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Application of a Stochastic Extension of the Analytical Design of Aggregated Regulators to a Multidimensional Biomedical Object

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Abstract: The results of the application of the methods of the synergetic control theory to a high-dimensional immunology object with uncertainty in its descriptions are reported. The control here is the therapy treated as a problem for constructing an optimal cure program. The control object is presented in continuous and discrete forms, i.e., mathematical models given by a system of ordinary differential equations with a bounded disturbance and a system of stochastic difference equations, respectively. Two algorithms for deriving robust regulators applicable to a 10-dimensional nonlinear multi-loop system with unstable limit states, which models an immune response to the hepatitis B infection, are obtained. Analytical control design for a continuous model relies on the method of nonlinear adaptation on the target manifold. The second algorithm represents a stochastic extension of the method of analytical design of aggregated discrete regulators minimizing the variance of the target macro variable. The numerical simulation of the developed control systems indicates the performance of the designed control algorithms. The results of this study can be used as a component part of the mathematical tools of expert systems and decision support systems.

Keywords: object of immunology; discrete stochastic system; system invariant; macro variable; variational problem; biomedical systems



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1. Introduction

The importance of new control problem statements for bioengineering plants, which are characterized by poor formalizability, incompleteness of the information on biological processes, and instability of the limit states is supported by the object capacity to resist control) and the absence of a general approach to analyzing the free states of the nonlinear systems. Furthermore, it is extremely important to search for new properties of such objects, which might result from a control based on their physical features [1–14].

Among the main reasons for designing an algorithm of a purposeful intervention in the work of a biomedical system (here, immunology) are the following [15–19]:

- The necessity of understanding the infection dynamics and verifying hypotheses that are hard (or impossible) to reproduce under laboratory conditions;
- The chaotic nature of the object under certain initial and parametric conditions [20–23]; for instance, the presence of predator–prey conditions, describing the main processes of infectious diseases, or adhering unstable properties to a controlled object;
- The consideration of the therapy as an optimal control problem has provided a number of successful theoretical and practical solutions [10,24–36];
- The modeling of the medical objects (here, an immune response to the hepatitis B virus) relies on n -dimensional ordinary differential equations (ODEs) or difference equations [15–18].

The main trends in the research into biomedical systems are at the moment presented, on the one hand, by methods that allow studying the dynamic stability (equilibrium) properties [20,24,25,31–33], the invariance, and the availability of periodic regimes applicable to such systems.

On the other hand, there is an evolving trend associated with the formation of a purposeful external impact on an unstable biochemical process aimed at adding the required properties to the system [26–35]. The diversity of the methods used in the solution of this problem is dictated by the following:

- The difference in the mathematical description (of the system of ODEs or difference equations) [17] and fractional reaction-diffusion modes [25];
- The level and types of the model uncertainties (deterministic [16,17] and stochastic [32]);
- The quality criteria of a target system and the restrictions on the object and control parameters, etc.

Thus, for plants considered in the class of ODE/difference systems, use is made of the method of differential games and the Pontryagin maximum principle [26–28], machine learning algorithms [34], the method of guaranteeing controllers [29], etc.

The diversity of the control methods, firstly, primarily indicates the absence of a single tool for researching such systems and, secondly, the presence of incompletely solved problems for the objects with uncertainties in the initial descriptions. This implies that the problem of stabilizing the state in a certain neighborhood of the target state with a minimal dispersion of the output parameters (macro variables as certain functions of the initial variables) is, in broad terms, open.

In this paper, we study the problem of correct intervention in an infectious model using hepatitis B as an example.

The mathematical model of the antiviral immune response, proposed by G.I. Marchuk and R.V. Petrov [16,17], is considered a system of ordinary differential equations with delayed arguments. An analysis of the condition of asymptotic stability as a whole of this model was carried out in [24].

Here, we pose the discrete and continuous problems of designing a system of control over an object of immunology with limited unknown disturbances in the control channel.

The control in this study, as earlier [26,27,30], will be understood as a program of drug delivery to a diseased organ, and the goal of control will be a stabilization of the target variable (antigen concentration) in a certain small-value neighborhood.

To solve the control problem, two new algorithms for the analytical design of regulators will be used, developed on the basis of the synergetic control theory (SCT) [8,9] for the case of an incomplete initial description of control plants.

The first of them is implemented via the integral adaptation method [12] and allows the design of robust control systems without obtaining any current information on variations of the object parameters and the external environment. This approach may be applied to solve urgent bioengineering and biomedicine problems. The second algorithm is a generalization relative to stochastic nonlinear high-dimensional objects with a goal to compensate for the additive random disturbances affecting the coordinates and/or the parameters [37].

The proposed algorithms to design continuous and discrete controllers have the following advantages:

- The control synthesis technique ensures the robust properties of the regulators;
- Provision of a minimal variance of the response variable;
- Clear priority of our method over the deterministic method of analytical design of aggregated regulators in the case of unmodelled stochastic dynamics, which is inevitably presented in unstable control plants;
- The quality functional of the synthesized control system meets the required properties of the target states, which meets the physical control theory [38].

1.1. State of the Art and Motivation Using SCT

Let us list the following arguments in favor of using methods based on SCT.

1. According to SCT, it is necessary that the control object be specified by a system of ordinary nonlinear differential (difference) equations with a bounded right-hand side.

In order to construct an immune system model of an organism, a class of nonlinear systems of ODEs with a delayed argument and a discontinuous right-hand part of the description is used. It is technically consistent with the concept of a “complex dynamic system” [39], with all the ensuing problems, since the results of research into stability analysis and designing control over nonlinear compound plants are far from being described as fruitful and systematic (e.g., see a review in [5]).

2. Designing a robust control for undefined nonlinear plants relies on the use of their robust linear approximations, which is not always correct due to the deterministic chaos typical for infectious disease models.

Specifically, it is known that a nonlinear model yields more accurate results in terms of different parameters of the regulator and control modeling errors [40–43] compared to linearized models.

3. An analysis of the current publications (e.g., see reviews in [14,26–35]) suggests that optimal strategies are the principal instruments for containment of the epidemics of hepatitis C and the infection caused by the hepatitis B virus.

The implementation of an optimal control over such an object is, however, very difficult, since it is associated with a necessity to search for solutions to the Riccati equations [29] with the state-dependent parameters. The numerical methods for solving such an equation require intensive computing procedures or point-wise solutions to nonlinear algebraic equations, which is not always acceptable for practical implementation in systems with chaotic dynamics [9,29].

4. There are algorithms for the analytical design of regulators based on adaptive control SCT and manifold invariance methods [12,37,44], which would meet the specified requirements in the cases of uncertainty in the parameters.

5. In [23,45,46], a survey of the current situation in immunology resulted in the following conclusion: a step towards an integration of systematic biology passes through “the epistemology of complexity”, which relies on cybernetics and the interdisciplinary synergetic approach or self-organization theory and other works). Synergetic control theory achieves these conclusions.

1.2. Main Principles of SCT as the Basis for the Analytical Design of Nonlinear Control Algorithms for a Complex Object under Conditions of Random and Systematic Disturbances

The mathematical method for designing controls is based on selecting the laws of external control ensuring the desired target properties of the system [8,9].

- The model of an object is defined by a system of nonlinear ordinary differential (or difference) equations.
- The target macro variable, $\psi(t) = \psi(X(t))$, is defined as a function of the state, and the goal of control is prescribed as a limit, $\psi(t) \xrightarrow{t \rightarrow \infty} 0$.
- The dimension of the macro variable coincides with that of the control, and the set of partial criteria represents the local requirements of the control system quality.
- The quality functional, $\Phi(\psi)$, represents the physical features of the target system via the least action principle: the initial system under the action of the found control would be in a self-organized manner and, due to this, most effectively change its state upon reaching the goal of control, $\psi(t) \xrightarrow{t \rightarrow \infty} 0$.
- The variational problem, $\{\Phi, \psi\}$, whose statement expresses the goal of control, is solved on a subset of solutions to the Euler–Lagrange equation for a *linear* form; the controls (external and internal) are sought on the extremals.
- The weight coefficients, emerging during the designing controls, have a convenient physical interpretation of a transient process duration.

- The controlling actions, determined from solutions to partial variational problems, transfer the object into the prescribed manifold of states and maintain it in this manifold, thus ensuring asymptotic stability to the control system as a whole.

The immune response is a phenomenon underlying immunity; it consists of the reaction of the immune system of an organism to the penetration of an antigen (an organism recognized as a foreign body). In order to define the control problem (Figure 1), let us take an extension of the base mathematical model of an antiviral immune response [17], where good agreement has been achieved between the laboratory data and the model solutions in terms of their application to the mechanisms of chronification during viral hepatitis B. This model allows the analysis of the antiviral cellular immune response, the antiviral humoral immune response, and the antiviral immune response in conditions of immunodeficiency.

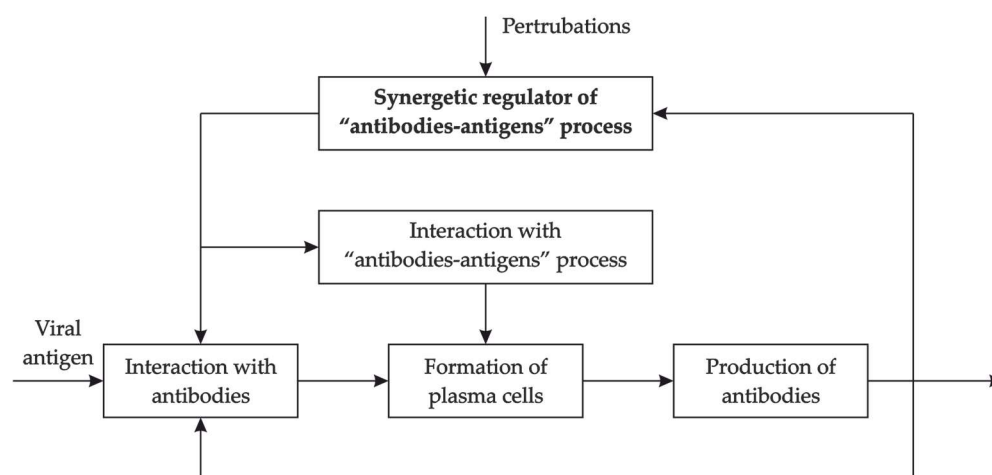


Figure 1. Rough scheme of influencing the immune response mechanism including a classical Burnet scheme [47].

