General description and pseudocode illustrating the basic features by which the Agent-Based Model Gransim operates

The overall structure of the agent-based model (ABM) for the immune response to Mtb infection in the lung is presented below and adapted from Cilfone et al. (2013)\(^1\).

Overall Structure of the ABM

The ABM was developed based on four considerations: an environment, agents (immune cells), ABM rules that govern the agents and their interactions, and the time-step (\(\Delta t\)) used to update events. The environment represents a two-dimensional section of lung parenchyma as a 200 × 200 square lattice that simulates an area of 4mm × 4mm. Each grid micro-compartment is thus scaled to the approximate size of a single human macrophage, 20 µm in diameter. 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 \(T_{moveT}\)). A T cell may also move into the same micro-compartment as a macrophage (with probability \(T_{moveM}\)). 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 \(^2\).

Extracellular Mtb and soluble molecules, including chemokines (CCL2, CCL5 and CXCL9/10/11), cytokines (TNF-\(\alpha\), shed TNFR2, and IL-10) and antibiotics (RIF and INH, if enabled) are simulated as continuous entities that can reside anywhere 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 cell death. In the ABM, caseation is defined to occur when a specific number (\(N_{caseum}\)) of infected or activated macrophages die in a micro-compartment. When a micro-compartment becomes caseated, any T cell present in the micro-compartment is killed and no further cells are permitted to enter the micro-compartment. Macrophages can initiate healing of caseation, wherein the tissue is remodeled with an associated time.

There are two major types of discrete agents in the model, macrophages and T cells. 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\(\gamma\) 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.

Cell-cell interactions are governed by ABM rules that are updated within every ABM time-step of \(dt = 10\) min and will be discussed in the next section. Diffusion and degradation of soluble molecules on the lattice and secretion of chemokines/cytokines from individual cells occurs is
solved within each ABM time-step at a time step of $dt_0 = 60$ seconds. TNF-$\alpha$/TNFR and IL-10/IL-10R dynamics and antibiotics at the single-cell level are approximated (if enabled) using a tuneable resolution approach at a time step of $dt_M = 6$ seconds. Thus, each single-cell event is updated 10 times within each diffusion time-step while the diffusion, degradation, and secretion events are updated 10 times with each ABM time-step.

Grid Initialization

A two-dimensional grid is created (ranging from 2 to 4 mm diameter lesion). 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 lung. Initial resting macrophages that represent resident alveolar macrophages are randomly placed on the grid ($M_{\text{init}}$). 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.

ABM Rules - Overview

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. Since 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.

Agent Movement

Macrophages

Macrophages may stay in place or move in 8 possible directions 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 smallest speed (zero) for $M_c$. The differences among macrophage speeds are shown in the model by time intervals in which each macrophage attempts to move ($t_{\text{move}M_r}$, $t_{\text{move}M_s}$, $t_{\text{move}M_a}$). There are minimum concentration thresholds and maximum saturating concentration thresholds ($\tau_{\text{chem}}$ and $s_{\text{chem}}$) for the effect of each chemokine on cell movement. Chemokine concentrations below $\tau_{\text{chem}}$ or above $s_{\text{chem}}$ 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 $\tau_{\text{chem}}$ or above $s_{\text{chem}}$. 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.

T cells

T cell movements are updated in time intervals of length $t_{\text{MoveT}}$ that is determined by the speed of T cell migration \textit{in vivo}. Movement of $T_\gamma$ 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, $T_{\text{moveM}}$ and $T_{\text{moveT}}$, respectively.
Cellular Recruitment

We recruit macrophages (Mr) and T cells (Tγ, Tc, and Tr) 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. 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. 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 TmoveM and TmoveT, respectively.

