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Computation and analysis of optimal disturbances of periodic solution of the hepatitis B dynamics model

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Abstract — Optimal disturbances of the periodic solution of the hepatitis B dynamics model corresponding to the chronic recurrent form of the disease are found. The dependence of the optimal disturbance on the phase of periodic solution is analyzed. Four phases of the solution are considered, they correspond to clinically different periods of development of the immune response and severity of the disease, namely, activation of antiviral immune reactions, attenuation of reactions, peak and minimum viral load. The possibility of using optimal disturbances to exit the domain of attraction of the considered periodic solution using minimal impact is studied. The components of disturbances that may underlie the phenomenon of spontaneous recovery from chronic hepatitis B observed in clinical practice are identified.

Keywords: Mathematical model, hepatitis B infection, delay differential equations, periodic solutions, optimal disturbances

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Nowadays, one of the widely used theoretical approaches to development of treatment methods for chronic infectious diseases is the use of mathematical models of the disease dynamics and immune response represented by systems of delay differential equations. Stable periodic solutions of such models can be interpreted as chronic forms of the disease. Therefore, in order to study possible ways of treating chronic infections, it is necessary to find multicomponent impacts leading the system out of a stable periodic solution. In [8], the authors proposed to use the so-called optimal disturbances as such impacts.

In this paper, we consider a model of the hepatitis B virus infection dynamics being a calibrated version of the Marchuk–Petrov antiviral immune response model represented by a system of 10 nonlinear delay equations [1, 13]. To study this model, the authors used algorithms and software developed by them earlier to compute stationary and periodic solutions, study their stability, and trace them along the parameters of the system [5–7, 10, 16], and compute optimal disturbances for periodic solutions [8, 9]. This technique was used to find the values of parameters of the hepatitis B dynamics model, at which it has a stable periodic solution with

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a least period of approximately 150 days, corresponding to the chronic form of the disease, and a stable stationary solution with zero viral load, corresponding to the state of a healthy organism. Technically, a periodic solution was sought in a neighborhood of an unstable stationary solution such that the leading (with the maximum real part) eigenvalue of the system linearized with respect to this stationary solution has a non-zero imaginary part.

One of the main goals of this paper is to study the dependence of the optimal disturbances on the solution phase. To do that, we computed and compared optimal disturbances corresponding to the moments of maximum and minimum viral loads of the periodic solution, and also to the moment of increase in the viral load at its average value, which corresponds to development of infection and activation of the immune response, and to the moment of decrease in the viral load at its average value which corresponds to elimination of infection and decrease in the immune response. The possibility to exit the domain of attraction of a stable periodic solution using optimal disturbances is also studied as well as the possibility of transition from a stable periodic solution corresponding to the chronic form of hepatitis B to a stable stationary solution corresponding to the state of a healthy organism.

The paper has the following structure. Section 1 briefly describes the Marchuk–Petrov mathematical model of antiviral immune response. In Section 2, we recall the definition of a disturbance of a stable periodic solution of a system with constant delays optimal at a given time moment introduced by the authors in [8]. The algorithms for computing such a disturbance proposed in [8, 9] are briefly described here. In Section 3, we present and discuss the results of the analysis of optimal disturbances of a stable periodic solution for the hepatitis B dynamics model. Section 4 summarizes the results of the paper.

1. Marchuk–Petrov model

In this paper we use the Marchuk–Petrov mathematical model of antiviral immune response proposed in [1, 13] and studied in [14]. The model is a system of 10 nonlinear differential equations with five constant delays written as

$$\frac{\mathrm{d}u}{\mathrm{d}t}(t) = \mathscr{F}\left(u(t), u(t-\tau_1), \ldots, u(t-\tau_5)\right) \tag{1.1}$$

where $0 < \tau_1 < \ldots < \tau_5$ are delays, u is a 10-component vector function of model variables, and the vector function $\mathscr{F}(v_0, v_1, \ldots, v_5)$ of vector arguments v_0, v_1,..., v_5 is continuously differentiable in the neighborhood $(u(t), u(t-\tau_1), \ldots, u(t-\tau_5))$ for all solutions $u(t)$ considered below and fixed time points t.

The system of equations of the model was given in [7] and describes the rate of change in the concentration of the following populations over time: viral particles V_f; virus-infected target organ cells C_V; destroyed target organ cells m; antigen-presenting cells (macrophages) M_V; $CD4^+$ T-helper lymphocytes of cellular immunity (Th1) H_E; $CD4^+$ T-helper lymphocytes of humoral immunity (Th2) H_B; $CD8^+$T-killer lymphocytes E destroying virus-infected cells; B-lymphocytes B;

Table 1. Varied parameters of the model.

Parameter	Biological meaning	Initial/final value
ρ_F	Rate constant of antibody synthesis by plasma cells	$1.7\cdot10^8/8.5\cdot10^6$ molecules/cell$\cdot$days^{-1}
b_m	Rate constant for destruction of infected hepatocytes due to cytopathicity of viruses	$0.068/0.052$ days^{-1}
ν	Rate constant of viral particle secretion by infected hepatocytes	$83/27.7$ particles/cell$\cdot$days^{-1}
γ_{MV}	The rate constant of antigenic stimulation of macrophages	$1.6\cdot10^{-11}/2.5\cdot10^{-11}$ (particles/ml)$^{-1}\cdot$days^{-1}
b_{CE}	The rate constant of destruction of infected hepatocytes by effector T-lymphocytes	$1.1\cdot10^{-6}/1.1\cdot10^{-5}$ (cells/ml)$^{-1}\cdot$days^{-1}
b_p^E	The rate constant of stimulation of effector T-lymphocytes	$4.1\cdot10^{-9}/4.1\cdot10^{-8}$ (cells/ml)$^{-2}\cdot$days^{-1}
γ_{VF}	The rate constant of neutralization of viral particles by antibodies	$5.0\cdot10^{-10}/5.0\cdot10^{-9}$ (molecules/ml)$^{-1}\cdot$days^{-1}

plasma cells P producing antibodies; antibodies F neutralizing viruses. The following dimensions were used for the variables: particles/ml for V_f, molecules/ml for F, cells/ml for the remaining variables. In the numerical experiments described in Section 3, we used the parameter values from [7] corresponding to acute hepatitis B with the exception of some parameters the values of which were varied when searching for a stable periodic solution. The biological meaning of the parameters being varied and their initial and final values are listed in Table 1.

