Effect of initial inoculum on the effectiveness of antiviral treatment

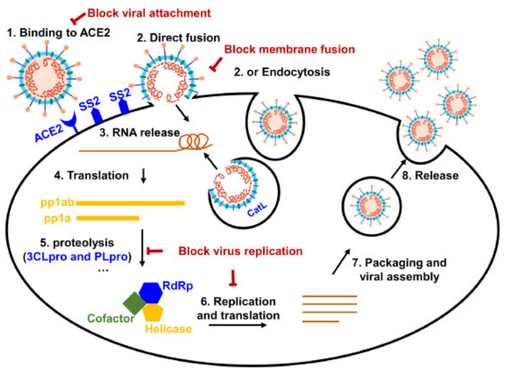
Sahana Talwar and Hana M. Dobrovolny

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

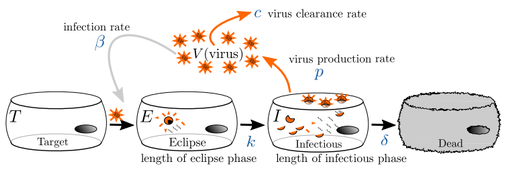
Background

- SARS-CoV-2 recently caused a pandemic that has resulted in over six million deaths and caused a global lockdown.
- There has been speculation that the amount of virus you are exposed to can affect the severity of the disease.
- Studies have shown that the initial dose of virus can alter the time course of the infection.
- This might affect when and how long drugs should be used.
- In this study, we examine whether the initial inoculum of SARS-CoV-2 affects the effectiveness of the antiviral.

SARS-CoV-2 replication



Mathematical Model



We use a mathematical model of infection to study the effect of antivirals,

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

In the model, T represents the target cells. E is the cells in the eclipse phase; I is the infectious cells, and V is the virus. The rate at which target cells are infected by the virus is represented by β. The time between the eclipse phase and when cells become infectious is $1/k$.

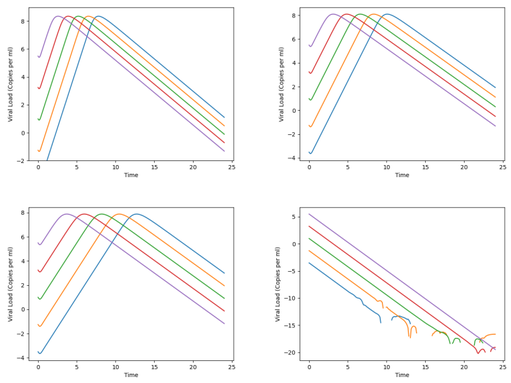
We use parameter values that describe SARS-CoV-2 infection (Hernandez-Vargas, 2020).

Parameter	SARS-CoV-2
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

Modeling drug treatment

- We model two different types of drugs: one that reduces infection rate of cells (spike protein inhibitor) and one that reduces release of virus (Paxlovid).
- Drugs are modeled using efficacy, ε, where ε ranges between 0 (completely ineffective) and 1 (100% effective).
- The two antivirals are applied in the model by multiplying either β or p by $(1-\varepsilon)$.

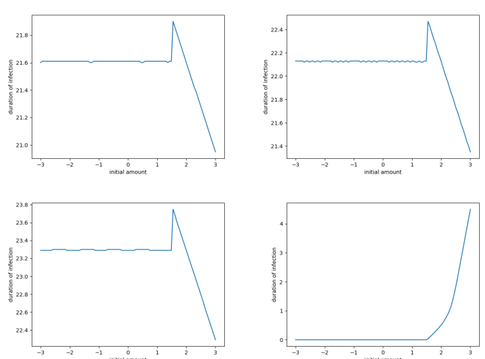
Drug that reduces production



- Each graph shows a different drug efficacy: 0.2, 0.4, 0.6, and 0.98.
- An efficacy of 0.98 is high enough to suppress the infection.
- Each line is a different initial viral dose.
- Visually, its difficult to see any difference in the viral curves other than the shift shift to an earlier time of peak as initial virus increases.

