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STOCHASTIC MODEL OF DRUG CONCENTRATION LEVEL DURING IV-ADMINISTRATION

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Abstract. A stochastic model describing the concentration of the drug in the body during its IV-administration is discussed. The paper compares a deterministic model created with certain simplifications with the stochastic model. Fluctuating and irregular patterns of plasma concentrations of some drugs observed during intravenous infusion are explained. An illustrative example is given with certain values of drug infusion rate and drug elimination rate.

Keywords: IV-administration, deterministic model, stochastic differential equation, mean value, delay differential equation.

Mathematics Subject Classification: 34F05, 60H10.

1. INTRODUCTION

From the point of view of both the doctor and the patient, it is very important to know what the body does with the drug. The effect of the drug on the organism can be determined by studying the relationship between the dosing regimen and the time profile of the concentration of the drug in the plasma, i.e. by observing and controlling the absorption, distribution, metabolism and excretion of the drug from the body over time.

Since the effect of a drug is related to its concentration at the site of action, it would be useful to control this concentration at that site. However, drug receptor sites are usually inaccessible or abundant in the body for such observations, making direct measurement of drug concentration at these sites impractical and often impossible. Therefore, indirect methods such as compartmental models are used to describe the process of drug action in the body.

Compartment models are based on the assumption of the existence of certain barriers that molecules of the active substance must overcome and that limit their movement. A key process of drug movement is the diffusion of molecules through biological barriers, which facilitates a mathematical description of the rate at which

the drug is distributed in the body. The compartment can be considered the only entity that has a capacity in which the drug is homogeneously dispersed. Drug delivery into the compartment and its removal are characterized by rate constants. Most drugs use one or two compartment models that are used to study their effects on the body, see [10] and references therein.

It follows from the published results of the pharmacokinetic study that deterministic models created in this way are the most suitable mathematical model for describing intravenous plasma drug concentrations.

However, the deterministic model is constructed assuming certain basic simplifications, which were discussed in [11]. Therefore, the deterministic equation expresses only a simplified model of the real process, which in most cases should not distort the time dependence of the plasma drug level, but in some cases the deterministic model may not reflect the real process.

Some phenomena modeled using stochastic systems or systems with a random structure were studied by the authors in [5–8, 12]. Specifically, in [12] the considered problem of navigating to a target is described by a differential equation with random parameters. In [6], the mathematical model of the foreign exchange market is considered in the form of a stochastic linear differential equation with coefficients dependent on the semi-Markov process. The stability of the zero solution to nonlinear differential equations under the influence of white noise is considered in [8]. A dynamical system with a random structure, which is very suitable for use as models for protecting information in cyberspace, is considered in [7].

In this paper, we first derive a deterministic model, then we recall the results of [11], and in the main part of the work we present a model describing the drug concentration in the body using a stochastic differential equation.

2. DETERMINISTIC MODEL

Due to the fact that the drug is rapidly absorbed into the body when administered intravenously, the one-compartment pharmacokinetic model is in many cases the most appropriate deterministic model for describing the distribution of IV-administered drugs. The one-compartment model is the simplest deterministic model representing the body as a whole, characterized by the entry of the drug into and out of its volume [2].

In the construction of the deterministic model, it is assumed that the drug input is equal to the infusion rate $I\left(\text{mg h}^{-1}\right)$ and the drug output is proportional to the elimination rate constant $k(\text{h}^{-1})$. The amount of drug in the body changes over time due to its elimination, and this change is described by the rate of elimination. Thus, in this simplest deterministic model, the rate of drug elimination is assumed to be proportional to its concentration, so the mathematical model of the process is equation

$$\frac{dA(t)}{dt} = I - kA(t) \tag{2.1}$$

where $A(\text{mg})$ is the amount of drug in the body.

It is obvious that the amount of drug in the body at any given time is equal to the difference between the amount of drug introduced into the body and the amount of drug eliminated from it, which varies over time depending on the amount of drug available for elimination. It should be noted that the equation (2.1) takes into account absolute values and does not take into account the so-called volume of compartment cells $V(\mathrm{L})$, i.e. the volume in which the drug is located. If it is desired to create a model that takes into account the cell volume of the compartment, it is necessary to introduce the concept of drug concentration in plasma, denoted as $C\big(\mathrm{mg\ L}^{-1}\big)$ and defined as the amount of drug in the body per unit volume, i.e. $C = \frac{A}{V}$. Than, the change in plasma drug concentration over time is determined by the differential equation

$$\frac{dC(t)}{dt} = \frac{I}{V} - k\,C(t). \tag{2.2}$$

Typically, drugs are eliminated from the body through various elimination processes, which involve many complex rate processes and may vary in each organ. Here we describe drug elimination in terms of a known factor in drug elimination from the body, known as clearance and referred to as $C_l(\mathrm{L\ h}^{-1})$.

