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Modelling a Therapeutic Hepatitis C Virus Dynamics

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Abstract: *This paper aims at designing a two compartmental mathematical model for determining the response of protein (Interferon) and drug (Ribarivin) for a patient who is suffering from hepatitis C virus. A two nonlinear coupled ordinary differential equations is provided. Stability conditions are established. The inverse techniques are used for identifying model parameters. To test efficiency and response of increasing of interferon and ribavirin, the validation of the model is achieved by considering a patient administrating the drugs during 12 months.*

Keywords: *Hepatitis C, Virus, Infection, Parameters identification, Modelling, Numerical simulation, Interferon, Ribavirin*

1. INTRODUCTION

Hepatitis C is a liver infection caused by the Hepatitis C virus (HCV): the virus can cause both acute and chronic hepatitis infection, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. Hepatitis C is a blood-borne virus. Today, most people become infected with the Hepatitis C virus by sharing needles or other equipment to inject drugs. For some people, hepatitis C is a short-term illness but for 70%-85% of people who become infected with Hepatitis 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. The hepatitis C virus is a bloodborne 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. 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-colored faces, 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 ribavirin 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.

WHO provides a limited example of primary prevention interventions (hand hygiene: including surgical hand preparation, hand washing and use of gloves, safe handling and disposal of sharps and waste, safe cleaning of equipment, testing of donated blood, improved access to safe blood and training of health personnel) and secondary and tertiary prevention (education and counseling on options for care and treatment, immunization with the hepatitis A and B vaccines to prevent co-infection from these hepatitis viruses to protect their liver, early and appropriate medical management including antiviral therapy if appropriate and regular monitoring for early diagnosis of chronic liver disease).

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. [1], 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. [2] improved upon [1] by including the effects of ribavirin , which in turn results in a fraction of the virions being rendered noninfectious. Their model is able to explain clinically observed biphasic decline patterns amongst patient population. Their study also shows that while IFN plays a pivotal role in the first phase decline of viral load, ribavirin has very little impact. However, in case of low IFN efficacy, ribavirin makes a significant contribution to the second phase of decline. The model could not successfully explain the triphasic decline patterns, as well as some cases of non-responders. Dahari et al. [3] in a subsequent and improved model, take into account the homeostatic mechanisms for the liver by incorporating a growth function. This model successfully explains the triphasic decline, as well as therapeutic failures.

Control theory has found wide ranging applications in biological and ecological problems [4]. In the case of HCV, Chakrabarty and Joshi [5] consider a model (motivated by [1, 2, 3] 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 [6] extended the results in [5] by considering a clinically validated functional form for the interferon efficacy and hence determined the optimal efficacy of ribavirin. Martin et al. [7] in a recent paper examine a three compartment model for HCV, involving the susceptible, chronically infected and treated injecting drug users (IDUs). They determine an optimal treatment program over a 10 year period taking into account several biomedical and economic objectives. The objective of this paper is to find a new mathematical model of therapeutic hepatitis C virus dynamics with treatment of two drugs, that is combination treatment with IFN and ribavirin.

This paper is organized as follows. In section 1, we build the mathematical model to be considered as

well as the inverse technique for computing unknown constants and functions of the model and stability analysis of the. Model parameters are computed in section 2. In section 3 we present numerical results for a healthy subject. The concluding remarks are presented in section 4.