In this study, we discuss the following:

- Section 2 gives the object's description and the formalized problem statements for the class of mathematical delays in the infectious disease models as the control problems under conditions of random and systematic disturbances.
- Section 3 provides a discrete algorithm of the analytical regulator design for a model whose difference equations system contains random disturbances in the control channel [13,37].
- Section 4 presents a continuous algorithm of analytical regulator design relying on the principles of nonlinear adaptation on a target manifold, whose equations system contains systematic disturbances.
- Section 5 gives the results of a numerical simulation of the control systems discussed here under conditions of systematic and random disturbances.
- Section 6 provides an analysis of the results of the numerical simulation of a control system for a high-dimensional immunology object under conditions of systematic and random disturbances.

2. Formulation of the Problem of a Discrete Stochastic Control on a Target Manifold and the Necessity of a Separate Consideration of the Discrete and Continuous Models

2.1. Initial Model of Object

There are the phase variables of the mathematical model of an antiviral immune response [16,17], which characterize the variation dynamics of the free virus, V_f , the antibodies to the viral antigens, F , the fraction of infected cells of the target organ, C_V , the fraction of the killed target, m , the number of specific killer cells, E , the number of helper cells for T-cells, H_E , the number of helper cells for B-cells of the given specificity, H_B , the

number of B-cells of the given specificity, B , the number of plasmatic cells synthesizing antibodies, P , and the number of stimulated macrophages, M_V .

In terms of immune therapy, the control in the infectious disease model is based on several processes, whose details will be omitted in what follows. Here we are going to consider the bioengineering component only—the possibility, in principle, to design an analytically validated impact (using the phase variable, F), which would provide stabilization of the model in the neighborhood of the given value of variable V .

Note that the choice of the Marchuk–Petrov model is not accidental, since the model under consideration was successfully calibrated according to acute forms of influenza A and hepatitis B [17].

The object's mathematical model is a 10th-order system of equations given by the following (here, the delay parameters are marked with a vertical bar):

$$\begin{aligned}
 \dot{V}_f &= (a_1 + a_2 E)C_V - a_3 V_f F - a_4 V_f - a_5(1 - C_V - m)V_f, \\
 \dot{C}_V &= a_{35} V_f(1 - C_V - m) - a_{36} C_V E - a_{37} C_V, \\
 \dot{m} &= a_{36} C_V E + a_{37} C_V - a_{38} m, \\
 \dot{M}_V &= a_6 V_f - a_7 M_V - a_8 M_V E, \\
 \dot{H}_E &= a_9 \xi(m) H_E \Big|_{t-a_{10}} M_V \Big|_{t-a_{10}} - a_{11} H_E M_V - a_{12} M_V E H_E + a_{13}(1 - H_E), \\
 \dot{E} &= a_{19} \xi(m) M_V \Big|_{t-a_{20}} H_E \Big|_{t-a_{20}} E \Big|_{t-a_{20}} - a_{21} M_V H_E E - a_{22} C_V E - a_{23} M_V E + a_{24}(1 - E), \\
 \dot{H}_B &= a_{14} \xi(m) H_B \Big|_{t-a_{15}} M_V \Big|_{t-a_{15}} - a_{16} H_B M_V - a_{17} M_V H_B B + a_{18}(1 - H_B), \\
 \dot{B} &= a_{25} \xi(m) M_V \Big|_{t-a_{26}} H_B \Big|_{t-a_{26}} B \Big|_{t-a_{26}} - a_{27} M_V H_B B + a_{28}(1 - B), \\
 \dot{P} &= a_{29} \xi(m) M_V \Big|_{t-a_{30}} H_B \Big|_{t-a_{30}} B \Big|_{t-a_{30}} + a_{31}(1 - P), \\
 \dot{F} &= a_{32} P - a_{33} F V_f - a_{34} F, \quad t \geq t_0,
 \end{aligned} \tag{1}$$

with the initial data for the dimensionless (rescaled) type [17]:

$$\begin{aligned}
 V_f(t_0) &= V_f^0, \quad C_V(t_0) = m(t_0) = M_V(t_0) = 0, \\
 H_E(t_0) &= E(t_0) = H_B(t_0) = B(t_0) = P(t_0) = F(t_0) = 1, \\
 H_E(t) M_V(t) &= 0 \quad \forall t \in [-a_{10}, t_0), \quad M_V(t) H_E(t) E(t) = 0 \quad \forall t \in [-a_{20}, t_0), \\
 M_V(t) H_E(t) E(t) &= 0 \quad \forall t \in [-a_{20}, t_0), \quad H_B(t) M_V(t) = 0 \quad \forall t \in [-a_{15}, t_0), \\
 M_V(t) H_B(t) B(t) &= 0 \quad \forall t \in [-s, t_0), \quad s = \max(a_{26}, a_{30}).
 \end{aligned}$$

Otherwise, introducing the notations

$$\begin{aligned}
 \mathbf{X} \in \mathbb{R}^n, \quad n = 10; \quad \mathbf{X} &= (X_1, \dots, X_{10})^T = (V_f, C_V, m, M_V, H_E, E, H_B, B, P, F)^T, \\
 \mathbf{A}_\tau &= \mathbf{A}_\tau(\mathbf{X}) = (A_{1\tau}, \dots, A_{10\tau})^T, \quad \dot{X}_i = A_{i\tau}(\mathbf{X}), \quad \tau = \{a_{10}, a_{15}, a_{16}, a_{20}, a_{26}, a_{30}\}, \quad u \in \mathbb{R},
 \end{aligned} \tag{2}$$

we can define the control problem similar to the problem statements for the base 4-dimensional model [17,26,27],

$$\dot{\mathbf{X}} = \mathbf{A}_\tau(\mathbf{X}) + \zeta(t) + \mathbf{U}(t), \quad \mathbf{U} = (0, \dots, 0, u)^T, \quad \zeta = (0, \dots, 0, \zeta)^T, \tag{3}$$

$$\psi^*(X_1) = X_1 - X_1^* = V_f - V^* \rightarrow 0, \quad X_1^* = V^* \approx 0 \tag{4}$$

as a problem of an intentional change in the concentration of antibodies, F , by an administration of medicinal preparations (donor antibodies, immunoglobulins, etc.).

In (1) and (2), the equations numbered 1–3 characterize the processes in the target organ, the equations numbered 4–6 are responsible for the dynamics of the T-cell immune response, and the other equations model the humoral immune response (via antibodies) [16,17,24], which could be influenced by the changing variable, $F(t)$ (antibodies to the viral antigens).

When no confusion is generated, we do not use arguments in function formulations. Expression (4) characterizes the goal of control; $X_1^* = V^* = \text{const}$ is the given value.

The subscript, $(\cdot)_{\tau}$, denotes here and below delays in variables X_4, X_5, X_6, X_7, X_8 , in accordance with the equations system (1); R^n is the n -dimensional Euclidean space.

Disturbances are the key components in the control problem, as, according to [48], without disturbances and process uncertainties, there is no need for feedback. Here, $\zeta(t)$ is the unknown bounded continuous (“worst”) disturbance.

In (2), according to (1) and the introduced notations, function A_i will acquire a form more convenient for the algorithmization of the control derivation:

$$\begin{aligned}
 A_{1\tau} &= (a_1 + a_2 X_6) X_2 - a_3 X_1 X_{10} - a_4 X_1 - a_5 (1 - X_2 - X_3) X_1, \\
 A_{2\tau} &= \dot{C}_V = a_{35} X_1 (1 - X_2 - X_3) - a_{36} X_2 X_6 - a_{37} X_2, F_3 = a_{36} X_2 X_6 + a_{37} X_2 - a_{38} X_3, \\
 A_{4\tau} &= a_6 X_1 - a_7 X_4 - a_8 X_4 X_6, \\
 A_{5\tau} &= a_9 \zeta(X_3) X_5|_{t-a_{10}} X_4|_{t-a_{10}} - a_{11} X_4 X_5 \\
 &\quad - a_{12} X_4 X_5 X_6 + a_{13} (1 - X_5), \\
 A_{6\tau} &= a_{19} \zeta(X_3) X_4|_{t-a_{10}} X_5|_{t-a_{10}} X_6|_{t-a_{10}} \\
 &\quad - X_6 (a_{21} X_4 X_5 + a_{22} X_2 + a_{23} X_4) + a_{24} (1 - X_6), \\
 A_{7\tau} &= a_{14} \zeta(X_3) X_4|_{t-a_{15}} X_7|_{t-a_{15}} - X_7 (a_{16} X_4 + a_{17} X_4 X_8) + a_{18} (1 - X_7), \\
 A_{8\tau} &= a_{25} \zeta(X_3) X_5|_{t-a_{26}} X_7|_{t-a_{26}} X_8|_{t-a_{26}} - a_{27} X_4 X_7 X_8 + a_{28} (1 - X_8), \\
 A_{9\tau} &= a_{29} \zeta(X_3) X_4|_{t-a_{30}} X_7|_{t-a_{30}} X_8|_{t-a_{30}} + a_{31} (1 - X_9), \\
 A_{10\tau} &= a_{32} X_9 - a_{33} X_1 X_{10} - a_{34} X_{10},
 \end{aligned} \tag{5}$$

$u \in R$ is the sought-for law regulating the supply of medicinal preparations delivered to the diseased organ with a goal of a reasonable impact on the immune response dynamics, $\zeta(t)$ is the uncontrollable bounded disturbance, $a_j, j = \overline{1, 38}$, are the model parameters whose values determine the disease stages (subclinical, acute, chronic, and lethal) and the delay values for a more detailed study of the immune response dynamics.

2.2. On the Nature of Disturbances and Their Modeling in Controlled Bioengineering Plants

In the study of the infectious disease models [15–23], a most reasonable assumption is that of an interval parametric uncertainty, uncertainty with respect to control, etc. (a priori and current, random and/or systematic).

From this standpoint, it becomes possible to construct an SCT-based regulator that would, given minimum information on the structure of the parametric and external impacts, ensure stability and acceptable quality of the transient processes in the synthesized nonlinear system. The so-called guaranteeing regulators [12] provide desirable properties for the synthesized systems under the worst disturbing impacts.

In order to model disturbances by the below-used integral adaptation method [12], firstly, we use the fact that continuous functions can be described as (partial) solutions of ODEs [49], and the real disturbances can be presented as superpositions of the piecewise continuous functions with unknown coefficients (varying in a stepwise manner within comparatively short time intervals). This disturbance model is termed wave representation [50].

