Vascular network remodeling via vessel cooption, regression and growth in tumors

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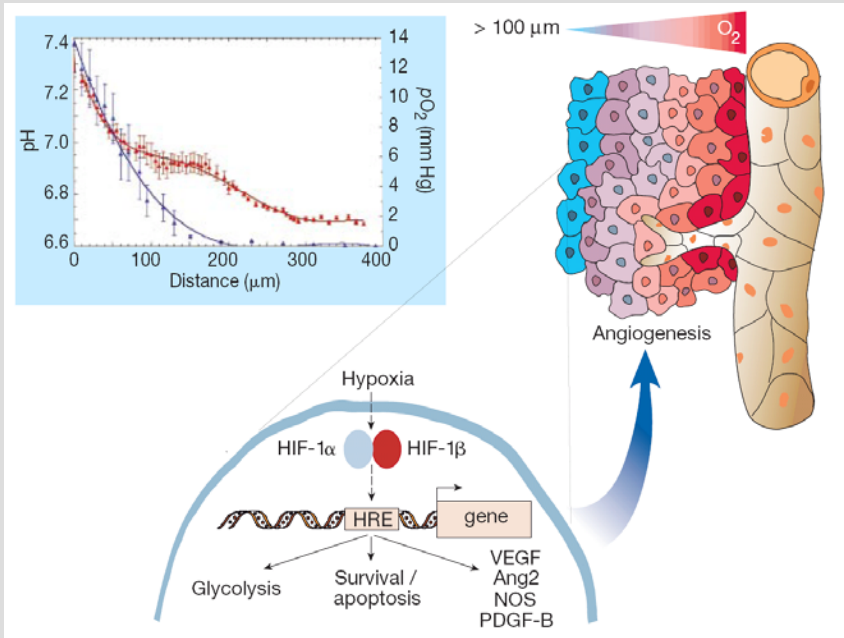# Normal vascularization vs. Tumor vessels

Normal capillary network (Steiner et.al.,1992).

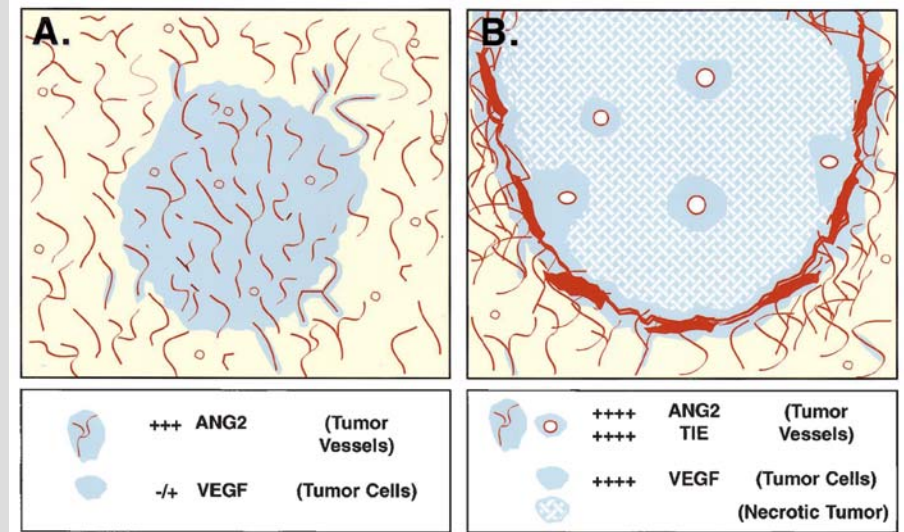Dilated vessels, brush border effect in the periphery of a melanoma (Steiner et.al.,1992)

Experimental basis confining the model

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)]

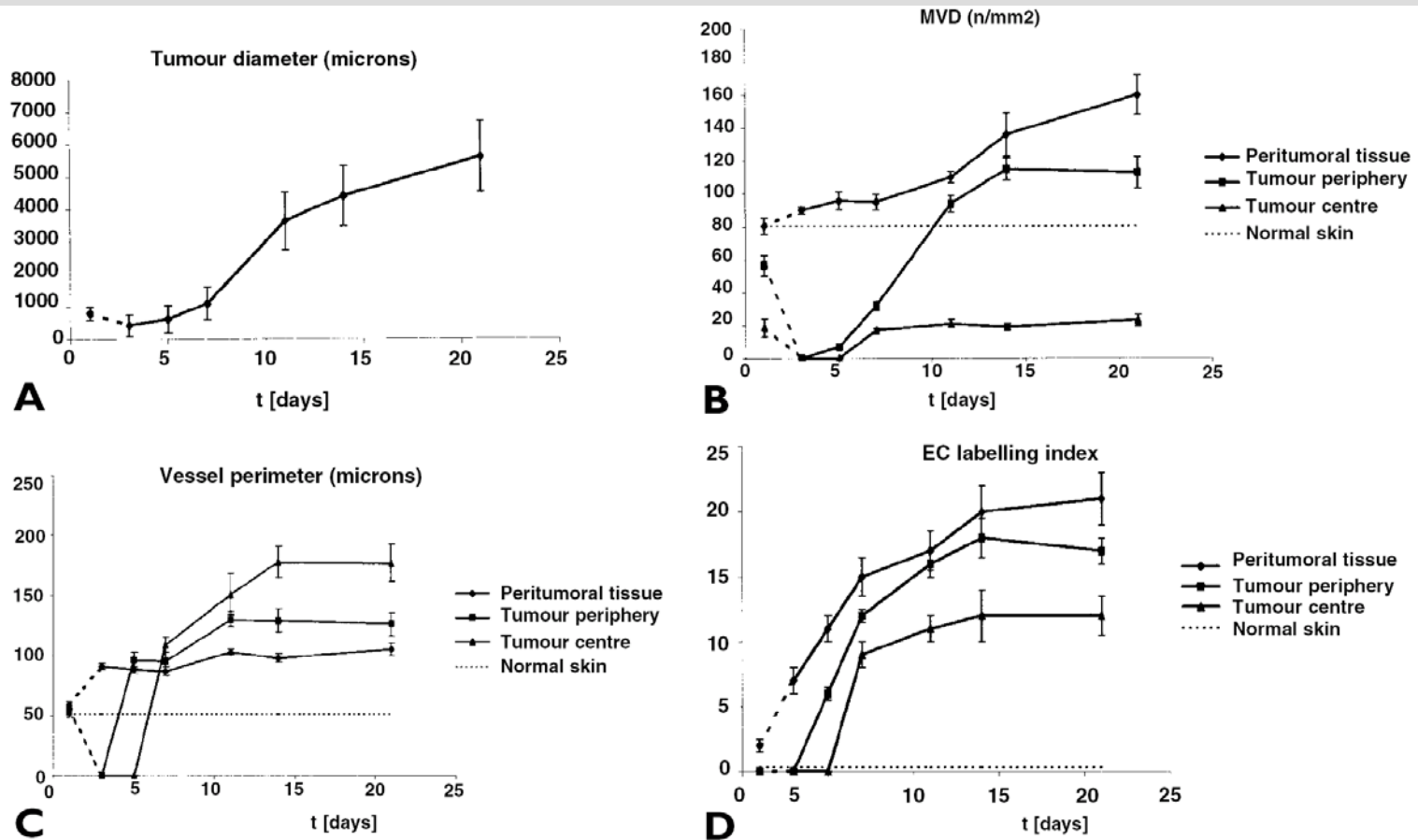# Experimental data obtained on melanoma vessels

