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Maximum response perturbation-based control of virus infection model with time-delays

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Abstract: A new method for constructing the multi-modal impacts on the immune system in the chronic phase of viral infection, based on mathematical models formulated with delay-differential equations is proposed. The so called, optimal disturbances, widely used in the aerodynamic stability theory for mathematical models without delays are constructed for perturbing the steady states of the dynamical system for maximizing the perturbation-induced response. The concept of optimal disturbances is generalized on the systems with delayed argument. An algorithm for computing the optimal disturbances is developed for such systems. The elaborated computational technology is tested on a system of four nonlinear delay-differential equations which represents the model of experimental infection in mice caused by lymphocytic choriomeningitis virus. The steady-state perturbations resulting in a maximum response were computed with the proposed algorithm for two types of steady states characterized by a low and a high levels of viral load. The possibility of correction of the infection dynamics and the restoration of virus-specific lymphocyte functioning of the immune system by perturbing the steady states is demonstrated.

Keywords: Virus infection, mathematical model, delay-differential equations, steady state, perturbation, multi-modal perturbations, persistence, optimal disturbances.

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The dynamics of human virus diseases is characterized by a variety of courses and outcomes including acute-, chronic-, and lethal infections. The establishment of chronic infection significantly increases the risk of development of other pathological states such as cancer, autoimmune diseases, concomitant infections and damage of cardiovascular or nervous systems. The problem of studying the mechanisms of the chronic virus infections development and approaches to their treatment was postulated as one of the central task of mathematical modelling in immunology in fundamental works of G.I. Marchuk [18, 19]. He proposed a new approach to cure the chronic infections using the results of stability analysis of the steady-states of the basic mathematical model of infectious disease. The approach is based on perturbing the chronic infection via exacerbation, leading to transition of the infection state from the chronic one to an acute with recovery. This paradigm of the system performance analysis by means of the perturbation of its dynamics was later extensively utilized in mathematical analysis of immune processes in various virus diseases, e.g., the human immunodeficiency virus (HIV) infection which is characterized by chronic dynamics and lethal outcome [23, 25].

Nowadays, the ideas of systems analysis postulated in biomedicine as 'system biology' [14] are widely used in mathematical immunology. The research focus of systems immunology is on the dynamics, structure and regulation mechanisms of immune processes. The property of robustness, i.e., the functional resistance of the immune system to external perturbations, is considered to be the major principle of its organization and functioning. In general, the robustness is a key feature of any self-regulating biological system organization

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[9, 16]. For example, HIV infection can be considered as a robust 'virus—host' system [15]. The robustness of self-regulating system implies the fragility of the system to certain combination of disturbances [9, 26]. The search for proper disturbances of system parameters or system states to develop effective treatment of the robust disease state can be performed via the sensitivity analysis of the underlying mathematical model of disease.

This study is aimed to investigate the possibility for constructing the compensatory impacts on the immune system during a chronic phase of virus infection by mathematical modelling methods. To this end, we consider previously developed mathematical model of experimental murine infection with lymphocytic choriomeningitis virus (LCMV) [1]. This model, formulated as a system of four non-linear delay-differential equations (DDEs), is briefly described in Section 1 of the paper.

To perturb stable steady states of the system, we propose to use optimal disturbances which are widely used in the aerodynamic stability theory for the mathematical models without delays. In aerodynamics, the following two scenarios of the laminar-turbulent transition (LTT) are considered: natural (at high Reynolds numbers) and bypass (at low Reynolds numbers) ones [5]. As the Reynolds number of a nearwall shear flow increases, it usually reaches a critical value, above which the flow loses its stability to infinitesimal disturbances that leads to its turbulization (natural scenario). However, in practice LTT often occurs at subcritical Reynolds numbers (bypass scenario) due to transient disturbances which consist of a large number of essentially mutually non-orthogonal stable modes and whose development is accompanied by a significant increase of their kinetic energy in finite time intervals. Among them, the maximum energy increase is attributed to so-called optimal disturbances. They develop to quasi-stationary streaks which modify the basic flow to a quasi-stationary linearly unstable state prone to LTT. Up to now, the analysis of bypass scenarios for systems with delays have not been carried out. For such systems one needs to introduce physically justified analogues of optimal disturbances. This new concept is described in Section 2 of the paper.

In Section 3 a direct algorithm for computing the optimal disturbances is proposed for delay systems. This algorithm is not optimal. Previously developed methods [3, 4, 22] allow one to compute optimal disturbances with a given accuracy for non-delay systems of ordinary differential equations using the Schur decomposition and a low-rank approximation. In future, it is advisable to generalize these significantly more efficient approaches, as well as the methods proposed in recent paper [21] for systems with large sparse matrices, on the delay-systems.

Section 4 presents computational results obtained with the developed technology for the model of LCMV infection. The disturbances providing the maximum response of the system were found for steady states of this model using proposed direct algorithm. We considered two types of steady states characterized by a low- and a high viral load, respectively [17]. The first type is relevant to the treatment of persistent virus infections characterized by the number of viruses in the organism below the conventional detection limit. Note that infections characterized by low level viral persistence present difficulties for organ transplantations which are often accompanied by exacerbation of latent infection due to immunosuppression. The high viral load persistence is typically observed in infections with HIV, viral hepatitis C and B. Their treatment is a problem of critical importance for public health. Both antiviral and immunomodulatory drugs which are used to control the infection dynamics, have side effects. Therefore, the issue of minimizing drug dozes while preserving the system response level is a crucial component of the efficient treatment strategy development. Taking this into account, we investigated the possibility for correction of LCMV infection dynamics and functional recovery of T lymphocyte responses by computing small perturbations of the steady states which result in a maximal response of the model solution.

The overall results of our study are summarized in Section 5.

1 Mathematical model of LCMV infection and its steady states

The basic mathematical model of LCMV infection in mice proposed and analyzed in [1, 17] is formulated as a system of non-linear delay-differential equations. The system describes the dynamics of the following time-

Table 1: Biological meaning of the model (1.1) parameters.

Parameter	Biological meaning
β	Viruses replication rate constant
γ_{VE}	Rate constant of virus clearance due to effector CTLs
V_{mvc}	Maximum possible virus concentration in spleen
τ	Typical duration of CTL division cycle
b_p	Rate constant of CTL stimulation
b_d	Rate constant of CTL differentiation
ϑ_p	Cumulative viral load threshold for anergy induction in precursor CTLs
ϑ_E	Cumulative viral load threshold for anergy induction in effector CTLs
α_{E_p}	Precursor CTL natural death rate constant
α_{E_e}	Effector CTL natural death rate constant
E_p^0	Concentration of precursor CTLs in spleen of unprimed mouse
τ_A	Typical duration of CTL commitment for apoptosis
α_{AP}	Precursor CTL apoptosis rate constant
α_{AE}	Effector CTL apoptosis rate constant
b_W	Rate constant of cumulative viral load increase
α_W	Rate constant of restoration from the inhibitory effect of cumulative viral load

dependent variables: concentration of viruses $V(t)$, population densities of two LCMV-specific cytotoxic lymphocytes (CTLs) — precursors $E_p(t)$ and effectors $E_e(t)$, and the cumulative viral load $W(t)$,

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}V(t) &= \beta V(t)\left(1-\frac{V(t)}{V_{mvc}}\right) - \gamma_{VE}E_e(t)V(t)\\
\frac{\mathrm{d}}{\mathrm{d}t}E_p(t) &= \alpha_{E_p}(E_p^0 - E_p(t)) + \beta_p g_p(W)V(t-\tau)E_p(t-\tau) - \alpha_{AP}V(t-\tau_A)V(t)E_p(t)\\
\frac{\mathrm{d}}{\mathrm{d}t}E_e(t) &= b_d g_e(W)V(t-\tau)E_p(t-\tau) - \alpha_{AE}V(t-\tau_A)V(t)E_e(t) - \alpha_{E_e}E_e(t)\\
\frac{\mathrm{d}}{\mathrm{d}t}W(t) &= b_W V(t) - \alpha_W W(t)
\end{aligned} \tag{1.1}$$

where $g_p(W) = 1/(1+W/\vartheta_p)^2$, $g_e(W) = 1/(1+W/\vartheta_E)^2$. The biological meaning of parameters is explained in Table 1.

