Supplementary Material

Granuloma equations

This model, composed of a system of 20 ODEs, captures bacterial, T cell, macrophage and cytokine dynamics within a single granuloma lesion. Below, we have listed equations, variable names and a brief explanation of the dynamics of each equation. Parameter symbols generally adhere to the following guidelines: α parameters are growth rates. k parameters are rate constants involving other variables. μ parameters are death or decay rates. c parameters are half-saturation values. Sr parameters are recruitment rate values to represent recruitment of cells from other areas of the body, for example. β and f parameters are scaling constants.

Extracellular bacteria concentrations within the granuloma are represented as B_E across time. Extracellular bacteria can grow ($alpha20$), or can be released when infected macrophages (M_I) undergo apoptosis from cytotoxic T cells (T_C) or TNF (F_α). Activated macrophages (M_A) or resting Macrophages (M_R) can kill extracellular bacteria.

$$\frac{dB_E}{dt} = \alpha_{20}B_E + k_{17}NM_I\left(\frac{B_I^2}{B_I^2 + N^2M_I^2}\right) + k_{14a}N_{fracc}\frac{B_I}{M_I}M_I\left(\frac{\left(\frac{T_C + w_3T_1}{M_I}\right)}{\left(\frac{T_C + w_3T_1}{M_I}\right) + c_4}\right) + k_{14b}N_{fraca}\frac{B_I}{M_I}M_I\left(\frac{F_\alpha}{F_\alpha + f_9I_{10} + s_{4b}}\right)$$
$$- k_2\frac{N}{2}M_R\left(\frac{B_E}{B_E + c_9}\right) - k_{15}M_AB_E - k_{18}M_RB_E - \mu_{B_E}B_E + \mu_{M_I}N_{fracd}\frac{B_I}{M_I}M_I$$

Intracellular bacteria concentrations are represented as B_I across time. B_I happens in the model as resting macrophages (M_R) engulf extracellular bacteria at a rate of k_2. Intracellular bacteria can die and can also become extracellular bacteria when infected macrophages undergo apoptosis. The intracellular bacterial growth term (beginning with α_{19}) has been slightly modified from *MultiGran* (36) so it now follows logistic growth function with a carrying capacity (N) per infected macrophage (M_I).

$$\frac{dB_I}{dt} = \alpha_{19}\frac{B_I}{M_I}M_I\left(1 - \frac{\frac{B_I}{M_I}}{N}\right) + k_2\frac{N}{2}M_R\left(\frac{B_E}{B_E + c_9}\right) - k_{17}NM_I\left(\frac{B_I^2}{B_I^2 + N^2M_I^2}\right) - k_{14a}\frac{B_I}{M_I}M_I\left(\frac{\left(\frac{T_C + w_3T_1}{M_I}\right)}{\left(\frac{T_C + w_3T_1}{M_I}\right) + c_4}\right)$$
$$- k_{14b}\frac{B_I}{M_I}M_I\left(\frac{F_\alpha}{F_\alpha + f_9I_{10} + s_{4b}}\right) - k_{52}\frac{B_I}{M_I}M_I\left(\frac{\left(\frac{\frac{T_C}{B_i + 1}\left(\frac{T_1}{T_1 + c_{T_1}}\right) + w_1T_1}{M_I}\right)}{\left(\frac{\frac{T_C}{B_i + 1}\left(\frac{T_1}{T_1 + c_{T_1}}\right) + w_1T_1}{M_I}\right) + c_{52}}\right) - \mu_{B_I}B_I + \mu_{M_I}\frac{B_I}{M_I}M_I$$

Resting macrophages (M_R) are recruited to the granuloma according to the number of activated Macrophages (M_A), the number of infected macrophages (M_I) and the concentration of TNF (F_α) in the granuloma. M_R can become activated or infected macrophages, or die.

$$\frac{dM_R}{dt} = Sr_M + \alpha_{4a}(M_A + w_2 M_I) + Sr_{4b}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b}}\right) - k_2 M_R\left(\frac{B_E}{B_E + c_9}\right) - k_3 M_R\left(\frac{B_E + wB_I + \beta F_\alpha}{B_E + wB_I + \beta F_\alpha + c_8}\right)\left(\frac{I_\gamma}{I_\gamma + f_1 I_4 + f_7 I_{10} + s_1}\right) - \mu_{M_R} M_R$$

Infected macrophages (M_I) become infected when a resting macrophage engulfs extracellular bacteria (B_E). M_I can burst when B_I growth exceeds carrying capacity (N) and can die through TNF- or cytotoxic T cell- mediated apoptosis.

$$\frac{dM_I}{dt} = k_2 M_R\left(\frac{B_E}{B_E + c_9}\right) - k_{17} M_I\left(\frac{B_I^2}{B_I^2 + N^2 M_I^2}\right) - k_{14a} M_I\left(\frac{\left(\frac{T_C + w_3 T_1}{M_I}\right)}{\left(\frac{T_C + w_3 T_1}{M_I}\right) + c_4}\right) - k_{14b} M_I\left(\frac{F_\alpha}{F_\alpha + f_9 I_{10} + s_{4b}}\right) - k_{52} M_I\left(\frac{\left(\frac{T_C\left(\frac{T_1}{T_1 + c_{T_1}}\right) + w_1 T_1}{M_I}\right)}{\left(\frac{T_C\left(\frac{T_1}{T_1 + c_{T_1}}\right) + w_1 T_1}{M_I}\right) + c_{52}}\right) - \mu_{M_I} M_I$$

Activated macrophages (M_A) become activated through resting Macrophages (M_R) interactions with extracellular bacteria (B_E) and IFN-γ (I_γ) in the granuloma. M_A can be de-activated by IL-10 ($I10$) cytokines or die.

$$\frac{dM_A}{dt} = k_3 M_R\left(\frac{B_E + wB_I + \beta F_\alpha}{B_E + wB_I + \beta F_\alpha + c_8}\right)\left(\frac{I_\gamma}{I_\gamma + f_1 I_4 + f_7 I_{10} + s_1}\right) - k_4 M_A\left(\frac{I_{10}}{I_{10} + s_8}\right) - \mu_{M_A} M_A$$

Primed CD4+ T cells (T_0) can proliferate at the site of the granuloma based on numbers of activated macrophages. Additionally, they are recruited to the site according to M_I, M_A, F_α concentrations in the granuloma. Differentiation of primed cells to effector states is based on cytokine concentrations across the granuloma. Primed cells can die.

