Tumor growth modeling under antiangiogenic therapy

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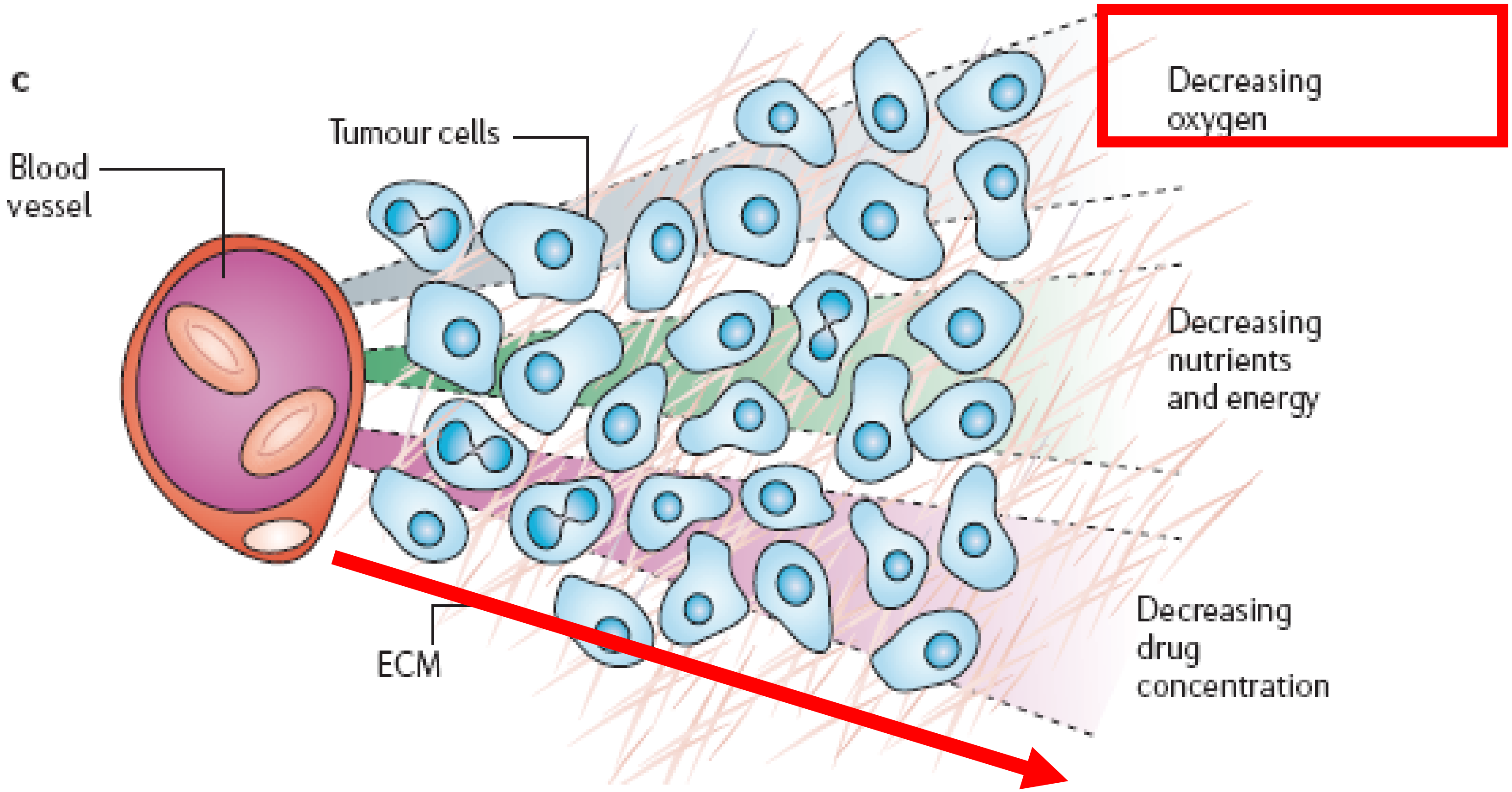
Characteristic of cancer

- self-sufficiency in growth signaling
- insensitivity to anti-growth signals
- evasion of apoptosis
- enabling of a limitless replicative potential
- induction and sustainment of angiogenesis
- activation of metastasis and invasion of tissue.

DIFFUSION – MAIN TRANSPORT IN TISSUE



PROGRESSIVE DECREASE

TRANSPORT PARAMETERS OF ENERGETIC NUTRIENTS

Oxygen level in:

Artery	85-100 mm Hg
Vein	40-50 mm Hg
Tissue	10-20 mm Hg
Cell	1-5 mm Hg

Glucose level:

Artery	5.5 mM/L
Vein in:	
brain	-12%
intestine	-9%
muscle	-7%
bud	-5%

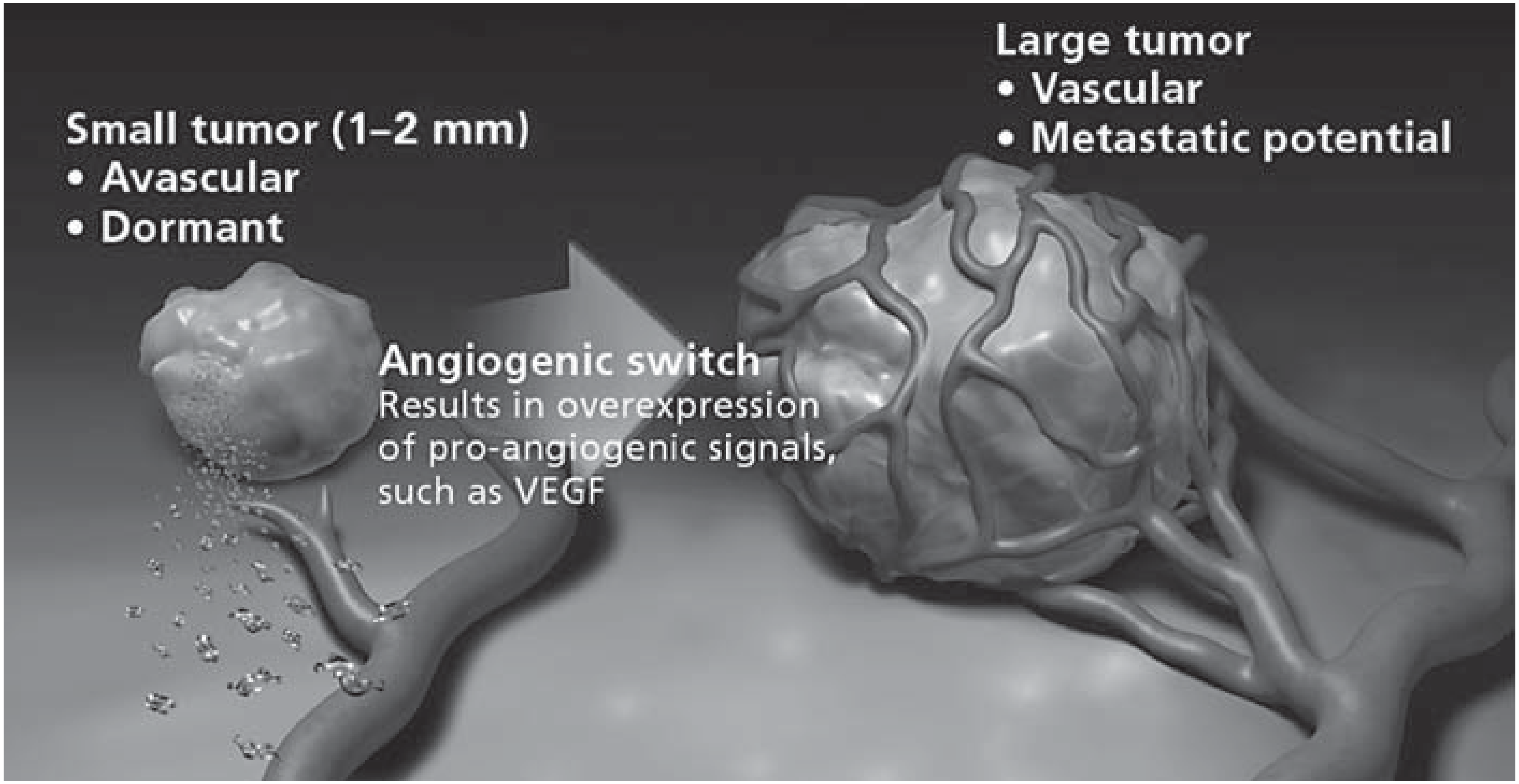
Коэффициент диффузии в ткани:

Oxygen $1.75*10^{-5}$ см^2/sec (in water - $2*10^{-5}$ – $2.5*10^{-5}$ см^2/sec)

Glucose $9.*10^{-6}$ см^2/sec (in water - $3.*10^{-6}$ см^2/sec)

