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Research paper

Numerical behavior of a fractional order dynamical model of RNA silencing

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Abstract

A class of fractional-order differential models of RNA silencing with memory is presented in this paper. We also carry out a detailed analysis on the stability of equilibrium and we show that the model established in this paper possesses non-negative solutions. Numerical solutions are obtained using a predictor-corrector method to handle the fractional derivatives. The fractional derivatives are described in the Caputo sense. Numerical simulations are presented to illustrate the results. Also, the numerical simulations show that, modeling the phenomena of RNA silencing by fractional ordinary differential equations (FODE) has more advantages than classical integer-order modeling.

Keywords: *Fractional Calculus; RNA Silencing Fractional Order Model; Predictor-Corrector Method.*

1. Introduction

DNA and RNA perform various functions in humans. RNA is vital to cells because it broadcast information encoded in DNA to tiny organs within the cell [34]. There are different kinds of RNAs like microRNAs (miRNAs), the so called messenger RNAs (mRNAs), the double-stranded RNA (dsRNA) which is RNA with two complementary strands, and small interfering RNA (siRNA) which is a class of double-stranded RNA [8]. Cells use miRNAs to control the number of protein molecules made from mRNAs [33]. In the last few decades, RNA silencing has become a major focus of genome sciences around the world [14]. RNA silencing (also known as RNA interference) is a sequence-specific RNA degradation mechanism that occurs in a broad range of eukaryotic organisms [25]. It is based on an immune system that protects eukaryotes against viruses [7]. RNA silencing also plays a primary antiviral role in plants and in insects [30]. So, RNA silencing-based resistance has been an impressive tool that has been used to engineer resistant crops [25]. Mathematical modeling has become an essential tool to understand the dynamics of RNA silencing [14], [30]. Different models have been presented to describe the dynamics of RNA silencing, but these models have been restricted to integer order (delay) differential equations [22], [26]. Hence, we propose in this paper a system of FODE for modeling RNA silencing based on the integer order model in [8]. The major reason of using is that FODE are naturally related to systems with memory which exists in most biological systems [3], [4], [9], [15], [17]. Also, they are closely related to fractals, which are abundant in biological systems [13], [16], [19], [20], [21]. FODE are, at least, as stable as their integer order counterpart [1], [2], [10], [11], [23], [24]. The rest of the paper is organized as follows. A brief review of the fractional calculus theory is given in Section 2. A discussion about the equilibrium points and stability is presented in section 3 while in section 4, we discuss the existence and uniqueness of the presented fractional order model. Section 5 is devoted for the numerical solution of the presented model.

2. Model derivation

First of all, some definitions of fractional order integrals and derivatives [5], [6] are presented here. For the concept of fractional derivative, we will adopt Caputo's definition, which is a modification of the Riemann–Liouville definition and has the advantage of dealing properly with initial value problems.

Definition 2.1: *The fractional integral of order* $\alpha > 0$ *of a function* $f : \Re^+ \to \Re$ *is given by*

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

$$J^0 f(x) = f(x)$$

Definition 2.2: *Riemann–Liouville and Caputo fractional order derivatives of a continuous function* $f : \Re^+ \to \Re$ *is given respectively by*

$$\begin{aligned} D^{(\alpha)} f(x) &= D^m (J^{m-\alpha} f(x)), \\ D_*^{(\alpha)} f(x) &= J^{m-\alpha} (D^m f(x)) \end{aligned} \tag{2}$$

Where

$$m-1 < \alpha \le m, \quad m \in N$$

The definition of fractional derivative involves an integration which is non-local operator (as it is defined on an interval) so fractional derivative is a non-local operator [27], [29], [31], [32]. In other words, calculating time-fractional derivative of a function $f(t)$ at some time $t=t_1$ requires all the previous history, i.e. all $f(t)$ from $t=0$ to $t=t_1$.

Now we introduce fractional-order into the model of RNA silencing [8]. The new system is described by the following set of FODE:

$$\begin{aligned} D^{(\alpha)}(S) &= -aS + gC, \\ D^{(\alpha)}(R) &= anS - d_R R - bRM, \\ D^{(\alpha)}(C) &= bRM - (g + d_C)C, \\ D^{(\alpha)}(M) &= h - d_M M - bRM. \end{aligned} \tag{3}$$

Where $0 < \alpha \le 1$, $S(t), R(t), C(t)$ and $M(t)$ present the concentrations of the dsRNA، RISC, RISC–mRNA complex, and mRNA at time t, respectively. The parameters can be defined as follows:

a is the rate of dsRNA degradation by Dicer.

b is mass action rate constant for RISC-mRNA formation.

h is the rate of target mRNA synthesis.

g is the rate of dsRNA synthesis from RISC–mRNA complex.

d_M is the rate of nonspecific mRNA degradation.

d_R is the rate of RISC dissociation.

d_C is the Rate at which complex is destroyed.

n is the Number of siRNAs produced from one secondary dsRNA.

