Australian Journal of Basic and Applied Sciences, 3(2): 1253-1265, 2009
ISSN 1991-8178

Stochastic Model for the Spread of the Hepatitis C Virus with Different Types of Virus Genome

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Abstract: 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. So far, 11 have been recognized with 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) (Ray, S.C., R.R. Arthur, 2000). In this paper, we construct a stochastic model to study the spread of HCV-subtype 4a amongst the Egyptian population. Also the relation between HCV-subtype 4a and the other subtypes is been studied. Also the effect of the mutation factor in the persistence of the disease is been addressed. In this paper we use the method of the stochastic partial differential equations given in (Kapur, J.N., 1988), (Kapur, J.N., 1992) and (Herbert, J., V.S. Isham, 1998), to derive our stochastic model and then try to solve this model. Threshold conditions for the value of the transmission rates k^1 and k_{02in} terms of R_{01}, R_{02} and the mutation factor have been determined. Also Monte Carlo simulations have been conducted for this disease using the infection rates k_1 and k^2 as random numbers.

Key words: Stochastic modelling, Monte carlo, Simulation, HCV, Deferent genome types.

INTRODUCTION

Hepatitis C virus infection is found in 0.5% to 8.0% of blood donors worldwide. Because the infection is chronic in more than 60% of infected persons, the disease is a major serious public health and economical problem . An estimation of the the World Health Organization (WHO) points out that nearly 3% of the world population are infected with HCV and about 20% to 30% of them may develop cirrhosis and 3% of them may develop liver cancer (Das, P., D. Mukherjee, 2005). Egypt has possibly the highest HCV prevalence in the world; 10-20% of the general population is infected and HCV is the leading cause of hepatocellular carcinoma (HCC) and chronic liver disease in the country (El-Zayadi, A., H. Abaza, 2001). The genomes of hepatitis C virus display significant sequence heterogeneity and have been classified into types and subtypes. Six types from 1 to 6 had 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 to 11. The worldwide presence of the virus and the geographic distribution of genotypes clearly indicate that HCV is an old killer of the human kind and (Dusheiko, G., W.H. Schmilovitz, 1994).

The majority of the Egyptian HCV carriers belong to a single subtype (4a), which responds less successfully to interferon therapy than the other subtypes (Ray, S.C., R.R. Arthur, 2000). Heterogeneous genomes which are called ”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 . To this date, there has not been a successful HCV vaccination or control strategy. So, we require an understanding of the nature and variability of epidemic behavior among subtypes.

A few qualitative studies have been done using the mathematical modelling techniques. For example Deuffic *et al.* (1999) constructed a mathematical model which is structured cording to age and gender of the population. They studied the HCV in France and gave a prediction of the transmission until the year 2025. Martcheva and Castillo-Vhavez (2003) studied an HCV model with chronic infectious stage in a non-constant population. Their study showed that disease free solution exists and is globally asymptotically stable. Also their results showed that, an endemic non-uniform state is locally asymptotically stable under certain conditions.

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Moneim and Mosa (2006) studied mathematically and numerically the effect of the mutation factor on the dynamics of the HCV in Egypt. We derived a formula for the secondary reproductive numbers $R_{01}R_{02}$ which, the expected number of secondary cases produced by a single infected individual entering a disease free population at equilibrium (Greenhalgh, D. and I.A. Moneim, 2003). $R_{01}R_{02}$ were the keys parameter for our study. We drived conditions on R_{01} R_{02} for the disease to be endemic or die out. Stochastic study of the mutation effect of the HCV is not studied in (Moneim, A.I. and G. Mosa, 2006).

As this disease is not studied enough, the problem still open and needs to be studied more and more to give a clearer insight to the dynamics of this mysterious disease, and possibly solve or try to solve this major worldwide problem.

In this paper we extend our previous work and to study a stochastic version of the deterministic model given in (Moneim, A.I. and G. Mosa, 2006). We use the stochastic partial differential equation described in Kapur's book (Kapur, J.N., 1992) to derive a model for the spread of the (HCV-subtype 4a). Also, by using appropriate approximations for the higher moments of the joint distributions, we obtain differential equations for the means, variances and co-variances of susceptibles, *S,* HCV-subtype 4a infectives, I_1, and HCV-all subtype except 4a infectives, I_2, (Herbert, J., V.S. Isham, 1998). Numerical simulations for stochastic version are conducted and compared with the corresponding results which obtained from deterministic model. As the way in which the disease is transmitted is undetermined precisely, it is more realistic to use random numbers for representing the values of the transmission rates k_1 and k_2. Monte Carlo simulations are also performed to highlight the effect of randomizing both of k_1 and k_2.

The Model:

We make the following assumptions in order to construct a model for the spread of the HCV disease:

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 can get infected or those who are ready to catch the disease;
   b) The Infective class, I_1, the individuals who are infected with HCV subtype 4a directly or with another subtype and had mutated to subtype 4a;
   c) The Infective class, I_2, comprising individuals from all subtypes of HCV except the subtype 4a.
2. All types of HCV infections can mutate to HCV subtype 4a at a positive constant rate (μ).
3. The virus vertical transmission is rare (Oliver, G.P., A.C. Michael, 2001). All ages of population can be infected by HCV virus. The basic way 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* move s 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 to getting in contact with an infected person.

