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Time delay in a basic model of the immune response

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Abstract

The effects of time delay on the two-dimensional system of Mayer et al., which represents the basic model of the immune response, are analysed (cf. Mayer H, Zaenker KS, an der Heiden U. A basic mathematical model of the immune response. Chaos, Solitons and Fractals 1995;5:155–61). We studied variations of the stability of the fixed points due to the time delay and the possibility for the occurrence of the chaotic solutions. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Time delay in models of population dynamics and in particular in macroscopic models of the immune response are natural and common [2,3]. Complex systems with many components and various interactions, often unknown, are replaced by systems with just a few measurable quantities and all the complexity is introduced by joint effect of the nonlinearities and the time delay. Most often, the nonlinearities are introduced by a reasonable theoretical model of the interaction between the several components (good surveys can be found in [4,5]). However, such approach fails to achieve the major goal of reducing the number of the necessary quantities to a minimum. On the other hand, the nonlinearities can be introduced by incorporating independently obtained models of the behaviour of particular components of the system into the model of the whole system. Partial aspects of the system's behaviour are treated as known, and are explicitly used in constructing the model for the whole system. One of the models obtained along these lines is the Mayer model of the immune response [1]. The model is described by a system of just two ODEs, and the rich behaviour is made possible by using highly nonlinear functions in order to model the joint effect of various processes. These functions are justified on the basis of previous models of the parts of the system. We shall analyse various effects of the time delay, introduced in these functions in a natural way.

The direct motivation for the introduction of the time delay is that the Mayer model consists of only two ODEs, and thus, it has only regular solutions, such as fixed points, periodic orbits and orbits asymptotic to these [6]. As Mayer et al. pointed out the model cannot describe, frequently observed, irregular or chaotic behaviour. In a recent paper, we have analyse a minimal extension of the Mayer model, based on the periodic parametric perturbations, which has the chaotic solutions [7]. It is the goal of this paper to present and analyse the effects of the time delay just sufficient to introduce the chaotic behaviour into the Mayer model.

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2. Description of the model

We shall be interested in the effects of the time delay on the dynamics in a very simple model of the immune response. The basic model [1] describes the immune response as an interaction between a target population, denoted T, and the most relevant (for such target) feature of the immune system, denoted E. The quantity E is called the immune competence, and refers to the concentration of the most relevant immune agents, like certain antibodies, NK cells or cytotoxic T-cells. The target can be some measurable property of anything susceptible to an immune response, like micro-organisms, macro-molecules (proteins, polysaccharides, lipids), or immunogenic tumour cells, etc. The class of models, which we shall analyse is given by the following equations:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = rT - kTE, \tag{1}$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = pf(aT(t) + (1-a)T(t-\tau_T)) + sg(bE(t) + (1-b)E(t-\tau_E)) - E, \tag{2}$$

where either a or b is necessarily equal to unity. In fact, the case with $a = 1, b \neq 1$ does not show long-term irregular behaviour, so we shall present in details the analyses of the case $a \neq 1, b = 1$, and the results for the other case shall be only indicated.

In the case of no time delay the Eqs. (1) and (2) give the model of Mayer et al. The functions f and g describe the rate of change of the immune competence E due to the presence of the target ($f(T)$), and due to auto-catalytic and/or co-operative reinforcement ($g(E)$) (see [1]). These processes are described by the following functions:

$$f(T) = \frac{T^4}{1+T^4}, \quad T \geqslant 0, \tag{3}$$

$$g(E) = \frac{E^3}{1+E^3}, \quad E \geqslant 0. \tag{4}$$

Such a choice describes, depending on the values of the parameters r, k, p and s, a large variety of biologically plausible situations. The effect of the immune response on the target is describe by the term $-kTE$ in the first equation. All the complexity of the interaction between the immune system and the target, and of the processes between various immuno-competent agents, leading to the reach variety of possible outcomes, is contained in the nonlinear functions f and g. The linear terms rT and $-E$ describe the average production rate of the target cells proportional to T, and the finite average life time of the immuno-competent agents.

