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The Fractional-Order Differential Equation Model of Psoriatic Pathogenesis: A Mathematical Study

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Abstract

Psoriasis is an autoimmune prevalent chronic skin disease discriminated by T-Cells mediated hyperproliferation of epidermal Keratinocytes. In this research article, we extend the research work [1] and consider a mathematical model for Psoriasis, involving a set of differential equations with T-Cells, Dendritic Cells (DCs) and epidermal Keratinocytes. We introduce here the fractional-order differential equations into the mathematical model of Psoriasis with effect of Cytokines release to observe the impact of it on the cell-biological system. Analytical study on the basis of stability analysis with fractional derivative is furnished. Moreover numerical simulation through non-standard finite difference methods has been applied for solving the fractional-order differential equations to support the analytical results. We have established that the effect of Cytokine network through exploring the suppressed memory, the inherited property of the system dynamics, in our mathematical model that contributes a greater impact for reducing the Keratinocyte cell population, causes the disease Psoriasis.

AMS Subject Classification: 34A08; 34K37; 37N25; 92B05; 92C37.

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1 Introduction

In present time, Psoriasis is measured as a frequent widespread skin disease, which is differentiated by T-Cells arbitrated hyperproliferation of Keratinocytes [2]. About 125 million population are affected worldwide by the severity of the disease. T-Cell population as well as Dendritic and Keratinocyte Cell populations take vital accountability for creating the disease Psoriasis. The inflammatory Cytokines, such as Tumour Necrosis Factor (TNF) are anticipated to assist an important pathogenic function in the disease [3]. Psoriasis can be observed in several forms in different episodes. Firstly, it is considered as a biochemical disturbance. Next it is measured as a Keratinocytes arbitrated condition. Finally, the immunological genetics related chaos is extremely relevant to this disease. Interleukin-2 (IL-2) is viewed as the powerful growth aspect of T-Cells. Cytokines of Th-1 types are produced by stimulated T-Cells in Psoriatic lesions. By limiting the excess production of Th-1 type Cytokines, Psoriatic disorder may be concentrated with Th-2 type Cytokines [4]. Roy and Bhadra [5] have studied the comparative analysis with respect to suppression taking place on T-Cells and DCs individually and have obtained a better result for the suppression on DCs rather than the other one. Roy and Datta have again furnished the research work [5], introducing Cytokines release with suppression taking place at DCs on the cell-biological system. In the domain of applied mathematics essentially in mathematical biology, fractional differential equation has presently come forward as an innovative avenue for better understanding of the disease dynamics. Further, this type of differential equation is also measured as a substitute model to mainly nonlinear differential equations [6]. Continuous and integrable functions in spaces with fractional order for the existence of solutions are also analyzed [7].

Leibnitz, one of the originators of calculus, predicted the concept of fractional calculus in a letter, which was written in 1695 [8]. In current age, fractional calculus has been broadly used in several research areas because of its prospective appliances [9], [10]. Now a day, fractional calculus is useful to describe the existent procedures. Mathematical model with fractional-order of a human root dentin is extended by Petrovic, Spasic and Atanackovic [11]. Modeling of the activities for brainstem vestibule-oculomotor neurons through fractional-order differential equations (FODEs) has more benefits rather than classical integer-order modeling [12]. Fractals, which are generous in biological structures, are normally associated with fractional-order differential equations. Further, FODEs are very much correlated to memory arrangements, which exist in most of the biological phenomenon [13], [14], [15]. Again cell-biological system must keep a memory that has a hidden nature inherited in that structures [16]. Any cell-biological system can be enhanced by the stimulation of the memory and that memory is actually recognized by means of activation of the cell-signaling network [17].

Roy and Bhadra [18] have proposed a basic mathematical model of Psoriasis, where proliferation of Keratinocytes takes place jointly with excess nitric oxide creation, which is the originators for the Psoriatic scratches. Researchers are paying their concentration for formulating the mathematical model of Psoriasis [1], [19], [20], [21], [22], [23], [24],

where most of the model systems have been studied through integer-order differential equations. But fractional-order differential equations on the model system with Cytokines release have not yet been explored till now. There are two main reasons for taking a fractional-order system in place of integer-order system. Fractional-order differential equations are the overview of integer-order system and the errors, coming from the ignored parameters for constructing model in practical situation, are reduced by using fractional-order differential equations [25]. Too much production of Keratinocyte cell population, generated by Cytokines release that is activated through interaction between T-Cells and Keratinocytes occurs through memory system of that cell population. Now for consideration of fractional-order differential equations that are nearly associated to memory managements, regulate the neural elements such that Psoriasis can be checked. On that outlook through cell-signaling communication, we are trying to stimulate the memory induced cell-biological system by means of the fractional-order method in the research work [1], so that the over production of Keratinocytes can be controlled.