$$\frac{dT_0}{dt} = \alpha_{1a}(M_A + w_2 M_I) + Sr_{1b}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b2}}\right) + \alpha_2 T_0\left(\frac{M_A}{M_A + c_{15}}\right) - k_6 I_{12} T_0\left(\frac{I_\gamma}{I_\gamma + f_1 I_4 + f_7 I_{10} + s_1}\right) - k_7 T_0\left(\frac{I_4}{I_4 + f_2 I_\gamma + s_2}\right) - \mu_{T_0} T_0$$

Effector Th1 T cells (T_1) are recruited to the granuloma according to M_I, M_A, and F_α. They are a differentiated T cell state originating from primed CD4+ T cells or effector memory CD8+ T cells. They can die from too much IFN-γ (I_γ).

$$\frac{dT_1}{dt} = \alpha_{3a}(M_A + w_2 M_I) + Sr_{3b}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}}\right) + k_6 I_{12} T_0\left(\frac{I_\gamma}{I_\gamma + f_1 I_4 + f_7 I_{10} + s_1}\right) + k_{31} T_{4EM} M_I - \mu_{T_\gamma}\left(\frac{I_\gamma}{I_\gamma + c}\right) T_1 M_A - \mu_{T_1} T_1$$

Effector Th2 T cells (T_2) are recruited to the granuloma according to M_I, M_A, and F_α. They are a differentiated T cell state originating from primed CD4+ T cells or effector memory CD4+ T cells.

$$\frac{dT_2}{dt} = \alpha_{3a2}(M_A + w_2 M_I) + Sr_{3b2}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}}\right) + k_7 T_0\left(\frac{I_4}{I_4 + f_2 I_\gamma + s_2}\right) + k_{32} T_{4EM} M_A - \mu_{T_2} T_2$$

Primed CD8+ T cells ($T80$) can proliferate at the site of the granuloma based on numbers of activated macrophages. Additionally, they are recruited to the site according to M_I, M_A, F_α concentrations in the granuloma. Differentiation of primed cells to effector states is based on cytokine concentrations across the granuloma. Primed cells can die.

$$\frac{dT_{80}}{dt} = \alpha_{1a}(M_A + w_2 M_I) + Sr_{1b}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b2}}\right) + \alpha_2 T_{80}\left(\frac{M_A}{M_A + c_{15}}\right) - k_6 I_{12} T_{80}\left(\frac{I_\gamma}{I_\gamma + f_1 I_4 + f_7 I_{10} + s_1}\right) - \mu_{T_{80}} T_{80}$$

Effector CD8+ T cells (T_8) are recruited to the granuloma according to M_I, M_A, and F_α. They are a differentiated T cell state originating from primed CD8+ T cells or effector memory CD8+ T cells and can die from IFN-γ (I_γ).

$$\frac{dT_8}{dt} = m\alpha_{3ac}(M_A + w_2 M_I) + mSr_{3bc}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}}\right) + mk_6 I_{12} T_{80}\left(\frac{I_\gamma}{I_\gamma + f_1 I_4 + f_7 I_{10} + s_1}\right) + k_{34} T_{8EM} M_I - \mu_{T_{c\gamma}}\left(\frac{I_\gamma}{I_\gamma + c_c}\right) T_8 M_A - \mu_{T_C} T_8$$

Cytotoxic CD8+ T cells (T_C) are recruited to the granuloma according to M_I, M_A, and F_α. They are a differentiated T cell state originating from primed CD8+ T cells or effector memory CD8+ T cells and can die from IFN-γ (I_γ).

$$\frac{dT_C}{dt} = m\alpha_{3ac}(M_A + w_2 M_I) + mSr_{3bc}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}}\right) + mk_6 I_{12} T_{80}\left(\frac{I_\gamma}{I_\gamma + f_1 I_4 + f_7 I_{10} + s_1}\right) + k_{33} T_{8EM} M_I - \mu_{T_{c\gamma}}\left(\frac{I_\gamma}{I_\gamma + c_c}\right) T_C M_A - \mu_{T_C} T_C$$

CD4+ effector memory T cells (T_{4EM}) can differentiate at the site of infection into effector cell states based on numbers of infected or activated macrophages. Additionally, they are recruited to the site according to F_α concentrations in the granuloma. These cells can die at the site of infection.

$$\frac{dT_{4EM}}{dt} = Sr_{4EM}\left(\frac{F_\alpha}{F_\alpha + hs_{4EM}}\right) - k_{31} T_{4EM} M_I - k_{32} T_{4EM} M_A - \mu_{T_{4EM}} T_{4EM}$$

CD8+ effector memory T cells (T_{8EM}) can differentiate at the site of infection into effector cell states based on numbers of infected macrophages. Additionally, they are recruited to the site according to F_α concentrations in the granuloma. These cells can die at the site of infection.

$$\frac{dT_{8EM}}{dt} = Sr_{8EM}\left(\frac{F_\alpha}{F_\alpha + hs_{8EM}}\right) - k_{33} T_{8EM} M_I - k_{34} T_{8EM} M_I - \mu_{T_{8EM}} T_{8EM}$$

CD4+ non-specific T cells (T_{4Non}) represent a generic class of T cells that do not respond to Mtb antigens but are recruited to the site according to F_α concentrations in the granuloma. These cells do not perform effector functions within the granuloma and die at the site of infection.

$$\frac{dT_{4N\,on}}{dt} = Sr_{4N\,on}\left(\frac{F_\alpha}{F_\alpha + hs_{4N\,on}}\right) - \mu_{T_{4N\,on}} T_{4N\,on}$$

CD8+ non-specific T cells (T_{8Non}) represent a generic class of T cells that do not respond to Mtb antigens but are recruited to the site according to F_α concentrations in the granuloma. These cells do not perform effector functions within the granuloma and die at the site of infection.

$$\frac{dT_{8N\,on}}{dt} = Sr_{8N\,on}\left(\frac{F_\alpha}{F_\alpha + hs_{8N\,on}}\right) - \mu_{T_{8N\,on}} T_{8N\,on}$$

TNF (F_α) is an inflammatory cytokine in the granuloma and is secreted by M_I, M_A, T_1, T_C and T_8 cells. It also decays in the granuloma.

$$\frac{dF_\alpha}{dt} = \alpha_{30}M_I + \alpha_{31}M_A\left(\frac{I_\gamma + \beta_2(B_E + wB_I)}{I_\gamma + \beta_2(B_E + wB_I) + f_1 I_4 + f_7 I_{10} + s_{10}}\right) + \alpha_{32}T_1 + \alpha_{33}\left(\frac{T_C + T_8}{2m}\right) - \mu_{F_\alpha}F_\alpha$$

