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PERIODIC DYNAMICS IN A MODEL OF IMMUNE SYSTEM

Abstract. The aim of this paper is to study periodic solutions of Marchuk's model, i.e. the system of ordinary differential equations with time delay describing the immune reactions. The Hopf bifurcation theorem is used to show the existence of a periodic solution for some values of the delay. Periodic dynamics caused by periodic immune reactivity or periodic initial data functions are compared. Autocorrelation functions are used to check the periodicity or quasiperiodicity of behaviour.

1. Introduction. In 1980 Marchuk proposed ([13]) a mathematical model of an infectious disease. It is a system of four (three in the simplified form) differential equations with time delay. Although many papers studying the properties of solutions were published (see [1–6, 8, 9, 14, 15, 17]), several problems are still open. One of them is the existence of periodic solutions of the model. Studying oscillations and periodicity in the models with delay is a challenging problem (see e.g. [7, 10, 12]). In the present paper we study Marchuk's model with the immune reactivity coefficient depending on time, as proposed in [3, 4] (in [13] it was assumed that, for small damage of the organ-target, the immune reactivity coefficient α is constant). We investigate the periodic dynamics of Marchuk's model caused by different reasons.

The first reason is Hopf bifurcation. Analytical and numerical results presented in [8] and [9] suggest that if a solution of Marchuk's model oscillates, then it has a limit equal to the positive stationary solution, which describes the chronic form of a disease. In this paper we prove that a Hopf bifurcation may occur. We consider the Hopf bifurcation with respect to

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the delay as bifurcation parameter. In such a case a non-trivial periodic solution exists, for some values of parameters and delay.

The second reason of periodic dynamics is that the immune reactivity coefficient is a periodic function of time. Fundamental properties of the model with time-dependent immune reactivity were studied in [3, 4].

The next reason is initial data. If one investigates Marchuk's model with constant immune reactivity but with periodic initial functions, then the solution may be periodic. This type of initial data has not been studied earlier. The most typical initial data used in the literature (see [1–4, 8, 9, 14, 15]) is such that a healthy organism is infected by some dose of an antigen at an initial time moment. Mathematically a healthy organism is described by one of the stationary solutions (where the antigen is absent in the organism).

We compare all these types of periodic dynamics using numerical simulations.

1.1. *Presentation of the model.* Marchuk's model is derived under the assumptions presented in detail in [14]. We consider the case of small damage of the organ-target. In this case Marchuk's model is written as a system of three ODEs with time delay.

The following notations are used:

1) $V(t)$ is the antigen concentration at time t,
2) $C(t)$ is the plasma cell concentration at time t,
3) $F(t)$ is the antibody concentration at time t.

We consider two types of immune reactivity: constant reactivity (as proposed in [13]) and periodic reactivity (as proposed in [3]). We study the system

$$\begin{cases} \dot{V}(t) = (\beta - \gamma F(t))V(t) \\ \dot{C}(t) = \alpha(t)V(t-\tau)F(t-\tau) - \mu_c(C(t) - C^*) \\ \dot{F}(t) = \varrho C(t) - (\mu_f + \eta\gamma V(t))F(t) \end{cases} \tag{1}$$

where:

- β is the antigen reproduction rate coefficient;
- γ is a coefficient expressing the probability of the antigen-antibody meeting and their interactions;
- $\alpha(t)$ is the immune reactivity coefficient; α is a constant or a smooth (at least C^1) periodic function;
- τ is a constant delay of immune reaction;
- μ_c is the plasma cell coefficient, with μ_c^{-1} equal to the mean plasma cell lifetime;
- ϱ is the antibody production rate per one plasma cell;
- η is the rate of antibodies necessary to suppress one antigen;

• μ_f is the antibody coeffcient, with μ_f^{-1} equal to the mean antibody lifetime;

and all coefficients are non-negative.

In this paper the model defined by (1) will be referred to as the MM.

We consider the MM with initial data $(0, X^0(t))$, where

$$X^0(t) = (V^0(t), C^0(t), F^0(t)), \qquad t \in [-\tau, 0], \tag{2}$$

and V^0, C^0, F^0 are given periodic functions of class C^1, or

$$X^0(t) = \begin{cases} (0, C^*, F^*) & \text{for } t \in [-\tau, 0), \\ (V_0, C^*, F^*) & \text{for } t = 0, \end{cases} \tag{3}$$

where $F^* = \varrho C^*/\mu_f$ is the physiological level of antibodies and V_0 is the level of antigen concentration at the beginning of an infection.