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 $\pm$ 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 $\pm$ 7, 51.5 $\pm$ 2.5 and 0.33 $\pm$ 0.15, respectively (mean $\pm$ SD, $n = 3$).

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

Table 1. Comparison of vascular parameters of the human malignant melanoma of the skin according to the thickness

Tumour thickness	Tumour centre		Tumour periphery		Peritumoural host tissue	
	MVD (n/mm^2)	Perimeter (µm)	MVD (n/mm^2)	Perimeter (µm)	MVD (n/mm^2)	Perimeter (µm)
<1.5 mm n=13	22.4±6.3	73±25.1	78.3±28.2	71±19.9	141±66.7	72.4±10.1
1.5–4 mm n=17	32.5±10	80.8±27.3	98.9±27.7	75.7±16.4	137±55.3	75.3±17
>4 mm n=15	31.3±7.9	104±31.7[a,b]	96.8±22.8	94.8±21.2	149±41.8	84.3±8.7

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

# Sketch of a model
combining tumor growth, cooption and neovascularization

- ● Start with a regular vessel network of given MVD (~100/mm^2)

- ● Start with a small tumor (e.g. Eden cluster of TCs)

- ● O$_2$ concentration field is produced by circulated vessels

- ● GF (Growth Factor) concentration field is produced by viable TCs

- ● TCs proliferate if local O$_2$ conc. is sufficient   (TC = Tumor Cell)

- ● ECs proliferate when GF conc. is sufficient   (EC = Endothelial Cell)

- ● Outside the tumor: EC form new vessels
  Inside the tumor: ECs increase vessel radius

- ● Vessels surrounded by TCs collapse if wall shear force is low

- ● Vessels regress if not circulated

- ● TCs die if too long under-oxygenated

Transition probabilities for the stochastic process

GF concentration: $c_{GF}(\mathbf{r},\tau) = \Sigma_{\mathbf{r}' \in \{TC\}(\tau)} \, \Delta c_{GF}(|\mathbf{r}-\mathbf{r}'|)$

O$_2$ concentration: $c_{Oxy}(\mathbf{r},\tau) = \Sigma_{\mathbf{r}' \in \{EC\}(\tau)} \, \Delta c_{Oxy}(|\mathbf{r}-\mathbf{r}'|)$
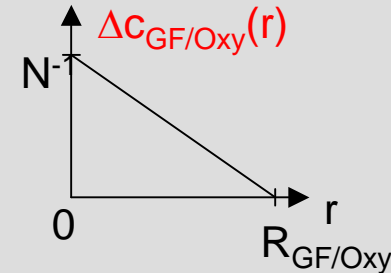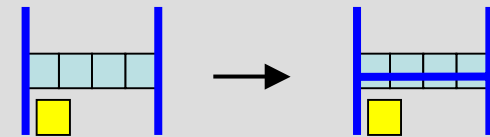

TC proliferation: If $c_{oxy}(\mathbf{r},\tau) \geq \theta_{oxy}$ at a tumor surface site $\mathbf{r}$:
$$w\{t(\mathbf{r})\to 1\} = \Delta\tau/T_t$$
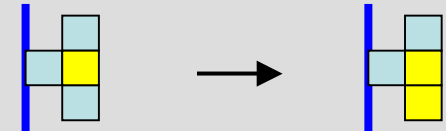
TC death: If $t(\mathbf{r})=1$ and $c_{oxy}(\mathbf{r},\tau) < \theta_{oxy}$ for time T_{uO}:
$$w\{t(\mathbf{r})\to 0\} = 1/2$$

Vessel growth: $\mathbf{r} \in \{EC\}(\tau)$ with $c_{GF}(\mathbf{r}) \geq \theta_{GF}$ are potential growth sites:
Insert new vessel along (unoccupied) path
$P_n(\mathbf{r})=(\mathbf{r}+d\mathbf{r}, \mathbf{r}+2d\mathbf{r},\ldots, \mathbf{r}+nd\mathbf{r})$ with rate $\sim 1/T_e$

Vessel dilatation: $\mathbf{r} \in \{EC\}(\tau)$ with $c_{GF}(\mathbf{r}) \geq \theta_{GF}$ and
neighbors occupied by TCs:
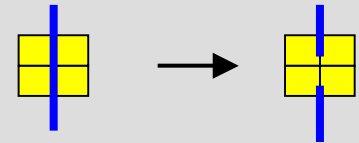$e_R(\mathbf{r}) \to e_R(\mathbf{r})+\Delta r/2\pi$ with rate $\sim 1/T_e$

cont.