IFN-γ (I_γ) is an inflammatory cytokine in the granuloma and is secreted by M_I, M_A, T_0, T_1, T_80, T_C and T_8 cells. It also decays in the granuloma.

$$\frac{dI_\gamma}{dt} = s_g\left(\frac{B_E + wB_I}{B_E + wB_I + c_{10}}\right)\left(\frac{I_{12}}{I_{12} + s_7}\right) + \alpha_{5a}T_1\left(\frac{M_A}{M_A + c_{5a}}\right) + \alpha_{5b}T_8\left(\frac{M_A}{M_A + c_{5b}}\right) + \alpha_{5c}M_I + \alpha_7 T_0\left(\frac{I_{12}}{I_{12} + f_4 I_{10} + s_4}\right) + \alpha_7 T_{80}\left(\frac{I_{12}}{I_{12} + f_4 I_{10} + s_4}\right) - \mu_{I_\gamma}I_\gamma$$

IL-12 (I_{12}) is secreted by M_R and M_A cells before decaying in the granuloma.

$$\frac{dI_{12}}{dt} = s_{12}\left(\frac{B_E + wB_I}{B_E + wB_I + c_{230}}\right) + \alpha_{23}M_R\left(\frac{B_E + wB_I}{B_E + wB_I + c_{23}}\right) + \alpha_8 M_A\left(\frac{s}{s + I_{10}}\right) - \mu_{I_{12}}I_{12}$$

IL-10 (I_{10}) is secreted by M_I, M_A, T_1, T_2, T_C and T_8 before decaying in the granuloma.

$$\frac{dI_{10}}{dt} = \delta_7(M_I + M_A)\left(\frac{s_6}{I_{10} + f_6 I_\gamma + s_6}\right) + \alpha_{16}T_1 + \alpha_{17}T_2 + \alpha_{18}\left(\frac{T_C + T_8}{2m}\right) - \mu_{I_{10}}I_{10}$$

IL-4 (I_4) is secreted by T_0 and T_2 before decaying in the granuloma.

$$\frac{dI_4}{dt} = \alpha_{11}T_0 + \alpha_{12}T_2 - \mu_{I_4}I_4$$

Blood and lymph node equations

This two-compartment model represents the dynamics of specific and non-specific T cells in the LN and blood following antigen presentation by antigen-presenting cells (APCs) in the LN. Measure units are cell counts in the lymph compartment and cell/mm^3 in the blood compartment. The term α represents the volume of blood in μL and is used for scaling cells when they traffic between the blood compartment and the lymph compartment.

Lymph Node CD4+ T cells
Antigen presentation and priming in LN compartment is driven by the following equation:

$$\frac{dAPC}{dt} = -\mu_5 APC \tag{0.1}$$

which tracks antigen presenting cells (APCs) in the LN at any time during or after infection. If the number of APCs doesn't increase (a reinfection event would be an example of increasing the APC population), the APC number decreases following an exponential decay, at the rate μ_5.
Naïve T cells (Eqn. (1.2)) represented by (N_4^{LN}) are recruited to the LN at a rate (k_1) dependent on cytokine production in the LN. Since we do not track cytokines in the LN model, we use APC also as a proxy for cytokine production (modeled as a Michaelis-Menten term in Eqn. (1.2)). Other terms included influx (ξ_1) and efflux (ξ_2), as well as mass action priming to precursor cells (k_2).

$$\frac{dN_4^{LN}}{dt} = \alpha\left(V_{primeN} + V_{Ninflux}\right) - V_{Nefflux} - V_{NdiffP} \tag{0.2}$$
$$V_{primeN} = k_1 N_4^B \left(\frac{APC}{APC + hs_1}\right)$$
$$V_{NdiffP} = k_2 N_4^{LN} APC$$
$$V_{Nefflux} = \xi_2 N_4^{LN}$$
$$V_{Ninflux} = \xi_1 N_4^B$$

Precursor CD4+ T cells (P_4^{LN}) (Eqn. (1.3)) are generated through priming of antigen-specific naïve T cells (k_2) as well as through re-activation of antigen-specific central memory T cells (k_3); both processes are expressed as mass action terms. Proliferation is modeled as logistic growth.

$$\frac{dP_4^{LN}}{dt} = \left(V_{NdiffP} + V_{CMdiffP}\right) + V_{prolif} - V_{PdiffE} - V_{PdiffCM} - \mu_6 P_4^{LN} \tag{0.3}$$

$$V_{CMdiffP} = k_3 CM_4^{LN} APC$$
$$V_{prolif} = k_4 P_4^{LN}\left(1 - \left(\frac{P_4^{LN}}{\rho_1}\right)\right)\left(\frac{APC}{APC + hs_4}\right)$$

$$V_{PdiffE} = k_5 P_4^{LN}\left(\frac{APC}{APC + hs_5}\right)$$
$$V_{PdiffCM} = k_6 P_4^{LN}\left(1 - \left(\frac{APC}{APC + hs_5}\right)\right)$$

A Michaelis-Menten term based on antigen stimulation (APC levels) was used to adjust proliferation (k_4) and differentiation rates (k_5 and k_6). The likelihood of precursor cells differentiating into effector cells is directly proportional to the amount of antigen stimulation (k_5). The opposite assumption was applied to the likelihood of precursor cells differentiating into central memory (k_6). A death term (μ_6) ensured that the precursor population did not persist in the absence of infection. No precursor populations exit the lymph node.
Effector CD4+ T cells are modeled in Eqn. (1.4), as E_4^{LN}:

$$\frac{dE_4^{LN}}{dt} = V_{PdiffE} - V_{Eefflux} - V_{EdiffEM} \quad (0.4)$$
$$V_{Eefflux} = \xi_3 E_4^{LN}$$
$$V_{EdiffEM} = k_7 E_4^{LN}$$

Terms in the equation include efflux to the blood (ξ_3), and a linear differentiation to the effector memory T cell population (k_7). We assumed that no effector T cells die in the LN (they can die in the blood).
Similar to naïve cells, central memory T cells (Eqn. (1.5)) are recruited to the lymph node (k_8) in addition to an influx rate (ξ_4). Other terms include differentiation from precursor cells (k_6), reactivation to precursor cells (k_3) and efflux into the blood (ξ_5). Given their relatively long lifespan compared to the length of the *in-silico* simulation (i.e., 200 days at most) we do not have a death term in Eqn. (1.5), as CM_4^{LN}:

$$\frac{dCM_4^{LN}}{dt} = \alpha\left(V_{primeCM} + \xi_4 CM_4^B\right) + V_{PdiffCM} - V_{CMdiffP} - V_{CMefflux} \quad (0.5)$$
$$V_{primeCM} = k_8 CM_4^B\left(\frac{APC}{APC + hs_8}\right)$$
$$V_{CMinflux} = \xi_4 CM_4^B$$
$$V_{CMefflux} = \xi_5 CM_4^{LN}$$

