Multiscale models for glioma invasion

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Joint work with:

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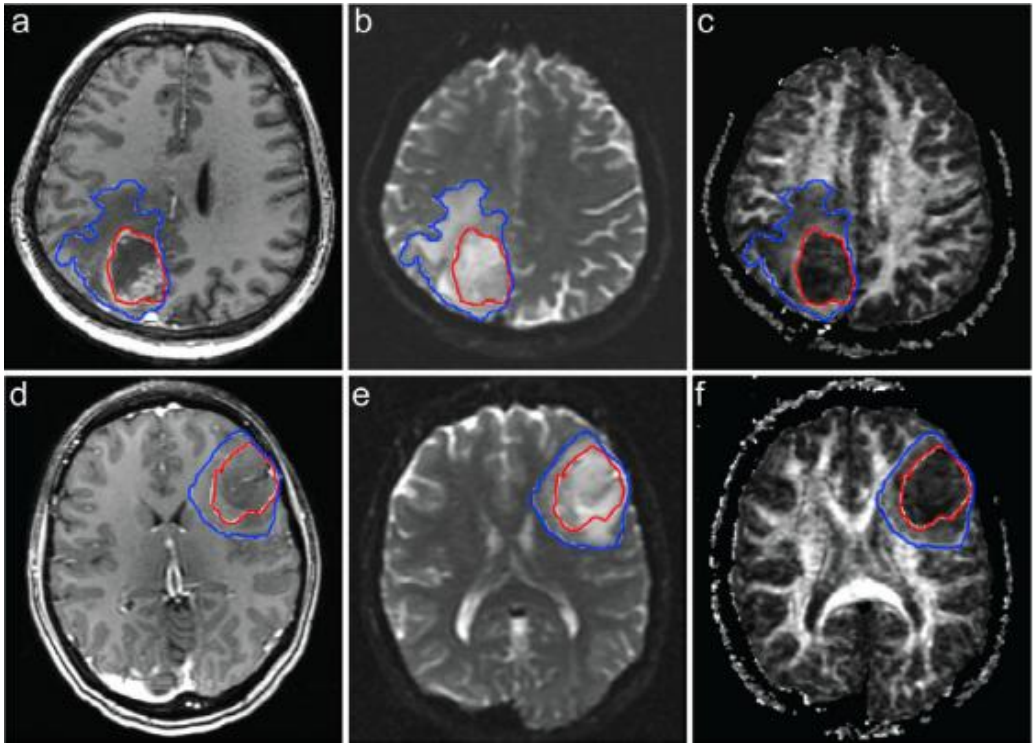
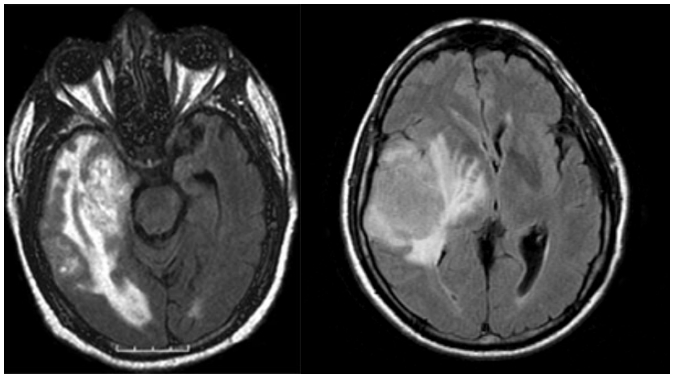
- Katarina Wolf (Radboud Univ. Nijmegen Medical Centre)
- Yvonne Dzierma (Uniklinikum des Saarlandes)

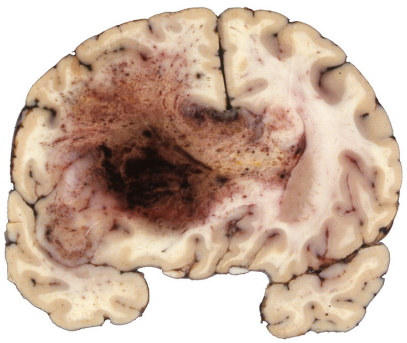
Glioblastoma multiforme (GBM)

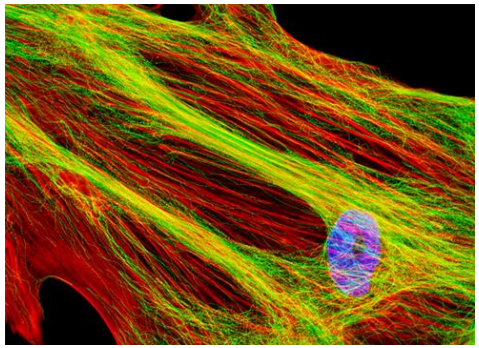


HIGH GRADE

LOW GRADE

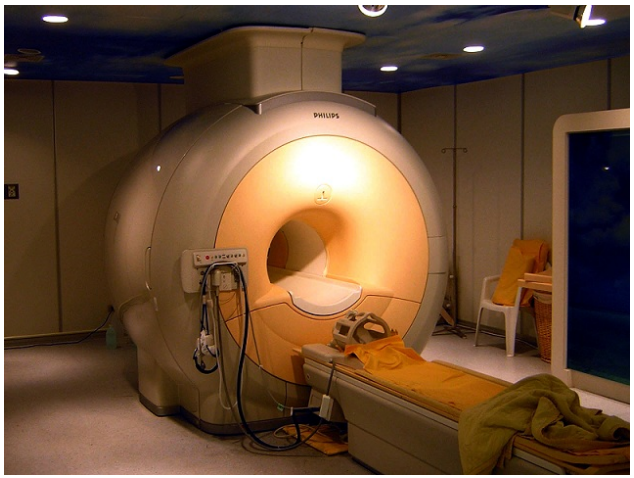






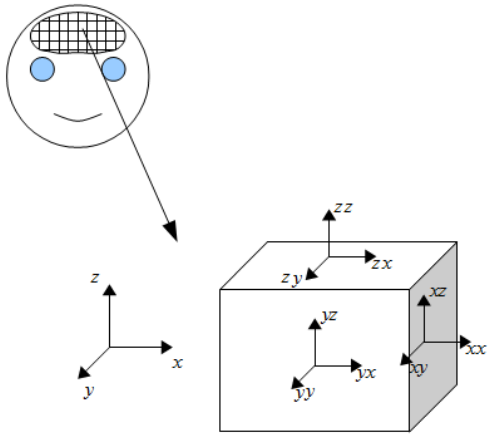
Diffusion tensor imaging

- Variant of diffusion-weighted magnetic resonance imaging, DW-MRI.
- Measures the spatial diffusion of water molecules by MRI per volume element (voxel) .



MRI-device (Philips Chieva 3.0 T)
http://upload.wikimedia.org/

Consider a single voxel:



This leads to a diffusion tensor

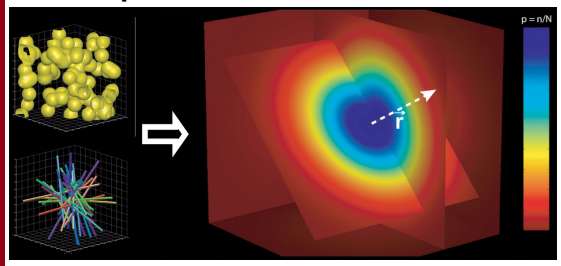
$$\mathbb{D}(\mathbf{x}) = \begin{pmatrix} d_{xx}(\mathbf{x}) & d_{xy}(\mathbf{x}) & d_{xz}(\mathbf{x}) \\ d_{yx}(\mathbf{x}) & d_{yy}(\mathbf{x}) & d_{yz}(\mathbf{x}) \\ d_{zx}(\mathbf{x}) & d_{zy}(\mathbf{x}) & d_{zz}(\mathbf{x}) \end{pmatrix}$$

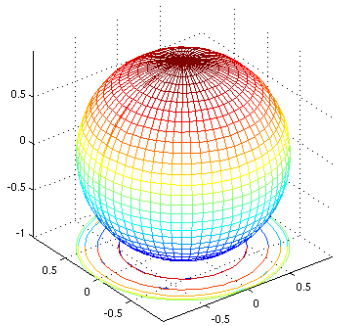
Representation of anisotropic diffusion tensor data

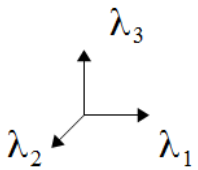
(see Hagmann et al. 2006)

Assume diffusion tensor in diagonal form: $\mathbb{D}(\mathbf{x}) = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix}$.

