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A PRELIMINARY MATHEMATICAL MODEL OF SKIN DENDRITIC CELL TRAFFICKING AND INDUCTION OF T CELL IMMUNITY

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ABSTRACT. Chronic inflammation is a process where dendritic cells (DCs) are constantly sampling antigen in the skin and migrating to lymph nodes where they induce the activation and proliferation of T cells. The T cells then travel back to the skin where they release cytokines that induce/maintain the inflammatory condition. This process is cyclic and ongoing. We created a differential equations model to reflect the initial stages of the inflammatory process. In particular, we modeled antigen stimulation of DCs in the skin, movement of DCs from the skin to a lymph node, and the subsequent activation of T cells in the lymph node. The model was able to simulate DC and T cell responses to antigen introduction taking place within realistic time scales. The goal of such a preliminary model is simply to be able to capture biologically realistic dynamics. Future models can then build on this preliminary model in directions that can potentially allow not only for model validation, but for predictions and hypothesis testing.

1. Background.

1.1. The motivation.

The primary function of the immune system is to protect the body from foreign, potentially pathogenic, invaders. The symptoms of the earliest stage of a normal immune response, inflammation, are redness, swelling, pain and increased local temperature. The initiation of inflammation by skin infections or damage to the skin triggers resident skin cells to release molecules that cause blood vessels near the skin surface to become permeable. This increase in blood vessel permeability allows immune cells and factors circulating in the blood to rapidly enter the infected or damaged area and, as a consequence, initiate the development of immunity. When infection or damage occurs for the first time, precursors of cells that initiate immunity are recruited out of the blood following a gradient of molecules called inflammatory chemokines that are induced at the site. In order to follow chemokine gradients produced during inflammation, these cells require receptors on their surface for specific types of inflammatory chemokines. The material, generally derived from microbes, that the immune cells react to at the site of inflammation is known as antigen. A subpopulation of immigrant cells rapidly develops into dendritic cells (DCs) in the skin that sample and process the antigen for presentation to T cells within local lymph nodes. Coincident with antigen uptake, DCs are activated by a "danger signal" that induces maturation of the cell resulting in receptor type changes displayed on the cell's surface (Figure 1). Microbial DNA, RNA from viruses, bacterial peptidoglycan and lipopolysaccharide (LPS) can all act as danger signals. Cytokines, soluble intercellular messenger molecules produced during inflammation, e.g., tumor necrosis factor alpha (TNF-α), also act as intrinsic danger signals for DCs, for example in the chronic disease model such as psoriasis [1, 10]. The new receptors resulting from the danger signal, referred to as CCR7 receptors, enable DCs to follow a gradient of another set of chemokines, the constitutive chemokines, termed CCL19 and CCL21, which guide the cells from the skin via lymphatic ducts to the lymph node. Within specialized areas of the lymph node, antigen is presented by DCs to T lymphocytes. These T lymphocytes are constantly circulating from the blood system through the lymph nodes. Those T cells that recognize antigen presented by DCs become activated and proliferate within the lymph nodes. Eventually, the T cells leave and travel to the skin to assist in the removal of the antigen by secreting molecules that drive inflammation. A gradient of chemokines is again required for this movement. During a normal response, inflammation ceases once the antigen is removed or healing

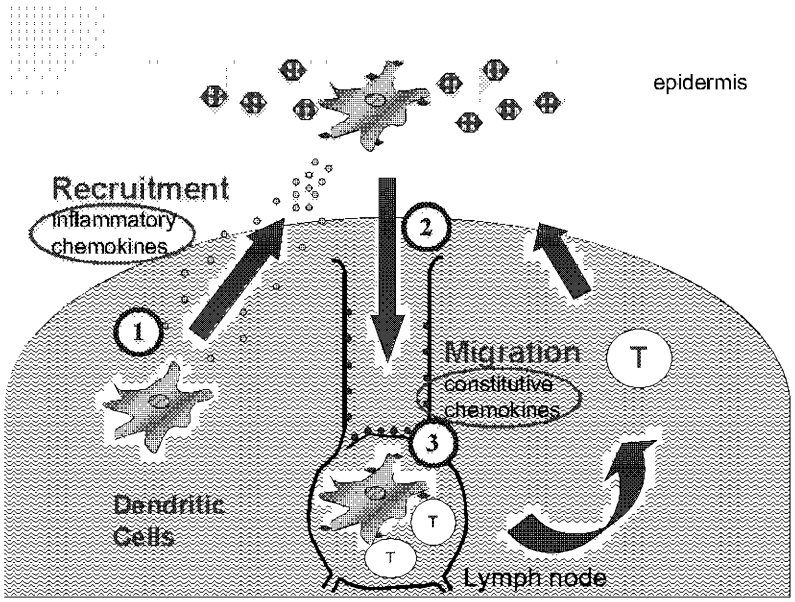

FIGURE 1. Chronic inflammation: A process where dendritic cells are constantly being recruited to the skin from the blood (1) sampling antigen in the skin and migrating to the lymph node (2) where they induce the activation and proliferation of T cells (3) that travel back to the skin where they release cytokines thus maintaining the inflammatory condition.

is complete. Some components of this immune cell movement are not restricted to the inflammatory response. In non-inflamed healthy skin, minor traffic of DCs from the skin to the lymph nodes consistently occurs. The purpose of this "steady state" migration is to assist the immune system in remaining tolerant towards body components, i.e., "self."