2.1 The Deterministic Model:

The model for the spread of Virus HCV can be written as a set of three coupled non-linear ordinary differential equations as follows:

$$\frac{dS}{dt} = -(k_1 I_1 + k_2 I_2)s - bS + bN \tag{1}$$

$$\frac{dI_1}{dt} = k_1 S I_1 - bI_1 + \mu I_2 \tag{2}$$

and

$$\frac{dI_2}{dt} = k_2 S I_2 - bI_2 + \mu I_2 \tag{3}$$

with $S + I_1 + I_2 = N$

We can say this model represents an SI_1I_2 model. This model is described by equations (1) - (3) which represent a nonlinear first order system of differential equations. So, the solution of the linearized system about the equilibrium points leads to useful information about the nonlinear system.

2.2 Equilibrium Points:

The system represented by equations (1) - (3) have three equilibrium points as follows:

1. 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 $P_1 \equiv (N00)$.
2. The HCV free infection from all types except subtype 4a. So that, ($I_2 = 0$) then the second equilibrium point is $P_2 \equiv (\frac{b}{k_1}, \frac{-b}{k_1} + N, 0)$
3. HCV from all types of infection. Then $(I_1 \neq 0 \neq I_2)$ Therefore the third equilibrium point is

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

2.3 The Basic Reproductive Numbers:

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 disease free equilibrium (Greenhalgh, D. and I.A. Moneim, 2003). Since, our model has two infection class (I_1 and I_2) then there are two basic reproductive numbers:

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

The analysis of this showed that 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. Details of the analysis of this model are given in (Moneim, A.I. and G. Mosa, 2006)

2.4 the Stochastic Version of the Model:

Now, we focus on the stochastic version of this pervious model. Let $p_{nmh}(t)$ be the probability that there are n susceptible persons, m infective persons with HCV subtype (4a) and h infective persons carrying HCV with a different subtype than (4a), and let $fijk\Delta' + o(\Delta t)$ denote the probability that the numbers (nmh) change to $(n + im + jh + k)$ in the time interval $(tt + \Delta t)$. So moving a person from a class to another or adding a person to any class by birth or removing one by death changes the system state from nmh to another and this depends on the disease parameters as follows:

$$f_{-1,1,0}(n,m,h) = k_1 mn \qquad f_{-1,1,0}(n,m,h) = k_2 mn$$
$$f_{0,1,-1}(n,m,h) = \mu m \qquad f_{1,0,0}(n,m,h) = b(n+m+h)$$
$$f_{-1,0,0}(n,m,h) = bn \qquad f_{0,-1,0}(n,m,h) = bm$$
$$f_{0,0,-1}(n,m,h) = bh$$

The general form of the stochastic partial differential equation describing our model is given as follows (Murthy, D.N.P. N.W. Page, 1990) and (Herbert, J., V.S. Isham, 1998): By substituting into the following partial differential equation,

$$\frac{\partial \phi(t;x,y,z)}{\partial t} = \sum_i \sum_j \sum_k (x^i y^j z^k - 1) f_{ijk}(x\frac{\partial}{\partial x}, y\frac{\partial}{\partial y}, z\frac{\partial}{\partial z})\phi(t;x,y,z) \tag{5}$$

where $\varphi(t; xyz)$ is a probability generating function which defined as,

$$\phi(t;x,y,z) = E(x^n y^m z^h) = \sum \sum \sum Pnmh(t)x^n y^m z^h \tag{6}$$

Equation (5) is the three dimensions version of the stochastic partial differential equation given in (Kapur, J.N., 1992)and (Isham, V.S., 1995). Using the definition of the generating function $\varphi(t; xyz)$ we can write:

$$\frac{\partial\phi(t,x,y,z)}{\partial t} = (x^{-1}y^1z^0 - 1)k_1((y\frac{\partial}{\partial y})(x\frac{\partial}{\partial x}))\phi$$

$$+(x^{-1}y^0z^1 - 1)k_2((z\frac{\partial}{\partial z})(x\frac{\partial}{\partial x}))\phi$$

$$+(x^0y^1z^{-1} - 1)\mu(z\frac{\partial}{\partial z}))\phi$$

$$+(x^1y^0z^0 - 1)b(x\frac{\partial}{\partial x} + y\frac{\partial}{\partial y} + z\frac{\partial}{\partial z})\phi \tag{7}$$

$$+(x^{-1}y^0z^0 - 1)b(x\frac{\partial}{\partial x})\phi$$

$$+(x^0y^{-1}z^0 - 1)b(y\frac{\partial}{\partial y})\phi$$

$$+(x^0y^0z^{-1} - 1)b(z\frac{\partial}{\partial z})\phi$$

or

$$\frac{\partial\phi(t;x,y,z)}{\partial t} = k_1y(y-x)\frac{\partial^2\phi}{\partial x\partial y} + k_2z(z-x)\frac{\partial^2\phi}{\partial x\partial z} + b(x-1)^2\frac{\partial\phi}{\partial x} \tag{8}$$
$$+b(y(x-2)+1)\frac{\partial\phi}{\partial y} + ((y-z)\mu + b(z(x-2)+1))\frac{\partial\phi}{\partial z}$$

