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Investigating Drug Diffusion Using Multi-Compartment Model

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دراسة انتشار الدواء بالجسم باستخدام نماذج متعددة الحجيرات

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الملخص

تلعب نماذج الحجيرات دورًا محوريًا في نمذجة انتشار الدواء في علم حركة الادوية في الجسم" الفارماكوكينتيك ". تعتبر النماذج المتعددة الحجيرات تمثيلا رياضيا معقدا يستخدم لشرح آليات توزيع الدواء وإزالته من الجسم. تهدف هذه الدراسة إلى استخدام نماذج متعددة الحجيرات متمثلة في نموذج ثلاثة وأربعة حجيرات لمحاكاة حركة الدواء وفهم سلوك الدواء في الجسم. بالإضافة الي تحديد معلمات الفارماكوكينتيك لحالتين من بيانات تركيز الدواء التجريبية. تم تنفيذ هذه النماذج عن طريق حل المعادلات التفاضلية التي تُمثل النظام المكون من ثلاثة وأربع حجيرات، وحساب المعلمات المتعلقة بفارماكوكينتيك, تم تصميم واجهة مستخدم رسومية للنظام. تم تطبيق طريقة المربعات الصغرى لملائمة البيانات التجريبية. خلصت الدراسة إلى أن دقة النموذج الرياضي المتحصل عليه تعتمد على جودة البيانات المدخلة. وأظهرت نتائج ان معدل الخطأ بين البيانات الفعلية وبيانات النموذج المتنبئ بها كانت اقل في نموذج أربع حجيرات.

Abstract

Compartment models play a central role in modeling drug diffusion in pharmacokinetics. Multi-compartment models are mathematical representations used to explain the mechanisms of drug distribution and elimination. The study aims to employ multi-compartmental models represented by three and four compartments in order to comprehend drug behavior in the body. Pharmacokinetic parameters were determined for two cases of experimental drug concentration data. The models were implemented by solving differential equations that represent the system of three and four compartments and then estimating pharmacokinetic parameters. These work utilize a graphical user interface (GUI) to facilitate entering data ad presenting the corresponding results. The least squares method was employed to fit the experimental data with the estimated ones. The study concluded that the accuracy of the obtained mathematical model depends on the quality of the input data. Moreover, the four-compartment model had the lowest error rate, indicating the best fit in both cases.

Keywords: Compartment, Pharmacokinetic, Drug, Concentration, Data Fitting.

Introduction

Nowadays, the compartmental model of drug concentration is a major challenge given its significance. Drug dosage, drug intake, and drug outflow through different bodily compartments can have both positive and negative consequences. A mathematical model is a crucial tool for understanding drug diffusion behavior. It is thought that the relationship between drug intake and drug concentration at the target site through different compartments in biological processes is very significant [1]. The human body is affected by drug dosage and the inflow and

outflow of the drug in processing compartments in both positive and negative ways. The behavior of a chemical or medicine supplied over time throughout the human body's numerous components was examined by pharmacokinetics researchers. It establishes the intended therapeutic response and aids in understanding the connections between the drug's rates of absorption, distribution, and elimination inside the body [2]. Drug diffusion mathematical modeling is a significant prediction technique for gaining a fundamental understanding of bio-transport mechanisms. Even if mathematical modeling is theoretical in nature, when compared and empirically confirmed, the established results lead to realistic outcomes. Many mathematical models and numerical simulations were performed with a high degree of efficiency in the absence of experiments[3]. Pharmacokinetics relies heavily on compartment modeling because of the local processes that occur in every area of the compartment[4]. A large number of researchers have dedicated their time to investigating the medication's compartmental activity in the human body over time and developing an appropriate pharmacological therapy procedure. Gajanan[5] investigated factors influencing blood flow concentration in cell compartments. Mathematical model with differential equations was utilized to analyze this phenomenon. Miskeen et.al [6] investigated one and two compartmental models, key pharmacokinetic parameters related to the behavior of the drug concentration in the body were calculated. Khanday et.al [4] developed mathematical models to understand how drugs are administered through oral and intravenous routes. One, two and three compartment models were formulated based on diffusion process. Ordinary differential equations were solved using Laplace transform and eigenvalue methods. Yan et.al [7] examined how dose omission affected the plasma concentrations of two-compartment models with two common drug administration routes: intravenous bolus and extravascular first-order absorption. The authors then compared the drug pharmacokinetics preference between one and two compartment pharmacokinetic models. Michalakis Savva[8] created a one-compartment model for constant rate repetitive intravenous intermittent infusions where drug concentration can be simulated as a function of real-time. In this work, the diffusion of drug in blood and tissue using three and four compartments model was considered and the pharmacokinetic parameters were calculated. These models were implemented utilizing MATLAB software with graphical user interface (GUI).

