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BEHAVIOUR OF SOLUTIONS TO MARCHUK'S MODEL DEPENDING ON A TIME DELAY

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Marchuk's model of an immune reaction is a system of differential equations with a time delay. The aim of this paper is to study the behaviour of solutions to Marchuk's model depending upon the delay of immune reaction and the history of an illness. We study Marchuk's model without delays, with a constant delay and with an infinite delay. A continuous dependence on the delay is considered. Bifurcation points are found using computer simulations.

Keywords: antigen, antibody, plasma cell, organ-target, delay differential equation, stationary state, stability, bifurcation point

1. Introduction

In 1980 Marchuk proposed (Marchuk, 1980) a mathematical model of an infectious disease. It is a system of four (or three in a simplest form) differential equations with a time delay. Although many papers studying the properties of solutions have been published (Belykh, 1988; Bofill *et al.*, 1996; Foryś, 1995; 2000; Marchuk, 1983; 1997; Szlenk and Vargas, 1995), several problems are still open. One of them is the dependence of solutions to the model on time delays. In the model, there appears a delay of reaction of the system with respect to the contamination moment. Accordingly, the system does not react immediately, and it needs some time to detect and investigate the contamination by an antigen.

The dependence on a time delay for functional-differential equations (FDE's) is a challenging problem. However, some types of FDE's have already been studied in detail (Cao *et al.*, 1998; Gopalsamy, 1992; Kolmanovskii and Nosov, 1986; Kuang, 1993; So *et al.*, 1996). In the case of RFDE's (Retarded Functional-Differential Equations) with a continuous right-hand side, a positive delay may be considered as any other parameter of the model and therefore, the dependence of solutions on it is continuous (Kuang, 1993). Furthermore, for linear RFDE's it is known (Kolmanovskii and Nosov, 1986) that for a sufficiently small delay the behaviour of the solutions is similar to the appropriate ODE's without delays. Many special types of RFDE's

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have been studied in much more detail. For example, Lotka-Volterra equations with delays, i.e.

$$\dot{X}_i(t) = X_i(t)\Big(r_i + a_{ij}X_j + \sum_{j=1}^{n} b_{ij}X_j(t-\tau_{ij})\Big), \quad i = 1,\dots,n \tag{1}$$

were studied in (Gopalsamy, 1992; Kuang, 1993; Lu and Wang, 1997), or FDE's of Lotka-Volterra type, i.e.

$$\dot{X}_i(t) = B_i(X_i(t))\Big(r_i - a_iX_i(t) + \sum_{j=1}^{n}\sum_{l=1}^{l_{ij}} b_{ijl}X_j(t-\tau_{ijl}) + \sum_{j=1}^{n}\int_0^{\infty} b_{ij}(t,s)X_j(t-s)\,\mathrm{d}s\Big), \quad i = 1,\dots,n \tag{2}$$

were studied e.g. in (Bereketoglu and Gyori, 1997).

Marchuk's model can also be considered as Lotka-Volterra equations, but there is a second-order term with delay (i.e. the term of the type $X_i(t-\tau)X_j(t-\tau)$) in the model which is absent in (1) and (2).

The paper is a first step in studying the behaviour of Marchuk's model and a larger class of equations of the type

$$\dot{X}_i = r_iX_i + X_i(t-\tau_i)\sum_{j=1}^{n} a_jX_j(t-\tau_{ji}), \quad i = 1,\dots,n$$

depending on the magnitudes of delays.

2. Presentation of the Model

In the paper, we consider the case of a slight damage to an organ-target. In this case Marchuk's model is written as a system of three DE's with a time delay.

The following notation is used in the model:

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.

Marchuk's model is derived under the following assumptions:

1. The number of antigens depends on their reproduction rate and the suppression by antibodies,

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \beta V(t) - \gamma F(t)V(t),$$

where β is the antigen reproduction rate coefficient, and γ is the coefficient expressing the probability of the antigen-antibody meeting and their interactions.

2. If no antigen is in the organism, then the plasma cell production depends on the deviation from the normal level C^*. If some antigen appears, then the so-called VT-complexes are formed (to simplify the model, it is assumed that the VT-complex rate depends on the number of antigen-antibody encounters). Stimulation of a B-cell by VT-complexes triggers off the plasma cell production process. The plasma cell production is delayed relative to the B-cell stimulation process

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \alpha V(t-\tau)F(t-\tau) - \mu_c(C - C^*),$$

where C^* is the level of plasma cells in the healthy organism, α is the immune process stimulation coefficient, μ_c is the plasma cell coefficient, with μ_c^{-1} equal to the mean plasma cell lifetime.

3. The number of antibodies depends on their production rate and their death due to immune reactions and ageing,

$$\frac{\mathrm{d}F}{\mathrm{d}t} = \varrho C(t) - \eta\gamma V(t)F(t) - \mu_f F(t),$$

where ϱ is the antibody production rate per one plasma cell, η is the rate of antibodies necessary to suppress one antigen, μ_f is an antibody coefficient, with μ_f^{-1} equal to the mean antibody lifetime.

