A hybrid model of tumour induced angiogenesis in 3D

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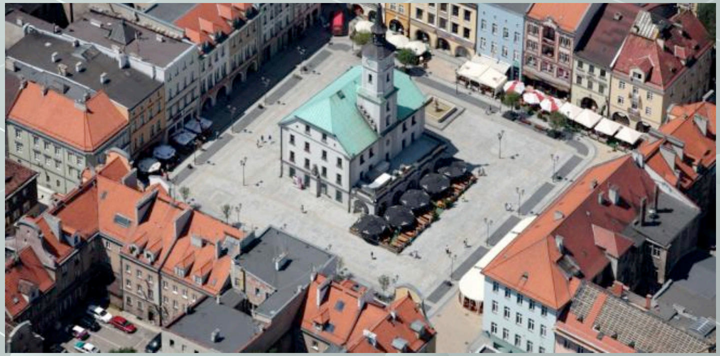


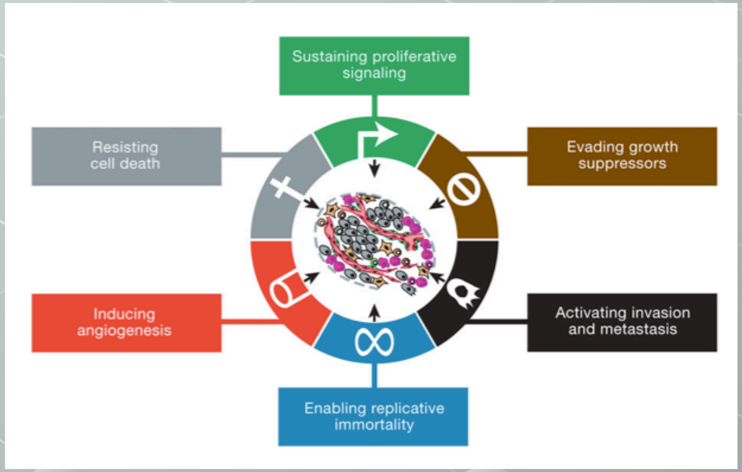
Presentation outline

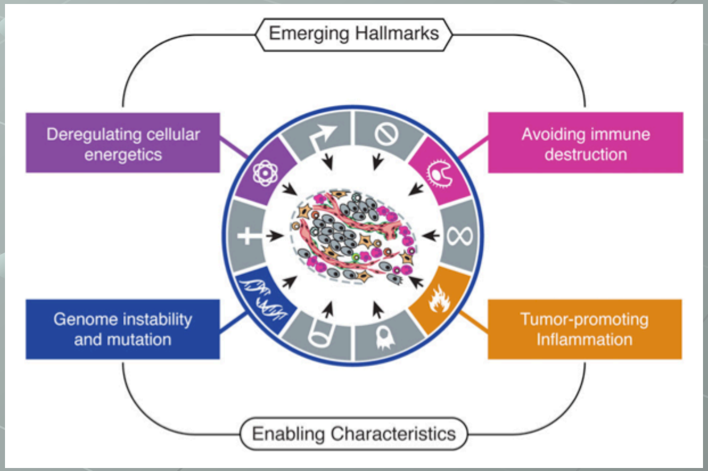
- Description of biological phenomena
- Motivation
- Mathematical model
- Results of computer simulations
- Summary

Hallmarks of Cancer

Hanahan & Weinberg: Hallmarks of Cancer. Cell (2000).
Hanahan & Weinberg: Hallmarks of Cancer: The Next Generation. Cell (2011).

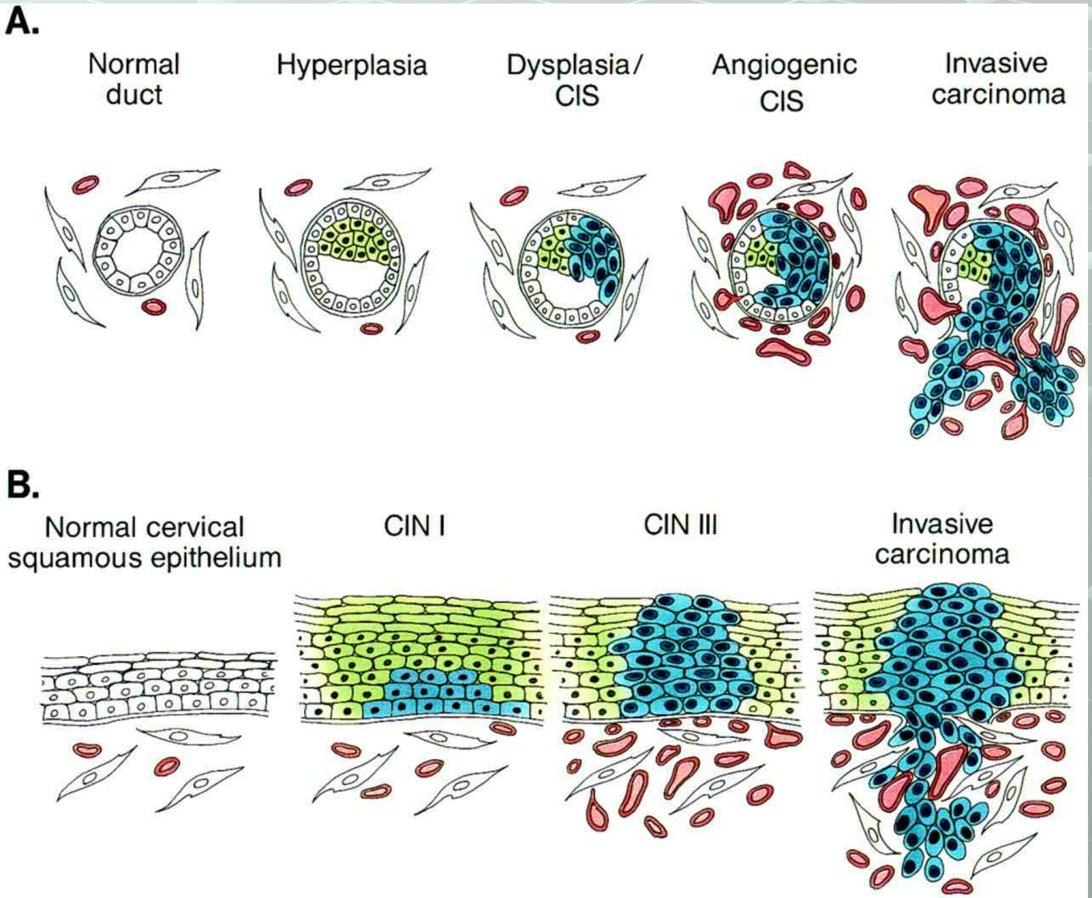
- Self-sufficiency in growth signals
- Evading apoptosis
- Limitless replicative potential
- Sustained angiogenesis
- Insensitivity to anti-growth signals