2. Hopf bifurcation. In this section we assume that the immune reactivity coefficient is constant. We apply the Hopf bifurcation theorem to show the existence of a non-trivial periodic solution of the MM, for some values of the parameters and the delay. We use the delay as a parameter of bifurcation. Therefore, the periodicity is a result of changing the type of stability—from a stable stationary solution to a limit cycle. The MM can have two stationary solutions. The first one, $(0, C^*, F^*)$, describes the healthy state of an organism. For this point a Hopf bifurcation cannot occur, because the characteristic values are always real (see e.g. [2, 15]). Such behaviour is possible for the second stationary solution of the MM, which is

$$\overline{X} = (\overline{V}, \overline{C}, \overline{F}) = \left(\frac{\mu_c \mu_f (\beta - \gamma F^*)}{\beta(\alpha\varrho - \eta\gamma\mu_c)}, \frac{\alpha\beta\mu_f - \eta\gamma^2\mu_c C^*}{\gamma(\alpha\varrho - \eta\gamma\mu_c)}, \frac{\beta}{\gamma} \right).$$

This stationary solution describes the chronic form of disease (for details see [8, 9]), and exists only if $\alpha\varrho > \eta\gamma\mu_c$ and $\beta > \gamma F^*$ or $\alpha\varrho < \eta\gamma\mu_c$ and $\beta < \gamma F^*$.

First, we write the MM in the form useful to check the assumptions of the Hopf bifurcation theorem (see e.g. [7] or [12]). Consider the equation

$$\dot{x}(t) = L(\alpha, x_t) + G(\alpha, x_t), \tag{4}$$

where $x_t(h) = x(t+h)$, $h \in [-\tau, 0]$, α is a parameter, L is a linear operator, G is continuous together with its first derivative, $G(\alpha, 0) = 0$ and $\frac{\partial G}{\partial x_t}(\alpha, 0) = 0$ for every α.

Let

$$x(t) = (v(t), c(t), f(t)) = (V(t) - \overline{V}, C(t) - \overline{C}, F(t) - \overline{F}).$$

Now, we can rewrite the MM using notation (4), where

$$L = (L_1, L_2, L_3), \qquad G = (G_1, G_2, G_3),$$

and

$$
\begin{aligned}
L_1(\tau, v_t, c_t, f_t) &= -\gamma\overline{V} f_t(0),\\
L_2(\tau, v_t, c_t, f_t) &= \alpha\overline{F} v_t(-\tau) + \alpha\overline{V} f_t(-\tau) - \mu_c c_t(0),\\
L_3(\tau, v_t, c_t, f_t) &= \varrho c_t(0) - (\eta\gamma\overline{V} + \mu_f) f_t(0) - \eta\gamma\overline{F} v_t(0),\\
G_1(\tau, v_t, c_t, f_t) &= -\gamma v_t(0) f_t(0),\\
G_2(\tau, v_t, c_t, f_t) &= \alpha v_t(-\tau) f_t(-\tau),\\
G_3(\tau, v_t, c_t, f_t) &= -\eta\gamma v_t(0) f_t(0).
\end{aligned} \tag{5}
$$

It is obvious that L is linear, G is continuous together with its derivative (as a polynomial of the second degree in $x_t(0)$ and $x_t(-\tau)$), $G(\tau, 0, 0, 0) = (0, 0, 0)$ and $\frac{\partial G}{\partial x_t}(\tau, 0, 0, 0) = (0, 0, 0)$.

THEOREM 1. *Assume that $\alpha\varrho > \eta\gamma(\mu_c + \beta)$, $\beta > \gamma F^* + \mu_c$ and μ_f is sufficiently small. Then there exists $\tau_0 > 0$ such that the MM has a Hopf bifurcation at τ_0.*

Proof. Calculating the characteristic function yields the quasipolynomial

$$\mathrm{M}(\tau, \lambda) = -\lambda^3 - a\lambda^2 - b\lambda + g(\lambda + \beta)e^{-\lambda\tau},$$

where

$$
\begin{gathered}
a = \mu_c + \mu_f + \eta\gamma\overline{V} > 0, \qquad b = \mu_c\mu_f + (\eta\gamma\mu_c - \eta\beta\gamma)\overline{V},\\
d = \eta\gamma\beta\mu_c\overline{V} > 0, \qquad g = \alpha\varrho\overline{V} > 0.
\end{gathered}
$$

