Available online at http://scik.org
Commun. Math. Biol. Neurosci. 2015, 2015:27
ISSN: 2052-2541

A FRACTIONAL-ORDER HBV INFECTION MODEL WITH CONSTANT VACCINATION STRATEGY

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Abstract. Fractional calculus represents a generalization of the ordinary differentiation and integration to non-integer and complex order. Motivated by this situation, the idea of modeling HBV infection involving constant vaccination by fractional order differential equations (FODE) arises. We developed a fractional SIRC model, in which they presented a detailed analysis for the asymptotic stability of disease-free and positive fixed point. First we show the positive solution of the HBV model in fractional order. However, analytical and closed solutions of these types of fractional equations cannot generally be obtained. As a consequence, approximate and numerical techniques are explored. We use the multi-step generalized differential transform method to approximate the numerical solution. Finally we compare our numerical results with nonstandard numerical method and forth order Runge-Kutta method.

Keywords: fractional order; HBV epidemic model; numerical method.

2010 AMS Subject Classification: 92C60.

1. Introduction

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Received February 18, 2015

Vaccination is a commonly used method for controlling disease, the study of vaccines against infectious disease has been a boon to mankind. Hepatitis B vaccine provides greater than 90% protection to infants, children, and adults immunized before being exposed to the virus. The efficacy of plasma-derived and recombinant hepatitis B vaccine in preventing acute and chronic infection has been demonstrated in controlled clinical trails conducted with adults, children and infants. In addition, a number of studies have examined various vaccination schedules and dosages and all have documented short-term vaccine safety [15]. Vaccine can be received by infants to adults and provides protection for 85%-90% of individuals [20, 14]. The main vaccinations include the 3-dose HepB vaccination and the timely Hepatitis B birth-dose (i.e., within 24 h of birth). In 1991, WHO recommended that hepatitis B vaccination should be included in national immunization system in all countries with an HBsAg carrier prevalence 8% by 1995 and all countries by 1997. By 2002, 154 countries had routine infant immunization with HepB [11, 9]. Mathematical models, of deterministic type, have often been used to provide deeper insights into the transmission HBV dynamics and to evaluate control strategies. The modelling of these systems by fractional-order differential equations has more advantages than classical integer-order mathematical modeling, in which such effects are neglected. Fractional-order differential equations are naturally related to systems with memory which exists in most biological systems. In some situations, the fractional-order differential equations (FODEs) models seem more consistent with the real phenomena than the integer- order models. This is due to the fact that fractional derivatives and integrals enable the description of the memory and hereditary properties inherent in various materials and processes. Hence there is a growing need to study and use the fractional-order differential and integral equations. Nowadays several researchers work on the fractional order differential equations because of best presentation of many phenomena. Fractional calculus represents a generalization of the ordinary differentiation and integration to non-integer and complex order. For this purpose [7] developed a fractional SIRC model, in which they presented a detailed analysis for the asymptotic stability of disease-free and positive fixed point. To our knowledge, no works are contributed to the analysis for a model of fractional order differential equations (FODEs) of describing the viral dynamics in the presence of HBV infection with constant vaccination. Motivated by this situation, the idea

of modeling HBV infection involving constant vaccination by FODE arises. First we show the positive solution of the HBV model in fractional order. However, analytical and closed solutions of these types of fractional equations cannot generally be obtained. As a consequence, approximate and numerical techniques are explored. We use the multi-step generalized differential transform method to approximate the numerical solution. Finally we compare our numerical results with nonstandard numerical method and forth order Runge-Kutta method.

2. Fractional order systems

Fractional calculus is generalization of integrals and derivatives to a non-integer or even complex order. Many systems in interdisciplinary fields describe a real object more accurately than the classical integer methods. There are many definitions of fractional derivatives. The Riemann-Liouville definition is given as

$$\frac{d^{\alpha}f(t)}{dt^{\alpha}} = \frac{1}{\Gamma(n-\alpha)}\frac{d^{n}}{dt^{n}}\int_{\alpha}^{t}\frac{f(\tau)}{(t-\tau)^{\alpha-n+1}}d\tau, \tag{1}$$

where $\Gamma(.)$ is the gama function, n is an integer number chosen in such a way that $n-1<\alpha<n$. α is order of derivative and a is the lower limit. Upon considering the inital values to be zero, the Laplace transform of the Riemann C Liouville fractional derevative is defined as

$$L\left\{\frac{d^{\alpha}f(t)}{dt^{\alpha}}\right\}(s) = s^{\alpha}L\{f(t)\}. \tag{2}$$

Hence fractional integral operator of order α is represented by the transfer function $F(s) = 1/s^{\alpha}$.

The Caputo derivative of order α and with the lower limit zero is defined as:

$$\frac{d^{\alpha}f(t)}{dt^{\alpha}} = \frac{1}{\Gamma(n-\alpha)}\frac{d^{n}}{dt^{n}}\int_{0}^{t}\frac{f(\tau)}{(t-\tau)^{\alpha-n+1}}d\tau. \tag{3}$$

In practice the fractional differential equation is hard to be solved in time domain; hence frequency domain techniques/Laplace transform is used. An algorithm for the numerical solution of differential equation of fractional order has been given by [5].

3. Stability of fractional order system

The stability analysis is important in control theory. Recently, there has been some advances in control theory of fractional differential systems for stability. In the fractional order systems the delay differential equation order is non-integer which makes it difficult to evaluate the stability by simply examining its characteristic equation or by finding its dominant roots or by using other algebraic methods. The stability of fractional order systems using polynomial criteria (e.g., Routh's or Jury's type) is not possible due to the fractional powers. A generalization of the Routh-Hurwitz criterion used for stability analysis for fractional-order systems is presented in [10]. However, this method is very complicated. Thus there remain only geometrical methods of complex analysis based on the argument principle (e.g; Nyquist type) which can be used for the stability check in the BIBO sense (bounded-input bounded-output). These are the techniques that inform about the number of singularities of the function within a rectifiable curve by observing the evolution of the function's argument through this curve. Root locus is another geometric method that can be used for analysis for fractional order systems. Also, for linear fractional differential systems of finite dimensions in state- space form, stability can be investigated. The stability of a linear fractional differential equation either by transforming the S-plane to the F-plane $F = s^{\alpha}$ or the w-plane $(w = s^{1/v})$, is explaned in [19].