Compartment model

Compartment model refers to a mathematical model used to examine physiological or pharmacological kinetic properties of the body or a portion of it. The body is shown as a collection of compartments that are grouped either parallel or in series, depending on how the material is being transported. These models can be used to comprehend the movement of medications or any other molecule throughout the body, as well as the transport mechanisms between related volumes. Understanding the biological mechanisms underlying the kinetic behavior of a medication injected into the body tissues is aided by the use of compartment models. Depending on the drug's behavior, the body is made up of one or multi compartment systems. In one compartment model, the entire human body is regarded as a homogenous unit where an administered drug diffuses instantly within the blood. In the case of multi compartment model, the body can be represented as separate but connected compartments viz. the central compartment and the peripheral compartments [6,9].

a. Single-compartment model

This model is the simplest way to prescribe the distribution of the drug as well as the disposal of the drug in the body. In this model, the body is assumed to act as a single unit that can easily enter or exit the body [5,6].

b. Multi-compartment model

Since the model of a single compartment is so simple, it does not represent the behavior of the spread of the drug in the body precisel. Therefore, multi-compartment models are used to study and predict more accurately the concentrations of these drugs in blood and tissues. In these models, it is assumed that the body can be divided into compartments according to the type of organs where there are high and low blood pumping organs. High blood pumping organs such as heart, brain, liver, lungs, kidneys, endocrinology, skin, muscles, fatty tissue and marrow, which composed of the central compartment. While low blood pumping organs such as bones, cartilage, teeth that are composed of the tissue or peripheral. The transfer rate processes for the passage of drug into or out of individual compartments are first-order processes [7].

1. Three compartments model

The pharmacokinetic three-compartment model divides the body into central and peripheral compartments, with drug administration in central compartment 1, distribution in peripheral compartments, and disposal in central compartment. Distribution volumes and transmission rates are determined using triple equivalents.

$$\mathrm{C(t)} = \mathrm{A}e^{-\alpha t} + \mathrm{B}e^{-\beta t} + \mathrm{C}e^{-\gamma t} \qquad (1)$$

The model consists of three compartments of central compartments, tissue compartment and inner tissue compartment as represent in Fig (1). The typical drug is distributed more quickly in the primary or central

compartment. The distribution speed in the second part or tissue is reduced very slowly to the third compartment such as bones and fat [9,10].

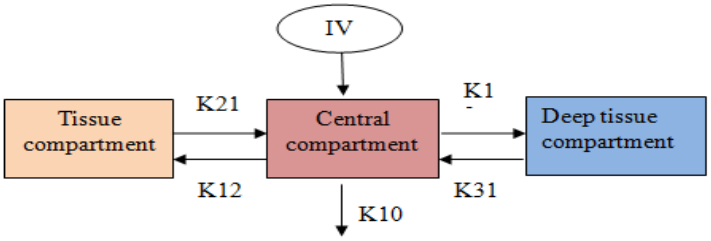

Figure 1 Represents of three compartments model.

