ON THE ROLE OF NONINFECTIOUS VIRIONS IN AN IN-HOST DENGUE INFECTION

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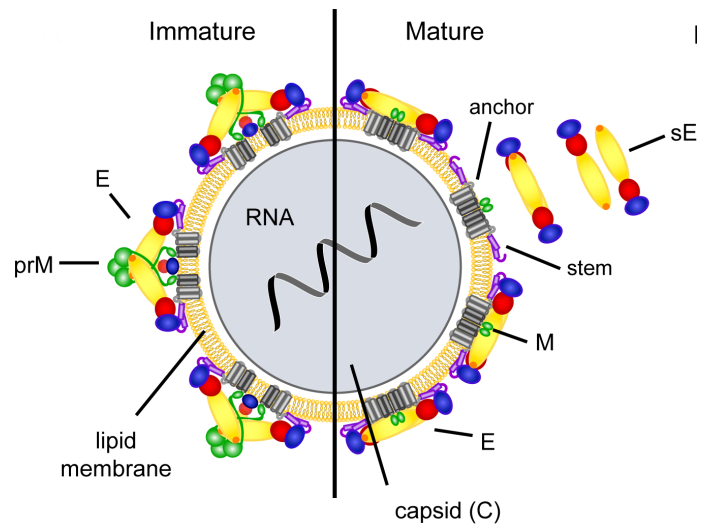


Synthesis of virions in DENV-infected cells

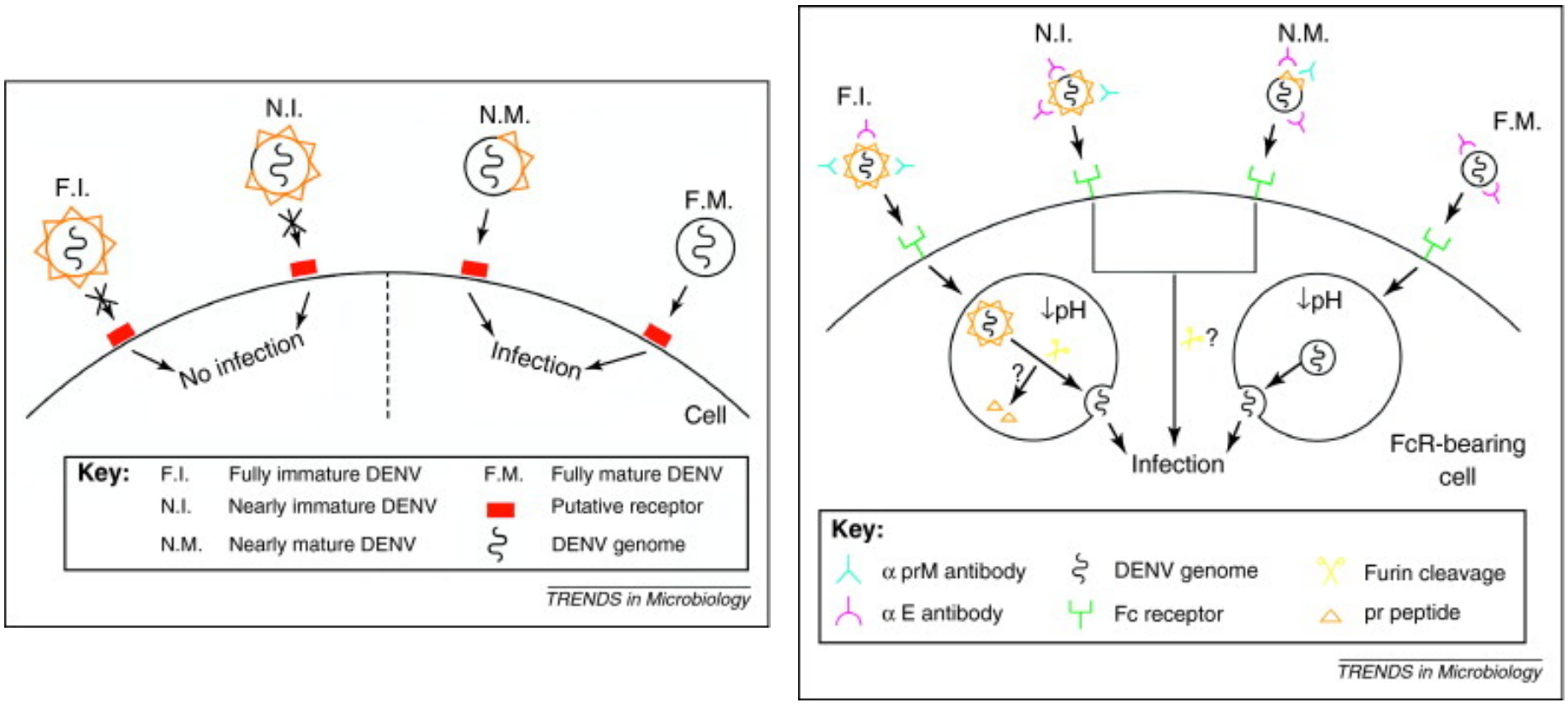


Figure: DENV infectivity in the absence and presence of antibodies (Rodenhuis-Zybert et al. 2011)

Degree of maturity = degree of infectivity

- blood samples from dengue patients contain a proportion of immature DENV containing uncleaved prM
- fully or nearly immature DENV is essentially not infectious to cells
- but they regain full infectivity when they interact with anti-prM antibodies
- such opsonised immature DENV enter Fc receptor-bearing cells and infect them (ADE)

