T2 Relaxometry:
A Comparison of Different Models and Different Cohorts

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Abstract

Myelin is an important tissue type in the brain which significantly aids cognitive functions. Therefore it is critical to have a robust and reliable method of estimating the amount of myelin in the brain, particularly during development. This paper aims to use Magnetic Resonance Imaging (MRI), a safe and non-invasive tool, as the data used to estimate myelin. The paper develops and compares a number of models and uses them to estimate different T2 relaxometry values for different tissue types. These T2 values are then used as priors to help estimate for the amount of Myelin.

1. Introduction

Magnetic Resonance Imaging (MRI) is a safe and non-invasive tool used to capture detailed images of the brain. These images can be used to provide valuable insights into different regions of the brain. However estimating myelin using MRI is still a challenge and is an active area of research (Pridham G, 2021). Myelin is the sheath around neuronal axons and it plays an important role in neurological functions, including increasing the conduction speed of neuron signals, and providing critical support for axons (mye, 2014). Development of myelin begins before birth, therefore myelin development could be hampered for extreme pre-term births (less than 25 weeks GAB - gestation at birth). This makes it critical to have a reliable, non-invasive method of estimating myelin in the brain to monitor development.

There have been different approaches to estimate myelin including, radial diffusivity (Aung WY, 2013), water fraction (Thiessen JD, 2013), and T2 relaxometry (Melbourne, 2014). This paper will be focusing on T2 relaxometry, this is the method of measuring the decay of the MRI signal through time for each voxel in the image. Each tissue type within the brain has a particular T2 relaxation time due to it's molecular makeup, this allows us to map different regions of the brain using T2. For example tissue with a high-water content, like CSF (cerebrospinal fluid), has a very slow signal decay, giving a relatively high T2. Whereas myelin is a fatty substance and it's MRI signal decays very quickly, giving a very low T2. The fast signal decay makes estimating myelin regions of the brain a challenge because multiple accurate MRI images are required in very quick succession to calculate a reasonable estimate.

The focus of this paper is estimating T2 relaxation times for different regions of the brain. We will use and compare different fitting methods; linear least squares, non-linear one-compartment, and non-linear multi-compartment models. We will then compare T2 estimates between extremely preterm individuals vs a full-term individuals using data from the EPICure study. Finally we will estimate and compare the proportions of myelin found within each cohort.

2. Methods

2.1. ***Data***

We are using data from the EPICure project, in particular MRI scans from 143 individuals aged 19 years old. For each individual there is; an MRI image with 10 different time to echos (TE) in mili seconds, segmentation mask for major regions of the brain with estimates of what proportions each region is, and information on the individual including gestation at birth (GAB).

2.2. ***Data Pre-processing***

Five of the individuals' data we discard due to either; individual being neither extremely pre-term (GAB $<$ 26w) nor full-term (GAB $\geq$ 37w), MRI scan data not able to load, or the MRI scan does not contain the full 10 time to echo (TE) images. Of the remaining 137 we later find (*Section 3.1*) 2 subjects have noisy measurements which we also discard. Therefore we have 135 subjects, 85 of these individuals have a GAB less than 26 weeks, this is our cohort of extremely pre-term individuals. The remaining 50 individuals have a GAB greater than 37 weeks, this is our full-term control cohort.

The segmentation mask for each individual represents what proportion of each region's tissue type (eg. white matter) is present in each voxel. Therefore each proportion should be between $[0, 1]$ and the total sum of all proportions in each voxel should be within $[0, 1]$. Note we aren't enforcing the sum of all proportions to be equal to one in each voxel because there could be other tissue types not classified in the voxel. Therefore we clip all proportions to be within $[0, 1]$ followed by normalising voxels when the sum of proportions is over 1 (we don't normalise voxels when the sum is within $[0, 1]$)

2.3. ***Models***

MRI applies a radio frequency and aligns protons in all tissue. Once the MRI signal stops the protons lose their alignment and decay back into their normal state. While decaying the protons emit a signal which can be measured at different TE times, producing MRI images.

Different tissue types decay at different rates due to their chemical composition. T2 is inversely proportional to the decay rate, therefore knowing T2 enables one to map different tissue types in the brain.