Effector memory cell formation is described in Eqn. (1.6), as EM_4^{LN}. A linear term captures the differentiation of CD4+ effector T cells into CD4+ effector memory (k_7). The last term represented efflux to the blood (ξ_6). Due to the longevity of these cells, we did not introduce a death term in the LN. Like effector T cells, effector memory T cells do not enter the LN directly from the blood.

$$\frac{dEM_4^{LN}}{dt} = V_{EdiffEM} - V_{EMefflux} \quad (0.6)$$
$$V_{EMefflux} = \xi_6 EM_4^{LN}$$

Blood CD4+ T cells

For the blood compartment, we track 4 different T cell antigen-specific phenotypes. The antigen-specific naïve CD4+ T cell blood population is modeled by Eqn. (1.7) (N_4^B). We have terms for a constant source supplied from the thymus (multiplied by the antigen-specific frequency λ, i.e. λs_{N_4}) to track specific and non-specific cells, migration from the lymph node (ξ_2), extra recruitment to the lymph node (k_1), migration to the lymph node (ξ_1), and death (μ_8).

$$\frac{dN_4^B}{dt} = \lambda s_{N_4} + \alpha^{-1} V_{Neff lux} - V_{primeN} - V_{Ninflux} - \mu_8 N_4^B \quad (0.7)$$

The values for s_{N_4} and μ_8 are chosen to maintain equilibrium in the total Naïve T cell populations (based on the initial conditions taken from the NHP blood data in previous work (48)).
Eqn. (1.8) describes effector CD4+ T cells dynamics (E_4^B) in the blood with two terms: migration from the lymph node (ξ_3) and death (μ_1).

$$\frac{dE_4^B}{dt} = \alpha^{-1} V_{Eefflux} - \mu_1 E_4^B \quad (0.8)$$

Central memory cells in the blood (Eqn. (1.9)) (CM_4^B) migrate from (ξ_5) and to the lymph node (ξ_4). Central memory cells are not recruited to the site of infection.

$$\frac{dCM_4^B}{dt} = \alpha^{-1} V_{CMefflux} - V_{CMinflux} - V_{primeCM} \quad (0.9)$$

Effector memory cells in the blood (Eqn.(1.10)) (EM_4^B) are modeled by two terms: migration from the lymph node (ξ_6) and death (μ_2). Similar to effector cells these were recruited to the site of infection.

$$\frac{dEM_4^B}{dt} = \alpha^{-1} V_{EMefflux} - \mu_2 EM_4^B \quad (0.10)$$

Non-Mtb-specific CD4+ lymphocytes
Our computational model similarly keeps track of non-specific T cells. However, non-Mtb-specific T cells do not respond to antigen, therefore, no priming occurs in any cell population and no precursor cells are generated. Also, since we assume neither effector nor effector memory T cells enter the lymph compartment from the blood, we do not model effector or effector memory cell populations within the LN compartment (as shown in Figure 2). The production of the non-specific effector cells was modeled as a source term in the blood compartment and was included to meet the assumption of homeostasis. The equations for non-Mtb-specific CD4+ T cells are shown below. Moreover, including non-Mtb-specific cells in the model makes model predictions more realistic due to the total cell numbers more accurately reflecting the actual numbers in blood.

Naïve CD4+ non-Mtb-specific (N_{nc4}^{LN})

$$\frac{dN_{nc4}^{LN}}{dt} = \alpha\left(k_1 N_{nc4}^B\left(\frac{APC}{APC + hs_1}\right) + \xi_1 N_{nc4}^B\right) - \xi_2 N_{nc4}^{LN} \quad (1.11)$$

Central Memory CD4+ non-Mtb-specific - LN (CM_{nc4}^{LN})

$$\frac{dCM_{nc4}^{LN}}{dt} = \alpha\left(k_8 CM_{nc4}^{B}\left(\frac{APC}{APC+hs_8}\right)+\xi_4 CM_{nc4}^{B}\right)-\xi_5 CM_{nc4}^{LN} \quad (1.12)$$

Naïve CD4+ non-Mtb-specific – Blood (N_{nc4}^{B})

$$\frac{dN_{nc4}^{B}}{dt} = (1-\lambda)s_{N_4}+\alpha^{-1}\xi_2 N_{nc4}^{LN}-k_1 N_{nc4}^{B}\left(\frac{APC}{APC+hs_1}\right)-\xi_1 N_{nc4}^{B}-\mu_8 N_{nc4}^{B} \quad (1.13)$$

Effector CD4+ non-Mtb-specific - Blood (E_{nc4}^{B})

$$\frac{dE_{nc4}^{B}}{dt} = s_{E_{nc4}}-\mu_1 E_{nc4}^{B} \quad (1.14)$$

As non Mtb-specific effector cells in the blood must be produced somewhere in the body, they are modeled as source and a death rate equal to that of their antigen-specific counterparts.

Central Memory CD4+ non Mtb-specific – Blood (CM_{nc4}^{B})

$$\frac{dCM_{nc4}^{B}}{dt} = \alpha^{-1}\xi_5 CM_{nc4}^{LN}-\xi_4 CM_{nc4}^{B}-k_8 CM_{nc4}^{B}\left(\frac{APC}{APC+hs_8}\right) \quad (1.15)$$

Effector Memory CD4+ non-Mtb-specific - Blood (EM_{nc4}^{B})

$$\frac{dEM_{nc4}^{B}}{dt} = s_{EM_{nc4}}-\mu_2 EM_{nc4}^{B} \quad (1.16)$$

Lymph Node and Blood Mtb-specific T cells

There are only slight differences in our modeling of CD8+ and CD4+ T cells. Importantly, the priming of Mtb-specific naïve CD8+ T cells is impacted by cytokines released by activated CD4+ T cells in the LN. Again, as we do not directly model cytokine expression in the LN; this is modeled indirectly by a Michaelis-Menten term that includes activated CD4+ T effector cells and a weighted term for precursor CD4+ T cells. We display these equations below:

$$\frac{dN_8^{LN}}{dt} = \alpha\left(k_{10} N_8^{B}\left(\frac{DC}{DC+hs_{10}}\right)+\xi_7 N_8^{B}\right)-\xi_8 N_8^{LN}- \\ -k_{11} N_8^{LN} DC\left(\frac{[E_4^{LN}+W_{P_4}P_4^{LN}]}{[E_4^{LN}+W_{P_4}P_4^{LN}]+hs_{11}}\right) \quad (1.17)$$

$$\frac{dP_8^{LN}}{dt} = k_{11}N_8^{LN}DC\left(\frac{[E_4^{LN} + W_{P_4}P_4^{LN}]}{[E_4^{LN} + W_{P_4}P_4^{LN}] + hs_{11}}\right) + k_{12}CM_8^{LN}DC$$
$$+k_{13}P_8^{LN}\left(1 - \frac{P_4^{LN} + P_8^{LN}}{\rho_1}\right)\left(\frac{DC}{DC + hs_{13}}\right) - k_{14}P_8^{LN}\left(\frac{DC}{DC + hs_{14}}\right) -$$
$$-k_{15}P_8^{LN}\left(1 - \left(\frac{DC}{DC + hs_{14}}\right)\right) - \mu_7 P_8^{LN} \tag{1.18}$$