3.1. Stability using Riemann surfaces

In a general way, the study of the stability of fractional order systems can be carried out by studying the solutions of the differential equations that characterize them. To carry out this study it is necessary to remember that a function of the type

$$a_n s^{\alpha_n} + a_{n-1} s^{\alpha_{-1}} + \ldots + a_0 s^{\alpha_0}, \tag{4}$$

where $\alpha_i \in \mathbb{R}^+$, is a multivalued function of the complex variable s whose domain can be seen as a Riemann surface of a number of sheets. The principle sheet is defined by $-\pi < arg(s) < \pi$. In the case of $\alpha \in \mathbb{Q}^+$, that is $\alpha = 1/v$, v being a positive integer, the v sheets of the Riemann surface are determined by

$$s = |s|e^{j\phi}, \qquad (2k+1)\pi < \phi < (2k+3)\pi, \tag{5}$$

$k = -1, 0, ..., v-2$ Correspondingly, the case of $k = -1$ is the principal sheet. For the conformal mapping (transformation) $w = s^{\alpha}$, these sheets become the regions of the plane w defined by:

$$w = |w|e^{j\theta}, \qquad \alpha(2k+1)\pi < \theta < \alpha(2k+3)\pi. \tag{6}$$

Thus, an equation of the type (4) which in general is not a polynomial, will have an infinite number of roots, among which only a finite number of roots will be on the principal sheet of the Riemann surface. It can be said that the roots which are in the secondary sheets of the Riemann surface are related to solutions that are always monotonically decreasing functions (they go to zero without oscillations when $t \to \infty$) and only the roots that are in the principal sheet of the Riemann surface are responsible for a different dynamics: damped oscillation, oscillation of constant amplitude, oscillation of increasing amplitude. For the case of commensurate-order systems, whose characteristic equation is a polynomial of the complex variable $w = s^{\alpha}$ the stability condition is expressed as, $|arg(w_i)| > \frac{\alpha\pi}{2}$, where w_i are the roots of the characteristic polynomial in w. For the particular case of $\alpha = 1$ the well known stability condition for the linear time-invariant system of integer-order is recovered: $|arg(w_i)| > \frac{\pi}{2}$.

4. Mathematical model derivation

To describe the viral dynamics in the presence of HBV infection with constant vaccination, the total population that is involved in the transmission of the infection is split into four(4) epidemiological classes: susceptible (S), vaccinated (V), infected (I), and recovered (R). The detailed transitions between these four classes is depicted in Figure 1. The class S of susceptibles is increased either by birth or immigration at a rate π. It is decreased by infection following contact with infected individuals at a time-varying rate β, and diminished by natural death at a rate μ. Furthermore, it is decreased by vaccination at a rate σ. This term naturally disappears in the absence of vaccine doses. The model also assumes that the vaccination wanes with time, leading to the migration of individuals from V to S at a rate φ [17, 21]. The class V of vaccinated individuals is generated through administration of the first-dose vaccine to the susceptible class S, either by vaccination of a fraction ω of recruited individuals. Since the vaccine may not induce complete protection to the infection, the individuals of this class might still become

infected, but at a lower rate of infectiousness, $\phi\beta I$, than susceptible individuals, where ϕ is the degree of protection induced by vaccination. This partial immunity may be due to the presence of antibodies which interfere with vaccine-induced seroconversion [3]. This leads to a response with a lower level of antibody titres and reduces vaccine efficacy [16]. This response could not entirely be attributed to the presence of antibodies (at the time of vaccination), as in addition the vaccine may not be sufficiently immunogenic in inducing adequate antibody response after a single dose [21]. Furthermore, the vaccine may wane with time, and thus vaccinated individuals gradually become susceptible to the disease again [17, 21]. The class V is decreased by administration of a vaccine (as a second dose) at a rate γ and diminished by natural death. The class I of infected individuals is generated through infection of susceptible and/or vaccinated individuals. This class is decreased by recovery from infection at a rate δ and diminished by natural death. The model assumes that both recovered and vaccinated individuals become permanently immune to the disease. This generates a class V of individuals who have complete protection to the disease.

