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Modelling and finite time stability analysis of psoriasis pathogenesis

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A new systems model of psoriasis is presented and analysed from the perspective of control theory. Cytokines are treated as actuators to the plant model that govern the cell population under the reasonable assumption that cytokine dynamics are faster than the cell population dynamics. The analysis of various equilibria is undertaken based on singular perturbation theory. Finite time stability and stabilisation has been studied in various engineering applications where the principal paradigm uses non-Lipschitz functions of the states. A comprehensive study of the finite time stability properties of the proposed psoriasis dynamics is carried out. It is demonstrated that the dynamics are finite time convergent to certain equilibrium points rather than asymptotically or exponentially convergent. This feature of finite time convergence motivates the development of a modified version of the Michaelis-Menten function, frequently used in biology. This framework is used to model cytokines as fast finite time actuators.

1. Introduction

Psoriasis is a chronic inflammatory skin disease that affects millions of people world-wide. The most common form of this disease is chronic plaque psoriasis which occurs in almost 90 % of cases [35]. Clinically, it is characterised by salmon colour plaques with silvery white scale that appear on the skin, commonly on the extensor elbows, knees and scalp. The outermost layer of skin is mainly comprised of keratinocytes; a type of cell that is considered important for psoriasis since they have been observed to hyperproliferate and abnormally differentiate in psoriatic skin. A role for the adaptive immune system in psoriasis is also acknowledged, with evidence coming from the presence of immune cells such as T-lymphocytes and dendritic cells in psoriatic lesions and the partially successful use of immunosuppressive and modulating drugs such as anti-TNF therapies [11, 29, 31, 42] in the treatment of psoriasis. The cytokines (signalling molecules) that mediate interactions between these cells are believed to be pro-inflammatory and linked to the occurrence of psoriasis.

The study of psoriasis benefits from the accessibility of the human normal and psoriatic tissues (i.e. skin) and several *in vitro* and *in vivo* models have been proposed [14]. Complementing experimental studies, computational and mathematical models have been proposed that are able to explain the hyper-proliferation of keratinocytes, the role of cytokines in psoriasis, and have generated the morphology of the normal and psoriatic epidermis. Based on the general approaches

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employed, existing models can be divided into two groups: (i) agent based models [51, 23, 48, 24, 54] and (ii) ordinary differential equation (ODE) based models [53, 43, 44, 47, 21]. A computational model to study the spatio-temporal dynamics of epidermis homoeostasis under normal and pathological conditions has been developed [59]. This model consists of a kinetic model of the central transition pathway of keratinocyte proliferation, differentiation and apoptosis and an agent-based model that propagates cell movements and generates the stratified epidermis. The model is used to study the onset, recurrence and phototherapy-induced remission of psoriasis. However, although the dynamics of cytokine interactions have been explored computationally [53], the ways in which these affect populations of the aforementioned cell types, therefore leading to psoriasis phenotypes, have not been explored.

In the present study, a mathematical model of psoriasis is developed that incorporates interactions between different cell types, mediated by the cytokines they produce. Using control engineering techniques, the possibility of some of the cytokines acting as fast actuators to the cell population dynamics is investigated. More specifically, singular perturbation methods are used to study cytokines as fast actuators. The analysis shows that the system can display two steady states reflecting normal and psoriatic skin conditions. Finite time stability of a healthy immune system is studied and the possibility of cytokines working as a fast finite time actuators to the cellular level dynamics is explored in this case. For both cases, a non-Lipschitz growth function approach is used. The study explores the inherent finite time nature of the underlying biology of psoriasis and demonstrates an analysis approach which could be used for other biological systems.

The paper is organised as follows. In Section 2 a new model for psoriasis is motivated and developed. Section 3 presents an analysis of the cell and cytokine dynamics where the possibility of some cytokines working as fast actuators for the cellular dynamics is explored. In section 4, the non-Lipschitz growth function approach to capture the finite convergence properties is discussed. Section 4.1 combines the approaches of sections 3 and 4 to model cytokines as fast finite time actuators. In section 5, a short conclusion is presented.

2. System components and model formulation

It is believed that the psoriatic skin is mainly populated with three cell types, namely keratinocytes, T cells (specifically CD4+ T lymphocytes) and dendritic cells [31, 36]. Other cell types have also been implicated in psoriasis pathogenesis, such as natural killer (NK) cells [15] and macrophages [12]. However, the level of information that is available from biology to inform modelling studies with regard to these cell types is sparse. In particular, there is a lack of understanding of the signalling pathways employed by these cells. Mainly for this reason, but also to simplify the system in order to investigate its finite-time behaviour and the effects of certain cytokines, only dendritic cells, T cells and Keratinocytes are considered. For these cell types, an extensive literature is available from biology to underpin the modelling effort. A single compartment model that consists of communication between immune cells in the dermis and keratinocytes in the epidermis is considered (see Figure 1). The keratinocyte population in the model includes a progenitor pool of keratinocyte stem cells and transit amplifying cells, which are exposed to signals from immune cells in the dermis. The keratinocyte desquamation in the model is neglected as cells are out of range of active immune cells long before desquamation. The present section motivates the incorporation of the modelled cell types and interactions among them, mediated by cytokines. These interactions are considered to influence the proliferation or apoptosis of cells, thus affecting the dynamics of cell population sizes. A list of cytokines incorporated in the model is shown in Table 1.

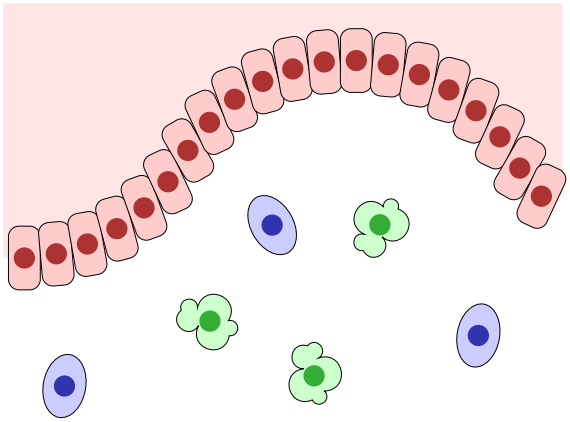

Figure 1. The cellular compartment modelled represents epidermal basal layer keratinocytes (red) interacting with dendritic cells (blue) and T-cells (green) via cytokine networks in the dermis.

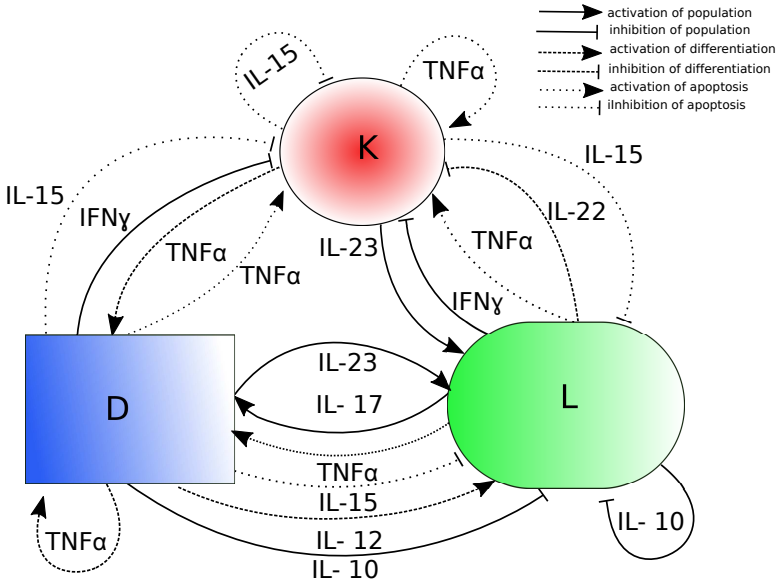

Figure 2. A schematic diagram of the cell types predominantly implicated in psoriasis and the interactions among them mediated via cytokines.

