UNIVERSITÄT DES SAARLANDES

# Angiogenesis and vascular network remodeling in a growing tumor

Physics of distributed information systems, NORDITA, May 2008

# Collaborators

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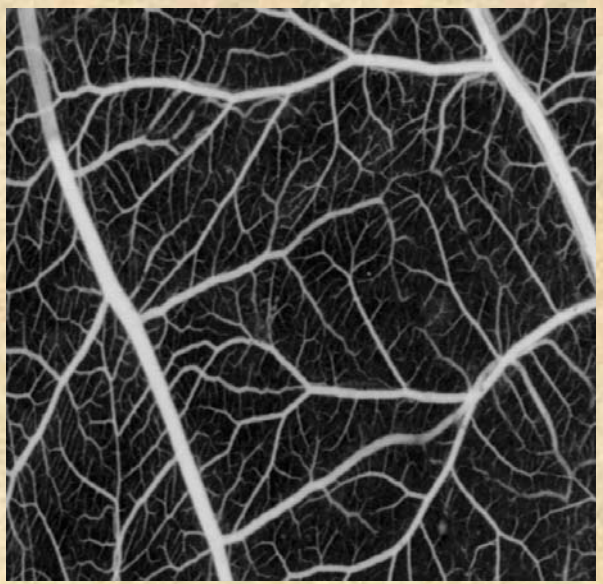
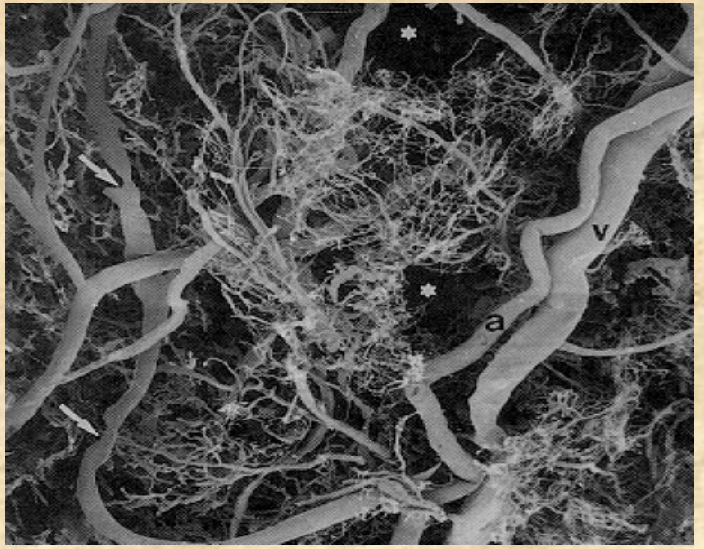
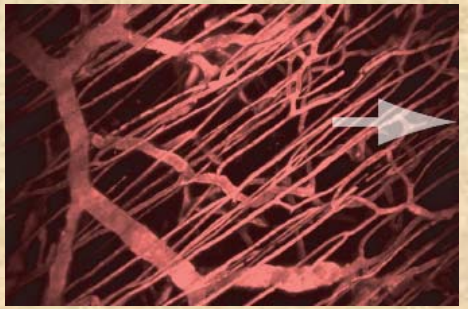
# Normal vascularization vs. tumor vessels



Normal capillary network (Oh et al. 1996)




Dilated vessels, brush border effect in the periphery of a melanoma (Steiner et.al.,1992)



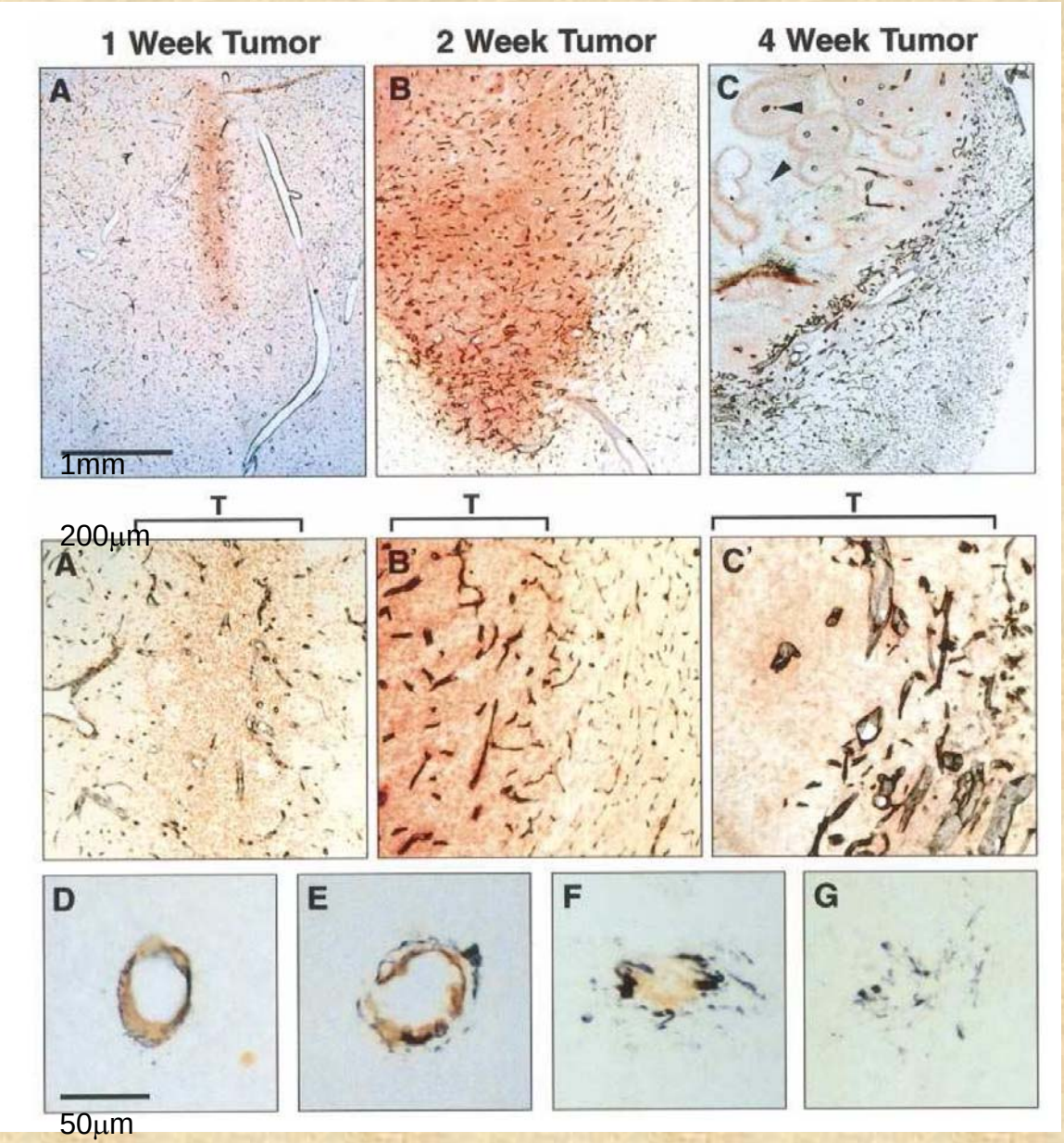
Capillaries in muscle tissue

# Progressive vessel regression in growing tumors

Sections from rat brain tumor

Black:
Vessel-walls

Red:
Tumor cells (TCs)

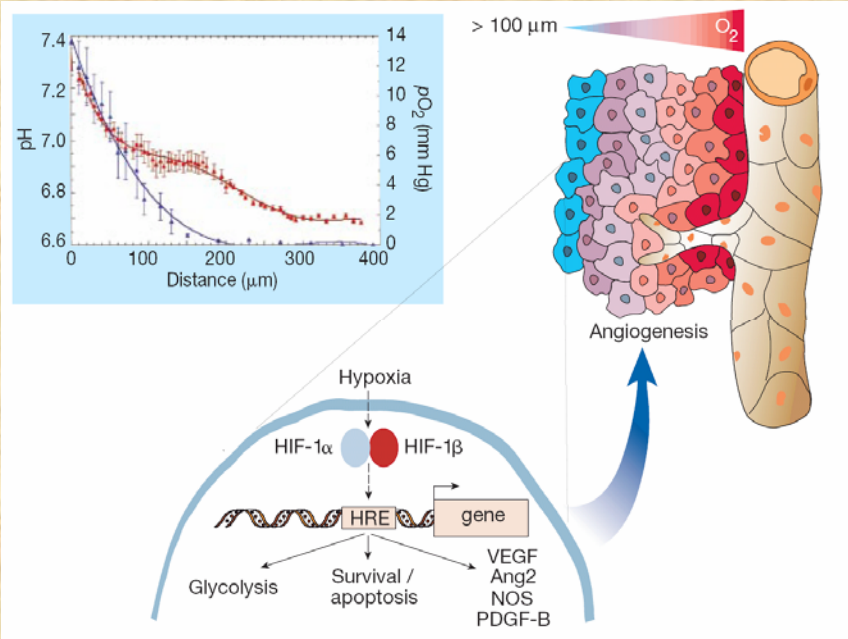



Section through normal vessel (D), tumor vessels (E-G)

[from Holash et al., Science 284, 1994 (1999)]

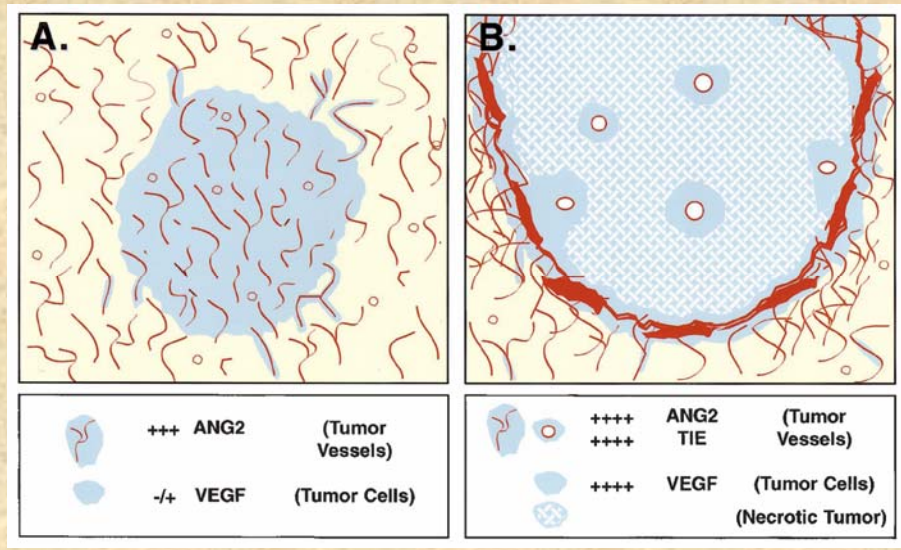
# Angiogenesis / Oxygen / HIF / Cooption

## Oxygen diffusion range / Hypoxia




[from Carmeliet and Jain, Nature 407, 249 (2000)]