Let $\lambda = x + \mathrm{i}y$. We are looking for a pure positive imaginary characteristic value. Then $x = 0$, $y > 0$ and

$$
\begin{cases}
0 = \mathrm{Re}(\mathrm{M}(\tau, y)) = ay^2 + d + g\beta\cos(y\tau) + gy\sin(y\tau),\\
0 = \mathrm{Im}(\mathrm{M}(\tau, y)) = y^3 - by - g\beta\sin(y\tau) + gy\cos(y\tau).
\end{cases} \tag{6}
$$

Now, let

$$y_0\tau_0 = \pi(2k + 1), \tag{7}$$

where k is an integer. In this case (6) takes the form

$$
\begin{cases}
ay_0^2 + d - g\beta = 0,\\
y_0^3 - by_0 - gy_0 = 0.
\end{cases} \tag{8}
$$

To have a positive solution of (8) one needs $g\beta - d > 0$ and $b + g > 0$. If $\alpha\varrho > \eta\gamma\mu_c + \eta\gamma\beta$, then both these inequalities are satisfied. Hence, if

$$\frac{g\beta - d}{a} = b + g, \tag{9}$$

then (8) has a positive solution. Now (9) is equivalent to

$$H(\overline{V}) = A\overline{V}^2 + B\overline{V} + D = 0, \tag{10}$$

where

$$A = \eta\gamma(\alpha\varrho + \eta\gamma\mu_c - \eta\beta\gamma),$$
$$B = \eta\gamma\mu_c\mu_f + (\mu_c + \mu_f)(\alpha\varrho + \eta\gamma\mu_c - \eta\beta\gamma) - \beta(\alpha\varrho - \eta\gamma\mu_c),$$
$$D = \mu_c\mu_f(\mu_c + \mu_f).$$

One can calculate

$$\Delta = B^2 - 4AD,$$

and if $\mu_c\mu_f = 0$, then $\Delta > 0$ and $B < 0$. Therefore, there exist values of μ_f such that $\Delta > 0$ and $B < 0$. Hence, (10) has a positive solution in this case.

If $\alpha\varrho > \eta\gamma\mu_c + \eta\gamma\beta$, $\beta > \gamma F^* + \mu_c$, and $H(\overline{V}) = 0$, then (8) has a solution, and then (6) has a solution of the form (7). It is easy to see that such a solution (τ_0, y_0) of (6) is unique for fixed τ_0.

Let (τ_0, y_0) denote the unique solution of (6). Using the implicit function theorem, one calculates $\frac{dx}{d\tau}(\tau)$ as

$$\frac{dx}{d\tau}(\tau) = \frac{\frac{\partial F_1}{\partial \tau}(\tau,x,y)\frac{\partial F_2}{\partial y}(\tau,x,y) - \frac{\partial F_2}{\partial \tau}(\tau,x,y)\frac{\partial F_1}{\partial y}(\tau,x,y)}{\frac{\partial F_2}{\partial x}(\tau,x,y)\frac{\partial F_1}{\partial y}(\tau,x,y) - \frac{\partial F_1}{\partial x}(\tau,x,y)\frac{\partial F_2}{\partial y}(\tau,x,y)}, \tag{11}$$

where

$$\mathrm{M}(\tau, x + \mathrm{i}y) = F_1(\tau,x,y) + \mathrm{i}F_2(\tau,x,y)$$

and

$$\begin{aligned} F_1(\tau,x,y) = {} & -x^3 + 3xy^2 - ax^2 + ay^2 - bx + d \\ & + e^{-x\tau}g(x+\beta)\cos(y\tau) + e^{-x\tau}gy\sin(y\tau), \\ F_2(\tau,x,y) = {} & -3x^2y + y^3 - 2axy - by \\ & - e^{-x\tau}g(x+\beta)\sin(y\tau) + e^{-x\tau}gy\cos(y\tau). \end{aligned}$$