Macrophages

Mr are recruited every time-step 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 Mr is given by:

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

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

\[ [CCL2] > \tau_{recMacCC} \quad \| \quad [CCL5] > \tau_{recMacCC} \quad \| \quad [TNF] > \tau_{recMacTNF} \]

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 (Text 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. Tγ are recruited every time-step 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$_r$ is given by:

$$P_{T_r} = T_{recTNF} \left[ \frac{V^{TNF}_{Max} [TNF - \tau_{recTNF}]}{[TNF - \tau_{recTNF} + h_{TNF}]} + \frac{V^{CCL2}_{Max} [CCL2 - \tau_{recTNF}]}{[CCL2 - \tau_{recTNF} + h_{CCL2}]} + \frac{V^{CCL5}_{Max} [CCL5 - \tau_{recTNF}]}{[CCL5 - \tau_{recTNF} + h_{CCL5}]} + \frac{V^{CXCL9}_{Max} [CXCL9 - \tau_{recTNF}]}{[CXCL9 - \tau_{recTNF} + h_{CXCL9}]} \right]$$

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):

$$[CCL2] > \tau_{recMacCC} \land [CCL5] > \tau_{recMacCC} \land [CXCL9] > \tau_{recMacCC} \land [TNF] > \tau_{recMacTNF}$$

T$_c$ are recruited every time-step 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:

$$P_{T_c} = T_{recCyt} \left[ \frac{V^{TNF}_{Max} [TNF - \tau_{recCytTNF}]}{[TNF - \tau_{recCytTNF} + h_{CytTNF}]} + \frac{V^{CCL5}_{Max} [CCL5 - \tau_{recCytCC}]}{[CCL5 - \tau_{recCytCC} + h_{CytCCL5}]} + \frac{V^{CXCL9}_{Max} [CXCL9 - \tau_{recCytCC}]}{[CXCL9 - \tau_{recCytCC} + h_{CytCXCL9}]} \right]$$

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

$$[CCL2] > \tau_{recMacCC} \land [CXCL9] > \tau_{recMacCC} \land [TNF] > \tau_{recMacTNF}$$

T$_r$ are recruited every time-step 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:
Along with the recruitment function the following threshold conditions must be met:

\[
[CCL5] > \tau_{\text{recMacCC}} \; \text{and} \; [TNF] > \tau_{\text{recMacTNF}}
\]

**Cell-Cell Interactions and State Transitions**

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

**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\(_{\text{ageMac}}\). T cells are also assigned a lifespan randomly distributed between zero and max\(_{\text{ageTcell}}\). M\(_{\text{a}}\) has a shortened lifespan of max\(_{\text{ageActive}}\). At death, M\(_{\text{r}}\) and T cells are removed from the grid. At death, M\(_{\text{i}}\) and M\(_{\text{ci}}\) are removed from the grid and any intracellular \(Mtb\) (\(B_{\text{int}}\)) is dispersed uniformly in the Moore neighborhood as extracellular bacteria (\(B_{\text{ext}}\)). M\(_{\text{a}}\) death contributes to caseation of the micro-compartment.
Rules for resting macrophages ($M_r$)

There is a chance of STAT-1 activation in a time-step as a result of interaction between a $M_r$ and IFN-γ producing $T_γ$ cells with a probability ($nT_γ \ast P_{STAT1}$); 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 $M_r$. $M_r$ can become NF-κB activated through TNF-α induced processes based on the equations given in the Tuneable 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 $t_{NFκB}$ 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 $B_{ext} \leq N_{rk}$, $M_r$ 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 $2 \ast P_k$ due to increased antimicrobial capacity. If both STAT1 and NF-κB are activated in a $M_r$ and it is not already down-regulated by a $T_r$, it becomes activated ($M_a$). Following $T_r$ down-regulation, $M_r$ does nothing but moves for a fixed period of time $t_{regMac}$. If the remaining lifespan of such an activated macrophage is greater than $\text{max}_{ageActive}$, it will be shortened to $\text{max}_{ageActive}$.

