A hybrid model of tumour induced angiogenesis in 3D

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Będlewo

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Presentation outline

- Description of biological phenomena
- Motivation
- Mathematical model
- Results of computer simulations
- Summary
Hallmarks of Cancer


- Self-sufficiency in growth signals
- Evading apoptosis
- Limitless replicative potential
- Sustained angiogenesis
- Insensitivity to anti-growth signals

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Stages of carcinogenesis

An example of the development of ductal cancer and cervical squamous cancer
Stages of carcinogenesis

An example of the development of ductal cancer and cervical squamous cancer

A. Normal duct  Hyperplasia  Dysplasia/CIS  Angiogenic CIS  Invasive carcinoma

B. Normal cervical squamous epithelium  CIN I  CIN III  Invasive carcinoma

The Angiogenic Switch

- Small tumor
  - Nonvascular
  - “Dormant”

- Larger tumor
  - Vascular
  - Metastatic potential
Angiogenesis – formation of new blood vessels (capillaries) from existing vasculature

- Angiogenic factor production (VEGF, FGF, EGF)
- BM degradation
- Proliferation of EC
- Directional migration of EC
- ECM remodeling
- Tube and loop formation
- Vessel remodeling

The characteristics of tumor tissue:
- Anomalies in the construction and function of blood vessels and lymph vessels
- The increased blood vessels density


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Angiogenesis process

Noninvasive imaging of growth of the implanted colorectal cancer and angiogenesis (*intravital microscopy of dorsal window*).


Vascular normalization process as a balance of pro- and anti-angiogenic factors.

New idea of therapy vs Folkman’s theory (1971)

RK Jain: Normalization of Tumor Vasculature: An Emerging Concept in Antiangiogenic Therapy.

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Angiogenesis process

Photoacoustic imaging of tumour vasculature of human colorectal tumour xenografts implanted in mice.

Motivation

A necessary condition to model distribution of the oxygen (nutrient) and drugs in the tissue is to construct a model which take into account the spatial structure of the vascular network.

Problems:
- coupling (math)
- heterogeneity (biology)

Primeau, et al. ’05
Spatio-temporal models of tumour growth and angiogenesis in 3D

- Cell-based modelling:
  - Potts models by Szabo and Merks (Frontiers in Oncology’13)
    - cell adhesion and tumour-stroma interaction taken into account

- Hybrid models:
  - Welter and Rieger (PlosONE’13)
    - discrete vessels defined on a face centered cubic lattice + PDEs
    - interstitial fluid flow, vessel remodeling and drug transport considered
  - H Perfahl et al. (PlosONE’11)
    - agent-based approach + PDEs,
    - nutrient-dependent cell cycle dynamics, vascular remodeling,
Mathematical model of tumour growth and angiogenesis
- multiphase model
- reaction-diffusion model

Multiphase model for tumour growth dynamics
(Farina & Preziosi’00, Byrne & Preziosi’03)

Model variables:
- \( n \) – volume fraction occupied by healthy cells
- \( a \) – volume fraction occupied by tumour cells
- \( c \) – oxygen concentration
- \( V \) – VEGF concentration

Constant:
- \( m \) – volume fraction occupied by ECM

Subscripts for cell classes:
- \( P \) – proliferating cells
- \( Q \) – quiescent cells
- \( A \) – apoptotic cells

\[
\begin{align*}
\rho_j \left[ \frac{\partial \phi_j}{\partial t} + \nabla \cdot (\phi_j \mathbf{v}_j) \right] &= \rho_j \Gamma_j \\
\frac{\partial u_i}{\partial t} + \nabla \cdot (u_i \mathbf{W}) &= \nabla \cdot (Q_i \nabla u_i) + G_i - D_i u_i
\end{align*}
\]

for \( i = 1, \ldots, m \) and \( j = 1, \ldots, n \)

<table>
<thead>
<tr>
<th>cells</th>
<th>chemical factors + nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \phi_j ) = volume ratio</td>
<td>( u_i ) = concentration</td>
</tr>
<tr>
<td>( \rho_j ) = density of a single cell</td>
<td>( \mathbf{W} ) = transport</td>
</tr>
<tr>
<td>( \mathbf{v}_j ) = cell velocity</td>
<td>( G_i ) = production</td>
</tr>
<tr>
<td>( \Gamma_j ) = birth/death</td>
<td>( D_i ) = degradation/uptake</td>
</tr>
<tr>
<td></td>
<td>( Q_i ) = diffusion</td>
</tr>
</tbody>
</table>

\[
\psi = n_P + n_Q + n_A + a_P + a_Q + a_A + m \leq 1.
\]
Mathematical model of tumour growth and angiogenesis
- multiphase model
- reaction-diffusion model