Effector CD8+ T cells in lymph node

$$\frac{dE_8^{LN}}{dt} = k_{14}P_8^{LN}\left(\frac{DC}{DC+hs_{14}}\right) - \xi_9 E_8^{LN} - k_{16}E_8^{LN} \tag{1.19}$$

Central Memory CD8+ T cells in lymph node

$$\frac{dCM_8^{LN}}{dt} = \alpha\left(k_{17}CM_8^B\left(\frac{DC}{DC + hs_{17}}\right) + \xi_{10}CM_8^B\right) +$$
$$k_{15}P_8^{LN}\left(1 - \left(\frac{DC}{DC + hs_{14}}\right)\right) - k_{12}CM_8^{LN}DC - \xi_{11}CM_8^{LN} \tag{1.20}$$

Effector Memory CD8+ T cells in lymph node

$$\frac{dEM_8^{LN}}{dt} = k_{16}E^{LN}{}_8 - \xi_{12}EM_8^{LN} \tag{1.21}$$

Naive CD8+ T cells in blood

$$\frac{dN_8^B}{dt} = \lambda s_{N_8} + \alpha^{-1}\xi_8 N_8^{LN} - k_{10}N_8^B\left(\frac{DC}{DC + hs_{10}}\right) - \xi_7 N_8^B - \mu_9 N_8^B \tag{1.22}$$

Effector CD8+ T cells in blood

$$\frac{dE_8^B}{dt} = \alpha^{-1}\xi_9 E_8^{LN} - \mu_3 E_8^B \tag{1.23}$$

Central Memory CD8+ T cells in blood

$$\frac{dCM_8^B}{dt} = \alpha^{-1}\xi_{11}CM_8^{LN} - \xi_{10}CM_8^B - k_{17}CM_8^B\left(\frac{DC}{DC + hs_{17}}\right) \tag{1.24}$$

Effector Memory CD8+ T cells in blood

$$\frac{dEM_8^B}{dt} = \alpha^{-1}\xi_{12}EM_8^{LN} - \mu_4 EM_8^B \tag{1.25}$$

Lymph Node and Blood non-Mtb-specific CD8+ T cells

Modeled in an identical approach as the CD4+ T cell pools that were non-Mtb-specific.

Non-Mtb-specific Naive CD8+ T cells in lymph node

$$\frac{dN_{nc8}^{LN}}{dt} = \alpha\left(k_{10}N_{nc8}^B\left(\frac{DC}{DC+hs_{10}}\right)+\xi_7 N_{nc8}^B\right) - \xi_8 N_{nc8}^{LN} \tag{1.26}$$

Non-Mtb-specific Central Memory CD8+ T cells in lymph node

$$\frac{dCM_{nc8}^{LN}}{dt} = \alpha\left(k_{17}CM_{nc8}^B\left(\frac{DC}{DC+hs_{17}}\right)+\xi_{10}CM_{nc8}^B\right) - \xi_{11}CM_{nc8}^{LN} \tag{1.27}$$

Non-Mtb-specific Naive CD8+ T cells in blood

$$\frac{dN_{nc8}^B}{dt} = (1-\lambda)s_{N_4} + \alpha^{-1}\xi_8 N_{nc8}^{LN} - k_{10}N_{nc8}^B\left(\frac{DC}{DC+hs_{10}}\right) - \xi_7 N_{nc8}^B - \mu_9 N_{nc8}^B \tag{1.28}$$

Non-Mtb-specific Effector CD8+ T cells in blood

$$\frac{dE_{nc8}^B}{dt} = s_{E_{nc8}} - \mu_3 E_{nc8}^B \tag{1.29}$$

Non-Mtb-specific Central Memory CD8+ T cells in blood

$$\frac{dCM_{nc8}^B}{dt} = \alpha^{-1}\xi_{11}CM_{nc8}^{LN} - \xi_{10}CM_{nc8}^B - k_{17}CM_{nc8}^B\left(\frac{DC}{DC+hs_{17}}\right) \tag{1.30}$$

Non-Mtb-specific Effector Memory CD8+ T cells in blood

$$\frac{dEM_{nc8}^B}{dt} = s_{EM_{nc8}} - \mu_4 EM_{nc8}^B \tag{1.31}$$

Supplementary Table 1. Parameter table for Granuloma Model and Lymph Node & Blood model parameters

Parameter Name Granuloma ODE	Units	Parameter Description	Minimum Value	Maximum Value
Srm	1/day	MR recruitment rate	0	0
alpha4a	1/day	Macrophage recruitment of MR	0.7	1.0
beta	1/pg	Scaling factor of Falpha for MR activation	8.65E+06	1.14E+07

