DRUG THERAPY BETWEEN T-CELLS AND DCS REDUCES THE EXCESS PRODUCTION OF KERATINOCYTES:AUSAL EFFECT OF PSORIASIS

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Abstract: Psoriasis is a widespread regular autoimmune inflammatory skin disease, categorized by a composite relationship of T-Cells, Dendritic Cells (DCs), Cytokines and also T-Cells mediated hyperproliferation of epidermal Keratinocytes. In this research article, we formulate a mathematical model of Psoriasis, which involves T-Cells, DCs and epidermal Keratinocytes. The interaction between T-Cells and DCs in the system generates Keratinocytes, whose over production is one of the foremost causes of Psoriasis. On that outlook, we introduce here the control approach (drug like biologic) between the interaction of T-Cells and DCs in the disease dynamics of Psoriasis to reduce the surplus production of Keratinocytes. Our analysis shows that the over production of Keratinocyte cell population can be reduced by applying the systemic medicines, for which we will be able to restrict the disease Psoriasis in a better way.

Keywords: T-Cells, Dendritic Cells (DCs), Keratinocytes, Antigen Presenting Cells, Biologic treatment, Control therapeutic strategy.

Introduction: The appearance of Psoriasis by means of immunotherapies reveals the important function of T-Cells, Dendritic Cells (DCs) and also Cytokines as element of a type 1 infammatory system [1]. It is generated from the activation of T-Cells in the corresponding dermal area by DCs. Psoriasis occurs due to the failure in the immune system. The immune T-Cells create an abnormal proliferation owing to some falls signaling [2]. So that, Psoriasis is considered as the T-Cell mediated autoimmune disease. DCs, one of the important factors in the immunopathogenic mechanisms of Psoriasis, have been documented as the Antigen Presenting Cells. It is vital for the appearance of molecules to T-Cells [3]. The upstream activation of DCs along with DC influenced Cytokines creation and antigen production to T-Cells performs significant role in disease dynamics of Psoriasis. Also Keratinocytes production performs a major part after the activation of the immune scheme. The thickness in epidermal layer (lower layer of Keratinocytes) recognizes the Psoriatic plaques, which are caused by hyperproliferation of Keratinocytes. Hence the Psoriatic plaques comprise the nitric oxide at a level more about hundred times advanced than that of our normal skin [4], [5]. In two space dimensions, Sherratt et al., [4] furnished numerical simulation of the mathematical model and thus the model was transformed into two coupled ordinary differential equations. After solving the model, the rate of release for nitric oxide was approximated as an explicit function of system parameters. Next Roy and Bhadra formulated the basic mathematical model of Psoriasis [6]. Furthermore Roy and Datta extended that mathematical model of Psoriasis integrating the half-saturation constant [7] and negative feedback control in delay induced structure [8].

Some hopeful advancement in the treatment of Psoriasis has been emerged in the last decade [9]. Biologic treatment is a novel method. Systemic medicines, which are produced from living creatures, are called Biologic. For the treatment of Psoriasis, FDA has accepted the biologic drugs like Enbrel, Humira, Stelara and Remicade [10]. Other drugs viz. Methotrexate and Cyclosporine disturb the immune system. On the other hand biologic drugs are actually more concentrated in their effects. This treatment strategy targets the origin of the cause, i.e., the interaction between the immunological cells like T-Cells and DCs. On that basis, we here try to introduce the drug biologic between the interaction of T-Cells and DCs to check the excess production of Keratinocytes.

The well known perception is that the interactions between T-Cells and DCs provide the negative effects on both T-Cells and DCs. Simultaneously this interaction helps to form Keratinocytes and increase the Keratinocyte population. The notion to check the over creation of Keratinocytes is still going on. But control of the disease Psoriasis through applying drugs systematically has not yet been explored till now properly. From that outlook in our present research article, we are trying to reduce the surplus production of Keratinocyte population through drug therapeutic approach (biologic), taken place between the interactions of T-Cells and DCs.

The Basic Assumptions and Formulation of the Mathematical Model: Here we assume $l(t)$, $m(t)$ and $k(t)$ to stand for the concentrations of T-Cells, Dendritic Cells and epidermal Keratinocytes respectively at a specific time t. We suppose that a as the constant rate of accumulation for T-Cells and b is the constant accumulation rate of Dendritic

Cells in the region proximity to the plaques.