The model with no time delay exhibits various stable and unstable fixed points with the corresponding asymptotic orbits. There are also large intervals of the parameter values when the system has got a limit cycle, corresponding to a periodic variations of the immune state. This limit cycle is born from a Hopf bifurcation of a stable fixed point. The bifurcation analyses of the model and its parametric perturbations were presented in the Ref. [7]. However the two-dimensional model has only regular solutions. There are several ways of extending it so that the new model might exhibit a chaotic behaviour. One possibility, analysed in [7], is to suppose a periodic time dependence for the parameters. Parametric oscillations coupled with the limit cycle oscillations in the model then generate the chaotic solutions.

It is also well-known that a single differential equation with a delayed argument could have very complex solutions [8,9]. Furthermore, introduction of the time delay into the functions f and g is obviously biologically justified.

3. Linear stability of the fixed points

The basic elements of the qualitative description of a dynamical system are the fixed points and the periodic orbits. The time delay introduces important qualitative changes in the dynamics of the system. We shall be concerned with the effects introduced by the time delay upon the stable fixed points and the periodic orbits (general theory of delayed-differential equation can be found in [10]). Linear stability of the fixed point will be analysed in this section, and the perturbations of the limit cycle will be analysed numerically in the next section.

There are two fixed points of the system. The first one is in the origin and is always unstable. The second one is given by:

$$E_0 = r/k \equiv \delta, \qquad T_0 = \sqrt[4]{\frac{\alpha}{1-\alpha}}, \quad \alpha = \frac{d}{p}\delta - \frac{s}{p}\frac{\delta^3}{(1+\delta^3)}. \tag{5}$$

As the time delay τ is varied this fixed point undergoes a Hopf bifurcation i.e. it is changed from a stable into an unstable fixed point, and a limit cycle is born. We want to find the critical value of the time delay τ_c, when the bifurcation from the stable into the unstable fixed point occurs. We shall present the analyses and the results for the case $a \neq 1, b = 1$, since, as we shall see, only in this case the long term irregular solutions are possible.

In order to determine stability of the fixed point we linearise the Eqs. (1) and (2) with $a \neq 1, b = 1$, in a neighbourhood of $E = E_0, T = T_0$ to obtain the matrix

$$A = \begin{pmatrix} a_1 & a_2 \\ b_1 + \frac{1-a}{a} b_1 \exp(-\lambda\tau) & b_2 \end{pmatrix} \tag{6}$$

and the characteristic equation

$$\det(A - \lambda I) \equiv \lambda^2 - \zeta_1\lambda + \zeta_2 + \zeta_2 \frac{1-a}{a} e^{-\lambda\tau} = 0, \tag{7}$$

where

$$\zeta_1 = -b_2, \qquad \zeta_2 = -a_2 b_1 \tag{8}$$

and

$$a_1 = 0, \qquad a_2 = -kT_0, \qquad b_1 = \frac{4apT_0^3}{(1+T_0^4)^2}, \qquad b_2 = \frac{3sE_0^2}{(1+E_0^3)^2} - d. \tag{9}$$

The characteristic equation is used to determine the linear stability of the fixed point. It is a transcendental equation, with an infinite number of solutions λ_i. The fixed point is unstable if there is at least one λ_i with $\mathrm{Re}\,\lambda_i > 0$. If all λ_i have $\lambda_i < 0$ then the fixed point is stable. The bifurcation occurs for those values of the parameters when there is at least one λ_i with $\mathrm{Re}\,\lambda_i = 0$.

The existence of τ_c and the number of purely imaginary λ_i for this τ_c is found by treating the characteristic equation as a complex variable mapping problem. Consider the transformation from the λ-plane to w-plane defined by

$$w = \lambda^2 + \zeta_1\lambda + \zeta_2 + \frac{1-a}{a}\zeta_2 e^{-\lambda\tau}, \quad \tau > 0. \tag{10}$$

Setting $\lambda = \mu + i\nu$ this gives

$$w = \left[\mu^2 - \nu^2 + \zeta_1\mu + \zeta_2 + \frac{1-a}{a}\zeta_2 e^{-\mu\tau}\cos(\nu\tau)\right] + i\left[2\mu\nu + \zeta_1\nu - \frac{1-a}{a}\zeta_2 e^{-\mu\tau}\sin(\nu\tau)\right]. \tag{11}$$

We wish to show that there is τ_c such that the image of the imaginary axes in the λ-plane by the complex map $w(\lambda)$, goes through the origin in the w-plane. Consider the contour in the λ-plane consisting of the imaginary axis and a semi-circle of infinite radius as shown schematically in Fig. 1a. We start by plotting the image of this contour by the mapping (11) in the case $\tau = 0$. Time delay will modify the image by just superposing oscillations proportional to τ.

