Mathematical Models for Angiogenic and Metabolic Activity in Solid Tumors

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June 19, 2012

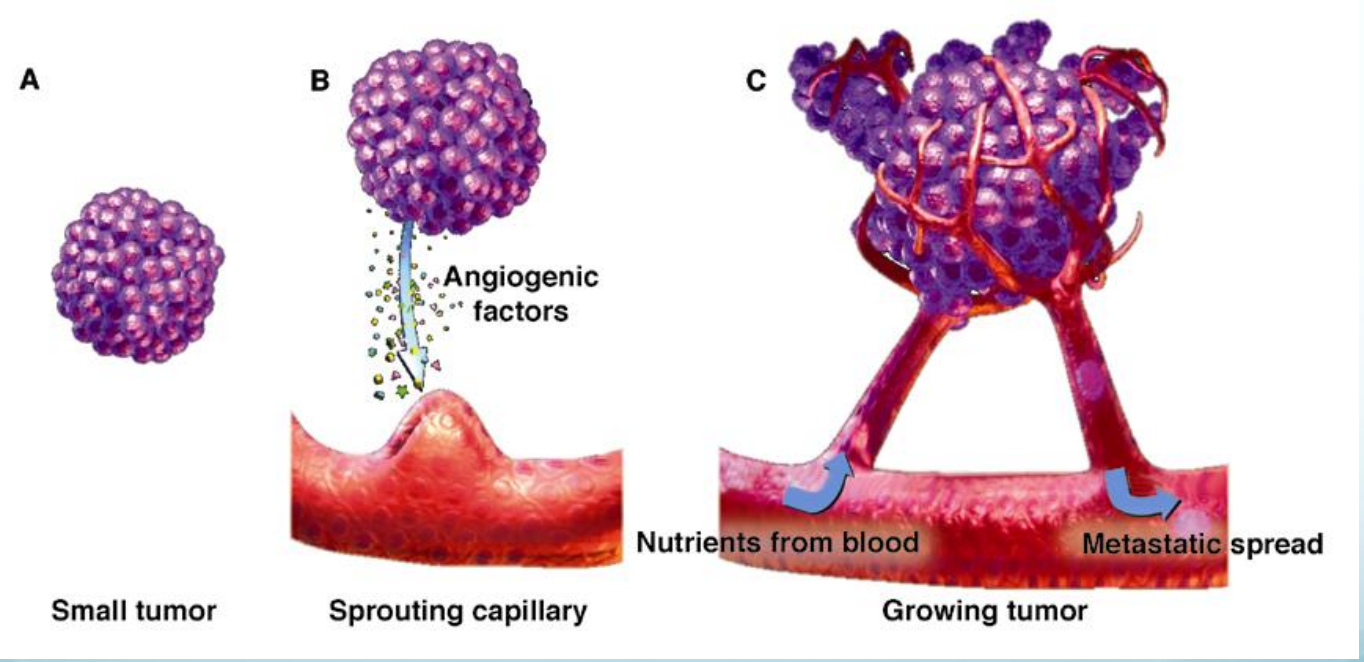
KITP

Outline

- Background
- Mathematical model
  - Angiogenic growth factor transport
  - Interstitial fluid pressure
- Results
- Other projects
  - Microvessel model for metabolism
  - Predicting cell viability from protein expression

Tumor angiogenesis

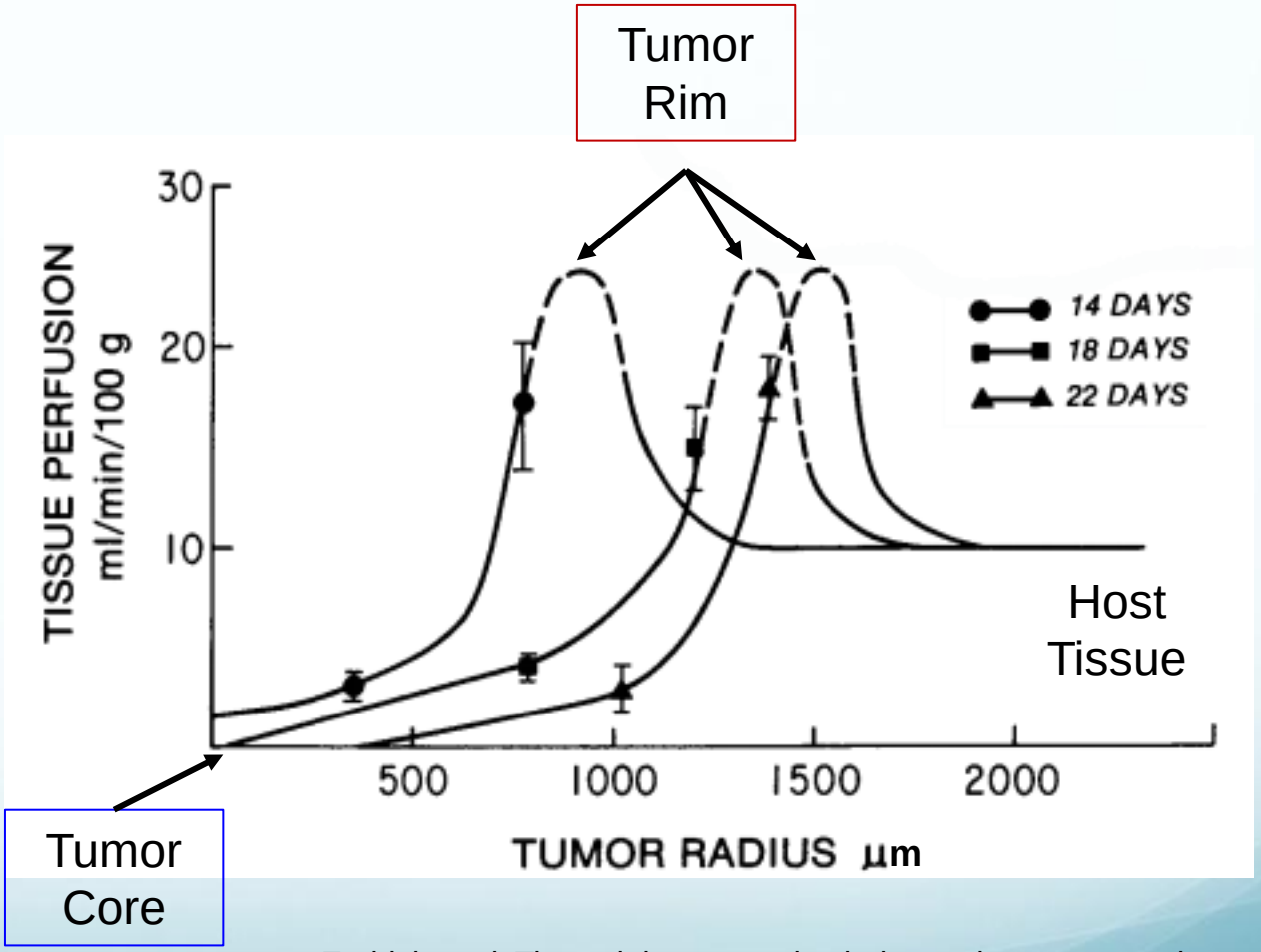
- Tumors initiate angiogenesis: formation of new blood vessels from pre-existing vessels
  - Hypoxia causes cells to produce angiogenic growth factors (AGFs)
    - e.g. proangiogenic: VEGF, antiangiogenic: angiostatin
  - Disrupts balance between proangiogenic and antiangiogenic factors
  - Blood vessels send sprouts toward tumor



Siemann DW., Vascular targeting agents. Horizons in Cancer Therapeutics: From Bench to Bedside. 2002;3(2):4-15

Tissue perfusion

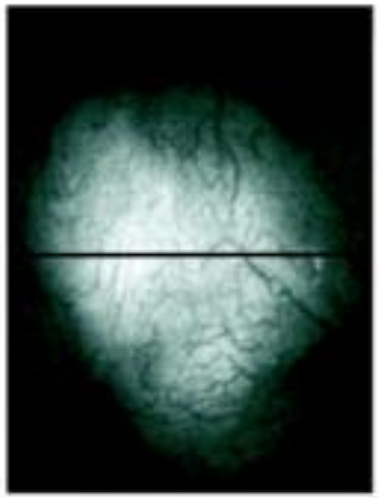
- Blood flow:
  - Highest at tumor rim
  - Lowest at tumor core
  - Reaches steady state in host tissue

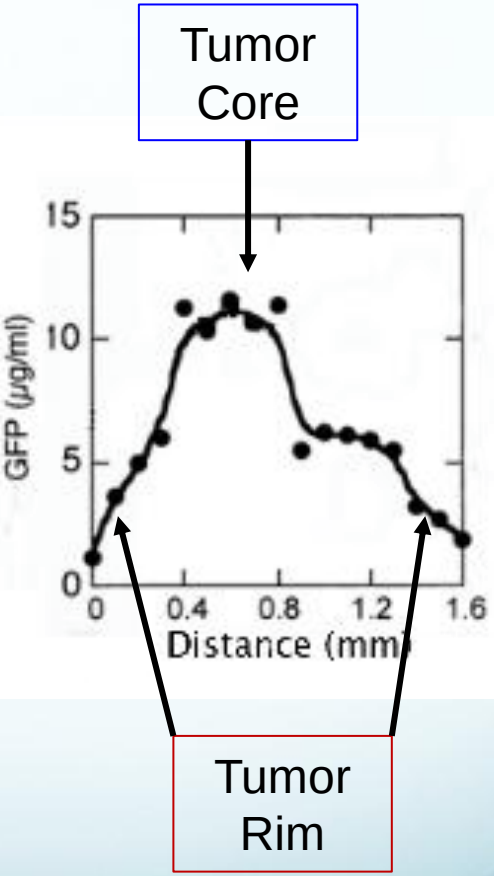


Endrich et al. Tissue inhomogeneity during early tumor growth in rats. J. Natl. Cancer Inst., 62 (1979), 387-395.