On occasion, the immune system induces prolonged skin inflammation. This chronic inflammation is due to an aberrant immune response to either foreign material or to normal body components that does not resolve. In this situation, cells continue to produce cytokines and chemokines and to move in and out of the skin which prolongs inflammation. One way to intervene in this process is to block the movement of immune cells. Molecules derived from viruses, termed chemokine binding proteins, have been identified that have the capacity to do this and therefore may have potential as anti-inflammatory therapeutics. We are interested in developing a mathematical model of this. Preliminary to this, we need to model (1) the recruitment of blood derived DCs in response to inflammatory stimuli and antigen in the skin, (2) the trafficking of antigen-loaded skin DCs to the node, and (3) subsequent T cell activation and proliferation under normal conditions. The mathematical model described in this paper represents these events.

2. **The model.** An ordinary differential equation (ODE) model was developed that enabled us to measure the levels of DCs in the lymph node, D_L (DCs/mg of lymph node), and in the skin, D_S (DCs/mg of skin), over time t (in hours). In addition, the antigen concentration, A (ng of antigen/mg of tissue) and the number of effector T cells (both CD4 and CD8), denoted T (with units of cells/mg of nodal tissue) were tracked. All model parameters and initial values are given in Table 1.

Regarding what "antigen" represents in the context of our model, we note that antigen that provokes DC movement in the first instance may be microbial, in which case it will replicate, and at a specific threshold (generally poorly defined), sufficiently activated DC will exit the skin. Alternatively, antigen may be a finite amount of protein which by definition will not increase. An example may be a contact allergen applied to the skin. And yet again, microbial antigen may mimic "self antigen" so that in an autoimmune disease, the immune response, initiated by antigen from the environment, may be perpetuated by a constant supply of "self" antigen, for example, cell components. Since our model is limited to incorporating the initiation of DC activation and movement to the draining lymph node in response to a given antigen, we have chosen to use a defined, finite quantity of proteinaceous antigen in this preliminary model. Since different microbes replicate at different rates under different conditions, it would be difficult to do otherwise.

We note that in a case of chronic inflammation, the model would be far more complicated, and more than one lymph node would be involved. However, in this preliminary model of DC trafficking, we focused on modeling the dynamics within only one lymph node. This model describes mathematically the induction of T cell immunity in the skin, as a first step toward developing a model of chronic inflammation. We incorporated only the simple elements of DC antigen acquisition, activation, movement, and T cell stimulation. Future, more complex, models can build on this preliminary model in directions that can potentially allow not only for model validation, but also for predictions and hypothesis testing.

2.1. **Assumptions and ODEs.** The mathematical model uses the following assumptions:

1. The concentration of DCs in the blood, D_B, remains relatively constant throughout the simulation. This implies that an ODE representing DCs in the blood would have the form $\frac{dD_B}{dt} \approx 0$ for the duration of the infection and subsequent inflammation, and thus an equation for D_B is not included.
2. Antigen accumulates in the skin linearly over time until it reaches a maximum level. There is no evidence that this is not the case, and it allows for a tractable mathematical implementation.
3. In the absence of sufficient antigen, the number of DCs that migrate to the lymph nodes is very small. Sufficiently high levels of antigen stimulate increased DC flow from the blood to the skin and thus from the skin to the lymph node.
4. Dendritic cells do not proliferate in the skin. This assumption is based on data derived from the inflammatory response when immigrant monocytes enter the skin, differentiate, acquire antigen in the presence of co-stimulatory danger signals and migrate to the draining nodes. Langerhans Cells, the normal residents, are known to turn over (that is, replicate) extremely slowly in the skin [6, 11]. Dendritic cells that are known to participate in an inflammatory

response are recruited primarily as monocytes from the blood and are not known to proliferate in the skin.

5. We know that between 0.01% and 3% of mature antigen-loaded DCs that leave the skin get to the node [8]. This suggests that there are probably quite large losses along the way possibly during migration. In the model, we are only interested in tracking those DCs that pick up antigen in the skin and are capable of activating T cells once they reach the lymph node. Therefore, we will assume that DCs that reach the node are all capable of activating T cells.
6. T cells do not begin to proliferate until the concentration of DCs in the lymph node reaches a certain threshold. This critical threshold is represented in the model by parameter $D_{L_{\text{crit}}}$.

