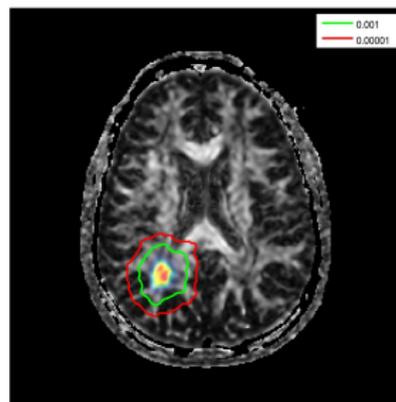


Mathematical Modelling with Fully Anisotropic Diffusion

Thomas Hillen (with K.J. Painter and M. Winkler)

University of Alberta



Fully Anisotropic Diffusion

$$u_t = \frac{\partial}{\partial x_i} \frac{\partial}{\partial x_j} (D^{ij}(x)u), \quad D(x) \in \mathbb{R}^{n \times n}.$$

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- Where does this model come from?
- What are mathematical properties?

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- Where does this model come from?
- What are mathematical properties?
- What can it be used for?

Outline

(1) Model derivations

(2) Mesenchymal motion

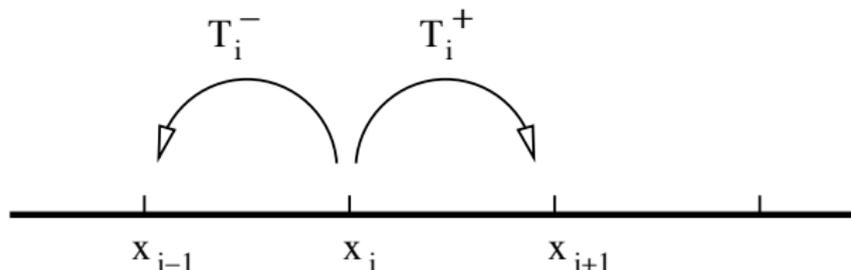
(3) Brain Tumors

(4) Wolf Movement

(5) A Blow-up result

(6) Conclusions

(1.1) Random walk



$u_i(t)$: Probability to find a particle at x_i at time t .

T_i^\pm : Transitional probabilities

Master equation:

$$\frac{du_i}{dt} = T_{i-1}^+ u_{i-1} + T_{i+1}^- u_{i+1} - (T_i^+ + T_i^-) u_i.$$

Three cases

1. look locally: $T_i^\pm(x) = (\Delta x)^{-2} T(x_i)$

$$u_t \approx (Tu)_{xx}$$

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2. look ahead: $T_i^\pm(x) = (\Delta x)^{-2} T(x_{i\pm 1})$

$$u_t \approx (Tu_x - T_x u)_x$$

3. look ahead half way $T_i^\pm(x) = (\Delta x)^{-2} T(x_{i\pm 1/2})$

$$u_t \approx (Tu_x)_x$$

(1.2) Ideal free distribution

“Species distribute themselves such that the fitness of each individual is the same.”
(Fretwell, Lucas, 1970)

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- Let $\mu(x)$, $x \in \mathbb{R}$ describe the resource landscape.
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(1.2) Ideal free distribution

“Species distribute themselves such that the fitness of each individual is the same.”
(Fretwell, Lucas, 1970)

- Let $\mu(x)$, $x \in \mathbb{R}$ describe the resource landscape.
- The population $u(x)$ has an **ideal free distribution**, if $u \sim \mu$.
- If individuals move faster in bad resources, such as

$$D(x) = \mu(x)^{-1}$$

then the ideal free distribution is realized by steady states of

$$u_t = (D(x)u)_{xx} + ru(\mu(x) - u).$$

Outline

(1) Model derivations

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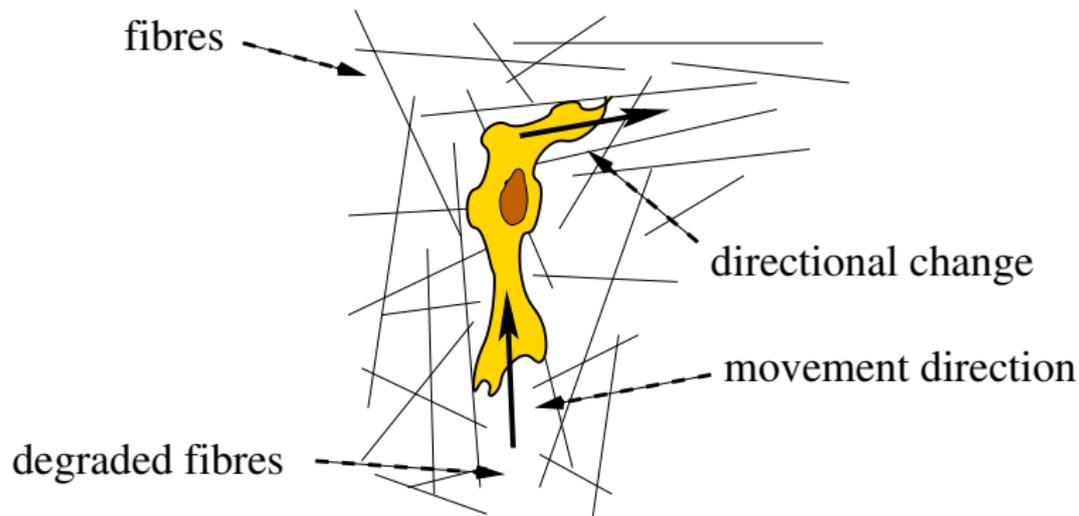
(3) Brain Tumors

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(6) Conclusions

(1.3) Cell movement in fiber networks



H', JMB, 2006

Tumor spheroid



Fibre Directional Distribution

- Orientation $\theta \in S^{n-1}$.
- Distribution of fibres $q(t, x, \theta)$

$$\int_{S^{n-1}} q(t, x, \theta) d\theta = 1.$$

Cell Velocities

Set of all possible cell velocities V :

$$V = [s_1, s_2] \times S^{n-1}, \quad 0 \leq s_1 \leq s_2 < \infty.$$

$$\hat{v} := \frac{v}{\|v\|}$$

Distribution on V

q is a distribution on S^{n-1} .

To make this into a distribution on V we consider

$$\frac{q(t, x, \hat{v})}{\omega}$$

where

$$\omega = \int_V q(t, x, \hat{v}) dv = \begin{cases} \frac{s_2^n - s_1^n}{s^{n-1}}, & s_1 < s_2, \\ s_1 = s_2 = s. \end{cases}$$

Transport Equation

$p(t, x, v)$: cell distribution at time t , location x , velocity v .

$$p_t(t, x, v) + v \cdot \nabla p(t, x, v) = -\mu p(t, x, v) + \mu \int_{\mathcal{V}} \frac{q(t, x, \hat{v})}{\omega} p(t, x, v') dv'$$

$\mu > 0$ constant turning rate.

