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SIMULATION RESULTS ON THE ASYMPTOTIC PERIODICITY OF COMPARTMENTAL SYSTEMS WITH LAGS*

ROLAND TÓTH†

Abstract. In this paper, we study the asymptotic behavior of solutions for a pharmacokinetic application, where the drug level is controlled between two boundary levels by repeated impulsive doses.

Key Words. asymptotic periodicity, impulsive state-dependent input, compartment, numerical simulation, estimation of the periodic solution

AMS(MOS) subject classification. 34K25, 34K28, 34K13

1. Introduction. More than fifty years ago, compartmental systems were originally introduced as the dynamic models of biological systems [1],[6]. Since then, this type of modeling have become an essential theory for medical sciences, because with it, the qualitative analysis of drugs in living organisms can be implemented. In many pharmacokinetic applications the biological systems are described by models consisting of three or two compartments, but in case of a very simplified system, the whole behavior can be described by one compartment. Although, one compartment seems to be a very sketchy representation of the original system, the presence of an inner delayed feedback in the model can make this level of resolution useful [2]. For a dosage model, impulsive input is very common, by which we would like to control the drug level, or the state of the system between an efficiency drug level c and an overdose level $a + c$. By considering this, a basic drug dosage model

* Many thanks to Prof. István Győri for being the supervisor of this work.
† University of Veszprém, H-8201 Veszprém, P. O. Box 158, Hungary, email: tothrola@vnet.hu

has the following form:

$$
\begin{array}{llll}
(1) & \dot{x}(t) & = & -\alpha x(t) + \beta x(t-\tau) \quad t > \sigma, \\
& x(t) & = & \varphi(t-\sigma), \quad \text{if } \sigma - \tau \le t \le \sigma, \\
& \varphi(0) & > & c, \quad \text{and if } x(t-) = c \text{ then } x(t+) = a + c, \text{ when } t \ge \sigma,
\end{array}
$$

where $\alpha, \beta, \tau \in \mathbb{R}_0^+$, the starting time is denoted by $\sigma \in \mathbb{R}_0^+$, $\varphi : [-\tau, 0] \to \mathbb{R}_0^+$ is integrable, and $\mathbb{R}_0^+ = [0, \infty)$. Because of the strong dissipativity of the original system, we assume $\alpha > \beta$. In this short note, our main goal is to verify and also to extend a conjecture (see [3]) on the asymptotic periodicity of the solutions of problem (1). We also give a brief explanation of the numerical methods which have been used to develop our computer programs.

2. Asymptotic periodicity of solutions. The fundamental solution $v : [-\tau, \infty) \to \mathbb{R}_0^+$ of (1) is defined as follows:

$$
\begin{array}{lll}
\dot{v}(t) & = & -\alpha v(t) + \beta v(t-\tau), \quad t > 0, \\
v(t) & = & \begin{cases} 1, & t = 0, \\ 0, & -\tau \le t < 0, \end{cases}
\end{array} \tag{2}
$$

where $v(t)$ exists, is unique on $[-\tau, \infty)$, and continuous on $[0, \infty)$. Because $\alpha > \beta$, it follows $\lim_{t\to\infty} v(t) = 0$, and the zero solution is asymptotically stable (see [3]). Moreover, we show

PROPOSITION 1. *Let v be the fundamental solution of (1), and assume $\alpha > \beta$. Then*

$$
e^{-\alpha t} \le v(t) \le e^{-\lambda_0 t}, \qquad t \ge 0, \tag{3}
$$

where λ_0 is the positive root of $\lambda_0 = \alpha - \beta e^{\lambda_0 \tau}$.

Proof. Clearly, such unique $\lambda_0 > 0$ exists. Equation (2) and the positivity of β and $v(t)$ yield $\dot{v}(t) \ge -\alpha v(t)$. Therefore

$$
\log(v(t)) - \log(v(0)) = \int_0^t \frac{\dot{v}(s)}{v(s)} ds \ge \int_0^t -\alpha ds = -\alpha t,
$$

which clearly leads to $v(t) \ge e^{-\alpha t}$. To get the upper estimation of $v(t)$ we introduce the function $w(t) = v(t)e^{\lambda_0 t}$, and consider

$$
\begin{aligned}
\dot{w}(t) &= \lambda_0 v(t) e^{\lambda_0 t} + e^{\lambda_0 t}(-\alpha v(t) + \beta v(t-\tau)) \\
&= (\lambda_0 - \alpha) w(t) + \beta e^{\lambda_0 \tau} w(t-\tau) \\
&= -\beta e^{\lambda_0 \tau}(w(t) - w(t-\tau)), \qquad t \ge 0.
\end{aligned}
$$