To determine the solution of system (1.1) for $t > 0$, it is necessary and sufficient to define the following initial functions: $V(t)$ for $-\tau_A \leqslant t \leqslant 0$, $E_p(t)$ for $-\tau \leqslant t \leqslant 0$, and the values $E_e(0)$ and $W(0)$. However, we will assume for the sake of generality that the initial conditions for all variables are specified on $\tau_A \leqslant t \leqslant 0$.

The initial value problem for system (1.1) with non-negative initial conditions and non-negative parameters has a unique non-negative solution in any finite time interval $[0, T]$. This can be proved using the technique described in [19], which is based on the Bellman's method of steps and makes use of a linear ordinary differential equations system majorizing the right-hand side of the DDEs system.

Let us denote the vector of system (1.1) state space variables as

$$U(t) = (V(t), E_p(t), E_e(t), W(t))^T \tag{1.2}$$

to express this system in the following compact form:

$$\frac{\mathrm{d}}{\mathrm{d}t}U(t) = F(U(t), U(t-\tau), U(t-\tau_A)). \tag{1.3}$$

As mentioned above, we assume that the vector of variables $U(t)$ is defined for $-\tau_A \leqslant t \leqslant 0$.

Model (1.3) has different steady states for different sets of parameters. In this study we used two parameter sets for which the stable steady states were found. The steady states were computed using Newton's method applied to non-linear equation $\Phi(U) = 0$, where $\Phi(U) = F(U, U, U)$. The numerical search of parameter sets which provide steady states of (1.3) with required properties, as well as the corresponding initial values for Newton's method, was based on results of numerical bifurcation analysis from [17]. The steady states

Table 2: The parameter values corresponding to stable steady states $\overline{U}_I$ and $\overline{U}_{II}$.

Parameter	Units	$\overline{U}_I$	$\overline{U}_{II}$
β	1/day	1.2	0.08
E_p^0	cell/ml	10^6	10^3
b_p	ml/(particle·day)	$7.73 \cdot 10^{-5}$	$1 \cdot 10^{-5}$
b_d	ml/(particle·day)	$7.73 \cdot 10^{-4}$	$5 \cdot 10^{-4}$
ϑ_p	particle/ml	$3 \cdot 10^6$	10
ϑ_E	particle/ml	$1 \cdot 10^5$	$1.8 \cdot 10^6$
γ_{VE}	ml/(cell·day)	$1.34 \cdot 10^{-6}$	
V_{mvc}	particle/ml	$4.82 \cdot 10^7$	
α_{E_p}	1/day	0.5	
α_{E_e}	1/day	0.1	
τ	day	0.4	
τ_A	day	5.6	
α_{AP}	$(\text{ml/particle})^2$/day	$7.5 \cdot 10^{-16}$	
α_{AE}	$(\text{ml/particle})^2$/day	$4.36 \cdot 10^{-14}$	
b_W	1/day	1	
α_W	1/day	0.11	

representing two types of chronic LCMV infection differing in the viral load were found by varying parameters in the admissible region specified in [17] and are described below.

The first steady state represents the latent form of infection with a low viral load and a high level of memory T cells [7]. The second one represents a symptomatic chronic infection with a high viral load and partial exhaustion/depletion of virus-specific T lymphocytes [8, 20]. In the first case, the perturbation of the system can be intended for the activation of infectious process with subsequent clearance of virus reservoir by immune response or for a direct infection elimination. In the second case, the perturbation-based treatment can be intended for the restoration of responsiveness of exhausted components of the immune system followed by decreasing the viral load. Both of these scenarios are relevant for HIV infection. They correspond to different infection phenotypes observed in 'elite-controllers' and 'progressors', respectively (see [11, 13]).

The parameter values, corresponding to the stable steady states $\overline{U}_I$ and $\overline{U}_{II}$, are given in Table 2. The values of the model variables of these steady states are given in Table 3.

2 Optimal disturbances of steady states

We are interested in the behaviour of system (1.3) near a stable steady state $\overline{U}$. Writing an arbitrary solution near the steady state as $U(t) = \overline{U} + \varepsilon U'(t) + O(\varepsilon^2)$, where ε is a real parameter with small magnitude, substituting this solution into (1.3) and requiring that the obtained equation holds for all ε in the neighbourhood of zero, we obtain the following system of linear differential equations for $U'(t)$:

$$\frac{\mathrm{d}}{\mathrm{d}t}U'(t) = L_0 U'(t) + L_\tau U'(t-\tau) + L_{\tau_A} U'(t-\tau_A) \tag{2.1}$$

where

$$L_0 = \begin{pmatrix} \beta - \frac{2\beta\overline{V}}{V_{vmc}} - y_{VE}\overline{E_e} & 0 & -y_{VE}\overline{V} & 0 \\ -\alpha_{AP}\overline{V}\,\overline{E_p} & -\alpha_{E_p} - \alpha_{AP}\overline{V}^2 & 0 & \frac{-2b_p\overline{V}\,\overline{E_p}g_p(\overline{W})}{\vartheta_p+\overline{W}} \\ -\alpha_{AE}\overline{V}\,\overline{E_e} & 0 & -\alpha_{E_e} - \alpha_{AE}\overline{V}^2 & \frac{-2b_d\overline{V}\,\overline{E_p}g_e(\overline{W})}{\vartheta_E+\overline{W}} \\ b_W & 0 & 0 & -\alpha_W \end{pmatrix}$$

Table 3: The values of steady state components and the maximum and minimum values of disturbed ones corresponding to Figs. 1–6 (up to three decimal digits).

		V	E_p	E_e	W
Steady state $\overline{U}_I$		11.5	$1.01 \cdot 10^6$	$8.96 \cdot 10^5$	104
	min	$2.75 \cdot 10^{-10}$	974	$3.98 \cdot 10^5$	$5.49 \cdot 10^{-3}$
Fig.1	$t_{\min}$	69.6	−0.92	-10^{-3}	123
	max	330	$1.08 \cdot 10^6$	$1.58 \cdot 10^6$	$1.12 \cdot 10^3$
	$t_{\max}$	6.63	10.3	11.9	9.13
	min	$1.64 \cdot 10^{-23}$	$9.6 \cdot 10^5$	$1.94 \cdot 10^5$	$8.02 \cdot 10^{-6}$
Fig.2	$t_{\min}$	92	−0.46	−0.46	184
	max	700	$1.13 \cdot 10^6$	$2.03 \cdot 10^6$	$1.82 \cdot 10^3$
	$t_{\max}$	5.55	8.45	9.58	7.46
	min	$5.38 \cdot 10^{-6}$	10^6	$5.37 \cdot 10^5$	$2.59 \cdot 10^{-2}$
Fig.3	$t_{\min}$	45.6	88.2	98.9	79.8
	max	174	$1.06 \cdot 10^6$	$1.39 \cdot 10^6$	703
	$t_{\max}$	107	111	-10^{-3}	110
	min	$9.44 \cdot 10^{-11}$	10^6	$4.4 \cdot 10^5$	$7.48 \cdot 10^{-4}$
Fig.4	$t_{\min}$	58.9	119	132	111
	max	272	$1.08 \cdot 10^6$	$1.6 \cdot 10^6$	947
	$t_{\max}$	139	143	−0.46	142
Steady state $\overline{U}_{II}$		$1.35 \cdot 10^5$	10^3	$5.95 \cdot 10^4$	$1.23 \cdot 10^6$
	min	$6.4 \cdot 10^3$	10^3	$9.45 \cdot 10^3$	$1.8 \cdot 10^5$
Fig.5	$t_{\min}$	8.92	−5.6	17.9	28.4
	max	$1.35 \cdot 10^5$	$3.14 \cdot 10^4$	$6.5 \cdot 10^5$	$1.23 \cdot 10^6$
	$t_{\max}$	−5.6	-10^{-3}	1.57	−5.6
	min	3.96	10^3	25.4	$2.34 \cdot 10^3$
Fig.6	$t_{\min}$	10.7	−5.6	34.4	65.4
	max	$1.35 \cdot 10^5$	$1.53 \cdot 10^5$	$2.45 \cdot 10^6$	$1.23 \cdot 10^6$
	$t_{\max}$	−5.6	-10^{-3}	1.08	−5.6

$$L_\tau = \begin{pmatrix} 0 & 0 & 0 & 0 \\ b_p\overline{E_p}g_p(\overline{W}) & b_p\overline{V}g_p(\overline{W}) & 0 & 0 \\ b_d\overline{E_p}g_e(\overline{W}) & b_d\overline{V}g_e(\overline{W}) & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad L_{\tau_A} = \begin{pmatrix} 0 & 0 & 0 & 0 \\ -\alpha_{AP}\overline{V}\,\overline{E_p} & 0 & 0 & 0 \\ -\alpha_{AE}\overline{V}\,\overline{E_e} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

System (2.1) is referred to as the linearized evolution equations for disturbances. The initial functions of this system are specified, as well as initial functions of system (1.3), for $-\tau_A \leqslant t \leqslant 0$.

