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IMPACT OF CYTOKINE RELEASE IN PSORIASIS: A CONTROL BASED MATHEMATICAL APPROACH

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Abstract.

Psoriasis is a frequent unremitting chronic autoimmune skin ailment, illustrated by T-Cells arbitrated hyperproliferation of Keratinocytes. It was also scrutinized that, psoriatic lesions are sharply demarcated, red and to some extent raised lesions along with silver whitish scales. This category of skin disorder is distinguished by macroscopic and microscopic skin adaptations. In this paper, we consider a mathematical model of Psoriasis, involving T-Cells, Dendritic Cells and epidermal Keratinocytes. After stimulation, the little polypeptides, secreted by abundant cells, are identified as Cytokines, which are also regarded as local hormones of immune organization.

Here we integrate the new idea, *i.e.*, effect of Cytokines release in our proposed model. Our analytical and numerical results reveal that, due to control effect, drug effort impedes the interaction between T-Cells and Keratinocytes by suppressing the Cytokines release to restrict Psoriasis and if the activation rate of Keratinocytes by T-Cells mediated Cytokines can be controlled, then Keratinocytes intensity is stabilized in the plaque of psoriatic pathogenesis.

Keywords: T-Cells, Dendritic Cells, Keratinocytes, Cytokine Release, Drug Efficacy, Optimal Control.

2010 Mathematics Subject Classification: 37N25, 37N35, 37N40, 92B05, 92C50.

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1 Introduction

In recent time, Psoriasis vulgaris is measured as the most widespread chronic seditious skin sickness, which is differentiated by T-Cell mediated hyperproliferation of Keratinocytes [1]. About 125 million populace are exaggerated worldwide by the diverse sternness of the autoimmune hyperproliferation skin ailment, named Psoriasis. In the precedent age, the unceasing disease, Psoriasis was viewed as a variety of leprosy. By many traits together with drugs, stress and bacterial infections, Psoriasis (psoriatic lesions) is expected to generate [2]. Our perceptive of pathogenesis is derived principally from clinical investigation and moreover translational knowledge, done in patients with the disease. T-Lymphocytes engage in recreation a most important responsibility as inducers of the sickness phenotype [3]. The pathogenesis of Psoriasis has not been completely illuminated, even though frequent studies has been transpired. The inflammatory unending disease, Psoriasis can be observed in different prototypse in different periods. Foremost, it was considered as a biochemical annoyance, next it was regarded as a Keratinocyte mediated situation. Lastly, in present circumstances, the perception of immunological genetics-related disorder is incredibly applicable to this disease [2]. We are also alarmed that, the inflammatory Cytokines, like Tumour Necrosis Factor (TNF) is expected to cooperate a significant pathogenic task in this sickness [3]. We are familiar with, from the cell-biological exploration, that the disease was due to collapse in the human resistant organization. On account of some falls indication, the invulnerable T-Cells reason an atypical proliferation of the vigorous skin cells. Here, Psoriasis is well thought-out as a T-Cell mediated autoimmune chaos. Cyclosporin and FK506 are exploited as drugs that perform as T-Cell suppressor [4].

Cell-biological and clinical investigations signify to a complex sequence of proceedings which guide to the manifestation of psoriatic plaques, which is in progress from the commencement of T-Cells accretion in the suitable dermal region by Dendritic Cells, resulting from diverse monocytes [4]. Within the psoriatic plaques as well as hyperproliferation of Keratinocytes, the cellular composition of the provocative penetration appears to be interceded by the Cytokines. The mechanism of accomplishment of various biological agents is illuminated by subsequent four strategies. (1) The diminution in the number of pathogenic T-Cells, (2) the embarrassment of T-Cell opening, (3) immunodeviation and (4) the stalemate of the movement of inflammatory Cytokines. The intention of the learning is to present the contact of Cytokines and their receptors in the pathogenesis of Psoriasis. Throughout stimulated T-Cells, Interleukin-1 (IL-1), being a Proinflammatory Cytokines, is exciting IL-2 and IFN-γ fabrication. Proliferation of Bone Marrow Cells, B Lymphocytes, Neutrophils, Dendritic Cells and Platelets are endorsed by IL-1. Development of inflammatory lesions with erythema and histological appearance of hyperkeratosis and inflammatory permeation are leaded by IL-1α construction in the basal stratum of the epidermis. For T-Cells, Interleukin-2 (IL-2) is measured to be the strongest development factor. The production of IFN-γ, TNF-α, IL-6, GMCSF, IL-2R and IL-2 self production are also enthused by IL-2. Basiliximab and Daclizumab (IL-2 receptors blockage with anti-alpha succession antibodies) appear to be safer policy. On immune system, pleiotropic effects is exercised by Interleukin-4. By adaptation the T-helper Cell phenotype into Th-2 cells, Th-1 mediated inflammation is straightforwardly concealed by IL-4. In psoriatic lesions, Th-1 type Cytokines is formed by activated T-Cells. The movement of Th-1 Cells is also suppressed by Th-2 type Cytokines (IL-4, IL-10 and IL-11). Through restraining the Th-1 kind Cytokine overproduction, psoriatic disorder may be condensed management of Th-2 type Cytokines. There are so many purposes to be done by Interleukin-6 (IL-6), which are concerned in the growth and differentiation of dermal and epidermal cells. The gathering are explained as (1) IL-6

assists to normalize growth and differentiation, (2) helping to trigger the NK Cells, (3) modifying the maturation of hematopoietic stem cells and (4) for T-Cells, IL-6 is considered as a chemotactic feature. In the course of this progression, T-Cell colonization to the epidermis is enthused in a straight line [2]. HLA-Cw* 0602 is itself a foremost susceptibility allele for unceasing disease, Psoriasis. This actuality is established by High resolution association studies. For commencing and preserving the pathogenic development of Psoriasis, CD4+ T-Cells are imperative, although it is argued that, the chief effector cells, reacting to antigens in the HLA-Cw* 0602, binding pocket of Keratinocytes, are the cross-primed CD8+ T-Cells [5].

In the optimal control, a number of mathematical workings have been completed, together with two non-cell-cycle-specific models (in all the stages of the cell cycle drugs are effectual) by Murray [6, 7]. In addition, Swan endow with a superior appraise of the role of optimum control in non-cell-cyclic-specific cancer chemotherapy [8]. We are most fascinated in optimum control problems as practicable to cell-cycle-specific chemotherapy (drug therapy). Eisen has premeditated a structure of scheme of linear differential equations, describing the development dynamics of the propagating (drug-sensitive phase) and dormant (drug-resistant phase) cells [9]. Over a given intermission while minimizing entire drug use, the control condenses the disease to a preset intensity. The toxicity to the bone marrow is one of the most important preventive aspects in cell-cyclic-specific chemotherapy and should be well thought-out straightforwardly. We desire to expand an optimal control problem, that will directly establish the possessions of cell-cyclic-specific treatment on the standard tissue, and we hope for endeavoring to communicate the mathematical consequences [10]. To establish the optimal drug dosages, the optimal control presumption can be used, if a mathematical representation of the infectivity and the values of the model parameters are accessible. For every patient, the job of estimation the model parameters may be very much easier said than done to be carried out [11]. By and large, parameter indecision in the demonstration and measurement noise are predictable in the real world (surroundings) [12].

