Bloch-Torrey equation and homogenization techniques

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Course schedule

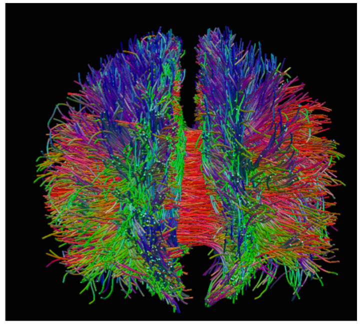
- May 31st, 8:30-10:30, alpha: Introduction to python
- June 07th, 8:30-10:30, alpha: How to obtain RM images and python lab (FFT)
- June 10th, 10:30-12:30, H: Bloch Torrey equation and homogenization techniques
- June 11th, 8:30-10:30, gamma: solution of Bloch Torrey equations in simple 2D geometry in FreeFem
- June 12th, 14:30-15:30, F: Numerical Convex Optimization applied to diffusion MRI

What is diffusion MRI (dMRI)?

is a non-invasive imaging technique which gives a measure of incoherent spins displacement.

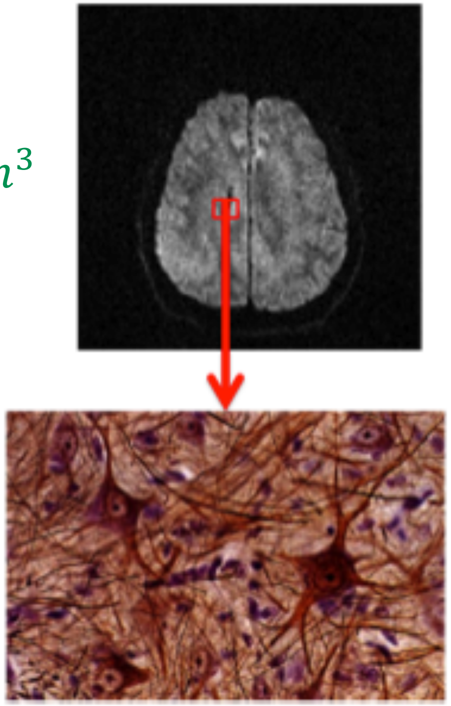
In biological tissues gives a measure of water diffusion characteristics.

- Water displacement can tell us about tissues microstructure
- Potential medical applications
  - Structure change in diseases: e.g. cells swell immediately after stroke, multiple sclerosis, ...
  - connectivity studies

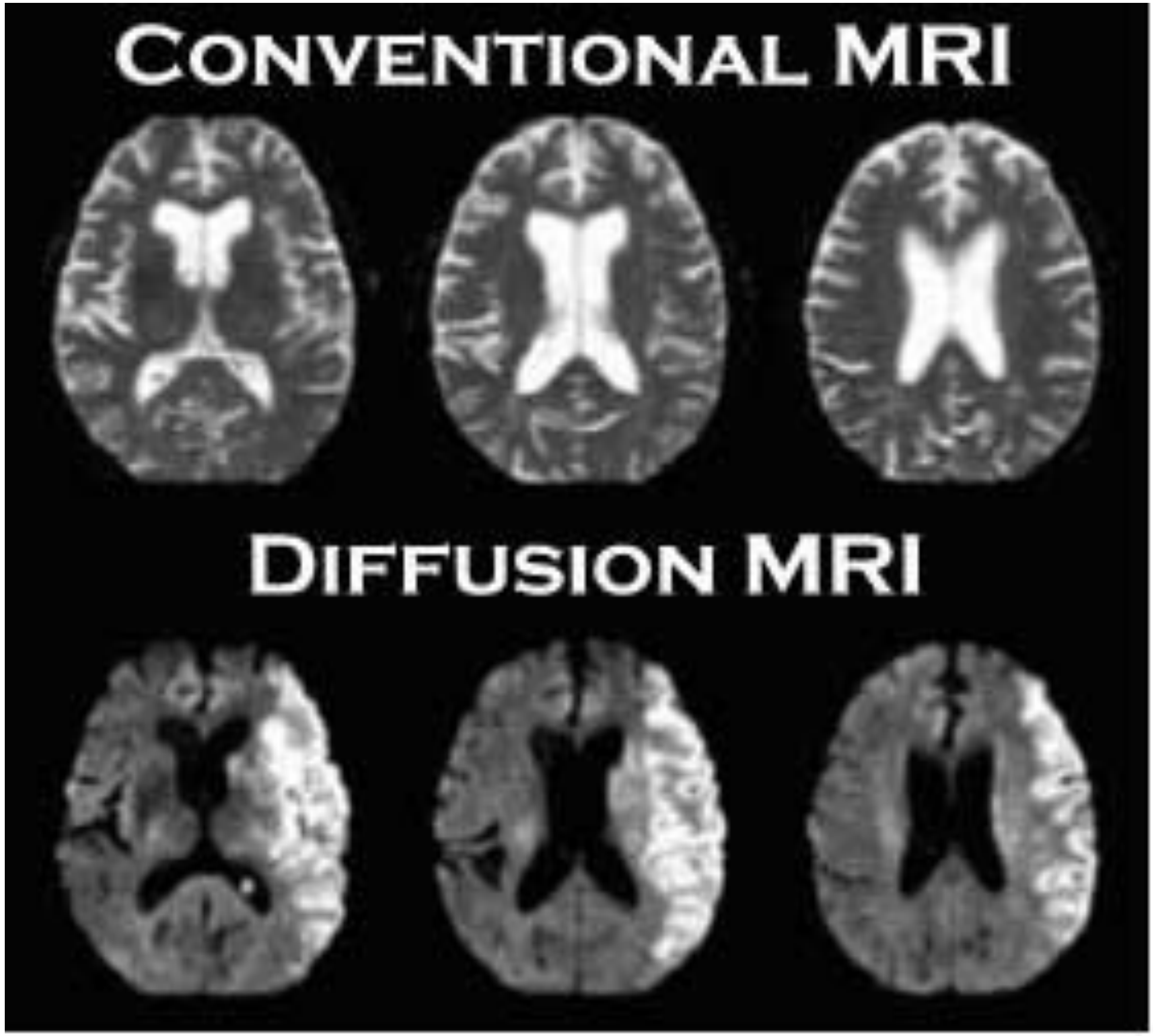


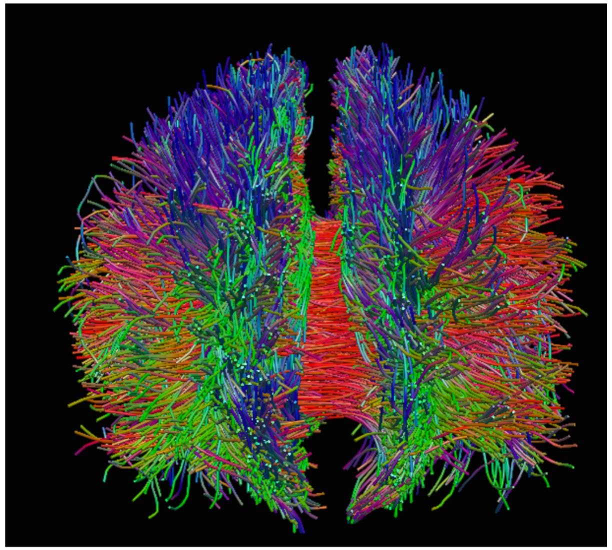
$\sim mm^3$

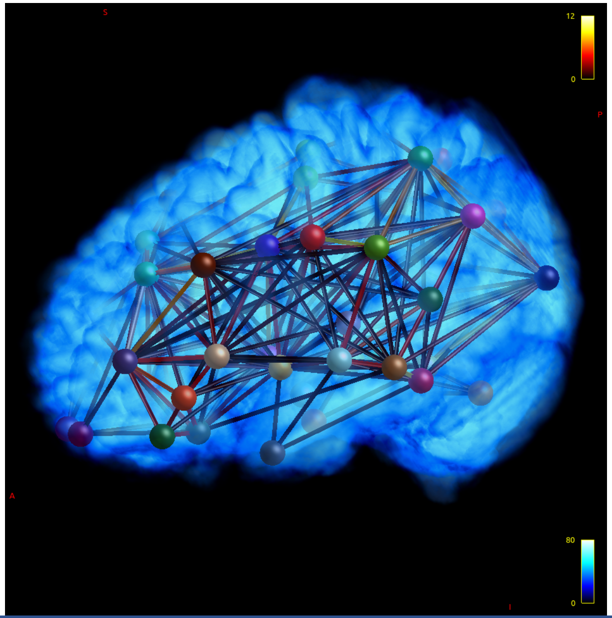
$\sim \mu m^3$



Conventional vs diffusion MRI







What is diffusion?

