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Mathematical modelling of the immune response to infectious diseases with the influence of environmental factors

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Abstract. The mathematical model of the immune response to infectious diseases with the influences of environmental factors is investigated. The conditions for the existence and uniqueness of the solution to the mathematical model for $t > 0$ have been established. Stationary solutions have been identified, along with the conditions for their existence and asymptotic stability. The results are illustrated using a model example.

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Keywords: immune response, infectious disease, mathematical model, stationary solution, stability of solutions, delay differential equations, Marchuk model, model of immune system.

Modelarea matematică a răspunsului imun la bolile infecţioase sub influenţa factorilor de mediu

Rezumat. Modelul matematic al răspunsului imun la bolile infecţioase sub influenţa factorilor de mediu este investigat. Au fost stabilite condiţiile de existenţă şi unicitate a soluţiei modelului matematic pentru $t > 0$. Soluţiile staţionare au fost identificate împreună cu condiţiile de existenţă şi stabilitate asimptotică. Rezultatele sunt prezentate folosind un exemplu model.

Cuvinte-cheie: răspuns imun, boală infecţioasă, model matematic, soluţie staţionară, stabilitatea soluţiilor, ecuaţii diferenţiale cu întârziere, modelul Marchuk, model al sistemului imunitar.

1. Introduction

Numerous works, including those [1]-[4], [8], [9] and others, are devoted to the mathematical modelling of the immune response. G.Bell proposed a predatory-prey model in an immune response to infections by antigens (viruses, bacteria or foreign cells) [1]. In 1980, G.I. Marchuk published a mathematical model that reflects the humoral immune response of the human body and is described by a system of delay differential equations [2]:

$$\begin{aligned}
\frac{dV}{dt} &= (\beta - \gamma F)V, \\
\frac{dC}{dt} &= \alpha\xi(m)V_\tau F_\tau - \mu_c(C - C^*), \\
\frac{dF}{dt} &= \rho C - \eta\gamma FV - \mu_f F, \\
\frac{dm}{dt} &= \sigma V - \mu_m m,
\end{aligned} \tag{1}$$

where variables represent the core factors of the infectious process. The immune response involves the production of specific objects (antibodies, $F(t)$), which are generated by a cascade of plasma cells $C(t)$. Antibodies are capable of neutralizing or destroying foreign materials (antigens), the amount $V(t)$ of which changes over time $t \geq t_0 = 0$. The models also include the relative mass of the affected target organ m(t), which serves as a generalized measure of organ damage caused by the virus, and $\xi(m) = 1$ for $m \in [0, m^*]$ and $\xi(m) = (m - 1)/(m^* - 1)$ for $m^* < m \leq 1$, having $m^* \in (0, 1)$ and considering for $m \in [0, m^*]$ the immune system functions normally; $V_\tau(t) = V(t - \tau)$, $F_\tau(t) = F(t - \tau)$.

The delay factor $\tau > 0$ plays a crucial role in the model as it sets the time from the moment of infection to the activation of immune response mechanisms. More complex delay models have been developed for the immune response to hepatitis B and C, tuberculosis, and other diseases [2]-[6]. Various aspects of immune response dynamics have been studied in the works of U. Forys and M. Bodnar [4].

The course of infectious diseases, such as hepatitis and acute respiratory diseases, is influenced by factors such as air pollution, water contamination, industrial waste, noise pollution, chemical pollution and other environmental pollutants. The model represented in the current work and described subsequently takes into account an integral factor $E(t)$, which is the sum of m factors $E_i(t)$ and is represented as follows:

$$E(t) = a_1E_1(t) + ... + a_mE_m(t),$$

where $a_i \geq 0$, $a_1 + ... + a_m = 1$.

Let us assume that the change of $E(t)$ occurs according to the generalized Hutchinson equation [5], [7], which has the following form:

$$\frac{dE(t)}{dt} = r\left(1 - \left(\frac{E(t - \Delta)}{E^*}\right)^n\right)E(t), t > 0, \tag{2}$$

where $r > 0$ - coefficient of linear growth, $0 < \Delta$ - the average time for the restoration of ecological balance, amount of which is $E^* > 0$. Using the parameter $n > 0$, a more accurate shape of the curve can be selected for a better representation of the system

dynamics. This flexibility allows the modelling of specific scenarios or data, ensuring a closer match to observed behavior in immune response or external factors dynamics (see Fig.1).