In what follows we discuss two disturbance models: the random functions with bounded variance and the functions resulting from a wave representation (with either discrete or continuous description of the control models, respectively).

It is well known [40,41] that the system’s robustness relative to the discretization operation is nontrivial for the nonlinear case and requires a separate study and validation. This implies that the robust properties of a control system obtained using a continuous description would not be transferred to a generally discrete case and vice versa. It is, therefore, reasonable to discuss both cases for a more complete analysis of a controlled object and a more correct selection of a consistent system for the regulator parameters, discretization, and object, respectively.

In this connection, we discuss an independent problem of a discrete control over a nonlinear object containing a stochastic uncertainty, based on a combined use of the modified method of designing aggregated regulators [8,9,12] and the control strategy, which minimizes the variance of the output macro variable [4,37,51]. The object of study is complicated by different values of delays in five variables [17].

3. Generalization of the Method of Analytical Design of Aggregated Regulators for a Discrete Stochastic Immunology Object

The acceptability of a description of the original model in the form of stochastic difference equations has been dictated by a greater physical validity, since the model, where randomness has a finite variance, is mathematically correct and plausible from the point of view of its practical content.

3.1. Features of the Discrete Description of the Control Object with Delay

The design of a discrete regulator requires that the initial mathematical model be presented in the form of a stochastic difference equation:

$$\begin{aligned} \mathbf{X}[k+1] &= \mathbf{F}[k] + \mathbf{u}[k] + \xi[k+1] + c\xi[k], \\ \mathbf{X}[k_0] &= \mathbf{X}_0, \quad k = k_0, k_0 + 1, \dots, \end{aligned} \quad (6)$$

where $\mathbf{X}[k] = (X_1[k], \dots, X_n[k])^T$, $\mathbf{F}[k] := \mathbf{F}(\mathbf{X}[k]) \in R^n$, and $\mathbf{u} \in R^m$, $m \leq n$ are the state vector, a nonlinear function describing it, and control, respectively, $\xi[k] \in R^l$, $l \leq m$ are the noncorrelated random quantities, $E\{\xi_i[k]\} = 0$, $D\{\xi_i[k]\} = \sigma^2$, $i = \overline{1, l}$, and $|c| < 1$ is the attenuation factor [4,13].

To define the control, we set a probability space, $\{\Omega, \mathfrak{F}, P\}$, with filtration, $\mathfrak{F}_k$, that satisfies the usual conditions; $\mathbf{u}[k]$ is a random measurable function.

Let E and D denote the operators of mathematical expectation and variance, respectively, and “a.s.” is short for “almost surely”. Note that for the random variables, the normal distribution is not assumed.

A relationship between (3), (5), and (6) is possible based on the discretization schemes (according to the Euler method (e.g., [43])):

$$\begin{aligned} \mathbf{F}[k] &= (F_1[k], \dots, F_n[k], F_{1\tau}[k], \dots, F_{n\tau}[k])^T, \\ F_i[k] &= X_i[k] + hA_{i\tau}(X_1[k], \dots, X_n[k]), \quad i = \overline{1, n}, \\ u[k] &= hU[k], \quad \zeta[k+1] = h(\xi[k+1] + c\xi[k]). \end{aligned} \quad (7)$$

During discretization, the differentiation operator, d/dt , in continuous description is approximated by a difference operator with the parameter $h > 0$, which is the right-hand difference derivative.

In order to design control in the state space using the discrete method of analytical design [9], we are going to use discrete analogs of the quality functional and the extremal equation for it:

$$\begin{aligned} \Phi_D &= \Phi_D(\Psi) = \sum_{k=k_0}^{\infty} \sum_{j=1}^m \left(\alpha_j^2 (\psi_j[k])^2 + (\Delta\psi_j[k])^2 \right) \rightarrow \min, \\ \Delta\psi_j[k] &= \psi_j[k] - \psi_j[k-1], \quad k = k_0 + 1, \dots; \\ \psi_j[k_0] &= \psi_j(\mathbf{X}[k_0]), \quad \mathbf{X}[k_0] = \mathbf{X}_0, \quad \Delta\psi_j[k_0] = 0, \end{aligned} \quad (8)$$

$$\psi_j[k+1] + \lambda_j \psi_j[k] = 0, \quad \lambda_j = \text{const}, \quad |\lambda_j| < 1, \quad j = \overline{1, m}, \quad k = k_0, k_0 + 1, \dots \quad (9)$$

Remark 1. The functional given by (8) is a generalization of the classical quadratic quality functional of the designed control. This is easily shown by substituting the object's equation into it. An advantage of this prescription for the control quality criterion consists, firstly, in an implementation of the physical control principles [3] and, secondly, in the possibility of controlling

the duration of achieving the steady state regime via parameters $\alpha, \lambda \in \mathbb{R}$. It is also assumed that the parameters α and λ in (8), and (9) ensure the finiteness of the functional Φ_D , according to the conditions of SCT [9].

Statement 1. Function $\psi[k]$, $k = k_0, k_0 + 1, \dots$, satisfying the following equation:

$$\psi[k+1] + \lambda\psi[k] = 0, \quad \lambda = \text{const}, \quad |\lambda| < 1$$

delivers a global minimum to the functional $\Phi_D = \sum_{k=k_0}^{\infty} (\alpha^2 \psi^2[k] + (\Delta\psi[k])^2)$ ($m = 1$). The parameters of the designed regulator, $\alpha, \lambda \in \mathbb{R}$, are related by $\lambda = 0.5 \left(2 + \alpha^2 - \left((2 + \alpha^2)^2 - 4 \right)^{1/2} \right)$.

A proof of Statement 1 (see Appendix A) follows immediately from the discrete analog of the corollary of the Euler–Lagrange equation [52] for the functional in the integral form (see Appendix B).

3.2. Algorithm for Designing a Regulator for System (6)

Consider the application of the algorithm for designing the stochastic regulator for a scalar control since, according to the condition for applying the Analytical Design of Aggregated Regulators (ADAR) method [8,9], the dimensions of the control vectors and the target macro variable must match.

Let us call an ADAR strategy a sequence, $\{U_1, U_2, \dots\}$, where the measurable function, $U_k : \mathbb{R}^n \rightarrow \mathbb{R}^m$, determines the control law at the moment, $t_k = kh$, $k \geq k_0$, $h > 0$, which implements a consistent solution to variational problems, (Φ^j, ψ_j) , $j = \overline{1, j_{\text{final}}}$, leading to the realization of the goal of control, $\psi^*[k] \xrightarrow{k \rightarrow \infty} 0$.

Assume that

- (1) All the conditions for the correct construction of the ADAR control are satisfied.
- (2) The control strategies are selected from a set of ADAR strategies in accordance with the discrete analog of ADAR method [9,12,37].
- (3) The control, $u[k]$, is formed according to the feedback principle:

$$\begin{aligned} u[k] &= u(\mathbf{X}^k; u^k), \quad u[k_0] = 0, \quad k = k_0, k_0 + 1, \dots, \\ \mathbf{X}^k &= (\mathbf{X}[k], \mathbf{X}[k-1], \dots, \mathbf{X}[k_0]), \quad u^k = (u[k-1], u[k-2], \dots, u[k_0]). \end{aligned} \quad (10)$$

Let us formalize the main points in constructing a stochastic discrete system of scalar control over a nonlinear immunology object, according to the requirements of (4) and (7) as the following algorithm.

1. Extend the phase space in order to compensate for the delay, relying on the feedback law $\mathbf{R}(\mathbf{X}, \mathbf{Y})$:

$$\begin{aligned} \mathbf{X}[k+1] &= \mathbf{F}(\mathbf{X}[k], \mathbf{Y}[k]) + \mathbf{u}[k] + \boldsymbol{\xi}[k+1] + c\boldsymbol{\xi}[k], \\ \mathbf{Y}[k+1] &= \mathbf{R}(\mathbf{X}, \mathbf{Y}), \quad k = k_0 + 1, \dots \end{aligned} \quad (11)$$

The vector variable, $\mathbf{Y} \in \mathbb{R}^{n_Y}$, is introduced to compensate for delays in five variables (see Appendix E) $X_j|_{k-v_{l_j}}$, $j = 4, 5, 6, 7, 8$, where

$$\begin{aligned} v_{l_j} &\in M_j; \quad M_4 = \{a_{l_4}, l_4 = 10, 15, 20, 30\}, \quad M_5 = \{a_{l_5}, l_5 = 10, 20, 26\}, \\ M_6 &= \{a_{20}\}, \quad M_7 = \{a_{l_7}, l_7 = 15, 30\}, \quad M_8 = \{a_{l_8}, l_8 = 26, 30\}, \\ a_{l_j} &= v_{l_j}h, \quad j \in \{4, 5, 6, 7, 8\}, \quad v_j = \max_{l_j} v_{l_j}, \quad n_Y = \sum_{j=4}^8 v_j. \end{aligned}$$

2. Determine the external control structure $u_{\xi}^A[k]$, $k = k_0, k_0 + 1, \dots$, using the deterministic ADAR method (at fixed functions realizing random disturbances).

- a. Introduce a macro variable:

$$\begin{aligned}\psi_1[k] &= X_{10}[k] - \phi[k], \\ \phi[k] &= \phi(X_1[k], \dots, X_9[k], Y_1[k], \dots, Y_{n_Y}[k]),\end{aligned}$$

and define the first variational problem, $\Phi_D^1(\psi_1) = \sum_{k=k_0}^{\infty} (\alpha_1^2 \psi_1^2[k] + (\Delta \psi_1[k])^2) \rightarrow \min$, where the sought-for function is given the role of internal control, under whose action the imaging point of the system will further tend towards the manifold, $\psi^*[k] \xrightarrow{k \rightarrow \infty} 0$.

