Applied Mathematics Letters 24 (2011) 982–986

Contents lists available at ScienceDirect

Applied Mathematics Letters

journal homepage: www.elsevier.com/locate/aml

Negativity of delayed induced oscillations in a simple linear DDE

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ARTICLE INFO

Article history:
Received 27 July 2009
Received in revised form 11 August 2010
Accepted 12 January 2011

Keywords:
Delay differential equations
Asymptotic analysis
Hopf bifurcation
Negativity of solutions
Biochemical reactions
Genetic regulatory network

ABSTRACT

In this work we study oscillations appearing in the simple linear delayed differential equation (DDE) of the form $\dot{x} = A - Bx(t) - Cx(t - \tau)$ with $B < C$ in the case of τ larger than the critical value τ_{cr} for which Hopf bifurcation occurs. We study the Cauchy problem proposed by Bratsun et al. (PNAS 102 (41) (2005)) as a description of some channel of biochemical reactions, that is we assume that $x(t) = 0$ for $t < 0$ and $x(0) = x^0 \geq 0$. We prove that for any $B < C$ and $\tau \geq \tau_{cr}$ there exists a t in the interval $(0, 4\tau)$ for which x loses positivity. We conclude that the proposed Cauchy problem is not a proper description of biochemical reactions or of other biological and physical quantities.

We also consider another Cauchy problem with constant positive initial data. There exists a large set of initial data for which the solution to such a problem becomes negative. Therefore, this Cauchy problem is not a proper description of biological or physical quantities.

1. Introduction

It is well known (compare e.g. [1] and references therein) that genetic regulatory networks can be modelled well using systems of ordinary differential equations (ODEs) that give good insight into intracellular mechanisms. Unfortunately, most biological processes inside a cell are very complicated and systems of ODEs that would take into account all the variables involved in those processes can be solved only numerically and in many cases their qualitative analysis is almost impossible.

Recently, to reduce the complexity of such regulatory networks or to include the fact that some reactions can take some time, delayed differential equations (DDEs) were introduced in the modelling of the networks, compare [2–4]. More precisely, in [3,4] it is assumed that the complicated pathway of protein transcription and translation can be reduced to one single process that takes some time. It is well known that even the simplest model with delay can yield interesting qualitative results, e.g. periodic oscillations (see e.g. [5] or [6]). Despite the question concerning the biological validity of that type of reduction, there appears the question of the form of the initial data. Most processes occurring in a cell are triggered if there is a demand for their results. Therefore, it seems natural to assume that initial data are expressed as a solution to ODEs describing that part of the pathway in which delayed reaction does not occur. This is equivalent to setting the noncontinuous initial data to the form

$$\mathbf{x}(t) = 0 \quad \text{for } t < 0 \quad \text{and} \quad \mathbf{x}(0) = \mathbf{x}^0 \geq 0 \tag{1}$$

where $\mathbf{x}(t)$ denotes the vector of densities of molecules taking part in reactions and $\mathbf{x}^0$ is the vector of initial densities of molecules present in the system.

In this work we study the deterministic description of the reaction channel proposed in [2] that reads

$$\emptyset \xrightarrow{A} P, \qquad P \xrightarrow{B} \emptyset, \qquad P \overset{C}{\Rightarrow} \emptyset, \tag{2}$$

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doi:10.1016/j.aml.2011.01.010

where A and B denote the rates (propensities) of non-delayed protein production and degradation, and C represents the rate at which delayed degradation of protein is initiated. Delayed reaction (indicated by the wide arrow) represents the initiation of the degradation machine, which eventually degrades the protein after time τ from the initiation (for more details see [2]). The linear DDE of the form

$$\dot{x} = A - Bx(t) - Cx(t-\tau) \tag{3}$$

was proposed in [2] as the deterministic description of the reaction channel (2). In this work we prove that periodic oscillations that occur for $B < C$ when delay exceeds the critical value $\tau_{cr} = \frac{\arccos(-B/C)}{\sqrt{C^2-B^2}}$ always lose positivity for the Cauchy problem described by (3), (1). Moreover, we show that there is a large set of other kinds of initial data for which solutions to Eq. (3) lose stability. Therefore, this equation seems not to be a proper description of oscillations appearing in biological, chemical or physical problems.

