Delta t = 0.001$

(0;0) is the only equilibrium point of this interaction system. In the figure 4.8, all lines go away from this point. Hence, this point is possibly a unstable equilibrium. In order to confirm this hypothesis, the linearisation of the differential equations around the equilibrium point needs to be done.

$$\begin{cases} \dfrac{dM_{GI}}{dt} &= f_1(M_{GI}, M_{Blood}) \\ \dfrac{dM_{Blood}}{dt} &= f_2(M_{GI}, M_{Blood}) \end{cases}$$

$$\Leftrightarrow \begin{cases} \dfrac{dM_{GI}}{dt} &= (M_{GI} - M_{GI_0}) \left.\dfrac{\partial f_1}{\partial M_{GI}}\right|_{(M_{GI_0}, M_{Blood_0})} + (M_{Blood} - M_{Blood_0}) \left.\dfrac{\partial f_1}{\partial M_{Blood}}\right|_{(M_{GI_0}, M_{Blood_0})} \\ \dfrac{dM_{Blood}}{dt} &= (M_{GI} - M_{GI_0}) \left.\dfrac{\partial f_2}{\partial M_{GI}}\right|_{(M_{GI_0}, M_{Blood_0})} + (M_{Blood} - M_{Blood_0}) \left.\dfrac{\partial f_2}{\partial M_{Blood}}\right|_{(M_{GI_0}, M_{Blood_0})} \end{cases}.$$

$$\Leftrightarrow \begin{cases} \dfrac{dM_{GI}}{dt} &= \dfrac{-2.7029}{10} M_{GI} + \dfrac{2.7029}{4.5} M_{Blood} \\ \dfrac{dM_{Blood}}{dt} &= \dfrac{2.7029}{10} M_{GI} + \dfrac{-2.7029 + 2.9565}{4.5} M_{Blood} \end{cases} \tag{4.4}$$

This linearised system then is written in matrix-vector form:

$$\begin{bmatrix} \dfrac{dM_{GI}}{dt} \\ \dfrac{dM_{Blood}}{dt} \end{bmatrix} = \left.\begin{bmatrix} \dfrac{\partial f_1}{\partial M_{GI}} & \dfrac{\partial f_1}{\partial M_{Blood}} \\ \dfrac{\partial f_2}{\partial M_{GI}} & \dfrac{\partial f_2}{\partial M_{Blood}} \end{bmatrix}\right|_{(M_{GI_0}, M_{Blood_0})} \begin{bmatrix} M_{GI} - M_{GI_0} \\ M_{GI_0}, M_{Blood_0} \end{bmatrix}.$$

$$\Leftrightarrow \frac{d\vec{X}}{dt} = J(\vec{X_0})(\vec{X}(t) - \vec{X_0})$$

Vector $\vec{X} - \vec{X_0}$ then is combined into $\vec{M}$:

$$\frac{d\vec{M}}{dt} = J(\vec{X_0})\vec{M}(t) \Leftrightarrow \frac{d\vec{M}}{dt} = \begin{bmatrix} \dfrac{-2.7029}{10} & \dfrac{2.7029}{4.5} \\ \dfrac{2.7029}{10} & \dfrac{0.2536}{4.5} \end{bmatrix} \vec{M}(t)$$

This Jacobian matrix has 2 distinct eigenvalues of $\lambda_1 = -0.5417$ and $\lambda_2 = 0.3278$. As a consequence, (0,0) is a saddle point, which fits the above hypothesis.

4.3 Interaction system in large time scale

LFDT 30mg is normally prescribed to use once a day for an adult, and it takes Lansoprazole from few days to few weeks to completely cure all symptoms of reflux or heartburn [5]. The reason is that it takes time for the plasma concentration builds up to a steady state, when the medicine gets therapeutically effective.

The shorter the time interval between uses, the faster the mass of LFDT in plasma reaches its steady state. However, the medicine should be used as prescribed to avoid any unwanted effects. Also, for the optimal results, the dose should not be skipped. In the firgure 4.12, it can be seen that if a dose is skipped, the amount of Lansoprazole in plasma reduces to zero, which means M_{Blood} needs to restart build-up procedure.