2.1 *Keratinocytes*

Keratinocytes are an obvious choice for inclusion in any model since this population of cells is known to form psoriatic plaques. They make up the bulk of the tissue of the epidermis, and keratinocyte hyperplasia is considered a distinguishing feature of psoriasis. These cells undergo differentiation as they travel up through the layers of the epidermis. In the stratum basale, keratinocytes start as stem cells (SC) or transit amplifying cells (TA) before differentiating to growth arrested cells (GA) and migrating to the stratum spinosum, where they differentiate into spinous cells (SP), then onto the stratum granulosum where they become granular cells (GC). Finally, when they reach the stratum corneum, they differentiate into corneocytes and are shed in the process of desquamation [59]. Only SC and TA cells are capable of proliferation, and back conversion is only possible between TA and SC or GA and TA [59]. For simplicity this study does not distinguish between these SC, TA, GA, SP and GC, lumping them instead into a single keratinocyte population. However, K does not include the terminally differentiated keratinocytes (corneocytes). The keratinocyte cell population is considered to be modulated largely by the opposing actions of proliferation and apoptosis, each of which can be up or down regulated to maintain homoeostasis. Keratinocyte

apoptosis is reported to be inhibited by IL-15 [45, 15] which is itself produced by keratinocytes and dendritic cells [5]. In addition, IL-22 which is produced by subsets of T-cells (Th17 and Th1) inhibits keratinocytes terminal differentiation [55]. IFNγ, which is produced by T-cells (by Th1 and Th17 [15, 49]) and dendritic cells [15] inhibits keratinocyte proliferation [50]. TNFα, which is produced by keratinocytes, T-cells and dendritic cells, drives keratinocyte apoptosis [35, 1, 60].

2.2 *T cells*

T cells or T lymphocytes are so named as their progenitors originate in the thymus and circulate around the body through the lymphatic system. There are many sub categories of T cell classified by the receptors and cytokines expressed by them as well as by their role in the immune system. However, it is widely acknowledged that the CD4+ super group of T cells is most critically associated with psoriasis [9]. Here, for simplicity, all mature CD4+ T lymphocytes are lumped into a single population. They are included in the model as they have long been implicated in the pathogenesis of psoriasis [2, 16, 20, 30, 58, 19]. As for keratinocytes, T cell populations are considered to be affected by proliferation and apoptosis, but also by migration from external sources or differentiation from other sub-populations. These behaviours are unsurprisingly governed by cytokines. For instance, IL-12 produced by dendritic cells has been shown to induce differentiation of naive CD4+ cells to Th1 [33]. Sub-populations of the CD4+ respond to other signals for instance Th-17 activity and proliferation is thought to be up regulated by IL-23 which is produced by macrophages, dendritic cells [4] and keratinocytes [39, 15]. The proliferation of CD4+ cells is reported to be inhibited by IL-10 [13], where T cells (subsets of CD4+ and CD8+ lymphocytes[13]) and dendritic cells are thought to be the major contributors of IL-10 [26, 46]. Furthermore, IL-15 causes T cell population increase via inhibition of apoptosis [8].

Table 1. List of cytokines considered in the model with their source and effect on different cell types.

Cell types / Cytokines	Keratinocytes	T	Dendritic
IL-10		- (inhibition of proliferation), s	s
IL-12		+ (differentiation in mature form)	s
IL-15	+ (inhibition of apoptosis), s	+ (inhibition of apoptosis)	s
IL-17		s	+ (indirect effect)
IL-22	+ (inhibition of differention)	s	
IL-23	s	+ (activation of proliferetaion)	s
IFN_γ	- (inhibition of proliferation)	s	s
TNF_α	- (activation of apoptosis), s	s	+ (maturation), s

where s denotes source of the cytokine, and + or - represent the net activation or inhibition of the cell population, respectively.

2.3 *Dendritic cells*

Dendritic cells are thought to straddle the gap between the innate and adaptive immune systems. Their primary role is as professional antigen presenting cells, however they are also capable of phagocytosis and are known to be prolific producers of cytokines. They are believed to be derived from monocytes and therefore the population dynamics is considered to be driven by migration and differentiation, as well as proliferation and apoptosis. In this study, only matured dendritic cells are incorporated. The population of dendritic cells increases due to the production of IL-17 by Th-17 cells via the stimulation of chemokine production in keratinocytes. TNFα stimulates maturation of dendritic cells [30].

2.4 *The model*

A schematic diagram of the cell-cell interactions among three types of cells: (i) keratinocytes, (ii) T- cells and (ii) dendritic cells via cytokines is shown in Figure 2. For simplicity, it is assumed that only four kinds of activity are accountable for the epidermis homeostasis. These are cell migration, proliferation, differentiation/maturation and apoptosis. It is also assumed that the rate of migration is independent of the local concentration for each cell type whereas the rate of proliferation and differentiation is dependent on the existing population. In addition, it is assumed that cell death is a stochastic event at the individual cell level, therefore the population average rate of cell death is proportional to the existing population. With these assumptions, the dynamics of each cell population, x, can be represented by the following ordinary differential equation

$$\frac{dx}{dt} = a_x + bx - cx - \mu_x x \tag{1}$$

where a_x is a parameter that denotes a basal rate of increase in cell population x (due to unmodelled migration or differentiation factors), b is a function that represents a rate of increase in x by cytokine-mediated differentiation/maturation and proliferation. Function c accounts for a net rate of decrease in x due to cytokine mediated apoptosis and parameter μ_x represents effects of additional apoptosis due to non-modelled processes. Based upon the interaction diagram (Figure 2) each of these additive terms can be modulated due to influences from other cells. These modulations can cause increases or decreases to the additive terms depending on the type of interaction (Figure 2). In order to model these effects, an approach previously employed to study up- and down-regulating interactions between biological components is used [34, 22]. In these previous studies, interactions are modelled by combinations of non-linear functions that are increasing or decreasing with respect to their arguments. Where different cytokines contribute to the same process (for example, proliferation) in the same cell, but with different direction of effect, this is modelled as a multiplication of terms. For example, IL-23 activates the proliferation of T cells, whereas IL-10 inhibits the proliferation of T cells. The proliferation term for T cells therefore contains an increasing function multiplied by a decreasing function. Taking into account the specific discussion above, within this framework the dynamics of a system of keratinocytes (K), T cells (L) and dendritic cells (D) can be written as

$$\begin{aligned}
\frac{\mathrm{d}L}{\mathrm{d}t} &= a_L + (f_{\mathrm{IL12}}(D) + f_{\mathrm{IL23}}(D,K)g_{\mathrm{IL10}}(D,L))L - (g_{\mathrm{IL15}}(D,K) + \mu_L)L \\
\frac{\mathrm{d}D}{\mathrm{d}t} &= a_D + (f_{\mathrm{TNF}}(D,K,L) + f_{\mathrm{IL17}}(L))D - \mu_D D \\
\frac{\mathrm{d}K}{\mathrm{d}t} &= a_K + (f_{\mathrm{IL22}}(L) + g_{\mathrm{IFN}}(L,D))K - (f_{\mathrm{TNF}}(D,K,L)g_{\mathrm{IL15}}(D,K) + \mu_K)K
\end{aligned} \tag{2}$$

