A model for in-host viral infection dynamics

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1 Model descriptions

1.1 Agent based model

Let $n, m \in \mathbb{N}$. For each $i \in \{1, \dots, n\}$, $j \in \{1, \dots, m\}$. Consider the following system.

$$\frac{dT_i}{dt} = b - \delta T_i - \frac{\kappa}{1 + \alpha A_i} T_i V_i, \tag{1}$$

$$\frac{dT_i^*}{dt} = \frac{\kappa}{1 + \alpha A_i} T_i V_i - q T_i^*, \tag{2}$$

$$\frac{dV_i}{dt} = p T_i^* - c V_i - c_A A_i V_i - X_i(t) + g\left(W_i + \sum_{j=1}^{m} \eta_{ij} Z_j\right), \tag{3}$$

$$\frac{dA_i}{dt} = b_A - \delta_A A_i + \kappa_A A_i(t - \tau) V_i(t - \tau), \tag{4}$$

$$\tag{5}$$

$$\frac{dZ_j}{dt} = \sum_{i=1}^{n} \xi_{ij} V_i - \delta_Z Z_j, \tag{6}$$

$$W_i(t) = \zeta \sum_{k=1}^{n} Y_{ik}(\lfloor t \rfloor) V_k(\lfloor t \rfloor), \tag{7}$$

$$g(x) = x \, \mathbf{1}_{(v, \infty)}(x). \tag{8}$$

Here, we define random variables $X_i(t) \sim \mathrm{Exp}(\lambda)$, $Y_{ik}(\lfloor t \rfloor) \sim \mathrm{Bernoulli}(s_{ik}\, p_{\mathrm{inf}})$.

The parameters ξ_{ij}, η_{ij} are to be thought of as weights linking agents with their environments; the parameters s_{ik} are to be thought of as strengths of connections between agents forming a network.

The model state is described by $(T, T^*, V, A, W, Z) \in \mathcal{S} \equiv \mathbb{R}_{\geq 0}^{3n} \times \mathcal{C}_\tau \times \mathcal{C}_\tau \times \mathbb{R}_{\geq 0}^{m}$, with $\mathcal{C}_\tau \equiv \mathcal{C}(0, \tau)$, $T \equiv (T_1, \dots, T_n)$, and so on.

The model parameters are $(b, \delta, \kappa, q, p, c, b_A, \delta_A, \kappa_A, c_A, \alpha, \tau, \delta_Z, v, \lambda, p_{\mathrm{inf}}, \zeta, \eta, \xi, s) \in \mathcal{P} \equiv \mathbb{R}_{\geq 0}^{17} \times \mathbb{R}_{\geq 0}^{mn} \times \mathbb{R}_{\geq 0}^{mn} \times [0, 1]^{n \times n}$, with $\eta \equiv [\eta_{ij}]_{ij}$, $\xi \equiv [\xi_{ij}]_{ij}$, and $s \equiv [s_{ik}]_{ik}$.

Table 1: Model state variables

Variable	Units	Interpretation
T	cells/ml	Concentration of target cells
T^*	cells/ml	Concentration of infected cells
V	copies/ml	Concentration of viral copies
A	imm/ml	Antibody/immunity level
W	copies/ml	Contact pressure of viral copies
Z	copies/m^2	Environmental viral copies

Table 2: Model parameters

Parameter	Units	Interpretation
b	cells ml^{-1}day^{-1}	Generation rate of target cells
δ	day^{-1}	Death rate of target cells
κ	cells^{-1}ml day^{-1}	Infection rate of target cells
q	day^{-1}	Death rate of infected cells
p	copies cells^{-1}day^{-1}	Production rate of viral copies
c	day^{-1}	Clearance rate of viral copies
b_A	imm ml^{-1}day^{-1}	Generation rate of antibodies
δ_A	day^{-1}	Clearance rate of antibodies
κ_A	copies^{-1}ml day^{-1}	Production rate of antibodies
c_A	imm^{-1}ml day^{-1}	Clearance rate of viral copies via antibodies
α	imm^{-1}ml	Inhibition of viral-target contact
τ	day	Delay in antibody production
δ_Z	day^{-1}	Removal rate of viral copies
v	copies ml^{-1}	Entry threshold of viral concentration
λ	copies^{-1}ml day	Reciprocal of mean of stochastic viral removal
p_{inf}	–	Probability of viral load transfer
ζ	–	Fraction of viral load transferred
η_{ij}	copies ml^{-1}cells^{-1}m^2 day^{-1}	Environment-Agent transmission rate of virus
ξ_{ij}	copies^{-1}ml cells m^{-2} day^{-1}	Viral shedding rate into environment
s_{ik}	–	Strength of contact between agents