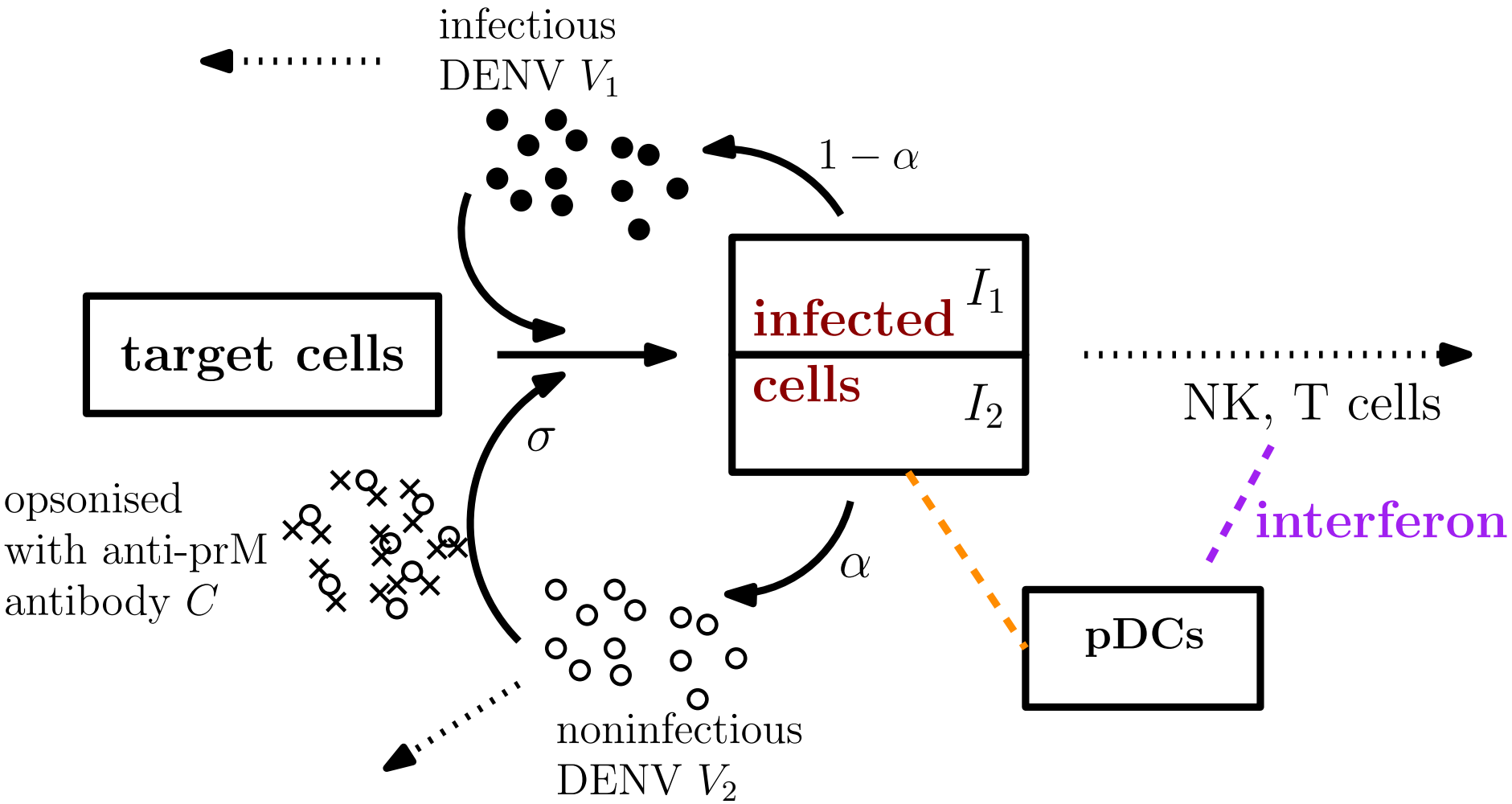
Immune response

- plasmacytoid dendritic cells (pDCs) sense invading pathogens and can release type I interferon up to thousand fold more than other cell types
- pDCs stimulate T cells by cell-cell contact
- infected cells that release immature DENV cause pDCs to produce much higher amounts of interferon than infected cells that release mature DENV (*in vitro*, Décembre et al. 2014)

The role of immature DENV in the disease progression

- is there any evolutionary advantage of immature, noninfectious DENV?
- why/how would DENV benefit from presence of noninfectious virions that induce a stronger immune response presumably targeted against DENV itself?
- fraction of noninfectious DENV and its effect on
  - disease progression: number of infected cells, peak viremia, time to peak viremia
  - immune response: "interferon bait" in recruitment of additional FcR-bearing target cells, antibody-dependent enhancement in DENV reinfection
- potential trade-offs, best strategy for host-to-vector transmission

In-host mathematical model of dengue



Asymptotic estimate

Our assumption is that α is the fraction of infected cells producing noninfectious DENV. We show that

$$\lim_{t\to+\infty} \frac{I_1(t)}{I_2(t)} = \frac{1-\alpha}{\alpha} \text{ and } \lim_{t\to+\infty} \frac{V_1(t)}{V_2(t)} = \frac{1-\alpha}{\alpha}$$

in a primary infection and

$$\lim_{t\to+\infty} \frac{I_1(t)}{I_2(t)} = \frac{1-\alpha}{\alpha} \text{ and } \lim_{t\to+\infty} \frac{V_1(t)}{V_2(t)+C(t)} = \frac{1-\alpha}{\alpha}$$

in a secondary infection, and numerical tests show this convergence is fast within the window of infection.
Hence, α is a good approximation to the experimentally observed fraction of noninfectious DENV in blood samples.

