Oncolytic Virotherapy

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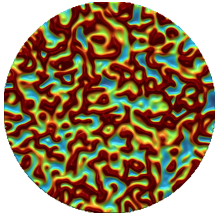
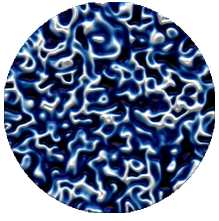


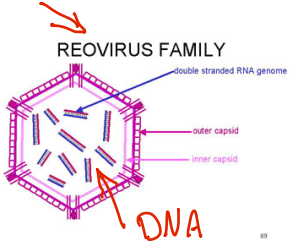


Oncolytic Virotherapy

Oncolytic viruses are genetically modified specialized viruses that selectively attack and replicate in tumor cells, while leaving normal tissues unharmed.

Two approved oncolytic viruses:

- T-VEC (herpes): melanoma
- Ad5-yCD/mutTKSR39rep-ADP (adenovirus): head and neck cancer



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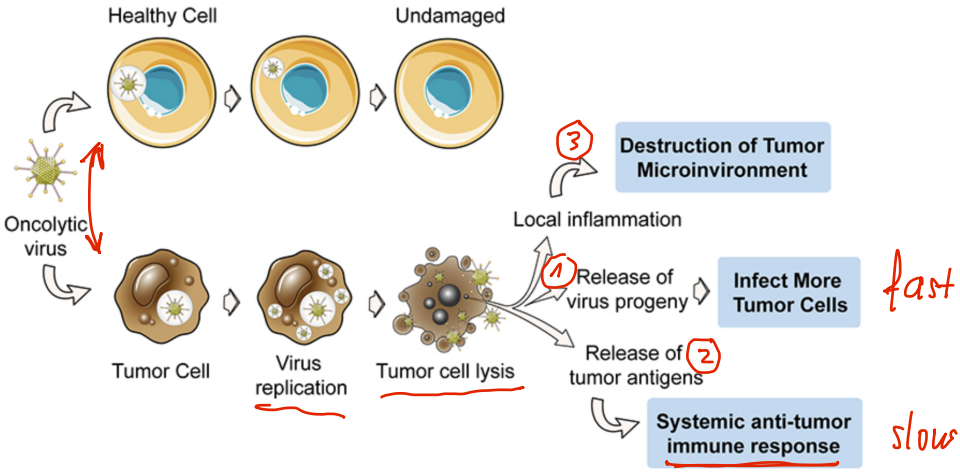

Mathematical Modelling

- Wu, Byrne, Kim, Wein 2001
- Wodarz 2003, Dingli 2006
- Friedman, Tian et al, 2006, 2011, 2013, 2017, 2019
- Eftimie 2011, 2016, 2019
- Storey, Jackson, 2020, 2021
- Pooladvand, Kim, Jenner, et al 2018, 2019, 2021

include immune response

Outline

1. AA. Baabdulla, TH, **Oscillations in a Spatial Oncolytic Virus Model.** Bulletin of Mathematical Biology, 2024, 86(8).

2. AA. Baabdulla, F. Cristi, M. Shmulevitz, TH, **Mathematical Modelling of Reoviruses in Cancer Cell Cultures**, in revision, 2024. bioRxiv 2024.07.12.603333

3. M. van Walsum, N. Mohammadnejad, TH, **Mathematical Modelling of Oncolytic Virotherapy**, 2024, manuscript.

4. TH. The Eye of the Needle in Oncolytic Virotherapy, Math Oncology Blog, 2024.

Base model

Cancer cells:
$$\frac{\partial C}{\partial t} = \underbrace{\tau C\left(1-\frac{C+I}{L}\right)}_{\text{logistic growth and competition}} - \underbrace{\beta CV}_{\text{infection}},$$

Infected cells:
$$\frac{\partial I}{\partial t} = \underbrace{\beta CV}_{\text{infection}} - \underbrace{\alpha I}_{\text{cell death}},$$

Virus particles:
$$\frac{\partial V}{\partial t} = \underbrace{\alpha b I}_{\text{virus production}} - \underbrace{\omega V}_{\text{virus loss}} - \underbrace{\kappa CV}_{\text{virus loss due to infection}}, \quad (1)$$

Very small!

burst size

Qualitative Behavior

Nondimensionalization

$$\begin{aligned} \dot{C} &= C\,(1 - C - I) - CV, \\ \dot{I} &= CV - aI, \\ \dot{V} &= \theta I - \gamma V - \kappa CV. \end{aligned} \tag{2}$$

Qualitative Behavior

Nondimensionalization

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A Bifurcation diagram with burst size $\theta = \frac{\alpha\beta bL}{\tau^2}$ as bifurcation parameter:

burst size

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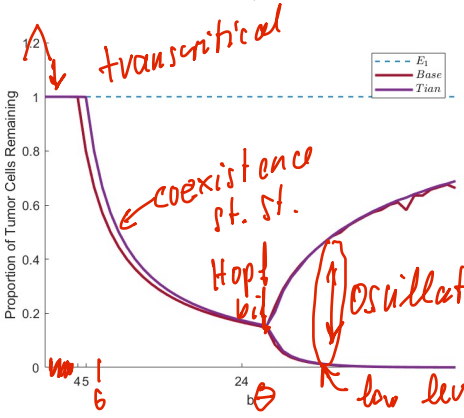

Simulations of ODE model

Using Pooladvand et al. parameters for adenovirus:
base value: $\Theta = 58.33$, Hopf bifurcation $\Theta_H = 338.45$.