However, the MRI imaging is discrete so the smallest voxel will likely contain multiple different types of tissue. To combat this we use increasingly complex models to estimate T2, and use a variety of methods to determine which we recommend.

For clarity we will label any measured signal from the data at TE time t as $S(t)$, and any estimated signal at TE time t using our models as $\hat{S}(t)$.

Model 1: One Compartment - The simplest model is assuming every voxel contains only one tissue type. Where $\hat{S}(t)$ is the estimated signal intensity at time to echo t, $\hat{S}_0$ is the estimated initial signal intensity at time zero.

$$\hat{S}(t) = \hat{S}_0 e^{-t/T2} \tag{1}$$

Model 2: Two Compartment - Extending the model we now assume there are two tissue types in each voxel contributing to the total measured signal $\hat{S}(t)$ from the voxel. Each tissue type has a $T2_i$ value and v_i is the percentage of the voxel being that tissue type.

$$\hat{S}(t) = \hat{S}_0 \left(v_1 e^{-t/T2_1} + v_2 e^{-t/T2_2} \right), \qquad v_1 + v_2 = 1, \qquad v_1, v_2 \in [0, 1] \tag{2}$$

Model 3: Multi Compartment - Generalising this we assume N tissue types in the voxel.

$$\hat{S}(t) = \hat{S}_0 \sum_i^N v_i e^{-t/T2_i}, \qquad \sum_i^N v_i = 1, \qquad v_i \in [0, 1] \tag{3}$$

*2.4. **Fitting***

To estimate a $T2$ value given a voxel, we fit our models to the MRI data. The data represents the measured signal, $S(t)$, at each voxel and for each TE timing. We use a number of fitting methods to then estimate T2.

Weighted Linear Least Squares - Using the one compartment model (*Equation 1*) we can transform the problem of estimating $T2$ into a linear equation. We assume all voxel signals have identically independent noise $\epsilon \sim \mathcal{N}(0, \sigma^2)$.

Using weighted linear least squares (WLLS) we can take the log of the signal, $S(T)$, without invalidating our noise assumption. This gives us the linear equation:

$$\begin{gathered} log(A) = B = Gx \\ \begin{bmatrix} log(S(t_1)) \\ \vdots \\ log(S(t_m)) \end{bmatrix} = \begin{bmatrix} 1 & t_1 \\ \vdots & \vdots \\ 1 & t_m \end{bmatrix} \begin{bmatrix} ln(S_0) \\ -\frac{1}{T2} \end{bmatrix} \end{gathered} \tag{4}$$

We can optimize this linear model by minimizing the weighted least squares between the model and the measured signals using (*Equation 5*). We take account of the different noise standard deviation of each log measurement with the matrix W, it is a $m \times m$ square matrix with the diagonal entries equal to the elements of B squared and all other entries zero. Taking the negative inverse of the second element of x gives us T2 for the voxel. Note that this method is estimating 2 parameters, therefore at least 2 different signal measurements are required to optimise the linear model.

$$x = (G^T W G)^{-1} G^T W B, \quad W_{i,i} = B_i^2 \tag{5}$$

Nonlinear Least Squares - To find T2 values for our more complex models we use non-linear optimization methods. We minimize the square difference between the estimated signals at each TE time and the measured signal. If we let $f(T2, v, TE) \in \mathbb{R}^m$ be the two or multi compartment model (*Equation 3*) with N compartments, and $A \in \mathbb{R}^m$ be the m measured signals for the voxel, then the scalar residual function we are minimizing will be:

$$r(A, T2, v, TE) = \| A - f(T2, v, TE) \|^2 \in \mathbb{R}, \quad A, TE \in \mathbb{R}^m, \quad T2, v \in \mathbb{R}^N \tag{6}$$

To minimize the the residual we use the L-BFGS-B method, which is based on Broyden-Fletcher-Goldfarb-Shanno algorithm. It is a quasi-Newton gradient descent optimisation method. It approximates the Hessian matrix and therefore requires the residual function to be differentiable and smooth. We are using the extended version L-BFGS-B to add linear constraints to our parameters, ie. $0 \leq v_i \leq 1$.

2.5. *Confidence Intervals*

When finding the average T2 values for each tissue type of the brain we will be quantifying a 95% confidence interval for our estimate, this does not assume any underlying noise models of the data. However it does assume our original sample is representative of the underlying population - we assume throughout the paper.