Therefore

$$\frac{d}{dt}\Big(w(t) + \beta e^{\lambda_0 \tau} \int_{t-\tau}^{t} w(s)\,ds\Big) = 0, \qquad t \geq 0,$$

and thus, using the initial condition of v, we get

$$w(t) = 1 - \beta e^{\lambda_0 \tau} \int_{t-\tau}^{t} w(s)\,ds, \qquad t \geq 0.$$

This concludes the proof, since $w(t) > 0$ for $t \geq 0$ implies $w(t) \leq 1$, $t \geq 0$. □

The exact solution of problem (1) has been constructed in [3]:

THEOREM 1. *There exist a sequence of constants $\{t_k\}$, $\sigma = t_0 < \ldots < t_k < \ldots$ called injection times, such that the original boundary value problem (1) has a unique solution $x(t) = x(\sigma, \varphi, \alpha, \beta, \tau, a, c)(t)$ which can be written into the following form:*

$$x(t) = v(t-\sigma)\varphi(0) + \beta \int_{-\tau}^{0} v(t-\sigma-s-\tau)\varphi(s)ds + a \sum_{i=1}^{\infty} v(t-t_i), \tag{4}$$

where $t \geq \sigma$, $t \notin \{t_k\}_{k \geq 1}$.

To show the asymptotic periodicity of solutions we consider a special, related problem:

$$\begin{aligned} \dot{y}(t) &= -\alpha x(t) + \beta y(t-\tau), \quad t > \sigma, \\ y(t) &= \varphi(t-\sigma), \quad \text{if } \sigma - \tau \leq t \leq \sigma, \\ y(\sigma + iT+) &= y(\sigma + iT-) + a, \quad i = 0, 1, 2, \ldots, \end{aligned} \tag{5}$$

where $T, \alpha, \beta, \tau, \sigma \in \mathbb{R}_0^+$ and $\alpha > \beta$. This related problem is very similar to (1) except of that the input of this model is a T periodic constant impulsive input sequence. For (5) the unique solution is (see [4]):

$$y(\sigma, \varphi, \alpha, \beta, \tau, a)(t) = y(\sigma, \varphi, \alpha, \beta, \tau, 0)(t) + a \sum_{i=0}^{[t/T]} v(t-\sigma-iT), t \geq \sigma, \tag{6}$$

where [.] is the greatest integer part function. Based on [4], we know that:

$$\lim_{t\to\infty} |y(\sigma, \varphi, \alpha, \beta, \tau, a)(t) - aW_{\sigma,T}(t)| = 0, \tag{7}$$

where $W_{\sigma,T}(t) = \sum_{i=0}^{\infty} v(t - \sigma - [t/T] + iT)$ is a T periodic, piecewise continuous function and

$$W_{\sigma,T}(T+) = \sum_{i=0}^{\infty} v(iT) = 1 + W_{\sigma,T}(T-) = (a+c)/a.$$

Relation (7) motivated the following conjecture in [3] for problem (1).

CONJECTURE 1. *(see [3]) For (1) if* $\lim_{t\to\infty} |t_{k+1} - t_k| = T$, *then there exists a* $\kappa \in \mathbb{R}$ *such that* $\lim_{t\to\infty} |x(\sigma, \varphi, \alpha, \beta, \tau, a, c)(t) - aW_{\kappa,T}(t)| = 0$ *holds.*

If this result is true, then asymptotic periodicity exists in (1). Our numerical experiments suggest the following extension of the above conjecture:

CONJECTURE 2. *For (1) there exists constants* $l \in \mathbb{N}$ *and* $\kappa \in \mathbb{R}$ *such that* $\lim_{t\to\infty} |t_{k+l} - t_k| = T$, *and* $\lim_{t\to\infty} |x(\sigma, \varphi, \alpha, \beta, \tau, a, c)(t) - aW_{\kappa,T}(t)| = 0$.

