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Homotopy Analysis of Explicit Solutions in a Chronic Hepatitis C Virus Model

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Abstract

Mathematical analysis of nonlinear models in epidemiology has generated a deep interest in gaining insights into the mechanisms that underlie hepatitis C virus (HCV) infections. In this article, we provide a study of a chronic HCV infection model with immune response, incorporating the effect of dendritic cells (DC) and cytotoxic T lymphocytes (CTL). Considering very recent developments in the literature related

to the Homotopy Analysis Method (HAM), we calculate the explicit series solutions of the HCV model, focusing our analysis on a particular set of dynamical variables. An optimal homotopy analysis approach is used to improve the computational efficiency of HAM by means of appropriate values for a convergence control parameter, which greatly accelerates the convergence of the series solutions. The approximated analytical solutions, with the variation of a parameter representing the expansion rate of CTL, are used to compute density plots, which allow us to discuss additional dynamical features of the model.

Mathematics Subject Classification: Primary 34A34; Secondary 92B05, 92C60, 34A05

Keywords: HCV infection model, Nonlinear differential equations, Explicit series solutions, Optimal homotopy analysis procedures

1 Motivation and preliminaries

Hepatitis C is an infectious liver disease that represents a significant global health problem. It is estimated by the World Health Organization (WHO) that around 150 million people are persistently infected with the Hepatitis C Virus (HCV) and are at risk of developing chronic liver disease, cirrhosis and hepatocellular carcinoma [1, 2]. The virus was identified in 1989, but its world wide presence suggests that it has been active for a much longer period. The new HCV infections per year occur in two basic stages - *acute* and *chronic* infections. The designations 'acute' and 'chronic' correspond to the duration and not to the severity of the disease. Acute infections have approximately 1% mortality rate [3, 4] and usually last up to 6 months. Those that last longer are considered chronic infections. It is estimated that around 80% of HCV infections develop into the chronic stage and can last asymptomatic for more than 20 years [3, 5]. In this context, hepatitis C is sometimes called 'silent epidemic', due to the long period of asymptomatic infections that makes difficult the diagnosis of the disease [3, 4]. Recently, a review of various existing models for the dynamics of hepatitis C infection has been presented based on different dynamical processes described in the literature [6].

In this article, our motivation is to provide insights into the study of a mathematical model with immune response for chronic HCV infection proposed by Li *et al.* in [7]. As pointed out in [8], given the importance of mathematical models in epidemiology, a great deal of numerical algorithms for approximating solutions have been used in the literature. Without doubt, the numerical algorithms have been particularly important in the study of complex dynamical systems. However, they allow us to analyze the dynamics at discrete points only, thereby making it impossible to obtain continuous solutions.

It is crucial to complement numerical analysis with the techniques for analytic approximation of solutions. Thereby, in recent years there has been a growing interest in obtaining continuous solutions for nonlinear dynamical systems by means of analytical or semi-analytical techniques [9, 10]. Such methods should preferably possess three fundamental properties: (i) their efficiency should not be influenced by the presence of small or large physical parameters; (ii) they should allow applications to different types of equations with the flexibility in choosing the expression for solution in the form of higher-order approximations; and (iii) the convergence of the series could be conveniently controlled by choosing the values of a convergence control parameter from an appropriate range. One such general analytical technique, used to get convergent series solutions of strongly nonlinear problems, is the so-called Homotopy Analysis Method (HAM), initially proposed by Liao [11, 12].

Due to its generality and versatility, homotopy analysis has been successfully applied to a wide range of nonlinear problems. In our work, we are going to carry out a modification of Liao's method, named as Step Homotopy Analysis Method (SHAM), which can be also applied to strongly nonlinear equations for large values of time. The approximated analytical solutions can motivate the discussion of additional features of the dynamics.

The paper is organized as follows. In Section 2, we present a brief overview of the chronic HCV infection model proposed in [7]. The structure of the homotopy analysis technique and the analytic solutions of the HCV model are discussed in Section 3. In the core of the analytical part of our approach, we construct explicit series solutions for the dynamical variables which are used for generating density plots and for exploring additional dynamic features of the model. Conducting an optimal homotopy analysis to improve the computational efficiency of the method, we present the procedure to compute optimal values of the auxiliary control parameter h based on squared residual errors, which ensures a fast convergence. We conclude the article with a summary of our analysis and final considerations.

2 Mathematical model for the HCV infection

We analyze the chronic HCV infection model with immune response proposed in [7], which includes the effect of Dendritic Cells (DC) and Cytotoxic T Lymphocytes (CTL) ([13]-[15]). More precisely, this model considers two biological effects:

(i) the effect of HCV infection, with the dynamical variables *healthy hepatocytes* (T) and *infected hepatocytes* (T^1);

(ii) the effect of immune system on HCV infection, with three dynamical variables, namely, *non-activated DC* (D), which do not present antigen, *loaded*

and activated DC (D^1), which have taken up antigen and display it, and *CTL* (C).

