Математически модел на имунен отговор на вируса на денга

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съвместна работа с Милен Борисов (ИМИ-БАН) и Gabriel Dimitriu (UMP-Iași, Romania)

Dengue fever is a vector-borne disease

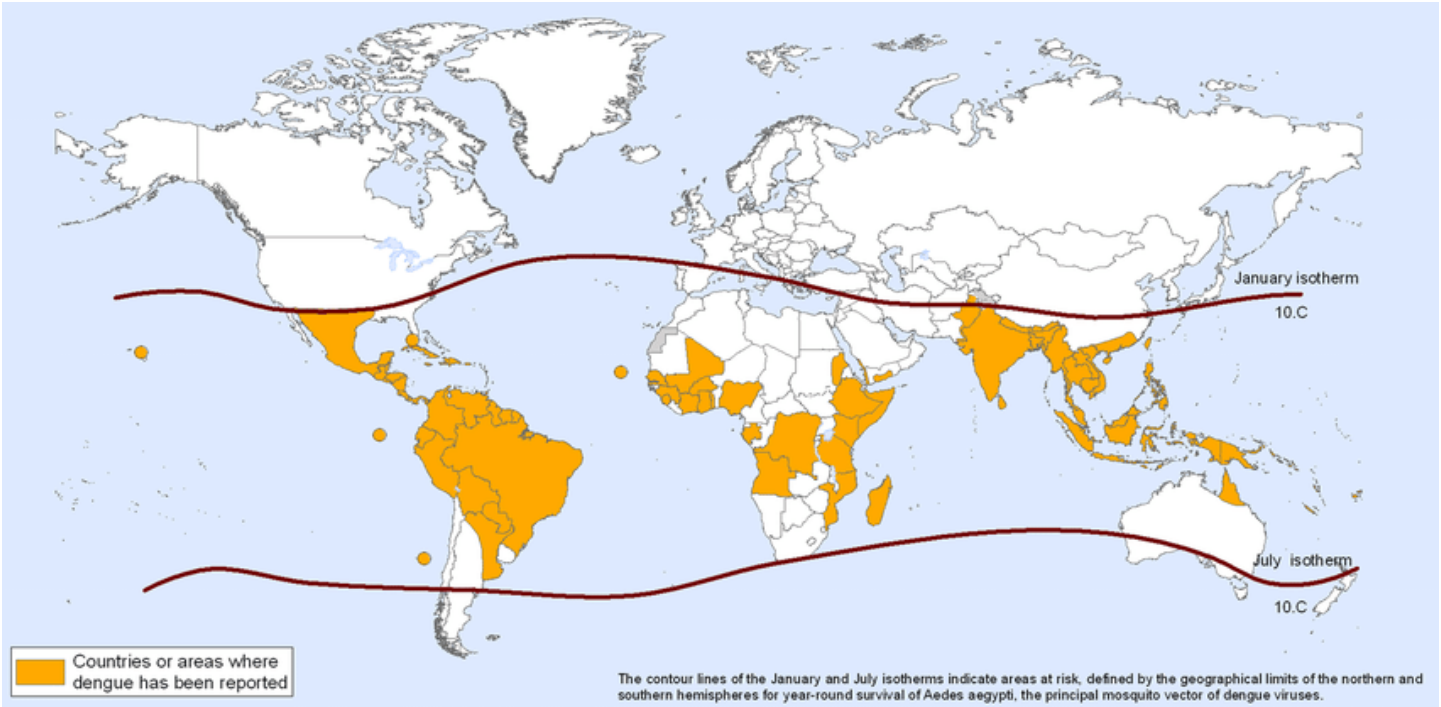
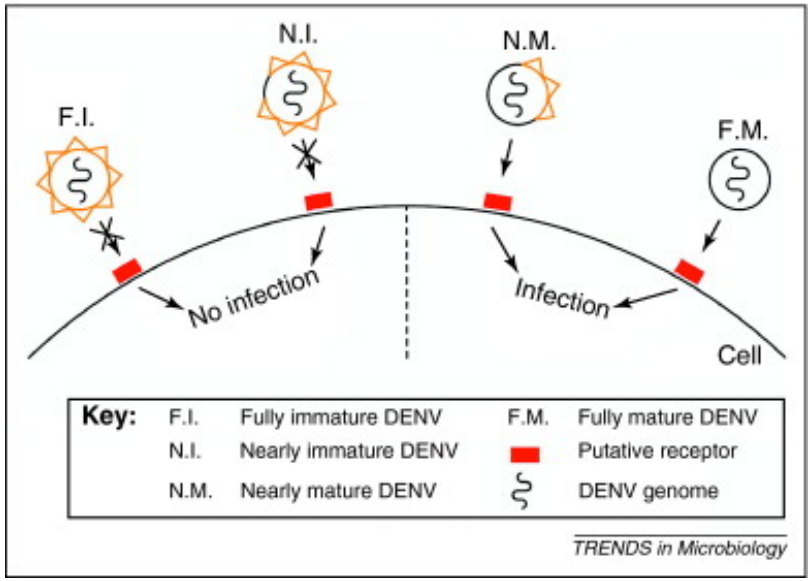
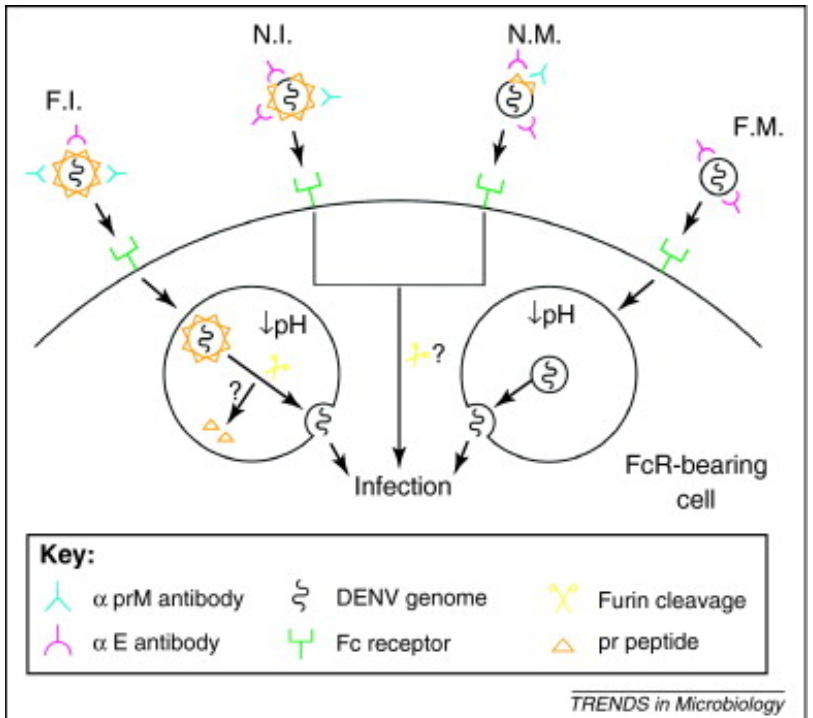


