NUMERICAL SIMULATIONS OF THE MICROCIRCULATORY BLOOD FLOW VARIATIONS DUE TO ANGIOGENESIS

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N Gorodnova , M. Kuznetsov, S. Simakov

Institute of Numerical Mathematics, Russian Academy of Sciences

Outline

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Background

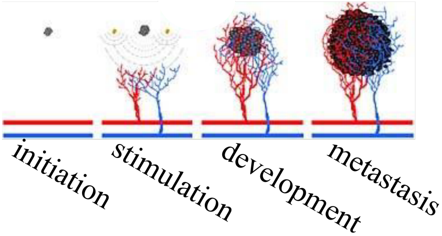
Angiogenesis — is the physiological process through which new blood vessels form from pre-existing vessels. Characteristics of angiogenesis in tumor-affected tissues:

- proceeding constantly
- faster than in healthy tissues
- another structure of blood vessel wall
- chaotic directions of vessel grow

Geometrical properties of capillaries:

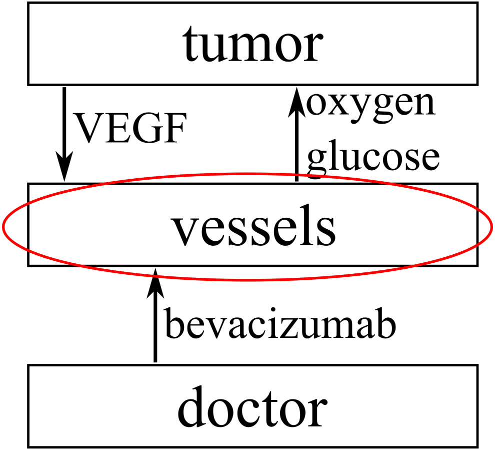
- Arterioles: length — 100-500 μm, diameter — 10-30 μm
- Capillaries: length — near 0.3 mm, diameter — 5-10 μm
- B 1 cm^3 in human organism — 200-250 thousands

Bevacizumab is medication used to treat a number of types of cancers.



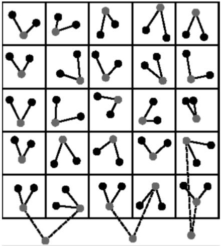
Motivation

Analysis of tumor Bevacizumab-treatment effectivenes and therapeutic strategy design



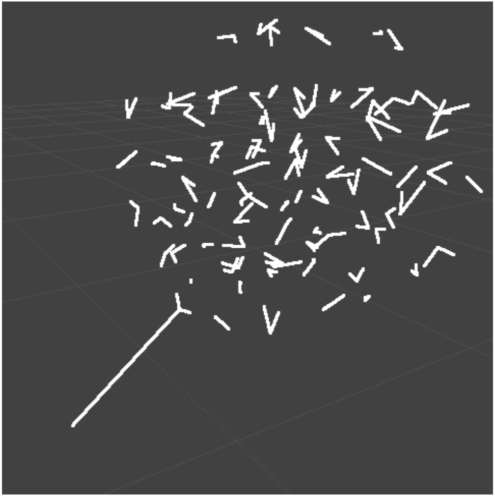
Algorithm of healthy vessel network construction

1. Divide cube into similar cubic cells
2. Place 3 nodes into every cell
3. Denote 1 node per cell as a boundary node, it is connected with 2 others
4. Place a node between 2 random boundary nodes, denote a new node as a boundary node instead of 2 others
5. Repeat item 4 until number of boundary nodes is greater than 1
6. Construct 2 networks using items 1–5: for arteries and veins
7. Connect 2 artery and vein networks via capillaries