Equation (8) represents our basic stochastic partial differential equation of the spread of the Hepatitis B Virus. Equation (8) is transformed into a system of ordinary differential equations for the means, variances and co-variances of the original variables *nm* and *h* by differentiating equation (6) with respect to *xy* and *z* respectively, and setting these variables to the value of one then we obtain, the differential equations governing the means *nm* and *h,* of the original variables *nm* and *h* respectively as follows:

$$\frac{d\mu_n}{dt} = \frac{d}{dt}E(n) = \frac{d}{dt}(\frac{\partial\phi}{\partial x})_{x=1,y=1,z=1} = b(\mu_h + \mu_m) - k_2(\mu_h\mu_n + \sigma_{nh}) - k_1(\mu_m\mu_n + \sigma_{nm}) \tag{9}$$

$$\frac{d\mu_m}{dt} = \frac{d}{dt}E(m) = \frac{d}{dt}(\frac{\partial\phi}{\partial y})_{x=1,y=1,z=1} = \mu\mu_h - b\mu_m + k_1(\mu_m\mu_n + \sigma_{nm}) \tag{10}$$

$$\frac{d\mu_n}{dt} = \frac{d}{dt}E(h) = \frac{d}{dt}(\frac{\partial\phi}{\partial z})_{x=1,y=1,z=1} = (-b-\mu)\mu_h + k_2(\mu_h\mu_n + \sigma_{nh}) \tag{11}$$

Differentiating Equation (6) again, we get the corresponding expressions for variances and co-variances of the original variables *nm* and *h* denoted by $\sigma_n^2, \sigma_m^2, \sigma_h^2, \sigma_{nm}, \sigma_{nh}$ **and** σ_{nh} espectively,

$$\frac{d\sigma_n^2}{dt} = \frac{d}{dt}(E(n^2) = \frac{d}{dt}(\frac{\partial\phi}{\partial x^2})_{x=1,y=1,z=1} + (1-2\mu_n)\frac{d}{dt}(\frac{\partial\phi}{\partial x})_{x=1,y=1,z=1}$$

$$= 2b\mu_2 + 2b(\mu_h\mu_n + \sigma_{nh}) + 2b(\mu_m\mu_n + \sigma_{nm}) \tag{12}$$

$$+(1-2\mu_n)(b\mu_h + b\mu_m - k_2(\mu_h\mu_n + \sigma_{nh}) - k_1(\mu_m\mu_n + \sigma_{nm}))$$

$$-2k_2(\frac{\partial^3 P_{nmh}}{\partial x^2\partial z})_{1,1,1} - 2k_1(\frac{\partial^3 P_{nmh}}{\partial x^2\partial z})_{1,1,1}$$

Similarly we find that,

$$\frac{d\sigma_m^2}{dt} = \mu\mu_h - 2k_1\mu_m^2\mu_n - 2b\sigma_m^2 + 2\mu\sigma_{mh} + \mu_m(b + k_1(3\mu_n - 2\sigma_{nm}))$$

$$+k_2(3\sigma_{nh} + 2(\frac{\partial^3 P_{nmh}}{\partial x\partial z^2})_{1,1,1}) \tag{13}$$

$$\frac{d\sigma_h^2}{dt} = -2k_2\mu_h^2\mu_n - 2(b+\mu)\sigma_h^2 + \mu_h(b + \mu + k_2(3\mu_n - 2\sigma_{nh}))$$

$$+k_2(3\sigma_{nh}) + 2(\frac{\partial^3 P_{nmh}}{\partial x\partial z^2})_{1,1,1} \tag{14}$$

$$\frac{d\sigma_{nm}}{dt} = \mu\sigma_{nh} + b(\sigma_m^2 + \sigma_{mb} - \sigma_{nm}) + k_2(\mu_m(\mu_h\mu_n + \sigma_{nh}))$$

$$-(\frac{\partial^3 P_{nmh}}{\partial x\partial y\partial z})_{1,1,1} + k_1(\mu_m(-1+\mu_m-\mu_n)\mu_n - \sigma_{nm})$$

$$+(\mu_m - \mu_n)\sigma_{nm} - (\frac{\partial^3 P_{nmh}}{\partial x\partial y^2})_{1,1,1} + (\frac{\partial^3 P_{nmh}}{\partial x^2\partial y})_{1,1,1} \tag{15}$$

$$\frac{d\sigma_{nh}}{dt} = b(\sigma_h^2 + \sigma_{mh}) - (b-\mu)\sigma_{nh}) + k_1(\mu_h(\mu_m\mu_n + \sigma_{nm})$$

$$-(\frac{\partial^3 P_{nmh}}{\partial x \partial y \partial z})_{1,1,1} + k_2(\mu_h(-1+\mu_n-\mu_n)\mu_n - \sigma_{nh}$$

$$+(\mu_h - \mu_n)\sigma_{nh} - (\frac{\partial^3 P_{nmh}}{\partial x \partial z^2})_{1,1,1} + (\frac{\partial^3 P_{nmh}}{\partial x^2 \partial z})_{1,1,1} \quad (16)$$

$$\frac{d\sigma_{mh}}{dt} = \mu\sigma_h^2 - (2b+\mu)\sigma_{mh} - k_2\mu_m\sigma_{nh} - \mu_h(\mu + (k_1+k_2)\mu_m\mu_n + k_1\sigma_{nm}$$

$$+(k_1+k_2)(\frac{\partial^3 P_{nmh}}{\partial x \partial y \partial z})_{1,1,1} \quad (17)$$

Some of the above equations involve third moments of our variables, alternatively we use an approximation to the third moments in terms of the mean, variances and co-variances by assuming our variables obey a specific distribution. Here we use a multivariate Normal distribution where, the third center moments of this distribution are zero, so tri-variate Normal variables W_1W_2 and W_3 satisfy the following equation (using the notation $m_i = {}^E(W_i)m_{ij} = E(W_iW_j)$).