Therefore, in this paper, we study the system

$$\begin{cases} \dot{V}(t) = (\beta - \gamma F(t))V(t), \\ \dot{C}(t) = \alpha V(t-\tau)F(t-\tau) - \mu_c(C(t) - C^*), \\ \dot{F}(t) = \varrho C(t) - (\mu_f + \eta\gamma V(t))F(t), \end{cases} \tag{3}$$

with non-negative coefficients and initial data $(0, X_0(t))$, where

$$X_0(t) = \begin{cases} (0, C^*, F^*) & \text{for} \quad t < 0, \\ (V_0, C^*, F^*) & \text{for} \quad t = 0, \end{cases} \tag{4}$$

and $F^* = \varrho C^*/\mu_f$ is the physiological level of antibodies. Model (3) will be referred to as the MM in this paper and will be considered together with the initial data (4).

It is known (Belykh, 1988; Marchuk, 1980; 1983; 1997) that the solution to the MM exists, and for every $t \geq 0$ is continuous and non-negative for non-negative initial data.

In parallel, we consider a model with an infinite delay, which is based on the same assumptions. Then the MM can be generalized as follows:

$$\begin{cases} \dot{V}(t) = \big(\beta - \gamma F(t)\big)V(t), \\ \dot{C}(t) = \alpha \displaystyle\int_{-\infty}^{0} w(h)V(t+h)F(t+h)\,\mathrm{d}h - \mu_c\big(C(t) - C^*\big), \\ \dot{F}(t) = \varrho C(t) - \big(\mu_f + \eta\gamma V(t)\big)F(t), \end{cases} \tag{5}$$

where $w(\cdot)$ is a probability distribution function, $\int_{-\infty}^{0} w(h)\,\mathrm{d}h = 1$, $w(h) \geq 0$ for every $h \in (-\infty, 0)$.

For the Dirac distribution at $h = -\tau$, it is obvious that (5) takes the form (3). Such a model was studied in (Foryś, 1993) with the distribution's support contained in $[-\tau, 0]$. Using the same arguments as in (Foryś, 1993), it is easy to prove that a non-negative continuous solution (5) exists for all non-negative initial data.

The MM and (5) have the same stationary states

$$X_1 = (0, C^*, F^*), \quad X_2 = (\bar{V}, \bar{C}, \bar{F}) = \left(\frac{\mu_c \mu_f (\beta - \gamma F^*)}{\beta(\alpha\varrho - \eta\gamma\mu_c)}, \frac{\alpha\beta\mu_f - \eta\gamma^2\mu_c C^*}{\gamma(\alpha\varrho - \eta\gamma\mu_c)}, \frac{\beta}{\gamma} \right).$$

X_2 exists only in the case of an efficient immune system but with a small physiological level of antibodies, i.e. $\alpha\varrho > \eta\gamma\mu_c$ and $\beta > \gamma F^*$, or in the case of immunodeficiency but with a weak antigen, i.e. $\alpha\varrho < \eta\gamma\mu_c$ and $\beta < \gamma F^*$. X_1 describes the healthy state of the organism, whereas X_2 corresponds to the chronic form of the disease.

The following theorems, describing the behaviour of the solutions to the MM, were proved in (Belykh, 1988; Foryś, 1995; 2000)

Theorem 1. *The state $X_1 = (0, C^*, F^*)$ of the MM is locally asymptotically stable if and only if $\beta < \gamma F^*$. Moreover, if the inequality*

$$\alpha\varrho > e^{\beta\tau}\eta\gamma(\mu_c + \beta) \tag{6}$$

holds, then this state is globally stable.

Theorem 2. *If $\beta > \gamma F^*$ and*

$$\alpha\varrho < e^{(\beta - \gamma F^*)\tau}\eta\gamma\mu_c, \tag{7}$$

then, for every solution to the MM, $V(t)$ increases to $+\infty$ and $F(t)$ has a limit equal to 0 as $t \to +\infty$.

Note that, for $\beta = 0$, (6) does not depend on τ. In this case the antigen cannot reproduce (e.g. the case of vaccinations). Therefore, if the immune system is efficient in Marchuk's meaning, i.e. $\alpha\varrho > \eta\gamma\mu_c$, then every infection leads to the recovery. Such types of infection were studied in (Bofill *et al.*, 1996; Foryś, 1999).

Also note that, in the case of a small physiological level of antibodies (i.e. $\gamma F^* < \beta$), even for $\alpha\varrho > \eta\gamma\mu_c$ (the system is efficient), if τ is large enough, then (7) is satisfied. It is obvious that, for τ large enough (6), is not fulfilled. This means that independently of other parameters, if τ is large enough, then, sooner or later, the organism must be destroyed.

3. Extreme Cases

In this section, we study two extreme cases. The first case (an infinite delay) has not been studied so far. The second case (no delay) was studied in (Szlenk and Vargas, 1995).

3.1. Infinite Delay

Consider the case of an infinite delay, i.e. (5) with initial data (4). Local stability of the stationary state X_1 does not depend on the delay. Therefore, there is no change of stability conditions with an increasing delay, i.e. X_1 is locally asymptotically stable if and only if $\beta < \gamma F^*$.

