Physics Tutorial 6: Diffusion MRI

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The purpose of this tutorial is to cover material related to Diffusion MRI, using a simple diffusion acquisition simulator. Questions without any asterisks are those that should be attempted by everyone, whereas more challenging questions are marked with one (*) or two (**) asterisks, and should be considered optional. Take these opportunities to think about these questions, and then discuss your answers with your tutor.

At the end of the tutorial period, you will receive a "take-home tutor", which is an annotated version of this tutorial guide that will help you complete the tutorial at home if you don't manage to make it all the way through with your tutor, or if you missed the tutorial session.

Attendance will be taken by the tutors, and marks will be given by participation. If you would like additional feedback or clarification on the tutorial material, you are welcome to submit your questions or comments to Weblearn, and a tutor will provide written feedback for you. Those unable to attend the tutorial must submit answers to all unstarred questions to receive credit for the tutorial.

Part 0 – Getting Started

Download and unzip the file containing the tutorial resources from Weblearn, or if you have access to the FMRIB internal network, copy them into your current directory from here:

~mchiew/GradCourse/6_Diffusion

Start MATLAB, and make sure you're inside the tutorial directory (i.e., the folder containing all the tutorial files).

Note to jalapeno00 users: please start with the -nojvm option, "matlab -nojvm"; *this should reduce server CPU load if lots of people are trying to use jalapeno00 simultaneously*

Part 1 – The Diffusion Simulator and the Tensor Model *[25-30 minutes]*

This tutorial uses a diffusion MRI MATLAB tool that simulates the acquisition and simple inspection of diffusion weighted MRI under semi-realistic conditions.
Type:
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>> dMRISim
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into the MATLAB command window to start the diffusion simulator

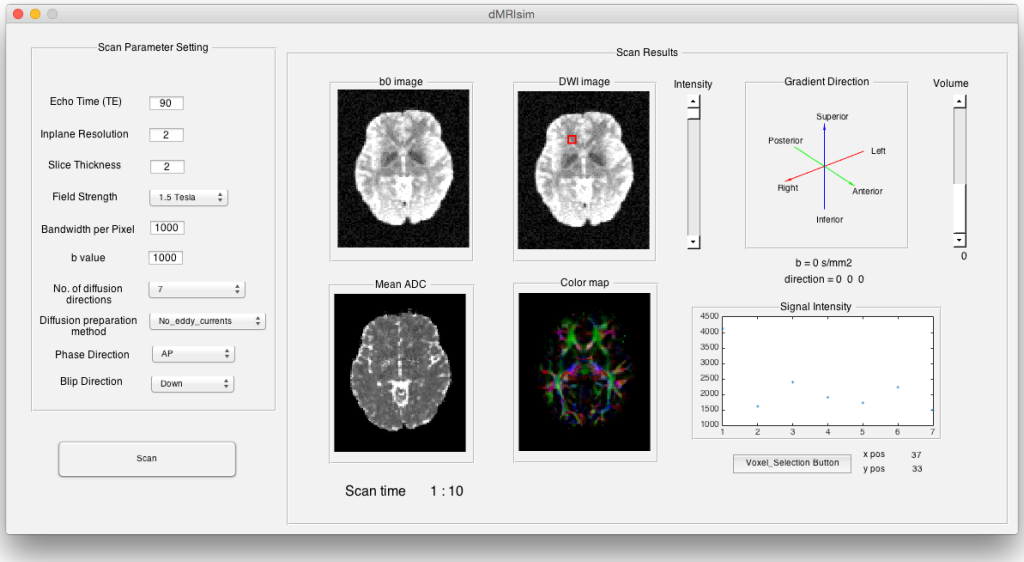

Figure 1

The simulator is able to realistically demonstrate the effects of changing:

- Echo time (TE)
- In-plane image resolution (Δx, Δy)
- Slice thickness (Δz)
- Magnetic field strength (B0)
- Acquisition Bandwidth
- Diffusion-weighting (b-value)
- Number of diffusion directions acquired
- Diffusion encoding method (type of diffusion encoding gradients)
- Phase encoding direction
- Phase encoding blip direction

At this stage, students should be reasonably comfortable with the effect of most of these simulator parameters on image properties. It may be useful to briefly review all the parameters, but focus on the diffusion-weighting, number of directions, and diffusion-encoding method parameters, which are the ones specific to this simulator.

