Mathematical Modeling on Immunopathogenesis in Chronic Plaque of Psoriasis: A Theoretical Study

Priti Kumar Roy [*†‡] **Jhumpa Bhadra** [†] **Biplab Chattopadhyay**[§]

Abstract—**Psoriasis is a chronic inflammatory human skin disorder characterized by T-cell mediated hyperproliferation of Keratinocytes. The exact nature of the triggering agent of psoriasis is not yet known. Cell biological findings on the disease revealed that Helper T-cells in the human blood as well as Dendritic Cells play an important role in inflicting the disease. Further, clinical research suggests that excessive generation of nitric oxide, through a complex chain of bio-chemical events, is causal to the scaliness of psoriatic plaques on human skin. We propose a mathematical model involving the densities of immune cells and Keratinocytes where proliferation of Keratinocytes together with excessive nitric oxide production is precursor to the psoriatic lesions. The model is studied both analytically and numerically. Results are observed to be consistent with the cell biological and clinical findings.**

Keywords* —*Dendritic Cells, Helper T-cells, Keratinocytes and Macrophages.

1 Introduction

Psoriasis is a commonly known disease which occurs as chronic inflammation of the skin. The disease has clinical appearance as red scaly lesions, known as plaques on the skin surface. As per existing statistics approximately $2-3\%$ of the world population is affected by psoriasis. Although the exact mechanism leading to the disease is yet to be fully understood, it is established by clinical and cell biological research that various genetic environmental and immunological factors contribute to the pathogenesis of the disease [1]-[3].

Before the mid-1980's scientist thought that psoriasis was altogether a skin disease having its root only to the epidermal area of the skin. Afterwards, cell-biological research established that the disease psoriasis was due to a breakdown in the human immune system. It is observed that the immune T-cells cause an abnormal proliferation of the healthy skin cells due to some falls signaling. Psoriasis is thus identified to be a T-cell mediated autoimmune disease [4],[5]. In some specific cases, drugs such as Cyclosporin and FK506 that act as T-cell suppressor, are found to be effective in the treatment of psoriasis [6],[7]. Further clinical research established that psoriatic lesions could be cured [8] by inducing bone marrow transplants [9], with a favorable response to anti-CD4 and anti-CD3 monoclonal antibodies as well as lymphocyte toxins.

Findings of cell-biological and clinical research so far, when put together, indicates to a complex chain of events leading to the appearance of psoriatic plaques, starting from the activation of T-cells' accumulation in the relevant dermal area by the Dendritic Cells that are derived from various Monocytes. Actually $CD14^+$ and $CD16^+$ monocytes in human blood give rise to tissue Macrophages or Dendritic Cells (DC). An upstream activation of DC's, in turn, activate lymphocytic T-cells. T-cells, by virtue of their stimulation, release tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and other cytokines [10]. It has been observed that the cytokines TNF-α and IFN-γ, through some intermediate mechanisms, leads to maturation of DC's. DC maturation again contributes to eventual activation of naive T-cells, forming a cyclic chain of mutual activation DCs and T-cells. The cytokines thus generated in the process of mutual activation, stimulate the proliferation of Keratinocytes in the epidermal region of the skin and also produce the antigenic adhesion molecules in the dermal blood vessels. Note that the normal skin has two layers; one is the epidermis, consisting of mostly a single close packed type of cells called Keratinocytes and below this, the dermis, made of collagen-based matrix holding fibroblast cells, blood vessels, nerve endings and epidermal appendages like hair-follicles and sweat glands. Infliction of psoriasis sees a significant thickening of epidermis due to Keratinocyte hyperproliferation and inhibition of apoptosis of the epidermal Keratinocytes.

Understanding of the diseases pathogenesis in psoriasis has further been enhanced with the discovery that psoriatic plaques contains nitric oxide at a level about hundred times higher than that of normal skin having normal level of Keratinocytes [11]. Kolb-Bachofen et al. [12] found

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†Centre for Mathematical Biology and Ecology, Department of Mathematics, Jadavpur University, Kolkata 700032, West Bengal, India.