Lemma 1. *If* $\beta < \gamma F^*$, $0 < V_0 < V^*$, *where*

$$V^* = \min\left(\frac{\mu_f}{\eta\beta\gamma}(\gamma F^* - \beta), \frac{\mu_c\mu_f}{\alpha\varrho}\right),$$

then for every solution $X(t)$ *to (5) we have* $\lim\limits_{t\to+\infty} X(t) = X_1$.

Proof. It is similar to the proof of Corollary 1 in (Foryś, 1993). ∎

Using the same framework as in (Foryś, 1993), we can prove the following result concerning the local stability of the state X_2.

Lemma 2. *Let* $m_1(w) = -\int_{-\infty}^{0} hw(h)\,\mathrm{d}h$ *and* $\mu_c m_1(w) \leq 1$. *If*

$$0 < \frac{H - D}{A - Gm_1(w)} < B - G - Hm_1(w), \tag{8}$$

where $A = \mu_c + \mu_f + \eta\gamma\bar{V}$, $B = \mu_c(\mu_f + \eta\gamma\bar{V}) - \eta\beta\gamma\bar{V}$, $D = \eta\beta\gamma\mu_c\bar{V}$, $G = \alpha\varrho\bar{V}$, $H = \beta G$, *then* X_2 *is locally stable.*

Remark 1. If $\alpha \to +\infty$, then condition (8) takes the simpler form

$$0 < \beta - \gamma F^* < \frac{1}{\frac{1}{\mu_c+\mu_f} + m_1(w)}. \tag{9}$$

It is obvious that the range of the parameters for which X_2 is locally stable depends on the distribution w. If the influence of memory is large (i.e. $w(h)$ is large for large values of $|h|$), then m_1 is also large and the right-hand side of (9) is small. In the case of a constant delay, m_1 cannot be as large as in the case of an infinite dalay. Therefore, it is possible that for fixed parameters and constant delay τ the state X_2 is stable and a chronic form of the disease can appear, but for an infinite delay with appropriate distribution the state X_2 is unstable and a chronic disease is not possible.

3.2. The Case Without Delay

In this paragraph, we study the case with no delay, i.e. the system of ordinary differential equations

$$\begin{cases} \dot{V}(t) = \big(\beta - \gamma F(t)\big)V(t), \\ \dot{C}(t) = \alpha V F - \mu_c\big(C(t) - C^*\big), \\ \dot{F}(t) = \varrho C(t) - \big(\mu_f + \eta\gamma V(t)\big)F(t). \end{cases} \tag{10}$$

Conditions for the stability of the healthy state (X_1) of the MM do not depend on the delay and therefore, are the same for the MM, (5) and (10). Consider stability conditions for the chronic state X_2. In this case the characteristic polynomial is equal to

$$\begin{aligned} W(\lambda) &= -\lambda^3 - a_1\lambda^2 - a_2\lambda - a_3, \\ a_1 &= \mu_c + \mu_f + \eta\gamma\bar{V}, \\ a_2 &= \mu_c\mu_f + (\eta\gamma\mu_c - \alpha\varrho - \eta\beta\gamma)\bar{V}, \\ a_3 &= \mu_c\mu_f(\beta - \gamma F^*). \end{aligned} \tag{11}$$

If $\beta < \gamma F^*$, then $W(0) < 0$ and therefore there exists a positive eigenvalue and the state X_2 is unstable. Applying Hurwitz's criterion (as in (Szlenk and Vargas, 1995)), we obtain the following condition of local asymptotical stability:

$$a_1 a_2 > a_3 > 0.$$

Therefore

$$\beta > \gamma F^*$$

and

$$\left(\mu_c + \mu_f + \frac{\eta\gamma\mu_c\mu_f(\beta - \gamma F^*)}{\beta(\alpha\varrho - \eta\gamma\mu_c)}\right)\left(\frac{\gamma F^*}{\beta} - \eta\gamma\frac{\beta - \gamma F^*}{\alpha\varrho - \eta\gamma\mu_c}\right) > \beta - \gamma F^*. \tag{12}$$

Now, we consider some special cases.

Assume that $\beta = \gamma F^*$. Then (12) takes the form $\mu_c + \mu_f > 0$. This means that there exists an interval $(\gamma F^*, \beta_1)$ such that if $\beta \in (\gamma F^*, \beta_1)$, then (12) is satisfied and X_2 is locally asymptotically stable.

For $\beta \to +\infty$, (12) leads to

$$-\left(\mu_c + \mu_f + \frac{\eta\gamma\mu_c\mu_f}{\alpha\varrho - \eta\gamma\mu_c}\right)\frac{\eta\gamma}{\alpha\varrho - \eta\gamma\mu_c} > 1. \tag{13}$$

It is easy to see that, for $\alpha\varrho > \eta\gamma\mu_c$, (13) is not fulfiled.

If $\alpha\varrho < \eta\gamma\mu_c$, then (13) is equivalent to

$$\mu_f > -\frac{\alpha\varrho}{\eta\gamma} + \frac{\eta\gamma\mu_c\mu_f}{\eta\gamma\mu_c - \alpha\varrho}, \tag{14}$$

which is satisfied.