Stages of carcinogenesis

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



Stages of carcinogenesis

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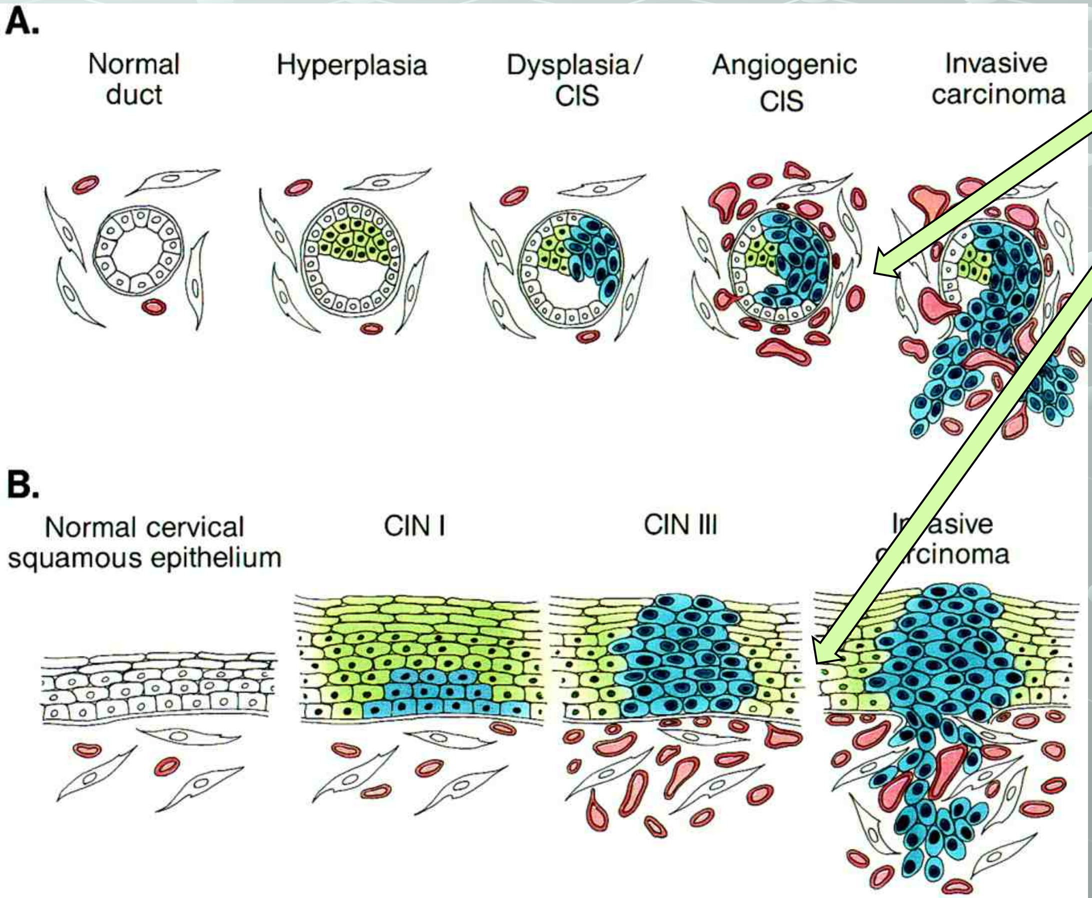
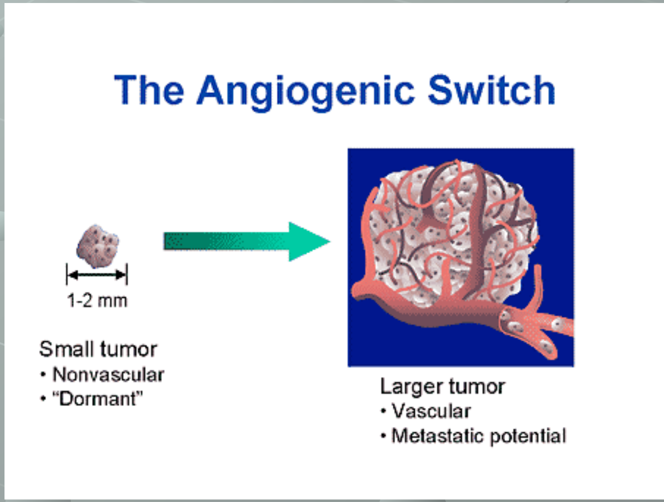
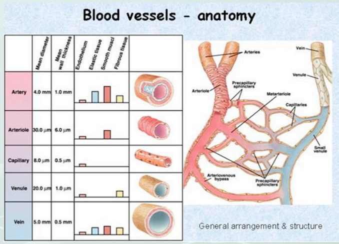
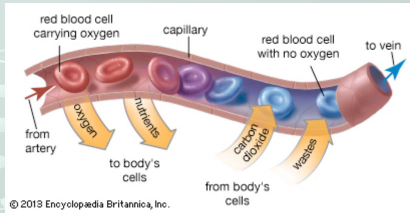


Angiogenic Switch



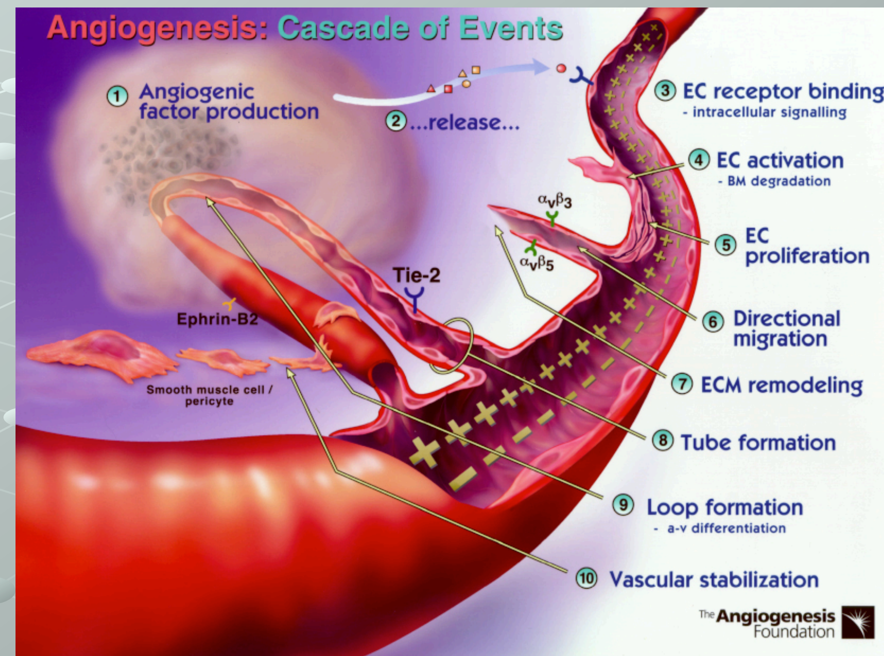
Angiogenesis process





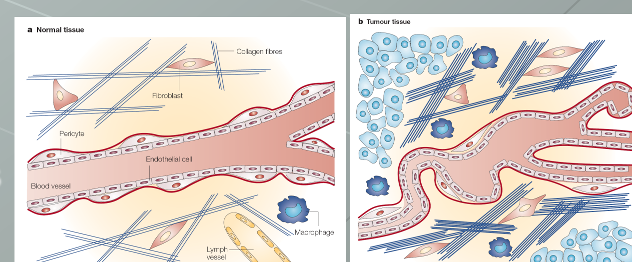
Angiogenesis – formation of new blood vessels (capillaries) from existing vasculature

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

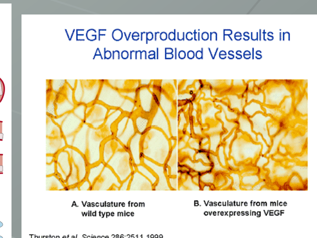


The characteristics of tumor tissue:

- Anomalies in the construction and function of blood vessels and lymph vessels
- The increased blood vessels density



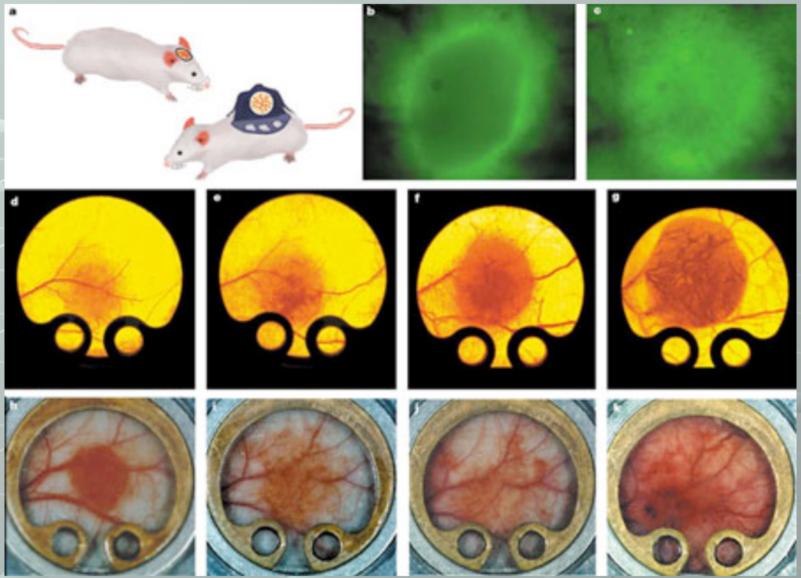
Heldin C.H.,et al., Nature Rev Cancer, 4:806-813, 2004.

