# The Value of Inflammatory Signals in Adaptive Immune Responses

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**Abstract.** Cells of the immune system must search among billions of healthy cells in order to find and neutralize a small number of infected cells before pathogens replicate to sufficient numbers to cause disease or death. The immune system uses information signals to accomplish this search quickly. Here we use a computationally tractable and scalable differential equation model and a spatially explicit agent based model to determine how much the information in capillary inflammation decreases the time taken by the first CTL to find infected cells, increases the number of CTLs by day 5 post activation in infected tissue and decreases the number of infected cells at day 5. We find that the inflammation signal localized in a small region of infected tissue significantly reduces search times. We suggest that simple models of infection and immune response can reveal the role of local information signals in improving immune function.

## 1 Introduction

Rapid search is crucial for an effective immune response: immune system cells must find, identify and neutralize pathogens before those pathogens replicate to sufficient numbers to cause disease or death. The natural immune system (NIS) has a small number of pathogen-specific cells that must search for and neutralize a small number of initially localized pathogens in a very large tissue space. We investigate the value of inflammatory signals by how they accelerate this search for a "needle in a haystack".

Lymph nodes are small localized locations where pathogens are presented to B-cells and T-cells to determine which of them can recognize antigens and eventually neutralize them. Previous work [1–3] shows how the architecture of the lymphatic network enables the NIS to detect antigen and respond by producing antibodies in time that is nearly invariant with animal size. In this work we focus on another phase of the search process, specifically how T-cells which have recognized pathogens within the LN can rapidly find and neutralize infected cells in tissue with the help of inflammatory signals.

We focus on how T-cells flow between the the LN and lung through the cardiovascular system and peripheral tissue, and how that flow facilitates rapid neutralization of influenza virus in the lung. We do not attempt to model the

entire immune system; nor do we consider how immune response differs for different pathogens. Instead we attempt to characterize a particular component of immune response to a particular pathogen in a particular organ. However the principles that guide search are relevant more broadly.

The immune response against influenza virus combines a local innate response (interferon production and cell recruitment) with the rapid development of cell mediated immunity. We focus here on the response of cytotoxic T lymphocytes (CTLs) because it has been clearly shown that recovery from influenza pneumonia requires neutralization of infected cells by CTLs [9].

CTLs are activated within the infected site LN and are released into the bloodstream. CTLs are delivered to the human lung by a cardiovascular network with on the order of $2^{14}$ arterioles which enter a large capillary network between the lung airspaces [16]. Capillaries in infected regions of the lung are permeated by an inflammatory signal which causes CTLs to exit the capillary and enter the lung tissue where a chemokine gradient guides the CTL to infected cells. When CTLs recognize the antigen displayed on the surface of infected cells, they neutralize those cells. The information represented by the inflammatory signals is local, and occurs in an initially small region of the lung surface, possibly as small as 1 in $2^{14}$ capillaries. We ask how much the local inflammatory signal reduces the time for CTLs to find the site of infection and eradicate the influenza pathogen.

If there were no inflammatory signal to inform lymphocytes circulating through capillaries that they had reached an area of inflammation and infection, then the search for infected tissue becomes a problem of search by random walking. Without any signal to indicate which capillaries are near infected tissue, a CTL would have to exit whatever capillary it was in and begin to crawl through the lung tissue to search for chemokines (other signals released near infected cells) or infected cells themselves. As we show below, this would require a long search because T-cells move at rates measured in microns per minute, and the surface area of a human lung is measured in roughly one hundred square meters. In this paper we examine how a simple highly localized inflammatory signal in capillaries in infected regions reduces the time for CTLs to find and eradicate influenza in the lung.

We use an ordinary differential equation (ODE) model and an agent based model (ABM) to quantify the value of the inflammatory signal in terms of reducing the time for CTLs to reach an influenza infected site in the lung, reducing the time to eradicate influenza from the lung, and reducing the number of CTLs that must be produced in order to clear influenza. The ABM has the advantage of being able to incorporate the spatial aspect of virus spread and CTL mediated killing of infected cells while the ODE model has the advantage of being able to scale up to billions of cells, for example in the human lung. First, we model an immune response without inflammatory signals in which CTLs exit in tissue at the first capillary they encounter and search by walking randomly through the lung until they find a chemokine gradient that then guides CTLs to infected cells. Second we model an immune response with inflammatory signals in which CTLs

exit into tissue only when the capillary has an inflammatory signal, and CTLs in capillaries without inflammatory signals recirculate through the cardiovascular network until they do end up in inflamed capillaries.