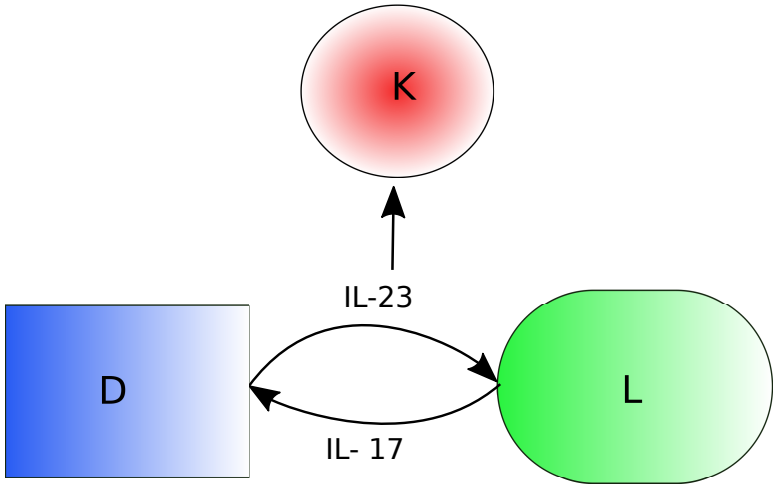

Figure 3. **Simplified network with IL-23 as an actuator.**

As described above, the functions f_i and g_i represent generic activation and inhibition functions, respectively.

3. A singular perturbation based analysis of the model

From a systems viewpoint, cytokines can be assumed to be actuators for the plant dynamics that govern the cell populations. The model described in Figure 2 and equation (2) is complex and one of the objectives of this study is to focus upon key phenomena that are pertinent to the pathogenesis and treatment of psoriasis. To achieve this objective, model simplification is required. In the following, the focus is on two cytokines, IL-23 and IFN$_\gamma$. In this study, these are considered as actuators and appear in the cell dynamics as control affine terms. The resulting models are analysed for stability. The selection of these specific cytokines as actuators is motivated by the consideration of cytokines within drug treatments for psoriasis which is well reported in the literature [4, 10, 27]. Initially the case where IL-23 is an actuator is considered.

IL-23 as an actuator

In order to study IL-23 as an actuator the model in equation (2) is simplified as shown in Figure 3. The mutually activating D to L loop is considered, which is reliant upon the cytokines IL-23 and IL-17 and produces the subsequent indirect activation of K (via L). The levels of K emerge from all the interactions of the network. Therefore to study the role of IL-23 in the general model (Eq.2) would require specification of all the functions and their parameters, and a sensitivity analysis of parameters relating to IL-23. Instead a simplified approach is adopted, lumping all the effects of IL-23 on$K$ into a single parameter, u_p. Specifically, the following relationships are assumed: $g_{\mathrm{IL15}}(D,K) = f_{\mathrm{IL12}}(D) = f_{\mathrm{IL22}}(L) = 0, f_{\mathrm{IL23}}(D,K,L) = \delta D$ where δ denotes the rate at which IL-23 is secreted from the dendritic cells, $g_{\mathrm{IL10}}(D,L) = 1, f_{\mathrm{TNF}}(D,K,L) = 0, f_{\mathrm{IL17}}(L) = \beta L$, $a_K = 0, g_{\mathrm{IFN}}(L,D) = 0$. Note that the unity in place of f_i and g_i represents a constant presence of that pathway.

These considerations produce the following reduced form:

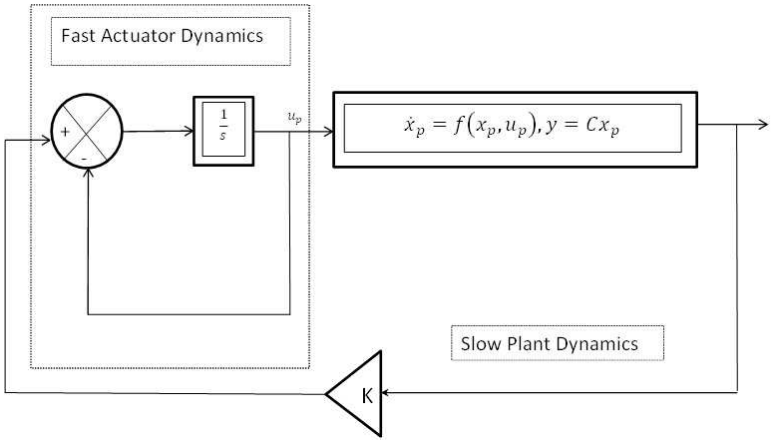

Figure 4. Fast-Slow Dynamics for singular perturbation analysis when IL-23 acts as an actuator.

$$\begin{aligned} \dot{L} &= a_L + \delta LD - \mu_L L \\ \dot{D} &= a_D + \beta LD - \mu_D D \\ \dot{K} &= u_p - \mu_K K, \end{aligned} \tag{3}$$

where, u_p is a control parameter representing the indirect effects of IL-23 on keratinocytes. A singular perturbation based approach is used to parameterise u_p as a function of the state (in particular as a function of the states D, K). Note that the control u_p is neither "synthesised" nor "proposed", but rather is derived naturally from the assumption of fast-slow dynamics. A block diagram of the control system is shown in Figure 4 where the output is defined as $y = x_p = [\ L \quad D \quad K\ ]^{\mathrm{T}}$ and the feedback gain matrix $\bar{K}$ is given by $\bar{K} = [\ 0 \quad k_2 \quad k_1\ ]$. The subscript '$p$' denotes plant (e.g. plant state x_p, control input u_p etc).

The function $f(x_p)$ is given by the right hand side of (3). The fast dynamics of the cytokine are proposed as follows:

$$\dot{u}_p = k_1 K + k_2 D - u_p \tag{4}$$

The motivation to choose this dynamic stems from the fact that u_p is thought to be the cause of inflammatory hyper-proliferation of keratinocytes. Such behaviour coincides with the pro-inflammatory nature of certain cytokines. More cytokines and higher order dynamics can be considered in a more detailed analysis. However, the above scalar dynamics of u_p are considered for ease of exposition.

