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Fractional calculus model of GATA-switching for regulating the differentiation of a hematopoietic stem cell

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Abstract

This paper deals with the fractional order model for GATA-switching for regulating the differentiation of a hematopoietic stem cell. We give a detailed analysis for the asymptotic stability of the model. The Adams-Bashforth-Moulton algorithm has been used to solve and simulate the system of differential equations.

Keywords: GATA-switching; fractional order dynamic system; stability; numerical methods

1 Introduction

Hematopoiesis is a highly orchestrated developmental process that comprises various developmental stages of hematopoietic stem cells (HSCs). During development, the decision to leave the self-renewing state and selection of a differentiation pathway is regulated by a number of transcription factors. Among them, genes GATA-1 and PU.1 form a core negative feedback module to regulate the genetic switching between the cell fate choices of HSCs. The transcription factors PU.1 and GATA-1 are known to be important in the development of blood progenitor cells. Specifically they are thought to regulate the differentiation of progenitor cells into the granulocyte/macrophage lineage and the erythrocyte/megakaryocyte lineage. Although extensive experimental studies have revealed the mechanisms to regulate the expression of these two genes, it is still unclear how this simple module regulates the genetic switching [1, 2].

The notion of fractional calculus was anticipated by Leibniz, one of the founders of standard calculus, in a letter written in 1695. Recently great considerations have been made to the models of FDEs in different areas of research. The most essential property of these models is their non-local property which does not exist in the integer order differential operators. We mean by this property that the next state of a model depends not only upon its current state but also upon all of its historical states [3–9].

In this paper, we consider the fractional model for GATA-switching for regulating the differentiation of a hematopoietic stem cell. We give a detailed analysis for the asymptotic stability of the model. The Adams-Bashforth-Moulton algorithm has been used to solve and simulate the system of differential equations.

2 Description of the model

In [2], Tian and Smith-Miles proposed a mathematical model for the GATA-PU.1 regulatory network including genes GATA-1, GATA-2 and PU.1. Under some assumptions, they proposed the model to realize the genetic switching of the GATA-PU.1 regulatory network of the following form:

$$\begin{aligned} \frac{dx}{dt} &= \frac{a_1x + a_2y}{a_3 + a_4x + a_5y + a_6z + a_7xz} - k_1x, \\ \frac{dy}{dt} &= \frac{b_1y}{b_2 + b_3x + b_4y + b_5z + b_6yz} - k_2y, \\ \frac{dz}{dt} &= \frac{c_1z}{c_2 + c_3x + c_4y + c_5z + c_6xz + c_7yz} - k_3z, \end{aligned} \tag{2.1}$$

where x , y and z are the concentrations of TFs GATA-1, GATA-2 and PU.1, respectively, a_1 , b_1 and c_1 represent the expression rates of genes GATA-1, GATA-2 and PU.1 auto-regulated by itself, respectively, a_2 is the expression rate of gene GATA-1 regulated by TF GATA-2, k_1 , k_2 and k_3 are the degradation rates of TFs GATA-1, GATA-2 and PU.1, respectively. There are 23 rate constants in the proposed mathematical model (2.1). Now we introduce fractional order into the ODE model by (2.1). The new system is described by the following set of fractional order differential equations:

$$\begin{aligned} D_t^\alpha x &= \frac{a_1x + a_2y}{a_3 + a_4x + a_5y + a_6z + a_7xz} - k_1x, \\ D_t^\alpha y &= \frac{b_1y}{b_2 + b_3x + b_4y + b_5z + b_6yz} - k_2y, \\ D_t^\alpha z &= \frac{c_1z}{c_2 + c_3x + c_4y + c_5z + c_6xz + c_7yz} - k_3z, \end{aligned} \tag{2.2}$$

where α is a parameter describing the order of the fractional time derivative in the Caputo sense defined as

$$D_t^\alpha f(t) = \frac{1}{\Gamma(n - \alpha)} \int_0^t \frac{f^{(n)}(s)}{(t - s)^{\alpha - n + 1}} ds, \quad n = [\alpha] + 1.$$

