Mathematical Assessment of Oncolytic Virotherapy

Ilyssa Summer

June 9, 2015

Cancer Therapies

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Cancer Therapies

Cancer is a complex collection of diseases involving unregulated cell growth. Common treatments include:

- Surgery
- Radiation therapy
- Chemotherapy
- Immunotherapy
- Targeted Therapy

Oncolytic Virus

- "Anti-cancer" Oncolytic virus is type of Virotherapy
  - Viral gene therapy
  - Viral Immunotherapy
- Virus that selectively infect and kill cancer cells

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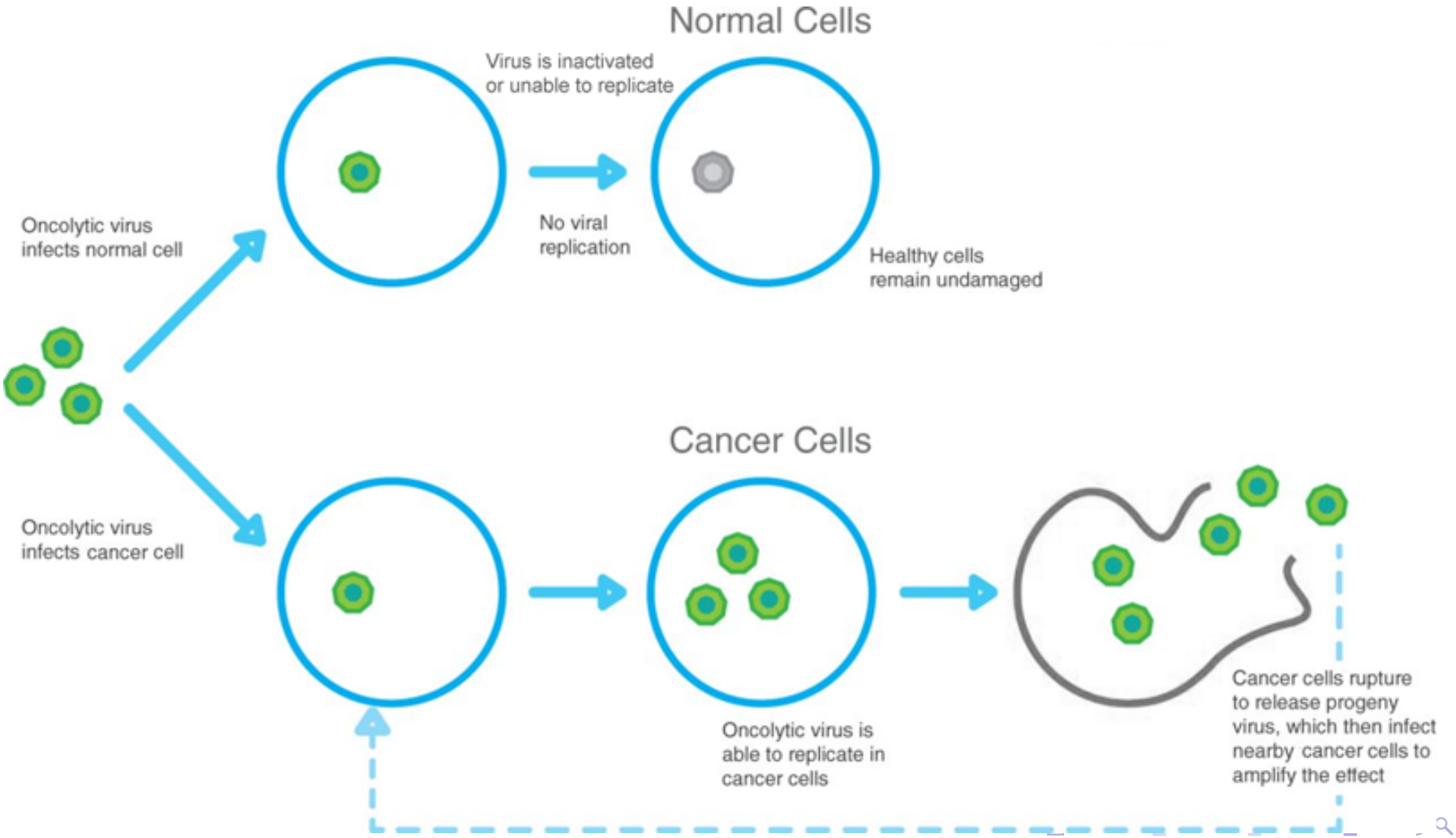
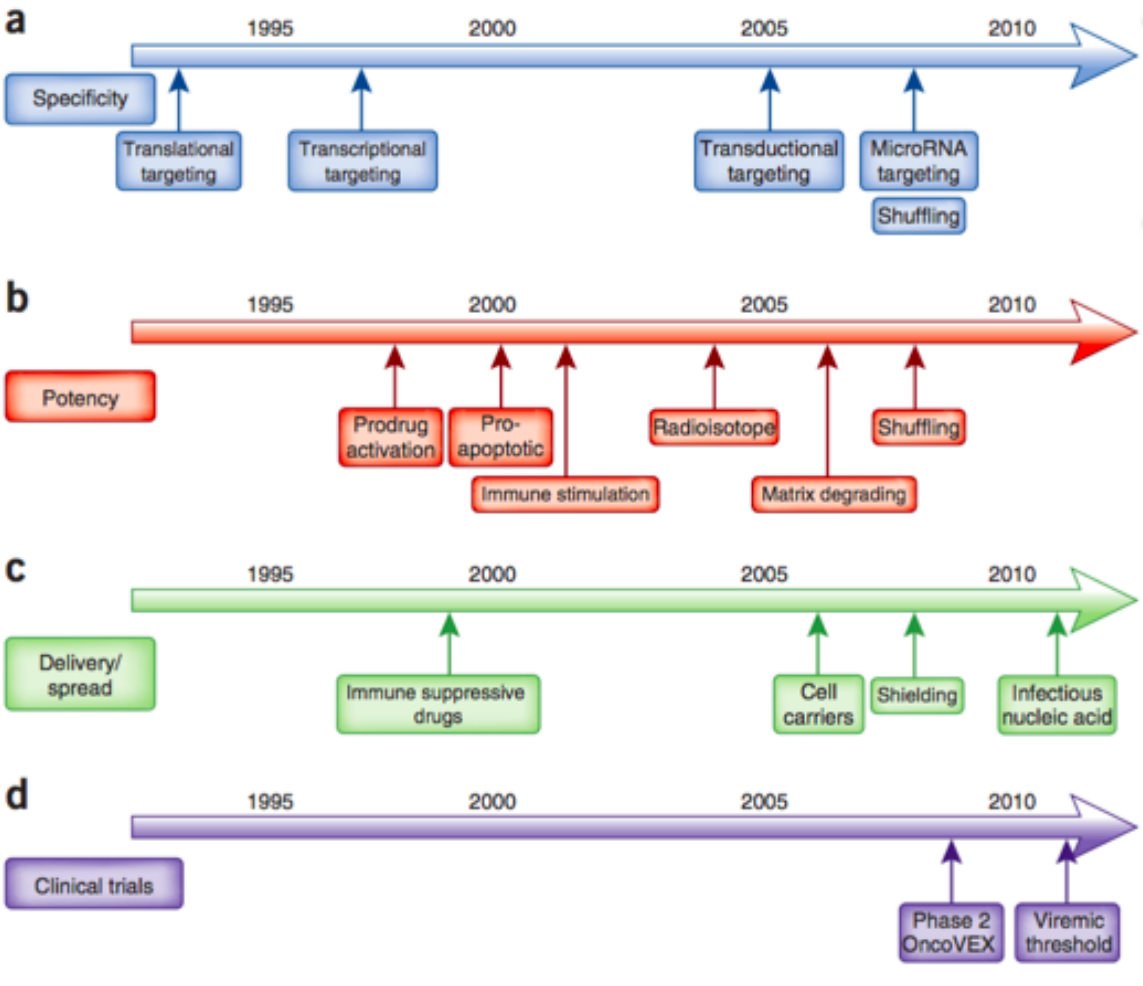


