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T-cell proliferation on immunopathogenic mechanism of psoriasis: a control based theoretical approach*

by

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Abstract: Psoriasis vulgaris is a common, worldwide autoimmune skin disorder characterized by T-cells mediated hyperproliferation of keratinocytes. The feature of T-cells arbitrated psoriatic lesions is the epidermal infiltration of oligoclonal $CD8^+$ T-cells and also of $CD4^+$ T-cells in the dermis. Psoriatic scratches are identified by red and enlarged lesions along with silver whitish scales. In this article, we propose a mathematical model for psoriasis, involving a set of differential equations, concerning T-cells, dendritic cells and epidermal keratinocytes. We introduce T-cell proliferation in the system, where T-cells are generated through expansion of accessible $CD4^+$ T-cells from precursors. We are interested in observing how the cell biological system develops through T-cell proliferation in presence of control with respect to T-cells and keratinocytes. We study the model in both implicit and explicit ways and measure the effect of drug on the system through impulsive drug therapy.

Keywords: T-cells, dendritic cells, keratinocytes, dermis, epidermis, cytokines, T-cell proliferation, drug efficacy, optimal control

1. Introduction

Psoriasis is considered to be a widespread continuous inflammatory skin disease, which is characterized by T-cells mediated hyperproliferation of keratinocytes. Psoriasis affects about 1.5% of the Caucasian population (Sabat et al., 2007). $CD8^+$ T-cells may act as the foremost effector in psoriatic pathogenesis. From the point of view of clinical investigation, we know that the immune organization plays an important role for the expansion of psoriasis (Gudjonsson et al., 2004). Psoriasis is also described as a genetically heterogeneous disorder. The two bases for the disease development are the attachment of multiple genes and

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the communication with the environment (Ghosh et al., 2008). The US Food and Drug Administration's (FDA's) approval demonstrates the achievement of translational research on this type of chronic disease. The biological concept considers Alefacept to be a fusion protein that connects to CD2 on T-cells, and Efalizumab a humanized antibody that can attach to leucocyte function associated antigen-1 (LFA-1). There are three types of HL-A specificities, with W17 and HL-A13 increased and HL-A12 reduced. The increase–related regularity for W17 and HL-A13 suggested that people with these forms of tissues are at increased threat of the disease, while those with HL-A12 are at a decreased risk (White et al., 1972). Cell biology and clinical investigation point toward a composite sequence of procedures that lead to the emergence of psoriatic plaques. The disease initiates from the activation of T-cells accretion in the appropriate dermal region through DCs. Besides, the inflammatory cytokines like Tumour Necrosis Factor-alpha (TNF-α) play an important pathogenic role in this disease (Krueger and Bowcock, 2005). Furthermore, TNF-α and also IFN-γ guide to the maturation of DCs, which once more furnish the activation of native T-cells through transitional cell mechanisms. To generate a cyclical series for activation of T-cells and DCs, the following three events that are relevant for excessive growth of keratinocytes, contribute to the causal effect of psoriasis. Firstly, the cytokines are produced through mutual formation. Secondly, proliferation of keratinocytes is stimulated in the epidermal area of the skin and finally, antigenic molecules are formed in the dermal blood vessels. In the above mentioned ways, psoriasis ultimately leads to the coagulation of epidermis, the lower layer of the keratinocytes (Krogstad et al., 1995; Roy et al., 2010; Vladirmirsson et al., 1986). The disease occurs as a result of collapse in the human immune arrangement. In definite conditions, Cyclosporin and FK506 are applied as drugs that proceed as T-cells suppressors (Baker and Fry, 1992; Griffiths et al., 1995). By introducing bone marrow transplants with a positive reaction to anti-CD3 and anti-CD4 monoclonal antibodies and lymphocyte toxins, psoriatic scratches may be treated (Eddy et al., 1990; Snowden and Heaton, 1997).

Over several years, extensive clinical and experimental investigations have been carried out for the pathogenesis of psoriasis. A lot of information has been gathered on genetic distinctions related to immune cells, pathogenesis and drugs. These genetic distinctions are due either to blocking the integration of RNA into the host $CD4^+$ T-cells or to restraining the appropriate proteins within an infected cell. Till now the basic questions are unanswered regarding this disease. In our previous article, we described the mathematical model, integrating the half saturation constant in presence of suppression together with cytokines release, taking place on DCs (Roy et al., 2011). Next, we noticed how the system changed due to impact of cytokines discharge in presence of suppression, taking place on DCs in the cell system (Roy and Datta, 2012). Furthermore, we described a set of differential equations for the process of stable control regarding the growth of epidermal keratinocytes by means of negative feedback, comparable to the introduction of a beneficial drug management. We introduced also a time delay in that model to represent the time related to

creation of T-cells and DCs until the expansion to the epidermal keratinocytes (Roy and Datta, 2012). It should be noted that T-cells suppression reduces the psoriatic pathogenesis and thus the asymptotic value of T-cell population is obtained concurrently. Roy and Bhadra (2010) stated that the suppression of DCs raises the concentration of T-cells, leading to a better condition than the suppression of T-cells.

For infectious diseases, it is proposed that T-cells can be produced by proliferation of some obtainable $CD4^+$ T-cells (Roy and Chatterjee, 2010). But in autoimmune disorder, some of T-cells are effectively enhanced. This process is identified as spontaneous proliferation (Campion et al., 2009). When the two signal activation is finished, T helper cells permit self-proliferation. This is accomplished by releasing Interleukin–2 (IL-2), which acts on itself in an autocrine manner. The thus stimulated T-cells must be detached by apoptosis at the end of an immune reply in order to uphold cellular homeostasis. Apoptosis can also be induced by cytokine deficiency (Akbara and Salmonb, 1997). The proliferating cells can be activated by antibodies, which are specific for a variety of cell types. Proliferating dermal cells display silver granules from tritium release. On the other hand, the proliferation and development of two constitutive cell types (Factor $XIIIa^+$ and Factor $VIII^+$) may result in maintaining the chance of $UCHL1^+$ ($CD45RO^+$) T-cells. The opening of antigen-reactive T-cells may enhance the dynamic strength of the dendritic cells and endothelial cell proliferation (Morganroth et al., 1991).

Significant advance on the study of state constrained optimal control problems is due to application of the technique called Alternative Optimality System. This procedure was initiated by Bryson, Denham and Dreyfus (1963), and Jacobson, Lele and Speyer (1971). The fundamental scheme shows that as soon as a state constraint is active over a particular time interval, the time derivative of the smallest order changes in such a way that the control changes accordingly (Bonnans and Hermant, 2009). An application of modern geometric control methods to quantum control arrangements is a novel approach in optimal control theory (Bonnard and Sugny, 2009). We have introduced the optimal control therapy strategy to optimize the use of drug for a long time in the sequence of days. The usual procedure is to control the drug for a few hours every few weeks. Nevertheless, our precise objective in the optimal control approach is to reduce the keratinocyte population, keeping the patient well by several measures (De Pillis and Radunskaya, 2001). The communication between psoriasis and stress was observed over 20 weeks by way of significant measures. Consequently, stress reduction may be observed as an aspect of treatment, for persons suffering from psoriasis (Gaston et al., 1987). In the optimal control mechanism, mathematical two non-cell-cycle-specific representations (in all the phases of the cell cycle, drugs are helpful) were developed by Murray (Murray, 1990 a, b). We desire to expand the optimal control problem, beginning with cell-cyclic-specific action on the normal tissues, and to determine the mathematical consequences (Fister and Panetta, 2000). For all patients, the identification of model parameters may, however be complicated (De Souza et al., 2000). Further, we have also studied

the explicit version of the model to explore the drug effects on the system.