2. Computation of optimal disturbances

Let the continuously differentiable vector function φ be a periodic solution to system (1.1) and T be its least period. We are interested in continuous solutions to the initial value problem for the following equations linearized with respect to φ:

$$\frac{\mathrm{d}w}{\mathrm{d}t}(t) = L_0(t)w(t) + \sum_{j=1}^{5} L_j(t)w(t-\tau_j) \tag{2.1}$$

where

$$L_j(t) = \frac{\partial \mathscr{F}}{\partial v_j}(\varphi(t), \varphi(t-\tau_1), \ldots, \varphi(t-\tau_5))$$

are real square matrices of order 10, and the initial value is taken as a continuous vector function determined in the interval $-\tau_5 \leqslant t \leqslant 0$.

For the vector of variables of system (2.1) introduce the following family of

local norms at the time moment t:

$$\|w\|_{D,\rho,t} = \left(\int_{t-\tau_5}^{t} \left(\|Dw(\xi)\|_2^2 + \rho \|D\frac{\mathrm{d}w}{\mathrm{d}\xi}(\xi)\|_2^2 \right) \mathrm{d}\xi \right)^{1/2} \tag{2.2}$$

where D is a given positive definite diagonal matrix of order 10, $\|\cdot\|_2$ is the second (Euclidean) vector norm, ρ is a nonnegative parameter. Below we use the L_2-norm $\|w\|_{L_2} = \|w\|_{D,0,t}$ and the W_2^1-norm $\|w\|_{W_2^1} = \|w\|_{D,1,t}$.

The optimal disturbance of the periodic solution φ to system (1.1) at the time moment $t_* \geqslant 0$ is the solution to linearized system (2.1) providing the maximal amplification of local norm (2.2) of the solution at the time moment t_* in comparison with its initial value, i.e., such nonzero $w = w_{\mathrm{opt},t_*}$ that maximizes the value

$$\frac{\|w\|_{D,\rho,t_*}}{\|w\|_{D,\rho,0}}. \tag{2.3}$$

By $\mathscr{Q}$ we denote the subspace of functions $[-\tau_5, 0] \to \mathbb{R}^{10}$ containing functions taken as initial ones in construction of the optimal disturbance. Following [8, 9, 12], for $\mathscr{Q}$ we take the linear span of a finite set of basis functions. Such a choice guarantees the existence of the maximum value of (2.3).

A basic method was proposed in [8] for computation of disturbances of a periodic solution to a time-delay system optimal at a given node $t_k > 0$ of the uniform grid

$$\{t_j = \delta j : \ j = -m_p + 1, -m_p + 2, \ldots\}$$

constructed in the semi-infinite interval $(-\tau_p, \infty)$ with the step $\delta > 0$, and [9] contains its modification using the Lanczos method. Here and below, $m_j = [\tau_j/\delta]$ is a discrete analogue of the delay τ_j, and p is the number of delays. These methods are based on time discretization of system (2.1) by the implicit second order scheme BDF2 [4]. The computation of the optimal disturbance is reduced to computation of the right singular vector of the matrix of transition from the node t_1 to the node t_k corresponding to its maximal singular value. In the basic method, this vector is computed using full singular value decomposition [3], the modification of the basic method uses the Lanczos method for this [15].

We normalize the obtained optimal disturbance in the local L_2-norm and use it to perturb the periodic solution of original nonlinear system (1.1) taking the initial value

$$u(t) = \varphi(t) + \varepsilon \widetilde{w}_{\mathrm{opt},t_*}(t) \tag{2.4}$$

for $-\tau_p \leqslant t \leqslant 0$, where $\widetilde{w}_{\mathrm{opt},t_*}$ means the optimal disturbance normalized in the indicated norm and ε is a real parameter. Varying the absolute value of this parameter, we can increase or decrease the initial disturbance. Depending on the sign of the parameter, a given component of the solution at $t = 0$ begins either to increase or decrease in comparison with the same component of the undisturbed periodic solution with the growth of t.

3. Results

This section describes the results of studying the dependence of optimal disturbances of a stable periodic solution on the solution phase and an analysis of the possibility to exit the domain of attraction of a stable periodic solution using optimal disturbances.

Using the methods for computations, analysis of stability and dependence of stationary and periodic solutions of time-delay systems on the parameters of the model developed earlier [5–7, 10, 16], the values of parameters of the hepatitis B dynamics model, at which it has a stable periodic solution corresponding to the chronic form of the disease, and a stable stationary solution with zero viral load, corresponding to the state of a healthy organism were obtained. Namely, for the final values of the parameters from Table 1, the model has three stationary solutions and the values of state variables from these solutions are given in Table 2. We note that stationary solution I is stable and corresponds to the state of healthy organism, whereas stationary solutions II and III are unstable. The leading eigenvalues of the systems linearized with respect to stationary solutions II and III are 0.003 ± 0.047i and 0.006, respectively. If the stationary solution is unstable and the leading eigenvalue of the system linearized relative to it has a nonzero imaginary part, then a stable periodic solution may exist in a neighborhood of such stationary solution. Only stationary solution II satisfies this condition. Using the method proposed in [6], a stable periodic solution was computed in a neighborhood of this stationary solution, it is shown in Fig. 1. The minimum and maximum values of variables in this solution are given in Table 3.