Spherical diffusion

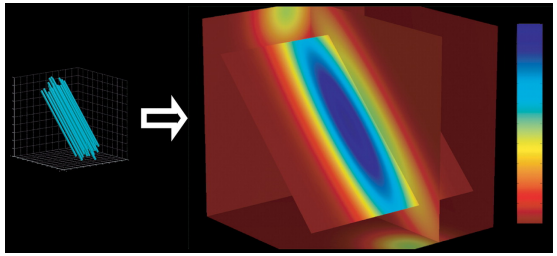


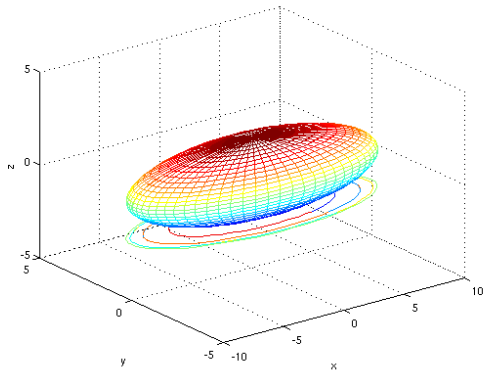


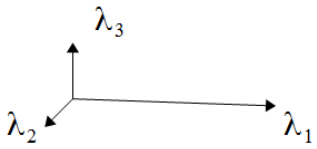


$\lambda_1 = \lambda_2 = \lambda_3$

Prolate diffusion

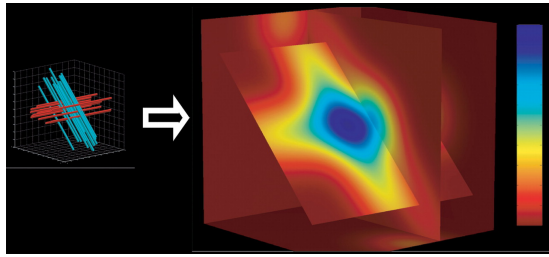


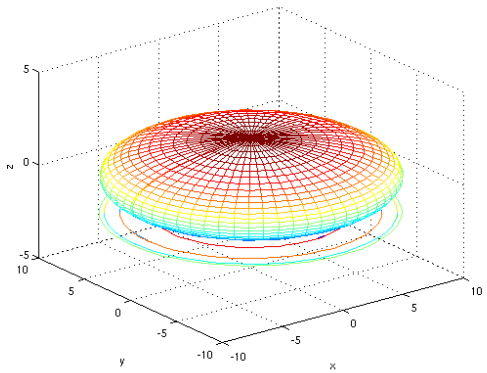


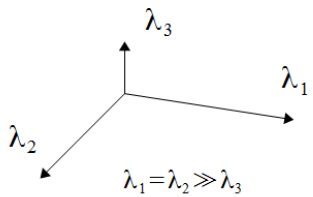


$\lambda_1 \gg \lambda_2 = \lambda_3$

Oblate diffusion



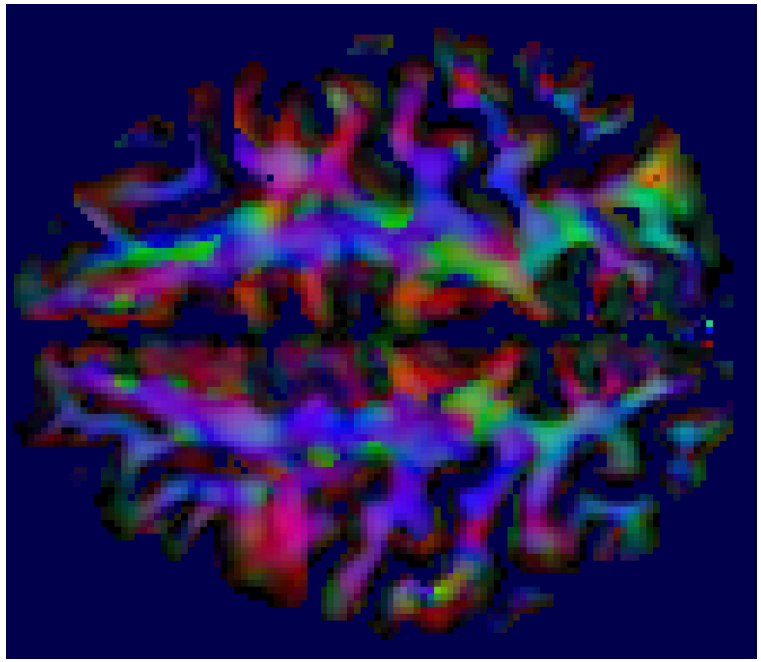


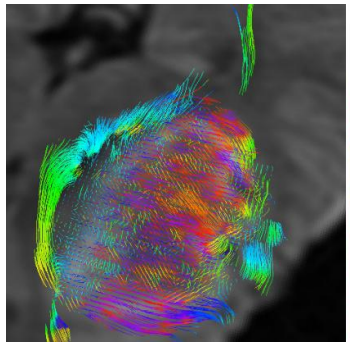


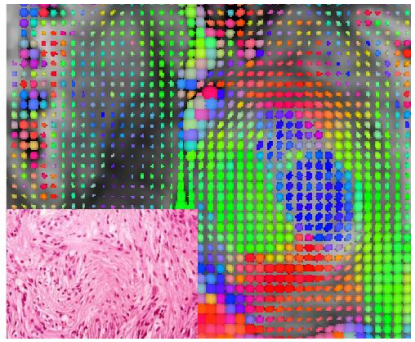
$\lambda_1 = \lambda_2 \gg \lambda_3$

Representation of the anisotropic DTI data

Glyphs & tractography

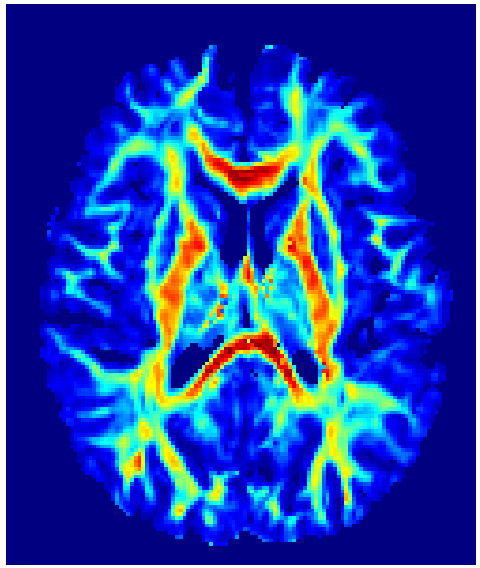






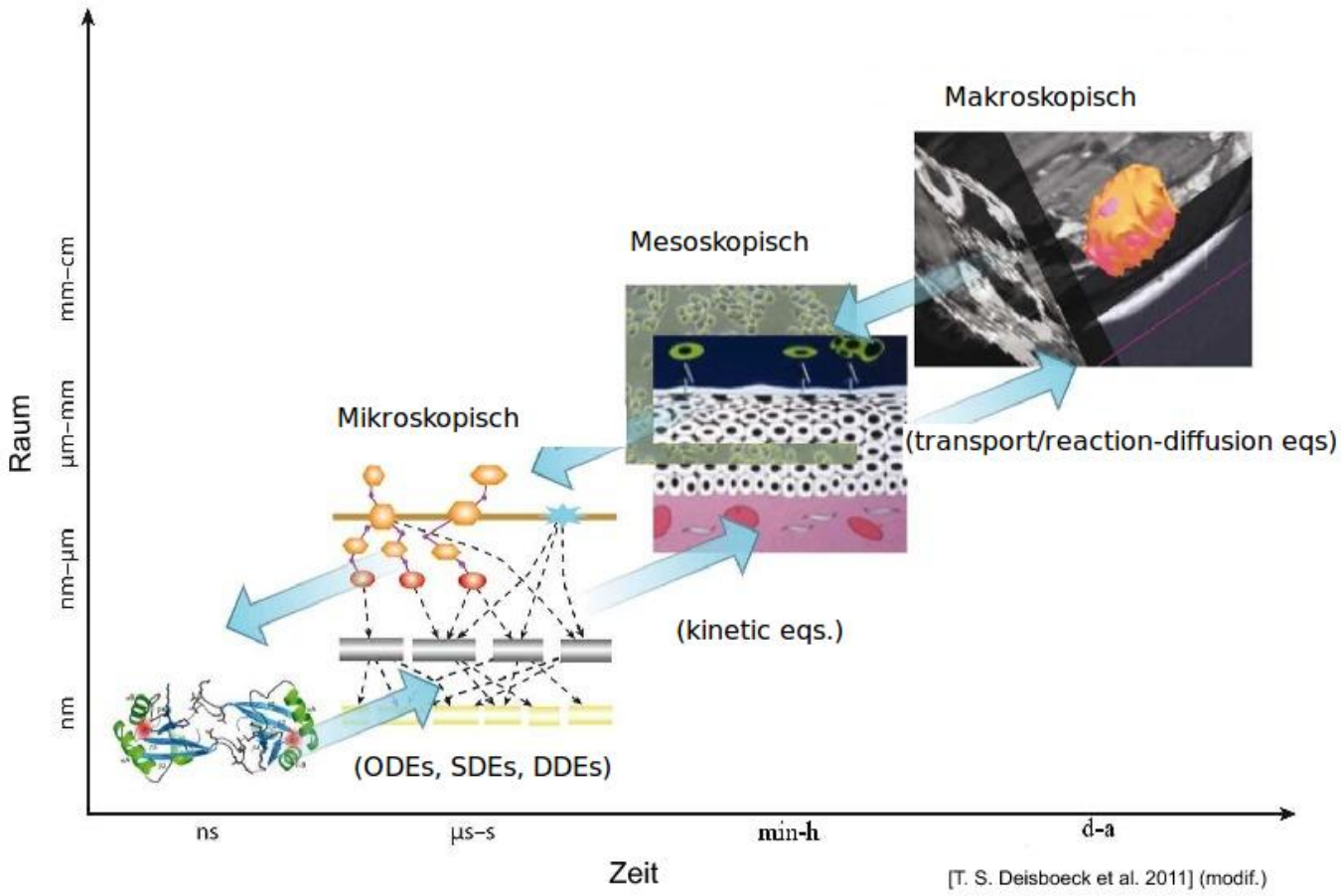
$$\frac{\theta_1^2}{\lambda_1} + \frac{\theta_2^2}{\lambda_2} + \frac{\theta_3^2}{\lambda_3} = 1$$

Fractional anisotropy



$$FA(\mathbf{x}) = \sqrt{\frac{3}{2}} \frac{\sqrt{\sum_{i=1}^{3} (\lambda_i - \bar{\lambda})^2}}{\sqrt{\sum_{i=1}^{3} \lambda_i^2}}$$

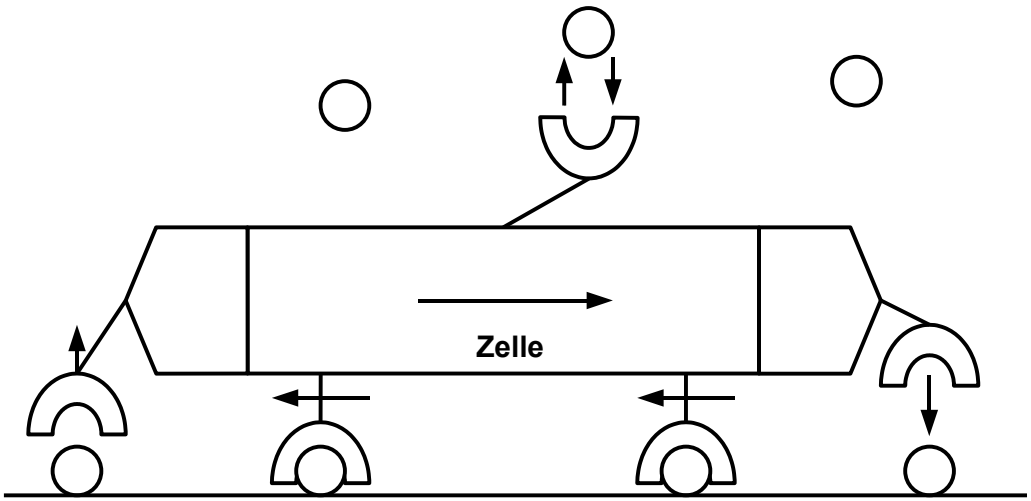
Modeling scales



Goal: multiscale descriptions

Biochemical basis of the microscopic model

- Cells interact with the neighbouring tissue in order to move forward (contact guidance)



- Receptor binding to unsoluble components Q

$$Q + (R_0 - y) \underset{k^-}{\overset{k^+}{\rightleftharpoons}} RQ$$

Notation: $y := RQ$.

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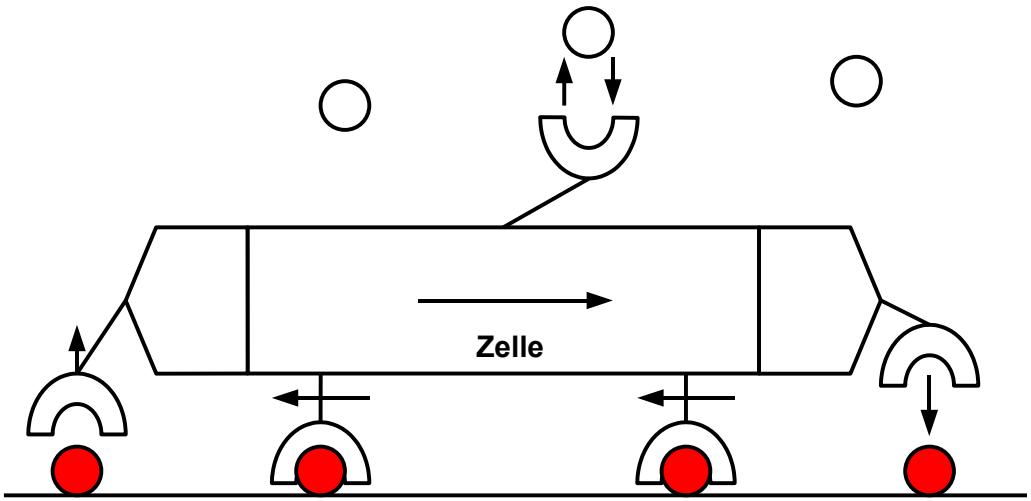

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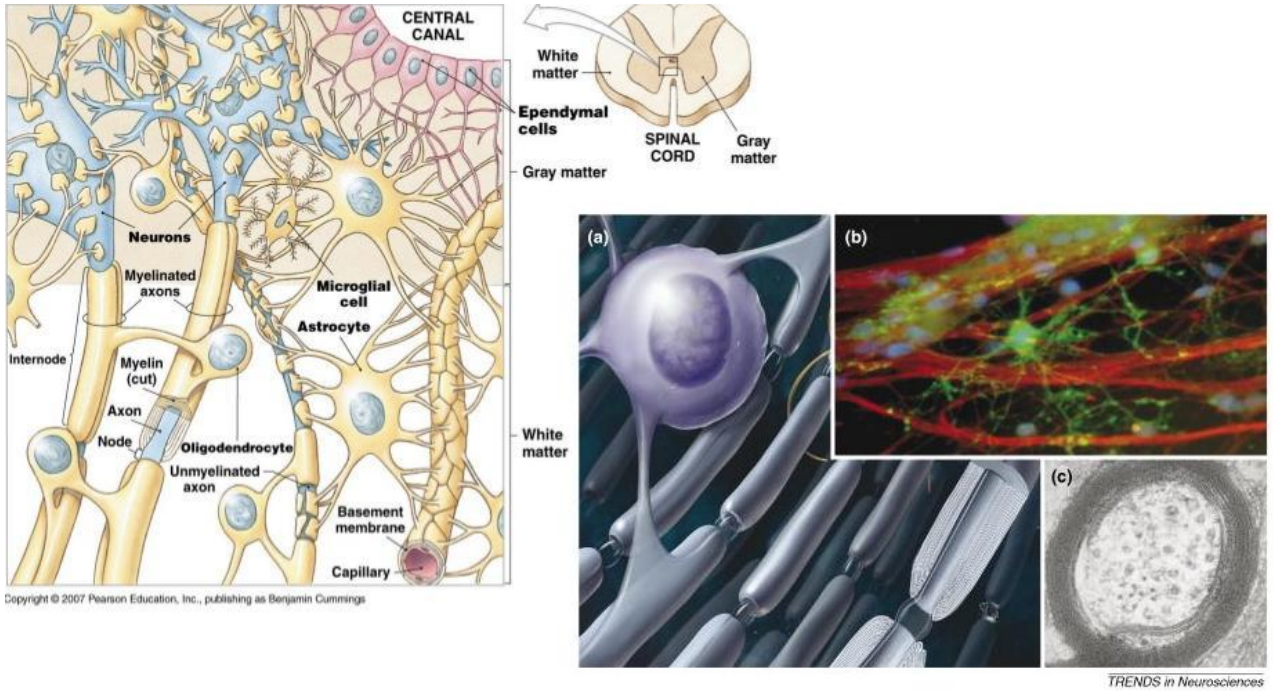
Glioma follow white matter tracts (Giese & Westphal, 1996)

Glia cells and myelinated axon bundles



Individual variables (N cells)

Position	$\mathbf{x}^{(j)} \in \mathbb{R}^n$
Velocity	$\mathbf{v}^{(j)} \in V = s\mathbb{S}^{n-1}$
Receptor state	$y^{(j)} \in Y \ (j = 1, ..., N).$

- Newton's law (in the absence of reorientations)

$$\frac{d\mathbf{x}^{(j)}}{dt} = \mathbf{v}^{(j)} \ , \ \frac{d\mathbf{v}^{(j)}}{dt} = 0$$

- ODE for receptor dynamics

$$\frac{dy^{(j)}}{dt} = G(y^{(j)}, Q(t, \mathbf{x}^{(j)}))$$

Micro-meso model: kinetic transport equations

Wanted: cell density $p(t, \mathbf{x}, \mathbf{v}, y)$ at time t, position $\mathbf{x} \in \mathbb{R}^n$, with velocity $\mathbf{v} \in V \subset \mathbb{R}^n$, and internal state $y \in Y \subseteq [0, R_0]$.

$$\partial_t p + \nabla_{\mathbf{x}} \cdot (\mathbf{v} p) + \partial_y \left(G(y) p \right) = -\lambda(y) p + \lambda(y) \int_V K(\mathbf{x}, \mathbf{v}, \mathbf{v}') p(\mathbf{v}') d\mathbf{v}'$$

We choose $K(\mathbf{x}, \mathbf{v}, \mathbf{v}') = \frac{q(\mathbf{x}, \hat{\mathbf{v}})}{\omega}$, where $q(\mathbf{x}, \theta)$ represents the directional distribution of tissue fibers and $\omega = \int_V q(\hat{\mathbf{v}}) d\mathbf{v} = s^{n-1}$ where $V = s\mathbb{S}^{n-1}$.

- $q(\mathbf{x}, \cdot) \in L^2(\mathbb{S}^{n-1})$, $q(\mathbf{x}, \theta) \geq 0$,
- For unoriented tissue $\mathbb{E}_q(\mathbf{x}) = \int_{\mathbb{S}^{n-1}} \theta q(\mathbf{x}, \theta) d\theta = \mathbf{0}$

Notation for turning operator

$$\mathcal{L}[\lambda(y)]p := -\lambda(y) p + \lambda(y) \frac{q(\mathbf{x}, \hat{\mathbf{v}})}{\omega} \int_V p(\mathbf{v}') d\mathbf{v}'.$$

Subcellular dynamics: $\frac{d}{dt}y(t) = G(y(t), Q(t, \mathbf{x}))$.