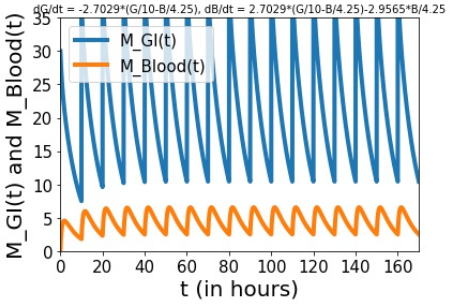

Figure 4.9: The mass of LFDT in GI tract and bloodstream over time,
A dose of 30mg tablet every 10 hours

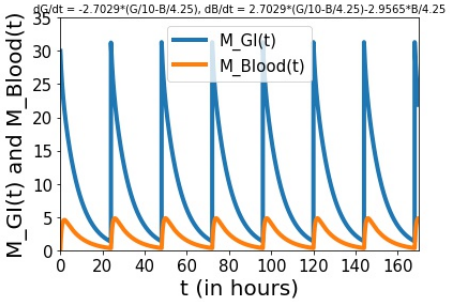

Figure 4.10: The mass of LFDT in GI tract and bloodstream over time,
A dose of 30mg tablet every 24 hours

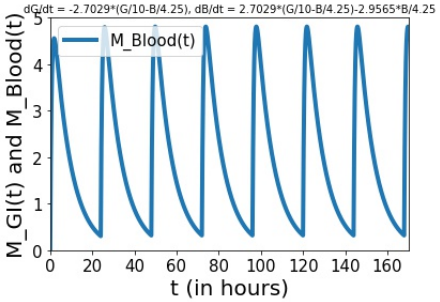

Figure 4.11: The mass of LFDT in bloodstream over time,
A dose of 30mg tablet every 24 hours

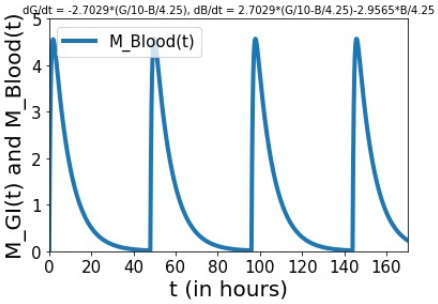

Figure 4.12: The mass of LFDT in bloodstream over time,
A dose of 30mg tablet every 48 hours

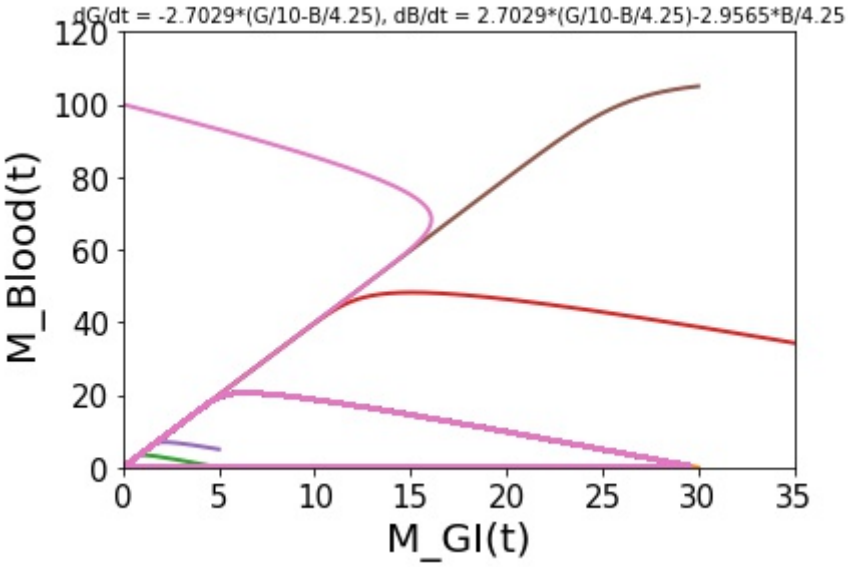

Figure 4.13: The mass of LFDT in GI tract versus in bloodstream,
A dose of 30mg tablet every 24 hours

In the figure above, it can be seen the similarity with the figure 4.8. This shows that no matter how much doses of LFDT is added every 24 hours, the equilibrium point of this system is still unstable.

