Brain regions analysis using T2 relaxometry on extremely preterm subjects

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T2 relaxometry has become a very reliable technique in the quest to unveil major health issues by means of Magnetic Resonance Imaging (MRI). Important discoveries on the strong correlations between physical measurements of tissue types and the T2 exponential decay have achieved wide acknowledgment among medical community on its reliability as additional evidence for diagnosis of different pathologies, with the additional advantage to the patients of a less invasive procedure. In this work, I analyzed a cohort of 143 subjects with information about their Gestational Birth Ages (GBA) making it possible split it into pre-term and full-term groups. Using their MRI T2-weighted images and their brain region labeling it is possible to get specific values for white matter (WM) intensities and 12 different regions of the brain. These values are then fitted into a T2 exponential decay multi compartment model looking after each of its parameters as they physically represent the water volume fraction (WVF) present on different tissues of the brain. Finally, this information is analyzed statistically in order to find out significant similarities between different tissues and mainly how correlated are the two different groups existing in the cohort. At the end of this study states that the two groups are not presenting major quantitative differences and therefore this means that an extremely preterm (EP) condition does not inhibit the proper functions of different brain regions.

1. Introduction

Preterm babies are at the same time low birth weight, more likely to die and might develop long-term neurological and developmental disorders than those born full term. The occurrence of major problems like learning difficulties, cerebral palsy or neurological disorders in general, has been shown to be a constant between EP subjects in the long-term and it has also been associated to the Periventricular leukomalacia which is one of the most frequent brain injuries in preterm infants [1]. Several statistics have shown that this kind of cases are increasing as many of preterm births are being reported year after year in developed countries. Specifically, in Europe the statistics point out that the rate of preterm birth is rising steadily, estimates are around figures between 5% and 10% for preterm births, a special case is for EP babies where the reported death rate is very high at above one third of fetal deaths and 40% of neonatal deaths [2]. Taking into account these numbers it is clear that a better understanding on the possible causes behind behavioral and functional outcomes is a very important task to be attended. Nowadays, there is no formal technology or treatments around this condition, but then quantitative information extracted by T2 relaxometry might be combined with some sort of prognosis or therapeutic intervention in order to lower down the risk of the aforementioned future problems for EP subjects.

Myelin is the multilayered membrane of insulation wrapped around axons by oligodendrocytes and is essential for nervous system function as it increases conduction speed by at least 50 times [3]. Preferential myelination or insulation of active brain cells is produced by electrical impulses coming from neurons being triggered by environmental stimuli. The process of insulation starts to form on axons in the very late stages of fetus development, but the process continues at earlier stages of childhood, adolescence and very likely into early adulthood. There are several motor axons specialized in specific functions that might not be enabled because of the myelination process starts at specific stages of brain development. For example, infants cannot hold their heads or walk, and the frontal lobes of the brain, responsible for judgement and more complex reasoning are not fully myelinated until the early twenties [4].

It was previously described how the myelin is formed and how it works at biological level. At chemical level the myelin is composed by big molecules like lipids and proteins and water being the smaller one. Then, at atomic level all the atoms from the molecules have protons whose behavior and physical properties are fundamental for the theory behind Magnetic Resonance Imaging (MRI) theory. Based on differences of these properties a Magnetic Resonance (MR) scanner is able to capture different zones or tissues in the Central Nervous System (CNS). Myelin decay rate is roughly 50 microseconds [5], this ultra-short decay rate makes this signal very difficult to capture only using highly specialized techniques which are not even designed to detect myelin tissue. Two factors are beneficial when using MRI in order to estimate myelin water fraction. First, it is well-known the T2 decay times for water interacting with different brain matter and as they are above 10ms they are accessible by MRI and second, they are adequate for showing soft tissue structure at different perspectives at different levels of granularity.

