

Mother-to-Child Transmission of Cytomegalovirus

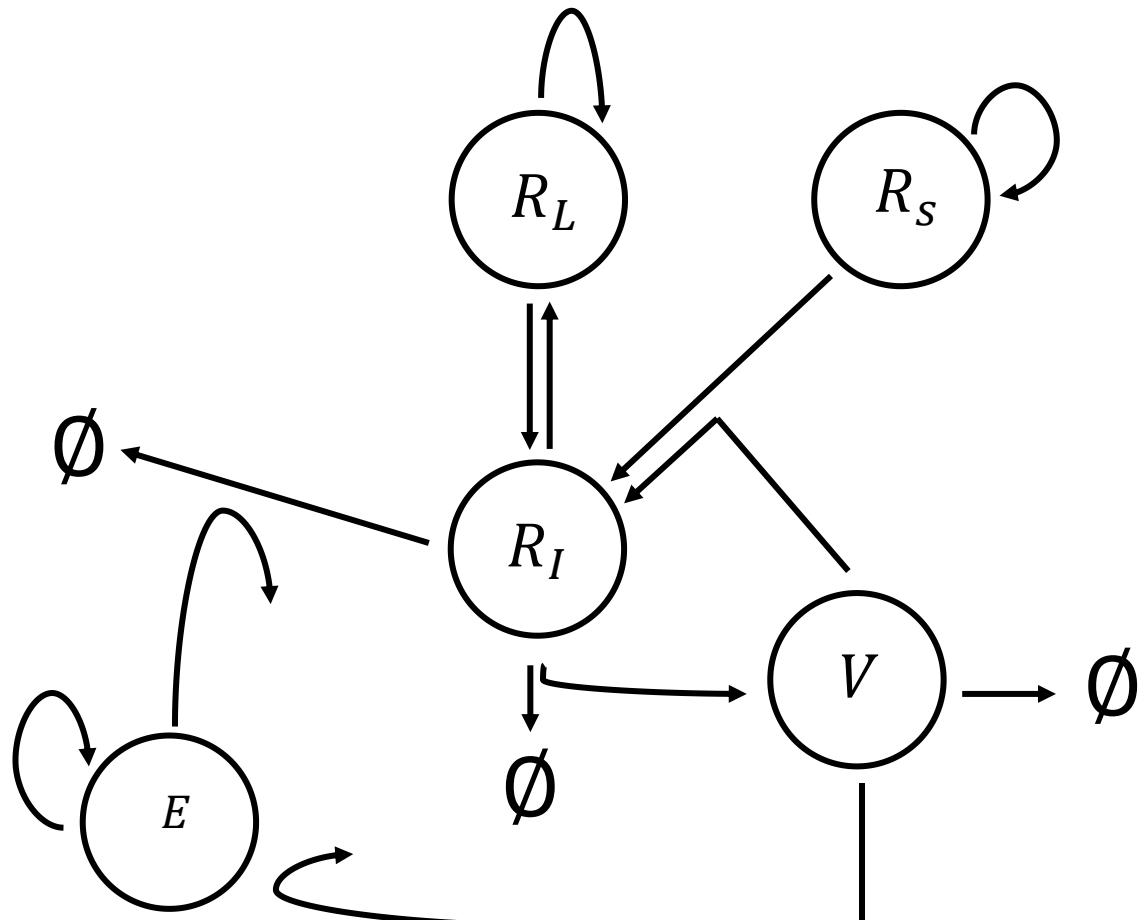
This project aims to provide a framework to

- 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



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

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

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

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

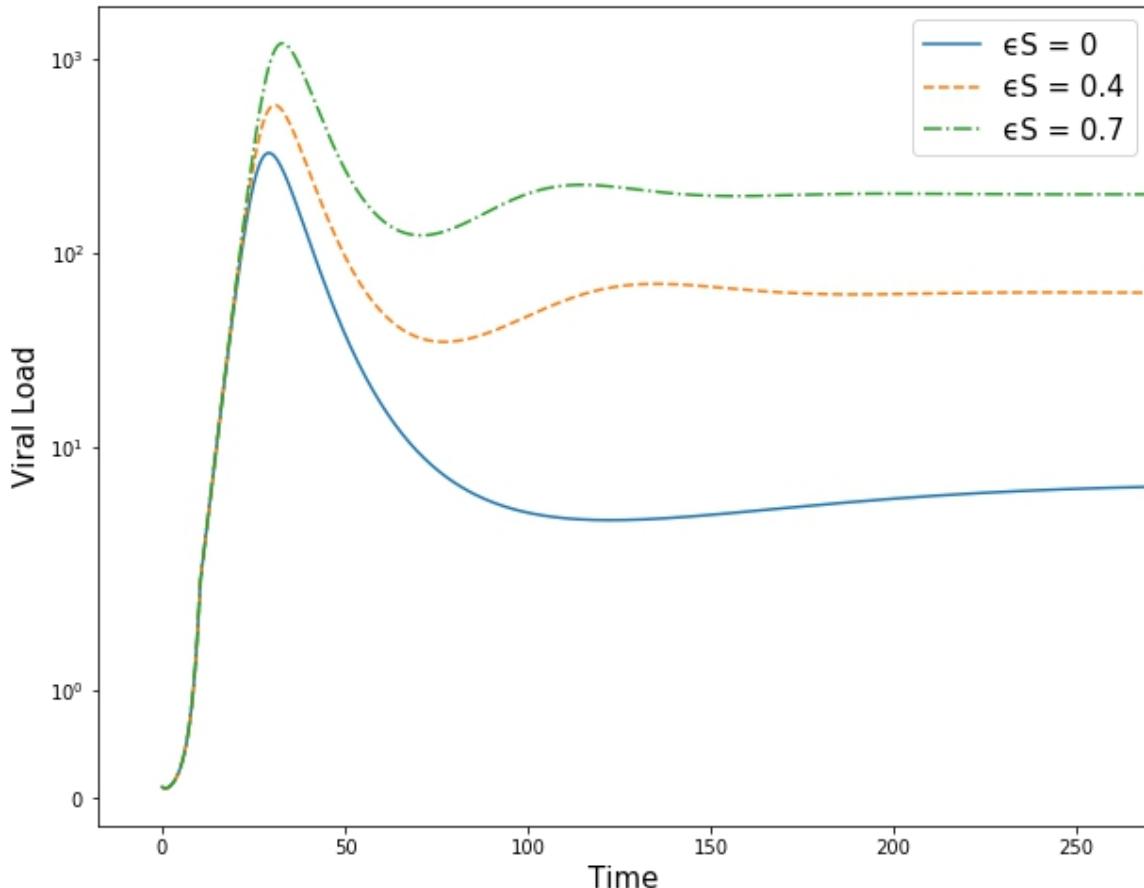
$$\frac{dR_L}{dt} = \lambda_{rep} \left(1 - \frac{R_L}{r_L} \right) R_S + \kappa R_I.$$

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

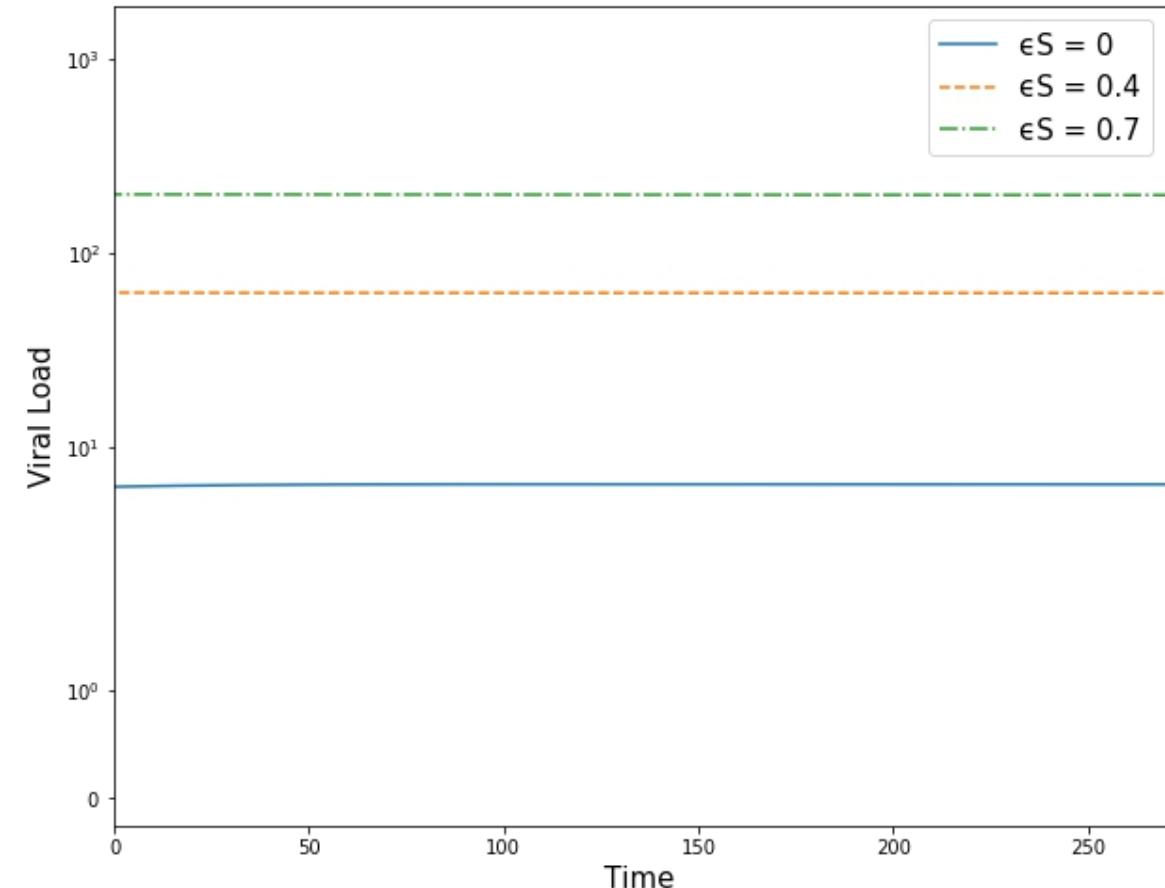
Maternal viral dynamics using ODE

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.

Spatial movement due to diffusion

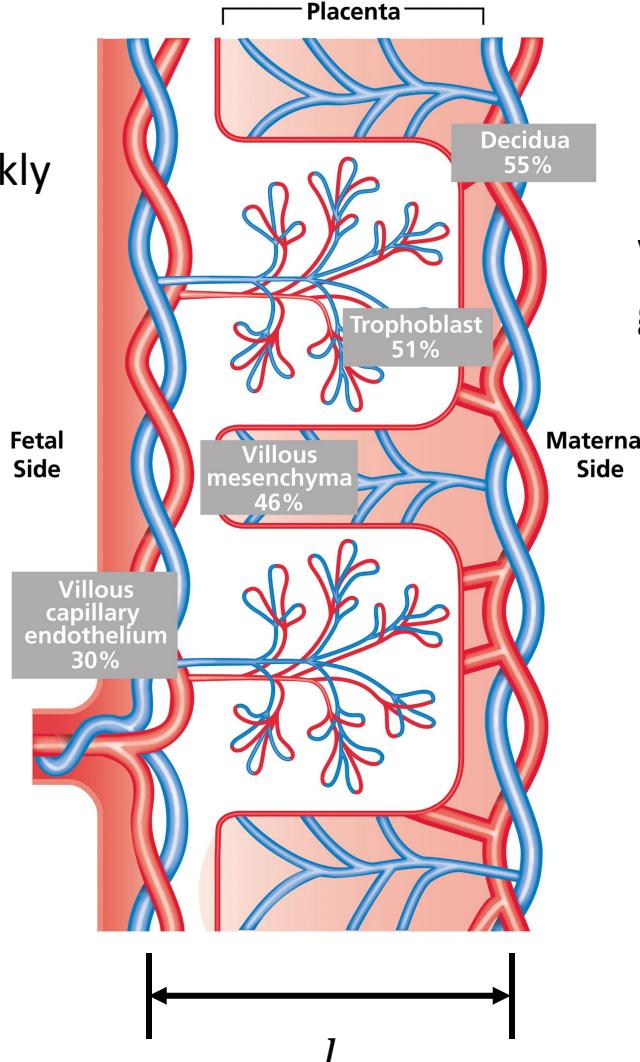
$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - \mu c,$$