Figure: Dengue distribution in 2011 (WHO data). DENV has 4 serotypes and infection with one serotype does not lead to immunity against the other serotypes, but may manifest as DHF/DSS.

Synthesis of virions in DENV-infected cells





Degree of maturity = degree of infectivity

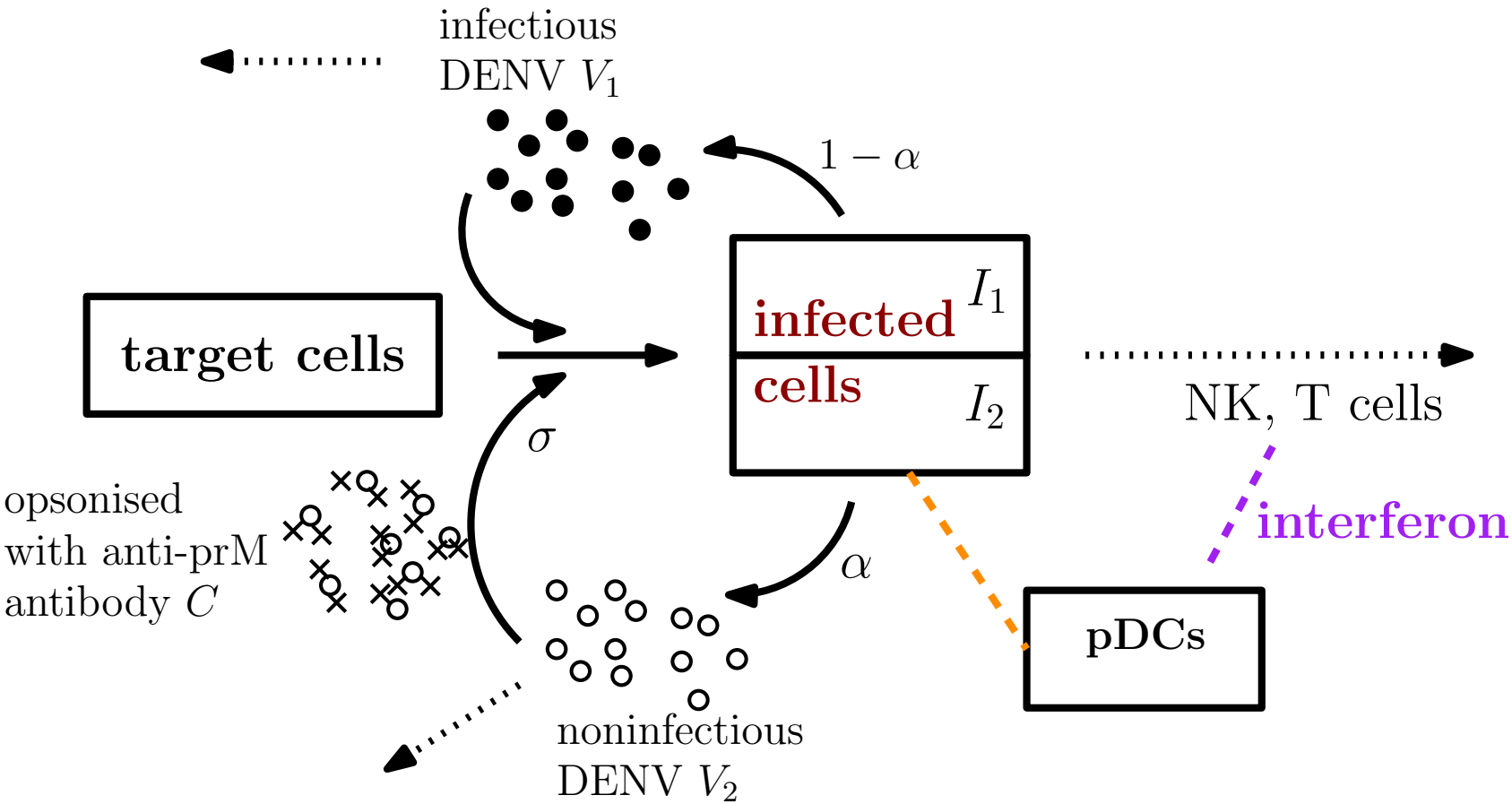
- blood samples from dengue patients contain a proportion of immature DENV containing uncleaved prM
- inhibition of furin leads to production of immature DENV (*in vivo*)
- fully or nearly immature DENV is essentially not infectious to cells *but* they regain full infectivity when they interact with 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

