# Mathematical Modelling of Cancer Stem Cells

Thomas Hillen

University of Alberta

June 21, 2024

Review article:
TH, A. Shyntar, Modelling of Cancer Stem Cell Driven Solid Tumors, book chapter, Springer 2024.

MOLECULAR CANCER THERAPEUTICS

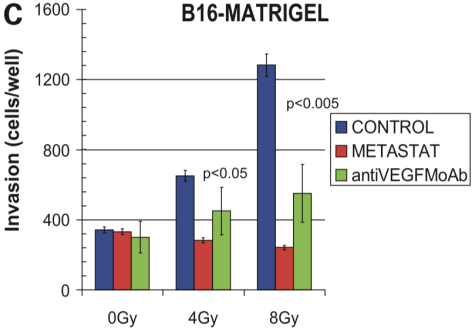


Article

# Angiogenesis and tumor growth inhibition by a matrix metalloproteinase inhibitor targeting radiation-induced invasion

Alexandre Kaliski, Laurence Maggiorella, Keith A. Cengel, Denis Mathe, Valerie Rouffiac, Paule Opolon, Nathalie Lassau, Jean Bourhis, and Eric Deutsch

**DOI:** 10.1158/1535-7163.MCT-05-0179 Published November 2005

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## uPA/uPAR downregulation inhibits radiation-induced migration, invasion and angiogenesis in IOMM-Lee meningioma cells and decreases tumor growth in vivo

**Authors:** Odysseas Kargiotis, Chandramu Chetty, Venkateswara Gogineni, Christopher S. Gondi, Sai Muralikrishna Pulukuri, Athanassios P. Kyritsis, Meena Gujrati, Jeffrey D. Klopfenstein, Dzung H. Dinh, Jasti S. Rao

- " Recently, ionizing radiation has been shown to enhance invasiveness of surviving tumor cells ..."

cancers

MDPI

*Article*

# The STAT3/Slug Axis Enhances Radiation-Induced Tumor Invasion and Cancer Stem-like Properties in Radioresistant Glioblastoma

**Jang-Chun Lin [1,2,3], Jo-Ting Tsai [2,3], Tsu-Yi Chao [1,4], Hsin-I Ma [5,6] and Wei-Hsiu Liu [5,6,*]**

- " Accumulating research indicates that GBM contains cancer stem-like cells (CSCs), which are radioresistant and result in therapeutic failure."
- " Transwell and microarray assay demonstrated that radioresistant GBM cells (GBM-R2I2) exhibit increased invasion and self-renewal abilities compared with parental GBM cells. "

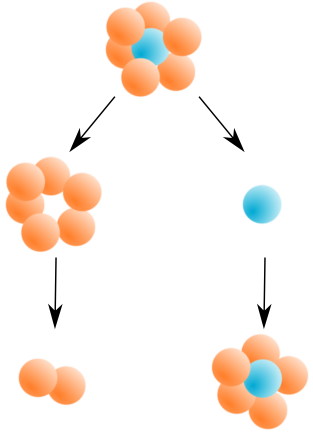
# Cancer Stem Cells

Cancer stem cells (**CSCs**)

- self-renewing
- able to repopulate a heterogeneous tumor
- less sensitive to treatment
- **Main drivers behind tumor growth!**

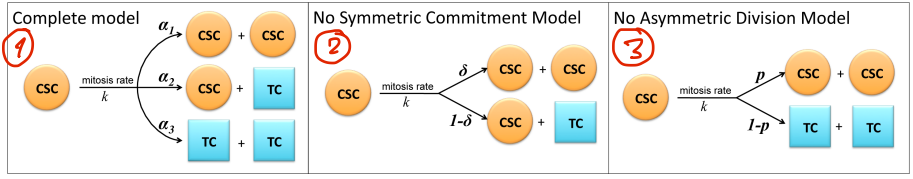
Non-stem Cancer cells (**TCs**)

- unable to repopulate the heterogeneous tumor
- relatively sensitive to treatment



* Figure from A. Rhodes

# Basic CSC models




(1) CSC $\dot{u} = -ku + 2k\alpha_1 u + k\alpha_2 u$

TC $\dot{v} = +2k\alpha_3 u + k\alpha_2 u$

$\dot{u} = k(-1 + 2\alpha_1 + \alpha_2)u$

$\dot{v} = k(2\alpha_3 + \alpha_2)u$

know: $\alpha_1 + \alpha_2 + \alpha_3 = 1$ $\quad \alpha_2 = 1 - \alpha_1 - \alpha_3$

$$\dot{u} = k(-1+2\alpha_1+1-\alpha_1-\alpha_3)u$$
$$= k(\alpha_1-\alpha_3)u$$
$$\dot{v} = k(2\alpha_3+1-\alpha_1-\alpha_3)u$$
$$= k(\alpha_3+1-\alpha_1)u$$

$$\left.\begin{aligned}\dot{u} &= (\alpha_1-\alpha_3)ku \\ \dot{v} &= (1-\alpha_1+\alpha_3)ku\end{aligned}\right\} \quad (1)$$

$\updownarrow$ Same !

