# Modeling of tumor growth and treatment with oncolytic viruses

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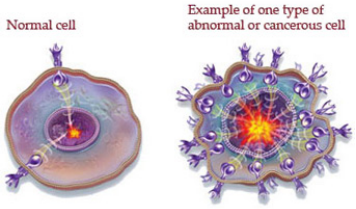
# Cancer

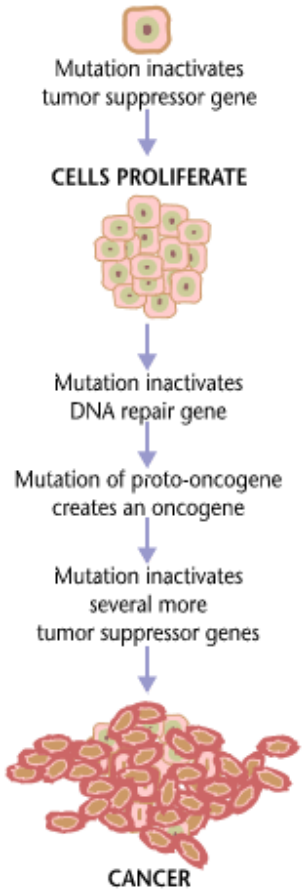
- About 14 million new cases of cancer are diagnosed every year worldwide.
- Cancer is responsible for $\sim$8 million deaths every year worldwide.
- The estimated cost of cancer is $1.16 trillion worldwide.
- Research is needed to help understand how cancer develops and how to best treat different types of cancers.

# Cancer Primer

- Cancer is a family of diseases, with each type of cancer having its own unique characteristics.
- Cancer is caused by a mutation that leads to abnormal cell proliferation.

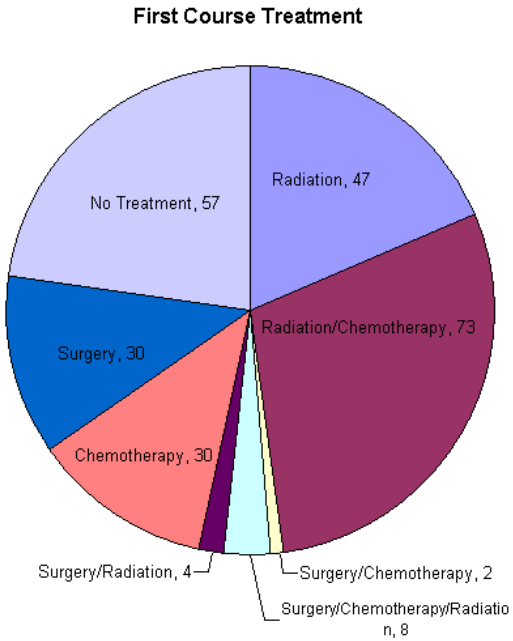



- The uncontrolled proliferation and lack of cell death allows the abnormal cells to infiltrate healthy orgrans.



# Cancer Treatment

- Current standard treatments include surgery, radiation, and chemotherapy.
- These treatments have serious and sometimes debilitating side effects.
- New treatment modalities aim to reduce side effects and include immunotherapy, oncolytic viruses, and gene therapy.



# Physics and Biology?

- Physicists build mathematical models to understand and predict the behaviour of a system.
- Physicists find connections between vastly different systems.
- Mathematical modeling of non-biological systems has led to the modern, technology-based society.
- Application of these physics techniques can help us understand biological systems.

# Mathematical Modeling of Cancer

- Mathematical models can help us understand the processes underlying cancer growth and treatment.
- Models can be used to help determine optimal doses and treatment regimens.
- Models can be used to study and optimize combination therapy.
- This talk will focus on ODE models and their use in modeling tumor growth and treatment with oncolytic viruses.

# Modeling Tumor Growth

Several ODE models of tumor growth have been proposed and are used to model tumor growth.

Exponential: $\dot{V} = \lambda V$

Mendelsohn: $\dot{V} = \lambda V^a$

Logistic: $\dot{V} = \lambda V (1 - bV)$

Linear: $\dot{V} = \frac{aV}{V+b}$

Surface: $\dot{V} = \frac{aV}{(V+b)^{\frac{1}{3}}}$

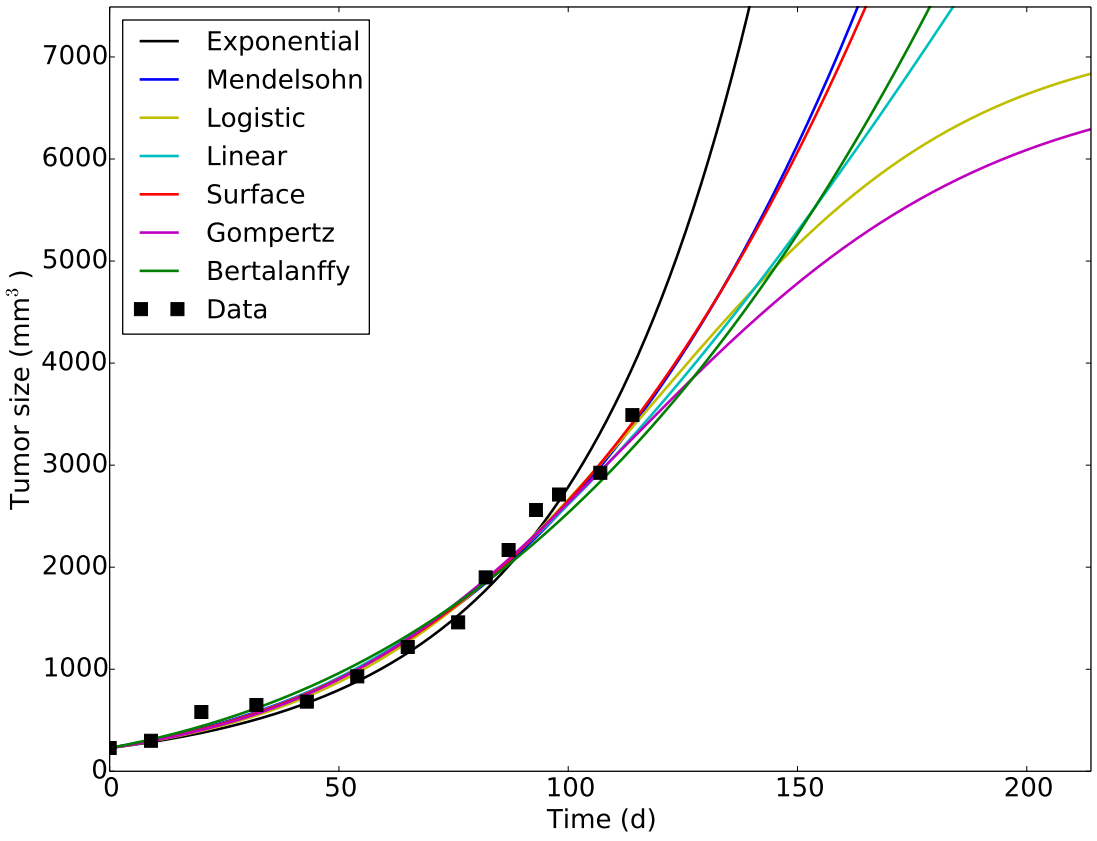
Gompertz: $\dot{V} = aV \ln\left(\frac{b}{V+c}\right)$

