ZASTOSOWANIA MATEMATYKI
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U. FORYŚ (Warszawa)

MATHEMATICAL MODEL OF AN IMMUNE SYSTEM WITH RANDOM TIME OF REACTION

1. Introduction. In Marchuk's model [3] of an immune system there appears a delay of reaction of the system with respect to the contamination moment. Accordingly, the system does not react immediately, it needs some time to detect and investigate the contamination by an antigen. Marchuk assumes this delay to be constant. According to the opinion of immunologists (a discussion at the Infant Health Center, Warsaw some years ago), this assumption is not satisfied in reality. The delay may depend on cells individually, so we rather have a family of delays, some of them being more probable than others. In this paper we try to answer the question raised by immunologists and to insert this phenomenon into Marchuk's model. We replace the fixed value of delay by the average of delays which appear in reactions of the immune system.

Mathematically, this means that in place of functions of delayed argument we are concerned with their averages with respect to a certain weight function.

2. The construction of the model. The following notation is used in the model:

1) $V(t)$ — antigen concentration at time t;
2) $C(t)$ — plasma cell concentration at time t;
3) $F(t)$ — antibody concentration at time t;
4) $m(t)$ — a characteristic of the damage of the organ-target in which the antigen is placed. m is defined as follows:

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

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where M_0 is a characteristic of a healthy organ (mass or area) and M_1 is a characteristic of a healthy part of this organ.

The model is derived under the following assumptions:

1) The number of antigens depends on their reproduction rate and the suppression by antibodies, according to the equation

$$\frac{dV}{dt} = \beta V(t) - \gamma F(t)V(t),$$

with the following meaning of the symbols:

β — antigen reproduction rate coefficient;

γ — a coefficient expressing the probability of the antigen-antibody meeting and their interactions.

2) Stimulation of B-cell by VT-complexes is a trigger of plasma cell production (the VT-complex rate depends on the number of antigen-antibody meetings). The plasma cell production process is delayed relative to the B-cell stimulation process. This stimulation also depends on the organ damage $m(t)$. The plasma cell production decreases with the increasing deviation from the normal level C^*:

$$\frac{dC}{dt} = \alpha\xi(m) \int_{-T}^{0} w(h)F(t+h)V(t+h)dh - \mu_c(C - C^*),$$

where:

T — the maximum time delay of the plasma cell production process;

$w(\cdot)$ — time delay probability distribution over the interval $[-T, 0]$;

α — an immune process stimulation coefficient;

μ_c — a plasma cell coefficient, with μ_c^{-1} equal to the plasma cell lifetime;

$\xi(\cdot)$ — a decreasing function which attenuates generation of plasma cells according to the magnitude of infection.

Typically, the function ξ is expressed as follows:

$$\xi(m) = \begin{cases} 1 & \text{if } m \in [0, m^*], \\ \dfrac{m-1}{m^*-1} & \text{if } m \in [m^*, 1]; \end{cases} \tag{X1}$$

this means that initially, immune processes do not depend on the organ damage rate; as soon as $m > m^*$ (where m^* is a certain level of organ damage), ξ begins to decrease to zero linearly, reflecting the rapid decrease of defence possibilities.

3) The number of antibodies depends on their production rate and their death due to the immune reactions and ageing:

$$\frac{dF}{dt} = \varrho C(t) - \eta\gamma V(t)F(t) - \mu_f F(t)$$

where:

ϱ — the antibody production rate per plasma cell;

η — rate of antibodies necessary to suppress one antigen;

μ_f — an antibody coefficient, with μ_f^{-1} equal to the antibody lifetime.

4) The work of the immune system depends on the normal work of other systems and organs, and also on the normal work of the organ-target. The organ damage depends on the antigen damage possibilities and the organ recovery rate:

$$\frac{dm}{dt} = \sigma V(t) - \mu_m m(t),$$

where:

σ — rate of organ damage by the antigen;

μ_m — an organ recovery coefficient, with μ_m^{-1} equal to the organ recovery time.

Summarizing, we obtain the following system of four equations:

$$\text{(s1)} \qquad \begin{cases} V' = (\beta - \gamma F)V, \\ C' = \alpha\xi(m)P_w(V,F) - \mu_c(C - C^*), \\ F' = \varrho C - (\mu_f + \eta\gamma V)F, \\ m' = \sigma V - \mu_m m \quad \text{if } m(t) \le 1\,. \end{cases}$$

The assumptions are as follows:

$$P_w(V,F)(t) = \int_{-T}^{0} w(h)F(t+h)V(t+h)dh\,,$$

$$w(h) \ge 0 \quad \text{for } h \in [-T,0], \qquad w \in C([-T,0],\mathbb{R}), \qquad \int_{-T}^{0} w(h)\,dh = 1,$$

$$\xi \in C([0,1],[0,1]), \qquad \xi(0) = 1, \qquad \xi(1) = 0,$$

$$m(t) \le 1 \quad \text{for every } t \ge 0,$$

$$\alpha, \beta, \gamma, \mu_c, \varrho, \mu_f, \eta, \sigma, \mu_m, C^* > 0.$$

If $x = (x_1, x_2, x_3, x_4) = (V, C, F, m)$, $x_t(h) = x(t+h)$ for $h \in [-T, 0]$, then the system (s1) takes the form

$$\text{(f1)} \qquad x' = f(x_t),$$

where the functional f represents the right sides of equations (s1). This is an autonomous system.

