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NEGATIVE FEEDBACK CONTROL MAY REGULATE CYTOKINES EFFECT DURING GROWTH OF KERATINOCYTES IN THE CHRONIC PLAQUE OF PSORIASIS: A MATHEMATICAL STUDY

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Abstract: Psoriasis is type-1 Cytokine mediated chronic, relapsing skin disease, that has been affecting millions of people worldwide and has a deep unpleasant effect on patient's physical, social and mental cheerfulness. Though it is debatable that, the pathogenesis of Psoriasis is based on immunological mechanisms and on defective growth control systems or possibly on a combination of both but it has been recently established that, different Cytokines, which are produced by Keratinocytes and T-Cells, both inhibit Keratinocytes terminal differentiation and persuade Psoriasis. Here, we formulate a set of differential equations to demonstrate a method of stable control to the growth of Keratinocytes concentration using negative feedback control term, that is analogous to the introduction of a therapeutic drug regime. We also introduce a time delay in our model of Psoriasis to describe the time from activation of T-Cells and DCs to the growth of epidermal Keratinocytes. Our analysis shows that, the Keretinocyte density can be controlled for increasing value of the control parameter. Furthermore, if the activation rate of Keratinocyte by T-Cells mediated Cytokines can be regulated, Keratonocyte density are normalized in the psoriatic plaque. Our exploration also reveals that, delay induced system exhibits changes in the progression pattern of Keratinocytes and also forbidden by the negative feedback control.

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1. Introduction

Psoriasis is a common, chronic, inflammatory and hyperproliferative state of the skin in which both genetic and environmental influence have a significant role. The most familiar form of lesion generally occurs on the extensor surface with red, scaly patch, affecting $2\% - 3\%$ of the world population. In early 1990s, it was considered that, immune T1 cells play the dominant role in the pathogenic mechanism of Psoriasis. Through a multifaceted sequence of bio-chemical proceedings, scaliness of psoriatic plaques have been occurred on human skin due to excessive production of nitric oxide, which was suggested by clinical research. In our previous work [1], we have presumed a mathematical representation, concerning the densities of immune cells and Keratinocytes, where propagation of Keratinocytes mutually with extreme nitric oxide erection is originator to the psoriatic lesions. Research from cell biological point of view on Psoriasis recognized that repression of epidermal T-Cells density restrains pathogenesis of Psoriasis. We have analyzed the comparative study in presence of suppression on T-Cells and DCs [2]. Dermal oedema, dilatation of vessels of papilla in the dermis and also perivascular cell infiltration occur in the earlier stages of psoriatic plaque. Through cell infiltration, T-Cells, Dendritic Cells and monocytes/ macrophages penetrate into the psoriatic plaque. High proportion of $CD8^+$T-Cells together with nutrophilic granulocytes in the epidermis of psoriatic lesions is a significant characteristic in Psoriasis, whereas $CD4^+$T-Cells are present in the upper dermis dominantly [3], [4], [5]. The prominent changes in chronic stages of epidermal come to the fore in the epidermis: acanthosis (raised number of Keratinocytes and thickening of the spinous layer), loss of granular layer, Parakeratosis (dysfunction of the cornification process with nucleus-containing Keratinocytes in the cornified layer) and Hyperkeratosis (thickening of the cornified layer) [3].

1.1. Pathophysiology and Cytokine Network in Psoriasis

Over the last few years, a lot of insights have been gained and also been changed in our opinion, concerning the view of the pathogenesis of Psoriasis, which is being reflected as T1-mediated skin disease. But the insightful success of the

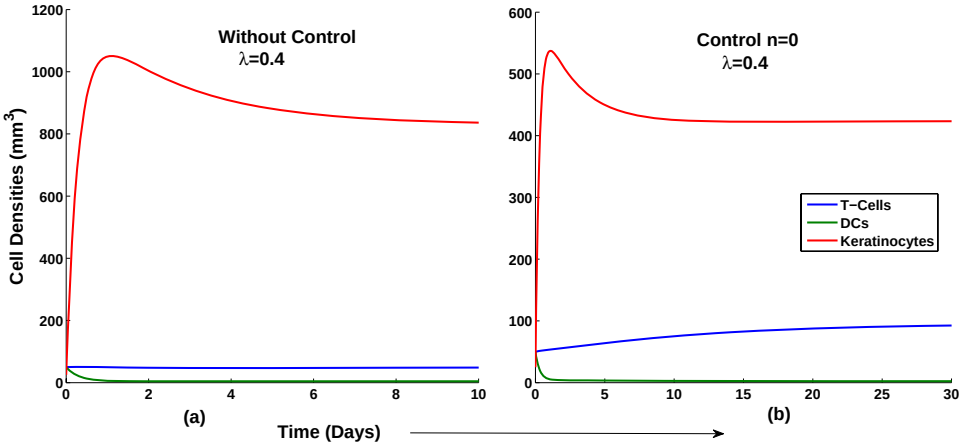

Figure 1: Time series solutions for different cell-biological masses of the system (3) without using the control and for variation of the positive constant parameter $n = 0$ where $\lambda = 0.4$, keeping other parameters at their standard values as in Table 1.

antitumor necrosis factor-α (TNF-α) therapy changes our idea through observation of the pathogenesis of Psoriasis [3], [6]. Several types of immune cells such as DCs, Th17 cells, T-Cells, Natural Killer (NK) T-Cells and regulatory T-Cells, the effect of signal transduction activation in the Keratinocytes (STAT3) and various noble Cytokines such as IL-2, IL-12, IFN-γ (Th1 regulatory Cytokines), IL-23 (DC induced Cytokines, Chemokines) are involved in the pathogenic mechanism of Psoriasis [4], [5], [7], [9].

The inception of the disease is poised by three phases, which is similar to an immune reaction. On that portrait, pathogenesis of the Psoriasis is to be completed through Sensitization phase, Silent phase and Effector phase [3]. For the duration of the Sensitization phase, immature Antigen Presenting Cells (APCs), DCs, macrophages uptake antigen (Ag) and migrate to the T-Cells areas of secondary lymphatic organs and in this process, DC undergoes a maturation process, due to the Cytokines TNF-α, IL-1β. Consequently, DCs stimulate the development of skin infiltrating effector/memory Th17 and T1 cells. DCs facilitate the conversion from naïve to the effector memory T-Cells, which takes place in a secondary lymphatic organs to acquire function and ability to immigrate into tissues. Through three signaling process, T-Cells turn into activated. The first signal is carried by interaction between TCR and MHC-II peptide complex, the second one is specified by co-stimulatory molecules and

