*Journal of Fractional Calculus and Applications*,
Vol. 8(2) July 2017, pp. 1-19.
ISSN: 2090-5858.
http://fcag-egypt.com/Journals/JFCA/

# GENERALIZED MATHEMATICAL MODEL OF CHRONIC HEPATITIS C INFECTION

SESHU KUMAR DAMARLA, MADHUSREE KUNDU

Abstract. A realistic fractional order mathematical model of chronic hepatitis C infection treated with combinational drug therapy (pegylated interferon-$\alpha$ (IFN-$\alpha$) plus antiviral drug ribavirin (RBV)) is presented. The proposed model shows the classical integer order model behaviour in the limit of fractional order tends to 1.0. The results reveal that the proposed fractional order chronic hepatitis C infection model can explain biphasic, triphasic and monophasic viral decline. Considering the fact, that simple new iterative method might not be helpful for analysing fractional order processes over large time span; multistage new iterative method is employed for approximate solution of fractional order chronic hepatitis C infection model.

## 1. Introduction

Hepatitis C virus (HCV) causes Hepatitis C, a highly spreadable disease infecting only humans and chimpanzees, disturbing chiefly the liver ([1, 2]). HCV was recognized in 1989 ([3]). It is a small, enveloped, single stranded and positive sense RNA virus ([4]). It belongs to *Hepacivirus* within *Flaviviridae* family. It frequently mutates and is extremely resilient and unstable. Hepatitis C is mainly spread by sharing injecting equipment for intravenous drug use, transfusion of unscreened blood and blood product, reuse or poorly sterilized medical equipment (especially syringes and needles) and less often by sharing personal items contaminated with infectious blood ([5]-[7]). Its transmission through sexual activity and from infected mother to her child are much less common ([8, 9]. According to WHO (World Health Organization), nearly 130 to 150 million people are infected with hepatitis C virus (HCV) and about 500000 infected individuals die every year from hepatitis C-related liver diseases (WHO 2015). Egypt is in first place with highest rate of chronic Hepatitis C infection (15%) and second and third places are occupied by Pakistan (4.8%) and China (3.2%), respectively (WHO 2015). Only 15% of infected individuals have acute symptoms like fever, fatigue, nausea, vomiting, joint or muscle pains, weight loss, decreased appetite, abdominal pain, dark urine, grey-coloured faeces and jaundice (acute infection is rarely associated with

2000 *Mathematics Subject Classification.* 34A12, 34A08, 92C45.
*Key words and phrases.* Fractional order chronic hepatitis C infection model, new iterative method, multistage new iterative method, Caputo fractional derivative.
Submitted Sep. 08, 2016.

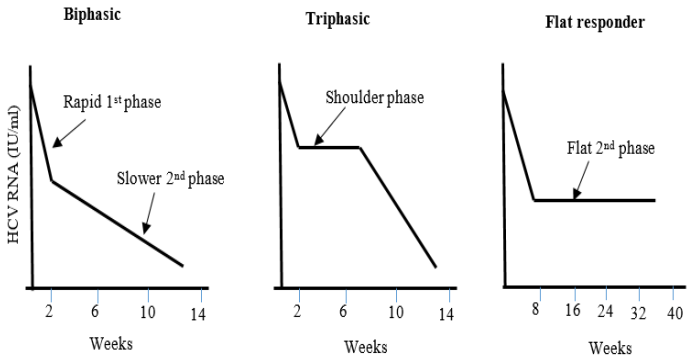


FIGURE 1. HCV RNA decline profiles observed in patients during antiviral therapy

jaundice) ([10]). 10-50% of patients with acute Hepatitis C infection spontaneously clear the infection within 6 months of infection without treatment, which occurs more frequently in individuals who are young and female ([11]). Remaining 85% of HCV infected patients develop to chronic infection which is the main cause of cirrhosis and liver cancer ([6]). 15-30% of those with chronic infection will develop cirrhosis, therefore, will lead to liver transplant (HCV may recur after transplantation) or even to death ([4]). HCV has a powerful reproductive strategy that prevents the development of effective vaccine against it. The combinational drug therapy; pegylated interferon-$\alpha$ (IFN-$\alpha$) and antiviral drug ribavirin (RBV) had been the standard treatment for chronic Hepatitis C for several years. Usually, the response to this therapy shows biphasic viral decline (Figure 1), which is characterized by a sharp decline followed by a slower decline ([12]). Sometimes, the therapy results in triphasic viral decline ([13]-[15]). The triphasic viral decline depicted in Figure 1 contains first phase of quick viral decline, second phase of constant viral load, which no longer exists when the ratio of uninfected hepatocytes and infected hepatocytes is greater than or equal to 1.0 and third phase of resumed gradual viral decay. In some patients (partial responders shown in Figure 1) treated with this combinational drug therapy, the viral load converged to a lower plateau during treatment ([13, 16]). Half of the HCV infected patients treated with this treatment were cured. But the treatment sometimes exhibited life-threatening adverse reactions. So new antivirals called direct antiviral agents (DAA) have been developed. Treatment with DAAs is more effective, safer and shorter (about 12 weeks) than the combinational drug therapy. Due to high prices, most HCV infected patients (even in high income countries) cannot have access to DAAs. No alternative treatment is available for non-responders.

Modelling the response of chronic Hepatitis C infection to antiviral therapy helps to know the origination and development of Hepatitis C, response of the immune system, effectiveness of therapy and mechanism of each drug action against HCV, etc. Most biological processes are memory (or history) dependent (they depend not only on the instant time but also on the history of previous time) and stochastic in nature. The principal merit (that is non-local) of fractional derivative made it possible to comprehend the underlying properties of biological processes exhibiting

fractional dynamics ([17]-[19]). The first attempt to apply fractional calculus concepts to predict the behaviour of chronic Hepatitis C disease during combinational drug therapy (IFN-$\alpha$ and RBV) is made by [20]. Their fractional order model could exactly reproduce the typical biphasic viral decline but failed to show clinically observed more complicated behaviours like triphasic viral decline, viral rebound to its pre-treatment level after cessation of therapy and convergence of viral load to a lower plateau. Moreover, they did not explain the role of RBV in curing Hepatitis C.

The objective of present work is to propose a fractional order mathematical model of chronic HCV infection responding to combinational drug therapy. The classical (integer order) model can explain i) triphasic behaviour for the HCV with a constant shoulder length (in terms of time period), where the death rate of virus and their proliferation rate are equal. However, the varying period of occurrence of this stationary phase followed by its decline with a specific slope to the below detection limit is not explained ii) biphasic behaviour. The classical model does not tell about a monophasic decline; that is a linear decline of viral load throughout therapy. The model proposed in this work has been a general one because it can explain the triphasic behaviour with varying stationary phase of curing HCV after drug therapy. The model can also describe biphasic as well as monophasic behaviour. Usually Hepatitis C takes at least 1 month to be cured with effective treatment. Therefore, to carry out numerical simulations for that duration, multistage new iterative method is considered.

The rest of the paper is organised as follows. Section 2 gives basic definitions and useful properties of fractional calculus. The proposed model is given in Section 3. Section 4 presents the evaluation of equilibrium points of proposed model and investigates their local asymptotic stability. We prove the existence of unique solution to the fractional order Hepatitis C model in Section 5. Section 6 expounds the procedure of solving the proposed model using multi-stage new iterative method. In Section 7, the model is simulated using various conditions to achieve above mentioned profiles of viral load. In Section 8, the paper gets concluded.

## 2. Basic definitions of fractional calculus

In this section, we provide the most commonly employed operators of fractional calculus, which were derived by generalizing the definition of $n-$fold integration ($n$ is an integer) ([21]).

**Definition 2.1**: A real function $f(t)$, $t>0$ is said to be in the space $C_\mu$, $\mu \in R$ if there exists a real number $p\,(>\mu)$, such that $f(t)=t^p f_1(t)$, where $f_1(t)\in C[0,\infty)$ and is said to be in the space $C_\mu^n$ if and only if $f^{(n)}\in C_\mu, n\in N$.