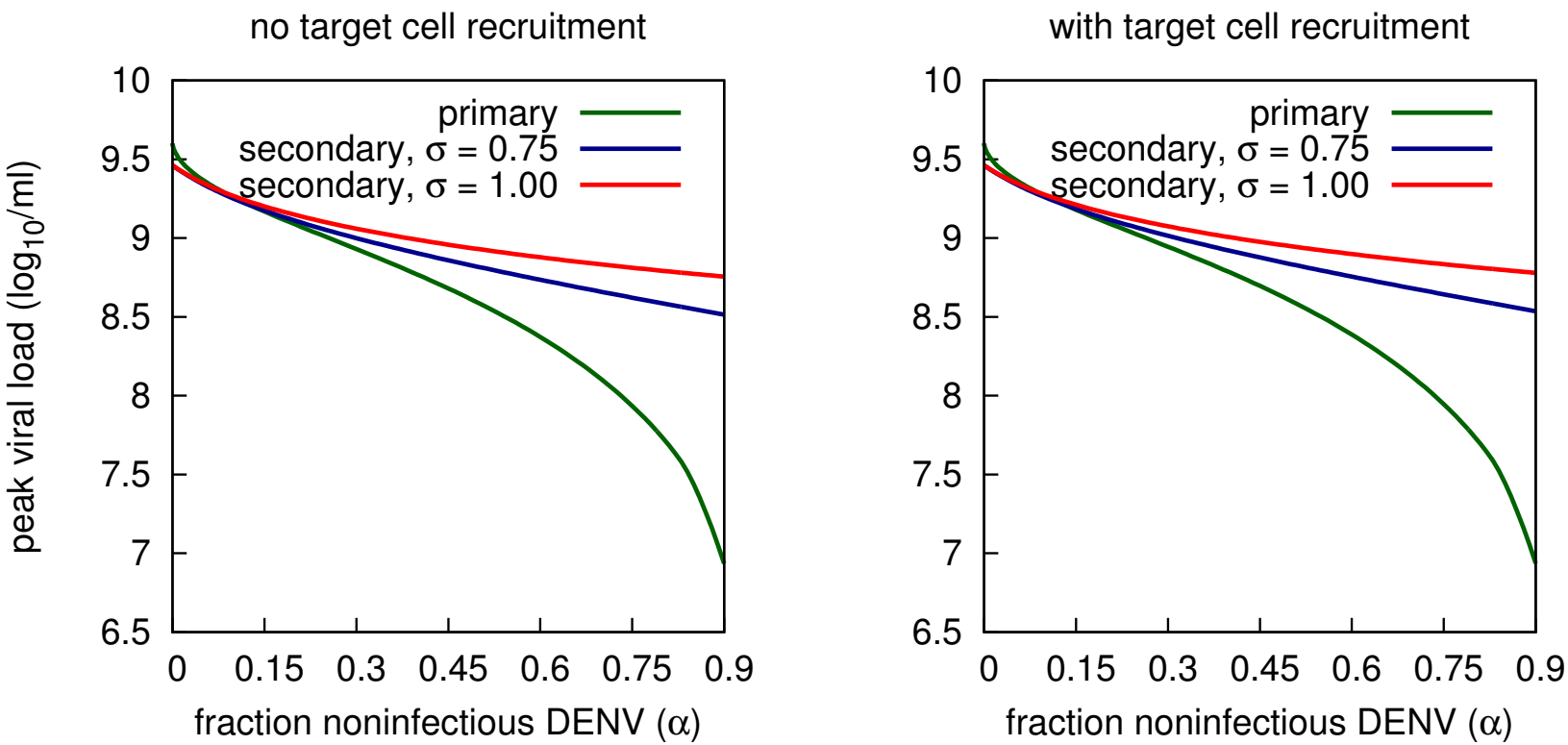
- is there any evolutionary advantage of immature, noninfectious DENV?
- why/how would DENV benefit from presence of noninfectious virions that induce a stronger immune response presumably targeted against DENV itself?
- fraction of noninfectious DENV and its effect on
  - disease progression: number 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