After choosing thresholds V' and A', we can count

$$S = \sum_{i=1}^{n} \mathbf{1}(A \leq A')\, \mathbf{1}(V \leq V') \tag{9}$$

$$I = \sum_{i=1}^{n} \mathbf{1}(V > V'), \tag{10}$$

$$R = n - S - I. \tag{11}$$

1.2 In-host submodel

Consider the in-host model described below.

$$\begin{aligned}
\frac{dT}{dt} &= b - \delta T - \frac{\kappa}{1+\alpha A} TV, \\
\frac{dT^*}{dt} &= \frac{\kappa}{1+\alpha A} TV - qT^*, \\
\frac{dV}{dt} &= pT^* - cV - c_A AV, \\
\frac{dA}{dt} &= b_A - \delta_A A + \kappa_A A(t-\tau)V(t-\tau).
\end{aligned}$$

Solving for an equilibrium, we demand

$$\frac{\kappa}{1+\alpha A} TV = b - \delta T = qT^*, \qquad pT^* = (c + c_A A)V, \qquad b_A - \delta_A A = -\kappa_A AV.$$

Thus,

$$\frac{p}{q}(b - \delta T) = -\frac{(c + c_A A)(b_A - \delta_A A)}{\kappa_A A},$$

whence

$$T = \frac{b}{\delta} + \frac{q(c + c_A A)(b_A - \delta_A A)}{p\delta\kappa_A A}.$$

Furthermore,

$$1 + \alpha A = \frac{\kappa TV}{b - \delta T} = -T\frac{(b_A - \delta_A A)/\kappa_A}{(b - \delta T)/\kappa},$$

whence

$$\frac{b - \delta T}{\kappa T} = -\frac{b_A - \delta_A A}{\kappa_A(1 + \alpha A)}.$$

Thus,

$$T = \frac{q(c + c_A A)(1 + \alpha A)}{p\kappa A}.$$

This gives

$$\frac{b}{\delta} = \frac{q(c + c_A A)}{pA}\left[\frac{1 + \alpha A}{\kappa} - \frac{b_A - \delta_A A}{\delta\kappa_A}\right].$$

Putting $T_0 = b/\delta$, $T = b_A/\delta_A$, we have

$$pAT_0 = q(c + c_A A)\left[\frac{1 + \alpha A}{\kappa} - \frac{\delta_A(A_0 - A)}{\delta\kappa_A}\right],$$

whence

$$p\kappa T_0 A = q(c + c_A A)\left[1 - \frac{\kappa/\delta}{\kappa_A/\delta_A}A_0 + \left(\alpha + \frac{\kappa/\delta}{\kappa_A/\delta_A}\right)A\right].$$

Setting $\beta = (\kappa/\delta)/(\kappa_A/\delta_A)$, $r = p/q$, $\gamma = c_A/c$, we have

$$\kappa r T_0 A = c(1 + \gamma A)[1 - \beta A_0 + (\alpha + \beta)A].$$

Thus,

$$\gamma(\alpha + \beta)A^2 + [\gamma(1 - \beta A_0) + (\alpha + \beta) - \kappa r T_0/c]A + (1 - \beta A_0) = 0,$$

or

$$A^2 + \left[\frac{1 - \beta A_0}{\alpha + \beta} + \frac{1}{\gamma} - \frac{\kappa r T_0}{c\gamma(\alpha + \beta)}\right]A + \frac{1 - \beta A_0}{\gamma(\alpha + \beta)} = 0.$$