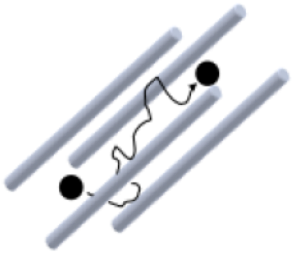
random walk of water molecules

Einstein equation: $\underbrace{<\Delta\mathbf{x}>^2}_{\text{quadratic displacement}} = 2 \underbrace{D}_{\text{diffusion tensor}} t$

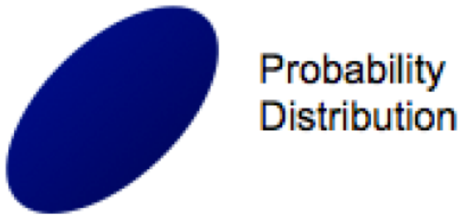
Free Diffusion

Isotropic Diffusion

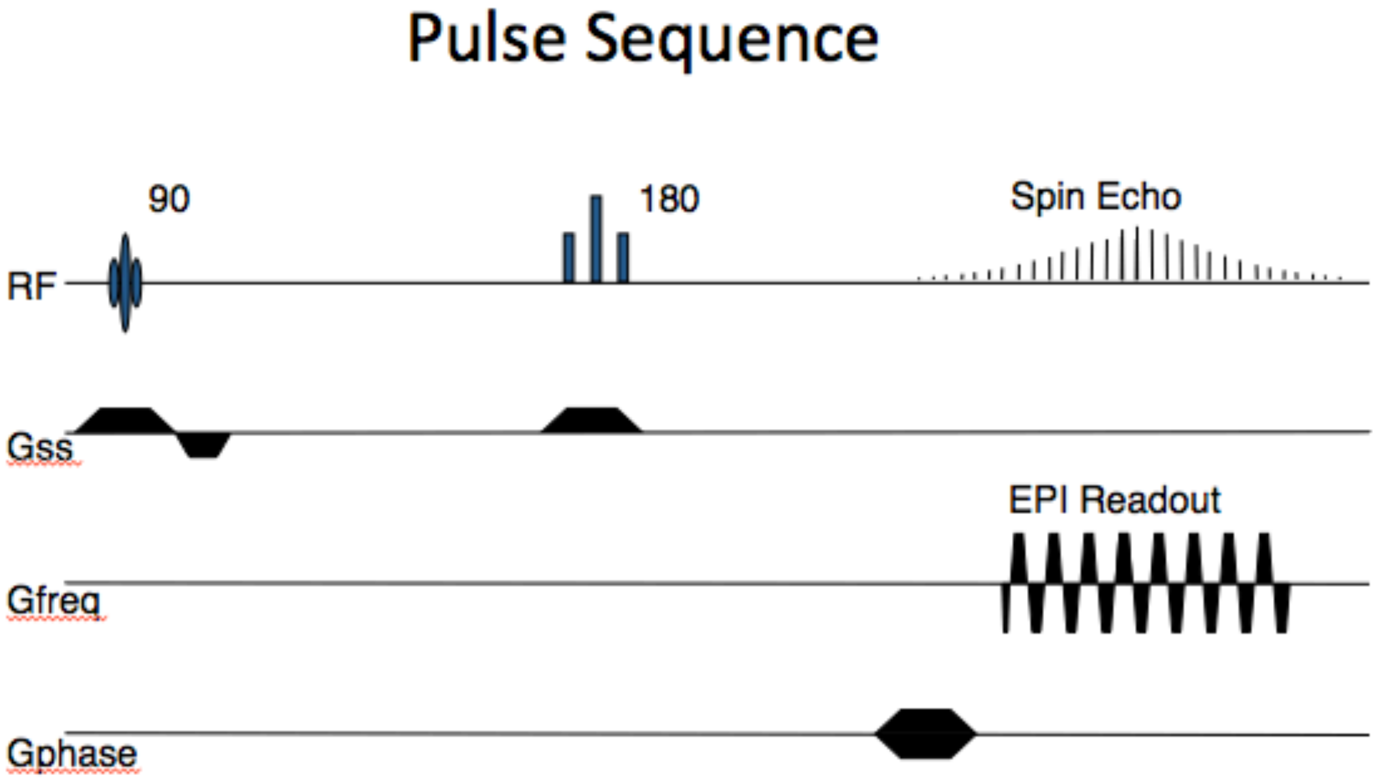
Restricted Diffusion



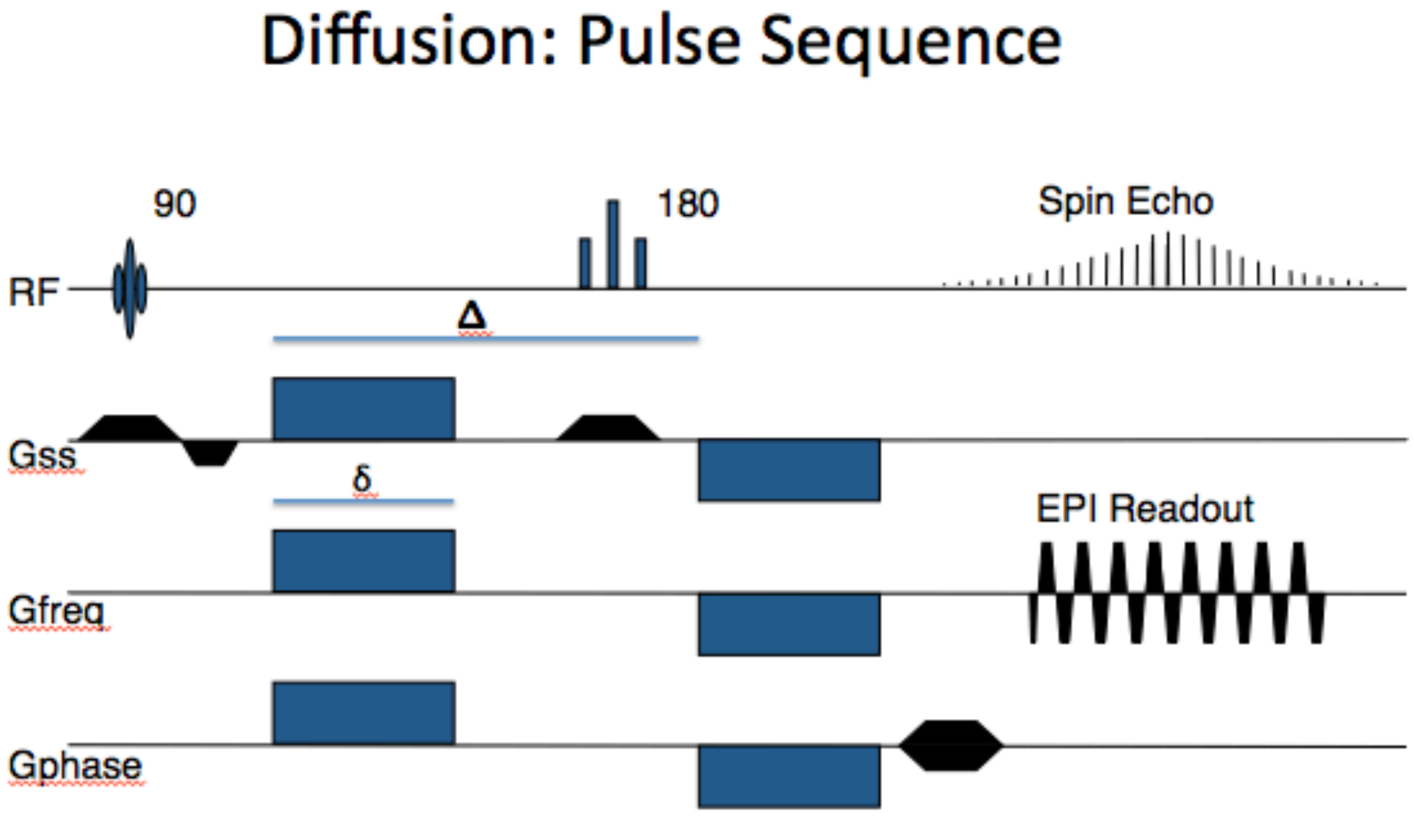
Anisotropic Diffusion



Spin echo for MRI



Spin Echo for diffusion MRI



Experimental setting and parameters of dMRI

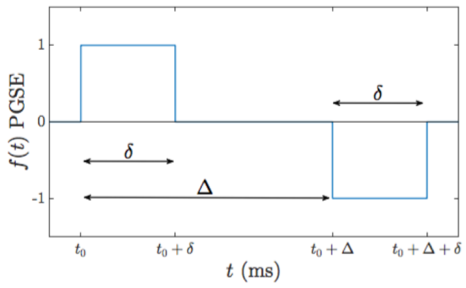
Diffusion-encoding magnetic gradient:

$$\mathbf{G}(\mathbf{x}, t) = g\, f(t)\mathbf{x} \cdot \mathbf{u_g}$$

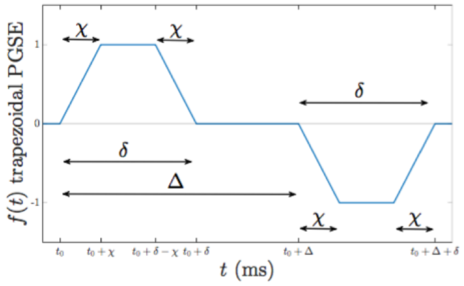
Experimental parameters:

- $\mathbf{q} = \gamma g \mathbf{u_g}$: gyromagnetic ratio $*$ intensity $*$ orientation of the magnetic field gradient, with $\|\mathbf{u_g}\|_2 = 1$,
- f: effective time profile of $\mathbf{G}$ (SE accounting for 180° RF pulse).

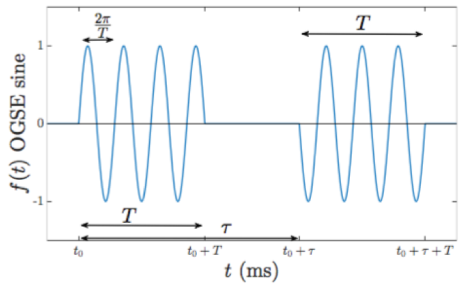
Example of used signals s.t. $\int_0^{T_E} f(t) = 0$ and $f(t) = -f(T_E - t)$



Pulsed Gradient Spin Echo
(PGSE)



Trapezoidal PGSE
(tPGSE)



Oscillating Gradient Spin Echo
(OGSE)

Experimental setting and parameters of dMRI

Diffusion-encoding magnetic gradient:

$$\mathbf{G}(\mathbf{x}, t) = g\, f(t)\mathbf{x} \cdot \mathbf{u_g}$$

Experimental parameters:

- $\mathbf{q} = \gamma g \mathbf{u_g}$: gyromagnetic ratio $*$ intensity $*$ orientation of the magnetic field gradient, with $\|\mathbf{u_g}\|_2 = 1$,
- f: effective time profile of $\mathbf{G}$ (SE accounting for 180° RF pulse).

