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Modelling the hepatitis C with different types of virus genome

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Hepatitis C virus (HCV) is one of the leading known causes of liver disease in the world. The HCV is a single-stranded RNA virus. The genomes of HCV display significant sequence heterogeneity and have been classified into types and subtypes. Types from 1 to 11 have so far been recognized, each type having a variable number of subtypes. It has been confirmed that 90% approximately of the isolates HCV infections in Egypt belong to a single subtype (4a) [10]. In this paper, we construct a mathematical model to study the spread of HCV-subtype 4a amongst the Egyptian population. The relation between HCV-subtype 4a and the other subtypes has also been studied. The values of reproduction numbers R_{01}, R_{02} have been derived [5]. Also, threshold conditions for the value of the transmission rates k_1 and k_{02}, in terms of R_{01}, R_{02} and the mutation factor μ have been determined to insure that the disease will die out. If the conditions fail to happen the disease takes off and becomes endemic.

Keywords: Modelling; Hepatitis C virus; RNA; Egypt

1. Introduction

It is known that hepatitis C virus (HCV) is one of the leading known causes of liver disease in the world. It is a common cause of cirrhosis and hepatocellular carcinoma HCC as well as the most common reason for liver transplantation. HCV infection is found in 0.5–8.0% of blood donors worldwide. Because the infection is chronic in more than 60% of infected persons, the disease is a serious economical problem [7]. The WHO organisation estimates that 3% of the world population is infected with HCV and about 20–30% of them may develop cirrhosis and 1–3% of the infected persons may develop liver cancer [2]. This problem needs to be studied more to give a clearer insight to the dynamics of this mysterious disease and possibly solve or try to solve this major worldwide problem.

Egypt has possibly the highest HCV prevalence in the world; 10–20% of the general population are infected and HCV is the leading cause of HCC and chronic liver disease in the country [4]. The genomes of HCV display significant sequence heterogeneity and have been classified into types and subtypes. Six types from 1 to 6 have been recognized, each type having a different number of subtypes like a, b, c, etc. Recently, new variants have been identified and assigned to proposed types 7–11. The worldwide presence of the virus and the geographic distribution of genotypes clearly indicate that HCV is an old companion of human kind [8].

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It is believed that the HCV has evolved over a period of several thousand years. This would explain the current general global patterns of genotypes and subtypes [3].

Most of the Egyptian HCV isolates belong to a single subtype (4a), which responds less successfully to interferon therapy than the other subtypes [10]. Within a hepatitis C subtypes, individual viruses differ from each other, ever so slightly. Such viral differences are not significant enough to form another subtype but instead form what's known as "quasispecies" [6]. Heterogeneous genomes "quasispecies" resulting from mutations due to high error rates in RNA replications are found within the same host. Many important biological features of several viruses are attributable to their "quasispecies" nature, including vaccination failure, persistent infection and resistance to antiviral drugs [8]. To date, there is no successful HCV vaccination nor control strategy. So, we require an understanding of the nature and variability of epidemic behavior among subtypes.

In the present work, this public health problem will be studied mathematically and using computer simulations. We construct a mathematical model to study the spread of HCV-subtype 4a in the Egyptian population and the relation between HCV-subtype 4a and other subtypes of HCV.

In the model, we assume that people from the Egyptian population have some factors which lead to substitutions or mutations of the different genotypes of HCV into HCV-subtype 4a. We analyze and solve our model and derive new results about the behavior of the spread of HCV. The mutation factor μ plays a key role for this study. We derive the R_{01}, R_{02} which are defined as the expected number of secondary cases produced by a single infected individual entering a disease free population at equilibrium [5]. These numbers are crucial to our study. We determine conditions on R_{01}, R_{02} for the disease to be endemic or die out. Intuitively, the disease will die out when both R_{01} and R_{02} are less than one in value otherwise the disease becomes endemic.

The numerical solutions of our models predict the behavior of the dynamics of the disease and estimate the numbers of persons in each stage. Mathematica 5.1, has been used to conduct our numerical simulations for our model.

