APPLICATIONES MATHEMATICAE
24,3 (1997), pp. 289–297

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IMMUNOLOGICAL BARRIER FOR INFECTIOUS DISEASES

Abstract. A nonlinear mathematical model with distributed delay is proposed to describe the reaction of a human organism to a pathogen agent. The stability of the disease free state is analyzed, showing that there exists a large set of initial conditions in the attraction basin of the disease-free state whose border is defined as the immunological barrier.

Introduction. In recent years several mathematical models for an infectious disease have been proposed [1, 3–6]. Marchuk [5] studied a model including four variables V, C, F and m: antigens, antibodies, plasma cells and the percentage of damage in the organism, respectively. The system has the following form:

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

The proofs of some of the results obtained by Marchuk for system (1) are based on the special form of the equations. For instance, it is crucial that V can be factored out in that special form on the right hand side of the first equation.

One can easily think of interactions of higher order, though. For instance, by changing the first equation into

$$\dot{V} = \beta V - \beta' V^2 - \gamma F V,$$

one can model the fact that there is room only for a limited number of

1991 *Mathematics Subject Classification*: 34K20, 92C50.
Key words and phrases: immunological barrier, delay equations, infectious disease, stability.

antigens in the organism. So the question remains whether or not results analogous to Marchuk's hold for more general systems.

Here, we propose a model that is locally equivalent to (1) around the disease-free state $(0, F^*, C^*, 0)$, but includes higher order interactions. Also, a distributed delay is allowed in the third equation, thereby modeling the fact that the time needed for detecting the presence of an antigen in the organism is not necessarily constant, nor is the influence of each detection the same. The system has the following form:

$$
\begin{aligned}
&\dot{x}_1(t) = f_1(x_1(t), x_2(t)) := x_1(t) \cdot f(x_1(t), x_2(t)),\\
&\dot{x}_2(t) = f_2(x_1(t), x_2(t), x_3(t)),\\
&\dot{x}_3(t) = f_3\Big(\int_{-r_1}^{-r_0} g(x_1(t+s), x_2(t+s))h(s)\,ds, x_3(t), x_4(t)\Big),\\
&\dot{x}_4(t) = f_4(x_1(t), x_4(t)),
\end{aligned}
\tag{2}
$$

and the following general conditions are assumed to hold true:

0. The functions $f : \mathbb{R}^2 \to \mathbb{R}, f_1 : \mathbb{R}^2 \to \mathbb{R}, f_2 : \mathbb{R}^3 \to \mathbb{R}, f_3 : \mathbb{R}^3 \to \mathbb{R}$, $f_4 : \mathbb{R}^3 \to \mathbb{R}, g : \mathbb{R} \to \mathbb{R}$ and $h : [-r_1, -r_0] \to \mathbb{R}$ are bounded in bounded sets in the C^1-norm.

1. $f_1(x, y)$ is a decreasing function of y, and the set $\{(x, y) \in \mathbb{R}^2 \mid f_1(x, y) = 0\}$ for $x > 0$ and $y \geq 0$ is given by a continuous function Ψ_1 of x, which is increasing and positive in $(0, x_{1\,\max}]$ for some positive $x_{1\,\max}$, decreasing in $(x_{1\,\max}, \overline{x}_1)$, for some $\overline{x}_1$, and equal to 0 for $x \geq \overline{x}_1$.

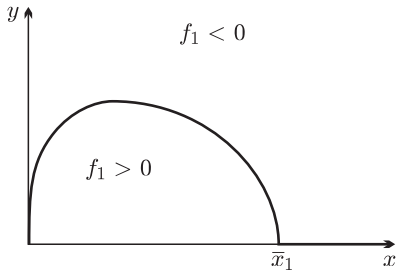

Fig. 1. $f_1(x, y) = 0$

2. For $x \geq 0$ and $z \geq 0$, the set $\{(x, y, z) \in \mathbb{R}^3 \mid f_2(x, y, z) = 0\}$ is given by a continuous surface $\Psi_2(x, z)$, which is identically equal to 0 for $z = 0$, and an increasing function of z for fixed x. For fixed $z > 0$ it is a decreasing function of x as long as it remains positive. If it becomes equal to zero, it remains constant.