Mean distance between capillaries - 100 mkM

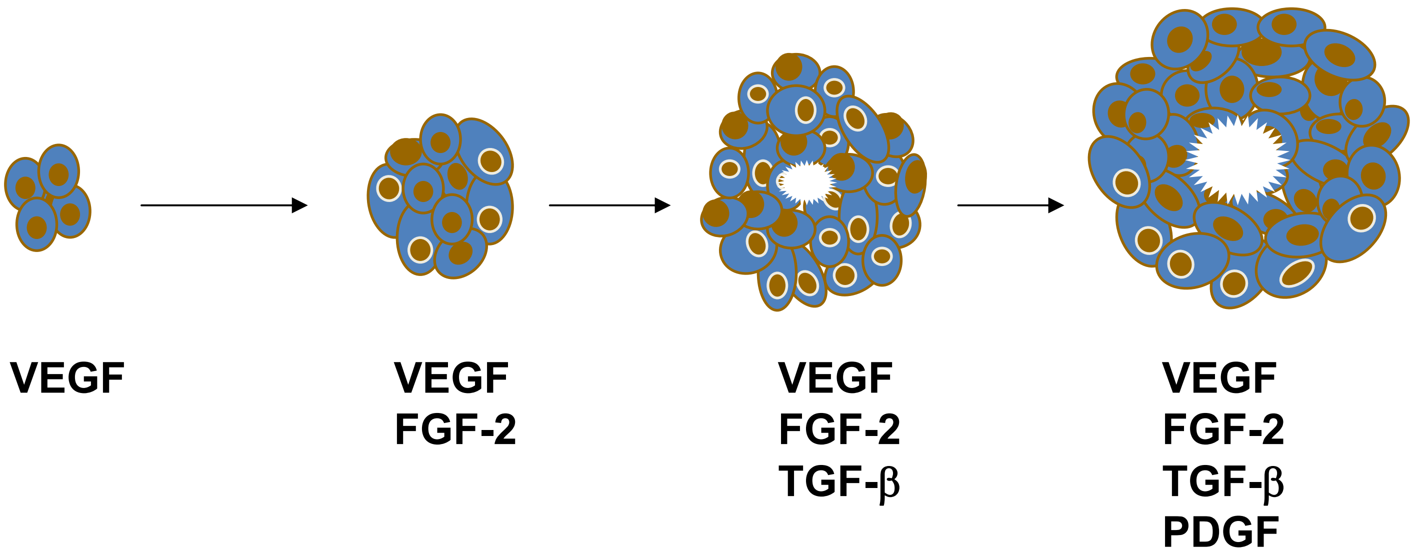
Tumor angiogenesis



Carcinoma in situ - 2-3 мм^3 in volume, no necrotic core, no angiogenesis

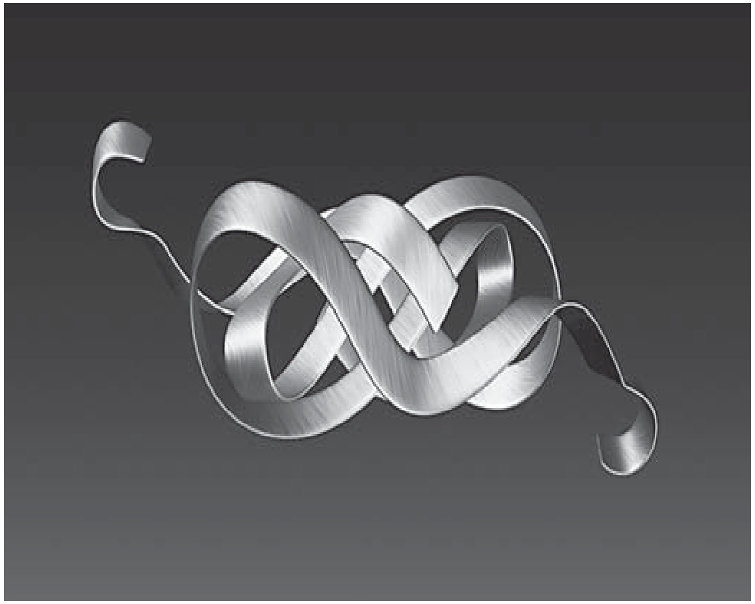
Large tumor – several см^3 in volume, necrotic core, neovascularization

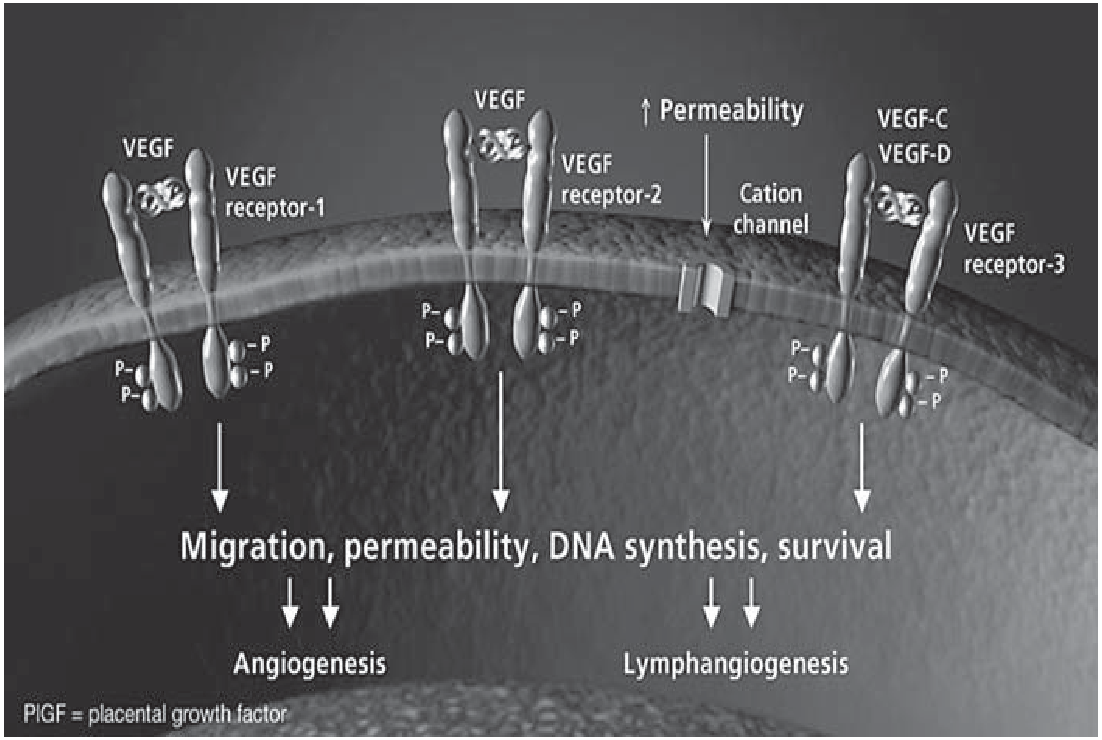
Multiple-factor regulation of tumor induced angiogenesis



VEGF induced angiogenesis at initial and through all other phases of tumor growth

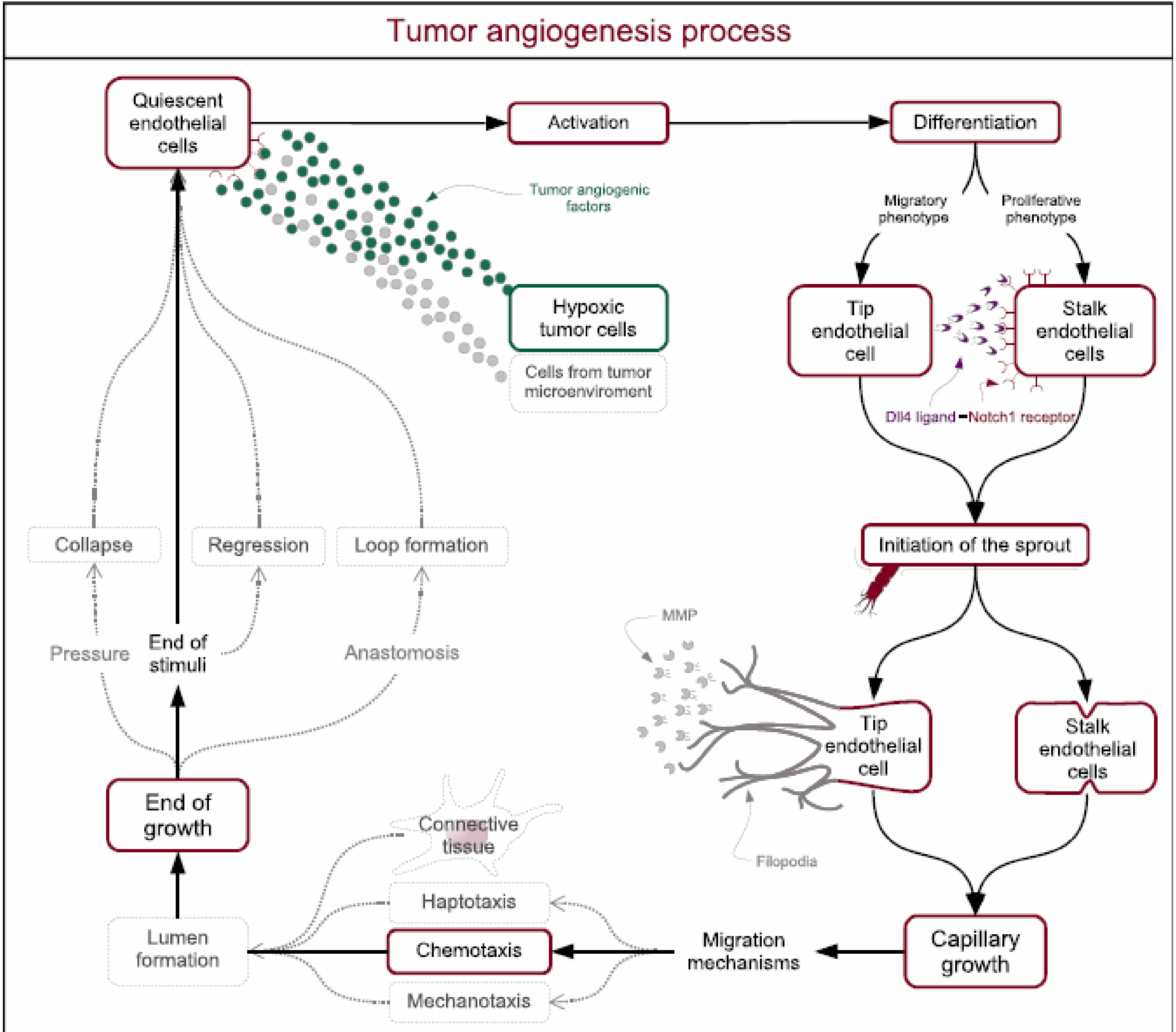
VEGF - Vascular endothelial growth factor





