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НЕСТАЦИОНАРНАЯ ФАРМАКОКИНЕТИКА НА МАТЕМАТИЧЕСКОЙ МОДЕЛИ

NONSTATIONARY PHARMACOKINETICS ON A MATHEMATICAL MODEL

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Аннотация
На практике более востребованы алгоритмы и модели сорбции и десорбции веществ живым организмом, когда регулярное их поступление неизменно на всём интервале времени наблюдения. Таковы, как правило, условия экологии, вредных производств или длительное лечение хронических заболеваний. Но не менее интересен более общий, нестационарный случай, и не только по одному ингредиенту, поступающему в организм сообразно некоторой функции, но и тогда, когда их несколько и априори известный для каждого из них период полувыведения оказывается зависимым от того, какие из них и в каком количестве уже накоплены в организме. В данной работе на математической модели рассматривается наиболее общий случай вплоть до возможности не нарушающего гомеостаз активного вмешательства в метаболизм.

Ключевые слова: накопление и вывод веществ в организме, математическое моделирование.

Abstract
In practice, algorithms and models of sorption and desorption of substances by a living organism are more in demand, when their regular intake is unchanged throughout the observation time interval. As a rule, these are environmental conditions, harmful industries or long-term treatment of chronic diseases. But no less interesting is the solution of a more general, non-stationary multidimensional problem, including both the case of sorption and desorption in the body of one ingredient acting according to some function, and cases when several ingredients are involved in the process. At the same time, the half-life a priori known for each of them is considered dependent on the already accumulated amount of other substances in the body. In this paper, the most general case is investigated using a mathematical model, up to the possibility of active intervention in metabolism that does not violate homeostasis.

Key words: accumulation and withdrawal of substances in the body, mathematical modeling

Previously, we have shown how important the idea of the half-life of substances from the body is, especially in conditions of unfavorable ecology and hazardous industries [1-4]. The dynamics of accumulation and excretion of substances by a living organism, as disclosed in [4-6], does not always cause a favorable state of the organism, where homeostasis indicators are set according to the characteristics of the habitat. However, homeostasis itself, as one of the most important representations of a biological organization, is customarily studied in the context of a structural-functional approach, detailing it for a specific subject that to some extent has the corresponding properties, although, in our opinion, no less interesting is its internal dynamics, in particular, the dynamics of accumulation and removal (more precisely, sorption and desorption) of substances by a living organism.

In 1964 by N. Rashevsky a model [5] was presented and studied in great detail, where the dynamics of the accumulation or loss of an ingredient in the body is considered as a manifestation of its ability to be released from a certain proportion of the substance in a certain time, even if there is a systematic, regular reinforcement in the form stationary, even a very small dose. More fully, in the development of such an approach, this is disclosed in the biophysics curriculum [6].

In our opinion, under stationary conditions, when the systematic intake of a substance into the body is unchanged over time, it is more convenient to use a discrete idea of the dose of a substance Δm per unit time.

Indeed, if it is known that some substance in the body is accumulated in the amount of M_0 and its half-life is T, then after time t , in the absence of its further intake into the body, the content will be equal to:

$$M_t = M_0 \cdot 2^{-t/T} \tag{1}$$

However, if at each time interval Δt the body additionally receives a dose of this substance equal to Δm, then its content initially turns out to be equal to

$$M_1 = (M_0 + \Delta m) \cdot 2^{-\Delta t/T}, \tag{2}$$

and on the time interval $t = n \Delta t$:

$$M_t = M_0 \cdot 2^{-t/T} + \Delta m \frac{1 - 2^{-t/T}}{1 - 2^{-\Delta t/T}} \tag{3}$$

Obviously, within

$$\lim_{t \to \infty} M_t = \frac{\Delta m}{1 - 2^{-\Delta t/T}} \tag{4}$$

The time to reach the limit can be found in comparison (3) and (4), based on the tolerance represented by the fraction of q from Δm:

$$abs(M_0 \cdot 2^{-t/T} + \Delta m \frac{1 - 2^{-t/T}}{1 - 2^{-\Delta t/T}} - \frac{\Delta m}{1 - 2^{-\Delta t/T}}) = q \Delta m,$$

where
$$t = T \log_2 \frac{abs(\frac{M_0}{\Delta m} - \frac{1}{1 - 2^{-\Delta t/T}})}{q} \qquad \text{(five)}$$

In practice, it often becomes necessary to find the time t, during which M_t of the accumulated substance can be reached, if the following are known: initial saturation - M_0 , half-life - T and stationary dose - Δm. Transforming (3), we get:

$$t = T \log_2 (\frac{M_0 - \frac{\Delta m}{1 - 2^{-\Delta t/T}}}{M_t - \frac{\Delta m}{1 - 2^{-\Delta t/T}}}) = T \log_2 (\frac{M_0 (1 - 2^{-\Delta t/T}) - \Delta m}{M_t (1 - 2^{-\Delta t/T}) - \Delta m}) \tag{6}$$