2 The Basic Assumptions and Formulation of the Mathematical Model

Of all the definitions for the fractional derivatives [9], [10], the Riemann-Liouville definition is the well-recognized. The definition of Riemann-Liouville fractional derivative of order α is described as

$$D^{\alpha}_{0_+} g(t) = \frac{1}{\Gamma(n-\alpha)}\Big(\frac{d}{dt}\Big)^n \int_0^t \frac{g(s)}{(t-s)^{\alpha-n+1}}\, ds, \quad n = [\alpha]+1. \tag{2.1}$$

Here, we denote Γ as the gamma function and n as an integer. Further, another definition is initiated by Caputo. In fact, definition explained by Caputo is a kind of regularization of the Riemann-Liouville definition of fractional derivative.

$$D^{\alpha}_{t} g(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{g^{(n)}(s)}{(t-s)^{\alpha-n+1}}\, ds. \tag{2.2}$$

As Caputo definition is broadly applied in real existent relevance, it is identified as the foremost general definition. The initial conditions of the Caputo derivative for the differential equations with the fractional-order are in similar type as the differential equations with the integer-order. Next, the definition of Grunwald-Letnikov (GL) for fractional derivative is defined as follows:

$$D^{\alpha}_{t} g(t) = \lim_{h\to 0} h^{-\alpha} \sum_{p=0}^{[(t-\alpha)/h]} (-1)^p \binom{\alpha}{p} g(t-ph). \tag{2.3}$$

After some simplifications, the GL definition can be transformed into:

$$D^{\alpha}_{t} x(t_q) = h^{-\alpha} \sum_{p=0}^{q} {v_p}^{(\alpha)} x_{q-p}. \tag{2.4}$$

Here, we indicate h as the time step and v_p^α as the Grunwald-Letnikov coefficients, described as $v_p^\alpha = (1-(1+\alpha)/p)v_{p-1}^\alpha$, $p = 0,1,2,...$ and $v_0^\alpha = h^{-\alpha}$ [8].

Roy et al., (2012) [1] has introduced the mathematical model of Psoriasis, integrating Cytokines release into the cell-biological system, in occurrence of suppression taking place on Dendritic Cells with the drug efficacy parameter. There are three distinct groups of cell population, incorporated into the model system: $l(t)$ is T-Cell population, $m(t)$ is Dendritic Cell population and $k(t)$ is Keratinocyte population at time t. On that basis the mathematical model, initiated by Roy et al., (2012) [1] is as follows:

$$\begin{aligned} \frac{dl}{dt} &= a - \delta lm - \gamma_1 lk - \mu l, \\ \frac{dm}{dt} &= b(1-u) - \beta lm - \mu' m, \\ \frac{dk}{dt} &= \beta lm + \delta lm + \gamma_2 lk - \lambda k. \end{aligned} \tag{2.5}$$

Here a and b are the constant rates of accumulation of T-Cells and Dendritic Cells respectively. The rate of activation of T-Cells by DCs is δ and β is the activation rate of DCs by T-Cells. Also γ_1 is the rate of activation of Keratinocytes due to T-Cells mediated Cytokines and growth of Keratinocytes takes place at a rate γ_2. Further μ is the per capita removal rate of T-Cells and the per capita removal rates of Dendritic Cells and epidermal Keratinocytes are μ' and λ respectively. Also u is the drug efficiency parameter with time in the limits $0 \le u < 1$.

