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CONTINUOUS DEPENDENCE AND STABILITY OF SOLUTIONS OF IMPULSIVE DIFFERENTIAL EQUATIONS ON THE INITIAL CONDITIONS AND IMPULSIVE MOMENTS

A.B. Dishliev[1] §, K.G. Dishlieva[2]

[1]Department of Mathematics
University of Chemical Technology and Metallurgy
8, Kliment Ohridsky, Sofia 1756, BULGARIA
e-mail: dishliev@uctm.edu

[2]Faculty of Applied Mathematics and Informatics
Technical University of Sofia
Sofia, BULGARIA
email: kgd@tu-sofia.bg

Abstract: Basic research object in the present paper are non-linear impulsive systems of differential equations with fixed moments of impulsive effects. For such type of equations are introduced the concepts continuous dependence and stability on the initial data and impulsive moments. Sufficient conditions are found under which the solutions have these properties. The results are applied to a mathematical model of pharmacokinetics.

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1. Introduction

Some processes are subjected to the short term perturbations caused by external interventions during their evolution. Very often the durations of these effects are negligible in comparison with the whole duration of the process. Therefore, it is natural to assume that these perturbations act instantaneously in the form of impulses (see [20], [23], [28]). Adequate mathematical apparatus

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§Correspondence author

for investigation of the above processes are impulsive differential equations. Depending on the way of determining the moments of impulses there are several types of impulsive differential equations:

- With fixed moments of impulsive effect;
- With impulsive moments, coinciding with the moments at which the integral curve of the equation meets predefined sets located in the extended phase space. Most often, these sets are non intercepting hypersurfaces;
- With impulsive moments, coinciding with the moments at which the solution minimizes a given functional;
- With impulsive moments with occasional nature which satisfy a certain law of distribution, etc.

In the present paper the object of investigation are impulsive equations with fixed moments of impulsive effects.

The theory of impulsive differential equations with fixed and variable times is relatively less developed due to the difficulties created by the state-dependent impulses. Recently, some interesting results have been done by R. Agarwal, M. Benchohra, J. Henderson, S. Ntouyas, A. Ouahab, M. Frigon, D. O'Regan, J. Nieto, etc (see [1], [2], [3], [6], [7], [8], [11], [12], [13], [24], [31]).

There are numerous applications of impulsive differential equations (see [4], [9], [16], [17], [19], [21], [22], [25], [27], [29], [30], [32], [34], [35], [36]) and their theory evolves intensively during last twenty years. On this relatively new theory are devoted dozen monographs, from which we indicate [5], [18], [26], [28] and [33].

2. Statement of the Problem

The main object of investigation in the present paper is the following initial problem for impulsive ordinary differential equations:

$$\frac{dx}{dt} = f(t, x), \qquad t \neq t_i, \tag{1}$$

$$x(t_i + 0) = x(t_i) + I_i(x(t_i)), \quad i = 1, 2, ..., \tag{2}$$

$$x(t_0) = x_0, \tag{3}$$

where: $f : \mathrm{R}^+ \times D \to \mathrm{R}^n$; $n \in \mathrm{N}$; D is a domain and $D \subset \mathrm{R}^n$; $t_i \in \mathrm{R}^+$; $0 \le t_0 < t_1 < t_2 < ...$; $I_i : D \to \mathrm{R}^n$; $(Id + I_i) : D \to D$ and $x_0 \in D$. The identity in R^n is Id.

The solution of the given problem is a piecewise continuous function. It is hold:

1. For $t_0 \leq t \leq t_1$ the solution of problem (1), (2), (3) coincides with the solution of problem (without impulses) (1), (3);

2. For $t_i < t \leq t_{i+1}$, $i = 1, 2, ...$, the solution of problem (1), (2), (3) coincides with the solution of the system (1) with initial value $x(t_i + 0) = (Id + I_i)(x(t_i))$.

Together with problem (1), (2), (3) we consider the corresponding perturbed problem

$$\frac{dx^*}{dt} = f(t, x^*), \qquad t \neq t_i^*, \tag{4}$$

$$x^*(t_i^* + 0) = x^*(t_i^*) + I_i(x^*(t_i^*)), \quad i = 1, 2, ..., \tag{5}$$

$$x^*(t_0^*) = x_0^*, \tag{6}$$

where $0 \leq t_0^* < t_1^* < t_2^* < ...$ and $x_0^* \in D$.

The solutions of the problems (1), (2), (3) and (4), (5), (6) we denote respectively by $x(t; t_0, x_0)$ and $x^*(t; t_0^*, x_0^*)$. We use the notation.

$$\langle a, b \rangle = \begin{cases} (a, b], & \text{if } a < b; \\ (b, a], & \text{if } a > b; \\ \emptyset, & \text{if } a = b. \end{cases}$$

Definition 1. We say that the solution of problem (1), (2), (3) depends continuously on the initial point (t_0, x_0) and impulsive moments $t_1, t_2, ...,$ if:

$$\begin{gathered}(\forall \varepsilon > 0)(\forall T > t_0)(\exists \delta = \delta(\varepsilon, T) > 0): \\ (\forall (t_0^*, x_0^*) \in [0, T] \times D, \quad |t_0^* - t_0| < \delta, \quad \|x_0^* - x_0\| < \delta) \\ \left(\forall t_1^*, t_2^*, ... \in \mathrm{R}^+, \quad t_0^* < t_1^* < t_2^* <, ..., |t_1^* - t_1| < \delta, \quad |t_2^* - t_2| < \delta, ...\right) \\ \Rightarrow \|x^*(t; t_0^*, x_0^*) - x(t; t_0, x_0)\| < \varepsilon, \quad t \in [t_0, T] \setminus \bigcup_{i=0,1,...} \langle t_i^*, t_i \rangle.\end{gathered}$$

Definition 2. We say that the solution of problem (1), (2), (3) is stable with respect to the initial point (t_0, x_0) and impulsive moments $t_1, t_2, ...,$ if:

$$\begin{gathered}(\forall \varepsilon > 0)(\exists \delta = \delta(\varepsilon) > 0): \\ \left(\forall (t_0^*, x_0^*) \in \mathrm{R}^+ \times D, \quad \|x_0^* - x_0\| < \delta\right)\end{gathered}$$

$$\left(\forall t_1^*, t_2^*, ... \in \mathrm{R}^+, \quad t_0^* < t_1^* < t_2^* <, ..., \quad \left(\sum_{i=0,1,...} |t_i^* - t_i|\right) < \delta\right)$$
$$\Rightarrow \|x^*(t; t_0^*, x_0^*) - x(t; t_0, x_0)\| < \varepsilon, \quad t \in [t_0, \infty) \setminus \bigcup_{i=0,1,...} \langle t_i^*, t_i \rangle.$$

The main aim of the paper is to find some sufficient conditions for continuous dependence and stability with respect to the initial point and impulsive moments of the solution of the initial problem (1), (2), (3).

3. Preliminary Remarks

Let us denote by $X(t; t_0, x_0)$ the solution of the initial problem without impulses (1), (3).