Milestones in Oncolytic Virotherapy



Viral Specificity-
Translational(1991), transcriptional (1997) and transductional (2005) targeting via engineering, and DNA shuffling (2008)

Potency-
Prodrug activation (1998), Introduction of proapoptotic genes (2000), immune stimulation (2001), inclusion of radioisotopic(2004), matrix degrading proteins(2006), DNA shuffling(2008)

Delivery and spread-
Immunosupressibve drugs(1999), introduction to cell carriers(2006), shielding approaches (2008), delivery of oncolyitc porconavirus (2011).

Clinical Trials-
Phase 2 OncoVEX(2009).
Viremic threshold(2011).

Russell et al, 2012

Clinically tested Oncolytic Viruses

- adenovirus

Clinically tested Oncolytic Viruses

- adenovirus
- reovirus

Clinically tested Oncolytic Viruses

- adenovirus
- reovirus
- measles

Clinically tested Oncolytic Viruses

- adenovirus
- reovirus
- measles
- herpes simplex (HSV)

Clinically tested Oncolytic Viruses

- adenovirus
- reovirus
- measles
- herpes simplex (HSV)
- Newcastle disease virus

Recent Experiments

Modified herpes virus therapy shows promise in melanoma

The Pharmaceutical Journal | , 5 JUN 2015 | By Joanna Lyford

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***NATURE REVIEWS DRUG DISCOVERY* | NEWS AND ANALYSIS**

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Lotte M.E. Berghauser Pont, Anne Kleijn, Jenneke J. Kloezeman, Wouter van den Bossche, Johanna K. Kaufmann, Jeroen de Vrij, Sieger Leenstra, Clemens M.F. Dirven, Martine L.M. Lamfers

Published: May 18, 2015 • DOI: 10.1371/journal.pone.0127058

Viruses as Antitumor Weapons

$$
\begin{aligned}
\frac{dx}{dt} &= rx\left(1-\frac{x+y}{K}\right)-dx-\beta xy \qquad (1)\\
\frac{dy}{dt} &= \beta xy+sy\left(1-\frac{x+y}{K}\right)-ay-pyz\\
\frac{dz}{dt} &= cyz-bz
\end{aligned}
$$

Wodarz, 2001

- x represents the uninfected tumor cells .
- y represents the infected tumor cells by virus.
- z represents the CTL cells

Oncolytic Viral Model

$$
\begin{aligned}
\frac{dx}{dt} &= rx\left(1-\frac{x+y}{K}\right)-\mu x-\beta xv \\
\frac{dy}{dt} &= \beta xv+sy\left(1-\frac{x+y}{K}\right)-\alpha y-\rho yz \\
\frac{dz}{dt} &= \sigma yz-\phi z \\
\frac{dv}{dt} &= N\alpha y-\xi v
\end{aligned}
\tag{2}
$$

- x represents the Uninfected Tumor cells .
- y represents the Infected Tumor cells by virus.
- z represents the CD8 T cells
- v represents the Viral Load