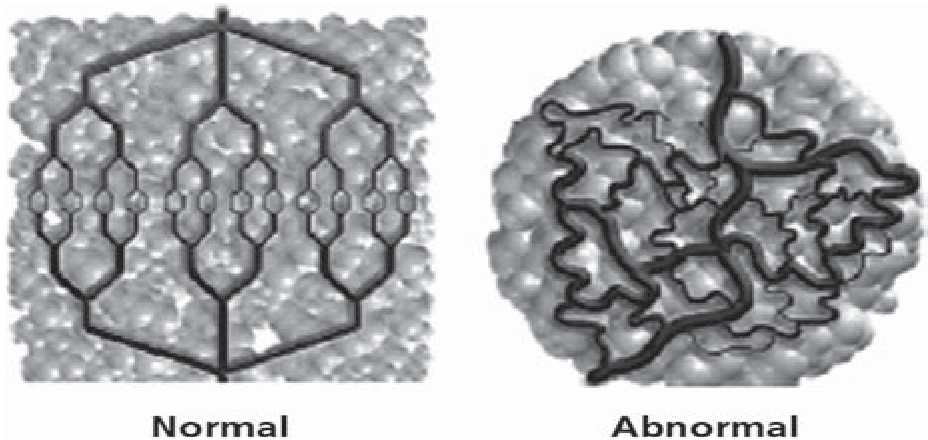
The VEGF family and its receptors. Ferrara et al., Copyright Nature Medicine 2003

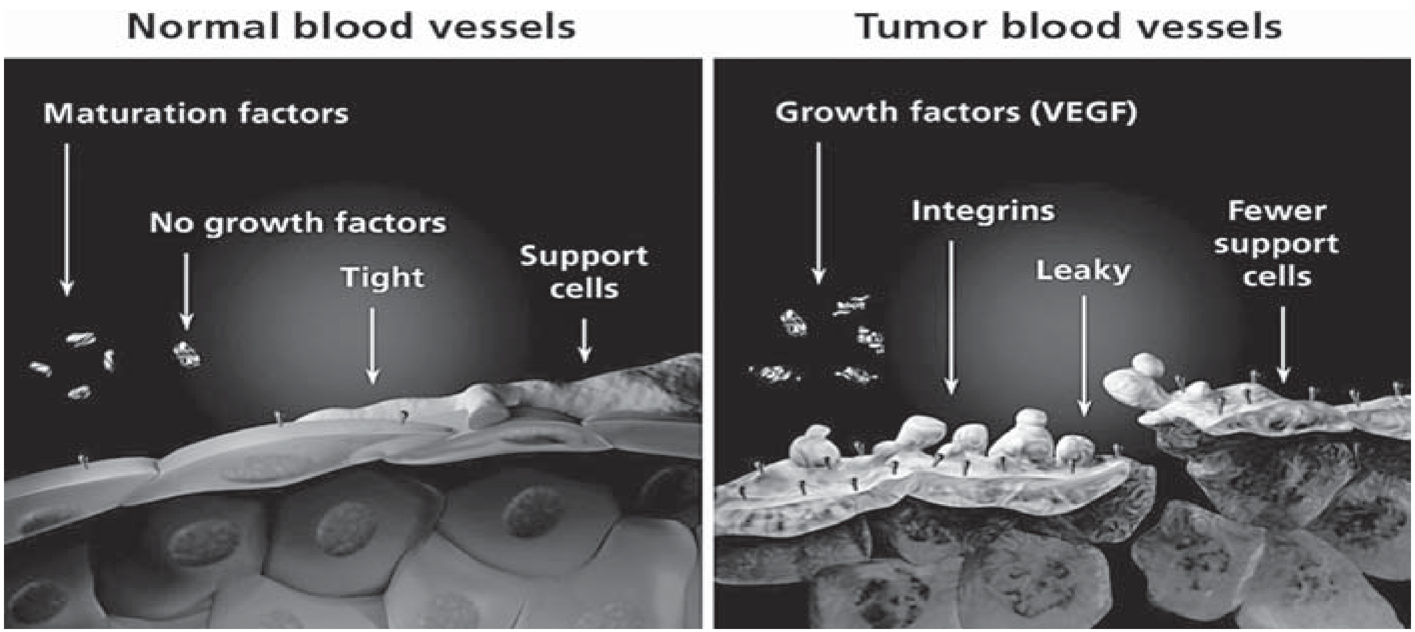
DIMER, Molecular mass - 34-42 kDa



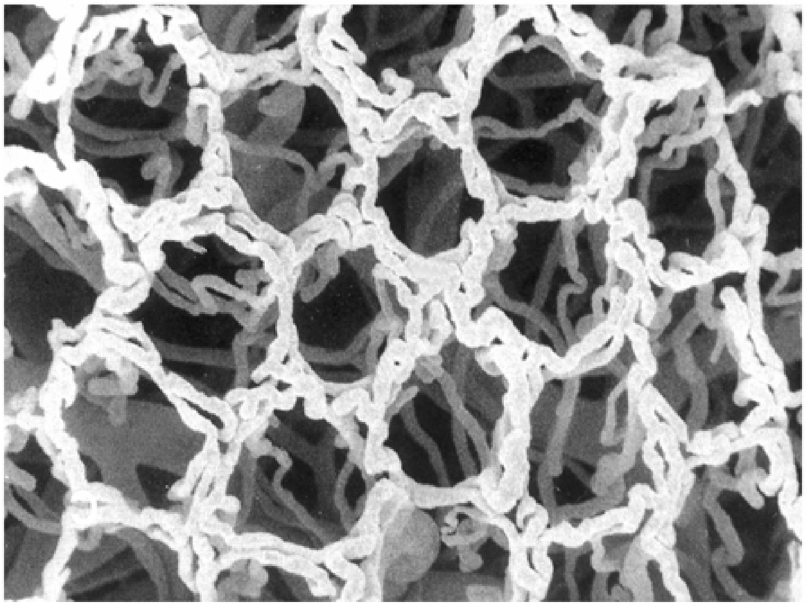
Tumor angiogenesis process
Quiescent endothelial cells
Activation
Differentiation
Tumor angiogenic factors
Migratory phenotype
Proliferative phenotype
Hypoxic tumor cells
Cells from tumor microenviroment
Tip endothelial cell
Stalk endothelial cells
Dll4 ligand
Notch1 receptor
Collapse
Regression
Loop formation
Initiation of the sprout
MMP
Pressure
End of stimuli
Anastomosis
Tip endothelial cell
Stalk endothelial cells
End of growth
Connective tissue
Filopodia
Haptotaxis
Lumen formation
Chemotaxis
Migration mechanisms
Capillary growth
Mechanotaxis