2. The model

We suggest that, the model of the spread of the HCV-subtype 4a disease has the following assumptions,

1. The total population size is a constant N and the population is divided into three groups:
    (a) The susceptible class, S, comprising those people who are capable of catching the disease;
    (b) the HCV subtype 4a infective class, I_1, the persons who are infected by virus HCV subtype 4a directly or by virus HCV other subtypes and had mutated to subtype 4a; and
    (c) the HCV from all subtype except 4a infective class, I_2, the persons who are infected by virus HCV-all subtype except 4a.
2. All types of HCV infections can mutate to HCV subtype 4a in their bodies at a positive constant rate (μ).
3. The virus vertical transmission is rare [9]. All ages of population can be infected by HCV virus. The basic role of the transmission is blood-to-blood, so susceptible class S moves in to the infective class (I_1), by a positive constant contact rate k_1. Also, S moves to the infected class I_2 by a positive constant rate k_2.

4. We assume that the birth and death rates are equal and positive constant rate b.
5. The population is mixing in a homogenous manner, i.e. every person has the same chance of coming in contact with an infected person.

The SI_1I_2 model for the spread of virus HCV-subtype 4a can be written as a set of three coupled nonlinear ordinary differential equations as follows:

$$\frac{dS}{dt} = -(k_1I_1 + k_2I_2)S - bS + bN, \tag{1}$$

$$\frac{dI_1}{dt} = k_1SI_1 - bI_1 + \mu I_2, \tag{2}$$

and

$$\frac{dI_2}{dt} = k_2SI_2 - bI_2 - \mu I_2, \tag{3}$$

with

$$S + I_1 + I_2 = N.$$

Equations (1)–(3) represent a nonlinear first order system of differential equations. So, the solution of the linearized system about an equilibrium points leads to useful information about the nonlinear system.

2.1 Equilibrium points

Equations (1)–(3) have three equilibrium points as follows:

1. The first is the disease free equilibrium (DFE) point, when the disease is absent in the population, in this case ($I_1 = I_2 = 0$), therefore the population is fully susceptible. Thus, the first equilibrium point is DFE $P_1 \equiv (N, 0, 0)$.
2. The second, is the free HCV infection from all types except 4a. So that ($I_2 = 0$) then the second equilibrium point is

$$P_2 \equiv \left(\frac{b}{k_1}, \frac{-b}{k_1} + N, 0 \right).$$

3. The third point is the endemic from all types of infection. Then ($I_1 \neq 0 \neq I_2$). Therefore the third equilibrium point is

$$P_3 \equiv \left(\frac{b+\mu}{k_2}, \frac{\mu}{k_2 - k_1} \left(\frac{Nk_2}{b+\mu} - 1 \right), \left(\frac{Nk_2}{b+\mu} - 1 \right) \left(\frac{bk_2 - k_1(b+\mu)}{k_2(k_2 - k_1)} \right) \right).$$

Remark. The free HCV type 4a infection, ($I_1^* = 0$ and $I_2 = +$ ve), does not exist, as there is a positive mutation rate μ from infective class, I_2, to infective class, I_1, so if $I_1^* = 0$ then it should be that, $I_2^* = 0$ is the (DFE) again.

2.2 The basic reproductive number

The basic reproductive number R_0 is defined as the expected number of secondary cases produced by a single infected individual entering the population at the DFE [5]. Since our

model has two infection classes (I_1 and I_2) then there are two basic reproductive numbers:

$$R_{01} = \frac{k_1 N}{b}, \quad R_{02} = \frac{k_2 N}{b + \mu} \tag{4}$$

Rewriting all the equilibrium points in terms of the basic reproductive numbers (R_{01}, R_{02}):

$$P_1 \equiv (N, 0, 0)$$

$$P_2 \equiv \left(S^*, I_1^*, I_2^* \right) \equiv \left(\frac{N}{R_{01}}, N \left(\frac{R_{01} - 1}{R_{01}} \right), 0 \right)$$

and

$$P_3 \equiv \left(S^{**}, I_1^{**}, I_2^{**} \right) \equiv \left(\frac{N}{R_{02}}, \frac{\mu}{k_2 - k_1}(R_{02} - 1), \frac{b}{k_2 - k_1}(R_{02} - 1) \left(\frac{R_{02} - R_{01}}{R_{02}} \right) \right)$$

DEFINITION 1. A point (P_i; $i = 1, 2, 3$) exists if and only if all it's components are nonnegative values.