the third signal is delivered by the soluble mediators. Naïve $CD4^+$T-Cells can be polarized into four different types Th1, Th2, Th17 and regulatory T-Cells, according to the presence of the Cytokines. Before the effector phase, there are silent phases of different length. The effector phase takes place cyclically and can be discriminated into three subsequent stages, skin infiltration of immune cells, immune cells activation in the skin and Keratinocytes response. T-Cells and other immune cells such as DCs and nutrophilic granulocytes, NK cells, monocytes/ macrophages infiltrate to the skin through intermediate five steps namely, rolling, triggering, adhesion, diapedesis and migration. In the dermis and epidermis, different antigen presenting cells may accelerate to activate the immune cells and vice versa. Different Cytokines released from various APCs such as IL-23, IL-6 play a dominant role. In the Keratinocytes response phase, epidermal Keratinocytes are activated by the mediators IFN-γ and IL-22 by T1 cells, IL-6, IL-17 by Th17, TNF-α by DCs and the activated Keratinocytes increase proliferation of themselves and their maturation and also produce various mediators, that can help further immigration of the immune cells. The Cytokines are released by activated or non-activated T-Cells thus to increase the Keratinocytes proliferation (Hancock et. al.) [3]. In our preceding research articles, we have established the mathematical representation, commencing the half saturation constant in presence of suppression together with Cytokines network, taking place DCs on the model dynamics. Thus in an essence, we can bring to an end that, if the Cytokines release is integrated with DCs and also the Negative Feedback Control is incorporated in our present analysis, we are enormously proficient to get hold an improved outcome than our foregoing work [17].

1.2. Approach to the Treatment of Psoriasis and a Mathematical Understanding

In the treatment of Psoriasis, immunologic therapies have generally been effective in targeting DC-T-Cell interactions and associated Cytokine networks within psoriatic lesions [7]. Whereas the beginning of biological therapy for treating Psoriasis and to maintain the disease under the development of improved and safer drugs, that has established in an exciting way. Moreover, depletion of T-Cell therapy, using the drug Cyclosporin gives an improvement in Psoriasis by diminishing the proliferation of T-Cells and Cytokines production. Systematic treatment of severe Psoriasis usually involves the use of oral Retinoids, Methotrexate, Cyclosporin and biological agents, that can significantly impact other bodily systems [8]. In the present time, TNF-α antagonists

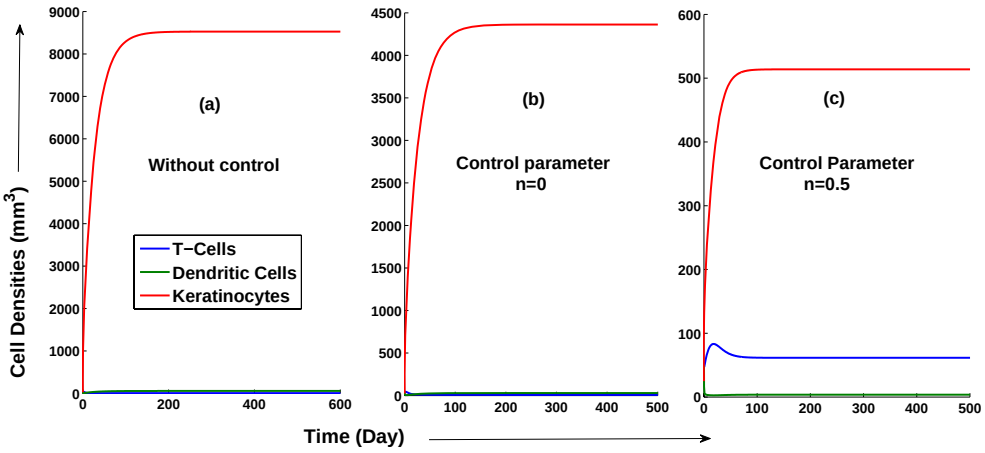

Figure 2: Time series solutions for different cell-biological masses of the system (3) without using the control and for variation of the positive constant parameter $n = 0$ and $n = 0.5$, where $\lambda = 0.04$, keeping other parameters at their standard values as in Table 1.

such as Infliximab and Etanercept result in a rapid clearing of psoriatic lesions [7]. Therapies like anti-p19, which is directed only against IL-23 or anti-IL-23R, also directed against Th17 cells will probably be more specific and safe for Psoriasis patients compared with traditional anti psoriatic agents, which impair both IL-23 and IL-12 signaling [15]. The consequence of Efalizumab (cultivated monoclonal IgG1 antibody) on dermatology-related HRQL in patients with reticent to harsh psoriatic plaque was scrutinized by means of a wide set of ending procedures [16]. Thus in a mathematical understanding, we expose that the activation of Keratinocyte Cells due to the T-Cells mediated Cytokines is the causal effect of excessive growth of Keratinocytes and reflects in the epidermal layer is to be formulated by a method of stable control to the growth of Keratinocytes concentration using negative feedback control term, that is analogous to the introduction of a therapeutic drug regime.

1.3. Why Negative Feedback Control should be used in Keratinocyte Growth?

From our previous discussion it is clear that, anti-TNF-α or therapies like anti-p19 or anti-IL-23R give the insightful success for Psoriasis patients compared with traditional anti psoriatic agents. Synergistic actions of different Cytokines

play an important role in the proliferation of Keratinocytes Cell population. Controls of growth factors are recognized to regulate the various cell functions, which are involved in the repair process. An interaction is defined as negative, if activation and accumulation of a component leads to activation or depletion of another component. If the structure of such a system is given by a certain component, which is influenced by its own activity or levels, then this component is said to regulate itself via a feedback loop. It is also known that feedback loops have been identified in a variety of regulatory systems [13]. Here in the present work, we concentrate to demonstrate a method of stable control to the growth of Keratinocytes concentration using negative feedback control term, that is analogous to the introduction of a therapeutic drug regime. Such kind of negative feedback control decreases the functioning response of Cytokines and reduces activation and proliferation of Keratinocytes.

In this research article, we explore the model dynamics of the disease Psoriasis involving model variables T-Cell, Dendritic Cell and epidermal Keratinocyte densities that pursue the cell biological events, connected with the disease Psoriasis. Furthermore, T-Cell depletion therapies, after treatment the drug gives an improvement in Psoriasis by diminishing the proliferation of T-Cells and Cytokines production. In the very last work [2], we have showed that, if a suppression made on Dendritic Cells will diminish the proliferation of Keratinocytes and gives better result than suppression on T-Cells. In case of suppression on T-Cells, when the drug is removed, the pathogenesis recur due to further activation in presence of DCs, whereas the suppression on DCs gives better result. But here, we demonstrate a method of stable control to the proliferation of Keratinocytes concentration using negative feedback control term, that is analogous to the opening of a therapeutic drug regime. Our analysis shows that, Keretinocyte density can be controlled for increasing value of the control parameter and if the activation rate of Keratinocyte by T-Cells mediated Cytokines can be kept in pace, for which Keratonocyte densities are normalized in the psoriatic plaque.

2. Mathematical Model of the Disease Psoriasis

In this section, we introduce a nonlinear ordinary differential equations model, that includes three model variables, specifically concentration of T-Cells ($l(t)$), DCs ($m(t)$) and epidermal Keratinocytes ($k(t)$), at a certain instant time t to describe the disease Psoriasis.