We draw attention on originating a populace form mathematical model, connecting an assortment of biological cells in our article. The three dynamical equations, consisting the intensity of Lymphotic T-Cells, Dendritic Cells and also Keratinocytes, are present in our representation of psoriatic pathogenesis. In a cyclic communication of shared foundation, T-Cells and Dendritic Cells are protected. This category of interface assists to the enlargement of Keratinocytes in the epidermis. We desire to proceed the learning of the dynamical activities of the scheme, and so immunopathogenesis of the disease, called Psoriasis, is centered. The dependence of the dynamical modification of model variables is investigated. The dynamics of Keratinocytes proliferation would be produced by analytical and numerical studies and also the methodical clinical management of Psoriasis concerning the T-Lymphocyte Cells and Dendritic Cells would be facilitated by Keratinocytes proliferation, guided to pathogenesis of Psoriasis [4]. From the genetics point of view, Psoriasis is measured as a genetically heterogeneous chaos. The two core foundations for the disease expansion are the involvement of multiple genes and interactions with the environment [13]. Thoughtful of the pathogenesis of chronic, immune-mediated, inflammatory disarray, Psoriasis has been significantly enlarged by genetic and immunological advancements [14]. Based on the topographical (geographical) region and the population groups (*i.e.*, ethnic groups) studies, contained by that region, the prevalence of Psoriasis comes into view to differ. Prevalence of Psoriasis may be prejudiced by the ethnic (*i.e.*, genetic and behavioral) features, which were depicted by a number of studies [15]. For suggesting effector reactions in a variety of skin categories in Psoriasis, proinflammatory Cytokines released as an outcome of T-Cell opening are dependable [16].

In our present research piece of writing, we expand an innovative thinking, impact of Cytokine

release, integrating with our model dynamics. We institute the control to the Cytokine release, so that the release of Cytokines should be synchronized. We are familiar with, from our preceding articles [4, 17, 25], the achieve of Cytokine release enhances the development of Keratinocytes, which facilitates to generate the chronic seditious skin sickness, Psoriasis. Thus our motivation is to control the release of Cytokines to standardize the surplus growth of Keratinocyte. The population of the T-Cells, Dendritic Cells and Keratinocytes are expressed by the differential equations and it is perceived that, the activities of dynamical system act accordingly. Our aim is to observe the revolutionization in the dynamical system for commencing the impact of Cytokine release. If the dynamics of the model changes, then the question is, how the system dynamics will take action. We accentuate on the up-to-the-minute contemplation to enlighten the new prospect on the psoriatic pathogenesis.

2 The Basic Assumptions and the Mathematical Model

Here, we reflect on the mathematical representation of Psoriasis, for the procession of dynamical cell biological systems, which broadcasts the happening of Psoriatic plaques. Let us presume $l(t)$, $m(t)$ and $k(t)$ to symbolize the concentrations of T-Cells, Dendritic Cells and epidermal Keratinocytes respectively at a specific time t. We presuppose following postulations to achieve a set of dynamical differential equations, involving the Lymphotic T-Cells, Dendritic Cells and Keratinocytes.

(A1) It is here considered that, the accumulation of T-Cells in the region proximity to the plaques. We suppose the constant a, as the rate of accumulation of the T-Cells. A similar accumulation rate of Dendritic Cells is considered to be constant b, at the relevant regime. At this juncture, we furthermore consider that T-Cells and Dendritic Cells do not get reproduced in any form and they are not increased by any other mechanism.

(A2) The activation or stimulation of T-Cells and Dendritic Cells take place, under mixing homogeneity of participating cells, through mutual interactions. Through a transitional chain of complex biochemical events, activation of these T-Cells and Dendritic Cells add to the augmentation of Keratinocytes in the epidermis effectively. It is also considered here that, the intensification of Keratinocytes density is assumed to be proportional to the product of instantaneous T-Cells and Dendritic Cells densities.

(A3) The per capita removal rate of T-Cells is designated by μ and the per capita removal rate of Dendritic Cells is denoted by μ', throughout natural progression.

(A4) The per capita removal rate of the epidermal Keratinocyte density, which sees profound growth by virtue of Cytokines, is indicated by λ.

(A5) It is moreover taken for granted that, the rate of activation of T-Cells by DCs is δ and β is the activation rate of DCs by T-Cells. It ought to be distinguished at this juncture that, T-Cell suppression eliminates the pathogenesis of Psoriasis and concurrently the asymptotic assessment of T-Cell concentration gets profoundly despoiled. Such deprivation of the immune system comes into view a normal agonize. Nevertheless, when we think about the suppression on DCs, T-Cell density acquires promoted importance all together and falls of DCs monotonically inferior, relatively than suppression on T-Cells [17]. Also at this point, u is reflected on as the drug efficiency parameter, which is shown a discrepancy with time in the limits $0 < u < 1$.

(A6) Last but not least, we infer that, the rate of interaction of T-Lymphocyte Cells by Dendritic Cells is γ_1 and Dendritic Cells by T-Lymphocyte Cells is γ_2.

Accumulating the on top of hypotheses (A1)–(A6), we can originate the mathematical representation, given underneath:

$$\begin{aligned} \frac{\mathrm{d}l}{\mathrm{d}t} &= a - \delta lm - \gamma_1 lk - \mu l, \\ \frac{\mathrm{d}m}{\mathrm{d}t} &= b(1-u) - \beta lm - \mu' m, \\ \frac{\mathrm{d}k}{\mathrm{d}t} &= \beta lm + \delta lm + \gamma_2 lk - \lambda k, \end{aligned} \tag{2.1}$$

where $l(0) > 0$, $m(0) > 0$, $k(0) > 0$, at any specific time t.

The communication is framed as follows: In section 2, we portray the mathematical formulation of the representation precursor to Psoriasis. Section 3 consists of a conjectural analysis of the model, containing existences and uniqueness of the system. This section is also included unique equilibrium (interior) of the system. Theoretical as well as biological interpretation of the model parameter, focusing on its stability and allied characteristics are accessible in the same section. Section 4 includes results from numerical simulation from the model. Section 5 contains the idea of Optimally Control Drug Therapy. Section 6 includes results from numerical simulation, applying Control (drug) therapy and finally, discussion and conclusion are given in section 7.

