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PHARMACOKINETIC MODEL OF INTRAVENOUS MEDICATION ADMINISTRATION

Model of intravenous medication administration is considered, i.e. Cauchy initial problem for a nonlinear differential equation. It is shown that, under certain assumption, there exists positive bounded solution of the considered model. In the proof of the main result, we apply the topological retract method. An illustrative example is solved for particular function describing elimination rate of medication from the compartment using programming system MATLAB.

Keywords: pharmacokinetic model, intravenous, medication

1. Introduction

Drugs are introduced into the body by several routes. The intramuscular route is preferred to the subcutaneous route when larger volumes of a drug product are needed. When given intravenously, a drug is immediately delivered to the bloodstream and tends to take effect more quickly than when given by any other route. Some drugs must be given by continuous infusion to keep their effect constant.

Living organism is so much complex system that the study of the movement of the active substance in the body requires some degree of simplification. This can be achieved by creating a substitute system or model. In the pharmacokinetic are known compartmental models based on the existence of certain barriers, which must be overcome by molecules of the active substance, and which restrict their movement to the part of the organism. Decisive process for the movement of the medicament is the diffusion of molecules through the biological barriers what facilitates the mathematical description of the fate of the drug in the body. Most of pharmacokinetic processes conform to the rules of the kinetics of chemical reactions first order, for which is the speed of process in any moment proportional to the concentration of the active substance. We can imagine the compartment as a single entity having a capacity in which the drug is homogeneously dispersed. Supply of drug into the compartment and its removal are characterized by rate constants. In practice, for most drugs are used one-compartment or two-compartment models [3].

We will focus on solving one-compartment pharmacokinetic model of intravenous administration of treatment medication. In the simplest case, this model is in the form of differential equation

$$y'(t) = -py(t) + y_0, \tag{1}$$

where p is the rate constant of medicament elimination and y_0 is a constant rate of infusion. Function $y(t)$ indicates the quantity of active substance in the compartment in time t.

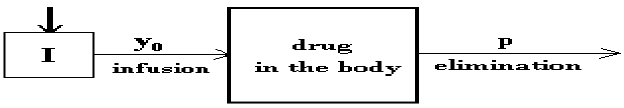

Fig. 1: Block diagram of one-compartment pharmacokinetic model

In generally, the rate of active substance elimination does not have to be constant, it can vary with time. This case describes real process more accurately.

Let us consider an initial Cauchy problem

$$y' = -p(t)y + y_{0,} \tag{2}$$

$$y(0) = 0, \tag{3}$$

where $t \geq 0, y_0 > 0$ and $p(t)$ is continuous function on $I_{\delta_2} = (0, \delta_2),\ \delta_2 > 0,$ which satisfies the inequality

$$0 < p_0 \leq p(t) \leq p_1.$$

The solution of Cauchy initial problem can be written in the form

$$y(t) = y_0 \left(e^{-\int_0^t p(s)\mathrm{d}s} - 1 \right).$$

We can see that this solution contains definite integral of the function $p(t)$. It is known that there exist such functions which integrals we cannot describe by elementary functions. The solution of Cauchy problem (2), (3) cannot be written without integral of these functions. In this case others accesses to the searching for quantity of medicament in the compartment are needed.

2. Preliminaries

In the proof of the main result the topological method of Ważewski is used. Therefore we give a short summary of it. Let us consider the system of differential equations

$$y' = f(x, y), \tag{4}$$

with known vector function *f* of two variables and unknown function *y* of one variable *x*. It will be assumed below that the right-hand side of the system (4) is a continuous function defined on the open (x, y)-set Ω. [1, p. 927]

Definition 1 [2, p. 281]. An open subset Ω^0 of the set Ω is called a (u, v)-subset of Ω with respect to the system (4) if the following conditions are satisfied:

1. There exist functions $v_i(x, y) \in C^1(\Omega),\ i = 1, \ldots, l$; $u_j(x, y) \in C^1(\Omega),\ j = 1, \ldots, m,$ such that

$$\Omega^0 = \{(x, y) : v_i(x, y) < 0,\ u_j(x, y) < 0 \ for\, all\, i, j\}.$$

2. $\dot{v}_\alpha(x,y) < 0$ *holds for the derivatives of the functions* $v_\alpha(x,y), \alpha = 1,\ldots,l,$ along the trajectories of (4) on the set

$$V_\alpha = \{(x,y) : v_\alpha = 0, v_i(x,y) \le 0, u_j(x,y) \le 0 \; for\, all\, i, j\, and\, \alpha, i \ne \alpha\}.$$

3. $\dot{u}_\beta(x,y) > 0$ *holds for the derivatives of the functions* $u_\beta(x,y), \beta = 1,\ldots,m,$ along the trajectories of (4) on the set

$$U_\beta = \{(x,y) : u_\beta = 0, u_j(x,y) \le 0, v_i(x,y) \le 0 \; for\, all\, i, j\, and\, \beta, j \ne \beta\}.$$

The number l *or the number* m can be zero in this definition.

