Biological Circuit Models of Immune Regulatory Response:
A Decentralized Control System

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Abstract— **The purpose of this paper is to present a model of immune control based on recently discovered regulatory properties of the immune system. The immune system is a control system which self optimizes over time to eliminate disease while avoiding harm to the host. The controller acts without centralized authority. Recent research has revealed new T-cell populations involved in regulating the immune response. We show how interactions of these populations at the cellular level can give rise to population dynamics which mimic a PID controller with on/off switching. We study these nonlinear dynamics and show stability using Lyapunov analysis. We also include the results of simulation.**

I. Introduction

The purpose of this paper is to improve our understanding of the immune system by understanding how it acts as a decentralized control system. The immune system is a collection of interacting biological and cellular processes which controls the body's response to infection. We consider the adaptive immune response which, in contrast to the innate immune response, can vary depending on the threat. One application of this research is harnessing the immune response for the treatment of cancer. In recent years, immunotherapy approaches to treatment of cancer have been proposed [1]. These approaches are based on an ability of the immune system to identify and destroy cancerous cells [2]. However, cancer immunotherapy efforts thus far have had little success. To understand why cancer immunotherapy fails, we need to better understand the immune system.

Modeling the immune response to cancer and other types of disease is typically based on experimental observation. Observation can be at either the cellular or population level. At the cellular level, we observe the mechanics of reproduction and interaction, and scale these mechanics to deduce population-level dynamics. At the population level, we observe the evolution of populations of cells and induce empirical laws governing the growth of these populations. In this paper, we observe that the immune system eliminates infectious disease while avoiding harmful interactions with the host - an effect. We deduce that the immune system must have an internal control system with mechanisms for detection, discrimination and elimination. We look for cellular interactions which produce this effect when scaled to population-level dynamics. This idea is similar to the concept of self-organized criticality [3].

There are several existing models of the immune response to infection, e.g. [4], [5]. Control of cancer has been treated in numerous works, e.g. [6] and recently [7], [8], [9]. The contribution of this paper is a focus on using new experimental research to describe control aspects of the immune system, such as determination of self/nonself and switching. We also focus on the decentralized control problem of how cells with limited knowledge and authority can collectively decide and act in the face of a threat.

We concentrate on two key decentralized control problems.

- How can the control system determine self from non-self without central memory?
- How can millions of cells coordinate a response with no central authority?

We use models of biological interaction to show that simple responses of individual cells, when scaled to a population-level interaction, result in a behavior similar to a biological circuit with PID control and on/off switching. The paper is organized as follows. In Section II, we present basics of the immune system. In Section III, we present a simplistic model of proportional response. In Section IV, we present a more complex model with differential response. In Section V, we present an even more complicated model which includes switching. Finally, in Section VI, we give a model which includes integral response. Next, we use computational tools to define the region of convergence of the model and use simulation to illustrate the dynamics.

The immune system is a robust, well designed control system. In the past, understanding of how this control system works has been poor. This paper leverages recent experimental research to shed light on this important question.

II. Background

A. Immune Functions

In this section, we review some of the elements of the immune response. The immune system is complex. We include only those elements used in defining our model. Additionally, there is uncertainty and overlap in many immune functions. For the purpose of of clarity, we make simplifications in categorizing these immune functions.

- An **Antigen** is any molecule with the potential for recognition by the immune system.
- **Antigen-Presenting Cells** (APCs) such as dendritic cells and macrophages process antigens throughout the body and present them to T-cells for potential targeting.

T-Cells: We model T-cells as controlling the decision-making aspect of immune system. They determine whether a target is a threat or not and regulate the response. While it is known that B-cells and dendritic cells also have a role in this process, we do not model these populations separately.

- A **Naïve T-Cell** is a T-cell which has not been activated.
- A **Cytotoxic T-Cell** (T_c, CD8+) is a cell which, once it has been activated, is capable of targeting cells which

express a specific antigen. T_c cells are not involved in decision-making per se, but rather in actuation.

- **Helper T-Cells** amplify immune response. Some examples include T_{h1}, T_{h2} and CD4+Foxp3- T cells.
- **Regulatory T-Cells** suppress immune response. Until recently their existence was controversial. Several distinct types of T_{reg} cells have been identified. e.g. iT_{reg}, CD4+Foxp3+ T_{reg}, Tr_1.