‡Corresponding Author E-mail: pritiju@gmail.com, Fax No. +913324146584, Ph.No. +919432095603

§Department of Physics, Barasat Government College, Kolkata 700124, West Bengal, India.

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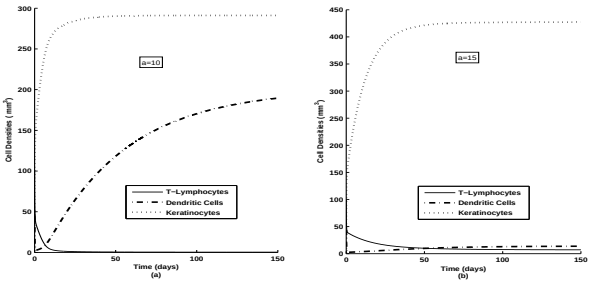

Figure 1: Time series solution for the variables in equation (1) representing the masses of T-Lymphocytes (l), Dendritic Cells/ Macrophages (m) and Keratinocytes (k) with changing a and keeping other parameters at their standard values as in Table 1.

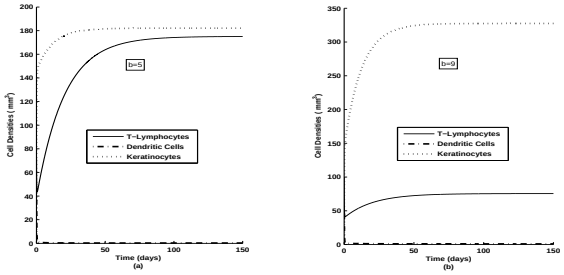

Figure 2: Plot of time series cell densities for $l(t)$, $m(t)$ and $k(t)$ with changing b. Other parameters are as in Table 1.

that epidermal Keratinocytes in plaques produce an enzyme called inducible nitric oxide synthase (iNOS) which is the major pathway of nitric oxide production.

In this paper, we focus on formulating a population/density type model involving different biological cells that are inherent in the chain of events, described so far, leading to psoriatic lesions on human skin. The mathematical model of psoriatic pathogenesis actually consists of three differential equations involving the densities of T-lymphocytes, Dendritic Cells (or Tissue Macrophages) and Keratinocytes. As observed in the literature, T-cells and DC's are locked in a cyclic interaction of mutual activation and such interaction, through an intermediate complex chemical process yields to the growth of epidermal Keratinocytes. It is to be noted here that while formulating the model an adhoc upstream accumulation of both T-cells and DC's are considered at the relevant spatial region of dermal blood vessels and tissues. Since we focus our attention to the immunopathogenesis of the diseases psoriasis we would remain content with the mentioned adhoc accumulation of the immune cells and proceed to study the dynamical behavior of the model system. We also explore the dependence of the dynamical changes of model variables on various model parameters. Analytical and numerical studies of the model would generate insights about the underlying dynamics of Keratinocyte proliferation leading to psoriatic pathogenesis and would enable us to formulate systematic clinical treatment of psoriatic patient involving probably the suppression of T-lymphocytes or Macrophages/Dendritic Cells. Note that analogous views regarding the treatment of psoriasis are contemplated in the clinical research and are documented well in the literature [11].

The communication is framed as follows: In section 2, we describe the mathematical formulation of the model precursor to immunopathogenesis in chronic plaque of psoriasis. In section 3 we do a theoretical analysis of the model focusing on its stability and allied characteristics. Results from global stability analysis of the model is presented in section 4. Section 5 includes results from numerical simulation of the model equations. Finally, discussion and conclusion are given in section 6.

2 The Basic Assumptions and the Mathematical Model

Let us consider $l(t)$ and $m(t)$ to be the concentrations of T-cells and Macrophages or Dendritic Cells respectively at an instant of time t. Let us also consider $k(t)$ to be the concentration of epidermal Keratinocytes at time t. Following assumptions are to be considered to lead the mathematical model.

