A Density Dependent Model of Influenza Infection Rate

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Assume that there is a bag of red and green marbles. In a standard probability calculation, the probability that a green marble would come into contact with a red marble would be calculated based on the percentage of red marbles present multiplied by the number marbles the green marble has surface area contact with. Standard viral kinetics models assume this well-mixed distribution. However, in the early stages of an infection, virus is localized and not well mixed. This model uses parameters to explore the impact of uneven spatial distribution on the properties of influenza infection.

Background

- The most common immunological models for analyzing viral infections assume even spatial distribution between virus particles and target cells.
- However, throughout an infection spatial distribution of virus and cells changes.
- Initially, virus is centered around infected cells so a target cell in an area with lower virus presence will be less likely to be infected than a cell closer to a viral source.
- A density-dependent infection rate has the potential to improve models that treat cellular infection probability as constant.

Standard Viral Kinetics Model

The standard model of viral kinetics analyzes the progression of infection in the context of β, the rate constant for the specific infection.

$$\begin{aligned}\frac{dT}{dt} &= -\beta VT\\ \frac{dE}{dt} &= \beta VT - kE\\ \frac{dI}{dt} &= kE - \delta I\\ \frac{dV}{dt} &= pI - cV\end{aligned}$$

- **T** represents uninfected target cells
- **V** represents virus
- **E** represents the eclipse phase (where the virus is undergoing intracellular replication)
- **I** represents infectious cells (which are producing new virus)
- Eclipse cells become infectious at rate k
- New virus is produced at rate of p per infectious cell
- Virus is cleared at rate c
- Cell death of infectious cells occurs at a rate of δ

Beddington-DeAngelis Model

- The standard approach relies on the multiplication of virus and healthy target cells to determine the rate of increase of the infection.
- By introducing constraining parameters on healthy target cells and virus, the rate of change is decreased to accommodate density dependent effects of virus and healthy cells not being well-mixed.

The Beddington-DeAngelis approach is characterized by the equations:

$$\begin{aligned}\frac{dT}{dt} &= \frac{-\beta VT}{1+\gamma T+\alpha V}\\ \frac{dE}{dt} &= \frac{-\beta VT}{1+\gamma T+\alpha V} - kE\\ \frac{dI}{dt} &= kE - \delta I\\ \frac{dV}{dt} &= pI - cV\end{aligned}$$

Setting Conditions with Parameters for Influenza Viral Infections

Parameters used for simulation are taken from fits of the basic model to patients infected with influenza A (Baccam et al. (2006) J. Virol.)

Parameter	Value
β	3.2 x 10^{-5} $(\mathrm{TCID}_{50}/ml \cdot d)^{-1}$
p	4.6 x 10^{-2} $\mathrm{TCID}_{50}/ml \cdot d$
k	4.0 /d
δ	5.2 /d
c	5.2 /d
V_0	7.5 x 10^{-2} TCID_{50}/ml
T_0	4 x 10^8 cells

α and γ are parameters that were varied to determine how changes in each parameter affects the severity of infection.

Measures of Infection Severity

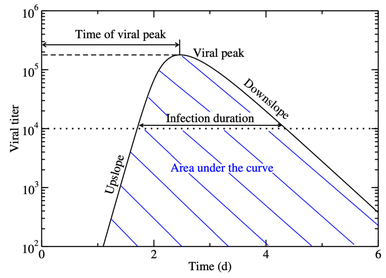

Figure 1. Measured Aspects of Viral Titer Curve

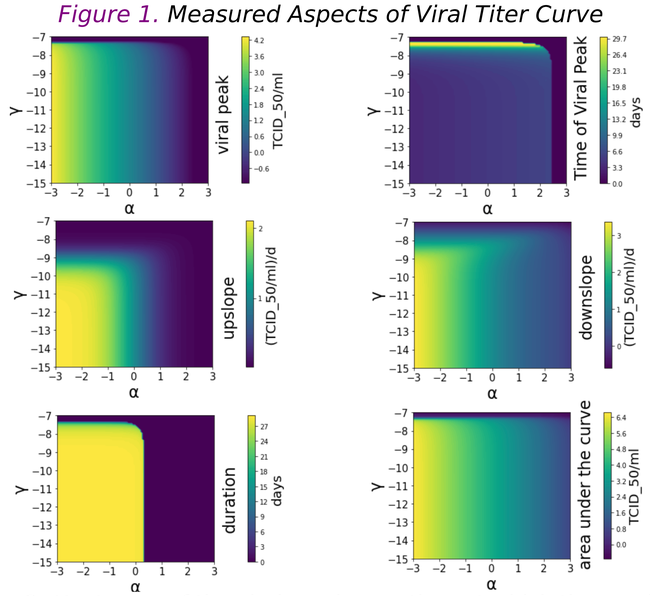

Figure 2. Heatmaps of the viral maximum, time at which the maximum occurs, viral upslope, viral downslope, infection duration, and area under the curve of the Beddington DeAngelis model based on varying parameters for α and γ.

Calculation of Indicators of Infection Intensity

The Beddington-DeAngelis model was simulated to determine viral load as a function of time. The curve was analyzed to understand how density dependence affects different aspects of infection progression.

- **Viral peak and time at maximum viral load** were determined by locating the maximum value of the curve.
- **Upslope** was determined by a linear fit using the `polyfit` function from initial significant observable increase to viral maximum.
- **Downslope** was determined by a linear fit using the `polyfit` function from viral maximum to when the function levels off approaching zero.
- **Infection duration** is the amount of time the virus spends over a particular threshold value.
- **Area under the curve** was calculated using trapezoidal approximations.

Summary

- **Viral peak** predicted values are higher for lower density dependence.
- **Time at which viral peak occurs** is greater for higher density dependence, which indicates a slower progression of the virus.
- **The predicted viral upslope** is steeper for lower density dependence.
- **Viral downslope** appears to descend faster for smaller parameter values for γ.
- **Duration of infection** is longer for greater parameter values for α in a two phase manner rather than a gradual increase.
- **Area under the curve** appears to be lower for greater density dependence.

Overall, increasing density dependence slows the initial progression of the infection. This is consistent with the idea that there is larger spatial heterogeneity in the early stages of infection.

Potential Future Applications

- Looking at other models as a means of analyzing the effect of density dependence on infection progression.
- Fitting the model to data with other density constraint models would allow for improved understanding of the best way to model density dependence.
- Comparing differences in how different density-dependent incident functions predict outcomes for aspects of infection severity

References

- Baccam P et al (2006) Kinetics of influenza A virus infection inhumans. J Virol 80(15):7590–7599
- Dobrovolny HM, Reddy MB, Kamal MA, Rayner CR, Beauchemin CA. Assessing mathematical models of influenza infections using features of the immune response. PLoS One. 2013;8(2):e57088. doi: 10.1371/journal.pone.0057088. Epub 2013 Feb 28. PMID: 23468916; PMCID: PMC3585335..