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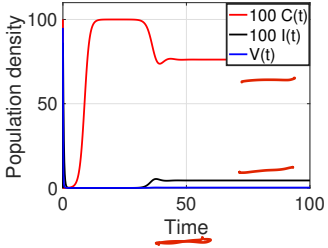
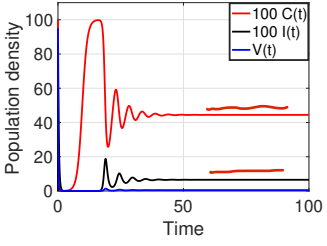
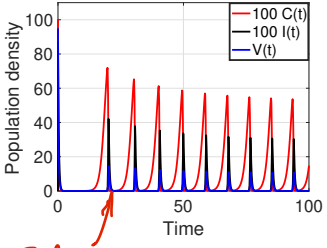


$\theta = 58.33$,



$\theta = 100$,



C low. $\theta = 500$.

Tumor Control Probability (TCP)

Poissonian: $$TCP(t) = e^{-C_0\, S(t)}, \qquad S(t) = \text{surviving fraction} \tag{3}$$

1 initial cond.

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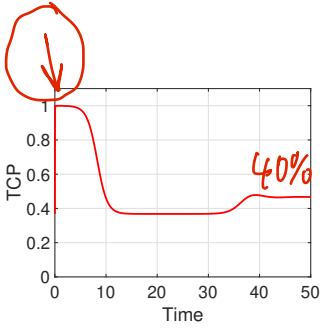

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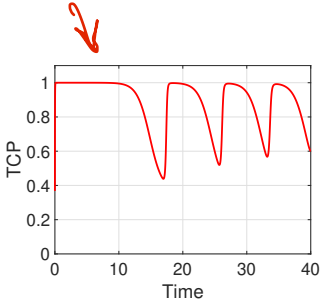
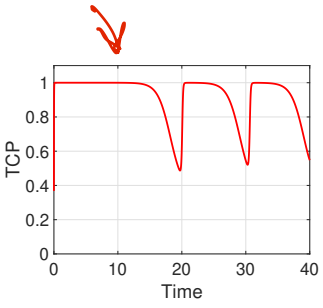


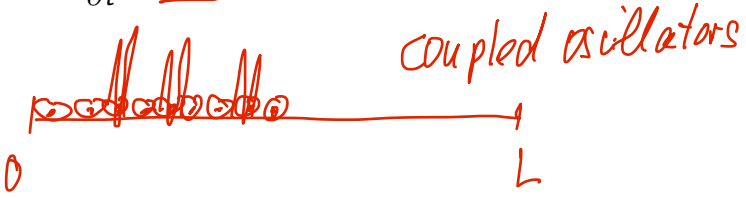
$\theta = 350,$



$\theta = 500.$

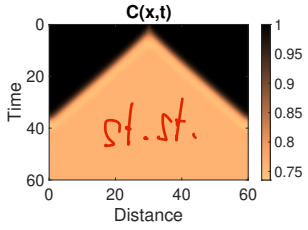
Including Space

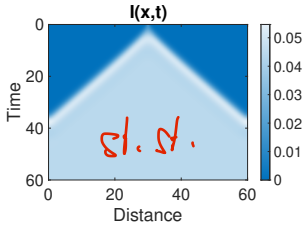
$$\begin{aligned}
\frac{\partial C}{\partial t} &= D_c \Delta C + C\,(1 - C - I) - CV, \\
\frac{\partial I}{\partial t} &= D_i \Delta I + CV - aI, \\
\frac{\partial V}{\partial t} &= \Delta V + \theta I - \gamma V,
\end{aligned} \tag{4}$$

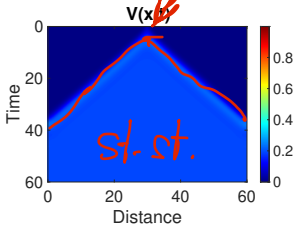


Simulations in 1-D

$\theta = 58.33$







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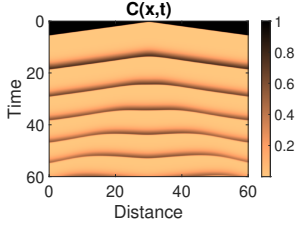
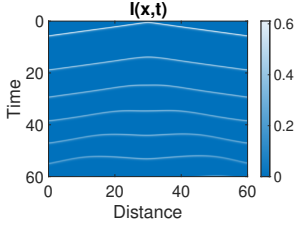
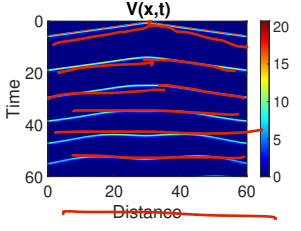
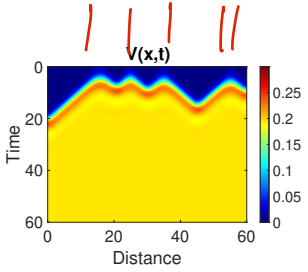






Five inoculations



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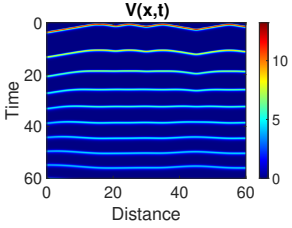