## Vessel cooption

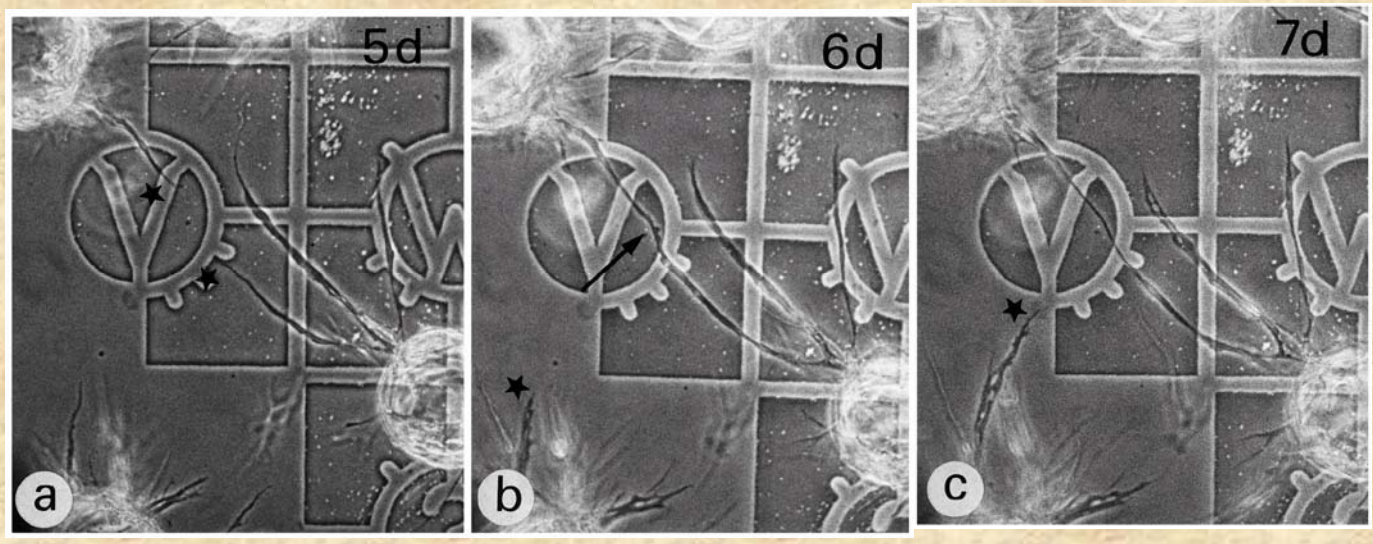



Changes in tumor vasculature during growth. After co-opting host vessels, tumors (gray) initially grow as well as vascularized masses (A).As tumor growth progresses, many of the central tumor vessels regress (B), resulting in massive TC death and necrosis (strippled region). Surviving TCs form cuffs around the few remaining internal vessels.

[from Holash et al., Science 284, 1994 (1999)]

# Capillary network remodeling in vitro:

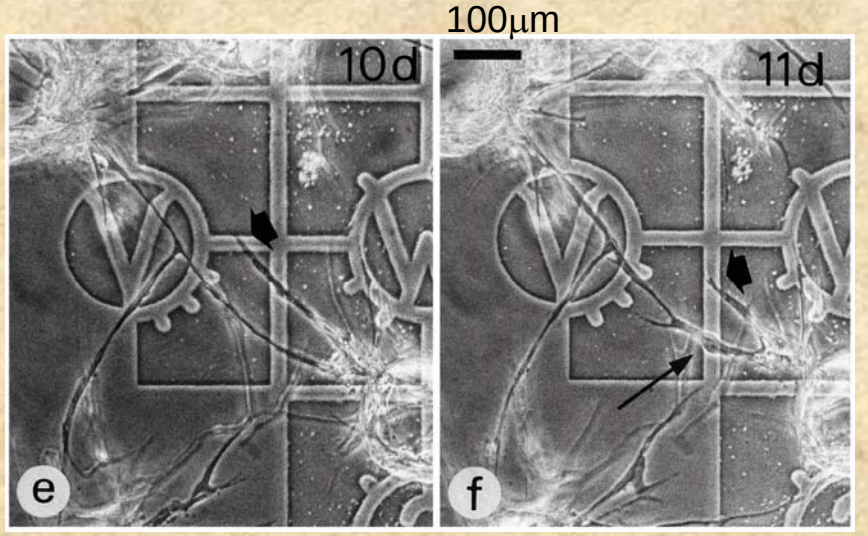
## Migration and anastomoisis of endothelial cells (EC)




Matrix:
Fibrin gel + bFGF

Microcarriers
coated with ECs

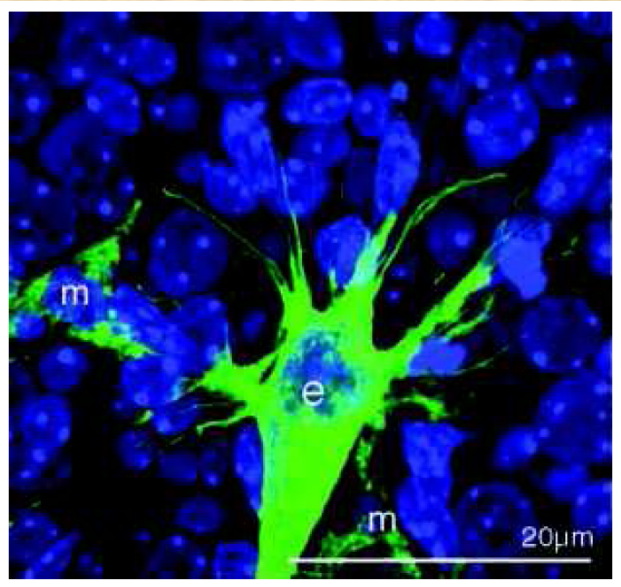
Nehls, Herrmann, Hühnken
Hist. Cell Biol. 109, 319
(1998)



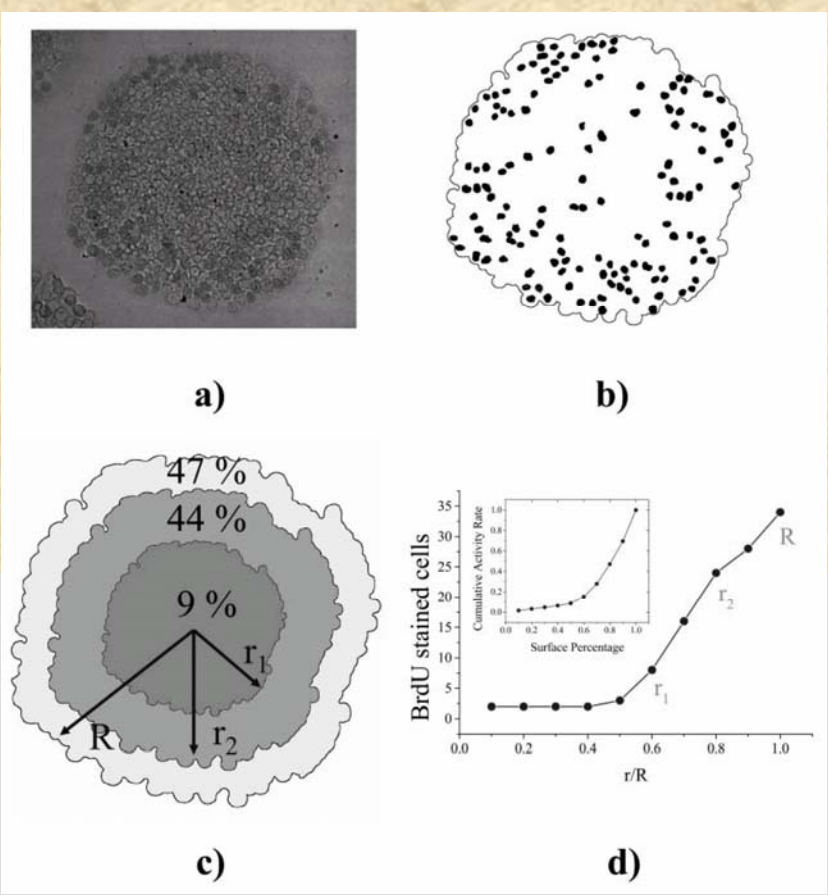

**In vivo:**
Filopodial
extensions
of a
sprouting tip

Green:
Endothelial
Cells (ECs)

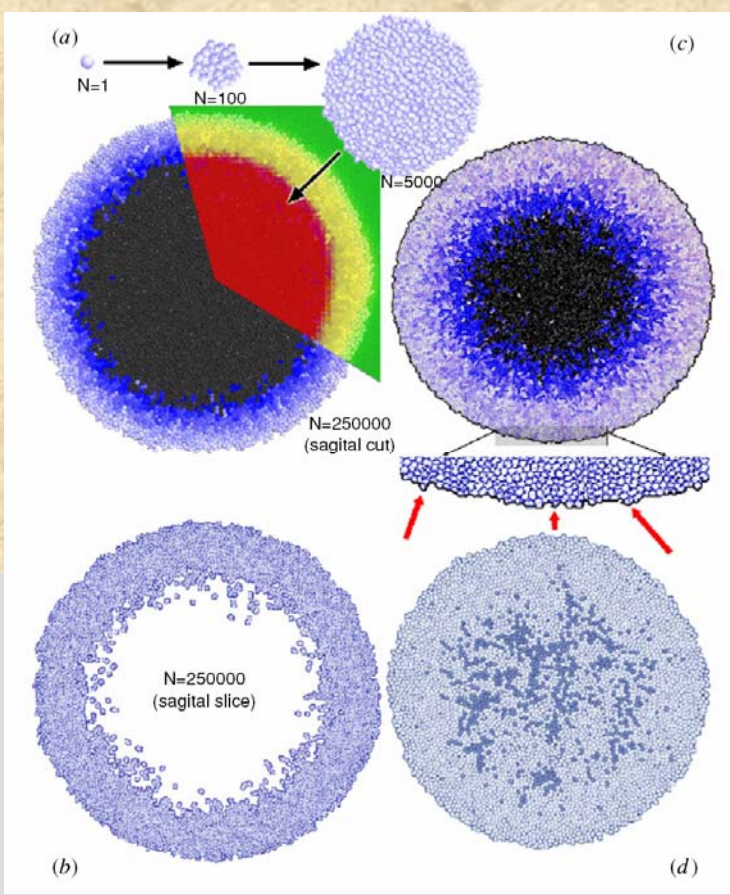
Blue:
Nuclei



# Tumor cell proliferation confined to outer rim:




Experiment, Brú et al.
Biophys. J. 85, 2948 (2003)

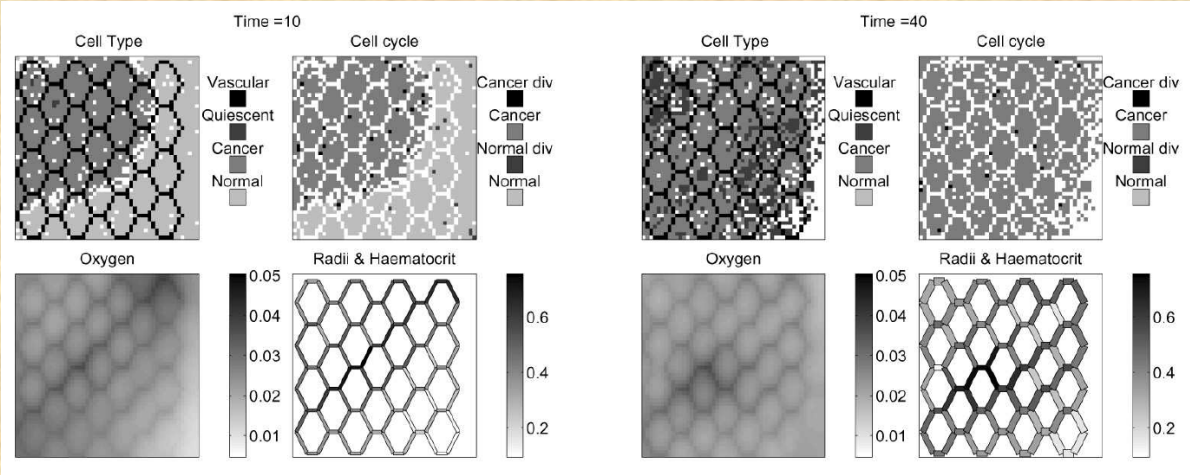



Theoretical model, Drasdo & Höhme
Phys. Biol. 2, 133 (2005)

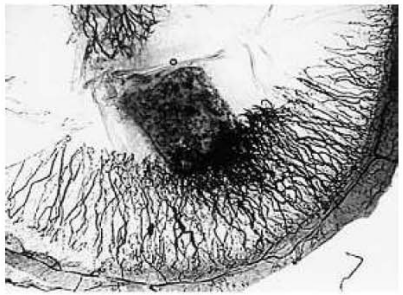
**Radius of an avascular tumor in vitro grows linearly in time**

# Earlier theoretical work

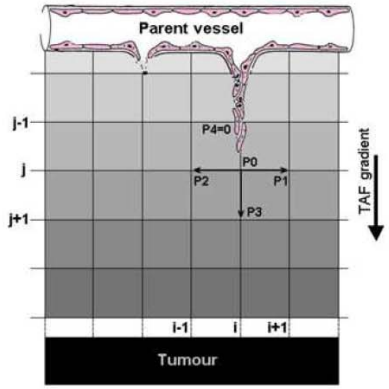
Fixed vessel network, proliferating tumor cells (Alarcon, Byrne, Maini)

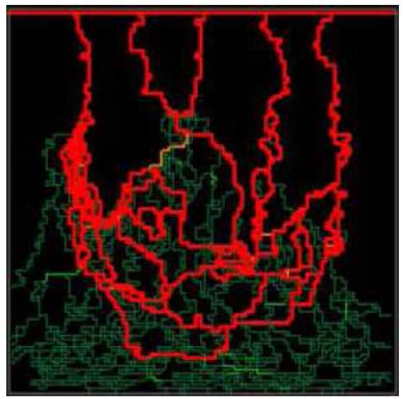



Fixed growth factor source, growing vessel network (Chaplain, Anderson, Sleeman,etc.)



