Mother-to-Child Transmission of Cytomegalovirus

This project aims to provide a framework to

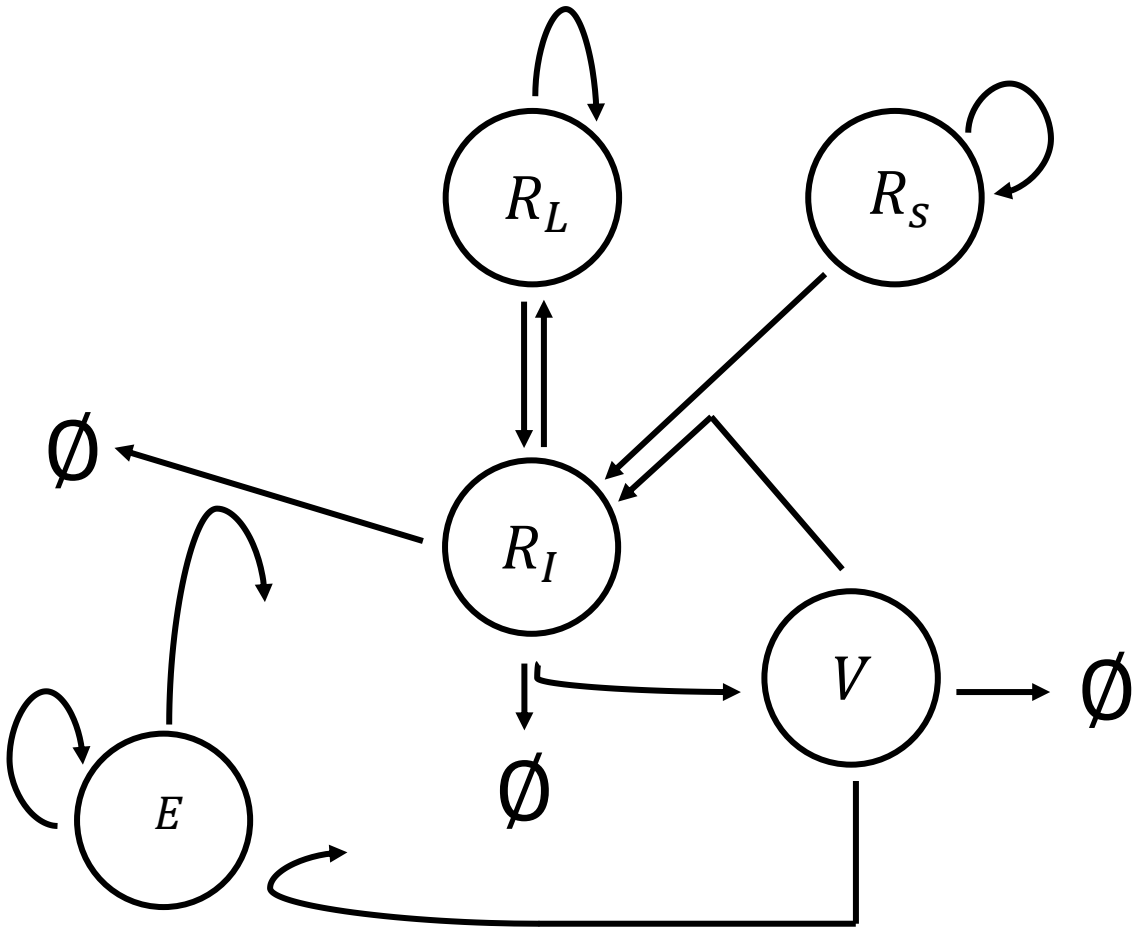
- deduce the possibility that the infant will be infected by CMV
- help test different hypotheses of what might affect the transmission

- Calibration required

Method Overview:

- Maternal viral dynamics:
  - System of ordinary differential equations
- Viral transmission through placenta:
  - (System of) partial differential equation(s) and analytic solution
- Viral dynamics in infant:
  - Stochastic simulation

Maternal viral dynamics using ODE



$$\frac{dV}{dt} = n\delta R_I - cV - fkR_S V,$$

$$\frac{dE}{dt} = (1 - \epsilon_S)\left(\lambda_E\left(1 - \frac{E}{e}\right)E + \rho V\right),$$

$$\frac{dR_I}{dt} = kR_S V - \delta R_I - (1 - \epsilon_S)mER_I + \alpha_0 R_L - \kappa\, R_I,$$

$$\frac{dR_S}{dt} = \lambda_{rep}\left(1 - \frac{R_S}{r_S}\right)R_S - kR_S V,$$

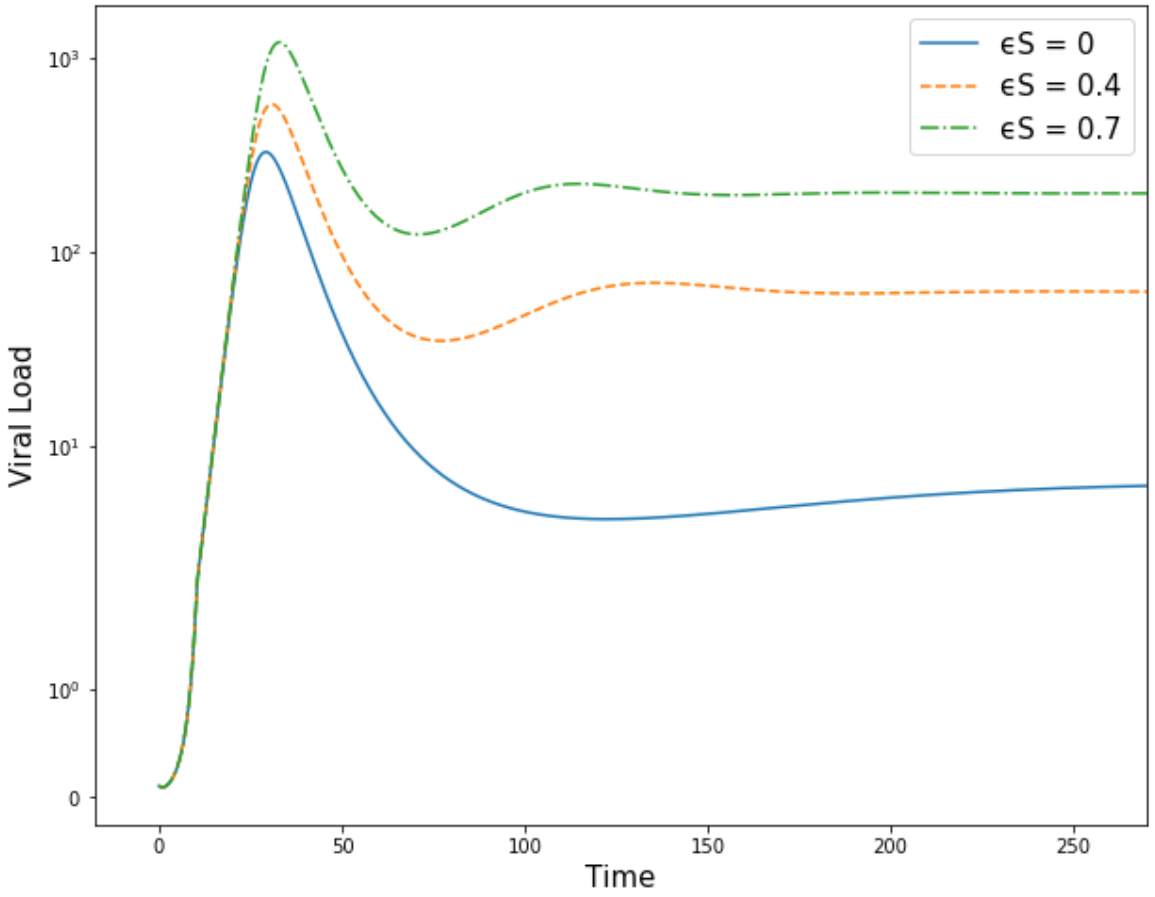
$$\frac{dR_L}{dt} = \lambda_{rep}\left(1 - \frac{R_L}{r_L}\right)R_S + \kappa\, R_I.$$

Variable	Description	Units
V	Viral load (free virus)	Virions/µl-blood
E	Virus-specific immune effector cells	Cells/µl-blood
R_I	Actively-infected cells	Cells/µl-blood
R_s	Susceptible cells	Cells/µl-blood
R_L	Latently-infected cells	Cells/µl-blood