«Inefficiency» of tumor angiogenic capillary network

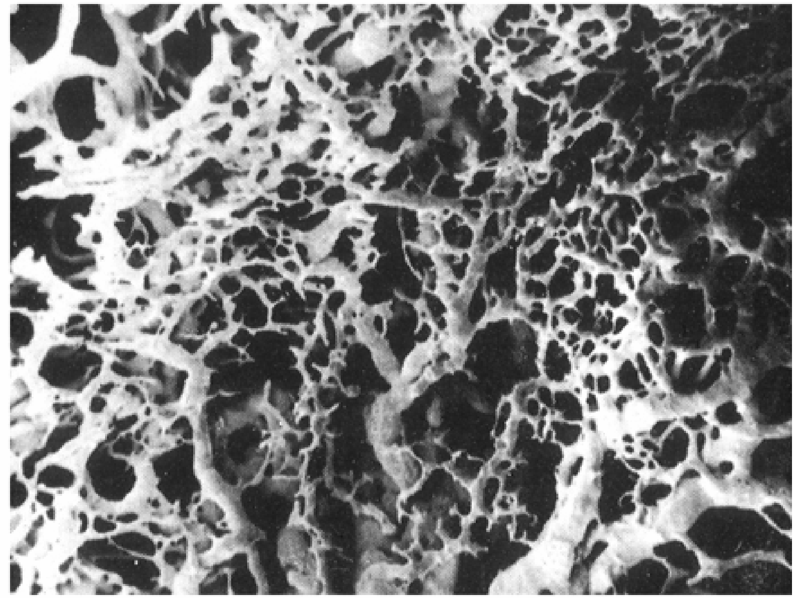




Normal colorectal mucosa

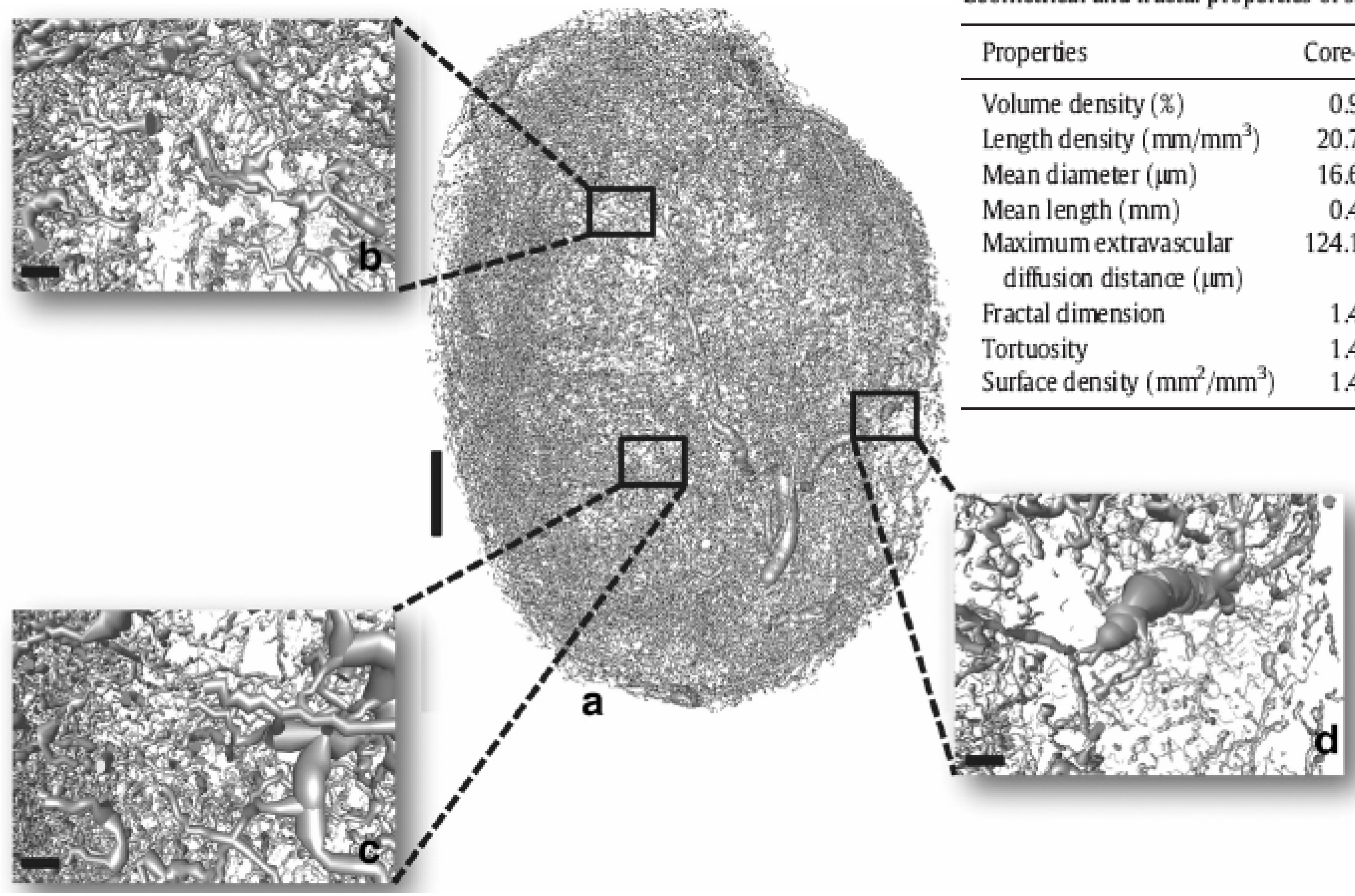


Nearby colorectal cancer



From Konerding et al. In Molls and Vaupel, eds. *Blood Perfusion and Microenvironment of Human Tumors*, 2002

Experimental capabilities



Geometrical and fractal properties of six regions of interest from tumor vasculature.

Properties	Core-1	Rim-1	Core-2	Rim-2	Core-3	Rim-3
Volume density (%)	0.9	3.4	0.38	2.06	0.2	1.08
Length density (mm/mm^3)	20.7	101.18	10.72	64.82	8.73	37.38
Mean diameter (µm)	16.66	15.12	17.95	15.77	19.24	14.15
Mean length (mm)	0.46	0.39	0.26	0.33	0.22	0.13
Maximum extravascular diffusion distance (µm)	124.1	56.1	172	70	191	92.3
Fractal dimension	1.46	1.45	1.1	1.55	1.01	1.29
Tortuosity	1.47	1.42	1.4	1.42	1.44	1.4
Surface density (mm^2/mm^3)	1.4	5.44	0.64	3.53	0.47	1.93

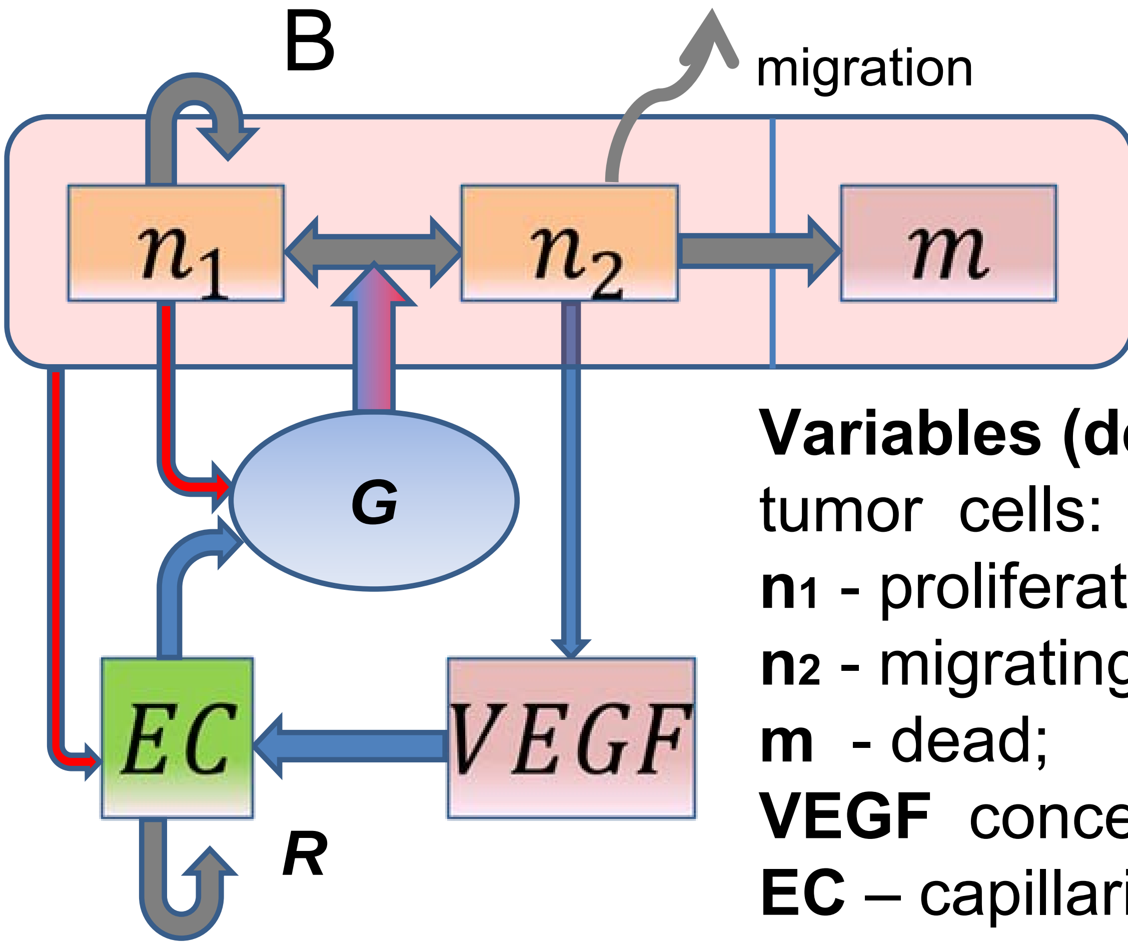
3Dmicro-CT derived whole-tumor microvasculature froma human triple-negative breast cancer xenograft (MDA-MB-231 cells). (a) Raw tumor vascular network. (b), (c) and (d) insets illustrate magnified regions of the raw vascular network. Scale bars: 1 mm (a), 100 µm (b), (c) and (d).

FROM: S.K. Stamatelos et al. / Microvascular Research 91 (2014) 8–21

Multi-scaling in tumor modeling

- Capillary diameter 5-10 microns (10^{-6} m)
- Cell size up from 5-6 microns (10^{-6} m)
- Distance between capillaries 100-200 microns (10^{-4} m)
- Carcinoma in situ 2-3 mm (10^{-3} m)
- Detectible tumor size more that 1 cm (10^{-2} m)
- Organ size 10^{-1} m

Model with account of tumor angiogenesis



Variables (densities):
tumor cells:
n_1 - proliferating;
n_2 - migrating;
m - dead;
VEGF concentration;
EC – capillaries surface area;
G - glucose concentration.

R – rate of angiogenesis intensity

Equations for capillary network density, glucose and VEGF concentrations

VEGF

production — degradation

$$\frac{dV}{dt} = D_V \Delta V + p(fn_1 + n_2) - (d_V + \omega EC)V$$

Capillaries surface area

Tumor angiogenesis — capillaries degradation

$$\frac{dEC}{dt} = \frac{RV}{V + V^*} EC(1 - EC / EC_{\max}) - Ln_t EC$$

$$EC|_{t=o} = 1$$

Glucose

Income — Consumption by: (tumor cells) (normal cells)

$$\frac{dG}{dt} = D_G \Delta G + EC \cdot Q_0 - \frac{q_t(n_1 + kn_2)G}{G + G*} - \frac{q_n(1 - n_t)G}{G + G*}$$

Equations for cell densities

proliferating cells
$$\frac{\partial n_1}{\partial t} = B_1 n_1 - P_1(G)n_1 + P_2(G)n_1 - \nabla(n_1 I),$$