w	N/A	Contribution of BI to MR activation	0.26	0.36
w3	N/A	Max contribution of Th1 to MI apoptosis	0.2	0.8
w2	N/A	Contribution of MI to MR recruitment	0.9	1.2
Sr4b	1/day	Falpha dependent recruitment of MR	592	864
f8	N/A	Ratio adjustment I10/Falpha on MR recruitment	1.74E-03	2.25E-03
f9	N/A	Ratio adjustment Falpha/I10	0.523	0.673
s4b	pg/ml	Half saturation of Falpha on MR recruitment	2920	5250
k4	1/day	MA deactivation by I10	0.08	0.17
s8	pg/ml	Half saturation of I10 on MA deactivation	244	1003
k2	1/day	MR infection rate	0.84	2.31
c9	count	Half saturation of BE on MR infection	1622	7868
k3	1/day	MR activation rate	0.034	0.045
f1	N/A	Adjustment I4/IGamma	126	165
s1	pg/ml	Half saturation of IGamma dependent MR activation	83	479
c8	count	Half saturation of BE and BI on MR activation	1.64E+05	4.09E+05
nuMR	1/day	MR death rate	0.004	0.006
k17	1/day	Max rate of MI bursting	0.088	0.238
N	count	Carrying capacity of MI	5	25
k14a	1/day	T cell induced apoptosis of MI	0.07	1.7
c4	count	Half saturation of Th1/MI ratio on MI apoptosis	397	951
k14b	1/day	Falpha induced apoptosis of MI	0.59	0.92
k52	1/day	Cytotoxic killing of MI	0.54	0.78
w1	N/A	Max contribution of Th1 to cytotoxic killing	0.22	0.74
c52	count	Half saturation of TC on MI killing	1.08E+05	2.51E+05
cT1	count	Half saturation of Th1 on cytotoxic killing	30	40
nuMI	1/day	MI death rate	0.003	0.004
nuMA	1/day	MA death rate	0.15	0.20
alpha1a	1/day	Macrophage recruitment of T0	0.08	0.57
Sr1b	1/day	F/alpha dependent T0 recruitment	25007	54088
s4b2	pg/ml	Half saturation of Falpha dependent T0 recruitment	4834	10175
alpha2	1/day	Max growth rate of T0	0.1	1
c15	count	Half saturation of MA proliferation of T0	5	25
k6	1/day	Max T0 to Th1 rate	0.10	0.23
f7	N/A	Effect of I10 on IGamma induced differentiation of T0 to Th1	8.2	32.3
k7	1/day	Max T0 to Th2 rate	0.24	0.61
f2	N/A	Adjustment IGamma/I4	0.2	0.4
s2	pg/ml	Half saturation I4	429	955

nuT0	1/day	T0 death rate	0.19	0.25
m	N/A	Percentage overlap between TC and T8	0.68	0.90
alpha3a	1/day	Macrophage recruitment of Th1	0.39	0.82
Sr3b	1/day	Falpha dependent recruitment of Th2	19	83
s4b1	pg/ml	Half saturation of Falpha dependent Th1 recruitment	6131	10162
alpha3a2	1/day	Macrophage recruitment of Th2	0.25	0.79
Sr3b2	1/day	Falpha dependent recruitment of Th2	47.5	99.0
nuTg	1/day	Igamma induced apoptosis of Th1	0.290	0.762
c	pg/ml	Half saturation Igamma on Th1 apoptosis	284	727
nuT1	1/day	Th1 death rate	0.28	0.37
nuT2	1/day	Th2 death rate	0.29	0.37
alpha3ac	1/day	Macrophage recruitment of TC and T8	0.25	0.80
Sr3bc	1/day	Falpha dependent recruitment of TC and T8	13	28
nuTCg	1/day	Igamma induced apoptosis of Tc and T8	0.46	0.90
cc	pg/ml	Half saturation IFN-g on TC and T8 apoptosis	337	673
nuTC	1/day	TC death rate	0.26	0.33
alpha30	pg/(ml* day)	Falpha production by MI	0.05	0.10
alpha31	pg/(ml* day)	Falpha production by MA	0.19	0.82
beta2	1/pg	Scaling factor of Mtb for Falpha production by MA	10466	13466
s10	pg/ml	Half saturation of Igamma on Falpha production by MA	103	313
alpha32	pg/(ml* day)	Falpha production by Th1	0.20	0.34
alpha33	pg/(ml* day)	Falpha production by T8	0.18	0.33
nuTNF	1/day	Falpha decay rate	0.93	1.21
sg	pg/(ml* day)	Igamma production by dendritic cells (DCs)	2667	7944
c10	count	Half saturation of Mtb on Igamma production by DCs	980813	6876625
s7	pg/ml	Half saturation of I12 on Igamma production by DCs	538	883
alpha5a	pg/day	Igamma production by Th1	0.54	0.87
c5a	count	Half saturation of MA on Igamma production by Th1	304	687
alpha5b	pg/day	Igamma production by T8	0.18	0.60
alpha5c	pg/day	Igamma production by MI	0.12	0.36
c5b	count	Half saturation of MA on Igamma production by T8	235.8	846.6
alpha7	pg/day	Igamma production by T0	0.04	0.17
f4	N/A	Adjustment of I10/I12 on Igamma	1.30	1.67
s4	pg/ml	Half saturation of I12 on Igamma	285	810

nuIG	1/day	Igamma decay rate	5.448	9.693
alpha23	pg/day	I12 production by MR	0.003	0.005
c23	pg/ml	Half saturation of Mtb on I12 production by MR	157	525
alpha8	pg/day	I12 production by MA	0.38	0.86
s12	pg/day	Dendritic cell production of I12	2361	4061
c230	count	Half saturation of Mtb on I12 production by DCs	366	762
nuI12	1/day	I12 decay rate	0.93	1.24
s	pg/ml	I10 effect on I12 production by MA	192	694
delta7	pg/day	I10 production by MA	0.38	0.85
s6	pg/ml	Half saturation of I10 self	587	859
f6	N/A	Adjustment Igamma on I10	0.30	0.39
alpha16	pg/day	I10 production by Th1	0.33	0.79
alpha17	pg/day	I10 production by Th2	0.28	0.53
alpha18	pg/day	I10 production by TC and T8	0.46	0.78
nuI10	1/day	I10 decay rate	1.80	4.53
alpha11	pg/day	I4 production by T0	0.01	0.06
alpha12	pg/day	I4 production by Th2	0.02	0.06
nuI4	1/day	I4 decay rate	2.37	3.09
alpha19	1/day	BI growth rate	0.82	1.36
alpha20	1/day	BE growth rate	0.25	0.43
Nfracc	N/A	Fraction BI released by T cell apoptosis of MI	0.05	0.07
Nfraca	N/A	Fraction BI released by TNF apoptosis of MI	0.05	0.07
k15	1/day	BE killing by MA	0.0003	0.0011
k18	1/day	BE killing by MR	0.0003	0.0008
Nfracd	N/A	fraction of BI released during MI natural death to become BE	0.0009	0.0011
power	N/A	scaling factor	2	2
nI	1/day	BI death rate	5.95E-05	9.04E-05
nE	1/day	BE death rate	4.11E-09	7.41E-09
Sr4Non	1/day	TNFalpha dependent recruitment of CD4 non-specific T cells	156	504
hs4Non	pg/ml	half sat of TNFalpha dependent recruitment of CD4 non-specific T cells	5	50
mui4Non	1/day	death rate of CD4 non-specific T cells	0.3	0.4
Sr8Non	1/day	TNFalpha dependent recruitment of CD8 non	153	509
hs8Non	pg/day	half sat of TNFalpha dependent recruitment of CD8 non	5	50
mui8Non	1/day	death rate of CD8 non-specific T cells	0.3	0.4
Sr4EM	1/day	TNFalpha dependent recruitment of CD4 EM T cells	48	102
hs4EM	pg/ml	half sat of TNFalpha dependent recruitment of CD4 EM T cells	0.001	0.001

