

Marchuk's Model of Immune System Dynamics with Application to Tumour Growth

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Marchuk's model of a general immune reaction is presented in the paper. The results of investigation of the model are summarized. The qualitative behaviour of solutions to the model and its simplification is described. Many illustrations of recovery process, oscillations or lethal outcomes of a disease are shown. The model with time-dependent immune reactivity is also considered. Periodic dynamics caused by different reasons are compared.

In the last section adaptation of the model to tumour-immune interactions is proposed. The role of interleukins in immune processes is taken into account to adapt Marchuk's model to tumour growth dynamics. Possible immunotherapy is also considered in the proposed model. Some preliminary analysis of the model is presented.

Keywords: Antigen; Antibody; Plasma cell; Humoral and cellular immune response; Delay differential equation; Local and global stability; Hopf bifurcation

THE MODEL—CONSTRUCTION AND BASIC PROPERTIES

The model of an immune reaction, presented in this paper, was proposed by Marchuk (1980). The model has very clear interpretation and simple mathematical form and therefore, it can play the similar role for immunology as the Lotka–Volterra model for ecology. This model describes a general immune reaction against some antigen. It is presented in the language of humoral immune reaction but cellular immune reaction may be modelled similarly.

Marchuk (1980; 1983) and Belykh (1988) proved some basic results about the model. Qualitative behaviour of the solutions was studied in Szlenk and Vargas (1995), Foryś (1997; 2000), Bodnar and Foryś (2000a,b). Many modifications and generalization of that model were made (see e.g. Marchuk, 1980; 1983; 1997; Belykh, 1988; Barradas, 1993; Foryś, 1993; 1995a,b; 1999; Asachenkov *et al.*, 1994; Borkowska and Szlenk, 1995; Foryś and Żołek, 1998; 2000; Bodnar and Foryś, 1999; 2000a). Marchuk's team fitted parameters of this model (and other similar ones) to experimental data in the case of several diseases (e.g. for hepatitis B) (see e.g. Asachenkov *et al.*, 1994; Marchuk, 1997). This model was also adapted to the case of immune reaction after vaccinations (against hepatitis B, see Borkowska and Szlenk, 1995; Bofill *et al.*,

1995; Foryś and Żołek, 1998; 2000; Foryś, 1999). Parameters of these models was also fitted to experimental data of Gesemann and Scheiermann (1993; 1995) very satisfactory.

Now, the considered model is presented. There are the following variables in the model:

- $V(t)$ is the antigen concentration at time t ;
- $C(t)$ is the plasma cell concentration at time t ;
- $F(t)$ is the antibody concentration at time t ;
- $m(t)$ is the characteristic of damage of the organ—target in which antigen is sited.

The function $m(t)$ is defined as follows

$$m(t) = \frac{M_0 - M_1(t)}{M_0},$$

where M_0 is the characteristic of healthy organ (mass or area) and $M_1(t)$ is the characteristic of a healthy part of this organ at time t .

Marchuk's model is derived under the following assumptions:

- The number of antigens depends on their reproduction rate (with the reproduction coefficient β) and the suppression by antibodies (with the coefficient γ which

express the probability of the antigen–antibody meeting and their interactions).

- If there is no antigen, then the plasma cell production is proportional to the deviation from the normal level C^* (with the coefficient μ_c , where μ_c^{-1} is equal to the mean plasma cell lifetime). If some antigen appears, then so-called VT-complexes are formed (to simplify the model, it is assumed that the VT-complex rate is proportional to the number of antigen–antibody encounters, with the coefficient α , which is called the immune reactivity coefficient). Stimulation of B-cell by VT-complexes is a trigger of the plasma cell production process. The plasma cell production is delayed relative to the B-cell stimulation process. It is assumed that this delay is constant, equal to $\tau > 0$. In most of immune reactions the delay is not close to 0 and it seems to be very important not to omit this delay in the model. The process of VT-complex formation depends also on the damage of the organ–target, according to the function $\xi(m)$. In Marchuk (1980) this function is defined as

$$\xi(m) = \begin{cases} 1 & \text{for } m \in [0, m^*], \\ \frac{m-1}{m^*-1} & \text{for } m \in (m^*, 1], \end{cases} \quad (1)$$

where $m^* \in (0,1)$ is certain level of the damage. This means that initially immune processes do not depend on the organ damage rate, but for large damage, ξ begins to decrease to zero, reflecting the rapid decrease of defence possibilities.

- The number of antibodies depends on their production rate per one plasma cell (with the production rate coefficient ϱ) and their death due to immune reactions and ageing, where η is the rate of antibodies necessary to suppress one antigen and μ_f is the mortality coefficient (where μ_f^{-1} is equal to the mean antibody lifetime).
- The organ damage depends on the antigen damage possibilities (with the coefficient σ) and the organ recovery rate μ_m (where μ_m^{-1} is equal to the mean organ recovery time). According to its definition, $m(t) \leq 1$, therefore, if $m(t)$ reaches the level 1 for some $\bar{t} > 0$, then $m(t) = 1$ for all $t > \bar{t}$, which means the lethal outcome of the disease.