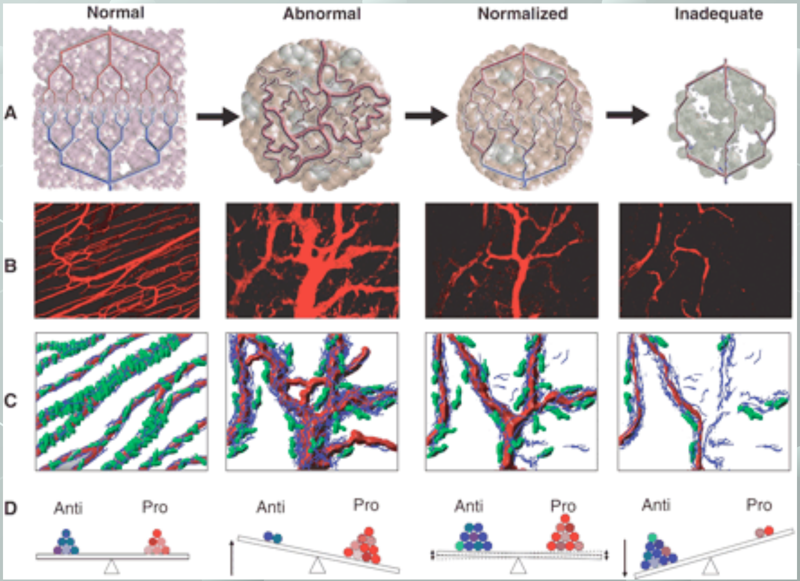


Angiogenesis process

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

P Carmeliet, RK Jain: Angiogenesis in cancer and other diseases.
Nature 407, 249-257 (2000).





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

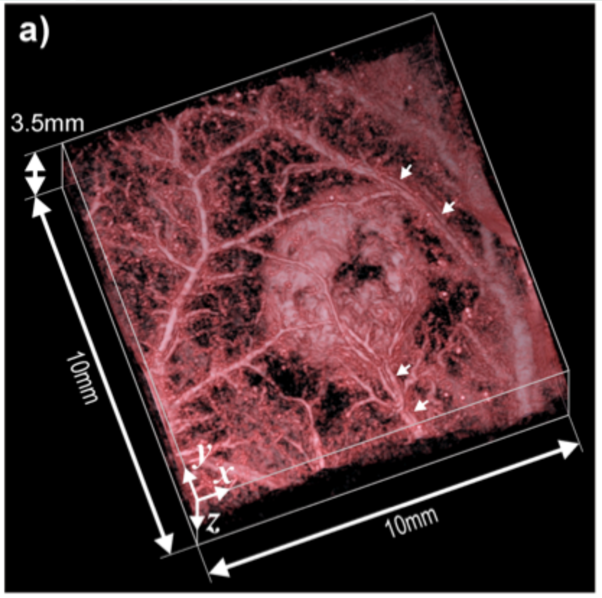
New idea of therapy vs Folkman's theory (1971)

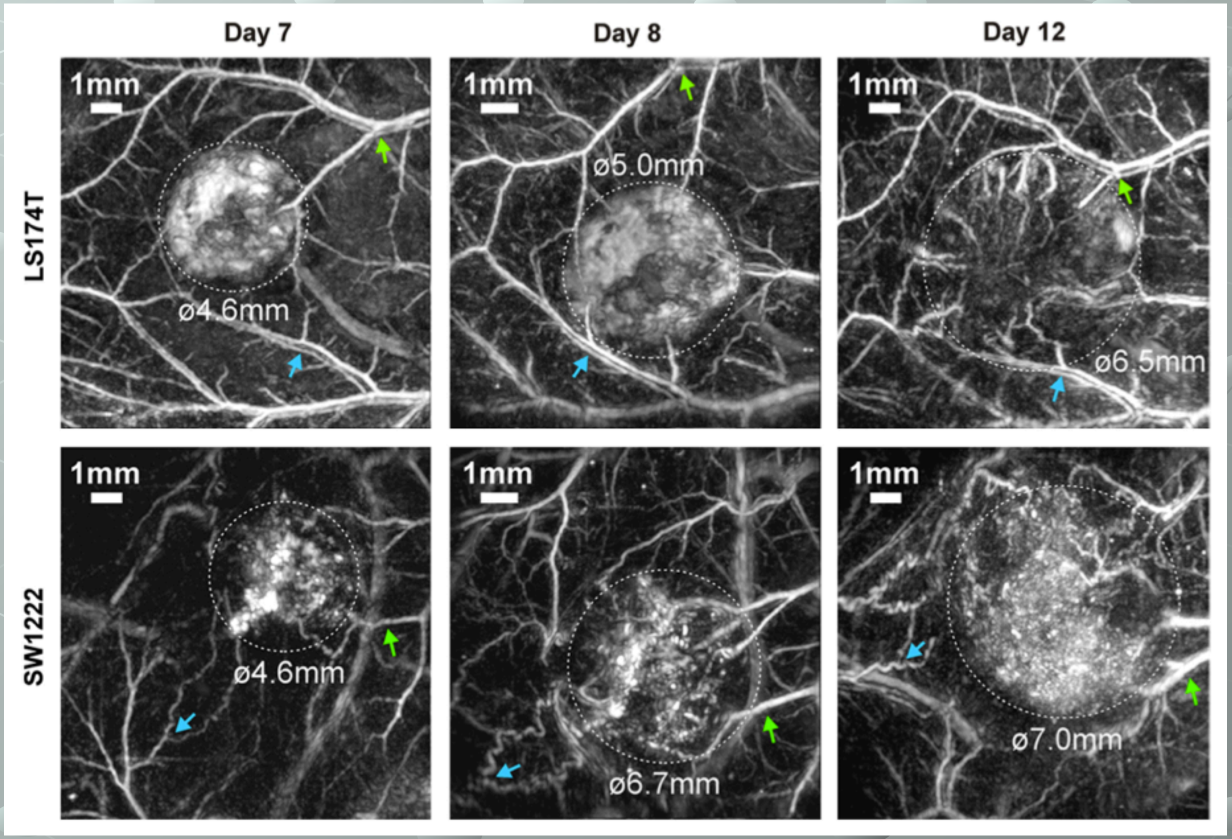
RK Jain: Normalization of Tumor Vasculature: An Emerging Concept in Antiangiogenic Therapy.
Science 307, 58-62 (2005).

Angiogenesis process

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

J. Laufen, *et al.*: In vivo preclinical photoacoustic imaging of tumor vasculature development and therapy. Journal of Biomedical Optics 17(5), 056016 (2012).



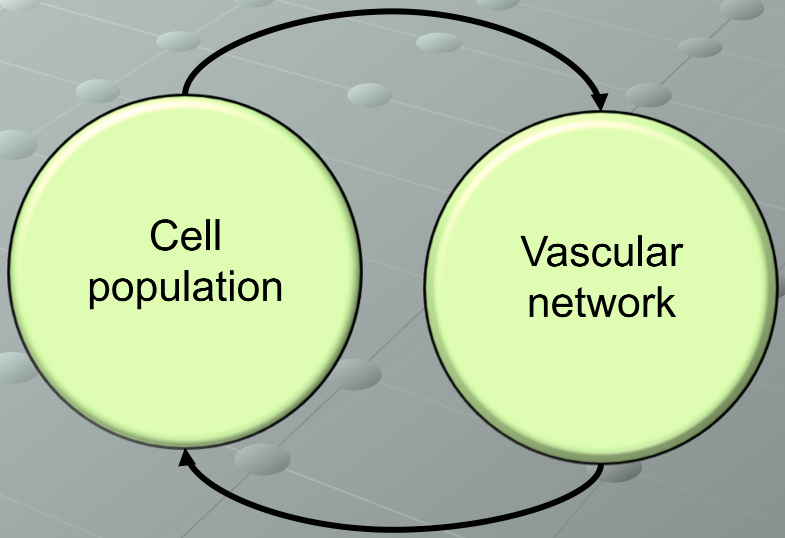


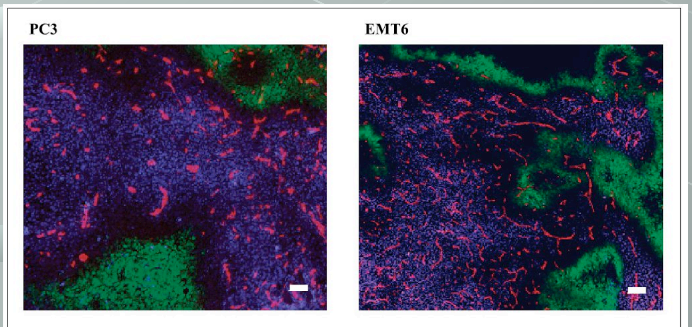
Motivation

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:

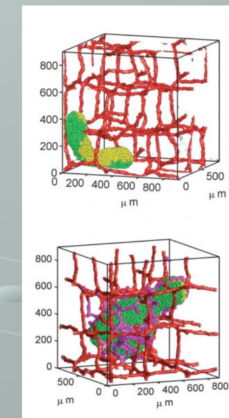
- coupling (math)
- heterogeneity (biology)



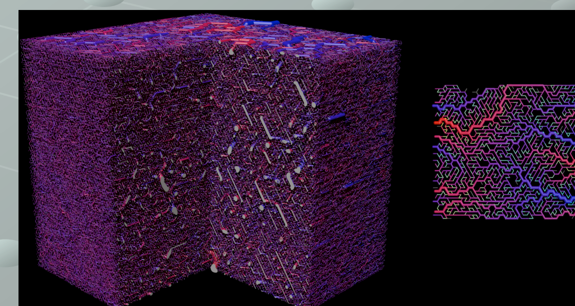


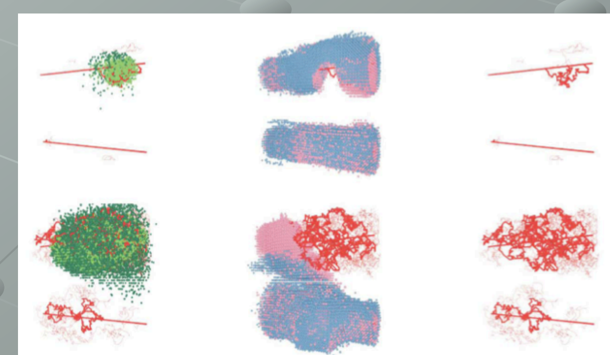
Primeau, *et al.* '05

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)

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

for $i = 1, \ldots, m$ and $j = 1, \ldots, n$

cells	chemical factors + nutrients
ϕ_j = volume ratio ρ_j = density of a single cell $\mathbf{v}_j$ = cell velocity Γ_j = birth/death	u_i = concentration $\mathbf{W}$ = transport G_i = production D_i = degradation/uptake Q_i = diffusion

Model variables:

n – volume fraction occupied by healthy cells

a – volume fraction occupied by tumourcells

c – oxygen concentration

V – VEGF concentration

Constant:

m – volume fraction occupied by ECM

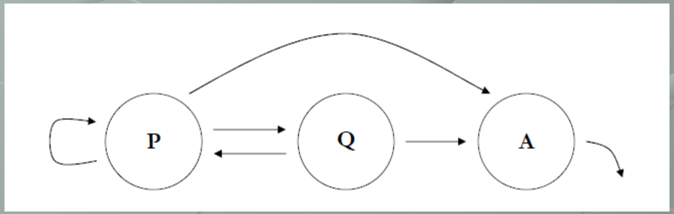
$$\psi = n_P + n_Q + n_A + a_P + a_Q + a_A + m \leq 1,$$

Subscripts for cell claces:

P – proliferating cells

Q – quiescent cells

A – apoptotic cells



Mathematical model of tumour growth and angiogenesis
- multiphase model
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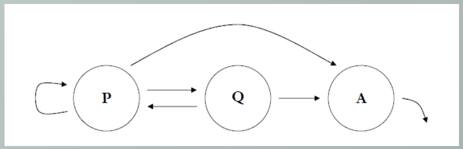


Model for normal and tumour cells:

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

$$\begin{cases} \partial_t a_P + \nabla \cdot (a_P \mathbf{v}_a) = \chi_a a_P (1-\psi) + \gamma_a(c) a_Q - \lambda_a(c) a_P - \alpha_a(c) a_P - k_2 d_1 a_P, \\ \partial_t a_Q + \nabla \cdot (a_Q \mathbf{v}_a) = -\gamma_a(c) a_Q + \lambda_a(c) a_P - \beta_a(c) a_Q, \\ \partial_t a_A + \nabla \cdot (a_A \mathbf{v}_a) = \alpha_a(c) a_P + \beta_a(c) a_Q - \mu_a a_A, \end{cases}$$

Model for O_2 and VEGF concentration:

$$\partial_t c = D_c \nabla^2 c - f_{P_n} n_P c - f_{P_a} a_P c - f_{Q_n} n_Q c - f_{Q_a} a_Q c + 2\pi R(x) P_c (H - c)$$

$$\partial_t V = D_V \nabla^2 V + \alpha_V (n_Q + a_Q) - \tau_V V - 2\pi R(x) V$$

Mathematical model of tumour growth and angiogenesis - model closure

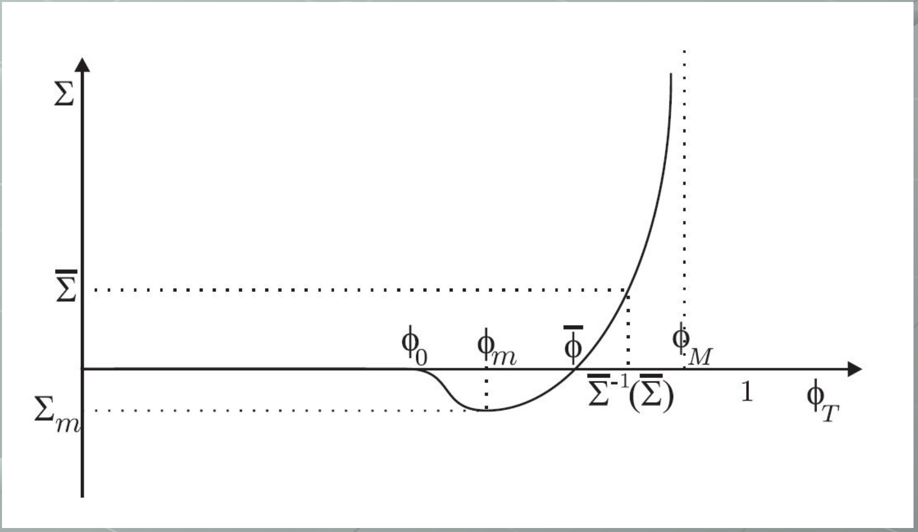
- Cellular velocity field based on DeAngelis & Preziosi ’00 and Ambrosi & Preziosi ’02
- Velocity field dependent on gradient of the cellular stress function

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

where:

K parametr associated with permeability of the tissue,

Σ stress function dependent on overall volume fraction.



Mathematical model of tumour growth and angiogenesis - random walk model

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

$$P_{\mathrm{sprout}} = \Delta t \frac{P_{\mathrm{sprout}}^{\max} V}{V_{\mathrm{sprout}} + V},$$

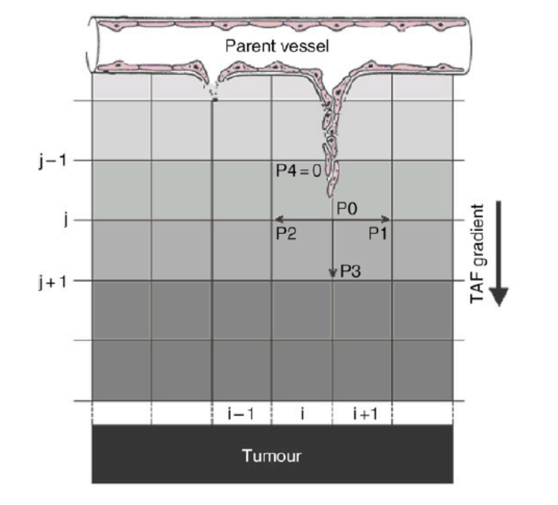
- probability of sprouting

Radius of exclusion, *Rex*
(Delta-Notch signalling)

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

- probability of „movement"