Clearance of CMV

$$c = 0, x = 0, t \geq 0,$$

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

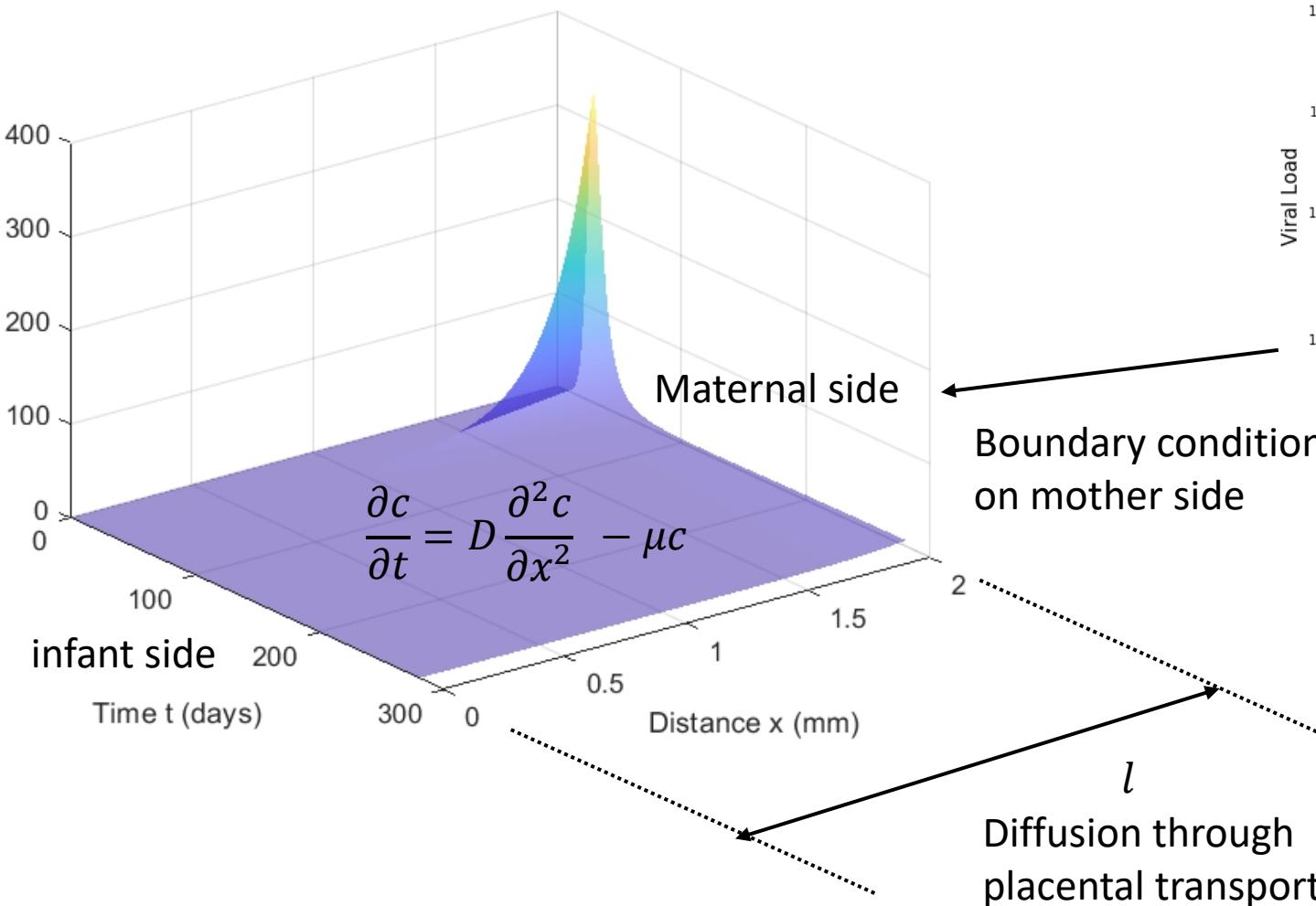
$$c = 0, 0 < x < l, t = 0.$$



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

Viral dynamics on mother side is given by the ODE system.

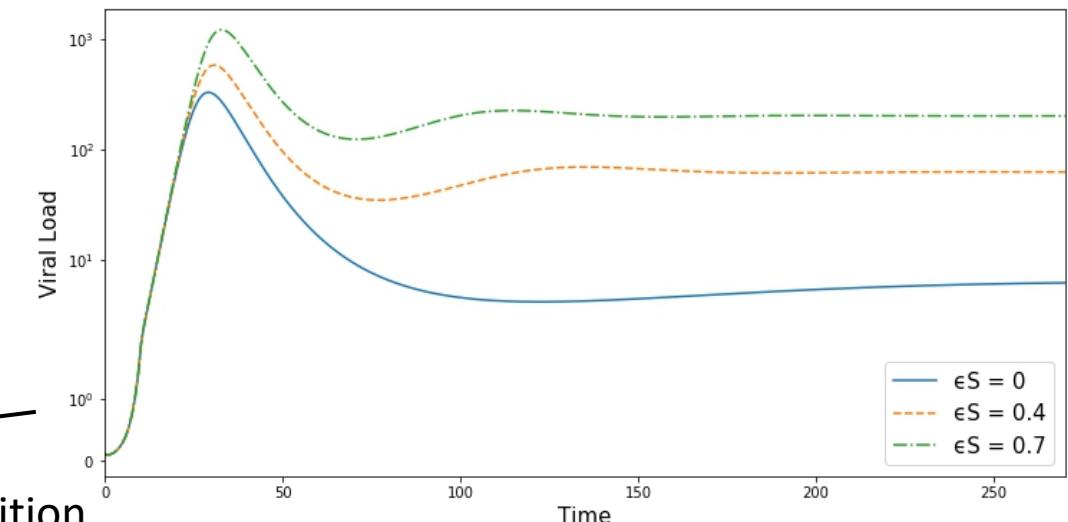
Viral Transmission through Placenta



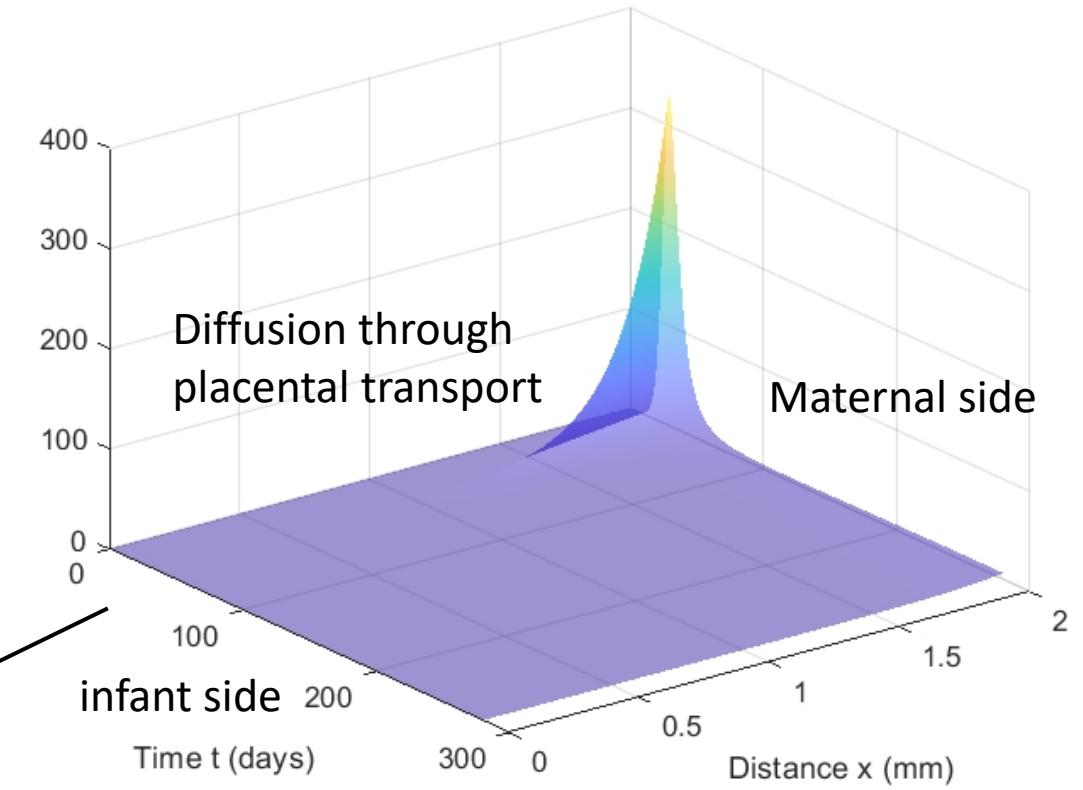
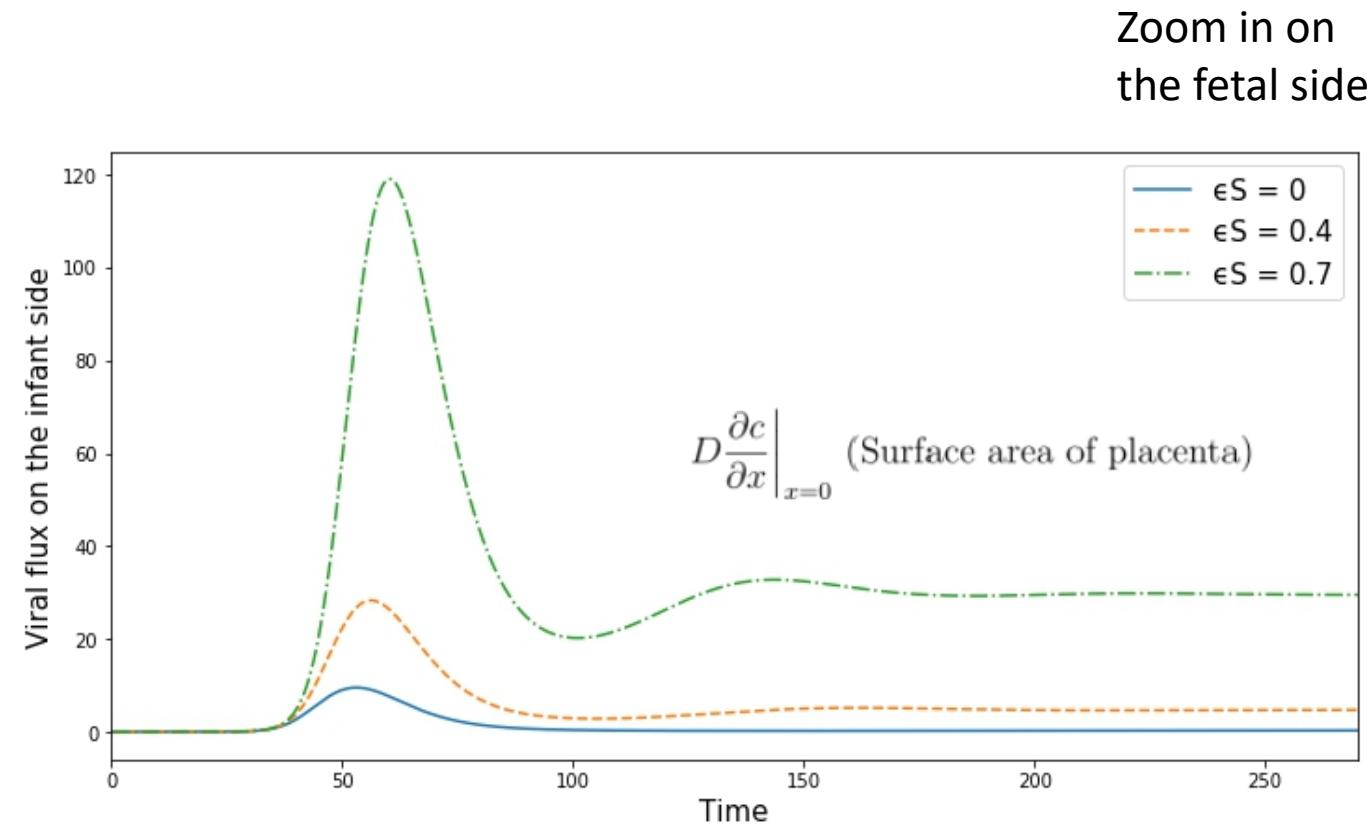
Boundary condition
on mother side

l
Diffusion through
placental transport

Maternal viral dynamics using ODE



Viral Transmission through Placenta



Number of viruses that reach the infant :

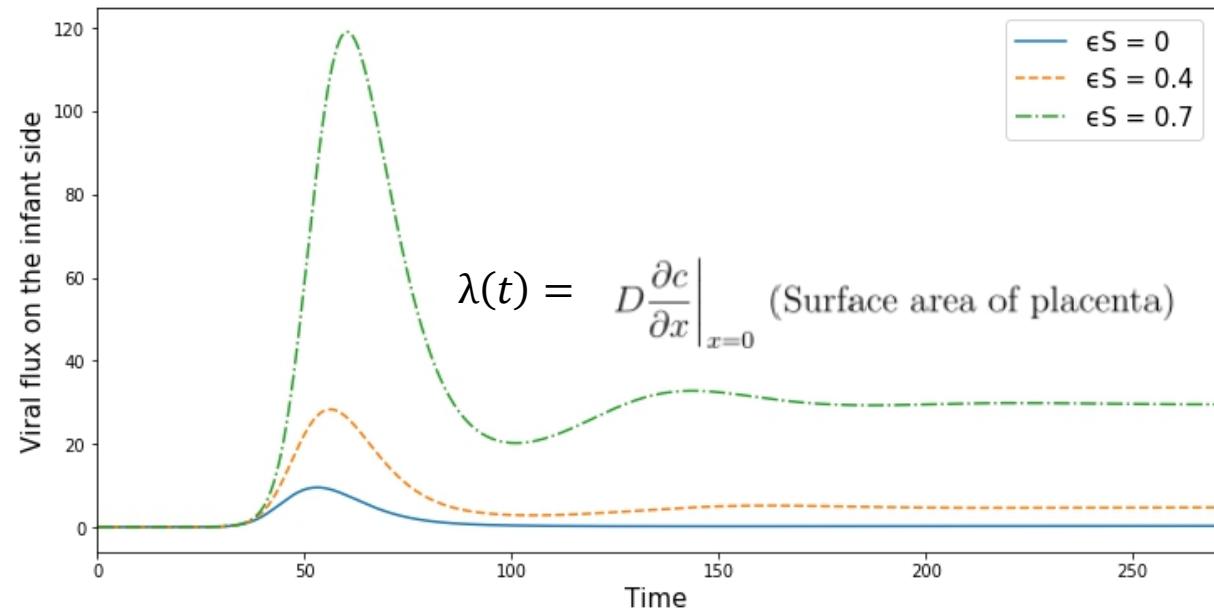
$$C = \int_0^T D \frac{\partial c}{\partial x} \Big|_{x=0} (\text{Surface area of placenta}) dt$$

But this information is not enough.

