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STABILITY OF THE MEDICATION DISTRIBUTION MODEL IN THE BODY AS AN OPEN SYSTEM FORMED BY SUBSYSTEMS

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Abstract. In the paper, the spread of medicine (toxin) in the body which is assumed to be an open system carrying out exchange with the environment is considered. The system itself is considered as a combination of two subsystems: blood and muscle. It is shown that the model can be unstable under some conditions and for a certain range of parameters. Solutions obtained with such parameter values do not correspond to the actual amount of the substance during intravenous injections.

Keywords: Mathematical model, medication distribution, the body as an open system

1. Introduction. The introduction of a certain medication into the body and its subsequent distribution to the blood and muscle subsystems is a task involving both intramuscular injections and intravenous injections and infusions. That is, the model describes a whole series of problems of treatment and anesthesia. Undoubtedly, each medication has its own characteristics, which are reflected in the model created using differential equations by different values of the coefficients. Therefore, the analysis of the stability of the medication distribution model for different cases is a relevant and important task in therapy, in anesthesia, in intoxication, and in the development of medicinal agents.

2. Model of medication distribution in the body as an open system exchanging with the environment.

In [1 – 3], the mathematical model of the distribution of a medication (toxin) that enters the body from a source is proposed. In this case, the body is treated as an open system, where the medication is introduced and excreted. In such a system, the kinetics of absorption and excretion of a medication is described by the following system of equations:

$$\begin{cases} \dfrac{dM_0}{dt} = -k_{in}M_0 \\ \dfrac{dM_1}{dt} = k_{in}M_0 - k_{el}M_1, \\ \dfrac{dM_2}{dt} = k_{el}M_2 \end{cases} \qquad (1)$$

In (1), the first equation describes the change in the concentration of the medication in the source due to its introduction into the system; the second equation describes the change in the concentration of the medication in the system as a result of its introduction from the source and due to its removal from the body; the third equation reflects the increase in the amount of the medication in the environment, as a result of its removal from the body. That is, $M(t)$ reflects the corresponding amount of the medication at the moment of time t: $M_0(t)$ in the source; $M_1(t)$ in the body and $M_2(t)$ in the environment. The analysis of the dimensions in (1) indicates that the coefficients k_{in}, k_{el} are values inverse to the times characteristic for the penetration of the substance into the system and the removal of the substance from the system, respectively. Initial conditions for the experiment are as follows:

$$\begin{aligned} &M_0\ t=0\ = M_0^0, \quad M_0\ t\to\infty\ = 0; \\ &M_1\ t=0\ = 0, \qquad M_1\ t\to\infty\ = 0; \\ &M_2\ t=0\ = 0, \qquad M_2\ t\to\infty\ = M_0^0. \end{aligned} \qquad (2)$$

The analytical solution of equation (1) under condition (2) determines the amount of toxin introduced into the body and extracted from it at the moment of time t:

$$\begin{aligned} M_1(t) &= \frac{M_0^0 k_{in}}{k_{in}-k_{el}}(e^{-k_{el}t} - e^{-k_{in}t}); \\ M_2(t) &= M_0^0\left(1 - \frac{1}{k_{in}-k_{el}}\right)(k_{in}e^{-k_{el}t} - k_{el}e^{-k_{in}t}). \end{aligned} \qquad (3)$$

It is considered that the time of absorption of the medication is significantly shorter than the time of its removal from the body, for the parameters used $k_{in} > k_{el}$.

Fig. 1 shows the time dependence of the medication in the body (*M1* is a red solid curve), the medication removed from the body (*M2* is a blue dashed curve) and the total amount (green dash-dotted curve), which practically reaches saturation during the characteristic time of removal and approaches the amount of the introduced medication.

As can be seen from Fig. 1, the concentration of the medication in the body (red solid curve) has a non-monotonous time dependence: first, an increase in the concentration to a certain maximum value can be observed; then, it is followed by a decrease due to the removal of the medications from the body.