We know that in the case $\zeta_1 > 0, \zeta_2 > 0$ and $\tau = 0$ the fixed point is stable and $\mathrm{Re}\,\lambda < 0$, so w as a function of λ does not pass through the origin in the w-plane. Actually, AE in Fig. 1, on which $\mu = 0$, is mapped by

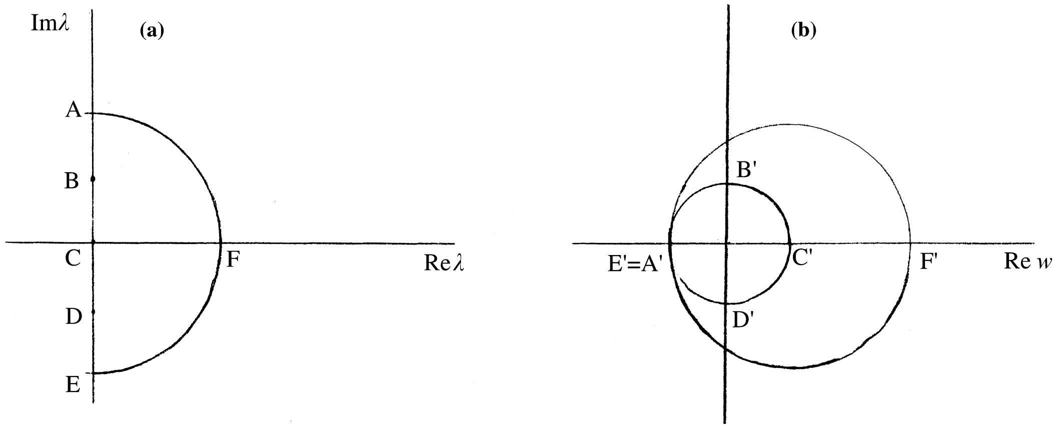


Fig. 1. A domain V in λ-plane, bounded by the curve AEF, is mapped by the characteristic polynomial into $A'E'F'$ in w-plane. AE is on the imaginary axes.

$$w = \left[-v^2 + \frac{\zeta_2}{a} \right] + \mathrm{i}[\zeta_1 v] \tag{12}$$

onto $A'E'$ in Fig. 1b with $C' = \zeta_2/a + \mathrm{i}0$ in the w-plane corresponding to $C = 0 + \mathrm{i}0$ in the λ-plane. The domain V is mapped into V'. The points A, B, C, D and E in Fig. 1a are mapped onto their primed equivalents as indicated in Table 1.

We now consider the mapping with $\tau > 0$. The line AE has $\mu = 0$ so it is mapped onto

$$w = \left[-v^2 + \zeta_2 + \frac{1-a}{a}\zeta_2 \cos(v\tau) \right] + \mathrm{i}\left[\zeta_1 v - \frac{1-a}{a}\zeta_2 \sin(v\tau) \right]. \tag{13}$$

The effect of the trigonometric terms is simply to add oscillations onto the curve $A'B'C'D'E'$, as is shown schematically on Fig. 2a. For τ larger than the critical τ_c, which depends on ζ_1, ζ_2 and a, the point B' is below and the point D' is above the $\mathrm{Re}\,w$ axes, as in Fig. 2b. The roots of the characteristic equation

Table 1

A	$(\infty \mathrm{e}^{i\pi/2})$	A'	$(\infty \mathrm{e}^{i\pi})$
B	$(\sqrt{\zeta_2/a}\,\mathrm{e}^{i\pi/2})$	B'	$(\zeta_1\sqrt{\zeta_2/a}\,\mathrm{e}^{i\pi/2})$
C	(0)	C'	(ζ_2/a)
D	$(\sqrt{\zeta_2/a}\,\mathrm{e}^{-i\pi/2})$	D'	$(\zeta_1\sqrt{\zeta_2/a}\,\mathrm{e}^{-i\pi/2})$
E	$(\infty \mathrm{e}^{-i\pi/2})$	E'	$(\infty \mathrm{e}^{-i\pi})$

