International Journal of Scientific and Innovative Mathematical Research (IJSIMR)
Volume 3, Issue 8, August 2015, PP 23-30
ISSN 2347-307X (Print) & ISSN 2347-3142 (Online)
www.arcjournals.org

Using Direct Approach for Solving an Optimal Control Problem of a Therapeutic Hepatitis C Virus Dynamics

Jean Marie Ntaganda

University of Rwanda
College of Science and Technology, School Sciences,
Department of Mathematics, Rwanda
jmnta@yahoo.fr, j.m.ntaganda@nur.ac.rw

Marcel Gahamanyi

College of Science and Technology,
School Sciences,
Department of Mathematics,
Rwanda
mgahamanyi@gmail.com

Abstract: *In the current study, the direct method has been chosen to serve for solving an optimal control problem for the dynamics of the hepatitis C virus in the human body. A two compartmental mathematical model of ordinary differential equations has been taken to constitute a set of constraints. In that model, protein (Interferon) and drug (Ribavirin) stand for controls. Assuming that the patient is administrating both interferon and Ribarivin; the efficiency of the method has been tested via the model validation by taking the values of the determinant parameters of the said disease. Results of the chosen numerical method are in good agreement with experimental data*

Keywords: *Hepatitis C, Virus, Infection, Optimal control problem, Numerical simulation, Interferon, Ribavirin*

1. INTRODUCTION

Hepatitis C, a blood-borne virus emanates from infection with the hepatitis C virus (HCV). It is an enveloped, single stranded and positive sense RNA virus [1]. The virus is susceptible to cause both acute (lasting a few period of time) and chronic (lifelong) hepatitis infection depending on the patients. Chronic Hepatitis C is a serious disease that can result in long-term health problems including the patient death. According to [2], 130-150 million of people globally have chronic hepatitis C infection and among them a significant number should develop liver cirrhosis or liver cancer. Each year, 350,000 to 500,000 people die from hepatitis C-related liver diseases. About 40% of HCV patients recover fully, but the remainder, whether they present symptoms or not, become chronic carriers. Of these, 20% develop cirrhosis. Of those with cirrhosis, up to 20% develop liver cancer [2].

Although HCV is less commonly transmitted through the infected blood than HBV and HIV [3]; HCV is usually spread by sharing infected needles with a carrier, by receiving infected blood or by accidental exposure to infected blood. Sometimes infection can also be acquired via nonparental means that is not yet fully defined including sexual transmission. The majority of infected persons might not be aware of their infection because they are not clinically ill. HCV is not spread by breast feeding, sneezing, coughing, hugging, sharing eating utensils or drinking glasses, other normal social contact, food or water and a person who has hepatitis C can still get other types of hepatitis, such as hepatitis A or hepatitis B [4]. Antiviral medicines can cure hepatitis C infection, but access to diagnosis and treatment is low. It has been shown that depending on the treatment used, antiviral treatment is successful about 50-90% of patients treated and reduces the development of both liver cancer and cirrhosis. For the time being, 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. It is well known that 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 six months of infection without any treatment. the remaining 55-85% of persons might develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15-30% within 20

years. The current standard treatment for hepatitis C is combination of 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 of these limitations, interferon and ribavirin treatment can be life-saving.

Some treatments of HCV infection are Pegylated interferon in combination with ribavirin, direct-acting antiviral 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. To ensure that these advances lead to greater access to treatment globally, much needs must be done.

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. [5], who examine the dynamics of HCV in presence of Interferon- α (IFN- α) treatment. They found that the primary role of IFN is to block 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. [6] improved upon [5] 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 crucial 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. [7] 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. Mathematical models can be a useful tool in controlling hepatitis C virus in order to put down the infection from the population.

Control theory has found wide ranging applications in biological and ecological problems [8]. In that context Chakrabarty and Joshi [9] considered a model (motivated by [5]) for HCV dynamics under control of the combination of interferon and ribavirin. An objective function is formulated to minimize the viral load, as well as the drug side-effects and the optimal system is solved numerically to determine optimal efficacy of the drugs. Chakrabarty [10] extended the results in [8] by considering a clinically validated function form for the interferon efficacy and hence determined the optimal efficacy of ribavirin. Martin et al. [11] 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 programme 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 structured as follows. In section one, we set an optimal control problem so be solved. The outline of direct method is presented in section two. In section three we present numerical results and the concluding remarks are presented in section four.