(2): Hillen

$$\left.\begin{aligned}\dot{u} &= \delta ku \\ \dot{v} &= (1-\delta)ku\end{aligned}\right\} \quad (2)$$

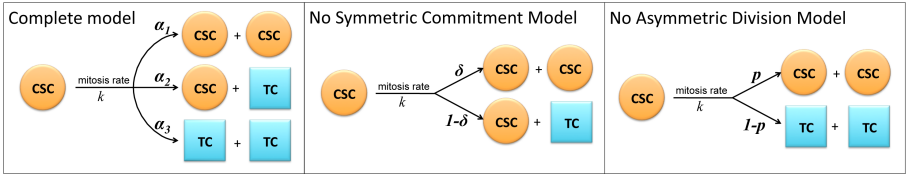
$$\delta = \alpha_1-\alpha_3$$
$$1-\delta = 1-\alpha_1+\alpha_3$$

(3): Natalia

$$\left.\begin{aligned}\dot{u} &= (2p-1)ku \\ \dot{v} &= \underline{2(1-p)}ku\end{aligned}\right\} \quad (3)$$

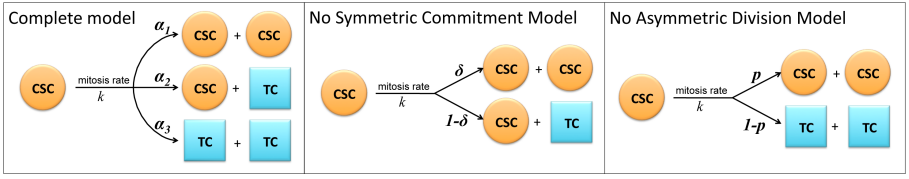
$$\delta = 2p-1$$
$$1-\delta = 1-2p+1 = 2(1-p)$$

# Basic CSC models




- All models are mathematically equivalent!

# Basic CSC models




- All models are mathematically equivalent!

For stem cells $u(t)$ and non-stem cells $v(t)$ we use the basic model

$$\begin{aligned} u_t &= \delta\gamma u \\ v_t &= (1-\delta)\gamma v \end{aligned}$$

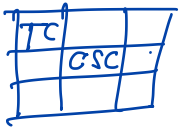
# Mathematical Models for Cancer Stem Cells

- Ganguli, Puri, *Cell Prolif.*, 2006
  Sole et al., *J. Theor. Biol.* 2006
  Carcinogenesis through mutations of normal stem cells
- Dingli, Michor, *Stem Cell*, 2006
  "Successful Therapy Must Eradicate Cancer Stem Cells"
- Marciniak-Czochra, et al, *Stem Cells and Development*, 2009
  Stem cell dynamics plus feedback control
- Lowengrub, Christini, Wise, et al, 2008-11
  Detailed cancer growth model in tissue, including spatial dynamics, tissue stiffness, force balances, growth factors and inhibitors, and cancer stem cells plus feedback control
- Enderling, et al 2009, TH et al 2012, Fasano et al 2016, Shyntar et al 2022
  The tumor growth paradox and tumor invasion paradox

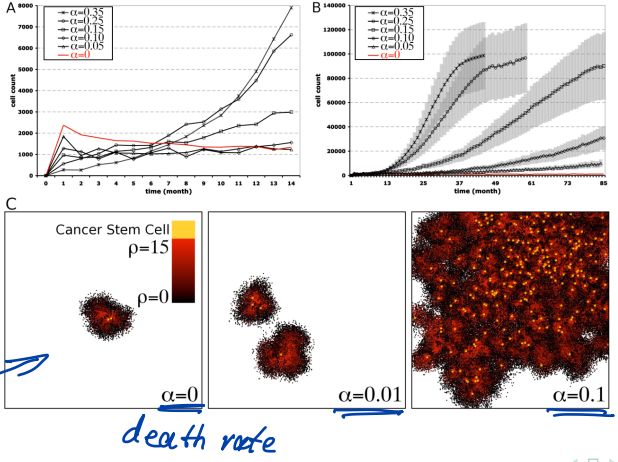
# Outline

- Model 1: An agent-based model: Simulations
- Model 2: A birth-jump model: Existence, uniqueness.
- Model 3: A reaction-diffusion model: The tumor invasion paradox
- Model 4: An ODE model: The tumor growth paradox

