Fractional order models of infectious diseases: a review

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Abstract

The aim of this paper is to present a succinct review on fractional order models of infectious diseases. Fractional order derivative is a potential tool which gives a better understanding of the impact of memory on spread of infectious diseases. This paper reviews different infectious diseases models with constant, variable or complex fractional order. Fractional order models with time delay are presented in this paper as well. We argue that, such models are essential for decision makers in health organizations.

Keywords: Constant/Variable Fractional Order Models-Models with Complex Fractional Order -Fractional Order Models with Time Delay-Infectious Diseases Models with Memory.

1. Introduction

Infectious diseases and epidemics have become one of the crucial global issues as they cause of death and disability not only in developing countries, but also worldwide. Every year, HIV, TB and malaria cause 10% of all deaths [37], [28]. Over the last few decades, the number of infectious diseases outbreaks has increased dramatically, resulting in economic crises and millions of disability and deaths [48], [61]. For example, West Africa suffered up to $32 billion loss by 2015 and more than 11,000 deaths during Ebola outbreak [60], [66]. Infectious diseases are spreading around the globe faster than ever before, and new diseases are emerging at a high rate [20]. Speed modern transportation has helped spread of some communicable diseases. International travelling and commerce drive the rapid, global distribution of microbial pathogens and the organisms that harbor them [45]. Recently, the Zika virus is now spreading explosively in the world through modern transportsations. There is no, no background immunity in the population, or vaccine currently available [70]. Outbreaks provide an opportunity to collect and analyze initial data. These gathered data are essential to predict the behavior of diseases and to adjust control strategies. But sometimes data collection is impossible due pathological limitations [37], [40], [54]. Also, testing spread of infectious diseases in human societies are unethical or needs big budgets [39], [40], [54]. So, mathematical models of infectious diseases should be used to give a better understanding of spread of diseases spread in human communities [36] and to predict crucial data that should be collected. It is worth mentioning that, mathematical modeling of diseases extends to ancient history. One of the earliest mathematical models in epidemiology was presented by Daniel Bernoulli (1700–1782) [50], [22]. He predicted the impact of immunity with smallpox disease that made the idea of eradication feasible [50], [22]. Nowadays, modern mathematical models of infectious diseases play an increasingly significant role to evaluate the potential impact of eradication and control programs in reducing morbidity and mortality [23], [25], [62], [46]. Such enormous models are significant to link between clinical data for selected subpopulations and population-level used [30]. Mathematical modelling can achieve a better understanding of the indirect protection provided by immunization [29]. For example, the spread of influenza virus in USA were simulated in 2009 from gathered data from different areas in [29]. Gathered data from the H1N1 epidemic have been used to approve SEIR mathematical model. Also, an estimate for the vaccination coverage needed to block the spread of infectious diseases can be obtained from such models after estimating its parameters from available medical and epidemiological data [29]. Mathematical models enable researchers to understand the development of drug resistance throughout therapy [47]. Although many of these models have been proposed in literature, it has been restricted to integer order models [17]. However, integer order systems do not convey any information about prior states [4-11]. Understanding the concept of memory in biological systems can be very essential to predict the future of infectious diseases outbreaks and to control infectious diseases. Studying immunological memory is essential to develop vaccines. Memory and learning process in vector and host are critical in vector-borne disease transmission like Malaria and dengue fever [56]. Learning behavior and memory in vectors like mosquitoes are important in vector borne diseases transmission [56]. Mosquitoes’ experience is considered as the ability for mosquitoes to accurately identify their hosts. Also memory and learning behavior is significant in immunological memory which is defined as the potential of the immune system to respond more effectively to threats that have been encountered previously [38]. Fractional order differential equations can be potential flexible tools for modelling epidemiological and biological systems related with memory.

Adding fractional-order parameter enhances the system potential as it adds a new degree of freedom which leads the model to more space [17], [19]. So, the fractional order is supposed to be the memory index [21]. However, if the fractional order value tends to unity, the system...
will have short memory dependence. Otherwise, if the fractional order approaches zero, so the system depends strongly on the previous states [28], [38]. So, of fractional-order models are more logical than the integer model [1], [5], [6].

In this paper, we summarize different recent fractional order models of infectious diseases including constant & variable fractional order models, fractional delay models, and fractional complex order models.

The rest of the paper is organized as follows: In section two, some basic definitions of the fractional calculus are presented. Section three introduces discussion about fractional order models of immune system while section four is devoted for the epidemic models with memory. Section five displays the role of mathematical models of with memory of Human immunodeficiency virus based on fractional order models. Two models are discussed in this section; the first is a constant fractional order model of HIV infection of $CD4^+ \text{T-cells}$, while the second model is a fractional complex-order model drug-resistance in HIV disease. A study on fractional order models of vector borne diseases is presented in section six. Section seven is devoted for Fractional variable-order model of multi-strain tuberculosis (TB). Fractional order model with time delay of HIV infection.

2. Preliminaries

Firstly, basic definitions of constant & variable fractional-order integration and fractional-order differentiation will be discussed [3], [6], [7], [9], [51], [52], [57], [58].

Definition 1: The fractional order integral of order of a function $f: \mathbb{R}^+ \to \mathbb{R}$ is given by

$$I^\alpha f(x) = \frac{1}{\Gamma(\alpha)} \int_0^x (x-t)^{\alpha-1} f(t) \, dt, \quad \alpha > 0, x > 0,$$

Where $\alpha \in (0, \infty)$

This integral is called integral with memory.