Von Bertalanffy: $\dot{V} = aV^{\frac{2}{3}} - bV$

# Choosing the Right Model

- There is little guidance on how to choose the best growth model.
- Is there a model that best describes most types of cancer?
- Should growth models be different for in vivo vs. in vitro studies?
- Do different types of cancer need different models?

# Why Model Choice Matters




Data from Worschech et al, BMC Genomics (2009)

We need to accurately predict growth in order to accurately assess treatment efficacy.

# Methods

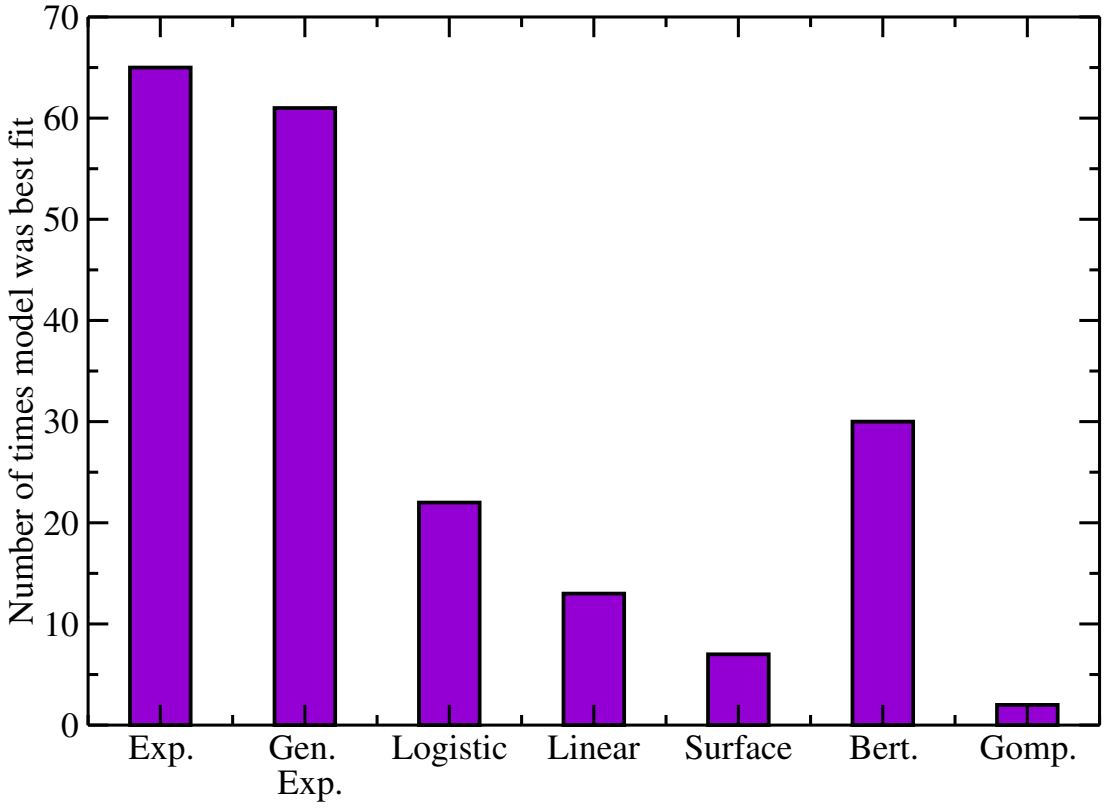
- Search literature for experimental data of tumor growth.
- Fit models to data using least-square fitting.
- Use Akaike's information criterion ($\mathrm{AIC_C}$) to determine which model best explains the data

$$\mathrm{AIC_C} = n \ln\left(\frac{SSR}{n}\right) + \frac{2(K+1)n}{n-K-2},$$

$n$ — number of data points
$K$ — number of parameters
$SSR$ — sum of squared residuals

