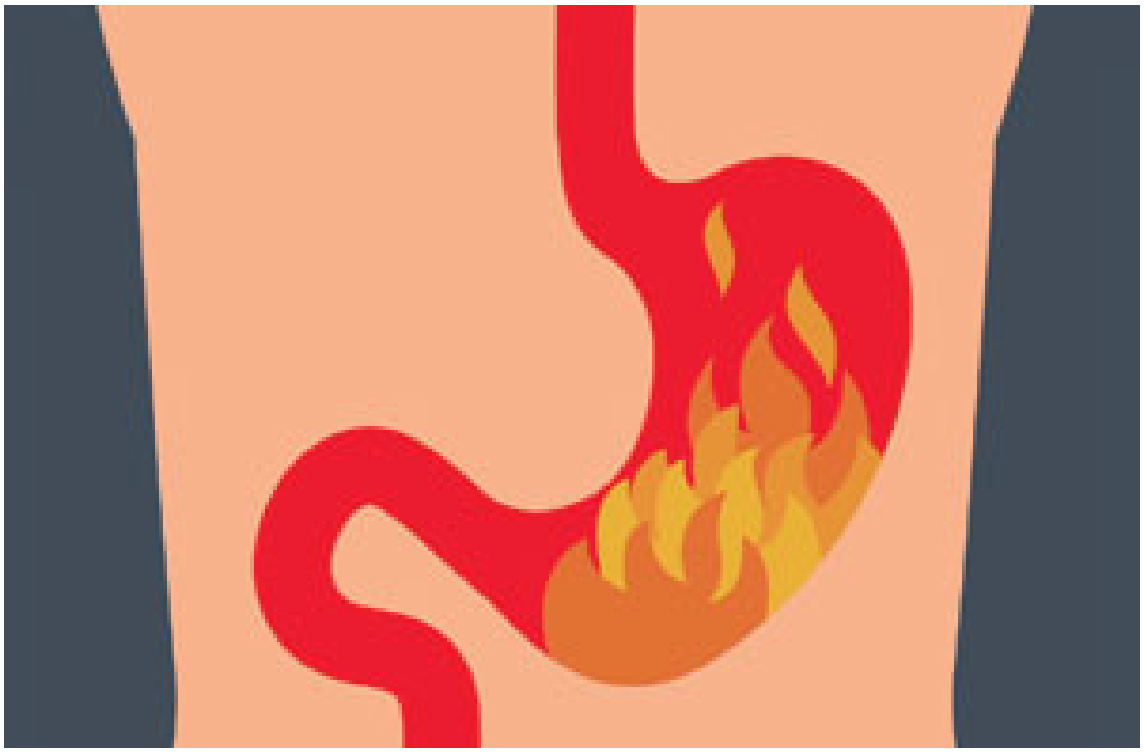

Lansoprazole in lactation

This is of the most popular stomach reflux medicine prescribed in the world. However, is it safe for infants if moms who are giving breastfeeding use the medicine?

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March 21, 2019

Summary

Introduction: Lansoprazole is a Proton Pump Inhibitor (PPI) used for the treatment of acid reflux. However, the impact of it on maternal and fetal health is still unknown.
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. Based on the original model, a new one is made to visualize how it actually works in maternal metabolism. A sample prescrition is assessed to check the safety rate.
Result and conclusion: The results of this model are only applied to patients without any other medical problems. LFDT is not compatible with women in lactation. If it is used, the infants will likely suffer from serious adverse reactions like diarrhoea, stomach ache or vomiting.

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)

$M_{\text{Milk}}(t)$: The mass of Lansoprazole in milk 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)

ΔM_{Milk}: The change in the mass of Lansoprazole in milk (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)

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

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)

d_3: The diffusion rate of Lansoprazole from bloodstream to milk (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). It can be used by both adults and children; however, for some people with special health condition, the dose might change.
The purpose of this report is to determine whether Lansoprazole can be used in women in lactation without any harm to infants.
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. The mother in this model is assumed to be a person without any additional medical problems and to have maximum 1L of milk per day; the infant is assumed to be 2-3 months old with a weight of 6 kg and having 0.9 L equally divided into 10 times in a day [2].
In this report, a systematical build-up of the mass determination of Lansoprazole will be done to check the safety rate when women giving breastfeeding use the medicine. First, in Chapter 2, the mathematical model for normal people will be developed. Additional factors in maternal metabolisms and an improved version of model is introduced in Chapter 3, followed by the safety assessment in Chapter 5. Chapter 6 will draw a conclusion for the result of this report.

Chapter 2

Mathematical model design of Lansoprazole in normal adults

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 brief procedure of buiding up this system of equations are presented. Firstly, Section 2.1 presents the theory of Lansoprazole pathway in humans body with the basic system model of LFDT in GI tract and plasma. Secondly, the diffusion rate d_1 and elimination rate d_2 are estimated and validated in section 2.2. Finally, multiple models of LFDT on long term are simulated in section 2.3. For a detailed program used in this chapter, see Appendix I.

2.1 Principle and basic system model of LFDT in GI tract and bloodstream

2.1.1 Pathway of LFDT 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[3]. 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[4].

2.1.2 Mathematical model

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:

$$\Delta M_{GI} = M_{GI}(t + \Delta t) - M_{GI}(t)$$

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

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:

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

Beside the diffusion rate d_1, the mass of LFDT in bloodstream also depends on the elimination rate d_2 of LFDT from bloodstream:

$$\Delta M_{Blood} = M_{Blood}(t + \Delta t) - M_{Blood}(t)$$

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

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:

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

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

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

2.2 Diffusion rate from GI tract to bloodstream d_1 and elimination rate d_2

2.2.1 Diffusion rate from GI tract to bloodstream d_1

d_2 is assumed to be zero:

$$\frac{dM_{Blood}}{dt} = d_1(3 - \frac{M_{Blood}(t)}{4.5}), \quad M_{Blood}(0) = 0 \tag{2.6}$$

The equation 2.6 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 $M_{Blood}(0)$:

$$c = -\ln 13.5$$

$$\Rightarrow -\ln(13.5 - M_{blood}) = \frac{d_1}{4.5} - \ln 13.5 \tag{2.7}$$

In reality, the amount of time for LFDT to reach its peak plasma concentration is from 1.5 hours to 2 hours [3]. 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 **??**), 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 2.7, 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 2.6 is simulated in Python with difference step-sizes $(0.1, \frac{0.1}{2}, \frac{0.1}{4}, \frac{0.1}{8})$:

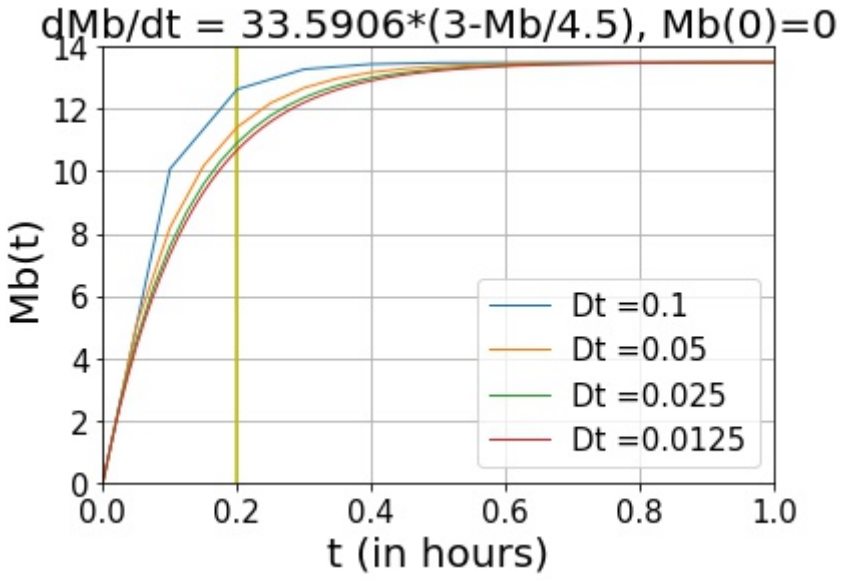

Figure 2.1: The mass of LFDT in bloodstream over time with different step-sizes Δt, $d_2 = 0$

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.

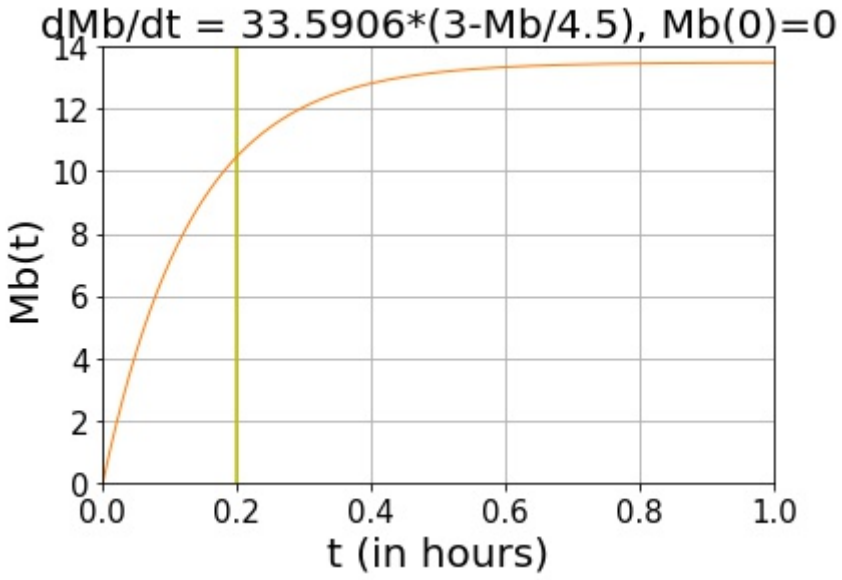

Figure 2.2: The mass of LFDT in bloodstream over time with $\Delta t = 0.001$, $d_2 = 0$

d_1 is assumed to be zero, and the mass of LFDT in plasma at $t = 0$ is the equilibrium point of model 2.6, $M_{Blood} = 13.5$:

2.2.2 Elimination rate d_2

$$\frac{dM_{Blood}}{dt} = -d_2\frac{M_{Blood}(t)}{4.5}, \quad M_{Blood}(0) = 13.5 \tag{2.8}$$

The equation 2.8 is solved analytically:

$$4.5\int \frac{1}{M_{blood}} dM_{Blood} = -d2\int dt \Leftrightarrow 4.5\ln\left(M_{Blood}\right) = -d_2t + c$$

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

$$c = 4.5\ln 13.5$$
$$\Rightarrow 4.5\ln\left(M_{Blood}\right) = -d_2t + 4.5\ln 13.5 \tag{2.9}$$

In reality, the half-life of LFDT in plasma is 1.5 ($\pm$1) hours [3]. However, the concentration of LFDT in GI tract is kept constant over time, $M_GI = 30$, 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 2.9 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 2.8 is simulated in Python difference step-sizes ($0.1, \frac{0.1}{2}, \frac{0.1}{4}, \frac{0.1}{8}$):

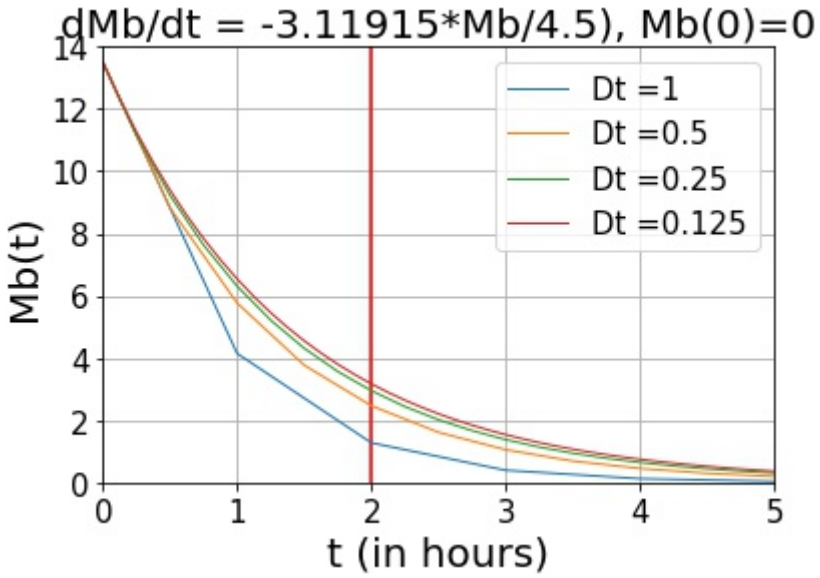

Figure 2.3: The mass of LFDT in bloodstream over time with different step-sizes Δt, $d_1 = 0$

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.

