Synergies between the dynamics of the immune response of T cells and the variable structure control paradigm

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Abstract— **This paper argues that strong synergies exist between the Variable Structure Control (VSC) paradigm and the dynamical behaviour of the immune response of T cells following vigorous infection. Sharp changes in T cell population kinetics in response to an infection have been revealed by experimental studies. Striking similarities are shown to exist between the phase portrait of a classical VSCS and the phase portrait of an accurate model of the T cell response with an on/off activation function. The robustness properties of the T cell response dynamics described in current experimental and mathematical studies are evaluated using Lyapanov stability theory and numerical simulations. The findings demonstrate that the T cell dynamics following vigorous infection behave as a closed-loop system under variable structure control. This control law effectively determines the immunological control structure and the metabolic energy regime required to ensure that the dynamics of the responding T cells maintain a healthy state. The VSC paradigm thus provides a mechanism to understand the transition from health to disease.**

I. Introduction

The immune response of T cells is a major immunological dynamic which opposes the progression of a bacterial or viral infection [4], [17]. The T cell itself is a type of lymphocyte (white blood cell) which mainly develops in the thymus and circulates in the blood and lymph [6], [5]. It is characterized by a unique antigen specific T-cell receptor (TCR) on the cell surface. The T cell population consists of different subtypes classified according to their immunological functions and phenotypes. For instance, CD8+ cytotoxic T cells respond typically to viral antigen and kill infected cells. Kinetic analysis in experimental studies of the T cell response following vigorous infection has provided accurate data on the time evolution of the population of responding T cells [6], [17]. Fundamentally, following activation of a small number of T cells by the pathogen, T cells rapidly proliferate at the maximum expansion rate. During this expansion phase, the infection may be removed. The expansion is suddenly **ceased** after some days and the number of activated T cells is drastically reduced. During this decay, or contraction phase, a small number of activated T cells become memory T cells. It follows that the population dynamic of the T cell response exhibits step-like changes between immunological dynamics which enhance or inhibit the immune response [6], [12], [17].

Various mathematical functions have been constructed to model the immunological mechanisms which underpin the dynamical behaviour of T cells responding to infection [3], [5], [10]. Different modelling approaches utilize a linear state feedback, a Michaelis-Menten function or other nonlinear versions of functional responses appearing in ecological models. They imply an immune activation which depends on the concentration of the pathogen [3], [5], [10]. These candidate immune response functions are not entirely appropriate because the population dynamic of T cells following vigorous infection does not entirely depend on the pathogen dynamic [4], [5], [17]. Further, the responses obtained are not fully in accordance with experimental observation because the corresponding stability and performance characteristics of the immune response are not robust to perturbations in biological rates and to model uncertainty [1], [5], [17]. However, modelling the T cell response using an on/off activation function such as in [1], [5] or a combination of feedback mechanisms such as in [4], [12] achieve a close match with experimental data. Importantly, neither changes in the initial number of responding T cells nor changes in biological rates associated with phenomenological factors perturb the qualitative behaviour of the system as is observed in practice. Therefore, models of the T cell response which switch replicate the robustness seen in experimental studies [4], [17], [18].

The motivation of this paper is to provide an analytical framework to evaluate the population dynamics of the T cell response using the VSC paradigm to further understand the switching mechanism occurring during the immune response. The novelty resides in the fact that the findings demonstrate the notion of the T cell dynamics following infection as a biological system which is a closed-loop system including a robust VSC law. This control law effectively determines the immunological control structure during the expansion and contraction phase and the metabolic energy regime required to ensure that the dynamics of the responding T cells maintain a healthy state [5], [17]. The VSC paradigm thus provides a mechanism to understand the transition from health to disease.

The paper is organised as follows: the fundamentals of variable structure control theory are revisited in Section 2. Section 3 presents the significant similarities between VSCS and the T cell response following vigorous infection using a mathematical model which has been validated by experimental data. Finally, a robustness analysis is conducted in Section 4 to assess the performance of the proposed immunological control law.