Clearance describes the process of drug elimination from the body without specifying the individual processes involved, so it can be defined as the volume of fluid cleared of the drug that is eliminated from the body per unit time. Since all drugs dissolve and distribute in body fluids, the volume concept is appropriate. However, clearance is not an indicator of how much drug is excreted from the body, it is just a hypothetical volume of blood that is completely cleared of the drug per unit time. The proportion of the drug eliminated per unit of time is represented by the elimination rate constant k. Since clearance expresses the rate of drug elimination divided by the plasma concentration, which expresses the volume of plasma from which the drug is completely eliminated per unit time, the relationship between the elimination rate constant k and the clearance C_l is $C_l = k\,V$, see [2]. Than equation (2.2) takes the form

$$\frac{dC(t)}{dt} = \frac{I - C_l\,C(t)}{V}, \tag{2.3}$$

which is a non-homogeneous linear differential equation of the first order. Such an equation is solvable, and if we assume that there is no drug in the body at the beginning of the infusion, then the initial condition can be written as $C(0) = 0$, and

$$C(t) = \frac{I}{C_l}\left(1 - e^{-\frac{C_l}{V}t}\right) \tag{2.4}$$

is the unique solution to (2.3) that satisfies this initial condition.

Graph of the solution with $\frac{C_l}{V} = 0.4\ (\mathrm{h}^{-1})$ and $\frac{I}{V} = 0.68\ (\mathrm{mg\ L}^{-1}\ \mathrm{h}^{-1})$ see in Figure 1. From (2.4) it can be seen that the amount of drug per volume increases gradually until it reaches equilibrium (steady state) $C_{ss} = \frac{I}{C_l}$, that is, if the rate of elimination is the same as the rate of infusion. Thus, the plasma drug concentration as a function of time using the equilibrium can be written as

$$C(t) = C_{ss}\left(1 - e^{-\frac{C_l}{V}t}\right). \tag{2.5}$$

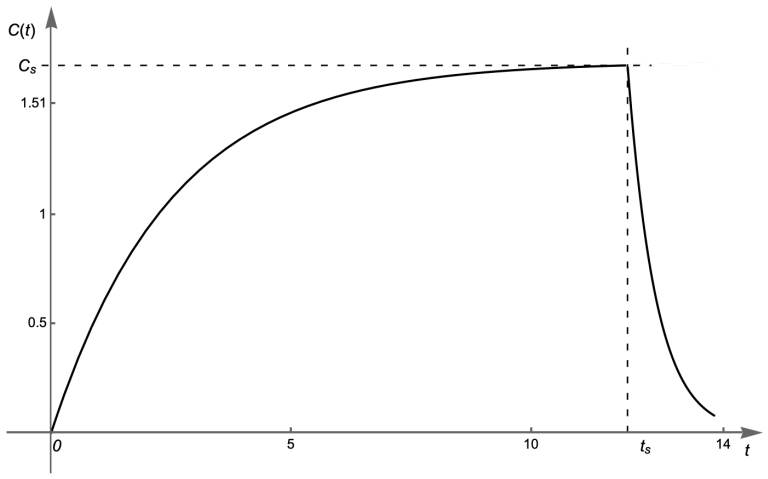

Fig. 1. The amount of drug (in mg / L) in the body during and after intravenous infusion, using models (2.3) and (2.6) with values $k = \frac{C_l}{V} = 0.4$ (h^{-1}), $\frac{I}{V} = 0.68$ (mg L^{-1} h^{-1}) and $C_s = 1.68$

Now consider that at time $t = t_s$, when the concentration reaches state $C(t_s) = C_s$, the infusion is stopped and therefore the plasma drug concentration starts to decrease in accordance with the rate of first-order kinetics. The differential equation describing the elimination of drugs from the body has the form

$$\frac{dC(t)}{dt} = -\frac{C_l}{V}\, C(t) \tag{2.6}$$

and its solution satisfying the initial condition $C(t_s) = C_s$ can be written in the form

$$C(t) = C_s \exp\left(-\frac{C_l}{V}(t - t_s)\right), \quad t \geq t_s, \tag{2.7}$$

which expresses an exponential decrease in plasma concentration. Graph of the solution with values $k = \frac{C_l}{V} = 0.4$ (h^{-1}), $C_s = 1.68$, see in Figure 1.

