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ПЛИСКА

БЪЛГАРСКИ МАТЕМАТИЧЕСКИ СТУДИИ

OPTIMIZATION PROBLEM IN A CLASS OF LINEAR SYSTEM. APPLICATION TO MULTIPLE DRUG ADMINISTRATION

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The optimal control settings are useful tools in studying the behavior of the plasma concentration of a drug (medicine) after its application. Linear compartmental systems are widely used as mathematical models for studying this behavior. In this paper we develop a strategy for minimizing the total amount of applied drug under the restriction: the mean plasma concentrations belongs to prescribed therapeutic interval. The aim of the article is to give to the therapeutist an simple and applicable formula for the optimal input sequence of multiple doses as a function of the time and rate constant of drug elimination. The desired formula is given as a result of the theorems for optimal input function which we proved. The optimal input is important specially for patients, which needs of treatment with antibiotics but they have kidney shortage function. Because of this the relationship between the optimal dose and the time intervals of administration to maintain a effective drug concentration in plasma is considered too. The results are applied to the two compartment stochastic model using experimental data of plasma concentration after single administration of antibiotic Tobramicin to a patient with kidney shortage function.

1. Introduction

Over the past decades, the treatment of illness has been accomplished by administering drugs to the human body via various pharmaceutical dosage forms,

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like tablets. These traditional pharmaceutical products are still commonly seen today in the prescription and over-the-counter drug marketplace. To achieve and maintain the drug concentration in the body within the therapeutic range required for a medication, it is often necessary to take this type of drug delivery system several times a day. This yields an undesirable drug level in the body.

A number of advancements have been made recently in the development of new techniques for drug delivery. These techniques are capable of regulating the rate of drug delivery, sustaining the duration of therapeutic action, and/or targeting the delivery of drug to a specific tissue. These advancements have already led to the development of several novel drug delivery systems that could provide one or more of the following benefits [8]:

1. Controlled administration of a therapeutic dose at a desirable rate of delivery.

2. Maintenance of drug concentration within an optimal therapeutic range for prolonged duration of treatment.

3. Maximization of efficacy-dose relationship.

4. Reduction of adverse side effects.

5. Minimization of the needs for frequent dose intake.

6. Enhancement of patient compliance.

Based on the technical sophistication of the controlled-release drug delivery systems (CrDDSs) that have been marketed so far, or that are under active development, the CrDDSs can be classified as follows [8]:

1. Rate-preprogrammed drug delivery systems.

2. Activation-modulated drug delivery systems.

3. Feedback-regulated drug delivery systems.

4. Site-targeting drug delivery systems.

One class of models that reflected the biological understanding of a system and is formulated in terms of the kinetics of the system is the class of linear compartment models. The method of compartmental analysis is frequently applied to pharmacokinetics [1]. These models are applied for analysis of feedback-regulated
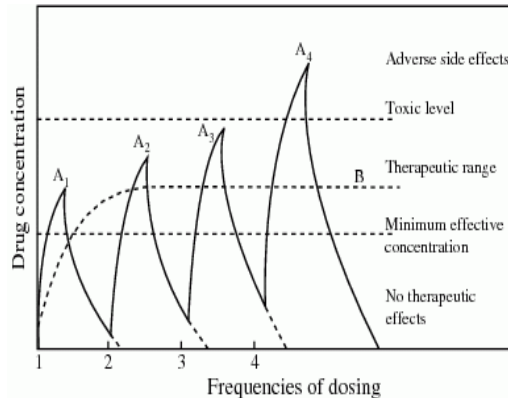
Figure 1: Drug concentration profiles in the systemic circulation as a result of taking a series of multiple doses of a conventional drug-delivery system $(A_1, A_2, \ldots)$ in comparison with the ideal drug concentration profile (B) (Adapted from Ref. [8]).

drug delivery systems. In [12] a feedback-regulated drug delivery systems with delay is considered for modeling HIV pathogenesis

On multiple administration of drug it is important (as the six benefits pointed in [8]) to maintain the concentration of drug in blood plasma in a appropriate range, while minimizing the total dosage of drug used in order to reduse side effects. In this paper we consider the optimal drug administration i.e. the mode of multiple drug application which satisfy the above two conditions.