„Rabbit eye“ model



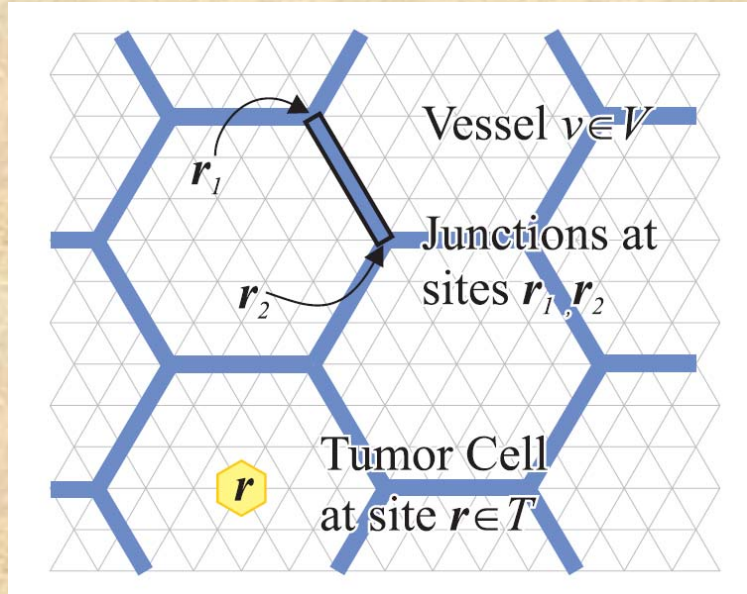



# Model concept

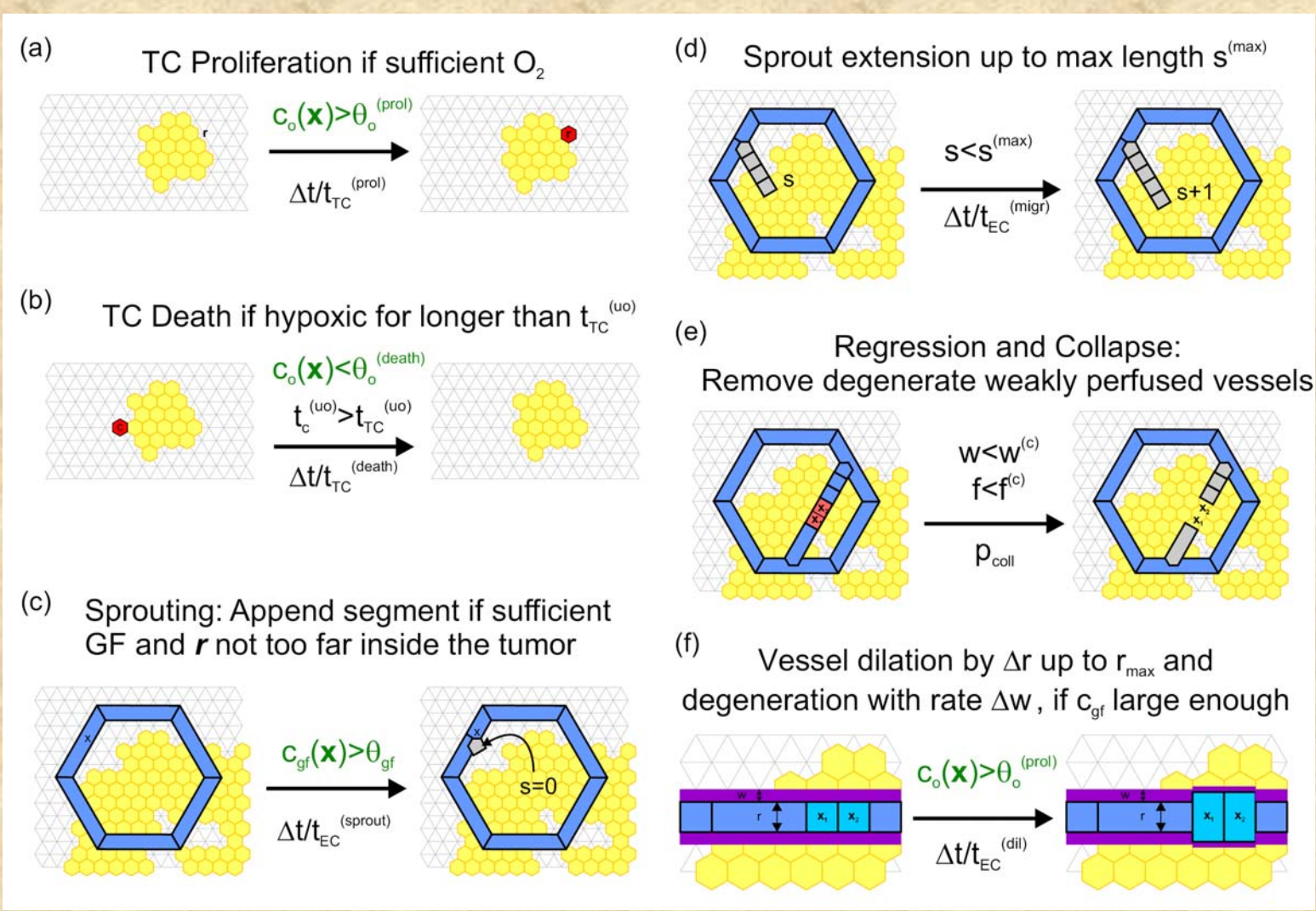
- Network of „vessels“ = pipe and pipe-segments
- Dynamics of segments / vessels
- „Blood“ flow = ideal pipe flow

- „Tumor cells“ = cellular automaton
- Dynamics: Proliferation & death

- Vessels and tumor interact via diffusive messengers:
- Perfused vessels emit oxygen / nutrients
- Tumor cells emit growth factors



# Dynamic processes (stochastic):




[Bartha, Rieger, J. Theor. Biol. 241, 903 (2006)]

# Details

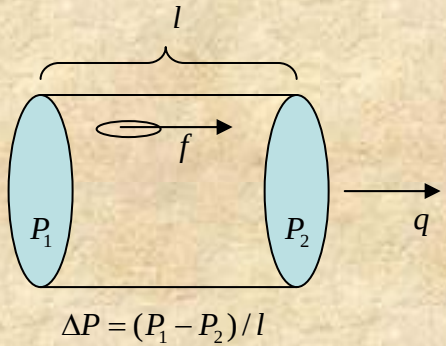
**Blood flow:**
(laminar, stationary)

Effective viscosity η from exp. Data, dep. on radius and hematocrit

Hagen-Poiseuille

Flow rate $q(v) = (\pi/8)\frac{r^4}{\eta}\Delta P$

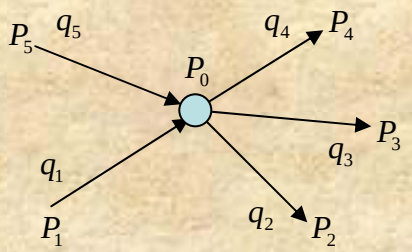
Shear force $f(v) = 1/2 r \Delta P$




$\Delta P = (P_1 - P_2)/l$

Mass conservation

$$0 = \sum q_i = \sum const_i \cdot (P_i - P_0)$$




**Oxygen / nutrient diffusion:**

$$\frac{\partial c_{oxy}}{\partial t} = D\Delta c_{oxy} - c_{oxy}k(r) + J(r)$$

$$J(r) = \begin{cases} q \cdot (c_{blood} - c(r)) & for \;\; r \in v \in V \\ 0 & otherwise \end{cases}$$

$$k(r) = \begin{cases} k_0 & in \;\; ECM \\ k_1 \geq k_0 & in \;\; tumor \end{cases}$$

**Growth factor diffusion:**

$$\frac{\partial c_{gf}}{\partial t} = \tilde{D}\Delta c_{gf} - k_0 c_{gf} + k_1 t(r)$$

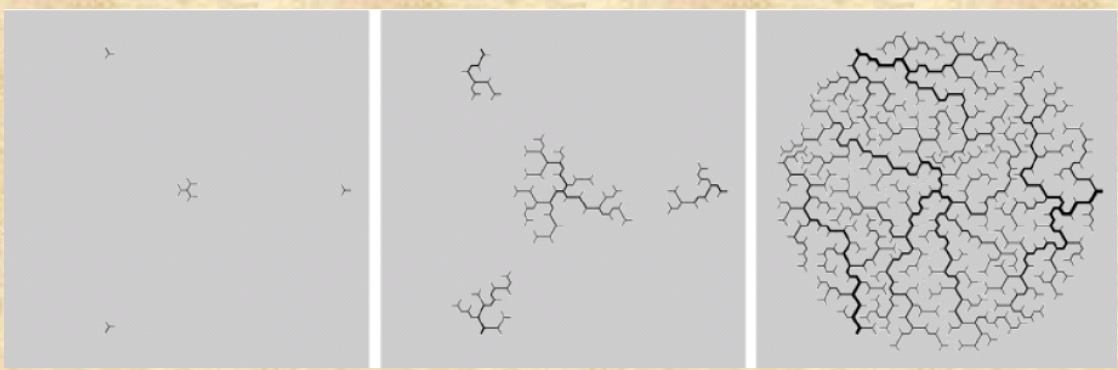
$$t(r) = \begin{cases} 1 \;\; for \;\; r \in T \;\; and \;\; c_{oxy}(r) < \theta_{oxy} \\ 0 \;\; otherwise \end{cases}$$