Ordinal differential equations corresponding to the three-compartment system are given by Eq. 2:

$$\frac{dc_{1(t)}}{dt} = c_2k_{21} + c_3(t)k_{31} - c_1(t)(k_{10} + k_{12} + k_{13}) \quad (2)$$
$$\frac{dc_2(t)}{dt} = -c_2(t)(k_{21}) + k_{12}c_1(t)$$
$$\frac{dc_3(t)}{dt} = -k_{31}c_3(t) + k_{13}c_1(t)$$

2. Four compartments model

Model of four compounds, represented in Fig (2), consists of the following compartments: central compartments, tissue compartment, inner tissue compartment and inner tissue compartment with special behavior. توحيد تسميات الحجيرات بما يتوافق مع شكل 2

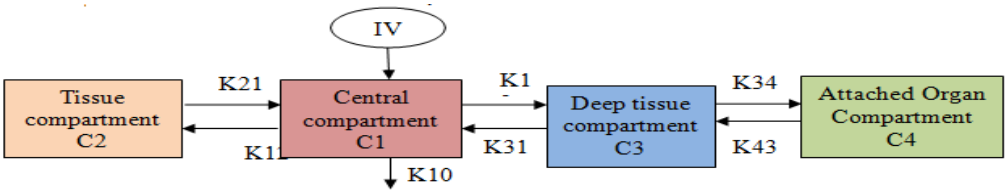

Figure 2 Represents of four compartments model.

Differential equations represented by 4-compartment model:

$$\frac{dc_1(t)}{dt} = -c_1k_{12} + c_2k_{21} - k_{10}c_1 - k_{13}c_1 + k_{31}c_3$$
$$\frac{dc_2(t)}{dt} = c_1k_{12} - c_2k_{21} \quad (3)$$
$$\frac{dc_3(t)}{dt} = -k_{31}c_3 - k_{34}c_3 + k_{43}c_4 + k_{13}c_1$$
$$\frac{dc_4(t)}{dt} = -k_{43}c_4 + k_{34}c_3$$

Pharmacokinetic parameters

In the following, five key parameters related to the compartment model are defined:

1. **Volume V**
   The formula in Eq. 4 is used to determine the volume of the medication is distributed in the main compartment [6,12]:
   $$V_1 = \frac{D_{i.v}}{C_1 + C_2 + C_3} \quad (4)$$
2. **Distribution size in stable state V_{ss}**
   The general equation of distribution size in stable state is given by the equation[11,13]:
   $$V_{ss} = \frac{D_{i.v}\sum_{i=1}^{n}\frac{c_i}{\lambda_i^2}}{(\sum_{i=1}^{n}\frac{c_i}{\lambda_i})^2} \quad (5)$$

3. **Area under curve AUC**
   This measure expresses the overall amount of the drug that enters the bloodstream following administration and is the total integrated area under the plasma level-time profile. AUC is calculated from the equation[6,11]:

$$AUC = \frac{c_1}{\lambda_1} + \frac{c_2}{\lambda_2} + \frac{c_3}{\lambda_3} + \frac{c_3}{\lambda_3} + \frac{c_{\mathrm{i}}}{\lambda_{\mathrm{i}}} \quad (6)$$

4. **Clearance cl**
   It refers to a drug's removal from the body and circulation. It is given as the drug concentration in a volume of blood divided by the time [6,12,13].

$$Cl = \frac{D_{i.v}}{AUC} \quad (8)$$

5. **Half-life $T_{1/2}$**
   It shows how long it takes for a drug's levels in the blood to drop to half of what it was at equilibrium [6,10,11].

$$T_{1/2} = \frac{0.693 v_d}{cl_t} \quad (7)$$

Data Fitting

Data fitting is the process of finding a mathematical function, typically a single f(x) formula, that accurately represents practical data. The goal is to determine the parameter values that make this function fit the data well. Linear and non-linear regression are commonly used for fitting practical data and determining the best-fit values for model parameters. It is not always necessary to use an ideal model with many parameters, as a simpler model can often provide a good approximation while facilitating compatibility with the data. Data fitting with exponential functions is particularly useful when solving compartmental systems, as the exponential function represents the solution to the differential equations, and the number of exponential terms corresponds to the number of compartments in the system [6].

GUI of the proposed system

Fig (3) shows the main interface designed for the system to calculate the concentration of the drug in the body by using the solution of the normal differential equation system .The data that can be entered through this main interface are:

1. Number of values (drug concentration versus time),
2. Drug concentration(mg/L),
3. Time the drug concentration was taken (hour),
4. The given dose (mg).