The cycle of DC activation begins with antigen stimulation. A few hours after initial antigen stimulation, antigen is assumed to reach a sufficiently high level to elicit an inflammatory response. In particular, we represent the process of infection initiation by allowing antigen concentration, A, to increase linearly with time from the start of the simulation until A reaches a maximum threshold, A_{thresh} (see Assumption (2)). The time at which this threshold is reached is t_{thresh}. For simplicity, we assume that antigen levels A increase by one ng per mg of tissue per hour, until reaching threshold A_{thresh}. Before that threshold is reached, a low level of DCs continuously flows from the blood into the skin. This constant inflow is represented by α_{D_B} (see equation (2) below). Once antigen levels in the skin hit the critical threshold, A_{thresh}, DCs are recruited from the blood into the skin at a higher rate. In the model, this is represented by having the value of α_{D_B} increase (see discussion in section 2.3). We make the assumption that the increase in the recruitment rate takes place on a short enough time scale that the increase in α_{D_B} can be approximated by a discrete jump from a non-inflamed value to an inflamed value, and that the use of a continuous function to represent this growth is not currently required. A continuously increasing recruitment parameter can be incorporated in a future model.

Dendritic cells in the skin, D_S, continuously flow out and travel to the lymph node. The rate of transfer from the skin to the lymph node is described by a rate function $K = K(D_S, D_L)$. As the number of DCs in the skin increases, the rate at which DCs migrate from the skin into the lymph node is moderated by the function K. The form of K is outlined in detail in section 2.2.

As noted in Assumption (4), there is no DC proliferation in the skin. This, along with the aforementioned antigen activation cycle, suggests that the rate of change of the DCs in the skin can be described by the equation

$$\frac{dD_S}{dt} = \alpha_{D_B} - K(D_S, D_L)D_S.$$

The DCs that arrive in the lymph node are assumed to come solely from the population of DCs in the skin. In this model, DCs leave the skin at a rate described by the rate function K and arrive in the lymph node at that same rate. The DCs in the lymph node diminish only through death at a rate δ (per hour). Hence, the differential equation describing the rate of change of the DC population in the lymph node is

$$\frac{dD_L}{dt} = K(D_S, D_L)D_S - \delta D_L.$$

Finally, the T cell population is assumed to grow logistically with growth rate $\alpha(D_L, t)$ (per mg per hour) to a carrying capacity m times the size of the maximum

number of DCs in the lymph node (we denote maximum number of DCs in lymph node by $D_{L_{\max}}$). This parameter m has a wide range, and we chose the value $m = 10$ which means that at carrying capacity, each DC presents antigen to 10 T cells in the lymph node. Note that the growth rate, $\alpha(D_L, t)$, is not constant but a function of the concentration of DCs in the lymph node as well as of time. By Assumption (6), T cells will not be stimulated until the concentration of DCs in the lymph node reaches a critical threshold, represented in the model by $D_{L_{\text{crit}}}$.

The time at which $D_{L_{\text{crit}}}$ is reached is stored as t_{crit} and $\alpha(D_L, t)$ increases linearly over time to its maximum value $\alpha_{\max}$. The equation describing the rate of change of the T cells is given by

$$\frac{dT}{dt} = \alpha T'(mD_{L_{\max}} - T).$$

where α is a function of D_L and time and is defined as

$$\alpha(D_L, t) = \begin{cases} 0 & \text{if} \quad D_L < D_{L_{\text{crit}}} \\ \min(\frac{\alpha_{\max}(t - t_{\text{crit}})}{t_\alpha}, \alpha_{\max}) & \text{if} \quad D_L \geq D_{L_{\text{crit}}}. \end{cases} \tag{1}$$

We chose α to have this time-dependent form for the following reasons. The T-cell population should not be stimulated to grow at all until the critical DC threshold is reached. At that time, the intention is not simply to discretely switch on the T-cell stimulation by DCs, but to allow T-cell stimulation by DCs to increase linearly with time until stimulation levels are at a maximum. This is achieved through the time-dependent form of α. We set $t_\alpha = 72$ hours, which is an arbitrary choice that allows the α function three days to achieve its maximum value.