The relevant derivatives at $(\tau_0, 0, y_0)$ are

$$\frac{\partial F_1}{\partial \tau}(\tau_0,0,y_0) = -gy_0\beta\sin(y_0\tau_0) + gy_0^2\cos(y_0\tau_0),$$
$$\frac{\partial F_2}{\partial y}(\tau_0,0,y_0) = 3y_0^2 - b + g(1-\beta\tau_0)\cos(y_0\tau_0) - gy_0\tau_0\sin(y_0\tau_0),$$
$$\frac{\partial F_2}{\partial \tau}(\tau_0,0,y_0) = -gy_0\beta\cos(y_0\tau_0) - gy_0^2\sin(y_0\tau_0),$$
$$\frac{\partial F_1}{\partial y}(\tau_0,0,y_0) = 2ay_0 + g(1-\beta\tau_0)\sin(y_0\tau_0) + gy_0\tau_0\cos(y_0\tau_0),$$
$$\frac{\partial F_1}{\partial x}(\tau_0,0,y_0) = 3y_0^2 - b + g(1-\beta\tau_0)\cos(y_0\tau_0) - gy_0\tau_0\sin(y_0\tau_0),$$
$$\frac{\partial F_2}{\partial x}(\tau_0,0,y_0) = -2ay_0 - g(1-\beta\tau_0)\sin(y_0\tau_0) - gy_0\tau_0\cos(y_0\tau_0).$$

Therefore,

$$\frac{\partial F_1}{\partial y}(\tau_0,0,y_0) = -\frac{\partial F_2}{\partial x}(\tau_0,0,y_0) \quad \text{and} \quad \frac{\partial F_2}{\partial y}(\tau_0,0,y_0) = \frac{\partial F_1}{\partial x}(\tau_0,0,y_0)$$

and then

$$\frac{\partial F_2}{\partial x}(\tau_0,0,y_0)\frac{\partial F_1}{\partial y}(\tau_0,0,y_0) - \frac{\partial F_1}{\partial x}(\tau_0,0,y_0)\frac{\partial F_2}{\partial y}(\tau_0,0,y_0)$$
$$= -\left(\frac{\partial F_1}{\partial y}(\tau_0,0,y_0)\right)^2 - \left(\frac{\partial F_1}{\partial x}(\tau_0,0,y_0)\right)^2 \le 0.$$

For the point (τ_0, y_0) one calculates

$$\frac{dx}{d\tau}(\tau_0) = -y_0^2 g \frac{-3y_0^2 + b + g - 2a\beta}{y_0^2(2a - g\tau_0)^2 + (3y_0^2 - b - g(1-\beta\tau_0))^2}.$$

Due to (10) we have $3y_0^2 \neq b+g-2a\beta$. Therefore, if $\tau_0 \neq 2a$, then $\frac{dx}{d\tau}(\tau_0) \neq 0$ and this completes the proof of the existence of a Hopf bifurcation for the MM. ∎

Remark 1. *Suppose $\beta < \gamma F^*$ and $\alpha\varrho$ is sufficiently small. Then a Hopf bifurcation with respect to τ cannot occur in the MM.*

Proof. Consider the first equation of (6). If $\tau = 0$, then

$$0 = \mathrm{Re}(\mathrm{M}(0,y)) = ay^2 + d + g\beta,$$

and this equation has no positive solutions.

Comparing the functions

$$\Phi(y) = ay^2 + d + g\beta\cos(y\tau) \quad \text{and} \quad \Psi(y) = -gy\sin(y\tau),$$

for arbitrary τ, we see that $\Phi(y) \in [ay^2 + d - g\beta, ay^2 + d + g\beta]$ and $\Psi(y) \in [-gy, gy]$, for every $y > 0$. Therefore, if $\Phi(y) > \Psi(y)$ for every $y > 0$, then there are no positive solutions of (6). Hence, if

$$ay^2 - gy + d - g\beta > 0 \quad \text{for every } y > 0, \tag{12}$$

then there are no solutions. Inequality (12) is equivalent to

$$4\beta(\eta\gamma\mu_c - \alpha\varrho)(\mu_c + \mu_f + \eta\gamma\overline{V}) > \alpha^2\varrho^2\overline{V}. \tag{13}$$

Inequality (13) holds only if $\alpha\varrho < \eta\gamma\mu_c$, and then $\beta < \gamma F^*$.