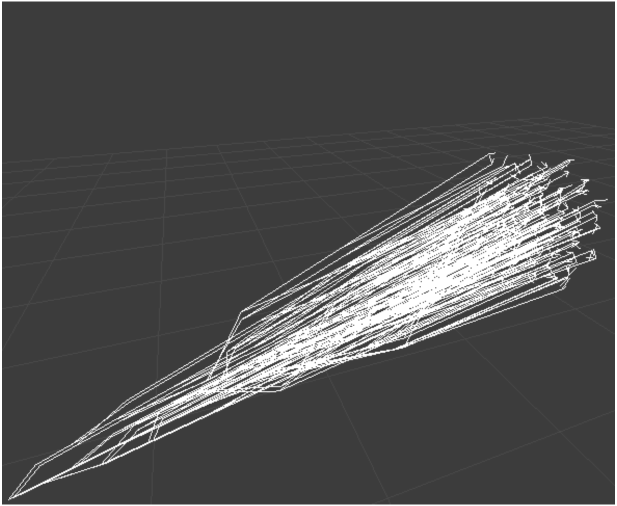
Algorithm result

The first step of the algorithm



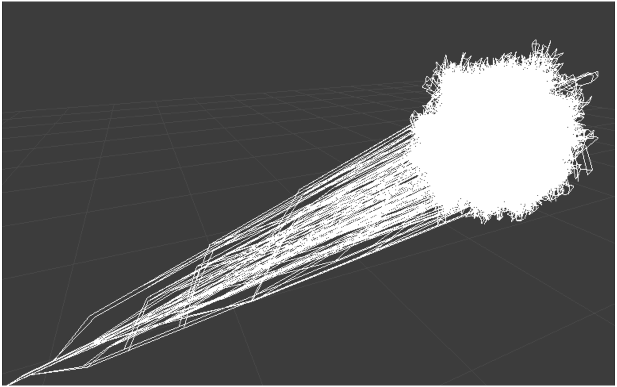
Algorithm result

Intermediate step of the algorithm



Algorithm result

The final step of the algorithm

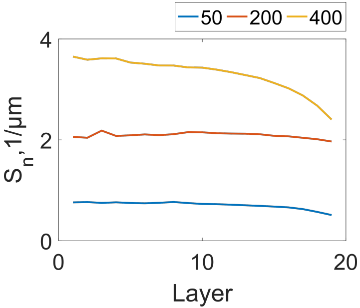


Distribution of vessel surface area

$$\delta = \frac{|S_n - S_{mean}|}{S_{mean}}$$

$$S_n = \frac{\sum_i S_i}{V_n}$$

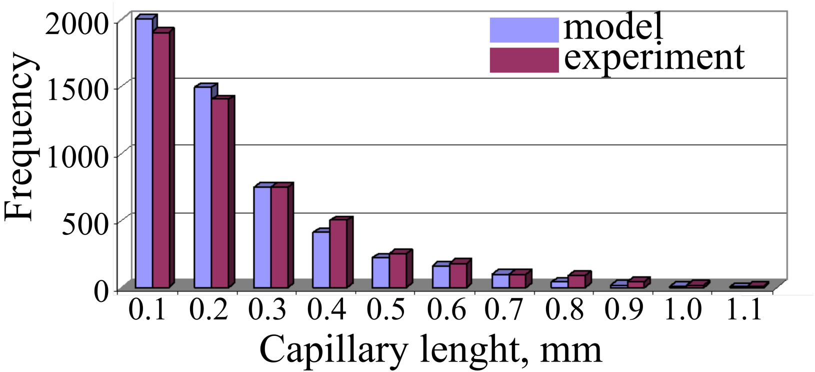
$$S_{mean} = \frac{\sum_n^N S_n}{N}$$



	50	200	400
δ_{mean}	0.068	0.05	0.027
δ_{max}	0.18	0.14	0.19

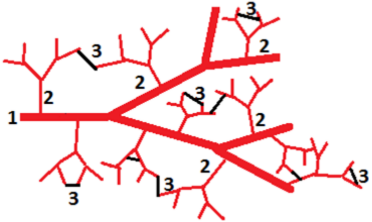
- δ_{mean} — mean deviation
- δ_{max} — maximum deviation
- N — number of layers
- V_n — layer volume
- S_i — vessel surface area

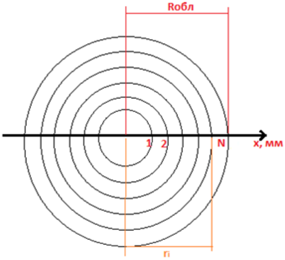
Comparison between experimental data and simulation results



Blue bars denote numerical results, purple bars denote experimental data obtained by microCT.

Tumor-affected growth of new capillaries





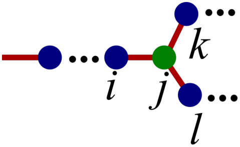
Radius of *n*-th layer:

$$r_n = \frac{n}{N} R_N, n = 1, ..., N$$

Spatial density of capillaries in a layer:

$$\rho_n = \frac{\sum_{i=1}^{K} S_i}{V_n}, n = 1, ..., N$$

Microcurculation mathematical modelling



$$Q_{ji} = G_{ji}\left(P_j - P_i\right),$$

$$Q_{jk} = G_{jk}\left(P_j - P_k\right),$$

$$Q_{jl} = G_{jl}\left(P_j - P_l\right),$$

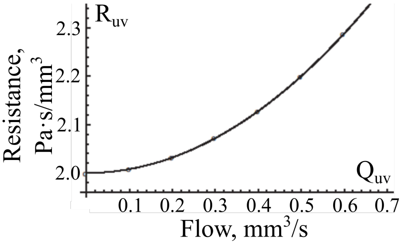
$$Q_{ji} + Q_{jk} + Q_{jl} = 0$$

- $Q_{j\beta}$ – blood volumetric flow in a vessel $j - \beta$, $\beta = i, k, l$,
- P_{β} – pressures in a node $\beta = i, j, k, l$,
- $G_{j\beta}$ – conductivity coefficient of a vessel $j - \beta$, $\beta = i, k, l$,

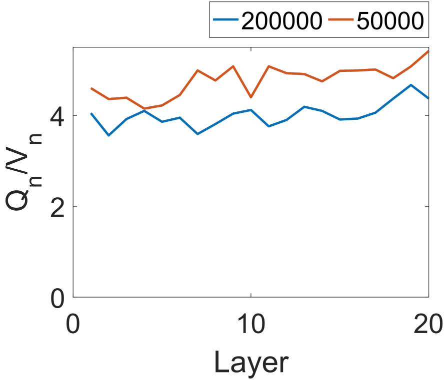
Vessel conductivity coefficient in linear and non-linear microcirculation models

$$G_{uv} = \begin{cases} \dfrac{8\mu l_{uv}}{\pi r_{uv}^4} \times (1 + \alpha Q_{uv}^2)^{-1} \\ \dfrac{8\mu l_{uv}}{\pi r_{uv}^4}, \end{cases}$$

- G_{uv} – conductivity of a vessel $u - v$,
- μ – blood viscosity,
- l_{uv} – length of a vessel $u - v$,
- r_{uv} – radius of a vessel $u - v$,
- α – coefficient of blood flow influence on vessel conductivity



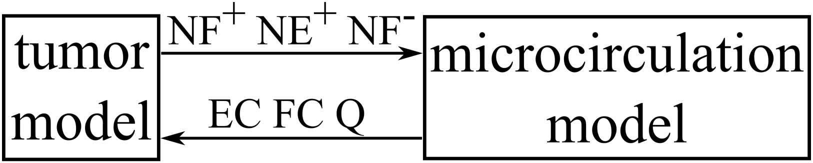
Volumetric perfusion



$$\bar{Q}_n = \frac{Q_i}{V_i}$$

N	max $2 \cdot 10^5$	mean $2 \cdot 10^5$	max $5 \cdot 10^4$	mean $5 \cdot 10^4$
1	35	15	47	30
2	34	15	42	17
3	29	13	17	12
4	12	6	32	13
5	29	12	18	9
6	32	11	18	9
7	28	12	27	15
8	17	7	18	8
9	19	8	24	11
10	22	10	11	5
11	23	7	20	9
12	12	5	19	7
13	9	5	10	7
14	9	4	19	11
15	12	4	21	9
16	7	3	11	4
17	7	4	6	4
18	12	6	12	6

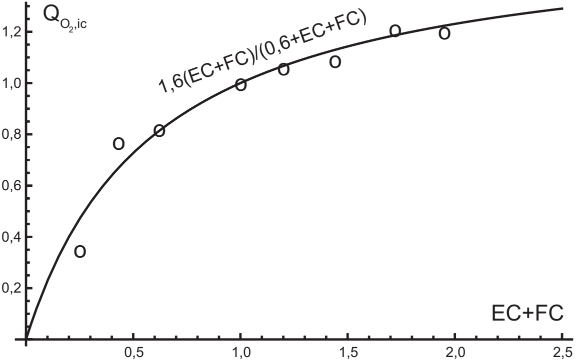
Intercoupling of the models



Schematic diagram of intercoupling of the models

- NF^{+} – number of capillaries grown due to angiogenesis,
- NE^{-}, NF^{-} – number of degraded pre-existed capillaries,
- EC, FC – surface area density of pre-existed and new capillaries,
- Q – blood flow volumetric desnity.

Intercoupling of the models



Blood flow through capillaries as a function of capillary network surface area density $Q_{O_2,ic}(EC+FC)$ obtained from numerical simulations. Circles denote experimental data, line denotes fitting function. The fitting function is used in further simulations.

Results

- Mathematical model of physiologically correct microcirculatory network construction is formulated.
- Mathematical model of blood microcirculation is formulated, numerically implemented and validated.
- Blood microcirculation and tumor growth mathematical models are intercoupled.

Thank you for your attention!