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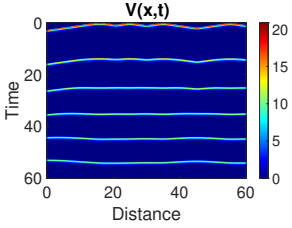
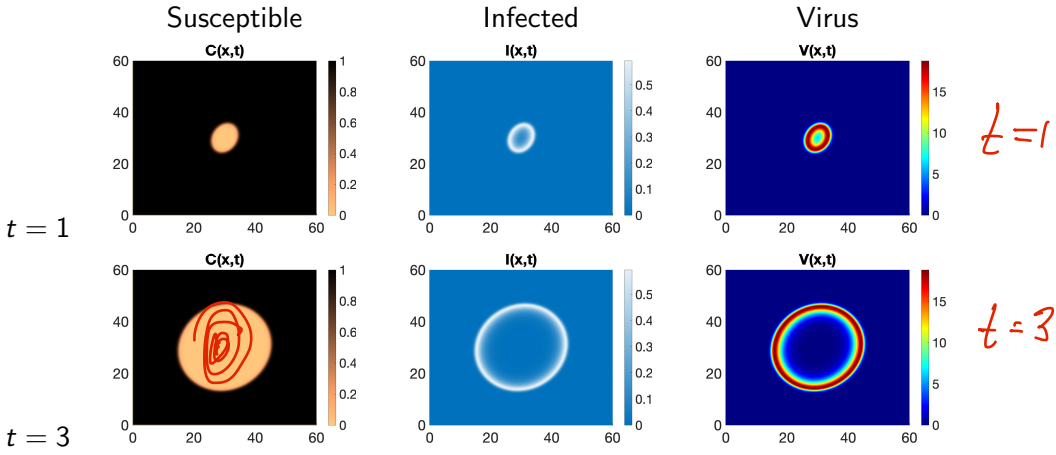
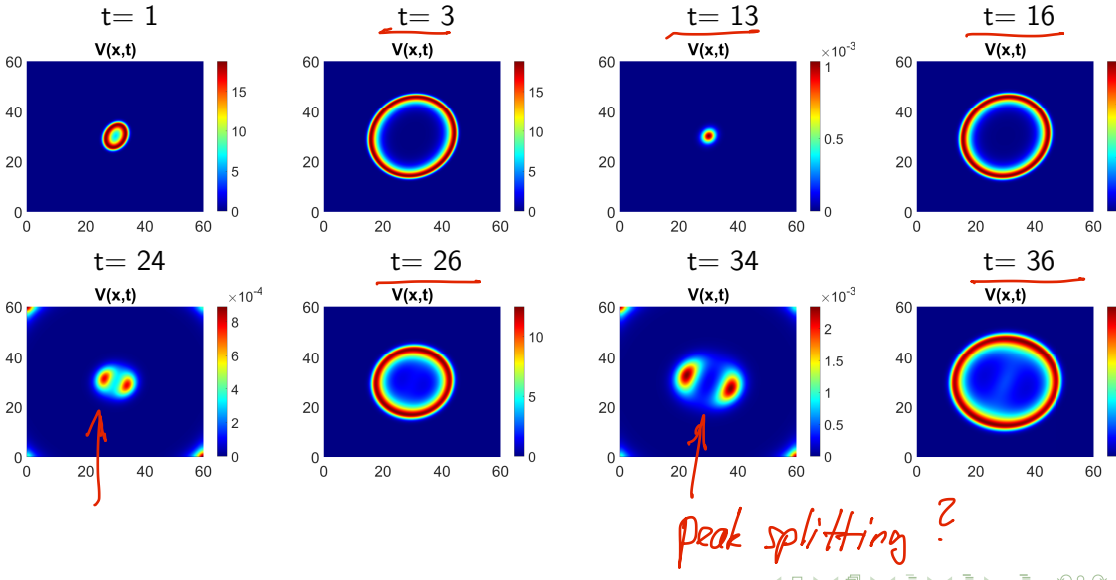


$\Theta = 500$

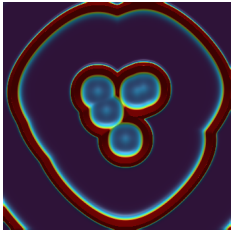
One inoculation in 2-D



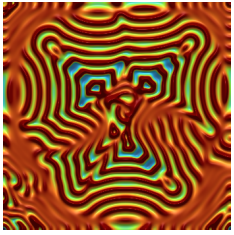
Longer time simulations



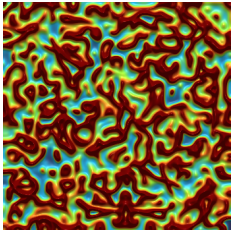
Chaotic dynamics



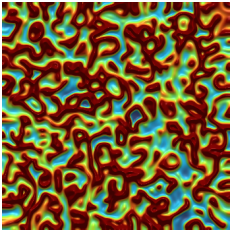
t= 46



t= 251



t= 600



t= 1000

AA. Baabdulla, TH, **Oscillations in a Spatial Oncolytic Virus Model.** Bulletin of Mathematical Biology, 2024, 86(8).

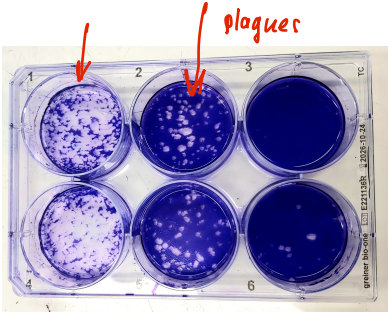
VisualPDE

(2) Reovirus

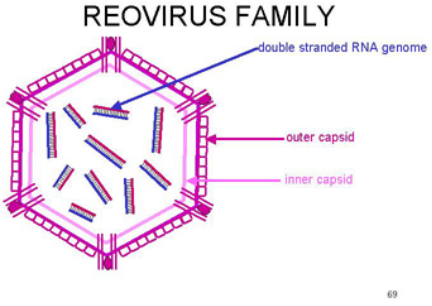
- AA. Baabdulla, F. Cristi, M. Shmulevitz, TH, **Mathematical Modelling of Reoviruses in Cancer Cell Cultures**, in revision, 2024.