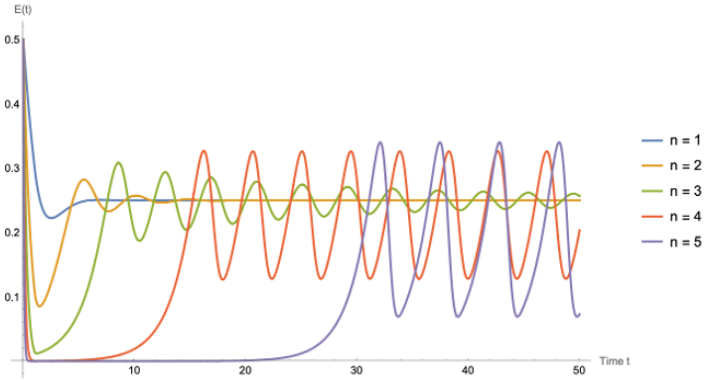


Figure 1. The dynamics of the generalized Hutchinson model for $n = 1, 2, 3, 4, 5$ and $r = 0.5, \Delta = 1, E^* = 0.25$

The change over time of the factors V, E, F, C and the measure m, $0 \le m(t) \le 1$ – the extent of organ damage against which the antigen V is directed – is proposed to be described by a system of equations:

$$\begin{aligned} \frac{dV}{dt} &= (\beta - \gamma F)V, \\ \frac{dC}{dt} &= \alpha\xi(m)V_\tau F_\tau - \mu_c(C - C^*) - \varepsilon_c E, \\ \frac{dF}{dt} &= \rho C - (\mu_f + \eta\gamma V)F, \\ \frac{dm}{dt} &= \sigma V - \mu_m m + \varepsilon_m E, \end{aligned} \tag{3}$$

The initial conditions for the system (3) solution have the following form:

$$\begin{aligned} &V(t) = 0, t \in [-\tau, 0), V(0) = V_0 \ge 0; \\ &F(t) = F_0(t) \ge 0, t \in [-\tau, 0]; C(0) = C_0 \ge 0; m(0) = m_0 \in [0, 1). \end{aligned} \tag{4}$$

The work explores issues of the existence and nonnegativity of solutions, identifies stationary solutions, establishes coefficient conditions for their stability, and conducts numerical modelling of the immune response for the model (3).

2. Nonnegativity and existence of a solution

It has been proven that the solution to the problem (3), (4) is nonnegative, which corresponds to the medical nature of the immune response process. It is known that the

solution to equation (2) with initial condition $E_0(t) \geq 0$ for $t > 0$ exists for $t > 0$ and is bounded, that means $0 \leq E(t) \leq M$.

Theorem 2.1. *Let the coefficients of the system of equations (3) be nonnegative, and suppose there exists a solution for $t > 0$ and the condition*

$$\varepsilon_c M < \mu_c C^* \tag{5}$$

is satisfied. Then the solution of system (3) with initial conditions (4) is nonnegative for $t > 0$.

Proof. The solution of the equation (2) with initial function $E_0(t) \geq 0$ for the $t \in [-\Delta, 0]$ exists for $t > 0$ and limited [7] by

$$0 \leq E(t) \leq M, t \geq 0. \tag{6}$$

From the first equation of (3) after integration we obtain the following:

$$V(t) = V_0 exp(\int_0^t (\beta - \gamma F(s))\, ds) \geq 0.$$

From that follows that $V(t) \geq 0$ for $t > 0$, if $V_0 \geq 0$ and $V(t) > 0$ for $V_0 > 0$. From the equation for the $m(t)$, we obtain

$$m(t) = m_0 e^{-\mu_m t} + \int_0^t e^{-\mu_m (t-s)} (\sigma V(s) + \varepsilon_m E(s)\, ds) \geq 0. \tag{7}$$

Since $m(0) \geq 0$, $V(t) \geq 0$ and $E(t) \geq 0$, then $m(t) > 0$ for $t > 0$. The initial function $V(t) = 0$ for $t < 0$, then on the interval $[0, \tau]$

$$\frac{dC}{dt} = -\mu_c C + \mu_c C^* - \varepsilon_c E. \tag{8}$$

The solution of the equation (8) is the following:

$$C(t) = C^* + (C_0 - C^*) e^{-\mu_c t} - \varepsilon_c \int_0^t e^{-\mu_m (t-s)} E(s)\, ds,$$

Since $E(t) \leq M$ for $t > 0$, then

$$C(t) \geq C^* - \frac{\varepsilon_c M}{\mu_c}(1 - e^{-\mu_c t}) \geq C^* - \frac{\varepsilon_c M}{\mu_c} > 0.$$

