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Modeling the Effect of Memory in the Adaptive Immune Response

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Abstract It is well understood that there are key differences between a primary immune response and subsequent responses. Specifically, memory T cells that remain after a primary response drive the clearance of antigen in later encounters. While the existence of memory T cells is widely accepted, the specific mechanisms that govern their function are generally debated. In this paper, we develop a mathematical model of the immune response. This model follows the creation, activation, and regulation of memory T cells, which allows us to explore the differences between the primary and secondary immune responses. Through the incorporation of memory T cells, we demonstrate how the immune system can mount a faster and more effective secondary response. This mathematical model provides a quantitative framework for studying chronic infections and auto-immune diseases.

Keywords Memory T cells · Secondary immune response · Immune memory · Chronic infections

1 Introduction

When studying T cell driven adaptive immunity, it is necessary to distinguish between a primary immune response and subsequent responses. Moreover, during a primary immune response, the immune system is primed to accelerate and amplify secondary and subsequent responses in comparison to a primary one. This difference is driven primarily by the presence of antigen specific memory T cells. These cells,

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while formed from T cells, require a lower amount of stimulation to be activated and perform as effector T cells faster than their non-antigen specific counterparts [31].

Given that memory T cells can have a half-life of up to 8–15 years, these cells allow for a prolonged and effective use of the immune system [2,24]. The formation and efficacy of these memory T cells is heavily dependent upon the duration of antigen exposure and the strength of inflammatory signaling. Shortening the duration of antigen exposure by introducing therapies, such as antibiotics, can prevent the formation of memory T cells. In contrast, overexposure to antigen, such as in chronic viral infections, can also prevent the formation of memory T cells through clonal exhaustion – continual antigen stimulation leading to terminally differentiated effector T cells [18].

From molecular to tissue-level interactions, there are numerous mathematical models that have been developed to answer immunological questions [9]. At the cellular level, models addressing T cell differentiation [14], T cell movement [5], and T cells in viral [26] and bacterial infections [3] all explore various aspects of the dynamics of adaptive immunity. In primary immmune response, models developed by [22,19,20] and [34] explore T cell expansion and regulation as well as the effects of regulatory T cell switching on immune contraction. mainly on the immune response following primary antigen stimulation. For other related works see [4,11,36,35] and the references therein. Recent studies have looked into the generation of memory cells and their differentiation [26,7]. For example, in regards to the development of memory cytotoxic T cells, in [12], Ganusov studies the varying ways in which the memory T cell development can occur. Other aspects of memory T cells have been mathematically modeled in various settings. Examples include [28,23,8,17,38,29]. None of these models address the interplay between regulatory T cells and memory T cells. Moreover, the majority of memory T cell models focus on the generation of memory cytotoxic T cells and less on the memory helper T cells and the activation of all effector memory T cells in a secondary infection.

In this work we develop a mathematical model in order to investigate the way in which memory T cells transition from mature effector T cells and their reactivation in response to the resurgence of the same antigen. Our model is constructed by incorporating memory T cells into the models of [22,19,20,34], hence incorporating both regulatory T cells and memory T cells. This model allows us to explore the differences in the dynamics of the immune cells present in a primary immune response versus a secondary response, stressing the role of memory T cells in a secondary immune response, and the corresponding role that the regulatory T cells play in the emerging dynamics. We study some of the challenging aspects that explain how in secondary immune response, memory T cells facilitate a rapid detection of antigen and expansion of immune cells effectively mounting a faster response than the primary immune response.

The paper is organized as follows: In Section 2.2 we explore the main differences between primary and secondary immune responses. In Section 2.3 we review the two main hypotheses on the formation and activation of memory T cells–the assumption that memory T cells differentiate from naïve T cells independently of the effector T cells and that memory T cells form from effector T cells. In Section 3 we develop a mathematical model using a system of delayed differential equation (DDEs) to study

the dynamics of memory T cells in relation to effector and regulatory T cells. The delays account for the differing amounts of time required for cell activation and proliferation. Simulations and a study of the robustness of the model parameters are given in Section 4. A detailed discussion of the results and issues that were encountered throughout the study in Section 5. Concluding remarks are made in Section 6.

2 Biological Background

2.1 Acute Immunology

The immune system fights organisms and substances that invade the body [1]. The immune system is composed of two main components: the innate immune system and the adaptive immune system. The innate immune system is the body's first line defense, incorporating factors such as anatomical barriers, natural killer cells, and antigen presenting cells (APCs), e.g., dendritic cells and macrophages. While the innate immune system provides a rapid response, these cells are neither antigen specific nor long lasting in the body. Conversely, the adaptive immune system, which includes B cells and T cells, may have a slower response to antigen stimulation, yet adaptive cells are antigen specific and can remain in the body for long periods of time. For the purposes of this study, we aim to focus on T cell driven adaptive immunity.

T cell driven adaptive immunity can be divided into three stages: activation, effector, and contraction. The activation of T cells comes as a consequence of immature APCs, including both innate immune system cells and B cells, encountering antigen and undergoing a maturation process. Subsequently, these mature APCs have the ability to present antigen molecules on their cell surface to naïve effector T cells. Once APCs bind with T cells that are specific to the antigen presented, these naïve cells undergo a minimal developmental program in which they proliferate multiple times until they reach maturation. This minimal delopment program as seen in [22, 19, 21, 20] is used to assume that following activation, each cell must undergo antigen-independent proliferation for a set number of times before they are fully mature effector T cells. And once matured, these effector T cells are ready to perform their individual effector functions.

The role of T cells in the effector stage depends on the type of T cell, the main two being CD8+ and CD4+ T cells. The primary role for CD8+ T cells, or cytotoxic T cells (CTLs), is to eliminate the antigen infected cells by inducing apoptosis, e.g, through the release of cytotoxins. The primary role of CD4+ T cells, also knowns as helper T cells (Ths), is to secrete the cytokines necessary to further expand the immune response, such as growth signal interleukin-2 (IL-2). Specifically, these secreted cytokines aid in the continual proliferation of CTLs. Moreover, a portion of CD4+ T cells will further differentiate into regulatory T cells (Tregs).

Throughout the immune response, Tregs are responsible for actively suppressing immune cells to prevent autoimmunity, and they continually proliferate in response to the secretion of IL-2 by the antigen-activated T cells. Furthermore, regulatory T cells play a key role in the final stage of an immune response, contraction. Once the CTLs have eliminated the antigen infected cells, through the secretion of inhibitory

cytokines, and are no longer needed, Tregs are responsible for eliminating the remaining effector T cells, leading to the full contraction of the adaptive immune response.