These assumptions lead to the following system of equations with time delay

$$\begin{aligned} \dot{V}(t) &= (\beta - \gamma F(t))V(t), \\ \dot{C}(t) &= \alpha \xi(m)V(t - \tau)F(t - \tau) - \mu_c(C(t) - C^*), \\ \dot{F}(t) &= \varrho C(t) - (\mu_f + \eta \gamma V(t))F(t), \\ \dot{m}(t) &= \sigma V(t) - \mu_m m(t) \text{ for } m \leq 1 \end{aligned} \quad (2)$$

and nonnegative coefficients.

The delay of reaction considered in the model seems to be very important in general immune reaction. Its mean value is equal to 1 for many infections, and therefore it cannot be neglected. For the models with time delay an initial data is not a point (as for ordinary differential equations) but a function defined on the interval $[-\tau, 0]$, i.e. on the interval of the length equal to the delay. The most typical initial data (considered in many papers, e.g. Marchuk, 1980; 1983; 1997; Belykh, 1988; Asachenkov *et al.*, 1994; Szlenk and Vargas, 1995; Foryś, 1997; 2000) is expressed as

$$X^0(t) = \begin{cases} (0, C^*, F^*, 0) & \text{for } t < 0, \\ (V_0, C^*, F^*, 0) & \text{for } t = 0, \end{cases} \quad (3)$$

where $V_0 > 0$ and $F^* = \varrho C^* / \mu_f$ is the physiological level of antibodies. This initial data describes the healthy organism (i.e. the organism with no antigen and some physiological levels of plasma cells and antibodies) infected at $t = 0$ by certain dose $V_0 > 0$ of the antigen.

In the case of tumour dynamics the cellular immune reactivity should be rather considered instead of the humoral one (see e.g. Kuznetsov *et al.*, 1994; Mayer *et al.*, 1995; Kirschner and Panetta, 1998). Therefore, the variables of the model may be interpreted as follows.

$V(t)$ denotes the amount of tumour cells, $F(t)$ —the concentration of immunocompetent cells (e.g. natural killers) in the region of tumour, $C(t)$ —the concentration of precursor cells and $m(t)$ may be the density of some inhibitory factors produced by tumour cells against the immune system.

In Marchuk (1980) such properties as existence, uniqueness and nonnegativity of solutions to Eq. (2) for nonnegative initial functions were proved. The system defined by Eq. (2) may have two stationary states, i.e. the solutions to

$$\begin{aligned} 0 &= (\beta - \gamma \bar{F})\bar{V}, & 0 &= \alpha \bar{V} \bar{F} - \mu_c(\bar{C} - C^*), \\ 0 &= \varrho \bar{C} - (\mu_f + \eta \gamma \bar{V})\bar{F}, & 0 &= \sigma \bar{V} - \mu_m \bar{m}, \end{aligned} \quad (4)$$

where $(\bar{V}, \bar{C}, \bar{F}, \bar{m})$ denote the stationary state. These stationary states are

$$X_1 = (0, C^*, F^*, 0) \quad (5)$$

and

$$X_2 = \left(\frac{\mu_c \mu_f (\beta - \gamma F^*)}{\beta (\alpha \varrho - \eta \gamma \mu_c)}, \frac{\alpha \beta - \eta \gamma^2 \mu_c C^*}{\gamma (\alpha \varrho - \eta \gamma \mu_c)}, \frac{\beta}{\gamma}, \frac{\sigma \mu_c \mu_f (\beta - \gamma F^*)}{\mu_m \beta (\alpha \varrho - \eta \gamma \mu_c)} \right). \quad (6)$$

If X_2 exists, then the inequality $\bar{V}_2 > 0$ is satisfied, and therefore,

$$(1) \beta > \gamma F^* \quad \text{and} \quad \alpha \varrho > \eta \gamma \mu_c \quad \text{or} \quad (2) \beta < \gamma F^*$$

$$\text{and} \quad \alpha \varrho < \eta \gamma \mu_c,$$

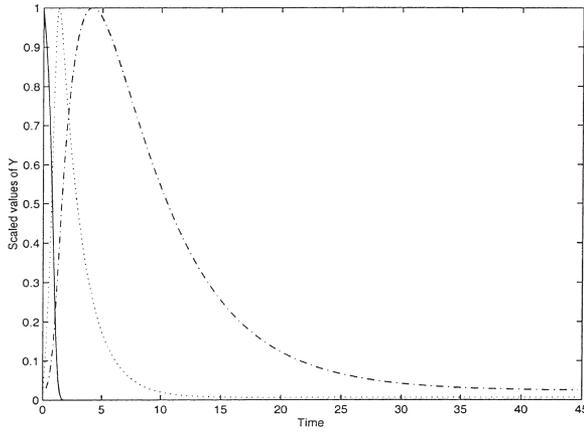


FIGURE 1 An example of acute form of the disease.

i.e. X_2 exists if the organism is strong (large reactivity coefficient α) but the physiological level of antibodies is small or, the second case—the organism is weak, i.e. α is small and the antigen reproduction rate is also small.

The solution X_1 corresponds to the healthy state of the organism and is called the healthy state. The solution X_2 corresponds to the chronic form of the disease (i.e. the antigen is still present in the organism) and is called the chronic state.

