Enhanced anti-tumoral immune response of oncolytic viruses

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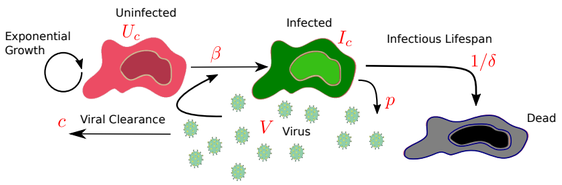
Background

- Cancer is among the leading causes of death worldwide.
- The herpes virus, like many other viruses, can be engineered to target and kill cancer cells.
- The herpes virus, when loaded with immune stimulating factors, like interleukin 12, can be even more effective at killing cancer cells.
- The goal of this project is to compare the parameter values obtained for the different viruses to both quantify differences between the viruses and to see if we can correlate any of the parameters to effectiveness in treating the cancer.

Oncolytic Virus Model



- The basic mathematical model for oncolytic virus is

$$\begin{aligned}\frac{dT}{dt} &= \lambda T\left(1-\frac{T+I}{K}\right)-\beta TV\\ \frac{dI}{dt} &= \beta TV-\delta I\\ \frac{dV}{dt} &= pI-cV.\end{aligned}$$

- Here, uninfected tumor cells, T, replicate according to the logistic model with growth rate, λ and carrying capacity K. These cells can be infected by virus, V, at infection rate β. The cells then become infectious, I, and produce virus at production rate p. The infected cells die at rate δ and the virus is cleared at rate c. This model quantifies some of the biological processes happening during the infection.

Experimental Data

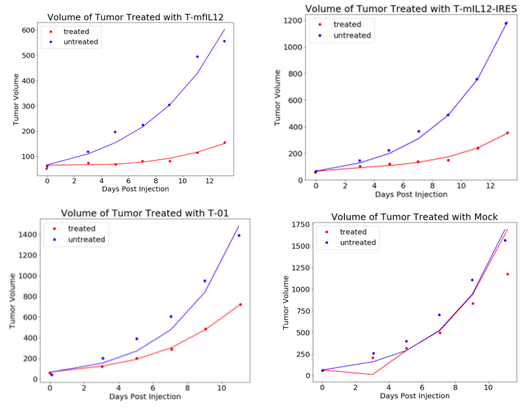
- Experimental data was taken from Fukuhara et al. (2023) Communications Medicine.
- Researchers constructed two variants of herpesvirus HSV-1 and tested their performance in vivo against Neuro2a tumors in mice.
- Mice had bilateral tumors, with one side being treated with oncolytic virus and one side left untreated.

Methods

- We fit the mathematical model to data using minimization of the sum of squared residuals.
- We estimated virus characteristics such as viral production rate and infectious lifespan of the different strains
- Bootstrapping was used to estimate the posterior distributions of the free parameters.
- All code was written using python.

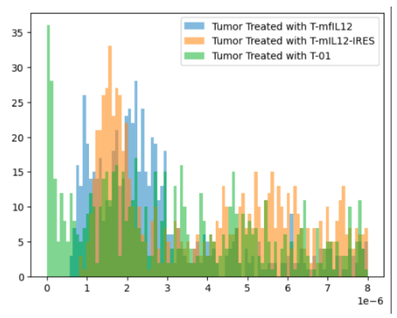
Original Model Fits

When fitting the data, we used the untreated tumor as a control for the treated tumor and fit both curves simultaneously for each viral strain.



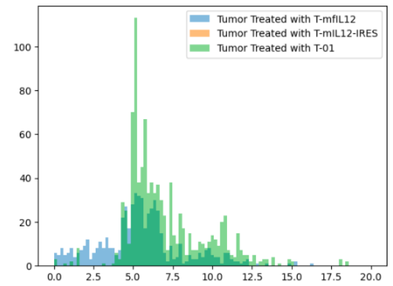
Infection rate

We compare the posterior distributions for the infection rate for each viral strain.



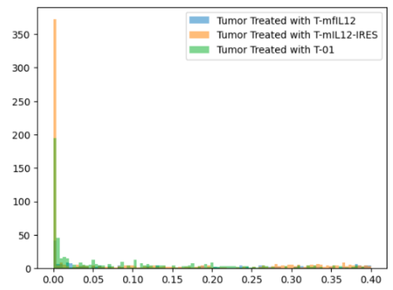
There is a significant overlap between all three strains suggesting that there is no difference in the infection rate between the three strains.

Production rate



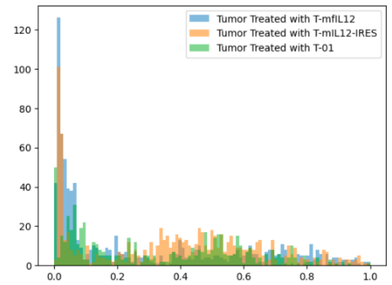
There is an overlap between T-mfIL12 and T-01 suggesting no difference in the production rate of the virus strains.

Infectious cell death rate



There is an overlap between TmIL12-IRES and T-01 suggesting no difference in the infectious cell death rate of the virus strains.

Viral clearance rate



There is an overlap between the distributions of all the strains suggesting no difference in the viral clearance rate. .

Conclusions

- We fit the mathematical model to the bilateral tumor data, getting estimates for important viral kinetics parameters.
- There does not appear to be any difference in infection rate between the three viral strains.
- Parameter values obtained for viral clearance rate between all three strains were also overlapping, indicating no difference.
- Parameter values obtained for cell death rate between T-mIL12-IRES and T-01 were similar, suggesting that the T-mIL12 variant had a different cell death rate.
- T-01 and T-mIL12 had similar production rates, suggesting that the creation of T-mIL12-IRES altered the production rate.

Future Directions

- To determine whether observed differences are statistically significant, we need to use statistical tests to check whether distributions overlap.
- Assess structural identifiability of the model using DAISY.
- Assess practical parameter identifiability by examining parameter correlations and likelihood profiles.
- We can use our parameter estimates to simulate different treatment protocols or combination therapy to determine the optimal application of the three different strains.
- The original paper also includes data for the same three strains in prostate cancer. We can apply the same methodology to this data to see if alterations in the virus have a similar effect in a different type of cancer.

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Some viruses can be modified using immune stimulating factors to kill and target cancer cells. We assessed the effectiveness of different modified herpes virus strains in killing cancer cells. Data from the literature was used to obtain the viral kinetic parameter values for the virus. The distributions of these parameter values were plotted to observe differences in the performance of the three strains of the modified herpes virus.