We suggest that localized signals like the inflammatory signal are enormously important to immune functionality. Here we take a first step toward quantifying the value of that signal in terms of time required to get T cells to sites of infection. This has important consequences for understanding the role of information signals in the NIS, and also the role that local information signals can play in other complex biological systems [12, 13] and in artificial immune systems where decentralized search requires effective use of local signals to solve computational problems [2, 3].

The rest of the paper is organized as follows: we review relevant features of the NIS, outline our hypothesis, and introduce our model. We first introduce the ODE model, and compare predictions to empirical data. We then use an ABM to verify some of the ODE predictions and produce more realisitic spatially explicit simulations that include spread of the pathogen during the CTL search. We conclude by quantifying how much inflammatory signals improve immune response in these models.

## 2 A Review of the Relevant Immunology

This study characterizes how a key type of adaptive immune cell (cytotoxic T lymphocytes, also called $CD8^+$ T cells or CTL) [6] searches for and neutralizes a common respiratory tract pathogen (influenza) in the principle target organ, the lung. Among the many immune cells and molecules involved in providing defense against influenza [15], there is a complex set of interactions to guide CTLs to the site of infection and to produce chemokines and other information signals to help contain the infection. We outline the role of only a few of these control pathways here. Influenza virus is inhaled and establishes infection in epithelial cells lining the airways and the air sacs (alveoli) of the lung. Epithelial cells provide the first line of innate defense through activation of interferon, and different strains express different replication efficiencies within the epithelial cells [10]. Epithelial cells also secrete chemokines to attract immigrant inflammatory cells such as macrophages capable of amplifying the chemokine signals [11]. Inflammation increases local blood flow to the infected region and amplifies the chemokine signal. To initiate the adaptive immune response, resident lung dendritic cells capture virus and carry it to the draining lymph nodes (LN) in the mediastinum and bronchus-associated lymphoid tissue (BALT) [7]. LNs provide a dense tissue in which T and B lymphocytes and antigen-loaded dendritic cells encounter each other efficiently. Antigen-specific CTLs are activated within the LN, undergo cell division, and leave the LN to enter the blood circulation. CTLs activated in BALT have a predilection to home to lung.

The cardiovascular network in the lung follows the fractal branching of the airways that bifurcate in a precise fashion 14 times in the human lung [16]. The arterioles nourishing the airway tissue also branch 14 times, ending in a deep cap-

illary network nourishing the airsacs (alveoli) of the lung. Entering the capillary network, the CTL has two outcomes, either encountering inflammation (very low probability early in infection) or most likely encountering un-inflamed capillaries. When an activated CTL reaches an un-inflamed capillary, it may wander short distances through the capillary network until it encounters a chemokine signal, or leave the network before any signal is encountered and recirculate in blood. When an activated CTL reaches an inflamed capillary within a chemokine gradient, however, its movement along the capillary endothelial wall is arrested and it exits the capillary into lung interstitial tissue. Climbing the chemokine gradient, the CTL locates the infected epithelial cells and reduces viral replication by multiple mechanisms. The chemotactic signals are composed of cytokines, chemokines and antigen. In this work we consider only one chemotactic signal which subsumes all its components.

## 3 Goals and Hypotheses

Inflammatory signals and chemotactic gradients are examples of signals which serve to guide search processes in the NIS. We hypothesize that these, and other, information signals enable the NIS cells to find and neutralize pathogens more quickly than in the absence of such signals. We hypothesize that inflammation in the capillaries that signals to CTLs that they have reached a site of infection greatly reduces the time for CTLs to find infected tissue and eradicate infection. We aim to quantify the value of information which serves as an exit signal for activated CTLs.