Angiogenic growth factors

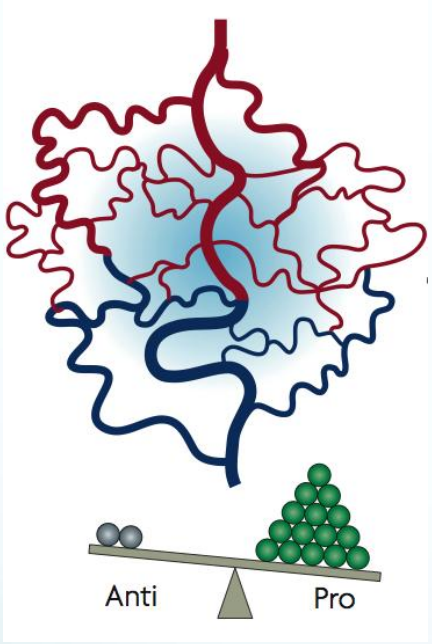
- VEGF concentration:
  - Highest at tumor core
  - Decreasing at rim
  - Reaches steady sate outside tumor
- [GFP] α [VEGF promoter]
- Observation:[vasculature] α [VEGF]
- Goal: Propose ‘next’ simplest relation





Fukumura et al. Hypoxia and acidosis independently upregulate VEGF… Cancer research (2001)

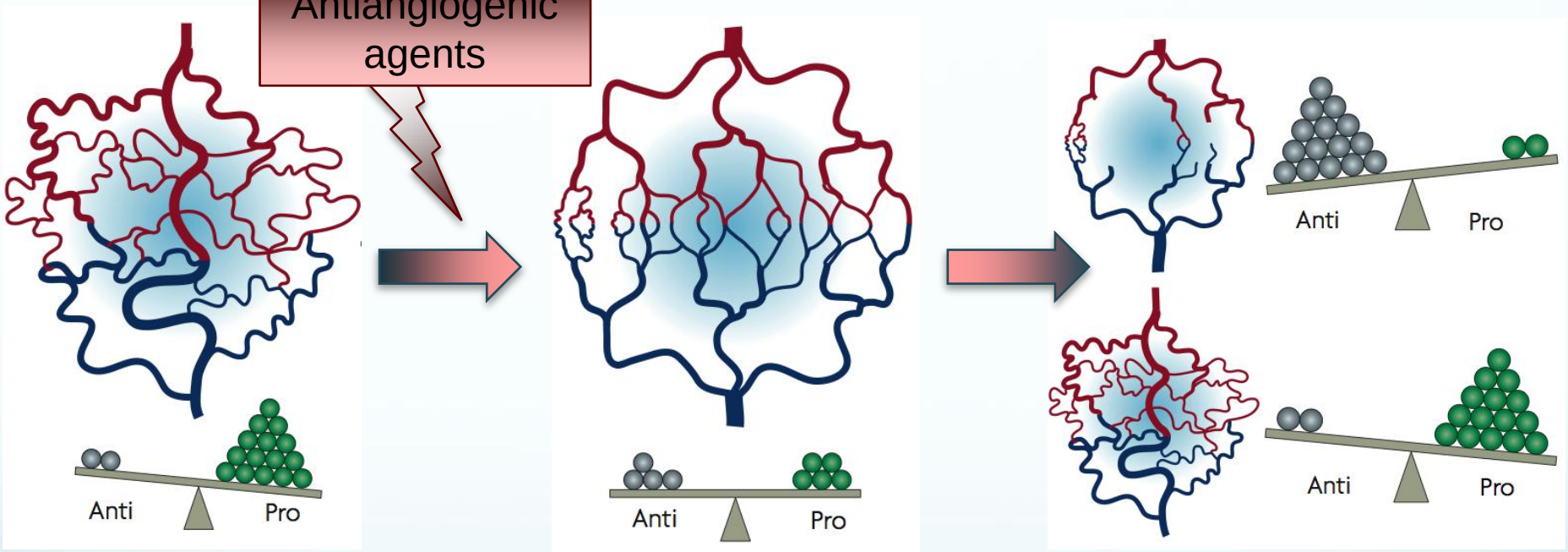
Tumor vessels



- Tumor angiogenesis:
  - poorly regulated and hasty
- Tumor blood vessel networks:
  - Tortuous, unorganized, inefficient and experience inconsistent perfusion
  - Hinders drug delivery
- Tumor vessels are leaky
  - Leads to elevated interstitial fluid pressure and outward convective transport
  - Helps short-term delivery
- Clinical goals
  - Normalize tumor blood vessel network
  - Alleviate elevated interstitial fluid pressure

R.K. Jain. Nat. Rev. Cancer 8:309-316 (2008).

Tumor normalization



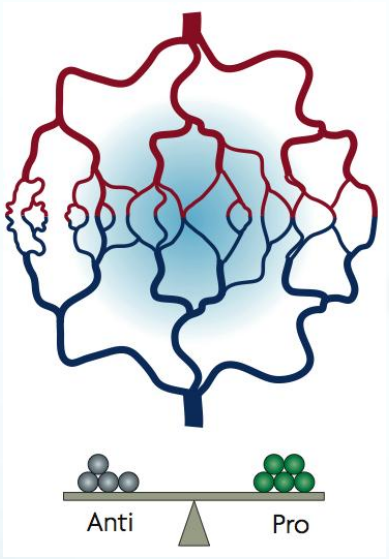
Abnormal tumor vasculature

Normalized

Reversion to abnormal structure

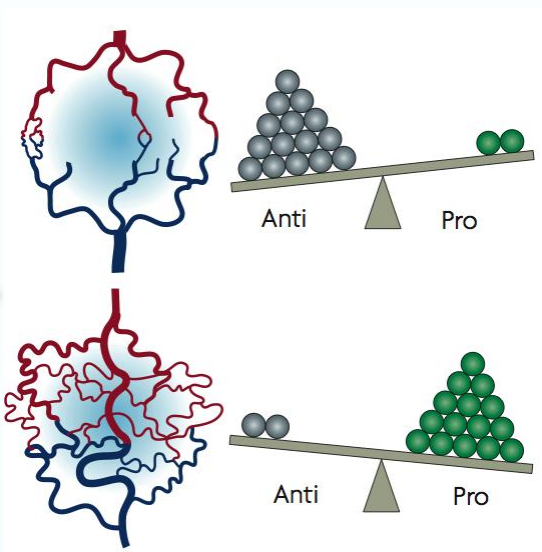
R.K. Jain. Nat. Rev. Cancer 8:309-316 (2008).

Normalization window

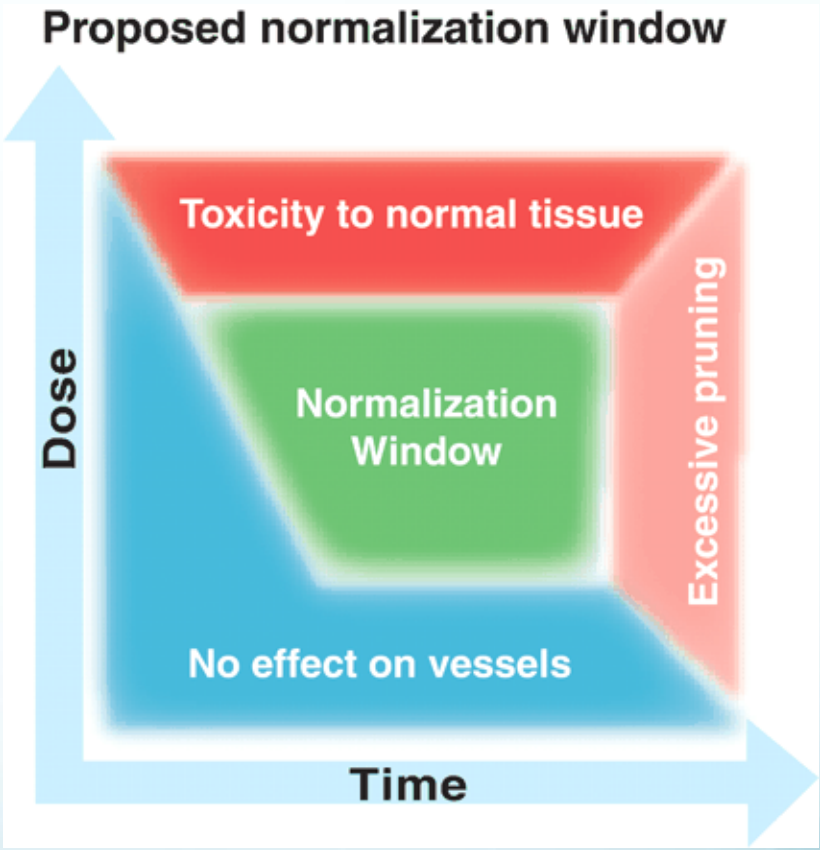


Normalized

Excessive pruning



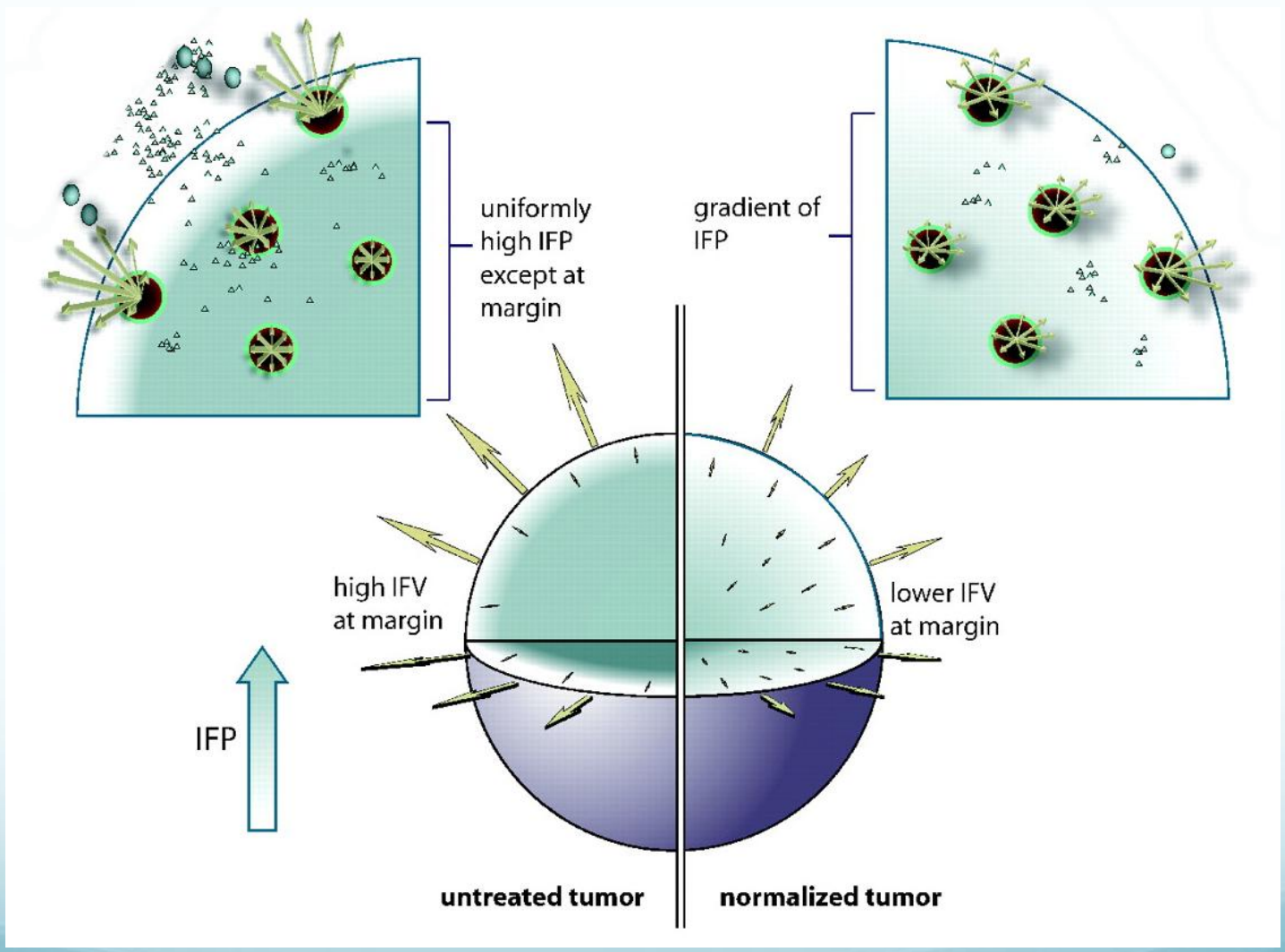
Reversion to abnormal structure



R.K. Jain. Nat. Rev. Cancer 8:309-316 (2008).

RK Jain. Science 7 (2005).

Pressure normalization



R.K. Jain. Nat. Rev. Cancer 8:309-316 (2008).