Moreover, the rate of activation of T-Cells by DCs is δ and also β is the activation rate of DCs by T-Cells. The per capita removal rates of T-Cells, Dendritic Cells and epidermal Keratinocytes are denoted by are μ, μ' and λ respectively throughout natural sequence. We consider that γ_1 be the rate of activation of Keratinocytes due to T-Cells mediated Cytokines and thus growth of Keratinocytes occurs at a rate γ_2. Further, drug efficacy parameter u, taken place on DCs, lies between the interval $0 < u < 1$. Finally, we introduce here the biologic drugs in terms of control parameters $u_1(t)$ and $u_2(t)$ at the places of interaction between T-Cells and DCs to restrict the excess growth of Keratinocytes. Assembling all the above assumptions, we can formulate the mathematical model of Psoriasis for $t_{start} \le t \le t_{final}$ given below:

$$\frac{dl}{dt} = a - \delta lm(1-u_1(t)) - \gamma_1 lk - \mu l,$$

$$\frac{dm}{dt} = b(1-u) - \beta lm(1-u_2(t)) - \mu' m, \quad (1) \qquad \frac{dk}{dt} = \delta lm(1-u_1(t)) + \beta lm(1-u_2(t)) + \gamma_2 lk - \lambda k,$$

with given initial values for $l(0) > 0$, $m(0) > 0$ and $k(0) > 0$ at t_{start}.

Theoretical Analysis of the System Dynamics:

3.1. Existence, Uniqueness and Boundedness of the System: To prove the existence, uniqueness and boundedness of the system (1), we first assume that the control parameters $u_1(t)$ and $u_2(t)$ are time independent, i. e., those are considered as u_1 and u_2. Thus the system of equations becomes:

$$\frac{dl}{dt} = a - \delta lm(1-u_1) - \gamma_1 lk - \mu l,$$

$$\frac{dm}{dt} = b(1-u) - \beta lm(1-u_2) - \mu m, \quad (2)$$

$$\frac{dk}{dt} = \delta lm(1-u_1) + \beta lm(1-u_2) + \gamma_2 lk - \lambda k.$$

The right hand sides of equations (2) are smooth functions of the variables l, m, k and also parameters, providing these quantities are obviously non-negative. So those in the positive octant, the local existence, uniqueness and boundedness of the system dynamics are guaranteed. It can be easily shown that the linear combination of T-Cells, DCs and Keratinocytes densities are less than a prearranged quantity. At the same time, the solution of the system is bounded.

3.2. Equilibria of the System Dynamics: The system of equations (2) may have only interior equilibrium point on the coordinate planes at $E^*(l^*, m^*, k^*)$, where l^*, m^* and k^* are the non-trivial solutions of the system (2). The only equilibrium point is $E^*(l^*, m^*, k^*)$, where

$k^* = \frac{b(1-u)l^* m^*[\delta(1-u_1)+\beta(1-u_2)]}{\lambda - \gamma_2 l^*}$, $m^* = \frac{b(1-u)}{\beta l^*(1-u_2)+\mu'}$ and l^* is the positive root of the equation

$[a + b(1-u) - \mu l^*][(\beta l^*(1-u_2) + \mu')(\lambda - \gamma_2 l^*)]$

$- \mu' b(1-u)(\lambda - \gamma_2 l^*) - \lambda b(1-u) l^*[\delta(1-u_1) + \beta(1-u_2)] = 0.$ Now, m^* is always positive and k^* is positive when $\lambda > \gamma_2 l^*$. Thus biologically the system has interior equilibrium if the per capita removal rate of epidermal Keratinocytes is greater than the predetermined positive quantity.

4. Optimal Control Theoretic Approach

The objective function is defined as $J(u_1, u_2) = \int_{t_{start}}^{t_{final}} [Au_1^2(t) + Bu_2^2(t) + Nk^2(t)]dt.$ (3)

The control term $u_1(t) = 0$ and $u_2(t) = 0$ are considered as the optimal utilization of the drug analysis. Here, the parameters $A \ge 0$ and $B \ge 0$ stand for the weight constant and the penalty multiplier is denoted by N. The "Pontryagin Minimum Principle" [11] is used to the optimal control problem, where the optimal control

parameters are valid in the interval $0 \le u_1(t), u_2(t) < 1$. Our aim is to minimize the objective function and also to find the optimal control pair $u^* = (u_1^*, u_2^*)$ such that $J(u_1^*, u_2^*) = \min(J(u_1, u_2) : (u_1, u_2) \in U)$, where $U = U_1 \text{X} U_2, U_1 = (u_1(t) : u_1$ is measurable and $0 \le u_1 \le 1, t \in [t_{start}, t_{final}])$ and $U_2 = (u_2(t) : u_2$ is measurable and $0 \le u_2 \le 1, t \in [t_{start}, t_{final}])$. We apply the "Pontryagin Minimum Principle" [11] to find u_1^* and u_2^*. The Hamiltonian is furnished by