$\frac{q(t, x, \hat{v})}{\omega}$: probability distribution of new chosen directions.

Transport Equation

$$\rho_t + v \cdot \nabla \rho = \mu \left(\frac{q}{\omega} \bar{\rho} - \rho \right)$$

$$\bar{\rho} = \int_V \rho(t, x, v) dv.$$

Transport Equation

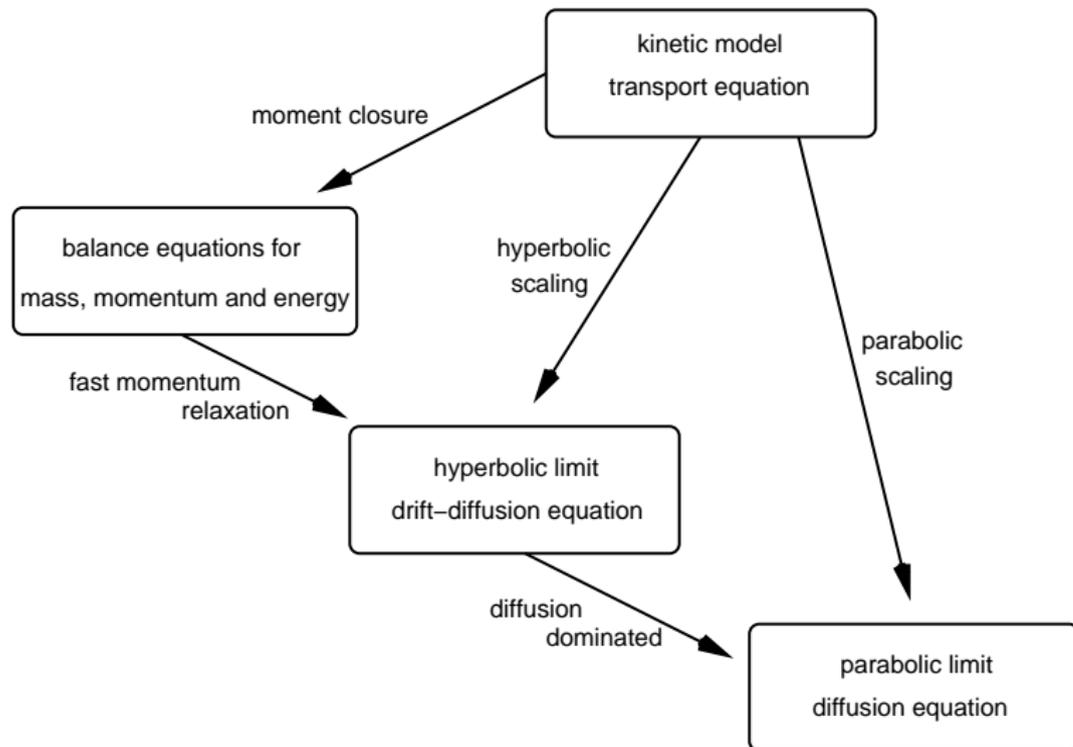
$$\rho_t + v \cdot \nabla \rho = \mu \left(\frac{q}{\omega} \bar{\rho} - \rho \right)$$

$$\bar{\rho} = \int_V \rho(t, x, v) dv.$$

Plus an equation for the tissue changes

$$q_t(t, x, v) = G(v, q, \rho).$$

Drift Diffusion Limits



H', Painter, *Kinetic Models for Movement in Oriented Habitats and Scaling Limits*, to appear 2012

Hyperbolic Scaling for Directed Tissue

$$\tau = \varepsilon t, \quad \xi = \varepsilon x,$$

$$\varepsilon p_\tau + \varepsilon v \cdot \nabla_\xi p = \mathcal{L}p$$

$$\mathcal{L}p = \mu \left(\frac{q}{\omega} \bar{p} - p \right)$$

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Use method of [Chapman Enskog](#) expansion.

Hyperbolic Scaling

$$\bar{\rho}_T + \nabla \cdot (u_c \bar{\rho}) = 0.$$

$$u_c(t, x) = \int_V v \frac{q(t, x, \hat{v})}{\omega} dv = \beta \langle q \rangle$$

Hyperbolic Scaling

$$\begin{aligned}\bar{p}_\tau + \nabla \cdot (u_c \bar{p}) &= 0. \\ u_c(t, x) &= \int_V v \frac{q(t, x, \hat{v})}{\omega} dv = \beta \langle q \rangle\end{aligned}$$

The drift velocity u_c is the **mean value** of q/ω over V .

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The drift velocity u_c is the **mean value** of q/ω over V .
Note that $u_c = 0$ for **undirected tissue**.

Parabolic Scaling

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$$\varepsilon^2 p_\tau + \varepsilon v \cdot \nabla_\xi p = \mathcal{L}p$$

Use method of **regular** expansion in ε .

Parabolic scaling (diffusion dominated)

$$\begin{aligned}\bar{p}_\tau &= \nabla(\nabla(D\bar{p})) \\ D(t, x) &= \frac{1}{\mu} \int_V v v^T \frac{q(t, x, \hat{v})}{\omega} dv\end{aligned}$$

Parabolic scaling (diffusion dominated)

$$\begin{aligned}\bar{p}_\tau &= \nabla(\nabla(D\bar{p})) \\ D(t, \mathbf{x}) &= \frac{1}{\mu} \int_{\mathcal{V}} \mathbf{v} \mathbf{v}^T \frac{q(t, \mathbf{x}, \hat{\mathbf{v}})}{\omega} d\mathbf{v}\end{aligned}$$

D is the **variance-covariance matrix** of $q(t, \mathbf{x}, \theta)$.

Moment closure (mixed case)

Moment closure with fast momentum relaxation:

$$\bar{p}_t + \nabla \cdot (u_c \bar{p}) = \nabla(\nabla D \bar{p})$$

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Procedure:

1. Define $q(t, x, \theta)$ based on biological insight
2. Compute mean and variance of q/ω :

$$u_c = \int v q/\omega dv$$

$$D = \int (v - u_c)(v - u_c)^T q/\omega dv$$

3. Use drift-diffusion model

Example: aligned and undirected tissue

Assume

$$q(t, x, \theta) := \begin{cases} 0.5 & \text{for } \theta = \mathbf{e}_1, \\ 0.5 & \text{for } \theta = -\mathbf{e}_1, \\ 0 & \text{otherwise.} \end{cases}$$

and assume that $V = sS^{n-1}$.