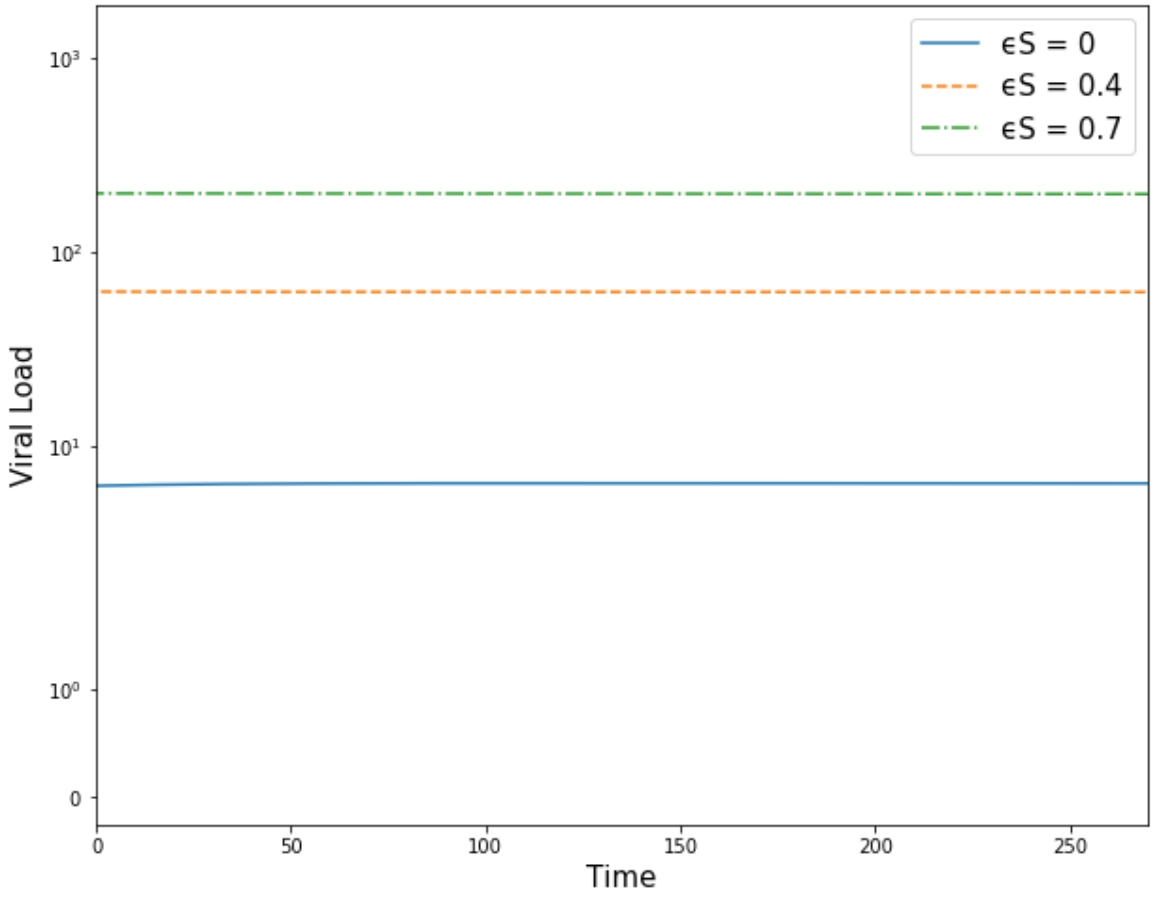
Maternal viral dynamics using ODE

ϵ_S : Level of immune suppression, corresponding to depletion of CD4+ level

Primary Infection of CMV



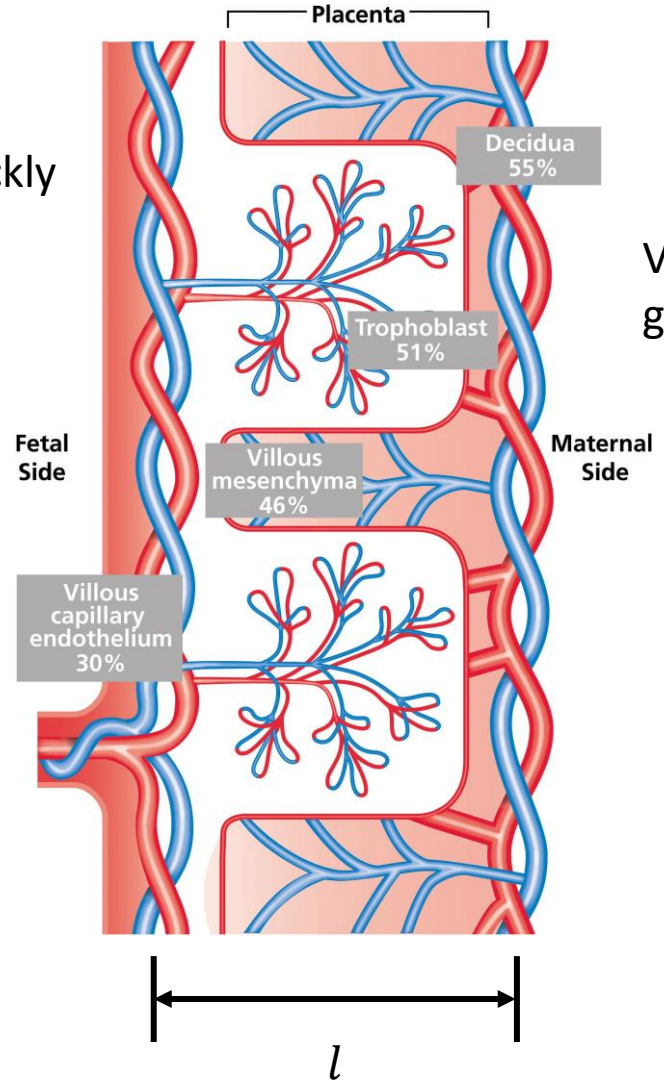
Chromic Infection of CMV



Viral Transmission through Placenta (PDE)

$c = 0, 0 < x < l, t = 0$, no virus inside placenta at first.

$c = 0, x = 0, t \geq 0,$
When virus enters the infant, it quickly gets washed away with blood.



$c = V_m(t), x = l, t \geq 0,$
Viral dynamics on mother side is given by the ODE system.

Spatial movement due to diffusion

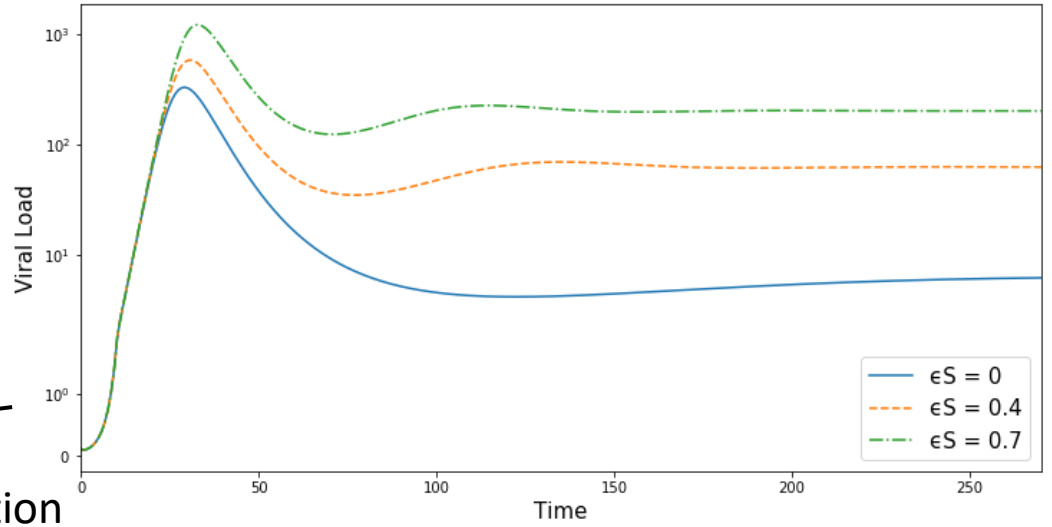
$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \mu c,$$

μc, → Clearance of CMV

$c = 0, x = 0, t \geq 0,$
$c = V_m(t), x = l, t \geq 0,$
$c = 0, 0 < x < l, t = 0.$

Viral Transmission through Placenta

Maternal viral dynamics using ODE



Maternal side

Boundary condition on mother side

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \mu c$$

infant side

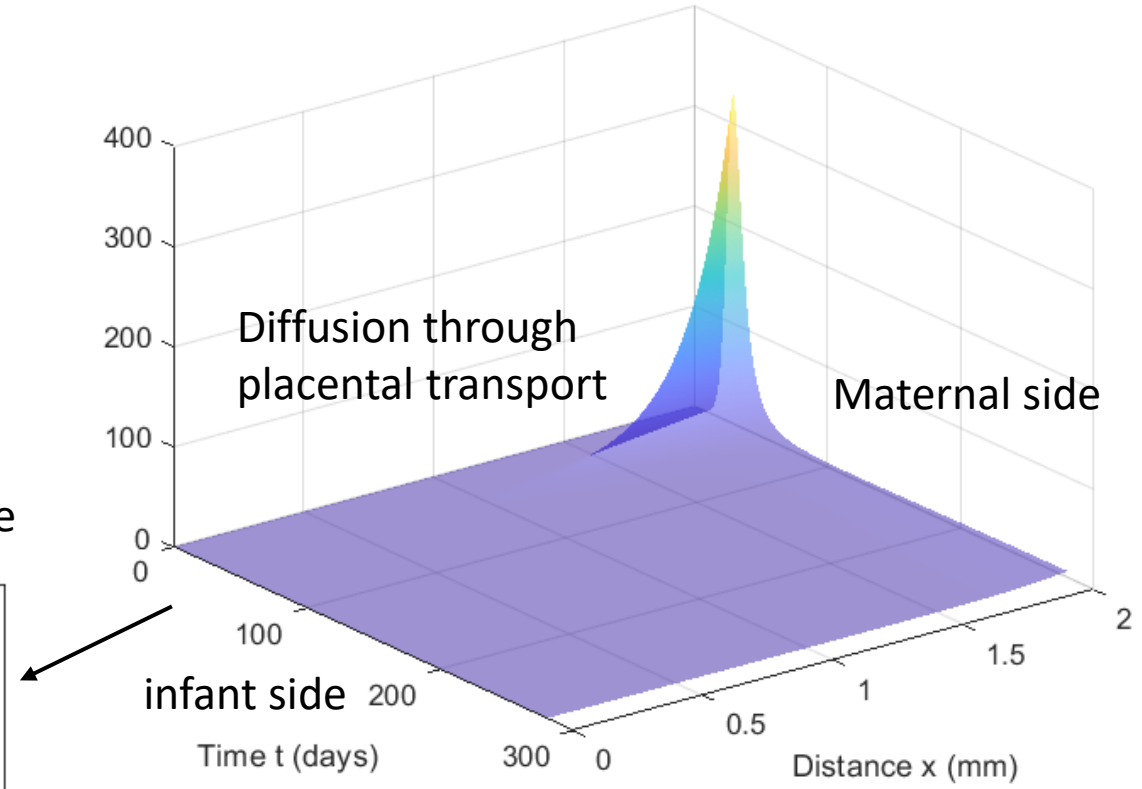
Time t (days)