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II. Philosophy of Variable Structure Control

The philosophy and characteristics of the VSC paradigm are reviewed using the classical example of the second order oscillatory system from [14] given as follows:

$$\frac{d^2y}{dt} - \xi\frac{dy}{dt} + uy = 0 \tag{1}$$

where ξ is a constant and u is the chosen control action. Consider a fixed structure design where the control gain is set to:

$$u = k \tag{2}$$

and the constant parameter k is a positive or a negative scalar. The phase portrait of the system (1) with the control (2) reveals that this strategy produces unstable dynamics and the desired stable motion of the system trajectories towards the equilibrium located at the origin is not exhibited as shown in Figure 1.

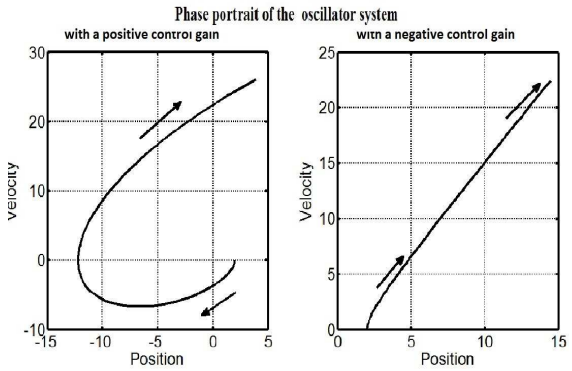

Fig. 1. Trajectories of the oscillator system with positive gain $k = 1$ and a negative gain $k = -1$. $y(0) = 2$; $\frac{y(0)}{dt} = 0$ and $\xi = 1$.

In contrast to this fixed structure design, the basic philosophy of VSC consists in formulating a decision rule to switch between different control structures to achieve stable dynamics and performance requirements [14]. A VSC law for the system (1) is constructed by combining a positive and a negative gain using the switching function $s(y(t), \frac{dy(t)}{dt})$ as follows:

$$u = \begin{cases} \alpha & \text{if } y(t)s(y(t), \frac{dy(t)}{dt}) > 0 \\ -\alpha & \text{if } y(t)s(y(t), \frac{dy(t)}{dt}) < 0 \end{cases} \tag{3}$$

$$s(y(t), \frac{dy(t)}{dt}) = cy(t) + \frac{dy(t)}{dt} \tag{4}$$

where α is the chosen controller gain and $0 < c \leq \lambda$ is a positive scalar designed using the stable poles of the system (1). λ is expressed as:

$$\lambda = \frac{\xi}{2} - \left(\frac{\xi^2}{4} + \alpha\right)^{\frac{1}{2}} \tag{5}$$

The example of the VSC law (3) applied to the system (1) highlights the significant advantages of allowing the control structure to change during the operation of the system [14], [8]. Although neither the positive nor the negative control gain alone could produce stable dynamics, an asymptotically stable motion towards the origin is achieved using the VSC (3) which effectively switches between suitable parts of the trajectories of the composite control structures, see Figure 2. Therefore, the application of a switched control mechanism has engendered a new system property i.e asymptotic stability which is not present in either of the single structure control designs alone. As observed in Figure 2, the system attains a sliding mode whereby it is forced to remain on the switching surface (4).

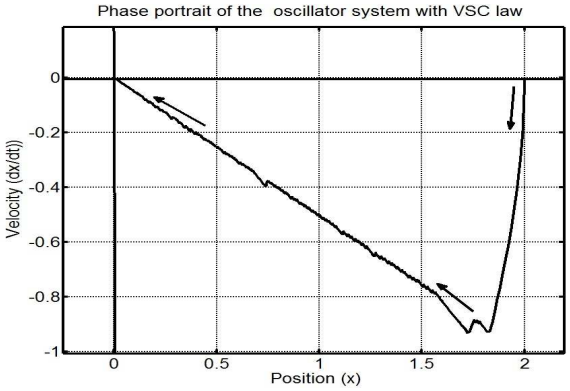

Fig. 2. Trajectories of the oscillator system under a VSC law. $y(0) = 2$, $\frac{y(0)}{dt} = 0$, $\alpha = 1$ and $c = .5$