From the condition $F(0) > 0$ we obtain $F(t) > 0$ on some interval $(0, t_1)$. Let us assume that $t_1 \leq \tau$ and $F(t_1) = 0$. Then $\frac{dF(t_1)}{dt} = 0$. At the same time,

$$\frac{dF(t_1)}{dt} = \rho C(t_1) - \eta\gamma F(t_1) V(t_1) - \mu_c F(t_1) = \rho C(t_1) > 0,$$

which contradicts the assumption. Thus, $F(t) > 0$ for $t \in [0, \tau]$. Since $\xi(m) \geq 0$ and, on the interval $[\tau, 2\tau]$, $F(t-\tau)V(t-\tau) \geq 0$, then

$$\frac{dC}{dt} = \xi(m(t))V(t-\tau)F(t-\tau) - \mu_c(C - C^*) - \varepsilon_c E \geq -\mu_c(C - C^*) - \varepsilon_c M.$$

From the estimate of the solution of the equation for F(t) on $[0, \tau]$, it follows that $C(t) > 0$ on $[\tau, 2\tau]$. Accordingly, $F(t) > 0$ on that interval. Using the step method, the positivity of $C(t)$ and $F(t)$ is similarly proven on $[2\tau, 3\tau]$, and so forth for subsequent intervals. ■

Theorem 2.2. *Let the coefficients and initial conditions at $t = 0$ for the solutions of equations (2) and (3) be positive numbers. Then there exists a unique solution to the problem (2), (3), defined on $[0, \infty)$ and differentiable on $(0, \tau) \cup (\tau, \infty)$.*

Proof. For equation (2), at each step $[k\Delta, (k+1)\Delta], k = 0, 1, ...$, a linear equation $\frac{dE}{dt} = qE(t)$ with a continuous function $q(t), t > 0$ is obtained. Therefore, there exists a unique solution to the equation (2) for $t > 0$, which is differentiable if the initial function $E_0 \in C[-\Delta, 0]$.

Let $V(0) > 0$. Then there exists a solution $V(t)$ on some interval $(0, a)$. Moreover, by Theorem 2.1, $V(t) > 0$. From this it follows that $F(t) > 0$ for $t \in (0, a)$. Thus on that interval

$$\frac{dV}{dt} = \beta V - \gamma FV \leq \beta V.$$

The solution to the linear equation $\frac{dV}{dt} = \beta V$ is defined for all $t > 0$. According to Wintner's theorem [6], the solution $V(t)$ of the first equation of (3) is defined for $t > 0$. Since the function $V_0(t)$ has a first-order discontinuity at $t = 0$, the function $V(t)$ is continuous for $(0, \infty)$ and differentiable over intervals $(0, \tau)$ and (τ, ∞).

From the form of the solution $m(t)$ according to formula (7), it follows that the solution $m(t)$ is defined for $t > 0$ and $m \in C^1(0, \infty)$.

The existence and uniqueness of solution $F \in C^1(0, \infty)$ is received from the differentiability of the right-hand side of the equation for F factor and an inequality

$$\frac{dF}{dt} = \rho C - (\eta\gamma F + \mu_f)F \leq \rho C,$$

using Winter's theorem.

■

3. Stationary solutions and their stability

By substituting $E(t) = \overline{E}(t) + E^*, t = s\Delta$, equation (2) is transformed into the form

$$\frac{d\overline{E}(s)}{ds} = -rn\Delta\overline{E}(s-1) + f(\overline{E}(s-1)),$$

where $\lim_{x\to 0}\frac{f(x)}{x} = 0$. The roots of the characteristic equation $\lambda + rn\Delta e^{-\lambda} = 0$ have negative real parts if the following condition is satisfied [7]

$$0 < rn\Delta < \pi/2. \tag{9}$$

According to the theorem on stability by linear approximation, the solution $E = E^*$ of equation (2) is asymptotically stable under the fulfilment of the condition (9).

The stationary solutions of system (3) are derived by the system of equations

$$\begin{aligned} &(\beta - \gamma F)V = 0,\\ &\alpha VF - \mu_c(C - C^*) - \varepsilon_c E = 0,\\ &\rho C - (\mu_f + \eta\gamma V)F = 0,\\ &\sigma V - \mu_m m + \varepsilon_m E = 0. \end{aligned} \tag{10}$$

The medical justification of the solutions requires $\xi(m) = 1$, which is achieved when $m \le m^*$ means that the damage to the target organ does not exceed the critical level.