We consider here that the growth of $CD4^+$ T-cells is logistic as T-cells cannot proliferate unboundedly. In this article, we integrate T-cell proliferation in the model system and our aim is to observe the performance of the immune system through drug stimulation with maximum proliferation of T-cells. We have also studied the optimal control therapeutic approach with respect to the interaction between T-cells and keratinocytes.

In Section 1, we have discussed the T-cell proliferation and optimal control therapeutic strategy. In Section 2, we have described the basic assumptions of the model and mathematical formulation of the model for psoriasis. Section 3 presents the theoretical analysis of the model, containing existence, uniqueness, permanence and boundedness of the system. This section also includes the unique equilibrium of the system including biological interpretation. In Section 4, we investigate the optimal control (drug) therapeutic approach, integrating existence, dynamical nature and uniqueness of the optimal control system. Section 5 includes analysis of the explicit version of the system through impulsive drug therapy and dynamical consequences thereof. Numerical simulation and discussion are given in Section 6, and, conclusion is given in Section 7. Finally, appendix to prove the uniqueness of the solution for the system is furnished in Section 8.

2. The basic assumptions and the mathematical model

Let $l(t)$, $m(t)$ and $k(t)$ denote the concentrations of T-cells, dendritic cells and epidermal keratinocytes corresponding to a specific time t. We wish to obtain a set of differential equations.

(A1): Locally the accumulation of T-cells in plaques occurs at a constant rate a, and the accumulation rate of dendritic cells is considered to be the constant b. It is also assumed that T-cells and dendritic cells are not produced by means of any other method.

(A2): The rate of activation of T-cells by DCs is denoted by δ and also β is the activation rate of DCs through T-cells. We assume that η is the proportion at which commonly stimulated T-cells and DCs join the expansion of epidermal keratinocytes. Interactions between T-cells and DCs help to form keratinocytes through some cell biological procedures and thus the population of both T-cells and DCs are reduced, as illustrated by the terms $-\delta lm$ and $-\beta lm$, respectively.

(A3): The rate of activation of keratinocytes due to T-cells mediated cytokines is indicated by γ_1 and the rate of keratinocytes growth is denoted by γ_2. Also interactions between T-cells and keratinocytes facilitate the generation of keratinocytes through some biological mechanisms and so T-cell population is reduced, as shown by the term $-\gamma_1 lk$.

(A4): As the total number of T-cells cannot increase unboundedly, we assume that the proliferation of T-cells is logistic, where p indicates the maximum proliferation rate, proliferation proceeding up to a certain maximum stage, given by l_{max} along with T-cell population. To formulate our mathematical model,

we consider the logistic term in the form $pl(1-\frac{l}{l_{max}})$.

(A5): The per capita removal rate of T-cells as given by μ and μ' is the per capita removal rate of dendritic cells in the course of normal progression. Further, the per capita removal rate of epidermal keratinocytes is given by λ.

(A6): To restrict the interaction between T-cells and epidermal keratinocytes, we introduce the drug efficacy parameter u to the term associated with the connection between the above two populations, as interactions between them help to develop the growth of keratinocytes, which in turn generates psoriasis. We introduce the same efficacy parameter u to the growth equations of both T-cells and keratinocytes as interactions between them reduce T-cell population simultaneously and develop the growth of keratinocytes.

Bringing together the above assumptions (A1)-(A6), we can organize the mathematical model given below:

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

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

3. Theoretical study of the system

3.1. Existence, uniqueness and boundedness of the system

The RHSs of equation (1) are smooth functions of the variables l, m, k, and parameters, providing these quantities are non-negative. Thus, local existence, uniqueness and boundedness of the system are ensured in the positive octant. In the subsequent theorem, we will illustrate that the linear combination of accumulation of T-cells, dendritic cells and keratinocytes densities is less than a predetermined quantity. In other words, the solution of the dynamical system is bounded.

THEOREM 1. *Solution y(t) of system (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

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

We notice that W is a well defined and differentiable function on some maximal interval $(0, t_f)$.

The time derivative of system (1) is

$$\frac{dW(t)}{dt} = (a+b) - (\delta+\beta-\eta)lm + [p(1-\frac{l}{l_{max}}) - \mu]l + (1-u)(\gamma_2-\gamma_1)lk - \mu' m - \lambda k.$$

For the sake of straightforwardness of computation, we here assume that the rate of activation of keratinocytes due to T-cells mediated cytokines, given by γ_1 and the rate of keratinocytes growth, denoted by γ_2, are the same ($\gamma_1 = \gamma_2$).

Therefore, the above equation takes the form,

$$\frac{dW(t)}{dt} = (a+b) - (\delta + \beta - \eta)lm + [p(1 - \frac{l}{l_{max}}) - \mu]l - \mu' m - \lambda k.$$

At this moment, for all $\psi > 0$, the following inequality holds (Roy and Bhadra, 2010),

$$\frac{dW(t)}{dt} + \psi W(t) \leq (a+b) - (\delta + \beta - \eta)(\frac{l^2+m^2}{2}) - [\mu - p(1 - \frac{l}{l_{max}}) - \psi]l$$
$$-(\mu^{'} - \psi)m - (\lambda - \psi)k \leq (a+b) + \frac{(\mu - p(1-\frac{l}{l_{max}}) - \psi)^2 + (\mu^{'} - \psi)^2}{2(\delta + \beta - \eta)} - (\lambda - \psi)k.$$

If we suppose that $0 < \psi < \lambda$, then there exists $\epsilon > 0$ such that,

$$\frac{dW(t)}{dt} + \psi W(t) \leq \epsilon \quad \text{for each } t \in (0, t_f).$$

Let H(t,y)=$\epsilon - \psi y$, which satisfies Lipschtiz condition everywhere. Evidently,

$$\frac{dW(t)}{dt} \leq \epsilon - \psi W(t) = H(t, W(t)) \quad \text{for all} \quad t \in (0, t_f).$$

Let $\frac{dx}{dt}$=$H(t,x)$=$\epsilon - \psi x$ and $x(0)$=$W(0)$=W_0. This ordinary differential equation has the solution

$$x(t) = \frac{\epsilon}{\psi}(1 - e^{-\psi t}) + W_0 e^{-\psi t}.$$

It is evident that $x(t)$ is bounded on $(0, t_f)$. By the Comparison Theorem (Birkhoff and Rota, 1982),

$$W(t) \leq x(t) = \frac{\epsilon}{\psi}(1 - e^{-\psi t}) + W_0 e^{-\psi t} \quad \forall \quad t \in (0, t_f).$$

Now consider $t_f < \infty$, then $W(t_f) \leq x(t_f) < \infty$. Then the solution is unique for some interval $(0, t_f)$ by the Picard-Lindelof Theorem. This contradicts the assumption that $t_f < \infty$. Consequently, $W(t)$ must be bounded for all non-negative t and as a result $y(t)$ is uniformly bounded on $R_{0,+}$ (Roy and Bhadra, 2010). ■

3.2. Permanence of the system

The system (1) is permanent (Tian et al., 2008) if there exists a compact set D in $R^3_+ = \{(l(t),\ m(t),\ k(t)) \in R^3_+ \mid l(t) > 0,\ m(t) > 0,\ k(t) > 0\}$ such that all solutions inside of R^3_+ finally come into D and stay in D.