Interstitial flow and angiogenesis

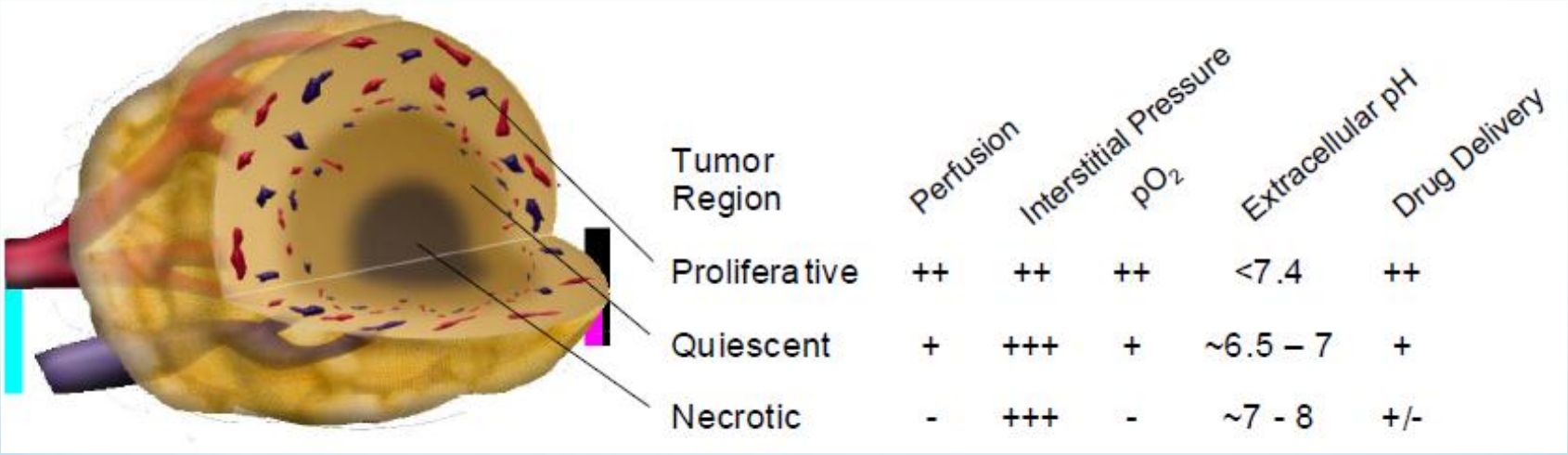
- Interstitial flow is crucial to capillary formation (Helm et al., PNAS, 2005):
  - VEGF or interstitial flow alone do not lead to capillary formation
  - BOTH must be present in order for capillaries to form
- Molecular weights of these factors suggest that convection could be important to their interstitial transport

Table 1: Molecular weights of common proangiogenic and antiangiogenic growth factors

Molecule	Angiogenic category	Size (kDa)
$VEGF_{165}$ dimer	Proangiogenic	45 (Ferrera *et al.*, 1989)
FGF family	Proangiogenic	17-34 (Ornitz *et al.*, 2001)
TSP-1	Antiangiogenic	140 (Rastinejad *et al.*, 1989)
angiostatin	Antiangiogenic	38 (O'Reilly *et al.*, 1994)
endostatin	Antiangiogenic	20 (O'Reilly *et al.*, 1997)

Tumor microenvironment

- High interstitial pressure
- Perfusion/Diffusion-limited hypoxia
- Low pH (altered metabolism)



Tumor Region	Perfusion	Interstitial Pressure	pO_2	Extracellular pH	Drug Delivery
Proliferative	++	++	++	<7.4	++
Quiescent	+	+++	+	~6.5 – 7	+
Necrotic	-	+++	-	~7 - 8	+/-

Jain RK, Forbes NS, PNAS 98, 14748 (2001).

Macromolecule transport

- Continuity equation for concentration of a macromolecule *c*, with flux *J* and production rate *P*

$$\frac{\partial c}{\partial t} + \nabla \cdot J = P$$

- Flux is sum of diffusive and convective fluxes:

$$J = J_D + J_C = -D\nabla c + \vec{v}c$$

- Concentration in steady state: $\nabla \cdot (-D\nabla c + \vec{v}c) = P$
- Constant diffusion coefficient and macromolecule velocity proportional to interstitial fluid velocity: $\vec{v} = r\vec{u}$

$$-D\nabla^2 c + r\nabla \cdot (\vec{u}c) = P$$

- Constant production and degradation rates:

$$-D\nabla^2 c + r\nabla \cdot (\vec{u}c) = g - kc$$

AGF equation

- Geometry: spherical tumor of fixed radius *R*, embedded in host tissue
- Two AGF categories: antiangiogenic, with concentration f_a, and proangiogenic, with concentration f_p, assume $r_j \approx 1$

$$-D_j \nabla^2 f_j + \nabla \cdot (\vec{u} f_j) = g_j - k_j f_j, \qquad j = p, a$$

where D_j, g_j and k_j differ inside and outside the tumor,

e.g.
$$D_j = \begin{cases} D_j^t & 0 \le r < R \\ D_j^h & r \ge R \end{cases}$$

- Spherical Laplacian and divergence:

$$-\frac{D_j}{r^2}\frac{d}{dr}\left(r^2 \frac{df_j}{dr}\right) + \frac{1}{r^2}\frac{d}{dr}\left(r^2 u f_j\right) = g_j - k_j f_j, \qquad j = p, a.$$

EA Swabb et al. Diffusion and convection in normal and neoplastic tissues. Cancer research (1974)

Boundary conditions

- Spherical symmetry at core:

$$-D_j^t \frac{df_j}{dr} + uf_j = 0, \qquad r = 0.$$

- Continuity of concentration and flux at boundary:

$$f_j(R^-) = f_j(R^+) \qquad \left(-D_j^t \frac{\P f_j}{\P r} + uf_j\right)\Big|_{r=R^-} = -\left(D_j^h \frac{\P f_j}{\P r} + uf_j\right)\Big|_{r=R^-}$$

- Far-field no flux:

$$-D_j^h \frac{df_j}{dr} + uf_j = 0, \qquad r \to \infty.$$

- Concentrations approach steady state in host tissue:

$$f_j^s = \frac{g_j^h}{k_j^h}$$

Interstitial fluid pressure and velocity

- Model for interstitial fluid pressure (IFP)
  - Continuity equation for steady state incompressible flow

$$\nabla \cdot u = f(r)$$

- Darcy's Law

$$u = -K\nabla p$$

  - u - interstitial fluid velocity (IFV)
  - p - interstitial fluid pressure
  - K – hydraulic conductivity of interstitium

- Starling's Law

$$f(r) = L_p \Phi \left(p_v - p - \sigma (p_v - p_i) \right)$$

  - L_p - hydraulic conductivity of vessel wall
  - Φ - surface area of vessel wall per unit volume of tumor
  - p_v - vascular pressure
  - $\pi_{v(i)}$ - plasma osmotic (interstitial) pressure
  - σ - average osmotic reflection coefficient for plasma proteins
    - LT Baxter, RK Jain, Microvascular Research 37 (1989)

- Pressure equation

$$\nabla^2 p = -\frac{L_p \Phi}{K}(p_e - p)$$

  - Effective pressure $p_e = p_v - \sigma (p_v - p_i)$
  - In tumors: $p_e \gg p_v$

Interstitial fluid pressure and velocity

- Spherical Laplacian:

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dp}{dr}\right) = -\frac{\alpha^2}{R^2}(p_e - p), \qquad \alpha = R\sqrt{\frac{L_p F}{K}}$$

  where α and p_e can differ between tumor and host tissue

- Spherical symmetry at core: $\left.\frac{dp}{dr}\right|_{r=0} = 0$
- Continuity of concentration and velocity at boundary:

$$p(R^-) = p(R^+), \qquad u(R^-) = u(R^+) \qquad \text{i.e. } -K^t \left.\frac{dp}{dr}\right|_{r=R^-} = -K^h \left.\frac{dp}{dr}\right|_{r=R+}$$

- Far-field zero flux:

$$\frac{dp}{dr} = 0, \qquad r \to \infty$$

- This leads to pressure approaching a steady state, assumed to be

$$p_e^h = 0$$

Non-dimensionalized system

- Radial distance $\tilde{r} = \frac{r}{R}$
- AGFs:

$$-\frac{1}{\tilde{r}^2}\frac{d}{d\tilde{r}}\left(\tilde{r}^2\frac{d\tilde{f}_j}{d\tilde{r}}\right)+\frac{\tilde{K}_j}{\tilde{r}^2}\frac{d}{d\tilde{r}}\left(\tilde{r}^2\tilde{u}\tilde{f}_j\right)=\tilde{g}_j-\tilde{k}_j\tilde{f}_j, \qquad \tilde{f}_j=\frac{f_j}{f_j^s}$$

- Pressure

$$\frac{1}{\tilde{r}^2}\frac{d}{d\tilde{r}}\left(\tilde{r}^2\frac{d\tilde{p}}{d\tilde{r}}\right)=-a^2(1-\tilde{p}), \qquad \tilde{p}=\frac{p}{p_e^t}$$

- Velocity

$$\tilde{u}=-\frac{d\tilde{p}}{d\tilde{r}}, \qquad \tilde{u}=\frac{u}{K^t p_e^t / R}$$

Non-dimensional parameters

AGFs

$$\tilde{k}_j^t = R^2 \frac{k_j^t}{D_j^t}$$

$$\tilde{g}_j^t = R^2 \frac{g_j^t}{D_j^t f_j^s}$$

$$\tilde{K}_j^t = \frac{K^t p_e^t}{D_j^t}$$

$$\tilde{k}_j^h = R^2 \frac{k_j^h}{D_j^h}$$

Production

$$\tilde{g}_j^h = R^2 \frac{k_j^h}{D_j^h} = \tilde{k}_j^h$$

Degradation

$$\tilde{K}_j^h = \frac{K^h p_e^t}{D_j^h}$$

Molecular Transport

$\tilde{r} = 0$ $\tilde{r} = 1$

Pressure

$$a^t = R\sqrt{\frac{L_p^t \mathsf{F}^t}{K^t}}$$

$$a^h = R\sqrt{\frac{L_p^h \mathsf{F}^h}{K^h}}$$

Fluid Transport

Angiogenic Activity

- Non-dimensional factor concentrations approach 1 in host tissue
- Measure of angiogenic activity from Stoll et al. (2003)

$$a(r) = \begin{cases} \dfrac{\tilde{f}_p}{\tilde{f}_a} - 1, & \tilde{f}_p \geq \tilde{f}_a \\ 1 - \dfrac{\tilde{f}_a}{\tilde{f}_p}, & \tilde{f}_p < \tilde{f}_a \end{cases}$$

  - If a>0 angiogenesis is initiated
  - If a=0 the vasculature is stable
  - If a<0 vessels are regressing

- Angiogenic activity classes:
  - Global angiogenesis: a>0 in the tumor
  - Focal suppression: a<0 at tumor core, a>0 at tumor rim
  - Global suppression: a<0 in the tumor
- Purpose: Analyze sensitivity to physiological parameters