Each of these points exists in the real life under certain conditions as follows:

1. P_1 always exists;
2. P_2 exists if and only if
3.

$$R_{01} > 1, \tag{5}$$

4. Finally, P_3 exists if and only if
5.

$$R_{02} > 1 \quad \text{and} \quad R_{02} > R_{01} \tag{6}$$

2.3 The stability analysis of the disease equilibrium points

To study the stability behaviour of the solutions at the equilibrium points of the system (1)–(3), we first use the following transformations:

$$U = N - S, \quad I_1 = I_1, \quad I_2 = I_2.$$

It follows that

$$\frac{dU}{dt} = (k_1 I_1 + k_2 I_2)(N - U) - bU, \tag{7}$$

$$\frac{dI_1}{dt} = k_1 I_1 (N - U) - bI_1 + \mu I_2, \tag{8}$$

and

$$\frac{\mathrm{d}I_2}{\mathrm{d}t} = k_2 I_2(N - U) - (b + \mu)I_2. \tag{9}$$

Therefore, the system (7)–(9) has the following equilibrium points $P_1 \equiv (0,0,0)$, $P_2 \equiv (U^*, I_1^*, I_2^*)$ and $P_3 \equiv (U^{**}, I_1^{**}, I_2^{**})$ where, $U^* = N - S^*$ and $U^{**} = N - S^{**}$.

Now, using Taylors approximation, we get the linearized version of system (7)–(9) near P_1 is

$$\begin{pmatrix} v' \\ w' \\ z' \end{pmatrix} = A \begin{pmatrix} v \\ w \\ z \end{pmatrix} \tag{10}$$

where,

$$v = U - 0, \quad w = I_1 - 0, \quad z = I_2 - 0$$

and

$$A = \begin{pmatrix} -b & k_1 N & k_2 N \\ 0 & k_1 N - b & \mu \\ 0 & 0 & k_2 N - (b + \mu) \end{pmatrix}. \tag{11}$$

It is a fact that, the stability behavior of the system (7)–(9) is the same as the stability behavior of its linearized system (10). The stability behavior of the system (10) depends on the eigenvalues of the matrix A of constants.

If all the eigenvalues of A has negative real parts then the equilibrium point P_1 is locally asymptotically stable. If at least one of the eigenvalues of the matrix A has a nonnegative real part then, the system is unstable at point P_1 [1].

LEMMA 1. *The equilibrium point P_1 is locally asymptotically stable if and only if*

$$\max(R_{01}, R_{02}) < 1.$$

Proof. The eigenvalues of the matrix A are $\lambda_{11} = -b$, $\lambda_{12} = k_1 N - b$ and $\lambda_{13} = k_2 N - (b + \mu)$.

Now, assume that the equilibrium point P_1 is locally asymptotically stable, then $(k_1 N - b) < 0$ and $(k_2 N - (b + \mu)) < 0$. Hence

$$\left(\frac{Nk_1}{b} < 1 \quad \text{and} \quad \frac{Nk_2}{b + \mu} < 1 \right)$$

i.e. ($R_{01} < 1$ and $R_{02} < 1$), so $\max(R_{01}, R_{02}) < 1$.

Conversely, assume that ($R_{01} < 1$ and $R_{02} < 1$), then

$$\left(\frac{Nk_1}{b} < 1 \quad \text{and} \quad \frac{Nk_2}{b + \mu} < 1 \right),$$

therefore $(k_1 N - b) < 0$ and $(k_2 N - (b + \mu)) < 0$. Thus we deduce that, all eigenvalues of the matrix A have negative real parts. Hence the equilibrium point P_1 is locally asymptotically stable.