The effects of modifying these parameters is reflected in the various output measures provided:

No diffusion weighting reference "b=0" image

The b=0 image is the reference image for all the subsequent directional, diffusion weighted images. It is an image acquired in the absence of any diffusion encoding gradients, with all other parameters the same. This produces the "S_0" image.

Note that in practice, it is difficult to be completely insensitive to diffusion weighting, as the readout gradient waveforms themselves can contribute small, but non-zero b-values.

Diffusion weighted images (one for each direction acquired)

When diffusion gradients are applied in a given direction, with a given b-value, the signals from the image that is produced can be expressed relative to the reference b=0 data as:

$$S_i = S_0 e^{-bD_i}$$

where S_i is the diffusion-weighted signal in the i^{th} direction, and D_i is the apparent diffusion coefficient in that same direction.

Question 1.1
Why is it necessary to measure diffusion weighting relative to a reference "b=0" image?
Because diffusion contrast is measured as a loss of signal, in order to specifically isolate the effects of diffusion, other factors that modulate signal intensity (like proton density or T2 decay) must be accounted for. The "b=0" image essentially measures the S_0, which makes estimation of the diffusion tensor simple, because:

$$\ln\left(\frac{S_0}{S_i}\right) = -b \cdot D_i$$

Estimated mean apparent diffusion coefficient (ADC) image
The mean ADC represents the average diffusion coefficient computed after estimation of the diffusion tensor:

$$\begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}$$

where mean ADC = $(D_{xx} + D_{yy} + D_{zz})/3$. This represents the *overall*, net effect of diffusion in all directions. A higher mean ADC represents a case where water molecules are able to produce larger net displacements in the same amount of time, compared to more restricted displacement in voxels with lower ADC.
Note that the diffusion tensor is symmetric, so that $D_{ij} = D_{ji}$, and that the diffusion tensor only has 6 unknowns.

Extra Information
Estimation of the diffusion tensor is performed by solving a uniquely determined (6 direction measurement) or an over-determined (more than 6 directions) linear system. Each measurement of diffusion in a different direction provides the following linear constraint to the variables D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{xz}, D_{yz}:

$$\ln\left(\frac{S_i}{S_0}\right) = -b \cdot \begin{pmatrix} u & v & w \end{pmatrix} \cdot \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix} \cdot \begin{pmatrix} u \\ v \\ w \end{pmatrix}$$

where $\begin{pmatrix} u \\ v \\ w \end{pmatrix}$ is a unit vector denoting the direction of the diffusion encoding gradient.

Estimated colour map fractional anisotropy (FA) image
The mean ADC does not provide any information of preferential diffusion directions. Instead colour-coded FA maps provide information about the primary diffusion direction, by colouring left-right directions red, anterior-posterior directions green, and inferior-superior directions red.
Refer to Figure 2 for discussion of preferential diffusion direction as the "long" axis of the diffusion ellipsoid. Consider drawing some ellipsoids with varying FA values on the whiteboard, to illustrate the round-ness of tensor fits with low FA, and the oblong-ness of fits with high FA.

Extra Information
The eigen-decomposition of the diffusion tensor is:

$$\begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} = [V_1 \quad V_2 \quad V_3] \begin{bmatrix} \lambda_1 & & \\ & \lambda_2 & \\ & & \lambda_3 \end{bmatrix} [V_1 \quad V_2 \quad V_3]'$$

where V_1, V_2, and V_3 are column vectors associated with the axes of the diffusion tensor ellipsoid (see Fig. 2). V_1 corresponds to the primary diffusion direction (and V_2 to the secondary, V_3 to the tertiary), and the colour assigned to the voxel in the FA colour map is determined by what degree V_1 is aligned with the left–right, anterior–posterior, or inferior–superior directions.

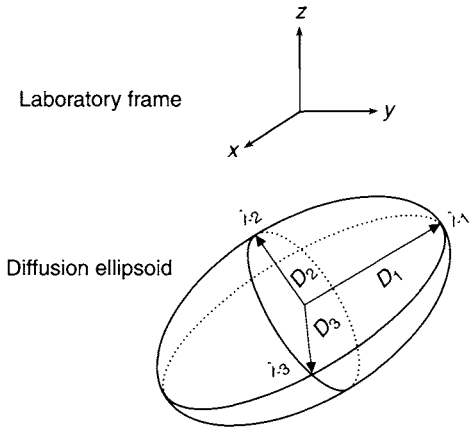

Figure 2 (*source: Bernstein et al., Handbook of MRI Pulse Sequences 2004*)

Start the diffusion simulator by typing:
`>> dMRISim`
into the MATLAB command window. Change the field strength to 7T and the number of diffusion directions to 21, then hit the "Scan" button. Use the voxel selection button to select a voxel in white matter where the fibres run anterior to posterior (i.e. they appear green in the colour map).