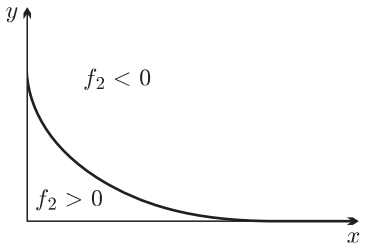

Fig. 2. $f_2(x, y, z) = 0$, for fixed $z > 0$

3.1. There exists an $x_3^* \geq 0$ such that $f_3(0, x_3^*, 0) = 0$.

3.2. $g(x, y)$ is a nonnegative function that is equal to zero if and only if at least one of its entries is equal to 0.

3.3. f_3 is an increasing function of x_1 and x_2, and a nonincreasing function of x_3 and x_4.

4. $f_4(x, y)$ is an increasing function of x, and for $x \geq 0$ and $y \geq 0$ the set $\{(x, y) \in \mathbb{R}_2 \mid f_4(x, y) = 0\}$ is given by a continuous increasing curve $\Psi_4(x)$ such that $\Psi_4(0) = 0$. Moreover Ψ_4 is an increasing function of x as long as it takes values less than 1. If $\Psi_4(x_0) = 1$ for some $x_0 > 0$, then $\Psi_4(x) = 1$ for all $x > x_0$.

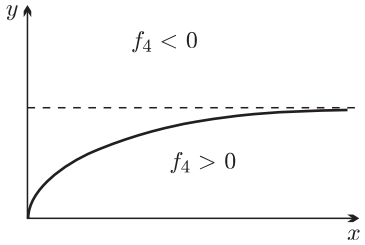

Fig. 3. $f_4(x, y) = 0$

The variables x_1, x_2, x_3 and x_4 generically represent antigens, antibodies, plasma cells and the percentage of damage in the organism, respectively. Condition 0 guarantees the global existence and uniqueness of solutions; it is not restrictive since, in applications, all interactions are bounded.

System (2) allows the modelling of a variety of processes that system (1) does not. We will point out some of them at the same time that we explain conditions 1 to 4.

The condition of positivity of Ψ_1 in particular means that for small both antigen and antibody populations (and neglecting random effects), the antigen population reproduces itself with a positive rate (in system (1), $f(0, 0) = \beta > 0$).

For small antigen populations and fixed amount of antibodies, a bigger population (usually) grows faster than a smaller one (for instance, proportionally to their size as in system (1)) but, due to competition and limiting factors, the growth rate can decrease with increasing antigen populations. The assumption that Ψ_1 is not constant in condition 1 allows modelling this kind of phenomena. This assumption is different from those in system (1), where f is constant for fixed F.

If the antigen population is big enough, inhibition factors outweigh reproduction and the growth rate becomes negative, that is, the antigen population always decreases if its size is bigger than $\overline{x}_1$, which can be seen as the carrying capacity for the antigen population. This condition is not satisfied by system (1).

Since condition 1 implies the existence of a maximum for Ψ_1, we are also taking into account the fact that for any given number of antigens, there is always an amount of antibodies large enough to cause a decrease in the antigen population. For system (1) that value is constant and equal to β/γ.

The boundary condition in 2 states that without plasma cells and antibodies, there is no production of the latter, no matter how many antigens are present. On the other hand, the disappearance of antibodies increases with their own number (Ψ_2 is a decreasing function of x, for fixed z), whereas their production increases with the number of plasma cells (Ψ_2 is increasing in z, for fixed x). These conditions are satisfied by system (1), too.

For a healthy organism, and in the absence of infection, condition 3.1 assumes the existence of a steady state x_3^* of plasma cells, to which population tends. That steady state corresponds to C^* in system (1). The production of plasma cells increases with the number of antigens attacking the organism, but that can only happen in the presence of receptors (antibodies). That is described in condition 3.3. Similarly, the production of plasma cells increases with the number of antibodies, but that can only happen in the presence of antigens (conditions 3.2 and 3.3). In system (1), these facts are modeled by the product of V and F.

