Non-Lipschitz Growth Functions as a Natural Way of Modelling Finite Time Behaviour in Auto-immune Dynamics [★]

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Abstract: This paper presents an analysis of healthy immune system dynamics from the perspective of finite time stability. Finite time stability and stabilisation have been well-studied in various engineering applications. The principal paradigm uses non-Lipschitz functions of the states. Recent studies on robustness of closed-loop non-Lipschitz dynamical systems are based on Lyapunov functions and show that finite time stability is both a special case of and superior to the asymptotic stability of the system. Such a finite time convergence property has not been studied extensively in the area of biological systems where it is evident that the dynamics are finite time convergent to certain equilibrium points rather than asymptotically or exponentially convergent. Furthermore, there are examples such as a healthy immune system response where robustness is found to the state of auto-immune disease. These inherent features of robustness and finite time convergence motivate the development of a modified version of the Michaelis-Menten function, which is frequently used in biology, based on the finite time stability paradigm. The paper hypothesizes a potential connection between finite time stability and the dynamics of a healthy immune system.

1. INTRODUCTION

Finite time stability has been studied rigorously and is an efficient robust control paradigm. It is a special case of asymptotic stability with the principal feature being that the states of the dynamical system reach the origin in finite time as opposed to infinite time. Several results exist in the area. The foundations can be traced back to results in the area of optimal control (see Fuller (1960)) where finite time convergence was shown to occur when a discontinuous controller was used.

Amongst the theoretical control studies, the convergence of the states to the origin can be achieved either via continuous or discontinuous control. Amongst the continuous control algorithms, early work by Haimo (1986) showed that the non-Lipschitz continuous controllers can produce a closed-loop system with states converging to the origin in finite time. Work by Bhat and Bernstein (2000) formalised Lyapunov theorems for continuous finite time stability. This area has developed from these early results and a brief literature review can be found in Bernuau et al. (2012). Amongst the discontinuous control paradigms, the area of first and second order sliding mode control belong to the class of robust control techniques where the states either reach a manifold or the origin in finite time. Since the first results of Utkin (1977), sliding mode control has been recognised as a popular robust control technique. The

theory of second order sliding mode control developed in Levant (1993) is a robust control result that ensures finite time convergence of the states of a second order system to the origin in the presence of bounded perturbations. A general result concerning finite time stability of discontinuous systems can be found in Orlov (2005). The latest advances in this area focus on studying explicit Lyapunov functions as can be seen by the recent literature of Polyakov and Poznyak (2009); Orlov et al. (2010) and Moreno (2012).

The main focus of this paper is in studying finite time stability properties of the dynamics of a healthy immune system. A new modelling environment for the immune system is thus hypothesized. Study of the immune system from a systems biology perspective continues to attract the interest of researchers. Immune system dynamics is a fundamental example of a biological system with bistable behaviour. Pathologies related to the immune system lead to a number of human diseases including psoriasis, arthritis, cancer, atherosclerosis, diabetes, inflammatory bowel disease and asthma. This paper studies the healthy equilibrium of the immune system dynamics.

Immune system dynamics, as with any other biological system, evolve over a finite time interval as opposed to infinite time. For example, individual clonal immune cell populations are required to expand and become activated for a limited time. The existing literature has rigorously provided systems theoretic results for studying asymptotic convergence of the states to certain equilibria (see for example Perelson (2002) and Rapin et al. (2011)). However,

rigorous study from a systems biology viewpoint has not been carried out to explore finite time stability. Given a rich mathematical background and the availability of sound results in the theory of continuous and discontinuous finite time stabilisation, there exists an opportunity to study the immune system dynamics from this control theoretic perspective. The principal motivation of the paper is to explore if there exists a connection between the mathematically known consequence of finite time stability when using non-Lipschitz functions and the natural observation of finite time convergence in biological system dynamics such as that of a healthy immune system.