Definition 2: The Caputo and Riemann–Liouville fractional order derivatives of order $\alpha$ are given respectively as follows [46]:

$$D^\alpha f(x) = D^m [f^m(x)],$$

$$\mathcal{D}^\alpha f(x) = f^m [D^m f(x)],$$

Where

$$m - 1 < \alpha \leq m, m \in \mathbb{N}.$$

Definition 3: Grunwald-Letnikov fractional order derivative of function $f(t)$ is given as follows [48]:

$$G_{\alpha}^D f(t) = \lim_{h \to 0} h^{-\alpha} \sum_{k=0}^{n} (-1)^k \binom{n}{k} f(t - kh)$$

Where $nh = x - \alpha$

The variable-order fractional derivative, is a powerful tool to characterize memory that may vary from point to point [57], [58]. Some of the basic definitions of the variable-order fractional derivative are presented as follows:

Definition 4: (Riemann–Liouville fractional derivatives of order)

Let $\alpha(t)$ be a continuous and bounded function, then Riemann–Liouville variable-order fractional derivative of $f(t): [a, b] \to \mathbb{R}$ is defined as [57]:

Left Riemann–Liouville derivative of order $\alpha(t)$ is defined by

$$G_{a^+}^D \alpha(t) f(t) = \frac{1}{\Gamma(1-\alpha(t))} \frac{d}{dt} \int_a^t (t-\tau)^{-\alpha(t)} f(\tau) \, d\tau,$$

Where $0 < \alpha(t) \leq 1$

Definition 5: (Caputo fractional derivatives of order $\alpha(t)$)

Let $\alpha(t)$ be a continuous and bounded function, then the Caputo variable-order fractional derivative of $f(t): [a, b] \to \mathbb{R}$ is defined as [57], [58]:

Left Caputo derivative of order $\alpha(t)$ is defined by

$$D_{a^+} \alpha(t) f(t) = \frac{1}{\Gamma(1-\alpha(t))} \int_a^t (t-\tau)^{-\alpha(t)} f'(\tau) \, d\tau,$$

Where $0 < \alpha(t) \leq 1$

Definition 6: (Grünwald-Letnikov fractional derivatives of order $\alpha(t)$)

Let $\alpha(t)$ be a continuous and bounded function, then the variable-order fractional derivative of $f(t): [a, b] \to \mathbb{R}$ is defined as [52]:

$$G_{a^+}^D \alpha(t) f(t) = \lim_{h \to 0} h^{-\alpha(t)} \sum_{k=0}^{n} (-1)^k \binom{n}{k} f(t - kh)$$

Where $nh = x - \alpha(t)$
\[ \frac{\alpha D^\alpha t}{\partial t} f(t) = \lim_{h \to 0} h^{-\alpha} \sum_{j=0}^{\lfloor n \rfloor} (-1)^j \binom{\alpha}{j} f(t - jh) \]

Where \( h \) is the step size, \( n = \frac{t}{\alpha} \lfloor n \rfloor \) is the integer part of \( n \) and \( 0 < \alpha(t) \leq 1 \).

### 3. Fractional order models with an immune response

All the immune system plays a vital role in human health as it protects the body from all harmful foreign substances like viruses and bacteria [32]. After defeating an infection, B and T cells create memory cells as they hold information about each hazard that attack the body. This creates the memory of immune system which makes it easier to identify and eliminate in the future [14]. There is no alternative to mathematical modeling to understand the behavior of immune system [39]. Numerous mathematical models have been presented to simulate the immune system [32]. The majority of such models proposed in the literature were integer order models. In [2], the authors presented a generalization of hepatitis C virus (HCV) model based on HCV basic model of Perelson et al [16] as follows

\[
\begin{align*}
D^\alpha(T) &= s - d T - (1 - \eta) \beta VT, \\
D^\alpha(I) &= (1 - \eta) \beta VT - \delta I (1 - \gamma c_2), \\
D^\alpha(V) &= (1 - \epsilon_p) p t - \epsilon V.
\end{align*}
\]

Where \( T, I \) and \( V \) present respectively uninfected hepatocytes, infected hepatocytes and virus density, and \( 0 < \alpha \leq 1 \) is the index of memory. The rate of production of uninfected hepatocytes is \( s \), while their rate of death is \( d \) per cell and rate of infection is \( \beta \). The rate of loss of infected hepatocytes is \( \delta \) per cell. The rate of production of virions is \( p \) per infected hepatocytes and their rate of clearness is \( c \) per virion. \( \epsilon_p \) and \( \eta \) present respectively the efficacy of treatment in blocking virion production and reducing new infections. The authors show that “fractional order results show the realistic biphasic decline behavior of HCV but at a slower rate”.

In [24], another example to show that fractional order models are more significant to model the immune system than classical integer order models. The authors consider two immune effectors \( y, z \) attacking an antigen \( x \). As follows:

\[
\begin{align*}
D^\alpha(x) &= x - axy - bxz, \\
D^\alpha(y) &= -cy + xy, \\
D^\alpha(z) &= -ez + xz.
\end{align*}
\]

Where \( a, b, c, e \) are positive constants and \( 0 < \alpha \leq 1 \).

Equilibrium points of (2) are locally asymptotically stable the condition \( \text{arg} \lambda_i > \frac{\pi}{2} \) is satisfied, where \( \lambda_i \) is the eigenvalue of the Jacobian matrix of the system at the equilibrium. It has been proved in [24] that, fractional order model is either stable as classical integer order model or more stable.