(A1): We assume that influx or accumulation of lymphocytic T-cells in the relevant spatial region of dermal layer of the skin is at a constant rate a. We also assume a similar accumulation of Dendritic Cells (Macrophages) at a constant rate b.
(A2): To be consistent with $A1$ it is imperative to assume that the T-cells and DC's are not reproduced in any form or by any mechanism other than the constant accumulation or influx of them at the spatial region under consideration.
(A3): We assume that the mutual interaction of stimulation/activation of T-cells and DC's take place under mixing homogeneity of the cells. This mutual activation/stimulation mechanisms eventually yields to the growth of epidermal Keratinocyte concentration. This growth of Keratinocyte is assumed to be proportional to the product of instantaneous T-cells and DC (Macrophage) concentrations. In mathematical language this whole process of immune cell activation and enrichment of Keratinocyte concentration follows the law of mass action. Note that the fractions of T-cells and DC's, once involved in mutual activation would be unavailable for further activation. A portion of these fractions is assumed to add to the Keratinocyte density.
(A4): We assume a per capita removal through natural process of T-cells denoted by $\mu(\in R_+)$ from the spatial dermal region under consideration. We also assume a per capita natural removal of DC (Macrophage) denoted by $\mu^{'}(\in R_+)$ where $\mu^{'} << \mu$. The T-cells remain as suspended particles in the blood serum, which

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makes their mobility significantly greater than that of DC (Macrophages).
(A5): We assume per capita loss of Keratinocyte mass denoted by $\lambda(\in R_+)$ by active production of nitric oxide through the $i-NOS$ pathway [13]. The above assumptions $A_1 - A_5$ lead us to formulate the model equations as

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

Where the parameter $\delta(\in R_+)$ denote the rate at which T-cell activates with their mutual counterpart Dendritic Cells or Macrophages. The parameter β is the rate of activation of DC's (Macrophages) with the T-cells. η denotes the proportion at which Keratinocyte concentration grows out of T-cells' and DC's (Macrophages) mutual activation.

3 Theoretical study of the system

3.1 Existence, Uniqueness and Boundedness

The right hand side of equation (1) are smooth functions of the variables l, m, k and the model parameters. As long as these quantities are non-negative, local existence, uniqueness and continuation properties hold in the positive octant. In the next theorem we show that the linear combination of accumulation of lymphocytic T-cells, accumulation of Dendritic Cells (Macrophages) and Keratinocyte concentration is less than a finite quantity which implies that the solution of the system is bounded.

Theorem 3.1. *The solution $y(t)$ of (1), where $y = (l, m, k)$, is uniformly bounded for $y_0 \in R^3_{0,+}$.*
Proof: We define a function $W(t) : R_{0,+} \to R_{0,+}$ by

$$W(t) = l + m + k$$

Observe that W is well defined and differentiable on some maximal interval $(0, t_f)$. The time derivative of (1) is

$$\frac{dW(t)}{dt} = (a+b) - (\delta + \beta - \eta)lm - \mu l - \mu^{'} m - \lambda k$$

Now, for each $\rho > 0$, the following inequality holds

$$\begin{aligned} \frac{dW(t)}{dt} + \rho W(t) &\le (a+b) - (\delta+\beta-\eta)(\tfrac{l^2+m^2}{2}) - (\mu-\rho)l \\ &\quad - (\mu^{'} - \rho)m - (\lambda - \rho)k \\ &\le (a+b) + \tfrac{(\mu-\rho)^2 + (\mu^{'}-\rho)^2}{2(\delta+\beta-\eta)} - (\lambda-\rho)k \end{aligned}$$

If we assume that, $0 < \rho < \lambda$, then there exists $B > 0$ such that $\frac{dW(t)}{dt} + \rho W(t) \le B$ for each $t \in (0, t_f)$. Let $G(t, y) = B - \rho y$, which satisfies Lipschtiz condition everywhere. Clearly,
$\frac{dW(t)}{dt} \le B - \rho W(t) = G(t, W(t))$ for all $t \in (0, t_f)$.

Let, $\dfrac{dx}{dt} = G(t, x) = B - \rho x$ and $x(0) = W(0) = W_0$.

