SARS-CoV-2 viral rebound after Paxlovid treatment

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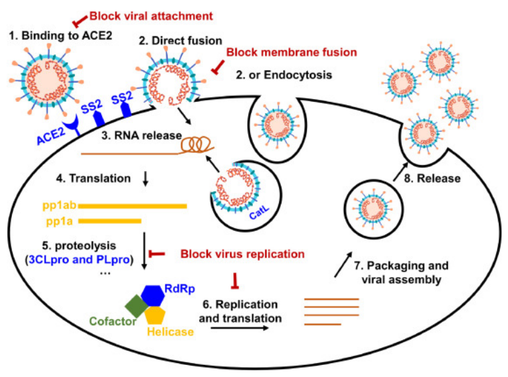
Background

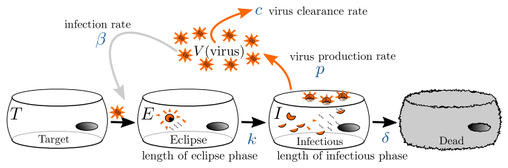
- COVID-19 is an infectious disease caused by the SARS-CoV-2 virus, which has resulted in over six million deaths.
- Paxlovid is a antiviral treatment for COVID-19 that is effective in preventing hospitalization.
- Paxlovid consists of two medications, nirmatrelvir and ritonavir, taken twice daily for 5 days.
- Currently, however anecdotal reports of rebound infection have been found with the use of Paxlovid.
- In this study we aim to use mathematical modeling to investigate the infection conditions that result in rebound of COVID-19 after antiviral treatment.

SARS-CoV-2 replication

SARS-CoV-2 is a single-stranded RNA virus. The spike protein on the viral capsid binds to the ACE2 receptor on the cell surface in order for the virus to gain entry to the cell. Once in the cell, the virus uses cell replication machinery to make copies of itself that are eventually released to infect other cells.



Mathematical model



In this model the target cells, T, are infected by the virus V, at a rate of β. Next these newly infected cells enter an eclipse phase, E. In phase E they are internally producing viral replicates but not releasing them. After a time $1/k$, the cell becomes productively infectious, I, and releases p infectious virions per unit time. Then the infectious virus decays at rate c.

$$\begin{aligned}\dot{T} &= -\beta TV\\ \dot{E} &= \beta TV - kE\\ \dot{I} &= kE - \delta I\\ \dot{V} &= pI - cV.\end{aligned}$$

Paxlovid

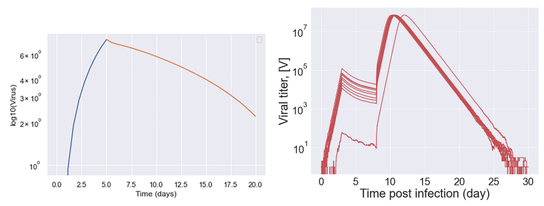
- Paxlovid consits of two separate medications, nirmatrelvir and ritonavir.
- Nirmatrelvir is a protease inhibitor. When the virus uses the cells machinery to replicate itself, it has to transfer its genome into a two large polypeptide proteins that then have to be broken down. The enzyme that breaks it down is SARS-CoV-2 is Mpro. Nirmatrelvir blocks Mpro, so it is unable bind to the polypeptide protein.
- This results in the virus being unable to create functioning protein and therefore being unable to replicate.
- Ritonavir is also a protease inhibitor and inhibits nirmatrelvir breakdown in the liver. This allows nirmatrelvir to have higher drug concentrations and stay in the body for a longer period of time.
- Since Paxlovid is a protease inhibitor it acts on part of the internal replication of the virus. So for our model we used the effect of Paxlovid as reducing the production rate of the virus.

$$p \to (1-\varepsilon)p,$$

where ε is the efficacy of the drug. An efficacy of 0 means the drug has no effect and 1 means the drug is 100% effective.

Stochastic simulations

- Stochastic modeling is a tool that brings randomness into the calculation.
- At each time step, a randomly chosen number of events occur, chosen based on the probability of those events happening.
- Therefore it accounts for random variance from patient to patient. This provides a more accurate depiction of the viral infection.