To examine the permanence of the system (1), we consider that $R^3_+ = \{(l(t),\ m(t),\ k(t)) \in R^3_+ \mid l(t) > 0,\ m(t) > 0,\ k(t) > 0\}$ is the positively invariant set of the system (1) and $(l(t),\ m(t),\ k(t))$ is a random positive solution of the system (1) for a positive initial value.

THEOREM 2. *For the system (1) satisfying the initial condition* $(l(0),\ m(0),\ k(0)) \in R^3_+$, *there exist positive* l^*_{max}, m^*_{max} *and* k^*_{max}, *such that for any* $(l(t),\ m(t),\ k(t)) \in R^3_+$, $l(t) \le l^*_{max}$, $m(t) \le m^*_{max}$ *and* $k(t) \le k^*_{max}$ *for large t.*

Proof. We have $W(t) = l + m + k$ is bounded, which is established for every non-negative t and as a result $y(t) = (l(t), m(t), k(t))$ is uniformly bounded on R_+. Hence proved. ∎

THEOREM 3. *For the system (1) satisfying the initial condition* $(l(0),\ m(0),\ k(0)) \in R^3_+$, *there exist positive* l^*_{min}, m^*_{min} *and* k^*_{min}, *such that for any* $(l(t),\ m(t),\ k(t)) \in R^3_+$, $l(t) \ge l^*_{min}$, $m(t) \ge m^*_{min}$ *and* $k(t) \ge k^*_{min}$ *for large t.*

Proof. For $l(t) \ge l^*_{min}$, $m(t) \ge m^*_{min}$, $k(t) \ge k^*_{min}$, where $k^*_{min} = \frac{\eta l^*_{max} m^*_{max}}{\lambda - \gamma_2 l^*_{max}(1-u)}$, $m^*_{min} = \frac{b}{\beta l^*_{max} + \mu'}$ and l^*_{min} is the positive root of the equation

$$a + p l^*_{min}(1 - \tfrac{l^*_{min}}{l_{max}}) - \delta l^*_{min} m^*_{max} - \gamma_1 l^*_{min} k(1-u) - \mu l^*_{min} = 0.$$

For large t,

$$\frac{dl}{dt} = a + pl(1 - \frac{l}{l_{max}}) - \delta lm - \gamma_1 lk(1-u) - \mu l \ \ge\ [a + pl(1 - \frac{l}{l_{max}}) - \delta l m^*_{max} - \gamma_1 lk(1-u) - \mu l] \ \ge\ 0,$$

$$\frac{dm}{dt} = b - \beta lm - \mu' m \ \ge\ [b - \beta m l^*_{max} - \mu' m] \ \ge\ 0,$$

$$\frac{dk}{dt} = \eta lm + \gamma_2 lk(1-u) - \lambda k \ \ge\ [\eta l^*_{max} m^*_{max} + \gamma_2 l^*_{max} k(1-u) - \lambda k] \ \ge\ 0.$$

Consequently, the system is bounded below.

Thus we come across a compact set $D = \{l(t),\ m(t),\ k(t) \mid l^*_{min} \le l(t) \le l^*_{max},\ m^*_{min} \le m(t) \le m^*_{max}$ and $k^*_{min} \le k(t) \le k^*_{max}\}$ corresponding to the system (1), where each solution of the system with positive initial value will go through the compact region D and stay in D.

Hence from definition of permanence, the whole solution of the system (1) is permanent (Roy and Bhadra, 2010). ∎

3.3. Equilibria of the system

The model equation (1) may have the unique equilibrium point (interior equilibrium) on the coordinate planes at $E^*(l^*, m^*, k^*)$, where l^*, m^*, and k^* are the non-trivial solutions of the model system (1). The other equilibria do not exist due to the choice of parameters and the restriction to equilibria of the biological system being in the positive octant. The only equilibrium point is $E^*(l^*, m^*, k^*)$, where $k^* = \frac{\eta l^* m^*}{\lambda - \gamma_2 l^*(1-u)}$, $m^* = \frac{b}{\beta l^* + \mu'}$ and l^* is the positive root of the equation $[(a+b) + (p(1 - \frac{l^*}{l_{max}}) - \mu) l^*][(\beta l^* + \mu')(\lambda - \gamma_2 l^*(1-u))] - \mu' b(\lambda - \gamma_2 l^*(1-u)) - \eta\lambda b l^* = 0$.

Now, k^* is positive when $\lambda > \gamma_2 l^*(1-u)$ and m^* is always positive. Thus, biologically, the system has an equilibrium if the per capita removal rate of epidermal keratinocytes is greater than a predetermined positive quantity.

Now, if we assume the relation $\mu < \mu' < \lambda$ then,

$$\frac{dT_{tot}}{dt} \equiv \frac{d(l+m+k)}{dt} < (a+b) - \mu(l+m+k),$$

if the density of T-cells is approaching its maximum level (l_{max}). Again we assume that the sum of the rate of activation of T-cells by DCs (δ) and activation rate of DCs through T-cells (β) is equal to the portion at which are commonly stimulated T-cells and DCs (η) i.e., $\delta + \beta = \eta$. We also assume that the rate of activation of keratinocytes due to T-cells mediated cytokines (γ_1) and rate of keratinocytes growth (γ_2) are the same i.e., $\gamma_1 = \gamma_2$.

Lemma 1. *Suppose x is a function satisfying $x'(t) < d - f(\phi)x(t)$, where d is a constant and $f(\phi)$ is independent of x and t. Then if $x(0) < \frac{d}{f(\phi)}$, it follows that $x(t) < \frac{d}{f(\phi)}$ for every t.*

Proof. See Smith and Wahl (2004, Lemma 4.1), Smith (2008). ■

Remark. If the inequalities are reversed, **Lemma 1** also holds.

Using the above **Lemma 1**, we can state that $T_{tot} < \frac{a+b}{\mu}$, if $T_{tot}(0) < \frac{a+b}{\mu}$. Therefore, if the above mentioned assumptions are satisfied, then the limiting value of the total cell population should not exceed the quantity $\frac{a+b}{\mu}$ (Lou, 2009).

4. Optimal control (drug) therapeutic approach

The system of ordinary differential equations, which describes the interactions of proliferated T-cells and epidermal keratinocytes in the immune system, is exploited and optimal control for the treatment strategies for this model is found. Existence and uniqueness for the optimal control are established. It is proposed to reduce the interaction between T-cells and keratinocytes and also to recover the immune system. This brings innovative expectation to the treatment of psoriasis and we are exploring approaches for such treatments by means of optimal control effort (Joshi, 2002). The control refers to the considerable effect of the drug on the disease. We have chosen our control set, defined on $[t_s, t_f]$ with the restriction $0 \leq u(t) < 1$, where t_s and t_f are t_{start} and t_{final}, respectively. Even though we do not consider the deviation or side effects, we can implement a condition that organizes the complete effects of this period: a controlled treatment, which is programmed for any treatment circumstances (Kirschner et al., 1997).

We here introduce a proliferation of T-cells in the system. During interaction between T-cells and kertinocytes, the cytokines are discharged and also stimulated. Then keratinocytes are produced through some biological procedures and excess amounts of keratinocytes help to develop psoriasis. Thus we put the control effort to the interaction between T-cells and keratinocytes at the time of production. In this situation, we desire to suppress the cytokines release using

control approach to the growth equation of T-cells and keratinocytes. Thus, for $t_s \leq t \leq t_f$, the system is:

$$\begin{aligned} \frac{dl}{dt} &= a + pl(1 - \frac{l}{l_{max}}) - \delta lm - \gamma_1 lk(1 - u(t)) - \mu l, \\ \frac{dm}{dt} &= b - \beta lm - \mu' m, \\ \frac{dk}{dt} &= \eta lm + \gamma_2 lk(1 - u(t)) - \lambda k, \end{aligned} \tag{2}$$

with known initial values for l, m, and k at t_s.