Shmulevitz Lab

- Dr. Maya Shmulevitz and Fran Cristi, Li Ka Shing Institute of Virology, U Alberta

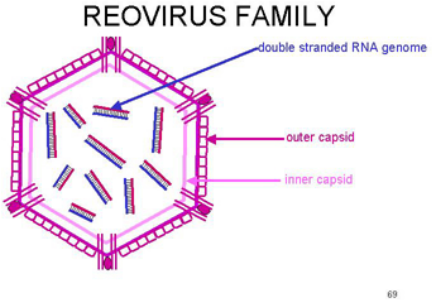


Reovirus



- Reovirus is a nonpathogenic double-stranded DNA virus

Reovirus



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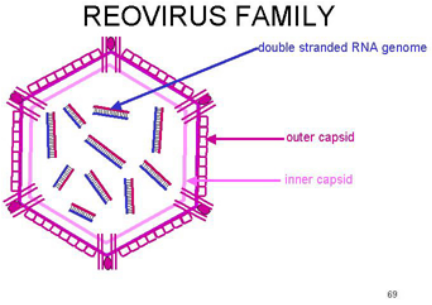
Reovirus



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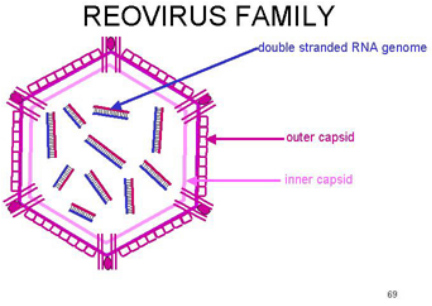
- It has shown anti-tumor abilities and is now in over 30 clinical trials targeting metastatic breast cancer, prostate cancer, colorectal cancer, etc.

Reovirus



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- The wild type T3wt resides in the digestive tract of mammals
- It has shown anti-tumor abilities and is now in over 30 clinical trials targeting metastatic breast cancer, prostate cancer, colorectal cancer, etc.
- There are currently two phase III clinical trials on reovirus for breast cancer.

T3wt mutations

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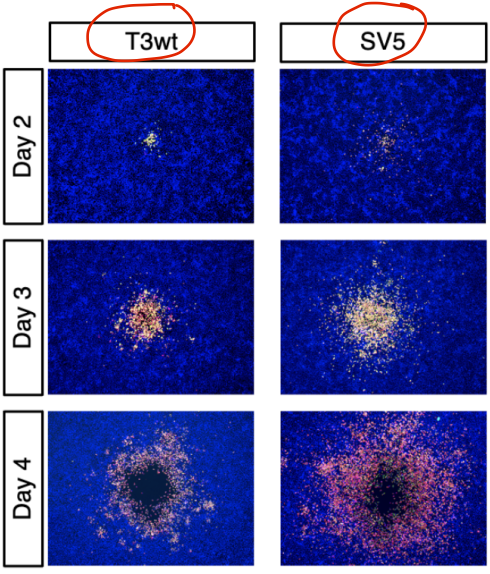
Question: Is there an optimal binding rate?

Data



Model 1: Short time

< 16hrs

$$V_t = D_V V_{xx} - \gamma_b V$$

- D_V diffusion coefficient
- γ_b binding rate

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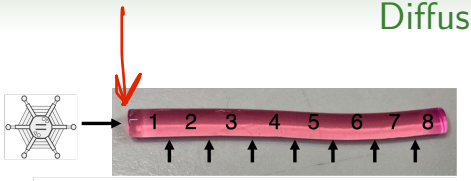
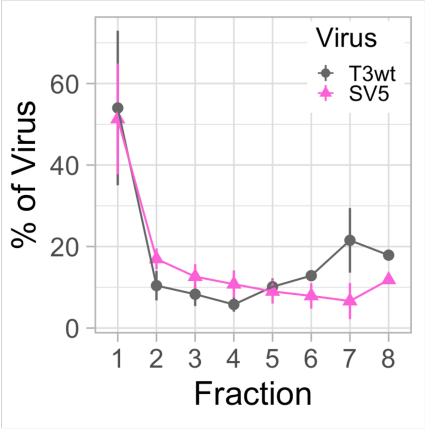
- γ_b binding rate

Virus was inoculated for 1 hour and then washed out from the cells. Bound virus was measured. We estimated

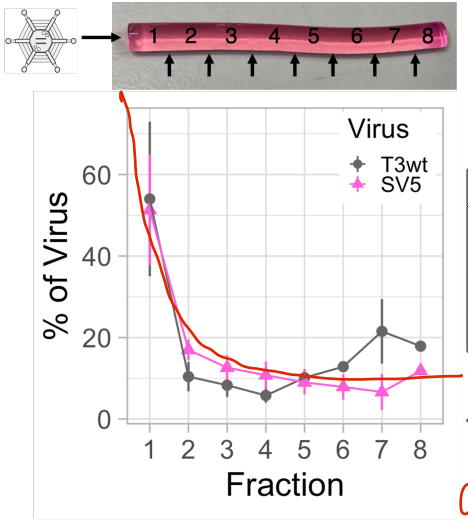
$$\gamma_{b,T3wt} = 61.63 \pm 10.14 \text{ per hour}, \qquad \gamma_{b,SV5} = 24.18 \pm 5.75 \text{ per hour}$$

Diffusion coefficient





Diffusion coefficient



D_v (**mm^2 per hour**)	
Our model fit estimation	0.01 ± 0.0015
Stokes-Einstein relation	0.02
Rioja et al. estimation	0.014
Poolandvand et al. estimation	0.01