# Model 1: Agent based modelling (ABM)

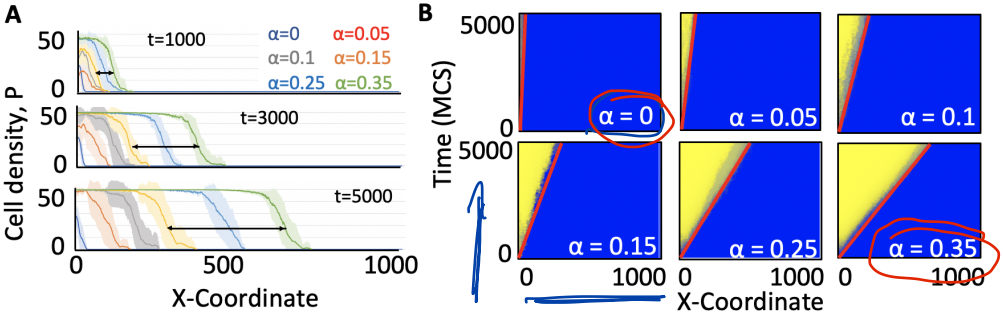



- Enderling et al. *Cancer Research* 2009.
- CSC: yellow, Tumor cells (TC) red-black. $\alpha$ death rate of TC.



# Individual Based Model

Ashna Patel and H. Enderling



## Model 2: Birth-jump model for cancer stem cells

$$\frac{\partial u}{\partial t} = D_u \Delta u + \delta \int_\Omega K(x, y, p(x,t)) \gamma u(y,t)\, dy - \alpha u \tag{1}$$

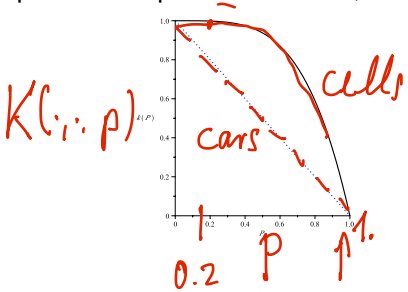
$$\frac{\partial v}{\partial t} = D_v \Delta v + (1-\delta) \int_\Omega K(x, y, p(x,t)) \gamma u(y,t)\, dy - \alpha v + \int_\Omega K(x, y, p(x,t)) \rho v(y,t)\, dy, \tag{2}$$

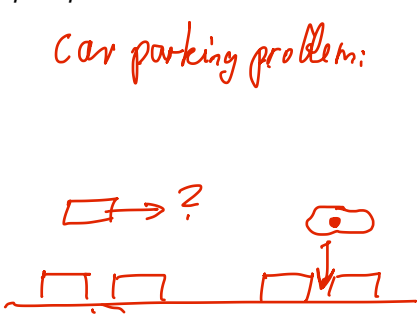
- $u(x,t)$ cancer stem cells, $v(x,t)$ differentiated cancer cells
  $p(x,t) = u(x,t) + v(x,t)$: total tumor population
- $D_u, D_v$: diffusion rates
- $\delta$: rate of symmetric mitosis of CSC
- $\gamma, \rho$: mitosis rates for SC and NSCC, respectively
- $K(x, y, p(x,t))$: volume constraint

# Volume constraint

$K(x, y, p(x, t))$:

- probability density of a cell at location $y$ to give rise to a daughter cell at location $x$.
- The dependence on $p$ expresses the volume effect (crowding effect), and proliferation is only possible if space is available, i.e. $p < p^*$.