The dynamical behaviour of this VSC is determined by the chosen formulation of the switching logic. The value of the parameter c of the switching function (4) determines the stability and the performance of the system (1) in the sliding mode as in [14]. The control gain α is tuned to satisfy the reachability condition which will determine when the sliding mode is reached. Perhaps most importantly, the desired stability and performance of the system are maintained despite variations in parameter values which are matched once the sliding mode is attained. This highlights the ability of the VSC paradigm to achieve robust stability and performance in the presence of uncertainty and disturbances [8], [13], [14]. Collectively, the features of VSC provide several benefits and motivate the use of the VSC paradigm in various applications from engineering. These include power electronics and robotics, and most recently assist the study of the robust switched control processes that naturally occur within biology [2], [3].

III. The Immune Response of T cells Behaves As A Switched Control System

This section argues that experimental studies along with mathematical investigations of the population dynamics of the immune response of T cells [5], [6], [17] present compelling evidence of the similarities between the dynamical behaviour and features of VSCS [8], [14] and those of the antigen specific T cell response.

A. Modelling the immune response of T cells

A second order model of the T cell response to vigorous infection has been established in the immunological literature

as the *program T cell response model* [4], [5], [12]. The state variables $A \geq 0$ and $M \geq 0$ represent the population dynamics of activated and memory T cells respectively. This model is considered here instead of higher order models both for ease of exposition but also because modelling of immunological dynamics has demonstrated that it fits experimental data on the T cell population kinetics of different viral and bacterial infections with 95% confidence [6], [5]. The corresponding dynamical equations are given by:

$$\begin{aligned} \frac{dA}{dt} &= \mathscr{F}(t)\rho A - (1-\mathscr{F}(t))(d_A+m)A \\ \frac{dM}{dt} &= mA(1-\mathscr{F}(t)) - d_M M \end{aligned} \tag{6}$$

where ρ and d_A are the proliferation and death rate of activated T cells. d_M is the death rate of memory T cells and m is the rate at which activated T cells become memory T cells. This piecewise linear model of the immune response of T cells incorporates a time based on/off activation function $\mathscr{F}(t)$ defined by:

$$\begin{aligned} &\mathscr{F}(t) = 1 \quad \text{if} \quad t_{on} \leq t \leq t_{off} \\ &\mathscr{F}(t) = 0 \qquad \text{otherwise} \end{aligned} \tag{7}$$

where experimental records have provided t_{on} as the time (in days) at which the number of activated T cells starts to increase to combat the infection whilst t_{off} is the time (in days) at which the decay of the population of activated T cells is enforced post infection [6], [17], [18].

B. A VSC perspective

The VSC viewpoint on modelling the dynamics of the immune response of T cells implies that there exists an inherent immunological switching logic associated with $\mathscr{F}(t)$ which governs the response of the T cells. Early work has argued that changes in the population dynamics of T cells post infection are orchestrated by an intrinsic time based autonomous program [4], [5], [6]. However, recent experimental and mathematical publications in immunology suggest that changes in the population dynamics of T cells after infection are the result of interactions between different immunological feedback mechanisms which increase or decrease the population size of responding T cells [4], [12], [17], [18]. The immunological dynamics involved in this inherent switching rule are still the topic of active research [17], [18]. The model (6) can be rewritten from the VSC perspective

$$\begin{aligned} \frac{dA}{dt} &= u_A(t) \\ \frac{dM}{dt} &= u_M(t) - d_M M \end{aligned} \tag{8}$$

where the immunological feedback control is determined by a switching function $\mathscr{F}(t)$ which defines the control as follows:

$$u_A(t) = \begin{cases} \rho A & \text{if } \mathscr{F}(t) = 1 \\ -(d_A+m)A & \text{if } \mathscr{F}(t) = 0 \end{cases} \tag{9}$$

$$u_M(t) = \begin{cases} 0 & \text{if } \mathscr{F}(t) = 1 \\ mA & \text{if } \mathscr{F}(t) = 0 \end{cases} \tag{10}$$

