Inferring Axon Diameter Sizes using Monte Carlo Simulations of Magnetic Resonance Oscillating Gradient Spin Echo Sequences

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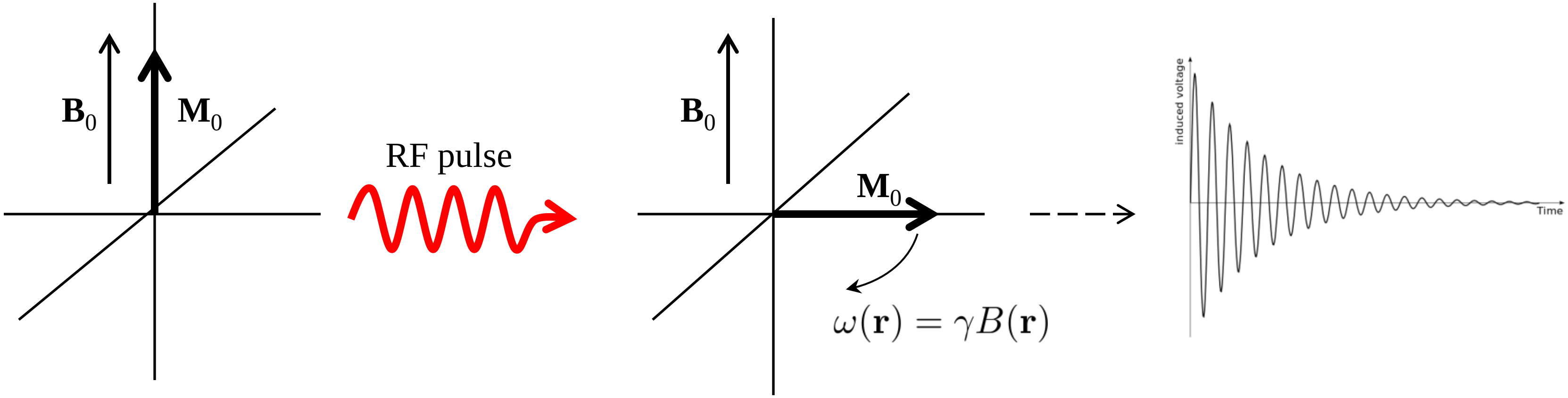
Introduction

- Diffusion-weighted magnetic resonance imaging (MRI) can be used to infer axon diameter distributions in brain tissue for axons > 5 μm.
- We have developed and are optimizing a new method for the measurement of the size of very small (less than or equal to 1 μm) axon diameters.

Magnetic Resonance Overview

- Ensemble of spins in a magnetic field $\mathbf{B}_0$ produces a net magnetization $\mathbf{M}_0$ along the direction of the field
- An RF pulse applied perpendicular to $\mathbf{B}_0$ will tip the magnetization into the transverse plane
- $\mathbf{M}_0$ precesses about $\mathbf{B}_0$ at a frequency proportional to the magnetic field, generating a signal in a detector coil (by Faraday's Law)



Diffusion

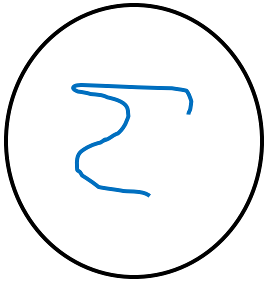
- Diffusion is the random migration of particles over time due to the vast number of collisions that occur at the microscopic level
- Mean-squared displacement depends on the diffusion time **Δ** as described by Einstein's relation:

$$\langle (\Delta \mathbf{r})^2 \rangle = 6D\Delta$$

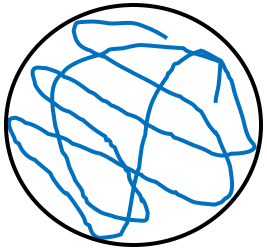
where D is the diffusion coefficient, a measurement of the amount of diffusion

Restricted Diffusion

- In a uniform medium, molecules are free to diffuse anywhere in the medium
- Barriers, such as those found in cellular tissues, can restrict molecular motion
- Measurements of diffusion as a function of **Δ** provides information about the structure in which the molecules are diffusing.