In addition to numerically verifying Conjecture 2, one of our main goal is to give an approximation on the fundamental time period T of the limiting periodic function $aW_{\kappa,T}$. These questions are important in constructing optimalized drug dosing strategies.

We can derive form (3)

$$\sum_{i=1}^{\infty} e^{-\alpha i T} \leq \sum_{i=1}^{\infty} v(iT) \leq \sum_{i=1}^{\infty} e^{-\lambda_0 i T}.$$

Using relation $W_{\sigma,T}(T+) - 1 = \sum_{i=1}^{\infty} v(iT) = c/a$ we get

$$\frac{e^{-\alpha T}}{1 - e^{-\alpha T}} \leq \frac{c}{a} \leq \frac{e^{-\lambda_0 T}}{1 - e^{-\lambda_0 T}}, \tag{8}$$

since $e^{-\alpha T}, e^{-\lambda_0 T} < 1$ by the positivity of α and λ_0. From (8) simple calculation implies

$$\frac{1}{\alpha} \ln \frac{c+a}{c} \leq T \leq \frac{1}{\lambda_0} \ln \frac{c+a}{c}. \tag{9}$$

The efficiency of estimation (9) will be investigated in the next section (see Fig. 7–10).

3. Numerical simulations. To investigate the problem numerically, we developed a software package in Matlab. We used a version of the explicit Euler method and the chain method, described in the next section, in our simulations. In all of our experiments we found that always exists an l, such that $\lim_{t\to\infty} |t_{k+l} - t_k| = T$, showing that with this input strategy, periodicity always reachable. Based on these investigations, we classified the solutions by speed of convergence and by order of periodicity:

Quickly convergent, $l = 1$ solutions: These solutions (Fig. 1) have a short transient and their limiting periodic function has an exponential decay. In this case $l = 1$, thus the difference between the consecutive injection points tends to a constant value (Fig. 2), which equals to the time period T of the limiting solution, as stated in Conjecture 1.

Slowly convergent, $l = 1$ solutions: These solutions (Fig. 3) have a much longer transient and their periodic function is the multiplication of a exponential function and a polynomial. We analytically computed these polynomials in several cases. For these systems, the relative value of α and β is much closer to each other than for quickly convergent systems. As in the previous case, Conjecture 1 holds (see Fig. 4).

Solutions with $l > 1$: As the relative value of α and β gets close enough to each other and the time delay is larger than an unknown value related to a, then $|t_{k+1} - t_k|$ will be asymptotically periodic, but not convergent (see Fig. 5), and, at the same time, the solution is also asymptotically periodic, and Conjecture 2 holds. In this case during an interval with length T there will be more than one injection points.

In Fig. 7-10 we investigate the effect of the parameters on the values of T on examples, where all parameters except one are fixed. We found that the time delay has no effect on the value of T. We observed that for small a or distant α and β, the lower and upper estimations given by (9) are efficient but if a increases and α, β get closer to each other, our knowledge about the true behavior of the system fades away. On Fig. 6 the efficiency of our estimation is presented when $l = 6$. We found numerically that our estimation (9) is also valid in the case, when we replace T in (9) by $|t_{k+1} - t_k|$ (see Fig. 6, where we plotted out the upper and lower estimates in (9) together with T and $|t_{k+1} - t_k|$).

4. Estimation of the periodic solution. In the following, we present a numerical method in case of $l = 1$, to approximate the periodic function W. With this method, we would like to give an easy way to describe the behaviour of (1) after a large number of inputs. To do this, we will use the chain method from [5]. By this method, any channel with time delay is substituted by the series connection of infinite number of compartments with no time lags. If we use only finite number $(r - 1) \in N$ of substituting compartments, then our system is approximated with a first order ODE system:

$$\dot{\tilde{\mathbf{x}}} = \mathbf{A}\tilde{\mathbf{x}}(t) + \mathbf{b}u(t), \tag{10}$$

$$\mathbf{A} = \begin{pmatrix} -\alpha & 0 & \cdots & 0 & r/\tau \\ \beta & -r/\tau & 0 & \cdots & 0 \\ 0 & r/\tau & -r/\tau & 0 & 0 \\ \vdots & \ddots & \ddots & \ddots & \ddots \\ 0 & \cdots & 0 & r/\tau & -r/\tau \end{pmatrix}_{r\times r}, \tilde{\mathbf{x}}(\sigma) = \begin{pmatrix} \varphi(\sigma) \\ \int_0^{-\tau/r} \varphi(s)ds \\ \vdots \\ \int_{-\tau}^{-(r-1)\tau/r} \varphi(s)ds \end{pmatrix}_{r\times 1}$$