### 4. Epidemic models with memory

An epidemic occurs when an infectious disease transmitted rapidly to many people than what was expected in a region during a given period. The Flu of 1918 was known as one of the most deadly outbreaks in recorded world history. This Flu killed more people than World War I (about 20 million victims) [54]. Recently, World Health Organization (WHO) has declared emergency state for Ebola outbreak in West Africa after thousands of deaths because of the virus in 2014. Mathematical models in epidemiology are able to describe and predict highly dynamic outbreaks. For example, the following model [12] presents a fractional order model of Ebola infection using SEIR model as follows:

\[
\begin{align*}
D^\alpha(S) &= \frac{\beta S(t)(aE(t)+I(t))}{N}, \\
D^\alpha(E) &= \frac{\beta S(t)(aE(t)+I(t))}{N} - \delta E(t), \\
D^\alpha(I) &= \delta E(t) - \gamma I(t), \\
D^\alpha(R) &= \gamma I(t).
\end{align*}
\]

Where \( 0 < \alpha \leq 1 \), while \( S(t), E(t), I(t), \) and \( R(t) \) are the susceptible, exposed, infected, removed populations respectively at time \( t \) and the number of total population \( N = S(t) + E(t) + I(t) + R(t) \). The parameter \( \beta = \frac{p}{q} \) is average number of infected people, \( p \) is the probability of infection, \( c \) is the per capita contact rate, \( q \in [0,1] \) and \( \gamma \) is the per-capita death rate. The authors have analyzed the WHO data in order to give an accurate prediction of the outbreak in Liberia, Guinea, and Sierra Leone. They achieved a good approximation to real gathered data.

### 5. Fractional order models of HIV infection

HIV is one of the most deadly viruses. It causes AIDS and destroys the immune system, so the body cannot defend itself against any threat. There were more than 36 million people living with HIV by the end of 2014 [67]. An estimated 21.8 million people have died of AIDS since the start of the epidemic. Mathematical models provide an essential tool to understand the interactions between HIV and the immune system. Fractional order models are helpful to provide a better understanding of the dynamics of HIV infection [19]. An impressive example has been shown in [19], where the authors have introduced a modified model of fractional order based on the ODE model proposed by Culshaw and Ruan [15] into a system of fractional-order as follows:
\[ D^\alpha(T) = s - \mu_I T + rT \left( 1 - \frac{t}{T_{\text{max}}} \right) - K_4 VT \]
\[ D^\alpha(I) = K_4 VT - \mu_I I, \]
\[ D^\alpha(V) = N\mu_I - K_4 VT - \mu_V V \]
\[ (4) \]

Where \( T(t) \) is the concentration of healthy CD4\(^+\)T-cells at time \( t \), \( I(t) \) is the concentration of infected CD4\(^+\)T-cells, and \( V(t) \) presents the concentration of free HIV at time \( t \). The parameters \( s, \mu_I, r \) and \( T_{\text{max}} \) are the source of CD4\(^+\)T-cells, the natural death rate of CD4\(^+\)T-cells, their growth rate and their carrying capacity respectively. \( K_4 \) is the infection rate of T-cells with free virus while \( K'_1 \) presents the rate at which infected cells become actively infected. \( \mu_I \) is a blanket death term for infected cells, \( \mu_V \) is the lytic death rate for infected cells, \( \mu_V \) is the loss rate of virus and \( N \) is the number of viral particles. In [19], it is assumed that \( 0.5 < \alpha \leq 1 \). The authors think that fractional derivatives cannot describe accurately the rate of change in number when \( 0 < \alpha \leq 0.5 \). It has been proven that in [19], there is a unique solution \( x(t) = (T, I, V)^T \) for on \( t \geq 0 \) and the solution will remain in \( \mathbb{R}_+^3 \). Furthermore, \( T(t) \) and \( I(t) \) are all bounded by \( T_{\text{max}} \). The authors showed that the model established in this paper possesses non negative solutions, as desired in any population dynamics. A restriction on the number of viral particles released per infectious has been obtained cell in [19], to sustain the infection. Another interesting study about a fractional complex-order model for HIV virus during therapy is presented in [44] as follows:

\[ \frac{1}{2} \left( D^{\alpha+\beta} + D^{\alpha-\beta} \right) T(t) = \lambda - dT - k_s(1-n_p)I(t)T(t) - k_r(1-n_p)I(t)T(t), \]
\[ \frac{1}{2} \left( D^{\alpha+\beta} + D^{\alpha-\beta} \right) T_2(t) = (1-u)k_s(1-n_p)I(t)T(t) - \delta T_2(t), \]
\[ \frac{1}{2} \left( D^{\alpha+\beta} + D^{\alpha-\beta} \right) V(t) = N_\delta(1-n_p)T(t) - cV(t), \]
\[ \frac{1}{2} \left( D^{\alpha+\beta} + D^{\alpha-\beta} \right) V_2(t) = uK_s(1-n_p)V(t)T(t) + K_r(1-n_p)I(t)T(t) - \delta T_2(t), \]
\[ \frac{1}{2} \left( D^{\alpha+\beta} + D^{\alpha-\beta} \right) V_3(t) = N_r(1-n_p)T(t) - cV(t). \]
\[ (5) \]

