Application of stochastic control method on manifold at immunology problem

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Abstract. The purpose of the paper is to study the principal appropriateness of the synergetic control theory to the simplest immunological object with the initial description in the form of a system of nonlinear differential equations. Physically, the control here refers to a regime to administer anti-disease substances. Based on the analytical synthesis, two control systems for an object were obtained: 1) for a continuous deterministic case; 2) for a discretized model with additive random noise in a controlled variable. The results of numerical modeling of the developed control systems that can be used in the respective decision support systems are presented.

1. Introduction
An application of technological advances to a non-technical problem is varied and has many studies conducted by prominent scientists [1].

The purpose of this research is to analyse the possibilities of the synergetic control theory (SCT) [2] to the simplest immunological object (according to G.I. Marchuk [3]).

Firstly, we note the basic features of SCT and its key method of synthesis for control systems that initiate this study:

- the control system synthesis method is analytical with all the ensuing conditions for its application;
- an initial description of the object is given in the form of a system of nonlinear ordinary differential (or difference) equations;
- the control target is given in the form of a limit equation (for example, \( \psi(t) = \psi(x(t)) = 0 \) when \( t \to \infty \), where \( \psi(t) \) is a well-known function, expertly defined and called a macro variable (in contrast to the initial vector state variable);
- the quality functional \( \Phi(\psi) \) contains a description of the physical features of the target system through the principal application of minimal action: the initial system under the action of the control found will be self-organized and, in this regard, will change its state most energy-efficiently when the control target \( \psi(t) \to 0 \) is achieved;
- the form of the quality functional is considered when the solution of the variation problem \( \{ \Phi, \psi \} \) is achieved by solving the Euler-Lagrange equation, which has a special linear form, and it leads to a rather simple technical plan to determine the control;
weight coefficients that arise in the process of control synthesis are controller settings and have a convenient physical interpretation as the duration of the transition process.

2. Control problem statement in deterministic description

Let the nonlinear object with delay $\tau$ be given [3]:

$$\dot{V} = a_1 V - a_2 F V,$$

$$\dot{S} = a_3 \zeta(m) F(t-\tau)V(t-\tau) - a_4 (S-1),$$

$$F = a_s (S-F) - a_5 F V + u,$$

$$m = a_6 V - a_7 m.$$ 

Here, the variables $V, S, F$ are concentrations of antigens in the affected organ, plasma cells, antibodies in blood, respectively; $m(t) = 1 - M(t)/M^*$ is the proportion of organ cells destroyed by the antigen, $M(t), M^*$ are the current number of cells in the organ (as target) at the time $t$ and the number in a normal condition, respectively; $a_i, i = 1, 8$ are model parameters, the value of which depends on the form and stage of the disease; the function $\zeta(m)$ characterizes the degree of disruption for normal functioning of the immune system due to organ damage $\zeta(m) = 1$ if $0 \leq m < m^*$, and $\zeta(m) = (m-1)/(m^*-1)$ if $m^* \leq m < 1$, where $m^*$ is the maximum allowable part of the cells destroyed by antigens when normal functioning of the immune system is possible.

The 1st equation of this system is a model to change the number of antigens in the organism; the 2nd equation characterizes the dynamics of the number of plasma cells; the 3rd equation describes the increase in the number of antibodies; the 4th equation characterizes the degree of organ damage.

Let us proceed to the discrete description without the delay due to the introduction of two additional phase variables $Y_1[k+1] = F[k], Y_2[k+1] = V[k]$:

$$V[k+1] = V[k] + \tau_0 \left( a_1 V[k] - a_2 F[k] V[k] \right),$$

$$S[k+1] = S[k] + \tau_0 \left( a_3 \zeta(m[k]) Y_1[k] Y_2[k] - a_4 (S[k] - 1) \right),$$

$$F[k+1] = F[k] + \tau_0 \left( a_s (S[k] - F[k]) - a_5 F[k] V[k] + u[k] \right),$$

$$m[k+1] = m[k] + \tau_0 \left( a_6 V[k] - a_7 m[k] \right),$$

$$Y_1[k+1] = F[k], Y_2[k+1] = V[k],$$ 

where $\tau_0 > 0$ is a discrete transform parameter (according to Euler).

Note. According to A.N. Kolmogorov [4] it is reasonable to conduct a study of the real phenomena and avoid the intermediate stage of their stylization through the ideas of mathematics infinite and continuous, going directly to discrete models.

