Moving toward faster live measurements of axon diameter

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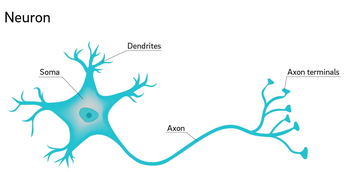
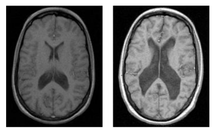
Motivation

Axon transmit message between neurons throughout the body. The corpus collosum, which connects 2 cerebral hemispheres, has more than **200 million** axon. [1]

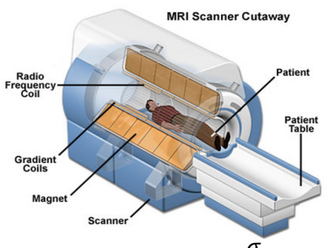


Schizophrenia is a central nervous system (CNS) related neurological disorder that autopsy studies indicate could be related to the distribution of axons throughout the brain. For instance, abnormalities in axonal integrity and organization were detected. [2]

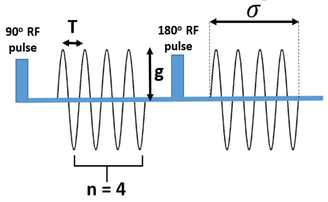
We are currently looking at methods to increase the efficiency of measuring axon properties for live animals and then move the method to live human imaging.[3]



Diffusion MRI + OGSE



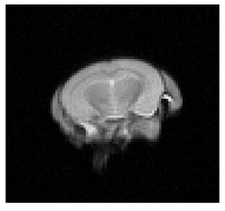
Magnetic Resonance Imaging (MRI) is a noninvasive diagnostic imaging tool that produces images with great contrast between tissues.[4] **Diffusion MRI** is an advanced MRI technique using special gradients to produce quantitative images giving information about the movement of water molecules in the body.



The highest resolution limit of clinical MRI is around 1 mm^3 per voxel but axons' diameters are of order 1 μm. **Oscillating Gradient spin echo sequence** is known for its ability to probe smaller structures with a shorter time frame.

Rodent experiments

Previous studies in the Martin lab imaged phantoms, or samples with known properties that mimic brain tissue. These studies required five days to collect many images. The goal is to have the method work in live human brains which requires a method that can collect fewer images in a matter of minutes.

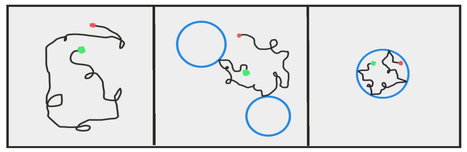


Accuracy assessment of our method can be done by sectioning the brain tissue and sending it for electron microscopy (EM) measurements. EM is the only known method for measuring axon diameters and packing fractions.

Methods

Experimental and simulated data were acquired with similar OGSE settings[5] . Images were registered and diffusion metrics were calculated. Diffusion information was fitted to the Ax-Caliber model[5] to find information about axonal packing fraction, axon mean diameter, and other information using different initial conditions.

Diffusion vs. Cell structures



Green and Red dots represent the initial and final position of a water molecule undergoing diffusion. Blue circles represent a cross-section of an axon. Movements of molecules are categorized into 3 types.

Ax-Caliber Model

$$S_{norm} = f_{axon}E_r(n, G) + (1 - f_{axon})E_h(n, G)$$

This is a simplified form of the analytic model called Ax-Caliber[6] which assumes single-sized axons within voxels. It was adapted for OGSE in the Martin lab. This model is based on the framework **Composite Hindered and Restricted Model of Diffusion** (CHARMED)[7] where the model assumes signal is coming from more than one compartment as shown above. MR signals from different areas in CNS tissue has to be modelled carefully into free, hindered, and restricted compartment. Modelling axons as cylinders, Bessel functions' solution and its derivatives were implemented to form a sophisticated model to calculate the restricted part of the diffusion. On the other hand, the hindered part is modelled with simple Gaussian distribution.

Input parameters:
S_{norm}: *normalized signals*
n: *gradient oscillation cycle*
G: *gradient strength*

Output parameters from LS fitting:
a: ***inferred radius***
D: *diffusion coefficient*
f_{axon}: *axon's packing fraction*

Scan time optimization

Columns are the gradient strength (G)

Rows are the gradient oscillation cycle number (n)

Numbers are shown in percentage of maximum gradient strength used.