Therefore, for a large β, i.e. if the immune system is efficient, the state X_2 is unstable, otherwise X_2 is stable.

Now, consider the changes in the left-hand side of (12) when changing coefficients α and ϱ. For $\alpha\varrho \to +\infty$, (9) takes the form

$$(\mu_c + \mu_f)\frac{\gamma F^*}{\beta} > \beta - \gamma F^*.$$

This implies that if $\beta \in \left(\gamma F^*, (1/2)\left(\gamma F^* 1 + \sqrt{1 + \frac{4(\mu_c+\mu_f)}{\gamma F^*}}\right)\right)$ and $\alpha\varrho \to +\infty$, then X_2 is locally asymptotically stable.

For $\alpha\varrho \to 0$, (12) takes the form

$$\left(\mu_c + \mu_f + \eta\gamma\mu_c\mu_f\frac{\beta - \gamma F^*}{\beta}\right)\left(\frac{\gamma F^*}{\beta} - \frac{\beta - \gamma F^*}{\mu_c}\right) > \beta - \gamma F^*. \tag{15}$$

For $\beta = \gamma F^*$, (15) is equivalent to $\mu_c + \mu_f > 0$, i.e. it is satisfied. For $\beta \to +\infty$, (15) is not satisfied. Therefore there exists an interval $(\gamma F^*, \beta_2)$, for $\beta \in (\gamma F^*, \beta_2)$ and $\alpha\varrho \to 0$, the state X_2 is locally asymptotically stable.

Equation (10), in the case of an efficient immune system with (V_0, C^*, F^*) as initial data, was studied in (Szlenk and Vargas, 1995) and the following results were proved.

Theorem 3. *If $\alpha\varrho > \eta\gamma(\mu_c + \beta)$ and $\gamma F^* > \beta$, then every solution $X(t)$ to (10) has a limit and $\lim_{t\to+\infty} X(t) = X_1$.*

Corollary 1. *If, in addition to the hypotheses of Theorem 3, we assume that $\mu_c < \mu_f < \gamma F^* - \beta$, then the function $C(t)$ converges to C^* faster than the exponential function with exponent μ_c, and the function $F(t)$ converges to F^* exponentially with exponent μ_c, i.e. there exist three constants K_1, K_2, K_3 such that*

$$0 < \quad C(t) - C^* \quad \leq K_1 e^{-\mu_c t},$$

$$K_2 e^{-\mu_c t} \leq \ |F(t) - F^*| \ \leq K_3 e^{-\mu_c t}$$

for large t.

If $\mu_f < \mu_c$, then $F(t)$ converges to F^* faster than the exponential function with exponent μ_f and slower than the exponential function with exponent μ_c.

Define an asymptotic time-average value of solution $X(t)$ as

$$\lim_{t\to+\infty} \frac{1}{t}\int_0^t X(s)\,\mathrm{d}s.$$

Theorem 4. *If $\alpha\varrho > \eta\gamma(\mu_c+\beta)$, $\beta < \gamma F^*$ and the state X_2 is locally asymptotically stable, or it is not stable, but there are two complex numbers with positive real parts among its characteristic values, then every solution $X(t)$ to (10) is bounded and there exists an asymptotic time-average of X and it is equal to X_2.*

4. Computer Simulations

In the previous sections, we have studied the behaviour of solutions to the MM for a small delay and for an infinite delay (eqn. (5)). We expect the following behaviour of numerical solutions: for a sufficiently small τ the behaviour is similar to the case without delay. Next, with an increasing delay it changes and for a large delay, the organism is destroyed, eventually. In all simulations we use initial data

$$\big(V(t),C(t),F(t)\big) = \begin{cases} (0,C^*,F^*) & \text{for} \quad t\in[-\tau,0), \\ (V_0,C^*,F^*) & \text{for} \quad t=0, \end{cases} \tag{16}$$

i.e. an infection of a healthy organism. Now we study what type of dynamics is expected for a large delay. It is obvious that we can calculate the solution only on a finite interval $[0,T]$. Therefore, for $t\in[0,T]$ the case for a large τ (i.e. $\tau>T$) is equivalent to $\alpha=0$ (due to initial data (16)). Therefore, the observed behaviour of the MM on the interval $[0,T]$ for a large τ is the same as the behaviour of the following system of ODE's

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}\hat{V}(t) = (\beta-\gamma\hat{F}(t))\hat{V}(t), \\ \dfrac{\mathrm{d}}{\mathrm{d}t}\hat{F}(t) = \mu_f F^* - \eta\gamma\hat{F}(t)\hat{V}(t) - \mu_f\hat{F}(t). \end{cases} \tag{17}$$

Assume that $\tau>T$. Thus we can study the solution to (17) with the initial condition (V_0,F^*), as the solution to the MM ($C(t)=C^*$ for $t<\tau$).

Consider stationary states of (17). The healthy state is equal to $(0,F^*)$ and the chronic state is equal to $(\mu_f(\gamma F^*-\beta)/\eta\beta\gamma,\beta/\gamma)$. It is obvious that the chronic state exists only in the case of a large physiological level of antibodies, i.e. for $\beta\le\gamma F^*$ (for $\beta=\gamma F^*$, the chronic level of antibodies and the physiological one are equal).