Let $M(\mathbf{x}, t)$ be the intravoxel complex transverse magnetization at position $\mathbf{x}$ and time t.
For each MRI voxel, we compute the signal at echo-time T_E:

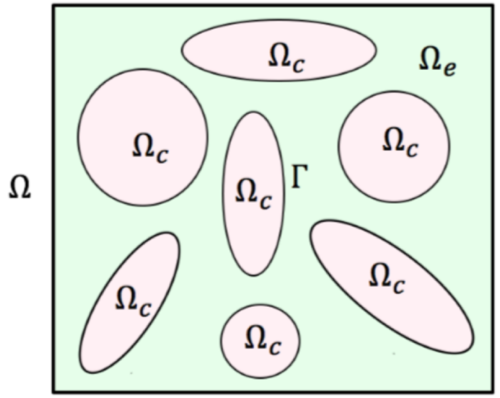
$$S(T_E) = \int_{\text{voxel}} M(\mathbf{x}, T_E)\, d\mathbf{x}$$

We define the signal attenuation: $S(T_E)/S_0$.

Multi-compartment Bloch-Torrey model

- Ω_e extra-cellular domain,
  Ω_c intra-cellular domain

Diffusion coefficient: $\mathcal{D}_0(\mathbf{x}) = \begin{cases} \mathcal{D}_0^e & \text{in } \Omega_e \\ \mathcal{D}_0^c & \text{in } \Omega_c \end{cases}$



- $\Gamma := \partial\Omega_c$, $\Omega := \bar{\Omega} \setminus \Gamma = \Omega_e \cup \Omega_c$

$$\begin{cases} \dfrac{\partial}{\partial t} M(\mathbf{x},t) + \iota\gamma \mathbf{g} \cdot \mathbf{x} f(t) M(\mathbf{x},t) - \operatorname{div}(\mathcal{D}_0(\mathbf{x}) \nabla M(\mathbf{x},t)) = 0 & \text{in } \Omega \times]0, T_E[\\ \mathcal{D}_0 \nabla M \cdot \nu|_\Gamma = \kappa [M]_\Gamma & \text{on } \Gamma \times]0, T_E[\\ [\mathcal{D}_0 \nabla M \cdot \nu]_\Gamma = 0 & \text{on } \Gamma \times]0, T_E[\\ M(\cdot, 0) = M_{ini} & \text{in } \Omega \end{cases}$$

κ: membrane permeability coefficient.

Remark: β = membrane's thickness, D_β = diffusion coefficient

$$\kappa = \lim_{\beta \to 0} \frac{D_\beta}{\beta}$$

Apparent Diffusion Coefficient (ADC)

For any gradient direction $\mathbf{u_g}$, in homogeneous medium $\frac{S(T_E)}{S_0} = e^{-\mathcal{D}_0 b}$, where b is the b-value

$$b := \gamma^2 g^2 \int_0^{T_E} \left(\int_0^t f(s) ds \right)^2 dt = q^2 \int_0^{T_E} F(t)^2 dt.$$

In heterogeneous medium,

$$\log \left(\frac{S(T_E)}{S_0} \right) = -ADC\, b + O(b^2)$$

ADC is the apparent (or effective) diffusion coefficient

$$ADC := \lim_{g \to 0} \frac{-1}{\gamma^2 \int_0^{T_E} F(t)^2 dt} \frac{\partial}{\partial g^2} \log \left(\frac{S(T_E)}{S_0} \right).$$

For free diffusion $ADC = \mathcal{D}_0$, and (Einstein equation)

$$\underbrace{< x^2(t) >}_{\textit{mean square displacement}} = 2 \quad t \quad \underbrace{ADC}_{\textit{apparent diffusion coefficient}}$$

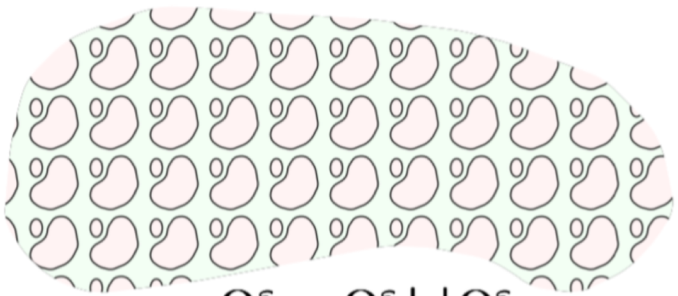
ADC approximations

In *in-vivo* experiment *ADC* is in general time-dependent (depends on $f(t)$)

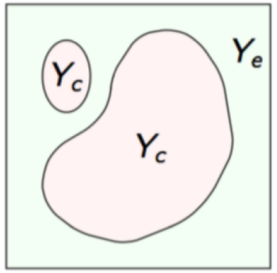
- **Short-time approximation** $(2\mathcal{D}_0 t_D \ll L^2)$
  - PGSE, narrow pulses $(\delta \ll \Delta)$ [Mitra *et al.* 1992, Axelrod *et al.* 2001,...]
  - OGSE [Novikov *et al.* 2011a, ...]
- **Long-time approximation** $(L^2 \ll 2\mathcal{D}_0 T_E)$
  - **Cheng and Torquato model** periodic domain, permeability, time independent [Cheng and Torquato 1997]
  - **Isolate cells** narrow pulses, eigenfunctions [Robertson 1966, Neumann 1974, ...]
  - **Tortuosity** $ADC_\infty = \mathcal{D}_0/\mathcal{T}$ [Callaghan 1991, Crick 1970, ...]
  - **Effective medium theory** smooth variation of $\mathcal{D}_0$, medium disorder [Novikov *et al.* 2010, Novikov *et al.* 2011, ...]
- **Anomalous diffusion** fractional derivatives or theory of diffusion in disordered media and fractals [Bennett *et al.* 2003, Özarslan *et al.* 2006, ...]
- **Geometric based models** entire signal [Behrens *et al.* 2003, Assaf and Basser 2005, Alexander 2008, Zhang *et al.* 2012, ...]
- ...

Homogenization technique

We assume that the volume to be modelled, Ω, can be described as a periodic domain. More precisely, we will assume that there exists a period ε, which represents the average size of a "representative" volume of Ω, and which is small compared to the size of Ω.



$$\Omega^\varepsilon = \Omega^\varepsilon_e \bigcup \Omega^\varepsilon_c$$



Scaled periodic cell Y, Zoom $\sim 1/\varepsilon$

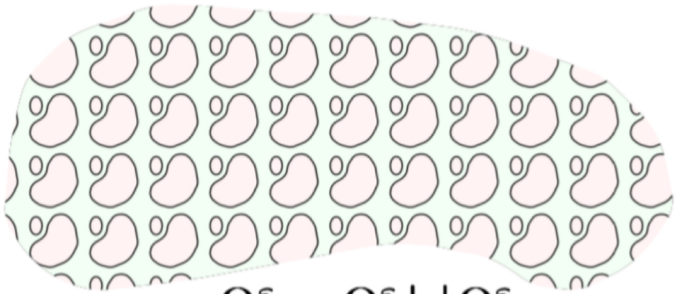
$$\overline{\Omega^\varepsilon_e} = \bigcup_{\xi\in\Xi_\varepsilon} \varepsilon(\xi+\overline{Y_e})\cap\overline{\Omega}, \quad \Omega^\varepsilon_c = \bigcup_{\xi\in\Xi_\varepsilon}\varepsilon(\xi+Y_c)\cap\Omega, \quad \Omega^\varepsilon_{ext}=\Omega^\varepsilon_e\cup\Omega^\varepsilon_c.$$

$$\partial\Omega^\varepsilon_c\cap\partial\Omega^\varepsilon_e = \partial\Omega^\varepsilon_e\setminus\overline{\partial\Omega} = \bigcup_{\xi\in\Xi_\varepsilon}\Gamma^{\varepsilon,\xi}_m, \quad \text{where} \quad \Gamma^{\varepsilon,\xi}_m = \varepsilon(\xi+\Gamma_m)\cap\Omega.$$

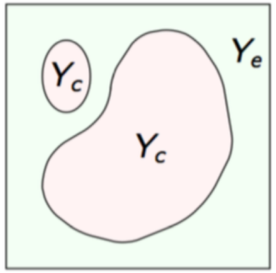
Of course, the diffusion coefficient will be assumed to be periodic as well

$$\mathcal{D}_0(\mathbf{x}) = \hat{\mathcal{D}}_0\left(\frac{\mathbf{x}}{\varepsilon}\right) = \hat{\mathcal{D}}_{0\varepsilon}(\mathbf{x})$$

Periodic homogenized model



$\Omega^\varepsilon = \Omega^\varepsilon_e \bigcup \Omega^\varepsilon_c$



Scaled periodic cell Y,
Zoom $\sim 1/\varepsilon$

M_ε **does not satisfy** the Bloch-Torrey equation in all Ω^ε_{ext}, but separately in Ω^ε_e and Ω^ε_c, with jump conditions on the Γ^ε_m.

$$\begin{cases} \frac{\partial}{\partial t} M_\varepsilon(\mathbf{x}, t) + \imath \mathbf{q} \cdot \mathbf{x} f(t) M_\varepsilon(\mathbf{x}, t) - \operatorname{div}(\hat{\mathcal{D}}_{0\varepsilon}(\mathbf{x}) \nabla M_\varepsilon(\mathbf{x}, t)) = 0 & \text{in } \Omega^\varepsilon \times]0, T_E[\\ \hat{\mathcal{D}}_{0\varepsilon} \nabla M_\varepsilon \cdot \nu|_{\Gamma^\varepsilon_m} = \kappa [M_\varepsilon]_{\Gamma^\varepsilon_m} & \text{on } \Gamma^\varepsilon_m \times]0, T_E[\\ [\hat{\mathcal{D}}_{0\varepsilon} \nabla M_\varepsilon \cdot \nu]_{\Gamma^\varepsilon_m} = 0 & \text{on } \Gamma^\varepsilon_m \times]0, T_E[\\ M_\varepsilon(\cdot, 0) = M_{ini} & \Omega^\varepsilon \end{cases}$$

Idea: asymptotic analysis ($\varepsilon \to 0$) to obtain an effective macroscopic description starting from the microstructure.

