A Mathematical Model of the Primary T Cell Response with Contraction Governed by Adaptive Regulatory T Cells

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Abstract— **The currently accepted paradigm for the primary T cell response is that effector T cells commit to minimal developmental programs in which these cells expand according to some predetermined expansion program. Current mathematical models that are based on these developmental programs do not show the robustness to precursor frequencies that is exhibited in experimental results. Recently we proposed a shift in paradigm wherein the expansion and contraction of effector T cells is the result of negative feedback from adaptive regulatory T cells. These regulatory T cells develop in the course of an immune response and suppress effector cells. In this work, we extend our mathematical model to include regulation of helper T cells. Simulations show that this feedback mechanism generates robust immune responses over a range of five orders of magnitude of precursor frequencies.**

Keywords— **Delay Differential Equations, Adaptive Regulatory T cells, Primary Immune Response.**

I. Introduction

The primary cell-mediated immune response is the process by which the human immune system responds to a foreign antigen. Upon pathogen invasion, immature antigen presenting cells (APCs) residing at the site of infection migrate to the lymph nodes and present the pathogen. A naïve T cell with the corresponding specificity will then proliferate and differentiate into cells with a range of functionality. Two classes of these T cells are helper T cells and cytotoxic effector T cells. The main functionality of helper T cells is to aid in activating and directing other immune cells, while cytotoxic T cells primarily induce apoptosis in infected cells [1]. The focus of this paper is to model the dynamics of the primary cell-mediated immune response. More specifically, we focus on the contraction of this response as a result of adaptive regulatory cells.

A number of experimental studies have shown that the dynamics of a cell-mediated immune response are determined shortly after antigen presentation [2,3,4]. A consequence of this fact is that the immune response is insensitive to the characteristics of the antigen exposure. This leads to the hypothesis that the immune response is determined shortly after the response initiates (i.e. that cells will commit apoptosis after a certain number of divisions or after a specified time period). As an alternative to these approaches, Kim et al. propose the hypothesis that the contraction of the immune response is controlled by adaptive regulatory mechanisms [5]. In [5], a model is proposed based on this concept. It is shown that contraction does not have to be pre-programmed by cells, but can come about as the result of negative feedback loops through cell interactions. When compared with both the Cell-Division and Time-Based Programs, this model shows robustness with respect to precursor frequencies that are more consistent with experimental studies. The work in this paper extends the work in [5] by considering the regulation of helper and effector cells separately.

II. Methods

We present a model of T cell expansion/contraction where contraction is controlled by adaptive regulatory T cells. During expansion, proliferating immune cells occasionally differentiate into adaptive regulatory T cells, iTregs. Over time, negative feedback provided by these regulatory cells, shuts down the immune response. In this model, we consider four populations of T cells: Naïve T cells, helper T cells, effector T cells and regulatory T cells. In addition, we consider concentrations of both immature and mature antigen presenting cells. We seek to discover the dynamics of how these populations interact when presented with a pathogen. This process is modeled in the following way (Figure 1):

1. Upon encountering an antigen, immature APCs become mature APCs and migrate to the lymph node.
2. Naïve T cells, which reside in the lymph nodes, encounter mature APCs and enter a minimal developmental program in which they divide *m* times.

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3. Upon completion of the minimal developmental program, naïve T cells differentiate into helper T cells. A proportion, *r*, of helper T cells further differentiates into regulatory T cells.
4. Existing cytotoxic effector T cells that are activated by helper cells enter into a minimal developmental program in proportion to the number of interactions between helper T cells and mature APCs.
5. After being differentiated from helper T cells, regulatory T cells enter into a minimal developmental program of their own. They then suppress both the helper and effector T cells.

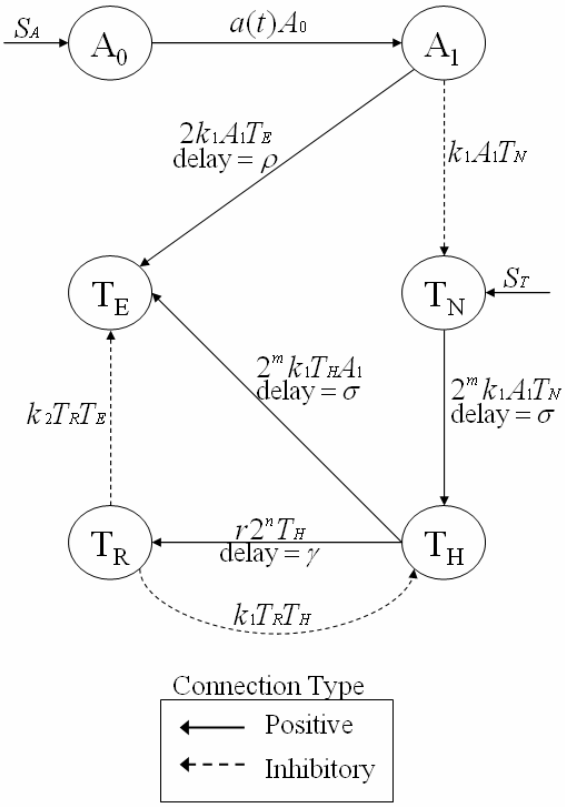

Fig. 1 Graphical representation for the model. Note that each compartment has an associated death rate, which is not represented in the diagram. The compartments are represented as follows: A_0: immature APCs, A_1: mature APCs, T_N: naïve T cells, T_H: helper T cells, T_E: effector T cells, and T_R: adaptive regulatory T cells