2. SETTING OF AN OPTIMAL CONTROL PROBLEM

In terms of constraints of our problem, we consider a two compartmental mathematical model proposed in [12]. This mathematical model is formulated from a diagram given in the figure 1.

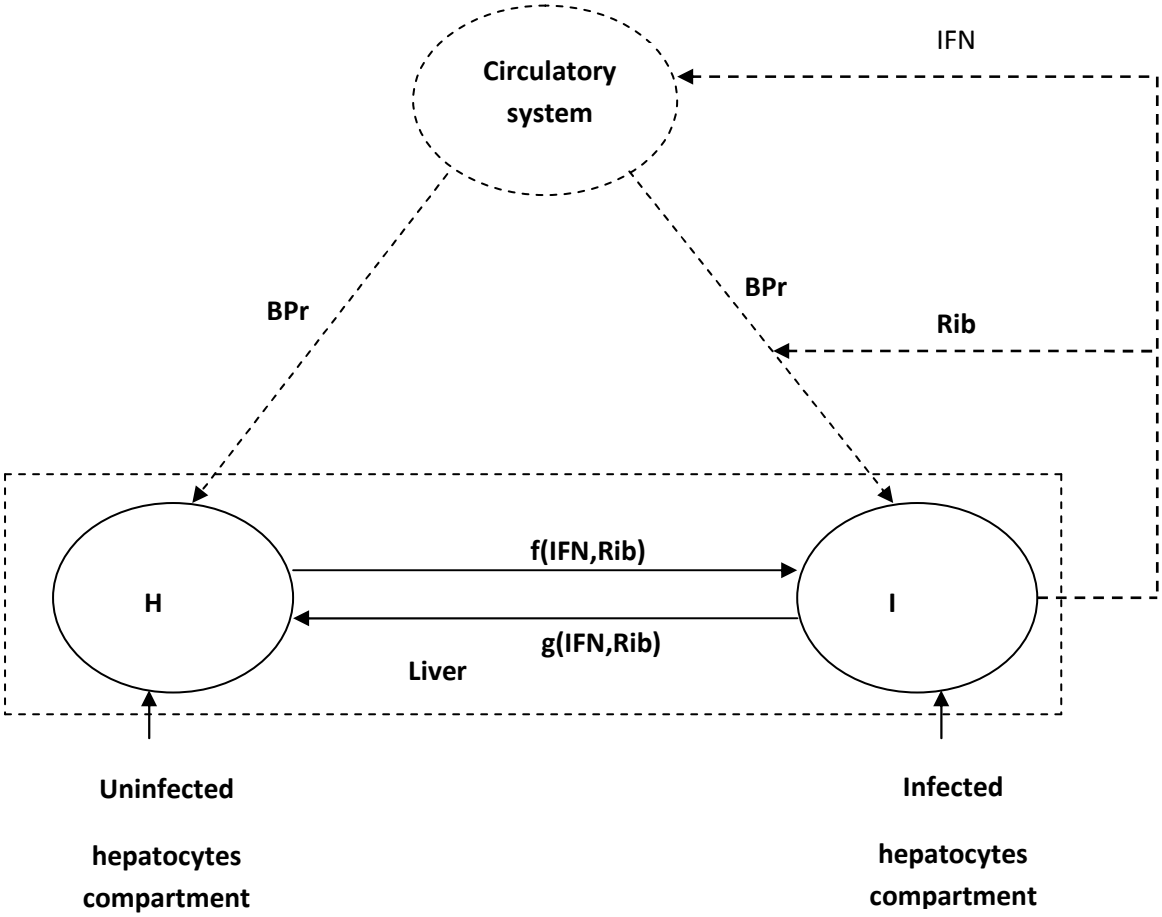

Figure 1. *A schematic diagram of two compartments for modeling human hepatitis C virus dynamics. PBr is blood pressure. IFN is interferon and Rib is ribavirin. H and I represent uninfected hepatocytes and infected hepatocytes respectively.*