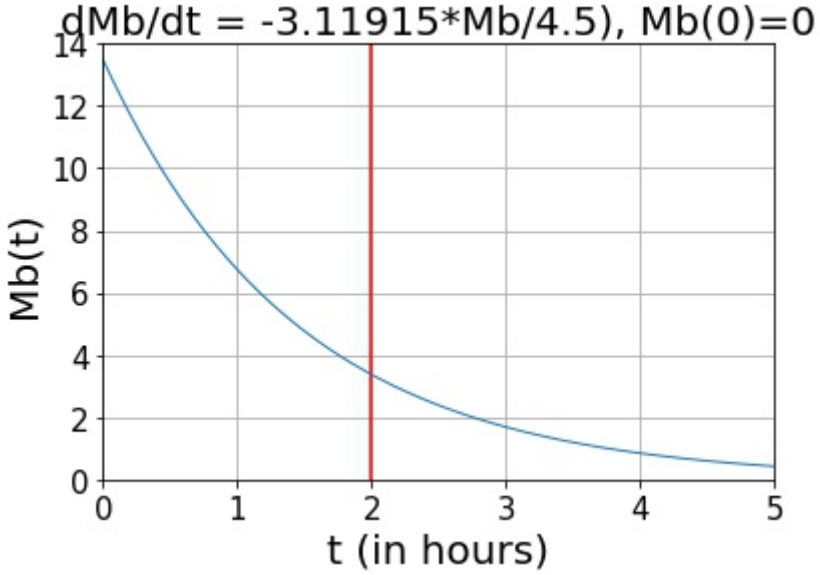

Figure 2.4: The mass of LFDT in bloodstream over time with $\Delta t = 0.001$, $d_1 = 0$

2.2.3 Validation of d_1 and d_2 on system model

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

$$\begin{cases} \frac{dM_{GI}}{dt} = -33.5906(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}), & M_{GI}(0) = 30 \\ \frac{dM_{Blood}}{dt} = 33.5906(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) - 3.11915\frac{M_{Blood}(t)}{4.5}, & M_{Blood}(0) = 0. \end{cases} \tag{2.10}$$

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 [5].
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 **??**, equilibrium point (13.5 mg) of 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}

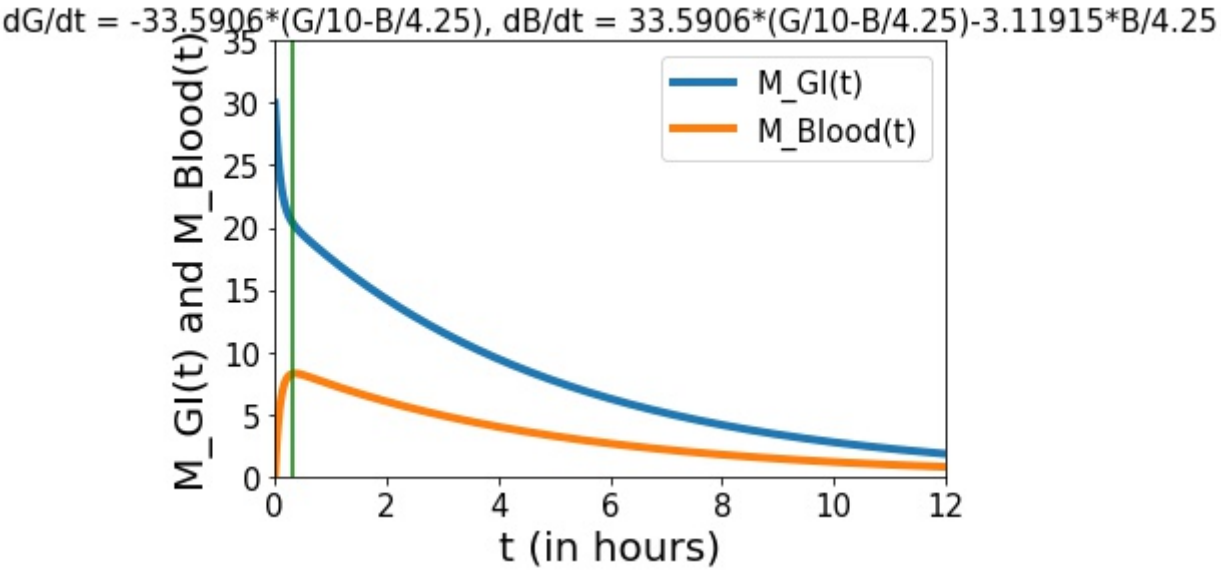

Figure 2.5: The mass of LFDT in GI tract and bloodstream over time with $\Delta t = 0.001$

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.

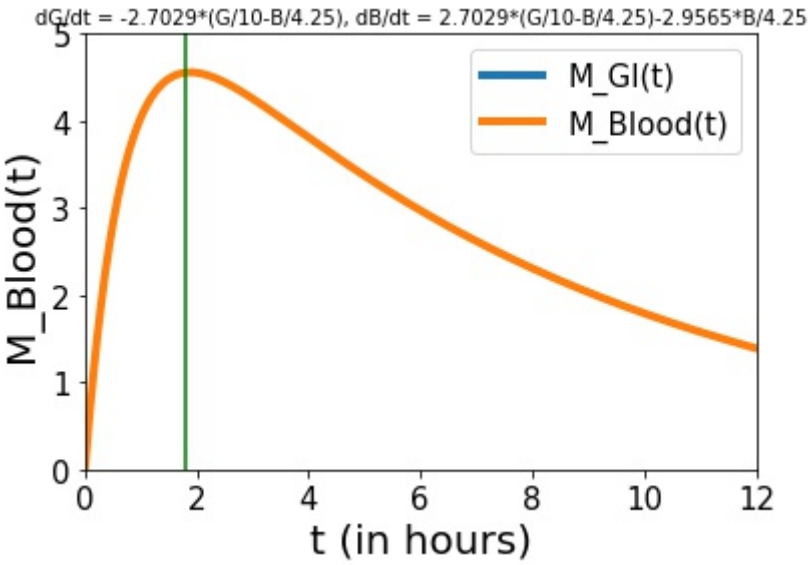

Figure 2.6: The mass of LFDT in bloodstream over time, $\Delta t = 0.001$

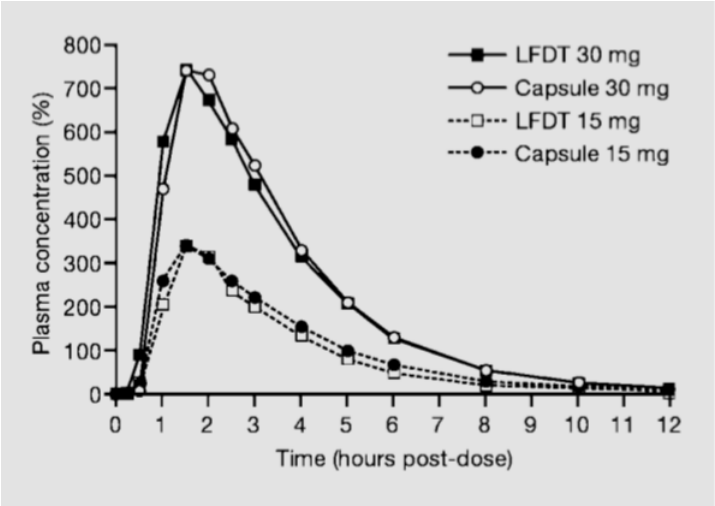

Figure 2.7: Comparison of mean lansoprazole plasma concentration time profiles between LFDT and lansoprazole capsule at 15- and 30-mg doses [5]

2.3 How the mass of LFDT changes in the long term

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 [6]. 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.