2.2 Primary vs. Secondary Immune Response

Within the adaptive immune system, there are significant differences between the mechanisms that drive a primary immune response and a secondary immune response. During the primary immune response, after antigen presenting cells (APCs) become mature, naïve T cells are activated to become the effector T cells that drive the elimination of the antigen. These effector T cells produce the growth factor cytokine interlukin-2 (IL-2), which not only drives the proliferation of mature effector T cells, but also drives the transition of these cells into memory T cells [30,25].

During a secondary immune response, the effector T cells are not only derived from activated naïve T cells; dormant memory T cells are also present. Since memory cells are antigen specific, the amount of APC and cytokine stimulation that is required to activate the cells is significantly lower than that of naïve T cells [6,37,30]. Memory T cells can be divided into two main compartments: central memory (CM) and effector memory (EM) T cells. When encountered with a secondary infection of an antigen, while EM cells require low stimulation for activation, CM cells require lower stimulation for proliferation [27,15]. Thus, the two memory compartments together facilitate an effector T cell response that is faster and of greater magnitude. Due to this fast response to antigen, it has been shown that memory cells are the driving force behind secondary immune responses, with the majority of effector T cells originating from dormant memory T cells [10].

2.3 Memory T Cell Dynamics

There are two main hypotheses as to when and how antigen specific memory T cells are formed (see Figure 1) [18]. The first hypothesis assumes that memory T cells differentiate from naïve T cells independently of the effector T cells (Figure 1 (left)). Experimental evidence suggests that it is somewhat unlikely that naïve T cells are primed to form either precursor memory cells or effector T cells [13].

A second hypothesis is that memory T cells form from effector T cells (Figure 1 (right)). As explained in [18], while still differentiating from effector T cells, there are a several mechanisms that could be at play. First, *the decreasing-potential model* assumes that throughout infection effector T cells keep a history of the signals they receive and will differentiate into the various memory T cells or remain as effector T cells based on these signals. When there is continuous signaling and interaction with antigen, cells are more likely to remain effector T cells and terminally differentiate. *The signal-strength model*, or *linear differentiation model*, suggests that memory T cells differentiate solely based on the strength of the signaling that effector T cells receive.

Other approaches that do not fall into the main two categories have been proposed, such as *the asymmetric cell fate model*. It suggests that while effector T cells

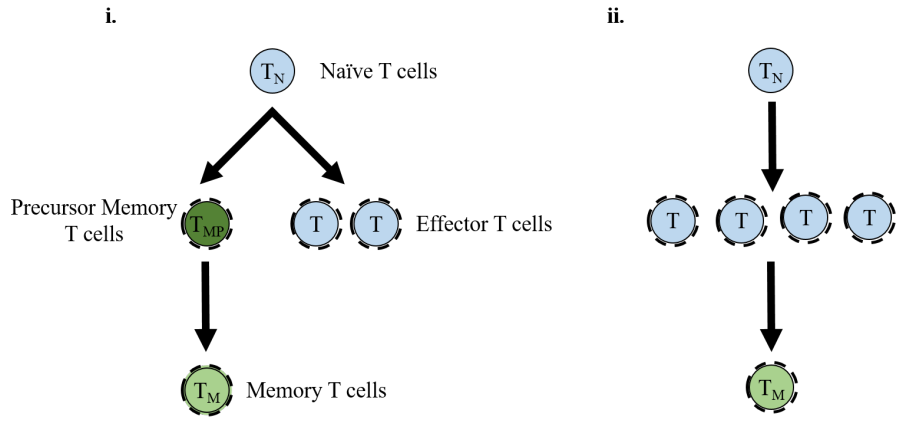

Fig. 1: **The formation of memory effector T cells.** Shown are two hypothesis regarding the formation of memory effector T cells: (i) A fraction of naïve T cells differentiate into precursor memory T cells that further differentiate into memory T cells. (ii) Memory T cells form from a fraction of the effector T cells during the contraction phase of an immune response.

are clonally expanding, based on the type of mature APC-T cell connection, effector T cells can divide asymmetrically into both effector T cells and memory T cells.

In this work, we assume a memory T cell differentiation model similar to that of the signal-strength model. Here, around 5–10% of effector T cells differentiate into dormant memory T cells based on the amount of APC and IL-2 stimulation throughout the entire immune response [18]. With this differentiation model, the majority of memory T cells will differentiate during the contraction phase of an immune response.

3 A Mathematical Model of Memory Induced Immune Dynamics

3.1 Reverse Transitions of Regulatory Cells to Helper Cells

We begin with an overview of the mathematical model for the dynamics of the primary immune response [34] (see also [19]). This model serves as the framework to which we incorporate memory T cells in Section 3.2. The model of [34] is based on the following assumptions:

1. The T cell response is mostly determined in the first hours of antigen presentation and is insensitive to precursor T cell frequencies.
2. Regulatory T cells are the mechanism of contraction following pathogen clearance.
3. Regulatory T cells can change their functionality and become immune promoting helper T cells [33].

The model is written as a system of DDEs that follow the dynamics of the concentrations of the following populations: immature APCs at the site of infection (A_0), mature APCs that are presenting antigen in the lymph nodes (A_1), naïve T cells (H^0) and mature helper T cell (H), naïve cytotoxic T cells (K^0) and mature cytotoxic T cells (K), interleukin-2 (P) and regulatory T cells (R). The model equations are:

$$\dot{A_0} = s_A - d_0 A_0(t) - a(t)A_0(t), \tag{1}$$

$$\dot{A_1} = a(t)A_0(t) - d_1 A_1(t), \tag{2}$$

$$\dot{H^0} = s_H - \delta_0 H^0(t) - kA_1(t)H^0(t), \tag{3}$$

$$\begin{aligned}\dot{H} = {} & 2^{m_1} kA_1(t-\sigma_1)H^0(t-\sigma_1) - kA_1(t)H(t) + 2kA_1(t-\rho_1)H(t-\rho_1) \\ & + \mu \frac{R(t)}{1+dP(t)} - (\delta_H + r)H(t) - kR(t)H(t),\end{aligned} \tag{4}$$

$$\dot{K^0} = s_k - \delta_0 K^0(t) - kA_1(t)K^0(t), \tag{5}$$

$$\begin{aligned}\dot{K} = {} & 2^{m_2} kA_1(t-\sigma_1)K^0(t-\sigma_1) - kP(t)K(t) + 2kP(t-\rho_2)K(t-\rho_2) \\ & - \delta_k K(t) - k_E R(t)K(t),\end{aligned} \tag{6}$$

$$\dot{P} = r_1 H(t) + r_2 K(t) - \delta_P P(t) - kP(t)K(t) - kP(t)R(t), \tag{7}$$

$$\dot{R} = rH(t) + 2kP(t-\rho_1)R(t-\rho_1) - kP(t)R(t) - \mu \frac{R(t)}{1+dP(t)} - \delta_H R(t). \tag{8}$$