Initial conditions. We may assume $t^0 = 0$ because the system is autonomous. An initial condition is a pair $(0, X^0(h))$, where X^0 is a function on $[-T, 0]$, $X^0 = (V^0, C^0, F^0, m^0)$. We assume that X^0 is continuous on

$[-T,0)$, V^0 can be discontinuous at $h=0$ and other functions are continuous also at $h=0$.

3. Fundamental properties of the model

THEOREM 1. *Assume* $V^0(h) \geq 0$, $F^0(h) \geq 0$ *for* $h \in [-T,0]$. *Suppose that there exists a solution of the system* (s1) *for every* $t > 0$ *and initial data satisfying*

$$(V(0), C(0), F(0), m(0)) \geq 0 \quad [V^0(0) > 0].$$

Then

$$(V(t), C(t), F(t), m(t)) \geq 0 \quad [(V(t), C(t), F(t), m(t)) > 0]$$

for every $t > 0$.

Proof. Since $V(t) = V_0 \exp(\int_0^t (\beta - \gamma F(s))\, ds)$, by our assumptions we obtain $V(t) \geq 0$ for $t \geq 0$. Further,

$$m(t) = m^0(0) \exp(-\mu_m t) + \sigma \int_0^t \exp(\mu_m(s-t)) V(s)\, ds,$$

and by our assumptions we get $m(t) \geq 0$ for $t \geq 0$.

To deal with C and F, consider three possibilities: either C or F becomes negative first, or they become negative simultaneously.

Suppose F becomes negative sooner than C. So there exists $t_1 > 0$ such that F becomes negative at t_1; we have $F(t_1) = 0$, $C(t) \geq 0$ and $F(t) \geq 0$ for $t \leq t_1$, $F'(t_1) \leq 0$ and there exists $t_2 > t_1$ such that $C(t) \geq 0$ and $F(t) < 0$ for $t \in (t_1, t_2)$. If $F'(t_1) < 0$ then $F'(t_1) = \varrho C(t_1) < 0$ and $C(t_1) \geq 0$, a contradiction. If $F'(t_1) = 0$ then there exists a sequence $(t_k)_{k=3}^{\infty}$ such that $\lim_{k\to\infty} t_k = t_1$, $t_k > t_1$, $F(t_k) < 0$ and $F'(t_k) < 0$. Therefore we can find $K \in \mathbf{N}$ such that for every $k \geq K$ we have $t_k \in (t_1, t_2)$ and $V(t_k) \geq 0$ so $F'(t_k) \geq \varrho C(t_k) \geq 0$, a contradiction again. The proofs in the other two cases are similar. Therefore the solutions of the system (s1) are nonnegative.

THEOREM 2. *Suppose that the initial data function* X^0 *is continuous. Then for any initial condition* $(0, X^0)$ *there exists a solution of the system* (s1) *and it is unique.*

Proof. We consider the system (s1) in the form (f1). It is easy to see that for $\xi(\cdot)$ differentiable the functional $f(\cdot)$ is of class C^1 in all variables, so we can apply the general theorem of RFDE (see [2]). The same argument can also be applied if $\xi(\cdot)$ is continuous and piecewise linear.

The same argument works in the case of the initial data function being discontinuous at one point and having one-sided limits at it.

THEOREM 3. *If* $(0, X^0)$ *is an initial condition such that* $X^0 \geq 0$ *then the solution of the system* (s1) *is defined for every* $t > 0$.

Proof. By Theorem 2 we know that there exists an interval $[0, t_*)$, $t_* > 0$, where the system (s1) has a unique solution. We show that this solution is defined for every $t > 0$. Solutions of the system (s1) for nonnegative initial data are bounded by a continuous function of the variable t:

$$V(t) = V^0(0) \exp\Big(\int_0^t (\beta - \gamma F(s))\, ds \Big) \leq V^0(0) e^{\beta t},$$

$$m(t) = m^0(0) e^{-\mu_m t} + \sigma \int_0^t \exp(\mu_m(s-t)) V(s)\, ds$$

$$\leq m^0(0) e^{-\mu_m t} + \frac{\sigma}{\beta} V^0(0) e^{\beta t}.$$

Now, if $C(t) \leq C^*$ for all t, we have a constant estimate; if there exists $t_1 \geq 0$ such that $C(t_1) > C^*$ then $C(t) > C^*$ for $t > t_1$, so $C' < \alpha \xi(m) P_w(V, F) \leq \alpha P_w(V, F)$.

