A Fractional Derivative Model of Anomalous Diffusion in White and Gray Matter

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A Workshop on Future Directions in Fractional Calculus Research and Applications, Oct 17-21, 2016

Department of Statistics and Probability  Michigan State University
“There is a rhythm and a pattern between the phenomena of nature which is not apparent to the eye, but only to the eye of analysis; and it is these rhythms and patterns which we call Physical Laws.”

Richard P. Feynman, The Messenger Lectures for 1964 at Cornell University on The Character of Physical Law
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By age 15, Feynman had mastered differential and integral calculus, and frequently experimented and re-created mathematical topics such as the half-derivative before even entering college.
How Does Microstructure Affect Water Diffusion In Brain Tissue?

Gray Matter

Diffusion Time

\[ \langle x^2 \rangle = 2Dt \]

Typical length scale for MRI

1-20 µm

White Matter

Dr Thomas. R. Barrick
St. George’s, University of London
Overview

- Diffusion weighted MRI and DTI are used to detect and stage neurodegenerative, malignant and ischemic disease.

- Correlation between pathology and the apparent diffusion coefficient relies on a model to design an efficient phase encoding pulse sequence.

- A common empirical approach to model the data encodes the diffusion coefficient as a stretched exponential, \( \exp[-(bD)^\alpha] \) and the Mittag-Leffler, \( E_\alpha[-(bD)^\alpha] \) functions.

- Here, we show how this functional behavior is a natural consequence of the Bloch-Torrey equation by using fractional-order calculus.

\[
0 I_t f(t) = \frac{1}{(1)} \int_0^t (t) \, 1 f( ) d
\]
Anomalous Behaviour

Why do we expect fractional calculus to be useful in describing relaxation and diffusion in biological tissues?
Universal power-law scaling of water diffusion in human brain defines what we see with MRI

Jelle Veraart, Els Fieremans and Dmitry S. Novikov
Dept. of Radiology, NYU School of Medicine

The viability of model-based “super-resolution” MRI rests on validating fundamental model assumptions. In white matter (WM), the most essential assumption underpinning most biophysical models\textsuperscript{1-13} is compartmentalization — i.e. representing the dMRI signal as a sum of independent contributions from separate pools of water, corresponding to locally anisotropic intra- and extra-axonal spaces, Fig. 1.

Here we argue that our experimental \textit{in vivo} observation of the universal power-law form (Fig. 2)

\[ S(b \to \infty) \sim \beta \cdot b^{-\alpha} + \gamma \]  

(1)

The asymptotic power-law (1) with exponent $\alpha = 1/2$ can only originate from the \textit{intra-axonal water}. Indeed, consider the dMRI signal (henceforth normalized to $S|_{b=0} \equiv 1$)

\[ S(\mathbf{g}, b) = \int d\mathbf{n} \mathcal{P}(\mathbf{n}) \psi_{\mathbf{A}}(\mathbf{g}, b) + \gamma + S_{0\text{ax}}^{\text{0ax}}(\mathbf{g}, b) \]  

(2)

\[ \mathbf{R} \]
“The remarkably slow decay of the signal, retaining much SNR even for very high $b$, provides an exciting avenue for probing brain tissue microstructure with extremely strong diffusion gradients on clinical systems, such as on Human Connectom scanners, …

…. thereby fostering the translation of advanced diffusion MRI methods into basic neuroscience research and clinical practice.”
Surprisingly, the above paper does not mention fractional calculus as a potential tool for deriving and expressing their results.

**Anomalous Behaviour**

“It was ever thus: whenever you introduce a new idea it is discredited. Then after it is accepted it is said to be obvious. And the final stage is that it was their idea all along, so why reference another person’s work?”

Email from Bruce West, 10/13/2016
Development of Fractional Magnetic Resonance Models

Brownian Motion → \( \langle x^2 \rangle \) → CTRW Model \( \alpha, \beta \) → Fractional Bloch-Torrey

Spin Translation \( \text{Pr}(x,t) \) → Spin Rotation \( \text{Pr}(\theta,\phi,t) \) → \( \langle B_0^2 \rangle \) → Bloch Equation

\( \Gamma(t), J(\omega), R_1, R_2 \) → \( \rho, T_1, T_2 \)

D, DTI, MD, FA

\( \alpha, \beta, \tau, \mu, D_f \)
Bloch Equation / Relaxation

Entropy

Energy

\[ \frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'} \]

\[ M_z(t) = M_z(0)e^{t/T_2^*} \]

\[ M_z(t) = M_0(1 - e^{t/T_1}) \]

\[ \frac{\partial M}{\partial t} = \gamma M \times B + \frac{M_o - M_z}{T_1} \hat{k} - \frac{M_x \hat{i} - M_y \hat{j}}{T_2} \]
Fractional NMR Relaxation