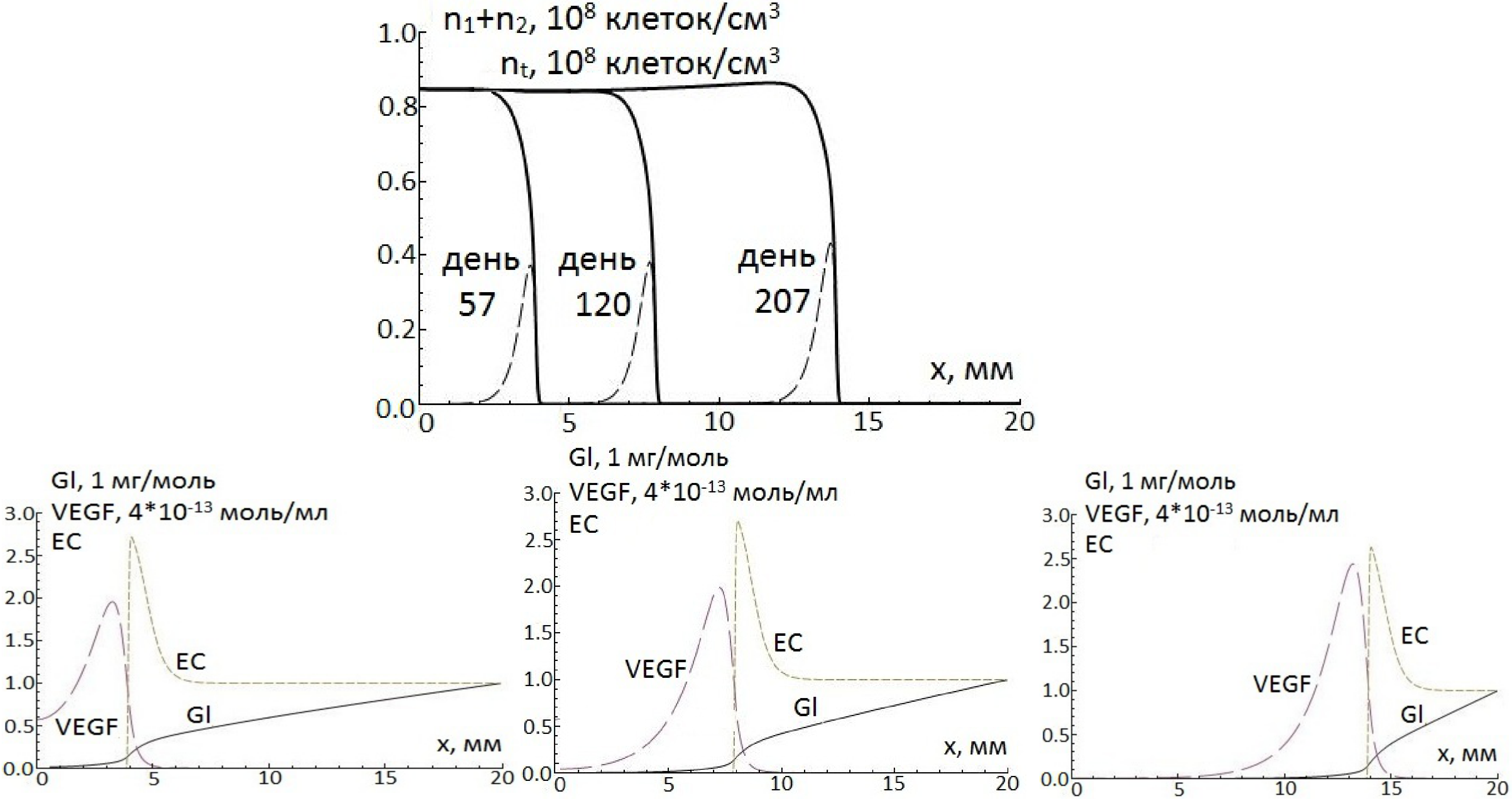
migrating cells
$$\frac{\partial n_2}{\partial t} = P_1(G)n_1 - P_2(G)n_2 - dn_2 - \nabla(n_2 I) + D_n \Delta n_2,$$

necrosis
$$\frac{\partial m}{\partial t} = dn_2 - \nabla(mI),$$

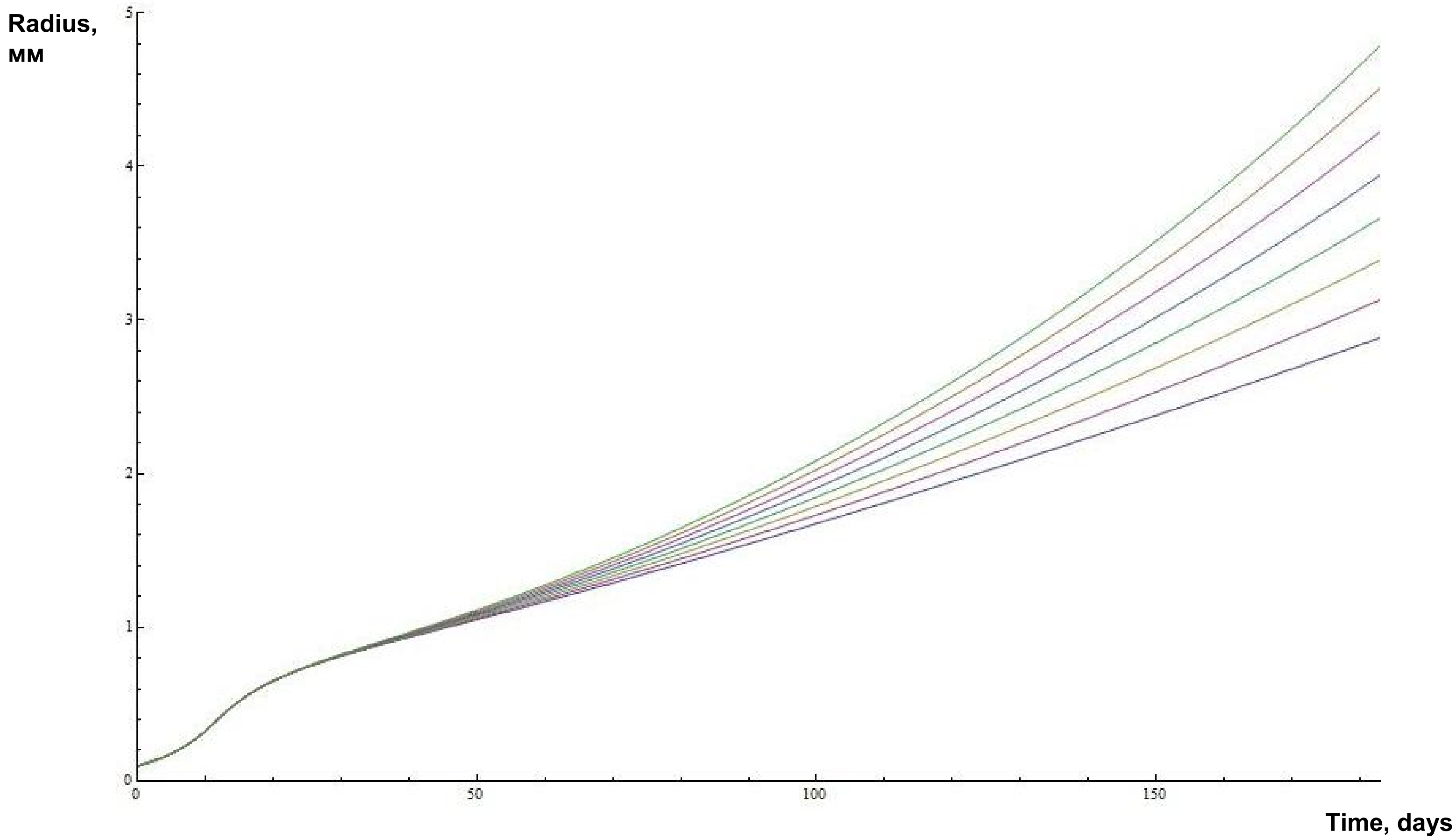
Tissue convection
$$I = U + D_n \nabla n_2$$
$$\nabla . U = \left[B_1 n_1 - Lis(n_1 + n_2)(1 - n_1 - n_2 - m)\right]$$

Transition functions
$$P_1(G) = k_1 \exp(-k_2 G)$$
$$P_2(G) = k_3(1 - th(\varepsilon(G^{cr} - G)))$$

Results for low invasive tumor ($D_n = 10^{-10}$ cm^2/sec)

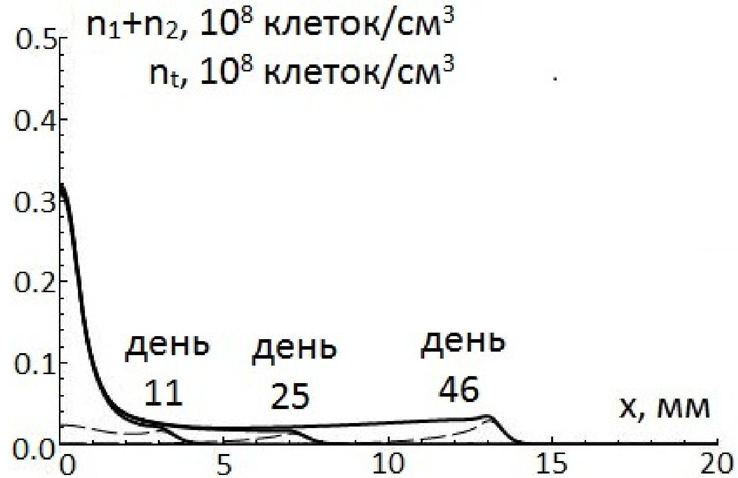


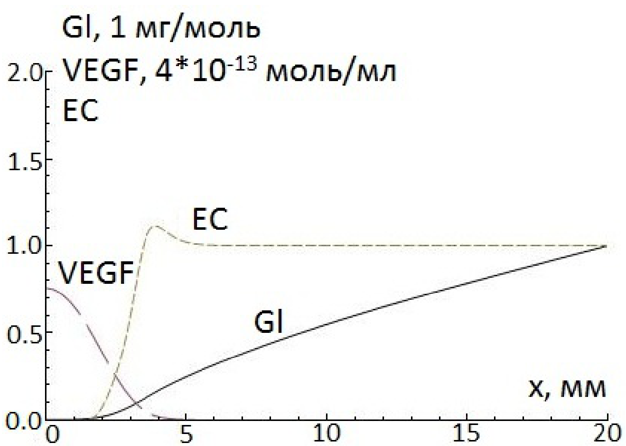
Dependence of low invasive tumor growth on angiogenesis