Let S be the total sample of voxel MRI signals we want to estimate the average T2 value for. To implement Classical Bootstrap we uniformly sample with replacement N times from S to create B many bootstrap samples, this gives us $\{S_1, S_2, \ldots, S_B\}$. For each sample S_i we calculate the average T2, this gives us $\{T2_1, T2_2, \ldots, T2_B\}$. From this set we take the 2.5th, and 97.5th percentiles as our 95% confidence interval of T2.

Ideally N and B would be very large to ensure all bootstrap samples are representative of the underlying population, but due to computation resource and time this is not possible. We compromise by having $N = 100$, and $B = 200$ which should be large enough to give robust estimates on the distribution of T2.

3. Experiments

3.1. ***Non-monotonic Voxels and Exploring the Data***

All voxels for all tissue types should have a decaying MRI signal through time. Example nonmonotonic voxel signals can be seen in *Figure 1 Left*. Therefore nonmonotonic voxels must be an indicator of noise. This could be from the patient moving during the MRI scan, or fluid movement between voxels.

We will do this by tissue type. First we classify each voxel with a threshold of 0.9, if the segmentation provided indicates the tissue type proportion is higher than the threshold, we classify the voxel as that tissue type. We then calculate for each individual, how many voxels are monotonic for that tissue type. This gives us 137 percentages for each tissue type. We then repeat the same calculations but with varying threshold values only for gray matter, we also remove major outliers in the final experiment. This is to check if changing threshold value alters the noise in voxels.

Results in *Middle Figure 1* show there is a clear difference between the different tissue types. White Matter and Gray Matter have far fewer nonmonotonic voxels than CSF. We also see some major outliers in the data which represent some individuals having much higher noise in their MRI scans than the rest of the population, we will remove subjects 17065 and 67358 from future calculations for this reason. Changing the threshold values doesn't change the distribution of noise in the voxel signals, therefore we will use a classification of 0.9 for all future calculations when classifying tissue types.

Finally, we plot the mean of the log signals for each tissue type from subject 13620. (We use subject 13620 because they have the least nonmonotonic voxel signals in the fullterm population - CSF 3%, less than 0.5% for GM and WM). The log of the signal should be a straight line if there is only one tissue type present (*Equation 1*). We clearly see in *Figure 2* the plot is fairly straight except for a strong 'kink' in the line between the first and second TE values. This could be an indicator of a signal from myelin with with a very short relaxation time. When we are fitting T2 for non-myelin tissue types the signal corresponding to TE = 13ms will be removed to allow for a better fit.

3.2. ***Comparing Models***

Now we have explored the data and have a better understanding of the noise, we will fit some data using our different models and compare which has performed best. We only fit data from subject 13620 to reduce noise.