Where \( T \) is the density of uninfected CD4\(^+\)T-cells with rate of production \( \lambda \) and rate of death \( d \). The parameter \( K_r \) is the infection rate of the CD4\(^+\) T-cells with drug-sensitive HIV viruses \( V \). The concentration of drug-sensitive infected CD4\(^+\)T is \( T_2(t) \) while the concentration of the drug-resistant infected CD4\(^+\)T is \( T_2(t) \). The CD4\(^+\)T-cells may be infected by drug-resistant viruses \( V \) at a rate \( K_r \). The efficacy rates of RTI for wild type and mutants are \( n_p^r \) and \( n_p^f \) respectively (The proportions of eliminated \( T_r \) and \( T_f \) cells by RTI). The parameter \( u \) is the proportion of \( T_r \) cells that can become resistant to the drug. The rate of death of \( T_r \) and \( T_f \) is \( \delta \) while \( c \) is the clearance rate of the viruses. \( V \) and \( V_2 \) are produced with bursting sizes drug-sensitive strains \( N_r \) and \( N_\delta \) respectively. The efficiency of PI for wild type strain and mutants are \( n_p^f \) and \( n_p^r \) respectively. Based on Grunwald-Letnikov formulation, the authors simulated the model for different values of the fractional derivative of complex order \( D^{\alpha+\beta} \) where \( \alpha, \beta \in C \). If \( \alpha = 1 \) and \( \beta = 0 \), the system will be converted to the integer order model. Applying fractional derivative complex-order to the system, results in complex valued outcomes. The authors fixed \( \beta = 0.8 \) and \( 0.5 \leq \alpha \leq 1 \). Faster declines in the density of viruses have been observed for decreasing values of \( \alpha \) [44]. In other words, increasing memory of T-cells leads to faster decreasing in density of HIV.

### 6. Fractional order vector borne diseases models

Vector-borne disease is a commonly used term that describes a disease transmitted to people by vectors like mosquitos and ticks through feeding activity [63]. Being a vector means that it carries a disease from one host to another. More than 1 million people die every year from mosquito-borne diseases like Malaria and Dengue Fever [65]. An interesting generalization of the basic deterministic ODE Dengue Fever disease model has been presented in [49]. The authors have modified the integer order model in [41] to be fractional order model as follows

\[ D^\alpha(S_H) = \mu_H(K - S_H) - \frac{b_H S_H I_H}{K}, \]
\[ D^\alpha(I_H) = \frac{b_H S_H I_H}{K} - (\mu_H + \gamma_H)I_H, \]
\[ D^\alpha(R_H) = \gamma_H I_H - \mu_H R_H, \]
\[ D^\alpha(I_V) = \frac{b_V I_V S_V}{K} - m I_V, \]
\[ D^\alpha(S_V) = A - \frac{b_V I_V S_V}{K} - m S_V. \]
\[ (6) \]

Where \( 0 < \alpha \leq 1, S_H, I_H \) and \( R_H \) are the populations of susceptible humans, infected human, and recovered human respectively. \( S_V \) and \( I_V \) are the populations of susceptible mosquitos, infected mosquitos. The total human population \( K \) at time \( t \) is denoted by \( N_H \) where \( N_H = S_H + I_H + R_H \). The authors considered that \( N_V = S_V + I_V \). The parameter \( \mu_H \) is the per capita mortality rate of the humans and \( m \) is the corresponding value for the mosquitos. \( \gamma_H \) is the humans recovery rate while \( b_V \) is the biting rate. The probabilities of transmission from human to mosquito and vice versa are denoted by \( b_H \) and \( b_V \) respectively while \( A \) is the recruitment rate of mosquito. Model (6) has some drawback, because the left-hand side of the system (6) has dimension \((\text{time})^{-\alpha}\) while the right-hand has the dimension \((\text{time})^{-1}\). So it is recommended to use the procedure presented in [18,49]. System (6) can be re-written as follows:
\[ D^\alpha(S_H) = \mu_H^0(K - S_H) - \frac{\beta_H S_H I_H}{K}, \]
\[ D^\alpha(I_H) = \frac{\beta_H S_H I_H}{K} - (\mu_H^0 + \gamma_H^0)I_H, \]
\[ D^\alpha(R_H) = \gamma_H^0I_H - \mu_R^0R_H, \]
\[ D^\alpha(S_V) = A_2 - \frac{\beta_V S_V I_V}{R_0}, \]
\[ D^\alpha(I_V) = \frac{\beta_V S_V I_V}{R_0} - \mu_V I_V. \]

Where \( A_2 = \mu_H^0 \times (S_V(0) + I_V(0)) \), and \( \mu_m \) is the birth rate of mosquito. In [48], two different orders \( \alpha \in (0, 1) \) and \( \beta \in (0, 1] \) are introduced to the system (6) to be more sensible, so the new system is as follows:

\[ D^\alpha(S_H) = \mu_H^0(K - S_H) - \frac{b_H S_H I_H}{K}, \]
\[ D^\alpha(I_H) = \frac{b_H S_H I_H}{K} - (\mu_H^0 + \gamma_H^0)I_H, \]
\[ D^\alpha(R_H) = \gamma_H^0I_H - \mu_R^0R_H, \]
\[ D^\beta(S_V) = A_2 - \frac{b_V S_V I_V}{R_0}, \]
\[ D^\beta(I_V) = \frac{b_V S_V I_V}{R_0} - \mu_V I_V. \]

The basic reproduction number has been derived in [48] for (6) to be

\[ R_0 = \frac{b_H K}{m} \times \frac{b_H A}{mK(\mu_H^0 + \gamma_H^0)} \]  