Similarly, we can show that, the linearized version of system (7)–(9) near P_2 is

$$\begin{pmatrix} v' \\ w' \\ z' \end{pmatrix} = B \begin{pmatrix} v \\ w \\ z \end{pmatrix} \tag{12}$$

where,

$$v = U - U^*, \quad w = I_1 - I_1^*, \quad z = I_2$$

and

$$B = \begin{pmatrix} -Nk_1 & b & \frac{bk_2}{k_1} \\ b - Nk_1 & 0 & \mu \\ 0 & 0 & \frac{bk_2}{k_1} - (b + \mu) \end{pmatrix} \tag{13}$$

LEMMA 2. *The equilibrium point P_2 is locally asymptotically stable if and only if*

$$1 < R_{02} < R_{01}$$

Proof. The eigenvalues of the matrix B are

$$\lambda_{21} = \frac{bk_2}{k_1} - (b + \mu), \quad \lambda_{22} = \frac{-Nk_1}{2} + \frac{\sqrt{(Nk_1)^2 - 4(-b^2 + Nbk_1)}}{2} \quad \text{and}$$

$$\lambda_{23} = \frac{-Nk_1}{2} - \frac{\sqrt{(Nk_1)^2 - 4(-b^2 + Nbk_1)}}{2}.$$

We start our proof by assuming that the equilibrium point P_2 is locally asymptotically stable. Then, $\lambda_{21} < 0$. Hence,

$$\left(\left(\frac{bk_2}{k_1} - (b + \mu) \right) < 0 \right).$$

So,

$$\left(\frac{k_2}{(b + \mu)} < \frac{k_1}{b} \right),$$

i.e. $(R_{02} < R_{01})$.

Conversely, assume that $R_{02} < R_{01}$ and if the equilibrium point P_2 is not locally asymptotically stable, then at least one of the following cases holds

- $\lambda_{21} \geq 0$ then $(k_2/(b + \mu)) \geq k_1/b)$. Thus $(R_{02} \geq R_{01})$ which is a contradiction.
- λ_{22} is a complex number with nonnegative real part, i.e. $(-Nk_1/2 \geq 0)$ which is also a contradiction with the fact that both $(N \geq 0$ and $k_1 \geq 0)$.
- λ_{22} is a real number and nonnegative, i.e.

$$\frac{-Nk_1}{2} + \frac{\sqrt{(Nk_1)^2 - 4(-b^2 + Nbk_1)}}{2} \geq 0.$$

Then, $(Nk_1/b < 1)$. This leads to $R_{01} < 1$ which contradicts the condition of the existence of $P2$. Finally, it is obvious that λ_{23} has a negative real part.

Therefore we can deduce that, the equilibrium point P_2 is locally asymptotically stable.

LEMMA 3. The equilibrium point P_3 is locally asymptotically stable if it exists.

Proof. We start of our proof by linearizing the system (7)–(9) near P_3. So we have that,

$$\begin{pmatrix} v' \\ w' \\ z' \end{pmatrix} = E \begin{pmatrix} v \\ w \\ z \end{pmatrix} \tag{14}$$

where,

$$v = U - U^{**}, \quad w = I_1 - I_1^{**}, \quad z = I_2 - I_2^{**}.$$

and

$$E = \begin{pmatrix} -\frac{bNk_2}{b+\mu} & \frac{k_1(b+\mu)}{k_2} & b+\mu \\ \frac{-k_1\mu}{k_2-k_1}\left(\frac{Nk_2}{b+\mu}\right) - 1 & \frac{k_1(b+\mu)}{k_2} - b & \mu \\ \left(1 - \frac{Nk_2}{b+\mu}\right)\left(\frac{bk_2-k_1(b+\mu)}{k_2-k_1}\right) & 0 & 0 \end{pmatrix} \tag{15}$$