**Definition 2.2**: (Riemann-Liouville fractional order integral)

The Cauchy formula for repeated integration, which reduces $n-$fold integration of $f(t)$ to a single integral, is

$$J^n f(t)=\frac{1}{n-1}\int_0^t (t-\tau)^{n-1} f(\tau)\,d\tau, n\in Z^+. \tag{1}$$

Equation (1) can be written as

$$J^n f(t)=\frac{1}{\Gamma(n)}\int_0^t (t-\tau)^{n-1} f(\tau)\,d\tau, \tag{2}$$

where $\Gamma(n)$ is well known Euler's Gamma function, $\Gamma(n) = \int_0^\infty e^{-x} x^{n-1} dx$.
Equation (2) enables us to replace $n$ with $\alpha$ to obtain the following Riemann-Liouville fractional order integral of $f(t)$.

$$J^\alpha f(t) = \begin{cases} \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f(\tau)\, d\tau, & \text{for } \alpha > 0, \\ f(t), & \text{for } \alpha = 0. \end{cases} \tag{3}$$

For the function $f(t) \in C_\mu$ $(\mu \geq -1)$, $\alpha, \beta \geq 0$ and $\gamma > -1$, we have the following semigroup and commutative properties of Riemann-Liouville fractional integral.

$$J^\alpha J^\beta f(t) = J^{\alpha+\beta} f(t). \tag{4}$$

$$J^\alpha J^\beta f(t) = J^\beta J^\alpha f(t). \tag{5}$$

$$J^\alpha t^\gamma = \frac{\Gamma(\gamma+1)}{\Gamma(\alpha+\gamma+1)} t^{\alpha+\gamma}. \tag{6}$$

**Definition 2.3**: (Riemann-Liouville fractional order derivative)
By using Equation (3), we can derive a formula for the fractional derivative of $f(t)$ of order $\alpha$ as

$${}_0^{RL}D_t^\alpha f(t) = \begin{cases} \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{dt^n} \int_0^t (t-\tau)^{n-\alpha-1} f(\tau)\, d\tau, & \text{for } n-1 < \alpha < n \text{ and } t > 0, \\ \frac{d^n}{dt^n} f(t), & \text{for } \alpha = n. \end{cases} \tag{7}$$

From pure mathematics perspective, this definition is rigorous and elegant but in applications, we encounter the problem of finding fractional order initial values in order to solve the corresponding fractional order differential equations involving Riemann-Liouville fractional derivative. Only in a few instances, the fractional order initial conditions have clear physical meanings so it is possible to determine them numerically from the experiment ([22]). However, the Riemann-Liouville fractional derivative cannot be utilised in practical applications where it is impossible to expound and find numerical values of the fractional order initial values. To circumvent this shortcoming, Caputo proposed a modification to the Riemann-Liouville fractional order derivative ([23]).
**Definition 2.4**: (Caputo fractional order derivative)
The Caputo fractional derivative of $f(t)$ of order $\alpha$ is

$${}_0^{C}D_t^\alpha f(t) = \begin{cases} \frac{1}{\Gamma(n-\alpha)} \int_0^t (t-\tau)^{n-\alpha-1} f^{(n)}(\tau)\, d\tau, & \text{for } n-1 < \alpha < n \text{ and } t > 0, \\ \frac{d^n}{dt^n} f(t), & \text{for } \alpha = n. \end{cases} \tag{8}$$

Contrary to Riemann-Liouville fractional derivative, the Caputo fractional differential equations necessitate classical (integer order) initial values, therefore, the Caputo fractional derivative is used in modelling real world processes which exhibit fractional order dynamics. In case of zero initial conditions, the Riemann-Liouville fractional derivative and the Caputo fractional derivative are equivalent. Like the classical operators (integral and derivative), the fractional order operators also have physical interpretation. The fractional order integral can be understood as area under shape changing curve whereas the fractional order derivative implies the integer order derivative of area under shape changing curve ([24]).
The mathematical properties of the Riemann-Liouville fractional derivative and the Caputo fractional derivative can be found in [21], [25] and [26]. We give below two properties of Caputo fractional derivative which we need in the subsequent sections.

For $f(t) \in C_\mu$, $\mu > -1$ and $n-1 < \alpha < n$,

$$J^\alpha {}_0^C D_t^\alpha f(t) = J^n D^n f(t) = \left( f(t) - \sum_{k=0}^{n-1} f^{(k)}(0) \frac{t^k}{\Gamma(k+1)} \right), \; {}_0^C D_t^\alpha c = 0, \quad (9)$$

where $c$ is a constant.

## 3. Fractional order chronic Hepatitis C infection model

Consider the following fractional order chronic HCV infection model, which is a generalization of the classical model proposed in [13], describing the behaviour of HCV during treatment with IFN-$\alpha$ and RBV.

$${}_0^C D_t^\alpha T(t) = s + r_T T(t) \left( 1 - \frac{T(t) + I(t)}{T\max} \right) - d_T T(t) - \beta V_I(t) T(t). \quad (10)$$

$${}_0^C D_t^\alpha I(t) = \beta V_I(t) T(t) + r_I I(t) \left( 1 - \frac{T(t) + I(t)}{T\max} \right) - \delta I(t). \quad (11)$$

$${}_0^C D_t^\alpha V_I(t) = (1 - \rho(t))(1 - \varepsilon_P) p I(t) - c V_I(t). \quad (12)$$

$${}_0^C D_t^\alpha V_{NI}(t) = \rho(t)(1 - \varepsilon_P) p I(t) - c V_{NI}(t). \quad (13)$$

$$\rho(t) = \rho_{\max} \left( 1 - \exp\left( {}^{-t}/_{t_a} \right) \right). \quad (14)$$

The population of uninfected hepatocytes ($T(t)$), infected hepatocytes ($I(t)$), non-infectious ($V_{NI}(t)$) and infectious viral particles ($V_I(t)$) in the chronic infection state before the treatment commences (i.e.at time $t = 0$) serve as the initial conditions; $T(0)$, $I(0)$, $V_{NI}(0)$ and $V_I(0)$ for the proposed model.

Equation (10) dictates that the target cells or uninfected hepatocytes are produced at constant rate$s$, died at constant rate $d$ and infected by HCV at constant rate $\beta$ per cell. The parameters, $r_T$ and $r_I$, are the maximum proliferation rates of uninfected and infected hepatocytes, respectively. As per the blind homeostasis process (in which the uninfected and the infected hepatocytes are indistinguishable), both the uninfected and the infected hepatocytes can flourish until the sum of $T(t)$ and $I(t)$ reaches the maximum size of liver, $T_{\max}$. Since HCV replicates itself, it is assumed that the proliferation rate of infected hepatocytes is slower than that of uninfected hepatocytes. The infected hepatocytes are lost at constant rate $\delta$ per cell. The HCV parti**c**les (virions) are produced at rate $p$per infected hepatocyte. The mutagenic effect of RBV makes a fraction ($\rho(t)$) of virus particles less infectious or non-infectious, $V_{NI}(t)$. The role of IFN-$\alpha$ in curing chronic infection is to block the secretion of new virions whereas RBV reduces *de novo* (afresh) infection. Both the infectious and the non-infectious viral particles are cleared at constant rate $c$ per virion. The effectiveness of IFN-$\alpha$ and RBV are described by $\varepsilon_p$and $\rho_{\max}$, respectively. The efficacy of RBV can increase with time on therapy (shown in (14)) as RBV slowly builds up in the blood plasma. Nonetheless, RBV's impact on HCV is insignificant when the efficiency of IFN-$\alpha$ is very high.

Dahari et al (2007)[13]utilized the following formula for critical drug efficacy to predict the behaviour of HCV during treatment.

$$e_c = 1 - \frac{c(\delta T_{\max} + r_I T_0 - r_I T_{\max})}{p\beta T_{\max} T_0}. \quad (15)$$

The successful treatment ($\varepsilon_{tot} > e_c$, $\varepsilon_{tot} = 1 - (1 - \rho_{\max})(1 - \varepsilon_p)$ is the overall drug efficacy) results in the complete eradication of HCV. If $\varepsilon_{tot} < e_c$, the viral

load converges to a new steady state below its pre-treatment level i.e. chronic Hepatitis C is not cured.