Now a day immense attentions have been concentrated towards the models of fractional-order equations in several research fields. The nonlocal characteristics, which do not exist with the integer-order differential operators, are the significant property of these type of models. It is understood by this feature that, the subsequent phase of the model not only depends upon it's present state but also upon all of it's chronological situations [8]. Now, we integrate fractional-order from the ordinary differential model equation of Roy et al., [1]. With the following set of fractional-order differential equations, the modified model system is furnished as follows:

$$\begin{aligned} D^\alpha l &= a - \delta lm - \gamma_1 lk - \mu l, \\ D^\alpha m &= b(1-u) - \beta lm - \mu' m, \\ D^\alpha k &= \beta lm + \delta lm + \gamma_2 lk - \lambda k, \end{aligned} \tag{2.6}$$

where Caputo fractional derivative is denoted by D^α. All the parameters, introduced into the model system, are considered as non-negative. Moreover it can be proved that all the state variables of the model equations are non-negative for time $t \ge 0$ [26].

3 Theoretical Study of the Model System

To find the equilibrium point, we assume

$$D^\alpha l = 0, D^\alpha m = 0 \text{ and} D^\alpha k = 0.$$

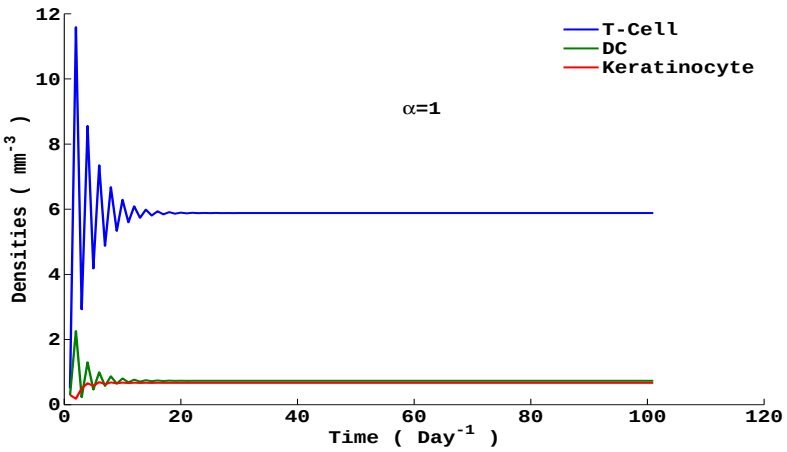

Figure 1. Population densities of T-Cells (l), Dendritic Cells (m) and Keratinocytes (k) are plotted as a function of time for the values of parameters are as in Table.

There is unique equilibrium (interior equilibrium) point $E^*(l^*, m^*, k^*)$ of the model equation (2.6), where $E^*(l^*, m^*, k^*)$ satisfies $m^* = \frac{b(1-u)}{\beta l^* + \mu'}$, which is always positive as $0 \leq u < 1$, $k^* = \frac{b(1-u)(\beta+\delta)l^*}{(\beta l^* + \mu')(\lambda - \gamma_2 l^*)}$, which is feasible if $\lambda > \gamma_2 l^*$ and l^* is the positive root of $f(l^*)=A(l^*)^3 - B(l^*)^2 + Cl^* + D = 0$,

where

$$\begin{aligned} A &= \beta\gamma_2\mu > 0, \\ B &= b\beta\gamma_1(1-u) + (1-u)[b\delta(\gamma_1 - \gamma_2)] + \mu(\beta\lambda - \gamma_2\mu') + a\beta\gamma_2 > 0, \\ C &= a(\beta\lambda - \gamma_2\mu') - \lambda[b\delta(1-u) + \mu\mu'] > 0 \text{ and} \\ D &= a\lambda\mu' > 0. \end{aligned}$$

Now, relating with Descartes' rule of sign, we can suggest that the cubic equation $A(l^*)^3 - B(l^*)^2 + Cl^* + D = 0$ have two positive real roots (multiplicities of roots are acceptable) [27] if and only if the subsequent conditions are hold:

$$(1)\ \gamma_1 > \gamma_2,\ \ (2)\ \beta\lambda > \gamma_2\mu'\ \text{ and }\ (3)\ a(\beta\lambda - \gamma_2\mu') > \lambda[b\delta(1-u) + \mu\mu'].$$

We now talk about the asymptotic nature of stability for the interior (positive) equilibrium of the system (2.6). The variational matrix J(E*) estimated at the interior equilibrium point $E^*(l^*, m^*, k^*)$ is furnished by

$$J(E^*) = \begin{pmatrix} -\delta m^* - \gamma_1 k^* - \mu & -\delta l^* & \gamma_1 l^* \\ -\beta m^* & -\beta l^* - \mu' & 0 \\ (\beta+\delta)m^* + \gamma_2 k^* & (\beta+\delta)l^* & \gamma_2 l^* - \lambda \end{pmatrix}$$