The initial conditions are $S(0)=S_0, R(0)=R_0, C(0)=C_0$, and $M(0)=M_0$ the basic reproductive number R_0 for dsRNA is presented in [8] as

$$R_0 = \frac{ngbh}{(g + d_C)(bh + d_R d_M)}.$$

If $R_0 < 1$, then the silencing reaction will take off.

3. Equilibrium points and stability

The authors in [8] deduced the equilibrium Points of the integer order system of the given model (3), i.e. when $\alpha = 1$ in (3). To evaluate the equilibrium points of the fractional-order system (3), let

$$D^{(\alpha)}(S) = 0, D^{(\alpha)}(R) = 0, D^{(\alpha)}(C) = 0, D^{(\alpha)}(M) = 0.$$

Model (1) has two steady states: $E_0 = (0,0,0,\frac{h}{d_M})$

and $E_1 = (S^*, R^*, C^*, M^*)$ where:

$$\begin{aligned} S^* &= \frac{g}{a} C^*, \\ R^* &= \frac{\beta C^*}{d_R}, \\ C^* &= \frac{\beta h - d_R d_M (g + d_C)}{\beta (d_C + g)}, \\ M^* &= \frac{(d_C + g) d_R}{\beta b}. \end{aligned}$$

Where $\beta = g(n-1) - d_C$.

The biological meaning of steady state E_0 is that, the silencing does not occur. The second steady state E_1 is biologically meaningful only if S^*, R^*, C^*, and M^* only are nonnegative [8], for which the condition $\beta h > (d_R d_M / b)(d_C + g)$ is both necessary and sufficient.

Also, a sufficient condition for the local asymptotic stability of the equilibrium points is that the eigenvalues λ_i of the Jacobian matrix of E_1 satisfy the condition $|arg(\lambda_i)| > \alpha \frac{\pi}{2}$ [2], [11], [23]. This confirms that fractional-order differential equations are, at least, as stable as their integer order counterpart.

4. Existence of uniformly stable solution

To prove the existence and uniqueness of solution for the system (3). Firstly we will recall the following lemma:

Lemma 4.1: *(Theorem 8.11, [12]) Let $0 < \alpha_j < 1$, for $j = 1,2,...,q$ and consider the initial value problem given by the multi-order fractional differential system (in Caputo sense)*

$$D^{\alpha} y_j = f_j(x, y_1(x), y_2(x), ..., y_q(x)), \quad j = 1,2,...,q \tag{4}$$

With initial condition

$$y_j(0) = p_j, \qquad j = 1,2,...,q.$$

Assume that the functions $f_j = [0,x] \times R^q \to R, j = 1,2,...,q$ are continuous and satisfy Lipschitz conditions with respect to all their arguments except for the first. Then the initial value problem (4) has a uniquely determined continuous solution. Since each $f_i = [0,T_1] \times R^4 \to R_+; i = 1,2,3,4$ is continuous.

To prove that the system (3) has a unique continuous solution, we want to show that each f_i satisfies the Lipschitz condition with respect to each of its argument except for the first.

Let

$$x_1(t) = S(t), x_2(t) = R(t), x_3(t) = C(t), x_4(t) = M(t)$$

$$D^{\alpha} x_1(t) = f_1(x_1(t), x_2(t), x_3(t), x_4(t)) \quad , t > 0 \quad and \quad x_1(0) = x_{01}, \tag{5}$$

$$D^{\alpha} x_2(t) = f_2(x_1(t), x_2(t), x_3(t), x_4(t)) \quad , t > 0 \quad and \quad x_2(0) = x_{02}, \tag{6}$$

$$D^{\alpha} x_3(t) = f_3(x_1(t), x_2(t), x_3(t), x_4(t)) \quad , t > 0 \quad and \quad x_3(0) = x_{03}, \tag{7}$$

$$D^{\alpha} x_4(t) = f_4(x_1(t), x_2(t), x_3(t), x_4(t)) \quad , t > 0 \quad and \quad x_4(0) = x_{04}, \tag{8}$$

Let $D = \{ x_1, x_2, x_3, x_4 \in R : |x_i(t)| \le r, t \in [0,T], i = 1,2,3,4 \}$,

The function f_i satisfy the Lipschitz condition on R_+^4 if

$$|f_i(S_1, R_1, C_1, M_1) - f_i(S_2, R_2, C_2, M_2)| \le \eta(|S_1 - S_2| +$$

$$|R_1 - R_2| + |C_1 - C_2| + |M_1 - M_2|$$

Where η is the Lipschitz constant. Then on D we have

$$\left| \frac{\partial}{\partial x_j} f_i(x_1, x_2, x_3, x_4) \right| \le \eta_n, \forall i, j = 1,2,3,4, and\, n = 1,2,3,...16$$

This implies that each of the four functions f_1, f_2, f_3, f_4 satisfies the Lipschitz condition with respect to the four arguments x_1, x_2, x_3, x_4 and then each of the four functions f_1, f_2, f_3, f_4 is absolutely continuous with respect to the four arguments x_1, x_2, x_3, x_4.

