Numerical exploration of the host immune response to mature and immature dengue virus

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Dengue fever is a vector-borne disease

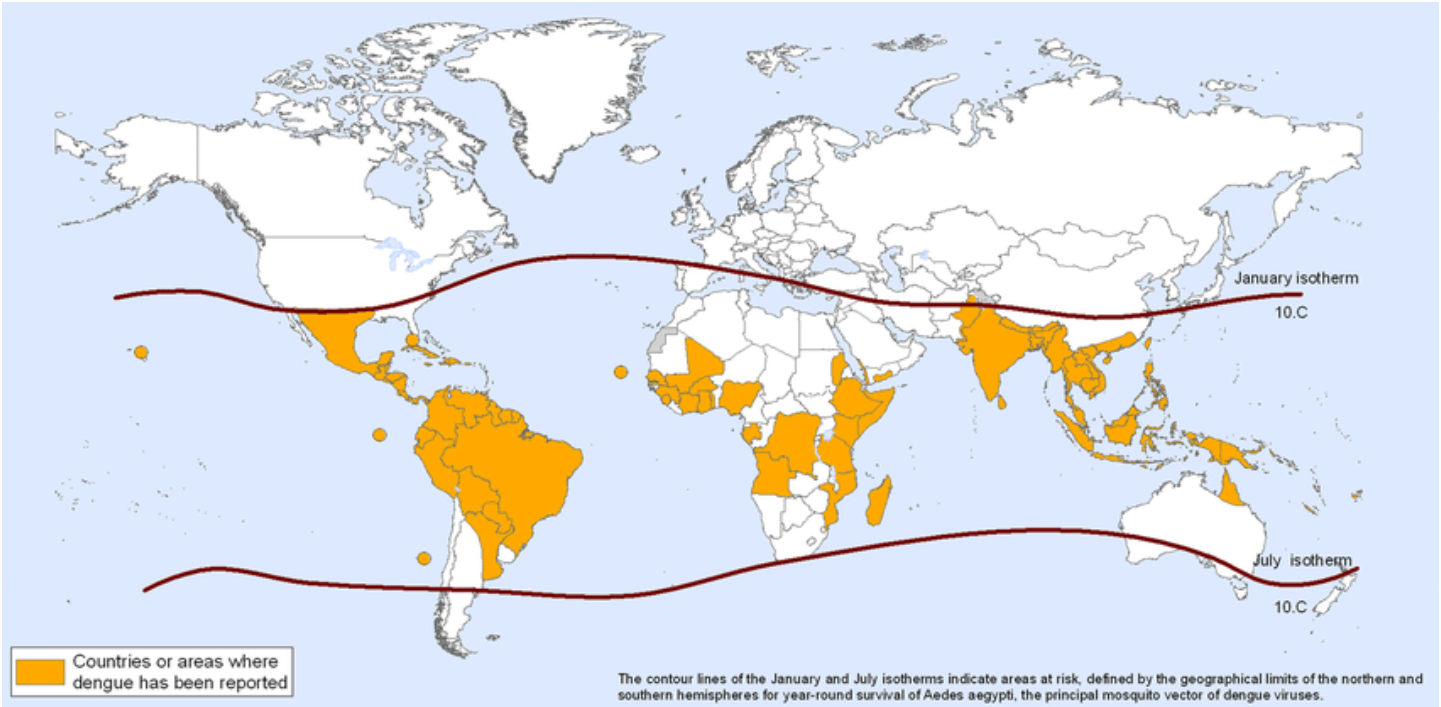
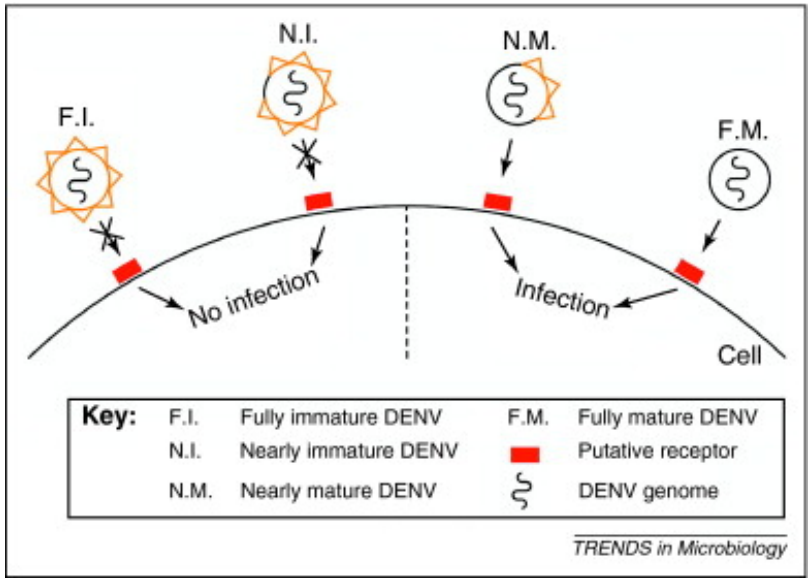
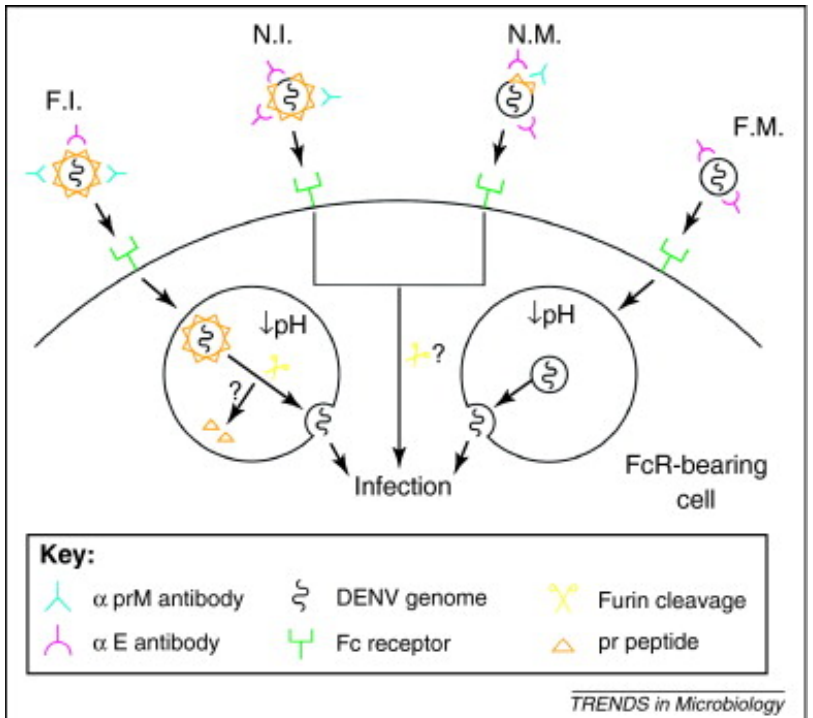