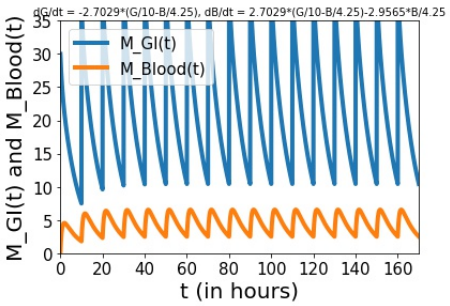

Figure 2.8: The mass of LFDT in GI tract and bloodstream over time,
A dose of 30mg tablet every 10 hours

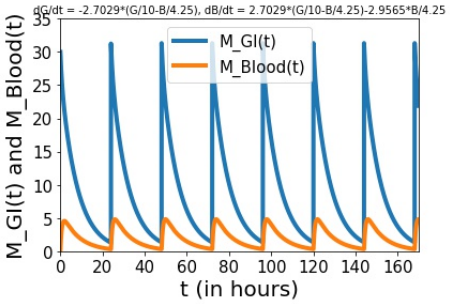

Figure 2.9: The mass of LFDT in GI tract and bloodstream over time,
A dose of 30mg tablet every 24 hours

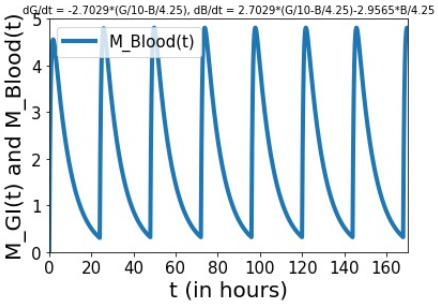

Figure 2.10: The mass of LFDT in bloodstream over time,
A dose of 30mg tablet every 24 hours

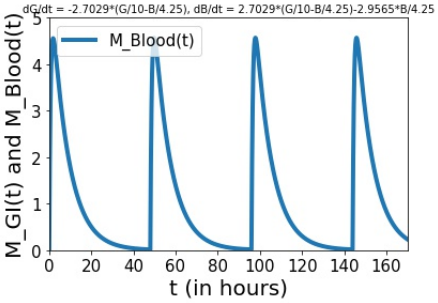

Figure 2.11: The mass of LFDT in bloodstream over time,
A dose of 30mg tablet every 48 hours

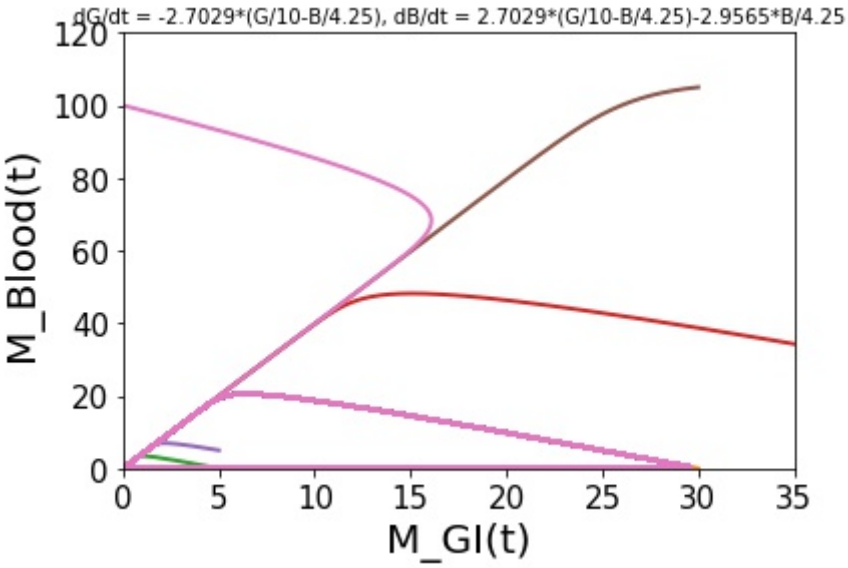

Figure 2.12: The mass of LFDT in GI tract versus in bloodstream,
A dose of 30mg tablet every 24 hours

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

$$\begin{cases} \dfrac{dM_{GI}}{dt} &= -2.7029(\dfrac{M_{GI}(t)}{10} - \dfrac{M_{Blood}(t)}{4.5}) \\ \dfrac{dM_{Blood}}{dt} &= 2.7029(\dfrac{M_{GI}(t)}{10} - \dfrac{M_{Blood}(t)}{4.5}) - 2.9565\dfrac{M_{Blood}(t)}{4.5}. \end{cases} \tag{2.11}$$

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.

Chapter 3

Mathematical model design of Lansoprazole in women in lactation

In the previous chapter, the basic model for Lansoprazole in normals adult is developed and validated. However, it will not be the same in case of women who is giving breastfeeding. The principle of how LFDT works in maternal metabolism will be explained in first section, followed by the validation of the diffusion rate from plasm to milk d_3 in section 3.2.

For a detailed program used in this chapter, see Appendix II.

3.1 Principle and basic system model of LFDT in GI tract, bloodstream and milk

3.1.1 Pathway of LFDT in maternal metabolism

When a women during lactation have medicines, the medicines will be distributed all over in her circulation, which means that there is high possibility that they will be passively diffused to the milk for infants.

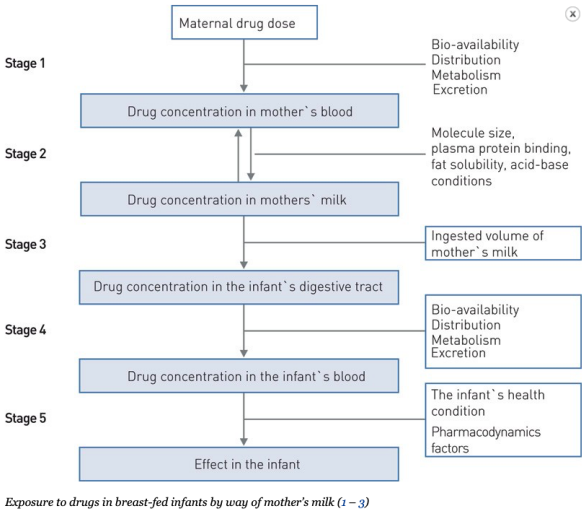

Figure 3.1: Pathway of medicines in maternal and fetal metabolisms

Therefore, a couple of new differential equations of the mass of LFDT in maternal milk $M_Milk$and the milk volume V_Milk will be introduced to the mathematical model.