Solution method

- Analytical solutions for pressure and velocity can be found:

$$\tilde{u}(\tilde{r}) = \begin{cases} \dfrac{1+a^h}{f+q}\dfrac{a^t\tilde{r}\cosh(a^t\tilde{r}) - \sinh(a^t\tilde{r})}{\tilde{r}^2} & 0 \le \tilde{r} < 1 \\ \dfrac{q}{f+q}\dfrac{(a^h\tilde{r}+1)\exp(a^h(\tilde{r}-1))}{\tilde{r}^2} & \tilde{r} \ge 1 \end{cases}$$

$$q = \frac{K^t}{K^h}(a^t\cosh(a^t) - \sinh(a^t)), \quad f = (1+a^h)\sinh(a^t)$$

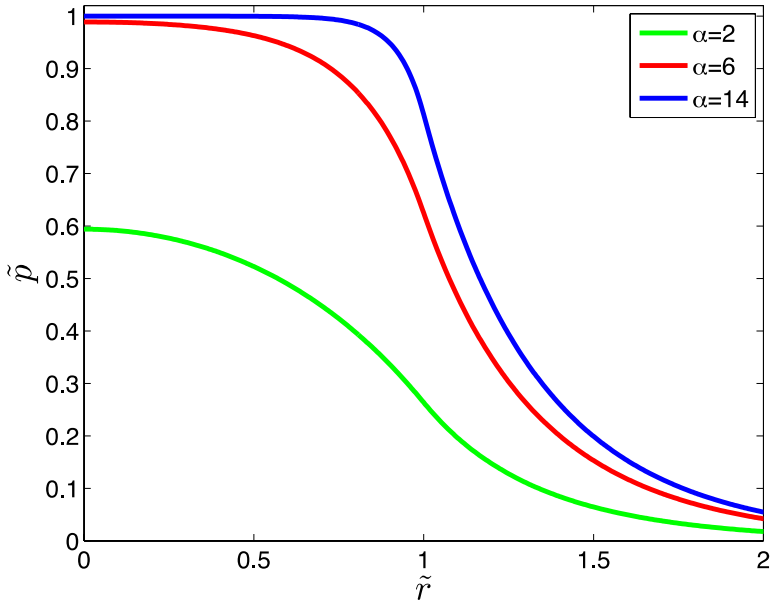
- If $\tilde{u}=0$ then we can find analytical solutions for AGFs [3], otherwise we rely on numerical integration schemes
- Determine measure of angiogenic activity

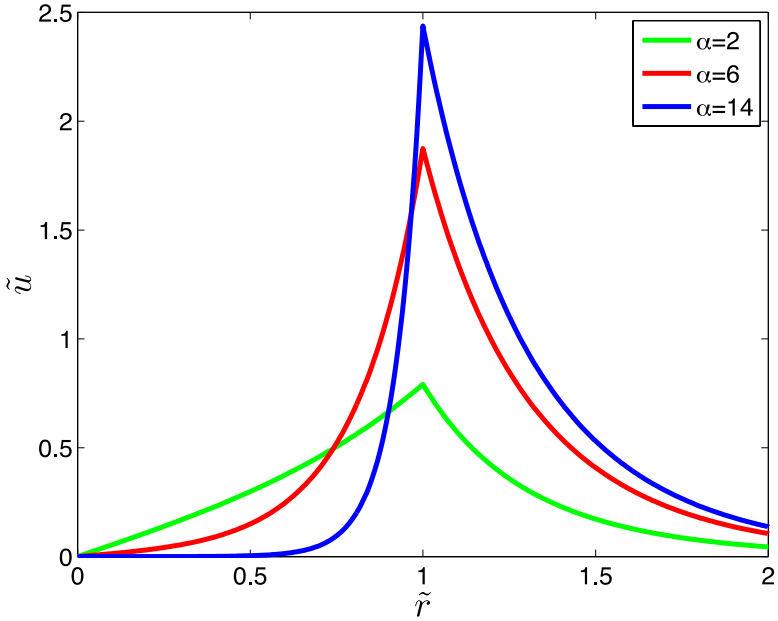
[3] Ramanujan et al. Cancer Res, 60: 1442-1448 (2000).

Interstitial fluid pressure and velocity

$$\nabla^2 \tilde{p} = -a^2(1 - \tilde{p})$$

$$\tilde{u} = -\nabla \tilde{p}$$

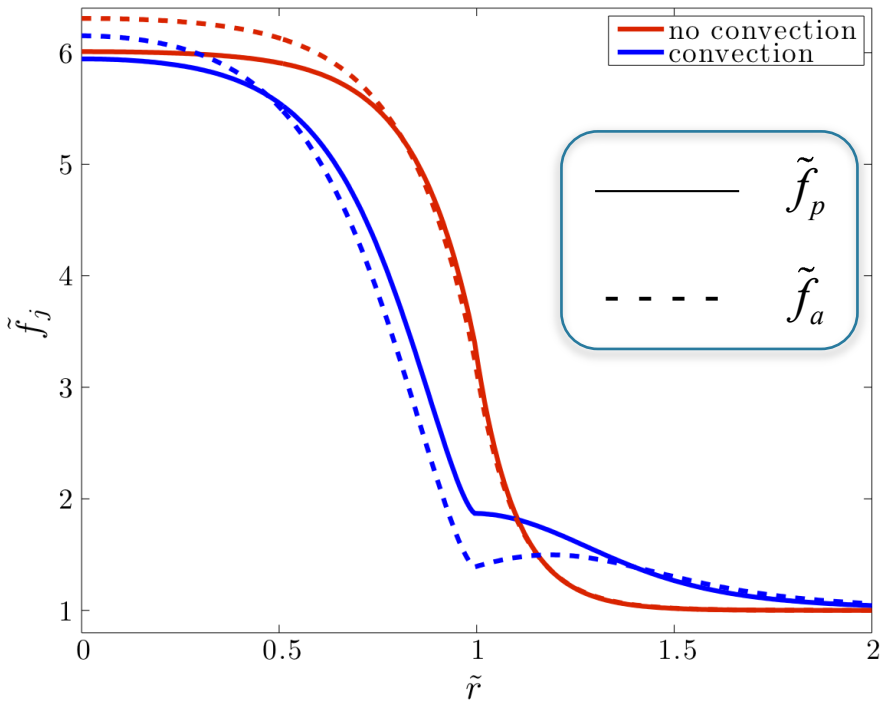




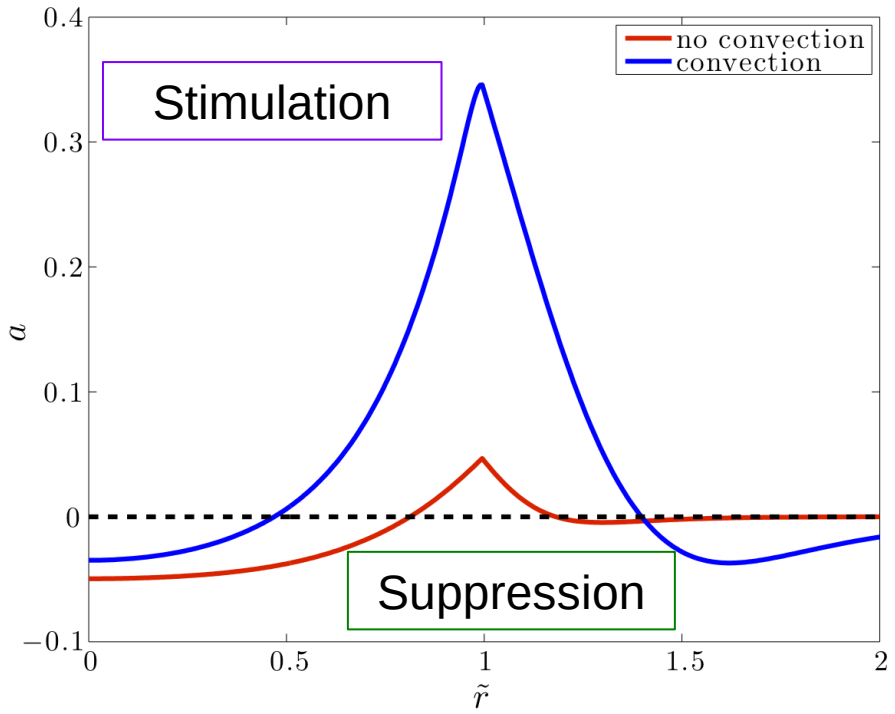
$$a^t = R\sqrt{\frac{L_p^t \mathrm{F}^t}{K^t}}$$ - Þ pressure rises in the tumor
drastic pressure drop at rim Þ low velocity in tumor core
high velocity at tumor rim

Convection

AGF concentrations



Angiogenic activity



add convection Þ factors pushed out of tumor

large difference at rim

Þ angiogenic suppression at core

high angiogenic activity at tumor rim

C. Phipps and M. Kohandel. Mathematical model of the effect of interstitial fluid pressure on angiogenic behavior in solid tumors. Comp Math Meth Med, 2011.

Correlation with necrotic volume

- Assume necrotic volume is proportional to suppressed volume: $V_n=\beta V_s$
- Best fit for quantitative agreement: $\beta=0.47$

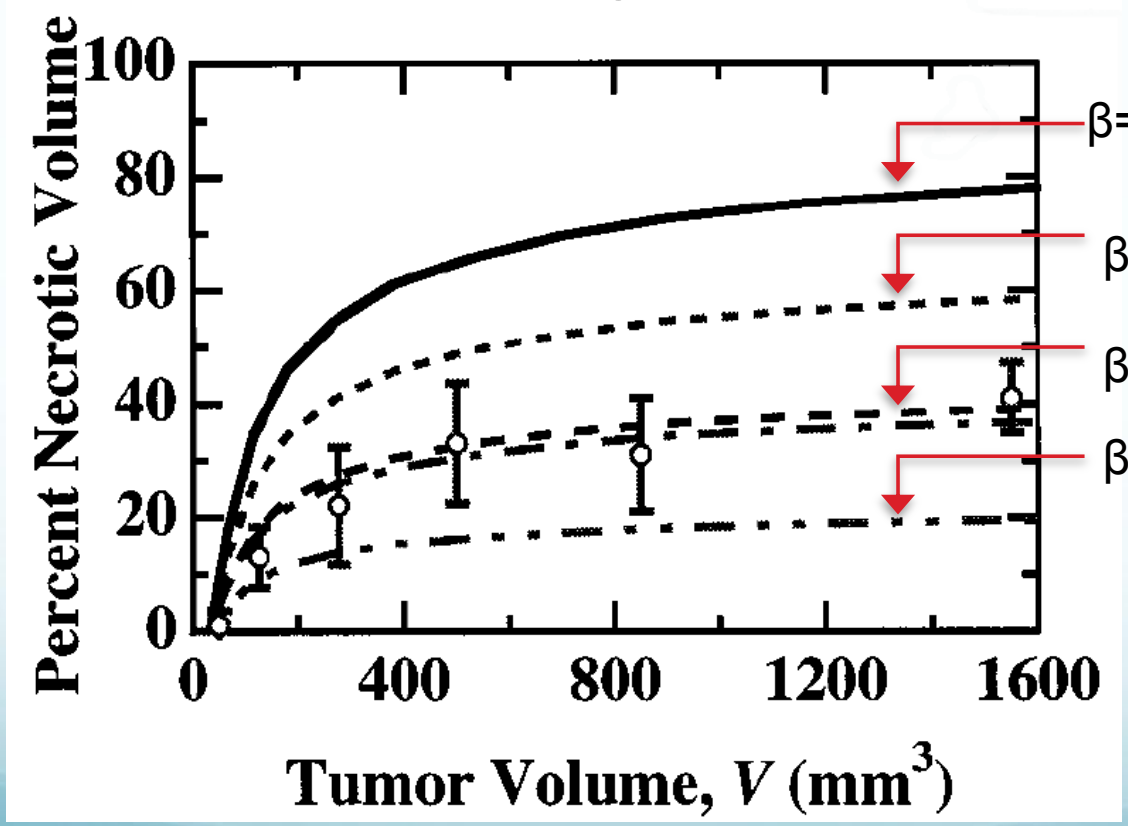
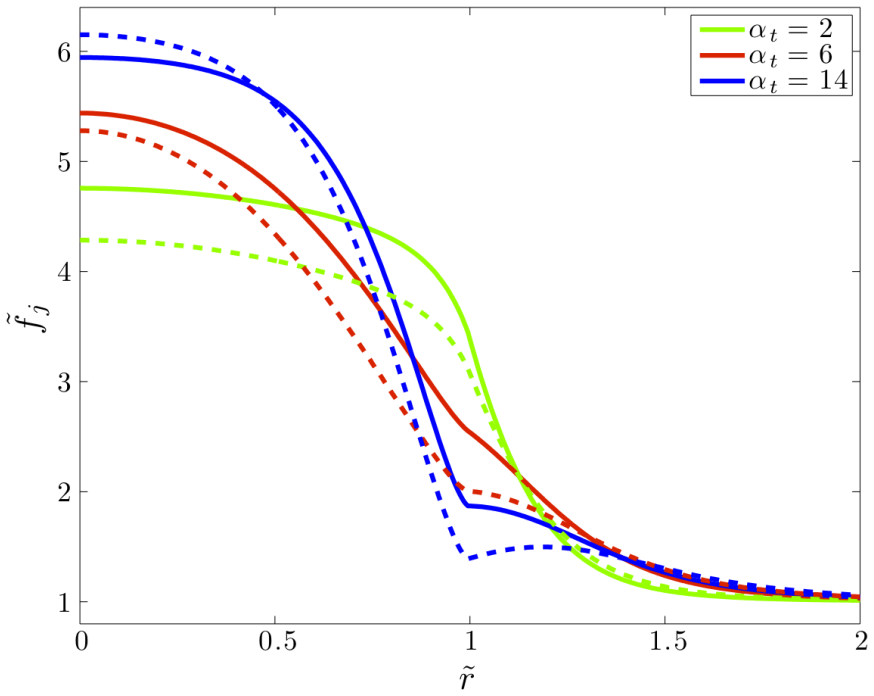