2.1. INACCURACIES OF DETERMINISTIC MODELS

Published results, for example in [1,2], show that (2.3) is the most suitable mathematical model describing plasma drug concentration during intravenous infusion. However, in some studies, when interpreting the experimental results, the concentration of the drug in the body at some time points does not fully correspond to the expected values, but one or more peaks or undulations occur, see Figure 2 ([3]). Significant inter-subject variability in the nature and magnitude of fluctuations or deviations from the normal smooth pattern was noted in the measurements [3].

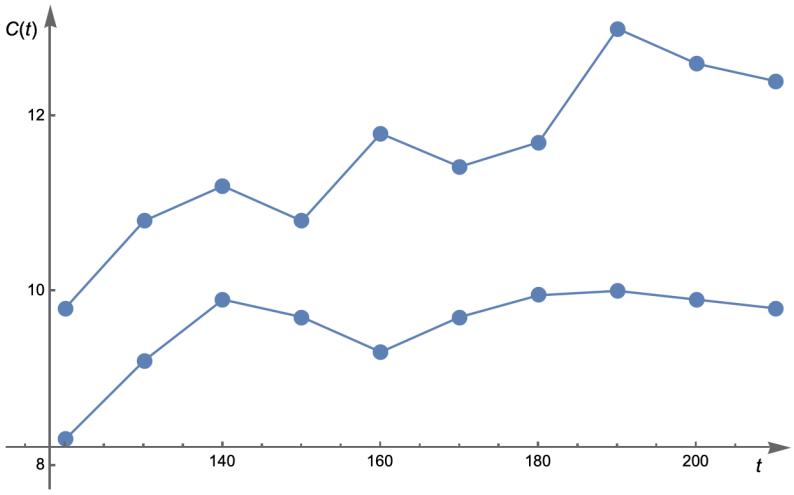

Fig. 2. Fluctuating plasma concentration apparent during intravenous infusion to a dog (taken over from [3])

The question arises: how to explain the fluctuations and irregular patterns of plasma concentrations of certain drugs that occur during intravenous administration? Several medical explanations of this phenomenon was suggested in [3]. However, these proposals cannot explain completely the undulations found in *in vivo* studies. We will propose a mathematical explanation of this phenomenon.

Deterministic models (2.3) and (2.6), like most mathematical models, are constructed with certain simplifications that usually do not distort the time-dependence of the drug concentration in plasma, but there are cases when the simplified model shows certain deviations from reality.

2.2. ELIMINATION RATE VALUE

In general, these deterministic models include some parameters, such as the elimination rate constant, corresponding to certain values that are not fully known. There are several ways to obtain the elimination rate constant k for an individual patient, but these typically involve taking multiple plasma samples at accurately recorded times. This pharmacokinetic approach carries a potentially significant degree of bias in the estimate of k and may lead to the development of an inappropriate dosing regimen with associated risks. A mathematical approach to determining the elimination constant k of an individual patient is described, for example, in paper [2].

Whatever method we use to determine the constant, it will always be inaccurate with a greater or lesser degree of calculation error. Therefore, it is appropriate to assume that the value of k varies between certain two constants $k_0, k_1 \in \mathbb{R}^+$, so that

the elimination rate is described by a bounded function $k(t)$ satisfying the inequalities $0 < k_0 \leq k(t) \leq k_1$. In this case, the plasma drug concentration is more accurately described by a differential equation of the form

$$\frac{dC(t)}{dt} = \frac{I}{V} - k(t)\, C(t). \tag{2.8}$$

With the initial condition $C(0) = 0$, the solution to the initial Cauchy problem, i.e., the drug concentration in the plasma at any time t, can be found as

$$C(t) = \frac{I}{V} \int_0^t \exp\left(- \int_0^s k(z)dz \right) ds. \tag{2.9}$$

Then the drug concentration in the body, as the solution (2.9) to equation (2.8) with initial condition $C(0) = 0$ is also bounded (see Figure 3) and the steady state C_{ss} satisfies the inequalities $I/Vk_1 < C_{ss} < I/Vk_0$.