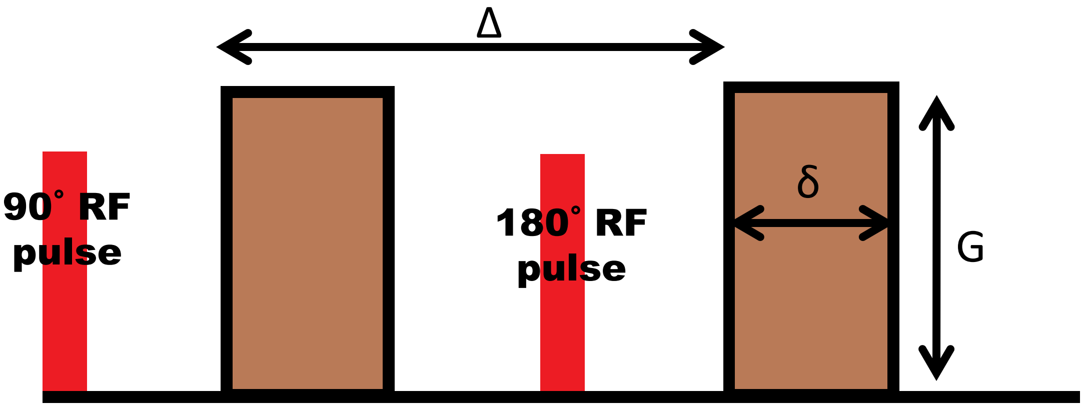
At short **Δ**, the particle appears to be free in its movement



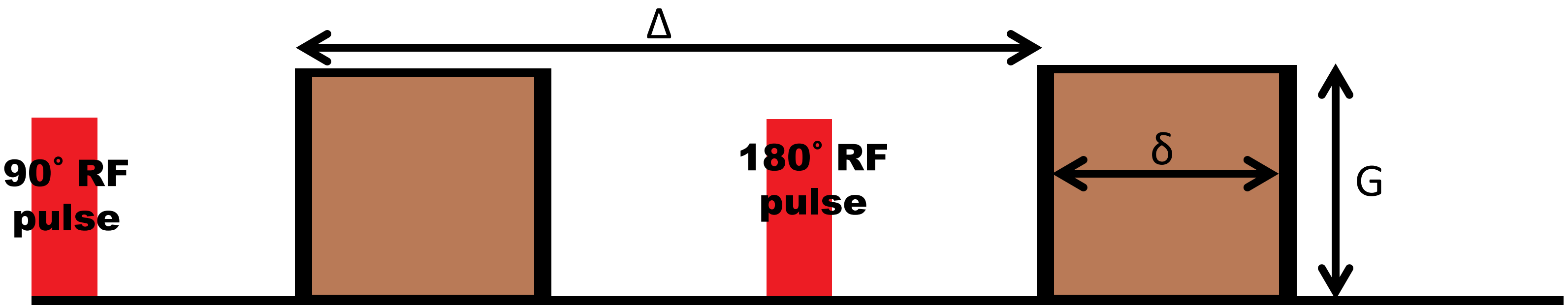
At long **Δ**, the particle is restricted in its movement