Two-scale expansion: $M_\varepsilon(\mathbf{x}, t) = \sum_{i=0}^{\infty} \varepsilon^i M_i\left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t\right)$, $\mathbf{y} = \frac{\mathbf{x}}{\varepsilon}$.

Scaling and Ansatz

- $\hat{\mathcal{D}}_0 = \begin{cases} \mathcal{D}_0^c & \text{in } Y_c \\ \mathcal{D}_0^e & \text{in } Y_e \end{cases}$
- introduce an appropriate scaling on $\kappa \to \kappa_\varepsilon = \kappa_0 \varepsilon^m$
  - m=0 [Cheng and Torquato 1997]
  - m=1 [Coatléven *et al.* 2014] $\longrightarrow$ $\kappa = \varepsilon \kappa_0$
  - general m [Coatléven 2015]

AIM: separate the "macroscopic" variations ($\boldsymbol{x}$) from the "microscopic" ones ($\boldsymbol{y}$) and obtain a new problem involving only the macroscopic

Periodic two-scale expansion

$$M_\varepsilon(\mathbf{x}, t) = \begin{cases} M_\varepsilon^e(\mathbf{x}, t) = \sum_{i=0}^{\infty} \varepsilon^i M_{ie}\left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t\right) & \text{in } \Omega_e^\varepsilon \\ M_\varepsilon^c(\mathbf{x}, t) = \sum_{i=0}^{\infty} \varepsilon^i M_{ic}\left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, t\right) & \text{in } \Omega_c^\varepsilon \end{cases}$$

$M_{ie}(\mathbf{x}, \mathbf{y}, t)$, $M_{ic}(\mathbf{x}, \mathbf{y}, t)$ defined on $\Omega \times Y_e \times]0, T_E[$ and $\Omega \times Y_c \times]0, T_E[$ and Y-periodic in y.

Homogenized model

The proof requires periodic unfolding method extended to the time-dependent cases. See Coatléven 2015

$$M_\varepsilon \rightharpoonup v_e M_{0e} + v_c M_{0c} \text{ weakly in } L^2(0, T_E, L^2(\mathbb{R}^d)),$$

where $v_e = \frac{|Y_e|}{|Y|}$ and $v_c = \frac{|Y_c|}{|Y|}$ are the volume fractions and

$$\begin{cases} \frac{\partial}{\partial t} M_{0e} - \operatorname{div}\left(D^e \nabla M_{0e}\right) + \imath q \mathbf{u_g} \cdot \mathbf{x} f(t) M_{0e} + \eta_e (M_{0e} - M_{0c}) = 0 & \Omega \times]0, T_E[\\ \frac{\partial}{\partial t} M_{0c} - \cancel{\operatorname{div}\left(D^c \nabla M_{0c}\right)} + \imath q \mathbf{u_g} \cdot \mathbf{x} f(t) M_{0c} + \eta_c (M_{0c} - M_{0e}) = 0 & \Omega \times]0, T_E[\\ M_{0e}(\cdot, 0) = M_{init}, \quad M_{0c}(\cdot, 0) = M_{init} & \text{in } \Omega \end{cases}$$

If Y_c does not touch the boundary of Y, then $D^c = 0$

with D^e and D^c some homogenized diffusion tensors

and $\eta_j := \frac{\kappa_0 |\Gamma|}{|Y_j|}$, $j = e, c$ model the exchange between compartments.

The approximate signal is then

$$S(T_E) = \int_{\mathbb{R}^d} v_e M_{0e}(\mathbf{x}, T_E) + v_c M_{0c}(\mathbf{x}, T_E) d\mathbf{x}.$$

and $ADC = v_e D^e + v_c D^c$.

Finite Pulse Kärger model (FPK)

Theorem [Coatléven *et al.* 2014]

Assuming that $M_{\text{ini}} \in L^1(\mathbb{R}^d)$ and $F(T_E) = \int_0^{T_E} f(t)dt = 0$ the signal attenuation can be computed as

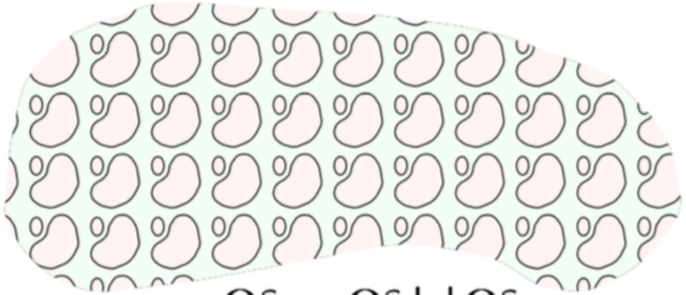
$$\frac{S(T_E)}{S_0} = m(T_E),$$

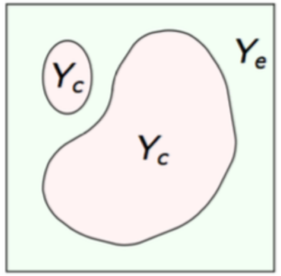
where $m(T_E) = m_e(T_E) + m_c(T_E)$, $m_j(T_E) = \int_{\mathbb{R}^d} M_{0j}(\mathbf{x}, T_E) e^{\imath q \mathbf{u_g} \cdot \mathbf{x} \int_0^t f(s) ds} d\mathbf{x}$ and $(m_e, m_c) \in C^1(0, T_E)^2$ is the unique solution of

$$\begin{cases} \dfrac{d}{dt} m_e(t) + q^2 F^2(t) D^e \mathbf{u_g} \cdot \mathbf{u_g} m_e(t) + \eta_e m_e(t) - \eta_c m_c(t) = 0 \\ \dfrac{d}{dt} m_c(t) + q^2 F^2(t) D^c \mathbf{u_g} \cdot \mathbf{u_g} m_c(t) + \eta_c m_c(t) - \eta_e m_e(t) = 0 \\ m_e(0) = v_e \quad \text{and} \quad m_c(0) = v_c \end{cases}$$

Remark: This model has a similar structure as the (phenomenological) Kärger model [Kärger 1985] designed for PGSE under the narrow pulses assumption $(\delta \ll \Delta)$.

Transformed equation


$\Omega^\varepsilon = \Omega^\varepsilon_e \bigcup \Omega^\varepsilon_c$



Scaled periodic cell Y,
Zoom $\sim 1/\varepsilon$

Change of variables: $\widetilde{M}_\varepsilon(\mathbf{x}, t) = M_\varepsilon(\mathbf{x}, t) e^{\iota q \mathbf{u_q} \cdot \mathbf{x} \int_0^t f(s)\, ds}$.

$$
\begin{cases}
\dfrac{\partial}{\partial t} \widetilde{M}_\varepsilon(\mathbf{x}, t) - \operatorname{div}\left(\mathcal{D}_{0\varepsilon}(\mathbf{x}) \nabla \widetilde{M}_\varepsilon(\mathbf{x}, t) - \iota q \mathbf{u_g} F(t) \mathcal{D}_{0\varepsilon}(\mathbf{x}) \widetilde{M}_\varepsilon(\mathbf{x}, t)\right) & \\
\quad + \iota q \mathbf{u_g} F(t) \mathcal{D}_{0\varepsilon}(\mathbf{x}) \nabla \widetilde{M}_\varepsilon(\mathbf{x}, t) + q^2 F(t)^2 \mathcal{D}_{0\varepsilon}(\mathbf{x}) \widetilde{M}_\varepsilon(\mathbf{x}, t) = 0 & \text{in } \Omega^\varepsilon \times]0, T_E[\\
\mathcal{D}_{0\varepsilon} \nabla \widetilde{M}_\varepsilon \cdot \nu - \iota q \mathbf{u_g} F(t) \mathcal{D}_{0\varepsilon} \widetilde{M}_\varepsilon \cdot \nu = \kappa^\varepsilon [\widetilde{M}_\varepsilon]_{\Gamma^\varepsilon_m} & \text{on } \Gamma^\varepsilon_m \times]0, T_E[\\
[\mathcal{D}_{0\varepsilon} \nabla \widetilde{M}_\varepsilon \cdot \nu - \iota q \mathbf{u_g} F(t) \mathcal{D}_{0\varepsilon} \widetilde{M}_\varepsilon \cdot \nu]_{\Gamma^\varepsilon_m} = 0 & \text{on } \Gamma^\varepsilon_m \times]0, T_E[\\
\widetilde{M}_\varepsilon(\cdot, 0) = M_{init} & \text{in } \Omega^\varepsilon
\end{cases}
$$

Multiscale Bloch-Torrey problem

$$
\begin{cases}
\displaystyle\sum_{i=0}^{\infty} \varepsilon^{i+2} \frac{\partial}{\partial t} \widetilde{M}_{ij} + \varepsilon^{i+2} q^2 \mathbf{u_g} \cdot \mathbf{u_g} F^2 \mathcal{D}_0^j \widetilde{M}_{ij} & \\
\quad + \varepsilon^{i+2} \imath q \mathbf{u_g} F \mathcal{D}_0^j (\nabla_{\mathbf{x}} \widetilde{M}_{ij} + \varepsilon^{-1} \nabla_{\mathbf{y}} \widetilde{M}_{ij}) & \\
\quad + \varepsilon^{i+2} \mathrm{div}_{\mathbf{x}} (\imath q \mathbf{u_g} F \mathcal{D}_0^j \widetilde{M}_{ij}) + \varepsilon^{i+1} \mathrm{div}_{\mathbf{y}} (\imath q \mathbf{u_g} F \mathcal{D}_0^j \widetilde{M}_{ij}) & \\
\quad - \varepsilon^{i+2} \mathrm{div}_{\mathbf{x}} (\mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{ij}) - \varepsilon^{i+1} \mathrm{div}_{\mathbf{x}} (\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{ij}) & \\
\quad - \varepsilon^{i+1} \mathrm{div}_{\mathbf{y}} (\mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{ij}) - \varepsilon^{i} \mathrm{div}_{\mathbf{y}} (\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{ij}) = 0 & \text{in } Y_j \times [0, T_E] \\
\displaystyle\sum_{i=0}^{\infty} \varepsilon^{i} \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{ij} + \varepsilon^{i+1} \left(\mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{ij} - \imath q \mathbf{u_g} F \mathcal{D}_0^j \widetilde{M}_{ij} \right) = \varepsilon^{i+2} \kappa_0 [\widetilde{M}_{ij}] & \text{on } \Gamma \times [0, T_E] \\
\displaystyle\sum_{i=0}^{\infty} [\varepsilon^{i} \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{ij} + \varepsilon^{i+1} \left(\mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{ij} - \imath q \mathbf{u_g} F \mathcal{D}_0^j \widetilde{M}_{ij} \right)] = 0 & \text{on } \Gamma \times [0, T_E] \\
\widetilde{M}_{0j}(\mathbf{x}, 0) = M_{\mathrm{ini}}, \quad \widetilde{M}_{ij}(\mathbf{x}, 0) = 0 \ \forall i \geq 1 & \text{in } Y_j
\end{cases}
$$

Matching the power of ε we can write the problem for $\widetilde{M}_{ij}$ and solve them recursively.