## 4. Equilibrium points and their local asymptotic stability

As the Caputo fractional derivative of a constant is zero, the system of Caputo fractional differential equations in (10) to (14) turns to the following system of nonlinear algebraic equations at steady state.

$$\left.\begin{array}{l} s + r_T T(t)\left(1 - \frac{T(t)+I(t)}{T\max}\right) - d_T T(t) - \beta V_I(t) T(t) = 0 \\ \beta V_I(t) T(t) + r_I I(t)\left(1 - \frac{T(t)+I(t)}{T\max}\right) - \delta I(t) = 0 \\ (1-\rho(t))(1-\varepsilon_P) pI(t) - cV_I(t) = 0 \\ \rho(t)(1-\varepsilon_P) pI(t) - cV_{NI}(t) = 0 \end{array}\right\}. \tag{16}$$

Upon solving Equation (16), we get the following equilibrium points.
Equilibrium point 1 (infection-free or uninfected steady state):
The first equilibrium point indicates that the person is healthy (uninfected by HCV or recovered from infection). In the uninfected state, there are no virions and infected hepatocytes. This situation is called sustained virological response. The population of uninfected hepatocytes or healthy liver cells in this state is given by

$$T_0 = \frac{T_{\max}}{2r_T}\left[r_T - d_T + \sqrt{(r_T - d_T)^2 + \frac{4r_T s}{T\max}}\right]. \tag{17}$$

Equilibrium point 1 is $\varepsilon_1 = (T_0, 0, 0)$.
Equilibrium point 2 (chronic infection):
The second equilibrium point emphases that the person has chronic HCV infection. The steady state values of uninfected cells, infected cells and viral load (infectious and non-infectious, $V_I + V_{NI}$) are given below.

$$\bar{T} = \frac{1}{2}\left[-\left(\frac{D}{H}\right) + \sqrt{\left(\frac{D}{H}\right)^2 + \frac{4sT_{\max}}{r_T H}}\right], \bar{I} = \bar{T}\left((A/r_I) - 1\right) + T_{\max} - B, \bar{V} = \frac{p\bar{I}}{c}, \tag{18}$$

where $A = \frac{p\beta T_{\max}}{c}, B = \frac{\delta T_{maxx}}{r_I}, H = \frac{A^2}{r_I r_T} + \frac{A}{r_I} - \frac{A}{r_T}$ ,
$D = A\left[\frac{T_{\max}}{r_T}\left(1 + \frac{d_T}{A}\right) - B\left(\frac{1}{A} + \frac{1}{r_T}\right)\right]$.
The second equilibrium point is$\varepsilon_2 = \left(\bar{T}, \bar{I}, \bar{V}\right)$.
We now carry out the stability analysis of the fractional order chronic Hepatitis C infection model during treatment.
The Jacobian matrix is computed as

$$J = \begin{bmatrix} a_{11} & a_{12} & a_{13} & 0 \\ a_{21} & a_{22} & a_{23} & 0 \\ 0 & a_{32} & -c & 0 \\ 0 & a_{42} & 0 & -c \end{bmatrix}. \tag{19}$$

where
$a_{11} = r_T - 2\frac{r_T}{T_{\max}} T(t) - \frac{r_T}{T_{\max}} I(t) - d_T - \beta V_I(t)$, $a_{12} = -\frac{r_T}{T_{\max}} T(t)$,
$a_{13} = -\beta T(t)$, $a_{21} = \beta V_I(t) - \frac{r_I}{T_{\max}} I(t)$, $a_{22} = r_I - \frac{r_I}{T_{\max}} T(t) - 2\frac{r_I}{T_{\max}} I(t) - \delta$,

$a_{23} = r_I - \frac{r_I}{T_{\max}} T(t) - 2\frac{r_I}{T_{\max}} I(t) - \delta$, $a_{32} = (1-\rho(t))(1-\varepsilon_P)p$, $a_{42} = \rho(t)(1-\varepsilon_P)p$.
Evaluating the Jacobian matrix at the first equilibrium point or infection-free state,

$$J(\varepsilon_1) = \begin{bmatrix} r_T - 2\frac{r_T}{T_{\max}} T_0 - d_T & -\frac{r_T}{T_{\max}} T_0 & -\beta T_0 & 0 \\ 0 & r_I - \frac{r_I}{T_{\max}} T_0 - \delta & \beta T_0 & 0 \\ 0 & (1-\rho(t))(1-\varepsilon_P)p & -c & 0 \\ 0 & \rho(t)(1-\varepsilon_P)p & 0 & -c \end{bmatrix}. \tag{20}$$

The eigenvalues of $J(\varepsilon_1)$ are

$$\lambda_1 = -\sqrt{(r_T - d_T)^2 + \frac{4 r_T s}{T \max}}. \tag{21}$$

$$\lambda_2 = -c. \tag{22}$$

$$\lambda_3 = \frac{1}{2}\left[ b_{11} + \sqrt{\left(-\delta + r_I - \frac{r_I T_0}{T_{\max}} - \beta T_0\right)^2 + 4p(1-\varepsilon)(1-\rho(t))\beta T_0} \right]. \tag{23}$$

$$\lambda_4 = \frac{1}{2}\left[ b_{22} - \sqrt{\left(-\delta + r_I - \frac{r_I T_0}{T_{\max}} - \beta T_0\right)^2 + 4p(1-\varepsilon)(1-\rho(t))\beta T_0} \right]. \tag{24}$$

where $b_{11} = -\delta + r_I - \frac{r_I T_0}{T_{\max}} + \beta T_0$, $b_{22} = -\delta + r_I - \frac{r_I T_0}{T_{\max}} + \beta T_0$.
Equilibrium point 1 is locally asymptotically stable if all eigenvalues of $J(\varepsilon_1)$ satisfies the following condition.

$$|\arg(\lambda_i)| > \frac{\alpha\pi}{2}, i = 1,2,3,4. \tag{25}$$

If the above condition is satisfied, during treatment, the viral load converges to uninfected or infection-free state that is viral particles are thoroughly removed and the patient is free of infection.
At the second equilibrium point, the Jacobian matrix is assessed as

$$J(\varepsilon_2) = \begin{bmatrix} b_{33} & -\frac{r_T}{T_{\max}}\bar{T} & -\beta\bar{T} & 0 \\ \beta\bar{V}_I - \frac{r_I}{T_{\max}}\bar{I} & r_I - \frac{r_I}{T_{\max}}\bar{T} - 2\frac{r_I}{T_{\max}}\bar{I} - \delta & \beta\bar{T} & 0 \\ 0 & (1-\rho(t))(1-\varepsilon_P)p & -c & 0 \\ 0 & \rho(t)(1-\varepsilon_P)p & 0 & -c \end{bmatrix}, \tag{26}$$

where $b_{33} = r_T - 2\frac{r_T}{T_{\max}}\bar{T} - \frac{r_T}{T_{\max}}\bar{I} - d_T - \beta\bar{V}_I$.
The characteristic equation is

$$a_4\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 1, \tag{27}$$

where,

$$a_4 = 1, a_3 = -a - e - j, a_2 = aj + ej + hj - gf - bd + ae + ah + eh - h, b = -\frac{r_T}{T_{\max}}\bar{T},$$

$$a_1 = jgf + jbd - jae - jah - jeh - cdg + afg + bdh - aeh, f = \beta\bar{T}, c = -\beta\bar{T},,$$

$$a = r_T - 2\frac{r_T}{T_{\max}}\bar{T} - \frac{r_T}{T_{\max}}\bar{I} - d_T - \beta\bar{V}, d = \beta\bar{V}_I - \frac{r_I}{T_{\max}}\bar{T}, j = -c, h = -c,$$

$$i = \rho(t)(1-\varepsilon_P)p, e = r_I - \frac{r_I}{T_{\max}}\bar{T} - 2\frac{r_I}{T_{\max}}\bar{I} - \delta, g = (1-\rho(t))(1-\varepsilon_P)p,$$

$$a_0 = jcdg - jafg - jbdh + jaeh - eh^3.$$

According to Routh-Hurwitz stability criterion, if the conditions as per the next equation are fulfilled, then the viral load remains unchanged that is the disease is persistently present.

$$a_i > 0, i = 1, 2, 3, 4, b_1 = \begin{vmatrix} a_2 & a_1 \\ a_4 & a_3 \end{vmatrix} > 0, c_1 = \begin{vmatrix} a_1 & a_3 & 0 \\ a_0 & a_2 & a_1 \\ 0 & a_4 & a_3 \end{vmatrix} > 0. \tag{28}$$

## 5. Existence of unique solution

Let us rewrite the fractional order chronic Hepatitis C infection model bestowed in Section 3 in a short form as follows.

$$_0^C D_t^\alpha X(t) = F(t, X(t)), t \in [0, T], Y \in [0, \infty), \tag{29}$$

where $X(t) = [T(t), I(t), V_I(t), V_{NI}(t)]$ and $F : [0, T] \times [0, \infty) \to [0, \infty)$ is a nonlinear function of $t$ and $X(t)$.
Let us define Banach space as

$$C = [0, T] \times [0, \infty), \tag{30}$$

with $d : [0, \infty) \times [0, \infty) \to [0, \infty)$, $d(X_1(t), X_2(t)) = \|X_2(t) - X_1(t)\|$.
We assume that the function $F$ satisfies the following condition of Lipschitz continuity.