Table of parameters

Variable/Parameter	Description
x	Uninfected tumor cells
y	Infected tumor cells
z	CTL cells
v	Free virus population
r	Uninfected tumor cell growth rate
μ	Uninfected tumor cell death rate
β	Viral infectious rate
s	Infected tumor cell growth rate
α	Lysing rate*
K	Tumor carrying capacity
ρ	Death from CTL cells
σ	CTL response rate
ϕ	CTL death rate
N	Burst size of virions
ξ	viral decay rate

*rate of cytotoxic cell death and viral replication

Equilibrium

$\mathbf{E_0(0,0,0,0)}$	Complete elimination of tumor .
$\mathbf{E_1}(\frac{\mathbf{K(r-\mu)}}{\mathbf{r}},\mathbf{0},\mathbf{0},\mathbf{0})$	Failure of viral therapy .
$\mathbf{E_2}(\mathbf{0},\frac{\mathbf{K(s-\alpha)}}{\mathbf{s}},\mathbf{0},\frac{\mathbf{NK}\alpha\mathbf{(s-\alpha)}}{\mathbf{s}(\xi\kappa)})$	Complete infection of tumor cells.
$\mathbf{E_3}(\mathbf{0},\frac{\mathbf{b}}{\mathbf{c}},\frac{\sigma\mathbf{K(s-\alpha)-s}\phi}{\sigma\rho\mathbf{K}},\frac{\phi\mathbf{N}\alpha}{\sigma(\xi)})$	Complete viral prevalence in the tumor cell population in the presence of virus specific CTL response.
$\mathbf{E_4}(\mathbf{x_4^*},\mathbf{y_4^*},\mathbf{0},\mathbf{v_4^*})$	Coexistence of uninfected and infected tumor cells with suppressed immune system.
$\mathbf{E_5}(\mathbf{x_5^*},\mathbf{y_5^*},\mathbf{z_5^*},\mathbf{v_5^*})$	Coexistence of uninfected and infected tumor cells with presence of CTL response.

Viral infection threshold

Theorem

Let $r > \mu, s < \alpha,$. *Then the model has boundary equilibrium. The Viral Free Equilibria (VFE)* $, E_1 = (\frac{K(r-\mu)}{r}, 0, 0, 0)$, *is L.A.S if* $\alpha - \frac{s\mu(\xi)}{r(\xi)-\beta KN(r-\mu)} > 0$ *whenever* $\beta < \frac{r(\xi)}{NK(r-\mu)}$.

The Virus Free Equilibrium(VFE)

$$\boxed{\alpha > \frac{s\mu(\xi)}{r(\xi)-\beta KN(r-\mu)} \text{ when } \beta < \frac{r(\xi)}{KN(r-\mu)}.}$$

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The Virus Free Equilibrium(VFE)

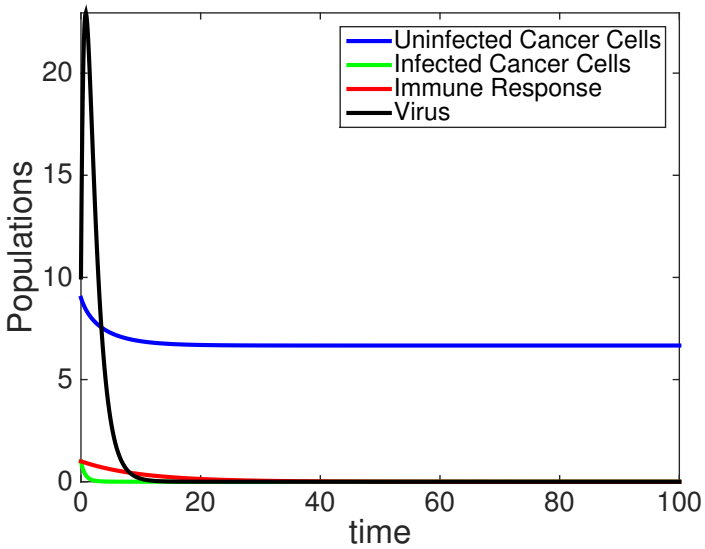
$$\boxed{\alpha > \frac{s\mu(\xi)}{r(\xi)-\beta KN(r-\mu)} \text{ when } \beta < \frac{r(\xi)}{KN(r-\mu)}.}$$

$$\boxed{R_0 = \frac{\beta N\alpha K(r-\mu)}{(\xi-\kappa)(\alpha r-\mu s)} < 1 \text{ when } \beta < \frac{r(\xi)}{NK(r-\mu)}.}$$

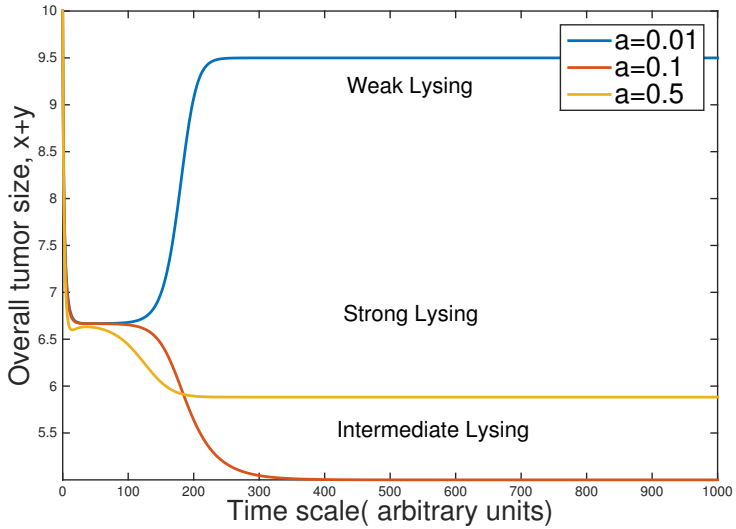
$$\text{Let } V_0 = \frac{s\mu(\xi)}{r(\xi)-\beta KN(r-\mu)} \quad \& \quad \beta_c = \frac{r(\xi)}{KN(r-\mu)}$$

