Available online at http://scik.org
J. Math. Comput. Sci. 10 (2020), No. 2, 262-276
https://doi.org/10.28919/jmcs/4329
ISSN: 1927-5307

NUMERICAL SOLUTION OF FRACTIONAL ORDER MATHEMATICAL MODEL OF DRUG RESISTANT TUBERCULOSIS WITH TWO LINE TREATMENT

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Abstract. In this paper, we have studied fractional order mathematical model that describes drug resistant tuberculosis with two line treatment by using Caputo fractional derivative. The present model has been solved successfully by applying generalised Euler method (GEM) and matched with the previous results in integer order. The properties and nature of physical states of these equations have been emphasised more precisely by taking fractional order. It is to be noted that the nature and kind of any type of tuberculosis is not uniform even though all circumstances remain similar. So it is challenging to define a mathematical model which considers the dynamics of its' class by taking fractional order derivatives. Numerical solutions are prominently demonstrated with the help of appropriate graphs that depicts practical utility than theoretical considerations.

Keywords: fractional order mathematical model [FOMM]; mathematical model for tuberculosis; fractional order mathematical model for tuberculosis with twin line treatment[FMMT]; generalised Euler method (GEM).

2010 AMS Subject Classification: 92B05, 34A12, 65L05.

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Received November 7, 2019

1. INTRODUCTION

Recently , the theory of fractional calculus [1], [2] has caught attention of scientists and researchers for analysing the mathematical models in the field of Science and Technology [3]. The concept of calculus evolved to fractional calculus by considering the fractional order of derivatives and integrals. It can be described in many fields accurately and more extensively as in Electrical engineering and electrodynamics [4], Physics and astrophysics, [5] Control systems [6], Signals and systems [7] , digital signal processing [7], Image processing [8], Biomedical and Biotechnology [9], Economics and Finance [10]. Researchers are now trying to pertain it to the field of medicine for analysis of epidemic diseases [11]. Fractional order mathematical model for diverse diseases which govern different factors at various stages has aroused wide interest among scientists.

Tuberculosis (TB) is caused by group of closely related *Mycobacterium tuberculosis* bacteria complex. The bacteria usually attacks lungs but can also attack any part of human body like kidney, spine and brain. According to WHO (2017) [12], Tuberculosis (TB) is one of the top 10 causes of death from this single infection. In 2017, Tuberculosis (TB) caused 1.3 million deaths among HIV negative people and additional 3 lack deaths from tuberculosis in HIV positive people. Among all these, maximum percentage of deaths accounting to 27% occurred in South Asia region including India [13].

In view of rapid infection rate of tuberculosis (TB), WHO has declared it as a serious world problem with efforts for eradication of the disease ranging from BCG vaccine in $18th$ century and DOTS strategy in the end of 19^{th} century [14]. To ensure the full impact, these policies demand not only assistance from the medical fraternity but also the public. To create awareness about life threatening effect of tuberculosis on humans in the world, analysis of mathematical model has become integral part of the treatment. [15], [16],[17]. Previously fractional order mathematical models of many epidemic diseases under considerable parameters and strategies have been analysed by different methods [18], [19]. There are various methods to get approximate solutions of system of non linear differential equations like Finite difference method (FDM) [22], Finite element method (FEA) [23], Adomain decomposition method (ADM) [24], Variation iteration method (VIM)[25], HE proposed Homotopy perturbation method (HPM)[26], Lio proposed Homotopy analysis method (HAM) [27]. These methods are effective for small time interval. Also chaotic systems have brought attention to failure of above methods. However, to some extent researchers have shown keen interest to apply these methods to get better approximation in versatile system of non linear differential equations in smaller classes [28].

The present fractional order mathematical model consist of system of non-linear ordinary differential equations with initial conditions have been operated by applying generalised Euler method successfully [29]. Classical Euler method has been generalised for the system of non-linear and linear differential equations of fractional order.