Consider the matrix (15), then the eigenvalues of this matrix are

$$\lambda_{31} = -b$$

$$\lambda_{32} = \frac{(M - \sqrt{H})}{(2k_2(b+\mu))}$$

$$\lambda_{33} = \frac{(M + \sqrt{H})}{(2k_2(b+\mu))}$$

where

$$M = b^2 k_1 - b k_2^2 N + 2b k_1 \mu + k_1 \mu^2$$

and

$$H = 4b(b(k_2 - k_1) - k_1\mu)k_2(b+\mu)^2(b - k_2 N + \mu) + (b^2 k_1 - b k_2^2 N + 2b k_1 \mu + k_1 \mu^2)^2$$

Since the equilibrium point P_3 is exist, therefore $R_{02} > 1$ and $R_{02} > R_{01}$. Then λ_{13} is obviously negative. To show that λ_{23} and λ_{33} have negative real parts, we start by showing that $M < 0$. Assume, $M \geq 0$, i.e. $(b^2 k_1 - b k_2^2 N + 2b k_1 \mu + k_1 \mu^2) \geq 0$. Hence, $k_1/b > k_2^2/(b+\mu)^2$ so $R_{01} \geq R_{02}^2$ which contradicts the existence of the equilibrium point P_3, then $M < 0$.

Now, we have the following possible cases,

- If $(H = 0)$, then $(\lambda_{32} = \lambda_{33} = M < 0)$,
- If $(H < 0)$, then the real part of λ_{32} and λ_{33} is M which is negative,
- If $(H > 0)$, then $(\lambda_{33} < 0)$ and to show that $(\lambda_{32} < 0)$, we will show $(\sqrt{H} < |M|)$, assume

that ($\sqrt{H} \geq |M|$) i.e.

$$\sqrt{4b(b(k_2 - k_1) - k_1\mu)k_2(b + \mu)^2(b - k_2N + \mu) + \left(b^2k_1 - bk_2^2N + 2bk_1\mu + k_1\mu^2\right)^2}$$
$$\geq \left|\left(b^2k_1 - bk_2^2N + 2bk_1\mu + k_1\mu^2\right)\right|.$$

So either ($R_{02} \leq 1$ and $R_{02} \geq R_{01}$) or ($R_{02} > 1$ and $R_{02} < R_{01}$) which is a contradiction. Therefore, ($\sqrt{H} < |M|$).

Then we deduce that the equilibrium point P_3 is locally asymptotically stable when exists.

THEOREM 1. The HCV disease dies out from the population if both $R_{01} < 1$ and $R_{02} < 1$ and the disease rises up when either $R_{01} > 1$ or $R_{02} > 1$ and becomes endemic.

Proof. By Lemmas (1)–(3), the proof has been completed.

3. Numerical simulation

In this section, we shall study our model numerically. The simulation results of our model have been performed using Mathematica 5.1. Because of the lack of data of this unclear virus, there is no real data that can be provided for our model. We use some documented data for some parameters like birth and death rate $b = 0.02$, take the number of population $N = 1,000,000$ and then suggest the other parameters such as mutation rate $\mu = 0.02$, the contact rates between S and both of I_1 and I_2 ($k_1 k_2$) respectively. Finally, the values of the basic reproductive numbers (R_{01}, R_{02}) have been suggested to be first, less than one in value and then larger enough than one to test the stability of the three different equilibrium points of our model.

The numerical simulations of the system (1)–(3) give the predicted numbers of the three compartments $S(t)$, $I_1(t)$ and $I_2(t)$ at any time. The basic reproductive numbers, R_{01}, R_{02}, are the key parameters in our study. First we simulate our system for values of $R_{01} < 1$ and $R_{02} < 1$, which are less than the threshold values. In this case, figure 1 shows that the disease dies out and the equilibrium point $P_1 = (N, 0, 0)$ is asymptotically stable. Secondly, figure 2 shows that, for a set of parameter values guaranteed that, $1 < R_{02} < R_{01}$, we found that from the simulation results the long term behaviour of our models tends asymptotically to the equilibrium point

$$P_2 \equiv \left(\frac{N}{R_{01}}, N\left(\frac{R_{01} - 1}{R_{01}}\right), 0\right).$$