In summary, the model equations are given by:

$$\frac{dD_S}{dt} = \alpha_{D_B}(A, A_{\text{thresh}}) - K(D_S, D_L)D_S \tag{2}$$

$$\frac{dD_L}{dt} = K(D_S, D_L)D_S - \delta D_L \tag{3}$$

$$\frac{dT}{dt} = \alpha T'(mD_{L_{\max}} - T). \tag{4}$$

2.2. **The rate function K.** To determine the rate function K, we first considered $0 < t < t_{\text{thresh}}$. At this time, we let $K = K_0$ since there will only be minimal numbers of antigen loaded DCs migrating to the lymph node before antigen levels reach their critical activation threshold. For $t > t_{\text{thresh}}$, we used results from [8] and estimated that the number of DCs in the skin doubles as the rate approximately triples. Therefore, $K = K_0\left(3^{\log_2(D_S/D_S^*)}\right)$, where K_0 is the initial rate at which activated DCs move from the skin into the lymph node. The value of D_S^* represents the number of DCs that have entered the skin by time t_{thresh}. D_S^* changes in magnitude with α_{D_B} to be consistent with experimental data. From the experiments of [7], the rate at which DCs enter uninflamed skin is 2 DCs per mg of skin per hour (see discussion of α_{D_B} in section 2.3). By the same experiment, the rate of DCs entering 1 mg of inflamed skin per hour is 100. Therefore, we will allow D_S^* to be the number of DCs in the skin at time t_{thresh}. Thus, $D_S^* = t_{\text{thresh}}\alpha_{D_B}$, for the uninflamed value of α_{D_B}. This equation holds as long as there is sufficient space in the lymph node for new DCs to enter, that is, $D_L < D_{L_{\max}}$. Once the threshold has been reached, $K(D_S, D_L)$ measures the rate at which DCs from the

TABLE 1. Table of model variables and parameters.

Quantity	Units	Initial Value	Change
	Variables		
D_S	dendritic cells / mg skin	0	$\frac{dD_S}{dt}$
D_L	dendritic cells / mg lymph node	0	$\frac{dD_L}{dt}$
T	Primed T cells / mg lymph node	1	$\frac{dT}{dt}$
	Parameters		
A	ng of antigen/mg of tissue	0	$\begin{cases} t & \text{if } A < A_{\text{thresh}} \\ A_{\text{thresh}} & \text{otherwise} \end{cases}$
t_{thresh}	hr	4	None
A_{thresh}	ng of antigen/mg tissue	4	None
$D_{L_{\text{crit}}}$	dendritic cells/mg lymph node	3×10^2	None
$D_{L_{\max}}$	dendritic cells/mg lymph node	2×10^4	None
α_{D_B}	dendritic cells/mg of skin/hr	$2 \le \alpha_{D_B} \le 125$	If $A > A_{\text{thresh}}$: $100 \le \alpha_{D_B} \le 6250$
D_S^*	dendritic cells / mg skin	$t_{\text{thresh}}\alpha_{D_B}$	None
δ	1/hr	1/72	None
$\alpha(D_L, t)$	1/(hr T cells/mg lymph node)	0	Linear function, see eq. (1)
m	T cells/dendritic cell	10	None
$\alpha_{\max}$	1/(hr T cells/mg lymph node)	0.1	None
K	1/hr	2.08×10^{-7}	See equation (5)

skin can replenish those DCs that died in the lymph node. If $D_L \ge D_{L_{\max}}$, then the maximum rate K is given by $K = (\delta D_L)/D_S$. This maintains the steady state population of $D_L = D_{L_{\max}}$.

Therefore, we have

$$K(D_S, D_L) = \begin{cases} K_0 & \text{if } 0 \le t \le t_{\text{thresh}} \\ K_0 \left(3^{\log_2(D_S/D_S^*)}\right) & \text{if } t > t_{\text{thresh}} \text{ and } D_L < D_{L_{\max}} \\ \min\left\{\delta D_L/D_S, K_0 \left(3^{\log_2(D_S/D_S^*)}\right)\right\} & \text{if } t > t_{\text{thresh}} \text{ and } D_L \ge D_{L_{\max}} \end{cases} \tag{5}$$

The rate function K uses the number of DCs in the skin as a proxy for the physiological roles of tumor necrosis factor (TNF), the chemokine gradient and other biological elements that influence DC migration.

2.3. **Parameters and initial conditions.** To allow for a numerical examination of the model system, we had to choose parameter values. In this section, we describe how we arrived at particular parameter values and initial conditions.

