

1 Granuloma Ordinary Differential Equations

*Note: in these equations m is the same as $CD8MultiFunc$ in the text. m is defined as $m = \frac{frac + 1}{2}$, where $frac$ is the fraction of all new CD8 cells that are multifunctional.

$$\begin{aligned} \frac{dB_E}{dt} = & \\ & + \alpha_{20} B_E \text{ (BE replication)} \\ & + k_{17} N M_I \left(\frac{B_I^2}{B_I^2 + N^2 M_I^2} \right) \text{ (MI bursting)} \\ & + k_{14a} N_{frac} \frac{B_I}{M_I} M_I \left(\frac{\left(\frac{T_C + w_3 T_1}{M_I} \right)}{\left(\frac{T_C + w_3 T_1}{M_I} \right) + c_4} \right) \text{ (Tcell-induced MI apoptosis)} \\ & + k_{14b} N_{frac} \frac{B_I}{M_I} M_I \left(\frac{F_\alpha}{F_\alpha + f_9 I_{10} + s_{4b}} \right) \text{ (TNF-}\alpha\text{-induced MI apoptosis)} \\ & - k_2 \frac{N}{2} M_R \left(\frac{B_E}{B_E + c_9} \right) \text{ (MR internalization)} \\ & - k_{15} M_A B_E \text{ (MA killing)} \\ & - k_{18} M_R B_E \text{ (MR killing)} \\ & - \mu_{B_E} B_E \text{ (BE natural death)} \\ & + \mu_{M_I} N_{frac} \frac{B_I}{M_I} M_I \text{ (MI natural death)} \end{aligned}$$

$$\begin{aligned}
\frac{dB_I}{dt} = & \\
& + \alpha_{19} B_I (NMI - B_I) \text{ (BI replication)} \\
& + k_2 \frac{N}{2} M_R \left(\frac{B_E}{B_E + c_9} \right) \text{ (MR internalization)} \\
& - k_{17} N M_I \left(\frac{B_I^2}{B_I^2 + N^2 M_I^2} \right) \text{ (MI bursting)} \\
& - k_{14a} \frac{B_I}{M I} M_I \left(\frac{\left(\frac{T_C + w_3 T_1}{M_I} \right)}{\left(\frac{T_C + w_3 T_1}{M_I} \right) + c_4} \right) \text{ (Tcell-induced MI apoptosis)} \\
& - k_{14b} \frac{B_I}{M I} M_I \left(\frac{F_\alpha}{F_\alpha + f_9 I_{10} + s_{4b}} \right) \text{ (TNF-}\alpha\text{-induced MI apoptosis)} \\
& - k_{52} \frac{B_I}{M I} M_I \left(\frac{\left(\frac{T_C \left(\frac{T_1}{T_1 + c_{T_1}} \right) + w_1 T_1}{M_I} \right)}{\left(\frac{T_C \left(\frac{T_1}{T_1 + c_{T_1}} \right) + w_1 T_1}{M_I} \right) + c_{52}} \right) \text{ (Tcell cytotoxic MI killing)} \\
& - \mu_{B_I} B_I \text{ (BI death inside living MI)} \\
& - \mu_{M_I} \frac{B_I}{M I} M_I \text{ (MI natural death)}
\end{aligned}$$

$$\begin{aligned}
\frac{dM_R}{dt} = & \\
& + S r_M \text{ (Background recruitment)} \\
& + \alpha_{4a} (M_A + w_2 M_I) \text{ (MA/MI recruitment)} \\
& + S r_{4b} \left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b}} \right) \text{ (TNF-}\alpha\text{ recruitment)} \\
& - k_2 M_R \left(\frac{B_E}{B_E + c_9} \right) \text{ (MR infection)} \\
& - k_3 M_R \left(\frac{B_E + w B_I + \beta F_\alpha}{B_E + w B_I + \beta F_\alpha + c_8} \right) \left(\frac{I_\gamma}{I_\gamma + f_1 I_4 + f_7 I_{10} + s_1} \right) \text{ (MR activation)} \\
& - \mu_{M_R} M_R \text{ (MR natural death)}
\end{aligned}$$