$$E(W_1W_2W_3) = m_1m_{23} + m_2m_{13} - 2m_1m_2m_3 \quad (18)$$

Now, the differential equations for variances and co-variances to variables are given as follows:

$$\frac{d\sigma_n^2}{dt} = 2b\mu_n + \mu_m(b + k_1(\mu_n - 2\sigma_n^2)) + \mu_h(b + k_2(\mu_n - 2\sigma_n^2))$$

$$+2b\sigma_{nh} + k_2\sigma_{nh} - 2k_2\mu_n\sigma_{nh} + (2b + k_1 - 2k_1\mu_n)\sigma_{nm} \quad (19)$$

$$\frac{d\sigma_m^2}{dt} = \mu\mu_h - 2(b - k_1\mu_n)\sigma_m^2 + 2\mu\sigma_{mh} + k_1\sigma_{mh} + \mu_m(b + k_1(\mu_n + 2\sigma_{nm})) \quad (20)$$

$$\frac{d\sigma_h^2}{dt} = -2(b + \mu - k_2\mu_n)\sigma_h^2 + k_2\sigma_{nh} + \mu_h(b + \mu + k_2(\mu_n + 2\sigma_{nh})) \quad (21)$$

$$\frac{d\sigma_{nm}}{dt} = b\sigma_m + (b - k_2\mu_n)\sigma_{mh} + \mu\sigma_{nh} - (b + k_2\mu_h)\sigma_{nm} - k_1(\mu_n(\sigma_m^2 - \sigma_{nm})$$

$$+\sigma_{nm} + \mu_m(\mu_n - \sigma_n^2 + \sigma_{nm})) \quad (22)$$

$$\frac{d\sigma_{nh}}{dt} = b\sigma_h^2 + (b - k_1\mu_n)\sigma_{mh} - (b + \mu + k_1\mu_m)\sigma_{nh} - k_2(\mu_n(\sigma_h^2 - \sigma_{nh})$$

$$+\sigma_{nh} + \mu_h(\mu_n - \sigma_n^2 + \sigma_{nh})) \quad (23)$$

$$\frac{d\sigma_{mh}}{dt} = \mu\sigma_h^2 - (2b + \mu - (k_1 + k_2)\mu_n)\sigma_{mh} + k_1\mu_m\sigma_{nh} + \mu_h(-\mu + k_2\sigma_{nm}) \quad (24)$$

Now we use the software Mathematica 5.1 to solve the system (9) - (11) and (19) - (24) numerically.

3 Numerical Simulation:

The system of the coupled non-linear ordinary differential equations (9) - (11) and (19) - (24) describe the means, variances and co-variances of the S, I_1 and I_2, is been solved numerically with the help of the software Mathematica 5.1. Because of the lack of clinical data of HCV, this unclear virus, there is no real data can be provided for our model. Then we use existing data for the parameter values for birth and death rates and play with other. In our simulation we have used b = 002 (Greenhalgh, D. and I.A. Moneim, 2003), and the total number of population N = 1000000. Then we suggest the value of the mutation rate to be = 002. Finally we chose different values of the contact rates (k_1, k_2), between S and both of I^1 and I_2 to have different values of the basic reproductive numbers $(R_{01}R_{02})$. First we chose values of (k_1,k_2) to force both of R_{01} and R_{02} to be less than one in value. Then we give (k_1,k_2) another values to guarantee that, both of R_{01} and R_{02} are large enough and satisfy: first $R_{01} > R_{02}$ and finally $R_{01} < R_{02}$ for another parameter set of (k_1,k_2), to test the behaviour of our stochastic model near the three different equilibrium points of the model given in(Moneim, A.I. and G. Mosa, 2006). We start of our simulation with initial values close to the equilibria. This is to accelerate the convergence of the numerical solution to approach its limiting value.

We start off our simulations with the case that, if both of the basic reproductive numbers , $(R_{01}R_{02})$, are less than one, the solution goes to an asymptotic value (N, 0, 0) which is the disease free solution. Equivalently the mean value of $(S(t),I1(t), I2(t))$ tend to the DFE as the time goes to infinity. Figure (1) shows that both of $I_1(t)$, $I_2(t)$ tend to zero as the time becomes large, while the mean value of the susceptible population S tends to the total population number N. This result is similar to the result obtained from the numerical simulation for deterministic model at the same conditions and also confirm the asymptotic stability of the equilibrium point P_1 = (N00) (Moneim, A.I. and G. Mosa, 2006).

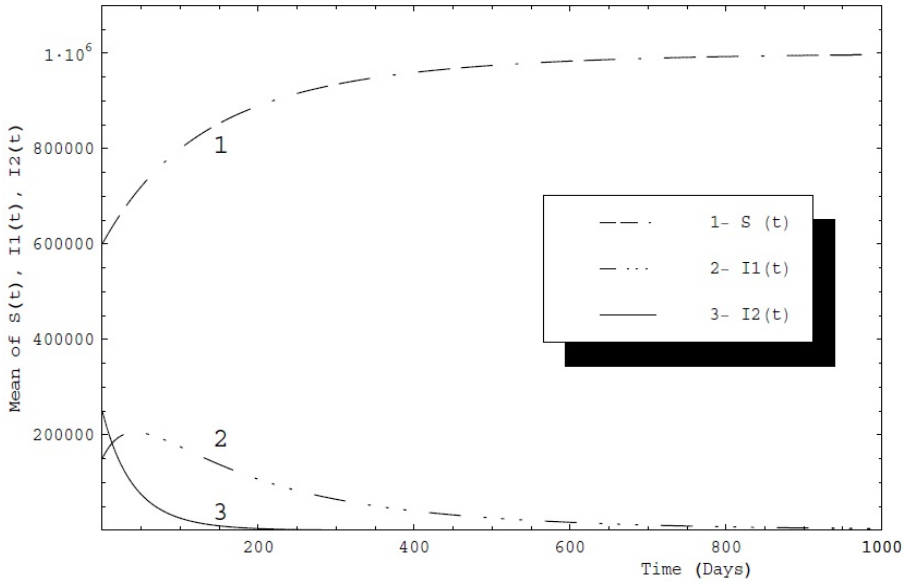

Fig. 1: The numerical simulation of our model, plotting results of the $(S(t), I_1(t), I_2(t))$ against the time, when the basic reproductive numbers have the values $(R_{01}R_{02})$= (0.8, 0.6)