1.3 Multiscale model

$$
\begin{aligned}
\frac{dS}{dt} &= -\beta_I(V,I)SI - \beta_Z(Z)SZ + \mu R, && (12)\\
\frac{dI}{dt} &= \beta_I(V,I)SI + \beta_Z(Z)SZ - \gamma I, && (13)\\
\frac{dR}{dt} &= \gamma I - \mu R, && (14)\\
& && (15)\\
\frac{dZ}{dt} &= \xi I - \delta_Z Z, && (16)\\
& && (17)\\
\epsilon\frac{dT}{dt} &= b - \delta T - \frac{\kappa}{1+\alpha A}TV, && (18)\\
\epsilon\frac{dT^*}{dt} &= \frac{\kappa}{1+\alpha A}TV - qT^*, && (19)\\
\epsilon\frac{dV}{dt} &= \eta Z + pT^* - cV - c_A AV, && (20)\\
\epsilon\frac{dA}{dt} &= b_A - \delta_A A + \kappa_A A(t-\tau)V(t-\tau). && (21)
\end{aligned}
$$

Here,

$$
\beta_I(V,I) = \frac{\beta_{I0} + C_0 V}{1 + C_1 I}, \qquad \beta_Z(Z) = \frac{\beta_{Z0}}{1 + C_2 Z}.
$$

1.4 SIRS model

$$
\begin{aligned}
\frac{dS}{dt} &= -\frac{\beta SI}{N} + \mu R, && (22)\\
\frac{dI}{dt} &= \frac{\beta SI}{N} - \gamma I, && (23)\\
\frac{dR}{dt} &= \gamma I - \mu R. && (24)
\end{aligned}
$$

Here, $N = S + I + R$.

2 Objectives

1. Compare the S, I, R curves with those obtained from a simplified model with one agent and one environment.
2. Identify/interpret infection phases (S, I, R) using the in-host variables (T, T^*, V, A).
3. Investigate the effects of heterogeneity in the agents and their contact network. For instance,
   (a) In-host parameters may be varied across agents, forming two or more groups.
   (b) Groups of agents may be vaccinated.
4. Investigate the effect of the stochastic term $X_i(t)$ in the in-host model.

3 Observations

1. The agent based model (1.1) is capable of producing infection curves with multiple waves/peaks.

2. Averaged infection curves from model (1.1) also show multiple peaks; the curve up to the first peak fits well against the SIRS model (1.4).

3. Individuals in model (1.1) become 'infected' when a pulse is applied on W_i. The viral load V_i rapidly increases, which after a short delay leads to a rapid increase in the antibody/immunity A_i. This V_i to fall sharply to zero. A_i gradually drops back to its baseline level. A sufficiently elevated A_i confers 'immunity' to the individual, preventing reinfection. The probability of reinfection, as a function of time since infection, can be calculated.