Our models of control do not include the effect of **Memory T-Cells**, which provide future immunity after an infection has been cleared, and act on longer time-scales.

Signalling: Cells of the immune system communicate in two ways; Either through direct interaction or through the release of and binding with signalling molecules.

- **Cytokines** are signalling molecules. Some of these cause cell activation and division. e.g. $IL-2$

III. A BASIC BIOLOGICAL CIRCUIT

We begin this section by describing how the immune system detects the concentration of antigens.

a) Sensing: As mentioned previously, antigens are present throughout the body. Antigen-Presenting Cells (APCs) process antigens and present them regularly to naïve T-cells with a frequency proportional to their concentrations in the body [10]. Thus the laws of mass-action dictate that the rate of creation of antigen-specific activated T-Cells is $r_{Ea}a(t)N(t)$, where $a(t)$ is the antigen concentration, $N(t)$ is the naïve T-Cell concentration and r_{Ea} is a reaction coefficient. We assume that the population of all naïve T-cells is always far greater than any population of antigen-specific T-cells and is replenished quickly. A basic population model for naïve T-cells can be found in, e.g. [11].

$$\dot{N}(t) = s_N - d_N N(t)$$

where d_N is the death rate and s_N is the rate at which the cells are replenished. Note that nominal estimates for all parameters are listed in Table VIII.1. Naturally, the dynamics are stable for any positive values of s_N and d_N. The equilibrium value is $N_{eq} = \frac{s_N}{d_N}$. In this initial model of sensing, we assume that the dynamics occur on a short time-scale and concentrations are small. If an infection is intense and extended, then activation of naïve T-cells may cause depletion of the equilibrium population. However, we discount this effect. This assumption can also be found in the models of [12], [13], [14].

The population dynamics for helper cell concentration, $E(t)$, become

$$\dot{E}(t) = r_{Ea}a(t)N_{eq} - d_E E(t),$$

where d_E is the death or deactivation rate of helper T-Cells. For a fixed reservoir of naïve T-cells, the helper cell dynamics are stable. Moreover, using the stated parameter values, the helper cell population will track the antigen concentration with rise time (time to 90%) $T_r = 2.2/d_R \cong 9 days$ for CD4+ helper cells. The equilibrium value is $E_{eq} = \frac{r_{Ea}N_{eq}}{d_E}a(t)$. Thus the helper cell population E is proportional to the concentration of antigen, $a(t)$, yet amplified by a factor of $\cong 324$. Simple mechanics of interaction give rise to a proportional response. Note that we do not specify which

helper cell population we use. The rate of response will vary depending on the subspecies of helper cell.

b) Actuation: In this section, we describe how the activation of CD8+ T-Cells by helper cells on an individual cellular level gives rise to a population of cytotoxic T-cells proportional to the concentration of helper cells.

We use the antigen-specific cytotoxic T-cell concentration, T_c, as the measure of actuator response. As was the case for helper cells, there is a stabilized pool of naïve CD8+ T-cells. The equilibrium concentration is $N_c = \frac{s_{Nc}}{d_{Nc}}$, where d_{Nc} is the death rate of naïve T-cells and s_{Nc} is the rate at which they are replenished. Naïve T-cells are activated by contact with certain helper cells, or through signalling compounds. Helper cells recruit T_c cells at rate proportional to concentration $E(t)N_c$. The T_c cell dynamics are

$$\dot{T}_c(t) = r_{Ec}E(t)N_c - d_{T_c}T_c(t).$$

where d_{T_c} is the death and deactivation rate of activated T_c-Cells. The population dynamics are stable and linear for any d_{T_c}. The T_c population will track the helper population with steady-state value $T_c = r_{Ec}\frac{N_c}{d_{T_c}}E$.