Image: Ramanujan et al. Cancer Res, 60: 1442-1448 (2000).

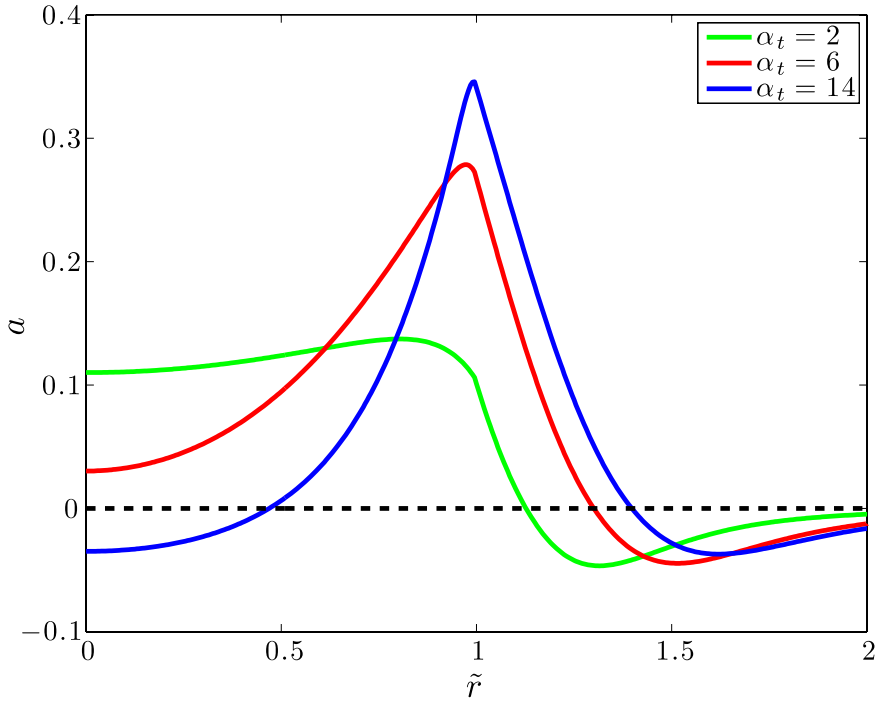
Pressure parameter

$$a^t = R\sqrt{\frac{L_p^t \mathsf{F}^t}{K^t}}$$

AGF concentrations



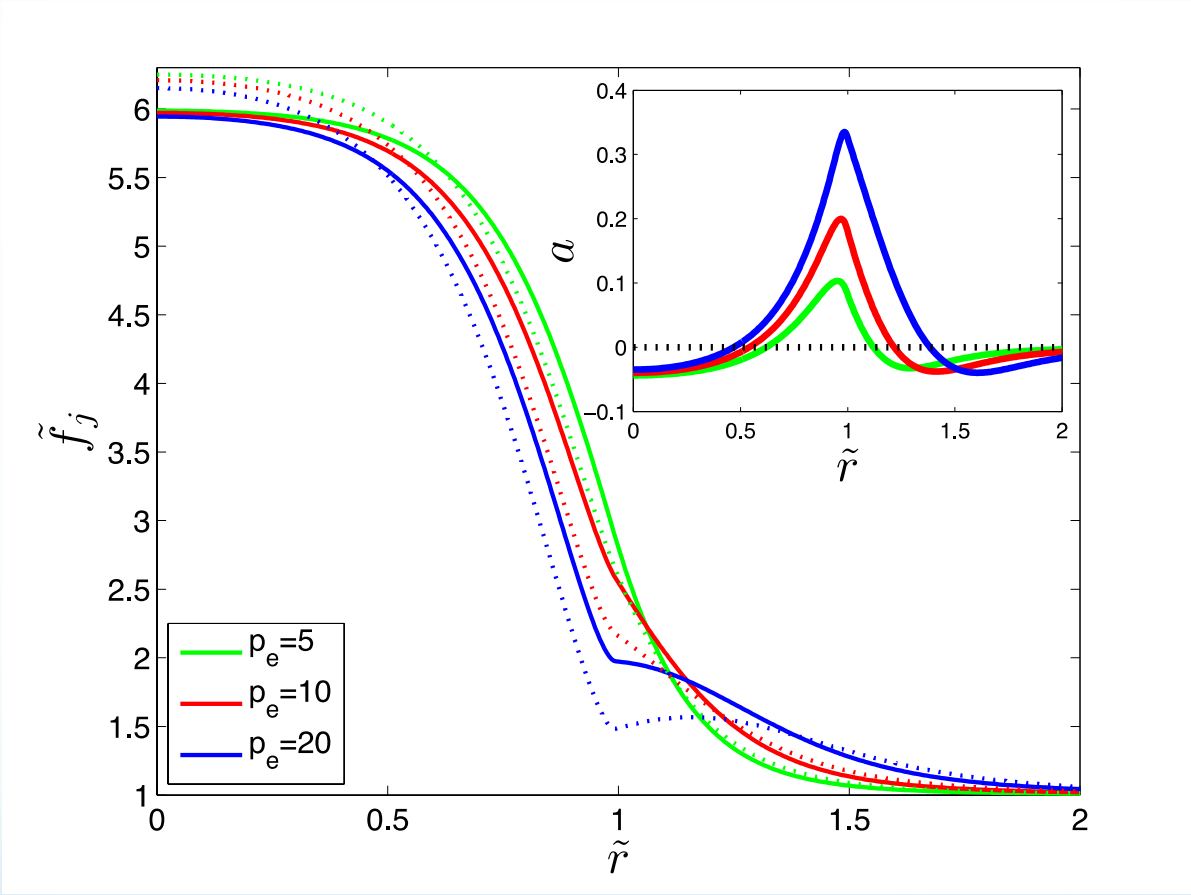
Angiogenic activity



L_p or F - Þ a^t - Þ low velocity in tumor core, high velocity at tumor rim Þ AGFs stay in tumor, AGFs pushed into host tissue

Convection parameter

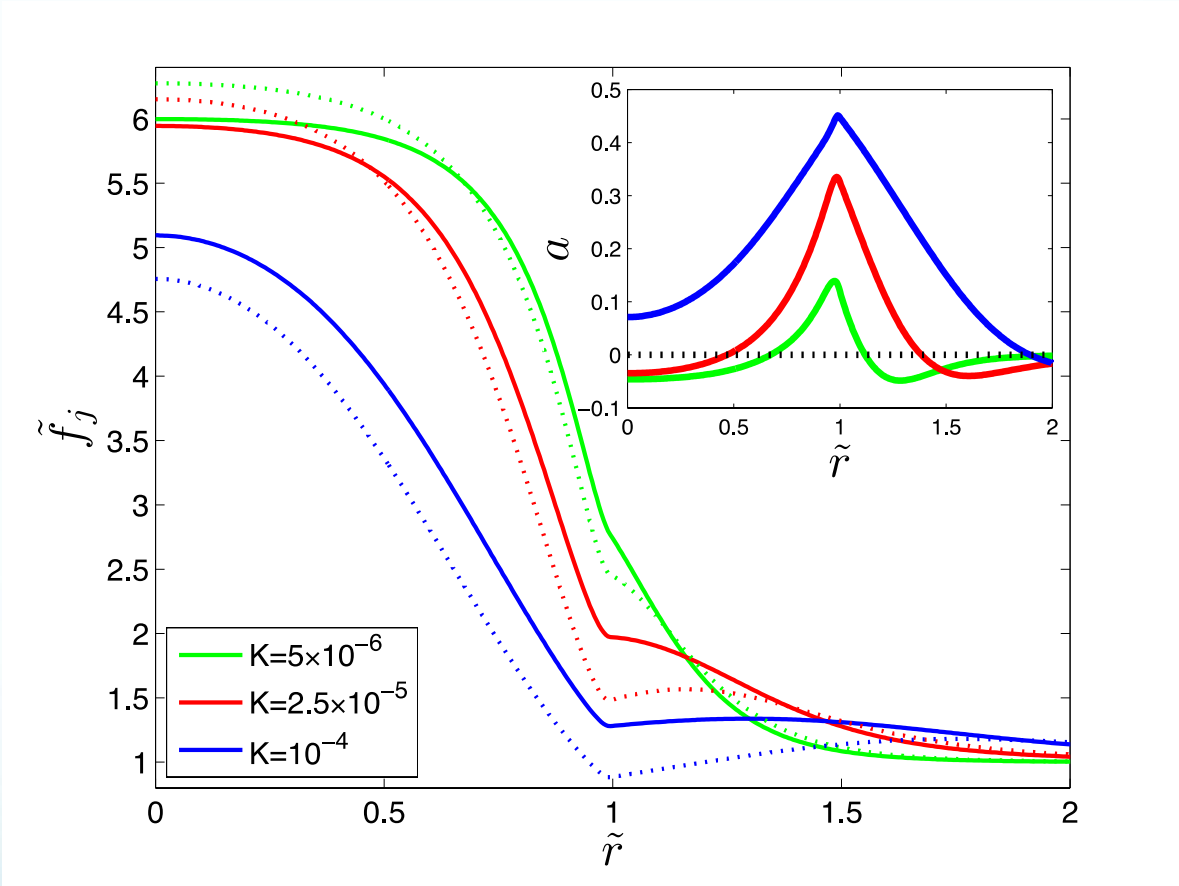
$$\tilde{K}_j = \frac{K p_e^t}{D_j}$$



p_e^t - Þ $\tilde{K}$ - Þ high velocity at tumor rim Þ AGFs pushed into host tissue

C. Phipps and M. Kohandel. Mathematical model of the effect of interstitial fluid pressure on angiogenic behavior in solid tumors. Comp Math Meth Med, 2011.