$$\begin{aligned}
\frac{dM_I}{dt} = & \\
& + k_2 M_R \left(\frac{B_E}{B_E + c_9} \right) \text{ (MR infection)} \\
& - k_{17} M_I \left(\frac{B_I^2}{B_I^2 + N^2 M_I^2} \right) \text{ (MI Bursting)} \\
& - k_{14a} M_I \left(\frac{\left(\frac{T_C + w_3 T_1}{M_I} \right)}{\left(\frac{T_C + w_3 T_1}{M_I} \right) + c_4} \right) \text{ (Tcell-induced MI apoptosis)} \\
& - k_{14b} M_I \left(\frac{F_\alpha}{F_\alpha + f_9 I_{10} + s_{4b}} \right) \text{ (TNF-}\alpha\text{-induced MI apoptosis)} \\
& - k_{52} M_I \left(\frac{\left(\frac{T_C \left(\frac{T_1}{T_1 + c_{T_1}} \right) + w_1 T_1}{M_I} \right)}{\left(\frac{T_C \left(\frac{T_1}{T_1 + c_{T_1}} \right) + w_1 T_1}{M_I} \right) + c_{52}} \right) \text{ (Tcell cytotoxic MI killing)} \\
& - \mu_{M_I} M_I \text{ (MI natural death)}
\end{aligned}$$

$$\begin{aligned}
\frac{dM_A}{dt} = & \\
& + k_3 M_R \left(\frac{B_E + w B_I + \beta F_\alpha}{B_E + w B_I + \beta F_\alpha + c_8} \right) \left(\frac{I_\gamma}{I_\gamma + f_1 I_4 + f_7 I_{10} + s_1} \right) \text{ (MA activation)} \\
& - k_4 M_A \left(\frac{I_{10}}{I_{10} + s_8} \right) \text{ (MA deactivation)} \\
& - \mu_{M_A} M_A \text{ (MA natural death)}
\end{aligned}$$

$$\begin{aligned}
\frac{dT_0}{dt} = & \\
& + \alpha_{1a} (M_A + w_2 M_I) \text{ (Mac T0 recruitment)} \\
& + S r_{1b} \left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b2}} \right) \text{ (TNF-}\alpha\text{ recruitment)} \\
& + \alpha_2 T_0 \left(\frac{M_A}{M_A + c_{15}} \right) \text{ (T0 proliferation)} \\
& - k_6 I_{12} T_0 \left(\frac{I_\gamma}{I_\gamma + (f_1 I_4 + f_7 I_{10}) + s_1} \right) \text{ (T0 to Th1 differentiation)} \\
& - k_7 T_0 \left(\frac{I_4}{I_4 + f_2 I_\gamma + s_2} \right) \text{ (T0 to Th2 differentiation)} \\
& - \mu_{T_0} T_0 \text{ (T0 natural death)}
\end{aligned}$$

$$\begin{aligned}
\frac{dT_1}{dt} = & \\
& + \alpha_{3a} (M_A + w_2 M_I) \text{ (Mac Th1 recruitment)} \\
& + S r_{3b} \left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}} \right) \text{ (TNF-}\alpha\text{ recruitment)} \\
& + k_6 I_{12} T_0 \left(\frac{I_\gamma}{I_\gamma + (f_1 I_4 + f_7 I_{10}) + s_1} \right) \text{ (T0 to Th1 differentiation)} \\
& - \mu_{T_\gamma} \left(\frac{I_\gamma}{I_\gamma + c} \right) T_1 M_A \text{ (IFN-}\alpha\text{ Th1 apoptosis)} \\
& - \mu_{T_1} T_1 \text{ (Th1 natural death)}
\end{aligned}$$

$$\begin{aligned}
\frac{dT_2}{dt} = & \\
& + \alpha_{3a2} (M_A + w_2 M_I) \text{ (Mac Th2 recruitment)} \\
& + S r_{3b2} \left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}} \right) \text{ (TNF-}\alpha\text{ Th2 recruitment)} \\
& + k_7 T_0 \left(\frac{I_4}{I_4 + f_2 I_\gamma + s_2} \right) \text{ (T0 to Th2 differentiation)} \\
& - \mu_{T_2} T_2 \text{ (Th2 natural death)}
\end{aligned}$$