3 Equilibrium points and stability

In the following, we discuss the stability of the commensurate fractional ordered dynamical system

$$D_t^\alpha x_i = f_i(x_1, x_2, x_3), \quad \alpha \in (0, 1), 1 \leq i \leq 3. \tag{3.1}$$

Let $E = (x_1^*, x_2^*, x_3^*)$ be an equilibrium point of system (3.1) and $x_i = x_i^* + \eta_i$, where η_i is a small disturbance from a fixed point. Then

$$\begin{aligned} D_t^\alpha \eta_i &= D_t^\alpha x_i \\ &= f_i(x_1^* + \eta_1, x_2^* + \eta_2, x_3^* + \eta_3) \\ &\approx \eta_1 \frac{\partial f_i(E)}{\partial x_1} + \eta_2 \frac{\partial f_i(E)}{\partial x_2} + \eta_3 \frac{\partial f_i(E)}{\partial x_3}. \end{aligned} \tag{3.2}$$

System (3.2) can be written as

$$D_t^\alpha \eta = J\eta, \tag{3.3}$$

where $\eta = (\eta_1, \eta_2, \eta_3)^T$ and J is the Jacobian matrix evaluated at the equilibrium points. Using Matignon's results [10], it follows that the linear autonomous system (3.3) is asymptotically stable if $|\arg(\lambda)| > \frac{\alpha\pi}{2}$ is satisfied for all eigenvalues of matrix J at the equilibrium point $E = (x_1^*, x_2^*, x_3^*)$.

If $p(x) = x^3 + a_1x^2 + a_2x + a_3$, let $D(p)$ denote the discriminant of a polynomial $p(x)$, then

$$D(p) = - \begin{vmatrix} 1 & a_1 & a_2 & a_3 & 0 \\ 0 & 1 & a_1 & a_2 & a_3 \\ 3 & 2a_1 & a_2 & 0 & 0 \\ 0 & 3 & a_1 & a_2 & 0 \\ 0 & 0 & 3 & 2a_1 & a_2 \end{vmatrix} = 18a_1a_2a_3 + (a_1a_2)^2 - 4a_3a_1^3 - 4a_2^3 - 27a_3^2.$$

Following [4, 10–13], we have the proposition.

Proposition *One assumes that E_1 exists in R_+^3 .*

- (i) *If the discriminant of $p(x)$, $D(p)$ is positive and the Routh-Hurwitz conditions are satisfied, that is, $D(p) > 0$, $a_1 > 0$, $a_3 > 0$, $a_1a_2 > a_3$, then E_1 is locally asymptotically stable.*
- (ii) *If $D(p) < 0$, $a_1 > 0$, $a_2 > 0$, $a_1a_2 = a_3$, $\alpha \in [0, 1)$, then E_1 is locally asymptotically stable.*
- (iii) *If $D(p) < 0$, $a_1 < 0$, $a_2 < 0$, $\alpha > \frac{2}{3}$, then E_1 is unstable.*
- (iv) *The necessary condition for the equilibrium point E_1 to be locally asymptotically stable is $a_3 > 0$.*

One can verify that system (2.2) has the following three steady states:

$$E_0 = (0, 0, 0), \quad E_1 = \left(\frac{a_1 - k_1a_3}{k_1a_3}, 0, 0 \right), \quad E_3 = \left(0, 0, \frac{c_1 - k_3c_2}{k_3c_5} \right).$$

Theorem 3.1 *The trivial steady state E_0 is locally asymptotically stable if the following conditions are satisfied: $\frac{a_1}{a_3} < k_1$, $\frac{b_1}{b_2} < k_2$, $\frac{c_1}{c_2} < k_3$.*