In [9] and [10] the optimal input is discussed but the model is without gastrointestinal tract, because of infusion administration of drug.

In [2] and [11] a linear two compartment model consisting of gastrointestinal tract and an apparent space of drug distribution is proposed. A control input to achieve the drug concentration in this space above a certain level (plateau effect in Fig. 1) is derived. In this model the transfer of drug between two compartments is assumed to be in one direction and treated neither optional time intervals nor the optimization of drug administration. In [3] and [4] the optimal impulsive control of compartmental models and a solution algorithm is reported. There is pointed out that the problem of optimal drug administration can be resolved into the optimal impulsive control.

In this article we consider the optimal impulsive control problem of arbitrary time intervals for a subclass of compartment linear systems, which usually describe the kinetics of drugs in a body. The impulse response of this system has

the unique maximum and is strictly monotone increasing before (decreasing after) the maximal point. Because of this the optimal solution is given in a more simple form than in [4]. For considered model the transfer of drug between the compartments is assumed to be in two directions (i.e. more complicate than in [2]. The choice of this particular compartment pharmacokinetic models is based on its popularity in the some pharmacokinetics investigations about kinetics of antibiotic Tobramicin and its generic [5], [6], [13].

2. Description of the model and mathematical problem statement

Let us consider N-compartment linear pharmacokinetics model, where the transfer of drug between two compartments is assumed to be occur in two directions. Let the application of drug is from depot i.e. oral, muscular, subcutant and etc. The administration is regarded as an impulsive input to the gastrointestinal tract or muscular tissue or etc. The compartment receiving a nonnegative input is assumed to be the first and an apparent space of drug distribution in the body containing the blood space to be $2, 3, \ldots, N$. On the Fig. 2 this model of the kinetics of the drug distribution is placed.
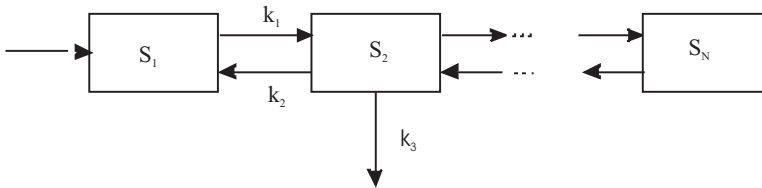

Figure 2: N-compartment pharmacokinetics model of drug distribution in the human body.

The kinetics of the drug is assumed to be first order. This means for instance that the outlet from compartment 1 per time unit at time t is $k_1 S_1(t)$.

Let the impulses $(i = 0, 1, \ldots, n)$ are loaded at the prescribed times t_i ($0 = t_0 < t_1 < \cdots < t_n$). Than the dynamics of the system is described by the following differential equations:

$$\frac{d\vec{S}}{dt} = K\vec{S}(t) + \vec{B}\epsilon, \ t \in [t_i, t_{i+1}], \ i = 0, \ldots, n$$

(1)

$$\vec{S}(t_0^-) = 0$$

where $\vec{S}(S_1, \ldots, S_N)^T$ (T – transpose of a matrix) is the state vector and its components S_i ($i = 1, \ldots, N$) are the drug concentrations in first and etc. compartments, K is the matrix, called compartment matrix [1] and $\vec{B}(1, 0, \ldots, 0)^T$ The impulse response of the system (1) after a single administration of a unit dose (δ-impulse) is the drug concentration in the blood plasma (second compartment) and it is given by [2]:

$$(2) \qquad\qquad y(t) = \sum_{i=1}^{N} A_i e^{-\alpha_i t}$$

where $t > 0$ and $0, \alpha_1, \alpha_2 < \cdots < \alpha_N$ are eigenvalues of the matrix K. A_i are real constants, which depends from the eigenvalues of K, $\sum_{i=1}^{N} A_i \leq 0$, $A_N < 0$. Let for the function $y(t)$ the following properties are valid:

(i) $y(t)$ has a unique maximum at the time $t_{\max}$.

(ii) $y(t)$ is strictly monotone decreasing for $t > t_{\max}$.

(iii) $y(t)$ is strictly monotone increasing for $t < t_{\max}$.