Here, we presume an accumulation of T-Cells, at a constant rate a in the

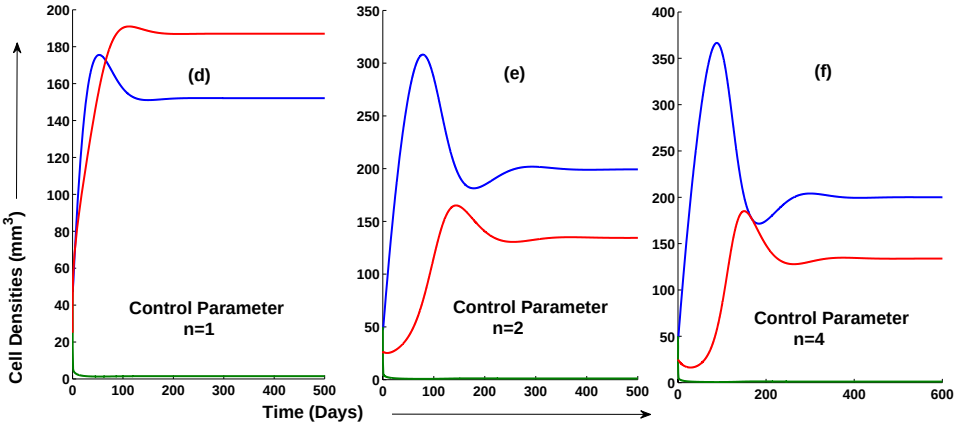

Figure 3: Time series solutions for different cell-biological masses of the system (3) for variation of the positive constant parameter $n = 1$, $n = 2$ and $n = 4$, where $\lambda = 0.04$, keeping other parameters at their standard values as in Table 1.

region proximity to the plaques with a similar accumulation of Dendritic Cells at a constant rate b. Also it is further assumed that, T-Cells and DCs do not get reproduced in any form and they are not increased by any other mechanism. The mutual activation of T-Cells and DCs take place under mixing homogeneity of these participating cells. Through this mutual activation effectively add to the growth of Keratinocytes in the epidermis, through an intermediate chain of complex biochemical events. Growth of Keratinocyte density is assumed to be proportional to the product of instantaneous T-Cells and DCs densities with a rate η. In view of this the following model [1] leads to:

$$\begin{aligned} \frac{dl}{dt} &= a - \delta lm - \mu l, \\ \frac{dm}{dt} &= b - \beta lm - \mu^{'} m, \\ \frac{dk}{dt} &= \eta lm - \lambda k. \end{aligned} \tag{1}$$

Here $\mu(\in R_+)$ and $\mu^{'}(\in R_+)$ denote per capita removal rate of T-Cells and DCs, through natural process, δ denotes the activation rate of T-Cells and DCs, β is the activation rate of DCs with T-Cells and a per capita loss of Keratinocyte density denoted by $\lambda(\in R_+)$.

This model has been extended to gain an understanding about the effects of systematic drug therapy using cyclosporin, where it has been included suppression of activated T-Cells within the model [2]. Further, they have introduced

another model equation with the same model variables and parameters including suppression on DCs, due to Antigen Presenting Cells (APCs), DCs, which play an important role in the pathogenesis of Psoriasis. In both cases, they have analyzed the model theoretically and numerically and result shows that T-Cell suppression eradicates the pathogenesis of Psoriasis and simultaneously the asymptotic value of T-Cell density gets heavily degraded and such degradation of the immune system emerges a natural worry, where as suppression on DCs, T-Cell densities gets upgraded value simultaneously and falls of DCs monotonically lower rather than suppression on T-Cells. But in that research article and also in [1], they have not been considered the effect of activated and non-activated T-Cells release factor, which increases the proliferation of Keratinocyte.

Now, it is to be noted here that, release factors of activated and non-activated T-Cells also increase the Keratinocytes proliferation (Hancockc et. al. [3]). So, we incorporate another term expressing this biological aspects in our model equation (1). We assume that, γ_1 be the rate of activation of Keratinocyte Cells due to the T-Cells mediated Cytokines and thus Keratinocytes growth take place at a rate γ_2. So our model equation (1) becomes,

$$\begin{aligned} \tfrac{dl}{dt} &= a - \delta lm - \gamma_1 lk - \mu l, \\ \tfrac{dm}{dt} &= b - \beta lm - \mu^{'} m, \\ \tfrac{dk}{dt} &= \eta lm + \gamma_2 lk - \lambda k. \end{aligned} \tag{2}$$

In formulating the mathematical model with negative feedback regulation [10] in the growth factor of Keratinocytes, the proposed equations are:

$$\begin{aligned} \tfrac{dl}{dt} &= a - \delta lm - \gamma_1 lk - \mu l, \\ \tfrac{dm}{dt} &= b - \beta lm - \mu^{'} m, \\ \tfrac{dk}{dt} &= \tfrac{\eta lm}{1+k^n} + \gamma_2 lk - \lambda k, \end{aligned} \tag{3}$$

under the initial condition $l(0) > 0$, $m(0) > 0$ and $k(0) > 0$, n is positive constant.

In this equation as $k \in [0, \infty)$, $(1 + k^n)^{-1}$ runs monotonically between 1 and 0. Hence the above mentioned function gives a negative effect on the proliferative term of Keratinocyte.

2.1. Local Stability Analysis

The right hand side of equation (3) is a smooth function of $l(t)$, $m(t)$ and $k(t)$ and of the parameter, as long as these quantities are non-negative, so local existence and uniqueness properties hold in the positive octant.

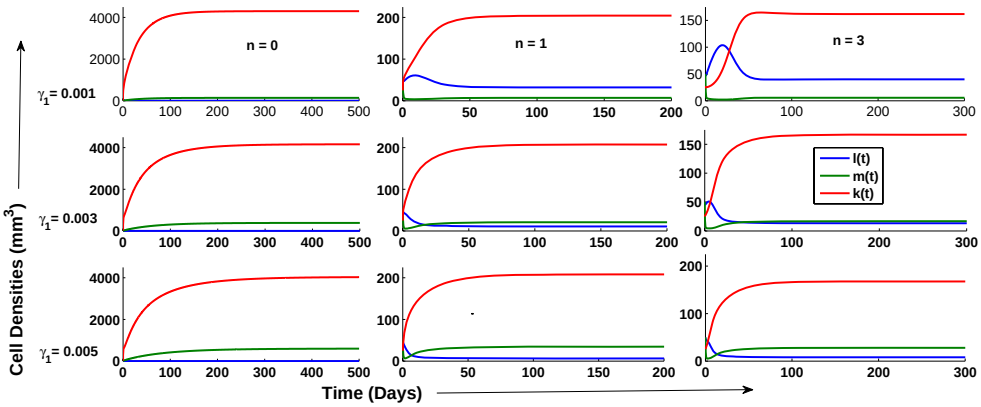

Figure 4: Time series solutions for different cell-biological masses of the system (3) for variation of $\gamma_1 = \gamma_2$ with the variation of control parameter $n = 0$, $n = 0.5$, $n = 1$ and $n = 3$, keeping other parameters at their standard values as in Table 1.