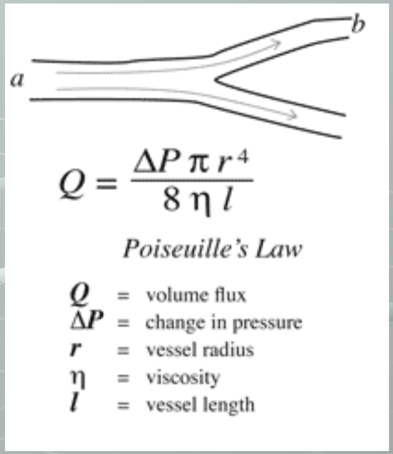
$$P_{ii} = 1 - \sum_{k\in\Omega_i} P_{ik} = 1 - \frac{\Delta t D}{\Delta x^2} \frac{\sum_{k\in\Omega_i} \frac{N_m - N_k}{d_{ik}^2}\left(1 + \gamma \frac{V_k - V_i}{d_{ik}\Delta x}\right)}{\sum_{k\in\Omega_i}(N_m - N_k) + N_m - N_i + N_m M}.$$



Mathematical model of tumour growth and angiogenesis - random walk model

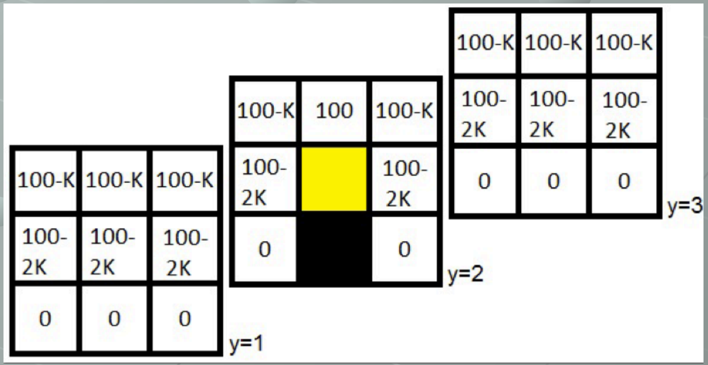
1) Making functional vessels

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



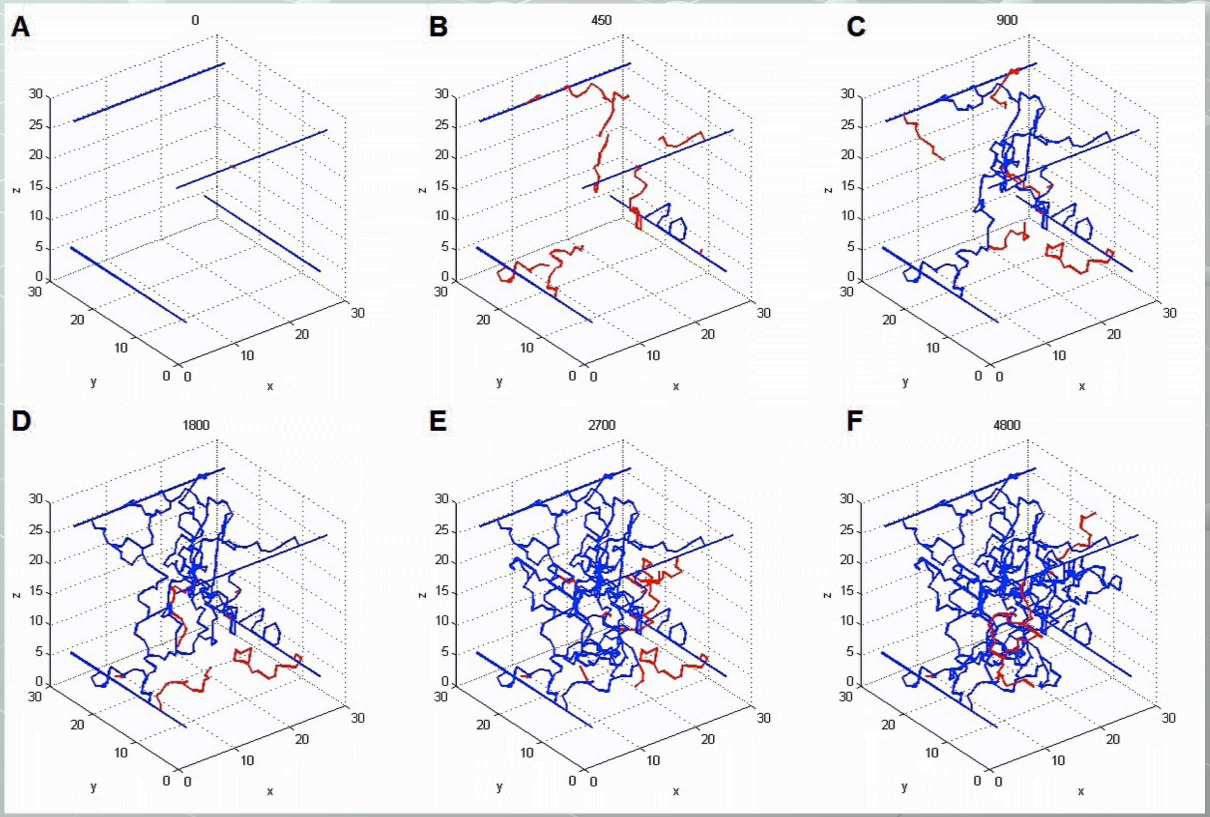
3) Wall shear stress for vascular normalization (pruning)

4) Probability modified by parameter K – tortuosity control



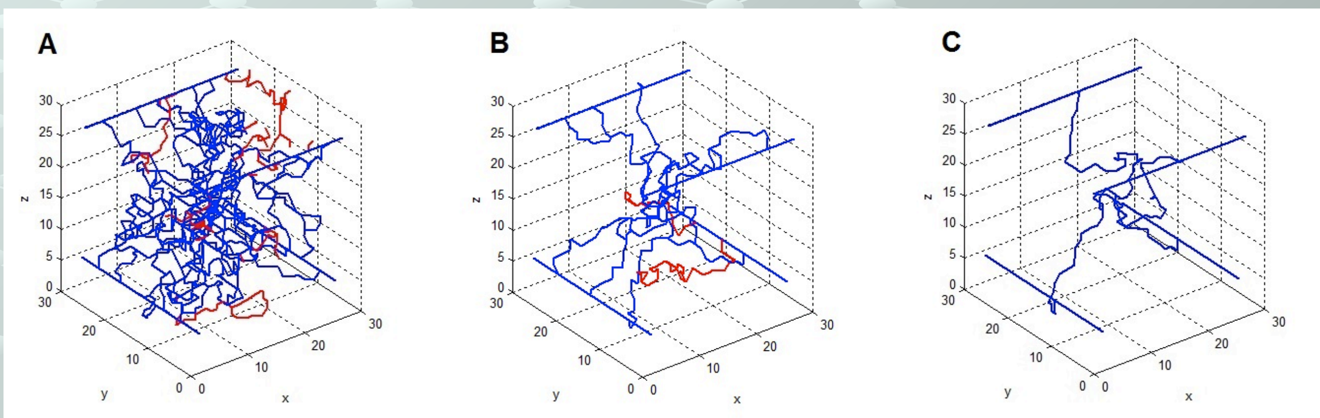
Results of numerical simulations

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

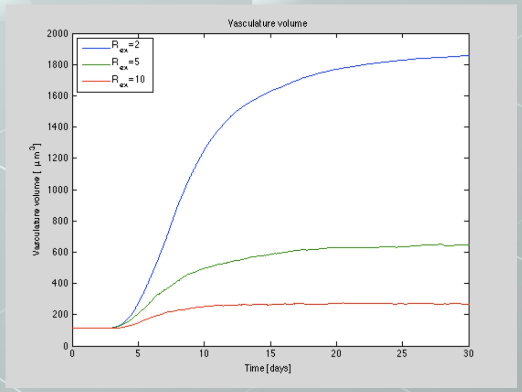


Results of numerical simulations

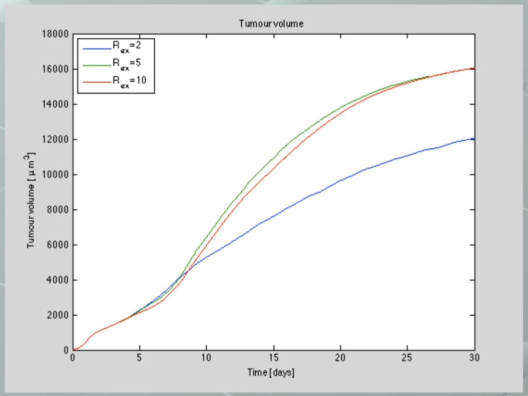
Changes in the network structure according to the model parameter Rex