# Results

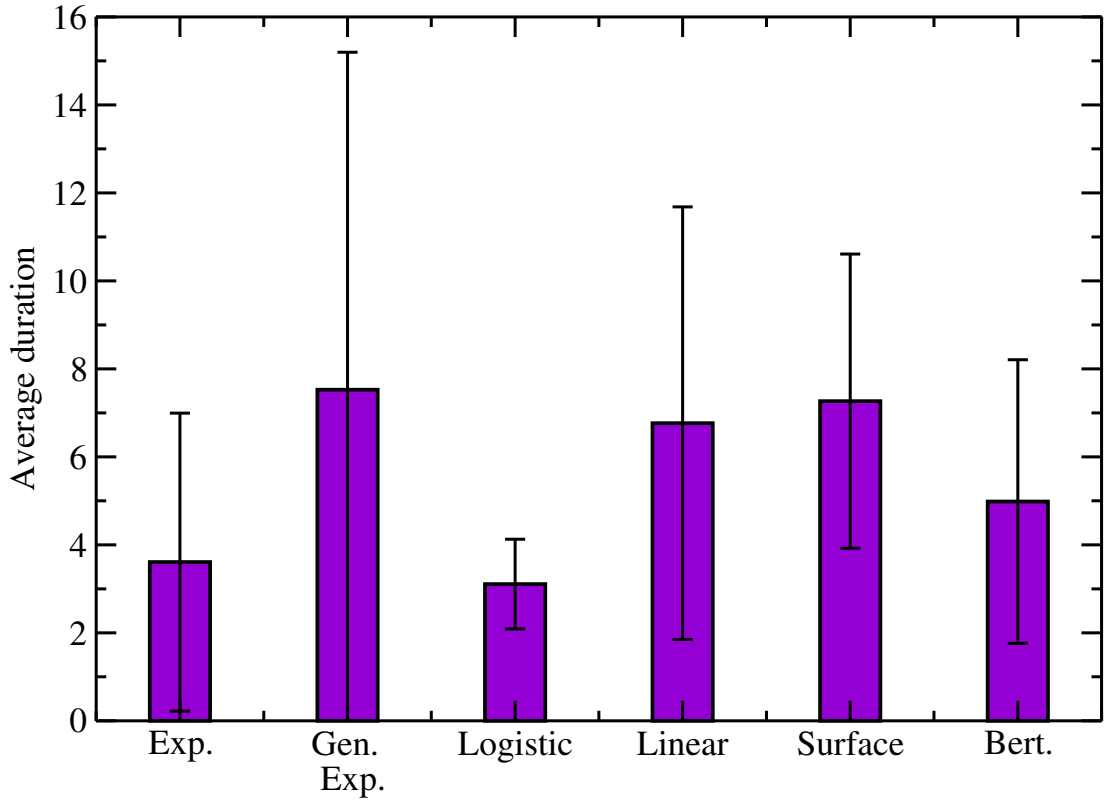
To date 204 data sets have been analyzed




The exponential and generalized exponential are the most frequent best fits.

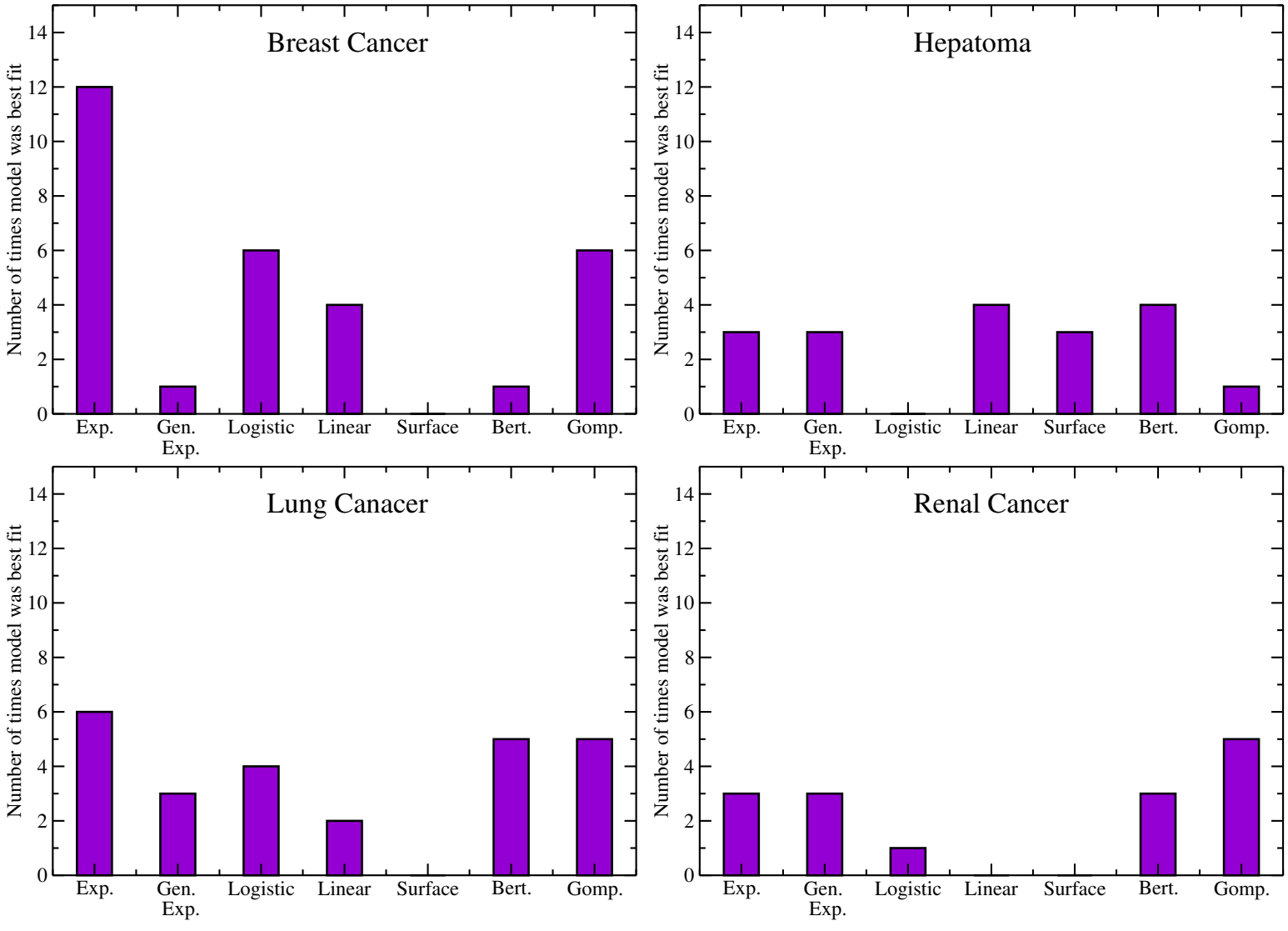
# Are the Data Sets Too Short?

