The Mesoscopic Physics of Diffusion MRI

St Petersburg, Russia, September 2017

Dmitry S. Novikov

Center for Biomedical Imaging, Department of Radiology
New York University School of Medicine

dmitry.novikov@nyumc.org
http://diffusion-mri.com

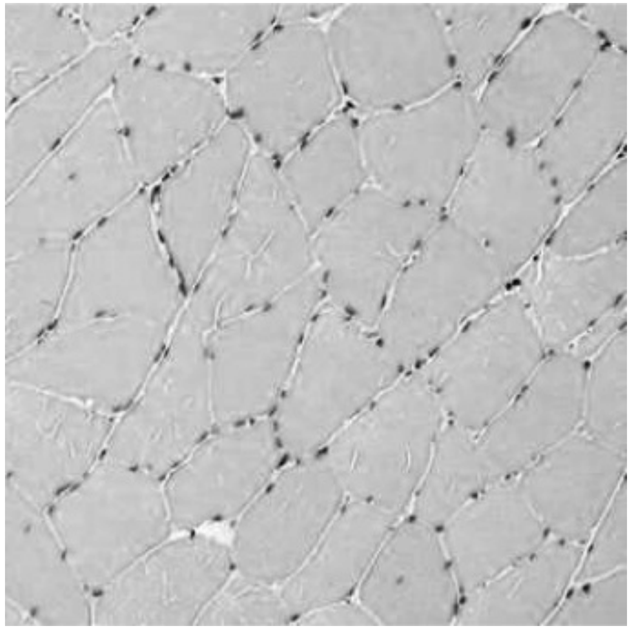
Funding:
NIH R01 NS088040
Litwin Foundation for Alzheimer's Research
Raymond & Beverly Sackler Fellowship

Disclaimer

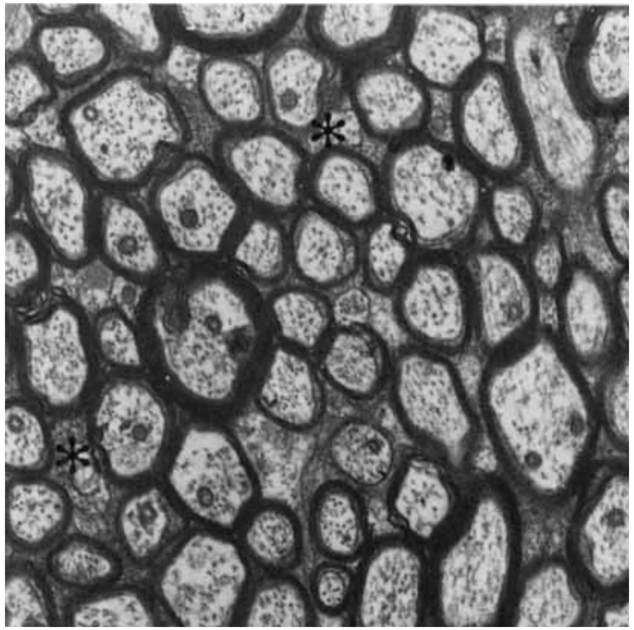
Please interrupt!!!

What does it mean to *quantify* microstructure?

Can we at least *distinguish* b/w 2 tissues?



Muscle fiber x-section

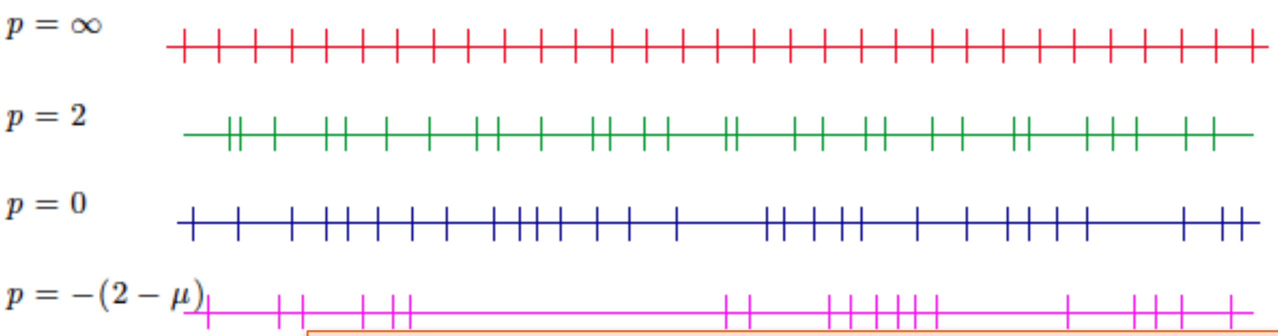


Neuronal white matter fiber x-section

1 major direction

Similar diffusion tensor eigenvalues

… at the very least, distinguish between these?



Novikov, Fieremans, et al., PNAS 111, 5088 (2014)

Identical permeable barriers with same avg density ➔ same D_0, D_∞

$$\vartheta = \frac{p+d}{2}$$

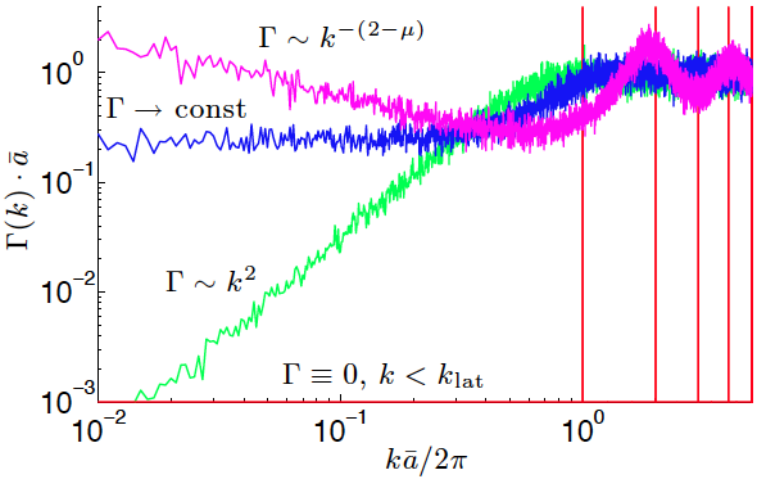
d = space dimension

- Structural exponent p:
  - p=0: uncorrelated (~Poissonian fluctuations); short-range
  - p>0: more ordered (smaller fluctuations); hyperuniform
  - p<0: less ordered (larger fluctuations); "strong disorder"

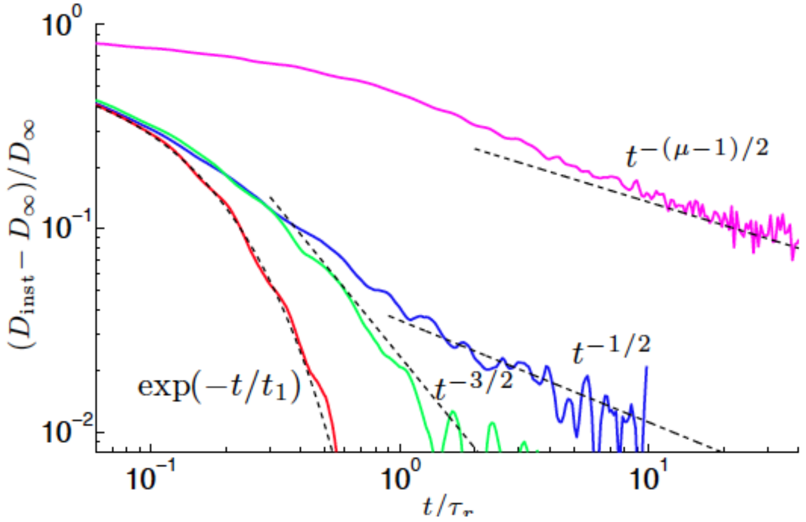
F.T.(barrier d

$$\Gamma(k) = \int dx\, \langle n($$

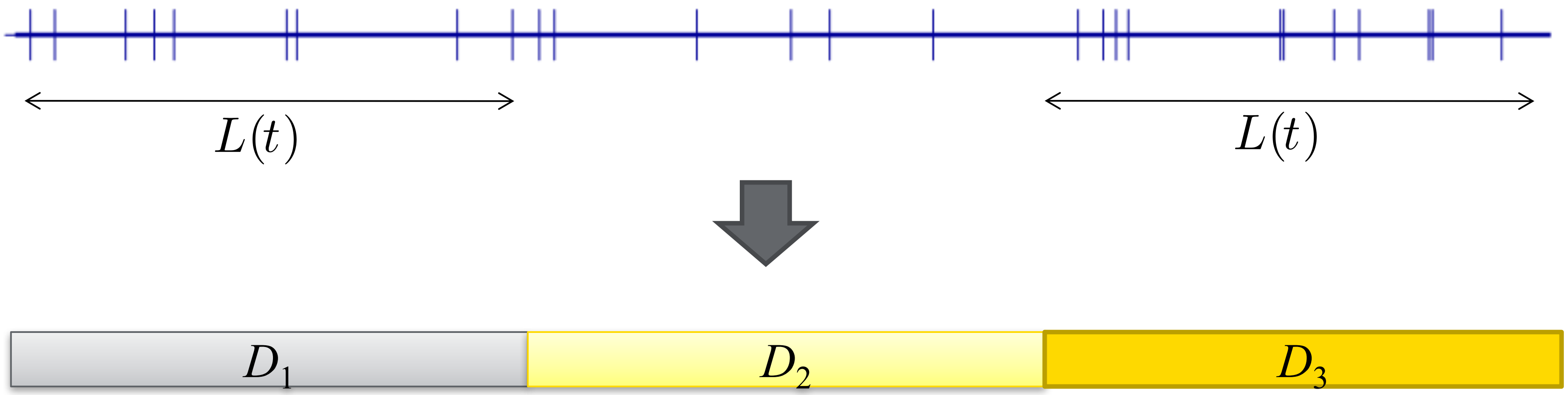
$$\Gamma(k) \sim k^{p}, \quad k \to 0$$



$$D_{\mathrm{inst}}(t) = \frac{\partial}{\partial t}\frac{\langle x^2\rangle}{2} \simeq D_\infty + \mathrm{const}\cdot t^{-\vartheta}$$



Long time limit: $L(t) \sim \sqrt{D_\infty t} \gg \bar{a}$



After coarse-graining: Slightly different D_j due to fluctuations in the # of barriers

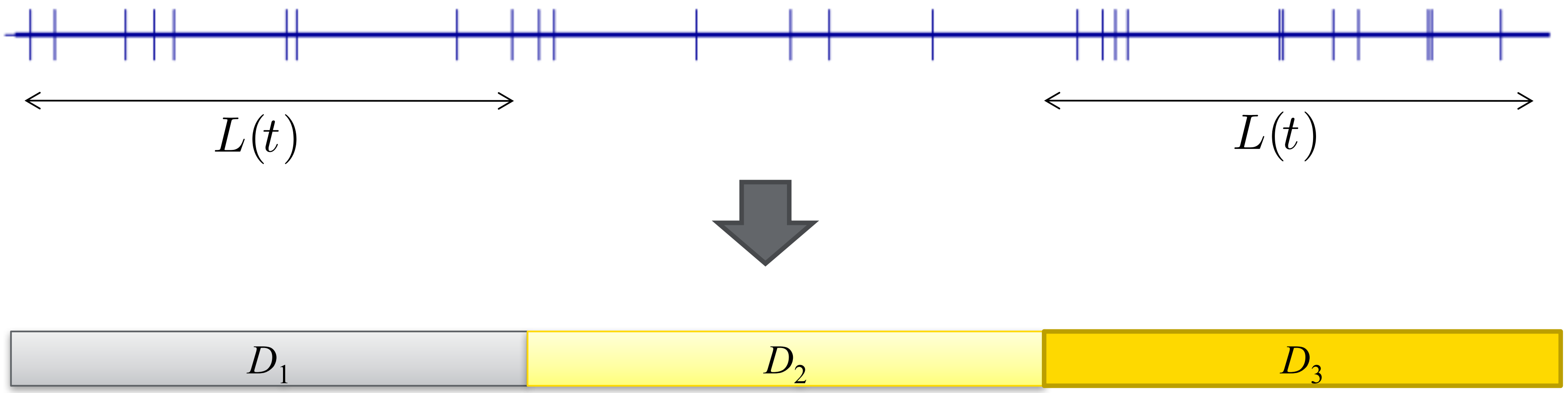
Add up "resistances", find $\frac{1}{D_\infty} = \left\langle \frac{1}{D_j} \right\rangle$ so that $D_\infty \simeq \langle D_j \rangle - \frac{\langle (\delta D_j)^2 \rangle}{\langle D_j \rangle}$

measured $D_{\text{inst}}(t)$

$$D_{\text{inst}}(t) \equiv \langle D_j \rangle \simeq D_\infty + \frac{\langle (\delta D_j)^2 \rangle}{D_\infty}$$

Fluctuation correction at a given diffusion length scale $L(t)$; decreases with time ("homogenization")

Long time limit: $L(t) \sim \sqrt{D_\infty t} \gg \bar{a}$



After coarse-graining: Slightly different D_j due to fluctuations in the # of barriers N_j

$$D_{\text{inst}}(t) - D_\infty \propto \langle (\delta D)^2 \rangle \propto \langle (\delta n)^2 \rangle \sim \frac{1}{\bar{N}} \sim \frac{1}{L(t)} \sim \frac{1}{\sqrt{t}}$$

(Poissonian)
[Ernst et al, 1983]

$$\sim \frac{1}{t^\vartheta}, \quad \vartheta$$ related to disorder class [DN et al., 2014]

$$\sim e^{-t/t_0},$$ periodic

How one really calculates this…

PNAS 111, 5088 (2014)

- Coarse-grain down to $L(t)$ ➔ effective diffusion eqn

$$\partial_t \psi = \overline{D}\partial_{\mathbf{r}}^2 \psi + \partial_{\mathbf{r}}(\delta D(\mathbf{r})\partial_{\mathbf{r}}\psi) \qquad D(\mathbf{r}) = \overline{D} + \delta D(\mathbf{r}), \qquad \overline{D} \equiv \langle D(\mathbf{r})\rangle$$