The characteristic polynomial for the healthy state has the form

$$W(\lambda) = -(\mu_f+\lambda)(\beta-\gamma F^*-\lambda).$$

Therefore this state is locally asymptotically stable (and then it is a node), if and only if $\beta<\gamma F^*$ and is unstable for $\beta>\gamma F^*$.

For the chronic state ($\beta\le\gamma F^*$), we have

$$W(\lambda) = \lambda^2 + \lambda\frac{\gamma\mu_f F^*}{\beta} - \mu_f(\gamma F^*-\beta).$$

We see that $W(0)=-\mu_f(\gamma F^*-\beta)<0$ and therefore the chronic state is a saddle point.

Let $(\mathbb{R}^+)^2$ denote the phase space of eqn. (17). Let I_1, I_2 denote the parts of the isocline for the first variable $\hat{V}(t)$ and I_3 denote the isocline for the second

variable $\hat{F}(t)$. Then

$$I_1 = \left\{(\hat{V},\hat{F}) \in (\mathbb{R}^+)^2 : \ \hat{F} = \frac{\beta}{\gamma}\right\},$$
$$I_2 = \left\{(\hat{V},\hat{F}) \in (\mathbb{R}^+)^2 : \ \hat{V} = 0\right\},$$
$$I_3 = \left\{(\hat{V},\hat{F}) \in (\mathbb{R}^+)^2 : \ \hat{F} = \frac{\mu_f F^*}{\mu_f + \eta\gamma\hat{V}}\right\}.$$

I_1 and I_2 are half-straight lines, I_3 is half of a hyperbola. I_2 and I_3 always have one common point—it is the healthy state. I_1 and I_3 have one common point for $\gamma F^* \geq \beta$—it is the chronic state.

Let us study the case of a large physiological level of antibodies, i.e. $\gamma F^* > \beta$.

Lemma 3. *If $\gamma F^* > \beta$, then, for every initial $\hat{V}_0$, the solution of the system defined by (17) has the following properties:*

- *For any initial condition $(\hat{V}_0, \hat{F}_0)$ lying in the upper region delimited by the stable manifold of the saddle chronic state, there exists a limit of the solution and it is equal to the healhty state, i.e. $(0, F^*)$ in this case.*
- *For any initial condition $(\hat{V}_0, \hat{F}_0)$ lying in the lower region delimited by the stable manifold of the saddle chronic state, we have*

$$\lim_{t\to+\infty} \hat{V}(t) = +\infty \quad \textit{and} \quad \lim_{t\to+\infty} \hat{F}(t) = 0.$$

Proof. Studying the phase space for $\gamma F^* > \beta$ (see Fig. 1) it is easy to see that either $(\hat{V},\hat{F})(t) \to (0, F^*)$ or $\hat{V}(t) \to +\infty$ as $t \to +\infty$. In the case $\lim_{t\to+\infty} \hat{V}(t) = +\infty$, the function $\hat{F}$ is decreasing for a sufficiently large t (because if $(\hat{V}(t_1),\hat{F}(t_1)) \in R_2$ for some t_1, then $(\hat{V}(t),\hat{F}(t)) \in R_2$ for $t > t_1$). Therefore $\lim_{t\to+\infty} \hat{F}(t) = g \geq 0$. Hence, if $g \neq 0$, then

$$\frac{\mathrm{d}\hat{F}}{\mathrm{d}t} < \mu_f F^* - \eta\gamma g\hat{V} \to -\infty \quad \text{for} \quad t \to +\infty. \tag{18}$$

Inequality (18) contradicts the condition that $\hat{F}$ is bounded. Consequently, $\lim_{t\to+\infty} \hat{F}(t) = 0$. ■

Now we study the phase space in the case of a small physiological level of antibodies, i.e. $\gamma F^* \leq \beta$. In this case the asymptotic behaviour of solutions does not depend on the initial condition.

Lemma 4. *If $\gamma F^* \leq \beta$, then*

- $\lim_{t\to+\infty} \hat{V}(t) = +\infty$ *and $\hat{V}$ is increasing, or $\hat{V}$ decreases at the beginning and then increases,*

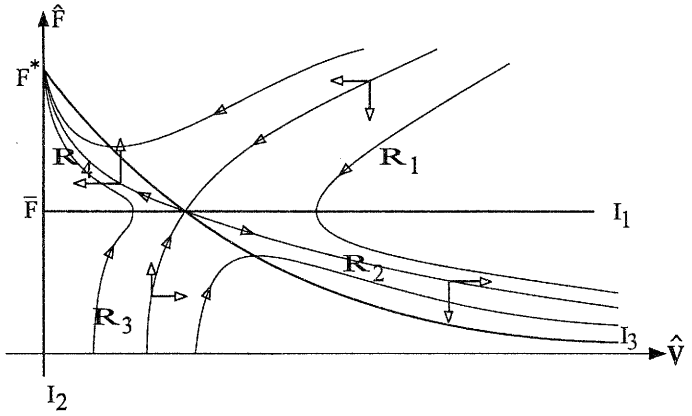

Fig. 1. Phase space for $\gamma F^* > \beta$.

