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Hopf bifurcation of a bicompartimental mathematical model of a therapeutic Hepatitis C virus dynamics

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Hepatitis C Virus, Interferon, Ribavirin, delay, numerical simu- lation, Hopf bifurcation

A B S T R A C T

In this paper, we are interested in looking for Hopf bifurcation solutions for bicompartimental mathematical model of a therapetic hepatitis C virus dynamics. The mathematical model is governed by a system of delay differ- ential equations. The algorithm for determining the critical delays that are convenable for Hopf bifurcation is used. The illustrative example for a patient administrating drugs during 12 months.

Introduction

Hepatitis C is a liver infection caused by the Hepatitis C virus (HCV). Hepatitis C is a blood-borne virus and the most common modes of infection are through unsafe injection practices; inadequate sterilization of medical equipment in some health-care settings; and unscreened blood and blood products. Antiviral medicines can cure hepatitis C infection, but access to diagnosis and treatment is low. Today, most people become infected with the Hepatitis C virus by sharing needles or other equipment to inject drugs. HCV can be transmitted by transfusion of blood and blood products, transplantation of solid organs from infected donors, injection drug abuse, unsafe therapeutic injections, and occupational exposure to blood (primarily contaminated needles) [1]. Transfusion-associated HCV infection was an important source of infection before HCV testing of blood donors was introduced in the early 1990s. Since then, transfusion-associated HCV infection has been virtually elim- inated in those countries where routine HCV-testing has been implemented (Safe Injection Global Network (SIGN), 2001). HCV is less efficiently transmitted by oc- cupational, perinatal and high-risk sexual exposures compared to those involving large or repeated percutaneous exposures to blood [1]. For some people, hepatitis C is a short-term illness but for 70%-85% of people who become infected with Hep-atitis C, it becomes a long-term, chronic infection. Chronic Hepatitis C is a serious disease than can result in long-term health problems, even death. 130-150 million people globally have chronic hepatitis C infection. A significant number of those who are chronically infected will develop liver cirrhosis or liver cancer. 350,000 to 500,000 people die each year from hepatitis C-related liver diseases. The majority of infected persons might not be aware of their infection because they are not clinically ill.

Antiviral treatment is successful in 50–90% of persons treated, depending on the treatment used, and has also been shown to reduce the

development of liver cancer and cirrhosis. There is no vaccine for Hepatitis C, however research in this area is ongoing. The best way to prevent Hepatitis C is by avoiding behaviors that can spread the disease, especially injecting drugs. Hepatitis C virus (HCV) causes both acute and chronic infection. Acute HCV infection is usually asymptomatic, and is only very rarely associated with life-threatening disease. About 15-45% of infected persons spontaneously clear the virus within 6 months of infection without any treatment. he remaining 55-85% of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15-30% within 20 years.

Hepatitis C is found worldwide. The most affected regions are Central and East Asia and North Africa. The hepatitis C epidemic can be concentrated in certain high-risk populations (for example, among people who inject drugs); and/or in general populations. There are multiple strains (or genotypes) of the HCV virus and their distribution varies by region. The incubation period for hepatitis C is 2 weeks to 6 months. Following initial infection, approximately 80% of people do not exhibit any symptoms. Those who are acutely symptomatic may exhibit fever, fatigue, decreased appetite, nausea, vomiting, abdominal pain, dark urine, grey-coloured faeces, joint pain and jaundice (yellowing of skin and the whites of the eyes). Hepatitis C does not always require treatment as the immune response in some people will clear the infection. When treatment is necessary, the goal of hepatitis C treatment is cure. The cure rate depends on several factors including the strain of the virus and the type of treatment given. Careful screening is necessary before starting the treatment to determine the most appropriate approach for the patient.

The current standard treatment for hepatitis C is combination antiviral therapy with interferon and ribavirin, which are effective against all the genotypes of hepatitis viruses (pan-genotypic). Unfortunately, interferon is not widely available globally and it is poorly tolerated in some patients. This means that management of the treatment is complex, and many patients do not finish their treatment. Despite these limitations, interferon and ribavirin treatment can be life-saving.