In Marchuk (1980) and Belykh (1988) conditions of local asymptotical stability of stationary states were studied. It occurs that the state X_1 is locally stable for $\beta < \gamma F^*$. This means that independently on other parameters if the antigen reproduction rate is small compared to the physiological level of antibodies, then the organism recovers when the initial dose of antigen is not too large. There are two possible behaviour of solutions in this case—one of them, when the concentration of antigen decreases rapidly (it may be decreasing or increasing at the beginning of infection) during the first few days, is called acute form of the disease, and the second, when the concentration of antigen decreases much slower, is called subclinical form. If the initial level of antigen is large, the infection may be ended lethally. Examples of these three types of infection are shown on Figs. 1–3, where the solid line represents V , dotted line represents C and dot-line-dot represents F (time is measured in days and scaled values of Y denote values of variables V , C , F scaled to the maximal values). More details about computer simulations, the reader can find in the next section. Figures in this section are only the sketches of possible dynamics.

For the second state X_2 the following is true. If $\beta \in (\gamma F^*, \gamma F^* + ((\mu_c + \mu_f)^{-1} + \tau)^{-1})$, $\mu_c \tau \leq 1$ and α is large enough, then X_2 is also locally asymptotically stable. This means that if the antigen reproduction rate is large, but not too large, and the organism is strong (large immune reactivity α), then the antigen is still present in the organism and this organism cannot recover (but the damage of organ–target is small, i.e. $\bar{m} < m^*$ and $\xi(m) = 1$), see Fig. 4.

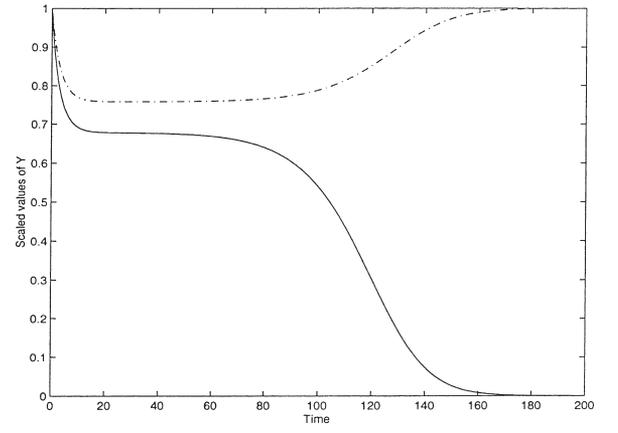


FIGURE 2 An example of subclinical form of the disease.

This type of chronic state is called the light chronic form of the disease in Belykh (1988). In the case when $\bar{m} > m^*$ the chronic state is called the heavy chronic form. Such a type of the disease also may exist and be locally asymptotically stable but the conditions of existence and stability are much more complicated (see Belykh, 1988).

Global asymptotical stability and bifurcations were studied in Foryś (1997; 2000) and Bodnar and Foryś (2000a,b) for simplified model. It is assumed that $m < m^*$ and then Eq. (2) reduce to the following system

$$\begin{aligned} \dot{V} &= (\beta - \gamma F)V, \\ \dot{C} &= \alpha V(t - \tau)F(t - \tau) - \mu_c(C - C^*), \\ \dot{F} &= \varrho C - (\mu_f + \eta\gamma V)F \end{aligned} \quad (7)$$

with the nonnegative coefficients. The model defined by Eq. (7) will be referred to as the MM in this paper, and will be considered together with the initial data defined by Eq. (3) where the last coordinate m is omitted.

The results of investigation of the MM are following.

- Case of strong immune system, i.e. large immune reactivity α

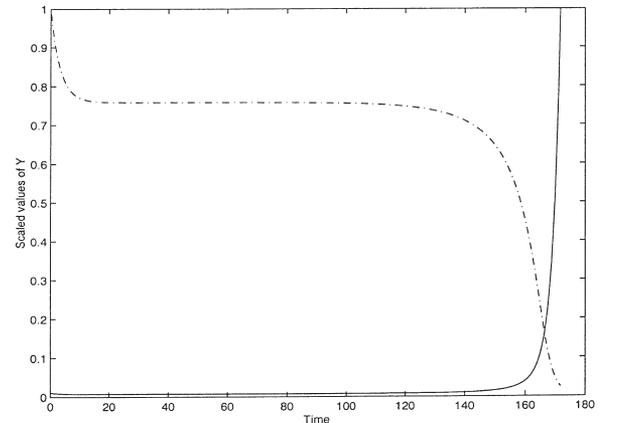


FIGURE 3 An example of lethal outcome of the disease.