In the other hand if we take the basic reproductive numbers R_{01} and R_{02} large enough so that, both of them is greater than one, we have two cases: the first one, is that, when $R_{01} > R_{02}$. As usual, we start our simulation from a level near the second expected equilibrium point (Moneim, A.I. and G. Mosa, 2006). Figure (2) represents this case and shows that the mean of susceptibles n decreases to approach its equilibrium value (S) as t becomes very large. This means that the equilibrium value of the mean of susceptibles is independent from the total population size. It also shows that the mean of infected persons m of kind I_1, and h of kind I_2 ,

approach an asymptotic endemic level for each compartment. The endemic level of the infected persons of kind I_1 is much larger than the one of the infected persons of kind I_2. These simulations results agree with the numerical simulations of the deterministic model with the same conditions. This is also agree with the asymptotic stability of the second equilibrium point stated in(Moneim, A.I. and G. Mosa, 2006).

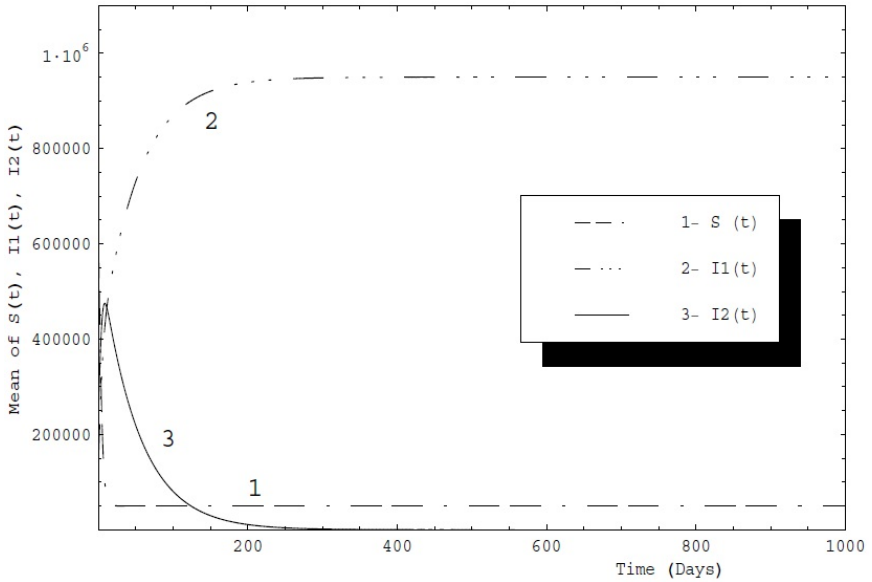

Fig. 2: The numerical simulation of our model, plotting results of the *(S(t), I_1(t), I_2(t))* against the time, when the basic reproductive numbers have the values ($^{R}01^{R}02)^{=}$, (20.0, 10.0)

Finally if, we take the basic reproductive number R_{02} is greater than R_{01} and greater than one, say (R_{01} = $^{1}0R_{02}$ = 20). Figure (3) a similar results to Figure (2) but with the endemic level of the infected persons of kind I_2 is much larger than the corresponding one of the infected persons of the same kind I_2 given in figure (2). Figure (3) also shows a very large of similarities of simulation results those of the corresponding results of the deterministic model when $R_{02} > R_{01} > 1$ and confirms the stability of the third equilibrium point (Moneim, A.I. and G. Mosa, 2006).

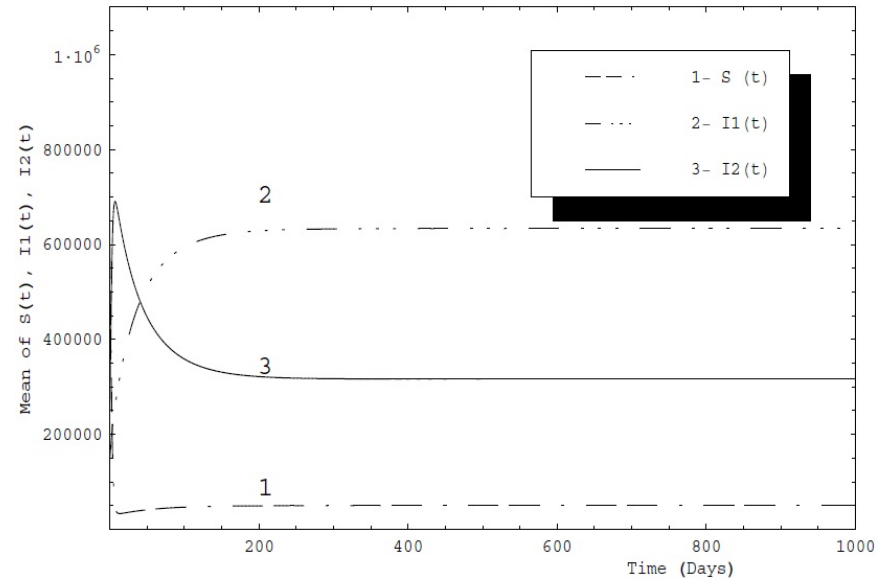

Fig. 3: The numerical simulation of our model, plotting results of the *(S(t) ,I_1(t), I_2(t))* against the time, when the basic reproductive numbers have the values ($R_{01}R_{02}$)= (10.0, 20.0)