Taking in consideration the assumptions stated in [7], it is derived the following model

$$\begin{cases} \frac{dT}{dt} = rT\left(1 - \frac{T+T^1}{K}\right) - \beta T T^1 \\ \frac{dT^1}{dt} = \beta T T^1 - d_1 T^1 - \beta_2 T^1 C \\ \frac{dD}{dt} = \lambda - \delta_1 D - \alpha D T^1 \\ \frac{dD^1}{dt} = \alpha D T^1 - \delta_2 D^1 \\ \frac{dC}{dt} = \eta D^1 C - \beta_3 T^1 C - \mu C \end{cases} . \quad (1)$$

Values and descriptions of the parameters of model (1), which were obtained from [7], are explained in the following table (for more details, see [7] and references therein).

Parameter	Value	Description
K	10	Carrying capacity of infected hepatocytes
β	2	Rate of infection of healthy hepatocytes
d_1	0.1	Death rate of infected hepatocytes
β_2	1	Rate of lyse of infected hepatocytes by variable C
λ	1	Constant production rate of variable D
δ_1	0.1	Death rate of variable D
α	0.2	Activation rate of variable D^1
δ_2	1.5	Death rate of variable D^1
β_3	0.5	Removal rate of variable C
μ	0.1	Death rate of variable C
r	0.91	Intrinsic proliferation rate of healthy hepatocytes
η	$1.0 \leq \eta \leq 1.038$	Expansion rate of variable C (Control Parameter)

Table 1: Values and descriptions of the parameters of model (1)

3 Structure of the homotopy analysis technique and the analytic solutions

The analytical approach of HAM ([16]) will be used in a sequence of intervals, giving rise to the step homotopy analysis method (SHAM). In the following

paragraph, we outline the description of SHAM applied to the chronic HCV infection model (1).

3.1 Explicit series expansion solutions

Based on the primary definitions of the HAM, we are able to perform an analytical approach of the HCV infection model. Our goal is to obtain the explicit series solutions for the state variables T, T^1, D, D^1 and C. Let us consider the initial conditions

$$T_0(t) = \alpha_T,\ T_0^1(t) = \alpha_{T^1},\ D_0(t) = \alpha_D,\ D_0^1(t) = \alpha_{D^1},\ C_0(t) = \alpha_C,$$

as our initial approximations of $T(t)$, $T^1(t)$, $D(t)$, $D^1(t)$ and $C(t)$, respectively. For our present analysis, we set the following values for the initial conditions:

$$\alpha_T = 2.068,\quad \alpha_{T^1} = 1.062,\quad \alpha_D = 6.297,\quad \alpha_{D^1} = 0.676 \ \text{ and } \ \alpha_C = 6.406.$$

In the context of HAM, there is freedom to choose auxiliary linear operators and we are going to simply consider

$$\mathcal{L}[\phi_i(t;q)] = \frac{\partial \phi_i(t;q)}{\partial t},\ i = 1, ..., 5,$$

where $\mathcal{L}(c_i) = 0$ and c_i $(i = 1, ..., 5)$ are integral constants. The nonlinear operators for the HCV infection model are

$$\mathcal{N}_1[\phi_1(t;q), \phi_2(t;q), \phi_3(t;q), \phi_4(t;q), \phi_5(t;q)] = \frac{\partial \phi_1(t;q)}{\partial t}$$
$$-r\phi_1(t;q) + \frac{r}{K}\phi_1^2(t;q) + \frac{r}{K}\phi_1(t;q)\phi_2(t;q) + \beta\phi_1(t;q)\phi_2(t;q),$$

$$\mathcal{N}_2[\phi_1(t;q), \phi_2(t;q), \phi_3(t;q), \phi_4(t;q), \phi_5(t;q)] = \frac{\partial \phi_2(t;q)}{\partial t}$$
$$-\beta\phi_1(t;q)\phi_2(t;q) + d_1\phi_2(t;q) + \beta_2\phi_2(t;q)\phi_5(t;q),$$

$$\mathcal{N}_3[\phi_1(t;q), \phi_2(t;q), \phi_3(t;q), \phi_4(t;q), \phi_5(t;q)] = \frac{\partial \phi_3(t;q)}{\partial t} - \lambda$$
$$+\delta_1\phi_3(t;q) + \alpha\phi_2(t;q)\phi_3(t;q),$$

$$\mathcal{N}_4[\phi_1(t;q), \phi_2(t;q), \phi_3(t;q), \phi_4(t;q), \phi_5(t;q)] = \frac{\partial \phi_4(t;q)}{\partial t}$$
$$-\alpha\phi_2(t;q)\phi_3(t;q) + \delta_2\phi_4(t;q)$$

and $$\mathcal{N}_5[\phi_1(t;q), \phi_2(t;q), \phi_3(t;q), \phi_4(t;q), \phi_5(t;q)] = \frac{\partial \phi_5(t;q)}{\partial t}$$
$$-\eta\phi_4(t;q)\phi_5(t;q) + \beta_3\phi_2(t;q)\phi_5(t;q) + \mu\phi_5(t;q).$$