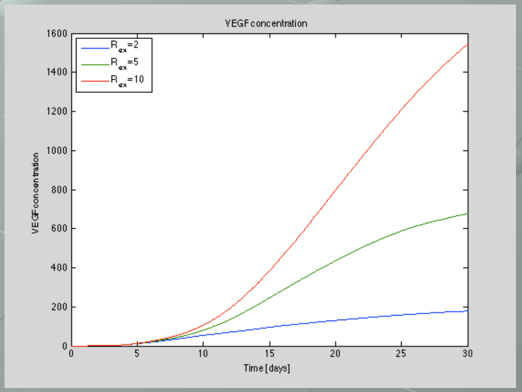
Volume of the vascular network



Volume of the tumor

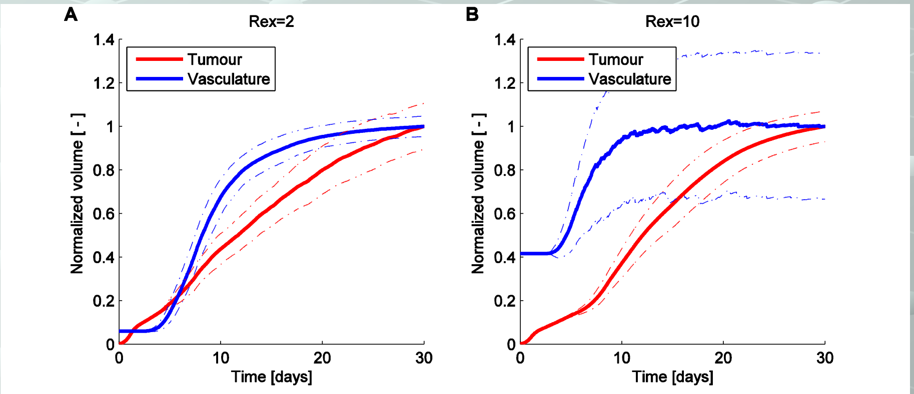


Overall concentration of VEGF



Results of numerical simulations

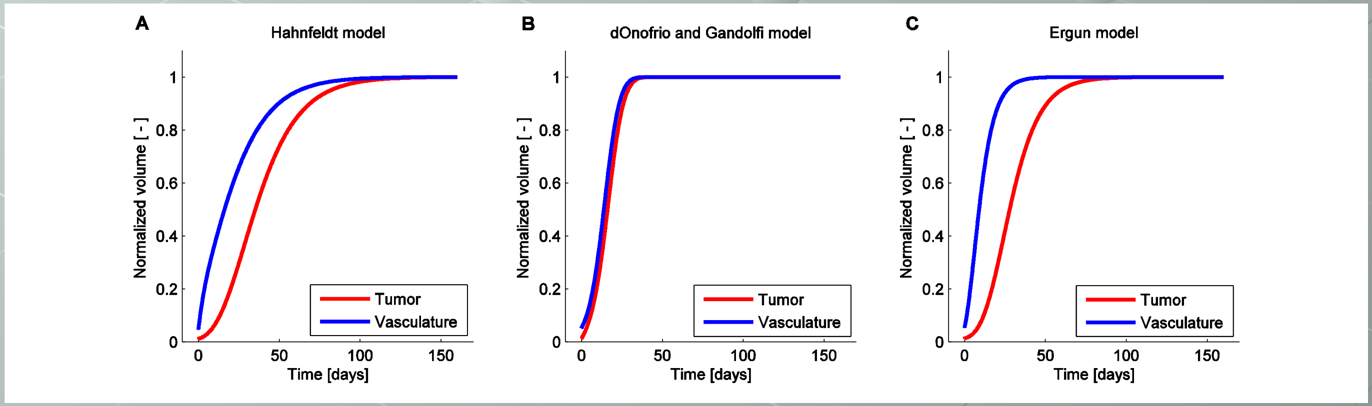
Dynamics of tumor growth according to the changes of Delta-Notch process parameter (multiple realization – 300 realisations)



Hahnfeldt Model

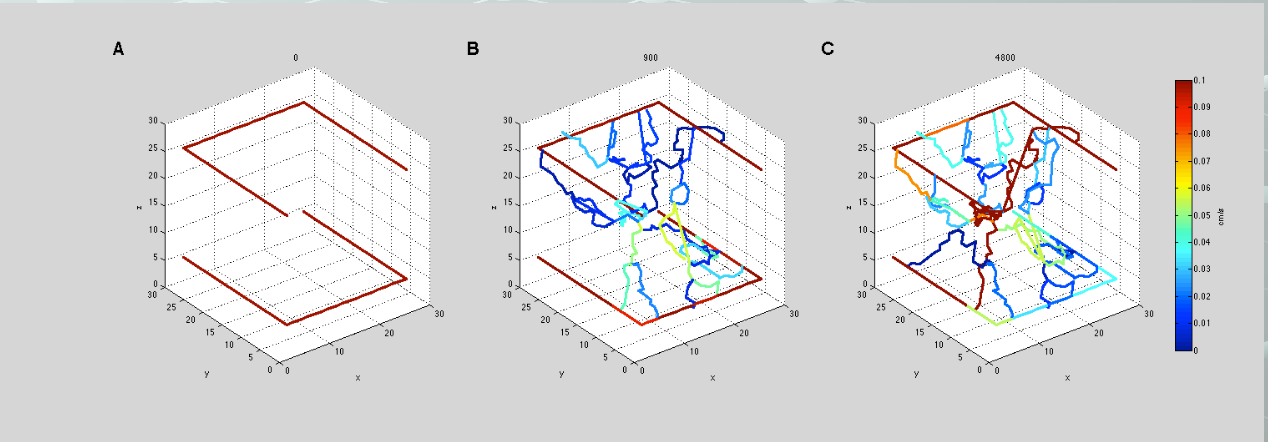
$$\dot{N} = -\beta N ln\left(\frac{N}{K}\right) - \psi v N$$