- b. Apply a corollary of the Euler–Lagrange Equation (9) for the functional Φ_D^1 in order to obtain a function for u_{ξ}^A accurately to an unknown function, $\phi[k]$, as follows:

$$\begin{aligned}u_{\xi}^A[k] &= -F_{10}[k] - (\xi[k+1] + c\xi[k]) + h^{-1}(-(\lambda_1 + 1)\psi_1[k] + \Delta\phi[k]), \quad u_{\xi}^A[k_0] = 0, \\ \Delta\phi[k] &= \phi[k+1] - \phi[k], \quad k = k_0, k_0 + 1, \dots\end{aligned}\quad (12)$$

- c. Decompose (11) on the manifold, $\psi_1[k] = 0$, $X_{10}[k] = \phi[k]$, $\phi[k] = \phi(\mathbf{X}[k])$, $k = k_0, k_0 + 1, \dots$. The dimension of system (11) will decrease by one:

$$\begin{aligned}\mathbf{X}_{\psi_1}[k+1] &= \mathbf{F}_{\psi_1}(\mathbf{X}_{\psi_1}[k], \mathbf{Y}[k]), \quad \mathbf{Y}[k+1] = \mathbf{R}(\mathbf{X}_{\psi_1}, \mathbf{Y}), \\ \mathbf{X}_{\psi_1}[k] &= (X_1[k], \dots, X_9[k])^T, \quad k = k_0, k_0 + 1, \dots\end{aligned}\quad (13)$$

The subscript, $(\cdot)_{\psi_1}$, in (13) means that system (11) describes the behavior of coordinates (11) on manifold $\psi_1 = 0$.

- d. Prescribe the second macro variable, $\psi_2[k] = \psi^*[k]$, $k = k_0, k_0 + 1, \dots$, in accordance with the hierarchy of the SCT design, and define the second variational problem:

$$\Phi_D^2(\psi_2) = \sum_{k=k_0}^{\infty} (\alpha_2^2 \psi_2^2[k] + (\Delta \psi_2[k])^2) \rightarrow \min.$$

- e. Obtain a formula for the function $\phi[k]$ from the extremal equation for the functional Φ_D^2 :

$$\begin{aligned}\psi_2[k+1] + \lambda_2 \psi_2[k] &= X_1[k+1] - X_1^* + \lambda_2 \psi^*[k] = 0 \Rightarrow \\ F_{1,\psi_1}(X_1[k], \dots, X_9[k], \phi[k], Y_1[k], \dots, Y_{n_Y}[k]) &= X_1^* - \lambda_2 \psi^*[k], \quad k = k_0, k_0 + 1, \dots\end{aligned}$$

or, in the explicit form, taking into account the representation (7):

$$\begin{aligned}\phi[k] &= (a_3 X_1)^{-1} \left(h^{-1}(\lambda_2 + 1) \psi^*[k] + \widehat{F}_{10}[k] \right), \\ \widehat{F}_{10}[k] &= (a_1 + a_2 X_6[k]) X_2[k] - a_4 X_1[k] \\ &\quad - a_5 (1 - X_2[k] - X_3[k]) X_1[k], \quad k = k_0, k_0 + 1, \dots\end{aligned}\quad (14)$$

3. Apply the operation of conditional mathematical expectation: $u^A[k] = \mathbf{E}\{u_{\xi}^A[k] | \xi^k\}$, $\xi^k = (\xi[k_0], \dots, \xi[k]), k = k_0, k_0 + 1, \dots$:

$$u^A[k] = -F_{10}[k] - c\xi[k] + h^{-1}(-(\lambda_1 + 1)\psi_1[k] + \Delta\phi[k]), \quad k = k_0 + 1, \dots\quad (15)$$

4. Reduce the system (11), taking into account the limit relations, $\lim_{k \rightarrow \infty} \psi_j[k] = 0$, $j = 1, 2$, and, in particular, obtain an expression given by

$$\psi_1[k+1] + \lambda_1 \psi_1[k] = h\hat{\xi}[k+1], \quad (16)$$

from which follows a formula for estimating $\hat{\xi}[k]$, whose calculation is provided by the current system state.

5. Substitute $\hat{\xi}[k]$ from (16) instead of $\xi[k]$ into expression (15). The designing of a stochastic discrete regulator is over, and the control is given by

$$u^A[k] = -F_{10}[k] - h^{-1}(c + (\lambda_1 + 1))\psi_1[k] - ch^{-1}\lambda_1\psi_1[k-1] + h^{-1}\Delta\phi[k], \quad k = k_0 + 1, \dots \quad (17)$$

The final control system represents a combination of the controlled object (11) and the regulator (14) and (17).

The regulator parameters, λ_1 and λ_2 , are responsible for a certain trade-off between the duration of reaching the target neighborhood, the parameter h , and the transient process quality.

Statement 2. Let the equation $\psi(t) = \psi(\mathbf{X}(t)) = 0, t \rightarrow \infty$ (a.s.) determine the invariant of the system (3) having the attractivity property of the manifold (4). Then, the control (17), $u^A[k], k = k_0 + 1, \dots$, provides the minimal variance for the output macro variable and

$$\begin{aligned} \mathbf{E}\{\psi_j[k+1] + \lambda_j\psi_j[k]\} &= 0, \quad |\lambda_j| < 1, \quad j = 1, 2, \quad k \rightarrow \infty; \\ \mathbf{D}\{\psi_j[k+1] + \lambda_j\psi_j[k]\} &\rightarrow \min, \\ \mathbf{E}\{\Phi\} = E\{\Phi_D^1 + \Phi_D^2\} &= E\left\{\sum_{k=k_0}^{\infty} \sum_{j=1}^2 \left(\alpha_j^2(\psi_j[k])^2 + (\Delta\psi_j[k])^2\right)\right\} \rightarrow \min. \end{aligned}$$

The proof of Statement 2 (see Appendix C) is based on the control provided by the main functional Equation (9) and discrete strategies [4,37] that minimize the variance of the output variable.

Remark 2. The output variable in the simplest one-dimensional model:

$$Y[k+1] = F[k] + u[k] + \xi[k+1] + c\xi[k], \quad k = k_0, k_0 + 1, \dots,$$

under the description given by (6) cannot have a variance smaller than that of the input noise, whatever the control:

$$\mathbf{D}\{Y[k]\} \geq \mathbf{D}\{\xi[k]\}, \quad k = k_0 + 1, \dots$$

4. Method of Nonlinear Continuous Design of a Control System for an Immunology Object

The integral adaptation method is used below [12], which relies on an analytical description of the target macro variables and the introduction of the integrators into the control channels based on them.

The control design algorithm based on this method makes it possible to synthesize adaptive systems without acquiring the current data on the changes in the plant and environment parameters.

Let us assume that the control is implemented in the state space, and the values of the variables in the infectious disease process can be measured. The phase trajectories of the variables selected for the construction of the regulator have to lie inside the “tube” constructed in a certain neighborhood of the stationary state of the object, which is consistent with the experimental data for the hepatitis B model [16,17].

4.1. Algorithm for Designing a Continuous Nonlinear Regulator for Object (3)

1. Ensure closedness of the system (3) using an extension of the system state:

$$\begin{aligned}\dot{\mathbf{X}} &= \mathbf{A}_\tau(\mathbf{X}) + \mathbf{Z}(t) + \mathbf{u}(t), \quad \mathbf{u} = (0, \dots, 0, u)^T, \quad \mathbf{Z} = (0, \dots, 0, Z)^T, \\ \dot{Z}(t) &= \eta\psi(t), \quad \eta = \text{const} > 0, \quad t \geq 0\end{aligned}\quad (18)$$

The correctness of modeling disturbance, $\zeta(t)$, via an additional phase variable, Z , goes back, in particular, to the paper [50] (see Appendix D). In (18), the proportionality coefficient, η , is a parameter of the synthesized system, which, together with parameter w (from Equation (A1)), affects the transient process quality. Therefore, the last two equations in (18) are given by:

$$\begin{aligned}\dot{X}_{10} &= F_{10} + Z + u, \\ \dot{Z} &= \eta\psi^*, \quad \eta = \text{const} > 0\end{aligned}$$

2. Obtain the structure of the continuous regulator according to the requirements (4) by virtue of the formulation and solution of the first variational problem (Φ_1, ψ_1) and taking into account the control scalar character:

$$\Phi_1(\psi_1) = \int_0^\infty (\psi_1^2 + w_1^2 \dot{\psi}_1^2) dt \rightarrow \min, \quad \psi_1 = X_{10} - \varphi, \quad (19)$$

where $\varphi = \varphi(X_1, \dots, X_9, Z)$ is the below-determined internal control, according to SCT terminology. In accordance with Appendix B, the extremal equation for Φ_1 has the form of (A1) with the parameters $w_1, \eta = \text{const} > 0$, from which follows that

$$u = -w_1^{-1}\psi_1 - F_{10} - Z + \dot{\varphi}, \quad Z = \eta \int \psi^* dt. \quad (20)$$

3. Decompose system (18) on the reached manifold, $\psi_1(t) = 0, t \rightarrow \infty$, which means applying the limit equality, $X_{10}(t) = \varphi(t), t \rightarrow \infty$, to this system, resulting in a reduced system:

$$\begin{aligned}\dot{\mathbf{X}}_{\psi_1} &= \mathbf{A}_\tau(\mathbf{X}_{\psi_1}), \quad \dot{Z}(t) = \eta\psi^*(t), \quad \eta = \text{const} > 0, \\ \mathbf{X}_{\psi_1,1} &= (X_{\psi_1,1}, \dots, X_{\psi_1,9}, Z)^T, \quad \varphi = \varphi(X_1, \dots, X_9, Z), \quad X_{\psi_1,10} = \varphi.\end{aligned}\quad (21)$$

The subscript, $(\cdot)_{\psi_1}$, in system (21) is used to indicate the difference from the behavior of object (18), since system (21) describes the trajectory of (18) on the reached manifold, $\psi_1(t) = 0, t \rightarrow \infty$, under the action of the external control (20).

4. Obtain the internal control structure, $\varphi = \varphi(X_1, \dots, X_9, Z)$, according to the requirements (4) by virtue of the formulation and solution of the second variational problem, (Φ_2, ψ_2) :

$$\Phi_2(\psi_2) = \int_0^\infty (\psi_2^2 + w_2^2 \dot{\psi}_2^2) dt \rightarrow \min, \quad \psi_2 = \psi^* + \kappa Z, \quad \kappa = \text{const} > 0, \quad (22)$$

κ is a regulator parameter.