It is assumed that the source of inflammation within u_p comes from D, the dendritic cells, and K the keratinocytes. Such a formulation of u_p is motivated by known biological information as described in the Introduction. The natural death rate of u_p is assumed to be unity for simplicity. In this way, a cytokine actuator is seen to have the role of a pseudo-control which inhibits the keratinocyte proliferation when it is prohibited using therapies.

Following the standard singular perturbation analysis method [28, Chapter 9], the following is considered:

$$\epsilon \dot{u}_p = \psi(x_p) = k_1 K + k_2 D - u_p \tag{5}$$

with ϵ being a small positive scalar. When $\epsilon = 0$, a closed-form solution for u_p results as follows:

$$u_p(x_p) \quad = \quad k_1 K + k_2 D \tag{6}$$

It should be noted that the analysis must consider that with singular perturbation methods, the right hand side of (4) is taken to zero since $\epsilon \dot{u}_p = 0$. However, $\dot{u}_p = \frac{1}{\epsilon}\psi(\cdot)$ can be very large when ϵ is very small but not zero. Large values of $\dot{u}_p$ may be attributed to the constant k_2 and not k_1 since it is reasonable to assume that it is the dendritic cells D that drive the proliferation of IL-23 more than the keratinocytes K. Hence, restricting $k_1 < \mu_K$, where μ_K is a positive scalar, in the following mathematical analysis is biochemically plausible. This requirement emerges as a condition for a meaningful biological equilibrium as motivated below.

Analysis of equilibria

Substituting (6) into (3) produces the following feedback system:

$$\begin{aligned} \dot{L} &= a_L + \delta LD - \mu_L L \\ \dot{D} &= a_D + \beta LD - \mu_D D \\ \dot{K} &= k_1 K + k_2 D - \mu_K K, \end{aligned} \tag{7}$$

The equilibria are given below where throughout the paper the notation * will be used to denote an equilibrium point.

$$\begin{aligned} L^* &= \frac{a_L}{\mu_L - \delta D^*} \\ D^* &= \frac{(\delta a_D - \beta a_L + \mu_L \mu_D) \pm \sqrt{(\delta a_D - \beta a_L + \mu_L \mu_D)^2 - 4\mu_L \mu_D \delta a_D}}{2\mu_D \delta} \\ K^* &= \frac{k_2}{\mu_K - k_1} D^*, \end{aligned} \tag{8}$$

where $k_1 < \mu_K$ and $\delta a_D > \beta a_L$. If $\mu_L \mu_D > (\delta a_D - \beta a_L)$ then D has two roots and therefore the system will have two equilibria. This dynamic behaviour has previously been suggested in the study of immunity [41].

IFN$_\gamma$ as an actuator

A simplified version of model (2) is analysed in the following as represented schematically in Figure 5. The activation and inhibition functions can be defined as follows:

$$\begin{aligned} f_i(x) &= \frac{1}{2}(1 + \text{sign}(x - \eta_i)) \\ g_i(x) &= \frac{1}{2}(1 - \text{sign}(x - \eta_i)) \end{aligned} \tag{9}$$

where the η_i are positive scalars representing the threshold values for activation or inhibition of a given cell population x and the signum function is defined as

$$\text{sign}(y) = \begin{cases} -1, & y < 0; \\ 1, & y \geq 0. \end{cases} \tag{10}$$

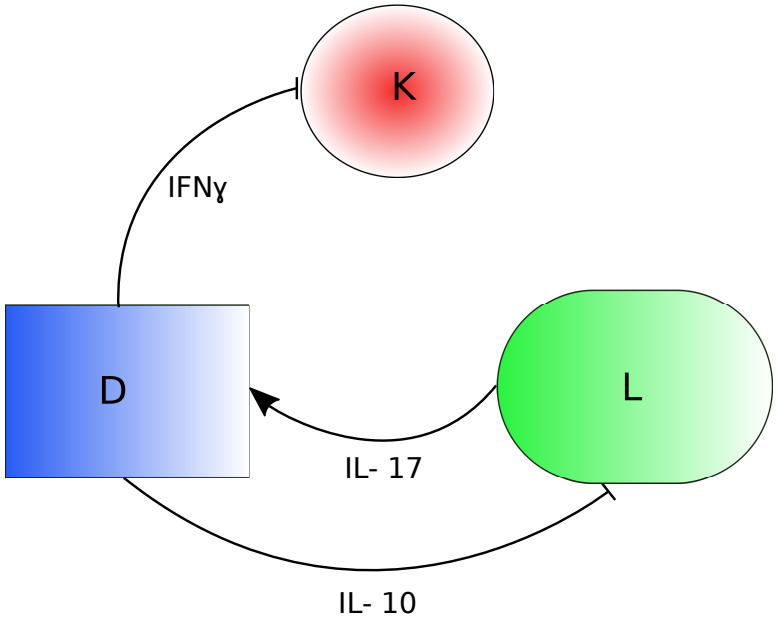

Figure 5. Simplified network with IFNγ as an actuator.

The functions f_i and g_i in (9) cannot be defined by a general multi-valued sign function. In the absence of a multi-valued definition [18] for the 'sign' functions at the point of discontinuity, the definition of the signum function in (9) is adequate to represent the biological switch in the functions f_i, g_i. Consider the particular case of the general model (2) under the following assumptions:

- $f_{\text{IL23}}(D,K) = f_{\text{TNF}}(D,K,L) = f_{\text{IL12}}(D) = 1$
- $g_{\text{IL15}}(D,K) = 1, f_{\text{IL22}}(L) = 0, a_K = 0$
- $f_{\text{IL17}}(L) = \frac{1}{2}(1 + \text{sign}(L - \eta_L))$
- $g_{\text{IL10}}(D,L) = \frac{1}{2}(1 - \text{sign}(D - \eta_D))$

The unity in place of f_i and g_i represents a constant presence of that pathway. In fact, a special case of psoriasis is considered whereby, of all the activation and inhibition functions, only $f_{\text{IL17}}(L)$ and $g_{\text{IL10}}(D,L)$ are defined and they are based on thresholds η_L, η_D.

Furthermore, it is assumed that the term $g_{\text{IFN}}(D,L)K = \bar{\epsilon}u_p$, where u_p denotes the control variable. This is motivated by an attempt to use IFN_γ as a therapy for an inflammation related disease [17] . The inhibition of the keratinocyte K via the function g_{IFN} is the same as the self-apoptosis of the IFN_γ dynamics (caused by an external signal). Biochemically, this means that controlling IFN_γ controls the proliferation of keratinocytes. The scalar $\bar{\epsilon}$ is introduced as a saturation parameter which gives direct control over the proliferation of K.