Assume that $F(t)$ is the maximal value of the function $F(s)$ over $s \leq t$. Then

$$P_w(V, F) \leq F(t) \int_{-T}^0 w(h) V(t+h)\, dh \leq V^0(0) F(t) e^{\beta t}.$$

Hence $C' < \alpha V^0(0) F(t) e^{\beta t}$, so

$$C(t) \leq C^0(0) + \alpha V^0(0) \int_0^t F(s) e^{\beta t} ds < C^0(0) + \frac{\alpha}{\beta} V^0(0) F(t) e^{\beta t}.$$

Therefore

$$F' \leq \varrho C^0(0) + \frac{\alpha \varrho}{\beta} V^0(0) F(t) e^{\beta t} - (\mu_f + \eta\gamma V) F$$

$$\leq \varrho C^0(0) + \frac{\alpha \varrho}{\beta} V^0(0) F(t) e^{\beta t}.$$

So we have

$$F(s) \leq F(t) \leq (F^0(0) + \varrho C^0(0) t) \exp\left(\frac{\alpha \varrho}{\beta^2} V^0(0) e^{\beta t} \right).$$

If F is increasing on $[0, t)$ for some $t \geq 0$ then this estimate is valid for $s \in [0, t]$. If F is increasing on $[0, t)$ and decreasing on (t, t_1) where $t > 0$ and $t_1 > t$ then just replace $F(s)$ by $F(t)$. If F is decreasing on $[0, t)$ where $t > 0$ then

$$F(s) \leq F^0(0) \leq F^0(0) \exp\left(\frac{\alpha \varrho}{\beta^2} V^0(0) e^{\beta t} \right)$$

and further estimation is similar. Hence the estimate for F is valid for the whole domain. Hence

$$C(t) < C^0(0) + \frac{\alpha}{\beta} V^0(0) e^{\beta t} (F^0(0) + \varrho C^0(0) t) \exp\left(\frac{\alpha\varrho}{\beta^2} V^0(0) e^{\beta t}\right).$$

Therefore for the finite time interval $[0, t_*)$, $t_* > 0$, the solution $x(t)$, $t \in [0, t_*)$, is bounded. Thus $x'(t)$, $t \in [0, t_*)$, is also bounded and the solution extends up to the point t_*.

Properties of the solutions:

1) If $x^0 \geq 0$ and $C^0(0) \geq C^*$ then $C(t) \geq C^*$ for every $t \geq 0$.
2) If $x^0 \geq 0$, $V^0(0) > 0$, $\xi(m) > 0$ then:
   a) if $C^0(0) > C^*$ then $C(t) > C^*$ for every $t \geq 0$;
   b) if $C^0(0) = C^*$ then $C(t) > C^*$ for every $t > 0$;
   c) if $C^0(0) < C^*$ then there exists $t_1 > 0$ such that $C(t) < C^*$ for $0 < t < t_1$, $C(t_1) = C^*$ and $C(t) > C^*$ for $t > t_1$.

Proof. It is similar to the proof of Theorem 1.

4. Stationary solutions. Assume that $\xi(m) = 1$. Suppose that $(\overline{V}, \overline{C}, \overline{F}, \overline{m})$ is a stationary solution, i.e.

$$\begin{cases} 0 = (\beta - \gamma\overline{F})\overline{V}, \\ 0 = \alpha P_w(\overline{V}, \overline{F}) - \mu_c(\overline{C} - C^*), \\ 0 = \varrho\overline{C} - (\mu_f + \eta\gamma\overline{V})\overline{F}, \\ 0 = \sigma\overline{V} - \mu_m\overline{m}\,. \end{cases}$$

This system has two solutions:

$$X_1 = (0, C^*, F^*, 0) = (\overline{V}_1, \overline{C}_1, \overline{F}_1, \overline{m}_1), \quad \text{where} \quad F^* = \frac{\varrho}{\mu_f} C^*;$$

$$X_2 = \left(\frac{\mu_c\mu_f(\beta - \gamma F^*)}{\beta(\alpha\varrho - \eta\gamma\mu_c)}, \frac{\alpha\beta\mu_f - \eta\gamma^2\mu_c C^*}{\gamma(\alpha\varrho - \eta\gamma\mu_c)}, \frac{\beta}{\gamma}, \frac{\sigma\mu_c\mu_f(\beta - \gamma F^*)}{\beta\mu_m(\alpha\varrho - \eta\gamma\mu_c)}\right)$$
$$= (\overline{V}_2, \overline{C}_2, \overline{F}_2, \overline{m}_2).$$

The interesting case is when $\overline{V}_2 > 0$ (since $\overline{V}_2$ is an antigen concentration). So we have:

1) $\beta > \gamma F^*$ and $\alpha\varrho > \eta\gamma\mu_c$ or 2) $\beta < \gamma F^*$ and $\alpha\varrho < \eta\gamma\mu_c$.

If $\beta = \gamma F^*$ then $\overline{V}_2 = \overline{V}_1 = 0$ (for $\alpha\varrho \neq \eta\gamma\mu_c$).

Let $x = X - \overline{X} = (V - \overline{V}, C - \overline{C}, F - \overline{F}, m - \overline{m}) = (v, c, f, n)$, where (v, c, f, n) is the vector of small perturbations of $\overline{X}$.