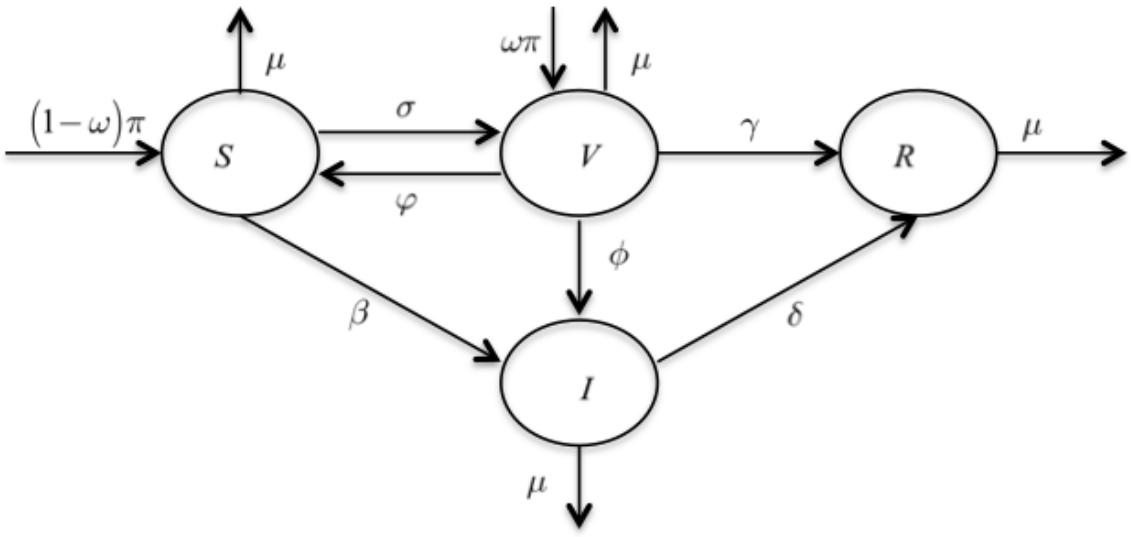


FIGURE 1. Transfer diagram of the HBV model

Using the above assumptions, the transitions between model classes can now be expressed by the following differential equations:

$$
\begin{aligned}
\tfrac{dS}{dt} &= (1-\omega)\pi - \beta SI - (\mu+\sigma)S + \varphi V,\\
\tfrac{dV}{dt} &= \omega\pi + \sigma S - \phi\beta VI - (\mu+\gamma+\varphi)V,\\
\tfrac{dI}{dt} &= \beta SI + \phi\beta VI - (\mu+\delta)I,\\
\tfrac{dR}{dt} &= \gamma V + \delta I - \mu R,
\end{aligned} \tag{7}
$$

where the parameter π is the birth rate for the population, ω is the proportion of recruited population who receieve vaccine, φ is the rate of waning vaccine-induced immunity, β is the rate of transmission with infected population, δ is the infection period, σ is the vaccination rate, and μ are the natural mortality, and ϕ is the vaccine-induced protection. Now we introduce fractional order into the ODE model by [1]. The new system is described by the following set of fractional order differential equations:

$$
\begin{aligned}
\mathscr{D}_t^{\alpha} S &= (1-\omega)\pi - \beta SI - (\mu+\sigma)S + \varphi V,\\
\mathscr{D}_t^{\alpha} V &= \omega\pi + \sigma S - \phi\beta VI - (\mu+\gamma+\varphi)V,\\
\mathscr{D}_t^{\alpha} I &= \beta SI + \phi\beta VI - (\mu+\delta)I,\\
\mathscr{D}_t^{\alpha} R &= \gamma V + \delta I - \mu R,
\end{aligned} \tag{8}
$$

where D_t^{α} is the Caputo fractional derivative. Because model (8) monitors the dynamics of human populations, all the parameters are assumed to be nonnegative. Furthermore, it can be shown that all state variables of the model are nonnegative for all time $t \geq 0$.

4.1. Non-negative solutions

It is important not to worry about negative values when dealing with a model of population dynamics is concerned. Hence, we prove the positivity of the solutions.

Theorem 4.1. *The closed set* $\Omega = \left\{(S,V,I,R) \in \mathbb{R}_+^4 : S+V+I+R = 1\right\}$ *is positively invariant with respect to model (5.8).*

Proof. Since the class of recovered group (R) does not appear in the first three equations of (5.8), the analysis will be restricted to the dynamics of the first three equations of (5.8). We also

note that the equation for the total population is

$$\mathscr{D}_t^{\alpha} N(t) = \pi - \mu N. \tag{9}$$

The solution to (5.9) is given by grouping and rearranging the variable of interest, thus

$$\mathscr{D}_t^{\alpha} N(t) + \mu N = \pi.$$

Now assume that $f(t) = \pi$, which is a constant function of time, then the equation is giving by

$$\mathscr{D}_t^{\alpha} N(t) + \mu N = f(t).$$

Taking the laplace transform, throughout, the new equation is given by

$$\mathscr{L}\left\{\mathscr{D}_t^{\alpha} N(t)\right\} + \mathscr{L}\left\{\mu N\right\} = \mathscr{L}\left\{f(t)\right\}$$

but

$$\mathscr{L}\left\{\mathscr{D}_t^{\alpha} N(t)\right\} = s^{\alpha}\tilde{N} - \sum_{n=0}^{n-1} s^{(\alpha-n-1)} N(0_+),$$

where

$$\sum_{n=0}^{n-1} s^{(\alpha-n-1)} N(0_+)$$

is the initial condition. Then, $\mathscr{L}\left\{\mu N\right\} = \mu\mathscr{L}\left\{N\right\} = \mu s^2\tilde{N}$ and $\mathscr{L}\left\{f(t)\right\} = F(s)$. This implies that

$$s^{\alpha}\tilde{N} - \sum_{n=0}^{n-1} s^{(\alpha-n-1)} N(0_+) + \mu s^2\tilde{N} = F(s).$$

Thus,

$$\left\{s^{\alpha} - \mu s^2\right\}\tilde{N} = \sum_{n=0}^{n-1} s^{(\alpha-n-1)} N(0_+) + F(s).$$

Taking the initial condition to be zero, then

$$\tilde{N} = \frac{F(s)}{s^{\alpha} + \mu s^2},$$

which involves two functions.