We model an adaptive immune response without inflammatory signals (CTLs walking randomly through lung tissue) and an adaptive immune response with inflammatory signals (CTLs recirculating through the circulatory network until the presence of inflammation signals them to exit). We model how fast the first CTL finds the infected region, how fast CTLs build up their numbers in infected tissue, and how many cells are infected in a specified time period in models with and without inflammatory signals. We quantify the value of the information signal as the ratio of these measures with the signal to the measures without the signal. We use an ODE to determine the value of the inflammatory signal in mice and humans that are vastly different sizes, and we use the ABM to incorporate spatial dynamics and growing infections.

## 4 Ordinary Differential Equation Model

We use an ODE model to analyze how quickly CTLs arrive a the site of infection with and without an inflamation signal. We model the region of infection as a circular region (region $A$) of infected tissue (expressing chemokines, inflammatory signals and antigen) of radius $r$. This region is surrounded by a region of uninfected tissue (a concentric circle of radius $R$ (region $B$)) without inflammation or chemokines. We assume that the $2^{14}$ capillaries are distributed evenly throughout the entire lung (region $A$ and $B$) (Fig. 1).

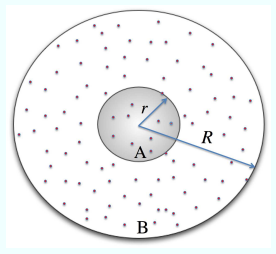


**Fig. 1.** A region of infected tissue of radius $r$ (shaded region $A$) expressing chemokines and inflammatory signals. This region is surrounded by region $B$ which does not have any infected cells and hence does not express either chemokines or inflammatory signals. The $2^{14}$ capillaries (red circles) are distributed evenly throughout the entire lung (region $A$ and $B$).

We assume that chemotactic signals only permeate the inside of region $A$ and do not reach region $B$. Hence any activated CTL that happen to flow to capillaries in region $A$ will have both an inflammatory signal that causes the CTL to exit the capillary, and surrounding the capillary there will be a chemokine gradient that will further direct CTLs to infected cells. In contrast, CTLs that arrive in the lung via capillaries in region $B$ will have no inflammatory signal and no chemokines to guide it to infected cells in region $A$. We assume that CTLs that exit into tissue do not back into circulation and ignore CTL death.

In the ODE model we ignore viral replication and just investigate the time taken for activated CTLs to reach the initial site of infection. We also ignore CTLs walking inside capillaries. We allow the infected region to grow over time in our ABM. The ODE model has the advantage of being fast and scalable up to billions of cells. It can also yield, in some cases, analytical results for biologically relevant parameters like the time to reach a steady state. The dynamics of the system are represented by three coupled ODEs. We parameterize the ODEs to consider two cases. In the first case, CTLs search for virus only via a random walk without an inflammation signal. In the second case CTLs receive an inflammation signal in capillaries in region $A$, exit and follow the chemotactic gradient or if they are in region $B$ which has no inflammation signal, the cells recirculate through the cardiovascular network until they find an inflamed capillary in region $A$.

### 4.1 Model 1: Dynamics with only Randomly Walking CTLs

We first model an immune response without inflammatory signals. In this scenario activated CTLs immediately exit into tissue as soon as they reach a capillary. There is no signal to inform CTLs in capillaries that they are in an infected region and hence they immediately exit into tissue. We assume that the infected site LN produces $\sigma$ activated CTLs per hour, the initial infection is in a region of radius $r$ and that the total lung area is described by a circle of radius $R$.

We assume that $r$ remains constant with time. The the time taken for CTLs to recirculate in blood is denoted by $t_{rc}$. We also assume that the infection is not growing with time ($r$ remains the same always). The system is represented by the following differential equations -

$$\frac{dN_c}{dt} = \sigma - \frac{N_c}{t_{rc}} \tag{1}$$

$$\frac{dN_w}{dt} = \frac{(R^2 - r^2) \cdot N_c}{R^2 \cdot t_{rc}} - \frac{D \cdot t_{rc} \cdot N_w}{\pi((2/3(R-r)+r)^2 - r^2)} \tag{2}$$

$$\frac{dN_f}{dt} = \frac{r^2 \cdot N_c}{R^2 \cdot t_{rc}} + \frac{D \cdot t_{rc} \cdot N_w}{\pi((2/3(R-r)+r)^2 - r^2)} \tag{3}$$

