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ON THE COEFFICIENT OF SENSITIVITY OF A CONTROLLED DIFFERENTIAL MODEL OF THE IMMUNE RESPONSE

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Abstract. A form of the system of differential equations is established, which satisfies the sensitivity coefficients of a controlled differential model of the immune response considering perturbations of the delay parameter, the initial and control functions.

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1. The coefficient of sensitivity and the equation in variations for the controlled differential equation with delay

Let $I = [t_0, t_1]$ be a given interval, suppose that $O \subset \mathbb{R}^n$ is an open set and $U \subset \mathbb{R}^r$ is a compact set. Let the n-dimensional function

$$f(t, x, y, u) = (f_1(t, x, y, u), ..., f_n(t, x, y, u))^T$$

be continuous on $I \times O^2 \times U$ and continuously differentiable with respect to x, y and u, where T is the sign of transposition. Furthermore, let $\tau_2 > \tau_1 > 0$ be given numbers; let Φ be a set of continuously differentiable functions $\varphi : I_1 = [\hat{\tau}, t_0] \to O$, where $\hat{\tau} = t_0 - \tau_2$ and let Ω be a set of piecewise-continuous functions $u(t) \in U, t \in I$.

To each element $\mu = (\tau, \varphi(t), u(t)) \in \Lambda := [\tau_1, \tau_2] \times \Phi \times \Omega$ we assign the delay controlled differential equation

$$\dot{x}(t) = f(t, x(t), x(t - \tau), u(t))), \ t \in I \tag{1}$$

with the initial condition

$$x(t) = \varphi(t), \ t \in I_1. \tag{2}$$

Definition. Let $\mu = (\tau, \varphi(t), u(t)) \in \Lambda$. A function $x(t; \mu) \in O$ for $t \in I_3 = [\hat{\tau}, t_1]$, is called a solution of equation (1) with the initial condition (2), or a solution corresponding to the element μ and defined on the interval I_3, if $x(t; \mu)$ satisfies condition (2), is absolutely continuous on the interval I and it satisfies equation (1) almost everywhere on I.

Let us introduce the notation:

$$|\mu| = |\tau| + \|\varphi\|_1 + \|u\|,$$

where

$$\|\varphi\|_1 = \sup\Big\{|\varphi(t)| + |\dot{\varphi}(t)| : t \in I_1\Big\}, \ \|u\| = \sup\Big\{|u(t)| : t \in I\Big\};$$

denote by

$$\Lambda_\varepsilon(\mu_0) = \Big\{\mu \in \Lambda : |\mu - \mu_0| \leq \varepsilon\Big\}$$

the set of perturbations of the fixed element $\mu_0 = (\tau_0, \varphi_0(t), u_0(t)) \in \Lambda$, where $\varepsilon > 0$ is a given number; furthermore,

$$\delta\tau = \tau - \tau_0,\ \delta\varphi(t) = \varphi(t) - \varphi_0(t),\ \delta u(t) = u(t) - u_0(t),$$
$$\delta\mu = \mu - \mu_0 = (\delta\tau, \delta\varphi, \delta u), |\delta\mu| = |\delta\tau| + \|\delta\varphi\|_1 + \|\delta u\|.$$

Theorem 1. *Let $x_0(t) := x(t;\mu_0)$ be the solution corresponding to the element $\mu_0 = (\tau_0, \varphi_0(t), u_0(t)) \in \Lambda$ and defined on the interval I_3. Then, there exists $\varepsilon_1 > 0$ such that for each element $\mu \in \Lambda_{\varepsilon_1}(\mu_0)$ there corresponds the solution $x(t;\mu)$ defined on the interval I_3 and the following representation holds:*

$$x(t;\mu) = x_0(t) + \delta x(t;\delta\mu) + o(t;\delta\mu),\ t \in (t_0, t_1), \tag{3}$$

where

$$\lim_{|\delta\mu|\to 0} \frac{|o(t;\delta\mu)|}{|\delta\mu|} = 0 \ \text{ uniformly for } \ t \in (t_0, t_1).$$