# Global existence

- (Maddalena 2014) Global existence and uniqueness of (1),(2).
- (Borsi, Fasano, Primicerio, TH, 2015) Global existence and uniqueness for model (1),(2) with no diffusion.
- (Delgado, Duarte, Suarez, 2016): Global existence and uniqueness for

$$\frac{\partial u}{\partial t} = D\Delta u + \delta \int_\Omega K(x, y, u(x,t))\gamma u(y,t)\, dy + f(u)$$

# Reduction 1

Expand integration kernel as

$$K(x, y, p) = q(x, y)k(p)$$

$$\int K(x, y, p(x, t))u(y, t)dy \approx k(p)(u + Bu_{xx})$$

where

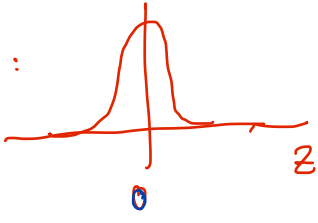
$$\int q\ dy, = 1, \qquad B = \frac{1}{2}\int (x - y)^2 q\ dy.$$

Moment expansion: $q(x-y)$

$$\int_\Omega q(x-y)\, u(y)\, dy = q * u(x)$$

$$= \int_\Omega q(z)\, u(x-z)\, dz$$

assume:




likely to move small steps $z$.

Use Taylor expansion

$$\int_\Omega q(z)\, u(x-z)\,dz = \int_\Omega q(z)\left(u(x) - z u'(x) + \frac{z^2}{2} u''(x) - \frac{z^3}{6} u'''(x) + \cdots\right)$$

$$= u(x)\underbrace{\int q(z)\,dz}_{=1} - u'(x)\underbrace{\int z\, q(z)\,dz}_{=0 \text{ if } q \text{ symmetric}} + \frac{u''(x)}{2}\underbrace{\int z^2 q(z)\,dz}_{\text{2nd moment}} - \frac{u'''(x)}{6}\underbrace{\int z^3 q(z)\,dz}_{=0 \text{ symmetry}} + \cdots$$

$dz$

$$\simeq u(x) + B\, u''(x)$$

## Model 3: A reaction-diffusion model

$$
\begin{aligned}
u_t &= Du_{xx} + \delta\gamma k(p)(u + Bu_{xx}) \\
v_t &= Dv_{xx} + (1-\delta)\gamma k(p)(u + Bu_{xx}) + \rho k(p)(v + Bv_{xx}) - \alpha v.
\end{aligned}
$$

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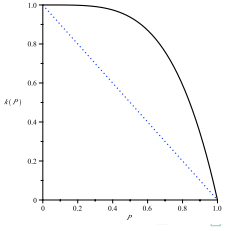
\end{aligned}
$$

**Model 4:** Focus on the kinetic part and remove all spatial derivatives.

$$
\begin{aligned}
U_t &= \delta\gamma k(P)U \\
V_t &= (1-\delta)\gamma k(P)U - \alpha V + \rho k(P)V.
\end{aligned}
$$

- $U(t)$: Cancer stem cells, mitosis rate $\gamma$
- $V(t)$: non-stem tumor cells, mitosis rate $\rho$
- $\delta$: fraction of symmetric mitosis events
- Volume constraint, $P = U + V$,
  $k(P) = \max\{1 - P^\sigma, 0\}$ , $\sigma \geq 1$.



# The Tumor Growth Paradox

**Definition**

Let $P_\alpha(t)$ denote the total tumor population at time $t$, with a non stem cell death rate of $\alpha$. The population exhibits a tumor growth paradox if there exists parameter values $\alpha_1 > \alpha_2$ and an open interval $(t_1, t_2)$ such that $P_{\alpha_1}(0) = P_{\alpha_2}(0)$ and

$$P_{\alpha_1}(t) > P_{\alpha_2}(t), \qquad \text{for } t \in (t_1, t_2).$$

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$$P_{\alpha_1}(t) > P_{\alpha_2}(t), \qquad \text{for } t \in (t_1, t_2).$$

**Theorem** (TH, Enderling, Hahnfeldt, 2013).

Model 4 shows a tumor growth paradox.

# Singular perturbation theory

Model 4:

$$\begin{aligned} U_t &= \delta\gamma k(P)U \\ V_t &= (1-\delta)\gamma k(P)U - \alpha V + \rho k(P)V. \end{aligned}$$

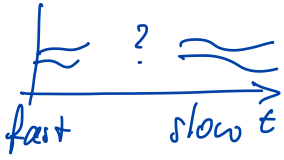
Small parameter: $\delta = 0.1 - 0.001$.

# Fast and slow systems

Fast system

$$\begin{aligned} U_t &= 0 \\ V_t &= \gamma k(P)U - \alpha V + \rho k(P)V. \end{aligned}$$

U const.