It's possible that the exponential models are the best models because we are dealing with short data sets.




Data sets best fit by exponential models are not of shorter duration than the others.

# Results by Strain



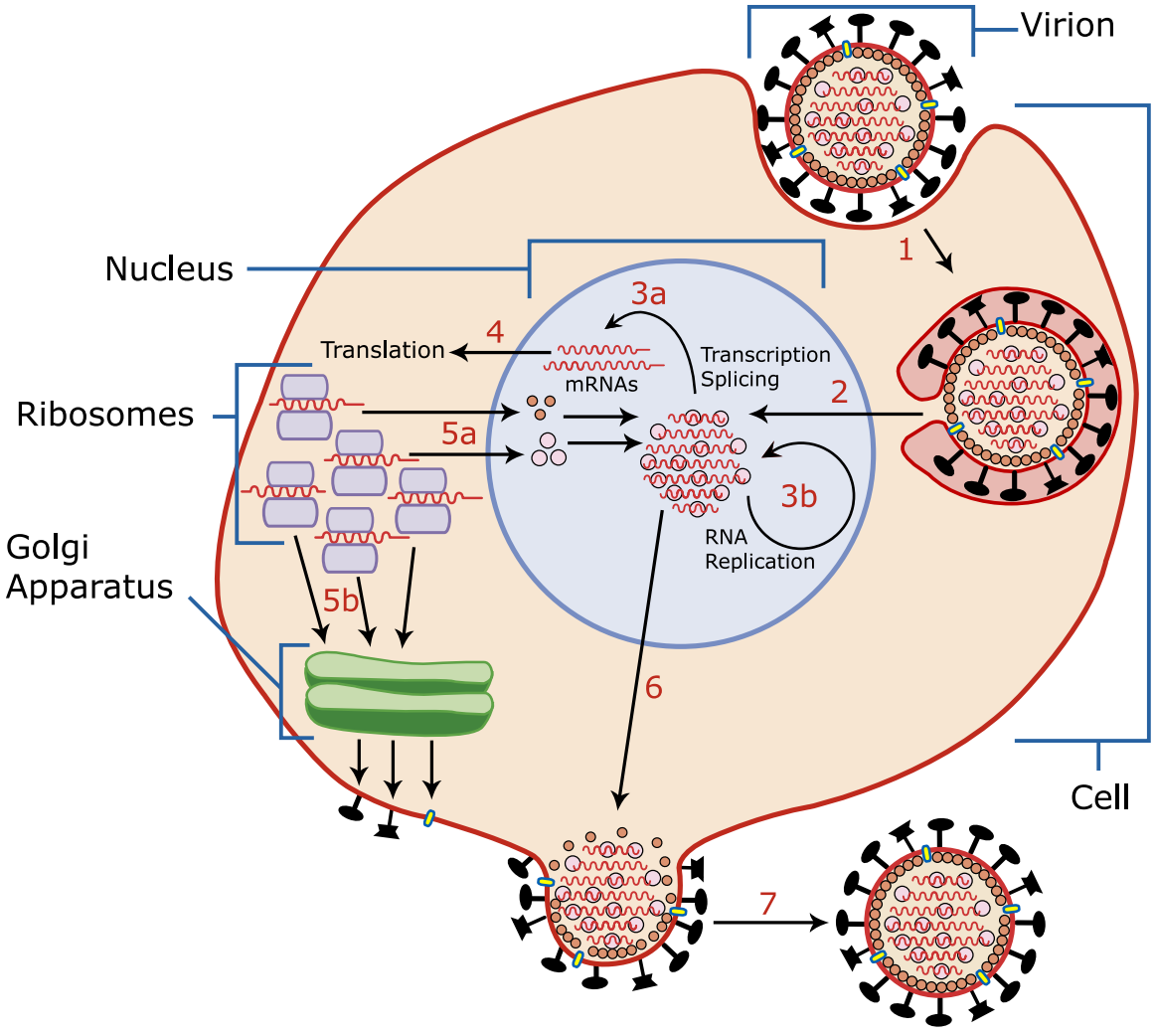
# Summary

- Exponential and generalized exponential models are most frequent best fits.
- This does not appear to be because the data is not collected over a long enough time span.
- There is not yet enough data to determine whether choice of model should depend on type of cancer.

# Oncolytic Virus Treatment

- Ability of certain viruses to destroy tumor cells and effect cancer remission is well known, with reports dating back more than 100 years
- Focus of significant research in 1950s, but by late 1960s interest declined
- By the 1990s, improved biotechnology and the potential for gene therapy led to renewed interest in oncolytic viruses
- A number of clinical trials are currently underway
- Oncolytic virus therapy currently approved and in use in China and Latvia
  - China - Oncorine (modified H101 adenovirus) for head and neck cancer
  - Latvia - RIGVIR (ECHO-7 enterovirus) for several types of cancer