- Disorder-averaged propagator up to $(\delta D)^2$

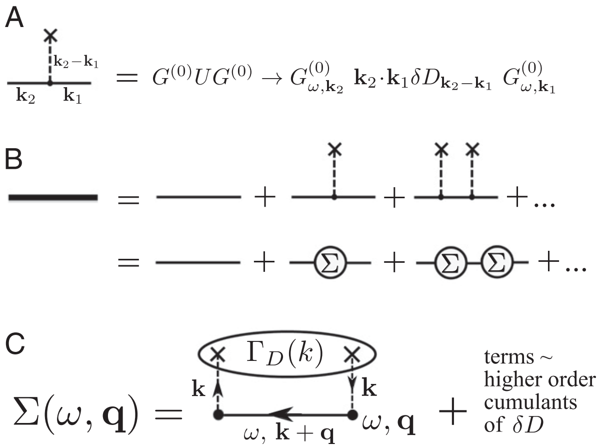
$$G_{\omega,\mathbf{q}} = \int \mathrm{d}\mathbf{r}\;\mathrm{d}t\; e^{i\omega t - i\mathbf{q}\mathbf{r}}\; G_{t,\mathbf{r}} = \frac{1}{-i\omega + \overline{D}q^2 - \Sigma(\omega,\mathbf{q})} \qquad \Sigma(\omega,\mathbf{q}) \simeq \int \frac{\mathrm{d}^d\mathbf{k}}{(2\pi)^d}\, \frac{[\mathbf{q}\cdot(\mathbf{k}+\mathbf{q})]^2\Gamma_D(k)}{-i\omega + \overline{D}(\mathbf{k}+\mathbf{q})^2}.$$

- Expand self-energy part up to q^2;
  obtain effective $D(\omega)$ as a pole of the propagator

$$G_{\omega,\mathbf{q}} = \frac{1}{-i\omega + D_\infty q^2 - \delta\Sigma(\omega,\mathbf{q})},$$

$$\delta\Sigma(\omega,\mathbf{q}) = \frac{i\omega\, q^2}{D_\infty d}\int \frac{\mathrm{d}^d\mathbf{k}}{(2\pi)^d}\,\frac{\Gamma_D(k)}{-i\omega + D_\infty k^2} + \mathcal{O}(q^4). \qquad \frac{\mathcal{D}(\omega) - D_\infty}{D_\infty} \simeq -\frac{i\omega}{D_\infty^2 d}\int \frac{\mathrm{d}^d\mathbf{k}}{(2\pi)^d}\,\frac{\Gamma_D(k)}{-i\omega + D_\infty k^2}$$

- In the time domain, $D_{\text{inst}}(t) - D_\infty \simeq \frac{1}{dD_\infty}\int \frac{\mathrm{d}^d\mathbf{k}}{(2\pi)^d}\Gamma_D(k)e^{-D_\infty k^2 t} \sim t^{-\vartheta}$, $\vartheta = \frac{p+d}{2}$



$$\Gamma_D(r) = \langle \delta D(\mathbf{r}_0 + \mathbf{r})\delta D(\mathbf{r}_0)\rangle$$

$$\Gamma_D(k) = \int \mathrm{d}^d\mathbf{r}\; e^{-i\mathbf{k}\mathbf{r}}\;\Gamma_D(r)$$

- From correlator of coarse-grained $D(\mathbf{r})$ to correlator of structure $n(\mathbf{r})$: Simple proportionality!

$$\delta D(\mathbf{r}) \simeq (\partial D_\infty/\partial\overline{n})\delta n(\mathbf{r}) \qquad ➔ \qquad \Gamma_D(k) \simeq C(\overline{n})\cdot\Gamma(k), \quad C(\overline{n}) = (\partial D_\infty/\partial\overline{n})^2$$

Diffusion = coarse-graining = low-pass filter

Novikov, Fieremans, et al., PNAS 111, 5088 (2014)

Identical permeable barriers with same avg density ➔ same D_0, D_∞

$$\vartheta = \frac{p+d}{2}$$

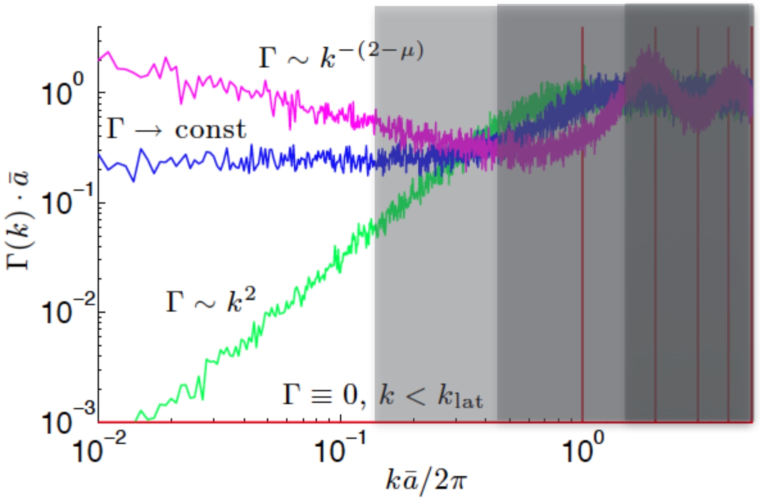
d = space dimension

F.T.(barrier density correlation function) = power spectrum

$$\Gamma(k) = \int dx\, \langle n(x_0+x)n(x_0)\rangle e^{-ikx} \propto |n(k)|^2$$

$$\Gamma(k) \sim k^p, \quad k \to 0$$

$$D_{\text{inst}}(t) = \frac{\partial}{\partial t}\frac{\langle x^2\rangle}{2} \simeq D_\infty + \text{const}\cdot t^{-\vartheta}$$

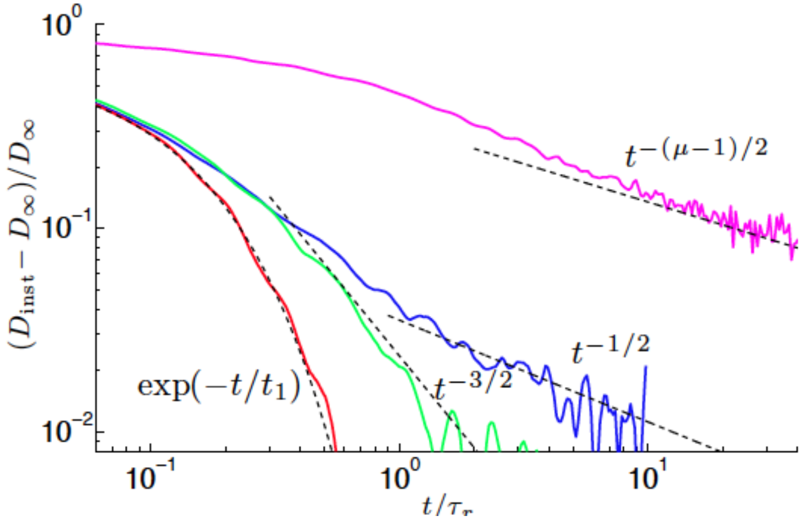


Diffusion = coarse-graining over increasing $L(t)$

~ Gaussian filter,

selecting $k \lesssim 1/L(t)$

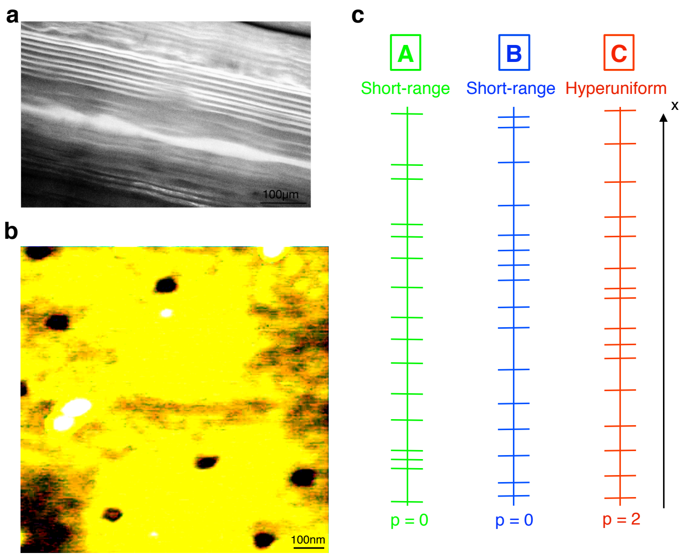
long t ➔ small k ➔ focus on **universal features** **of structural organization**



Experiment in $d = 1$

Permeable films with holes

Papaioannou, **Novikov, Fieremans, Boutis**
Preprint http://arxiv.org/abs/1607.08639
CUNY/NYU



$$\vartheta = \frac{p+d}{2}$$

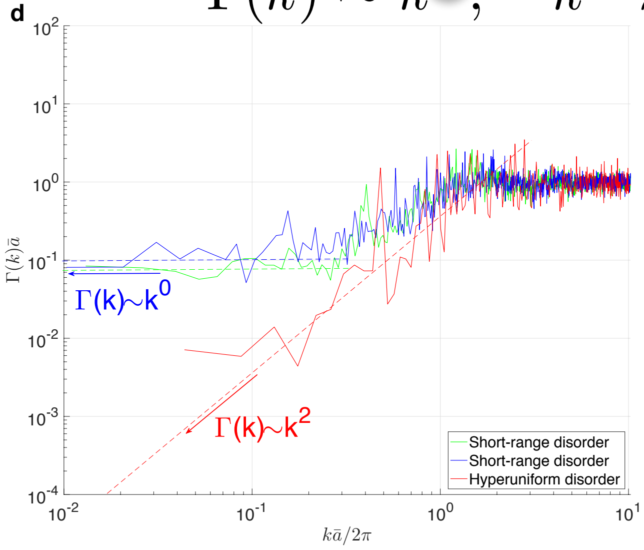
d = space dimension

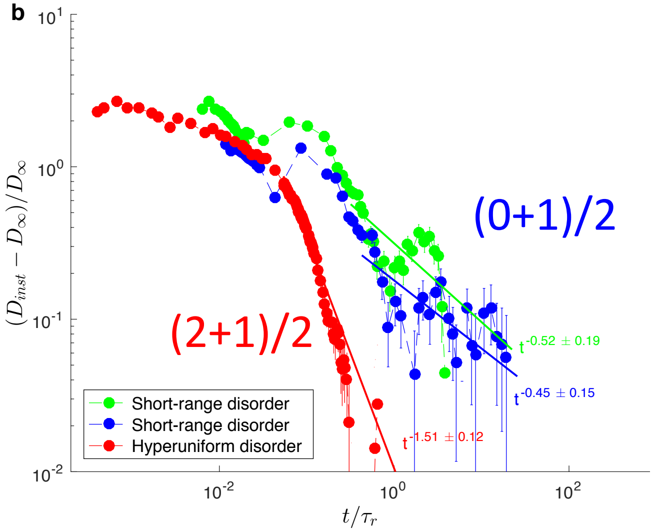
F.T.(barrier density correlation function) = power spectrum

$$\Gamma(k) = \int dx\, \langle n(x_0+x)n(x_0)\rangle e^{-ikx} \propto |n(k)|^2$$

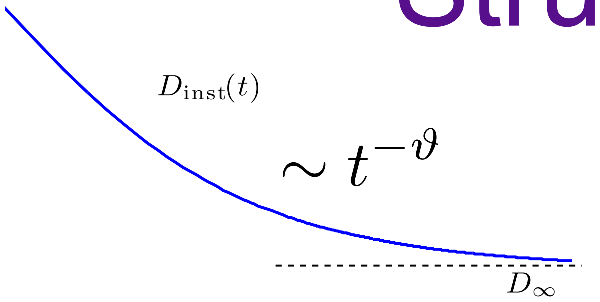
$$\Gamma(k) \sim k^{p}, \quad k \to 0$$

$$D_{\text{inst}}(t) = \frac{\partial}{\partial t}\frac{\langle x^2\rangle}{2} \simeq D_\infty + \text{const}\cdot t^{-\vartheta}$$





Structural universality classes



PNAS 111, 5088 (2014)

$\vartheta = \frac{p+d}{2}$ "dynamical exponent"

Short-scale differences become irrelevant

Relevant: Statistics of large-scale structural fluctuations

Stronger fluctuations = smaller ϑ = slower approach to D_∞

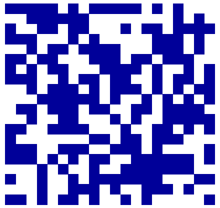
$$D_{\mathrm{inst}}(t) \equiv \frac{\partial}{\partial t}\frac{\langle \delta x^2 \rangle}{2} \simeq D_\infty + \mathrm{const}\cdot t^{-\vartheta}$$

- Media can be disordered in a few distinct ways
- Relate structure classes to diffusive dynamics
- Exponent ϑ = marker for the type of structural order/disorder
- Robust wrt biological variability!
- Focus on the <u>relevant part of tissue structure</u>

extended, random rods

$D_{\mathrm{inst}} \simeq D_\infty + \mathrm{const}\cdot t^{-1}$

$p = -(d-2)$ $\vartheta = 1$

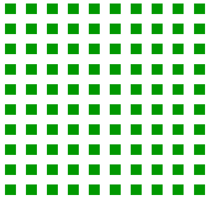


$D_{\mathrm{inst}} \simeq D_\infty + \mathrm{const}\cdot t^{-d/2}$

Short-range disorder (random) in d spatial dimensions

$p=0$ $\vartheta = d/2$

Ernst et al. 1983

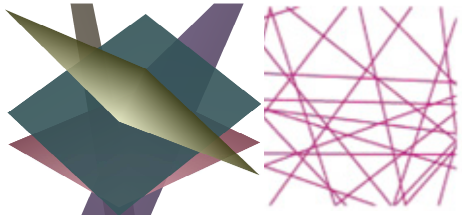


$D_{\mathrm{inst}} \simeq D_\infty + \mathrm{const}\cdot e^{-t/t_c}$

periodic
(in any spatial dimension)