Some treatments of HCV infection are Pegylated interferon in combination with ribavirin, direct-acting antivirals telaprevir or boceprevir, given in combination with pegylated interferon and ribavirin, Sofosbuvir, given in combination with rib- avirin with or without pegylated interferon (depending on the HCV genotype) and Simeprevir, given in combination with pegylated interferon and ribavirin. Scientific advances have led to the development of new antiviral drugs for hepatitis C, which are much more effective, safer and better-tolerated than existing therapies. These therapies, known as oral directly acting antiviral agent (DAAs) therapies simplify hepatitis C treatment by significantly decreasing monitoring requirements and by increasing cure rates. Although the production cost of DAAs is low, the initial prices set by companies are very high and likely to make access to these drugs difficult even in high-income countries. Much needs to be done to ensure that these advances lead to greater access to treatment globally.

Mathematical modelling and quantitative analysis of hepatitis C infections has been explored extensively over the last decade. Most of the modelling has been restricted to the short term dynamics of the model. One of the earliest models was proposed by Neumann et al. [2], who examine the dynamics of HCV in presence of Interferon-α (IFN-α) treatment. They find that the primary role of IFN is in blocking the production of virions from the infected hepatocytes. However, IFN has little impact when it comes to controlling the infection of the hepatocytes. Dixit et al. [3] improved upon [2] by including the effects of ribavirin , which in turn results in a fraction of the virions being rendered noninfectious. Control theory has found wide ranging applications in biological and ecological problems [5]. In the case of HCV, Chakrabarty and Joshi [6] consider a model (motivated by [2, 3, 4] for HCV dynamics under

combination therapy of interferon and ribavirin. An objective functional is formulated to minimize the viral load, as well as the drug side-effects and the optimal system is solved numerically to determine optimal efficacies of the drugs. Chakrabarty [7] extended the results in [6] by considering a clinically validated functional form for the interferon efficacy and hence determined the optimal efficacy of ribavirin. Martin et al. [8] in a recent paper examine a three compartment model for HCV, involving the susceptible, chronically infected and treated injecting drug users (IDUs).Recently, a bicompartmental mathematical model for determining hepatitis C virus dynamics has been designed [9]. Taking two delays we can deal with determining the Hopf bifurcation points of this model during physical acticity where we consider three cases: Walking, Jogging, and Running fast.

This paper is organised as follows. In section 2, we set mathematical model equations as well as equilibrium points. The section 3 deals with the asymptotic states and algorithm for determining the bifurcation points. In section 4 we present test results for a patient who administrating the drugs. The concluding remarks are presented in section 5.

Setting mathematical model equations

One of an important phenomena to human health is the control of hepatitis C virus. The question that often arises is of determining interferon and ribavirin for controlling the dynamics of HCV. For a patient, it is well known that Interferon is a protein made by the immune system, named because it interferes with viral reproduction. In addition, interferon signals the immune system to recognize and respond to microorganisms, including viral and bacterial infections. Ribavirin, also known as Copegus, Rebetol, Virazole, or a component of Rebetron, is a type of antiviral medicine called a nucleoside analogue.

This medicine blocks the ability of the hepatitis C virus (HCV) to make more copies of itself. The models generally consist of solving control optimal problems of nonlinear differential equations with cumbersome terms, leading to unstable solutions. In literature, we have generally the mathematical models where the determinant parameters describe at least the dynamics of uninfected hepatocytes, infected hepatocytes and virions under therapy [2, 6]. These models require that we must, first, search stable equilibrium states and, secondly, compute the solution on an interval (0, T) with small value of time T for the initial state which is very closed to the equilibrium state. Sometime, such mode doesn't permit to understand a long-term of hepatitis C dynamics virus. In this paper, we would like to be interested in a two compartmental model developed in [9] and its diagram of a two compartment is shown in the figure 1 where we consider the uninfected hepatocytes compartment (H) and infected hepatocytes (I) and the blood flows in liver through circulatory system. Two positive delays are added in a two compartmental mathematical model for showing the role of drugs in controlling the plasma uninfected hepatocytes and infected hepatocytes levels. The variation of these physiological parameters are function of interferon and ribavirin. In this way we consider that the flow plasma of uninfected hepatocytes cells and infected hepatocytes cells in liver is delayed by two positive constants τ_h and τ_i respectively.Based on the diagram presented in the figure 1 and physiology properties of hepatitis C virus in human body the mathematical model equations are [9]: The effectiveness of the control of interferon and ribavirin is influenced by the transport delays because through the corculatory system, a certain distance is needed so that blood flows in capillary to the sensory sites of the liver. The control thery can be used to find the optimal control of hepatitis C virus from the mathematical model equations (1)-(2). Therefore, the role of controls is to stabilize the determinant parameters aroung their equilibrium values [5]. In this work we adapt model equations (1)-(2) to include the effects of two transport delays as follows,