1.1. Basic definitions and some properties of fractional calculus. We give some basic idea of fractional calculus and properties which are used further [1][2].

1.1.1. *Definition.* A real function $h(t)$, $t > 0$, is said to be in the space C_μ, $\mu \in R$ if there exist a real number $p\,(>\mu\,)$ such that $h(t\,) = tph_1(t)$ where $h_1(t) \in C[0,\infty]$ and it is said to be in the space C^n_μ if and only if $h^n \in C_\mu$, $n \in N$.

1.1.2. *Definition.* Riemann-Liouville fractional integral operator (J^α_t) of order $\alpha \geq 0$ of a function $h \in C_\mu$, $\mu \geq -1$ is defined as

$$\cdot_a J^\alpha_t\, h(t) = \frac{1}{\Gamma\alpha}\int_a^t (t-\tau)^{\alpha-1}.h(\tau)\,d\tau \qquad (\alpha > 0)$$

Where $t \geq a \geq 0$ and $\Gamma(.)$ is a well known gamma function.

Some of the properties of Riemann -Liouville fractional integral operator have been explained For $h(t) \in C_\mu$, $\mu \in R$, $\mu > -1$,
$a, \alpha, \beta \geq 0$ and $\nu \geq -1$.

1. $\cdot_a J^\alpha_t\, h(t)\, \cdot_a J^\beta_t\, h(t) = \cdot_a J^{\alpha+\beta}_t\, h(t)$

2. $\cdot_a J^\alpha_t\, h(t)\, \cdot_a J^\beta_t\, h(t) = \cdot_a J^\beta_t\, h(t)\, \cdot_a J^\alpha_t\, h(t)$

3. ${}_{\cdot a}J_t^{\alpha}\,(t-a)^{\nu} = \frac{\Gamma \nu+1}{\Gamma \alpha+\nu+1}(t-a)^{(\alpha+\nu)}$

1.1.3. *Definition.* Riemann-Liouville Fractional Derivative:

If $f(t) \in C[a,b]$ and $a < t < b$ then

$$ {}_0D_t^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)}\frac{d}{dt}\int_a^t \frac{f(\tau)}{(t-\tau)^{\alpha}}d\tau, \tag{1} $$

where $\alpha \in (0,1)$ is called the Riemann-Liouville fractional derivative of order α.

1.1.4. *Definition.* The Caputo fractional derivative $({}_{\cdot a}D_t^{\alpha})$ of $h(t)$ is defined as

$$ {}_{\cdot a}D_t^{\alpha}\, h(t) = \frac{1}{\Gamma n-\alpha}\int_a^t (t-\tau)^{n-\alpha-1} h^{(n)}\,(\tau)\, d\tau $$

For $n-1 < \alpha \leq n \quad n \in \mathbb{N}$

$t \geq a \geq 0$ and $h \in C_{-1}^{n}$

Some of the properties of Caputo fractional integral are as follows

If $n-1 < \alpha \geq n\;\; n \in \mathbb{N}$ and $h \in C_{\mu}^{n}$, $\mu \geq -1$ then

1. ${}_{\cdot a}D_t^{\alpha}\, {}_{\cdot a}J_t^{\alpha}\, h(t) = h(t)$

2. ${}_{\cdot a}D_t^{\alpha}\, {}_{\cdot a}J_t^{\alpha}\, h(t) = h(t) + \sum_{j=0}^{n-1} h^k(a)\frac{(t-a)^k}{k!}$