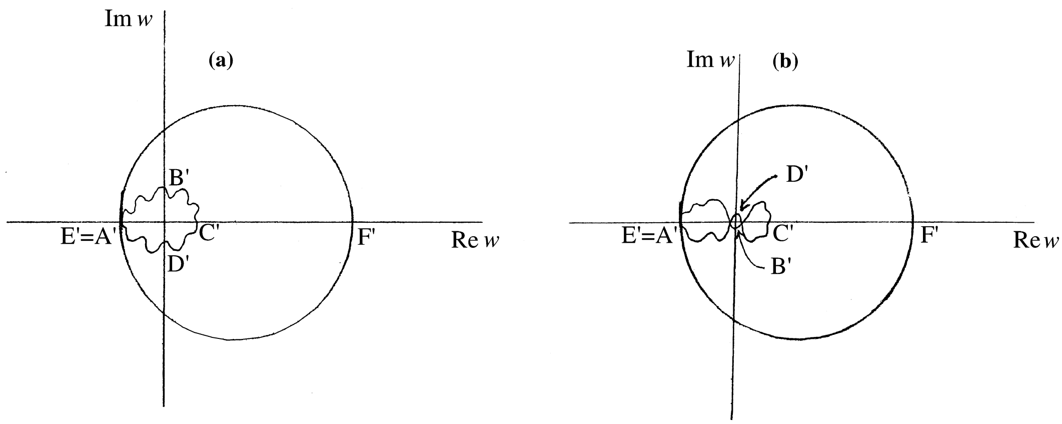


Fig. 2. Images of the curve AEF from Fig. 1a by the characteristic equation with: (a) small τ; (b) larger τ.

$w(\lambda) = 0$ are always complex conjugate pairs. The number of roots with $\mathrm{Re}\,\lambda > 0$ is obtained by computing the change in the argument of w upon traversing the boundary of V'. In the supercritical case, represented in the Fig. 2b, the change in arg w is 4π, corresponding to two complex conjugate roots with $\mathrm{Re}\,\lambda > 0$.

We shall not go into the analyses of the dependence of τ_c on the parameters ζ_1, ζ_2 and a. This could be investigated by graphical or numerical solutions of the following system of equations:

$$\zeta_1 = -\frac{1-a}{a} v \frac{\sin(v\tau_c)}{1 + ((1-a)/a)\cos(v\tau_c)}, \tag{14}$$

$$\zeta_2 = \frac{v^2}{1 + ((1-a)/a)\cos(v\tau_c)}, \tag{15}$$

or analytically in the case of small and large τ. Let us just mention in order that there is the critical τ_c, i.e. a solution with real v, the parameter a must be $a > 1/2$.

4. Nonlinear effects

We expect that the nonlinear terms in the two-dimensional system, coupled with the time delay, could introduce the chaotic solutions in the case when the original system, with no time delay, has a limit cycle. There are large intervals of the parameter values when the instability domain of the unstable fixed point of the Mayer model is bounded by the stable limit cycle. We shall now analyse what happens with this limit cycle due to the time delay. In particular we want to investigate if the chaotic solutions could appear by introducing the time delay in only one term of the original model.

Systematic numerical computations lead us to conclude that there are three qualitatively different situations, which could occur for the values of the parameters corresponding to the existence of the limit cycle in the original model. Two of these could occur for any of the time-delayed models i.e. for any values of a and b and the third one is possible only in the case when the time delay is introduced in the function $f(T)$ i.e. for $a \neq 1, b = 1$. In order to obtain a particular solution of the system of delayed differential equations we need an initial function defined on the interval $(t_0 - \tau, t_0)$, which corresponds to a relatively short interval before the complex interactions and processes between E and T cells started. In our numerical computations we used the class of linear functions for the initial data, which is biologically plausible. Our conclusions are thus restricted to this class of the initial functions, but they are qualitatively the same for the functions in this class.