It should be noted that as a biological system, the state variables (6) and (8) are only meaningful when they are non-negative. Also, parameters of the system are always positive because they represent biological rates. Consequently, the trajectories of this system evolve in the positive quadrant of the phase portrait as in [12]. The Jacobian of (8) is:

$$J = \begin{pmatrix} \mathscr{F}(t)(\rho + d_A + m) - (d_A + m) & 0 \\ m(1-\mathscr{F}(t)) & -d_M \end{pmatrix} \tag{11}$$

From (11) with $\mathscr{F}(t) = 1$, the system has an unstable trivial equilibrium $A_{ss0} = 0, M_{ss0} = 0$ with poles at ρ and $-d_M$. Consequently, the system exhibits an exponential proliferation of activated T cells. The phase portrait of the system shown in Figure 3 during the expansion phase depicts an unstable positive feedback with motion of the trajectories away from the origin. This motion is desirable from the perspective of immunity because it enables the trajectories to leave the low steady-state population and ensures the initial increase in the number of activated T cells required to respond to infection [1], [17], [18]. During the contraction phase where $\mathscr{F}(t) = 0$, the immunological control structure enforces decay of the activated T cells and the generation of memory T cells is imposed on the system. As a result, the corresponding trivial equilibrium acquires stable poles located at $-(d_A+m)$ and $-d_M$. The stable dynamics of the contraction and memory phase are illustrated in the phase portrait shown in Figure 3.

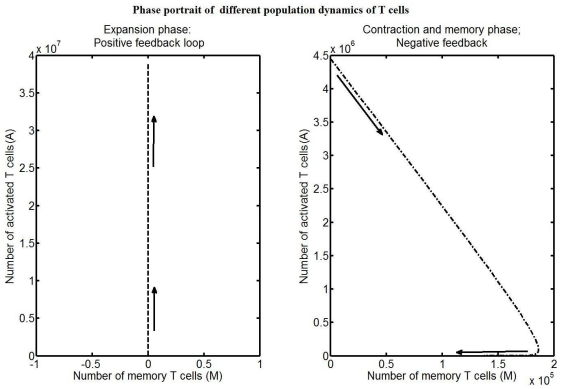

Fig. 3. Phase portrait of the trajectories of the T cell population dynamic with positive and negative feedback

It is clear that the different immunological structures have different properties and induce different population dynamics, see Figure 3. Individually, each feedback structure is inappropriate to reproduce the T cell response observed post infection. Therefore, without a suitable switching mechanism between these different immunological feedback structures, the population dynamic of the T cell response is not consistent with experimental data. Hence, models of the T cell response dynamics which do not incorporate switching behaviour are unable to replicate the dynamic behaviour observed in practice [4], [5], [10], [12].

Using the time based on/off activation function $\mathscr{F}(t)$, a switched control system is defined which enables the system to exhibit appropriate immunological feedback control.

Figure 4 shows the resulting phase portrait which reveals that changes in the T cell population dynamic from the expansion phase to the contraction phase is underpinned by a sharp switching from a positive to a negative feedback. This matches the results obtained in [3], [4], [10].

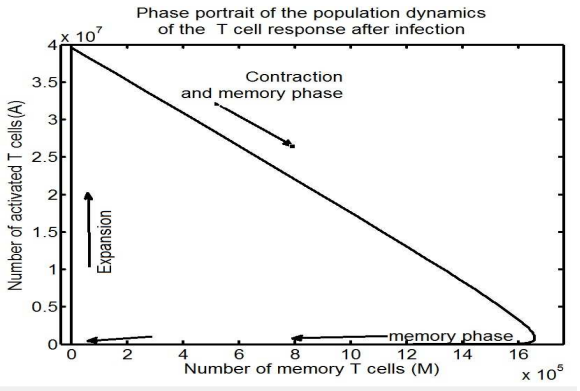

Fig. 4. Phase portrait of the trajectories of the system with a time based on/off activation function

Furthermore, the phase portrait in Figure 4 demonstrates striking similarities between the stable motion of the trajectories of the T cell immune response towards the origin and the stable trajectories produced by classical VSCS, see Figure 2 and [8], [13], [14].

The output dynamics of (6) shown in Figure 5 are consistent with experimental data [5], [17], [18]. Hence, the population dynamic of the T cell response following vigorous infection can be interpreted as an immunological system which incorporates an inherent VSC law.