The state of the second compartment — S_2 — at the time $t \in [t_k, t_{k+1}]$, ($k = 1, \ldots, N$) may be expressed by the discrete analog of Duhamel's integral:

$$(3) \qquad\qquad S_2(t) = \sum_{i=0}^{k} \epsilon y(t - t_i).$$

We consider the following two problems:

Problem 1. The total amount $\Phi(\epsilon) = \sum_{i=1}^{n} \epsilon_i$ of the input doses $\epsilon_0, \epsilon_1, \ldots, \epsilon_n$, to be minimum and the state of the second compartment (S_2) to be maintained above the given constant $c > 0$ (c – minimal effective plasma concentration of the drug in steady-state):

$$S_2(t) \geq c, \quad t \in [t_i, t_{i+1}];$$

Problem 2. The total amount $\Phi(\epsilon) = \sum_{i=0}^{n} \epsilon_i$ of the input doses $\epsilon_0, \epsilon_1, \ldots, \epsilon_n$, to be minimum and the mean value of the state of the second compartment (S_2):

$$(4) \qquad\qquad m_i = \frac{1}{t_i - t_{i-1}} \int_{t_{i-1}}^{t_i} S_2(\tau) d\tau \geq C, \; i = 1, 2, \ldots, n$$

to be maintained above the given constant $C > 0$ (C – maximal effective plasma concentration of the drug in steady-state).

Consideration of Problem 1. If we denote: s_i – the state of S_2 at time t_i and $S = (s_1, \ldots, s_{n+1})^T$, then the equation (3) will be rewritten as $S = Y\epsilon$, where the elements of the matrix Y are

$$(5) \qquad y_{ij} = \begin{cases} y(t_i - t_{j-1}), & i \geq j \\ 0, & i < j \end{cases} \qquad \text{for} \qquad i, j = 1, 2, \ldots, n+1,$$

where $y(t)$ is the function given by (2).

We shall prove the following theorem, which give the optimal solution of the Problem 1.

Theorem 1. *If the impulse response $y(t)$ of the system* (1) *corresponding to the unit impulse is*

$$y(t) = \sum_{i=1}^{N} A_i e^{-\alpha_i t}, \qquad (0 < \alpha_1 < \alpha_2 < \cdots < \alpha_N)$$

which satisfy the properties (**i**)–(**iii**) *and the length of all input intervals satisfy*

$$|t_{i+1} - t_i| > t_{\max}, \ i = 0, 1, \ldots, n,$$

then there exists a positive input sequence $\epsilon = (\epsilon_0, \epsilon_1, \ldots, \epsilon_n)$, which minimizes the function

$$\Phi(\epsilon) = \sum_{i=0}^{n} \epsilon_i = I^T \epsilon$$

under the constrains $Y\epsilon \geq c$, where $c > 0$ is a given constant, and the input sequence is given by $\hat{\epsilon} = cY^{-1}I$.

Consideration of Problem 2. Let us denote the vector $M = (m_1, \ldots, m_{n+1})^T$, where m_i is the mean value of the state of S_2 during the input interval $[t_{i-1}, t_i]$. Than the equation (3) will be rewritten as $M = \tilde{Y}\epsilon$, where the elements of the matrix $\tilde{Y}$ are

$$(6) \qquad \tilde{y}_{ij} = \begin{cases} \dfrac{1}{t_i - t_{j-1}} \displaystyle\int_{t_{i-1}}^{t_i} d\tau, & i \geq j \\ 0, & i < j \end{cases} \qquad \text{for} \qquad i, j = 1, 2, \ldots, n+1,$$

where $y(t)$ is function given by (2). From the mean value theorem it follows that the elements of the matrix $\tilde{Y}$ for $i \geq j$, satisfy $\tilde{y}_{ij} = y(\tau_i - t_{j-1})$, for some τ_i where $t_{i-1} < \tau_i < t_i$.

We shall prove the following theorem, which give the optimal solution of the Problem 2.

