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 $i \in \{1, \ldots, n\}$, $j \in \{1, \ldots, m\}$. 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 $X_i(t) \sim \text{Exp}(\lambda)$, $Y_{ik}(\lfloor t \rfloor) \sim \text{Bernoulli}(s_{ik}\, p_{\text{inf}})$.

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 $(T, T^*, V, A, W, Z) \in \mathcal{S} \equiv \mathbb{R}^{3n}_{\geq 0} \times \mathcal{C}_\tau \times \mathcal{C}_\tau \times \mathbb{R}^m_{\geq 0}$, with $\mathcal{C}_\tau \equiv \mathcal{C}(0, \tau)$, $T \equiv (T_1, \ldots, T_n)$, and so on.

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

Simplifications: Given i, let $\eta_{ij} = \eta$, $\xi_{ij} = \xi$ for precisely one j and $\eta_{ij}, \xi_{ij} = 0$ for the rest. In other words, let each agent belong to precisely one environment. Furthermore, let $s_{ik} \in \{0, 1\}$, with all $s_{ii} = 0$.

With the underlying agent-environment and agent-agent connections fixed, the parameter space reduces to $\mathbb{R}^{19}_{\geq 0}$.

Description: This model accommodates n agents, each of which belongs to one of m environments. The agents also form the nodes of a contact network. Each agent maintains its own in-host variables T, T^*, V, A which evolve over time. Each environment accumulates viral copies from its member agents, which decay over time. At the start of every day, each agent is stochastically assigned a subset of its contact neighbours, which together with the agent's environment contribute an 'external pressure' of viral copies. If this crosses a threshold v, then the agent becomes infected and experiences a rapid increase in its in-host viral load V.

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

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

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

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

Here, S denotes the number of susceptible agents, I denotes the number of infectuous agents, and R denotes the number of recovered agents. The threshold V' is chosen such that its contribution to the external pressure of viral copies is enough to cross the barrier v. The threshold A' is chosen such that a typical individual with that level of antibodies is immune to infection.

1.2 In-host submodel

Consider the in-host model described below.

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

Equilibria: Note that $(b/\delta, 0, 0, b_A/\delta_A)$ is a trivial infection-free equilibrium. Solving for other equilibria, 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

$$\frac{dS}{dt} = -\beta_I(V, I) SI - \beta_Z(Z) SZ + \mu R, \tag{12}$$

$$\frac{dI}{dt} = \beta_I(V, I) SI + \beta_Z(Z) SZ - \gamma I, \tag{13}$$

$$\frac{dR}{dt} = \gamma I - \mu R, \tag{14}$$

$$\tag{15}$$

$$\frac{dZ}{dt} = \xi I - \delta_Z Z, \tag{16}$$

$$\tag{17}$$

$$\epsilon \frac{dT}{dt} = b - \delta T - \frac{\kappa}{1 + \alpha A} TV, \tag{18}$$

$$\epsilon \frac{dT^*}{dt} = \frac{\kappa}{1 + \alpha A} TV - qT^*, \tag{19}$$

$$\epsilon \frac{dV}{dt} = \eta Z + pT^* - cV - c_A AV, \tag{20}$$

$$\epsilon \frac{dA}{dt} = b_A - \delta_A A + \kappa_A A(t - \tau) V(t - \tau). \tag{21}$$

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

$$\frac{dS}{dt} = -\frac{\beta SI}{N} + \mu R, \tag{22}$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} - \gamma I, \tag{23}$$

$$\frac{dR}{dt} = \gamma I - \mu R. \tag{24}$$

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). Individual infection curves from model (1.1) up to the first peak also fit well against model (1.4).
3. There is a narrow range of p_{inf}, with all other parameters in model (1.1) fixed, in which a significant proportion of infection curves display multiple prominent peaks without damping. For lower p_{inf}, infection curves become more stochastic in nature.
4. 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 forces V_i to fall sharply to zero, after which 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.