Assume that $\alpha\varrho = 0$. In this case (13) takes the form

$$4\eta\gamma\mu_c(\beta\mu_c + \gamma F^*\mu_f) > 0,$$

which is obviously satisfied, and therefore, for sufficiently small values of $\alpha\varrho$, (6) has no solutions. ∎

Remark 1 means that if the organism is weak (small $\alpha\varrho$) and the antigen reproduction rate β is small (i.e. $\beta < \gamma F^*$), then a Hopf bifurcation cannot occur, independently of the magnitude of the delay. This is not

surprising. In this case the stationary state $\overline{X}$ is not stable (see [2]), and for a small initial value of the antigen the solution has a limit equal to the stationary solution $(0, C^*, F^*)$, but for larger initial values of the antigen, the concentration of the antigen increases to infinity in time (see [9]).

3. Periodic immune reactivity. In this section we show some interesting numerical results about the behaviour of solutions of the MM for periodic functions α. Our numerical methods are similar to those presented in [11]. In order to use the values of the coefficients published in [2] and [13], we define new variables, without changing the notation of the previous section:

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

where V_M is the maximal value of the antigen concentration in the organism, and therefore, $v \leq 1$.

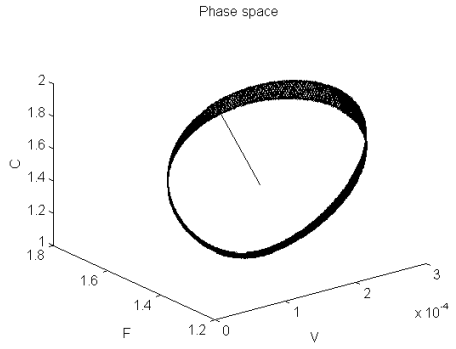

Fig. 1. Phase space of the MM for $\beta = 1.2$ and $\delta = 0.9$

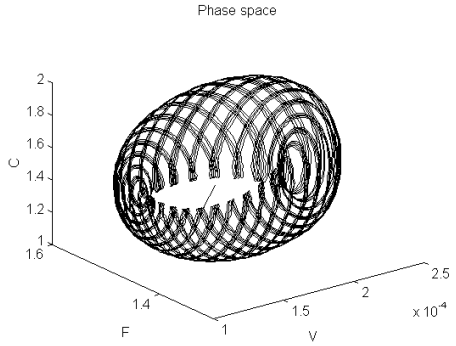

Fig. 2. Phase space of the MM for $\beta = 1.16$ and $\delta = 0.9$

Let

$$\gamma_1 = \gamma F^*, \qquad \eta_1 = \eta\gamma V_M, \qquad \alpha_1(t) = \frac{\alpha(t) F^* V_M}{C^*}.$$

In computations we use the immune reactivity of the form

$$\alpha_1(t) = \alpha_c\left(1 + \delta \sin\left(\frac{2\pi}{\tau}t\right)\right).$$

In the case of time-dependent immune reactivity, the MM has only one stationary solution—the healthy state $(0, C^*, F^*)$ (see [3, 4]), but we have calculated the solution in the neighbourhood of the second stationary state $\overline{X}$ for an appropriate model with constant coefficient, i.e. $\alpha = \alpha_c$. In the paper we present the most interesting results of computations. One of such results was observed for the coefficients

$$\gamma_1 = 0.8,\ \mu_F = 0.17,\ \mu_C = 0.5,\ \eta_1 = 8,\ \alpha_c = 1000,$$

and the time delay $\tau = 0.5$ and $\beta = 1.16$ or $\beta = 1.2$.

The result for $\beta = 1.16$ and $\delta = 0.9$ is presented in Fig. 2 as the phase space of the MM.

For $\beta = 1.2$ and $\delta = 0.9$ we have got a phase portrait which looks like a ring or Möbius strip (see Fig. 1). In the second case it is possible that the

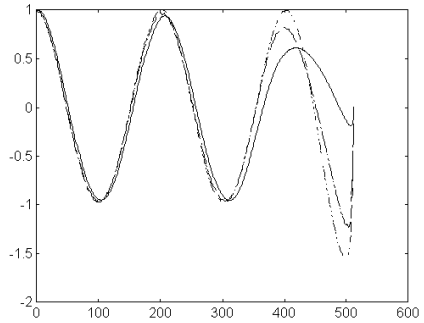

Fig. 3. Autocorrelation functions for solutions of MM for $\beta = 1.2$

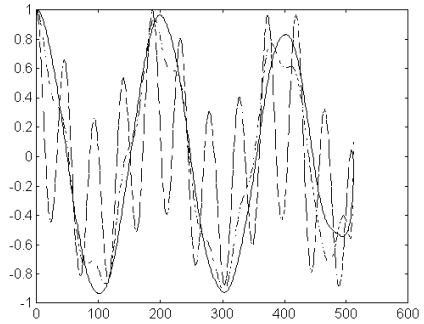

Fig. 4. Autocorrelation functions for solutions of MM for $\beta = 1.16$

dynamics is chaotic. In order to check it we calculate an autocorrelation function (see [16]). Let the time average of the function f be given