$Q(t, \mathbf{x})$: volume fraction of tissue fibres.

$$\dot{y} = k^+(R_0 - y)Q - k^- y.$$

Together with the kinetic transport equation

$$\partial_t p + \nabla_{\mathbf{x}} \cdot (\mathbf{v}p) + \partial_y (G(y)p) = \mathcal{L}[\lambda(y)]p$$

this leads to a micro-meso model (the tissue informations Q and q serve as input).

Issues:

- Proliferation not included.
- Numerical handling too complicated.
- Actually wanted: macroscopic cell density.

Receptor dynamics in a static field

Steady state: $y^* = \frac{k^+ Q R_0}{k^+ Q + k^-}$.

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Turning rate: $\lambda(z) = \lambda_0 - \lambda_1 z \geq 0$, with adequate $\lambda_0,\ \lambda_1 > 0$.

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Wanted: macroscopic cell density

$$M(t, \mathbf{x}) := \iint_{V \times Z} p(t, \mathbf{x}, \mathbf{v}, z) dz d\mathbf{v},$$

where $Z \subseteq [R_0 - y^*, y^*]$ is the shifted domain for internal states.

Notations: $\mathbf{x} = \mathbf{x}_0 + \mathbf{v}t, \qquad f(Q(\mathbf{x})) = \frac{k^+ Q(\mathbf{x}) R_0}{k^+ Q(\mathbf{x}) + k^-}$

Then for any t

$$\frac{d}{dt} f\big(Q(\mathbf{x}_0 + \mathbf{v}t)\big) = f'\big(Q(\mathbf{x}_0 + \mathbf{v}t)\big)\, \mathbf{v} \cdot \nabla Q(\mathbf{x}_0 + \mathbf{v}t)$$

and hence

$$\begin{aligned} \dot{z} &= -(k^+ Q(\mathbf{x}) + k^-) z + f'(Q(\mathbf{x})) \mathbf{v} \cdot \nabla Q(\mathbf{x}) \\ &= -(k^+ Q(\mathbf{x}) + k^-) z + \frac{k^+ k^- R_0}{(k^+ Q(\mathbf{x}) + k^-)^2}\, \mathbf{v} \cdot \nabla Q(\mathbf{x}). \end{aligned}$$

Assume for simplicity that the receptor dynamics equilibrates rapidly, s.t. the system is close to steady-state. Then

$$\partial_t p + \mathbf{v} \cdot \nabla p - \partial_z (((k^+ Q + k^-) z - f'(Q) \mathbf{v} \cdot \nabla Q) p) = \mathcal{L}[\lambda_0] p + \mathcal{L}[\lambda_1] z p$$

Modeling proliferation: interactions with tissue

$$\mathcal{P}(p) = \underbrace{\mu(\mathbf{x}, M, \mathbf{v})}_{\text{growth rate}} \int_Z \chi(\mathbf{x}, z, z') p(t, \mathbf{x}, \mathbf{v}, z') Q(\mathbf{x}) \, dz',$$

$$\text{with } M(t, \mathbf{x}) = \int_V \int_Z p(t, \mathbf{x}, \mathbf{v}, z) \, dz \, d\mathbf{v}.$$

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Then our kinetic transport equation (KTE) becomes

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Remark: KTAP by N. Bellomo assumes cell-cell interactions

$$P_i[p](t, y) = \sum_{h,k=1}^{n} \mu_{hk} \iint_{Y \times Y} \chi^i_{hk}(y', y''; y) p_h(t, y') p_k(t, y'') dy' dy''.$$

Moments

$$m(t,\mathbf{x},\mathbf{v}) = \int_Z p(t,\mathbf{x},\mathbf{v},z)dz,$$

$$M(t,\mathbf{x}) = \iint_{V\times Z} p(t,\mathbf{x},\mathbf{v},z)dzd\mathbf{v}$$

$$m^z(t,\mathbf{x},\mathbf{v}) = \int_Z zp(t,\mathbf{x},\mathbf{v},z)dz,$$

$$M^z(t,\mathbf{x}) = \iint_{V\times Z} zp(t,\mathbf{x},\mathbf{v},z)dzd\mathbf{v}$$

Higher order moments are set to zero, due to the small deviations z from the steady-state y^*.
We assume the data to be compactly supported in the $(\mathbf{x},\mathbf{v},z)$ space; this allows to perform the computations for the subsequent macroscopic scaling.

Macroscopic scaling

- Integrate the KTE w.r.t. z to obtain

$$\partial_t m + \nabla_{\mathbf{x}} \cdot (\mathbf{v} m) = -\lambda_0 m + \lambda_1 m^z + \lambda_0 \frac{q}{\omega} M - \lambda_1 \frac{q}{\omega} M^z + \mu(\mathbf{x}, M, \mathbf{v}) Q(\mathbf{x}) \int_Z \int_Z \chi(\mathbf{x}, z, z') p(z') \, dz' \, dz$$

- Multiply the KTE by z and integrate w.r.t. z to obtain

$$\partial_t m^z + \nabla_{\mathbf{x}} \cdot (\mathbf{v} m^z) = -(k^+ Q + k^- + \lambda_0) m^z + f'(Q) \mathbf{v} \cdot \nabla Q m + \lambda_0 \frac{q}{\omega} M^z + \mu(\mathbf{x}, M, \mathbf{v}) Q(\mathbf{x}) \int_Z \int_Z z \chi(\mathbf{x}, z, z') p(z') \, dz' \, dz.$$

Macroscopic scaling

Parabolic scaling: $\hat{t} = \varepsilon^2 t$, $\hat{\mathbf{x}} = \varepsilon \mathbf{x}$ leads to (drop the hats!):

$$\epsilon^2 \partial_t m + \epsilon \nabla \cdot (\mathbf{v} m) = -\lambda_0 m + \lambda_1 m^z + \lambda_0 \frac{q}{\omega} M - \lambda_1 \frac{q}{\omega} M^z + \epsilon^2 \mu(\mathbf{x}, M, \mathbf{v}) Q(\mathbf{x}) \int_Z \int_Z \chi(\mathbf{x}, z, z') p(z') \, dz' \, dz$$

$$\epsilon^2 \partial_t m^z + \epsilon \nabla \cdot (\mathbf{v} m^z) = -(k^+ Q + k^- + \lambda_0) m^z + \lambda_0 \frac{q}{\omega} M^z + \epsilon f'(Q) \mathbf{v} \cdot \nabla Q m + \epsilon^2 \mu(\mathbf{x}, M, \mathbf{v}) Q(\mathbf{x}) \int_Z \int_Z z \chi(\mathbf{x}, z, z') p(z') \, dz' \, dz.$$

Remark. The proliferation rate is rescaled with ϵ^2 to let it act on the correct new time scale.

Macroscopic scaling

Hilbert expansions of the moments:

$$m = \sum_{k=0}^{\infty} \epsilon^k m_k \qquad M = \sum_{k=0}^{\infty} \epsilon^k M_k$$

$$m^z = \sum_{k=0}^{\infty} \epsilon^k m_k^z \qquad M^z = \sum_{k=0}^{\infty} \epsilon^k M_k^z$$

Collect the coefficients of the powers of ϵ and integrate w.r.t. $\mathbf{v}$ to obtain:

$$m_0 = \frac{q}{\omega} M_0, \qquad m_0^z = 0$$

$$M_0^z = 0, \qquad m_1 = -\frac{1}{\lambda_0}\left(\nabla \cdot \left(\mathbf{v}\frac{q}{\omega} M_0\right) - \lambda_1 m_1^z\right)$$

$$m_1^z = \frac{f'(Q)}{k^+ Q + k^- + \lambda_0} \nabla \cdot \left(\mathbf{v} Q \frac{q}{\omega}\right) M_0,$$

$$M_1 = 0, \qquad M_1^z = 0.$$

Effective equations on macroscale

$$\partial_t M_0 - \nabla \cdot (\mathbb{D}_T(\mathbf{x})\nabla M_0) + \nabla \cdot (g(Q(\mathbf{x}))\mathbb{D}_T(\mathbf{x})\nabla Q(\mathbf{x}) - \mathbf{u}(\mathbf{x}))M_0) = Q(\mathbf{x})\mu(\mathbf{x}, M_0)M_0,$$

with

$$g(Q(\mathbf{x})) = \lambda_1(k^+ Q + k^- + \lambda_0)^{-1} f'(Q(\mathbf{x})), \quad \text{where}$$

$$f(Q(\mathbf{x})) = \frac{k^+ Q(\mathbf{x}) R_0}{k^+ Q(\mathbf{x}) + k^-} \text{ (subcellular level information)},$$

$$\mathbf{u}(\mathbf{x}) = \frac{1}{\lambda_0 \omega} \int_V \mathbf{v} \otimes \mathbf{v} \nabla q \, d\mathbf{v} \quad \text{(drift velocity)}$$

$$\mathbb{D}_T(\mathbf{x}) = \frac{1}{\lambda_0 \omega} \int_V q \mathbf{v} \otimes \mathbf{v} \; d\mathbf{v} \quad \text{(tumor diffusion tensor)}$$

Semilinear advection-diffusion equation $\rightsquigarrow$ globally well posed (with Neumann BCs and adequate ICs).

Determine explicit forms of the coefficients

Choices of $Q(\mathbf{x})$:

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- Fractional anisotropy (FA), from data.

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  Problem: assumes Q to be high where tissue is strongly aligned $\rightsquigarrow$ also true in regions of isotropic (non-aligned) and densely packed tissue??

Determine explicit forms of the coefficients

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- Fractional anisotropy (FA), from data.

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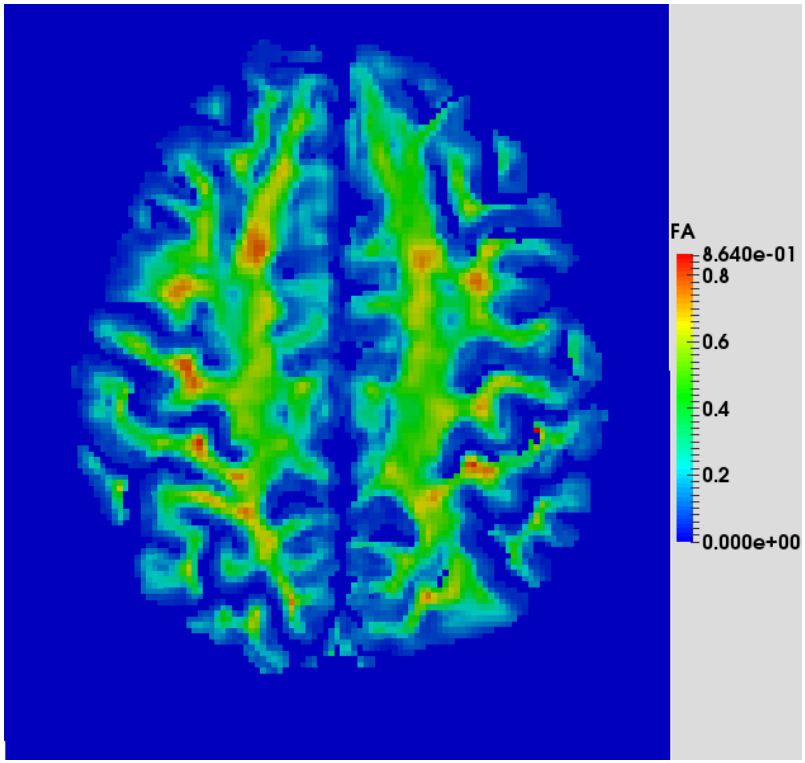
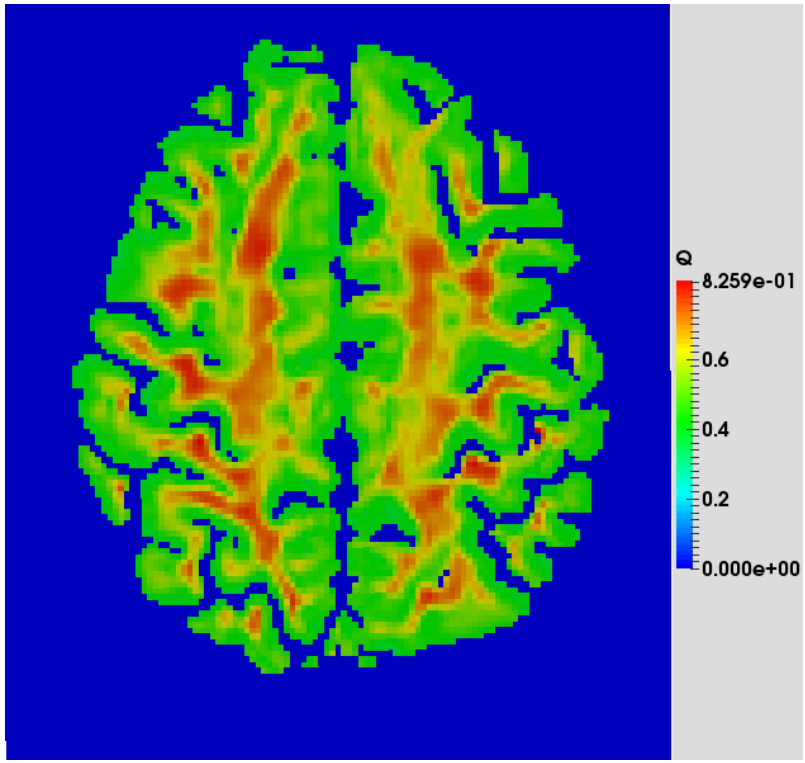
The free volume fraction of one voxel is l_c^3/h^3.

So the occupied volume is $Q = 1 - \frac{l_c^3}{h^3}$.