1.1.5. *Analysis of generalised Euler method [GEM].* Let's consider system of fractional order linear differential equations as in [28]

$$ D_a^{\alpha} y_i(t) = f(t, y_1(t),\, y_2(t),\, y_3(t), \ldots, y_n(t)) \qquad 0 < \alpha \leq 1, \qquad t > 0 \tag{2} $$

with initial conditions $y_i(0) = y_{i_0},\ for\ i = 1,\ 2,\ 3, \ldots n$

We have to find the solution in finite interval $[0,\ a]$. Particularly, in the prescribed method we will solve the system in $'k'$ subintervals of $[0,\ a]$by taking h as a width of each interval such that $h = a/k$ so that node of the interval will be $t_j = jh$ for $j = 0, 1, 2, 3, \ldots k$ Assume that $y_i(t),\ D_a^{\alpha} y_i(t),\ D_a^{2\alpha} y_i(t)\ for\ all\ i's$ are continuous on $[0,\ a]$

Now we can use the generalised Taylor series formula about t_0. for each value of t there is a value ζ_1 such that

$$y_i(t) = y_{i_0} + (D_a^{\alpha} y_i(t))(t_0) \frac{t^{\alpha}}{\Gamma(\alpha+1)} + \left(D_a^{2\alpha} y_i(t)\right)(\zeta_1) \frac{t^{2\alpha}}{\Gamma(2\alpha+1)} + \ldots \tag{3}$$

$$for\ all\ i = 1,\ 2,\ 3, \ldots n$$

Let's take $t_0 = 0$ that gives $t = h$ and so on. By substituting in 3, we get

$$y_i(t_0 + h) = y_i(t_0) + f(t_0, y_i(t_0)) \frac{h^{\alpha}}{\Gamma(\alpha+1)} + \left(D_a^{2\alpha} y_i(t_0)\right)(\zeta_1) \frac{h^{2\alpha}}{\Gamma(2\alpha+1)} + \ldots \tag{4}$$

By taking h sufficiently small, we get the free hand to eliminate the higher power terms from the series 4. The general formula for generalised Euler method (GEM) for $t_{j+1} = t_j + h\ for\ all\ j = 0,\ 1\ 2\ 3 \ldots k$ is

$$y_i(t_{j+1}) = y_i(t_j) + f(t_j, y_i(t_j)) \frac{h^{\alpha}}{\Gamma(\alpha+1)} \tag{5}$$

$for\ all\ i = 1, 2, \ldots n$

1.2. Fractional order mathematical model of tuberculosis with twin line treatment.

Tuberculosis being an air-borne disease is transmitted when droplets from infectious individuals are inhaled and reach the alveoli of the lung via nasal passages, respiratory tract and bronchi. On infection, the exposed individual may have a latent period having no symptoms or full blown symptoms (cough, fever, weight loss, etc.) as in active infection. The individual in this stage has a large amount of active TB bacteria in the body.

The risk of progression to TB disease is such that infected individuals shall develop TB if untreated. When infected, if TB treatment is inadequate or transmission is directly from an individual having drug resistant tuberculosis, the first line of treatment fails and the person may develop a multi-drug resistance TB (MDR-TB).Rarely extensively drug resistance TB (XDR-TB) develops wherein, the second line of treatment also fails.A third type of drug resistance TB referred to as totally drug resistant TB (XXDR-TB or TDR- TB) has been found.

In this study,we will first extend standard fractional order mathematical model for transmission of tuberculosis with twin line treatment of Mycobacterium tuberculosis in human host in which we have considered multi drug resistant(MDR) tuberculosis. To understand the dynamics of the disease, we have analysed the following system of fractional order ordinary differential equations which defines the model of Tuberculosis with drug resistant to two line treatment presuming population remains constant (N).

Assuming the following variables:

Sr. No.	Class	Description of class
1	S(t)	Susceptible individuals
2	E(t)	Exposed individuals
3	I(t)	Infected individuals
4	$R1(t)$	Resistance to first line of treatment
5	$R2(t)$	Resistance to second line of treatment
6	R(t)	Recovered individuals