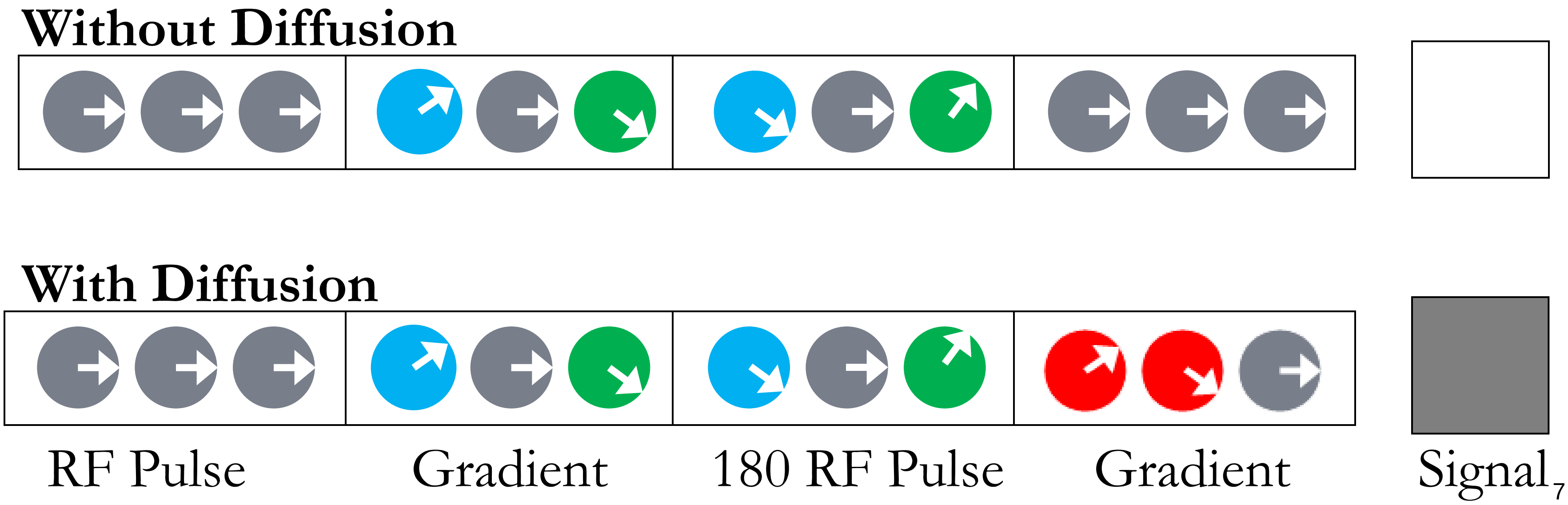
Pulse Sequences

- In diffusion MRI, a sequence of magnetic fields, or a pulse sequence, is used to weight the signal to the diffusive motion of the particles
- Traditional pulse sequence used to measure diffusion is known as the Pulsed Gradient Spin Echo sequence (PGSE)
- PGSE involves two gradients of constant strength G applied back-to-back for duration δ, with the second gradient pulse applied at a time Δ after the first gradient pulse



PGSE (Pulsed Gradient Spin Echo)





Without Diffusion

With Diffusion

RF Pulse

Gradient

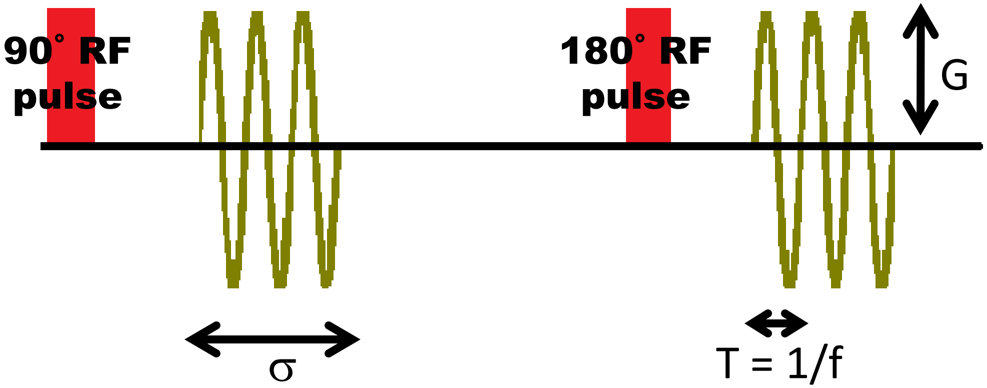
180 RF Pulse

Gradient

Signal

OGSE (Oscillating Gradient Spin Echo)

- Used to make measurements at short diffusion times
- Replaces the rectangular pulses of PGSE with sinusoidally varying gradient pulses
- In OGSE, each period of the sine acts a diffusion weighting so that the spins are dephased by the first lobe, and rephased by the second lobe, similar to the rectangular gradients of the PGSE