2. MODEL DESIGN

2.1. Outline of the Model

In this section we would like to design a mathematical model for determining uninfected hepatocytes and infected hepatocytes with respect to IFN and ribavirin. Let us describe briefly overview of IFN and ribavirin. 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. Infected cells release interferon to trigger the immune response. There are three types of interferon: alfa (IFN-α), beta (IFN-β) and gamma (IFN-γ). Interferon alfa is used to treat viral hepatitis and some types of cancer. The type 1 IFNs [interferon alpha and beta (IFN-α/β)] comprise a family of distinct proteins [8] that are produced by a wide variety of cells, including fibroblasts, epithelial cells, and hepatocytes [9], although plasmacytoid dendritic cells (DCs) are probably the major source in most viral infections. In contrast, type II IFN [interferon gamma (IFN-γ)] is a single gene cytokine unrelated in structure to IFN-α/β that is produced largely by macrophages, natural killer (NK) cells, and T lymphocytes. Both types of IFNs interact with cells via distinct cellular receptors. The details of the signaling mechanisms by which IFN-α/β and IFN-γ induce the transcription of interferon-stimulated genes (ISGs) and depress the transcription of others are still being defined [10]. However, it is increasingly clear that the complex transcriptional programs induced differ significantly depending on the IFN type, the cellular target, and the nature of the infection/host challenge. IFN-α/β produced by DCs activates NK cells, enhancing their cytotoxic potential and stimulating their production of IFN-γ, whereas other cytokines such as interleukin-15 (IL-15) induced by IFN-α/β stimulates the proliferation and accumulation of NK cells [11, 12]. IFN- α/β produced by DCs also modulates the activation of CD8+ T cells, which produce additional IFN-γ and represent the central players in the pathogen-specific adaptive immune response [13].

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. Ribavirin is not active against HIV. Ribavirin is used in combination with interferon alfa-2a or -2b or peginterferon alfa-2a or -2b to treat HIV infected patients who are also infected with HCV. Ribavirin capsules are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 18 years of age and older with compensated liver disease previously untreated with alpha interferon or in patients 18 years of age and older who have relapsed following alpha interferon therapy. Ribavirin is a broad spectrum antiviral agent that is used with pegylated IFN (Peg-IFN) for HCV treatment. Ribavirin does not significantly reduce HCV viral load when used alone but increases rates of sustained virologic response (SVR) when combined with Peg-IFN. HCV genotype 1 infected patients require higher doses of ribavirin administered for a longer duration of time versus HCV genotypes 2 and 3 patients who respond effectively to Peg-IFN with lower doses of ribavirin and shorter duration of therapy. Higher serum concentrations of ribavirin are associated with higher response rates but also higher rates of hemolytic anemia which is a dose limiting side effect.

To find the equations of our mathematical model, we first consider a dimensional model given by Dahari et al. [3]. This model is based on the mathematical model developed by Neumann et al. [1]. It describes the dynamics of the the uninfected and infected hepatocytes as well as the hepatitis C virus. Since this model excludes the role of IFN in blocking the infection and it was observed to have minimal effect in this case , it was extended to include the therapeutic effects of ribavirin [2]. Taking into account those consideration and the mechanisms of action of interferon and ribavirin in chronic hepatitis C we propose a two compartmental model composed of the uninfected hepatocytes compartment (UH) and the infected hepatocytes compartment (IH) by hepatitis virus as shown in the figure 1