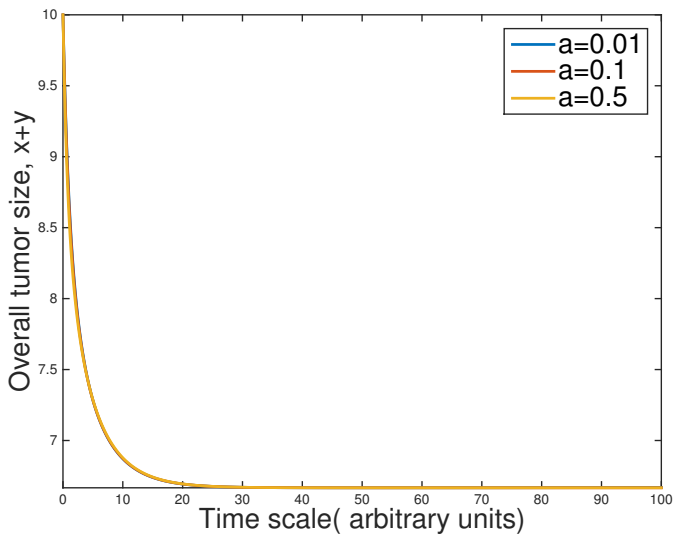
Changes in VFE

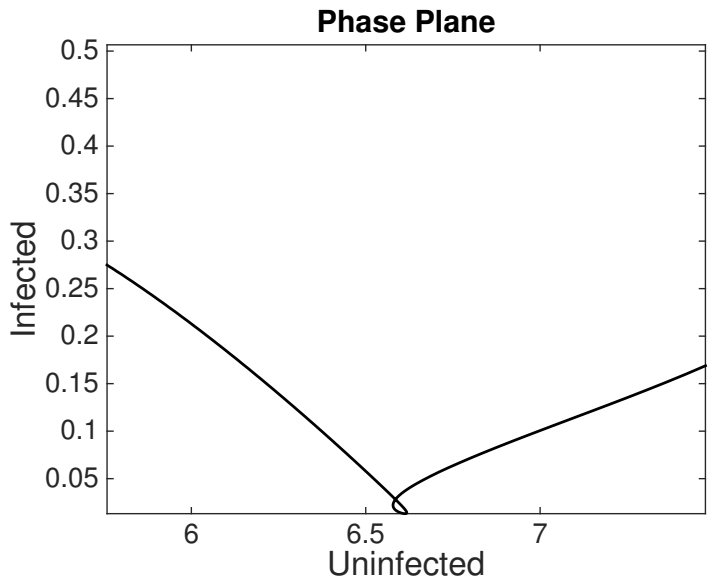
$\alpha > V_0, \beta < \beta_c$



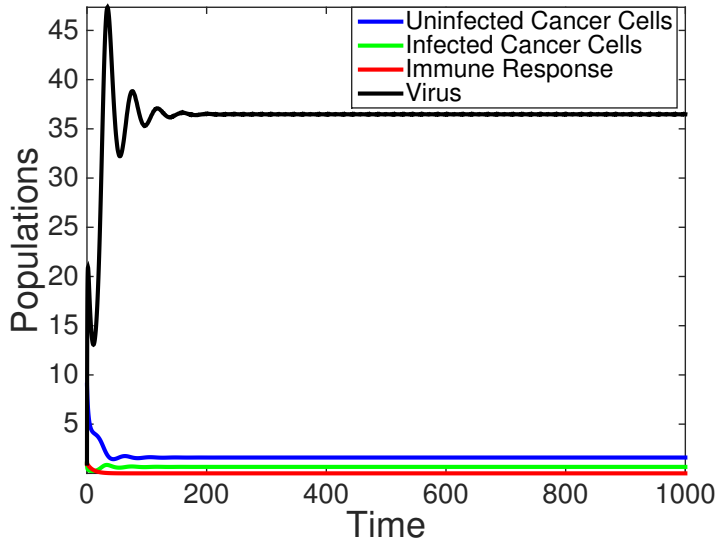
$\beta = \beta_c$

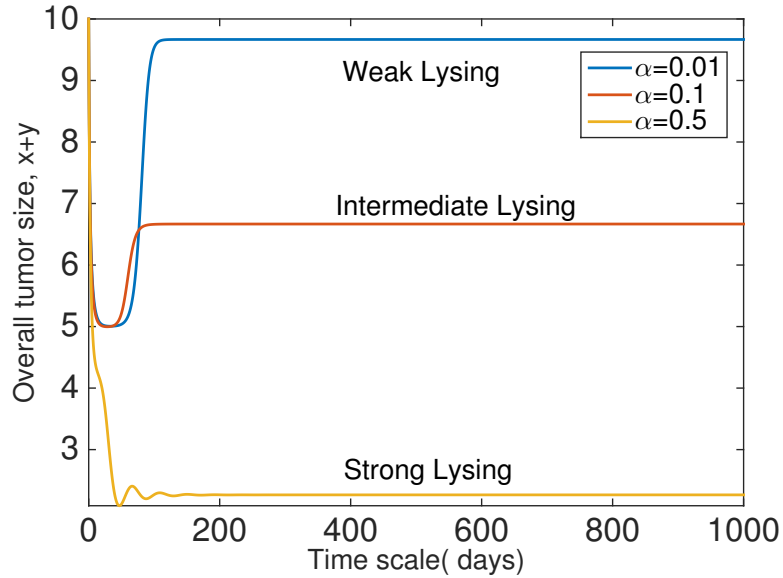


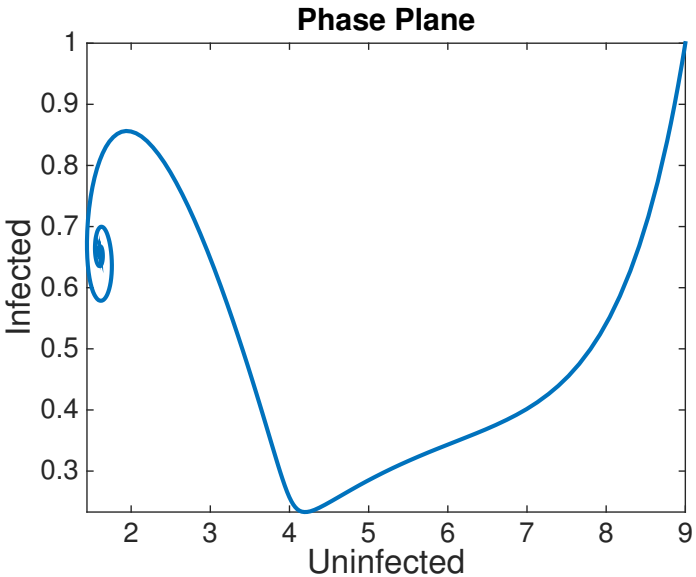




$\beta > \beta_c$


Uninfected Cancer Cells
Infected Cancer Cells
Immune Response
Virus
Populations
Time
0
200
400
600
800
1000
5
10
15
20
25
30
35
40
45


Weak Lysing
Intermediate Lysing
Strong Lysing
α=0.01
α=0.1
α=0.5
Overall tumor size, x+y
Time scale(days)
0
200
400
600
800
1000
3
4
5
6
7
8
9
10


Phase Plane
Infected