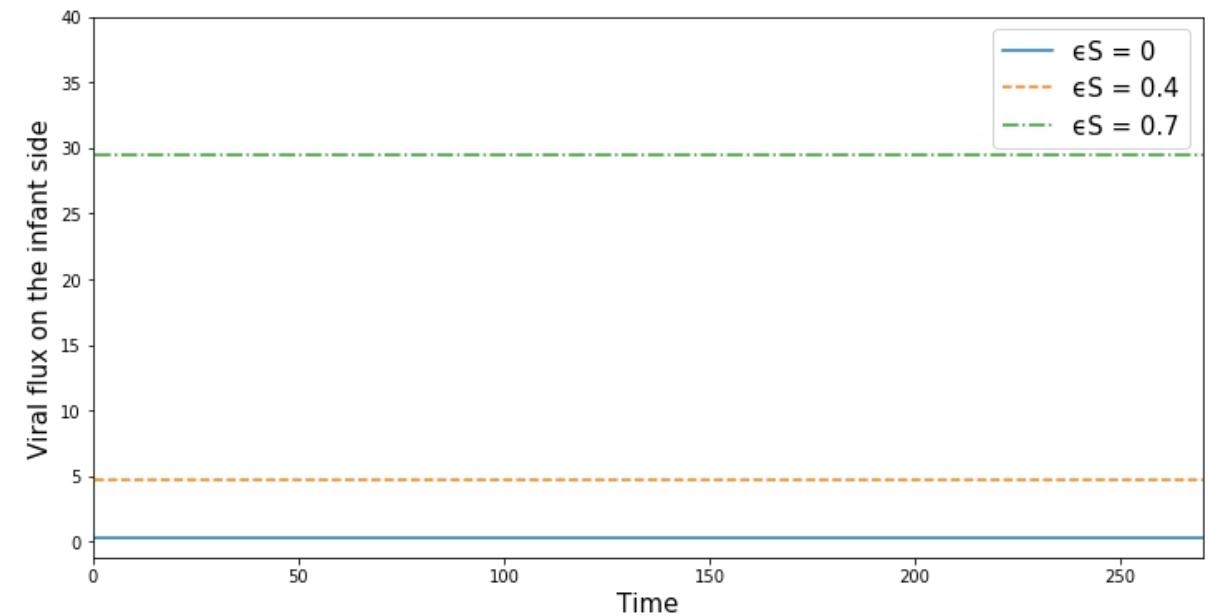
Infection of CMV

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



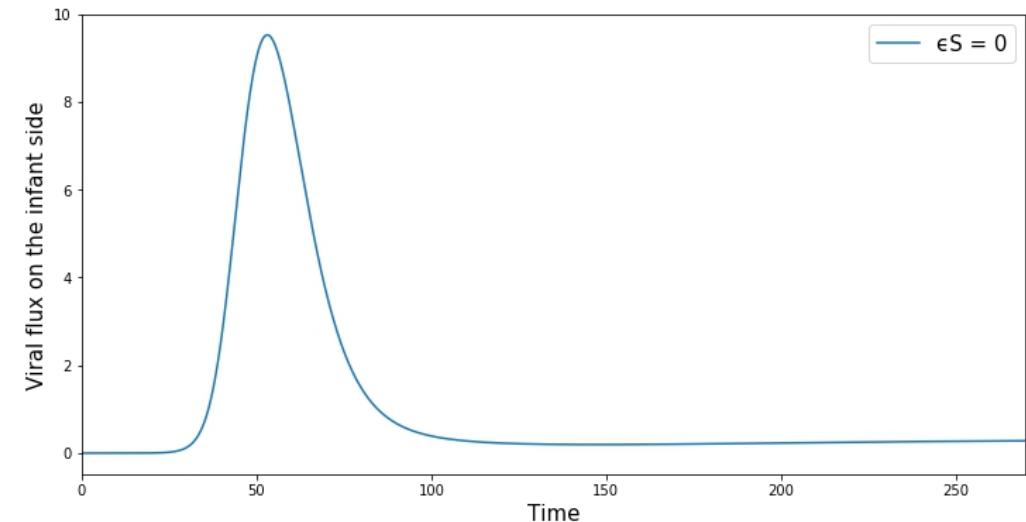
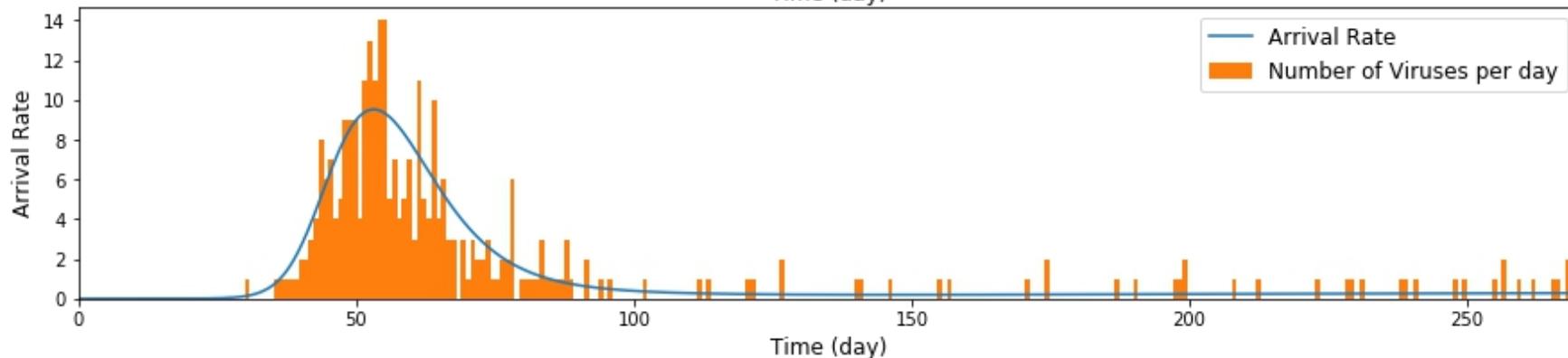
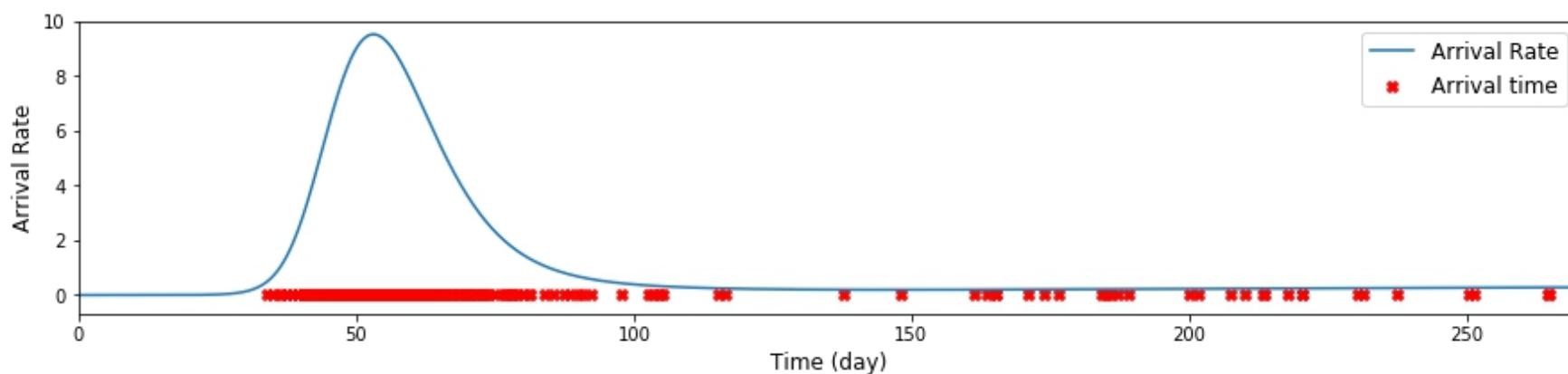
Chronic infection



Primary Infection of CMV

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

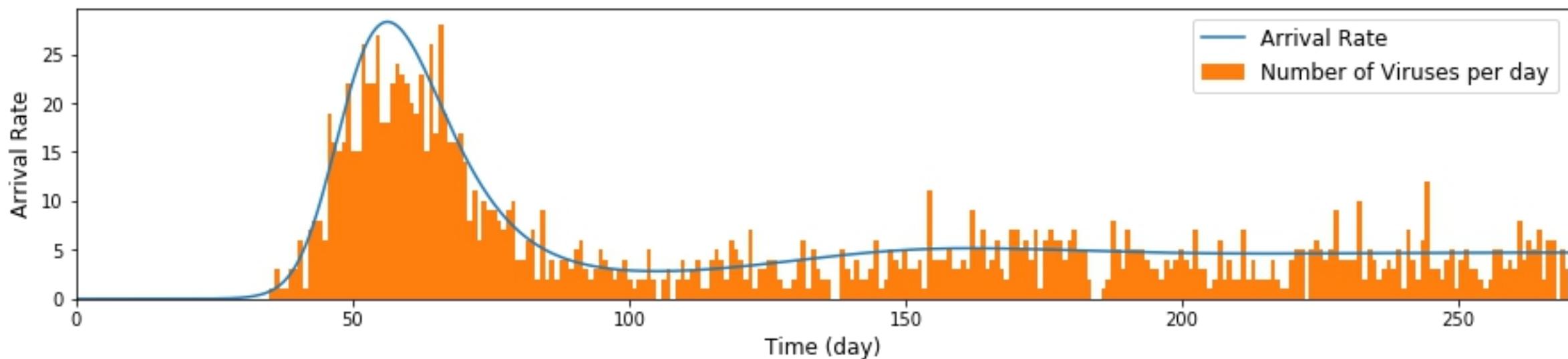
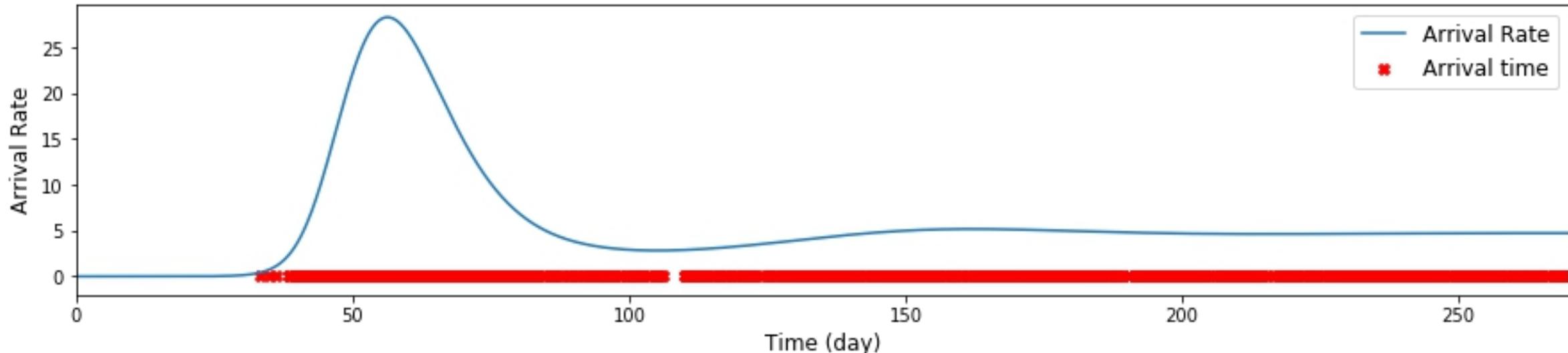
Healthy $\epsilon_S = 0$



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.

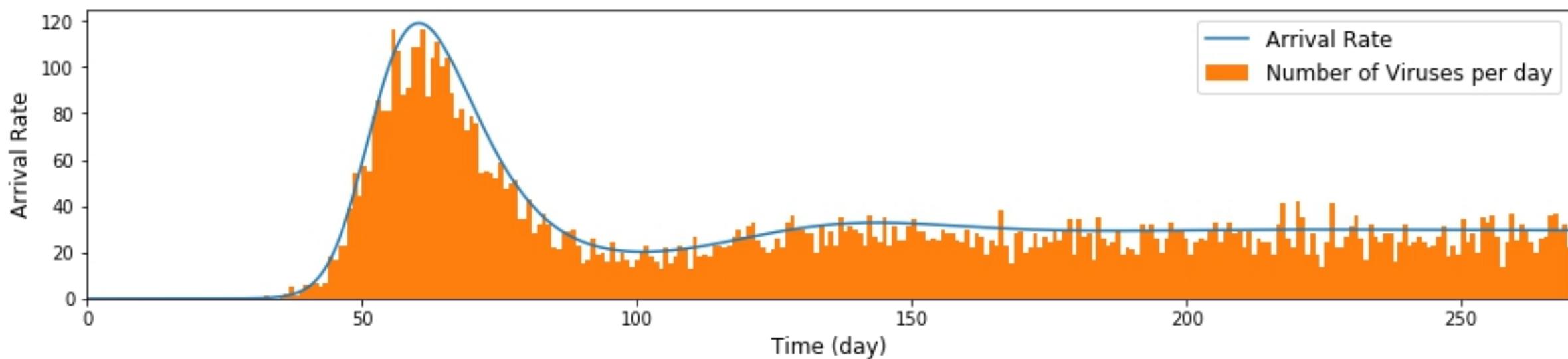
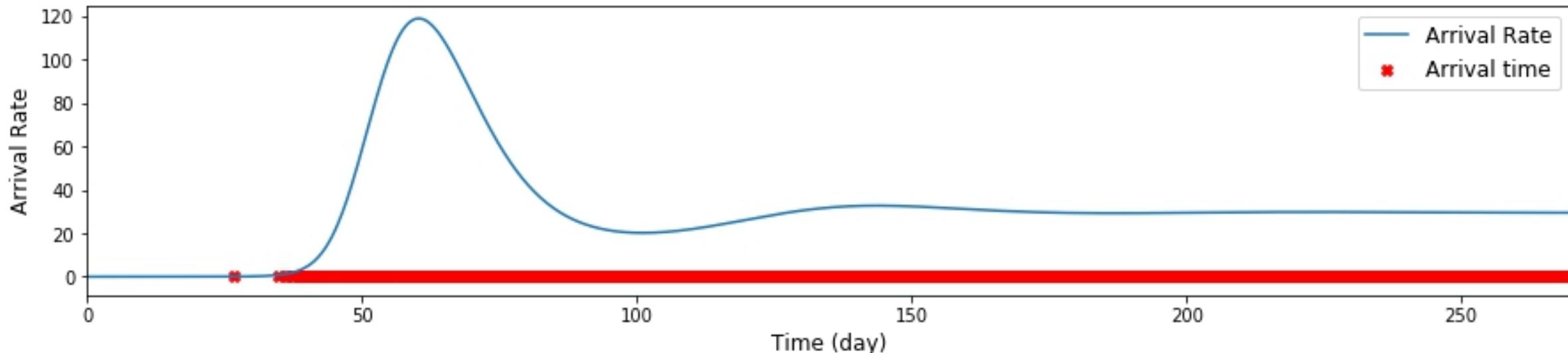
Primary Infection of CMV