Definition 2 [4, p. 595]**.** The point $(x_0, y_0) \in \Omega \cap \delta\Omega^0$ is called an *egress point* (or *ingress point*) of Ω^0 with respect to the system (2) if, for every solution of the problem $y(x_0) = y_0,$ there exists an $\varepsilon > 0$ *such that* $(x, y(x)) \in \Omega^0$ *for* $x_0 - \varepsilon \le x < x_0$ $(x_0 < x \le x_0 + \varepsilon)$. An egress point (ingress point) (x_0, y_0) *of* Ω^0 is called a *strict egress point* (*strict ingress point*) of Ω^0 *if* $(x, y(x)) \notin \bar{\Omega}^0$ *on the interval* $x_0 < x \le x_0 + \varepsilon_1$ $(x_0 - \varepsilon_1 \le x < x_0)$ *for a small* $\varepsilon_1 > 0$. The set of all points of egress (strict egress) is denoted by Ω_e^0 (Ω_{se}^0). Finally, the point $(x_0, y_0) \in \Omega \cap \delta\Omega^0$ is called an *outward tangency point* of Ω^0 with respect to the system (2) if, for every solution of the problem $y(x_0) = y_0,$ there exists an $\varepsilon > 0$ *such that* $(x, y(x)) \notin \bar{\Omega}^0$ *for* $x_0 - \varepsilon < x < x_0 + \varepsilon,\; x \ne x_0.$

The points distinguished in the above definition can be visualized in Figure 2, where the fragments of trajectories of some planar equation near the boundary of the square are shown. The open vertical sides of the square consist of strict egress points, the open horizontal sides consist of strict ingress points and the four vertices form the set of outward tangency points [4, p. 595].

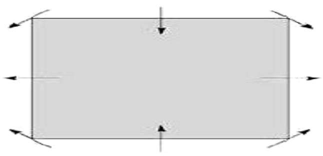

Fig. 2: Ingress, egress and outward tangency points

Lemma 1 [2, p. 281]**.** *Let* Ω^0 *be a* (u,v) *-subset of* Ω *with respect to the system* (4). *Then*

$$\Omega_{se}^0 = \Omega_e^0 = \left(\bigcup_{\beta=1}^{m} U_\beta\right) \setminus \left(\bigcup_{\alpha=1}^{l} V_\alpha\right)$$

The following theorem formulates sufficient conditions for the existence of at least one solution, having its graph in Ω^0 [1, p. 928].

Theorem 1 (Theorem of Ważewski) [2, p. 282]**.** *Let* Ω^0 *be some* (u,v) *-subset of* Ω *with respect to the system* (4). *Let* S *be a nonempty compact subset of* $\Omega^0 \cup \Omega_e^0$ *such that the set* $S \cap \Omega_e^0$ *is not a retract of* Ω_e^0. *Then there is at least one point* $(x_0, y_0) \in S \cap \Omega^0$ *such that the graph of a solution* $y(x)$ *of the Cauchy problem* $y(x_0) = y_0$ *lies in* Ω^0 *on its right-hand maximal interval of existence*.

3. Main result

Now, we consider one-compartment pharmacokinetic model of intravenous medication administration in the case when the rate of active substance elimination can vary with time.

Theorem 2 *Let* $p(t)$ *be a continuous function on* $I_{\delta_2} = (0, \delta_2),\; \delta_2 > 0,$ *and let the function* $p(t)$ *be bounded by positive constants* $p_0,\, p_1,$ *i.e. the inequality* $0 < p_0 \le p(t) \le p_1$ *holds. Let* y_0 *be a positive constant. Then there exist a positive solution of the problem* (2), (3) *on an interval* $I_{\delta_3} \subset I_{\delta_2}$. *Moreover, the solution satisfies the inequality*

$$\frac{y_0}{p_1} < \lim_{t\to\infty} y(t) < \frac{y_0}{p_0}$$

on the interval I_{δ_3}.