Figure: Dengue distribution in 2011 (WHO data). DENV has 4 serotypes and infection with one serotype does not lead to immunity against the other serotypes, and in a secondary infection with a different serotype may manifest as DHF/DSS.

Synthesis of virions in DENV-infected cells





Degree of maturity = degree of infectivity

- blood samples from dengue patients contain a proportion of immature DENV containing uncleaved prM
- inhibition of furin leads to production of immature DENV (*in vivo*)
- 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 (*antibody-dependent enhacement*)

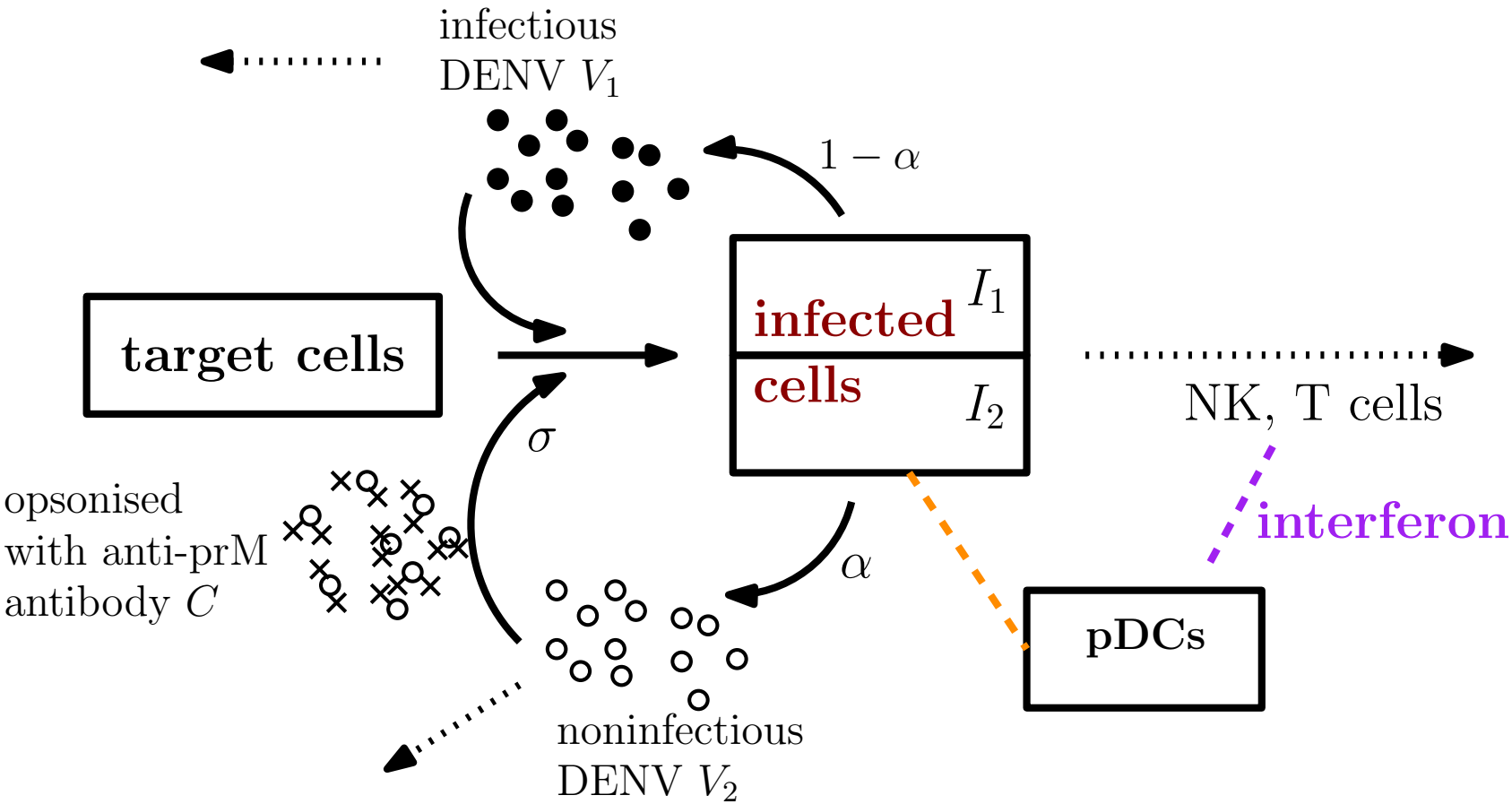
- plasmacytoid dendritic cells (pDCs) sense invading pathogens and can release type I interferon up to thousand fold more than other cell types
- DENV-infected cells producing immature vs. mature virions elicit antiviral response of different intensity (interferon and inflammatory cytokine secretion) from pDCs (*in vitro*, Décembre et al. 2014)
- DENV-infected cells that release immature DENV cause pDCs to produce much higher amounts of interferon than cells that release mature DENV (ibid, *in vivo*)

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: recruitment of additional target cells, antibody-dependent enhancement in a secondary infection?
- indication for new experimental work

- compartmental model – ODEs
- modelling assumptions based on biomedical observations as well as *in vitro* experiments gathered from the literatue
- quantities of biomedical interest
  - *disease indicators*: peak viral load, time to peak viral load since limit of detection (LOD), maximum count of infected cells
  - *immune indicators*: strength of pDC response maximum counts of activated NK cells, T cells, peak interferon level, peak antibody level