In-host mathematical model of dengue

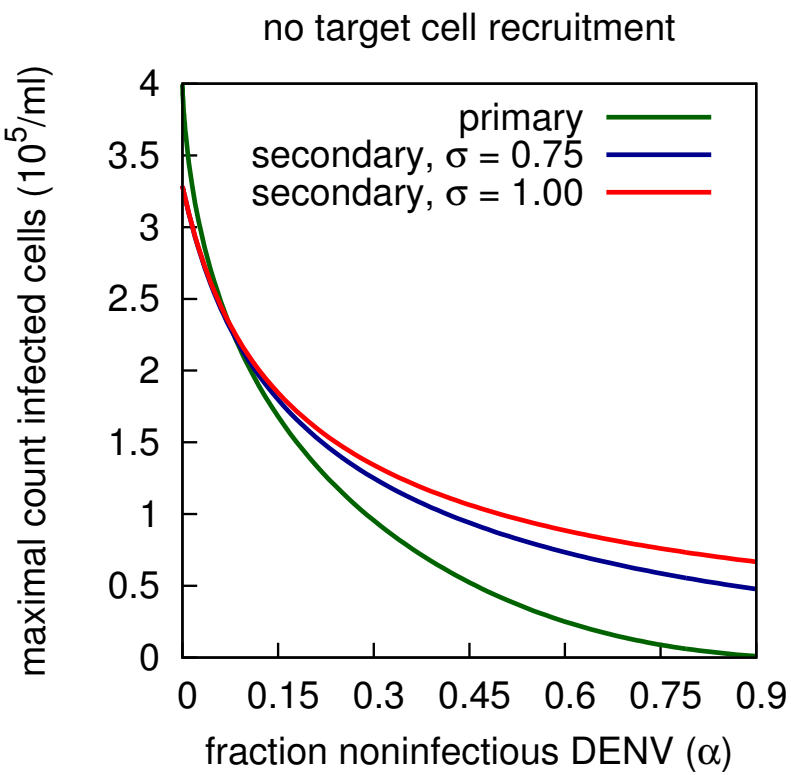


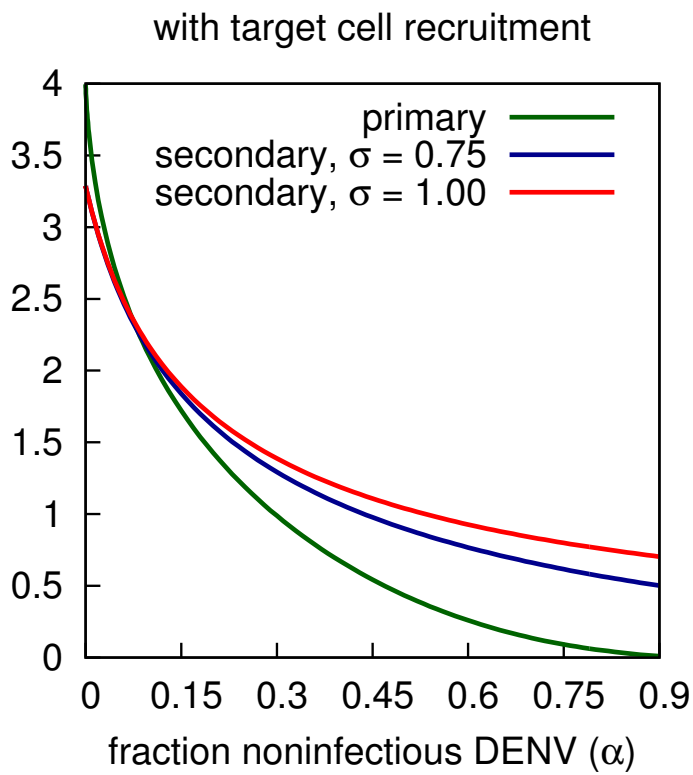
- randomly sample model parameters and run simulations to account for the uncertainty of the parameter values
- consider several scenarios
- vary the proportion α of infected cells producing noninfectious DENV and record the peak viral load, time to peak viral load, maximum of infected cells, immune indicators
- consider the scenario when only a fraction of the opsonised noninfectious DENV enters Fc receptor-bearing cells ($\sigma = 0.75$) 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