$$f_{\mathrm{av}} = \lim_{T\to+\infty} \frac{1}{T} \int_0^T f(s)\,ds.$$

In [3] it was shown that this limit exists for the strong immune system, i.e. for large values of $\alpha\varrho$ (and then $\beta > \gamma F^*$). Now, we calculate the autocorrelation function for f using the formula

$$a_f(t) = \lim_{T\to+\infty} \frac{1}{T} \int_0^T \widehat{f}(s+t)\widehat{f}(s)\,ds,$$

where $\widehat{f}(s) = f(s) - f_{\mathrm{av}}$. The autocorrelation functions for v and c are also calculated using similar expressions (averages for v and c are calculated only numerically). In Figs. 3, 4 we can see the results. The autocorrelation function for v is presented as a line, for c as "line-space-line" and for f as "line-dot". The regular behaviour of the autocorrelation functions suggests that the dynamics is periodic or quasiperiodic.

3.1. *Symmetric solutions for symmetric $\alpha(t)$.* Now, we compare solutions of the MM for symmetric functions α, i.e. we consider the function α of the form

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

where α_0 is periodic, i.e. $\alpha_0(t)=\alpha_0(t+T)$ for some $T>0$, and $\int_0^T \alpha_0(s)\,ds=0$ (for example $\alpha_0(t)=\sin t$, $T=2\pi$).

Let $v(t) = V(t)$, $c(t) = C(t) - C^*$, $f(t) = F(t) - F^*$. Then $(0,0,0)$ is the unique stationary solution of the model with time-dependent immune reactivity (see [3, 4]). Linearizing the MM around this point yields

$$\begin{cases} \dot{v}(t) = (\beta - \gamma F^*)v(t), \\ \dot{c}(t) = -\mu_c c(t) + \alpha(t)F^* v(t-\tau), \\ \dot{f}(t) = \varrho c(t) - \mu_f f(t) - \eta\gamma F^* v(t). \end{cases} \tag{14}$$

Therefore,

$$v(t) = V_0 e^{(\beta-\gamma F^*)t} = V_0 e^{\beta_1 t},$$

where $\beta_1 = \beta - \gamma F^*$, and

$$c(t) = V_0 F^* e^{-\mu_c t} \int_0^t \alpha(s) e^{(\beta_1+\mu_c)s}\,ds.$$

Now, denote by $(v(t), c(t), f(t))$ the solution for the constant coefficient $\alpha = \alpha_c$, by $(v(t), c_+(t), f_+(t))$ the solution for α_+, and by $(v(t), c_-(t), f_-(t))$

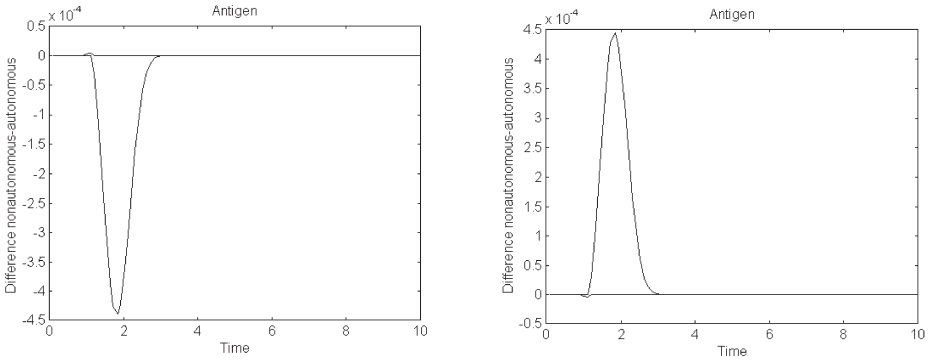

Fig. 5. The difference between the antigen coefficients of solutions of the autonomous and noautonomous models (left: $\delta = 0.9$, right: $\delta = -0.9$)