The numerical simulations of the stochastic model confirm that the behaviour of our system depends mainly on the model parameter especially the values of the basic reproductive numbers , $(R_{01}R_{02})$. When the maximum value of R_{01} and R_{02} is less than one, the solution of the model goes to (N00), which represents the DFE of the corresponding deterministic model described in (Moneim, A.I. and G. Mosa, 2006). In this case the DFE always exists and stable in both of the deterministic and stochastic models. Therefore when both R_{01} and R_{02} > 1 are less than one, the disease will die out. But if, R_{01} > R_{02} > 1 or R_{02} > R_{01} > 1 then the solutions of the model go to endemic equilibrium levels. These levels are equivalent to the second and third equilibrium points the corresponding deterministic model respectively. At both of these points the disease will become an endemic in the population.

4 Monte-Carlo Simulation:

Now, we use the Monte-Carlo technique to simulate our model again with initial conditions similar to those which are used in the numerical simulation for the stochastic model in the previous section. Here we take the infection rate as a random values of specific uniform distribution. This is more realistic due to uncertainty of data available and the concern about the approximate value of the infection rate of this disease in many developing countries like Egypt. In this section we use the Monte-Carlo Simulation simulation technique to simulate our model. Then compare the results with the results which obtained in section 3 and in (Moneim, A.I. and G. Mosa, 2006). The results of both numerical simulations of the deterministic and the stochastic models are similar. We use the same parameter values used previously in both deterministic and stochastic numerical simulations.

Since we assume that the population is mixing in a homogenous manner i.e. every person has the same chance to become in contact with an infected person.

$$\frac{dS}{dt} = -(k_1^* I_1 + k_2^* I_2)S - bS + bN \tag{25}$$

$$\frac{dI_1}{dt} = k_1^* S I_1 + bI_1 + \mu I_2 \tag{26}$$

and

$$\frac{dI_2}{dt} = k_2^* S I_2 + bI_2 + \mu I_2 \tag{27}$$

with

$$S + I_1 + I_2 = N$$

Where k_1 and k_2 are random numbers generated by specific uniform distribution. The present system (25) - (27) is solved by using the fourth order Rung-Kutta method with time step h = 4 and evaluate the mathematical mean of $S(t)I_1(t)$ and $I_2(t)$ of 20 samples at each step to produce numerical solutions for means of $S(t)I_1(t)$ and $I_2(t)$ at any time. A computer program to solve our model using fourth order Rung-Kutta method is written in the language of Visual-Basic under Excel and the package Zrandom to produce a random numbers.

Monte-Carlo Model is built to predict the values of the mean of each compartment $S(t)$, $I_1(t)$ and $I_2(t)$ at any time. As expected the results of Monte-Carlo simulation depend on the values of basic reproductive numbers $(R_{01}R_{02})$ as shown in the following figures. These figures start of when the maximum value of R_{01} and R_{02} less than one in this case the solution of our model goes to , (N00) which is the disease free equilibrium point DFE of the deterministic model (1)-(3), so the disease will die out. Otherwise if, R_{01} is greater than R_{02} and both are greater than one then the solution of the model goes to the second equilibrium point P_2 *(1)-(3)*. Finally the solution of the model goes to the third equilibrium point P_3 of (1)-(3). When R_{02} > R_{01} > 1. These results means that the disease at the maximum value of R_{01} and R_{02} is greater than one, becomes endemic. The results obtained in this section are not only similar to the results which obtained from

the numerical simulation of the deterministic model (Moneim, A.I. and G. Mosa, 2006), but also confirms the result which obtained in the numerical simulation of the stochastic model in the previous section.

Now, we use the Monte-Carlo technique to simulate our model again with initial conditions similar to those which are used in the numerical simulation for the stochastic model in the previous section.

Figure (4) shows that, when the values of the basic reproductive numbers , (R_{01} R_{02}) are (0806), the Mean of susceptibles, increases monotonically until it reaches its equilibrium value (N) as t becomes very large, and shows that, the mean of infectives type 4a, I_1, increases in the beginning of the disease until it reaches a maximum value, and then decreases exponentially to approach its equilibrium value zero, as the time t increases. Finally the mean of infectives from all subtypes I_2, except type 4a, decreases monotonically and similar to a strong exponential decay to approach zero (its equilibrium value). Therefore the disease will die out in this case. These results confirm the asymptotic stability of the equilibrium point (N, 0, 0) from the analytical study (Moneim, A.I. and G. Mosa, 2006). Also these results are quite similar to the results of the numerical simulation for the stochastic model at the same conditions.