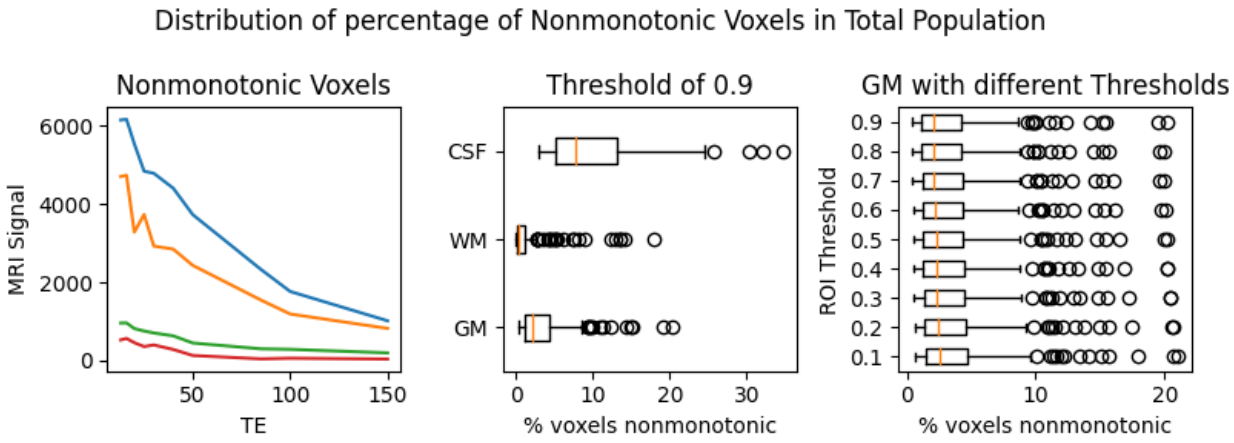

Figure 1: **Left**: Example of 4 nonmonotonic signals **Middle**: Using a tissue type threshold of 0.9 to classify each voxel, the percentage of non-monotonic voxels for each individual is calculated. The resulting distribution for each tissue type is plotted. **Right**: The middle plot is repeated for a range of classification thresholds, but only for gray matter.

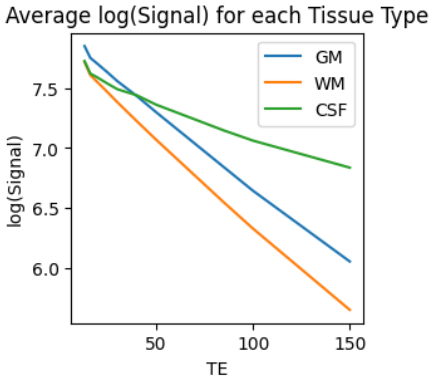

Figure 2: Mean log signal for each tissue type in subject 13620

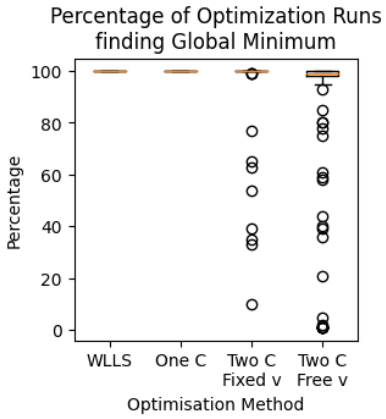

Figure 3: Fitting 200 voxels, 100 times with perturbed starting conditions

To compare models we will take a subset (200) of MRI signals from subject 13620 that are classified as 'brain'. For each fitting, initial start points are required for each parameter so we will repeat the fitting 100 times with slightly perturbed starting conditions (using Gaussian noise with standard deviation of one fifth original starting conditions).

To compare which is the best fit we will use root mean square error (RMSE) between the true signal and the estimate signal. Therefore we will have 100 RMSE values for each voxel and model. The different fitting methods we use are:

- **WLLS** - Fitting parameters $(S_0, T2)$ using model 1 and using weighted least squares *Equation 4*. No bounds or starting conditions required. However any negative results we discard and replace with zero.
- **One Compartment** - Fitting parameters $(S_0, T2)$ using Model 1 (*Equation 1*) with non-linear fitting. We use the bounds $S_0 \in (2000, 15000)$, $T2 \in (20, 2000)$. We use starting conditions of $S_0 = 5000$,

$T2 = 50$.

- **Two C + fixed v** - Fitting parameters $(S_0, T2_1, T2_1)$ using the 2 compartment model (*Equation 2*) and using non-linear fitting with the bounds $S_0 \in (2000, 15000)$, $T2_1, T2_2 \in (20, 2000)$. For each voxel we have starting conditions of $S_0 = 5000$, $T2_1 = 50$, $T2_2 = 60$, and we set v_1 to be the greatest voxel segmentation proportion given in the segmentation mask (or 0.5, whichever is greater) and $v_2 = 1 - v_1$.
- **Two C + free v** - Fitting parameters $(S_0, T2_1, T2_1, v_1)$ with the same setup as the previous model except now we are fixing v_1 to the data. Note: we only need to fit v_1, because $v_2 = 1 - v_1$. Initial conditions are same as above.

Results

Results of fitting multiple times can be seen in *Table 1*. As expected when increasing the complexity of the model the average error (RMSE) reduces. However there is additional computation cost with higher complexity.

We also see the minimum RMSE is quite different from the mean RMSE for the more complex models, indicating the optimisation needs to be run multiple times with different starting conditions to find the best fit. Assuming after fitting 100 random perturbed starting conditions the global minimum was found at least once, we can calculate the probability of finding the global minimum in each run (shown in the table). Therefore we can calculate the number of runs required to have a 95% chance of finding the global minimum at least once. For all models this comes to running the fitting once, except the most complex *Two C + free v* model which would require 8 optimization runs. In *Figure 3* it is clear that the most complex model some voxels don't find the global minimum and so would require many runs with many different starting conditions to find the optimal solution.

