1 Example 1 Equations: predator-prey model

All equations and parameters are included in the main body of the text for this two equation model. Additionally, we provide a directory for download that includes all Matlab scripts for running a fully automated version of *CaliPro* on this predator-prey model example. This includes model parameters, equations and execution. The webpage address where a reader can download the zipped directory is: http://malthus.micro.med.umich.edu/CaliPro

2 Example 2 Equations: ODE granuloma lesion model

As the second example, we apply *CaliPro* to a system of 16 ODEs that caputre 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 ($alpha_{20}$), 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.

$$\frac{dB_E}{dt} = \alpha_{20}B_E + k_{17}NM_I\left(\frac{B_I^2}{B_I^2+N^2M_I^2}\right) + k_{14a}N_{fracc}\frac{B_I}{MI}M_I\left(\frac{\left(\frac{T_C+w_3T_1}{M_I}\right)}{\left(\frac{T_C+w_3T_1}{M_I}\right)+c_4}\right)$$

$$+ k_{14b}N_{fraca}\frac{B_I}{MI}M_I\left(\frac{F_\alpha}{F_\alpha+f_9I_{10}+s_{4b}}\right) - k_2\frac{N}{2}M_R\left(\frac{B_E}{B_E+c_9}\right)$$

$$- k_{15}M_AB_E - k_{18}M_RB_E - \mu_{B_E}B_E + \mu_{M_I}N_{fracd}\frac{B_I}{MI}M_I$$

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.

$$\frac{dB_I}{dt} = \alpha_{19} B_I \left(NMI - B_I\right) + k_2 \frac{N}{2} M_R \left(\frac{B_E}{B_E + c_9}\right) - k_{17} N M_I \left(\frac{B_I^2}{B_I^2 + N^2 M_I^2}\right)$$

$$- k_{14a} \frac{B_I}{MI} M_I \left(\frac{\left(\frac{T_C + w_3 T_1}{M_I}\right)}{\left(\frac{T_C + w_3 T_1}{M_I}\right) + c_4}\right) - k_{14b} \frac{B_I}{MI} M_I \left(\frac{F_\alpha}{F_\alpha + f_9 I_{10} + s_{4b}}\right)$$

$$- k_{52} \frac{B_I}{MI} M_I \left(\frac{\left(\frac{T_C \left(\frac{T_1}{T_1 + c_{T_1}}\right) + w_1 T_1}{M_I}\right)}{\left(\frac{T_C \left(\frac{T_1}{T_1 + c_{T_1}}\right) + w_1 T_1}{M_I}\right) + c_{52}}\right)$$

$$- \mu_{B_I} B_I - \mu_{M_I} \frac{B_I}{MI} M_I$$

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 IFNgamma (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.

$$\frac{dT_0}{dt} = \alpha_{1a} \left(M_A + w_2 M_I\right) + Sr_{1b} \left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b2}}\right) + \alpha_2 T_0 \left(\frac{M_A}{M_A + c_{15}}\right)$$

$$- k_6 I_{12} T_0 \left(\frac{I_\gamma}{I_\gamma + (f_1 I_4 + f_7 I_{10}) + s_1}\right) - k_7 T_0 \left(\frac{I_4}{I_4 + f_2 I_\gamma + s_2}\right) - \mu_{T_0} T_0$$

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. They can die from too much IFNgamma (I_γ).

$$\frac{dT_1}{dt} = \alpha_{3a}\left(M_A + w_2 M_I\right) + Sr_{3b}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}}\right)$$

$$+ k_6 I_{12} T_0 \left(\frac{I_\gamma}{I_\gamma + (f_1 I_4 + f_7 I_{10}) + s_1}\right) - \mu_{T_\gamma}\left(\frac{I_\gamma}{I_\gamma + c}\right) T_1 M_A - \mu_{T_1} T_1$$

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.

$$\frac{dT_2}{dt} = \alpha_{3a2}\left(M_A + w_2 M_I\right) + Sr_{3b2}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}}\right)$$

$$+ k_7 T_0 \left(\frac{I_4}{I_4 + f_2 I_\gamma + s_2}\right) - \mu_{T_2} T_2$$

Primed CD8+ T cells ($T_8 0$) 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.