For solutions of (2.1) we introduce the following family of local norms at time t:

$$\|U'\|_{D,t} = \left(\int_{t-\tau_A}^{t} \|DU'(\xi)\|_2^2 \, \mathrm{d}\xi \right)^{1/2} \tag{2.2}$$

where D is a given positive-definite diagonal matrix and $\|\cdot\|_2$ is the second (Euclidean) vector norm.

A solution $U'(t) = U'_{\mathrm{opt}}(t)$ of system (2.1) providing the maximum amplification of (2.2) (in comparison with its value at $t = 0$) will be referred to as the optimal disturbance. According to this definition the optimal disturbance gives the value of

$$\max_{t \geqslant 0} \frac{\|U'\|_{D,t}}{\|U'\|_{D,0}}.$$

Since by definition the optimal disturbance is a solution of linear system (2.1) and, hence, it is completely determined by its values for $-\tau_A \leqslant t \leqslant 0$, in construction of optimal disturbances along with the choice of norm, in which the optimization is carried out, it is important to choose an appropriate subspace of functions $[-\tau_A, 0] \to \mathbb{R}^4$ from which we take initial functions. This subspace will be denoted by Ω. For the correctness of considered optimization problems the subspace Ω has to be complete with respect to $\|\cdot\|_{D,0}$. In practice it

is sufficient to choose $\mathcal{Q}$ as the linear span of some finite set of basic functions. This particularly ensures its completeness.

It is convenient to find optimal disturbances in two steps. First we compute the maximum amplification

$$\Gamma(t) = \max_{U'} \frac{\|U'\|_{D,t}}{\|U'\|_{D,0}} \tag{2.3}$$

over all solutions of (2.1) with initial functions being non-zero and belonging to $\mathcal{Q}$. Then we find $t = t_{\text{opt}}$ at which the function $\Gamma(t)$ reaches its maximum value. If there are more than one such t, then for definiteness we choose the smallest of them. Thus,

$$t_{\text{opt}} = \min \arg \max_{t \geqslant 0} \Gamma(t).$$

Then we find

$$U'_{\text{opt}} \in \arg \max_{U'} \frac{\|U'\|_{D,t_{\text{opt}}}}{\|U'\|_{D,0}}.$$

If D and $\mathcal{Q}$ are fixed, then any optimal disturbance provides the same maximum value of the local solution norm. Usually the maximum amplification has only one global maximum while the solution of the second optimization problem is unique up to a non-zero multiplicative constant.

We will use optimal disturbances for perturbing the stable steady states of the original non-linear model (1.3). To do that, we will take

$$U(t) = \overline{U} + \varepsilon \widetilde{U}'_{\text{opt}}(t) \tag{2.4}$$

for $-\tau_A \leqslant t \leqslant 0$ as an initial function where $\widetilde{U}'_{\text{opt}}(t)$ means the normalized optimal disturbance and ε is a real parameter. By varying this parameter, it is possible to increase or decrease the initial perturbation of steady state. If absolute value of ε is small, then it should be expected, that obtained solution $U(t)$ of system (1.3) will be close to (2.4) for $t > 0$. When absolute value of ε is large, due to influence of non-linearity the solution of (1.3) will be significantly different from (2.4) for $t > 0$. The sign of ε plays an important role as well. Depending on it density of the virus population increases or decreases at $t = 0$. If the optimal disturbance in (2.4) is normalized such that the first component of the vector

$$L_0 \widetilde{U}'_{\text{opt}}(0) + L_\tau \widetilde{U}'_{\text{opt}}(-\tau) + L_{\tau_A} \widetilde{U}'_{\text{opt}}(-\tau_A)$$

is positive, then density of the virus population increases at $t = 0$ when $\varepsilon > 0$.

3 Computation of optimal disturbances

Optimal disturbances can be computed on the basis of any difference scheme suitable for solving initial value problems for systems of linear ordinary differential equations with delayed argument. In the present work we use implicit scheme of the second order BDF2 [12] on the uniform grid

$$\{t_k = \delta k : \ k = -m_A + 1, -m_A + 2, \dots\}$$

built in $(-\tau_A, \infty)$ with step $\delta > 0$. Values $m = [\tau/\delta]$ and $m_A = [\tau_A/\delta]$ are the discrete analogues of delays τ and τ_A, respectively, where $[\cdot]$ denotes the integer part. After discretization described above system (2.1) takes the following form

$$\frac{1.5U_k - 2U_{k-1} + 0.5U_{k-2}}{\delta} = L_0 U_k + L_\tau U_{k-m} + L_{\tau_A} U_{k-m_A}, \quad k = 1, 2, \dots \tag{3.1}$$

where U_k is a grid function which approximates $U(t_k)$. It is necessary to set $U_{-m_A+1}, \dots, U_0$ as initial values for solving the initial value problem.

Let us write equation (3.1) in the form

$$U_k = C_1 U_{k-1} + C_2 U_{k-2} + C_m U_{k-m} + C_{m_A} U_{k-m_A} \tag{3.2}$$

where

$$C_1 = 2(1.5I - \delta L_0)^{-1}, \quad C_2 = -0.5(1.5I - \delta L_0)^{-1}$$

$$C_m = (1.5I - \delta L_0)^{-1}\delta L_\tau, \quad C_{m_A} = (1.5I - \delta L_0)^{-1}\delta L_{\tau_A}$$

and I means the identity matrix of order 4, and add to (3.2) the identities $U_j = U_j$, $j = k-1, \ldots, k-m_A+1$. The obtained system of m_A equations can be written in the form

$$X_k = MX_{k-1}, \quad k = 1, 2, \ldots \tag{3.3}$$

where

$$X_k = \begin{pmatrix} U_k \\ \vdots \\ U_{k-m_A+1} \end{pmatrix}, \quad M = \begin{pmatrix} M_{11} & \cdots & M_{1m_A} \\ \vdots & & \vdots \\ M_{m_A1} & \cdots & M_{m_Am_A} \end{pmatrix}. \tag{3.4}$$

Block matrix M in (3.4) is of block order m_A with blocks of order 4. All blocks of this matrix are zero except the subdiagonal blocks $M_{j+1,j} = I$, $j = 1, \ldots, m_A - 1$, and the following four blocks $M_{11} = C_1$, $M_{12} = C_2$, $M_{1m} = C_m$, and $M_{1m_A} = C_{m_A}$ of the first block row.

Due to (3.3) and (3.4), the grid analogue Γ_k of the maximum amplification (2.3) of solution norm can be written as follows:

$$\Gamma_k = \max_{X_0 \in \mathrm{span}Q\setminus\{0\}} \frac{\|HM^kX_0\|_2}{\|HX_0\|_2}$$

where Q is a matrix of size $4m_A \times p$ ($p \leqslant 4m_A$) whose columns form basis in a grid analogue of subspace Ω, span(Q) means the linear span of matrix Q columns, $H = I_{m_A} \otimes D$, D is a diagonal matrix defining the local norm in which optimal disturbances are computed and $\otimes$ means the Kronecker product.

Taking into account that $HX_0 = HQ\xi = \widetilde{Q}\widetilde{\xi}$, where $\widetilde{Q}$ is a matrix obtained by the orthonormalization of columns of HQ, $\xi = Q^*X_0$ and $\widetilde{\xi} = \widetilde{Q}^*HX_0$, we have:

$$\frac{\|HM^kX_0\|_2}{\|HX_0\|_2} = \frac{\|HM^kH^{-1}HX_0\|_2}{\|HX_0\|_2} = \frac{\|HM^kH^{-1}\widetilde{Q}\widetilde{\xi}\|_2}{\|\widetilde{Q}\widetilde{\xi}\|_2} = \frac{\|HM^kH^{-1}\widetilde{Q}\widetilde{\xi}\|_2}{\|\widetilde{\xi}\|_2}$$

and, hence,

$$\Gamma_k = \max_{\widetilde{\xi}\neq 0} \frac{\|HM^kH^{-1}\widetilde{Q}\widetilde{\xi}\|_2}{\|\widetilde{\xi}\|_2} = \|HM^kH^{-1}\widetilde{Q}\|_2.$$

Thus, the computation of Γ_k reduces to computations of $Y_0 = H^{-1}\widetilde{Q}$ and Y_k with recurrent formula $Y_k = MY_{k-1}$ and $\|HY_k\|_2$.

