Lab - 2

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CS302, Modeling and Simulation

In this lab we numerically and analytically analyze the one compartment and two compartment models that model the drug dosage in human bodies.

I. INTRODUCTION

Drugs administered in the human body have prescribed dosages which, if not adhered to, can cause the drug to either be ineffective or may even prove to be fatal. The appropriate dosage of a drug depends on factors like absorption, distribution, metabolism and elimination. In this lab, we use two models for drug dosage while taking into account, the above factors. Each drug has a Minimum Effective Concentration, MEC (the minimum concentration of drug in required in the body for it to be effective) and a Maximum Therapeutic Concentration, MTC (the maximum concentration of drug that the body can tolerate after which it becomes toxic). The aim of modeling drug dosage is to determine effective dosage, and in case of periodic doses, the effective time interval of injection/ingestion of the drug in the body. [1].

II. MODELS AND RESULTS

A. One Compartment Model for Drug Dosage

- Simplifying assumptions:

  1. The entire body is a single homogeneous compartment.
  2. Distribution and absorption of drug in the body is instantaneous.
  3. Concentration of the drug in the system is proportional to the dosage.
  4. Elimination is proportional to the concentration of the drug in the body.

- Equations:
  Let Q be the mass of the drug. Let the initial mass administered be Q_0 and let it be administered periodically in the body. Per our assumptions, we can say that

$$\frac{dQ}{dt} = -KQ \tag{1}$$

  which is a differential equation with the solution:

$$Q = Q_0 e^{-Kt} \tag{2}$$

1. As seen in Eq. 2, $Q = Q_0 e^{-Kt}$. At half-life, $Q = Q_0/2$, hence, $0.5 = e^{-Kt}$, which gives us $ln(0.5) = -Kt_{1/2}$. Hence, we get the following equation for K:

$$K = -\frac{ln(0.5)}{t_{1/2}} \tag{3}$$

2. (a) MEC and MTC have units of concentration, i.e. $\mu g/mL$.
(b) The unit of dosage is that of mass, i.e. μg.
(c) The initial dosage of Dilantin is 100mg but we convert it to μg and hence, we multiply it by 1000.

3. Let

$$GP = 1 + a + a^2 + ... + a^{n-1} \tag{4}$$

represent the sum of a geometric progression with common ratio, a. Multiplying Eq. 4 by a on both sides and subtracting the resultant equation from Eq. 4, we get:

$$(1 - a)GP = 1 - a^n \tag{5}$$

which gives us the required formula:

$$GP = \frac{1 - a^n}{1 - a} \tag{6}$$

4. (a) As the half-life of Dilantin increases, the elimination constant decreases in value, and this follows from the equation:

$$elimination\_constant = \frac{0.693}{t_{1/2}} \tag{7}$$

(b) For $t_{1/2} = 7h$, $elimination\_constant = 0.099/h$.
(c) For $t_{1/2} = 22h$, $elimination\_constant = 0.0315/h$.
(d) For $t_{1/2} = 42h$, $elimination\_constant = 0.0165/h$.

5. (a) Here, Dilantin follows a one compartment model with multiple doses.
The patient takes 300mg of Dilantin once a day.
Simulating the above scenario we get the concentration versus time graph as shown in Fig. 1
(b) In this model Q is the quantity of Dilantin in blood in mg and the drug is administered every 24h, hence, t=24 and K=$eliminating\_constant$.

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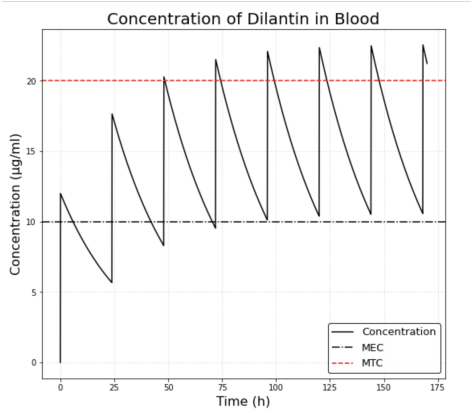

FIG. 1. Concentration of Dilatin in blood stream with respect to time: 300mg of Dilantin is administered every 24h. We can see that after 4th dose, the concentration of Dilantin in the body is more than MTC, absorption_constant=0.12.

