

# A Spatial Model of Tumor-Host Interaction: Application of Chemotherapy

Peter Hinow

Institute for Mathematics and its Applications, University of Minnesota,  
Minneapolis, MN 55455, USA

INRIA Rocquencourt, January 6th 2009



## Vanderbilt Integrative Cancer Biology Center 2nd Annual Workshop Nashville, TN, July 2006

Participants:  $\approx$  40 cancer biologists, biomedical engineers and mathematicians from the US and the UK.



- ▶ **Philip Gerlee**, Alexander R. A. Anderson (Division of Mathematics, University of Dundee, Scotland)
- ▶ Jason M. Graham, Bruce P. Ayati (Department of Mathematics, University of Iowa, Iowa City, IA)
- ▶ Lisa J. McCawley, Shizhen Wang, Vito Quaranta (Department of Cancer Biology, Vanderbilt University, Nashville, TN)
- ▶ Madalina Ciobanu (Department of Chemistry, Vanderbilt University, Nashville, TN)
- ▶ Mary Loveless (Department of Biomedical Engineering, Vanderbilt University, Nashville, TN)
- ▶ Jonathan Claridge, Kristin R. Swanson (Department of Applied Mathematics, University of Washington, Seattle, WA)

# Overview of the talk

- ▶ Introduction to the biological background
- ▶ Formulation of the mathematical model
- ▶ Numerical simulations
- ▶ Outlook, conclusion

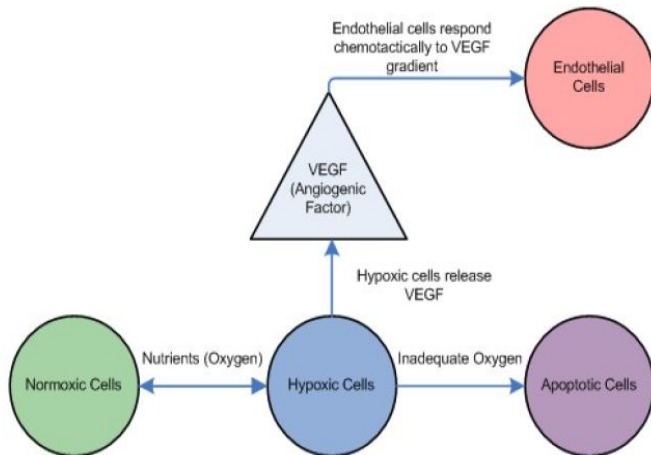
# General picture of cancer progression

- ▶ Disruption of cell growth regulation leads to primary tumor.
- ▶ The growth of the initial tumor mass limited by the diffusion of nutrients and oxygen towards the tumor.
- ▶ Necrotic cells in the center of the tumor secrete endothelial growth factors (e.g. VEGF).
- ▶ Endothelial cells are migrating towards the source of VEGF and new vasculature is established.
- ▶ Tumor cells enter the blood stream and form metastases in distant parts of the organism.

# Variables of the model

notation	concentration of
$n(x, t)$	normoxic (healthy, proliferating) tumor cells
$h$	hypoxic (quiescent) tumor cells
$a$	apoptotic tumor cells
$m$	endothelial cells (vasculature)
$f$	extracellular matrix
$g$	vascular endothelial growth factor (VEGF)
$w$	O <sub>2</sub> (or another nutrient)
$c$	cytotoxic drug

# Flow chart of tumor progression



# Specific features of the model

- ▶ Normoxic tumor cells undergo biased and unbiased migration.
  - ▶ haptotaxis with respect to a gradient of extracellular matrix density
  - ▶ additional pressure driven migration
- ▶ Lack of oxygen causes the hypoxic cells to produce VEGF.
- ▶ Gradient of VEGF provides chemotactic signal to the endothelial cells.

# Sample equation 1

The equation for oxygen concentration is

$$\frac{\partial w}{\partial t}(x, t) = D_w \frac{\partial^2 w}{\partial x^2} + \alpha_w m(w_{max} - w) - \beta_w(n + h + m) - \gamma_w w,$$

where  $D_w$  is the coefficient of oxygen diffusion,  $w_{max}$  is the maximum oxygen density,  $\beta_w$  is the uptake rate of oxygen by normoxic, hypoxic and endothelial cells and  $\gamma_w$  the loss rate of oxygen.