$$\frac{d}{dt}H(t) = -H(t) + (I(t-\tau_i))^{\gamma} f(IFN(t), Rib(t)) \quad (1)$$

$$\frac{d}{dt}I(t) = -I(t) + (H(t-\tau_h))^{\sigma} g(IFN(t), Rib(t)) \quad (2)$$

where

$$\gamma = -0.0089 \text{ and } \sigma = -0.4678$$

$$f(IFN, Rib) \approx 73.8550 \times Rib \times IFN^{2.0320} - 1090.2213 \times Rib + 996.5871 \times IFN + 152.4584 \quad (3)$$

$$g(IFN, Rib) \approx 884.9682 \times \sin(Rib \times IFN) + 350.8518 \times Rib + 48.3569 \times IFN \quad (4)$$

and τ_h, τ_i are respectively uninfected hepatocytes and infected hepatocytes delays.

In the context of determining the equilibrium of the system (1)-(2), let IFN_e, Rib_e, H_e and I_e be the equilibrium states. At the equilibrium we have

$$\begin{aligned} H(t) &= H(t-\tau_g) = H_e \\ I(t) &= I(t-\tau_i) = I_e \\ W(t) &= W_e \\ Z(t) &= Z_e \end{aligned}$$

where we have set

$$W(t) = f(H(t), I(t)) \text{ and } Z(t) = g(H(t), I(t)),$$

so that

$$W_e = f(IFN_e, Rib_e) \quad and \quad Z_e = g(IFN_e, Rib_e)$$

Therefore we have the system

$$\begin{cases} -H_e + (I_e)^{\gamma} W_e = 0 \\ -I_e + (H_e)^{\sigma} Z_e = 0, \end{cases} \quad (5)$$

Since it is known that uninfected hepatocytes and infected hepatocytes take the values that satisfy the following expression

$$H(t) > 0 \text{ and } I(t) \geq 0, \qquad \forall t.$$

It follows that the equilibrium state is determined by

$$\begin{cases} I_e = (W_e)^{\frac{\gamma}{1-\sigma\gamma}} (Z_e)^{\frac{1}{1-\sigma\gamma}} \\ H_e = (W_e)^{\frac{1}{1-\sigma\gamma}} (Z_e)^{\frac{\sigma}{1-\sigma\gamma}} \end{cases} \qquad (\sigma\gamma \neq 1) \quad (6)$$

Proposition 2.1 *[9]*

Assume that

$$0 < \delta\gamma < 1$$

then the equilibrium state defined by (6) is stable.

□

Proposition 2.2 *[9]*

Assume that f and g are positive functions and differentiable with respect to their argument, then for given positive constants H_0 and I_0, there exist control functions IFN, and Rib such that the system (1)-(2) admits a unique positive solution $(H, I) \in (C_1(0,T))^2$ that satisfies $H(0) = H_0$ and $I(0) = I_0$. Moreover this solution is asymptotically stable.

□

To determinine the equilibrium points we take

$$x(t) = H(t),\ y(t) = I(t),$$

$$u_1(t) = f(IFN, Rib),\ u_2(t) = g(IFN, Rib),$$

then the model system (1)-(2) becomes

$$\begin{cases} \dfrac{dx(t)}{dt} = -x(t) + y^{\gamma}(t-\tau_i)u_1(t) \\ \dfrac{dy(t)}{dt} = -y(t) + x^{\sigma}(t-\tau_h)u_2(t) \end{cases}. \tag{7}$$

Let $(x^*, y^*)^T$ be an equilibrium point of variable state $(x, y)^T$ and $(u_1^*, u_2^*)^T$ be the equilibrium of corresponding control parameters $(u_1, u_2)^T$. At the equilibrium point we have

$$x(t) = x(t-\tau_h) = x^*, \quad y(t) = y(t-\tau_i) = y^*, \quad u_1(t) = u_1^* \text{ and } u_2(t) = u_2^*.$$

and the system (7) becomes

$$\begin{cases} -x^* + (y^*)^{\gamma}u_1^* = 0 \\ -y^* + (x^*)^{\sigma}u_2^* = 0. \end{cases} \tag{8}$$

which can be written as follows

$$\begin{cases} (y^*)^{\gamma}u_1^* = x^* \\ (x^*)^{\sigma}u_2^* = y^*. \end{cases} \tag{9}$$