$p=\infty$ $\vartheta = \infty$

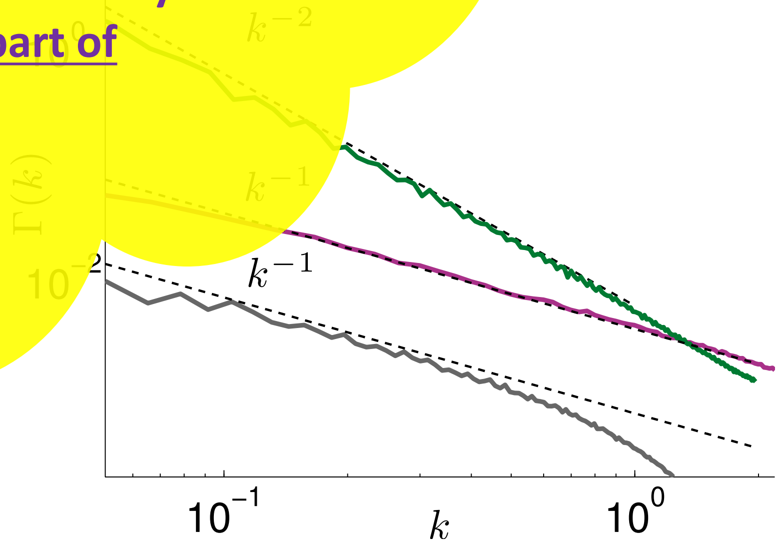
Tanner 1978; Dunn & Bergman 1995



$D_{\mathrm{inst}} \simeq D_\infty + \mathrm{const}\cdot t^{-1/2}$

extended, any d
random membranes: DN et al., Nat. Phys. 2011

$p = -(d-1)$ $\vartheta = 1/2$



Universality and dynamical exponents

- <u>The idea</u> comes from theory of critical phenomena:

At the phase transition, many systems behave in a similar way, with same **critical exponents**;
Group them into **“universality classes”**
L Landau, ~1930s; and A Migdal, V Pokrovsky, L Kadanoff, K Wilson, ~1970

Critical dynamics near a phase transition – **dynamical exponents**
P Hohenberg, B Halperin, ~1980

- In our case, the classification in terms of **structural universality classes**, distinguished by the Brownian dynamics

$$D_{\text{inst}}(t) = \frac{\partial}{\partial t}\frac{\langle x^2\rangle}{2} \simeq D_\infty + \text{const}\cdot t^{-\vartheta}$$

diffusion

structure

dimension

$$\vartheta = \frac{p+d}{2}$$

- Structural exponent p:
  - $p=0$: uncorrelated (~Poissonian fluctuations)
  - $p>0$: more ordered (smaller fluctuations); $p<0$: less ordered (larger fluctuations)

- Finite D_∞ ➔ Normal (not anomalous) diffusion,

$$\langle x^2\rangle \sim t^1\,, \quad t\to\infty$$

$$\langle x^2\rangle \sim D_\infty t + \text{const}\cdot t^{\overbrace{1-\vartheta}^{<1}}$$

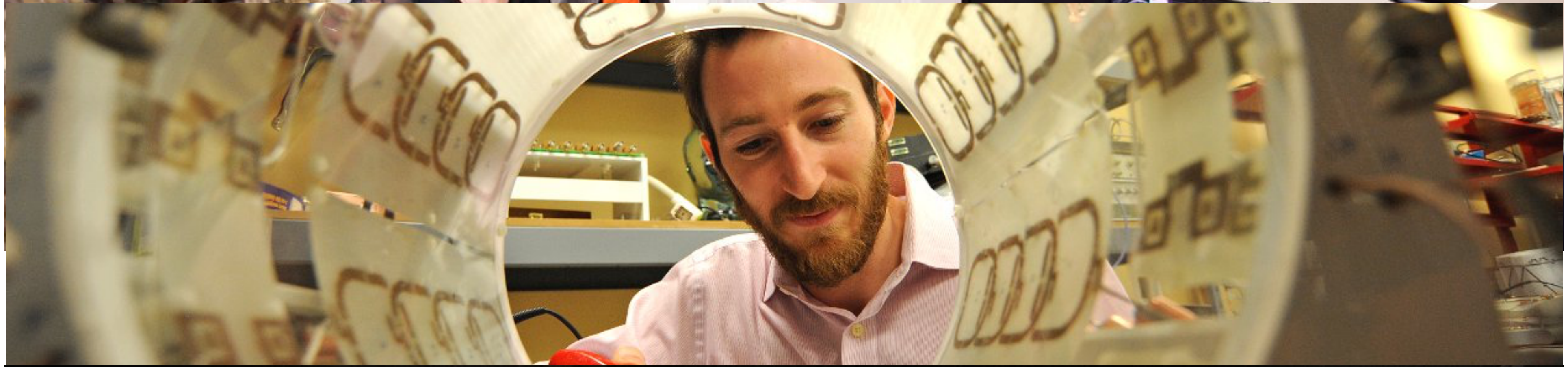
The Real World…

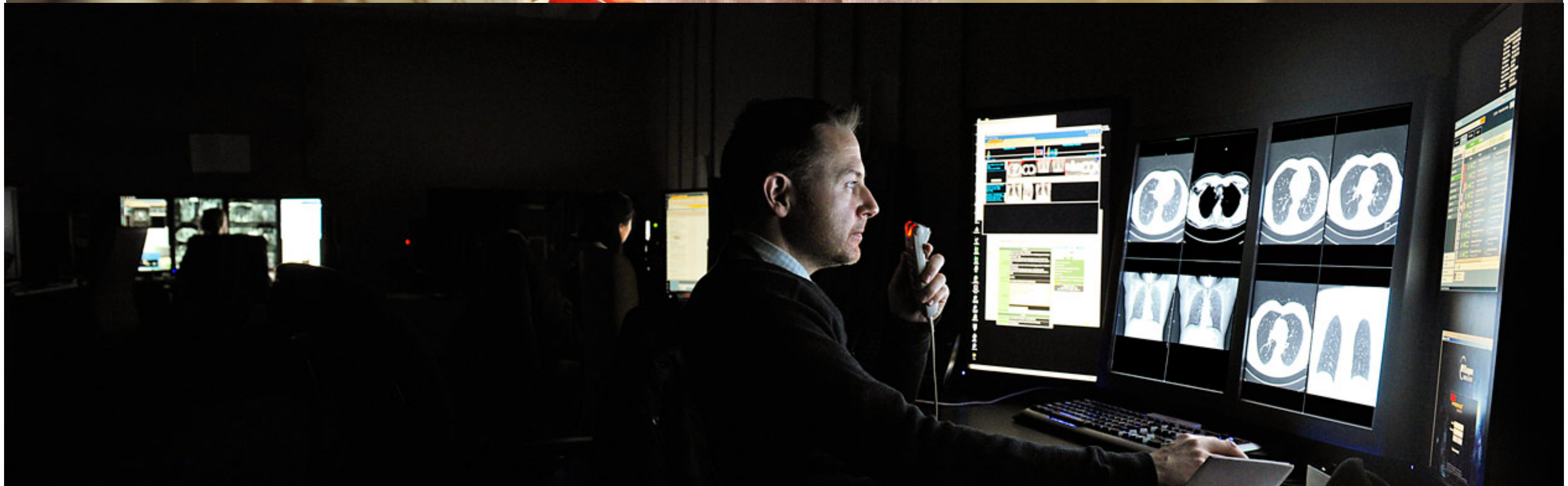
New York University School of Medicine
Department of Radiology

40+ MRI scanners
~ 200 MDs
> 1.5•10^6 exams/year

Center for Biomedical Imaging (660 First ave @38th st) = research division
100+ PhD researchers:
RF coil development; fast acquisition methods (compressed sensing, MR fingerprinting); MR spectroscopy; tissue electrical properties mapping; mesoscopic MRI (diffusion, R_2*)

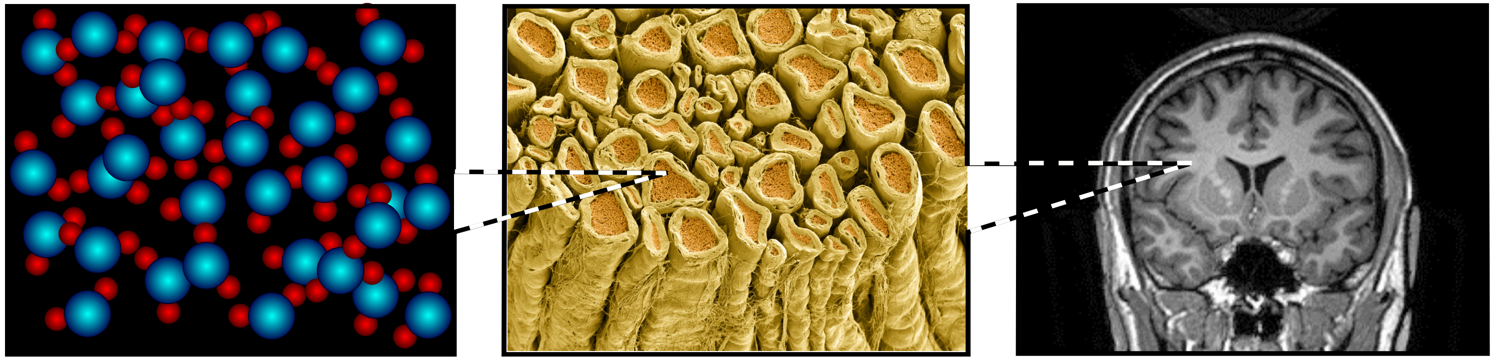
Radiology / MRI: What comes to mind?





Mesoscopic physics @ μm scale

arXiv:1612.02059 (2016)



mesoscopic Bloch-Torrey equation

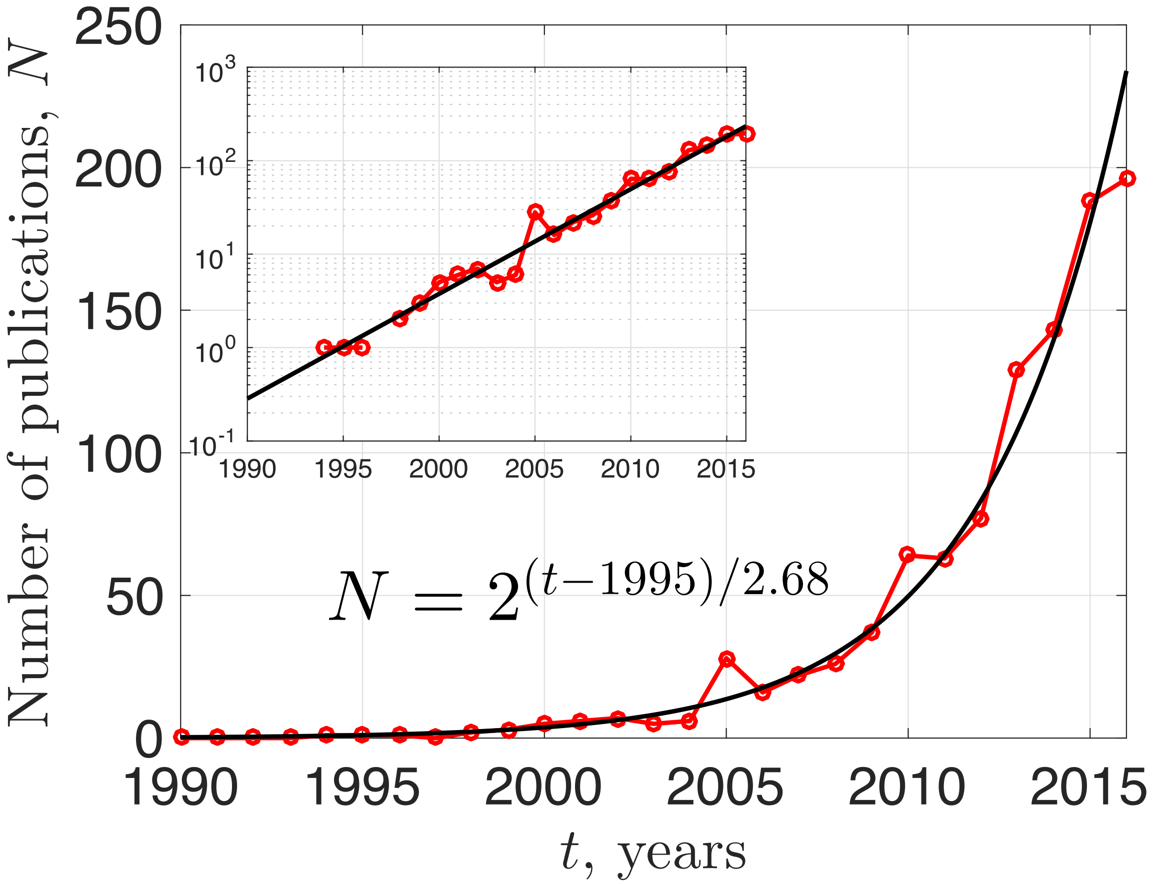
$$\partial_t M = \underbrace{\partial_{\mathbf{r}}\left(D(\mathbf{r})\partial_{\mathbf{r}} M\right)}_{\text{Diffusion term}} - \underbrace{i\Omega(\mathbf{r})}M - \underbrace{R_2(\mathbf{r})}M$$

Diffusion term:
HC Torrey, PhysRev 1956
(e.g. cell walls, tumor vs benign tissue, etc)

Locally varying Larmor freq. offset (e.g. blood, iron)

Locally varying transverse relaxation rate (e.g. myelin vs water vs cytoplasm)