This ordinary differential equation has the solution

$$x(t) = \tfrac{B}{\rho}(1 - e^{-\rho t}) + W_0 e^{-\rho t}$$

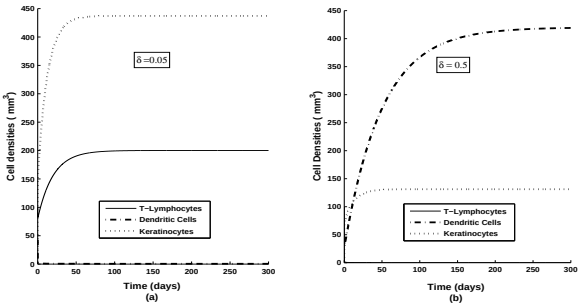

Figure 3: Time series solutions of different masses with changing δ, the rate of activation of T-cells by DCs. Other parameters are as in Table 1.

It is clear that $x(t)$ is bounded on $(0, t_f)$. By comparison theorem (Birkhoff and Rota (1989)
$W(t) \le x(t) = \frac{B}{\rho}(1 - e^{-\rho t}) + W_0 e^{-\rho t} \quad \forall \quad t \in (0, t_f)$.

Now suppose $t_f < \infty$. Then $W(t_f) \le x(t_f) < \infty$, but then the solution exists uniquely for some interval $(0, t_f)$ by the Picard-Lindelof Theorem. This contradicts the supposition that $t_f < \infty$. Therefore $W(t)$ must be bounded for all non-negative t and thus $y(t)$ is uniformly bounded on $R_{0,+}$.

3.2 Equilibria

The model equation (1) may has the following equilibria on all the co-ordinate planes either (i) $E_1(l_1^*, 0, 0)$ where $l_1^* = \frac{\beta a - b\delta}{\mu\beta}$ or (ii) $E_2(0, m_2^*, 0)$ where $m_2^* = \frac{b\delta - \beta a}{\mu^{'}\delta}$ and (iii) $E^*(l^*, m^*, k^*)$ where $k^* = \frac{\eta l^* m^*}{\lambda}$, $m^* = \frac{b}{\beta l^* + \mu^{'}}$, and l^* is the positive root of

$$\mu\beta(l^*)^2 + (\delta b + \mu\mu^{'} - a\beta)l^* - a\mu^{'} = 0 \tag{2}$$

Note that equation (2) has a unique positive root, given by

$$l^* = \frac{-(\delta b + \mu\mu^{'} - a\beta) + \sqrt{(\delta b + \mu\mu^{'} - a\beta)^2 + 4a\beta\mu\mu^{'}}}{2\mu\beta} \tag{3}$$

The existence condition for the interior equilibrium, E^* is $\delta b + \mu\mu^{'} > a\beta$ and that of E_1 and E_2 are according as $\beta a - b\delta > 0$ or < 0.

Biological Interpretation: The existence of interior equilibrium signifies that the multiplicative combination of the accumulation rate of T-cells and the activation rate of DCs with T-cells is always less than the additive effects of two terms, one term being the activation rate of T-cells with DCs multiplied by activation rate of DCs and the other term being per capita removal of T-cells by natural processes multiplied by that of the DCs (Macrophage). The existence of E_1 and E_2 biologically represent that the ratio of accumulation rate of the T-cells with the activation rate of T-cells by DCs is greater or less than that of influx rate of DCs with the rate of activation of DCs by T-cells accordingly.

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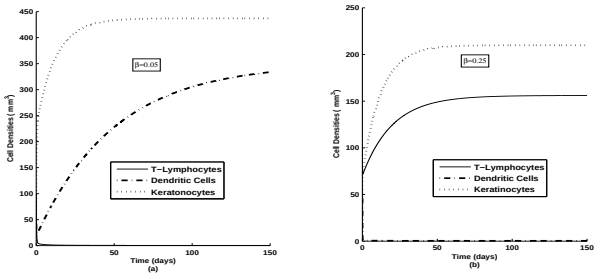

Figure 4: Time series solution of different masses $l(t)$, $m(t)$ and $k(t)$ changing β, the rate of activation of DCs with T-cells.