Blood flow computation: Identify vessel segments with pipes,
Boundary conditions for pressure p:
$\Rightarrow$ homogeneous flow / shear force,
global net flow in (1,-1)-direction
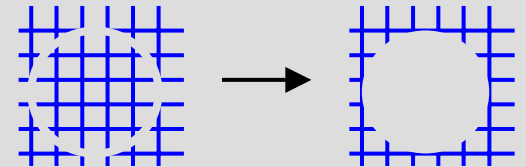
Hagen-Poisseuille
$$q(\vec{r}) = c \cdot \Delta p \cdot r^4$$
$$f(\vec{r}) = c \cdot \Delta p \cdot r^1$$

Vessel collapse: $\mathbf{r} \in \{EC\}(\tau)$ with low shear force $f(\mathbf{r}) < f_{crit}$
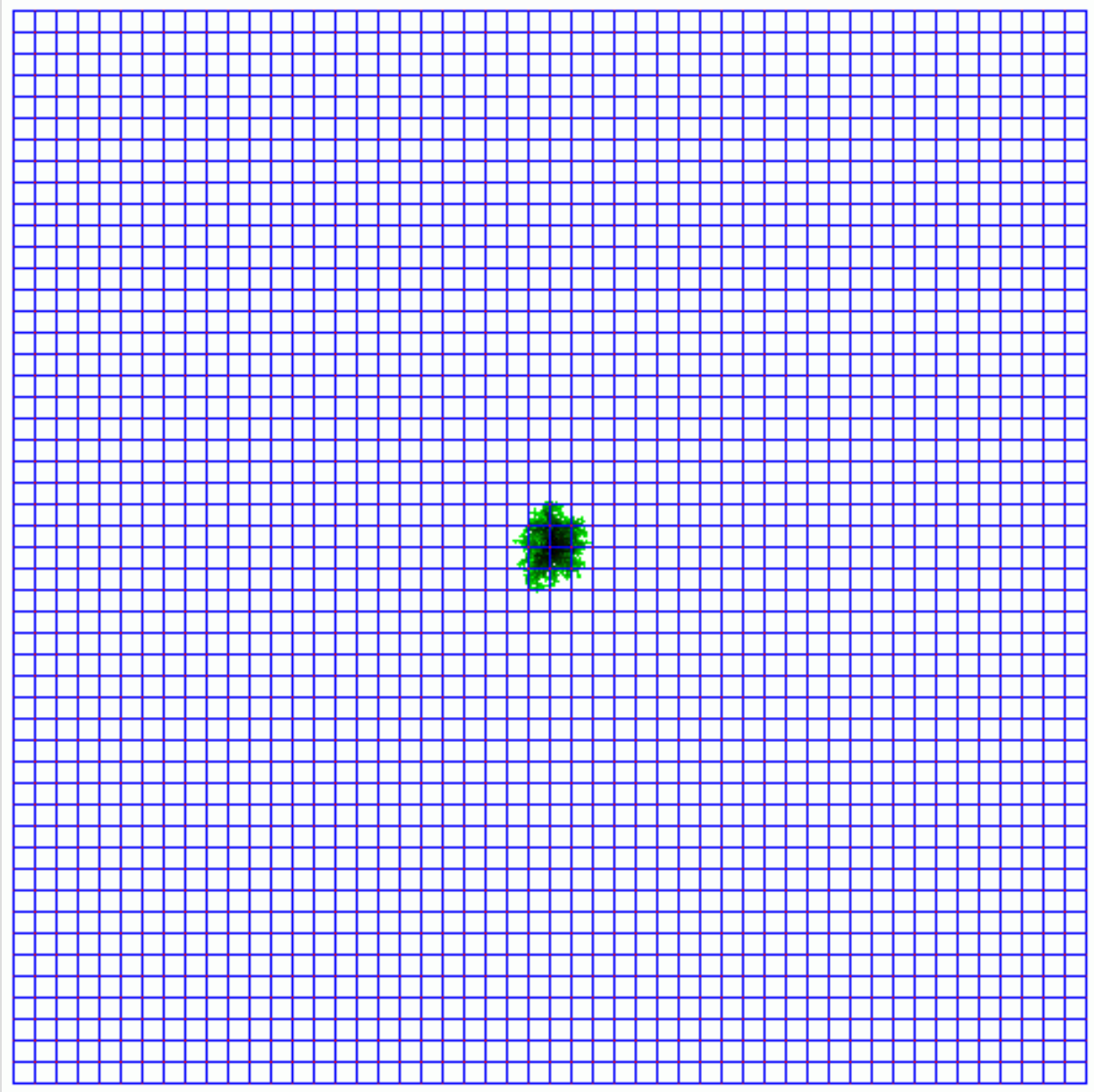can collapse: $w\{e(\mathbf{r}) \to 0\} = p_{collapse} \Delta\tau / T_t$

Vessel regression: $\mathbf{r} \in \{EC\}(\tau)$, which do not belong to the
circulated component of the network,
die if $c_{oxy}(\mathbf{r},\tau) < 10 \cdot \theta_{oxy}$: $w\{e(\mathbf{r}) \to 0\} = 1/2$