Basic reproduction numbers

- using the next generation matrix method (van der Driesche and Watmough 2002), we are able to
  - compute R_0^p for the primary infection exactly
  - estimate R_0^s for the secondary infection using the formula for cubic roots
- in a heterotypic DENV reinfection where preexisting, non-neutralising anti-prM antibody would not opsonise with infectious DENV but with noninfectious DENV, we establish $R_0^s > R_0^p$

Basic reproduction numbers

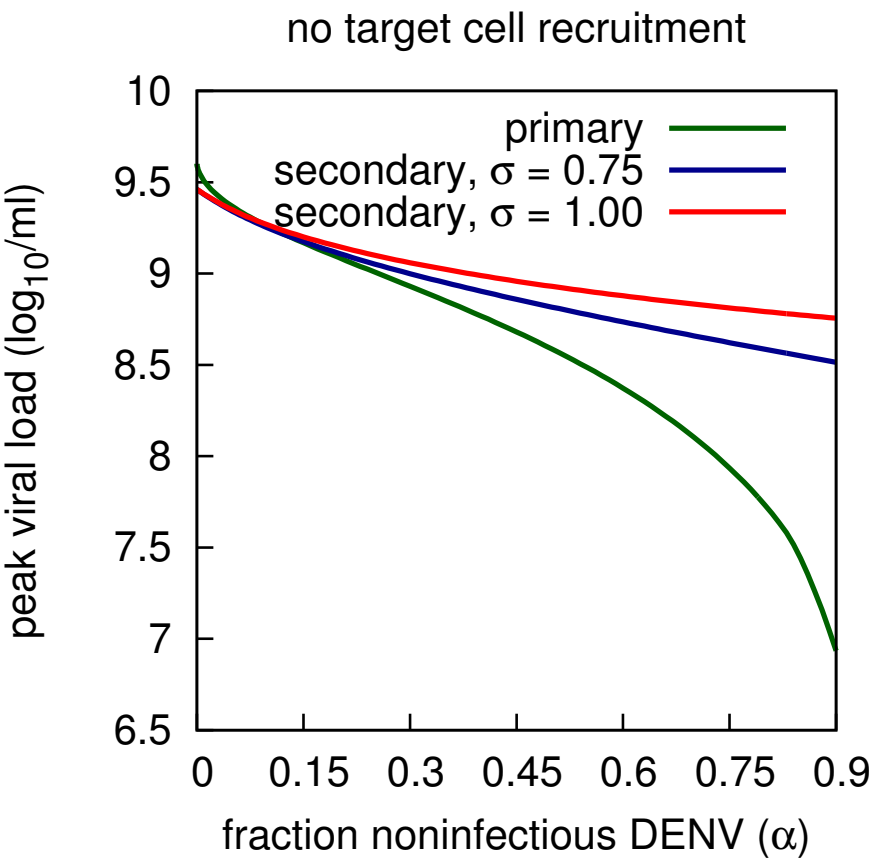
In a homotypic DENV reinfection most studies report lack of viremia. Thus, R_0^s would be expected to be less than 1 or at least low enough so that viral loads remain below the detection threshold. Our estimate poinpoints several options:

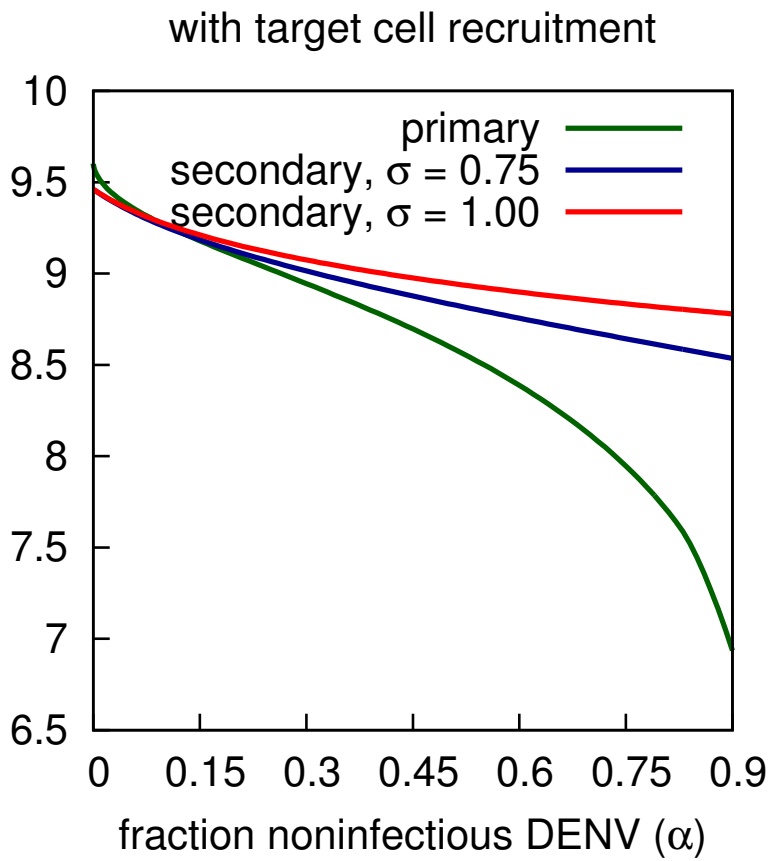
- reduce the infectivity rate (by action of neutralising antibody)
- increase the binding rate of anti-prM antibody to infectious DENV, viral clearance rate, kill rate of NK cells
- reduce the proportion of opsonized noninfectious DENV that are not cleared by phagocytosis but may infect target cells

