A mathematical model of triple viral infection

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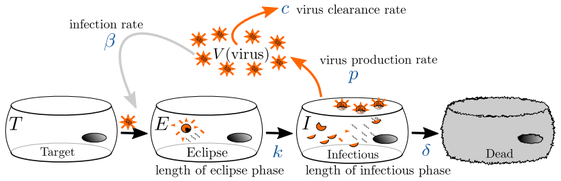
Background

- Studying triple infections, especially involving influenza (IAV), respiratory syncytial virus (RSV), and SARS-CoV-2, is crucial for public health preparedness, since all three viruses circulate promarily during the winter months.
- All three viruses infect cells lining the respiratory tract, replicating within these cells, causing cell damage and the release of viral particles to infect neighboring cells.
- The incubation period for COVID-19 is typically 2 to 14 days, with most cases showing symptoms within 4 to 5 days after exposure.
- Influenza (IAV) is a single stranded respiratory virus with an incubation period for typically 1 to 4 days.
- The incubation period for RSV is typically 4 to 6 days, with symptoms appearing within 4 to 5 days after exposure.
- We use mathematical modeling to help us understand how viruses interact during these infections.

Single virus model

The triple infection model is based on a single virus infection model.



Parameters of the model include viral infection rate (β, transition rate k, death rate of infectious cells δ, viral production rate p, and viral clearance rate c. Values of these parameters differ for the three different viruses we model (IAV, RSV, SARS-CoV-2).

Methods

- We extend the single virus model to describe a triple infection system involving influenza (IAV), respiratory syncytial virus (RSV), and SARS-CoV-2.
- To study what happens during a triple infection, we calculate maximum virus populations and infection durations for all three viruses as infection rates are varied.
- All code was written using python.

Model equations

1. Target Cells (T):

$$\frac{dT}{dt} = -\beta_1 T V_1 - \beta_2 T V_2 - \beta_3 T V_3$$

2. Eclipse Phase Infected Cells (E_1, E_2, E_3):

$$\frac{dE_1}{dt} = \beta_1 T V_1 - k_1 E_1 \qquad \frac{dE_2}{dt} = \beta_2 T V_2 - k_2 E_2$$

$$\frac{dE_3}{dt} = \beta_3 T V_3 - k_3 E_3$$

3. Productively Infectious Cells (I_1, I_2, I_3):

$$\frac{dI_1}{dt} = k_1 E_1 - \delta_1 I_1 \qquad \frac{dI_2}{dt} = k_2 E_2 - \delta_2 I_2$$

$$\frac{dI_3}{dt} = k_3 E_3 - \delta_3 I_3$$

4. Viral Particles (V_1, V_2, V_3):

$$\frac{dV_1}{dt} = p_1 I_1 - c_1 V_1 \qquad \frac{dV_2}{dt} = p_2 I_2 - c_2 V_2$$

$$\frac{dV_3}{dt} = p_3 I_3 - c_3 V_3$$

The viruses interact by competing for target cells.

Parameters

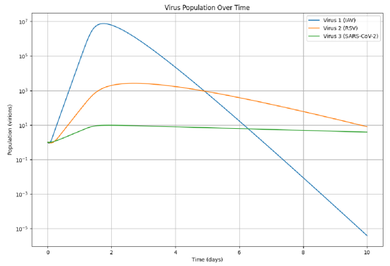
Different parameter values characterize different viruses. We found parameter values for influenza, RSV and SARS-CoV-2 from the literature:

- Influenza — Pinky et al. Plos One (2016)
- RSV — Pinky et al. Plos One (2016)
- SARS-CoV-2 — Pinky et al. Journal of Medical Virology (2020)

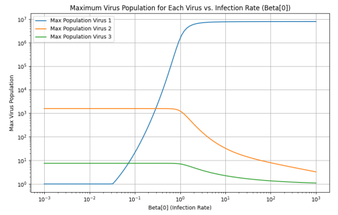
Parameter	Influenza	RSV	SARS-CoV-2
T_0	1.0	1.0	1.0
V_0	1.0	1.0	1.0
β (/[V] $\cdot$ d)	82.73×10^{-7}	0.03	2.32×10^{-4}
k (/d)	4.20	1.27	4.08
δ (/d)	4.20	1.27	38.1
p ([v]/d)	0.12×10^{9}	76.45×10^{2}	4.78×10^{5}
c (/d)	4.03	1.27	0.117

Infection time courses

These parameter values lead to the following viral time courses:

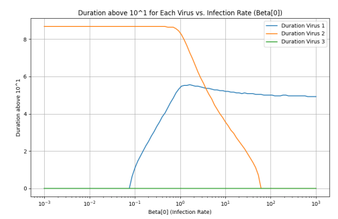


Maximum viral load



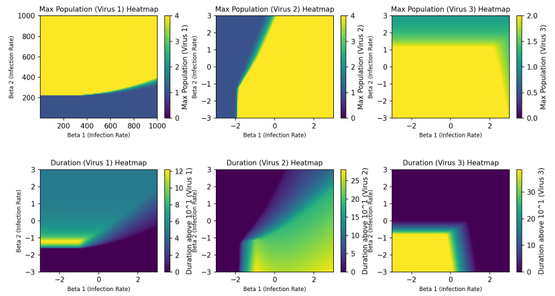
- We vary the infection rate of virus 1 and measure the maximum viral load of all three viruses.
- Peak viral load of virus 1 starts to rise at $\sim 10^{-1.5}$. When virus 1 reaches its peak, the maximum viral load of the other two viruses declines.
- The simulation identifies critical thresholds for each virus, where their responses to infection rates change significantly.

Infection Rates VS Duration



- We vary the infection rate of virus 1 and measure the infection duration of all three viruses.
- Virus 3 is suppressed by the other two viruses.
- Virus 2 initially suppresses virus 1, but this is reversed as virus 1 infection rate increases.

Virus interactions



- Three heatmaps are generated, each representing the duration of time that each virus remains above a threshold population (in this case, 10^1.
- Similar to the maximum population heatmaps, the x-axis and y-axis represent the values of Beta 1 and Beta 2.
- The color intensity in each cell of the heatmap indicates the duration of time that the corresponding virus remains above the threshold population under the given combination of Beta 1 and Beta 2 values.

Conclusions

- Each virus has a region where it has the longest infection durations and highest viral loads.
- Virus 1 and Virus 2 dominate when their respective infection rates are large.
- Virus 3 dominates only when the infection rates of the other two viruses are low.

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This study presents a mathematical model analyzing triple infection dynamics involving influenza, respiratory syncytial virus, and SARS-CoV-2. These three viruses circulate at the same time of year, so it's possible to that people might be exposed to all three viruses at the same time. This presents challenges for doctors trying to treat patients since it's not clear whether having multiple viruses will result in more severe disease. Treating one virus might increase disease severity because of the complex interactions between the viruses. Our model can help guide treatment decisions by helping doctors understand how the viruses interact during a triple infection.