Hydraulic conductivity



$$a^t = R\sqrt{\frac{L_p^t \mathrm{F}^t}{K^t}}$$

$$\tilde{K}_j = \frac{K p_e^t}{D_j}$$

K - Þ a^t — Þ high velocity in tumor core Þ AGFs pushed into host tissue

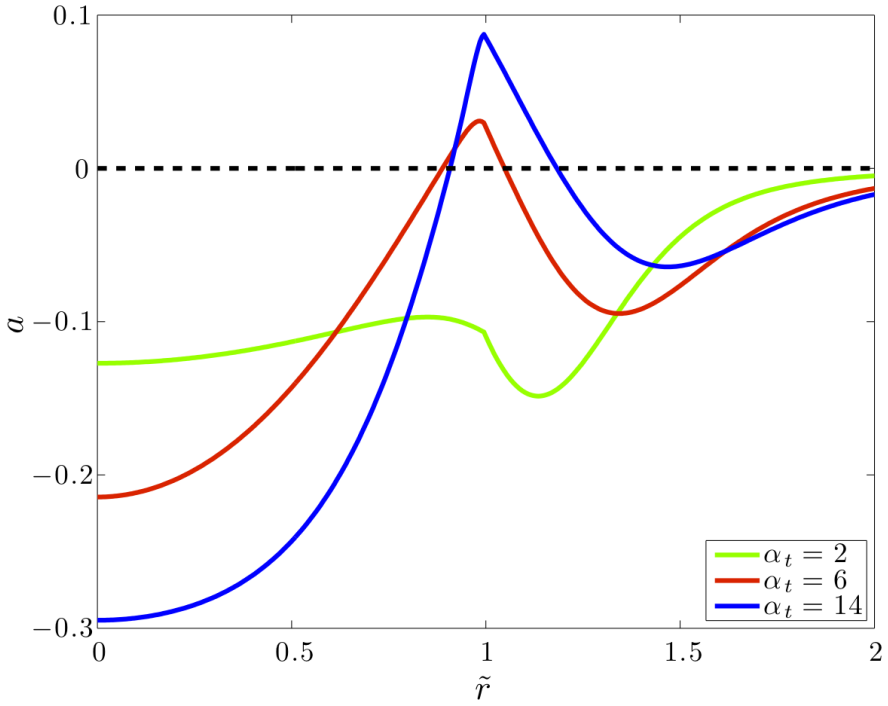
$\tilde{K}$ - high velocity at tumor rim

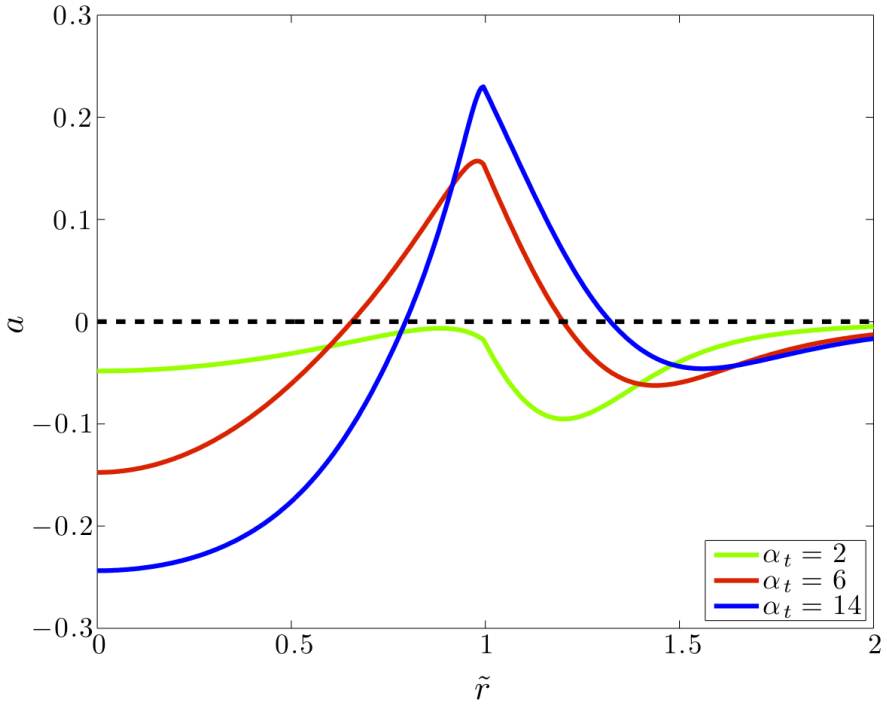
C. Phipps and M. Kohandel. Mathematical model of the effect of interstitial fluid pressure on angiogenic behavior in solid tumors. Comp Math Meth Med, 2011.

Therapeutic implications

- Antiangiogenic treatment
  - Proangiogenic inhibition
    - Increased proangiogenic deactivation: $\tilde{k}_p^t$ -
  - Antiangiogenic factors
    - Increased antiangiogenic production: $\tilde{g}_a^t$ -
  - Vessel normalization
    - Decreased vessel permeability: $L_p^t \neg \Rightarrow a^t \neg$
    - Decreased resistance: $p_v \neg \Rightarrow \tilde{K} \neg$
    - Decreased surface area: $F \neg \Rightarrow a^t \neg$
- Matrix-degrading enzymes
  - Less dense tissue
    - Increased hydraulic conductivity: $K - \Rightarrow \frac{\tilde{K} -}{a \neg}$
- Cytotoxic agents
  - Decreased proangiogenic production: $\tilde{g}_p^t \neg$

Other therapy effects





k_p^t - Þ $\tilde{k}_p^t$ -

g_a^t - Þ $\tilde{g}_a^t$ -

Conclusions

- Angiogenic growth factors concentrations are influenced by convective transport in solid tumors
- Angiogenesis can be partially suppressed by modifying physiological parameters
- Treatments: decreasing vascular pressure or vessel permeability may discourage angiogenesis (along with improved chemotherapy delivery)
- Despite reducing IFP, decreasing hydraulic conductivity may be detrimental to treatment efficacy
- AGF imbalance is a simple way to incorporate angiogenesis into a tumor model, hopefully can be used as a predictive tool for treatment combinations

Tumor metabolism

- Hypoxia: Leads to increased glycolysis
- Warburg effect: Aerobic glycolysis

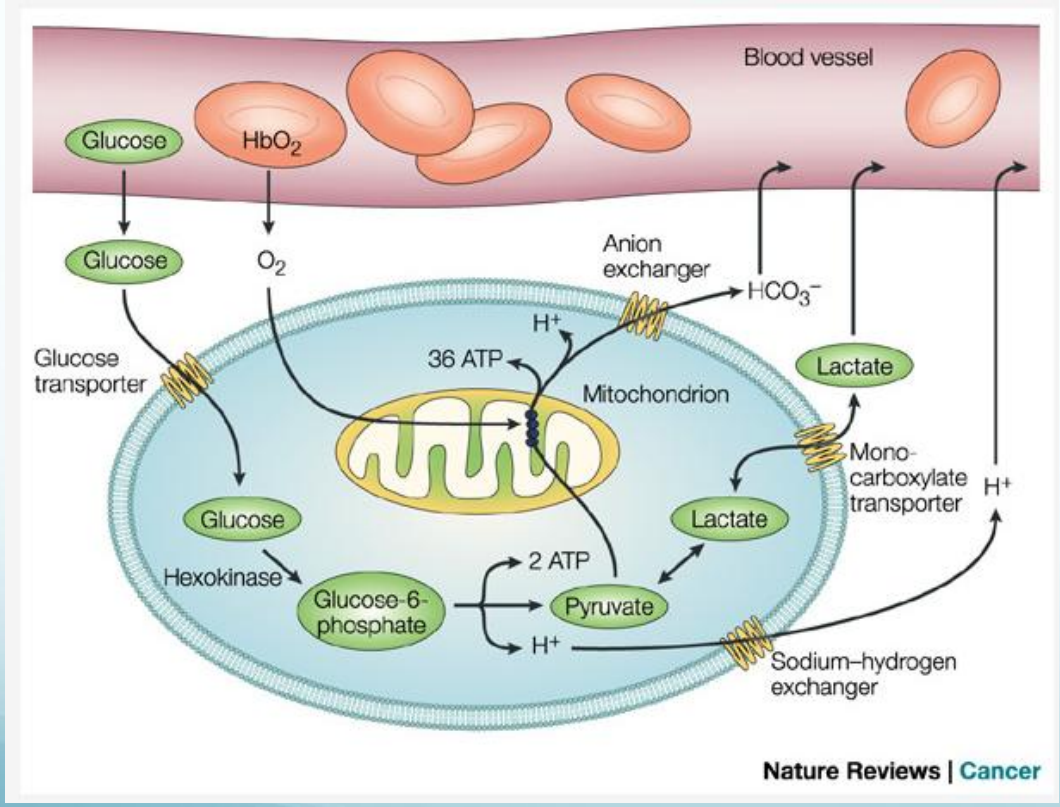


Image from: Gatenby et al., Nature Rev Cancer 4, 2004.