Moreover, the function

$$\delta x(t) = \begin{cases} \delta\varphi(t),\ t \in I_1, \\ \delta x(t;\delta\mu),\ t \in (t_0, t_1] \end{cases}$$

is a solution of the "equation in variations"

$$\dot{\delta x}(t) = f_x[t]\delta x(t) + f_y[t]\delta x(t-\tau_0) - f_y[t]\dot{x}_0(t-\tau_0)\delta\tau$$
$$+ f_u[t]\delta u(t),\ t \in (t_0, t_1) \tag{4}$$

with the initial condition

$$\delta x(t) = \delta\varphi(t),\ t \in [\hat{\tau}, t_0]. \tag{5}$$

Here

$$f_x[t] = f_x(t, x_0(t), x_0(t-\tau_0), u_0(t)). \tag{6}$$

Remark. The Theorem 1 is proved in [1-2]. The function $\delta x(t;\delta\mu)$ in formula (3) is called the coefficient of sensitivity. Finding the sensitivity coefficient is an important tool for establishing properties of the mathematical models. For example, in an immune model, this coefficient allows one to determine dependence of viruses concentrations on the initial data and controls. Formulas for the sensitivity coefficients are obtained in [3-17] for the various classes of functional differential equations.

2. The coefficients of sensitivity and the equation in variations for a model of the immune response

Let us consider a simple modified Marchuk's controlled model about viruses attack on an organism and its immune response [18-20] as the following system of differential equations

$$\begin{cases} \dot{x}_1(t) = p_1 x_1(t) - p_2 x_1(t) x_3(t), \\ \dot{x}_2(t) = p_3 x_1(t-\tau) x_3(t-\tau) - p_4(x_2(t) - x_2^*) + u_1(t), \\ \dot{x}_3(t) = p_5 x_2(t) - p_6 x_3(t) - p_7 x_1(t) x_3(t) + u_2(t), \\ t \in [0, t^*], \tau \in (0, \tau^*]. \end{cases} \tag{7}$$

with the initial condition

$$x_i(t) = \varphi_i(t), t \in [-\tau^*, 0], i = 1, 2, 3. \tag{8}$$

Here: $x_1(t)$ is the viruses concentration at time t; the first equation

$$\dot{x}_1(t) = p_1 x_1(t) - p_2 x_1(t) x_3(t)$$

of system (7) describes changes of $x_1(t)$, here the first term $p_1 x_1(t)$ supports to reproduction of viruses and the second term $p_2 x_1(t) x_3(t)$ characterizes to struggle between viruses and antibody and do not support to reproduction of viruses;
$x_2(t)$ is the plasma cells concentration, which are producers of antibodies; the plasma cells after a certain time give the immune response characterized by this term

$$p_3 x_1(t-\tau) x_3(t-\tau),$$

where $\tau \in (0, \tau^*]$ is a delay of the immune reaction, i. e. this expression supports reproduction of the antibodies;
$x_3(t)$ is the antibody which kills viruses; x_2^* is the physiological level of plasma cells, in the absence of viruses plasma cells stay;
$p_1, p_2, ...$ are positive constants; $u_1(t) \in [0, v_1]$ is control: enhancer of the plasma cell; $u_2(t) \in [0, v_2]$ is control: enhancer of the antibody.

In the paper, for the sensitivity coefficients of model (7) the system of differential equations is established considering perturbations of the delay parameter, the initial and control functions.

For the consideration model we have: $n = 3, r = 2, t_0 = 0, t_1 = t^*, \tau \in (0, \tau^*]$;

$$O^* \subset \{x = (x_1, x_2, x_3)^T : x_i \in [0, \infty), i = 1, 2, 3\}$$

is an open set;

$$U^* = \{u = (u_1, u_2)^T : u_i \in [0, v_i), i = 1, 2\}$$

is the compact set;