Theorem 2. *If the impulse response $y(t)$ of the system (1) corresponding to the unit impulse is*

$$y(t) = \sum_{i=1}^{N} A_i e^{-\alpha_i t}, \qquad (0 < \alpha_1 < \alpha_2 < \cdots < \alpha_N)$$

which satisfy the properties (**i**)–(**iii**) *and the length of all input intervals satisfy*

$$|t_{i+1} - t_i| > t_{\max}, \ i = 0, 1, \ldots, n,$$

then there exists a positive input sequence $\epsilon = (\epsilon_0, \epsilon_1, \ldots, \epsilon_n)$, which minimizes the function

$$\Phi(\epsilon) = \sum_{i=0}^{n} \epsilon_i = I^T \epsilon$$

under the constrains $\tilde{Y}\epsilon \geq C$, where $C > 0$ is a given constant, and the input sequence is given by $\epsilon_{opt} = C\tilde{Y}^{-1}I$.

At first we shall prove two lemmas.

Lemma 1. *Let $I = (1, 1, \ldots, 1)^T$ and let Y is $(n \times n)$ lower triangular matrix with positive elements and $C > 0$ is a given constant.*
The minimum of the function

(7)
$$\Phi(\epsilon) = \sum_{i=0}^{n} \epsilon_i = I^T \epsilon$$

under the constrains

(8)
$$Q\epsilon \geq C \qquad and \qquad \epsilon_i > 0$$

is given by

(9)
$$\hat{\epsilon} = CQ^{-1}I$$

if and only if all components of the vector $Q^{-1}I$ are nonnegative.

Proof. The necessary and sufficient conditions for existence of an optimal solution $\hat{\epsilon}$ of this optimization problem given in [7] are the following:

The equations

(10)
$$\left|\begin{array}{l} -I + (\mathrm{grad}\Psi(\hat{\epsilon}))^T\mu = 0 \\[2mm] (\Psi(\hat{\epsilon}))^T\mu = 0, \end{array}\right.$$

where

$$(\Psi(\epsilon))^T = \begin{pmatrix} CI - Q\epsilon \\ -\epsilon \end{pmatrix}$$

to be satisfy for some no positive vector μ, which component are no positive.

Necessary: Let us suppouse that

(11)
$$\hat{\epsilon} = CQ^{-1}I$$

is the optimal solution and that all components of $\hat{\epsilon}$ are nonnegative:

(12)
$$\hat{\epsilon} \geq 0.$$

Then from the second equation of (10)

$$(\Psi(\hat{\epsilon}))^T\mu = \begin{pmatrix} CI - QCQ^{-1}I \\ -CQ^{-1}I \end{pmatrix} \begin{pmatrix} \mu_1 \\ \dots \\ \mu_{2n} \end{pmatrix} = \begin{pmatrix} 0 \\ -CQ^{-1}I \end{pmatrix} \begin{pmatrix} \mu_1 \\ \dots \\ \mu_{2n} \end{pmatrix} = \begin{pmatrix} 0 \\ \dots \\ 0 \end{pmatrix},$$

it follows that there exist an vector $\mu = (\mu_1, \dots, \mu_n, 0, \dots, 0)^T$, which satisfy the equation. Now, substituting μ into first equation of (10), we get:

(13) $-I + \begin{pmatrix} -Q \\ -E \end{pmatrix}^T (\mu_1, \dots, \mu_n, 0, \dots, 0)^T = -I + (-Q)^T \begin{pmatrix} \mu_1 \\ \dots \\ \mu_n \end{pmatrix} = 0.$

Let us denote $\hat{\mu} = (\mu_1, \dots, \mu_n)^T$. Than from (13) it follows: $-Q^T\hat{\mu} = I$ and $-\hat{\mu}^T = (I^T Q^{-1})^T$. Now from (12) it follows that the components of the vector $\hat{\mu}$ and corresponding - components of μ, are no positive.

Sufficiency: Let us assume that components of the vector $(Q^{-1}I)$ are non-negative i.e. $Q^{-1}I \geq 0$.

Let us define vector $\mu = \begin{pmatrix} -(Q^T)^{-1}I \\ 0 \end{pmatrix}$ i.e. all components $\mu_i \leq 0$ $(i = 1, \dots, 2n)$. We shall proof that equations (10) are satisfied for this μ.