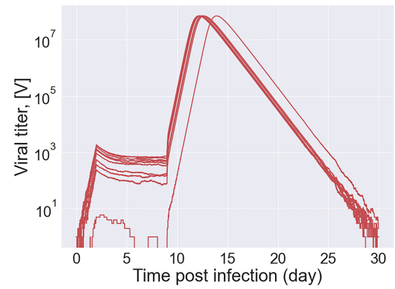
Simulating SARS-CoV-2

We used parameter values representing SARS-Cov-2 infection, taken from Hernandez-Vargas, 2020:

Parameter	Value
β	4.71×10^{-8} (copies/mL $\cdot$ d)$^{-1}$
p	3.07 copies/d $\cdot$ mL
k	5.0 /d
δ	1.07 /d
c	2.4 /d
V_0	0.31 copies/mL
T_0	4×10^8 cells

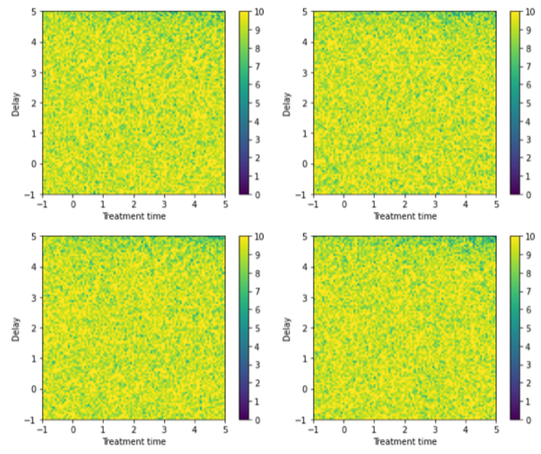
Methods

- We changed treatment time by setting up a range of 3 to 10 days in .07 increments in order to run simulations for different time durations.
- We changed treatment delay by setting a range of .5 to 7 days in .065 increments in order to simulate different delay times before treatment begins.
- For each combination of treatment time and duration, we simulated 10 patients then counted how many patients experienced rebound.
- We counted an infection as having rebound if the maximum viral load after treatment was 10% bigger than the last count during treatment.



Results for Paxlovid

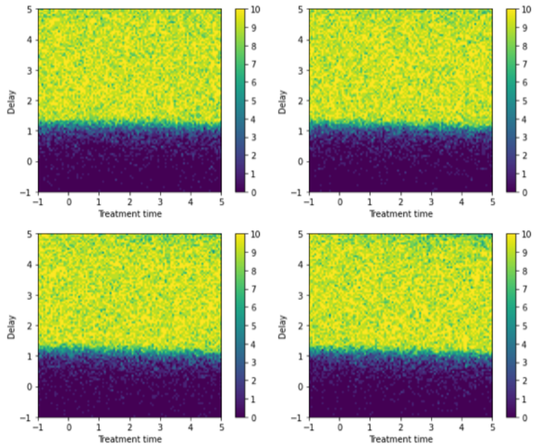
We simulate 10 patients at each treatment duration and treatment delay. The plots below show how many of the 10 had rebound at different drug efficacies.



- With Paxlovid viral rebound is virtually guaranteed no matter how effective the dose.
- This is because Paxlovid does not prevent infection of the cells, only blocks release of virus.
- Once the antiviral is removed, the infected cells that still remain start to produce virus again.

Results for a fusion inhibitor

We examined a drug that prevents infection to see if it was more effective at preventing rebound.



- Antivirals that prevent infection can prevent rebound if they are given early enough.
- The drug dose and the duration of treatment have little effect on the chance of viral rebound.
- If the drug is given too late, most cells have already been infected and the antiviral will not prevent rebound.

Conclusions

- Antivirals that disrupt processes after the cell has been infected are almost guaranteed to have viral rebound.
- Antivirals that prevent cell infection can prevent rebound, but only if the antiviral is given before too many cells are infected.
- The duration of treatment has little effect on whether there is rebound.

Future Directions

- Incorporate realistic time-varying drug treatment.
- Examine the relationship between infectious cell lifespan and treatment duration needed to prevent rebound.
- Model other antiviral mechanisms of action.

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Covid-19 is an infectious disease that has spread across the world. Paxlovid is a medication that has been given to treat COVID-19. However rebound cases have occurred after taking Paxlovid. In our study we found that Paxlovid is almost guaranteed to cause rebound because it only stops the release of the virus but not the infection itself. Therefore after treatment is done the virus will start replicating again. So we also tested a drug that prevents infection and if given early enough we found that it can prevent rebound.