For the problem (2),(3), there always exists such a stationary solution

$$E_1 = E^*, V_1 = 0, C_1 = C^* - \frac{\varepsilon_c E^*}{\mu_c}, F_1 = \frac{\rho C_1}{\mu_f}, m_1 = \frac{\varepsilon_m E^*}{\mu_m} \tag{11}$$

that defines the state of a healthy organism under permissible environmental pollution levels. The stationary solution (11) has a medical justification, if it is nonnegative. This holds if the following conditions are met:

$$\varepsilon_c E^* < C^*\mu_c, \varepsilon_m E^* \le \mu_m m^* \tag{12}$$

Theorem 3.1. *If condition (9), (12) and condition*

$$\beta - \gamma F_1 < 0 \tag{13}$$

are satisfied, then solution (11) is locally asymptotically stable.

Proof. Let us perform a substitution in system (3): $E = \overline{E} + E^*, V = \overline{V}, C = \overline{C} + C_1, F = \overline{F} + F_1, m = \overline{m} + m_1$. Let $(\overline{V}, \overline{F}, \overline{C}, \overline{m})$ be a solution of (10), then the linearized system

corresponding to (3) for this solution takes the form

$$\begin{aligned}
\frac{d\overline{V}}{dt} &= (\beta - \gamma\overline{F})V,\\
\frac{d\overline{C}}{dt} &= \alpha\overline{V}F_\tau + \alpha\overline{F}V_\tau - \mu_c C - \varepsilon_c E,\\
\frac{d\overline{F}}{dt} &= \rho\overline{C} - \mu_f\overline{F} - \eta\gamma(\overline{V}F + V\overline{F}),\\
\frac{d\overline{m}}{dt} &= \sigma\overline{V} - \mu_m\overline{m} + \varepsilon_m E.
\end{aligned} \tag{14}$$

If the conditions of the theorem are satisfied, the nonnegativity of the solution (11) is evident. The characteristic equation for the linearized system (14) for solution (11) takes the form

$$(\lambda + rne^{-\Delta})\begin{vmatrix} \beta - \gamma F_1 - \lambda & 0 & 0 & 0\\ \alpha F_1 e^{-\lambda\tau} & -\mu_c - \lambda & 0 & 0\\ -\eta\gamma F_1 & \rho & \mu_f - \lambda & 0\\ \sigma & 0 & 0 & -\mu_m - \lambda \end{vmatrix} =$$

$$= (\beta - \gamma F_1 - \lambda)(\mu_c + \lambda)(\mu_f + \lambda)(\mu_m + \lambda) = 0,$$

If conditions (9) and (13) are satisfied, the roots are negative, and the stationary solution is locally asymptotically stable. It is worth noting that solution (11) can be interpreted as the state of a healthy organism under an acceptable level of environmental pollution. ■

Theorem 3.2. *Let condition (13) hold, and for the initial values C_0 and V_0 the inequalities*

$$C_0 > C^* + \frac{\varepsilon M}{\mu_c}, 0 < V_0 < V^* = \frac{\mu_f(\gamma F_1 - \beta)}{\eta\gamma\beta} + \frac{2\rho\varepsilon_C M}{\mu_c} \tag{15}$$

are satisfied. Then, the function $V(t)$ decreases for $t > 0$ and

$$\lim_{t\to\infty} V(t) = 0.$$

Proof. Let $c(t) = C(t) - C^*$, $c_0 = C_0 - C^*$. For $t \in [0, \tau]$ from second equation of model (3) and initial functions (4); the following equation is received:

$$\frac{dc}{dt} = -\mu_C c - \varepsilon_c E.$$

From the first inequality from (15) and the boundedness of the solution of equation (2) by the constant M is received:

$$c(t) = c_0 e^{-\mu_c t} - \varepsilon_c \int_0^t e^{-\mu_c(t-s)} E(s)\, ds \geq c_0 e^{-\mu_c t} - \frac{\varepsilon_c M}{\mu_c}(1 - e^{-\mu_c t}) \geq \frac{c_0}{2}. \tag{16}$$

Thus, for $t \in [0, \tau]$

$$C(t) \geq C^* + \frac{2\varepsilon_c M}{\mu_c}. \tag{17}$$

On the interval $[\tau, 2\tau]$, taking into account that $F(t) > 0$, we obtain

$$\frac{dc}{dt} = \alpha\xi(m)F(t-\tau)V(t-\tau) - \mu_c c(t) - \varepsilon_c E(t) \geq -\mu_c c(t) - \varepsilon_c E(t),$$

from which assessment (16) is received. So forth for subsequent intervals $[2\tau, 3\tau]$.

