Uttaranchal Journal of Applied and Life Sciences
U. J. App. Life. Sci. Vol: 3 (1): 83-91 **Dec 2022**

ODE Based Modeling of Drug Concentrations in Human Bloodstream

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Received: (15 Oct 2022) Revised: (15 Nov 2022) Accepted: (7 Dec 2022)

Abstract: In the last few years, mathematician & Scientist used numerous scientific studies to model the real world problems related in the field of pharmacology or pharmaceutical sciences. In this paper we emphasis on the mathematical modeling of drug concentration in human blood stream. For this we formulate ordinary differential equation (ODE) based two models, in which first model is compartment model and second is the modified model when multiple drug doses are given to a patient at a regular time interval gap. For the solution of models we use some mathematical techniques like, Laplace transformation, delta function, Step function and interpreted the resultant equation of model from which we can evaluate the drug amount in human blood stream at any time t.

Keywords: Bloodstream, Drug doses, Compartment model, GI tract, metabolism, ODE, Pharmacokinetics

INTRODUCTION

The branch of medicine science that deals with actions, use, effects, impacts of drugs into the human body known as pharmacology. This drug may act as a natural or artificial molecule that endeavours a physico-chemical or biological impact on the organism or any organ. To know the correct compositions of drugs are required to taken by a patient is understood by two main discipline of pharmacology which are pharmacodynamics and pharmacokinetics. In the pharma science, how an organism affected by a drug studied in pharmacokinetics whereas

pharmacodyanamics explains the drug affects into the organism. The models related to pharmacokinetics and pharmacodyanamics are showing the adverse effects and dose benefits together. The principle of pharmacokinetics is safest to applied for effective therapeutic of drugs on a patient under clinical pharmacokinetics. Although, this is not easy to identify the site where drugs are becoming effective into the organs, but easy to measure the concentration in between given time slot through urine, blood or saliva by pharmacokinetics. The known amount of drug's concentration is necessary to determine the drug's amount by calculating the distribution of drug in a human body that will explain the exact quantity of drug distributed through human blood. A large amount of distribution represents the drug amount has been dispensed fully into the human's blood. The cubic measure of distribution differs considerably between patients responsible to the fact which are genetically different as well as weaknesses can impact to the plasma volume within that individual body (Feizabadi, Volk and Hirshbeck. 2009). Thus, a patient who carries lower-plasma concentration will need to require a lesser quantity of drug's dose to reach complete drug dispersion throughout the person body; this is important to notice that check over the patients haemorrhaging while experiencing medication. The drug's concentration and its distribution is changing continuously due to excretion. Although, the amount of drug's concentration in bloodstream is increases while the amount is high into the tissue that may ultimately diffused the tissue by high drug concentration or high dose (Gordon and Michael 2015).

Pharmacodynamics is the combination of two Greek words "pharmakon" and "dynamikos" which means "drug" and "power" respectively. It describes about the drug's biochemical, molecular and physiologic actions in body. The association between drug assemblage on the target site and out coming effect includes the strength of therapeutic and time course adverse effects. Some factors are responsible, for example, the first variable is the time course, which describes the time taken of a drug will remain at the receiver site, which also controls its effects. Another is tolerability, which suggests that an increased quantity at the target site over time may eventually respond to diminishing drug effects (Jennifer 2020). When drug's dose increases, human body increases the metabolism level to resistance the effect of drug. Similarly, some beneficial bacteria also create barriers to build a protective layer from drug's concentration exposure. So that, use of anti-inflammatory drugs for a long time, as like antibiotics and ibeprophen, might be detrimental to living body. Different type of drugs may

target differently to the receptor site. Such like, a medicine use to lower blood pressure will directly hit to the auto rhythmic cells in heart to reduce calcium level, thereby seeing quantity in the heart and reducing mean-arterial pressure. But, the antibiotic such as penicillin, which hits foreign bacteria, and its cell, stopping the cell to form a protective cell wall and cause to dead. Every receptor's site may vary that's why each drug has different mechanisms (Wang and Husan 1996).

After the deep knowledgeable understanding of pharmacodynamics & pharmacokinetics,let us take a look into some mathematical systems.