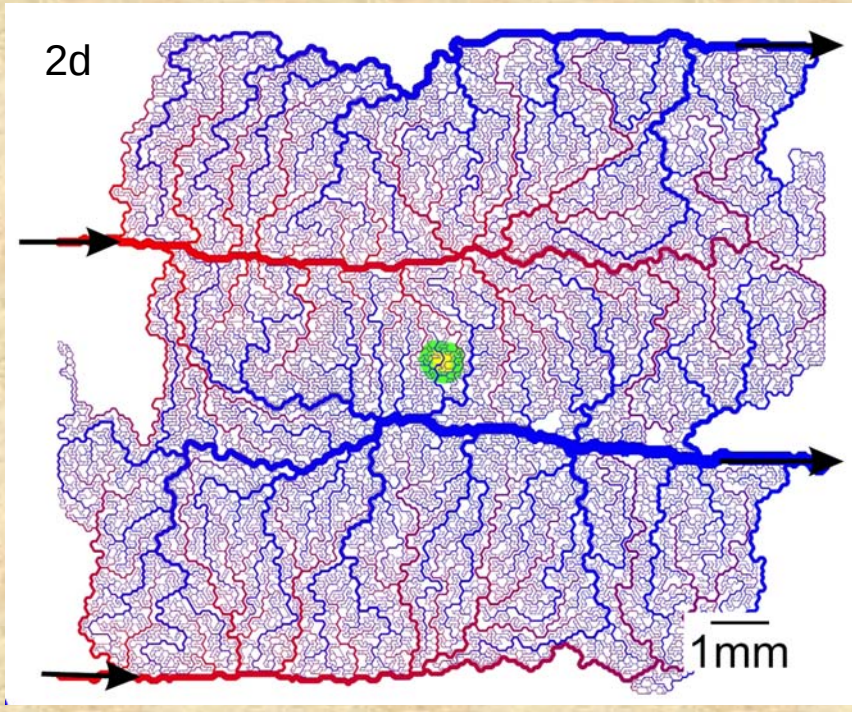
# Initial arterio-venous network

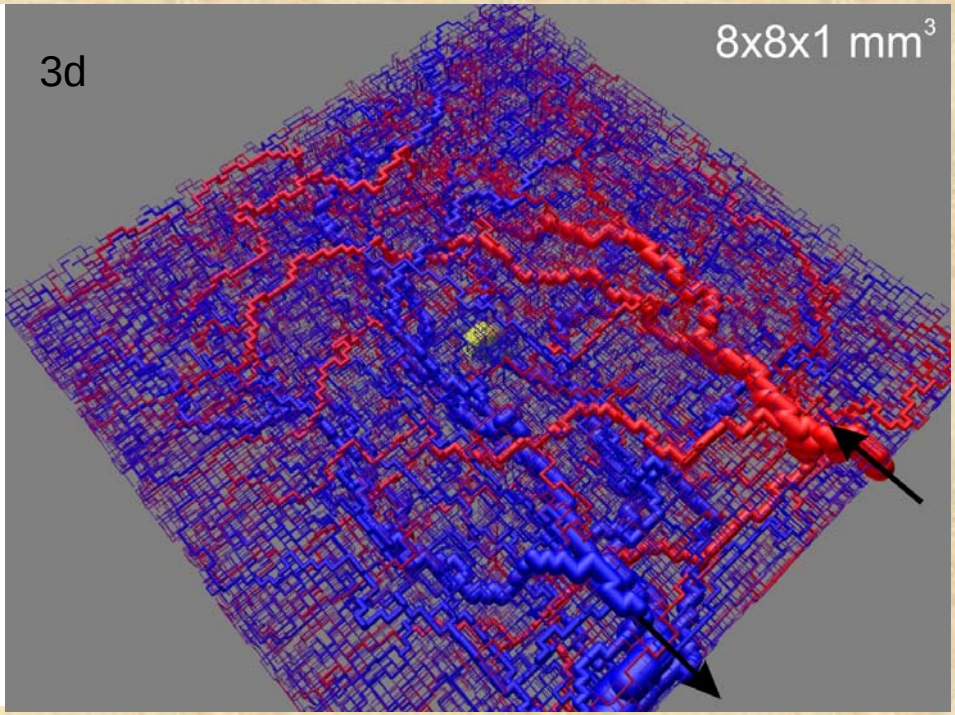
2d model:
[Gödde & Kurz, Dev. Dyn 220, 387 (01)]

Branchings obey Murrays law:

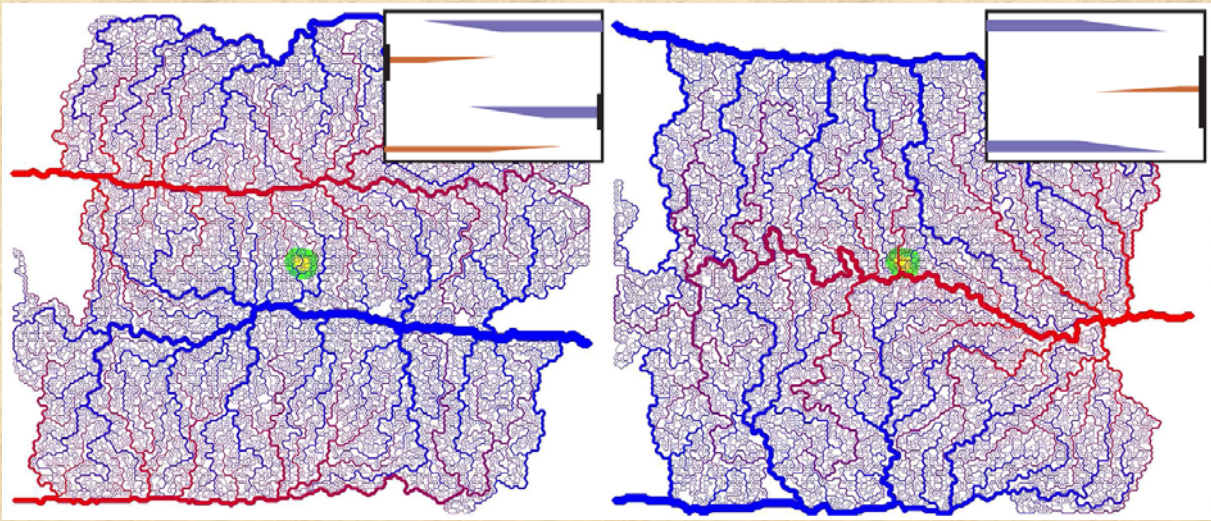
$$r_\rho^\alpha = r_1^\alpha + r_2^\alpha \qquad \alpha \approx 2.7$$

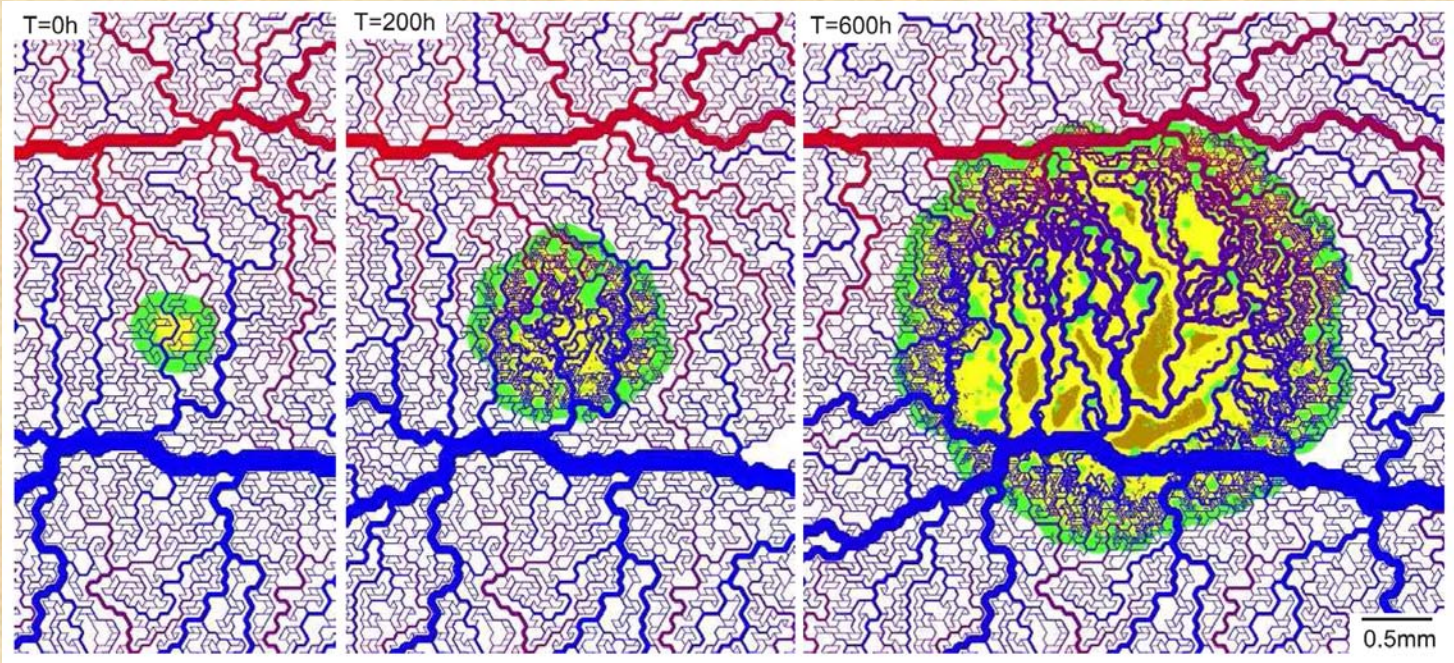




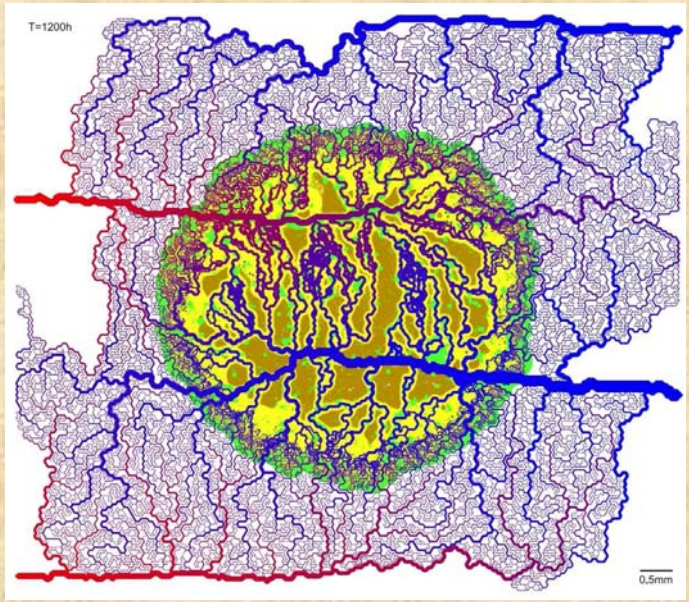



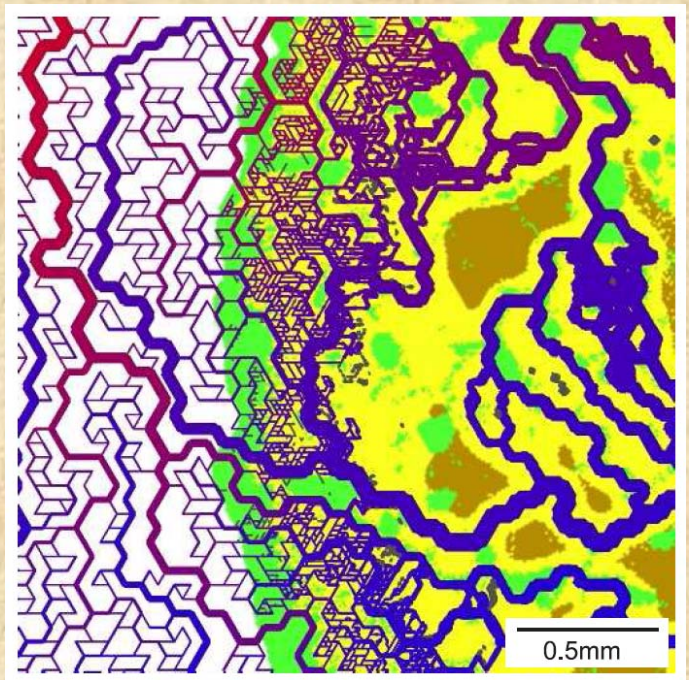
# Tumor growth in arterio-venous network