## Sample equation 2

The normoxic cells are governed by

$$\begin{aligned} \frac{\partial n}{\partial t}(x, t) = & \frac{\partial}{\partial x} \left( (D_n \max\{n - v_c, 0\} + D_m) \frac{\partial n}{\partial x} \right) - \frac{\partial}{\partial x} \left( \chi_n n \frac{\partial f}{\partial x} \right) \\ & + \alpha_n n (v_{max} - v) - \alpha_h \mathcal{H}(w_h - w) n + \frac{1}{10} \alpha_h \mathcal{H}(w - w_h) h. \end{aligned}$$

$\mathcal{H}$  = Heaviside function,  $v_c$  is the threshold for pressure driven migration.

## Sample equation 3

The equation for endothelial cells is

$$\frac{\partial m}{\partial t}(x, t) = \frac{\partial}{\partial x} \left( D_m \frac{\partial m}{\partial x} - m \chi_m \frac{\partial g}{\partial x} \right) + \alpha_m m g (v_{max} - v).$$

( $g$  is the concentration of angiogenic factor VEGF.)  $\dots + 6$  more.

# Nondimensionalization

Factor	Value	Meaning
$T$	$16 h$	cell cycle time
$L$	$1 cm$	typical length scale
$v_{max}$	$10^8 \text{ cells}/cm^3$	maximum density of cells
$w_{max}$	$6.7 \times 10^{-6} \text{ moles}/cm^3$	saturation level of oxygen
$g_{tot}$	$10^{13} \text{ moles}/cm^3$	maximal VEGF concentration

# Sample parameter values

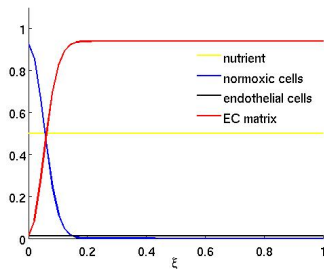
Parameter	Value	Reference
$D_w$	$10^{-5} \text{ cm}^2 \text{ s}^{-1}$	Anderson 2005
$\beta_w$	$6.25 \times 10^{-17} \text{ mol cell}^{-1} \text{ s}^{-1}$	Casciari et al. 1992
$D_m$	$10^{-9} \text{ cm}^2 \text{ s}^{-1}$	Bray 1992
$\beta_h$	$5.6 \times 10^{-6} \text{ s}^{-1}$	Borutaite 2005
$\chi_m$	$2.6 \times 10^3 \text{ cm}^2 \text{ s}^{-1} \text{ M}^{-1}$	Stokes et al. 1991
	...	

Some parameters are published in the literature, others have to be estimated.

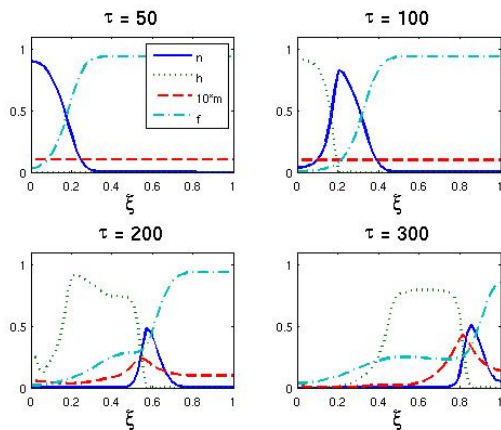
# Initial and boundary conditions

$$\begin{aligned}w(\xi, 0) &= 1.0, & \xi \in [0, 1], \\n(\xi, 0) &= 0.93 \exp(-200\xi^2), \\m(\xi, 0) &= 0.01, \\f(\xi, 0) &= 1 - n(\xi, 0) - m(\xi, 0) - 0.05,\end{aligned}$$

No-flux conditions for all species are imposed.



# Results: baseline scenario



The spatial distribution of normoxic, hypoxic,  $10 \cdot$ endothelial cells and extracellular matrix at  $\tau = 50, 100, 200, 300$  for the baseline scenario (300 cell cycles  $\approx$  200 days).

# Cytostatic and cytotoxic chemotherapy

- ▶ Cytostatic drugs inhibit cell division or some other function of tumor or host cells (e.g. angiogenesis).
- ▶ Cytotoxic drugs actively kill proliferating tumor (and healthy) cells.