The extremal equation for Φ_2 has the form (A1) with the parameter $w_2 = \text{const} > 0$, from which follows that

$$\varphi = (a_3 X_1)^{-1} \left(\psi^* (w_2^{-1} + k\eta) + \kappa Z w_2^{-1} + (a_1 + a_2 X_6) X_2 - X_1 (a_4 + a_5 (1 - X_2 - X_3)) \right), \quad (23)$$

and, therefore, the total derivative is determined from the following formulas:

$$\begin{aligned}
\dot{\varphi} &= \frac{\partial \varphi}{\partial X_1} F_1 + \frac{\partial \varphi}{\partial X_2} F_2 + \frac{\partial \varphi}{\partial X_3} F_3 + \frac{\partial \varphi}{\partial X_6} F_6 + \frac{\partial \varphi}{\partial Z} \kappa \eta \psi^*, \\
\frac{\partial \varphi}{\partial X_1} &= (a_3 X_1^2)^{-1} \left(X_1^* (w_2^{-1} + \kappa \eta) - \kappa Z w_2^{-1} - (a_1 + a_2 X_6) X_2 \right), \\
\frac{\partial \varphi}{\partial X_2} &= (a_3 X_1)^{-1} (a_1 + a_2 X_6 - a_5 X_1), \quad \frac{\partial \varphi}{\partial X_3} = (a_3 X_1)^{-1} a_5 X_1, \\
\frac{\partial \varphi}{\partial X_6} &= (a_3 X_1)^{-1} a_2 X_2, \quad \frac{\partial \varphi}{\partial Z} = (a_3 X_1)^{-1} \kappa w_2^{-1}.
\end{aligned} \tag{24}$$

- Form the final control system (controlled object and regulator) in the form of Equations (3), (4), (20), (23), and (24).

The constants w_1, w_2, κ and η are the regulator parameters determining the consistency between both the duration and quality of the transient process.

Remark 3. Let us comment on the form of the macro variable, $\psi_2(t) = \psi^*(t) + \kappa Z(t)$, $\kappa > 0$. Reaching the manifold, $\psi_2(t) = 0$, $t \rightarrow \infty$, or $\psi^*(t) = -\kappa Z(t)$, leads to the following form of the last equation: $\dot{Z}(t) = -\kappa \eta Z(t)$, $\kappa \eta > 0$, which guarantees an asymptotically stable achievement of the zero solution, $Z(t) = 0$, $t \rightarrow \infty$.

Statement 3. Let the limit equation, $\psi^*(t) = \psi^*(X(t)) = 0$, $t \rightarrow \infty$, determine the invariant of the controlled biomedical object (3) having the attractivity property of the target manifold (4). Then, the control in the state space from (20) would transfer object (3) from its initial point, $X(t_0) = X_0$, to a certain neighborhood, $\psi^*(X(t)) = 0$, and provide an asymptotically stable holding of this object in this neighborhood.

The proof of Statement 3 is given in Appendix D and is based on the results of theoretical mechanics [49,53,54] and the wave representation of perturbations [50].

5. Simulation Results for Acute Disease Stage

Here, we study the most interesting, from the practical viewpoint, uncertainties in the right-hand side of the description: non-random (piecewise-constant and harmonic functions) and random uncertainty (off-design conditions for the ADAR algorithm) (Figures 2–6). The initial data correspond to the acute stage [17] (Table 1).

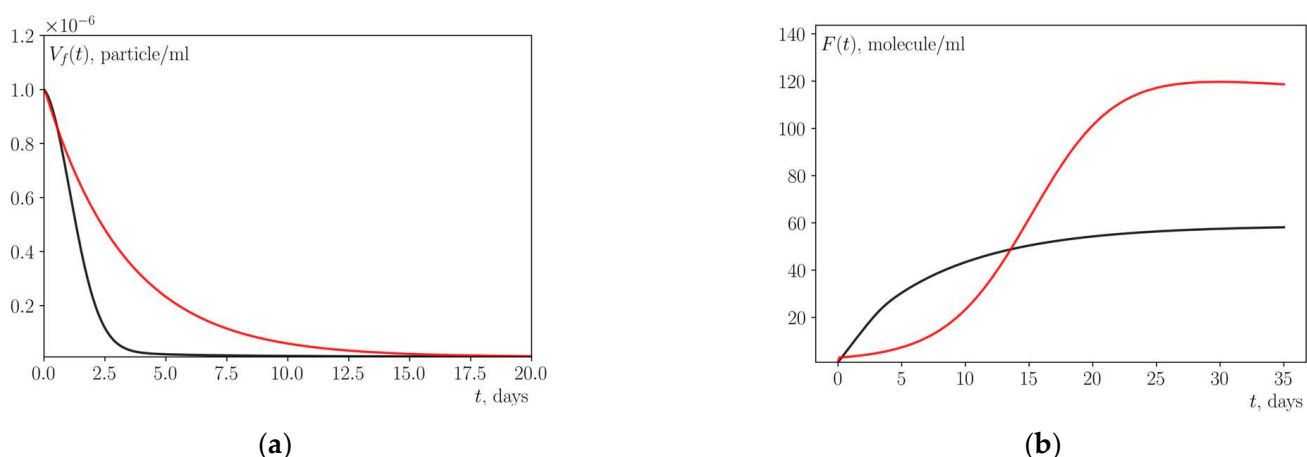


Figure 2. Comparative trajectories of main discrete model characteristics in conditions of normal noises ($N(0;0.05)$, $\lambda_1 = -0.5$, $\lambda_2 = -0.997$): (a) antigen concentrations; (b) antibody variation dynamics (red/black lines for behaviors with stochastic/deterministic ADAR control under off-design conditions, respectively). The values of the antigen variable reach the specified neighborhood. The duration of the treatment program does not exceed natural treatment (24.98).

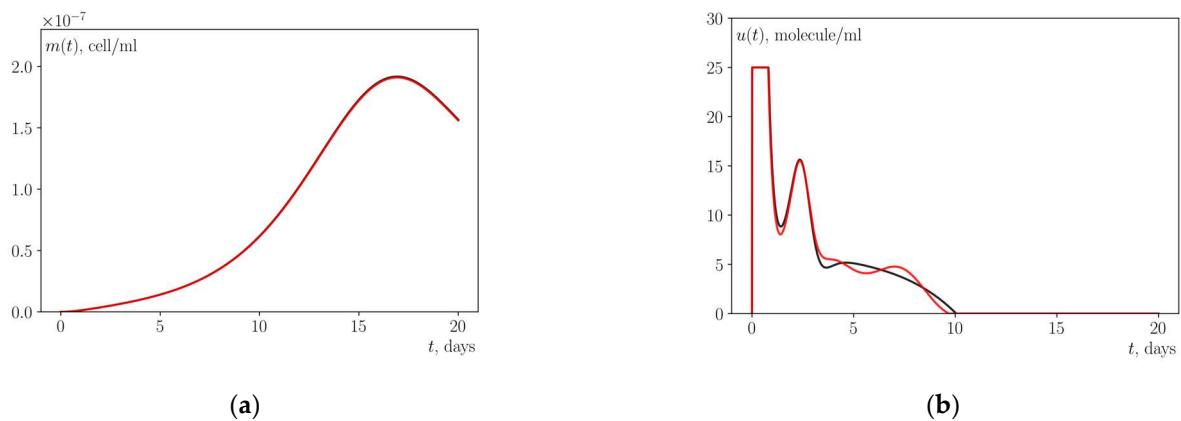


Figure 3. Trajectories of the main continuous model (1) characteristics: (a) dynamics of relative characteristic ($m(t)$) as the proportion of target organ cells destroyed by antigen; and (b) control variation dynamics (red/black lines for behaviors with control in conditions of harmonic ($\zeta = \sin(\pi t/2)$)/constant noises ($\zeta = 0.1$), respectively). The trajectories for $m(t)$ coincide for both types of disturbances. The controls take values within acceptable limits.

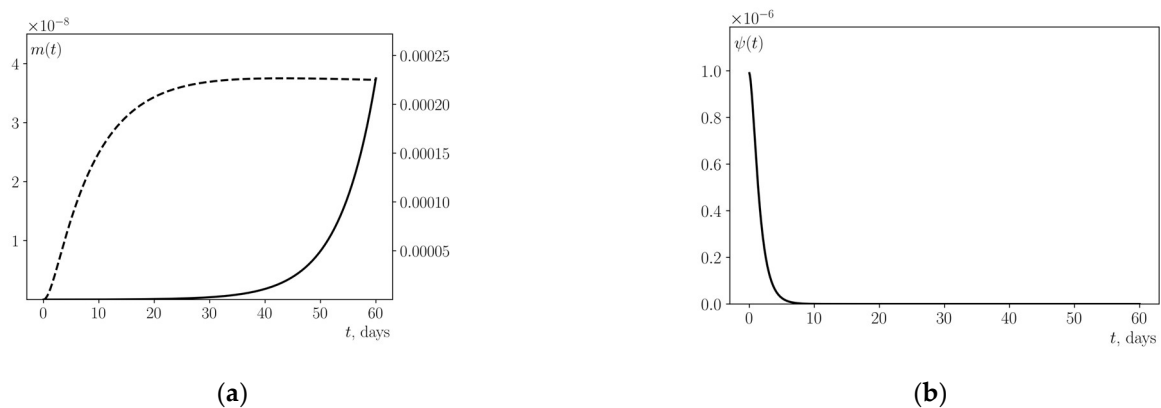


Figure 4. Comparative trajectories of main continuous base model [17] characteristics in conditions of constant noises, $\zeta = 0.5$: (a) dynamics of relative characteristic ($m(t)$) as the proportion of target organ cells destroyed by the antigen (dashed/solid lines for behaviors with/without control, respectively); and (b) trajectory of target macro variable, $\psi(t) = V(t) - V^*$, with control, $V^* = 10^{-14}$. The duration of the treatment program is less than natural treatment (~ 20 – 25).

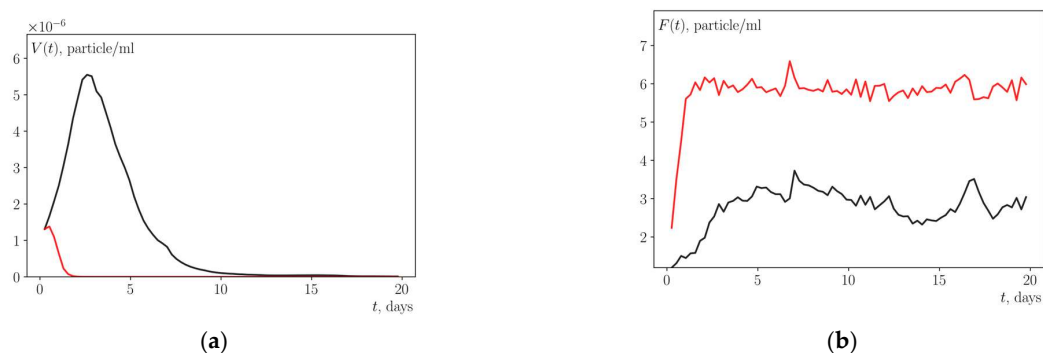


Figure 5. Comparative trajectories of main continuous base model [17] characteristics in conditions of normal noises, $N(0; 0.07)$: (a) antigen concentrations; and (b) antibody variation dynamics (red/black lines for behaviors with stochastic/deterministic ADAR control under off-design conditions, respectively). The graphs illustrate a significantly better control result in accordance with the stochastic algorithm.