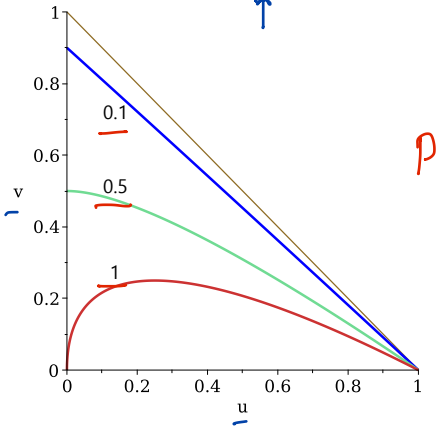

Slow system, $(\tau = \delta t)$

$$\begin{aligned} U_\tau &= \gamma k(P)U \\ 0 &= \gamma k(P)U - \alpha V + \rho k(P)V \end{aligned}$$

slow manifold

# Slow manifold

$$\mathcal{M} = \{(U, V) : \gamma k(P)U - \alpha V + \rho k(P)V = 0\}$$

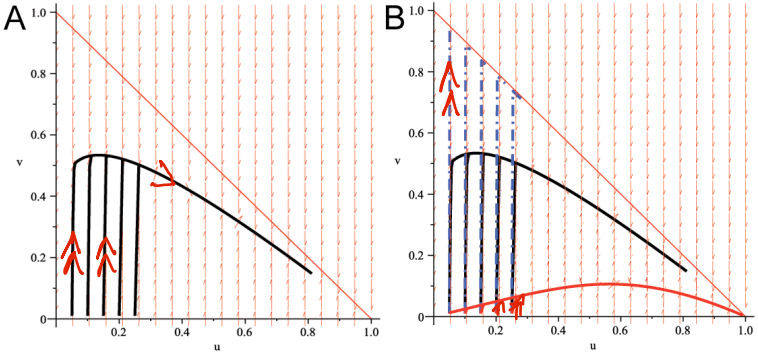



$p = u + v \leq 1$

# Fast dynamics

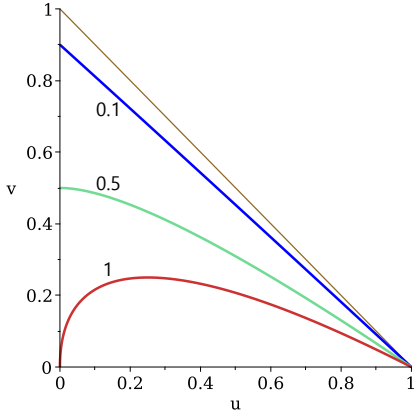
The fast dynamics relaxes quickly onto the slow manifold

$$\mathcal{M} = \{(U, V) : \gamma k(P)U - \alpha V + \rho k(P)V = 0\}$$




$\alpha = 0.05$ (blue), $\alpha = 1$ (black), $\alpha = 5$ (red).

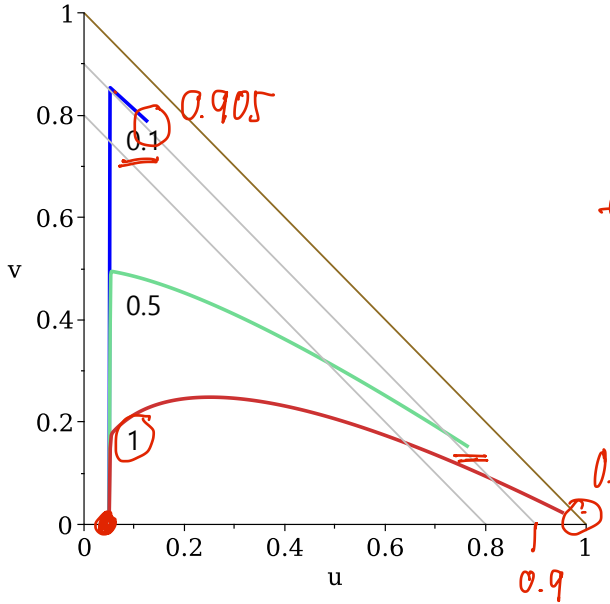
# Slow dynamics




## Lemma

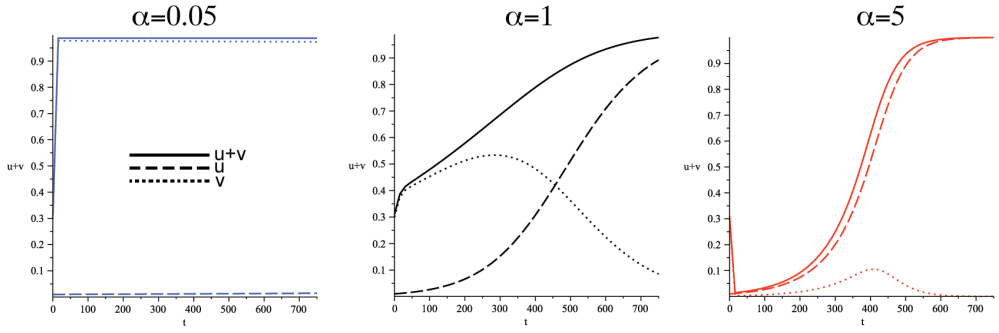
*Consider two clonogenic death rates $\alpha_1 > \alpha_2 > 0$. Then, on the slow manifold, the stem cell growth rate is larger for the population with the larger death rate $\alpha_1$.*