Glycolysis

$$C_6H_{12}O_6 \rightarrow 2C_3H_5O_3^- + 2H^+$$

Yield: 4-2=2 ATP

Respiration

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$$

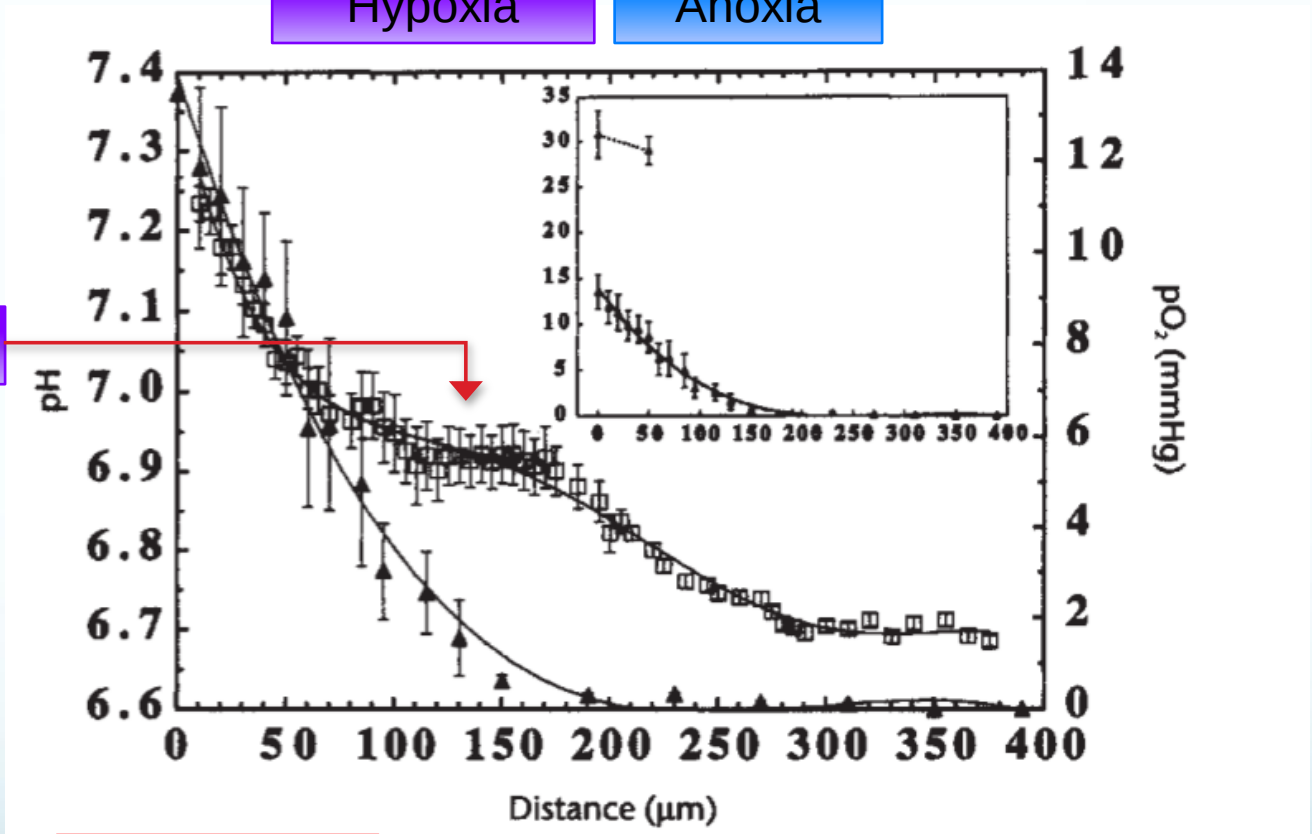
Yield: ≤38 ATP

Microvessel experiment

Hypoxia

Anoxia

pH plateau



Hypothesis:

Respiration-dominated

Downregulated Respiration/Glycolysis

Glycolysis-dominated

Image from: Helmlinger et al., Nature Med 3, 1997.

Mathematical model

- Metabolism:

Respiration

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$$

Glycolysis

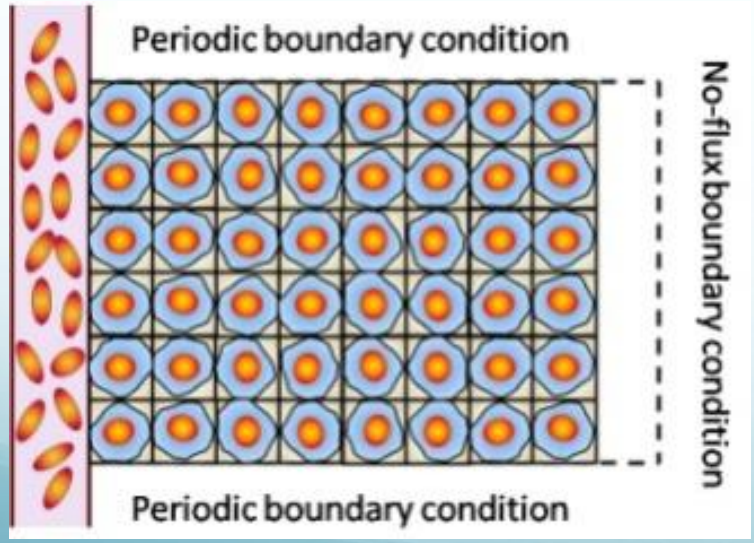
$$C_6H_{12}O_6 \rightarrow 2C_3H_5O_3^- + 2H^+$$

- Buffer:

$$CO_2 + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} HCO_3^- + H^+$$

- Na^+ and Cl^- to ensure electroneutrality
- Interested in pH=-log(c_H)

$$\frac{\partial C_i}{\partial t} = D_i \nabla^2 C_i + P_i$$

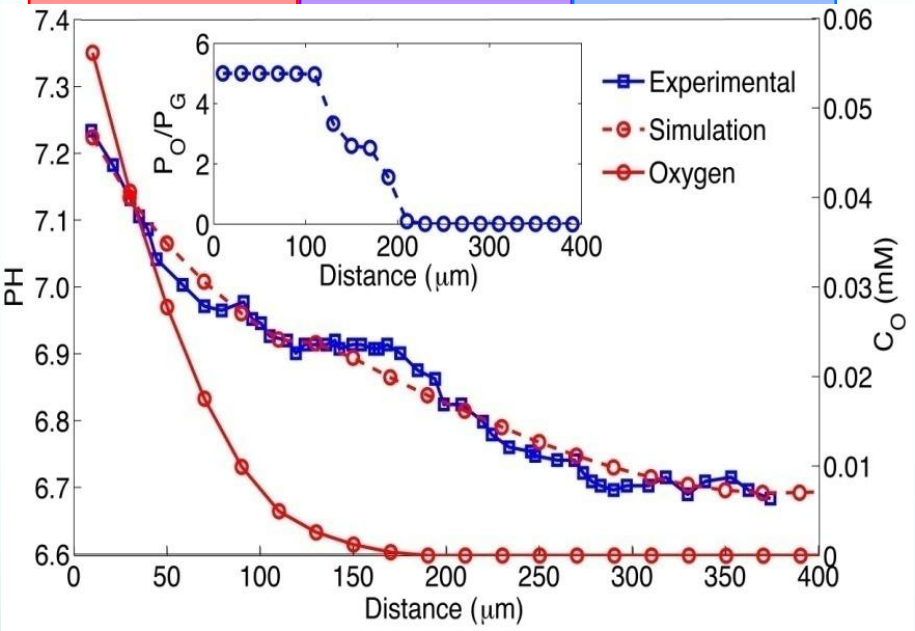


Molavian et al.Cancer Res 69 (2009).

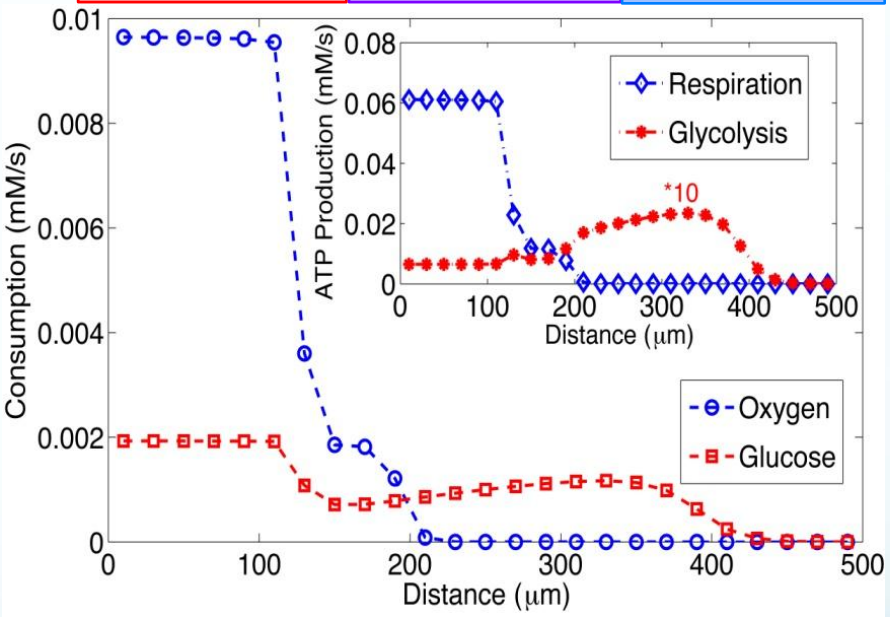
Compound	i	P_i (10^{-2}mM/s)
Cl^-	Cl	0
Na^+	Na	-
Glucose	G	$-p_G \frac{C_G}{C_G + k_G} f_1(C_O)$
O_2	O	$RP_G \frac{C_O}{C_O + k_O} f_2(C_O)$
$Lactate^-$	L	$-2P_G + \frac{1}{3}P_O$
CO_2	CO	$k_r C_H C_B - k_f C_{CO}$
$Bicarbonate^-$	B	$k_f C_{CO} - k_r C_H C_B - P_O$
H^+	H	$k_f C_{CO} - k_r C_H C_B - P_O + P_L$

Results

Respiration-dominated | Respiration/Glycolysis | Glycolysis-dominated



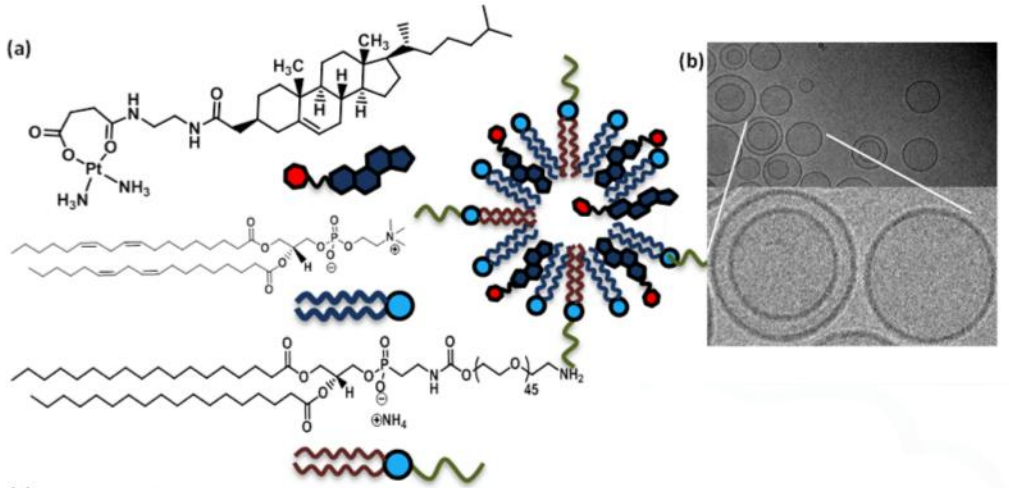
Respiration-dominated | Respiration/Glycolysis | Glycolysis-dominated

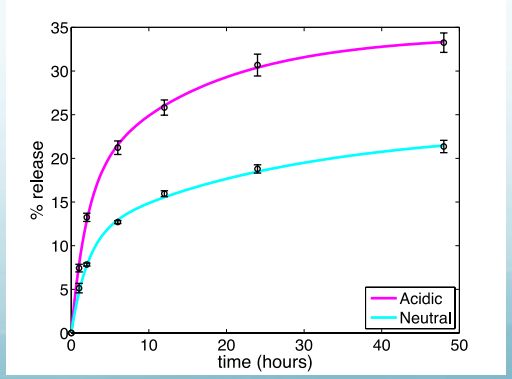


Molavian et al.PLoS one 6(12)..