Equilibria. For simplicity we take $n = 1$, then the model equation (3) has the following equilibrium $\bar{E} = (\bar{l}, \bar{m}, \bar{k})$, where $\bar{m} = \frac{b}{\beta\bar{l}+\mu'}$, $\bar{k} = \frac{1}{\gamma_1}(\frac{a}{\bar{l}} - \frac{\delta b}{\beta\bar{l}+\mu'} - \mu)$ and $\bar{l}$ is the positive real root of the equation

$$l^5 + A_1 l^4 + A_2 l^3 + A_3 l^2 + A_4 l + A_5 = 0, \tag{4}$$

where

$$\begin{aligned}
A_1 &= \tfrac{1}{\zeta}[\gamma_1\gamma_2(\xi_2\beta + \xi_3\mu') + 2\gamma_2\xi_2\xi_3 + \gamma_1^2\eta b\beta - \xi_3\lambda(\xi_3 + \gamma_1\beta)],\\
A_2 &= \tfrac{1}{\zeta}[2\xi_1\xi_3\gamma_2 + \gamma_1\gamma_2(\mu'\xi_2 + \beta\xi_1) + \gamma_2\xi_2^2 + \gamma_1^2\eta b\mu' - \lambda\gamma_1(\beta\xi_2 + \mu'\xi_3)\\
&\qquad - 2\xi_2\xi_3\lambda],\\
A_3 &= \tfrac{1}{\zeta}[2\xi_1\xi_2\gamma_2 + \gamma_1\gamma_2\xi_1\mu' - 2\xi_1\xi_3\lambda - \gamma_1\lambda(\xi_1\beta + \xi_2\mu' - \lambda\xi_2^2)],\\
A_4 &= \tfrac{1}{\zeta}[\gamma_2\xi_1^2 - (2\xi_1\xi_2\lambda + \xi_1\gamma_1\lambda\mu')],\\
A_5 &= -\tfrac{\xi_1^2\lambda}{\zeta},\\
\zeta &= \gamma_2\xi_3(\xi_3 + \gamma_1\beta),\\
\xi_1 &= a\mu',\\
\xi_2 &= a\beta - b\delta - \mu\mu',\\
\xi_3 &= -\mu\beta.
\end{aligned} \tag{5}$$

If $\gamma_1 < \mu$, i.e. rate of activation of Keratinocyte due to T-Cell mediated Cytokines, then $A_5 < 0$ and the equation (4) must have atleast one positive

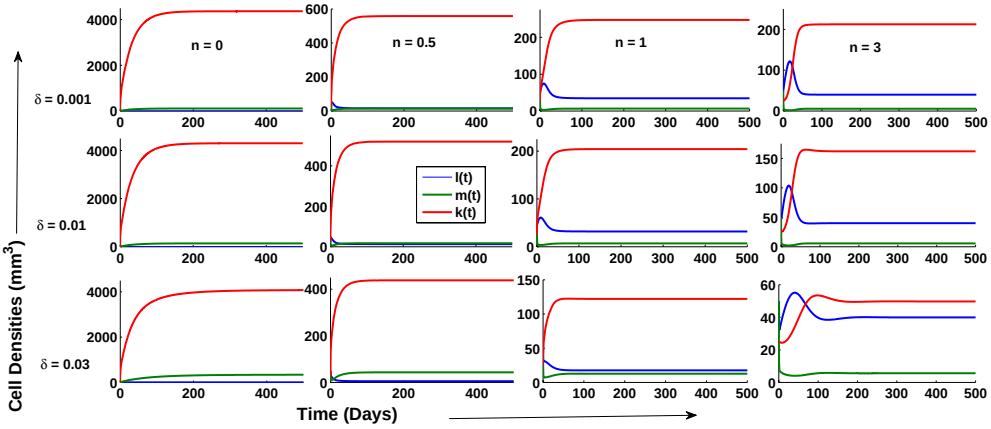

Figure 5: Time series solutions for different cell-biological masses of the system (3) for variation of δ with the variation of control parameter $n = 0$, $n = 0.5$, $n = 1$ and $n = 3$ and $\gamma_1 = \gamma_2 = 0.001$, where $\lambda = 0.04$, keeping other parameters at their standard values as in Table 1.

real root, whatever may be the sign of the real coefficients A_1, A_2, A_3 and A_4. The interior equilibrium point $\bar{E}$ exists if $\frac{a}{l} > \frac{\delta b}{\beta \bar{l} + \mu'} + \mu$.

Biological Interpretation: The rate of activation of Keratinocyte Cells due to the T-Cells mediated Cytokines, denoted by γ_1, should be less than the per capita removal rate of T-Cells, symbolized by μ, then we can suggest that, the equation (4) must have one positive real root. The existence of the interior equilibrium $\bar{E}$ biologically exposes that, the productive effect of the concentration rate of T-Cells with activation rate of DCs by T-Cells, must be greater than additive affect of activation of T-Cells by DCs together with constant accumulation rate of DCs and product of natural per capita removal rate of T-Cells and DCs.

The characteristic equation is

$$\sigma^3 + B_1\sigma^2 + B_2\sigma + B_3 = 0, \tag{6}$$

where

$$\begin{aligned}
B_1 &= \beta\bar{l} + \delta\bar{m} + \gamma_1\bar{k} + \mu + \mu^{'} + \tfrac{\eta\bar{l}\bar{m}}{(1+k)^2} - \gamma_2\bar{l} + \lambda,\\
B_2 &= \gamma_1\bar{k}(\beta\bar{l} + \mu^{'}) + \beta\mu\bar{l} + \delta\mu^{'}\bar{m} + \mu\mu^{'}\\
&\quad +(\tfrac{\eta\bar{l}\bar{m}}{(1+\bar{k})^2} - \gamma_2\bar{l} + \lambda)(\beta\bar{l} + \delta\bar{m} + \mu + \mu^{'})\\
&\quad +\gamma_1\bar{k}(\tfrac{\eta\bar{l}\bar{m}}{(1+\bar{k})^2} + \lambda) + \tfrac{\eta\gamma_1\bar{l}\bar{m}}{1+\bar{k}},\\
B_3 &= \gamma_1\bar{l}(\beta\gamma_2\bar{l}\bar{k} + \gamma_2\mu^{'}\bar{k} + \tfrac{\eta\mu^{'}\bar{m}}{1+k}) + (\tfrac{\eta\bar{l}\bar{m}}{(1+k)^2} - \gamma_2\bar{l} + \lambda)\\
&\quad \{\gamma_1\bar{k}(\beta\bar{l} + \mu^{'}) + \beta\mu\bar{l} + \delta\mu^{'}\bar{m} + \mu\mu^{'}\}.
\end{aligned} \tag{7}$$

Using the Routh-Hurwitz criterion, the system will be locally asymptotically stable around $\bar{E}$, if the following condition is satisfied

$$\frac{\gamma_2}{\gamma_1} < \frac{\lambda}{\mu}. \tag{8}$$

Here, we assume at the interior equilibrium point $\bar{E} = (\bar{l}, \bar{m}, \bar{k})$, the condition

$$\frac{\eta\bar{l}\bar{m}}{(1+\bar{k})^2} - \gamma_2\bar{l} + \lambda > 0 \tag{9}$$

which does not violate the parameter restriction.