$H = Au_1^2(t) + Bu_2^2(t) + Nk^2(t) + \rho_1[a - \delta lm(1 - u_1(t)) - \gamma_1 lk - \mu l] + \rho_2[b(1 - u) - \beta lm(1 - u_2(t)) - \mu' m] + \rho_3[\delta lm(1 - u_1(t)) + \beta lm(1 - u_2(t)) + \gamma_2 lk - \lambda k]$,

where ρ_1, ρ_2 and ρ_3 are considered as adjoint variables. By applying the "Pontryagin Minimum Principle" for existence condition of the optimal control theory [11], [12], we obtain two optimal control variables, i.e., one is u_1^* and another is u_2^* that satisfy the condition $\frac{\partial H}{\partial u_1^*(t)} = \frac{\partial H}{\partial u_2^*(t)} = 0$.

Again H can be written as, $H = Au_1^2(t) + Bu_2^2(t) - \delta lm(1 - u_1(t))(\rho_1 - \rho_3) - \beta lm(1 - u_2(t))(\rho_2 - \rho_3)$ + terms without $u_1(t)$ and $u_2(t)$. Therefore from the above two equations we have, $\frac{\partial H}{\partial u_1^*(t)} = 2Au_1^* + \delta lm(\rho_1 - \rho_3) = 0$ and $\frac{\partial H}{\partial u_2^*(t)} = 2Bu_2^* + \beta lm(\rho_2 - \rho_3) = 0$. Solving we have, $u_1^*(t) = \frac{\delta lm(\rho_3 - \rho_1)}{2A}$ and $u_2^*(t) = \frac{\beta lm(\rho_3 - \rho_2)}{2B}$. Hence the compact form of $u_1^*(t)$ is given by $u_1^*(t) = max(0, min(1, \frac{\delta lm(\rho_3 - \rho_1)}{2A}))$. In a similar fashion, we can achieve the compact form of $u_2^*(t)$ as $u_2^*(t) = max(0, min(1, \frac{\beta lm(\rho_3 - \rho_2)}{2B}))$. The above equations are the necessary conditions satisfying the optimal control $u_1(t)$, $u_2(t)$ and also the state variables of the system. The existence conditions for the adjoint variables are furnished by the corresponding adjoint equations:

$\frac{d\rho_1}{dt} = -\frac{\partial H}{\partial l}, \frac{d\rho_2}{dt} = -\frac{\partial H}{\partial m}$ and $\frac{d\rho_3}{dt} = -\frac{\partial H}{\partial k}$ where

$\frac{\partial H}{\partial l} = -\rho_1(\delta m(1 - u_1(t)) + \gamma_1 k + \mu) - \rho_2 \beta m(1 - u_2(t)) + \rho_3(\delta m(1 - u_1(t)) + \beta m(1 - u_2(t)) + \gamma_2 k)$,

$\frac{\partial H}{\partial m} = -\rho_1 \delta l(1 - u_1(t)) - \rho_2(\beta l(1 - u_2(t)) + \mu') + \rho_3(\delta l(1 - u_1(t)) + \beta l(1 - u_2(t)))$,

$\frac{\partial H}{\partial k} = 2Nk - \rho_1 \gamma_1 l + \rho_3(\gamma_2 l - \lambda)$.

5. Numerical Simulation: In previous part, we have illustrated the analytical method using optimal control theoretic approach for the qualitative analysis of the system (1). In this section, we carry out the numerical simulation of the model (1) on the basis of the analytical behaviors. The numerical values of the model parameters for our computations are as follows: a = 15 $mm^{-3}day^{-1}$, b = 12 mm^{-3} day^{-1}, δ = 0.005 mm^3 day^{-1}, β = 0.4 mm^3 day^{-1}, $\boldsymbol{\gamma_1}$ = 0.8 mm^3 day^{-1}, $\boldsymbol{\gamma_2 = 0.05}$ mm^3 day^{-1}, μ = 0.01 day^{-1}, μ' = 0.02 day^{-1}, λ = 0.9 day^{-1} and u = 0.7 [6], [7], [13].