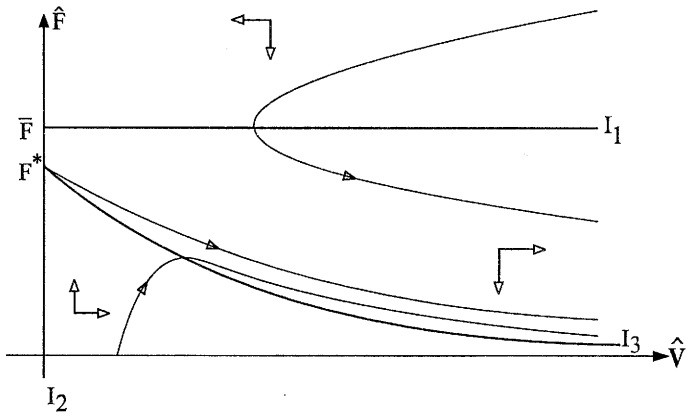

Fig. 2. Phase space for $\gamma F^* < \beta$.

- $\lim_{t\to+\infty} \hat{F}(t) = 0$ *and* $\hat{F}$ *is decreasing, or* $\hat{F}$ *increases at the beginning and then decreases.*

Proof. For every positive initial condition $(\hat{V}_0, \hat{F}_0)$ the function $\hat{V}$ either increases to $+\infty$, or (for a large $\hat{F}_0$, i.e. $\hat{F}_0 > \bar{F} = \beta/\gamma$) the function $\hat{V}$ decreases at the beginning and next increases to $+\infty$. The function $\hat{F}$ may increase at the beginning, but is always decreasing for a sufficiently large t (see Fig. 2).

As in Lemma 3, $\lim_{t\to+\infty} \hat{F}(t) = 0$. ■

Lemma 4 means that each of the functions $\hat{V}$ and $\hat{F}$ has at most one change in the slope.

Applying Lemma 3, we see that for any initial condition $(\hat{V}_0, F^*)$ such that $\gamma F^* > \beta$ there are two possible types of behaviour. There exists a point (V_0^*, F^*)

which lies on the stable manifold for the chronic state such that for any initial condition with $\hat{V}_0 < V_0^*$ the solution converges to the healthy state. For any initial condition with $\hat{V}_0 > V_0^*$ $\lim_{t\to+\infty} V(t) = +\infty$ and $\lim_{t\to+\infty} F(t) = 0$.

Applying Lemma 4, we see that if $\beta < \gamma F^*$, then for every $\hat{V}_0$ we have $\lim_{t\to+\infty} V(t) = +\infty$ and $\lim_{t\to+\infty} F(t) = 0$.

Now we present simulation results. We use a computation method similar to that used in (Kim and Pimenov, 1999). We take the values of the coefficients from (Marchuk, 1980) and then we need to rewrite the MM. Let

$$v(t) = \frac{V(t)}{V_m}, \quad c(t) = \frac{C(t)}{C^*}, \quad f(t) = \frac{F(t)}{F^*}.$$

In terms of the new variables, the MM has the following form:

$$\begin{cases} \dot{v}(t) = (\beta - \gamma_1 f)v, \\ \dot{c}(t) = \alpha_1 v(t-\tau)f(t-\tau) - \mu_c(c-1), \\ \dot{f}(t) = \mu_f(c-f) - \eta_1 v f, \end{cases} \tag{19}$$

where

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

We assume that V_m is the maximal level of the antigen concentration, i.e. the organism is destroyed when the antigen concentration reaches the level V_m. We also assume that if $v(t) < 10^{-16}$, then the antigen is eliminated from the organism and the organism recovers.

The healthy state is equal to $(0,1,1)$ in the new variables. We consider the following initial condition:

$$x(t) = \begin{cases} (v_0,1,1) & \text{if} \quad t = 0, \\ (0,1,1) & \text{if} \quad t \in (-\tau, 0). \end{cases} \tag{20}$$

At the beginning we study the behaviour of the solutions for a large τ. In this case, we change β while the other parameters are constant. For $\beta = 0$, $v(t)$ decreases to 0 very fast (see Fig. 3).

For a larger v_0, the recovery process is only a little slower. On the other hand, for a large value of β (for example, $\beta = 0.8$) the antigen concentration increases rapidly to $+\infty$. We look for the smallest value of β at which the function v increases to $+\infty$ (see Fig. 4).

Let $v_0 = 0.1$. We get the following results: for $\beta = 0.121803$ the antigen concentration decreases to 0 but for $\beta = 0.121804$ it increases to $+\infty$. We observe a similar behviour for $v_0 = 0.01$, $\beta = 0.37903$ and $\beta = 0.37904$ (see Figs. 5 and 6).

For $v_0 = 10^{-3}$, a bifurcation point appears for β between 0.4976 and 0.4977. If v_0 decreases, the bifurcation point moves to greater values. We observe that for $v_0 = 10^{-1}$ or $v_0 = 10^{-2}$ the time of recovery or death is almost the same, i.e. about 170 days, but for 10^{-3} it is much longer—more than 2,000 days.