# Tumor Growth Paradox




$\epsilon_{max} = 1000$

# Stem cells versus differentiated cancer cells




Cell populations as functions of time

- stem cells (dashed), differentiated cells (dotted), total population (solid)

# Inclusion of treatments

$$
\begin{aligned}
u_t &= \delta k(p)u - R_u(t)u \\
v_t &= (1-\delta)k(p)u + \rho k(p)v - \alpha v - R_v(t)v.
\end{aligned}
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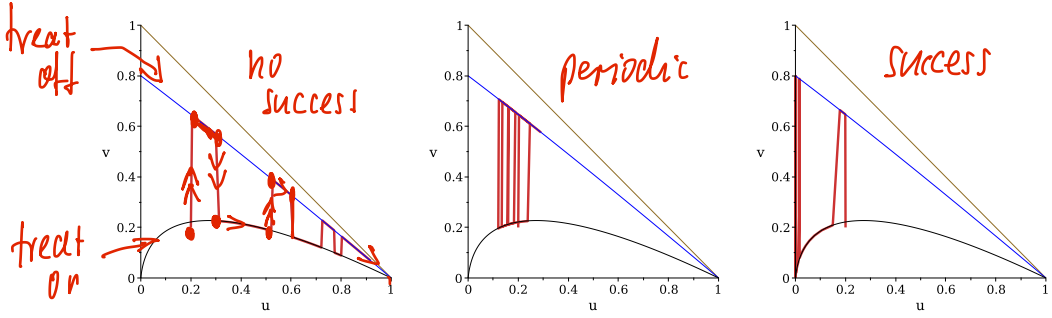


(A) insufficient treatment, (B) treatment oscillations, (C) successful treatment

# Differentiation promoters

- CSC are less sensitive to treatments.
- Differentiation promoters can be used to push CSC into differentiation and make them more sensitive.
- In (Bachman et al 2012), we included differentiation promoters into the model and calibrated it on cancer data.

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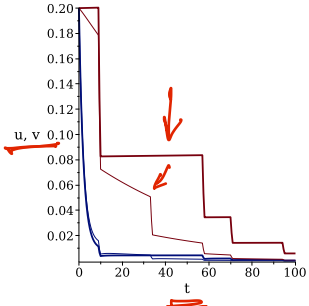
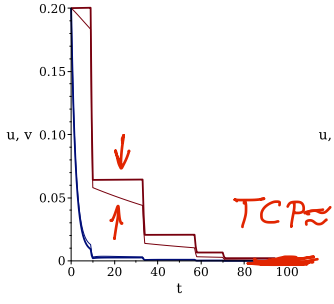
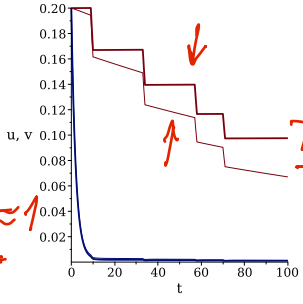
- CSC are less sensitive to treatments.
- Differentiation promoters can be used to push CSC into differentiation and make them more sensitive.
- In (Bachman et al 2012), we included differentiation promoters into the model and calibrated it on cancer data.
- CSC, TC, **thick: no diff. promoter**, thin: with diff. promoter




head and neck



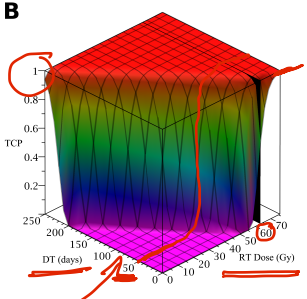

metastatic brain cancer




breast cancer

# Tumor Control Probability (w. Bachman)

TCP = probability that the cancer is cured.