- large number of model parameters with unidentified or uncertain values
- *Latin hypercube* sampling of the parameter space (a statistical method for generating a near-random sample of parameter values from a multidimensional distribution)
- uniform distribution for the parameter values, 200 sample intervals
- run the models and generate the disease and immune indicators
- perform statistical hypothesis testing


infectious
DENV V_1
$1-\alpha$
target cells
infected cells
I_1
I_2
NK, T cells
interferon
σ
opsonised
with anti-prM
antibody C
α
pDCs
noninfectious
DENV V_2

$$
\begin{aligned}
S' &= -\beta S V_1 + \gamma_S F \\
I_1' &= (1-\alpha)\beta S V_1 - k_N I_1 N \\
I_2' &= \alpha\beta S V_1 - k_N I_2 N \\
V_1' &= p I_1 - \beta V_1 S - d_V V_1 \\
V_2' &= p I_2 - d_V V_2 \\
F' &= q_1 D I_2 + q_2 (I_2 + I_1) - d_F F \\
D' &= D_0 + \frac{K_D F}{\kappa_F + F} - d_D D \\
N' &= \gamma_N F - d_N N
\end{aligned}
$$

Equations of the model: secondary infection

$$
\begin{aligned}
S' &= -\beta S V_1 - \beta S C + \gamma_S F \\
I_1' &= (1-\alpha)\beta S(V_1 + C) - k_N I_1 N - k_T I_1 T \\
I_2' &= \alpha\beta S(V_1 + C) - k_N I_2 N - k_T I_2 T \\
V_1' &= p I_1 - \beta V_1 S - d_V V_1 - k_{a1} A V_1 \\
V_2' &= p I_2 - d_V V_2 - k_{a2} A V_2 \\
C' &= \sigma k_{a2} A V_2 - \beta C S - d_V C \\
F' &= q_1 D I_2 + q_2(I_2 + I_1) - d_F F \\
D' &= D_0 + \frac{K_D F}{\kappa_F + F} - d_D D \\
N' &= \gamma_N F - d_N N \\
T' &= \gamma_{T1} T(I_1 + I_2) + \gamma_{T2} T D - d_T T \\
A' &= rA\left(1 - \frac{A}{K_a + m(V_1 + V_2)}\right) - k_{a1} A V_1 - k_{a2} A V_2
\end{aligned}
$$

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 proxy for the experimentally observed fraction of noninfectious DENV in blood samples.

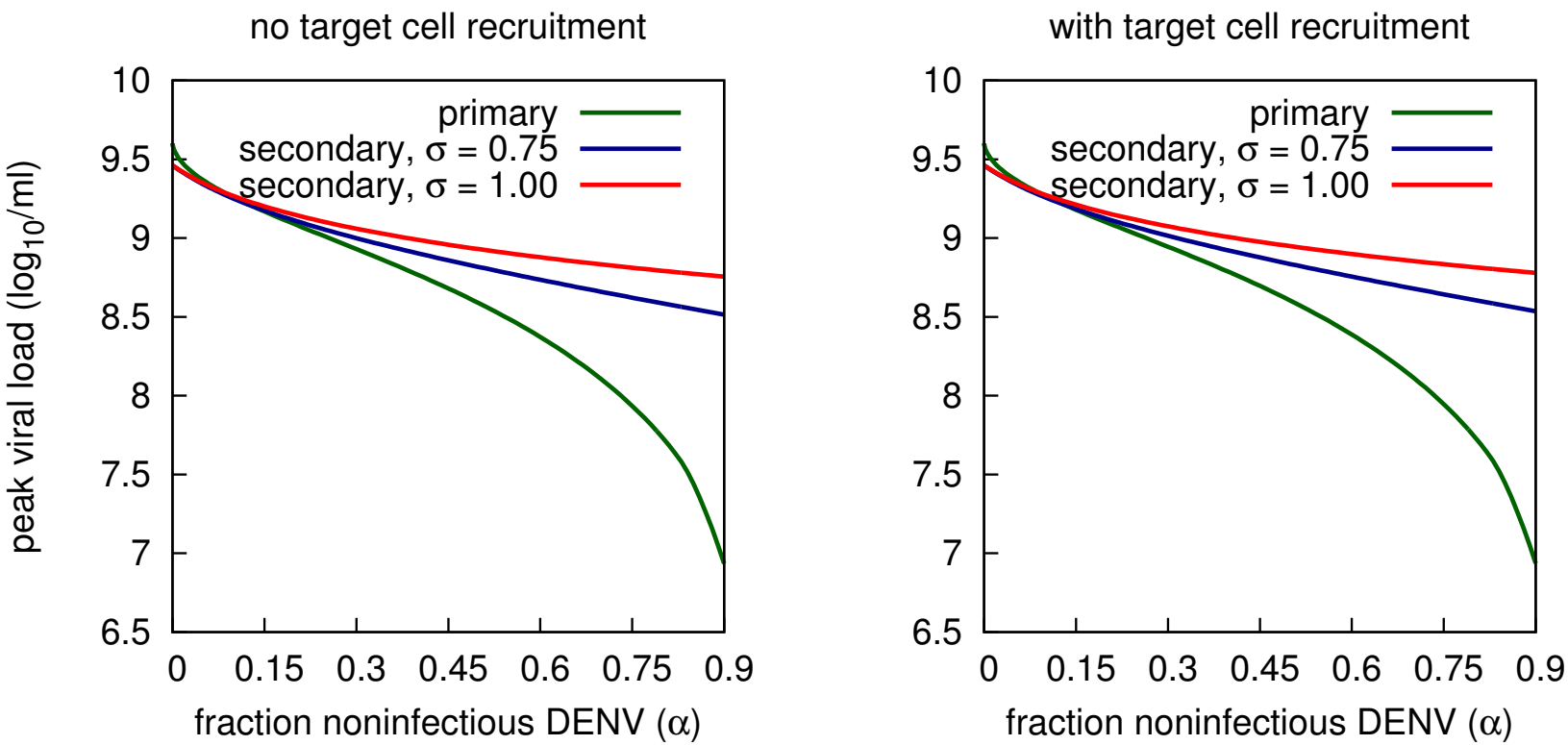
Numerical experiment 1: fraction of noninfectios virus