Solving system (9) we get

$$x^* = (u_1^*)^{\frac{1}{1-\gamma\sigma}} \times (u_2^*)^{\frac{\gamma}{1-\gamma\sigma}}$$

and

$$y^* = (u_1^*)^{\frac{\sigma}{1-\gamma\sigma}} \times (u_2^*)^{\frac{1}{1-\gamma\sigma}}.$$

3 Asymptotic states

Assuming

$$y_{\tau_i}(t) = y(t-\tau_i)$$

and

$$x_{\tau_h}(t) = y(t-\tau_h)$$

the system (7) is written as follows

$$\begin{cases} \dfrac{dx(t)}{dt} = f_1(x, y_{\tau_i}, u_1) = -x(t) + y_{\tau_i}^{\gamma}(t)u_1(t) \\ \dfrac{dy(t)}{dt} = f_2(y, x_{\tau_h}, u_2) = -y(t) + x_{\tau_h}^{\sigma}(t)u_2(t) \end{cases}.$$

Using the first order Taylor series around the equilibrium point, we get

$$\begin{cases} \dfrac{dx(t)}{dt} = \dfrac{\partial f_1(x^*,y^*,u_1^*)}{\partial x}(x-x^*) + \dfrac{\partial f_2(x^*,y^*,u_1^*)}{\partial y_{\tau_i}}(y_{\tau_i}-y^*) \\ \qquad + \dfrac{\partial f_3(x^*,y^*,u_1^*)}{\partial u_1}(u_1-u_1^*) + \ldots \\ \dfrac{dy(t)}{dt} = \dfrac{\partial f_1(x^*,y^*,u_2^*)}{\partial y}(y-y^*) + \dfrac{\partial f_2(x^*,y^*,u_2^*)}{\partial x_{\tau_h}}(x_{\tau_h}-x^*) \\ \qquad + \dfrac{\partial f_3(x^*,y^*,u_2^*)}{\partial u_2}(u_2-u_2^*) + \ldots \end{cases}$$

After calculations, the linearized system becomes

$$\begin{cases} \dfrac{dx(t)}{dt} = -(x-x^*) + \gamma(y^*)^{\gamma-1}u_1^*(y_{\tau_i}-y^*) + (y^*)^{\gamma}(u_1-u_1^*) \\ \dfrac{dy(t)}{dt} = -(y-y^*) + \sigma(x^*)^{\sigma-1}u_1^*(x_{\tau_h}-x^*) + (x^*)^{\delta}(u_2-u_2^*) \end{cases},$$

which can be written in matrix form as follows

$$\begin{cases} \dfrac{dX(t)}{dt} = A_1X(t) + A_2X(t-\tau_{as}) + A_3X(t-\tau_{vs}) + DU(t) \\ X(t) = X_0, \quad -\tau \le t \le 0, \end{cases} \tag{10}$$

where we set

$$X(t) = \begin{pmatrix} x - x^* \\ y - y^* \end{pmatrix}, \; A_1 = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix}, \; U = \begin{pmatrix} u_1 - u_1^* \\ u_2 - u_2^* \end{pmatrix},$$

$$A_2 = \begin{pmatrix} 0 & 0 \\ \sigma(x^*)^{\sigma-1}u_2^* & 0 \end{pmatrix}, \; A_3 = \begin{pmatrix} 0 & \gamma(y^*)^{\gamma-1}u_1^* \\ 0 & 0 \end{pmatrix}.$$

The solution of the system (10) can be written as

$$\begin{cases} X(t) = M(t)e^{\lambda t} \\ X(0) = M(0). \end{cases} \tag{11}$$

Calculating the derivative from (11) we obtain

$$\frac{dX(t)}{dt} = \frac{dM(t)}{dt}e^{\lambda t} + \lambda M(t)e^{\lambda t}. \tag{12}$$

Taking into account (11) and (12) the system (10) becomes

$$\frac{dM(t)}{dt}e^{\lambda t} + \lambda M(t)e^{\lambda t} = A_1 M(t)e^{\lambda t} + A_2 M(t)e^{\lambda(t-\tau_h)} + A_3 M(t)e^{\lambda(t-\tau_i)} + DU(t),$$

that is

$$\frac{dH(t)}{dt}e^{\lambda t} = (A_1 + A_2 e^{-\lambda\tau_h} + A_3 e^{-\lambda\tau_i} - \lambda I)H(t)e^{\lambda t} + DU.$$