$$d(F(t, X_1(t)), F(t, X_2(t))) \leq Ld(X_1(t), X_2(t)), \tag{31}$$

where$L$ is a Lipschitz constant, $L \in (0, 1)$.
We now rewrite Equation (29) as

$$X(t) = X(0) + \frac{1}{\Gamma(\alpha - 1)} \int_0^t (t - \tau)^{\alpha-1} F(\tau, X(\tau)) d\tau. \tag{32}$$

Any function satisfying Equation (29) also satisfies the above Volterra integral equation.
By considering the following successive approximations, we prove that Equation (29) has a unique solution.

$$\varphi_0 = X(0). \tag{33}$$

$$\varphi_{k+1}(t) = X(0) + \frac{1}{\Gamma(\alpha - 1)} \int_0^t (t - \tau)^{\alpha-1} F(\tau, \varphi_k(\tau)) d\tau, k = 0, 1, 2, 3, \ldots. \tag{34}$$

Let us define the Picard operator on Banach Space $C$ as

$$\Gamma\varphi = X(0) + \frac{1}{\Gamma(\alpha - 1)} \int_0^t (t - \tau)^{\alpha-1} F(\tau, \varphi(\tau)) d\tau. \tag{35}$$

We now show that the Picard operator is a contraction on Banach space.
Let $t$ be such that $\|(\Gamma\varphi_2 - \Gamma\varphi_1) t\| = \|\Gamma\varphi_2(t) - \Gamma\varphi_1(t)\|$.

$$\begin{aligned} &\left\| e^{-Nt} (\Gamma\varphi_2(t) - \Gamma\varphi_1(t)) \right\| \\ &\quad = \left\| \frac{1}{\Gamma(\alpha)} \int_0^t (t - \tau)^{\alpha-1} e^{-N\tau} (F(\tau, \varphi_2(\tau)) - F(\tau, \varphi_1(\tau))) d\tau \right\| \\ &\quad = \left| \frac{1}{\Gamma(\alpha)} \int_0^t (t - \tau)^{\alpha-1} e^{-N\tau} \|F(\tau, \varphi_2(\tau)) - F(\tau, \varphi_1(\tau))\| d\tau \right| \\ &\quad \leq \left| \frac{1}{\Gamma(\alpha)} \int_0^t (t - \tau)^{\alpha-1} e^{-N\tau} L \|\varphi_2(\tau) - \varphi_1(\tau)\| d\tau \right| \end{aligned} \tag{36}$$

$$\leq \frac{L\left\|\varphi_2(\tau)-\varphi_1(\tau)\right\|}{\Gamma(\alpha)}\left|\int_0^t (t-\tau)^{\alpha-1}e^{-N\tau}d\tau\right|$$
$$\leq L\left\|\varphi_2(\tau)-\varphi_1(\tau)\right\|\left|\frac{e^{-Nt}}{N^\alpha}\right|.$$

Choose $N$ such that $N^\alpha > L$.
From Equation (36), we can obtain the following.

$$\left\|\Gamma\varphi_2(t)-\Gamma\varphi_1(t)\right\| \leq \frac{L}{N^\alpha}\left\|\varphi_2(t)-\varphi_1(t)\right\|. \tag{37}$$

According to Banach fixed point theorem, the Picard operator has a unique fixed point that is a unique function $\varphi(t)$ satisfying $\Gamma\varphi(t)=\varphi(t)$. This affirms that there exists a unique solution to the fractional order chronic Hepatitis C infection model.

## 6. Solving fractional order chronic Hepatitis C infection model using multistage new iterative method

Using Equation (9), an equivalent form for the fractional order chronic HCV infection model can be obtained as follows.

$$T(t)=b_{55}-\frac{r_T}{T\max}\left(J^\alpha(T(t)T(t))+J^\alpha(T(t)I(t))\right)-d_TJ^\alpha(T(t))-b_{66}, \tag{38}$$

where $b_{55}=T(0)+J^\alpha(s)+r_TJ^\alpha(T(t))$, $b_{66}=\beta J^\alpha(V_I(t)T(t))$.

$$I(t)=b_{77}-\frac{r_I}{T\max}\left(J^\alpha(I(t)T(t))+J^\alpha(I(t)I(t))\right)-\delta J^\alpha(I(t)), \tag{39}$$

where $b_{77}=I(0)+\beta J^\alpha(V_I(t)T(t))+r_IJ^\alpha(I(t))$.

$$V_I(t)=V_I(0)+(1-\rho(t))(1-\varepsilon_P)pJ^\alpha(I(t))-cJ^\alpha(V_I(t)). \tag{40}$$

$$V_{NI}(t)=V_{NI}(0)+\rho(t)(1-\varepsilon_P)pJ^\alpha(I(t))-cJ^\alpha(V_{NI}(t)). \tag{41}$$

Following the new iterative method ([27]), we approximate the solution of the above system of Volterra integral equations as

$$T(t)=\sum_{i=0}^{\infty}T_i(t), I(t)=\sum_{i=0}^{\infty}I_i(t), V_I(t)=\sum_{i=0}^{\infty}V_{I_i}(t), V_{NI}(t)=\sum_{i=0}^{\infty}V_{NI_i}(t). \tag{42}$$

Linearizing the nonlinear terms,

$$A_T=\left(\sum_{i=0}^{\infty}T_i(t)\right)^2=(T_0(t))^2+\sum_{i=1}^{\infty}\left(\left(\sum_{j=0}^{i}T_j(t)\right)^2-\left(\sum_{j=0}^{i-1}T_j(t)\right)^2\right). \tag{43}$$

$$A_I=\left(\sum_{i=0}^{\infty}I_i(t)\right)^2=(I_0(t))^2+\sum_{i=1}^{\infty}\left(\left(\sum_{j=0}^{i}I_j(t)\right)^2-\left(\sum_{j=0}^{i-1}I_j(t)\right)^2\right). \tag{44}$$

$$A_{TI}=\left(\sum_{i=0}^{\infty}T_i(t)\right)\left(\sum_{i=0}^{\infty}I_i(t)\right)=T_0(t)I_0(t)+\sum_{i=1}^{\infty}(A-B), \tag{45}$$

where $A=\left(\sum_{j=0}^{i}T_j(t)\right)\left(\sum_{j=0}^{i}I_j(t)\right)$, $B=\left(\sum_{j=0}^{i-1}T_j(t)\right)\left(\sum_{j=0}^{i-1}I_j(t)\right)$.

$$A_{TV}=\left(\sum_{i=0}^{\infty}T_i(t)\right)\left(\sum_{i=0}^{\infty}V_{I_i}(t)\right)=T_0(t)V_{I_0}(t)+\sum_{i=1}^{\infty}(A1-B1), \tag{46}$$

where $A1 = \left(\sum_{j=0}^{i} T_j(t)\right)\left(\sum_{j=0}^{i} V_{I_j}(t)\right)$, $B1 = \left(\sum_{j=0}^{i-1} T_j(t)\right)\left(\sum_{j=0}^{i-1} V_{I_j}(t)\right)$.
From Equations (38) to (46),

$$\sum_{i=0}^{\infty} T_i(t) = a_0 + r_T J^\alpha\left(\sum_{i=0}^{\infty} T_i(t)\right) - \frac{r_T}{T\max} J^\alpha\left(A_T + A_{TI}\right) - d_T J^\alpha\left(\sum_{i=0}^{\infty} T_i(t)\right), \tag{47}$$

where $a_0 = T(0) + J^\alpha(s) - \beta J^\alpha(A_{TV})$.

$$\sum_{i=0}^{\infty} I_i(t) = a_1 - \frac{r_I}{T\max} J^\alpha\left(A_I + A_{TI}\right) + r_I J^\alpha\left(\sum_{i=0}^{\infty} I_i(t)\right) - \delta J^\alpha\left(\sum_{i=0}^{\infty} I_i(t)\right), \tag{48}$$

where $a_1 = I(0) + \beta J^\alpha(A_{TV})$.

$$\sum_{i=0}^{\infty} V_{I_i}(t) = V_I(0) + (1-\rho(t))(1-\varepsilon_P) p J^\alpha\left(\sum_{i=0}^{\infty} I_i(t)\right) - c J^\alpha\left(\sum_{i=0}^{\infty} V_{I_i}(t)\right). \tag{49}$$

$$\sum_{i=0}^{\infty} V_{NI_i}(t) = V_{NI}(0) + \rho(t)(1-\varepsilon_P) p J^\alpha\left(\sum_{i=0}^{\infty} I_i(t)\right) - c J^\alpha\left(\sum_{i=0}^{\infty} V_{NI_i}(t)\right). \tag{50}$$