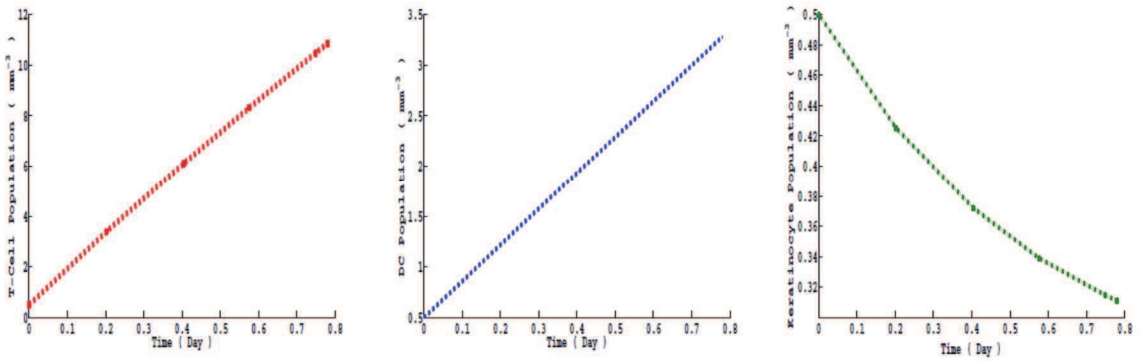

Figure 1: Population densities of T-Cells, DCs and Keratinocytes after applying Optimal Control, which are plotted as a function of time and values of the other parameters are given in Table.

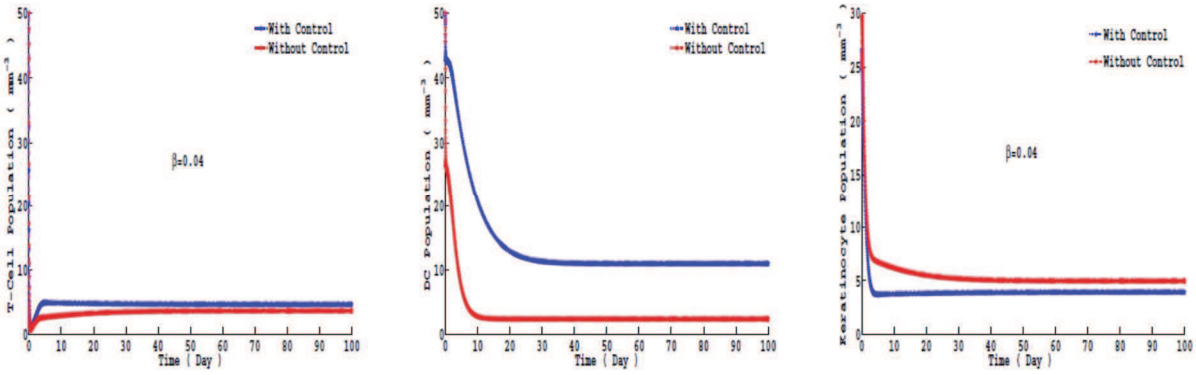

Figure 2: Control behavior (with control and without control) at $u_1(t) = u_2(t) = 0.8$ for densities of T-Cells, DCs and Keratinocytes, which are plotted as a function of time and values of the other parameters are given in Table.In first two panels, upper curve stands for with control and lower curve stands for without control and reverse characteristic for third panel.

In Figure 1 we observe that, T-Cell population increases gradually from it's initial position because of it's constant production from bone marrow or thymus though control theoretic approach is introduced at the place of interaction with DCs. Same characteristic is noticed in case of DCs. We also notice that, Keratinocyte population decreases from it's initial value to the lower level after applying the control theoretic strategy on the interaction between T-Cells and DCs. In the first two cases, T-Cells and DCs have an increasing nature in a straight line mode to be noticed in the time period of 80 days. On the other hand in the third case, Keratinocyte population has a decreasing trend, but not in a direct straight line fashion. In the time span of 80 days, the straight line is divided into four segments. In Figure 2, we plot the graphical presentations of three different cells with respect to the control parameters $u_1(t)$ and $u_2(t)$, for which we consider the value as 0.8 each. In the same figure, we are trying to show the behavioral pattern of those three different cells without control theoretic strategy. We observe that, in the case of T-Cells and DCs, population is increased. Rather the increasing nature is more prominent in case of DCs. On the other hand, Keratinocyte population is reduced for applying control theoretic method.

Discussion and Biological Conclusion: Psoriasic disease dynamics reveals that the surplus production of Keratinocyte population, mainly the causal effect of Psoriasis, is generated from the interactions between T-Cells and DCs. On that outlook, we are trying to restrict the over production of Keratinocyte population through control theoretic approach under formulating a mathematical model. In this research article, we are furnishing the control effort at the place of interaction between T-Cells and DCs to restrict the excess production of Keratinocytes through the drug biologic. Our mathematical and numerical analysis show that the effect of the drug biologic reflects the reduction of Keratinocyte population gradually from it's initial value. Again from our numerical simulation we show that since the angle of inclination has been varied in different positions in the case of Keratinocyte population, so different dosage of drugs biologic may be applied.

Thus applying control theoretic approach by means of drugs biologic, we get better result for Keratinocyte population related to without any control. At the same time the population becomes stable more quickly rather than the without control feature of the drug. Hence condensing the excess production of Keratinocyte population through systematic application of drug like biologic, we are capable to restrain the chronic skin disease Psoriasis in the global scenario.

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