$$\dot{K} = \gamma N - \lambda K N^{\frac{2}{3}} - \mu K - \eta u K - \xi v K$$

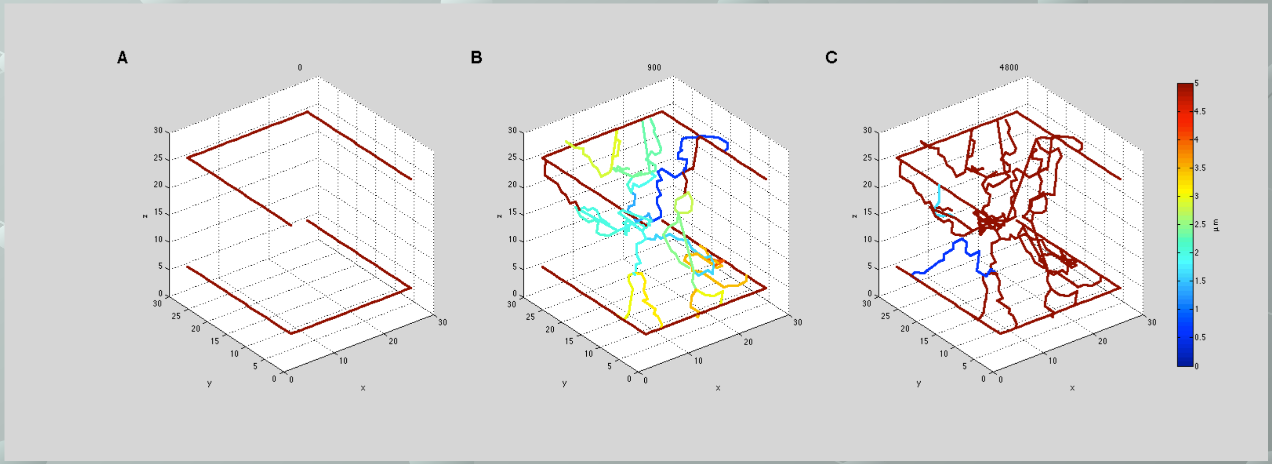


Results of numerical simulations

Blood flow distribution in vascular network

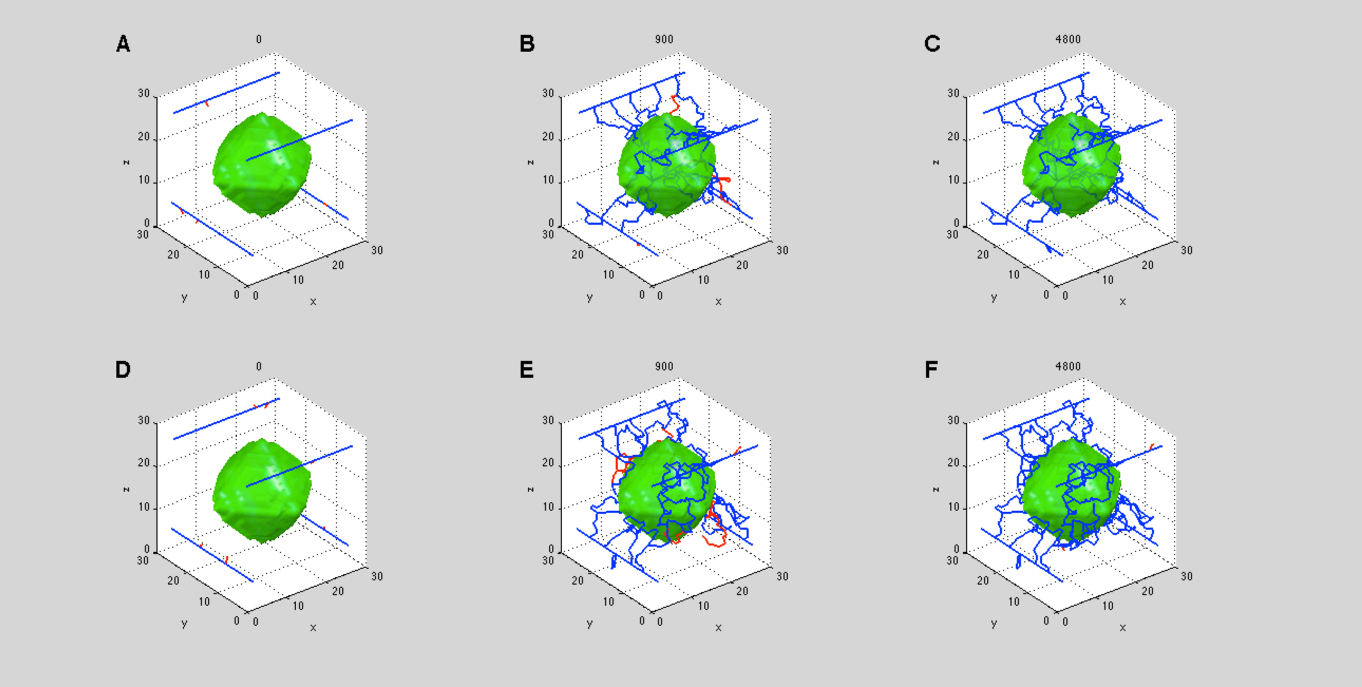


Blood vessel diameter distribution (pruning + maturation)

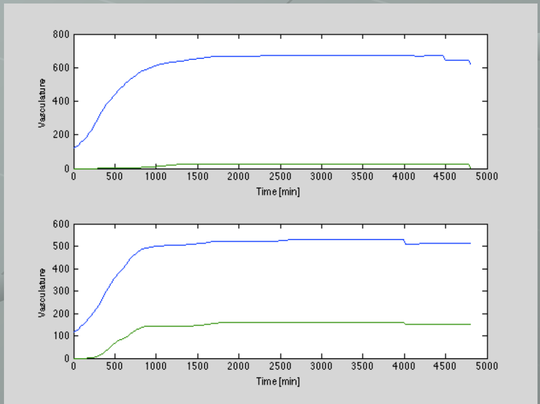


Results of numerical simulations

Penertation of the tumour by the vessels – cell density dependance.

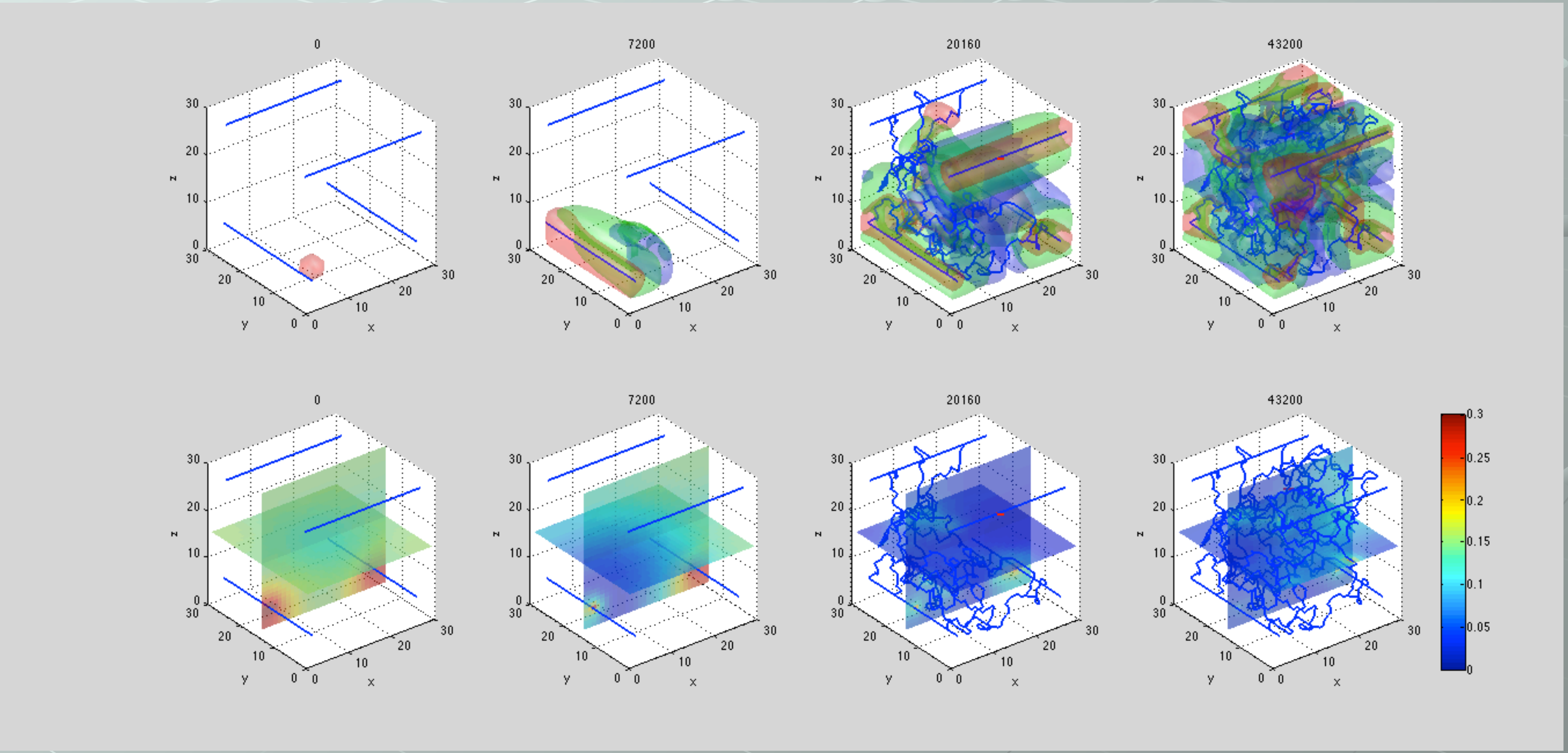


Overall volume of the vascular network (inside and outside)