Definition 3. We say that system (1) is gravitating with a constant κ, if:

$$(\forall t_0 \geq 0)\,(\forall x_0, x_0^* \in D)\,(\forall t \geq t_0) \Rightarrow \|X(t; t_0, x_0^*) - X(t; t_0, x_0)\| < \kappa \|x_0^* - x_0\|.$$

Remark 1. Let the eigenvalues of matrix $A \in (n \times n)$ are different and have no positive real parts.

Then the system

$$\frac{dx}{dt} = Ax$$

is a gravitating with constant 1.

Further we use the following conditions:

H1. The function $f \in C[\mathrm{R}^+ \times D, \mathrm{R}^n]$.

H2. There exists a constant $M > 0$ such that

$$\left(\forall (t, x) \in \mathrm{R}^+ \times D\right) \Rightarrow \|f(t, x)\| \leq M.$$

H3. There exists a constant $L > 0$ such that

$$\left(\forall (t, x^*),\ (t, x) \in \mathrm{R}^+ \times D\right) \Rightarrow \|f(t, x^*) - f(t, x)\| \leq L \|x^* - x\|.$$

H4. The relation $\lim_{i \to \infty} t_i = \infty$ holds.

H5. $(\forall (t_0^*, x_0^*) \in \mathrm{R}^+ \times D) \Rightarrow$ the problem without impulses (4), (6) has a unique solution in interval $[t_0^*, \infty)$.

H6. The functions $I_i \in C[D, \mathrm{R}^n]$, $i = 1, 2, ...$.

H7. There are constants $L_i > 0$ such that:

H7.1. $\prod_{i=1,2,...} (1 + L_i) < \infty$;

H7.2. $(\forall x^*, x \in D) \Rightarrow \|I_i(x^*) - I_i(x)\| \leq L_i \|x^* - x\|, i = 1, 2, ...$

H8. There exists a constant $C_I > 0$ such that

$$(\forall x^*, x \in D) \Rightarrow \|(x^* + I_i(x^*)) - (x + I_i(x))\| \leq C_I \|x^* - x\|, \quad i = 1, 2, ...$$

Theorem 1. *Let the conditions H4 and H5 be satisfied.*

Then $(\forall (t_0^*, x_0^*) \in \mathrm{R}^+ \times D)$ *the solution of the problem with impulses (4), (5), (6) exists and it is unique on the interval* $[t_0^*, \infty)$.

In particular the assertion of Theorem 1 concerns the solution of the problem (1), (2), (3).

We introduce the notations $t_i^{\min} = \min\{t_i^*, t_i\}$, $t_i^{\max} = \max\{t_i^*, t_i\}$ and hence

$$\langle t_i^*, t_i \rangle = \left(t_i^{\min}, t_i^{\max}\right], \quad i = 0, 1, ...$$

4. Main Results

Theorem 2. *Let the conditions H1–H6 be satisfied.*

Then the solution of problem (1), (2), (3) depends continuously on the initial point and the impulsive moments $t_1, t_2, ...$

Proof. According to the condition H4 there exists a number $k \in \mathrm{N}$ such that

$$t_k < T \leq t_{k+1}.$$

We assume that $\|x_0^* - x_0\| < \delta$, $|t_i^* - t_i| < \delta$, $i = 0, 1, ...$ Then if δ is a sufficiently small positive constant the following inequalities are valid:

$$T < t_{k+2}^{\min}, t_i^{\max} < t_{i+1}^{\min}, \quad i = 0, 1, ... (k+1) .$$

Moreover we have

$$[t_0, T] \setminus \bigcup_{i=0,1,...} \langle t_i^*, t_i \rangle = [t_0, T] \setminus \bigcup_{i=0,1,...} \left(t_i^{\min}, t_i^{\max}\right]$$

$$= \left(\bigcup_{i=0,1,\dots,k-1} \left(t_i^{\max}, t_{i+1}^{\min}\right] \right) \cup \left(t_k^{\max}, T^{\min}\right],$$

where $T^{\min} = \min\left\{T, t_{k+1}^{\min}\right\}$. For convenience from now on we assume that $T^{\min} = t_{k+1}^{\min}$. In the case when $T < t_{k+1}^{\min}$ the remaining part of the proof of Theorem 2, the point $t_{k+1}^{\min}$ should be replaced by T. Under the given assumption it follows:

$$[t_0, T] \setminus \bigcup_{i=0,1,\dots} \langle t_i^*, t_i \rangle = \bigcup_{i=0,1,\dots,k} \left(t_i^{\max}, t_{i+1}^{\min}\right].$$

First, we will get an estimation for the difference $\|x^*(t; t_0^*, x_0^*) - x(t; t_0, x_0)\|$ for $t \in \left(t_0^{\max}, t_1^{\min}\right]$. We assume that $t_0^{\min} = t_0^*$ and $t_0^{\max} = t_0$. The proof of the case $t_0^{\min} = t_0$ and $t_0^{\max} = t_0^*$ is similar. We have

$$\begin{aligned}
&\|x^*(t_0^{\max}; t_0^*, x_0^*) - x(t_0^{\max}; t_0, x_0)\| \\
&= \left\| x^*\left(t_0^{\min}; t_0^*, x_0^*\right) + \int_{t_0^{\min}}^{t_0^{\max}} f(\tau, x^*(\tau; t_0^*, x_0^*)) d\tau - x(t_0^{\max}; t_0, x_0) \right\| \\
&\le \left\| x^*\left(t_0^{\min}; t_0^*, x_0^*\right) - x(t_0^{\max}; t_0, x_0) \right\| + \int_{t_0^{\min}}^{t_0^{\max}} \|f(\tau, x^*(\tau; t_0^*, x_0^*))\| d\tau \\
&\le \|x_0^* - x_0\| + \int_{t_0^{\min}}^{t_0^{\max}} M d\tau \\
&= \|x_0^* - x_0\| + M\left(t_0^{\max} - t_0^{\min}\right) \le (1+M)\,\delta.
\end{aligned} \tag{7}$$

For $t \in \left(t_0^{\max}, t_1^{\min}\right]$ the solution of problem (1), (2), (3) coincides with the solution of the initial problem

$$\frac{dx}{dt} = f(t, x), \quad x(t_0^{\max}) = x_0$$

or equivalently with the solution of the integral equation

$$x(t) = x_0 + \int_{t_0^{\max}}^{t} f(\tau, x(\tau))\, d\tau.$$

Consequently

$$x(t;t_0,x_0) = x_0 + \int\limits_{t_0^{\max}}^{t} f(\tau, x(\tau;t_0,x_0))\,d\tau \qquad (8).$$

On the considered interval the solution of problem (4), (5), (6) coincides with the solution of the problem

$$\frac{dx^*}{dt} = f(t,x^*), \quad x^*(t_0^{\max}) = x^*(t_0^{\max};t_0^*,x_0^*),$$

whence it follows

$$x^*(t;t_0^*,x_0^*) = x^*(t_0^{\max};t_0^*,x_0^*) + \int\limits_{t_0^{\max}}^{t} f(\tau, x^*(\tau;t_0^*,x_0^*))\,d\tau. \qquad (9)$$