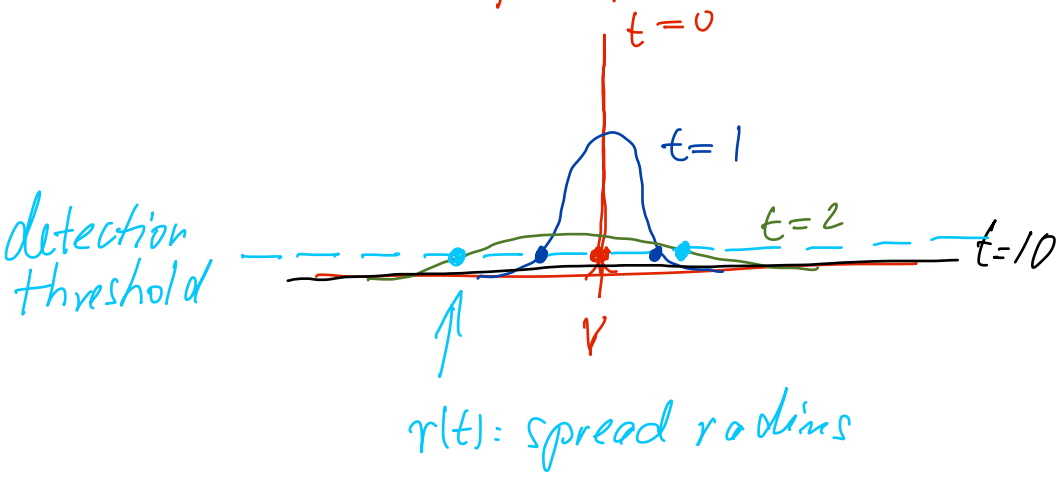
fundamental sol. of diffusion eq $V_t = D V_{xx}$

Estimate the spread radius in short times

The equation

$$V_t = D_V V_{xx} - \gamma_b V$$

has an explicit solution.



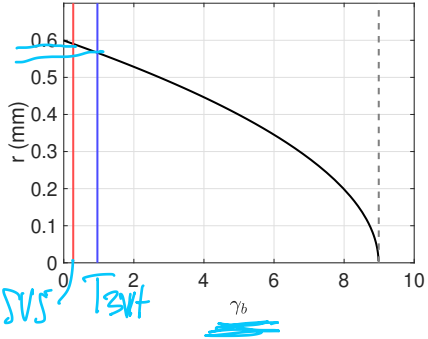
Estimate the spread radius in short times

The equation

$$V_t = D_V V_{xx} - \gamma_b V$$

has an explicit solution. We assume that the spread radius corresponds to the level where the virus concentration is lower than V_{min}, and we compute

$$r = \sqrt{4 D_V t \left(\ln \left[\frac{V_0}{4\pi D_V V_{\min} t} \right] - \gamma_b t \right)}.$$



- blue: T3wt
- red: SV5

Model 2: Long time

$t > 16h$

$C_t = 0 \rightarrow C = \text{const.}$

infected virus

$$
\begin{aligned}
I_t &= \gamma_b \nu V - aI \\
V_t &= D_V V_{xx} + \theta I - \gamma_b V
\end{aligned}
$$

Three new parameters:

- ν: percentage of virus binding that leads to an infection
- a: death rate of infected cells
- θ: burst size

Model 2: Long time

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$$

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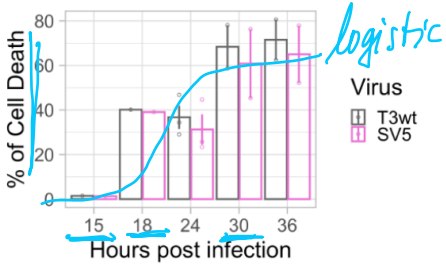
- a: death rate of infected cells
- θ: burst size

Marcato, Shmulevitz, Mol. Therapy 2007: $\nu = 0.01$.

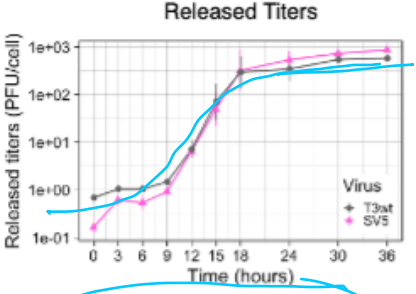
Death rate and burst size

Death rate estimation



$a = 0.057 \pm 0.03$

Burst size estimation

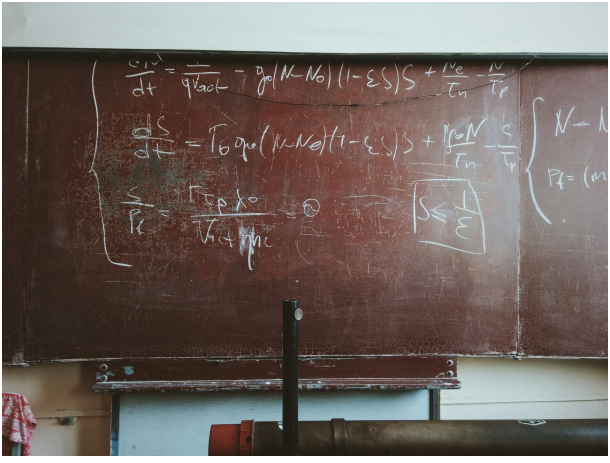


$\theta_{T3wt} = 514 \pm 114$

$\theta_{SV5} = 732 \pm 146$

Travelling Wave Analysis

Lets do some Math:



Traveling Wave Analysis

$$
\begin{aligned}
I_t &= \gamma_b \nu V - aI \\
V_t &= D_V V_{xx} + \theta I - \gamma_b V
\end{aligned}
$$

Traveling Wave Analysis

$$\begin{aligned} I_t &= \gamma_b \nu V - aI \\ V_t &= D_V V_{xx} + \theta I - \gamma_b V \end{aligned}$$