Rules for infected macrophages ($M_i$)

$B_{int}$ replicates in $M_i$ every ABM time-step according to the following equation:

$$B_{int}(t + \Delta t) = (1 + \alpha_{Bi})B_{int}(t) \quad \text{(Eq. 1)}$$

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

$$P_{uptakeMi} = \left(\frac{N_c - B_{int}}{100}\right) \quad \text{(Eq. 2)}$$

$M_i$ takes up $N_{rk}$ of extracellular bacteria if $B_{ext} > N_{rk}$. 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 ($M_i$). There is a chance of STAT-1 activation in a time-step as a result of interaction between a $M_i$ and IFN-γ producing $T_γ$ cells with a probability ($nT_γ \ast P_{STAT1}$); where, $nT_γ$ is the number of $T_γ$ cells surrounding the $M_i$ in the Moore neighborhood including the micro-compartment occupied by the $M_i$. $M_i$ can become NF-κB activated based on the equations given in the Tuneable 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 $t_{NFκB}$ after which STAT-1 or NF-κB activation, respectively, is lost. $M_i$ that are either STAT1 or NF-κB can be down-regulated by a $T_r$ in which the $M_i$ loses either STAT1 or NF-κB activation respectively. Following $T_r$ down-regulation, $M_i$ does nothing but moves for a fixed period of time $t_{regMac}$, but continues to secrete chemokines. If both STAT1 and NF-κB 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 $\text{max}_{ageActive}$, it will be shortened to $\text{max}_{ageActive}$.
Rules for chronically infected macrophages (Mci)

B_{int} replicates in Mci every time-step according to Eqn. 1. If the B_{int} exceeds a threshold (N_{burst}), the Mci bursts and its B_{int} are evenly distributed as whole numbers to the Moore neighborhood surrounding the Mci. Mci bursting contributes to caseation of the micro-compartment. Mci are always NF-κB activated and cannot become STAT1 activated. Mci cannot be down-regulated by a T_r.

Rules for activated macrophages (Ma)

Ma is capable of effectively killing B_{ext}. Each time-step, Ma kills N_{ak} of the B_{ext} in its micro-compartment. Ma that transitions from M_i kill B_{int} at the same rate that it kills B_{ext} each time-step. Ma can be down-regulated by a T_r in which the Ma loses both STAT1 and NF-κB activation. Following T_r down-regulation, Ma does nothing but moves for a fixed period of time t_{regMac} and subsequently transitions back to M_i after its down-regulated state. Ma 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.

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 (Text S2).

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_{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 down-regulated, T_c cells lose their cytotoxic capabilities for a fixed period of time t_{regTcyt}.

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 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 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_{cil} is given by the probability $P_{\text{apop/Fas}}$. As a result of apoptosis, half of the $B_{\text{int}}$ in $M_i$ or $M_{cil}$ will be killed and the other half will be equally distributed in the Moore neighborhood as $B_{\text{ext}}$. When down-regulated, $T_\gamma$ cells lose their apoptotic capabilities for a fixed period of time $t_{\text{regTgam}}$.

**Rules for regulatory T cells ($T_r$)**

$T_r$ suppresses or down-regulates the action of $T$ cells and macrophages through non interleukin-10 mechanisms (CTLA-4, TGF-β, etc.), which are still poorly understood. Thus, the probability of alternative suppressive functions of $T_r$ occurring is linearly dependent upon the following ratio (Eq. 3), 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 up regulated by a specified factor.

$$BoundRatio = \frac{[\text{TNF} \cdot \text{TNFR1}]}{[\text{TNF} \cdot \text{TNFR1}] + [\text{IL10} \cdot \text{IL10R}]} \quad (\text{Eq. 3})$$

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

**Extracellular Mtb Growth**

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

$$B_{\text{ext}}(t + \Delta t) = B_{\text{ext}}(t) + \alpha_{\text{Be}}B_{\text{ext}}(t) \left[1 - \frac{B_{\text{ext}}(t)}{1.1K_{\text{be}}}\right] \quad (\text{Eq. 4})$$