Now find the laplace inverse transform of $\tilde{N}$ to get $N(t)$, then let $\tilde{g}(s) = \frac{1}{s^{\alpha}+\mu s^2}$ and $\tilde{k}(s) = F(s)$. Now, $\tilde{g}(s) = \frac{1}{s^{\alpha}+\mu s^2} = \frac{1}{s^2}\left(\frac{1}{s^{\alpha-2}+\mu}\right) = \frac{1}{\mu}\left(\frac{s^{-2}}{\frac{s^{\alpha-2}}{\mu}+1}\right)$. Then

$$\tilde{g}(s) = \frac{1}{\mu}\left(\frac{s^{-2}}{1-\left(-\frac{s^{\alpha}-2}{\mu}\right)}\right) = \frac{1}{\mu}\sum_{k=0}^{\infty}(-1)^k s^{-2}\left(\frac{s^{-(\alpha-2)}}{\mu}\right)^k,$$

which gives

$$\tilde{g}(s) = \frac{1}{\mu}\sum_{k=0}^{\infty}(-1)^k\left(\frac{s^{-[k(\alpha-2)+2]}}{\mu^k}\right)$$

but $\mathscr{L}^{-1}\{s^{-p}\} = \frac{t^{p-1}}{\Gamma(p)}$.

Now we let $p = k(\alpha-2)+2$, and by substitute into the above formula, thus

$$\mathscr{L}^{-1}\left\{s^{-[k(\alpha-2)+2]}\right\} = \frac{t^{k(\alpha-2)+2-1}}{\Gamma(k(\alpha-2)+2)}$$

implies

$$\tilde{g}(t) = \frac{1}{\mu}\sum_{k=0}^{\infty}\left(\frac{-1}{\mu}\right)^k\frac{t^{k(\alpha-2)+2-1}}{\Gamma(k(\alpha-2)+2)}, \quad \mu > 0.$$

Thus,

$$\tilde{g}(t) = \frac{1}{\mu}t\sum_{k=0}^{\infty}\frac{\left(-\frac{t^{\alpha-2}}{\mu}\right)^k}{\Gamma(k(\alpha-2)+2)}, \quad \mu > 0.$$

Now assuming $z = \frac{-t^{\alpha-2}}{\mu}, u = \alpha-2, v = 2$, we have

$$\tilde{g}(t) = \frac{1}{\mu}t\sum_{k=0}^{\infty}\frac{z^k}{\Gamma(uk+v)}.$$

Then, by Mittag-Leffler function. Considering the fact that the Mittag-Leffler function has an asymptotic behavior [8],

$$E_{u,v}(z) \sim -\sum_{k=1}^{p}\frac{z^{-k}}{\Gamma(v-uk)} + O\left(|z|^{-1-p}\right), \quad \left(|z|\to\infty, \frac{\alpha\pi}{2} < |arg(z)| \le \pi\right). \tag{10}$$

Thus, $N \to \pi/\mu$ as $t \to \infty$, and hence $R = \pi/\mu - S - V - I$. This shows that the feasible region

$$\Omega = \{(S,V,I,R) : S,V,I,R \ge 0, S+V+I+R = \pi/\mu\},$$

is a positively invariant set for the model. Therefore, we restrict our attention to the dynamics of the model in Ω.

For the proof of the non-negative solution, consider the following Theorem and Corollary.

Theorem 4.2. [Generalized Mean Value Theorem] *Let* $f(x) \in C(0,a]$ *and* $\mathscr{D}^{\alpha}f(x) \in C(0,a]$, *for* $0 < \alpha \le 1$. *Then we have*

$$f(x) = f(0+) + \frac{1}{\Gamma(\alpha)}(\mathscr{D}^{\alpha}f)(\xi)(x)^{\alpha}$$

with $0 \le \xi \le x, \forall x \in (0,a]$.

Corollary 4.1. *Suppose that* $f(x) \in C[0,a]$ *and* $\mathscr{D}^{\alpha} f(x) \in C(0,a]$ *for* $0 < \alpha \leq 1$. *It is clear from Theorem 4.2 that if* $\mathscr{D}^{\alpha} f(x) \geq 0$, $\forall x \in (0,a)$, *then* $f(x)$ *is non-decreasing and if* $\mathscr{D}^{\alpha} f(x) \leq 0$, $\forall x \in (0,a)$, *then* $f(x)$ *is non-increasing for* $\forall x \in [0,a]$.

Theorem 4.3. *There is a unique solution* $\Omega(t) = (S,V,I,R)^T$ *for (8) at* $t \geq 0$ *and the solution will remain in* $\mathbb{R}^4_+$.

Proof. The existence and uniqueness of the solution of (8) in $(0,\infty)$ can be obtained from [[12], Theorem 3.1 and Remark 3.2]. Now we need to show that the domain $\mathbb{R}^4_+$ is positively invariant. Since

$$\begin{aligned}
&\mathscr{D}_t^{\alpha} S|_{S=0} = \pi(1-\omega) + \varphi V \geq 0,\\
&\mathscr{D}_t^{\alpha} V|_{V=0} = \pi\omega + \sigma S \geq 0,\\
&\mathscr{D}_t^{\alpha} I|_{I=0} = 0,\\
&\mathscr{D}_t^{\alpha} R|_{R=0} = \gamma V + \delta I \geq 0.
\end{aligned}$$

On each hyperplane bounding the nonnegative orthant, the vector field points into $\mathbb{R}^4_+$.

For convenience in calculations we consider the following system, which can be obtained from

$$\begin{aligned}
&\mathscr{D}_t^{\alpha} S = (1-\omega)\pi - \beta SI - (\mu+\sigma)S + \varphi V,\\
&\mathscr{D}_t^{\alpha} V = \omega\pi + \sigma S - \phi\beta VI - (\mu+\gamma+\varphi)V,\\
&\mathscr{D}_t^{\alpha} I = \beta SI + \phi\beta VI - (\mu+\delta)I,\\
&\mathscr{D}_t^{\alpha} R = \gamma V + \delta I - \mu R,
\end{aligned} \tag{11}$$

with initial conditions

$$S(0) = S_0, V(0) = V_0, I(0) = I_0, R(0) = R_0. \tag{12}$$

4.2. Disease-free equilibruim (DFE)

TABLE 1. Description and estimation of fractional order model parameters

Para.	Description	Value	Reference
π	Birth rate	0.0121	[18]
μ	Natural mortality rate	0.00693	[18]
β	rate of transmission with acute infection	0.95 -20.49	[6]
γ	rate of transmission with chronic infection	0.16	[6]
δ	Rate of moving from acute to chronic infection	0.3	[6]
σ	Vaccination rate	(1-100%)	
ϕ	Vaccine induce protection	(90-99%)	
ω	Proportion of birth without successful vaccination	(1-100%)	
φ	Rate of waning vaccine - induced immunity	0.1	[6]