After linearization the system (s1) takes the following form:

$$\text{(s2)} \qquad \begin{cases} v' = (\beta - \gamma\overline{F})v - \gamma\overline{V}f, \\ c' = \alpha\overline{F}\int_{-T}^{0} w(h)v(t+h)dh + \alpha\overline{V}\int_{-T}^{0} w(h)f(t+h)dh - \mu_c c, \\ f' = \varrho c - (\eta\gamma\overline{V} + \mu_f)f - \eta\gamma\overline{F}v, \\ n' = \sigma v - \mu_m n\ . \end{cases}$$

The vector neglected in the linearization process is

$$R(x_t) = \Big(-\gamma f v,\ \alpha \int_{-T}^{0} w(h) f_t(h) v_t(h) dh,\ -\eta\gamma f v,\ 0 \Big),$$

where $x_t = (v_t, c_t, f_t, n_t)$, $x_t(h) = x(t+h)$ for $h \in [-T, 0]$.

The vector $R(x_t)$ satisfies the assumptions of the linearization theorem (see [2]). Thus we can study the stability of the solutions of (s2) instead of those of (s1). In our case it is enough (to satisfy the linearization theorem) to check that $\lim_{\|x_t\|\to 0} \|R(x_t)\|/\|x_t\| = 0$, $R(0) = 0$, $DR(0) = 0$ and $DR(x_t)$ is continuous. It is easy to see that the last three conditions are satisfied.

Since $\|R(x_t)\| \le A\|x_t\|^2$, where $A = T\sup(w(h) : h \in [-T, 0])$, we have

$$\lim_{\|x_t\|\to 0} \|R(x_t)\|/\|x_t\| = 0\,.$$

Denote $\int_{-T}^{0} w(h)e^{\lambda h}dh$ by $g(\lambda)$. Then the characteristic matrix of (s2) takes the following form:

$$\bar{A}(\lambda) = \begin{pmatrix} \beta - \gamma\overline{F} - \lambda & 0 & -\gamma\overline{V} & 0 \\ \alpha\overline{F}g(\lambda) & -(\mu_c + \lambda) & \alpha\overline{V}g(\lambda) & 0 \\ -\eta\gamma\overline{F} & \varrho & -(\mu_f + \eta\gamma\overline{V} + \lambda) & 0 \\ \sigma & 0 & 0 & -(\mu_m + \lambda) \end{pmatrix}.$$

5. Stability of the solution X_1. For X_1 we have

$$\bar{A}(\lambda) = \begin{pmatrix} \beta - \gamma F^* - \lambda & 0 & 0 & 0 \\ \alpha F^* g(\lambda) & -(\mu_c + \lambda) & 0 & 0 \\ -\eta\gamma F^* & \varrho & -(\mu_f + \lambda) & 0 \\ \sigma & 0 & 0 & -(\mu_m + \lambda) \end{pmatrix}.$$

The characteristic quasipolynomial is of the form

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

THEOREM 4. *If $\beta < \gamma F^*$ then the stationary solution $X_1 = (0, C^*, F^*, 0)$ is asymptotically stable.*

Proof. $W(\lambda) = 0$ if and only if $\lambda_1 = -\mu_c$, $\lambda_2 = -\mu_m$, $\lambda_3 = -\mu_f$, $\lambda_4 = \beta - \gamma F^*$. The numbers $\lambda_1, \lambda_2, \lambda_3$ are apparently negative and $\lambda_4 < 0$ because $\beta < \gamma F^*$. So X_1 is asymptotically stable.

Now consider the following case: $V^0(h) = 0$ for $h \in [-T, 0)$, $F^0(0) = F^*$, $C^0(0) = C^*$, $m^0(0) = 0$, $V^0(0) > 0$ (which means that we have a healthy organism infected by a small dose of the antigen).

THEOREM 5. *If* $X^0 = (V^0, C^*, F^*, 0)$, $\beta < \gamma F^*$, $0 < V^0 < V^*$, *where*

$$V^* = \frac{\mu_f}{\eta\gamma\beta}(\gamma F^* - \beta)$$

then $V(t)$ *decreases for* $t \geq 0$, $\lim_{t\to\infty} V(t) = 0$ *and* $V(t) \leq V^0 e^{-At}$, *where*

$$A = \frac{\gamma\varrho C^*}{\mu_f + \eta\gamma V^0} - \beta > 0\,.$$

Proof. See the proof of Theorem 4 in [1].

COROLLARY 1. *If* $X^0 = (V^0, C^*, F^*, 0)$, $0 < V^0 < V^*$, $\beta < \gamma F^*$ *then*

$$\lim_{t\to\infty}(V(t), C(t), F(t), m(t)) = (0, C^*, F^*, 0)\,.$$

Proof ([1]). We have $\lim_{t\to\infty} V(t) = 0$ by Theorem 5 and $m' = \sigma V - \mu_m m$, $m(t) > 0$ for $t > 0$.

For any $\varepsilon > 0$ there exists $\bar{t} > 0$ such that $V(t) < \varepsilon\mu_m/\sigma$ for $t > \bar{t}$. Then $m' < \varepsilon\mu_m - \mu_m m$ so $m(t) \leq \varepsilon(1 - e^{-\mu_m t}) < \varepsilon$. Therefore $\lim_{t\to\infty} m(t) = 0$.