Model for normal and tumour cells:

\[
\begin{align*}
\partial_t n_P + \nabla \cdot (n_P \mathbf{v}_n) &= \chi_n n_P (1 - \psi) + \gamma_n(c) n_Q - \lambda_n(c) n_P - \alpha_n(c) n_P - k_1 d_1 n_P, \\
\partial_t n_Q + \nabla \cdot (n_Q \mathbf{v}_n) &= -\gamma_n(c) n_Q + \lambda_n(c) n_P - \beta_n(c) n_Q, \\
\partial_t n_A + \nabla \cdot (n_A \mathbf{v}_n) &= \alpha_n(c) n_P + \beta_n(c) n_Q - \mu_n n_A,
\end{align*}
\]

Model for O$_2$ and VEGF concentration:

\[
\begin{align*}
\partial_t c &= D_c \nabla^2 c - f_{Pn} n_P c - f_{Pa} a_P c - f_{Qn} n_Q c - f_{Qa} a_Q c + 2\pi R(x) P_c (H - c) \\
\partial_t V &= D_V \nabla^2 V + \alpha_V (n_Q + a_Q) - \tau_V V - 2\pi R(x) V
\end{align*}
\]

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Mathematical model of tumour growth and angiogenesis - model closure

- Cellular velocity field based on DeAngelis & Preziosi ’00 and Ambrosi & Preziosi ’02
- Velocity field dependent on gradient of the cellular stress function

\[ \mathbf{v} \equiv \mathbf{v}_a = \mathbf{v}_n = -K \nabla \Sigma(\psi), \]

where:

\( K \) parametr associated with permeability of the tissue,

\( \Sigma \) stress function dependent on overall volume fraction.

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Mathematical model of tumour growth and angiogenesis
- random walk model

Random walk model for endothelial cells forming vessels
(Owen, et al. JTB’09)

\[
P_{\text{sprout}} = \Delta t \frac{p_{\text{max sprout}} V}{V_{\text{sprout}} + V}
\]

Radius of exclusion, \(R_{\text{ex}}\)
(Delta-Notch signalling)

- probability of sprouting

\[
P_{ij} = \frac{\Delta t D}{d_{ij}^2 \Delta x^2} \sum_{k \in \Omega_i} \frac{(N_m - N_j)(N_m - N_k) + N_m - N_i + N_m M}{N_m - N_k + N_m N_i + N_m M} \left(1 + \gamma \frac{V_j - V_i}{d_{ij} \Delta x}\right)
\]
for \(i \neq j\),

- probability of „movement”

\[
P_{ii} = 1 - \sum_{k \in \Omega_i} P_{ik} = 1 - \frac{\Delta t D}{\Delta x^2} \sum_{k \in \Omega_i} \sum_{k \in \Omega_i} \frac{(N_m - N_k)(N_m - N_k) + N_m - N_i + N_m M}{N_m - N_k + N_m N_i + N_m M} \left(1 + \gamma \frac{V_k - V_i}{d_{ik} \Delta x}\right)
\]

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Mathematical model of tumour growth and angiogenesis - random walk model

1) Making functional vessels

2) Poiseuille law used for calculation volume flowrate (laminar flow)

3) Wall shear stress for vascular normalization (pruning)

4) Probability modified by parameter K – tortuosity control
Results of numerical simulations

Simulations of angiogenesis in 3D (source of VEGF in centre)

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Results of numerical simulations

Changes in the network structure according to the model parameter Rex

Volume of the vascular network

Volume of the tumor

Overall concentration of VEGF

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Results of numerical simulations

Dynamics of tumor growth according to the changes of Delta-Notch process parameter (multiple realization – 300 realisations)

Hahnfeldt Model

\[ \dot{N} = -\beta N \ln \left( \frac{N}{K} \right) - \psi \nu N \]

\[ \dot{K} = \gamma N - \lambda K N^2 - \mu K - \eta \nu K - \xi \nu K \]
Results of numerical simulations

Blood flow distribution in vascular network

Blood vessel diameter distribution (pruning + maturation)

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Results of numerical simulations

Penetration of the tumour by the vessels – cell density dependence.

Overall volume of the vascular network (inside and outside)

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Results of numerical simulations

Distribution of tumour cell population (proliferative, quiescent and apoptotic).
Distribution of oxygen concentration within the tissue.
Results of numerical simulations

Distribution of tumour cell population (proliferative, quiescent and apoptotic).
Distribution of VEGF concentration within the tissue.
Results of numerical simulations

Distribution of normal cell population (proliferative, quiescent and apoptotic).

Distribution of overall tumour vs normal cell population.

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Construction of the model of growing tumour which take into account geometry of vascular network
Simulations are in three-dimensional space
Model captures heterogeneity of the tissue

Ongoing research:
• Validation of the model
• Part of the larger project aimed for simulations of cerebral pathologies (including blood flow)
• Simulations of chemotherapy and/or antiangiogenic therapy
• Optimization of the therapeutic protocols
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