We deduced the disease-free equilibruim point by considering the interger system of the given fractional-order system (8) with $\alpha = 1$. To evaluate the equilibrium points of the system (8), let

$$\begin{aligned}
\mathscr{D}_t^{\alpha}(S) &= 0,\\
\mathscr{D}_t^{\alpha}(V) &= 0,\\
\mathscr{D}_t^{\alpha}(I) &= 0,\\
\mathscr{D}_t^{\alpha}(R) &= 0.
\end{aligned}$$

In the absence of infection, the model has a unique disease-free equilibruim $\mathscr{E}_0 = (S_0, V_0, 0, R_0)$ where

$$S_0 = \frac{[(1-\omega)(\mu+\gamma)+\varphi]\pi}{(\mu+\gamma)+\mu\varphi},$$
$$V_0 = \frac{(\mu\omega+\sigma)\pi}{(\mu+\gamma)+\mu\varphi},$$
$$R_0 = \frac{\gamma(\mu\omega+\sigma)\pi}{\mu[(\mu+\gamma)+\mu\varphi]}.$$

To analyze the stability of the DFE, the first three equation of the model is linearized around $\mathscr{E}_0$ by setting:

$$S(t) = S_0 + s(t), \quad V(t) = V_0 + v(t), \quad I(t) = i(t).$$

Then, we have:

$$\mathscr{D}_t^{\alpha} s = -(\mu+\sigma)s - \frac{[(1-\omega)(\mu+\gamma)+\varphi]\beta\pi}{(\mu+\gamma)(\mu+\sigma)+\mu\varphi} i + \varphi v, \tag{13}$$

$$\mathscr{D}_t^{\alpha} v = \sigma s - (\mu+\gamma+\varphi)v - \frac{\phi(\mu\omega+\sigma)\beta\pi}{(\mu+\gamma)(\mu+\sigma)+\mu\varphi} i, \tag{14}$$

$$\mathscr{D}_t^{\alpha} i = \frac{[(1-\omega)(\mu+\gamma)+\varphi+\phi(\mu\omega+\sigma)]\beta\pi}{(\mu+\gamma)(\mu+\sigma)+\mu\varphi} i - (\mu+\delta)i. \tag{15}$$

A fundamental matrix of (13)-(15) consists of the solutions $X_j = \left(s_j(t), v_j(t), i_j(t)\right), j = 1,2,3$ which satisfy the following initial conditions:

$$X_1(0) = (1,0,0), \quad X_2(0) = (0,1,0), \quad X_3(0) = (0,0,1).$$

It is easy to see that the set of these solutions is given by:

$$X_1 = \begin{pmatrix} exp[-(\mu+\sigma)t] \\ 0 \\ 0 \end{pmatrix}, \quad X_2 = \begin{pmatrix} s_2^*(t) \\ exp[-(\mu+\gamma+\varphi)t] \\ 0 \end{pmatrix},$$

and

$$X_3 = \begin{pmatrix} s_3^*(t), \\ v_3^*(t), \\ exp\left\{\int_0^t \left(\frac{[(1-\omega)(\mu+\gamma)+\varphi+\phi(\mu\omega+\sigma)]\beta\pi}{(\mu+\gamma)(\mu+\sigma)+\mu\varphi} - (\mu+\delta)\right) d\tau\right\} \end{pmatrix},$$

where $s_2^*(0) = s_3^*(0) = v_3^*(0) = 0$. The monodromy matrix is the fundamental matrix $M(t) = [X_1(t), X_2(t), X_3(t)]$ evaluated at the period T.

Theorem 4.4. *The disease-free equilibrium $\mathscr{E}_0$ of the system (8) is locally asymptotically stable if*

$$\mathscr{R}_0 = \frac{[(1-\omega)(\mu+\gamma)+\varphi+\phi(\mu\omega+\sigma)]\beta\pi}{(\mu+\delta)[(\mu+\gamma)(\mu+\sigma)+\mu\varphi]} < 1.$$

Proof. The local stability of $\mathscr{E}_0$ is determined by the modulus of the eigenvalues of $M(T)$. These eigenvalues are

$$\lambda_1 = exp[-(\mu+\sigma)T],$$

$$\lambda_2 = exp[-(\mu+\gamma+\varphi)T]$$

and

$$\lambda_3 = exp\left\{\int_0^T \left(\frac{[(1-\omega)(\mu+\gamma)+\varphi+\phi(\mu\omega+\sigma)]\beta\pi}{(\mu+\gamma)(\mu+\sigma)+\mu\varphi} - (\mu+\delta)\right) d\tau\right\}.$$

Since $0 < \lambda_1, \lambda_2 < 1$ the equilibrium $\mathscr{E}_0$ is locally asymptoticaly stable if $\lambda_3 < 1$. A simple calculation shows that $\lambda_3 < 1$ if and only if

$$\frac{1}{T}\int_0^T \beta d\tau < \frac{(\mu+\delta)[(\mu+\gamma)(\mu+\sigma)+\mu\varphi]}{[(1-\omega)(\mu+\gamma)+\varphi+\phi(\mu\omega+\sigma)]\pi}. \tag{16}$$