Fractional $T_1$ Relaxation

$$ ^C_0 D_t M_z(t) = \frac{M_0}{T_1} M_z(t) $$

$$ M_z(t) = M_z(0) + \left[ M_0 \ M_z(0) \right] \left[ 1 \ E \left( \frac{t}{T_1} \right) \right] $$

Fractional $T_2$ Relaxation

$$ ^C_0 D_t M_{xy}(t) = i \int_0^1 M_{xy}(t) \frac{1}{T_2} M_{xy}(t) $$

$$ M_{xy}(t) = M_{xy}(0) E \left[ \left( \frac{t}{T_2} \right) \right] + M_{xy}(\infty) $$

Fractional $T_1$ Relaxation

Fractional-order $T_1$ relaxation curves. Plots of $M_z(TI)$ versus TI (inversion recovery) for different values of $\beta$ in the range from $\beta = 0.6$ (bottom curve) to $\beta = 1$ in steps of 0.1 ($M_0 = 1$, $T_1 = 1.5$ s, $A = 1$).
Fractional $T_2$ Relaxation

Fractional-order $T_2$ relaxation curves. Plots of $M_{xy}(TE)$ versus TE (Spin Echo) for different values of $\alpha$ in the range from $\alpha = 0.6$ (top curve at TE = 1,200 ms) to $\alpha = 1$ in steps of 0.1 ($M_{xy}(0) = 1$, $T_2 = 80$ ms).
Fractional $T_2$ Relaxation

Fractional-order $T_2$ relaxation curves. Plots of $M_{xy}(TE)$ versus TE (Spin Echo) for different values of $\alpha$ in the range from $\alpha = 0.6$ (top curve at $TE = 1,200$ ms) to $\alpha = 1$ in steps of 0.1 ($M_{xy}(0) = 1$, $T_2 = 80$ ms). Decay appears to be multi-exponential, which suggests multiple compartments.
Anomalous Relaxation

Anomalous T2 relaxation in normal and degraded cartilage

David A. Reiter, Richard L. Magin, Weiguo Li, Juan J. Trujillo, M. Pilar Velasco, and Richard G. Spencer


Anomalous NMR relaxation in cartilage matrix components and native cartilage: fractional-order models.

Magin RL, Li W, Pilar Velasco M, Trujillo J, Reiter DA, Morgenstern A, Spencer RG.


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Cartilage Ultrastructure

- **Collagen** provides tissue integrity and tensile strength
- **Proteoglycans (PGs)** provide compressive resistance
- **Water** exists in several compartments of different mobility

Relaxation time of water protons is influenced by its local environment

Courtesy of Basic Biomechanics of the Musculoskeletal System (1989)
$T_2$ Relaxation Models

**Stretched Exponential**

$$M_{xy}(TE \cdot n) = b + M_{xy}(0) \cdot \exp\left(\frac{-(TE \cdot n)^{\alpha_{se}}}{T_{2,se}}\right)$$

**Stretched Mittag-Leffler**

$$M_{xy}(TE \cdot n) = b + M_{xy}(0) \cdot E_\alpha\left(\frac{-(TE \cdot n)^{\alpha_{sml}}}{T_{2,sml}}\right)$$

**Two Exponential**

$$M_{xy}(TE \cdot n) = b + M_{xy}(0) \cdot \left( w_1 \cdot \exp\left(\frac{-TE \cdot n}{T_{2,1}}\right) + (1 - w_1) \cdot \exp\left(\frac{-TE \cdot n}{T_{2,2}}\right) \right)$$

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Stretched Exponential $T_2$ Relaxation

Chondroitin Sulfate (CS) Solutions

---

$T_{2,se} = 2867$
$\alpha = 1.0$

$T_{2,se} = 390$
$\alpha = 0.97$

$T_{2,se} = 216$
$\alpha = 0.96$

$T_{2,se} = 161$
$\alpha = 0.94$

Source: Basic Biomechanics of the Musculoskeletal System (1989)

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Anomalous T2 Relaxation in Normal and Degraded Cartilage

Comparison of different models: i) the exponential function $\exp(-t)$, ii) the stretched exponential function $\exp(-t^{0.5})$, iii) the stretched Mittag-Leffler function $E_{1/2}(-t^{0.5})$, and iv) the power function $t^{-0.5}/\Gamma(1/2)$.