Since $F(t) > 0$ for $t > 0$ and $\beta - \gamma F^* < 0$, then function $V(t)$ decreases on the interval $(0, t_1)$, $t_1 > 0$ and $\frac{dV(t_1)}{dt} = 0$. Then $F(t_1) = \frac{\beta}{\gamma}$ and on the certain interval (t_1, t_2) the following conditions are satisfied: $\frac{dV(t)}{dt} \geq 0$,

$$\frac{dF(t)}{dt} \leq 0. \tag{18}$$

Let us consider the value of the derivative

$$\frac{dF(t_1)}{dt} = \rho C(t_1) - \eta\gamma F(t_1)V(t_1) - \mu_f F(t_1) > \rho(C^* + \frac{2\varepsilon_c M}{\mu_c}) - \eta\beta V_0 - \mu_f \frac{\beta}{\gamma}.$$

From the estimate (17) follows:

$$\frac{dF(t_1)}{dt} = \eta\beta\left(\frac{\gamma F_1 - \beta}{\beta\gamma\eta} + \frac{2\rho\varepsilon_c E}{\beta\eta\mu_c} - V_0\right) = V^* - V_0 \geq 0,$$

This contradicts estimate (18). Hence, the function $V(t)$ decreases for $t > 0$ and the limit for $t \to \infty$ is the stationary solution $V_1 = 0$. ■

Remark 3.1. *In the monograph* [2] *number V^* is called an immunological barrier. If, during antigen infection, its degree does not exceed V^*, then the disease will not develop.*

The problem (2), (3) may have another stationary solution that corresponds to the state of a chronic disease:

$$\begin{aligned}
E_2 &= E^*, F_2 = \frac{\beta}{\gamma}, \\
V_2 &= \frac{\mu_c\mu_f\beta - \rho\gamma\mu_c C^* + \rho\gamma\varepsilon_c E^*}{\beta(\alpha\rho - \mu_c\eta\gamma)}, \\
C_2 &= \frac{\alpha\beta\mu_f - \eta\gamma^2\mu_c C^* + \eta\gamma^2\varepsilon_c E^*}{\gamma(\alpha\rho - \mu_c\eta\gamma)}, \\
m_2 &= \frac{\delta V_2 + E_2}{\mu_m}.
\end{aligned} \tag{19}$$

A stationary solution (19) exists if either

$$\alpha\rho > \mu_c\eta\gamma, \rho\gamma\mu_c C^* < \mu_c\mu_f\beta + \rho\gamma\varepsilon_c E^*$$

or the inequality with the opposite sign is satisfied. If $V_2 > 0$, then $C_2 > 0$ accordingly.

The characteristic equation for system (19), corresponding to the stationary solution $X := (E_2, V_2, C_2, F_2, m_2)$ takes the form:

$$P_5(\lambda) := -(\mu_m + \lambda)(\lambda + rne^{-\lambda\Delta}) * \begin{vmatrix} -\lambda & 0 & -\gamma V_2 \\ 2F_2 e^{-\lambda\tau} & -\mu_c - \lambda & \alpha V_2 e^{-\lambda\tau} \\ -\eta\gamma F_2 & \rho & \eta\gamma V_2 - \mu_f - \lambda \end{vmatrix} =$$
$$= (\mu_m + \lambda)(\lambda + rne^{-\lambda\Delta})(\lambda^3 + c_1\lambda^2 + +c_2\lambda + c_3) = 0,$$

where $c_1 = \mu_c + \mu_f - \eta\gamma V_2$, $c_2(\lambda) = \mu_c\mu_f - (\eta\gamma + \alpha\rho e^{-\lambda\tau} + \eta\beta)V_2$,
$c_3(\lambda) = (\alpha\rho e^{-\lambda\tau} - \eta\mu_c)\Delta V_2$.