Volume fraction of tissue fibers



FA



Estimated Q

Determine explicit forms of the coefficients

Choices of $q(\mathbf{x}, \theta)$ ($\theta \in \mathbb{S}^{n-1}$ gives the fiber orientation):

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Choices of $q(\mathbf{x},\theta)$ ($\theta \in \mathbb{S}^{n-1}$ gives the fiber orientation):

- peanut (Hillen): $q(\mathbf{x},\theta) = \frac{n}{|\mathbb{S}^{n-1}|\mathrm{tr}\mathbb{D}_W(\mathbf{x})}\theta^t\mathbb{D}_W(\mathbf{x})\theta$.
  Advantage: very simple, convenient for calculations.
  Drawback: cannot resolve crossings fiber tracts
- bimodal von Mises-Fisher (Painter & Hillen, 2013):
  $q(\mathbf{x},\theta) = \frac{k(\mathbf{x})}{8\pi\sinh(k(\mathbf{x}))}\left(\exp(k(\mathbf{x})\phi(\mathbf{x})\cdot\theta) + \exp(-k(\mathbf{x})\phi(\mathbf{x})\cdot\theta)\right)$
  with $k(\mathbf{x}) = \kappa FA(\mathbf{x})$ and ϕ the leading eigenvector of the water diffusion tensor for each voxel.
  Drawbacks:
  - concentration parameter κ cannot be determined by measurements (ought to be assessed from many different DTI data sets)
  - FA is not satisfactory enough as indicator for anisotropy

Determine explicit forms of the coefficients

- orientation distribution function (ODF):

$$q(\mathbf{x},\theta) = ODF(\theta) := \int_0^\infty \Pi(r\theta) r^2 \, dr,$$

describes the probability of diffusion in direction θ, where $\Pi(r\theta)$: displacement probability of a spatial point in spherical coordinates.
It can be shown (Aganj et al 2010) that

$$q(\mathbf{x},\theta) = \frac{1}{4\pi |\mathbb{D}_W(\mathbf{x})| \left(\theta^t \mathbb{D}_W(\mathbf{x})^{-1} \theta\right)^{\frac{3}{2}}}$$

Advantages:

- available for different medical imaging techniques, including Q-Ball and HARDI;
- allows to use medical data in different forms;
- does not need supplementary parameters which are difficult to assess.

Example: peanut distribution

$$q(\mathbf{x},\theta)=\frac{n}{|\mathbb{S}^{n-1}|\mathrm{tr}\mathbb{D}_W(\mathbf{x})}\theta^t\mathbb{D}_W(\mathbf{x})\theta.$$

Tumor diffusion tensor:

$$\mathbb{D}_T(\mathbf{x})=\frac{s^2}{\omega\lambda_0(n+2)}\left(\mathbb{I}_n+2\frac{\mathbb{D}_W}{\mathrm{tr}\ \mathbb{D}_W}\right),$$

Drift velocity:

$$\mathbf{u}(\mathbf{x})=\frac{s^2}{\omega\lambda_0(n+2)}\left[-\frac{1}{(\mathrm{tr}\ \mathbb{D}_W)^2}\left(\mathrm{tr}\ \mathbb{D}_W\mathbb{I}_n+2\ \mathbb{D}_W\right)\cdot\nabla\mathrm{tr}\ \mathbb{D}_W+\frac{1}{\mathrm{tr}\ \mathbb{D}_W}\left(\nabla\mathrm{tr}\ \mathbb{D}_W+2\nabla\cdot\ \mathbb{D}_W\right)\right].$$

The values of the water diffusion tensor $\mathbb{D}_W$ are known from DTI measurements.

A useful lemma

Lemma (Hillen, 2005)

Consider the mean of velocity tensors $\bar{\mathbf{v}}^{i_1\dots i_k} := \int_V v^{i_1}\dots v^{i_k}\,d\mathbf{v}$

- *If* $k \in \mathbb{N}$ *is odd, then* $\bar{\mathbf{v}}^{i_1\dots i_k} = \mathbf{0},\ \forall\ i_1,\dots,i_k \in \{1,\dots,n\}$.
- *If* $k \in \mathbb{N}$ *is even, then there is a constant* $c_k > 0$ *s.t.*

$$\bar{\mathbf{v}}^{i_1\dots i_k} = s^{k+n-1} c_k \Big(\sum_{\pi(i_1,\dots,i_k)} \delta^{i_{j_1} i_{j_2}} \dots \delta^{i_{j_{k-1}} i_{j_k}} \Big),$$

where the set of all pairs of indices out of $(i_1,\dots,i_k)$ *is*

$$\pi(i_1,\dots,i_k) := \{((i_{j_1}, i_{j_2}),\dots,(i_{j_{k-1}}, i_{j_k}))\ :\ \{j_1,\dots,j_k\} = \{1,\dots,k\}\}.$$

The constants c_k *are given by*

$$c_0 = |\mathbb{S}^{n-1}|, \quad , c_2 = \frac{1}{n}|\mathbb{S}^{n-1}|, \quad , c_k = \frac{c_{k-2}}{k-2+n},\ \text{for } k \geq 4.$$

Setting $\mathbf{v} = s\theta$ with $\theta \in \mathbb{S}^{n-1}$ we get (let $\omega_n := |\mathbb{S}^{n-1}|$)

$$\begin{aligned}
\mathbb{D}_T(\mathbf{x}) &= \frac{1}{\lambda_0 \omega} \int_V \mathbf{v} \otimes \mathbf{v} q d\mathbf{v} \\
&= \frac{s^2}{\omega \lambda_0} \int_{\mathbb{S}^{n-1}} \theta \otimes \theta \frac{n}{\omega_n \mathrm{tr}\mathbb{D}_W(\mathbf{x})} \theta^t \mathbb{D}_W(\mathbf{x}) \theta d\theta \\
&= \frac{ns^2}{\omega \lambda_0 \omega_n \mathrm{tr}\mathbb{D}_W} \int_{\mathbb{S}^{n-1}} \sum_{i,j}^{n} \theta^i \theta^j \sum_{k,l}^{n} \theta^k \theta^l D_w^{kl} d\theta \\
&= \frac{ns^2}{\omega \lambda_0 \omega_n \mathrm{tr}\mathbb{D}_W} \sum_{i,j,k,l}^{n} D_w^{kl} \int_{\mathbb{S}^{n-1}} \theta^i \theta^j \theta^k \theta^l d\theta
\end{aligned}$$

By Lemma

$$\int_{\mathbb{S}^{n-1}} \theta^i\theta^j\theta^k\theta^l d\theta = c_4(\delta^{ij}\delta^{kl}+\delta^{ki}\delta^{lj}+\delta^{kj}\delta^{il})$$
$$= \frac{\omega_n}{n(n+2)}(\delta^{ij}\delta^{kl}+\delta^{ki}\delta^{lj}+\delta^{kj}\delta^{il})$$

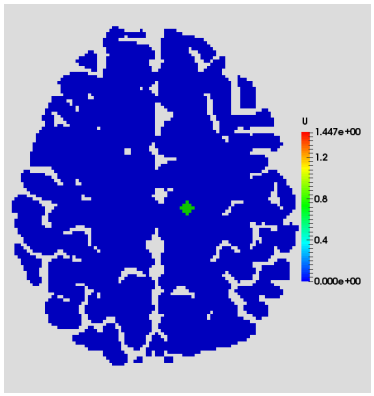
thus

$$\mathbb{D}_T(\mathbf{x}) = \frac{ns^2}{\omega\lambda_0\omega_n \mathrm{tr}\mathbb{D}_W}\frac{\omega_n}{n(n+2)}\sum_{i,j,k,l}^{n} D_w^{kl}(\delta^{ij}\delta^{kl}+\delta^{ki}\delta^{lj}+\delta^{kj}\delta^{il})$$
$$= \frac{s^2}{\omega\lambda_0(n+2)\mathrm{tr}\mathbb{D}_W}\sum_{i,j}^{n}(\mathrm{tr}\mathbb{D}_W\ \delta^{ij}+D_w^{ij}+D_w^{ji}).$$

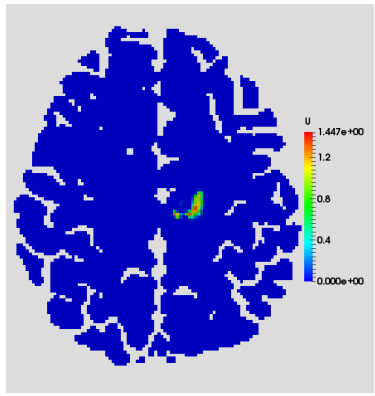
Assume $\mathbb{D}_w$ is symmetric. This implies

$$\mathbb{D}_T(\mathbf{x}) = \frac{s^2}{\omega\lambda_0(n+2)}\left(\mathbb{I}_n + 2\frac{\mathbb{D}_W}{\mathrm{tr}\ \mathbb{D}_W}\right).$$

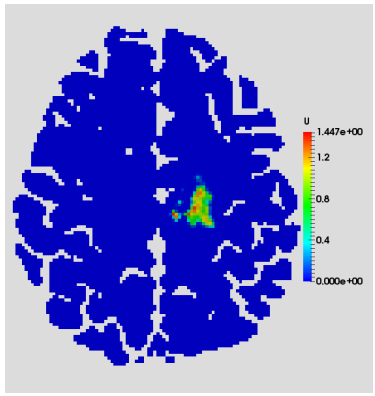
Simulation results (with peanut)



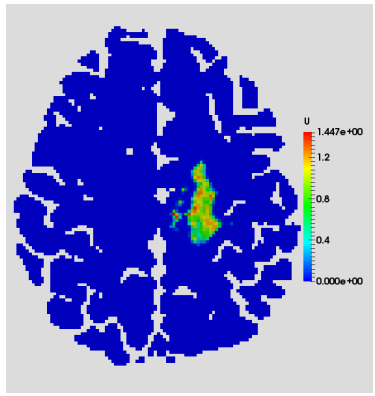
day 0, FA



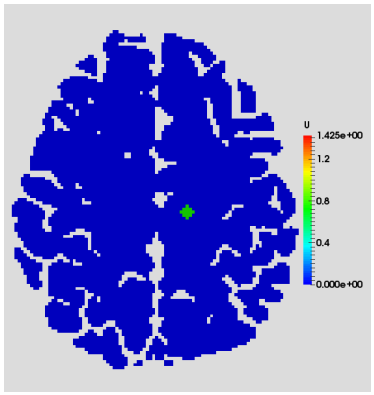
day 200, FA



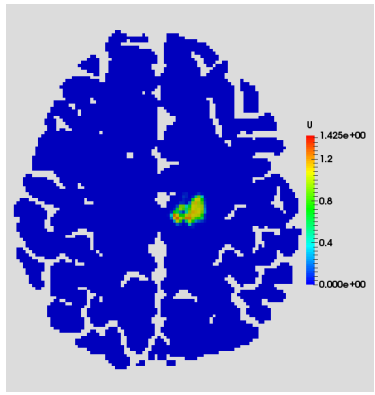
day 400, FA



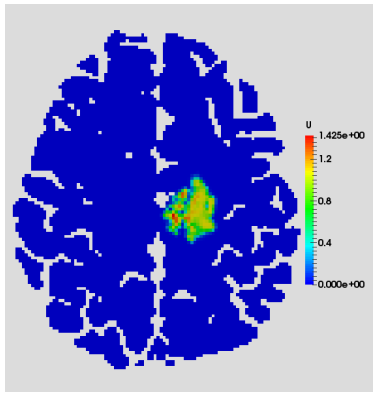
day 600, FA



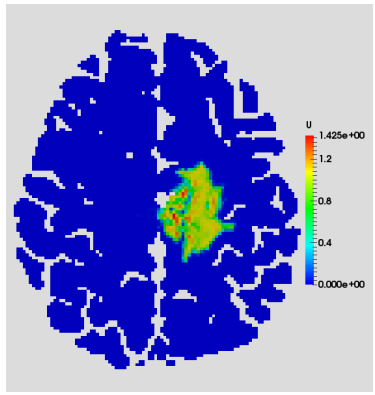
day 0, Q



day 200, Q

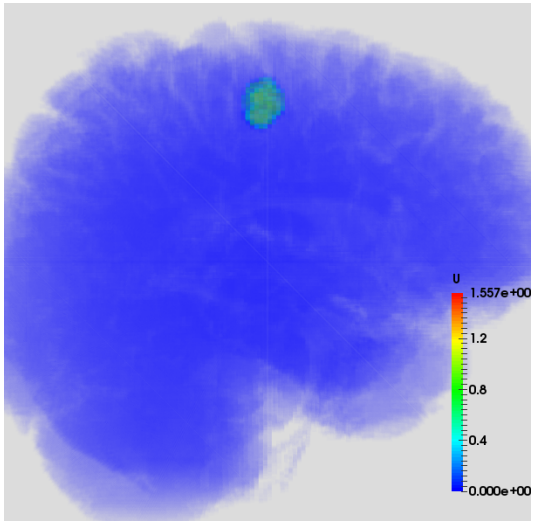


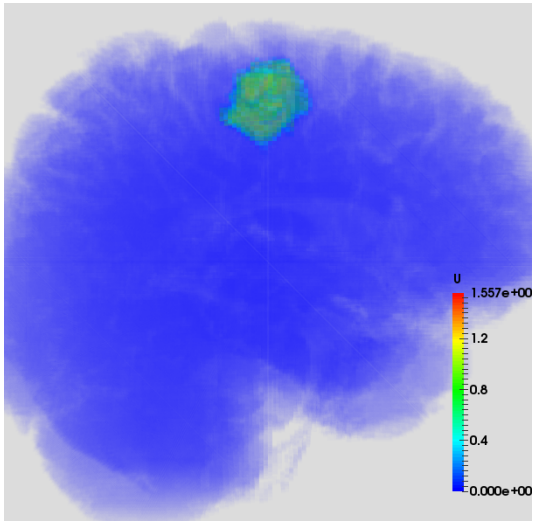
day 400, Q

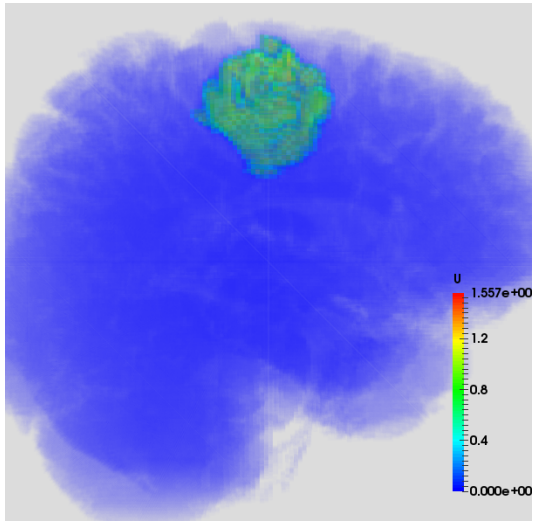


day 600, Q

Simulation results in 3D (with estmated Q and peanut)