- choose a random sample of the model parameters
- vary the proportion α of infected cells producing noninfectious DENV, solve the ODE model and generate the disease and immune indicators
- consider also a scenario where only a fraction of the opsonised noninfectious DENV enters Fc receptor-bearing cells ($\sigma = 0.75$) in a heterotypic reinfection
- test the effect of additional recruiment of target cells ($\gamma_S = 0, \gamma_S > 0$) due to the action of interferon on the disease indicators

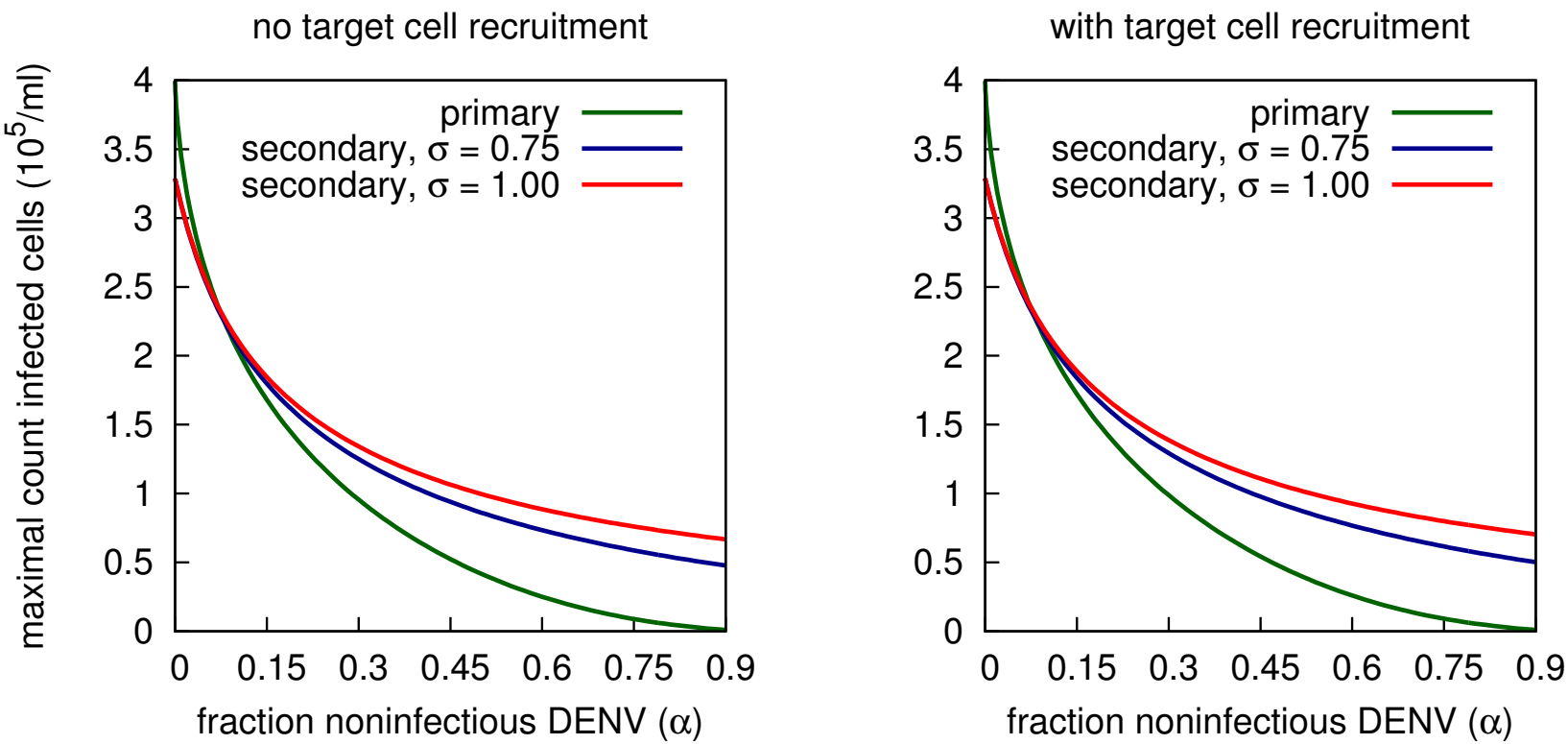
Numerical experiment 2: "interferon bait" hypothesis

- explore the "interferon bait" hypothesis, which states interferon-mediated additional recruitment of target cells leads to higher viremia in a DENV infection
- do a Latin hypercube sample
- solve the ODE models and generate the disease indicators in the scenarios $\gamma_S = 0, \gamma_S > 0$
- perform a Kolmogorov-Smirnov statistical test for H_0 "peak viral loads and times to peak viral loads in both scenarios have the same distribution "