MSE

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Anomalous Relaxation


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Relaxation models

- Classical monoexponential model for transverse magnetisation
  \[ |M_+(t)| = |M_+(0)|e^{-t/T_2^*} \]

- Magin’s time-fractional model transverse magnetisation
  \[ |M_+(t)| = |M_+(0)|E_\alpha\left(-\frac{t^\alpha}{T_2^*}\right) \]

- Our extended time-fractional model transverse magnetisation model
  \[ |M_+(t)| = |M_+(0)|\sqrt{E_\alpha\left(-\frac{t^\alpha}{T_2^*} + i\Delta \omega t^\alpha\right)E_\alpha\left(-\frac{t^\alpha}{T_2^*} - i\Delta \omega t^\alpha\right)} \]
  \[ = M_+(0)|E_\alpha\left(-\frac{t^\alpha}{T_2^*} + i\Delta \omega t^\alpha\right)| \]

- Fitting equation
  \[ S(t) = A_0 |M_+(t)| + C \]
Fractional model for $T_2^*$ decay

- We take the frequency shift $\Delta \omega$ into consideration

\[
\begin{align*}
\mathcal{C} D^\alpha_t M_z(t) &= \frac{M_0 - M_z(t)}{T_1} , \\
\mathcal{C} D^\alpha_t M_{x'}(t) &= -\frac{1}{T_2^*} M_{x'}(t) + \Delta \omega M_{y'}(t) , \\
\mathcal{C} D^\alpha_t M_{y'}(t) &= -\frac{1}{T_2^*} M_{y'}(t) + \Delta \omega M_{x'}(t) ,
\end{align*}
\]

- By using the matrix method and diagonalising the parameter matrix

\[
\begin{align*}
M_{x'}(t) &= \frac{M_x(0) - iM_y(0)}{2} E_\alpha(-\frac{t^\alpha}{T_2^*} + i\Delta \omega t^\alpha) + \frac{M_x(0) + iM_y(0)}{2} E_\alpha(-\frac{t^\alpha}{T_2^*} - i\Delta \omega t^\alpha) , \\
M_{y'}(t) &= \frac{M_y(0) + iM_x(0)}{2} E_\alpha(-\frac{t^\alpha}{T_2^*} + i\Delta \omega t^\alpha) + \frac{M_y(0) - iM_x(0)}{2} E_\alpha(-\frac{t^\alpha}{T_2^*} - i\Delta \omega t^\alpha) , \\
M_z(t) &= M_z(0) E_\alpha(-\frac{t^\alpha}{T_1}) + \frac{M_0}{T_1} t^\alpha E_{\alpha,\alpha+1}(-\frac{t^\alpha}{T_1}) ,
\end{align*}
\]

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In vivo experiment

- **Subjects**: 5 healthy participants (two females and three males) aged 30-41 years were scanned.

- **MRI data**: 7T MRI data collected on the Siemens Magnetom Research scanner with a 32 channel head coil (Nova Medical, Wilmington, USA).

- **Data processing**: Individual channel data were combined using the sum-of-squares approach in a voxel-by-voxel manner.

Voxel-based fitting results

Fitting method: lsqcurvefit (a standard nonlinear fitting function in Matlab)

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(A) Sagittal, (B) Coronal and (C) Axial

fornix  putamen  thalamus  caudate  insula  pallidum
internal capsule  red nucleus  substantia nigra

R_2^* = 1 / T_2^*

\Delta f = \Delta \omega / 2\pi

**Fitting Results of the Monoexponential and Time-Fractional Models to Signal Decays in Nine ROIs**

| ROI | #  | WM  | GM  | CSF | WM/GM | A_0    | R_2 (Hz) | MSE  | A_0    | R_2 (Hz) | \(|\Delta f| (Hz)\) | \(\alpha\) | MSE  |
|-----|----|-----|-----|-----|-------|--------|----------|------|--------|----------|----------------|--------|------|
| CA  | 419| 37  | 43  | 20  | 0.87  | 691    | 43.07    | 9.54 | 668    | 34.91    | 21.76           | 0.979  | 1.71 |
| FO  | 57 | 42  | 45  | 13  | 0.94  | 567    | 39.68    | 3.21 | 611    | 30.31    | 1.59            | 0.949  | 2.35 |
| IN  | 190| 30  | 61  | 9   | 0.49  | 804    | 32.19    | 2.08 | 855    | 26.52    | 2.49            | 0.964  | 1.47 |
| IC  | 235| 59  | 39  | 2   | 1.50  | 619    | 47.76    | 2.94 | 668    | 36.26    | 0.02            | 0.947  | 1.39 |
| PA  | 431| 56  | 42  | 2   | 1.33  | 733    | 93.06    | 16.11| 718    | 74.17    | 19.70           | 0.965  | 0.21 |
| PU  | 461| 39  | 59  | 2   | 0.67  | 779    | 44.73    | 8.28 | 743    | 37.45    | 17.21           | 0.972  | 0.41 |
| RN  | 142| 42  | 53  | 5   | 0.79  | 636    | 60.93    | 8.51 | 602    | 38.75    | 11.76           | 0.907  | 3.56 |
| SN  | 230| 50  | 46  | 4   | 1.09  | 658    | 73.99    | 10.92| 642    | 58.11    | 27.13           | 0.976  | 2.17 |
| TH  | 978| 32  | 51  | 17  | 0.63  | 611    | 37.50    | 6.09 | 663    | 28.49    | 0.01            | 0.951  | 5.27 |