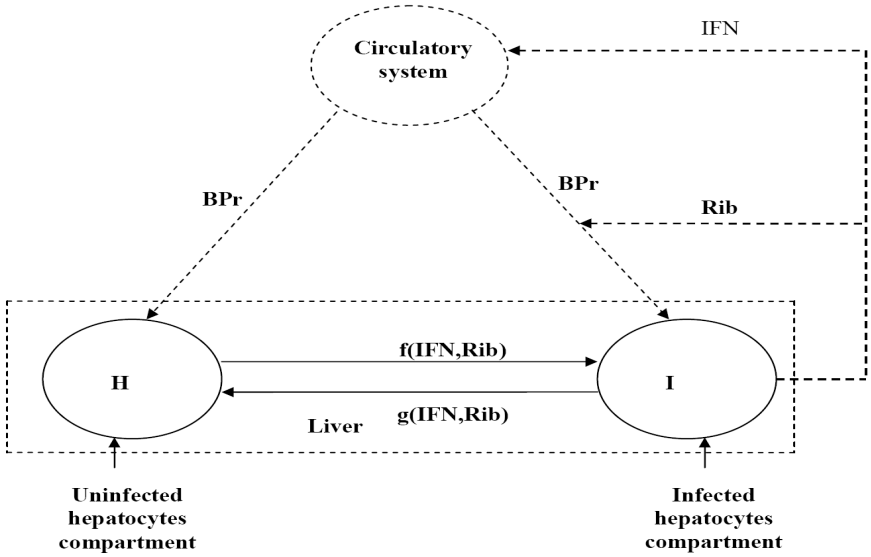

Figure1. *A schematic diagram of two compartments for modeling human hepatitis C virus dynamics. PBr is blood pressure. IFN is interferon and Rib is ribavirin. H and I represent uninfected hepatocytes and infected hepatocytes respectively.*

The model has two compartments: compartment (UH) and the infected hepatocytes compartment (IH). From circulatory system the the drugs in the blood flow in liver where we have two those compartment due to blood pressure. Two controls IFN and ribavirin that control the dynamics of hepatocytes. The mechanism of this control is not direct and can be represented by outflow functions between uninfected hepatocytes and infected hepatocytes compartments that depend on interferon (IFN) and ribavirin (Rib) [figure 1] which flow in lever through circulatory system by blood pressure. Therefore a nonlinear compartment analysis leads on the following new global model

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

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

where the functions $H(t)$ and $I(t)$ denote respectively uninfected hepatocytes and infected hepatocytes at time t, α and β are model constants and f, g model functions to be identified. Equation (1) and (2) arise from straightforward development of mass balance between uninfected hepatocytes and infected hepatocytes compartments. They are obtained from Fick's law, Boyle's law related to the concentration of interferon and ribavirin in human blood.

2.2. Stability Analysis

Let H_e and I_e be the equilibrium states. According to equations (1) and (2) we have

$$\begin{cases} -H_e + (I_e)^{\alpha} f_e = 0 \\ -I_e + (H_e)^{\beta} g_e = 0, \end{cases} \tag{3}$$

where $f_e = f(IFN_e, Rib_e)$ and $g_e = g(IFN_e, Rib_e)$. Since it is known that uninfected hepatocytes and infected hepatocytes take the values strictly positive that is

$H(t) > 0$ and $I(t) \geq 0, \quad \forall t$

it follows that the equilibrium state is determined by

$$\begin{cases} I_e = f_e^{\frac{\beta}{1-\alpha\beta}} g_e^{\frac{1}{1-\alpha\beta}} \\ H_e = f_e^{\frac{1}{1-\alpha\beta}} g_e^{\frac{\beta}{1-\alpha\beta}} \end{cases} \qquad (\alpha\beta \neq 1). \tag{4}$$

Proposition 1

Let us assume that

$$0 < \alpha\beta < 1 \tag{5}$$

then the equilibrium state defined by (3) is stable.

Proof

According to the dynamic system theory, the stability of an equilibrium state of two ordinary differential equations is determined by analyzing the behavour of the Hessian matrix. When it is definite negative this equilibrium is stable. Since the corresponding Hessian matrix defined by the the equilibrium state (4) is given as follows

$$\mathbf{H} = \begin{bmatrix} -1 & \alpha f_e^{\frac{1-\beta}{1-\alpha\beta}} g_e^{\frac{\alpha-1}{1-\alpha\beta}} \\ \beta f_e^{\frac{\beta-1}{1-\alpha\beta}} g_e^{\frac{1-\alpha}{1-\alpha\beta}} & -1 \end{bmatrix}.$$

The characteristic equation becomes

$$\lambda^2 + 2\lambda + 1 - \alpha\beta = 0, \tag{6}$$

where λ is eigenvalue.

It is easy to verify that the equation () has two strictly negative real roots if and only if $0 < \alpha\beta < 1$ so that the proposition 1 yields.

The consequence of the proposition 1 is that the solutions of proposal model (1) and (2) converge toward the equilibrium state. Therefore we have the following result·

Proposition 2

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 a couple of control functions $(IFN(t), Rib(t))$ with $t \in [0, T_{\max}]$ such that the system ()-() admits a unique positive solution $(IFN(t), Rib(t)) \in (C^1(0, T_{\max}))^2$ that satisfies $H(0) = H^0$ and $I(0) = I^0$. Furthermore this solution is asymptotically stable.