The disappearance of plasma cells depends directly on their number (condition 3.3). In the same way, if the damage suffered by the organism increases, the production of plasma cells cannot increase (condition 3.3). The last fact is included in system (1) by making the function $\xi(m)$ not increasing in m.

Finally, condition 4 models the fact that the greater the infection the more extensive the damage to the organism. On the other hand, the organism tends to recover, but that process can slow down with increasing damage (Ψ_4 is bounded).

Some additional conditions have to be stated to guarantee invariance of the positive region under system (2). They are of technical nature and are

stated also for negative entries:

$$f_i \geq 0 \quad \text{for } i = 1, 2, 3, 4$$

if any argument is less than or equal to 0, or if x_4 is greater than 1, and

$$f_4(x, y) \leq 0 \quad \text{if } y \geq 1.$$

The interpretation in each case is very simple. For instance, $y \geq 1$ in $f_4(x, y)$ means that if the damage to the organism is complete, then there is nothing more to be damaged. In some cases this makes system (2) more realistic than system (1). In the case of plasma cells, for instance, system (1) allows their production up to C^*, even if the damage to the organism is complete. There would exist a stronger similitude between both models if the coefficient μ depended on m and if $\mu(1) = 0$, which is very reasonable, since a completely damaged organism cannot be expected to produce plasma cells anymore.

An initial condition for equation (2) is a function

$$\varphi \in \mathbf{G} := C([-r_1, 0], \mathbb{R}) \times C([-r_1, 0], \mathbb{R}) \times \mathbb{R} \times \mathbb{R},$$

but for applications we are interested in initial conditions

$$\varphi \in \mathbf{G}^+ := C([-r_1, 0], \mathbb{R}^+) \times C([-r_1, 0]), \mathbb{R}^+) \times \mathbb{R}^+ \times [0, 1].$$

The conditions stated above guarantee that $\mathbf{G}^+$ is invariant under (2) as in the following

LEMMA 1. *Let $\varphi \in \mathbf{G}^+$. Then the solution $x(t) := (x_1(t), \ldots, x_4(t))$ of (2) with initial condition φ satisfies $x_i(t) \geq 0$ and $x_4(t) \leq 1$ for $t \geq 0, i = 1, \ldots, 4$.*

Proof. If $x_1(t_1) = 0$ for some $t_1 \geq 0$, it follows that $x_1(t) = 0$ for $t \geq t_1$, since otherwise the mean value theorem implies that there exists a $t^* > t_1$ such that $x_1(t^*) < 0$ and $\dot{x}_1(t^*) < 0$. That contradicts the fact that f_1 is nonnegative for negative entries.

A similar argument shows that the other variables cannot become negative, neither can x_4 become greater than one.

In order to prove the existence of a stationary solution of (1), we need the following

LEMMA 2. *Let $\Gamma = \{(y, z) \mid f_2(0, y, z) = 0,\ y, z \geq 0\}$. Then there exists $\Psi : [0, \infty) \to \mathbb{R}$ such that $\Gamma = \{(\Psi(z), z) : z \geq 0\}$.*

Proof. Given $z \geq 0$, $\Psi(z)$ is defined as the only value y such that $f_2(0, y, z) = 0$, which is well defined for $z \geq 0$, since so is Ψ_2. Actually, $\Psi(z) = \Psi_2(0, z)$ for $z \geq 0$.

The existence of a stationary solution of (2) is stated in the following

LEMMA 3. $(0, \Psi(x_3^*), x_3^*, 0)$ *is a stationary solution of* (2), *with* x_3^* *the same as in condition* 3.1.

P r o o f. The special form of f_1 in (2) guarantees that the right hand side of the first equation is identically zero for $x_1 = 0$. Conditions 3.1 and 3.2 together with the definition of Ψ in Lemma 2 guarantee the same for the second and third equations in (2). Finally, condition 4 states that the right hand side of the last equation in (2) is also identically zero.