**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 ($1/10^{th}$).

**Chemokine Secretion**

$M_i$, $M_{cil}$, $M_a$, NF-κB activated $M_r$, and NF-κB activated $M_i$ are able to secrete chemokines, provided that they are not down-regulated by $T_r$. The rates of chemokine secretion for different cell types are as follows. $M_{cil}$, $M_a$ and NF-κB activated $M_i$ are able to secrete chemokines with full secretion rates ($r_{\text{CCL2}}$, $r_{\text{CCL5}}$, and $r_{\text{CXCL9}}$) 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 ($0.5 \times r_{\text{CCL2}}$, $0.5 \times r_{\text{CCL5}}$, and $0.5 \times r_{\text{CXCL9}}$). Caseated micro-compartments also secrete attractants that attract immune cells. For simplicity, we use quarter-full rates of
chemokine secretion to simulate the effect of such attractants \((0.25 \times r_{CCL2}, 0.25 \times r_{CCL5}, \text{and} 0.25 \times r_{CXCL9})\). Chemokine secretions to the micro-compartments on the grid are updated in time intervals of \(dt_0\). Secretion of TNF and IL-10 is discussed in the Tuneable Resolution section.

**Diffusion of Soluble Molecules**

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

\[
\frac{\partial C}{\partial t} = D \left( \frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2} \right) \quad \text{(Eq. 5)}
\]

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 \(^{10-14}\). 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 \(^{15}\). For an in depth explanation please refer to \(^{13}\). 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 \(^{15,16}\).

**Tuneable 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 \(^{1,17}\). Our focus is to understand the treatment of TB using inhaled formulations of 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 \(^{18}\). Briefly, the system of non-linear ordinary differential equations in \(^{1}\) is replaced with the following equations describing the change in soluble TNF and soluble IL-10 concentrations in a compartment containing an agent:

\[
\frac{d[sTNF]}{dt} = k'_{sTNF} - k_{cTNF} \left( \frac{[sTNF]}{K_{DT1} + [sTNF]} - \frac{[sTNF]}{K_{DT2} + [sTNF]} \right) \quad \text{(Eq. 6)}
\]

\[
\frac{d[sIL10]}{dt} = k'_{sIL10} - k_{cIL10} \left( \frac{[sIL10]}{K_{DI} + [sIL10]} \right) \quad \text{(Eq. 7)}
\]
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:

$$P_{NFkB} = \begin{cases} 
0 & \frac{[sTNF]}{K_{DT1}+\frac{N}{V}+[sTNF]} < \tau'_{NFkB} \\
-k_{NFkB}' \left( \frac{[sTNF]}{K_{DT1}+\frac{N}{V}+[sTNF]} - \tau'_{NFkB} \right) \Delta t & \frac{[sTNF]}{K_{DT1}+\frac{N}{V}+[sTNF]} \geq \tau'_{NFkB} 
\end{cases}$$

(Eqn. 8)
\[ P_{apop} = \begin{cases} 0 & f_{int} < \tau'_{apop} \\ -k'_{apop} \left( \frac{[sTNF]}{K_{DT1} \cdot \frac{N}{V} + [sTNF]} \right) f_{int} - \tau'_{NFkB} \Delta t & f_{int} \geq \tau'_{apop} \\ 1 - e^{-k'_{apop} \left( \frac{[sTNF]}{K_{DT1} \cdot \frac{N}{V} + [sTNF]} \right) f_{int} - \tau'_{NFkB}} \Delta t & \end{cases} \] (Eqn. 9)

\[ k'_{NFkB}, k'_{apop}, \tau'_{NFkB} \text{ and } \tau'_{apop} \] are modified rate constants and thresholds for TNF-induced NF-κB 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.

\[ k'_sTNF = \frac{1}{\log[sIL10] + \alpha} \frac{1}{1 + e^{\frac{\alpha}{\beta}}} \] (Eqn. 10)

Where \( k'_sTNF \) is the apparent secretion rate of TNF, \( \alpha \) is the threshold parameter, and \( \beta \) is the shape parameter.
References