IV. Robustness Analysis

In VSC, the robustness properties of the control law are a fundamentally important feature which guarantee the stability and the desired performance in the presence of uncertainty and disturbances [8], [13], [14]. The robustness of a VSC is underpinned by the choice of the switching function and the control gain because they provide some invariance properties with respect to changes in parameter values and modelling uncertainty [8], [13].

Various experimental studies along with mathematical work on the kinetics of the T cell response have demonstrated that it is not affected by a number of biological factors such as changes in the phenotype of T cells, the initial number of responding T cells, the duration of the expansion phase, changes in biological rates and changes in the biological environment [5], [17], [18].

In this section, the stability and performance of the model presented in (8) is evaluated in the presence of biologically realistic variations in parameter values and modelling uncertainty to support the evidence of the robustness properties of the population dynamic of T cells following vigorous infection presented in experimental findings [5], [17], [18].

Considering the nominal system representations (6) and (8), an uncertain system is constructed using experimental data on the kinetics of the immune response of memory T

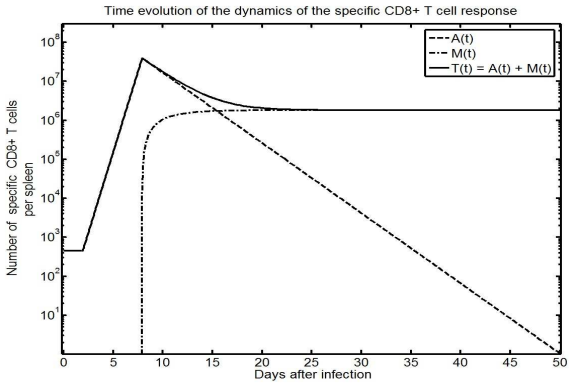

Fig. 5. Simulation of the immune response dynamics with an on/off switching function. Matching experimental data on the time course of the population dynamics of specific CD8+ T cells after LCMV infection [5]. $A(0) = 445$, $M(0) = 0$, $\rho = 1.90\text{day}^{-1}$, $d_A = 0.395\text{day}^{-1}$, $m = 0.019\text{day}^{-1}$ $t_{on} = 1.93$ day; $t_{off} = 7.91 day$

cells following a high dose viral infection as reported in [1], [17]. The corresponding dynamical equations are given as follows

$$\begin{aligned} \frac{dA}{dt} &= \mathscr{F}(t)(\rho A + a_M M) - (1 - \mathscr{F}(t))(d_A + m)A + d_u \\ \frac{dM}{dt} &= mA(1 - \mathscr{F}(t)) - d_M M - \mathscr{F}(t) a_M M \end{aligned} \quad (12)$$

where a_M is the activation rate of memory T cells and d_u is a parameter accounting for biological perturbations influencing the population dynamic of activated T cells. The uncertain system (12) is chosen for the robustness analysis because it models a realistic immunological scenario in which the infection with a high viral load perturbs a number of biological rates and the timings of the inherent immunological switching mechanism [1], [17].

A. Stability analysis

A comparative analysis of the nominal and the uncertain models of the dynamics of the T cell response is conducted by considering a Lyapunov analysis as is frequently used to investigate the stability of VSC designed for engineering systems [8], [11], [14]. From Lyapanov stability theory, if a positive definite function V can be constructed using an algebraic combination of the state variables of the system, the equilibrium of interest is asymptotically stable if the corresponding derivative is a negative definite function of the state variables of the system [11]. Let $V(A,M)$ be a Lyapanov function candidate for the T cell response

$$V(A,M) = A + M \quad (13)$$

where the state variables $A \geq 0$ and $M \geq 0$ are always nonnegative because they represent the variation over time of cell numbers in the spleen [1], [5]. As a result, $V(A,M)$ is positive definite as required. The temporal derivative of (13) for the nominal system is given by

$$\frac{dV(A,M)}{dt} = \mathscr{F}(t)(\rho + d_A)A - d_A A - d_M M \quad (14)$$

The ranges of the biological parameters can be determined from experimental analysis [5], [6] and are given in Table I.