$$\begin{aligned}
\frac{dT_{80}}{dt} = & \\
& + \alpha_{1a} (M_A + w_2 M_I) \text{ (Mac T80 recruitment)} \\
& + S r_{1b} \left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b2}} \right) \text{ (TNF-}\alpha\text{ T80 recruitment)} \\
& + \alpha_2 T_{80} \left(\frac{M_A}{M_A + c_{15}} \right) \text{ (T80 proliferation)} \\
& - k_6 I_{12} T_{80} \left(\frac{I_\gamma}{I_\gamma + (f_1 I_4 + f_7 I_{10}) + s_1} \right) \text{ (T80 to TC/T8 differentiation)} \\
& - \mu_{T_0} T_{80} \text{ (T80 natural death)}
\end{aligned}$$

$$\begin{aligned}
\frac{dT_8}{dt} = & \\
& + m \alpha_{3ac} (M_A + w_2 M_I) \text{ (Mac T8 recruitment)} \\
& + m S r_{3bc} \left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}} \right) \text{ (TNF-}\alpha\text{ T8 recruitment)} \\
& + m k_6 I_{12} T_{80} \left(\frac{I_\gamma}{I_\gamma + (f_1 I_4 + f_7 I_{10}) + s_1} \right) \text{ (T80 to TC/T8 differentiation)} \\
& - \mu_{T_{c\gamma}} \left(\frac{I_\gamma}{I_\gamma + c_c} \right) T_8 M_A \text{ (IFN-}\alpha\text{ T8 apoptosis)} \\
& - \mu_{T_C} T_8 \text{ (T8 natural death)}
\end{aligned}$$

$$\begin{aligned}
\frac{dT_C}{dt} = & \\
& + m \alpha_{3ac} (M_A + w_2 M_I) \text{ (Mac TC recruitment)} \\
& + m S r_{3bc} \left(\frac{F_\alpha}{F_\alpha + f_8 I_{10} + s_{4b1}} \right) \text{ (TNF-}\alpha\text{ TC recruitment)} \\
& + m k_6 I_{12} T_{80} \left(\frac{I_\gamma}{I_\gamma + (f_1 I_4 + f_7 I_{10}) + s_1} \right) \text{ (T80 to TC/T8 differentiation)} \\
& - \mu_{T_{c\gamma}} \left(\frac{I_\gamma}{I_\gamma + c_c} \right) T_C M_A \text{ (IFN-}\alpha\text{ TC apoptosis)} \\
& - \mu_{T_C} T_C \text{ (TC natural death)}
\end{aligned}$$

$$\begin{aligned}
\frac{dF_\alpha}{dt} = & \\
& + \alpha_{30} M_I \text{ (MI TNF-}\alpha\text{ production)} \\
& + \alpha_{31} M_A \left(\frac{I_\gamma + \beta_2(B_E + wB_I)}{I_\gamma + \beta_2(B_E + wB_I) + f_1 I_4 + f_7 I_{10} + s_{10}} \right) \text{ (MA TNF-}\alpha\text{ production)} \\
& + \alpha_{32} T_1 \text{ (Th1 TNF-}\alpha\text{ production)} \\
& + \alpha_{33} \left(\frac{T_C + T_8}{2m} \right) \text{ (CD8+ TNF-}\alpha\text{ production)} \\
& - \mu_{F_\alpha} F_\alpha \text{ (TNF-}\alpha\text{ natural decay)}
\end{aligned}$$

