Modelling chronic hepatitis B using the Marchuk-Petrov model

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Abstract. Systems of time-delay differential equations are widely used to study the dynamics of infectious diseases and immune responses. The Marchuk-Petrov model is one of them. Stable non-trivial steady states and stable periodic solutions to this model can be interpreted as chronic viral diseases. In this work we briefly describe our technology developed for computing steady and periodic solutions of time-delay systems and present and discuss the results of computing periodic solutions for the Marchuk-Petrov model with parameter values corresponding to the hepatitis B infection.

1. Introduction
Mathematical modelling in immunology is a powerful tool for analyzing the defense mechanisms in the body during infectious diseases of various nature. The classical models of mathematical immunology include the Marchuk-Petrov model of antiviral immune response \cite{1}. This model is formulated as a system of ten nonlinear delay differential equations. Using the model, the quantitative regularities of the dynamics of acute human infections caused by influenza A viruses and hepatitis B viruses were studied. Unlike influenza, viral hepatitis B has along with the acute form also chronic forms of the disease course, differing in the level of a viral load, the degree of damage to liver cells and the intensity of immune reactions. A detailed description of the viral infection and the immune response in the Marchuk-Petrov multiparameter model makes it possible to investigate, based on this model, the fundamental regularities of the development of chronic viral hepatitis B infection \cite{2}.

In the Marchuk-Petrov model, chronic forms of the disease correspond to its steady and periodic solutions. To study the conditions of existence of these solutions and the parameters of their stability, efficient numerical algorithms for searching in multidimensional spaces of parameters of time-delay models for parameter values that correspond to such solutions with given characteristics are required. This study is aimed at presenting a new technology implemented in the MATLAB environment for computing and analyzing steady and periodic solutions of complex multiparameter time-delay models and at demonstrating the applicability of this technology for studying chronic modes of the dynamics of the viral hepatitis B using the Marchuk-Petrov model of antiviral immune response.

Note that the study of chronic forms of diseases using a model of such a complexity as the Marchuk-Petrov model has not been performed before. However, for a much simpler model of
the viral hepatitis B, consisting of two time-delay differential equations (DDEs), the conditions of persistence of viruses below the detection threshold by existing standard methods [3] were investigated. For this, the authors used the well-known software package DDE_BIFTOOL [4] designed for bifurcation analysis of DDEs. In [5], the algorithms from this package were compared with the presented new algorithms by the example of the model of infection with lymphocytic choriomeningitis viruses proposed in [6]. This model, consisting of four DDEs, is more complex than the small-size model of the viral hepatitis B but is much simpler than the Marchuk-Petrov model. The significant advantage of the new algorithms was illustrated. In particular, it was shown that computation of the periodic solution using new algorithms is more accurate than and almost twice as fast as computation using the algorithms from the DDE_BIFTOOL package. Moreover, it was shown that the new algorithms make it possible to compute periodic solutions for those values of the model parameters for which it is impossible to compute periodic solutions using algorithms from the DDE_BIFTOOL package.

Everywhere in this paper, \( \| \cdot \|_2 \) denotes the matrix or vector second norm, \( i \) is the imaginary unit, \( \text{Real}(\cdot) \) and \( \text{Imag}(\cdot) \) denote the real and imaginary parts of a complex number, \( [\cdot] \) denotes the integer part of a real number.