T2 relaxometry is an MRI technique that is able to look into different water environments where the signal from mobile protons is categorized into different water storages based on their T2 relaxation time. One of these usages is the estimation of the Myelin Water Fraction (MWF) within the brain. By taking images at different echo-times it is possible to form a sequence which shows an exponential decay curve, representing how the signal intensity gets low through time. Using these facts is possible to propose a mathematical model based on the physical behavior seen then it is possible to fit the parameters corresponding to the loss of energy for each voxel on the sequence of images. The expected amount of water present in myelin tissue is small compared to other tissues and so the T2 time must also be very short. Consequently, the T2 value of a voxel is characterizing the tissue composition, so it makes possible to determine the volume of White/Grey matter, Cerebrospinal fluid (CSF) and even the MWF.

[6] previously reported the comparison between T2 relaxometry values on WM based on the inspection of T2 weighted MR images, in order to assess the possible linkage between the quantitative T2 relaxometry values and the more qualitative apparent diffusion coefficient (ADC). Their conclusion was the discovery of differences between preterm and full-term babies T2 values and also those values were correlated with traits in development scores at two years of age for preterm babies. However, these values are not reliable as it is acknowledged that a specific brain tissue type may contain different kinds of tissues at distinct T2 values. For these reasons, it makes more sense to approach this solution as a multi-compartment and multi-exponential model, analyzed by [7], aimed to have a better intuition of how the brain is shaped at voxel, tissue and region levels. It has also been estimated and described by [7] the typical T2 value ranges expected for different tissues. The important ones for this work are the Myelin Water Fraction, which is the water contained between the layers of the myelin sheath, with values between 10 and 50 ms; next it is the White Matter (WM)/Grey Matter (GM) fraction with values around 70-90 ms and last is the cerebrospinal fluid component with observed values above 2 s.

[8] researched on finding out the possible causes and correlations in WM myelin density estimated quantitatively between two groups of subjects, born preterm and full-term. They also used Magnetic resonance (MR) T2 relaxometry as a way to look into different brain zones in order to estimate the values of specific regions. With these estimations at hand, it was possible to compare statistically how significantly correlated are these two groups and also looking at additional subgroups configurations, specifically male and female, as they could give additional insights on the proposed question. At the end, no significant differences were found between subjects at study.

In this work, I try to investigate the possible relationships of different estimated quantitative measures as the MWF and GM/WM fraction with respect to different T1 labeled regions of the brain. By analyzing a cohort of 143 subjects, separated into two study groups, choosing 20 of them as control subjects born at full term and other 20 selected EP subjects. It is also analyzed the noise within different subjects before proceeding with the design of a suitable model. For this study, I am focusing on single, two and three compartment models. A previous work [8] related to a similar dataset was constrained to look after differences between pre-term and full-term subjects' brains features at four different tissue types, WM, GM, CSF and intracranial water, the difference is I focus on finding significant differences at twelve different regions given by parcellation labels.

2. Materials and Methods

2.1 Dataset description

Data was released in two different cohorts, imaged at 3 Teslas. The first one consisting of 6 adult subjects cohort was released for analysis. MRI images were taken with a Siemens Trio MR equipment with separate definition of echo times for each subject. A second cohort of 143 subjects were imaged using a Philips Achieva MR, with the following echo-times {13, 16, 20, 25, 30, 40, 50, 85, 100, 150} ms.

Both datasets are delivered as NIFTY format images, together with region of interest (ROI) mask, parcellation and segmentation from regions of the brain. For the second dataset, there are also general characteristics of the subjects under analysis like Gender and Gestational Age at Birth (GAB). In addition, each subject is accompanied of more specific features like 'Height', 'Weight' and 'Full Scale Intelligent Quotient' (FSIQ). Furthermore, 4 out of 143 subjects are not considered for the initial analysis as they have different echo time images possibly because of repeated data among the cohort. Some of the subgroups observed are 29 full-term, 85 EP and 25 preterm subjects. Dividing the dataset based on gender, it is observed 81 females and 58 males, then splitting them based on term time there are 49 and 36 EP born females and males respectively, while the control groups are formed as 16 females and 13 males full term born. The segmentation maps corresponding to different tissues within the brain and label parcellation are all coming from T1-weighted data which was masked, segmented and labeled according to the unified Geodesic Information Flow Strategy [9].