Pharmacokinetic parameters are calculated and the user can choose the model type (i.e, whether three or four compartments)

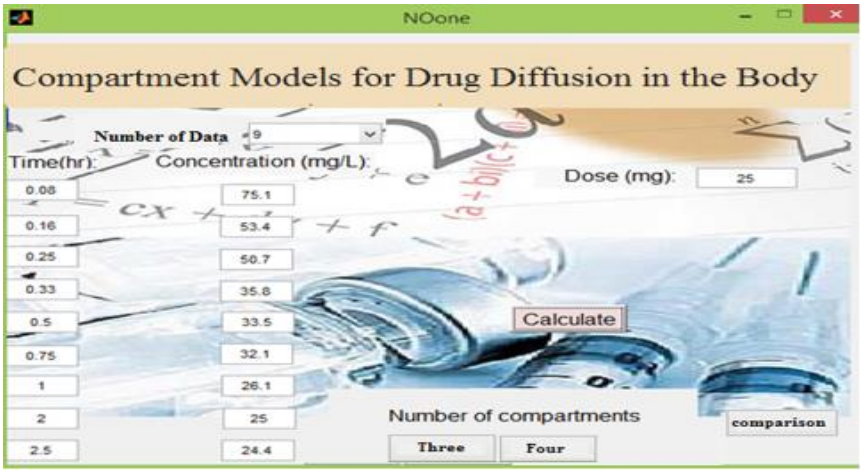

Figure 3 Graphic interface(main interface).

Results

1. **Case Study 1**

   Data for this case study is adopted from [14]. It considers estimating of the concentration of the medicine insulin in plasma produced by injection at a dose of 80 milligrams and Table (1) shows the empirical data sampling according to [14]. The drug concentrations in plasma at eight periods of time (Note that: data has not been taken for enough time as the drug's concentration has not approached zero).

Table 1 Concentration of drug for condition(first case) [14]

Time (hr)	0.06	0.1	0.133	0.166	0.2	0.233	0.266	0.316
Medicine concentration (mg/L)	130	85	51	49	45	41	35	30

The three compartment data are plotted on the GUI and the pharmacokinetic parameters are displayed in the Fig. 4. While Fig. 5 depicted the results for four-compartment model using the same data. The more points the curve passes over, the better the representation.

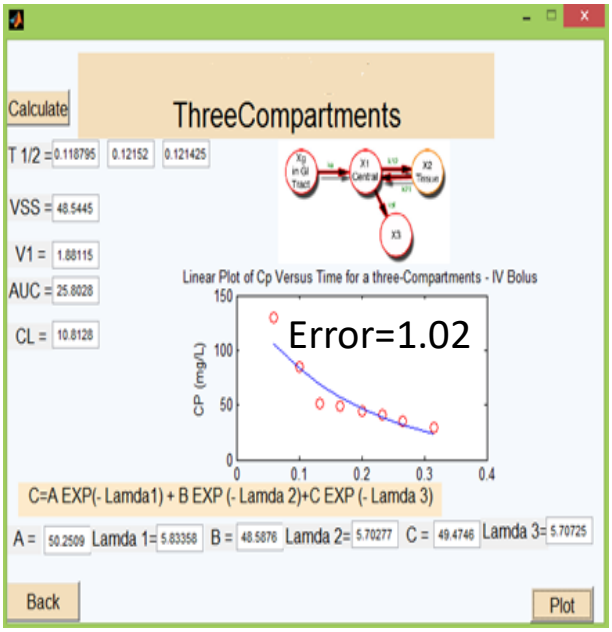

Figure 4 Graphic interface for three compatment model(case one)