Since β is a periodic function with the period T, then the inequality (16) can be written as $\mathscr{R}_0 < 1$ where

$$\mathscr{R}_0 = \frac{[(1-\omega)(\mu+\gamma)+\varphi+\phi(\mu\omega+\sigma)]\beta\pi}{(\mu+\delta)[(\mu+\gamma)(\mu+\sigma)+\mu\varphi]}. \tag{17}$$

According to stability conditions in [5, 13] the disease-free equilibrium $\mathscr{E}_0$ is locally asymptotically stable if all of the eigenvalues $\lambda_i (i = 1,2,3)$ satisfy $|arg\lambda_i| > \alpha\frac{\theta}{2}$. If $0 < \mathscr{R}_0 < 1$, then the above three characteristic roots will have negative real parts. Thus the disease-free equilibrium $\mathscr{E}_0$ is locally asymptotically stable. If $\mathscr{R}_0 > 1$, then at least one eigenvalue will be positive real root. Thus, the disease-free equilibrium $\mathscr{E}_0$ is unstable. Therefore Theorem 4.4 is complete.

5. Sensitivity of a fractional order system to its $\mathscr{R}_0$ ratios

This section focuses on the sensitivity analysis of a fractional order system. Sensitivity analysis aims to describe how much model output values are affected by changes in model input

values. Thus, sensitivity analysis can address the change in optimal system performance associated with changes in various parameter values, and also how optimal decisions would change with changes in resource constraint levels or target output requirements. For the computation of the sensitivity analysis, we employ the normalised forward sensitivity index of a variable to be the ratio of the relative change in a variable to a change in a parameter [2].

Definition 5.1. Let $h = f(x_1, x_2, ..., x_n)$, be a differentiable function that depends on the parameters x_i, then the normalised forward sensitivity index of x_i with respect to parameter, p, is defined as:

$$\zeta_p^{\mathscr{R}_0} = \frac{\partial h}{\partial x_i} \times \frac{x_i}{h}. \tag{18}$$

This index measures the relative change in h due to relative changes in x_i. The normalized forward sensitivity indices of $\mathscr{R}_0$ relative to its parameters are presented in Table 2.

TABLE 2. Sensitivity indices of fractional order model to $\mathscr{R}_0$

Para.	Description	Sensitivity index
π	Birth rate	+(ve)
μ	Natural mortality rate	-(ve)
β	rate of transmission with acute infection	+(ve)
γ	rate of transmission with chronic infection	-(ve)
δ	Rate of moving from acute to chronic infection	-(ve)
σ	Vaccination rate	-(ve)
ϕ	Vaccine induce protection	+(ve)
ω	Proportion of birth without successful vaccination	+(ve)
φ	Rate of waning vaccine - induced immunity	+(ve)

6. Multi-step generalized differential transform method

We applying the multi-step generalized differential transform method to find the approximate solution of equations (8), which gives an accurate solution over a longer time frame as compared to the standard generalized differential transform method. Taking the differential transform of

equations (8) with respect to time we obtain,

$$S(k+1)=\frac{\Gamma(\alpha k+1)}{\Gamma((\alpha k+1)+1)}\left((1-\omega)\pi+\varphi V(k)-\beta\sum_{i=0}^{k}S(k-i)I(i)-(\mu+\sigma)S(k)\right),$$

$$V(k+1)=\frac{\Gamma(\alpha k+1)}{\Gamma((\alpha k+1)+1)}\left(\omega\pi+\sigma S(k)-\phi\beta\sum_{i=0}^{k}V(k-i)I(i)-(\mu+\gamma+\varphi)V(k)\right),$$

$$I(k+1)=\frac{\Gamma(\alpha k+1)}{\Gamma((\alpha k+1)+1)}\left(\beta\sum_{i=0}^{k}S(k-i)I(i)+\phi\beta\sum_{i=0}^{k}V(k-i)I(i)-(\mu+\delta)I(k)\right),$$

$$R(k+1)=\frac{\Gamma(\alpha k+1)}{\Gamma((\alpha k+1)+1)}\left(\gamma V(k)+\delta I(k)-\mu R(k)\right).$$

Here $S(k),V(k),I(k)$ and $R(k)$ are thr differential transformation of $S(t),V(t),I(t)$ and $R(t)$. The differential transform of the initial conditions are $S(0)=S_0,V(0)=V_0,I(0)=I_0$ and $R(0)=R_0$.

In view of the differential inverse transform, the differential transform series solution for the system can be obtained as

$$\begin{cases} S(t)=\sum_{k=0}^{k}S(k)t^{\alpha k}, \\ V(t)=\sum_{k=0}^{k}V(k)t^{\alpha k}, \\ I(t)=\sum_{k=0}^{k}I(k)t^{\alpha k}, \\ R(t)=\sum_{k=0}^{k}R(k)t^{\alpha k}. \end{cases} \tag{19}$$

Now according to the multi-step generalized differential transform method the series solution for the equations (8) is suggested by

$$S(t)=\begin{cases} \sum_{k=0}^{k}S_1(k)t^{\alpha k} & t\in[0,t_1] \\ \sum_{k=0}^{k}S_2(k)(t-t_1)^{\alpha k} & t\in[t_1,t_2] \\ \vdots & \\ \sum_{k=0}^{k}S_M(k)(t-t_{M-1})^{\alpha k} & t\in[t_{M-1},t_M] \end{cases} \tag{20}$$

$$V(t) = \begin{cases} \sum_{k=0}^{k} V_1(k) t^{\alpha k} & t \in [0, t_1] \\ \sum_{k=0}^{k} V_2(k)(t-t_1)^{\alpha k} & t \in [t_1, t_2] \\ \vdots & \\ \sum_{k=0}^{k} V_M(k)(t-t_{M-1})^{\alpha k} & t \in [t_{M-1}, t_M] \end{cases} \tag{21}$$