Numerical simulations

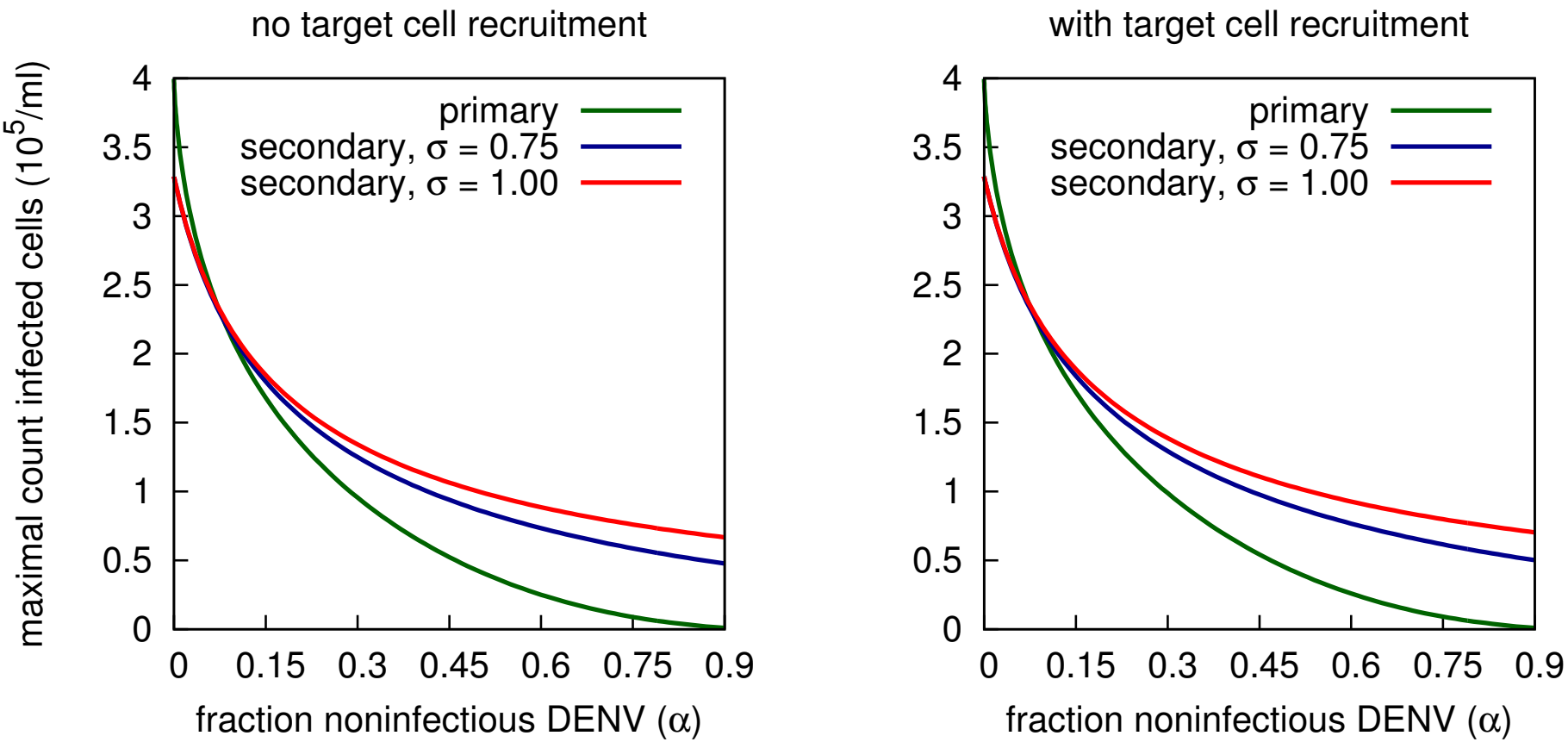
- randomly sample model parameters and run simulations to account for the uncertainty of the parameter values
- consider several scenarios
- vary the proportion α of infected cells producing noninfectious DENV and record the peak viral load, time to peak viral load, maximum of infected cells, immune indicators
- consider the scenario when only a fraction ($\sigma = 0.75$) of the opsonised noninfectious DENV enters FcR-bearing cells in a heterotypic reinfection
- perform hypothesis testing for effect of additional recruiment of target cells due to the action of interferon on disease indicators