If $\hat{\epsilon} = -C(Q^{-1}I)^T$ is the optimal solution,

$$-I+(\mathrm{grad}\Psi(\epsilon))^T\mu = -I + \begin{pmatrix} -Q \\ -E \end{pmatrix}\begin{pmatrix} -(Q^T)^{-1}I \\ 0 \end{pmatrix} = -I + Q^T(Q^T)^{-1}I = -I + I = 0,$$

and

$$(\Psi(\hat{\epsilon}))^T\mu = \begin{pmatrix} CI - Q\hat{\epsilon} \\ \hat{\epsilon} \end{pmatrix}\begin{pmatrix} -(Q^T)^{-1}I \\ 0 \end{pmatrix} =$$
$$= (CI^T - \hat{\epsilon}^T Q^T)(-(Q^T)^{-1}I) = (-C(Q^{-1}I)^T + \hat{\epsilon}^T)I =$$
$$= (-C(Q^{-1}I)^T + -C(Q^{-1}I)^T) = 0$$

This complete the proof. □

Therefore, if we prove, that the matrices Y and $\tilde{Y}$ are lower triangular matrix with positive elements, then the proof of the Theorem 1 and Theorem 2 will be completed.

Let us consider the matrix Y from the Problem 1.

Let us assume that the length of the inputs interval $|t_{i+1} - t_i| > t_{\max}$, $(i = 0, 1, \ldots, n)$. Than for $j < i_1 < i_2$ we have

$$(14) \qquad y_{i_1 j} - y_{i_2 j} = y(t_{i_1} - t_{j-1}) - y(t_{i_2} - t_{j-1}) > 0,$$

because of (**i**)–(**iii**).

After this consideration, it is easy to prove the following:

Lemma 2. *If Y is $(n \times n)$ lower triangular matrix with positive elements defined by (10) and $y_{i_1 j} > y_{i_2 j}$ for $1 \le j < i_1 < i_2 \le n$, $j = 1, \ldots, n - 1$, than components of the vector $(Y^{-1}I)$ are nonnegative.*

P r o o f. (by the method of mathematical induction):
Let $n = 2$ i.e. we consider the matrix

$$\begin{pmatrix} y_{11} & 0 \\ y_{21} & y_{22} \end{pmatrix}$$

with elements

$$(15) \qquad y_{11} > y_{21} \qquad \text{and} \qquad y_{ij} > 0 \ (i \ge j).$$

Than the components of $(Y^{-1}I)$ i.e. the row sum of the invert matrix

$$Y_2^{-1} = \begin{pmatrix} \frac{1}{y_{11}} & 0 \\ \frac{-y_{21}}{y_{11}y_{22}} & \frac{1}{y_{22}} \end{pmatrix}$$

are positive because of (15):

$$\sum_{j=1}^{2}(Y_2^{-1})_{1j} = \frac{1}{y_{11}} > 0,$$

$$\sum_{j=1}^{2}(Y_2^{-1})_{2j} = \frac{1}{y_{22}} - \frac{y_{21}}{y_{11}y_{22}} = \frac{1}{y_{22}}\left(1 - y_{21}\left(\frac{1}{y_{11}}\right)\right) > 0,$$

Let us suppose that the Lemma is thought for $n = k - 1$, i.e. the row sum of for the matrix

(16)
$$Y_{k-1}^{-1} = \begin{pmatrix} Y_{k-2}^{-1} & 0 \\ -\sum_{i=1}^{k-2}\frac{y_{k-1,i}}{y_{k-1,k-1}}\left(\sum_{j=1}^{k-2}(Y_{k-2}^{-1})_{ij}\right) & \frac{1}{y_{k-1,k-1}} \end{pmatrix}$$

are positive. We shall prove the Lemma for $n = k$. The matrix Y_k^{-1} has the kth row sum equal to:

(17)
$$\sum_{j=1}^{k}(Y_k^{-1})_{kj} = \frac{1}{y_{kk}}\left(1 - \sum_{i=1}^{k-1}y_{ki}\sum_{j=1}^{k-1}(Y_{k-1}^{-1})_{ij}\right)$$