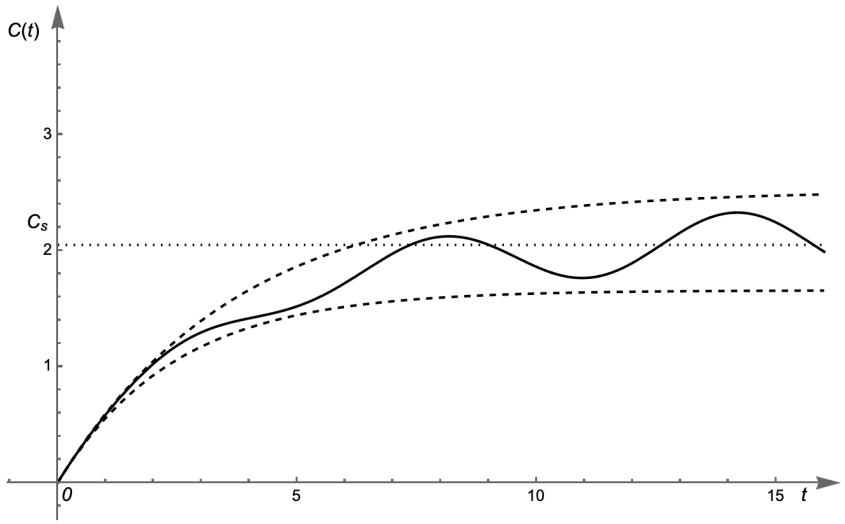

Fig. 3. The amount of drug (in mg / L) in the body in the case if the drug infusion rate divided by volume is $I/V = 0.68\,(mg\,h^{-1}L^{-1})$ and the drug elimination rate depends on a bounded function $k(t)$, $0.27 \leq k(t) \leq 0.41$

It is obvious that if the function $k(t)$ is not monotonic, but k varies between certain two constants, undulations may appear on the time curve of the plasma level. Such mathematical model can explain the measured values obtained in the experiments listed in [1] and shown in Figure 2. The obtained result can be formulated in the form of the following theorem.

Theorem 2.1. *Let $k(t)$ be a continuous function defined on $[0, t_s)$ and let there be constants $k_0, k_1 \in \mathbb{R}^+$ such that $0 < k_0 \leq k(t) \leq k_1$. Then the unique solution to Eq.* (2.8) *satisfying the initial condition $C(0) = 0$ satisfies the iequality*

$$\frac{I}{Vk_1}\left(1 - e^{-k_1 t}\right) < C(t) < \frac{I}{Vk_0}\left(1 - e^{-k_0 t}\right). \tag{2.10}$$

2.3. ELIMINATION OF THE DRUG WITH A DELAY

All pharmacokinetic models assume that elimination begins simultaneously with drug administration. The administration, distribution, and elimination of the drug from the body does not begin immediately, but some time passes from the beginning of the individual phases.

In the phenomena under consideration, the administration of the drug does not manifest its effect immediately at the moment of its onset, but affects the future level of the drug concentration. The time elapsed from the start of the infusion to the start of the elimination of the drug from the body is called the delay and is denoted by τ (h), $\tau > 0$. Therefore, the drug concentration level in this case is better described by the so-calleddifferential equation with delayed argument

$$\frac{dC(t)}{dt} = \frac{I - C_l\, C(t-\tau)}{V} \tag{2.11}$$

than (2.3). If the infusion is stopped, the plasma concentration of the drug is also described by a differential equation with a delay of the form

$$\frac{dC(t)}{dt} = -k\, C(t-\tau), \quad k := \frac{C_l}{V} > 0. \tag{2.12}$$

Such a mathematical model can explain the observed phenomenon where, after intravenous administration, there is no gradual increase in plasma levels, but one or more peaks or waves occur during the increase in plasma concentration, as reported in [3]. The conditions under which a ripple in the plasma concentration occurs or does not occur, in accordance with the results in [9], are formulated in the following theorem.

Theorem 2.2. *Taking into account the elimination of the drug with a delay τ, the ripple of plasma concentration in accordance with Eq.* (2.12) *occurs if and only if $k\tau\mathrm{e} > 1$.*

Therefore, in the case of elimination with a delay τ, undulations may appear depending on the product of the values of k and τ, see Figure 4. Otherwise, if $k\tau\mathrm{e} \leq 1$, the behavior of the solutions can be explained using the results in [4].