The control target is to provide asymptotic stabilization of the function $V[k]$ in the vicinity of the given value (the number of antigens) $V^*$ (for example, $V^* = 0$)

$$\psi[k] = V[k] - V^* \to 0, k \to \infty,$$ 

in the sense of the minimum of the following quality control criteria

$$\Phi(\psi) = \sum_{t=0}^{\infty} \left( \alpha^2 \psi^2[t] + (\Delta \psi[t])^2 \right), \alpha = \text{const.}$$
3. Problem solution of deterministic control

Omitting technical details, we use the discrete analogue for the classical method of analytical design of aggregated regulators (ADAR) that lead to the control:

\[ u[k] = \tau_0^{-1} (\varphi[k + 1] + \omega \varphi[k] - (\omega_i + 1) F[k]) - a_i \left(S[k] - F[k]\right) + a_i F[k] V[k], \]

\[ \varphi[k] = \left(\tau_0 a_k V[k]\right)^{-1} (\omega V(k) + V[k]) + a_i a_k^{-1}, \quad 0 < \omega_i < 1, \ i = 1,2. \]  

(3)

3.1. Results of numerical simulation of the control system

The control system (1)-(3) was modeled for the following cases (figures 1–4).

3.1.1. Example 1. Object parameters (1) that correspond to the fatal disease outcome.

\[ a_1 = 1.54, a_2 = 0.77, a_3 = 880, a_4 = 0.15, a_5 = 0.5, a_6 = 12, a_7 = 0.12, a_8 = 8, \]

\[ \omega_1 = 0.05, \omega_2 = 0.1, V(0) = 10^{-6}, S(0) = 1, F(0) = 1, m(0) = 0.1, t_0 = 1, V' = 0. \]

3.1.2. Example 2. Object parameters (1) that correspond to the chronic form of disease.

\[ a_1 = 1, a_2 = 0.8, a_3 = 1000, a_4 = 0.17, a_5 = 0.5, a_6 = 10, a_7 = 0.12, a_8 = 8, \]

\[ \omega_1 = 0.05, \omega_2 = 0.1, V(0) = 10^{-6}, S(0) = 1, F(0) = 1, m(0) = 0.1, t_0 = 1, V' = 0. \]

a) Figure 1. Trajectories of variable \( V[k] \) \( a) \) – without control; \( b) \) – with control for example 1; sampling interval \( \Delta \) has a value of 1.

b) Figure 2. Trajectories of variable \( V[k] \) \( a) \) – without control; \( b) \) – with control for example 2; sampling interval \( \Delta \) has a value of 1.
3.1.3. Example 3. Object parameters (1) that correspond to the acute form of disease.

\[ a_1 = 2, a_2 = 0.8, a_3 = 10000, a_4 = 0.17, a_5 = 0.5, a_6 = 10, a_7 = 0.12, a_8 = 8, \]
\[ \omega_1 = 0.05, \omega_2 = 0.1, V(0) = 10^{-6}, S(0) = 1, F(0) = 1, m(0) = 0.1, t_0 = 1, V' = 0. \]

![Figure 3](image1.png)

**Figure 3.** Trajectories of variable \( V[k] \) a) – without control; b) – with control for example 3; sampling interval \( \Delta \) has a value of 0.1.

3.1.4. Example 4. Object parameters (1) that correspond to the subclinical form of disease.

\[ a_1 = 8, a_2 = 10, a_3 = 10000, a_4 = 0.17, a_5 = 0.5, a_6 = 10, a_7 = 0.12, a_8 = 8, \]
\[ \omega_1 = 0.05, \omega_2 = 0.1, V(0) = 10^{-6}, S(0) = 1, F(0) = 1, m(0) = 0.1, t_0 = 1, V' = 0. \]

![Figure 4](image2.png)

**Figure 4.** Trajectories of variable \( V[k] \) a) – without control; b) – with control for example 4; sampling interval \( \Delta \) has a value of 0.1.

4. Problem statement of stochastic discrete control

We add random functions \( \xi[k] + \xi[k], k \geq 0 \), \( E[\xi[k]] = 0 \), \( D[\xi[k]] = \sigma^2 \) to the right side of the equation, which is responsible for the dynamics of the controlled variable:
\[ V[k+1] = V[k] + \tau_0 (a_1 V[k] - a_F[k] V[k]), \]
\[ S[k+1] = S[k] + \tau_0 (a_3 (m[k]) Y_1[k] Y_2[k] - a_S (S[k] - 1)), \]
\[ F[k+1] = F[k] + \tau_0 (a_4 (S[k] - F[k]) - a_F[k] V[k] + u[k]) + \xi[k+1] + c \xi[k], \quad (4) \]
\[ m[k+1] = m[k] + \tau_0 (a_6 V[k] - a_m[m[k]]), \]
\[ Y_1[k+1] = F[k], Y_2[k+1] = V[k], k \geq 0. \]