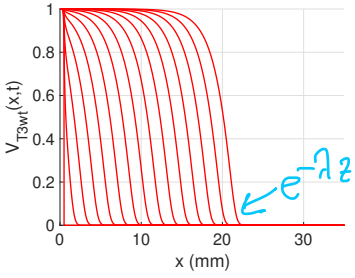
Look for traveling wave solutions

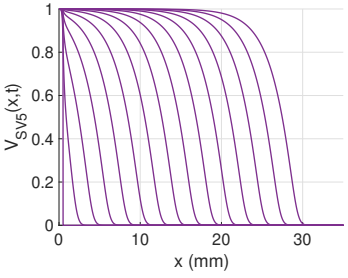
$$(I(x,t), V(x,t)) = (\varepsilon_i e^{-\lambda(x-ct)}, \varepsilon_v e^{-\lambda(x-ct)})$$

- c invasion speed
- λ decay rate of the wave front
- $\varepsilon_i, \varepsilon_v$ small parameters

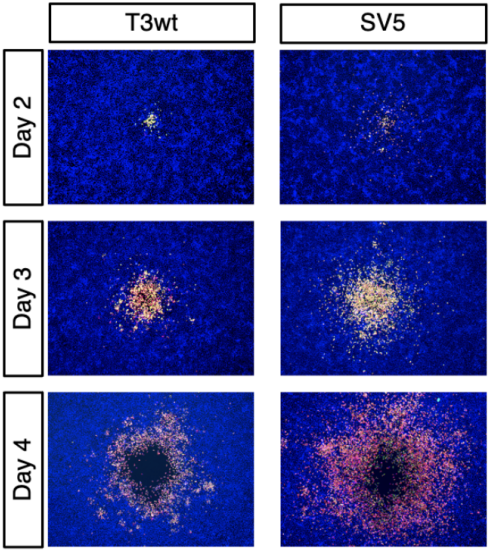
Traveling waves

T3wt	SV5
$c = 0.044$ mm per hour	$c = 0.059$ mm per hour
$\lambda = 6.9$ per mm	$\lambda = 5.4$ per mm

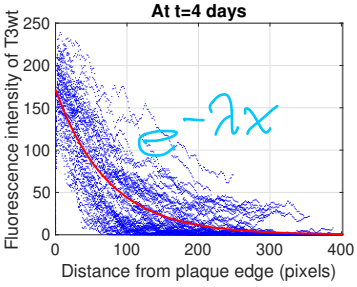
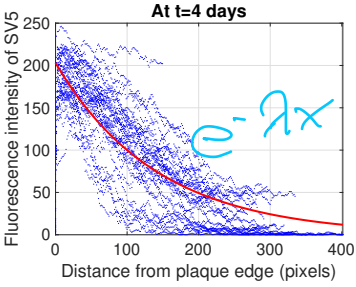




Validation



Validation

	T3wt	SV5
		
measured:	$\lambda = 9.8$ per mm	$\lambda = 4.9$ per mm
computed:	$\lambda = 6.9$ per mm	$\lambda = 5.4$ per mm

So What?

So What?

Question: Is there an optimal binding rate?

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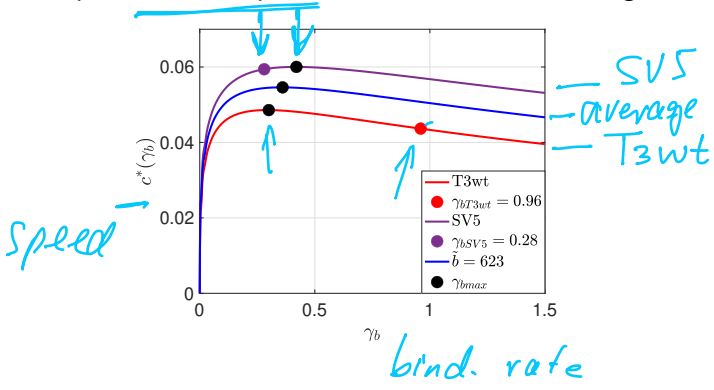
Compute invasion speed as function of the binding rate:



Varying burst size θ

θ	γ_{bmax}	$\frac{\gamma_{bmax}}{\theta}$	c^*_{max}	**Plaque Size**
virus per cell	per hour	10^{-5}	mm per hour	mm^2
500	0.28	56	0.047	5
550	0.32	58	0.050	20
600	0.36	60	0.053	32
650	0.36	55	0.056	43
700	0.39	56	0.058	55
750	0.43	57	0.060	69
800	0.47	59	0.063	82
850	0.47	55	0.065	95
900	0.51	57	0.067	106
950	0.51	54	0.069	121
1000	0.50	50	0.071	129

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950	0.51	54	0.069	121
1000	0.50	50	0.071	129

The Shmulevitz lab is now looking for the optimal virus.

(3) Including Immune Response, a theoretical study

- M. van Walsum, N. Mohammadnejad, TH, **Mathematical Modelling of Oncolytic Virotherapy**, 2024, manuscript.