From (8) and (9) for $t \in \left(t_0^{\max}, t_1^{\min}\right]$ we get

$$\begin{aligned}
&\|x^*(t;t_0^*,x_0^*) - x(t;t_0,x_0)\| \\
&\le \left\| x^*(t_0^{\max};t_0^*,x_0^*) + \int\limits_{t_0^{\max}}^{t} f(\tau, x^*(\tau;t_0^*,x_0^*))\,d\tau - x_0 - \int\limits_{t_0^{\max}}^{t} f(\tau, x(\tau;t_0,x_0))\,d\tau \right\| \\
&\le \|x^*(t_0^{\max};t_0^*,x_0^*) - x_0\| + \left\| \int\limits_{t_0^{\max}}^{t} \left(f(\tau, x^*(\tau;t_0^*,x_0^*)) - f(\tau, x(\tau;t_0,x_0))\right)d\tau \right\| \\
&\le \|x^*(t_0^{\max};t_0^*,x_0^*) - x(t_0^{\max};t_0,x_0)\| + L\int\limits_{t_0^{\max}}^{t} \|x^*(\tau;t_0^*,x_0^*) - x(\tau;t_0,x_0)\|\,d\tau.
\end{aligned}$$

Now using the estimate (7) we find

$$\begin{aligned}
&\|x^*(t;t_0^*,x_0^*) - x(t;t_0,x_0)\| \\
&\qquad \le (1+M)\,\delta + L\int\limits_{t_0^{\max}}^{t} \|x^*(\tau;t_0^*,x_0^*) - x(\tau;t_0,x_0)\|\,d\tau. \qquad (10)
\end{aligned}$$

From (10), using Gronwall's inequality [15], we get the estimate

$$\|x^*(t;t_0^*,x_0^*) - x(t;t_0,x_0)\|$$

$$\begin{aligned}&\leq \delta\left(1+M\right)e^{L\left(t-t_0^{\max}\right)}\\&\leq \delta\left(1+M\right)e^{L\left(t_1^{\min}-t_0^{\max}\right)}\\&\leq \delta\left(1+M\right)e^{LT},\quad t\in\left(t_0^{\max},t_1^{\min}\right]. \end{aligned}\tag{11}$$

Let δ_0 be an arbitrary positive number. From the above estimate it follows that if δ is a sufficiently small constant then we have

$$\left\|x^*\left(t;t_0^*,x_0^*\right)-x\left(t;t_0,x_0\right)\right\|<\delta_0,\quad t\in\left(t_0^{\max},t_1^{\min}\right].$$

After that, we will get an estimate for the difference $\|x^*(t;t_0^*,x_0^*)-x(t;t_0,x_0)\|$ for $t\in\left(t_1^{\max},t_2^{\min}\right]$. Assume that $t_1^{\min}=t_1$ and $t_1^{\max}=t_1^*$. The case $t_1^{\min}=t_1^*$ and $t_1^{\max}=t_1$ can be considered similarly. As $t_1^{\min}$ is the first impulsive moment of the problem (1), (2), (3) we find

$$\begin{aligned}x\left(t_1^{\min}+0;t_0,x_0\right)&=x\left(t_1+0;t_0,x_0\right)\\&=x\left(t_1;t_0,x_0\right)+I_1\left(x\left(t_1;t_0,x_0\right)\right)\\&=x\left(t_1^{\min};t_0,x_0\right)+I_1\left(x\left(t_1^{\min};t_0,x_0\right)\right).\end{aligned}$$

The same solution, when $t\in\left(t_1^{\min},t_2^{\min}\right]$, coincides with the solution of the initial problem:

$$\frac{dx}{dt}=f\left(t,x\right),x\left(t_1^{\min}\right)=x\left(t_1^{\min};t_0,x_0\right)+I_1\left(x\left(t_1^{\min};t_0,x_0\right)\right).$$

This means it is a solution of the integral equation

$$x\left(t\right)=x\left(t_1^{\min};t_0,x_0\right)+I_1\left(x\left(t_1^{\min};t_0,x_0\right)\right)+\int_{t_1^{\min}}^{t}f\left(\tau,x\left(\tau\right)\right)d\tau.$$

In particular if $t=t_1^{\max}+0$ we get

$$\begin{aligned}x\left(t_1^{\max}+0;t_0,x_0\right)=&x\left(t_1^{\min};t_0,x_0\right)+I_1\left(x\left(t_1^{\min};t_0,x_0\right)\right)\\&+\int_{t_1^{\min}}^{t_1^{\max}}f\left(\tau,x\left(\tau;t_0,x_0\right)\right)d\tau.\end{aligned}\tag{12}$$

For $t\in\left(t_1^{\min},t_1^{\max}\right]=\left(t_1,t_1^*\right]$ the solution of the problem (4), (5), (6) does not undergo impulsive perturbation and satisfies the equality

$$x^*\left(t;t_0^*,x_0^*\right)=x^*\left(t_1^{\min}+0;t_0^*,x_0^*\right)+\int_{t_1^{\min}}^{t}f\left(\tau,x^*\left(\tau;t_0^*,x_0^*\right)\right)d\tau,$$

from which, we find

$$x^*\left(t_1^{\max};t_0^*,x_0^*\right)=x^*\left(t_1^{\min}+0;t_0^*,x_0^*\right)+\int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x^*\left(\tau;t_0^*,x_0^*\right)\right)d\tau$$
$$=x^*\left(t_1^{\min};t_0^*,x_0^*\right)+\int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x^*\left(\tau;t_0^*,x_0^*\right)\right)d\tau.$$

From the impulsive equality (5) for $i=1$, we obtain

$$x^*(t_1^{\max}+0;t_0^*,x_0^*)=x^*\left(t_1^*+0;t_0^*,x_0^*\right)$$
$$=x^*\left(t_1^{\min};t_0^*,x_0^*\right)+\int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x^*\left(\tau;t_0^*,x_0^*\right)\right)d\tau$$
$$+I_1\left(x^*\left(t_1^{\min};t_0^*,x_0^*\right)+\int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x^*\left(\tau;t_0^*,x_0^*\right)\right)d\tau\right). \quad (13)$$

From (12) and (13) it follows

$$\|x^*(t_1^{\max}+0;t_0^*,x_0^*)-x(t_1^{\max}+0;t_0,x_0)\|$$
$$\leq\left\|x^*\left(t_1^{\min};t_0^*,x_0^*\right)-x\left(t_1^{\min};t_0,x_0\right)\right\|+\int\limits_{t_1^{\min}}^{t_1^{\max}}\|f\left(\tau,x^*\left(\tau;t_0^*,x_0^*\right)\right)\|d\tau$$
$$+\int\limits_{t_1^{\min}}^{t_1^{\max}}\|f\left(\tau,x\left(\tau;t_0,x_0\right)\right)\|d\tau$$
$$+\left\|I_1\left(x^*\left(t_1^{\min};t_0^*,x_0^*\right)+\int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x^*\left(\tau;t_0^*,x_0^*\right)\right)d\tau\right)\right.$$
$$\left.-I_1\left(x\left(t_1^{\min};t_0,x_0\right)\right)\right\|. \quad (14)$$