We show that F is a bounded function for $t \to \infty$. We know that $V(t) \leq V^0 e^{-At}$. Assume that $F(t) = \max\{F(s) : s \leq t\}$. Then

$$\begin{aligned} C' &= \alpha \int_{-T}^{0} w(h)F(t+h)V(t+h)dh - \mu_c(C - C^*) \\ &\leq \alpha V^0 e^{A(T-t)}F(t) - \mu_c(C - C^*). \end{aligned}$$

Since $C^0 = C^*$, we have

$$\begin{aligned} C(t) &\leq C^* + \alpha V^0 e^{At} \int_{-T}^{0} e^{-As-\mu_c(t-s)}F(s)\,ds \\ &\leq C^* + \alpha V^0 e^{AT}F(t)\frac{e^{-At} - e^{-\mu_c t}}{\mu_c - A}. \end{aligned}$$

Applying this inequality we get

$$F' < \varrho C - \mu_f F \leq \varrho C^* + \left(\frac{\alpha\varrho V^0}{\mu_c - A}e^{AT}(e^{-At} - e^{-\mu_c t}) - \mu_f\right)F.$$

Estimating solutions of the equation

$$F' = \varrho C^* + \left(\frac{\alpha\varrho V^0}{\mu_c - A}e^{AT}(e^{-At} - e^{-\mu_c t}) - \mu_f\right)F$$

([1]) In [1] and [3] it is claimed that Corollary 1 is an easy consequence of Theorem 5. In the author's opinion the implication is not so obvious.

we show that $F(t) \leq G(t)$ where

$$G(t) = F^* \exp\left(-\mu_f t + \frac{\alpha\varrho V^0}{\mu_c - A} e^{AT}\left(\frac{1-e^{-At}}{A} + \frac{e^{-\mu_c t}-1}{\mu_c}\right)\right)$$
$$+ F^* \exp\left(\frac{\alpha\varrho V^0}{\mu_c - A} e^{AT}\frac{1-e^{-At}}{A}\right)(1-e^{-\mu_f t}).$$

It is easy to see that

$$\lim_{t\to\infty} G(t) = F^* \exp\left(\frac{\alpha\varrho V^0 e^{AT}}{A(\mu_c - A)}\right).$$

In the same way as in the proof of Theorem 3 we obtain $F(t) \leq G(t)$ for every $t > 0$. Therefore F is a bounded function. Then $\lim_{t\to\infty} F(t)V(t) = 0$. Hence we get our assertion applying the same argument as in the proof that $m(t) \to 0$ as $t \to \infty$.

6. Stability of the solution X_2. The characteristic matrix for X_2 takes the following form:

$$\bar{A}(\lambda) = \begin{pmatrix} -\lambda & 0 & -\gamma\overline{V}_2 & 0 \\ \frac{\alpha\beta}{\gamma} g(\lambda) & -(\mu_c + \lambda) & \alpha\overline{V}_2 g(\lambda) & 0 \\ -\eta\beta & \varrho & -(\mu_f + \eta\gamma\overline{V}_2 + \lambda) & 0 \\ \sigma & 0 & 0 & -(\mu_m + \lambda) \end{pmatrix}.$$

The characteristic quasipolynomial is

$$W(\lambda) = \det \bar{A}(\lambda) = -(\mu_m + \lambda)Y(\lambda);$$
$$Y(\lambda) = -\lambda^3 - A\lambda^2 - B\lambda + D + (G\lambda + H)\int_{-T}^{0} w(h)e^{\lambda h}dh;$$
$$A = \mu_c + \mu_f + \eta\gamma\overline{V}_2 > 0, \quad B = \mu_c(\mu_f + \eta\gamma\overline{V}_2) - \eta\gamma\beta\overline{V}_2,$$
$$D = \eta\gamma\beta\mu_c\overline{V}_2 > 0, \quad G = \alpha\varrho\overline{V}_2 > 0, \quad H = \alpha\beta\varrho\overline{V}_2 > 0.$$

The proof bases on the so-called Mikhailov Criterion. We present here the extended Mikhailov Criterion:

THEOREM 6. *Consider an arbitrary system of differential equations with a characteristic quasipolynomial of the form*

$$D(p) = N(p) + M(p)g(p) = 0,$$

where N and M are polynomials, $\deg N > \deg M$, g is the functional given by $g(p) = \int_{-T}^{0} w(h)e^{ph}dh$. ($g(p) = e^{-p\tau}$ in Marchuk's model.) The solution of such a system is asymptotically stable if and only if the argument of $D(i\omega)$ increases by $\frac{\pi}{2}\deg N$ while ω varies from 0 to ∞.

Proof. We consider the curve $S_R = \Gamma_R + C_R$ on the complex plane, where Γ_R is the interval $[-R, R]$ on the imaginary axis and C_R is the half-circle in the right half-plane with center at 0 and radius R.

The quasipolynomial $D(p)$ has no poles. If the solution is asymptotically stable then, for every radius R, $D(p)$ has no zeros inside the domain bounded by S_R and on S_R (and conversely). Hence the increase of the argument of $D(p)$ on S_R is equal to 0, that is, $\Delta_{S_R} \arg D(p) = 0$.