Equation (1) describes the change in the number of recirculating activated CTLs in the cardiovascular system ($N_c$) due to the rate of production of new CTLs in the LN ($\sigma$), and CTLs that exit capillaries and enter tissue regardless of a signal to search using a random walk. Since the "time step" in this setting is the minimum time taken for CTLs to complete one circuit through the arterial and venous circulation system (the recirculation time $t_{rc}$) and is different from the simulation time step ($dt$), we adjust by dividing all rate constants by $t_{rc}$.

Equation (2) describes the change in the number of CTLs ($N_w$) that are in tissue and searching for infected cells by executing a random walk. The change in $N_w$ is due to rate at which CTLs exit into region $B$ from circulation (a fraction of $\frac{N_c}{t_{rc}}$) and a rate at which CTLs leave the pool of walking CTLs and find region $A$. The fraction of circulating CTLs that enter capillaries in region $B$ is given by the relative area of region $B$ ($\frac{R^2-r^2}{R^2}$). The number of CTLs that find region $A$ at each time step is calculated as follows: an average CTL in region $B$ will be at a distance 2/3 from the periphery of region $A$ (obtained by integrating over all CTLs at each distance in region $B$). The mean area that this CTL will cover before reaching region $A$ is given by the quantity $\pi((2/3(R-r)+r)^2-r^2)$, and the mean time in which this area is covered is this quantity divided by the diffusion constant for random walk ($D$), again adjusted for the recirculation time. The reciprocal of this time gives the rate at which a single CTL enters region $A$. To complete the analysis we multiply this quantity by the number of randomly walking CTLs. Finally, Equation (3) describes the change in the number of CTLs ($N_f$) that have found infected cells (in region $A$), and this is composed of the loss term from the pool of randomly walking CTLs from Equation (2) and the fraction of the recirculating CTLs that enter capillaries in region $A$ (represented by the area of region $A$ relative to the total lung area).

In order to numerically integrate Equations (1)-(3) we first estimate the diffusion speed. Since we are not aware of any published values of diffusion speeds of activated CTLs within tissue, we used measured mean square displacements of T cells within the LN from literature [4]. Following Beauchemin et al. [4], the equation relating mean square displacement of a random walking particle in two dimensions at time $t$ is given by $\mid m \mid = \sqrt{4Dt}\frac{\Gamma(\frac{3}{2})}{\Gamma(\frac{1}{2})}$ where $\mid m \mid$ is the mean

square displacement, $D$ is the diffusion constant and $\Gamma$ is the gamma function. Analyzing data on mean square displacement from [4] we found that the diffusion constant ($D$) was approximately $56(\mu m)^2$ / hour.

We assume that the infected site LN in mice produces 2900 activated CTLs per hour (calculated from experimental data and detailed in the next section) and the time to recirculate ($t_{rc}$) is 6 seconds [14]. The initial infection is in a region of radius ($r$) 1 mm (personal observation for seasonal strains in mice) and that the total lung area is described by a circle of radius ($R$) 10 cm. The latter number comes from a lung area of approximately $100m^2$ in humans [5] scaled down 10000 times for mice.

We observe that the number of circulating CTLs reaches a steady state at approximately 50 activated CTLs. So few CTLs are in circulation because they exit the LN, spend only 6 seconds in blood, and go immediately to search in the lung. We numerically simulated the ODE system and found that the time for the first randomly walking CTL to reach the site of infection (region $A$) is approximately 4 hours post activation in the LN (Fig. 2, Panel A). Approximately 40 CTLs find the infected region at day 5 post activation.

The ODE model has the advantage of being able to scale up and produce predictions for even larger organisms. Scaling up to a human which is approximately 10,000 times larger than mice, we see that $R$ is 10 meters, $r$ remains the same, the CTL recirculation time ($t_{rc}$) increases to 6 seconds since recirculation times scale as $M^{1/4}$ where $M$ is the mass of the animal [18]. Lastly, we expect the LN output rate ($\sigma$) to scale as $M^{3/7}$ since LNs in larger animals are expected to be larger and have more high endothelial venules to release activated CTLs at a faster rate [3]. The calculation yields a value of $\sigma$ of approximately $10^7$ CTLs per hour and numerically simulating the ODE system we see that the predicted time for a CTL to find an infected cell in a human lung is approximately 28 days, which is much longer than the time taken to resolve influenza infections (approximately 10 days) [9].