# Viral Replication Cycle

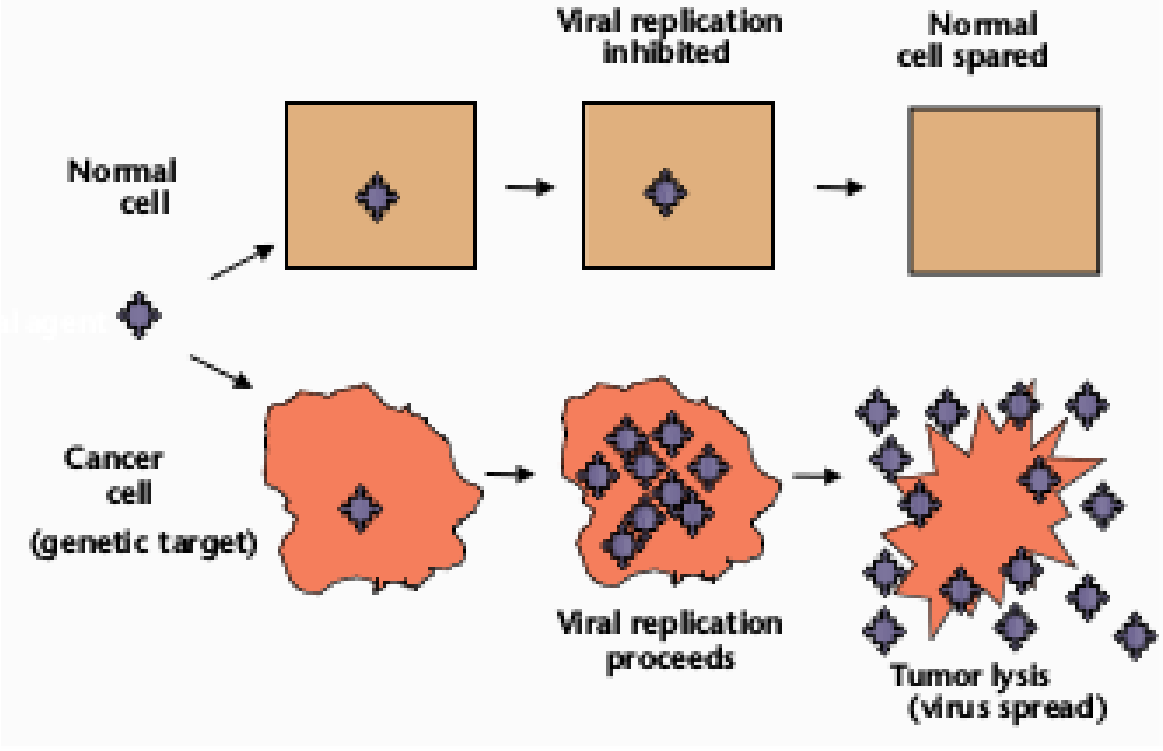


# Oncolytic Viruses

- Many viruses can kill tumor cells, but we would also like them to NOT kill healthy cells.
- Many viruses have a natural preference for cancer cells, although the mechanism varies:
  - Viruses can more easily bind to receptors on cancer cells than receptors on healthy cells.
  - Viruses can replicate more efficiently in cancer cells than in healthy cells.
  - Viruses can kill cancer cells more effectively than healthy cells.
  - Viruses can stimulate the immune response to attack cancer cells due to a lack of IFN response in tumors.

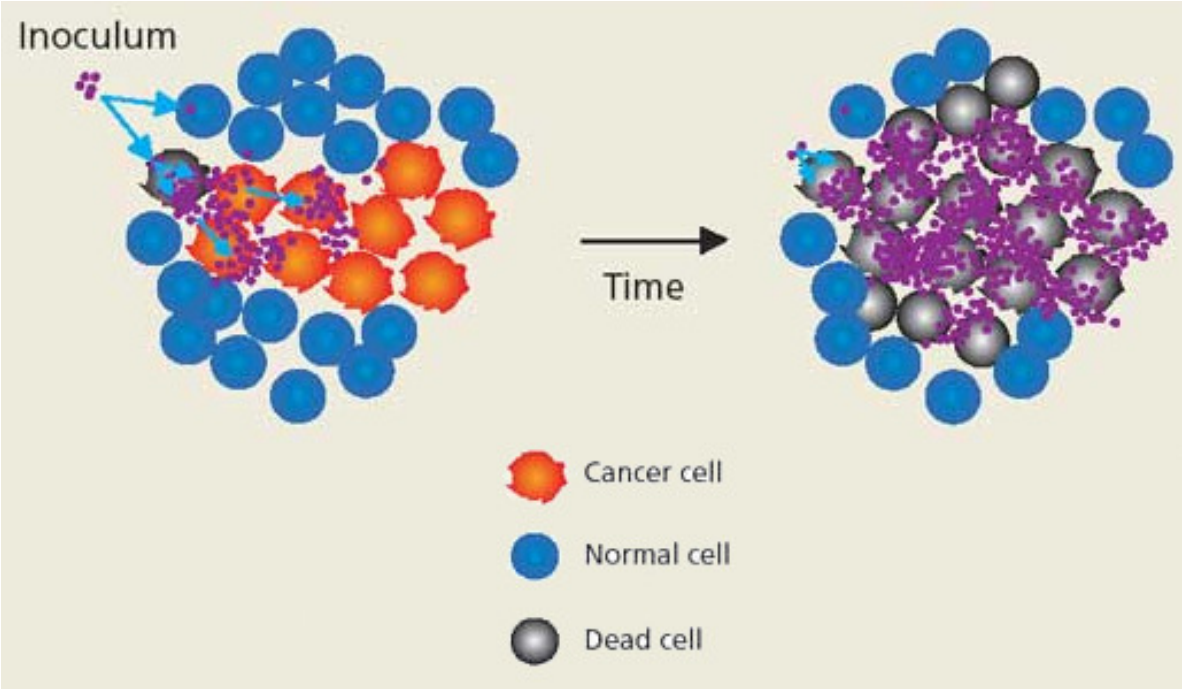
# Replication Selective Virotherapy

Assumes no virus replication in normal cells




Reproduced from Kirn D *et al.* (Nat. Med., 2001)