And when it is necessary to establish what the initial saturation was, if the time to reach the final one is known, from expression (3) we find:

$$M_0 = M_t - \Delta m \frac{1 - 2^{-t/T}}{1 - 2^{-\Delta t/T}} \cdot 2^{t/T} \tag{7}$$

And, of course, knowing M_0 and M_t, as well as the corresponding time interval - t, it is easy to find the value of the stationary dose - Δm :

$$\Delta m = (M_t - M_0 \cdot 2^{-t/T}) \frac{1-2^{-\Delta t/T}}{1-2^{-t/T}} . \qquad (8)$$

If necessary, using the recursive representation of equation (6), you can also find the value of the half-life:

$$T = t / \log_2 \left(\frac{M_0 (1-2^{-\Delta t/T}) - \Delta m}{M_t (1-2^{-\Delta t/T}) - \Delta m} \right) . \qquad (9)$$

A, dividing both sides of equation (9) by T, we come to an expression that will allow us to interpret the result obtained in the form of the law of accumulation and withdrawal (or sorption and desorption) of substances by a living organism:

$$\frac{t}{T} / \log_2 \left(\frac{M_0 (1-2^{-\Delta t/T}) - \Delta m}{M_t (1-2^{-\Delta t/T}) - \Delta m} \right) = 1 \text{ or } \frac{M_0 (1-2^{-\Delta t/T}) - \Delta m}{M_t (1-2^{-\Delta t/T}) - \Delta m} = 2^{t/T} \qquad (10)$$

Of course, the above calculations are not complicated and useful in practice, opening up the possibility of calculating the indicators necessary, in particular, for the control of drug therapy, laboratory and clinical trials in pharmacology, the corresponding calculations in experimental and clinical toxicology and forensic medicine, as well as for laboratory and field research by ecologists, but in practice we often deal not with some stable dose Δm , but with a time-dependent discrete function Δm_i , which characterizes the doses of a substance entering the body at each i -th time interval, or with a continuous function $m(t)$, which makes it possible to take into account the dynamics of the intake of a substance into the body in a more general formulation of the problem.

Let us first consider the case when the intake of a substance into the body can be represented by a time-discrete function Δm_i. An example of this can be a single contamination of a drinking water reservoir, where the content of a polluting ingredient decreases in accordance with an exponential or other continuous function, where the function of the intake of a substance into the body is discrete, determining the time and volume of fluid consumed. In this case, the amount of the substance in the body after the first time period will be equal to

$$M_{t=1} = \Delta m_0 \cdot 2^{-t/T} + \Delta m_1 ,$$

and after the second interval:

$$M_{t=2} = \Delta m_0 \cdot 2^{-t/T} + \Delta m_1 \cdot 2^{-(t-1)/T} + \Delta m_2 ,$$

after the third:

$$M_{t=3} = \Delta m_0 \cdot 2^{-t/T} + \Delta m_1 \cdot 2^{-(t-1)/T} + \Delta m_2 \cdot 2^{-(t-2)/T} + \Delta m_3 , \ldots$$

And as a result, the mass of a substance in the body after t intervals can be determined based on the following ratio:

$$M_t = \sum_{i=0}^{t} \Delta m_i \cdot 2^{-(t-i)/T} . \qquad (11)$$

And if there is some amount of this substance M_0 accumulated in the body, we get:

$$M_t = M_0 \cdot 2^{-t/T} + \sum_{i=0}^{t} \Delta m_i \cdot 2^{-(t-i)/T} . \qquad (12)$$

It is quite obvious that when the intake of a substance is characterized by a continuous function (for example, in conditions of industrial aggression, which entails environmental trouble in the form of regularly manifested emissions into the air or water environment), the ratio for calculating the mass of a substance in the body at time *t* will take the following form:

$$M(t) = M(0) \cdot 2^{-t/T} + \int_0^t m(\tau) \cdot 2^{-(t-\tau)/T} d\tau. \qquad (13)$$