The zeroth-order deformation equations have the form

$$\begin{aligned}
(1-q)\mathcal{L}[\phi_1(t;q)-T_0(t)] &= qh\mathcal{N}_1[\phi_1(t;q),\phi_2(t;q),\phi_3(t;q),\phi_4(t;q),\phi_5(t;q)],\\
(1-q)\mathcal{L}[\phi_2(t;q)-T_0^1(t)] &= qh\mathcal{N}_2[\phi_1(t;q),\phi_2(t;q),\phi_3(t;q),\phi_4(t;q),\phi_5(t;q)],\\
(1-q)\mathcal{L}[\phi_3(t;q)-D_0(t)] &= qh\mathcal{N}_3[\phi_1(t;q),\phi_2(t;q),\phi_3(t;q),\phi_4(t;q),\phi_5(t;q)],\\
(1-q)\mathcal{L}[\phi_4(t;q)-D_0^1(t)] &= qh\mathcal{N}_4[\phi_1(t;q),\phi_2(t;q),\phi_3(t;q),\phi_4(t;q),\phi_5(t;q)],\\
(1-q)\mathcal{L}[\phi_5(t;q)-C_0(t)] &= qh\mathcal{N}_5[\phi_1(t;q),\phi_2(t;q),\phi_3(t;q),\phi_4(t;q),\phi_5(t;q)],
\end{aligned} \tag{2}$$

with initial conditions

$$\begin{aligned}
\phi_1(0;q) &= 2.068,\ \phi_2(0;q)=1.062,\ \ \phi_3(0;q)=6.297,\\
\phi_4(0;q) &= 0.676 \ \text{ and } \ \phi_5(0;q)=6.406.
\end{aligned}$$

Solutions to the zeroth-order equations (2) for the values $q=0$ and $q=1$ are

$$\begin{gathered}
\phi_1(t;0)=T_0(t),\ \phi_2(t;0)=T_0^1(t),\ \ \phi_3(t;0)=D_0(t),\\
\phi_4(t;0)=D_0^1(t),\ \ \phi_5(t;0)=C_0(t)
\end{gathered} \tag{3}$$

$$\begin{gathered}
\text{and } \phi_1(t;1)=T(t),\ \phi_2(t;1)=T^1(t),\ \ \phi_3(t;1)=D(t),\\
\phi_4(t;1)=D^1(t),\ \ \phi_5(t;1)=C(t),
\end{gathered} \tag{4}$$

respectively. By increasing q from 0 to 1, the functions $\phi_i(t;q)$ $(i=1,...,5)$ vary from $T_0(t)$, $T_0^1(t)$, $D_0(t)$, $D_0^1(t)$ and $C_0(t)$ to $T(t)$, $T^1(t)$, $D(t)$, $D^1(t)$ and $C(t)$, respectively. Expanding each of the functions $\phi_i(t;q)$ $(i=1,...,5)$ in MacLaurin series with respect to q, we obtain the homotopy-Maclaurin series

$$\begin{aligned}
\phi_1(t;q) &= T_0(t)+\sum_{m=1}^{+\infty}T_m(t)q^m,\ \ \phi_2(t;q)=T_0^1(t)+\sum_{m=1}^{+\infty}T_m^1(t)q^m,\\
\phi_3(t;q) &= D_0(t)+\sum_{m=1}^{+\infty}D_m(t)q^m,\ \ \phi_4(t;q)=D_0^1(t)+\sum_{m=1}^{+\infty}D_m^1(t)q^m,\\
\phi_5(t;q) &= C_0(t)+\sum_{m=1}^{+\infty}C_m(t)q^m,\quad \text{where}
\end{aligned} \tag{5}$$

$$T_m(t) = \frac{1}{m!}\left.\frac{\partial^m \phi_1(t;q)}{\partial q^m}\right|_{q=0}, \quad T_m^1(t) = \frac{1}{m!}\left.\frac{\partial^m \phi_2(t;q)}{\partial q^m}\right|_{q=0},$$

$$D_m(t) = \frac{1}{m!}\left.\frac{\partial^m \phi_3(t;q)}{\partial q^m}\right|_{q=0}, \quad D_m^1(t) = \frac{1}{m!}\left.\frac{\partial^m \phi_4(t;q)}{\partial q^m}\right|_{q=0}, \tag{6}$$

$$\text{and} \quad C_m(t) = \frac{1}{m!}\left.\frac{\partial^m \phi_5(t;q)}{\partial q^m}\right|_{q=0}.$$