Let k_{opt} be the value of k at which maximum of Γ_k is reached. Computing the normalized right singular vector η of

$$HM^{k_{\mathrm{opt}}}H^{-1}\widetilde{Q} \tag{3.5}$$

corresponding to its largest singular value [10], the initial value X_0^{opt} of the grid analogue X_k^{opt} of optimal disturbance can be found by formula $X_0^{\mathrm{opt}} = H^{-1}\widetilde{Q}\eta$.

It should be noted that to increase the effectiveness of the above algorithm matrix M has to be saved and multiplied by vectors in sparse format.

4 Results of numerical experiments

We found optimal disturbances in subspace Ω of piece-wise constant functions. To this end we split $[-\tau_A, 0]$ into l equal subintervals on which the functions take constant values. The uniform grid with step $\delta = 10^{-2}$ was used for computing the optimal disturbances. We computed two optimal disturbances corresponding to $l = 6$ and 12 for the first steady state $\overline{U}_I$, and one optimal disturbance with $l = 6$ for the second steady state $\overline{U}_{II}$. The local norm weights (diagonal entries of matrix D) for the first two disturbances were taken equal to the inverse values of corresponding components of $\overline{U}_I$. For the second steady state, the optimal disturbance

Table 4: The results of computing the maximum amplification.

Steady state	l	t_{opt}	$\Gamma(t_{opt})$	$\widetilde{\Gamma}(t_{opt})$
$\overline{U}_I$	6	17.0	$2.98 \cdot 10^2$	2.72
$\overline{U}_I$	12	17.0	$4.19 \cdot 10^2$	3.83
$\overline{U}_{II}$	6	23.5	$3.16 \cdot 10^2$	$5.57 \cdot 10^{-2}$

was found in the subspace $\mathbb{Q}$ of functions with zero components $V(t)$ and $W(t)$. As D it was taken the identity matrix of order 4. In all three cases the maximum amplification defined as the largest singular value $\Gamma(t_{opt})$ of matrix (3.5) and the second largest singular value $\widetilde{\Gamma}(t_{opt})$ of this matrix were well separated (see Table 4) that ensures the uniqueness of the computed optimal disturbance up to some non-zero multiplicative constant.

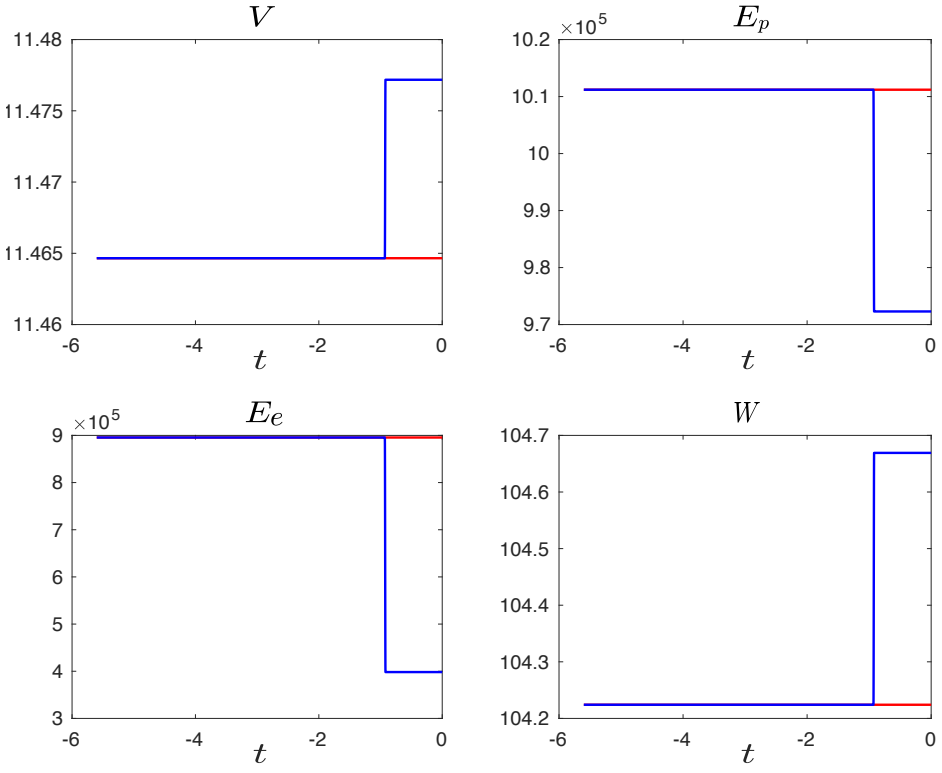
For integrating system (1.3) with initial functions (2.4) we use the same BDF2 scheme as for computing optimal disturbances with the grid step equal 10^{-3}. Optimal disturbances were interpolated on a finer grid using the shape-preserving piece-wise cubic interpolation. The absolute value of parameter ε was selected in order to generate a strong response for a small initial disturbance. Note that the authors of model (1.1) have used the code DIFSUB-DDE [2]. It was designed for solving the stiff systems of nonlinear differential equations with constant delays. The code implements a modification of the linear multistep Gear's method based on BDF schemes of variable order $p \leqslant 6$. The derivative discontinuities up to order $p + 1$ are followed and the Nordsieck interpolation vector is used for approximating the delayed components of the state vector. We used this code as well to verify our computations based on BDF2, and the results were in a good agreement.

For steady state $\overline{U}_I$ initial functions and the results of numerical integration of the corresponding initial value problem are presented in Figs. 1–4. The red lines correspond to the steady states, and the blue ones to the perturbed steady states. In Table 3, the maximum and minimum values of the solution components shown in Figs. 1–4 are displayed rounded to three decimal digits.

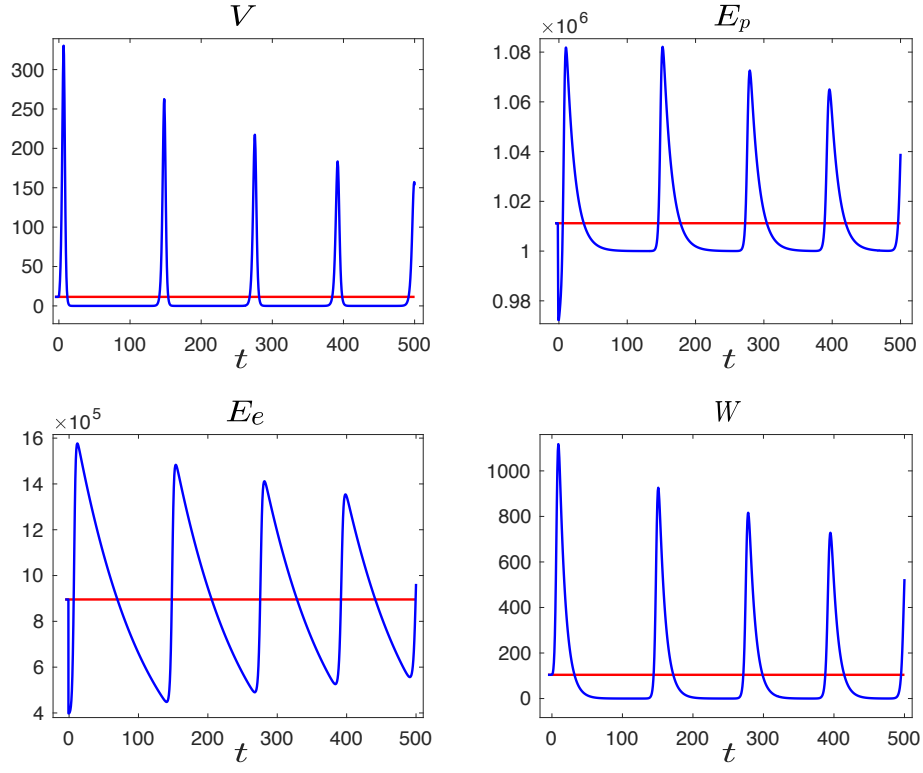
Figure 1 demonstrates the evolution of infectious process as a result of steady state perturbation by increasing the viral load, the cumulative viral load and simultaneously decreasing the T cell population. The steady state with a low level viral load is considered. The perturbation is intended for activation of the infectious process via exacerbation with its subsequent elimination. As illustrated in the figure, the considered optimal disturbance provides the means to reach this goal. It results in a significant increase (by several orders of magnitude) of the viral load followed by clearance of viruses due to strong immune response (see Table 3). This scenario of steady state perturbation corresponds to treatment regimen which temporarily, i.e. for about one day, suppress the immunity and activate the virus growth.