Immune suppressed $\epsilon_S = 0.4$



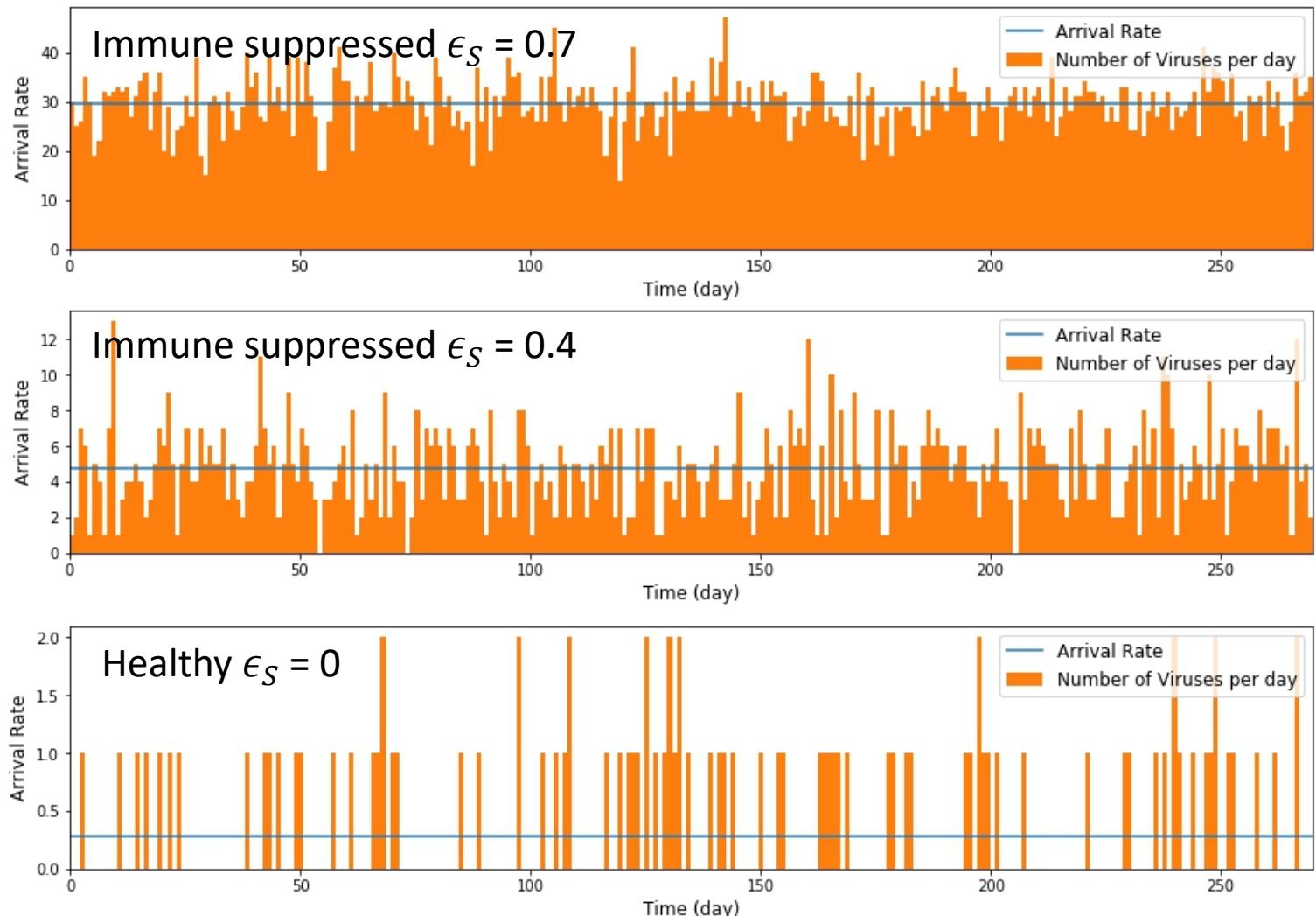
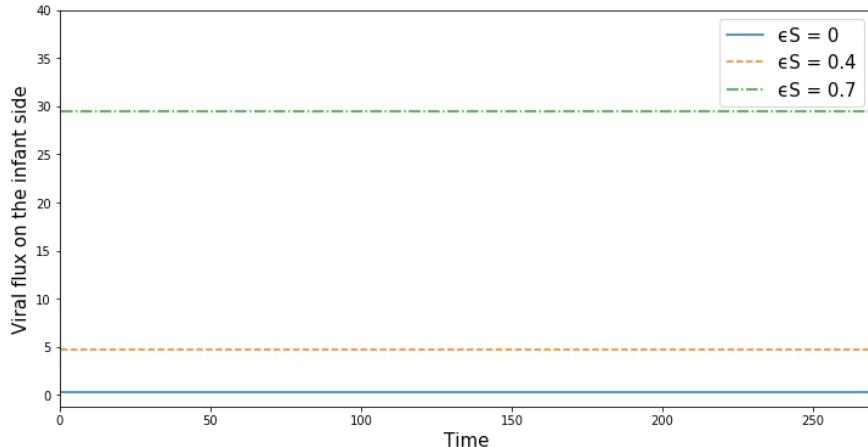
Primary Infection of CMV

Immune suppressed $\epsilon_S = 0.7$



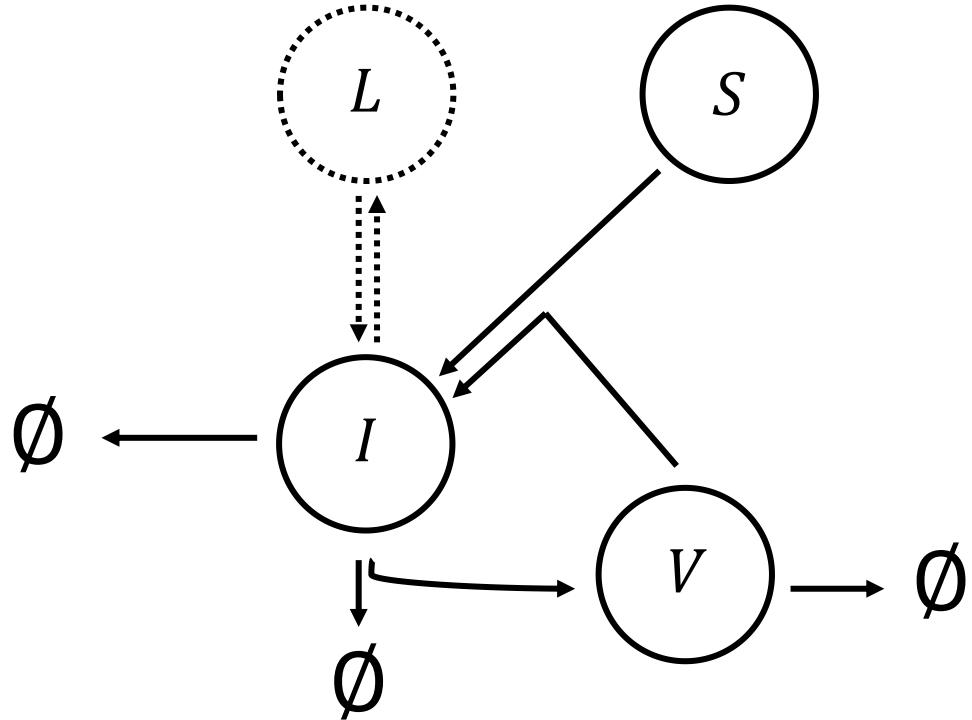
Chronic Infection of CMV

Chronic infection



# of viruses entered	Healthy $\epsilon_S = 0$	Immune suppressed $\epsilon_S = 0.4$	Immune suppressed $\epsilon_S = 0.7$
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.

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

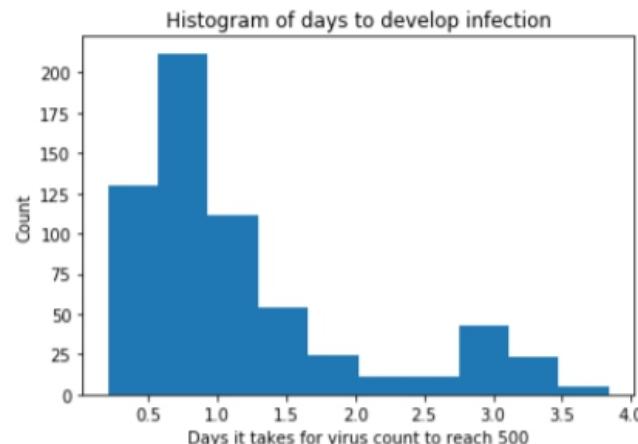
$S \rightarrow I$ with $c_1 = \beta SV$,
 $I \rightarrow \emptyset$ with $c_2 = \delta_I$,
 $\emptyset \rightarrow V$ with $c_3 = p$,
 $V \rightarrow \emptyset$ with $c_4 = \mu$.

Probability of infection

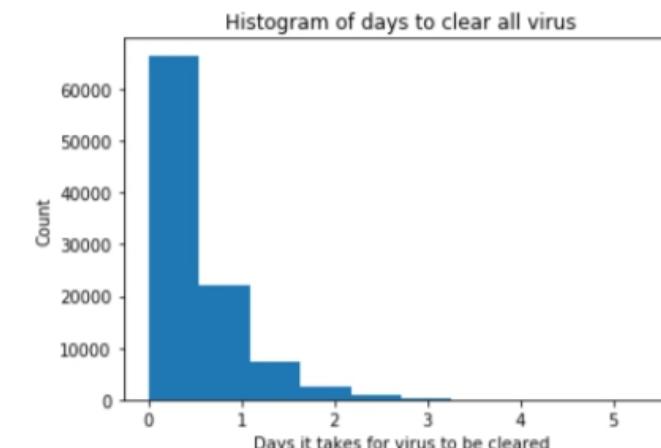
Heuristic

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

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

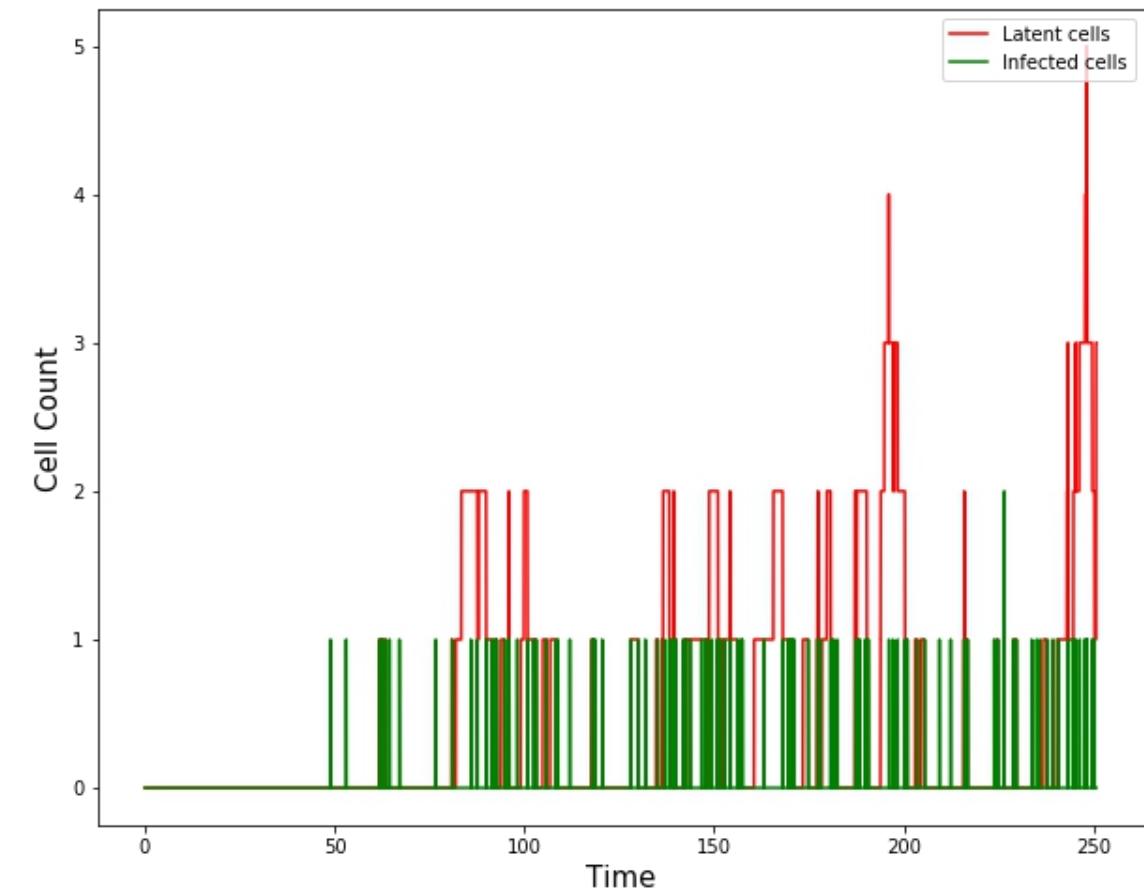
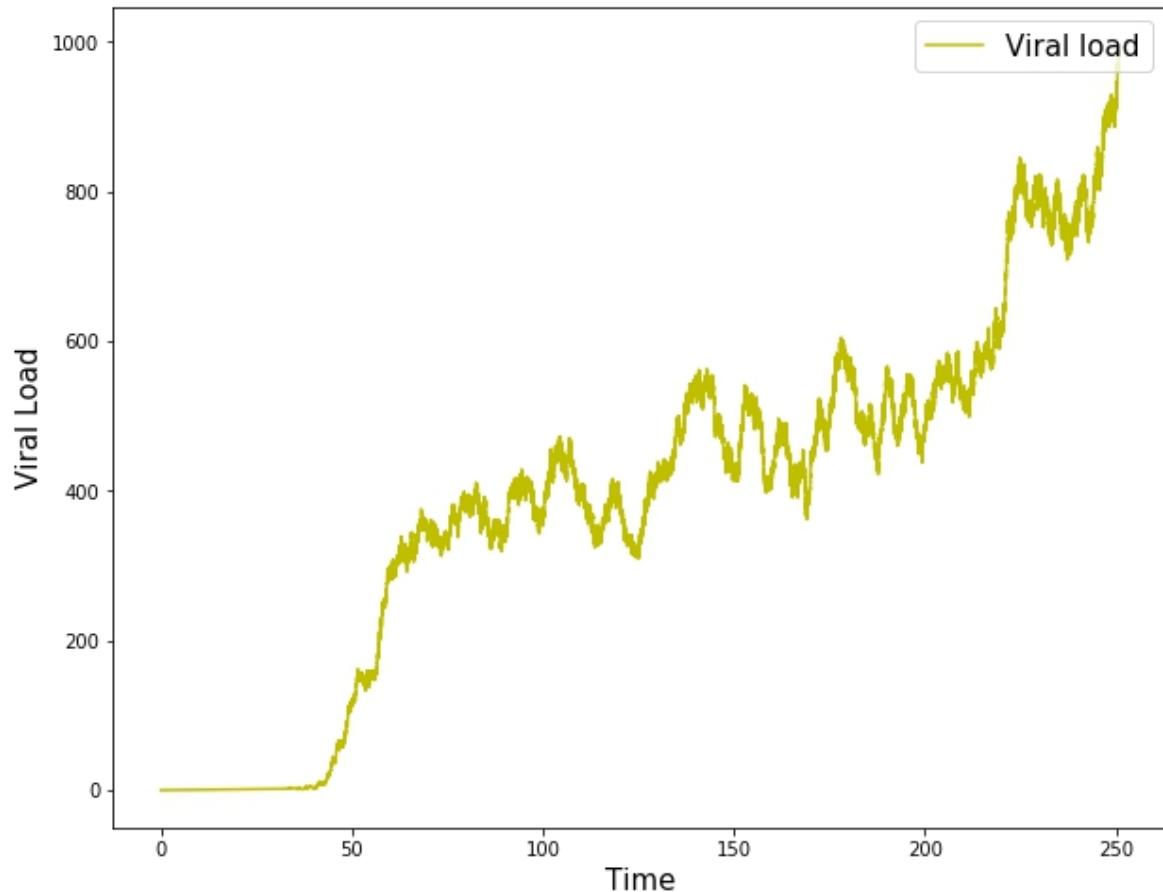