The model (1)–(8) describes the following dynamics: Upon encountering antigen, immature APCs become mature APCS and migrate to the lymph nodes. Naïve helper and cytotoxic T cells residing in the lymph nodes encounter mature APCs and enter a minimal developmental program in which they divide m_1 or m_2 times, respectively. Mature helper and cytotoxic T cells secrete the positive growth signal IL-2. Mature helper and cytotoxic T cells that have completed the minimal developmental program become effector cells that continue dividing upon further antigenic stimulations. In response to antigenic stimulation, some proportion of helper T cells differentiate into regulatory T cells. These Tregs suppress mature helper and cytotoxic T cells, proliferate after consuming free positive growth signal, and may transition back into the helper T cells at a rate that depends on the growth signals received from mature T cells.

The model (1)–(8) was shown to express the expansion and contraction of the primary immune response. Varying the initial T cell concentrations over 4 orders of magnitude led to a change in the peak immune response that varied by one order of magnitude. This is consistent with biological experiments. For more details we refer to [34];

3.2 Mathematical Model Framework

Following the framework developed in [19,34], we develop a mathematical model that incorporates memory T cells. The model is written as a system of ordinary and

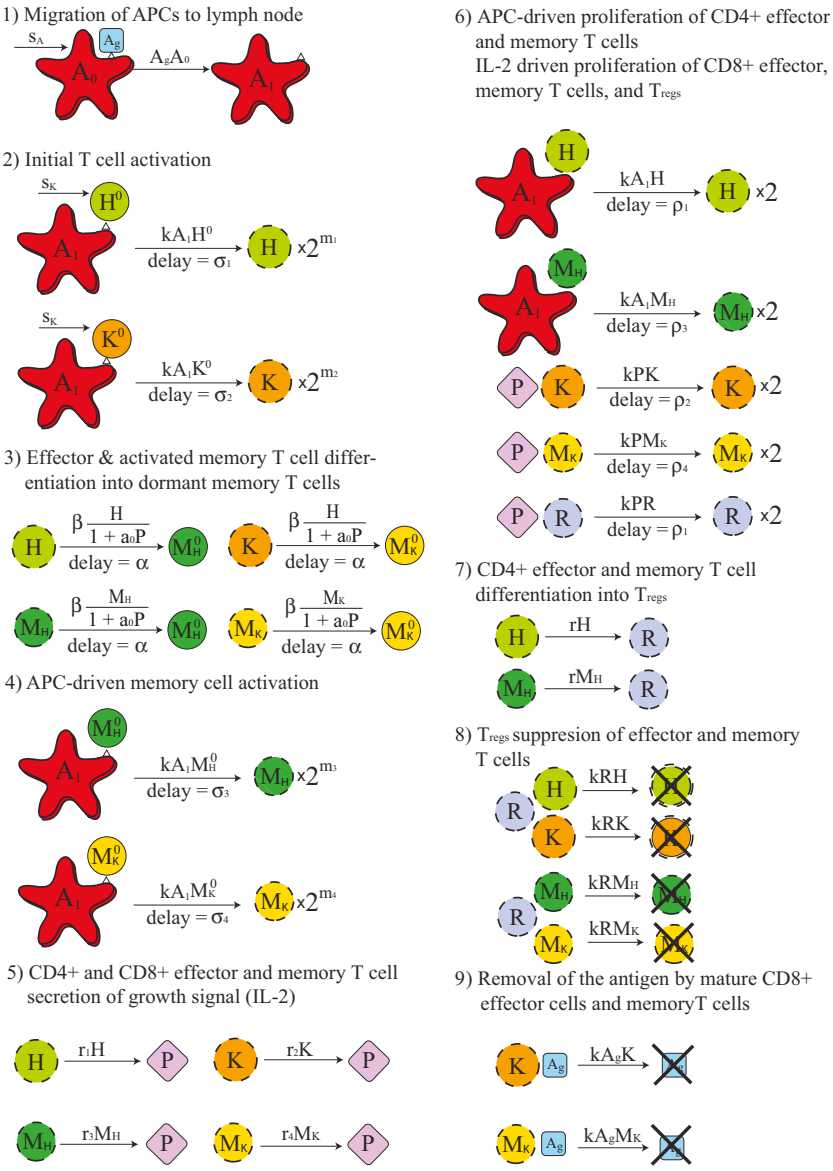

Fig. 2: A diagram of the adaptive immunity model including memory cells, corresponding to equations (9)–(21). The diagram includes the following compartments: immature APCs (A_0), mature APCs (A_1), naïve helper T cells (H^0), mature helper T cells (H), naïve cytotoxic T cells (K^0), mature cytotoxic cells (K), dormant memory helper T cells (M_H^0), activated memory helper T cells (M_H), dormant memory cytotoxic T cells (M_K^0), activated memory cytotoxic cells (M_K), IL-2 (P), regulatory T cells (R), and antigen (A_g).

delayed differential equations. We combine central memory (CM) and effector memory (EM) cells into a singular memory T cell compartment. Memory T cells require less stimulation to respond, and clonally expands faster than their non-memory counterparts. The inclusion of memory T cells allows us to expand the framework of [19, 34] and capture both primary and secondary immune responses.