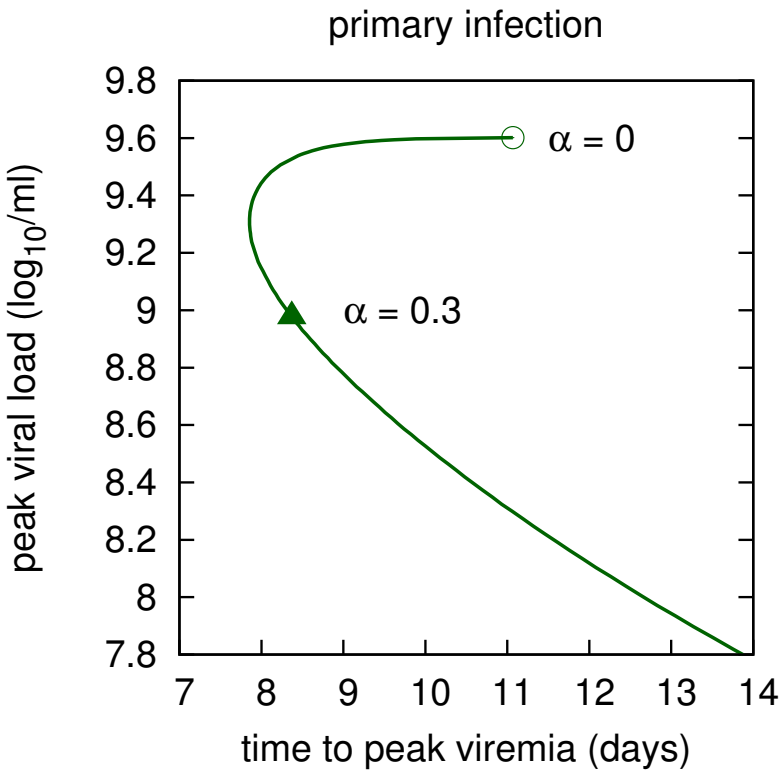


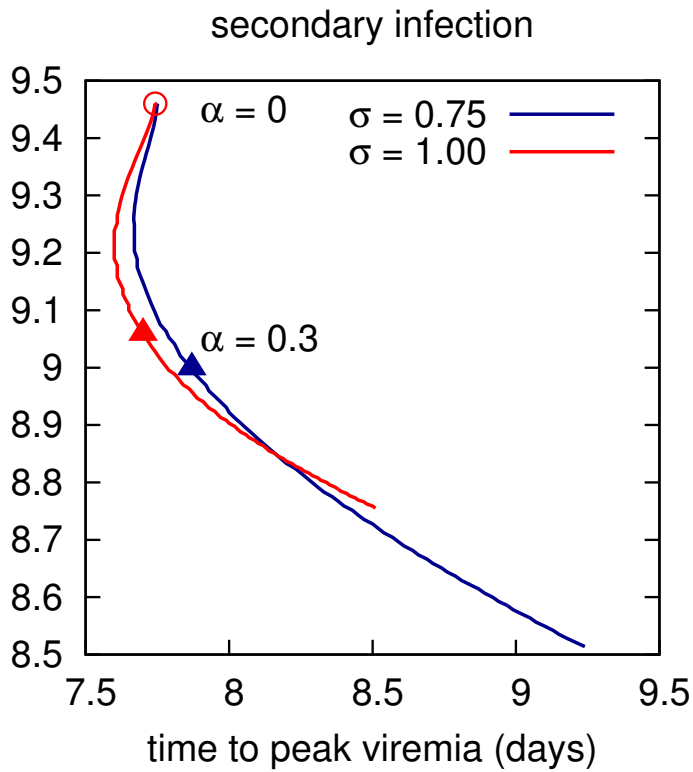
maximal count DENV infected cells