Note: Data were averaged across voxels in selected regions of five subjects. "#" denotes the average number of voxels contained in each region. We also computed the tissue parameters, such as white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) proportions, and WM-GM ratio. The fitted parameters are amplitude \(A_0\), relaxation rate \(R_2\), frequency shift \(|\Delta f|\) \((|\Delta f| = |\Delta \omega| / 2\pi)\), time-fractional order \(\alpha\), and MSE.

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Anomalous Diffusion

Development of Fractional Magnetic Resonance Models

Brownian Motion

Spin Translation $Pr(x,t)$

Spin Rotation $Pr(\theta,\phi,t)$

$\langle x^2 \rangle$

Bloch - Torrey Equation

$\langle B_0^2 \rangle$

$\Gamma(t)$ $J(\omega)$ $R_1, R_2$

CTRW Model $\alpha, \beta$

Fractional Bloch-Torrey

$\rho, T_1, T_2$

$D, DTI, MD, FA$

$\alpha, \beta, \tau, \mu, D_f$
Fractional Generalization of Bloch-Torrey Equation

\[ 1 \, ^{1}_0 C D^\alpha_t \, M_{xy}(r,t) = M_{xy}(r,t) + D^2 \, ^{2}_0 C D^\beta_t \, M_{xy}(r,t) \]

where \( \alpha, \beta \) = \( i \, (r \times G) \); \( 0 < \alpha, \beta < 1 \)

- \( ^{1}_0 C D^\alpha_t \) - fractional order time derivative

- \( ^{2}_0 C D^\beta_t \) - fractional order spatial Laplacian

- \( ^{1}_0 C D^\alpha_t \), \( ^{2}_0 C D^\beta_t \) - fractional order time and space constants needed to maintain correct units

Note: for \( \alpha = 1, \beta = 1 \), we recover the classical Bloch-Torrey equation

Magin et al., JMR, 190: 255-270, 2008
For fixed, bipolar and Stejskal-Tanner gradient pulses we find

\[
M_{xy} = \begin{cases} 
M_0 \exp\left( i G_z zt \right) D^{2(1)} t^2 \frac{1}{(2 \beta + 1)} \\
M_0 \exp\left( 2D \right) G_z^2 T_b^2 \frac{1}{(2 \beta + 1)} \\\nM_0 \exp[ D^{2(1)} \left( G_z \right)^2 \left( \frac{2}{2 \beta + 1} \right) ]
\end{cases}
\]

Note that here \( 0 < \beta < 1 \) and that for \( \beta = 1 \), we recover the classical results.
PGSE (Stejskal-Tanner)
Changing $\beta (0.3 - 1.0)$ and $\mu (5 - 55 \, \mu m)$
Brain MRI at 3 T
DW-EPI at 3T TR/TE = 4000/97 ms, slice thickness = 3 mm, matrix 256 x 256 and FOV = 22 x 22 cm$^2$. Max b-value = 3300 s/mm$^2$
Axial Slice 2

- T2
- ADC
- Beta
- Mu
Anomalous Diffusion

Fractional diffusion as a window into Duchenne Muscular Dystrophy pathology

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Duchenne Muscular Dystrophy (DMD) is a genetic muscle-wasting condition affecting around 1 in 3,600 boys.

Muscle structure

- Muscle tissue is hierarchical
  → **Myofibres, Myofibrils, Myofilaments**

Images: Wiley
Most diffusion is confined to small pores, but occasionally spins transition to neighbouring regions.

Changes to muscle structure change the distribution of pores and waiting times between transitions.
Diffusion MRI

• Regular diffusion imaging (including DTI) assumes that diffusion is averaged out across the sample

• This predicts that the log of the signal vs diffusion weighting will be a straight line
• If we measure this in tissue, however, we get the following, which we fit to the Mittag-Leffler function, \( E_\alpha(-D_{\alpha,\beta} q^\beta \Delta^\alpha) \)
Preclinical results (mice)
Comparison with Histology
Conclusions

The non-monoexponential curve contains information about the tissue hierarchical structure, which provides a model of the decay curve.

Changes in fibre distribution, packing, and permeability change the signal’s curvature. The Mittag-Leffler function can capture these changes.

Parameter maps for mouse data show darkened regions in Mdx models which are not present in wild type. These regions are observed consistently across N=8 subjects.