From the following recursive relations, the components of the series solutions in (42) can be determined.

$$T_0(t) = T(0) + J^\alpha(s). \tag{51}$$

$$T_1(t) = J^\alpha\left(a_2 - \beta T_0(t) V_{I_0}(t) - \frac{r_T}{T\max}\left(T_0(t)\right)^2 - \frac{r_T}{T\max} T_0(t) I_0(t)\right), \tag{52}$$

where $a_2 = r_T T_0(t) - d_T T_0(t)$.

$$T_{i+1}(t) = -\frac{r_T}{T\max} J^\alpha\left(a_3 + a_4 - a_5\right) - \beta J^\alpha(a_6) + J^\alpha\left(r_T T_i(t) - d_T T_i(t)\right), \tag{53}$$

where $a_3 = \left(\sum_{j=0}^{i} T_j(t)\right)^2 - \left(\sum_{j=0}^{i-1} T_j(t)\right)^2$, $a_4 = \left(\sum_{j=0}^{i} T_j(t)\right)\left(\sum_{j=0}^{i} I_j(t)\right)$,
$a_6 = \left(\sum_{j=0}^{i} T_j(t)\right)\left(\sum_{j=0}^{i} V_{I_j}(t)\right) - \left(\sum_{j=0}^{i-1} T_j(t)\right)\left(\sum_{j=0}^{i-1} V_{I_j}(t)\right)$,
$a_5 = \left(\sum_{j=0}^{i-1} T_j(t)\right)\left(\sum_{j=0}^{i-1} I_j(t)\right)$.

$$I_0(t) = I(0). \tag{54}$$

$$I_1(t) = J^\alpha\left(\beta V_{I_0}(t) T_0(t) + r_I I_0(t) - \frac{r_I}{T\max}\left(T_0(t) I_0(t) + \left(I_0(t)\right)^2\right) - \delta I_0(t)\right). \tag{55}$$

$$I_{i+1}(t) = \beta J^\alpha(a_7) + J^\alpha\left(r_I I_i(t) - \delta I_i(t)\right) - \frac{r_I}{T\max} J^\alpha(a_8) - \frac{r_T}{T\max} J^\alpha(a_9), \tag{56}$$

where $a_7 = \left(\sum_{j=0}^{i} T_j(t)\right)\left(\sum_{j=0}^{i} V_{I_j}(t)\right) - \left(\sum_{j=0}^{i-1} T_j(t)\right)\left(\sum_{j=0}^{i-1} V_{I_j}(t)\right)$,
$a_8 = \left(\sum_{j=0}^{i} I_j(t)\right)^2 - \left(\sum_{j=0}^{i-1} I_j(t)\right)^2$,
$a_9 = \left(\sum_{j=0}^{i} T_j(t)\right)\left(\sum_{j=0}^{i} I_j(t)\right) - \left(\sum_{j=0}^{i-1} T_j(t)\right)\left(\sum_{j=0}^{i-1} I_j(t)\right)$.

$$V_{I_0}(t) = V_I(0). \tag{57}$$

$$V_{I_{i+1}}(t) = J^\alpha\left(\left(1-\rho(t)\right)\left(1-\varepsilon_P\right) p I_i(t) - c V_{I_i}(t)\right), i \geq 0. \tag{58}$$

$$V_{NI_0}(t) = V_{NI}(0). \tag{59}$$

$$V_{NI_{i+1}}(t) = J^\alpha\left(\rho(t)\left(1-\varepsilon_P\right) p I_i(t) - c V_{NI_i}(t)\right), i \geq 0. \tag{60}$$

To achieve practical solution, we truncate the infinite series in (39) to $N$($N$ is a finite integer) terms as shown in the next equation.

$$T(t) \approx \sum_{i=0}^{N} T_i(t), I(t) \approx \sum_{i=0}^{N} I_i(t), V_I(t) \approx \sum_{i=0}^{N} V_{I_i}(t), V_{NI}(t) \approx \sum_{i=0}^{N} V_{NI_i}(t). \quad (61)$$

The approximate solutions obtained by the new iterative method can predict the real nature of Hepatitis C virus only for a short treatment duration but to know whether the patient is cured or not, we need to have approximate solution which can valid for whole treatment duration (i.e at least more than one month). Therefore, we adopt here the multistage new iterative method proposed in [28].
We divide the interval $[0, T]$ into $m$ subinterval using the constant step size $h$ as $[0, t_1]$, $[t_1, t_2]$, $[t_3, t_4]$, $\cdots\cdots\cdots$, $[t_{m-1}, t_m]$, where $t_i = ih$.
Now, the fractional order chronic HCV infection model in (10) to (13) becomes

$$T(t) = T(t_*) + \int_{t_*}^{t} (t-\tau)^{\alpha-1} \left(s + r_T T(\tau) a_{10} - d_T T(\tau) - \beta V_I(\tau) T(\tau)\right) d\tau, \quad (62)$$

where $a_{10} = \left(1 - \frac{T(\tau)+I(\tau)}{T\max}\right)$.

$$I(t) = I(t_*) + \int_{t_*}^{t} (t-\tau)^{\alpha-1} \left(\beta V_I(\tau) T(\tau) + r_I I(\tau) a_{10} - \delta I(\tau)\right) d\tau. \quad (63)$$

$$V_I(t) = V_I(t_*) + \int_{t_*}^{t} (t-\tau)^{\alpha-1} \left((1-\rho(\tau))(1-\varepsilon_P) p I(\tau) - c V_I(\tau)\right) d\tau. \quad (64)$$

$$V_{NI}(t) = V_{NI}(t_*) + \int_{t_*}^{t} (t-\tau)^{\alpha-1} \left(\rho(\tau)(1-\varepsilon_P) p I(\tau) - c V_{NI}(\tau)\right) d\tau(t). \quad (65)$$

where $t \in [t_{i-1}, t_i)$, $t_* = t_{i-1}$, $i = 1, 2, 3, \ldots\ldots\ldots, m$.
Following the procedure expounded in (42) to (60), we compute the solution of the system of Volterra integral equations in (62) to (65) in the first subinterval $[0, t_1]$.

$$T(t) = T(0) + \sum_{j=1}^{N} T_j(t), I(t) = I(0) + \sum_{j=1}^{N} I_j(t), t \in [0, t_1). \quad (66)$$

$$V_I(t) = V_I(0) + \sum_{j=1}^{N} V_{I_j}(t), V_{NI}(t) = V_{NI}(0) + \sum_{j=1}^{N} V_{NI_j}(t), t \in [0, t_1). \quad (67)$$

At the second stage (second subinterval), we evaluate the solution acquired in the first subinterval at $t = t_1$ and use $T(t_1)$, $I(t_1)$, $V_I(t_1)$, $V_{NI}(t_1)$ as the initial values.

$$T(t) = T(t_1) + \sum_{j=1}^{N} T_j(t), I(t) = I(t_1) + \sum_{j=1}^{N} I_j(t), t \in [t_1, t_2). \quad (68)$$

$$V_I(t) = V_I(t_1) + \sum_{j=1}^{N} V_{I_j}(t), V_{NI}(t) = V_{NI}(t_1) + \sum_{j=1}^{N} V_{NI_j}(t), t \in [t_1, t_2). \quad (69)$$

At the $i^{th}$ stage, the solution is estimated as

$$T(t) = T(t_{i-1}) + \sum_{j=1}^{N} T_j(t), I(t) = I(t_{i-1}) + \sum_{j=1}^{N} I_j(t), t \in [t_{i-1}, t_i). \quad (70)$$

$$V_I(t) = V_I(t_{i-1}) + \sum_{j=1}^{N} V_{I_j}(t), V_{NI}(t) = V_{NI}(t_{i-1}) + \sum_{j=1}^{N} V_{NI_j}(t), t \in [t_{i-1}, t_i). \tag{71}$$

In this manner, we predict the response of healthy or uninfected hepatocytes, infected hepatocytes and Hepatitis C virus in whole treatment duration.