It is clear that susceptible individuals $(S(t))$ with recruitment rate in population size N be 'a' may become infected $(I(t))$. Let the rates at which an individual shifts from susceptible individuals $(S(t))$ to exposed individuals $(E(t))$ be 'c',and exposed individuals $(E(t))$ to infected individual $(I(t))$ be 'f'. On infection, the person goes for first line of treatment $(R1(t))$ or second line of treatment $(R2(t))$ with resistance rates to treatment 'h' and 'k' respectively. After proper and adequate treatment, they shall shift to recovered class $(R(t))$. However, since there exist no permanent immunity to TB, the recovered can again be susceptible to the disease at rate 'd'. Considering the rates of disease roused mortality from class $I(t), R1(t), and\ R2(t)$ as

’g’, ’l’, and ’n’ respectively. Rate of natural death ’b’. The resistant classes $R1(t)$ and $R2(t)$ on convalescence move to recovered class $R(t)$ at the rate ’m’ and ’p’ respectively.

Thus parameters governing the model are as follows

Sr. No.	Class	Description of class
1	a	Recruitment rate in population to susceptible individuals
2	b	Rate of natural death
3	c	Rate at which susceptible individuals be exposed
4	d	Rate at which recovered individuals becomes susceptible again
5	f	Rate at which exposed individuals be infected
6	g	Rate of diseased roused mortality in I(t)
7	h	Resistance to first line of treatment
8	k	Resistance to second line of treatment
9	l	Rate of diseased roused mortality in R1(t)
10	m	Rate of recovery after first line of treatment
11	n	Rate of diseased roused mortality in R2(t)
12	p	Rate of recovery after second line of treatment

Now we will first extend standard fractional order mathematical model for transmission of tuberculosis with twin line treatment of mycobacterium tuberculosis in human host in which we have considered multi drug resistant(MDR) tuberculosis. To understand the dynamics of the disease, we have analysed the following system of fractional order ordinary differential equations which defines the model of tuberculosis with drug resistant to two line treatment presuming population remains constant (N).

$$ {}_0D_t^{\alpha}S(t) = aN - bs(t) - cS(t)I(t) + dR(t) \tag{6} $$

$$ {}_0D_t^{\alpha}E(t) = cS(t)I(t) - (b+f)E(t) \tag{7} $$

$$ {}_0D_t^{\alpha}I(t) = fE(t) - (b+g+h+k)I(t) \tag{8} $$

$$ {}_0D_t^{\alpha}R1(t) = hI(t) - (b+l+m)R1(t) \tag{9} $$

$$ {}_0D_t^{\alpha}R2(t) = kI(t) - (b+n+p)R2(t) \tag{10} $$

$$ {}_0D_t^{\alpha}R(t) = mR1(t) + pR2(t) - (b+d)R(t) \tag{11} $$

where α is real number such that $0 < \alpha \leq 1$.

1.2.1. *Non-negative solutions of mathematical model.* Denote $R_+^6 = \{X \in R_6 \, / X \geq 0\}$ and $X(t) = (S, E, I, R1, R2, R)$ .The following theorem and corollary prove the non negativity of the solution,

Theorem 1.1. *(Mean value theorem in the form of fractional order derivative)*[28], [29] *Let $f(t)$ and it's derivative of order α i.e. $D^{\alpha} f(t)$ are continuous in $C(0, a]$ for $0 < \alpha \leq 1$ then*

$$ f(t) = f(0_+) + \frac{t^{\alpha}}{\Gamma(\alpha)} (D^{\alpha} f)(\vartheta) \tag{12} $$

where $0 \leq \vartheta \leq t, \; \forall \, t \in (0, a]$.