Note: Shear force is determined by the blood flow through the individual vessels
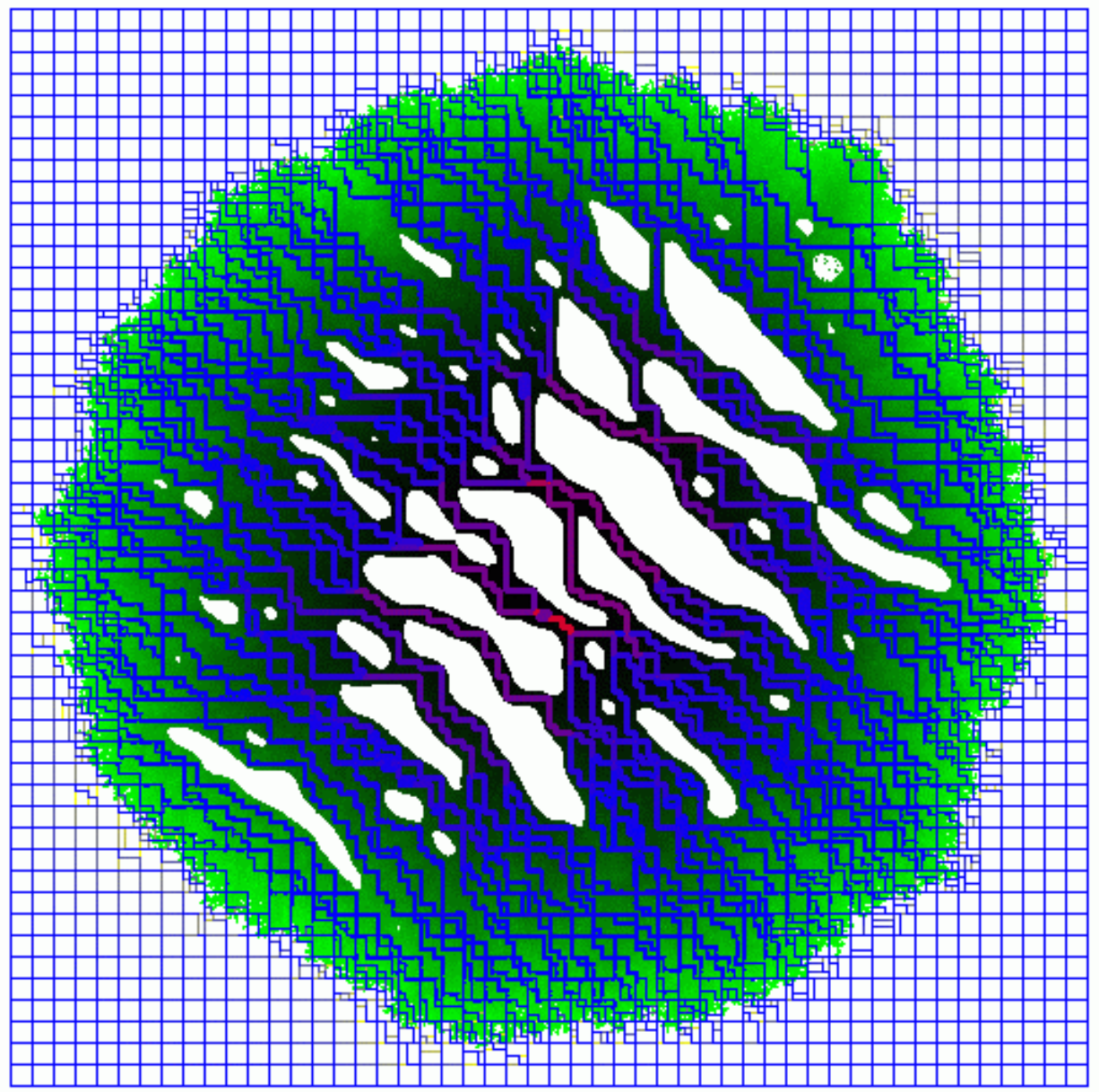Circulation is determined by the topological condition of bi-connectedness

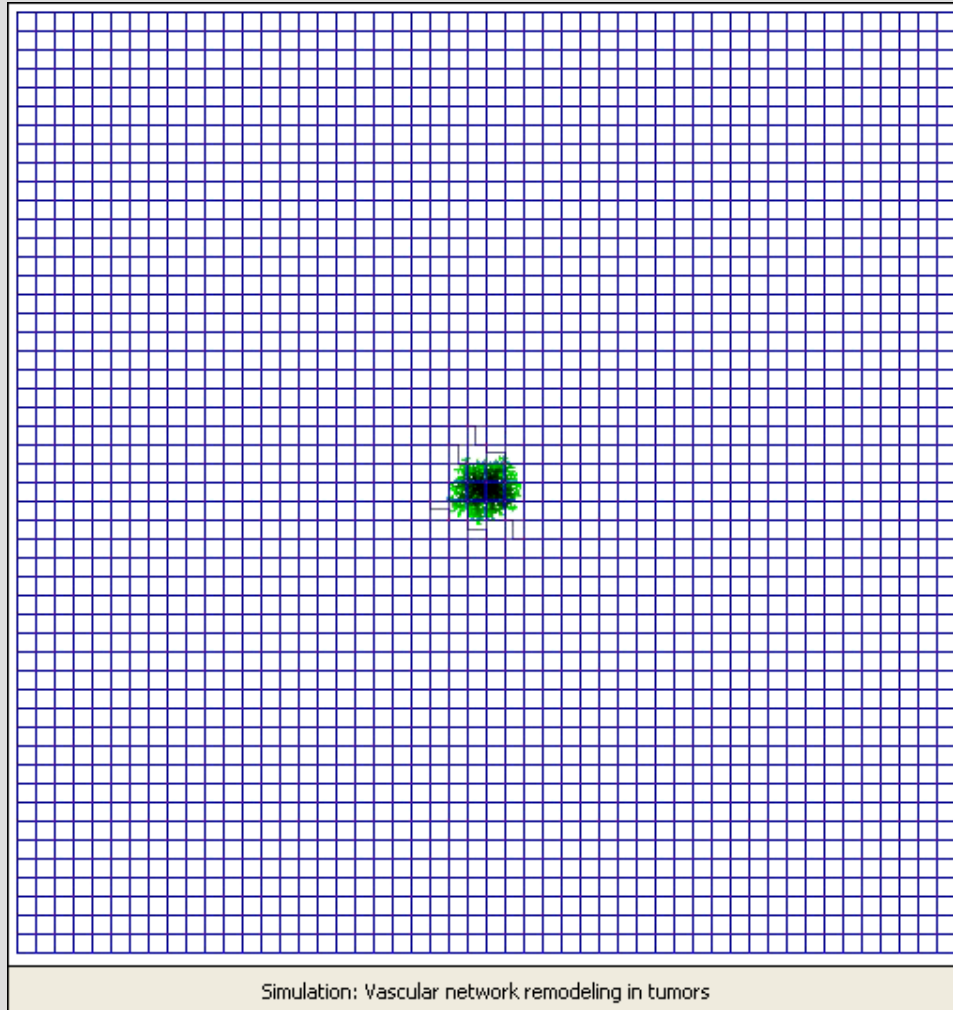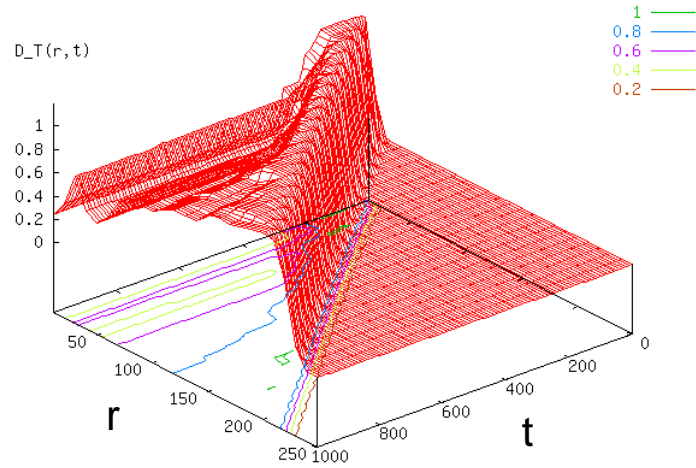# Initial state