Within this framework, the system dynamics in equation (2) becomes

$$\begin{aligned} \dot{L} &= a_L + (1 + \frac{1}{2}(1 - \text{sign}(D - \eta_D)))L - (1 + \mu_L)L \\ \dot{D} &= a_D + (1 + \frac{1}{2}(1 + \text{sign}(L - \eta_L)))D - \mu_D D \\ \dot{K} &= \bar{\epsilon}u_p - (1 + \mu_K)K \end{aligned} \tag{11}$$

Next, scalar cytokine dynamics are considered as discussed previously. From the discussion in the preceding sections, it is plausible to choose a cytokine that is a good candidate for control. As mentioned previously, the choice should be commensurate with the biochemical degrees of freedom, i.e., the choice of cytokine should be such that it becomes reasonable to think about the particular

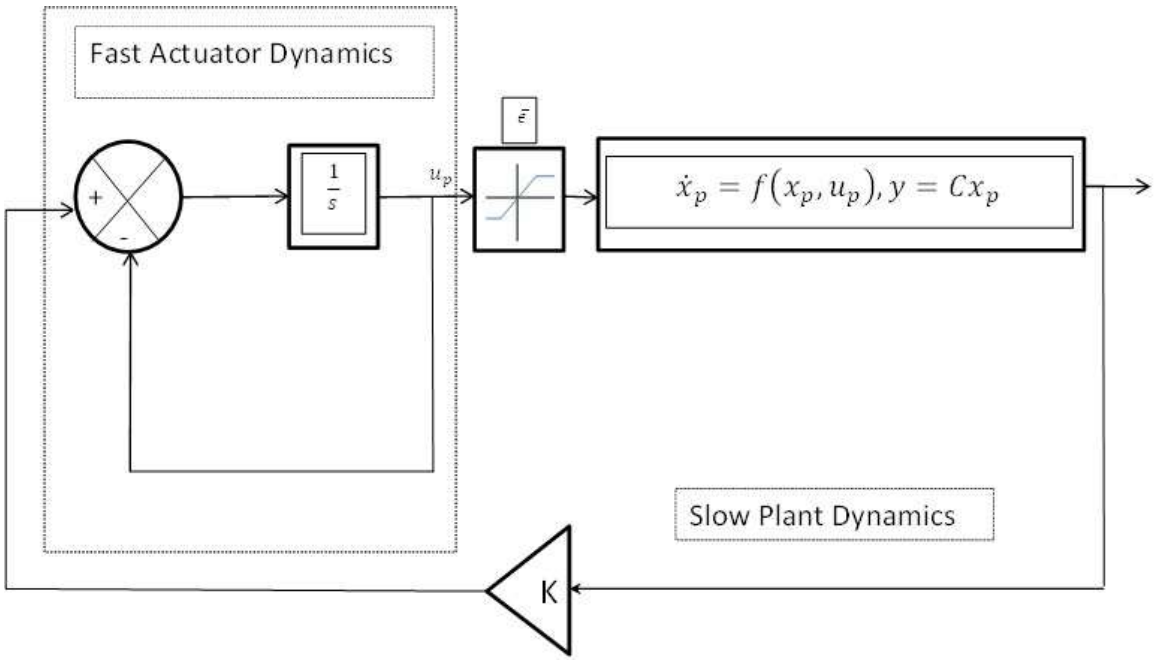

Figure 6. Fast-Slow Dynamics for singular perturbation analysis when IFN_γ acts as an actuator.

cytokine as a fast acting control variable.

Assuming cytokine IFN_γ as the actuator, the following equation for the cytokine dynamics is chosen:

$$\dot{u}_p = D - u_p \tag{12}$$

where, $u_p = IFN_\gamma$. It can be seen that this simple choice of scalar dynamics accommodates the up-regulation of IFN_γ by the dendritic cells D as discussed in Subsection 2.1 above and in [15], also assuming that L makes a negligible contribution.

The structure of the dynamics from the control view-point is depicted in Figure 6 where the cytokine behaves as a fast actuator producing the control action u_p for the slow plant dynamics corresponding to the cell populations. These cell populations are effectively driven by the saturated control $\bar{\epsilon}u_p$.

Following a similar analysis as carried out for cytokine IL-23 and assuming as before that the cytokine dynamics are much faster than the cell population dynamics, the following holds true:

$$\dot{u}_p = 0 \Rightarrow D = u_p \tag{13}$$

Analysis of Equilibria

As can be seen from (11), the first two equations contain linear decay and non-linear terms that contain the signum function. A case by case study can be carried out for each of the four possible combinations due to the two signum functions.

Case 1: $\frac{1}{2}(1 - \text{sign}(D - \eta_D)) = \frac{1}{2}(1 + \text{sign}(L - \eta_L)) = 0$

The following is obtained from (11):

$$\begin{aligned}\dot{L} &= a_L - \mu_L L \\ \dot{D} &= a_D + (1-\mu_D)D \\ \dot{K} &= \bar{\epsilon}u_p - (1+\mu_K)K\end{aligned} \tag{14}$$

It is straightforward to show that the equilibrium is given by $(L^*, D^*, K^*) = (\frac{a_L}{\mu_L}, \frac{a_D}{\mu_D - 1}, \frac{\bar{\epsilon}(a_D)}{(\mu_D-1)(1+\mu_K)})$. It can be seen that as $\bar{\epsilon} \to 0$, the concentration of keratinocytes K tends to zero.

Case 2: $\frac{1}{2}(1 - \text{sign}(D - \eta_D)) = \frac{1}{2}(1 + \text{sign}(L - \eta_L)) = 1$

The following is obtained from (11):

$$\begin{aligned}\dot{L} &= a_L + (1-\mu_L)L \\ \dot{D} &= a_D + (2-\mu_D)D \\ \dot{K} &= \bar{\epsilon}u_p - (1+\mu_K)K\end{aligned} \tag{15}$$

One can easily show that equilibrium is given by $(L^*, D^*, K^*) = (\frac{a_L}{\mu_L - 1}, \frac{a_D}{\mu_D - 2}, \frac{\bar{\epsilon}a_D}{(\mu_D-2)(1+\mu_K)})$ for $\mu_L > 1$ and $\mu_D > 2$. Again, as $\bar{\epsilon} \to 0$, the concentration of keratinocytes K tends to zero.

Case 3: $\frac{1}{2}(1 - \text{sign}(D - \eta_D)) = 0, \frac{1}{2}(1 + \text{sign}(L - \eta_L)) = 1$

The following is obtained from (11):

$$\begin{aligned}\dot{L} &= a_L - \mu_L L \\ \dot{D} &= a_D + (2-\mu_D)D \\ \dot{K} &= \bar{\epsilon}u_p - (1+\mu_K)K\end{aligned} \tag{16}$$

Then the equilibrium is given by $(L^*, D^*, K^*) = (\frac{a_L}{\mu_L}, \frac{a_D}{\mu_D - 2}, \frac{\bar{\epsilon}a_D}{(\mu_D-2)(1+\mu_K)})$ for $\mu_D > 2$.

Case 4: $\frac{1}{2}(1 - \text{sign}(D - \eta_D)) = 1, \frac{1}{2}(1 + \text{sign}(L - \eta_L)) = 0$

$$\begin{aligned}\dot{L} &= a_L + (1-\mu_L))L \\ \dot{D} &= a_D + (1-\mu_D)D \\ \dot{K} &= \bar{\epsilon}u_p - (1+\mu_K)K\end{aligned} \tag{17}$$

The corresponding equilibrium is given by $(L^*, D^*, K^*) = (\frac{a_L}{\mu_L - 1}, \frac{a_D}{(\mu_D - 1)}, \frac{\bar{\epsilon}a_D}{(\mu_D-1)(1+\mu_K)})$ for $\mu_L > 1$ and $\mu_D > 1$.