We also calculate the mean AIC for each model optimization run, which takes into account the complexity of the model and the performance. According to AIC the *One Compartment* method is the best model. However, we know for our goals in this paper we need to model voxels with multiple compartments, therefore going forward we will use the *Two C + fixed v* method as our primary method of calculating estimates on T2 values for each region. This is a model which fits the data better than the one compartment models, while also requiring fewer, faster optimization fittings than the *Two C + free v* method.

Fitting Model	Mean RMSE	min(RMSE)	Time per fit (s)	P(finding global min)	Mean AIC
WLLS	91.2	91.2	0.02	1.00	91.51
One Compartment	79.4	79.4	1.65	1.00	90.93
Two C + fixed v	76.8	76.1	2.49	0.94	92.21
Two C + free v	71.7	68.3	7.90	0.31	92.23

Table 1: Fitting 200 random brain voxels 100 times from subject 13620 with models. RMSE mean of all fits and minimum RMSE is shown for each model. Probability of each optimisation run finding the global minimum (assuming the global min was found in 100 runs). Mean AIC from each optimisation run

3.3. ***T2 Image Map***

Before we generate T2 estimates for each tissue type, we will first fit our model to one image slice of MRI data to check the estimates are reasonable estimates. For this we again use subject 13620, on z slice 25, using the *Two C + fixed v* fitting method. We discard the first TE=13 signal as discussed previously. As

reasoned in the previous experiment, we only need to run the fitting procedure once to have a 95% chance of finding the global minimum.

Figure 4 visualises the results of the T2 fitting. The parameters $S_0, T2_0, T2_1$ were fitted, v_0, v_1 were pre determined using the largest compartment in the segmentation for v_0 (or 0.5, whichever was greater). This gives the interpretation that $T2_0$ is the predominant T2 value for each voxel. This can be visualised in the first image. The second image is $T2_1$ which has less interpretation and has many more values above the max mapped value of 200 for readability.

When fitting it was found having a lower bound of zero found for a good fit but did not find reasonable values. Most voxels would fit a very low (around 3) $T2$ value, meaning S_0 would be much too large to compensate when fitting the signal. Therefore we have introduced a lower bound of 20 for $T2$ which improved the fitting significantly as can be seen in the figure. As expected the majority of $T2_0$ values lie between 50 and 80 which matches what we should expect for White and Gray matter. The large tail of T2 values above 100 potentially could be related to T2 values for CSF, we will investigate this further in the next experiment.

Overall the fitting looks very reasonable, with a fairly uniform RMSE across the whole brain slice.

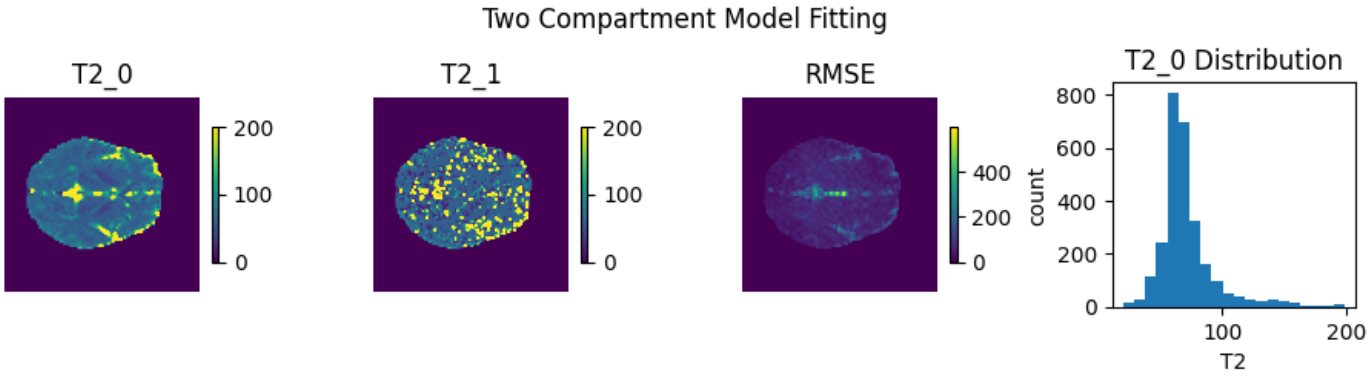

Figure 4: Fitted parameters $T2$ for 2 compartments using the Two compartment model with fixed v fitting. $T2_0$ is the primary $T2$ value in the predominant modelled compartment. The last plot shows the distribution of $T2_0$