Proof: Let the functions $\varphi(\delta t),\, \varphi(kt)$ be defined on the interval I_{δ_2} in the form

$$\varphi(\delta t) = -\frac{y_0}{p_1} e^{-\delta t} + \frac{y_0}{p_1},$$

$$\varphi(kt) = -\frac{y_0}{p_0} e^{-kt} + \frac{y_0}{p_0},$$

where $\delta\, and\, k$ are constants satisfying the inequality

$$0 < \delta < p_0 < 1 < k.$$

With regard to this it is easy to verity, that the functions $\varphi(\delta t)$, $\varphi(kt)$ satisfy the inequality

$$\varphi(\delta t) < \varphi(kt).$$

Let us define domain Ω_0 in the form

$$\Omega_0 = \{(t,y) \in \mathbb{R}\times\mathbb{R} : t \in (0,\delta_3), \varphi(\delta t) < y(t) < \varphi(kt)\}, \delta_3 > 0,$$

and the auxiliary functions

$$u(t,y) \equiv (y - \varphi(\delta t))(y - \varphi(kt)),$$
$$v(t,y) \equiv v(t) \equiv t - \delta_3.$$

Then

$$\Omega_0 = \{(t,y) \in \mathbb{R}\times\mathbb{R} : u(t,y) < 0, v(t,y) < 0\}.$$

Next, we will show that all the points of the set

$$U = \{(t,y) \in \mathbb{R}\times\mathbb{R} : u(t,y) = 0, v(t,y) \le 0\}$$

are the points of strict ingress of the set Ω_0 with respect to the equation (2) and all the points of the set

$$V = \{(t,y) \in \mathbb{R}\times\mathbb{R} : u(t,y) \le 0, v(t,y) = 0\}$$

are the points of strict egress of set Ω_0 with respect to the equation (2).

For verifying this, we compute the full derivative of the function $u(t,y)$ along the trajectories of the equation (2) on corresponding set U at first. We get

$$\frac{\mathrm{d}u}{\mathrm{d}t} = (y' - \delta\varphi'(\delta t))(y - \varphi(kt)) + (y - \varphi(\delta t))(y' - k\varphi'(kt))$$

If $(t,y) \in U$, then either $y = \varphi(\delta t) or\, y = \varphi(kt)$.

In the first case we have

$$\frac{\mathrm{du}}{\mathrm{dt}}/_{(\mathrm{t,y})\in \mathrm{U},\ \ \mathrm{y}=\varphi(\delta\mathrm{t})} = (-\mathrm{p}(\mathrm{t})\mathrm{y} + \mathrm{y}_0 - \delta\varphi'(\delta\mathrm{t}))(\varphi(\delta\mathrm{t}) - \varphi(\mathrm{kt})) < 0.$$

Thus, if $\mathrm{y} = \varphi(\delta\mathrm{t})$ then all the points $(\mathrm{t,y}) \in \mathrm{U}$ are points of strict ingress.

In the second case, i.e., if $\mathrm{y} = \varphi(\mathrm{kt})$, we get

$$\frac{\mathrm{du}}{\mathrm{dt}}/_{(\mathrm{t,y})\in \mathrm{U},\ \ \mathrm{y}=\varphi(\mathrm{kt})} = (\varphi(\mathrm{kt}) - \varphi(\delta\mathrm{t}))(-\mathrm{p}(\mathrm{t})\mathrm{y} + \mathrm{y}_0 - \mathrm{k}\varphi'(\mathrm{kt})) < 0.$$

This means that if $\mathrm{y} = \varphi(\mathrm{kt})$ then all the points $(\mathrm{t,y}) \in \mathrm{U}$ are also points of strict ingress. Therefore, in both considered cases we have obtained

$$\frac{\mathrm{du}}{\mathrm{dt}}/_{(\mathrm{t,y})\in \mathrm{U}} < 0.$$

Now let us compute the full derivative of the function $v(t,y)$ along the trajectories of the equation (2) on corresponding set V. We have

$$\frac{\mathrm{d}v}{\mathrm{d}t} = 1 > 0.$$

Thus, all the points $(t,y) \in V$ are points of strict egress. So the set Ω_0 is the (u,v)-set and therefore we can apply the theorem of Ważewski. This means that the domain Ω_0 contains the graph of the solution of considered problem (2), (3) and this solution is bounded, i.e.

$$-\frac{y_0}{p_1}e^{-\delta t} + \frac{y_0}{p_1} < y(t) < -\frac{y_0}{p_0}e^{-kt} + \frac{y_0}{p_0}.$$

If we pass to the limit for $t \to \infty$ we get

$$\frac{y_0}{p_1} < \lim_{t\to\infty} y(t) < \frac{y_0}{p_0}.$$

On the basis of the last inequality, we can conclude that the level of the medicament in the compartment after long-lasting infusion will be close to the value, which is always greater than the ratio of infusion rate y_0 and p_1 of the function $p(t)$ and less than the ratio of y_0 and lower limit p_0 of the same function $p(t)$.