The infection persists if \( R_0 > 1 \), and dies out if \( R_0 < 1 \). Using the next generation matrix approach, the basic reproduction numbers \( R_0, \hat{R}_0, \) and \( \check{R}_0 \) have been derived for systems (7) and (8) respectively in [49] to be:

\[ \hat{R}_0 = \frac{b_H \beta_I}{m^2} \times \frac{b_H A}{m^2K(\mu_H^0 + \gamma_H^0)} \]

And

\[ \check{R}_0 = \frac{b_H \beta_I}{m^2} \times \frac{b_H A}{m^2K(\mu_H^0 + \gamma_H^0)} \]

It is clear that, \( \hat{R}_0 \) and \( \check{R}_0 \) carry information about the persistence of the disease. Involvement of the index of human memory (\( \alpha \)) and the index of mosquitoes memory (\( \beta \)) in (10) and (11) has some effects on the values of the reproduction numbers \( \hat{R}_0 \) and \( \check{R}_0 \). The authors in [49] observed the relation between the memory of mosquitoes and the dengue transmission. Also they studied the effect of the memory of humans on dengue transmission. Increasing human memory (\( \alpha \to 0 \)) will reduce the disease transmission. The authors in [49] presented a strategy for controlling dengue disease through studying the memory effects of the host, and the vector. They believe that, increasing human memory and learning behavior through different kinds of media awareness is essential to reduce the disease transmission. Also the memory of the mosquito (like detecting host sites and suitable locations for their eggs) plays a significant role in the disease transmission. So, increasing mosquitoes memory and learning behavior (\( \beta \to 0 \)), leads to increasing the disease transmission. The authors observed that the results of (8) have a better agreement with a real measured data in [64]. Such observations support using the models with memory.

### 7. Fractional variable-order model of multi-strain tuberculosis (TB)

TB is an infectious disease is one of the most dangerous diseases [42], [66]. It is often affect the lungs. According to reports of World Health Organization (WHO) in 2014, 9.6 million people have been infected with TB and 1.5 million died from the disease [69]. TB is one of the major killers of HIV-positive people. In 2015, 1 in 3 HIV deaths was due to TB [67]. Ending the TB epidemic by 2030 is among the World Health Organization (WHO) future plans [69]. Mathematical models help the decision makers to put their plans to control TB diseases and to achieve public health and economic benefits [27]. Anti (TB) drug resistance is one of the most dangerous problems that delayed progress made in TB care [13]. In [52], multi-strain TB model of variable-order fractional derivatives is presented as follows

\[ D^{\alpha(S)} = b - dS - \beta_S S_N - \beta_m S_N - \beta_x S_N, \]
\[ D^{\alpha(L)} = \lambda_S b_x S_N + \sigma_S \lambda_S I_N + \gamma_S I_N - \alpha_S b_S \frac{I_N}{N} - \alpha_S b_m \frac{I_N}{N} - \alpha_S b_x \frac{I_N}{N} - (d + \varepsilon_S + \tau_S)I_N, \]
\[ D^{\alpha(L_m)} = \lambda_m b_m S_N + \sigma_m \lambda_m I_N + \gamma_m I_N + \alpha_m b_m \lambda_m \frac{I_N}{N} + (1 - P_1)\varepsilon_S I_N + (1 - P_2)\varepsilon_x I_N - \alpha_m b_m \lambda_m \frac{I_N}{N} - \alpha_m b_m \lambda_m \frac{I_N}{N} - \frac{(d + \varepsilon_m) I_N}{N}. \]
\[ D^{\alpha(t)}(L_x) = \lambda_x \beta_x \frac{S_t}{N} + \alpha_x \lambda_x \beta_x \frac{R_t}{N} + \gamma_x I_x + \alpha_x \lambda_x \beta_x \frac{I_t}{N} + \alpha_{mx} \lambda_x \beta_x \frac{m_t}{N} + (1 - P_3) t_{2m} l_m - \alpha_x \beta_x \frac{I_t}{N} - (d + \varepsilon_x) L_x. \]

\[ D^{\alpha(t)}(I_t) = \alpha_{mx} \beta_x \frac{m_t}{N} + (1 - \lambda_x) \beta_x \left( \frac{S_t}{N} + \alpha_x \frac{I_t}{N} \right) + \varepsilon_x L_x - (d + \delta_x + t_{2x} + \gamma_x) I_x. \]

\[ D^{\alpha(t)}(l_m) = \alpha_{mm} \beta_m \frac{l_{m_t}}{N} + (1 - \lambda_m) \beta_m \left( \frac{S_m}{N} + \alpha_m \frac{I_m}{N} \right) + \alpha_{sx} \lambda_x \beta_x \frac{I_t}{N} + \alpha_{mx} \lambda_x \beta_x \frac{m_t}{N} - \alpha_m \beta_m \frac{R_m}{N} - \delta_x \frac{I_t}{N} \frac{l_{m_t}}{N} - dR. \]

\[ D^{\alpha(t)}(R) = P_1 t_{13} I_x + P_2 t_{23} I_x + P_3 t_{2m} l_m + t_{2x} I_x - \alpha_g \beta_r \frac{R_t}{N} - \alpha_m \beta_m \frac{R_m}{N} - \sigma_x \beta_x \frac{I_t}{N} - dR \quad (12) \]