To conclude, in this chapter, new reasonable values of diffusion rate d_1 and elimination rate d_2 are chosen to fit the information in reality (2.7029 and 2.9565 respectively). Moreover, the equilibrium of this interaction model is found out to be a saddle point (an unstable point), which is the same even when a dose of LFDT 30 mg is administered every 24 hours. Finally, LFDT only works effectively if the correct dose is used as prescribed.

Chapter 5

How ages influences the effectiveness of LFDT

[This chapter will be completed in the 2^{nd} report.]

Chapter 6

Conclusions

For LFDT 30mg, a mathematic model was made that fit 80% to the plotted graph of real administration:

$$\begin{cases} \frac{dM_{GI}}{dt} &= -2.7029(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) \\ \frac{dM_{Blood}}{dt} &= 2.7029(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) - 2.9565\frac{M_{Blood}(t)}{4.5}. \end{cases} \tag{6.1}$$

Based on this model, we can predict the concentration of LFDT in humans' body at a moment of time. This will help prevent the overdose of or the low effectiveness of this medicine. Also, the infants (2–3 months old) have higher exposure to LFDT than adults, and the elderly that use the medicine have higher chance of bone fractures. A careful test on the model should be made to ensure that the patients are appropriate to use the medicine.

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Appendix A

Python code for estimating the values of diffusion rate d_1 and elimination rate d_2 in the simplified model of the mass of LFDT in plasma

```
"""
@author: trangnguyen
"""

import numpy as np
import matplotlib.pyplot as plt


Dt = 1                        # timestep Delta t
Mb_init =0                    # initial population of M_Blood
t_init = 0                    # initial time
t_end = 6000                  # stopping time
n_steps = int(round((t_end-t_init)/Dt)) # total number of timesteps

t_arr = np.zeros(n_steps + 1)  # create a storage array for t
Mb_arr = np.zeros(n_steps + 1) # create a storage array for Mb
t_arr[0] = t_init              # add the initial t to the storage array
Mb_arr[0] = Mb_init            # add the initial Mb to the storage array
# Plot the results
fig = plt.figure()
#set title
plt.title('dMb/dt = 33.5906*(30/10-Mb/4.5)-3.11915*Mb/4.5  , Mb(0)=0', fontsize = 15)
plt.xlabel('t (in hours)', fontsize = 20) # set axis name
plt.ylabel('Mb(t)', fontsize = 20)

plt.xticks(fontsize = 15) # set fontsize
```

```
plt.yticks(fontsize = 15)
plt.grid(True)
plt.axis([0, 1 , 0, 14])

k1= 0.5                        # coefficient for t_max in plasma (0 < k1 < 1)
k2= 2                          # coefficient for t_1/2 in plasma (k2 > 1)
d1=16.7953/k1     # d1, d2 value after solving the differiential analytically
d2=6.2383/k2

Mbe = d1*3*4.5/(d1+d2)       #Equilibrium point
print('Mbe= ', Mbe)

print('k1=', k1)
print('k2=', k2)
print('d1=', d1)
print('d2=', d2)

#Euler's method
for Dt in (0.001,0.002):
    for i in range (1, n_steps + 1):
        Mb = Mb_arr[i-1     ]# load the value of Mb
        t = t_arr[i-1]       # load the time
        dMbdt = d1*(30/10-Mb/4.5)-d2*Mb/4.5 # calculate the derivative dMB/dt
        Mb_arr[i] = Mb + Dt*dMbdt   # store new values
        t_arr[i] = t + Dt
    plt.plot(t_arr, Mb_arr, linewidth = 1) # plot Mb vs. t for each Dt
plt.show()

#Save graph as a picture
fig.savefig('d12(2).jpg',dpi=fig.dpi, bbox_inches = "tight")
```