The auxiliary parameter h is chosen properly to ensure the convergence of all series for $q = 1$. The homotopy series solutions are obtained from equations (3)-(6).

$$\begin{aligned} T(t) &= T_0(t) + \sum_{m=1}^{+\infty} T_m(t), \quad T^1(t) = T_0^1(t) + \sum_{m=1}^{+\infty} T_m^1(t), \\ D(t) &= D_0(t) + \sum_{m=1}^{+\infty} D_m(t), \quad D^1(t) = D_0^1(t) + \sum_{m=1}^{+\infty} D_m^1(t) \\ \text{and } C(t) &= C_0(t) + \sum_{m=1}^{+\infty} C_m(t). \end{aligned} \tag{7}$$

Differentiating the zeroth-order Equations (2) m times and using the properties

$$\mathcal{D}_m(\phi_i) = x_{i,m},$$

$$\mathcal{D}_m q^k \phi_i = \mathcal{D}_{m-k}(\phi_i) = \begin{cases} x_{i,m-k}, & 0 \le k \le m, \\ 0, & \text{otherwise} \end{cases}$$

$$\mathcal{D}_m(\phi_1^2) = \sum_{k=0}^{m} x_{i,m-k}\ x_{i,k},$$

$$\mathcal{D}_m(\phi_i \psi_i) = \sum_{k=0}^{m} \mathcal{D}_k(\phi_i)\mathcal{D}_{m-k}(\psi_i) = \sum_{k=0}^{m} x_{i,k}\ y_{i,m-k},$$

where $\mathcal{D}$ stands for the m^{th}-order derivative with respect to the homotopy parameter q and $\overrightarrow{u}_{m-1}(t) = \big(T_{m-1}(t), T_{m-1}^1(t), D_{m-1}(t), D_{m-1}^1(t), C_{m-1}(t)\big)$,

we obtain the m^{th}-order deformation equations

$$\begin{aligned}
\mathcal{L}[T_m(t) - \chi_m T_{m-1}(t)] &= hR_{1,m}[\overrightarrow{u}_{m-1}(t)] \\
\mathcal{L}[T^1_m(t) - \chi_m T^1_{m-1}(t)] &= hR_{2,m}[\overrightarrow{u}_{m-1}(t)], \\
\mathcal{L}[D_m(t) - \chi_m D_{m-1}(t)] &= hR_{3,m}[\overrightarrow{u}_{m-1}(t)], \\
\mathcal{L}[D^1_m(t) - \chi_m D^1_{m-1}(t)] &= hR_{4,m}[\overrightarrow{u}_{m-1}(t)], \\
\mathcal{L}[C_m(t) - \chi_m C_{m-1}(t)] &= hR_{5,m}[\overrightarrow{u}_{m-1}(t)],
\end{aligned} \tag{8}$$

where

$$\chi_m = \begin{cases} 0, & \text{for } m \leq 1 \\ 1, & \text{for } m > 1 \end{cases},$$

subject to the initial conditions

$$T_m(0) = 0,\ T^1_m(0) = 0, D_m(0) = 0,\ D^1_m(0) = 0,\ \ C_m(0) = 0. \tag{9}$$

Then we have

$$R_1[\overrightarrow{u}_{m-1}] = \frac{dT_{m-1}(t)}{dt} - rT_{m-1}(t)$$
$$+\frac{r}{K}\sum_{k=0}^{m-1} T_{m-1-k}(t)T_k(t) + \frac{r}{K}\sum_{k=0}^{m-1} T_{m-1-k}(t)T_k^1(t)$$
$$+\beta\sum_{k=0}^{m-1} T_{m-1-k}(t)T_k^1(t),$$

$$R_2[\overrightarrow{u}_{m-1}] = \frac{dT_{m-1}^1(t)}{dt} - \beta\sum_{k=0}^{m-1} T_{m-1-k}(t)T_k^1(t)$$
$$+d_1T_{m-1}^1(t) + \beta_2\sum_{k=0}^{m-1} T_{m-1-k}^1(t)C_k(t),$$

$$R_3[\overrightarrow{u}_{m-1}] = \frac{dD_{m-1}(t)}{dt} - (1-\chi_m)\lambda + \delta_1 D_{m-1}(t)$$
$$+\alpha\sum_{k=0}^{m-1} D_{m-1-k}(t)T_k^1(t),$$

$$R_4[\overrightarrow{u}_{m-1}] = \frac{dD_{m-1}^1(t)}{dt} - \alpha\sum_{k=0}^{m-1} D_{m-1-k}(t)T_k^1(t)$$
$$+\delta_2 D_{m-1}^1(t),$$

$$\text{and } R_5[\overrightarrow{u}_{m-1}] = \frac{dC_{m-1}(t)}{dt} - \eta\sum_{k=0}^{m-1} D_{m-1-k}^1(t)C_k(t)$$
$$+\beta_3\sum_{k=0}^{m-1} T_{m-1-k}^1(t)C_k(t) + \mu C_{m-1}(t).$$