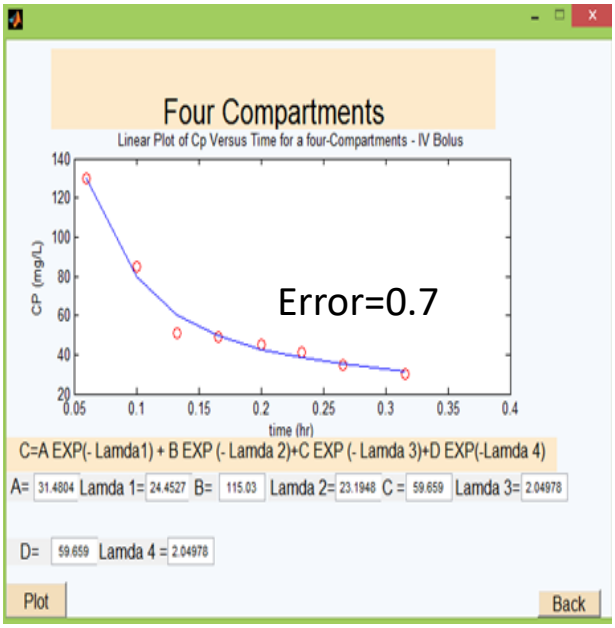

Figure 5 Graphic interface for three compatment model(case one)

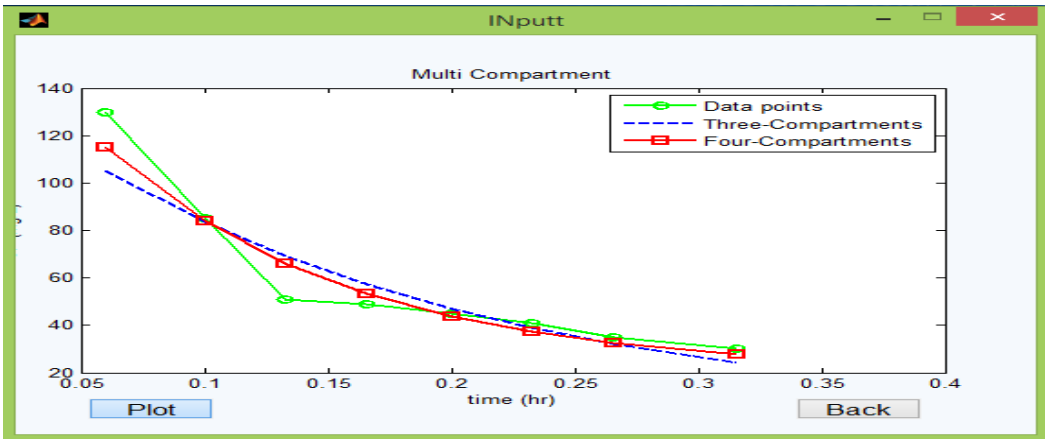

Figure 6 Comparison between three compartments and four compartments in the first case.

The four-compartment model showed better data representation and a reduced error ratio as shown in Fig(6) between the curve and actual data compared to the three-compartment model.

2. Case study 2

Data for this case study is adopted from [15]. The drug dose of 25 mg is intravenously injected and exchanges take place between the compartments, drug concentrations vs. points of time are shown in Table(2).

Table 2 Concentration of drug for condition(second case) [15]

Time (hr)	0.08	0.16	0.25	0.33	0.5	0.75	1	2	2.5
Medicine concentration (mg/L)	75.1	53.4	50.7	35.8	33.5	32.1	26.1	25	24.4

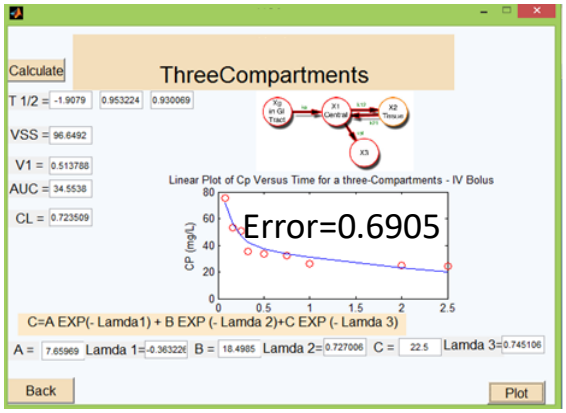

Figure 7 Three compartment model(case two)