2.2 Data Analysis

All the tasks carried out throughout this work were done using Matlab R2017b (Mathworks, Inc., MA). The data is regrouped in two different groups whose conditions full-term or extremely preterm status. Then, group-wise comparisons are carried out over aforementioned subgroups using their volume fraction parameter map on the parcel labels using analysis of variance (ANOVA) tests and setting a significance p-value of less than 0.05. Parameter values within parcel labels are concatenated across subjects to form the final dataset which is going to be tested.

As discussed previously, the expected shape of the signal intensities in MRI imaging is exponential. More specifically this signal has been observed to behave as monotonic and mono-exponential. Additionally, as mentioned in [7] different tissue types within brain regions decay at different rates. Based on this fact, it is possible to take T1 weighted images representing segments of the brain then it is feasible to look at the expected average behavior of each segment and conclude that the images are overall in a consistent average state free of noise in order to continue with the analysis as shown in **Fig 1** for the first 6 subjects dataset and **Fig 2** for the 139 one. In addition to this, a noise analysis postprocessing is done in order to determine which cases are really representing good fitting together with the lowest amount of noise.

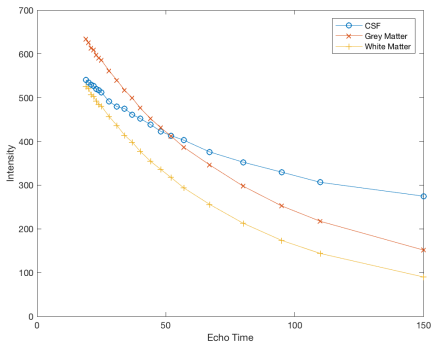


***Figure 1**: 6-subject dataset curves per segment*

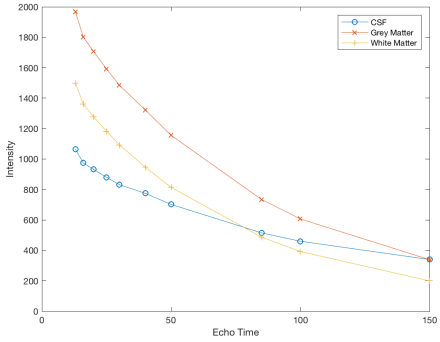


***Figure 2**: 139-subject dataset exponential decay*

2.3 Noise Analysis

In engineering problems dealing with signal processing is important to determine if any external factor could affect the data acquisition, for this project the MRI imaging process. There are some environmental factors affecting the signal acquired by the MR scanner, amongst them are detune of the device, random body noise or thermal fluctuations, motion effects, magnetic fields due to metallic objects and even body implants.

The first insight about the behavior of signals in the dataset is reflected in **Fig. 1** and **Fig. 2**. It can be observed that the average trend on each of the segments is following the expected exponential decay curve. In order to confirm this fact at a lower level, a deeper analysis on different voxels is done. The first thing to be taken into account is that there is not any prior knowledge of noise for each of the signals or the images in general. For these reasons an algorithm proposed by [10] is used to estimate the variance of the noise, it is thought for signals of multiple dimensions, but for this project it is used the one-dimensional case per-voxel. Once the variances are calculated, their exponential probability distribution is computed, which because of its nature is analyzed using power-law fitting at 5% and 1% of the tail, in this way it allows to know more about how the noisy signals are distributed whether they are mostly packed in the tail then the coefficient of determination R^2 calculated in the linear regression will be high otherwise they will be low.

2.4 T2 Relaxometry models

By means of mathematical models representing the exponential decay signal of T2 in each voxel, it is possible to relate the parameter values of the model to the physical features present in the brain. There have been different proposals about mathematical models presented in [11] and [12]. In the former, they try to get more granular representation of different features inside the brain, for the latter they do a review about the mono-exponential model by including an offset as a fitting parameter.