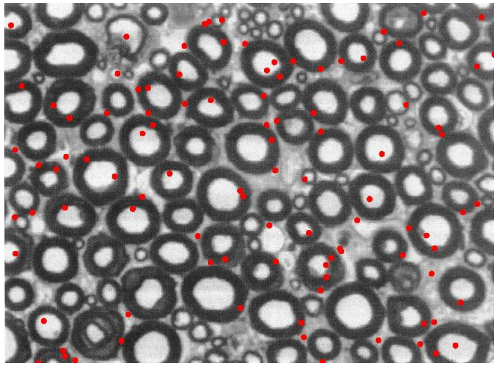
Monte Carlo Simulations

- Test ability of OGSE to infer small axon sizes using Monte Carlo simulations

Steps:

- Distribute N particles on a lattice
- Each particle undergoes a random walk
- After each time step, do the following for each particle:
  1. Update its position ($\boldsymbol{r}_k \rightarrow \boldsymbol{r}_k + \Delta\boldsymbol{r}_k$)
  2. Update its phase ($\varphi_k \rightarrow \varphi_k + d\varphi_k$)
     - Phase increment $d\varphi_k$ depends on the magnetic field experienced by the particle
- The total signal collected at the end of the simulation (S) will be

$$S = \left| \frac{1}{N} \sum_{j=1}^{N} e^{i\phi_j} \right|$$



These particles (red) are diffusing on a lattice.

AxCaliber Model

- AxCaliber is a model for estimating axon distributions using diffusion MRI
- Model signal as coming from two compartments:

$$S = \underbrace{e^{-bD_h}}_{\text{Extracellular signal}} + \underbrace{\sum_i \frac{w(r_i,\boldsymbol{\theta}) r_i^2 e^{-\beta(r_i,D_i)}}{\sum_k w(r_k,\boldsymbol{\theta}) r_k^2}}_{\text{Intracellular signal}}$$

f_h: volume fraction of extracellular space

D_h: hindered diffusion coefficient (apparent extracellular diffusion coefficient)

D_i : Intracellular diffusion coefficient

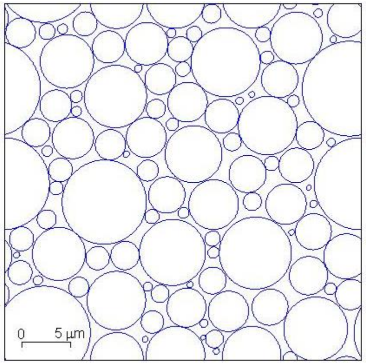
$w(r_i,\theta)$: Axon radius distribution (parameterized by θ)

$e^{-\beta(r_i,D_i)}$: Analytical signal from single cylinder

Simulation Setup and Methods

- We model white matter as a collection of parallel, non-overlapping, impermeable cylinders
- Synthesize 400 diffusion-weighted signals using a cosine gradient spin echo sequence
  - Acquire signals at different cosine frequencies and amplitudes
- Repeat for different axon diameter distributions
  - Single radius
  - Gamma distribution
  - Gaussian distribution
- Fit signal data to AxCaliber model

  using χ^2 minimization



Example of a simulated
axon environment

Single Cylinder Simulation

- 57344 particles initialized inside a cylinder
  - Choose a radius
  - Set diffusion coefficient in cylinder to 1.0 μm^2/ms
- Fit signal to analytical expression for cylinder signal
  - Extract radius and diffusion coefficient

Actual values	Fit values	
Radius (μm)	Radius (μm)	D (μm^2/ms)
1.0	1.004 ± 0.001	0.992 ± 0.007
2.0	2.017 ± 0.006	1.001 ± 0.001
3.0	3.037 ± 0.006	0.9984 ± 0.0007

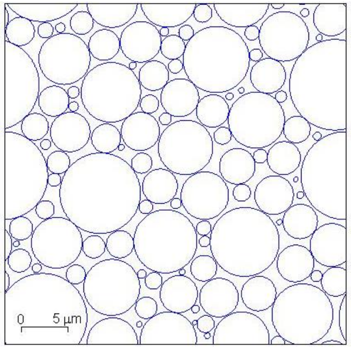
Single Cylinder Simulation

- Lattice of squared packed cylinders
  - Radius: 2 μm
  - Diffusion coefficients: 1.0 $\mu m^2/ms$ (intracellular) and 2.5 $\mu m^2/ms$ (extracellular)
  - Choose packing fraction
- 57344 particles uniformly distributed over substrate
- Fit to two compartmental model ($w(r,\theta) = \delta[r-r_0]$)
  - Extract f_h and D_h

f_h (actual)	0.8	0.7	0.6	0.5
f_h (fit)	0.776 ± 0.002	0.670 ± 0.003	0.558 ± 0.003	0.456 ± 0.003
D_h ($\mu m^2/ms$)	2.482 ± 0.009	2.46 ± 0.01	2.41 ± 0.02	2.34 ± 0.02