$$I(t) = \begin{cases} \sum_{k=0}^{k} I_1(k) t^{\alpha k} & t \in [0, t_1] \\ \sum_{k=0}^{k} I_2(k)(t-t_1)^{\alpha k} & t \in [t_1, t_2] \\ \vdots & \\ \sum_{k=0}^{k} I_M(k)(t-t_{M-1})^{\alpha k} & t \in [t_{M-1}, t_M] \end{cases} \tag{22}$$

$$R(t) = \begin{cases} \sum_{k=0}^{k} R_1(k) t^{\alpha k} & t \in [0, t_1] \\ \sum_{k=0}^{k} R_2(k)(t-t_1)^{\alpha k} & t \in [t_1, t_2] \\ \vdots & \\ \sum_{k=0}^{k} R_M(k)(t-t_{M-1})^{\alpha k} & t \in [t_{M-1}, t_M] \end{cases} \tag{23}$$

Here $S_j(k), V_j(k), I_j(k)$ and $R_j(k)$ for $j = 1, 2, ..., M$ satisfy the following recurrence relations

$$S_j(k+1) = \frac{\Gamma(\alpha k+1)}{\Gamma((\alpha k+1)+1)} \left((1-\omega)\pi + \varphi V_j(k) - \beta \sum_{i=0}^{k} S_j(k-i) I_j(i) - (\mu+\sigma) S_j(k) \right),$$

$$V_j(k+1) = \frac{\Gamma(\alpha k+1)}{\Gamma((\alpha k+1)+1)} \left(\omega\pi + \sigma S_j(k) - \phi\beta \sum_{i=0}^{k} V_j(k-i) I_j(i) - (\mu+\gamma+\varphi) V_j(k) \right),$$

$$I_j(k+1) = \frac{\Gamma(\alpha k+1)}{\Gamma((\alpha k+1)+1)} \left(\beta \sum_{i=0}^{k} S_j(k-i) I_j(i) + \phi\beta \sum_{i=0}^{k} V_j(k-i) I_j(i) - (\mu+\delta) I_j(k) \right),$$

$$R_j(k+1) = \frac{\Gamma(\alpha k+1)}{\Gamma((\alpha k+1)+1)} \left(\gamma V_j(k) + \delta I_j(k) - \mu R_j(k) \right).$$

With the initial conditions $S_j(0) = S_{j-1}, V_j(0) = V_{j-1}, I_j(0) = I_{j-1}$ and $R_j(0) = R_{j-1}$. Finally, we start with initial conditions $S(0) = S_0, V(0) = V_0, I(0) = I_0$ and $R(0) = R_0$, and use the recurrence relation given in the above system, we can obtain the multi-step generalized differential transform solution given in (20)-(23)

7. Numerical methods and simulation

Since most of the fractional-order differential equations do not have exact analytic solutions, so approximation and numerical techniques must be used. Several analytical and numerical methods have been proposed to solve the fractional-order differential equations. For the numerical solution, we will study the effect of vaccination on the dynamics of a HBV disease described by the SVIR model (8) using multi-step generalized differential transform method according to the different values of the parameters in Table 1.

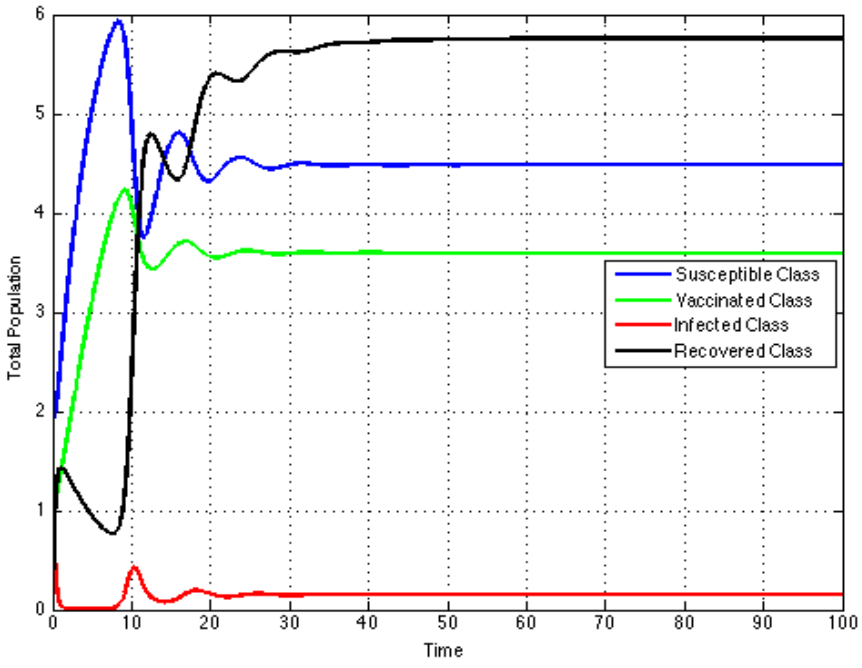
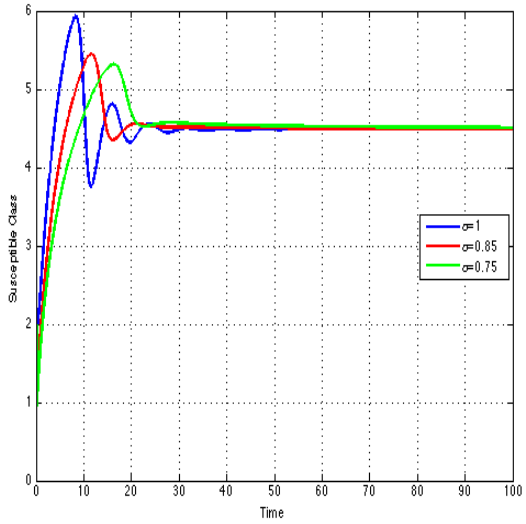
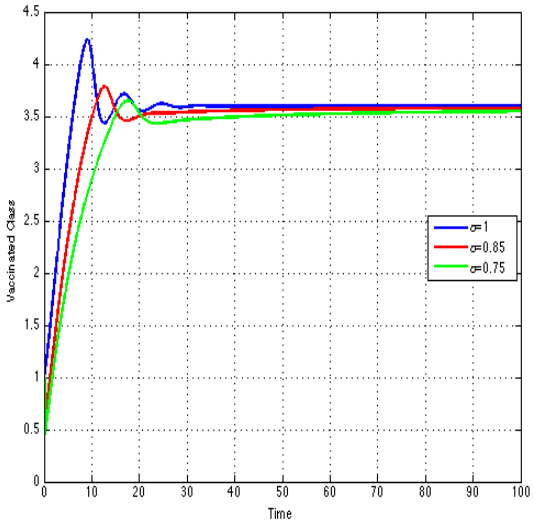
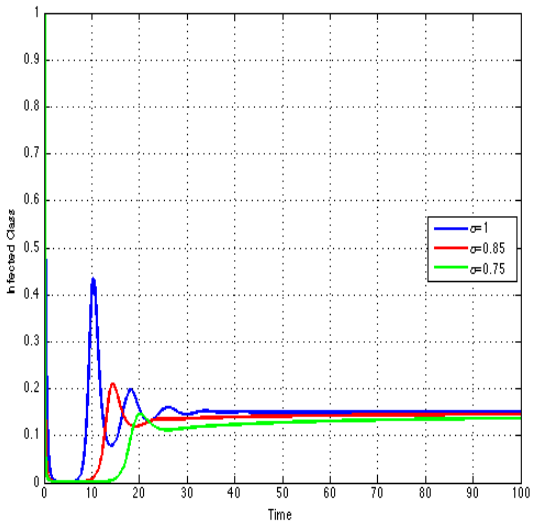