TABLE I

LIKELY VARIATION OF THE BIOLOGICAL PARAMETER VALUES

Parameter	ρ	d_A	m	d_M	a_M
Range (day^{-1})	1.4-3.0	0.19-0.84	0.008-0.019	0.001-0.01	1-10

When $\mathscr{F}(t) = 0$, (14) is found to be negative definite and the equilibrium of (6) is stable. During the expansion phase, $\mathscr{F}(t) = 1$, $\rho > d_A$ and A increases whilst M is reduced to feed A. Therefore, the sign of (14) becomes positive and the equilibrium of the model (6) is unstable. Thus, $\mathscr{F}(t) = 1$ destabilizes the equilibrium for a finite time period; this ensures the rapid response of activated T cells as required. After switching to $\mathscr{F}(t) = 0$, the system equilibrium becomes stable. The combination of the two behaviours using (9)-(10) produces a stable motion of this immunological VSC towards the manifold $A = 0$.

For the uncertain system (12), $\frac{dV(A,M)}{dt}$ may be expressed by

$$\frac{dV(A,M)}{dt} = \mathscr{F}(t)(\rho + d_A)A - d_A A - d_M M + d_u \quad (15)$$

For the desired performance to be attained it is essential that the parameter variations and the disturbance permit both the unstable and stable immunological dynamics to be enforced appropriately, otherwise the immune system will fail to respond appropriately following infection [17]. Considering (13) and (15) with $d_u = 0$, variations in the biological rates as per Table I do not affect the qualitative behaviour of the immune response models, see [5], [6]. Clearly, the sign and the magnitude of the biological disturbance signal d_u can impose undesirable immunological dynamics. The T cell response dynamics are maintained when $\rho A - d_u > 0$ or $d_u - d_A A < 0$. The stability of the T cell response dynamics changes when the immunological control structures do not satisfy these conditions. This aligns with immunopathology when improper activation or inhibition of the T cell response occurs [16], [17]. Hence, the stability of the T cell response dynamics is analogous to that of a VSC [8], [14].

Interestingly, there are some notable analogies between the evolution of the Lyapanov function (13) as a function monitoring the energy of the system [11] and the evolution of the energy consumption of the metabolism of the immune response. In engineering systems, changes in the sign of $\frac{dV}{dt}$ are often associated with changes in the energy regime of the system [8], [11], [14]. $\frac{dV}{dt} > 0$ implies an increase in the energy of the system whilst $\frac{dV}{dt} < 0$ denotes a decrease in energy and a stable motion towards a steady-state [8], [13], [14]. It has been pointed out in [7], [9], [15] that resting T cells and immunological homeostasis have a small uptake of nutrients whereas the nutrient uptake and the energy production of activated T cells is higher to enable cell growth during the expansion phase.

Although the formulation of the Lyapanov function $V(A,M)$ is not an explicit expression of the energy of the immune response, the evolution of the magnitude of this Lyapanov function along with the changes in sign of $\frac{dV(A,M)}{dt}$ are in accordance with the dynamics of the metabolic energy regime of the immune response of T cells. Hence, as in engineering VSC, the switching mechanism of the immune response switches between different energy regimes, see [7], [9], [15], to achieve the desired immunological performance [8], [14].

B. Performance analysis

Numerical simulations inspired by experimental studies are used to assess the performance of the dynamics of the T cell response in the presence of biological perturbations and model uncertainty. Using the nominal system (8) or the uncertain system (12), simulations involving changes in the biological rates or in initial conditions reveal that these perturbations have quantitative effects which can be seen by fluctuations in the number of T cells at the peak of the expansion and variations in the number of generated memory T cells [1], [5]. However, the qualitative behaviour of the T cell response dynamic is preserved.

Figure 6 reproduces experiments from [17] in which the population kinetics of the memory T cell response following infection with a high viral load is analysed. Although the shape of the phase portrait of the T cell response dynamics is preserved, the population dynamic of T cells is impaired by some biological perturbations encompassed in d_u. Importantly, the changes in the timings of the switching mechanisms and in the biological rates of each immunological feedback structure deregulate the response and the pathogen is not removed. This reinforces that following infection with a high viral load, the switching mechanism of the T cell dynamics is disturbed [17] and the desired operation of the T cell response fails to hold.