Writing $D(p)$ in the form

$$D(p) = N(p)\left(1 + \frac{M(p)}{N(p)} g(p)\right) = 0,$$

we get

$$0 = \Delta_{S_R} \arg D(p) = \Delta_{S_R} \arg N(p) + \Delta_{S_R} \arg \left(1 + \frac{M(p)}{N(p)} g(p)\right).$$

Assume that $N(p)$ has q zeros in the right half-plane and no zeros on the imaginary axis. Then for sufficiently large R, $\Delta_{S_R} \arg N(p) = 2\pi q$, so

$$\Delta_{S_R} \arg \left(1 + \frac{M(p)}{N(p)} g(p)\right) = -2\pi q.$$

Since $\deg N > \deg M$, on C_R we have $p = R(\cos\phi + i \sin\phi)$ where $\phi \in (-\pi/2, \pi/2)$, $\|M(p)/N(p)\| \to 0$ uniformly as $R \to \infty$, and $\|g(p)\| \leq 1$. Hence

$$\Delta_{C_R} \arg \left(1 + \frac{M(p)}{N(p)} g(p)\right) \to 0 \quad \text{as } R \to \infty.$$

Therefore

$$\Delta_{\Gamma_R} \arg \left(1 + \frac{M(p)}{N(p)} g(p)\right) \to -2\pi q \quad \text{as } R \to \infty.$$

So

$$\Delta_{-\infty < \omega < \infty} \arg \left(1 + \frac{M(i\omega)}{N(i\omega)} g(i\omega)\right) = 2\pi q.$$

We have

$$\Delta_{-\infty < \omega < \infty} \arg N(i\omega) = (\deg N - q)\pi + q(-\pi) = (\deg N - 2q)\pi.$$

Thus $\arg N(i\omega) = -\arg N(-i\omega)$ so $\Delta_{0 \leq \omega < \infty} \arg N(i\omega) = (\deg N - 2q)\pi/2$. Also $\arg D(i\omega) = -\arg D(-i\omega)$ and therefore

$$\Delta_{0 \leq \omega < \infty} \arg D(i\omega) = \deg N \cdot \pi/2.$$

Corollary 2. *If* $-\mu_c m_1(w) \leq 1$ *and*

$$0 < \frac{H - D}{A + G m_1(w)} < B - G + H m_1(w),$$

where $m_1(w) = \int_{-T}^{0} hw(h)dh$, *then the solution* X_2 *of the system* (s1) *is asymptotically stable.*

Proof. See the proof of Theorem 6 in [1].

COROLLARY 3. *The solution* X_2 *is stable only if* $\alpha\varrho > \eta\gamma\mu_c$ *and* $\beta > \gamma F^*$.

Proof. By Theorem 6 we have $H - D > 0$, so $\alpha\beta\varrho\overline{V}_2 - \eta\beta\gamma\mu_c\overline{V}_2 > 0$. Therefore $\alpha\varrho > \eta\gamma\mu_c$. From the assumption $\overline{V}_2 > 0$ we have $\beta > \gamma F^*$.

COROLLARY 4. *If* $\alpha \to \infty$ *and*

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

then the solution X_2 *is asymptotically stable.*

Proof. See the proof of this fact in [1].

7. Stationary solutions for $\xi(m) < 1$

Remark. Proofs in this section are similar to those in Section 3.5 of [1].

Assume that ξ has the typical form (X1).

Let $X_2' = (\overline{V}_2', \overline{C}_2', \overline{F}_2', \overline{m}_2')$ be a stationary solution in the case of $\overline{m}_2' > m^*$.

In the same way as in [1] we can show that

$$(*) \qquad (\overline{m}_2')^2 + \frac{\mu_c\eta\gamma - \alpha\varrho\delta}{\alpha\varrho\delta}\overline{m}_2' + \frac{\sigma\mu_c\mu_f(\beta - \gamma F^*)}{\alpha\beta\varrho\delta\mu_m} = 0,$$

where $\delta = 1/(1 - m^*) > 1$.

LEMMA 1. *If* $\beta < \gamma F^*$, $\alpha\varrho > \eta\gamma\mu_c$ *and there exists a solution* X_2 *with* $\overline{m}_2 < m^*$ *then there exists a unique stationary solution* X_2' *with* $\overline{m}_2'$ *equal to the greater root of the equation* $(*)$.

COROLLARY 5. *If there exist two roots of the equation* $(*)$ *then there is no stationary solution for* $\overline{m}_2 < m^*$.