Distance x (mm)

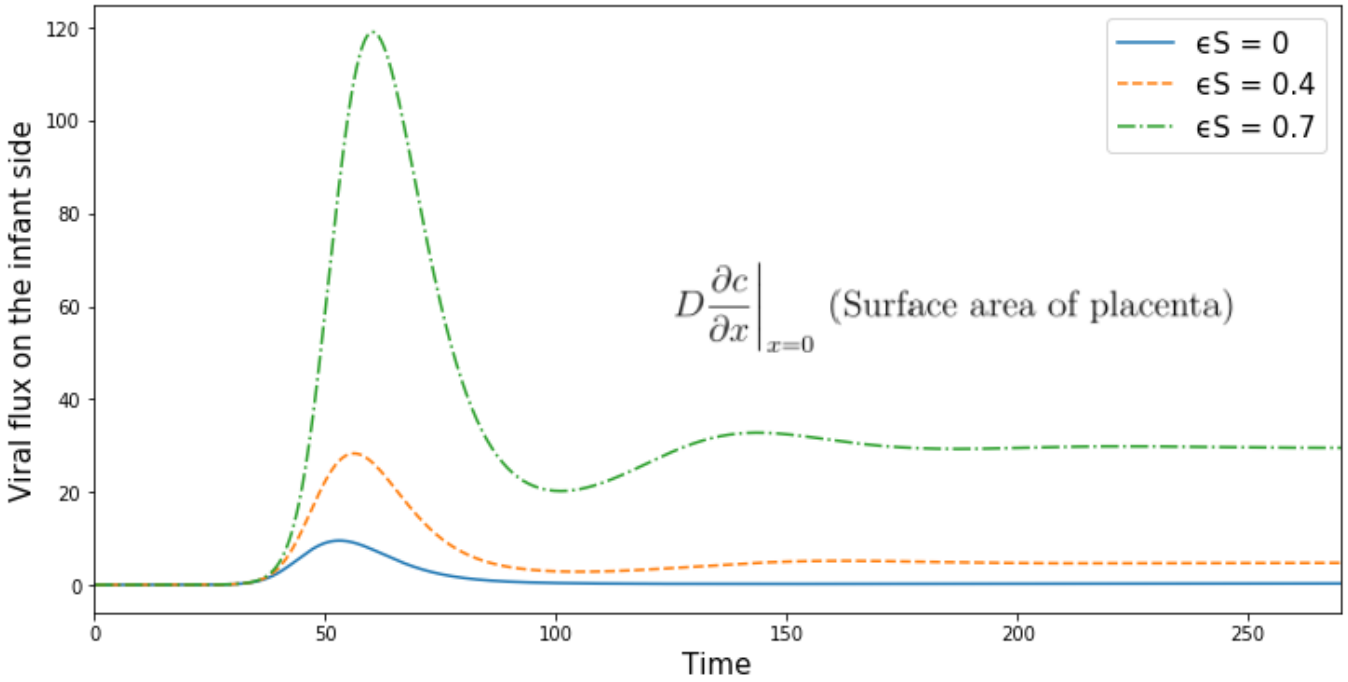
l

Diffusion through placental transport

Viral Transmission through Placenta



Zoom in on
the fetal side



Number of viruses that reach the infant :

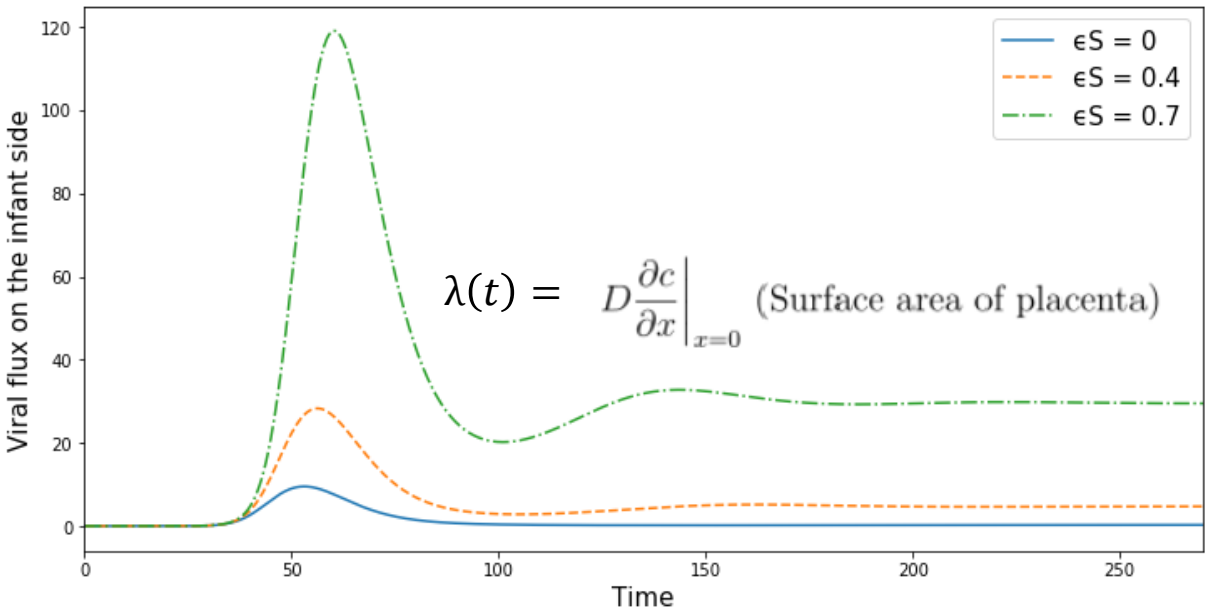
$$C = \int_0^T D\frac{\partial c}{\partial x}\Big|_{x=0} \text{(Surface area of placenta)}\ dt$$

But this information is not enough.

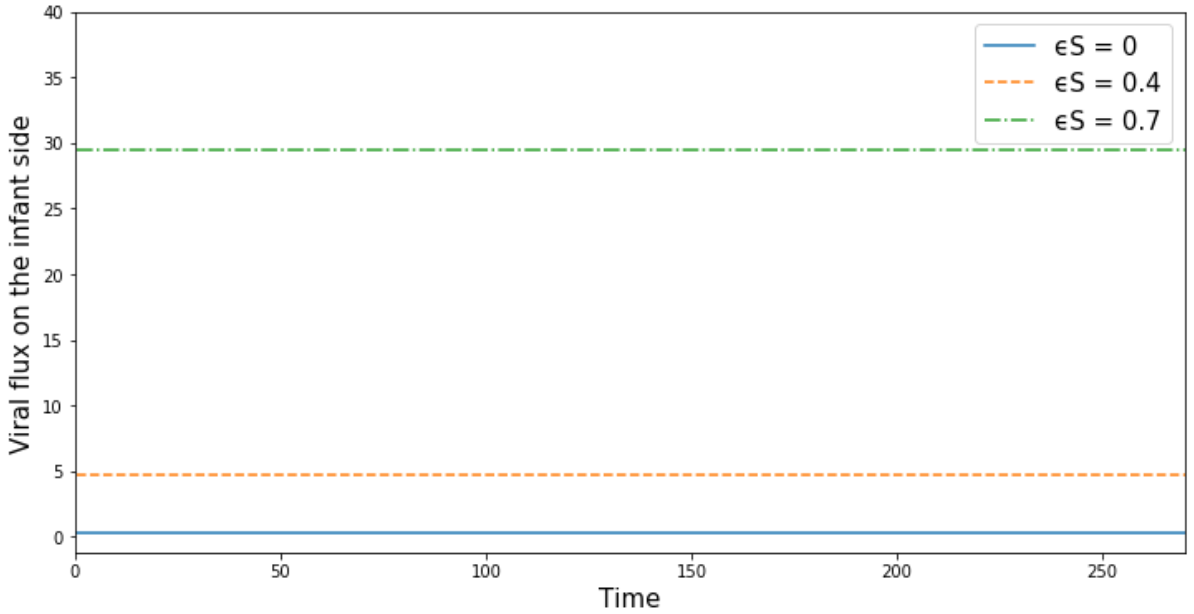
Infection of CMV

Treat the viral flux as the rate for an inhomogeneous Poisson point process, so we can obtain the time that each virus enters the infant.