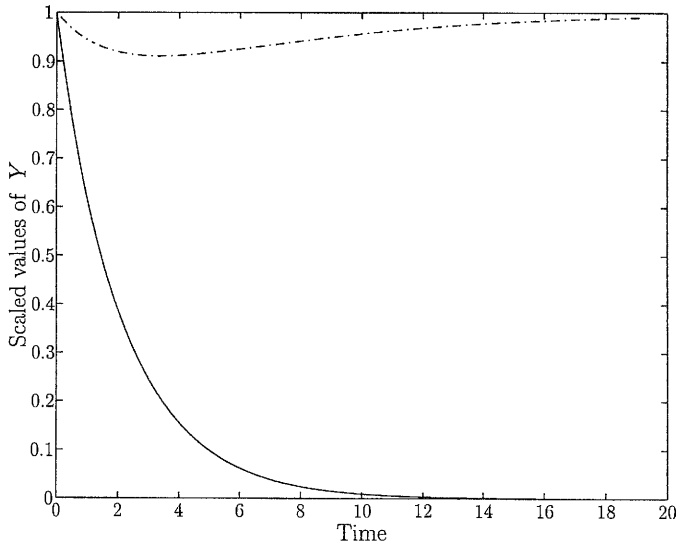

Fig. 3. Solution to the MM for $\tau > T$ and $\beta = 0$.

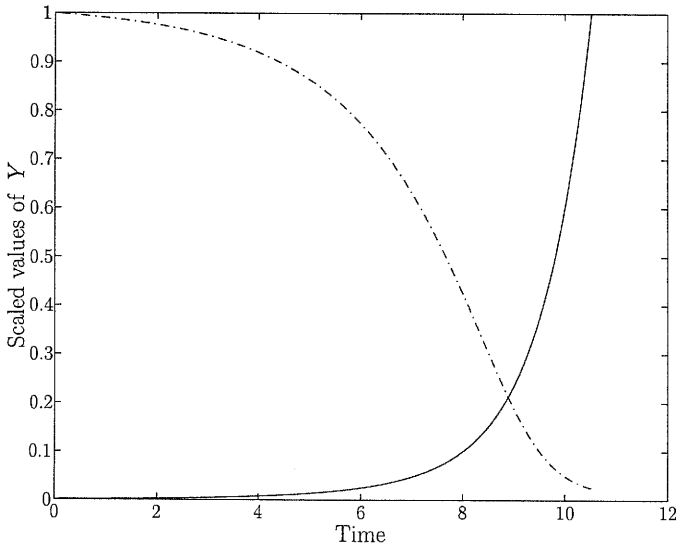

Fig. 4. Solution to the MM for $\tau > T$ and a large β.

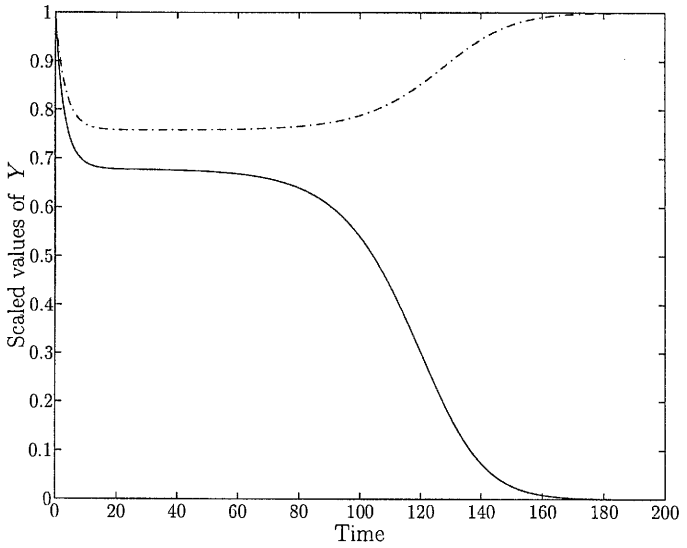

Fig. 5. Solution to the MM for $\tau > T$ before bifurcation.

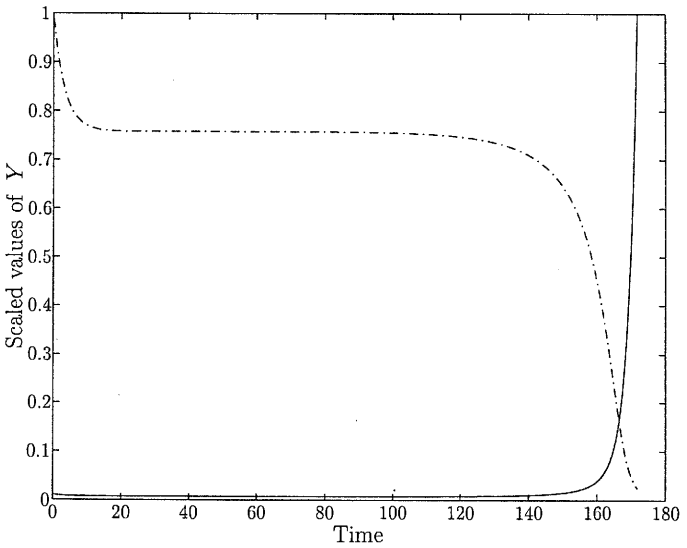

Fig. 6. Solution to the MM for $\tau > T$ after bifurcation.