Equations satisfied by the first orders

$$\begin{cases} -\mathrm{div}_{\mathbf{y}}(\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{0j}) = 0 & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{0j} \cdot \nu = 0 & \text{on } \Gamma \\ \widetilde{M}_{0j} \text{ is } Y \text{ periodic} & \end{cases}$$

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$\widetilde{M}_{0j}$ does not depend on $\mathbf{y}$.

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$\widetilde{M}_{0j}$ does not depend on $\mathbf{y}$.

$$\begin{cases} -\mathrm{div}_{\mathbf{y}}\left(\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{1j} + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{0j} - \imath q F \mathcal{D}_0^j \widetilde{M}_{0j} \mathbf{u_g}\right) = 0 & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{1j} \cdot \nu + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{0j} \cdot \nu - \imath q F \mathcal{D}_0^j \widetilde{M}_{0j} \mathbf{u_g} \cdot \nu = 0 & \text{on } \Gamma \\ \widetilde{M}_{1j} \text{ is } Y \text{ periodic} \end{cases}$$

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$$\begin{cases} -\mathrm{div}_{\mathbf{y}}(\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{0j}) = 0 & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{0j} \cdot \nu = 0 & \text{on } \Gamma \\ \widetilde{M}_{0j} \text{ is } Y \text{ periodic} \end{cases} \longrightarrow$$

$\widetilde{M}_{0j}$ does not depend on $\mathbf{y}$.

$$\begin{cases} -\mathrm{div}_{\mathbf{y}} \left(\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{1j} + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{0j} - \imath q F \mathcal{D}_0^j \widetilde{M}_{0j} \mathbf{u_g} \right) = 0 & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{1j} \cdot \nu + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{0j} \cdot \nu - \imath q F \mathcal{D}_0^j \widetilde{M}_{0j} \mathbf{u_g} \cdot \nu = 0 & \text{on } \Gamma \\ \widetilde{M}_{1j} \text{ is } Y \text{ periodic} \end{cases}$$

$$\widetilde{M}_{1j}(\mathbf{x}, b\mathbf{y}, t) = u^j \cdot \left(\nabla_{\mathbf{x}} \widetilde{M}_{0j} - \imath q F \widetilde{M}_{0j} \mathbf{u_g} \right)$$

where u_l^j, $l = 1, \dots, d$ solves

$$\begin{cases} -\mathrm{div}_{\mathbf{y}} \left(\mathcal{D}_0^j \nabla_{\mathbf{y}} u_l^j + \mathcal{D}_0^j \mathbf{e}_l \right) = 0 & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} u_l^j \cdot \nu + \mathcal{D}_0^j \mathbf{e}_l \cdot \nu = 0 & \text{on } \Gamma \\ u_l^j \text{ is } Y \text{ periodic} \end{cases}$$

Equations satisfied by the first orders

$$\begin{cases} -\mathrm{div}_{\mathbf{y}}(\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{0j}) = 0 & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{0j} \cdot \nu = 0 & \text{on } \Gamma \\ \widetilde{M}_{0j} \text{ is } Y \text{ periodic} \end{cases} \longrightarrow$$

$\widetilde{M}_{0j}$ does not depend on $\mathbf{y}$.

$$\begin{cases} -\mathrm{div}_{\mathbf{y}}\left(\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{1j} + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{0j} - \imath q F \mathcal{D}_0^j \widetilde{M}_{0j} \mathbf{u_g}\right) = 0 & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{1j} \cdot \nu + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{0j} \cdot \nu - \imath q F \mathcal{D}_0^j \widetilde{M}_{0j} \mathbf{u_g} \cdot \nu = 0 & \text{on } \Gamma \\ \widetilde{M}_{1j} \text{ is } Y \text{ periodic} \end{cases}$$

$$\widetilde{M}_{1j}(\mathbf{x}, by, t) = u^j \cdot \left(\nabla_{\mathbf{x}} \widetilde{M}_{0j} - \imath q F \widetilde{M}_{0j} \mathbf{u_g}\right)$$

where u_l^j, $l = 1, \ldots, d$ solves

$$\begin{cases} -\mathrm{div}_{\mathbf{y}}\left(\mathcal{D}_0^j \nabla_{\mathbf{y}} u_l^j + \mathcal{D}_0^j \mathbf{e}_l\right) = 0 & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} u_l^j \cdot \nu + \mathcal{D}_0^j \mathbf{e}_l \cdot \nu = 0 & \text{on } \Gamma \\ u_l^j \text{ is } Y \text{ periodic} \end{cases}$$

$$\begin{cases} -\mathrm{div}_{\mathbf{y}}\left(\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{2j} + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{1j} - \imath q F \mathcal{D}_0^j \widetilde{M}_{1j} \mathbf{u_g}\right) = -\frac{\partial}{\partial t} \widetilde{M}_{0j} & \\ \qquad - q^2 F^2 \mathcal{D}_0^j \widetilde{M}_{0j} - \imath q F \mathcal{D}_0 \mathbf{u_g} \cdot (\nabla_{\mathbf{y}} \widetilde{M}_{1j} + \nabla_{\mathbf{x}} \widetilde{M}_{0j}) & \\ \qquad + \mathrm{div}_{\mathbf{x}}(\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{1j} + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{0j} - \imath q F \mathcal{D}_0^j \mathbf{u_g} \widetilde{M}_{0j}) & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{2j} \cdot \nu + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{1j} \cdot \nu - \imath q F \mathcal{D}_0^j \widetilde{M}_{1j} \mathbf{u_g} \cdot \nu = \kappa_0[\widetilde{M}_{0j}] & \text{on } \Gamma \\ \widetilde{M}_{2j} \text{ is } Y \text{ periodic} \end{cases}$$

Equations satisfied by the first orders

$$\begin{cases} -\mathrm{div}_{\mathbf{y}}(\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{0j}) = 0 & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{0j} \cdot \nu = 0 & \text{on } \Gamma \\ \widetilde{M}_{0j} \text{ is } Y \text{ periodic} \end{cases} \longrightarrow$$

$\widetilde{M}_{0j}$ does not depend on $\mathbf{y}$.

$$\begin{cases} -\mathrm{div}_{\mathbf{y}} \left(\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{1j} + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{0j} - \imath q F \mathcal{D}_0^j \widetilde{M}_{0j} \mathbf{u_g} \right) = 0 & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{1j} \cdot \nu + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{0j} \cdot \nu - \imath q F \mathcal{D}_0^j \widetilde{M}_{0j} \mathbf{u_g} \cdot \nu = 0 & \text{on } \Gamma \\ \widetilde{M}_{1j} \text{ is } Y \text{ periodic} \end{cases}$$

$$\widetilde{M}_{1j}(\mathbf{x}, by, t) = u^j \cdot \left(\nabla_{\mathbf{x}} \widetilde{M}_{0j} - \imath q F \widetilde{M}_{0j} \mathbf{u_g} \right)$$

where u_l^j, $l = 1, \ldots, d$ solves

$$\begin{cases} -\mathrm{div}_{\mathbf{y}} \left(\mathcal{D}_0^j \nabla_{\mathbf{y}} u_l^j + \mathcal{D}_0^j \mathbf{e}_l \right) = 0 & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} u_l^j \cdot \nu + \mathcal{D}_0^j \mathbf{e}_l \cdot \nu = 0 & \text{on } \Gamma \\ u_l^j \text{ is } Y \text{ periodic} \end{cases}$$

$$\begin{cases} -\mathrm{div}_{\mathbf{y}} \left(\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{2j} + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{1j} - \imath q F \mathcal{D}_0^j \widetilde{M}_{1j} \mathbf{u_g} \right) = -\frac{\partial}{\partial t} \widetilde{M}_{0j} & \\ \quad - q^2 F^2 \mathcal{D}_0^j \widetilde{M}_{0j} - \imath q F \mathcal{D}_0 \mathbf{u_g} \cdot (\nabla_{\mathbf{y}} \widetilde{M}_{1j} + \nabla_{\mathbf{x}} \widetilde{M}_{0j}) & \\ \quad + \mathrm{div}_{\mathbf{x}} (\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{1j} + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{0j} - \imath q F \mathcal{D}_0^j \mathbf{u_g} \widetilde{M}_{0j}) & \text{in } Y_j \\ \mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{2j} \cdot \nu + \mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{1j} \cdot \nu - \imath q F \mathcal{D}_0^j \widetilde{M}_{1j} \mathbf{u_g} \cdot \nu = \kappa_0 [\widetilde{M}_{0j}] & \text{on } \Gamma \\ \widetilde{M}_{2j} \text{ is } Y \text{ periodic} \end{cases}$$