Proof The trivial steady state E_0 is locally asymptotically stable if all the eigenvalues λ_i , $i = 1, 2, 3$, of the Jacobian matrix $J(E_0)$ satisfy the following condition [9, 14–16]:

$$|\arg(\lambda_i)| > \frac{\alpha\pi}{2}. \tag{3.4}$$

The Jacobian matrix $J(E_0)$ for the system given in (2.2) evaluated at the steady state E_0 is as follows:

$$J(E_0) = \begin{pmatrix} \frac{a_1}{a_3} - k_1 & \frac{a_2}{a_3} & 0 \\ 0 & \frac{b_1}{b_2} - k_2 & 0 \\ 0 & 0 & \frac{c_1}{c_2} - k_3 \end{pmatrix}.$$

The eigenvalues of the Jacobian matrix $J(E_0)$ are $\lambda_1 = \frac{a_1}{a_3} - k_1$, $\lambda_2 = \frac{b_1}{b_2} - k_2$, $\lambda_3 = \frac{c_1}{c_2} - k_3$.

Hence E_0 is locally asymptotically stable if the following conditions are satisfied: $\frac{a_1}{a_3} < k_1$, $\frac{b_1}{b_2} < k_2$, $\frac{c_1}{c_2} < k_3$. \square

Theorem 3.2 *The steady state E_1 with high expression level of gene GATA-1 is stable if the following conditions are satisfied:*

$$\frac{a_3 k_1}{a_1} < 1, \quad \frac{a_4 k_1 b_1}{a_4 k_1 b_2 + b_3(a_1 - a_3 k_1)} < k_2, \quad \frac{a_4 k_1 c_1}{a_4 k_1 c_2 + c_3(a_1 - a_3 k_1)} < k_3.$$

Proof The Jacobian matrix of nonlinear system (2.2) for this steady state E_1 is

$$J(E_1) = \begin{pmatrix} k_1 \left(\frac{a_3 k_1 - a_1}{a_1} \right) & \frac{k_1(a_2 a_4 + a_5(-a_1 + a_3 k_1))}{a_1 a_4} & -\frac{(a_1 - a_3 k_1)(a_4 a_6 k_1 + a_7(a_1 - a_3 k_1))}{a_1 a_4^2} \\ 0 & \frac{a_4 k_1 b_1}{a_4 k_1 b_2 + b_3(a_1 - a_3 k_1)} - k_2 & 0 \\ 0 & 0 & \frac{a_4 k_1 c_1}{a_4 k_1 c_2 + c_3(a_1 - a_3 k_1)} - k_3 \end{pmatrix}.$$

The three eigenvalues of the Jacobian matrix are:

$$\begin{aligned} \lambda_1 &= k_1 \left(\frac{a_3 k_1 - a_1}{a_1} \right), \\ \lambda_2 &= \frac{a_4 k_1 b_1}{a_4 k_1 b_2 + b_3(a_1 - a_3 k_1)} - k_2, \\ \lambda_3 &= \frac{a_4 k_1 c_1}{a_4 k_1 c_2 + c_3(a_1 - a_3 k_1)} - k_3. \end{aligned}$$

Theorem 1 of [2] has the same results for the integer order model (and has some misprints in the first condition). They claimed that λ_1 is negative, but the sign of λ_1 depends on the quantity $\left(\frac{a_3 k_1 - a_1}{a_1}\right)$. \square

Theorem 3.3 *The steady state E_3 with high expression level of gene PU.1 is stable if the following conditions are satisfied:*

$$\frac{c_2 k_3}{c_1} < 1, \quad \frac{a_1 c_5 k_3}{a_3 c_5 k_3 + a_6(c_1 - c_2 k_3)} < k_1, \quad \frac{b_1 c_5 k_3}{c_5 k_3 b_2 + b_5(c_1 - c_2 k_3)} < k_2.$$