We can refer to [14] and [13] for the proof of the proposition. It is should be mentioned that the bifurcation analysis technique may predict the existence of the Hopf bifurcation at parameter values where the equilibrium loses its stability and periodical stable solutions exist when the value of parameter increases. In this work we mainly focus our attention on the identification of the model parameters that leads to asymptotically stable solutions.

3. COMPUTING MODEL PARAMETERS

Let us be interested in identifying the constant α and β and the functions f and g· We take $T_{\max}$ as a positive time parameter and N as integer parameter. We consider

$$\underline{H}^{\mu} = (H^{\mu}(t_1), ..., H^{\mu}(t_N))^T$$

$$\underline{I}^{\mu} = (I^{\mu}(t_1), ..., I^{\mu}(t_N))^T,$$

where $H^{\mu}(t_k)$ and $I^{\mu}(t_k)$ are measured data at the time $t_k = \frac{kT_{\max}}{N}$ representing ideal values $H(t_k)$ and $I(t_k)$; μ is the perturbation parameter due to some imprecision on measured data. Mathematically the identification problem can be formulated as follows.

Find $=(\alpha,\beta,\bar{f},\bar{g})$ solution of the output least squares problem

$$J(\underline{u})=\min_{\underline{u}=(\alpha,\beta,\underline{f},\underline{g})} J(\underline{u}), \tag{7}$$

where

$$J(\underline{u})=\left\|\underline{H}^{\mu}-H^{\mu}\right\|^2+\left\|\underline{I}^{\mu}-I^{\mu}\right\|^2 \tag{8}$$

and

$$\underline{f}=(f(IFN(t_k),Rib(st_k))^T, \qquad \underline{g}=(g(IFN(t_k),Rib(st_k))^T, \tag{9}$$

and where $\underline{H}$ and $\underline{I}$ are $\mathbb{R}^N$ vector solutions at time grid points of the system (1)-(2) depending of the parameter vector $\underline{u}$ and $IFN(t_k)$ and $Rib(t_k)$ are the values of hepatitis C virus control IFN and IFN at the time t_k respectively.

We should mention that (7) is a nonlinear inverse problem that is generally ill-posed in the sense that a couple $(\underline{H},\underline{I})$ does not depend continuously on $\underline{u}$. That is, a little perturbation on data produces a solution that is very different of the original ones. For getting a well posed problem the regularization techniques are used [16, 17]. Therefore based upon Tikhonov regularization [17], we consider the problem of finding $\underline{\bar{u}}^{\eta}$ solution of

$$J(\underline{\bar{u}}^{\eta})=\min_{\underline{u}=(\alpha,\beta,f,g)} J^{\eta}(\underline{u}), \tag{10}$$

where we have set

$$J^{\eta}(\underline{u})=\left\|\underline{H}^{\mu}-H^{\mu}\right\|^2+\left\|\underline{I}^{\mu}-I^{\mu}\right\|^2+\eta\left\|\mathbf{L}u\right\|^2 \tag{11}$$

for a given η such that $\underline{u}^{\eta}$ converges toward the solution $\underline{u}$ as $\eta\to 0$. Here $\mathbf{L}$ is an operator used for stabilization (i.e., $\mathbf{L}$ is the identity, a differentiation operator, etc.).

Our numerical simulation aims at identification of coefficients and functions parameters of the mathematical model. Therefore, the purpose is to consider the control observed data corresponding to patient administrating the drugs during 12 months. Thereafter numerical solutions are carry out using a collection of MATLAB routines for solving the optimization problem () and the ordinary differential system (1)-(2).

Observed data of interferon and ribavirin are plotted in figures 2. The solution of uninfected hepatocytes and infected hepatocytes obtained from the model and its observed data are given in figures 3. Computed values obtained with MATLAB routines are

$$\alpha=-0.0089 \text{ and } \beta=-0.4678 \tag{12}$$

and the corresponding identified functions f and g are represented in figures 4.