c) Proportional Response: In experimental immunology, detailed time-series data is not available. Although some planning for higher resolution data is in the works, at present the best human data will give three or four measurements of E and a over the course of several months. Due to the granularity of measurement, model validation requires a simplified framework. Therefore, we summarize the Sensor-Actuation model presented in this section as a proportional feedback with gain

$$K = r_{Ec}r_{Ea}\frac{N_c}{d_{T_c}}\frac{N_{eq}}{d_E}$$

As a system, the APC-CD4+-CD8+ interactions predict a proportional response to antigen concentration. This prediction can be readily tested experimentally. Experience tells us, however, that such a simple response is not possible. Taking our model at face value, the logical implication would be that there would be a larger response to internal antigen targets than to external ones, resulting in deadly autoimmune disease. Specifically, the proportional response model does not admit a mechanism for self-tolerance. In the next section, we show how the behavioral difference between self-antigens and non-self-antigens can be distinguished using differential feedback. We also show how maturation delay in regulatory cells can create a circuit for this differential feedback.

IV. THREAT DETECTION: DERIVATIVE RESPONSE

The problem we address in this section is how to differentiate a 'friendly' target from a 'hostile' target without centralized coordination. Individual cells, when presented with an antigen, can choose to ignore the antigen or to activate. Once activated, the cell can recruit CD8+ cells or release cytokines to increase immune response. However, the cell must make the determination of friend or foe without any knowledge of the biological difference between a friendly or hostile antigen [15].

The answer to this dilemma lies in the existence of the recently-discovered species of cell called regulatory T-cells [16]. Regulatory T-cells, once activated, reduce immune

response either through direct interaction with helper cells or indirectly via cytokine signalling. The negative influence of regulatory cells balance the positive action of helper cells.

The only recognizable difference between a threat and a friendly antigen is that friendly antigens already exist in abundance, while threats start small and quickly build in quantity. This behavioral difference can be detected as a deviation from equilibrium. The balance created by equal and opposing populations of helper and regulatory cells is disrupted when helper cells respond more quickly than regulatory cells. This deviation is the trigger for the immune system. This means that the immune system responds not to antigen concentration, but the rate of change of antigen concentration.

The mechanism for creation and action of T_{reg} cells is hotly debated. For our purposes, we suppose that the method of creation/activation of regulatory cells is similar to that for helper cells. There is a stabilized reservoir of naïve T_{reg} cells. Antigen-specific T_{reg} cells, denoted $R(t)$, are recruited from this reservoir by direct contact with antigen. The rate of recruitment is $r_R a(t)$, where r_R is a reaction rate which is proportional to the naïve T_{reg} population. As was the case for helper cells, regulatory cells in this model experience stable linear growth.

$$\dot{R}(t) = r_R a(t) - d_R E(t)$$

Although the mechanism of T_{reg} creation is unclear, experimental results consistently show that the regulatory response is delayed with respect to the helper response. This may be due to slower dynamics or a maturation delay. In either case, we model a delay, τ, in evaluating the steady-state response of the regulatory population $R(t) = \frac{r_R}{d_R} a(t - \tau)$. This yields a population of regulatory cells which mirrors the population of helper cells, but with delay. At the population level, down-regulation of helper cells occurs at rate $r_{RE} R(t) E(t)$, where r_{RE} is a reaction coefficient. The combined Regulatory-Helper dynamics become

$$\dot{E}(t) = r_{Ea} a(t) E(t) - r_{RE} R(t) E(t)$$
$$= (r_{Ea} a(t) - K_{RE} a(t - \tau)) E(t)$$

where $K_{RE} := r_{RE} \frac{r_R}{d_R}$. This expression can be put in the form of a first-order difference equation:

$$\dot{E}(t) = (r_{Ea} - K_{RE}) a(t) E(t)$$
$$+ \tau K_{RE} \frac{(a(t) - a(t - \tau))}{\tau} E(t). \quad \text{(IV.1)}$$

Because derivatives are impossible to detect directly, a first-order hold is a standard method used for approximating the derivative in a PD controller.

$$\dot{a}(t) \cong \frac{a(t) - a(t - \tau)}{\tau}$$

Note that if there were no delay, the response would be simply proportional:

$$\dot{E}(t) \cong (r_{Ea} - K_{RE}) a(t) E(t).$$

Since proportional response can be achieved by growth of the helper cell population alone, we conclude that one of the reasons for the existence of regulatory cells is to create derivative feedback.