Where \( 0 < \alpha(t) \leq 1 \) is the fractional variable order,
\[ S(t) \] is the susceptible individuals,
\[ L_x(t) \] is the latently infected individuals with the drug-sensitive TB strain,
\[ l_m(t) \] is the latently infected population with MDR-TB,
\[ I_x(t) \] is the infected individuals with the drug-sensitive TB strain who are infectious to others,
\[ I_m(t) \] presents the infectious individuals with the MDR-TB strain,
\[ I_x(t) \] presents the individuals who infectious with the XDR-TB strain,
\[ R(t) \] is the populations for who have been treated successfully,
\[ N(t) = S(t) + L_x(t) + L_m(t) + I_x(t) + l_m(t) + I_x(t) + R(t) \] is the total population

\( b \) is the rate of birth/recruitment,
\( d \) is per capita natural death rate,
\( \beta_r \) is transmission coefficient for strain \( r \),
\( \lambda_x \) is the proportion of newly infected individuals developing LTBI with strain \( r \),
\( \varepsilon_x \) is per capita rate of endogenous reactivation of \( L_x \),
\( \alpha_{x1}, \alpha_{x2} \) are the proportion of exogenous reinfection of \( L_x \) due to contact with \( I_x \),
\( \gamma_x \) is per capita rate of natural recovery to the latent stage \( L_x \),
\( \delta_x \) is per capita rate of death due to TB of strain \( r \),
\( t_{1x} \) is per capita rate of treatment for \( L_x \),
\( t_{2x} \) is per capita rate of treatment for \( I_x \),
\( 1 - \sigma_x \) is the efficiency of treatment,
\( P_1, P_2, \) and \( P_3 \) are the probabilities of treatment success for \( L_x, I_x, \) and \( l_m \) respectively.

The notation \( t_1, t_2, t_3 \in \{ s, m, x \} \) is used. This model presents three strains: drug-sensitive, emerging multi-drug resistant (MDR) and extensively drug-resistant (XDR), as an extension for multi-strain TB integer order model which was developed in [13]. From the numerical results obtained in [52], the integer order model can be used to describe the short memory of the model, and the variable-order fractional model can be used to present the variable memory of TB model. The basic reproduction number has been derived in [ ] for (12) to be:

\[ R_{0x} = \frac{\beta_x e^{(1-\lambda_x) (d+t_{1x})}}{(e+\delta+t_{1x}) e^{(e+\delta+t_{1x})+\gamma x (e+\delta+t_{1x})}} \]

\[ R_{0m} = \frac{\beta_m e^{(1-\lambda_m) (d)}}{(e+\delta+t_{1x}) (e+\delta+t_{1x})+\gamma m d} \]

\[ R_{0x} = \frac{\beta_x e^{(1-\lambda_x) (d)}}{(e+\delta+t_{1x}) e^{(e+\delta+t_{1x})+\gamma x (e+\delta+t_{1x})}} \]

8. Fractional order models of infectious diseases with time delay

Many researchers introduce the fractional order derivative into the infectious diseases models for its memory property. Time delay in these models plays a significant role in the process of spreading infectious diseases [34,35,59] as it introduces the dependence of the present state of the model on the past history. This time delay takes into account certain hidden processes like the viral life cycle and duration of immunity to diseases. Time delays increase the risk of epidemic and the difficulty of epidemic control. Fractional order derivative and time delays in infectious diseases models give a better understanding of the dynamics of infectious diseases. Several works have been proposed to study the fractional order models with time delay of infectious diseases. In this section, three examples of such models will be illustrated.

8.1. Fractional order model of HIV with time delay

The authors in [59] have introduced the following system to model HIV infection of \( CD^4^+T \)-cells with time delay:

\[ D^{\alpha(t)}(T) = s - \mu_T T(t) + r T(t) \left( 1 - \frac{r(t)+s(t)}{r_{max}} \right) - kT(t) V(t) \]

\[ D^{\alpha(t)}(I) = k T(t - \tau) V(t - \tau) - \mu_I I(t) \]

\[ D^{\alpha(t)}(V) = N \mu_J (t) - k T(t) V(t) - \mu_V V(t) \]

(13)
Where

\[ T(\theta) = T_0 I(0) = 0, V(\theta) = V_0, \theta \in [-\tau, 0]. \]

The authors in [34] present a new fractional order time-delay model which is as an extension of the work in [59]. This model includes full logistic growth terms of both healthy and infected CD4+ T-cells, and cure rate items. The new model is described by the following fractional differential time-delay model:

\[
D^\alpha(T) = s - \mu_T T(t) + r T(t) \left(1 - \frac{\tau(t) + r(t)}{\tau_{\text{max}}}ight) - k T(t) V(t) + \rho I(t) \\
D^\alpha(l) = k T(t - \tau)V(t - \tau) + r l(t) \left(1 - \frac{\tau(t) + r(t)}{\tau_{\text{max}}}ight) - (\mu_t + \rho) l(t) \\
D^\alpha(V) = N \mu_I J(t) - \mu_V V(t)
\]

Where \( T(\theta) = T_0 I(0) = 0, V(\theta) = V_0, \theta \in [-\tau, 0], 0 < \alpha \leq 1, \) and \( \tau \geq 0 \) is the length of the delay in days, \( T(t), I(t), \) and \( V(t) \) represent the concentration of healthy CD4+ T cells, infected CD4+ T-cells, and density of HIV RNA in the blood, respectively. The parameters are defined in [1], [2] as follows:

- \( s \) is the source term for uninfected CD4+ T cells,
- \( \mu_T \) is the natural death rate of CD4+ T cells,
- \( \mu_I \) is the blanket death rate of the infected cells,
- \( \mu_v \) is the death rate of free virus,
- \( \mu_b \) is the rate of lytic death of infected cells,
- \( k \) is the rate of infections of CD4+ T-cells,
- \( k' \) is the rate of activation of infected cells,
- \( \rho \) is the rate of reverting from infected cells to the uninfected state,
- \( r \) is the growth rate of CD4+ T-cells.

