Description of the *GranSim* Agent-Based Model

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1 Overall Structure of the ABM

The ABM was developed based on four considerations: (i) an environment, (ii) agents (immune cells and bacteria), (iii) ABM rules that govern the agents and their interactions, and (iv) the timestep (Δt) used to update events. The environment represents a two-dimensional section of lung parenchyma as a square lattice that is typically 200×200 compartments that simulates an area of 4mm $\times$ 4mm. Other size grids are also occasionally used to simulate larger or smaller granulomas. Each grid micro-compartment is thus scaled to the approximate size of a single human macrophage, 20µm $\times$ 20µm. Discrete agents (macrophages and T cells) are recruited from specific micro-compartments on the lattice that represent vascular sources. Cells move on the lattice and interact with each other and the environment based on the ABM rules that are defined based on known biological activities. Due to the size difference between macrophages and T cells, up to two T cells are permitted to enter the same micro-compartment (with probability P_{moveT}). A T cell may also move into the same micro-compartment as a macrophage (with probability P_{moveM}). This model of cell spacing is a compromise between a realistic spatial representation and computational tractability and is consistent with observations on macrophage and T cell dynamics during development of mycobacterial granulomas that show granuloma-associated T cells squeeze through cell junctions created by a dense macrophage network[6].

Soluble molecules, including chemokines (CCL2, CCL5 and CXCL9), cytokines (TNF-α, shed TNFR2, and IL-10), and antibiotics (if enabled) are simulated as continuous numbers that can reside in any square discretization on the lattice. Extracellular *Mtb* grow in each micro-compartment. Soluble molecules diffuse and degrade among micro-compartments. Caseation represents inflammation of and damage to the lung parenchyma from macrophage T cell death. In the ABM, caseation is defined to occur when a specific number (N_{caseum}) of infected or activated macrophages die, or if any cell dies due to TNF-induced apoptosis in a micro-compartment. When a micro-compartment becomes caseated, any immune cell present in the micro-compartment is killed and immune cells are not permitted to enter the micro-compartment. Macrophages can initiate healing of caseation, wherein the tissue is remodeled with an associated time.

The major types of discrete agents in the model are macrophages, T cells, and bacteria. Macrophages are either resting (M_{r}; uninfected), infected (M_{i}; have taken up *Mtb*), chronically infected (M_{ci}; are unable to clear their intracellular *Mtb* due to a high bacterial load), or activated (M_{a}; can effectively kill bacteria). Three distinct T cell classes, based on their functions, are modeled. The T_{γ} class represents CD4 and CD8 pro-inflammatory T cells; T_{c} class represents cytotoxic T cells (CTLs); and T_{r} class represents regulatory T cells including FOXP3+ and FOXP3- cells. Bacteria as agents can exist in three distinct subpopulations: intracellular (inside macrophages), replicating extracellular, or non-replicating extracellular.

Cell-cell interactions are governed by ABM rules that are updated within every agent timestep of $dt_{\mathrm{A}} = 10$min and will be discussed in the ABM rules section. Diffusion and degradation of soluble molecules on the lattice and secretion of chemokines/cytokines from individual cells occurs and is solved within each ABM timestep at a diffusion or molecular timestep, defined based on the relevant mechanisms modeled. TNF-α/TNFR and IL-10/IL-10R dynamics at the single-cell level are approximated (if enabled) using a tunable resolution approach at a timestep of $dt_{\mathrm{M}} = 6$s. Thus, each single-cell event is updated 10 times within each diffusion timestep while the diffusion, degradation, and secretion events are updated 10 times with each ABM timestep.

2 Grid Initialization

A two-dimensional grid is created (typically 4mm $\times$ 4mm). Periodic boundary conditions are used for cell movement, Dirichlet boundary conditions (zero outside grid perimeter) are used for chemokine/cytokine diffusion, and no-flux boundary conditions are used for antibiotics (if enabled). Vascular source locations are randomly distributed on the grid based on an approximate vascularization density estimated from non-human primate lungs. Initial resting macrophages, that represent resident alveolar macrophages, are randomly placed on the grid (M_{init}). One infected macrophage with one

intracellular *Mtb* is placed at the center of the grid. This is consistent with estimations of the minimum infection dose of *Mtb* that range from a single bacterium upward[8, 13].

