MCIT Modeling, control & information technologies

Mathematical modeling of the body's immune response to infectious disease with external factors

https://doi.org/10.31713/MCIT.2024.067

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The article investigates a mathematical model of the immune response to an infectious disease, considering external factors that influence the course of the disease. Stationary solutions and their existing conditions have been identified, along with their medical interpretation and sufficient conditions for asymptotic stability.

Keywords — mathematical model of infectious disease, модель імунна відповідь, стаціонарний розв'язок, стійкість, антигени, антитіла, плазмоклітини, запізнення.

Mathematical immunology aims to utilize mathematical methods and information technologies to model immune processes, enabling their study and prediction. The adequacy of the mathematical model of the immune response significantly depends on the mathematical formulation, particularly on the selection of factors that influence the immune response in an infectious disease.

This field of applied mathematics has been actively developing since the works of G. Bell. A foundational model is G.I. Marchuk's mathematical model of the immune response to an infectious disease, proposed in 1975 [1]. Several significant results have been obtained in the works of U. Forish and M. Bodnar [2], V.P. Martsenyuk and O.H. Nakonechnyi [3], A.Ya. Bomba [4], S. Rusakov [5], among others.

In this study, the research presented in [6] has been continued, focusing on the impact of external factors on the immune response to an infectious disease, which is modeled as a solution to the generalized Hutchinson model

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

where $E(t)$ is the integrated dimensionless factor of external influence, such as environmental pollution, $0 \leq E(t) \leq 1, r > 0$ is the linear growth coefficient, $0 < \Delta$ is the average time for ecological equilibrium restoration, $n > 1$ and provides flexibility in describing the dynamics of the process.

If the condition

$$0 < rn\Delta < \frac{\pi}{2} \qquad (2)$$

is satisfied, it has been proven that the stationary solution $E = E^*$ is locally asymptotically stable.

A generalization of G.I. Marchuk's model includes considering the influence of the factor $E(t)$ on the formation of the plasma cell cascade $C(t)$ and the extent of damage to the target organ $m(t), 0 \leq m(t) \leq 1$. The mathematical model takes the form:

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

$$\frac{dC}{dt} = \alpha\xi(m)V_\tau F_\tau - \mu_c(C - C^*) - \varepsilon_c E, \qquad (3)$$

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

$$\frac{dm}{dt} = \sigma V - \mu_m m + \varepsilon_m E,$$

where $V(t)$ is the population of antigens (viruses, bacteria, etc.), $F(t)$ is the population of antibodies, $0 < \tau$ is the time required for the formation of the plasma cell cascade, $V_\tau(t) = V(t-\tau), F_\tau(t) = F(t-\tau), \xi(m) = 1$ when $0 \leq m \leq m^*$, while $\xi(m) = 1 + (m-1)/(m^*-1)$ for $m > m^*$, where the stationary solution does not exist due to immune system dysfunction.

Theorem 1. If the coefficients of the mathematical model (1), (3) are non-negative numbers, and the initial functions for the factors E, F i V are are non-negative functions on the initial intervals $[-\Delta; 0]$ i $[-\tau; 0]$ respectively, then there exists a unique continuous solution for $t > 0$. ■

In the system (1)-(3) exists a stationary solution:

$$E_1 = E^*, V_1 = 0,$$

$$C_1 = C^* - \frac{\varepsilon_c E^*}{\mu_c}, F_1 = \frac{\rho C_1}{\mu_f}, m_1 = \frac{\varepsilon_m E^*}{\mu_m}, \qquad (4)$$

when

$$C^*\mu_c > \varepsilon_c E^*, \varepsilon_m E^* \leq \mu_m m^*. \qquad (5)$$

This solution corresponds to the state of a healthy human organism.

Theorem 2. Let the conditions (2) and (5) hold, and

$$\beta - \gamma F_1 < 0, \qquad (6)$$

then the stationary solution (4) is locally asymptotically stable. ■

Corollary. If the conditions of Theorem 1 are satisfied and $V_0 = V^*$, then the disease will not occur. In this case, the stability depends on the delay Δ and is independent of the delay $\tau > 0$.

The system of equations (1), (3) may have another stationary solution, which corresponds to the state of a chronic disease:

$$E_2 = E^*, F_2 = \frac{\beta}{\gamma}, m_2 = \frac{\delta V_2 + E_2}{\mu_m},$$
$$V_2 = \frac{\mu_c \mu_f \beta - \rho\gamma\mu_c C^* + \rho\gamma\varepsilon_c E^*}{\beta(\alpha\rho - \mu_c\eta\gamma)}, \quad (7)$$
$$C_2 = \frac{\alpha\beta\mu_f - \eta\gamma^2\mu_c C^* + \eta\gamma^2\varepsilon_c E^*}{\gamma(\alpha\rho - \mu_c\eta\gamma)}.$$

The stationary solution (7) exists if either

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

or the inequality with the opposite sign is satisfied.