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and assume that $V = sS^{n-1}$.

Then the drift diffusion limit is

$$\bar{p}_t = \frac{s^2}{\mu} \bar{p}_{x_1 x_1}$$

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Brain tumors

[Swanson 2000]

$$u_t = \nabla(D(x)\nabla u) + \rho u$$

$$D(x) = \begin{cases} 5 & x \in \{\text{white matter}\} \\ 1 & x \in \{\text{gray matter}\} \end{cases}$$

Brain tumors

[Swanson 2000]

$$u_t = \nabla(D(x)\nabla u) + \rho u$$

$$D(x) = \begin{cases} 5 & x \in \{\text{white matter}\} \\ 1 & x \in \{\text{gray matter}\} \end{cases}$$

However

$$D(x) = \frac{1}{\omega} \int_V vv^T q(x, \hat{v}) dv$$

is the variance-covariance matrix. Swansons assumption does not reflect the fibrous structure of white matter.

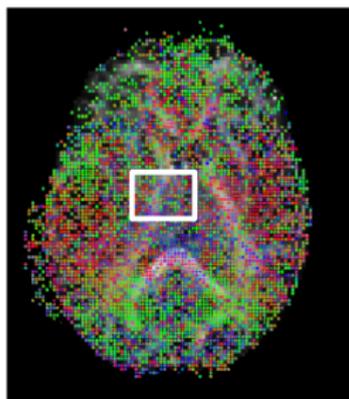
White Matter

If at a point $x \in$ white matter we find a dominant direction of e_1 , say, then we would expect

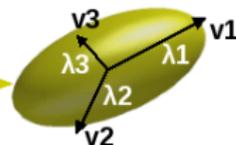
$$D(x) = \begin{pmatrix} 5 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

DTI - diffusion tensor imaging

[Jägersand, Murtha, Beaulieu, 2000s]



DTI with tensors represented as ellipsoids



Diffusion Ellipsoid
Surface is an
isosurface of the
probability of diffusion

Tumor diffusion tensor

- Water diffusion tensor $D_w \in \mathbb{R}^{3 \times 3}$:

$$D_w = \lambda_1 v_1 v_1^T + \lambda_2 v_2 v_2^T + \lambda_3 v_3 v_3^T$$

(λ_j, v_j) are the eigenvalues and eigenvectors of the water diffusion coefficient.

Tumor diffusion tensor

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- [Jbabdi, Swanson et al. 2005]:
Tumor diffusion tensor

$$D_T = a_1(r) \lambda_1 v_1 v_1^T + a_2(r) \lambda_2 v_2 v_2^T + a_3(r) \lambda_3 v_3 v_3^T,$$

where r is a scaling parameter.

Jbabdi et al. 2005, Figure 3

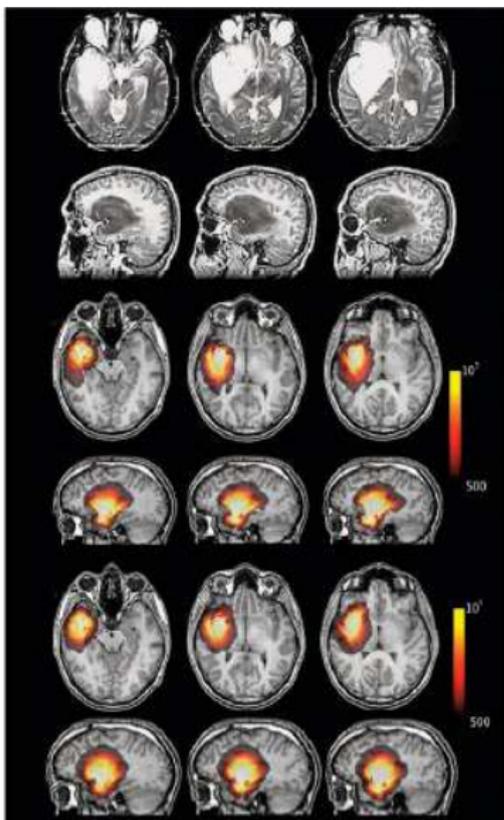


FIG. 3. Simulations with a starting point located in the insular part of the uncinate fasciculus. (a) Patient data, (b) Anisotropic simulations ($r = 10$), (c) Isotropic simulations. Visualization threshold : 500 cells per mm^3 .

Research stimulated by Swanson, Jbabdi et al.

Question:

How to relate DTI information to tissue structure and to tumor diffusion?

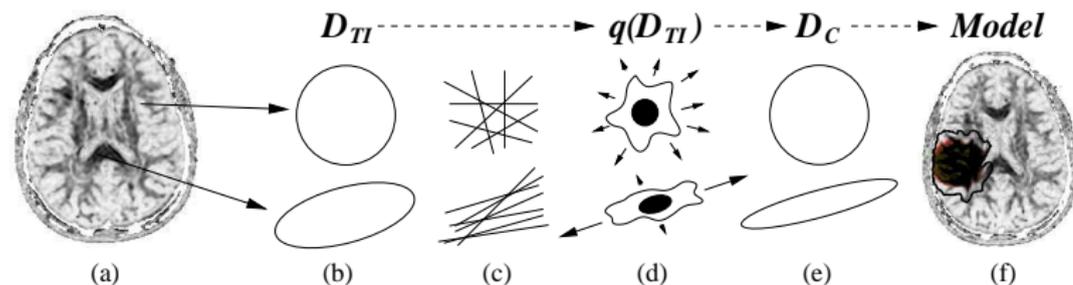
Research stimulated by Swanson, Jbabdi et al.

Question:

How to relate DTI information to tissue structure and to tumor diffusion?

Possible answer:

Using transport equation framework and the von-Mises distribution.



von Mises distribution

Let $\gamma \in S^{n-1}$ be a given direction. Define the **von Mises distribution**

$$q(x, \theta) = \frac{1}{2\pi I_0(k)} e^{k(x)\theta \cdot \gamma},$$

where $k(x)$ is the parameter of concentration.

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- q becomes uniform for $k \rightarrow 0$.
- q becomes a singular delta-distribution in direction γ for $k \rightarrow \infty$.