We can now find λ such that

$$(A_1 + A_2 e^{-\lambda\tau_h} + A_3 e^{-\lambda\tau_i} - \lambda I) = 0,$$

thus due to this condition $M(t)$ is the solution:

$$\begin{cases} \frac{dM(t)}{dt}e^{\lambda t} = DU(t) \\ M(0) = X_0, \end{cases}$$

where

$$M(t) = D\int_0^t U(s)e^{-\lambda s}ds + X_0.$$

Consequently from (11)we have

$$X(t) = e^{\lambda t}[D\int_0^t U(s)e^{-\lambda s}ds + X_0].$$

We know that the stability of this solution depend on the property of the parameter λ. Therefore, to find the stability of the solution of equation (10) is to study the stability of the homogeneous equation of the form

$$\frac{dX(t)}{dt} = A_1X(t) + A_2X(t-\tau_h) + A_3X(t-\tau_i) \tag{13}$$

that is

$$\frac{dX(t)}{dt} = 0.$$

From the equation (13) we deduce the characteristic equation of the form:

$$\left|A_1 + A_2e^{-\lambda\tau_h} + A_3e^{-\lambda\tau_i} - \lambda I\right| = 0. \tag{14}$$

which is written as

$$\begin{vmatrix} -1-\lambda & \gamma(y^*)^{\gamma-1}(u_1^*)e^{-\lambda\tau_i} \\ \sigma(x^*)^{\sigma-1}(u_2^*)e^{-\lambda\tau_h} & -1-\lambda \end{vmatrix} = 0,$$

After the calculations we get

$$(-1-\lambda)^2 - \sigma(x^*)^{\sigma-1}(u_2^*)e^{-\lambda\tau_h}\gamma(y^*)^{\gamma-1}(u_1^*)e^{-\lambda\tau_i} = 0,$$

that is

$$\lambda^2 + 2\lambda + 1 - \sigma(x^*)^{\sigma-1}\gamma(y^*)^{\gamma-1}(u_2^*)e^{-\lambda\tau_h}(u_1^*)e^{-\lambda\tau_i} = 0. \tag{15}$$

Since

$$(y^*)^{\gamma} = \frac{x^*}{u_1^*} \text{ and } (x^*)^{\sigma} = \frac{y^*}{u_2^*} \text{ (see (9))}$$

we get

$$\lambda^2 + 2\lambda + 1 - \sigma\frac{y^*}{u_2^*}\frac{1}{x^*}\gamma\frac{x^*}{u_1^*}\frac{1}{y^*}u_2^*e^{-\lambda\tau_h}u_1^*e^{-\lambda\tau_i} = 0.$$

Finally we obtain the characteristic polynomial of the form

$$P(\lambda) \equiv \lambda^2 + 2\lambda + 1 - \gamma\sigma e^{-\lambda(\tau_h+\tau_i)} = 0. \tag{16}$$

Let us set $\lambda = i\omega$, the determination of Hopf bifurcation points for the equation (16) results in solving the system

$$\begin{cases} K(\omega, \tau_a, \tau_b) = 0 \\ L(\omega, \tau_a, \tau_b) = 0 \end{cases}$$

where

$$K(\omega, \tau_a, \tau_b) = Re(P(i\omega)) \quad and \quad L(\omega, \tau_g, \tau_i) = Im(P(i\omega)) \tag{17}$$

are respectively real and imaginary part of P (iω) [10]. The purpose of calculation is to try and find out bifurcation points using the α-dense curves in R^2. The general algorithm for computing the bifurcation points of the system that being have the general form as (13) constitutes the main outcomes presented in [10]. We adopt the algorithm to our situation as follows.

1. Set $\alpha > 0$ and define h_α as α-dense curve in $\mathbb{R}^2$
2. Write the functions K and L as defined in (17)
3. Define $K_\alpha(\omega, \phi) = K(\omega, h_\alpha(\phi))$ and $L_\alpha(\omega, \phi) = L(\omega, h_\alpha(\phi))$ where ϕ is angle to be determined
4. Find $(\omega_\alpha^*, \phi_\alpha^*)$ solution of $K_\alpha(\omega, \phi) = 0$ and $L_\alpha(\omega, \phi) = 0$
5. Set $\tau_\alpha^* = h_\alpha(\phi_\alpha^*)$ as bifurcation point.