Corollary 1.1.1. *Suppose that $f(t)$ and it's derivative of order α i.e. $D^{\alpha} f(t)$ are continuous in $C(0, a]$ for $0 < \alpha \leq 1$ then by 1.1, if $D^{\alpha} f(t) \geq 0$ for all $t \in (0, 1)$ then $f(t)$ is non decreasing and if $D^{\alpha} f(t) \leq 0$ for all $t \in (0, 1)$ then $f(t)$ is non increasing for all $t \in (0, 1)$.*

Theorem 1.2. [28] *Existence and uniqueness of solution of system of fractional order differential equations with initial conditions in $(0, \infty)$ Now, We show that R_+^6 is positive invariant domain as*

$$ {}_0D_t^{\alpha}S(t) = aN - bs(t) - cS(t)I(t) + dR(t) \geq 0 $$

$$ {}_0D_t^{\alpha}E(t) = cS(t)I(t) - (b+f)E(t) \geq 0 $$

$$ {}_0D_t^{\alpha}I(t) = fE(t) - (b+g+h+k)I(t) \geq 0 $$

$$ {}_0D_t^{\alpha}R1(t) = hI(t) - (b+l+m)R1(t) \geq 0 $$

$$ {}_0D_t^{\alpha}R2(t) = kI(t) - (b+n+p)R2(t) \geq 0 $$

$$ {}_0D_t^{\alpha}R(t) = mR1(t) + pR2(t) - (b+d)R(t) \geq 0 $$

where α is a real number such that $0 < \alpha \leq 1$

It is to be noted that by corollary 1.1.1, the solution will remain in R_+^6

1.2.2. *Equilibrium points and stability of mathematical model.* The equilibrium points of the integer order system [21], [22], [23], i. e. for $\alpha = 1$. To evaluate equilibrium points of the fractional order system 6 to 11 are $A_1 = \left(\frac{aN}{b}, 0, 0, 0, 0, 0\right)$ and epidemic equilibrium points are $A_2\left(\bar{S}, \bar{E}, \bar{I}, \bar{R}1, \bar{R}2, \bar{R}\right)$ are expressed as

$$\bar{S} = \frac{(b+f)(b+g+h+k)}{cf} \qquad \bar{E} = \frac{c\bar{S}(b+d)(aN-b\bar{S})}{(b+f)(c\bar{S}(b+d)-\rho)}$$

$$\bar{I} = \frac{(b+d)(aN-b\bar{S})}{c\bar{S}(b+d)-d} \qquad \bar{R}1 = \frac{h(b+d)(aN-b\bar{S})}{(b+l+m)(c\bar{S}(b+d)-\rho)}$$

$$\bar{R}2 = \frac{k(b+d)(aN-b\bar{S})}{(b+n+p)(c\bar{S}(b+d)-\rho)} \qquad \bar{R} = \frac{(aN-b\bar{S})\rho}{(c\bar{S}(b+d)-\rho)d}$$

$$where \qquad \rho = d\left(\frac{hm}{b+l+m} + \frac{pk}{b+n+p}\right)$$

The local asymptotic stability of the equilibrium points have sufficient condition as the Jacobian of matrix A_1 and A_2 having eigen values λ_i for $i = 1, 2, 3, 4, 5, 6$ such that $|arg.(\lambda_i)| \geq \alpha\,\frac{\pi}{2}$. These sufficient conditions extends the stability of fractional order system by taking an integer order (i. e. $\alpha = 1$).

1.3. Numerical results of mathematical model. We have solved fractional ordered mathematical model by using general Euler method(GEM). The graphical results for $\alpha = 1$ have been examined by taking initial conditions $S(0) = 1$, $E(0) = 2$, $I(0) = 1$, $R1(0) = 1$, $R2(0) = 1$, $R(0) = 1$. It has been observed that in this particular state, the results of the model matches exactly as [23]. In these graphical results, Susceptible population increases up the limit point and then takes steady state. The remaining classes of population decrease in various fashion and take constant value as time increases. This endorses that both first and second line of treatments are useful to control Mycobacterium tuberculosis. It has to be noted that the graph of Recovered individuals returns to zero under appropriate and effective treatment as time progresses .