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Recall

$$u_c = \int v \frac{q}{\omega} dv, \quad D = \int (v - u_c)(v - u_c)^T \frac{q}{\omega} dv.$$

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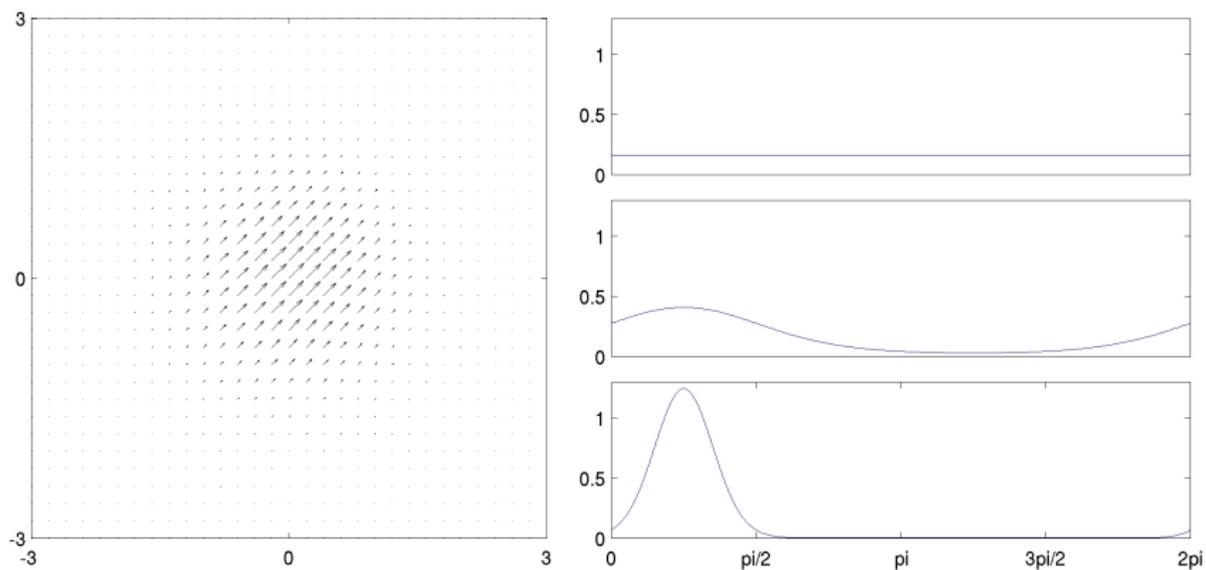
$$u_c = \int v \frac{q}{\omega} dv, \quad D = \int (v - u_c)(v - u_c)^T \frac{q}{\omega} dv.$$

For the advection-diffusion limit in 2D with $V = sS^1$:

$$u_c = s \frac{I_1(k)}{I_0(k)} \gamma$$

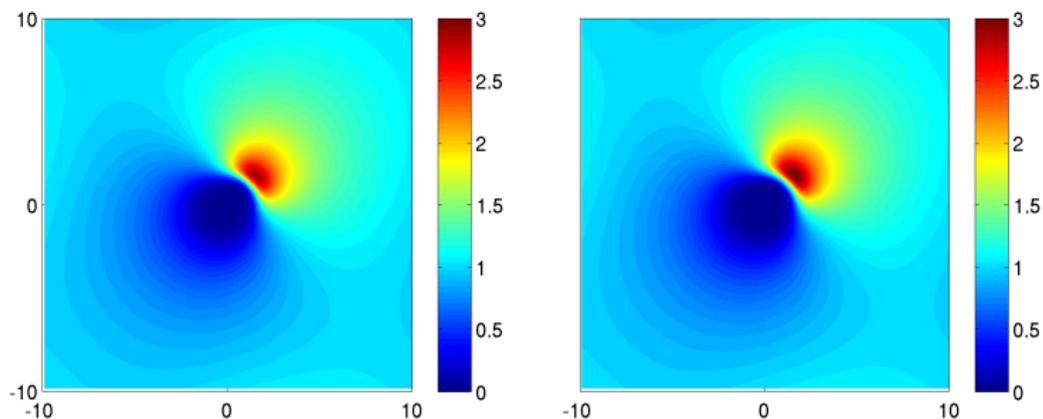
$$\frac{2\mu}{s^2} D = \left(1 - \frac{I_2(k)}{I_0(k)}\right) \mathcal{I} + \left(\frac{I_2(k)}{I_0(k)} - \left(\frac{I_1(k)}{I_0(k)}\right)^2\right) \gamma \gamma^T$$

Example 2: Oriented



Solution of

$$u_t = \nabla \nabla (D(x)u)$$



(A) $s = 10, \mu = 100$, (B) parabolic limit.

Bimodal von-Mises distribution

Let $\gamma \in S^1$ be a given direction. Define the bimodal von Mises distribution

$$q(x, \theta) = \frac{1}{4\pi I_0(k)} \left(e^{k(x)\theta \cdot \gamma} + e^{-k(x)\theta \cdot \gamma} \right),$$

where $k(x)$ is the parameter of concentration.