“MRI” & “microstructure” in *PubMed*

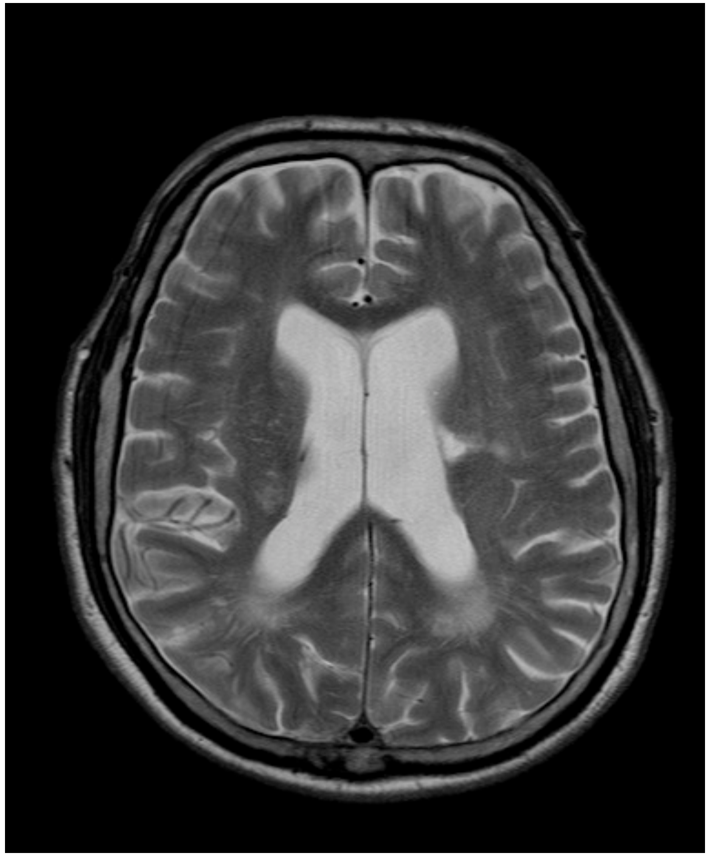


DN, VK, S.Jespersen (to appear)

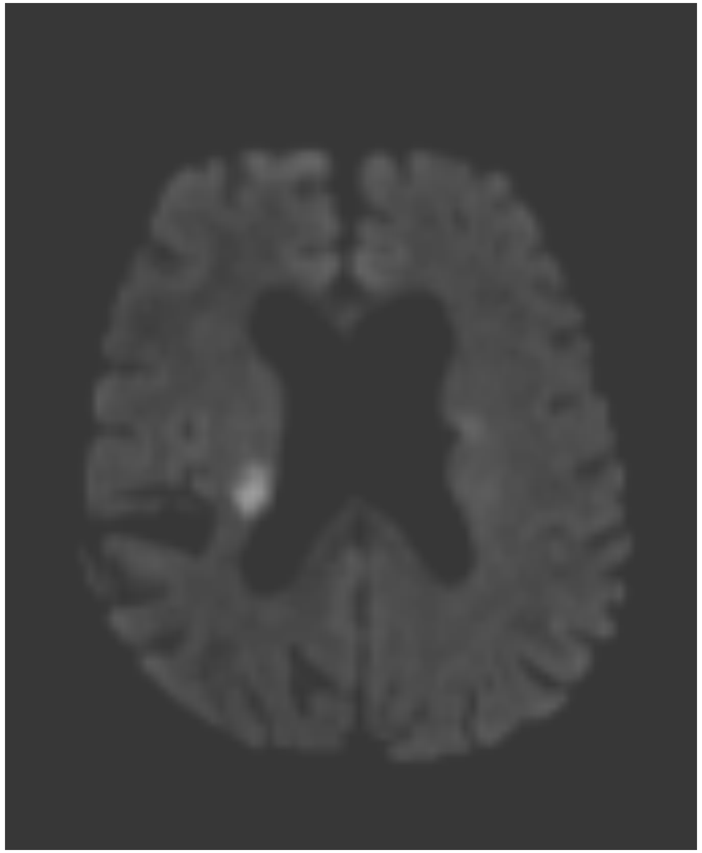
Current state of dMRI in clinic

Early detection of regional cerebral ischemia in cats: comparison of **diffusion**-and T2-weighted **MRI** and spectroscopy
ME Moseley, Y Cohen, J Mintorovitch... - Magnetic ..., 1990 - Wiley Online Library
Abstract **Diffusion**-weighted MR images were compared with T2-weighted MR images and correlated with 1 H spin-echo and 31 P MR Spectroscopy for 6-8 h following a unilateral middle cerebral and bilateral carotid artery occlusion in eight cats. **Diffusion**-weighted ...
Cited by 1423 Related articles All 4 versions Web of Science: 1144 Cite More

$$e^{-bD}, \quad D\downarrow$$



T2w



DWI

Clinical applications: Empirical so far

- Disease processes associated with diffusion abnormality:

  Ischemia, Demyelinating lesions, Tumors, Seizures, Drug toxicity, Abscess, Marrow abnormalities, Prion disease, …

- Biophysical mechanisms underlying diffusion changes are often unclear; sensitive but not yet specific!

- E.g., the cause of the drop in the diffusion observed in acute stroke is still under debate: cell swelling, exchange, active transport mechanisms, axonal beading, etc.

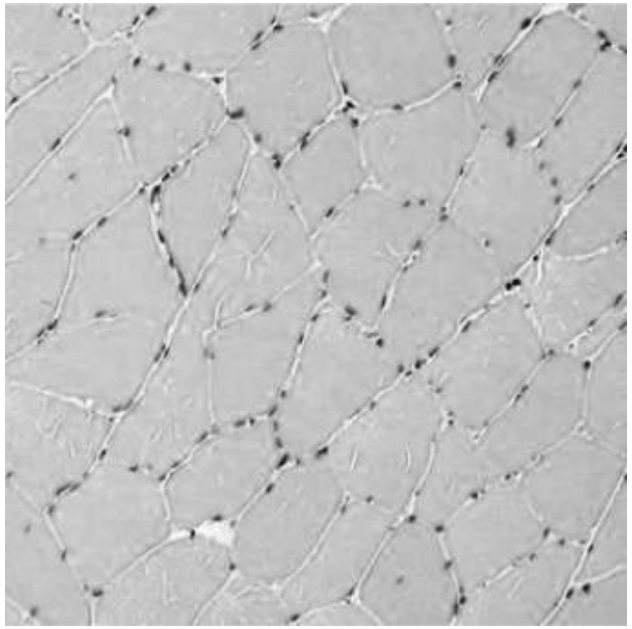
Benveniste *et al*, Stroke 23 746 (1992);
Nevo *et al*, NMR Biomed 23 734 (2010);
Ackerman *et al*, NMR Biomed 23 725 (2010);
Budde MD *et al* PNAS 107 14472 (2010);
Fieremans E et al. ISMRM (2012), 3600;
Hui ES et al. Stroke. 43 2968 (2012);
Novikov DS et al, PNAS 111, 5088 (2014)

dMRI Goal: “to see the invisible”

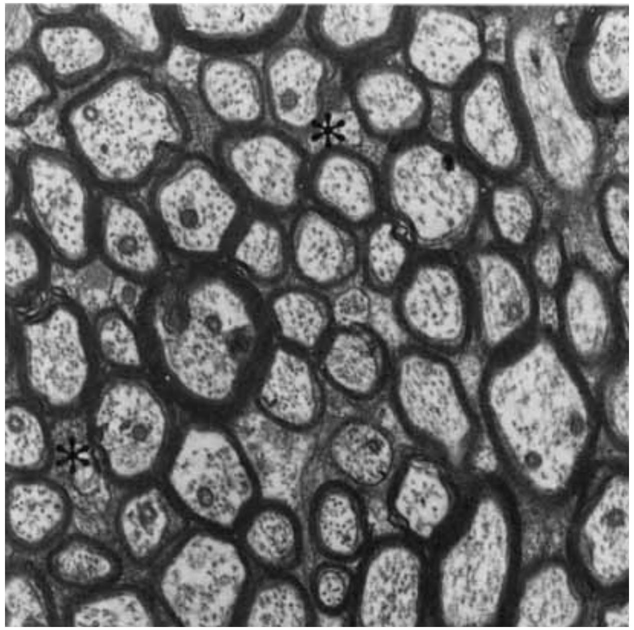
To become specific to pathological changes at the mesoscopic scale, ~ 1 – 50 μm

- **Brain:** Demyelination, axonal loss, inflammation…
  - AD, MS, TBI, stroke
- **Body:** Cell size, membrane permeability, cell density…
  - Tumor grading (e.g. prostate)
  - Atrophy, rehabilitation, dystrophy (muscle)

Can we at least *distinguish* b/w 2 tissues?



Muscle fiber x-section



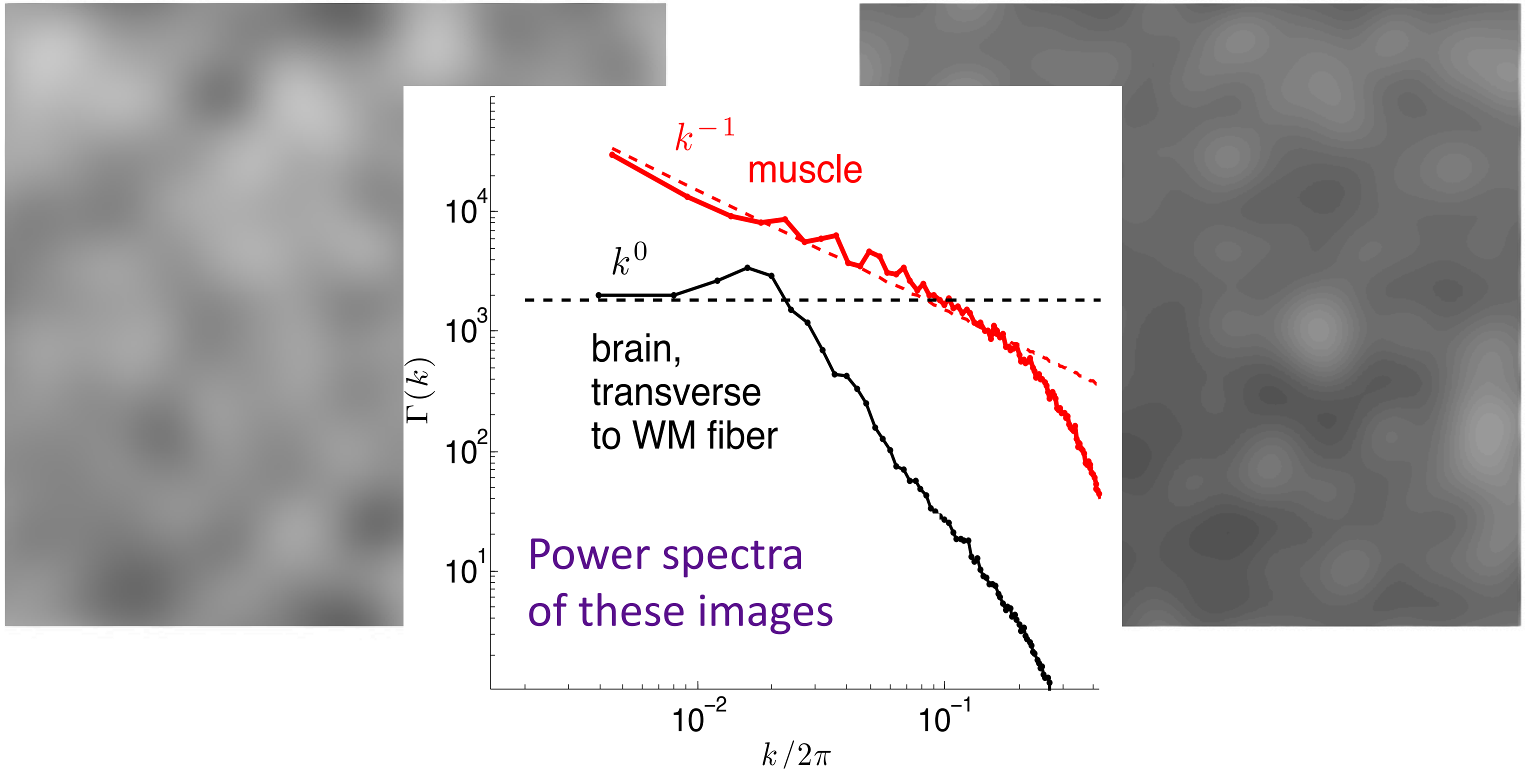
Neuronal white matter fiber x-section

1 major direction

Similar diffusion tensor eigenvalues

Focus on large-scale fluctuations

- short scale features gradually lost
- long range correlations survive

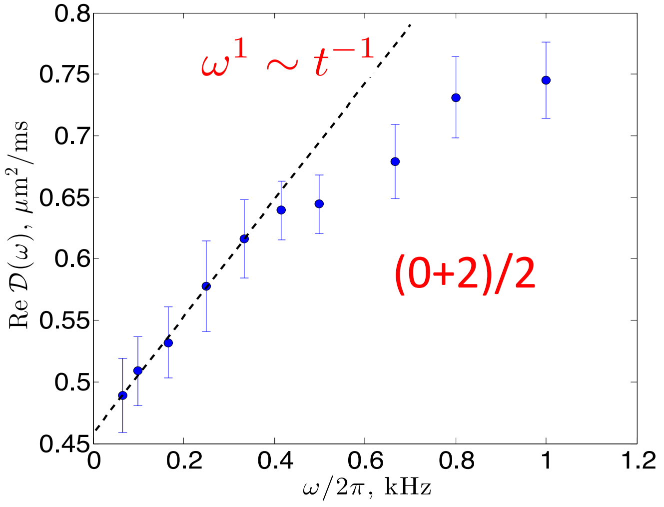


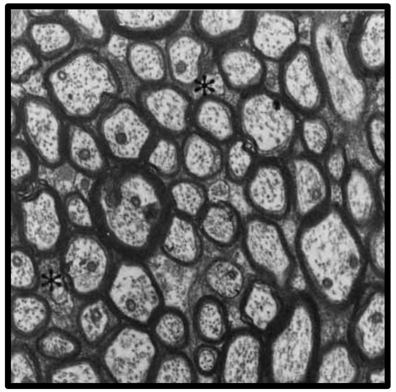
Muscle fiber x-section

Neuronal white matter fiber tract x-section

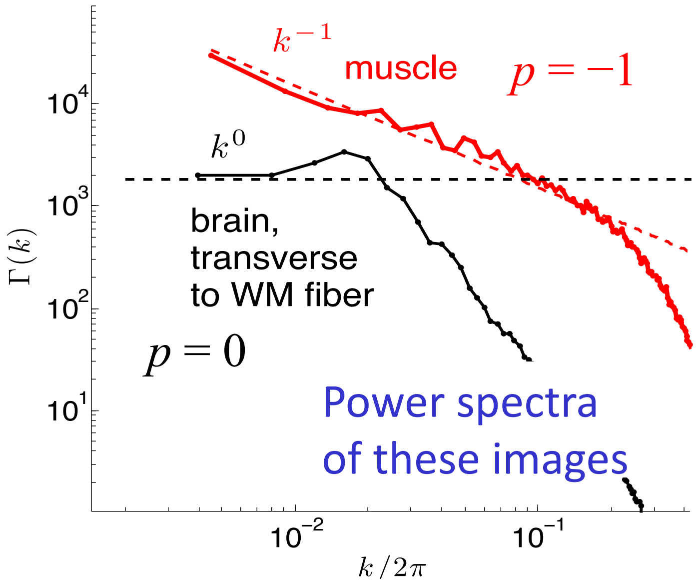
So, can we distinguish b/w these 2 tissues?