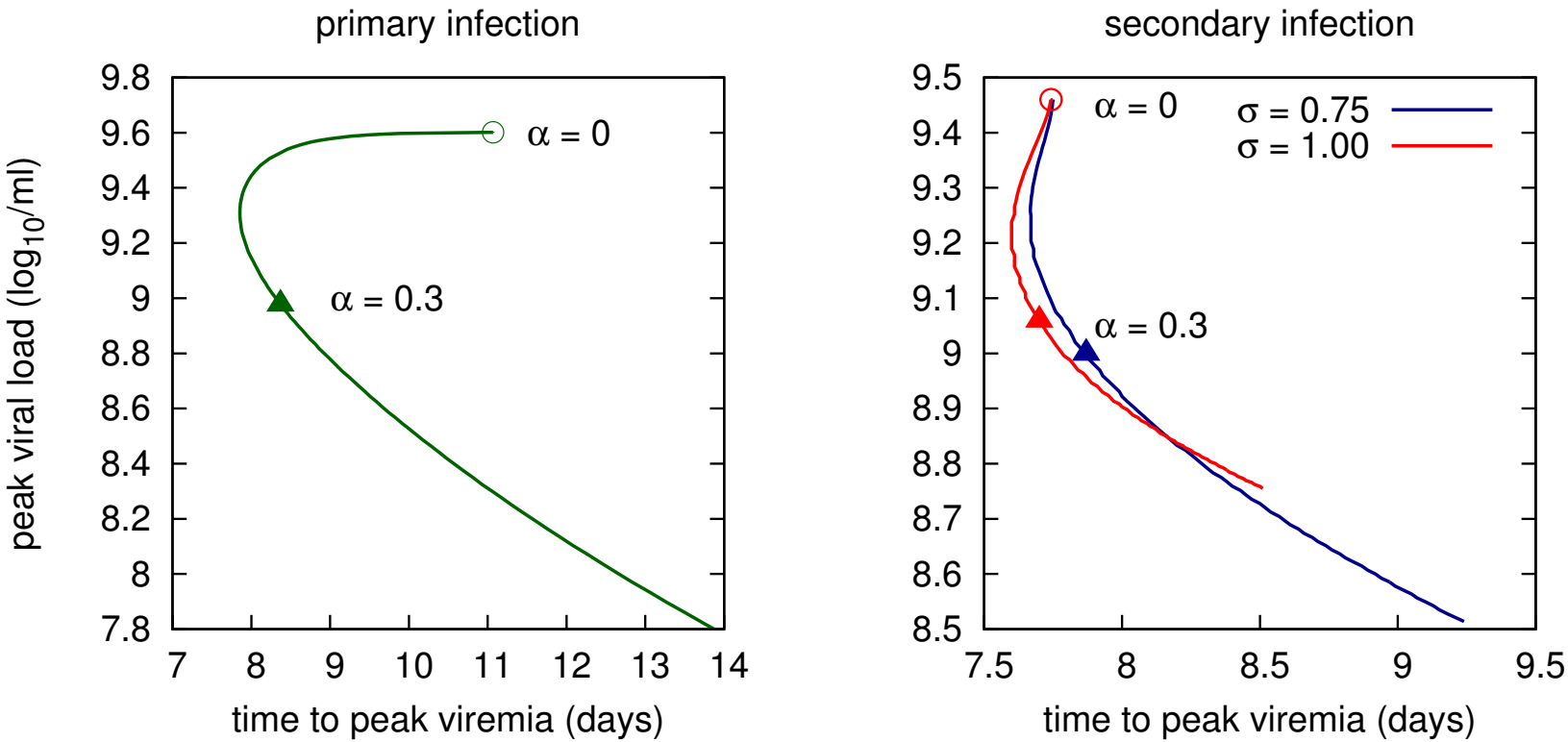
peak viral load



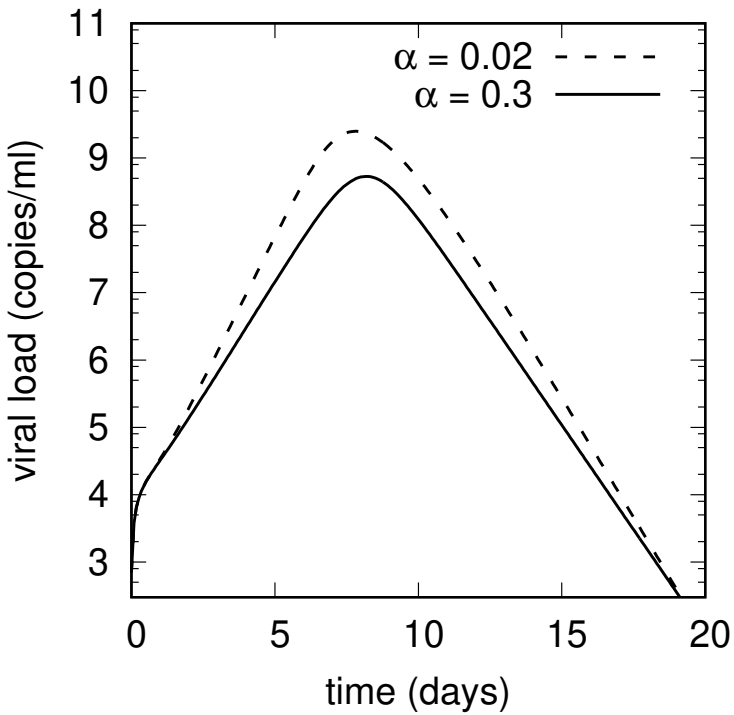
maximal count DENV infected cells

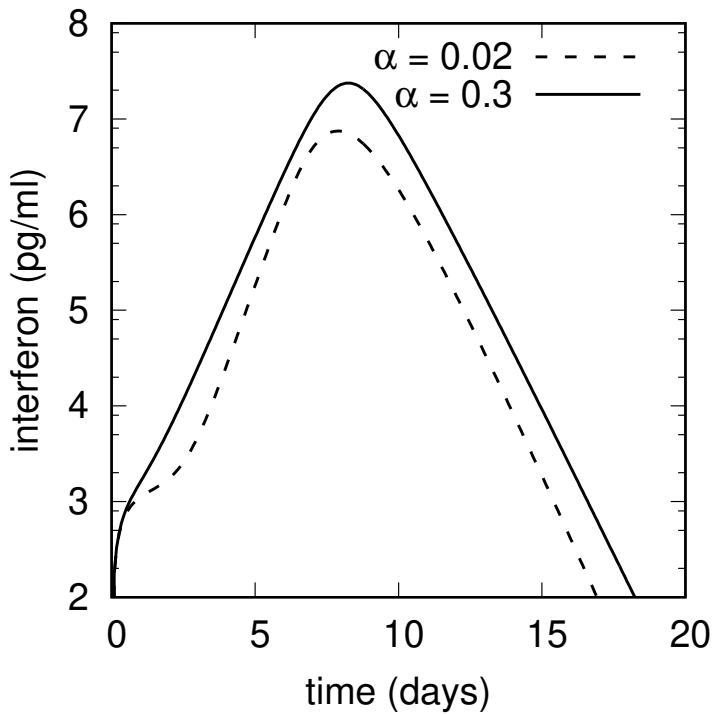


fraction noninfectious DENV causes a trade-off



primary infection



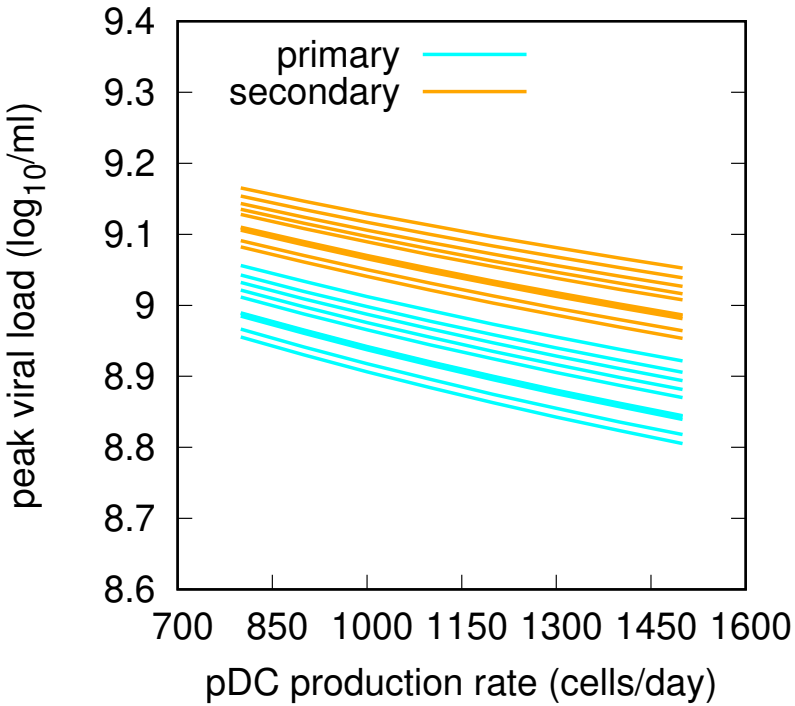


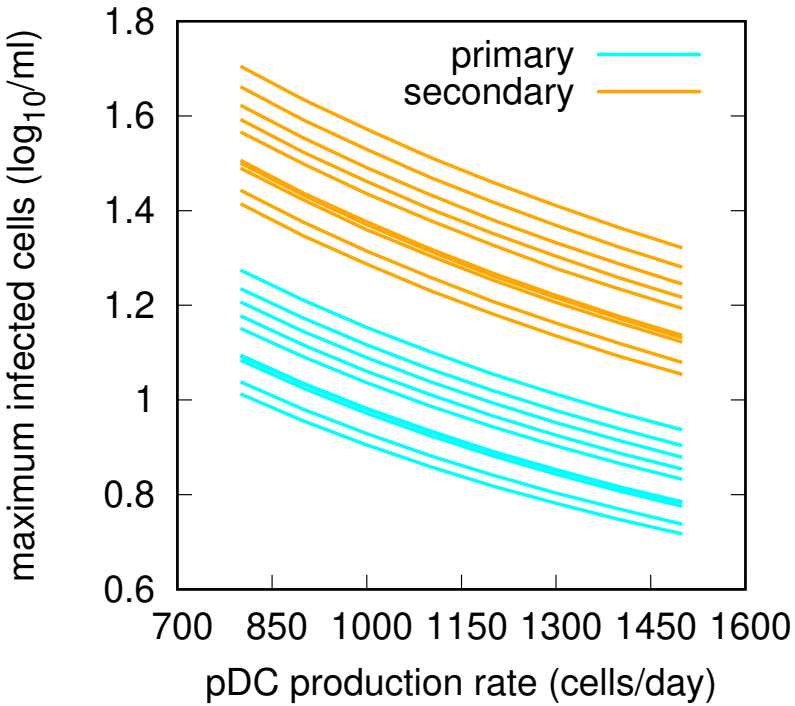
- no statistical evidence that interferon-mediated additional recruitment of target cells leads to higher viremia in primary or secondary DENV infection (*statistics not shown*)
- noninfectious DENV production enables DENV to increase its odds of transmission by several instruments: timing and level of peak viremia
- suggestions for further experimental reasearch