Φ^* is a set of continuously differentiable functions $\varphi : [-\tau^*, 0] \to O^*$; Ω^* is a set of piecewise-continuous functions $u(t) \in U^*, t \in [0, t^*]$;

$$f(t, x, y, u) = (f_1(t, x, y, u), f_2(t, x, y, u), f_3(t, x, y, u))^T, x \in O^*,$$
$$y = (y_1, y_2, y_3)^T \in O^*, u \in U^*,$$

where

$$f_1(t, x, y, u) = p_1 x_1 - p_2 x_1 x_3,$$
$$f_2(t, x, y, u) = p_3 y_1 y_3 - p_4(x_2 - x_2^*) + u_1,$$
$$f_3(t, x, y, u) = p_5 x_2 - p_6 x_3 - p_7 x_1 x_3 + u_2;$$

furthermore,

$$\mu = (\tau, \varphi(t), u(t)) \in \Lambda^* = (0, \tau^*] \times \Phi^* \times \Omega^*,$$

$$\varphi(t)=(\varphi_1(t),\varphi_2(t),\varphi_3(t))^T, u(t)=(u_1(t),u_2(t))^T;$$

$$\begin{gathered}\mu_0=(\tau_0,\varphi_0(t),u_0(t))\in\Lambda^*, x_0(t):=x(t;\mu_0)\\ =(x_{10}(t),x_{20}(t),x_{30}(t))^T, t\in[-\tau^*,t^*];\\ x_0(t)=\varphi_0(t)=(\varphi_{10}(t),\varphi_{20}(t),\varphi_{30}(t))^T, t\in[-\tau^*,0];\\ u_0(t)=(u_{10}(t),u_{20}(t))^T, t\in[0,t^*];\end{gathered}$$

$$\begin{gathered}\delta x(t)=(\delta x_1(t),\delta x_2(t),\delta x_3(t))^T:=\delta x(t;\delta\mu)\\ =(\delta x_1(t;\delta\mu),\delta x_2(t;\delta\mu),\delta x_3(t;\delta\mu))^T, t\in[-\tau^*,t^*];\\ \delta x(t)=\delta\varphi(t)=(\delta\varphi_1(t),\delta\varphi_2(t),\delta\varphi_3(t))^T, t\in[-\tau^*,0];\end{gathered}$$

$$\Lambda^*_\varepsilon(\mu_0)=\Big\{\mu\in\Lambda^*:|\mu-\mu_0|\le\varepsilon\Big\};$$

now let us find the matrices $f_x[t]$, $f_y[t]$ and $f_u[t]$ (see (6))

$$f_x[t]=\begin{pmatrix} f_{1x_1}[t] & f_{1x_2}[t] & f_{1x_3}[t]\\ f_{2x_1}[t] & f_{2x_2}[t] & f_{2x_3}[t]\\ f_{3x_1}[t] & f_{3x_2}[t] & f_{3x_3}[t]\end{pmatrix},$$

where

$$\begin{gathered}f_{1x_1}[t]=p_1-p_2x_{30}(t),\quad f_{1x_2}[t]=0,\quad f_{1x_3}[t]=-p_2x_{10}(t),\\ f_{2x_1}[t]=0,\quad f_{2x_2}[t]=-p_4,\quad f_{2x_3}[t]=0,\\ f_{3x_1}[t]=-p_7x_{30}(t),\quad f_{3x_2}[t]=p_5,\quad f_{3x_3}[t]=-p_6-p_7x_{10}(t);\end{gathered}$$

$$f_y[t]=\begin{pmatrix} f_{1y_1}[t] & f_{1y_2}[t] & f_{1y_3}[t]\\ f_{2y_1}[t] & f_{2y_2}[t] & f_{2y_3}[t]\\ f_{3y_1}[t] & f_{3y_2}[t] & f_{3y_3}[t]\end{pmatrix},$$

here

$$\begin{gathered}f_{1y_1}[t]=0,\quad f_{1y_2}[t]=0,\quad f_{1y_3}[t]=0,\\ f_{2y_1}[t]=p_3x_{30}(t-\tau_0),\quad f_{2y_2}[t]=0,\quad f_{2y_3}[t]=p_3x_{10}(t-\tau_0),\\ f_{3y_1}[t]=0,\quad f_{3y_2}[t]=0,\quad f_{3y_3}[t]=0;\end{gathered}$$

$$f_u[t]=\begin{pmatrix} f_{1u_1}[t] & f_{1u_2}[t]\\ f_{2u_1}[t] & f_{2u_2}[t]\\ f_{3u_1}[t] & f_{3u_2}[t],\end{pmatrix},$$

where

$$f_{1u_1}[t] = 0,\ f_{1u_2}[t] = 0,$$

$$f_{2u_1}[t] = 1\ f_{2u_2}[0] = 0,$$

$$f_{3u_1}[0] = 0\ f_{3u_2}[t] = 1.$$

After elementary calculations we get (see (5))