3 Theoretical Study of the System

The coordination of equation (1) enjoys only the interior equilibrium point namely, $E^*(l^*, m^*, k^*)$, where $m^* = \frac{b(1-u)}{\beta l^* + \mu'}$, $k^* = \frac{(\beta+\delta) l^* b(1-u)}{(\lambda - \gamma_2 l^*)(\beta l^* + \mu')}$ and l^* is the positive root of

$$A(l^*)^3 - B(l^*)^2 + Cl^* + D = 0$$

where

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

Now, applying Descartes' rule of sign, we can conclude that the equation $A(l^*)^3 - B(l^*)^2 + Cl^* + D = 0$ has two positive real roots (multiplicities of roots are permitted) [18] if and only if the following conditions hold:

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

Here, for the case of condition (iii), $\beta\lambda > \gamma_2\mu'$ comes from condition (ii) and u < 1 is considered from our fundamental assumption. This cubic equation has positive root if coefficients of $(l^*)^3$, $-(l^*)^2$ and l^* are positive. For this, we ought to have,

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

As a consequence, if the stipulation (i), (ii) and (iii) are persuaded, then we can bring to a close that, the equation (1) have two positive real roots.

Accordingly, the scheme possesses positive interior equilibrium $E^*(l^*, m^*, k^*)$ if

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

At this moment, in nature, we can conclude that, if the rate of interface of T-Lymphocyte Cells by Dendritic Cells, denoted by γ_1 is superior than the rate of interaction of Dendritic Cells by T-Lymphocyte Cells, termed as γ_2, at that time, the interior equilibrium exists. The per capita removal rate of the epidermal Keratinocyte density, which sees profound growth by virtue of Cytokines, designated by λ, be required to be larger than some pre-assigned positive magnitude. These are crucial features for the subsistence of the interior equilibrium point $E^*(l^*, m^*, k^*)$.

From second equation of system (1), we include, m^*= $\frac{b(1-u)}{\beta l^* + \mu'}$, which is for ever and a day positive by our indispensable postulation.

From third equation of system (1), we search out, $k^* = \frac{(\beta+\delta)l^* b(1-u)}{(\lambda - \gamma_2 l^*)(\beta l^* + \mu')}$, which is practicable if $\lambda - \gamma_2 l^* > 0,\ i.e.,\ \lambda > \gamma_2 l^*$.

The variational matrix at the interior equilibrium point $E^*(\ l^*, m^*, k^*\ )$ is

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

The characteristic equation is illustrated by

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

where

$$\begin{aligned} A_1 &= l^*\beta + k^*\gamma_1 - l^*\gamma_2 + m^*\delta + \lambda + \mu + \mu', \\ A_2 &= k^*l^*\beta\gamma_1 + l^*m^*\beta\gamma_1 - (l^*)^2\beta\gamma_2 + l^*m^*\gamma_1\delta - l^*m^*\gamma_2\delta + l^*\beta\lambda + k^*\gamma_1\lambda \\ &\quad + m^*\delta\lambda + l^*\beta\mu - l^*\gamma_2\mu + \lambda\mu + k^*\gamma_1\mu' - l^*\gamma_2\mu' + m^*\delta\mu' + \lambda\mu' + \mu\mu', \\ \text{and}\quad A_3 &= k^*l^*\beta\gamma_1\lambda - (l^*)^2\beta\gamma_2\mu + l^*\beta\lambda\mu + l^*m^*\beta\gamma_1\mu' + l^*m^*\gamma_1\delta\mu' - l^*\gamma_2\mu\mu' \\ &\quad + \lambda\mu\mu' - l^*m^*\gamma_2\delta\mu' + k^*\gamma_1\lambda\mu' + m^*\delta\lambda\mu'. \end{aligned}$$

As a result from the Routh-Hurwitz criterion, we may bring to a close that, the equilibrium point E^* is locally asymptotically stable, if the three subsequent state of affairs embrace:

$$(1):\ \ A_1 > 0\ ,\ \ (2):\ \ A_3 > 0\ \text{ and }\ (3):\ \ A_1A_2 - A_3 > 0.$$

At this instant,

$$\begin{aligned} &(1)\ \ A_1 > 0\ \text{ if }\ \beta > \gamma_2\ , \\ &(2)\ \ A_3 > 0\ \text{ if }\ (a)\ \gamma_1 > \gamma_2\ ,\ \ (b)\ \beta\lambda > \gamma_2\mu'\ ,\ \ (c)\ \frac{k^*}{l^*} > \frac{\gamma_2\mu}{\gamma_1\lambda} \\ \text{and}\quad &(3)\ \ A_1A_2 - A_3 > 0\ \text{ if }\ \beta > 2\gamma_2\ . \end{aligned}$$

Now combining $(1),\ (2)$ and (3), we can state the conditions, which are given below:

$$(A)\ \beta > 2\gamma_2,$$
$$(B)\ \gamma_1 > \gamma_2,$$
$$(C)\ \beta\lambda > \gamma_2\mu',$$
$$(D)\ \frac{k^*}{l^*} > \frac{\gamma_2\mu}{\gamma_1\lambda}.$$

We may biologically say that, if (1) the creation rate of DCs by T-Cells, renowned as β should be greater than double of γ_2, where γ_2 is the rate of contact of Dendritic Cells by T-Lymphocyte Cells, (2) the rate of interface of T-Lymphocyte Cells by Dendritic Cells, termed as γ_1 is superior than the rate of interaction of Dendritic Cells by T-Lymphocyte Cells, phrased as γ_2, (3) the per capita removal rate of the epidermal Keratinocyte density, which perceives profound growth by virtue of Cytokines, nominated by λ, be obligatory to be larger than some pre-assigned affirmative magnitude, then the interior equilibrium $E^*(\ l^*, m^*, k^*\ )$ exists.

If the above pointed out circumstances clutch along, we can wrap up that, the interior equilibrium point $E^*(\ l^*, m^*, k^*\ )$ will be asymptotically stable.

4 Numerical Illustration

List and unit of the parameters used for System (1): λ , γ_1, γ_2, δ, β, μ, μ' all are $(\mathrm{mm}^3\,\mathrm{day}^{-1})$; a, b are $(\mathrm{mm}^{-3}\mathrm{day}^{-1})$, u is varied with time in the limits $0 < u < 1$. Parameter values are mainly taken from [4, 17, 25].

Table 1. *List of parameters for System* (1) used in Figure 1.