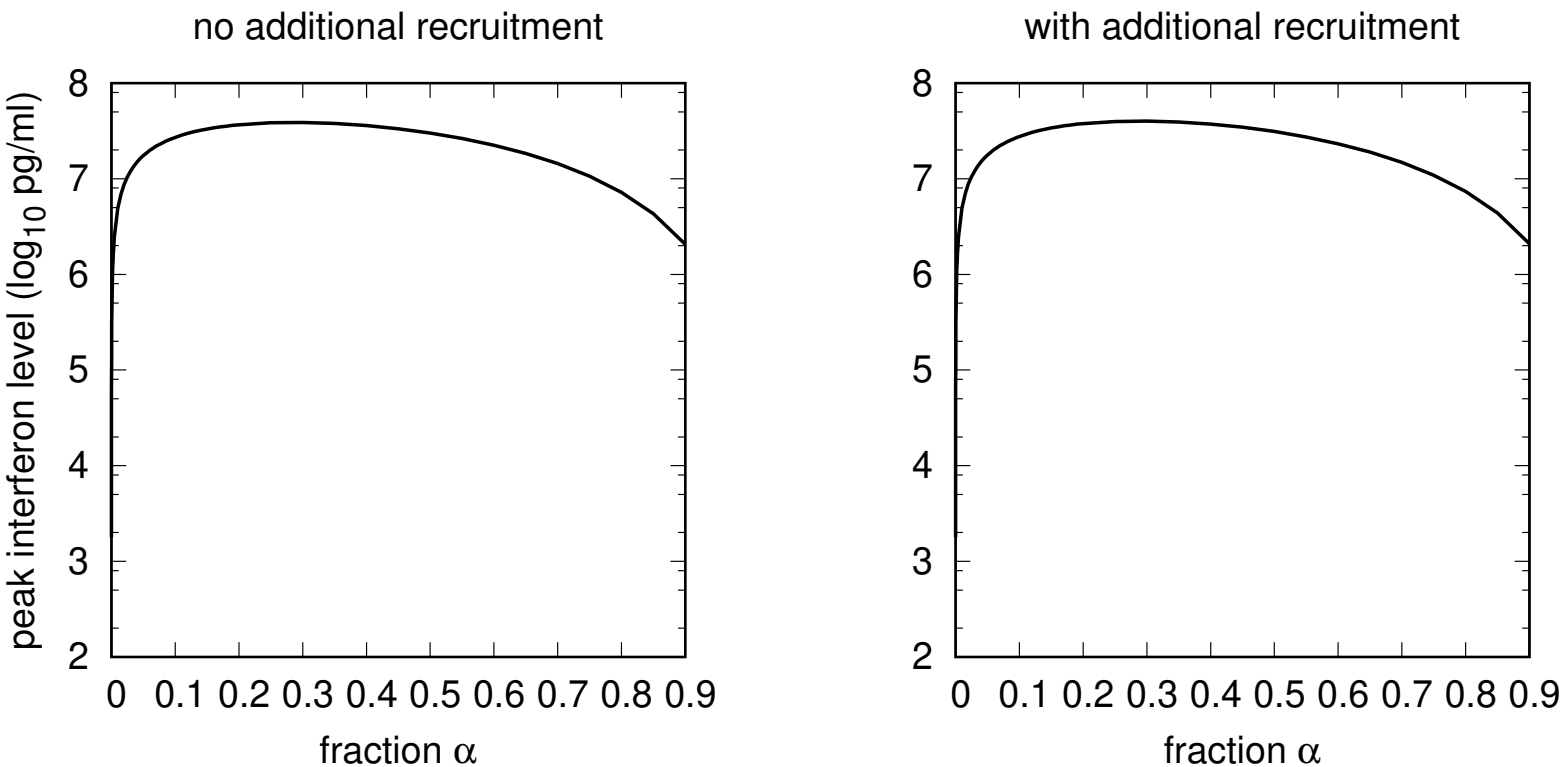
fraction noninfectious DENV causes a trade-off