Consider the following initial value problem which represents the fractional-order RNA silencing (3)

Definition 4.1: *By a solution of the fractional –order RNA silencing (5), (6), (7), and (8) which is a column vector*

$$X(T)=(x_1(t),x_2(t),x_3(t),x_4(t))^{\tau},\ x_1,x_2,x_3,x_4$$

And $x_4 \in C[0,T], T<\infty$ where $C[0,T]$ the class of continuous functions defined on the interval $[0,T]$ and τ denotes the transpose of the matrix [18].

Theorem 4.1: *The fractional order model which describes a vector-borne plant disease model (5), (6), (7), and (8) has a unique uniformly Lyapunov stable solution [18].*

Proof: Write the model 5, 6, 7 and 8 in the matrix form

$$D^{\alpha}X(t)=F(X(t)), t>0 \text{ and } X(0)=x_0 \text{ where}$$

$$X(t)=(x_1(t),x_2(t),x_3(t),x_4(t))^{\tau}, F(X(t))=(f_1,f_2,f_3,f_4)^{\tau}$$

By applying Theorem 2.1 [18], we deduce that the fractional order RNA silencing system (5), (6), (7), and (8) has a unique solution. Also by Theorem 3.2 [18] this solution is uniformly Lyapunov stable.

5. Numerical simulation and discussion

In this section, predictor-corrector method is applied to get numerical solutions of the system (1). The values of the parameters are considered as in [8] as follows:

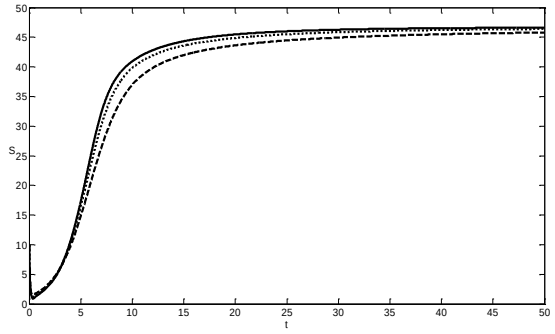
$$a=10, b=0.001, h=1000, g=1, d_M=1, d_R=0.1, d_C=1, n=5.$$

The initial conditions are:

$M(0)=1000, R(0)=0, C(0)=0, S(0)=10$ (Fig. 1 and Fig. 2) or $S(0)=1000$ (Fig. 3).

By using these values of parameters, it is clear that $R_0>1$. It means that a small amount of dsRNA will be sufficient to trigger a silencing reaction in this case.

(A)



(B)

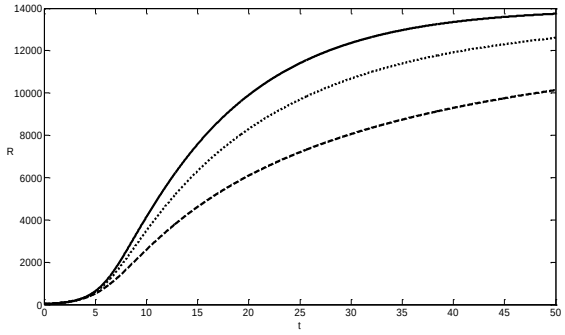
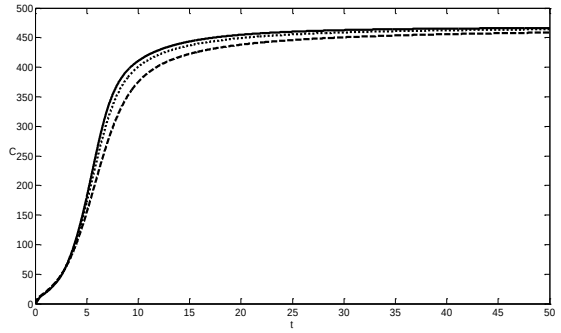


Fig. 1: A) the Concentration of the $S(t)$, B) the Concentration of the $R(t)$ for $\alpha=1$ (the Solid Line) $\alpha=0.9$ (the Dotted Line), $\alpha=0.75$ (The Dashed Line) in the 1st Case: t=Time, S=Concentration of dsRNA, R=Concentration of RISC.