Figure 2 demonstrates the effect of decreasing the duration of perturbation from 1 to 0.5 days and consisting of (i) a more complicated pattern of viral load disturbance consisting of the combination of decline and successive rise of the viral load, (ii) an increase of the cumulative viral load and (iii) a decrease of T lymphocytes population. This type of optimal disturbance also reaches the goal, i.e., it results in a significant increase (by several orders of magnitude) of the viral load with a minor influence on the population of specific T lymphocytes, followed by the decrease of viral population to the level corresponding to a complete clearance. This scenario of perturbation can be viewed as a hypothetical regime of structured treatment of persistent infection, consisting of initially decreasing the virus population and followed by increasing the viral load and by suppressing the specific T cell reactions.

Figure 3 demonstrates the development of infectious process as a result of initial steady state perturbation by decreasing both the viral load and the cumulative viral load and in parallel by increasing the T lymphocyte population. The perturbation of the steady state characterized by a low level viral load is intended for infection elimination without exacerbation. The perturbation duration is 1 day. As the figure shows, this type of optimal disturbance allows one to reach the goal of a significant decrease of viral load to the level of a complete infection elimination. This scenario of perturbation corresponds to the treatment regimen temporarily (for about 1 day) reducing the virus population and in parallel increasing the level of specific T cells (e.g., via to adoptive transfer).

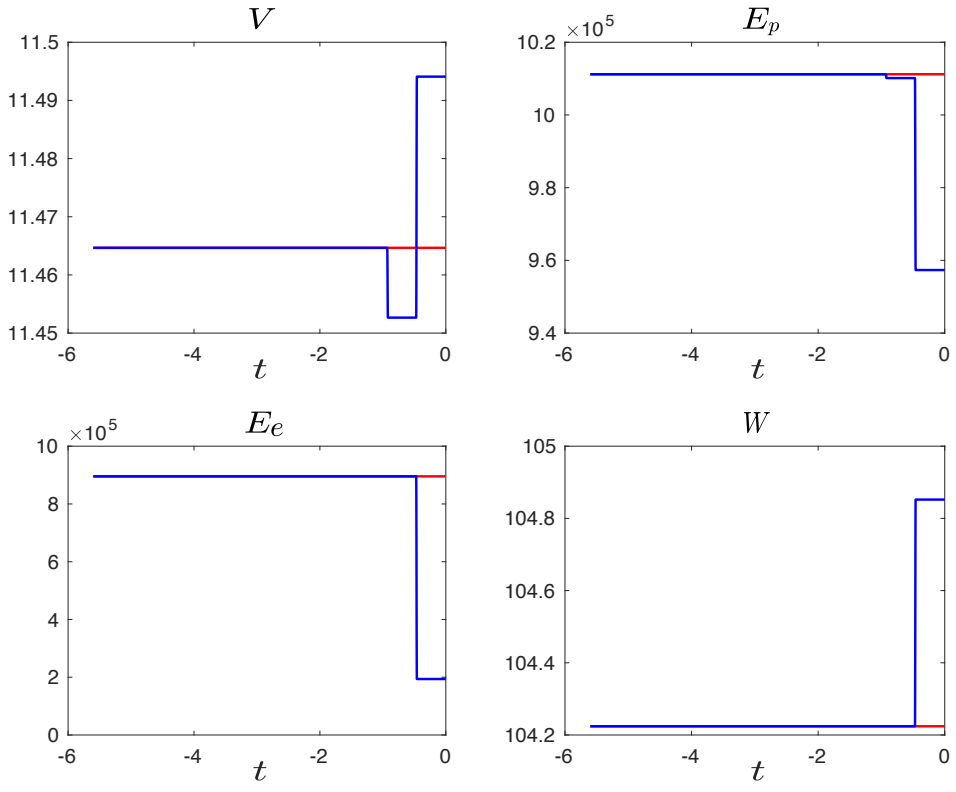


(A)

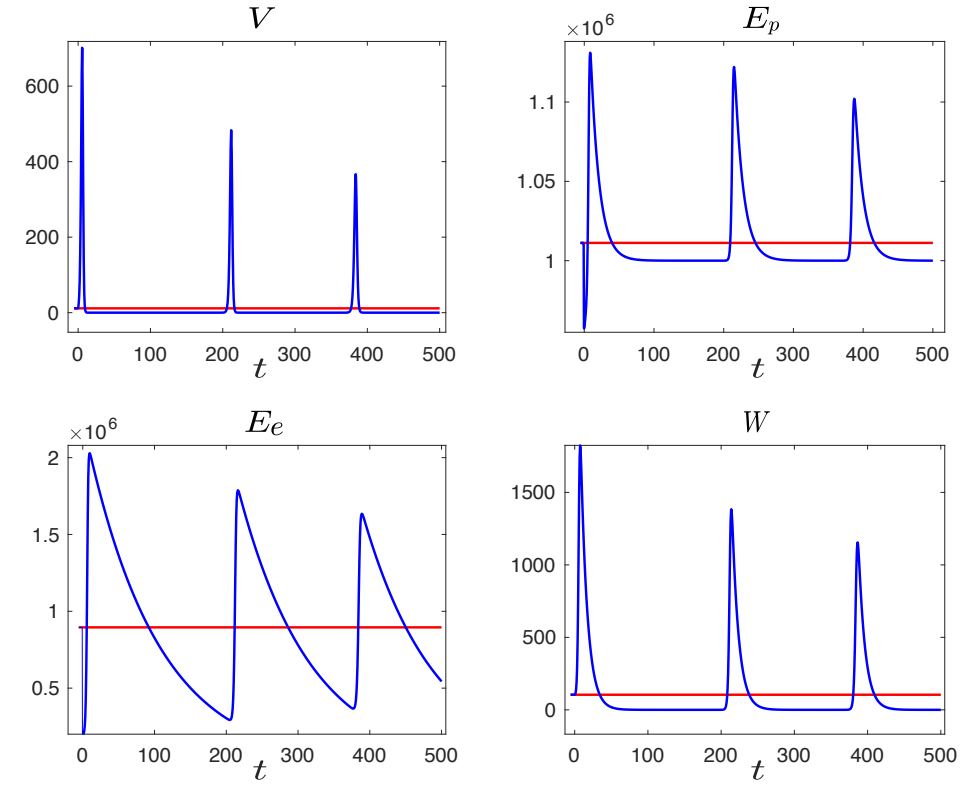


(B)

Figure 1: The initial values (A) and the result of integration of perturbed steady state $\overline{U}_l$ (B) for $l = 6$ and $\varepsilon = 0.15$.