Primary infection

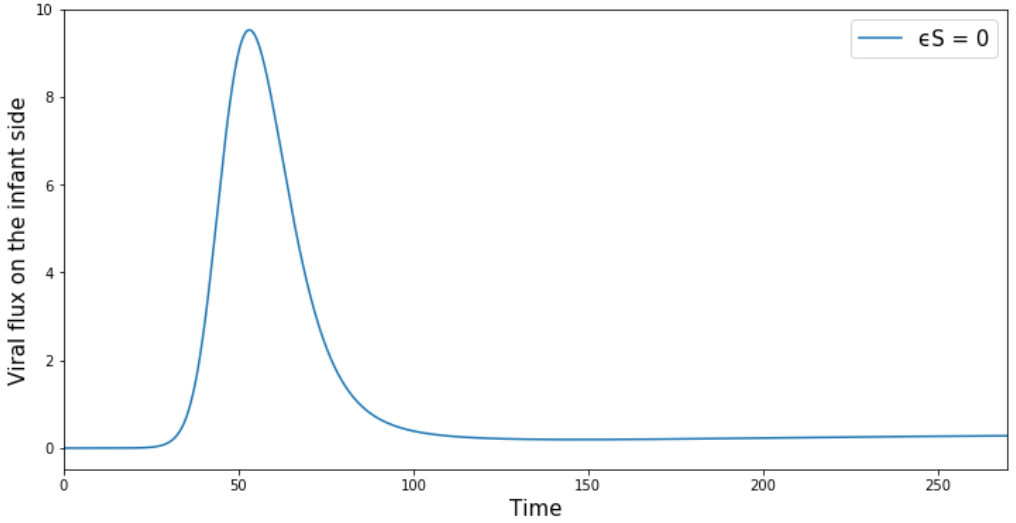


Chronic infection

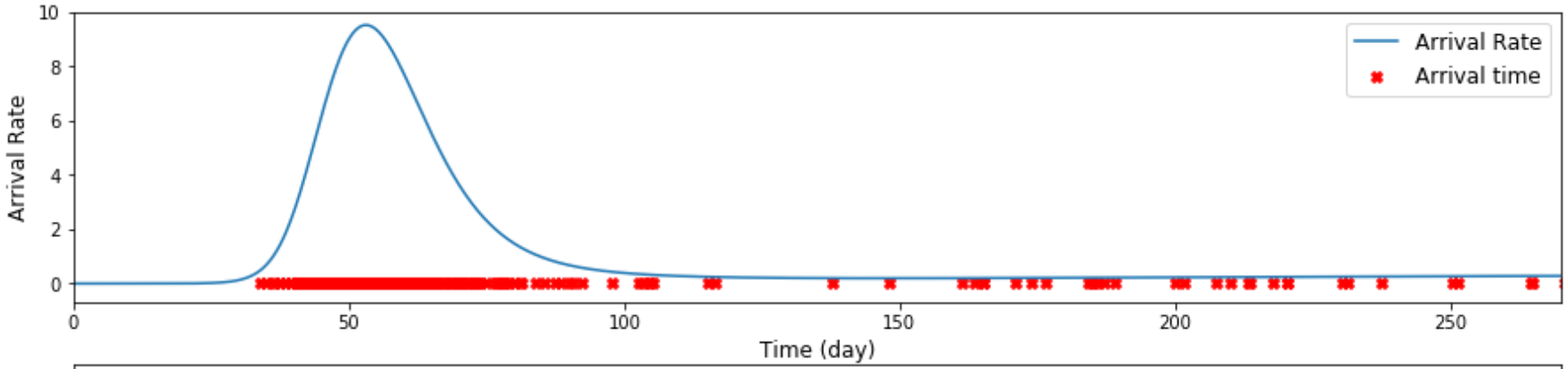


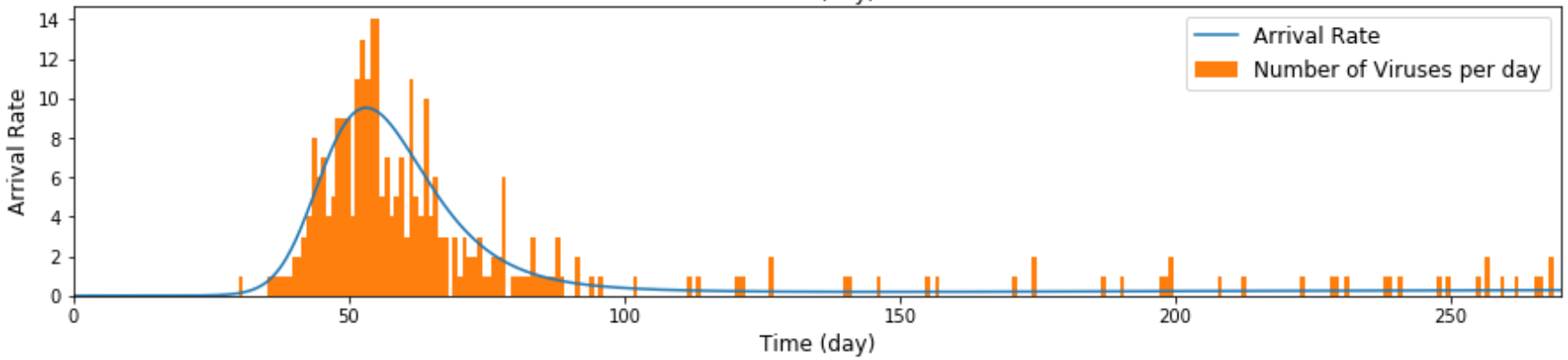
Primary Infection of CMV

Think of this flux function as probability of a virus arrives at the fetal side.



Healthy $\epsilon_S = 0$

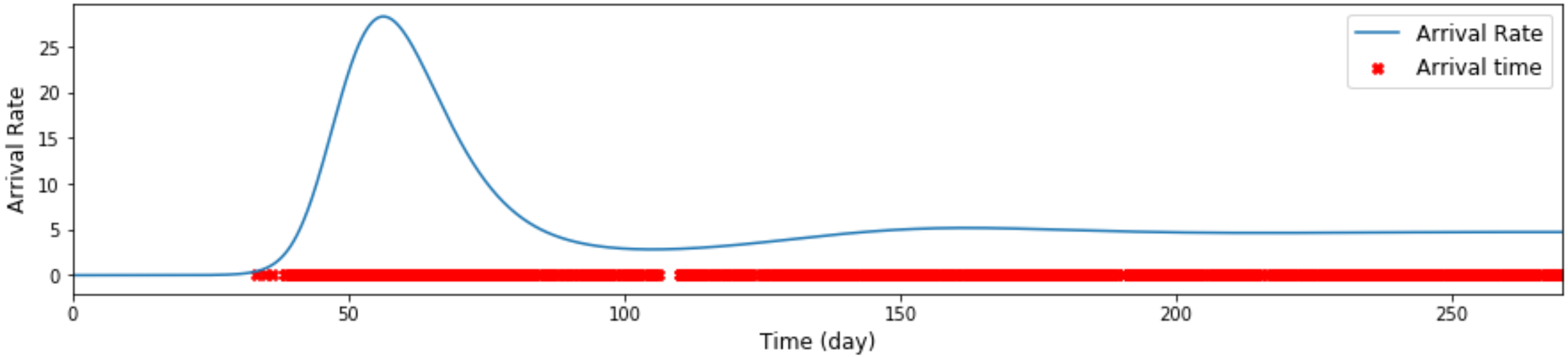


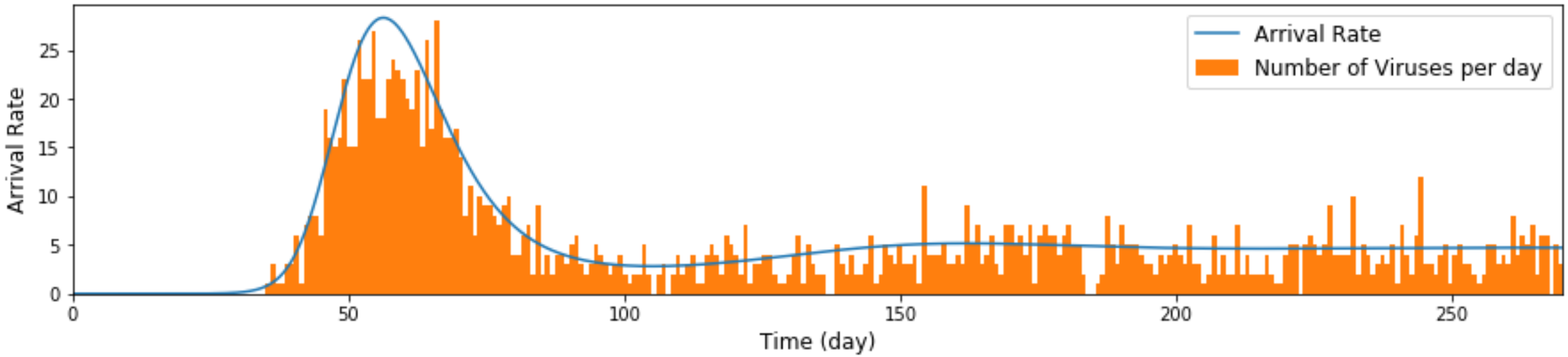


Here we have a list of time stamp for each virus, however, just the viruses entering the infant does not mean the infant is infected.