The interactions captured by the model are schematically shown in Figure 2. The figure includes the following elements:

1. Immature APCs, $A_0(t)$, become mature APCs, $A_1(t)$ when they interact with antigen, $A_g(t)$. Mature APCs travel to the lymph nodes.
2. In the lymph nodes, the naïve helper T cells, $H^0(t)$, and naïve cytotoxic T cells, $K^0(t)$, interact with the mature APCs and begin to undergo the minimal developmental program. Helper T cells divide m_1 times over time σ_1, while CTLs divide m_2 times over time σ_2.
3. In primary immune response, during the contraction phase, when the amount of mature APCs, $A_1(t)$, is low, mature helper T-cells and mature CTLs, transition into dormant memory helper cells, $M_H^0(t)$, and dormant memory CTLs, $M_K^0(t)$, respectively. In the contraction phase of secondary and subsequent immune responses, mature helper T cells and activated memory helper cells, $M_H(t)$, both transition to $M_H^0(t)$. Similarly, mature CTLs and activated memory CTLs, $M_K(t)$, both transition to $M_K^0(t)$ during the contraction phase of secondary and subsequent immune responses. The duration of the transition into $M_H^0(t)$ and $M_K^0(t)$ is α.
4. In secondary and subsequent immune responses, the dormant memory T cells, interact with mature APCs causing them begin the minimal developmental program. Memory helper T cells divide m_3 times over time σ_3, while memory CTLs divide m_4 times over time σ_4.
5. Both mature effector T cells and activated memory T cells secrete the growth signal IL-2, $P(t)$.
6. Once mature T cells and activated memory T cells complete the minimal developmental program, they become effector T cells and continue to divide. The CD4+ T cells continue to proliferate in response to an interaction with the mature APCs, while CD8+ cells proliferate in response to stimulation by IL-2.
7. A proportion of mature helper T cells and activated memory helper cells transition into regulatory T cells in response to stimulation by antigen.
8. Regulatory T cells suppress mature effector T cells as well as activated memory T cells. They also proliferate in response to IL-2 stimulation.
9. Mature CTLs and activated memory CTLs induce apoptosis in antigen cells.

A corresponding model for the adaptive immune dynamics that includes memory T cells and regulatory T cells, is given by the following equations:

$$\dot{A}_0 = s_A - d_0 A_0(t) - A_g(t)A_0(t), \tag{9}$$

$$\dot{A}_1 = A_g(t)A_0(t) - d_1 A_1(t), \tag{10}$$

$$\dot{H}^0 = s_H - \delta_0 H^0(t) - kA_1(t)H^0(t), \tag{11}$$

$$\dot{H} = 2^{m_1} kA_1(t-\sigma_1)H^0(t-\sigma_1) - kA_1(t)H(t) + 2kA(t-\rho_1)H(t-\rho_1)$$

$$- (\delta_H + r)H(t) - kR(t)H(t) - \beta \frac{H(t)}{1 + a_0 P(t)}, \tag{12}$$

$$\dot{K}^0 = s_k - \delta_0 K^0(t) - kA_1(t)K^0(t), \tag{13}$$

$$\dot{K} = 2^{m_2} kA_1(t - \sigma_2)K^0(t - \sigma_2) - kP(t)K(t) + 2kP(t - \rho_2)K(t - \rho_2) - \delta_k K(t) - k_E R(t)K(t) - \beta \frac{K(t)}{1 + a_0 P(t)}, \tag{14}$$

$$\dot{M}_H^0 = \beta \frac{H(t - \alpha)}{1 + a_0 P(t - \alpha)} + \beta \frac{M_H(t - \alpha)}{1 + a_0 P(t - \alpha)} + (r_{MH} - \delta_{MH})M_H^0(t) - k_{MH} A_1(t) M_H^0(t), \tag{15}$$

$$\dot{M}_H = 2^{m_3} k_{MH} A_1(t - \sigma_3)M_H^0(t - \sigma_3) - kA_1(t)M_H(t) + 2kA_1(t - \rho_1)M_H(t - \rho_1) - (\delta_H + r)M_H(t) - kR(t)M_H(t) - \beta \frac{M_H(t)}{1 + a_0 P(t)}, \tag{16}$$

$$\dot{M}_K^0 = \beta \frac{K(t - \alpha)}{1 + a_0 A_1(t - \alpha)} + \beta \frac{M_K(t - \alpha)}{1 + a_0 P(t - \alpha)} + (r_{MK} - \delta_{MK})M_K^0(t) - k_{MK} A_1(t) M_K^0(t), \tag{17}$$

$$\dot{M}_K = 2^{m_4} k_{MK} A_1(t - \sigma_4)M_K^0(t - \sigma_4) - kP(t)M_K(t) + 2kP(t - \rho_2)M_K(t - \rho_2) - \delta_k M_K(t) - k_E R(t)M_K(t) - \beta \frac{M_K(t)}{1 + a_0 P(t)}, \tag{18}$$

$$\dot{P} = r_1 H(t) + r_2 K(t) + r_3 M_H(t) + r_4 M_K(t) - \delta_P P(t) - kP(t)K(t) - kP(t)M_K(t) - kP(t)R(t), \tag{19}$$

$$\dot{R} = r(H(t) + M_H(t)) + 2kP(t - \rho_1)R(t - \rho_1) - kP(t)R(t) - \delta_H R(t), \tag{20}$$

$$\dot{A}_g = [(r_A - \delta_A)A_g(t) - k_A A_g(t)K(t) - k_A A_g(t)M_K(t)] \times \theta(A_g(t) - 10^{-18}) + a(t). \tag{21}$$

Here, A_0 represents the concentration of immature APCs at the site of infection, while A_1 is the concentration of mature APCs that are presenting antigen in the lymph nodes. H^0 represents the concentration of naïve helper T cells and H is the concentration of mature helper T cells. Similarly, K^0 and K represent the concentration of naïve and mature cytotoxic T cells, respectively. M_H^0 and M_H represent the concentration of dormant and activated memory helper T cells, while M_K^0 and M_K represent the concentration of dormant and activated memory cytotoxic T cells. Finally, P is the IL-2 concentration, R represents regulatory T cell concentration, and A_g represents antigen concentration.

Equation (9) describes the immature APCs that are available to respond to antigen stimulation. We assume a constant supply of cells, s_A, and a death rate, d_0. Immature APCs are stimulated by the antigen, A_g, and through this stimulation immature APCs become the mature APCs in the lymph nodes described by (10). Mature APCs die at rate d_1.

Equations (11) and (13) describe naïve helper T cells and naïve cytotoxic T cells (CTLs). Both populations have constant supply, s_H and s_K, and an identical death

rate, δ_0. These naïve T cells transition into their respective effector T cell populations following interactions with mature APCs.

The mature helper T cell population is described by Equation (12). After the naïve CD4+ T cells become activated by mature APCs, the first term corresponds to a minimal development program where they undergo m_1 cell divisions over a time period σ_1. Once the cells are fully mature, CD4+ T cells are further stimulated by APCs and proliferate. This division is represented by the second and third terms. The amount of time required for mature helper T cells to divide is ρ_1. Mature helper T cells are removed from the system by either natural cell death, δ_H, differentiation into regulatory T cells, r, regulatory T cells suppression, or differentiation into dormant memory T cells. Since we assume that dormant memory T cells are formed during the contraction phase of an immune response, the last term represents the switching of CD4+ T cells to dormant memory T cells which occurs at low levels of IL-2.