As mentioned, the existence of a proportional response is not realistic. Thus we expect $r_{Ea} \cong K_{RE}$. In this case there is no steady-state response. T_{reg} cells suppress auto-immune disease (response to persistent self-antigens) while permitting a response to fast-acting infections. For slow-growing diseases such as cancer, this model predicts the immune response will be mild.

We conclude that although individual cells do not have the capacity to determine self from non-self, at a population level, the cells create a circuit which is able to make such a distinction.

V. AN ON/OFF SWITCH FROM IL-2 SIGNALING

The collective decision-making power of regulatory T-cells was discussed in the previous section. However, it is well-known that differential response alone is not capable of eliminating a threat. This is because there is no mechanism for eliminating steady-state error. Steady-state error implies persistent (chronic) infection. Furthermore, it has been shown in several studies [17], [18], [19], [20], [21], [22], that the strength of immune response does not vary substantially with the initial concentration, as would be predicted from a purely differential model of response. The differential response, therefore, is only a trigger to recognize the threat and signal a much larger immune reaction.

To understand how the immune system creates a large-scale response, we turn to the phenomenon of cytokine signalling. Cytokines such as IL-2 are known to be both secreted and bound by several different cells. In helper cells, binding of IL-2 triggers clonal expansion which causes the cell to divide into two activated helper cells which, in turn, secrete more of the compound. When present in sufficient numbers, this binding and secretion can create a positive feedback loop leading to exponential growth in the immune response. In pathological cases, the positive feedback loop results in a saturation of various cytokines, such as seen in septic shock. In this paper, we use an amalgamated population of positive cytokines represented by $p(t)$. These cytokines are both produced by and bind to the helper cell population. They are secreted by all activated helper cells at rate $r_p E(t)$. Upon binding, they stimulate growth at rate $r_E p(t) E(t)$. The dynamics of the helper cell population are now

$$\dot{E}(t) = -d_E E(t) + r_E p(t) E(t) + u(t),$$

where $u(t)$ is an input which represents the effect of antigen stimulation, as modeled in Equation IV.1. The cytokine-helper relationship is illustrated in Figure V.1.

Production of signalling compound is described by

$$\dot{p}(t) = r_p E(t) - d_p p(t).$$

where r_p is the production rate and d_p is the loss rate. Because p is absorbed by many different actors, we assume that the loss due to reabsorption by E is negligible. Because the signalling molecules are produced significantly faster than cell activation, we can make the quasi-steady-state approximation

$$p(t) = \frac{r_p E(t)}{d_p}.$$

By including the expression for $p(t)$ in the helper-cell dynamics, we obtain
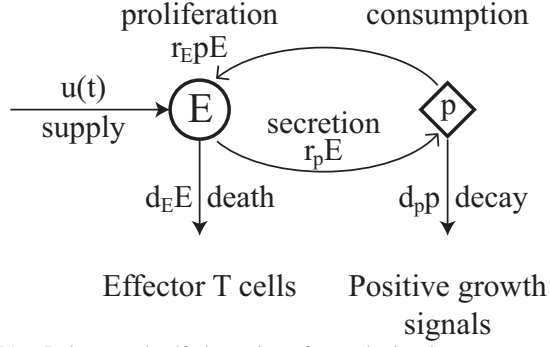
Fig. V.1. Release and self-absorption of growth signals creates a positive feedback loop

$$\dot{E}(t) = -d_E E(t) + r_E E(t)^2 \frac{r_p}{d_p} + u(t)$$

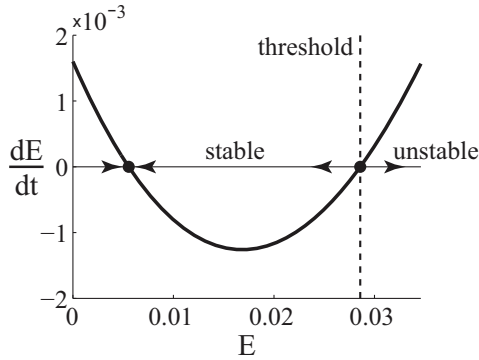For small values of $u(t)$, the system has two equilibrium