λ	γ_1	γ_2	δ	β	μ	μ'	a	b	u
0.9	0.8	0.05	0.005	0.4	0.01	0.02	15	12	0.7

Table 2. *List of parameters for System* (1) used in Figure 2.

λ	γ_1	γ_2	δ	β	μ	μ'	a	b	u
1.5	0.8	0.05	0.005	0.4	0.01	0.02	15	12	0.7

Table 3. *List of parameters for System* (1) used in Figure 3.

λ	γ_1	γ_2	δ	β	μ	μ'	a	b	u
2.3	0.8	0.05	0.005	0.4	0.01	0.02	15	12	0.7

Table 4. *List of parameters for System* (1) used in Figure 4.

λ	γ_1	γ_2	δ	β	μ	μ'	a	b	u
3.1	0.8	0.05	0.005	0.4	0.01	0.02	15	12	0.7

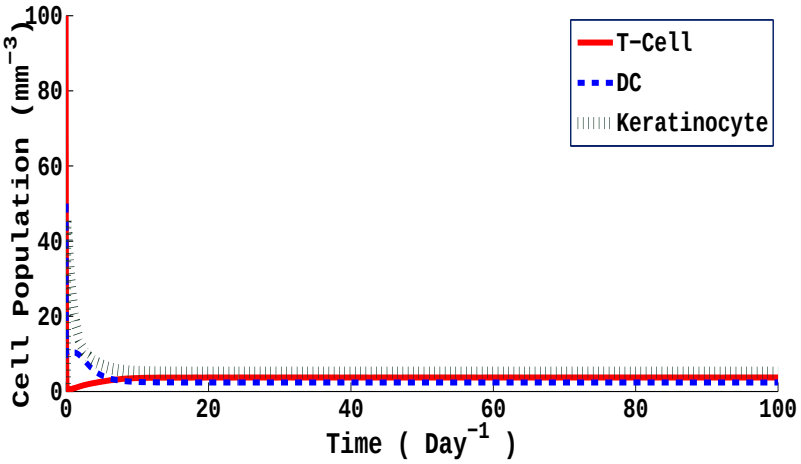

Figure 1: Population densities of T Cell (l), Dendritic Cell (m) and Keratinocyte (k) are plotted as a function of time for the parameters are as in Table 1.

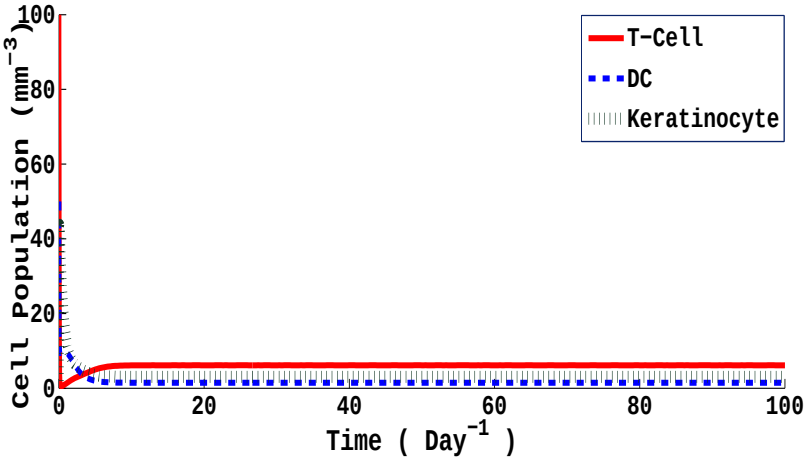

Figure 2: Population densities of T Cell (l), Dendritic Cell (m) and Keratinocyte (k) are plotted as a function of time for the parameters are as in Table 2.

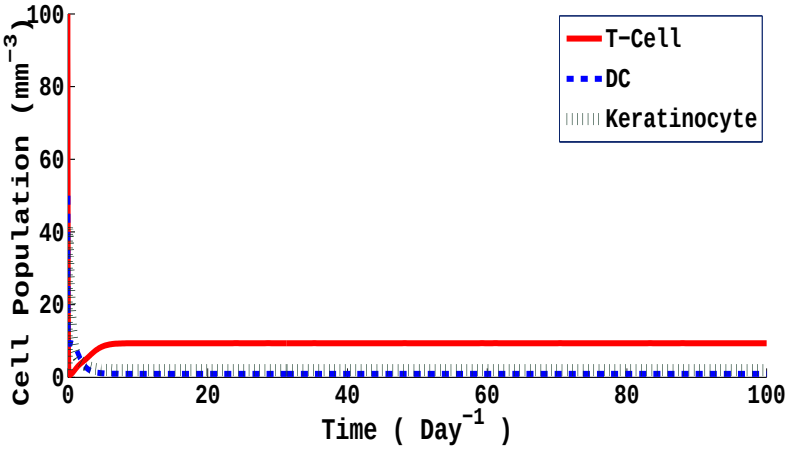

Figure 3: Population densities of T Cell (l), Dendritic Cell (m) and Keratinocyte (k) are plotted as a function of time for the parameters are as in Table 3.

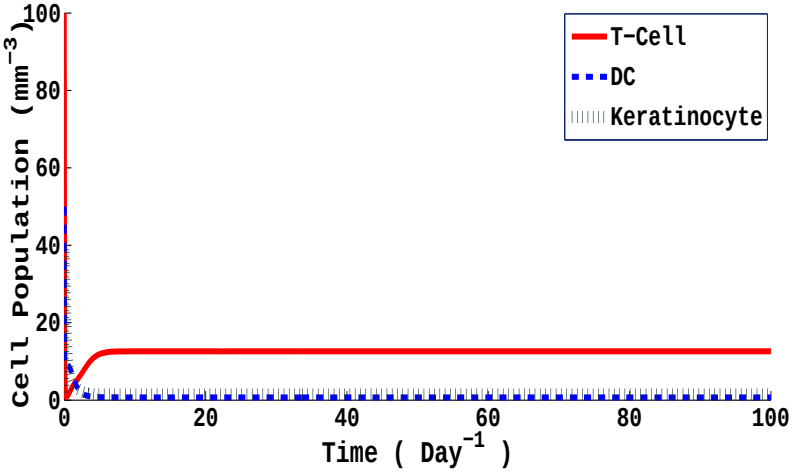

Figure 4: Population densities of T Cell (l), Dendritic Cell (m) and Keratinocyte (k) are plotted as a function of time for the parameters are as in Table 4.