peak viral load

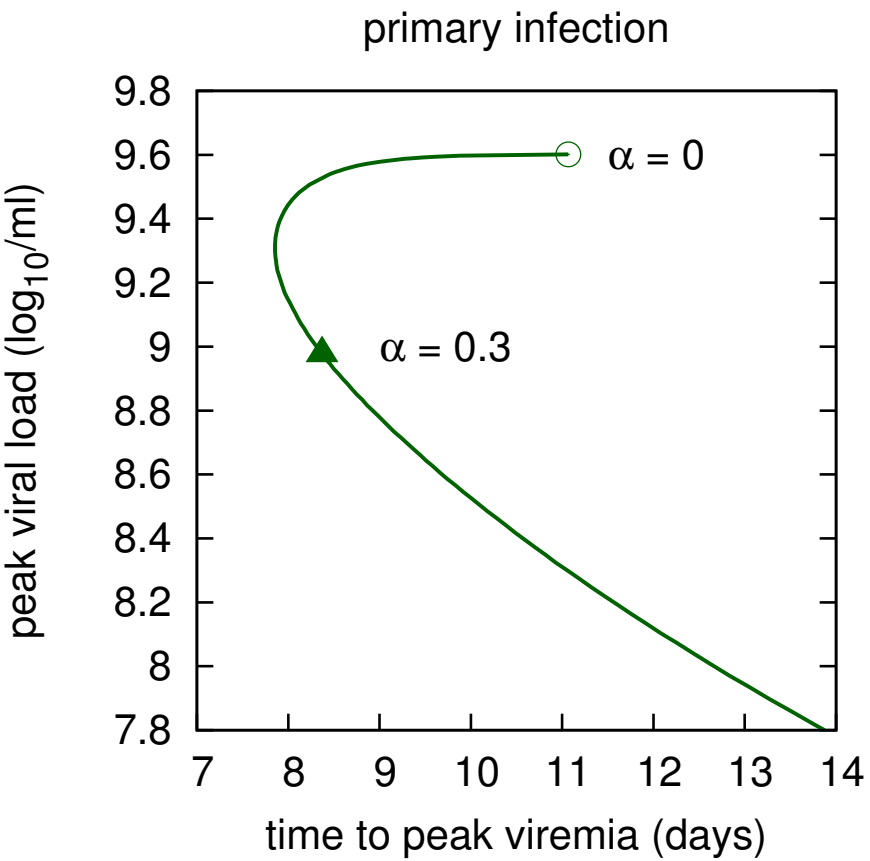


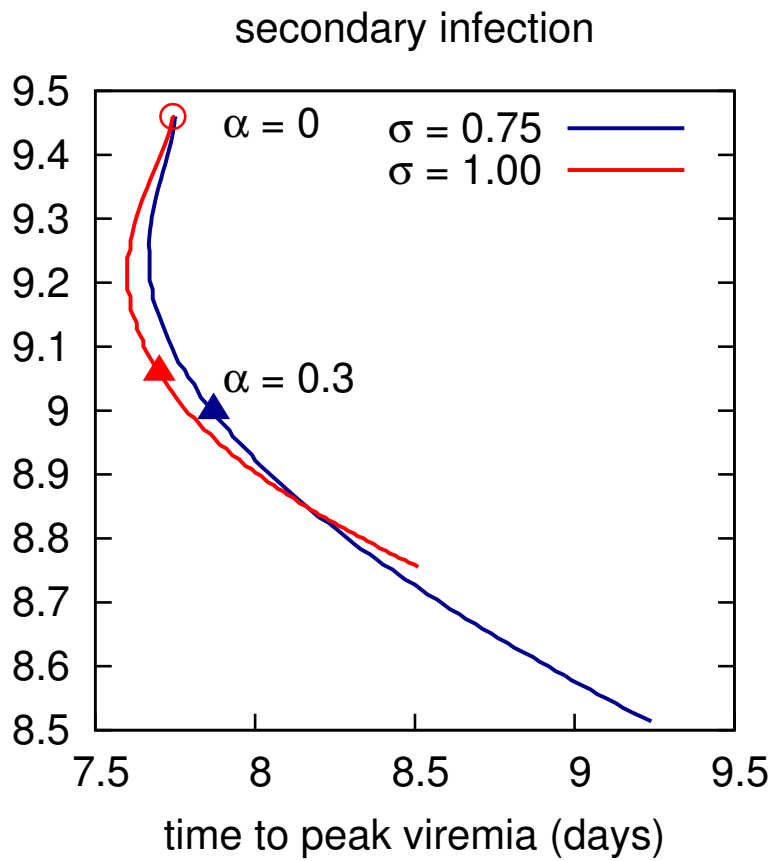


maximal count DENV infected cells



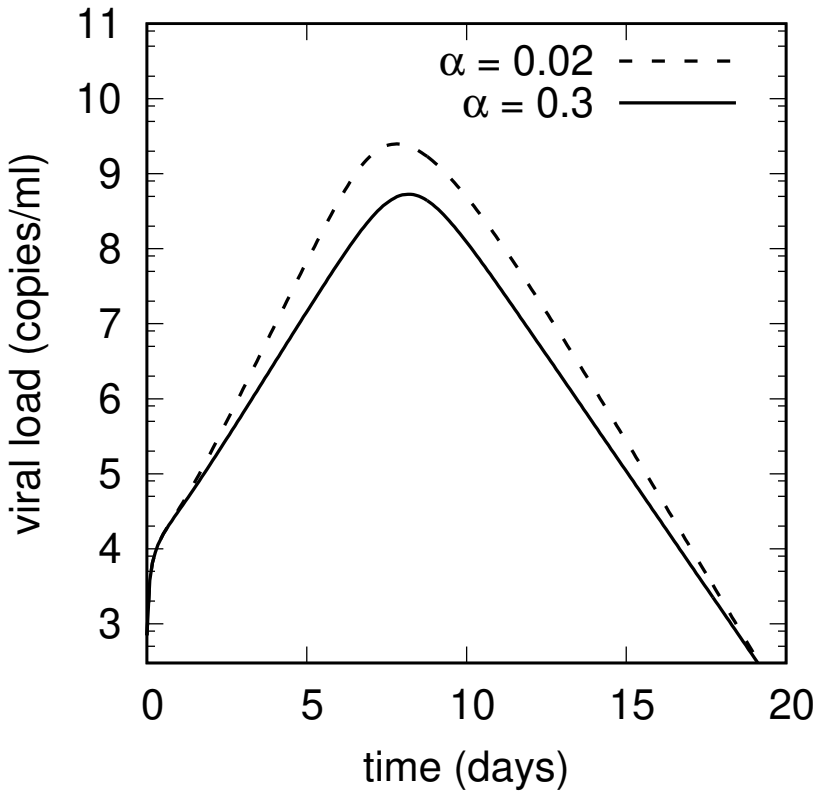
fraction noninfectious DENV causes a trade-off