Solutions of linear m^{th}-order deformation equations (8), satisfying the initial

conditions (9) for all $m \geq 1$, are given by

$$T_m(t) = \chi_m T_{m-1}(t) + h \int_0^t R_{1,m}[\overrightarrow{u}_{m-1}(t)]d\tau,$$

$$T_m^1(t) = \chi_m T_{m-1}^1(t) + h \int_0^t R_{2,m}[\overrightarrow{u}_{m-1}(t)]d\tau,$$

$$D_m(t) = \chi_m D_{m-1}(t) + h \int_0^t R_{3,m}[\overrightarrow{u}_{m-1}(t)]d\tau,$$

$$D_m^1(t) = \chi_m D_{m-1}^1(t) + h \int_0^t R_{4,m}[\overrightarrow{u}_{m-1}(t)]d\tau,$$

$$C_m(t) = \chi_m C_{m-1}(t) + h \int_0^t R_{5,m}[\overrightarrow{u}_{m-1}(t)]d\tau.$$

Truncating the homotopy series (7) at the M^{th} step, we obtain the M^{th}-order approximate solutions in the form

$$\begin{aligned} &T_M(t) = T_0(t) + \sum_{m=1}^{M} T_m(t), \quad T_M^1(t) = T_0^1(t) + \sum_{m=1}^{M} T_m^1(t), \\ &D_M(t) = D_0(t) + \sum_{m=1}^{M} D_m(t), \quad D_M^1(t) = D_0^1(t) + \sum_{m=1}^{M} D_m^1(t) \\ &\text{and } C_M(t) = C_0(t) + \sum_{m=1}^{M} C_m(t). \end{aligned} \tag{10}$$

The exact solutions of (1) are obtained by passing to the limit as $M \to \infty$,

$$T(t) = \lim_{M \to +\infty} T_M(t), \qquad T^1(t) = \lim_{M \to +\infty} T_M^1(t),$$

$$D(t) = \lim_{M \to +\infty} D_M(t), \qquad D^1(t) = \lim_{M \to +\infty} D_M^1(t),$$

$$C(t) = \lim_{M \to +\infty} C_M(t).$$

In order to obtain approximations to solutions for large values of t, we use the SHAM, which corresponds to the application of the HAM on a sequence of intervals with the time step Δt considering, as an illustrative example, the eighth order approximations defined by equations (11):

$$\begin{aligned} T(t) &= T_0(t) + \sum_{m=1}^{8} T_m(t), \qquad T^1(t) = T_0^1(t) + \sum_{m=1}^{8} T^1(t), \\ D(t) &= D_0(t) + \sum_{m=1}^{8} D_m(t), \qquad D^1(t) = D_0^1(t) + \sum_{m=1}^{8} D_m^1(t), \\ C(t) &= C_0(t) + \sum_{m=1}^{8} C_m(t). \end{aligned} \tag{11}$$

In this case, initial values for T_0, T_0^1, D_0, D_0^1 and C_0 change at each subinterval, i.e., $T(t^*) = T_0$, $T^1(t^*) = T_0^1$, $D(t^*) = D_0$, $D^1(t^*) = D_0^1$ and $C(t^*) = C_0$, with initial conditions $T_m(t^*) = T_m^1(t^*) = D_m(t^*) = D_m^1(t^*) = C_m(t^*) = 0$ satisfied for all $m \geq 1$. As a consequence, approximate solutions are given by

$$\begin{aligned} T(t) &= T(t^*) + \sum_{m=1}^{8} T_m(t - t^*), \qquad T^1(t) = T^1(t^*) + \sum_{m=1}^{8} T_m^1(t - t^*), \\ D(t) &= D(t^*) + \sum_{m=1}^{8} D_m(t - t^*), \qquad D^1(t) = D^1(t^*) + \sum_{m=1}^{8} D_m^1(t - t^*), \\ C(t) &= C(t^*) + \sum_{m=1}^{8} C(t - t^*). \end{aligned} \tag{12}$$

In the beginning, only the initial data at $t = 0$ are known for the variables $T(t)$, $T^1(t)$, $D(t)$, $D^1(t)$ and $C(t)$. Corresponding values at $t = t^*$ at each step are obtained by using the values of approximate solutions computed at the previous step, thus ensuring smoothness of solutions.