Proof The Jacobian matrix of nonlinear system (2.1) for this steady state E_3 is

$$J(E_3) = \begin{pmatrix} \frac{a_1 c_5 k_3}{a_3 c_5 k_3 + a_6(c_1 - c_2 k_3)} - k_1 & \frac{a_2 c_5 k_3}{a_3 c_5 k_3 + a_6(c_1 - c_2 k_3)} & 0 \\ 0 & \frac{b_1 c_5 k_3}{c_5 k_3 b_2 + b_5(c_1 - c_2 k_3)} - k_2 & 0 \\ -\frac{(c_1 - c_2 k_3)(c_3 c_5 k_3 + c_6(c_1 - c_2 k_3))}{c_1 c_5^2} & -\frac{(c_1 - c_2 k_3)(c_4 c_5 k_3 + c_7(c_1 - c_2 k_3))}{c_1 c_5^2} & k_3 \left(\frac{c_2 k_3 - c_1}{c_1} \right) \end{pmatrix}.$$

The three eigenvalues of the Jacobian matrix are:

$$\begin{aligned} \lambda_1 &= k_3 \left(\frac{c_2 k_3}{c_1} - 1 \right), \\ \lambda_2 &= \frac{a_1 c_5 k_3}{a_3 c_5 k_3 + a_6(c_1 - c_2 k_3)} - k_1, \\ \lambda_3 &= \frac{b_1 c_5 k_3}{c_5 k_3 b_2 + b_5(c_1 - c_2 k_3)} - k_2. \end{aligned}$$

Table 1 The equilibrium points and the eigenvalues of the system

Equilibrium point	Eigenvalues
$E_4 = (659.2192685, 0, 0)$	$\{-0.909177, 0.435225, -0.234831\}$
$E_5 = (322.17148, 1.36478, 0)$	$\{-0.909177, 0.435225, -0.234831\}$
$E_6 = (3.812275, 13.9889, 0)$	$\{-1.37375, 0.948121, -0.560537\}$
$E_7 = (15.99, 2.19 \times 10^{-12}, 1.153)$	$\{26.522544, -0.929339, 0.0585563\}$
$E_8 = (3.6329, 13.065, 1.17301)$	$\{-1.38529, -0.591193, -0.203561\}$
$E_9 = (0.00054, 0.0042, 241.024)$	$\{-0.622622, -0.345295, 0.0472589\}$

Under the conditions of Theorem 3.3, we can conclude that steady state E_3 with high expression level of gene PU.1 is stable. \square

Following [2], parameters of the model are as follows:

$$(a_1, a_2, a_3, a_4, a_5, a_6, a_7) = (731.7409, 856.1247, 1, 1.6, 398.9719, 44.8982, 53.0),$$

$$(b_1, b_2, b_3, b_4, b_5, b_6) = (18470.6419, 1, 37.3615, 942.1939, 55.0375, 53.0),$$

$$(c_1, c_2, c_3, c_4, c_5, c_6, c_7) = (12391.1968, 1, 710.4490, 522.4385, 170.0, 1700.0, 1700.0)$$

and

$$(k_1, k_2, k_3) = (0.6931, 1.3863, 0.2888).$$

Using these parameters, one can verify that the system has six nontrivial equilibrium points. The equilibrium points and the eigenvalues of corresponding Jacobian matrix are given in Table 1.

It is clear from the table, that the equilibrium point E_8 is a stable point. The other points are unstable.

4 Numerical methods and simulations

Since most of the fractional-order differential equations do not have exact analytic solutions, approximation and numerical techniques must be used. Several analytical and numerical methods have been proposed to solve the fractional-order differential equations. For numerical solutions of system (2.2), one can use the generalized Adams-Bashforth-Moulton method. To give the approximate solution by means of this algorithm, consider the following nonlinear fractional differential equation [17]:

$$D_t^\alpha y(t) = f(t, y(t)), \quad 0 \leq t \leq T,$$

$$y^{(k)}(0) = y_0^k, \quad k = 0, 1, 2, \dots, m - 1, \text{ where } m = [\alpha].$$