$$f_x[t]\delta x(t) = \begin{pmatrix} (p_1 - p_2 x_{30}(t))\delta x_1(t) - p_2 x_{10}(t)\delta x_3(t) \\ -p_4\delta x_2(t) \\ -p_7 x_{30}(t)\delta x_1(t) + p_5\delta x_2(t) - (p_6 + p_7 x_{10}(t))\delta x_3(t) \end{pmatrix},$$

$$f_y[t]\delta x(t-\tau_0) = \begin{pmatrix} 0 \\ p_3 x_{30}(t-\tau_0)\delta x_1(t-\tau_0) + p_3 x_{10}(t-\tau_0)\delta x_3(t-\tau_0) \\ 0 \end{pmatrix},$$

$$f_y[t]\dot{x}_0(t-\tau_0) = \begin{pmatrix} 0 \\ p_3 x_{30}(t-\tau_0)\dot{x}_{10}(t-\tau_0) + p_3 x_{10}(t-\tau_0)\dot{x}_{30}(t-\tau_0) \\ 0 \end{pmatrix},$$

$$f_u[t]\delta u(t) = \begin{pmatrix} 0 \\ \delta u_1(t) \\ \delta u_2(t) \end{pmatrix},$$

Using the above given expressions from Theorem 1 it follows

Theorem 2. *Let $x_{i0}(t), i = 1, 2, 3$ be the solution of the equation*

$$\begin{cases} \dot{x}_1(t) = p_1 x_1(t) - p_2 x_1(t) x_3(t), \\ \dot{x}_2(t) = p_3 x_1(t-\tau_0) x_3(t-\tau_0) - p_4(x_2(t) - x_2^*) + u_{10}(t), \\ \dot{x}_3(t) = p_5 x_2(t) - p_6 x_3(t) - p_7 x_1(t) x_3(t) + u_{20}(t), \\ t \in [0, t^*], \tau_0 \in (0, \tau^*]. \end{cases}$$

with the initial condition

$$x_{i0}(t)=\varphi_{i0}(t), t\in[-\tau^*,0],$$

i. e. the solution corresponding to the element $\mu_0=(\tau_0,\varphi_0(t),u_0(t))\in\Lambda^*$ *and defined on the interval* $[-\tau^*,t^*]$. *Then, there exists* $\varepsilon_1>0$ *such that to each perturbation* $\mu\in\Lambda^*_{\varepsilon_1}(\mu_0)$ *of the element* μ_0, *there corresponds the solution* $x_i(t;\mu), i=1,2,3$ *of problem (7)-(8) defined on the interval* $[-\tau^*,t^*]$ *and the following representation holds:*

$$x_i(t;\mu)=x_{i0}(t)+\delta x_i(t;\delta\mu)+o_i(t;\delta\mu),\ t\in(0,t^*), i=1,2,3$$

(see (4)), where

$$\lim_{|\delta\mu|\to 0}\frac{|o_i(t;\delta\mu)|}{|\delta\mu|}=0, i=1,2,3 \text{ uniformly for } t\in(0,t^*).$$

Moreover, the coefficients of sensitivity $\delta x_i(t), i=1,2,3, t\in[0,t^*]$ *satisfies the "equation in variations"*

$$\begin{cases} \dot{\delta} x_1(t)=(p_1-p_2x_{30}(t))\delta x_1(t)-p_2x_{10}(t)\delta x_3(t),\\ \\ \dot{\delta} x_2(t)=-p_4\delta x_2(t)+p_3x_{30}(t-\tau_0)\delta x_1(t-\tau_0)+p_3x_{10}(t-\tau_0)\delta x_3(t-\tau_0)\\ -[p_3x_{30}(t-\tau_0)\dot{x}_{10}(t-\tau_0)+p_3x_{10}(t-\tau_0)\dot{x}_{30}(t-\tau_0)]\delta\tau+\delta u_1(t)),\\ \\ \dot{\delta} x_3(t)=-p_7x_{30}(t)\delta x_1(t)+p_5\delta x_2(t)-(p_6+p_7x_{10}(t))\delta x_3(t)+\delta u_2(t). \end{cases}$$

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