3.3 Local Stability Analysis

The variational matrix about any arbitrary equilibrium $E(l, m, k)$ is given by

$$\begin{pmatrix} -\delta m - \mu & -\delta l & 0 \\ -\beta m & -\beta l - \mu^{'} & 0 \\ \eta m & \eta l & -\lambda \end{pmatrix}$$

Theorem 3.3.1 *The system (1) is locally asymptotically stable around E_1 if $\beta a > \delta b$.*

Proof: The eigenvalues of the corresponding variational matrix are

$$\xi_1 = -\mu, \;\; \xi_2 = -(\beta l_1^* + \mu^{'}), \;\; \xi_3 = -\lambda$$

From the existence condition of E_1, all the characteristic roots corresponding to E_1 are negative, and hence with the existence condition of E_1 the system (1) is locally asymptotically stable around E_1.

Theorem 3.3.2 *The system (1) is locally asymptotically stable around E_2 if $\beta a < \delta b$.*

Proof: The eigenvalues of the corresponding variational matrix are

$$\xi_1 = -\mu^{'}, \;\; \xi_2 = -(\delta m_2^* + \mu), \;\; \xi_3 = -\lambda$$

From the existence condition of E_2, all the characteristic roots corresponding to E_2 are negative, and hence with the existence condition of E_2 the system (1) is locally asymptotically stable around E_2.

Theorem 3.3.3 *The system (1) is locally asymptotically stable around E^*.*

Proof: The characteristic equation corresponding to the variational matrix of E^* can be put in the form

$$\xi^3 + A_1\xi^2 + A_2\xi + A_3 = 0$$

$$A_1 = \delta m^* + \beta l^* + \lambda + \mu + \mu^{'}$$
$$A_2 = \delta\mu^{'} m^* + \beta\mu l^* + \lambda\beta l^* + \lambda\delta m^* + \mu\mu^{'} + \lambda\mu + \lambda\mu^{'}$$
$$A_3 = \delta\lambda m^*\mu^{'} + \beta\lambda\mu l^* + \mu\mu^{'}\lambda$$

From Routh-Hurwitz criterion, E^* is locally asymptotically stable if and only if

$$A_1 > 0, \;\; A_3 > 0 \text{ and } A_1A_2 - A_3 > 0.$$

Considering the existence condition of E^*, we can state that the system is locally asymptotically stable around E^*.

Table.1. Values of parameters used for models dynamics calculations.

Parameter	Definition	Default Value (day $^{-1}$)
a	Rate of influx of T-cells	15 mm^{-3} Day^{-1}
b	Rate of influx of DCs	12 mm^{-3} Day^{-1}
δ	Rate of activation of l by m	0.15 mm^3 Day^{-1}
β	Rate of activation of m by l	0.12 mm^3 Day^{-1}
η	Growth rate of Keratinocytes	0.35 mm^3 Day^{-1}
μ	Per capita removal of T-cells	0.05 Day^{-1}
μ'	Per capita removal of DCs	0.02 Day^{-1}
λ	Decay rate of Keratinocytes	0.08 Day^{-1}

3.4 Global Stability Analysis

We consider the system (1) and we denote the nontrivial equilibrium of (1) by $E^* = (l^*, m^*, k^*) > 0$. We shall prove the global stability of system (1) by constructing a suitable Lyapunov function.

Theorem 3.4.1 *The interior equilibrium point E^* is asymptotically stable if*

$(i) \;\; \mu + \delta m > 0$
$(ii) \;\; 4(\mu + \delta m)(\beta l^* + \mu^{'}) > (\delta l^* + \beta m)^2$
$(iii) \;\; detA > 0$

$$A = \begin{pmatrix} \mu + \delta m & \frac{(\delta l^* + \beta m)}{2} & -\frac{\eta m}{2} \\ \frac{\delta l^* + \beta m}{2} & \beta l^* + \mu^{'} & -\frac{\eta l^*}{2} \\ -\frac{\eta m}{2} & -\frac{\eta l^*}{2} & \lambda \end{pmatrix}$$

Proof: We define the positive definite function $V(l, m, k)$ as $V(l, m, k) = \frac{1}{2}[(l - l^*)^2 + (m - m^*)^2 + (k - k^*)^2]$. It can be easily verified that the function V is zero at the equilibrium (l^*, m^*, k^*) and positive for all other positive real values of l, m and k. The time derivative along the solutions of (1) is

$$\begin{aligned} \dot{V} &= (l - l^*)\dot{l} + (m - m^*)\dot{m} + (k - k^*)\dot{k} \\ &= -(l - l^*)^2(\mu + \delta m) - (m - m^*)^2(\beta l^* + \mu^{'}) \\ &\quad - (k - k^*)^2\lambda - (l - l^*)(m - m^*)(\delta l^* + \beta m) \\ &\quad + (k - k^*)(m - m^*)\eta l^* + (k - k^*)(l - l^*)\eta m \end{aligned}$$

The above equation should be considered as quadratic form in the variables $(l - l^*)$, $(m - m^*)$ and $(k - k^*)$, which is negative definite if the above conditions does hold.