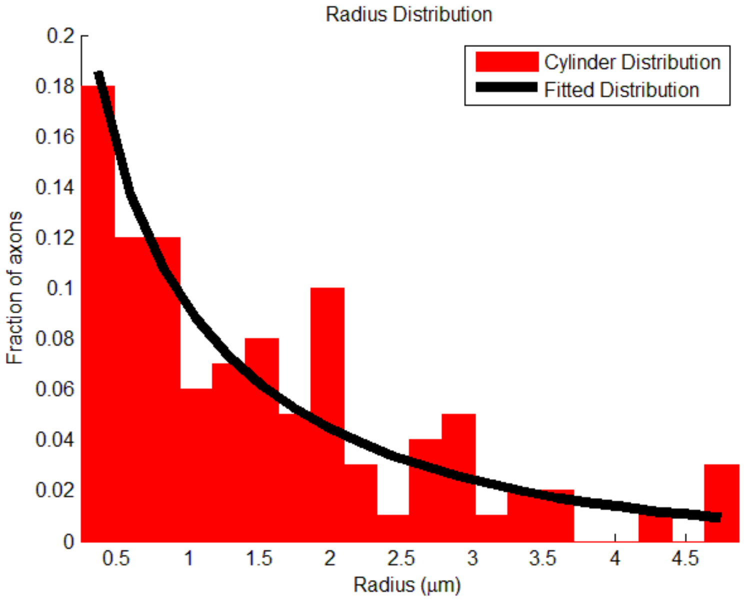
Gamma Distribution of Axon Diameters

- 100 cylinders chosen from a Gamma distribution on a periodic lattice
- Simulations for different packing fractions (vary lattice size)
  - Five packing fractions ranging from approximately 0.3 to 0.8
- Allow water to diffuse:
  - Inside cylinders ($D_i = 1.0\ \mu m^2/ms$)
  - Inside and around cylinders ($D_{ex} = 2.5\ \mu m^2/ms$)
- Fit data to AxCaliber model
  - Extract distribution parameters (intracellular water only)
  - Also extract *f*h, and *D*h (for intracellular and extracellular water)
  - Keep D_i fixed



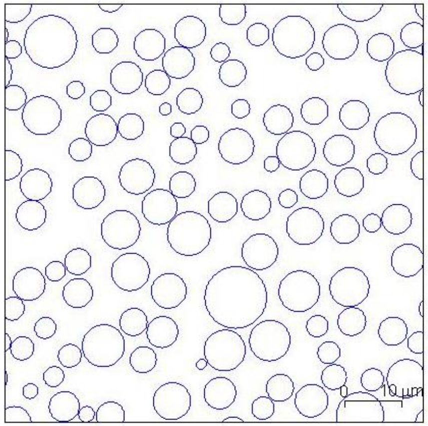
Gamma Distribution of Axon Diameters

- Water allowed to diffuse only within the cylinders
- In this case, we only need to fit the signal to the modeled intracellular signal
  - Extract Gamma distribution parameters
- Fitted distribution agrees fairly well with the actual distribution over the entire range of radii