The equations the model are presented in the following form:

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

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

where

$\alpha = -0.0089$ and $\beta = -0.4678$

and

1) Model 1

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

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

2) Model 2

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

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

If $X = (H, I)^T$ is a state vector, then the healthy improvement conditions for an uninfected human should look for reaching uninfected steady state $X_e = (H_e, I_e)^T$ where H_e is the constant that must be found out. Since $I_e = 0$, next the cost function (objective function) was formulated in the following way.

Find $IFN^*(t)$ and $Rib^*(t)$ solution of

$$J(IFN, Rib) = \int_0^{T_{\max}} q_H \left(H - H_e\right)^2 + q_{IFN} IFN(t)^2 + q_{Rib} Rib(t)^2 \tag{3}$$

subject to the system (1)-(2).

The positive scalar coefficients q_H, q_{IFN}, and q_{Rib} determine how much weight is attached to each cost component term in the integrand whereas $T_{\max}$ denotes the maximum time that the physical activity can take.

3. OUTLINE OF DIRECT APPROACH AND DISCRETIZATION OF OBJECTIVE FUNCTION

In order to approximate the system (1)-(2), we consider

$$\mathbf{B}^N = \left\{\psi_j^N,\ j = 1,..., N\right\} \tag{4}$$

a linear B-splines basis functions on the uniform grid

$$\Omega_N = \left\{t_k = \frac{kT_{\max}}{N},\ \ k = 0,..., N\right\}, \tag{5}$$

such that

$\psi_i^N(t_k) = \delta_{ik}$.

Let us introduce the vector space W^N whose the basis is $\mathbf{B}^N$. In this context we have

- $\dim W^N = N$
- $W^N \subset W^{N+1}$.

Let us consider again $W = C^0(0,T)$ and take the following interpolation operator

$$\begin{array}{rccl} \Pi^N & : & W & \to & W^N \\ & & \phi & \mapsto & \Pi^N \phi. \end{array} \tag{6}$$

This satisfies the following condition

$$\Pi^N \phi(t_k) = \phi(t_k), \quad k = 1, \cdots, N. \tag{7}$$

We verify easily that

$$\left\|\Pi^N \phi - \phi\right\|_W \underset{N\to\infty}{\to} 0 \quad \forall \phi \in W \tag{8}$$

$$\left\|\Pi^N\right\| = \sup_{\substack{\phi \neq 0 \\ \phi \in W}} \frac{\left\|\Pi^N \phi\right\|_W}{\left\|\phi\right\|_W} = 1. \tag{9}$$

Therefore, the system (1)-(2) can be approached by the following form.

Find $(H^N, I^N) \in (W^N)^2$ solution of the system

$$\frac{d}{dt} H^N(t) = -H^N(t) + \left(I^\alpha\right)^N f^N(IFN(t), Rib(t)) \tag{10}$$

$$\frac{d}{dt} I^N(t) = -I^N(t) + \left(H^\beta\right)^N g^N(IFN(t), Rib(t)) \tag{11}$$

$$H^N(0) = H_0^N, \quad I^N(0) = I_0^N, \tag{12}$$

such that

$$\left|H_0 - H_0^N\right| \underset{N\to\infty}{\to} 0 \tag{13}$$

$$\left|I_0 - I_0^N\right| \underset{N\to\infty}{\to} 0. \tag{14}$$

The discretization of the optimal problem (3) is done as follows.

$$\min_{\lambda \in Q} J^N(\lambda) = \int_0^{T_f} \left(q_H (H^N(t) - H_e)^2 + \sum_{j=1}^{2} q_j . (\lambda_j(t))^2 \right) dt \ , \tag{15}$$

where

$\lambda = (IFN, Rib)^T$ and $q = (q_{IFN}, q_{Rib})^T$

with λ_j and q_i respectively the j^{th} component of the vectors λ and q respectively.

