Nonlinear tumor modeling III: Angiogenesis, vascular growth and future directions

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Motivation

• Provide biophysically justified *in silico* virtual system to study
• Help experimental investigations; design new experiments
• Therapy protocols
Outline

• Review of tumor growth model
• Angiogenesis (experiment)
• Angiogenesis (model)
• Numerical implementation
• Results
Example of solid tumor growth

- Genetic mutations
- Avascular growth: Diffusion dominated
- Angiogenesis
- Vascular growth: invasive metastasis, malignancy

• Goal: Model all Phases of growth
Present model

• Continuum approximation: super-cell macro scale

• Role of cell adhesion and motility on tissue invasion and metastasis
  Idealized mechanical response of tissues

• Coupling between growth and angiogenesis (neo-vascularization): necessary for maintaining uncontrolled cell proliferation

• Genetic mutations: random changes in microphysical parameters cell apoptosis and adhesion

• Limitations: poor feedback from macro scale to micro scale
  (Greenspan, Byrne & Chaplain, Anderson & Chaplain, Levine…)

Healthy tissue (may have vessels)
Necrotic core
highly-vascularized exterior
Captured region
Proliferating Tumor region (may have vessels)

[Diagram showing Healthy tissue, Captured region, Proliferating Tumor region, Necrotic core, highly-vascularized exterior]
Cell proliferation and tissue invasion

Assume constant tumor cell density: cell velocity

Cell-to-cell adhesion

Assume 1 diffusing nutrient of concentration $\sigma$

Spatial distribution of the oncotic pressure

Cell mobility: reflect strength of cell adhesion to other cells and to the Extra-Cellular Matrix (ECM), the other main factor leading to tissue invasion

Viability concentration

Rate of enzymatic breakdown of necrotic cells (death due to lack of nutrient)

Cell death responsible for release of angiogenic factors: INPUT TO ANGIOGENESIS

Darcy-Stokes

$\nabla \cdot \mathbf{u} = \begin{cases} 
\lambda_M(\sigma) - \lambda_A & \text{in } \Omega_P \\
-\lambda_N & \text{in } \Omega_N = \{ \mathbf{x} | \sigma(\mathbf{x}, t) \leq \sigma_N \} 
\end{cases}$

Cell proliferation: in the tumor is a balance of mitosis and apoptosis (mitosis is responsible for reproduction of mutated genes) and is one of the two main factors responsible for tissue invasion

Assume constant tumor cell density: cell velocity

Cell-to-cell adhesion

Viscosity

Darcy-Stokes

$\mathbf{u} - \nu \Delta \mathbf{u} = -\mu \nabla P$
Evolution of nutrient: Oxygen/Glucose

Greenspan, Chaplain, Byrne, …

\[ \frac{\partial \sigma}{\partial t} = \nabla \cdot (D \nabla \sigma) - \lambda_C \cdot \sigma + \lambda_B (\sigma_B - \sigma, P_B - P, x, t) \]

Nutrient consumption by the cells

Diffusion

Oncotic pressure: affects blood flow and delivery of nutrients (and chemotherapy drugs)

Blood-to-tissue nutrient transfer rate function. Spatial distribution of capillaries: OUTPUT FROM ANGIOGENESIS

=0 (quasi-steady assumption). Tumor growth time scale (~1 day) large compared to typical diffusion time (~1 min)
More complex Biophysics

• Simplified cell-cycling model \( \lambda_M (\sigma) = b \sigma \)

• Blood-tissue transfer of nutrient

\[
\lambda_B (\sigma_B - \sigma, P_B - P, x, t) = \lambda_B h(\sigma_B - \sigma) \cdot (P_B - P)_+
\]

\[
h(\sigma_B - \sigma) = (\sigma_B - \sigma) \delta_{\text{Capillary}}
\]

• Avascular, angiogenesis and fully vascularized growth

• Nonlinear interaction between developing vasculature and tumor growth
Angiogenesis

Angiogenic factors:
- VEGF (Vascular Endothelial cell Growth Factor)
- FGF (Fibroblast Growth Factor)
- Angiogenin
- TGF (Transforming Growth Factor), ….
ECM/MMP Regulation of VEGF


VEGF-A isoforms

- Insoluble VEGF + Matrix Metalloproteinases (ECM) → Soluble VEGF (Endothelial cells) + MMPs
- Different signaling outcomes through VEGFR2
Effect on EC growth

Beads containing cells embedded in fibrin/fibronectin gels

- VEGF 113: Sheets
- VEGFD108-118: Chords
- VEGF 164: Both

(stain to measure proliferation)
Effect on Vessel Morphology

Wild  Soluble  Insoluble

- Morphology strongly depends on type

(diameters)  15 µm  109 µm  16 µm

- Number density perimeter

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Number density

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Vessel perimeter/µm²
Effect on tumor growth

• Soluble VEGF poor prognosticactor of tumor progression

• Matrix-bound VEGF yields more efficient angiogenic response
Mathematical model

Anderson, Chaplain, Macdougall, Levine, Sleeman, Zheng, Wise, Cristini BMB 2005, ...