Homogenized model

Applying the Green's Theorem we get

$$\int_{Y_j}\left(\frac{\partial}{\partial t}\widetilde{M}_{0j} + q^2F^2\mathcal{D}_0^j\widetilde{M}_{0j} + \imath qF\mathcal{D}_0^j\mathbf{u_g}\cdot(\nabla_{\mathbf{y}}\widetilde{M}_{1j} + \nabla_{\mathbf{x}}\widetilde{M}_{0j})\right)d\mathbf{y}$$

$$-\int_{Y_j}\mathrm{div}_{\mathbf{x}}(\mathcal{D}_0^j\nabla_{\mathbf{y}}\widetilde{M}_{1j} + \mathcal{D}_0^j\nabla_{\mathbf{x}}\widetilde{M}_{0j} - \imath qF\mathcal{D}_0^j\mathbf{u_g}\widetilde{M}_{0j})\,d\mathbf{y} = \int_{\Gamma}\kappa_0[\widetilde{M}_{0j}]ds_{\mathbf{y}}$$

But remembering that

$\widetilde{M}_{0j}$ does not depend on $\mathbf{y}$ and $\widetilde{M}_{1j}(\mathbf{x}, b\mathbf{y}, t) = u^j\cdot\left(\nabla_{\mathbf{x}}\widetilde{M}_{0j} - \imath qF\widetilde{M}_{0j}\mathbf{u_g}\right)$

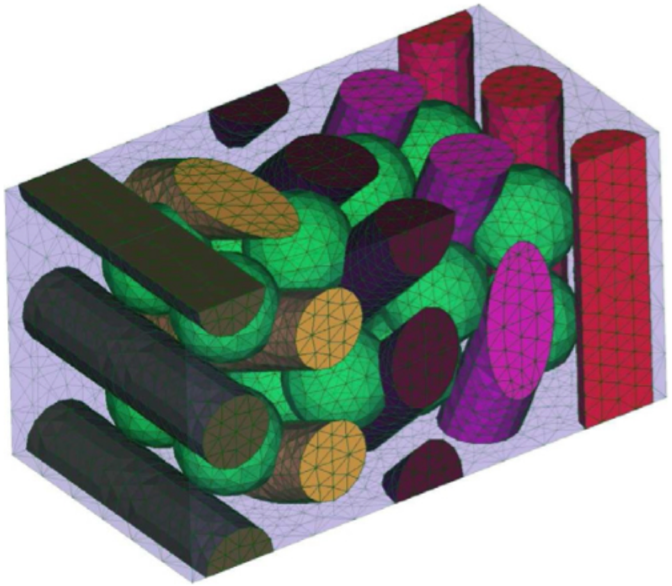
and defining the effective diffusion tensor $D^j_{lk} = \frac{1}{|Y_j|}\int_{Y_j}\mathcal{D}_0^j\left(u^j_l\cdot\mathbf{e}_k + \mathbf{e}_l\cdot\mathbf{e}_k\right)$ we get

$$\begin{cases}\frac{\partial}{\partial t}\widetilde{M}_{0e} - \mathrm{div}\left(D^e\nabla\widetilde{M}_{0e}\right) + 2\imath qD^e\nabla\widetilde{M}_{0e}\cdot\mathbf{u_g} \\ \qquad + q^2F^2D^e\mathbf{u_g}\cdot\mathbf{u_g}\widetilde{M}_{0e} + \eta_e(\widetilde{M}_{0e} - \widetilde{M}_{0c}) = 0 \quad \Omega\times]0,T_E[\\ \frac{\partial}{\partial t}\widetilde{M}_{0c} - \mathrm{div}\cancel{\left(D^c\nabla\widetilde{M}_{0c}\right) + 2\imath qD^c\nabla\widetilde{M}_{0c}\cdot}\mathbf{u_g} \\ \qquad + \cancel{q^2F^2D^c\mathbf{u_g}\cdot\mathbf{u_g}\widetilde{M}_{0c}} + \eta_c(\widetilde{M}_{0c} - \widetilde{M}_{0e}) = 0 \quad \Omega\times]0,T_E[\\ \widetilde{M}_{0e}(\cdot,0) = M_{init}, \quad \widetilde{M}_{0c}(\cdot,0) = M_{init} \quad \text{in } \Omega\end{cases}$$

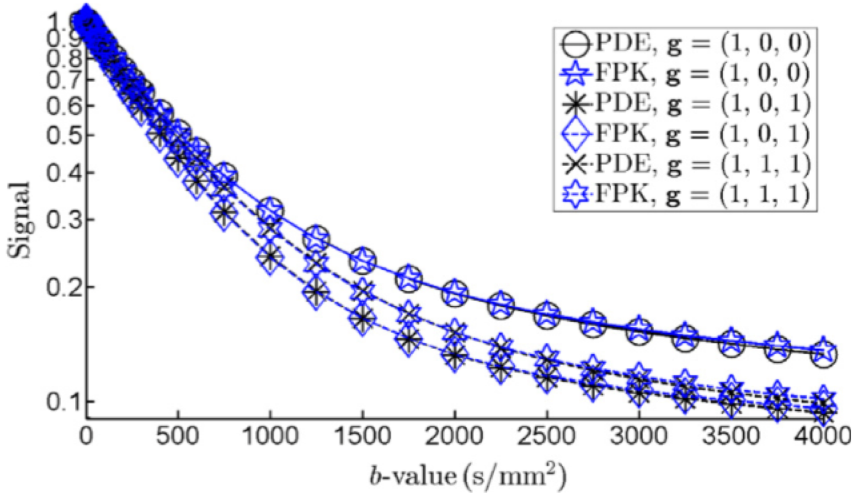
with $\eta_j := \frac{\kappa_0|\Gamma|}{|Y_j|}$

If Y_c does not touch the boundary of Y, then $D^c = 0$

Numerical results



(a) Finite elements mesh of C.



(b) DMRI signals

Fig. 5. (a) Finite elements mesh of $C = [-3.75, 3.75] \times [-7.03, 7.03] \times [-3.75, 3.75]$ µm³ containing 5 layers of cylinders and 4 layers of spheres. In each layer, the cylinders have the same orientation. (b) The signals $S_{PDE}(b)$ and $S_{FPK}(b)$. Simulation parameters: $D^0 = 3 \times 10^{-3}$ mm²/s, $\kappa = 10^{-5}$ m/s; the gradient directions are $\mathbf{g}_1 = (1,0,0)$, $\mathbf{g}_2 = (1,0,1)$, and $\mathbf{g}_3 = (1,1,1)$; the pulse sequence is PGSE, with $\delta = \Delta = 40$ ms.

Convergence

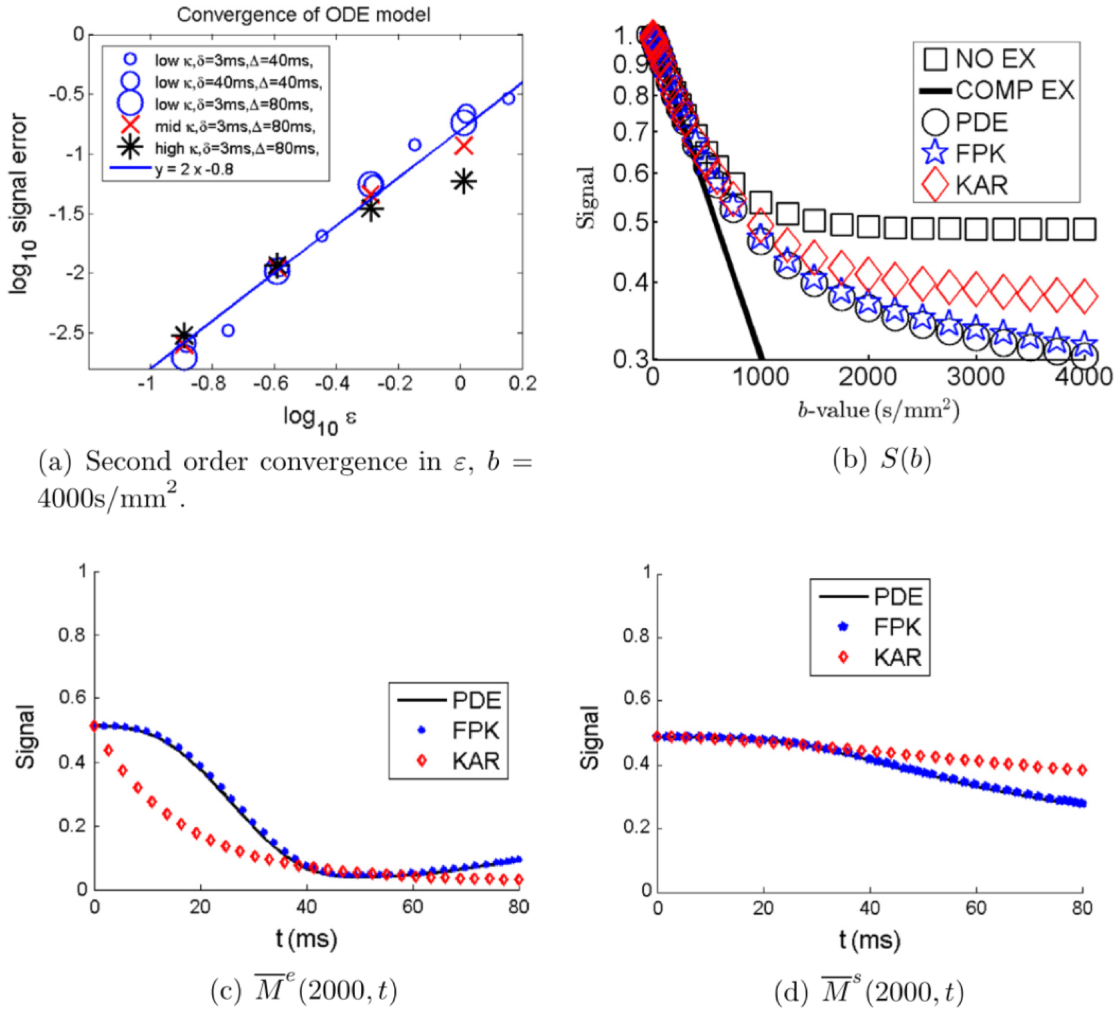


Fig. 1. (a) The FPK model signal converges to the reference signal with second order convergence in $\varepsilon = l/L$, where l is the side length of the representative volume C and L is a measure of the diffusion displacement. (b) DMRI signals: $S_{PDE}(b)$, $S_{FPK}(b)$, $S_{KAR}(b)$, $S_{NOEX}(b)$, $S_{COMPEX}(b)$. Simulation parameters: sphere radius $R^s = 2.45$ µm, $D^0 = 3 \times 10^{-3}$ mm²/s, $\kappa = 10^{-5}$ m/s, PGSE sequence with $\delta = 40$ ms, $\Delta = 40$ ms. (c) Compartment magnetization in the extra-cellular compartment at $b = 2000$ s/mm²: $\overline{M}^e_{PDE}(2000,t)$, $\overline{M}^e_{FPK}(2000,t)$, $\overline{M}^e_{KAR}(2000,t)$, same simulation parameters as (b). (d) Compartment magnetization in the sphere compartment at $b = 2000$ s/mm²: $\overline{M}^s_{PDE}(2000,t)$, $\overline{M}^s_{FPK}(2000,t)$, $\overline{M}^s_{KAR}(2000,t)$, same simulation parameters as (b).