OVT Models

We can incorporate the immune system into the model using cell and virus specific lymphocytes L_x and L_y.

$$\frac{dx}{dt} = rx\left(1 - \frac{x+y}{K}\right) - avx - pxL_x$$
$$\frac{dy}{dt} = avx - \delta y - qyL_v - pyL_x$$
$$\frac{dv}{dt} = \theta\delta y - cv - psL_v$$
$$\frac{dL_x}{dt} = gxL_x - wL_x \quad \text{cell specific}$$
$$\frac{dL_v}{dt} = hyL_v - wL_v \quad \text{virus specific}$$

L_x: the population of tumor-specific leukocytes
L_v : the population of virus-specific leukocytes

2-OVT Model

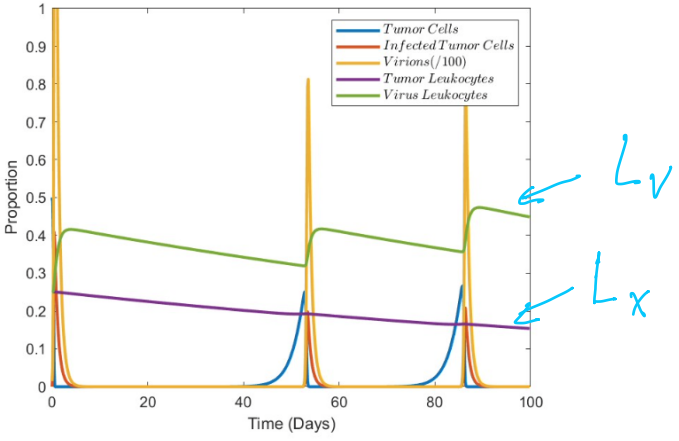


Figure: Treatment simulations of oncolytic virotherapy when the immune system is considered

Combination Therapies Models

We combine OVT with these following therapies:

1. Continuous infusion chemotherapy
2. Fractionated chemotherapy
3. Brachytherapy (insertion of radioactive seeds)
4. External beam radiotherapy (fractionated)
5. Immunosuppression with an immunosuppressant
6. Immune boost (stimulate lymphocytes and increasing their efficiency)
7. CAR-T cell immunotherapy

(1) Continuous infusion chemotherapy

$$
\begin{aligned}
\dot{x} &= rx(1-x-y) - axy - pxL_x - x\theta_x(1-E_x(C)) \\
\dot{y} &= axv - y - qyL_v - y - pyL_x - y\theta_y(1-E_y(C)) \\
\dot{v} &= \theta y - cv - svL_v \\
\dot{L_x} &= gxL_x - \omega L_x - L_x\theta_I(1-E_I(C)) \\
\dot{L_v} &= hyL_v - \omega L_v - L_v\theta_I(1-E_I(C)) \\
\dot{C} &= 1 - \gamma C
\end{aligned}
$$

chemo

where $E_i(C) = e^{-\mu_i C}$ for $i \in \{x, y, I\}$

(2)-Fractionated chemotherapy

$$
\begin{aligned}
\dot{x} &= rx(1-x-y) - axy - pxL_x - x\theta_x(1-E_x) \\
\dot{y} &= axv - y - qyL_v - y - pyL_x - y\theta_y(1-E_y) \\
\dot{v} &= \theta y - cv - svL_v \\
\dot{L_x} &= gxL_x - \omega L_x - L_x\theta_I(1-E_I) \\
\dot{L_v} &= hyL_v - \omega L_v - L_v\theta_I(1-E_I) \\
\dot{C} &= D(t) - \gamma C
\end{aligned}
\tag{5}
$$

Where $E_i(C) = e^{-\mu_i C}$ for $i \in \{x, y, I\}$

(3)-Brachytherapy

$$
\begin{aligned}
\dot{x} &= rx(1-x-y) - axy - pxL_x - mxR \\
\dot{y} &= axv - y - qyL_v - pyL_x - myR \\
\dot{v} &= \theta y - cv - svL_v \\
\dot{L_x} &= gxL_x - \omega L_x - nL_xR \\
\dot{L_v} &= hyL_v - \omega L_v - nL_vR \\
\dot{R} &= \lambda(1-R)
\end{aligned}
$$

(4)- External beam radiotherapy

$$
\begin{aligned}
\frac{dx}{dt} &= rx\left(1 - \frac{x+y}{K}\right) - avx - pxL_x \\
\frac{dy}{dt} &= avx - y - qyL_v - pyL_x \\
\frac{dv}{dt} &= \theta y - cv - psL_v \\
\frac{dL_x}{dt} &= gxL_x - wL_x \\
\frac{dL_x}{dt} &= hyL_x - wL_v
\end{aligned}
$$

Assume only a surviving fraction of tumor cells and leukocytes after each treatment period where

$$S(d) = exp\{-\alpha d - \beta d^2\}$$

α_i: radiosensitivity of cells to a single does of radiation, β_i :the radiosensitivity of cells to two doses of radiation

(5)-Immunosuppression

$$
\begin{aligned}
\dot{x} &= rx(1-x-y) - axv - pxL_x \\
\dot{y} &= axv - y - qyL_v - pyL_x \\
\dot{v} &= \theta y - cv - svL_v \\
\dot{L_x} &= gxL_x - \omega L_x - L_x\vartheta(1-e^{-\varepsilon I_0 I}) \\
\dot{L_v} &= hyL_v - \omega L_v - L_v\vartheta(1-e^{-\varepsilon I_0 I}) \\
\dot{I} &= 1 - \eta I
\end{aligned}
\tag{6}
$$

(6)-Immune boost

$$
\begin{aligned}
\dot{x} &= rx(1-x-y) - axv - \kappa pxL_x \\
\dot{y} &= axv - y - qyL_v - pyL_x \\
\dot{v} &= \theta y - cv - svL_v \\
\dot{L_x} &= \zeta gxL_x - \omega L_x \\
\dot{L_v} &= hyL_v - \omega L_v
\end{aligned}
\tag{7}
$$

(7)-CAR-T cell immunotherapy

$$
\begin{aligned}
\dot{x} &= rx(1-x-y) - axy - pxL_x \\
\dot{y} &= axv - y - qyL_v - pyL_x \\
\dot{v} &= \theta y - cv - svL_v \\
\dot{L_x} &= gxL_x - \omega L_x + \varphi \\
\dot{L_v} &= hyL_v - \omega L_v
\end{aligned}
\tag{8}
$$

Tumor control probability

Probability that cancer will be effectively controlled Poissonian model:

$$TCP(\tau) = exp\{-N_0 S(\tau)\}$$

close to 1 ?