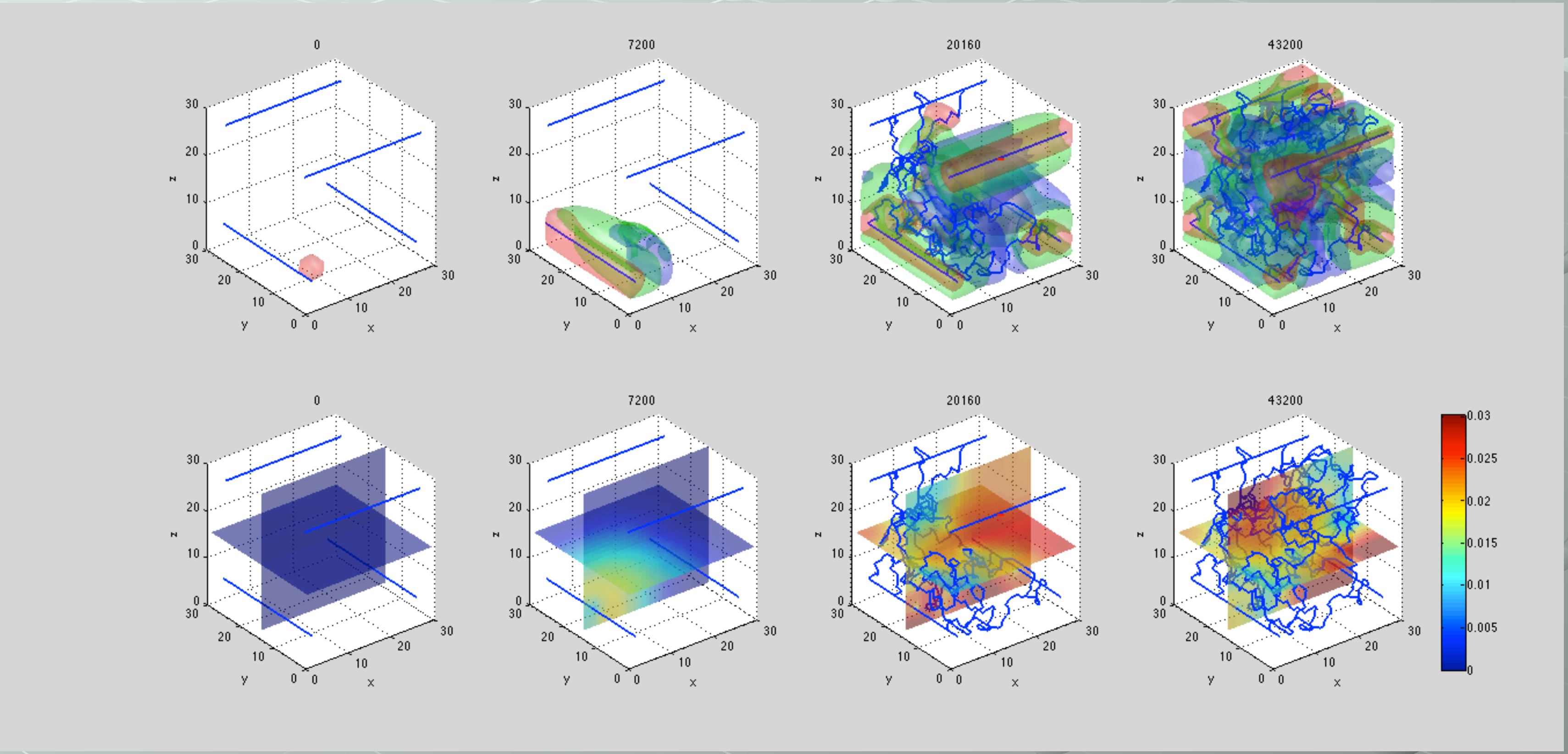
Results of numerical simulations

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



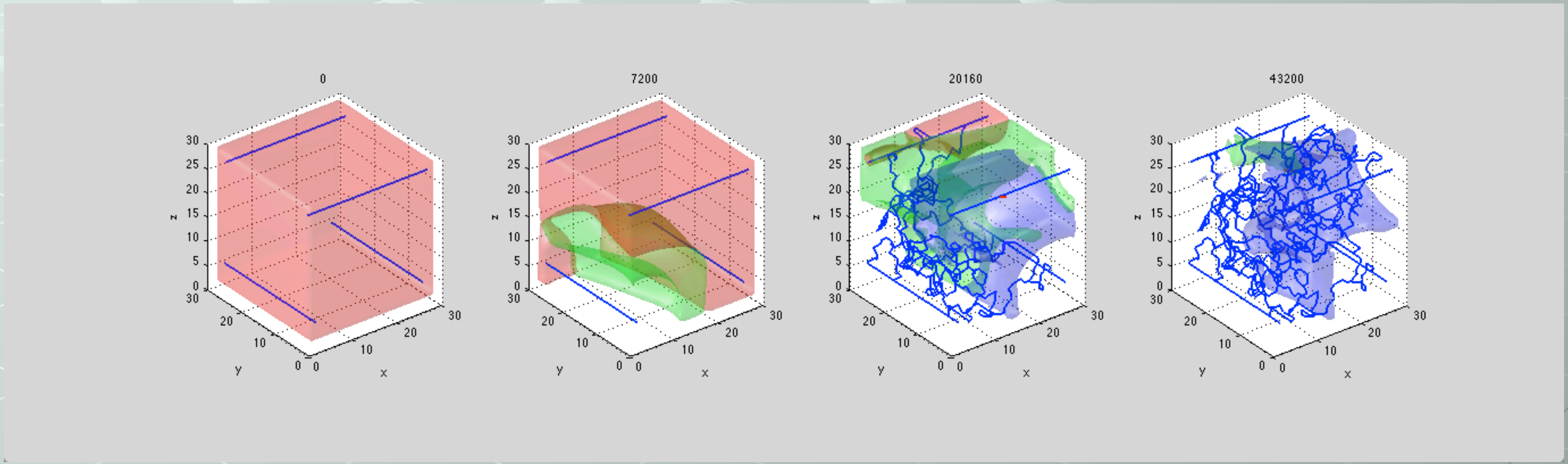
Results of numerical simulations

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

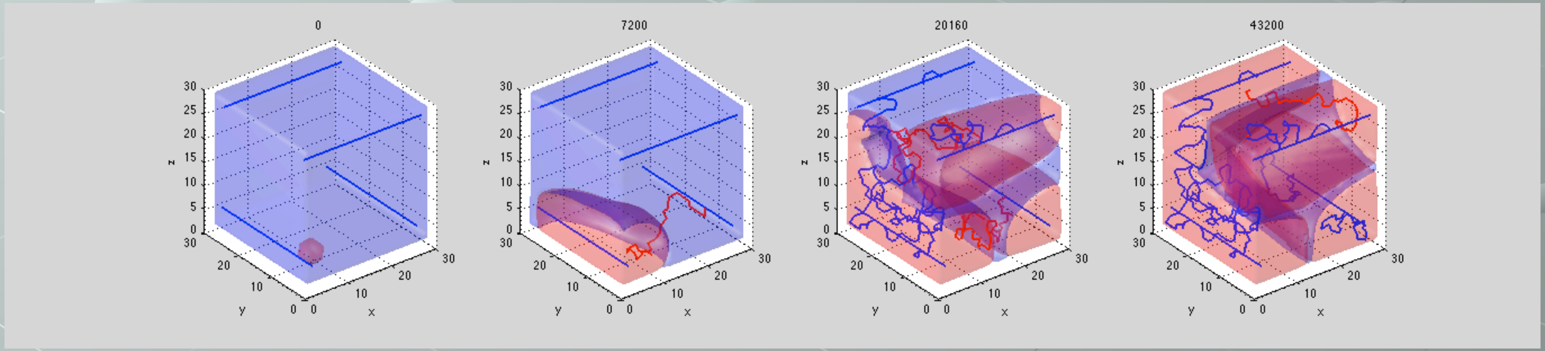


Results of numerical simulations

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



Distribution of overall tumour vs normal cell population.

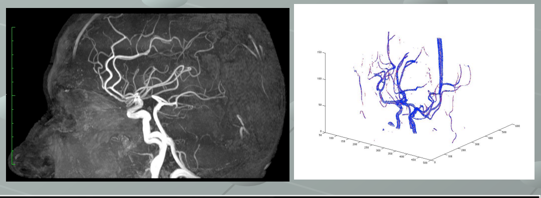


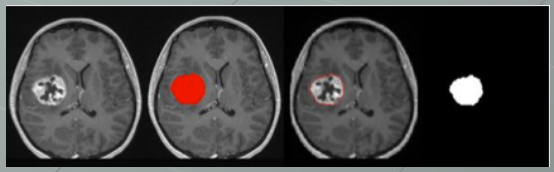
Summary

- Construction of the model of growing tumour which take into account geometry of vascular network
- Simulations are in three-dimensional space
- Model capturoes 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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  - prof. dr hab. inż. Andrzej Świerniak

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Thank you for your attention!