3.1.2 Mathematical model

The mass of LFDT in bloodstream

An amount of LFDT is diffused from plasma to milk, so the new equation for the mass of LFDT in bloodstream is:

$$\frac{dM_{Blood}}{dt} = -d_1(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) - d_2\frac{M_{Blood}(t)}{4.5} - d_3(\frac{M_{Blood}(t)}{4.5} - \frac{M_{Milk}(t)}{V_{Milk}(t)}) \quad (3.1)$$

The volume of milk

It assumed that at $t = 0$, the volume of milk is at maximum of 1L. An infant is fed 10 times with a total volume of 0.9 L in a day (0.09L every 2.4 hours on average):

$$\Delta V_{Milk} = V_{Milk}(t + \Delta t) - V_{Milk}(t)$$

$$\Leftrightarrow \Delta V_{Milk} = -0.09\frac{\Delta t}{2.4} \quad (3.2)$$

Then, the balance equation 3.2 is divided by Δt:

$$\frac{\Delta V_{Milk}}{\Delta t} = \frac{-0.09}{2.4}$$

And the limit for Δt to zero is taken:

$$\frac{dM_{Milk}}{dt} = \frac{-0.09}{2.4} \tag{3.3}$$

The mass of LFDT in milk

The amount of LFDT in milk depends on the amount of it in plasma as well as the diffusion rate $d_3$from plasma to milk. Moreover, breastfeeding is given multiple times a day, making the volume of milk changes followed by the decrease of the mass of LFDT in milk:

$$\Delta M_{Milk} = M_{Milk}(t + \Delta t) - M_{Milk}(t)$$

$$\Leftrightarrow \Delta M_{Milk} = d_3 \Delta t(\frac{M_{Blood}(t)}{4.5} - \frac{M_{Milk}(t)}{V_{Milk}(t)}) - \frac{0.09}{2.4}\frac{M_{Milk}(t)}{V_{Milk}(t)} \tag{3.4}$$

Then, the balance equation 3.4 is divided by Δt:

$$\frac{\Delta M_{Milk}}{\Delta t} = d_3(\frac{M_{Blood}(t)}{4.5} - \frac{M_{Milk}(t)}{V_{Milk}(t)}) - \frac{0.09}{2.4}\frac{M_{Milk}(t)}{V_{Milk}(t)}$$

And the limit for Δt to zero is taken:

$$\frac{dM_{Milk}}{dt} = d_3(\frac{M_{Blood}(t)}{4.5} - \frac{M_{Milk}(t)}{V_{Milk}(t)}) - \frac{0.09}{2.4}\frac{M_{Milk}(t)}{V_{Milk}(t)} \tag{3.5}$$

The complete model for the mass of LFDT in maternal metabolism is:

$$\begin{cases} \frac{dM_{GI}}{dt} &= -d_1(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}), \\ \frac{dM_{Blood}}{dt} &= d_1(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) - d_2\frac{M_{Blood}(t)}{4.5} - d_3(\frac{M_{Blood}(t)}{4.5} - \frac{M_{Milk}(t)}{V_{Milk}(t)}, \\ \frac{dM_{Milk}}{dt} &= d_3(\frac{M_{Blood}(t)}{4.5} - \frac{M_{Milk}(t)}{V_{Milk}(t)}) - \frac{0.09}{2.4}\frac{M_{Milk}(t)}{V_{Milk}(t)}, \\ \frac{dM_{Milk}}{dt} &= \frac{-0.09}{2.4} \end{cases} \tag{3.6}$$

The woman in this model is assumed not to have any additional medical problems, so the values of d_1 and d_2 are the same as in normal people. The values of d_3 is estimated in the next section.

3.2 Diffusion rate from bloodstream to milk d_2

In reality, there is no record about how concentration or mass of LFDT changes in women in lactation; therefore, the value of d_3 will be estimated based on $\frac{m}{p}(AUC)$, which means the ratio between area under curve of the concentration of the drug in the milk and that of the concentration in maternal plasma. For a medicine that can be used during lactation, the value range is from 0.5 to 1.0 on average. Moreover, the dose for women giving beastfeeding is always reduced, so the initial value for M_{GI} decreases to 15 mg, half dose of normal people.

$$\frac{m}{p}(AUC) = \frac{\int_0^{24} \frac{M_{Milk}}{V_{Milk}} d_t}{\int_0^{24} \frac{M_{Blood}}{V_{Blood}} d_t} \tag{3.7}$$

In order to calculate the values of those integrals in Python, Simpson's rule is used (How it is used is shown in Appendix II.) After multiple simulations, it can be see in the table 3.1 that, the $\frac{m}{p}(AUC)$ is smaller than 1 until d_3 reaches 229.39, which is a great number when d_3 is considered as a diffusion rate in humans body. As validated in chapter 1, the value of diffusion rate from GI tract to plasma d_1 is 2.7029; therefore, it is only reasonable that the value of d_3 is smaller or equal 10. To estimate the highest risk in using LFDT, a maximum of 10 is chosen as the value of d_3.

d_3	AUC_{Milk}	AUC_{Blood}	$\frac{m}{p}(AUC)$
0.5	3.9660	4.6863	0.8463
1	4.2872	4.6764	0.9168
5	4.5841	4.6673	0.9822
10	4.6241	4.6661	0.9910
100	4.6607	4.6649	0.9991
200	4.6628	4.6649	0.9995
229.385	4.5662	4.6671	0.9984
229.39	4.7139	4.6637	1.0108

Table 3.1: $\frac{m}{p}(AUC)$ values at different d_3 values

In conclusion, different from the pathway of medicine in normal people, that in women giving breastfeeding includes the passive diffusion of medicine from plasma to milk and vice versa. The value of this diffusion rate d_3 is estimated based on the $\frac{m}{p}(AUC)$ ratio. Then, the full model for the mass of LFDT in maternal metabolism is:

$$\begin{cases} \frac{dM_{GI}}{dt} &= -2.7029(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}), \\ \frac{dM_{Blood}}{dt} &= 2.7029(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) - 2.9565\frac{M_{Blood}(t)}{4.5} - 10(\frac{M_{Blood}(t)}{4.5} - \frac{M_{Milk}(t)}{V_{Milk}(t)}, \\ \frac{dM_{Milk}}{dt} &= 10(\frac{M_{Blood}(t)}{4.5} - \frac{M_{Milk}(t)}{V_{Milk}(t)}) - \frac{0.09}{2.4}\frac{M_{Milk}(t)}{V_{Milk}(t)}, \\ \frac{dM_{Milk}}{dt} &= \frac{-0.09}{2.4} \end{cases} \tag{3.8}$$

Chapter 4

Safety of LFDT use in lactation

In chapter 2, a model of the amount of LFDT in metabolism that can be used for women in lactation is developed. In section 4.1 of this chapter, the model will be simulated in Python program to check whether it is good for mom and infants to use LFDT. Finally, an assessment about a prescription of 4 days using LFDT is presented in section 4.2. For a detailed program used in this chapter, see Appendix II.