3.2 The convergence-control and the optimal value of h: optimal homotopy analysis procedures for the solutions

Using an optimal approach, the homotopy analysis method might be applied to solve complicated differential equations with strong nonlinearity. With the purpose of determining the optimum value of h, an exact Squared Residual Error (SRE) is defined and efficiently used to find optimal convergence values for the convergence control parameter h, corresponding to dynamical variables T and D.

It is found that this optimal homotopy analysis approach greatly accelerates the convergence of series solution.

3.2.1 Squared residual error and the optimal value of h

A procedure to check the convergence of a homotopy-series solution is to substitute this series into the original governing equations and initial conditions, and then to evaluate the corresponding squared residual errors - the more quickly the residual error decays to zero, the faster the homotopy-series converges. In this context, and as an illustration, an error analysis is performed in the following lines for the dynamical variables T and D.

Taking the expressions (10), let us consider $\varphi_T(t,h_T) = T_M(t)$, $\varphi_{T^1}(t,h_{T^1}) = T_M^1(t)$, $\varphi_D(t,h_D) = D_M(t)$, $\varphi_{D^1}(t,h_{D^1}) = D_M^1(t)$ and $\varphi_C(t,h_C) = C_M(t)$. With the substitution of these solutions into Eqs. (1), we are able to construct *Residual Error* (RE) functions as follows ((13)-(15)):

$$\begin{aligned} RE_T(h_T,t) &= \frac{\partial\varphi_T(t,h_T)}{\partial t} - r\varphi_T(t,h_T) \\ &\quad -r\phi_T(t,h_T) + \frac{r}{K}\phi_T^2(t,h_T) + \frac{r}{K}\phi_T(t,h_T)\phi_{T^1}(t,h_{T^1}) \\ &\quad +\beta\phi_T(t;h_T)\phi_{T^1}(t,h_{T^1}), \end{aligned} \tag{13}$$

$$\begin{aligned} RE_{T^1}(h_{T^1},t) &= \frac{\partial\varphi_{T^1}(t,h_{T^1})}{\partial t} - \beta\phi_T(t,h_T)\phi_{T^1}(t,h_{T^1}) \\ &\quad +d_1\phi_{T^1}(t,h_{T^1}) + \beta_2\phi_{T^1}(t,h_{T^1})\phi_C(t,h_C), \end{aligned} \tag{14}$$

$$RE_D(h_D,t) = \frac{\partial\varphi_D(t,h_D)}{\partial t} - \lambda + \delta_1\phi_D(t,h_D) + \alpha\phi_{T^1}(t,h_{T^1})\phi_D(t,h_D), \tag{15}$$

$$RE_{D^1}(h_{D^1},t) = \frac{\partial\varphi_{D^1}(t,h_{D^1})}{\partial t} - \alpha\phi_{T^1}(t,h_{T^1})\phi_D(t,h_D) + \delta_2\phi_{D^1}(t,h_{D^1}) \tag{16}$$

$$\begin{aligned} RE_C(h_C,t) &= \frac{\partial\varphi_C(t,h_C)}{\partial t} - \eta\phi_{D^1}(t,h_{D^1})\phi_C(t,h_C) + \\ &\quad +\beta_3\phi_{T^1}(t,h_{T^1})\phi_C(t,h_C) + \mu\phi_C(t,h_C) \end{aligned} \tag{17}$$

In 2007, Yabushita *et al.* [17] suggested an *optimization method* for convergence control parameters. Their work is based on the Squared Residual Error. Inspired by this approach, and following the studies carried out in [18], we consider the exact *Squared Residual Error* (SRE) for the M^{th}-order approximations to be

$$SRE_T(h_T) = \int_0^1 \left[RE_T(h_T,t)\right]^2 dt, \tag{18}$$

$$SRE_{T^1}\left(h_{T^1}\right) = \int_0^1 \left[RE_{T^1}\left(h_{T^1}, t\right)\right]^2 dt, \tag{19}$$

$$SRE_D\left(h_D\right) = \int_0^1 \left[RE_D\left(h_D, t\right)\right]^2 dt, \tag{20}$$

$$SRE_{D^1}\left(h_{D^1}\right) = \int_0^1 \left[RE_{D^1}\left(h_{D^1}, t\right)\right]^2 dt, \tag{21}$$

$$SRE_C\left(h_C\right) = \int_0^1 \left[RE_C\left(h_C, t\right)\right]^2 dt. \tag{22}$$

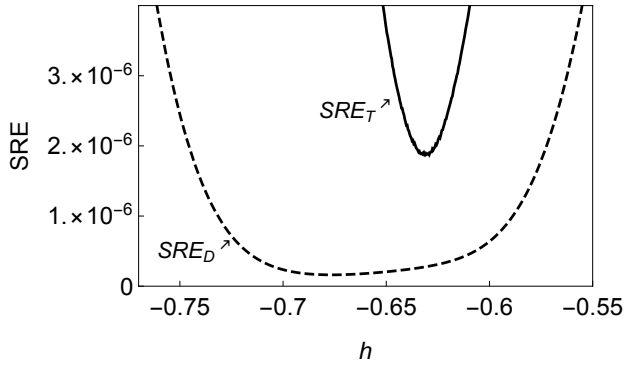

Figure 1: Exact Squared Residual Error functions, SRE_T and SRE_D versus h, corresponding to the 8^{th}-order approximation ($r = 0.91$ and $\eta = 1.013$). Each optimum value of h gives rise to the minimum value of the SRE.