3.1. Dependence of the optimal disturbance on the phase of the periodic solution

As the subset of functions $\mathscr{Q}$ from which initial functions were taken for computation of optimal disturbances was taken as the linear span of 60 functions qualitatively approximating the behavior of drugs within the framework of single-compartment and two-compartment pharmacokinetic models describing the absorption and elimination of drugs, i.e.,

$$\psi(t,t_j) = \begin{cases} 0, & -\tau_5 \leqslant t < t_j \\ \exp\{-3(t-t_j)\} - \exp\{-9(t-t_j)\}, & t_j \leqslant t \leqslant 0 \end{cases}$$

where $j = -m_5 + [im_5/60] + 1$, $i = 0, 1, \ldots, 59$. The grid step δ was taken equal to $5 \cdot 10^{-3}$, which resulted in $m_5 = 600$. The optimal disturbances were computed in the W_2^1-norm. This provided a sufficiently smooth dependence of the initial value of the optimal disturbance on time [2]. We took the diagonal matrix with diagonal entries equal to values inverse to the components of stationary solution II whose neighborhood contained the considered periodic solution as D.

To analyze the dependence of the optimal disturbance of a periodic solution on the solution phase, consider the disturbances optimal at the time moment equal to the least period T assuming that the solution is in the considered phase at time

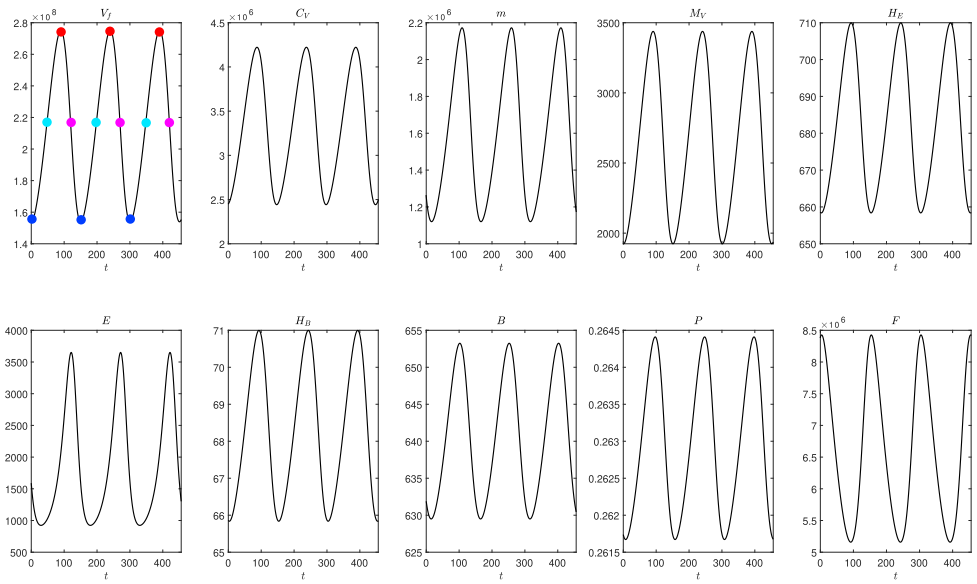

Figure 1. Periodic solution $\varphi(t)$ with the least period $T = 150.24$. Colour code: blue circle — the remission phase $V_f = V_{\min}$, red circle — the phase of exacerbation $V_f = V_{\max}$, turquoise — the phase $V_f = (V_{\max} + V_{\min})/2$ with increasing V_f, violet — the phase $V_f = (V_{\max} + V_{\min})/2$ with decreasing V_f.

$t = 0$. We consider disturbances for the following four phases of the solution: those with the minimum viral load $V_f = V_{\min}$, with the maximum viral load $V_f = V_{\max}$, for $V_f = (V_{\max} + V_{\min})/2$ with increasing V_f, and for $V_f = (V_{\max} + V_{\min})/2$ with decreasing V_f (coloured circles in Fig. 1). Denote these disturbances by $w_{\min}(t)$, $w_{\max}(t)$, $w_{\text{up}}(t)$, and $w_{\text{down}}(t)$, respectively, and note that the selected time points correspond to the stages of remission, exacerbation, development of infection and activation of the immune response, and elimination of infection and reduction of the immune response, respectively. The computed disturbances are shown in Fig. 2, and a component-by-component comparison of the ratio of norms of the computed disturbances to the norm of the periodic solution are shown in Fig. 3.

The analysis of curves presented in Fig. 2 and diagrams shown in Fig. 3 results in the following conclusions. For the phases of remission and exacerbation, the amplitude of the optimal disturbance for all variables except for H_B is less than for the phases of development and elimination of infection. At the same time, the disturbance of the variables C_V, M_V, H_E, E have a multidirectional character for these two groups of phases of an infectious disease.

The optimal disturbance for the phase of minimum viral load $w_{\min}(t)$ significantly changes all components of the state vector except for the B-cellular immune response (components H_B, B, P, F) and the proportion of destroyed hepatocytes (component m). The optimal disturbance for the maximum viral load phase $w_{\max}(t)$ significantly has the same structure and qualitative characteristics as for the minimum viral load phase. However, there is some quantitative difference between the