Now we fix all parameters and initial conditions in the present model and numerical simulations of the model have been studied by varying order of fractional differential equations so that it interprets as change in varied classes. Thereby alteration in order produces a modification in nature of graph that can be investigated. The numerical solution for present fractional

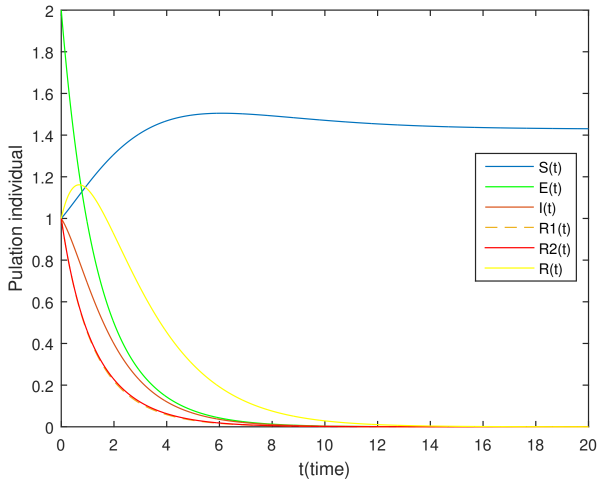
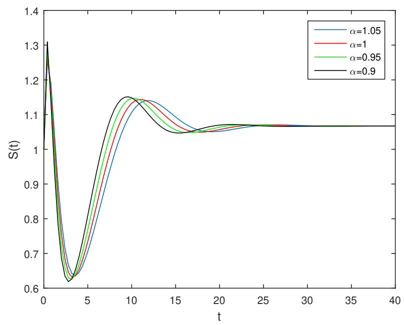


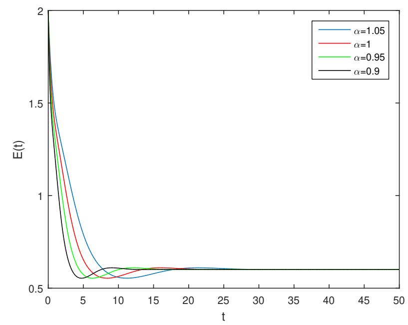
FIGURE 1. Mathematical model of $S(t)$, $E(t)$, $I(t)$, $R1(t)$, $R2(t)$, $R(t)$, at a=0.015, N=1000, b=0.7, c=0.398, d=0.4, e=1, f=0.0998, g=0.008, h=0.4, k=0.5, l=0.4, m=1, p=1.2, n=0.3 and $\alpha = 1$

order mathematical model has been illustrated by two dimensional graph in two types of initial conditions and values of parameters as in figure. 2 and figure 3. In figure 2(a), Susceptible population decrease until some period of time, thereafter there is an increment followed by steady state. Figure 2(b) gives the graph of Exposed population. It is to be noted that on account of first line treatment and second line treatment there occurs a decrement in number of Exposed individuals followed by constant value.These individuals emerge as part of Recovered individuals ($R(t)$). Figure 2(c) suggests an increase in Infected individuals upto certain level until the number comes down gradually to steady level. Figure2(d) and figure 2(e) on Resistant individuals to first line of treatment $R1(t)$ and to second line of treatment $R2(t)$ supports the assumption that line one treatment and line two treatments efficiently control the Mycobacterium tuberculosis. Whereas figure 2(f) exposes the considerable decrease in Recovered population ($R(t)$. This elicits the fact that immunity is temporary and individuals from class R(t) may shift to class S(t). It is observed that in all the cases,there is gradual variation in asymptotic nature of the classes as the order of derivatives changes.

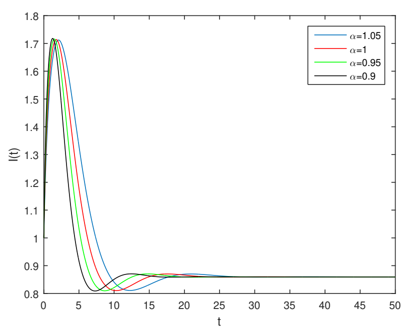
In figure 3, We have changed the initial conditions to observe therein the nature of classes of fractional order model keeping all parameters uniform. The model is set to equilibrium while varying the relative initial conditions as in [23]. This is to survey the alteration in numerical results by variation in initial conditions and comparing it with the previous case.