Equation (14) describes the mature cytotoxic T cell population. Similar to the mature helper T cells, the first term corresponds to naïve CD8+ T cells entering the mature cell population after undergoing the minimal developmental program of m_2 cell divisions, over a time period ρ_2. Further proliferation of CD8+ cells is activated by IL-2 (the second and third terms) with the duration of one cell division of CD8+ T cells, ρ_2. CD8+ cells exit the system by either natural cell death, δ_K, suppression by regulatory T cells or by differentiating into dormant memory CTLs when the amount of IL-2 is low.

Equations (15) and (17) describe the dormant helper and CTL memory cells, respectively. The first two terms of each equation represents the transitioning from either their respective mature T cell populations or their respective activated memory T cell compartment. We assume that after the transition from the effector T cell compartments, dormant memory T cells can be activated only after a time α passes. The third terms describe the growth at rate r_{M*}, and natural death at rate δ_{M*}. The final terms describe the activtation of dormant cells as a result of their interaction with mature APCs.

The activated memory T cell populations are described by Equations (16) and (18), representing CD4+ and CD8+ T cells, respectively. Similar to the activation of non-memory T cells, after the dormant memory cells become activated by mature APCs, the first term corresponding to the minimal developmental program where they undergo m_3 and m_4 cell divisions. The amount of time required for this developmental program is characterized by the time delays σ_3 and σ_4. Once the cells are fully activated, CD4+ T cells are further stimulated by APCs and proliferate, while CD8+ cells are further stimulated by IL-2. The amount of time required for activated memory CD4+ and CD8+ T cells to divide is represented by the time delays ρ_1 and ρ_2, respectively.

Activated memory CD4+ T cells are removed from the system by either natural cell death, δ_H, differentiation into regulatory T cells, r, regulatory T cells suppression, or differentiation into dormant memory T cells. Similarly, activated memory CD8+ T cells are removed from the system by either natural cell death, δ_K, regulatory T cells suppression, or differentiation into dormant memory T cells. Since we assume that dormant memory T cells are formed during the contraction phase of an immune

response, the last term of both equations shows the rate of activated memory cells switching to dormant memory cells at low levels of IL-2.

Equation (19) describes the amount of IL-2 in the system. The first four terms describe the secretion of IL-2 by mature helper T cells (r_1), mature CTLs (r_2), activated memory CD4+ T cells (r_3), and activated memory CD8+ T cells (r_4). The cytokine has a decay rate, δ_P. IL-2 is also consumed by mature CTLs, activated memory CTLs, and Tregs, described by the last three terms.

The dynamics of regulatory T cells is governed by equation (20). The first term is the differentiation of mature helper T cells and activated memory T cells into Tregs. The next two terms describe the additional proliferation of Tregs due to IL-2 activation, with the duration of Treg cells division given by ρ_1. Tregs exit the system by the same natural death rate of helper T cells, δ_H.

The final equation, (21), describes the dynamics of antigens. The first term describes their growth at rate r_A, and death at rate δ_A. Antigens are removed from the system via interaction with mature CTLs (the second term) and activated memory CTLs (the third term). $\theta(t)$ is the Heaviside equation, with

$$\theta(t) = \begin{cases} 0 & t < 0, \\ \frac{1}{2} & t = 0, \\ 1 & t > 0. \end{cases}$$

Here, $\theta(t)$ prevents the antigen compartment from changing once its population falls below a threshold which we set as 10^{-18} K/mm^3. Finally, the last term, $a(t)$, describes the source of antigens, which is used to stimulate the system and activate the immune response.

4 Results

4.1 Numerical Model Simulations and Results

Using the parameter values shown in Table 1 we numerically solve the model (9)-(21).. All simulations were carried out using the Matlab solver DDESD. The majority of the parameters are taken from [19] and [34]. Assumptions that are made for these simulations are as follows:

1. Memory T cells are slowly growing and slowly dying. Specifically, they proliferate and go through natural cell death at the same rate.
2. Activated memory T cells produce substantially more IL-2 than their non-memory counterparts. For the simulations we choose a factor of 10.
3. Memory T cells have the same kinetic coefficients when interacting with IL-2 and mature APCs as their non-memory counterparts, i.e. k, k_{MH}, and k_{MK} all have the same value.
4. The secondary antigen stimulation is identical to the primary stimulation. In order to induce both primary immune response and a secondary immune response 70

Table 1: Estimates of parameters for model (9)-(21). All concentrations are measured in K/mm^3 and time is in days. Initial conditions not provided in the table are zero. We note that the estimate parameters are based on general assumptions regarding the characteristics of memory T cell dynamics.

Parameter	Description	Estimate	Source
$A_0(0)$	Initial concentration of immature APCs	10	[19]
$H_0(0)$	Initial concentration of naïve CD4+ T cells	0.06	[19]
$K_0(0)$	Initial concentration of naïve CD8+ T cells	0.04	[19]
s_A	Supply rate of immature APCs	0.3	[19]
d_0	Death rate of immature APCs	0.03	[19]
d_1	Death rate of mature APCs	0.8	[19]
s_H, s_K	Supply rate of naïve CD4+ and CD8+ T cells, respectively.	0.0018, 0.0012	[34]
k	Kinetic coefficient	5	[34]
δ_0	Death rate of naïve T cells	0.03	[34]
δ_H, δ_K	Death rate of mature CD4+ and CD8+ T cells, respectively.	0.23, 0.4	[34]
m_1, m_2	Number of divisions in the minimal development program for naïve CD4+ and CD8+ T cells, respectively.	2, 7	[34]
σ_1, σ_2	Duration of the minimal development program for naïve CD4+ and CD8+ T cells, respectively.	1.46, 4	[34]
ρ_H, ρ_K	Duration of one T cell division for mature CD4+ and CD8+ T cells, respectively	11/24, 1/3	[34]
k_E	Kinetic coefficient for CTL-Treg interactions	20	[34]
β	Rate of differentiation of mature effector T cells into dormant memory effector T cells	0.3	estimated
α	Duration of time for cells to switch into dormant memory effector T cells	20	estimated
r_{MH}, r_{MK}	Growth rate of dormant memory CD4+ and CD8+ T cells, respectively.	0, 0	assumed
δ_{MH}, δ_{MK}	Death rate of dormant memory CD4+ and CD8+ T cells, respectively.	0, 0	assumed
k_{MH}, k_{MK}	Kinetic coefficient for mature APC- memory T cell interactions	5, 5	estimated
m_3, m_4	Number of divisions in the minimal development program for dormant memory CD4+ and CD8+ T cells, respectively.	3, 8	estimated
σ_3, σ_4	Duration of the minimal development program for dormant memory CD4+ and CD8+ T cells, respectively.	1, 3	estimated
a_0	Magnitude of dependence of dormant memory T cell differentiation on IL-2 and mature APCs	5	estimated
r_1, r_2	Rate of IL-2 secretion by mature CD4+ and CD8+ T cells, respectively	10, 1	[19]
r_3, r_4	Rate of IL-2 secretion by activated memory CD4+ and CD8+ T cells, respectively	12.3, 3.3	estimated
δ_P	Decay rate of free IL-2	5.5	[34]
r	Rate of differentiation of mature and activated memory CD4+ T cells into regulatory T cells	10	estimated
r_A	Growth rate of antigen cells	1	set
δ_A	Death rate of antigen cells	0.4	set
k_A	Kinetic coefficient for CTL-antigen interactions	2	set