- \( N \) is the number of virions produced by infected CD4+ T-cells,
- \( \tau_{\text{max}} \) is the maximal population level of CD4+ T-cells,
- \( T_0 \) is the CD4+ T-cells population for HIV-negative persons.

The numerical solutions in [34] indicate that, when \( \alpha \) increases, the trajectory of the model is close to the integer-order model and when \( \tau \) increases, the fluctuation of the trajectory of the model is smaller during the previous period of time. Also numerical solutions in [34] show that if the cure rate gets large, the HIV infection cannot be controlled.

8.2. Fractional order TB model with time delay

In [53], fractional order TB model with time delay is proposed. This model is based on Grünwald–Letnikov fractional order derivative. In this work, the fractional order system which has been presented in [53] as follows:

\[
D^\alpha(S) = b_S - d_S S - \beta_S S I / N - \beta_S I R / N - \beta_S I L / N - \beta_S I \alpha / N,
\]

\[
D^\alpha(L) = \lambda^2 \beta_S S I / N + \lambda^2 \beta_S I R / N + \gamma^2 I - \alpha^2 \beta_S S I / N - \alpha^2 S S / N - \alpha^2 S R / N - \alpha^2 S L / N - \alpha^2 S \alpha / N - (d_S + \epsilon_S + \delta_S) L / N.
\]

\[
D^\alpha(R) = \lambda^2 \beta_S S I / N + \lambda^2 \beta_S I R / N + \gamma^2 I + \alpha^2 \beta_S S I / N + \alpha^2 S S / N + \alpha^2 S R / N + \alpha^2 S L / N + \alpha^2 S \alpha / N - (d_S + \epsilon_S + \delta_S) L / N.
\]

\[
D^\alpha(I) = \lambda^2 \beta_S S I / N + \lambda^2 \beta_S I R / N + \gamma^2 I + \alpha^2 \beta_S S I / N + \alpha^2 S S / N + \alpha^2 S R / N + \alpha^2 S L / N + \alpha^2 S \alpha / N - (d_S + \epsilon_S + \delta_S) L / N.
\]

\[
D^\alpha(R) = \lambda^2 \beta_S S I / N + \lambda^2 \beta_S I R / N + \gamma^2 I + \alpha^2 \beta_S S I / N + \alpha^2 S S / N + \alpha^2 S R / N + \alpha^2 S L / N + \alpha^2 S \alpha / N - (d_S + \epsilon_S + \delta_S) L / N.
\]

The basic reproduction number has been derived in [53] for (15) to be:

\[
R_{0S} = \frac{\beta_S (\gamma^2 + (1 - \gamma^2) (d_S + \delta_S))}{( \epsilon_S + d_S + \alpha_S \gamma_S + \beta_S I R / N + \gamma_S \beta_S I L / N + \beta_S I / N + d_S \alpha_S)}
\]

\[
R_{0R} = \frac{\beta_S (\gamma^2 + (1 - \gamma^2) (d_S + \delta_S))}{( \epsilon_S + d_S + \alpha_S \gamma_S + \beta_S I R / N + \gamma_S \beta_S I L / N + \beta_S I / N + d_S \alpha_S)}
\]
\[ R_{0x} = \frac{\beta_x \gamma x (1 - \lambda x) \mu x}{(\xi_x + \alpha x) \mu x + \mu x + \gamma x \mu x + \alpha x} \]

\[
8.3. \text{Fractional order model for malaria transmission with time delay under impact of vaccination control}
\]

Malaria disease is caused by the bites of infected Anopheles mosquitoes. It is one of the most fatal vector borne diseases. About 216 million people have been infected with malaria in 2016 [71]. 91% of such cases were in Africa. 445 000 people died in 2016 because of malaria infection [71]. Fractional order models can be used to study the impact of vaccination strategies against malaria transmission. A delayed fractional order model of Malaria transmission is proposed in [43]. The effect of impact of vaccination control is implemented in this model.

\[
D^{\alpha}(N_h(t)) = \Lambda_h - \xi_h(I_h(t) + (1 - \theta_2)Y_h(t) + (1 - \nu)T_h(t)) - \mu_h N_h(t),
\]

\[
D^{\alpha}(S_h(t)) = (1 - p)\Lambda_h - f_m(t)S_h(t) + r_h(I_h(t) + \theta_1 Y_h(t) + \delta T_h(t)) + \sigma V_h(t) - \mu_h S_h(t)
\]

\[
D^{\alpha}(V_h(t)) = p\Lambda_h - f_h(t)(1 - \gamma) V_h(t) - (\sigma + \mu_h)V_h(t)
\]

\[
D^{\alpha}(I_h(t)) = f_h(t - \tau_h)S_h(t - \tau_h)e^{-\mu_h \tau_h} - (k + r_h + \xi_h + \mu_h)I_h(t)
\]

\[
D^{\alpha}(Y_h(t)) = f_h(t - \tau_h)(1 - \gamma)V_h(t - \tau_h)e^{-\mu_h \tau_h} - (k + \theta_1 r_h + (1 - \theta_2)\xi_h + \mu_h)Y_h(t)
\]

\[
D^{\alpha}(T_h(t)) = k(I_h(t) + Y_h(t)) - (\delta r_h + (1 - \nu)\xi_h + \mu_h)T_h(t)
\]

\[
D^{\alpha}(N_m(t)) = \Lambda_m - \xi_m I_m(t) - \mu_m N_m(t)
\]

\[
D^{\alpha}(S_m(t)) = \Lambda_m - f_m(t)S_m(t) - \mu_m S_m(t)
\]

\[
D^{\alpha}(I_m(t)) = f_m(t - \tau_m)S_m(t - \tau_m)e^{-\mu_m \tau_m} - (\mu_m + \xi_m)I_m(t) + \Lambda_m
\]