Comparison with histology suggests we’re seeing changes in fibre size distribution.
Anomalous Diffusion

Fractional Order Calculus (FROC) Model for Pediatric Brain Tumor Differentiation

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Brain Tumor Differentiation

- The diffusion weighted signal attenuation according to the FROC Model

\[
\frac{S}{S_0} = \exp\left(-D\mu^2(\beta^{-1})(G_d \delta)^2\left(\Delta - \frac{2\beta - 1}{2\beta + 1}\delta\right)\right)
\]

- Application of the FROC Model to Differentiate Low- and High-grade Pediatric Brain Tumors

**Low-grade (WHO II - 4y) Astrocytoma**

**High-grade (WHO IV - 6y) Medulloblastoma**

T1-weighted | Contrast enhanced T1-weighted | T2-weighted
--- | --- | ---

A | B | C

D | E | F

\(D\) | \(\beta\) | \(\mu\)

Sui et al., Radiology, 2015.

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Fractional Order Calculus (FROC) Model for Pediatric Brain Tumor Differentiation

- Group Comparison on the Basis of the FROC Model

Scatter diagrams and box plots of the mean values

Receiver operating characteristics (ROC) curves

Area, 95% Confidence Interval, and Asymptotic Significance of ROC Curves by using FROC Parameters for Differentiating Low- and High-grade Pediatric Brain Tumors

<table>
<thead>
<tr>
<th>FROC Parameter</th>
<th>Area</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area</td>
<td>0.910</td>
<td>0.840, 0.981</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.763</td>
<td>0.884, 1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>P value</td>
<td>0.962</td>
<td>0.646, 0.879</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note.—P₀ = a combination of D and β.
Fractional Order Calculus (FROC) Model for Glioma Differentiation

Low-grade (WHO I - 41y) Oligodendroglioma

High-grade (WHO IV - 38y) Glioblastoma Multiforme

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Continuous-time Random Walk (CTRW) Model for Brain Tumor Differentiation

- The diffusion weighted signal attenuation according to the CTRW Model

\[ \frac{S}{S_0} = E_\alpha \left( -b D_m \right)^\beta \]

- Application of the CTRW Model to Differentiate Low- and High-grade Pediatric Brain Tumors

\[ D_m \]: anomalous diffusion coefficient
\[ \alpha \]: diffusion waiting time parameter (temporal heterogeneity)
\[ \beta \]: diffusion jump length parameter (spatial heterogeneity)

Low-grade (WHO II - 17m) Ependymoma

High-grade (WHO IV - 18m) Medulloblastoma

Karaman et al., MRM, 2015. mkaraman@uic.edu
Continuous-time Random Walk (CTRW) Model for Brain Tumor Differentiation

- Group Comparison on the Basis of the CTRW Model

Box and whisker plots of the mean values

Receiver operating characteristics (ROC) curves

The area under the curves are 0.951 ($D_m$, $\alpha$), 0.952 ($D_m$, $\beta$), 0.898 ($\alpha$, $\beta$), 0.957 ($D_m$, $\alpha$, $\beta$), and 0.804 (ADC).

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Karaman et al., MRM, 2015.
An Alternative Non-Gaussian Diffusion Model: Fractional Motion Model

The diffusion weighted signal attenuation according to the FM Model*

\[
\frac{S}{S_0} = \exp\left(-\eta' D_{fm} b^{\varphi/2} \left(\Delta - \frac{\delta}{3}\right)^{-\varphi/2} \Delta^{\varphi+\psi} \delta^{-\varphi}\right)
\]

\(D_{fm}\): anomalous diffusion coefficient  
\(\varphi\): parameter that governs the variance of increments  
\(\psi\): parameter that governs the correlation properties of

We would like to compare CTRW and FM diffusion models at the level of an *imaging voxel* unlike recent studies performed in *cell culture**.


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An Alternative Non-Gaussian Diffusion Model: Fractional Motion Model

- Comparison of the CTRW and FM Models to Differentiate Low- and High-grade Pediatric Brain Tumors

**ROC Results:**

The CTRW and FM models provide similar performance for discriminating malignancy of pediatric brain tumors, which challenges several reports on the drastic difference between the two models observed in cell cultures.


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Anomalous Diffusion

Parsimonious continuous time random walk models and kurtosis for diffusion in magnetic resonance of biological tissue.