Cell viability prediction

- Experiments measure pAkt (pro-survival) and Caspase-3 (apoptosis trigger) proteins
- Cisplatin nanoparticles
  - Increase caspase-3
  - Increase pAkt
- Potential solution:
  - PI3K inhibitor: PI828
  - Prevents Akt phosphorylation
- Mathematical goal:
  - Optimize treatment combination





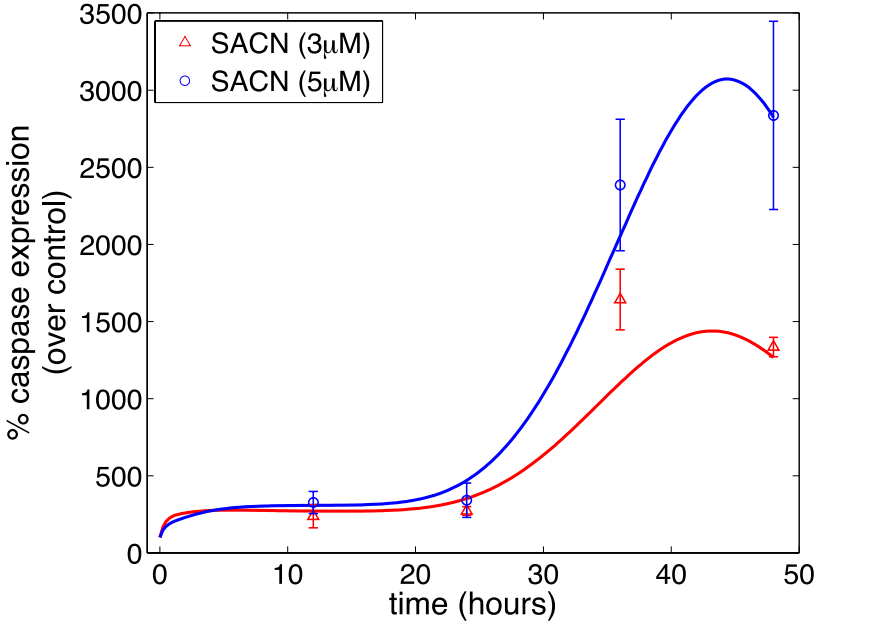
Protein expression

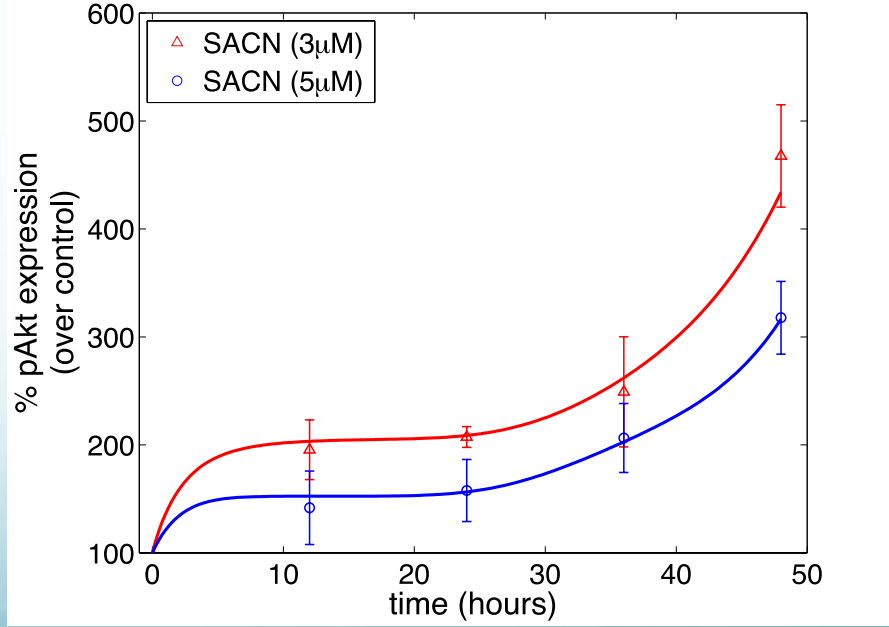
- Protein equations:
  - Mutually inhibitory
  - Treatment effects

$$\frac{dP}{dt} = \frac{k_p + l_p f_p(t)}{1 + a_p C + g_p g_i(t)} - d_p P$$

$$\frac{dC}{dt} = \frac{k_c + l_c f_c(t)}{1 + a_c P} - d_c C$$

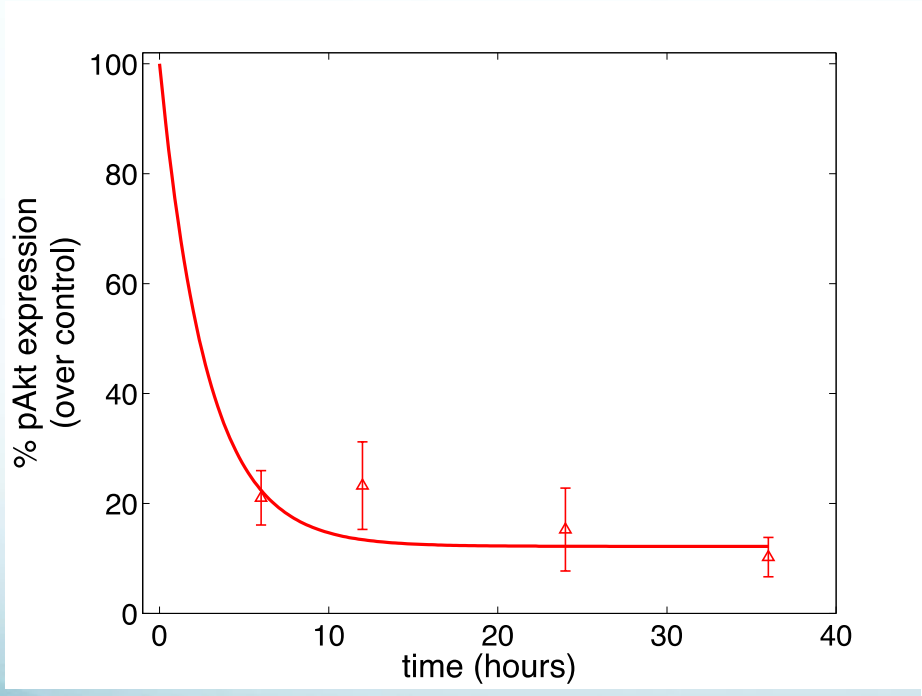
- Chemotherapy increases Caspase-3 and pAkt



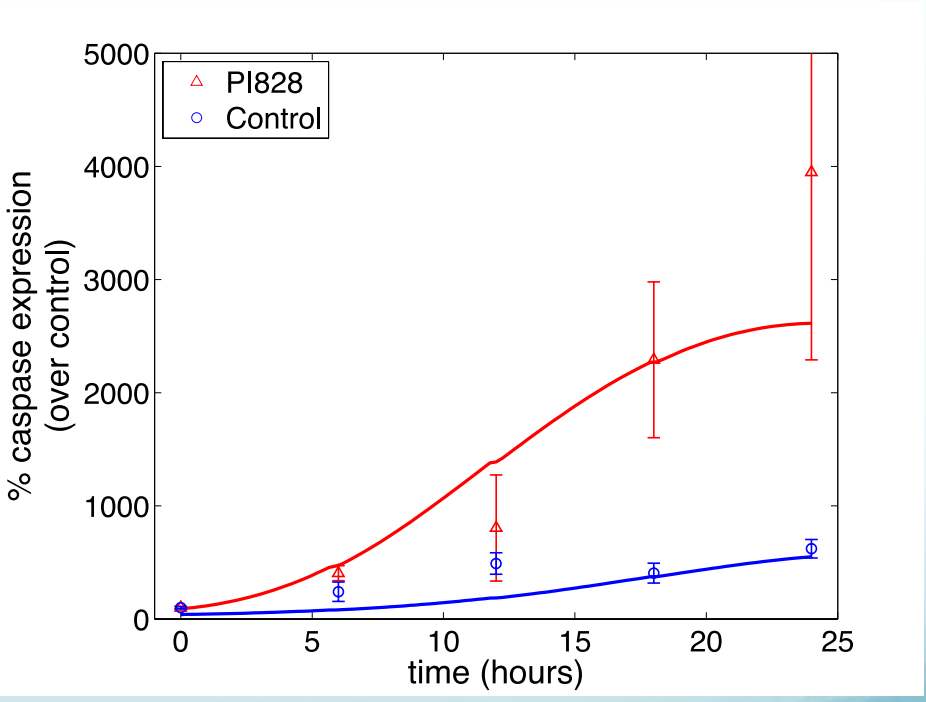


Protein expression

- PI828 blocks Akt phosphorylation



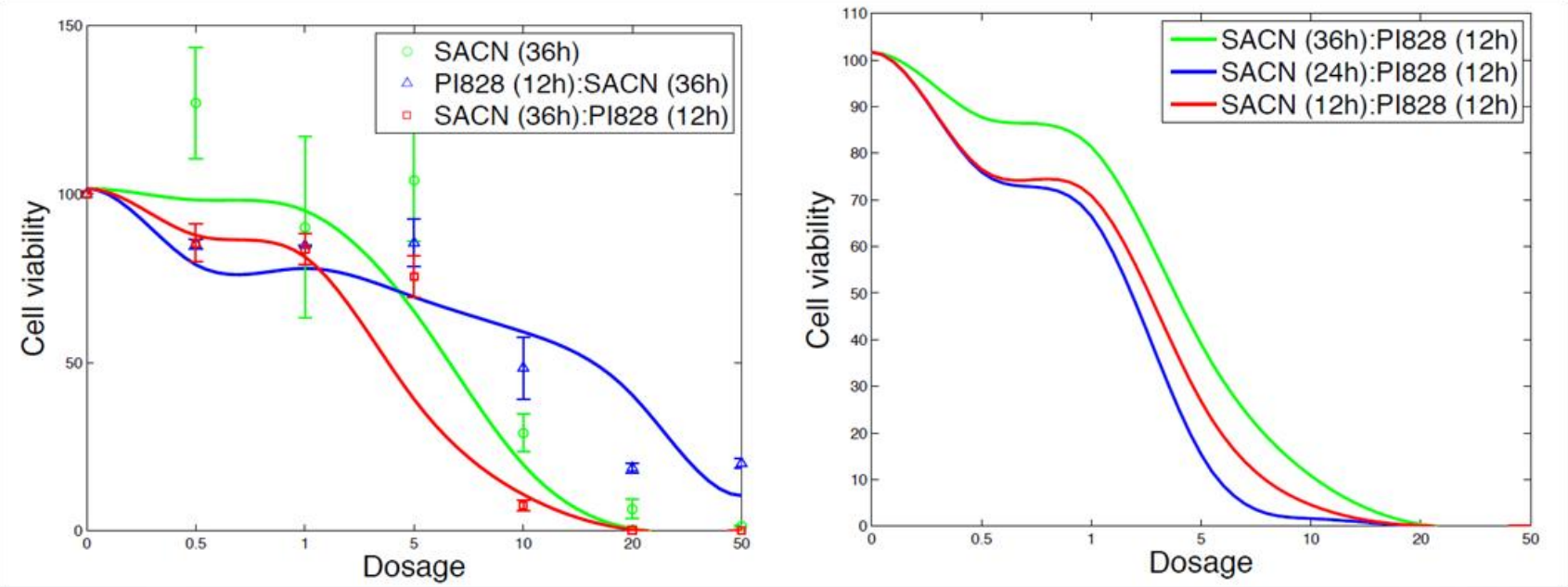
- CisNP + PI828 has synergistic effect



Cell viability

- Equation:

$$\frac{dN}{dt} = [\lambda_N P - \delta_N C] N$$



- Prediction: Synergistic effect if PI828 administered after 24 hours
  - 12 hours: limited cisplatin exposure
  - 36 hours: cisplatin effect is wearing off

- Collaborators
  - Mohammad Kohandel (supervisor, U. Waterloo)
  - Hamid Molavian (U. Waterloo)
  - Ambarish Pandey (U. Texas Southwestern)
  - Shiladitya Sengupta (MIT)
- Funding
  - NSERC
  - Waterloo Institute for Nanotechnology