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Influence of delay on character of stability of stationary points for mathematical model of purchased immunity.

A mathematical model of purchased immunity, which is described by a system of nonlinear differential equations with delay. Influence of delay is analyzed on stability of stationary points, and in the end, we give the biological consequences.

Keywords: system of nonlinear differential equations, the immune system, antigen, the stability of the stationary point.

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Вплив запізнення на характер стійкості стаціонарних точок в математичній моделі надбаного імунітету.

Розглядається математична модель надбаного імунітету, яка описується системою нелінійних диференціальних рівнянь із запізненням. Аналізується вплив запізнення на стійкість стаціонарних точок, наводяться біологічні наслідки.

Ключові слова: система нелінійних диференціальних рівнянь, імунітет, антиген, стійкість стаціонарного стану.

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To study the effect of reaction delay lymphocytes to change amount of infections we will consider a nonlinear system of ordinary differential equations describing the effect of purchased immunity:

$$\frac{dN}{dt} = N(\mu_N - \gamma_1 L - \gamma_2 X),\quad \frac{dL}{dt} = (L^* - L)(\mu_L - \gamma_3 N(t-\tau) - \gamma_4 G). \tag{1}$$

The initial conditions are given by

$$N(t_0) = N_0, L(t_0) = L_0,\quad N(t) \equiv 0 \text{ for } t_0 - \tau < t < t_0. \tag{2}$$

Suppose the parameter τ small. Replace function $N(t-\tau)$ its linear approximation:

$$N(t-\tau) \cong N(t) - \tau\frac{dN(t)}{dt}.$$

Thus, we have

$$\frac{dN}{dt} = N(\mu_N - \gamma_1 L - \gamma_2 X),\quad \frac{dL}{dt} = (L^* - L)(\mu_L - \gamma_3 N(1 + \tau(\mu_N - \gamma_1 L - \gamma_2 X)) - \gamma_4 G). \tag{3}$$

Stationary points found from the system:

$$N(\mu_N - \gamma_1 L - \gamma_2 X) = 0,\quad (L^* - L)(\mu_L - \gamma_3 N(1 + \tau(\mu_N - \gamma_1 L - \gamma_2 X)) - \gamma_4 G) = 0. \tag{4}$$

The first stationary point

$$N_1 = 0,\ L_1 = L^*, \tag{5}$$

describes a healthy organism,
and the second stationary point

$$L_2 = \frac{\mu_N - \gamma_2 X}{\gamma_1},\ N_2 = \frac{\mu_L - \gamma_4 G}{\gamma_3}, \tag{6}$$

responds for a sick organism.

Investigate the stability of stationary points.

Theorem 1. *A stationary point* (5) *will be asymptotic stable at implementation of such condition* $\mu_N - \gamma_2 X < \gamma_1 L^*$, *if the condition* $\mu_N - \gamma_2 X > \gamma_1 L^*$, *the stationary point is unstable, and if* $\mu_N - \gamma_2 X = \gamma_1 L^*$, *the stationary point is stable.*

Proof:

Linearized system of differential equations (3) in around of this point (5) will look like

$$\frac{dN}{dt} = (\mu_N - \gamma_1 L^* - \gamma_2 X)N,\quad \frac{d\tilde{L}}{dt} = (\gamma_4 G - \mu_L)\tilde{L}, \tag{7}$$

where $\tilde{L} = L - L_1$.

We write the matrix coefficients for the linearized system

$$A_1 = \begin{pmatrix} \mu_N - \gamma_1 L^* - \gamma_2 X & 0 \\ 0 & \gamma_4 G - \mu_L \end{pmatrix}.$$

Characteristic equation $\det(A_1 - \lambda E) = 0$ will look like

$$\begin{vmatrix} (\mu_N - \gamma_1 L^* - \gamma_2 X) - \lambda & 0 \\ 0 & (\gamma_4 G - \mu_L) - \lambda \end{vmatrix} = 0$$

or

$$\big((\mu_N - \gamma_1 L^* - \gamma_2 X) - \lambda\big)\big((\gamma_4 G - \mu_L) - \lambda\big) = 0,$$

here received

$$\lambda_1 = \mu_N - \gamma_1 L^* - \gamma_2 X,$$
$$\lambda_2 = \gamma_4 G - \mu_L.$$

Clearly, that $\lambda_2 < 0$ always (due to the fact that $N_2 > 0$). As for the sign λ_1, then if $\lambda_1 < 0$ – singular point is asymptotic stable, if $\lambda_1 > 0$ – singular point is unstable, and if $\lambda_1 = 0$ – singular point is stable.

The theorem is proved.

Results. In the case of the stable node ($\lambda_1 < 0$, $\lambda_2 < 0$), the existing population of lymphocytes in the body exceeds the speed of propagation of antigen and with it the content of corticosteroids G did not significantly affect the rate of reproduction and recovery of lymphocytes in the body [1]. Under this situation, the immune system described situation is stable and even a small perturbation of the steady state does not put it out of balance. Human remains healthy.

In the case of the saddle ($\lambda_1 > 0$, $\lambda_2 < 0$), despite the fact that the content of corticosteroids does not substantially affect the reproduction rate and the recovery of lymphocytes in the body, yet the rate of reproduction and dissemination of antigen exceeds the lymphocyte population in the body (weak immune status), which can result in chronic disease.