(A)



(B)

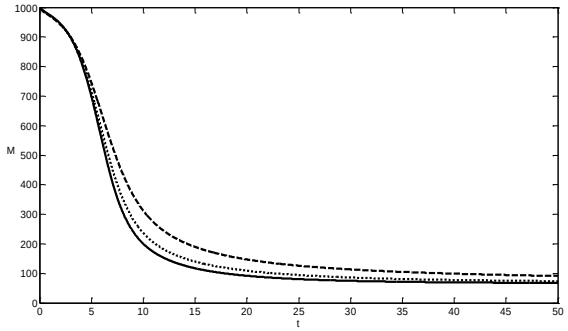
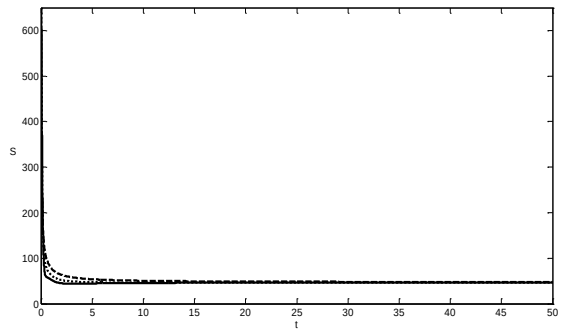


Fig. 2: A) the Concentration of the $C(t)$, B) the Concentration of $M(t)$ for $\alpha=1$ (the Solid Line) $\alpha=0.9$ (the Dotted Line), $\alpha=0.75$ (the Dashed Line) in the 1st Case, t=Time, C=Concentration of RISC-mRNA, M=Concentration of mRNA.

(A)



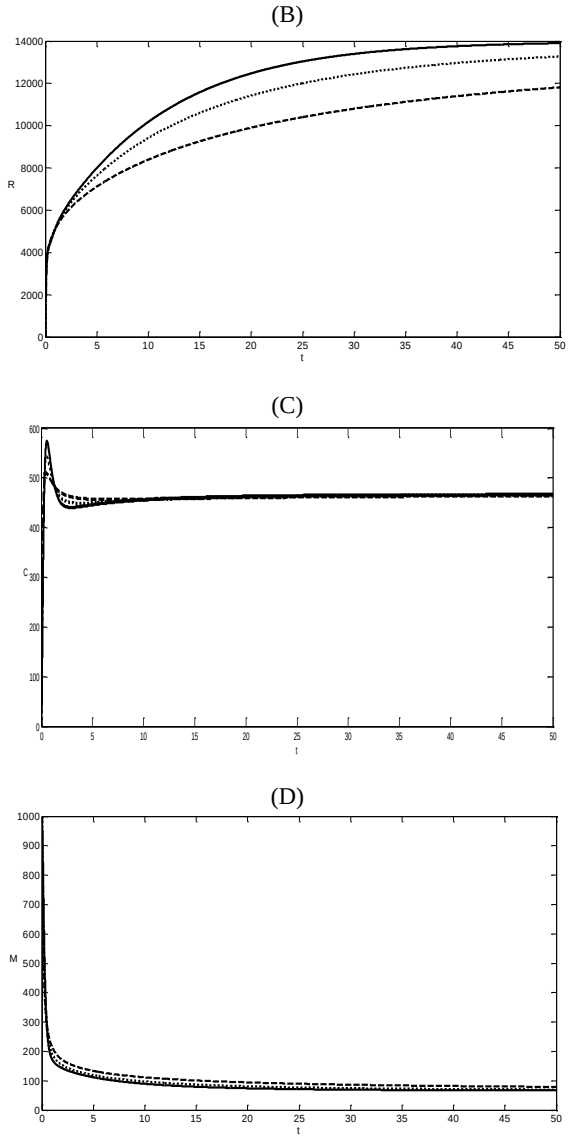


Fig. 3: (A) the Concentrations of the $S(t)$, (B) the Concentrations of the $R(t)$, (C) the Concentrations of the $C(t)$, (D) the Concentrations Of the $M(t)$ for $\alpha = 1$ (the Solid Line) $\alpha = 0.9$ (the Dotted Line), $\alpha = 0.75$ (The Dashed Line) in the 2nd Case, t=Time, S=Concentration of dsRNA, R=Concentration of RISC, C=Concentration of RISC-mRNA, M=Concentration Of mRNA.

6. Conclusion

In this paper, the numerical solution of fractional order model of RNA silencing is discussed. We show that, fractional-order differential equations are generalizations of integer-order differential equations. In Fig. 1, Fig. 2 and Fig.3, the same degree of silencing is obtained for both low and high initial dsRNA concentrations. When $\alpha \to 1$ the solution of the fractional model (3) $S_\alpha(t), R_\alpha(t), C_\alpha(t), M_\alpha(t)$ reduce to the standard solution $S(t), R(t), C(t), M(t)$, (see Fig.1, Fig.2 and Fig.3). In addition of proving the existence and uniqueness of a stable solution. Also the results show that the numerical simulations confirm the advantages of the numerical technique and using fractional-order differential models in biological systems over the differential equations with integer order.

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