Modeling polymerase inhibitor treatment of RSV

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Background

Respiratory syncytial virus, or RSV, is a virus that causes lower respiratory tract infections throughout childhood and infancy. Agents that can effectively combat RSV are still not available for widespread clinical use, but one of the targets being investigated is PC786, a novel inhaled L-protein polymerase inhibitor. Given the promising experimental data, we are trying to find the best mathematical model for the drug, so we can use modeling to help optimize treatment.

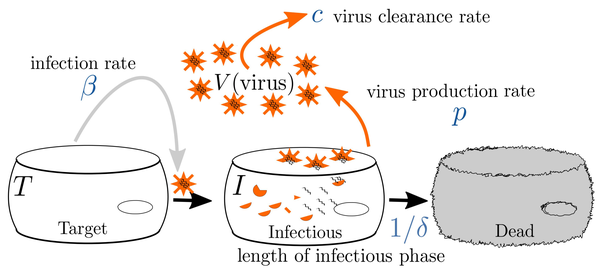
Respiratory Syncytial Virus

RSV spreads through bodily fluids and direct contact. Most infections come with mild, cold-like symptoms that typically last 2 weeks or less. However, the virus can have much more adverse effects on the young, elderly, and immunocompromised. It's the most common cause of bronchiolitis (inflammation of small airways in the lung) and pneumonia in infants in the United States. It's also a significant cause of respiratory illness in the elderly. Researchers are working to develop vaccines for RSV, but none are available yet.

PC786

PC786, the drug being studied, is a potent nonnucleoside L-protein polymerase inhibitor, designed to treat RSV through inhalation. Previous studies have found that it inhibits viral replication, thereby decreasing the viral load. In order to further develop the drug, we need to determine optimal dosing, which can be helped by modeling the effect of the drug. Unfortunately, we do not yet know how to best model the mechanism of action of this drug.

Virus Life Cycle



Model Equations

$$\frac{dT}{dt} = -\beta TV$$
$$\frac{dI}{dt} = \beta TV - \delta I$$
$$\frac{dV}{dt} = pI - cV$$

In this model, target cells T are infected with virus V at a rate β. Once infected, the cells enter the infectious phase I, where they produce virus at a rate p. The cells die at a rate δ and the virus is cleared at a rate c. β, δ, c, and p are the parameters of the model while T, I, and V are the variables of the model.

Modeling the Drug Effect

$$\varepsilon = \frac{\varepsilon_{max} D}{D + IC_{50}}$$

where ε represents the efficacy of the drug, D represents dosage, and IC_{50} is a measure of how much drug is required to inhibit a biological process by half. Applying the drug effect entails inhibiting one step of the process by multiplying it by a factor of (1-ε), so if efficacy is 1, the drug is 100% effective and the process is entirely inhibited.

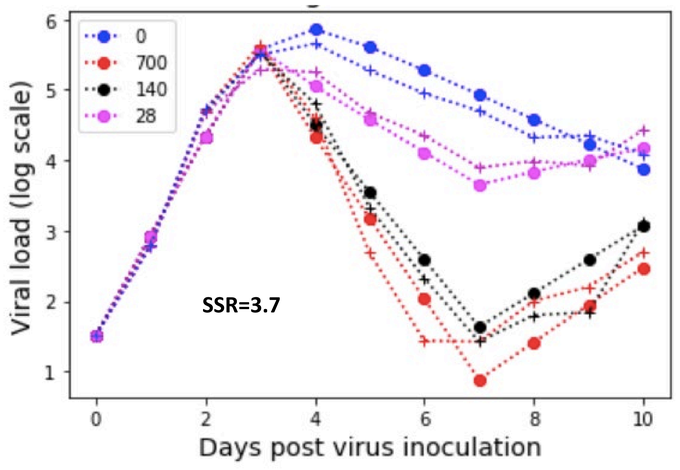
Methods

Using data from previous publications, we created models of the relationship between volume of PC786 and viral load in patients with RSV to try to determine how to best model the action of this drug.

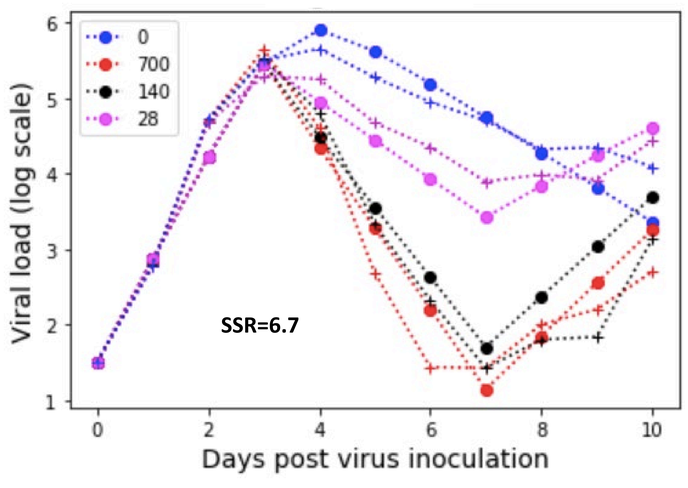
WebPlotDigitizer was used to extract data from a previous publication (D W Brookes, British Journal of Pharmacology. Python was used to create code and fit data. The mathematical model was fit to data by minimizing the sum of squared residuals (SSR).

Model Fits to Experimental Data

We tested two mechanisms of action:
The drug reduces the infection rate



or the drug reduces the production rate



Parameter Estimates

Parameter	Model 1	Model 2
$\varepsilon_{\mu\alpha\xi}$	1.91	1.47
IC_{50} (nM)	18.0	13.7
β (/day)	2.56×10^{-6}	1.96×10^{-6}
p (/day)	1.23×10^{10}	1.44×10^{16}
c (/day)	0.848	1.20
δ (/day)	7630	6.50×10^{9}
SSR	3.7	6.7

- In Model 1, the drug effect was applied to β, meaning the model acts as if the drug decreases the virus infection rate.
- In Model 2, the drug effect was applied to p, meaning the model acts as if the virus production rate is inhibited.
- Both models fit the data with a fairly small SSR, indicating a good fit to the data.
- Model 1 resulted in a slightly better SSR.
- However, both models had inconsistencies or errors, since the value of ε_{max} can not be more than 1.
- The estimated values of δ are also larger than previous estimates.
- Values of IC_{50} for both models are in good agreement and are consistent with experimental estimates.

Sources of Error

- Within the extracted data points, y-values less than 1.5 may be inaccurate due to data-collecting limitations.
- Viral titer measurements are known to be dependent on temperature, humidity, and freeze-thaw cycles.
- Minimization algorithms do not necessarily find the global minimum, so re-fitting with a different initial guess might lead to better results.
- The viral dynamics model used here might be too simple to properly model the effect of PC786.

Conclusion

PC786 may be an effective treatment for RSV. We created models of previously published data in an attempt to learn how to better model the action of this drug. Although the models fit the data well, they were inconsistent and inaccurate in the ε_{max} values used to fit the data, which were unrealistic and unreasonable values. However, our preliminary results indicate that the most appropriate mathematical model for PC786 is one that assumes a reduction in infection rate.

Future Work

- We will try other assumptions for the mechanism of action of PC786.
- We will extend the viral dynamics model to include other steps of the viral replication cycle in order to better model the effect of PC786.
- There is more experimental data for PC786 that can be used to help determine whether the model is correctly representing the effect of PC786, so we will incorporate that into our analysis.