In order to study the stability of the stationary solution established in Lemma 3, we consider the linearization of (2) around the point $(0, \Psi(x_3^*), x_3^*, 0)$. Its characteristic equation is $\det \Delta(\lambda) = 0$ with $\lambda \in \mathbb{C}$ and

$$\Delta(\lambda) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} - \lambda & 0 & 0 & 0 \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} - \lambda & \frac{\partial f_2}{\partial x_3} & 0 \\ \frac{\partial f_3}{\partial x1} \int_{-r_1}^{-r_0} e^{\lambda s} h(s)\, ds & 0 & \frac{\partial f_3}{\partial x_3} - \lambda & \frac{\partial f_3}{\partial x_4} \\ \frac{\partial f_4}{\partial x_1} & 0 & 0 & \frac{\partial f_4}{\partial x_4} - \lambda \end{pmatrix}$$

(all the derivatives being evaluated at $x_1 = 0,\ x_2 = \Psi(x_3^*),\ x_3 = x_3^*$, and $x_4 = 0$). The first and third elements in the second column vanish because of the special form of f_1 and the fact that $\frac{\partial g}{\partial x}(0, \Psi(x_3^*)) = 0$.

With this information we can easily prove the following

PROPOSITION 4. *The stationary solution* $(0, \Psi(x_3^*), x_3^*, 0)$ *is stable if*

$$\left. \frac{\partial f_1}{\partial x_1} \right|_{x_1 = 0,\, x_2 = \Psi(x_3^*)} < 0. \tag{3}$$

P r o o f. The characteristic equation is

$$\left(\frac{\partial f_1}{\partial x_1} - \lambda \right) \left(\frac{\partial f_2}{\partial x_2} - \lambda \right) \left(\frac{\partial f_3}{\partial x_3} - \lambda \right) \left(\frac{\partial f_4}{\partial x_4} - \lambda \right) = 0,$$

with all the derivatives evaluated at $x_1 = 0,\ x_2 = \Psi(x_3^*),\ x_3 = x_3^*$ and $x_4 = 0$. The negativity of the first root is a consequence of the hypothesis. Condition 2 for $x \equiv 0$ implies that $y = \Psi_2(0, z)$ is an increasing function of z. Therefore, on such a curve $\partial f_2 / \partial x_2$ is negative. The nonnegativity of the remaining roots is guaranteed by conditions 3.3 and 4.

Proposition 4 guarantees that a healthy organism recovers if (3) is satisfied. But because of applications we want to know "how small" the infection must be for the organism to recover. To do this, we need three lemmas that follow from the general conditions.

To begin with, the conditions on f_1 imply

LEMMA 5. *The function* $\Psi_1 : (0, \infty) \to \mathbb{R}^+$ *has the following properties*:

(i) $f_1(x, \Psi_1(x)) = 0$ *for* $x \in (0, \infty)$.

(ii) $f_1(x,y) < 0$ *if* $x > 0$ *and* $y > \Psi_1(x)$.
(iii) $f_1(x,y) > 0$ *if* $x > 0$ *and* $y < \Psi_1(x)$.

Similarly, the conditions on f_2 imply

LEMMA 6. *For every fixed* $z > 0$ *the function* $\Psi_2 : \mathbb{R}^+ \times \mathbb{R}^+ \to \mathbb{R}$ *has the following properties*:

(i) $f_2(x, \Psi_2(x,z), z) = 0$ *for* $x \geq 0$.
(ii) $f_2(x,y,z) < 0$ *if* $x \geq 0$ *and* $y > \Psi_2(x,z)$.
(iii) $f_2(x,y,z) > 0$ *if* $x \geq 0$ *and* $y < \Psi_2(x,z)$.

Finally, the conditions on f_4 imply

LEMMA 7. *The function* $\Psi_4 : [0,\infty) \to [0,1]$ *has the following properties*:

(i) $f_4(x, \Psi_4(x)) = 0$ *for* $x \in [0,\infty)$.
(ii) $f_4(x,y) < 0$ *for* $y > \Psi_4(x)$.
(iii) $f_4(x,y) > 0$ *for* $0 < y < \Psi_4(x)$.