5,12mm
(L=512)

Snapshots

t=1000

5,12mm

Time evolution:
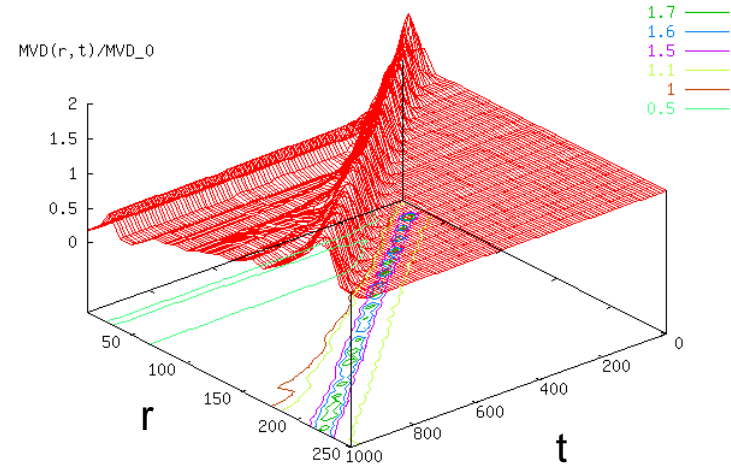

Simulation: Vascular network remodeling in tumors

Quantitative analysis

Tumor density

$D_T(r,t)$

Microvascular density

$MVD(r,t)/MVD_0$

Growth factor concentration

$c_{GF}(r,t)$

O_2 concentration

$c_{oxy}(r,t)/c_0$
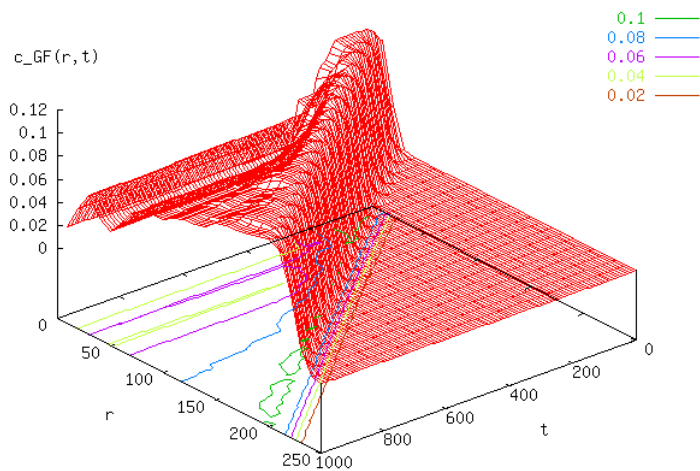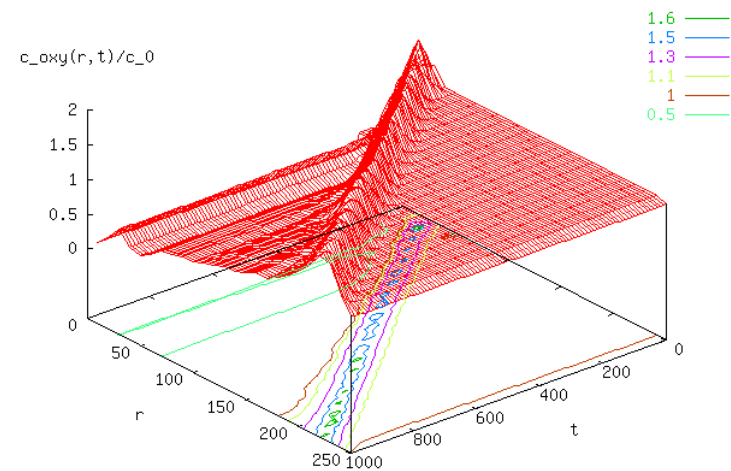
Quantitative analysis (2)