It can be seen that by controlling epsilon desirable keratinocyte levels (i.e. comparatively lower levels) can be attained. Hence, the above modelling approach elucidates the role of the saturated output corresponding to the fast cytokine dynamics as a control variable in the dynamics of psoriasis.

In this section the effect of two cytokines has been considered by considering saturated and non-saturated actuators as fast acting control variables for the dynamics of psoriasis using a singular perturbation based analysis. The next section utilises the natural fact of finite time stability of the biological dynamics and introduces non-Lipschitz growth functions.

4. Non-Lipschitz growth functions for modelling finite time behaviour

Non-Lipschitzian dynamics are central to producing finite time stable dynamics [25, 3, 37]. This section establishes a connection between using non-Lipschitz growth functions for cell population dynamics and their finite time convergence via the study of auto-immune disease dynamics. A preliminary analysis motivating the use of finite time stability considerations within the modelling of autoimmune disease appears in [38].

In order to study finite time behaviour, an explicit functional form for the interactions described by our general model is sought. First, a modified version of the Michaelis-Menten function is introduced as follows:

$$f(x) = \frac{k_{\max} x}{k_m + x}, \tag{18}$$

where x is the concentration of the cell population, $k_{\max}$ is the maximum or the saturation value attainable in the range of the function $f(x)$ and $\frac{k_{\max}}{k_m}$ defines the slope of the graph of $f(x)$ at $x = 0$. A normalized version of (18) as given in [53] is as follows:

$$f(x) = \frac{x}{1 + x} \tag{19}$$

A non-Lipschitz modification of the above function is given by:

$$\bar{f}(x) = (\frac{x}{1 + x})^{\alpha} \tag{20}$$

where $\alpha \in (0, 1)$. The non-Lipschitz function $\bar{f}(x)$ of (20) coincides with $f(x)$ of (19) when $\alpha = 1$. The limiting values of $\bar{f}(x)$ as x tends to zero and infinity remain the same as those for $f(x)$. The main difference between these two functions is that the slope of $\bar{f}(x)$ at $x = 0$ is infinite as it is non-Lipschitz in x whereas $f(x)$ has a slope $(1 + x)^{-2}$ everywhere. The graphs of $f(x)$ and $\bar{f}(x)$ against x are shown in Figure 7 with $\alpha = 0.5$. It should be noted that $f(x)$ takes the value $\frac{1}{2}$ at $x = 1$ whereas $\bar{f}(x) = (\frac{1}{2})^{\alpha}$ at $x = 1$. Small values of the constant k_m in (18) correspond to (i) a higher slope closer to the origin, and (ii) to stronger attraction of the trajectories towards the resulting equilibrium. The modified Michaelis-Menten function (20) exhibits this feature for those values of α smaller than unity (Figure 7). The motivation behind such a modification stems from the viewpoint of modelling a personalised immune response that is healthy with a strong attraction towards a healthy equilibrium.

Modelling and corresponding analysis in the existing literature focusses on asymptotic stability of healthy or unhealthy equilibria of the immune system (see [41]). Such an analysis gives good insight into the qualitative asymptotic behaviour of the system close to the equilibrium. However, it is evident from the observation of biological systems that the dynamics are finite time convergent to the given equilibrium point rather than asymptotically or exponentially convergent. There is limited work available which rigorously models the finite time behaviour which is a key characteristic of the underpinning biology. This section is motivated by the need to analyse the decay in the concentration or cell population to the equilibrium in a finite time as this may be a more realistic approach than to perform modelling and analysis on an infinite time scale. The tools for stability analysis from linear system theory can no longer be applied to the resulting non-Lipschitz dynamical system. However, there are well defined mathematical tools available in the literature as defined in [25, 3, 37]. Furthermore, the motivation to study a new modelling framework also lies in the possibility of proposing new treatment regimes which, as in existing cases, need to be defined on a finite time scale.

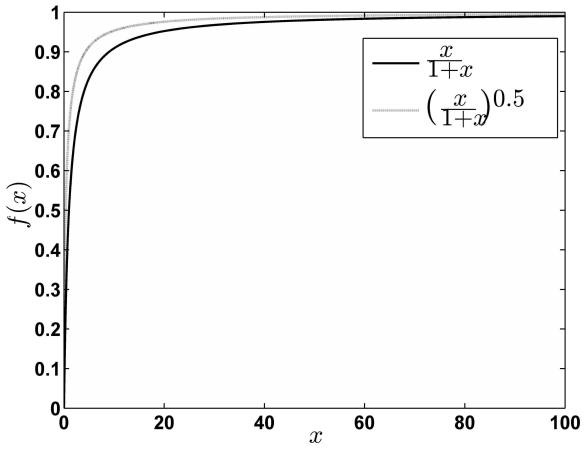

Figure 7. A normalised modified Michaelis-Menten function and a non-Lipschitz modification of that with $\alpha = 0.5$.

A systems model prescribing finite time stability: a case study

With the above viewpoint, the modified Michaelis-Menten functions as defined in (20) can be used to model the dynamics of auto-immune disease i.e. the class of disease in which psoriasis is thought to lie. For this case study, non-Lipschitz equations are used that build on the linearised immune system model given by [41].

The immune system model given in [41] is as follows:

$$\dot{x}_1 = l - dx_1 - k\,x_1\,x_3, \quad \dot{x}_2 = -e\,x_2 + k\,x_1\,x_3, \quad \dot{x}_3 = m\frac{x_2\,x_3}{h + x_2\,x_3} - f\,x_3 \tag{21}$$

where, x_1 represents the tissue cells, x_2 represents the damaged cells and x_3 represents the immune cells. The positive scalars l, d, k, e, m, h, f are defined in [41]. Consider the following linear model derived by linearising the non-linear dynamics around the equilibrium point $(x_1, x_2, x_3) = (\frac{l}{d}, 0, 0)$ as derived in [41]:

$$\dot{x}_1 = -dx_1 - \frac{k\,l}{d}x_3, \quad \dot{x}_2 = -ex_2 + \frac{k\,l}{d}x_3, \quad \dot{x}_3 = -fx_3 \tag{22}$$

The model parameters d, e, f represent respectively the death rate constants of the three states. The proposed modification of the model using the non-Lipschitz function (20) is given as follows:

$$\begin{gathered}\dot{x}_1 = -d\left(\frac{x_1}{1+x_1}\right)^{\alpha} - \frac{k\,l}{d}\left(\frac{x_3}{1+x_3}\right)^{\alpha}, \dot{x}_2 = -e\left(\frac{x_2}{1+x_2}\right)^{\alpha} + \frac{k\,l}{d}\left(\frac{x_3}{1+x_3}\right)^{\alpha}, \\ \dot{x}_3 = -f\left(\frac{x_3}{1+x_3}\right)^{\alpha}\end{gathered} \tag{23}$$

where $\alpha = 0.98$ is used. The model in equation (23) possesses a different set of equilibria when compared to (22). The equilibria depend on α. The justification for introducing such variability lies in the fact that it is unlikely that every immune system possesses a distinctly defined equilibrium and the same model parameters. Thus, the parameter α represents various responses for a class of immune system dynamics. There are a number of properties of this model that can be observed.