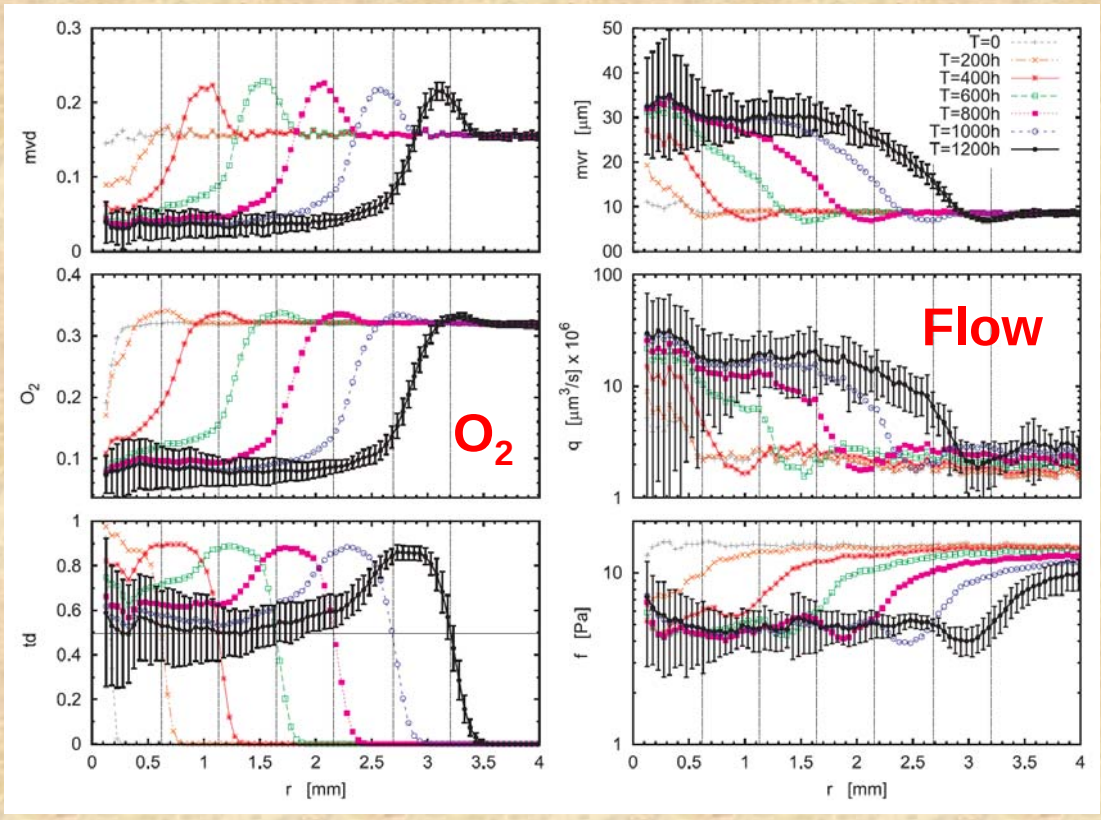
# Radial distributions




MVD

Vessel radius




Tumor density

Shear force

[Welter, Bartha, Rieger, arXiv:0801.0654v2 [q-bio.TO]

# Comparison w. experimental data obtained on melanoma vessels

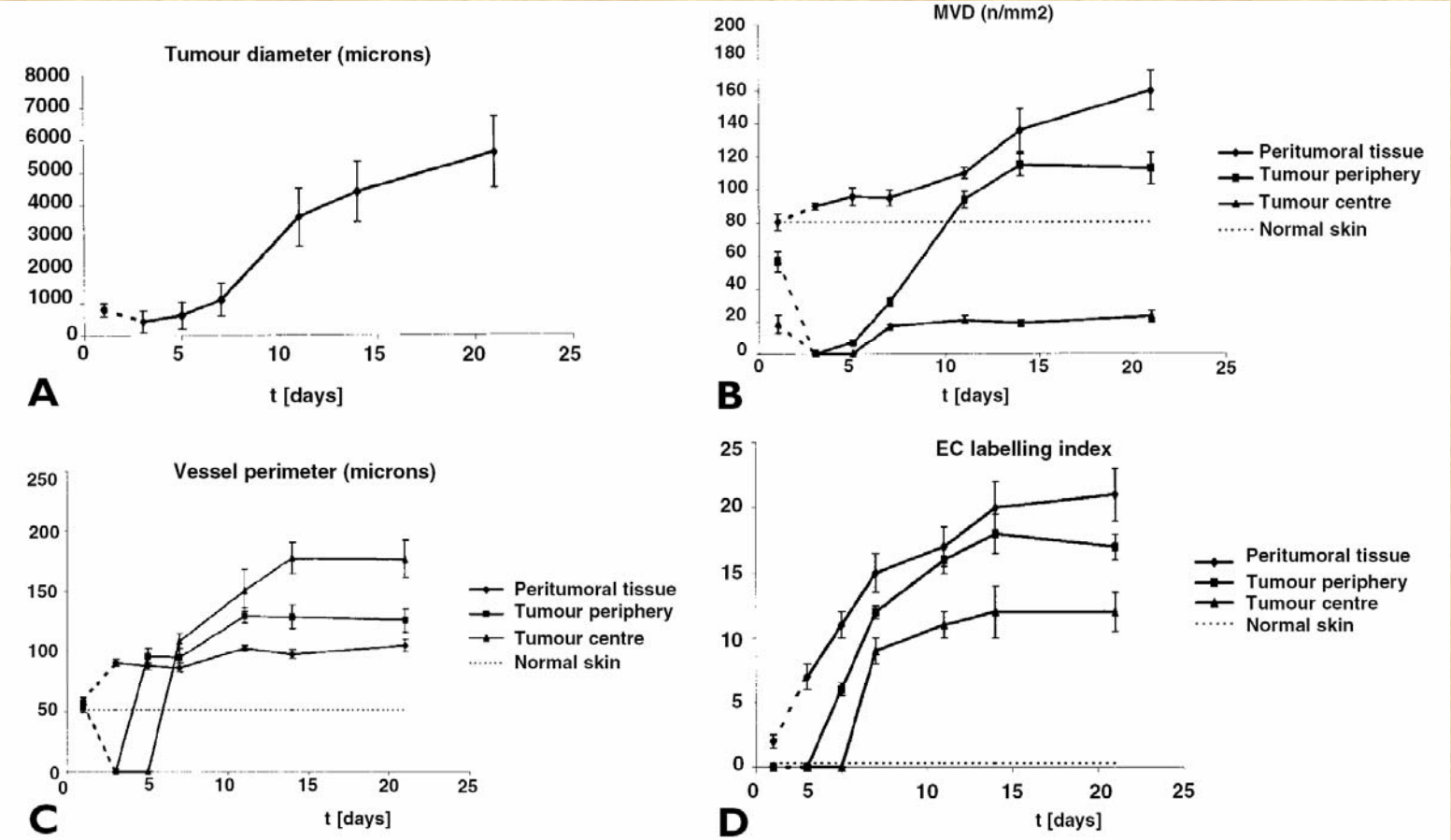
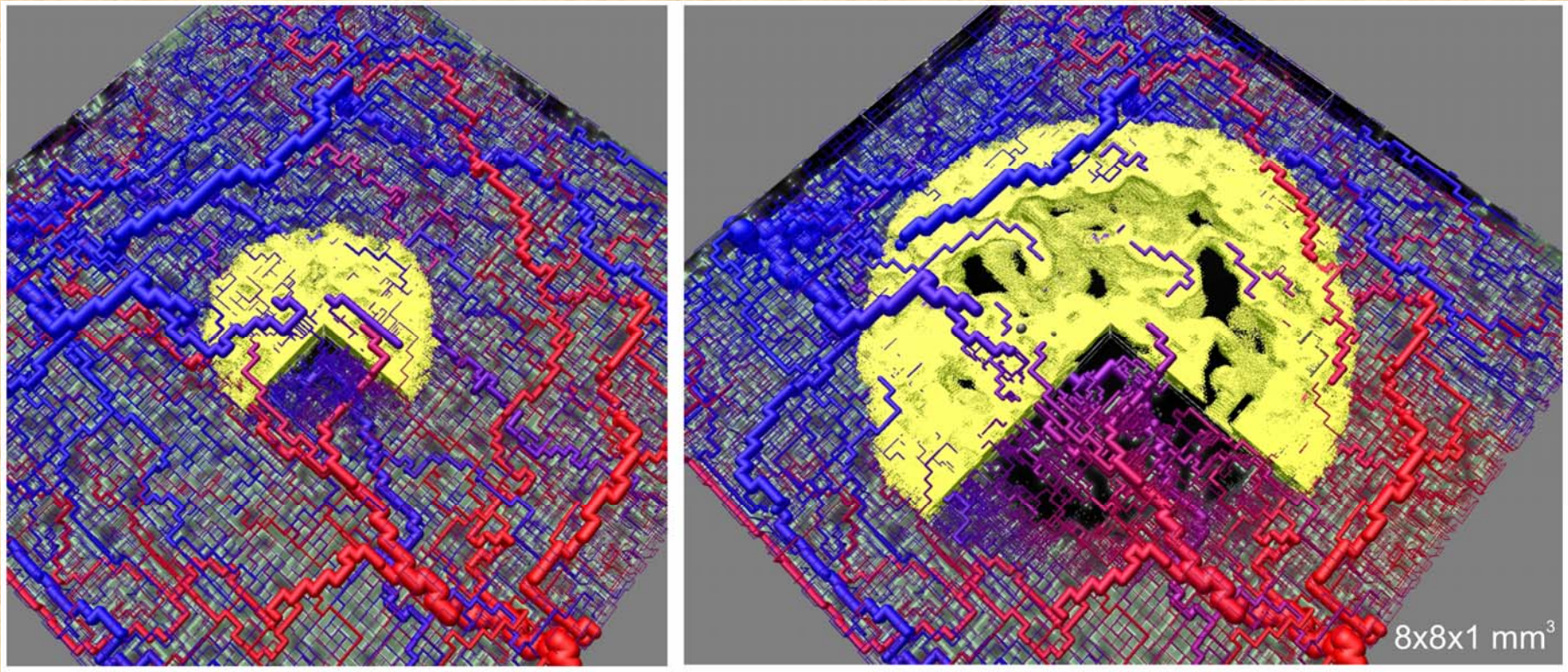