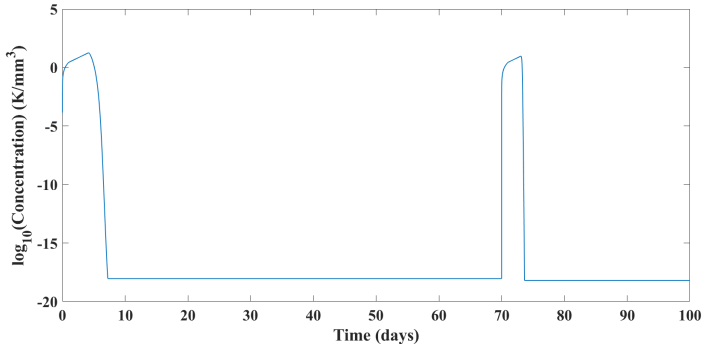

Fig. 3: The dynamics of antigen. Antigen is cleared approximately twice as fast in the secondary response compared with the primary response.

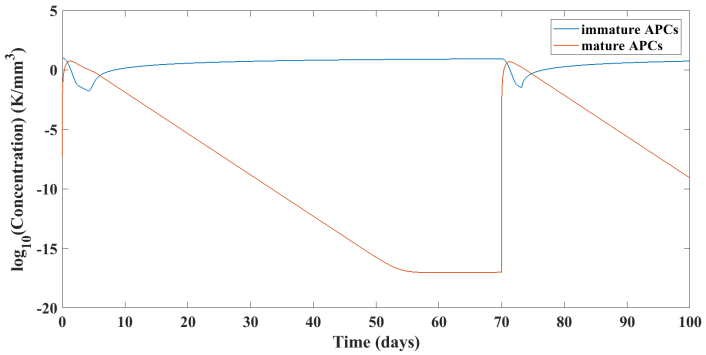

Fig. 4: The dynamics of immature and mature APCs. We do not observe much of a dynamical change from primary immune response to the secondary immune response other than a reduced time to return to the initial population levels following the secondary immune response.

days later, we set the function $a(t)$ in our antigen compartment to the following:

$$a(t) = \begin{cases} 2 & 0 \leq t < 1, \\ 2 & 70 \leq t < 71, \\ 0 & \text{otherwise.} \end{cases}$$

The number 70 days, corresponding to the time of the secondary stimulation is arbitrary. It is set to be greater than 20 days, which is the delay in the reactivation of memory cells.

Figure 3 shows the antigen compartments for both primary and secondary. We see indication that the antigen compartment is cleared more rapidly in the secondary immune response, with primary antigen clearance around 8 days and secondary antigen

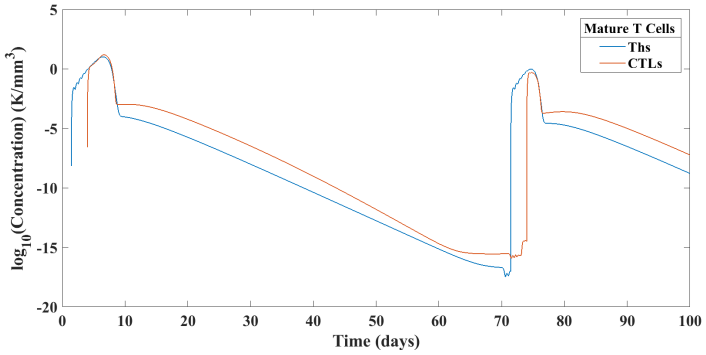

Fig. 5: The dynamics of mature helper T cells and CTLs. We see a reduction in the amount of mature non-memory cells that are present in the secondary immune response compared with the primary immune response.

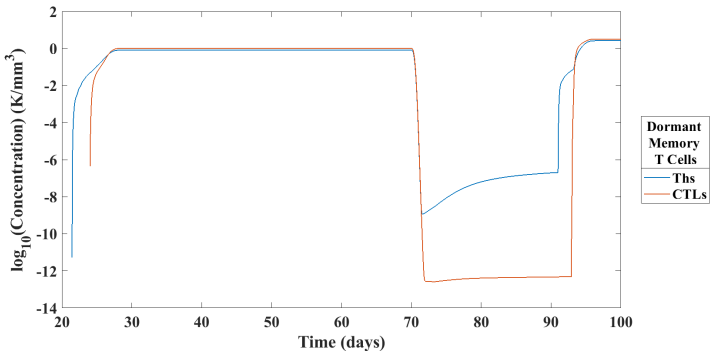

Fig. 6: The dynamics of dormant memory helper T cells and memory CTLs. Memory cells are created and remain steady at low levels, around 5–10% of the total amount of mature and activated cells during both immune responses. We note that the formation of the dormant memory T cell population begins around day 20. This aligns with the assumption that dormant memory T cells appear near the end of the primary immune response.

clearance in less than 5 days. Moreover, the maximum amount in the antigen concentration over the course of the secondary response is slightly lower than the peak of antigen concentration during the primary response. The dynamics of immature and mature APCs is shown in Figure 4.