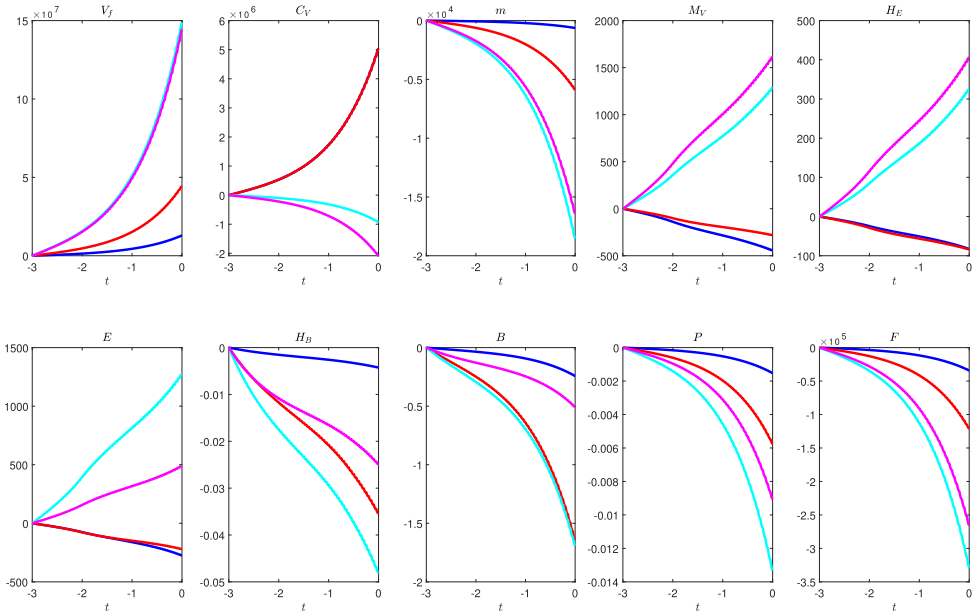

Figure 2. Disturbances optimal in the W_2^1-norm and normalized in the L_2-norm for different stages of infection. Blue line is for the remission $V_f = V_{\min}$, red line is for the stage of exacerbation $V_f = V_{\max}$, turquoise line is for the moment $V_f = (V_{\max} + V_{\min})/2$ with increasing V_f, purple line is for the moment $V_f = (V_{\max} + V_{\min})/2$ with decreasing V_f.

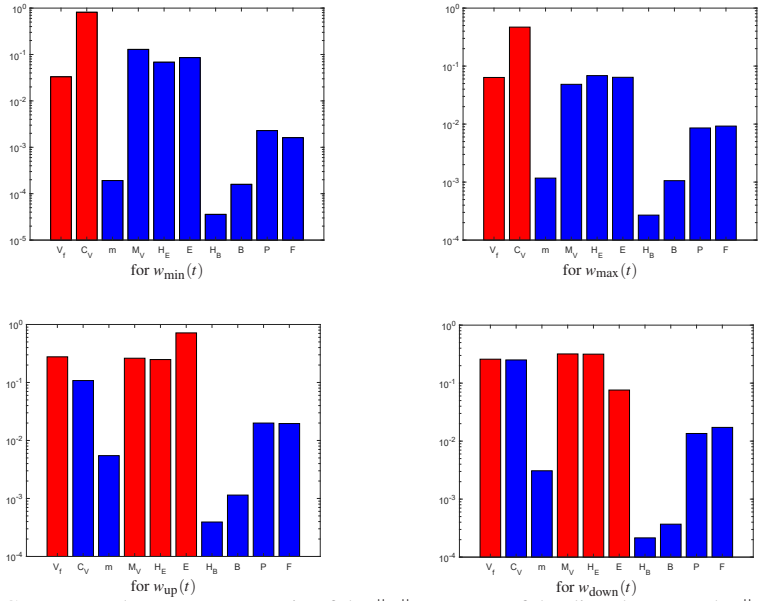

Figure 3. Component-by-component ratio of the $\|\cdot\|_{I,0,t}$ norm of the disturbance to the $\|\cdot\|_{I,0,t}$ norm of the periodic solution, where I is the identity matrix. Red bars correspond to a variable increasing relative to the periodic solution, blue bars are for decreasing ones.

Table 2. Values of model variables in stationary solutions.

	I	II	III
V_f	0	$2.284 \cdot 10^8$	$2.324 \cdot 10^7$
C_V	0	$3.538 \cdot 10^6$	$4.565 \cdot 10^5$
m	0	$1.721 \cdot 10^6$	$1.778 \cdot 10^5$
M_V	0	$2.855 \cdot 10^3$	$2.905 \cdot 10^2$
H_E	602	$6.893 \cdot 10^2$	$6.100 \cdot 10^2$
E	602	$1.910 \cdot 10^3$	$5.853 \cdot 10^2$
H_B	60.2	$6.893 \cdot 10^1$	$6.099 \cdot 10^1$
B	602	$6.437 \cdot 10^2$	$6.056 \cdot 10^2$
P	0.259	0.263	0.259
F	$5.117 \cdot 10^7$	$6.060 \cdot 10^6$	$2.892 \cdot 10^7$

Table 3. Maximum and minimum values of variables in the periodic solution.

	MIN	MAX
V_f	$1.539 \cdot 10^8$	$2.751 \cdot 10^8$
C_V	$2.442 \cdot 10^6$	$4.222 \cdot 10^6$
m	$1.120 \cdot 10^6$	$2.172 \cdot 10^6$
M_V	$1.924 \cdot 10^3$	$3.438 \cdot 10^3$
H_E	$6.584 \cdot 10^2$	$7.100 \cdot 10^2$
E	$9.234 \cdot 10^2$	$3.651 \cdot 10^3$
H_B	65.84	71.00
B	$6.295 \cdot 10^2$	$6.532 \cdot 10^2$
P	0.262	0.264
F	$5.159 \cdot 10^6$	$8.427 \cdot 10^6$

components of the optimal disturbances $w_{\min}(t)$ and $w_{\max}(t)$ in terms of viral load (V_f), the number of infected cells (C_V), activated macrophages (M_V), and the T-cell immune response (H_E, E). The remaining components of the state vector change quantitatively in a similar way or biologically insignificantly.