Figure 7 reflects the case of an undesirable proliferation of activated T cells. When the disturbance signal d_u is

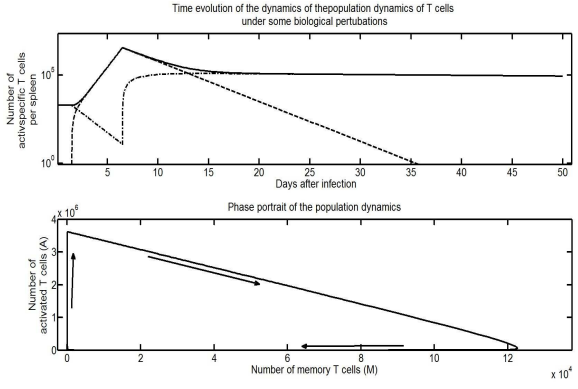

Fig. 6. Simulation of the immune response dynamics with an on/off switching function using the uncertain system (12). Representative output dynamics and phase portrait of the memory T cell response after infection with a high viral dose [17], [1]. $A(0) = 0$, $M(0) = 44500$. $\rho = 1.755\text{day}^{-1}$,, $m = 0.09\text{day}^{-1}$, $t_{on} = 1.5\text{day}^{-1}$,$t_{off} = 6.5\text{day}^{-1}$. For $t_{onn} \leq t \leq t_{off}$, $d_u = -.055day^{-1}$. For $t > t_{off}$, $d_u = -.105day^{-1}$

sufficiently high, the stability properties are altered and the desired timings of the switching mechanisms are violated as seen in Figure 6 and Figure 7. In immunology, this relates to cases of improper immune responses [16], [17], [1], [2]. These undesirable immunological dynamics caused by biological perturbations are analogous to cases where the gain of an engineering VSCS is not sufficient to reject the effects of the disturbance and a reachability condition fails to hold [8], [14]. These simulation results are consistent with

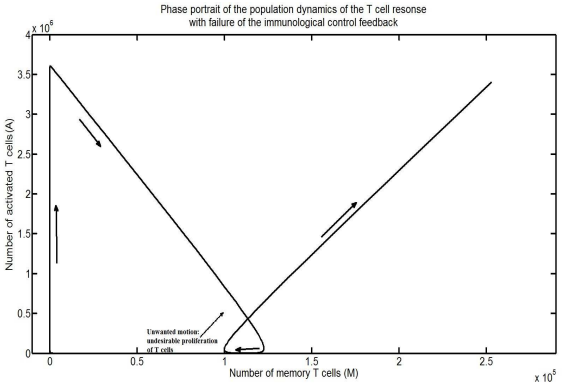

Fig. 7. Phase portrait of the immune response dynamics with an on/off switching function using the uncertain system in presence of the large disturbance signal $d_u = 1.1A$ when $t > 25$ days

experimental observations and mathematical results reported in the immunological literature [1], [5], [16], [17]. It can be concluded that the population dynamic of the T cell response exhibits robust stability and performance consistent with that achieved by engineering systems with a VSC [8], [14].

V. Conclusion

In this paper, current experimental and mathematical results on the immune response of T cells are discussed from the standpoint of control engineering. Strong similarities are found between the dynamics induced by the immunological switching mechanism governing the T cell response [5], [17] and the dynamics of an engineering system controlled using a VSC law [8], [14]. Although an explicit expression of the inherent immunological switching logic has not been formulated here, a piecewise linear system with an on/off switching logic appropriately models experimental data [1], [5]. The population dynamic of the T cell response is analysed as a biological system which is a closed-loop system including a robust VSC law. This control law effectively determines the immunological control structure and the metabolic energy regime required to ensure that the dynamics of the responding T cells maintain a healthy state. Using Lyapanov stability analysis and simulations of realistic immunological scenarios, this VSC formulation of the immune response is shown to achieve the robust stability and performance in the presence of biological perturbations as observed experimentally. Hence, the VSC paradigm provides a mechanism to understand the transition from health to disease.

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