By the induction assumption and by the condition $y_{k-1,i} > y_{ki}$ it follows:

(18)
$$\sum_{j=1}^{k-2}(Y_{k-2}^{-1})_{ij} = \sum_{j=1}^{k-1}(Y_{k-1}^{-1})_{ij}, \quad i = 1, \ldots, k-2,$$

and

(19)
$$1 > \sum_{i=1}^{k-2}y_{k-1,i}\sum_{j=1}^{k-2}(Y_{k-2}^{-1})_{ij} > \sum_{i=1}^{k-2}y_{ki}\sum_{j=1}^{k-2}(Y_{k-2}^{-1})_{ij}.$$

After some simple transformations, take into a count (18) and (19), we obtain

(20)
$$\sum_{i=1}^{k-1}y_{ki}\sum_{j=1}^{k-1}(Y_{k-1}^{-1})_{ij} < 1.$$

Therefore from (17) it follows that the Lemma 2 is thought for $n = k$. □

The statement of the Lemma 2, for the matrix $\tilde{Y}$, which elements are given by (6) can be proved by the analogues way.

Now, using the above proved Lemma 1 and the Lemma 2 we complete the proof of the Theorem 1 and Theorem 2, which gives the optimal solution of the Problem 1 and Problem 2.

3. Application to the two compartment model
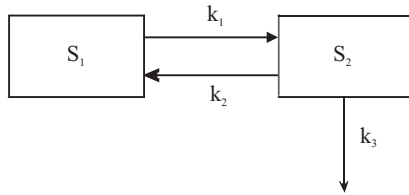
Let us consider two compartment model:

Figure 3: Two compartment model of drug distribution in the human body.

Let the impulses $\epsilon_i (i = 0, 1, \ldots, n)$ are loaded at the prescribed times t_i, $(0 = t_0 < t_1 < \cdots < t_n)$. Then the dynamics of this system is described by the following differential equations:

$$\frac{d\vec{S}}{dt} = K\vec{S}(t), \quad t \in [t_i, t_{i+1}]$$

$$\vec{S}(t_i^+) = \vec{S}(t_i^-) \begin{pmatrix} 1 \\ 0 \end{pmatrix} \epsilon_i$$

$$\vec{S}(t_0) = 0, \quad i = 0, 1, \ldots, n,$$

where $\vec{S}(S_1, S_2)^T$ is the state vector and its components S_1 and S_2 are the drug concentration in first and second compartment, and compartment matrix K is

$$K = \begin{pmatrix} -k_1 & k_2 \\ k_1 & -k_2 - k_3 \end{pmatrix}.$$

The drug concentration in the blood plasma after a single administration of a unit dose i.e impulse response of the second compartment is given by

(21) $$y(t) = \frac{k_1}{\alpha_1 - \alpha_2}(e^{-\alpha_1 t} - e^{-\alpha_2 t}) = A(e^{-\alpha_1 t} - e^{-\alpha_2 t})$$

where $0 < \alpha_1 < \alpha_2$ are eigenvalues of K given by:

(22) $$\alpha_{1,2} = \frac{1}{2}\left(-(k_1 + k_2 + k_3) \pm \sqrt{(k_1 + k_2 + k_3)^2 - 4k_1 k_3}\right).$$

It must be emphasized that for the function $y(t)$ the properties **(i)** - **(iii)** are valid:

(i) $y(t)$ has a unique maximum at time

(23) $$t_{\max} = \frac{1}{\alpha_2 - \alpha_1} \ln\left(\frac{\alpha_2}{\alpha_1}\right);$$

(ii) $y(t)$ is strictly monotone decreasing for $t > t_{\max}$;

(iii) $y(t)$ is strictly monotone increasing for $t < t_{\max}$.

The state of the compartment 2 - S_2, at time $t \in [t_k, t_{k+1}]$ is expressed by (3) i.e.

$$S_2(t) = \sum_{i=0}^{k} \epsilon_i y(t - t_i).$$

Let us consider the Problem 1 for this two compartment model. In order to give to the therapeutist an simple and applicable formula for the optimal input sequence $\epsilon_{opt} = (\epsilon_0, \ldots, \epsilon_n)$, we shall consider relationship between the optimal dose and the time intervals of administration to maintain a minimal effective drug concentration in plasma $c > o$ (c-const.).