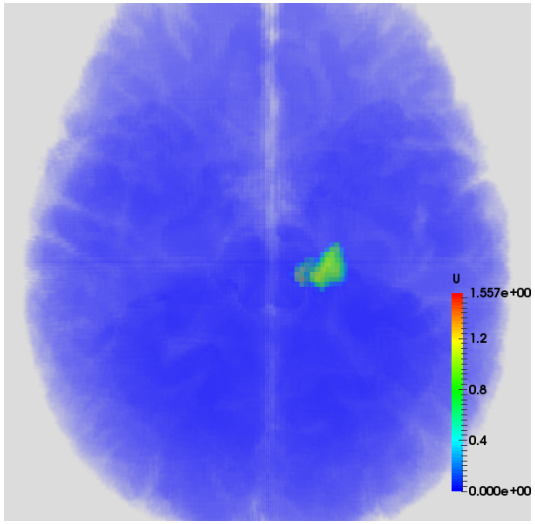


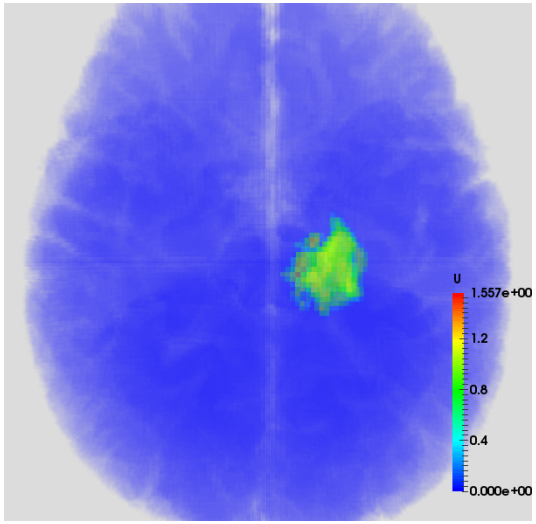


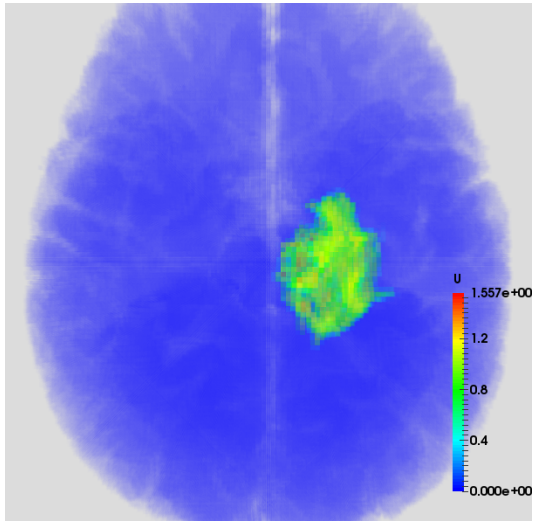
day 200

day 400

day 600

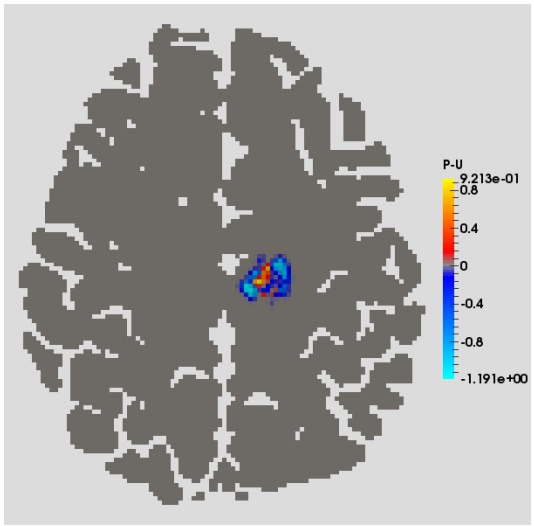




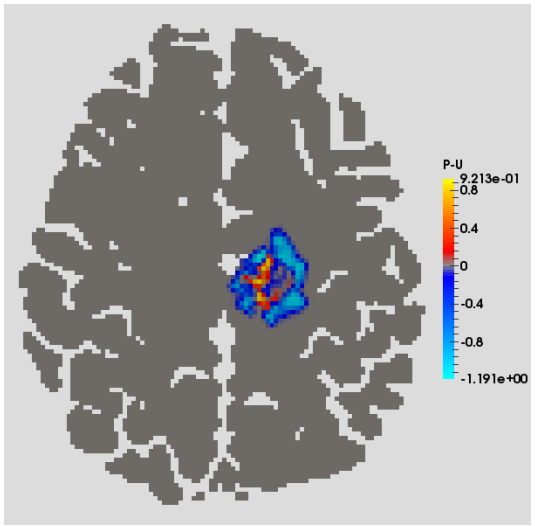


Comparison with a pure macroscopic model

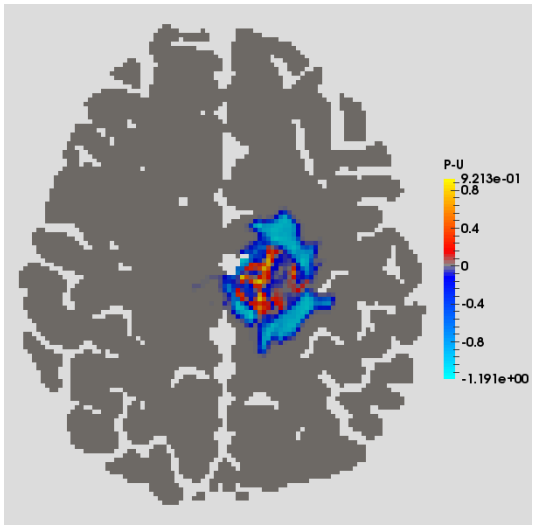
$$\partial_t M_0 - \nabla \cdot (\mathbb{D}_T(\mathbf{x}) \nabla M_0) = Q(\mathbf{x}) \mu(M_0) M_0.$$



day 200, Q



day 400, Q



day 600, Q

Alternative proliferation modeling: Go-or-grow

- Moving cancer cells:

$$\partial_t p + \nabla_{\mathbf{x}} \cdot (\mathbf{v} p) + \partial_y \left(G(y, Q) p \right) = \mathcal{L}[\lambda] p - a(\mathbf{x}) p + \frac{bq}{\omega} r - \ell(N) p$$

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- Non-moving (proliferating) cancer cells:

$$\partial_t r = a(\mathbf{x}) \int_V p d\mathbf{v} - br + g(N) r - \ell(N) r.$$

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- Subcellular (receptor) dynamics:

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- Subcellular (receptor) dynamics:

$$\frac{d}{dt} y(t) = G(y(t), Q),$$

- Total cell density (macroscopic):

$$N(t, \mathbf{x}) = \int_V \int_Y p(t, \mathbf{x}, \mathbf{v}, y) dy \; d\mathbf{v} + \int_Y r(t, \mathbf{x}, y) dy$$

Deducing the effective macroscale equations

Assumptions:

- system is close to steady-state;
- time scale on which birth and death events occur is much slower than the (biased) random walk process.

Wanted moments:

$$M(t,\mathbf{x}) := \iint_{V\times Z} p(t,\mathbf{x},\mathbf{v},z)dzd\mathbf{v}$$

$$w(t,\mathbf{x},\mathbf{v}) := \int_{Z} r(t,\mathbf{x},\mathbf{v},z)dz$$

to recover the macroscopic cell density $N(t,\mathbf{x})$.

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to recover the macroscopic cell density $N(t,\mathbf{x})$.
Parabolic scaling again: $\hat{t}=\varepsilon^2 t$, $\hat{\mathbf{x}}=\varepsilon\mathbf{x}$.

$$g(N)\to\varepsilon^2\hat{g}(\hat{N})$$

$$\ell(N)\to\varepsilon^2\hat{\ell}(\hat{N}).$$

We obtain

$$\partial_t N_0 - \nabla \cdot \left(\frac{1}{\lambda_0 + a(\mathbf{x})} \nabla \cdot \left(\frac{b}{a(\mathbf{x}) + b} \mathbb{D}_T(\mathbf{x}) N_0 \right) \right)$$
$$+ \nabla \cdot \left(\frac{\lambda_1}{\lambda_0 + a(\mathbf{x})} \gamma(\mathbf{x}) f'(Q) \frac{b}{a(\mathbf{x}) + b} \mathbb{D}_T(\mathbf{x}) \cdot \nabla Q \; N_0 \right)$$
$$= \frac{a(\mathbf{x})}{a(\mathbf{x}) + b} g(N_0) N_0 - N_0 \ell(N_0),$$

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$$= \frac{a(\mathbf{x})}{a(\mathbf{x}) + b} g(N_0) N_0 - N_0 \ell(N_0),$$

with the tumor diffusion tensor $\mathbb{D}_T(\mathbf{x}) = \frac{1}{\omega} \int_V \mathbf{v}\mathbf{v}^t q(\hat{\mathbf{v}}) \, d\mathbf{v}$.

Effective equations on the macroscale

With the logistic growth choice $g(N_0) = c_g$, $\ell(N_0) = c_\ell N_0$, where $N_0 = \frac{a+b}{b} M_0$, we get

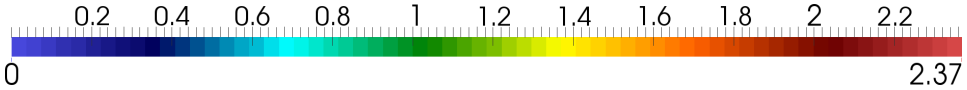
$$\partial_t N_0 - c_D(\mathbf{x})\nabla\nabla\left(\mathbb{D}_T(\mathbf{x})N_0\right) - \lambda_1 c_D(\mathbf{x})\nabla\left(\mathbf{u}(\mathbf{x})N_0\right) = \frac{a}{a+b} c_g N_0 - c_\ell N_0^2,$$

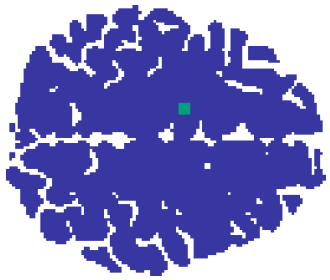
with $c_D(\mathbf{x}) = \frac{b}{(\lambda_0 + a(\mathbf{x}))(a(\mathbf{x})+b)}$ and the drift velocity

$$\mathbf{u}(\mathbf{x}) = \gamma(\mathbf{x}) f'(Q(\mathbf{x}))\mathbb{D}_T(\mathbf{x})\nabla Q,$$

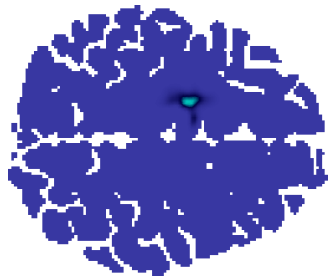
where $\gamma(\mathbf{x}) = (k^+ Q + k^- + \lambda_0 + a)^{-1}$ and $f(Q(\mathbf{x})) = \frac{k^+ Q(\mathbf{x}) R_0}{k^+ Q(\mathbf{x}) + k^-}$.