The proposed study of finite time stability is carried out as follows. The paper considers two existing models of the immune system dynamics and proposes modifications to generate finite time stability of the healthy equilibrium. The first model is the cell-level dynamics given by Rapin et al. (2011) and the second model is that given by Valeyev et al. (2010) for the cytokine level dynamics. As discussed in the reported literature, finite time stability cannot be modelled in the absence of non-Lipschitz functions on the right hand side of differential equations. This becomes the main basis for proposing a non-Lipschitz version of the well-known Michaelis-Menten function (see references Lebl (2013); Porter and Miller (2012) for a survey and references Valeyev et al. (2008a,b) for recent applications). The paper considers if the existing qualitative features of a healthy immune system remain while giving mathematical evidence of finite time convergence thereby narrowing the gap between the natural biological occurrence of finite time stability and the underlying models that should capture such observed behaviour.

The paper is structured as follows. Section 2 begins the discussion with a modified version of the Michaelis-Menten function. Section 3 then explores connections with finite time stability for two system models of the immune system dynamics. Section 4 presents the conclusions.

2. A MODIFIED VERSION OF THE MICHAELIS-MENTEN FUNCTION

A modified version of the Michaelis-Menten function is discussed in this section. The motivation to introduce a new version lies in the possibility of modelling the naturally occuring finite-time behaviour of the healthy immune system. This is discussed in more detail in the next section. The Michaelis-Menten function involving the concentration x of a cell population is given as follows:

$$f(x) = \frac{k_{\max} x}{k_m + x}, \qquad (1)$$

where $k_{\max}$ 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 (1) as utilised in Valeyev et al. (2010) can be written as follows:

$$f(x) = \frac{x}{1+x} \qquad (2)$$

A non-Lipschitz modification of the above function is proposed in this paper as follows:

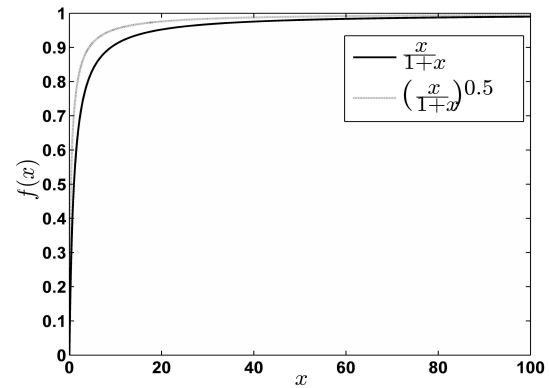$$\bar{f}(x) = \left(\frac{x}{1+x}\right)^{\alpha} \qquad (3)$$

Fig. 1. Modified Michaelis-Menten function

where $\alpha \in (0,1)$. The non-Lipschitz function $\bar{f}(x)$ of (3) equals $f(x)$ of (2) for $\alpha = 1$. The limiting values of $\bar{f}(x)$ as x tends to zero and infinity remain the same as those of $f(x)$. The main difference between these two functions is that $\bar{f}(x)$ approaches zero with an infinite slope 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 Fig. 1 with $\alpha = 0.5$. It is 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 (1) correspond to a higher slope closer to the origin and to stronger attraction of the trajectories towards the resulting equilibrium. The modified Michaelis-Menten function (3) mimics this characteristic for those values of α smaller than unity.

3. MODELS PRESCRIBING FINITE TIME STABILITY

Such a modification as proposed above comes from the viewpoint of modelling a personalised immune response that is healthy with a stronger attraction towards a healthy equilibrium. Modelling analysis in the existing literature focusses on asymptotic stability of healthy or unhealthy equilibria of the immune system (see Rapin et al. (2011)). Typically, the vector field is linearised about the equilibrium and the eigenvalues of the resulting system matrix are analysed. 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. To the authors' knowledge, there is no existing work which can rigorously model 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 populations to the equilibrium in a finite time as this may be a more realistic way of modeling compared to that 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 Bhat and Bernstein (2000). Furthermore, the motivation to study a new modelling framework also lies in the possibility of proposing new

treatment regimes which, like the existing ones, inherently need to be defined on a finite time scale as do cell deaths.

With the above viewpoint, the modified Michaelis-Menten functions as defined in (3) can be used to model a personalised immune response function. Two different models are considered relating to the immune system in the following sub-sections. The first model builds on the linearised immune system model given by Rapin et al. (2011) which captures cell level dynamics and the second model builds on the cytokine dynamics presented in Valeyev et al. (2010).