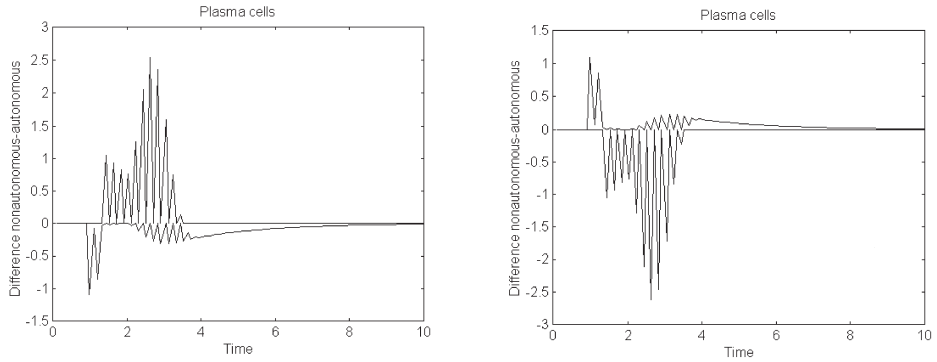

Fig. 6. The difference beetween the plasma cell coefficients of the solution of the autonomous and noautonomous models (left: $\delta = 0.9$, right: $\delta = -0.9$)

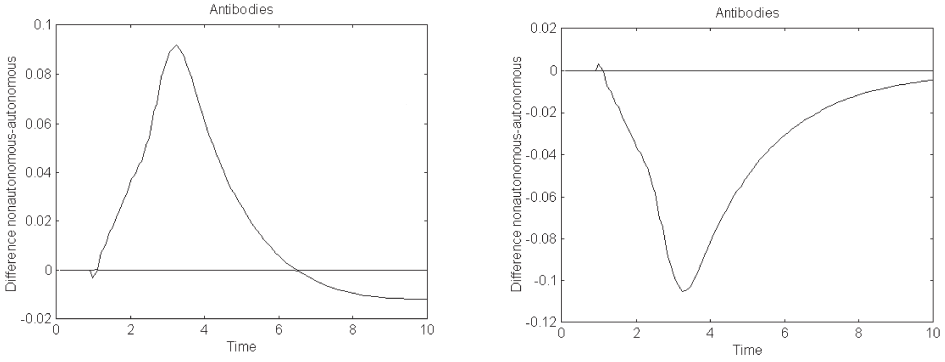

Fig. 7. The difference between the antibody coefficients of solutions of the autonomous and noautonomous models (left: $\delta = 0.9$, right: $\delta = -0.9$)

the solution for α_-. Then

$$c_+(t) - c(t) = V_0 F^* e^{-\mu_c t} \int_0^t \alpha_0(s) e^{(\beta_1+\mu_c)s}\, ds,$$

and

$$c_-(t) - c(t) = -(c_+(t) - c_-(t)).$$

It is obvious that the functions f_+ and f_- are also symmetric, i.e.

$$f_-(t) - f(t) = -(f_+(t) - f(t)).$$

In the case of the MM the function C can also be calculated as a functional of V. Integrating by parts (as in [9]) yields

$$C(t) = C^* + \frac{1}{\gamma}\Big[e^{-\mu_c t}\int_0^t V(s-\tau)e^{\mu_c s}(\mu_c + \beta + \dot\alpha(s))\, ds + V_0 e^{-\mu_c t} e^{-\beta_1 \tau}\alpha(0) - V(t-\tau)\alpha(t)\Big].$$

Assume that $V(t)$ behaves as in the linear case. Then

$$c(t) = \frac{V_0 e^{-\beta_1\tau}}{\gamma}\Big[e^{-\mu_c t}\int_0^t e^{(\beta_1+\mu_c)s}(\mu_c + \beta + \dot\alpha(s))\, ds + \alpha(0)e^{-\mu_c t} - \alpha(t)e^{\beta_1 t}\Big]. \tag{15}$$

Hence

$$c_+(t) - c(t) = \frac{V_0 e^{-\beta_1\tau}}{\gamma}\Big[e^{-\mu_c t}\int_0^t e^{(\beta_1+\mu_c)s}\alpha_c\dot\alpha_0(s)\, ds + \alpha_c\alpha_0(0)e^{-\mu_c t} - \alpha_c\alpha_0(t)e^{-\beta_1 t}\Big]$$

and again

$$c_-(t) - c(t) = -(c_+(t) - c(t)), \qquad f_-(t) - f(t) = -(f_+(t) - f(t)).$$

Our computer simulations (see Figs. 5–7) show that every relevant coefficient of the solution of the MM for $\alpha_+(t) = \alpha_c(1 + \delta\sin(\frac{2\pi}{\tau}t))$ and $\alpha_-(t) = \alpha_c(1 - \delta\sin(\frac{2\pi}{\tau}t))$, $\delta = \text{const}$, is symmetric.