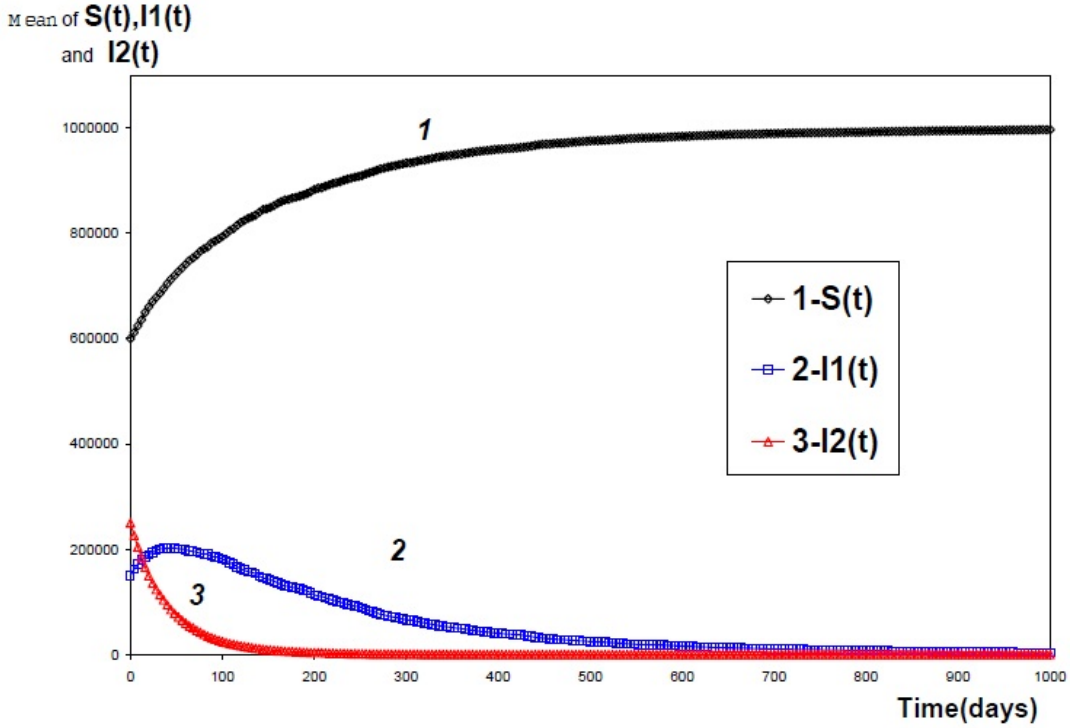

Fig. 4: Mont Carlo simulations for the system (25)- (27) Plotting the Susceptibles S (t), Infectives ($I_1(t)$ and Infectives ($I_2(t)$ against the time when both (R_{01} and R_{02} are both less than one, precisely ($R_{01}R_{02}$) = (0806)

Now we turn our attention when the values of the basic reproductive numbers, R_{01} and R_{02} are both grater than one. The first case when (R_{01} > R_{02} > 1). Figure (5) shows that, when ($R_{01}R_{02}$) = (2010) the mean of susceptibles, decreases to an asymptotic value with fluctuates around this level to the end of range. Figure(5) also shows that, the mean of infectives by (HCV subtype 4a), I_1, increases with clear fluctuation around an asymptotic value as the time t increases. In the other hand Figure (5) shows that, the mean of infectives of type I_2 (HCV all subtypes except subtype 4a), increases in the beginning of the disease until it reaches a maximum value, then decreases exponentially to approach zero as the time t increases. This behaviour is quite similar to that of the deterministic model when R_{01} > R_{02} > 1, as the solution approaches the equilibrium value P_2. In this case the disease will be endemic and persist in the population.

Finally, we study the simulation results when (R_{02} > R_{01}) > 1. Figure (6) shows that, the mean of susceptibles decreases to a certain asymptotic value and fluctuate around it to the end of the time. On the other hand, the mean of infectives of 4a subtype I_1, increases with clear fluctuation around its asymptotic value as the time t increases. Figure (6) also shows that, the mean of infectives I_2, of HCV from all subtypes except subtype 4a, increases in the beginning of the disease until it reaches a maximum value then decreases