mui4EM	1/day	death rate of CD4 EM T cells	0.16	0.32
k31	1/day	differentiaton rate of CD4 EM T cells to Th1 cells	0.04	0.11
k32	1/day	differentiaton rate of CD4 EM T cells to Th2 cells	0.07	0.11
Sr8EM	1/day	TNFalpha dependent recruitment of CD8 EM T cells	53	107
hs8EM	pg/ml	half sat of TNFalpha dependent recruitment of CD8 EM T cells	0.001	0.001
mui8EM	1/day	death rate of CD8 EM T cells	0.17	0.31
k33	1/day	differentiaton rate of CD8 EM T cells to cytotoxic CD8 T cells	0.05	0.11
k34	1/day	differentiaton rate of CD8 EM T cells to Effector CD8 T cells	0.05	0.11
k99	1/day	killing rate constant of BI by TRM	0.3	0.8
APCtimeStart	day	when APCs leave and enter the lymph node	5	28
APCtimeEnd	day	APCs stop leaving granuloma	50	105
APCleave	N/A	Percentage of infected macs considered APCs in granuloma	5	25
localDissemCFUHalf	count	half sat CFU for local dissemination events	6.98E+03	9.71E+03
localDissemLambda	N/A	max probability of local dissemination	0.0005	0.025
nonLocalDissemCFUHalf	count	half sat CFU for non local dissemination	5.22E+03	1.06E+04
nonLocalDissemLambda	N/A	max probability of non local dissemination	0.0001	0.005
MR (initial condition)	count	Resting macrophages	0	0
MI (initial condition)	count	Infected macrophages	1	1
MA (initial condition)	count	Activated macrophages	0	0
T0 (initial condition)	count	Primed CD4+ T cells	0	0
T1 (initial condition)	count	Th1 cells	0	0
T2 (initial condition)	count	Th2 cells	0	0
T80 (initial condition)	count	Primed CD8+ T cells	0	0
TC (initial condition)	count	Cytotoxic T cells	0	0
T8 (initial condition)	count	Effector CD8+ T cells	0	0
TNF (initial condition)	pg/ml	Tumour Necrosis Factor	0	0
IFNG (initial condition)	pg/ml	interferon	0	0
IL12 (initial condition)	pg/ml	Interleukin	0	0
IL10 (initial condition)	pg/ml	Interleukin	0	0
IL4 (initial condition)	pg/ml	Interleukin	0	0
BI (initial condition)	count	Intracellular Bacteria	1	1
BE (initial condition)	count	Extracellular Bacteria	0	0
CD4Non (initial condition)	count	Nonspecific CD4 T cells	0	0
CD8Non (initial condition)	count	Nonspecific CD8 T cells	0	0

EMCD4 (initial condition)	count	Effector Memory CD4 T cells	0	0
EMCD8 (initial condition)	count	Effector Memory CD8 T cells	0	0
Parameter Name (LN & Blood)	**Units**	**Parameter Description**	**Minimum Value**	**Maximum Value**
alfa	uL	Conversion from Blood to LN	360000	360000
host_Ln	count	Involved Lymph Nodes in Host	5	5
lambda	count	frequency of specific Naive T cells in system	0.0001	0.0001
hs1	count	half sat of Naive CD4+ T cell recruitment	14	71
hs10	count	half sat of Naive CD8+ T cell recruitment	46	88
hs11	count	half sat of Naive CD8+ T cell priming	13	48
hs13	count	half sat of precursor CD8+ T cell proliferation	2684	4056
hs14	count	half sat of precursor CD8+ T cell differentiation	1904	4144
hs17	count	half sat of Central Memory CD8+ T cell recruitment	66	403
hs4	count	half sat of Precursor CD4+ T cell proliferation	1319	4318
hs5	count	half sat of Precursor CD4+ T cell differentiation	1257	3719
hs8	count	half sat of Central Memory CD4+ T cell recruitment	40	57
k1	1/day	Naive CD4+ T cell recruitment rate	0.12	0.47
k10	1/day	Naive CD8+ T cell recruitment rate	0.77	0.97
k11	1/day	Naive CD8+ T cell priming rate	0.00010	0.00023
k12	1/day	Central Memory CD8+ T cell reactivation rate	0.00012	0.00075
k13	1/day	Precursor CD8+ T cell proliferation rate	0.20	0.80
k14	1/day	Precursor CD8+ T cell differentiation to Effector rate	0.25	0.74
k15	1/day	Precursor CD8+ T cell differentiation to CM rate	0.53	0.86
k16	1/day	Precursor CD8+ T cell differentiation to EM rate	0.16	0.82
k17	1/day	Central Memory CD8+ T cell recruitment rate	0.35	0.90
k2	1/day	Naive CD4+ T cell priming rate	0.33	0.87
k3	1/day	Central Memory CD4+ T cell reactivation rate	0.022	0.080
k4	1/day	Precursor CD4+ T cell proliferation rate	0.30	1.36
k5	1/day	Precursor CD4+ T cell differentation to effector T cell	0.27	0.90
k6	1/day	Precursor CD4+ T cell differentiation to central memory T cell	0.3	0.9
k7	1/day	Effector CD4+ T cell differentiation to EM	0.1	0.6
k8	1/day	Central Memory CD4+ T cell recruitment rate	0.026	0.070
mu1	1/day	Effector CD4+ T cell death rate	0.2	0.2
mu2	1/day	Effector Memory CD4+ T cell death rate	0.04	0.04
mu3	1/day	Effector CD8+ T cell death rate	0.2	0.2
mu4	1/day	EM CD8+ T cell death rate	0.018	0.018
mu5	1/day	APC death rate	0.05	0.05

mu6	1/day	Precursor CD4+ T cell death rate	0.0005	0.0005
mu7	1/day	Precurosr CD8+ T cell death rate	0.015	0.015
mu8	1/day	Naive CD4+ T cell death rate	0.3	0.3
mu9	1/day	Naive CD8+ T cell death rate	0.05	0.05
rho1	count	Precursor Carrying Capacity	300000000	300000000
Wp4	N/A	Weight factor for Precursor CD4+ T cell in CD8+ T cell priming	0.7355	0.7355
xi11	1/day	Central Memory CD8+ Lymph efflux rate	0.275	1.223
xi12	1/day	EM CD8 Lymph efflux rate	0.219	1.521
xi2	1/day	Naive CD4+ Lymph Efflux rate	2	5
xi3	1/day	Effector CD4+ Lymph Efflux rate	1	4
xi5	1/day	Central Memory CD4+ Lymph Efflux rate	1	4
xi6	1/day	Effector Memory CD4+ Lymph Efflux rate	3	4
xi8	1/day	naive CD8 lymph efflux rate	1	2
xi9	1/day	effector CD8 lymph efflux rate	2	4

Supplementary Table 2. Effect Measure comparisons for Figure 6C.