Representing the antigen presenting cells, A_0 is the concentration of immature APCs at the infection site and A_1 is the concentration of mature APCs in the lymph nodes. The T cell compartments are modeled as follows: T_N is the concentration of naïve cells, T_H is the concentration of helper cells, T_E is the concentration of effector cells, and T_R is the concentration of regulatory cells.

The model is described as the following system of delay differential equations:

$$\dot{A}_0(t) = S_A - d_0A_0(t) - a(t)A_0(t) \tag{1}$$

$$\dot{A}_1(t) = a(t)A_0(t) - d_1A_1(t) \tag{2}$$

$$\dot{T}_N(t) = S_T - \delta_0T_N(t) - k_1A_1(t)T_N(t) \tag{3}$$

$$\begin{aligned}\dot{T}_H(t) = {} & 2^m k_1A_1(t-\sigma)T_N(t-\sigma) - \delta_1T_H(t) \\ & -k_1T_R(t)T_H(t) - rT_H(t)\end{aligned} \tag{4}$$

$$\begin{aligned}\dot{T}_E(t) = {} & 2^m k_1T_H(t-\sigma)A_1(t-\sigma) - k_2T_R(t)T_E(t) \\ & +2k_1A_1(t-\rho)T_E(t-\rho) - k_1A_1(t)T_E(t) - \delta_1T_E(t)\end{aligned} \tag{5}$$

$$\dot{T}_R(t) = r2^nT_H(t-\gamma) - \delta_1T_R(t) \tag{6}$$

Equation (1) describes the immature APCs maintained throughout the body. There is a constant supply rate, S_A and proportional death rate, d_0, of these cells. The invasion by an immunogen is represented by the rate, $a(t)$, with which the immunogen stimulates immature APCs to become mature APCs.

Mature APCs are given in equation (2). The source of these cells is provided by immature APCs that have been stimulated by the antigen. These cells have a natural death rate of d_1.

The third equation characterizes the dynamics of the naïve T cell population. These cells have a constant supply rate, S_T, and proportional death rate, δ_0. The last term describes the rate with which naïve T cells enter into a proliferative state. This rate is proportional to the mass action interactions of naïve T cells and mature APCs.

Helper T cells are given by equation (4). At a given point in time, *t*, the source of these cells is proportional to product of concentrations of A_1 and T_N at time, t-σ, with σ denoting the time needed for a naïve T cell to undergo *m* cell divisions. The next term denotes the natural death rate of these cells. The third term captures the effect of regulatory cell suppression on helper T cells. The final term of this equation signifies the rate with which helper T cells further differentiate into regulatory T cells.

The effector cell compartment is governed by equation (5). Here, the first term describes the source from cells that have undergone a minimal development program. This source is proportional to the number of interactions of helper T cells and mature APCs. It includes a time delay of magnitude σ, during which the effector cell undergoes *m* cell divisions. Next, we have the effect of negative feedback from regulatory cells. When effector cells are further stimulated by mature APCs, they exit the system, undergo a

single cell division and return to the system at a time ρ units in the future. This phenomenon is captured by the expression $2k_1A_1(t-\rho)T_E(t-\rho) - k_1A_1(t)T_E(t)$ in equation (5).

The final equation describes the regulatory T cell compartment. These cells differentiate from helper T cells, and divide n times with a delay of γ days. They have a natural death rate of δ_1.

Most of the parameter estimates used in this model were obtained from [5] and are contained in Table 1. The additional parameters: k_1, k_2, n, and γ were estimated based on their related parameters in [5].

Table 1 Parameter Values

Parameter	Description	Estimate
S_A	Supply rate of immature APCs	0.3
S_T	Supply rate of naïve T cells	0.0012
d_0	Death rate of immature APCs	0.03
d_1	Death rate of mature APCs	0.8
δ_0	Death rate of naive T cells	0.03
δ_1	Death rate of helper and effector T cells	0.4
k_1	Kinetic coefficient of helper/regulatory cell interaction	20
k_2	Kinetic coefficient of effector/regulatory cell interaction	30
r	Proportion of helper T cells that become regulatory T cells	0.01
m	Number of divisions in minimal developmental program for helper and effector T cells	7
n	Number of divisions in minimal developmental program for regulatory T cells	3
σ	Duration of minimal developmental program for helper and effector T cells	3
ρ	Duration of one T cell division	⅓
γ	Duration of minimal developmental program for regulatory T cells	2.5
a(t)	Rate of APC stimulation	$c\mathbf{1}_{[0,b]}$
b	Duration of antigen availability	10
c	Level of APC stimulation	1

III. Results

Using Matlab's DDE function, the system of delay differential equations (1)-(6) was numerically simulated for varying initial concentrations of naïve T cells. Across all simulations, this was the only varying initial condition. The initial condition of immature APCs was 10 k/ L and all initial conditions not specifically mentioned were set to zero. We concentrate on the relationship between the initial concentration of naïve T cells and the corresponding expansion and contraction of the helper and effector T cell populations.