3 Overview of ABM Rules

Cells move, become recruited to the site of infection, and respond to local conditions depending on their type and state according to rules that represent known biological activities *in vivo*. ABM rules that govern cell behaviors and interactions are as follows. Because chemokine single cell-level dynamics are not included in our model we discuss chemokine-related secretion and cellular recruitment in addition to cellular-scale immunological details of the ABM in this section. All immune cell agents may move anywhere in their Moore neighborhood, either by staying in place or moving to the 8 possible micro-compartments surrounding the cell's current location on the grid.

4 Agent Movement

4.1 Macrophages

Macrophages move to a new location on the grid based on CCL2 and CCL5 chemokine concentrations in their Moore neighborhood — the nine micro-compartments around the cell location including the micro-compartment occupied by the cell. Speed of movement only depends on the state of macrophages with the highest speed for M_{r} and the lowest speed (zero) for M_{ci}. The differences among macrophage speeds are shown in the model by time intervals during which each macrophage attempts to move (t_{moveMr}, t_{moveMi}, t_{moveMa}). There are minimum concentration thresholds and maximum saturating concentration thresholds (τ_{chem} and s_{chem}) for the effect of each chemokine on cell movement. Chemokine concentrations below τ_{chem} or above s_{chem} do not have any extra effect on direction of movement. For simplicity, we assume similar threshold values for all chemokines and cell types. Movement is random if chemokine concentrations in the Moore neighborhood are below τ_{chem} or above s_{chem}. Otherwise, CCL2 and CCL5 concentrations in the Moore neighborhood determine a linear probability distribution for movement. We assume a bias for macrophage movement to the micro-compartment with the highest chemokine concentration. Hence, the highest chemokine concentration in the Moore neighborhood is multiplied by a factor 1.5 before calculation of movement probabilities. Movement is blocked by a caseous micro-compartment or macrophage presence and, if blocked, no extra attempt for moving is made.

4.2 T cells

T cell movements are updated in time intervals of length t_{moveT} that is determined by the speed of T cell migration *in vivo*. Movement of T_{Υ} cells depends on CCL2, CCL5 and CXCL9/10/11 concentrations in the Moore neighborhood. T_{c} cells move based on CCL5 and CXCL9/10/11 concentrations and T_{r} cells move based on CCL5 concentrations. The details of T cell chemotactic movements are similar to macrophages as described above. T cell movement is blocked by caseation. However, T cell movement to a micro-compartment that contains one macrophage or one T cell is possible with reduced probabilities, P_{moveM} and P_{moveT}, respectively.

5 Cellular Recruitment

We recruit macrophages (M_{r}) and T cells (T_{Υ}, T_{c}, and T_{r}) from vascular sources randomly distributed across the lung environment. The recruitment rate at each vascular source is dependent upon the concentrations of CCL2, CCL5, CXCL9, and TNF-α in the specified micro-compartment[1, 19]. A time delay exists such that T cell recruitment rates increase linearly to the maximum rates over a specified interval as the adaptive immune response is not instantaneous[10]. Recruitment at a vascular source that contains one macrophage or one T cell is subject to the same rules as movement with recruitment probabilities reduced by P_{moveM} and P_{moveT}, respectively.

5.1 Macrophages

M_{r} are recruited every timestep from vascular sources based on available TNF-α and CCL2, and CCL5 concentrations at the specific vascular source, provided that the vascular source is not caseated nor blocked by a macrophage or two T cells.