This results confirm our analytical results that, when $1 < R_{02} < R_{01}$ the disease rises up and becomes endemic in the level of the equilibrium point

$$P_2 \equiv \left(\frac{N}{R_{01}}, N\left(\frac{R_{01} - 1}{R_{01}}\right), 0\right).$$

Finally figure 3 shows that when $R_{02} > 1$ and $R_{02} > R_{01}$, the solution of our system tends asymptotically to the equilibrium point

$$P_3 \equiv \left(\frac{N}{R_{02}}, \frac{\mu}{k_2 - k_1}(R_{02} - 1), \frac{b}{k_2 - k_1}(R_{02} - 1)\left(\frac{R_{02} - R_{01}}{R_{02}}\right)\right).$$
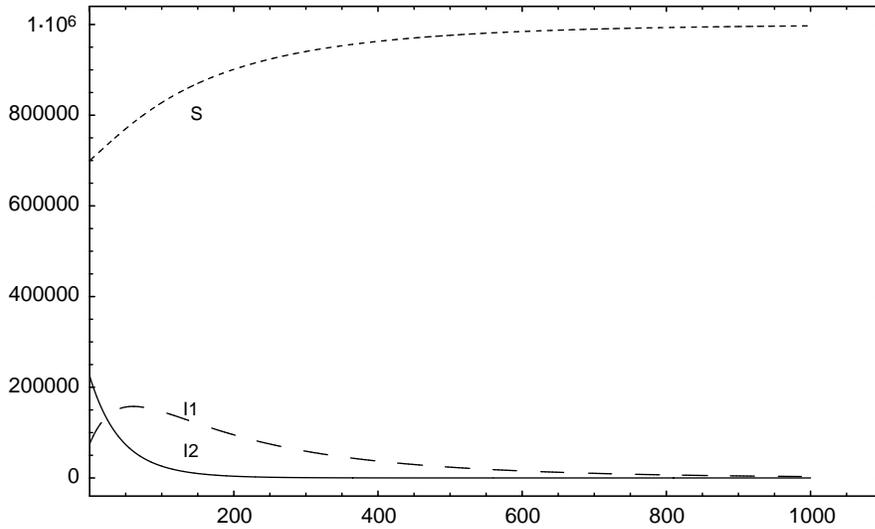
Figure 1. Shows the numerical simulation of our model and gives approximate results of the $(S(t), I_1(t), I_2(t))$, when the basic reproductive numbers have the values $(R_{01}, R_{02}) = (0.8, 0.6)$.

Therefore, the disease becomes endemic at the level of the equilibrium point P_3. This also supports our theoretical results obtained in this paper.

So from our simulation results, we can conclude that, if both R_{01} and R_{02} are less than one then the solutions go to the DFE, $P_1 = (N, 0, 0)$ and the disease will die out. On the other hand if either R_{01} or R_{02} is greater than one the solutions go to an endemic equilibrium point which is either P_2 or P_3. The existence of one of these two endemic equilibrium points depends on the values of R_{01} and R_{02}, who is greater than the other. In this case, the existed endemic point becomes stable and the disease will take off and becomes endemic on the
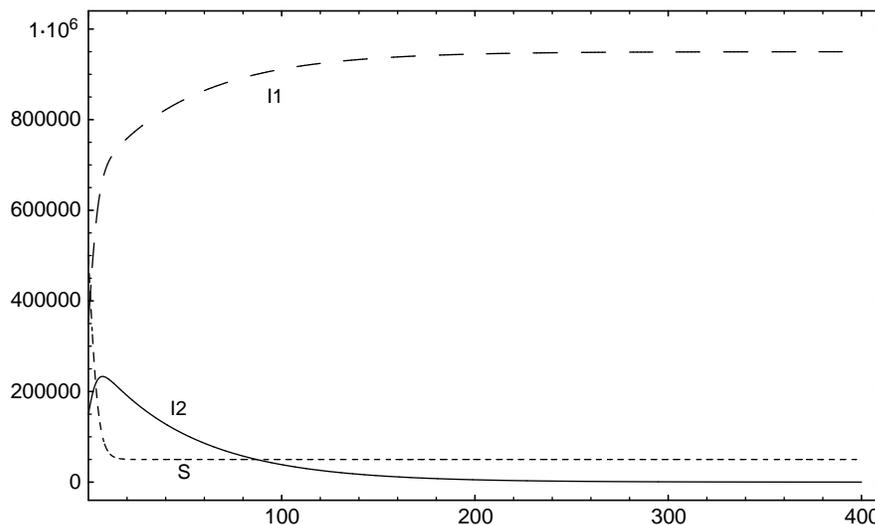