The optimal disturbance for the phase of infection development and activation of the immune response $w_{\text{up}}(t)$ significantly ($>1\%$) changes all components of the state vector except for the B-cellular immune response (components H_B, B) and the proportion of destroyed hepatocytes (component m), the relative change of which is less than 1%. The same pattern holds with respect to the optimal disturbance for the phase of infection elimination and reduction of the immune response $w_{\text{down}}(t)$. The structure of the components of the optimal disturbances $w_{\text{up}}(t)$ and $w_{\text{down}}(t)$ differs significantly in the values of the number of infected cells (C_V) and the concentration of cytotoxic immune response cells (E). The other components of the state vector change quantitatively in a similar way or biologically insignificantly.

3.2. Transition of the system from a stable periodic solution

The computed optimal disturbances $w_{\min}(t)$, $w_{\max}(t)$, $w_{\text{up}}(t)$, and $w_{\text{down}}(t)$ were also used to analyze the possibility of transition of the system from the obtained stable periodic solution corresponding to the chronic form of hepatitis B to the infection-

free stable stationary solution I with $V_f = 0$ using these disturbances. It should be noted that in all four cases it was possible to make the transition, that is, to achieve the elimination of infection both with the help of an optimal disturbance taken with a negative weight that lowers the viral load, which can be interpreted as treatment with antiviral drugs, and with the help of the same disturbance taken with a positive weight that increases the viral load, which can be interpreted as an exacerbation-type of treatment.

The initial values of the perturbed periodic solution in the interval $[-\tau_5, 0]$ for each of the four disturbances taken with positive (red lines) and negative weights (blue lines) are shown in Figs. 4, 6, 8, and 10. The transitions resulting from disturbance by each of the four perturbations are shown in Figs. 5, 7, 9, and 11. Figures 4 and 6 show that for the phases of remission and exacerbation the disturbances $w_{\min}(t)$ and $w_{\max}(t)$ taken with negative weight suppress viral reproduction, suppress infection of target cells, and enhance the immune response, while the same disturbances taken with positive weight enhance viral reproduction and weaken the immune response. However, as can be seen from Figs. 8 and 10, for the phase of infection development and activation of the immune response and for the phase of infection reduction and weakening of the immune response, the disturbances $w_{\text{up}}(t)$ and $w_{\text{down}}(t)$ taken with positive weight (exacerbation of infection) are characterized by decrease in the intensity of infection and destruction of target cells accompanied by an increase in T-cell immune response.

Figures 4 and 5 show that for successful transition to the infection-free state using the optimal disturbance for the phase of minimal viral load $w_{\min}(t)$, this disturbance can be used with the same absolute magnitude both for the negative weight reducing the viral load and the positive weight increasing the viral load. Figures 6 and 7 show that for successful transition using the optimal disturbance for the phase of maximal viral load $w_{\max}(t)$, the negative weight must be taken two and a half times greater in absolute value than the positive weight. For successful transition using optimal disturbance for the phase of increasing viral load at its average value $w_{\text{up}}(t)$, the positive weight must be taken twice as much in absolute value as the negative weight as shown in Figs. 8 and 9. And for successful transition using the optimal disturbance for the phase of decreasing viral load at its average value $w_{\text{down}}(t)$, this disturbance can be taken with negative and positive weights of the same absolute magnitude as presented in Figs. 10 and 11. Notice that the optimal disturbance for the phase of minimal viral load in the amplification mode and the suppression mode of viral infection leads to elimination of infection in 300 and 450 days, respectively. The optimal disturbance for the phase of maximal viral load in the mode of amplification of viral infection leads to elimination of infection in significantly shorter time, about 350 days, than in the mode of suppression of viral infection which requires about 700 days. Optimal disturbances for the phases of increasing viral load at its average value and of decreasing viral load at its average value lead to elimination of infection in about the same time. In virus infection amplification mode, this happens in about 450 days, and in virus suppression mode in about 700 days. Thus, the best result in terms of the minimality of the local norm of

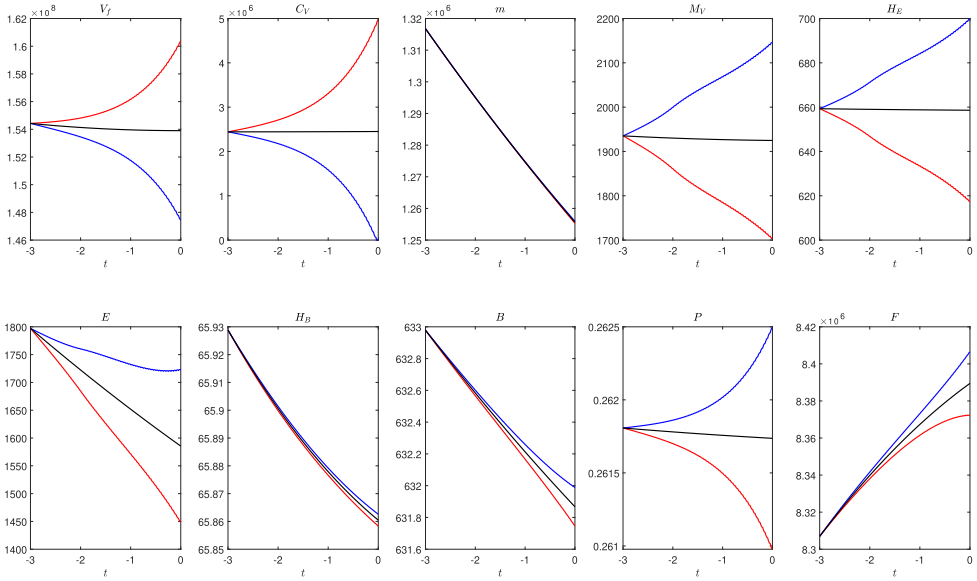

Figure 4. Initial values of the periodic solution (black line) and its disturbed values at the stage of remission with the weight $\varepsilon = -0.5$ (blue line) and with the weight $\varepsilon = 0.5$ (red line).