Define the objective function

$$J(u) = \int_{t_s}^{t_f} [k(t) + \frac{1}{2} B(u(t))^2] dt. \tag{3}$$

Our aim is to minimize the objective function. The objective function is a non-linear function of u. A quadratic objective function can also be chosen. Enormous drug doses can be harmful. If the control $u(t) = 0$ corresponds to optimal consumption of drug, then the optimal cost is $(1-u(t))$. The parameter $B \geq 0$ is the preferential weight on the benefit and cost. The goal is to attain the optimal control u^*, corresponding to $J(u) = J(u^*)$ in the interval $0 \leq u(t) < 1$. If u^* is an optimal control, then the "Pontryagin's Minimal Principle" may be functional to the reversed control approach (Kirschner et al., 1997). One of our objectives is to simulate qualitatively the drug efficiency for the interaction of T-cells and keratinocytes. So, we have built the model to represent the corresponding activity. Our another goal is to recognize treatment procedures that may achieve a better regularized drug therapy schedule. The optimal control therapies furnish results in the population over time (De Pillis and Radunskaya, 2001).

4.1. Existence of the optimal control

The existence of the optimal control can be achieved by applying the result as suggested by Fleming and Rishel (1975, Th. 4.1, pp. $68 - 69$).

THEOREM 4. *Let us consider the control problem with system equation (2). There exists $u^* \in U$, where U is the control set such that $J(u) = J(u^*)$.*

Proof. To utilize the existence result, Theorem III.4.1 from Fleming and Rishel (1975), we have to ensure the following:

1. The control set and analogous state variable sets are nonempty.
2. The control set, denoted by U, is convex and closed.
3. The RHS of the system dynamics is bounded by means of a linear function in the state and control variables.
4. The integrand of the objective function is concave on the control set U.

5. There exists a constant $c > 0$ and $\alpha > 1$ such that the integrand of the objective function assures

$$k(t) + \frac{1}{2}B(u(t))^2 \ \leq \ c(|u|^2)^{\alpha/2}.$$

For confirmation of these conditions, we use the result by Lukes (1982, Th. 9.2.1, pp. 182) to provide the existence of solutions of ODE's with bounded coefficient, which furnishes the condition 1. We observe that the solutions are bounded. Our control satisfies the condition 2. Because of our linear state system, the RHS of the equation satisfies the condition 3.

We note that the integrand of the objective function is concave. Also we have the final condition needed

$$k(t) + \frac{1}{2}B(u(t))^2 \ \leq \ c(|u|^2)^{\alpha/2},$$

where $c > 0$ depends on the upper bound of keratinocyte population k and $B > 0$. Hence, we may conclude that there exists a unique optimal control (Joshi, 2002). ■

4.2. Dynamics of the optimal system

For optimal control system, we define the Hamiltonian,

$H = k + \frac{1}{2}B(u(t))^2 + \rho_1[a + pl(1 - \frac{l}{l_{max}}) - \delta lm - \gamma_1 lk(1 - u(t)) - \mu l] + \rho_2[b - \beta lm - \mu' m] + \rho_3[\eta lm + \gamma_2 lk(1 - u(t)) - \lambda k] + v_1 u(t) + v_2(1 - u(t))$,
where ρ_1, ρ_2, and ρ_3 are adjoint variables and v_1, and v_2 are penalty multipliers, subject to the conditions,
$u = 0$ when $v_1 \neq 0$ and $v_2 = 0$ and $u = 1$ when $v_1 = 0$ and $v_2 \neq 0$.

The corresponding adjoint equations are stated as:

$$\frac{d\rho_1}{dt} = -\frac{\partial H}{\partial l}, \tag{4}$$

$$\frac{d\rho_2}{dt} = -\frac{\partial H}{\partial m}, \tag{5}$$

$$\frac{d\rho_3}{dt} = -\frac{\partial H}{\partial k}, \tag{6}$$

where

$$\frac{\partial H}{\partial l} = \rho_1(p(1 - \frac{2l}{l_{max}}) - \delta m - \gamma_1 k(1 - u(t)) - \mu) - \rho_2 \beta m + \rho_3(\eta m + \gamma_2 k(1 - u(t))), \tag{7}$$

$$\frac{\partial H}{\partial m} = -\rho_1 \delta l - \rho_2(\beta l + \mu') + \rho_3 \eta l, \tag{8}$$

$$\frac{\partial H}{\partial k} = 1 - \rho_1\gamma_1 l(1-u(t)) + \rho_3(\gamma_2 l(1-u(t)) - \lambda). \tag{9}$$

Again H can be represented as,

$$H = \frac{1}{2}B(u(t))^2 - \rho_1\gamma_1 lk(1-u(t)) + \rho_3\gamma_2 lk(1-u(t)) + v_1 u(t) \tag{10}$$
$$+v_2(1-u(t)) + \text{ terms without } u.$$

Now, differentiating the above expression for H with respect to u yields,

$$\frac{\partial H}{\partial u} = Bu(t) + \rho_1\gamma_1 lk - \rho_3\gamma_2 lk + v_1 - v_2. \tag{11}$$

This expression should be equal to zero at $u^*(t)$. Thus, $Bu(t) + \rho_1\gamma_1 lk - \rho_3\gamma_2 lk + v_1 - v_2 = 0$ at $u^*(t)$.

Solving for the optimal control, we have,

$$u^*(t) = \frac{lk(\rho_3\gamma_2 - \rho_1\gamma_1) - v_1 + v_2}{B}. \tag{12}$$

Now, there are three cases to be observed.

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

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

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

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

$$u^*(t) = \frac{lk(\rho_3\gamma_2 - \rho_1\gamma_1)}{B}. \tag{13}$$

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

$$lk(\rho_3\gamma_2 - \rho_1\gamma_1) = v_1. \tag{14}$$

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

$$lk(\rho_3\gamma_2 - \rho_1\gamma_1) + v_2 = B. \tag{15}$$

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

$$u^*(t) = \begin{cases} 0, & \dfrac{lk(\rho_3\gamma_2 - \rho_1\gamma_1)}{B} \leq 0, \\ \dfrac{lk(\rho_3\gamma_2 - \rho_1\gamma_1)}{B}, & 0 < \dfrac{lk(\rho_3\gamma_2 - \rho_1\gamma_1)}{B} < 1, \\ 1, & \dfrac{lk(\rho_3\gamma_2 - \rho_1\gamma_1)}{B} \geq 1. \end{cases} \tag{16}$$

4.3. Uniqueness of the optimal control

THEOREM 5. *The solution of the system of non–linear bounds is unique for a small time interval.*

Proof. See Appendix. ∎

5. Analysis of the explicit version of the system through impulsive drug therapy

In the preceding part, we have studied the implicit version of the system, incorporating control (drug) therapeutic approach, taking place between the interaction of proliferated T-cells and epidermal keratinocytes. We now wish to analyze the model system explicitly through impulsive drug therapy. Our aim is to observe, how the system behaves after integrating impulsive drug therapeutic strategy. So, we have formulated the model with impulsive differential equations, given below:

$$\begin{aligned}
\frac{dl}{dt} &= a + pl(1 - \frac{l}{l_{max}}) - \delta lm - \gamma_1 lk - \mu l - ql\tilde{R}, \\
\frac{dm}{dt} &= b - \beta lm - \mu' m, \\
\frac{dk}{dt} &= \eta lm + \gamma_2 lk - \lambda k, \\
\frac{d\hat{l}}{dt} &= ql\tilde{R} - \mu\hat{l},
\end{aligned} \tag{17}$$

where $l(0) > 0,\ m(0) > 0,\ k(0) > 0$ and $\hat{l}(0) > 0$ at a specific time t. In these equations, notations are the same as in (1). Here, $\hat{l}$ is the concentration of T-cells, which are separated through interaction with drug ($\tilde{R}$) and q is the rate of interaction between proliferated T-cells and drug ($\tilde{R}$). Also μ is the per capita removal rate of separated T-cells, having interacted with drug ($\tilde{R}$).