Bimodal von-Mises distribution

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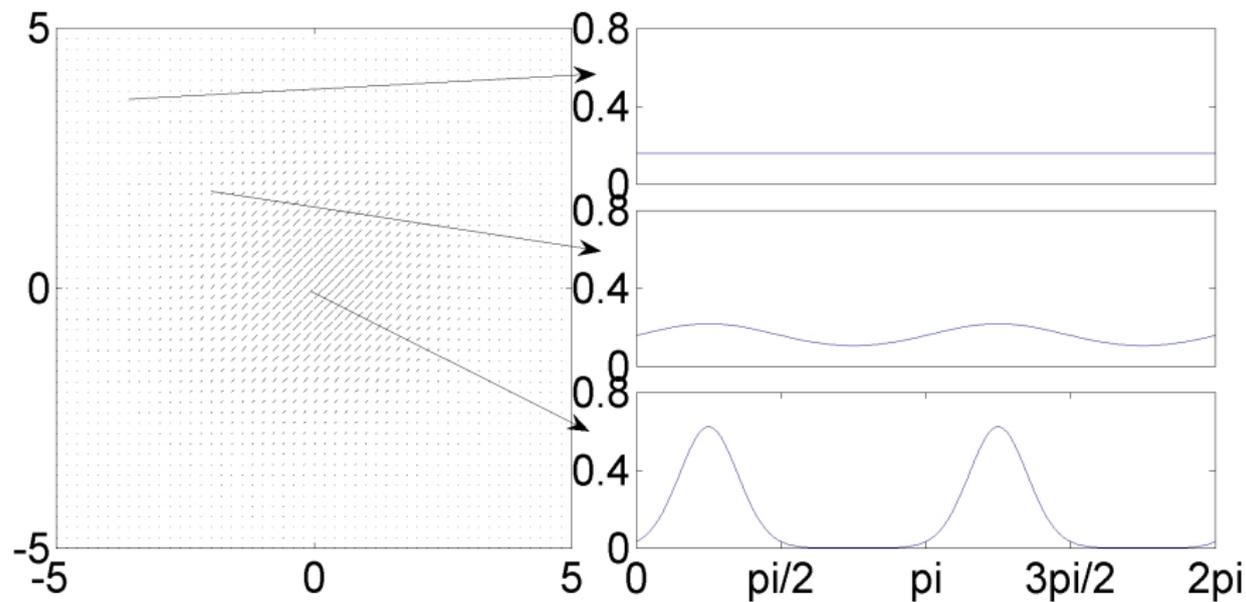
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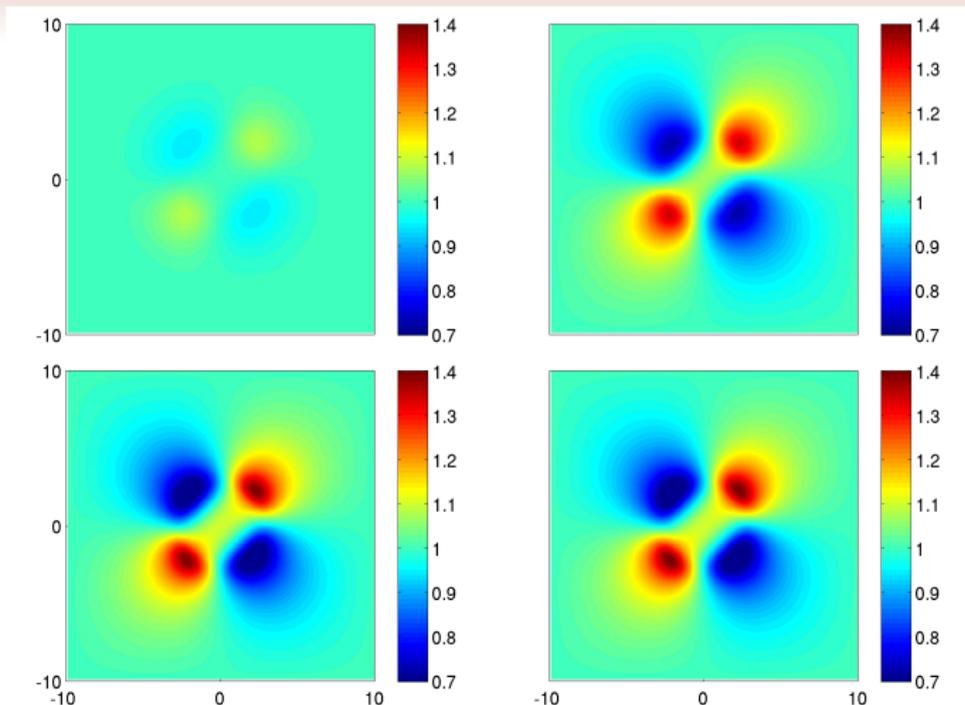
where $k(x)$ is the parameter of concentration.

For the advection-diffusion limit:

$$\begin{aligned} u_c &= 0 \\ \frac{2\mu}{s^2} D &= \left(1 - \frac{I_2(k)}{I_0(k)} \right) \mathcal{I} + \frac{I_2(k)}{I_0(k)} \gamma \gamma^T \end{aligned}$$

Example 2: Nonoriented





(A) $s = 0.1, \mu = 0.01$, (B) $s = 1, \mu = 1$, (C) $s = 10, \mu = 100$
(D) parabolic limit.

Application to DTI data

- Water diffusion tensor D_{TI} with eigenvectors and eigenvalues (λ_i, e_i) .
- dominating direction $\gamma := e_1$
- Fractional anisotropy

$$\text{FA}(D_{TI}) := \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_1 - \lambda_3)^2}}{\sqrt{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

- concentration coefficient

$$k := \kappa \text{FA}(D_{TI}), \quad \kappa > 0.$$

Fractional Anisotropy

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- $D_1 = \text{diag}(1, 1, 1)$, then $\text{FA}(D_1) = 0$.
- $D_2 = \text{diag}(1, 1, 0)$, then $\text{FA}(D_2) = 1/\sqrt{2}$.
- $D_3 = \text{diag}(1, 0, 0)$, then $\text{FA}(D_3) = 1$

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- $\text{FA}(D) \in [0, 1]$

Procedure

1. Obtain measured DTI data

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2. Define $q(x)$ as von-Mises distribution with dominating direction $\gamma = e_1$ and concentration parameter $k = \kappa FA$. Use $\kappa > 0$ as adjustable parameter.

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3. Compute tumor diffusion tensor as second moment of $q(x)$:

$$D(x) = \int vv^T q(x) / \omega dv.$$

Procedure

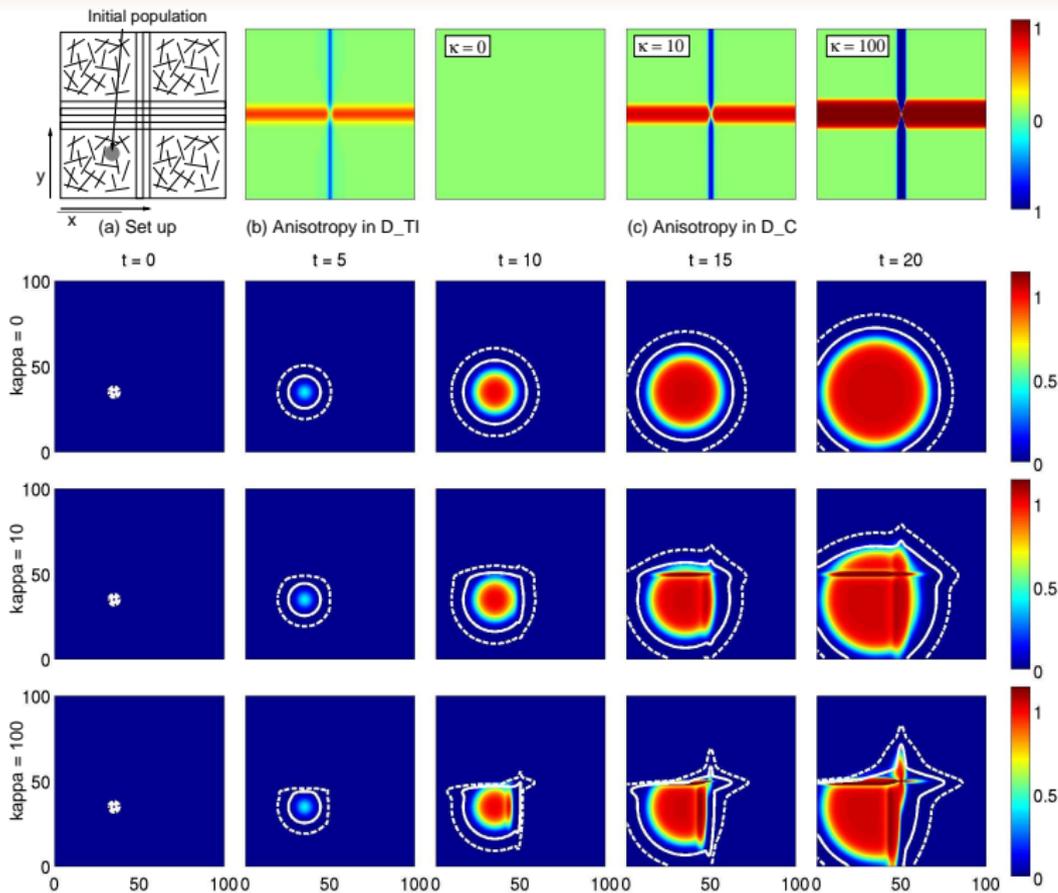
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4. Solve fully anisotropic diffusion equation on brain domain