### 4.2 Model 2: Dynamics with only CTL Recirculation and no Randomly Walking CTLs

Here we model an immune response with inflammatory signals. CTLs only recirculate and exit into tissue only when there is an inflammatory signal, i.e. CTLs never exit into tissue if there is no inflammatory signal. All the other parameters are exactly the same as in the last case. The system is represented by the following differential equations -

$$\frac{dN_c}{dt} = \sigma - \frac{r^2 \cdot N_c}{R^2 \cdot t_{rc}} \tag{4}$$

$$\frac{dN_f}{dt} = \frac{r^2 \cdot N_c}{R^2 \cdot t_{rc}} \tag{5}$$

Equation (4) describes the change in the number of recirculating activated CTLs in the cardiovascular system ($N_c$) due to the rate of production of new

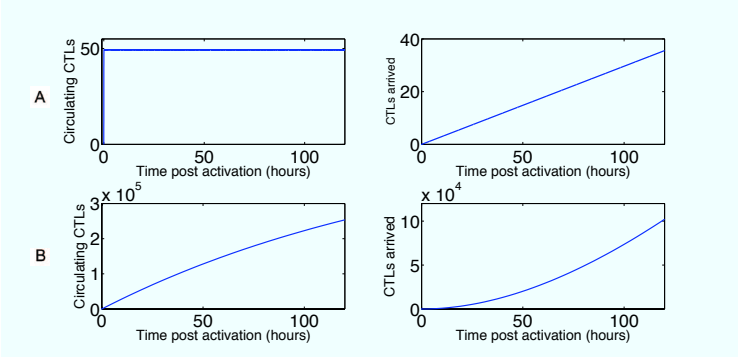


**Fig. 2.** Panel A: Plot of the number of recirculating CTLs ($N_c$) and CTLs that have found infected cells ($N_f$) vs. time post activation of the first CTL in LN for CTLs only walking randomly (Model 1). The number of recirculating CTLs reaches a steady state because once they enter the lung they never recirculate. Panel B: Plot of $N_c$ and $N_f$ vs. time post activation for CTLs recirculating (Model 2 fit to experimental data).

CTLs in the LN ($\sigma$), and CTLs that exit capillaries expressing inflammatory signals and enter infected tissue (region $A$). The latter quantity is a fraction of all the recirculating CTLs ($N_c$) where the fraction is the relative area represented by region $A$ ($\frac{r^2}{R^2}$). Since the "time step" in this setting is the time taken for CTLs to complete one circuit (the recirculation time $t_{rc}$) and is different from the simulation time step ($dt$), we adjust by dividing all rate constants by $t_{rc}$. Equation (5) describes the change in the number of CTLs which find infected cells and this is just composed of the loss term from the pool of recirculating CTLs from Equation (4).

We fit Model 2 (with an inflammatory signal) to experimental numbers of CTLs in lung at various time points post infection for influenza in mice [9]. We fit our ODE Model 2 to this dataset until the peak of CTL activation and do not consider the dynamics causing the decline of CTLs after the infection is cleared.

The ordinary differential equations describing Model 2 (Equations 4 and 5) were solved numerically using Berkeley Madonna [8]. The Runge-Kutta 4 method of integration was employed with a step size of 0.0004. The "curve fitter" option in Berkeley Madonna was used to establish the best-fit parameter estimates. The curve-fitting method uses nonlinear least-squares regression that minimizes the sum of the squared residuals between the experimental and predicted values of $N_f$. We weighed all the data points equally in our fitting procedure.