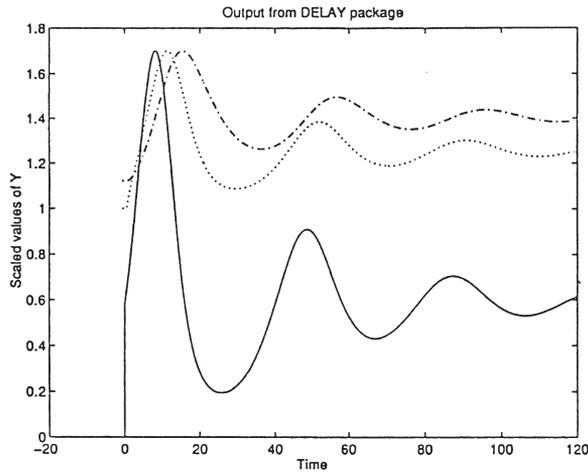


FIGURE 4 An example of chronic form of the disease.

If the immune reactivity coefficient α is large, the delay of reaction τ and the reproduction rate of antigen β are small, i.e. inequalities

$$\alpha\varrho > \eta\gamma(\mu_c + \beta)e^{\beta\tau} \quad (8)$$

and $\beta < \gamma F^*$ hold, then independently on the initial dose of antigen, the organism recovers, i.e. $V(t)$ tends to 0, $C(t)$ and $F(t)$ tend to physiological levels, as $t \rightarrow +\infty$.

If the immune reactivity coefficient α is large and the delay of reaction τ is small, but the reproduction rate of antigen β is large enough, i.e. inequalities (8) and $\beta > \gamma F^*$ are fulfilled, then independently on the initial dose of antigen, every solution to the MM oscillates around the chronic state X_2 .

There exist such values of parameters and $\tau_0 > 0$, that the MM has a Hopf bifurcation at τ_0 , i.e. the stationary state X_1 loses stability and the nontrivial periodic solution appears.

- Case of weak immune system (immunodeficiency), i.e. small immune reactivity.

If the immune reactivity coefficient is small and the reproduction rate of antigen is large, i.e. inequalities $\beta > \gamma F^*$ and

$$\alpha\varrho < \eta\gamma\mu_c e^{(\beta - \gamma F^*)\tau} \quad (9)$$

are satisfied then every solution to the MM has the following properties— $V(t)$ increases to $+\infty$ and $F(t)$ tends to 0, as $t \rightarrow +\infty$.

If the immune reactivity coefficient is small (one need to assume much more complicated inequality then Eq. (9) and therefore, the explicit expression for this inequality is omitted) and the reproduction rate of antigen is also small ($\beta < \gamma F^*$), then for small initial V_0 the organism recovers, but for larger V_0 the end of infection is lethal, i.e. $V(t) \rightarrow +\infty$ and $F(t) \rightarrow 0$, as $t \rightarrow +\infty$.

These results show the importance of delay in immune reactions. Even if the immune reactivity is large, Eq. (8) is not able to be satisfied for large τ , e.g. if Eq. (8) is satisfied for $\tau = 0$, i.e. $\alpha\varrho > \eta\gamma(\mu_c + \beta)$, then there exists such $\tau_0 > 0$ that for $\tau > \tau_0$ the inverse inequality holds, which may lead to lethal outcome of the disease not only for large V_0 but also for V_0 very small.

The dynamics of the MM is rather simple. More complicated behaviour one obtains, e.g. under the assumption that the immune reactivity α depends on time (see Bodnar and Foryś, 1999; 2000b).

COMPUTER SIMULATIONS

In this section, we describe how computer solutions to the MM were prepared. Numerical methods used to prepare the simulations are similar to those presented in Kim and Pimenov (1999), i.e. Adam's and BDF methods.

At the beginning we need to rescale variables in order to obtain nondimensional form. It is the standard procedure, which was also used in original books of Marchuk (1980; 1983; 1997) and Belykh (1988) from which the main values of parameters are taken. Define

$$v = \frac{V}{V_M}, \quad c = \frac{C}{C^*}, \quad f = \frac{F}{F^*},$$

where V_M is a maximal possible concentration of V in the organism, and denote

$$\gamma_1 = \gamma F^*, \quad \eta_1 = \eta\gamma V_M, \quad \alpha_1 = \frac{\alpha F^* V_M}{C^*}.$$

Due to the definition $v(t) \leq 1$, for every $t \geq 0$, and therefore, the time moment \bar{t} for which $v(\bar{t}) = 1$ is identified with the lethal outcome.

Now, $(0, 1, 1)$ is the stationary solution to the MM in new variables which reflexes the healthy state and

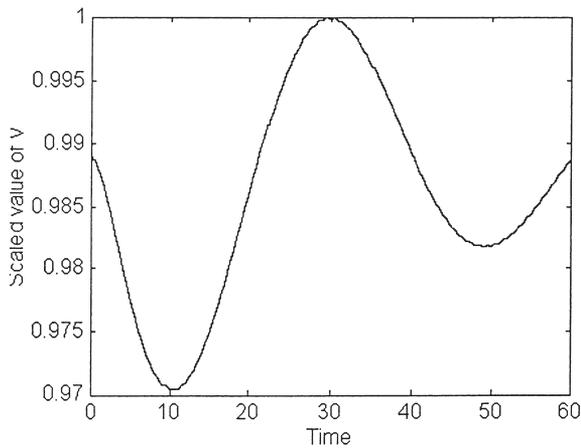
$$\begin{aligned} & (\mu_c \mu_f (\beta - \gamma_1) / \beta (\alpha_1 \mu_f - \eta_1 \mu_c), \alpha_1 \mu_f \beta \\ & - \eta_1 \mu_c \gamma_1 / \gamma_1 (\alpha_1 \mu_f - \eta_1 \mu_c), \beta / \gamma_1) \end{aligned}$$

describes the chronic state. The initial data defined by Eq. (3) changes to $(0, 1, 1)$ for $t < 0$ and $(v_0, 1, 1)$ for $t = 0$, where $v_0 < 1$ is the initial dose of antigen. In all simulations we use $\gamma_1 = 0.8$, $\mu_f = 0.17$, $\mu_c = 0.5$, $\eta_1 = 8$ and different values of α_1 , β and v_0 .