2. Marchuk-Petrov mathematical model of the antiviral immune response

The Marchuk-Petrov mathematical model of the antiviral immune response was formulated in [1, 2] in the form of a system of nonlinear DDEs. The system describes the rate of a change in the concentration of the following populations: the viral particles \( V_f \); the virus-infected cells \( C_V \) of the target organ; destroyed cells \( m \) of the target organ; 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 \( B \); plasma cells \( P \) producing antibodies; antibodies \( F \) neutralizing viruses. The variables \( V_f \) and \( F \) have the dimensionality of particles/ml and the other variables have the dimensionality of cells/ml. The system is formulated as follows:

\[
\frac{d}{dt} V_f(t) = \nu C_V(t) + nb_CE C_V(t) E(t) - \gamma_V F(t) F(t) - \\
- \gamma_M V_f(t) - \gamma_V C_V(t) [C^0 - C_V(t) - m(t)] ,
\]

\[
\frac{d}{dt} C_V(t) = \sigma V_f(t) [C^0 - C_V(t) - m(t)] - \\
- b_CE C_V(t) E(t) - b_m C_V(t) ,
\]

\[
\frac{d}{dt} m(t) = b_CE C_V(t) E(t) + b_m C_V(t) - \alpha_m m(t) ,
\]

\[
\frac{d}{dt} M_V(t) = \gamma_M M^0 V_f(t) - \alpha_M M_V(t) ,
\]

\[
\frac{d}{dt} H_E(t) = b_H^E [\xi(m) + \rho_H^E M_V(t - \tau_H^E) - M_V(t) H_E(t)] - \\
- b_p^E H_E(t) + \alpha_H^E (H_E^E - H_E(t)) ,
\]
\[
\frac{d}{dt} E(t) = b_p^E [\xi(m) \rho_E M_V(t - \tau_E) H_E(t - \tau_E) E(t - \tau_E) -
-M_V(t) H_E(t) E(t)] -
-b_E C V(t) E(t) + \alpha_E (E^0 - E(t)),
\]
\[
\frac{d}{dt} H_B(t) = b_p^B [\xi(m) \rho_H M_V(t - \tau_H) H_B(t - \tau_H) -
-M_V(t) H_B(t)] - b_p^H M_V(t) H_B(t) B(t) +
+\alpha_p^H (H_B^0 - H_B(t)),
\]
\[
\frac{d}{dt} B(t) = b_p^B [\xi(m) \rho_B M_V(t - \tau_B) H_B(t - \tau_B) B(t - \tau_B) -
-M_V(t) H_B(t) B(t)] + \alpha_B (B^0 - B(t)),
\]
\[
\frac{d}{dt} P(t) = b_p^P [\xi(m) \rho_P M_V(t - \tau_P) H_B(t - \tau_P) B(t - \tau_P) +
+\alpha_P (P^0 - P(t)),
\]
\[
\frac{d}{dt} F(t) = \rho_F P(t) - \gamma_{FV} F(t) V_f(t) - \alpha_F F(t),
\]

where \( \xi(m) = 1 - m/C^0 \).

Denote the vector of the variables of this system by
\[
U = (V_f, C_V, m, M_V, H_E, E, H_B, B, P, F)^T,
\]
and write down this system in the following compact form:
\[
\frac{dU}{dt}(t) = F(U(t), U(t - \tau_1), \ldots, U(t - \tau_3)),
\]
where \( \tau_1, \ldots, \tau_3 \) mean the delays enumerated in non-descending order.

For numerical integration of system (2) we used the implicit second order BDF2 scheme [7] on the uniform grid
\[
\{ \delta k : k = -m_5 + 1, -m_5 + 2, \ldots \},
\]
built on the interval \((-\tau_3, \infty)\) with the step \( \delta > 0 \), i.e.,
\[
\frac{1.5U_k - 2U_{k-1} + 0.5U_{k-2}}{\delta} = F(U_k, U_{k-m_1}, \ldots, U_{k-m_5}), \quad k = 1, 2, \ldots,
\]
where \( m_j = [\tau_j/\delta] \) are discrete analogues of the delays \( \tau_j \). Further, we will replace all computations with the original system (2) for computations with a discrete system (4), where the grid step \( \delta \) is chosen sufficiently small.