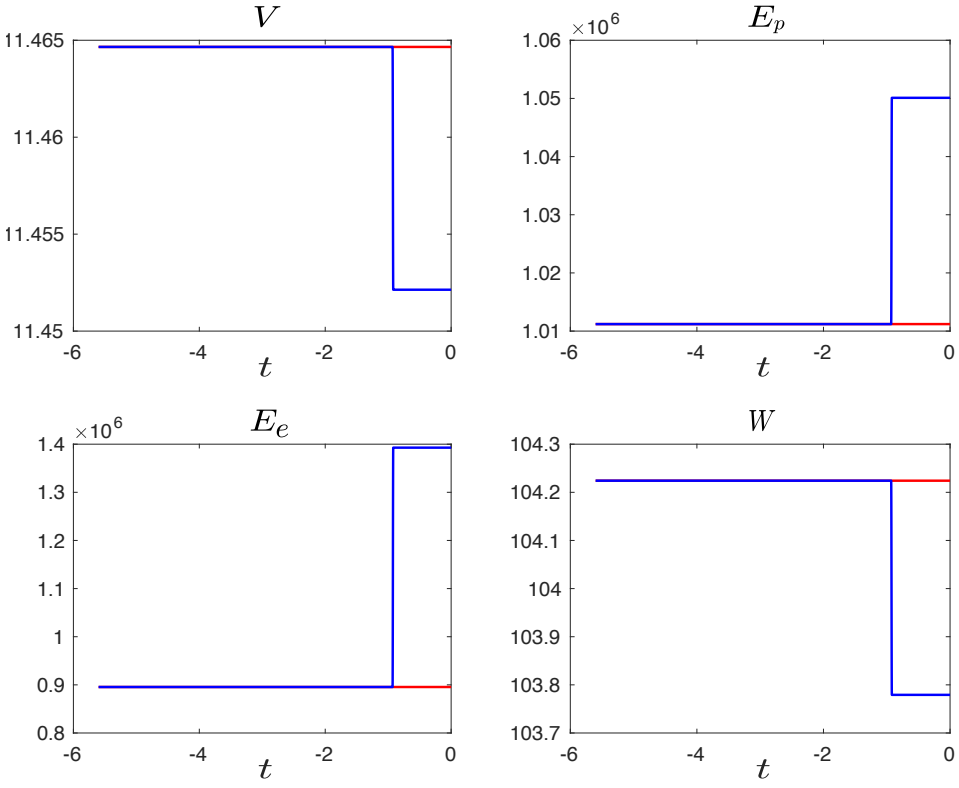


(A)

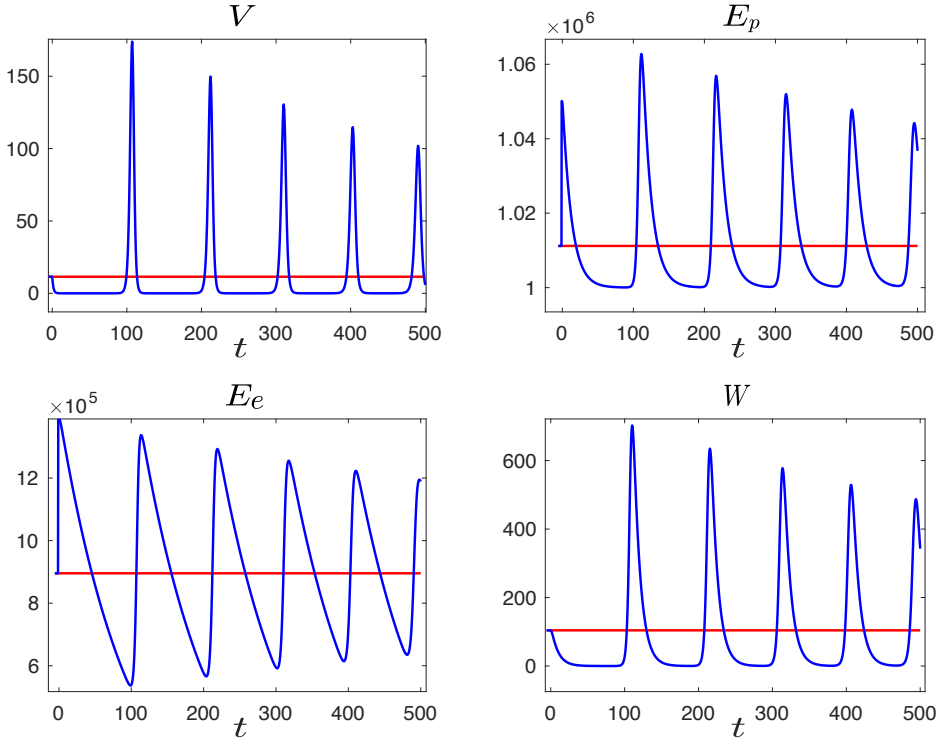


(B)

Figure 2: The initial values (A) and the result of integration of perturbed steady state $\overline{U}_l$ (B) for $l = 12$ and $\varepsilon = 0.15$.

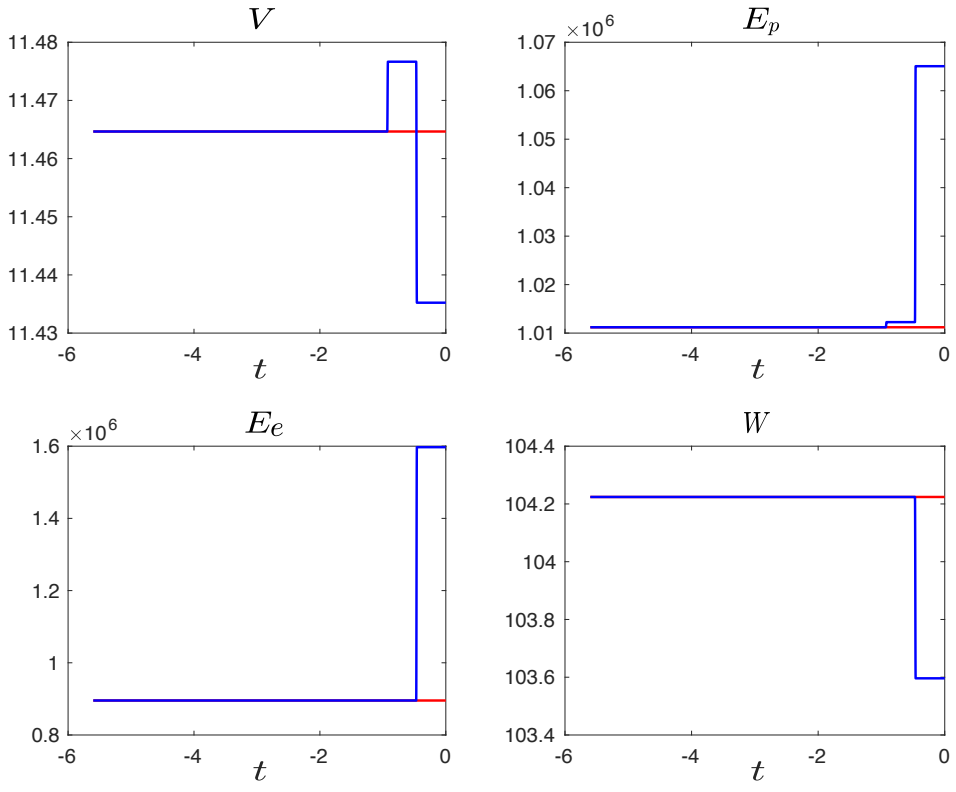


(A)

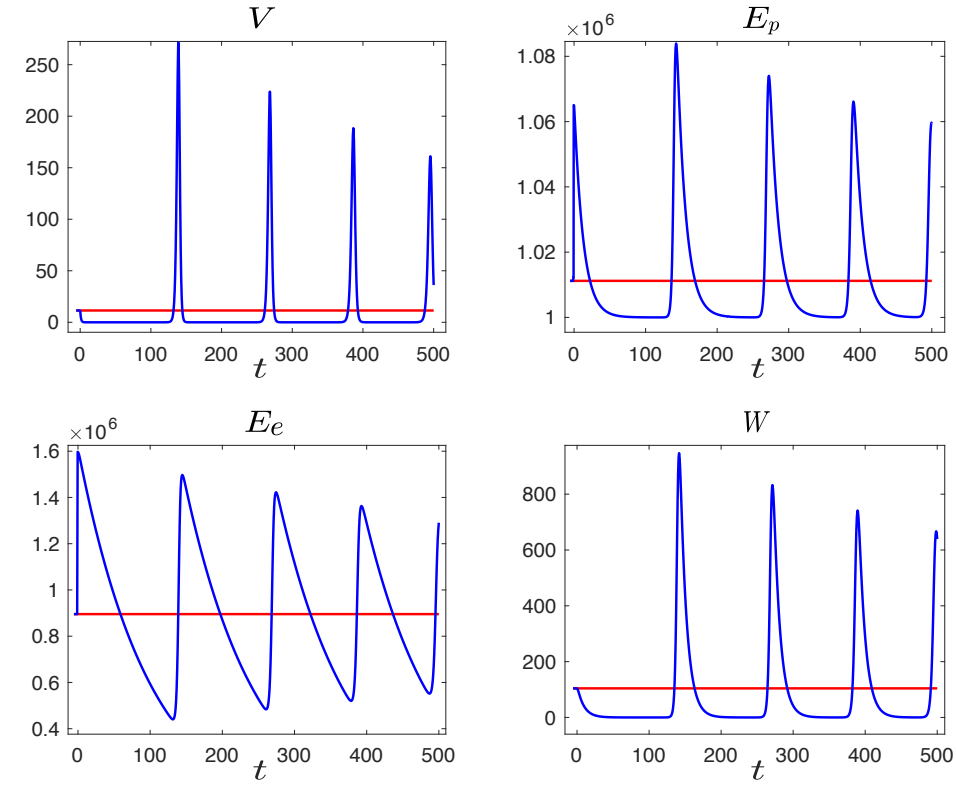


(B)

Figure 3: The initial values (A) and the result of integration of perturbed steady state $\overline{U}_l$ (B) for $l = 6$ and $\varepsilon = -0.15$.