Portnoy MRM 2013
Burcaw NeuroImage 2015

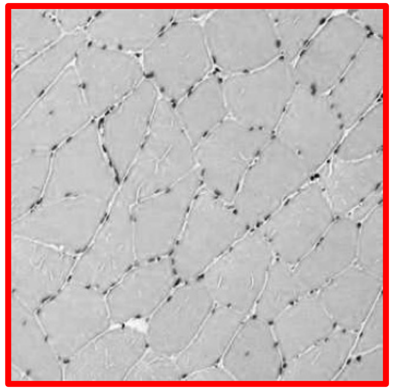


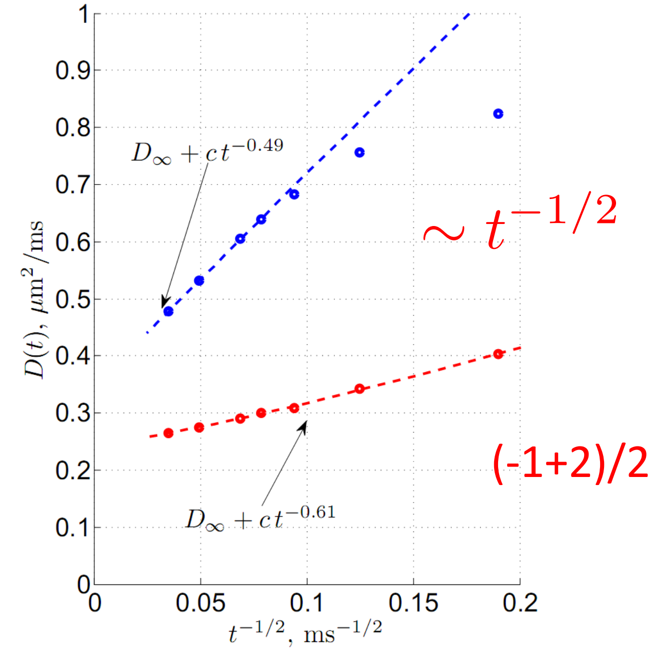


$$\vartheta = \frac{p+d}{2}$$



Novikov PNAS 2014
Burcaw NeuroImage 2015





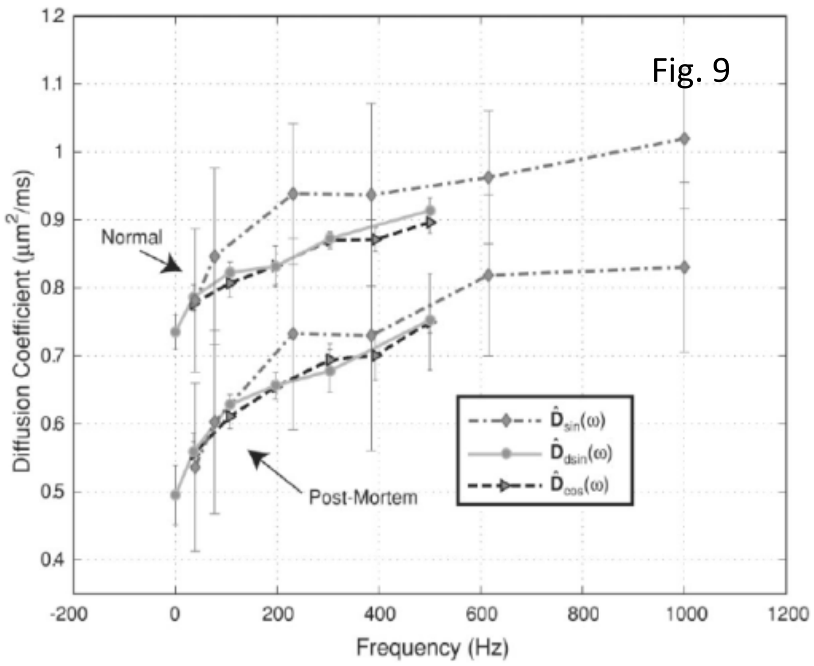
Kim MRM 2004
Novikov Nature Physics 2011
Novikov PNAS 2014

Cortical gray matter (rat)

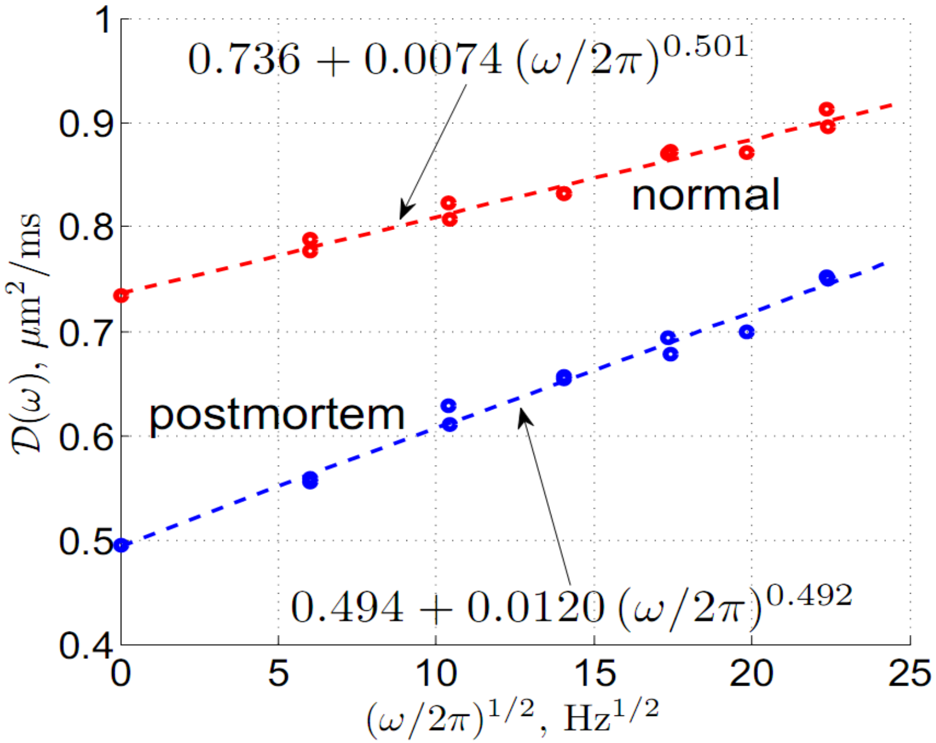
Magnetic Resonance in Medicine 49:206–215 (2003)

Oscillating Gradient Measurements of Water Diffusion in Normal and Globally Ischemic Rat Brain

Mark D. Does,[1*] Edward C. Parsons,[2] and John C. Gore[1–3]



Replot wrt $\sqrt{\omega}$



$d = 3$ isotropic random medium:

$p = 0,\ \vartheta = (0+3)/2 = 3/2$

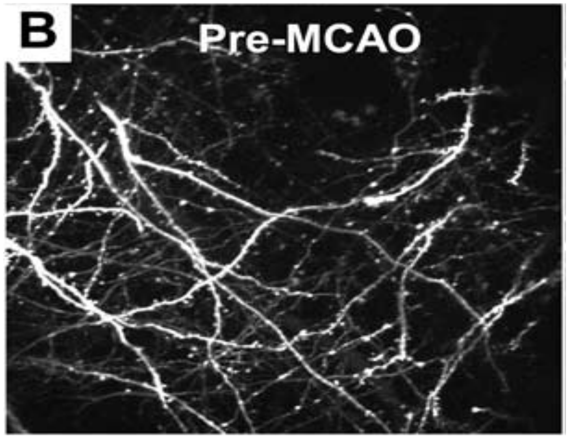
Expect $\omega^{3/2}$

$D(t) = D_\infty + \mathrm{const}\cdot t^{-1/2}$ before and after ischemia!

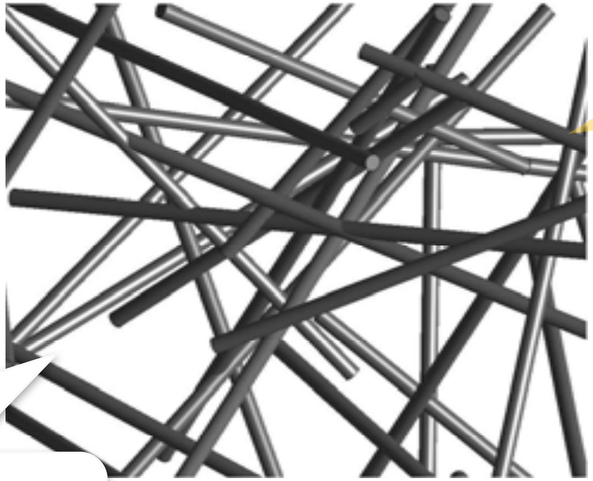
$$\vartheta = \frac{p+d}{2} = \frac{1}{2}$$

Why $\vartheta = \frac{1}{2}$? Disorder *along* neurites

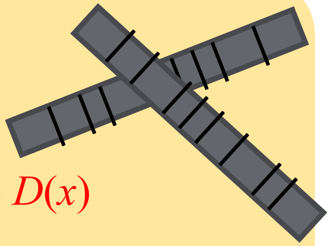
Li, Murphy, J Neurosci 2008



Randomly oriented cylinders in GM:
Kroenke 2004; Jespersen 2007, 2010



$d = 1,\ p = 0$: ➔ $\vartheta = \frac{1}{2}$
randomly oriented 1-dimensional neurites
with short-range disorder in $D(x)$ inside



Extra-neurite water:
$d = 3,\ p = -1$ ➔ $\vartheta = 1$

$$|\omega| + \omega^{1/2} \sim \omega^{1/2}$$

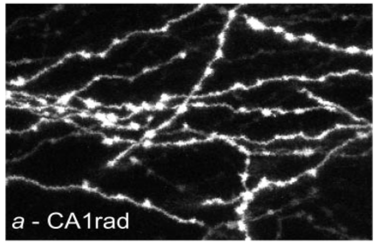
outside inside

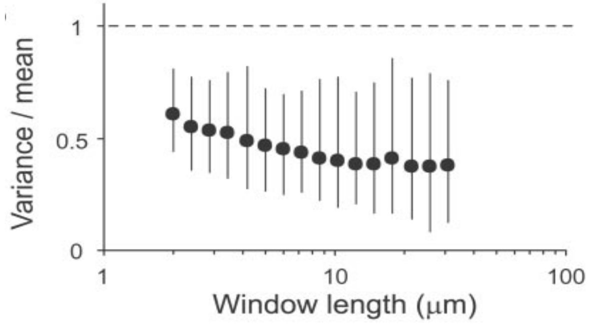
- Fill cylinders with disordered "stuff"
- Extra-neurite water invisible

General and variable features of varicosity spacing along unmyelinated axons in the hippocampus and cerebellum

Gordon M. G. Shepherd*, Morten Raastad, and Per Andersen

6340–6345 | PNAS | April 30, 2002 | vol. 99 | no. 9

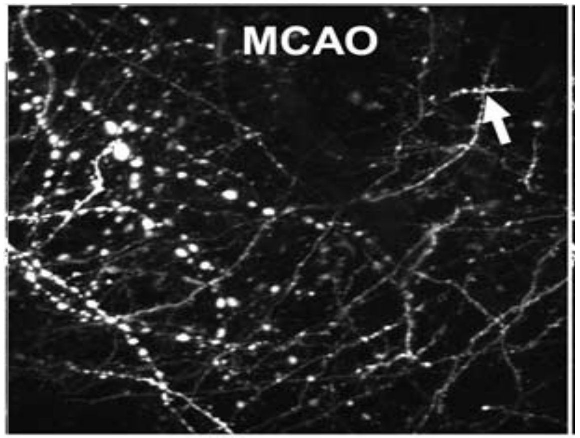




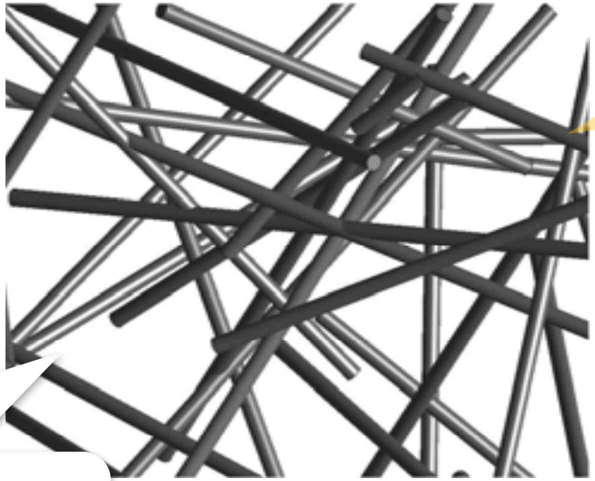
Short-range disorder
$d = 1, p = 0$

What reduces D in ischemia?