We are looking for $\lambda^M = (\lambda_1^M, \lambda_2^M) \in Q^M$ an approximated solution of (15) in the set $Q^M = (W^M)^2$ such that

$$\lambda_j^M = \sum_{k=0}^{M} \lambda_{j,k}^M \psi_k(t), \quad j = 1,2. \tag{16}$$

Therefore the cost function (15) becomes

$$J^N(\lambda^M \quad \approx \quad \sum_{k=1}^{M} \left(q_H \left(H^N(t_k) - H_e \right)^2 + \sum_{j=1}^{2} q_j \left(\lambda_{j,k}^M \right)^2 \right) h, \qquad \text{with } h = \frac{T_{\max}}{M}, \tag{17}$$

where (17) is determined using rectangular method such that the discretization is done on a regular grid Ω_M .

The discrete formulation of optimal problem (3) subject to (1)-(2) is written as follows.

$$\min_{\lambda^M \in \mathbb{R}^{(M+1)} \times \mathbb{R}^{(M+1)}} J^N(\underline{\lambda}^M) \approx \Delta t \left((Y^T R Y) + \left(\underline{\lambda}^M \right)^T B \underline{\lambda}^M \right) \tag{18}$$

where $\underline{\lambda}^M$ is a matrix $(M+1) \times 2$ such that the components $\lambda_{j,k}^M$ are components of the function λ_j^N in the set $\mathbf{B}^N$ and Y represents the matrix with $(i,k)^{th}$ component, $H^N(t_k) - H_e$ denotes the first components of solution of the system ()-() associated to $\lambda = \lambda^N$, R and B are matrix defined by

$$R = \begin{pmatrix} q_H & 0 \\ 0 & q_H \end{pmatrix}, \qquad B = \begin{pmatrix} q_{IFN} & 0 \\ 0 & q_{Rib} \end{pmatrix}.$$

Finally, the optimal control problem (3), (1)-(2) is a minimisation problem with constraint. The discrete formulation of such problem can be written as follows.

Find $\lambda^{*,M} \in \mathbb{R}^{(M+1)} \times \mathbb{R}^{(M+1)}$ solution of

$$\min_{\lambda^M \in \mathbb{R}^{(M+1)} \times \mathbb{R}^{(M+1)}} J^N(\underline{\lambda}^M) \approx \Delta t \left((Y^T R Y) + \left(\underline{\lambda}^M \right)^T B \underline{\lambda}^M \right), \tag{19}$$

subject to

$$\begin{cases} \dfrac{d}{dt} H^N(t) = -H^N(t) + \left(I^{\alpha} \right)^N f^N(IFN(t), Rib(t)) \\ \dfrac{d}{dt} I^N(t) = -I^N(t) + \left(H^{\beta} \right)^N g^N(IFN(t), Rib(t)), \end{cases} \tag{20}$$

where $\underline{\lambda}^M$ is a matrix $(M+1) \times 2$ such that the components $\lambda_{j,k}^M$ are those function λ_j^N in $\mathbf{B}^N$ and Y is the matrix such that the $(j,k)^{th}$ component is $x_j^N(t_k) - x_j^e$, where $x^N = (H^N, I^N)^T$ is the solution of (3) subject to (1)-(2) associated to $\lambda = \lambda^N$ and $x^e = (H_e, I_e)^T$.

4. NUMERICAL TEST RESULTS

The treatment used and its duration 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. 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. In some cases, HCV treatment may be limited by the 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 the interferon is increasing as protein in the body during 12 months. It is known that the role of interferon and ribavirin for hepatitis C virus is to allow uninfected hepatocytes cells to be around the equilibrium value. In this case the equilibrium value has been considered to be $H_e = 1000$ cells/dl as uninfected hepatocytes and $I_e = 0$ as infected hepatocytes. In the same way, in numerical simulation we take $N = 100$ and $T_{\max} = 12$. We take also the initial values of a patient of HCV that is $H_0 = 500$ and $I_0 = 300$. Test results of numerical simulation are illustrated in figure 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 trajectories of determinant parameters, that is uninfected hepatocytes, infected hepatocytes, interferon and ribavirin.