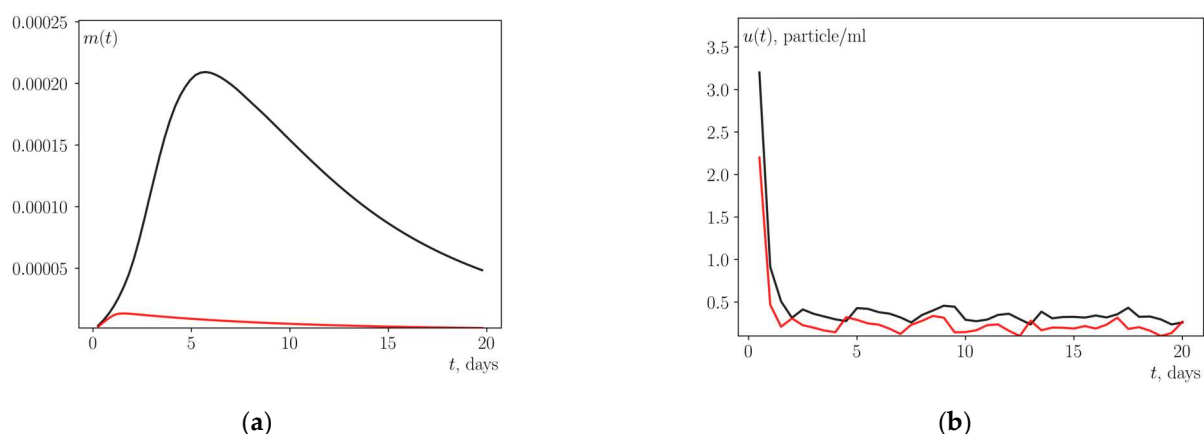


Figure 6. Comparative trajectories of the main continuous base model [17] characteristics in conditions of normal noises, $N(0;0.07)$: (a) dynamics of relative organ-damage characteristics; and (b) control variation dynamics (red/black lines for behaviors with stochastic/deterministic ADAR control under off-design conditions, respectively). The value of the generalized relative characteristic of the damage that the antigen inflicts on the target organ is significantly less for the stochastic algorithm, with comparable control values for both algorithms (stochastic and deterministic).

Table 1. Model (1) parameters in dimensionless form.

Parameters				
$a_1 = 0.1$	$a_{10} = 0.8$	$a_{19} = 0.8$	$a_{28} = 0.1$	$a_{37} = 0.005$
$a_2 = 0.0001$	$a_{11} = 0.001$	$a_{20} = 2$	$a_{29} = 0.5$	$a_{38} = 0.12$
$a_3 = 0.1$	$a_{12} = 0.0001$	$a_{21} = 0.08$	$a_{30} = 3$	$m^* = 0.5$
$a_4 = 0.0001$	$a_{13} = 0.05$	$a_{22} = 0.00015$	$a_{31} = 0.16$	$C^* = 1$
$a_5 = 0.0001$	$a_{14} = 0.01$	$a_{23} = 0.0001$	$a_{32} = 0.17$	$x_1^* \in (10^{-15}, 10^{-8})$
$a_6 = 0.05$	$a_{15} = 0.7$	$a_{24} = 0.1$	$a_{33} = 0.2$	
$a_7 = 0.02$	$a_{16} = 0.001$	$a_{25} = 0.8$	$a_{34} = 0.17$	
$a_8 = 0.0001$	$a_{17} = 0.0001$	$a_{26} = 2$	$a_{35} = 0.4$	
$a_9 = 0.01$	$a_{18} = 0.05$	$a_{27} = 0.08$	$a_{36} = 0.002$	

The delayed arguments that determine the required time for the variables to interact with each other are defined by parameters $a_{10}, a_{15}, a_{16}, a_{20}, a_{26}, a_{30}$ associated with variables M_V, H_E, H_B, E, B , respectively. A study of the behavior of model solutions depending on the delay coefficient was carried out in the article [55]. The simulation of the control algorithms (Sections 3.2 and 4.1) was carried out with fixed values of the delay arguments.

Assume $t_0 = 0$, since the system of equations of the antiviral immune response model is autonomous. The initial conditions are:

$$x_1(0) = 10^{-8}, \quad x_2(0) = 0, \quad x_3(0) = 0, \quad x_4(0) = 0, \quad x_5(0) = 1; \\ x_6(0) = 1, \quad x_7(0) = 1, \quad x_8(0) = 1, \quad x_9(0) = 1, \quad x_{10}(0) = 1$$

Remark 4. The base mathematical model of an infectious disease [17] based on Burnet's clonal selection theory [47] is a subsystem of (1). The model describes the interaction of the four most significant characteristics of the disease: the concentration of antigens, $V(t)$, plasma cells, $C(t)$, antibodies, $F(t)$, and the relative characteristic, $m(t)$, as the proportion of target organ cells destroyed by antigen.

Remark 5. The parameters of the mathematical model of the antiviral response and the ranges of their acceptable values for viral hepatitis B can be clarified in the papers [16,17,26].

Table 2 presents comparative data for the model (1) according to four algorithms and parameters from Table 1. The algorithm comparison indicators used are as follows [26,56,57]:

- The average rate of body damage (AR_V/AR_{Vd}) (subscript “d” indicates discrete case);
- The ratio of the volume of donor antibodies administered to the normal level of antibodies in a healthy body (R_u/R_{ud});
- Recovery time for the body (T_δ), where

$$AR_V = (T_\delta)^{-1} \int_0^{T_\delta} V_f(t) dt \left(AR_{Vd} = (T_\delta)^{-1} \sum_{i=1}^{[T_\delta]} V_f[i] \right);$$

$$R_u = (F^*)^{-1} \int_0^{T_\delta} u(t) dt \left(R_{ud} = (F^*)^{-1} \sum_{i=1}^{[T_\delta]} u[i] \right);$$

$$T_\delta = \operatorname{argmin}_t (m(u(t)) < \delta), \quad \delta = 0.01,$$

where $[x]$ is the integer part of a number, x , and F^* is the normal level of antibodies in a healthy body.

Table 2. Average comparative characteristics of control algorithms in conditions of normal noises, $N(0; 0.05)$.

Algorithm	AR_V	R_u	T_δ
Discrete adaptation algorithm [26]	3.6×10^{-4}	3.7	20–23
Integral adaptation SCT algorithm (Section 4.1)	3.5×10^{-3}	3.1	10
Stochastic SCT algorithm (Section 3.2)	3.8×10^{-4}	3.9	12
ADAR algorithm [30]	3.1×10^{-4}	3.5	10

The data presented in Table 2 suggests an acceptable quality of all the compared object control algorithms. There is a certain advantage of the synergetic algorithms in terms of the time to achieve conditional recovery of the organism model. However, the greatest interest is in the dynamics of the quality of the algorithms for the base [17] and extended (1) models under conditions of physically acceptable values of the signal-to-noise ratio. The design and comparison of controls for object (1) with these additional requirements is the subject of further investigations.

6. Discussion

A statistical analysis of the results of simulation control systems allows us to draw the following conclusions.

The plots presented above (Figures 2–6) suggest an acceptable quality of both controls over the biomedical object, which ensures that the goal is achieved in terms of the global minimum (on average) of the quality functional with a synergistic effect. The control object is sustained in the fairly small neighborhood of the value of antigens.

Table 3 shows the dependence of the root mean square (RMS) on the target value of the main indicator, V , depending on the RMS of the noise level, ξ .

Table 3. Dependence of the standard deviation of the controlled object coordinates on the noise level.

$\sigma(\xi)$	$\sigma_A(V) \times 10^{-6} (N/U)^1$	$\sigma_S(V) \times 10^{-6} (N/U)^1$
0.01	3.80/3.89	3.75/3.95
0.1	3.85/3.99	3.70/3.95
0.5	4.05/4.08	3.75/3.90
0.9	7.85/7.90	3.74/4.00

¹ N and U denote normal and uniform distribution, respectively.

Here, we use the notations $\sigma_A(V)$ and $\sigma_S(V)$ for the RMS of the controlled variable on the basis of the classical ADAR algorithm (off-design conditions), and the stochastic algorithm, respectively.

From Table 3, it follows that the stochastic control (in relation to the model under consideration) demonstrates less variance than the deterministic ADAR control, starting from a certain threshold value of the RMS noise.

Let us note the following advantages and disadvantages of control design algorithms based on SCT:

- Ensuring the robust properties of both controllers if the target manifold has attractive properties;
- The algorithm based on nonlinear stochastic adaptation has a certain superiority over the deterministic control algorithm under conditions of physically acceptable values of the signal-to-noise ratio;
- A signal-to-noise ratio, when the control still provides the expected behavior of the object, should be estimated on the training set;
- There is a high sensitivity to the parameters of the discreteness of time and the regulator under conditions of an unstable target state;
- Setting different target values of the macro variable may lead to the discovery of new properties of the controlled object.

The last statement represents a motivation towards the formulation of the inference rules of the IF...THEN type as the basis for databases and knowledge; the creation of such databases is the primary task for the digital healthcare service.

7. Conclusions

The two algorithms for designing control over a nonlinear high-dimensional object presented in this work have a number of properties making them attractive candidates for applications in the current expert and decision support systems as mathematical tools for modeling a delicate intervention into the immune system functioning, as follows:

- A control can be of the vector type in terms of the number of channels of possible impacts.
- A “prescription” of different target invariants allows the identification and study of new regularities of the object in focus.
- The inclusion of systematic and random disturbances in the control model improves the reliability of the prognostic analysis of the modeled object’s behavior in cases of parametric inaccuracies and estimation errors.

The control in this study and earlier ones has been understood as a program of drug delivery to the diseased organ, and the goal of control was a stabilization of the target variable (antigen concentration) in a certain small-value neighborhood. Notably, for an unstable mode, the goal was not to completely suppress the chaoticity but to somewhat reduce it.

An advantage of the design technique used in this study is the simplicity of the mathematical technique, whose validation entirely relies on the results of theoretical mechanics and principles of physical control theory [3,38]. The proposed algorithms for designing control have been derived analytically.