For non-negative initial conditions, the quantity $\frac{x_i}{1+x_i}, i = 1, 2, 3$ always remains positive. Furthermore, the time varying scalar $\bar{k}(x_3) = \frac{1}{(1+x_3)^{\alpha}}$ remains positive. The third equation in (23) can

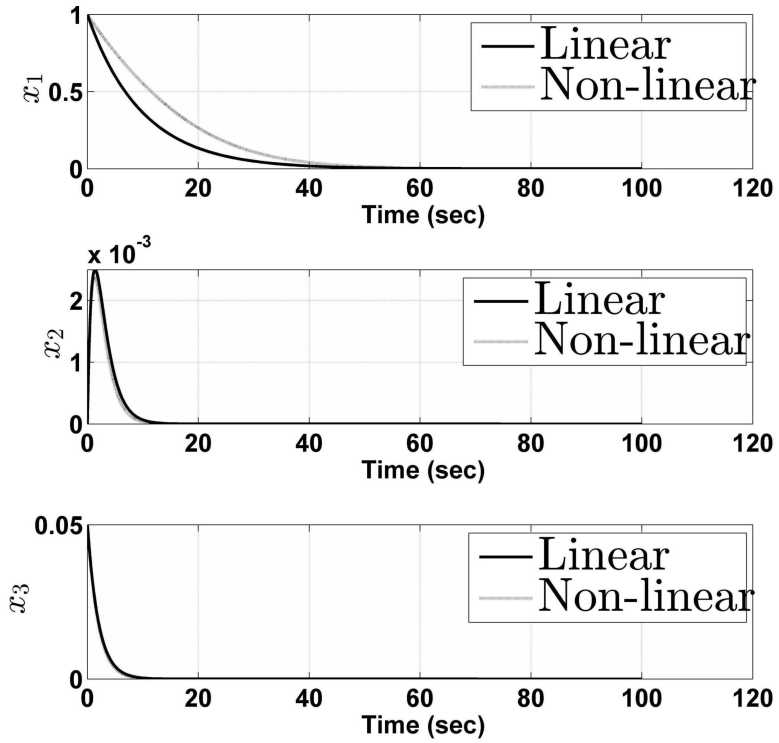

Figure 8. Comparison of evolution of states of the dynamics (23).

be re-written as

$$\dot{x_3} = -f\bar{k}(x_3)x_3^{\alpha}, \tag{24}$$

which is a finite time stable equation as per [3, Th. 4.2]. This can be formally verified by analysing the Lyapunov function $V(x_3) = \frac{1}{2}\,x_3^2$ and its temporal derivative along the scalar system equation (24) $\dot{V} = -f\bar{k}(x_3)x_3^{\alpha+1}$. Since $x_3^{\alpha+1} = (2V)^{\frac{\alpha+1}{2}}$, the equality

$$\dot{V} \leq -2^{\frac{\alpha+1}{2}} f\kappa V^{\frac{\alpha+1}{2}} \tag{25}$$

holds true for some scalar $1 \geq \bar{k}(x_3) \geq \frac{1}{2} > \kappa > 0$. Such a scalar $\kappa \in (0, \frac{1}{2})$ can always be found globally for all x_3. This is because (25) shows global asymptotic stability and there exists a finite time $t = t_1$ after which the expressions $\sup_{x_3 \geq 0} \bar{k}(x_3) = 1, x_3 < 1, (1 + x_3)^{\alpha} \leq 2$ and

$$\frac{1}{(1+x_3)^{\alpha}} \geq \frac{1}{2} \Rightarrow -\frac{1}{(1+x_3)^{\alpha}} = -\bar{k}(x_3) \leq -\frac{1}{2} \leq -\kappa$$

hold true for all $\alpha \in (0, 1)$. Hence, the well-known result of finite time stability using Lyapunov analysis (Theorem 4.2 of [3]) applies since $\frac{\alpha+1}{2} \in (0, 1)\ \forall \alpha \in (0, 1)$. This leads to the equality $x_3 = 0$ in finite time instead of asymptotically.

After a finite time instant $t = T < \infty$ for which the identity $x_3 = 0$ holds true for all $t \geq T$, the

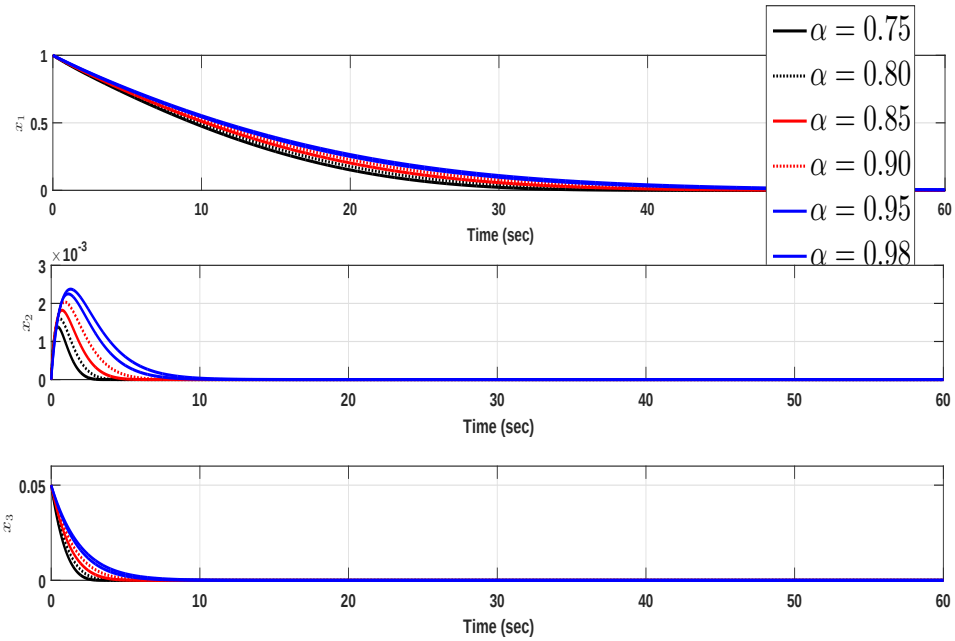

Figure 9. Sensitivity of state time histories of the dynamics (23) with varying α.

remaining dynamics in (23) can then be given as follows:

$$\dot{x}_1 = -d\left(\frac{x_1}{1+x_1}\right)^{\alpha}, \quad \dot{x}_2 = -e\left(\frac{x_2}{1+x_2}\right)^{\alpha}. \tag{26}$$

These, in turn, are finite time convergent to the origin $x_1 = 0, x_2 = 0$ following a similar analysis as carried out for the state x_3. This analysis shows that the model (23) imitates the linear model (22) in that the stability of the healthy equilibrium point is maintained. The comparative plots in Figure 8 show the behaviour of the linear model in (22) and the proposed model which prescribes finite time convergence in (23). The traces show good agreement. The stability of the states in (23) is a finite time behaviour, which is a special case of asymptotic stability (see [3]). Hence, the proposed model (23) captures a class of finite time healthy immune system responses that have the same qualitative stability properties as the linear model for the healthy equilibrium.