Vessel radius

R(r,t)
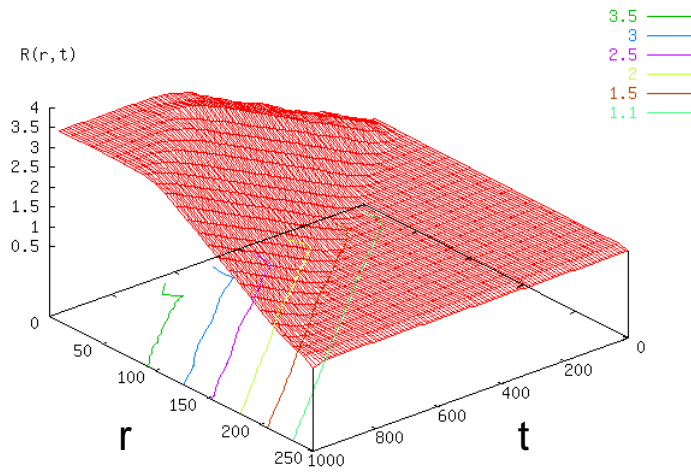
Blood flow per vessel

Q(r,t)/Q_0
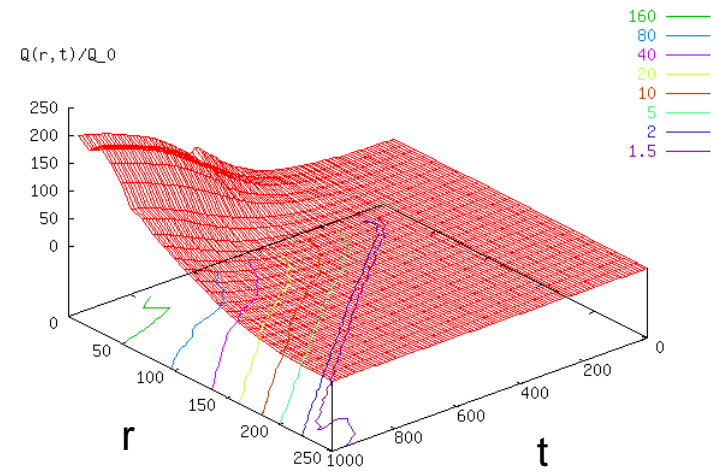
Shear force on vessel walls

F(r,t)/F_0
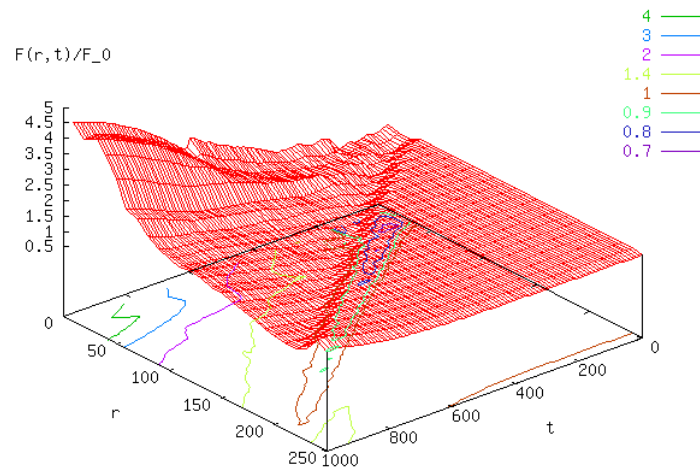
Results (summary):

Model predicts compartmentalization of the tumor into different regions:

- Highly vascularized peritumoral region (outside tumor)
- Increased MVD in tumor periphery (inside tumor)
- Low MVD in the tumor center
- Vessel radius increases with decreasing distance from the center
- Necrotic regions (void of TCs and ECs)
  threaded by thick vessels
  surrounded by cuffs of viable TCs

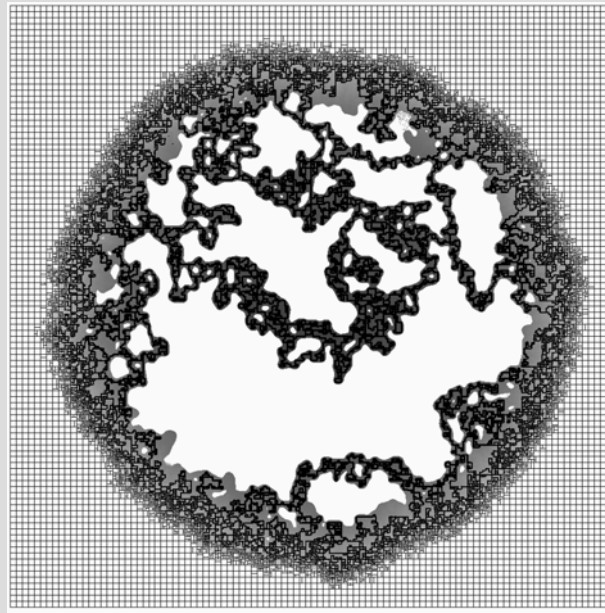Comparison with data for melanoma:

[Döme et al. J. Pathol. `02]
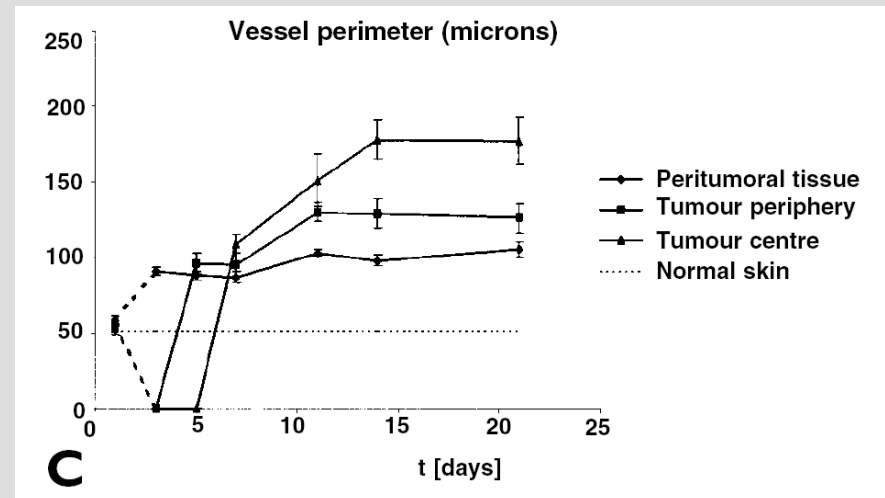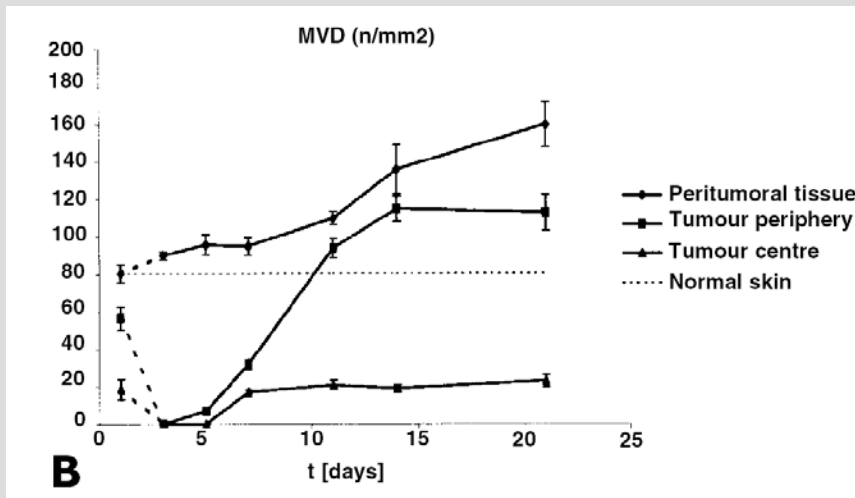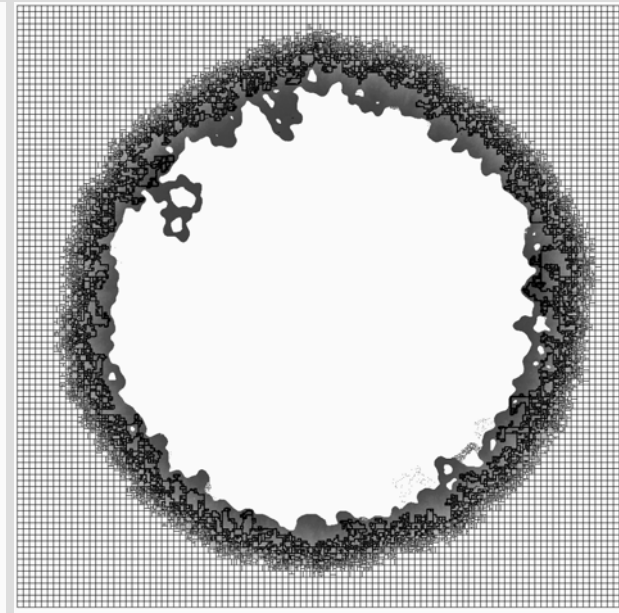
Flow correlated collapse avoids percolation transition

