The Characterization of Oncolytic Herpes Simplex Virus

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Background

- Oncolytic herpes simplex viruses (oHSVs) are selectively engineered to infect and kill cancer cells while sparing normal tissue.
- The oHSV's efficacy is determined by tumor characteristics, viral replication dynamics, and immune system interactions.
- Epidermal growth factor receptors (EGFRs) are particularly susceptible to oHSV infection.
- Mathematical models help optimize treatment strategies by quantifying tumor, viral, and immune interactions.
- Accurate parameter estimation is essential to predict treatment outcomes.

Basic model of viral infection

Here, uninfected tumor cells, T, replicate exponentially with growth rate λ. These cells can be infected by virus, V, at infection rate β. The cells then enter an eclipse phase, where they are infected, but not yet producing virus. The virus stimulates an interferon response (F), where ϵ characterizes the virus' sensitivity to interferon, and α is the decay rate of interferon. Interferon reduces production of the virus. This model quantifies some of the biological processes happening during the infection.

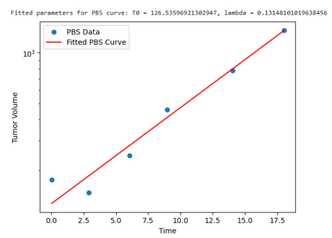
$$\begin{aligned}
\frac{dT}{dt} &= \lambda T - \beta T V \\
\frac{dE}{dt} &= \beta T V - kE \\
\frac{dI}{dt} &= kE - \delta I \\
\frac{dV}{dt} &= I\left(\frac{p}{1+\epsilon F}\right) - cV \\
\frac{dF}{dt} &= I - \alpha F.
\end{aligned}$$

Methods

- Extraction:Experimental data was extracted from graphs via WebPlotDigitizer.
- Optimization:The model parameters were estimated by minimizing the sum of squared residuals between the experimental data and model predictions.
- Bootstrapping:Used to generate confidence intervals for the parameters by resampling and refitting the model several times.

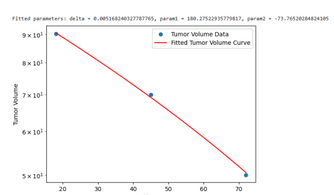
Tumor growth rate

The parameter λ, indicating the tumor growth rate, is derived from an optimization program fitting the tumor growth model to PBS control data by minimizing squared residuals (SSR). The process includes manual data entry, model definition, and using SciPy's minimize function.



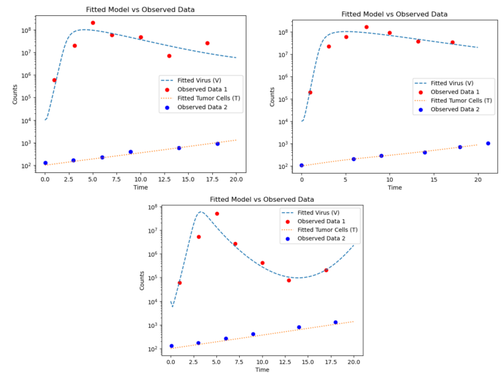
Infected cell death rate

The parameter δ, indicating infected cell death rate, is derived from an optimization program fitting a decay curve to cell death by minimizing squared residuals (SSR). The process includes manual data entry, model definition, and using SciPy's minimize function.



Best Fit and Data

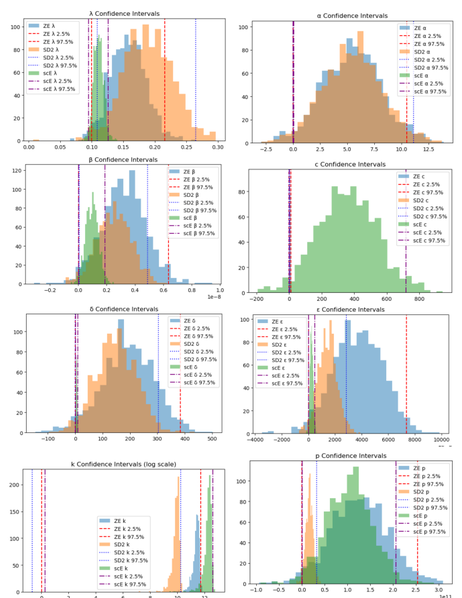
Experimental data collected from different oHSV strains in U251 tumor-bearing mice were used for parameter estimation.



Best fit parameters account for both viral and tumor cells.

Distributions and Histograms

Bootstrapping generated distributions of key parameters, revealing variability across viral strains. Histograms of viral burst size (p), infection rate (β), and tumor growth rate (λ) showed that effective strains had higher p and β values. These distributions guided the identification of viral strains with enhanced therapeutic potential.



Conclusions

- We quantified the interactions between oncolytic herpes simplex virus (oHSV) and tumor cells using effective mathematical modeling.
- A system of differential equations was implemented to identify key mechanisms underlying viral infection, replication, and tumor response.
- Parameter fitting and optimization techniques were used to replicate experimental data for tumor growth and assess the efficacy of different oHSV strains on EGFR-bearing tumors.
- Viral titer dynamics and tumor regression were compared to determine the efficacy of various oHSV strains.
- Incorporating the interferon variable improved parameter prediction, while bootstrapping techniques established confidence intervals and assessed statistical significance.
- This study contributes to the growing field of computational approaches aimed at predicting treatment outcomes for clinical applications.

Future directions

- Investigate the efficacy of different oncolytic herpes simplex virus strains on a wider range of tumor types to determine the generalization of the method.
- Further study the immune system's role in oncolytic virus therapy, particularly the effects it has on tumor regression and viral efficacy.
- Begin to expand clinical applications by using the model to predict and personalize treatment for cancer therapy.

We used mathematical modeling to study how different strains of oncolytic herpes simplex virus (oHSV) impact tumor cells. By creating systems of differential equations, we simulated tumor growth, virus spread, and immune response. Fitting these models to experimental data allowed us to determine how effective each virus strain was at reducing tumor size. We also examined how interferons, a part of the immune system, influence the virus-tumor interaction. Statistical techniques like bootstrapping helped confirm our findings. This approach offers a powerful tool to predict how viral therapies behave, guiding the development of more effective cancer treatments in the future.

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