$$\frac{dT_{80}}{dt} = \alpha_{1a}\left(M_A + w_2 M_I\right) + Sr_{1b}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b2}}\right)$$

$$+ \alpha_2 T_{80}\left(\frac{M_A}{M_A + c_{15}}\right) - k_6 I_{12} T_{80}\left(\frac{I_\gamma}{I_\gamma + (f_1 I_4 + f_7 I_{10}) + s_1}\right) - \mu_{T_0} T_{80}$$

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 and can die from IFNgamma (I_γ).

$$\frac{dT_8}{dt} = m\alpha_{3ac}\left(M_A + w_2 M_I\right) + mSr_{3bc}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}}\right)$$

$$+ mk_6 I_{12} T_{80}\left(\frac{I_\gamma}{I_\gamma + (f_1 I_4 + f_7 I_{10}) + s_1}\right) - \mu_{T_{c\gamma}}\left(\frac{I_\gamma}{I_\gamma + c_c}\right) T_8 M_A - \mu_{T_C} T_8$$

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 and can die from IFNgamma (I_γ).

$$\frac{dT_C}{dt} = m\alpha_{3ac}\left(M_A + w_2 M_I\right) + mSr_{3bc}\left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}}\right)$$

$$+ mk_6 I_{12} T_{80}\left(\frac{I_\gamma}{I_\gamma + (f_1 I_4 + f_7 I_{10}) + s_1}\right) - \mu_{T_{c\gamma}}\left(\frac{I_\gamma}{I_\gamma + c_c}\right) T_C M_A - \mu_{T_C} T_C$$

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.

$$\frac{dF_\alpha}{dt} = \alpha_{30} M_I + \alpha_{31} M_A\left(\frac{I_\gamma + \beta_2(B_E + wB_I)}{I_\gamma + \beta_2(B_E + wB_I) + f_1 I_4 + f_7 I_{10} + s_{10}}\right)$$

$$+ \alpha_{32} T_1 + \alpha_{33}\left(\frac{T_C + T_8}{2m}\right) - \mu_{F_\alpha} F_\alpha$$

IFNgamma (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.

$$\frac{dI_{10}}{dt} = \delta_7 \left(M_I + M_A\right) \left(\frac{s_6}{I_{10} + f_6 I_\gamma + s_6}\right) + \alpha_{16} T_1 + \alpha_{17} T_2$$

$$+ \alpha_{18} \left(\frac{T_C + T_8}{2m}\right) - \mu_{I_{10}} I_{10}$$

IL-4 (I_4) is secreted by T_0 and T_2 before decaying in the granuloma.
$\frac{dI_4}{dt} = \alpha_{11} T_0 + \alpha_{12} T_2 - \mu_{I_4} I_4$

3 Example 3 Equations: transmission model of infectious disease

The model used for this example was initially shown in Menzies et al.[35] . More information can be found in their original paper, but briefly, the model includes 6 states including non-susceptible individuals (N), susceptible individuals (S), early disease cases (E), late disease cases (L) treatment cases (T) and dead individuals (D). The number of individuals by state and year (t) is given by N_t, S_t, E_t, L_t and T_t, respectively. Individuals enter the model as either non-susceptible or susceptible states, and transition between states to allow for infection (S to E) disease progression (E to L), treatment initiation (E and L to T), and death (all other states to D) via background and disease-specific mortality. μ parameters are death rates, λ_t is the force of infection based on contact rate, and a represents annual birth rate.

$$\begin{aligned}
\frac{dN}{dt} &= ab - \mu^B N \\
\frac{dS}{dt} &= a(1-b) - \mu^B S - \lambda_t S \\
\frac{dE}{dt} &= \lambda_t S - (\mu^B + \mu^E) E - r_t^E E - cE \\
\frac{dL}{dt} &= cE - (\mu^B + \mu^L) L - r^L L \\
\frac{dT}{dt} &= r_t^E E + r^L L - (\mu^B + \mu^T) T \\
\frac{dD}{dt} &= \mu^B (N + S + E + L + T + \mu^E E + \mu^L L + \mu^T T)
\end{aligned}$$

4 Example 4 Model: agent-based model of granuloma formation

GranSim is an agent-based model of granuloma formation during *Mycobacterium tuberculosis* infection that has been curated for approximately 15 years within our lab. For this model example, we execute a 2D version of *GranSim* representing 4mm by 4mm section of lung tissue that tracks molecular, cellular, and tissue-scale events. We host a website (http://malthus.micro.med.umich.edu/GranSim) devoted to *GranSim*'s development and rules. Interested readers can download model parameter sets and a model executable as well.