4.1 Is the amount of LFDT in safe zone?

It is advised that the baby is fed before mom has medicine to minimise the concentration of medicine in milk [7]. Hence, it is assumed that at $t = 0$, the woman in this women has a maximum volume of milk and starts giving her first breastfeeding in the morning. After 30 minutes, she takes the first dose of LFDT 15mg. How the amount of medicine changes in her body is illustrated in the below figure:

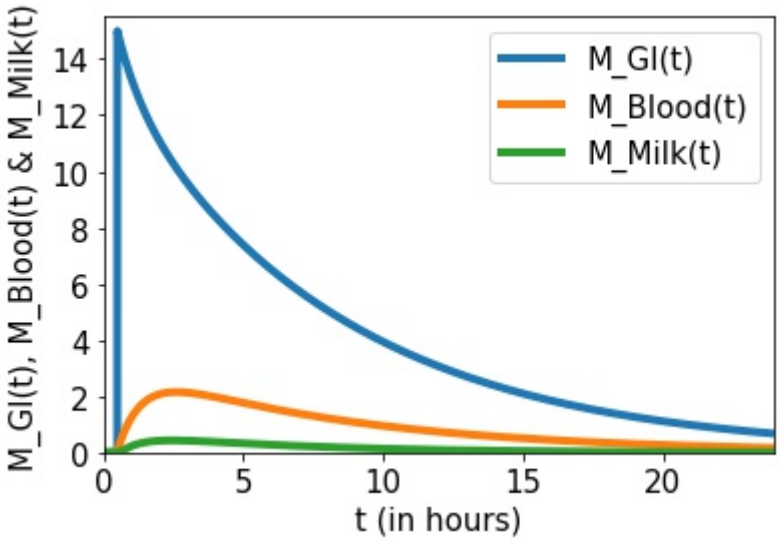

Figure 4.1: The mass of LFDT in GI tract, bloodstream and milk over time with a dose of 15 mg,$\Delta t = 0.001$

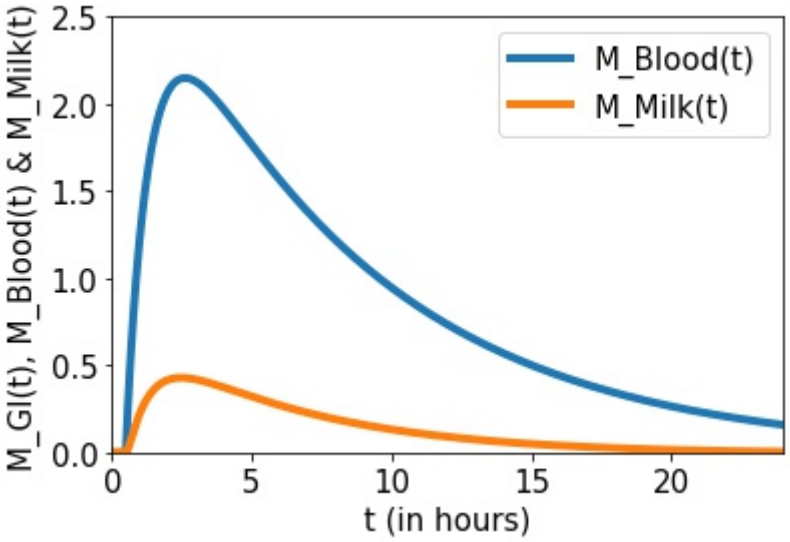

Figure 4.2: The mass of LFDT in bloodstream and milk over time with a dose of 15 mg,$\Delta t = 0.001$

Firgure 3.3 shows that the maximum mass of LFDT in milk is below 0.5 mg, which means it is below 25% of the mass in plasma at the same time. However, in order to assess the safety of the medicine, we need to look at the total mass of LFDT in milk for a dose or AUC of the mass of milk over time. The model is simulated in Python, and the total mass of LFDT in milk for 24 hours is 3.2407 mg, which accounts for 21.60% of a 15 mg dose used by the woman. Compared to the standard of drug safety in lactation of under 10% for infant dose [8], this level is too high. This leads to a conclusion that LFDT 15 mg is not appropriate for women giving breastfeeding. Because the values are proportional to each other, even the dose is reduced, the infant dose percentage is still the same.

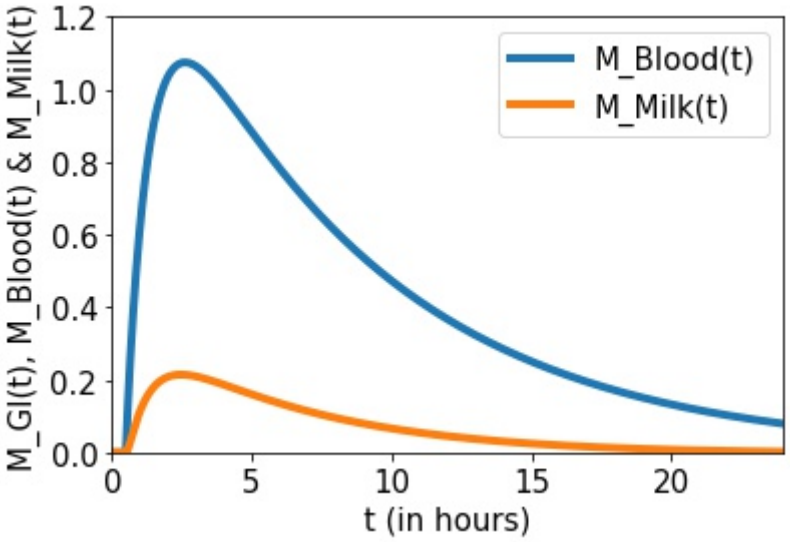

Figure 4.3: The mass of LFDT in bloodstream and milk over time with a dose of 7.5 mg,$\Delta t = 0.001$

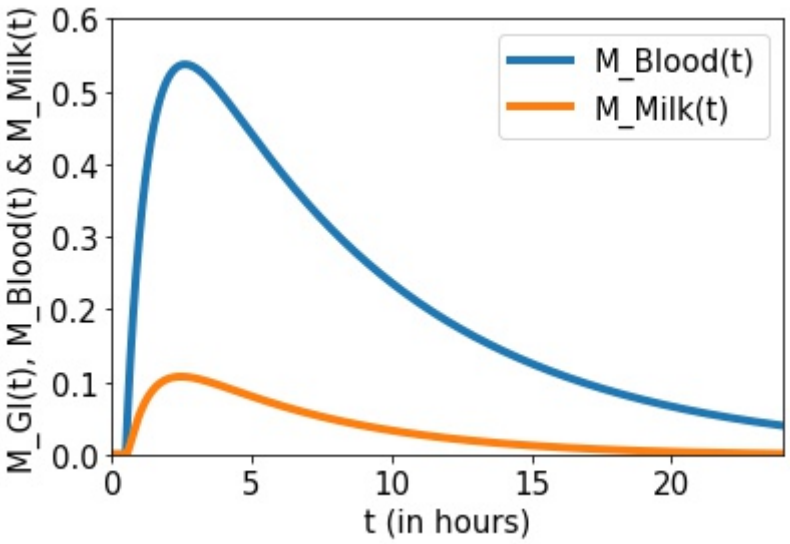

Figure 4.4: The mass of LFDT in bloodstream and milk over time with a dose of 3.75 mg,$\Delta t = 0.001$

4.2 What if the woman keeps using the medicine?

In some cases, maybe due to the habit, women might take the medicine without considering about the risk. In the figure 4.5 for normal people and figures 4.6, 4.7 for women in lactation with the same prescription of 15 mg, it can be seen that the stable state in maternal metabolism is comparable to that in normal one. Therefore, if the relief is shown when using, the woman is likely to continue until all symptoms disappear. This means that each day, the infant has to expose to a high amount of LFDT of approximately 3.2407 mg, which can cause some common serious adverse reactions in infants such as diarrhoea, stomach ache or vomiting [9].