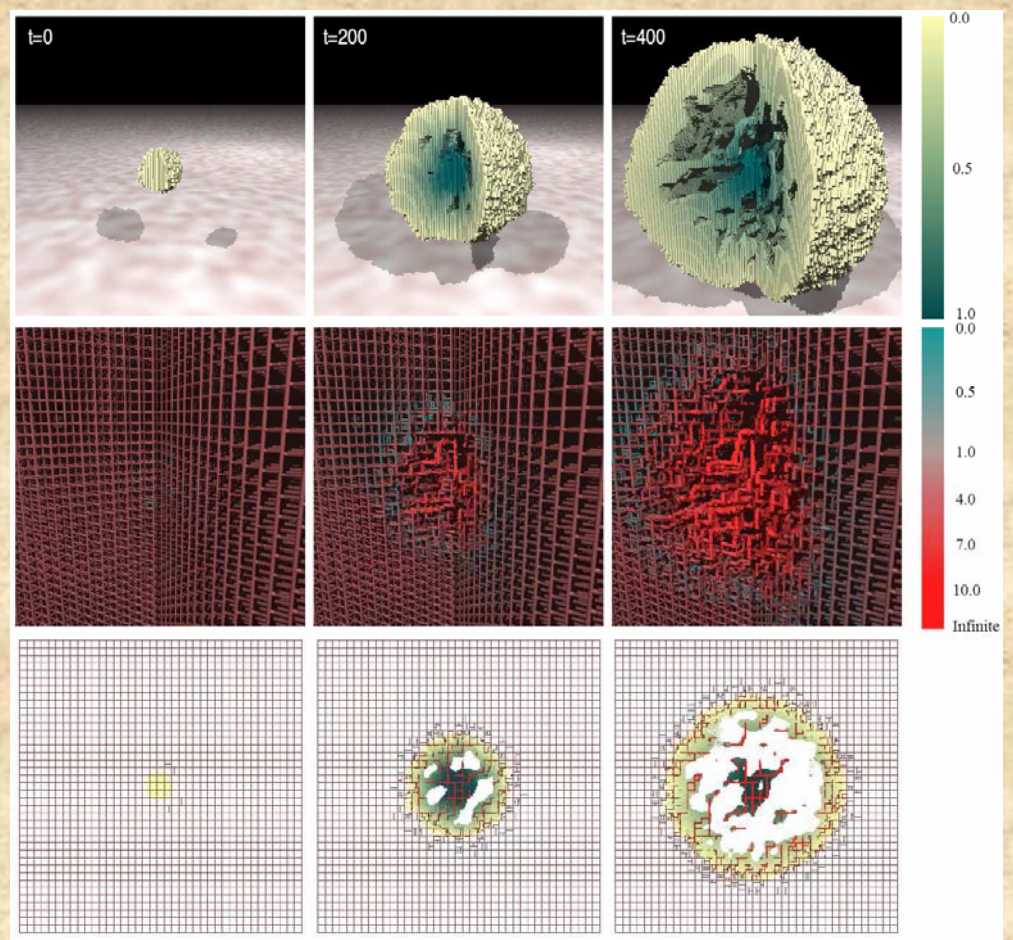

**Figure 2.** Tumour diameters (A) and alterations of vascular parameters (B, C, D) of B16 murine melanoma. Groups of three mice were sacrificed by anaesthesia at 1, 3, 5, 7, 11, 14 and 21 days. Data are means ± SEM. The decrease of MVD and vessel perimeter between days 1 and 3 can be explained by the regression of the existing host vessels of the dermis, following the injection of the tumour cell suspension. The mean MVD, vessel perimeter and EC labelling index in normal mouse skin were 80.7 ± 7, 51.5 ± 2.5 and 0.33 ± 0.15, respectively (mean ± SD, $n = 3$).

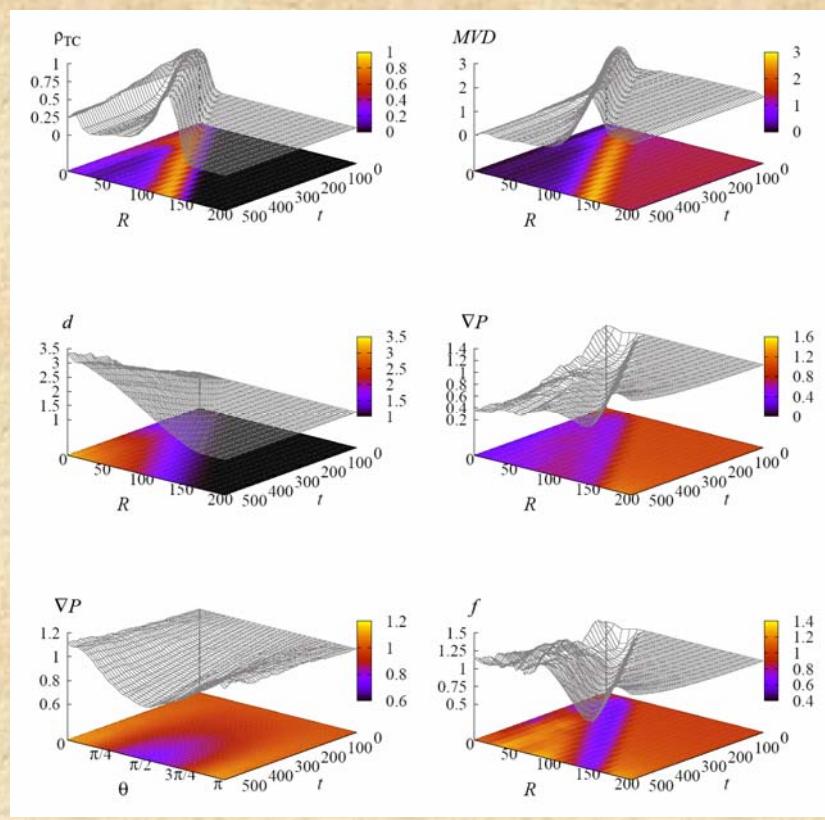
From Döme *et al.,* J. Path. **197**, 355 (2002).

# … in 3d (prel.)



# Three dimensional model for tumor vascularization:

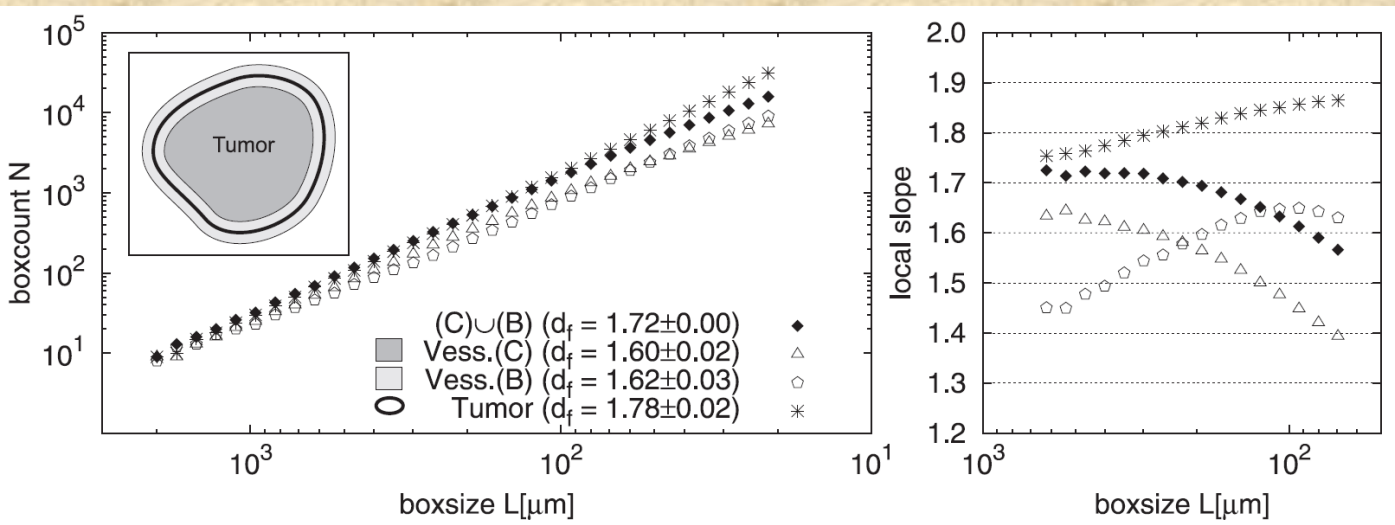


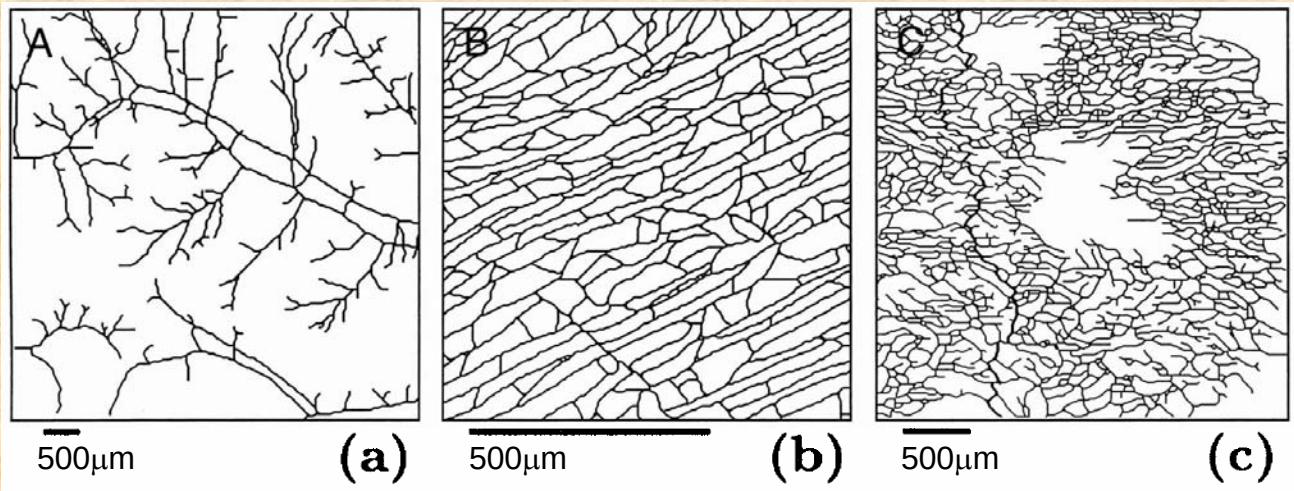

Quantitatively similar to 2d version!

[Lee, Rieger, Bartha, PRL 96, 058104 (2006)]

# Fractal analysis:




Fractal dimension in different regions of the tumor Vasculature
$D_f$ ~ 1.8




Experiment

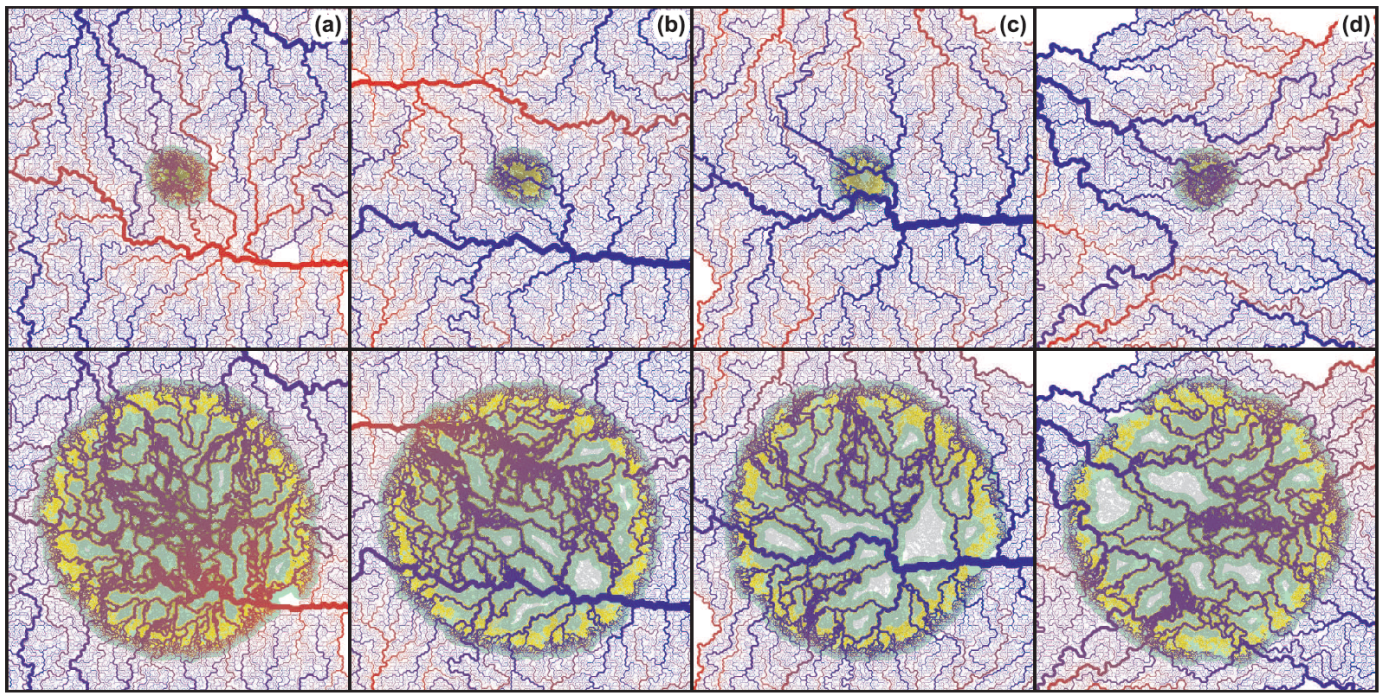
Gazit et al.,
Phys. Rev. Lett. 75, 2428 (1995)

