Nonlinear Tumor Modeling II: Tissue inhomogeneities and necrosis

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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 basic model and results

• Extension to a (simple) model of tissue inhomogeneity

• Numerical methods

• Results
Mathematical 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...)
Cell proliferation and tissue invasion

Greenspan, Chaplain, Byrne, …

Assume constant tumor cell density: cell velocity

Cell-to-cell adhesion

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

Darcy’s law

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

\[ P = \tau \kappa \text{ on } \Sigma \]

\[ \mathbf{u} = -\mu \nabla P \]

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

Spatial distribution of the oncotic pressure

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
Evolution of nutrient: Oxygen/Glucose

Greenspan, Chaplain, Byrne, …

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

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

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

Diffusion

nutrient concentration in blood

Blood-to-tissue nutrient transfer rate function.

Spatial distribution of capillaries: OUTPUT FROM ANGIOGENESIS

Nutrient consumption by the cells
Limited Biophysics

- Simplified cell-cycling model: \( \lambda_M(\sigma) = b\sigma \)
- Simplified Blood-tissue transfer: \( \lambda_B(\sigma_B - \sigma, P_B - P, x, t) = \lambda_B \cdot (\sigma_B - \sigma) \)
- Avascular or fully vascularized growth (i.e. no angiogenesis)

- Insight to biophysical system
- Benchmark for more complicated systems
Previous (basic) model
Greenspan, Chaplain, Byrne, Friedman-Reitich, Cristini-Lowengrub-Nie,…

Nutrient

\[ 0 = D \nabla^2 \sigma + \Gamma, \]
\[ \Gamma = -\lambda_B (\sigma - \sigma_B) - \lambda \sigma. \]
\[ (\sigma)_{\Sigma} = \sigma^\infty \]

Pressure

\[ u = -\mu \nabla P, \quad \nabla \cdot u = \begin{cases} \lambda_p & \text{in } \Omega_p \\ -\lambda_N & \text{in } \Omega_N \end{cases} \]
\[ (P)_{\Sigma} = \gamma \kappa \]
\[ \lambda_p = b\sigma - \lambda_A, \]
\[ V = -\mu \mathbf{n} \cdot (\nabla P)_{\Sigma}. \]

normal velocity
Extended model

- Healthy tissue (may have vessels)
- Necrotic core
- Highly-vascularized exterior
- Captured region
- Proliferating Tumor region (may have vessels)
Extended Model
Macklin, Lowengrub, In preparation.

Nutrient

\[ 0 = \nabla \cdot (D \nabla \sigma) + \Gamma \]

\[ \Gamma = \begin{cases} 
-\lambda_B (\sigma - \sigma_B) - \lambda \sigma & \text{in } \Omega_P \\
-\lambda_{B,H} (\sigma - \sigma_B) - \lambda_H \sigma & \text{in } \Omega_H \\
0 & \text{in } \Omega_N 
\end{cases} \]

\[ [\sigma]_\Sigma = [D \nabla \sigma \cdot n]_\Sigma = 0 \]

\[ [\sigma]_{\Sigma_N} = [D \nabla \sigma \cdot n]_{\Sigma_N} = 0 \]

\[ (\sigma)_{\partial \Omega_0} = \sigma_\infty \]

• Let \( D \) and \( \mu \) vary in \( \Omega_P \) and \( \Omega_H \)

Pressure

\[ u = -\mu \nabla P, \]

\[ \nabla \cdot u = \begin{cases} 
\lambda_p & \text{in } \Omega_P \\
0 & \text{in } \Omega_H \\
-\lambda_N & \text{in } \Omega_N 
\end{cases} \]

\[ [P]_\Sigma = \gamma \kappa, \quad [\mu \nabla P \cdot n]_\Sigma = 0 \]

\[ [P]_{\Sigma_N} = [\mu \nabla P \cdot n]_{\Sigma_N} = 0 \]

\[ (p)_{\partial \Omega_0} = p_\infty \]

\[ V = -\mu \ n \cdot (\nabla P)_\Sigma. \quad \text{normal velocity} \]
Interpretation

In $\Omega_H$,

- $D$ is an indirect measure of perfusion
  *i.e.*, $D$ large $\rightarrow$ nutrient rich

- $\mu$ is a measure of mechanical properties of extra-tumoral tissue
  *i.e.*, $\mu$ small $\rightarrow$ tissue hard to penetrate (less mobile)

- Although a very simplified model of these effects, this does provide insight on how inhomogeneity influences tumor growth.
Nondimensionalization


Intrinsic length scale: \[ L_D = D_P^{1/2} (\lambda_B + \lambda)^{-1/2} \]
Adhesion time scale: \[ \lambda_R^{-1}, \quad \lambda_R = \gamma \mu_p / L_D^3 \]