3.4. ***Bootstrap - Mean T2 Values for each Tissue Type***

To calculate the mean T2 value for each tissue type we use the same *Two Compartment + Fixed v* fitting method described in the previous experiment, and we fit on a random sample of size 100 from the total available voxels in the fullterm control group, and the extremely preterm group. However we only sample from voxels that are monotonic, have a tissue type threshold above 0.9, and we remove the first signal from TE=13ms. As discussed before this is to reduce the noise and maximise the signal from the tissue type we are fitting to.

We do this 300 times using the classical bootstrap method (*Section 2.5*), each sample gives us a mean T2 for that tissue type. This enables us to estimate the mean T2 distribution for each tissue type with a 95% confidence interval from each cohort. The results can be seen in *Figure 5*, and *Table 2*.

Qualitatively from the figure white matter and grey matter have very similar distributions for both preterm and fullterm. In contrast CSF for each cohort has very different distributions. The Fullterm seems to have a much lower T2 mean T2 value than the preterm cohort. However the 95% confidence interval does intersect so we can not conclude they have different T2s without further work (ie. larger sample size with more bootstrap samples).

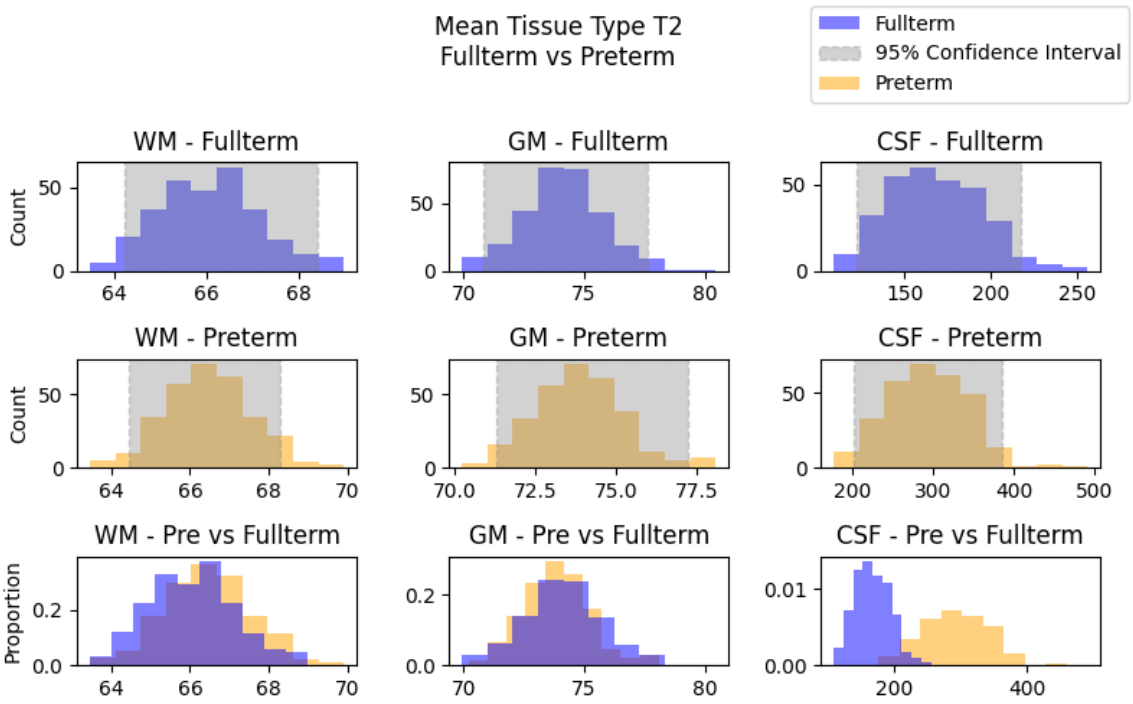

Figure 5: Fitting for T2 in control fullterm cohort and preterm cohort. 300 random bootstrap samples of size 100 were used to estimate the distribution of mean T2 values