The variation of controls of the mathematical model (1)-(2) is illustrated in figure (a) and (b).

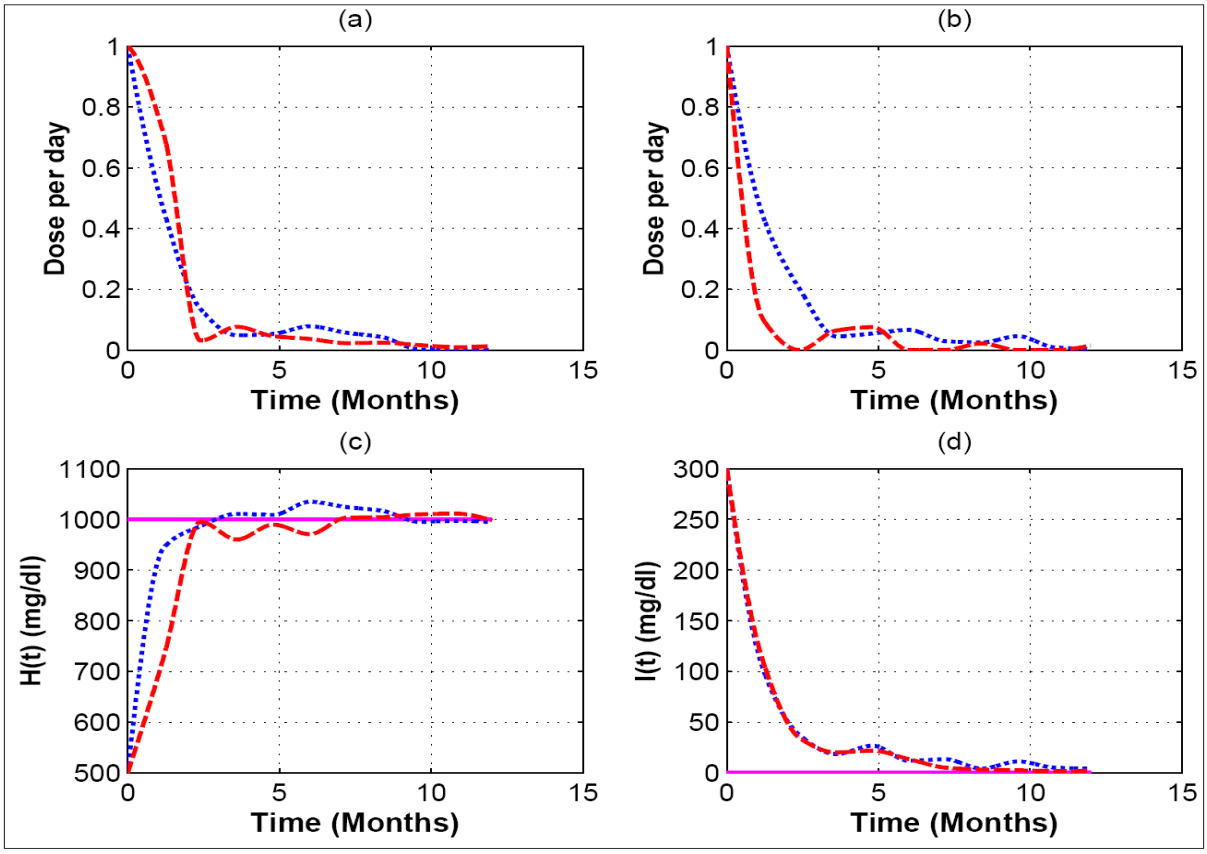

Figure 2. *Variation of optimal trajectories of interferon (a), ribavirin (b), uninfected hepatocytes (c) and infected hepatocytes (d) where dotted lines correspond to the first model while the dashed lines are related to the second model. The solid lines represent desired mean values.*

This figure shows the decrease from 1 (when the treatment is absent) of both interferon (IFN) and ribavirin (Rib) to be closer to the lower value 0 (maximal use of therapy). The response of those two controls is represented in the figure (c) and (d). Furthermore, during the treatment period, the number of infected hepatocytes is decreasing ((d)) and one of uninfected hepatocytes is increasing ((c)). When IFN and Rib as protein and drug respectively act on its minimal level (at this stage the controls reach their minimum value equals 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)) whereas uninfected hepatocytes

increases. 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, that is the drugs reduce the risk of disease and therefore the protein and drug play a crucial role such that any patient becomes healthy.