For Model 2, we fixed $r$ to 1 mm, $R$ to 10 cm, the recirculation time ($t_{rc}$) to 6 seconds and estimated the LN rate of output of CTLs ($\sigma$). The best fit parameter estimate of $\sigma$ was approximately 2900 activated CTLs per hour. The Model 2 output thus parameterized is shown in Fig. 2 Panel B (a list of all ODE model parameters is given in Table 1). However Model 1 (CTLs only walking randomly) cannot fit the empirical data since it predicts that the number of

CTLs that find infected cells should increase linearly whereas the empirical data shows a quadratic increase.

Numerically simulating the ODE system, we estimated the time taken for the first CTL to reach infected tissue to be approximately 30 minutes (Fig. 2 Panel B). Approximately $10^5$ CTLs find the infected region at day 5 post activation. Finally the ODE Model 2 can produce predictions for CTL search times in human lung. We used the same values as in the previous section ($R = 10$ meters, $t_{rc} =$ 1 minute and $\sigma = 10^7$ CTLs per hour) and numerically simulated the ODE system. The predicted time for an activated CTL to first find an infected cell in a human lung is approximately 5 hours.

In summary, the presence of an inflammatory signal and a chemokine gradient around infected cells results in faster trafficking of activated CTLs to sites of infection (5 hours compared to 28 days without an inflammatory signal in humans and 30 minutes compared to 4 hours without an inflammatory signal in mice for first detection of infected cells by CTLs).

**Table 1.** The parameters used in the ODE and ABM with a short description of their role and default value ($^{\S}$ measured in human cell lines)

| Description | Value | Source |
|---|---|---|
| Release rate of activated CTLs ($\sigma$) | $2900/h$ | Fit to data in [9] |
| CTL recirculation time ($t_{rc}$) | $6\ s$ | [14] |
| CTL diffusion coefficient ($D$) | $56(\mu m)^2/h$ | Calculated from [4] |
| Radius of lung area ($R$) | $10cm$ | Calculated from [5] and scaled down to mice |
| Radius of circle lung infected area ($r$) | $0.1cm$ | Personal observation |
| Length of cubic ABM simulation compartment | $2000\mu m$ | - |
| Time between infection and secretion $^{\S}$ | $10.5h$ | [10] |
| Duration of productive infection $^{\S}$ | $17.15h$ | [10] |
| ABM virus secretion rate $^{\S}$ | $2.6\ virions/h$ | [10] |
| ABM CTL sensing radius | $10\mu m$ | Model parameter |
| ABM Epithelial cell diameter | $10\mu m$ | Model parameter |
| ABM CTL diameter | $4\mu m$ | Model parameter |

## 5 Agent Based Model

We use a spatially explicit ABM in order to explore the spatial and stochastic effects of CTL migration and recirculation, and incorporate CTL mediated killing of infected cells. We use the CyCells [17] modeling tool to explicitly represent healthy cells, infected cells, T-cells and influenza virions, and we represent cytokines and chemokines as concentrations. We model the release of virions from

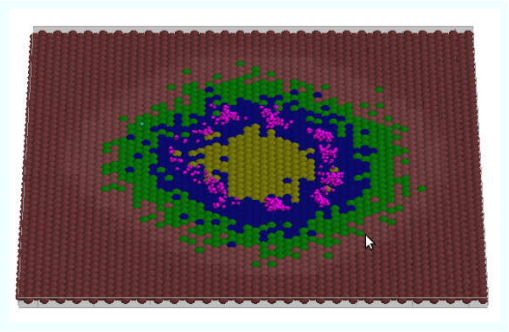

**Fig. 3.** A snapshot of the CyCells ABM in action. The epithelial cell layer is made up of healthy cells (dark red), infected incubating cells (green), virus expressing cells (blue), and dead cells (yellow). The area of lighter red surrounding the infection shows that free virus particles (semi-transparent white) are present. T-cells (pink) are seen swarming over locations with high virus concentration.