Biological Interpretation: The condition (8) biologically reveals that, the ratio of the activation rate of Keratinocyte due to the T-Cells mediated Cytokines and rate of growth of Keratinocyte cause of these Cytokines must be less than the relative amount of the decay rate of Keratinocytes and T-Cells.

3. Numerical Simulation of the System

In our preceding section, we initiated analytical tools for a qualitative analysis of both the non-delayed and delayed system along with negative feedback control loop. In this section, we carry out a numerical simulation of the model (3) on the basis of analytical discussion. Since, no such clinical data is accessible in various amassed literature mentioned in our reference list thus, we estimate the parameter through analytical results and conditions. Numerical values of the model parameters are used in our calculations have been given in Table 1. Initial values of the model variables are chosen to be $(0) = 50$, $m(0) = 50$ and $k(0) = 25$.

Initially in this research article, we have tried to focus the effects of negative feedback on Keratinocyte growth and what will be the mathematical perceptive in expression of pathogenesis of the disease Psoriasis within the formulated

Parameters	Definition	Default Values assigned
a	Rate of accumulation of T-Cells	9 mm^{-3} Day^{-1} [14]
b	Rate of accumulation of DCs	14 mm^{-3} Day^{-1}[1]
δ	Rate of activation of l by m	0.01 mm^3 Day^{-1}[1]
β	Rate of activation of m by l	0.065 mm^3 Day^{-1}[1]
γ_1	Rate of activation of k by l due to T-Cells mediated Cytokines	0.0002 mm^3 Day^{-1}
γ_2	Rate of growth of k due to T-Cells mediated Cytokines	0.0002 mm^3 Day^{-1}
η	Growth rate of Keratinocytes	1.5 mm^3 Day^{-1}
μ	Per capita removal rate of T-Cells	0.007 Day^{-1}[14]
μ'	Per capita removal rate of DCs	0.002 Day^{-1} [1]
λ	Decay rate of Keratinocytes	0.04 - 0.4 Day^{-1} [4]

Table 1: Variables and parameters used in the model equation (3)

model. Therefore, we have emphasized here the variation of control parameter n as in model equations (3).

To see the mean Keratinocyte cell cycle period, when it is about 311 h in the normal skin, we have fixed parameter $\lambda = 0.4$ in the Figure 1 (panel (a)) and keeping all other parameters value as same in the Table 1 and also in the panel (b), that shows the progression of cell densities when the proliferation of Keratinocytes is just half of η.

Since in psoriatic lesions, the mean Keratinocyte cell cycle period is reduced to 36 h, thus we take $\lambda = 0.04$ in Figure 2 and Figure 3, which depict the progression of Cell densities (T-Lymphocyte (l), Dendritic Cell (m), Keratinocyte (k)) with respect to time. Panel (a) is shimmering without the control parameter i.e. when the feedback control is not being applied to the Keratinocyte and panel (b) and (c) of Figure 2, focus the time series plot with $n = 0$, $n = 0.5$ and $n = 1$, $n = 2$ and $n = 4$ in panel (d), (e) and (f) of Figure 3 respectively. Here we first notice that, since the apoptosis rate λ decreases, the Keratinocytes density hence gets much higher value rather than $\lambda = 0.4$ in normal skin. Furthermore, with the increasing of drugs efficiency in the anti-TNF-α therapy i.e. with increasing value of the negative feedback control parameter n, variable masses l, m and k are asymptotically stable towards lowered value. While the constant value of control parameter (n) approaches to a higher value, asymptotic value of Keratinocyte mass rolls back to a small numerical value and moves towards stable region. Moreover, the T-Cell density gets little bit upper value and ultimately goes towards stability.

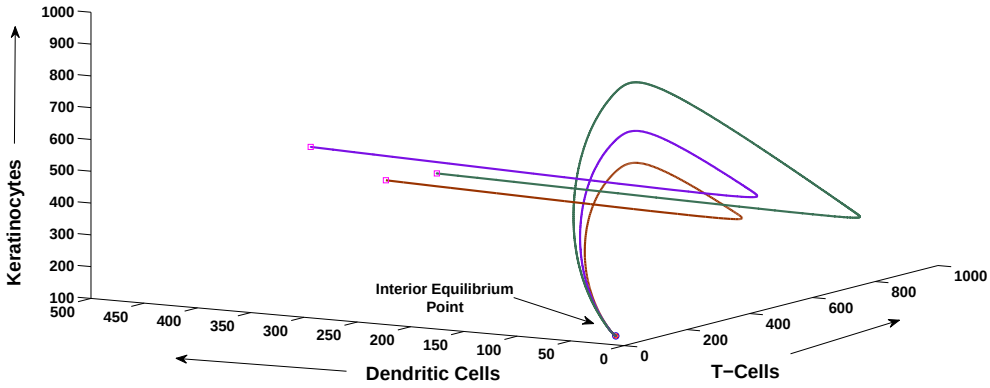

Figure 6: Phase plane population densities of T-Cells ($l(t)$), Dendritic Cells ($m(t)$) and Keratinocytes ($k(t)$) with $\gamma_1 = \gamma_2 = 0.001$, $\delta = 0.03$, $\lambda = 0.04$ and keeping other parameters as in Table 1

Further, we have also tried to focus on the effects of the parameter γ_1 (rate of activation of Keratinocyte due to T-Cells mediated Cytokines), which has been introduced as a new parameter in the model equation (3). In this case, we set $\gamma_2 = \gamma_1$, where γ_2 is rate of growth of Keratinocytes due to T-Cell mediated Cytokines. These parameters play an important role to the growth of Keratinocytes in the psoriatic plaque. Numerical simulation also shows that, with the increasing value of γ_1 and the control parameter n (see Figure 4), Keratinocyte density undergoes lower asymptotic stable value. Simultaneously DCs concentration did not attain to a higher value for which the additional activation of DCs will be less effectual. Hence if T-Cell mediated Cytokines can be controlled, the pathogenesis of Psoriasis may be keeping pace.

In Figure 5, we have fixed the value $\gamma_1 = 0.001$ and differed the parameter δ (activation rate of T-Lymphocytes by DCs) together with the control parameter n. Clearly it inflicts that, with the increasing value of the parameter δ, Keratinocyte density gets much lower value at the superior value of control parameter n.