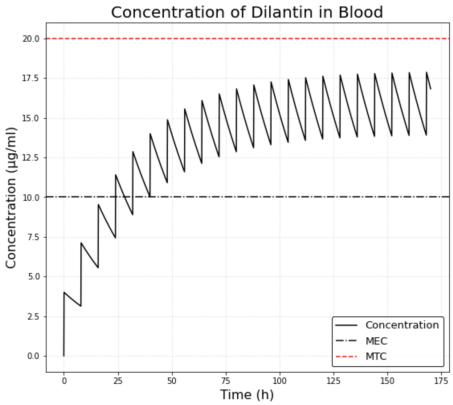

FIG. 2. Concentration of Dilatin in blood stream with respect to time: 100mg of Dilantin administered every 8h. This dosage schedule is safe and effective as the concentration lies between MTC and MEC, absorption_constant=0.12.

$$Q(0) = 0$$

$$Q(1) = 0.09 * 300 = 27mg$$

$$Q(2) = Q(1)e^{-24k} + Q(1)$$

$Q(3) = Q(2)e^{-24K} + Q(1)$, which implies

$$Q(1)[1 + e^{-24k} + e^{-24k*2} + e^{-24k*3} + ... + e^{-24k*N}] \quad (8)$$

Eq. 8 is a GP with common ratio r=e^{-24k}=0.4695. Hence, following Eq. 6 we get:

$$Q(n) = Q(1)(\frac{1-(0.4695)^n}{1-(0.4695)}) \quad (9)$$

6. (a) To measure the quantity of Dilantin before the fifth dose we follow the formula in Eq. 10. Here the value

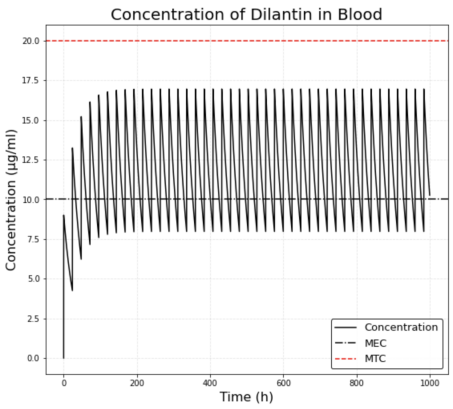

FIG. 3. Concentration of Dilantin in blood stream with respect to time: 100mg of Dilantin administered every 8h, absorption_constant=0.09.

of n is 5. The quantity at just after the fifth dose is:

$$Q(5) = Q(1)(\frac{1-0.2835}{1-0.7772})$$

$$Q(5) = 12(\frac{0.7164}{0.2228}) = 38.58mg$$

The quantity before the fifth dose is:

$$Q(5-) = Q(4)e^{-K(7.99)} = 37.5mg$$

$$Q(4) = 34.21mg$$

$$Q(5) = 26.59mg$$

Concentration of Aspirin at that time is 8.866μg which matches with the values in Fig. 4.

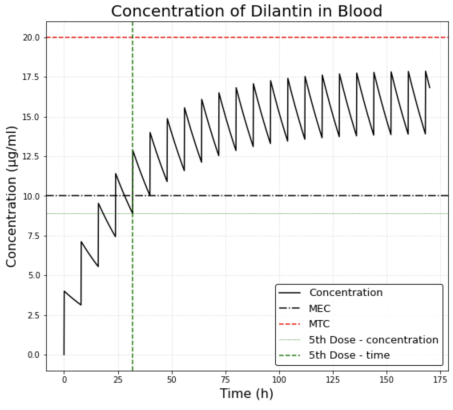

FIG. 4. Concentration of Dilantin in blood stream with respect to time: the concentration just before the 5th dose is 8.866μg , absorption_constant=0.12.

(b) Right before the n^{th} dose: Following Eq. 2, the formula for the long-term value of the quantity of Dilantin in the system immediately before the nth dose is

$$Q_n = Q_{n-1}e^{-K*(interval-0.1)} \tag{10}$$

When n tends to infinity (after a long time) we know from examining Eq. 6 that:

$$Q(n-1) = 12\frac{1}{1-0.7772} = 53.856mg$$

$$Q(n) = 41.99mg$$

(c) We get results similar to the OneCompartDilantin model.

7. For a male of 90kg, the total fluid volume will be (0.65)*(90)*(1000) ml. Hence to increase the concentration of drug in the blood stream, we would need to give a really high dose. Here, we adjust the dose to $100\mu g$, after which the concentration rises above MEC.

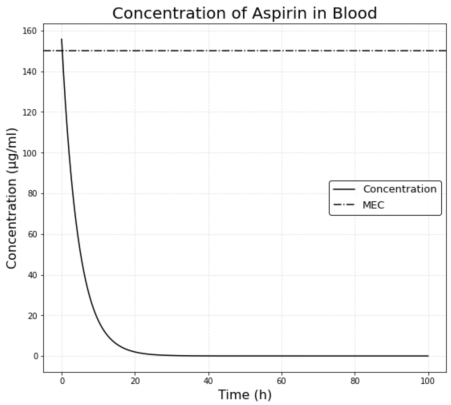

FIG. 5. Concentration of Dilantin in blood stream with respect to time: For a male of 90kg with the mentioned constraints. Here, we adjust the dose to $100\mu g$ and absorption_constant=0.12.