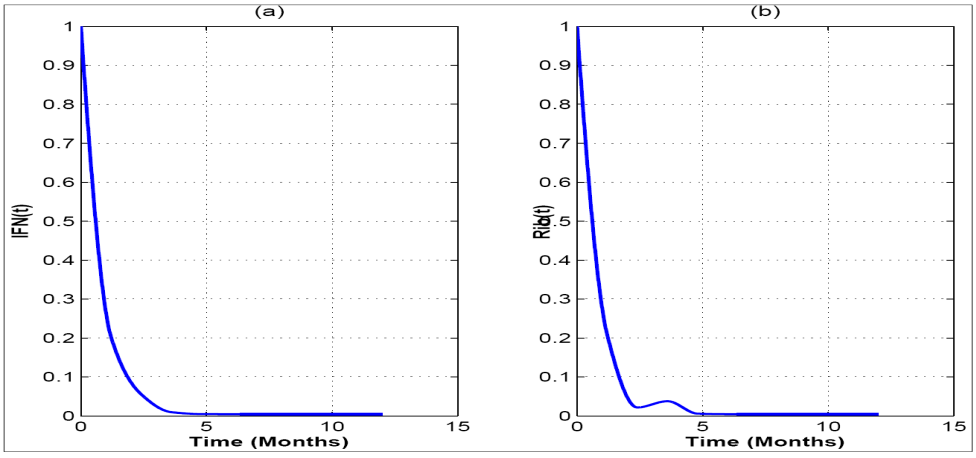

Figure2. *Observed data for interferon (a) and ribavirin (b) for a patient administrating those drugs during 12 months.*

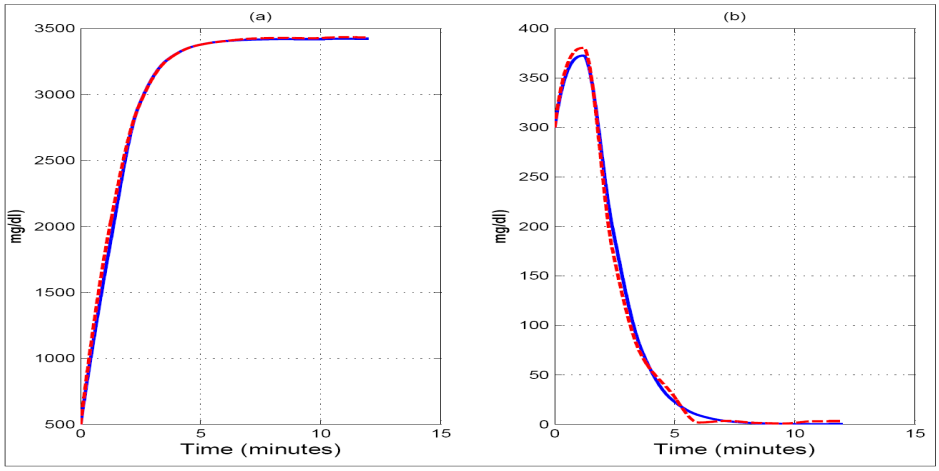

Figure3. *The uninfected hepatocytes (a) and infected hepatocytes (b) where dashed line denotes the observed data while solid line is the output of the model solution. We see that the two curves are very closed*