In the case of periodic function α the following function was used

$$\alpha(t) = \alpha_c (1 + \delta \sin(2\pi t/T)), \quad (10)$$

where $\alpha_c = 1000$, $\delta = 0.9$ and now, $\alpha_1(t) = \alpha(t) F^* V_M / C^*$. The value of T is equal to the main period of $\alpha(t)$, e.g. if $T = 1$ (the value used in simulations) then α reflexes the changes of immune reactivity within 1 day.

FIGURE 5 The solution for time-dependent reactivity. Value of V .

Similarly, the periodic initial conditions were defined as

$$\Phi_i(t) = \bar{x}_i(1 + a_i \sin(2\pi t/\tau)), \quad i = v, c, f, \quad (11)$$

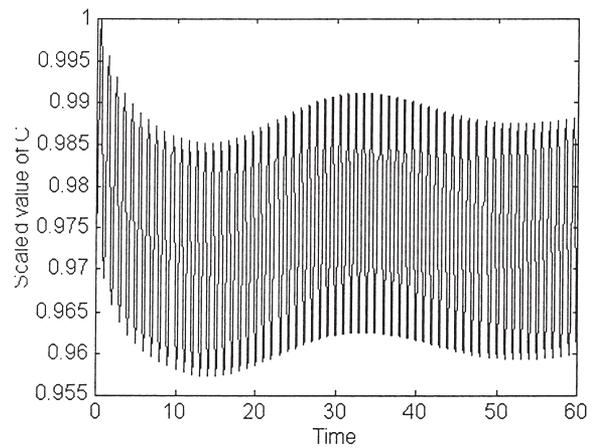
where $\bar{x} = (\bar{v}, \bar{c}, \bar{f})$ denotes the chronic state in scaled variables v, c, f , and a_i are some constants.

Scaled values of variables on the vertical axis denote these values scaled to the maximum. Time is measured in days, as the delay τ .

PERIODIC DYNAMICS

In this section the periodic dynamics of Marchuk's model will be presented. Such dynamics may be caused by different reasons. Periodic solutions may appear after the Hopf bifurcation. The next possibility to obtain such solutions is the periodicity of coefficient α , i.e. we assume that α is not constant but $\alpha = \alpha(t)$ is a periodic, nonnegative, smooth function of t . Such type of immune reactivity may reflexes, e.g. the seasonal changes of weather. In this case the period of α should be 365 days, i.e. 1 year. The third possibility is periodic initial data, which may also be connected with the seasonal changes of weather.

In the case of time-dependent immune reactivity the solutions to Marchuk's model may behave similarly to the MM or may be more complicated. The example of the solution with more complicated behaviour is presented in Figs. 5–7, where the periodic immune reactivity is defined by Eq. (10), $T = 1$, $\beta = 1$, $\tau = 1$, $v_0 = 10^{-3}$ and other parameters are as presented in "Computer simulations" section. One can see that for periodic immune reactivity the solution oscillates but these oscillations are not so regular as for constant α . It turns out that the phase portrait may be very interesting (see Fig. 8 with $\beta = 1.2$ and Fig. 9 with $\beta = 1.16$, where the vertical axis is C and the horizontal ones are V and F). It is possible to obtain something like a ring or Mobius strip as in Fig. 9. These oscillations (regular or irregular one) can be identified with some type of chronic disease where the state of patient still changes.

FIGURE 6 The solution for time-dependent reactivity. Value of C .

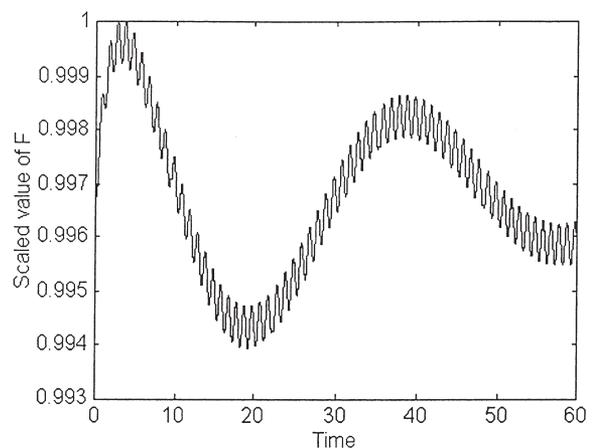
Another interesting behaviour of solutions to the model with periodic α is observed if one consider two models with symmetric functions α , i.e.

$$\alpha_+(t) = \alpha_c(1 + \alpha_0(t)) \quad \text{and} \quad \alpha_-(t) = \alpha_c(1 - \alpha_0(t)),$$

where $\alpha_c > 0$ is some constant and $\alpha_0(t)$ is periodic, then these solutions are also symmetric. In Figs. 10–12 we see the difference between the solution (variables V, C, F , equivalently) to the model with constant reactivity α_c and the reactivity defined by Eq. (10) with $\delta = 0.9$ on the left-hand side and $\delta = -0.9$ on the right-hand side.