If inequality (9) holds, the study of the asymptotic stability of the solution X reduces to finding the conditions under which $Re(\lambda) < 0$ for the roots of the quasi-polynomial $P_3 = 0$. Let us consider the case when $\tau = 0$, which is the case of an instantaneous immune system response to the infection of the human body. In this case, the problem reduces to studying the roots of a cubic equation

$$P_{3,0}(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{20}$$

where $a_1 = c_1$, $a_2 = \mu_c\mu_f - ((1+\beta)\eta\gamma + \alpha\rho)V_2$, $a_3 = \beta(\alpha\rho - \eta\gamma\mu_c)V_2$. Let us consider the case of a strong immune response [2], when

$$\alpha\rho > \eta\gamma\mu_c, \tag{21}$$

in that case $a_3 > 0$.

From the Routh-Hurwitz criterion [6], it follows that the necessary and sufficient conditions for the asymptotic stability of solution X are the fulfilment of condition (21) and

$$a_1 > 0, a_1a_2 - a_3 > 0. \tag{22}$$

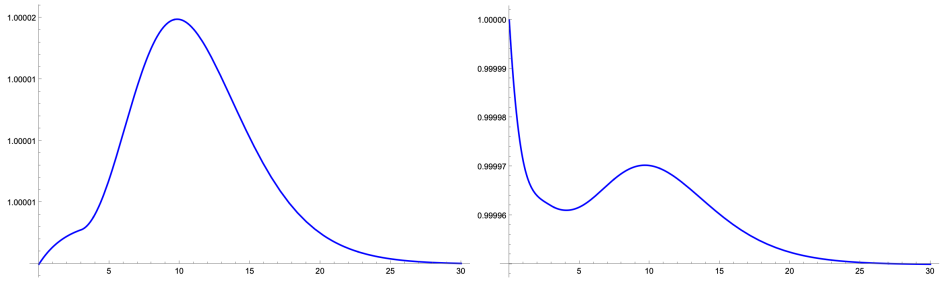
From the analysis of the roots of the characteristic equation of the linearized system, the conditions for the asymptotic stability and instability of solution (19) have been found. Therefore, sufficient conditions for either maintaining a chronic disease state or transitioning from a chronic condition to an acute form have been obtained.

4. Numerical modelling

Numerical simulations of the immune response were conducted using the Wolfram Mathematica computer algebra system, considering the influence of environmental factors. These simulations were based on the system (2), (3) with the following parameters: $\beta = 0.6, \gamma = 0.2, \alpha = 0.9, \mu_c = 0.5, C^* = 1, \rho = 0.9, \mu_f = 0.17, \eta = 0.8, \sigma = 0.35, \mu_m = 0.4, r = 0.5, \Delta = 1, E^* = 0.25, n = 1; V_0 = 0.000001, C_0 = F_0 = 1, E_0 =$

0.5, $m_0 = 0$. Simulations were performed under two distinct scenarios: Figures 2(a), 3(a) with $\varepsilon_c = \varepsilon_m = 0$, and Figures 2(b), 3(b) with $\varepsilon_c = \varepsilon_m = 0.0001$.

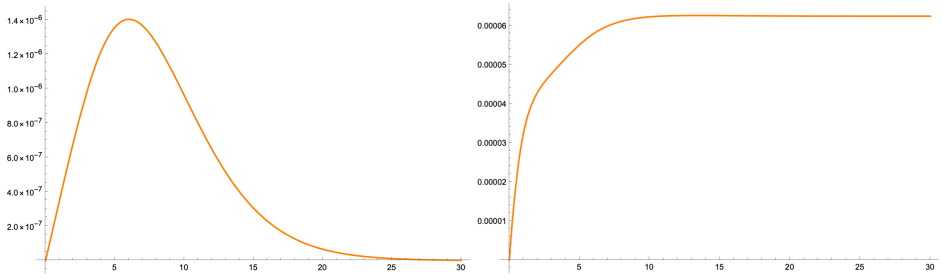
Figure 2(a) illustrates the change in the level of plasma cells $C(t)$ without the influence of the environmental factors $E(t)$. In Figure 2b, under the influence of $E(t)$, oscillations occur in the plasma cell population, and the weakened overall immune response is demonstrated.



a) b)

Figure 2. Dynamics in the immune response model factor $C(t)$ without (a) and with (b) the influence of environmental factors.

Figures 3(a) and 3(b) show the dynamics of the extent of damage $m(t)$ to the target organ. With pollution (Figure 3b), there remains relatively minor damage to the target organ according to the parameters set by this model example. The presence of the ecological factor leads to an overall destabilizing effect on the system's equilibrium. When $E(t) = 0$, then $m(t) \to 0$ for $t \to \infty$.



a) b)

Figure 3. Dynamics in the immune response model factor $m(t)$ without (a) and with (b) the influence of environmental factors.

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