Let us denote by τ the length of each time intervals between the administrations. Let the optimal dose ϵ_k from (21) is applied at the time $t_k = k\tau$. Then from (3) it follows

(24) $$S_2(t) = \sum_{i=0}^{k} \epsilon_i y(t - t_i) = \sum_{i=0}^{k} y(t - i\tau) = c, \qquad k\tau \le t < (k+1)\tau.$$

If we denote $t = k\tau$, then (24) have a form

(25) $$S_2(k\tau) = \sum_{i=0}^{k-1} \epsilon_i y((k-1)\tau) = c.$$

In order to obtain ϵ_k, let us substitute $i = j + 1$ in (25):

$$\sum_{j=1}^{k-1} \epsilon_j y(k - j + 1)\tau) + \epsilon_k y(\tau) = c,$$

i.e.

$$(26) \qquad \epsilon_k = \frac{c}{y(\tau)} - \frac{1}{y(\tau)} \sum_{j=1}^{k-1} \epsilon_j y((k-j+1)\tau).$$

From (21) we obtain

$$y((k-j+1)\tau) = A(e^{-\alpha_1(k-j+1)\tau} - e^{-\alpha_2(k-j+1)\tau}) =$$
$$= \frac{A(e^{-\alpha_1(k-j)\tau} - e^{-\alpha_2(k-j)\tau}).A(e^{-\alpha_1\tau} - e^{-\alpha_2\tau})}{A} +$$
$$A(e^{-\alpha_2(k-j)\tau}(e^{-\alpha_1\tau} - e^{-\alpha_2\tau}) + e^{-\alpha_2\tau}(e^{-\alpha_1(k-j)\tau} - e^{-\alpha_2(k-j)\tau}) =$$
$$= \frac{y(k-j\tau)y(\tau)}{A} + y(\tau)e^{-\alpha_2(k-j)\tau} + y(k-j)\tau)e^{-\alpha_2\tau}$$

Substituting in (26) and take into account (25), we get for the kth component of $\hat{\epsilon}$:

$$(27) \qquad \epsilon_k = c\left(\frac{1 - e^{-\alpha_2\tau}}{y(\tau)} - \frac{1}{A}\right) - \sum_{j=0}^{k-1} \epsilon_j e^{-\alpha_2(k-j)\tau}.$$

Now we shall give an approximate relationship between ϵ_k and τ. Let us present ϵ_k from (27) in the form

$$(28) \quad \epsilon_k = c\left(\frac{e^{\alpha_1\tau}}{A(1 - e^{-(\alpha_2-\alpha_1)\tau})} - \frac{1}{A(e^{(\alpha_2-\alpha_1)\tau} - 1)} - \frac{1}{A}\right) - \sum_{j=0}^{k-1} \epsilon_j e^{-\alpha_2(k-j)\tau}.$$

Because of $\alpha_2 > \alpha_1 > 0$ and (i)–(iii), the term with in $y(t)$ is negligible for $t \gg t_{\max}$. So, if τ is sufficiently large, then $\lim_{\tau\to\infty} e^{-\alpha_2\tau} = 0$, $\lim_{\tau\to\infty} e^{-(\alpha_2-\alpha_1)\tau} = 0$ and $\lim_{\tau\to\infty} \frac{1}{A(e^{(\alpha_2-\alpha_1)\tau} - 1)} = 0$. Therefore

$$(29) \qquad \epsilon_k = \frac{c}{A}(e^{\alpha_1\tau} + \mathrm{sgn}(e^{(\alpha_1-\alpha_2)\tau} - 1)).$$

From the above given considerations it follows, that if τ is sufficiently large, then the maintenance dose ϵ_k, $k = 1, \ldots, n$ is independent of t_k and it is approximately constant.