The probability of recruitment of M_{r} is given by:

$$P_{\mathrm{Mr}} = M_{\mathrm{recMax}} \left[\frac{V_{\mathrm{max}}^{\mathrm{TNF}}([\mathrm{TNF}] - \tau_{\mathrm{recMacTNF}})}{([\mathrm{TNF}] - \tau_{\mathrm{recMacTNF}}) + h_{\mathrm{MacTNF}}} + \frac{V_{\mathrm{max}}^{\mathrm{CCL2}}([\mathrm{CCL2}] - \tau_{\mathrm{recMacCC}})}{([\mathrm{CCL2}] - \tau_{\mathrm{recMacCC}}) + h_{\mathrm{MacCC}}} + \frac{V_{\mathrm{max}}^{\mathrm{CCL5}}([\mathrm{CCL5}] - \tau_{\mathrm{recMacCC}})}{([\mathrm{CCL5}] - \tau_{\mathrm{recMacCC}}) + h_{\mathrm{MacCC}}} \right] \tag{1}$$

Along with the recruitment function, the following threshold conditions must be met:

$$\begin{aligned} [\mathrm{TNF}] &> \tau_{\mathrm{recMacTNF}} \| \\ [\mathrm{CCL2}] &> \tau_{\mathrm{recMacCC}} \| \\ [\mathrm{CCL5}] &> \tau_{\mathrm{recMacCC}} \end{aligned} \tag{2}$$

5.2 T cells

Note

T cell recruitment rules for the 3-compartmental model submitted in the manuscript "Computational and empirical studies predict *Mycobacterium tuberculosis*-specific T cells as a biomarker for infection outcome" are given in the Supplementary Materials section S2. However, the threshold conditions outlined below for enabling a vascular source for T cell recruitment are always enforced.

Recruitment of T cells begins after a threshold of number of *Mtb* (N_{MtbTcell}) is reached that represents the time required for activation of the adaptive immune response following *Mtb* infection. T_{γ} are recruited every timestep from vascular sources based on available TNF-α, CCL2, CCL5, and CXCL9/10/11 (written as only CXCL9 from here forth) concentrations at the specific vascular source, provided that the vascular source is not caseated nor blocked by a macrophage or two T cells. The probability of recruitment of T_{γ} is given by:

$$P_{\mathrm{T}\gamma} = T_{\mathrm{recTgamMax}} \left[\frac{V_{\mathrm{max}}^{\mathrm{TNF}}([\mathrm{TNF}] - \tau_{\mathrm{recTgamTNF}})}{([\mathrm{TNF}] - \tau_{\mathrm{recTgamTNF}}) + h_{\mathrm{TgamTNF}}} + \frac{V_{\mathrm{max}}^{\mathrm{CCL2}}([\mathrm{CCL2}] - \tau_{\mathrm{recTgamCC}})}{([\mathrm{CCL2}] - \tau_{\mathrm{recTgamCC}}) + h_{\mathrm{TgamCC}}} + \frac{V_{\mathrm{max}}^{\mathrm{CCL5}}([\mathrm{CCL5}] - \tau_{\mathrm{recTgamCC}})}{([\mathrm{CCL5}] - \tau_{\mathrm{recTgamCC}}) + h_{\mathrm{TgamCC}}} + \frac{V_{\mathrm{max}}^{CXCL9}([\mathrm{CXCL9}] - \tau_{\mathrm{recTgamCC}})}{([\mathrm{CCL5}] - \tau_{\mathrm{recTgamCC}}) + h_{\mathrm{TgamCC}}} \right] \tag{3}$$

Along with the recruitment function the following threshold conditions must be met (this condition determines if a vascular source is enabled for recruitment of a specific T cell phenotype):

$$\begin{aligned} [\mathrm{TNF}] &> \tau_{\mathrm{recMacTNF}} \| \\ [\mathrm{CCL2}] &> \tau_{\mathrm{recMacCC}} \| \\ [\mathrm{CCL5}] &> \tau_{\mathrm{recMacCC}} \| \\ [\mathrm{CXCL9}] &> \tau_{\mathrm{recMacCC}} \end{aligned} \tag{4}$$

T_{c} are recruited every timestep from vascular sources based on available TNF-α, CCL5, and CXCL9 concentrations at the specific vascular source, provided that the vascular source is not caseated nor blocked by a macrophage or two T cells.