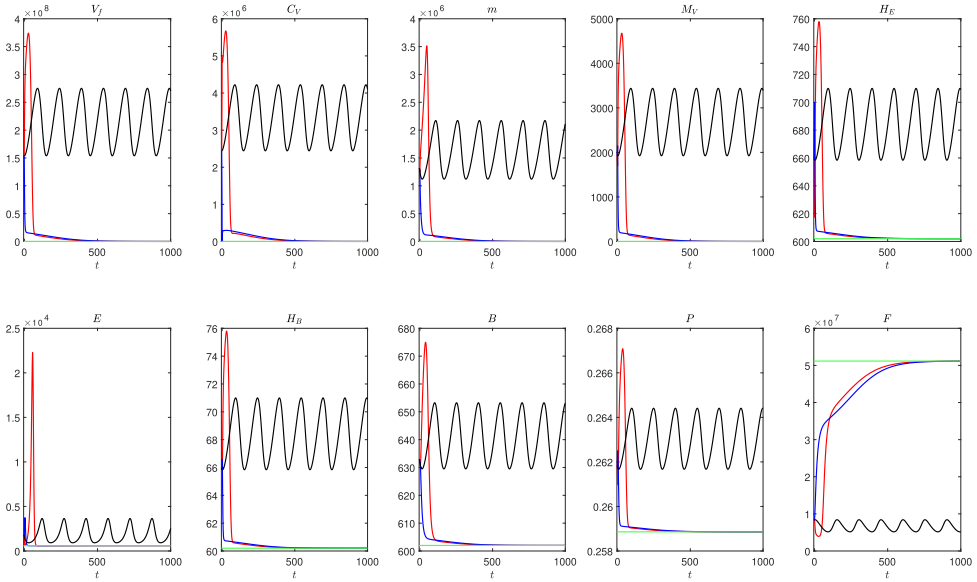

Figure 5. The periodic solution $\varphi(t)$ (black line), its disturbed values at the stage of remission with the weight $\varepsilon = -0.5$ (blue line), with the weight $\varepsilon = 0.5$ (red line), and stationary solution I with $V_f = 0$ (green line).

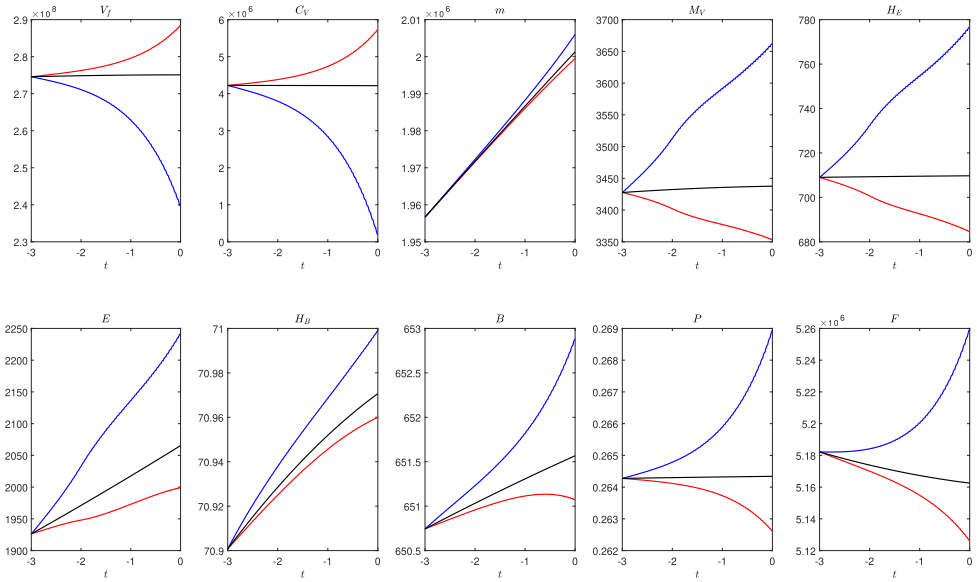

Figure 6. Initial values of the periodic solution (black line) and its disturbed values at the stage of exacerbation with the weight $\varepsilon = -0.8$ (blue line) and with the weight $\varepsilon = 0.3$ (red line).

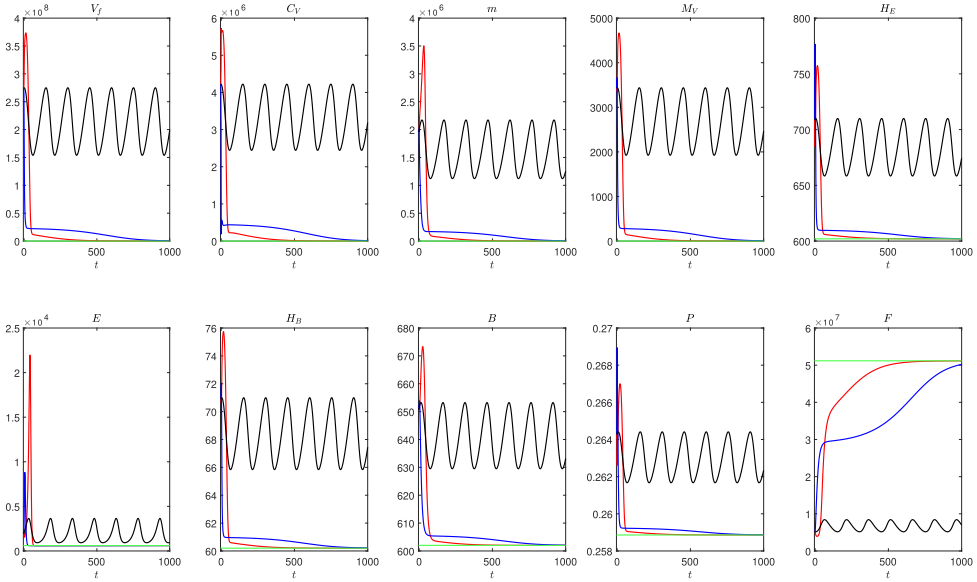

Figure 7. The periodic solution $\varphi(t)$ (black line), its disturbed values at the stage of exacerbation with the weight $\varepsilon = -0.8$ (blue line), with the weight $\varepsilon = 0.3$ (red line), and stationary solution I with $V_f = 0$ (green line).