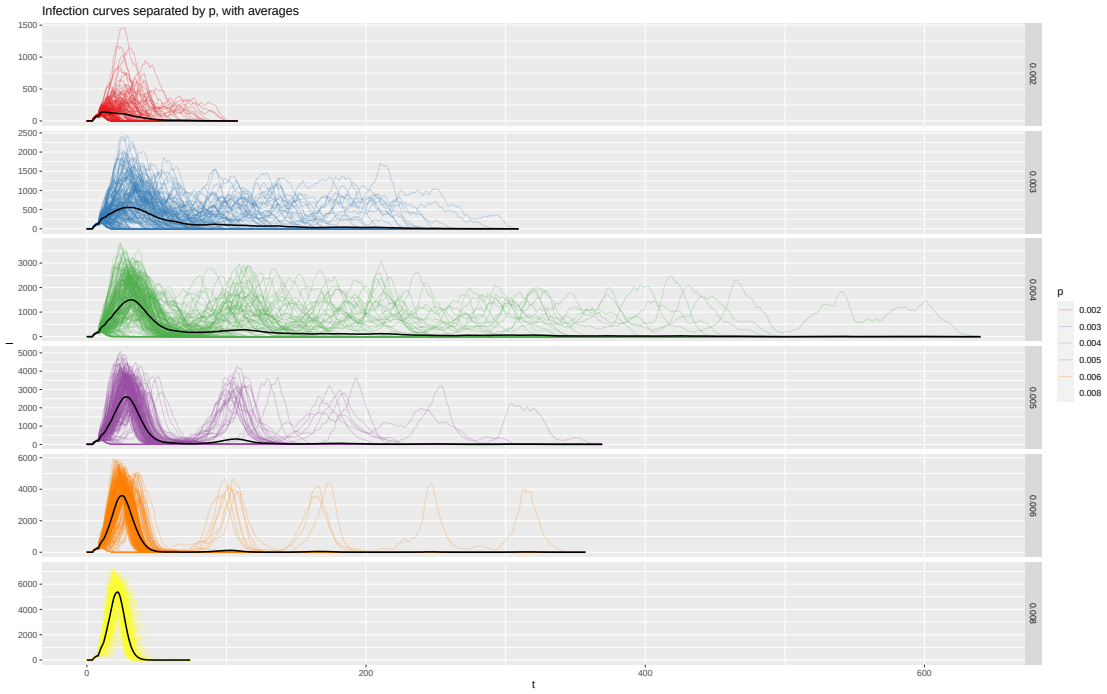

Figure 1: Infection curves, by varying infection probabilities p_{inf}.