Other interesting results may be obtained for periodic initial functions. These results are presented in next figures. In these figures the vertical axis represents scaled values of all variables V, C, F and the solid and dotted lines have the same interpretation as in the first section.

The periodicity of initial data leads to periodic solution, but to obtain the periodic solution one need only the periodic initial function V^0 and F^0 , C^0 may not be periodic. If one consider V^0 periodic only, then C and F

FIGURE 7 The solution for time-dependent reactivity. Value of F .

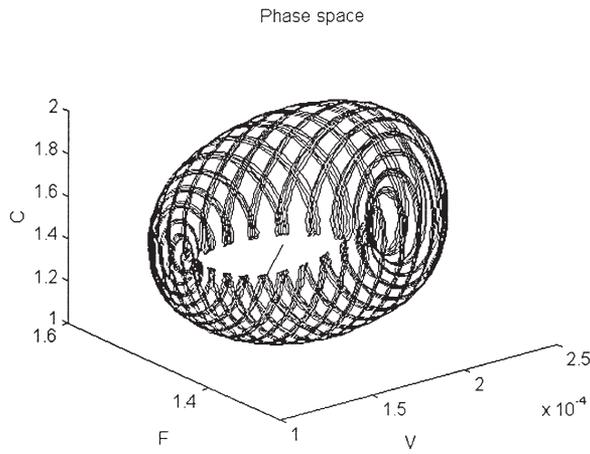


FIGURE 8 Phase space.

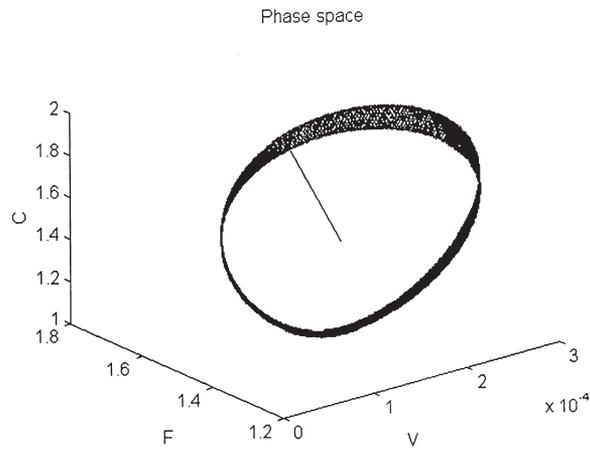


FIGURE 9 Phase space. Another example.

are also periodic, but V reaches the stationary value very fast. Initial data used in simulations is defined by Eq. (11), in Fig. 13 with $a_i = 0.8$, $i = v, c, f$ (almost identical solutions one obtain for $a_c = 0$). Figure 14 with $a_v = 0.8$, $a_c = a_f = 0$ illustrates the behaviour of solutions in the case of periodic first variable and constant two other ones.

ADAPTATION TO TUMOUR GROWTH DYNAMICS

There are many models similar to the MM which describe tumour growth dynamics (e.g. Asachenkov *et al.*, 1994; Kuznetsov *et al.*, 1994; Kirschner and Panetta, 1998). These models are built on the basis of cellular immune response and therefore, the model presented in the paper should be also interpreted in the same way. Now, as we mentioned in the first section, $V(t)$ is the amount of tumour cells, $F(t)$ denotes the concentration of immunocompetent cells, $C(t)$ —precursor cells. In the author’s opinion, the last variable $m(t)$ may be interpreted as a concentration of some inhibitory factors (chemicals) produced by tumour cells against the immune system. It seems to be obvious that in the case of high concentration of such factors it is not possible to simplify Marchuk’s model. In such case in the original model, even if the organism is strong but V_0 is sufficiently large, then the damage $m(t)$ increases very fast, such that $m(t) = 1$ at a very short time interval, which leads to the lethal outcome of the disease and which is not possible for the MM. In the case of tumour–immune interactions it is not necessary to identify $m(t) = 1$ with a patient’s death and therefore, the model may be also valid for $m(t) > 1$ and we should reformulate the definition of $\xi(m)$. This function may be defined as a smooth function with $\xi(0) = 1$ and $\lim_{m \rightarrow +\infty} \xi(m) = 0$ (so called switching