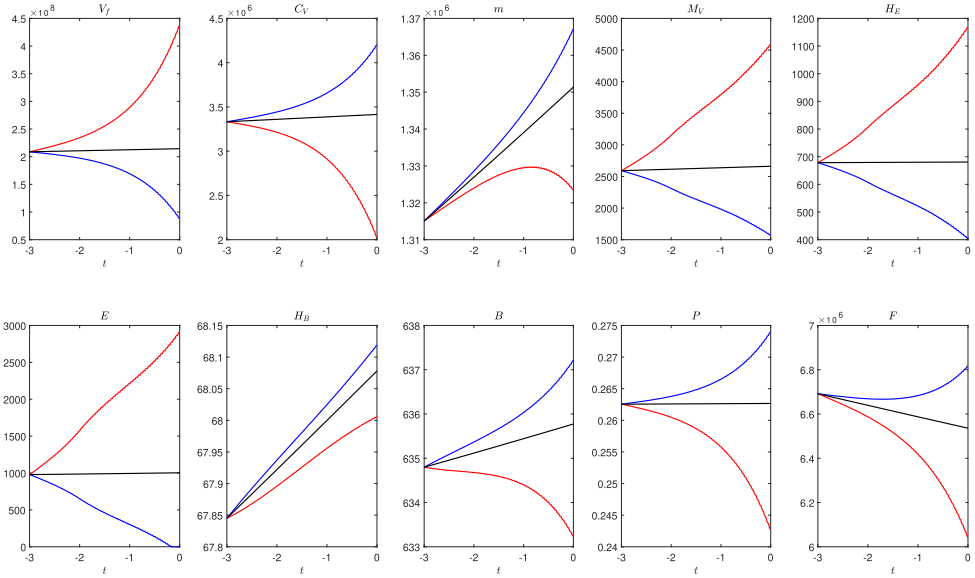

Figure 8. Initial values of the periodic solution (black line) and its disturbed values at the stage of infection development and activation of the immune response with the weight $\varepsilon = -0.85$ (blue line) and with the weight $\varepsilon = 1.5$ (red line).

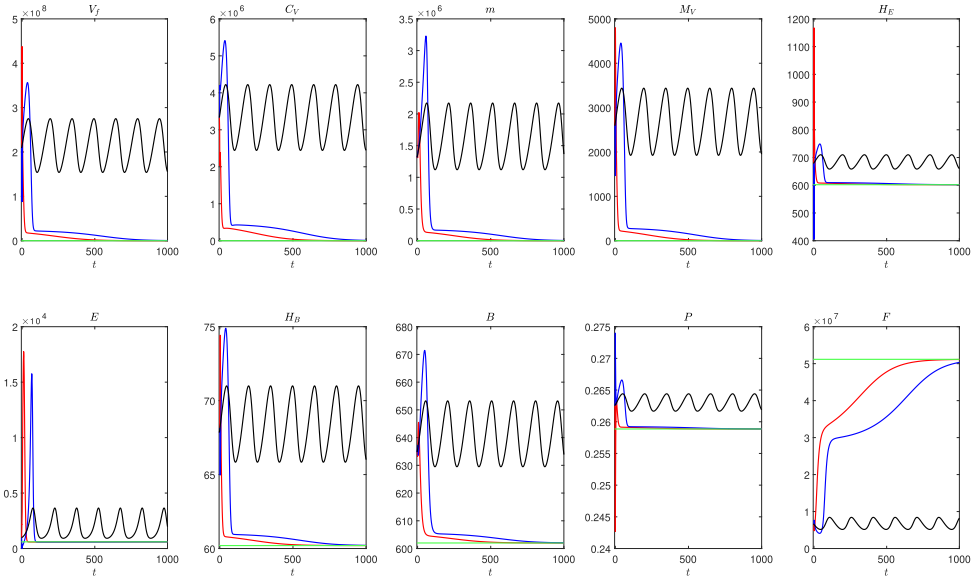

Figure 9. The periodic solution $\varphi(t)$ (black line), its disturbed values at the stage of infection development and activation of the immune response with the weight $\varepsilon = -0.85$ (blue line), with the weight $\varepsilon = 1.5$ (red line), and stationary solution I with $V_f = 0$ (green line).