3. Computation of the steady states and their stability analysis

The steady states of the discrete system (4) for given values of the parameters coincide with the steady states of the original system (2) and are non-negative solutions of form (1) of the system of algebraic equations
\[
F(U, U, \ldots, U) = 0,
\]
where \( F \) is the mapping appearing in the right-hand sides of equations (2) and (4). To solve systems of algebraic equations, the methods of computer algebra [8], which are also called methods of symbolic computation, are currently used. In particular, such methods are
implemented in the NSolve procedure of the Mathematica package. This procedure is based on computing the Groebner basis using monomial ordering and theoretically allows one to obtain an approximation of solutions to an arbitrary system of algebraic equations. However, the complexity of computations grows as \( d^n \) with the increasing number of equations \( s \) and their maximum degree \( d \) [9], which limits the possibilities of the method in practice. When applying the NSolve procedure directly to system (5), the algorithm returns an empty set as a solution. Some preliminary transformations are required to avoid this.

Firstly, note that system (5) has a trivial solution

\[
V_f = C_V = M_V = 0, \quad H_E = H^n_E, \quad E = E^0, \\
H_B = H^0_B, \quad B = B^0, \quad P = P^0, \quad F = \frac{\rho_F P^0}{\alpha_F}.
\]  

(6)

In [10] it was shown that if we exclude this solution, then the remaining system can be reduced to the following system of four equations for the variables \( V_f, C_V, H_B \) and \( H_E \):

\[
\begin{align*}
|b_H^B(\xi(m))\rho^B_H - 1)|M_V H_B - b_H^{Hn} K + \alpha^B_H(H^0_B - H_B) &= 0, \\
M_V H_B B &= R, \\
|b_p^E(\xi(m))\rho^E_H - 1)|M_V H_E - b_p^{Hn} M_V H_E E + \alpha^E_H(H^0_E - H_E) &= 0, \\
|b_p^E(\xi(m))\rho_E - 1)|M_V H_E E - b_E C_V E + \alpha_E(E^0 - E) &= 0,
\end{align*}
\]  

(7)

where \( m, \ E, \ M_V, \ F, \ P, \ B \) are the functions obtained by an explicit expression of the corresponding system variables (5) in terms of the variables \( V_f, C_V, \) and \( R \) is some algebraic function of these two variables. Unlike the original system (5), system (7) is successfully solved by the NSolve procedure. Therefore, the steady states of system (4) with fixed values of the parameters can be computed using the Mathematica package.

To study the stability of the found steady state \( \overline{U} \) of system (4), we write its solution near this steady state in the form \( \overline{U}_k = \overline{U} + \varepsilon \overline{U}'_k + o(\varepsilon) \), where \( \varepsilon \) is a small parameter in absolute value. Substituting this solution into (4) and assuming that the obtained equalities hold for all arbitrarily small values of \( \varepsilon \), for the grid function \( \overline{U}'_k \) we obtain the following system of finite difference equations:

\[
\frac{1.5U'_k - 2U'_{k-1} + 0.5U'_{k-2}}{\delta} = L_0 U'_k + \sum_{j=1}^5 L_j U'_{k-m_j},
\]  

(8)

where \( L_0 \) and \( L_j \) denote constant square matrices of order 10, which are, respectively, the values in the steady state of the partial derivatives \( \partial F/\partial U_k \) and \( \partial F/\partial U_{k-m_j} \) of the right-hand side of system (4).

The steady state \( \overline{U} \) is asymptotically stable if any solution of system (8) of the form

\[
U'_k = \mu^k Z,
\]  

(9)

where \( \mu \) is a complex number, and \( Z \) is a constant 10-component non-zero vector, monotonically decreases as \( k \to \infty \). Substituting (9) into (8), after simple transformations we obtain the following polynomial eigenproblem:

\[
\left(\frac{1.5\mu^{m_5} + 2\mu^{m_5-1} + 0.5\mu^{m_5-2}}{\delta} I - L_0 \mu^{m_5} - \sum_{j=1}^5 L_j \mu^{m_5-m_j}\right) Z = 0,
\]  

(10)
where $I$ means the identity matrix of order 10. This problem is reduced in the usual way to a linear eigenproblem with a square sparse matrix of order 10 $m_5$, all solutions of which can be found, for example, by the QR algorithm [11]. If for the considered value of $\delta$ the matrix of the linear problem turns out to be too large, then the described approach can be applied to a polynomial problem of form (10) with a larger value of $\delta$. After that, to increase reliability, a certain number of the found eigenvalues $\mu$ maximum in absolute value can be used as initial approximations to compute the leading eigenvalues of problem (10) with the original value of $\delta$ using the method of successive linear problems [12].