3.1 Cell population dynamics

The first model considered is the immune systems model given in Rapin et al. (2011) as follows:

$$\dot{x}_1 = l - dx_1 - k\,x_1\,x_3, \quad \dot{x}_2 = -e\,x_2 + k\,x_1\,x_3$$
$$\dot{x}_3 = m\frac{x_2\,x_3}{h + x_2\,x_3} - f\,x_3 \tag{4}$$

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 Rapin et al. (2011). 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 Rapin et al. (2011):

$$\dot{x}_1 = -dx_1 - \frac{k\,l}{d}x_3, \quad \dot{x}_2 = -ex_2 + \frac{k\,l}{d}x_3, \quad \dot{x}_2 = -fx_3 \tag{5}$$

The model parameters d, e, f represent respectively the death rate constants of the three states [1]. The proposed modification of the model using the non-Lipschitz function (3) is given as follows:

$$\dot{x}_1 = -d\left(\frac{x_1}{1+x_1}\right)^\alpha - \frac{k\,l}{d}\left(\frac{x_3}{1+x_3}\right)^\alpha$$
$$\dot{x}_2 = -e\left(\frac{x_2}{1+x_2}\right)^\alpha + \frac{k\,l}{d}\left(\frac{x_3}{1+x_3}\right)^\alpha \tag{6}$$
$$\dot{x}_3 = -f\left(\frac{x_3}{1+x_3}\right)^\alpha$$

where $\alpha = 0.98$ is used. Model (6) possesses a different set of equilibria when compared to (5). 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 (6) can be re-written as

$$\dot{x}_3 = -f\bar{k}(x_3)x_3^\alpha, \tag{7}$$

which is a finite time stable equation as per Bhat and Bernstein (2000, Th. 4.2). This can be formally verified by analysing the Lyapunov function $V(x_3) = \frac{1}{2}\,x_3^2$ and its

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[1] Refer to Rapin et al. (2011) for values of the model constants
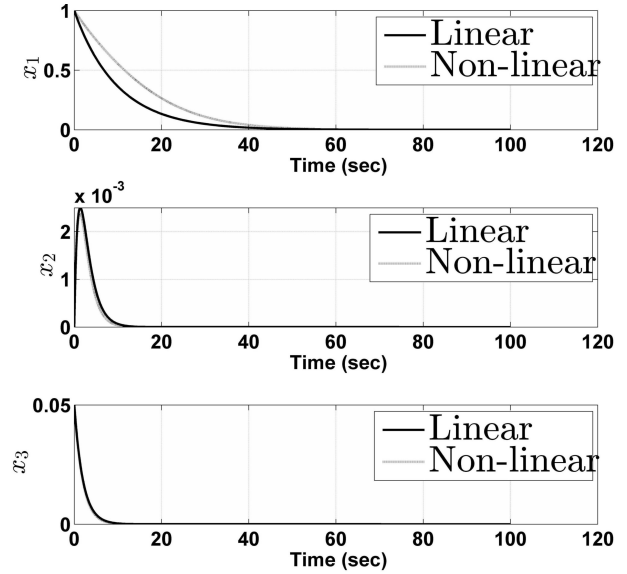

Fig. 2. Comparison of evolution of state x_1 of the dynamics (6)

temporal derivative along the scalar system equation (7) $\dot{V} = -f\bar{k}(x_3)x_3^{\alpha+1}$. Since $x_3^{\alpha+1} = (2V)^{\frac{\alpha+1}{2}}$, the equality

$$\dot{V} \leq -2^{\frac{\alpha+1}{2}}f\kappa V^{\frac{\alpha+1}{2}} \tag{8}$$

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 (8) 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

$$\frac{1}{(1+x_3)^\alpha} \geq \frac{1}{2} \Rightarrow -\frac{1}{(1+x_3)^\alpha} = -\kappa(\bar{x}_3) \leq -\frac{1}{2} \leq -\kappa$$

hold true for all $\alpha \in (0, 1)$. Hence, the well-known result of finite time stability using Lyapunov analysis (Theorem 4.2 of Bhat and Bernstein (2000)) 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 remaining dynamics in (6) can then be given as follows:

$$\dot{x}_1 = -d\left(\frac{x_1}{1+x_1}\right)^\alpha, \quad \dot{x}_2 = -e\left(\frac{x_2}{1+x_2}\right)^\alpha. \tag{9}$$

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 (6) imitates the linear model (5) in that the stability of the healthy equilibrium point is maintained. However, the stability of the states is a finite time behaviour, which is a special case of asymptotic stability (see Bhat and Bernstein (2000)). Hence, the proposed model (6) 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.