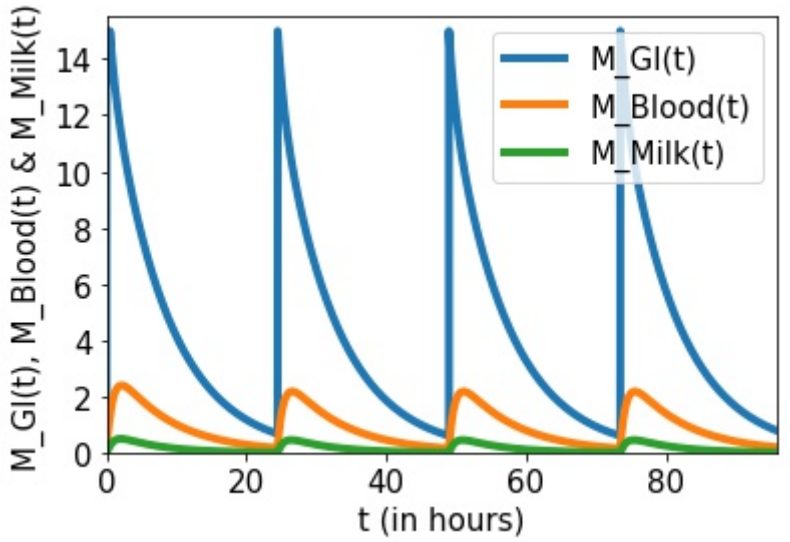

Figure 4.5: The mass of LFDT in GI tract, bloodstream and milk over time with a dose of 15 mg for 4 days in normal people,$\Delta t = 0.001$

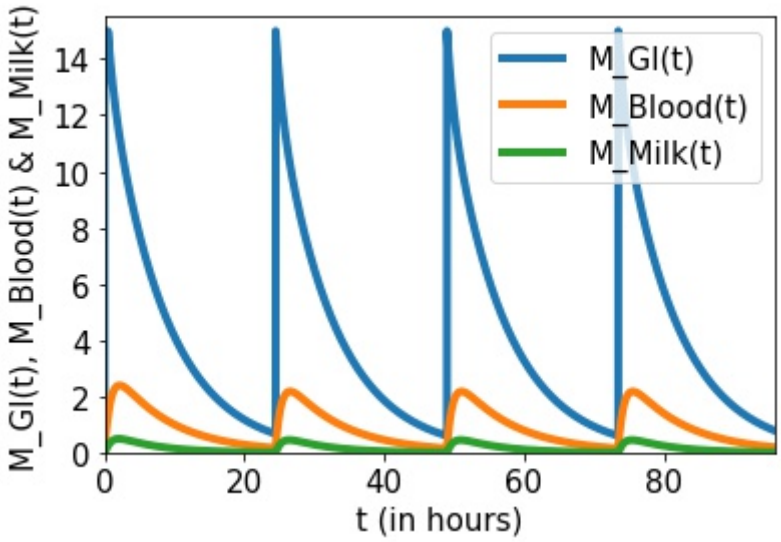

Figure 4.6: The mass of LFDT in GI tract, bloodstream and milk over time with a dose of 15 mg for 4 days in women in lactation,$\Delta t = 0.001$

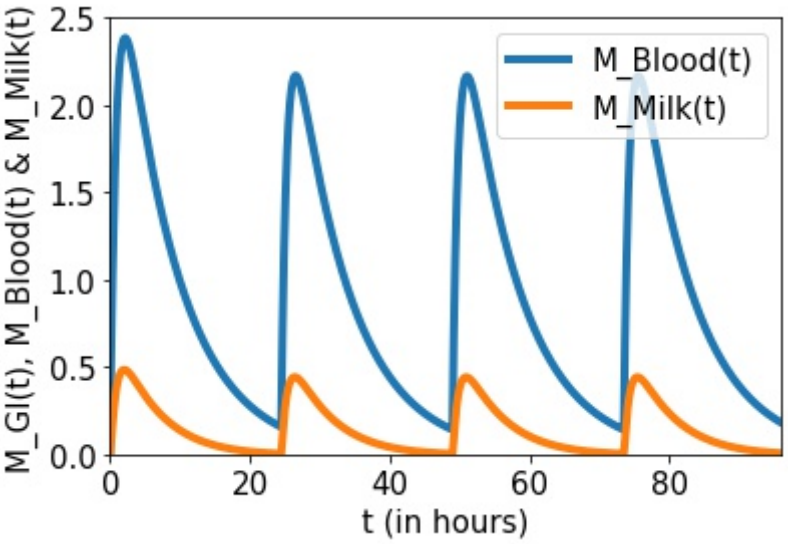

Figure 4.7: The mass of LFDT in bloodstream and milk over time with a dose of 15 mg for 4 days in women in lactation,$\Delta t = 0.001$

After some simulations in Pythons, it is concluded that LFDT is not safe for infants given breastfeeding. If the exposure is maintained, there is high possibility that they will suffer from serious adverse reactions.

Chapter 5

Conclusions

In summary, a complete model system of the mass of Lansoprazole for women giving breastfeeding is built up based on that for normal people. The value of diffusion rate from GI tract to plasma d_1, elimination rate from plasma d_2 and diffusion rate from plasma to milk d_3 are estimated and validated (2.7029, 2.9565 and 10 respectively).

$$\begin{cases} \frac{dM_{GI}}{dt} &= -2.7029(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}), \\ \frac{dM_{Blood}}{dt} &= 2.7029(\frac{M_{GI}(t)}{10} - \frac{M_{Blood}(t)}{4.5}) - 2.9565\frac{M_{Blood}(t)}{4.5} - 10(\frac{M_{Blood}(t)}{4.5} - \frac{M_{Milk}(t)}{V_{Milk}(t)}, \\ \frac{dM_{Milk}}{dt} &= 10(\frac{M_{Blood}(t)}{4.5} - \frac{M_{Milk}(t)}{V_{Milk}(t)}) - \frac{0.09}{2.4}\frac{M_{Milk}(t)}{V_{Milk}(t)}, \\ \frac{dM_{Milk}}{dt} &= \frac{-0.09}{2.4} \end{cases} \tag{5.1}$$

Multiple simulations are done in Python shows that LFDT is not compatible with women in laction. If the women keep using the medicine, the infants have to suffer a high exposure of about 21.6% everyday, which may cause some common serious adverse reactions in infants such as diarrhoea, stomach ache or vomiting.
(This result is only based on mathematical model, more factors must be considered for more accuracy.)