Carson Ingo, Yu Fen Chen, Todd B. Parrish, Andrew G. Webb, and Itamar Ronen


C.J. Gorter Center for High Field MRI, Univ. of Leiden, The Netherlands
Northwestern University, Chicago
Gaussian Diffusion

Partial Differential Equation

\[ \frac{\partial P(x, t)}{\partial t} = D_{1,2} \frac{\partial^2 P(x, t)}{\partial |x|^2} \]

Fourier Transform Solution

\[ p(q, t) = \exp(-D_{1,2}|q|^2t) \]

Anomalous Subdiffusion

Fractional Partial Differential Equation

\[ \frac{\partial^\alpha P(x, t)}{\partial t^\alpha} = D_\alpha \frac{\partial^2 P(x, t)}{\partial |x|^2} \]

Fourier Transform Solution

\[ p(q, t) = E_\alpha \left[ -D_\alpha |q|^2t^\alpha \right] \]

Mittag-Leffler Function (MLF)


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Mittag-Leffler Function (MLF)


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Diffusional Kurtosis Imaging (DKI)

\[ K \equiv \frac{\langle x^4 \rangle}{\langle x^2 \rangle^2} - 3 \]

\[ \frac{S}{S_0} = \exp(-bD + \frac{1}{6}b^2D^2K_{app}) \]

\[ \ln \frac{S(g)}{S(0)} = -\kappa_2 \frac{(\gamma g \delta)^2}{2} + \kappa_4 \frac{(\gamma g \delta)^4}{4!} + \kappa_6 \frac{(\gamma g \delta)^6}{6!} + \ldots \]

Kurtosis in the Mittag-Leffler function

\[ K \equiv \frac{\langle x^4 \rangle}{\langle x^2 \rangle^2} - 3 \]

\[ p(q, t) = E_\alpha \left[ -D_\alpha |q|^2 t^\alpha \right] \]

\[ \langle x^2(t) \rangle = \frac{2D_\alpha}{\Gamma(\alpha + 1)} t^\alpha \]

\[ \langle x^4(t) \rangle = \frac{24(D_\alpha)^2}{\Gamma(2\alpha + 1)} t^{2\alpha} \]

\[ K_{MLF} = \frac{6 \Gamma^2(\alpha + 1)}{\Gamma(2\alpha + 1)} - 3 \]


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Methods

- Northwestern University Memorial Hospital
- 1 chronic stroke patient
- 3T Siemens Trio
- Diffusion weighted SE–EPI sequence
- 3 diffusion directions
- b-values: 0, 500, 1000, 3000, 4000 s/mm² with NA = 6
- TE = 102 ms, TR = 6 s, Δ = 41.2 ms, δ = 30.6 ms
- In-plane resolution = 2x2 mm, slice thickness = 4 mm
- 20 slices, scan time ~ 4 min

\[ \frac{S}{S_0} = \exp(-bD + \frac{1}{6}b^2D^2K_{app}) \]
\[ p(q, t) = E_{\alpha}\left[-D_{\alpha}|q|^2t^\alpha\right] \]
\[ K_{MLF} = 6\frac{\Gamma^2(\alpha + 1)}{\Gamma(2\alpha + 1)} - 3 \]


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Results

![Graphs showing diffusion coefficient values for WM, GM, and CSF.](image-url)

**TABLE 1** Mean and standard deviation of $\alpha$, $K_{\text{MLF}}$, $K_{\text{app}}$, $D_{\text{MLF}}$, $D_K$, and ADC values for selected regions of interest (ROI) in the white matter (WM), gray matter (GM), ischemic tissue (IT), and cerebrospinal fluid (CSF) of a chronic ischemic stroke patient’s brain.

<table>
<thead>
<tr>
<th>ROI</th>
<th>$\alpha$</th>
<th>$K_{\text{MLF}}$</th>
<th>$K_{\text{app}}$</th>
<th>$D_{\text{MLF}}$</th>
<th>$D_K$</th>
<th>ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) WM</td>
<td>0.49 ± 0.04</td>
<td>1.75 ± 0.12</td>
<td>0.99 ± 0.07</td>
<td>0.72 ± 0.03</td>
<td>0.75 ± 0.03</td>
<td>0.68 ± 0.02</td>
</tr>
<tr>
<td>(B) GM</td>
<td>0.77 ± 0.03</td>
<td>0.75 ± 0.09</td>
<td>0.58 ± 0.05</td>
<td>0.97 ± 0.02</td>
<td>1.02 ± 0.02</td>
<td>0.93 ± 0.01</td>
</tr>
<tr>
<td>(C) IT</td>
<td>0.94 ± 0.03</td>
<td>0.18 ± 0.09</td>
<td>0.35 ± 0.03</td>
<td>3.12 ± 0.12</td>
<td>3.26 ± 0.11</td>
<td>2.97 ± 0.10</td>
</tr>
<tr>
<td>(D) CSF</td>
<td>0.97 ± 0.01</td>
<td>0.12 ± 0.08</td>
<td>0.29 ± 0.06</td>
<td>3.27 ± 0.11</td>
<td>3.46 ± 0.12</td>
<td>3.12 ± 0.08</td>
</tr>
</tbody>
</table>

The estimated diffusion coefficient values are reported with units $\times 10^{-3} \text{ mm}^2/\text{s}$.