- $D_S(0) = 0$: $D_S(0)$ is the number of DCs in the skin at time zero, and is zero initially, since we don't expect there be any activated DCs in the skin prior to the introduction of antigen.
- $D_L(0) = 0$: $D_L(0)$ is the number of DCs in the lymph node at time zero, and is zero initially, since we don't expect there be any activated DCs in the lymph node prior to the introduction of antigen.
- $T(0) = 1$: There can be on the order of 10^6 T cells per lymph node, but before antigen stimulation, there should be no primed T cells. For the purposes of streamlining the mathematical model, we chose to represent T cell dynamics by a logistic growth term, which requires mathematically a non-zero initial condition in order to allow for any population growth. Therefore, we allowed for a negligible number of sensitized T cells per mg of lymph tissue when we initiated the simulation (one per mg of lymph tissue).
- $m = 10$: We estimate that there are approximately 10 T cells per DC in the lymph node, and therefore, the carrying capacity of T is $mD_{L_{\max}}$ [3].
- $t_{\text{thresh}} = 4$: The time at which antigen levels A reach A_{thresh}. See further explanation below for A_{thresh}.
- $A_{\text{thresh}} = 4$: In our model, we allow antigen levels to increase at a rate of 1 ng/mg of tissue per hour. This is a guess, and will vary depending on the organism. For this reason, we allow $A_{\text{thresh}} = t_{\text{thresh}}$ times 1 ng per mg of tissue per hour. In our case, we estimated A_{thresh} to be 4 ng/mg of tissue, the point at which DCs start getting recruited from the blood to the skin, after which the DCs take up the antigen, and migrate to the lymph node. The process of T cell activation by DCs in the lymph node is initiated once the concentration of DCs in the lymph node reaches $D_{L_{\text{crit}}}$ cells/mg of lymph node. Since there is evidence that DC activation takes place about 2 to 4 hours after initial antigen stimulation [5], we set t_{thresh} at 4 [8].

  We note that inflammation is initiated by a danger signal, and this danger signal comes from the same micro-organism as the antigen, as discussed in the introduction of this paper. Such danger signals are not explicitly accounted for in our model, but instead we allow the threshold antigen level to dictate the initiation of the inflammation response. We assume that there is sufficient accompanying danger signal to initiate the inflammatory response, allowing DC recruitment from the blood to the skin.
- $D_{L_{\text{crit}}} = 3 \times 10^2$: According to [3, 9] 3000 antigen-presenting cells per lymph node, or 300 cells/mg lymph node (assuming a 10 mg lymph node), is adequate for T cell response. In our model, we record the first time $D_{L_{\text{crit}}}$ is reached as t_{crit}. Thereafter, the T-cell growth coefficient $\alpha(D_L, t)$ grows linearly with time until its value reaches the maximum, $\alpha_{\max}$.
- $D_{L_{\max}} = 2 \times 10^4$: The lymph node in a mouse can hold about 2×10^5 DCs [8], which is 2×10^4 cells/mg of lymph node with the assumption that the lymph

node is approximately 10 mg. We let $D_{L_{\max}}$ denote the maximum number of DCs per mg of lymph node.

- $2 \leq \alpha_{D_B} \leq 125$ (uninflamed), $100 \leq \alpha_{D_B} \leq 6250$ (inflamed range):

This is the rate of the DCs entering 1 mg of skin from the blood per hour. Rate values for α_{D_B} are pre and post-threshold levels of antigen. The lower bound for the pre-threshold levels are based on the experiments of [7], and the upper bound pre-threshold value is chosen to be a percent of the upper bound post-threshold rate of DC entering inflamed skin. When α_{D_B} represents the rate of blood-derived DCs that are recruited to uninflamed skin per hour, the lower bound value is $\alpha_{D_B} = 2\pm$ (1 SD)/mg of skin per hour. This value of α_{D_B} was obtained from experiments in which DC recruitment from the blood was performed using egfp DC (DC expressing green fluorescent protein) adoptively transferred into syngeneic recipients. Bone marrow DCs were cultured from C57Bl/6 mice as previously described [2]. 3×10^7 egfp DCs were administered into sex matched C57Bl/6 recipients via the tail vein [1]. Forty hours later mice were sacrificed and an area of skin from the abdomen was excised, weighed and the immune cells isolated by enzymatic digestion. The egfp DCs were enumerated by staining the cells with a monoclonal antibody to the cell surface glycoprotein CD11C. The data were obtained using 3 mice per experimental group and 2 experiments were performed. 89 DC ± 54 (1 SD)/mg of tissue were found to be recruited to uninflamed skin over a 48 hour period. The experiment described here and experiments described below for determining α_{D_B} in the inflamed state were approved by the Animal Ethics Committee, University of Otago. The upper bound value for the uninflamed rate α_{D_B} is chosen to be 2% of the upper bound value of the inflamed α_{D_B}, since the lower bound uninflamed value is 2% of the lower bound inflamed value. Since the upper bound on the inflamed value is 6250 (see discussion below), we have the upper bound on the uninflamed set at 125.