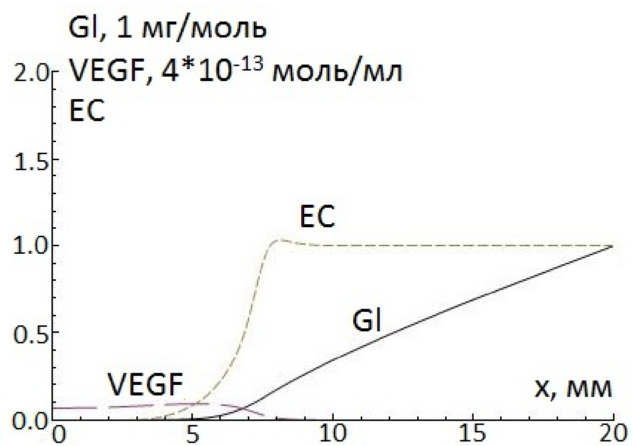


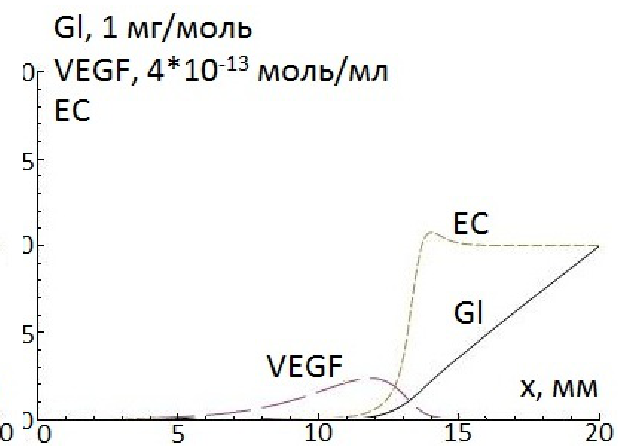
Increase of angiogenesis rate R (from *0,0015 to 0,015 – 2* days capillaries density doubling time) significantly increase low invasive tumor growth rate

Results for invasive tumor ($D_n = 10^{-9}$ cm^2/sec)

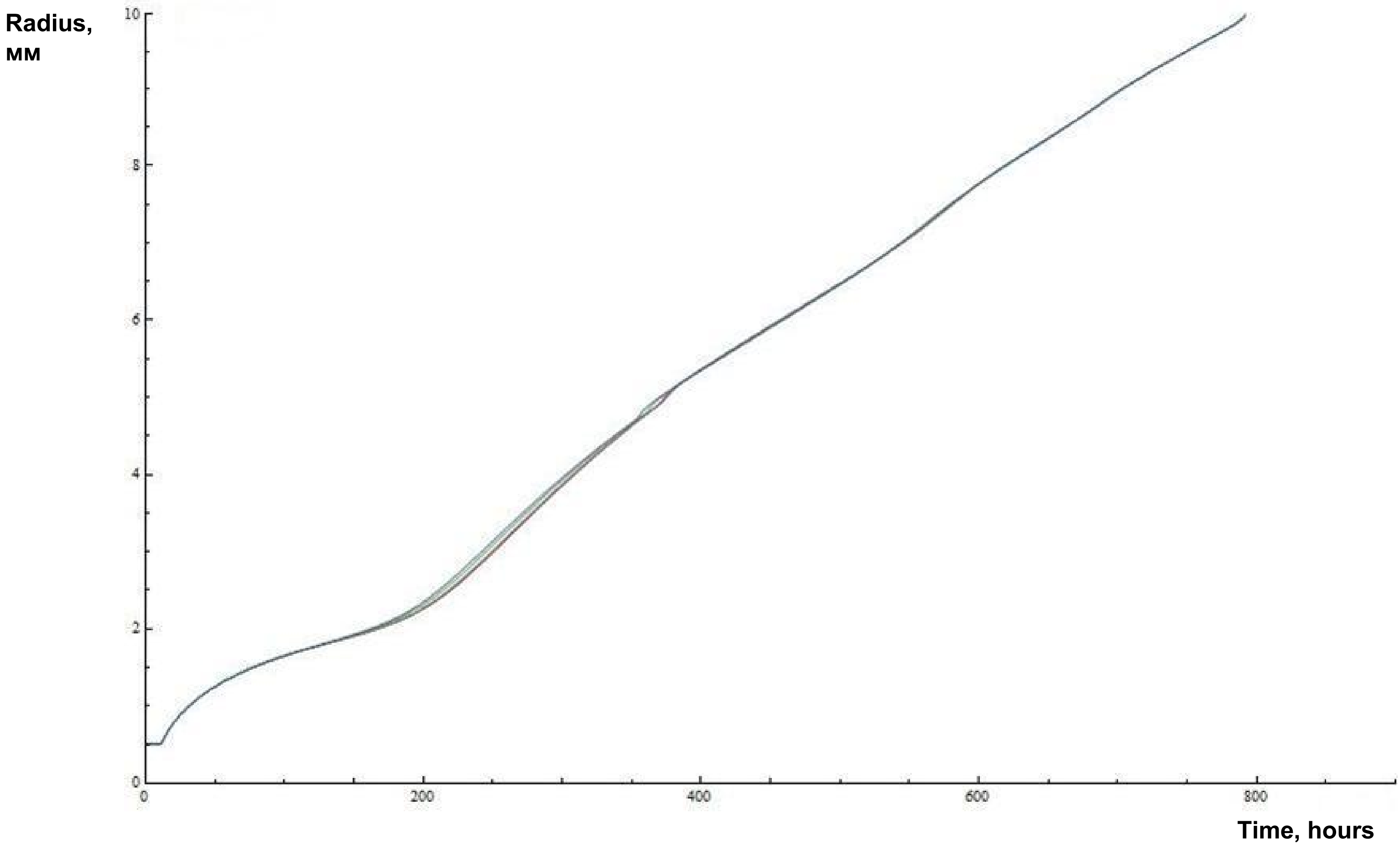








Dependence of invasive tumor growth n angiogenesis



Invasive tumor growth does not depend on angiogenesis

Bevacizumab

Bevacizumab - recombinant humanized monoclonal antibody for VEGF

Molecular mass - approximately 149 kDa, $D_A = 2*10^{-7}$ cm^2/sec

Half-life (non-specific degradation k_{eff}) - 20 days (11–50 days)

Constant of Bevacizumab-VEGF interaction k_A=1,9 $*10^{12}$ sec^{-1} M^{-1}

Character concentrations of VEGF in blood of oncological patients:

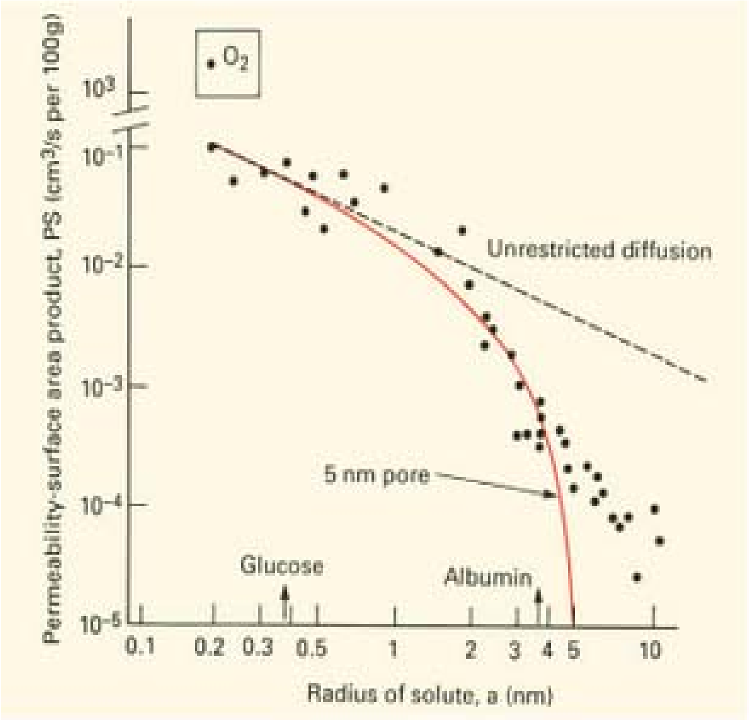
V_0=(1-10)* 10^{-10} mol/l

$$Q = P \cdot S \cdot (A_{capillary} - A_{tissue})$$

$A_{cappilary}$=const

P – permeability may differs dramatically in preexist capillaries and that formed during tumor angiogenesis!!!

Permeability from capillaries



Renkin equation

$$P = D'(S_a / S)(1 - \frac{a}{r})^2$$

$$D' = D(1 - \frac{a}{r})^2 (1 - 2.1\left(\frac{a}{r}\right) + 2.09\left(\frac{a}{r}\right)^3 - 0.95\left(\frac{a}{r}\right)^5)$$

$S=EC_0=50\ cm^2/cm^3$

Permeability capillaries	Preexisting	Angiogenic	Ratio
Glucose (180 Da)	1.1*10^{-5} см/sec	1.54*10^{-5} см/sec	1.4
VEGF (38-42 kDa)	1.5*10^{-7} см/sec	5,6*10^{-6} см/sec	37
Bevacizumab (149kDa)	1,1*10^{-8} см/sec	1,8*10^{-6} см/sec	158

