Antiviral Treatment in Syncytia Forming Viruses

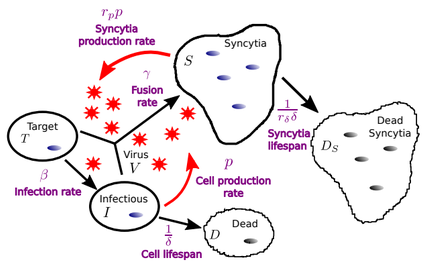
Kiara Johnson and Hana M. Dobrovolny

Department of Physics and Astronomy, Texas Christian University, Fort Worth, USA

Background

- Some viruses have the ability to form syncytia, multi-nucleated cells formed via membrane fusion.
- Syncytia formation allows viruses to spread infection to other cells without entering the extracellular space where it could be exposed to antiviral drugs or antibodies.
- The goal is to personalize mathematical models to individual patients in order to optimize treatment.
- This project explores how syncytia formation can help viruses avoid the effect of the antiviral drugs.
- Antiviral efficacy parameters are applied to a mathematical model to simulate infections and investigate the effect of antiviral drugs on syncytia formation in respiratory syncytial virus (RSV).

Model of Virus Infection



Model Equations

$$\begin{aligned}
\frac{\mathrm{d}T}{\mathrm{d}t} &= -\beta TV - \gamma T(I+S) \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta TV - \gamma I(T+2I+S) - \delta I \\
\frac{\mathrm{d}S}{\mathrm{d}t} &= \gamma T(2I+S) + \gamma I(2I+S) - r_\delta \delta S \\
\frac{\mathrm{d}V}{\mathrm{d}t} &= pI + r_p pS - cV.
\end{aligned}$$

In this model,

- virus, V, infects healthy target cells, T, at a rate β;
- target cells become infected, I, and will produce more virus at rate p, or fuse with other cells to create syncytia, S, at rate γ;
- syncytia then produce virus at a rate of $r_p p$;
- both infected cells and syncytia continue to produce virus until they die after lifetimes of $1/\delta$ and $1/r_\delta \delta$ respectively;
- virus is cleared from the system at a rate c.

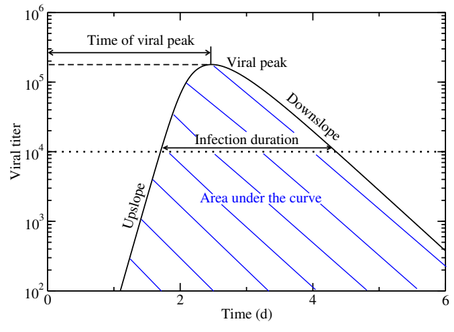
Mechanism of Action: Comparison of Drugs Applied

Antivirals acting on a parameter is represented by multiplying the parameter by the efficacy factor $(1-\epsilon)$. The efficacy, ϵ, is between 0 (no drug) and 1 (perfectly effective drug.

1. **Acting on β:** The infection rate, β, is multiplied by the efficacy parameter to simulate the effect of antivirals blocking the virus's ability to enter healthy cells, which stops the spread of infection.
2. **Acting on p:** The viral production rate, p, is multiplied by the efficacy parameter to simulate the effect of antivirals blocking the spread of the virus by stopping the cells fusing into syncytia.

Measurements

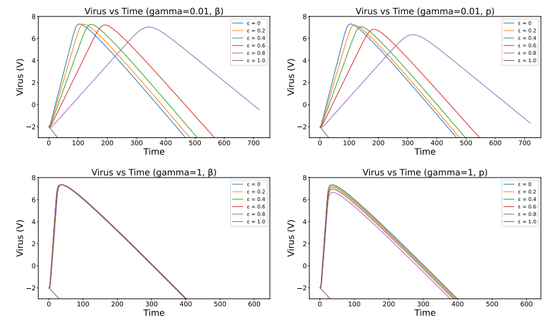
The following measurements are used to assess the effect of the antiviral drugs on the infections simulated.