Due to the finite time convergence properties shown, the proposed model can be seen to capture a more robust immune system. Consider the initial condition response for models (5) and (6). The evolution of each of the states

is shown in Fig. 2 with the initial condition $(x_1^0, x_2^0, x_3^0) = (1, 0, 0.05)$. The immune cells x_3 and the damaged cells x_2 go to zero slightly quicker for the non-linear model. Here, α is seen as a modelling parameter dictating the finite time behaviour.

3.2 A Cytokine dynamics of an immune system

This section proposes the study of finite time stability with respect to a model proposed in Valeyev et al. (2010). Valeyev et al. (2010) proposed a systems model for immune cell interactions to study the mechanism of inflammatory disease in human skin. The authors highlighted the need for development of a model that gives more insight into how various cytokine production scenarios can complement the genome-wide association studies and expression level comparison studies for studying how the immune system operates. The normalised model given in the Section "Materials and Methods" of the article Valeyev et al. (2010) for capturing the interdependence of cytokines x_1 and x_2 can be formulated by coupled ordinary differential equations as follows:

$$\dot{x}_1 = a_1 \frac{x_1}{1+x_1} \frac{1}{1+x_2} - a_2 \frac{x_1}{(1+x_1)\left(1 + \frac{x_1}{1+x_1} + \frac{d}{1+x_1}\right)}$$
$$\qquad - D(x_1 - c_k) - MP\frac{x_1}{k_{MP} + x_1} + i_1(t)$$
$$\dot{x}_2 = a_3 \frac{x_1}{1+x_1} \frac{x_2}{1+x_2} - a_4 \frac{x_2}{(1+x_2)\left(1 + \frac{x_2}{1+x_2} + \frac{d}{1+x_2}\right)}$$
$$\qquad - D(x_2 - c_k) - MP\frac{x_2}{k_{MP} + x_2} + i_2(t)$$

$$(10)$$

The variables $x_1(t)$ and $x_2(t)$ represent the concentrations of cytokine A and B respectively. The corresponding non-normalised equations and the definitions of the units of the associated model entities can be found in Valeyev et al. (2010). The model parameters can be found in Table 1 of the reference of Valeyev et al. (2010). In the following analysis, it is assumed that $i_1(t) = i_2(t) = 0$. The system model (10) is a highly non-linear model and unlike the linear dynamics, the stability points are generally difficult to find. The approach in Valeyev et al. (2010) is to find the equilibrium points numerically by setting the right hand sides of each of the equations in (10) to zero and locating the intersection. Fig. 3 shows typical *null clines*, or *lines of*
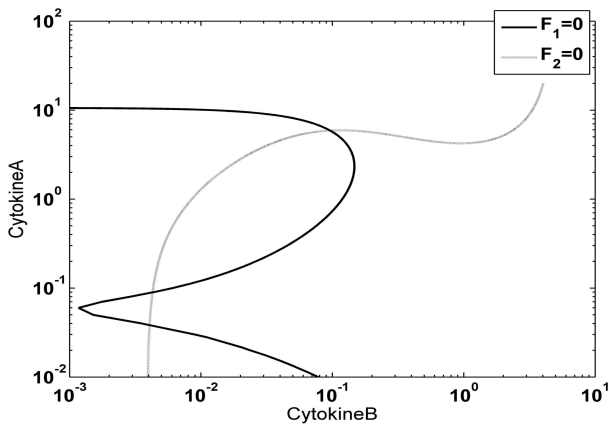