Using the Wolfram Mathematica computer algebra system, numerical immune response modeling, accounting for external influence, was conducted. Figure 1 shows the variation in the magnitude of external influence depending on certain parameter n = 1, 2 and 3.

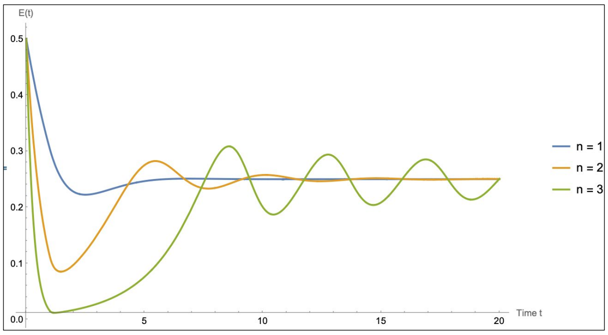

Figure 1. The dynamics of the generalized Hutchinson model for $n = \{1,2,3\}$ *and* $r = 0.5, \Delta = 1, E^* = 0.25$.

In Figure 2, the functions' graphs are presented in the absence of external influence. When external influence is present (Figure 3), a weaker immune response is observed, along with oscillations in the number of plasma cells and damage to the target organ.

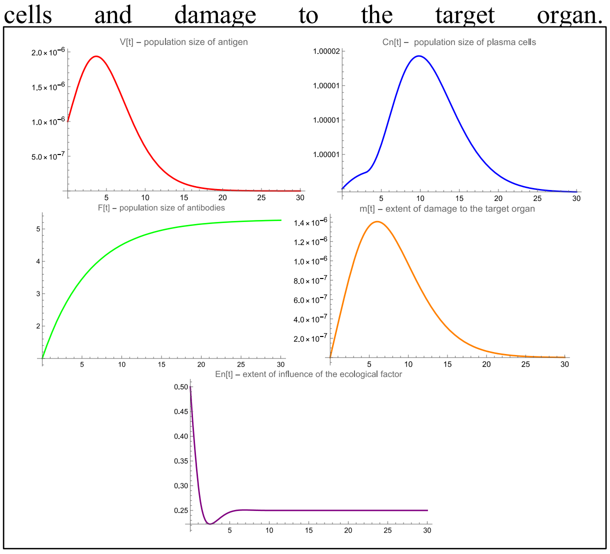

Figure 2. Dynamics in the immune response model without external influence. Parameters: $\beta = 0.6, \gamma = 0.2, \alpha = 0.9, \mu_c = 0.5, C^* = 1, \varepsilon_c = \varepsilon_m = 0, \rho = 0.9, \mu_f = 0.17, \eta = 0.8, \sigma = 0.35, \mu_m = 0.4, r = 0.5, \Delta = 1, E^* = 0.25, n = 1; V_0 = 0.000001, C_0 = F_0 = 1, E_0 = 0.5, m_0 = 0$

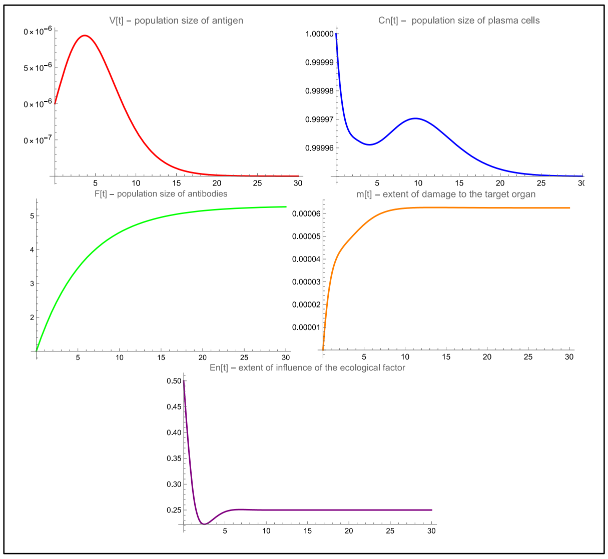

Figure 3. Dynamics in the immune response model with external influence. Parameters: $\beta = 0.6, \gamma = 0.2, \alpha = 0.9, \mu_c = 0.5, C^* = 1, \varepsilon_c = 0.0001, \rho = 0.9, \mu_f = 0.17, \eta = 0.8, \sigma = 0.35, \mu_m = 0.4, \varepsilon_m = 0.0001, r = 0.5, \Delta = 1, E^* = 0.25, n = 1; V_0 = 0.000001, C_0 = F_0 = 1, E_0 = 0.5, m_0 = 0$

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