  - heterogeneity of furin expression in target cell pool
  - better clinical data to validate the model - especially in the period before peak viral load
  - better data on link between increased cytokine secretion and physiological state (e.g. fever)
  - window of transmission from host to vector?
  - case of asymptomatic dengue patients

Numerical experiment 3: DENV and pDCs

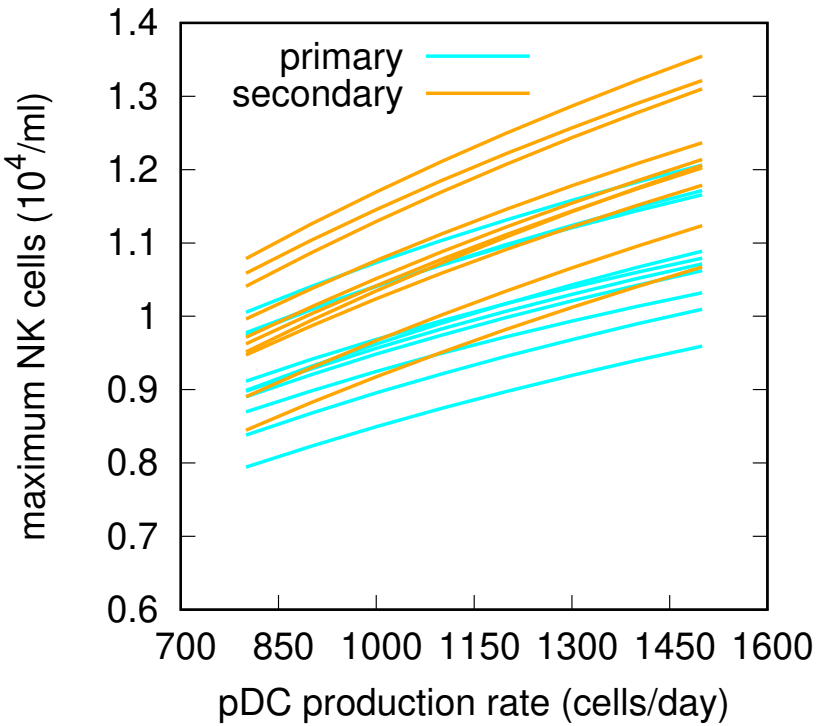
- pDCs as very potent producers of interferon
- *in silico* test of their role in disease progression
- randomly sample model parameters and vary the production rate of pDCs
- generate and compare the disease and immune indicators