Fig. V.2. Positive feedback with antigen stimulation creates stable and unstable equilibria

points. The lesser equilibrium point is always stable, while the greater equilibrium is always unstable. Thus, absent perturbation, the helper cell population will remain contained at some low level. Now suppose $u(t)$ is nonzero. The equilibria are

$$E_{eq} = \frac{d_p}{r_p r_E} \left(d_E \pm \sqrt{d_E^2 - 4\frac{r_E r_p}{d_p} u(t)} \right)$$

Because the term under the square root decreases with u, for some value of u the equilibria no longer exist, leading to exponential growth. Note that even if $u(t)$ later returns to zero, helper cell growth will continue as the population will have surpassed the greater equilibrium point. This situation is illustrated in Figure V.2. The dynamics mimic the effects of a switch between stable and unstable growth where $u(t)$ acts as a switch with a trigger value of

$$u_{trigger} = d_E^2 \frac{d_p}{4 r_p r_E}$$

When $u(t)$ exceeds this value, unregulated exponential growth ensues.

To summarize, by the secretion of positive cytokines, individual helper cells contribute to the overall decision of the immune system as to the level of response. Similarly, through the binding of signalling molecules, helper cells take into account the collective knowledge of other cells. Once a sufficient number of helper cells decide that an antigen constitutes a threat, the dynamics of the helper cell population responds with unregulated exponential growth.

Naturally, unregulated exponential growth is not a realistic model of response. Once a threat has been eliminated, the response must contract. This question is addressed in the following section.

VI. INTEGRAL FEEDBACK: CONTRACTION FROM REGULATORY GROWTH

The problem with the positive feedback model of switching, as presented in the previous section is that once triggered, we have indefinite increase in immune response even if antigen stimulation is absent. While this is reasonable on short term time scales, eventually the response must contract if the infectious agent has been eliminated.

To account for this effect, we look at a different class of regulatory T-cells called iT_{reg} cells. Activated iT_{reg} cells are thought to arise from the helper cell population [23]. We model these iT_{reg} cells as being activated by or differentiating from the population of helper cells acting under the influence of positive growth cytokines. Thus the growth rate of these cells is $\nu_R p(t)E(t)$ where ν_R is a reaction coefficient. The population dynamics of iT_{reg} cells are

$$\dot{R}_i(t) = \nu_R p(t)E(t) - d_{Ri}R_i(t).$$

where d_{Ri} is the death/deactivation rate. Using the expression $p(t) = \frac{r_p}{d_p}E(t)$, we have

$$\dot{R}_i(t) = \nu_R \frac{r_p}{d_p}E(t)^2 - d_{Ri}R_i(t).$$

The constants ν_R, d_{Ri} are both small as the creation rate of these cells is less than the helper rate, yet they are longer-lived. iT_{reg} deactivate helper cells at rate $r_{R_iE}R_i(t)E(t)$ using reaction coefficient r_{R_iE}. The combined helper-regulatory dynamics are

$$\dot{E}(t) = -r_{R_iE}R_i(t)E(t) - d_E E(t) + r_E E(t)^2 \frac{r_p}{d_p} + u(t)$$

$$\dot{R}_i(t) = \nu_R \frac{r_p}{d_p}E(t)^2 - d_{Ri}R_i(t).$$

$u(t)$ represents the antigen stimulation. The effect of the iT_{reg} cells is to ensure contraction of the helper response. In the following section, we obtain a proof of this contractive property. However, a rough explanation for the stabilizing effect of the iT_{reg} cells is that if one ignores the relatively low death rate of these cells, then

$$R_i(t) \cong \int_0^t \frac{\nu_R r_p}{d_p}E(s)^2 ds.$$

This is a form of integral feedback. Integral feedback is necessary to balance the unbounded growth of the helper cells. Once the helper cell population has become sufficiently small, the lesser equilibrium becomes stable and the immune response ceases.