4. Periodic initial conditions. In this section we study the behaviour of solutions of the MM for periodic initial conditions and constant immune reactivity α. We use the following initial functions:

$$\varphi_i(t) = \overline{x}_i\left(1 + a_i \sin\left(\frac{2\pi t}{b_i\tau}\right)\right), \qquad i = v, c, f,$$

where $\overline{x} = (\overline{x}_1, \overline{x}_2, \overline{x}_3) = (\overline{v}, \overline{c}, \overline{f})$ denotes the chronic stationary solution of the MM.

Our simulations show that the periodicity of the solution is the result of the periodicity of φ_f and φ_v. The periodicity of φ_c has no influence on the periodicity of the solutions.

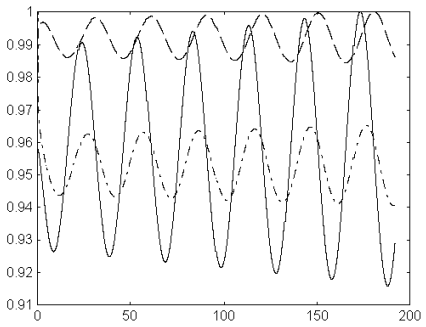

Fig. 8. The solution of the MM for $a_v = a_c = a_f = 0.8$

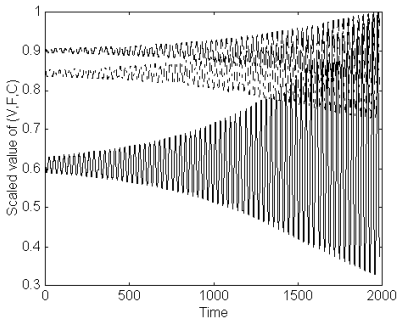

Fig. 9. The solution of the MM for $a_v = a_c = a_f = 0.8$

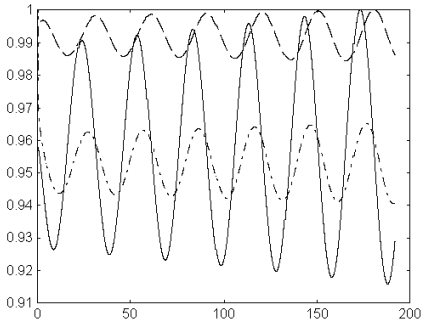

Fig. 10. The solution of the MM for $a_v = a_f = 0.8$ and $a_c = 0$

In Fig. 8 we can see the behaviour of the solution of the MM when every initial function is periodic. In Fig. 9 we can see the same solution

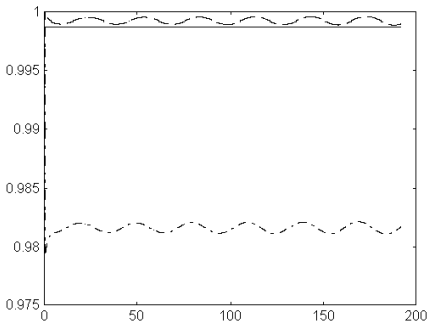

Fig. 11. The solution of the MM for $a_v = 0.8$ and $a_c = a_f = 0$

but in a longer time interval. Let us compare Fig. 8 and Fig. 10 which shows the behaviour of solutions of the MM for the initial condition with $a_v = 0.8$, $a_f = 0.8$ and $a_c = 0$. We see that these figures are almost identical. This is not surprising, because the periodicity of φ_v and φ_f implies the periodic behaviour of c on the interval $[0, \tau]$, and later the behaviour should be periodic, too.

In Fig. 11 we present the solution of MM when only φ_v is periodic. What is now surprising is that the periodic dynamics of φ_v produces the periodicity of c and f, but v reaches the stationary value $\overline{v}$ very fast.

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