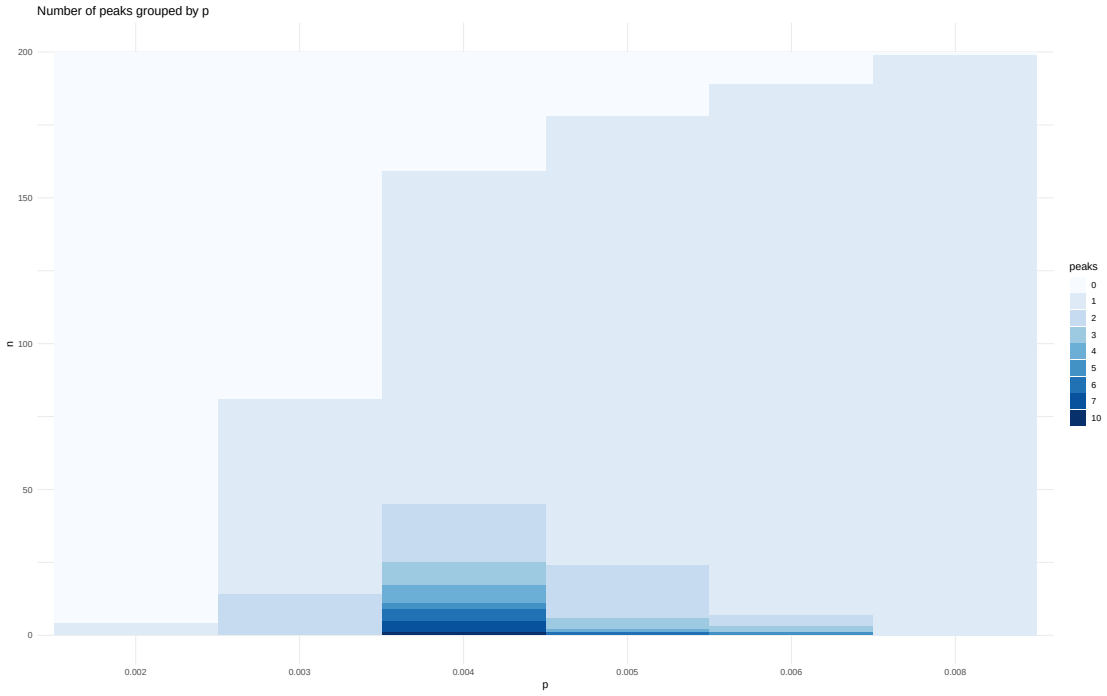

Figure 2: Number of runs (out of 200) with n peaks in the infection curve, by varying infection probabilities p_{inf}.

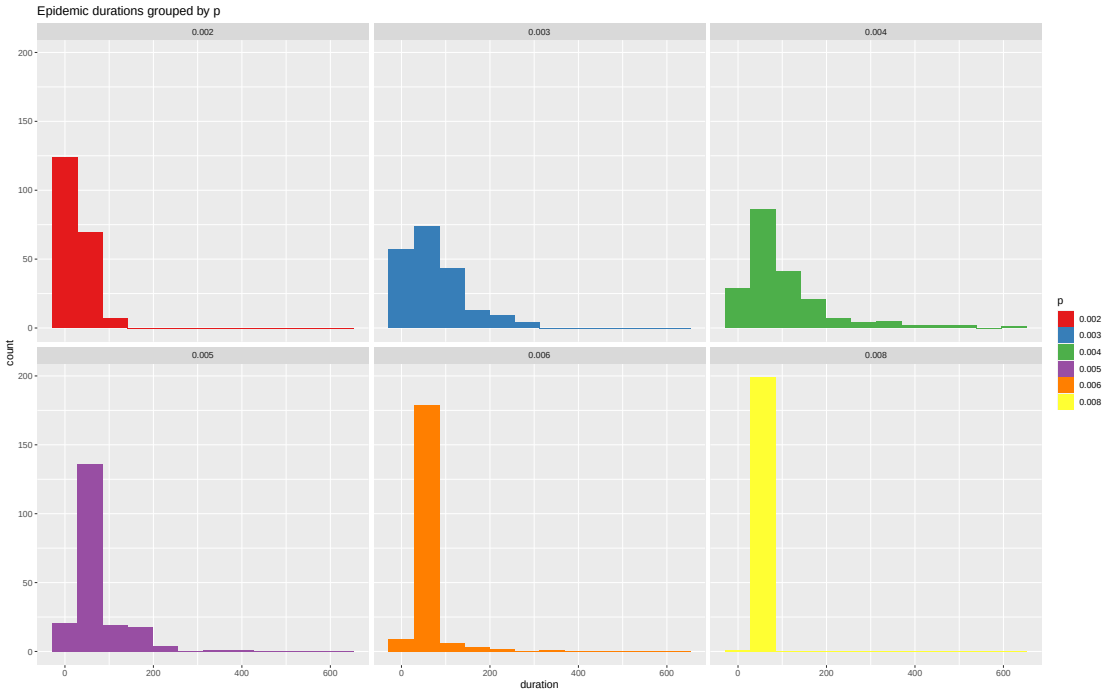

Figure 3: Distribution of epidemic durations, by varying infection probabilities p_{inf}.