Uninfected
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
2
3
4
5
6
7
8
9

Complete Viral Prevalence

Theorem

Let $r < \mu, s > \alpha, .$ *The model has complete viral prevalence at* $E_2 = \left(0, \frac{K(s-\alpha)}{s}, 0, \frac{NK\alpha(s-\alpha)}{s(\xi)}\right)$.

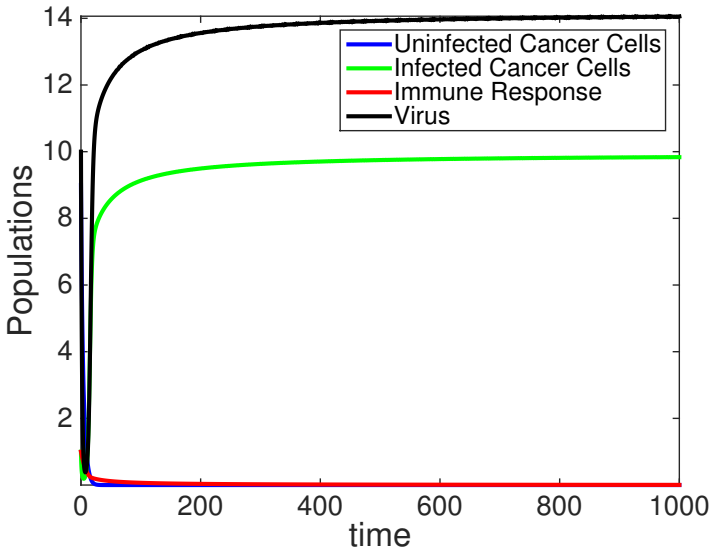
E_2 *is L.A.S whenever* $\sigma < \frac{\phi s}{K(s-\alpha)}$.

$$\boxed{\sigma < \frac{\phi s}{K(s-\alpha)}}$$

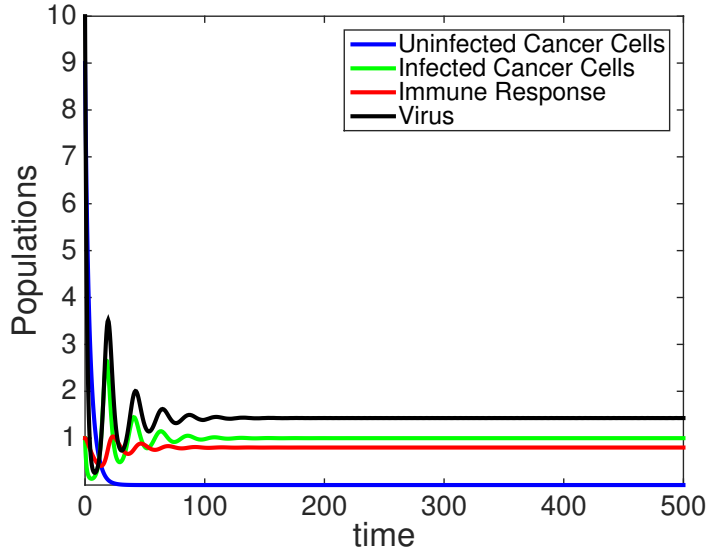
When $\sigma > \frac{\phi s}{K(s-\alpha)}$, the immune response rate is large enough to respond to the infected tumor cell population