VII. STABILITY ANALYSIS USING SUM-OF-SQUARES

In this section, we show that the iT_{reg} population modeled previously is capable of controlling the helper cell population in the absence of antigen stimulation. Recall that we have the following dynamics for $E(t)$ and $R_i(t)$.

$$\dot{E}(t) = -r_{R_iE}R_i(t)E(t) - d_E E(t) + r_E E(t)^2 \frac{r_p}{d_p} = f_1(E, R_i)$$

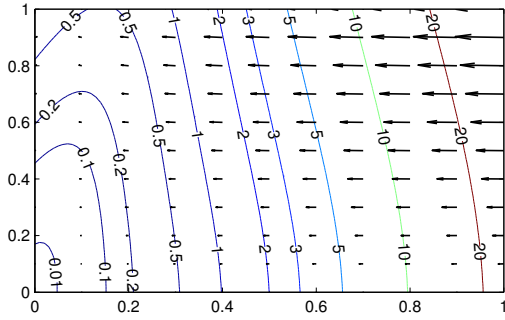$$\dot{R}_i(t) = \nu_R \frac{r_p}{d_p}E(t)^2 - d_{Ri}R_i(t) = f_2(E, R_i)$$

Fig. VII.3. Lyapunov Level Sets and Vector Field: Helper vs. Regulatory Cell Concentration

Sum-of-Squares optimization is a computational method for solving optimization problems with polynomial variables [24]. If we consider a Lyapunov function to be a polynomial variable, then this method can be used to analyze stability of nonlinear systems [25]. In this paper, we use Sum-of-Squares optimization to search for a polynomial Lyapunov function, $V(E, R_i)$ such that the following holds for all $E, R_i > 0$.

$$V(0,0) = 0, \qquad V(E,R_i) \geq \varepsilon(E^2 + R_i^2) \qquad \dot{V}(E,R_i) \leq 0.$$

Let $Z(x)$ be the vectors of monomials of degree 6 or less. We parameterize V using a vector of coefficients c as $V(E,R_i) = c^T Z(E,R_i)$. We search for a vector c and sum-of-squares polynomials s_1, s_2, s_3 and s_4 such that

$$c^T Z(E,R_i) - \varepsilon(E^2 + R_i^2) = s_1$$

$$c^T \nabla Z(E,R_i)^T \begin{bmatrix} f_1(E,R_i) \\ f_2(E,R_i) \end{bmatrix} + Es_2 + R_i s_3 = -s_4.$$

This ensures that the stability conditions are met. The constraints were implemented in SOSTOOLS [26] and SeDuMi [27]. For the nominal parameters listed in Table VIII.1, the SOS program was feasible. The level sets of the Lyapunov function can be seen in Figure VII.3, along with the vector field.

Because parameters involving *iTregs* are speculative, we estimated the parameter region of stability by testing parameter values on a grid. For v_r and r_{RE}, the stable regions of the parameter space are shown in Figure VII.4. The results are obtained from SeDuMi. The z-axis is feasibility. A feasibility of 1 implies the existence of a Lyapunov function. A feasibility of -1 implies that a Lyapunov function of degree 6 or less does not exist. The plot indicates that a combination of v_R and r_{RiE} contribute to stability. An approximate condition for stability which which is consistent with the data in Figure VII.4 is

$$v_R \cdot r_{RiE} > 12.$$

VIII. SIMULATION

We summarize the paper with a Simulink demonstration. We use the parameter values indicated in Table VIII.1 without any steady-state assumptions. A square antigen input is used with helper response shown in FigureVIII.5. Note the three different response regimes. From day 0 to 1, there is a sharp differential in antigen concentration, which triggers the switch and causes exponential increase. At time $t = 1day$,
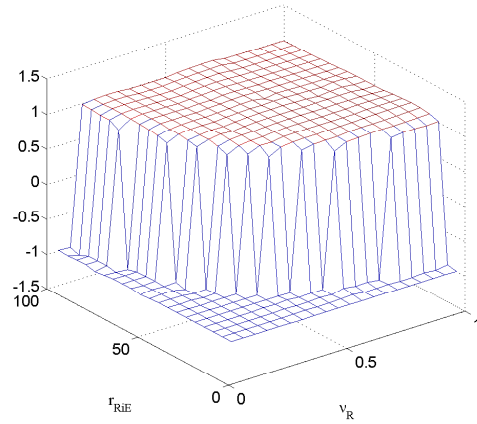