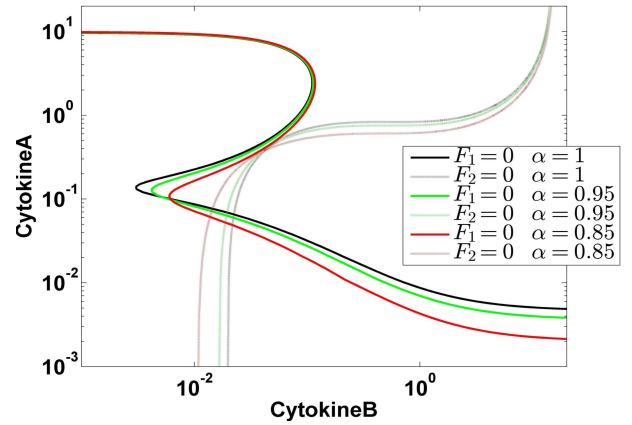Fig. 3. Lines of equilibrium of the dynamics (10) with bistable behaviour

Fig. 4. Lines of equilibrium of the dynamics (11) for the stable homeostasis

equilibrium for the dynamics of (10) for the case when the model parameters induce a bistable behaviour. The legend entry $F_1 = 0$ represents that set of points in the (x_1, x_2) state-plane where the expression $\dot{x}_1 = 0$ holds. Similarly, the legend entry $F_2 = 0$ represents that set of points in the (x_1, x_2) state-plane where the expression $\dot{x}_2 = 0$ holds. Refer to Valeyev et al. (2010) for a detailed analysis of the resulting dynamics of the immune system.

It can be seen that model (10) makes use of the Michaelis-Menten function in its original normalised form (2). Similar to Section 3.1, the intention is to explore the behaviour of the model by substituting the non-Lipschitz growth function (3) for (2) in the model (10). Hence, the following model results:

$$\dot{x}_1 = \frac{a_1}{1+x_2}\left(\frac{x_1}{1+x_1}\right)^\alpha - \frac{a_2}{1 + \frac{x_1}{1+x_1} + \frac{d}{1+x_1}}\left(\frac{x_1}{1+x_1}\right)^\alpha$$
$$\qquad - D(x_1 - c_k) - MP\left(\frac{x_1}{k_{MP} + x_1}\right)^\alpha$$
$$\dot{x}_2 = a_3\left(\frac{x_1}{1+x_1}\right)^\alpha\left(\frac{x_2}{1+x_2}\right)^\alpha - MP\left(\frac{x_2}{k_{MP}+x_2}\right)^\alpha$$
$$\qquad - a_4\left(\frac{x_2}{1+x_2}\right)^\alpha\frac{1}{\left(1 + \frac{x_2}{1+x_2} + \frac{d}{1+x_2}\right)} - D(x_2 - c_k)$$

$$(11)$$

where the scalar $\alpha > 0$ becomes a model constant that parameterises the immune system response. It should be noted that when going from (10) to (11), the non-Lipschitz growth function is performed only for the terms of the form $x_i/(k + x_i)$ for some $k = 1$ or $k = k_{MP}$ and $i = 1, 2$ with the exception of the term