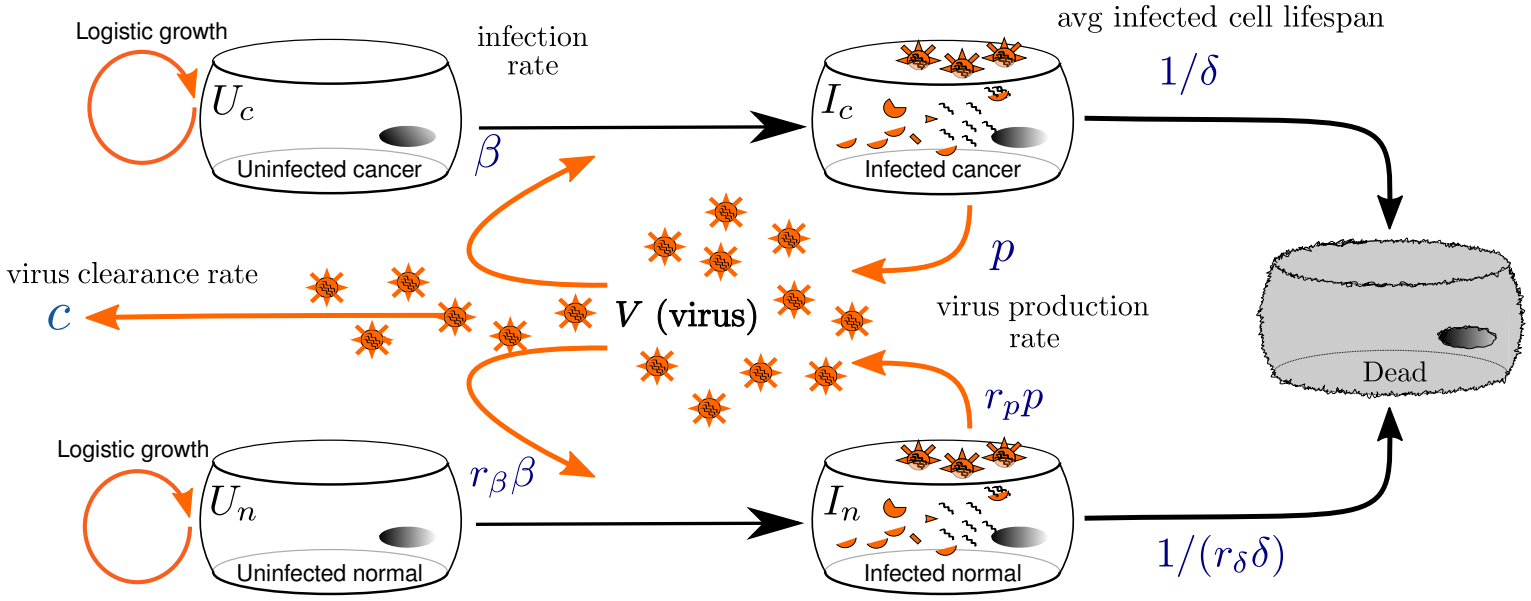
# Reality




Modified from Aguilar-Cordova, E. (Nat. Biotech., 2003)

In reality, we cannot completely prevent viruses from replicating in normal cells.

# Two Cell Model




- Previous OV models have typically focused on effects upon cancer cells and tumor size reduction.
- Do not address potential infection of surrounding normal cells and resulting changes in virus population.