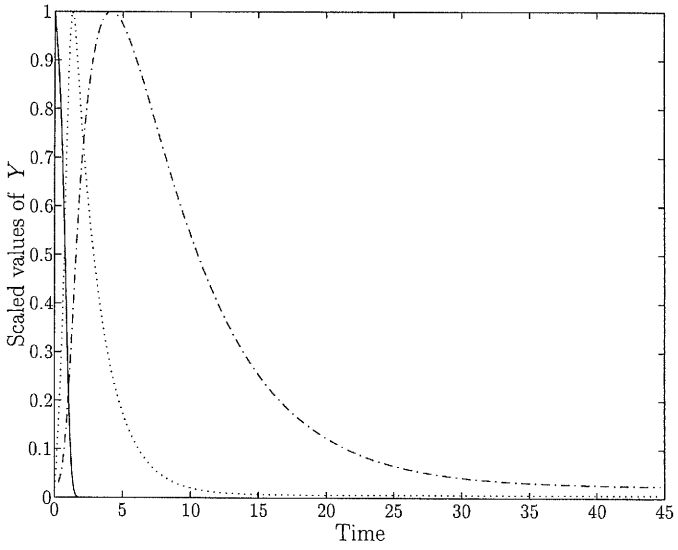

Fig. 7. Solution to the MM for a small τ.

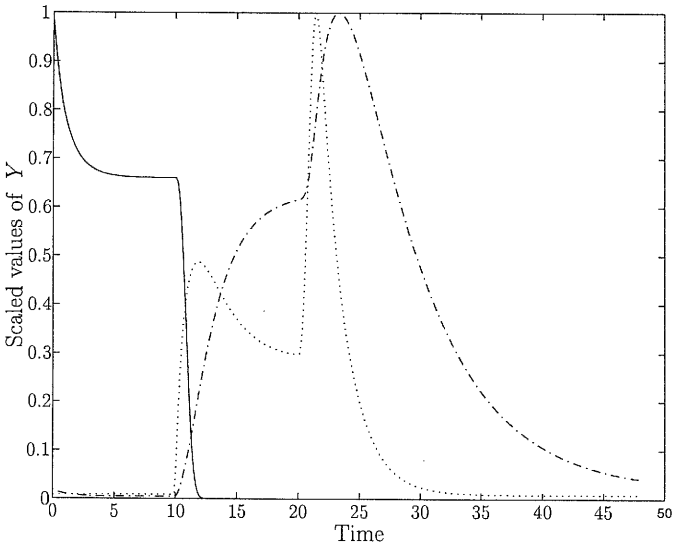

Fig. 8. One of more complicated behaviours of solutions to the MM.

Now, we study the case of $\beta = 0.121804$ and $v_0 = 0.1$ for different τ's. As we expected, for $\tau \leq 1$ the recovery process is very fast. The antigens are eliminated after less than 5 days (see Fig. 7).

For $\tau = 10.0$ this process is slower. The organism is healed after 10 days. We observe that the antigen concentration rapidly decreases at the beginning, then it is stopped, until the immune response begins, i.e. the organism starts to produce more antibodies (see Fig. 8).

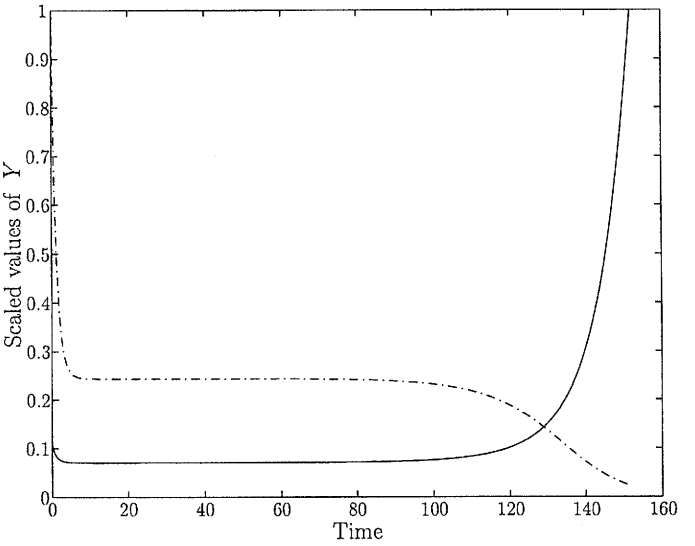

Fig. 9. Solution to the MM for a large τ.

For a large τ ($\tau \geq 160$) (see Fig. 9) the organism is destroyed. We observe the same behaviour for $\beta = 0.37904$ and $v_0 = 0.01$, and for $\beta = 4.977$ and $v_0 = 0.001$.

We see that the results of simulations are as we expected. If we fix all the parameters of the MM except τ, then τ cannot be greater than some critical level τ^* which depends on other parameters. For delays greater than τ^*, the organism is always destroyed.

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