4. Application to the real data. Results and conclusion

In our disposition there were six experimental data points (t_i, y_i) of plasma concentration $y(t)$, obtained after single intramuscular input of antibiotic Tobramicin to the patient A.G. who had serious tissue infection (after motor-car accident) and needs of antibiotic therapy. Employing the method of nonlinear regression to the experimental points (t_i, y_i), $i = 1, \ldots, 6$, the individual parameters $\alpha_1 = 0.031/h$, $\alpha_2 = 9 \ 1/h$, $A = 3.96$ were estimated according to the function $y(t)$ from (2). Therefore in this case (29) obtains the form:

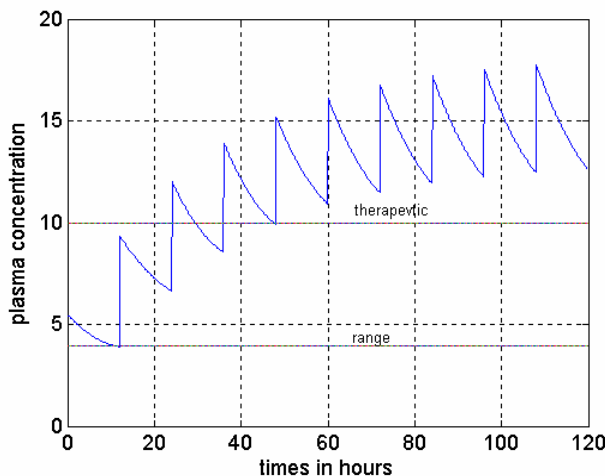$$(30) \qquad \epsilon_k = \frac{c}{A}(e^{\alpha_1 \tau} - 1)$$

Figure 4: The plasma concentrations levels $S(t)$ if the conventional mode of administration of Tobramicin is applied.

The therapeutic range (the effective levels of drug plasma concentrations) of Tobramicin is $[2.8 - 3, 8.5 - 10]\ \mu g/ml$ i.e. $c = 3\ \mu g/ml$. The results (after application of (30)) for the plasma concentrations levels $S(t)$, if the conventional mode of administration of Tobramicin: $\tau = 12$ h, $\epsilon_k = 80$ mg is taken, are shown in Fig. 4. As it can be seen on Fig. 4, the minimal concentration of drug in plasma would be about 12 $\mu g/ml$, i.e. greater than the limits of levels of therapeutic range. It is because of the very long half-life of excretion $t_{1/2}(\alpha_1) \approx 23$ h of this patient $(t_{1/2}(\alpha_1) = (\ln 2)/\alpha_1$ (in hours)). The first two doses are applied for $\tau = 12$ h in order to reach quickly the prescribed maximal effective levels in plasma.
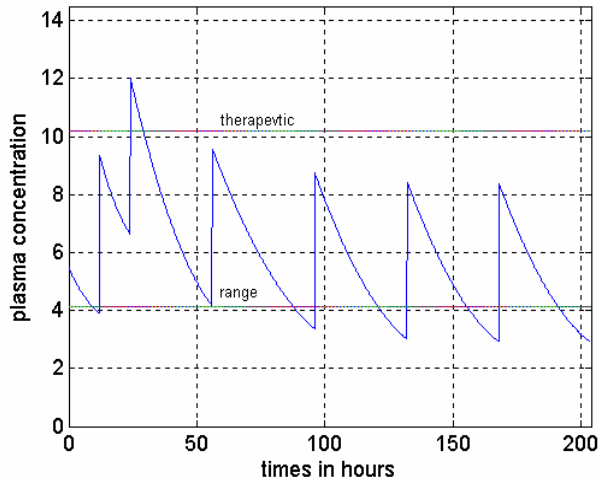
Figure 5: The plasma levels $S(t)$ of Tobramicin predicted using (30).

The optimal time interval $\tau_k = 36$ h, $(k = 3, \ldots, 7)$ is calculated using (30) and the resulting predicted plasma levels are shown in Fig. 5. There were taken four test-samples: $S(48) = 5.5\ \mu\text{g/ml}$, $S(96) = 3.1\ \mu\text{g/ml}$, $S(140) = 8.8\ \mu\text{g/ml}$ and $S(168) = 3.1\ \mu\text{g/ml}$. They satisfy the prescribed therapeutic range of plasma concentrations.

The results above shows that optimal control settings are useful tools in studying the behavior of the plasma concentration of a drug after multiple its administration.

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