(a) On average, it takes 1.23 days to develop an infection.

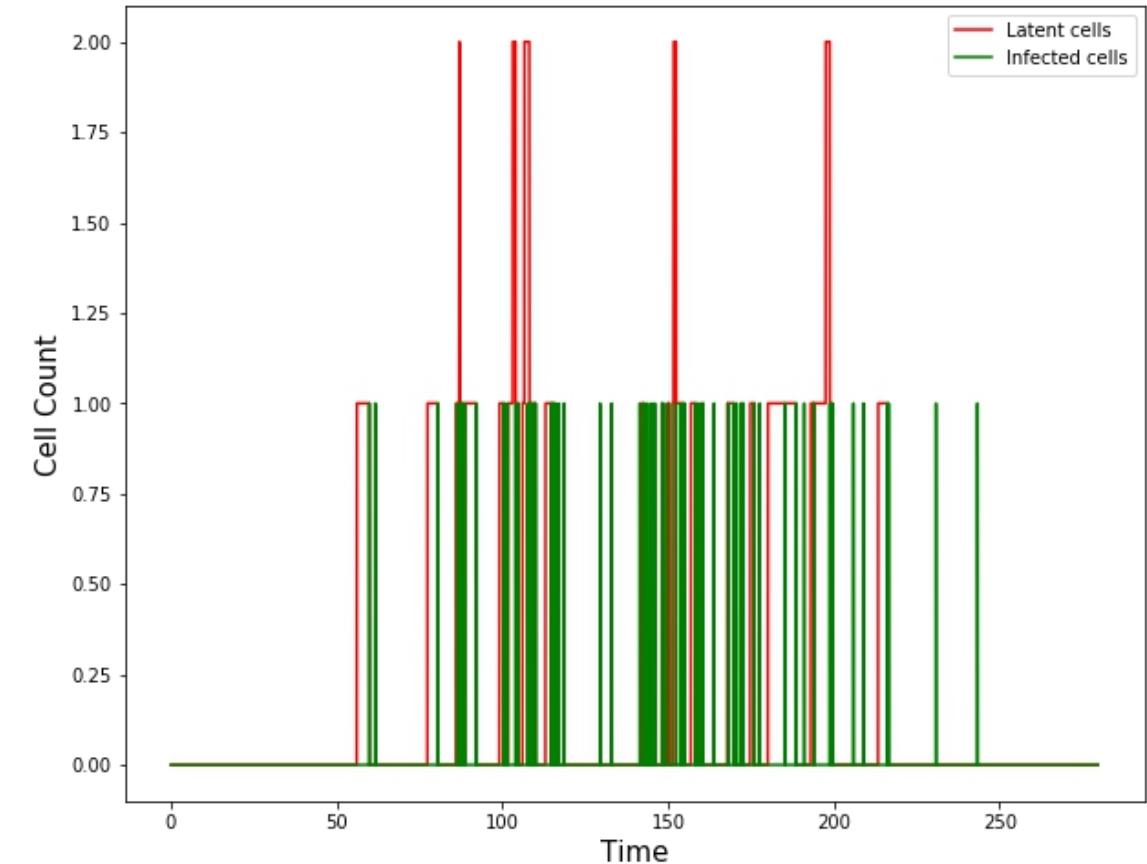
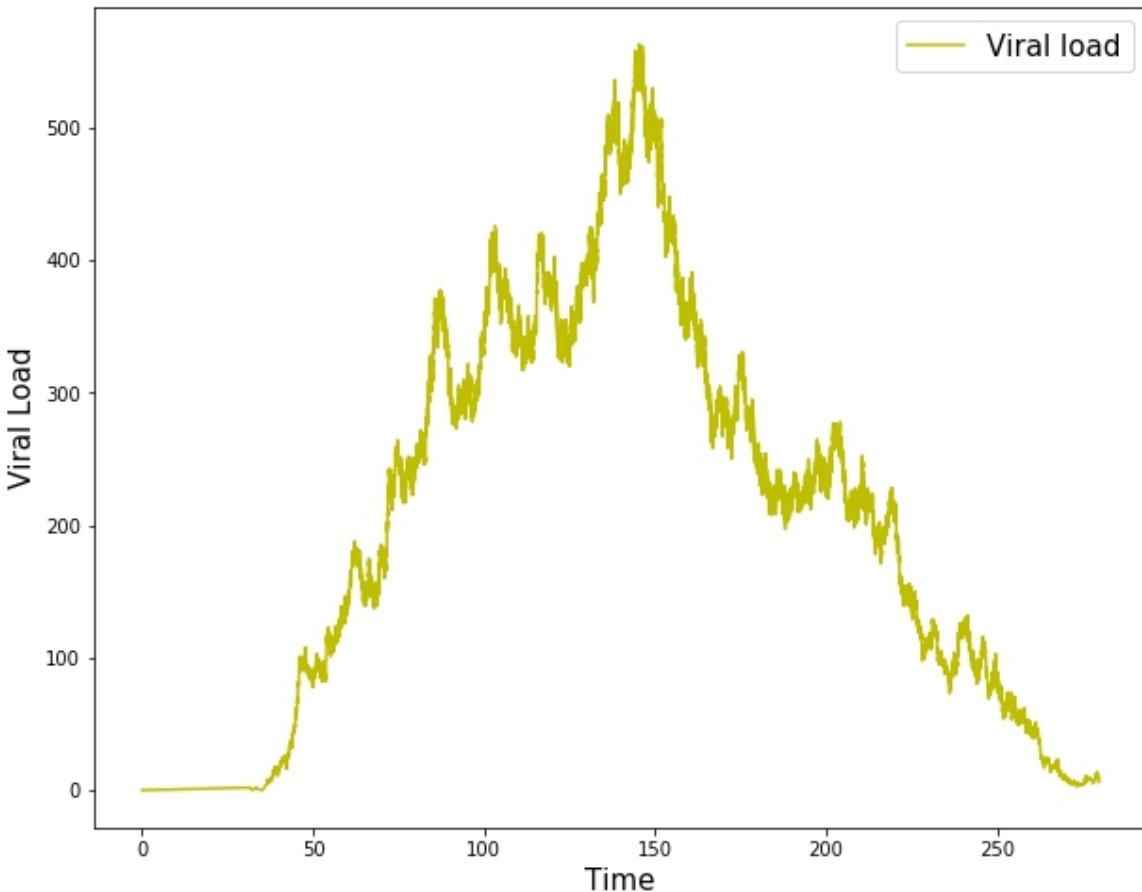


-(b) On average, it takes 0.49 days to clear all viruses.

Persistent infection



Infection that got cleared



Summary

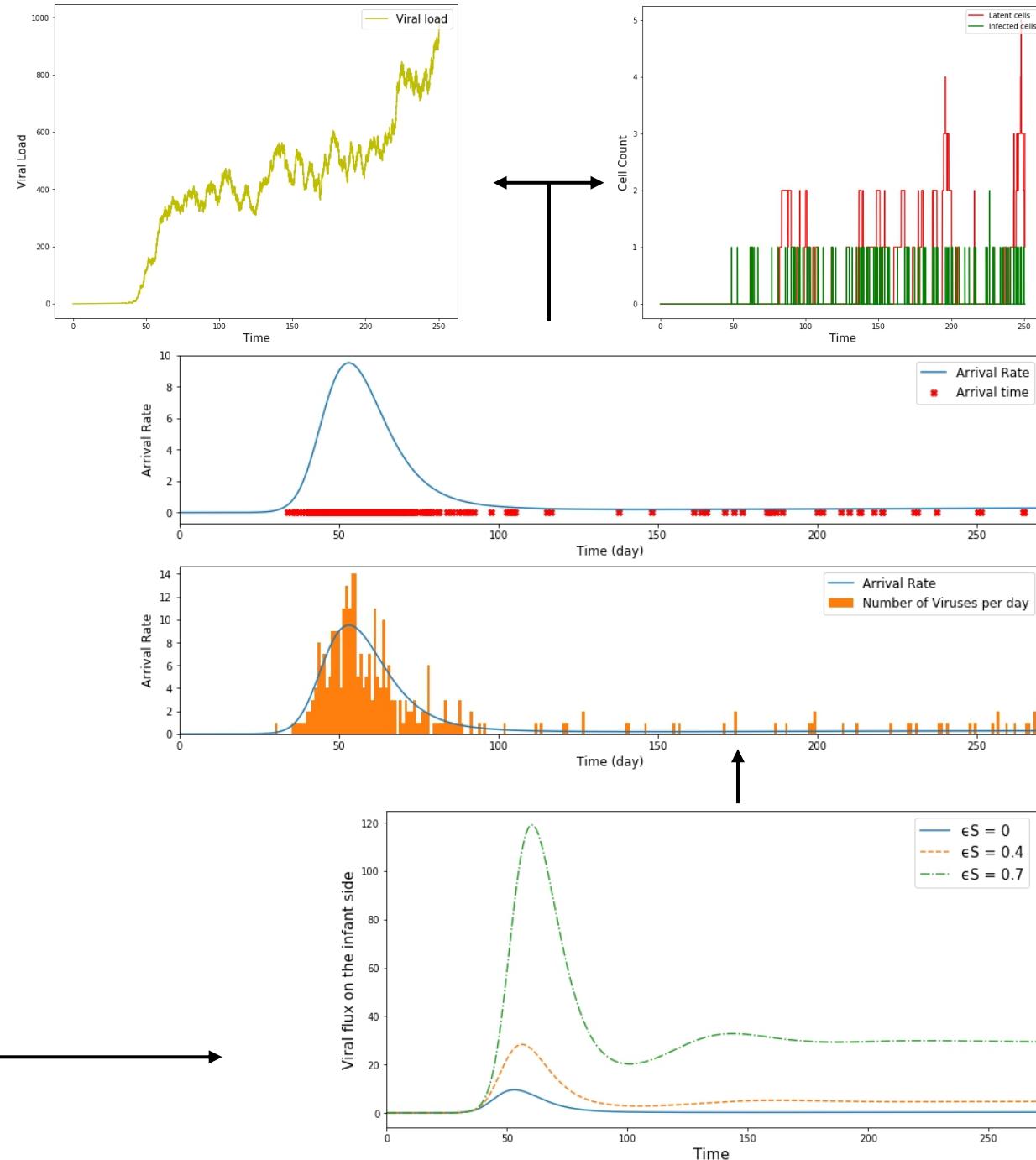
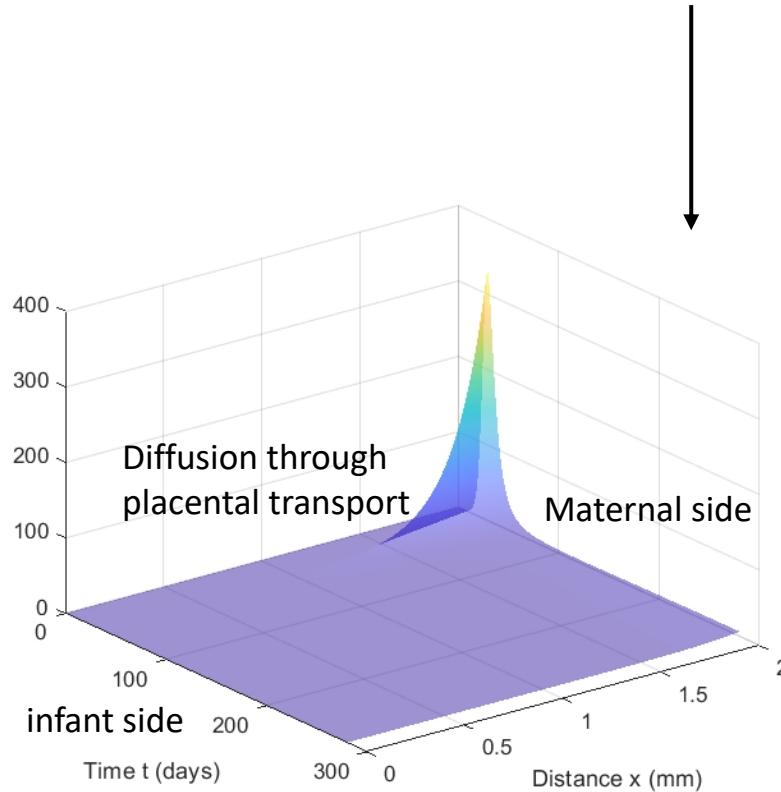
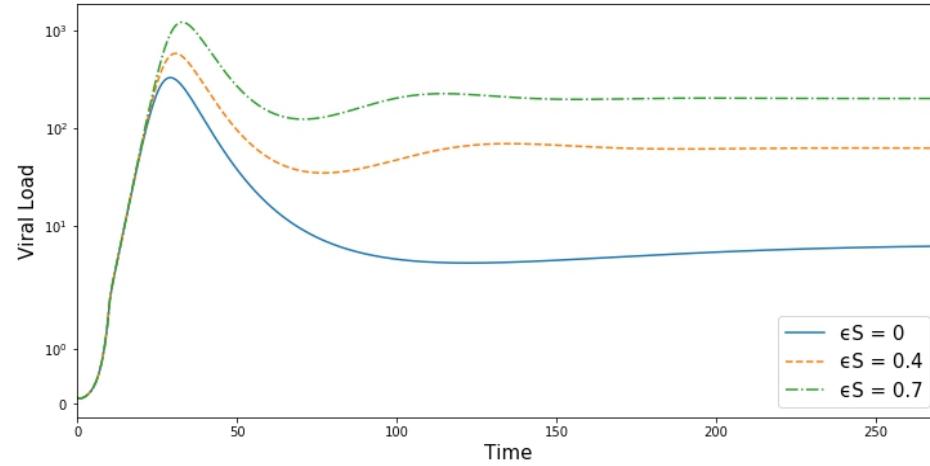
This model can predict infections in two situations