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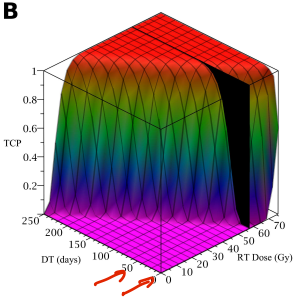


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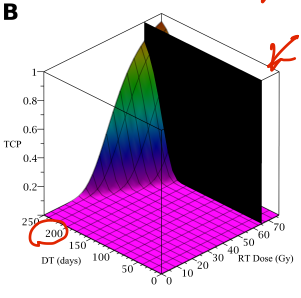


breast cancer

# More on treatments

- In (Konstorum et al 2016) we included various feedback mechanisms and found an Allee effect.

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- In (Konstorum et al 2016) we included various feedback mechanisms and found an Allee effect.
- In (Jilkine, Gutenkunst 2014, Rhodes, TH, 2016) study of de-differentiation. We include a de-differentiation promoter survivin and a survivin inhibitor YM155 and fitted the model to mouse data. Inhibition of survivin leads to better treatment.

# Back to the reaction-diffusion model (Model 3)

$$
\begin{aligned}
u_t &= Du_{xx} + \delta\gamma k(p)(u + Bu_{xx}) \\
v_t &= Dv_{xx} + (1-\delta)\gamma k(p)(u + Bu_{xx}) + \rho k(p)(v + Bv_{xx}) - \alpha v.
\end{aligned}
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**Theorem:** (Fasano et al 2016): Local and global existence of classical solutions.

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Simplify with $\gamma = \rho = 1$ and $B \approx 0$.

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**Theorem:** (Fasano et al 2016): Local and global existence of classical solutions.

Simplify with $\gamma = \rho = 1$ and $B \approx 0$.
**Model 3a:**

$$
\begin{aligned}
u_t &= Du_{xx} + \delta k(p)u \\
v_t &= Dv_{xx} + (1-\delta)k(p)u + \rho k(p)v - \alpha v.
\end{aligned}
$$

# The Tumor Invasion Paradox

$$\begin{aligned} u_t &= Du_{xx} + \delta k(p)u \\ v_t &= Dv_{xx} + (1-\delta)k(p)u + \rho k(p)v - \alpha v. \end{aligned}$$

**Theorem:** (A. Shyntar et al. 2022)
Assume $k(p)$ is decreasing and $k(0) = 1$.

# The Tumor Invasion Paradox

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**Theorem:** (A. Shyntar et al. 2022)
Assume $k(p)$ is decreasing and $k(0) = 1$.

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2. If $\alpha < 1$, then each front-like initial condition converges to a travelling wave with minimal wave speed
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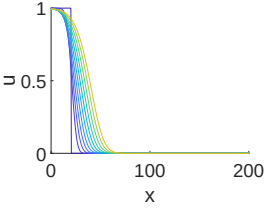
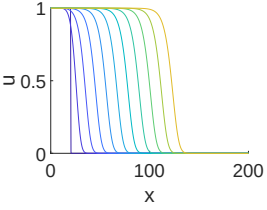
# Simulations (A. Shyntar)




$\alpha = 0.05$

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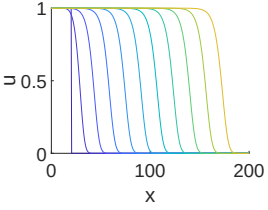
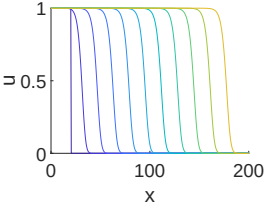



$\alpha = 1$




$\alpha = 5$

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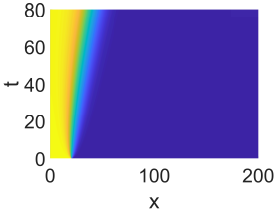
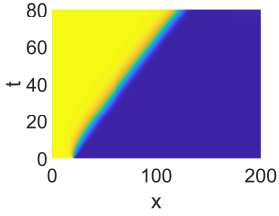



$\alpha = 0.05$

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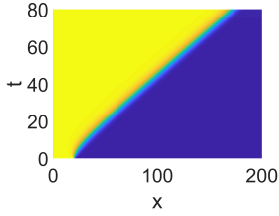
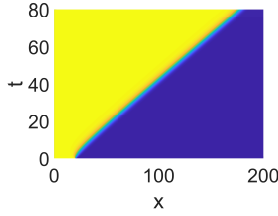



$\alpha = 1$

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- We show that this is of Fisher-KPP type and use the known results.