Simulation results, full multiscale model

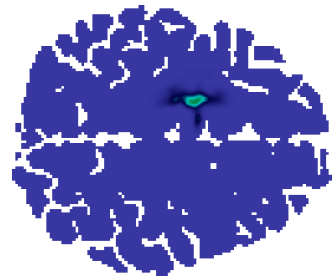




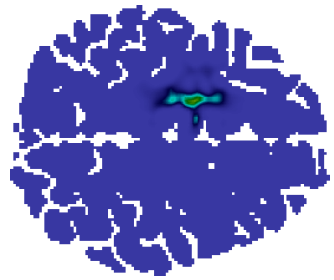
$t = 0$



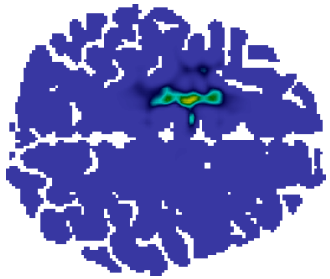
$t = 100 \cdot 10^4 s$



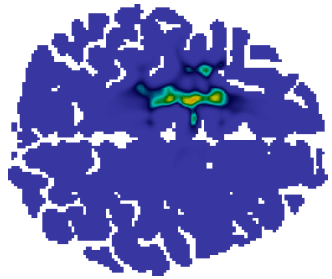
$t = 200 \cdot 10^4 s$



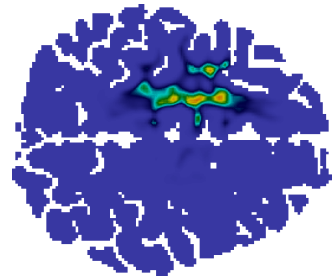
$t = 300 \cdot 10^4 s$



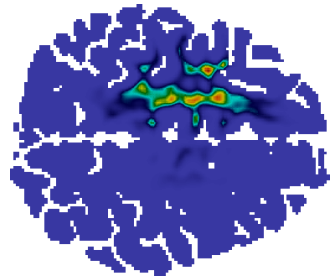
$t = 400 \cdot 10^4 s$



$t = 500 \cdot 10^4 s$

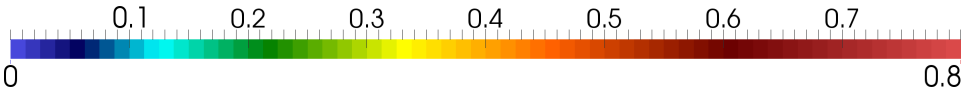


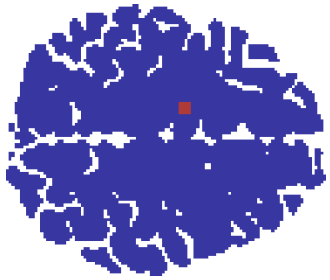
$t = 600 \cdot 10^4 s$



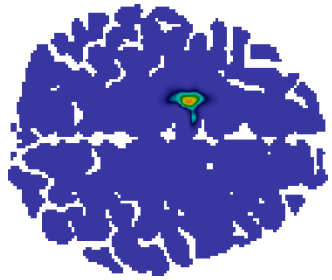
$t = 700 \cdot 10^4 s$

Simulation results, model without proliferation

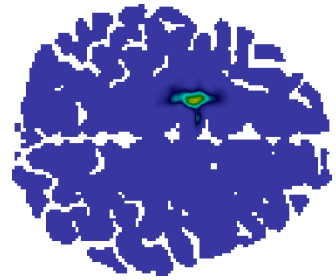




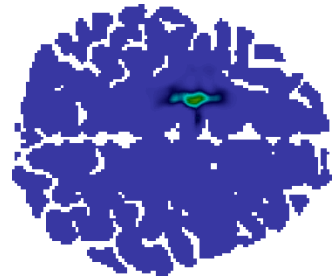
$t = 0$



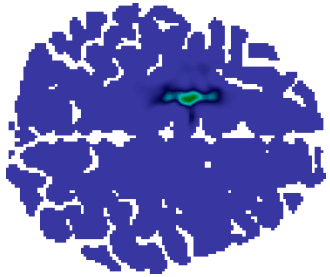
$t = 100 \cdot 10^4 s$



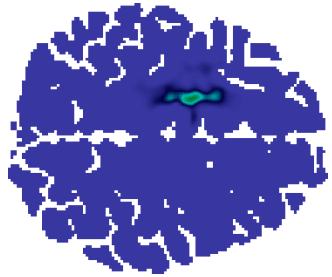
$t = 200 \cdot 10^4 s$



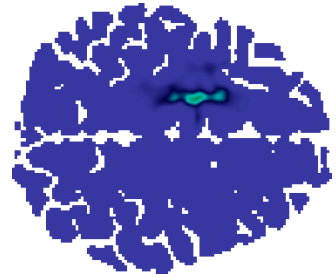
$t = 300 \cdot 10^4 s$



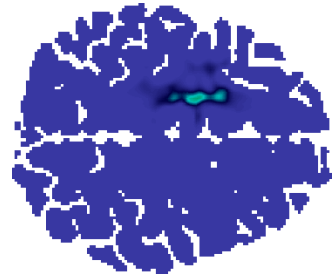
$t = 400 \cdot 10^4 s$



$t = 500 \cdot 10^4 s$



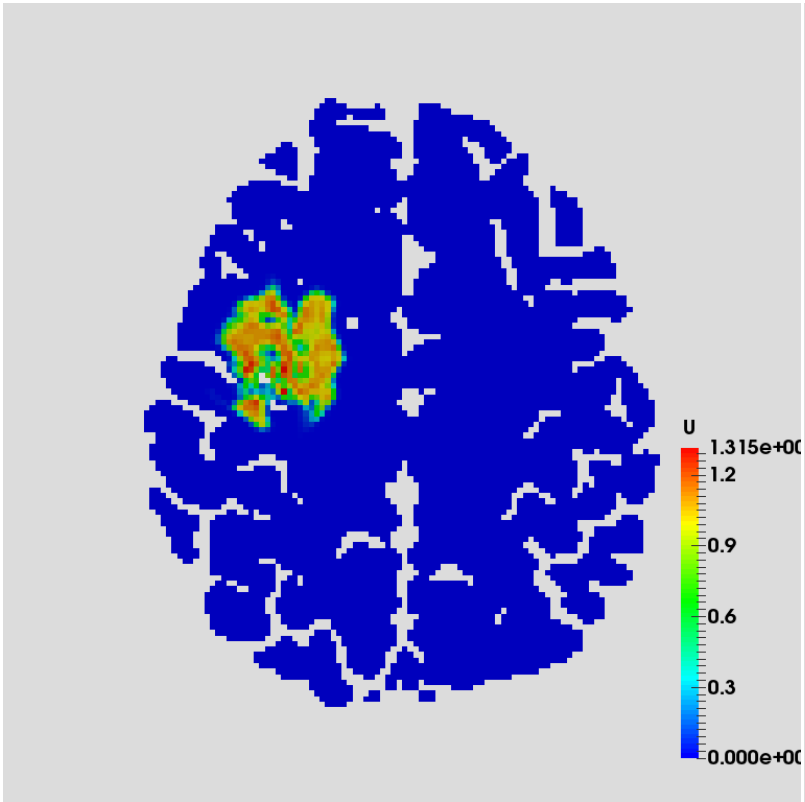
$t = 600 \cdot 10^4 s$



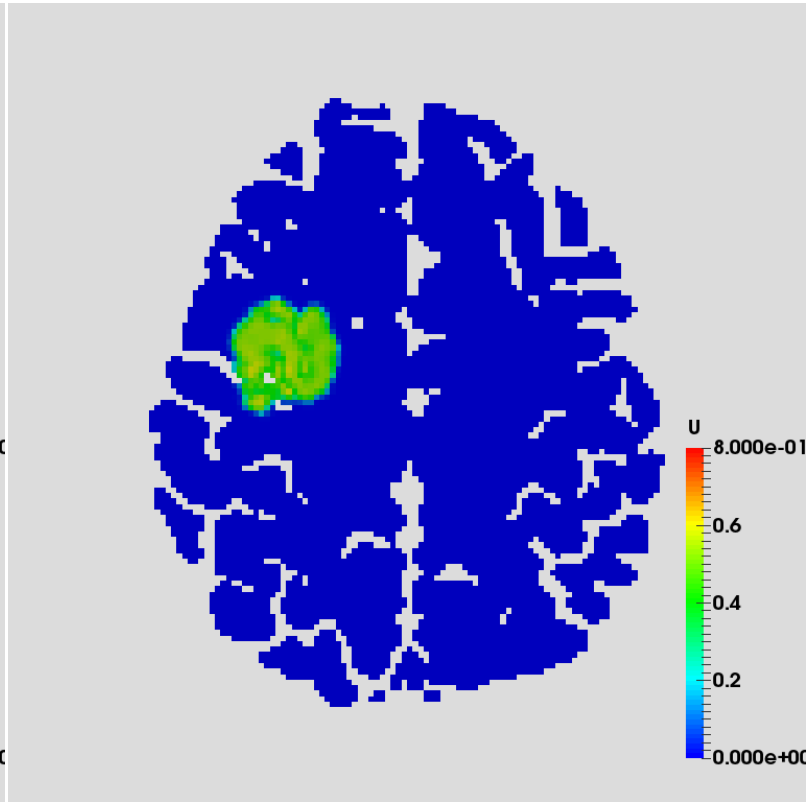
$t = 700 \cdot 10^4 s$

Comparison between the two types of proliferation (time: 1 year, estimated Q, ODF)

Mesoscopic cell-tissue



Go-or-grow



Micro-meso model via go-or-grow, with therapy

- Chemotherapy: inhibition of receptor binding (by peptidomimetics), with dosis d_c
- Radiotherapy: cell killing by ionizing radiation, with dosis d_r

Micro-meso model via go-or-grow, with therapy

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$$\partial_t p + \nabla_{\mathbf{x}} \cdot (\mathbf{v} p) + \partial_y \left(G(y, Q, d_c, d_r) p \right)$$
$$= \mathcal{L}[\lambda(y)]p - a(\mathbf{x}, d_c)p + b(\mathbf{x}, d_c)\frac{q(\hat{\mathbf{v}})}{\omega} r - L_1(N, \alpha_1, d_r)p$$

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$$\partial_t r = a(\mathbf{x}, d_c) \int_V p(\mathbf{v}) d\mathbf{v} - b(\mathbf{x}, d_c) r + g(N, d_c) r - L_2(N, \alpha_2, d_r) r$$

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with $L_l(N, \alpha_l, d_r) := \ell_l(N) + R_l(\alpha_l, d_r)$ $(l = 1, 2)$.

Micro-meso model via go-or-grow, with therapy

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- Radiotherapy: cell killing by ionizing radiation, with dosis d_r

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with $L_l(N, \alpha_l, d_r) := \ell_l(N) + R_l(\alpha_l, d_r)$ $(l = 1, 2)$.

$$\dot{y} = G(y, Q, d_c, d_r) = k^+(d_c)(R_0 - y) Q \; S(\alpha_3, d_r) - k^-(d_c) y.$$

$$R_j(\alpha_j, d_r) = \sum_{i=1}^{\nu} (1 - S(\alpha_j, d_r))\eta_\delta(t - t_i), \qquad t_i \in \text{radiotherapy},$$

supp $\eta_\delta \subset (-\delta, \delta)$, $\delta << 1$, $j = 1, 2, 3$.

Survival fractions (LQ model): $S(\alpha_j, d_r) = \exp(-\alpha_j d_r - \beta_j d_r^2)$.

For ν fractions, each of dosis $\hat{d}_r$:
$S(\alpha_j, d_r) = \exp(-\nu(\alpha_j \hat{d}_r + \beta_j \hat{d}_r^2)) = \exp(-\alpha_j d_r(1 + \hat{d}_r/(\alpha_j/\beta_j)))$.

- α_j represents lethal lesions produced by a single radiation track ($\alpha_j d_r$, cell kill per Gy)
- β_j characterizes lethal lesions produced by two radiation tracks ($\beta_j d_r^2$, cell kill per Gy^2)
- $\frac{\alpha_j}{\beta_j}$: radiation sensitivity, correlates with cell cycle length

Effective equation on macroscale

Remember $N(t,\mathbf{x}) = \int_V \int_Y p(t,\mathbf{x},\mathbf{v},y)dy\ d\mathbf{v} + \int_Y r(t,\mathbf{x},y)dy.$

Effective equation on macroscale

Remember $N(t,\mathbf{x}) = \int_V \int_Y p(t,\mathbf{x},\mathbf{v},y)dy\ d\mathbf{v} + \int_Y r(t,\mathbf{x},y)dy$.

$$\partial_t N_0 - \nabla\cdot\left(\frac{1}{\lambda_0+a}\nabla\cdot\left(\frac{b}{a+b}\mathbb{D}_T(\mathbf{x})N_0\right)\right)$$
$$+\nabla\cdot\left(\frac{\lambda_1 f'(Q)}{\gamma(\mathbf{x})}\frac{b}{(\lambda_0+a\ )(b\ +a\ )}\mathbb{D}_T(\mathbf{x})\nabla QN_0\right)$$
$$=\left((g(N_0)-L_2(N_0))\frac{a}{a\ +b}-L_1(N_0)\frac{b}{a\ +b}\right)N_0,$$

Effective equation on macroscale

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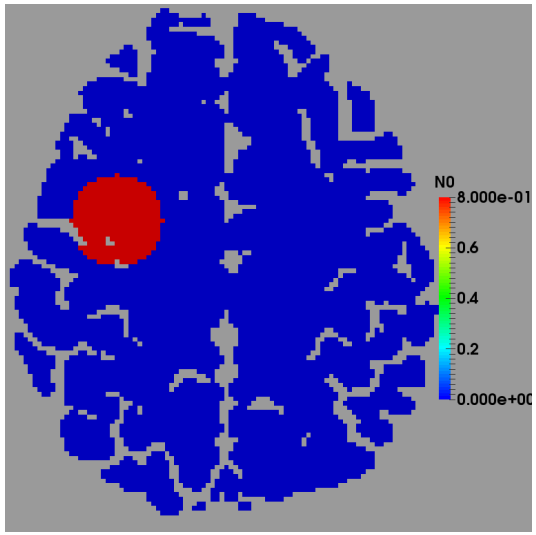
$$=\left((g(N_0)-L_2(N_0))\frac{a}{a\ +b}-L_1(N_0)\frac{b}{a\ +b}\right)N_0,$$

where $\gamma(\mathbf{x}) := k^+QS + k^- + \lambda_0 + a$.

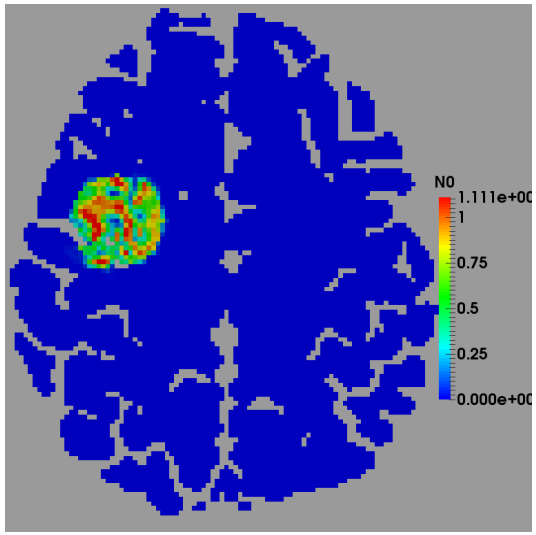
Therapy strategies

- Strategy 1: resection (2 weeks after start), no further therapy.
- Strategy 2: resection (2 weeks after start), followed after 3 weeks by radiotherapy (weekends excluded) for 6 weeks.
- Strategy 3: resection (2 weeks after start), followed after 3 weeks by concurrent chemotherapy and radiotherapy (weekends excluded) for 6 weeks.