- Primary vs chronic
- Different level of immune suppression

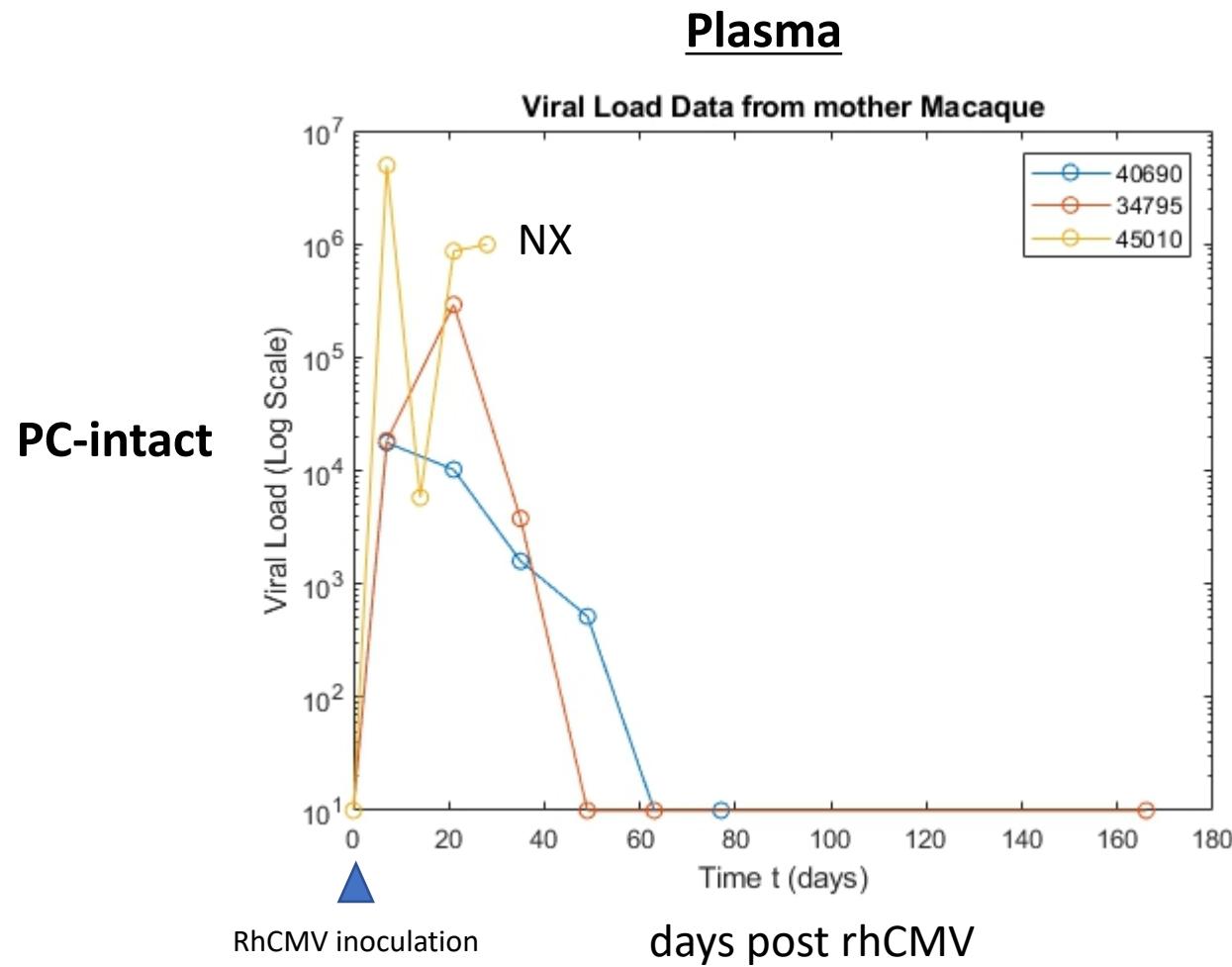
# of viruses entered	Healthy $\epsilon_S = 0$	Immune suppressed $\epsilon_S = 0.4$	Immune suppressed $\epsilon_S = 0.7$
Primary	~300	~1600	~8700
Chronic	~100	~1300	~8100

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

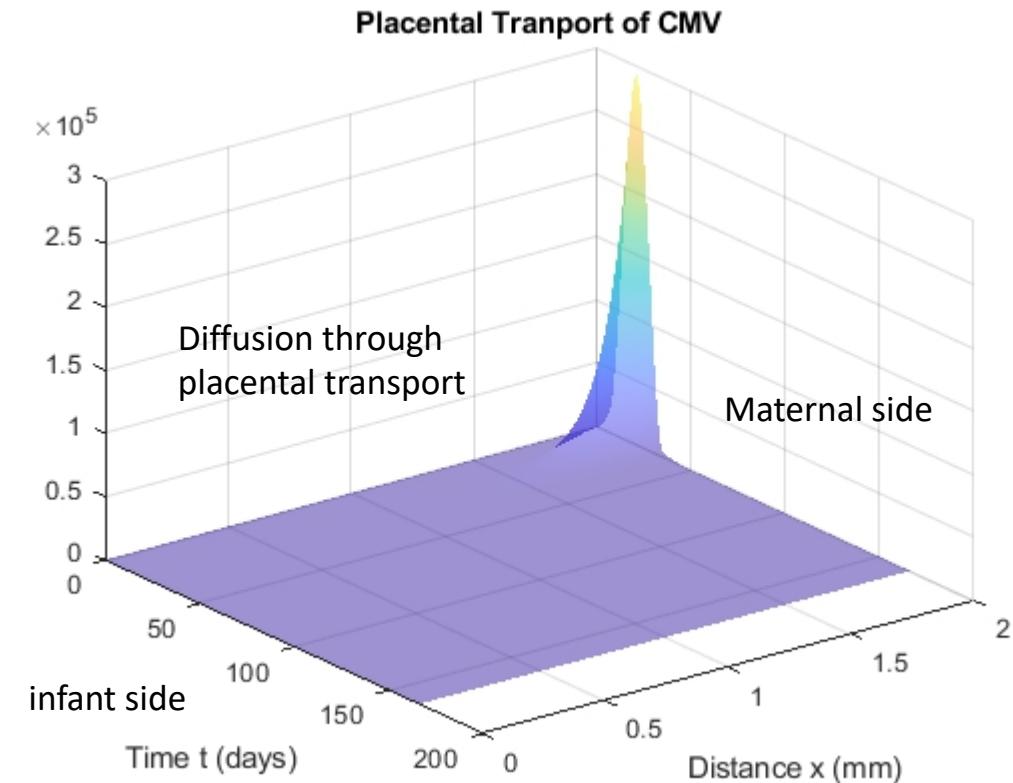
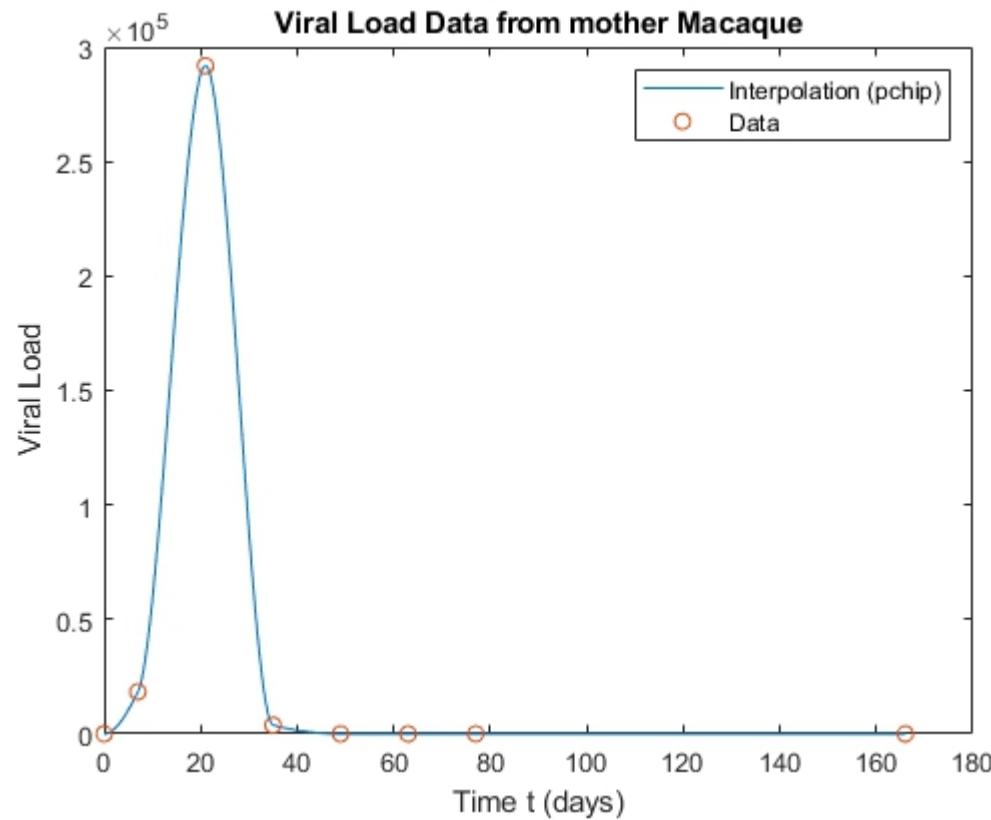
Maternal viral dynamics using ODE