Modified Equations for capillary network densities, glucose, VEGF and Bevacizumab concentrations

$$\frac{dEC}{dt} = -Ln_t EC \Leftrightarrow EC\Big|_{t=0} = 1$$

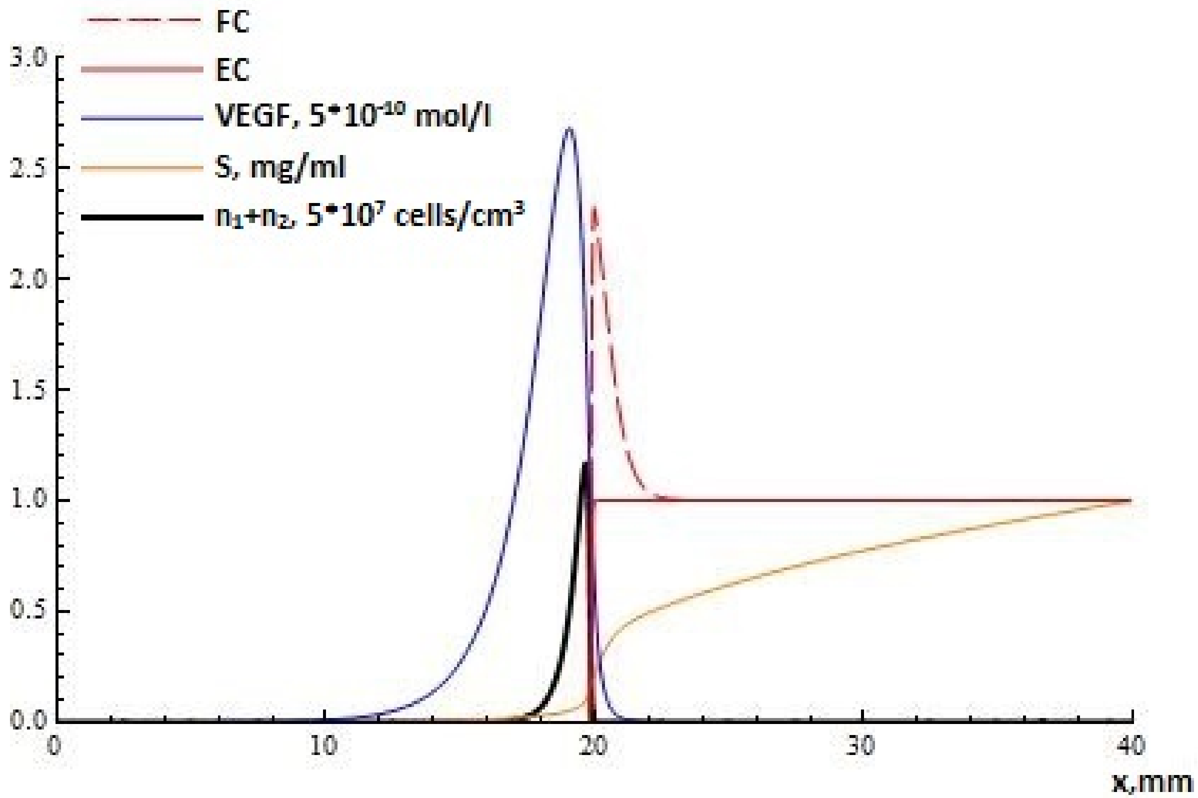
$$\frac{dFC}{dt} = \frac{RV}{V+V^*}(EC+FC)\left(1-\frac{(FC+EC)}{(FC+EC)_{\max}}\right) - Ln_t EC$$

$$\frac{dG}{dt} = D_G \Delta G + EC \cdot Q_{EC} + FC \cdot Q_{FC} - \frac{q_t(n_1+kn_2)G}{G+G^*} - \frac{q_n(1-n_t)G}{G+G^*}$$

$$\frac{dV}{dt} = D_V \Delta V + p(fn_1+n_2) - (d_V + \omega EC)V$$

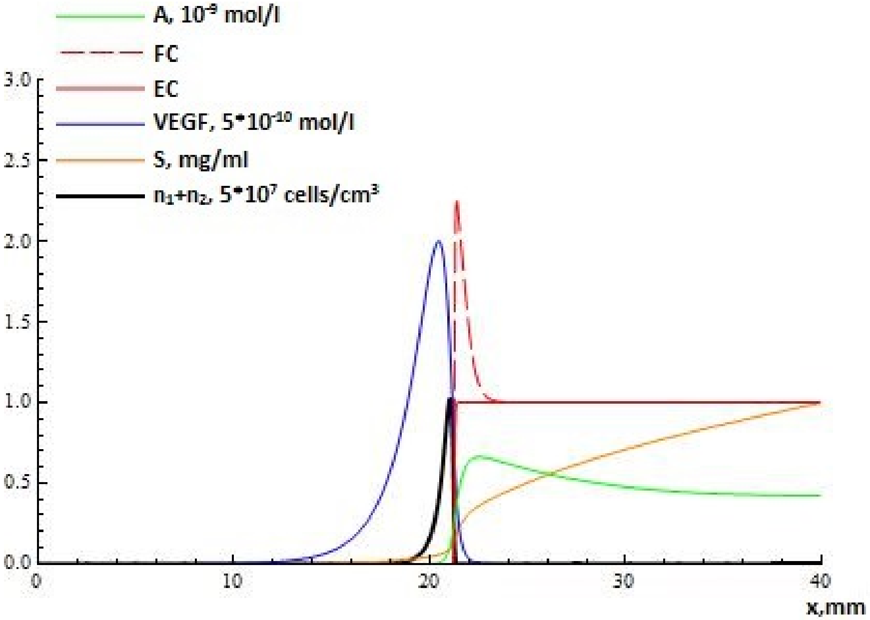
$$\frac{dA}{dt} = D_A \Delta A + P_{A,EC} EC(1-A) + P_{A,FC} FC(1-A) - (k_A V_o)AV - k_{eff} A$$