Previous nondimensional parameters:

• Vascularization: \[ B = \frac{\sigma_B}{\sigma_\infty} \frac{\lambda_B}{\lambda_B + \lambda} \]
• Apoptosis vs. mitosis \[ A = \frac{\lambda_A/\lambda_M - B}{1 - B} \]
• Mitosis vs. adhesion \[ G = \frac{\lambda_M}{\lambda_R} (1 - B) \]
• Necrosis vs. mitosis \[ G_N = \lambda_N / \lambda_M \quad \lambda_M = b \sigma_\infty \]
• Viability \[ N = \frac{\sigma_N}{\sigma_\infty} - B \]

New nondimensional parameters:

• Diffusion ratio: \[ \chi_D = D_H / D_P \]
• Mobility (adhesion) ratio: \[ \chi_\mu = \mu_H / \mu_P \]
• Transfer ratio: \[ \chi_B = \frac{\lambda_B,H}{\lambda_B} \]
• Uptake ratio: \[ \chi_\lambda = \frac{\lambda_H}{\lambda} \]

• Reduces to basic model when: \[ \chi_D, \chi_\mu \to \infty, \quad \chi_\lambda, \chi_B \quad \text{bounded} \]
Nondimensional System

Nutrient: \( c = (\sigma / \sigma_\infty - B)/(1 - B) \)
Pressure: \( p = (P - P_\infty) / (\gamma / L_D) \)

Generic Poisson-type problems for \( c \) and \( p \):

\((w = c \text{ or } p)\)

\[
\nabla \cdot (\chi \nabla w) = f(x, w), \quad \text{in } \Omega = \Omega_N \cup \Omega_P \cup \Omega_H
\]

\[
[w]_\Sigma = g, \quad [\chi \nabla w \cdot n]_\Sigma = 0
\]

\[
[w]_{\Sigma_N} = [\chi \nabla w \cdot n]_{\Sigma_N} = 0
\]

\[
(w)_{\partial \Omega_0} = w_\infty
\]

\[
n \cdot \frac{dx}{dt}_\Sigma = V = -\nabla p \cdot n
\]
More Complex Biophysics

• Non-uniform parameters
• Necrosis
• Complex morphology
• Angiogenesis

Level-set method

\[ \phi_t + V | \nabla \phi | = 0 \]

\[ V = u \cdot n \]

Difficulties:
• Stability—sensitive to geometry  \( V \sim H(\kappa_s) \)
• Accurate extension/interpolation
• Stable discretizations of  \( n \) and  \( \kappa \)
**2\textsuperscript{nd} Order Accurate**

**Ghost Fluid/Level-Set Method**


- Embed in Rectangular domain
- Incorporate sub-cell resolution and physical boundary conditions
- Solve equations on full Cartesian mesh

Difficulties:
- Stability – sensitive to geometry $V \sim H(\kappa_s)$
- Accurate extension/interpolation
- Stable discretizations of $n$ and $\kappa$

\[
\frac{\partial^2 u}{\partial x^2} = \frac{u_{i-1} - 2u_i + \hat{u}_{i+1}}{\Delta x^2} + O(\Delta x^2)
\]
2nd Order Accurate Method

Extension

Cubic extrapolation

Normal Vector/ Curvature

Bilinear interpolation

1-sided method

Fig. A.3: Gradient Extension. We extend a scalar function beyond \( \Omega \cup \Sigma \) by one-dimensional, grid-aligned extrapolation. The points used in the extrapolation are chosen according to the direction of the normal vector. We preserve curvature information by choosing the next point for extension according to the value of the level set function at the remaining points (open circles).

Fig. A.4: Finding the closest point on the interface. \( \mathbf{W} = -\varphi(x_0)\mathbf{n}(x_0) \).

Fig. A.5: Effect of Level Set Irregularity on \( \kappa \) and \( \mathbf{n} \): In the left figure, two interfaces are close together. The middle curve shows the points equidistant from both interfaces, and the level set function is irregular along this curve. The standard techniques for calculating \( \kappa \) and \( \mathbf{n} \) work well at \( x_0 \) (where \( \varphi_x \) and \( \varphi_y \) are continuous), whereas they break down numerically at \( x_1 \). The right figure shows a cross-section through \( x_1 \) of the level set function; the “peak” in the middle is equidistant from the two interfaces and a point of irregularity in \( \varphi \).
Gaussian smoothing

\[ \hat{f}_I = \frac{1}{A} \frac{1}{N \sqrt{2\pi}} \sum_{i=-3N}^{3N} f_{I-i} \exp\left( -\frac{1}{2} \left( \frac{i}{N} \right)^2 \right), \quad N=3 \]

Fig. A.8. Effect of Smoothing on Overall Stability and Accuracy: Initially small perturbations have grown to grossly distort the shape of the interface by \( t = 0.01 \). The dashed curve shows the solution at the same time with speed smoothing.