FPK limitations

- The effective diffusion tensors are constants, i.e. they don't depend on the chosen $f(t)$. Indeed

$$D^j_{lk} = \frac{1}{|Y_j|}\int_{Y_j} \mathcal{D}^j_0(\nabla u^j_l \cdot e_k + e_l \cdot e_k)$$

with u^j_l, $l = 1, \dots, d$, $j = e, c$, solutions of the cell problems

$$\begin{cases} -\mathrm{div}_{\mathbf{y}}\left(\mathcal{D}^j_0 \nabla_{\mathbf{y}} u^j_l + \mathcal{D}^j_0 \mathbf{e}_l\right) = 0 & Y_j \\ \mathcal{D}^j_0 \nabla_{\mathbf{y}} u^j_l \cdot \nu + \mathcal{D}^j_0 \mathbf{e}_l \cdot \nu = 0 & \Gamma \\ u^j_l \text{ is } Y \text{ periodic} \end{cases}$$

Remark: D^j have the same form of the ones in [Cheng and Torquato 1997] assuming $\kappa = 0$.

- It's a more suited approximation for the long-time regime, i.e. when

$$L^2 \ll 2\mathbf{u}_g^T \min_{c,e}(D^c, D^e)\mathbf{u}_g T_E$$

Idea: introduce an appropriate scaling on time $t_\varepsilon = \varepsilon^\alpha t_0$ which links the spatial and time scales.

Other scalings including time

- $\hat{\mathcal{D}}_0 = \begin{cases} \mathcal{D}_0^c & \text{in } Y_c \\ \mathcal{D}_0^e & \text{in } Y_e \end{cases}$
- $\kappa_\varepsilon = \kappa_0 \varepsilon.$

Periodic two-scale expansion

$$\widetilde{M}_\varepsilon(\mathbf{x}, t) = \begin{cases} \widetilde{M}_\varepsilon^e(\mathbf{x}, t) = \sum_{i=0}^{\infty} \varepsilon^i \widetilde{M}_{ie}\left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, \frac{t}{\varepsilon^\alpha}\right) & \text{in } \Omega_e^\varepsilon \\ \widetilde{M}_\varepsilon^c(\mathbf{x}, t) = \sum_{i=0}^{\infty} \varepsilon^i \widetilde{M}_{ic}\left(\mathbf{x}, \frac{\mathbf{x}}{\varepsilon}, \frac{t}{\varepsilon^\alpha}\right) & \text{in } \Omega_c^\varepsilon \end{cases}$$

$\widetilde{M}_{ie}(\mathbf{x}, \mathbf{y}, \tau)$, $\widetilde{M}_{ic}(\mathbf{x}, \mathbf{y}, \tau)$ defined on $\Omega \times Y_e \times]0, T_E/\varepsilon^\alpha[$ and $\Omega \times Y_c \times]0, T_E/\varepsilon^\alpha[$ and Y-periodic in y.

- b small $\longrightarrow$ $q = \dfrac{q_0}{\varepsilon^\gamma}$.

  Because $b = q^2 \int_0^{T_E} F^2(t)dt = \varepsilon^{3\alpha - 2\gamma} q_0^2 \int_0^{\tilde{T}_E} F_0^2(\tau)d\tau$.

Choice of scaling

Resulting PDE in $Y_j \times [0, T_E]$

$$\sum_{i=0}^{\infty} \varepsilon^{i-\alpha+2} \frac{\partial}{\partial \tau} \widetilde{M}_{ij} + \varepsilon^{i+2\alpha-2\gamma+2} q_0^2 \mathbf{u_g} \cdot \mathbf{u_g} F_0^2 \mathcal{D}_0^j \widetilde{M}_{ij}$$
$$+ \varepsilon^{i+\alpha-\gamma+2} \imath q_0 \mathbf{u_g} F_0 \mathcal{D}_0^j (\nabla_{\mathbf{x}} \widetilde{M}_{ij} + \varepsilon^{-1} \nabla_{\mathbf{y}} \widetilde{M}_{ij}) - \varepsilon^{i+2} \mathrm{div}_{\mathbf{x}} (\mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{ij})$$
$$- \varepsilon^{i+1} \mathrm{div}_{\mathbf{x}} (\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{ij}) - \varepsilon^{i+1} \mathrm{div}_{\mathbf{y}} (\mathcal{D}_0^j \nabla_{\mathbf{x}} \widetilde{M}_{ij}) - \varepsilon^{i} \mathrm{div}_{\mathbf{y}} (\mathcal{D}_0^j \nabla_{\mathbf{y}} \widetilde{M}_{ij})$$
$$+ \varepsilon^{i+\alpha-\gamma+2} \mathrm{div}_{\mathbf{x}} (\imath q_0 \mathbf{u_g} F_0 \mathcal{D}_0^j \widetilde{M}_{ij}) + \varepsilon^{i+\alpha-\gamma+1} \mathrm{div}_{\mathbf{y}} (\imath q_0 \mathbf{u_g} F_0 \mathcal{D}_0^j \widetilde{M}_{ij}) = 0$$

Mathematical parameters limitations:

1. To avoid incompatibilities with the B.C. → $0 \leq \alpha \leq 2$,
2. Small b-value → $3\alpha - 2\gamma > 0$.

Possible choices:

- $\alpha = \gamma = 0$ gives the FPK model already discussed
- $\alpha = 1$ For all the choice of γ which respect the condition 2 we obtain a model whose *ADC* does not depend on time (like FPK).

Model for $\boldsymbol{\alpha = \gamma = 2}$

The signal attenuation results

$$\frac{S(T_E)}{S_0} = 1 - ADC_{new}\, b + O(\varepsilon^3)$$

$$ADC_{new} := v_e \overline{D}_e^{eff}(T_E)\mathbf{u_g} \cdot \mathbf{u_g} + v_c \overline{D}_c^{eff}(T_E)\mathbf{u_g} \cdot \mathbf{u_g},$$

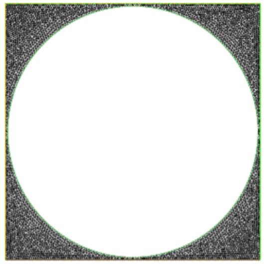
and for $k, l = 1, \ldots, d,, j \in \{ e, c \}$

$$\left(\overline{D}_j^{eff}\right)_{kl}(T_E) := \mathcal{D}_0^j \left(\mathbf{e}_k \cdot \mathbf{e}_l - \frac{1}{\int_0^{T_E} F^2(t)dt} \int_0^{T_E} \left(F(t) \frac{1}{|Y_j|} \int_{Y_j} \nabla \omega_l^j(\mathbf{y}, t) \cdot \mathbf{e}_k dy \right) dt \right)$$

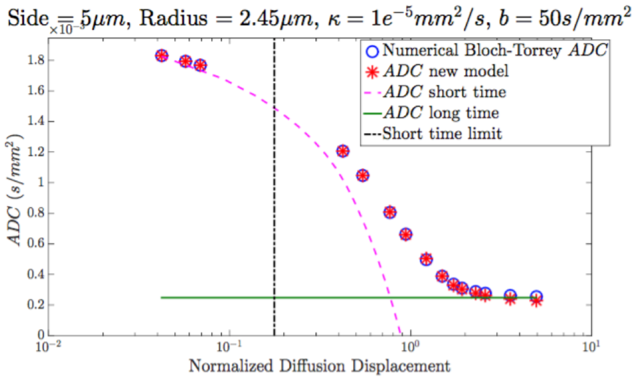
and ω_l^j solves the cell problem

$$\begin{cases} \dfrac{\partial}{\partial t}\omega_l^j(\mathbf{y}, t) - \mathrm{div}_\mathbf{y}\left(\mathcal{D}_0^j \nabla_\mathbf{y} \omega_l^j(\mathbf{y}, t) - \mathcal{D}_0^j F(t)\mathbf{e}_l\right) = 0 & \text{in } Y_j \times [0, T_E] \\ \mathcal{D}_0^j \nabla_\mathbf{y} \omega_l^j(\mathbf{y}, t) \cdot \nu - F(t)\mathcal{D}_0^j \mathbf{e}_l \cdot \nu = 0 & \text{on } \Gamma \times [0, T_E] \\ \omega_l^j(\cdot, 0) = 0 & \text{in } Y_j \\ \omega_l^j \text{ is } Y\text{-periodic} & \end{cases}$$