fraction noninfectious DENV causes a trade-off

primary infection

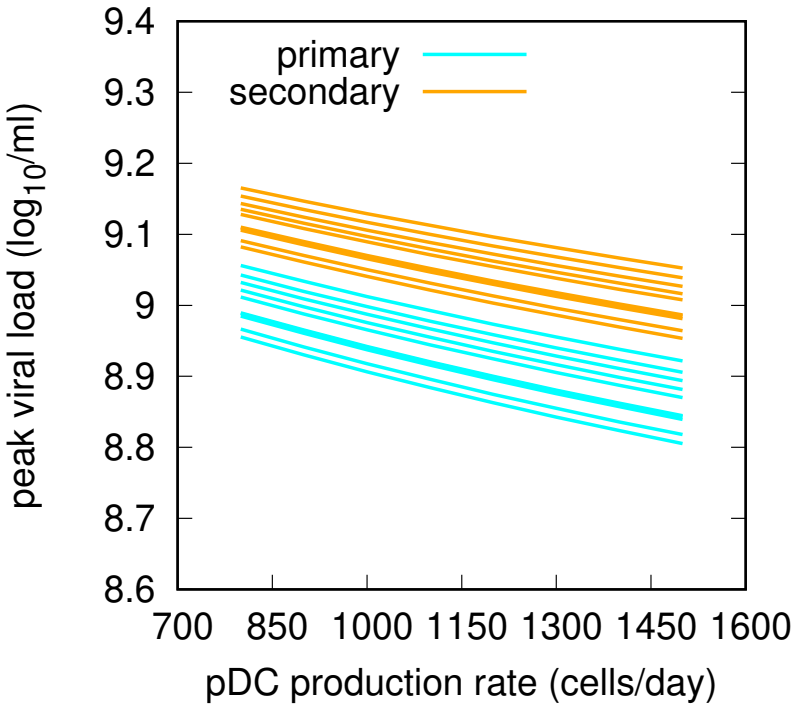


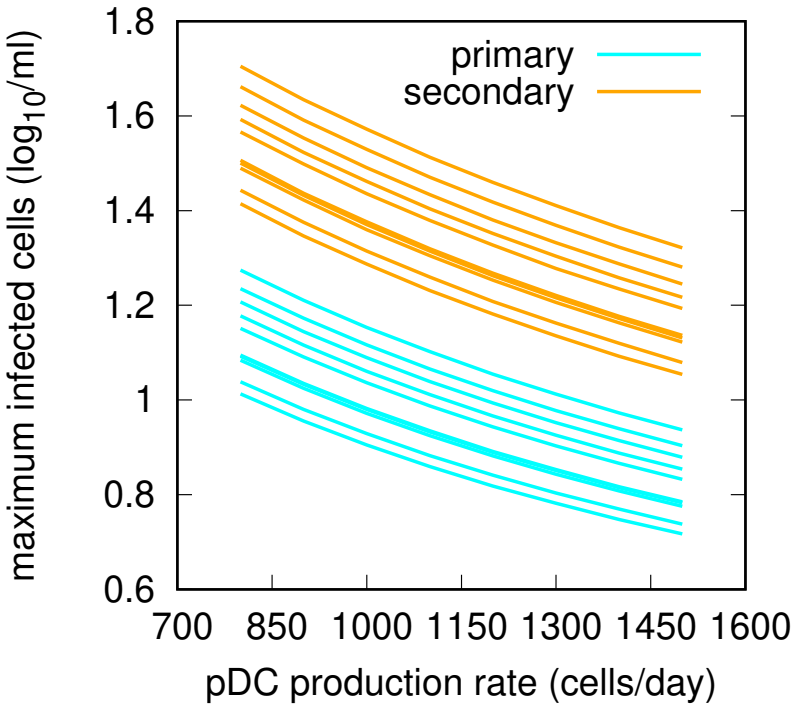
- no statistical evidence that interferon-mediated additional recruitment of target cells leads to higher viremia in primary or secondary DENV infection
- noninfectious DENV production enables DENV to increase its odds of transmission by several instruments: timing and level of peak viremia
- suggestions 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 viremia
  - 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

DENV and plasmacytoid dendritic cells

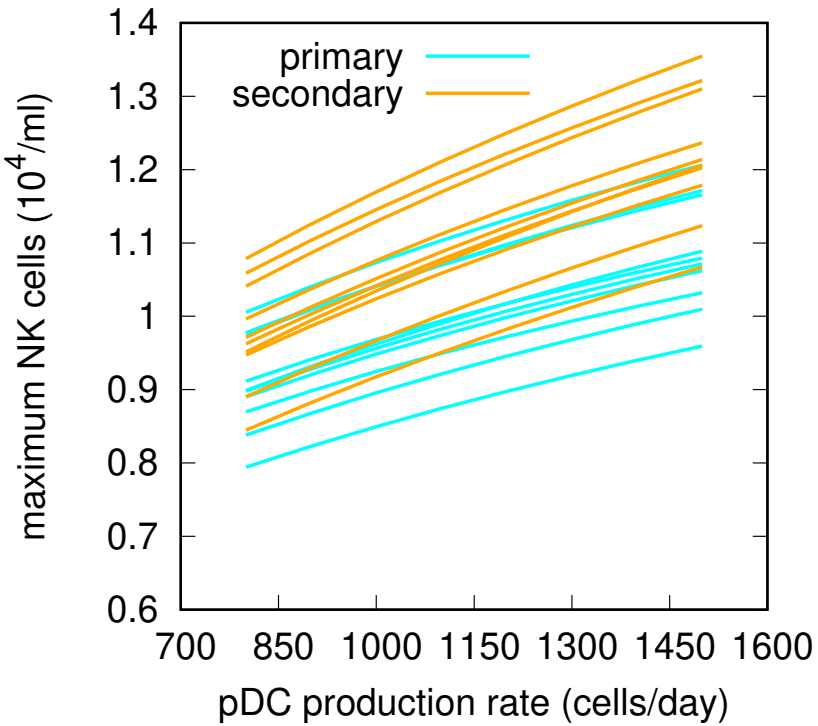
- test *in silico* the role of pDCs in disease progression
- randomly sample model parameters and vary the production rate of pDCs
- record disease indicators: peak viremia, maximum count of infected cells
- record immune indicators: the maximum counts of NK cells, T cells, peak interferon level