Figure 2. Shows the numerical simulation of our model and gives approximate results of the $(S(t), I_1(t), I_2(t))$, when the basic reproductive numbers have the values $(R_{01}, R_{02}) = (20.0, 10.0)$.
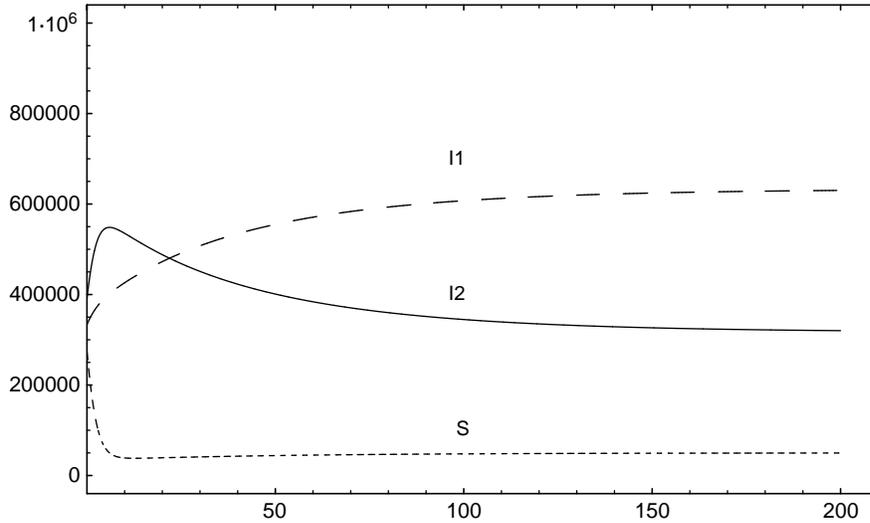
Figure 3.   Shows the numerical simulation of our model and gives approximate results of the $(S(t), I_1(t), I_2(t))$, when the basic reproductive numbers have the values $(R_{01}, R_{02}) = (10.0, 20.0)$.

population. While if both of R_{01} and R_{02} are greater than one, the mutation rate μ plays an important role to determine which endemic point exists.

4. Discussion

In this paper, we analyze an HCV model with susceptible, infected type one and type four hepatitis C. We observe from our analysis that the mutation rate in the body of the infected persons is a major factor to make the HCV endemic in the population. The less the mutation rate is the less number of infected with type 4a. When the mutation disappears, there is a chance to control the disease and the model becomes a simple SI epidemic model. Birth rate of susceptible individuals and the effective contact rates of infected individuals, from the two investigated types, are important ways to free the population from hepatitis C. Further more, when the effective contact rates of infected individuals with hepatitis C is sufficiently large, then two endemic equilibrium points exist. In the other hand, if the effective contact rates of infected individuals with hepatitis C is insufficient so that, $R_{01} < 1$ and $R_{02} < 1$, then DFE point exists and becomes asymptotically stable. Threshold values under which the disease dies out have been derived. These threshold values are given in terms of the mutation rate, birth rate, total number of susceptibles and the contact rates. Moreover, our simulation shows clearly that the solutions given in figures 1−3 represent the stable behavior of our model, which validate our theoretical analysis of our model. Using our model which is the system of differential equations (1)−(3), we generate these figures with the help of Mathematica 5.1.

Finally, the impact of the mutation rate μ of the disease inside the human body is a key parameter on the persistence of the disease on the population. This important factor should be studied more. Also, it interesting to focus on estimating the value of this important factor. This mutation rate works as a switch from the endemic point P_2 to P_3. So, μ plays an important role to determine which one of the endemic points exists.

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