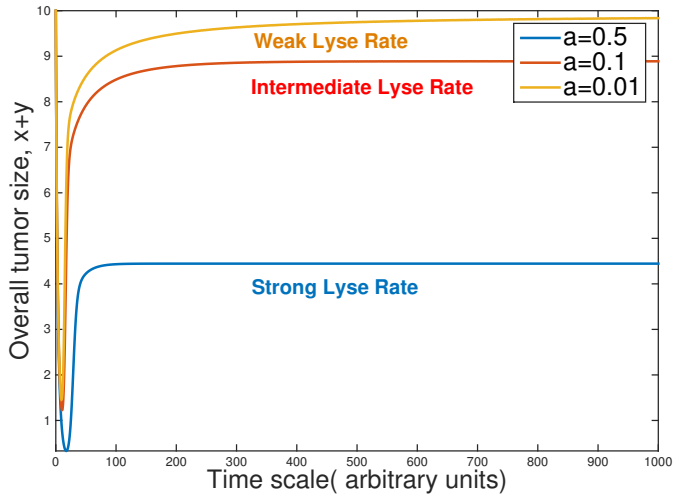
CTL response

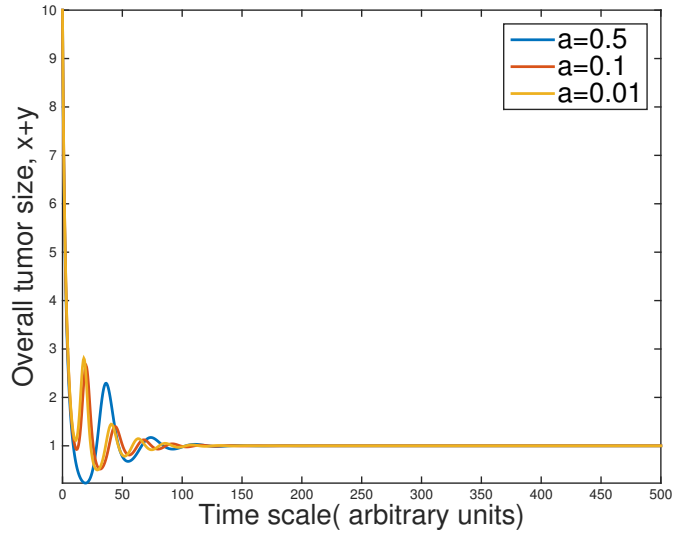
$$\sigma < \frac{\phi s}{K(s-\alpha)}$$



$$\sigma > \frac{\phi s}{K(s-\alpha)}$$







Complete Viral Prevalence in the Presence of Immune Response

Theorem

Let $s > \alpha, r < \mu, , \sigma > \frac{\phi s}{K(s-\alpha)}$. *The model has complete viral prevalence in the presence of CTL response at* $E_3 = (0, \frac{\phi}{\sigma}, \frac{\sigma K(s-\alpha) - s\phi}{\sigma \rho K}, \frac{\phi N \alpha}{\sigma(\xi)})$. E_3 *is an unstable saddle point whenever* $\sigma K[(\xi)(r-\mu)] - r\phi(\xi) - \beta K N \alpha \phi < 0$.

$$\boxed{\frac{\sigma \beta N K \alpha \phi + r\phi(\xi)}{K(\xi)(r-\mu)} < 0}$$

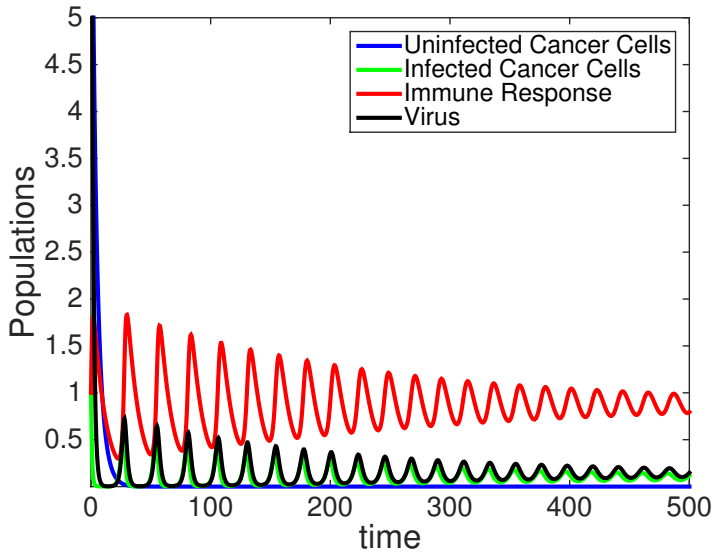
Coexistence of Uninfected and Infected Populations in Presence of Immune Response

Theorem

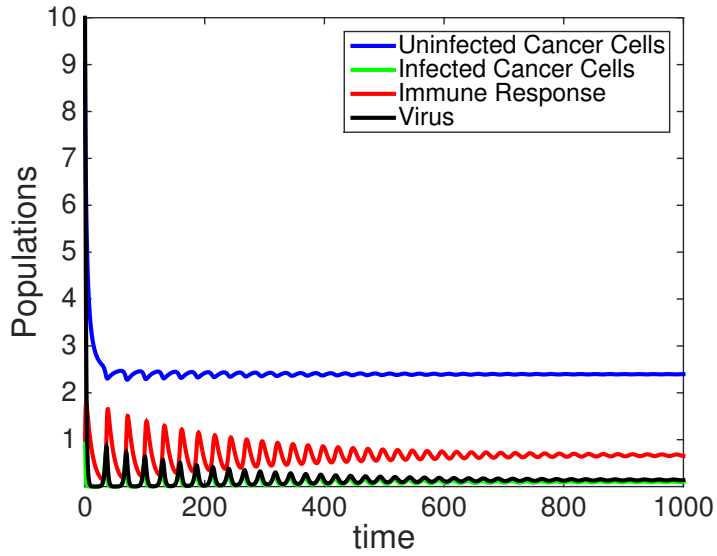
Let $s > \alpha, r > \mu, , \sigma > \frac{\phi s}{K(s-\alpha)}$. *The equilibria of the coexistence of uninfected and infection cells in the presence of CTL cells is* $E_5 = (x_5^*, y_5^*, z_5^*, v_5^*)$. *The model has an unstable point whenever* $\frac{\sigma\beta NK\alpha\phi + r\phi(\xi)}{K(\xi)(r-\mu)} > 0$.