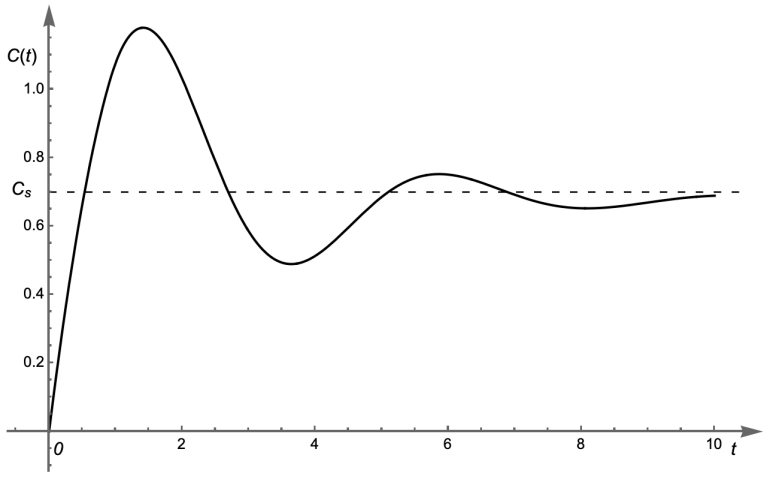

Fig. 4. Plasma concentration during intravenous infusion, with respect to a delay, using model (2.11)

3. STOCHASTIC MODEL

In the previous Section, we explained the discrepancies between the solutions to equations and the experimental ones based on simplifications in creating deterministic models. However, in general we do not have sufficient information about the parameters in deterministic models due to noise. Therefore, it is reasonable to modify the deterministic model by adding this noise term to obtain a stochastic model. This type of mathematical modeling can provide more accurate information about phenomena occurring in the real world than their deterministic counterparts. Using the stochastic differential equation, we can better explain the variable and irregular fluctuations in plasma levels of some drugs.

3.1. ADMINISTRATION OF THE DRUG INTO THE BODY

We now modify the deterministic model (2.3) obtained with certain simplifications by adding random variables to the equation. Mathematically, this means adding white noise to Eq. (2.3), namely

$$dC(t) = \frac{I - C_l C(t)}{V} dt + \text{white noise}.$$

Then, assuming that

$$\text{white noise } = \xi(t)dt = \sigma dW(t)$$

where $W(t)$ is Brownian motion and σ is the variability parameter, we get equation

$$dC(t) = \left(\frac{I}{V} - \frac{C_l}{V}C(t)\right)dt + \sigma dW(t).$$

If we denote $X(t) = C(t)$ and the parameters $\frac{I}{V} = \alpha$, $\mu = \frac{C_l}{V}$, we get the stochastic equation

$$dX(t) = \big(\alpha - \mu X(t)\big)dt + \sigma dW(t), \tag{3.1}$$

which is the equation of the so-called Ornstein–Uhlenbeck process.

To find a solution to the stochastic differential equation (3.1), we first consider the differential of the expression $e^{\mu t}(\alpha - \mu X(t))$. By the usual calculations we get

$$\begin{aligned} d\big(e^{\mu t}(\alpha - \mu X(t))\big) &= e^{\mu t}d\big(\alpha - \mu X(t)\big) + de^{\mu t}\big(\alpha - \mu X(t)\big) \\ &= -\mu e^{\mu t}dX(t) + \mu e^{\mu t}\big(\alpha - \mu X(t)\big)dt. \end{aligned} \tag{3.2}$$

Substituting the expression $-\mu e^{\mu t}dX(t)$ into equation (3.2) with the right side of equation (3.1) multiplied by $-\mu e^{\mu t}$, we have

$$\begin{aligned} d\big(e^{\mu t}(\alpha - \mu X(t))\big) &= -\mu e^{\mu t}\big(\big(\alpha - \mu X(t)\big)dt + \sigma dW(t)\big) + \mu e^{\mu t}\big(\alpha - \mu X(t)\big)dt \\ &= -\mu e^{\mu t}\sigma dW(t). \end{aligned}$$

The obtained equation

$$d\big(e^{\mu t}(\alpha - \mu X(t))\big) = -\mu e^{\mu t}\sigma dW(t)$$

can be easily integrated.

We assume that the initial condition is the same as we considered in the deterministic model, i.e. $X(0) = 0$, so we integrate from zero to t, which leads us to the relationship

$$e^{\mu t}\big(\alpha - \mu X(t)\big) - \big(\alpha - \mu X(0)\big) = -\mu\sigma \int_0^t e^{\mu s}dW(s),$$

from where we get the solution

$$X(t) = X(0)e^{-\mu t} + \frac{\alpha}{\mu}\left(1 - e^{-\mu t}\right) + \sigma \int_0^t e^{\mu(s-t)}dW(t) \tag{3.3}$$

to stochastic equation (3.1).