Endothelial cell concentration $e$: form the lining of the capillary

\[
\frac{\partial e}{\partial t} = \bar{D}_e \nabla^2 e - \nabla \cdot \left( \left( \frac{\bar{\chi}_c}{1 + \alpha c / \bar{c}_0} \nabla c + \bar{\chi}_f \nabla f + \chi_{u\cdot u} \right) e \right)
\]

Chemotaxis

Haptotaxis

Tumor angiogenic factor (e.g., VEGF-A): potent mitogen, drives motion

Decay

Uptake by the endothelial cells

\[
0 = \bar{D}_c \nabla^2 c - \bar{\beta}_D c - \bar{\beta}_U c e / \bar{e}_0,
\]

c = 1 on $\Sigma_N$

Recast in a biased random-walk model to follow the evolution of the capillaries (Anderson, Chaplain)

Cell receptor ligand (e.g., Fibronectin) in the ECM. Regulates cell adhesion and motion

\[
\frac{\partial f}{\partial t} = \eta_P e - \eta_U f e - \eta_N \chi_{\Omega_N} f,
\]

production degradation
Numerical method

• Level-set/Finite-element formulation (Mixed methods, LDG, EPC)

• Adaptive computational mesh

Mesh: System of springs (energy)
Local Operations → Minimum energy → Optimal mesh

Resolution of physical scales \( l_{eq} = \min(l_1, l_2, \ldots) \)
• Vary $D_c$ and $\beta_D$ to mimic Soluble/Insoluble VEGF-A Parameters from literature.

Day 0

Day 10

Day 20

Insoluble

Partly soluble

Soluble

• Chemotaxis/
  Branching enhanced with insoluble VEGF

• Qualitative agreement with experiments
Mechanism

Distribution of VEGF:

Day 0  Day 10  Day 20

Insoluble  Partly soluble  Soluble

• Uptake of ECM-bound VEGF-A by EC produces large gradient in insoluble case

• Gradients enhance chemotaxis
Later times

Partly Soluble

Soluble

• Brush-border effect
• Penetration

• Irregular vascular development
• No penetration

• Qualitative agreement with experiment

• Experimental results consistent with increased $D_c$ and/or decreased $\beta_c$
Movies

Insoluble

Soluble
More sophisticated model

**Insoluble**

\[
\frac{\partial C_I}{\partial t} = \nabla (D \nabla C_I) - \beta_D C_I - \beta_U C_I \frac{e}{e_0} - \beta_{\text{cleave}} \frac{e}{e_0} C_I
\]

**Soluble**

\[
0 = D_{sc} \nabla^2 C_S - \beta_{SD} C_S - \beta_{SU} C_S \frac{e}{e_0} + \beta_{\text{cleave}} \frac{e}{e_0} C_I
\]

- Variable diffusion for insoluble TAF
- Test coupling with full tumor model
  - tumor and vessel development nonlinearly coupled
Fully coupled model

- Brush-border effect
- Penetration
- Growth of tumor

- Irregular vascular development
- Little penetration
- Less growth
Stills
VEGF

**Insoluble**

**Soluble**
Vascular cooption

• Initial capillaries present
• Growing tumor surrounds vessels
• Uses up available vasculature
• Secondary angiogenesis
• Observe bursts of growth as the nutrient supply increases (like a fire)

• Note nutrient supply localized near red (nutrient-releasing) vessels
• Observe corresponding (tumor) near vessels cell growth
• Regions of hypoxia separate cell clusters
Vascular co-option

- Initial capillary present
- Growing tumor surrounds vessels
- Continuous angiogenesis.
Effect of vessel aging

• As vessels age, the perfusion is reduced.
• Typically angiogenesis occurs very close to the tumor
• Observe bursts of growth as the nutrient supply increases and decreases (like a fire)
Implications for therapy

- Anti-angiogenic therapy
- Vascular normalization
- Anti-invasive therapy

Rubinstein et al. (2000)

Increase adhesion

Anti-invasive therapy

Increase adhesion

Anti-angiogenic therapy

Vessel disruption

Vascular normalization

2D: Cristini, et al., Cancer Res. (2006)
Conclusions

• Developed a framework to model tumors through all phases of growth

• Nonlinear coupling of neovascular development and tissue/tumor growth

• Qualitative agreement with experiments by Iruela-Arispe for neovascular morphology
  morphology controlled by diffusion/degradation of VEGF-A

• Needs further work: MMPs, identification of biophysical mechanisms

• Vascular remodeling/flow, etc.
Ongoing and Future work

- 3D

- Direct modeling of VEGF-A/ECM/MMP interaction on Neovascular morphology.

- Realistic mechanical/diffusional description of tissue

- Cell-signaling– macro/micro nonlinear coupling