The characteristic equation is illustrated by

$$\xi^3 + \rho_1\xi^2 + \rho_2\xi + \rho_3 = 0,$$

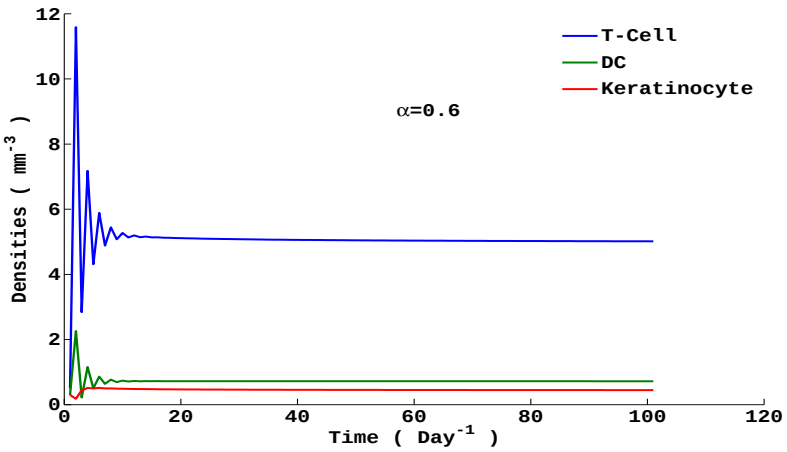

Figure 2. Population densities of T-Cells (l), Dendritic Cells (m) and Keratinocytes (k) are plotted as a function of time for the values of parameters are as in Table.

where

$$\rho_1 = l^*\beta + k^*\gamma_1 - l^*\gamma_2 + m^*\delta + \lambda + \mu + \mu',$$

$$\begin{aligned}\rho_2 &= k^*l^*\beta\gamma_1 + l^*m^*\beta\gamma_1 - (l^*)^2\beta\gamma_2 + l^*m^*\gamma_1\delta - l^*m^*\gamma_2\delta + l^*\beta\lambda + k^*\gamma_1\lambda + m^*\delta\lambda \\ &\quad + l^*\beta\mu - l^*\gamma_2\mu + \lambda\mu + k^*\gamma_1\mu' - l^*\gamma_2\mu' + m^*\delta\mu' + \lambda\mu' + \mu\mu',\end{aligned}$$

$$\begin{aligned}\rho_3 &= k^*l^*\beta\gamma_1\lambda - (l^*)^2\beta\gamma_2\mu + l^*\beta\lambda\mu + l^*m^*\beta\gamma_1\mu' + l^*m^*\gamma_1\delta\mu' - l^*\gamma_2\mu\mu' + \lambda\mu\mu' \\ &\quad - l^*m^*\gamma_2\delta\mu' + k^*\gamma_1\lambda\mu' + m^*\delta\lambda\mu'.\end{aligned}$$

From the Routh-Hurwith criterion, we may conclude that, the interior equilibrium point E^* is locally asymptotically stable, if the three following conditions are hold:

$$(i)\ \beta > 2\gamma_2,\ \ (ii)\ \gamma_1 > \gamma_2,\ \ (iii)\ \beta\lambda > \gamma_2\mu' \text{ and } (iv)\ \frac{k^*}{l^*} > \frac{\gamma_2\mu}{\gamma_1\lambda}.$$

Let us consider, the discriminant of a polynomial g is indicated by $D(\psi)$. If $\psi(y) = y^3 + \rho_1 y^2 + \rho_2 y + \rho_3 = 0$, then

$$D(\psi) = -\begin{vmatrix} 1 & \rho_1 & \rho_2 & \rho_3 & 0 \\ 0 & 1 & \rho_1 & \rho_2 & \rho_3 \\ 3 & 2\rho_1 & \rho_2 & 0 & 0 \\ 0 & 3 & \rho_1 & \rho_2 & 0 \\ 0 & 0 & 3 & 2\rho_1 & \rho_2 \end{vmatrix}$$

$= 18\rho_1\rho_2\rho_3 + (\rho_1\rho_2)^2 - 4\rho_1^3\rho_3 - 4\rho_2^3 - 27\rho_3^2$. Applying the outcomes from [15], [28], [29], [30], we obtain the following proposition.