This equation is equivalent to the Volterra integral equation

$$y(t) = \sum_{k=0}^{m-1} y_0^{(k)} \frac{t^k}{k!} + \frac{1}{\Gamma(\alpha)} \int_0^t (t-s)^{\alpha-1} f(s, y(s)) ds. \tag{4.1}$$

Diethelm *et al.* used the predictor-correctors scheme [11, 12] based on the Adams-Bashforth-Moulton algorithm to integrate Eq. (4.1). By applying this scheme to the fractional-order model GATA-switching for regulating the differentiation of a hematopoietic stem

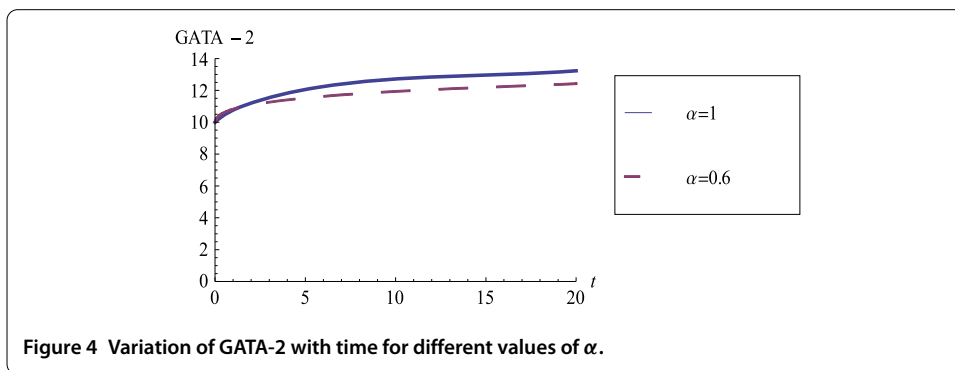
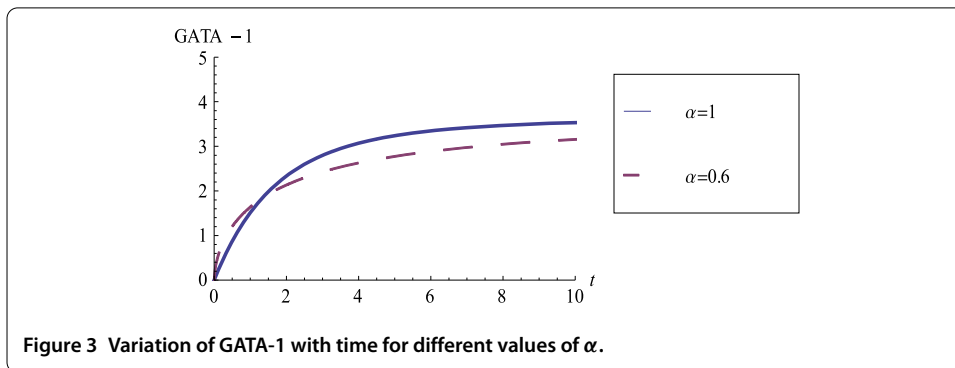
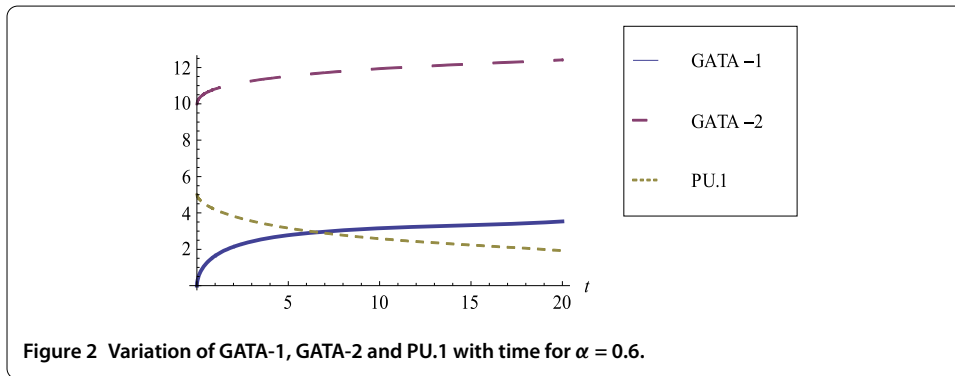
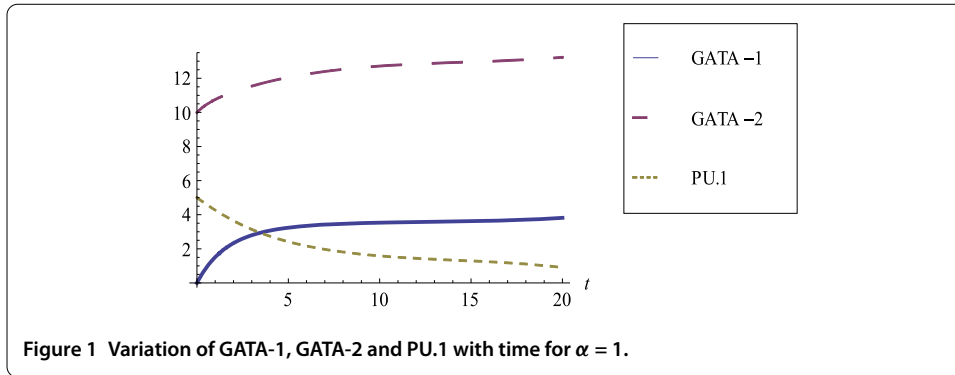
cell, and setting $h = \frac{T}{N}$, $t_n = nh$, $n = 0, 1, 2, \dots, N \in \mathbb{Z}^+$, Eq. (4.1) can be discretized as follows [17]:

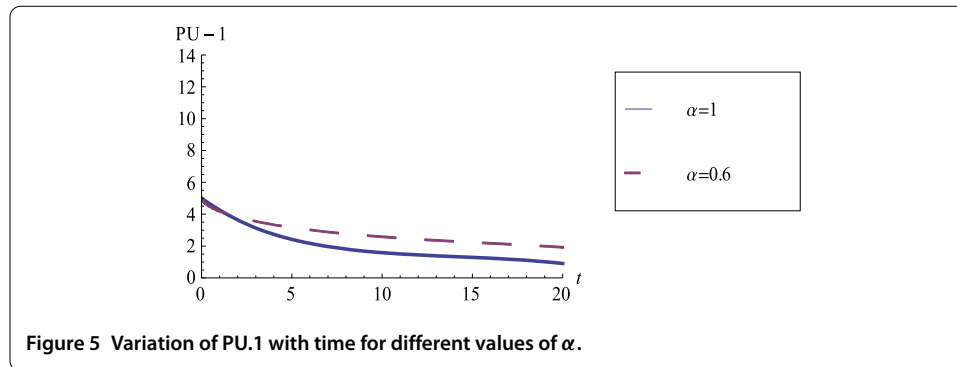
$$\begin{aligned}
 x_{n+1} &= x_0 + \frac{h^\alpha}{\Gamma(\alpha + 2)} \left(\frac{a_1 x_{n+1}^p + a_2 y_{n+1}^p}{a_3 + a_4 x_{n+1}^p + a_5 y_{n+1}^p + a_6 z_{n+1}^p + a_7 x_{n+1}^p z_{n+1}^p} - k_1 x_{n+1}^p \right) \\
 &\quad + \frac{h^\alpha}{\Gamma(\alpha + 2)} \sum_{j=0}^n a_{j,n+1} \left(\frac{a_1 x_j + a_2 y_j}{a_3 + a_4 x_j + a_5 y_j + a_6 z_j + a_7 x_j z_j} - k_1 x_j \right), \\
 y_{n+1} &= y_0 + \frac{h^\alpha}{\Gamma(\alpha + 2)} \left(\frac{b_1 y_{n+1}^p}{b_2 + b_3 x_{n+1}^p + b_4 y_{n+1}^p + b_5 z_{n+1}^p + b_6 y_{n+1}^p z_{n+1}^p} - k_2 y_{n+1}^p \right) \\
 &\quad + \frac{h^\alpha}{\Gamma(\alpha + 2)} \sum_{j=0}^n a_{j,n+1} \left(\frac{b_1 y_j}{b_2 + b_3 x_j + b_4 y_j + b_5 z_j + b_6 y_j z_j} - k_2 y_j \right), \\
 z_{n+1} &= z_0 + \frac{h^\alpha}{\Gamma(\alpha + 2)} \left(\frac{c_1 z_{n+1}^p}{c_2 + c_3 x_{n+1}^p + c_4 y_{n+1}^p + c_5 z_{n+1}^p + c_6 x_{n+1}^p z_{n+1}^p + c_7 y_{n+1}^p z_{n+1}^p} - k_3 z_{n+1}^p \right) \\
 &\quad + \frac{h^\alpha}{\Gamma(\alpha + 2)} \sum_{j=0}^n a_{j,n+1} \left(\frac{c_1 z_j}{c_2 + c_3 x_j + c_4 y_j + c_5 z_j + c_6 x_j z_j + c_7 y_j z_j} - k_3 z_j \right),
 \end{aligned}$$