The simplest model is the single compartment model, which is an exponential function of the T2 relaxation time along different echo-times and weighted by the initial signal S_0, expressed in the following way:

$$S(S_0, T2) = S_0 e^{-TE/T2} \quad (1)$$

The parameters S0 and T2 of this model can be estimated by Linear Least Squares (LLS) algorithm once the single compartment model has been linearized. Additionally, parameter can be estimated by Non-Negative Least Squares (NNLS) or Non-Linear estimation.

As the single compartment model has limited inference capacity, then an improved model is analyzed with two compartments:

$$S(S_0, T2_1, T2_2 m_1, m_2) = S_0\left(m_1 e^{-TE/T2_1} + m_2 e^{-TE/T2_2}\right) \quad (2)$$

At the end, it is possible to generalize the most robust model whose parameters be precise enough to represent different facts in the physical world. In this way, the compartmentation is generalized as follows:

$$S(v_i, T2_i) = S_0 \sum_i v_i e^{-t/T2_i} \quad where\ v_i \geq 0\ and \sum_i v_i = 1 \quad (3)$$

All these models were tested along this work and the results on their evaluation by means of AIC and BIC are presented later. Additionally, to this, at high level it is clear that the more parameters a model have the more able to describe what is happening and, in specific, how each voxel is composed by different tissues. Based on this last statement is clear that the single compartment model despite being simple does not describe something biologically meaningful in contrast the three-compartment one is the selection for this work because is able to describe the MWF and WM/GM fraction. The way to set this assumption within the model is letting the respective T2s to previously referred values by [8] of 20ms for MWF, 80ms for GM/WM and 2s for CSF, in this way is expected that v^{20ms} will be the MWF, v^{80ms} representing the tissue of GM/WM and finally v^{2s} or the rest of the volume per voxel being the CSF water. Finally, it is seen how using the different segmentations labels combined with prior information on the percentage of MWF expected according to [7], is helping on getting a better starting point before doing the proper estimation of parameters. In this way, the corresponding MWF is initialized at 25% of

WM and 3% of GM while the tissue fraction takes complementary percentages below 100% and free water component is just the difference between the sum of the previous compartments.

2.5 Fitting techniques

Non-linear least squares optimization is the approach mostly used in recent years as it is well-posed to solve this kind of multi-dimensional problems. Additionally, is the obvious choice for almost any kind of real world application either in science or engineering. The trade-off is that it is very expensive computationally as it keeps using high quantities of memory, processor cycles and storage capacity especially for nowadays Big Data problems. Despite the aforementioned reasons, this is the fitting technique utilized across this work. The mathematics around this are related to the gradient descent algorithm which formulates that at each step a set of parameters x will be updated according to this rule:

$$x_{t+1} = x_t + \gamma \nabla f(x) \quad (4)$$

Then, in case of the single component function, $f(x)$ will be as eq. (1), and the parameters for S0 and T2 will be expressed in the following way:

$$x_t = \begin{bmatrix} S_0^t \\ T2^t \end{bmatrix} \quad (5)$$

Then, for the case of single compartment model, plugging in (1) and (5) in (4), the resulting update rule will be similar to:

$$\begin{bmatrix} S_0^{t+1} \\ T2^{t+1} \end{bmatrix} = \begin{bmatrix} S_0^t \\ T2^t \end{bmatrix} + \gamma \nabla \left(S_0 e^{-TE/T2} \right) \quad (6)$$

Eq. (6) can be solved by finding the gradient of each different model, but the numerical approximation has been found very useful and reliable, so at the end it is preferred to use them as they also lead to fulfill more experiments towards a more precise and accurate response. Finally, the procedure followed across this work for finding the optimal set of parameters for eq. (1), (2) and (3) begins by running the Linear Least Squares algorithm and finding parameter values. Then, these values will be used as starting points and an iterative fitting is executed by using the first order algorithm 'Levenberg-Marquardt'. This will run until convergence is reached or until the set tolerance of $1e^{-6}$ is achieved.