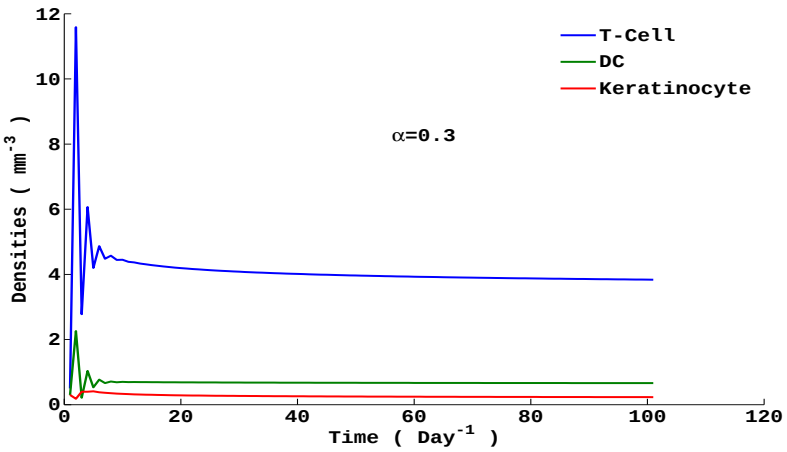

Figure 3. Population densities of T-Cells (l), Dendritic Cells (m) and Keratinocytes (k) are plotted as a function of time for the values of parameters are as in Table.

Proposition 3.1. *We suppose that E^* exists in R^3_+.*
(1) If the discriminant of $\psi(y)$, $D(\psi)$ is positive and Routh-Hurwitz criterion are satisfied, i.e., $D(\psi) > 0$, $\rho_1 > 0$, $\rho_3 > 0$ and $\rho_1\rho_2 > \rho_3$, then the interior equilibrium E^* is locally asymptotically stable,
(2) if $D(\psi) < 0$, $\rho_1 > 0$, $\rho_2 > 0$, $\rho_1\rho_2 = \rho_3$ and $\alpha \in [0,1)$, then the interior equilibrium E^* is locally asymptotically stable and
(3) if $D(\psi) < 0$, $\rho_1 < 0$, $\rho_2 < 0$ and $\alpha > 2/3$, then the interior equilibrium $E^*$is unstable.

4 Numerical Simulation

We are to apply approximation and numerical procedures in most of the cases as the fracti onal-order differential equations do not obtain exact analytical results. There are different analytical as well as numerical techniques for solving the fractional-order differential equations. Here we apply the Nonstandard Finite Difference Method (NFDM) for resolving of the system (2.6) numerically. The NFDM was established by Mickens in 1980s. The notion of this process is described in [31]. Essential characteristics of exact solutions for the concerned fractional-order differential equations are attained by this method, so that this procedure is indicated as a dominant numerical method [32]. Using NFDM, the fractional-order system of equations (2.6) may be discretized in the following form:

$$\sum_{p=0}^{j+1} v_p^{\alpha} l_{j+1-p} = a - \delta l_{j+1} m_j - \gamma_1 l_{j+1} k_j - \mu l_{j+1}, \tag{4.1}$$

$$\sum_{p=0}^{j+1} v_p^{\alpha} m_{j+1-p} = b(1-u) - \beta l_j m_{j+1} - \mu' m_{j+1}, \tag{4.2}$$

$$\sum_{p=0}^{j+1} v_p^{\alpha} k_{j+1-p} = \beta l_j m_{j+1} + \delta l_{j+1} m_j + \gamma_2 l_{j+1} k_j - \lambda k_{j+1}. \tag{4.3}$$

After some algebraic calculations to equations (4.1), (4.2) and (4.3), we acquire the following relations:

$$l_{j+1} = \frac{a - \sum_{p=1}^{j+1} v_p^{\alpha} l_{j+1-p}}{v_0^{\alpha} + \delta m_j + \gamma_1 k_j + \mu}, \tag{4.4}$$

$$m_{j+1} = \frac{b(1-u) - \sum_{p=1}^{j+1} v_p^{\alpha} m_{j+1-p}}{v_0^{\alpha} + \beta l_j + \mu'}, \tag{4.5}$$

$$k_{j+1} = \frac{\beta l_j m_{j+1} + \delta l_{j+1} m_j + \gamma_2 l_{j+1} K_j - \sum_{p=1}^{j+1} v_p^{\alpha} k_{j+1-p}}{v_0^{\alpha} + \lambda}. \tag{4.6}$$

Numerical values of model parameters, used in the numerical simulation, have been mainly taken from [1], [18], [21] and are displayed in **Table**. Units of the parameters are taken as usual.