The dynamics of the drug ($\tilde{R}$) is described by,

$$\frac{d\tilde{R}}{dt} = -h\tilde{R},\ t \neq t_k, \tag{18}$$

along with impulsive conditions,

$$\Delta\tilde{R} = \Delta\tilde{R}_k\ (or\ \tilde{R}^i),\ t = t_k, \tag{19}$$

where $t_k = k\tau,\ k = 0, 1, ..., h$ is the rate at which the drug is depleted and $\Delta\tilde{R}_k$ ($or\ \tilde{R}^i$) is the dosage of the drug.

We also notice that

$$\tilde{R}(t_k^+) = \tilde{R}(t_k^-) + \Delta\tilde{R}_k,$$

where t_k^- and t_k^+ represent the time just before and after one dose being taken, respectively. The impulse period t_k can be presumed to be unchanged, describing normal dosing phases. We can also state t_1 to be considerably large to express the fact that drugs are not in use until the disease has been diagnosed. We will similarly suppose that $\tilde{R}(0) = 0$. Thus, system (17), with (18) and (19) determines our model of impulsive differential equations (Smith and Wahl, 2005). There is an impulsive periodic orbit that satisfies

$$\frac{\tilde{R}^i e^{-h\tau}}{1 - e^{-h\tau}} \leq \tilde{R} \leq \frac{\tilde{R}^i}{1 - e^{-h\tau}} \quad \text{(Lou and Smith, 2011)} \tag{20}$$

where τ is the time between subsequent doses.

Let us suppose that the total number of T-cells be $l_{tot} \equiv l + \hat{l}$. Now,

$$l'_{tot} = a - l(\delta m + \gamma_1 k + \mu - p + \frac{pl}{l_{max}}) - \mu\hat{l},$$

i.e., $l'_{tot} = a - Ml - \mu\hat{l}$, where $\mathrm{M} = \delta m + \gamma_1 k + \mu - p + \frac{pl}{l_{max}} > 0$. If $\mu > p$, this implies

$$l'_{tot}(t) < a - \mu l_{tot}(t),$$

if $\mathrm{M} > \mu$. Then from the above mentioned Lemma (Smith and Wahl, 2004, Lemma 4.1; Smith, 2008), we have,

$$l_{tot}(t) < \frac{a}{\mu}, \text{ if } l_{tot}(0) < \frac{a}{\mu}. \tag{21}$$

The limiting value of the total amount of T-cells should be less than $\frac{a}{\mu}$ in the immune system for the effectiveness of the impulsive drug therapy, providing the per capita removal rate of T-cells greater than the maximum proliferation rate constant.

5.1. Dynamical consequences of drug

Now, we talk about the dynamical nature of the drug. To begin with, we provide the general explanation of

$$\frac{d\tilde{R}}{dt} = -h\tilde{R}, \ t \neq t_k,$$

$$\tilde{R}(0) = \tilde{R}_0 \ \text{ for } \ t = 0,$$

$$\tilde{R}(t^+_{k+1}) = \tilde{R}(t^-_{k+1}) + \Delta\tilde{R}_{k+1} \ \text{ for } \ t = t_{k+1},$$

where $t_k = k\tau, \ k = 0, 1, ...$ Here, $\Delta\tilde{R}_{k+1} \geq 0$ and the initial dosage of drug is denoted by $\tilde{R}_0$. The impulse periods t_k are assumed fixed, as normal dosing episodes. Time between subsequent doses is assumed to be constant. That is, $\tau = t^+_k - t^-_{k+1}$. In the interval $t \in [t^+_k, t^-_{k+1}]$, we have

$$\tilde{R}(t) = \tilde{R}(t^+_k)e^{-h(t-t_k)}, \ t \in [t^+_k, t^-_{k+1}]. \tag{22}$$

Assuming $t \to t^-_{k+1}$, we have $\tilde{R}(t^-_{k+1}) = \tilde{R}(t^+_k)j$, where $j = e^{-h\tau}$. Consequently, the perfect drug concentration immediately before or after, the amount for dosage being used is given by,

$$\lim_{k\to\infty} \ \tilde{R}(t^+_k) = \frac{\tilde{R}_0}{1-j}, \ \lim_{k\to\infty} \ \tilde{R}(t^-_{k+1}) = \frac{\tilde{R}_0 j}{1-j}. \tag{23}$$

We obtain a stable (in fact, asymptotically stable) impulsive episodic trajectory in drug application with endpoints $\frac{\tilde{R}_0}{1-j}$ and $\frac{\tilde{R}_0 j}{1-j}$. In addition, the endpoints of every cycle monotonically increases (Lou, 2009).

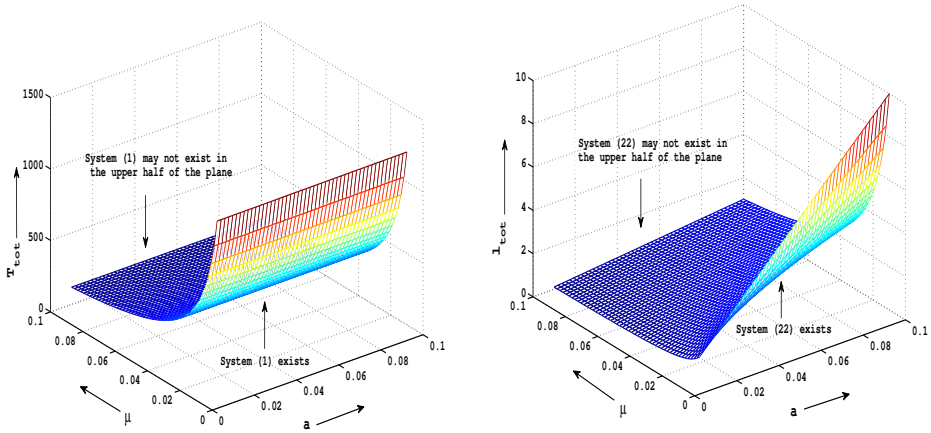

Figure 1. Graphical representations (mesh diagram) of existence condition of the system (1) in a-μ-T_{tot} parametric space (left) and existence condition of the system (22) in a-μ-l_{tot} parametric space (right) with value of the parameters $a = 15$ and $\mu = 0.04$.