Duration of the infection

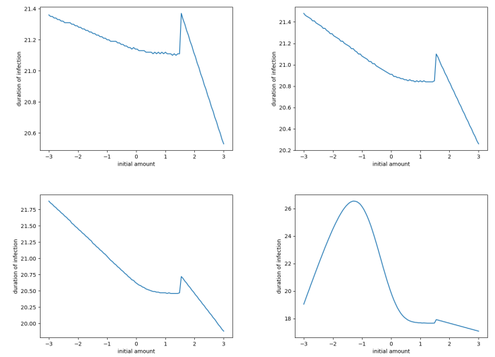
To better assess if the viral dose changed the infection in a way that matters to patients, we measured the duration of the infection. Infection duration is defined as the time the virus is above 10 TCID_{50}/ml.



Duration does not change much as the initial dose of virus is changed, except for at high efficacy where the duration increases once the initial dose is above threshold.

5 day treatment

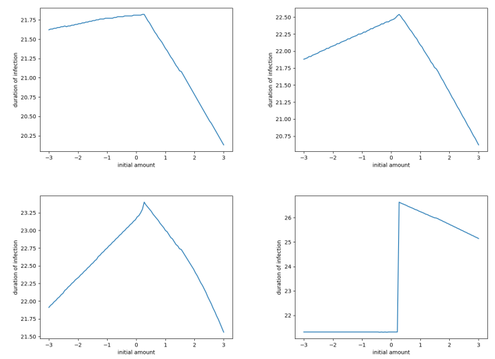
Since Paxlovid is only given for 5 days, we looked at the effect of only having 5 days of antiviral treatment.



At low drug efficacy, the duration mostly decreases as the initial viral dose increases. At high efficacy, the duration first increases before decreasing again.

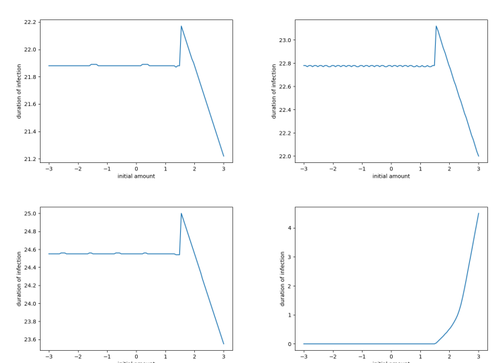
Treatment Delay

In real life treatment is not usually started immediately, so we investigated the effect of a treatment delay of 1 day with the 5 day treatment.



Delaying treatment allows all initial virus doses to rise above threshold before the antiviral is applied, changing the dependence of duration on initial viral dose.

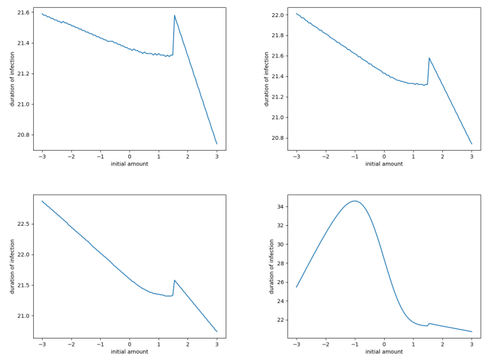
Drug that reduces infection



The dependence of duration on initial viral dose is similar to what was seen for a drug that reduces production.

5 day treatment

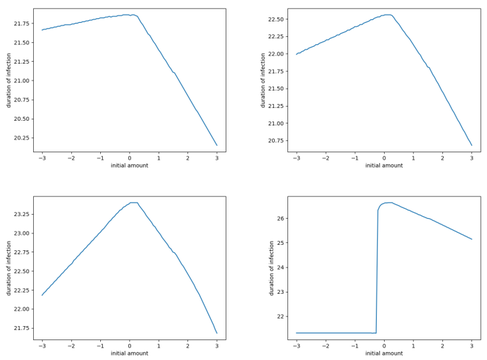
We again assumed a treatment course of 5 days.



While the trend is similar to the other antiviral, the infection duration is longer when using a drug that blocks infection.

Treatment delay

We assumed a 5-day treatment course after a delay of 1 day.



Durations are again similar to those observed for the other antiviral.

Conclusions

- For prophylactic treatment, the duration shows little dependence on viral dose until high viral dose or high drug efficacy.
- In most cases, the effect is small, with duration changing by less than 1 day.
- An antiviral that reduces infection tends to have longer durations than an antiviral that reduces production.

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Since some studies suggest that initial viral dose can affect the severity of illness, this research focuses on discovering if the initial dose of virus also affects the effectiveness of the antivirals. We tested both antivirals that reduce production and antivirals that reduce infections. We find that initial viral dose can affect the duration of a treated infection, particularly when the efficacy of the drug is high.