A further sensitivity analysis can also be studied. Figure 9 shows the evolution of all the three cell types against time when α is varied from 0.75 to 0.98. The initial conditions are kept constant for all simulation runs at $(1, 0, 0.05)$. It can be clearly seen that reduction in the parameter α is accompanied with a reduced settling time for the finite time stable equations contained in (23). From a systems biology viewpoint, it is reasonable to view α as a model constant that parameterizes the convergence to the healthy equilibrium. It should be noted here that the conventional model constants d, e, f are kept constant and it is the modified Michaelis-Menten function that affects the behaviour of the dynamics of psoriasis via α. Hence, the proposed model captures many possible immune responses for the same model structure, a more realistic and intuitive outcome than having a specific model for each type of immune response. Of course, setting $\alpha = 0$ captures the limiting discontinuous case as can be seen from (24) which enforces what is known in the paradigm of control theory as a sliding mode on $x_3 = 0$. Studies on such discontinuous dynamics can be found in [57]. Such a general parameterization of the immune response can motivate devising future therapeutic regimes.

Finally, sensitivity of the new model can be studied with respect to changes in the model constants

d, e, f. Let the right hand sides of the equations (22) and (23) be re-written as follows. The linear dynamics from (22) are given by

$$\dot{x}_1 = \Psi_1(d, \gamma, x_1, x_3), \quad \dot{x}_2 = \Psi_2(e, \gamma, x_2, x_3), \quad \dot{x}_3 = \Psi_3(f, x_3), \tag{27}$$

where $\gamma = \frac{kl}{d}$. The non-linear dynamics from (23) are given by

$$\dot{x}_1 = \Psi_4(\alpha, d, \gamma, x_1, x_3), \quad \dot{x}_2 = \Psi_5(\alpha, e, \gamma, x_2, x_3), \quad \dot{x}_3 = \Psi_6(\alpha, f, x_3), \tag{28}$$

It can be clearly seen that computing $\frac{\partial \Psi_3}{\partial f}$ results in $-x_3$ whereas computing $\frac{\partial \Psi_6}{\partial f}$ results in $-\left(\frac{x_3}{1+x_3}\right)^{\alpha}$. Hence, the non-linear differential equation is more sensitive in a favourable way when the parameter f changes, for example when $x_3 << 1$, as the non-Lipschitz entity $-\left(\frac{x_3}{1+x_3}\right)^{\alpha}$ represents faster convergence than $-x_3$ for given value of f. Certainly, the sensitivity may become less or more favourable when partial derivatives of Ψ_4 and Ψ_5 with respect to d and e respectively are taken into account. However, the underlying finite time behaviour is ensured by the parameter α.

4.1 *Cytokines as fast finite time actuators*

The concept of non-Lipschitz growth functions introduced above can be utilised to remove the approximation within the earlier singular perturbation based analysis [28] of the dynamics of psoriasis. The main idea is to treat the actuator as a finite time stable actuator which is obviously faster than the asymptotically stable cell dynamics. Consider again the case of IFN_γ acting as a control variable u_p having fast dynamics (see Figure 6). In place of the Lipschitz right hand side in (12), the following choice of non-Lipschitz dynamics for the finite time actuator can be made:

$$\dot{u}_p = \left(\frac{|u_p^* - u_p|}{1 + |u_p^* - u_p|}\right)^{\alpha} \text{sign}(u_p^* - u_p) \tag{29}$$

where, the scalar $\alpha \in (0, 1)$ and u_p^* is the steady-state value of the cytokine concentration. It can be seen that $u_p = u_p^*$ is an equilibrium of this system. A candidate Lyapunov function can then be constructed as follows:

$$V(u_p) = |u_p^* - u_p| \tag{30}$$

It should be noted that the concentrations u_p^* and u_p take only positive values due to their biological definitions. Hence, the function V is always positive definite. The temporal derivative of V along the trajectories of the dynamics (29) can be obtained as follows:

$$\dot{V} = \text{sign}(u_p^* - u_p) \left(-\left(\frac{|u_p^* - u_p|}{1 + |u_p^* - u_p|}\right)^{\alpha} \text{sign}(u_p^* - u_p)\right) \tag{31}$$

It is reasonable to restrict the study to finite concentrations in biology, i.e., consider only the local case $|u_p^* - u_p| < \rho$ where ρ is an arbitrary and *a priori* known positive scalar. Hence, the expression $1 + |u_p^* - u_p| < 1 + \rho \Rightarrow -\frac{1}{(1+|u_p^* - u_p|)^{\alpha}} < -\frac{1}{(1+\rho)^{\alpha}}$ holds true. The expression (31) can then be

re-written as follows:

$$\begin{aligned}\dot{V} &= |u_p^* - u_p|^\alpha \left(-\frac{1}{(1+|u_p^* - u_p|)^\alpha} \right) \\ &< -\frac{1}{(1+\rho)^\alpha} V^\alpha \end{aligned} \tag{32}$$

Since $\frac{1}{(1+\rho)^\alpha}$ is a positive constant, finite time stability of (29) follows from [3, Theorem 4.2] due to (32). Since, $V = 0$ in finite time, $u_p = u_p^*$ is also achieved in finite time. This is a very similar expression to that obtained in (13) in that $u_p^* \approx D$ when the concentration D is changing slowly when compared to u_p. It should be noted that the above analysis follows the naturally occurring finite time convergent cytokine dynamics rather than using the singular perturbation approach where $\epsilon \dot{u}_p$ is approximated as zero for some very small ϵ.

5. Conclusion

An ordinary differential equation based mathematical model of psoriasis pathogenesis has been developed which incorporates the different cell types and cytokines involved in this disorder. Specifically, the model considers T-cells, dendritic cells and keratinocytes. In order to keep the model simple, the role of only a few cytokines have been incorporated. Assuming the cell population dynamics as a plant model, the role of two cytokines as fast actuators is explored. A stability analysis using a singular perturbation approach is presented in which the inherent fast-slow dynamics is utilised. The two stable steady-states of the model correspond to a normal and psoriatic epidermis. In addition, the use of finite time stability analysis is motivated for biological systems as this seems very natural. An analysis framework is proposed that has the potential to provide new insights into how to exploit the role of cytokines in future treatments for psoriasis.

Moving forward, informative data to further validate the model could include measurements of cytokine levels along with rates of proliferation, differentiation and apoptosis of cell populations as functions of time. As more information becomes available regarding the interactions of other cell populations within this system (for example natural killer cells), such cells can also be incorporated into the model. This could include an extension to consider histological imaging that identifies psoriasis effects on natural killer cells [6], [32].

The model that has been developed contains crucial ingredients that can be extended to study autoimmune systems more generally and their involvement in an array of diseases. Pertinent examples would be psoriatic arthritis, which often co-occurs with psoriasis [52]. In addition, the pro-inflammatory state in psoriasis is correlated to the presence of co-morbidities such as metabolic syndrome [7]. In this case the model may provide insight into the complex interplay and the common mechanisms involved [56]. Moreover, the modelling framework lends itself to the study of wider diseases of cytokine and T-cell dysfunction including autoimmune type 1 diabetes and multiple sclerosis [40].

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