5. CONCLUDING REMARKS

In this work we have been investigating an optimal control problem of 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 different 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 direct approach used in the present work provides interesting answers to the question of determining optimal trajectories due to the best treatment capacity during a certain period of administration of drugs. Numerical simulations give interesting conclusions. Notably the model would be helpful for the control of some HCV patients.

REFERENCES

[1]. Houghton M, *Hepatitis C viruses. In: Fields BN*, Knipe DM, Howley PM, eds. Fields Virology, 3rd ed. Philadelphia, Lippincott - Raven, 1996:1035-1058.

[2]. EASL, *International Consensus Conference on Hepatitis C. Consensus Statement*, Journal of Hepatology, 1999, 31:3-8.

[3]. Alter MJ, *Hepatitis C virus infection in the United States*, Journal of Hepatology, 1999, 31:88-91.

[4]. Mast EE, Alter MJ, Margolis HS, *Strategies to prevent and control hepatitis B and C virus infections: a global perspective.* Vaccine, 1999, 17:1730-1733.

[5]. Neumann AU, Lam NP, Dahari H, Gretch DR,Wiley TE, Layden TJ, Perelson AS. (1998), *Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-α therapy*, Science 282: 103-107.

[6]. Dixit NM, Layden-Almer JE, Layden TJ, Perelson AS, (2004), *Modelling how ribavirin improves interferon response rates in hepatitis C virus infection*, Nature 432:922924.

[7]. Dahari H, Lo A, Ribeiro RM, Perelson AS, (2007), *Modeling hepatitis C virus dynamics: liver regeneration and critical drug efficacy*, Journal of Theoretical Biology 247: 371-381.

[8]. Lenhart S, Workman JT, *Optimal control applied to biological methods*. Mathematical and Computational Biology Series, Chapman & Hall/CRC, London, UK, 2007.

[9]. Chakrabarty SP, Joshi HR (2009), *Optimally controlled treatment strategy using interferon and ribavirin for hepatitis C*, Journal of Biological Systems, 17(1): 97-110

[10]. Chakrabarty SP (2009), *Optimal efficacy of ribavirin in the treatment of hepatitis C*, Optimal Control Applications and Methods, 30(6): 594-600

[11]. Martin NK, Ashley B, Pitcher AB, Vickerman P, Vassal A, Hickman M (2011), *Optimal control of hepatitis C antiviral treatment programme delivery for prevention amongst a population of injecting drug users*, PLos One, 6(8): e22309.

[12]. Jean Marie Ntaganda, (July 2015), *Modelling a Therapeutic Hepatitis C Virus Dynamics*; International Journal of Scientific and Innovative Mathematical Research (IJSIMR), Volume 3, Issue 7, July 2015, PP 1-10, ISSN 2347-307X (Print) & ISSN 2347-3142 (Online)

AUTHORS' BIOGRAPHY

Prof. Ntaganda Jean Marie, PhD holder in Numerical Analysis from Cheikh Anta Diop University of Dakar, Senegal (2004-2006) and Ouagadougou University, Burkina Faso (2004-2007). He is Associate Professor in Applied Mathematics at University of Rwanda, College of Science and Technology, School of Sciences, Department of Mathematics where he is module leader of many modules related to computation and numerical analysis. Since 2005 he is active researcher in Biomathematics where more than 20 publications have been published in international peer-reviewed journals.

Marcel Gahamanyi, is a Rwandan Lecturer of mathematics at the University of Rwanda-College of science and Technology. Marcel Gahamanyi is a Bsc, Msc holder in Pure mathematics, Med and PhD holder in Mathematics education. His research interest is widened in various area of mathematics including Ordinary and partial differential equations, Numerical analysis and Mathematics education.