We apply this algorithm in order to get the critical delays of the system (13). From the results presented in [?] the curve defined by

$$x_1 = \alpha\theta_k \cos\theta_k, \quad x_2 = \alpha\theta_k \sin\theta_k, \ k = 0, 1, 2, ...$$

is $\pi\alpha$-dense in $\mathbb{R}^2$ where α is a constant to be correctly chosen. The critical delays for Hopf bifurcations are given by

$$\tau_g^* = \alpha\theta^* \cos\theta^*, \quad \tau_i^* = \alpha\theta^* \sin\theta^*,$$

where θ^* is obtained at step 4 of above algorithm.

Test results

Our numerical simulations aims to determine the Hopf bifurcation points for a two delays model for a patient who administrating the drugs. For this purpose we illustrate the variation of determinant parameters vis- a-vis their equilibrium values given in the table 1. Taking α = 1.76 to have a curve that covers the space R^2 of the delay parameters and setting initial value θ_0 = 1.2460 we obtain the delay parameters as given in the tables 2. The results illustrated in the figures 2 and 3 are outcome of the numerical simulation by implementing the algorithm presented in the section 3 and taking the value of table 1 and 2. The figure 2 deals with the variation of uninfected hepatocytes and infected hepatocytes.

The variation of uninfected hepatocytes vs infected hepatocytes is shown in the figure 3 for three possible phases (phase asymptotically stable, unstable phase and Hopf bifurcation) through the phase portraits of transition phases.

For a patient who administrating the drugs (Interferon and ribavirin), we find that a small perturbation of Hopf bifurcation's delay parameters allows the subject to pass from stable state (figures 2(a) and (d)) to unstable state (figures 2(c) and (f)) through an intermediate transition (Hopf bifurcation) [figures 2(b) and (e)]. In the case of instability, it appears that the state of subject causes to grow worse from the greatest value to the state closed to the equilibrium. The case of

stability is due to the behaviour of uninfected hepatocytes and infected hepatocytes that vary such that the state of the subject remains stationary around the equilibrium (figure 2(a) and (c)) while a small perturbation causes oscillations which correspond to Hopf bifurcations (figure 2 (b) and (e)). A small perturbation of Hopf bifurcation's delay parameters can be used to suffer a sudden downfall to an unstable state. The stability and instability behaviors of transition phase of uninfected hepatocytes and infected hepatocytes are also shown by the phase portrait where we have a stable spiral in the case of Hopf bifurcation as shown in figure3(b).

Conclusion

In this work the investigation of uninfected hepatocytes and infected hepatocytes in the case of Hopf bifurcation is done for a bicompartmental mathematical model. The curves show the responses of uninfected hepatocytes and infected hepatocytes of patient with hepatitis to ts controls (interferon and ribavirin). An algorithm is used to find delay parameters of stability, instablility and Hopf bifurcation for this patient so that Hopf bifurcations are the intermediate oscillation solutions from stability to instability regions.

Table.1 The equilibrium and initail value for a patient with hepatitis C virus

Variable	H	I
Initial value (cells/dl)	500	250
Equilibrium value (cells/dl)	1000	0

Table.2 Delay parameters from the resolution of algorithm in the walking case

Delay parameters	Stability	Hopf bifurcation	Instability
τ_h	0.0176	0.5973	1.6707
τ_i	2.0122	3.2592	4.8135

Figure.1 A schematic diagram of two compartments for modeling human hepatitis C virus dynamics. PBr is blood pressure. IFN is interferon and Rib is ribavirin. H and I represent uninfected hepatocytes and infected hepatocytes respectively

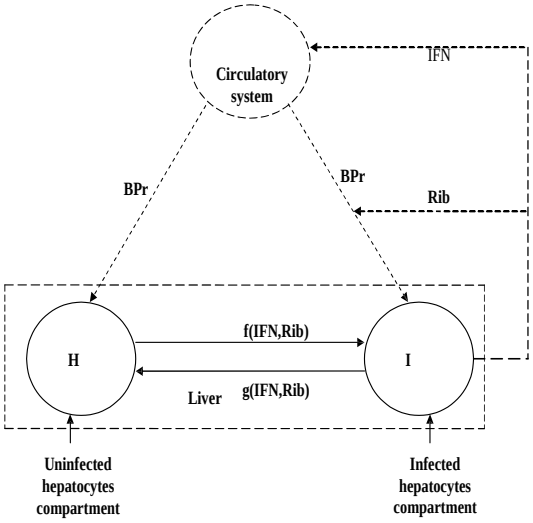


Figure.2 Variation trajectory of uninfected hepatocytes ((a), (b), (c)) and infected hepatocytes ((d), (e), (f)) compared to their respective equilibrium (dashed line) for a patient who administrates drugs during 12 months. The transition phases are illustrated from left to right (phase asymptotically stable towards unstable phase) and the curve in the middle correspond to Hopf bifurcation parameters.