Tissue Type	**WM**		**GM**		**CSF**	
Cohort	Mean T2	95% Interval	Mean T2	95% Interval	Mean T2	95% Interval
Fullterm	65.9	(64.0, 68.2)	74.5	(71.7, 77.4)	170.7	(124.0, 236.5)
Preterm	66.3	(64.3, 68.5)	73.9	(71.1, 76.3)	303.1	(217.0, 404.3)

Table 2: 300 Bootstrap random samples of size 100 to estimate mean T2 for each region - fitting using only monotonic voxels with classification threshold 0.9. Mean T2 is 50th percentile of distribution of mean T2

*3.5. **Bootstrap - Myelin Estimation***

Myelin is predominantly present in white matter and in grey matter (Stadelmann et al. (2019)). Therefore we will only be looking at WM and GM to estimate myelin. We can use the previous experiments results of the mean T2 to provide priors in fitting, and then leave the T2 value free for myelin, along with the compartment proportions. We will use the average T2 value between the two cohorts because they are so similar.

Our method to estimate myelin will be using a 4 compartment model (*Section 2.3*), each compartment being WM, GM, Myelin and Other respectively. Initially we first fit the data using weighted linear least squares (WLLS) (*Section 2.4*) to estimate S_0. Then we fit again using the 4 compartment model with the prior S_0 estimated from WLLS, and $T2_0$, $T2_1$ using the the T2 values estimated in the previous section for WM and GM tissue types.

We will only fit on voxels that are 90% white matter and gray matter. This is to minimise the number of significant tissue types in the voxel. The hope is the remaining T2 signal we are fitting will be predominantly myelin. Therefore we will include the constraint that the ratio of white matter to grey matter will remain fixed according to the ratio in the segmentation given.

Due to myelin having such a short decay time (small T2) we will include the signal from TE=13 in our fitting data. I'm expecting the 'noise' we saw previously from this TE time is actually the myelin signal. $T2_3$ represents the T2 value for Myelin in the 3rd compartment, $T2_4$ is the T2 value for the fourth compartment which doesn't have any interpretation. To ensure the 3rd compartment represents Myelin we will bound $T2_3$ between (5,35), and $T2_4$ is bounded between (40,2000). This ensures the 4th compartment can not represent Myelin.

Due to having a fourth compartment we add the following constraints to the model:

- $z = v_3 + v_4$
- $r = v_3/(v_3 + v_4)$
- $c = v_1/(v_1 + v_2)$

z and r are dummy variables that are being fitted, from z and r we can calculate v_3 and v_4. c is fixed variable calculated from the segmentation mask. It represents the ratio of WM and GM which remains constant, however the total amount of WM and GM can change depending on z and r.

To summarise. We are Fitting only on white and gray matter voxels (combined threshold 0.9), we first fit with WLLS to get a prior for S_0. We use T2 priors for White and Grey matter for $T2_1, T2_2$. A constraint of compartment ratios between white and grey matter will be fixed. The free fitting parameters are; $T2_3, T2_4, z$, and r, where r and z are defined above. All other parameters are either fixed or calculated from the fitted parameters. We then repeat this procedure 200 times to implement Classical Bootstrap with each bootstrap sample having a size of 100.

Myelin Proportion Metric

After completing the fitting if $T2_3$ is between (5,35), then that voxel is classified as having a v_3 proportion of myelin. There were many voxels where the T2 fitting hadn't changed from the initial conditions ($T2_3 = 35$), in this case the voxel is not classified as myelin. To get the final metric of Myelin proportion, we sum the total amount of myelin compartment proportions and divide by the total number of voxels we fitted on.

Results

Results are shown in *Figure 6* and *Table 3*. There is no evidence there is a different amount of myelin within each cohort. The distributions of Myelin proportions look very similar and with similar confidence intervals.

The results of this do not look correct because there a considerable amount of myelin is in white matter, indicating the myelin percentages should be much higher. Therefore this fitting method to estimate myelin proportions is not effective.