In Figure 2, we show the dynamics of the T cell populations. This begins with the expansion of the Helper T cells, which peak approximately 4 days after initial antigen presentation. This peak is followed by an increase in the population of effector cells which peaks approximately 3 days later. This coincides with the estimates that the immune response takes approximately **7** days to peak. Also, we see that contraction of the effector cells begins when the regulatory cells reach their maximal concentration.

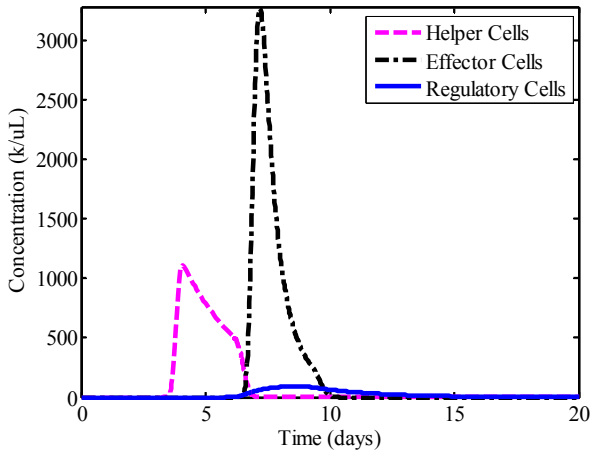

Fig. 2 Time Course of Helper, Effector, and Regulatory T Cells for $T_N(0)$= 0.1 k/ L

Figure 3 shows the phase portrait of effector versus regulatory cells over varying initial concentrations of naïve T cells. Here, we see how the regulatory cell response scales in order to control the effector cell response. The maximum concentration of the regulatory T cell concentration scales on the order of 10 times the initial concentration, while the effector response remains on the same order of magnitude for each of the initial conditions shown.

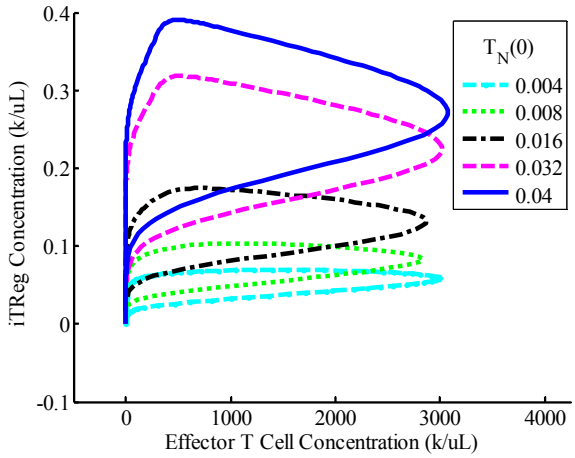

Fig. 3 Phase Portrait of iTregs versus Effectors Over 20 Days

A further examination of the relationship between effector response and initial conditions is shown in figure 4. Over a span of 5 orders of magnitude difference in initial T cell concentration, we see a difference on the order of 2 orders of magnitude in peak effector responses. This insensitivity to initial conditions is similar to what was seen in [6].

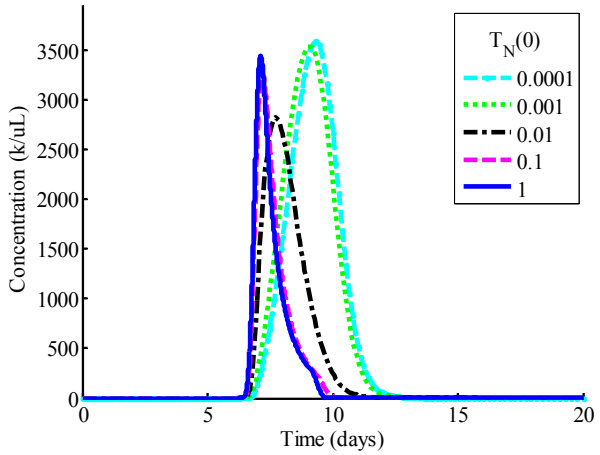

Fig. 4 Effector T Cell Population Over Time

IV. Discussion

As helper T cells and their regulation are considered, this model is an improvement over the model of [5]. When compared to the model of Kim et al., the present model shows similar results in terms of stability to precursor frequencies. The model presented here differentiates iTregs from helper T cells. A result of iTregs differentiating from such a small population is that the kinetic coefficient, k_2, must be increased. We also follow the dynamics of these adaptive regulatory cells by allowing them to proliferate in order to generate a sufficient number to handle the regulation of the effector population. Here, we were able to show that the model presented in [5] can be extended to consider the aforementioned modifications while maintaining the biologically consistent stability results.

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