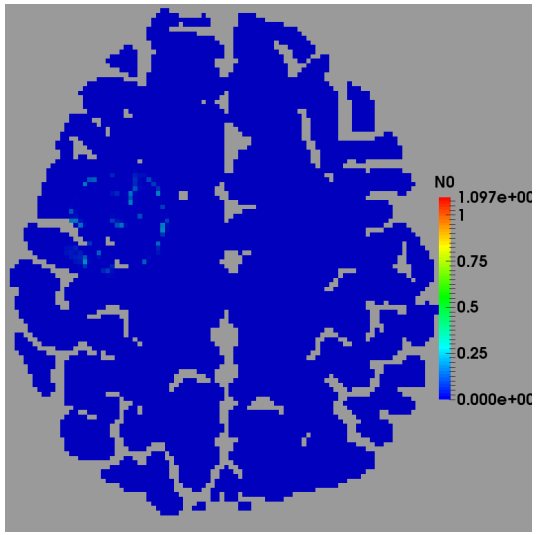
Results



start

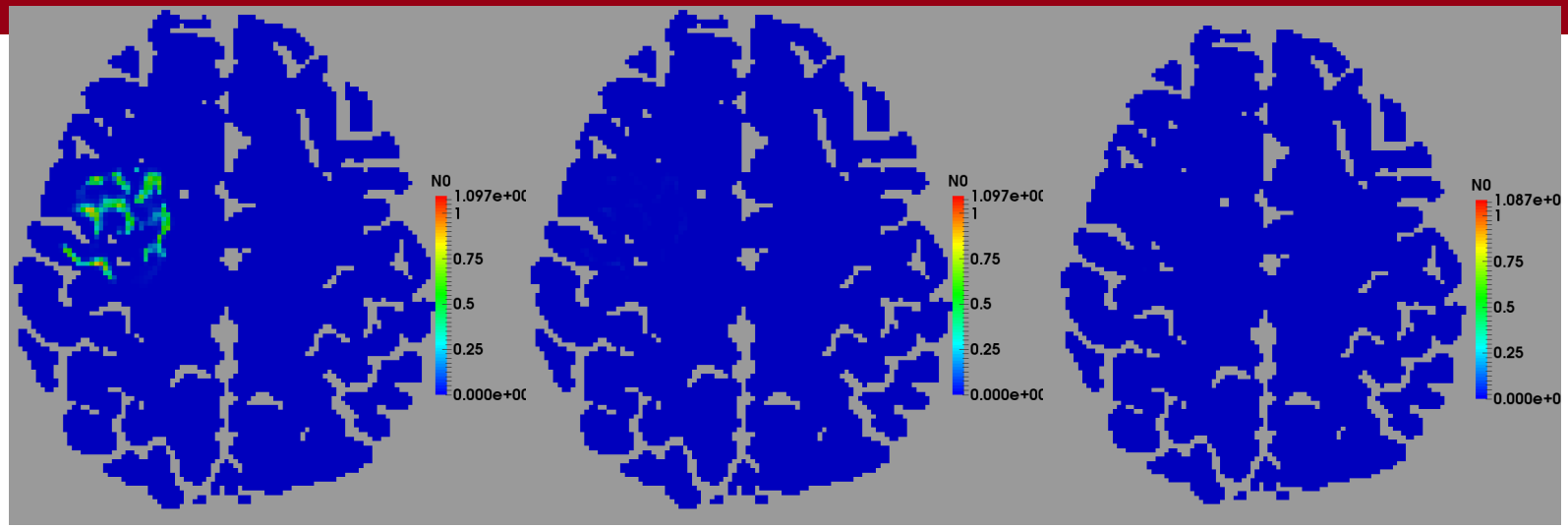


before resection

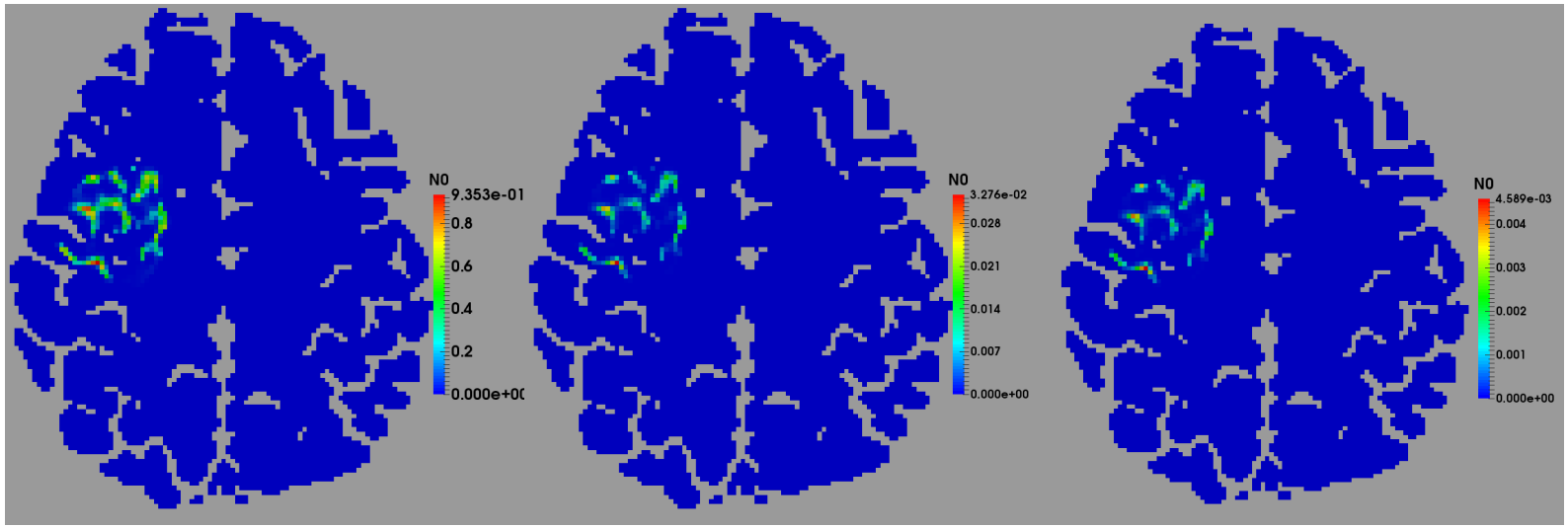


after resection

Results

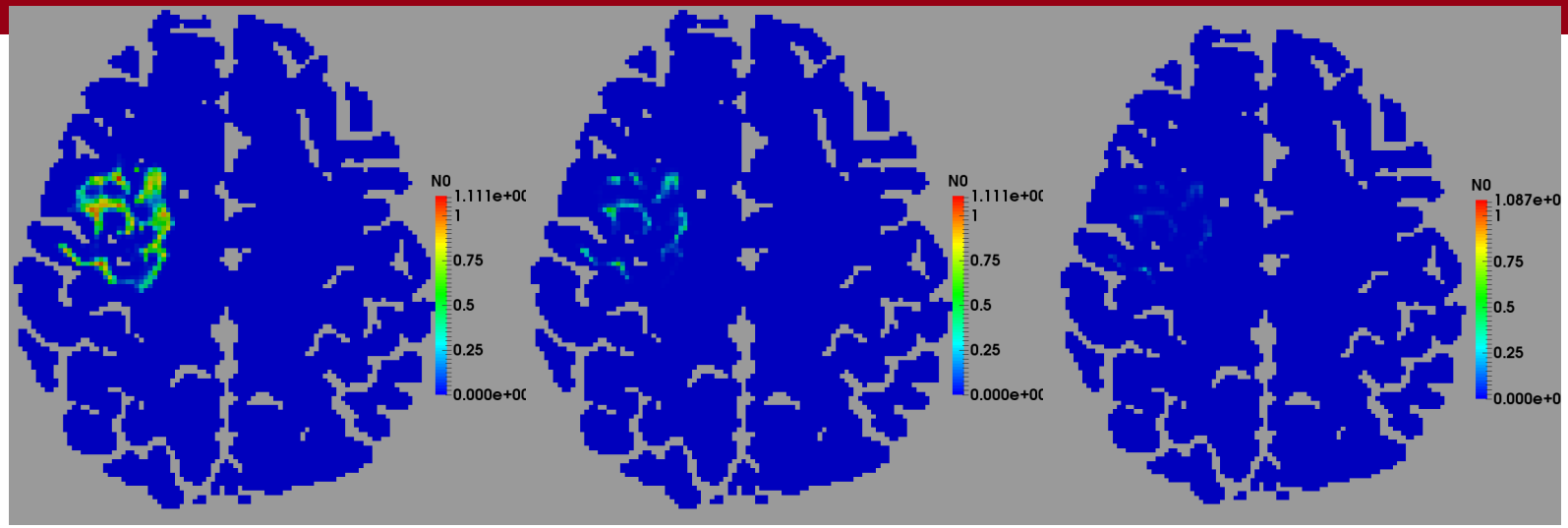


end of therapy

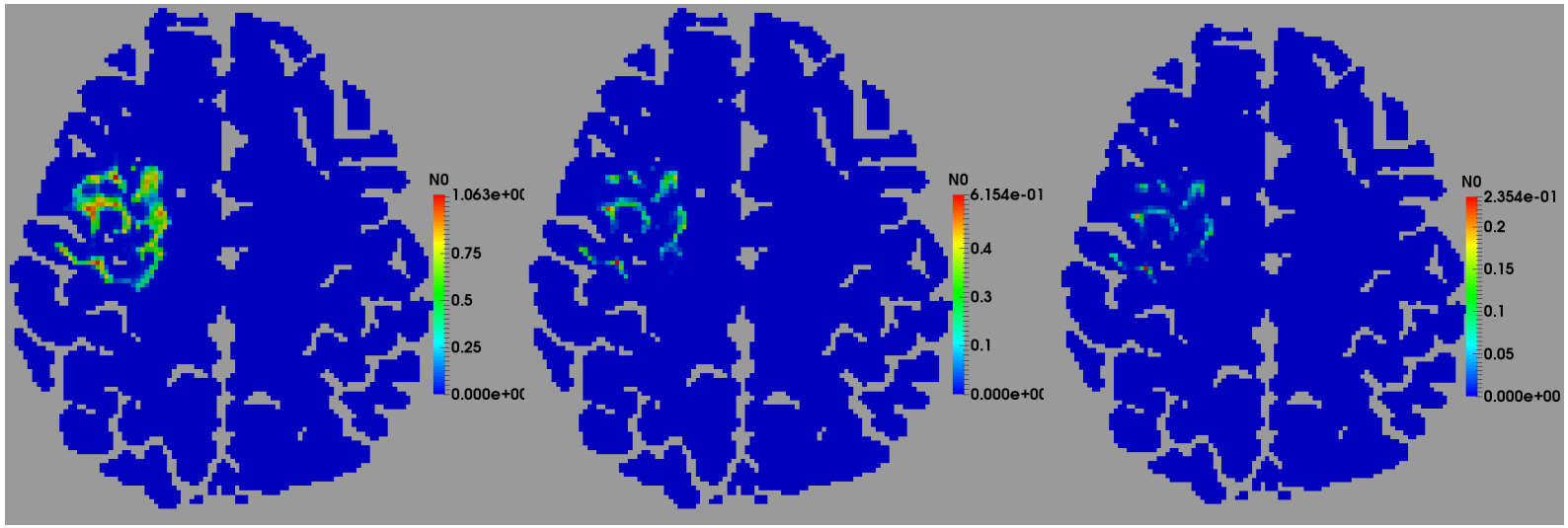


end of therapy, scaled

Results



follow-up after two months



follow-up, scaled

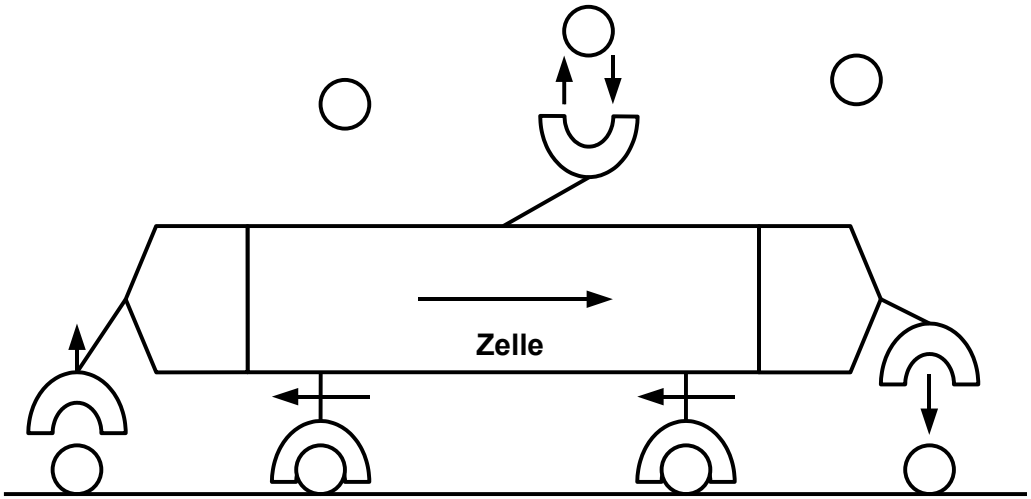
Moving on...

Goal: Multiscale model with tactic reorientations and tissue degradation.

- Involve on the mesolevel both hapto- and chemotaxis to describe cell reorientations $\rightsquigarrow$ more complex subcellular dynamics.
- Model tissue degradation dependent on direction of cell motion (mesolevel description).