The range of values for the inflamed state were determined as follows: they are based partially on the experiments carried out in [7], and partially on the data provided in [8]. In the experiments of [7], 10^7 white blood cells were injected into the blood (through the tail vein) of three BLB/6 mice in two experiments (for a total of six mice). The injected cells were marked with CD11c for the tracking of the number of DCs. After 24 hours, a mean of 2400 (± 94) DCs per mg of skin were harvested from the mice. So in this experiment, about 100 DCs per mg of skin appear to enter the skin per hour. We will allow this to determine the lower end value of α_{D_B}, setting it to 100. According to [3], about 300 DC/mg of lymph node are needed to initiate a T cell response. The experiments of [7] are consistent with this.

In order to get an upper bound on α_{D_B}, we look at [8], in which we see that in some cases, as few as about 0.1% of activated DCs in the skin manage to migrate to the lymph node. If we work backwards from the threshold of 300 DCs/mg of lymph node needed to activated a T cell response, assume that it takes about 2 days, or 48 hours, for the activated DCs to build up to that level in the lymph node, and then suppose that only 0.1% of activated DCs actually make it to the lymph node (according to [8]), we have the following outcome: 300 DC/mg of lymph node built up over 48 hours means an average of 6.25 DCs/mg of lymph node are entering the lymph node per hour. If this represents only 0.1% of the activated DCs that make it from the skin to the

lymph node, then there must be about 6250 activated DCs/mg of skin per hour. We choose this to be our upper bound on α_{D_B}.

- $D_S^* = t_{\text{thresh}}\alpha_{D_B}$: This represents the number of activated DCs that have arrived in the skin at the time t_{thresh} when antigen levels have reached their critical threshold.
- $\delta = 1/72$: Dendritic cells die in the lymph node after approximately 3 days, so the rate of D_L dying in the lymph node per hour, δ, is $1/72$. The estimates of a three day life span are given in [6].
- $\alpha_{\max} = 0.1$, $0 \leq \alpha(D_L, t) \leq \alpha_{\max}$: This is the growth rate of T cells in 1 mg of lymph node per hour. We chose $\alpha_{\max} = 0.1$, which is a guess, and a value that allows the T cell population to increase at a biologically reasonable rate. See equation (1) for further discussion of $\alpha(D_L, t)$.
- $K_0 = 2.08 \times 10^{-7}$/hour: The initial rate at which mature DCs are recruited from the skin into the lymph node prior to antigen levels reaching their critical threshold A_{thresh}. The value for K_0 was estimated by taking values from an experiment in [8]. In this experiment, when 10^5 DCs were injected into the skin, the rate of migration was 0.0001 after 2 days, which is equivalent to 2.08×10^{-6} per hour. Since we expect the rate of migration to be lower before critical antigen levels are reached, we will assume that the rate K_0 is an order of magnitude less than this measured rate, and therefore we let the value of K_0 be 2.08×10^{-7}/hour. Plots of various rate functions K are shown in Figures 2 through 5.

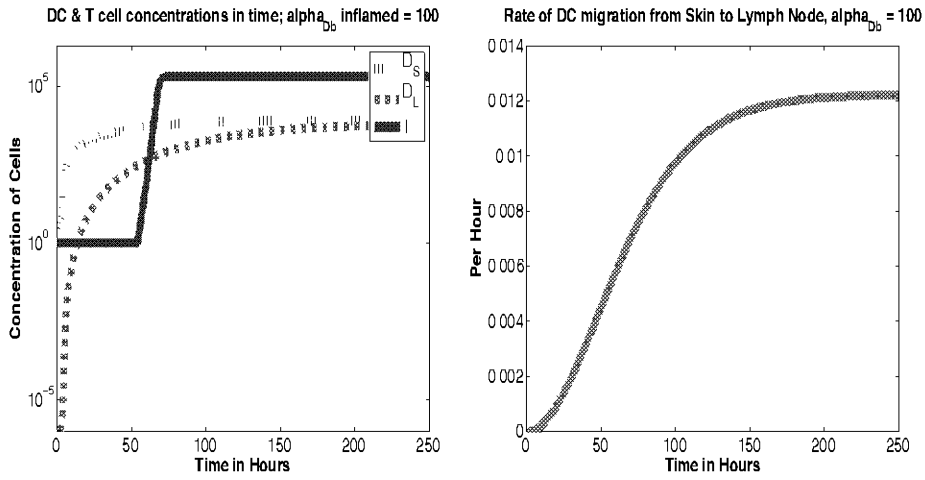

FIGURE 2. Numerical simulation of cell concentrations, with corresponding K rate function. Initial parameters and variables in Table 1. $\alpha_{D_B} = 100$.