2.6 Markov-Chain Monte Carlo estimation

The data for each subject in a group is taken and fed into a Monte Carlo Markov-Chain (MCMC) algorithm. It is being considered only the white matter segment where masks are not zero within the ROI then voxel intensities are taken for each subject creating a vector for each study group and then estimate parameter value ranges for MWF and Tissue. Roughly 800000 voxels are taken in total per group. The priors selected for parameters are, Gaussian for intensities and Uniform for MWF and Tissue Fraction. The number of MCMC samples used are 100000 with burn-in parameter of 50000 and thinning of 5000.

3. Results

3.1 Noise estimation results

Assuming that the worst fitting may contain the noisiest signals, it is taken subject with id 88 who has a sum of square difference (SSD) of 1.5873e+06 and it is contrasted with the best fitting coming from subject 20 with SSD of 1.0597e+04. Then the highest, middle and lowest noisy voxel signal from those subjects are shown in **Fig. 3** and **Fig 4** respectively, it can be seen clearly how the SSD value is correlated to noisy signals.

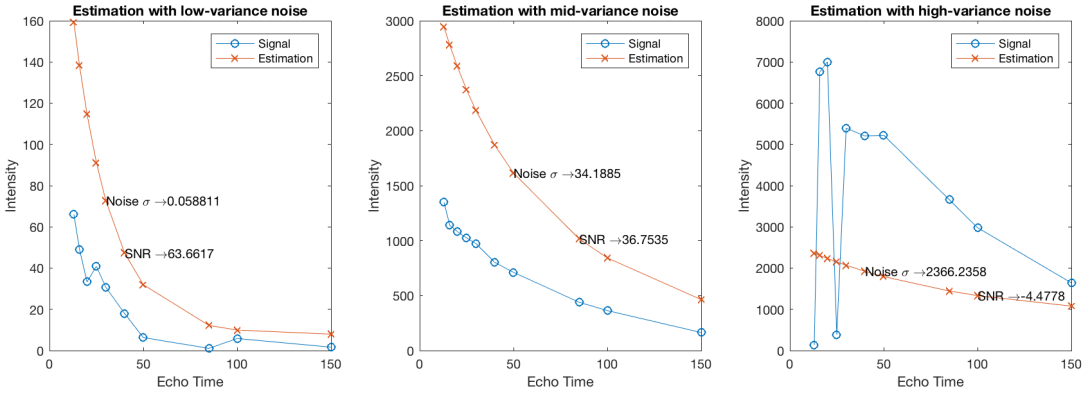


***Figure 3**: Subject 88 noise analysis on sampled voxels*

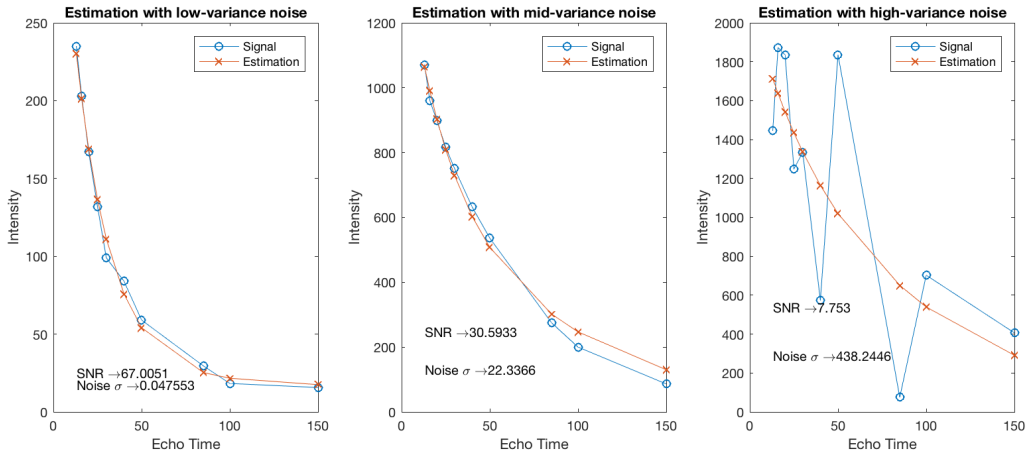


***Figure 4**: Subject 20 sampled signals shown much less noise*

In addition, to verify that the estimated noise standard deviation is representative of what is happening to the signal, it is also important to find out how these values are behaving for each subject. Once having the distribution of standard deviations for each subject, it is done a linear regression fitting to look at how the noisy signals are distributed across the tail. In **Table 2**, there is a summary of subjects with calculated R^2 for 5% and 1% elements of the