Table 1. Parameters used in the model equation (1)

Parameters	Definition	Default values assigned (Day^{-1})
a	The rate of accumulation of T-cells	15 mm^{-3}
b	The rate of accumulation of DCs	12 mm^{-3}
δ	The rate of activation of T-cells by DCs	0.15 mm^3
β	The rate of activation of DCs by T-cells	0.12 mm^3
η	The fraction at which stimulated T-cells and DCs add to keratinocytes density	0.35 mm^3
γ_1	The rate of activation of keratinocytes due to T-cells mediated cytokines	0.8 mm^3
γ_2	The rate of keratinocytes growth	0.06 mm^3 (estimated)
μ	The per capita removal rate of T-cells	0.04 (estimated)
μ'	The per capita removal rate of DCs	0.05
λ	The decay rate of keratinocytes	0.08
p	The maximum proliferation rate constant	0.03 mm^{-3}
l_{max}	T-cell proliferation to a certain maximum stage	1500 mm^{-3}

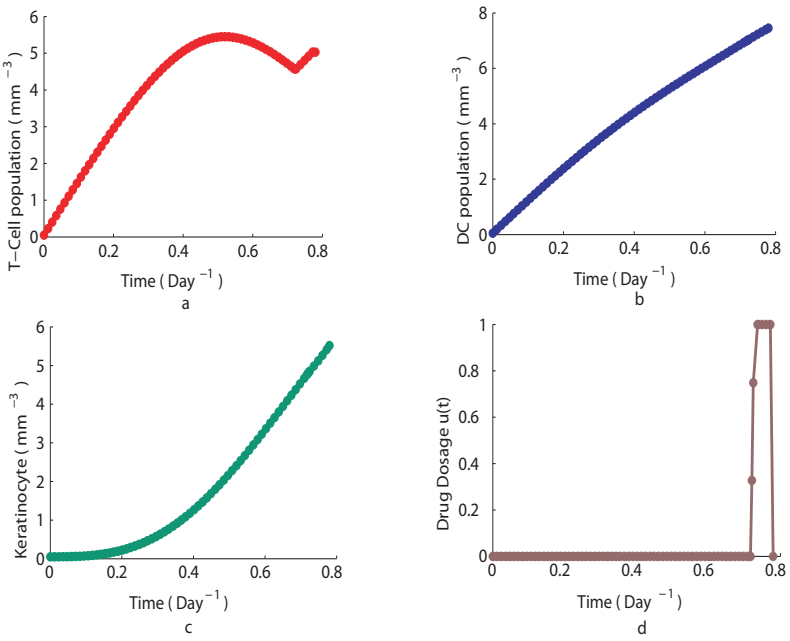

Figure 2. Population densities of T-Cells (l)(b), Dendritic Cells (m)(c), Keratinocytes (k)(a) and drug dosage u(t)(d) are plotted as a function of time after applying control (drug) for the parameters used in Table 1.

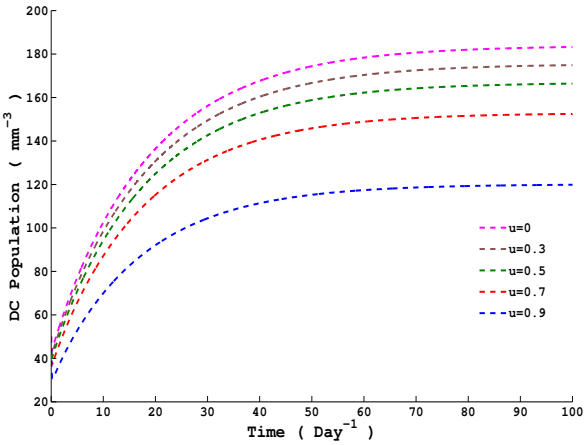

Figure 3. Dendritic Cell population is plotted as a function of time after applying different dosages of drug for the parameters used in Table 1. The curves are going downward for the increasing values of u.

6. Numerical simulation and discussion

In the earlier section, we have described the analytical techniques for the qualitative study of the system (1). Here, we present the numerical simulation of the model (1) on the basis of the analytical behavior and parameters estimated. Most of the numerical values of the model parameters, used in our computations, have been taken from the literature (Roy and Bhadra, 2010, Roy and Chatterjee, 2010), and are specified in Table 1.

In this section, we analyze the behavior of three types of cell populations after applying control approach numerically. Graphical representation of existence condition of the system (1) in a-μ-T_{tot} parametric space is given in Fig. 1 left and existence condition of the system (17) in a-μ-l_{tot} parametric space is displayed in Fig. 1 right. T-cell population increases to a certain level (up to **50** days) and then decreases for a while. It increases again because of its constant production, as shown in Fig. 2a. DC population increases gradually from initial position (Fig. 2b). We observe in Fig. 2c that at the beginning (about first **20** days), keratinocyte population behaves stably, though in the next phase (after **20** days), it increases gradually up to **80** days. In Fig. 2d, drug dosage is portrayed. Very little drug is applied until **75** days. Subsequently, the dose is increased very sharply to the highest point after which it is reduced to the ground level in close proximity of **80** days. In Fig. 3, we study the behavior of DC population, which has been constantly decreased as the quantity of the drug dose is increased step by step.

In this article, we included the T-cell proliferation in the system of psoriasis

and obtained a unique equilibrium point (interior equilibrium) because the axial and planar equilibrium did not exist as the value of $u(t)$ was always less than 1.

In the first part, we analyzed the system in implicit way, with the control upshot in the interaction between T-cells and keratinocytes. If the per capita removal rate of T-cells is less than the same of dendritic cells, which is also less than the per capita removal rate of keratinocytes in the course of normal progression, then the limiting value of the total cell population should not exceed $\frac{a+b}{\mu}$. Existence of the system (1) takes place in the **lower** portion of the mesh diagram of Fig. 1 left, while in the **upper** portion, the system may not exist.

Further, we studied the system with control. If the adjoint variable (ρ) of optimal system was greater than some preassigned positive value and the final time (t_f) of optimal system was less than some predetermined positive quantity, then the solution of the non-linear bounds was unique for a certain period of time span. Due to proliferation and constant production, T-cell population increased to a certain level and for the interaction with keratinocytes, T-cell population was compelled to decrease. As the control approach was not directly placed on DCs, the DCs increased gradually because of their constant production. Interaction between T-cells and DCs and contact between T-cells and keratinocytes helped to increase keratinocytes density. Owing to control affecting the interaction between T-cells and keratinocytes, we were able to restrict the cytokines release to some extent. At the initial stage (before **20** days), keratinocyte population behaved in a stable manner and in the next phase, it increased gradually. It was natural to study the behavior of T-cells and keratinocytes after applying the drug, as the drug was directly applied to both of these populations. But there was no straight relation between DCs and control approach according to our model system. Therefore, we were interested in analyzing the behavioral pattern of DCs after applying the drug, as DC population was also involved in the system. As the drug dosage was increased gradually, DC population decreased correspondingly. Hence, we may conclude that though drug was not directly applied to DCs, drug dosage was inversely proportional to the growth of DCs. This result has great impact on the dynamics of psoriasis.

7. Conclusion

In the present study, the impulsive drug application was calculated explicitly by incorporating the drug dosage $\tilde{R}$. Our aim was to observe the effect of the drug on the system. Existence of the system (17) took place in the **lower** section of the mesh diagram of Fig. 1 (right) and at the same time in the **upper** portion, the system might not exist. Further, the per capita removal rate of T-cells should be greater than the maximum proliferation rate constant for the existence of the impulsive drug application effect. Hence psoriasis, with causal effect of T-cell proliferation in the cell system may be restricted through optimal control therapeutic approach by impulsive drug therapy.

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8. Appendix

Let us assume that $(l,\ m,\ k, \rho_1, \rho_2, \rho_3)$ and $(\bar{l}, \bar{m}, \bar{k}, \bar{\rho_1}, \bar{\rho_2}, \bar{\rho_3})$ are two solutions of the system. Further, we suppose that

$l = e^{\rho t}p_1$, $m = e^{\rho t}p_2$, $k = e^{\rho t}p_3$, $\rho_1 = e^{-\rho t}q_1$, $\rho_2 = e^{-\rho t}q_2$ and $\rho_3 = e^{-\rho t}q_3$.