Modeling of antiangiogenic therapy

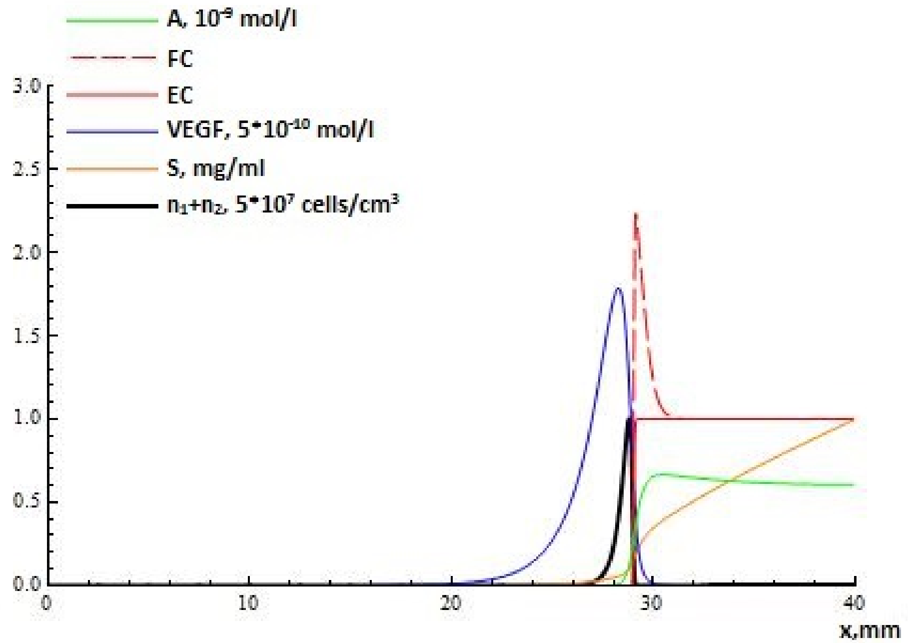


Variables distribution in the moment of bevacizumab injection

$A_0 = 10^{-9}$ mol/l

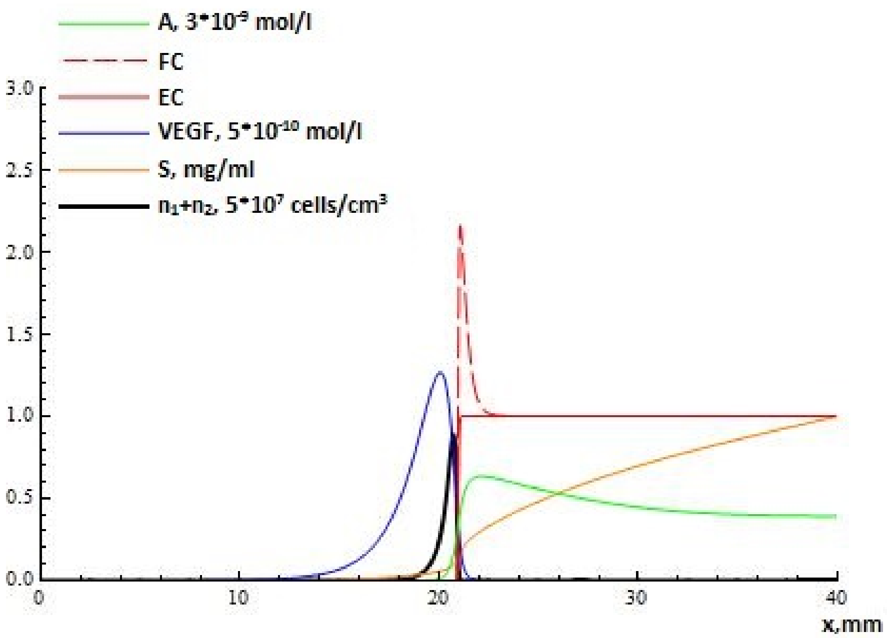


16th day after injection

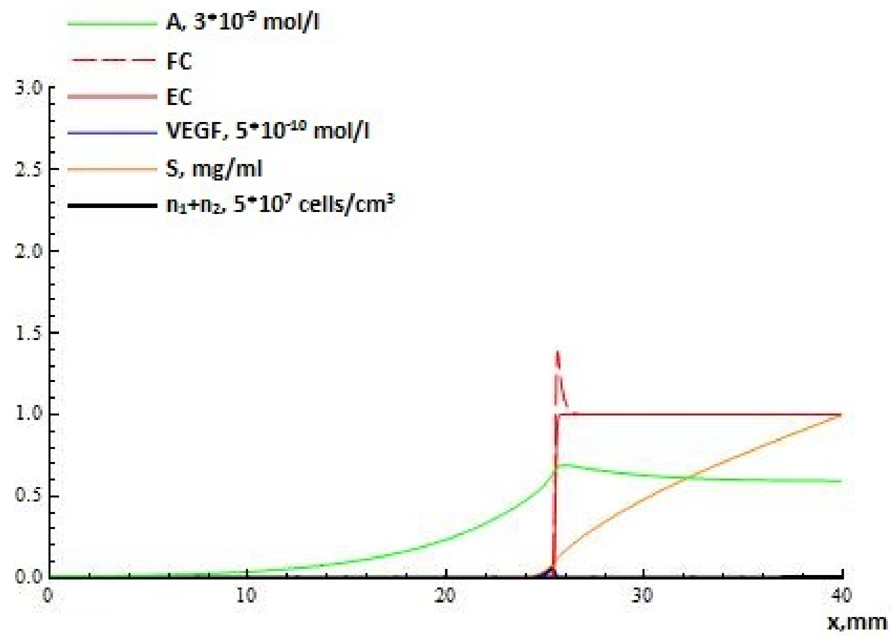


120th day after injection

$A_0 = 3*10^{-9}$ mol/l

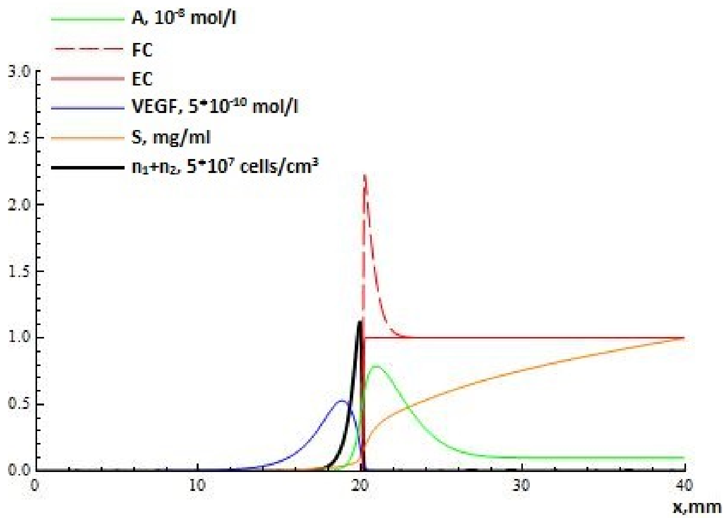


14th day after injection

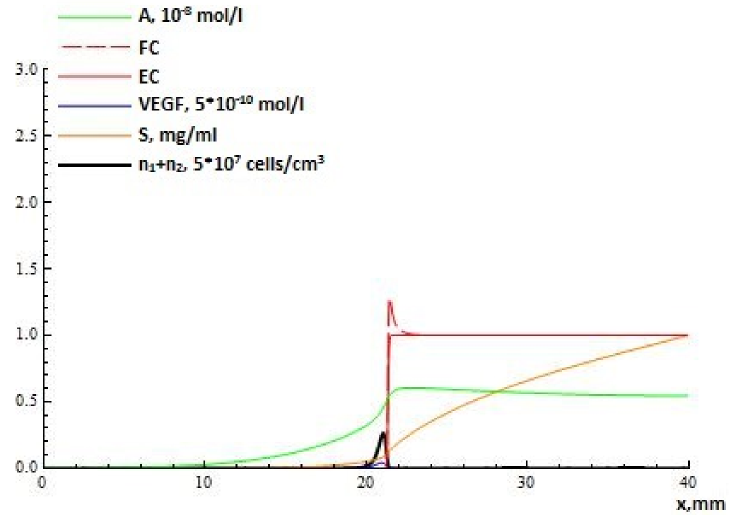


135th day after injection

$A_0 = 10^{-8}$ mol/l

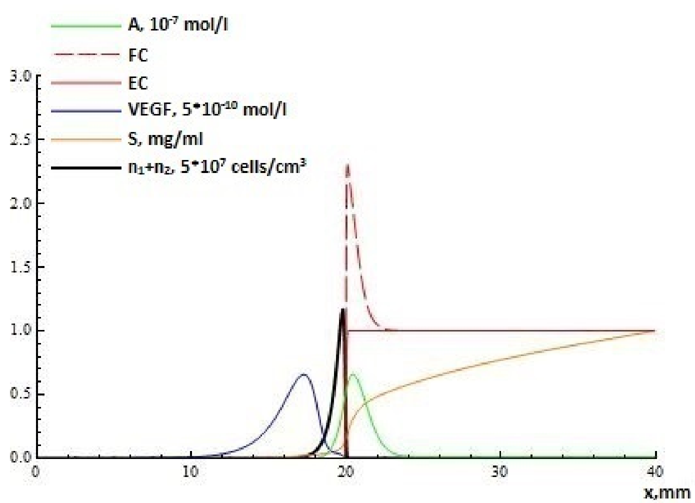


3rd day after injection

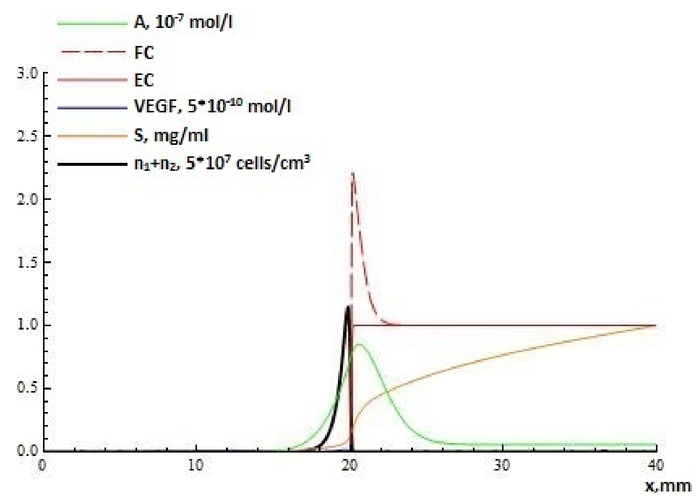


30th day after injection

$A_0 = 10^{-7}$ mol/l

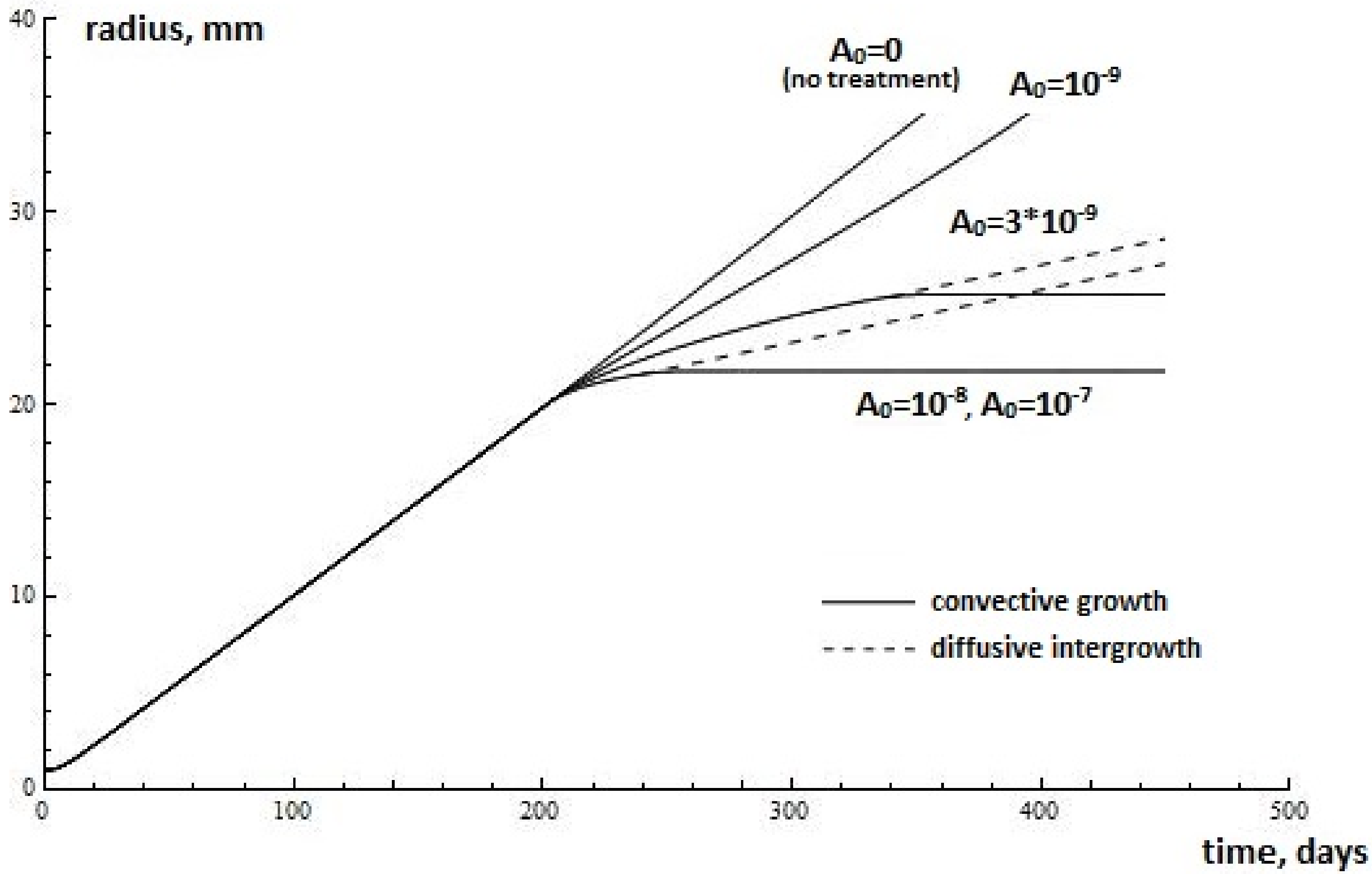


1st day after injection



2nd day after injection

Tumor growth under bevacizumab therapy



Medics give oncological patients avastin (bevacizumab)5 mg/kg

that corresponds to blood concentration $A_0 = 10^{-6}$ mol/l

Thank you