The phase plane l-m-k (Figure 4) signifies the different trajectories starting from different initial points, which go through the interior equilibrium points.

4. Effect of Delay during Growth of Keratinocyte

Psoriatic patients have become adversely affected their lives and limited their activities of daily living due to rigorous attack of the disease and it thus appears to be appreciative of the cell dynamics together with control of the disease. No such mathematical model including delay has emerged in the last few years except fundamental research based on clinical and experimental understanding. Delay-differential equations exhibit very complicated dynamics, rather than ordinary differential equations, since a time lag could cause a stable equilibrium to become unstable and cause the population to fluctuate [12]. A time delay thus naturally comes in our mathematical point of view for realistic emulation of the discrete biological process in the proliferation of Keratinocyte. Since the proliferation of Keratinocyte in our immune system are partially dependent on the activation of T-Cells and DCs density and since the process is simultaneous but not instantaneous, so we have incorporated a realistic time lag in our model of Psoriasis to describe the time from activation of T-Cells and DCs to the growth of epidermal Keratinocytes. Also it has been shown that, delay induced system exhibits changes in the progression pattern of Keratinocytes and subsequently forbidden by the negative feedback control.

4.1. Mathematical Model of Delayed Disease Dynamics

In the model (3), it may be considered that, as soon as the mutual interaction made between T-Cells and the Dendritic Cells and Keratinocytes growth occur simultaneously. However, in reality, there is a time delay between these two events. Incorporating this idea in the model equation of the system (3), we formulate the following delay differential equations with τ as delay parameter:

$$\begin{aligned} \tfrac{dl}{dt} &= a - \delta lm - \gamma_1 lk - \mu l, \\ \tfrac{dm}{dt} &= b - \beta lm - \mu^{'} m, \\ \tfrac{dk}{dt} &= \tfrac{\eta l(t-\tau)m(t-\tau)}{1+k^n} + \gamma_2 lk - \lambda k, \end{aligned} \tag{10}$$

where n is positive integer and with the initial condition, $l(\theta) \geq 0$, $m(\theta) \geq 0$, $k(\theta) \geq 0$ and $\theta \in (-\infty, 0]$.

We analyze the delay system for $n = 1$. Hence the system becomes:

$$\begin{aligned} \tfrac{dl}{dt} &= a - \delta lm - \gamma_1 lk - \mu l, \\ \tfrac{dm}{dt} &= b - \beta lm - \mu^{'} m, \\ \tfrac{dk}{dt} &= \tfrac{\eta l(t-\tau)m(t-\tau)}{1+k} + \gamma_2 lk - \lambda k, \end{aligned} \tag{11}$$

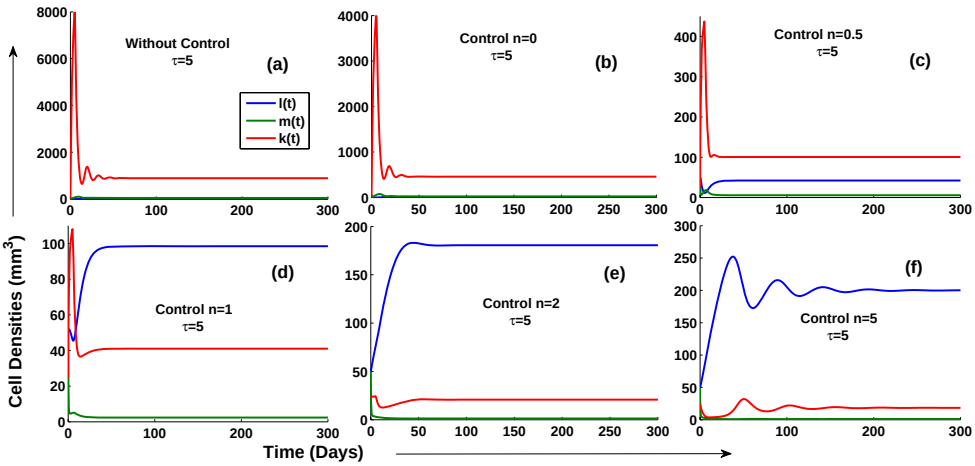

Figure 7: Time series solution of the model variables T-Cells ($l(t)$), DCs ($m(t)$) and Keratinocytes ($k(t)$) with delay parameter $\tau = 5$, without control and using feedback control parameter $n = 0$, $n = 0.5$, $n = 1$, $n = 2$ and $n = 5$.

with the initial condition $x(\theta) \geq 0$, $y(\theta) \geq 0$, $z(\theta) \geq 0$ and $\theta \in (-\infty, 0]$.

4.2. Local Stability Analysis

Here, we are interested to investigate the local stability of the interior equilibrium $\bar{E}$ of the delay induced system (11).

We linearize the system (11) by substituting $L(t) = l(t) - \bar{l}$, $M(t) = m(t) - \bar{m}$ and $K(t) = k(t) - \bar{k}$, as perturbed variables. The linearized form at $\bar{E}$ is given by

$$\begin{aligned} \frac{dL}{dt} &= -\delta\bar{m}L - \delta\bar{l}M - \gamma_1\bar{k}L - \gamma_1\bar{l}K - \mu L, \\ \frac{dM}{dt} &= -\beta\bar{l}M - \beta\bar{m}L - \mu^{'}M, \\ \frac{dK}{dt} &= \frac{\eta[\bar{m}L(t-\tau)+\bar{l}M(t-\tau)]}{1+\bar{k}} - \frac{\eta\bar{l}\bar{m}}{(1+\bar{k})^2}K + \gamma_2\bar{k}L + \gamma_2\bar{l}K - \lambda K. \end{aligned} \tag{12}$$

This linearized system can be put in the form:

$$\frac{dX}{dt} = J_1X(t) + J_2X(t-\tau),$$

where

$$J_1 = \begin{pmatrix} -\delta\bar{m} - \gamma_1\bar{k} - \mu & -\delta\bar{l} & -\gamma_1\bar{l} \\ -\beta\bar{m} & -\beta\bar{l} - \mu^{'} & 0 \\ \gamma_2\bar{k} & 0 & -\frac{\eta\bar{l}\bar{m}}{(1+\bar{k})^2} + \gamma_2\bar{l} - \lambda \end{pmatrix},$$

$$J_2 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ \frac{\eta\bar{m}}{1+\bar{k}} & \frac{\eta\bar{l}}{1+\bar{k}} & 0 \end{pmatrix},$$

and

$$X(.) = (L(.), M(.), K(.))^T.$$

The characteristic equation of the linearized system (12) is

$$\sigma^3 + a_1\sigma^2 + a_2\sigma + a_3 + (a_4\sigma + a_5)e^{-\sigma\tau} = 0, \tag{13}$$