1. **Peak Viral Load:** An indicator of the transmissibility of an infection.
2. **Time of Viral Peak:** The time it takes the maximum amount of virus to spread within the host.
3. **Viral Upslope:** The exponential growth rate of the virus during the first phase of infection.
4. **Area Under the Curve (AUC):** The total amount of viral production and spread throughout the duration of the infection.
5. **Infection Duration:** The amount of time the viral titer, concentration of infectious viral particles, is over 10^4, which indicates how long the infected individual might experience symptoms.

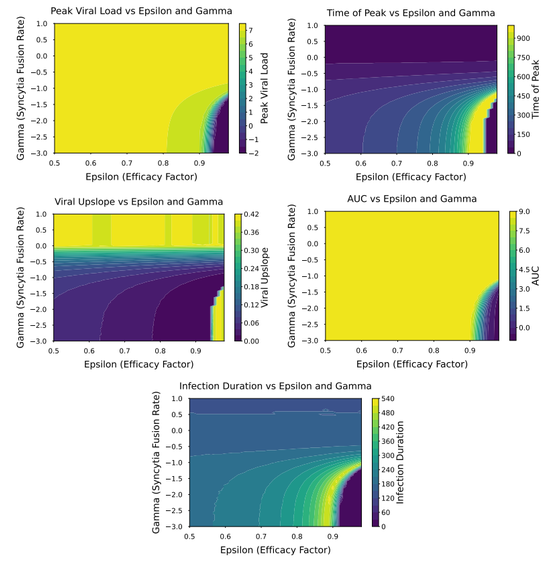
Virus vs Time

We measured viral concentration over time under conditions of both high and low syncytia formation rates (γ), for various drug efficacy values (ϵ) applied to the infection rate (β) or the viral production rate (p).



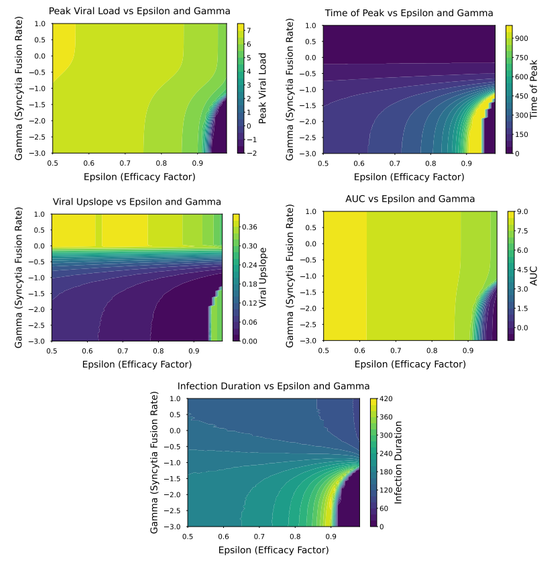
Drug Acting on β

We varied the syncytia formation rate (γ) and the drug efficacy, then measured the 5 characteristics of the viral load.



The antiviral suppresses infection when the antiviral effectiveness is high and the syncytia formation rate is low. High amounts of syncytia formation make the antiviral ineffective.

Drug Acting on p



Conclusion

- Antivirals suppress the infection when the drug efficacy is high and syncytia formation rate is low.
- High rates of syncytia formation lower antiviral effectiveness since infection can still spread through cell fusion.
- The infection duration was shorter and the peak viral load was lower when the antiviral reduced viral production.

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Antiviral drugs are used to block the spread or replication of viruses. Some viruses can form syncytia, multi-nucleated cells that allow viruses to spread by cells fusing together, which allow the viruses to avoid immune responses and antiviral drugs. In this study, a mathematical model is used to simulate how antivirals affect infections. Applying different antiviral treatments to these infections allows us to assess how effective the drugs are at lowering the transmission rate, reducing the amount of virus produced, and shortening the infection duration. Understanding syncytia formation is important for creating more effective antiviral drugs.