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Conclusions and Future Work

- Established mathematical connection between subdiffusion and kurtosis
- No limit on maximum b-value to estimate kurtosis
- $K_{MLF}$ provided improved tissue contrast compared to $K_{app}$
- Quantify microstructural plasticity with language therapy in chronic stroke patients

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Anomalous Diffusion

Tissue microstructure features derived from anomalous diffusion measurements in magnetic resonance imaging.

Yu, Q., Reutens, D., O’Brien, K., & Vegh, V


Centre for Advanced Imaging, the University of Queensland, Brisbane, Queensland, Australia

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Extract axon radius and volume fraction using tissue model

- Corpus callosum is a white matter structure consisting of highly oriented fibre bundles of varying radii and volume fractions

- We aimed to map axon radii and volume fraction across the corpus callosum using a tissue model and space fractional anomalous diffusion

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**Ex vivo experiment**

- **Subject**: A single brain was obtained from the Queensland Brain Bank, Australia (male aged 60).

- **EM**: Electron microscopy images were used to evaluate axon radius and volume fraction in specific regions-of-interest.

- **MRI structural data**: 7T Siemens Clinscan animal scanner was used to acquire 100 micron$^3$ gradient recalled echo structural data.

- **MRI diffusion data**: 7T Siemens Clinscan animal scanner was used to acquire 300 micron$^3$ diffusion data with b-values from 0 to 5,000s/mm$^2$ in steps of 500s/mm$^2$, and number of directions increased with b-value to ensure trace of data had consistent SNR across all b-values.

Electron microscopy validation (ex vivo experiment)
Results

*ex vivo*

![Graph showing EM and MRI mean radius changes across different conditions.]
In vivo experiment

- **Subjects**: 9 healthy males aged 23-66 years were scanned
- **Structural MRI data**: 7T MRI gradient recalled echo collected on the Siemens Magnetom Research scanner at 750 micron$^3$ resolution
- **Anomalous diffusion data**: 1.5mm$^3$ DWI data with b-values from 0 to 5,000s/mm$^2$ in steps of 500s/mm$^2$, number of directions increased with b-value such that SNR does not degrade
- **Tractography data**: DWI with b-value = 3,000s/mm$^2$ and 64 directions
- **Segmentation of the corpus callosum**: MRtrix-based probabilistic tracotorgraphy was performed to segment the corpus callosum into areas projecting into various cortical regions

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Segment corpus callosum using tractography (**in vivo** experiment)
Data Processing

Fractional model

\[ M_0 \exp \left( -D\mu^{2(\beta-1)}(\gamma G\delta)^{2\beta} \left( \Delta - \frac{2\beta - 1}{2\beta + 1} \delta \right) \right) \]

\[ D \text{ map} \quad \beta \text{ map} \quad \mu \text{ map} \]

Tissue model

\[ f_{ls} S_{ls} + f_{ls} S_{ld} + f_{csf} S_{csf} + f_{tw} S_{tw} \]

Axon attributes

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Results

in vivo

![Box plot showing radius in vivo](image-url)
Anomalous Diffusion

Probing Features Of Tissue Microstructure Using The Continuous Time Random Walk Diffusion Model

Dr Thomas. R. Barrick
St. George’s, University of London
How Does Microstructure Affect Water Diffusion In Brain Tissue?

Diffusion Time

$$\langle x^2 \rangle = 2Dt$$

Typical length scale for MRI

1-20μm
Image Acquisition

- 3T diffusion-weighted MRI data
  - 2 scanners
    - St George’s, University of London (SGUL)
      - Philips Achieva TX clinical system
        - 80 mTm\(^{-1}\) maximum gradient strength
    - Human Connectome Project (HCP)
      - Purpose built enhanced Siemens system
        - 300 mTm\(^{-1}\) maximum gradient strength
Image Acquisition

- SGUL
  \( \delta = 23.5 \, \text{ms}, \ \Delta = 43.9 \, \text{ms}, \ \Delta = 36.1 \, \text{ms} \)
  Voxel resolution \( 2 \times 2 \times 5 \, \text{mm}^3 \)
  b-values 0, 500, 750, 1000, 1500, 2250, 3500, 5000 \, \text{s} \, \text{mm}^{-2} \)
  3 or 6 diffusion gradient directions,
  Acquisition time 6.5 or 13 minutes

- HCP
  \( \delta = 10.6 \, \text{ms}, \ \Delta = 41.7 \, \text{ms}, \ \Delta = 38.2 \, \text{ms} \)
  Voxel resolution \( \text{Isotropic} 1.25 \, \text{mm}^3 \)
  b-values 5, 1000, 2000, 3000 \, \text{s} \, \text{mm}^{-2} \)
  180 diffusion gradient directions,
  Acquisition time 1 hour

Van Essen et al., 2012
Data Fitting

(a) Signal (arbitrary units) vs. b-value (s mm⁻²) for Cerebrospinal Fluid, Grey Matter, and White Matter.