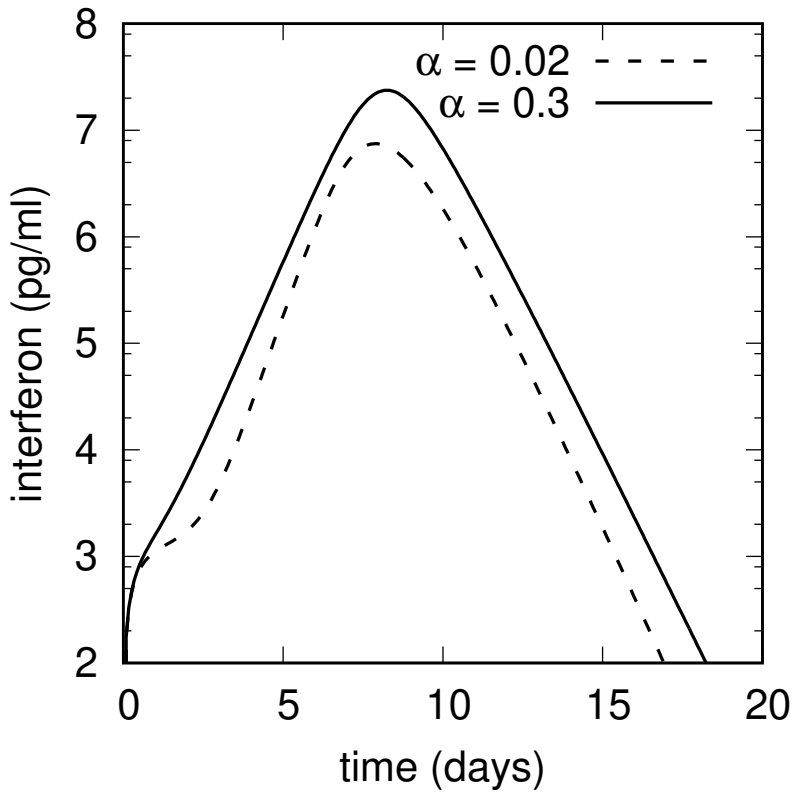




fraction noninfectious DENV causes a trade-off

primary infection





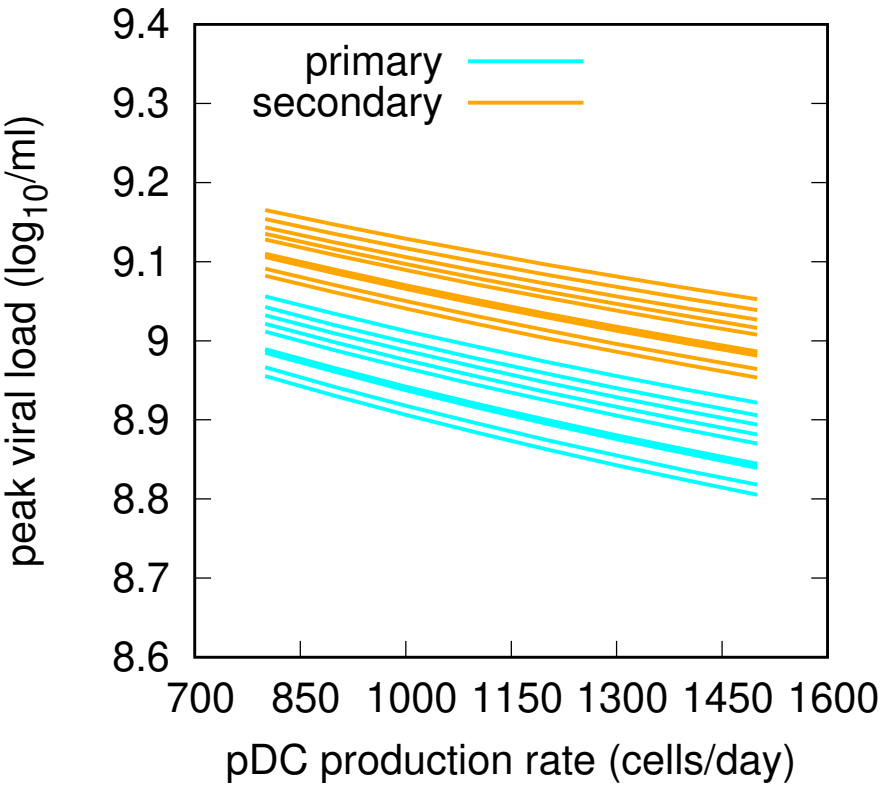
Discussion

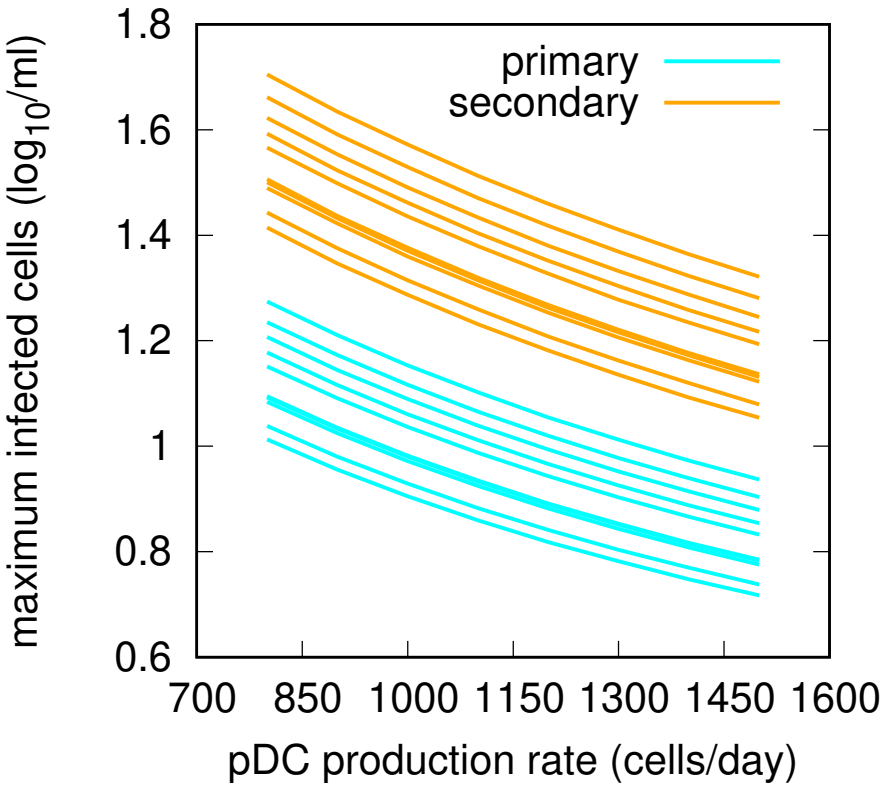
- noninfectious DENV is no "interferon bait"
- no statistical evidence that interferon-mediated additional recruitment of target cells leads to significantly higher viremia in primary or secondary DENV infection
- noninfectious DENV production enables DENV to increase its odds of transmission by several instruments: timing and level of peak viremia, as well as causing febrile symptoms through increased cytokine secretion
- eco-evolutionary questions (Nguyen et al. 2013)
  - window of transmission from host to vector
  - threshold levels of host viremia, days post infection