Compartment Model

According to Koch Noble GA. 2011, we have a pair of ordinary differential equation

$$\left.\begin{aligned} \frac{dz}{dt} &= y(t) - b \cdot z(t) \\ \frac{dx}{dt} &= b \cdot z(t) - a \cdot x(t) \end{aligned}\right\} \qquad (1.1)$$

Where

$y(t) =$ initial injection dosage at instant t = 0

$x(t) =$ drug amount in blood stream at time t

$z(t) =$ drug amount in GI Tract at time t

$a, b =$ drug metabolism in blood stream and GI Tract respectively

Suppose we have a second order differential equation

$$A\frac{d^2 f}{dt^2} + B\frac{df}{dt} + Cf = 0 \qquad (1.2)$$

If $f = e^{kt}$ is a solution of equation (1.2) then

$$k^2 e^{kt} + k e^{kt} + e^{kt} = 0 \qquad \Rightarrow \quad k^2 + k + 1 = 0 \qquad (1.3)$$

Equation (1.3) is the characteristic equation of (1.2), we will use this equation later.

If we solve equation (1.3) suppose we will have different real values for k then the solution of this homogeneous equation is given by the complementary function

$f_c = C_1 e^{-k_1 t} + C_2 e^{-k_2 t}$

Now to factor out $z(t)$, we rewriting model equation (1.1)

$$\{D+b\}\cdot\{z(t)\}=1 \quad \text{and} \quad -b\cdot\{z(t)\}+\{D+a\}\cdot\{x(t)\}=0$$

Where D denotes the differential coefficient w.r.t. t and let$y(t) = 1$. Multiplying above equation by b we get

$b\{D + b\}\{z(t)\} = b$ (1.4)

$[D + b]\{-b[z(t)] + [D + a][x(t)]\} = 0$ (1.5)

For the elimination of $z(t)$, adding (1.4) & (1.5), we get

$\{D + b\}\{D + a\}\{x(t)\} = b$, which can be written as

$$\frac{d^2x}{dt^2} + (a+b)\frac{dx}{dt} + abx = b \tag{1.6}$$

For the solution of (1.6) now using characteristic equation (1.3), the we have

$$k^2 + (a + b)k + ab = 0 \implies (k + a)(k + b) = 0 \implies k = -a \; and \; k = -b$$

Then homogeneous solution is

$$x_c = C_1 e^{-at} + C_2 e^{-bt} \tag{1.7}$$

And let particular solution of (1.6) is given by

$x_p = K$, using in (1.6) we get $abK = b \implies K = \frac{1}{a}$

So complete solution of model equation (1.6) is given by

$$x(t) = C_1 e^{-at} + C_2 e^{-bt} + \frac{1}{a} \tag{1.8}$$

In the solution (1.8) $x(t)$ is the drug amount in the blood at any time t and $C_1 \& C_2$are the drug amount in the Ist and IInd compartments respectively, $a \; and \; b$ are constant for decline rate. Using equation (1.8) we can model or evaluate the drug amount in the human blood stream at a particular instant or time t when drug passes through two compartment models.

MODIFIED MODEL

Suppose drug doses given to a patient at a regular time interval and drug would be metabolized between each injected dose. We can start from the equation

$$\frac{dx}{dt} = y(t) - a \cdot x(t) \tag{2.1}$$

Where $x(t)$ is the drug amount in blood at time t and (t) , drug injection pattern at time t, which is a discrete value, a is the drug metabolism. When $y(t) = 0$ then there will be exponential decay of drug in the blood stream.

To solve the modeled equation (2.1) we required some mathematical concepts from Dirac delta function& its Laplace transformation.

The Laplace transformation of $y(t)$ is defined by

$$L[y(t)] = \int_0^\infty e^{-st} y(t)dt = F(s) \tag{2.2}$$

And Dirac delta function is defined by the rate of change in step function or derivative of step function w.r.to. t [3]. Therefore

$$\frac{du}{dt} = \delta(t) \tag{2.3}$$

Where $u(t) = \begin{cases} 1 & \text{when } t > 0 \\ 0 & \text{when } t < 0 \end{cases}$ is step function.