Note that stochastic removal of vessels inside the tumor would lead to a (unrealistic) percolation transition $\Rightarrow$ blood flow is essential model ingredience
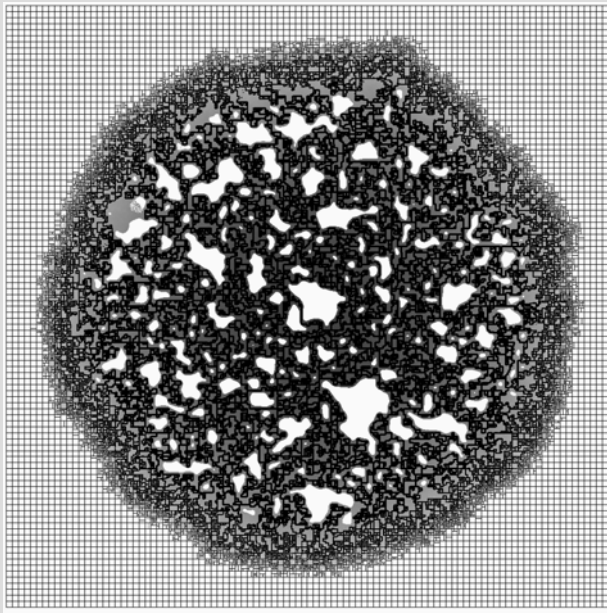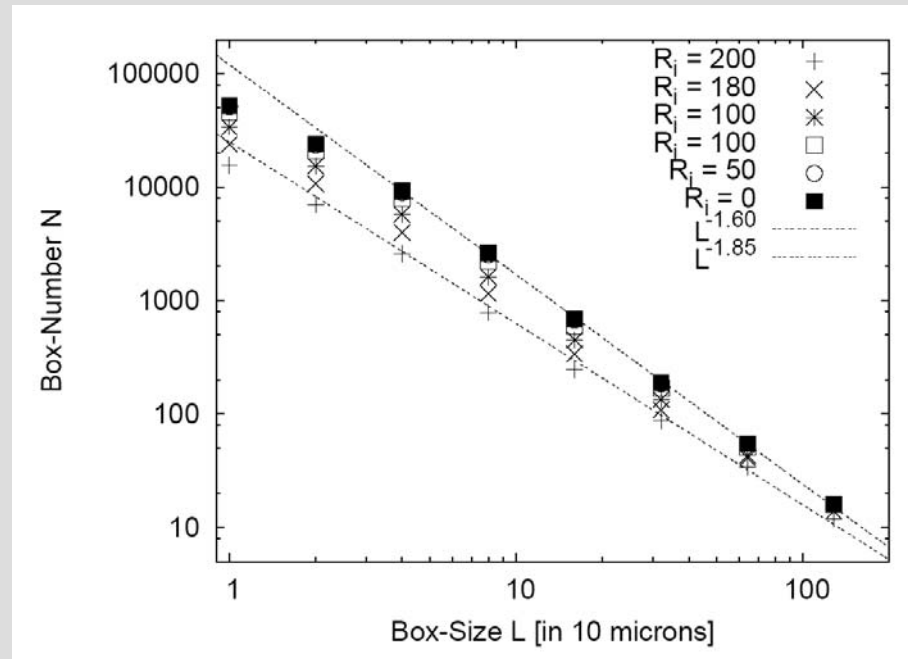

$p_{collapse} < p_c$ $\qquad$ $p_{collapse} = p_c$ $\qquad$ $p_{collapse} > p_c$

Fractal dimension of the tumor vessel network

Box-Counting Method.

$d_f = 1.85 \pm 0.05$

d_f of percolation cluster: 1.891   [random removal of segments with prob. p_c]

d_f of vasculature in carcinoma: 1.89±0.04 [Jain et al. (1995)]

Fractal structure is exclusively determined by collapse events,
Correlation of collapse with blood flow drives the structure into the critical state

N.b.: The fractal structure appears inside the tumor due to remodelling,
not due to vessel growth (c.f. Jain et al.).