4. Computation of the periodic solutions

From the theory of bifurcation analysis [13] of nonlinear dynamic systems dependent on a parameter, it is known that if the system linearized with respect to one of the steady states has a complex conjugate pair of leading (with the maximum real part) eigenvalues with nonzero imaginary part and this pair passes from the left half-plane to the right one with the growth of the parameter, then after such a transition the stable periodic solution may appear in the neighborhood of the unstable steady state. The value of the parameter at which the stability loss occurs is called the Andronov-Hopf bifurcation point. The method for computing the stable periodic solution in the neighborhood of the unstable steady state was proposed in [5]. This section is devoted to a brief description of this method.

The method from [5] is applied to a system of form (4) to compute the initial grid function $U_k, k = -m_5 + 1, \ldots, 0$, which determines its approximate periodic solution, and also to compute the least period $K$ of this periodic solution. The accuracy of the obtained approximate periodic solution and its least period is determined with the following residual functional:

$$\left(\sum_{k=0}^{m_5+1} h_k \|D(U_{K+k} - U_k)\|_2^2\right)^{1/2} \left(\sum_{k=-m_5+1}^{0} h_k \|DU_k\|_2^2\right)^{1/2},$$

(11)

where $h_{-m_5+1} = h_0 = \delta/2$ and $h_k = \delta$ for $-m_5 + 2 \leq k \leq 1$, and $D$ is the diagonal matrix of order 10 whose diagonal entries are inverse to the components of the vector $\mathbf{\overline{U}}$. The method consists of three stages.

The first stage consists in computation of the approximate periodic solution by the relaxation method with the initial grid function

$$U_k = \mathbf{\overline{U}} + \varepsilon \text{Real} \left(\mu^k Z\right), \quad k = -m_5 + 1, \ldots, 0,$$

(12)

where $\mu$ is the leading eigenvalue of problem (10) (it is assumed that the leading eigenvalue has a nonzero imaginary part), $Z$ is the normalized eigenvector corresponding to this eigenvalue, $\varepsilon$ is a given positive number (parameter of the algorithm). The initial guess of the least period is taken as $K = [2\pi/|\text{Imag}(\log(\mu))|]$, where $\log(\cdot)$ denotes a natural logarithm. The relaxation method consists of substages, each of which is a discrete-time integration of system (4) during $N_eK$ steps. Function (12) was chosen as the initial function for the first substage while the values of $U_k$ for $k = (i-1)N_eK - m_5 + 1, \ldots, (i-1)N_eK$ obtained at the substage $(i-1)$, were chosen as the initial function for the substage number $i > 1$. The relaxation method continues its work until either a given maximum number of substages $N_{f,\text{max}}$ (parameter of the algorithm) is executed, or until

$$\frac{|\text{var}V_{f,i} - \text{var}V_{f,i-1}|}{\text{var}V_{f,i}} > \theta_V,$$
where \( \text{var} V_{E,i} \) is the difference between the maximum and minimum values of \( V_f \) at the \( i \)-th substage and \( \theta V \) is a small positive number (parameter of the algorithm). We will assume that \( N_f \) substages of the relaxation method have been performed in total, that is, the solution has been computed at all grid nodes (3) up to the node with the number \( N_fN_eK \).