$$u_t = \nabla \nabla (D(x)u).$$

Artificial brain



Outline

(1) Model derivations

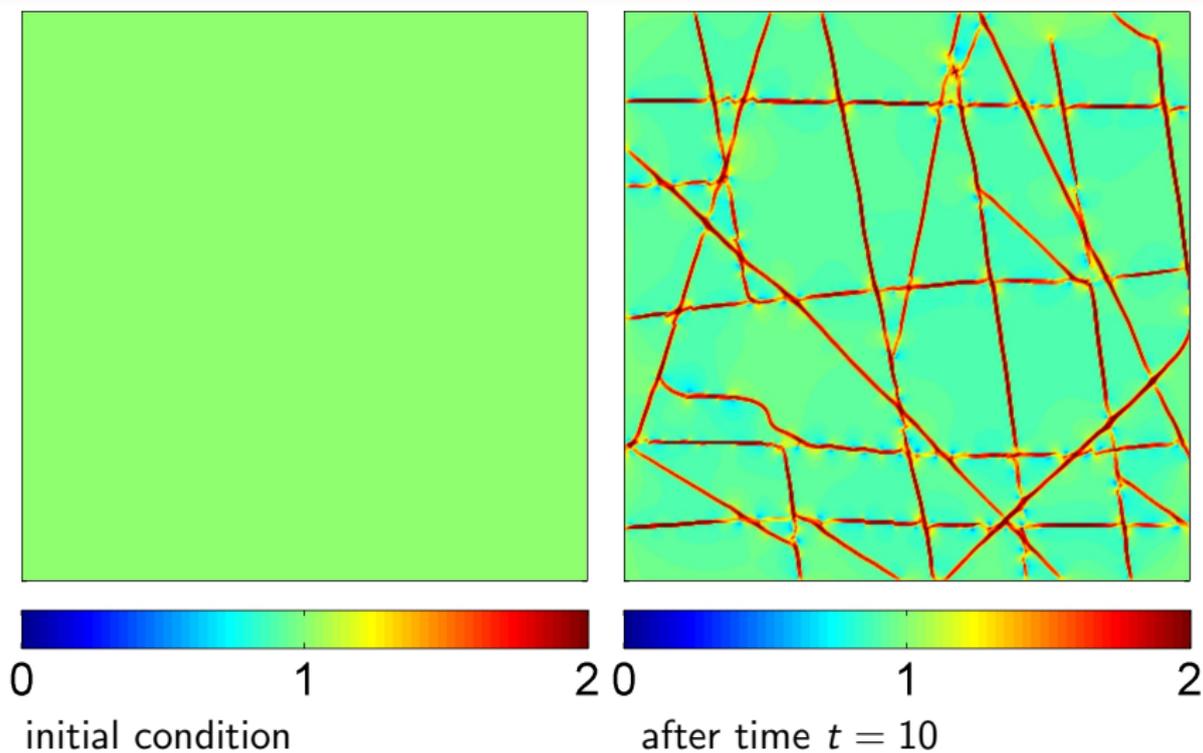
(2) Mesenchymal motion

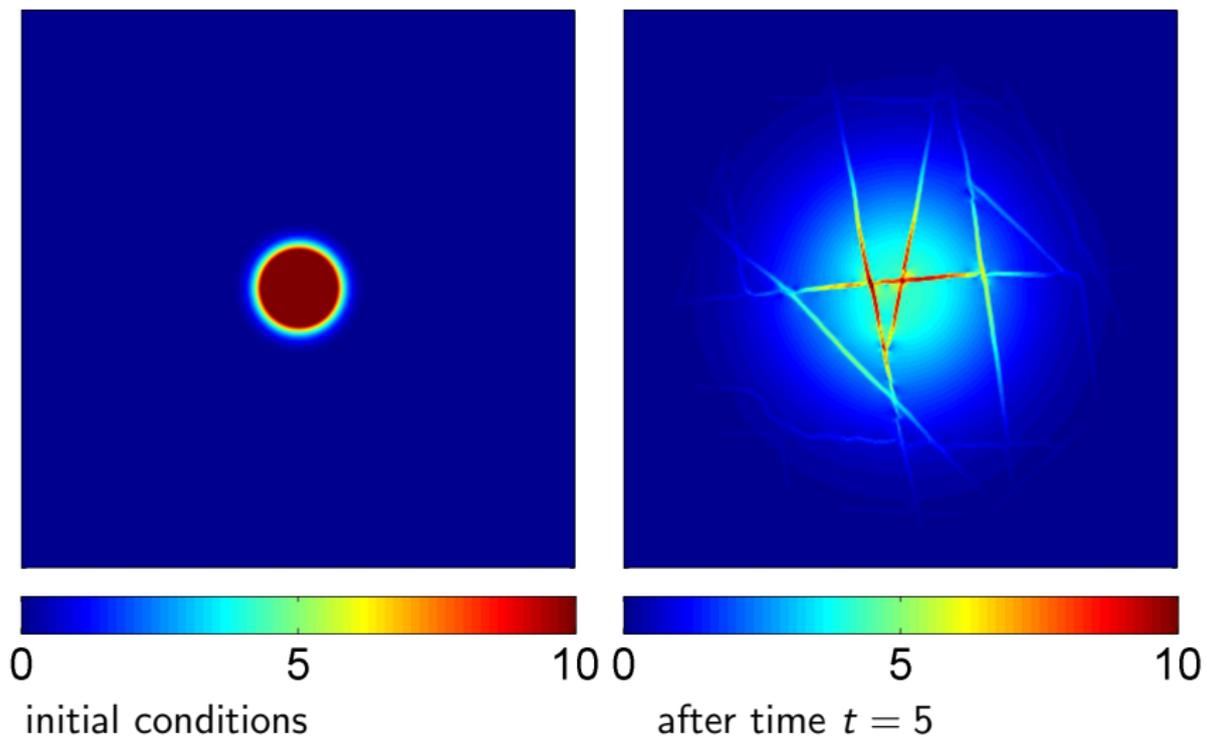
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(6) Conclusions