# Treatments (A. Shyntar)

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u_t &= D u_{xx} + \delta\gamma k(p) u - \varepsilon h(t) u \\
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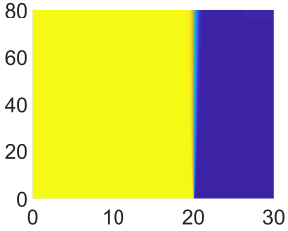
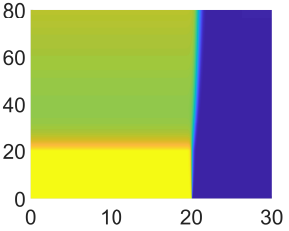
and two radiation dose rates $R_0 = 5.71$ Gy/day (realistic) and $R_0 = 50.0$ Gy/day (unrealistic).

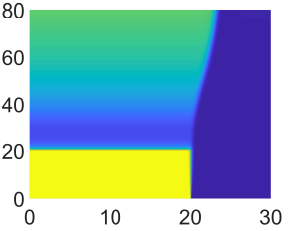
# Brachytherapy




no treatment

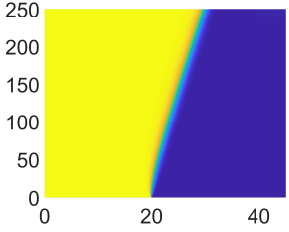



$R_0$ low

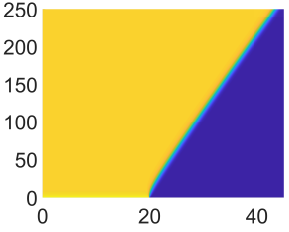



$R_0$ high

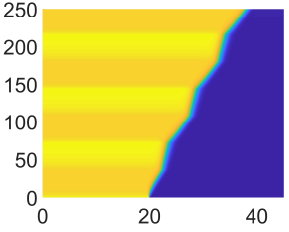
# Intermittent therapy




no treatment

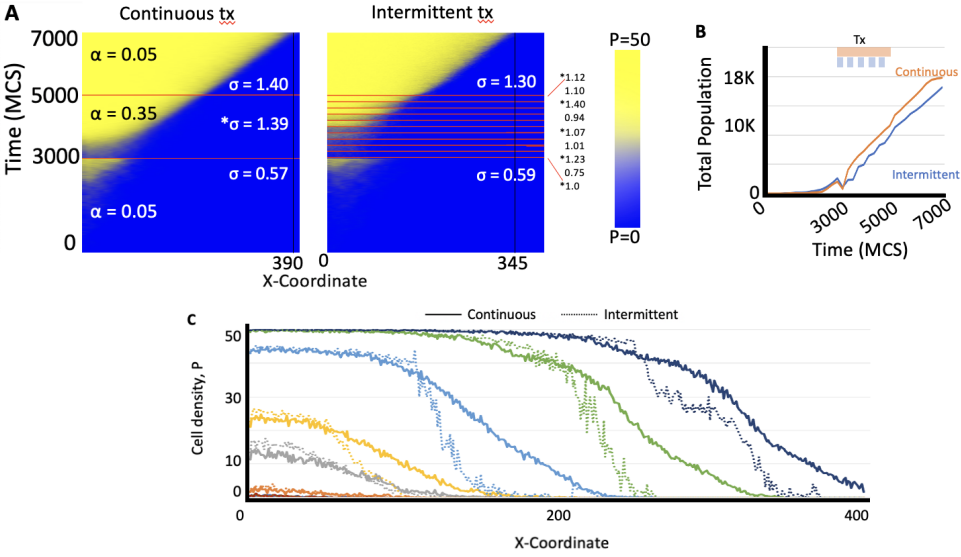



continuous

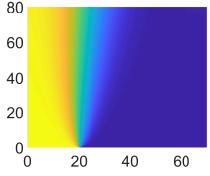



intermittent

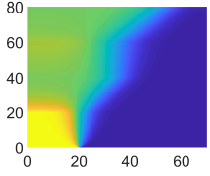
# Intermittent therapy (ABM)



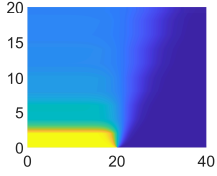
# Fractionation therapy (glioma parameters)



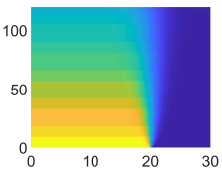

no treatment




20 days




2 days




10 min

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Thank you

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A. Shyntar, M. Rhodes, A. Patel, H. Enderling, P. Hahnfeldt, I. Borsi, A. Fasano, M. Primicerio