Cohort	Myelin Proportion	Confidence Interval
Fullterm	0.0012	(0.000, 0.120)
Preterm	0.0017	(0.000, 0.138)

Table 3: 200 Bootstrap random samples of size 100 to estimate the myelin proportion of tissue type in voxels containing at least 90% grey or white matter. Fitting only monotonic voxels from either cohort

4. Discussion

To summarise, the first experiment was exploring the data to understand any noise or issues by analysing the non-monotonic voxels in each individual. Some individuals were outliers and therefore removed from

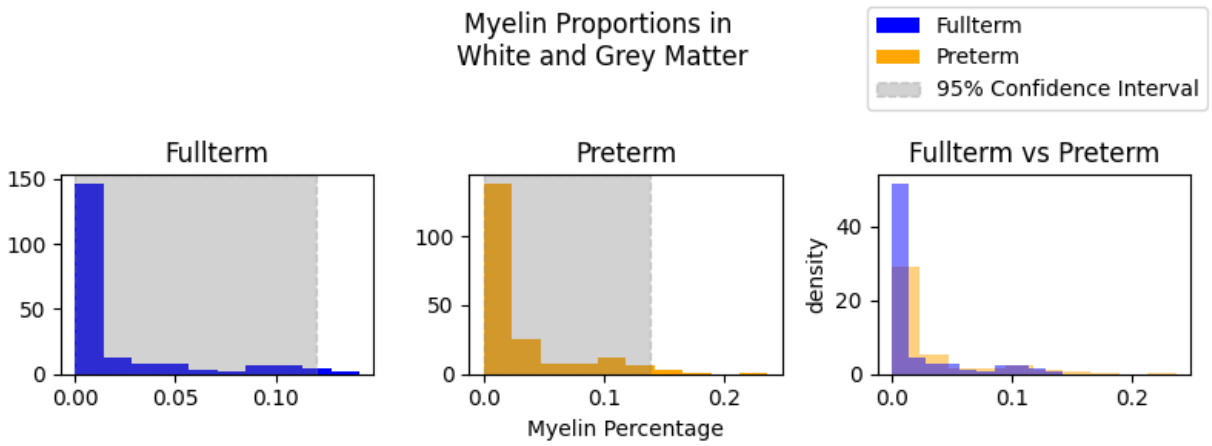

Figure 6: Estimating average Myelin tissue proportion in voxels that contain at least 90% white or grey matter. Calculated using Bootstrap 200 times on random samples of size 100

the rest of the study. The tissue type classification threshold was found to not have much affect on noise, and therefore a threshold was used of 0.9 was used for the remaining experiments. It was also observed the first MRI signal at TE=13ms had evidence of being either noisy or being predominantly from a very small T2 value, therefore most analysis was completed without this first signal.

The second experiment compared our models and fitting methods. As complexity increased so did the performance of fit. But with complexity also came computational cost and interpret-ability. Therefore the two compartment model with fixed v was used for most of the paper.

In the third experiment the fitting of T2 was visualised. Overall the fitting was as expected. The next step was to fit on all individuals' data using Classical Bootstrap which we did in experiment 4. The mean T2, with a 95% confidence interval, for each tissue type was calculated. This gave promising and expected results. When comparing the fullterm and very preterm cohorts there was a considerable difference noted, although more investigation is required to conclude anything from this.

In the final experiment all previous work was combined to estimate the myelin proportions within grey and white matter tissue. Bootstrap was applied again but the results were not promising because it looks like this fitting method is not effective in estimating Myelin.

Further Work

There are a number of avenues to explore with this work. Completing p-value tests on the mean T2 distributions would be an effective way to conclude if there is a statistical difference between the cohorts. Only WM, GM and CSF tissue types were considered, but there are plenty of other tissue types and segmentation masks available for this dataset. Estimating Myeline proportions, this paper tried one method but there are many different approaches that could be tried, we encourage different methods to be applied.

5. Conclusion

Having a robust and reproducible method to estimate Myelin from MRI scans is important to be able to monitor the development of myelin in the brain. Even though this paper did not develop a robust method to do this, I hope that the methods of estimating the mean T2 values for major tissue types in the brain will be useful for future work.

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