where

$$\begin{aligned}
a_1 &= \beta\bar{l} + \delta\bar{m} + \gamma_1\bar{k} + \mu + \mu^{'} + \tfrac{\eta\bar{l}\bar{m}}{(1+\bar{k})^2} - \gamma_2\bar{l} + \lambda, \\
a_2 &= \gamma_1\bar{k}(\beta\bar{l} + \mu^{'}) + \beta\mu\bar{l} + \delta\mu^{'}\bar{m} + \mu\mu^{'} \\
&\quad + (\tfrac{\eta\bar{l}\bar{m}}{(1+\bar{k})^2} - \gamma_2\bar{l} + \lambda)(\beta\bar{l} + \delta\bar{m} + \mu + \mu^{'}) \\
&\quad + \gamma_1\bar{k}(\tfrac{\eta\bar{l}\bar{m}}{(1+\bar{k})^2} + \lambda), \\
a_3 &= \gamma_1\gamma_2\bar{l}\bar{k}(\beta\bar{l} + \mu^{'}) \\
&\quad + (\tfrac{\eta\bar{l}\bar{m}}{(1+\bar{k})^2} - \gamma_2\bar{l} + \lambda)\{\gamma_1\bar{k}(\beta\bar{l} + \mu^{'}) + \beta\mu\bar{l} + \delta\mu^{'}\bar{m} + \mu\mu^{'}\}, \\
a_4 &= \tfrac{\eta\gamma_1\bar{l}\bar{m}}{1+\bar{k}}, \\
a_5 &= \tfrac{\eta\mu\ \gamma_1\bar{l}\bar{m}}{1+\bar{k}}.
\end{aligned} \tag{14}$$

Let

$$\psi(\sigma, \tau) = \sigma^3 + a_1\sigma^2 + a_2\sigma + a_3 + (a_4\sigma + a_5)e^{-\sigma\tau} = 0. \tag{15}$$

For $\tau = 0$, i.e. for non-delayed system,

$$\psi(\sigma, 0) = \sigma^3 + a_1\sigma^2 + (a_2 + a_4)\sigma + (a_3 + a_5) = 0.$$

From the Routh-Hurwitz criterion, the necessary and sufficient condition for locally asymptotically stable is $a_1(a_2 + a_4) > (a_3 + a_5)$, which is equivalent with the condition (8), derived in the non-delayed system.

For $\tau > 0$, the characteristic equation (13) is a transcendental equation and it has infinitely many roots. Now substituting $\sigma = u(\tau) + v(\tau)$ in (13) and separating real and imaginary parts, we obtain the following transcendental equations:

$$\begin{aligned}
u^3 - 3uv^2 + a_1(u^2 - v^2) + a_2u + a_3 \\
+ e^{-u\tau}\{(a_4u + a_5)\cos v\tau + a_4v\sin v\tau\} = 0
\end{aligned} \tag{16}$$

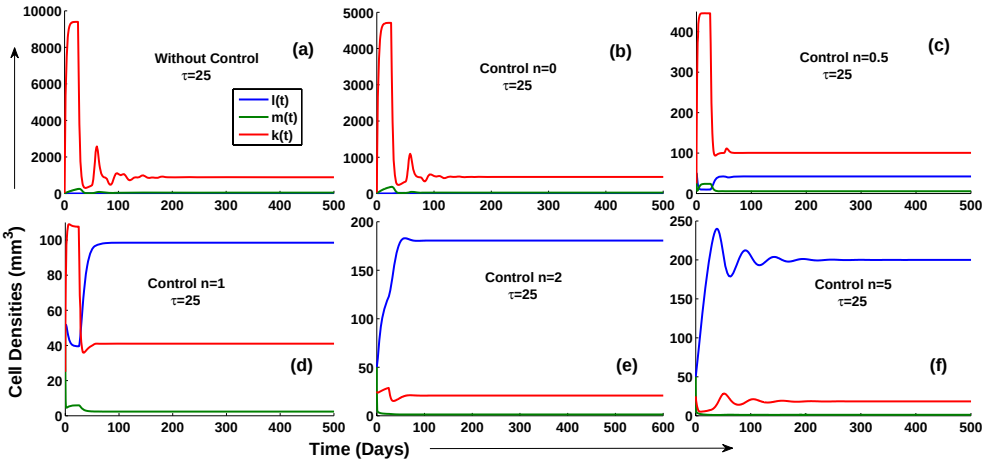

Figure 8: Time series solution of the model variables T-cells ($l(t)$), DCs ($m(t)$) and Keratinocytes ($k(t)$) with delay parameter $\tau = 25$, without control and using feedback control parameter $n = 0$, $n = 0.5$, $n = 1$, $n = 2$ and $n = 5$.

and

$$-v^3 + 3u^2v + 2a_1uv + a_2v + e^{-u\tau}\{a_4v\cos v\tau - (a_4u + a_5)\sin v\tau\} = 0. \quad (17)$$

To find the conditions for non-existence of delay induced instability, we now use the following theorem of Gopalsamy (1992), see [11].

Theorem. *A set of necessary and sufficient conditions for the equilibrium $\bar{E}$ to be asymptotically stable for all $\tau \geq 0$ is the following: (i) the real parts of all the roots of $\psi(\sigma, 0) = 0$ are negative, (ii) for real v and $\tau \geq 0$, $\psi(iv, \tau) \neq 0$, where $i = \sqrt{-1}$.*

Proof. Here $\psi(\sigma, 0) = 0$ has roots whose real parts are negative provided (8) holds. Now for $v = 0$,

$$\psi(0, \tau) = a_3 + a_5 > 0$$

and for $v \neq 0$

$$\psi(iv, \tau) = -iv^3 - a_1v^2 + ia_2v + a_3 + e^{-iv\tau}(ia_4v + a_5) = 0. \quad (18)$$

Let us suppose that, τ varies in the interval $[0, \frac{2\pi}{|v|}]$ which implies that $\mid v\tau \mid \in [0, 2\pi]$. Thus $e^{iv\tau}$ varies over a unit circle. Thus for $v \neq 0$, separating real and imaginary parts, we get,

$$a_1 v^2 - a_3 = a_5 \cos v\tau + a_4 v \sin v\tau \tag{19}$$

and

$$v^3 - a_2 v = a_4 v \cos v\tau - a_5 \sin v\tau. \tag{20}$$

Squaring and adding the above two equations, we get

$$U(v) = v^6 + (a_1^2 - 2a_2)v^4 + (a_2^2 - 2a_1 a_3 - a_4^2)v^2 + (a_3^2 - a_5^2) = 0. \tag{21}$$

Equation (21) is of the form

$$G(\omega) = \omega^3 + P_0\omega^2 + P_1\omega + P_2 = 0, \tag{22}$$

where

$$v^2 = \omega, \quad P_0 = a_1^2 - 2a_2, \quad P_1 = a_2^2 - 2a_1 a_3 - a_4^2, \quad P_2 = a_3^2 - a_5^2. \tag{23}$$

If $P_0 \geq 0$, $P_1 > 0$ and $P_2 \geq 0$ then,

$$G'(\omega) = 3\omega^2 + 2P_0\omega + P_1 > 0 \quad \text{for all} \ \ \omega \geq 0.$$

Thus, the function $G(\omega)$ is monotonic increasing function of $\omega \geq 0$ and hence delayed system is asymptotically stable for all $\tau \geq 0$.