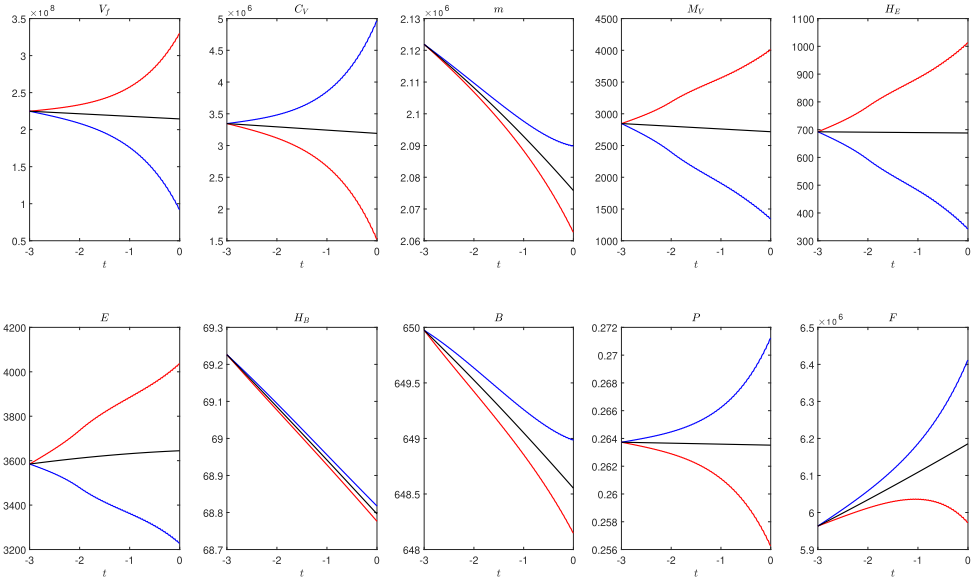

Figure 10. Initial values of the periodic solution (black line) and its disturbed values at the stage of infection elimination and decreased immune response with the weight $\varepsilon = -0.85$ (blue line) and with the line $\varepsilon = 0.8$ (red line).

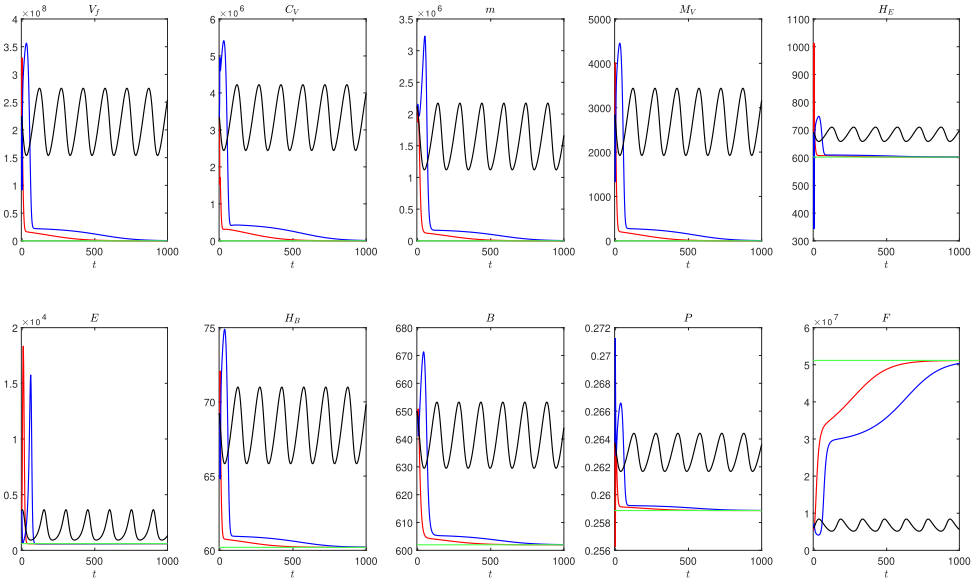

Figure 11. The periodic solution $\varphi(t)$ (black line), its disturbed values at the stage of infection elimination and decreased immune response with the weight $\varepsilon = -0.85$ (blue line), with the weight $\varepsilon = 0.8$ (red line), and stationary solution I with $V_f = 0$ (green line).

the initial disturbance and the time of elimination of infection could be achieved using the optimal disturbance for the phase of maximum viral load taken with positive weight, which increases the viral load and weakens the components of the immune response.

4. Conclusion

The dependence of optimal disturbances of a stable periodic solution of the hepatitis B dynamics model corresponding to the chronic form of the disease on the solution phase was studied in the paper. For this purpose, optimal disturbances computed for four different phases of the periodic solution were considered. Those are phases of minimum viral load, maximum viral load, infection development, and infection elimination. It was shown that for all four phases of infection and immune response the optimal disturbance significantly changes all components of the state vector except for the B-cell immune response. It was also shown that the structure of the optimal disturbance for the phases of minimum and maximum viral load is the same. However, it differs qualitatively from the structure of optimal disturbance for the phases of development and elimination of infection in the following components: infected cells, activated macrophages, Type 1 T-helper cells, and cytotoxic T-lymphocytes. At the same time, the computed relative deviations of optimal disturbances from the components of the periodic solution do not exceed 80%, which allows us to conclude that periodic solutions corresponding to chronic active hepatitis with the viral load level greater than 10^8 virions/ml can be accompanied by spontaneous recovery within the framework of the multiplicative noise model examined earlier in [11]. Indeed, the required relative variations of the components of the viral load, infected cells, activated macrophages, Type 1 T-helper cells, cytotoxic T-lymphocytes, plasma cells, and antibodies vary from 1 to 100% according to the structure of the component-by-component ratio of the disturbance norm to the norm of the periodic solution.

Moreover, it was shown that the transition from a stable periodic solution corresponding to the chronic recurrent form of hepatitis B to a stable stationary solution with zero viral load corresponding to the state of a healthy organism is possible with the use of optimal disturbances computed for the four phases of the periodic solution described above. In all four cases, the transition could be performed both by reducing the viral load, which can be interpreted as treatment with antiviral drugs, and by increasing the viral load, which can be interpreted as treatment by exacerbation. The best result in terms of minimization of the magnitude of impact on the system and the time required for elimination of infection can be achieved by using an exacerbation-type of treatment for the phase of the maximal viral load.

The periodic solution studied here is characterized by a small amplitude of variation of the model variables. Further research may be related to consideration of other bifurcation parameters and the study of their effect on the amplitude and period of oscillating solutions observed in clinical practice for viral hepatitis B [11] and the study of possibility of using optimal disturbances for design of combination type therapies.

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