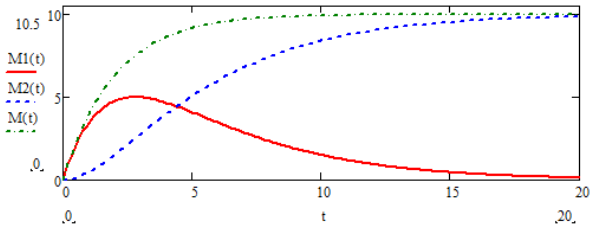


Fig. 1.Connections (3) obtained for the values: $M_0^0 = 10,= 0.5; k_{in} k_{el} = 0,25.$

The blue dashed curve has a monotonous character and is asymptotic to the value M_0^0. The total amount of toxin (green dash-dotted curve) reaches saturation almost at times equal to $\frac{1}{k_{el}}$. The temporal change in the amount of the medication in the body and environment at different characteristic times was investigated, various parameters given in Table 1. The surfaces describing solutions (3) of the amount of the medication in the body (M1) and in the environment (M2) for parameters from Table 1 depending on time (j), are shown in Fig. 2.

Table 1

Values of the parameters used for the results obtained

i	*now*	a few	*J*	*i.e*
1	0.3	0.25	0.1...200	*0.1 j*
2	0.4	0.35		
3	0.7	0.6		
4	0.9	0.75		
5	1	0.8		

To carry out the verification, the sum of M1 and M2 was also analyzed, which practically reached saturation for the times $2\ \ k_{in}$ and was equal to M0 for all subsequent times.

3. Distribution of the toxin within the system, conventionally divided into 2 subsystems.

The kinetics of the distribution of a toxic substance in the system (organism) can be considered, representing it as two subsystems: blood and muscle tissue. Here, it is necessary to introduce the third distribution constant k_d which is inverted to the characteristic time of the transition of the toxin from the blood to the muscular system.

During the process, the toxin influences the corresponding receptors. The authors [1 – 3] obtained the following expressions to define the amount of the substance in the blood and the amount of the substance in the muscle tissues:

$$M_k\ t\ = \frac{M_1\ t\ m_k}{m_{eff} - m_{tk} e^{-k_d t}}$$
$$M_{tk}\ t\ = \frac{M_1\ t\ m_{tk}\ 1 - e^{-k_d t}}{m_{eff} - m_{tk} e^{-k_d t}}. \qquad (4)$$

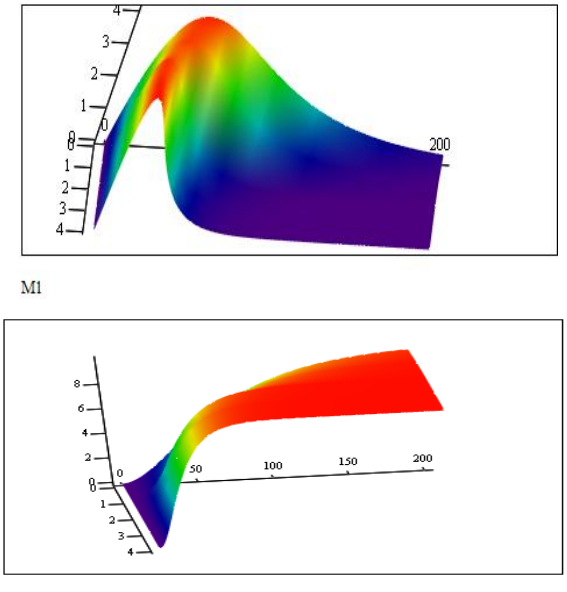


Fig. 2. The surface showing the dependence of the concentration of the medication in the body (M1) and in the environment (M2) for different moments of time (j) and different parameters of the task (i) from Table 1.

In (4), m_{eff} is an effective body mass (mass in which the toxin acts), m_k is the blood mass, and m_{tk} is the mass of tissues under the toxin influence.

Table 2 shows the parameters used in the numerical experiment.

Table 2

Parameter sets used in numerical experiments

$m_{eff} = 50; , m_k = 0.07 m_{eff}; m_{tk} = m_{eff} - m_k$			
a)		*b)*	
$k_{in} = 0.5;\quad k_{el} = 0,25$		$k_d = 0.02$	
i	k_d	k_{in}	k_{el}
1	0.1	0.3	0.25
2	0.2	0.4	0.35
3	0.3	0.7	0.6
4	0.4	0.9	0.75
5	0.5	1	0.8

Fig. 3 represents the surfaces obtained as a function of the amount of substance in the root and muscle subsystems. For illustrating this dependence, only those parameter values for which the results were fundamentally different were used.