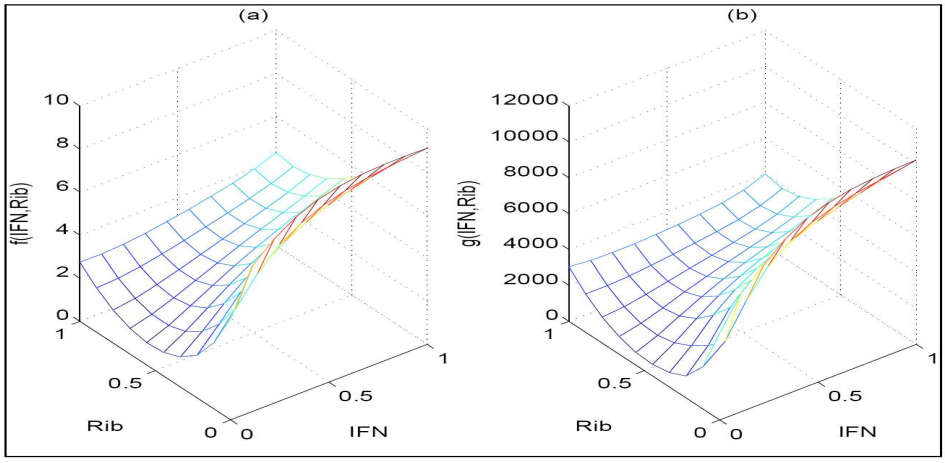

Figure4. *The identified functions f and g*

The expressions of the functions f and g must be fitted to achieve the identification of our model. Based on data illustrated in figure 4, we use numerical iterative techniques for the minimization of a merit function that gives information about the goodness of the fitting process. The following are solutions of fitting curves of functions f and g.

1. Model 1

$$f(IFN, Rib) \approx 75.7961 IFN \times Rib - 536.6375 Rib + 475.4780 IFN$$

$$g(IFN, Rib) \approx -155.0246 \sin(IFN) \times Rib + 386.3074 \sin(Rib) + 444.9382 .$$

2. Model 2

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

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

4. TEST RESULTS

We know that the goal of HCV treatment is to cure the virus, which can be done with a combination of drugs. The specific meds used and the duration of treatment depend on a number of factors, including HCV genotype (genetic structure of the virus), viral load, past treatment experience, degree of liver damage, ability to tolerate the prescribed treatment, and whether the person is waiting for a liver transplant or is a transplant recipient. In some cases, HCV treatment may be limited by your health insurance plan or drug formulary. To test our models we consider a patient who is infected with the Hepatitis C virus. The patient is administrating the ribavirin as drug and increasing the interferon

as protein in the body during 12 months. The role of interferon and ribavirin for hepatitis C virus is to allow uninfected hepatocytes cells to be around the equilibrium value ($H_e = 1000$ cells/dl) and to remove all infected hepatocytes ($I_e = 0$) in the body of patient. These mean values are for healthy subjects. The autoregulation process evolves in formulating the optimal way toward these values. This suggests us to solving the following optimal control problem:

Find IFN^* and Rib^*

$$\min_{(IFN,Rib)\in\mathbb{R}^2} \|H - H_e\|^2 + \|I - I_e\|^2 + IFN^2 + Rib^2$$

subject to the system (1)-(2). Test results for our model are plotted in figure 5 where the dotted lines correspond to the first model while the dashed lines are related to the second model. The solid lines represent desired mean values. In this figure we have depicted the curves of optimal solutions for each model described above.