Primary Infection of CMV

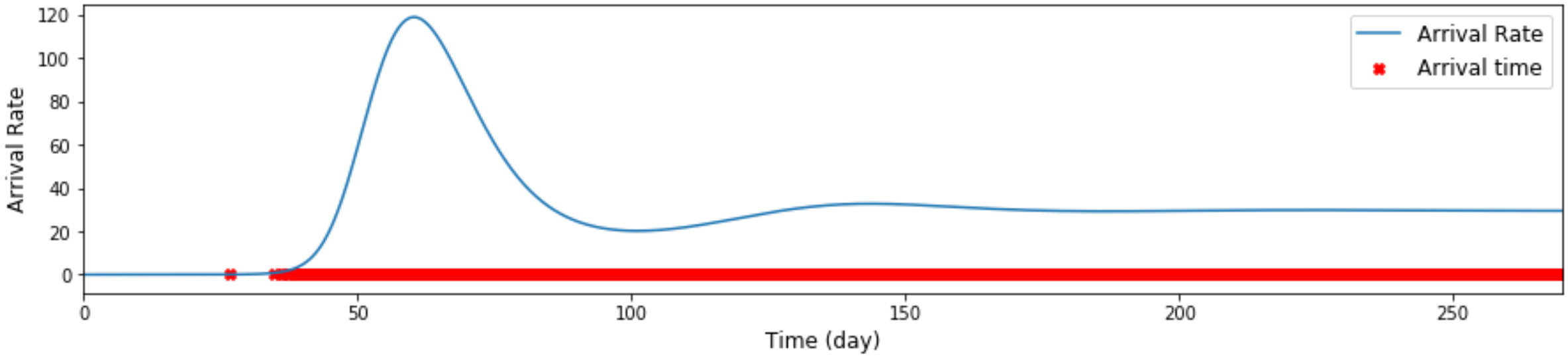
Immune suppressed ϵ_S = 0.4

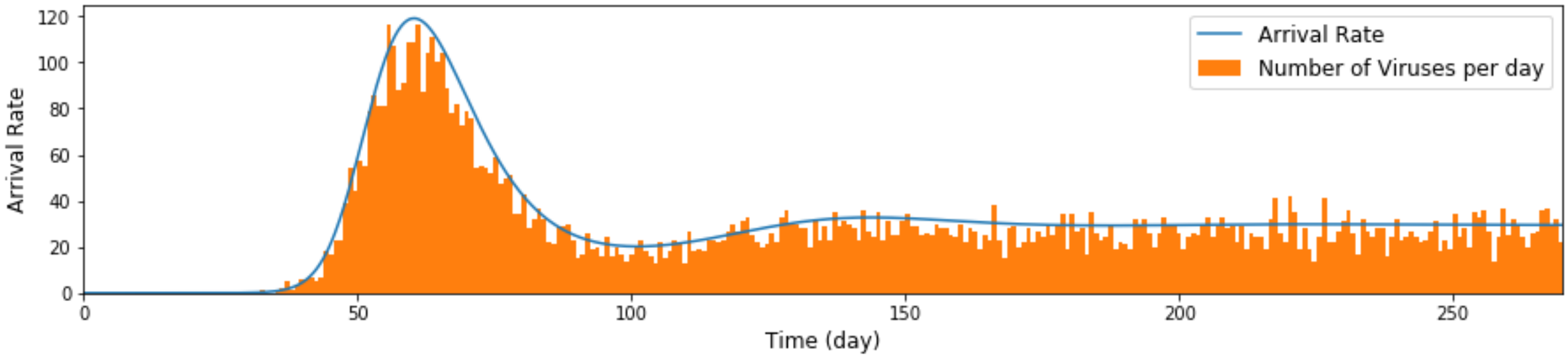




Primary Infection of CMV

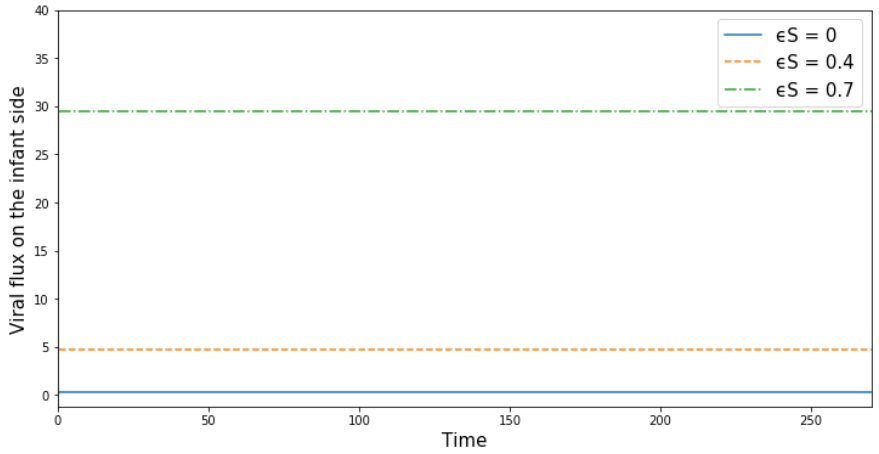
Immune suppressed ϵ_S = 0.7

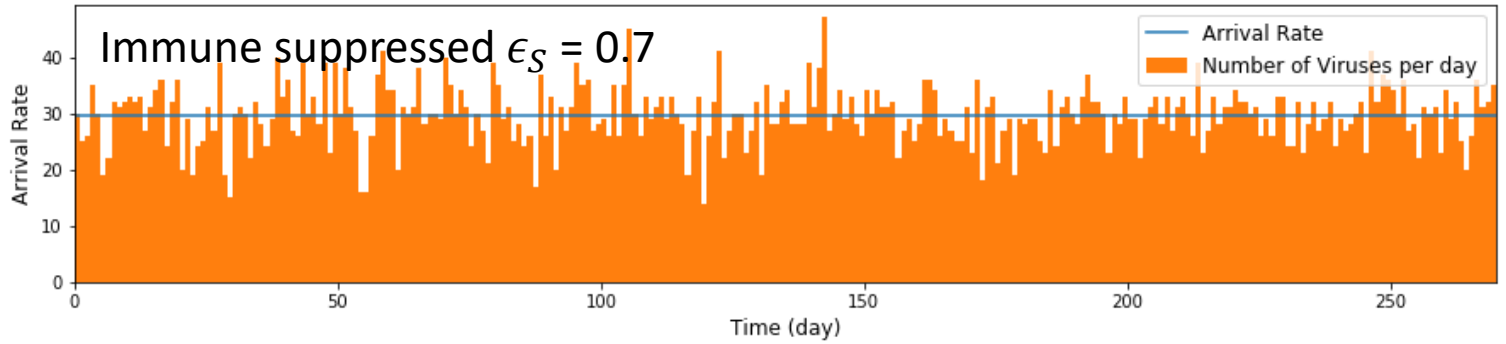


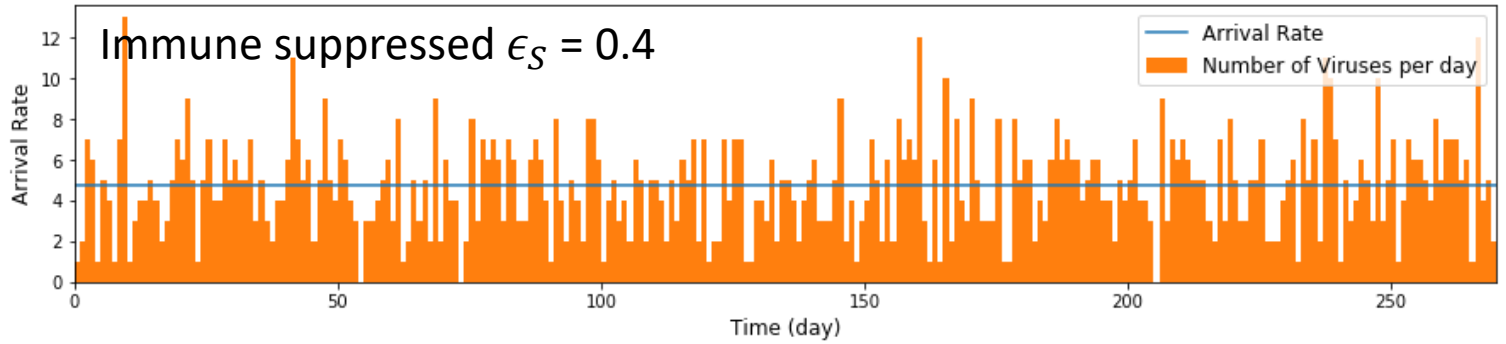


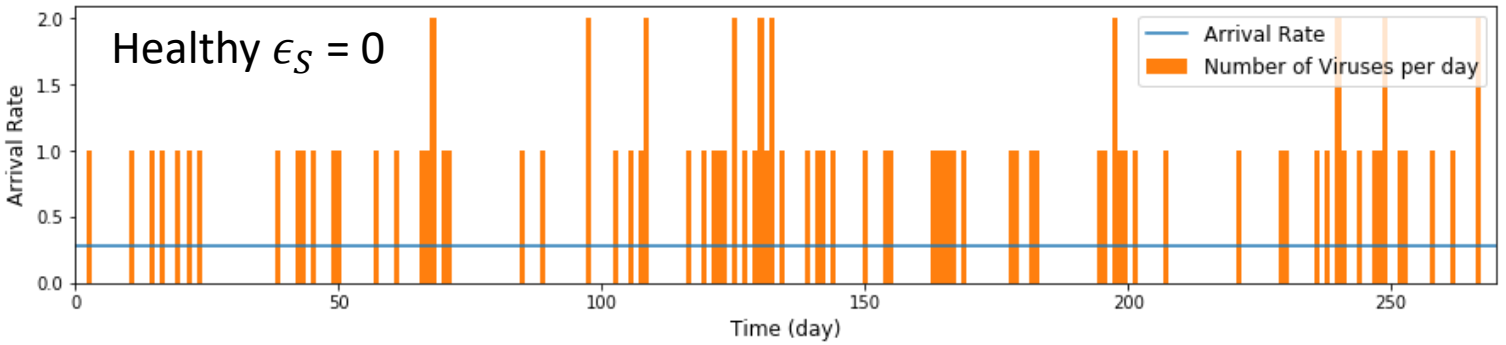
Chronic Infection of CMV

Chronic infection



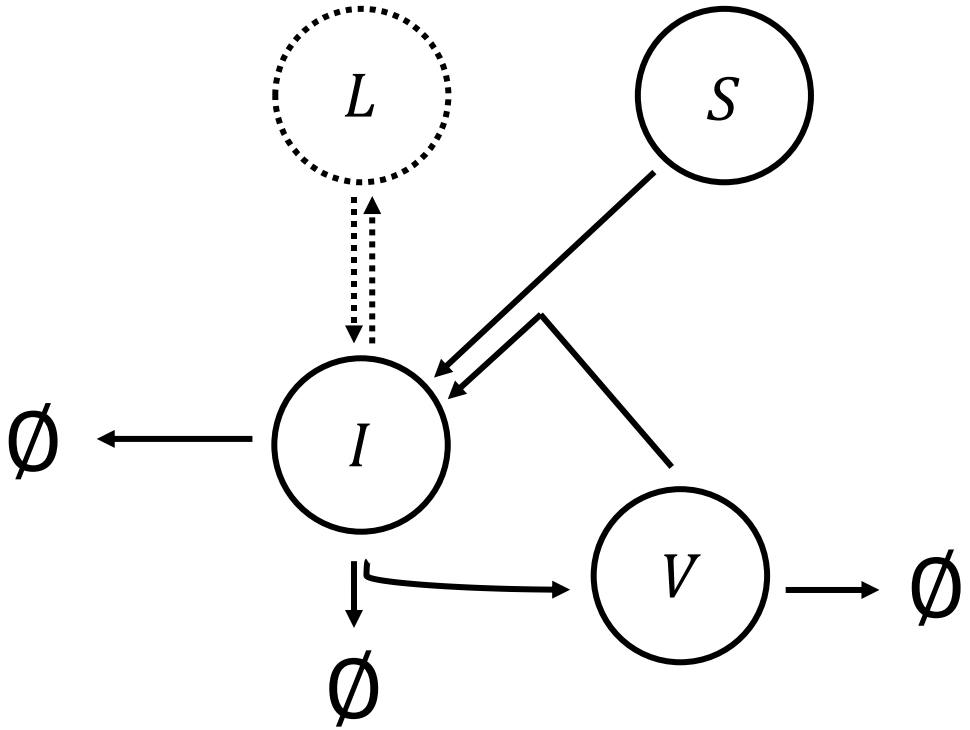






# of viruses entered	Healthy ϵ_S = 0	Immune suppressed ϵ_S = 0.4	Immune suppressed ϵ_S = 0.7
Primary	~300	~1600	~8700
Chronic	~100	~1300	~8100

Stochastic simulation on the infant side