Variable	Optimal value h^*	Minimum value of SRE (8^{th}-order approximation)
T	-0.631204	1.84176×10^{-6}
D	-0.676395	1.61835×10^{-7}

Table 2: Optimal values h_T^* and h_D^* and minima of the respective squared residual error functions, corresponding to the dynamical regime presented in Fig. 1.

Values of h_T, h_{T^1}, h_D, h_{D^1} and h_C for which $SRE_T\left(h_T\right)$, $SRE_{T^1}\left(h_{T^1}\right)$, $SRE_D\left(h_D\right)$, $SRE_{D^1}\left(h_{D^1}\right)$ and $SRE_C\left(h_C\right)$ are minimum can be obtained. For

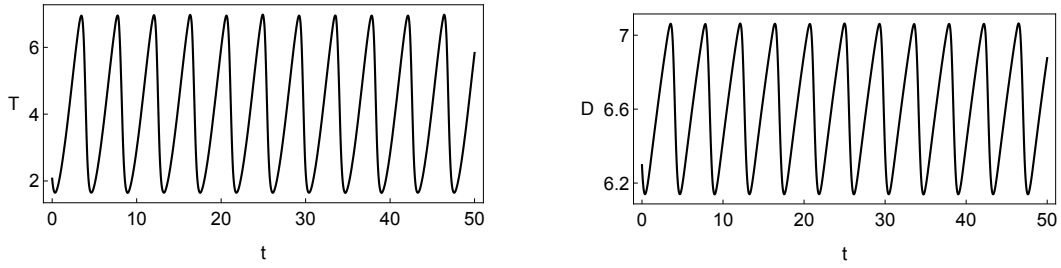

Figure 2: The SHAM analytical solutions of $T(t)$ and $D(t)$ of the HCV infection model, considering $r = 0.91$ and $\eta = 1.013$.

a given M^{th}-order of approximation, the optimal values of h_T, h_{T^1}, h_D, h_{D^1} and h_C are given by solving the nonlinear algebraic equations

$$\begin{aligned} \frac{d\left[SRE_T\left(h_T\right)\right]}{dh_T} &= 0, \quad \frac{d\left[SRE_{T^1}\left(h_{T^1}\right)\right]}{dh_{T^1}} = 0, \quad \frac{d\left[SRE_D\left(h_D\right)\right]}{dh_D} = 0, \\ \frac{d\left[SRE_{D^1}\left(h_{D^1}\right)\right]}{dh_{D^1}} &= 0, \quad \frac{d\left[SRE_C\left(h_C\right)\right]}{dh_C} = 0, \end{aligned}$$

respectively. The optimal values for all of these considered cases are h_T^*, $h_{T^1}^*$, h_D^*, $h_{D^1}^*$ and h_C^*. As an illustration, the curves of SRE_T and SRE_D, regarding the 8^{th}-order of approximation ($M = 8$) is shown in Fig. 1. Central information regarding the optimal values of h_T, h_D and minima of the respective squared residual error functions is summarized in the table of Table 2.

Indeed, the use of the squared residual error functions, by solving the equations mentioned above, allows us to obtain and optimal value that ensures the convergence for the artificial parameter h. This represents a central advantage in the study of the convergence of HAM. In Fig. 2, we illustrate the SHAM analytical solutions for T and D with the numerical results using precisely the optimum values presented in the table.

3.2.2 Density plots and dynamics of T and D using the optimization procedures

Following the previous procedure, we analyze the dynamics of *healthy hepatocytes* (variable T) and *non-activated dendritic cells* (variable D) using the homotopy solutions constructed above, taking as control parameter η, the *expansion rate of the Cytotoxic T Lymphocytes (*variable C), considering the range $1.0 \leq \eta \leq 1.038$. Time series and density plots for variables T and D, within the same parameter range, are depicted in Fig. 3. A noteworthy and eye-catching feature of these figures is the periodicity of the solutions.