It is also important that the designed control is not terminal, where the strict requirements are set to the final state only while admitting the other parts of the target trajectory to be comparatively arbitrary. The available regulator parameters are transparently interpretable and consistent with the quality and duration requirements of a transient process.

It seems reasonable to associate further studies with the construction of a control system in the observation space, provided with a synergistic observer of states for estimating variables that are not directly measurable.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Proof of Statement 1. The validity of the statement follows from a direct substitution of the increment $\Delta\Phi_D(\psi) = \Phi_D(\psi + \delta) - \Phi_D(\psi)$ into the respective expression, and the relationship between parameters $\alpha, \lambda \in R$ follows from the basic principles of a discrete analog of the ADAR method [9,12]. Indeed, denoting individual terms in (8) as $T[k] = T(\psi[k], \Delta\psi[k]) = \lambda^2\psi^2[k] + (\Delta\psi[k])^2$, $k = k_0 + 1, \dots$, considering the discrete derivatives $T_{\Delta\psi}[k], T_\psi[k]$ of the function $T(\psi[k], \Delta\psi[k])$ relative to the arguments $\Delta\psi[k], \psi[k]$, respectively, obtain the following:

$$T_{\Delta\psi}[k] = 2\Delta\psi[k], \quad T_\psi[k+1] = 2\lambda^2\psi[k+1],$$

and substitute the resulting expressions into the discrete analogs of corollaries of the Lagrange equation:

$$\Delta T_{\Delta\psi}[k] - T_\psi[k+1] = 0, \quad \Delta T_{\Delta\psi}[k] = T_{\Delta\psi}[k+1] - T_{\Delta\psi}[k].$$

After elementary manipulations, obtain an equation $\alpha^2\psi[k] + (2 + \alpha^2)\lambda\psi[k] + \psi[k] = 0$, that implies a formula relating the regulator parameters α and λ . $\square$

Appendix B

Consider the Euler–Lagrange equation for the functional in the integral form. Let a continuous variational problem (Φ_C, ψ) is given by

$$\Phi_C = \int_0^\infty \left(\vartheta^2(\psi) + w^2\dot{\psi}^2 \right) dt \rightarrow \min, \quad \psi(t) = 0, \quad t \rightarrow \infty, \\ \vartheta(\psi)\psi > 0 \quad \forall \psi \neq 0, \quad \vartheta(0) = 0,$$

where $\vartheta(\psi)$ is a single-valued, continuous, differentiable function.

Solutions to the equation

$$w\dot{\psi} + \vartheta(\psi) = 0 \tag{A1}$$

would determine the stable extremals providing a minimum to the functional Φ_C .

The validity of this statement follows directly from the Euler–Lagrange equation for Φ_C :

$$F(t, \psi, \dot{\psi}) = \vartheta^2(\psi) + w^2\dot{\psi}^2, \\ \frac{\partial F}{\partial \psi} - \frac{d}{dt} \frac{\partial F}{\partial \dot{\psi}} = 2\vartheta(\psi) \frac{d\vartheta}{d\psi} - 2w^2\ddot{\psi} = 0$$

Multiply the latter equation by $\dot{\psi}$ and then integrate it with respect to t :

$$\vartheta(\psi) \frac{d\vartheta}{d\psi} \dot{\psi} - w^2\ddot{\psi}\dot{\psi} = 0 \Rightarrow \int \vartheta d\vartheta - w^2 \int \dot{\psi} d\dot{\psi} = 0 \Rightarrow \vartheta^2(\psi) - w^2\dot{\psi}^2 = C,$$

wherefrom, considering the conditions $\psi = 0, \dot{\psi} = 0, \vartheta(0) = 0, t \rightarrow \infty$, constant $C = 0$. Since $\vartheta^2(\psi) - w^2\dot{\psi}^2 = (\vartheta(\psi) - w\dot{\psi})(\vartheta(\psi) + w\dot{\psi}) = 0$, we note that solutions to the Equation (A1) have the necessary properties.

Appendix C

Proof of Statement 2. Proof of Statement 2 follows from the resulting estimate of the perturbation as a function of the current state (16). It follows from the last equation of system (6) that, under a best control, we have the inequality $\mathbf{D}\{\psi_1[k] + \lambda_1\psi_1[k-1]\} \geq h^2\mathbf{D}\{\xi[k]\}$, $k = k_0 + 1, \dots$

We substitute the found control (17) into the initial system (6), (7) as a result, after simplification, we obtain the expression:

$$\psi_1[k+1] + \lambda_1\psi_1[k] = -c(\psi_1[k] + \lambda_1\psi_1[k-1]) + h\xi[k+1] + hc\xi[k].$$

Let us represent the last equation as a difference equation $q[k+1] = -cq[k]$, where $q[k] = (\psi_1[k] + \lambda_1\psi_1[k-1]) - h\xi[k]$.

Taking into account the initial condition $q[k_0] = q_0$, we obtain $q[k] = (-c)^{k-k_0}q_0$.

Since the condition $|c| < 1$ holds, then $q[k] = (\psi_1[k] + \lambda_1\psi_1[k-1]) - h\xi[k] \xrightarrow{k \rightarrow \infty} 0$, or $\psi_1[k] + \lambda_1\psi_1[k-1] \rightarrow h\xi[k]$.

The last expression implies the minimum variance of the macro variable $\psi_1[k]$ for the steady state. $\square$

Appendix D

Proof of Statement 3. The results of the theory of invariant dynamical systems [53] imply the validity of the following statement: for the relation $\psi = \psi(X_1, \dots, X_n) = 0$ (here for simplicity the control is scalar) to be an invariant manifold of the system $\dot{X}_i = F_i(X_1, \dots, X_n)$, $i = \overline{1, n}$, it is necessary and sufficient that the following condition be fulfilled:

$$\frac{d\psi}{dt} = \sum_{i=1}^n \frac{\partial \psi(X_1, \dots, X_n)}{\partial X_i} R_i(X_1, \dots, X_n) = \vartheta(\psi) = \vartheta(\psi(X_1, \dots, X_n)),$$

$$R_i(X_1, \dots, X_n) = F_i(X_1, \dots, X_n) + u,$$

where $\vartheta(\psi, X_1, \dots, X_n)$ is a certain single-valued with respect to ψ continuous differentiable function, $\psi = 0 : \vartheta(0) = 0$, $\vartheta(\psi)\psi > 0 \forall \psi \neq 0$, in particular, here we have $\vartheta(\psi, X_1, \dots, X_n) = \omega\psi(X_1, \dots, X_n)$, $\omega = \text{const}$, $\omega > 0$.

The invariant equality $\psi(x_1) = 0$ (see Section 4.1) is provided by the algorithm in two steps. First, from the solution to the functional equation $w_1\dot{\psi}_1(t) + \psi_1(t) = 0$, $t \rightarrow \infty$, for the problem (Φ_1, ψ_1) , $\psi_1 = X_{10} - \varphi$ we obtain external control (20) taking into account the equations of the extended system (18). At step 2, after the decomposition of system (18) on the manifold $X_{10}(t) = \varphi(t)$, $t \rightarrow \infty$, we obtain the expression for internal control (23) from the solution to the functional equation $w_2\dot{\psi}_2(t) + \psi_2(t) = 0$, $t \rightarrow \infty$, for the problem (Φ_2, ψ_2) , $\psi_2 = \psi + \kappa Z$.

The regulator for the object (3) for the purpose (4) of control $\psi^*(x_1) = 0$ is determined by a set of Equations (20) and (23). Substituting the resulting control into system (3), we obtain

$$w_1\dot{\psi}_1 + \psi_1 = w_1(\zeta - Z), \quad Z = \eta \int \psi^* dt.$$

The control (20) obtained from the requirement $w_1\dot{\psi}_1(t) + \psi_1(t) = 0$, $t \rightarrow \infty$, in the state space of the object (3) provides an estimate $|\zeta - Z| < \varepsilon$, $\varepsilon > 0$, starting from some $t_\varepsilon = t_\varepsilon(w_1, w_2, \kappa, \eta)$.

It is also easy to verify that the control designed in accordance with the specified requirement, ensures that the derivative of the Lyapunov function, taken in the form $V = 0.5\psi_1^2$, is negative. Statement 3 has been proved. $\square$

Appendix E

Commentary to Section 3.2 and Formula (11). It is assumed that the delay $\tau_0 > 0$ is a multiple of the value of discretization: $\tau_0 = \nu_0 h$, $\nu_0 = 1, 2, \dots, \nu_*$ (a value ν_* is known). Then, for $\nu_0 = 1$ a transformation of the initial system into a system extended for the immunology model (6), (9) would result in the appearance of five phase variables to compensate for delays in respect of the variables $X_j[k - \nu_j]$, followed by a replacement of the variables $X_j[k - \nu_j]$ by $Y_{j-3}[k]$, $j = 4, 5, 6, 7, 8$, respectively in the right-hand part of the Formula (11), and $\mathbf{Y}[k] = (Y_1, Y_2, Y_3, Y_4, Y_5)^T$, $Y_{j-3}[k+1] = X_j[k]$, $k = k_0, k_0 + 1, \dots$

It should be noted that the high dimension of control plants is not an obstacle to the synergistic design of aggregated controllers due to a specific technique that does not require the solution to systems of difference (differential) equations [9,12].