If $P_0 \geq 0$, $P_1 > 0$ and $P_2 < 0$ then $G(0) < 0$ also $\lim_{\omega\to\infty} G(\omega) \to \infty$, then (22) must have one positive root say ω_0 and hence (21) must has one positive root, denoted by $v_0 = \sqrt{\omega_0}$.

A necessary and sufficient condition for $U(v) = 0$ not to have non-zero real root is $a_3^2 - a_5^2 \geq 0$. If $U(v) = 0$ has non-zero real root, then $a_3^2 - a_5^2 < 0$. Thus we get the condition $\gamma_1 \leq \mu$, that is presumed for the existence of the interior equilibrium point. □

5. Numerical Simulation for Delayed System

In the delayed system, we have studied the effect of delay parameter τ in the model equation (10) with the variation of control parameter n. For that purpose, we use the same parameter value as used in non-delayed system (3). We have observed that, for any value of τ, the system is asymptotically stable.

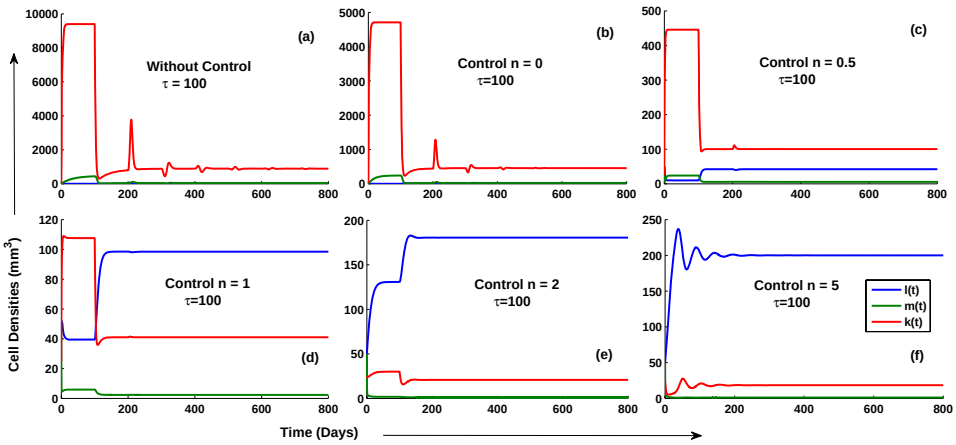

Figure 9: Time series solution of the model variables T-cells ($l(t)$), DCs ($m(t)$) and Keratinocytes ($k(t)$) with delay parameter $\tau = 100$, without control and using feedback control parameter $n = 0$, $n = 0.5$, $n = 1$, $n = 2$ and $n = 5$.

Here, we do not able to trace out any τ across that value, for which delayed system induces an instability. In Figure 7, we attain the small value of $\tau = 5$ and alter in control parameter n. Panel (a) represents the progression of cell concentrations (T-Cells $l(t)$, DCs $m(t)$ and Keratinocytes $k(t)$), where we have considered $\lambda = 0.4$. Firstly, within 5 days Keratinocytes density gets a high peak and turn around impulsively and oscillate in 50 days approximately. But ultimately it shows stable nature. Then we rise control parameter $n = 0$ to $n = 5$, keeping the value τ unchanged. We observe that if we increase the value of τ for initial $150 - 200$ days, the system behavior gets some changes. But with the increase of time, Keratinocyte density undergoes towards the same asymptotic value.

Subsequently, we increase in the delay parameter $\tau = 5$ to $\tau = 25$ and try to examine the changes of the system behavior. In Figure 8, we plot time series again for different cell densities at $\tau = 25$. Here, also within very few days Keratinocyte gets to the high peak but gradually fall down within a short period and again oscillates after few days. But if the control parameter n gets large value $n = 0$ to $n = 5$, the system shows near about same dynamical pattern.

Further, we increase delay parameter $\tau = 100$ in the delayed system and we notice that with this increasing value of τ, the oscillatory behavior increases

in the uncontrolled delayed system (see Figure 9, Panel (a)). Next we have increased the control parameter $n = 0$ to $n = 5$ (Panel (b), (c), (d), (e), (f)), that reflects the same stable behavior as in Figure 7, Figure 8.

Thus, delay induced system exhibits changes in the progression pattern of Keratinocytes and also has forbidden by the negative feedback control.

6. Discussion and Conclusion

In this research article, we have considered a mathematical model on the basis of population dynamics, concerning with three major population variable T-Cells, Dendritic Cells and Keratinocytes, interrelated to the pathogenesis of chronic plaque of Psoriasis. Here, we have emphasized the effect on T-Cells mediated Cytokines in the proliferation of Keratinocytes by incorporating the Cytokines effective term and tried to control the pathogenesis of the disease by giving negative feedback control on the growth term of Keratinocytes. In order to study the detailed dynamical progression of the model variables, we carry out both analytical and numerical techniques.

Analytical analysis illustrates on the qualitative aspects within the model. The system is bounded. We get only the interior equilibrium point and condition for existence, which depicts that, productive effect of the concentration rate of T-Cells with the activation rate of DCs by T-Cells must be less than additive affect of activation of T-Cells by DCs together with constant accumulation rate of DCs and product of natural per capita removal rate of T-Cells and DCs. Next, we find the condition, under which the model system undergoes asymptotically stable. Here, we show that, if the ratio of the activation rate of Keratinocytes due to the T-Cells mediated Cytokines and rate of Keratinocytes, (causing of Cytokines) must be less than the relative amount of the natural death rate of Keratinocytes and T-Cells, then the system is asymptotically stable around the interior equilibrium point.

In the mechanism of Psoriasis, Keratinocytes growth increases because of mutual activation process of DCs and T-Cells. But in reality, there must be time lag in between this process. That's why, we introduce the delay term in the last equation. We also apply the negative feedback control on the growth term of Keratinocytes. Analytical discussion shows that, for any value of delay parameter $\tau \geq 0$, delayed system undergoes in a asymptotically stable region.

In our numerical studies, we have considered the different model parameters to observe their effects on the model variables. Furthermore, we have studied the dynamical behavior of the system with the different value of the control

parameter n. We notice that, if the value of the control parameter is high nearly $n = 3$ to $n = 4$, Keratinocytes density is to be controlled. Also, if the activation rate (γ_1) of Keratinocyte by T-Cells mediated Cytokines can be regulated, then the time series progression shows that Keratonocyte density is to be normalized in the psoriatic plaque (see Figure 2).

It has also been shown that, incorporating a realistic time lag in the production term of Keratinocytes of our basic mathematical model, the delay induced system can also be controlled, using negative feedback function on that term which exhibits strong effect on the excessive proliferation of Keratinocytes in the pathogenesis of Psoriasis.

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