and $\mathbf{b} = \begin{pmatrix} a, & 0, & \cdots, & 0 \end{pmatrix}^T_{1\times r}$, $u(t) = \sum_{k=1}^{\infty} \delta(t-t_k)$, where t_k denotes the injection points and δ is the Dirac-delta function. By solving (10), the estimation of the unique solution of (1) can be obtained between each injection points:

$$\text{(11)} \quad \tilde{\mathbf{x}}(\alpha,\beta,\tau,a,c)(t,r) = e^{\mathbf{A}(t-\sigma)}\tilde{\mathbf{x}}(\sigma) + \sum_{i=0}^{n-1} \int_{t_i}^{t} e^{\mathbf{A}(t-s-t_i)}\mathbf{q}(s-t_i)ds,$$

where $\mathbf{q}(s) = \begin{pmatrix} a\delta(s), & 0, & \cdots, & 0 \end{pmatrix}^T_{1\times r}$ and $t \in [\sigma, t_n)$. After large number of inputs the solution of (11) gets close enough to its periodic state, which can be described by its fundamental time period $\tilde{T}$, and initial values $z_1, \ldots, z_{r-1} \in \mathbb{R}_0^+$ of the substituting compartments at the beginning of the period. These parameters can be obtained by solving

$$\text{(12)} \qquad \mathbf{z}_0 = e^{\mathbf{A}\tilde{T}}\mathbf{z}_1,$$

where $\mathbf{z}_0 = \begin{pmatrix} c, & z_1, & \cdots, & z_{r-1} \end{pmatrix}^T$ and $\mathbf{z}_1 = \begin{pmatrix} a+c, & z_1, & \cdots, & z_{r-1} \end{pmatrix}^T$. If we assumes that $\tilde{T} = T$, then from these parameters, the estimated periodic solution of (1) can be constructed, which one period is as follows:

$$\text{(13)} \qquad \tilde{\mathbf{x}}(\alpha,\beta,\tau,a,c)(t,r) = e^{\mathbf{A}t}\mathbf{z}_1, \quad t \in (0+, T-).$$

Conjecture 3. *There exists a $\kappa \in \mathbb{R}$ such that the unique solution of (1) satisfies:*

$$\text{(14)} \qquad \lim_{t,r\to\infty} |x(\sigma,\varphi,\alpha,\beta,\tau,a,c)(t) - \mathbf{p}\tilde{\mathbf{x}}(\alpha,\beta,\tau,a,c)(t-\kappa,r)| = 0,$$

where $\mathbf{p} = \begin{pmatrix} 1, & 0, & \cdots, & 0 \end{pmatrix}$.

In Fig. 11 an example is given which affirms that Conjecture 3 is valid. By analyzing Fig. 12, it can be concluded that the estimated solution is a bit faster due to the finite resolution, but in between consecutive injection points the difference of the two solutions is relatively small.