Bibliography

[1] C. D. Fryar, M.S.P.H., J. P. Hughes, M.P.H., K. A. Herrick, Ph.D., MSc., N. Ahluwalia, Ph.D (October, 2018).Fast Food Consumption Among Adults in the United States, 20132016. Retrieved on date, year from https://www.cdc.gov/nchs/products/databriefs/db322.htm.

[2] K. Bonyata, BS, IBCLC (January 14, 2018). How much expressed milk will my baby need? Retrieved on date, year from https://kellymom.com/bf/pumpingmoms/pumping/milkcalc/.

[3] DrugBank (June 13, 2005). Lansoprazole. Retrieved on date, year from https://www.drugbank.ca/drugs/DB00448.

[4] Lupin Healthcare (UK) Ltd (January 23, 2014). Lansoprazole 30mg Orodispersible Tablets. Retrieved on date, year from https://www.medicines.org.uk/emc/product/7183.

[5] F. Baldia, P. Malfertheinerb (2003). Lansoprazole Fast Disintegrating Tablet: A New Formulation for an Established Proton Pump Inhibitor. Retrieved from https://www.karger.com/article/pdf/70393.

[6] H. Marshall (May 05, 2016). Lansoprazole: uses, action, dosage, side effect and brand information: Lansoprazole reduces stomach acid and is prescribed for heartburn, acid reflux and stomach ulcers - read on for advice on taking this medicine. Retrieved on date, year from https://www.netdoctor.co.uk/medicines/digestion/a26460/lansoprazole-uses-and-action/.

[7] N. Hotham, E. Hotham (October 1, 2015). Drugs in breastfeeding. Retrieved on date, year from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4657301/.

[8] S. Gardiner, Drug Information Pharmacist, Christchurch Hospital, E. Begg, Clinical Pharmacologist, Christchurch School of Medicine (May 2001). Drug Safety in Lactation. Retrieved from https://medsafe.govt.nz/profs/puarticles/lactation.htm.

[9] Lupin Healthcare (UK) Ltd (January 23,2014). Lansoprazole 15mg Orodispersible Tablets. Retrieved from https://www.medicines.org.uk/emc/product/7182.

Appendix A

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")
```

Appendix B

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

```
@author: trangnguyen
"""
import numpy as np
import matplotlib.pyplot as plt

# Initializations
Dt = 0.001                          # timestep Delta t
G_init = 0                          # initial population of M_GI
B_init = 0                          # initial population of M_Blood
M_init = 0                          # initial population of M_Milk
Vm_init = 1                         # initial population of V_milk
t_init = 0                          # initial time
t_end = 100                         # stopping time

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

X = np.zeros(4)                         # create space for current X=[G,B]^T
dXdt = np.zeros(4)                      # create space for current derivative
t_arr = np.zeros(n_steps + 1)           # create a storage array for t
X_arr = np.zeros((4,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
X_arr[2,0] = M_init                     # add the initial M to the storage array
X_arr[3,0] = Vm_init                    # add the initial Vm to the storage array

k=0
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
d3 = 10

odd1=0                                    # Sum of values with odd index
even1=0                                   # Sum of values with even index
odd2=0
even2=0
odd23=0
even23=0
# 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
    M = X_arr[2,i-1]                      # load the value of M
    Vm= X_arr[3,i-1]                      # load the value of Vm
    if np.remainder(t,2.4)<0.001:
        k=0.09
    if np.remainder(t,0.5)<0.001 and t>0 and t<1:
        G =+ 15
    if np.remainder(t,24.5)<0.001:
        G=+15
        Vm=+1
    X[0] = G                              # fill current state vector X=[G,B]^T
    X[1] = B
    X[2] = M
    X[3] = Vm
    dGdt = -d1*(G/10-B/4.5)               # calculate the derivative dG/dt
    dBdt =  d1*(G/10-B/4.5)-d2*B/4.5-d3*(B/4.5-M/Vm)   # calculate the derivative dB/dt
    dMdt =  d3*(B/4.5-M/Vm)-k*M/Vm
    dVmdt=  -0.09/2.4
    dXdt[0] = dGdt                        # fill derivative vector dX/dt
    dXdt[1] = dBdt
    dXdt[2] = dMdt
    dXdt[3] = dVmdt
    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
    if i<23900 and np.remainder(i,2)<0.001:
        even1 = even1 + X_arr[1,i]
        even2 = even2 + X_arr[2,i]
        even23= even23+ X_arr[2,i]/X_arr[3,i]
    if i<23900 and i%2==1:
        odd1 = odd1 + X_arr[1,i]
        odd2 = odd2 + X_arr[2,i]
        odd23= odd23+ X_arr[2,i]/X_arr[3,i]
AUC1 = (B_init + 4*odd1 + 2*even1 + X_arr[1,23900])/3000 #AUC of M_Blood
AUC2 = (M_init + 4*odd2 + 2*even2 + X_arr[2,23900])/3000 #AUC of M_Milk
```

```
AUCC1= AUC1/4.5 #AUC of C_Blood
AUCC2= (M_init/Vm_init + 4*odd23 + 2*even23 + X_arr[2,23900]/X_arr[3,23900])/3000
#AUC of C_Milk

print('odd1=',odd1)
print('even1=',even1)
print('AUC1=', AUC1)
print('odd2=',odd2)
print('even2=',even2)
print('AUC2=', AUC2)
print('AUCC1=', AUCC1)
print('AUCC2=', AUCC2)

# Plot the results
fig = plt.figure()

plt.plot(t_arr, X_arr[1,:], linewidth = 4,label="M_Blood(t)")  # plot B vs. time
plt.plot(t_arr, X_arr[2,:], linewidth = 4,label="M_Milk(t)")  # plot M vs. time

plt.xlabel('t (in hours)', fontsize = 15)   # name of horizontal axis
plt.ylabel('M_GI(t), M_Blood(t) & M_Milk(t)', fontsize = 15) # name of vertical axis

plt.xticks(fontsize = 15)              # adjust the fontsize
plt.yticks(fontsize = 15)              # adjust the fontsize
plt.axis([0, 96, 0, 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('GBM6.jpg',dpi=fig.dpi, bbox_inches = "tight")
```