The probability of recruitment of T_{c} is given by:

$$P_{\mathrm{Tc}} = T_{\mathrm{recTcytMax}} \left[\frac{V_{\max}^{\mathrm{TNF}}([\mathrm{TNF}] - \tau_{\mathrm{recTcytTNF}})}{([\mathrm{TNF}] - \tau_{\mathrm{recTcytTNF}}) + h_{\mathrm{TcytTNF}}} + \frac{V_{\max}^{\mathrm{CCL5}}([\mathrm{CCL5}] - \tau_{\mathrm{recTcytCC}})}{([\mathrm{CCL5}] - \tau_{\mathrm{recTcytCC}}) + h_{\mathrm{TcytCC}}} + \frac{V_{\max}^{\mathrm{CXCL9}}([\mathrm{CXCL9}] - \tau_{\mathrm{recTcytCC}})}{([\mathrm{CCL5}] - \tau_{\mathrm{recTcytCC}}) + h_{\mathrm{TcytCC}}} \right] \tag{5}$$

Along with the recruitment function, the following threshold conditions must be met:

$$\begin{aligned} [\mathrm{TNF}] &> \tau_{\mathrm{recMacTNF}} \| \\ [\mathrm{CCL5}] &> \tau_{\mathrm{recMacCC}} \| \\ [\mathrm{CXCL9}] &> \tau_{\mathrm{recMacCC}} \end{aligned} \tag{6}$$

T_{r} are recruited every timestep from vascular sources based on available TNF-α and CCL5 concentrations at the specific vascular source, provided that the vascular source is not caseated nor blocked by a macrophage or two T cells. The probability of recruitment of T_{r} is given by:

$$P_{\mathrm{Tr}} = T_{\mathrm{recTregMax}} \left[\frac{V_{\max}^{\mathrm{TNF}}([\mathrm{TNF}] - \tau_{\mathrm{recTregTNF}})}{([\mathrm{TNF}] - \tau_{\mathrm{recTregTNF}}) + h_{\mathrm{TregTNF}}} + \frac{V_{\max}^{\mathrm{CCL5}}([\mathrm{CCL5}] - \tau_{\mathrm{recTregCC}})}{([\mathrm{CCL5}] - \tau_{\mathrm{recTregCC}}) + h_{\mathrm{TregCC}}} \right] \tag{7}$$

Along with the recruitment function, the following threshold conditions must be met:

$$\begin{aligned} [\mathrm{TNF}] &> \tau_{\mathrm{recMacTNF}} \| \\ [\mathrm{CCL5}] &> \tau_{\mathrm{recMacCC}} \end{aligned} \tag{8}$$

6 Cell-Cell Interactions and State Transitions

All cell-cell interactions and state transitions described below are updated every ABM timestep for all cells.

6.1 Cell Death Due to Age

All macrophages that are initially distributed or recruited on the grid are assigned a lifespan selected from a uniform distribution between zero and $\max_{\mathrm{ageMac}}$. T cells are also assigned a lifespan randomly distributed between zero and $\max_{\mathrm{ageTcell}}$. M_{a} has a shortened lifespan of $\max_{\mathrm{ageActive}}$. At death, M_{r} and T cells are removed from the grid. At death, M_{i} and M_{ci} are removed from the grid and any intracellular *Mtb* (B_{int}) is dispersed uniformly in the Moore neighborhood as extracellular bacteria (B_{ext}). M_{a} death contributes to caseation of the micro-compartment.