arteriovenous net.:
$d_f$= 1.70±0.03

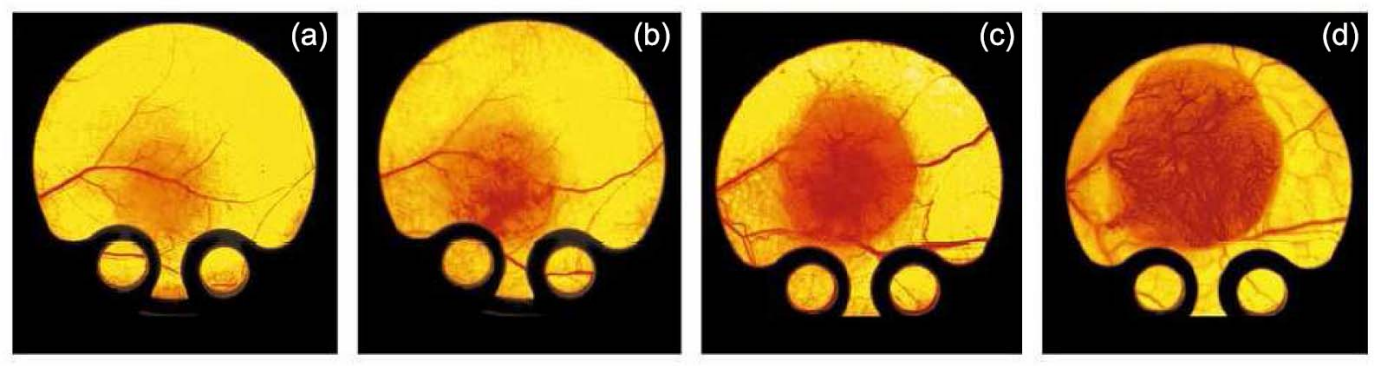
Norm. capillary net.:
$d_f$= 1.98±0.02

carcinoma network:
$d_f$= 1.88±0.04

# Formation of „hot spots“ – dependence on initial network

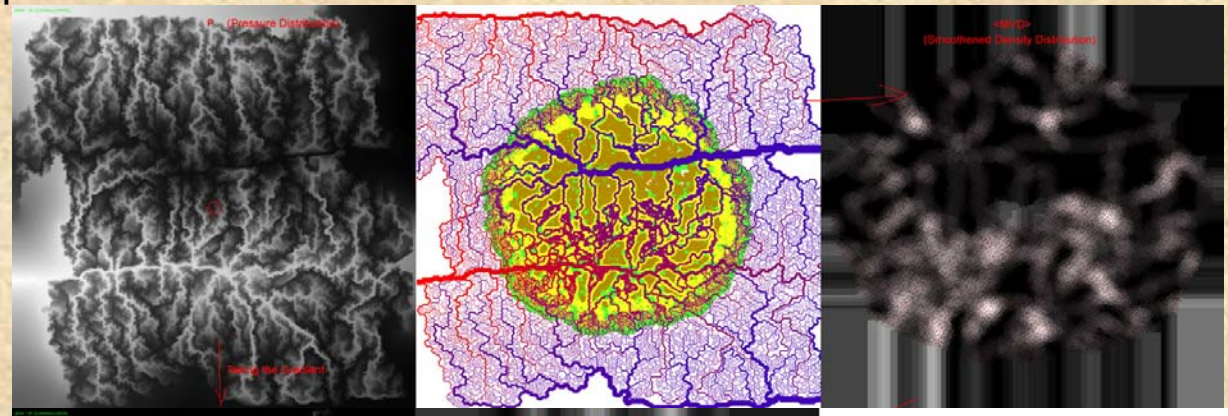


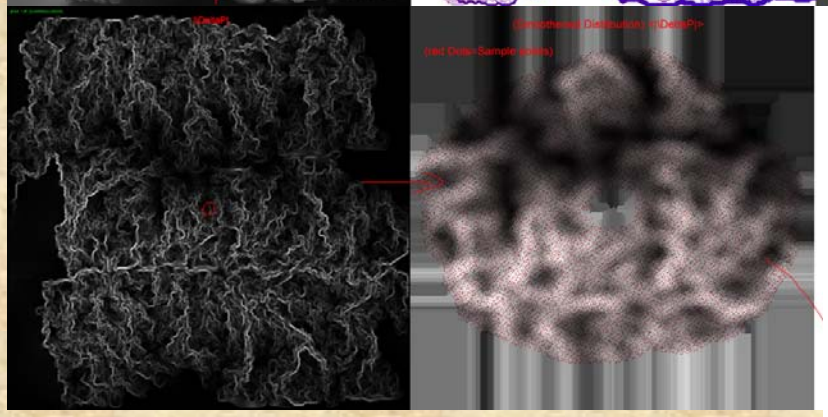

**comparison w. experiment (dorsal skinfold chamber):**



# Correlationof hot-spot formation with pressure gradients

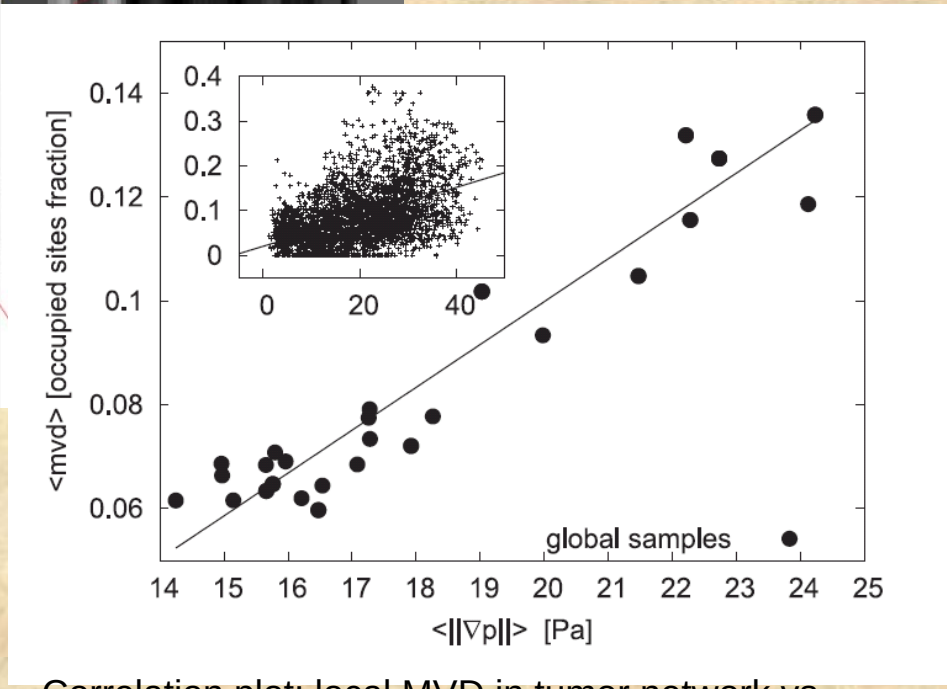
pressure in initial netw. tumor network local MVD of tumor network





pressure gradients in initial network

pressure gradients goarse grained




Correlation plot: local MVD in tumor network vs. local pressure gradient in initial network

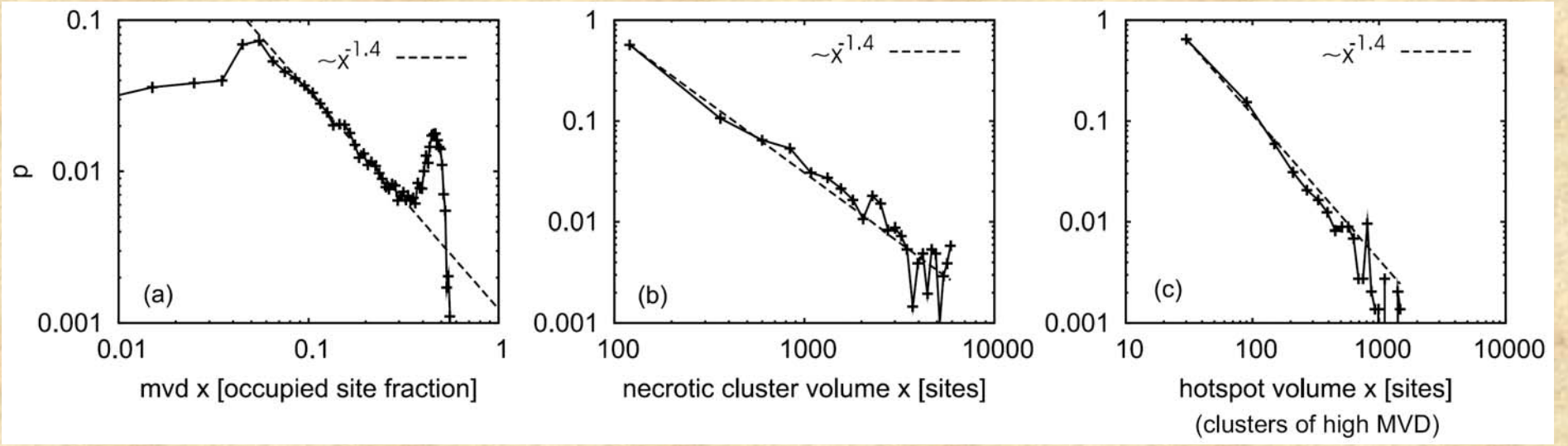
# Spatial inhomogeneities display self similar behavior