$$\begin{aligned}
\frac{dI_\gamma}{dt} = & \\
& + s_g \left(\frac{B_E + wB_I}{B_E + wB_I + c_{10}} \right) \left(\frac{I_{12}}{I_{12} + s_7} \right) \text{ (DC IG production)} \\
& + \alpha_{5a} T_1 \left(\frac{M_A}{M_A + c_{5a}} \right) \text{ (Th1 IG production)} \\
& + \alpha_{5b} T_8 \left(\frac{M_A}{M_A + c_{5b}} \right) \text{ (T8 IG production)} \\
& + \alpha_{5c} M_I \text{ (MI IG production)} \\
& + \alpha_7 T_0 \left(\frac{I_{12}}{I_{12} + f_4 I_{10} + s_4} \right) \text{ (T0 IG production)} \\
& + \alpha_7 T_{80} \left(\frac{I_{12}}{I_{12} + f_4 I_{10} + s_4} \right) \text{ (T80 IG production)} \\
& - \mu_{I_\gamma} I_\gamma \text{ (IG natural decay)}
\end{aligned}$$

$$\begin{aligned}
\frac{dI_{12}}{dt} = & \\
& + s_{12} \left(\frac{B_E + wB_I}{B_E + wB_I + c_{230}} \right) \text{ (DC I12 production)} \\
& + \alpha_{23} M_R \left(\frac{B_E + wB_I}{B_E + wB_I + c_{23}} \right) \text{ (MR I12 production)} \\
& + \alpha_8 M_A \left(\frac{s}{s + I_{10}} \right) \text{ (MA I12 production)} \\
& - \mu_{I_{12}} I_{12} \text{ (I12 natural decay)}
\end{aligned}$$

$$\begin{aligned}
\frac{dI_{10}}{dt} = & \\
& + \delta_7 (M_I + M_A) \left(\frac{s_6}{I_{10} + f_6 I_\gamma + s_6} \right) \text{ (MI I10 production)} \\
& + \alpha_{16} T_1 \text{ (Th1 I10 production)} \\
& + \alpha_{17} T_2 \text{ (Th2 I10 production)} \\
& + \alpha_{18} \left(\frac{T_C + T_8}{2m} \right) \text{ (CD8 I10 production)} \\
& - \mu_{I_{10}} I_{10} \text{ (I10 natural decay)}
\end{aligned}$$

$$\begin{aligned}
\frac{dI_4}{dt} = & \\
& + \alpha_{11} T_0 \text{ (T0 I4 production)} \\
& + \alpha_{12} T_2 \text{ (T2 I4 production)} \\
& - \mu_{I_4} I_4 \text{ (I4 natural decay)}
\end{aligned}$$

2 Dissemination Equations

2.1 Local Dissemination

2.1.1 Probability

$$Prob_{Local}(t) = \lambda_{Local} \frac{CFU(t)}{CFU(t) + CFU_{half}^{Local}}$$

2.1.2 Expected Value

$$E_{Local}(t+dt) = E_{Local}(t) + \int_t^{dt} Prob_{Local}(s) ds \approx E_{Local}(t) + \lambda_{Local} \frac{CFU(t)}{CFU(t) + CFU_{half}^{Local}} dt$$

2.2 Number of Dissemination Events

$$\begin{aligned}
NumDiss_{Local}(t+dt) &= Floor(Res_{Local}(t) + E_{Local}(t+dt) - E_{Local}(t)) \\
Res_{Local}(t+dt) &= (Res_{Local}(t) + E_{Local}(t+dt) - E_{Local}(t)) - NumDiss_{Local}(t+dt)
\end{aligned}$$

2.2.1 Updated Counts/Concentrations

$$MI^{Parent} = \begin{cases} MI^{Parent} - 1 & \text{if } MI^{Parent} \geq 1 \\ 0 & \text{if } MI^{Parent} < 1 \end{cases}$$

$$BI^{Parent} = \begin{cases} BI^{Parent} - \frac{BI^{Parent}}{MI^{Parent}} & \text{if } MI^{Parent} \geq 1 \\ 0 & \text{if } MI^{Parent} < 1 \end{cases}$$

$$T_0^{Parent, New}(t) = T_0^{Parent, Old}(t) - Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_0^{Parent, Old}(t)$$

$$T_1^{Parent, New}(t) = T_1^{Parent, Old}(t) - Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_1^{Parent, Old}(t)$$

$$T_2^{Parent, New}(t) = T_2^{Parent, Old}(t) - Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_2^{Parent, Old}(t)$$

$$T_{80}^{Parent, New}(t) = T_{80}^{Parent, Old}(t) - Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_{80}^{Parent, Old}(t)$$

$$T_C^{Parent, New}(t) = T_C^{Parent, Old}(t) - Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_C^{Parent, Old}(t)$$

$$T_8^{Parent, New}(t) = T_8^{Parent, Old}(t) - Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_8^{Parent, Old}(t)$$