Figures 5-7 show the evolution of the mature effector T cell and the memory T cell population concentration. Just as demonstrated experimentally, the dormant memory T cell population forms primarily during the contraction phase of the immune response. We observe that the formation of the memory T cell population, both dormant and activated, begin around day 20. This aligns with the assumption that

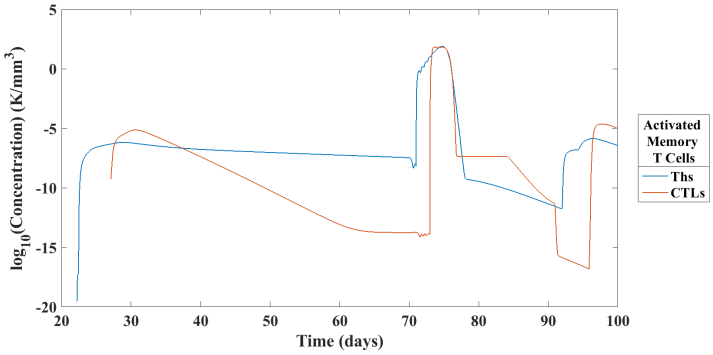

Fig. 7: The dynamics of activated memory helper T cells and memory CTLs. We observe a faster activation speed and an increased magnitude of the secondary response compared with the non-memory T cells during the primary immune response. Just as with the dormant memory T cells the formation of activated memory T cell population begin around day 20. This is consistent with having no dormant memory T cells to activate prior to this time.

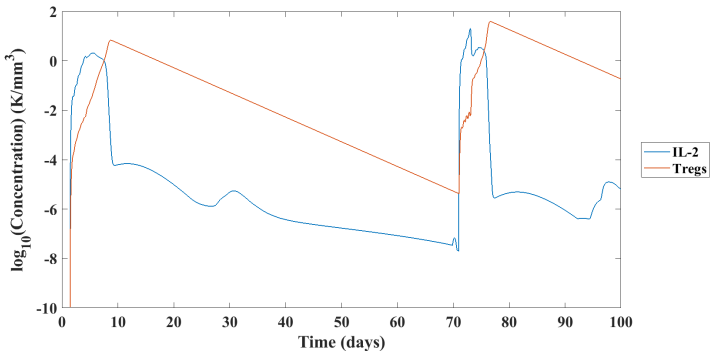

Fig. 8: The dynamics of IL-2 and Tregs. We observe an increase in both the secretion of IL-2 and the number of Tregs in the secondary immune response. These observations illustrate the 10% increase in IL-2 production by memory T cells and the increased regulation required for the contraction of the secondary immune response.

memory T cells appear near the end of the primary immune response. Moreover, when comparing the primary immune response to the secondary response, activated memory T cells dominate with far less non-memory effector T cells becoming activated. We do see a slight increase in the amount of activated memory T cells after 90 days (shown in Figure 7). This small increase in the amount of activated memory T cells is due to the fact that within our model, the concentration of mature APCs (shown in Figure 4) does not reach a level that is low enough to avoid activating a small portion of the dormant memory T cells.

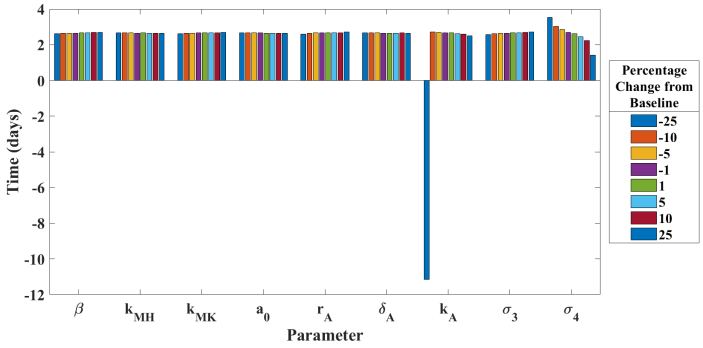

Fig. 9: Sensitivity analysis of the parameters related to memory T cells and antigen compartments. We varied the listed parameters by percentage increments from the baseline parameter values found in Table 1. We compare the difference in time of antigen clearance between primary and secondary infections.

Even though the difference in the evolution of APCs between primary and secondary immune responses (shown in Figure 4) is negligible, the amount of IL-2 and the number of Tregs that are created during the secondary response are significantly greater, see Figure 8. This increase in IL-2 and Tregs is in direct response to the increase of the amount of activated memory T cells in the system. These memory T cells create more IL-2 and at the same time require more regulation than the mature effector T cells during the primary immune response. Similar to the activated memory T cells, there is an increase followed by a decrease in the amount of IL-2 in the system after 90 days. This increase is expected given that IL-2 is secreted by the small amount of activated memory T cells.

4.2 Parameter Analysis

When testing the robustness of the parameters in our model, we compare the amount of time that is required to clear a primary infection with the amount of time required to clear a secondary infection. Here, we vary each parameter centered around a baseline value. As seen in Figure 9 the majority of the parameters guiding the memory T cell and antigen compartments do not significantly change the clearance time of the secondary infection when varied from the baseline. The main parameter that affects the results with slight perturbation is the delay required for dormant helper cells to mature, σ_3. As shown, the difference in the length of time of antigen clearance decreases with an increasing amount of time required to mature. Thus, as expected by slightly lowering the time required for the mature memory T cells to become active, the clearance of antigen in a secondary infection happens faster than in primary infection. We further assessed the effects that varying the values of parameters k_A and α has on the antigen cell concentration as seen in Figures 10 and 11.

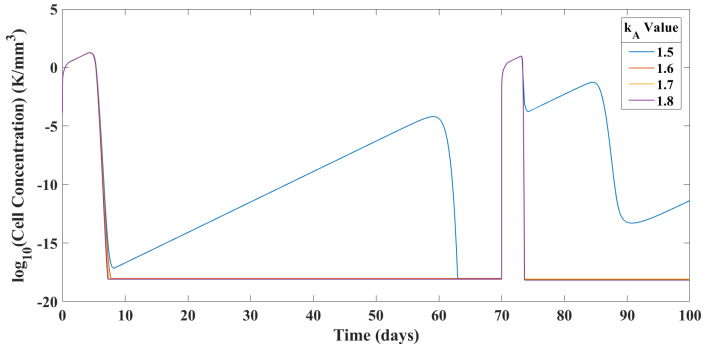

Fig. 10: The dynamics of antigen cell concentrations with varying values of CTL-antigen kinetic coefficient k_A. Once the parameter reaches below 1.6, the concentration of antigen does not reach the threshold, 10^{-18}, required by the Heaviside equation in Equation (21) in order to prevent any change in the antigen compartment.