Figure 5 shows ten possible paths of the stochastic process described by Eq. (3.1) with solution (3.3) i.e. the ten possible time courses of drug levels in the body. For comparison, the mean value of these ten paths is shown in blue, and the solution to the deterministic equation is shown in red. Graphs were made with parameters $\alpha = 0.68$, $\mu = 0.34$, $\sigma = 0.3$.

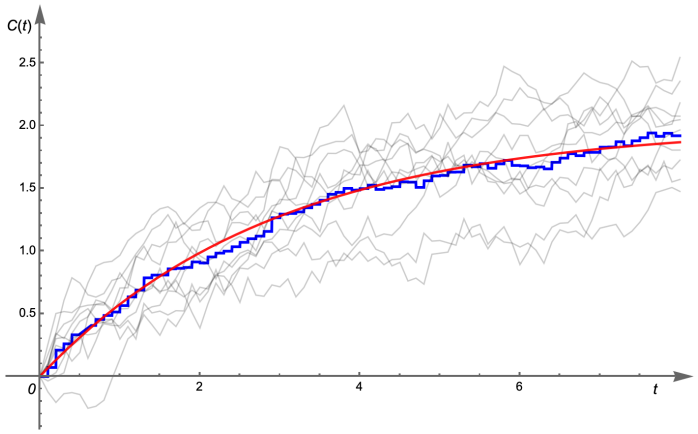

Fig. 5. Plasma concentration of the drug during intravenous infusion, with the addition of white noise (mean value - blue color), according to model (3.1) with parameters $\alpha = 0.68$, $\mu = 0.34$, $\sigma = 0.3$ and the deterministic model (red color)

Remark 3.1. Each of the stochastic pathways contains several peaks and may reflect plasma concentration fluctuations that occur during intravenous infusion in dogs.

Figure 6 shows a one of these paths, chosen at random. The points on the graph represent the measured values of one measurement from Figure 2. Therefore, the variable and irregular characteristics of some drugs observed during intravenous infusion can be explained in this way.

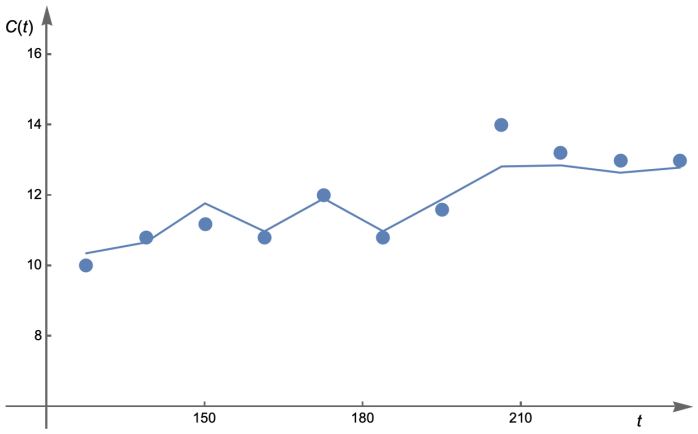

Fig. 6. One randomly chosen path of the stochastic process (3.1). The points represent the measured values of one measurement from Figure 2

Using more of paths of the stochastic process described by Eq. (3.1) with solution (3.3), it can be confirmed that the solution to deterministic model (2.3) behaves like the mean value of the considered stochastic process. One hundred random solutions of the stochastic process for the values $\alpha = 0.68$, $\mu = 0.34$, $\sigma = 0.3$ are shown in Figure 7. Their mean value is a very good approximation of the solution to the deterministic model (2.3). By increasing the number of simulations to a thousand we get an almost perfect match with the mean value.

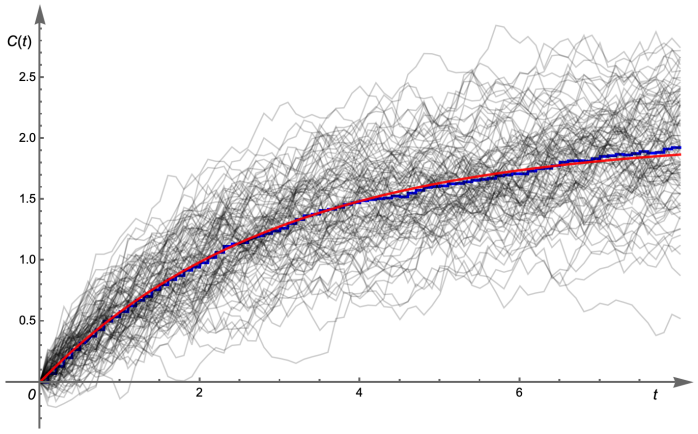

Fig. 7. Plasma concentration of the drug during intravenous infusion with the addition of white noise (mean value - blue color) according to model (3.1) with parameters $\alpha = 0.68$, $\mu = 0.34$, $\sigma = 0.3$ and deterministic model (Red color)