## 7. Results

We take the parameters;
$T_{\max} = 9.13 \times 10^6$cells, $d_T = 0.013$ day$^{-1}$, $p = 4.3$ virions cell$^{-1}$ day$^{-1}$,
$c = 3.5$ day$^{-1}$, $\beta = 3.5 \times 10^{-7}$ml day$^{-1}$ virions$^{-1}$, $\delta = 0.22$ day$^{-1}$, $r_T = 0.5$ day$^{-1}$,
$\rho_{\max} = 0$, $r_I = 0.5 r_T$ day$^{-1}$, $s = 4$cells ml$^{-1}$ day$^{-1}$, $\varepsilon_{tot} \approx 1$, $\varepsilon_c = 0.9442$,
and the initial values;
$T(0) = 89.3854, I(0) = 1.0969 \times 10^6, V_I(0) = 1.3476 \times 10^6, V_{NI}(0) = 0$.
In case of successful antiviral therapy ($\varepsilon_{tot} > \varepsilon_c$), the fractional order model must exhibit sustained virological response with triphasic viral decline. The NIM solution obtained for $\alpha = 1$ and $t \in [0, 1]$ is in good agreement with the solution attained by the fourth order Runge-Kutta (RK) method as shown in Figure 2. However, for $t \in [0, 6]$, the new iterative method ($N = 8$) became incapable to offer realistic approximate solutions (Figure 3) whereas the multistage new iterative method ($N = 3$, $t \in [0, 90]$) succeeded in predicting the actual response of uninfected hepatocytes, infected hepatocytes and viral load (Figure 4). For the selected values of model parameters, the eigenvalues of the Jacobian matrix evaluated at $\varepsilon_1 = (892628.213, 0, 0)$ are real and negative ($\lambda_1 = -3.5008$, $\lambda_2 = -3.5$, $\lambda_3 = -1.461$, $\lambda_4 = -0.456$), hence, the infection-free state is locally asymptotically stable as displayed in Figure 4. Both the population of uninfected and infected hepatocytes reach the uninfected state. The final (third) phase slope of viral decline indicates the death rate of infected hepatocytes. According to the homeostasis process, the proliferation rate of infected hepatocytes is sensitive to the total number of liver cells (uninfected plus infected hepatocytes). The uninfected hepatocytes take reasonably long time to level the infected ones, therefore, during this period, the loss of infected hepatocytes is compensated by recently born infected cells. So that the level of infected hepatocytes remains constant until $T = I$. Since the infected hepatocytes are the major producers of viral particles, the population of HCV does not change as long as the level of infected hepatocytes stays constant, leading to the formation of shoulder phase. When $T \geq I$, the viral load begins to decay i.e. the end of the shoulder phase.
The fractional order chronic HCV infection model is simulated using MNIM for various values of $\alpha$ and Figure 5 displays the corresponding responses of $T$ and $I$. We notice from Figure 5 that as the value of fractional order decreases from 0.9 to 0.52, the population of uninfected and infected hepatocytes quickly converge to the uninfected steady state ($T = T_0$, $I = 0$). The shoulder phase of HCV decline (Figure 6) keeps on shrinking until $\alpha = 0.6$ and at $\alpha = 0.55$, the triphasic HCV decline turns to biphasic and becomes monophasic when $\alpha = 0.52$. The viral load eventually reaches the lowest value of $1.71437 \times 10^{-9}$. We now examine the dynamics of HCV when the proliferation rate of infected hepatocytes is much slower than that of uninfected hepatocytes($r_T/r_I = 5$). Figure 7 shows the profiles of $T$, $I$ and $V$ for diverse values of $\alpha$. At each value of $\alpha$, the population of uninfected hepatocytes increases from its initial value to the steady state value of 8892628.2135 and the

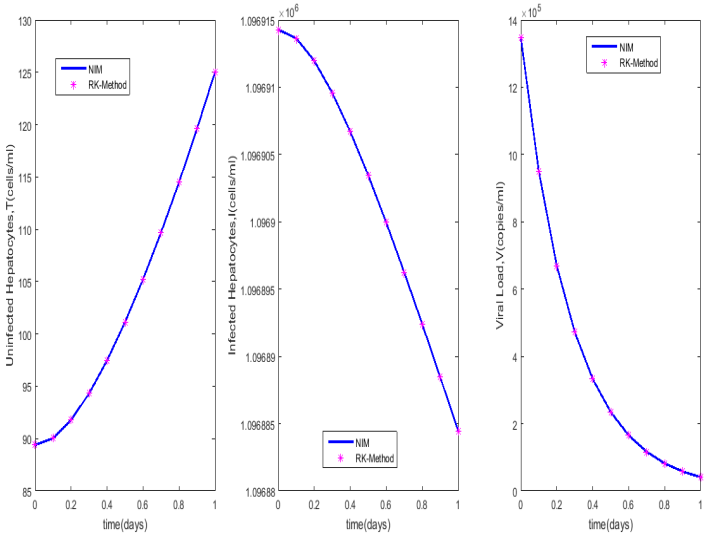


FIGURE 2. Comparison between NIM solution and RK solution for $\alpha = 1$, $h = 0.1$ and $t \in [0, 1]$

lowest value of $\alpha$ induces the population of uninfected hepatocytes to quickly reach its steady state. As the value of $\alpha$reduces from 1, the infected hepatocytes rapidly converges to the uninfected steady state of 0. Since the infected hepatocytes are slowly regenerating, their loss is not compensated, hence, the infected hepatocytes are continuously decaying thus there is no shoulder phase in the viral decline and this type of decline of viral load is called biphasic decline. The viral load rapidly drops beyond the undetectable limit at the lowest value of $\alpha$. It is evident from Figures 5 to 7 that the infection-free state is locally asymptotically stable even in the fractional order case. When the overall drug efficacy is not high enough ($\varepsilon_{tot} = 0.94$), one of the eigenvalues of the Jacobian matrix calculated at infection-free state is positive. Therefore, the infection-free state is unstable and the viral load does not converge to the first equilibrium point instead reaches a lower plateau (8) i.e. chronic HCV infection is not cured. It is also noticed that the shoulder phase occurs even in partial responders. As found before, the duration of the shoulder phase reduces as the fractional order approaches zero. Because of the inadequate drug efficacy, there is no appreciable growth in the population of healthy liver cells and no significant decay in the population of infected cells. We assume that the effectiveness of RBV is constant throughout the therapy and we simulate the fractional order HCV model for $\varepsilon_{tot} = 0.95$, $\rho_{\max} = 0.9$ and $\alpha = \{1, 0.85, 0.75, 0.55\}$. Figure 9 shows that the mutagenic effect of RBV enhances the third phase slope of HCV decay and further improvement in the third phase slope is caused by $\alpha$ as demonstrated in Figure 10.

## 8. CONCLUSIONS

The mathematical model presented in this paper is about the response of patient with chronic Hepatitis C infection in the face of therapeutic drug (IFN-$\alpha$ and RBV).

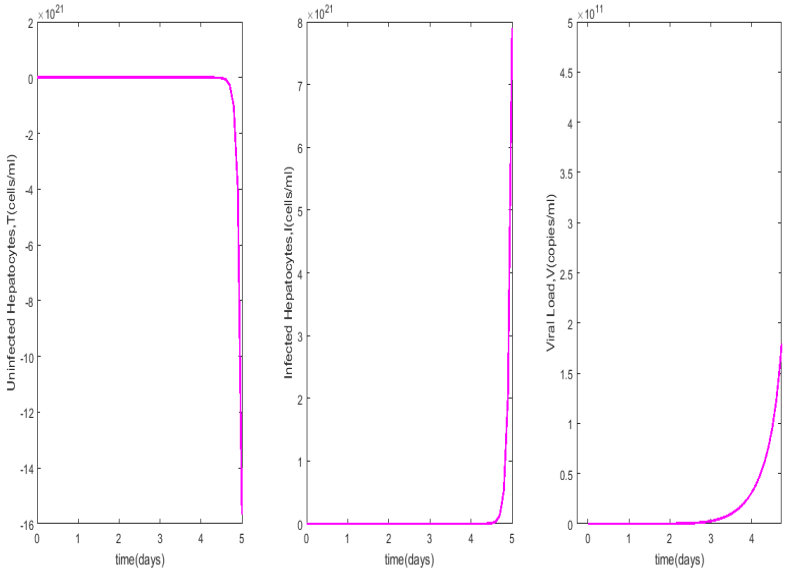


FIGURE 3. NIM solution for $t \in [0, 6]$

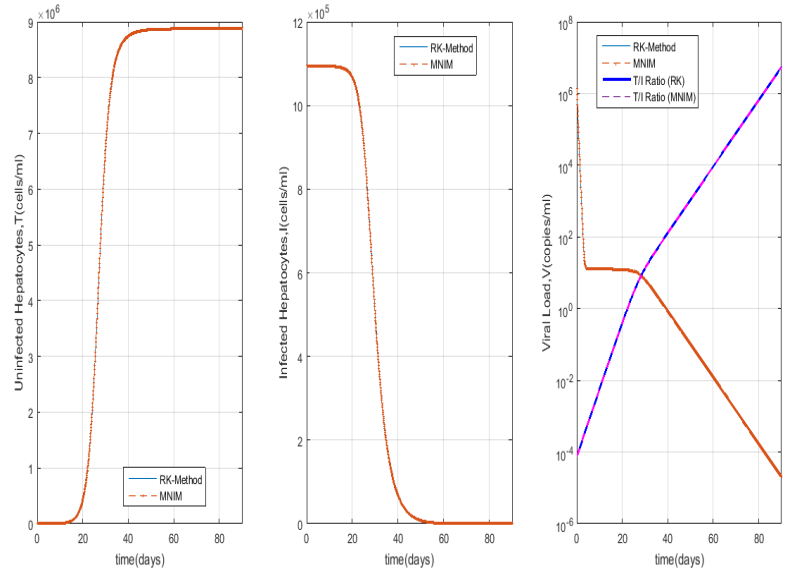


FIGURE 4. Comparison between MNIM and RK Method for $\alpha = 1$ and $t \in [0, 90]$