B. Two Compartment Model

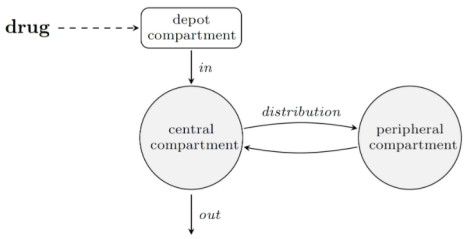

FIG. 6. [2]

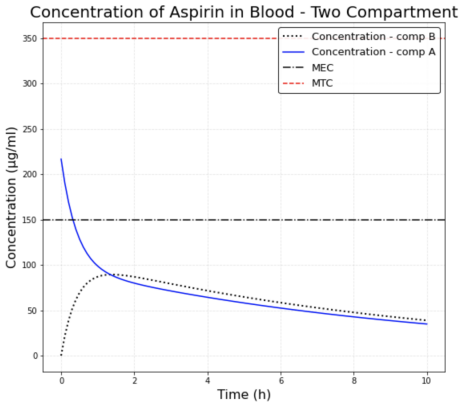

FIG. 7. Two Compartment Model of Aspirin - Single dose: $a_{12} = 1$, $a_1 = 1$, $K = \frac{ln2}{3.2}$ with one dose of 325 mg

We have taken the two-compartment model as shown in Fig. 6. Here, compartment A is the GI tract and Compartment B is the blood/serum. The diffusion constant from GI to blood stream is $a_{12} = a_{21}$, the diffusion constant from blood stream to the GI tract. The distribution in the first compartment, i.e. the GI tract is assumed to be instantaneous and the distribution in the second compartment is comparatively slower. K is the elimination constant.

The governing differential equations are:

$$\frac{dA}{dt} = -a_{12}A + a_{21}B - kA \tag{11}$$

$$\frac{dB}{dt} = a_{12}A - a_{21}B \tag{12}$$

1. Modeling single dose aspirin as seen in Fig. 7. Here the $a_1 = 1$, $a_{12} = 1$ and dose of Aspirin is 650 mg, considering 325 mg already present in blood plasma. We see that for this dose, the concentration of plasma does not exceed MEC level.

2. A person takes three aspirin tablets initially and takes 2 other after 2 hours. If we consider the absorption constant to be 1 then the diffusion constant needs to be 0.2 in order to bring the total concentration between MEC and MTC. Refer to plot in Fig. 8

3. To raise the concentration of drug above MEC, the doctor gives a loading dose. Here, we take the value of diffusion constant to be 0.8, assuming the absorption constant of Dilantin in the intestine is 0.12. If we take the absorption constant to be greater then the concentration of the drug will increase in the body and will cross MTC.

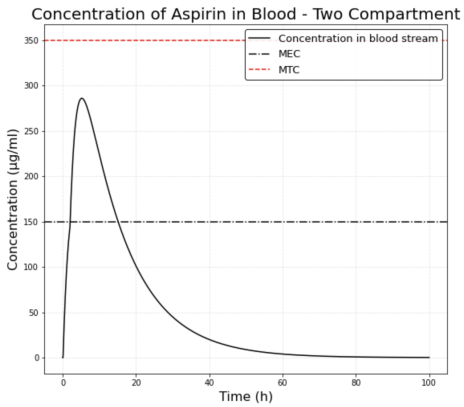

FIG. 8. Two Compartment Model of Aspirin - Multiple dose: $a_{12} = 1$, $a_1 = 0.2$, $K = \frac{ln2}{3.2}$ with one dose of 325 mg

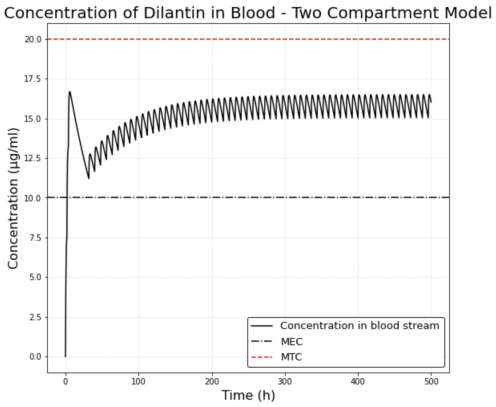

FIG. 9. Two Compartment Model of Aspirin - Multiple dose: $a_{12} = 0.8$, $a_1 = 0.12$, $K = \frac{ln2}{22}$ with one dose of 325 mg

III. CONCLUSIONS

We draw the following conclusions:

- We see that the compartment models are useful in giving us insights about the correct dosage schedules of drugs.
- The amount of dosage and the intervals at which it needs to be administered depends on the absorption and elimination constants.
- We see that two compartment models are more appropriate for modeling drugs that take more time to get absorbed in the body since, in such a model, the second compartment takes more time to absorb the drug.

[1] A. Shiflet and G. Shiflet, *Introduction to Computational Science: Modeling and Simulation for the Sciences*, Princeton University Press.3, 276 (2006).
[2] http://sia.webpopix.org/pharmacokinetics.html