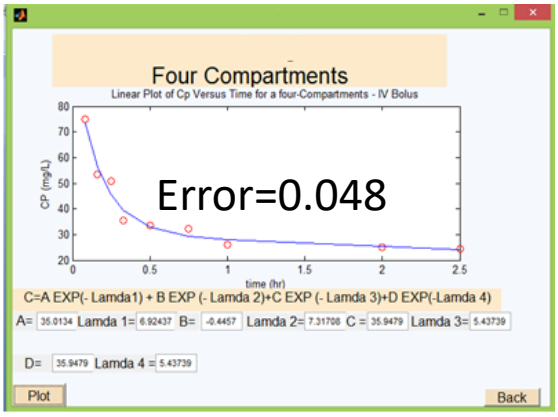

Figure 8. Four compartment model(second case)

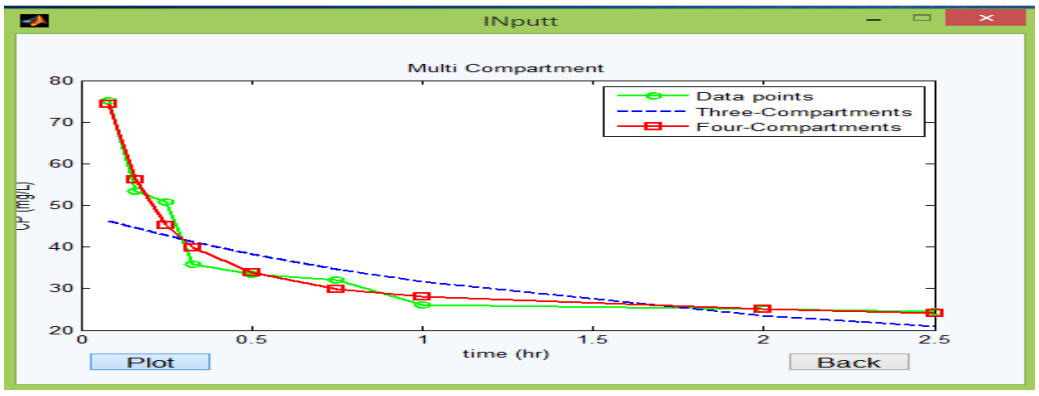

Figure 9 Comparison between three compartments and four compartments in the second case

The drug's concentrations results for the second case are shown in the previous Fig 7 and 8. By comparing the curves in Fig (9), it is obvious that the four-compartment model's representation had the lowest error ratio and was the best. When comparing the two cases' data quality, it was found that the second case's data was of higher quality because it had more data (9 samples) taken for closed periods of time and enough time to take because the concertation was closer to zero than the first case. As a result, the error rate was lower in the second case. Table (3) displays the results of the calculations for the pharmacokinetic parameters of the three- and four-compartment models.

Table 3 Pharmacokinetic parameters.

Number of compartments	Case study	Cl	AUC	V_1	Vss	$T_{1/2}$			
3	1	10.8128	25.8028	1.88115	48.5445	0.121425	0.12152		0.118795
		0.72350	34.5538	0.51378	96.6492	0.930069	0.953224		1.9079
4	2	25.86	10.78	1.434	4.67	0.0645	0.806	0.255	0.0688
		0.0592	422	0.2297	343	0.072	0.07262	0.232	0.0592

Conclusion

A multi-compartment model was presented to estimate the concentration of the drug in the body, (which was taken intravenously) through solving differential equations. The model included data representing time of sampling and the concentration of the drug in the blood for two different conditions (in terms of the type of drug, the period between sampling, and the number of samples). A graphical user interface was designed using Matlab for the input of data and result presentation. Data fitting and modeling for three and four compartments were compared and the pharmacokinetic parameters were estimated. The results showed that the greater the number of data representing the concentrations, the greater the number of compartments and thus higher accuracy of the model. For future research, the study recommends investigating other drug delivery systems, such as drug tablets taken orally, and the underlying mathematical models. It also suggests considering a generic model to represent N compartments, and consider several data samples with patient information such as weight, age, and sex to account for different factors.

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