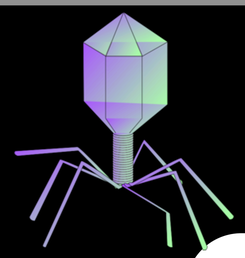
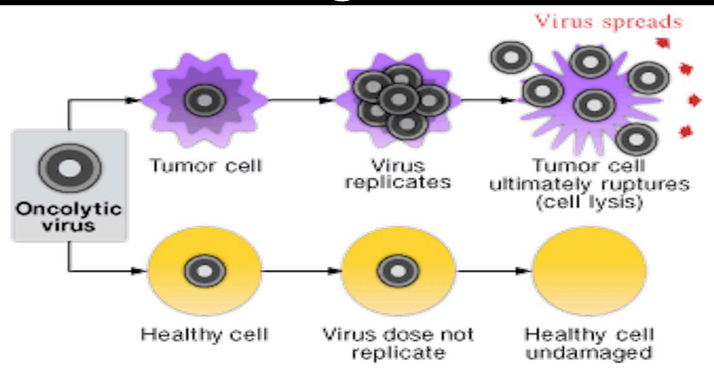
Math to fight cancer

Johnathon Joey Irani[1,2,3], James H.K. Ooi[2,3] and Mads Kaern[2,3,4]



Background



Oncolytic viruses are promising anticancer therapeutics as they infect and destroy cancer cells without compromising normal tissue.

Mathematical modeling is an innovative approach to identify strategies that improve the therapeutic potential of the oncolytic virus[1].

Our research goal is to use mathematical modelling to identify potential drug targets that can sensitize cancer cells to oncolytic virus treatment, while minimizing their impact on non-cancerous cells.

Aim

→ To identify potential drug targets, we will conduct a sensitivity analysis of how viral efficacy changes when model parameters are systematically varied.

Why model parameters? Each parameter represents an important biological process. Parameters that are sensitive to variation are potential targets for optimal therapeutic outcomes.

Hypothesis

→ Key parameters will be most sensitive to variation:

- $K_{Bud\ IP}$ (rate of virus budding from the infected population)
- $K_{Bud\ AP}$ (rate of virus budding from the activated population)
- K_{VI} (infection rate)
- $K_{DR\ IP}$ (rate of the decoy receptor from the infected population)
- $K_{DR\ AP}$ (rate of the decoy receptor from the activated population)

Methods

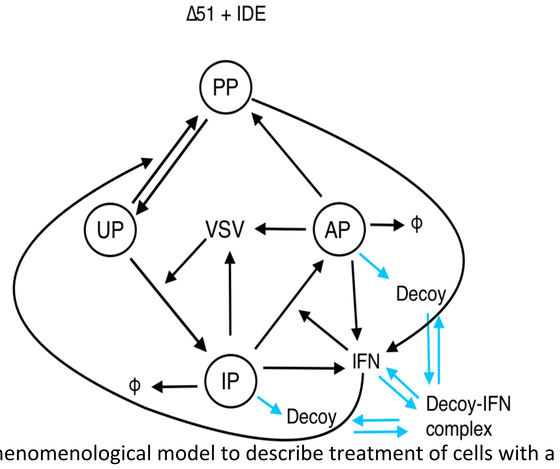


Figure 1: Phenomenological model to describe treatment of cells with a virus called "Δ51 + IDE" (Δ51-mediated expression of the IFN DR). This virus is a vesicular stomatitis virus (VSV) reengineered from the VSV wild type. A positive feedback loop is represented by the blue arrows and it allows further production of IFN.