Now scroll through the different diffusion weighted images using the "Volume" scroll bar at the top right. You may wish to use the "intensity" scroll bar to show the diffusion-weighted images more clearly.

Question 1.4
Using **only** the diffusion weighted images and the signal intensity plot, state which volume numbers correspond to the following cases and how you deduced this:
a) no diffusion weighting (b = 0).
b) diffusion weighting in approximately the anterior–posterior direction.
a) There are three b = 0 images (volume numbers 1, 10 and 19). These have the highest signal intensity in all voxels since no signal is lost due to diffusion weighting.
b) Volumes 4, 8, 13 and 18 use diffusion gradients approximately along the anterior–posterior direction. We can tell this because in voxels with fibres running in this direction we get the strongest signal loss in those volumes since water can diffuse relatively freely along the direction of the tracts. Note that other volume numbers have some diffusion weighting along this direction too, so you may get slightly different results depending the precise direction of the fibres in the voxel you picked.

Part 2 –Diffusion Acquisition Parameters *[20–30 minutes]*

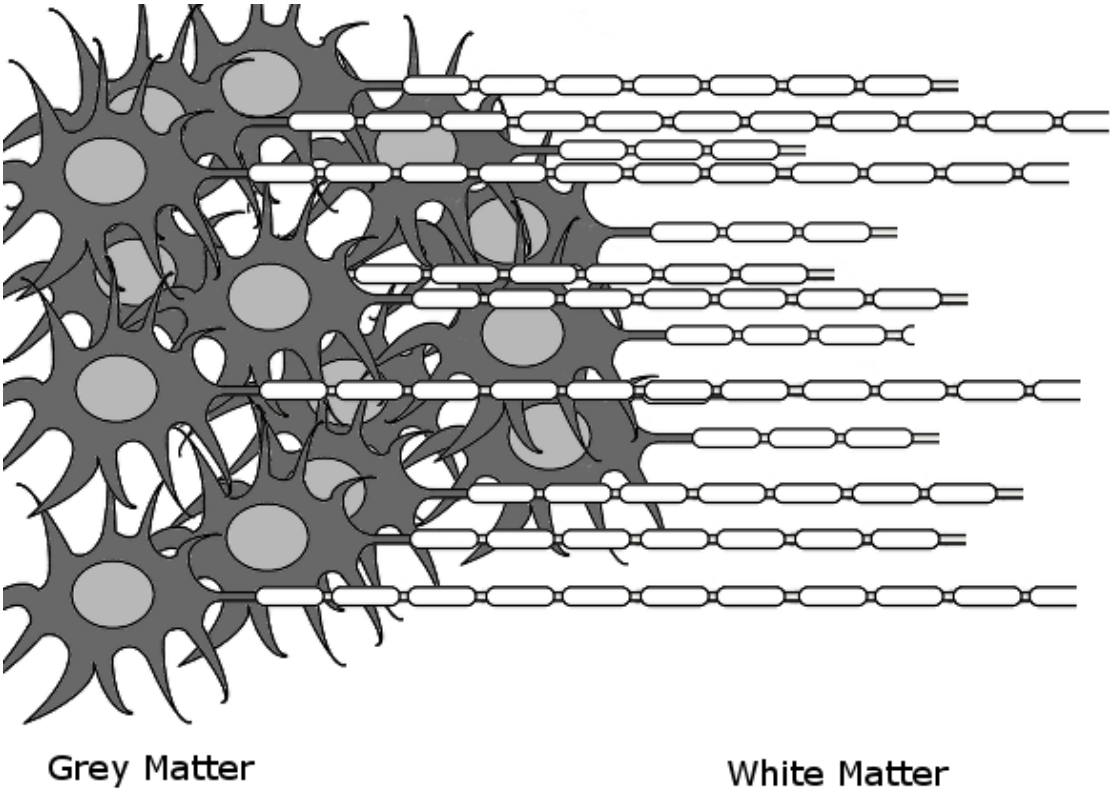

Figure 3

Diffusion-weighted measurements are designed to reveal information about the microstructural properties of the tissues under investigation. Grey matter (neuron bodies), white matter (neuron projections, or axons) and cerebral-spinal fluid all have distinct diffusion tensor signatures that reflect their respective structures (or lackthereof).