When the number of viruses is very small, it is possible that the viruses go extinct before causing persistent infection.

$$R_0 = \frac{\beta S_0 p}{c\delta\left(1+\frac{\mu}{\alpha}\right)} \approx 1.36$$

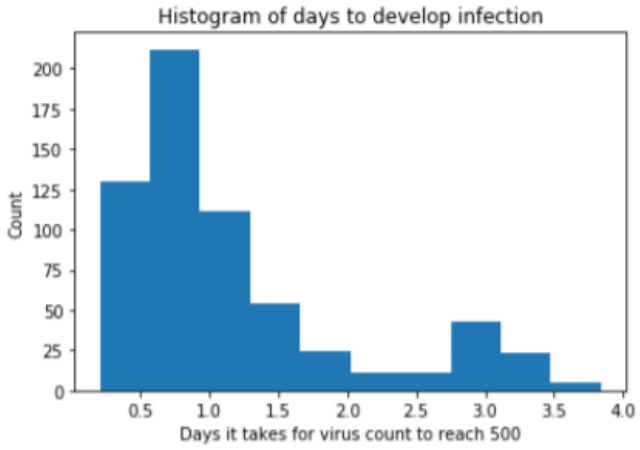
$$S \to I \; with \; c_1 = \beta SV,$$
$$I \to \emptyset \; with \; c_2 = \delta_I,$$
$$\emptyset \to V \; with \; c_3 = p,$$
$$V \to \emptyset \; with \; c_4 = \mu.$$

Probability of infection

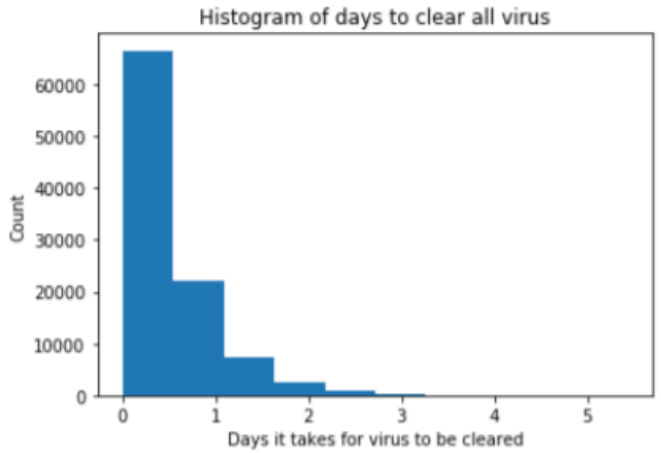
Heuristic

$$\left(\frac{\beta SV}{\beta SV + \mu V}\right)\left(\frac{pI}{pI + \delta_I I}\right)^N \approx \left(\frac{0.0012}{0.0012 + 1.5}\right)\left(\frac{1400}{1400 + 0.77}\right)^{1000} = 0.00046$$