At preliminary phase, while the removal rate of Keratinocyte, indicated by λ, is 0.9 mm^3/day, subsequently T-Cell population heightens very faintly within roughly first 10 days and after that, turns into stable. It sustains its stability all through the entirety time duration (here, we deem 100 days as the total time phase). T-Cell first augments due to it's steady (constant) production. Dendritic Cell population be, to begin with, at the level of 15 (approx) mm^3/day and after that, increases very vaguely. After increasing, DC population declines within first 10 days, because of suppression, applied on it. Eventually, DC population develops as well into stable, revealed in our Figure 1. Keratinocyte population, at the beginning, be at the level of 45 (approx) mm^3/day. It diminishes very sharply within first 10 (approx) days and the population retains the stabilized character throughout the complete time period (Figure 1).

We observe the parameter λ as very decisive, as the value of parameter λ (removal rate of Keratinocyte) is enlarged, the Keratinocyte population be converted into decreased feature. We are immensely fascinated about the crucial parameter λ. Subsequently, the deletion rate of Keratinocyte (λ) is assumed as 1.5 mm^3/day. The behaviors of three categories of cell populations are same as that of the preceding case (Figure 1). We bump up the value of the removal rate of Keratinocyte, named as λ, bit by bit. These values are 2.3 mm^3/day and 3.1 mm^3/day correspondingly in Figure 3 and Figure 4. The values of the other parameters stay behind unaltered. We perceive the same experience (like as Figure 1), taken place in the Figure 3 and Figure 4.

It is an incredibly illustrious piece of information that, during the contact, sandwiched between T-Cell and Keratinocyte populations, the Cytokines are released and it provides a negative upshot to the escalation in T-Cell population. As an outcome, Keratinocyte (some proration of Cytokines are transformed into Keratinocytes) population is amplified regularly. Most entertainingly, we scrutinize that, when we increase the confiscation rate of Keratinocyte (λ), afterward the rate of interaction between T-Cell and Keratinocyte population is osmotically reduced and noticeably, the rate of Cytokine release is decreased concurrently. As a consequence, T-Cell population raises gradually, symbolized in Figure 1, Figure 2, Figure 3 and Figure 4 respectively. After increasing upto 10 (approx) days, it turns out to be stable in nature. These are obtainable in the above four figures. An additional happening is that, when the removal rate of Keratinocyte (λ) is increased little by little, as a consequence, the separation of growth curves between DCs and Keratinocytes befall smaller and smaller and in the Figure 4, it becomes insignificant, also going to overlap with the x-axis. Accordingly the Keratinocyte population is decreased as the time to raise.

5 Optimally Control Drug Therapy

The control corresponds to the prerogative effect, the drug therapy has on the viral fabrication. We take for granted that, the drug therapy condenses the viral consignment. We prefer our control set quantifiable functions, defined on $[t_{\text{start}}, t_{\text{final}}]$, with the constraint $0 \leq u_1(t) < 1$. Even though, we do not propose to model belongings of confrontation or side effects, we can enforce a stipulation, that supervises the comprehensive effects of this happening: a restricted treatment casement. The treatment phase is predetermined in any treatment situation [19].

We commence a suppression on DCs in the system dynamics of this article and as a consequence, we have achieved a improved outcome than our preceding work [4, 17]. In the similar piece of article, we, at this time, integrate the control effect to the Cytokine release to attain an enhanced output. It is a incredibly well-known reality that, during interaction flanked by T-Cells and Keratinocytes, Cytokine is released and it reduces the T-Cell population. This Cytokine is transformed

into Keratinocytes in the course of some cell-biological mechanisms and it facilitates to generate the growth of Keratinocytes, which in turn, originates to form the chronic seditious skin sickness, Psoriasis. Thus, in this circumstance, we wish to suppress the Cytokine release using control effects in the growth equation of T-Cells and Keratinocytes to thwart the disease, Psoriasis. We comprise the control parameter $u_1(t)$ (*i.e.*, the term $1-u_1(t)$) in the first and third equation of the dynamical model system (1). Thus, for $t_{\text{start}} \leq t \leq t_{\text{final}}$, the state system would be:

$$\begin{aligned} \frac{\mathrm{d}l}{\mathrm{d}t} &= a - \delta lm - \gamma_1 lk(1-u_1(t)) - \mu l, \\ \frac{\mathrm{d}m}{\mathrm{d}t} &= b(1-u) - \beta lm - \mu' m, \\ \frac{\mathrm{d}k}{\mathrm{d}t} &= \beta lm + \delta lm + \gamma_2 lk(1-u_1(t)) - \lambda k, \end{aligned} \tag{5.1}$$

with given initial values for $l, m\ and\ k$ at t_{start}.

Define the objective function

$$J(u_1) = \int_{t_{\text{start}}}^{t_{\text{final}}} [k(t) + \frac{1}{2} B(u_1(t))^2]\,\mathrm{d}t \tag{5.2}$$

Our intention is to minimize the objective function. Since huge drug deliberation can be detrimental, for this cause, we have reason to consider that the cost function is a non-linear function of u_1^*. A quadratic cost can be preferred. It is based on the actuality that, there is not a linear association involving the effects of treatment on T-Cells. If the control $u_1(t) = 0$ represents to optimal utilization of drug therapy, then the optimal cost is characterized as $(1-u_1(t))$. The parameter $B \geq 0$ be a symbol of the preferred 'weight' on the benefit and cost. The ambition, thus to exemplify the optimal control, u_1^* satisfying the condition, $J(u_1) = J(u_1^*)$ in the intermission $0 \leq u_1(t) < 1$. If u_1^* is an optimal control, then the "Pontryagin's Minimal Principle" may be applied to the inhibited control problem [19]. In the United States, the Centers for Disease Control, informed that, about 22% of patients at present fail to complete their treatment within a 12-month phase and in several parts, the failure rate arrives at 55% . For the duration of the course of treatment, throughout home appointments and administration, numerous places in the world have approved the DOTS (Directly Observed Therapy Strategy), in which communal health nurses, community outreach workers and others take most of the responsibility for keeping an eye on [20].

Define the Hamiltonian

$$\begin{aligned} H = k(t) + \frac{1}{2} B(u_1(t))^2 + \rho_1[a - \delta lm - \gamma_1 lk(1-u_1(t)) - \mu l] + \rho_2[b(1-u) - \beta lm - \mu' m] \\ + \rho_3[\beta lm + \delta lm + \gamma_2 lk(1-u_1(t)) - \lambda k] + v_1 u_1(t) + v_2(1-u_1(t))\,. \end{aligned}$$

where ρ_1, ρ_2 and ρ_3 are regarded as adjoint variables and v_1 and v_2 are considered as penalty multipliers subject to the condition,

$u_1 = 0$, where $v_1 \neq 0$ and $v_2 = 0$

$u_1 = 1$, where $v_1 = 0$ and $v_2 \neq 0$.