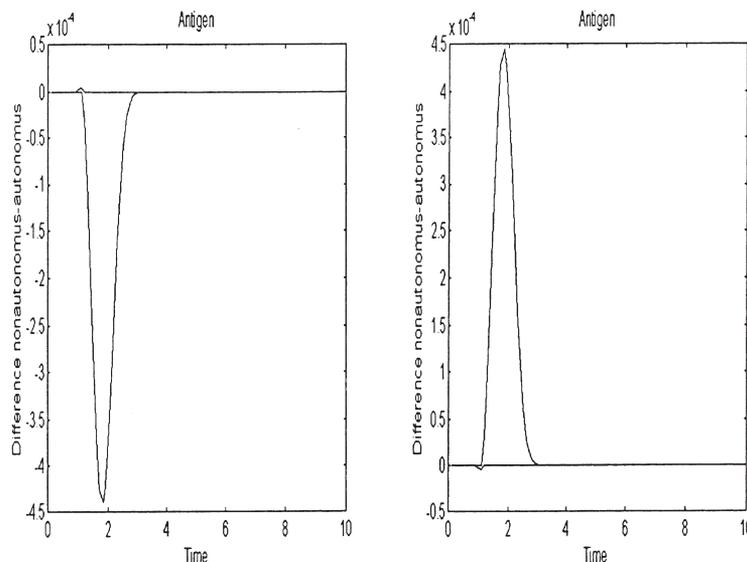


FIGURE 10 Symmetricity of solutions. Variable V .

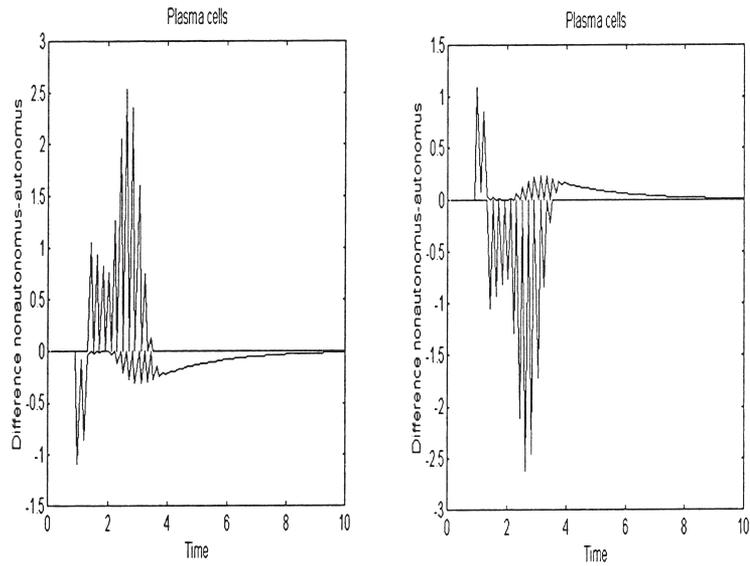


FIGURE 11 Symmetricity of solutions. Variable C .

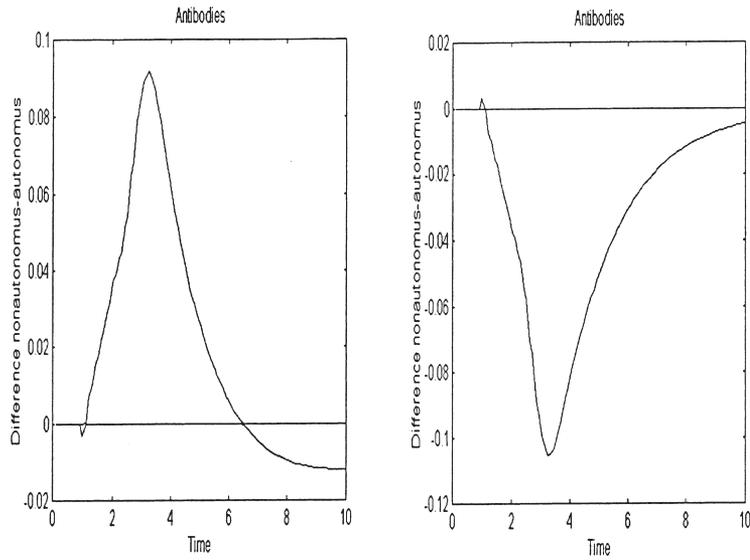


FIGURE 12 Symmetricity of solutions. Variable F .

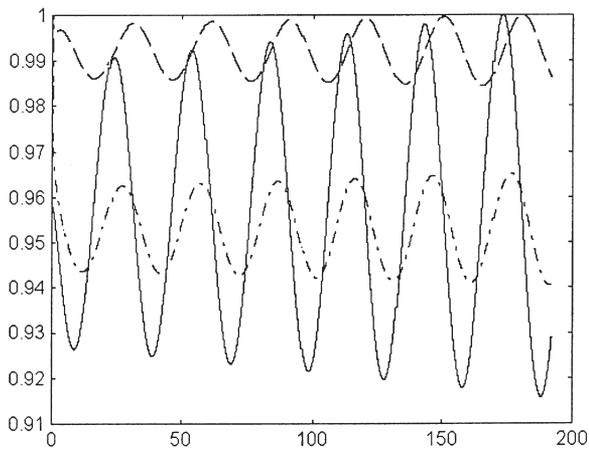


FIGURE 13 The solution for periodic initial functions.