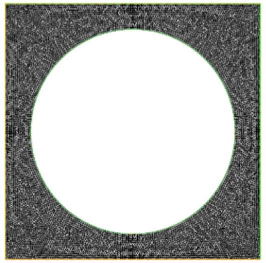
Numerical Results



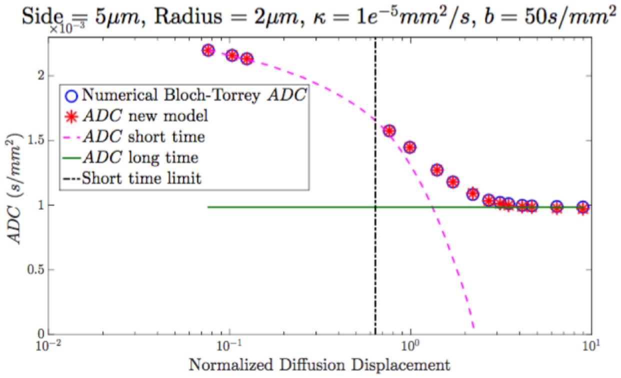
(a) Configuration



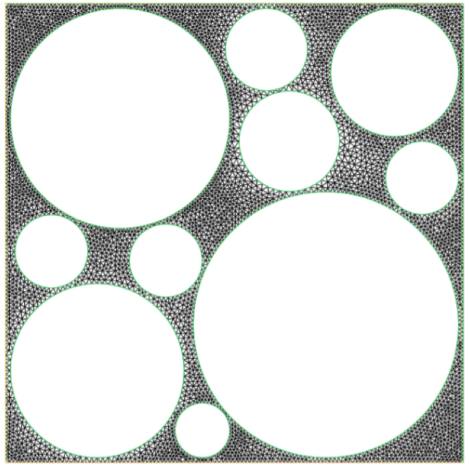
(b) $R = 0.49L$



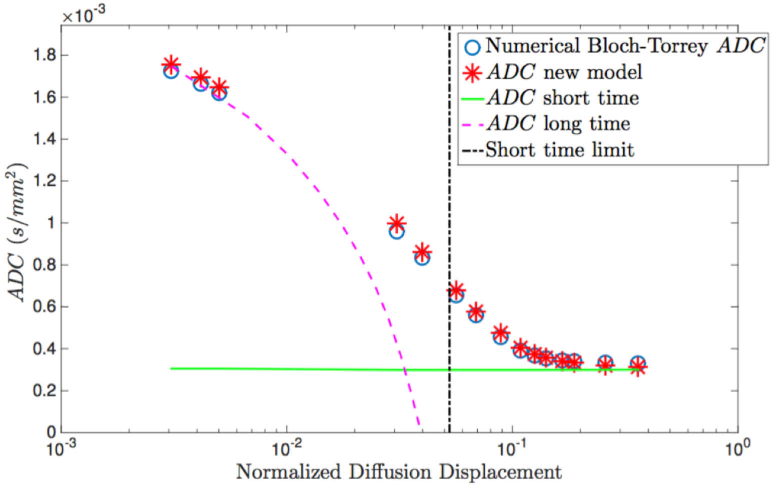
(c) Configuration



(d) $R = 0.4L$



(a) Configuration

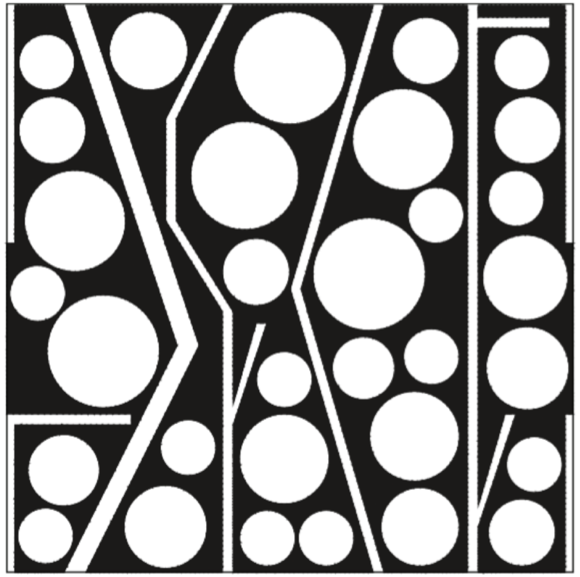


(b) *adc*

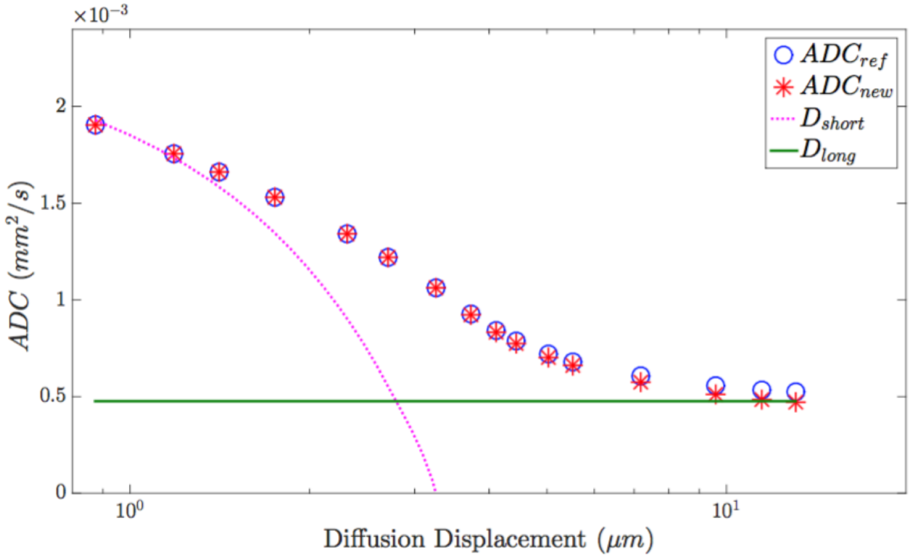
Figure: ADC approximation for a group of circular biological cells in a periodicity cell with $\kappa = 1 \times 10^{-5}$ m/s, $\sigma_e = 3 \times 10^{-3} mm^2/s$, $\sigma_c = 1.6 \times 10^{-3} mm^2/s$.

ADC approximation with $\sigma_e = 3 \times 10^{-3} mm^2/s$, $\sigma_c = 1.6 \times 10^{-3} mm^2/s$.

Numerical Results



(a) Configuration

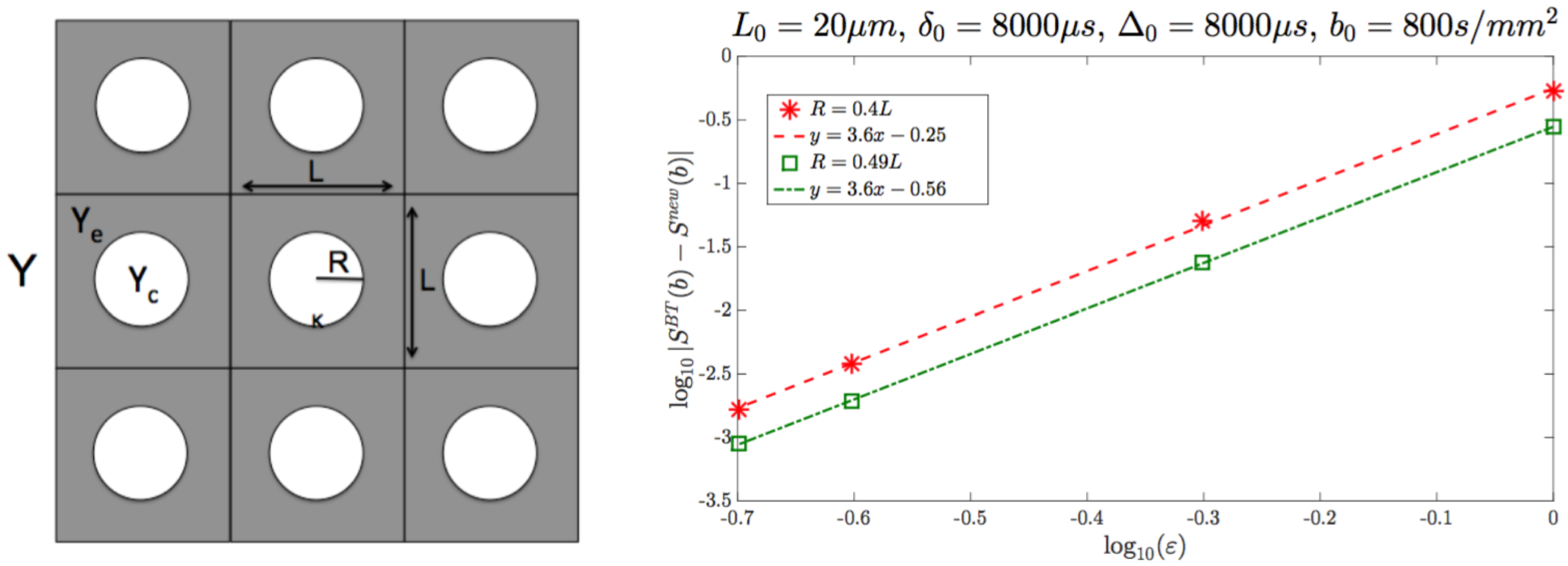


(b) *ADC*

Figure: Periodicity cell of $L = 50\mu\text{m}$, external volume fraction $v_e = 0.4$, $\mathcal{D}_0^e = 3 \times 10^{-3}\text{mm}^2/\text{s}$, $\mathcal{D}_0^c = 2 \times 10^{-3}\text{mm}^2/\text{s}$, $\kappa = 1 \times 10^{-5}\text{m/s}$, $\mathbf{u_g} = [1, 1]$.

- ADC_{ref} fitted using a polynomial fit of the signal obtained solving Bloch-Torrey problem for ten b until $b = 100 s/mm^2$.
- D_{short} computed using Mitra's model [Mitra *et al.* 1992].
- D_{long} computed using [Cheng and Torquato 1997] with $\kappa = 0\text{m/s}$.

Numerical convergence



(a) Geometry (b) Signal absolute error

Figure: Signal numerical convergence for a circular biological cells placed at the center of a periodicity cell with $\kappa = 1 \times 10^{-5}$ m/s, $\mathcal{D}_0^e = 3 \times 10^{-3} mm^2/s$, $\mathcal{D}_0^c = 1.6 \times 10^{-3} mm^2/s$.