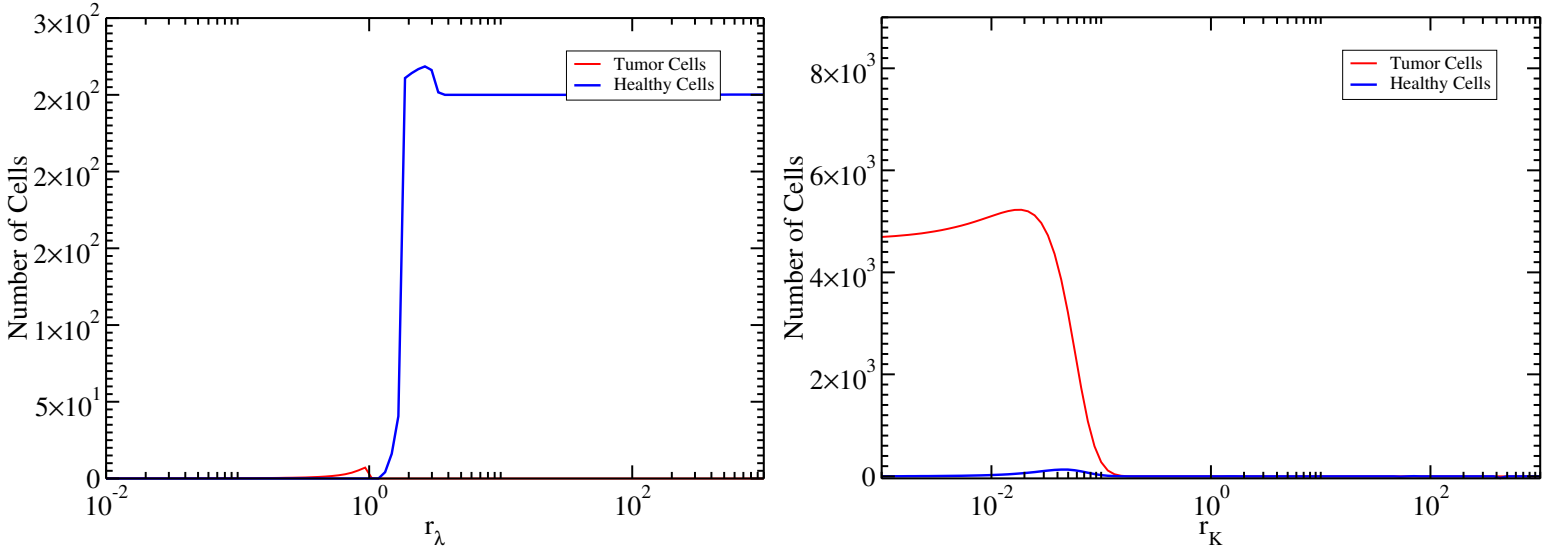
# Model Equations

$$
\begin{aligned}
\frac{\mathrm{d}U_c}{\mathrm{d}t} &= \lambda U_c \left(1 - \frac{U_c + I_c}{K}\right) - \beta U_c V \\
\frac{\mathrm{d}I_c}{\mathrm{d}t} &= \beta U_c V - \delta I_c \\
\frac{\mathrm{d}U_n}{\mathrm{d}t} &= r_\lambda \lambda U_n \left(1 - \frac{U_n + I_n}{r_K K}\right) - r_\beta \beta U_n V \\
\frac{\mathrm{d}I_n}{\mathrm{d}t} &= r_\beta \beta U_n V - r_\delta \delta I_n \\
\frac{\mathrm{d}V}{\mathrm{d}t} &= p(r_p I_n + I_c) - cV
\end{aligned}
$$

- There is no explicit immune response.
- We are currently using logistic growth for both cancer and healthy cells.
- ODEs assume that cancer and healthy cells are well-mixed, i.e. no spatial structure.

# No Cell Tropism

Are differences in cell growth enough to eradicate the tumor?




- The tumor will be eradicated and healthy cells preserved if $r_\lambda > 1$. Unfortunately tumors typically grow faster than healthy cells.
- Changes in $r_K$ do not lead to cure.

# Possible Outcomes

We have the following possible steady states:

$$\begin{aligned} U_c &= I_c = U_n = I_n = V = 0 \\ U_c &= I_c = I_n = V = 0, U_n = r_K K \\ I_c &= U_n = I_n = V = 0, U_c = K \\ I_c &= I_n = V = 0, U_c = K, U_n = r_K K \end{aligned}$$

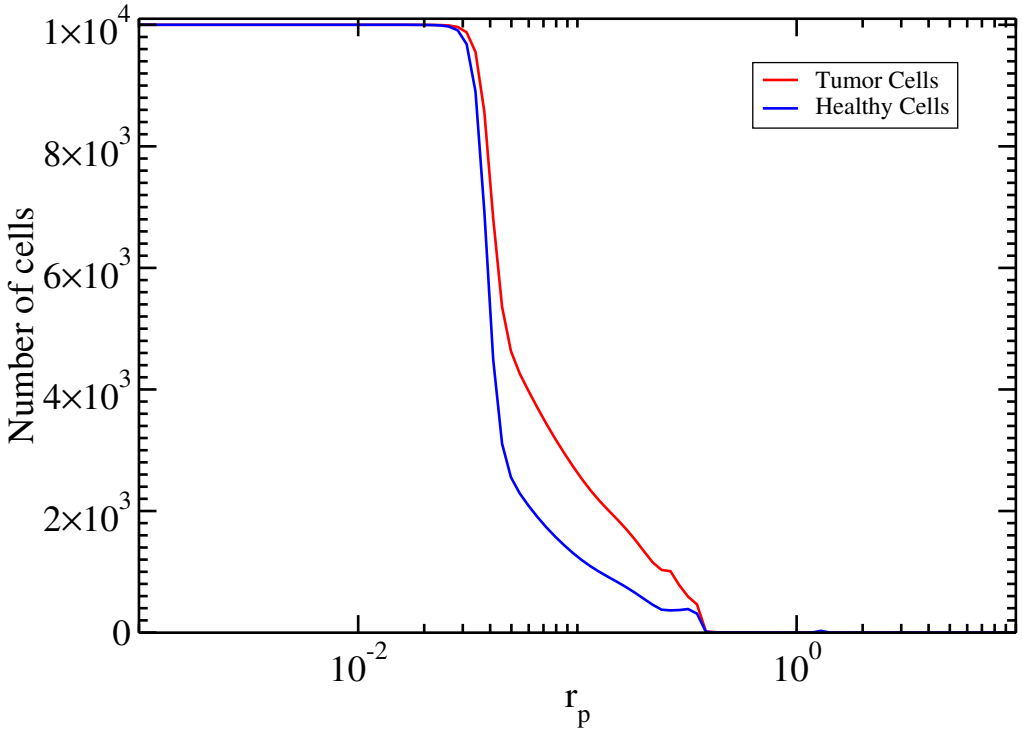
where the steady states correspond to

- Everything dies.
- The cancer is cured.
- Healthy cells die, but the tumor remains.
- Both healthy cells and tumor are unaffected by virus.