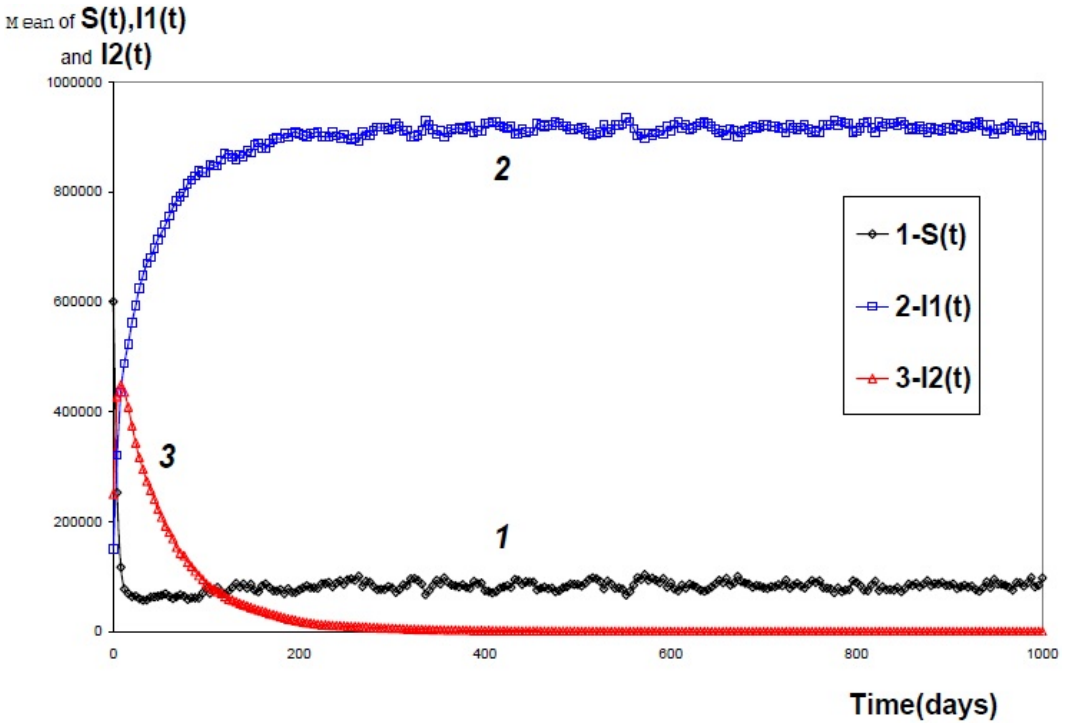

Fig. 5: Mont Carlo simulations for the system (25)-(27) Plotting the Susceptibles S(t), Infectives ($I_1(t)$ and Infectives ($I_2(t)$ against the time when $R_{01} > R_{02} > 1$

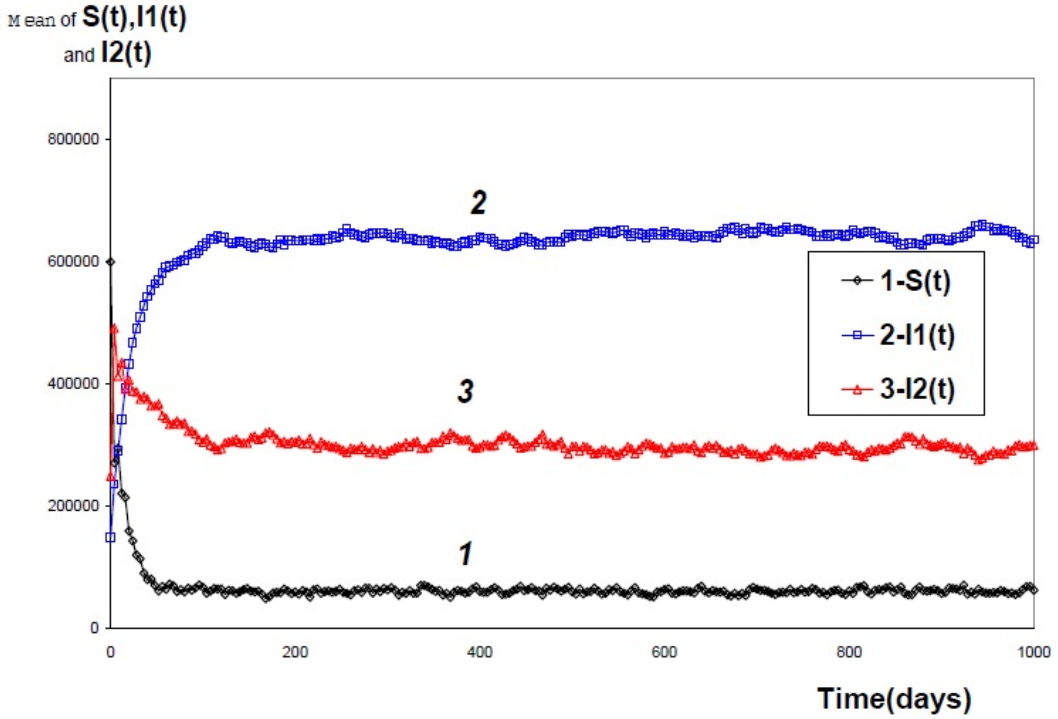

Fig. 6: Mont Carlo simulations for the system (25)-(27) Plotting the Susceptibles S(t), Infectives ($I_1(t)$ and Infectives ($I_2(t)$ against the time when ($^R02 > {}^R01$) > 1

exponentially to an asymptotic level and oscillates around this value until the time lasts. These results are quite similar to those of the numerical simulations for the deterministic and stochastic models solved in (Moneim, A.I. and G. Mosa, 2006) and in the previous section.

5 Discussion:

In this paper, we analyze a stochastic model for the hepatitis C virus with three compartments, susceptible, infected of type one and of type two. We observe from our analysis that the mutation rate in the body of the infected persons is a major factor to determine when the HCV will be endemic in the population or die out. The less the mutation rate is the less number of infected with type 4a. When the mutation disappears $I_2 = 0$ in this case there is a chance to control the disease and the model becomes a simple SI stochastic epidemic model. 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 we choose parameter values which insure that, the effective contact rates of infected individuals with hepatitis C is sufficiently large, then the solutions of the stochastic model converge to an asymptotic endemic level depends on the values of R_{01} and R_{02}. On the other hand if the model parameters are small enough so that, R_{01} and R_{02} are both less than one in value the solution converges to a disease free equilibrium value asymptotically. Threshold values under which the disease dies out is 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, 2 and 3 always converge to asymptotic values which are equivalent to the stable behaviour of the solutions of the deterministic model given in (Moneim, A.I. and G. Mosa, 2006). This also agree with theoretical analysis of the same model.

Next we add more realism to our model by taking k_1 and k_2* as random numbers generated by specific uniform distribution. Here we use the same initial condition and similar parameter values to that used in numerical simulation of Stochastic model. The results of Monte-Carlo Simulation of (HCV subtype 4a) at, are very similar to the results of the numerical simulation of the stochastic model. The only and most important different is that, the Mont carlo results show a small amplitude fluctuation around an asymptotic level, while the stochastic solution always approaches an asymptotic value.

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 and more. Also it is interesting to focus on estimating the value of this important factor. This mutation rate works as a switch from the endemic stat from level to anther level. So the value of μ plays an important role to determine which level the solution of the stochastic model converges to it.

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