effect of pDC production

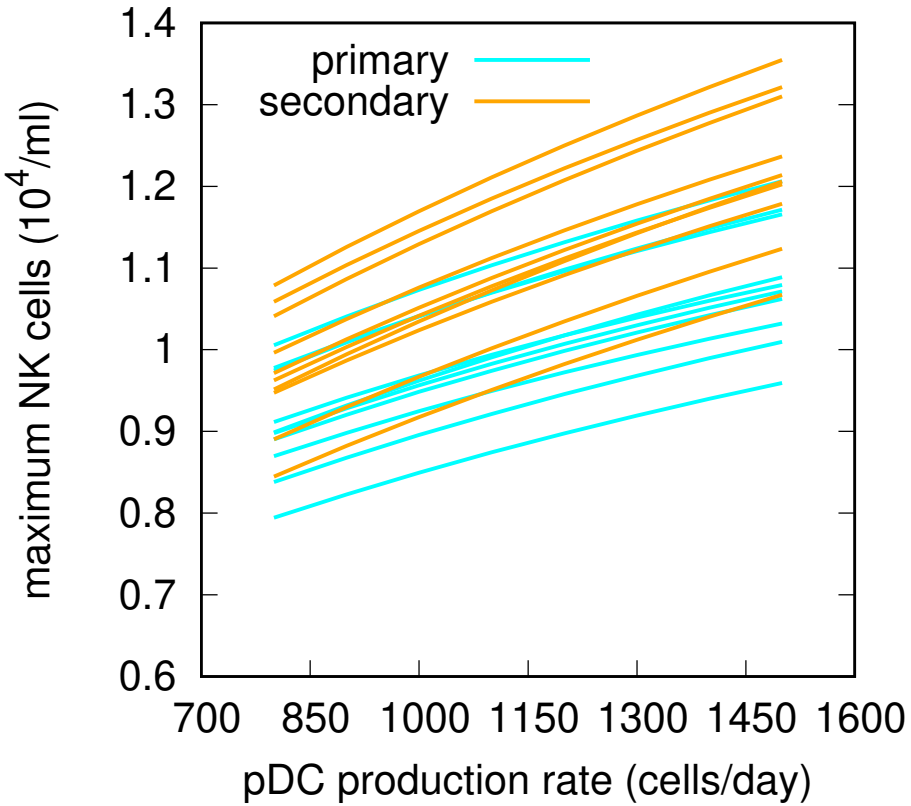
- test *in silico* the role of pDCs in disease progression
- randomly sample model parameters and vary the production rate of pDCs
- record disease indicators: peak viremia, maximum count of infected cells
- record immune indicators: the maximum counts of NK cells, T cells, peak interferon level

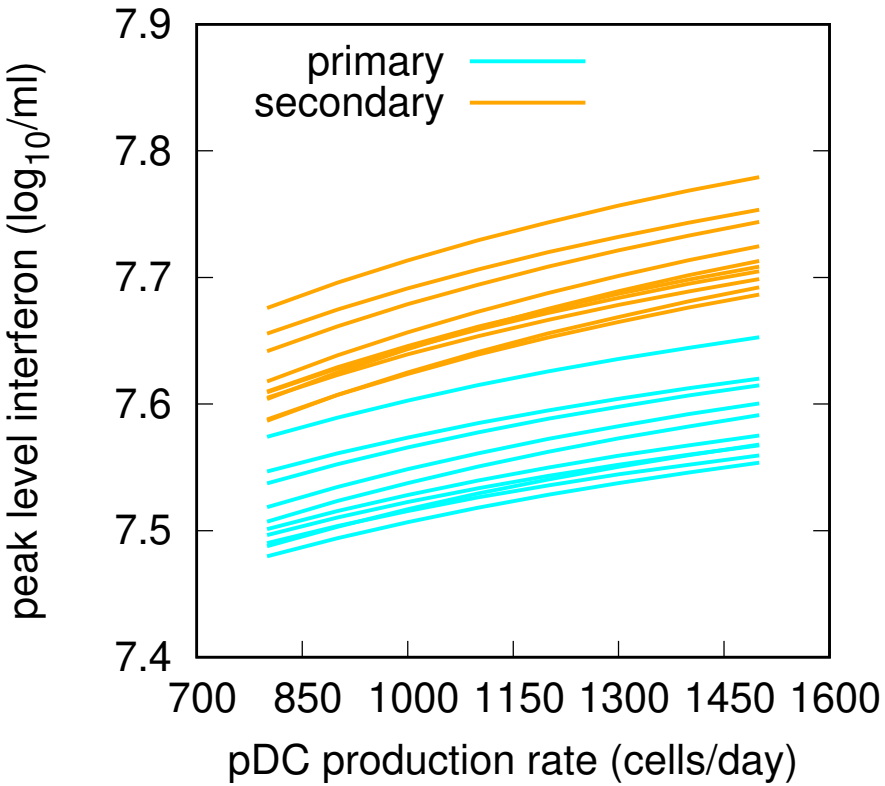
effect of pDC production on disease indicators