Algebraic tails in probability distributions of

Local MVD

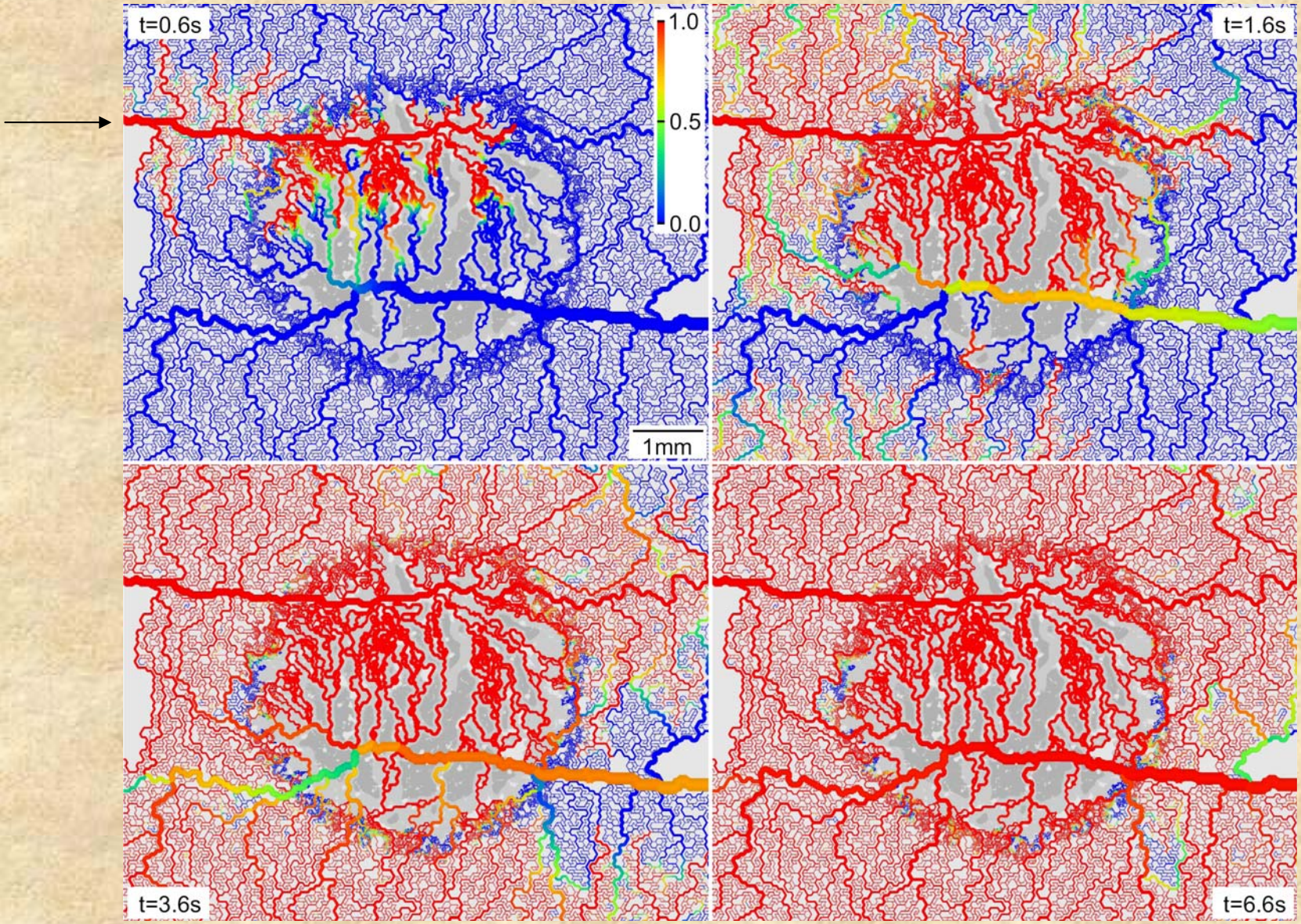
Size of necrotic clusters

Size of hot spots

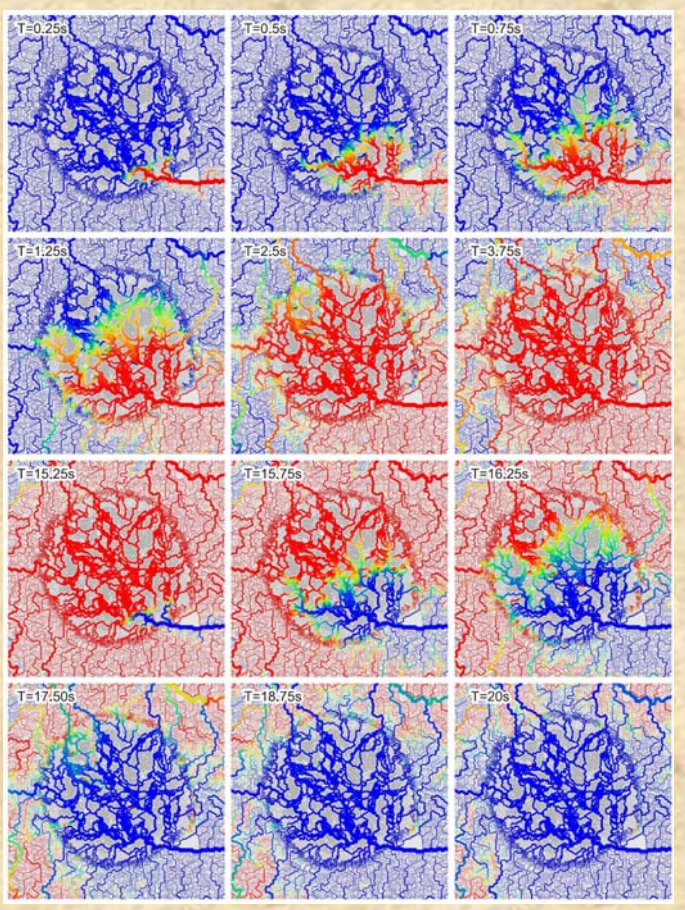


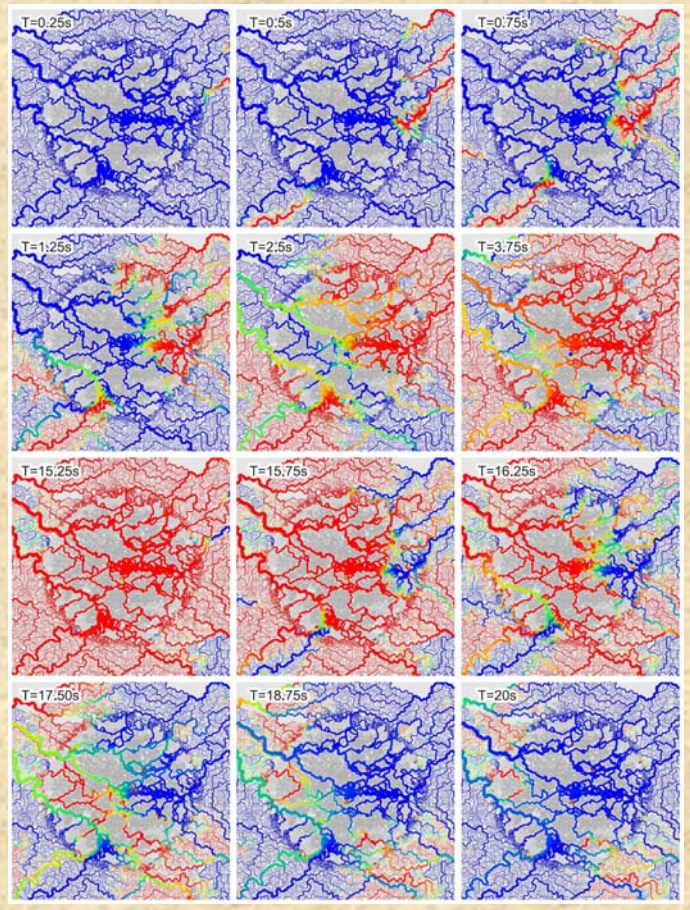
# Drug flow simulation

(continuous injection into blood stream of main artery)



# Drug flow



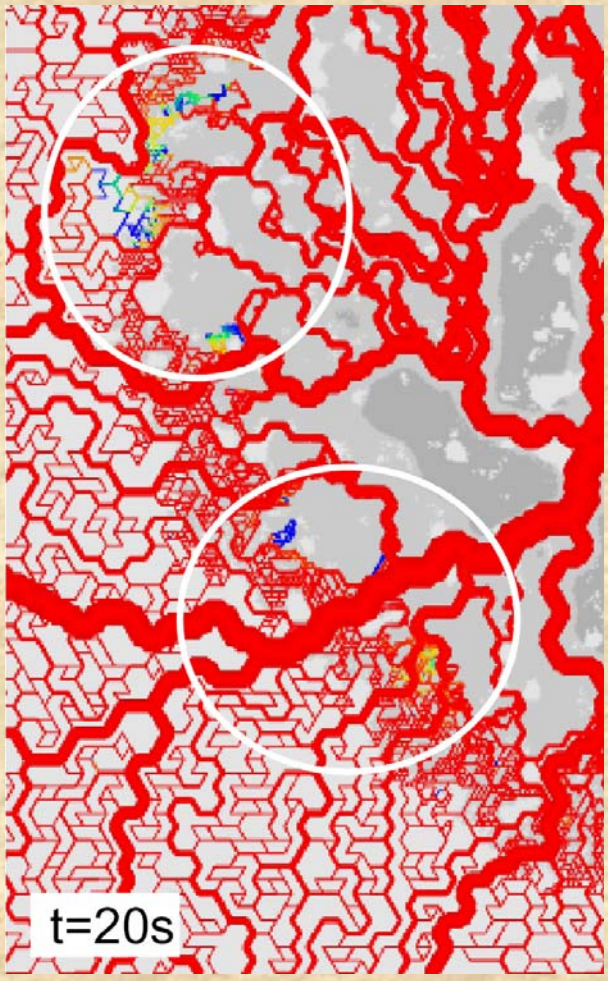

→ Drug reaches all vascularized regions of the tumor!

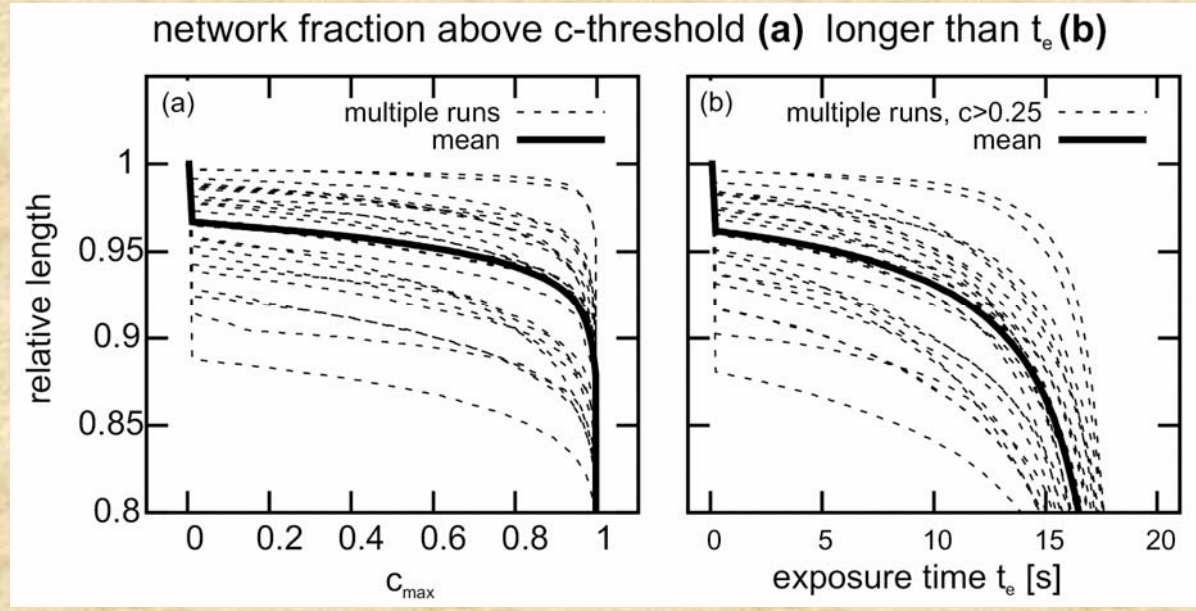
Reasons for drug delivery problems during therapy?

[Welter, Bartha, Rieger, J. Theor. Biol. 250, 257 (2008)]

# Drug flow (2)

Tiny nests of badly-perfused vessels in tumor periphery



# Conclusions

- Morphology of tumor vasculature:
  Compartmentalization into peritumoral plexus, tumor periphery and necrotic core
  Result of flow-correlated percolation process, independent of initial network
- Fractal properties: Dependent upon parameters and location in tumor
  Not a well defined concept in tumors
- Low pressure gradient and
  small shear forces in tumor vessels
- Location of “hot spots“ of well perfused tumor regions
  determined by initial network
- Drug transport through surviving tumor vessels is good
  Drug delivery to TCs is known to be bad: Why?
- Next steps:
  Institial fluid in porous medium $\rightarrow$ convective transport of drugs;
  solid pressure in tumor tissue $\rightarrow$ origin of vessel collapse;
  …