3. **Numerical experiments.** In this section, we present simulation outcomes using a range of parameter values. We investigated the effect of the parameter α_{D_B} on the outcome of the model in an inflamed state. As noted, we assumed that in the inflamed state, α_{D_B} may range from around 100 up to approximately 6250. As can be seen in Figures 2 through 5, a change in α_{D_B} affected not only the cell concentrations over time but also the rate function K. When antigen levels are

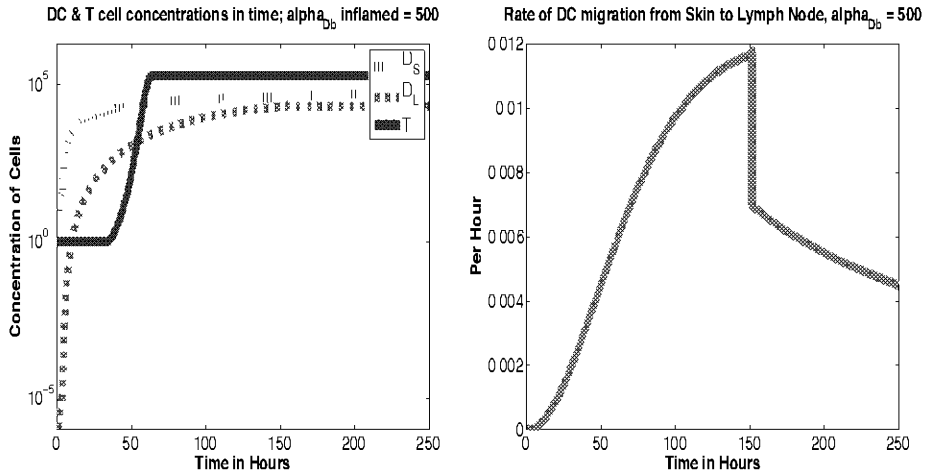

FIGURE 3. Numerical simulation of cell concentrations, with corresponding K rate function. Initial parameters and variables in Table 1. $\alpha_{D_B} = 500$.

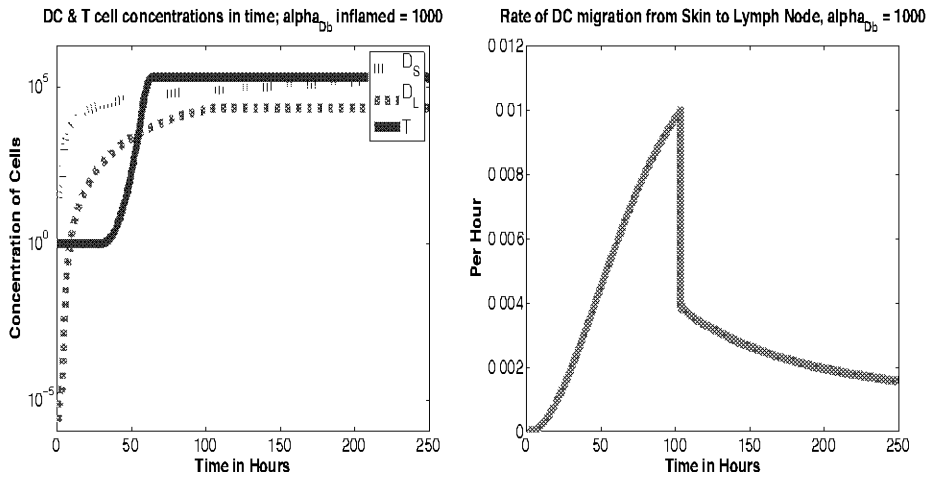

FIGURE 4. Numerical simulation of cell concentrations, with corresponding K rate function. Initial parameters and variables in Table 1. $\alpha_{D_B} = 1000$.

low, α_{D_B} is set to be between 2 and 125 cells per mg per hour (that is, 2% of the inflamed α_{D_B} value). When the antigen level is beyond a fixed threshold, the higher inflamed value of α_{D_B} kicks in. Note that for all values of α_{D_B}, we observe cell-concentration dynamics that appear to be biologically realistic. Namely,

- T cells do not respond until about 2 days after infection. It takes around one day for cells to migrate from the skin to the lymph node [8], and thereafter around 20 hours for the T cell response to kick in [4]. Thus the 2 day lag time seems to be a reasonably realistic time scale.
- Dendritic cells in the skin and lymph node begin to grow quickly.