Table. Parameters used in the model equation (2.6)

Parameters	Definition	Default Values Assigned (Day^{-1})
a	Rate of accumulation of T-Cells	15 mm^{-3}
b	Rate of accumulation of DCs	12 mm^{-3}
δ	Rate of activation of T-Cells by DCs	0.005 mm^3
β	Rate of activation of DCs by T-Cells	0.4 mm^3
γ_1	Rate of activation of Keratinocytes by T-Cells due to T-Cells mediated Cytokines	0.8 mm^3
γ_2	Rate of growth of Keratinocytes due to T-Cells mediated Cytokines	0.05 mm^3
μ	Per capita removal rate of T-Cells	0.01
μ'	Per capita removal rate of DCs	0.02
λ	Decay rate of Keratinocytes	0.9
u	Efficacy parameter	0.7

We are trying to notice the cell-biological behavior of three different types of cells (T-Cells, DCs and Keratinocytes) for several values of α, where D^{α} is the Caputo fractional derivative for introducing fractional-order differential equations into our model system (2.6). In **Figure 1** (α**=1**), T-Cell population oscillates very sharply within the range 2 to 12 cells/mm^3 and after 20 days (approx.), it becomes stable near about 6 cells/mm^3 up to our observation of 100 days (approx.). DC population oscillates firstly and thereafter turns into stable position after 15 days (approx.). Keratinocytes slightly oscillate and after more or less 10 days become stable in nature. The last two populations stay near about 1 cell/mm^3.

In **Figure 2** (α**=0.6**), T-Cells initially oscillate and become stable after 15 days (approx.) and exist between 4 to 6 cells/mm^3. Likewise, DC and Keratinocyte population oscillate at first and develop into stable nature after 10 days and 5 days (approx.) respectively. Also Keratinocyte population is decreased than the previous case.

In **Figure 3** (α**=0.3**), all the three populations on the verge oscillate and finally be converted into stabilized character but number of oscillations is less than the earlier cases. In this case, T-Cell and Keratinocyte populations are reduced than the previous case but DC population remains unaltered. Again it is observed that, for lower values of α, a curving tendency is noticed mainly in T-Cell population. A basic difference is observed with respect to the same model equations between the integer-order and fractional-order system. For the integer-order process, there is not at all any oscillation criteria observed in the cell population. On the other hand, oscillating feature is viewed for the fractional-order system and number of oscillation is varied for the change in the value of α.

5 Discussion and Biological Conclusion

In our present research article, we incorporate the fractional-order derivative into the model system. We find only one interior equilibrium point as axial and planer equilibrium points do not exist as the value of the efficacy parameter u can never become 1 and after that make its stability analysis both analytically and numerically. We can biologically express that, if the rate of activation of DCs by T-Cells is greater than twice of the rate of growth for Keratinocytes and the rate of activation of Keratinocytes by T-Cells is greater than the rate of Keratinocytes growth, then the interior equilibrium point is locally asymptotically stable. Further the per capita removal rate of Keratinocytes should exceed some pre-assigned positive threshold value for the local asymptotical stability of the interior equilibrium. We biologically may conclude that if the value of α, where D^α is the Caputo fractional derivative, is decreased, then the cell population reaches it's stable position more rapidly. At the same time, oscillating criteria and also the number of oscillations are also reduced for the smaller value of α in the system. Furthermore, T-Cells as well as Keratinocytes are reduced simultaneously, if the value of α is comparatively small rather than the higher values. There is not at all any significant effect on DCs. It always maintains the same level, which is independent of Caputo fractional derivative. The limelight here is to activate or stimulate the suppressed memory by considering the effect of Cytokine release through fractional derivative that has a great impact on cell-biological dynamics of the disease Psoriasis. Basically in this research article the memory based cell-biological system of Psoriasis is explored so that the surplus creation of Keratinocyte cell population, which is generated by Cytokine release, is reduced. Hence we can conclude that, motivating the hidden or suppressed memory by fractional-order method into our model system methodically or systematically, we are capable to reduce the excess Keratinocytes production to fight against Psoriasis.

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