In the first two cases the system is eventually attracted towards a simple attractor. Depending on the values of the parameters r, k, s, p and the time delay τ the attractor is either the stable fixed point or the stable limit cycle, bounding the instability domain of the unstable fixed point. This limiting long term behaviour is presided either by a short period of irregular or by a regular transient oscillations. The combination of the critical values of the parameters and the time delay, r_c, k_c, s_c, p_c and τ_c, corresponding to the transition from the one to the other limiting behaviour, can be determined using the linear stability analyses of the fixed point in each case of interest. The analyses, using a method (D-resolution) different from the one of the last section is rather lengthy and will not be given here [11]. These two types of behaviour are the only possible types in the case the time delay is introduced in the function $g(E)$ ($a = 1, b \neq 1$) or in the first term of the equation for T. T components of the typical orbits are illustrated in Fig. 3a and b. Fourier amplitude spectrum (Fig. 4), and the largest Lyapunov exponents also correspond to the regular attractors. Very large time delay leads to unbounded solutions. No solution with a long term chaotic behaviour is found.

The chaotic solutions are found only in the case of the time delay in the function $f(T)$. A typical chaotic orbit in the phase space is represented in Fig. 5, together with its T component and the Fourier amplitude spectrum in Fig. 6a and b. For fixed values of the parameters r, k, s, p, admitting a limit cycle in the original model ($\tau = 0$), and for fixed $a = 0.75, b = 1$, increasing the value of the time delay τ changes the limiting set of a typical orbit from a circle to a multiply periodic orbit, for even larger τ, the orbit becomes chaotic. The

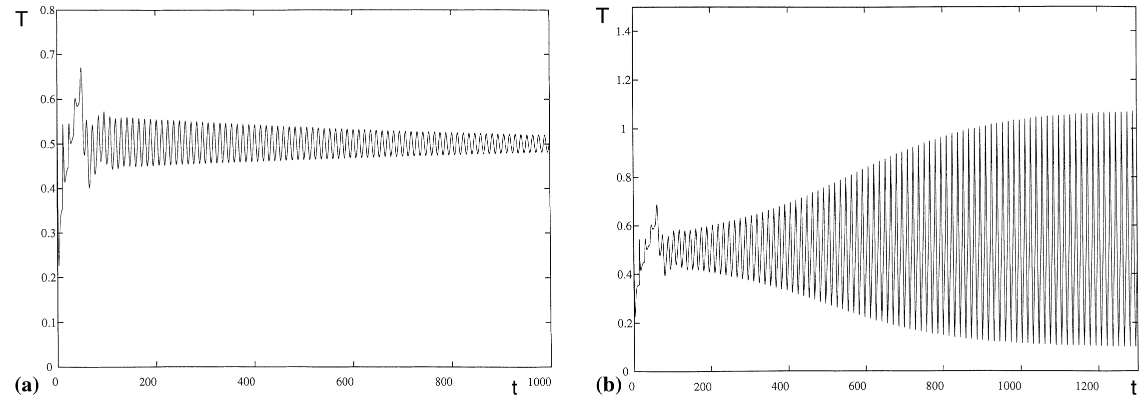
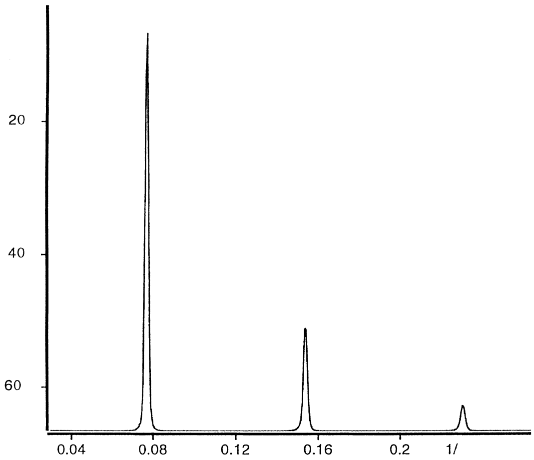


Fig. 3. T component of typical orbits attracted towards: (a) the stable fixed point; (b) the stable limit circle.



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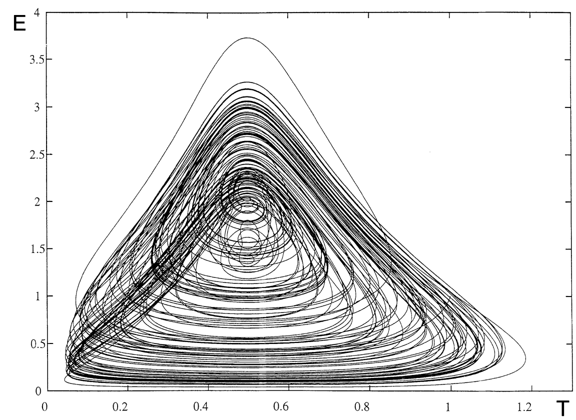

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Fig. 4. Amplitude Fourier spectrum of the T component of the orbit in Fig. 3b.