For verification, it was revealed that for all analyzed cases the sum *Mk(t) + Mtk(t)* coincides with *M1(t).*

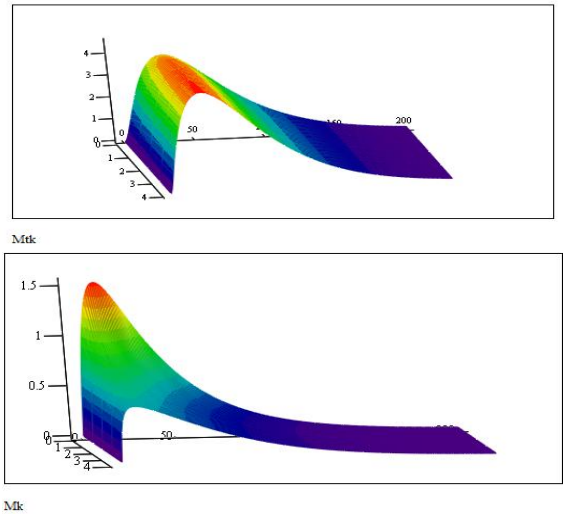


Fig. 3.a).Time dependences of the medication concentration in muscle tissue (Mtk) and in blood (Mk) for parameters (column a) from Table. 2

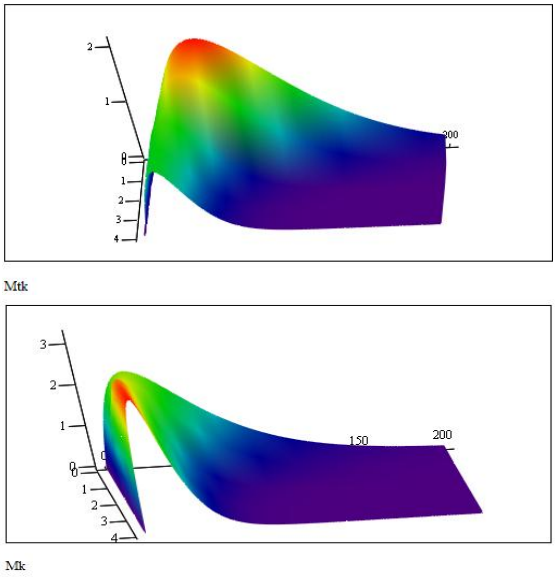


Fig. 3.b).Time dependences of drug concentration in muscle tissue (Mtk) and in blood (Mk) for parameters (column b) from Table. 2.

4. Results and conclusions.

As it can be seen from Fig. 2, the amount of the medications in the body has the following features:

- non-monotonous character with a maximum whose position and half-width changes, depending on the coefficients;
- a sharp maximum with the largest concentration value and a small half-width of the curve occurs during growth of the *i-th parameter*, which corresponds both to the increase in the inverse times of the problem and to the increase in the difference between them;
- the smooth nature of the peak with a large half-width and a slightly smaller value at the maximum corresponds to the smallest value of *i*.
- the maximum numerical value of the amount of the substance increases slightly with the increase in *i*.

Slight differences in the positions of the peaks due to a change in the parameters of the problem are also observed.

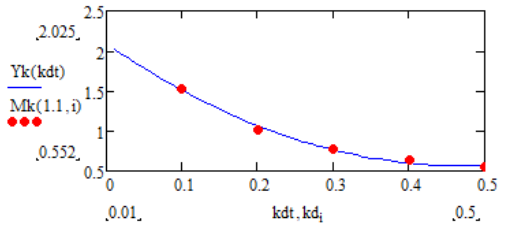
Similar calculations of the amount of the substance in the environment obtained for the parameters from Table 1 have shown that:

- the amount of matter in the external environment increases monotonically as saturation is reached;
- the rate of saturation is determined by the characteristic times of the processes. For small times (large values of coefficients), saturation occurs quickly. For large characteristic times (small values of the coefficients), an almost linear nature of the time dependence of the amount of the removed substance is obtained.

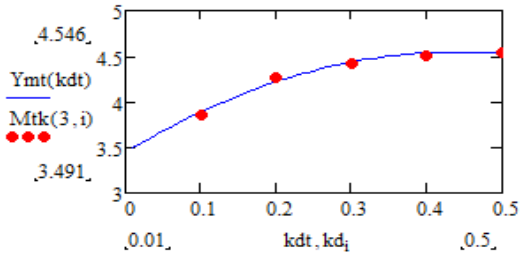
Such dependencies are understandable: long characteristic times mean slow relaxation and slow removal of the medications from the body.