3.2. EXCRETION OF THE DRUG FROM THE BODY

As in the case of drug administration into the body, we modify the deterministic model (2.6) describing drug excretion. Since we consider this part of the process separately, we use the start time $t = 0$ for simplicity.

This means that we have the equation and the initial condition in the form of the initial Cauchy problem

$$\begin{cases} dC(t) = -\frac{C_l}{V} C(t)dt, \\ C(0) = C_s, \end{cases} \tag{3.4}$$

which has the unique solution

$$C(t) = C(0)e^{-\frac{C_l}{V}t}. \tag{3.5}$$

Now we will model the metabolic processes responsible for the elimination of the drug from the body under the influence of some random phenomena. This means adding white noise to Eq. (3.4)

$$dC(t) = -\frac{C_l}{V} C(t)dt + \xi(t)dt.$$

Then, since $\xi(t)dt = \sigma dW(t)$ where $W(t)$ is the Brownian motion and σ variability parameter, we get

$$dC(t) = -\frac{C_l}{V}C(t)dt + \sigma dW(t).$$

We denote

$$X(t) = C(t)$$

and the parameter

$$\mu = \frac{C_l}{V},$$

then we get equation

$$dX(t) = -\mu X(t)dt + \sigma dW(t), \tag{3.6}$$

which is also the equation for the Ornstein-Uhlenbeck process.

We solve this equation in the same way as before, but first consider the differential of the expression $e^{\mu t}X(t)$). Thus we get

$$\begin{aligned} d\big(e^{\mu t}X(t)\big) &= e^{\mu t}dX(t) + de^{\mu t}X(t) \\ &= e^{\mu t}dX(t) + \mu e^{\mu t}X(t)dt. \end{aligned} \tag{3.7}$$

Replacing the expression $e^{\mu t}dX(t)$ in equation (3.7) with the expression on the right side of equation (3.6) multiplied by $e^{\mu t}$, we obtain

$$d\big(e^{\mu t}X(t)\big) = e^{\mu t}\big(-\mu X(t)dt + \sigma dW(t)\big) + \mu e^{\mu t}X(t)dt = e^{\mu t}\sigma dW(t).$$

Then, integrating both sides of the equation

$$d\big(e^{\mu t}X(t)\big) = e^{\mu t}\sigma dW(t)$$

from zero to t, we obtain

$$e^{\mu t}\big(X(t) - X(0)\big) = \sigma \int_0^t e^{\mu s}dW(s),$$

from where we can write

$$X(t) = X(0)e^{-\mu t} + \sigma \int_0^t e^{\mu(s-t)}dW(t),$$

which is the solution to stochastic process (3.6). The drug level in the body described by equation (3.6) shown in Figure 8.

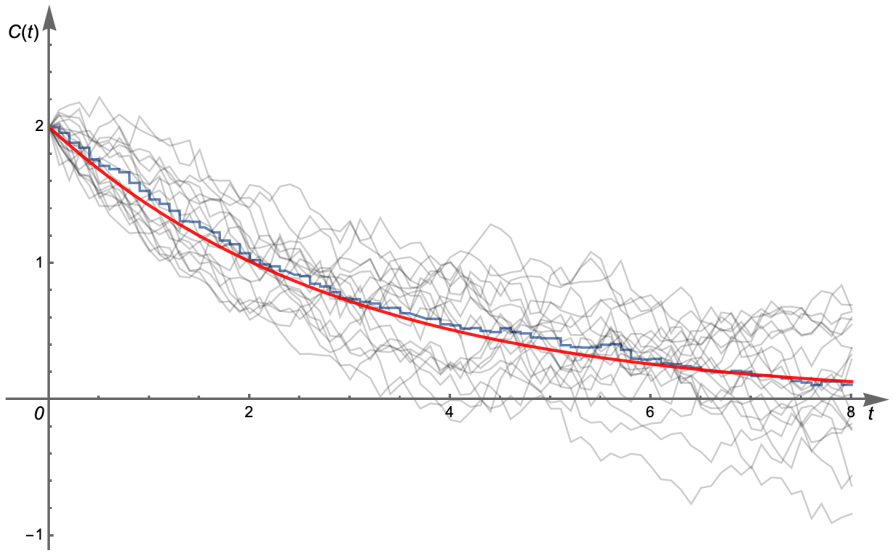

Fig. 8. Plasma drug concentration during its excretion from the body under the influence of white noise (mean value – blue color) according to model (3.6) and deterministic model (red color)