Fig. 5. Typical chaotic orbit ($k = 1$, $r = 0.5$, $s = 1.75$, $p = 0.35$, $a = 0.75$, $\tau = 20$).

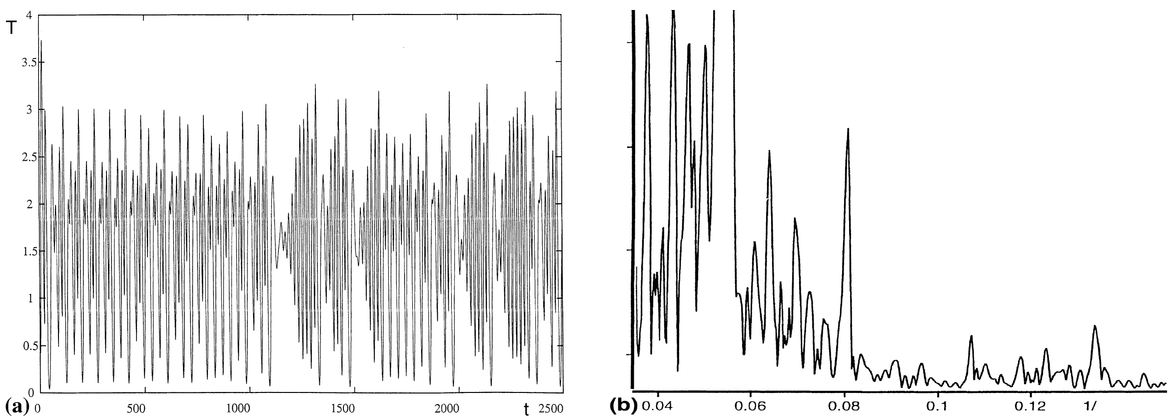

Fig. 6. (a) T component. (b) Its amplitude spectrum of the chaotic orbit in Fig. 5.

chaotic solutions appear for the values of τ which are close to the period of the limit cycle of the system with no delay. There is a small interval (about 10% of the time delay) of the time delay τ for which the orbits are chaotic. Then follows a small interval of τ for which periodic limiting behaviour is restored. Larger time delays lead again to the chaotic solutions, which continue to appear for all large τ. Similar chaotic solutions are found for other values of a lying approximately in the interval $(0.65, 0.8)$ and $b = 1$. No chaotic solutions are found for the values of r, k, s, p which corresponding to the stable fixed point in the original $\tau = 0$ model and for any τ, (or a and b) although, as shown in the last section, the time delay can destabilise the fixed point.

To summarise, extensive numerical computations show that: For any values of the parameters r, s, p, d, for which there is a limit circle in the model with no time delay, there are sufficiently large time delay τ and an interval of $a \neq 1$ and $b = 1$, such that the system is chaotic. The case $a = 1, b < 1$ has no chaotic solution for any value of the parameters and the time delay.

5. Conclusion

The model analysed in this paper is a typical example of an approach to the modelling of the immune system. The approach is based on the guiding idea that the model should satisfy the basic requirement, one should need as little as possible of the input data in order to be able to describe many typical situations occurring in the real system. The Mayer model without the time delay contains only two characteristic variables. All variety of different dynamical behaviour is made possible by the two nonlinear functions, introduced on the bases of an independent analyses. However, the model is to simple to be able to reproduce (at least qualitatively) the irregular oscillations of the state of the immune system, which are observed quite often. What are possible minimal additions which would make a model with irregular behaviour? We have partially answered this question by analysing a class of systems with the time-delayed arguments, introducing the time delay in each and only one of the terms in the Mayer model. The main result of our analyses is that the irregular behaviour can be introduced by the time delay in the function which describes the increased production of the immuno competent cells due to the presence of the target cells. Time delay in any other single term of the equations produces stabilisation of the transient irregular behaviour onto the simple attractor i.e. the fixed point or the periodic orbit. This conclusion seems to be generally valid for all tested initial data functions.

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