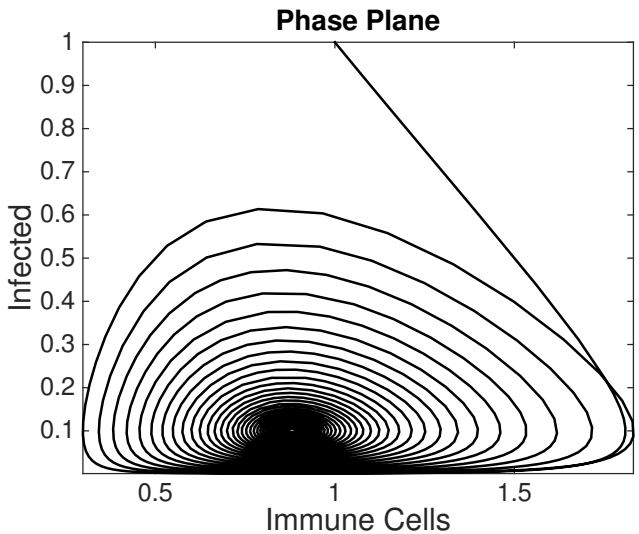
CTL response

$$\frac{\sigma\beta NK\alpha\phi + r\phi(\xi)}{K(\xi)(r-\mu)} < 0$$



$$\frac{\sigma\beta NK\alpha\phi + r\phi(\xi)}{K(\xi)(r-\mu)} > 0$$

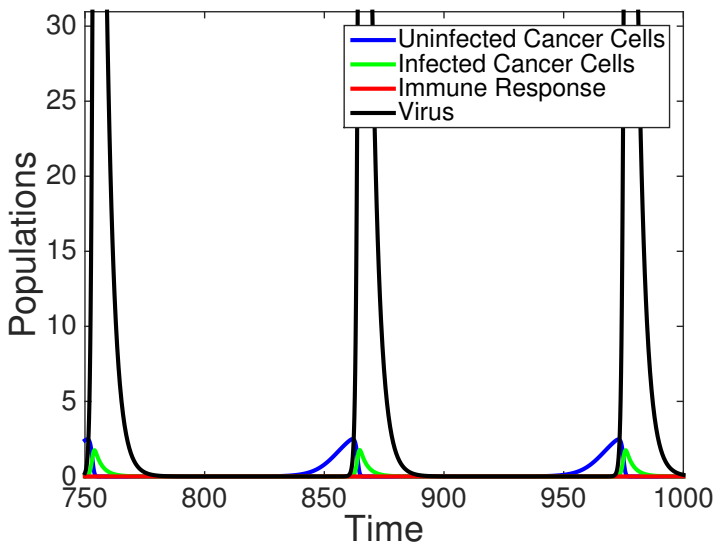


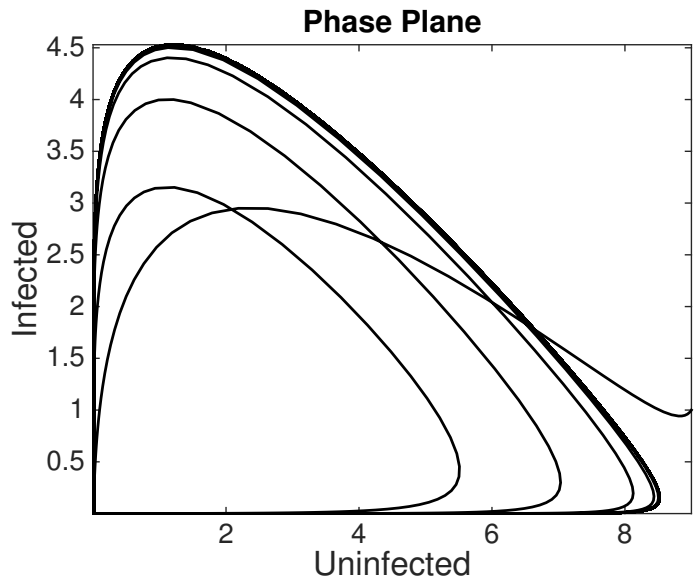


Coexistence of Uninfected and Infected Populations without Immune Response

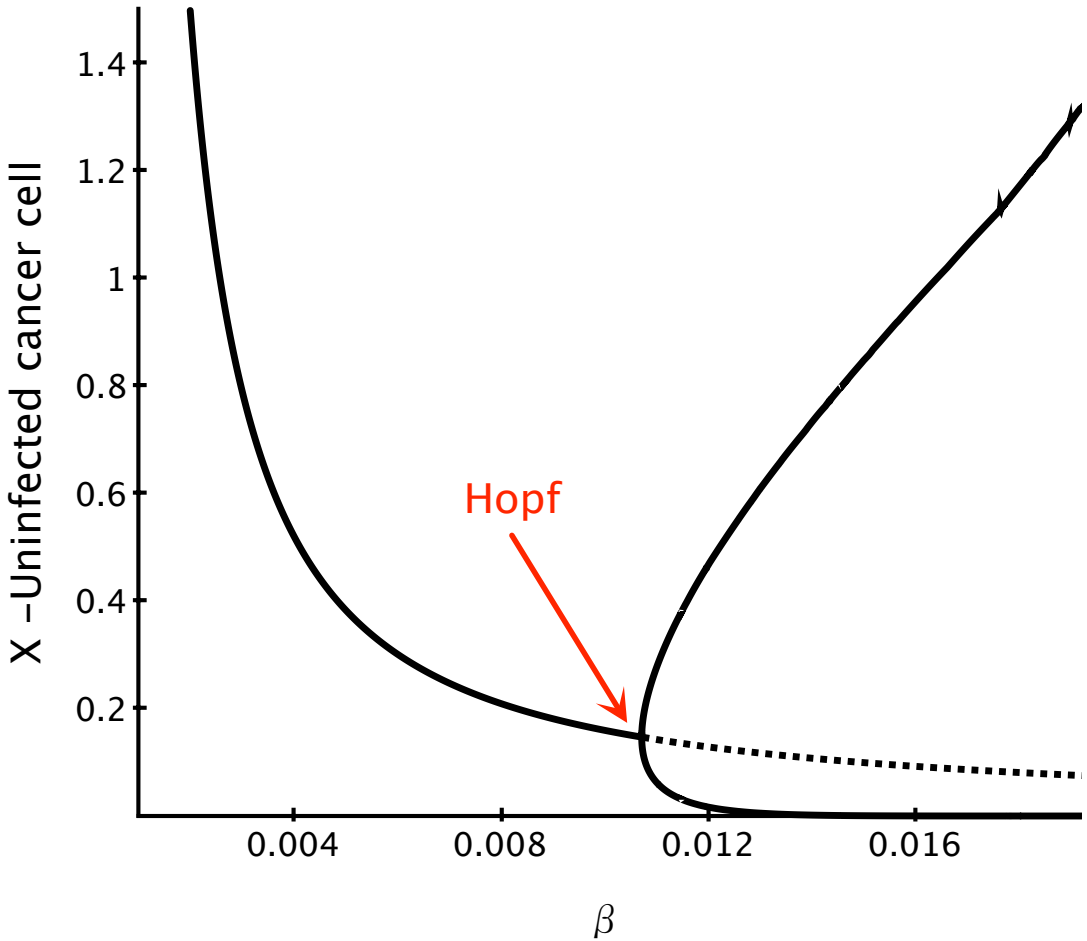
Theorem

Let $s < \alpha, r > \mu, , \beta > \beta_1, \sigma > \frac{\beta NK\alpha b + rb(\xi)}{K(\xi)(r-\mu)}$. *The equilibria of the coexistence of uninfected and infection cells in the absence of CTL cells is* $E_4 = (x_4^*, y_4^*, 0, v_4^*)$. *The model has an unstable point at* E_4 *whenever* $\sigma < \frac{\phi s}{K(s-\alpha)}$.