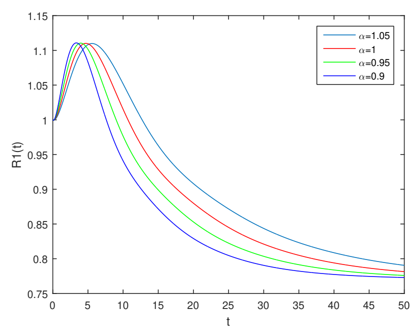
(a) 2D plot for $S(t)$



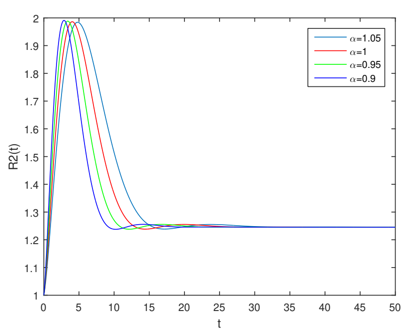
(b) 2D plot for $E(t)$



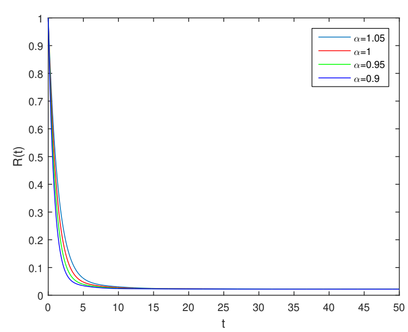
(c) 2D plot for $I(t)$



(d) 2D plot for $R1(t)$

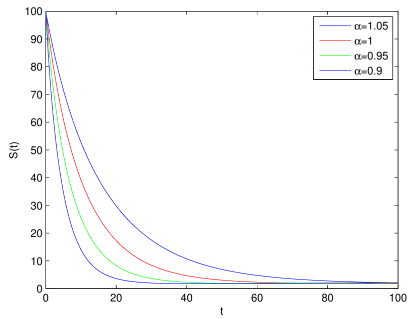


(e) 2D plot for $R2(t)$

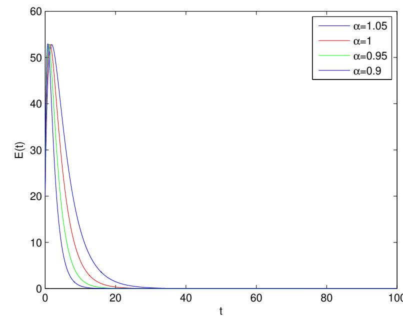


(f) 2D plot for $R(t)$

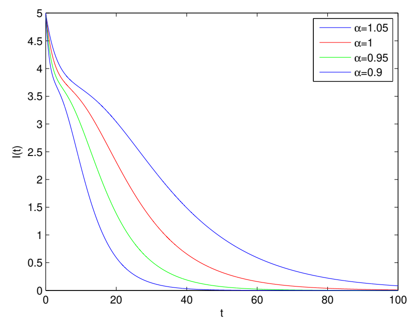
FIGURE 2. Fractional order mathematical model taking initial conditions $S(0) = 1$, $E(0) = 2$, $I(0) = 1$, $R1(0) = 1$, $R2(0) = 1$, $R(0) = 1$, at a=0.0007, N=1000, b=0.07, c=0.7, d=0.75, f=0.998, g=0.008, h=0.07, k=0.55, l=0.00004, m=0.008, p=0.0095, n=0.3 and $\alpha = 1.05, 1, 0.95, 0.9$