Appendix B

Python code for interaction system model of the mass of LFDT in GI tract and in bloodstream

```
"""
@author: trangnguyen
"""

import numpy as np
import matplotlib.pyplot as plt

print("Solution for dG/dt = -d1*(G-B/4.25), dB/dt = d1*(G-B/4.25)-d2*B/4.25")

# Initializations
Dt = 0.001                      # timestep Delta t
G_init = 30                     # initial population of M_GI
B_init = 0                      # initial population of M_Blood
t_init = 0                      # initial time
t_end = 6000                    # stopping time

n_steps = int(round((t_end-t_init)/Dt)) # total number of timesteps

X = np.zeros(2)                 # create space for current X=[G,B]^T
dXdt = np.zeros(2)              # create space for current derivative
t_arr = np.zeros(n_steps + 1)   # create a storage array for t
X_arr = np.zeros((2,n_steps+1)) # create a storage array for X=[G,B]^T
t_arr[0] = t_init               # add the initial t to the storage array
X_arr[0,0] = G_init             # add the initial G to the storage array
X_arr[1,0] = B_init             # add the initial B to the storage array

k1= 0.45                        # coefficient for t_max in plasma (0 < k1 < 1)
k2= 2.11                        # coefficient for t_1/2 in plasma (k2 > 1)
d1= 1.2163 /k1      # d1, d2 value after solving the differiential analytically
d2=6.2383/k2
```

```
print('k1=', k1)
print('k2=', k2)
print('d1=', d1)
print('d2=', d2)

# Euler's method
for i in range (1, n_steps + 1):
    t = t_arr[i-1]              # load the time
    G = X_arr[0,i-1]            # load the value of G
    B = X_arr[1,i-1]            # load the value of B
    if np.remainder(t,24)<0.001 and t>0: # a dose of LFDT 30 mg added every 24 hours
        G += 30
    X[0] = G                    # fill current state vector X=[G,B]^T
    X[1] = B
    dGdt = -d1*(G/10-B/4.5)     # calculate the derivative dG/dt
    dBdt =  d1*(G/10-B/4.5)-d2*B/4.5  # calculate the derivative dB/dt
    dXdt[0] = dGdt              # fill derivative vector dX/dt
    dXdt[1] = dBdt
    Xnew = X + Dt*dXdt          # calculate X on next time step
    X_arr[:,i] = Xnew           # store Xnew
    t_arr[i] = t + Dt           # store new t-value

# Plot the results
fig = plt.figure()

plt.plot(t_arr, X_arr[0,:], linewidth = 4,label="M_Blood(t)")  # plot G vs. time
plt.plot(t_arr, X_arr[1,:], linewidth = 4,label="M_Blood(t)")  # plot B vs. time
# plot G vs. B
plt.plot(X_arr[0,:], X_arr[1,:], linewidth = 2, label= "M_GI(t) vs M_Blood(t)")
# set title
plt.title('dG/dt=-d1*(G/10-B/4.25),dB/dt=d1*(G/10-B/4.25)-d2*B/4.25',fontsize=10)
plt.xlabel('t (in hours)', fontsize = 20)   # name of horizontal axis
plt.ylabel('M_GI(t) and M_Blood(t)', fontsize = 20) # name of vertical axis

plt.xticks(fontsize = 15)              # adjust the fontsize
plt.yticks(fontsize = 15)              # adjust the fontsize
plt.axis([0, 170, 0, 5])               # set the range of the axes

plt.legend(fontsize=15)                # show the legend
plt.show()                             # necessary for some platforms

# Save the graph as a picture
fig.savefig('30mg every 24 hours.jpg',dpi=fig.dpi, bbox_inches = "tight")
```