Similarly, we suppose that

$\bar{l} = e^{\rho t}\bar{p_1}$, $\bar{m} = e^{\rho t}\bar{p_2}$, $\bar{k} = e^{\rho t}\bar{p_3}$, $\bar{\rho_1} = e^{-\rho t}\bar{q_1}$, $\bar{\rho_2} = e^{-\rho t}\bar{q_2}$ and $\bar{\rho_3} = e^{-\rho t}\bar{q_3}$.

Substituting $l = e^{\rho t}p_1$ into the first equation of the system (1), we have

$$\dot{p_1} + \rho p_1 = ae^{-\rho t} + pp_1(1 - \frac{e^{\rho t}p_1}{l_{max}}) - \delta p_1 p_2 e^{\rho t} - \gamma_1 p_1 p_3 (1 - u(t))e^{\rho t} - \mu p_1. \quad (24)$$

Now, $\frac{1}{2}(p_1 - \bar{p_1})^2 + \rho \int_{t_s}^{t_f}(p_1 - \bar{p_1})^2 dt = \int_{t_s}^{t_f} p(p_1 - \bar{p_1})^2 dt - \frac{p}{l_{max}} \int_{t_s}^{t_f} e^{\rho t}(p_1 - \bar{p_1})^2(p_1 + \bar{p_1})dt - \delta \int_{t_s}^{t_f} e^{\rho t}(p_1 p_2 - \bar{p_1}\bar{p_2})(p_1 - \bar{p_1})dt - \gamma_1 \int_{t_s}^{t_f} e^{\rho t}[(1 - u(t))p_1 p_3 -$

$(1-\bar{u}(t))\bar{p_1}\bar{p_3}](p_1-\bar{p_1})dt-\mu\int_{t_s}^{t_f}(p_1-\bar{p_1})^2dt.$

Substituting $m=e^{\rho t}p_2$ into the second equation of the system (1), we have

$$\dot{p_2}+\rho p_2=be^{-\rho t}-\beta e^{\rho t}p_1p_2-\mu' p_2. \tag{25}$$

Now, $\frac{1}{2}(p_2-\bar{p_2})^2+\rho\int_{t_s}^{t_f}(p_2-\bar{p_2})^2dt=\int_{t_s}^{t_f}p(p_2-\bar{p_2})^2dt-\beta\int_{t_s}^{t_f}e^{\rho t}(p_1p_2-\bar{p_1}\bar{p_2})(p_2-\bar{p_2})dt-\mu'\int_{t_s}^{t_f}(p_2-\bar{p_2})^2dt.$

Substituting $k=e^{\rho t}p_3$ into the third equation of the system (1), we have

$$\dot{p_3}+\rho p_3=\eta e^{\rho t}p_1p_2+\gamma_2e^{\rho t}(1-u(t))p_1p_3-\lambda p_3. \tag{26}$$

Again, $\frac{1}{2}(p_3-\bar{p_3})^2+\rho\int_{t_s}^{t_f}(p_3-\bar{p_3})^2dt=\eta\int_{t_s}^{t_f}e^{\rho t}(p_1p_2-\bar{p_1}\bar{p_2})(p_3-\bar{p_3})dt+\gamma_2\int_{t_s}^{t_f}e^{\rho t}[(1-u(t))p_1p_3-(1-\bar{u}(t))\bar{p_1}\bar{p_3}](p_3-\bar{p_3})dt-\lambda\int_{t_s}^{t_f}(p_3-\bar{p_3})^2dt.$

Putting $\rho_1=e^{-\rho t}q_1$ into the first adjoint equation of the system (1), we have

$$\begin{aligned}\dot{q_1}-\rho q_1=&-pq_1+e^{\rho t}\frac{2pp_1q_1}{l_{max}}+\delta e^{\rho t}p_2q_1+\gamma_1e^{\rho t}(1-u(t))p_3q_1\\&+\mu q_1+\beta e^{\rho t}p_2q_2-\eta e^{\rho t}p_2q_3-\gamma_2e^{\rho t}(1-u(t))p_3q_3.\end{aligned} \tag{27}$$

Now, $\frac{1}{2}(q_1-\bar{q_1})^2+\rho\int_{t_s}^{t_f}(q_1-\bar{q_1})^2dt=-p\int_{t_s}^{t_f}(q_1-\bar{q_1})^2dt+\frac{2p}{l_{max}}\int_{t_s}^{t_f}e^{\rho t}(p_1q_1-\bar{p_1}\bar{q_1})(q_1-\bar{q_1})dt+\delta\int_{t_s}^{t_f}e^{\rho t}(p_2q_1-\bar{p_2}\bar{q_1})(q_1-\bar{q_1})dt+\gamma_1\int_{t_s}^{t_f}e^{\rho t}[(1-u(t))p_3q_1-(1-\bar{u}(t))\bar{p_3}\bar{q_1}](q_1-\bar{q_1})dt+\mu\int_{t_s}^{t_f}(q_1-\bar{q_1})^2dt+\beta\int_{t_s}^{t_f}e^{\rho t}(p_2q_2-\bar{p_2}\bar{q_2})(q_1-\bar{q_1})dt-\eta\int_{t_s}^{t_f}e^{\rho t}(p_2q_3-\bar{p_2}\bar{q_3})(q_1-\bar{q_1})dt-\gamma_2\int_{t_s}^{t_f}e^{\rho t}[(1-u(t))p_3q_3-(1-\bar{u}(t))\bar{p_3}\bar{q_3}](q_1-\bar{q_1})dt.$

Replacing $\rho_2=e^{-\rho t}q_2$ in the second adjoint equation of the system (1), we have

$$\dot{q_2}-\rho q_2=\delta e^{\rho t}p_1q_1+\beta e^{\rho t}p_1q_2+\mu' q_2-\eta e^{\rho t}p_1q_3. \tag{28}$$

Again, $\frac{1}{2}(q_2-\bar{q_2})^2+\rho\int_{t_s}^{t_f}(q_2-\bar{q_2})^2dt=\delta\int_{t_s}^{t_f}e^{\rho t}(p_1q_1-\bar{p_1}\bar{q_1})(q_2-\bar{q_2})dt+\beta\int_{t_s}^{t_f}e^{\rho t}(p_1q_2-\bar{p_1}\bar{q_2})(q_2-\bar{q_2})dt+\mu'\int_{t_s}^{t_f}(q_2-\bar{q_2})^2dt-\eta\int_{t_s}^{t_f}e^{\rho t}(p_1q_3-\bar{p_1}\bar{q_3})(q_2-\bar{q_2})dt.$

Substituting $\rho_3=e^{-\rho t}q_3$ into the third and final adjoint equation of the system (1), we have

$$\dot{q_3}-\rho q_3=-e^{\rho t}+\gamma_1e^{\rho t}(1-u(t))p_1q_1-\gamma_2e^{\rho t}(1-u(t))p_1q_3+\lambda q_3. \tag{29}$$

Now, $\frac{1}{2}(q_3-\bar{q_3})^2+\rho\int_{t_s}^{t_f}(q_3-\bar{q_3})^2dt=p\int_{t_s}^{t_f}(q_3-\bar{q_3})^2dt+\gamma_1\int_{t_s}^{t_f}e^{\rho t}[(1-u(t))p_1q_1-(1-\bar{u}(t))\bar{p_1}\bar{q_1}](q_3-\bar{q_3})dt-\gamma_2\int_{t_s}^{t_f}e^{\rho t}[(1-u(t))p_1q_3-(1-\bar{u}(t))\bar{p_1}\bar{q_3}](q_3-\bar{q_3})dt+\lambda\int_{t_s}^{t_f}(q_3-\bar{q_3})^2dt.$