References

1. Åström, K.; Albertos, P.; Blanke, M.; Isidori, A.; Schaufelberger, W.; Sanz, R. *Control of Complex Systems*; Springer: London, UK, 2001; pp. 239–261.
2. Miroshnik, I.V.; Nikiforov, V.O.; Fradkov, A.L. *Nonlinear and Adaptive Control of Complex Dynamic Systems*; Nauka: Saint Petersburg, Russia, 2000; pp. 325–487.
3. Krasovskii, A.A. *Mathematical and Applied Theory. Selected Works*; Nauka: Moscow, Russia, 2002; pp. 169–238.
4. Åström, K.J. *Introduction to Stochastic Control Theory*; Academic Press: New York, NY, USA; London, UK, 1970; pp. 174–229.
5. Xi, R.; Zhang, H.; Wang, Y.; Sun, S. Overview of the recent research progress for stability and control on random nonlinear systems. *Annu. Rev. Control* **2022**, *53*, 70–82. [\[CrossRef\]](#)
6. Li, W.; Krstic, M. Prescribed-time control of stochastic nonlinear systems with reduced control effort. *J. Syst. Sci. Complex.* **2021**, *34*, 1782–1800. [\[CrossRef\]](#)
7. Kokotovic, P.; Arcak, M. Constructive nonlinear control: A historic perspective. *Automatica* **2001**, *37*, 637–662. [\[CrossRef\]](#)
8. Tyukin, I.Y.; Terekhov, V.A. *Adaptation in Nonlinear Dynamical Systems*; LKI: Saint Petersburg, Russia, 2008; pp. 34–190.
9. Kolesnikov, A.A. *Synergetics and Problems of Control Theory: Collected Articles*; Kolesnikov, A.A., Ed.; Fizmatlit: Moscow, Russia, 2004; pp. 130–204.
10. Andrievskii, B.R.; Fradkov, A.L. Control of chaos: Methods and applications. II. Applications. *Autom. Remote Control* **2004**, *65*, 505–533. [\[CrossRef\]](#)
11. Ott, E.; Grebogi, C.; Yorke, J. Controlling chaos. *Phys. Rev. Lett.* **1990**, *64*, 1196–1199. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Kolesnikov, A.A. *Synergistic Methods of Control Complex Systems: The Theory of System Synthesis*; Librokom: Moscow, Russia, 2012; pp. 71–148.
13. Kolesnikova, S.I. A multiple-control system for nonlinear discrete object under uncertainty. *Optim. Methods Softw.* **2019**, *34*, 578–585. [\[CrossRef\]](#)
14. Din, A.; Ain, Q.T. Stochastic optimal control analysis of a mathematical model: Theory and application to non-singular kernels. *Fractal Fract.* **2022**, *6*, 279. [\[CrossRef\]](#)
15. Nowak, M.; May, R.M. *Virus Dynamics: Mathematical Principles of Immunology and Virology: Mathematical Principles of Immunology and Virology*; Oxford University Press: Oxford, UK, 2000.
16. Marchuk, G.I.; Petrov, R.V.; Romanyukha, A.A.; Bocharov, G. Mathematical model of antiviral immune response. I. Data analysis, generalized picture construction and parameters evaluation for hepatitis B. *J. Theor. Biol.* **1991**, *151*, 1–40. [\[CrossRef\]](#)
17. Marchuk, G.I. *Mathematical Modeling in Immunology and Medicine. Selected Works*; Russian Academy of Sciences: Moscow, Russia, 2018; pp. 62–154.
18. Li, M.; Zu, J. The review of differential equation models of HBV infection dynamics. *J. Virol. Methods* **2019**, *266*, 103–113. [\[CrossRef\]](#)
19. Andrew, S.M.; Baker, C.T.H.; Bocharov, G.A. Rival approaches to mathematical modelling in immunology. *J. Comput. Appl. Math.* **2007**, *205*, 669–686. [\[CrossRef\]](#)
20. Foryś, U. Stability and bifurcations for the chronic state in Marchuk’s model of an immune system. *J. Math. Anal. Appl.* **2009**, *352*, 922–942. [\[CrossRef\]](#)
21. Souza, E.; Lyra, M.; Gleria, I. Critical bifurcations and chaos in a delayed nonlinear model for the immune response. *Chaos Solit. Fractals* **2009**, *42*, 2494–2501. [\[CrossRef\]](#)
22. Singh, A.; Sharma, V.S. Bifurcations and chaos control in a discrete-time prey–predator model with Holling type-II functional response and prey refuge. *J. Comput. Appl. Math.* **2023**, *418*, 114666. [\[CrossRef\]](#)
23. Ivanitsky, G.R. Self-organizing dynamic stability of biosystems far from equilibrium. *Phys.-Usp.* **2017**, *187*, 757–784.
24. Karatueva, N.A.; Kharchenko, R.V. Problems of control for immunological models. *Nonlinear Anal. Real World Appl.* **2006**, *7*, 829–840. [\[CrossRef\]](#)
25. Owolabi, K.M. Numerical solution of diffusive HBV model in a fractional medium. *SpringerPlus* **2016**, *5*, 1643. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Chirkov, M.V. Methodology for Modeling the Control of the Immune Response Process under Conditions of Uncertainty. Ph.D. Thesis, Perm State National Research University, Perm, Russia, 2017.

27. Bolodurina, I.P.; Lugovskova, Y.P. Optimal management of the dynamics of the interaction of the human immune system with infectious diseases. *Bull. Samara State Univ. Nat. Sci. Ser.* **2009**, *8*, 138–153.
28. Kumar, A.; Srivastava, P.K.; Dong, Y.; Takeuchi, Y. Optimal control of infectious disease: Information-induced vaccination and limited treatment. *Phys. A Stat. Mech. Appl.* **2020**, *542*, 123196. [\[CrossRef\]](#)
29. Andryukhina, V.N.; Afanasiev, V.N. Guaranteed control in the problem of the use of antiviral drugs and the results of mathematical modeling. *Control Sci.* **2012**, *3*, 41–48.
30. Kolesnikova, S.I.; Avramyonok, V.A. Synergetic control algorithms for a multidimensional biomedical model under conditions of nonrandom and random disturbances using kernel regression. *J. Phys. Conf. Ser.* **2021**, *1745*, 012094. [\[CrossRef\]](#)
31. Alrabaiah, H.; Safi, M.A.; DarAssi, M.H.; Al-Hdaibat, B.; Ullah, S.; Khan, M.A.; Ali Shah, S.A. Optimal control analysis of hepatitis B virus with treatment and vaccination. *Results Phys.* **2020**, *19*, 103599. [\[CrossRef\]](#)
32. Azanov, V.M. Optimal control of a discrete-time stochastic system with a probabilistic criterion and a non-fixed terminal time. *Autom. Remote Control* **2020**, *81*, 2143–2159. [\[CrossRef\]](#)
33. Elaiw, A.M.; AlShamrani, N.H. Stability of a general adaptive immunity virus dynamics model with multi-stages of infected cells and two routes of infection. *Math. Methods Appl. Sci.* **2019**, *43*, 1145–1175. [\[CrossRef\]](#)
34. Khodaei-mehr, J.; Tangestanizadeh, S.; Vatankhah, R.; Sharifi, M. ANFIS-based optimal control of hepatitis C virus epidemic. *IFAC-Papers Online* **2018**, *51*, 539–544. [\[CrossRef\]](#)
35. Qaiser, H.; Ahmad, I.; Kashif, M. Fuzzy, synergetic and non-linear state feedback control of chemotherapy drug for a cancerous tumor. *Biomed. Signal Process. Control* **2020**, *62*, 102061. [\[CrossRef\]](#)
36. Khatun, Z.; Islam, M.S.; Ghosh, U. Mathematical modeling of hepatitis B virus infection incorporating immune responses. *Sens. Int.* **2020**, *1*, 100017. [\[CrossRef\]](#)
37. Kolesnikova, S.I. Synthesis of controller for vector plant, based on integral adaptation method for disturbance suppression. *Differ. Uravn. Protsey Upr.* **2022**, *3*, 27–45. Available online: <https://diffjournal.spbu.ru/pdf/22303-jdecp-kolesnikova.pdf> (accessed on 1 October 2023).
38. Krasovskii, A.A. Problems of physical control theory. *Autom. Remote Control* **1990**, *51*, 1459–1479.
39. Rastrigin, L.A. *Adaptation of Complex Systems*; Zinatne: Riga, USSR, 1981; pp. 13–47.
40. Derevitsky, D.P.; Fradkov, A.L. Two models for analyzing dynamics of adaptation algorithms. *Autom. Remote Control* **1974**, *35*, 59–67.
41. Ljung, L. Analysis of recursive stochastic algorithms. *IEEE Trans. Automat. Contr.* **1977**, *22*, 551–575. [\[CrossRef\]](#)
42. Kailash, C.P.; Shikongo, A. The application of asymptotic analysis for developing reliable numerical method for a model singular perturbation problem. *J. Numer. Anal. Ind. Appl. Math.* **2007**, *2*, 193–207.
43. Jerray, J.; Saoud, A.; Fribourg, L. Asymptotic error in Euler’s method with a constant step size. *Eur. J. Control* **2022**, *68*, 100694. [\[CrossRef\]](#)
44. Astolfi, A.; Karagiannis, D.; Ortega, R. *Nonlinear and Adaptive Control with Applications*, 187; Springer: London, UK, 2008; pp. 115–150. [\[CrossRef\]](#)
45. Kesić, S. Rethinking the pragmatic systems biology and systems-theoretical biology divide: Toward a complexity-inspired epistemology of systems biomedicine. *Med. Hypotheses* **2019**, *131*, 109316. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Saridis, J. *Self-Organizing Stochastic Control Systems*; Nauka: Moscow, USSR, 1980; pp. 308–370.
47. Burnet, F.M. A modification of Jerne’s theory of antibody production using the concept of clonal selection. *Aust. J. Sci.* **1957**, *20*, 67–69. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Åström, K.J.; Kumar, P.R. Control: A perspective. *Automatica* **2014**, *50*, 3–43. [\[CrossRef\]](#)
49. Yerugin, N.P. Construction of the whole set of differential equations having a given integral curve. *Appl. Math. Mech.* **1952**, *10*, 659–670.
50. Johnson, S. Theory of regulators adapting to disturbances. In *Filtering and Stochastic Control in Dynamical Systems*; Leondes, K.T., Ed.; Mir: Moscow, USSR, 1980; pp. 254–296.
51. Åström, K.J.; Wittenmark, B. *Adaptive Control*, 2nd ed.; Dover Publications: New York, NY, USA, 2008; pp. 137–369.
52. Forsyth, A.R. *Calculus of Variations*; Dover: New York, NY, USA, 1960; pp. 17–20.
53. Galiullin, A.S. Inverse problems of dynamics and control problems of motions of material systems. *Differ. Equ.* **1972**, *8*, 1535–1541.
54. Averina, T.A.; Karachanskaya, E.V.; Rybakov, K.A. Statistical analysis of diffusion systems with invariants. *Russ. J. Numer. Anal. Math. Model.* **2018**, *33*, 1–13. [\[CrossRef\]](#)
55. Bodnar, M.; Forsys, U. Behavior of solutions to Marchuk’s model depending on a time delay. *Intern. J. Appl. Math. Comput. Sci.* **2000**, *10*, 101–116.
56. Pogozhev, I.B. *Application of Mathematical Models of Diseases in Clinical Practice*; Nauka: Moscow, USSR, 1988; pp. 35–174.
57. Buldayev, A.S. A numerical method of control optimization in delay systems for immune response modelling. *USSR Comput. Math. Math. Phys.* **1990**, *30*, 18–28. [\[CrossRef\]](#)

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