6.2 Rules for resting macrophages (M_{r})

There is a chance of STAT-1 activation in a timestep as a result of interaction between a M_{r} and IFN-γ producing T_{γ} cells with a probability ($nT_{\gamma} \times PSTAT1$); where, nT_{γ} is the number of T_{γ} cells surrounding the M_{r} in the Moore neighborhood including the micro-compartment occupied by the M_{r}. M_{r} can become NF-ϰB activated through TNF-α induced processes based on the equations given in the Tunable Resolution section. NF-ϰB activation can also occur if the B_{ext} in the Moore neighborhood exceeds B_{actM}. STAT-1 and NF-ϰB activation last for the time interval t_{STAT1} and $t_{\mathrm{NF\varkappa B}}$ after which STAT-1 or NF-ϰB activation, respectively, is lost. M_{r} that are either STAT1 or NF-ϰB can be down-regulated by a T_{r} in which the M_{r} loses either STAT1 or NF-ϰB activation respectively. M_{r} is able to uptake or to kill B_{ext} that reside in the same micro-compartment. If the number of $B_{\mathrm{ext}} \leq N_{\mathrm{rk}}$, M_{r} kills them. Otherwise, it either kills N_{rk} of the B_{ext} with probability P_{k} or becomes infected (M_{i}) after uptake of N_{rk} of the B_{ext} as its initial B_{int}. M_{r} that are either STAT1 or NF-ϰB activated kill B_{ext} with a probability $2 \times P_{\mathrm{k}}$ due to increased antimicrobial capacity. If both STAT1 and NF-ϰB are activated in a M_{textr} and it is not already downregulated by a T_{r}, it becomes activated (M_{a}). Following T_{textr} downregulation, M_{r} does nothing but moves for a fixed period of time t_{regMac}. If the remaining lifespan of such an activated macrophage is greater than $\max_{\mathrm{ageActive}}$, it will be shortened to $\max_{\mathrm{ageActive}}$.

6.3 Rules for infected macrophages (M_{i})

B_{int} replicates in M_{i} every ABM timestep according to the following equation:

$$B_{\mathrm{int}}(t + \Delta t) = (1 + \alpha_{\mathrm{Bi}})B_{\mathrm{int}}(t) \tag{9}$$

M_{i} is able to uptake but not kill $B_{textext}$ from its micro-compartment with a probability (P_{uptakeMi}) that is computed as a function of B_{int} as follows:

$$P_{\mathrm{uptakeMi}} = \frac{N_{\mathrm{c}} - B_{\mathrm{int}}}{100} \tag{10}$$

M_{i} takes up N_{rk} of extracellular bacteria if $B_{\mathrm{ext}} > N_{\mathrm{rk}}$. Otherwise, it takes up all extracellular bacteria that are available in the micro-compartment. If the number of B_{int} exceeds a threshold N_{c}, the M_{i} becomes chronically infected (M_{ci}). There is a chance of STAT-1 activation in a timestep as a result of interaction between a M_{i} and IFN-γ producing T_{γ} cell with a probability ($nT_{textg} \times P_{\mathrm{STAT1}}$); where, nT_{γ} is the number of T_{γ} cells surrounding the M_{r} in the Moore neighborhood including the micro-compartment occupied by the M_{r}. M_{i} can become NF-$\varkappa$B activated based on the equations given in the Tunable Resolution section. NF-$\varkappa$B activation can also occur if the B_{ext} in the Moore neighborhood exceeds B_{actM}. STAT-1 and NF-$\varkappa$B activation last for the time interval t_{STAT1} and $t_{\mathrm{NF\varkappa B}}$ after which STAT-1 or NF-$\varkappa$B activation, respectively, is lost. M_{i} that are either STAT1 or NF-$\varkappa$B can be downregulated by a T_{r} in which the M_{i} loses either STAT1 or NF-$\varkappa$B activation respectively. Following T_{r} downregulation, M_{i} does nothing but moves for a fixed period of time t_{regMac}, but continues to secrete chemokines. If both STAT1 and NF-$\varkappa$B are activated in a M_{i} and it is not already down-regulated by a T_{r}, it becomes activated (M_{a}). If the remaining lifespan of such an activated macrophage is greater than $\mathrm{max}_{\mathrm{ageActive}}$, it will be shortened to $\mathrm{max}_{\mathrm{ageActive}}$.