$$-\frac{1}{1 + \frac{x_i}{1+x_i} + \frac{d}{1+x_i}} \qquad (12)$$

where $i = 1, 2$ since this term is not non-Lipschitz and does not affect the overall dynamics in the way that the other non-Lipschitz terms do. In other words the term (12) can be shown to be bounded from above by the term $-1/(2+d)$ and does not contribute towards any finite time convergence characteristics. It is interesting to study if the original qualitative behaviour remains for the healthy equilibrium despite the above changes. Fig. 4 shows the behaviour of the vector field (11) for the stable homeostasis in terms of the equilibrium lines $F_1 = 0, F_2 = 0$ for three cases. The black lines represent the original case, i.e. $\alpha = 1$,
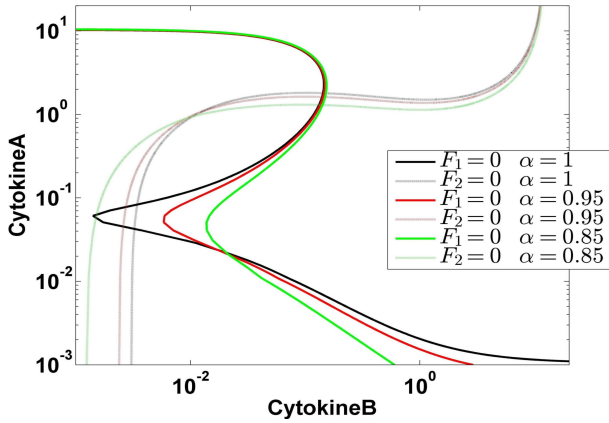
Fig. 5. Lines of equilibrium for dynamics (11) for the oscillatory homeostasis
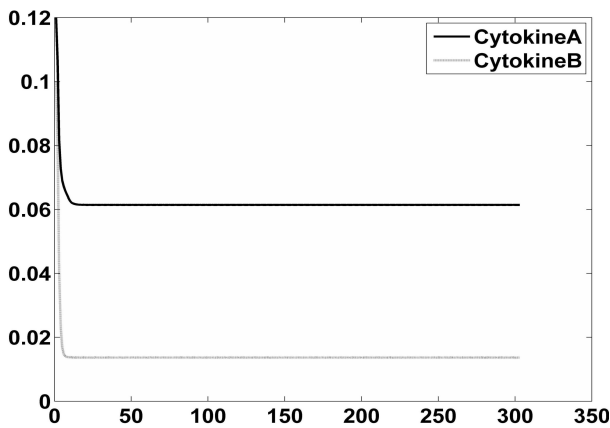

Fig. 6. State response for the dynamics (11) for the stable homeostasis

the red lines represent the case when $\alpha = 0.95$ and the green lines represent the case when $\alpha = 0.85$ is used. A similar qualitative behaviour is shown for the oscillatory homeostasis in Fig. 5. The equilibrium manifolds $F_1 = 0, F_2 = 0$ vary with the variation in α. However, the qualitative behaviour of the systems model remains the same, representing a stable healthy equilibrium mode (see Fig. 4) and an unstable oscillatory mode (see Fig. 5) for auto-immune disease for the presented range of α since the location of the equilibrium points of interest do not change drastically. Fig. 6 shows the time response of the cytokine concentrations x_1, x_2 for the stable homeostasis of Fig. 4.

Parameterisations of Model constants based on finite time stability analysis

Finite time stability of dynamical systems has been studied extensively. There are two generic problems that are of relevance to the study carried out in this section. Amongst discontinuous systems, results on second and higher order sliding mode systems pertaining to finite time stabilisation solve the first problem via Lyapunov analysis, namely, proving that the system states converge to the desired ones in finite time (see references Orlov (2005); Moreno (2012); Orlov et al. (2010)). The results that make use of non-Lipschitz continuous controllers for second order systems can be found in Bhat and Bernstein (1998); Hong et al. (2001). The converse problem then becomes one of finding

the gains of the controller given the desired convergence time of the closed-loop system. Results in this area of study can be found in Oza et al. (2012).

The preceding sections studied the first problem for the healthy immune system dynamics, namely, if the system settles at the equilibrium given the structure of the model and fixed values of model constants. This section attempts to study the converse problem for the proposed modifications of the model. More precisely, the intention is to find parameterisations or sets of values for the model constants for which finite time convergence of the states is guaranteed. Motivation for such an analysis lies in the ultimate goal of gaining more insight into stable behaviour of the auto-immune dynamics and exploring opportunities for building a desired model for therapeutic purposes as the model constants can be influenced by drug regimes.

To this effect, consider the stable homeostasis of the dynamics (11). The approach used in the following is that of analysing bounding solutions (or the majorant curves as utilised in Levant (1993)) to find the conditions for finite time convergence while treating the model constants as controller gain-like terms. It is reasonable to assume $|x_1| < 1$ close to the stable origin as can be seen from Fig 4. It is also true that the expression $\sup_{x_2 \geq 0} 1/(1 + x_2) = 1$ always holds true. Furthermore, the expression $-1/(k_{MP} + x_1)^\alpha \leq -\frac{1}{(1+x_1)^\alpha}$ can be derived for all $k_{MP} < 1$. Finally, the expression