Walk through selection of voxels in GM, WM and CSF with students, and examine the signal vs. direction plot. Describe the large fractional anisotropy in WM, compared to the relatively isotropic diffusion in GM and CSF. Similarly, note that ADC in CSF is higher than in GM, due to the lack of motion-impeding structures, referring to Fig. 3.

Question 2.1

How might diffusion change in WM axons with increasing radius?

Given the change in radius with respect to the diffusion coefficient (or more accurately, the mean free path due to diffusion) this could have a very small or a very large effect. If the radius is on the order of that of the MFP, then increasing it will make diffusion appear less anisotropic, where as decreasing it will increase apparent anisotropy. In many cases of white matter disease, the structure of the axon or myelin sheath is disrupted, leading to increased diffusion perpendicular to the axon fibre direction. Diffusion anisotropy measurements can be sensitive to these changes.

The high degree of fractional anisotropy in white matter is what people are often interested in when acquiring diffusion data for the purpose of axonal fibre characterisation. There are many choices of acquisition parameters that can be made to balance the quality of the diffusion tensor estimates with scan time and image quality.

One parameter is the number of diffusion directions. At a bare minimum, the diffusion tensor has 6 free parameters, so 6 non-collinear directions must be

acquired (in addition to the directionless b=0 reference image). In practice, measurements can be made on up to *hundreds* of different directions.
Examine and discuss the effect of increasing the number of directions. Generally, robust estimation of the diffusion tensor requires at least 20–30 measurements. Note that in the tensor model, more directions only provides more data for the least squares estimation of the single ellipsoid, and does not provide additional information on more complex orientation dependence (see section 3.2 on crossing fibres).

Another parameter is the b-value, or strength of diffusion encoding. Increasing the b-value increases the diffusion contrast, but can often result in increasing TE. The optimal b-value for measuring diffusion in the human brain is around b=1000 s/mm^2, which is large enough to ensure diffusion has a strong impact on the signal intensity, but not so large as to cause too much signal loss.
Examine and discuss the effect of changing b-values, or diffusion encoding strength, using the simulator. It may also be instructive to explain the b-value in terms of the properties of the diffusion encoding gradient, and its impact on the measured MR signal from an intuitive perspective.

Question 2.2
What effect does increasing TE have on the diffusion data?
Assuming the diffusion encoding gradient is unchanged, the increased TE results in a reduced signal-to-noise ratio. Generally, in diffusion imaging the TE is limited by the time needed to play out the diffusion encoding gradients, so increasing TE allows longer diffusion gradients, and therefore higher b-values.

Question 2.3**
Estimate the optimal b-value for measuring diffusion contrast
Given $S = S_0 e^{-bD}$, compute the rate of change of S with respect to D, which represents how sensitive diffusion changes are reflected in the MR signal:

$$\frac{\partial S}{\partial D} = -b \cdot S$$

Then, to find the optimal b-value, this sensitivity should be optimised with respect to b, which determines the b-value that provides maximum diffusion sensitivity:

$$\frac{\partial^2 S}{\partial b \partial D} = -S + bD \cdot S = 0$$

which is solved when

$$b = \frac{1}{D}$$

Other parameters can include field strength, and image resolution.
Briefly demonstrate and discuss the effect of modifying field strength and resolution on the ADC and colour FA maps.

Part 3 – Artefacts and Complications *[35–40 minutes]*

3.1 Distortion and Eddy Currents [25–30 minutes]

In a typical diffusion imaging protocol a spin-echo EPI readout is used.

Question 3.1.1
How much do dropout and distortion affect the images produced in the simulator (you may like to change the TE and bandwidth to test this)? Can you explain why this is?

There is no dropout in these images because we are using a spin-echo sequence. Any magnetisation that dephases due to magnetic field inhomogeneity is refocused at the echo time by the 180° refocusing RF pulse. Distortion is still a problem though because magnetic field inhomogeneities still cause the magnetisation to precess at different frequencies at different locations in the brain throughout the EPI readout, leading to signal mislocalisation.

Distortion in diffusion acquisitions also arises due to eddy current effects from the diffusion encoding gradients.