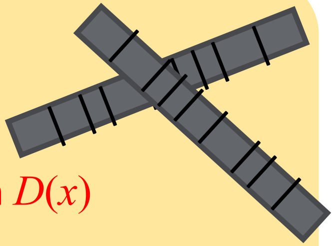
Li, Murphy, J Neurosci 2008



Randomly oriented cylinders in GM:
Kroenke 2004; Jespersen 2007, 2010



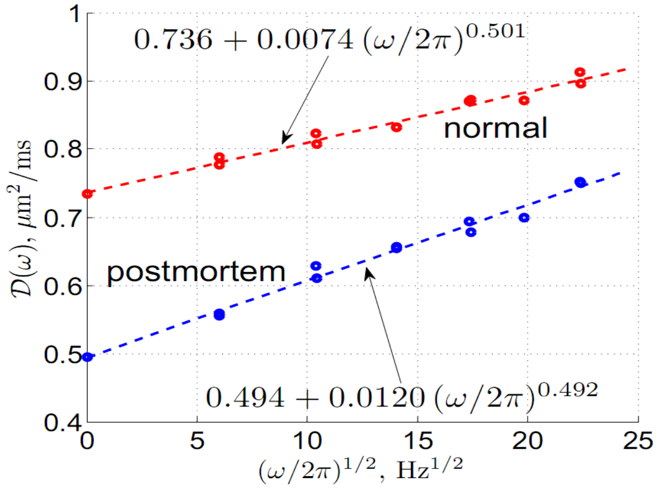
$d = 1,\ p = 0$: ➔ $\vartheta = ½$
randomly oriented 1-dimensional neurites
with short-range disorder in $D(x)$ inside



Extra-neurite water:
$d = 3,\ p = -1$ ➔ $\vartheta = 1$

$$|\omega| + \omega^{1/2} \sim \omega^{1/2}$$

outside inside



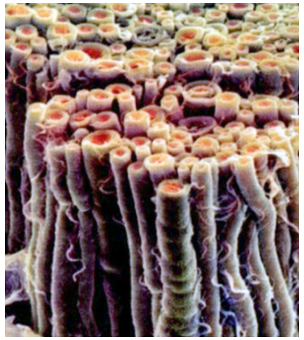
- **Disorder universality class unchanged**
➔ **no qualitative change**

- **Disorder amplitude increases (e.g. beading, cf. Budde *et al.* 2010)**
➔ **D_∞ drops, coefficient of $\omega^{1/2}$ increases**

White matter tracts (human)

$D(t)$ in Brain WM

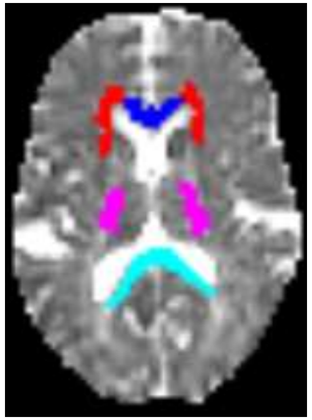
Fieremans, Novikov, et al. NeuroImage 2016

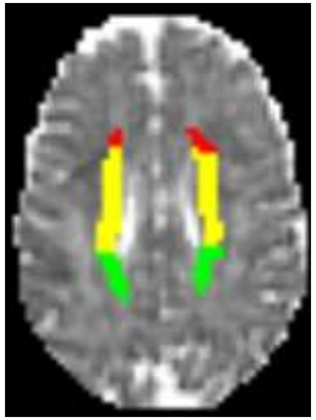


$D_{\parallel}$

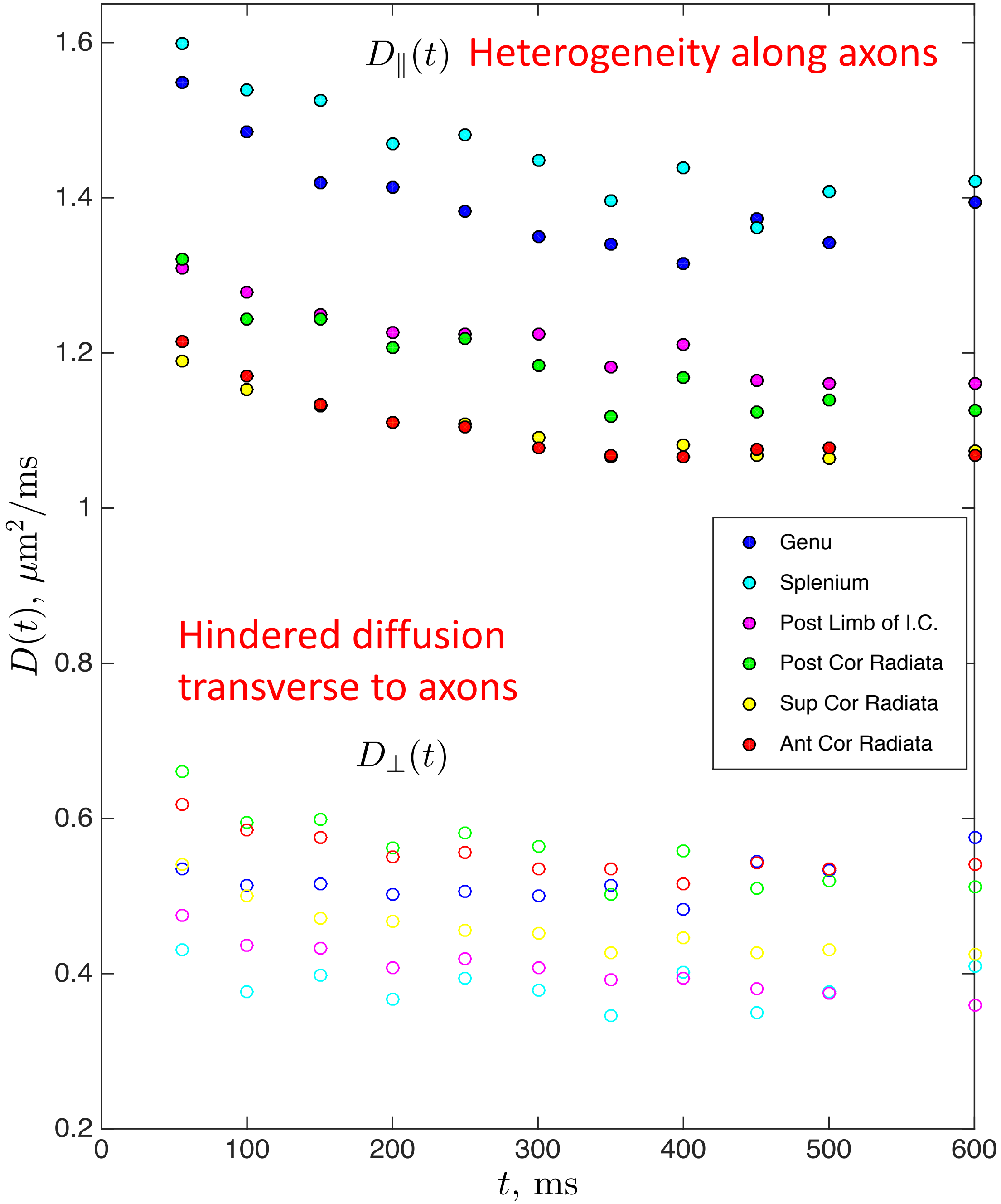
$D_{\perp}$

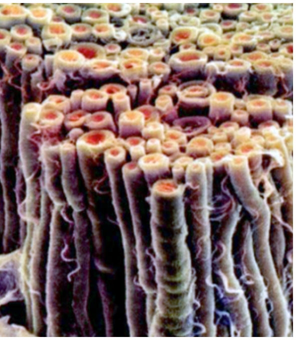
Highly aligned





5 healthy volunteers, 25-41 years old
3T Siemens Tim Trio
STEAM EPI, 20 directions, b_{max} = 0.5

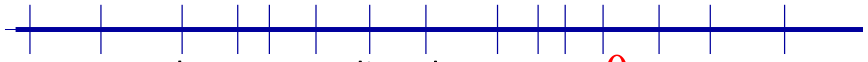




$D_{||}(t)$: axons are not straight hollow tubes

	Fit parameters	
ROI	D_∞	$l_c^{\|\|}$, µm
Genu	1.20	4.48
Splenium	1.24	5.13
Ant. Cor. Radiata	0.98	3.3
Sup. Cor. Radiata	0.99	2.97
Post. Cor. Radiata	1.05	3.66
Post. Limb of I.C.	1.08	3.36
FA > 0.3	1.01	3.02
FA > 0.4	1.03	3.50
FA > 0.5	1.08	3.95
FA > 0.6	1.15	4.31
FA > 0.7	1.25	4.42

$d = 1$ $\vartheta = (0+1)/2$



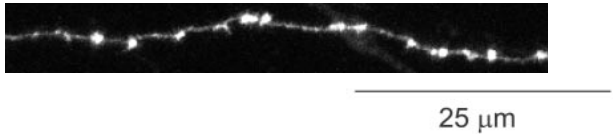
Short-range disorder $p = 0$

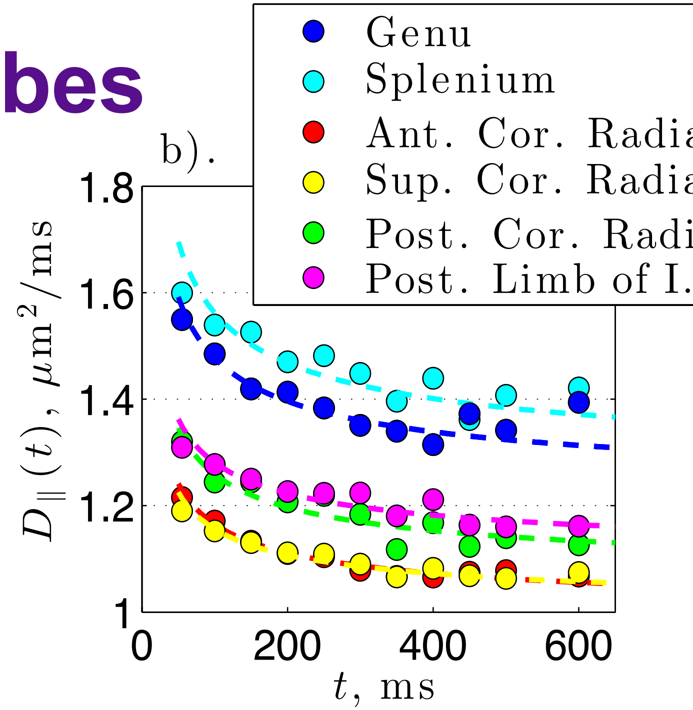
Disordered 1d restrictions

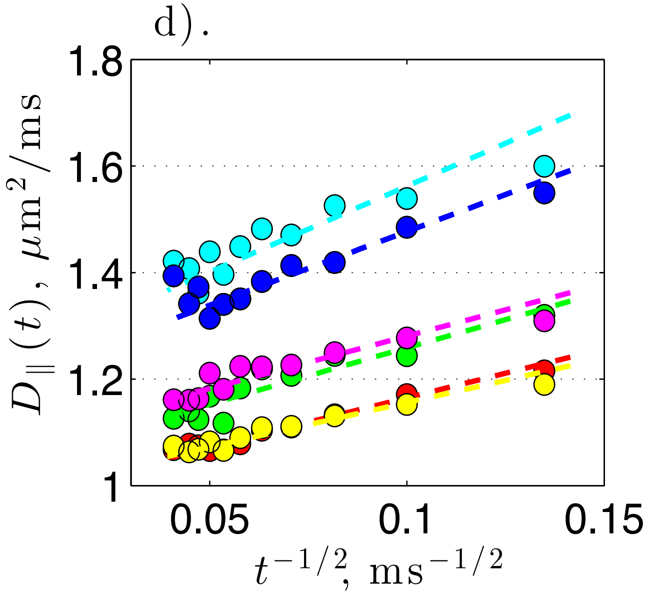
$$D_{||}(t) \simeq D_\infty + \frac{c_2}{\sqrt{t}}, \quad c_2 = \frac{\Gamma_D(0)}{D_\infty}\frac{1}{\sqrt{\pi D_\infty}}$$

$$l_c^{||} \simeq c_2\sqrt{\frac{\pi}{D_\infty}}$$

"structural disorder"
correlation length $l_c^{||}$ = 3-5 µm
Likely to be distance b/w varicosities along axons
[Shepherd et al., PNAS 2002]



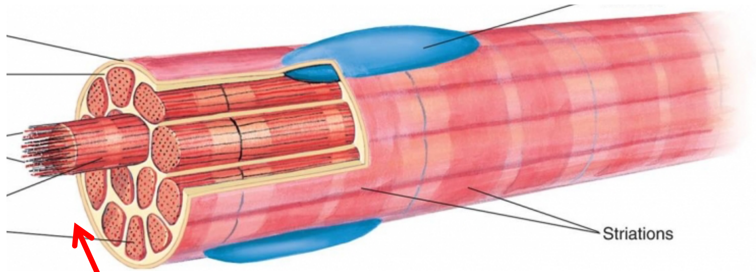


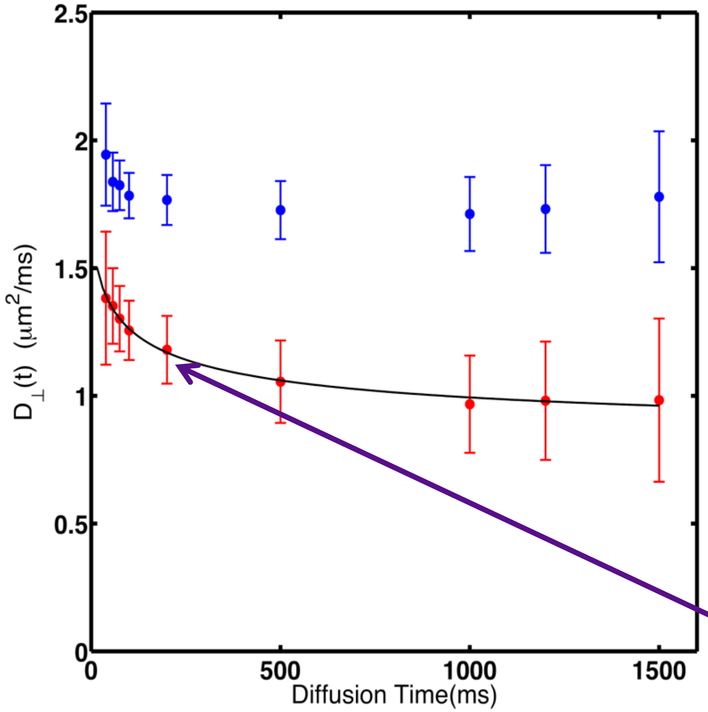


Fieremans, Novikov, et al. NeuroImage 2016

Human Skeletal Muscle
(calf, shoulder)