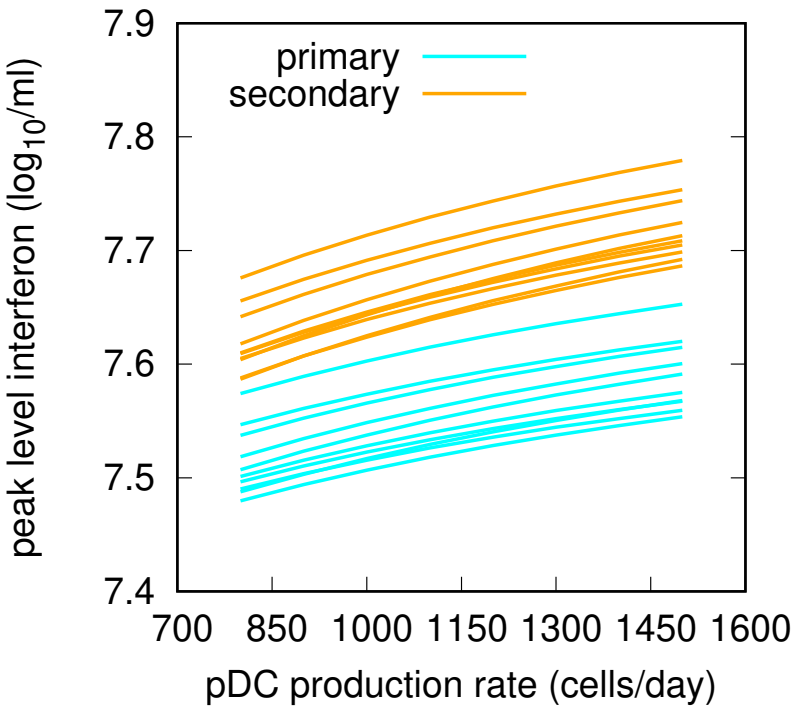
effect of pDC production on disease indicators



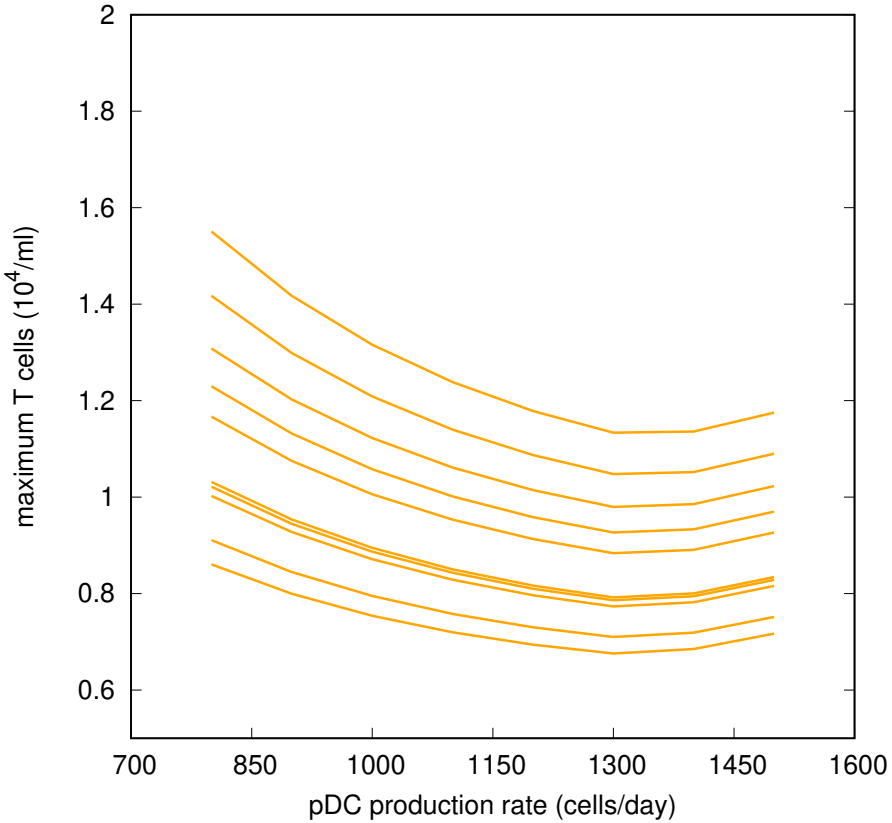


effect of pDC production on the immune response





effect of pDC production on the immune response



higher maximum counts of T cells at lower pDC production rates

- 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?

- 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
- single-cell experiments: understand better the heterogeneity of virus produced by infected cells

БЛАГОДАРЯ ЗА ВНИМАНИЕТО!

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