OGSE_parameters.g

	1	2	3	4	5
1	0	10	8.1854	5.8310	1
2	0	19.3218	15.8156	11.2665	1.9322
3	0	28.6660	23.4641	16.7150	2.8666
4	0	38.0153	31.1169	22.1665	3.8015
5	0	47.3666	38.7712	27.6192	4.7367
6	0	56.7188	46.4263	33.0725	5.6719
7	0	66.0702	54.0819	38.5260	6.6072
8	0	75.4247	61.7378	43.9797	7.5425
9	0	84.7781	69.3939	49.4337	8.4778
10	0	94.1316	77.0500	54.8877	9.4132
11	0	92	84.7063	60.3417	10.3485
12	0	92.3627	65.7959	40	11.2839
13	0	92	71.2500	40	12.2193
14	0	92	76.7042	40	13.1547
15	0	92	82.1584	50	14.0900
16	0	92	87.6126	50	15.0254
17	0	93.0668	50	30	15.9608
18	0	90	80	70.0000	16.8962
19	0	90	80	70.0000	17.8316
20	0	90	80	70.0000	18.7670

The average time for scanning in previous experiments was 72 hours. Most of them were repetitive scans. By averaging, signal-to-noise ratio can be increased. However, humans cannot tolerate a 72-hour imaging session. The total scan time for the method is needed to be shortened.

Data acquisition structure is mainly represented by the "OGSE_parameters" shown in the table. **Gradient strength, gradient oscillation cycle and the number of gradient strengths** are 3 main parameters. Eliminating any numbers from the table will result in a drop of total imaging time. A **proposed method** is to make *a priori* assumption of the axon's radius and approximate diffusion coefficient. By relating that with **Einstein's mean diffusion displacement**, one can calculate the gradient oscillation cycle number with effective diffusion time for an ideal measurement. Data with a desired range of gradient oscillation cycles centered at the the ideal calculated value were collected to determine if imaging sessions could be shortened.

$$< x^2 > = N_d D \frac{\tau}{2N_{OG}}$$

This is Einstein's relation for diffusion displacement [8] combining-effective diffusion time equation with gradient oscillation cycle.

N_d: motional degree of freedom
D: diffusion coefficient
τ: gradient duration
N_{OG}: number of gradient oscillation cycle

Main findings

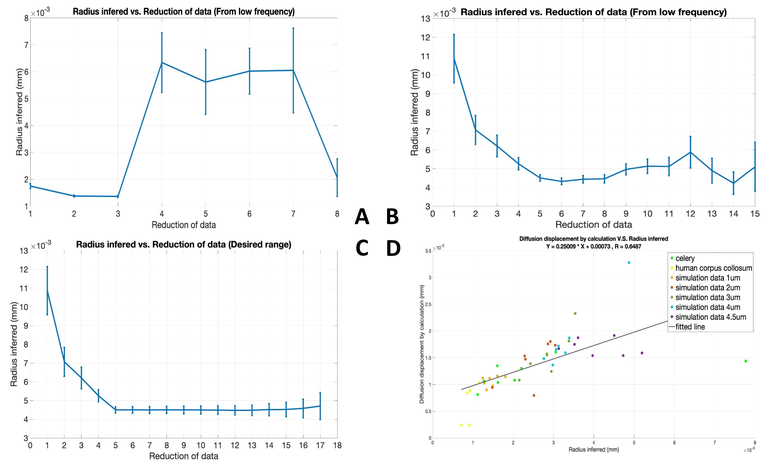


Figure A,B and C uses the same data set (**4.5 μm simulation data**) with different data dropping method. **Figure D** is the correlation between the ***inferred radius*** and the ***diffusion displacement*** .

- **Figure A**, Model used: **AxCaliber model(C)**, Data are dropped from **lower n's** end.
- **Figure B**, Model used: **AxCaliber model(R)**, Data are dropped from **lower n's** end.
- **Figure C**, Model used: **AxCaliber model(R)**, Data are dropped from **both n's** ends.

The **restricted** part **(R)** of the **Completed** equation **(C)** describes the water signals trapped inside the axons, the **hindered** part **(H)** of the equation describes the water signals in the spaces between axons.

By Comparing Figure **A's** and Figure **B's** error bar and output parameter trends, **AxCaliber model(R)** did a better job inferring a close result to 4.5 μm even though the model was fed fewer terms. Figure **C** is telling us that the model still works well if a suitable range of n's is centered at a calculated ideal gradient oscillation cycle. Through Figure **D**, we could determine the range of n's needed to perform analytical scans by the **linear relation** and the **Einstein diffusion displacement equation.** Although it requires rough estimates on diffusion coefficient.

Conclusion

As a moderate correlation suggested(R = 0.6487), OGSE's oscillation cycle can be potentially pre-determined by the axon sizes. Also, with the combination that Melissa's gradient reducing method(using only 2 gradient for each n's)[9], **imaging time can be reduced from an initial period of 3 days to *5 hours 45 mins*.** (Due to the pandemic, additional data acquisition is limited)

"~12.5 times decrease of our scanning time."

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