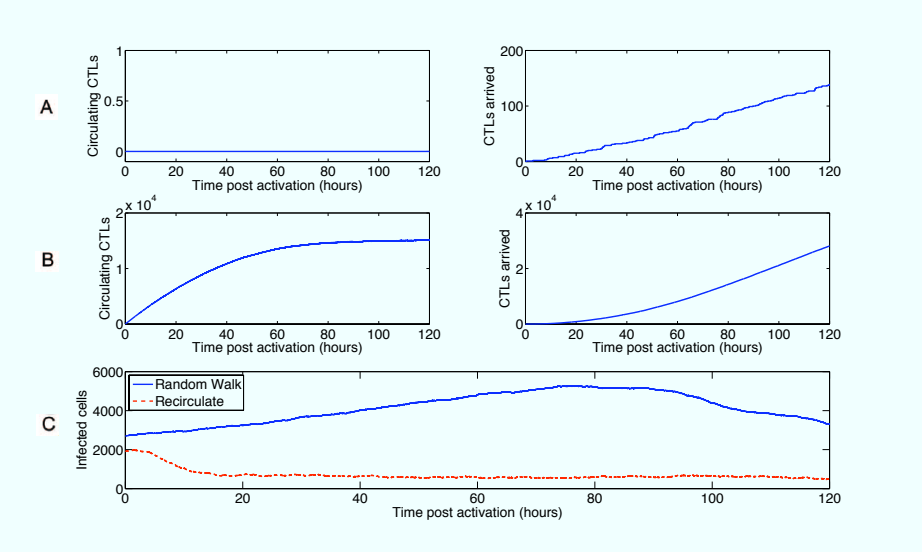


**Fig. 4.** Panel A: Plot of the number of recirculating CTLs ($N_c$) and CTLs that have found infected cells ($N_f$) vs. time post activation for CTLs only walking randomly (Model 1) in the ABM. Panel B: Plot of $N_c$ and $N_f$ vs. time for CTLs only recirculating (Model 2) in the ABM. Panel C: Plot of the number of infected cells over time for Model 1 and Model 2 in the ABM.

infected cells, the diffusion of chemokines and inflamatory signals and chemotaxis of cells towards a chemokine gradient. A snapshot of the environment is shown in Fig. 3.

### 5.1 Model 1: Dynamics with Randomly Walking CTLs

We start by modelling a $2mm$ by $2mm$ grid with a single infected cell in the middle. CTLs enter the grid at a rate that accounts for the size of the grid and the rate that CTL exit the LN, $\sigma = 2900/hour$. Infected cells produce virions which then infect healthy cells. Virus infected cells were differentiated into two populations: infected cells that are incubating but not secreting virus, and expressing cells which are actively producing new virions. The parameters describing the infection of healthy cells are taken from a previous study [10] in human cell lines (summarized in Table 1). Some parameters (labeled as Model parameter in Table 1) have been adjusted to yield reasonable infection sizes at day 5 post activation. Our primary results that compare system dynamics with and without inflammation signals do not depend on the these model parameters.

First we model a hypothetical immune response without inflammatory signals. The time taken for the first CTL to detect an infected cell is 3 minutes. The number of CTLs which find infected cells in the discrete event simulator is 138 at day 5 post activation (Fig. 4 Panel A). The ABM also allows us to calculate the number of cells that are infected which is 3308 at day 5 post activation.

### 5.2 Model 2: Dynamics with CTL Recirculation and no Randomly Walking CTLs

Here we model an immune response with inflammatory signals. We simulated an influenza infection in the same grid as ABM 1, but CTLs recirculate until they encounter an inflammation signal. We evaluate the value of the inflammatory signal by comparing the results of ABM 1 and ABM 2.

The time taken for the first CTL to find an infected cell is one hour and four minutes. This is longer than the three minutes in model 1, however this is due to 1 run of a highly stochastic event. Additional model runs are ongoing. The number of CTLs which find infected cells reaches 28,104. Finally, we observe that the number of infected cells remaining in the simulation is much lower for ABM 2 (500) compared to ABM 1(3300). Hence the value of the inflammation signal is a reduction in the number of infected cells at day 5 (from approximately 3300 without an inflammatory signal to approximately 500 with the signal).