Fig. VII.4. Stability for v_R vs. r_{RiE}. Generated from SeDuMi on a grid. 1 implies stability. -1 means indeterminate
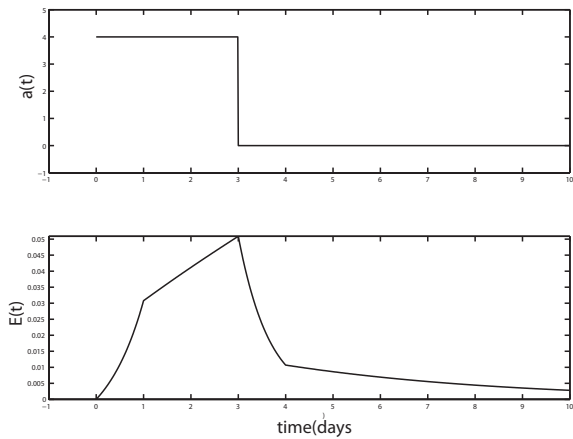

Fig. VIII.5. Simulation results using antigen stimulation and zero initial conditions

this differential goes away as the pulse amplitude is constant over the period of delay ($\tau = 1$). We continue to see increase in helper response, but this is balanced by a growing integral response. At time day 3, the antigen stimulation disappears, resulting in an imbalance of T_{reg} cells due to the negative differential. This causes a rapid decline in response until day 4 when the Helper-Regulator balance is restored. At this point integral feedback eliminates the remaining helper cells.

IX. CONCLUSION

In this paper, we have shown how the local interaction of individual cells with limited information and authority can yield intelligent response to an external threat. The population dynamics are delayed and nonlinear, with several interacting populations. However, we have shown that the effect of these population dynamics can be interpreted as a biological circuit. This circuit contains a differential sensor, on/off switching and integral feedback. We have shown that the dynamics of response are stable for regions of the parameter space using sum-of-squares optimization.

The work presented in this paper is still preliminary in that there are many aspects of the immune response that are not well modeled or understood. Additionally, there is no experimental validation using detailed time-series data. We hope to conduct such experiments in the future. An

Parameter	Description	Estimate
s_N	Supply rate of naïve CD4+ T cells	0.0024k/μL day^{-1}
d_E	Helper CD4+ cell death rate	0.23/day
d_N	Naïve CD4+ cell death rate	0.03/day
$a(t)$, a_0	Antigen stimulation rate, steady state value	$a_0 = 4\%$/day
d_{T_c}	Effector CD8+ cell death rate	0.35/day
s_{Nc}	Supply rate of naïve CD8+ T cells	0.0016k/μL day^{-1}
d_{Nc}	Naïve CD8+ cell death rate	.03/day
r_E	Helper CD4+ growth rate upon interacting with positive growth signal	0.33(k/μL)$^{-1}$ day^{-1}
r_p	Positive signal secretion rate by helper CD4+ cells	100/day
d_p	Positive growth signal decay rate	5.5/day
d_R	T_{reg} death rate	0.23/day
r_R	Relative stimulation rate of T_{reg} cells to antigen	1
r_{RE}	Suppression rate of helper cells by T_{reg} cells	20 interactions
r_{R_iE}	Suppression rate of helper cells by iT_{reg} cells	40 interactions
r_{Ea}	Clonal expansion rate of stimulated helper cells	.35/day
r_{Ec}	Clonal expansion rate of recruited cytotoxicT cells	1/day
ν_R	Differentiation rate of iT_{reg} cells	0.3(k/μL)$^{-1}$ day^{-1}
d_{Ri}	Death rate of iT_{reg} cells	.03/day
τ	T_{reg} maturation delay	1 day

TABLE VIII.1

PARAMETERS FOR THE COMBINED MODEL [11]. CONCENTRATIONS ARE IN UNITS OF K/μL, AND TIME IS MEASURED IN DAYS.

important unresolved question is the mechanics of T cell memory. We would like to create a model of how the immune system responds to a previously identified threat without triggering a full immune response. For answer, we will look at the dynamics of other known helper and regulatory T cells. Another area of research is to deduce values of the system parameters based by considering the optimal control of simple models of infection. Since the immune system is highly optimized by an evolutionary process, these values of the parameters should correspond with the ones found in nature.

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