$$\frac{dUP}{dt} = -K_{IV} * [V] * [UP] - \left(\frac{-K_{IFN\ on}}{1+\left(\frac{[IFN]}{EC50}\right)^2} + K_{IFN\ on}\right) * [UP] + K_{IFN\ off} * [PP]; \quad (1)$$

$$\frac{dIP}{dt} = K_{IV} * [V] * [UP] - \left(\frac{-K_{IFN\ on}}{1+\frac{[IFN]^2}{EC50}} + K_{IFN\ on}\right) * [IP] - \gamma_c + * [IP]; \quad (2)$$

$$\frac{dAP}{dt} = \left(\frac{-K_{IFN\ on}}{1+\frac{[IFN]^2}{EC50}} + K_{IFN\ on}\right) * [IP] - K_{VC} * [AP] - \gamma_c * [AP]; \quad (3)$$

$$\frac{dPP}{dt} = \left(\frac{-K_{IFN\ on}}{1+\frac{[IFN]^2}{EC50}} + K_{IFN\ on}\right) * [UP] - K_{VC} * [AP] - K_{IFN\ off} * [PP]. \quad (4)$$

$$\frac{dV}{dt} = K_{Bud\ IP} * [IP] + K_{Bud\ AP} * [AP] - K_{VI} * [V] * [UP] - \gamma_V * [V]; \quad (5)$$

$$\frac{dIFN}{dt} = K_{IFN1} * [IP] + K_{IFN2.1} * [AP] - K_{IFN2.2} * [PP] - \gamma_{IFN} * IFN - K_f * [DR] * [IFN] - K_r * [DR - IFN]; \quad (6)$$

$$\frac{dDR}{dt} = K_{DR\_IP} * [IP] + K_{DR_{AP}} * [AP] - \gamma_{DR} * [DR] * [IFN] - K_r * [DR] * [IFN]; + K_R * [DR - IFN]; \quad (7)$$

$$\frac{dDR-IFN}{dt} = K_f * [DR] * [IFN] - K_r * [DR - IFN]. \quad (8)$$

A set of four mathematical equations describing the transition between the four different populations: Uninfected Population, UP (1) , Infected Population, IP (2), Activated Population, AP (3) and Protected Population, PP (4).
A set of four mathematical equations describing the concentration of the four different substances present in the media during treatment: virus, V (5), interferon, IFN (6), decoy receptor, DR (7) and DR-IFN complex, DR-IFN (8).

→ Approach to the sensitivity analysis: Latin hypercube sampling method will be used to sample parameters

Results

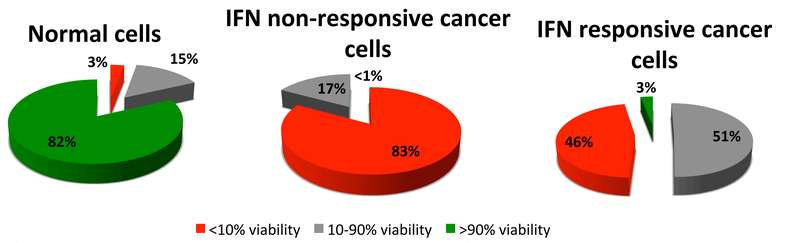


Figure 4: Δ51+IDE treatment for 72h in normal cells (left), IFN non-responsive cancer cells (center) and IFN responsive cancer cells (right). A Mont Carlo sampling method is used to generate the probability distribution of the viable population following treatment[1].

→ After treating cells with the virus, most normal cells survived (green) and both types of cancer cells were greatly affected (red).

Conclusions

→ The proposed phenomenological model shows encouraging results. It has the best efficacy and specificity to cancer cells compared to other validated models.
→ The viral efficacy and specificity is not perfect as there is room for improvement. The model is not yet able to propose a virus suitable for clinical trials
→ Sensitivity analysis is work in progress

Impacts
→ This has a significant importance in the field of cancer therapeutics since cancer is today's leading cause of death in Canadian population.

→ Results obtained from this project will help conduct further feasible experiments to test the model predictions.

→ Even if no therapeutic strategy is identified, this research project will nonetheless improve the understanding of cause-effect relationships and of the experimentally-validated model of OV dynamics.

Future Work

→ Improve the phenomenological model

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[1]Biomedical Sciences Program, [2]Ottawa institute of Systems Biology, [3]Department of Cellular and Molecular Medicine and [4]Department of Physics, University of Ottawa, Jiran101@uottawa.ca