6.4 Rules for chronically infected macrophages (M_{ci})

B_{int} replicates in M_{ci} every timestep according to eq. (9). If the B_{int} exceeds a threshold (N_{burst}), the M_{ci} bursts and its B_{int} are evenly distributed as whole numbers to the Moore neighborhood surrounding the M_{ci}. M_{ci} bursting contributes to caseation of the micro-compartment. M_{ci} are always NF-$\varkappa$B activated and cannot become STAT1 activated. M_{ci} cannot be down-regulated by a T_{r}.

6.5 Rules for activated macrophages (M_{a})

M_{a} is capable of effectively killing B_{ext}. Each timestep, M_{a} kills N_{ak} of the B_{ext} in its micro-compartment. M_{a} that transitions from M_{i} kill B_{int} at the same rate that it kills B_{ext} each timestep. M_{a} can be downregulated by a T_{r} in which the M_{a} loses both STAT1 and NF-$\varkappa$B activation. Following T_{r} downregulation, M_{a} does nothing but moves for a fixed period of time t_{regMac} and subsequently transitions back to M_{r} after its downregulated state. M_{a} have an associated probability of initiating a healing event. If the compartment is marked for healing, there is an associated time with the healing process. Once the time interval is passed, the compartment changes from caseated to non-caseated.

6.6 Rules for T cells

> **Note**
>
> By definition, the rules outlined below refer to *Mtb*-specific T cells. Specific T cell rules for T cell interactions and state transitions in the 3-compartmental model submitted in the manuscript "Computational and empirical studies predict *Mycobacterium tuberculosis*-specific T cells as a biomarker for infection outcome" are given in the Supplementary Materials section S2.

6.7 Rules for cytotoxic T cells (T_{c})

T_{c} are classified by the ability to secrete TNF-α based on a specified probability when it is born. If T_{c} is not already down-regulated by a T_{r} and there is a M_{i} or M_{ci} present in its Moore neighborhood there is a chance of perforin/granulysin-mediated killing of M_{i} or M_{ci} with probability P_{cytKill}. If there are more than one M_{i} or M_{ci} in the Moore neighborhood one is chosen at random and the chance of perforin/granulysin-mediated killing of M_{i} or M_{ci} is given by the probability P_{cytKill}. M_{i} killing by a T_{c} kills all B_{int} and contributes to caseation of the micro-compartment. In the case of M_{ci} killing, the B_{int} are killed with probability $P_{\mathrm{cytKillClean}}$. Otherwise, half of the B_{int} will be uniformly distributed in the Moore neighborhood. M_{ci} killing by T_{c} also contributes to caseation of the micro-compartment. When downregulated, T_{c} cells lose their cytotoxic capabilities for a fixed period of time t_{regTcyt}.

6.8 Rules for pro-inflammatory T cells (T_γ)

T_γ are classified by the ability to secrete IFN-γ (and activate STAT1) and TNF-α based on specified probabilities when it is born. If T_γ is not already downregulated by a T_r and there is a M_i or M_{ci} present in its Moore neighborhood there is a chance of Fas/FasL-induced apoptosis of M_i or M_{ci} with probability $P_{apop/Fas}$. If there are more than one M_i or M_{ci} in the Moore neighborhood one is chosen at random and the chance of Fas/FasL-induced apoptosis of M_i or M_{ci} is given by the probability $P_{apop/Fas}$. As a result of apoptosis, half of the B_{int} in M_i or M_{ci} will be killed and the other half will be equally distributed in the Moore neighborhood as B_{ext}. When downregulated, T_γ cells lose their apoptotic capabilities for a fixed period of time, $t_{regTgam}$.