Moreover,

$$\int_{-\infty}^{\infty} z(t) \cdot \delta(t-\tau)dt = z(\tau) \tag{2.4}$$

$$\delta(t) = \begin{cases} \infty, & \text{if } t = 0 \\ 0, & \text{if } t \neq 0 \end{cases} \quad \text{and} \quad \int_{-\infty}^{\infty} \delta(t)dt = 1 \tag{2.5}$$

$$\delta(t-\tau) = \begin{cases} \infty, & \text{if } t = \tau \\ 0, & \text{if } t \neq \tau \end{cases}$$

Since $y(t)$ is a discrete pulse function so $y(t)$ can be represented as

$$y(t) = \delta(t-\tau_1) + \delta(t-\tau_2) + ... + \delta(t-\tau_n) \tag{2.6}$$

Where n is the number of doses given to the patient.

For the solution of (2.1) taking Laplace transform into account we have

$$L\left[\frac{dx}{dt}\right] = L\left[y(t) - a \cdot x(t)\right] = L\left[y(t)\right] - a \cdot L\left[x(t)\right] \qquad \text{(Using Linearity Property)}$$

$$L\left[\frac{dx}{dt}\right] = \int_0^\infty e^{-st}\frac{dx}{dt}dt = \left[e^{-st}x(t)\right]_0^\infty + \int_0^\infty se^{-st}x(t)dt$$

$$L\left[\frac{dx}{dt}\right] = -x(0) + s\int_0^\infty e^{-st}x(t)dt$$

$$L\left[\frac{dx}{dt}\right] = -x(0) + s\cdot I \tag{2.7}$$

Where $I = \int_0^\infty e^{-st}x(t)dt = L\left[x(t)\right]$ and $x(0)$is the drug amount at initial time $= 0$. Also,

$$L\left[y(t)\right] - a\cdot L\left[x(t)\right] = L\left[\delta(t-\tau_1) + \delta(t-\tau_2) + ... + \delta(t-\tau_n)\right] - a\cdot L\left[x(t)\right] \tag{2.8}$$

Taking Laplace transformation of the delta function, this gives

$$L\left[\delta(t-\tau)\right] = \int_0^\infty e^{-st}\delta(t-\tau)dt = e^{-s\tau} \tag{2.9}$$

Applying (2.9) in the right hand side of Equation (2.8) and comparing with equation (2.7), which turn out as

$$s\cdot I - x(0) = \left\{e^{-s\tau_1} + e^{-s\tau_2} + e^{-s\tau_3} + ... + e^{-s\tau_n}\right\} - a\cdot I$$

$$I(s+a) = x(0) + \left\{e^{-s\tau_1} + e^{-s\tau_2} + e^{-s\tau_3} + ... + e^{-s\tau_n}\right\}$$

$$I = \frac{x(0) + \left\{e^{-s\tau_1} + e^{-s\tau_2} + e^{-s\tau_3} + ... + e^{-s\tau_n}\right\}}{s+a} \tag{2.10}$$

Now inserting the value of I and formulating inverse Laplace transform of each parts of the equation (2.10), we get

$$L[I] = L^{-1}\left[\frac{x(0)}{s+a}\right] + L^{-1}\left[\frac{e^{-s\tau_1}}{s+a}\right] + L^{-1}\left[\frac{e^{-s\tau_2}}{s+a}\right] + ... + L^{-1}\left[\frac{e^{-s\tau_n}}{s+a}\right] \tag{2.11}$$

Suppose $L^{-1}\left[\frac{e^{-s\tau_n}}{s+a}\right] = L^{-1}\left[e^{-s\tau_n}\cdot R\right]$, where $R = \frac{1}{s+a}$

To find out the final solution, we have now four steps process. First we have to identify the R then we will evaluate the inverse of laplace transformation of function R to get $y(t)$, replace t by the $t-\tau_n$ and at last multiply $y(t)$ by the $u(t)$ (i.e. step function). After this procedure we get

$$L^{-1}\left[e^{-s\tau_n}\cdot R\right] = y(t-\tau_n)\cdot u(t-\tau_n) \tag{2.12}$$

Also from the definition of Laplace transform we have $y(t) = e^{-at}$, if we apply this for every component of the equation (2.11) then using (2.11) and (2.12) we got the final solution of model equation for drug concentration, we have

$$x(t) = x(0)e^{-at} + u(t-\tau_1)e^{-a(t-\tau_1)} + u(t-\tau_2)e^{-a(t-\tau_2)} + \ldots + u(t-\tau_n)e^{-a(t-\tau_n)} \qquad (2.13)$$

Equation (2.13) is the solution to our modified model. Using this equation, the amount of drug in the body can be determined over time t. Graphical representation of equation (2.13) using MATLAB software is shown in fig-1.