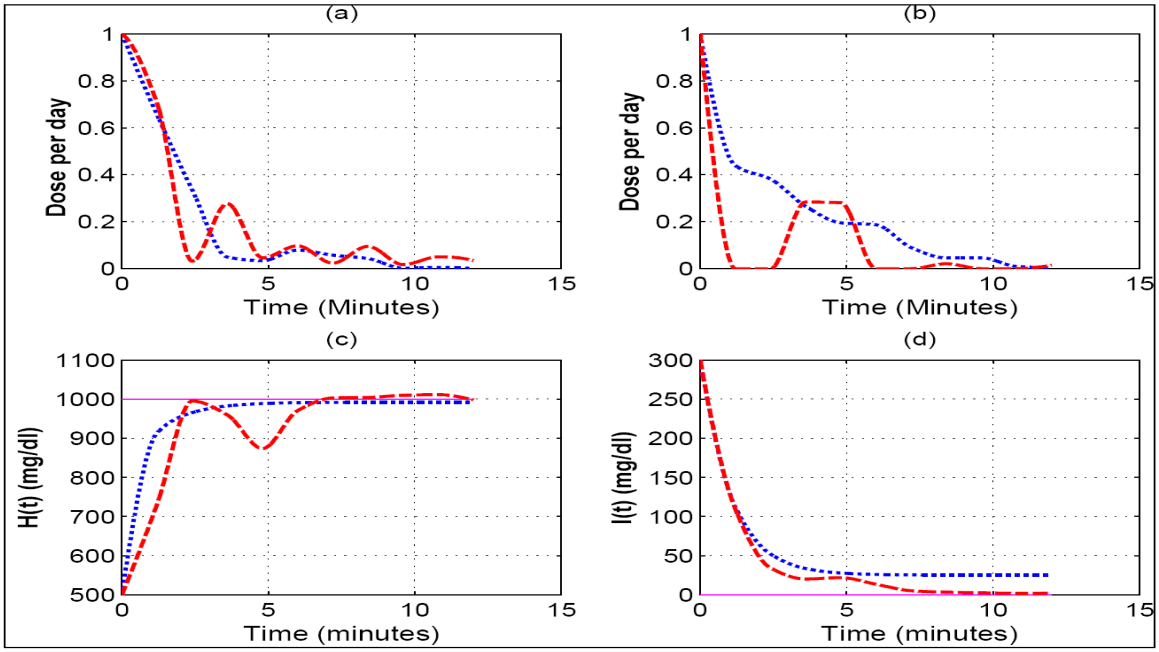

Figure5. *Variation of optimal trajectories of interferon (a), ribavirin (b), uninfected hepatocytes (c) and infected hepatocytes (d) where dotted lines correspond to the first model while the dashed lines are related to the second model. The solid lines represent desired mean values.*

It is known that the main aim of treatment for chronic hepatitis C is to suppress HCV replication before there is irreversible liver damage. Furthermore, the role of drugs on chronic hepatitis C virus is to reduce the risk of liver disease and prevent you from passing the infection to others. The controls variation of hepatitis C virus are represented in figure (a) and (b) which shows the decrease from 1 (when and treatment is absent) of both interferon (IFN) and ribavirin (Rib) to be closer to the lower value 0 (maximal use of therapy). During the treatment period, the number of infected hepatocytes is decreasing and one of uninfected hepatocytes is increasing. This mechanism is due to the response of drugs. When IFN and Rib as protein and drug respectively act on its minimal level (at this stage the controls reach their minimum value equal to zero as shown in the figure (a) and (b)), they fight against the antibodies and the number of infected hepatocytes decreases rapidly until when it reaches the value zero (no virus in the body as illustrated in the figure (d)). This makes all liver cells to be free; and consequently, no infected liver cells. The response of control is also shown in the figure (c) where there is a increase of uninfected hepatocytes to its desired value. The results obtained in this work are rather satisfactory. In particular, the reaction of the disease to drugs can be modeled and a feedback can be approximated by the solution of an optimal control problem. The drugs reduce the risk of disease. Therefore the drugs play a crucial role such that any patient becomes healthy.

5. CONCLUDING REMARKS

In this work we have investigated a two compartmental mathematical model that describes the variation of uninfected hepatocytes and infected hepatocytes for hepatitis C virus due to the response of protein (Interferon) and drug (Ribavirin). The treatment of HCV depends on a number of factors. The increasing necessity to interpret the meaning of measurable variables such as interferon and ribavirin under both physiological and pathological conditions for a patient has imposed the need for relatively simple models that should be able to describe as accurately as possible the mechanical behavior of the disease. The modelling technique used in present work provides interesting answers to the question of determining the best treatment capacity capacity during administration of drugs. Numerical simulations give interesting conclusions. Notably the model would helpful for the control of some HCV patients.

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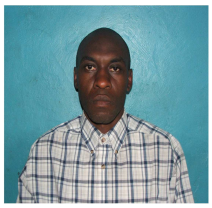

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