Using (11), we estimate the first addend on the right hand side of (14) at $t=t_1^{\min}$

$$\left\|x^*\left(t_1^{\min};t_0^*,x_0^*\right)-x\left(t_1^{\min};t_0,x_0\right)\right\|\leq\delta_0. \quad (15)$$

For the second addend on the right hand side of (14) using condition H2, we obtain

$$\int_{t_1^{\min}}^{t_1^{\max}} \|f(\tau, x^*(\tau; t_0^*, x_0^*))\| d\tau \le M\left(t_1^{\max} - t_1^{\min}\right) \le M\delta. \tag{16}$$

In similar way, we get

$$\int_{t_1^{\min}}^{t_1^{\max}} \|f(\tau, x(\tau; t_0, x_0))\| d\tau \le M\delta \qquad (17).$$

It is true that

$$\begin{aligned} &\left\| x^*\left(t_1^{\min}; t_0^*, x_0^*\right) + \int_{t_1^{\min}}^{t_1^{\max}} f(\tau, x^*(\tau; t_0^*, x_0^*)) d\tau - x\left(t_1^{\min}; t_0, x_0\right) \right\| \\ &\qquad \le \left\| x^*\left(t_1^{\min}; t_0^*, x_0^*\right) - x\left(t_1^{\min}; t_0, x_0\right) \right\| \\ &\qquad\quad + \int_{t_1^{\min}}^{t_1^{\max}} \|f(\tau, x^*(\tau; t_0^*, x_0^*))\| d\tau \le \delta_0 + M\delta. \end{aligned} \tag{18}$$

Let $\delta_1^{\min}$ be an arbitrary positive number. Then from (18) and from the continuity of the function I_1 it follows that there exist sufficiently small positive values of δ and δ_0 such that

$$\left\| I_1\left(x^*\left(t_1^{\min}; t_0^*, x_0^*\right) + \int_{t_1^{\min}}^{t_1^{\max}} f(\tau, x^*(\tau; t_0^*, x_0^*)) d\tau \right) - I_1\left(x\left(t_1^{\min}; t_0, x_0\right)\right) \right\| < \frac{1}{2}\delta_1^{\min}. \tag{19}$$

From (14), (15), (16), (17) and (19) we obtain

$$\|x^*(t_1^{\max} + 0; t_0^*, x_0^*) - x(t_1^{\max} + 0; t_0, x_0)\| < \delta_0 + 2M\delta + \frac{1}{2}\delta_1^{\min}.$$

Again, if δ and δ_0 are sufficiently small, then from the above inequality it follows the estimate

$$\|x^*(t_1^{\max} + 0; t_0^*, x_0^*) - x(t_1^{\max} + 0; t_0, x_0)\| < \delta_1^{\min}. \tag{20}$$

For $t \in \left(t_1^{\max}, t_2^{\min}\right]$ the solution of problem (1), (2), (3) does not undergo impulsive perturbation and therefore it satisfies

$$x\left(t; t_0, x_0\right) = x\left(t_1^{\max} + 0; t_0, x_0\right) + \int\limits_{t_1^{\max}}^{t} f\left(\tau, x\left(\tau; t_0, x_0\right)\right) d\tau.$$

In the similar way, for $t \in \left(t_1^{\max}, t_2^{\min}\right]$ the solution of problem (1), (2), (3) satisfies the integral equation

$$x^*\left(t; t_0^*, x_0^*\right) = x^*\left(t_1^{\max} + 0; t_0^*, x_0^*\right) + \int\limits_{t_1^{\max}}^{t} f\left(\tau, x^*\left(\tau; t_0^*, x_0^*\right)\right) d\tau.$$

Therefore,

$$\begin{aligned}
\left\|x^*\left(t; t_0^*, x_0^*\right) - x\left(t; t_0, x_0\right)\right\| \leq & \left\| x^*\left(t_1^{\max} + 0; t_0^*, x_0^*\right) + \int\limits_{t_1^{\max}}^{t} f\left(\tau, x^*\left(\tau; t_0^*, x_0^*\right)\right) d\tau \right. \\
& \left. - x\left(t_1^{\max} + 0; t_0, x_0\right) - \int\limits_{t_1^{\max}}^{t} f\left(\tau, x\left(\tau; t_0, x_0\right)\right) d\tau \right\| \\
& \leq \left\|x^*\left(t_1^{\max} + 0; t_0^*, x_0^*\right) - x\left(t_1^{\max} + 0; t_0, x_0\right)\right\| \\
& + \left\| \int\limits_{t_1^{\max}}^{t} \left(f\left(\tau, x^*\left(\tau; t_0^*, x_0^*\right)\right) - f\left(\tau, x\left(\tau; t_0, x_0\right)\right)\right) d\tau \right\| \\
& < \delta_1^{\min} + L \int\limits_{t_1^{\max}}^{t} \left\|x^*\left(\tau; t_0^*, x_0^*\right) - x\left(\tau; t_0, x_0\right)\right\| d\tau.
\end{aligned}$$

We apply Gronwall's inequality and obtain the estimate

$$\left\|x^*\left(t; t_0^*, x_0^*\right) - x\left(t; t_0, x_0\right)\right\| \leq \delta_1^{\min}\left(1 + M\right) e^{L\left(t - t_0^{\max}\right)} \leq \delta_1^{\min}\left(1 + M\right) e^{LT}, \quad t \in \left(t_1^{\max}, t_2^{\min}\right].$$

Let δ_1 be an arbitrary positive number. From above estimate it follows that if $\delta_1^{\min}$ is sufficiently small constant, i.e. if δ and δ_0 are small enough, we have

$$\left\|x^*\left(t; t_0^*, x_0^*\right) - x\left(t; t_0, x_0\right)\right\| < \delta_1, t \in \left(t_1^{\max}, t_2^{\min}\right]. \tag{21}$$

In the similar way, from (21) we derive that

$$(\forall\delta_i > 0)\,(\exists\delta > 0, \exists\delta_0 > 0, \exists\delta_1 > 0, ..., \exists\delta_{i-1} > 0) :$$
$$\|x^*(t; t_0^*, x_0^*) - x(t; t_0, x_0)\| < \delta_i, \quad t \in \left(t_i^{\max}, t_{i+1}^{\min}\right], \quad i = 0, 1, ..., k. \tag{22}$$

Let ε be an arbitrary positive number and $\delta_k = \varepsilon$. According to (22) there exist positive constants $\delta, \delta_0, ..., \delta_{k-1}$, for which is fulfilled the inequality

$$\|x^*(t; t_0^*, x_0^*) - x(t; t_0, x_0)\| < \varepsilon, \quad t \in \left(t_k^{\max}, t_{k+1}^{\min}\right]. \tag{23}$$

Without loss of generality we may assume that $\delta_{k-1} \le \varepsilon$. Again, using (22), it follows that there exist positive constants $\delta, \delta_0, ..., \delta_{k-2}$, for which the following estimate

$$\|x^*(t; t_0^*, x_0^*) - x(t; t_0, x_0)\| < \varepsilon, \quad t \in \left(t_{k-1}^{\max}, t_k^{\min}\right] \tag{24}$$

is valid. We may also impose an additional requirement $\delta_{k-2} \le \varepsilon$. Finally from (11) or equivalently from (22), it follows that if $i = 0$ then there exists a constant $\delta > 0$ such that

$$\|x^*(t; t_0^*, x_0^*) - x(t; t_0, x_0)\| < \varepsilon, \quad t \in \left(t_0^{\max}, t_1^{\min}\right]. \tag{25}$$