For the solution X_2' the characteristic quasipolynomial is

$$W(\lambda) = -((\mu_m + \lambda)Z(\lambda) + p),$$

where

$$p = \alpha\beta\varrho\sigma\delta(\overline{V}_2')^2, \quad Z(\lambda) = -\lambda^3 - a\lambda^2 - b\lambda + d + (g\lambda + h)\int_{-T}^{0} w(s)e^{\lambda s}ds$$

and

$$a = \mu_c + \mu_f + \eta\gamma\overline{V}_2' > 0, \quad b = \mu_c(\mu_f + \eta\gamma\overline{V}_2') - \eta\gamma\beta\overline{V}_2',$$
$$d = \eta\gamma\beta\mu_c\overline{V}_2' > 0, \quad \alpha\varrho\xi(\overline{m}_2')\overline{V}_2' > 0, \quad h = \beta g > 0.$$

COROLLARY 6. *If* $-\mu_c m_1(w) \leq 1$,

$$0 < \frac{h-d}{a+gm_1(w)} < b-g+hm_1(w),$$

$$m_1(w) = \int_{-T}^{0} sw(s)\,ds,$$

$$\Delta = \left(1 - \frac{\eta\gamma\mu_c}{\alpha\varrho\delta}\right)^2 - 4A_0 > 0,$$

$$A_0 = \frac{\sigma\mu_c\mu_f(\beta-\gamma F^*)}{\alpha\beta\varrho\delta\mu_m} > m^*\left(1 - \frac{\eta\gamma\mu_c}{\alpha\varrho\delta} - m^*\right)$$

then there exists a unique stationary solution X_2' *such that*

$$0 < m^* < \frac{1}{2}\left(1 - \frac{\eta\gamma\mu_c}{\alpha\varrho\delta} - \sqrt{\Delta}\right) = \overline{m}_2' < 1$$

and it is asymptotically stable. The solution X_2 *with* $\overline{m}_2 < m^*$ *does not exist.*

QUESTION: Under what conditions may a light chronic stable form of disease ($\overline{m}_2 < m^*$) become a heavy chronic stable form ($\overline{m}_2' > m^*$)?

LEMMA 2. *If*

$$0 < \frac{H-D}{A+Gm_1(w)} < b-g+hm_1(w)$$

and $\mu_c m_1(w) \geq -1$ *then the assumptions of Corollaries* 2 *and* 6 *are satisfied.*

8. Results of computer simulation. In this section we present the computer simulation results for the model. This simulation is based on a number of data published by Marchuk and Belykh in [1] and [3]. It turns out that our results do not differ from Marchuk's results and, generally, agree with the experimental data.

There exist three basic types of infection evolution: subclinical, acute and chronic. In Figs. 1–6, $V_{\max}$ is the maximum admissible concentration of the antigen in the organism.

1) $\beta < \gamma F^*$

In Fig. 1, a subclinical form of disease with normal stimulation of the immune system is shown. This means that $\alpha\varrho > \eta\gamma\mu_c$.

For Fig. 1a, $w_1(h) = 1/T$; for 1b, $w_2(h) = e^{-h}/(e^T - 1)$; for 1c, we have a constant delay (Marchuk's model). In the other cases the curves are presented only for $w_1(h)$.