4 Numerical simulation

Analytical study of the model representing immunopathogenesis of psoriasis has been carried focusing predominantly the stability of the solutions for different masses. In particular, the global stability of the system has been studied extensively. In order to have an understanding of the detailed dynamics of the system comprising of three different masses, we do numerical simulations

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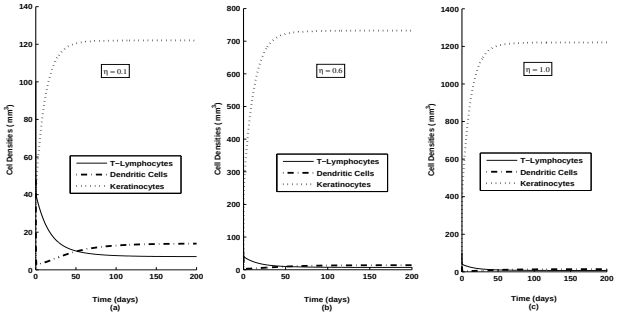

Figure 5: Time varying solutions of different variables $l(t)$, $m(t)$ and $k(t)$ as in equation (1) for different values of the η, the growth rate of Keratinocyte density. Other parameters are as in Table 1.

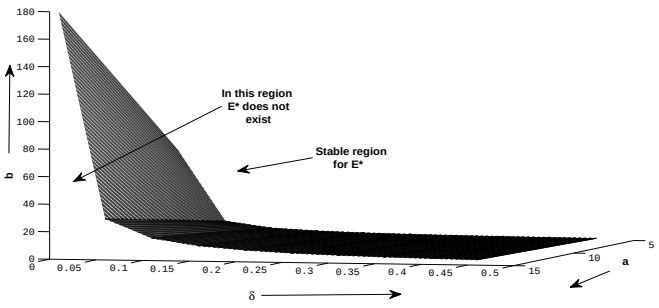

Figure 6: Graphical representation of existence and stability condition of E^* in a-δ-b parametric space with $\beta = 0.12$, $\mu = 0.05$ and $\mu^{'} = 0.02$.

of the model equations. For the purpose numerical values of the model parameters are standardized based on available clinical data, reflections from analytical solutions of the model systems and by exploring the preliminary numerical solutions of the equations. The model parameters, as standardized, are given in Table.1. Initial values of the variables are chosen as $l(0) = 100$, $m(0) = 50$, $k(0) = 2$.

In Figure 1, we see that with the increase of accumulation rate of T-Lymphocytes (a) the asymptotic stable values of lymphocyte mass (l) goes up and this inflicts a strong upward change to the asymptotic value of Keratinocyte mass (k). We observe in Figure 2, that a lowering of accumulation rate of DCs/Macrophage (b) inflicts a similar lowering of Keratinocyte growth. Asymptotically all the variables (cell densities) assume their respective stable values. We see in Figure 3 that with the increase rate of activation of T-Lymphocytes by DCs (δ) asymptotic stable values of l gets progressively degraded. This in turn, reduces the asymptotic stable value of Keratinocyte mass. Figure 4, shows that an increase rate of activation of DCs by T-Lymphocytes (β) inflicts a degradation in the stable value of m (Dendritic Cells/Macrophage density). This degradation in m causes a reduction in the stable value of Keratinocyte density in the system. Figure 5 reflects clearly that the qualitative features of time variation of different masses do not suffer any significant change with the variation of Growth rate of Keratinocytes (η). The increase of η reduces the asymptotic stable value of l and m significantly and cause a strong upward change to the asymptotic value of (k).