Theorem 2. *For* $\tau > 0$, *if the condition is* $\gamma_1 L^* = \mu_N - \gamma_2 X$, *then a stationary point* (6) *is a type of unstable degenerate node, if* $\gamma_1 L^* < \mu_N - \gamma_2 X$, *then stationary point – is unstable focus, if* $\gamma_1 L^* > \mu_N - \gamma_2 X$, *then the stationary point* (6) *is a saddle.*

Proof:

Linearized system of differential equations (3) in around of the second point (6) will look like

$$\frac{d\tilde{N}}{dt} = \frac{\gamma_1}{\gamma_3}(\mu_L - \gamma_4 G)\tilde{L},$$
$$\frac{d\tilde{L}}{dt} = -\gamma_3\Big(L^* - \frac{\mu_N - \gamma_2 X}{\gamma_1}\Big)\tilde{N} + \tau(\mu_L - \gamma_4 G)(\mu_N - \gamma_2 X)\tilde{L},$$

where $\tilde{L} = L - L_2$, $\tilde{N} = N - N_2$.

Matrix coefficients for the linearized system has the form

$$A_2 = \begin{pmatrix} 0 & -\frac{\gamma_1}{\gamma_3}(\mu_L - \gamma_4 G) \\ -\gamma_3\Big(L^* - \frac{\mu_N - \gamma_2 X}{\gamma_1}\Big) & \tau(\mu_L - \gamma_4 G)(\mu_N - \gamma_2 X) \end{pmatrix}$$

Characteristic equation $\det(A_2 - \lambda E) = 0$ will look like

$$\begin{vmatrix} -\lambda & -\frac{\gamma_1}{\gamma_3}(\mu_L - \gamma_4 G) \\ -\gamma_3\Big(L^* - \frac{(\mu_N - \gamma_2 X)}{\gamma_1}\Big) & \tau(\mu_L - \gamma_4 G)(\mu_N - \gamma_2 X) - \lambda \end{vmatrix}.$$

Then we have

$$\lambda^2 - \lambda\tau(\mu_L - \gamma_4 G)(\mu_N - \gamma_2 X) - \\ - \gamma_1(\mu_L - \gamma_4 G)\Big(L^* - \frac{\mu_N - \gamma_2 X}{\gamma_1}\Big) = 0.$$

Roots of this quadratic equation have the form

$$\lambda_1 = \frac{\tau(\mu_L - \gamma_4 G)(\mu_N - \gamma_2 X)}{2} + \\ + \sqrt{\gamma_1(\mu_L - \gamma_4 G)\Big(L^* - \frac{(\mu_N - \gamma_2 X)}{\gamma_1}\Big)},$$
$$\lambda_2 = \frac{\tau(\mu_L - \gamma_4 G)(\mu_N - \gamma_2 X)}{2} - \\ - \sqrt{\gamma_1(\mu_L - \gamma_4 G)\Big(L^* - \frac{(\mu_N - \gamma_2 X)}{\gamma_1}\Big)}. \quad (8)$$

We must evaluate the sign

$$D_1 = \gamma_1(\mu_L - \gamma_4 G)\Big(L^* - \frac{(\mu_N - \gamma_2 X)}{\gamma_1}\Big).$$

Because of $\tau > 0$, then we have for $D_1 = 0$:

$\lambda_1 = \lambda_2 = \dfrac{\tau(\mu_L - \gamma_4 G)(\mu_N - \gamma_2 X)}{2} > 0$ – the roots are multiples and positive, so we have an unstable degenerate node;

for $D_1 < 0$

roots of the characteristic equation are

$$\lambda_{1,2} = \frac{\tau(\mu_L - \gamma_4 G)(\mu_N - \gamma_2 X)}{2} \pm$$

$$\pm i\sqrt{\gamma_1(\mu_L - \gamma_4 G)(L^* - \frac{(\mu_N - \gamma_2 X)}{\gamma_1})}$$

and $\mathrm{Re}\lambda > 0$, therefore, we have an unstable focus;

for $D_1 > 0$, then $\lambda_1 > 0$, $\lambda_2 < 0$ – stationary point is saddle, but if τ grows, we have ($\lambda_1 > 0, \lambda_2 > 0$) an unstable node.

The theorem is proved.

Results. In the case of a singular point of saddle - the body or be able to overcome the disease, or may be lost. In the case where the singular point is the center, the body will have a chronic disease that periodically will escalate.

In the case of a singular point of the body of an unstable focus will continue to experience some "hesitation": the aggravation of the disease and a weakened immune system (including the reduction of hormones (corticosteroids)) that suppress the production of lymphocytes), and then will increase the production of lymphocytes and a slight weakening of the disease. With increasing content of lymphocytes increased hormone (G), which will result inhibit the production of lymphocytes and lead to a new outbreak. Such constant stress on the immune system result in an exhaustion [1, 2], whereby the body can not cope with the disease and die.

In the case where the singular point is an unstable node, depending on the state of the immune system (the system parameters and the ratio of (3)), or the body can overcome the disease or inhibit the growth of populations of antigen specific "long" period of time, or in the case of a weakened immune system - will be the rapid growth of the population of antigens, the body with the disease eventually can not cope and die [3, 4].

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