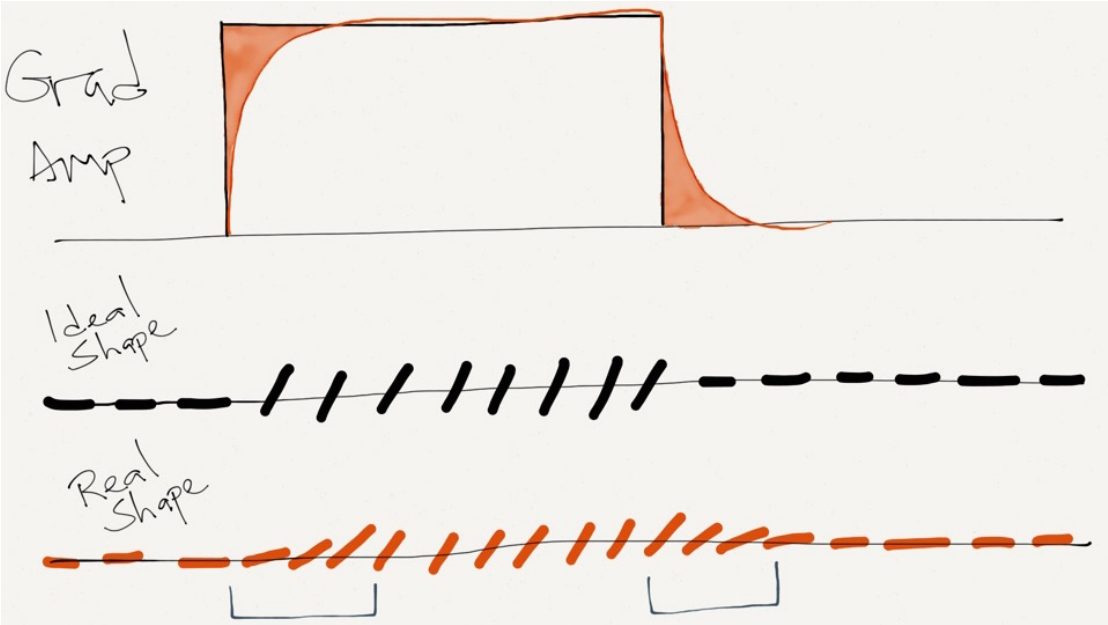

Figure 4

Eddy currents cause the gradient waveforms to deform, where the effect can be understood as a "resistance to change" behaviour of the magnetic field gradients. Fig. 4 illustrates the principle with a simple gradient pulse, showing the sluggish response of the orange, realistic gradients to being turned on and off, relative to the ideal gradient pulse (controlled by the input current to the gradient coil).
Discuss the figure with students. You could use an analogy with physical inertia: e.g. when you put your foot down on a car's accelerator pedal it doesn't immediately go at full speed, but takes some time to get there (i.e. there is resistance to change in speed), and the same applies in reverse for braking.
With more advanced students you could point out that eddy currents don't actually change the area under the gradient waveform, so the direct action of the gradients (i.e. the diffusion encoding) is relatively unaffected, but they do become a problem if you are trying to acquire k-space data shortly after a large gradient has been switched off.

Because eddy currents alter the strength of the gradient, but do not affect the direction, eddy current effects follow the same directional dependence as the diffusion encoding. Therefore, different diffusion-weighted images will each have unique image distortions depending on the direction of diffusion encoding. This distortion is also dependent on the EPI phase-encoding and blip directions.
Turn on monopolar gradients, scroll through images and discuss the distortion-dependence on direction. Sketch on the white board two cases where the diffusion gradients are parallel to and orthogonal to the EPI phase-encoding direction to help explain why you can get either stretching/compression or image shearing, respectively.

Question 3.1.2

Turn on the eddy current simulation by selecting the monopolar diffusion encoding gradients. Examine the effect of eddy currents on the FA colour maps. How might you explain the bright "ring" artefact you see?
Eddy currents cause different distortions in different images. Therefore, in voxels near the edge of the brain in some images there may be tissue present (strong signal) and in other images it is not present (no signal). The signals in those voxels therefore vary strongly with the direction of the applied diffusion gradients, which is entirely consistent with a diffusion tensor that is strongly directional. These voxels are therefore assigned high FA values. Note that this ring is primarily present along edges which are orthogonal to the phase-encoding direction, since distortions always occur along the phase-encoding direction.

Question 3.1.3*
Why are eddy currents specific to diffusion-encoding gradients?
Actually, they are not. However, eddy currents scale with gradient strength, so they are particularly prominent in diffusion imaging where very strong gradients are used. In addition, in many other sequences the eddy currents result from gradients that are always applied in the same direction, giving consistent image distortion, which is much less problematic than distortion that varies between images.