From (23), (24) and (25) we conclude that

$$(\forall\varepsilon > 0)\,(\exists\delta > 0) : (\|x_0^* - x_0\| < \delta, \quad |t_i^* - t_i| < \delta, \quad i = 0, 1, ...k)$$
$$\Rightarrow \|x^*(t; t_0^*, x_0^*) - x(t; t_0, x_0)\| < \varepsilon, \quad t \in \left(t_i^{\max}, t_{i+1}^{\min}\right], \quad i = 0, 1, ..., k.$$

The theorem is proved. □

Theorem 3. *Let the following conditions be satisfied:*

1. *Conditions H1–H5 and H7 hold.*
2. *The system (1) is a gravitating with constant 1.*
3. *The constant $M \le 1$.*

Then the solution of the problem with impulses (1), (2), (3) is stable with respect to the initial point (t_0, x_0) and the impulsive moments $t_1, t_2, ...$.

Proof. We assume that there exist positive constants: $\delta_x, \delta_0, \delta_1, ...$ and δ such that:

$$\|x_0^* - x_0\| < \delta_x, \quad |t_i^* - t_i| < \delta_i, \quad i = 0, 1, ..., \quad \delta_x \le \delta_0, \quad \sum_{i=0,1...} \delta_i = \delta.$$

From condition H4 we have

$$(\exists \Delta_t = \text{const.} > 0) : (\forall i = 1, 2, ...) \Rightarrow t_i - t_{i-1} > \Delta_t.$$

It follows that if δ is a small enough positive constant (for example $\delta < \Delta_t$), then the following inequalities are valid:

$$t_i^{\max} < t_{i+1}^{\min}, i = 0, 1, ...$$

Alsowehave

$$[t_0, \infty) \setminus \bigcup_{i=0,1,...} \langle t_i^*, t_i \rangle = [t_0, \infty) \setminus \bigcup_{i=0,1,...} \left(t_i^{\min}, t_i^{\max}\right] = \bigcup_{i=0,1,...} \left(t_i^{\max}, t_{i+1}^{\min}\right].$$

Similarly to (7), we get the estimate

$$\|x^* \left(t_0^{\max}; t_0^*, x_0^*\right) - x \left(t_0^{\max}; t_0, x_0\right)\| \leq \delta_x + M\delta_0 \leq (1 + M)\, \delta_0.$$

Taking into account the fact that system (1) is a gravitating with constant 1, we obtain the conclusion

$$\|x^* \left(t; t_0^*, x_0^*\right) - x \left(t; t_0, x_0\right)\| \leq (1 + M)\, \delta_0, \quad t \in \left(t_0^{\max}, t_1^{\min}\right]. \tag{26}$$

Let ε be an arbitrary positive number. From the above estimate it follows that if δ_0 is sufficiently small (respectively, if δ is small enough), it is fulfilled

$$\|x^* \left(t; t_0^*, x_0^*\right) - x \left(t; t_0, x_0\right)\| < \varepsilon, \quad t \in \left(t_0^{\max}, t_1^{\min}\right]. \tag{27}$$

We will obtain an estimate for the difference$\|x^* \left(t; t_0^*, x_0^*\right) - x \left(t; t_0, x_0\right)\|$ for $t \in \left(t_1^{\max}, t_2^{\min}\right]$.

Assume that $t_1^{\min} = t_1^*$ and $t_1^{\max} = t_1$. The case $t_1^{\min} = t_1$ and $t_1^{\max} = t_1^*$ can be considered in the similar way. Since $t_1^{\min}$ is the first impulsive moment of the problem (4), (5), (6), then we have

$$\begin{aligned} x^* \left(t_1^{\min} + 0; t_0^*, x_0^*\right) =& x^* \left(t_1^* + 0; t_0^*, x_0^*\right) = x^* \left(t_1^*; t_0^*, x_0^*\right) + I_1 \left(x^* \left(t_1^*; t_0^*, x_0^*\right)\right) \\ =& x^* \left(t_1^{\min}; t_0^*, x_0^*\right) + I_1 \left(x^* \left(t_1^{\min}; t_0^*, x_0^*\right)\right). \end{aligned}$$

For $t \in \left(t_1^{\min}, t_1^{\max}\right]$ the solution of the problem (4), (5), (6) does not undergo impulsive perturbation and it coincides with the solution of initial problem

$$\frac{dx^*}{dt} = f\left(t, x^*\right), x^*\left(t_1^{\min}\right) = x^*\left(t_1^{\min}; t_0^*, x_0^*\right) + I_1\left(x^*\left(t_1^{\min}; t_0^*, x_0^*\right)\right),$$

i.e. the following equation is satisfied

$$\begin{aligned} x^*\left(t;t_0^*,x_0^*\right) =& x^*\left(t_1^{\min};t_0^*,x_0^*\right)+I_1\left(x^*\left(t_1^{\min};t_0^*,x_0^*\right)\right) \\ &+\int\limits_{t_1^{\min}}^{t} f\left(\tau,x^*\left(\tau;t_0^*,x_0^*\right)\right)d\tau. \end{aligned}$$

If $t=t_1^{\max}$ we find

$$\begin{aligned} x^*\left(t_1^{\max};t_0^*,x_0^*\right) =& x^*\left(t_1^{\min};t_0^*,x_0^*\right)+I_1\left(x^*\left(t_1^{\min};t_0^*,x_0^*\right)\right) \\ &+\int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x^*\left(\tau;t_0^*,x_0^*\right)\right)d\tau. \end{aligned} \tag{28}$$

On the same interval $t\in\left(t_1^{\min},t_1^{\max}\right]$, the solution of the problem (1), (2), (3) coincides with the solution of the problem

$$\frac{dx}{dt}=f\left(t,x\right), x\left(t_1^{\min}\right)=x\left(t_1^{\min};t_0,x_0\right),$$

or equivalently

$$x\left(t;t_0,x_0\right)=x\left(t_1^{\min};t_0,x_0\right)+\int\limits_{t_1^{\min}}^{t} f\left(\tau,x\left(\tau;t_0,x_0\right)\right)d\tau.$$

For $t=t_1^{\max}$ we derive

$$x\left(t_1^{\max};t_0,x_0\right)=x\left(t_1^{\min};t_0,x_0\right)+\int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x\left(\tau;t_0,x_0\right)\right)d\tau.$$

Since $t_1^{\max}=t_1$, we have

$$\begin{aligned} x\left(t_1^{\max}+0;t_0,x_0\right) =& x\left(t_1^{\max};t_0,x_0\right)+I_1\left(x\left(t_1^{\max};t_0,x_0\right)\right) \\ =& x\left(t_1^{\min};t_0,x_0\right)+\int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x\left(\tau;t_0,x_0\right)\right)d\tau \\ &+I_1\left(x\left(t_1^{\min};t_0,x_0\right)+\int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x\left(\tau;t_0,x_0\right)\right)d\tau\right). \end{aligned} \tag{29}$$