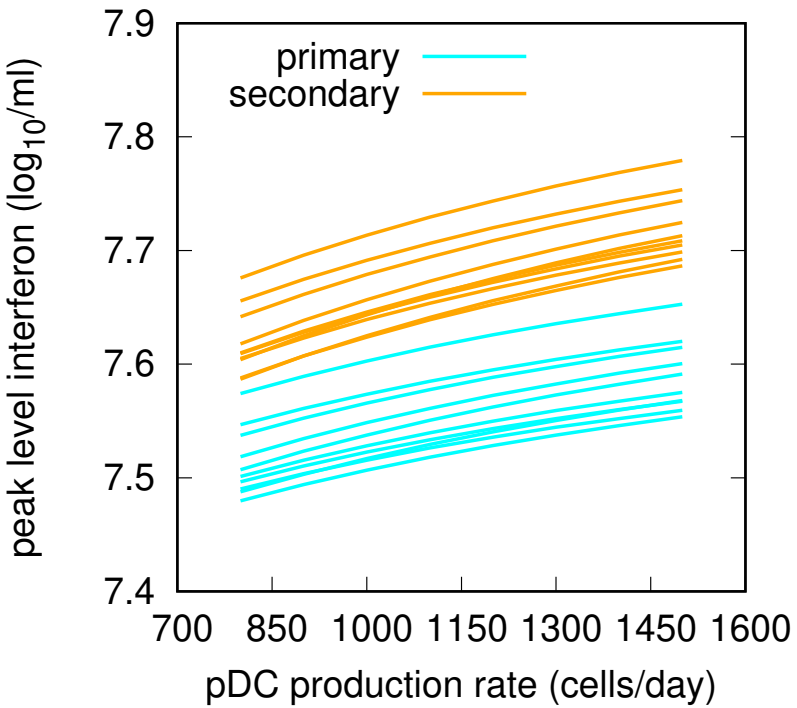
effect of pDC production on disease indicators