6.9 Rules for regulatory T cells (T_r)

T_r suppresses or downregulates the action of T cells and macrophages through non-interleukin-10 mechanisms (CTLA-4, TGF-β, etc.), which are still poorly understood[15, 16, 17]. Thus, the probability of alternative suppressive functions of T_r occurring is linearly dependent upon the following ratio in eq. (11), which coarsely simulates the mechanisms of other regulatory mechanisms. T_r have a baseline deactivation capacity, thus when IL-10 production is deleted from regulatory T cells, the deactivation capacity is upregulated by a specified factor.

$$\text{Bound Ratio} = \frac{[\text{TNF}] \cdot [\text{TNFR1}]}{[\text{TNF}] \cdot [\text{TNFR1}] + [\text{IL10}] \cdot [\text{IL10R}]} \tag{11}$$

T_r here down-regulates all cells (macrophages, T_c and T_γ) in its Moore neighborhood. Downregulated states last for t_{regMac}, $t_{regTgam}$ and $t_{regTcyt}$ for macrophages, T_c and T_γ cells, respectively. T_r downregulation for each cell type is explained in sections that describe ABM rules for that specific cell type.

7 Extracellular *Mtb* Growth (B_{ext})

Growth of extracellular *Mtb* (B_{ext}) in all micro-compartments is calculated based on the following equation:

$$B_{ext}(t + \Delta t) = B_{ext}(t) + B_{ext}(t)\left[1 - \frac{B_{ext}(t)}{1.1K_{be}}\right] \tag{12}$$

8 Non-Replicating Extracellular *Mtb*

Non-replicating *Mtb* trapped in caseated compartments in the Moore neighborhood of an M_a can be killed at a reduced rate of activated macrophage killing ($1/10^{th}$).

9 Chemokine Secretion

M_i, M_{ci}, M_a, NF-κB activated M_r, and NF-κB activated M_i are able to secrete chemokines, provided that they are not downregulated by T_r. The rates of chemokine secretion for different cell types are as follows. !M_{ci}, M_a and NF-κB activated M_i are able to secrete chemokines with full secretion rates (r_{CCL2}, r_{CCL5}, and r_{CXCL9}) as listed in Table S3 in Appendix S3. NF-κB activated M_r and M_i cells that are not NF-κB activated secrete chemokines with half-full secretion rates ($0.5 \times r_{CCL2}$, $0.5 \times r_{CCL5}$, and $0.5 \times r_{CXCL9}$). Caseated microcompartments also secrete attractants that attract immune cells. For simplicity, we use quarter-full rates of chemokine secretion to simulate the effect of such attractants ($0.25 \times r_{CCL2}$, $0.25 \times r_{CCL5}$, and $0.25 \times r_{CXCL9}$). Chemokine secretions to the microcompartments on the grid are updated in time intervals of dt_D. Secretion of TNF and IL-10 is discussed in the Tunable Resolution section.

10 Diffusion of Soluble Molecules

The two-dimensional partial differential equation (PDE), for diffusion of chemokines, cytokines, and antibiotics, is given by the following equation.

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2}\right) \tag{13}$$

C is the concentration of diffusing molecule that changes with time t in the x and y directions and D is the diffusion coefficient for the molecule in the tissue environment. This equation can be implemented numerically on the grid by using Spectral Methods. Spectral methods for solving PDEs are a class of collocation methods that analyze the discretized system in a global instead of a local manner[4, 5, 9, 14, 18]. The solution to the entire system is assumed by a basis function and time-varying coefficients are determined such that the solution to the system is satisfied. Importantly, spectral methods reduce PDEs into ODEs thus drastically reducing the computational burden of the numerical approximation[14]. For an in depth explanation please refer to Mugler and Scott [14]. We adapt the basic method for our needs to allow insulating boundary conditions and apply simple smoothing pre-processing steps to limit errors associated with discontinuous concentration fields[2, 11].

11 Tunable Resolution

Previous versions of *GranSim* were focused on understanding the roles of cytokine dynamics (TNF and IL-10) at a molecular scale and how receptor-ligand trafficking events (modeled as a system of non-linear differential equations) influenced infection outcomes[3, 7]. Our focus is to understand the treatment of TB using antibiotics at a single granuloma level. Thus, we apply the concept of tunable resolution to our model in order to retain our understanding of the roles of TNF and IL-10 during infection, yet reducing model complexity and computational burden in order to focus on a detailed description of antibiotic treatment[12]. Briefly, the system of non-linear ordinary differential equations in Cilfone et al. [3] is replaced with the following equations describing the change in soluble TNF and soluble IL-10 concentrations in a compartment containing an agent:

$$\frac{d[\text{sTNF}]}{dt} = k'_{\text{sTNF}} - k_{\text{cTNF}} \left(\frac{[\text{sTNF}]}{K_{\text{DT1}} \frac{N_{\text{AV}}}{V} + [\text{sTNF}]} - \frac{[\text{sTNF}]}{K_{\text{DT2}} \frac{N_{\text{AV}}}{V} + [\text{sTNF}]} - \right) \tag{14}$$

$$\frac{d[\text{sIL10}]}{dt} = k'_{\text{sIL10}} - k_{\text{cIL10}} \left(\frac{[\text{sIL10}]}{K_{DI} \frac{N_{\text{AV}}}{V} [\text{sIL10}]} \right) \tag{15}$$

Where k'_{sTNF} and k'_{sIL10} are the apparent secretion rates of TNF and IL-10, k_{cTNF} and k_{cIL10} are the apparent rate constants for consumption (which incorporate estimates for total receptors and any scaling factors for both TNF and IL-10), and K_{DT1}, K_{DT2}, and K_{DI} are affinities for TNFR1, TNFR2, and IL-10R respectively. Each quotient represents the bound fraction of surface receptors assuming a pseudo-steady state.

Additionally, we re-write any probability functions that relied on molecular scale details in terms of soluble TNF and IL-10 concentrations:

$$P_{\text{NF}\varkappa\text{B}} = \begin{cases} 0 & \dfrac{[\text{sTNF}]}{K_{\text{DT1}} \frac{N_{\text{AV}}}{V} + [\text{sTNF}]} < \tau'_{\text{NF}\varkappa\text{B}} \\ 1 - \exp\left(-k'_{\text{NF}\varkappa\text{B}} \left(\dfrac{[\text{sTNF}]}{K_{\text{DT1}} \frac{N_{\text{AV}}}{V}} - \tau'_{\text{NF}\varkappa\text{B}} \right) \Delta t \right) & \dfrac{[\text{sTNF}]}{K_{\text{DT1}} \frac{N_{\text{AV}}}{V} + [\text{sTNF}]} \geq \tau'_{\text{NF}\varkappa\text{B}} \end{cases} \tag{16}$$

$$P_{\text{apop}} = \begin{cases} 0 & \dfrac{[\text{sTNF}]}{K_{\text{DT1}} \frac{N_{\text{AV}}}{V} + [\text{sTNF}]} < \tau'_{\text{apop}} \\ 1 - \exp\left(-k'_{\text{apop}} \left(f_{\text{int}} \dfrac{[\text{sTNF}]}{K_{\text{DT1}} \frac{N_{\text{AV}}}{V}} - \tau'_{\text{apop}} \right) \Delta t \right) & \dfrac{[\text{sTNF}]}{K_{\text{DT1}} \frac{N_{\text{AV}}}{V} + [\text{sTNF}]} \geq \tau'_{\text{apop}} \end{cases} \tag{17}$$

$k'_{\text{NF}\varkappa\text{B}}$, k'_{apop}, $\tau'_{\text{NF}\varkappa\text{B}}$ and τ'_{apop} are modified rate constants and thresholds for TNF-induced NF-$\varkappa$B activation and apoptosis, respectively, while f_{int} is a partition factor for estimating internalized bound receptors from the pseudo-steady state estimate of surface bound receptors. These resulting rate constants and parameters can be estimated from their corresponding parameters when the increased molecular scale detail is turned on.

Lastly, inhibition of TNF synthesis by IL-10 is reduced to a simple dose dependence function based on the soluble IL-10 concentration in the compartment.

$$k'_{\text{sTNF}} = \frac{1}{1 + \exp\left(\dfrac{\log[\text{sIL10}] + \alpha}{\beta}\right)} \tag{18}$$

Where k'_{sTNF} is the apparent secretion rate of TNF, α is the threshold parameter, and β is the shape parameter.

References

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