The corresponding adjoint equations are given by

$$\frac{\mathrm{d}\rho_1}{\mathrm{d}t} = -\frac{\partial H}{\partial l} \tag{5.3}$$

$$\frac{\mathrm{d}\rho_2}{\mathrm{d}t} = -\frac{\partial H}{\partial m} \tag{5.4}$$

$$\frac{\mathrm{d}\rho_3}{\mathrm{d}t} = -\frac{\partial H}{\partial k} \tag{5.5}$$

where

$$\frac{\partial H}{\partial l} = -\rho_1(\delta m + \gamma_1 k(1-u_1(t)) + \mu) - \rho_2 \beta m + \rho_3(\beta m + \delta m + \gamma_2 k(1-u_1(t))\,, \tag{5.6}$$

$$\frac{\partial H}{\partial m} = -\rho_1 \delta l - \rho_2(\beta l + \mu') + \rho_3(\beta l + \delta l)\,, \tag{5.7}$$

$$\frac{\partial H}{\partial k} = 1 - \rho_1\gamma_1 l(1-u_1(t)) + \rho_3(\gamma_2 l(1-u_1(t)) - \lambda)\,. \tag{5.8}$$

Again H can be written as

$$\begin{aligned} H &= \tfrac{1}{2}\,B(u_1(t))^2 - \rho_1\gamma_1 lk(1-u_1(t)) + \rho_3\gamma_2 lk(1-u_1(t)) \\ &\quad + v_1 u_1(t) + v_2(1-u_1(t)) + \text{ terms without } u_1\,. \end{aligned} \tag{5.9}$$

Now, differentiating this expression for *H* with respect to u_1 gives

$$\frac{\partial H}{\partial u_1} = Bu_1(t) + \rho_1\gamma_1 lk - \rho_3\gamma_2 lk + v_1 - v_2\,. \tag{5.10}$$

This expression should be equal to zero at $u_1^*(t)$. Thus, $Bu_1(t) + \rho_1\gamma_1 lk - \rho_3\gamma_2 lk + v_1 - v_2 = 0$ at $u_1^*(t)$. Solving for the optimal control yields

$$u_1^*(t) = \frac{lk(\rho_3\gamma_2 - \rho_1\gamma_1) - v_1 + v_2}{B}\,. \tag{5.11}$$

There are three cases to be considered:

Case 1: $0 < u_1^*(t) < 1$,

Case 2: $u_1^*(t) = 0$,

Case 3: $u_1^*(t) = 1$.

Case 1: $0 < u_1^*(t) < 1$, subject to the condition $v_1 = v_2 = 0$.

$$u_1^*(t) = \frac{lk(\rho_3\gamma_2 - \rho_1\gamma_1)}{B} \tag{5.12}$$

Case 2: $u_1^*(t) = 0$, subject to the condition $v_1 \neq 0$ and $v_2 = 0$.

$$lk(\rho_3\gamma_2 - \rho_1\gamma_1) = v_1 \tag{5.13}$$

Case 3: $u_1^*(t) = 1$, subject to the condition $v_1 = 0$ and $v_2 \neq 0$.

$$lk(\rho_3\gamma_2 - \rho_1\gamma_1) + v_2 = B \tag{5.14}$$

Therefore, we can propose the optimal value of $u_1(t)$, *i.e.*, $u_1^*(t)$ as stated below:

$$u_1^*(t) = \max(\min\Big(\frac{lk(\rho_3\gamma_2 - \rho_1\gamma_1)}{B}, 1\Big), 0) \tag{5.15}$$

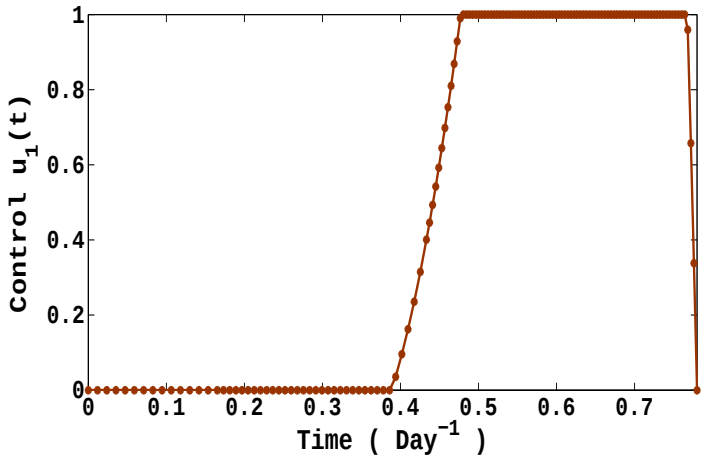

Figure 5: Control (Drug) effects are plotted as a function of time

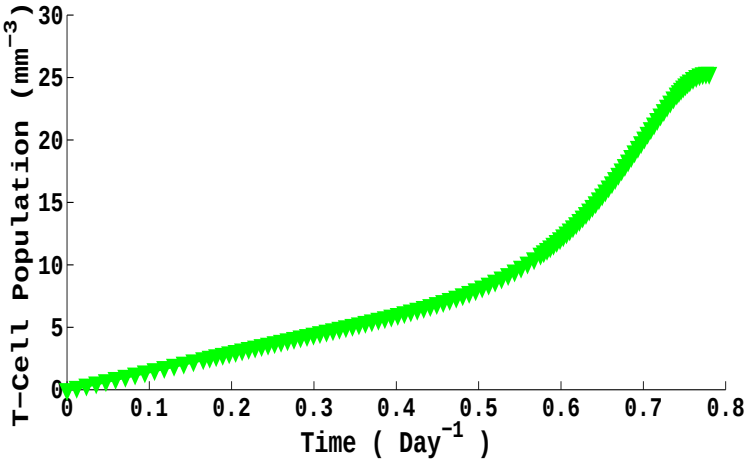

Figure 6: Population density of T-Cell (l) after applying Control (Drug) is plotted as a function of time

6 Numerical Illustration

In the Figure 5, we explain the control (drug) effects. Surrounded by first (approx.) 38 days, drug dosage is relatively constant. After that, drug input is leisurely but surely improved upto near about 50 days. Drug effort hits the highest point between 48^{th} to 78^{th} day, cf. in Figure 5. It reaches highest peak during these days. Control (drug) is dwindled very piercingly and at last, the input is clogged near about 80^{th} day, approx.