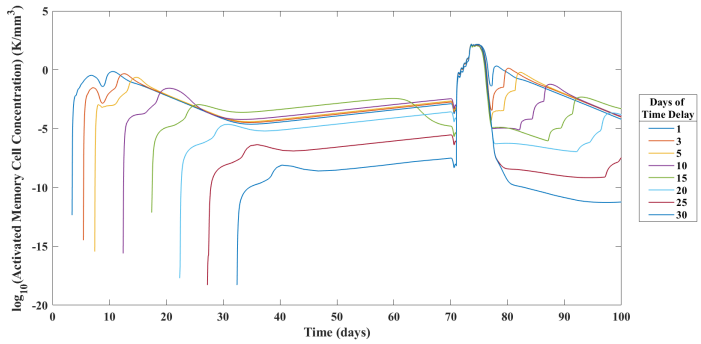

Fig. 11: The dynamics of the total activated memory T cells with varying delays, α, in transition to dormant memory T cells. We do not observe a significant change in the activation of dormant memory cells after 20 days.

Given that k_A is the kinetic coefficient for the CTL-antigen interaction, though performing similarly as the other parameter for the majority of changes from the baseline, once the parameter is lowered significantly, the time necessary to clear the secondary infection increases significantly. When varying k_A, we observe that once the kinetic coefficient reaches below around 1.6 the clearance of antigen from the primary infection does not reach below the 10^{-18} threshold required by the Heaviside equation in Equation (21) to prevent a change in the antigen compartment (see Figure 10).

The final parameter we address is the parameter which governs the delay from when a mature effector T cell becomes a dormant memory T cell. The choice of α is done in order to prevent dormant memory T cells from being activated immediately once they are created. In our model dormant memory T cells are created all the

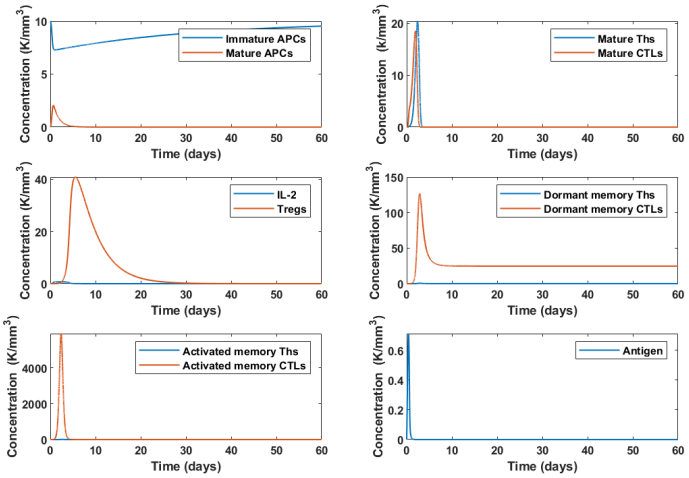

Fig. 12: The dynamics of the full system without time delays. We observe a full activation of of the immune system, including memory T cells, during the first couple of days, which is not in line with our assumptions on when memory cells form and activate.

time and not just at the very end of the process. As seen in Figure 11, if we set α at five days or below, the dormant memory cells become activated within the infection that produced them. Given that our system has residual IL-2 and antigen cells post immune response, dormant memory cells become activated between infections. However, the choice of twenty days guarantees that these activated memory cells remain in relatively low levels while ensuring that they will be available for activation for a subsequent infection within a reasonable timespan.

In Figure 12 we show model simulations that were obtained without time delays. We observe that without these delays, there is a quick full activation of the immune system as both the memory and non-memory T cells activate approximately at the same time during the primary immune response. The activation happens so fast that a full activation of the APCs in the primary immune response does not happen since memory T cells require lower stimulation to activate. Moreover, for the secondary immune response, there is a complete breakdown due to the larger numbers of dormant memory cells, which gives rise to a large response of memory cells, far too many cells for the system to respond efficiently.

5 Discussion

During the construction of this model, we ran into some challenges. First, since we want effector T cells to convert into memory T cells based on a decrease of IL-2 in the system, though in small numbers, dormant memory T cells are created through-

out the entire primary immune response. Moreover, since dormant memory T cells are activated by APCs, if we allow dormant memory T cells to have the ability to activate too soon after conversion from effector T cells, APCs then have the ability to activate dormant memory cells throughout the primary immune response as well. Considering that it is unknown if memory T cells are immediately functional, even during a primary response, we assume that even though dormant memory cells are created throughout an immune response, there is a delay in the time from conversion from effector T cells to having the ability to activate into functioning memory T cells. Given that we assume a primary immune response that lasts for roughly ten days, we set the delay in the ability to activate to twenty days.

Another issue we encountered during this study was that some populations do not go extinct in the mathematical model. For example, *in vivo*, it is safe to assume that at the end of an immune response, the antigen has been completely eliminated. However, given that we are working with a system of differential equations, though antigen may drop to very low levels, the residual antigen can still activate the system. We address this issue by incorporating the Heaviside equation into the equation governing the kinetics of the antigen compartment. This prevents the antigen compartment from changing once its population falls below $10^{-18}K/mm^3$, While this does not fully prevent the immune system from being activated, the amount of activation simulated by our mathematical model becomes negligible.

We would like to emphasize that due to the uncertainty in the values of many of the parameters that were not estimated from experiments, the results of this work should be cautiously interpreted.

A direct implementation of the model of [19,34] to a secondary immune response, we see almost identical behavior to the primary response, no increase in IL-2 or speed in antigen clearance, which gave rise to adding a memory compartment. While it is possible to formulate more complex models with varying degrees of detail within T cell memory formation and activation, we observe that having one population of memory T cells for both CD4+ and CD8+ T cells results in the desired overall dynamics. Our aim was to observe how memory T cells play an overall role in antigen clearance and to capture key features of memory T cell activation and expansion, which was accomplished. Through our parameter analysis, we observed that the behavior of the overall system is robust with regards to large perturbations in the majority of the model parameters.

6 Conclusion

Adaptive immunity in both primary and secondary immune responses encompasses a complex system of cells and cytokines that allow for both recognition and response to many antigens. In this work we derived a mathematical model to describe these dynamical interactions. We showed that, for the parameter values used, memory T cells are the main contributor to a swift elimination of antigen in secondary immune system activation.

This model can be potentially used for studying the immune response to repeated encounters with the same antigen, which is the case, e.g., with chronic infections

and autoimmune diseases. Given that there may be evidence of differing types of regulation for effector T cells and memory T cells, one can expand this model to capture the differences in the contraction of memory T cells and non-antigen specific T cells. Further studies on the expansion and contraction of memory T cells can lead to models tackling questions surrounding vaccines and other immune stimulatory processes that involve memory cells.

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