$$Probability\ of\ infection = 1 - (1 - 0.046\%)^M$$

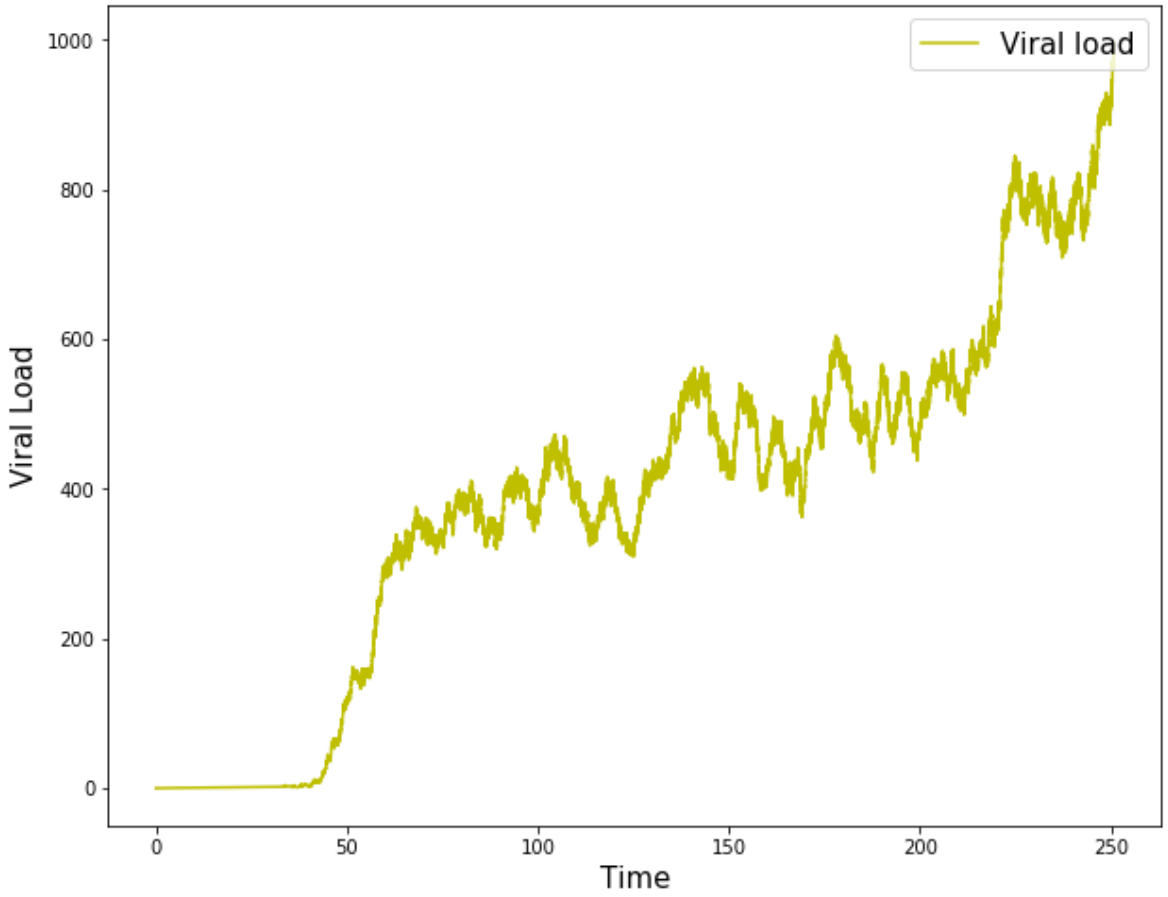


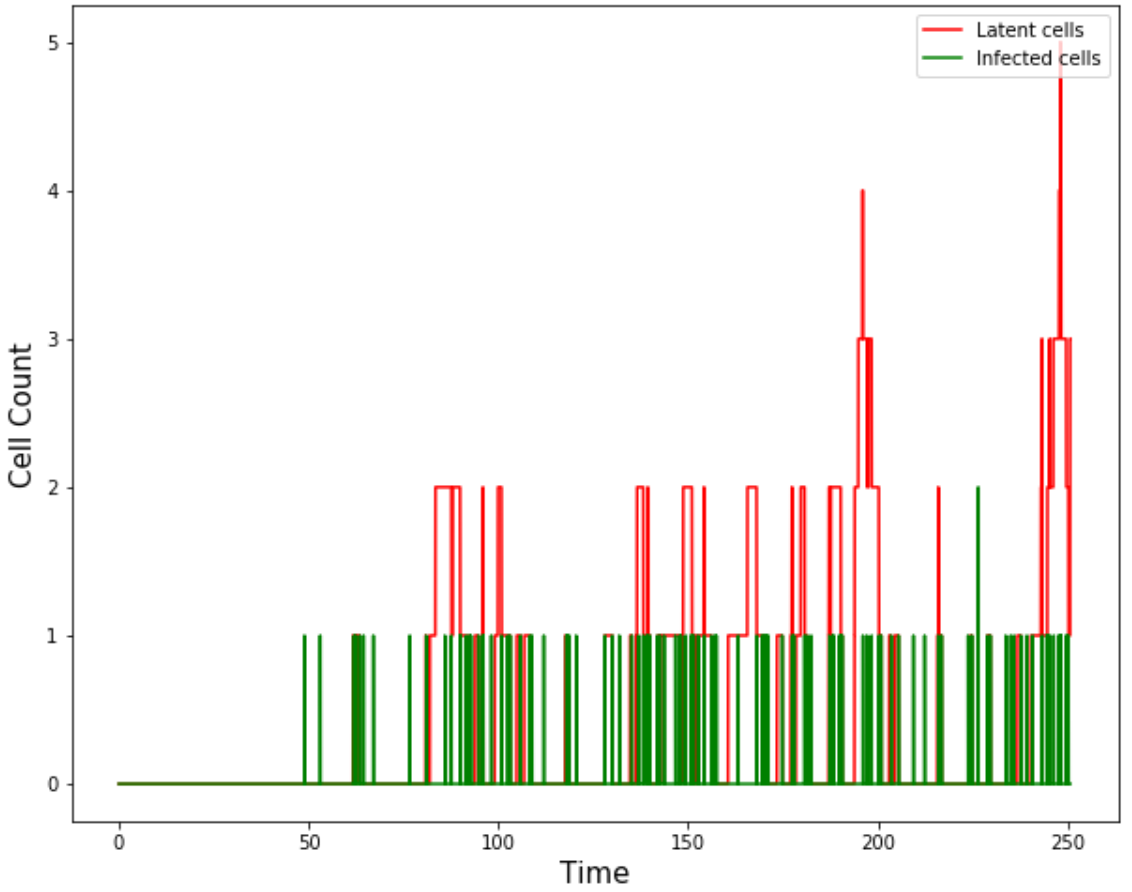
(a) On average, it takes 1.23 days to develop an infection.



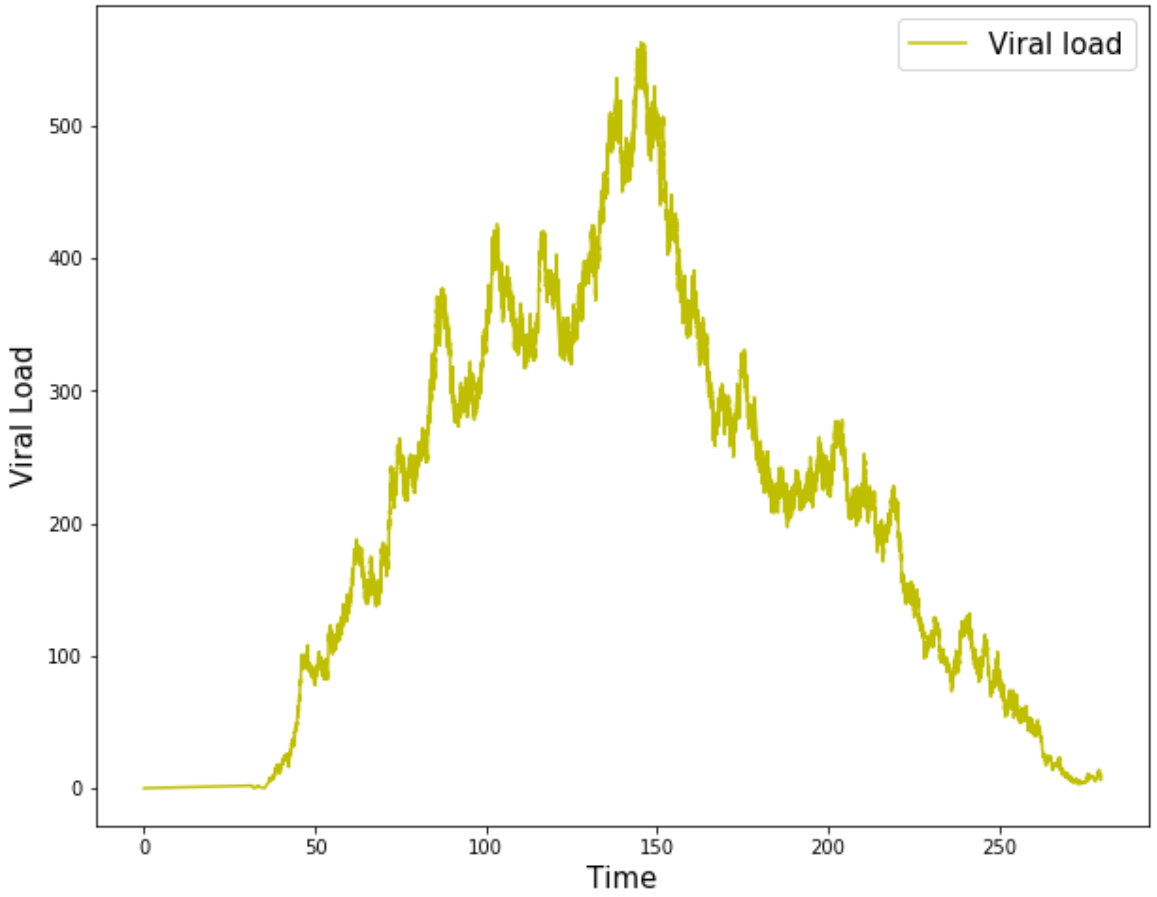
(b) On average, it takes 0.49 days to clear all viruses.