$$\sup_{x_1 \geq 0} 1 + \frac{1}{1 + x_1} + \frac{d}{1 + x_1} \leq 2 + d$$
$$\Rightarrow \frac{-1}{1 + \frac{1}{1+x_1} + \frac{d}{1+x_1}} \leq -\frac{1}{2 + d} \tag{13}$$

always holds true for all $1 > x_1 \geq 0$. Combining these simplifications, the first equation in (11) can be re-written as follows for $k_{MP} = 0.6$:

$$\dot{x}_1 \leq \left(a_1 - \frac{a_2}{2 + d} - MP\right)\left(\frac{x_1}{1 + x_1}\right)^\alpha - D(x_1 - c_k) \tag{14}$$

In the vicinity of the origin where $1 > |x_1| > c_k = 0.25$, the finite time convergence of the state x_1 to the set $\{(x_1, x_2) : \max\{|x_1|, |x_2|\} \leq c_k\}$ is always guaranteed for the finite time stable equation (14). This can be formally proved by employing a Lyapuov analysis as presented in Section 3.1 provided the following condition holds true:

$$a_1 - \frac{a_2}{2 + d} - MP < 0 \tag{15}$$

It can be seen that the set $\{(x_1, x_2) : \max\{|x_1|, |x_2|\} \leq c_k\}$ contains the stable equilibrium which is the intersection of the two equilibrium lines for all the cases in Fig. 4. A similar analysis can be performed for the second equation in the vicinity of the stable equilibrium where $x_1 < 1$ so that $x_1/(1 + x_1) \leq 1$ holds true. The resulting majorant solution for the second equation can be obtained as follows:

$$\dot{x}_2 \leq \left(a_3 - \frac{a_4}{2 + d} - MP\right)\left(\frac{x_2}{1 + x_2}\right)^\alpha - D(x_2 - c_k) \tag{16}$$

The condition for finite time convergence of the state x_2 to the set $\{(x_1, x_2) : \max\{|x_1|, |x_2|\} \leq c_k\}$ is thus obtained:

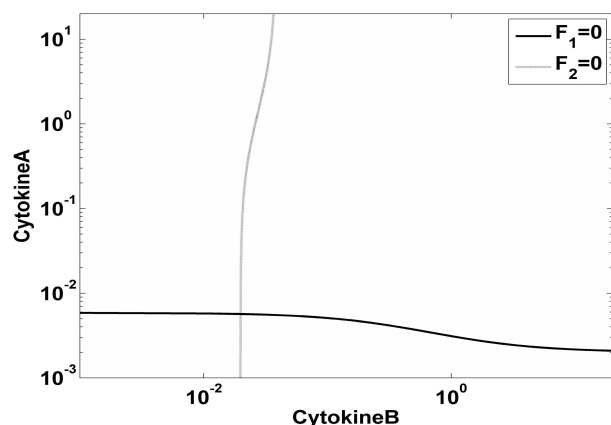$$a_3 - \frac{a_4}{2 + d} - MP < 0 \tag{17}$$

Fig. 7. State response for the dynamics (11) for the a priori guaranteed stable homeostasis

Equations (15) and (17) prescribe conditions on the model parameters in a similar way to the controller tuning analysis presented in Oza et al. (2012) for a general perturbed double integrator system. Hence, the above analysis builds an analogue to the existing control theoretical results for the reported immune system dynamics while extending the modelling framework to encompass a more general immune system response. The equilibrium lines for the system with an priori guarantee of finite time stability are shown in Fig. 7 where the parameters $a_1 = 0.16, a_2 = 0.34, a_3 = a_4 = 0.03, MP = 0.024, c_k = 0.25, k_{MP} = 0.6, d = 0.5$ are used such that conditions (15) and (17) are satisfied. It can be seen from Fig. 7 that such an immune system does not exhibit any unstable modes and hence finite time convergence to the set containing the resulting healthy equilibrium is the only possible outcome.