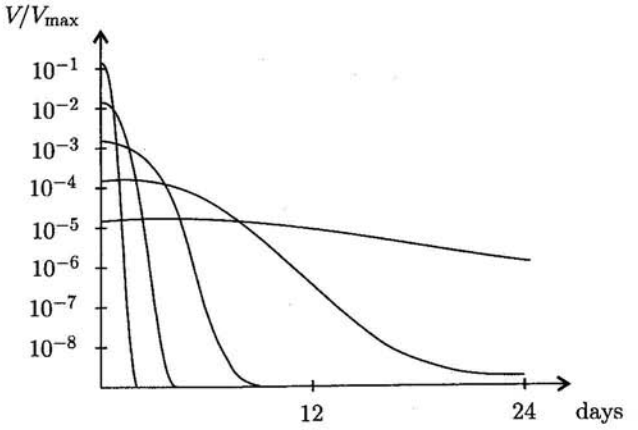

Fig. 1a

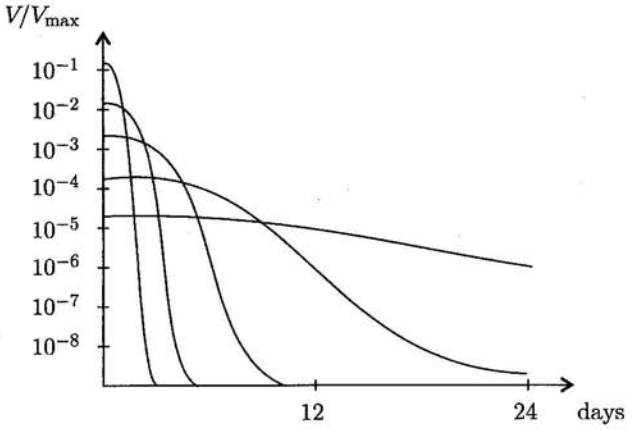

Fig. 1b

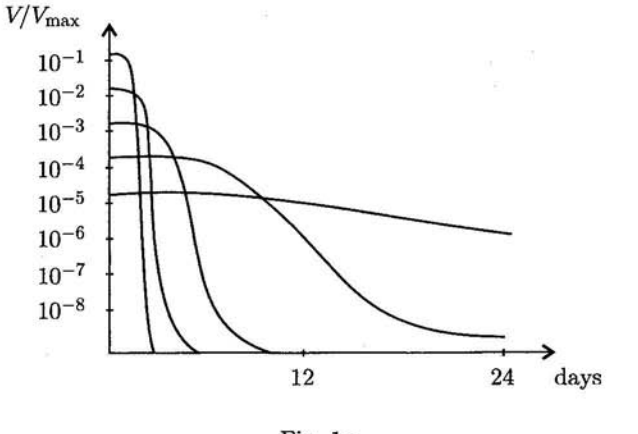

Fig. 1c

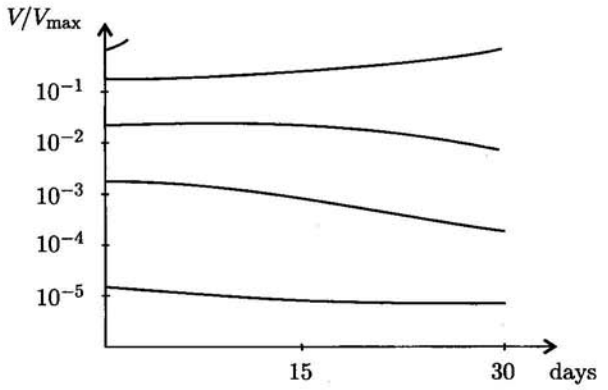

Fig. 2

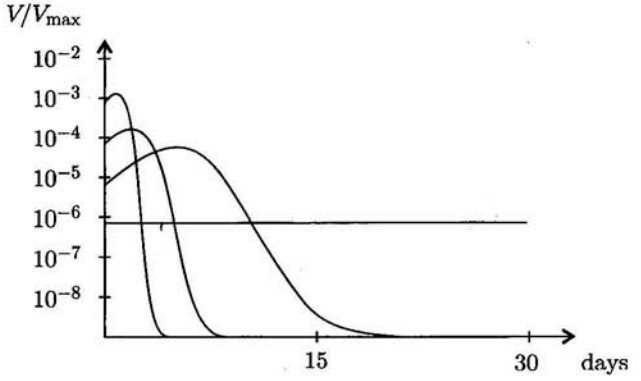

Fig. 3

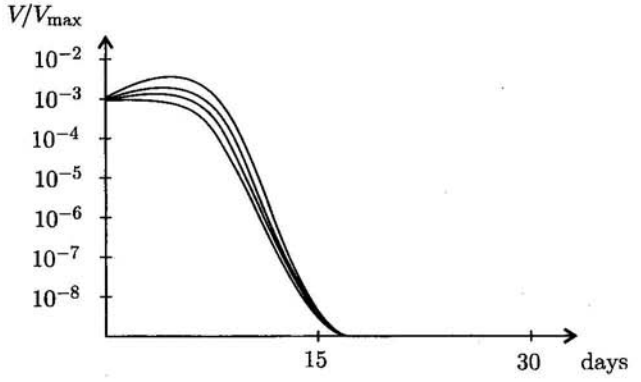

Fig. 4

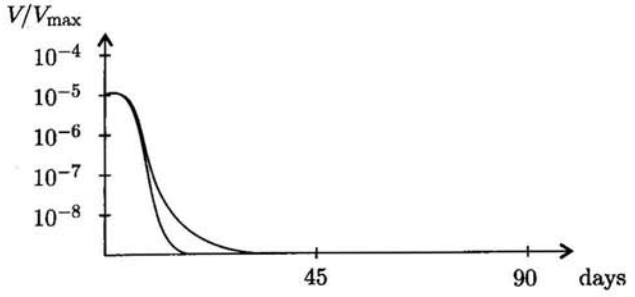

Fig. 5

In Fig. 2 we have a subclinical form of disease with weak stimulation. This means that $\alpha\varrho < \eta\gamma\mu_c$. Here, we obtain a lethal form of disease for large initial concentration of the antigen.

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

In Figs. 3, 4 and 5 an acute form of disease is shown: in Fig. 3 depending on the initial concentration, in Fig. 4 depending on the coefficient β, in Fig. 5 depending on the coefficient σ.

For greater values of the coefficient β (i.e. for greater reproduction rate of the antigen) we have a greater maximal concentration of the antigen, also for greater values of σ (i.e. for greater antigen-damage possibilities) we observe a longer duration of the disease processes.

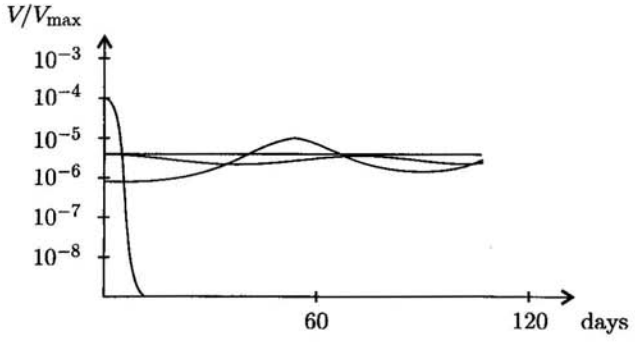

Fig. 6

In Fig. 6 a chronic form of disease is shown. V_{chr} is the chronic level of antigen concentration. From the shape of these curves we deduce that the increase of the antigen concentration in the organism may be one of the treatment methods.

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URSZULA FORYŚ
INSTITUTE OF APPLIED MATHEMATICS
UNIVERSITY OF WARSAW
UL. BANACHA 2
02-097 WARSZAWA, POLAND

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