Subcellular dynamics revisited

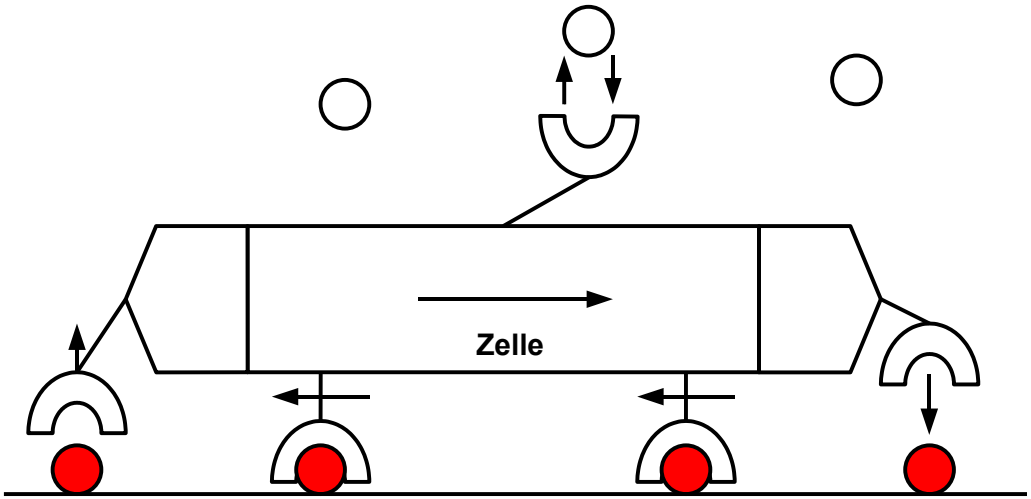
- Cells interact with the neighbouring tissue in order to move forward (contact guidance)



- Integrin receptor binding:

Subcellular dynamics revisited

- Cells interact with the neighbouring tissue in order to move forward (contact guidance)



- to insoluble components Q

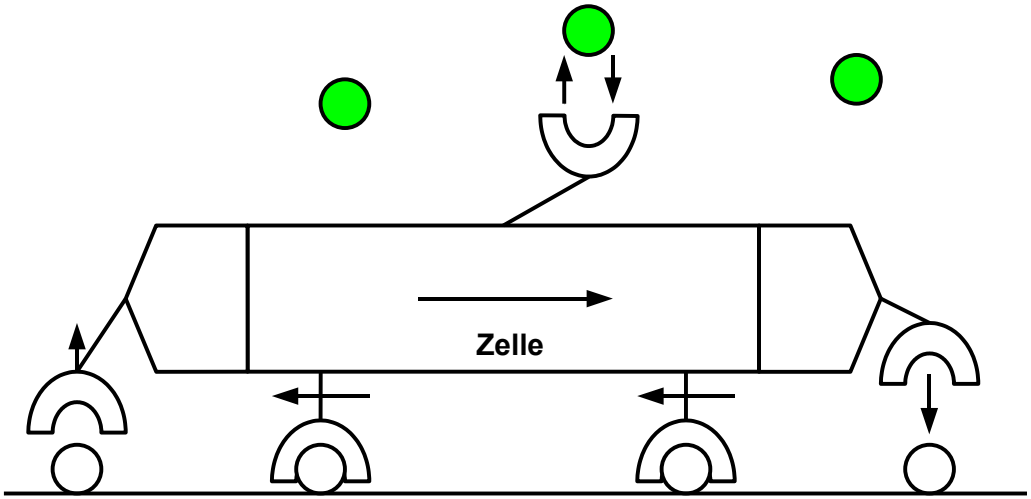
- Integrin receptor binding:

$$Q + (R_0 - y_1 - y_2) \underset{k_1'}{\overset{k_1}{\rightleftharpoons}} RQ$$

Notations: $y_1 := RQ$, $y_2 := RL$.

Subcellular dynamics revisited

- Cells interact with the neighbouring tissue in order to move forward (contact guidance)



- Integrin receptor binding:
  - to insoluble components Q
  - to soluble components L

$$Q + (R_0 - y_1 - y_2) \underset{k_1'}{\overset{k_1}{\rightleftharpoons}} RQ \qquad L + (R_0 - y_1 - y_2) \underset{k_2'}{\overset{k_2}{\rightleftharpoons}} RL$$

Notations: $y_1 := RQ$, $y_2 := RL$.

ODE for receptor dynamics ($j = 1, \dots, N$, N: number of cells)

$$\frac{d\mathbf{y}^{(j)}}{dt} = \underbrace{\begin{pmatrix} k_1(R_0 - y_1 - y_2)Q(t, \mathbf{x}^{(j)}) - k_1' y_1 \\ k_2(R_0 - y_1 - y_2)L(t, \mathbf{x}^{(j)}) - k_2' y_2 \end{pmatrix}}_{\mathbf{G}(\mathbf{y}^{(j)}, Q(t,\mathbf{x}^{(j)}), L(t,\mathbf{x}^{(j)}))}$$

R_0 total receptor concentration

y_1, y_2 concentration of receptors bound to $\bar{Q}$, resp. L.

In the absence of reorientations:

$$\frac{\partial p}{\partial t} + \underbrace{\mathbf{v} \cdot \nabla_{\mathbf{x}} p}_{\text{Transport with velocity } \mathbf{v}} + \underbrace{\nabla_{\mathbf{y}} \cdot (\mathbf{G}(\mathbf{y}, Q, L)p)}_{\text{Receptor dynamics}} = 0$$

Changes in orientation (and speed) have to be incorporated in the right-hand side.

Reorientation mechanisms - Haptotaxis

- Cells tend to align their movement direction to the direction of the fibers in the tissue.
- Haptotaxis:

$$\mathcal{H}(p,q) = \mathcal{H}_+(p,q) - \mathcal{H}_-(p,q).$$

  - Gain term

$$\mathcal{H}_+(p,q) = \int_V \int_{\mathbb{S}^{n-1}} \eta_h(t,\mathbf{x},\mathbf{v}',\mathbf{y})\psi(\mathbf{v};\mathbf{v}',\theta')p(\mathbf{v}')Q(\theta')d\mathbf{v}'d\theta'.$$

  - Loss term

$$\mathcal{H}_-(p,q) = f(\mathbf{v})\int_V \int_{\mathbb{S}^{n-1}} \eta_h(t,\mathbf{x},\mathbf{v},\mathbf{y})\psi(\mathbf{v}';\mathbf{v},\theta')q(\theta')d\mathbf{v}'d\theta'.$$

η_h is the rate for haptotactic reorientation
$\psi(\mathbf{v};\mathbf{v}',\theta')$ probability kernel for a reorientation $\mathbf{v}' \to \mathbf{v}$ after encounter with a fibre in direction θ'. E.g.,

$$\psi(\mathbf{v};\mathbf{v}',\theta') \;=\; |\hat{\mathbf{v}}'\cdot\theta'|\, K_H^{(1)}(\mathbf{v},\theta') + (1-|\hat{\mathbf{v}}'\cdot\theta'|)\, K_H^{(2)}(\mathbf{v},\mathbf{v}').$$

Reorientation mechanisms - Chemotaxis

- Chemotaxis: $\mathcal{C} = \mathcal{C}_+ - \mathcal{C}_-$.
  - Gain term

$$\mathcal{C}_+(p, L, \mathbf{y}) = \int_V \eta_c(t, \mathbf{x}, \mathbf{v}', \mathbf{y}) K[L](\mathbf{v}, \mathbf{v}', \mathbf{y}) p(\mathbf{v}') d\mathbf{v}'.$$

  - Loss term

$$\mathcal{C}_-(p, L, \mathbf{y}) = \eta_c(t, \mathbf{x}, \mathbf{v}, \mathbf{y}) p(\mathbf{v}).$$

  - Turning kernel

$$K[L](\mathbf{v}, \mathbf{v}', \mathbf{y}) = \alpha_1(\mathbf{y}) K(\mathbf{v}, \mathbf{v}') + \alpha_2(\mathbf{y}) K(\mathbf{v}, \nabla L).$$

$\alpha_1, \alpha_2 : Y \to [0, 1]$ with $\alpha_1(\mathbf{y}) + \alpha_2(\mathbf{y}) = 1$, $\forall \mathbf{y} \in Y$.

Full mesoscopic equation for cells

$$\frac{\partial p}{\partial t} + \underbrace{\mathbf{v}\cdot\nabla_{\mathbf{x}} p}_{\text{Transport with velocity } \mathbf{v}} + \underbrace{\nabla_{\mathbf{y}}\cdot(\mathbf{G}(\mathbf{y},Q,L)p)}_{\text{Receptor dynamics}} = \underbrace{\mathcal{H}(p,q)+\mathcal{C}(p,L)}_{\text{Changes in velocity}}$$

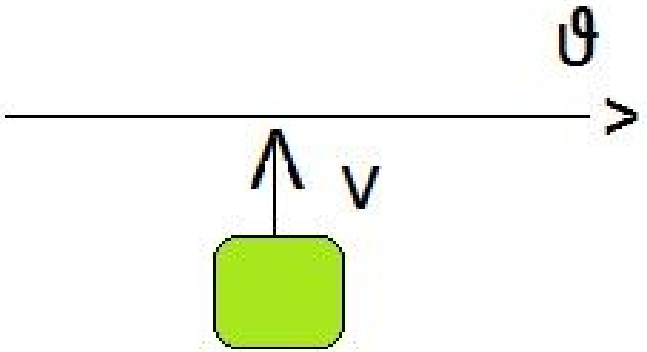
The macroscopic population density at time t and position $\mathbf{x}$ is given by

$$M(t,\mathbf{x}) := \int_Y \int_V p(t,\mathbf{x},\mathbf{v},\mathbf{y})\,d\mathbf{v}\,d\mathbf{y}$$

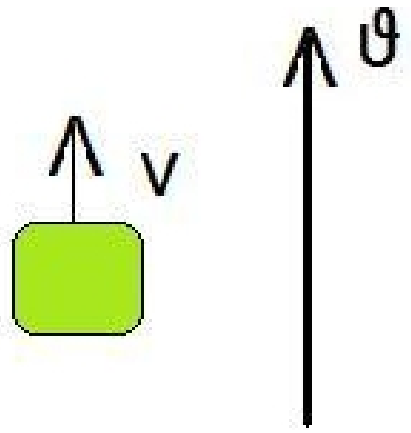
Tissue modification (Hillen 2005)

- Cell motion is both based on and can be impeded by ECM;
- Cells cut ECM-fibres using enzymes (proteolysis);
- Mean projection of movement direction on fiber orientation:

$$\Pi[p](t,\mathbf{x},\theta) = \frac{1}{M(t,\mathbf{x})} \begin{cases} \int_Y \int_V |\theta \cdot \hat{\mathbf{v}}| p(t,\mathbf{x},\mathbf{v},\mathbf{y}) d\mathbf{v} d\mathbf{y}, & \text{undirected} \\ \int_Y \int_V \theta \cdot \hat{\mathbf{v}}\ p(t,\mathbf{x},\mathbf{v},\mathbf{y}) d\mathbf{v} d\mathbf{y}, & \text{directed} \end{cases}$$



(a) $1 - \Pi = 1$ high proteolytic activity



(b) $1 - \Pi = 0$ no proteolytic activity

Tissue degradation and production of soluble ligand

- Tissue equation based on mass-action kinetics:

$$\frac{\partial q}{\partial t} = \kappa(\Pi[p](t,\mathbf{x},\theta) - 1)M(t,\mathbf{x})q(t,\mathbf{x},\theta).$$

- Tissue degradation leads to production of a soluble ligand which then diffuses and degrades:

$$\frac{\partial L}{\partial t} = D_L \triangle L + \int_{\mathbb{S}^{n-1}} \kappa(1-\Pi[p](t,\mathbf{x},\theta))M(t,\mathbf{x})q(t,\mathbf{x},\theta)d\theta - r_L L$$

D_L: diffusion coefficient of L
r_L: degradation rate of L
κ: rate for proteolytic degradation of q.

Multiscale cell migration model

- **Cells** $p : [0, T] \times \mathbb{R}^n \times V \times Y \to \mathbb{R}$

$$\boxed{\frac{\partial p}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} p + \nabla_{\mathbf{y}} \cdot (\mathbf{G}(\mathbf{y}, Q, L)p) = \mathcal{H}(p, q) + \mathcal{C}(p, \nabla L)}$$

with $p(0, \mathbf{x}, \mathbf{v}, \mathbf{y}) = p_0(\mathbf{x}, \mathbf{v}, \mathbf{y})$ and $\partial_n p = 0$ on ∂Y.

- **Tissue** $q : [0, T] \times \mathbb{R}^n \times \mathbb{S}^{n-1} \to \mathbb{R}$

$$\boxed{\frac{\partial q}{\partial t} = \kappa(\Pi[p](t, \mathbf{x}, \theta) - 1)M(t, \mathbf{x})q(t, \mathbf{x}, \theta)}$$

with $q(0, \mathbf{x}, \theta) = q_0(\mathbf{x}, \theta)$.

- **Soluble product of fibre cutting** $L : [0, T] \times \mathbb{R}^n \to \mathbb{R}$

$$\boxed{\frac{\partial L}{\partial t} = D_L \triangle L + \int_{\mathbb{S}^{n-1}} \kappa(1 - \Pi[p](t, \mathbf{x}, \theta))M(t, \mathbf{x})q(t, \mathbf{x}, \theta)d\theta - r_L L}$$

with $L(0, \mathbf{x}) = L_0(\mathbf{x}) = 0$.

Global existence and uniqueness

Theorem (Kelkel & S. 2012)

There exists a global unique solution of the multiscale model in $L^1 \cap L^\infty$.

Theorem (Lorenz & S. 2014)

There exists a global unique solution of a more general multiscale model (allowing e.g., for nonlocal cell-tissue interactions) in L^2.

Nonlocal cell-tissue interactions:

$$\frac{\partial q}{\partial t} = \kappa \, (\Pi[p](t,\mathbf{x},\theta) - 1) \; M(t,\mathbf{x}) \; \mathcal{K} \star \frac{q(t,\mathbf{x},\theta)}{1+\gamma_Q \, |q(t,\mathbf{x},\theta)|},$$

$\mathcal{K} \star \phi$: convolution of a given spatial kernel $\mathcal{K}$ with a function ϕ.

Conclusions

Multiscale models:

- allow testing the influence of many factors;
- are more difficult to handle numerically and analytically:
  - high dimensionality;
  - different scales both w.r.t. space and time;
  - highly nonlinear coupling;

Conclusions

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Micro-meso-macro models:

- Other cells (no tissue): Erban & Othmer (Multiscale Model. Simul. 2005); Xue & Othmer (SIAP 2009).
- Tumor cells (moving in tissue networks): Bellomo et al. (M3AS 2010); Kelkel & S. (MBE 2011); Kelkel & S. (M3AS 2012); Lorenz & S. (M3AS 2014); Engwer, Hillen, Knappitsch, S. (JMB 2015); Engwer, Hunt & S. (IMA Math. Med. Biol. 2015); Engwer, Knappitsch & S. (MBE 2015); Hunt & S. (2015).

Outlook

- Goal: predict better CTVs and PTVs to allow for patient-specific treatment planning.
- tissue degradation modeled on mesoscale $\rightsquigarrow$ chemotaxis equations on macroscale?
- lymph and blood angiogenesis;
- cell-cell interactions $\rightsquigarrow$ effects on proliferation & invasion; can we recover macroscopic adhesion models?
- effects of hypoxia, acid-mediated invasion, tumor heterogeneity w.r.t. treatment response.