We can assume the following inequalities given below:

$\frac{1}{2}(p_1-\bar{p_1})^2(t_f)+\rho\int_{t_s}^{t_f}(p_1-\bar{p_1})^2dt\le p\int_{t_s}^{t_f}|p_1-\bar{p_1}|^2dt+2p\int_{t_s}^{t_f}|p_1-\bar{p_1}|^2dt+c_1e^{\rho t_f}\int_{t_s}^{t_f}[|p_1-\bar{p_1}|^2+|p_2-\bar{p_2}|^2]dt+c_2e^{3\rho t_f}[|p_1-\bar{p_1}|^2+|p_3-\bar{p_3}|^2+|q_1-\bar{q_1}|^2+|q_3-\bar{q_3}|^2]dt+\mu\int_{t_s}^{t_f}|p_1-\bar{p_1}|^2dt,$

$\frac{1}{2}(p_2-\bar{p_2})^2(t_f)+\rho\int_{t_s}^{t_f}(p_2-\bar{p_2})^2dt \le p\int_{t_s}^{t_f}|p_2-\bar{p_2}|^2dt + c_3e^{\rho t_f}[|p_1-\bar{p_1}|^2 + |p_2-\bar{p_2}|^2]dt + \mu'\int_{t_s}^{t_f}|p_2-\bar{p_2}|^2dt,$

$\frac{1}{2}(p_3-\bar{p_3})^2(t_f)+\rho\int_{t_s}^{t_f}(p_3-\bar{p_3})^2dt \le c_4e^{\rho t_f}\int_{t_s}^{t_f}[|p_1-\bar{p_1}|^2+|p_2-\bar{p_2}|^2+|p_3-\bar{p_3}|^2]dt + c_5e^{3\rho t_f}\int_{t_s}^{t_f}[|p_1-\bar{p_1}|^2+|p_3-\bar{p_3}|^2+|q_1-\bar{q_1}|^2+|q_3-\bar{q_3}|^2]dt + \lambda\int_{t_s}^{t_f}|p_3-\bar{p_3}|^2dt,$

$\frac{1}{2}(q_1-\bar{q_1})^2(t_s)+\rho\int_{t_s}^{t_f}(q_1-\bar{q_1})^2dt \le p\int_{t_s}^{t_f}|q_1-\bar{q_1}|^2dt + c_6e^{3\rho t_f}\int_{t_s}^{t_f}[|p_1-\bar{p_1}|^2+|q_1-\bar{q_1}|^2]dt + c_7e^{\rho t_f}\int_{t_s}^{t_f}[|p_2-\bar{p_2}|^2+|q_1-\bar{q_1}|^2]dt + c_8e^{3\rho t_f}\int_{t_s}^{t_f}[|p_1-\bar{p_1}|^2+|p_3-\bar{p_3}|^2+|q_1-\bar{q_1}|^2+|q_3-\bar{q_3}|^2]dt + \mu\int_{t_s}^{t_f}|q_1-\bar{q_1}|^2dt + c_9e^{\rho t_f}\int_{t_s}^{t_f}[|p_2-\bar{p_2}|^2+|q_1-\bar{q_1}|^2+|q_2-\bar{q_2}|^2]dt + c_{10}e^{\rho t_f}\int_{t_s}^{t_f}[|p_2-\bar{p_2}|^2+|q_1-\bar{q_1}|^2+|q_3-\bar{q_3}|^2]dt + c_{11}e^{3\rho t_f}\int_{t_s}^{t_f}[|p_3-\bar{p_3}|^2+|q_1-\bar{q_1}|^2+|q_3-\bar{q_3}|^2]dt,$

$\frac{1}{2}(q_2-\bar{q_2})^2(t_s)+\rho\int_{t_s}^{t_f}(q_2-\bar{q_2})^2dt \le c_{12}e^{\rho t_f}\int_{t_s}^{t_f}[|p_1-\bar{p_1}|^2+|q_1-\bar{q_1}|^2+|q_2-\bar{q_2}|^2]dt + c_{13}e^{\rho t_f}\int_{t_s}^{t_f}[|p_1-\bar{p_1}|^2+|q_2-\bar{q_2}|^2]dt + \mu'\int_{t_s}^{t_f}|q_2-\bar{q_2}|^2dt + c_{14}e^{\rho t_f}\int_{t_s}^{t_f}[|p_1-\bar{p_1}|^2+|q_2-\bar{q_2}|^2+|q_3-\bar{q_3}|^2]dt$

and

$\frac{1}{2}(q_3-\bar{q_3})^2(t_s)+\rho\int_{t_s}^{t_f}(q_3-\bar{q_3})^2dt \le p\int_{t_s}^{t_f}|q_3-\bar{q_3}|^2dt + c_{15}e^{3\rho t_f}\int_{t_s}^{t_f}[|p_1-\bar{p_1}|^2+|q_1-\bar{q_1}|^2+|q_3-\bar{q_3}|^2]dt + c_{16}e^{3\rho t_f}\int_{t_s}^{t_f}[|p_1-\bar{p_1}|^2+|p_3-\bar{p_3}|^2+|q_1-\bar{q_1}|^2+|q_3-\bar{q_3}|^2]dt + \lambda\int_{t_s}^{t_f}|q_3-\bar{q_3}|^2dt.$

Now, $\frac{1}{2}[(p_1-\bar{p_1})^2(t_f)+(p_2-\bar{p_2})^2(t_f)+(p_3-\bar{p_3})^2(t_f)+(q_1-\bar{q_1})^2(t_s)+(q_2-\bar{q_2})^2(t_s)+(q_3-\bar{q_3})^2(t_s)]+\rho\int_{t_s}^{t_f}[(p_1-\bar{p_1})^2+(p_2-\bar{p_2})^2+(p_3-\bar{p_3})^2+(q_1-\bar{q_1})^2+(q_2-\bar{q_2})^2+(q_3-\bar{q_3})^2]dt \le (\tilde{c_1}+\tilde{c_2}e^{3\rho t_f})\int_{t_s}^{t_f}[(p_1-\bar{p_1})^2+(p_2-\bar{p_2})^2+(p_3-\bar{p_3})^2+(q_1-\bar{q_1})^2+(q_2-\bar{q_2})^2+(q_3-\bar{q_3})^2]dt,$
which implies

$(\rho-\tilde{c_1}+\tilde{c_2}e^{3\rho t_f})\int_{t_s}^{t_f}[(p_1-\bar{p_1})^2+(p_2-\bar{p_2})^2+(p_3-\bar{p_3})^2+(q_1-\bar{q_1})^2+(q_2-\bar{q_2})^2+(q_3-\bar{q_3})^2]dt \le 0,$
where $\tilde{c_1}, \tilde{c_2}$ depend on the coefficients and the bounds of p_1, p_2, p_3, q_1, q_2 and q_3. If we choose $\rho > \tilde{c_1}+\tilde{c_2}$ and $t_f < \frac{1}{3\rho}\ln(\frac{\rho-\tilde{c_1}}{\tilde{c_2}})$, then $p_1=\bar{p_1}, p_2=\bar{p_2}, p_3=\bar{p_3}, q_1=\bar{q_1}, q_2=\bar{q_2}$ and $q_3=\bar{q_3}$.

Hence we can conclude that the solution of the system of such non–linear bounds is unique for a small time interval (Joshi, 2002).