Other counts/concentrations remain unchanged

$$MI^{Daughter} = \begin{cases} 1 & \text{if } MI^{Parent} \geq 1 \\ MI^{Parent} & \text{if } MI^{Parent} < 1 \end{cases}$$

$$BI^{Daughter} = \begin{cases} BI^{Parent} & \text{if } MI^{Parent} \geq 1 \\ \frac{BI^{Parent}}{MI^{Parent}} & \text{if } MI^{Parent} < 1 \end{cases}$$

$$T_0^{Daughter}(t) = Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_0^{Parent, Old}(t)$$

$$T_1^{Daughter}(t) = Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_1^{Parent, Old}(t)$$

$$T_2^{Daughter}(t) = Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_2^{Parent, Old}(t)$$

$$T_{80}^{Daughter}(t) = Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_{80}^{Parent, Old}(t)$$

$$T_C^{Daughter}(t) = Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_C^{Parent, Old}(t)$$

$$T_8^{Daughter}(t) = Norm(\mu_{Local}^{Tfrac}, \sigma_{Local}^{Tfrac}) * T_8^{Parent, Old}(t)$$

Other counts/concentrations are 0

2.2.2 Location

$$x_{Daughter} = x_{Parent} + R_{rand} * \cos(\theta_{rand}) * \sin(\phi_{rand})$$

$$y_{Daughter} = y_{Parent} + R_{rand} * \sin(\theta_{rand}) * \sin(\phi_{rand})$$

$$z_{Daughter} = z_{Parent} + R_{rand} * \cos(\phi_{rand})$$

where:

$$R_{rand} = Norm(\mu_{Local}^{Dist}, \sigma_{Local}^{Dist})$$

$$\theta_{rand} = Unif(0, 1) * 2 * \pi$$

$$\phi_{rand} = Unif(0, 1) * \pi$$

and:

$$(x_{Daughter}, y_{Daughter}, z_{Daughter}) \in \Gamma$$

2.3 Nonocal Dissemination

2.3.1 Probability

$$Prob_{Nonlocal}(t) = \lambda_{Nonlocal} \frac{CFU(t)}{CFU(t) + CFU_{half}^{Nonlocal}}$$

2.3.2 Expected Value

$$E_{Nonlocal}(t+dt) = E_{Nonlocal}(t) + \int_t^{dt} Prob_{Local}(s)ds \approx E_{Nonlocal}(t) + \lambda_{Nonlocal} \frac{CFU(t)}{CFU(t) + CFU_{half}^{Nonlocal}} dt$$

2.4 Number of Dissemination Events

$$\begin{aligned} NumDiss_{Nonlocal}(t+dt) &= Floor(Res_{Nonlocal}(t) + E_{Nonlocal}(t+dt) - E_{Nonlocal}(t)) \\ Res_{Nonlocal}(t+dt) &= (Res_{Nonlocal}(t) + E_{Nonlocal}(t+dt) - E_{Nonlocal}(t)) - NumDiss_{Nonlocal}(t+dt) \end{aligned}$$

2.4.1 Updated Counts/Concentrations

$$BE^{Parent} = BE^{Parent} - 1$$

Other counts/concentrations remain unchanged

$$MI^{Daughter} = 1$$

$$BI^{Daughter} = 1$$

Other counts/concentrations are 0

2.4.2 Location

$$x_{Daughter} = x_{min} + Unif(0, 1) * (x_{max} - x_{min})$$

$$y_{Daughter} = y_{min} + Unif(0, 1) * (y_{max} - y_{min})$$

$$z_{Daughter} = z_{min} + Unif(0, 1) * (z_{max} - z_{min})$$

where:

$$(x_{Daughter}, y_{Daughter}, z_{Daughter}) \in \Gamma$$