At the second stage we estimate the least period of the approximate periodic solution. This stage consists of three substages. At the first substage, the interval \([N_f - 1]N_eK, N_fN_eK\) is clipped from the left so that the length of the obtained interval \([L, N_fN_eK]\) is an approximate period of the approximate periodic solution. At the second substage, the least period is estimated based on the expansion of the variable \( V_f \) in a discrete Fourier series. The approximate least period is set equal to \((N_fN_eT - L)/p\), where \( p \) is the greatest common divisor of the numbers \( j_1, \ldots, j_r \) of harmonics whose absolute values divided by their maximum are larger than \( \rho \), where \( \rho \) is some small positive value (parameter of the algorithm). At the third substage, the approximate least period is corrected by minimization of the residual (11) in the neighborhood of this approximate least period.

The third stage consists in alternating refinement of the initial values of the approximate periodic grid function and the approximate least period obtained at the first two stages. For a fixed least period \( K \), one step of the Newton-type method is performed to solve the equation

\[
G(Y_0; K) = Y_K - Y_0 = 0
\]

for \( Y_0 \), where

\[
Y_k = (H \otimes D)(U_k^T, U_{k+1}^T, \ldots, U_{k-m+1}^T)^T, \quad H = \text{diag}(\delta/2, \delta, \ldots, \delta, \delta/2).
\]

Then the least period is corrected as it was done at the second stage. After that, the step of the Newton-type method is performed again, and so on. The iteration stops when the residual norm \( \|G(Y_0^{\text{new}}; K^{\text{new}})\|_2/\|Y_0^{\text{old}}\|_2 \) does not exceed a given value \( \text{tol}_{NM} \) or when a given maximum number of steps \( N_{NM} \) is accomplished (parameters of the algorithm). The step of the Newton-type method has the form

\[
Y_0^{\text{new}} = Y_0 - \alpha \Delta,
\]

where

\[
\Delta = J^{-1}G(Y_0; K), \quad J = \frac{\partial G}{\partial Y_0}(Y_0; K),
\]

and \( \alpha \) is a scalar parameter whose value is selected so as to minimize \( \|G(Y_0^{\text{new}}; K)\|_2 \). The Newton step \( \Delta \) is computed by solving the system of linear equations with the Jacobi matrix

\[
\frac{\partial G}{\partial Y}(Y_0; K)
\]

and the right-hand side \( G(Y_0; K) \) by the GMRES method with given maximum number of steps \( N_{LS} \) and the threshold ratio of the system residual norm to the norm of its right-hand side \( \text{tol}_{LS} \) (parameters of the algorithm). The Jacobi matrix itself is not computed, but a procedure for its approximate multiplication by a given vector based on a finite difference approximation is used.

5. Numerical experiments

Using the technology described in sections 3 and 4, steady states and periodic solutions of model (2) were computed for three different sets of values of the model parameters, which will be referred to as sets (a), (b) and (c). The set (a) consists of the values specified in Table 1 from [14], except for the values of the parameters \( \gamma_{MV}, \delta_p, \delta_{B} \), taken as \( 1.86 \cdot 10^9 \text{ M}^{-1}\text{day}^{-1} \), \( 2.62 \cdot 10^{32} \text{ M}^{-2}\text{day}^{-1} \), \( 5 \cdot 10^{30} \text{ M}^{-2}\text{day}^{-1} \). The set (b) consists of the same parameter values as the set (a), except for the parameter \( b_B^H \), taken as \( 5 \cdot 10^{15} \text{ M}^{-1}\text{day}^{-1} \). The set (c) consists of the
same parameter values as the set (b), except for the parameter $\gamma_{MV}$, taken as $10^{12}$ M$^{-1}$day$^{-1}$.

For each of the three sets, the system has two steady states, which will further be denoted by the numbers I and II. States I are trivial and are the same in all the three cases. The rounded values of the variables in the steady states and the leading eigenvalues $\mu$ corresponding to these states are presented in table 1.