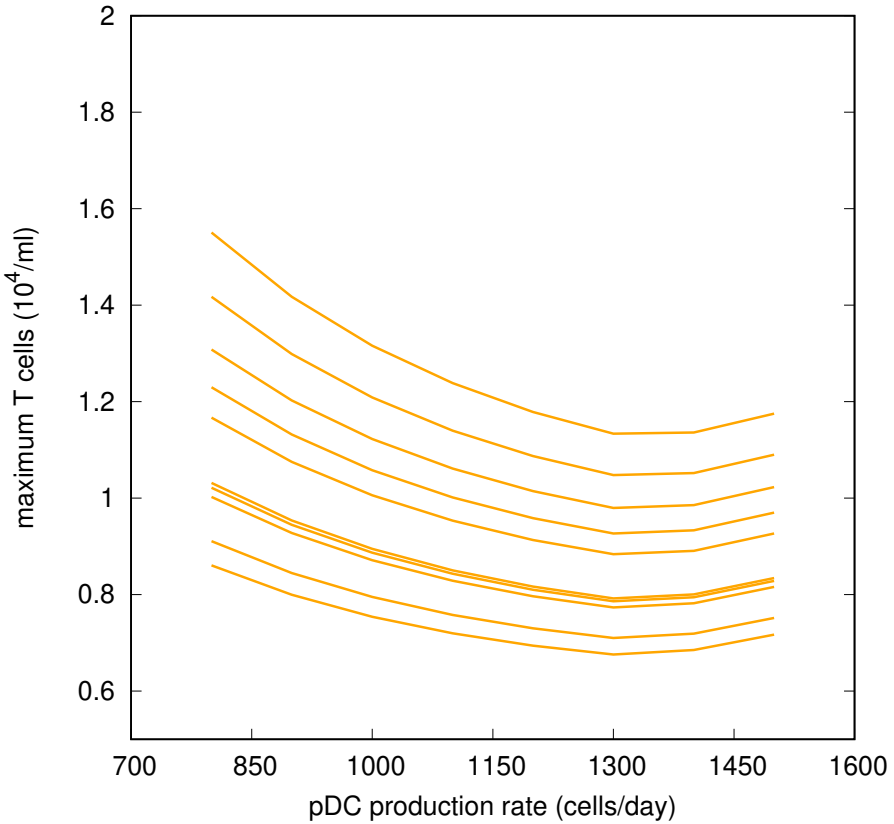


effect of pDC production on the immune response





effect of pDC production on the immune response



higher maximum counts of T cells at lower pDC production rates

Discussion

- pDCs serve as mediators between innate and adaptive immune response in DENV infection
- consistent with clinical evidence: insufficient pDC levels associated with higher viremia and higher risk of dengue hemorrhagic fever (Pichyangkul et al. 2003)
- model suggests a possible mechanism: stimulation of T cells which produce pro-inflammatory cytokines?

THANK YOU FOR YOUR ATTENTION!
GRAZIE PER L'ATTENZIONE!

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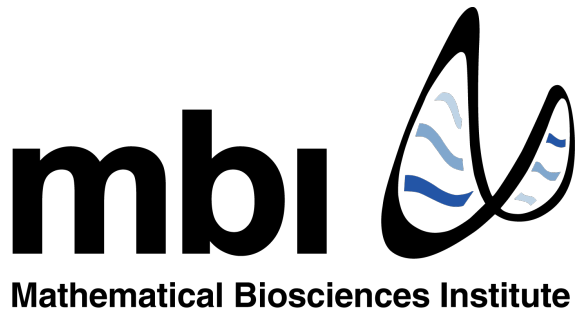

Equations of the model: primary infection

$$S' = -\beta S V_1 + \gamma_S F \tag{1a}$$
$$I_1' = (1-\alpha)\beta S V_1 - k_N I_1 N \tag{1b}$$
$$I_2' = \alpha\beta S V_1 - k_N I_2 N \tag{1c}$$
$$V_1' = p I_1 - \beta V_1 S - d_V V_1 \tag{1d}$$
$$V_2' = p I_2 - d_V V_2 \tag{1e}$$
$$F' = q_1 D I_2 + q_2(I_2 + I_1) - d_F F \tag{1f}$$
$$D' = D_0 + \frac{K_D F}{\kappa_F + F} - d_D D \tag{1g}$$
$$N' = \gamma_N F - d_N N \tag{1h}$$

Equations of the model: secondary infection

$$S' = -\beta S V_1 - \beta S C + \gamma_S F \tag{2a}$$
$$I_1' = (1-\alpha)\beta S(V_1 + C) - k_N I_1 N - k_T I_1 T \tag{2b}$$
$$I_2' = \alpha\beta S(V_1 + C) - k_N I_2 N - k_T I_2 T \tag{2c}$$
$$V_1' = pI_1 - \beta V_1 S - d_V V_1 - k_{a1} A V_1 \tag{2d}$$
$$V_2' = pI_2 - d_V V_2 - k_{a2} A V_2 \tag{2e}$$
$$C' = \sigma k_{a2} A V_2 - \beta C S - d_V C \tag{2f}$$
$$F' = q_1 D I_2 + q_2(I_2 + I_1) - d_F F \tag{2g}$$
$$D' = D_0 + \frac{K_D F}{\kappa_F + F} - d_D D \tag{2h}$$
$$N' = \gamma_N F - d_N N \tag{2i}$$
$$T' = \gamma_{T1} T(I_1 + I_2) + \gamma_{T2} T D - d_T T \tag{2j}$$
$$A' = rA\left(1 - \frac{A}{K_a + m(V_1 + V_2)}\right) \tag{2k}$$

Disease-free equilibrium

Neglecting the clearance of NK cells during the window of infection ($d_N = 0$), we have the disease free equilibrium

$$E^p = (S_0, 0, 0, 0, 0, 0, \frac{D_0}{d_D}, N_0)$$

for the primary infection (1), and

$$E^s = (S_0, 0, 0, 0, 0, 0, 0, \frac{D_0}{d_D}, N_0, 0, K_a)$$

for the secondary infection (2).

Basic reproduction numbers

Using the next generation matrix, we compute R_0^p for the primary infection

$$R_0^p = \sqrt{\frac{(1-\alpha)p\beta S_0}{k_N N_0(d_V + \beta S_0)}}$$

and estimate R_0^s for the secondary infection

$$R_0^s \approx \sqrt{\frac{(1-\alpha)p\beta S_0}{k_N N_0(d_V + \beta S_0 + k_{a1}K_a)}} + \frac{3}{2} \cdot \frac{\alpha\sigma k_{a2}K_a(\beta S_0 + k_{a1}K_a + d_V)}{(1-\alpha)(d_V + k_{a2}K_a)(d_V + \beta S_0)}.$$

Basic reproduction numbers

In a heterotypic DENV reinfection where preexisting, non-neutralising anti-prM antibody would not opsonise with infectious DENV, we assume $k_{a1} = 0$ (no clearance from phagocytosis). Then

$$R_0^s \approx R_0^p + \frac{3}{2} \cdot \frac{\sigma k_{a2} K_a}{k_{a2} K_a + d_V} \cdot \frac{\alpha}{1 - \alpha}.$$

Due to the presence of anti-prM antibody $K_a > 0$, however, $R_0^s > R_0^p$ holds.