where

$$\begin{aligned}
 x_{n+1}^p &= x_0 + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n b_{j,n+1} \left(\frac{a_1 x_j + a_2 y_j}{a_3 + a_4 x_j + a_5 y_j + a_6 z_j + a_7 x_j z_j} - k_1 x_j \right), \\
 y_{n+1}^p &= y_0 + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n b_{j,n+1} \left(\frac{b_1 y_j}{b_2 + b_3 x_j + b_4 y_j + b_5 z_j + b_6 y_j z_j} - k_2 y_j \right), \\
 z_{n+1}^p &= z_0 + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n b_{j,n+1} \left(\frac{c_1 z_j}{c_2 + c_3 x_j + c_4 y_j + c_5 z_j + c_6 x_j z_j + c_7 y_j z_j} - k_3 z_j \right), \\
 a_{j,n+1} &= \begin{cases} n^{\alpha+1} - (n - \alpha)(n + 1), & j = 0, \\ (n - j + 2)^{\alpha+1} + (n - j)^{\alpha+1} - 2(n - j + 1)^{\alpha+1}, & 1 \leq j \leq n, \\ 1, & j = n + 1, \end{cases} \\
 b_{j,n+1} &= \frac{h^\alpha}{\alpha} ((n - j + 1)^\alpha - (n - j)^\alpha), \quad 0 \leq j \leq n.
 \end{aligned}$$

Figure 1 illustrates the distribution of the concentration GATA-1, GATA-2 and PU.1 with time. It is observed that GATA-1 is increasing with time and reaches its equilibrium point (3.6329), while PU.1 seems to decrease with time and reaches its steady state (1.17301). On the other hand, the GATA-2 gene seems to decrease with time and reach its equilibrium point (13.065). Figure 2 indicates the behavior of the approximate solutions for system (2.2) obtained for the values of $\alpha = 0.6$. In Figure 3, the variation of GATA-1 vs. time t is shown for different values of $\alpha = 1, 0.6$ by fixing other parameters. Figure 4 depicts GATA-2 vs. time t . Figure 4 shows similar variations of GATA-1 with various values of α . In Figure 5, the variation of PU.1 vs. time t is shown for different values of α that increase, α decreases with the concentration of PU.1 gene.





5 Conclusions

In this paper, we consider the fractional model for GATA-switching for regulating the differentiation of a hematopoietic stem cell. We have obtained a stability condition for equilibrium points. We have also given a numerical example and verified our results. 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. One also needs to mention that when dealing with real life problems, the order of the system can be determined by using the collected data.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed equally to the writing of this paper. All authors read and approved the final manuscript.

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