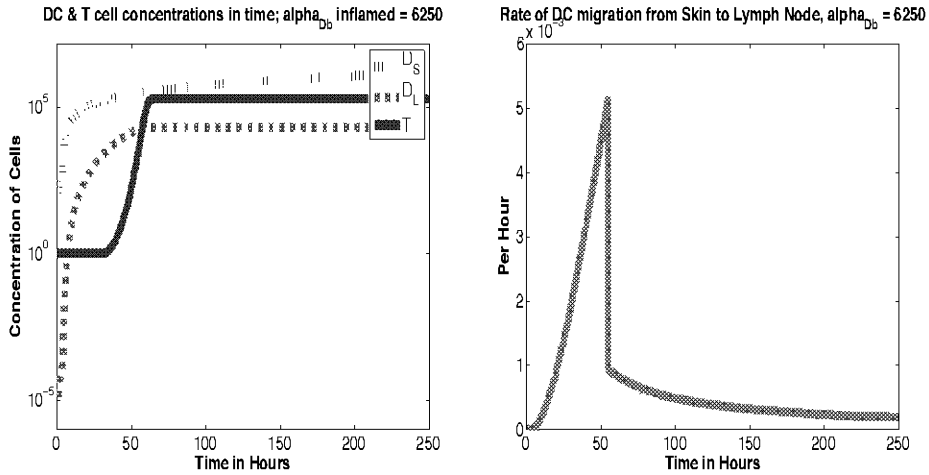

FIGURE 5. Numerical simulation of cell concentrations, with corresponding K rate function. Initial parameters and variables in Table 1. $\alpha_{D_B} = 6250$.

- $D_L < D_S$ since DCs in the lymph node come from DCs in the skin. This difference becomes more pronounced for higher values of α_{D_B}.
- T cells reach a maximum equilibrium value.
- Once D_L reaches its maximum value, D_S begins to grow since DCs in the skin migrate at a lower rate from the skin to the lymph node.
- D_L achieves its steady state value roughly at the same time T cells do. This is appropriate since D_Ls stimulate T cell production.

In the inflamed state, when α_{D_B} increases to 500 and higher, we notice that the T cell response takes place more quickly (see Figures 2 through 5). As expected, the concentrations of DCs in the skin and in the lymph node increase more rapidly in the initial hours. For α_{D_B} at 100, steady state values are achieved for DCs in the skin and lymph node, and are about equal. For the larger values of α_{D_B}, the DCs in the skin appear still to be increasing, even at time 250, but the DCs in the lymph node have achieved their steady state value of around 10^4 DCs per mg of lymph node (the maximum that can be held in the lymph node tissue). For $\alpha_{D_B} = 100$, the steady state value for the DCs in the lymph node is achieved around hour 250, but for the larger value of $\alpha_{D_B} = 6250$, the steady state value is achieved as early as hour 50.

Notice, also, that the rate function K is affected by the change in the value of α_{D_B}, becoming increasingly narrow, as well as decreasing in maximum height, as α_{D_B} increases. See Figures 2 through 5. A nice feature of the K function is that at its maximum, it never exceeds 1.2%, which is consistent with the measurements in [8].

4. **Discussion.** The model presented here is an initial step toward solving the problem of chronic inflammation. The model reflects the basic biology behind the immune response to antigen, and the simulations show biologically reasonable results. However, some additional steps need to be taken in order for this model to be

usable as a foundation for realistically addressing how a chemokine-binding protein can inhibit DC movement.

The next steps in developing this model will include:

- *Cell loss in transition.* Currently, we assume that DCs leave the skin and arrive in the lymph node at a rate K. It may be useful to explore the effect of concurrent cell loss. In the model, this is easy to implement. We can introduce a parameter ρ, where $0 \leq \rho \leq 1$, and simply modify the equation for the DCs in the lymph node to read as follows: $\frac{dD_L}{dt} = \rho K(D_S, D_L)D_S - \delta D_L$.
- *The rate function K.* $K(D_S, D_L)$ is a simplified function in which the physiological roles of tumor necrosis factor (TNF) and the chemokine gradient are not included explicitly, but their roles in DC migration are only approximated by the number of DCs in the skin. Future models will incorporate secondary chemokines such as CCL19 and CCL21 as well as the TNF's effect on inflammation and secondary chemokine production. In addition, we hope to find better values for parameters, potentially through designing experiments in collaboration between the mathematicians and the biologists. Since movement of DCs from the skin to the lymph node is not an instantaneous process biologically, we plan to investigate the introduction of a time delay between DC loss from skin and arrival at the lymph node. We note here that we model the lymph node, and not the lymph, because we can obtain data from the literature and from our own experiments. Deriving data from lymph is not easy in the mouse. It can be done in larger experimental animals by cannulating lymphatic vessels, for example in the rat [12].
- *Capturing chronic inflammation.* In this preliminary model, we have not yet included T-cell clearing of antigen, and the persistence of the T-cell population once it is activated is essentially imposed. In a future model that will build on this model, and in which we intend to capture the mechanisms that lead to chronic inflammation, the dynamics will have to be modified to allow the inflamed state to emerge from a set of rules that do not explicitly impose such a state.
- *The value of α_{D_B}.* α_{D_B} is the rate at which DCs are recruited into skin, which depends on the antigen concentration. When the antigen concentration has not yet reached a threshold, A_{thresh}, we consider that inflammation has not been triggered. We are currently investigating an implementation of a more biologically accurate definition of α_{D_B}.

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