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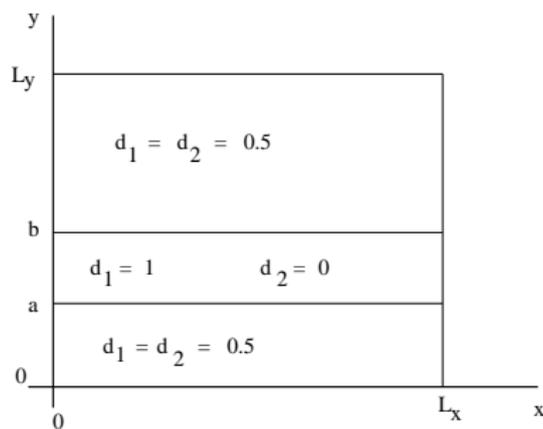
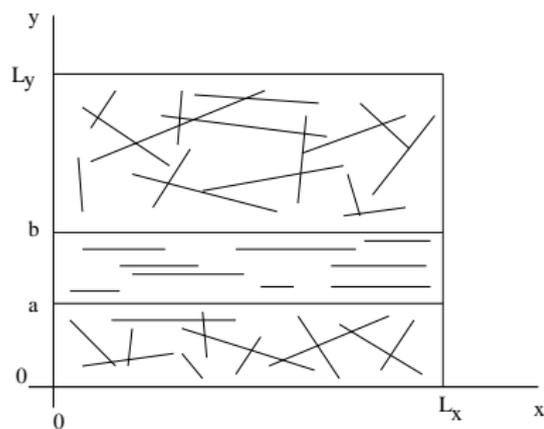
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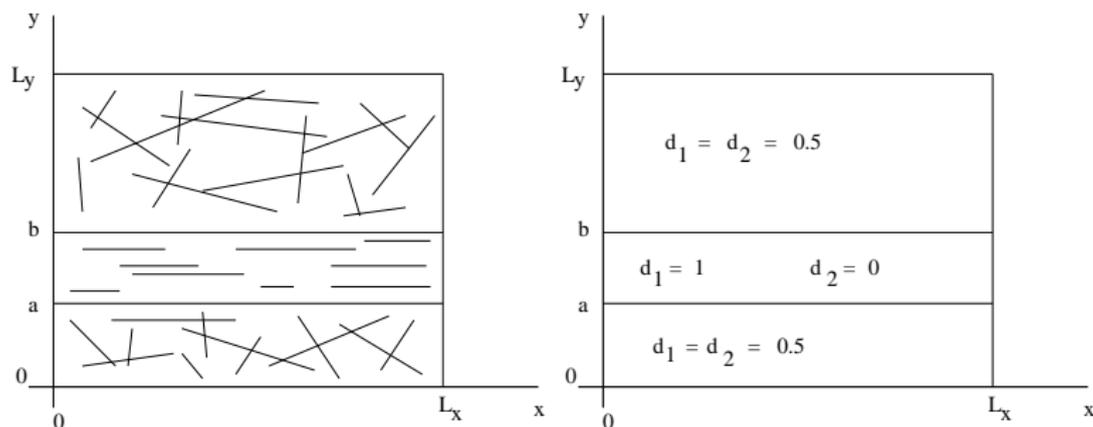
(5) A Blow-up result

(6) Conclusions

Example of a road or white matter track



Example of a road or white matter track



D is diagonal and

$$u_t = (d_1(x, y)u)_{xx} + (d_2(x, y)u)_{yy}$$

- regular diffusion: $d_1 = d_2 = \text{const.}$
- diffusion biased in x direction: $d_1 \gg d_2$.

A Mathematical problem

On $\Omega = (0, L_x) \times (0, L_y)$ consider

$$u_t = (d_1(x, y)u)_{xx} + (d_2(x, y)u)_{yy}$$

under no-flux boundary conditions and

$$d_1 = d_2 = 1/2, \quad \text{for } y \notin (a, b),$$

$$d_1 = 1, d_2 = \varepsilon \quad \text{for } y \in (a, b).$$

A Mathematical problem

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under no-flux boundary conditions and

$$d_1 = d_2 = 1/2, \quad \text{for } y \notin (a, b),$$

$$d_1 = 1, d_2 = \varepsilon \quad \text{for } y \in (a, b).$$

Goal: Understand behavior as $\varepsilon \rightarrow 0$.

Blow-up result

Theorem (H', Painter, Winkler, 2012)

Assume $\varepsilon = 0$. Let

$$U(y, t) = \int u(x, y, t) dx.$$

Then in the sense of regular Borel measures over $[0, L_y]$ we have

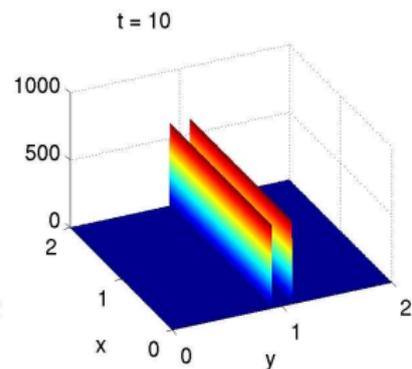
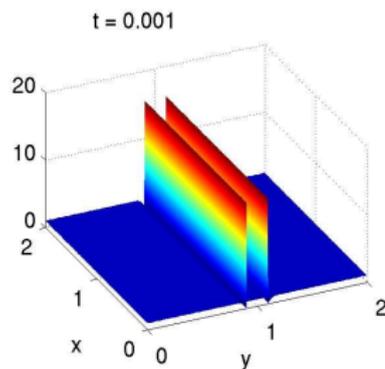
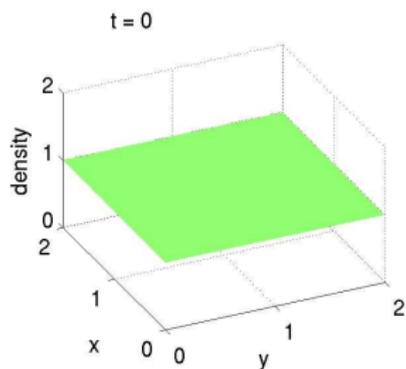
$$U(y, t) \rightharpoonup^* \frac{1}{L_x} \chi_{(a,b)}(y) U_0(y) + m_1 \delta(y - a) + m_2 \delta(y - b),$$