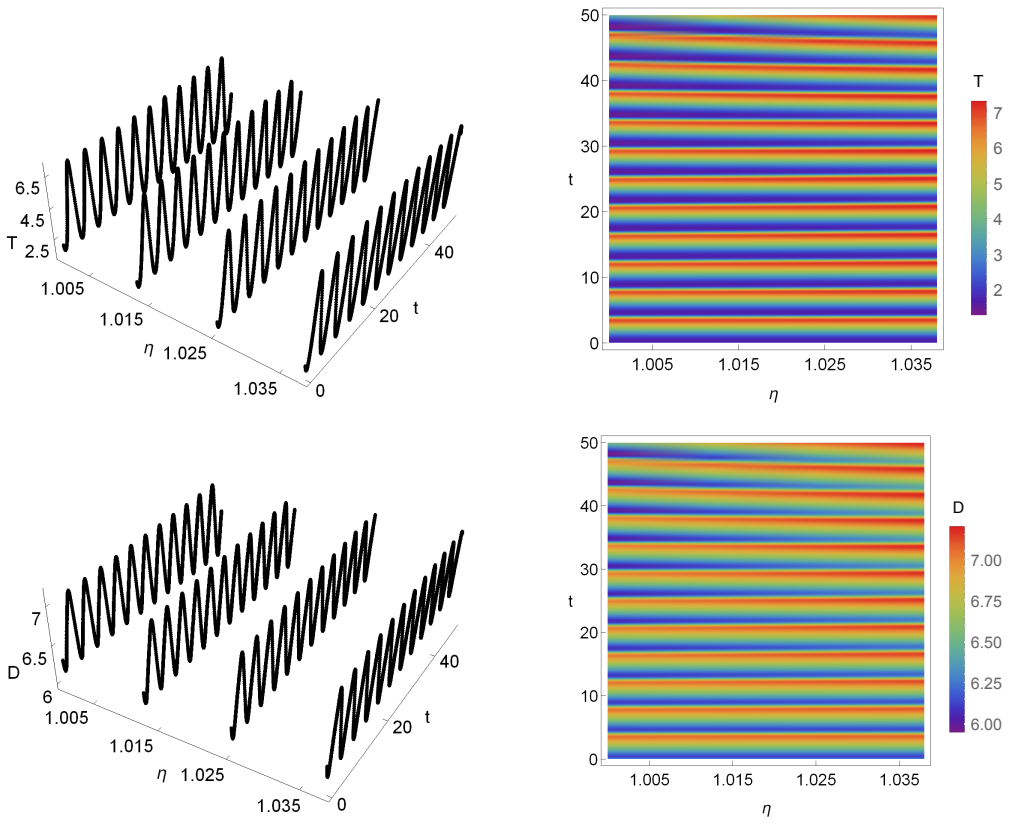

Figure 3: *Left* -Samples of time series of variables T and D for different combinations of $\eta \in [1.0, 1.038]$, corresponding to the derived analytical solutions. *Right* - Density plots for T and D for the same range of the control parameter.

4 Final considerations

In this paper we have provided new insights into the study of a chronic HCV infection model with immune response, incorporating the effect of dendritic cells and cytotoxic T lymphocytes. It is well-known that nonlinear equations are particularly difficult to solve, especially in terms of analytical methods. In general, and as stated in [19], there are two standards for a *satisfactory* approach of nonlinear equations: (i) it can always give approximation expressions *efficiently*; (ii) it can guarantee that approximation expressions are *accurate* enough in the studied region of biophysical parameters. Using these two standards as a criterion, we have successfully applied an analytical method for nonlinear differential equations, the Step Homotopy Analysis Method (SHAM), to construct the explicit series solution of the HCV infection model. With this analytical algorithm, based on a modification of the Homotopy Analysis Method (HAM), the five coupled original nonlinear differential equations are replaced by an infinite number of linear sub-problems. This technique has the advantage of giving continuous solutions within each time interval, which is not possible by purely numerical methods. Associated to the explicit series solutions is a convergence-control parameter h. This auxiliary parameter represents a convenient way to adjust and control the convergence of the resulting series solution, which is a significant qualitative difference compared with other methods.

In order to increase the computational efficiency, an optimal homotopy analysis approach has been here developed to obtain optimal values for the convergence-control parameter h by means of the definition of exact Squared Residual Error functions. This analysis provides a fast convergence of the homotopy series solutions and illustrates that, in fact, the homotopy analysis method satisfies the two standard aspects (i) and (ii), mentioned previously.

The optimized SHAM method has been used to characterize the dynamics of *healthy hepatocytes* (variable T) and *non-activated dendritic cells* (variable D), taking as control parameter η, the *expansion rate of the Cytotoxic T Lymphocytes (*variable C). In perfect agreement with numerical solutions, and under appropriate parameter values, both variables T and D undergo a regime of periodic dynamics for the studied parameter region.

The authors hope that the results presented in this article will inspire further applications of the HAM for the analysis of highly nonlinear problems in theoretical biology. This study illustrates how integration of theoretical reasonings and numerical experiments contributes to our understanding of important biological models and provides trustworthy explanation of complex phenomena witnessed in biological systems.

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