Fitting to animal data

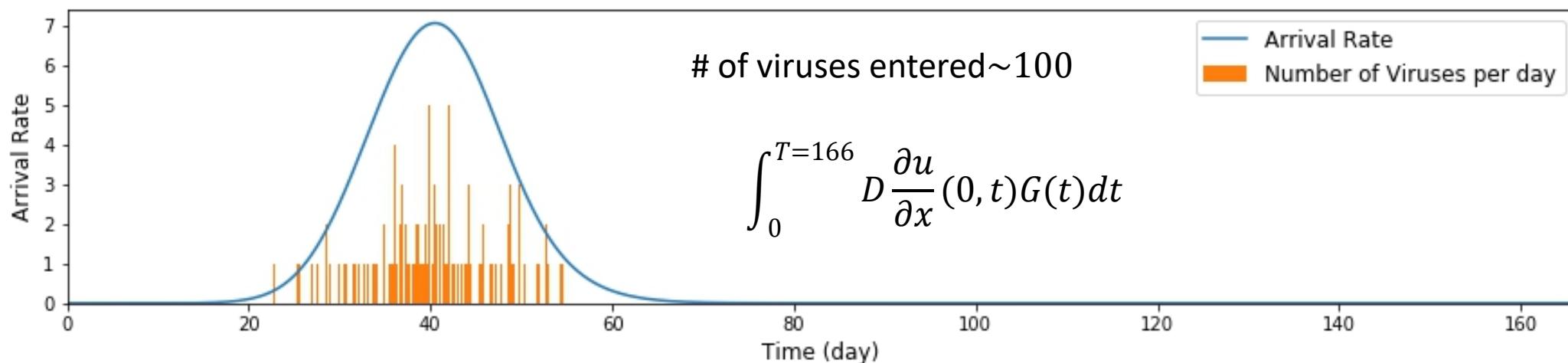
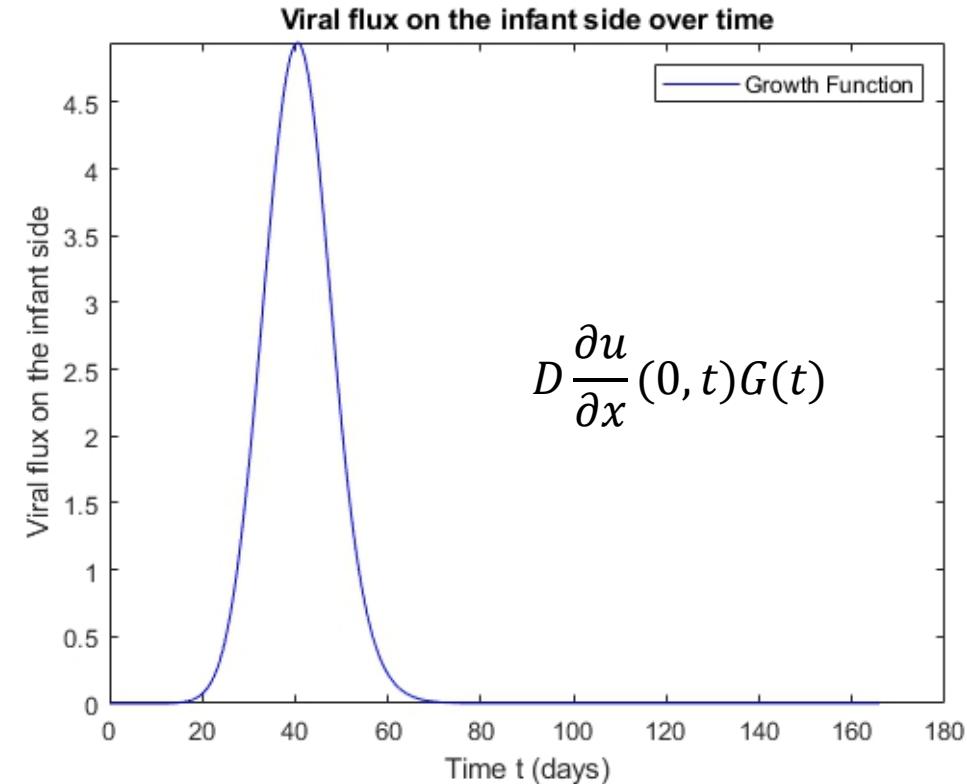
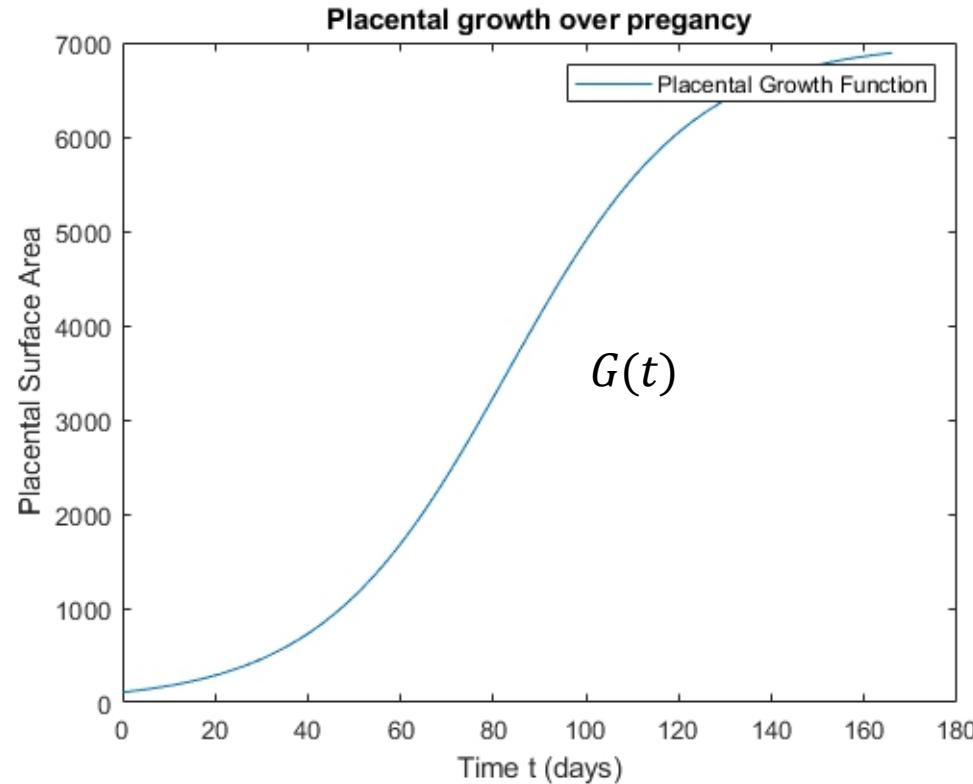


RM animal ID = 34795

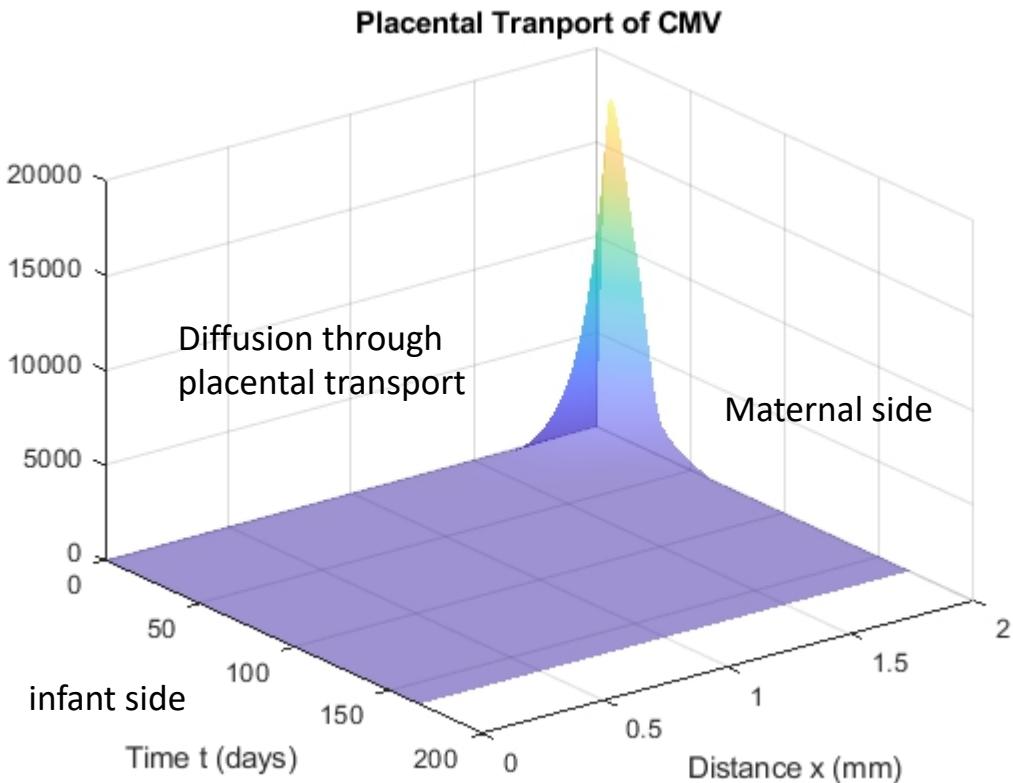
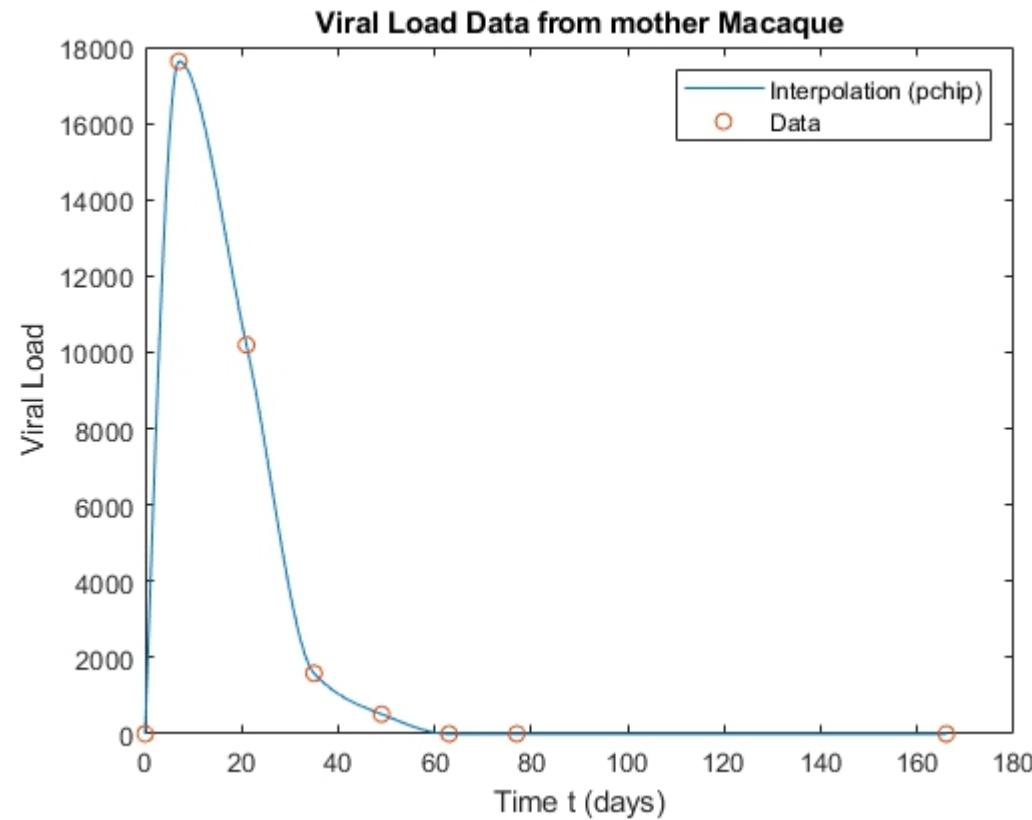


Viral clearance rate = 0.4

RM animal ID = 34795

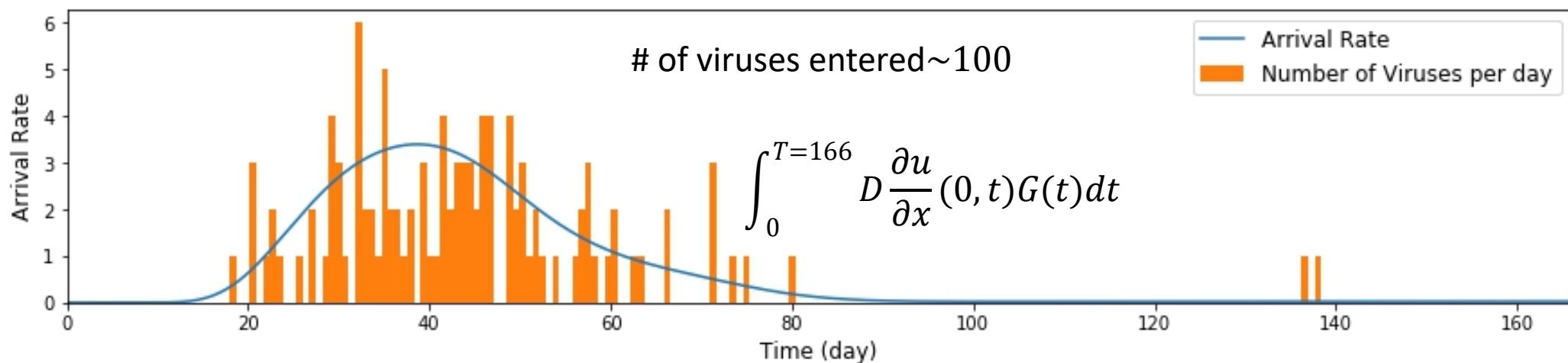
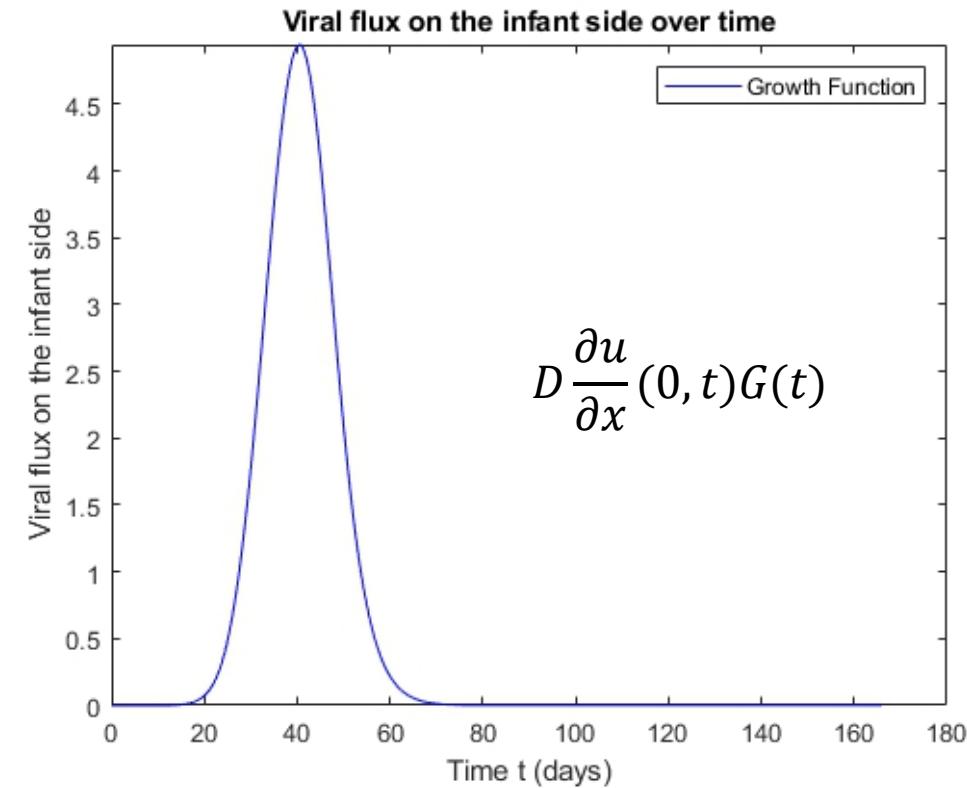
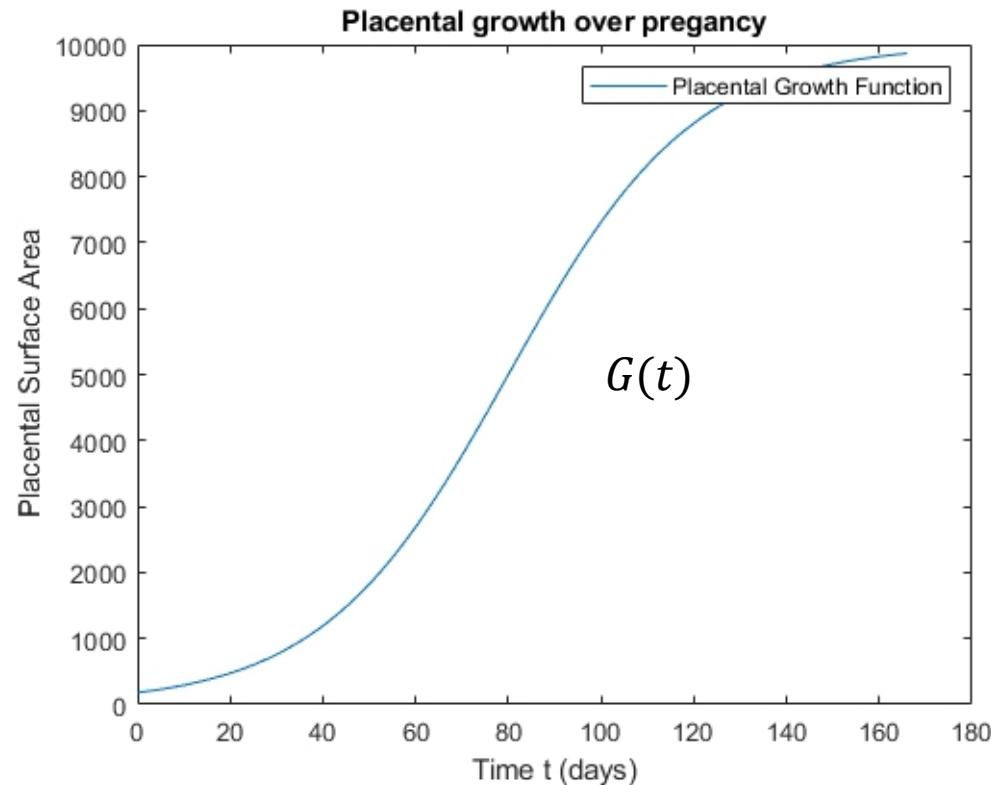