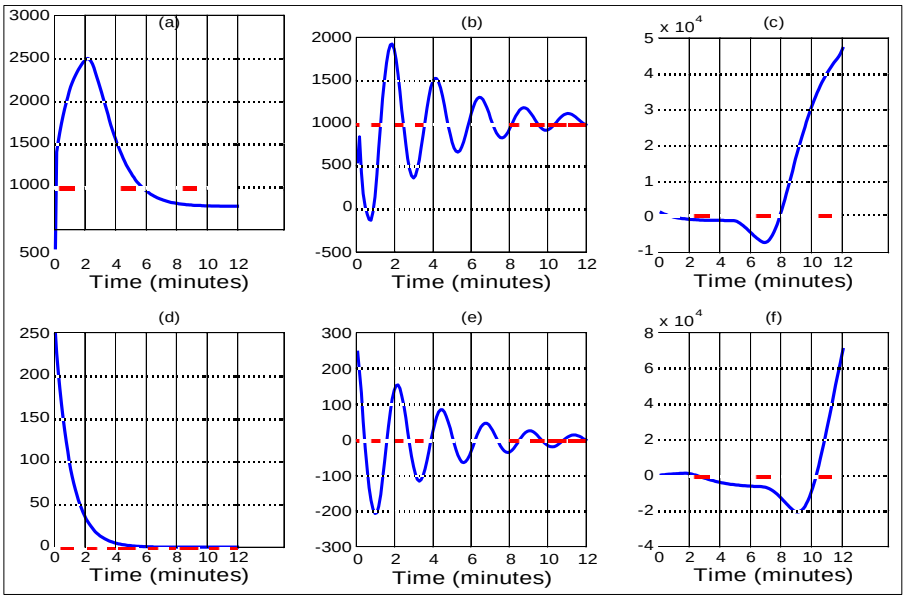
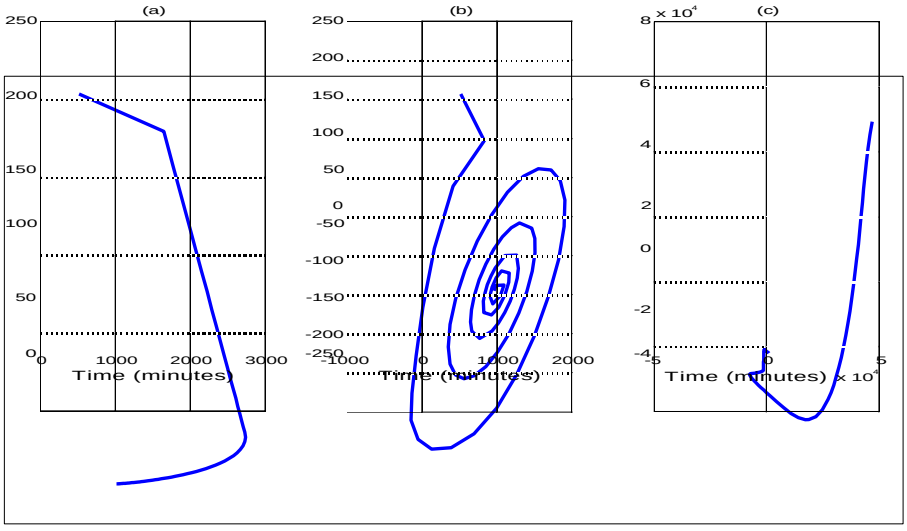


Figure.3 The phase portrait (systemic arterial pressure versus systemic venous pressure according to variation of transition phases plotted in the figure ?? for a 30 years old woman during walking physical activity. The curves are illustrated from (a) to (c) (phase asymptotically stable towards unstable phase) and the curve in (b) corresponds to Hopf bifurcation.



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