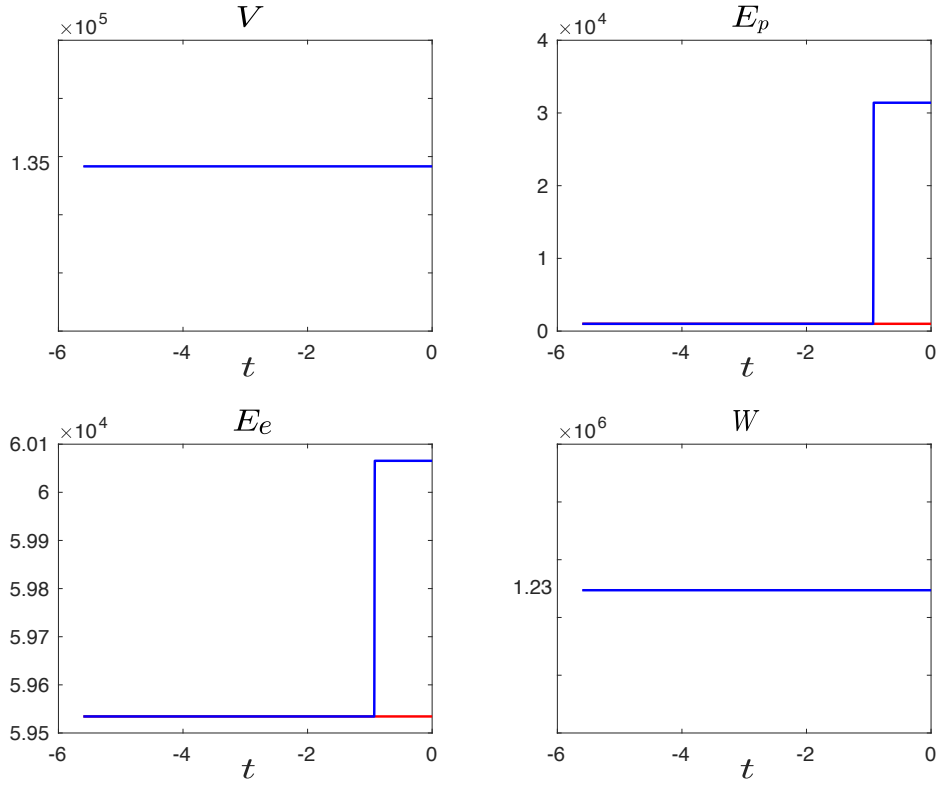


(A)

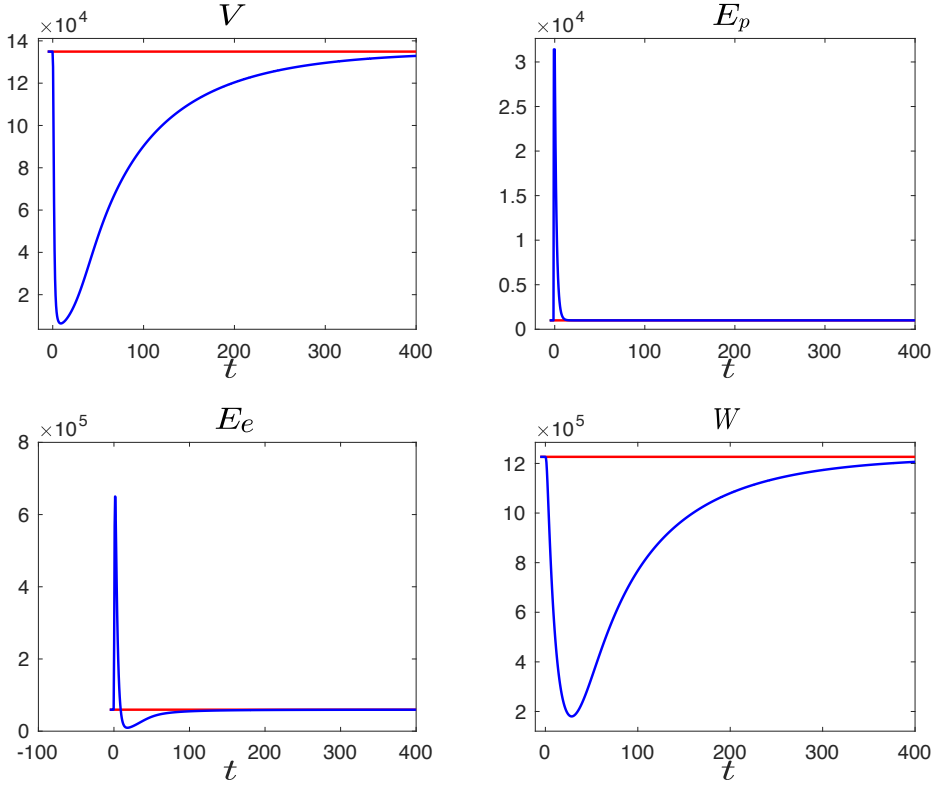


(B)

Figure 4: The initial values (A) and the result of integration of perturbed steady state $\overline{U}_I$ (B) for $I = 12$ and $\varepsilon = -0.15$.

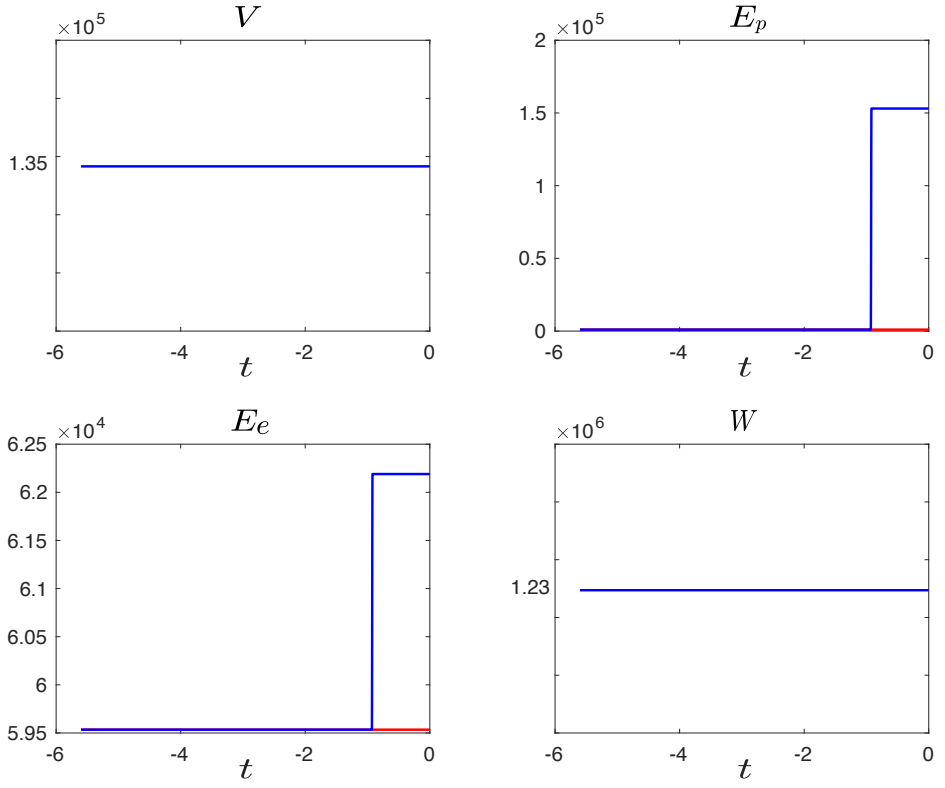


(A)