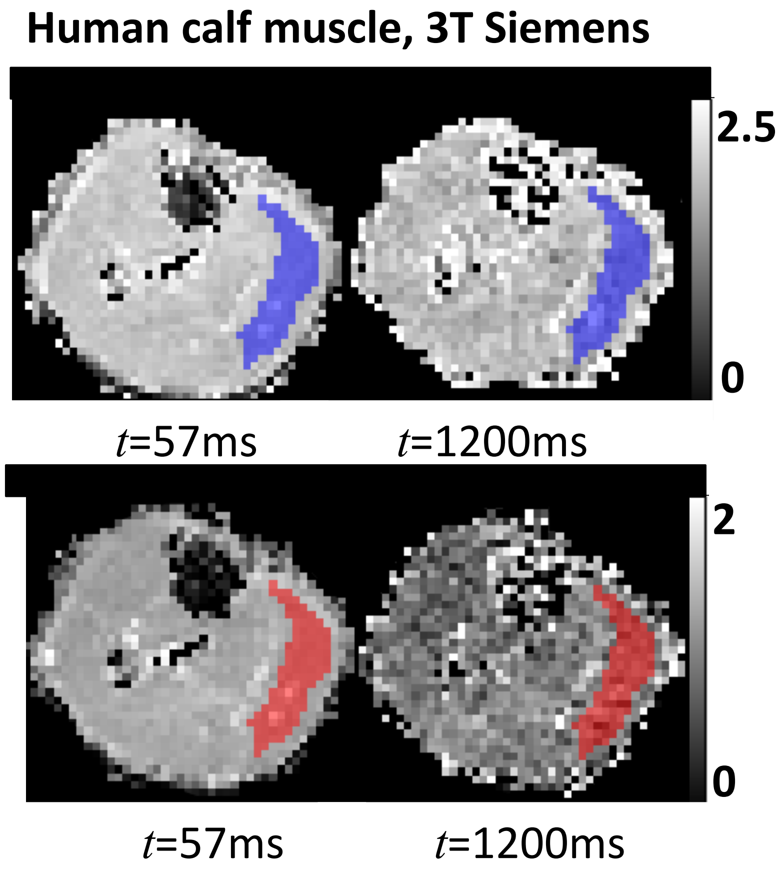
Time Dependent Diffusion: Human Calf Muscle





$D_{Longitudinal}$

D_{Radial}



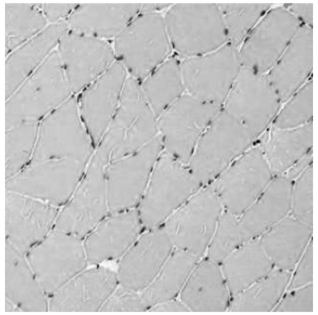
$$t = \frac{\langle x_t - x_0 \rangle^2}{2D_{Muscle}} = \frac{(25\ \mu m)^2}{2(1.5\ \mu m^2/ms\ )} \approx 200\ \text{ms}$$

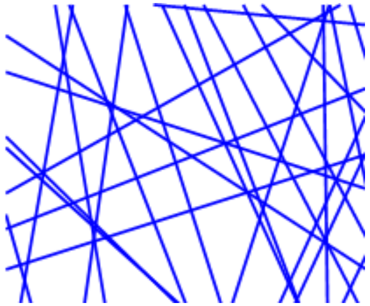
ARTICLES
PUBLISHED ONLINE: 6 MARCH 2011 | DOI: 10.1038/NPHYS1936
nature physics

Random walks with barriers

Dmitry S. Novikov[1]*, Els Fieremans[1], Jens H. Jensen[1,2] and Joseph A. Helpern[1,2,3]†

$$\Gamma(k) \sim k^{-1}\,, \quad k \to 0$$





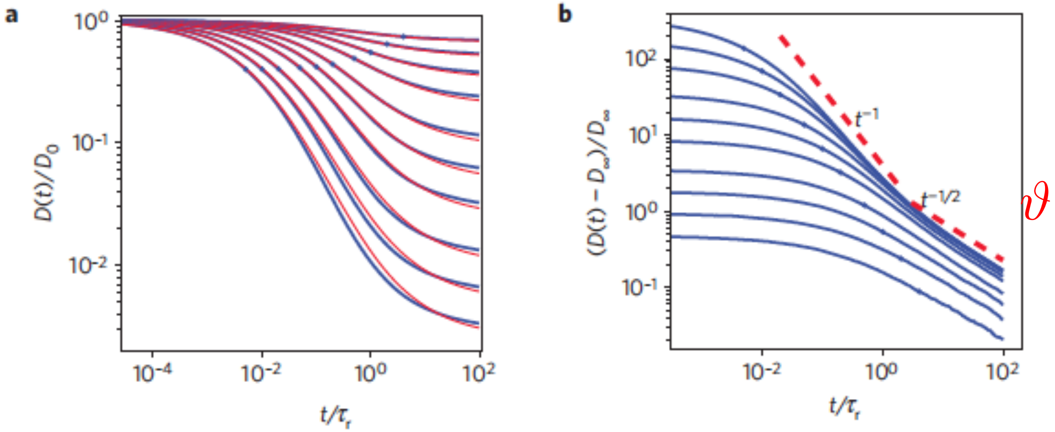
RPBM = Random permeable barrier model

3 Parameters:

D_0 (w/o membranes)

S/V surface-to-volume (to obtain size)

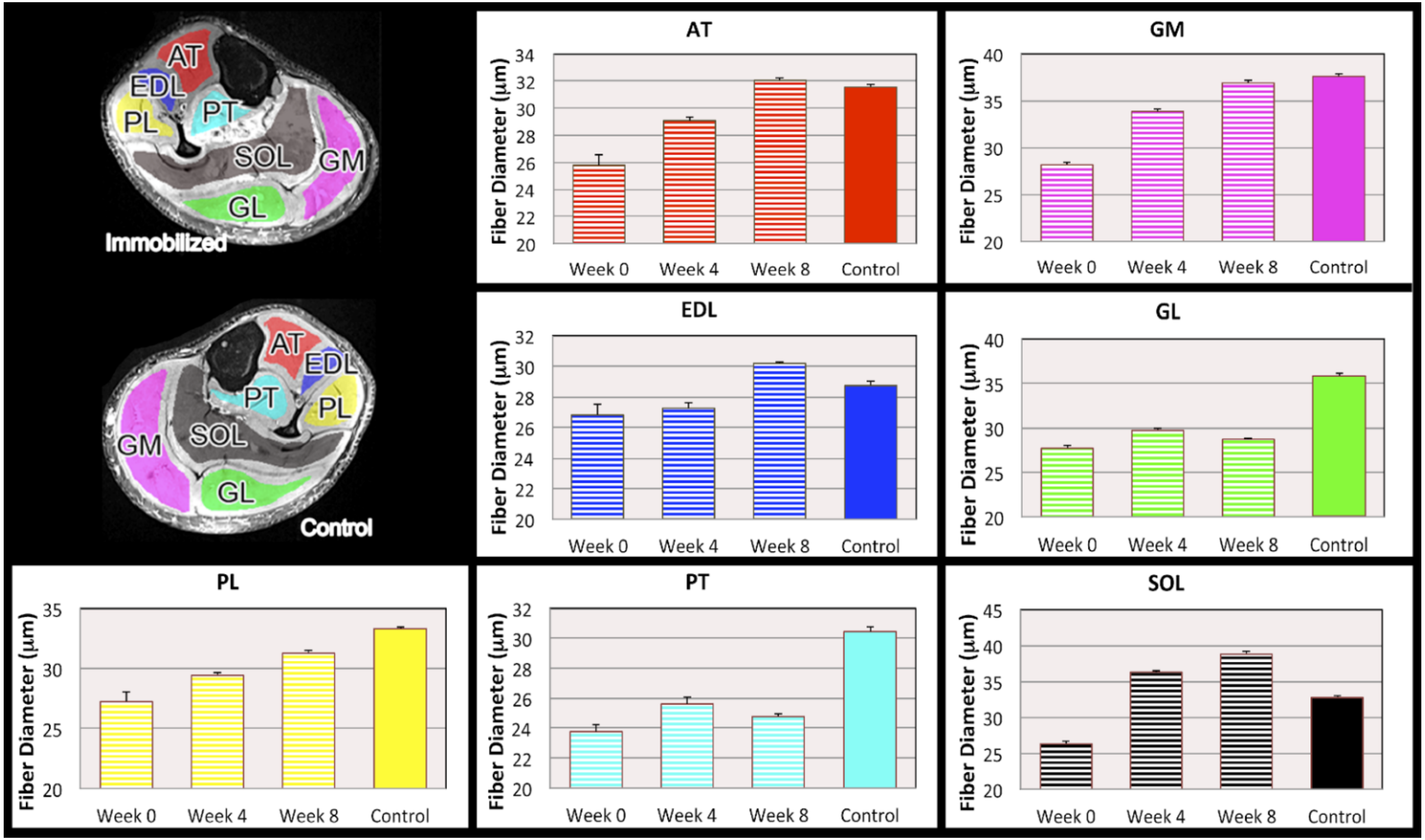
κ membrane permeability



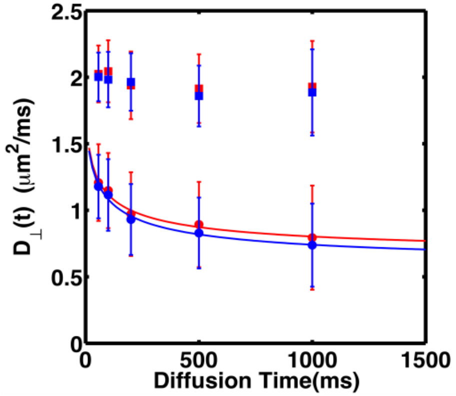
$$\vartheta = \frac{1}{2}$$

Scattering theory + real-space RG: ***D*(*t*) for all *t***

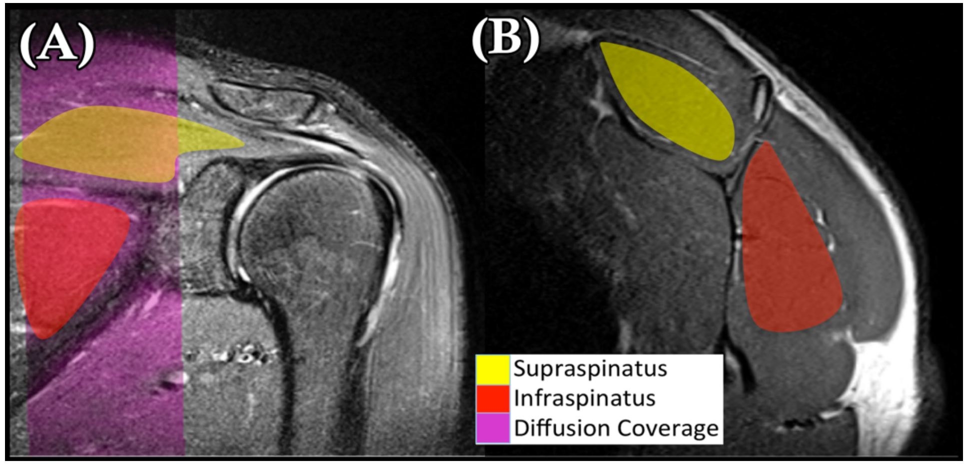
Longitudinal Follow up 31 y/o M (Posterior Tibialis Tendon Tear)

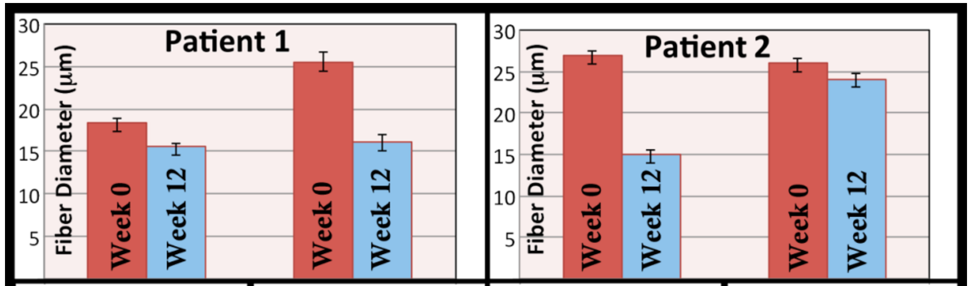


Post-operative outcomes in rotator cuff muscle



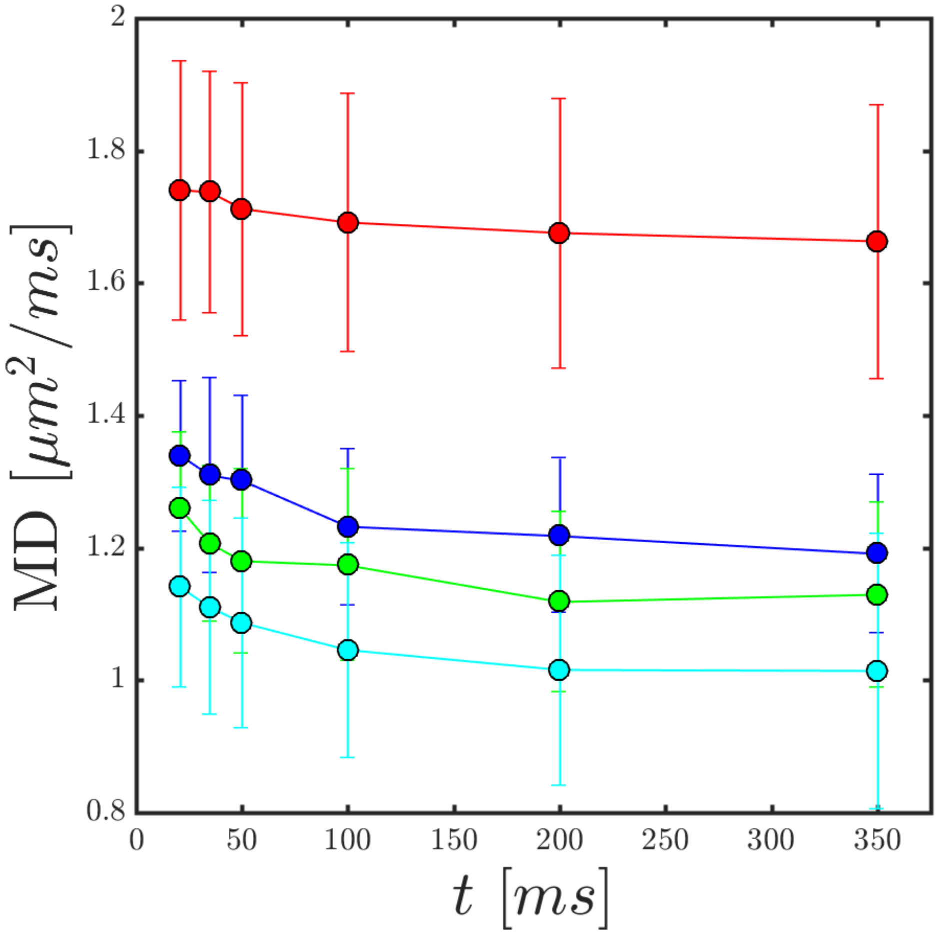
- Setting of rotator cuff tendon
- Gold standard: muscular atrophy
- Outcomes diminish as rotator cuff atrophy and fatty infiltration worsen
- Current methods (CT, MRI) quantify shoulder atrophy <u>indirectly</u> as a function of fatty infiltration
- We focus on atrophy <u>directly</u>, via myofiber diameter using $D(t)$