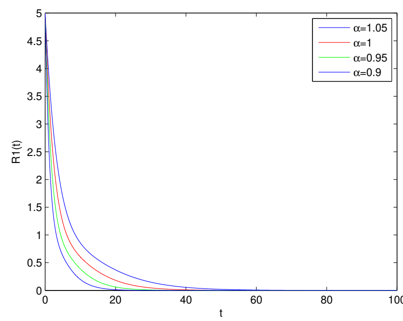
(a) 2D plot for $S(t)$



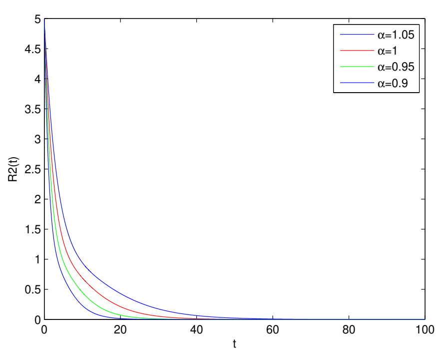
(b) 2D plot for $E(t)$



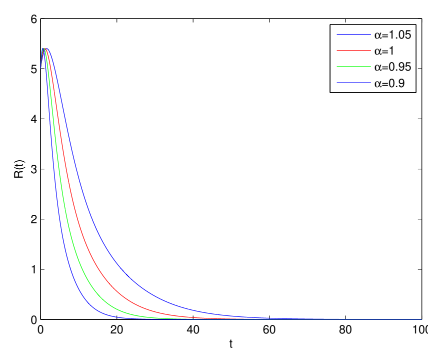
(c) 2D plot for $I(t)$



(d) 2D plot for $R1(t)$



(e) 2D plot for $R2(t)$



(f) 2D plot for $R(t)$

FIGURE 3. Fractional order mathematical model with initial conditions $S(0) = 100$, $E(0) = 20$, $I(0) = 5$, $R1(0) = 5$, $R2(0) = 5$, $R(0) = 5$, at a=0.0015, N=1000, b=0.7, c=0.398, d=0.4, f=0.008, g=0.008, h=0.4, k=0.5, l=0.4, m=1, p=1.2, n=0.3 and $\alpha = 1.05, 1, 0.95, 0.9$

Here in figure 3(a), Susceptible class shows decrement to steady state while exposed population shows a slight increase and then slowly decrease as in figure 3(b). The Infected population, class of population who are Resistant to line one and two treatment and Recovered individuals show reflection of current treatments' effect. Since this phenomenon is a natural phenomenon, we must consider possible variation in the population. The graphs for fractional order mathematical model reflect dynamic nature of the classes under same initial conditions and parameters.

2. CONCLUSION

In view of the current scenario, integrated patient centred care and prevention, early diagnosis, systematic screening, preventive treatment of patients with high risk and vaccinations against tuberculosis is imperative. Bold policies and supportive systems, political commitment with adequate resources, engagement of communities universal health coverage policies coupled with intensified research and innovation will be critical in ending the tuberculosis epidemic [15]. With the WHO coming up with the ”End TB” , strategy owing to the global TB epidemic that can cause serious public health consequences, the relevance of such models has greatly increased.

Fractional order mathematical model for tuberculosis considering two line treatment has been handled successfully by using generalised Euler method [GEM]. The results obtained by generalised Euler method [GEM] match with [23] for $\alpha = 1$. By taking suitable values of parameters and initial conditions for all classes, Fractional order mathematical model gives an identical configuration of graphs with proper distinctive orientation on account of change in order of derivatives.

Proposed fractional order mathematical model provides a useful insight into the transmission and further treatment of the disease for a variable population size and time varying state. It is to be noted that while applying the model practically we may not get exact results in the output of the integer order model,while a variety of possible illustrations may be obtained by changing order of system of ordinary differential equations in mathematical model. Further, it is firmly stated that fractional order mathematical model satisfies the hypothesis more accurately without changing initial conditions and values of parameters. It is predicted that the proposed model based on fractional calculus gives a wide scope to analyse the disease scientifically. It is clear that general Euler method [GEM] is a powerful, efficient and reliable method for investigation of fractional mathematical model.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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