3d model:
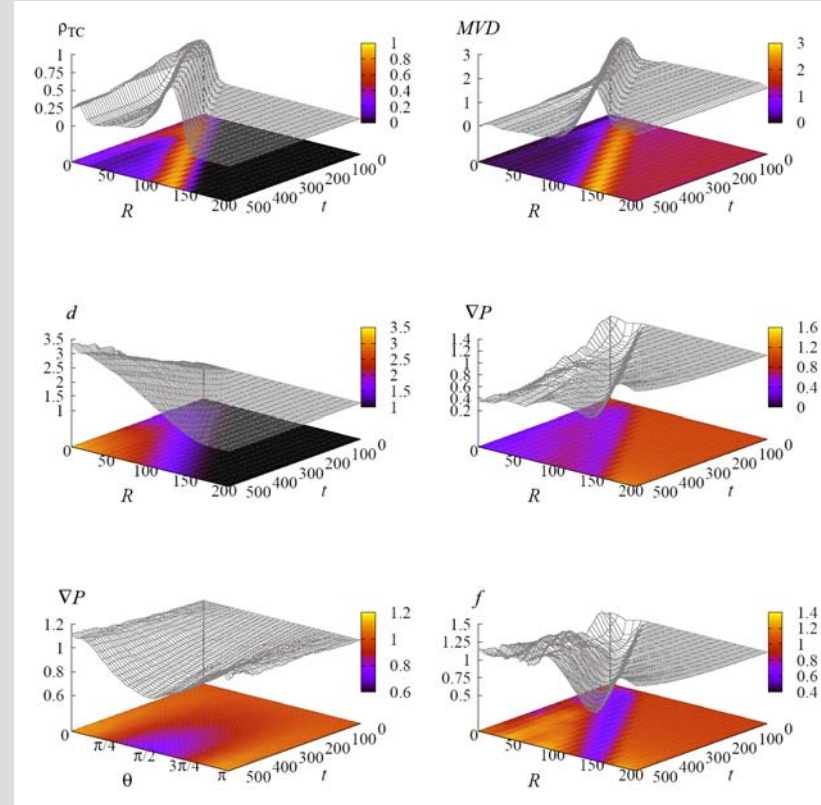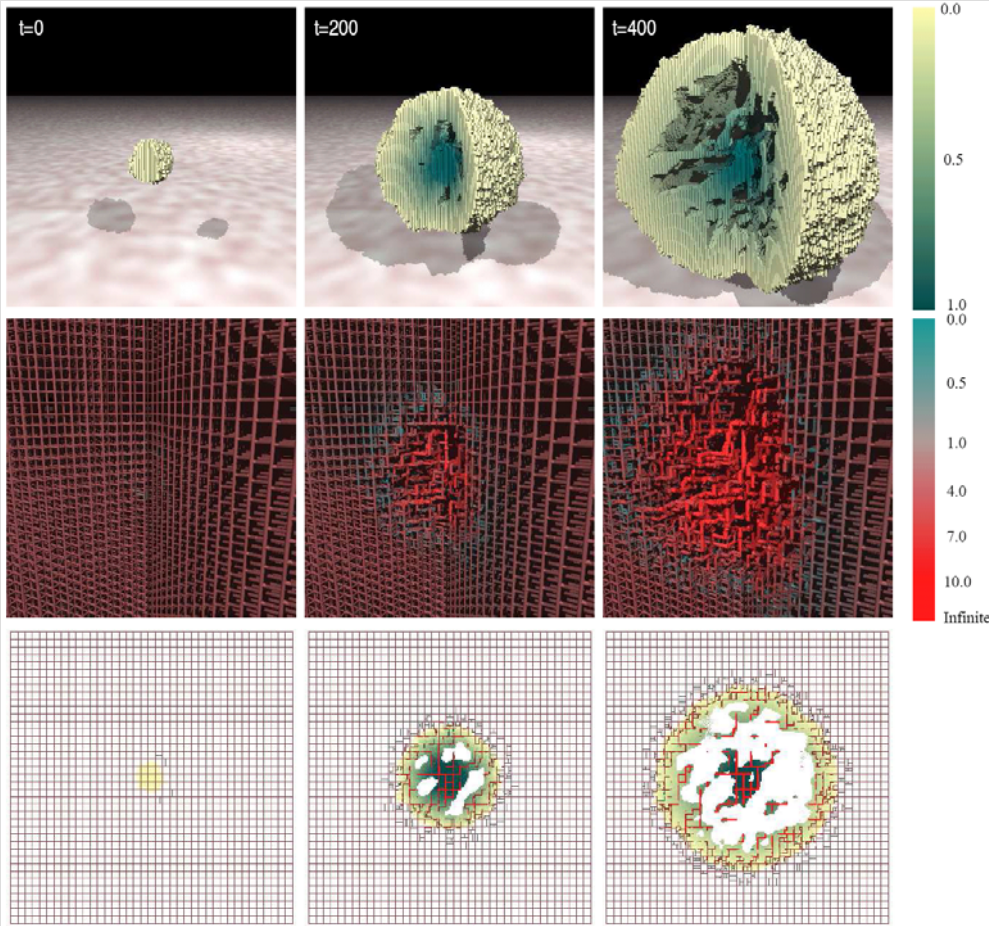
Quantitatively similar to 2d version!
[D.-S. Lee, H. Rieger, K. Bartha ´05]

Implications for vascular assembly

The simplistic model of capillary sprouting is replaced here by a
more complex cascade of events including vascular assembly and network formation:

- The original network of the host is remodeled by the tumor, blood flow is redirected.

- Pressure gradient is decreased within tumor vasculature

- Fractal structure due to collapse events inside the tumor (flow correlated percolation) not due to the growth process (c.f. Jain et al.: invasion percolation)

Implications for tumor growth

- Tumor pushes peritumoral plexus into the host tissue during growth.

- Is MVD a useful prognostic tool for tumor growth?
  Apparently (according to our model) not:
  MVD in the tumor can be high or low – independent of growth rate.

- Main parameter determining the tumor growth is the TC proliferation time –
  O_2 will not be a crucial factor as long as R_{GF} is sufficiently large.