4. CONCLUSION

In this article, a deterministic one-compartment pharmacokinetic model was obtained as the most appropriate mathematical model to describe plasma drug concentration during intravenous infusion. Derived-type deterministic models include some parameters that are not fully known, so they carry a potentially significant degree of bias in the parameter estimates and may lead to an incorrect dosing regimen with associated risks. In fact, considerable intersubjective variability in nature and magnitude of fluctuations or deviations from a normal smoothed pattern has been reported in measurements, for example in [3].

In this article, we have discussed the mathematical explanation of fluctuating and irregular patterns of plasma concentrations of some drugs observed during intravenous infusion. Some solutions to this problem offer modified deterministic models in which two changes are taken into account: the elimination rate constant varies within a certain interval or the elimination time of the drug is delayed from the start of its intravenous administration.

Since we do not have enough information about the parameters in deterministic models to be able to determine them precisely, it is convenient to estimate these inaccuracies using white noise. Mathematical modeling using stochastic differential equations can provide more accurate information about phenomena occurring in the real world than their deterministic counterparts. The solution to such a stochastic

model is a random process, each path of which contains multiple peaks and may reflect the fluctuations in plasma concentration observed during intravenous infusion in a dog.

It would be interesting to understand the stochastic model of the investigated phenomenon, which additionally includes a delay in the elimination of the drug from the start of its intravenous administration. We leave this as an open problem.

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REFERENCES

[1] T.A. Ahmed, *Basic Pharmacokinetic Concepts and Some Clinical Applications*, Technology & Medicine, 2015.

[2] T. Buclin, M. Nicod, S. Kellenberger, *Pharmacokinetics.* UNIL, University of Lausanne, 2009.

[3] V. Claassen, *Neglected factors in pharmacology and neuroscience research*, Techniques in the Behavioral and Neural Sciences, vol. 12, Elsevier Science B.V., Amsterdam, 1994.

[4] J. Diblík, M. Růžičková, *Asymptotic behavior of solutions and positive solutions of differential delayed equations*, Funct. Differ. Equ. **14** (2007), no. 1, 83–105.

[5] J. Diblík, I. Dzhalladova, M. Michalková, M. Růžičková, *Modeling of applied problems by stochastic systems and their analysis using the moment equations*, Adv. Difference Equ. **2013** (2013), Article no. 152.

[6] J. Diblík, I. Dzhalladova, M. Michalková, M. Růžičková, *Moment equations in modeling a stable foreign currency exchange market in conditions of uncertainty*, Abstr. Appl. Anal. **2013** (2013), Art. ID 172847.

[7] I. Dzhalladova, M. Růžičková, *Dynamic system with random structure for modeling security and risk management in cyberspace,* Opuscula Math. **39** (2019), no. 1, 23–37.

[8] I. Dzhalladova, M. Růžičková, V. Štoudková Růžičková, *Stability of the zero solution of nonlinear differential equations under the influence of white noise*, Adv. Difference Equ. **2015** (2015), Article no. 143.

[9] I. Gyori, G. Ladas, *Oscillation Theory of Delay Differential Equations*, Clarendon Press, 1991.

[10] M.A. Khanday, A. Rafiq, K. Nazir, *Mathematical models for drug diffusion through the compartments of blood and tissue medium*, Alexandria Journal of Medicine **53** (2017), 245–249.

[11] M. Růžičková, J. Diblík, G. Vážanová, *Mathematical Modeling of the IV-administered Drug Concentration Level*, AIP Conference Proceedings **1978**, 430011 (2018).

[12] M. Růžičková, I. Dzhalladova, J. Laitochová, J. Diblík, *Solution to a stochastic pursuit model using moment equations*, Discrete Contin. Dyn. Syst. Ser. B **23** (2018), 473–485.

[13] G. Scutt, D. Waxman, *Improved estimates of mean pharmacokinetic parameters for increased accuracy in dosing and reduced risk to patients*, British Journal of Clinical Pharmacology **87** (2021), no. 9, 3518–3530.

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