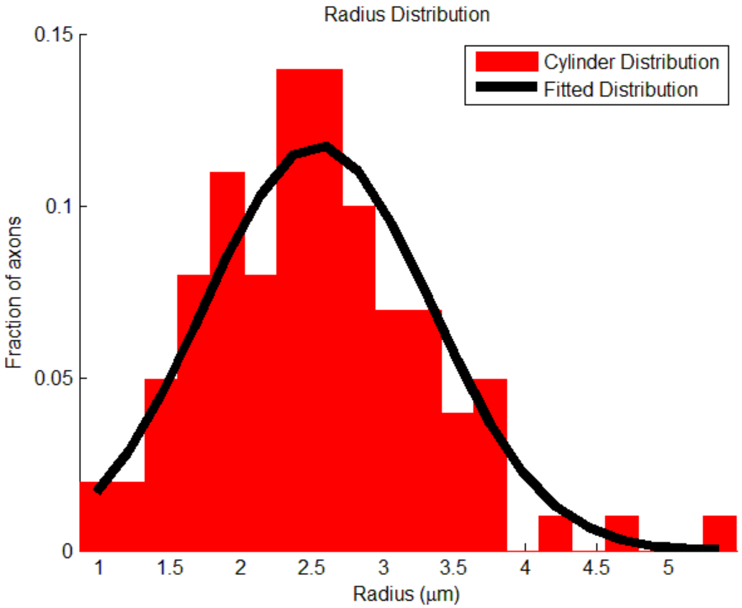
Gaussian Distribution of Axon Diameters

- 100 cylinders chosen from a Gaussian distribution on a periodic lattice
  - Mean radius (μ) ≈ 2.56 µm
  - Standard Deviation (σ) ≈ 0.77 µm
- Simulations for different packing fractions (vary lattice size)
  - Packing fractions of 0.1, 0.3, and 0.4
- Allow water to diffuse:
  - Inside cylinders ($D_i = 1.0\ \mu m^2/ms$)
  - Inside and around cylinders ($D_{ex} = 2.5\ \mu m^2/ms$)
- Fit data to AxCaliber model
  - Extract μ, σ (intracellular water only)
  - Also extract fh and Dh (for intracellular and extracellular water)
  - Keep D_i fixed



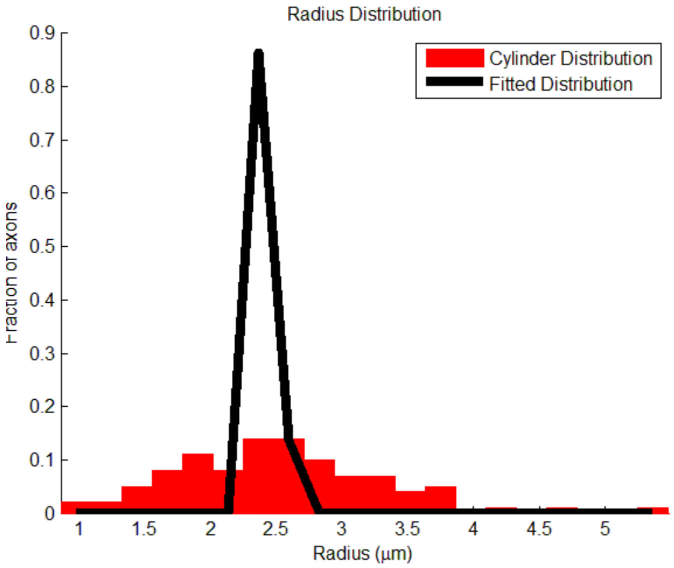
Intracellular signal – Gaussian distribution

- Water allowed to diffuse only within the cylinders
- In this case, we only need to fit the signal to the modeled intracellular signal
- Extract Gaussian distribution parameters (mean and standard deviation)
- Fitted distribution agrees fairly well with the actual distribution over the entire range of radii



Gaussian Distribution: Full Signal

- When water is allowed to diffuse inside and around the cylinders, the model has trouble finding the correct axon distribution
- For a Gaussian distribution of radii, it can predict the mean radius, but not the width of the distribution
- Indicates that the extracellular signal used in the AxCaliber model needs to be modified



Gaussian distribution of diameters with a packing fraction of 0.4

Conclusions

- First step towards combining oscillating gradient measurements with axon diameter distribution models to infer distributions of small axon diameters in tissues
- Accurately predicted mean diameters of various models of white matter using oscillating gradients.
  - These diameters were at least a factor of two smaller than the smallest possible inferred diameters used in other simulations.
- We will improve the model of extracellular space to infer the total distributions more accurately
- Eventually would like to compare white matter fibre integrity in healthy and diseased mouse brains

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