And in approaching reality, of course, one should present the dynamics in multidimensional terms, for several ingredients with different characteristics at once, which is exemplified by living in ecologically unfavorable territories, and occupational hazards for workers in some industries, as well as both accidental and intentional due to necessity, active multicomponent interventions in metabolism. At the same time, the half-life for each of the substances entering the body should now be considered at least linearly dependent on the ratio of the accumulated mass of each of the others to the body weight, that is:

$$\begin{cases} M_1(t) = M_1(0) \cdot 2^{-t/T_1(M_2, M_3 \ldots, M_n, M_m)} + \int_0^t m_1(\tau) \cdot 2^{-(t-\tau)/T_1(M_2, M_3 \ldots, M_n, M_m)} d\tau, \\ M_2(t) = M_2(0) \cdot 2^{-t/T_2(M_1, M_3, \ldots, M_n, M_m)} + \int_0^t m_2(\tau) \cdot 2^{-(t-\tau)/T_2(M_1, M_3, \ldots, M_n, M_m)} d\tau, \\ \ldots \\ M_n(t) = M_n(0) \cdot 2^{-t/T_n(M_1, M_2, \ldots, M_{n-1}, M_m)} + \int_0^t m_n(\tau) \cdot 2^{-(t-\tau)/T_n(M_1, M_2, \ldots, M_{n-1}, M_m)} d\tau, \\ \dfrac{dT_1(M_2, M_3 \ldots, M_n, M_m)}{dt} M_m(t) = a_{12} \cdot M_2(t) + a_{13} \cdot M_3(t) + \ldots + a_{1n} \cdot M_n(t), \\ \dfrac{dT_2(M_1, M_3, \ldots, M_n, M_m)}{dt} M_m(t) = a_{21} \cdot M_1(t) + a_{23} \cdot M_3(t) + \ldots + a_{2n} \cdot M_n(t), \\ \ldots \\ \dfrac{dT_n(M_1, M_2, \ldots, M_{n-1}, M_m)}{dt} M_m(t) = a_{n1} \cdot M_1(t) + a_{n2} \cdot M_2(t) + \ldots + a_{n\,n-1} \cdot M_{n-1}(t). \end{cases}$$

(14)

$M_i(t)$ is the mass of the *i* -th substance in the body at time *t*;

$m_i(\tau)$ is a function that characterizes the dynamics of the intake of the *i* -th substance into the body;

$M_t(t)$ – body mass at time *t*;

T_i – half-life of the *i* - th substance;

aij _ – coefficient characterizing the influence of the mass of the *j* -th substance in the body on the half-life of the *i* - th substance.

Undoubtedly, effective control that meets the goals of ensuring a stable image of homeostasis in a living system becomes possible from the standpoint of the theory of dynamic systems. Previously, we have shown the possibility of predicting discrete changes in each of the objective functions for known initial values of each of them and the magnitudes of the control and perturbing effects on the system [7].

Let us now consider the parameters of homeostasis as state variables, and drug therapeutic interventions and other substances entering the body and exerting an active influence on metabolism as input effects and describe the dynamics of the system:

$$\begin{cases} \dfrac{dx_1(t)}{dt} = a_{11} \cdot x_1(t) + a_{12} \cdot x_2(t) + ... + a_{1k} \cdot x_k(t) + b_{11} \cdot M_1(t) + b_{12} \cdot M_2(t) + ... + b_{1n} \cdot M_n(t), \\ \dfrac{dx_2(t)}{dt} = a_{21} \cdot x_1(t) + a_{22} \cdot x_2(t) + ... + a_{2k} \cdot x_k(t) + b_{21} \cdot M_1(t) + b_{22} \cdot M_2(t) + ... + b_{2n} \cdot M_n(t), \\ ... \\ \dfrac{dx_k(t)}{dt} = a_{k1} \cdot x_1(t) + a_{k2} \cdot x_2(t) + ... + a_{kk} \cdot x_k(t) + b_{k1} \cdot M_1(t) + b_{k2} \cdot M_2(t) + ... + b_{kn} \cdot M_n(t), \end{cases} \quad (15)$$

where $x_i(t)$ is the value of the i -th homeostasis parameter at time t,

$M_i(t)$ is the mass of the i - th active substance in the body at time t,

aij _ – coefficient characterizing the dependence of the rate of change of the i -th homeostasis parameter on the value of the j - th homeostasis parameter,

b_{ij} – coefficient characterizing the dependence of the rate of change of the i -th parameter of homeostasis on the mass of the j -th active substance.

The system of equations (15) can be solved numerically, which makes it possible to predict the consequences of given active interventions in metabolism by choosing the appropriate strategies for directed actions.

Thus, it becomes possible not only for one component and not only under stationary conditions to represent the dynamics of accumulation and excretion of substances by a living organism, but it is also possible to reflect a multidimensional picture of the homeokinetic response to changing environmental conditions, which opens up the possibility of targeted interventions in metabolism, as well as necessary corrections when appropriate rehabilitation algorithms, measures to overcome critical and borderline conditions are in demand, or, on the contrary, if necessary, targeted harmonizing influences

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