FIGURE 2. Show the approximate solutions for $S(t), V(t), I(t)$ and $R(t)$ obtained for value of $\alpha = 1$ using the multi-step generalized differential transform method.


Susceptible Class
Time
σ=1
σ=0.85
σ=0.75


Vaccinated Class
Time
σ=1
σ=0.85
σ=0.75


Infected Class
Time
σ=1
σ=0.85
σ=0.75

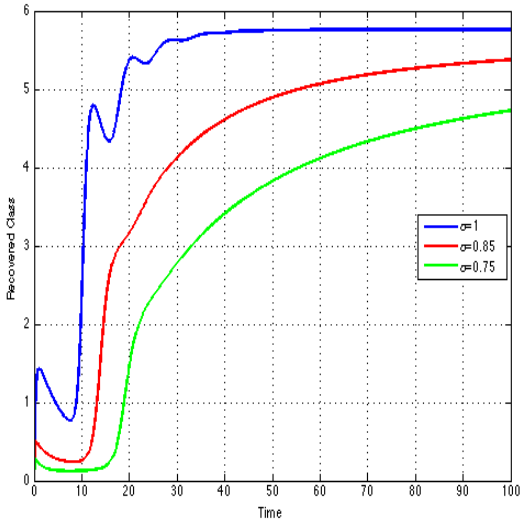


FIGURE 3. Numerical Simulations of the FODEs model (8) for different values of α, with $\alpha = 1, \alpha = 0.85, \alpha = 0.75$. The system converges to the stable steady state $\mathscr{E}_0$. The fraction derivative damps the oscilation behavior.

8. Concluding remarks

In this paper we study some fractional order models for HBV transmission with constant vaccination. Fractional-order differential equations are generalizations of integer-order differential equations. As a definition of fractional calculus: $\lim_{\alpha\to 1} D_t^{\alpha} f(t) = Df(t)$ has been provided. Fractional-order differential equations can be used to reduce the errors arising from the neglected parameters in modeling biological systems with memory and systems distributed parameters. In the presented problem, the susceptible class $S(t)$, the vaccinated class $V(t)$, the infected class $I(t)$, and the recovered class $R(t)$, have been obtained, the results obtained show that when $\alpha \to 1$ the solution of the fractional model (8), $D_t^{\alpha}(S), D_t^{\alpha}(V), D_t^{\alpha}(I), D_t^{\alpha}(R)$, reduce to the standard solution $S(t), V(t), I(t), R(t)$. The models possess non-negative solutions, as desired in any population dynamics. We have obtained a stability condition for equilibrium points and the threshold parameter $\mathscr{R}_0$ is estimated. One should note that although the equilibrium points are the same for both integer order and fractional order models, the solution of the fractional order model tends to the fixed point over a longer period of time.

The transformation of a classical model into a fractional-order makes it very sensitive to the order of differentiation α : a small change in α may result in a big change in the final result.

Numerical solutions of these models are given and the simulations have been used to verify the theoretical analysis. The results show that the solution continuously depends on the time-fractional derivative and on the values of the parameters described in Table 1. These figures show the effect of the constant-vaccination coverage on the disease free initial population groups. In figure 2, the population of the susceptible class decreases with time while that of the recovered class gradually increases due to inclusion of vaccinated-susceptible class. The entire population generally remains disease free with all the time and the endemic equilibrium remains stable.

From the numerical results in Figure 3, it is clear that the approximate solutions depend continuously on the fractional derivative α. The stability of the numerical scheme was established theoretically, under the assumption that the nonlinear source term satisfies a Lipschitz condition and the drift coefficient decreases monotonically. The approximate solutions obtained by multi-step generalized differential transform method are highly accurate and valid for a long time in the integer case. This method is very applicable and also this is a good approach for the solutions of differential equations of such order.

Conflict of Interests

The authors declare that there is no conflict of interests.

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