Given that

\[
f_h(t) = \beta_h c (1 - b_2) \frac{I_m(t)}{N_h(t)}
\]

\[
f_m(t) = \beta_m c (1 - b_2) \frac{I_m(t) + I(u(t)) + (1 - \gamma) Y_h(t) + (1 - \eta) T_h(t)}{N_h(t)}
\]

Where

- \( \alpha_i \in [0,1] \) for \( i = 1, 2, 3, ... , 9 \)
- \( N_h(t) \) is the total human population,
- \( S_h(t) \) is the number of susceptible human individuals,
- \( V_h(t) \) is the number of vaccinated human individuals,
- \( I_h(t) \) is the number of infectious human individuals,
- \( Y_h(t) \) is the number of infectious vaccinated human individuals,
- \( T_h(t) \) is the number of treated human individuals,
- \( N_m(t) \) is the total number of mosquito population,
- \( S_m(t) \) is the number of susceptible mosquitos,
- \( I_m(t) \) is the number of infectious mosquitos,
- \( \Lambda_h \) is the rate of recruitment of human population,
- \( p \) is the proportion of vaccinated individuals,
- \( \sigma \) is the rate of loss of immunity due to vaccination,
- \( r_h \) is the rate of recovery,
- \( c \) is the biting rate,
- \( \beta_h \) is the probability of transmission,
- \( b \) is the personal protection efficacy,
- \( z \) is the compliance of personal protection,
- \( \xi_h \) is the death rate due to the disease,
- \( \mu_h \) is the human’s natural death rate,
- \( \gamma \) is the pre-erythrocytic vaccine efficacy,
- \( \epsilon \) is the efficacy of transmission blocking vaccine,
- \( \tau_h \) is the latent period of humans,
- \( k \) is the Treatment rate,
- \( \eta \) is the drug efficacy,
- \( \Lambda_m \) is the rate of recruitment of human population,
- \( \beta_m \) is the probability of infection transmission to mosquitos,
- \( \mu_m \) is the natural death rate of mosquitos,
- \( \tau_m \) is the latent period for mosquitos,
- \( \xi_m \) is the rate of death due to presence of parasites,

Infectious vaccinated humans recover at the rate of \( \theta_2 r_h \) or die at the rate \( (1 - \theta_2) \xi_h \), while treated humans recover at the rate of \( \delta r_h \) or die at the rate of \( (1 - \nu) \xi_h \).
9. Fractional order SIR model based on stochastic process

In [5], a new sophisticated approach has been proposed to derive fractional order SIR model. Instead of replacing first order derivatives in the classical SIR model by a Caputo fractional order derivatives, the authors in [5] developed a new Fractional order SIR recovery model based on physical stochastic process. They follow an interesting technique in their approach by replacing the constant parameters in the classical SIR model with time dependent parameters. In addition, they use a Mittag-Leffler waiting time distribution, to derive the following generalized master SIR model with fractional recovery:

\[
\frac{dS(t)}{dt} = \lambda(t) - \omega(t)S(t)I(t) - \gamma(t)S(t),
\]

\[
\frac{dI(t)}{dt} = \omega(t)S(t)I(t) - \gamma(t)I(t) - \theta(t,0)\left(\mu D^\gamma \left(\frac{l}{\alpha(\theta)} - \frac{l_0}{\alpha(\theta)}\right) - \frac{d}{dt} \left(\frac{l_0}{\alpha(\theta)}\right)\right),
\]

\[
\frac{dR(t)}{dt} = \theta(t,0)\left(\mu D^\gamma \left(\frac{l}{\alpha(\theta)} - \frac{l_0}{\alpha(\theta)}\right) - \frac{d}{dt} \left(\frac{l_0}{\alpha(\theta)}\right)\right) - \gamma(t)R(t).
\]

Where

- \(S\) is the susceptible population
- \(I\) is the infected populations
- \(R\) is the recovered population

\(\theta(t, t')\) is the death surviving probability of from \(t'\) to time \(t\)

\(\theta(t, 0) = \theta(t, t')\theta(t', 0), \text{ for } 0 < t' < t\).

\(\omega(t)\) is the rate of becoming infected

If the probability of death happens in the interval \(t\) to \(t + \delta t\) is \(\gamma(t)\delta t + o(\delta t)\), then:

\[\theta(t, t') = e^{-\int_t^{t'} \gamma(t) dt}\]

10. Conclusion

As the fractional-order dynamical systems possess memory, it offers a deep insight into the mathematical modeling of infectious diseases. In this paper, we have provided some fractional order models of infectious diseases to show how memory effect changes the dynamics of diseases. Fractional order models exhibit much more realistic dynamics than integer order models because such models carry information about the memory of living systems and its associative learning mechanisms. The fractional order derivative is the parameter of memory.

References