Figures 1-3 show the periodic solutions computed for the values of the model parameters from the sets (a), (b), (c) respectively, on the intervals $[-\tau_5, 0]$ (red) and $[0, T]$ (blue), where $T = K\delta$ denotes the approximate least period of the solution. For computing periodic solutions, the parameters of the algorithm specified in table 2 from [5] were used, except for the parameters $\epsilon, N_e, \rho$ described in section 4 and taken as $10^6$, 70, 0.01. Note that the periodic solution for each of the sets (a), (b), (c) was sought for in the neighborhood of unstable steady states II. The periodic solution shown in figure 1 corresponds to a set of parameters specifying a weak immune response. The periodic solution shown in figure 2 is characterized by large amplitude fluctuations in the viral load and significant liver damage. This solution occurs when the humoral immune response is weakened. The periodic solution shown in figure 3 is characterized by a lower viral load and a lesser liver damage, which is a consequence of the values of the model parameters setting a lower activation threshold for antigen-presenting macrophages.

| Table 1. Variable values in steady states. |
|------------------|------------------|------------------|------------------|
|                  | I    | IIa  | IIb  | IIc  |
| $V_f$            | 0    | $2.5 \cdot 10^{10}$ | $2.7 \cdot 10^{10}$ | $2.0 \cdot 10^{7}$ |
| $C_V$            | 0    | $1.4 \cdot 10^8$    | $1.3 \cdot 10^8$    | $1.8 \cdot 10^5$    |
| $m$              | 0    | $6.4 \cdot 10^7$    | $7.0 \cdot 10^7$    | $1.5 \cdot 10^5$    |
| $M_V$            | 0    | $3.8 \cdot 10^4$    | $4.1 \cdot 10^4$    | $1.7 \cdot 10^4$    |
| $H_E$            | 602  | $1.1 \cdot 10^5$    | $1.0 \cdot 10^5$    | $2.4 \cdot 10^3$    |
| $E$              | 602  | $1.7 \cdot 10^3$    | $1.2 \cdot 10^4$    | $5.7 \cdot 10^4$    |
| $H_B$            | 60.2 | $1.1 \cdot 10^4$    | 73.8              | 69.9              |
| $B$              | 602  | $2.0 \cdot 10^5$    | 604.9             | 603.5             |
| $P$              | 0.26 | 24.1             | 0.31              | 0.28              |
| $F$              | $10^9$ | $1.2 \cdot 10^8$ | $1.4 \cdot 10^6$ | $6.7 \cdot 10^8$  |
| $\mu$            | 1.0003 | 1.0001 ± 0.0009i | 1.0005 ± 0.0012i | 1.0007 ± 0.0013i  |
Figure 1. Periodic solution for the set (a) on the interval $[-\tau_3, T]$.

Figure 2. Periodic solution for the set (b) on the interval $[-\tau_3, T]$.

Figure 3. Periodic solution for the set (c) on the interval $[-\tau_3, T]$.
6. Conclusion

This paper presents a new technology for computing and analyzing steady states and periodic solutions of systems of nonlinear DDEs, which are actively used in modeling infectious diseases in humans and animals [1, 15]. To study the practical efficiency of the proposed methods, the Marchuk-Petrov mathematical model of the antiviral immune response was used. This model has been previously applied to study the acute forms of influenza and hepatitis infections. In this study, for the first time, the periodic solutions of the model corresponding to various courses of chronic hepatitis were found. These solutions differ in the level of a viral load, the intensity of the immune response and the degree of liver damage, and allow for an intuitive biological interpretation in the categories of specific phenotypes of chronic hepatitis B infection. It was shown that the developed technology makes it possible to effectively find in the multidimensional spaces of parameters of the time delay models the values of the parameters which correspond to steady and periodic solutions with given characteristics. Thus, universal computational tools have been developed to study the mechanisms of pathogenesis of persistent and acute forms of hepatitis and to develop an original approach to their analysis and treatment based on optimal disturbances.

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