Curvature/Normal Vector

Poisson 2: Quadratic extrapolation of ghost-value linear approximation of ghost-point

WENO5: Reinitialization/Advection
Validation with benchmark boundary integral result

Solid: BI  
Dashed: GF

• Excellent agreement
Post-transition dynamics

- Repeated capture of healthy tissue
  
  Observed in tumors
  \textit{In vivo}

- Captured tissue acts like blood vessels (nutrient supply from 3D)
  
  Mimics tumor growing into uniformly vascularized tissue
Growth with necrosis and without 3D nutrient supply

- Captured regions do not act as nutrient source

- Many topology transitions of tissue and necrotic core
- Quite different morphology
Morphology diagram

\[ A = 0, \quad G = 20, \quad G_N = 1 \]

\[ N = 0.35 \]

Effect of extra-tumoral tissue

- 3 distinct regimes:
  - Fragmented (nutrient-poor)
  - Fingered (high tissue resistance)
  - Hollowed (low tissue resistance, nutrient-rich)

Increased tissue resistance (decreased mobility)

Higher degree of vascularization
Fragmented

\[ \chi_D = 1, \quad \chi_\mu = \infty \]

- Hypoxia leads to invasion
  \( \text{i.e.,} \) inhomogeneous nutrient distribution,
  imperfect vasculature
- Strong metastatic potential
- Implications for antiangiogenic therapy

Combine with anti-invasive therapy
Dependence on other parameters

\[ \chi_D = 1, \quad \chi_\mu = 1 \]

- Increasing \( G \) or \( G_N \) enhances instability
- Increasing \( G_N \) decreases necrotic core
Dependence on $N$

$N=0.175$

$\chi_D = 1,$
$\chi_{\mu} = 1,$
$G = 20,$
$G_N = 1$

$N=0.35$

$N=0.70$

• Strong effect on size
\[ \chi_D = 50, \quad \chi_\mu = 1 \]

- Growth into less mobile tissue results in invasive fingering
Dependence on other parameters

- Increasing $G$ or $G_N$ enhances instability
- Increasing $G_N$ decreases necrotic core
- Strong effect on morphology—compact, 1D-like, hollow
Dependence on $N$

$\chi_D = 50,$
$\chi_\mu = 1,$
$G = 20,$
$G_N = 1$

- Strong effect on size
Hollowed

\[ \chi_D = 100, \quad \chi_\mu = 50 \]

- Repeated capture and coalescence leads to hollow structure
Dependence on other parameters

- Increasing $G$ or $G_N$ enhances instability
- Increasing $G_N$ decreases necrotic core
- Strong effect on morphology—compact, 1D-like, hollow

$\chi_D = 50, \; \chi_\mu = \infty$

In vitro tumor spheroid

Cristini et al, Cancer Res, in review

adhesiveness

Necrosis (degradation)
Growth into highly vascularized tissue

\[ G = 20, \quad G_N = 1, \quad \chi_D = \chi_{\mu} = \infty \]

- Multifocal tumor
- Statistically self-similar

Effect of vascularization in captured regions

\[ G = 20, \quad G_N = 1, \]

\[ \chi_D = \chi_\mu = \infty \quad \text{vascularized} \]

\[ \text{unvascularized} \]

- Vascularized tumor is more compact as predicted by previous theory.
Phase Diagram: Highly vascularized tissue

\[ \chi_D = \infty, \quad \chi_\mu = \infty \]

Macklin, Lowengrub, in preparation

- 3 distinct morphologies
- Evolution becomes independent of \( G \) for \( G >> 1 \)

In vitro tumor spheroid

Cristini et al, Cancer Res, in review

Necrosis (degradation)
Conclusions

• Extra-tumoral tissue strongly affects the size and morphology of growing tumors

• Inhomogeneity in nutrient distribution may lead to invasion, fragmentation and metastasis through diffusional instability

• Additional instability introduced by growth into less mobile tissue
Next Steps

• More complex/realistic biophysics
  • Angiogenesis
  • Multiphase/Multiscale models
  • More realistic mechanical response
  • Finite, complex domains
  • Stochastic models
Future work

• Genetic mutations, cell-differentiation and spatial structure

Non-random

Random

Komarova, Macklin, L.

Highly simplified model: \( dX_2 = dt + dW \)

• Strong interaction among length scales with geometry of domain leads to delayed invasion
Modeling growth in real organs

Breast cancer model