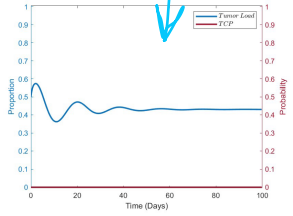
traditionally used as a means of predicting the success of radiotherapy We define the surviving fraction of cells at any time τ to be

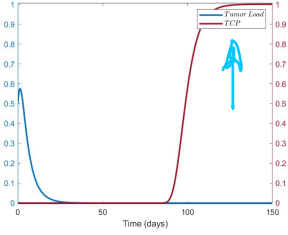
$$S(\tau) = x(\tau) + y(\tau).$$

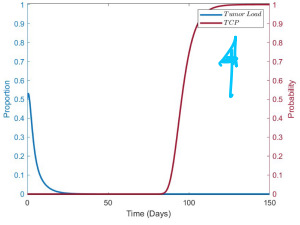
(3)- Brachytherapy

$$\theta < \theta_H$$

blue: tumor cells, purple: TCP







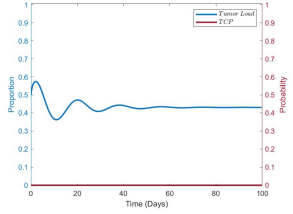
OVT alone | alternative treatment alone | combination

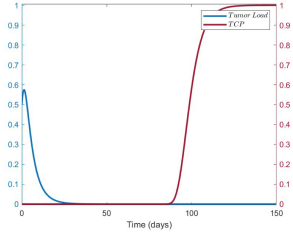
not successful

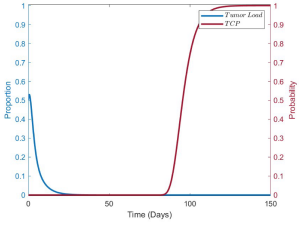
(3)- Brachytherapy

$$\theta < \theta_H$$

blue: tumor cells, purple: TCP







OVT alone ✗

alternative treatment alone ✓

combination ✓

(3)- Brachytherapy

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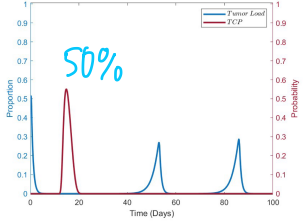
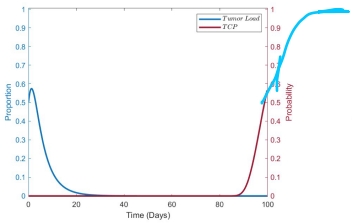
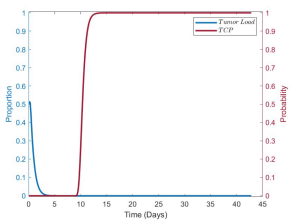






OVT alone

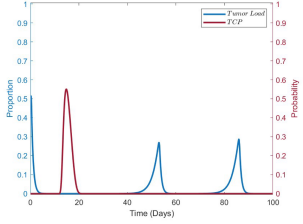
alternative treatment alone

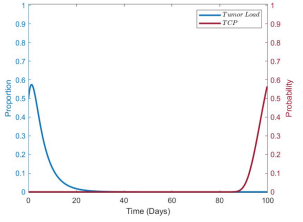
combination

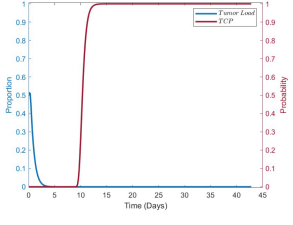
(3)- Brachytherapy

$$\theta > \theta_H$$

blue: tumor cells, purple: TCP







OVT alone

0.5

alternative treatment alone

✔

combination

✔++

OVT insufficient, $\theta < \theta_H$

Treatment	OVT alone	alt. alone	combined
1) continuous infusion chemo	✗	✓	✓
2) fractionated chemo	✗	✗	✗
3) brachy	✗	✓	✓
4) external beam	✗	✗	✗
5) immuno suppression	✗	✗	✗
6) immuno boost	✗	✗	✗
7) CAR-T	✗	✓	✓

OVT sufficient, $\theta > \theta_H$

Treatment	OVT alone	alt. alone	combined
1) continuous infusion chemo	0.5	✔	✔++
2) fractionated chemo	0.5	✘	✔
3) brachy	0.5	✔	✔++
4) external beam	0.5	✔	✔
5) immuno suppression	0.5	✘	✔
6) immuno boost	0.5	✘	✔
7) CAR-T	0.5	✔	✔++

- When OVT is not successful on it's own, other treatments do not improve OVT or gain benefit from combination with OVT.
- When OVT is partially successful, benefit can be gained from combination treatments.

Conclusions and Future Work

- Spatial models
  - The basic oncolytic virus model shows interesting spatio-temporal dynamics.

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  - Van Walsum, Day: Oncolytic virus resistance.

Thank You

1. AA. Baabdulla, TH, **Oscillations in a Spatial Oncolytic Virus Model.** Bulletin of Mathematical Biology, 2024, 86(8).

2. AA. Baabdulla, F. Cristi, M. Shmulevitz, TH, **Mathematical Modelling of Reoviruses in Cancer Cell Cultures**, in revision, 2024. bioRxiv 2024.07.12.603333

3. M. van Walsum, N. Mohammadnejad, TH, **Mathematical Modelling of Oncolytic Virotherapy**, 2024, manuscript.

4. TH. The Eye of the Needle in Oncolytic Virotherapy, Math Oncology Blog, 2024.