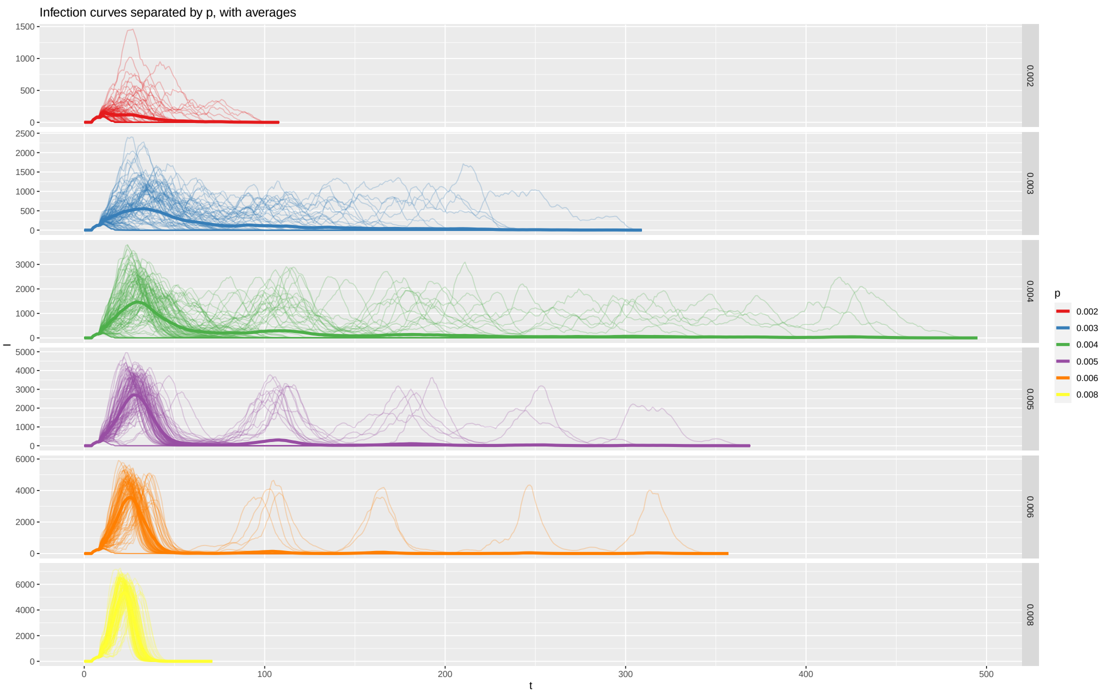

Figure 1: Infection curves, by varying infection probabilities p_{inf}.

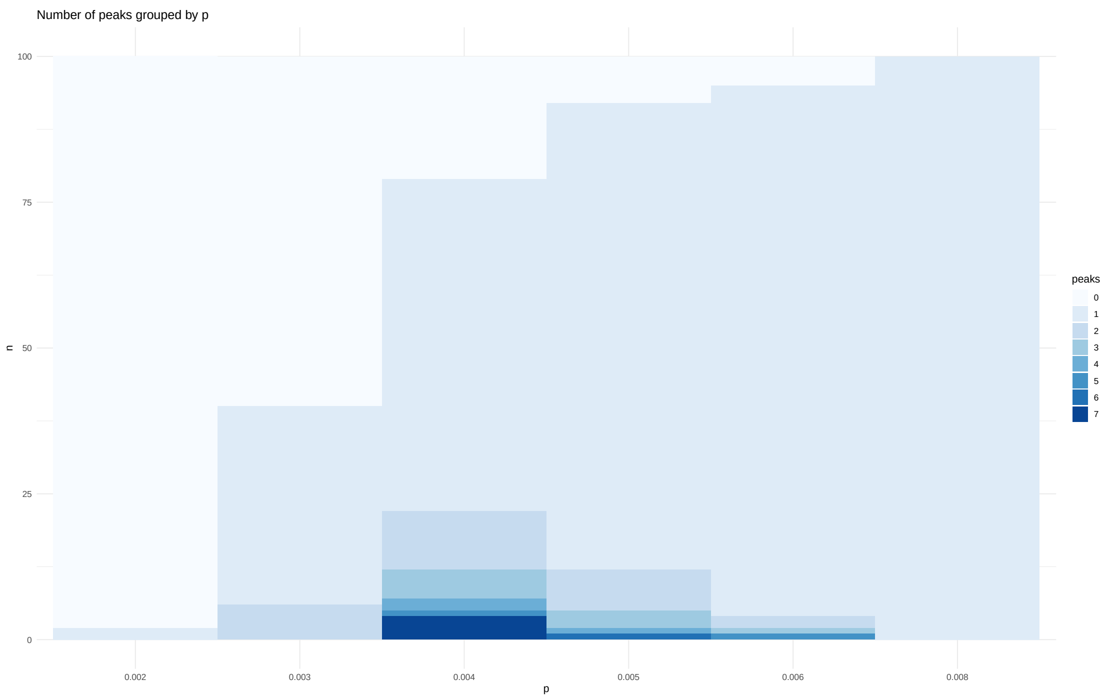

Figure 2: Number of runs (out of 100) with n peaks in the infection curve, by varying infection probabilities p_{inf}