# Antiangiogenic chemotherapy (e.g. Avastin)

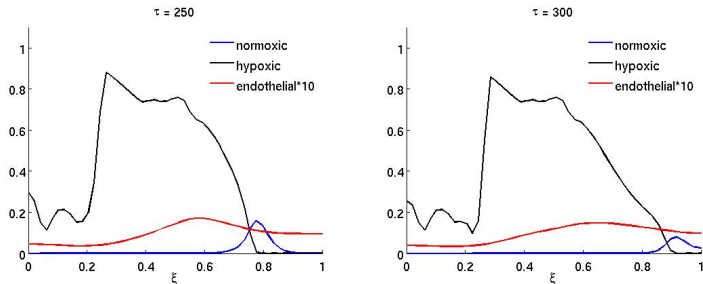
Recall the equation for endothelial cells

$$\frac{\partial m}{\partial t}(x, t) = \frac{\partial}{\partial x} \left( D_m \frac{\partial m}{\partial x} - m \chi_m \frac{\partial g}{\partial x} \right) + \alpha_m m g (v_{max} - v).$$

The drug can reduce the proliferation rate of endothelial cells  $\alpha_m$  or their chemotactic sensitivity  $\chi_m$ .

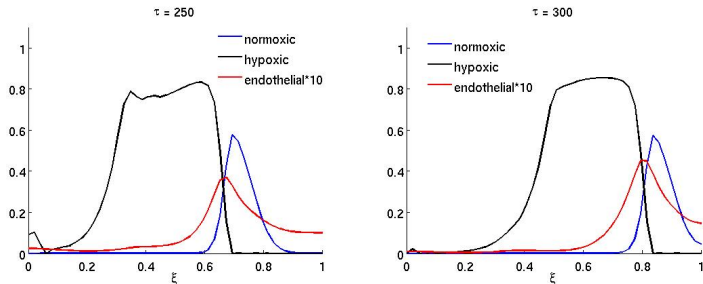
We let  $\alpha_m \rightarrow \alpha_m/10$  or  $\chi_m \rightarrow \chi_m/10$ .

# Results: Antiangiogenic therapy



Spatial distribution of normoxic, hypoxic and endothelial cells if  $\alpha_m$  is replaced by  $\alpha_m/10$ .

# Results: Antiangiogenic therapy



Spatial distribution of normoxic, hypoxic and endothelial cells if  $\chi_m$  is replaced by  $\chi_m/10$ .

We include a new equation for a cytotoxic drug,

$$\frac{\partial c}{\partial \tau}(\xi, \tau) = D_c \frac{\partial^2 c}{\partial \xi^2} + \alpha_c(\tau)m(1 - c) - \gamma_c c - \gamma_n n c.$$

- ▶ The drug enters the tissue from the blood stream, hence its production rate is proportional to the density of endothelial cells.
- ▶ The scheduling of the drug is time-dependent through the production rate  $\alpha_c(\tau)$ .
- ▶ The drug is cleared from the body at a constant rate  $\gamma_c$ .

The normoxic cells are driven into apoptosis at a rate proportional to the drug concentration

$$\begin{aligned}\frac{\partial n}{\partial t}(x, t) &= \dots - \gamma_n n c \\ \frac{\partial a}{\partial t}(x, t) &= \dots + \gamma_n n c,\end{aligned}$$

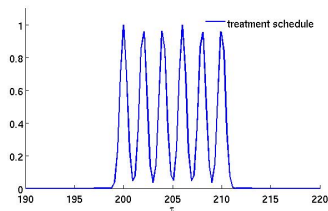
with rate constant  $\gamma_n > 0$ .

*Question:* Given a fixed treatment schedule, how do the kill rate  $\gamma_n$  and decay rate  $\gamma_c$  of the drug affect the tumor growth?

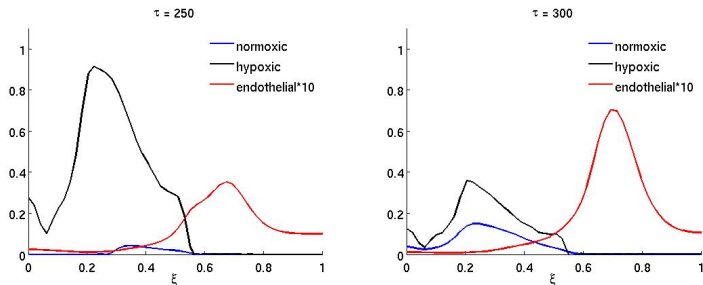
# Treatment schedule

$$\alpha_c(\tau) = 100 \sum_{k=0}^5 \exp(-4(\tau - (200 + 2k))^2)$$

6 infusions of the drug are given, each infusion lasts approximately 1 cell cycle (= 16 h), the interval between two infusions is 2 cell cycles.