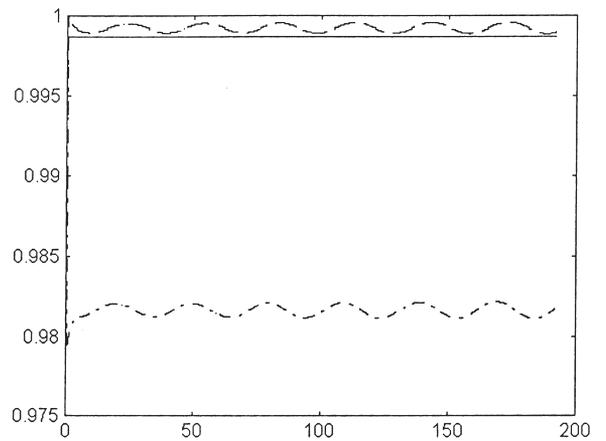


FIGURE 14 The solution for periodic V_0 only.

function). Of course one can consider ξ defined by Eq. (1) as well.

Also some other improvements are possible. For example one can study a role of interleukins in defence possibilities of the organism (see e.g. Foryś, 1995b; Kirschner and Panetta, 1998). In Kirschner and Panetta (1998) the similar to the MM model with interleukins IL_2 is proposed. Taking into account the role of interleukins and inhibitory factors, and following the ideas of Kirschner and Panetta (1998) considering the immunotherapy, we propose the following model

$$\begin{aligned}\dot{V}(t) &= (\beta - \gamma_1 F(t))V(t), \\ \dot{C}(t) &= c_1 + \alpha_c \xi(m)V(t - \tau_1)F(t - \tau_1) \\ &\quad - \mu_c(C(t) - C^*), \\ \dot{F}(t) &= c_2 + \varrho_0 C(t)(1 + \varrho_1 I(t)) - (\mu_f + \eta\gamma_1 V(t))F(t), \\ \dot{I}(t) &= c_3 + \alpha_0 F(t - \tau_2)V(t - \tau_2) + \alpha_1 F(t)I(t) \\ &\quad - \mu_1 I - \gamma_2 C(t)I(t), \\ \dot{m}(t) &= \sigma V(t) - \mu_m m(t),\end{aligned}\quad (12)$$

where $I(t)$ denotes the concentration of interleukin at time t , and c_i , $i = 1, 2, 3$, denote constant external flow of considered variables (immunotherapy).

The very basic properties as the existence and uniqueness of solutions to Eq. (12) may be studied similarly as for the MM, but we are not able to prove prolongability of solutions. There is some kind of “interleukin loop” in the model and therefore, the solution is supposed to explode.

Looking for stationary solutions to Eq. (12) one conclude that in the case without immunotherapy, i.e. $c_i = 0$, $i = 1, 2, 3$, there is a stationary state which describes a healthy organism, namely $(0, C^*, F^*, 0, 0)$ where F^* is defined similarly as for the original model, $F^* = \varrho_0 C^* / \mu_f$. Assuming $\xi(m) = 1$ and linearizing Eq. (12) one obtain the characteristic equation

$$\begin{aligned}(\beta - \gamma_1 F^* - \lambda)(\mu_c + \lambda)(\mu_f + \lambda) \\ (\alpha_1 F^* - \mu_1 - \gamma_2 C^* - \lambda) = 0\end{aligned}$$

and hence, if $\beta < \gamma_1 F^*$ (which is the same inequality as for the MM) and

$$\alpha_1 F^* < \mu_1 + \gamma_2 C^* \quad (13)$$

then this state is stable. Equation (13) is equivalent to

$$(\alpha_1 \varrho_0 - \gamma_2 \mu_f) C^* < \mu_f \mu_1,$$

which means that the healthy state cannot be stable if the organism produces too much interleukins and

immunocompetent cells (large coefficients ϱ_0 and α_1). This is the effect of “interleukin loop”.

If there is some immunotherapy, then the variable I at the stationary state with $V = 0$ need to satisfy

$$\begin{aligned}\frac{\alpha_1 \varrho_0 \varrho_1}{\mu_f} \left(\frac{c_1}{\mu_c} + C^* \right) I^2 \\ + \left(\frac{\alpha_1 c_2}{\mu_f} + \frac{\alpha_1 \varrho_0 - \gamma_2 \mu_f}{\mu_f} \left(\frac{c_1}{\mu_c} + C^* \right) - \mu_1 \right) I \\ + c_3 = 0.\end{aligned}\quad (14)$$

The above quadratic cannot be satisfied in the case of large coefficients α_1 , ϱ_0 (the “interleukin loop” effect again). If, e.g. $\alpha_1 = 0$, then Eq. (14) has the unique solution $I = c_3 / \mu_1 + \gamma_2 (c_1 / \mu_c + C^*)$. Therefore, for small α_1 the positive solution to Eq. (14) exists, but it is not unique, there are two solutions. It turns out that if such solution exists, then it is always unstable. This shows that the immunotherapy cannot last long time.

The proposed model can be useful in studying effects of immunotherapy in two cases—when there are some inhibitory factors in the organism ($\xi < 1$) or the level of such factors can be omitted ($\xi = 1$). In order to know properties of the solutions to Eq. (12) we need to do much more studies and it is the possible aim of a next paper.

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