4. CONCLUSION

A non-Lipschitz growth function has been proposed in this paper. Motivated by the observation of naturally occurring finite time convergence in biological systems and by the recent advances in robust control systems, a new modelling framework for immune system dynamics was proposed and analysed. The problem of parameterising the constants of the proposed model was undertaken based on both the intuitively known fact of biological finite time stability of naturally occurring dynamics and the corresponding mathematical analysis. Extending this approach to higher dimensional models can be identified as a future objective.

REFERENCES

Bernuau, E., Perruquetti, W., Efimov, D., and Moulay, E. (2012). Finite-time output stabilization of the double integrator. In *IEEE 51st Annual Conference on Decision and Control (CDC)*, 5906–5911.

Bhat, S. and Bernstein, D. (1998). Continuous finite-time stabilization of the translational and rotational double integrators. *IEEE Transactions on Automatic Control*, 678–682.

Bhat, S. and Bernstein, D. (2000). Finite-time stability of continuous autonomous systems. *SIAM J. Control Optim.*, 38(3), 751–766.

Fuller, A. (1960). Relay control systems optimized for various performance criteria. In *Proceedings of the 1st IFAC Triennial World Congress*, 510–519.

Haimo, V.T. (1986). Finite time controllers. *SIAM Journal on Control and Optimization*, 24(4), 760–770.

Hong, Y., Huang, J., and Xu, Y. (2001). On an output feedback finite-time stabilization problem. *IEEE Transactions on Automatic Control*, 46(2), 305–309.

Lebl, J. (2013). Ordinary differential equations. In B. Reisfeld and A. Mayeno (eds.), *Computational Toxicology*, volume 930 of *Methods in Molecular Biology*, 475–498. Humana Press.

Levant, A. (1993). Sliding order and sliding accuracy in sliding mode control. *International Journal of Control*, 58(6), 1247–1263.

Moreno, J.A. (2012). A Lyapunov approach to output feedback control using second-order sliding modes. *IMA Journal of Mathematical Control and Information*, 29(3), 291–308.

Orlov, Y. (2005). Finite time stability and robust control synthesis of uncertain switched systems. *SIAM Journal on Control and Optimization*, 43(4), 1253–1271.

Orlov, Y., Aoustin, Y., and Chevallereau, C. (2010). Finite time stabilization of a perturbed double integrator - part I: Continuous sliding mode-based output feedback synthesis. *IEEE Transactions on Automatic Control*, 56(3).

Oza, H., Orlov, Y., and Spurgeon, S. (2012). Lyapunov-based settling time estimate and tuning for twisting controller. *IMA Journal of Mathematical Control and Information*, 29(4), 471–490.

Perelson, A.S. (2002). Modelling viral and immune system dynamics. *Nature reviews. Immunology*, 2(1), 28–36. PMID: 11905835.

Polyakov, A. and Poznyak, A. (2009). Lyapunov function design for finite-time convergence analysis: "Twisting" controller for second-order sliding mode realization. *Automatica*, 45(2), 444–448.

Porter, C.M. and Miller, B. (2012). Cooperativity in monomeric enzymes with single ligand-binding sites. *Bioorganic chemistry*, 43, 44–50.

Rapin, N., Mosekilde, E., and Lund, O. (2011). Bistability in autoimmune diseases. *Autoimmunity*, 44(4), 256–260. PMID: 21244341.

Utkin, V. (1977). Variable structure systems with sliding modes. *IEEE Transactions on Automatic Control*, 22(2), 212–222.

Valeyev, N., Bates, D., Heslop-Harrison, P., Postlethwaite, I., and Kotov, N. (2008a). Elucidating the mechanisms of cooperative calcium-calmodulin interactions: a structural systems biology approach. *BMC Systems Biology*, 2(1), 48.

Valeyev, N., Heslop-Harrison, P., Postlethwaite, I., Kotov, N., and Bates, D. (2008b). Multiple calcium binding sites make calmodulin multifunctional. *Mol. BioSyst.*, 4, 66–73.

Valeyev, N., Hundhausen, C., Umezawa, Y., Kotov, N., Williams, G., Clop, A., Ainali, C., Ouzounis, C., Tsoka, S., and Nestle, F. (2010). A systems model for immune cell interactions unravels the mechanism of inflammation in human skin. *PLoS Comput Biol*, 6(12), e1001024.