Question 3.1.4**
Ideally, magnetic field gradient strength would be directly proportional to the current in the gradient coil. In practice, eddy current effects cause the gradient strength to have characteristic delayed and smoothed responses to change. Where do the eddy currents come from, and what do they tell you about the impulse response of the gradient system?
They come from Lenz's law, where the opposing eddy currents are generated in the conducting structures of the magnet. This means that the gradient system has a characteristic, non-ideal (delta function) impulse response.

One way of mitigating eddy current effects is by trying to design gradient waveforms in a way that accounts for the anticipated eddy-current delays (known as "pre-emphasis") or by trying to design gradient pulses that elicit eddy currents which tend to cancel each other out.
Ask the students to suggest how gradient pulses could be modified to reduce the effect of eddy currents and sketch these on the white board.

Bipolar diffusion encoding gradients (i.e. those with both positive and negative lobes) are designed to produce the latter effect, in order to minimise eddy current distortion in images.
Sketch the eddy currents induced by monopolar and bipolar gradients to show why they tend to cancel out (but not perfectly) in the latter case. Use the simulator to compare monopolar and bipolar gradient images, showing the reduction in distortion and the "ring" artefact noted above.

Question 3.1.5
Why aren't bipolar gradients always used?
When bipolar gradients are used, more time is required to play out these gradients to achieve the same b value. Since these gradients are all played out after the RF excitation pulse, the echo time must be increased in order to accommodate them, leading to greater T2 decay and reduced SNR.

3.2 Multiple Fibres [~10 minutes]

Figure 5 shows a colour map of the primary diffusion direction (left) and the FA map (right) from the same coronal slice. Notice how the white matter tracts appear bright,

e.g. the corpus callosum running left-right between hemispheres appears red in the colour map and bright in the FA map. We usually observe high FA in WM tracts due to the strong dependence of the measured signal on a particular diffusion encoding direction – i.e. the signal decreases (diffusion contrast increases) as the gradient direction becomes closer to the tract orientation.

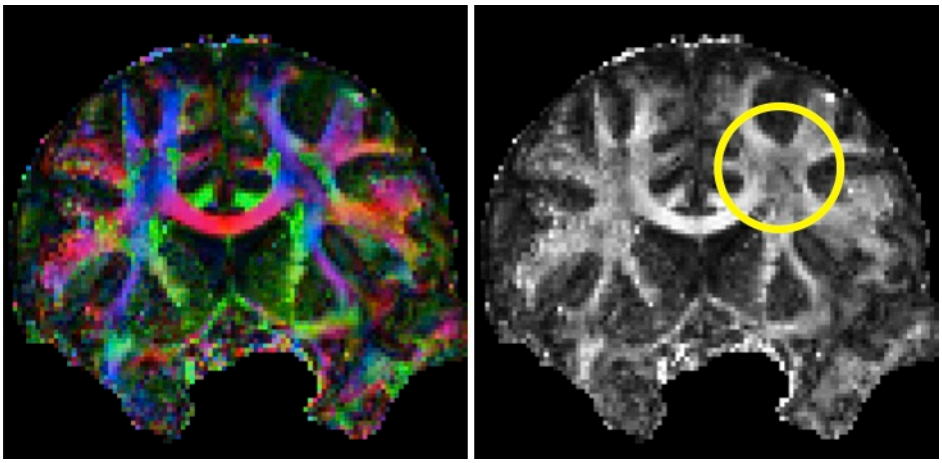

Figure 5

Question 3.2.1
The region highlighted by the yellow circle in the FA map is a white matter region, however it has low FA. Why do you think is?
Looking at the colour map, we see that WM tracts running in different directions are crossing here: projections from the corpus callosum (red), the corticospinal tract (blue) and the superior longitudinal fasciculus (green). Signal is attenuated by diffusion gradients that are parallel to any of these tracts. Hence, voxels in this region will not have a dominant diffusion direction and the diffusion appears closer to isotropic (a sphere) rather than anisotropic (an ellipsoid). As the eigenvalues are of a similar magnitude we observe low FA in these regions where there are crossing fibres.

It can be useful to think about what the tensor model assumes about how diffusion behaves within a voxel, and how this can be insufficient to capture more complex diffusion geometries, like cases with crossing fibres or “kissing” fibres.

Models other than the tensor model are used to describe the dependence of diffusion signals on measurement orientation and how this reflects the underlying internal voxel geometry, which you will learn about in the Analysis Course next term.