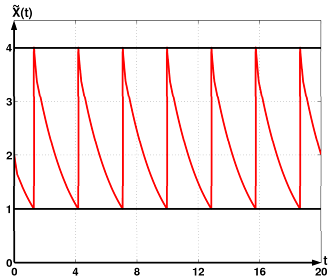

Fig. 1: $x(0, 2, 1, 0.5, 0.2, 1, 3)(t)$

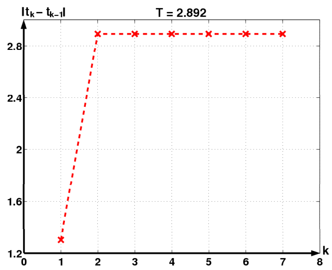

Fig. 2: $|t_{k+1} - t_k|$ for $x(0, 2, 1, 0.5, 0.2, 1, 3)(t)$

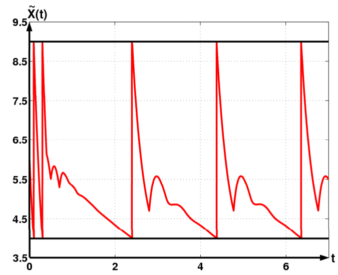

Fig. 3: $x(0, 6, 4, 3.5, 0.4, 4, 5)(t)$

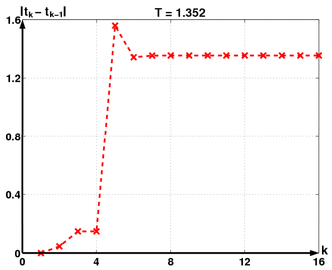

Fig. 4: $|t_{k+1} - t_k|$ for $x(0, 6, 4, 3.5, 0.4, 4, 5)(t)$

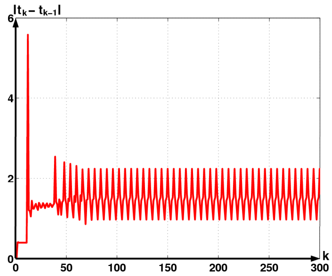

Fig. 5: $|t_{k+1} - t_k|$ for $x(0, 14, 3, 2.75, 4, 9, 5)(t)$

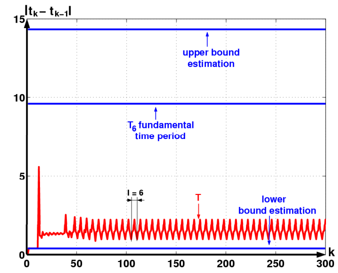

Fig. 6: Estimations for $T_{l=6}$, $x(0, 14, 3, 2.75, 4, 9, 5)(t)$

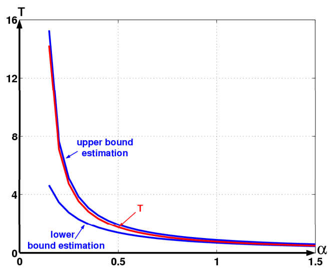

Fig. 7: Effect of α on T for $x(0, 1, \alpha, 0.1, 1, 1, 1)(t)$

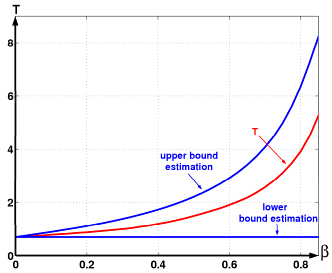

Fig. 8: Effect of β on T for $x(0, 1, 1, \beta, 1, 1, 1)(t)$

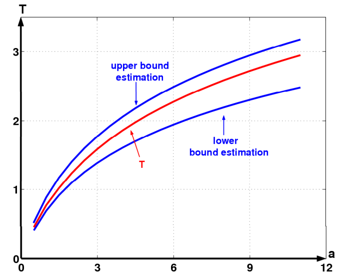

Fig. 9: Effect of a on T for $x(0, 1, 1, 0.1, 1, 1, a)(t)$

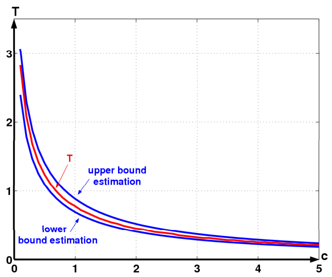

Fig. 10: Effect of c on T for $x(0, 1, 1, 0.1, 1, c, 1)(t)$

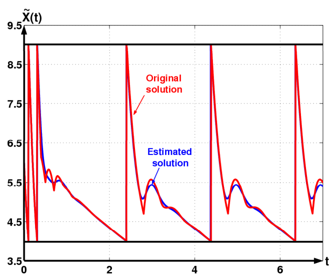

Fig. 11: $x(t)$ and $\tilde{x}(t, 25)$, $x(0, 14, 3, 2.75, 4, 9, 5)(t)$

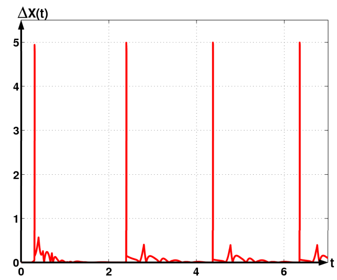

Fig. 12: $|x(t) - \tilde{x}(t, 25)|$, $x(0, 14, 3, 2.75, 4, 9, 5)(t)$

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