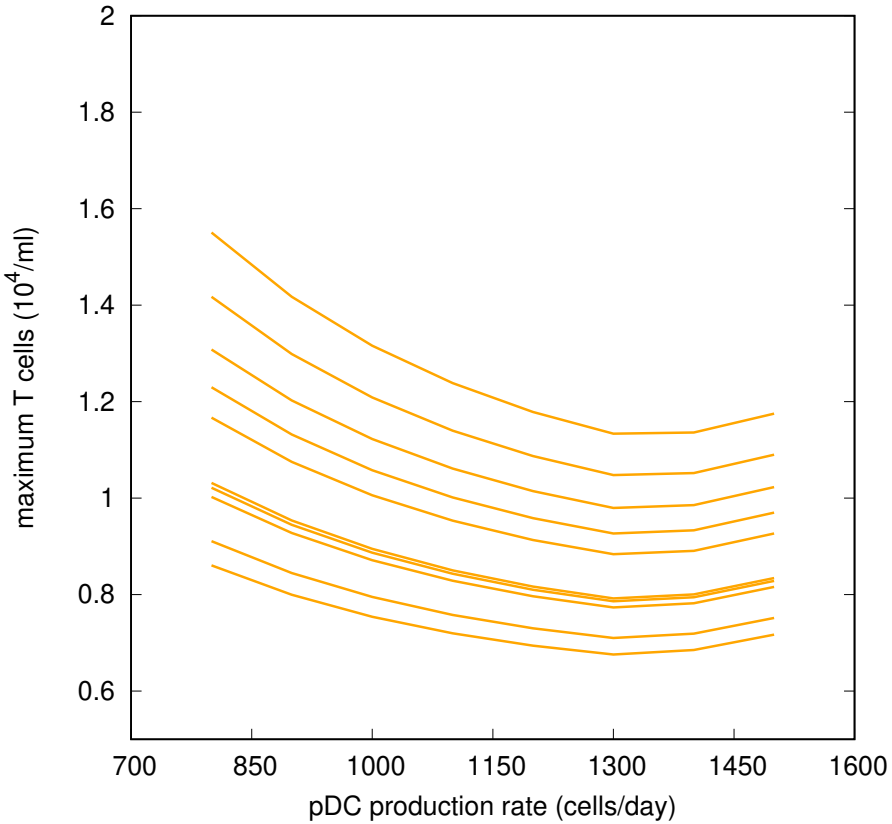


effect of pDC production on the immune response





effect of pDC production on the immune response



higher maximum counts of T cells at lower pDC production rates

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

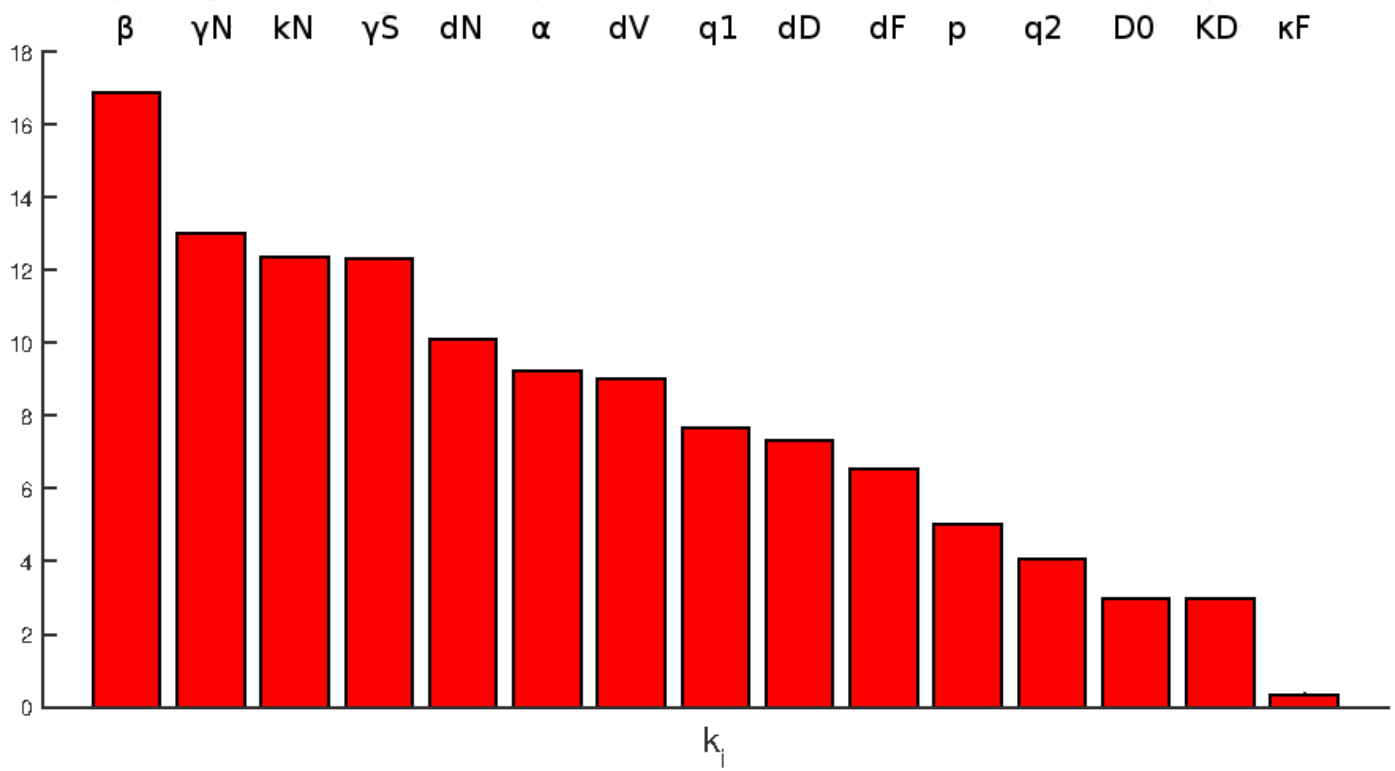


Figure: Parameter sensitvity spectrum, primary infection.

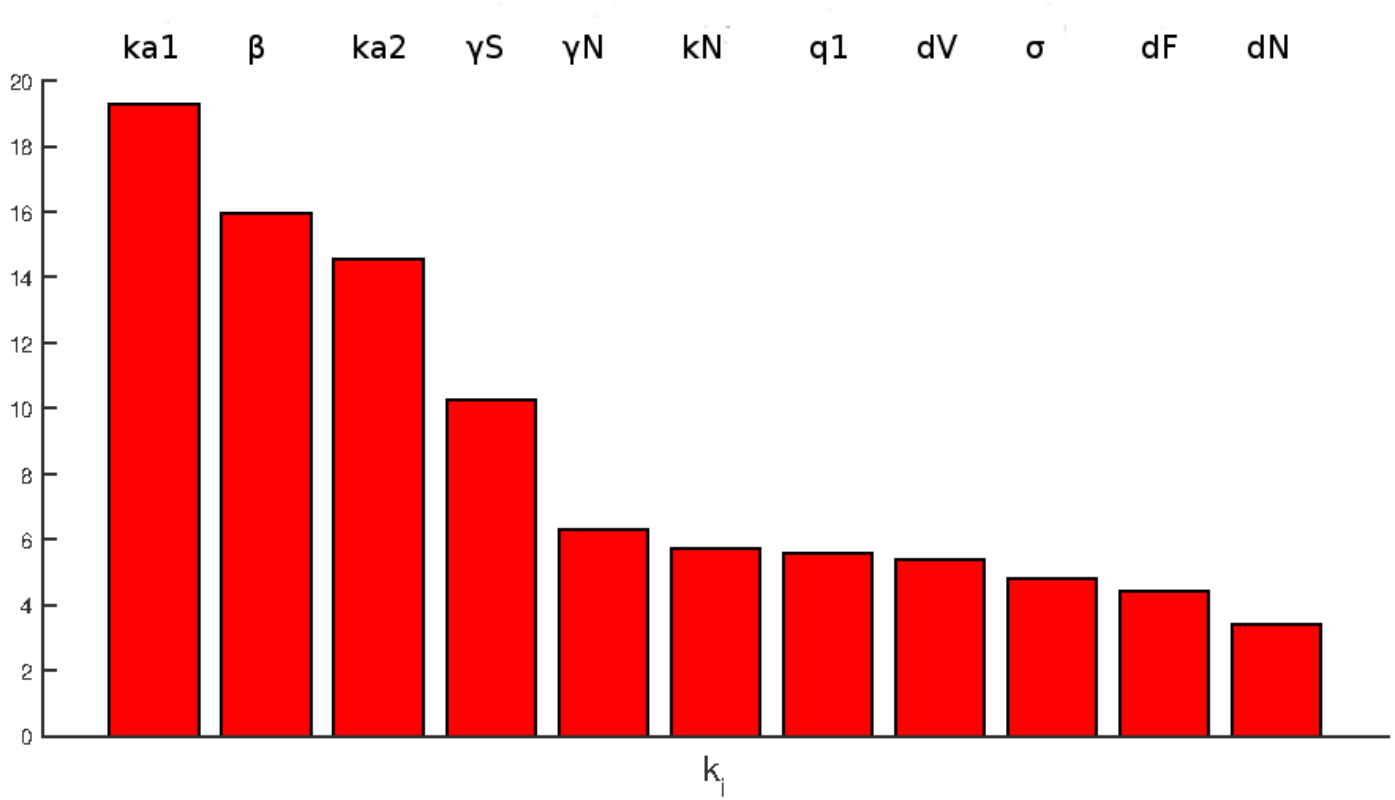


Figure: Parameter sensitvity spectrum, secondary infection.

- our model is based on the assumption of a stable dichotomy between two types of populations of infected cells
- whether such subpopulations persist stably over time could be examined through additional *in vitro/in vivo* experiments
- potential for single-cell experiments: understand better the heterogeneity of virus produced by infected cells

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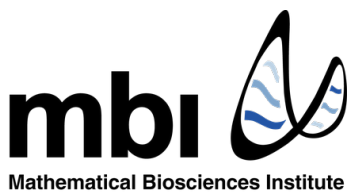
ИКТвНОС



M. Borisov, G. Dimitriu and P. Rashkov. Modelling the host immune response to mature and immature dengue virus (under review, 2019)

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