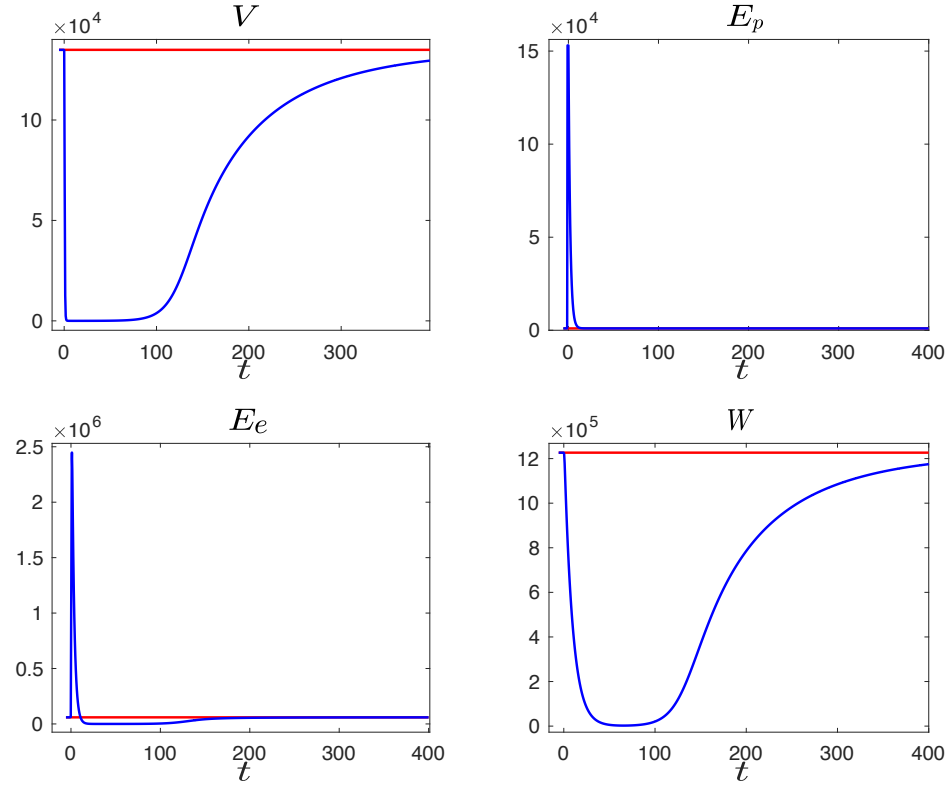


(B)

Figure 5: The initial values (A) and the result of integration of perturbed steady state $\overline{U}_{II}$ (B) for $l = 6$ and $\varepsilon = -0.01$.



(A)



(B)

Figure 6: The initial values (A) and the result of integration of perturbed steady state $\overline{U}_{II}$ (B) for $l = 6$ and $\varepsilon = -0.05$.

Figure 4 illustrates the analysis of the influence of structured treatment regimen on the infectious process development as a result of initial steady state perturbation by combination of increasing and subsequent decreasing of viral load, reduction of cumulative viral load and increase of T lymphocytes population level. The steady state perturbation is intended for elimination of viruses. The duration of initial perturbation is two times shorter than in previous case (see Fig. 3). The figure shows that this type of optimal disturbance permits of a significant decrease (by several orders of magnitude) of the viral load having a minor impact on the level of specific T cells (see Table 3). This perturbation scenario corresponds to the treatment regimen eliminating viruses which persist below the detection limit without activating the infectious process.

The steady state $\overline{U}_{II}$ is characterized by a high viral load. The results of numerical integration corresponding to the perturbed steady state are shown in Figs. 5–6. In the lower part of Table 3 the values of the steady state components along with the maximum and minimum values of the perturbed solution are presented rounded to three decimal digits. Both figures illustrate the development of infectious process caused by the perturbation of the high viral load steady state. The analysis was intended for searching the optimal disturbances which result in activation of the specific immunity and the decrease of viral load. The disturbance duration is set to 1 day.

The structure of perturbed steady state presented in Fig. 5 is characterized by 10-fold increase of the precursor CTLs number, a minor increase (1%) of effector CTLs, and no perturbation of the viral- and cumulative viral loads results in the development of strong immune response, i.e., the effector CTLs increase by 10-fold, and 20-fold decrease of the viral load, which however is not enough for eradication of infection. Figure 6 demonstrates the development of infectious process characterized by 5-fold increase of the perturbation parameter ε. The corresponding perturbation results in the development of immune response which is strong enough for 4000-fold reduction of viral load. This solution can be interpreted as complete elimination of viruses from the organism. Relevant quantitative details of the respective solution are given in Table 3. Thus, we demonstrated the existence of optimal disturbances of the high viral load steady state which lead to transient dynamics with a high-amplitude variation of solution components (primarily, the virus concentration component). This was exactly the main objective of applying external forcing to the system steady state.

5 Conclusion

In this study we examined the response of the mathematical model of experimental infection with LCMV to multimodal perturbation-based control. The primary aim was to develop a computational algorithm for the initial perturbations of the steady states of the system of delay-differential equations, which would result in the system reaction dynamics characterized by a maximal deviation from the respective steady state. This problem is considered to be of crucial relevance for systems immunology as its solution will allow one to design more effective multicomponent treatment regimens of virus diseases, in particular, the HIV infection [6].

To the best of our knowledge, it is the first study in mathematical immunology focusing on implementation of the algorithm for constructing the initial perturbation of the system steady state based on the methodology of 'optimal disturbances' developed in aerodynamics, which are characterized by maximum amplification of the perturbation norm, as the system evolves in time. For two types of stable steady states of the model corresponding to the biologically different phenotypes of virus infections:

(i) low level viral persistence below the detection limit,

(ii) chronic virus infection with a high level viral load and T lymphocyte depletion/exhaustion,

we computed several structurally different types of the initial state perturbations and analyzed their impact on the infection dynamics.

For the first steady state, the perturbations targeting (1) the infectious process activation by means of viral load increase followed by subsequent clearance of the virus reservoir, and (2) the subclinical elimination of infection, were considered. For the second steady state, the perturbations were aimed to reduce the activity of the infectious process with successive clearance of viruses from the host. It should be noted, that in the cases presented above, there was a significant amplification of the initial perturbations for the considered variants

of the system steady state perturbations. Overall, we presented a proof-of-concept concerning the possibility of identifying specially selected optimal disturbances with a small initial (local) norm which have a maximal impact on the system dynamics in terms of some specified criteria.

There remain important issues requiring further study: (1) the significance of the perturbations with small amplitude in specific components of the steady state of model, which are obtained as solution to the optimization problem as described in Section 3; (2) the uniqueness of the solution to the problem of constructing the optimal disturbances under given restrictions on the duration of the disturbances. The definition of the subspace in which the disturbances are looked for must be linked to the characteristics of reaction of infection- and immune processes to the impact of antiviral and immunomodulating drugs and it will be formalized in our future work.

The proposed methodology opens the possibility of developing novel therapeutic approaches in clinical immunology to treat the persistent and chronic infections with minimal dozes of multicomponent drugs having a maximal cure effect. The practical complexity of this problem is caused by necessity to consider multicomponent medical drugs, their pharmacodynamics and pharmacokinetics, and the need to parameterize their effects in models as certain functional relations. In turn, this requires further multidisciplinary studies, including both the problem of development of (1) biologically relevant mathematical models of 'virus—host' interactions taking into account immunopathological processes of infection development, and (2) robust algorithms for computing optimal disturbances of multiparametric mathematical models with a large state space.

In closing, it is appropriate to quote one of the outstanding immunologists William Paul [24] concerning the expected role of mathematics in immunology: '...the immune system offers challenges sufficient to test the growing power of mathematical attack on a biological problem. It is to the quantitative prediction of the outcome of given perturbations in the immune system that we envisage our mathematical/modelling colleagues will apply themselves'. This statement provides a strong motivation for further studies on the development of mathematical methods and models for immunology applications targeted to provide more effective and rational approaches to the treatment of unfavourable courses of infectious diseases.

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