Vargha and Delaney's A measure calculated pairwise between the three separate groups for differences between fold change of cell entry into lung. When A measure < 0.56, differences are considered small, if A measure > 0.71, the differences are considered to be large. Values are rounded to the nearest hundredth.

	LTBI vs Active TB groups	TB eliminator vs Active TB groups	TB eliminator vs LTBI groups
CD4+ Effector T cell	0.9	0.91	0.54
CD4+ Effector Memory T cell	0.53	0.64	0.6
CD8+ Effector T cell	0.64	0.84	0.7
CD8+ Effector Memory T cell	0.52	0.67	0.65

Supplementary Table 3: PRCC values for host-scale sensitivity analysis

Parameter Names	Description	PRCC values
LN_k13	Precursor CD8+ T cell proliferation	0.22
LN_k14	CD8+ Precursor differentiation rate to CD8+ Effector T cell	-0.18

LN_k4	Precursor CD4+ T cell proliferation	0.32
LN_k5	CD4+ Precursor differentiation rate to CD4+ Effector T cell	-0.15

Supplementary Table 4: PRCC values from granuloma-scale sensitivity analysis for active TB case

Parameter Names	Description	PRCC values
w3	Max percentage contribution of Th1 cells to Fas-FasL apoptosis of MI	-0.12
s4b		0.13
k2	MR infection rate	0.11
c9	Half-sat of BE on MR infection	-0.14
k17	MI death rate due to BI	0.36
N	Carrying capacity of MI	0.26
k14a	Fas-FasL induced apoptosis of MI	-0.17
k14b	TNF induced apoptosis of MI	-0.15
Sr1b	TNF dependent recruitment of primed CD4+ T cells	-0.21
s4b2	Half-sat of TNF dependent recruitment of primed CD4+ T cells	0.19
k6	Max rate of primed CD4+ T cells differentiating to Th1	-0.22
k7	Max rate of primed CD4+ T cells differentiating to Th2	0.11
s2	Half-sat of IL-4 production	-0.1
c	Half-sat of IFN-γ on Th1 death	-0.12
alpha32	TNF produced by Th1 cells	-0.24
nuTNF	Decay rate of TNF	0.12
alpha7	IFN-γ production by primed CD4+ T cells	-0.19
s12	IL-12 production	-0.19
c230	Half-sat of BI on IL-12 production	0.19
nuIL12	Decay rate of IL-12	0.13
nuIL10	Decay rate of IL-10	-0.13

alpha11	IL-4 produced by primed CD4+ T cells	0.26
alpha20	BE growth rate	0.17
k18	BE killing by MR	-0.22

Supplementary Table 5: PRCC values from granuloma-scale sensitivity analysis for TB eliminator case

Parameter Names	Description	PRCC values
k2	MR infection rate	0.11
c9	Half-sat of BE on MR infection	-0.14
k17	MI death rate due to BI	0.22
N	Carrying capacity of MI	0.11
k14a	Fas-FasL induced apoptosis of MI	-0.62
c4	Half-sat of cytotoxic and Th1 cells per MI on MI apoptosis	0.17
alpha11	IL-4 produced by primed CD4+ T cells	0.11
k18	BE killing by MR	-0.12

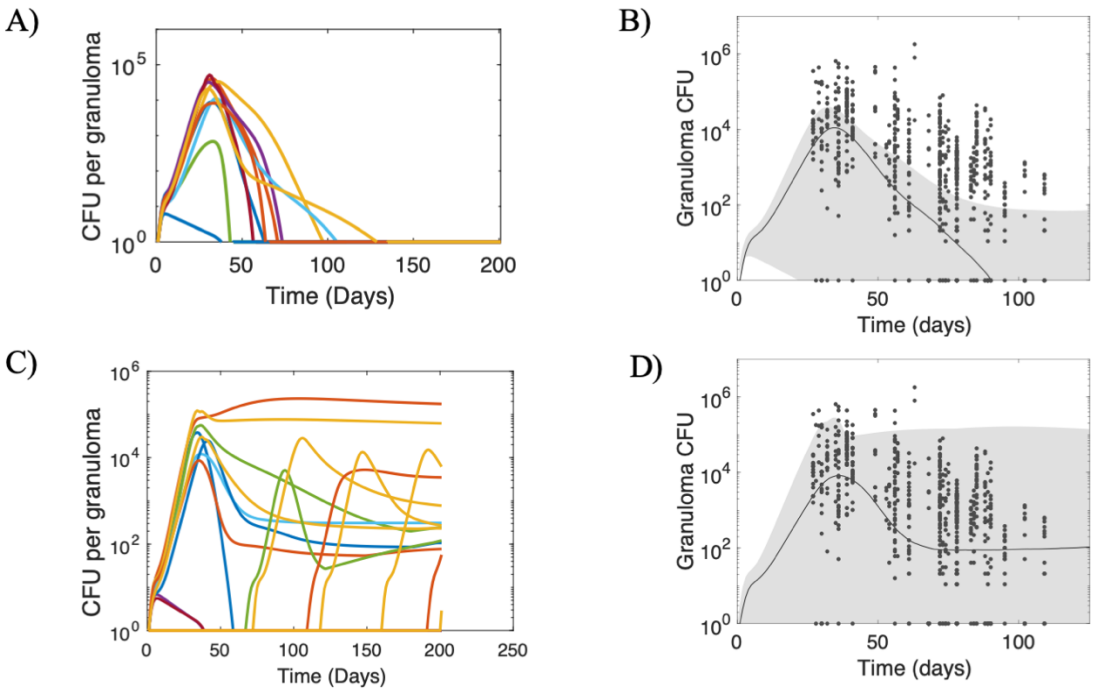

Figure S1: Representative simulations for intra-compartment sensitivity analysis. A) CFU trajectories within a single TB eliminator host. B) Minimum, median and maximum CFU trajectories for the TB eliminator host, re-simulated 500 times, varying only granuloma-scale parameters. C) CFU trajectories within a single active TB host. D) Minimum, median and maximum CFU trajectories for the active TB host, re-simulated 500 times, varying only granuloma-scale parameters.