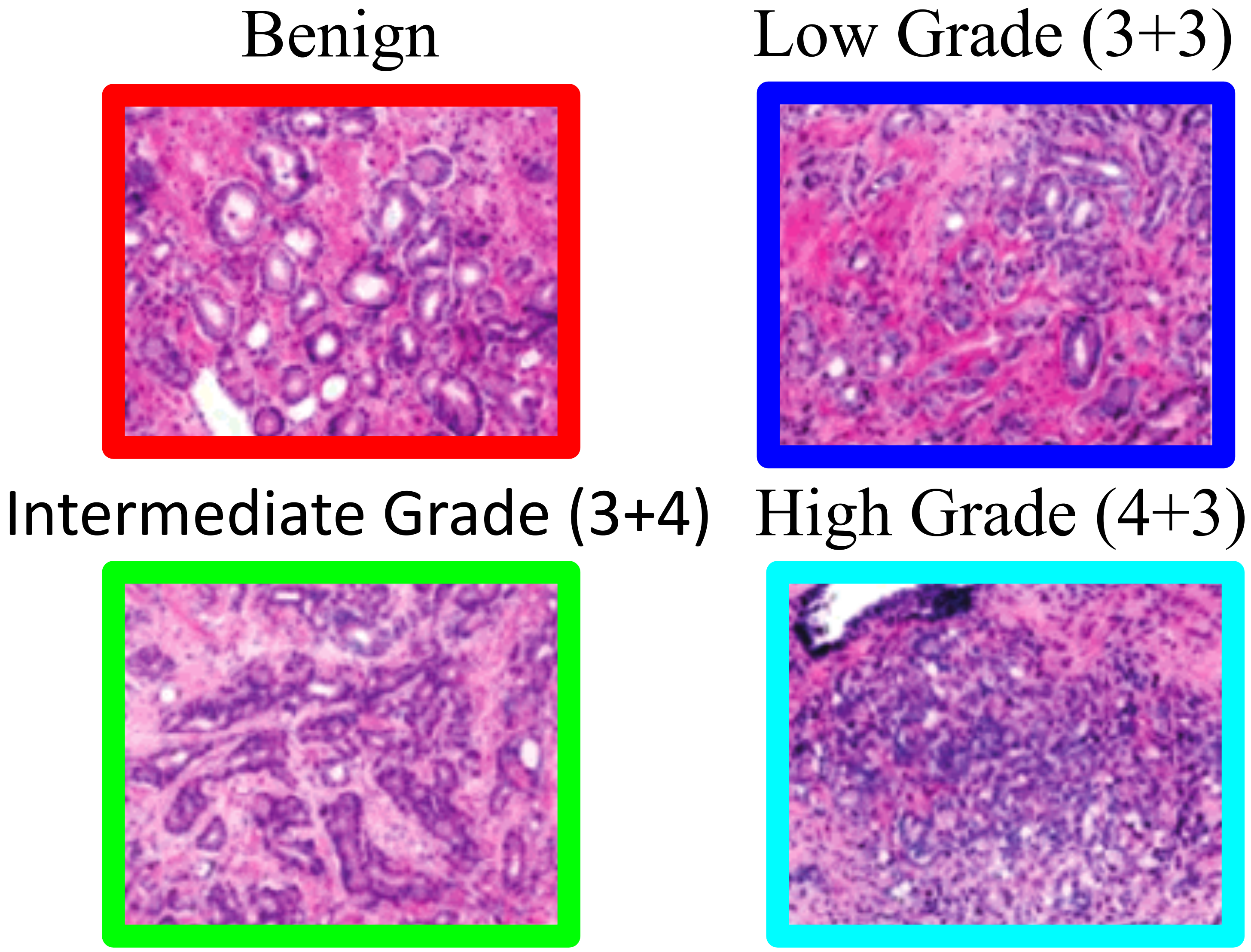




Supraspinatus	Infraspinatus	Supraspinatus	Infraspinatus
18.3626 ± 0.5992	25.4372 ± 0.3205	26.8991 ± 0.5909	25.9523 ± 0.5268
15.5763 ± 1.2198	16.0484 ± 0.8986	14.9659 0.6937	24.0613 ± 0.7300

D(*t*) in prostate cancer





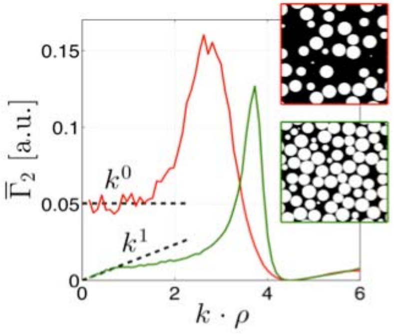
Lemberskiy et al. Investigative Radiology 2017

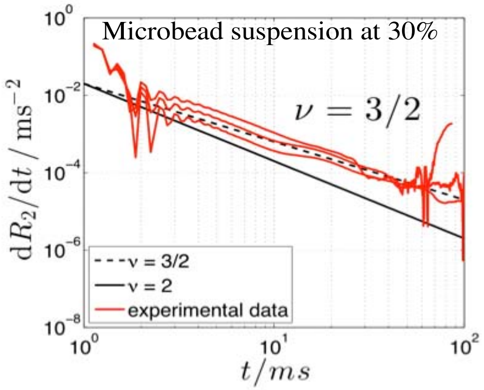
Generalizations:
$R_2^*(t)$ ~ meso magnetic structure

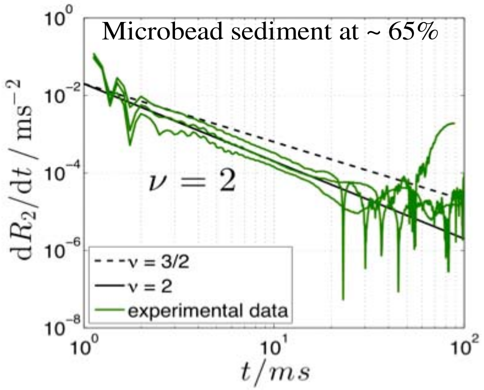
$$\frac{dR_2^*}{dt} \sim t^{\nu} \qquad \nu = \frac{p+d}{2}$$

Signature of jamming transition in dense bead suspensions

Ruh, Kiselev *et al.*
Proc ISMRM 2015, p.1667







Donev Stillinger Torquato
PRL 2005

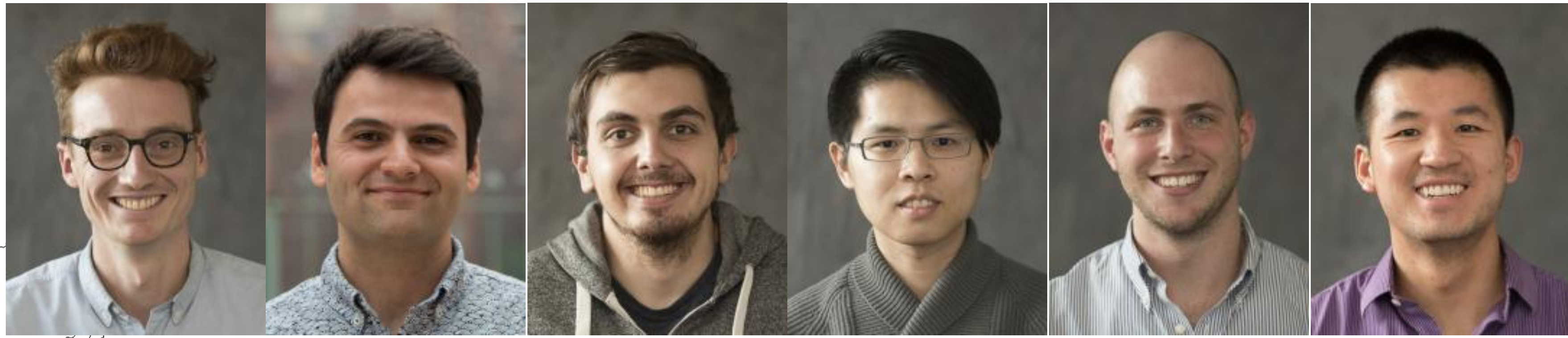
p=0

p=1

NIH R01 NS088040
Litwin Foundation for Alzheimer’s Research
Raymond & Beverly Sackler Fellowship

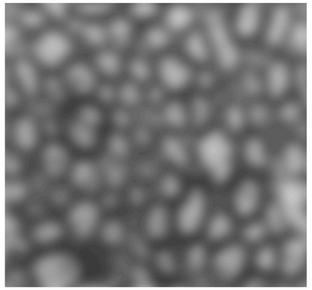
MRI Biophysics (est. 2012)

diffusion-mri.com



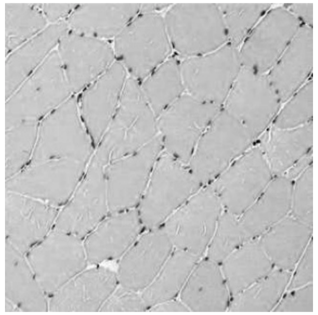
alumni:

Conclusions

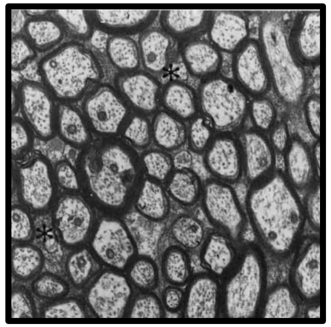


- Diffusion = coarse-graining
- Universality; power-law approach to D_∞
- In-vivo model validation tool

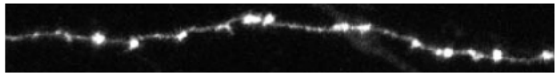
$$\vartheta = \frac{p+d}{2}$$



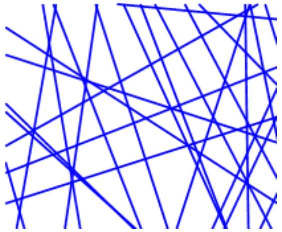
$t^{-1/2}$

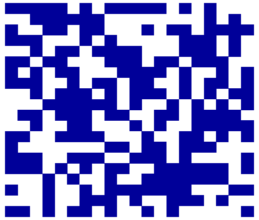


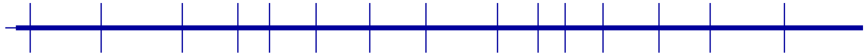
t^{-1}



$t^{-1/2}$







Applications:

- Stroke
- Neurodegeneration (MS, AD)
- Muscle atrophy
- Tumors

- Review on dMRI modeling

arXiv:1612.02059

Quantifying brain microstructure with diffusion MRI: Theory and parameter estimation

Dmitry S. Novikov,[1,*] Sune N. Jespersen,[2,†] Valerij G. Kiselev,[3,‡] and Els Fieremans[1,§]

[1]Center for Biomedical Imaging, Department of Radiology, NYU School of Medicine, New York, NY, USA
[2]CFIN/MINDLab, Department of Clinical Medicine and Department of Physics and Astronomy, Aarhus University, Aarhus, Denmark
[3]Department of Diagnostic Radiology, Medical Physics, University Medical Center Freiburg, Germany

(Dated: December 8, 2016)

We review, systematize and discuss models of diffusion in neuronal tissue, by putting them into an overarching physical context of coarse-graining over an increasing diffusion length scale. From this perspective, we view research on quantifying brain microstructure as occurring along the three major avenues. The first avenue focusses on the transient, or time-dependent, effects in diffusion. These effects signify the gradual coarse-graining of tissue structure, which occurs qualitatively differently in different brain tissue compartments. We show that studying the transient effects has the potential to quantify the relevant length scales for neuronal tissue, such as the packing correlation length for neuronal fibers, the degree of neuronal beading, and compartment sizes. The second avenue corresponds to the long-time limit, when the observed signal can be approximated as a sum of multiple non-exchanging anisotropic Gaussian components. Here the challenge lies in parameter estimation and in resolving its hidden degeneracies. The third avenue employs multiple diffusion encoding techniques, able to access information not contained in the conventional diffusion propagator. We conclude with our outlook on the future research directions which can open exciting possibilities for developing markers of pathology and development based on methods of studying mesoscopic transport in disordered systems.

CONTENTS

* dima@alum.mit.edu
† sune@cfin.au.dk
‡ kiselev@ukl.uni-freiburg.de
§ els.fieremans@nyumc.org