T-Cell population swells gradually with increasing drug effect. It enhances stridently in first 40 days and from then on increases step by step. When drug effect is bunged (near about 80^{th} day), T-Cell population happens to stable at 25 cell/mm^3/day and as well persists. Whenever, drug effect is applied progressively more, then Cytokine release is restricted and as a consequence, T-Cell population grows progressively (as Cytokines release give a negative effect to the intensification of T-Cell population). The escalating nature of T-Cell population is blocked, at whatever time drug

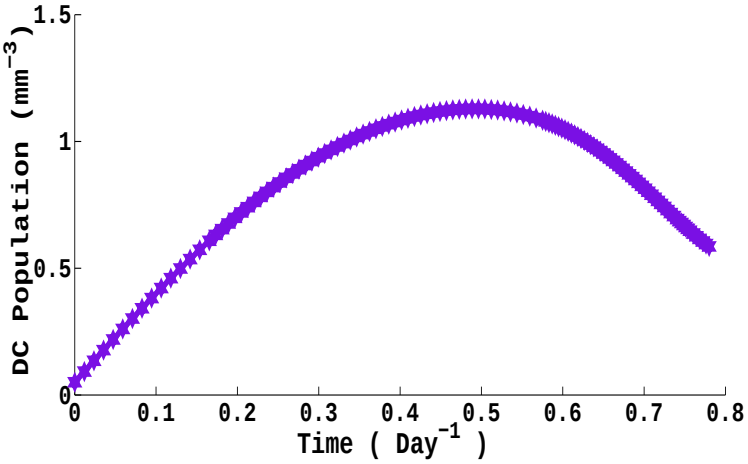

Figure 7: Population density of Dendritic Cell (m) after applying Control (Drug) is plotted as a function of time

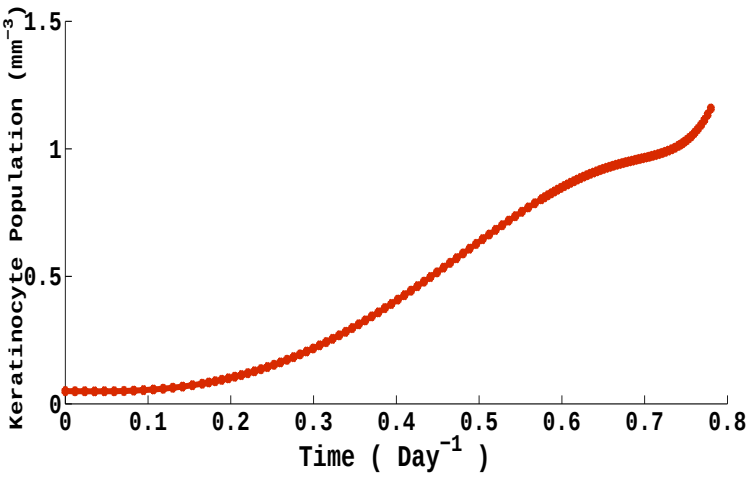

Figure 8: Population density of Keratinocyte (k) after applying Control (Drug) is plotted as a function of time

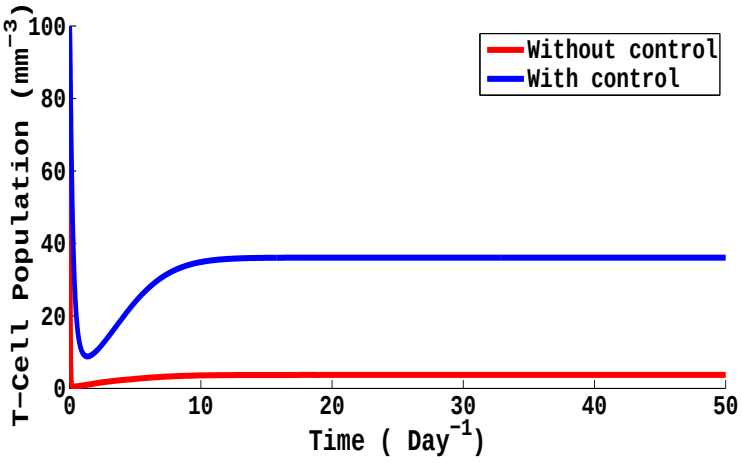

Figure 9: Behaviors of T-Lymphocyte Cell population (l) without and with Control (Drug) effects are plotted as a function of time

effect is congested, shown in Figure 6.

As remedy (drug) is not straightforwardly applied on the DCs, it is independent of drug effort. DCs increase within first 45 days on account of it's constant production and then decrease due to interface with T-Cell population and also for its own removal rate (Figure 7), as we notice that, the interaction with T-Cell facilitates to decrease its population.

The Keratinocyte population preserves its stabilized nature in first $15-20$ days, then it gradually enhance and grow upwards (Figure 8). Even though there is a continuous removal of its population, it is obligated to increase by the positive effect of (Cytokines release) the interaction between T-Cell and Keratinocyte populations.

We portray the cell-biological performances of the three forms of cells (T-Cell, DC, Keratinocyte) in two segments. Phase (1) behavior without control effort, Phase (2) behavior with control effort. The activities of T-Lymphocytes Cell (without control and with control) are established in Figure 9. The behaviors of DC (without control and with control) are exemplified in Figure 10. Finally, Keratinocyte's cell-biological actions (Without control and with control) are obtainable in Figure 11.

We watch the change in behavior of T-Lymphocyte Cell due to control effects (Figure 9). The population of T-Lymphocyte Cell increases, after applying control efforts, since control (drug) effects decrease the contact rate between T-Lymphocyte Cells and Keratinocytes, which in turn, restricts the release of Cytokines.

As the control is not directly applied on the Dendritic Cell, the difference of behaviors of DC population without control and with control is not significant enough (Figure 10). Although insignificant, the population of DC should be decreased after applying control upshot.

Like the earlier case, the alteration in behavior of Keratinocyte population is not momentous. The population density of Keratinocyte is reduced, after applying control (drug) effects (Figure 11). The one of the imperative rationale of this inconsequential features is that, despite the fact that, we restrict the fabrication of Keratinocyte, through interaction between T-Cell and Keratinocyte population (Cytokine release), we could not be in command of the production of Keratinocyte population

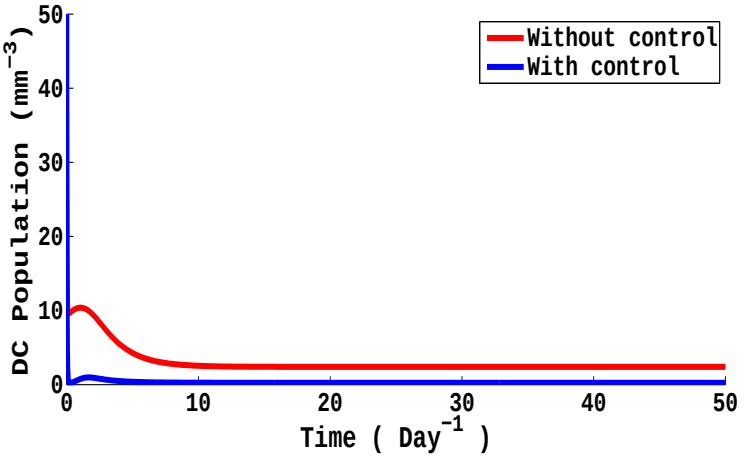

Figure 10: Behaviors of Dendritic Cell population (m) without and with Control (Drug) effects are plotted as a function of time