## 6 Summary and Conclusions

In this study we used ODE and ABM to quantify how much inflammation in the capillary at the local site of infection decreases the time for the first CTL to reach the site of infection, increases the number of CTL that reach the site of infection by 5 days post activation, and decreases the number of infected cells at 5 days post activation. The ODE shows that the time for the first CTL to arrive in the infected region is approximately 8 times faster in mice, and 100 times faster in humans when the inflammatory signal is present. The ODE shows that the number of CTLs that reach the infected region by day 5 post activation is

**Table 2.** The value of inflammation in mice and humans for the ODE and ABM ([§] measured at 5 days post activation). [*] Based off of two high-variance parameters from a single model run.

| Mice | | Without Inflammation | With Inflammation | Benefit of Inflammation |
|---|---|---|---|---|
| Time to first detection | **ODE** | 4 h | 30 m | **8** |
| | **ABM** | 3m | 64m | **.0469** [*] |
| Arrived CTLs | **ODE** | 40 | $10^5$ | **2500** |
| | **ABM** | 138 | 28,104 | **204** |
| Infected cells | **ODE** | - | - | - |
| | **ABM** | 3308 | 499 | **6.63** |

| Humans | | Random Walk | Recirculate | Difference |
|---|---|---|---|---|
| Time to first detection | **ODE** | 28d | 5h | **134** |
| Arrived CTLs [§] | **ODE** | 0.2 | 600 | **3000** |
| Infected Cells [§] | **ODE** | - | - | - |

approximately 2500 times more in mice, and approximately 3000 times more in humans when the inflammatory signal is present. Finally, the ABM predicts that the number of infected cells at day 5 post activation is approximately 7 times lower in mice with an inflammatory signal.

The ODE model has the advantage of being computationally tractable, scalable to billions of cells, for example in humans, and yielding analytical solutions in this case. This simple model with inflammation and recirculation is able to replicate peak number of influenza specific CTL in the lung and the time to reach that peak from empirical data on mice. The ODE model is able to produce predictions for the time taken for CTLs to find infected cells in lung and the number of CTLs in lung at any given time post infection. We are then able to use the ODE to extrapolate from small laboratory mice to make predictions for humans.

We build an ABM incorporating the spatial aspects of virus spread and CTL mediated killing of infected cells. Our ABM shows that the predictions of the model in which CTLs walk randomly is in close agreement with the corresponding ODE model. The ABM shows that the time for the first CTL to arrive in the infected region in mice is approximately the same with or without a signal. The ABM also shows that the number of CTLs that reach the infected region by day 5 post activation is approximately 200 times more in mice with an inflammatory signal. In the model with an inflammatory signal (Model 2) the ABM predicts that a higher number of CTLs should find infected cells. This could be because of the interplay between a growing infected cell population and hence a higher amount of information to the immune system in form of inflammation, and CTLs killing infected cells and reducing the amount of information available to the immune system. The ABM predicts that the information in inflammation should allow CTLs to kill more infected cells and eradicate the virus faster than would have been possible without inflammatory signals and chemokines to direct CTLs. The value of the inflammatory signal is a reduction in the number of infected cells at day 5 (from approximately 4400 without an inflammatory signal to around 800 with the signal).

Together, these two models allow us to quantify the value of an information signal in biologically relevant terms. The local inflammation signal in the capillary allows search to be faster because it allows CTLs to recirculate when they arrive in capillaries in uninflamed regions of the lung. Because the lung surface area is so large, and CTL that have exited capillaries move so slowly relative to circulating CTL, this information signal drastically changes the ability of CTL to search the lung quickly. It allows CTL to effectively search the large surface area of the lung in the relatively fast flow of the blood circulatory system, and to exit only very near the site of infection.

By understanding the role of information signals in the immune system we can build models to estimate biologically relevant parameters, for example, in this case, the rate that LN produce activated CTL. More generally, this approach allows us to understand how immune systems form distributed information exchange networks to search, adapt and respond to infections. Without central control, the interactions among millions of communicating components enable immune systems to search and respond to complex, dynamic landscapes effectively. We hypothesize that ant colonies, immune systems and other complex biological systems use common informational strategies to allocate components effectively to tasks and direct their search in space [12]. This study shows that a local inflammation signal can quickly direct CTL to sites of infection.

Our approach is useful for developing decentralized search in Artificial Immune Systems [2, 3]. We anticipate that a quantitative characterization of information flow and its effect on performance will help in understanding why systems of different sizes and in different environments use different information, organizational structures and strategies to accomplish similar tasks.

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