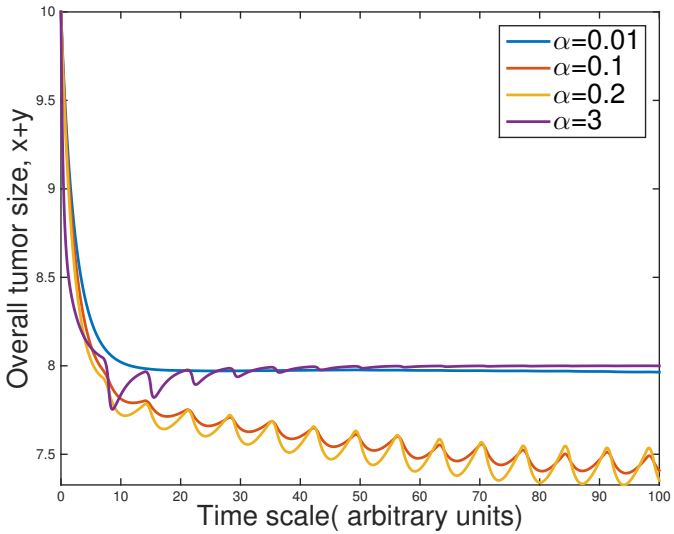


Bifurcation at E_4

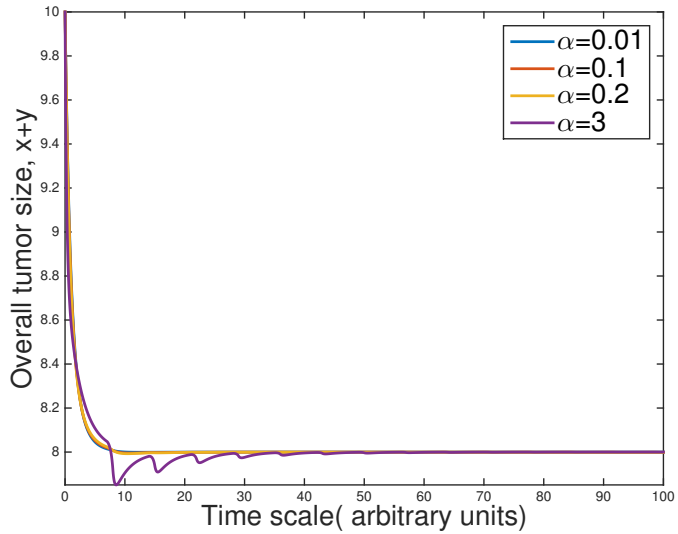


Immune-Viral Interactions

Immunosuppression



Immune Response



- What are the viral-immune dynamics for oncolytic viruses?
- How much time delay is needed from the immune response in order to allow for infection?
- Is the immune system infected by virus?

Future Work

- Add immune response to cancer population
- Extend model to include a Hill function for immune response term
- Incorporate a delayed immune response on cancer-viral interactions
- Incorporate data for partial/full model

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- Dr.Abba Gumel
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Thank you!

Dziękuję!