Experiments have shown that if the damage to the organism is not great, its capacity to respond to an infection does not change. That means that there is an $\overline{x}_4 > 0$ such that $\frac{\partial f_3}{\partial x_4}(x,y,z) = 0$ for $x, y > 0$ and $0 < z < \overline{x}_4$.

With this information we can prove the following.

PROPOSITION 8. *Let* $(x_1(t), x_2(t), x_3(t), x_4(t))$ *be the solution of* (1) *with initial condition* $(x_1^0(t), x_2^0(t), x_3^0, x_4^0)$, *and let the following conditions be satisfied*:

$$x_2^0(0) > \Psi_1(x_1^0(0)), \tag{4}$$

$$\Psi_2(x, \overline{x}_3) > \Psi_1(x) \quad \text{for } x \leq x_1^0(0) \tag{5}$$

and

$$\overline{x}_4 > \max\{x_4^0, \Psi_3(x_1^0(0))\}$$

with $\overline{x}_3 = \min\{x_3^*, x_3^0\}$ (x_3^* *the same as in condition* 3.1). *Then* $x_1(t)$ *is decreasing for* $t \geq 0$, *and* $\lim_{t\to\infty} x_1(t) = 0$ (*i.e., the infection will die out*).

P r o o f. Note that (4) and Lemma 5(ii) yield a $t_0 > 0$ such that $\dot{x}_1(t) < 0$ for $t \in (0, t_0)$. Now, suppose there is a first $t_1 \geq t_0$ such that $\dot{x}_1(t_1) = 0$. Then

$$x_1(t_1) < x_1^0(0) \tag{7}$$

and

$$f_1(x_1(t_1), x_2(t_1)) = 0, \tag{8}$$

i.e.,

$$\Psi_1(x_1(t_1)) = x_2(t_1). \tag{9}$$

Now, combining (5) with the previous equality we get

$$\Psi_2(x_1(t_1), \overline{x}_3) > x_2(t_1) \tag{10}$$

or, by Lemma 6(iii),

$$f_2(x_1(t_1), x_2(t_1), \overline{x}_3) > 0.$$

On the other hand, (6), Lemma 7, and the fact that $x_1(t)$ is decreasing on $(0, t_1)$ guarantee that $x_4(t) < \overline{x}_4$ for $0 \le t \le t_1$, and therefore, $\partial f_3/\partial x_4 = 0$ for $0 < t < t_1$. Moreover, it is clear from 3.1 and 3.3 that $\dot{x}_3 \ge 0$ if $x_3(t) \le x_3^*$ and $x_1(t)$ and $x_2(t)$ are nonnegative. This, in turn, implies that

$$f_2(x_1(t_1), x_2(t_1), x_3(t_1)) \ge f_2(x_1(t_1), x_2(t_1), \overline{x}_3) > 0,$$

i.e.,

$$\dot{x}_2(t_1) > 0. \tag{11}$$

Finally, (11) guarantees the existence of an interval I such that $t_1 \in I$ and $\dot{x}_2(t) > 0$ for $t \in I$. This, together with (8) and the fact that f_1 is a decreasing function of the second argument implies

$$\dot{x}_1(t) = f_1(x_1(t_1), x_2(t)) > 0$$

just before t_1. This contradiction finishes the proof.

Conditions (4) and (5) are natural generalizations of the ones obtained by Marchuk: $\beta < \lambda F$ and $v_0 < \mu_f(\lambda F^* - \beta)/(\beta\eta\lambda)$. The first condition guarantees that the antigen population decreases for small values of t, and the second implies that it goes monotonically to zero. Restriction (6) corresponds to the assumption $\xi(m(0)) = 1$ in Marchuk's work.

In the present work the immunological barrier can be defined as the first value of x_1 for which $\Psi_2(x_1, \overline{x}_3) = \Psi_1(x_1)$. If the initial antigen population does not break the immunological barrier, then recovery occurs, i.e., the number of antigens in the organism tends to zero in time and any damage in the organism will be corrected.

Moreover, the fact that Ψ_2 is an increasing function of the second component (Condition 2) implies that the organism becomes more resistent by increasing x_3^0. That suggests an effective method of preventing and, even, treating a disease.

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Received on 15.2.1996