2. The equation $\dot{x} = A - Bx(t) - Cx(t-\tau)$ as a description of biochemical reactions

In this section we study the solutions to linear DDE (3) with initial data of the form (1). General properties of solutions to Eq. (3) are well known and described in many articles and textbooks; compare e.g. [5–8] and references therein. The main property of solutions for $B < C$ is stability of the steady state $\bar{x} = \frac{A}{B+C}$ for $\tau < \tau_{cr}$ and the occurrence of Hopf bifurcation at $\tau = \tau_{cr}$ which leads to the periodic behaviour of solutions for $\tau \geq \tau_{cr}$. It is also obvious that solutions to this equation can lose positivity (compare [9]). From [9] it can be deduced that the general reasons for losing positivity for solutions to DDEs are negative values of the terms with delay. In such a case, if the values of solution are sufficiently large at $t-\tau$ and sufficiently small at t, then the derivative of the solution can take such negative values that the solution decreases very fast and loses positivity as a consequence. In the problem considered, initial functions have to be biochemically reasonable and cannot behave so badly. However, the interesting issue is whether the amplitude of the oscillations that appear due to Hopf bifurcation can be so large that solutions become negative. We show that this is the case.

We are interested in the case where the positive steady state $\bar{x}$ loses stability and Hopf bifurcation occurs, that is $\tau \geq \tau_{cr} = \frac{\arccos(-B/C)}{\sqrt{C^2-B^2}}$; compare e.g. [10]. Scaling the space and time variables allow us to reduce the number of parameters from 3 to 1. Therefore, without loss of generality, we study the Cauchy problem

$$\dot{\phi} = 1 - b\phi(t) - \phi(t-\tau), \quad \phi(t) = 0 \text{ for } t < 0 \quad \text{and} \quad \phi(0) = \phi^0 \geq 0 \tag{4}$$

with $b < 1$ and $\tau \geq \tau_{cr}$. Notice that for $b > 1$ there is no change of stability; compare e.g. [5]. In this section we prove that the solution to this problem loses positivity on the interval $[0, 4\tau]$.

Due to the different forms of solutions, one needs to study two cases: for $b = 0$ and for $b \in (0, 1)$, separately. Therefore, in the work we deal with the following Cauchy problems:

$$\dot{x} = 1 - x(t-\tau), \qquad x(t) = 0 \quad \text{for } t \leq 0, \tag{5}$$

$$\dot{y} = 1 - y(t-\tau), \qquad y(t) = 0 \quad \text{for } t < 0 \text{ and } y(0) = y^0 > 0, \tag{6}$$

$$\dot{z} = 1 - bz(t) - z(t-\tau), \qquad z(t) = 0 \quad \text{for } t \leq 0, \tag{7}$$

$$\dot{w} = 1 - bw(t) - w(t-\tau), \qquad w(t) = 0 \quad \text{for } t < 0 \text{ and } w(0) = w^0 > 0, \tag{8}$$

with $\tau \geq \tau_{cr} = \frac{\pi - \arccos(b)}{\sqrt{1-b^2}} \geq \frac{\pi}{2}$, where $\tau_{cr} = \frac{\pi}{2}$ is the critical value for $b = 0$.

First, we propose an explicit formula for solutions to all problems (5)–(8).

Lemma 2.1. *The solutions to problems (5)–(8) for $t \in [(n-1)\tau, n\tau)$, $n \geq 1$ are given by the following formulae:*

$$x(t) = \sum_{k=1}^{n} \frac{(-1)^{k+1}}{k!}(t-(k-1)\tau)^k, \tag{9}$$

$$y(t) = x(t) + y^0\dot{x}(t) = \sum_{k=1}^{n} \frac{(-1)^{k+1}}{(k-1)!}(t-(k-1)\tau)^{k-1}\left(\frac{t-(k-1)\tau}{k} + y^0\right), \tag{10}$$

$$z(t) = \frac{1}{b}\sum_{k=0}^{n-1} \frac{(-1)^k}{b^k}\left(1 - e^{-b(t-k\tau)}\sum_{i=0}^{k} \frac{b^i(t-k\tau)^i}{i!}\right), \tag{11}$$

$$\begin{aligned} w(t) &= z(t) + w^0\dot{z}(t) \\ &= \frac{1}{b}\sum_{k=0}^{n-1} \frac{(-1)^k}{b^k}\left(1 - e^{-b(t-k\tau)}\left(1-w^0 b\right) - e^{-b(t-k\tau)}\sum_{i=1}^{k} \frac{b^i(t-k\tau)^{i-1}}{i!}\left((t-k\tau)(1-w^0 b) + w^0 i\right)\right). \end{aligned} \tag{12}$$

Notice that for $k = 0$ the second term in the formula (12) disappears since $k = 0 < 1$.