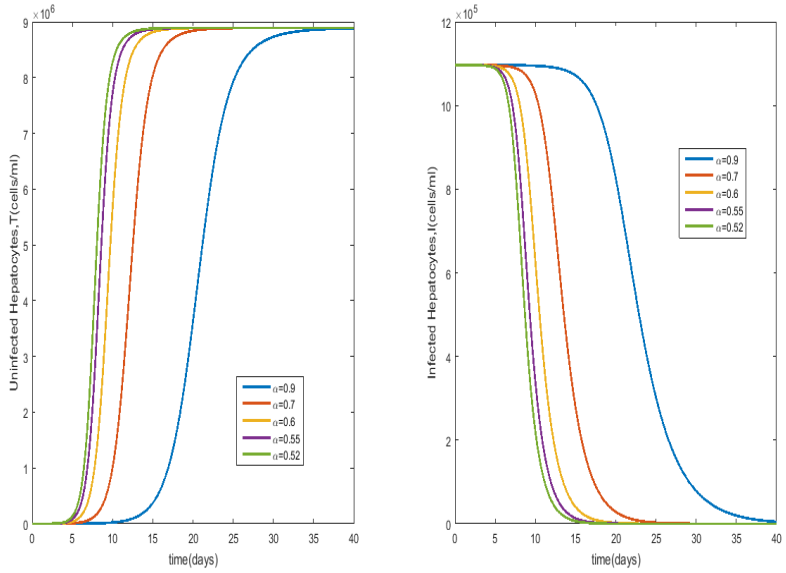


FIGURE 5. Profiles of uninfected and infected cells

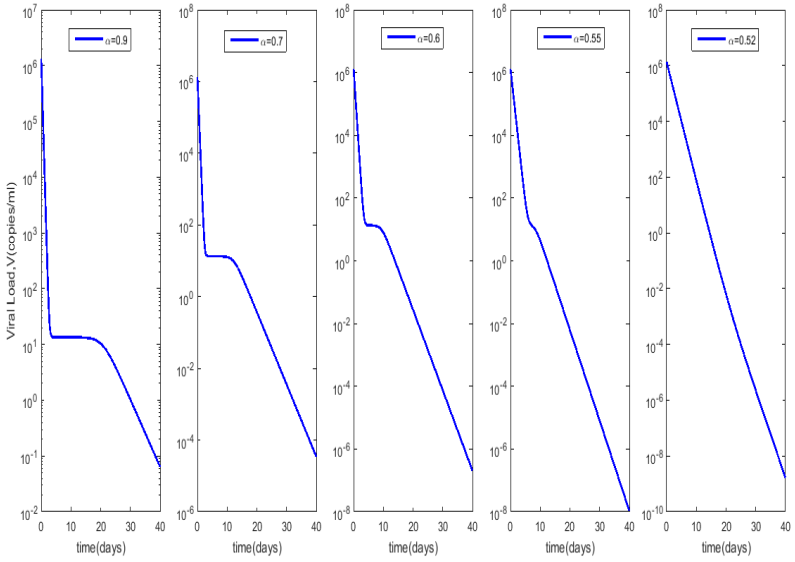


FIGURE 6. Response of viral load for various values of $\alpha$

The classical integer order ($\alpha = 1$) model cannot explain biphasic, triphasic, flat partial HCV response varying for individuals and monophasic HCV decay as it is

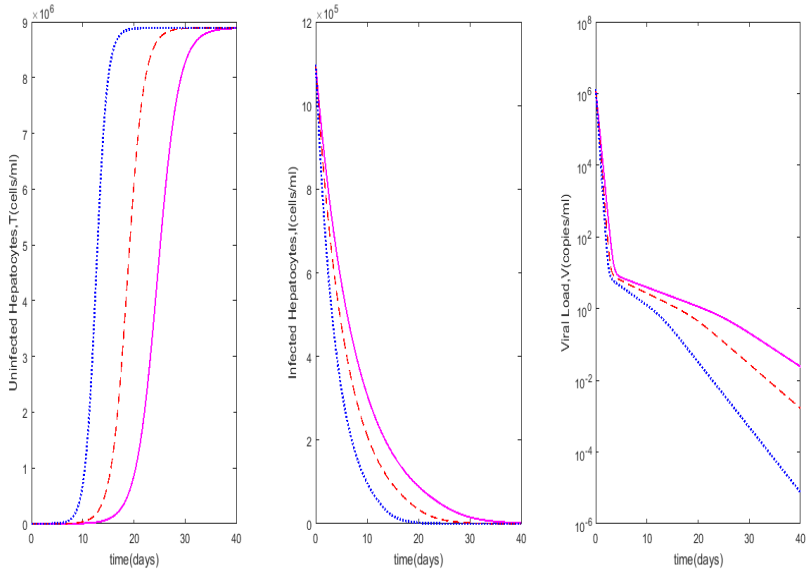


FIGURE 7. Response of fractional order chronic HCV infection model for $r_T = 5r_I$ and $\alpha = 1$(solid line), $\alpha = 0.9$(dashed line), $\alpha = 0.75$(dotted line)

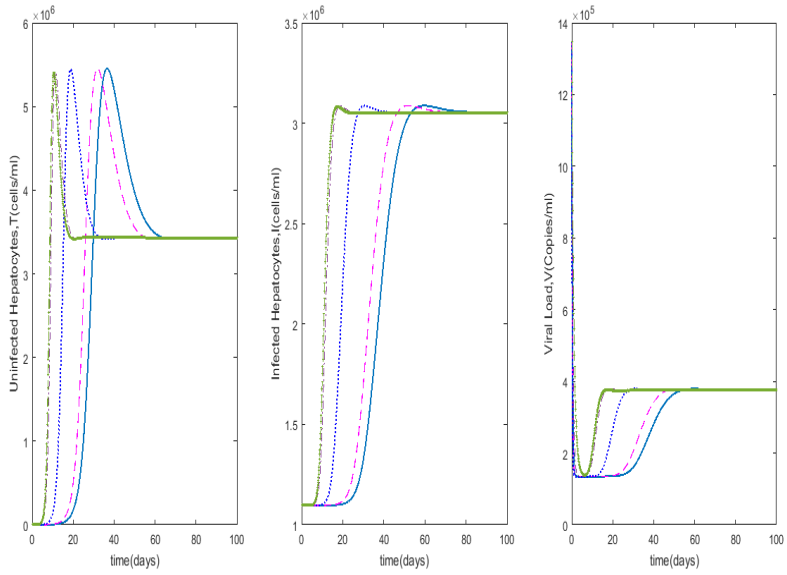


FIGURE 8. Response of fractional order chronic HCV infection model for $\varepsilon_{tot} < e_c$ and $\alpha = 1$(solid line), $\alpha = 0.95$(dashed line), $\alpha = 0.75$(dotted line), $\alpha = 0.55$(dashed-dotted line), $\alpha = 0.52$(dashed-starred line)