The problem is to stabilize the variable \( V[k] \) in the vicinity of a given value \( V^* \)
\[ E\{\psi(V[k])\} = E\{V[k] - V^*\} \rightarrow 0, \quad k \rightarrow \infty, \]
where \( E\{\zeta\} \) is the sign of mathematical expectation for the random variable \( \zeta \). The control quality requirements are as follows:
\[ D\{\psi[k + 1] + T \psi[k]\} \rightarrow \min, \quad k \rightarrow \infty; \]
\[ E\{\Phi\} = E\left\{ \sum_{i=0}^{\infty} \left( \alpha^2 \left( \psi[i]\right)^2 + (\Delta \psi[i])^2 \right) \right\} \rightarrow \min. \]

5. **Problem solution of stochastic control**

There are main algorithmic steps that lead to stochastic control of the object (4) to achieve the target (5) (for example, see [5]).

**Step 1.** We apply the ADAR method as for an object with a deterministic description:
\[ \bar{u}[k] = \tau_0 \left( -\omega_0 \psi^{(i)}[k] - F[k] + \varphi[k+1]\right) - a_S (S[k] - F[k]) + a_F[k] V[k] - \tau_0 \xi[k+1] - c \tau_0 \xi[k]. \]

**Step 2.** We use the conditional expectation operation:
\[ u[k] = E\{\bar{u}[k] | \xi[k]\} = \tau_0 \left( -\omega_0 \psi^{(i)}[k] - F[k] + \varphi[k+1]\right) - a_S (S[k] - F[k]) + \]
\[ + a_F[k] V[k] - c \tau_0 \xi[k]. \]

**Step 3.** We consider the last expression and the initial description, and obtain the dependence for
\[ \psi^{(i)}[k] + \omega_0 \psi^{(i)}[k-1] = \xi[k] \]
\[ u^{ui}[k] = -\tau_0 \psi^{(i)}[k] (\omega_0 + c) - c \tau_0 \omega_0 \psi^{(i)}[k-1] - a_S (S[k] - F[k]) + a_F[k] V[k]. \]

The simulation (figures 5-7) was performed with the following parameter values:
\[ a_1 = 1.54, \quad a_2 = 0.77, \quad a_3 = 880, \quad a_4 = 0.15, \quad a_5 = 0.5, \quad a_6 = 12, \quad a_7 = 0.12, \quad a_8 = 8, \quad \Delta = 0.1, \quad \tau_0 = 1; \]
\[ T_1 = 0.05, \quad T_2 = 0.1, \quad V[0] = 10^{-6}, \quad F[0] = S[0] = 1, \quad m[0] = 0, \quad m_0 = 0.1, \quad c = 0.1; \quad u_{max} = 5. \]

The given control requirements were considered \( U_{\min} \leq u(t) \leq U_{\max} \) by the rule:
\[ u[k] = \begin{cases} 0, & \text{if } u^{ui}[k] < 0, \\ u^{ui}[k], & \text{if } 0 \leq u^{ui}[k] \leq u_{\max}, \\ u_{\max}, & \text{if } u^{ui} > u_{\max}. \end{cases} \]

is the maximum injection rate of ready-made immunoglobulins or donor antibodies, depending on the \( u_{\max} \) physiologically acceptable drug doses.
Figure 5. Transient processes for phase coordinates $V[k]$ of the control system (solid line) and behavior of the uncontrolled variable (dashed line); noise has a normal distribution with parameters $a) - (0; 0.1)$, $b) - (0; 0.5)$, respectively.

Figure 6. Transient processes $a)$ - for control variable $u[k]$ and $b) - behavior of the macrovariable; noise has a normal distribution with parameters $(0; 0.1)$.

Figure 7. Transient processes $a)$ - for control variable $u[k]$ and $b) - behavior of the macrovariable $\psi[k]$; noise has a normal distribution with parameters $(0; 0.5)$. 
Comment. Such parameters as a sampling rate \( (\Delta) \) and a duration of reaching the vicinity of the target state \( (T_1, T_2) \) are very interconnected and require careful selection for the given individual characteristics of the model (4).

The values of the above parameters correspond to the form of the acute disease with a possible fatal outcome. Figure 5 shows that immunotherapy can reduce the number of antigens. The graphs illustrate clinical and laboratory data with the dynamics of viral hepatitis B (G.I. Marchuk, [6]).

6. Conclusion
The paper considers the example of principal application of the synergetic control theory for a biomedical problem.

The form of the used quality criteria for synthesized control is fully consistent with the physical control theory [7] and the principle of the minimal action, which can provide the most careful intervention in the behavior of a living organism.

As you know, the creation and implementation of decision support systems is a critical technology, the development of which directly affects the social well-being of the population. The results of the research can be the mathematical basis of the decision support system in the corresponding subject area.

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