Then from (28) and (29) it follows:

$$
\begin{aligned}
&\left\|x^*\left(t_1^{\max}+0;t_0^*,x_0^*\right)-x\left(t_1^{\max}+0;t_0,x_0\right)\right\| \\
&\quad=\left\|x^*\left(t_1^{\max};t_0^*,x_0^*\right)-x\left(t_1^{\max}+0;t_0,x_0\right)\right\| \\
&\quad=\Bigg\|x^*\left(t_1^{\min};t_0^*,x_0^*\right)+I_1\left(x^*\left(t_1^{\min};t_0^*,x_0^*\right)\right)+\int_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x^*\left(\tau;t_0^*,x_0^*\right)\right)d\tau \\
&\qquad-x\left(t_1^{\min};t_0,x_0\right)-\int_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x\left(\tau;t_0,x_0\right)\right)d\tau \\
&\qquad-I_1\left(x\left(t_1^{\min};t_0,x_0\right)+\int_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x\left(\tau;t_0,x_0\right)\right)d\tau\right)\Bigg\| \\
&\quad\le\left\|x^*\left(t_1^{\min};t_0^*,x_0^*\right)-x\left(t_1^{\min};t_0,x_0\right)\right\|+\left\|\int_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x^*\left(\tau;t_0^*,x_0^*\right)\right)d\tau\right\| \\
&\qquad+\left\|\int_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x\left(\tau;t_0,x_0\right)\right)d\tau\right\| \\
&\qquad+\left\|I_1\left(x^*\left(t_1^{\min};t_0^*,x_0^*\right)\right)-I_1\left(x\left(t_1^{\min};t_0,x_0\right)+\int_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x\left(\tau;t_0,x_0\right)\right)d\tau\right)\right\|.
\end{aligned}
$$

From (26), conditions H2 and H7 and using the inequality $M\le 1$, we find

$$
\begin{aligned}
&\left\|x^*\left(t_1^{\max}+0;t_0^*,x_0^*\right)-x\left(t_1^{\max}+0;t_0,x_0\right)\right\| \\
&\quad\le(1+M)\,\delta_0+2M\delta_1 \\
&\qquad+L_1\left\|x^*\left(t_1^{\min};t_0^*,x_0^*\right)-x^*\left(t_1^{\min};t_0^*,x_0^*\right)+\int_{t_1^{\min}}^{t_1^{\max}} f\left(\tau,x\left(\tau;t_0,x_0\right)\right)d\tau\right\| \\
&\quad\le(1+M)\,\delta_0+2M\delta_1+L_1\left((1+M)\,\delta_0+M\delta_1\right) \\
&\quad=(1+L_1)\,(1+M)\,\delta_0+(2+L_1)\,M\delta_1 \\
&\quad\le(1+L_1)\,(1+M)\,(\delta_0+\delta_1)\,. \qquad (30)
\end{aligned}
$$

Again, taking into account that system (1) is a gravitating, we obtain the inequality

$$\begin{aligned}\left\|x^*\left(t;t_0^*,x_0^*\right)-x\left(t;t_0,x_0\right)\right\| &\leq \left\|x^*\left(t_1^{\max}+0;t_0^*,x_0^*\right)-x\left(t_1^{\max}+0;t_0,x_0\right)\right\| \\ &\leq (1+L_1)\,(1+M)\,(\delta_0+\delta_1) \\ &\leq (1+M)\prod_{j=1,2,\ldots}(1+L_j)\sum_{j=0,1,\ldots}\delta_j \\ &\leq \delta\,(1+M)\prod_{j=1,2,\ldots}(1+L_j), t\in\left(t_1^{\max},t_2^{\min}\right]. \quad (31)\end{aligned}$$

For sufficiently small values of δ from the last inequality, we get

$$\left\|x^*\left(t;t_0^*,x_0^*\right)-x\left(t;t_0,x_0\right)\right\|<\varepsilon, t\in\left(t_1^{\max},t_2^{\min}\right]. \quad (32)$$

In the similar way for $i=2,3,\ldots$we find

$$\begin{aligned}&\left\|x^*\left(t_i^{\max}+0;t_0^*,x_0^*\right)-x\left(t_i^{\max}+0;t_0,x_0\right)\right\| \\ &\qquad\leq (1+L_1)\ldots(1+L_i)\,(1+M)\,(\delta_0+\delta_1+\ldots+\delta_i);\end{aligned}$$

$$\left\|x^*\left(t;t_0^*,x_0^*\right)-x\left(t;t_0,x_0\right)\right\|\leq\delta\,(1+M)\prod_{j=1,2,\ldots}(1+L_j),\quad t\in\left(t_i^{\max},t_{i+1}^{\min}\right];$$

$$\left\|x^*\left(t;t_0^*,x_0^*\right)-x\left(t;t_0,x_0\right)\right\|<\varepsilon,\quad t\in\left(t_i^{\max},t_{i+1}^{\min}\right].$$

From (27), (32) and last inequality it follows that for sufficiently small values of δ, the following inequality is satisfied

$$\left\|x^*\left(t;t_0^*,x_0^*\right)-x\left(t;t_0,x_0\right)\right\|<\varepsilon, t\in\bigcup_{i=0,1,\ldots}\left(t_i^{\max},t_{i+1}^{\min}\right].$$

The theorem is proved. □

Theorem 4. *Let the following conditions be satisfied:*

1. *Conditions H1–H5 and H8 hold.*
2. *The system (1) is a gravitating with a constant κ.*
3. *The inequalities $C_IM\leq 1$ and $C_I\kappa\leq 1$ are valid.*

Then the solution of the problem with impulses (1), (2), (3) is stable with respect to the initial point (t_0,x_0) and the impulsive moments $t_1,t_2,\ldots$.

Proof. Similarly to the previous theorem we obtain an estimate

$$\|x^*(t_0^{\max};t_0^*,x_0^*)-x(t_0^{\max};t_0,x_0)\|\le(1+M)\,\delta_0,$$

from where using the condition 2 of the theorem we get

$$\|x^*(t;t_0^*,x_0^*)-x(t;t_0,x_0)\|\le\kappa\,(1+M)\,\delta_0,\quad t\in\left(t_0^{\max},t_1^{\min}\right].$$

Let $t_1^{\min}=t_1$ and $t_1^{\max}=t_1^*$ are valid. Then

$$\begin{aligned}x\left(t_1^{\min}+0;t_0,x_0\right)=&x(t_1+0;t_0,x_0)=x(t_1;t_0,x_0)+I_1(x(t_1;t_0,x_0))\\=&x\left(t_1^{\min};t_0,x_0\right)+I_1\left(x\left(t_1^{\min};t_0,x_0\right)\right).\end{aligned}$$

Similarly to (28) we have

$$\begin{aligned}x(t_1^{\max}+0;t_0,x_0)=&x(t_1^{\max};t_0,x_0)\\=&x\left(t_1^{\min};t_0,x_0\right)+I_1\left(x\left(t_1^{\min};t_0,x_0\right)\right)\\&+\int\limits_{t_1^{\min}}^{t_1^{\max}}f(\tau,x(\tau;t_0,x_0))d\tau.\end{aligned}$$