as $t \rightarrow \infty$, where

$$m_1 = \int_{\{y < a\}} u_0 dx dy, \quad m_2 = \int_{\{y > b\}} u_0 dx dy.$$

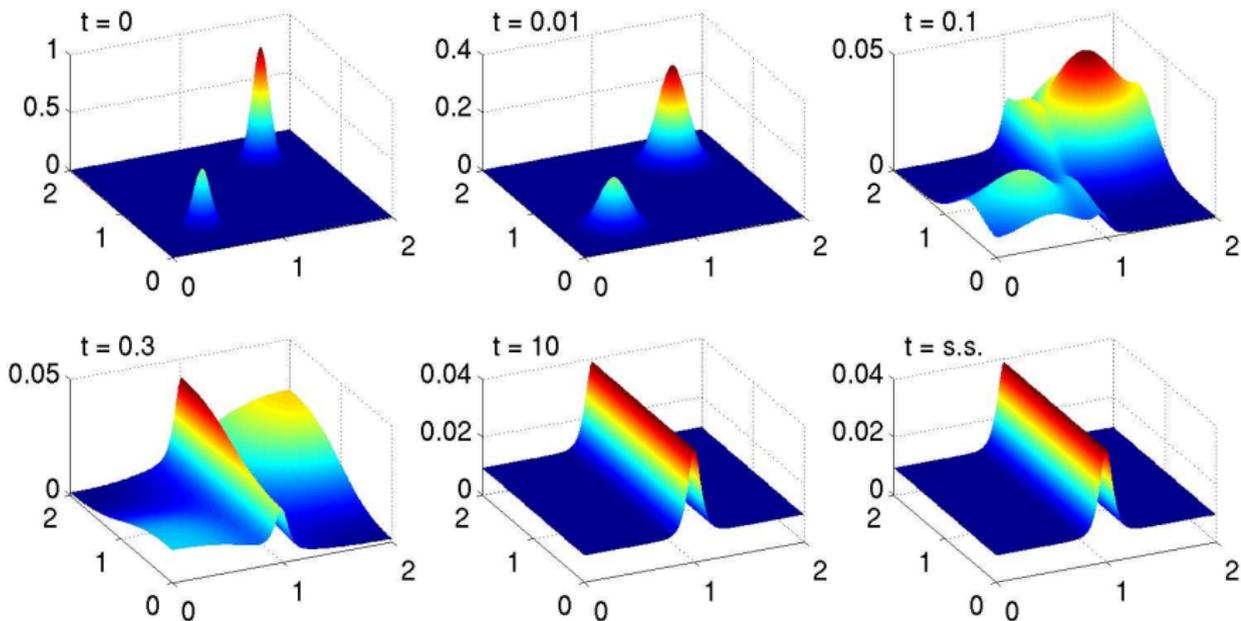
Simulations

(K.J. Painter)



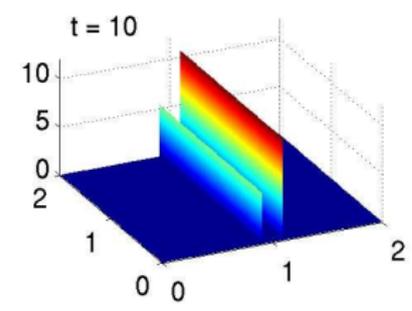
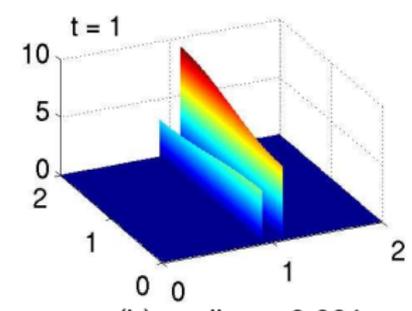
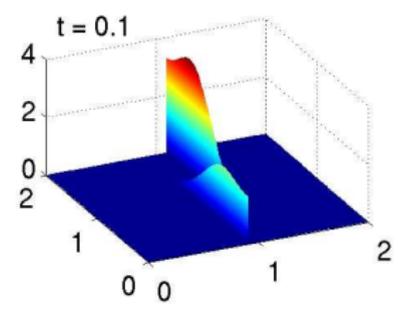
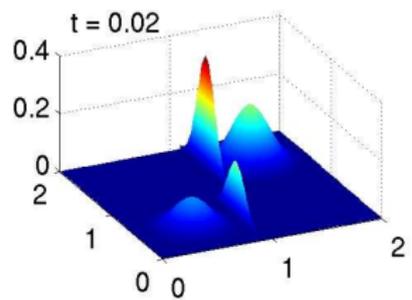
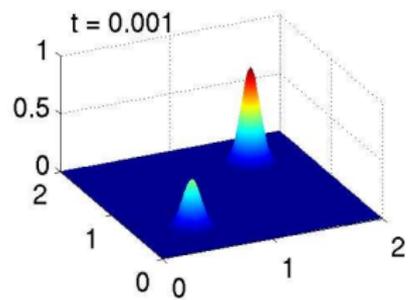
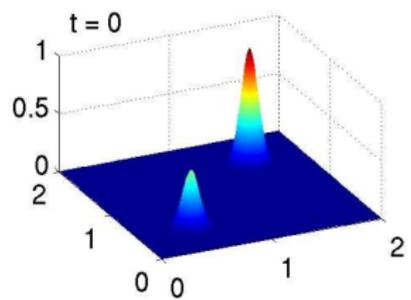
Simulations

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(a) epsilon = 0.1

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(b) epsilon = 0.001

Outline

(1) Model derivations

(2) Mesenchymal motion

(3) Brain Tumors

(4) Wolf Movement

(5) A Blow-up result

(6) Conclusions

Conclusions

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- Where does it come from?
random walk, ideal free distribution, transport equations

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- What can it be used for?
glioma growth and wolf movement

Open Problems

Glioma:

- Fully develop 3D model

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Math:

- Pattern formation and travelling waves
- Uniqueness of very weak solutions
- Other blow-up?

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