The mesh diagram (see Fig 6) of the model, plotted in the a-δ-b parametric space, keeping all other parameters as in table 1, gives the surface above which the interior equilibrium of the system of psoriatic pathogenesis exists and stable, and below the surface interior equilibrium does not exists. With the increase of b and δ the system undergoes towards the stable region.

5 Discussion and conclusion

We have considered a mathematical model to study the dynamical behaviour of immunopathogenesis in chronic plaque of psoriasis in human skin. In order to study the detailed dynamical progression of the model variables representing different cell densities, we performed both analytical and numerical techniques.

In the analytical study, we focus on the qualitative aspects within the model. In our analytical study we observe that the existence, uniqueness and boundedness of the solutions of the dynamical variables l (T-Lymphocyte), m (DCs/Macrophages), k (Keratinocytes) holds in the positive octant where we assume all the model parameters are non-negative. Our analytical study shows that the multiplicative combination of the accumulation rate of T-cells and the activation rate of DCs with T-cells is less than the additive effects of two terms, one term being the activation rate of T-cells with DCs multiplied by activation rate of DCs and the other term being per capita removal of T-cells by natural processes multiplied by that of the DCs (Macrophage) for existence and stability of the interior equilibrium point. We find the condition under which the solution of the system becomes globally stable.

In our numerical studies we considered the variation in the model parameters to observe their effect on the model variables. We find that a lowering in the accumulation rate of T-cells make the Keratinocyte growth as well as the asymptotic value of T-lymphocyte density lowered. However, such lowering of the parameter accumulation rate of T-Lymphocytes a (accumulation rate of T-Lymphocytes) favors the growth of Dendritic Cells whose asymptotic stable value gets increased. This implies that a lowering in the parameter a progressively lowers the stable Keratinocyte density and the psoriatic pathogenesis may suffer a roll-back at small values of a (see Fig 1). A similar lowering in the accumulation rate of DCs/Macrophages again reduces the concentrations of Keratinocyte and DC/Macrophage, although T-

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lymphocyte density gets a significant boost. Thus, one may conclude that a roll-back from pathogenesis is possible for very small value of the parameter b (rate of accumulation of DCs/Macrophage). Note that in all this cases the asymptotic cell densities are single valued and stable.

Time series solutions of model variables, plotted for various values of δ show that a decreasing δ drastically enhances the asymptotic value of T-lymphocyte density and lowers that of DCs/Macrophages. The Keratinocyte density suffers a moderate enhancement with the decreasing δ and it implies a stronger pathogenesis (see Fig 3). With lower value of β the asymptotic stable value of T-lymphocyte density suffers considerable abasement whereas that of DCs/Macrophages gets enhanced moderately. It is observed that the asymptotic Keratinocyte density towards lower β rises, again implying a progressively stronger pathogenesis (see Fig 4). A change in η towards higher values, seems not to perturb much the asymptotic values of model variables as apparent in Fig 5, even the asymptotic values of l and m remain nearly unchanged for varying η. Clearly the asymptotic values of all three variables l, m and k are not controlled by the Keratinocyte growth rate η. This is plausible from the structure of the model equations where the Keratinocyte density gets enriched only when the activation of l and m are in excess of η.

To understand how different model parameters control the dynamical behaviour of the system of psoriatic pathogenesis, existence condition of the system and stable criterion of the interior equilibrium E^*, we look into the mesh diagram in the parametric space a-δ-b. Our analytical and numerical study are reflected through mesh diagram (Figure 6) which depicts the region where the interior equilibrium point E^* exists and stable in the a-δ-b parametric space. In the lower part of the surface the interior equilibrium does not exist. With the increasing rate of accumulation of DCs/Macrophages the system moves towards stable region. On the other hand the system gives a similar behaviour with the enhance value of the activation of T-Lymphocytes by DCs/Macrophages. However the change of accumulation rate of T-Lymphocytes does not affect the nature of the system of psoriatic pathogenesis significantly. Our numerical analysis reveal that the pathogenesis of the psoriatic lesions become more stable towards the higher value of the rate of accumulation of DCs/Macrophages and the activation of T-Lymphocytes by DCs/Macrophages.

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