Analogously to (29) we find

$$x^*(t_1^{\max};t_0^*,x_0^*)=x^*\left(t_1^{\min};t_0^*,x_0^*\right)+\int\limits_{t_1^{\min}}^{t_1^{\max}}f(\tau,x^*(\tau;t_0^*,x_0^*))d\tau.$$

Since $t_1^{\max}=t_1^*$, then it follows from the above equality

$$\begin{aligned}x^*(t_1^{\max}+0;t_0^*,x_0^*)=&x^*(t_1^{\max};t_0^*,x_0^*)+I_1(x^*(t_1^{\max};t_0^*,x_0^*))\\=&x^*\left(t_1^{\min};t_0^*,x_0^*\right)+\int\limits_{t_1^{\min}}^{t_1^{\max}}f(\tau,x^*(\tau;t_0^*,x_0^*))d\tau\\&+I_1\left(x^*\left(t_1^{\min};t_0^*,x_0^*\right)+\int\limits_{t_1^{\min}}^{t_1^{\max}}f(\tau,x^*(\tau;t_0^*,x_0^*))d\tau\right).\end{aligned}$$

Then

$$\|x^*(t_1^{\max}+0;t_0^*,x_0^*)-x(t_1^{\max}+0;t_0,x_0)\|$$

$$
\begin{aligned}
&= \Bigg\| x^*\left(t_1^{\min}; t_0^*, x_0^*\right) + \int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau, x^*\left(\tau; t_0^*, x_0^*\right)\right) d\tau \\
&\quad + I_1\left(x^*\left(t_1^{\min}; t_0^*, x_0^*\right) + \int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau, x^*\left(\tau; t_0^*, x_0^*\right)\right) d\tau \right) \\
&\quad - x\left(t_1^{\min}; t_0, x_0\right) - I_1\left(x\left(t_1^{\min}; t_0, x_0\right)\right) - \int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau, x\left(\tau; t_0, x_0\right)\right) d\tau \Bigg\| \\
&\le \Bigg\| \Bigg[x^*\left(t_1^{\min}; t_0^*, x_0^*\right) + \int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau, x^*\left(\tau; t_0^*, x_0^*\right)\right) d\tau \\
&\quad + I_1\left(x^*\left(t_1^{\min}; t_0^*, x_0^*\right) + \int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau, x^*\left(\tau; t_0^*, x_0^*\right)\right) d\tau \right) \Bigg] \\
&\quad - \left[x\left(t_1^{\min}; t_0, x_0\right) + I_1\left(x\left(t_1^{\min}; t_0, x_0\right)\right) \right] \Bigg\| \\
&\quad + \left\| \int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau, x\left(\tau; t_0, x_0\right)\right) d\tau \right\| \\
&\le C_I \left\| x^*\left(t_1^{\min}; t_0^*, x_0^*\right) + \int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau, x^*\left(\tau; t_0^*, x_0^*\right)\right) d\tau - x\left(t_1^{\min}; t_0, x_0\right) \right\| + M\delta_1 \\
&\le C_I \left\| x^*\left(t_1^{\min}; t_0^*, x_0^*\right) - x\left(t_1^{\min}; t_0, x_0\right) \right\| + C_I \left\| \int\limits_{t_1^{\min}}^{t_1^{\max}} f\left(\tau, x^*\left(\tau; t_0^*, x_0^*\right)\right) d\tau \right\| + M\delta_1 \\
&\le C_I \kappa \left(1 + M\right) \delta_0 + C_I M \delta_1 + M\delta_1 \\
&\le \left(1 + M\right)\left(\delta_0 + \delta_1\right).
\end{aligned}
$$

Again, taking into account that system (1) is a gravitating, we obtain the inequality

$$
\begin{aligned}
\left\| x^*\left(t; t_0^*, x_0^*\right) - x\left(t; t_0, x_0\right) \right\| &\le \left\| x^*\left(t_1^{\max} + 0; t_0^*, x_0^*\right) - x\left(t_1^{\max} + 0; t_0, x_0\right) \right\| \\
&\le \kappa \left(1 + M\right)\left(\delta_0 + \delta_1\right)
\end{aligned}
$$

$$\leq \kappa (1+M) \sum_{j=0,1,...} \delta_j$$
$$< \kappa (1+M) \delta, t \in \left(t_1^{\max}, t_2^{\min}\right].$$

For sufficiently small values of δ from the last inequality, we get

$$\left\| x^* \left(t; t_0^*, x_0^*\right) - x\left(t; t_0, x_0\right) \right\| < \varepsilon, \quad t \in \left(t_1^{\max}, t_2^{\min}\right].$$

In the similar way for $i = 2, 3, ...$we find

$$\left\| x^* \left(t_i^{\max} + 0; t_0^*, x_0^*\right) - x\left(t_i^{\max} + 0; t_0, x_0\right) \right\| \leq (1+M)\left(\delta_0 + \delta_1 + ... + \delta_i\right);$$

$$\left\| x^* \left(t; t_0^*, x_0^*\right) - x\left(t; t_0, x_0\right) \right\| \leq \kappa (1+M)\left(\delta_0 + \delta_1 + ... + \delta_i\right) < \kappa (1+M)\delta,$$
$$t \in \left(t_i^{\max}, t_{i+1}^{\min}\right];$$

$$\left\| x^* \left(t; t_0^*, x_0^*\right) - x\left(t; t_0, x_0\right) \right\| < \varepsilon, \quad t \in \left(t_i^{\max}, t_{i+1}^{\min}\right].$$

It follows that for sufficiently small values of δ the following inequality is satisfied

$$\left\| x^* \left(t; t_0^*, x_0^*\right) - x\left(t; t_0, x_0\right) \right\| < \varepsilon, \quad t \in \bigcup_{i=0,1,...} \left(t_i^{\max}, t_{i+1}^{\min}\right].$$

The theorem is proved.

5. Application of the Main Results

In general, the treatment of many medical conditions is achieved by maintaining a therapeutic drug concentration in the blood (plasma) of the patient. This concentration can be achieved in two ways:

- By continuous administration of the drug;
- By intermittent (impulsive) administration of the drug at certain time intervals.

From the pharmacokinetic point of view the first model is preferable. Unfortunately this method of treatment is difficult in its practical realization. More precisely, in the common case, it is impossible for one patient to take continuously one or more drugs during the treatment period (this period may have lasting several weeks or months). Therefore, the maintenance of therapeutic drug concentration in the blood via discrete impulsive applications of the drug is more common. It is natural to assume that the amount of drug is bounded from below, i.e., there exists a minimum quantity of drug that could be taken as a single dose at once. By using this type of treatment, a physician can manipulate two pharmacokinetic parameters: the size of single dose of drug D_i and the length of dosing interval T_{i+1}, $i = 1, 2, ...$ More precisely, D_i is the dose of i^{-th} application of drug, and T_{i+1} is the time between moment of i^{-th} and $(i+1)^{-th}$ application of the drug $i = 1, 2, ...$ In the cases when the dosing intervals are shorter than required time for complete elimination of the drug in the body, the drug begins to cumulate. This cumulating is useful for the treatment of the patient, if it is kept in intervals determined by the minimum and maximum plasma levels, called therapeutic range (therapeutic window) of the drug concentration. Pharmacokinetic model for the therapeutic treatment consist in appropriate choice of dose scheme of treatment which guarantees the maintenance of drug concentration within the therapeutic window.