# Results: Cytotoxic chemotherapy



The spatial distribution of normoxic, hypoxic and endothelial cells after chemotherapy has been applied with the drug parameters  $\gamma_n = 10$  and  $\gamma_c = 0.1$ .

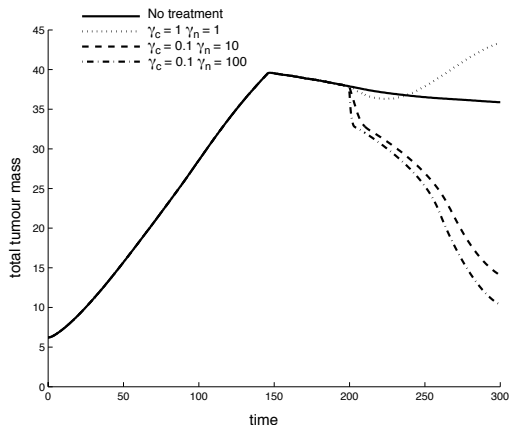
# Results: Cytotoxic chemotherapy

Define the normalized post-treatment mass at the final time  $\tau_s = 300$  by

$$M = \frac{1}{M_0} \int_0^1 (n(\xi, \tau_s) + h(\xi, \tau_s)) d\xi,$$

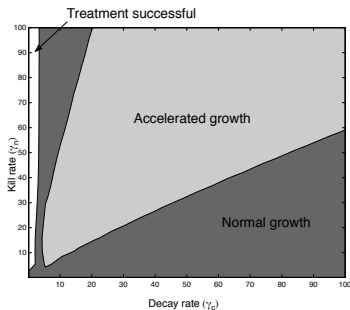
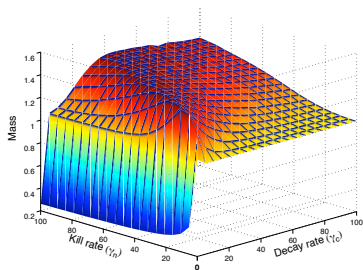
where  $M_0$  is the final tumor mass in case of no treatment.

# Examples of treatment outcomes



The time evolution of the total tumor mass (normoxic plus hypoxic cells) for the baseline scenario and three different chemotherapy parameter sets.

# Treatment surface



The division of drug parameter space ( $\gamma_c =$  decay rate,  $\gamma_n =$  kill rate) into three distinct regions: (i) successful treatment (ii) normal growth and (iii) accelerated growth.

# Conclusions

- ▶ We have built a mathematical model of reaction-diffusion type that takes into account the complex interactions between the tumor and surrounding stromal cells.
- ▶ It is possible to simulate cytostatic and cytotoxic chemotherapies in a spatial context.
- ▶ Endothelial cells supply the tumor with essential nutrients, but also, when therapy is applied, with detrimental drugs.
- ▶ In an antiangiogenic therapy the prevention of proliferation carries more weight than the prevention of chemotaxis of endothelial cells.
- ▶ Cytotoxic therapy can have indirect effects on the micro-environment of the tumor and can even make the growth conditions more beneficial for the tumor.

# Acknowledgments

- ▶ National Cancer Institute ICBP program (U54-CA113007)
- ▶ Dr. Lourdes Estrada, Vanderbilt Integrative Cancer Biology Center (VICBC)

Thank you for your attention

P. Hinow, P. Gerlee et al. A Spatial Model of Tumor-Host Interaction: Application of Chemotherapy *Math. Biosci. Eng*, to appear [arXiv:0810.1024](https://arxiv.org/abs/0810.1024)

Shanks conference on mathematical biology (organizer: Glenn Webb): May 18–21, 2009 [www.math.vanderbilt.edu](http://www.math.vanderbilt.edu)

Vanderbilt Integrative Cancer Biology Center (VICBC)  
[www.vanderbilt.edu/VICBC](http://www.vanderbilt.edu/VICBC), annual workshops in July or August