4. Examples

Let us consider a nonlinear Cauchy problem:

$$y' = p(t)y(t) + y_0,$$
$$y(0^+) = 0,$$

with

$$p(t) = 0.6e^{-\frac{1}{t}} + 0.2, \qquad y_0 > 0.$$

Let the function $p(t)$ be bounded for $t > 0$, i.e.

$$0.2 \le p(t) \le 0.8, \quad \forall t > 0.$$

This problem has, by Theorem 2, one positive solution, which is bounded on $I = (0, \infty)$ (see figure 3).

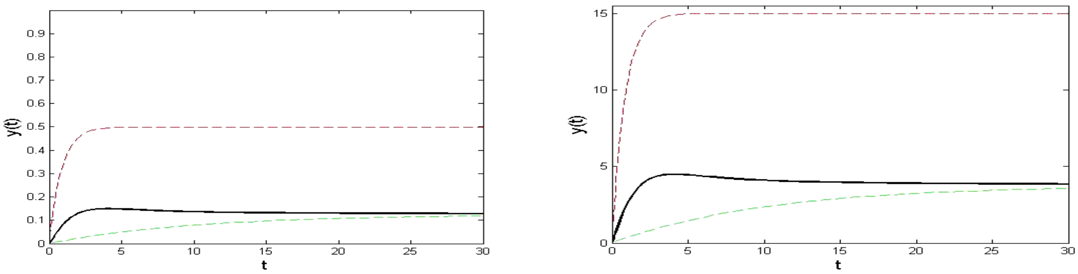

Fig. 3. The level of the medicament for $0 \le t \le 30$ **and** $\delta = 0.1, k = 2, y_0 = 0.1$ $\delta = 0.1, k = 2, y_0 = 0.1$ **or** $\delta = 0.1, k = 1.2, y_0 = 3$

We can make conclusion: In the case when the rate of active substance elimination is described by bounded function $0 < p_0 \le p(t) \le p_1$, the level of the medicament in the compartment after long-lasting infusion is between values $\frac{y_0}{p_1}$ and $\frac{y_0}{p_0}$. Moreover, if the function $p(t)$ is the exponential function of the form mentioned above, the level of the medicament in the compartment convergent to the value $\frac{y_0}{p_1}$. For two considered values of the parameters $\delta = 0.1, k = 2, y_0 = 0.1;\ \delta = 0.1, k = 1.2, y_0 = 3$ the limit value is 0.125 or 3.75 respectively.

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ФАРМАКОКІНЕТИЧНА МОДЕЛЬ ВНУТРИВЕННОГО ВВЕДЕННЯ ЛІКІВ

Розглядається модель внутривенного введення препарату побудована на вихідній завдачі Коші для нелінійного диференціального рівняння. Показано, що при деяких умовах існує позитивне обмеження розв'язку розглянутої моделі. При доказі основного результату, ми застосовуємо метод топологічних відмовлення. Наочний приклад вирішується для конкретної функції, що описує швидкість виведення лікарського засобу з відсіку, застосувавши системи програмування MATLAB.

Ключові слова: фармакокінетичні моделі, внутрішньовенно, ліки.

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ФАРМАКОКИНЕТИЧЕСКАЯ МОДЕЛЬ ВНУТРИВЕННОГО ВВЕДЕНИЯ ЛЕКАРСТВ

Рассматривается модель внутривенного введения препарата построена на исходной завдачи Коши для нелинейного дифференциального уравнения. Показано, что при некоторых условиях существует положительное ограничения решения рассматриваемой модели. При доказательстве основного результата, мы применяем метод топологического отказа. Наглядный пример решается для конкретной функции, описывающей скорость выведения лекарственного средства из отсека, применив системы программирования MATLAB.

Ключевые слова: фармакокинетические модели, внутривенно, лекарства.

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ДИНАМІКА НЕЛІНІЙНОЇ МОДЕЛІ СИСТЕМИ ПОПУЛЯЦІЇ ЛЕСЛІ

В роботі проведено дослідження нелінійної моделі популяції Леслі. Модель записана у векторно-матричному вигляді різницевих рівнянь. Зроблено припущення про нелінійний вплив щільності популяції на динаміку системи. Визначено точки спокою. Досліджено вплив параметрів системи на її "грубість".

Ключові слова: динамічна система, різницеві рівняння, точки спокою, асимптотична стійкість, фазовий портрет.

Вступ

В наступній роботі продовжується дослідження динаміки моделі популяції Леслі, що проводилась в роботах [1-3]. Розглянута нелінійна (квазілінійна) модель. Модифікуємо Лінійна модель динаміки популяції Леслі, що була записана у векторний-матричному вигляді в роботі [8], модифікується наступним чином. Для обліку впливу щільності популяції на її плодючість, введена величина, що є зваженим розміром популяції [4-5]

$$w(x) = \sum_{j=1}^{n} \alpha_j x_j \ , \qquad (0.1)$$