(b) Normalised signal vs. b-value (s mm⁻²) for Cerebrospinal Fluid, Grey Matter, and White Matter.

(c) Anomalous Diffusion Imaging results with $D_{1,2}$ and $\chi^2$ maps.
Parameter Maps

St George’s Data

HCP Data

Trace of 6 diffusion gradient directions

Trace of 180 diffusion gradient directions

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Anomalous Diffusion Imaging

30th June 2015
Tissue Histograms

HCP data
Anomalous Diffusion Imaging
Dr Thomas. R. Barrick
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Brain Tissue Signatures

HCP data (N=10)

$D_{1,2}$ shows significant differences between acquisitions

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Anomalous Diffusion Imaging

30th June 2015
Corpus Callosum

Group Average Tractography (N=40)

3T HARDI, δ=10.6ms, Δ=41.7ms
180 diffusion directions, b=0,1000, 2000, 3000 s mm⁻²
1 hour

Human Connectome Project Data

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Van Essen et al., 2012

30th June 2015
Corpus Callosum

Group Average Tractography (N=40)

Human Connectome Project Data

Van Essen et al., 2012

Dr Thomas. R. Barrick
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30th June 2015
Corpus Callosum

Dr Thomas. R. Barrick
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Anomalous Diffusion Imaging

30th June 2015
Brain Tumour Patients

Grade I Meningioma

Grade II Astrocytoma

Grade I Glioblastoma

Grade IV Metastasis

aDWI, trace of 3 diffusion gradient directions, 6.5 minutes

30th June 2015
Dr Thomas. R. Barrick
St. George’s, University of London
Acute Stroke Patient

aDTI, 6 diffusion gradient directions, 13 minutes
MLF computed in each direction, tensor fitted to each parameter
Conclusions

- CTRW diffusion model provide parameters that may be interpreted in terms of tissue microstructure
  - Provides tissue contrast
  - Similar parameter values for SGUL and HCP
    - Different effective diffusion times
    - Different voxel sizes
    - Relationship between $\alpha$ and $\beta$ in tissue?
  - Identifies pathological brain regions
    - Consistent with kurtosis and stretched MLF/exponential results for brain tumour
    - Rodent data for stroke
    - Needs further studies with large patient numbers to identify utility

Kwee et al., 2009
Yi Sui et al., 2015
Grinberg et al., 2014
Rudrapatna et al., 2014
Other Approaches

1. Computing Kurtosis and Spectral Entropy as Anomalous Diffusion Measures
   Carson Ingo, Yu Fen Chen, Todd B. Parrish, Andrew G. Webb, and Itamar Ronen
   C.J. Gorter Center for High Field MRI, Department of Radiology, Leiden University Medical Center, Leiden, NL, Department of Radiology, Northwestern University, Chicago, IL, United States

2. Fractional and Fractal Derivative Models for the Characterization of Anomalous Diffusion in MRI
   Yingjie Liang, Wen Chen, and Richard L. Magin
   Hohai University, Nanjing, China and University of Illinois at Chicago, United States

3. Anisotropic Fractional Diffusion Tensor Imaging
   Mark M. Meerschaert, Richard L. Magin and Allen Q. Ye
   Michigan State University, East Lansing, MI and University of Illinois at Chicago, United States
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Matt Hall, UCL
Tom Barrick, St. George’s, UL
Viktor Vegh, U Queensland
Qiang Yu, U Queensland
Development of Fractional Magnetic Resonance Models: What next?

- Brownian Motion
- Spin Rotation $\text{Pr}(\theta, \phi, t)$
- Spin Translation $\text{Pr}(x, t)$
- $\langle x^2 \rangle$
- $\langle B_0^2 \rangle$
- CTRW Model $\alpha, \beta$
- Bloch Equation $\Gamma(t)$, $J(\omega)$, $R_1, R_2$
- Fractional Bloch-Torrey $\rho, T_1, T_2$, $\alpha, \beta, \tau, \mu, D_f$

D, DTI, MD, FA
Linear and Complex Systems

Chaos
- Hodgkin-Huxley
- Chua-Hartley

Non-Linear
- Turbulence
- Combustion

Deterministic

Linear
- Fractals
- Fractional Calculus

Random
- LTIC
- White Noise
- Brownian Motion

White Noise
Brownian Motion