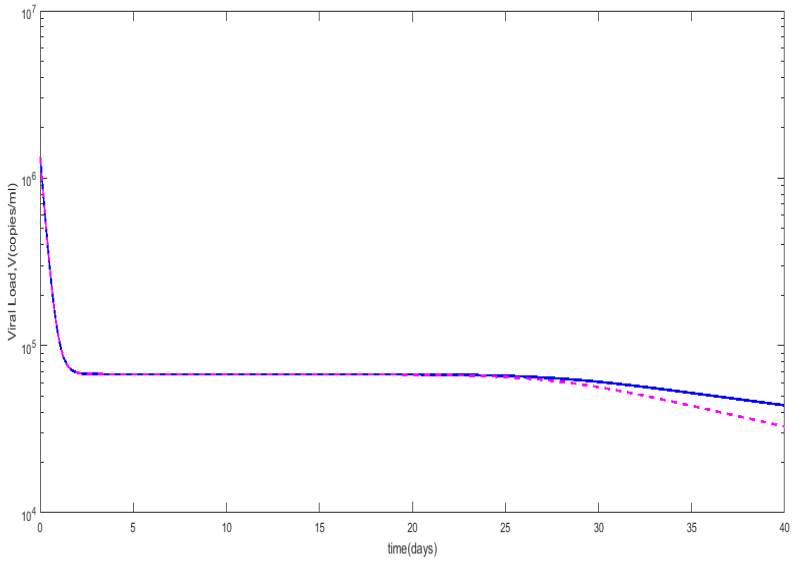


FIGURE 9. Profile of viral load for $\varepsilon_{tot} = 0.95$, $\rho_{\max} = 0$, $\alpha = 1$ (solid line) and $\varepsilon_{tot} = 0.95$, $\rho_{\max} = 0.9$, $\alpha = 1$ (dashed line)

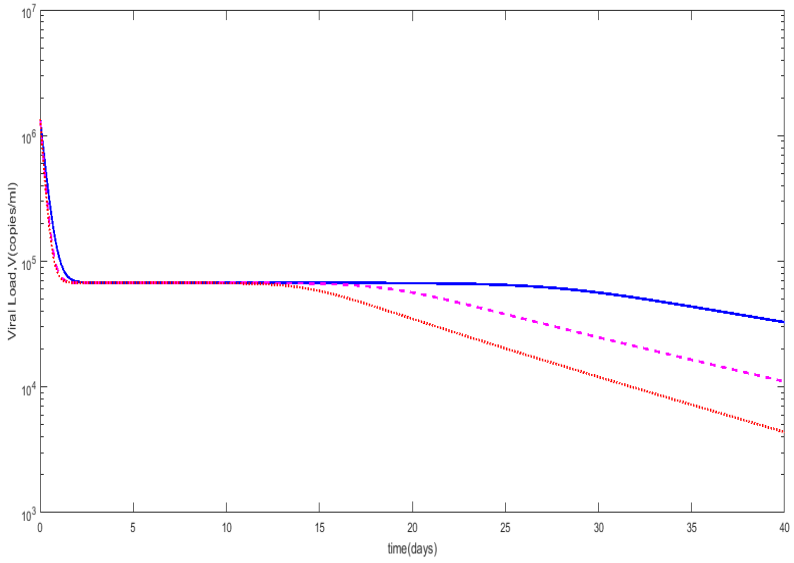


FIGURE 10. Response of viral load for $\varepsilon_{tot} = 0.95$, $\rho_{\max} = 0.9$ and $\alpha = 1$(solid line), $\alpha = 0.85$(dashed line), $\alpha = 0.75$(dotted line), $\alpha = 0.55$(dashed-dotted line)

predicting generalized behaviours (biphasic and triphasic) under certain circumstances manifested by drug efficacy; rate of infection and death rate of the infected cells. In view of this, the proposed model of non-integer order appears to be perfect and a model of broad generality, which provides the classical model predictions as one of the possible solution at $\alpha = 1$.

## References


[1] K.J. Ryan, C.G. GRay, Sherris Medical Microbiology (4th ed.), McGraw Hill, USA, 2004.
[2] S. Teri, Understanding Viruses ($2^{nd}$ ed.), Jones & Bartlett Learning, Burlington, MA, 2011.
[3] M. Houghton, The long and winding road leading to the identification of the hepatitis C virus, Journal of Hepatology 51 939-948, 2009.
[4] H.R. Rosen, Clinical practice. Chronic hepatitis C infection. New Engl J Med 364 2429-2438, 2011.
[5] G. Lock, M. Dirscherl, F. Obermeier, C.M. Gelbmann, C. Hellerbrand, A. Knoll, J. Scholmerich, W. Jilg, Hepatitis C-contamination of toothbrushes: myth or reality?, J Viral Hepat 13 571–573, 2006.
[6] P.K. Nelson, B.M. Mathers, B. Cowie, H. Hagan, D. Des Jarlais, D. Horyniak, L. Degenhardt, Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: Results of systematic reviews, Lancet 378 571–583, 2011.
[7] T. Wilkins, J.K. Malcolm, D. Raina, R.R. Schade, Hepatitis C: Diagnosis and treatment, American Family Physician 81 1351–1357, 2010.
[8] N.C. Lam, P.B. Gotsch, R.C. Langan, Caring for pregnant women and newborns with hepatitis B or C, American family physician 82 1225–1229, 2010.
[9] R.A. Tohme, S.D. Holmberg, Is sexual contact a major mode of hepatitis C virus transmission?, Hepatology 52 1497–1505, 2010.
[10] A. Maheshwari, S. Ray, P.J. Thuluvath, Acute hepatitis C, Lancet 372 321-332, 2008.
[11] L.S. Mitchell, Chronic hepatitis C virus: Advances in treatment, promise for the future, Springer Verlag, New York, 2011.
[12] A.U. Neumann, N.P. Lam, H. Dahari, D.R. Gretch, T..E. Wiley, T.J. Layden, A.S. Perelson, Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy, Science 282 103–107, 1998.
[13] H. Dahari, R.M. Ribeiro, A.S. Perelson, Triphasic decline of hepatitis C virus RNA during antiviral therapy, Hepatology 46 16-21, 2007.
[14] J.M. Pawlotsky, H. Dahari, A.U. Neumann, C. Hezode, G. Germanidis, I. Lonjon, L. Castera, D. Dhumeaux, Antiviral action of ribavirin in chronic hepatitis C, Gastroenterology 126 703–714, 2004.
[15] R.E. Sentjens, C.J. Weegink, M.G. Beld, M.C. Cooreman, H.W. Reesink, Viral kinetics of hepatitis C virus RNA in patients with chronic hepatitis C treated with 18 MU of interferon alpha daily, Eur J Gastroen Hepat 14 833–840, 2002.
[16] M.W. Fried, M.L. Shiffman, K.R. Reddy, C. Smith, G. Jr. Marinos, F.L. Goncales, D. Haussinger, M. Diago, G. Carosi, D. Dhumeaux, A. Craxi, A. Lin, J. Hoffman, J. Yu, Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection, New Engl J Med 347 975–982, 2002.
[17] F.A. Abdullah, Using fractional differential equations to model the Michaelis-Menten reaction in a 2-d region containing obstacles, ScienceAsia 37 75-78, 2011.
[18] E. Ahmed, A.S. Elgazzar, On fractional order differential equations model for nonlocal epidemics, Physica A 379 607–614, 2011.
[19] A.M.A. El-Sayed, S.Z. Rida, A.A.M. Arafa, Exact solutions of fractional-order biological population model, Commun Theor Phys 52 992–996, 2009.
[20] E. Ahmed, H.A. El-Saka, On fractional order models for hepatitis C, Nonlinear Biomed Phys 4:1, 2010.
[21] I. Podlubny, Fractional Differential Equations, Academic Press, New York, 1999.
[22] N. Heymans, I. Podlubny, Physical interpretation of initial conditions for fractional differential equations with Riemann-Liouville fractional derivatives, Rheol Acta 45 765–771, 2006.

[23] M. Caputo, Linear models of dissipation whose Q is almost frequency independent-II, Geophys J R Astr Soc 13 529–539, 1967.
[24] S. Das, Functional Fractional Calculus, Springer-Verlag Berlin, Heidelberg, 2011.
[25] G. Jumarie, Table of some basic fractional calculus formulae derived from a modified Riemann-Liouville derivative for non-differentiable functions, Appl Math Lett 22 378-385, 2009.
[26] C. Li, W. Deng, Remarks on fractional derivatives, Appl Math Comput 187 777-784, 2007.
[27] D-G. Varsha, J. Hossein, An iterative method for solving nonlinear functional equations, J Math Anal Appl 316 753–763, 2006.
[28] S.K. Damarla, M. Kundu, Approximate solution of nonlinear fractional order biochemical reaction model by multistage new iterative method, Journal of Fractional Calculus and Applications 5 113-126, 2014.

Seshu Kumar Damarla
Department of Chemical Engineering, National Institute of Technology Rourkela, Odisha, India
*E-mail address*: seshud769@gmail.com, venugopalaraod769@gmail.com

Madhusree Kundu
Department of Chemical Engineering, National Institute of Technology Rourkela, Odisha, India
*E-mail address*: mkundu@nitrkl.ac.in