RM animal ID = 40690

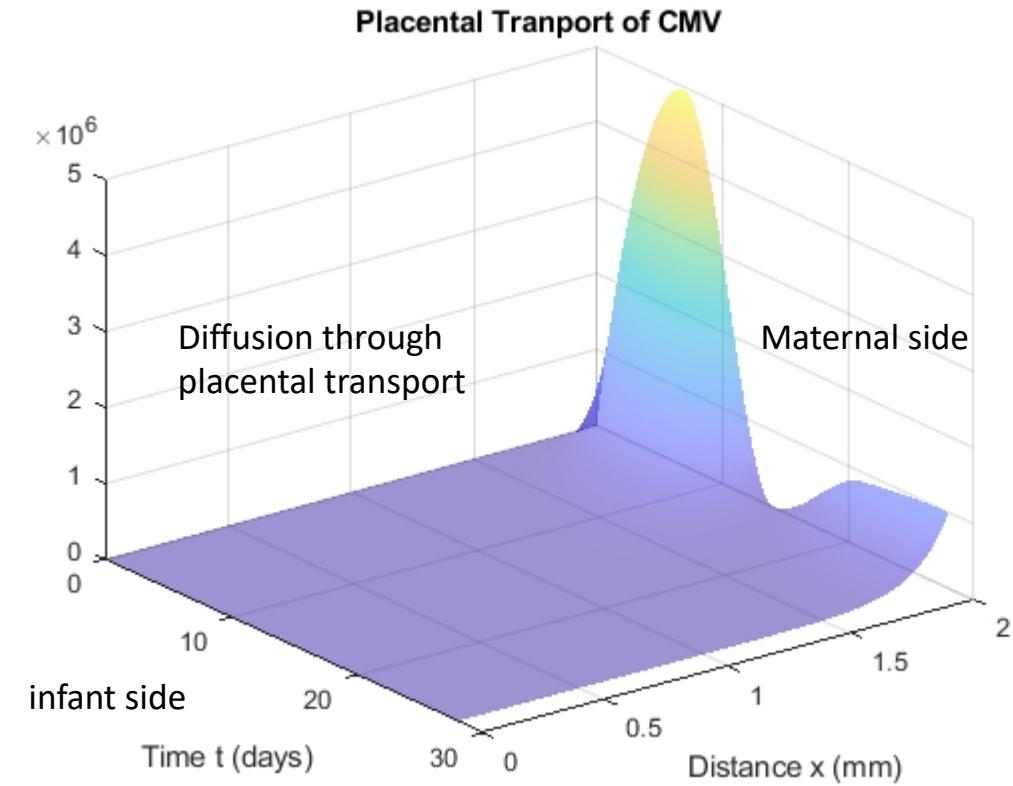
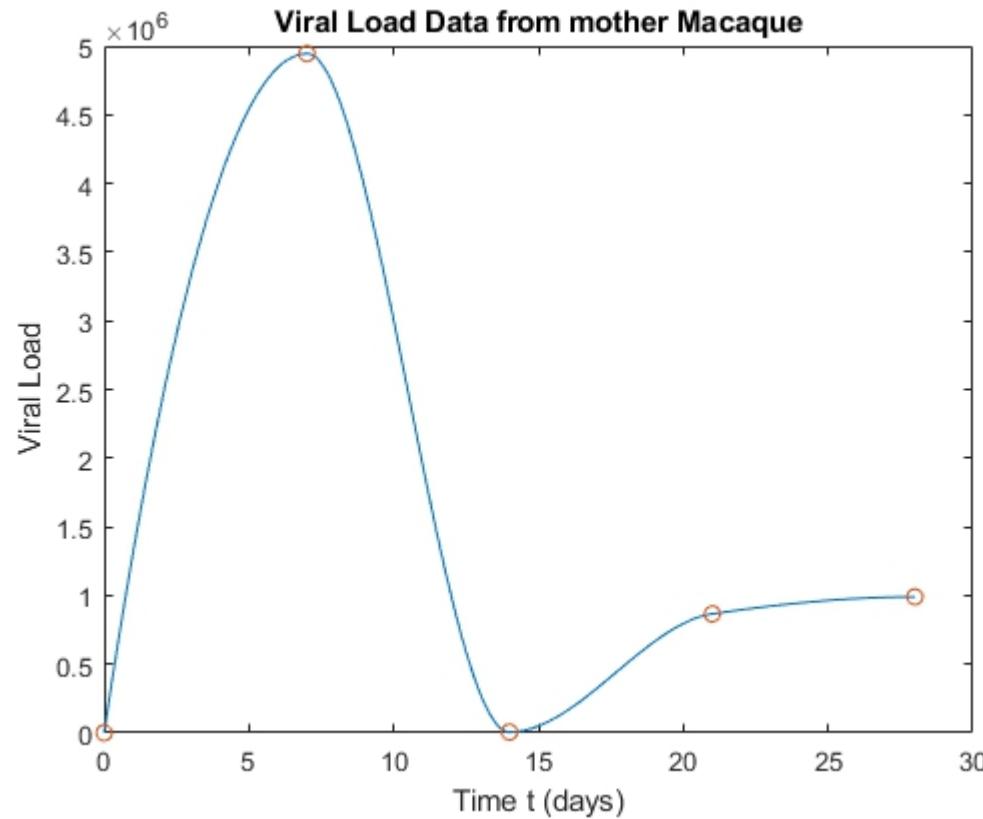


Viral clearance rate = **0.28**

RM animal ID = 40690

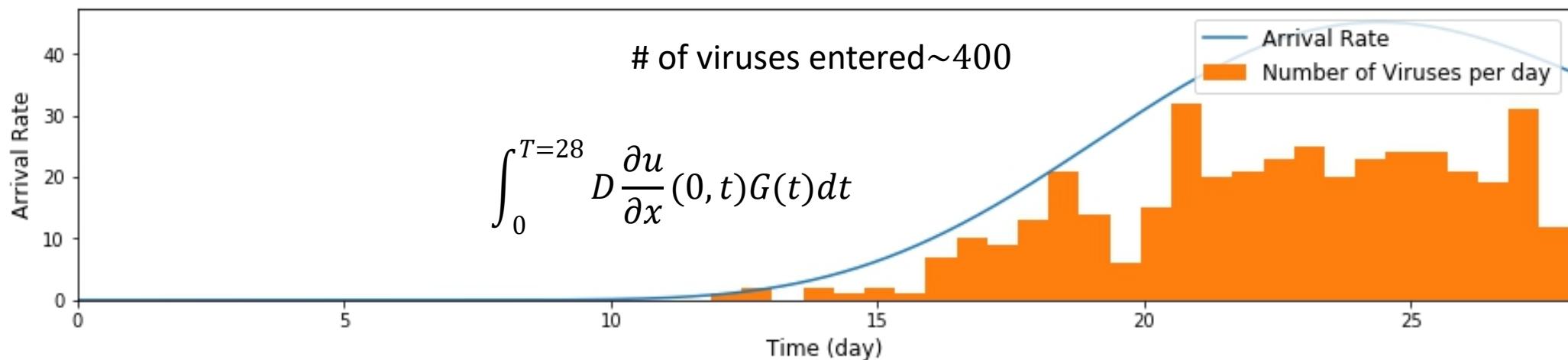
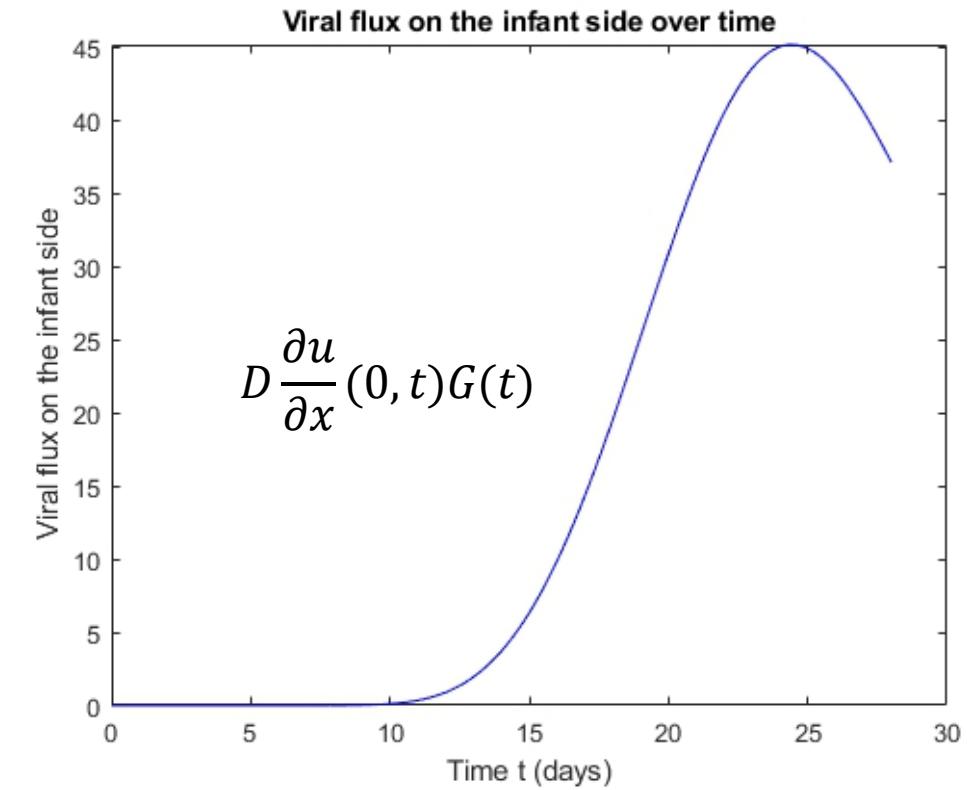
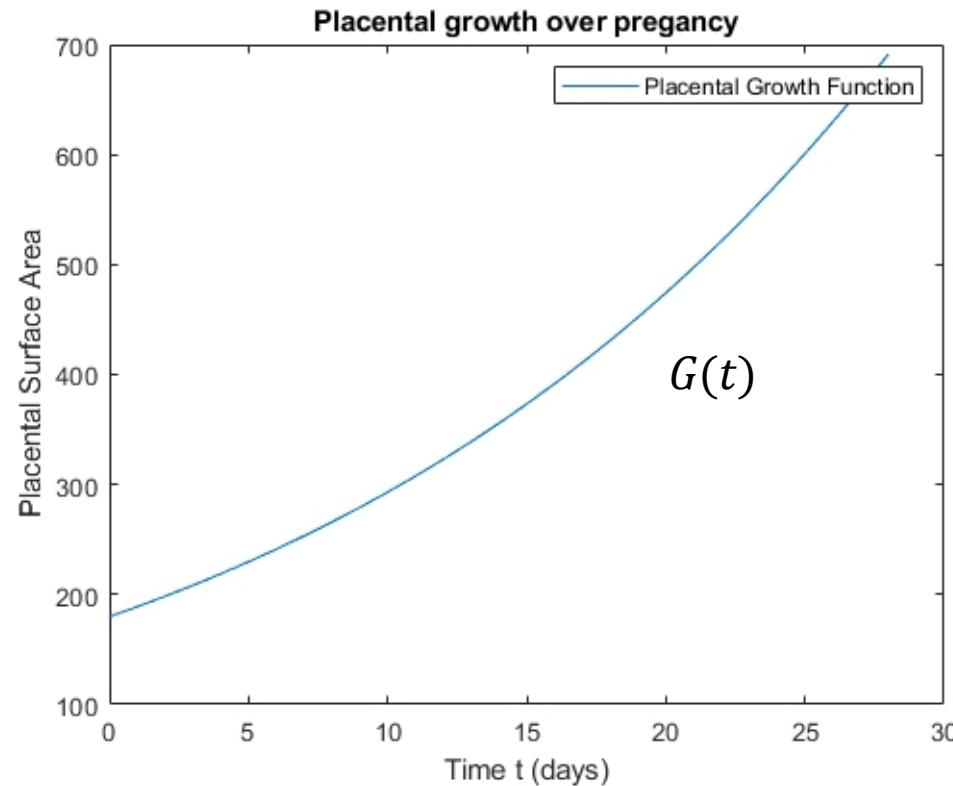


RM animal ID = 45010



Viral clearance rate = 0.4

RM animal ID = 45010



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
- Adoptions to the model so that it can be applied to other viruses?
- Incorporate population genomic information about CMV into the model?