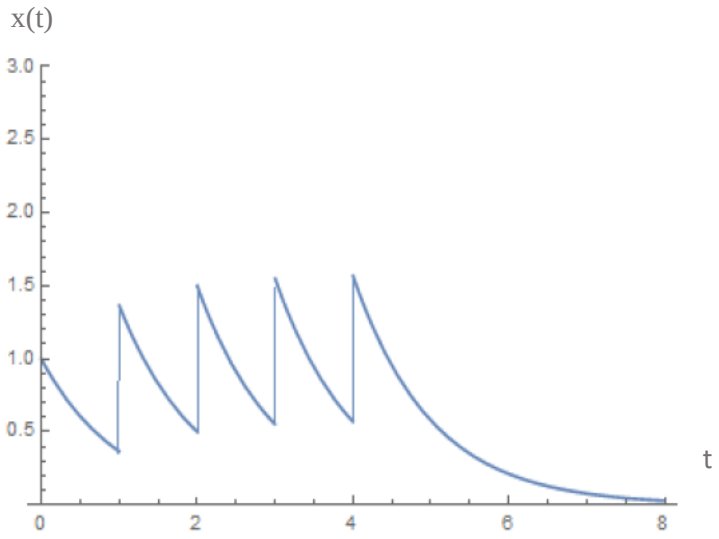

Figure 1: Amount of Drug in Blood Stream

The actions are triggered as time passes, and the result shows temporary surge in drug concentration levels. The exponential decay function does not allow for much of the increase in this spike that is associated with it thus reducing the concentration of drug. When x(t) is plotted, the result obtained is what we expected. This graph shows that the lowest point of the graph (curve) is here indicating that the drug level touches its lowest effective drug concentration, and the highest peak point is represented by its greater toxic drug amount. The full graph shows a therapeutic-window representing arrange of drug efficiency. It has been studied before, that each type of drug has accumulated its own chemical properties that react differently in the body. Some drugs are used to administer small doses at repeated intervals, while some are used to administer higher doses over a longer period of time. The therapeutic

range for small doses of the drug is large. This may be a drawback as there is a reason for sub therapeutic long-distance stays. Similarly, more frequent use of drugs is not attractive for administration

CONCLUSION

To conclude, very few focused on models that support modeling drug injection. types in the field of pharmacokinetics. While the resolution of each formulation may change according to different factors varies, although the result coincides, we are therefore able to control the concentration of the drug in the human blood at any instant. Although, this is very important to consider all the responsible factors. Patients have different capacities to metabolize the different doses. Interconnectivity between medications may also affect the decay rate. With working principles of pharmacodynamics, these components may be considered or adjusted to calculate the mathematical interpretations. These models may lead to a broader understanding of the drugs used to improve the efficacy of drug administration and achieve the ultimate aim of truly improving patient overall health.

REFERENCES

[1] Koch Noble GA. 2011. Drugs in Classroom: Using Pharmacokinetics to introduce bio mathematical modeling. Math Model Nat Phen, 6(6): 227-44.

[2] Feizabadi MS, Volk C, Hirshbeck S. 2009. A two compartment model interacting with dynamic drugs. Applied Mathematics Letter, 22:1205-9

[3] Dawkins, Paul. 2016. “Table of Laplace Transforms” Paul’s Online Math Notes. Lamar University.

[4] Gordon, Michael. 2015. Pharmacokinetics for Nursing Pharmacology: Drug Half-Life Pharmacokinetics for Nursing Pharmacology: Drug Half-Life.

[5] Khanday MA, Najar A. 2015. Maclaurin’s series approach for the analytical solution of oxygen transport to the biological tissues through capillary bed. J Med Imag Health Informatics, 5(1).

[6] Jennifer Le. Oct 2020. 'Drug Administration', School of Pharmacy and Pharmaceutical Sciences, University of California San Diego.

[7] Wang.W and Husan. F. 1996. The impact of patient compliance on drug concentration profile in multiple doses, Statistics in Medicine,15(6): 659-669.

[8] S.P. Ellner and J. Guckenheimer. 2006. Dynamic Models in Biology, Princeton UniversityPress, (Chapter 6).