We introduce the following restrictions and notations:

1. The body is presented as a compartment with volume V_d in which the active drug is distributed. It is possible the concentration of the drug to vary in different parts of the body. We assume constant ratio between the levels of the drug in any part of the body during treatment period. This means that any change of the drug concentration in plasma reflects in a strictly defined relevant quantitative change of the drug concentration in tissue;

2. Initial moment of the treatment is denoted with t_0;

3. The duration between the initial moment of medication t_0 and first moment t_1 in which drug with volume D_1 is imported into the body, is denoted by T_1, i.e. it is satisfied $t_1 = t_0 + T_1$;

4. Dose D_i of the medicinal product is imported directly into a compartment at the moment $t_i = t_{i-1} + T_i = t_0 + \sum_{j=1,2,...,i} T_j$, $i = 1, 2, ...$;

5. Elimination of the drug is implemented with a speed proportional to its current amount in the body, i.e. it is considered as a process of first order which is characterized by a speed constant K. The latter constant is the sum of the constant of metabolism and the constant of extraction of the unchanged drug K_e. It is satisfied: $K = K_m + K_e$;

6. Denote by $A(t)$ the quantity of the drug in the body at the moment $t \geq t_0$. In general, the quantity of this substance, located in the body of the patient at any time, cannot be determined experimentally. Actually the concentration of medication in some biological fluids (mostly blood) is possible to be determined. For mathematical modeling of the treatment process it is

convenient to introduce the volume in which the drug is distributed. This value is called the volume of distribution and it is denoted by V_d. It is defined so that the following equality

$$C(t) = \frac{A(t)}{V_d}, \quad t \geq t_0$$

is satisfied, where $C(t)$ is concentration of the drug measured in the blood or more generally in the plasma. We note that the volume of the distribution does not have a physiological sense. We could consider that as a fictitious volume and if a drug of quantity $A(t)$ is distributed evenly, the concentration in it will be in concentration $C(t)$ measured in the plasma. In fact, a part of the drug is connected with the plasma proteins and with the tissue proteins, so that its distribution is not uniformly. Therefore, the volume of the distribution is possible to be different from the volume of the body's fluids;

7. In the initial moment t_0 we assume that the drug concentration is C_0. In some cases it is assumed that $C_0 = 0$.

Idealized mathematical model of the above process is described in [20] by using the following initial value problem for impulsive differential equation:

$$\frac{dC}{dt} = -KC, \qquad t \neq t_i, \tag{7}$$

$$C(t_i + 0) = C(t_i) + \frac{D_i}{V_d}, \quad i = 1, 2, ..., \tag{8}$$

$$C(t_0) = C_0. \tag{9}$$

The solution of the previous initial problem can be obtained easily:

— For $t_0 \leq t \leq t_1$ it is satisfied

$$C(t) = C_0 \exp(-K(t - t_0));$$

— For $t_1 < t \leq t_2$ we get

$$\begin{aligned} C(t) = & \left(C_0 \exp(-K(t_1 - t_0)) + \frac{D_1}{V_d} \right) . \exp(-K(t - t_1)) \\ = & C_0 \exp(-K(t - t_0)) + \frac{D_1}{V_d} \exp(-K(t - t_1)); \end{aligned}$$

— For $t_i < t \leq t_{i+1}$, $i = 2, 3, ...$, the following equality

$$\begin{aligned} C(t) = & C_0 \exp(-K(t - t_0)) + \frac{D_1}{V_d} \exp(-K(t - t_1)) \\ & + \frac{D_2}{V_d} \exp(-K(t - t_2)) + ... + \frac{D_i}{V_d} \exp(-K(t - t_i)), \end{aligned}$$

is valid, i.e.

$$C(t) = \frac{\exp(-Kt)}{V_d} \sum_{j=0,1,\ldots,i} D_j \exp(Kt_j) = C_i \exp(-Kt),$$

where

$$C_i = \frac{1}{V_d} \sum_{j=0,1,\ldots,i} D_j \exp(Kt_j) \quad \text{and} \quad D_0 = C_0 V_d.$$

Different aspects in the qualitative theory of impulsive models in pharmacokinetics are considered in [10] and [14].

We apply the obtained basic result to the model (33), (34), (35). We denote $f(t, C) = f(C) = -KC$ and $I_i(x) = \frac{D_i}{V_d}$. In addition we assume that the dose intervals T_i are bounded from below, i.e. there exists a positive constant Δ_t such that $t_{i+1} - t_i = T_{i+1} \geq \Delta_t, i = 0, 1, ...$ This means that $\lim_{i \to \infty} t_i = \infty$ and therefore the condition H4 holds. The conditions H1, H3, H5, H6 and H7 (with constants $L_i = 0, i = 1, 2, ...$) can be easily verified. It is natural to assume that concentration of the drug is bounded above, i.e., the variable $C = C(t)$ is bounded. Since the solution is a positive piecewise monotonous decreasing function, then the constant $C_{\max} = C_0 + \frac{1}{V_d} \sum_{t_i \leq T} D_i$ is one upper limit for $C = C(t), t_0 \leq t \leq T$. In other words, we have $0 \leq C \leq C_{\max}$ for $t_0 \leq t \leq T$. Then we get

$$\|f(t, C)\| = |f(C)| = |-KC| \leq KC_{\max} = M, \tag{36}$$

so the condition H2 is also valid. This means that the conditions of Theorem 2 are fulfilled and therefore the solution of problem (33), (34), (35) depends continuously on the initial point and the impulsive moments. This fact has the following interpretation:

The concentrations of pharmaceuticals in the patient's body in two different schemes of treatment are approximately equal if the following conditions are fulfilled:

- The schemes of treatment are applied to the one and same patient;
- Manipulation period (the period during which the drugs are taken) is limited;
- The concentrations of drugs in the initial moment of both schemes of treatment are negligibly different;

- The initial moments of both treatment schemes approximately coincide;
- For both schemes of treatment dosages for each discrete drug's intake are equal;
- Dosing intervals (the intervals between two consecutive moments of drug's intake) are bounded from below;
- The moments of drug's intake approximately coincide in both schemes of treatment.

We determine that equation (33) is a gravitating with constant 1 by means of remark 1. In addition, if we find out that the solution $C = C(t)$ is bounded from above by a constant $\frac{1}{K}$, then from (36) it follows that $M \leq 1$ and therefore the solution of the problem (33), (34), (35) is stable on the initial data and impulsive moments. The interpretation of this fact is similar to the described one with the difference that the manipulation period is not bounded.

It is easy to check that the estimate $C \leq \frac{1}{K}$ is valid if the following inequalities are fulfilled:

$$C_0 \leq \frac{1}{K}, \quad \exp(-KT_i) + \frac{KD_i}{V_d} \leq 1, \quad i = 1, 2, \dots .$$

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