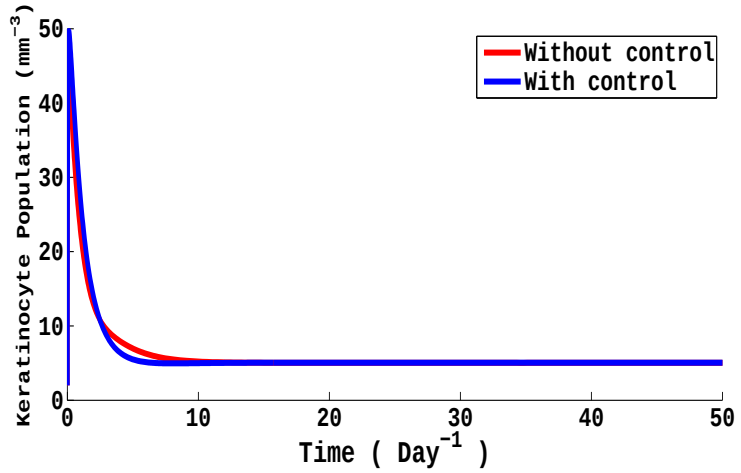

Figure 11: Behaviors of Keratinocyte population (k) without and with Control (Drug) effects are plotted as a function of time

through interaction between T-Cell and DC.

7 Discussion and Conclusion

It was reported that, the key players in the pathogenesis of Psoriasis are the stimulated CD4+ T-Cells, which is occurred by a good correlation of L-selectin levels on CD4+ T-Cells with disease sternness [21]. In our previous working [4], we have studied on the mathematical modeling on the immunopathogenesis in chronic plaque of Psoriasis. To get a better outcome, we also have done a comparative study on the suppression on T-Cells and DCs in a mathematical model of Psoriasis in the next article [17]. Now to obtain a more enhanced and superior result, here we have introduced the concept of Cytokines discharge during dealings between T-Cells and Keratinocytes. In our current working, we integrate suppression on Dendritic Cell and in addition embrace the thought of Cytokines release (Cytokines are released for the interaction between T-cells and Keratinocytes). At this point, we locate only the interior equilibrium point and next construct its stability analysis both analytically as well as numerically. We have only the interior equilibrium, ever since axial and planer equilibrium do not subsist as the value of "u" can by no means become 1. Merely, the interior equilibrium exists if the subsequent conditions hold which are demonstrated above elaborately.

We possibly will biologically articulate that, if (1) the creation rate of DCs by T-Cells, distinguished as β should be greater than double of γ_2, where γ_2 is the rate of contact of Dendritic Cells by T-Lymphocyte Cells, (2) the rate of interface of T-Lymphocyte Cells by Dendritic Cells, named as γ_1 is superior than the rate of interaction of Dendritic Cells by T-Lymphocyte Cells, phrased as γ_2, (3) The per capita deletion rate of the epidermal Keratinocyte density, which perceives profound growth by virtue of Cytokines, nominated by λ, be mandatory to be larger than some pre-assigned affirmative and confirmatory magnitude (extent), then the interior equilibrium $E^*(\ l^*,\ m^*,\ k^*\ )$ persists.

At beginning segment, consequently T-Cell population heightens very indistinctly within approximately first 10 days and after that, turns into stable. It prolongs its stability all through the entirety time length (here, we deem 100 days as the overall time phase). T-Cell first augments due to its steady (constant) production. Dendritic Cell population enhances very vaguely. After increasing, DC population declines within initial 10 days, because of suppression, applied on it. In the long run, DC population expands as well into stable as the interactions between T-Cells and Keratinocytes do not have any impact on the DC population. Keratinocytes population diminishes very penetratingly within first 10 (approx) days and the population retains the stabilized character throughout the complete time period. We observe the parameter, *i.e.*, the removal rate of Keratinocytes population, as very decisive, as the value of parameter λ (removal rate of Keratinocyte) is enlarged, the Keratinocyte population be converted into decreased feature. We are immeasurably enthralled about the crucial parameter λ. The behaviors of three categories of cell populations are same as that of the preceding case. We put up the value of the removal rate of Keratinocyte, named as λ, progressively (the values of the other parameters stay behind unaltered). We perceive the same experience. Most entertainingly, we inspect that, when we boost the confiscation rate of Keratinocyte (λ), afterward the rate of interaction between T-Cell and Keratinocyte population is osmotically reduced and noticeably, the rate of Cytokine release is decreased. As a corollary, T-Cell population raises gradually, symbolized in Figure 1, Figure 2, Figure 3 and Figure 4, respectively. Accordingly the Keratinocyte population is shrinking as the time to raise.

It was earlier suggested that, this chronic inflammatory skin ailment is related with cardiovascu-

lar disorders, diabetes mellitus and rheumatoid arthritis. These associated diseases are considered as oxidative stress state of affairs [22]. Elevated echelons of IFN-γ and IL-2 but stumpy of IL-10 and IL-4 was described by Schlaak et al [23]. There was a negative feedback in the IL-4 construction, which was considered by Mozzanica et al [24], [2]. It is well-known information, derived from our mathematical representation that, contacts between T-Cell and Dendritic Cell cause reduction in the both of the population. This decrease produces the growth in the Keratinocyte population. During contact between T-Cell and Keratinocyte population, Cytokines are released. This Cytokines is one of the significant reasons for the growth of the skin ailment, Psoriasis. We are proficient to suppress the dealings between T-Cell and Keratinocyte population by applying control (drug) effort. As a result, the concentration of T-Cell would not be decreased (T-Cell population engorges gradually with increasing drug effect), which is presented in Figure 6 (Cytokine release lessens the T-Cell population). Thus, applying control (drug), Cytokines release are controlled, so that the recurrent unrelenting and chronic autoimmune stimulating skin ailment, Psoriasis is restricted. We desire to suppress the growth of Keratinocytes using control effect to restrict the autoimmune skin ailment, Psoriasis. Applying control (drug) effect between T-Cells and Keratinocytes, we are able to suppress the growth of Keratinocytes (Cytokines release are checked). Thus the disease should be controlled, *i.e.*, restricted. Hence in an essence, we can bring to an end that, if the control (drug) is incorporated with T-Cells and certainly to the release of Cytokine in our nearby demonstration, we are capable to get hold an enhanced and improved conclusion than our previous work.

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