The analysis of the medication distribution among the subsystems (Fig. 2.a, Fig. 2.b) for all considered cases has the following features:

- the non-monotonous nature of the distribution of the medications in both the blood and muscle subsystems, which is explained by the competition of the two streams of the introduction of the drug and its removal from the subsystems;
- the maximum of the medications in the blood precedes the maximum of the medications in the muscle subsystem, and the half-width of the peak in the muscles exceeds the half-width of the peak in the blood subsystem, which is due to the difference in characteristic times (used coefficients);



a



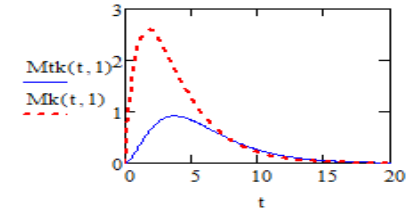
b

Fig. 4. Changes in the maximum drug concentrations in blood (a) and muscle (b) depending on the kd parameter. The solid curve corresponds to the regression (5), the red dots indicate the obtained numerical values.

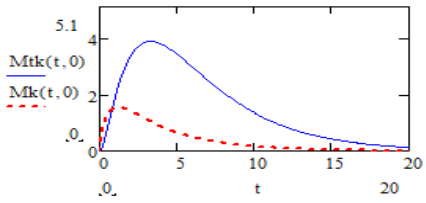
- for a number of studies, when the same coefficients k_{in}, k_{el} are used and coefficient k_d changes (case (a) from Table 2), the position of drug maxima in subsystems does not change over time. Here, the maximum of the medication in the blood is reached at t = 1.1, and in the muscle subsystem at t = 3 (in relative units).
- dependence of the maximum values on the parameter k_d can be described as:

$$Ymt\ kd = 3.441 + 5.04\,kd - 5.748\,kd^2,$$
$$Yk\ kd = 2.089 - 6.528\,kd + 6.994\,kd^2$$

Fig. 4 a, b show the reduced dependence, and the points indicate the data obtained in the numerical experiment.



a



b

Fig. 5. The amount of drug in muscle tissue (blue solid curves) and blood (red dashed curves). a) kd = 0.01; kin = 0.4; kel = 0.5; b) kd = 0.1; kin = 0.5; kel = 0.25 (red dashed curves). a) kd = 0.01; kin = 0.4; kel = 0.5; b) kd = 0.1; kin = 0.5; kel = 0.25.

For the analyzed data, the largest relative deviation of numerical data and function (5) does not exceed 6.5% for the medications in the blood and 1.5% for the amount of the medications in the muscles.

The study of the amount of medications in subsystems for increasing coefficients of *kin*, *kel* and constant *kd* (series (b) of values) showed that the growth of these coefficients leads to the displacement of both maxima in the region of shorter times. The obtained numerical data indicate the limitations of the application of this model for anesthesia and in the case when the drug is administered intravenously.

Therefore, in Fig. 5, two solutions obtained for different parameters of the problem are shown. There it can be seen that the analyzed model is not suitable for describing the amount of the drug injected into the body intravenously, for parameters b).

In fact, after integrating the obtained dependences over time, it was clarified that the amount of the medications injected into the blood (area under the red dotted curve) is less than the amount of the drug injected into the muscles. This indicates the instability of this model and the need to identify criteria for its application.

СТІЙКІСТЬ МОДЕЛІ ПОШИРЕННЯ ПРЕПАРАТУ В ОРГАНІЗМІ, ЯК ВІДКРИТІЙ СИСЕМІ, УТВОРЕНІЙ ПІДСИСТЕМАМИ

Теодор Онутчак, Корнелія Товстюк

Розглядається поширення медикаменту (токсину) в організмі як відкритій системі, що здійснює обмін із довкіллям. Сама система розглядається як сукупність двох підсистем: кров'яної та м'язевої. Ми показуємо нестійкість моделі за деяких умов і для певної області параметрів. Отримані таких значеннях параметрів розв'язки не відповідають фактичній кількості речовини при внутрішньовенних ін'єкціях.

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