# Goals

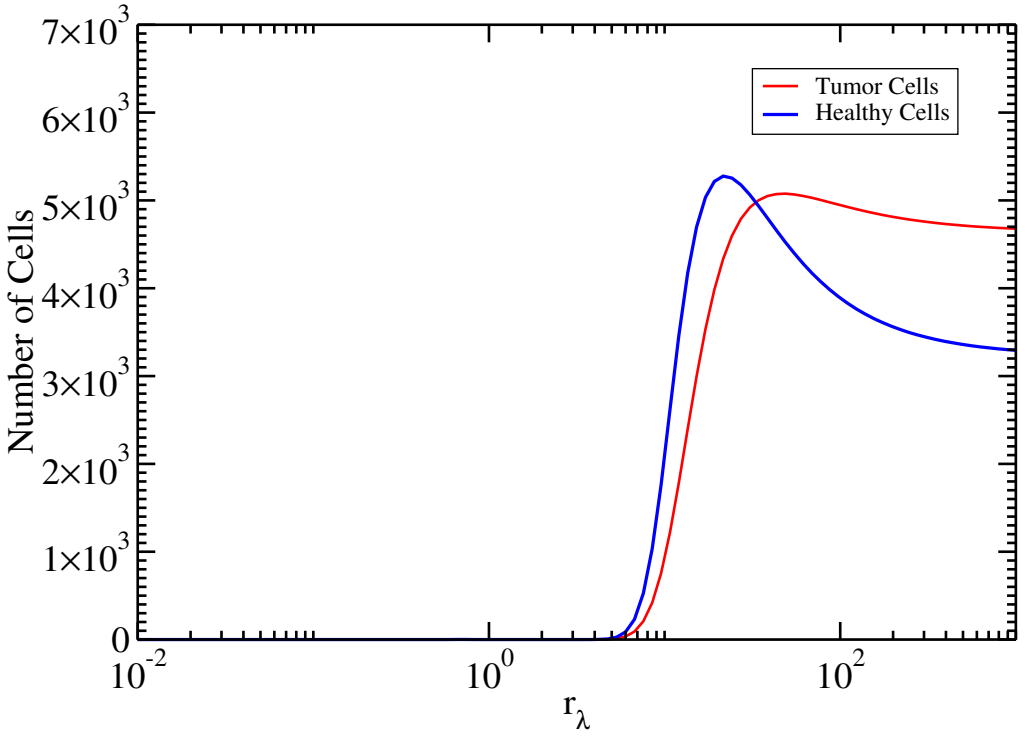
- We want to find parameter ranges corresponding to the second steady state (cancer is cured).
- We examine the different mechanisms of viral preference to see if a particular mechanism is preferable.
- We varied $r_p, r_\delta, r_\beta$ along with $r_\lambda$ to find which parameter values eradicate cancer cells but still preserve normal cells.

# Difference in Viral Production



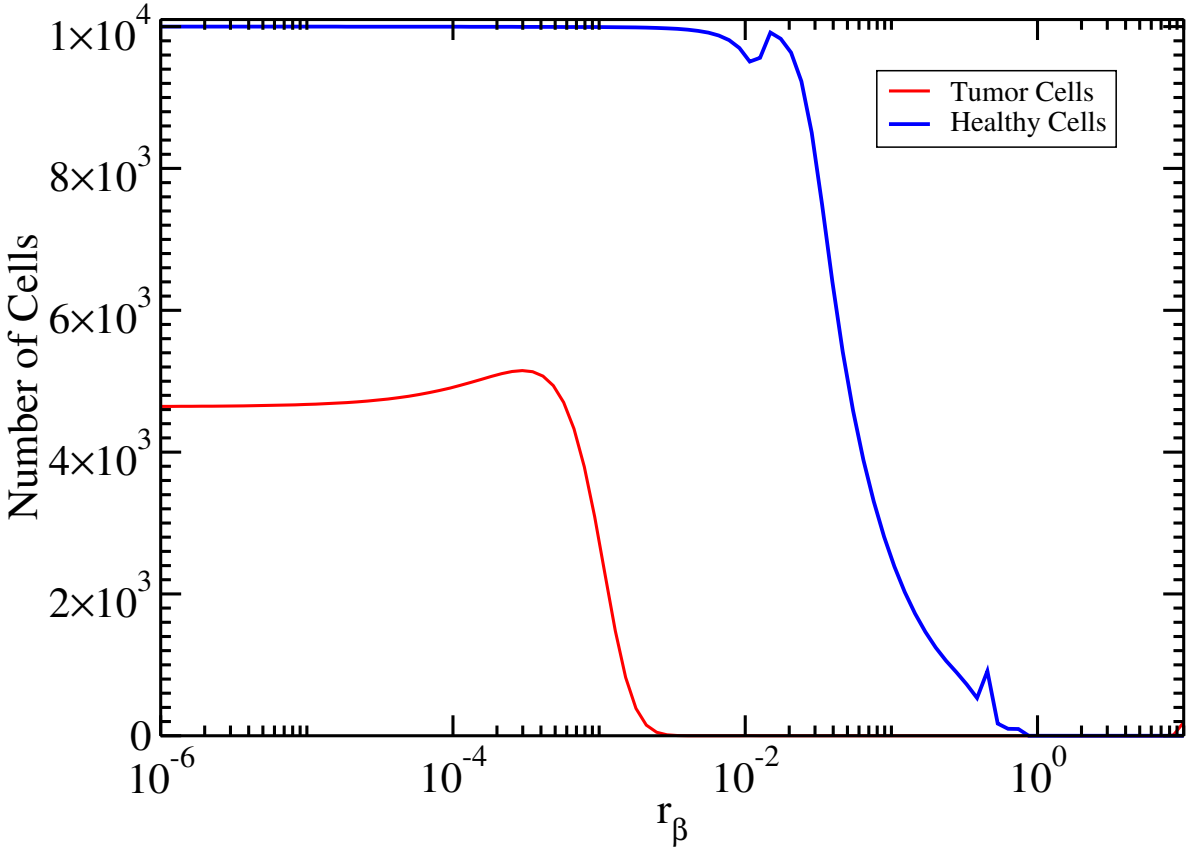

- Differences in viral production will not lead to a cure.
- Either both cell populations remain or both cell populations die.

# Difference in Viral Kill Rate




- Differences in viral kill rate do not lead to a cure.
- Again either both cell populations survive or both die.

# Difference in Viral Infection Rate




- At low values of $r_\beta$, we see a small controlled tumor with no healthy cell damage.
- For a range of values near $10^{-2}$, the tumor disappears, but healthy cells remain.

# Conclusions

- Our model suggests that only viruses that preferentially infect cancer cells will be able to cure the cancer.
- Differences in production rate or kill rate alone will not be able to eradicate the tumor.
- There is a small range of infection rates that will lead to eradication of the tumor.
- Large differences in infection rate lead to a controlled tumor.

# Future Work

- Determine guidelines for choosing ODE tumor growth models.
- Investigate how growth model choice affects oncolytic virus treatment predictions.
- Develop a model that includes spatial effects to see if tumor structure can help limit spread of virus to neighboring cells.
- Incorporate immune response to study the last mechanism of cell preference.

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