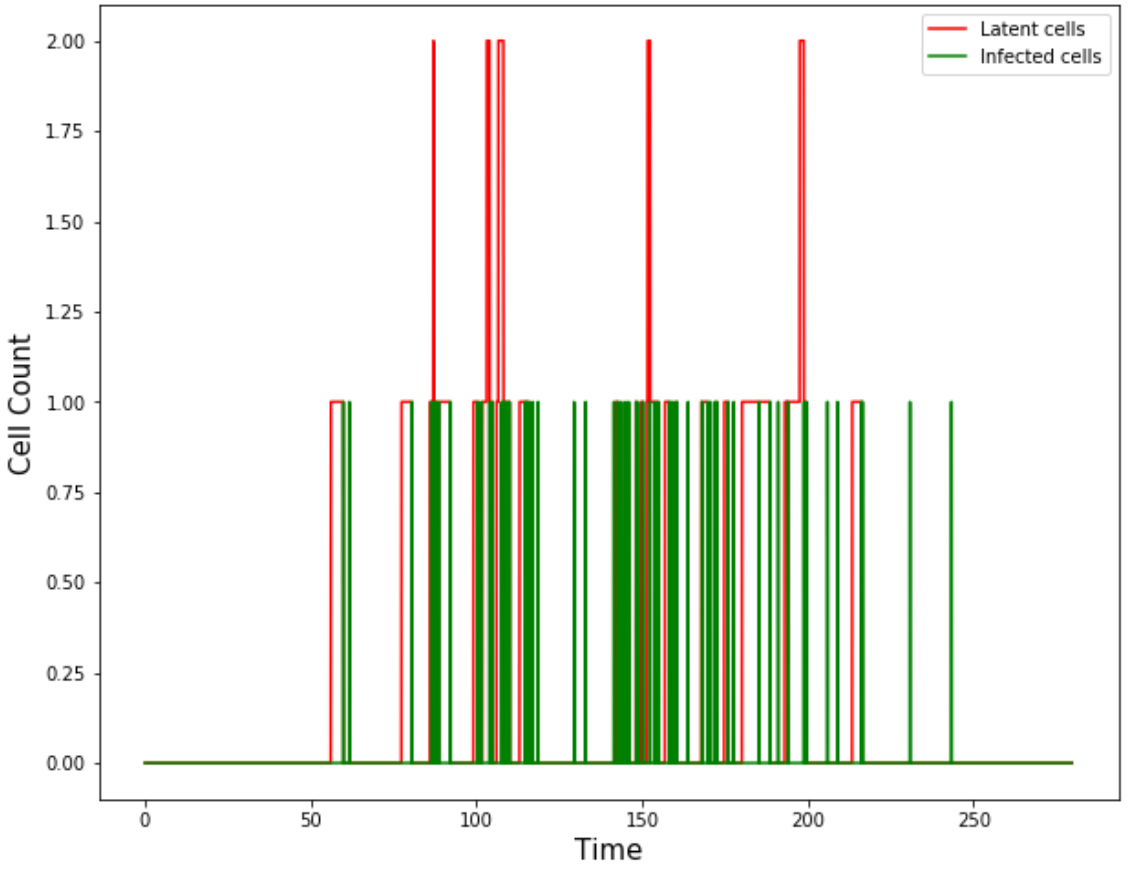
Persistent infection





Infection that got cleared





Summary

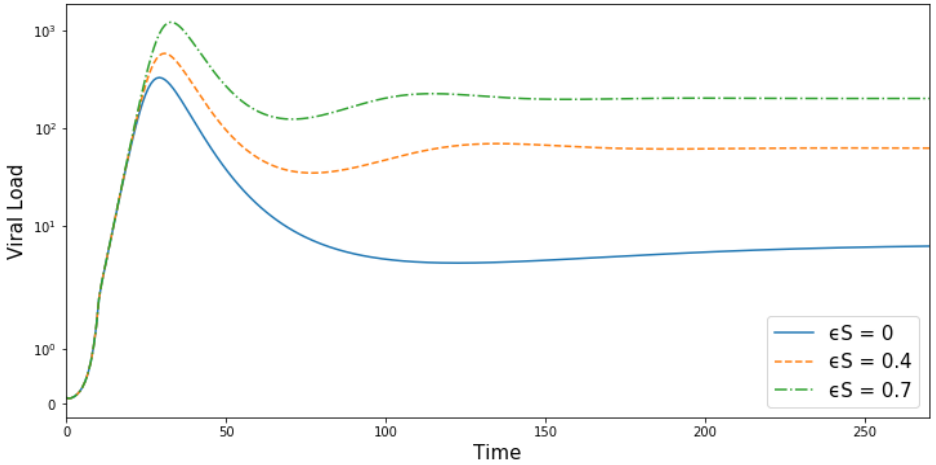
This model can predict infections in two situations

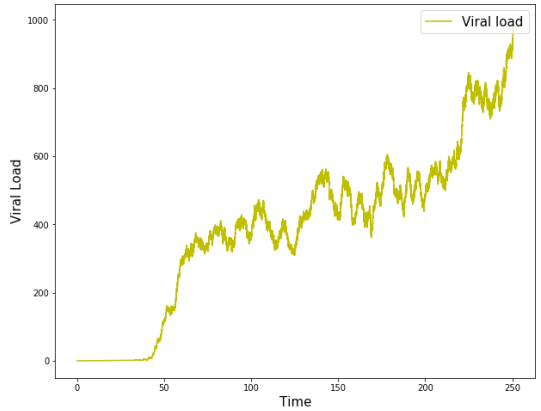
- Primary vs chronic
- Different level of immune suppression

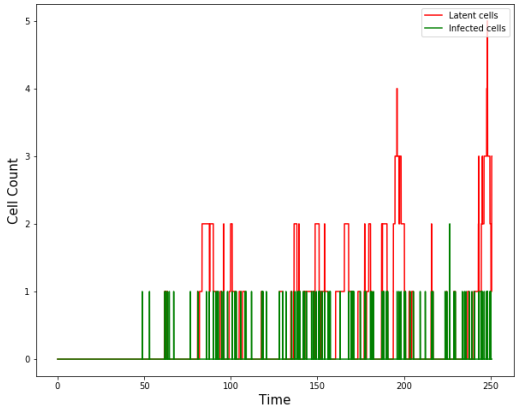
# of viruses entered	Healthy ϵ_S = 0	Immune suppressed ϵ_S = 0.4	Immune suppressed ϵ_S = 0.7
Primary	~ 300	~ 1600	~ 8700
Chronic	~ 100	~ 1300	~ 8100

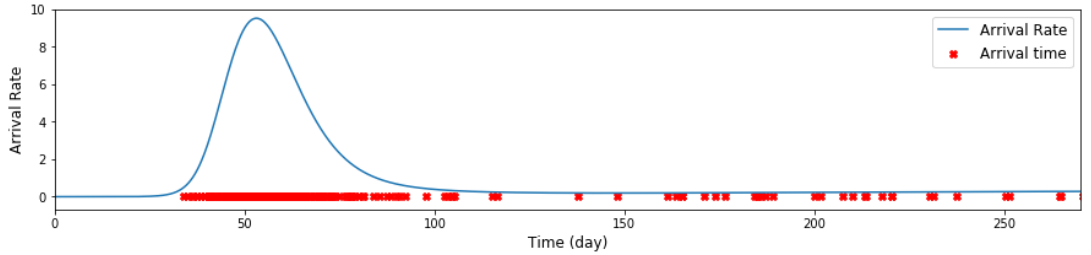
Infection rate	Healthy ϵ_S = 0	Immune suppressed ϵ_S = 0.4	Immune suppressed ϵ_S = 0.7
Primary	12.89%	52.19%	98.17%
Chronic	4.5%	45.02%	97.59%

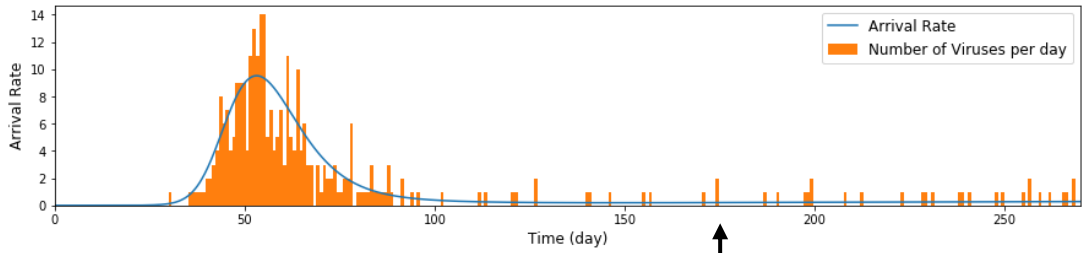
Maternal viral dynamics using ODE

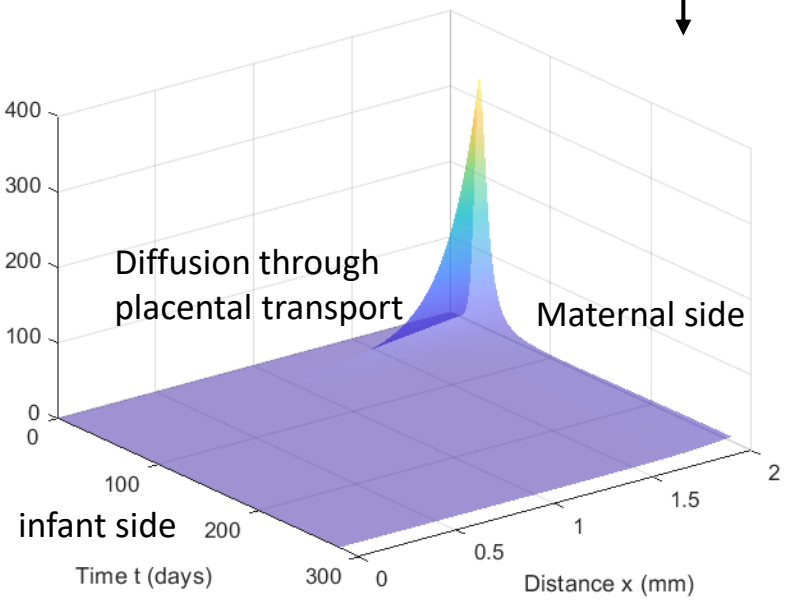


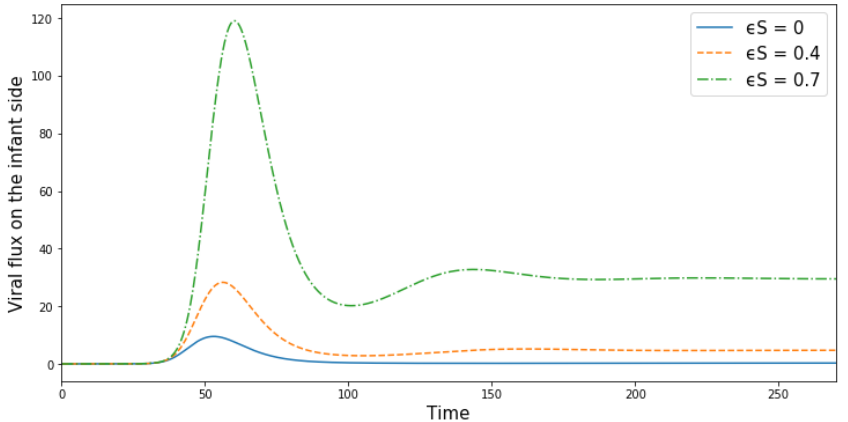












Next step

- Feedback if the model is biologically plausible
  - Different route of infection
  - Perturbation to model
- **Calibrate the model for human and RM data**
  - Viral load in mother
  - Total number of viruses the infant
- Other applicable situations for this model besides different level of immune suppression and primary vs. chronic
- Adaptions to the model so that it can be applied to other viruses?
- Incorporate population genomic information about CMV into the model?