tail, it can be seen how the coefficient grows despite less elements are used, verifying the exponential nature of the distribution and then **Fig. 5** shows the tail fitting for subject 118. Furthermore, what is interpretable from these results is that the estimation of parameters is being affected for noisy signals and also inferred by the figures above, where the noisier the signals the higher the calculated SSD. Additionally, it is clear that given the power law fitting results the elements in the tail are not evenly distributed, in one hand the noisy elements in the tail may be beyond the 5% and on the other it is just enough the 1% constraint. For example, subject 137 has a very low coefficient of determination, 0.34 at 1% and 0.55 at 55%, meaning that few noisy signals are present in its tail. In contrast, subject 116 shows higher figures meaning more noisy signals are concentrated in the tail. **Fig 6** and **7** show each of these subjects respectively. Finally, combining this data together it is possible to get a heuristic for choosing the best cases based on their SSD mainly but also considering their tail distribution not being higher than 0.85.

***Table 1**: Results of fitting compared to SSD*

Subject Id	R^2 at 5%	R^2 at 1%	SSD
20	0.5008	0.6889	1.0597e4
1	0.5994	0.7909	1.1954e4
137	0.3941	0.5586	1.2495e4
.			
.			
116	0.7772	0.9395	7.9785e5
57	0.4996	0.7001	1.1048e6
83	0.2803	0.5436	1.1383e6
103	0.6064	0.8216	1.5873e6

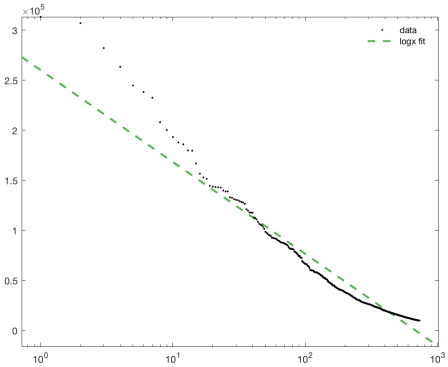


***Figure 5**: Subject 118 fitting at 1% elements of tail. R^2 0.9410*

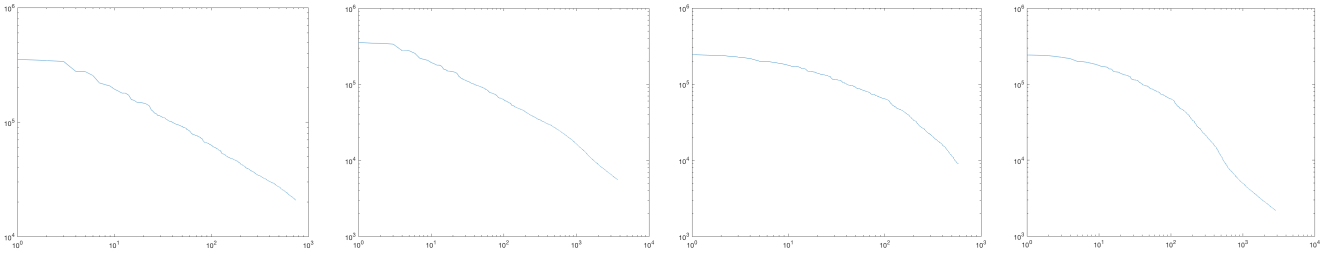


***Figure 6**: Subject 116 tail showing more noisy elements in its tail*

***Figure 7**: Subject 137 with less noisy signal at the end of its tail*

3.2 Model Evaluation

Single Compartment Model

This model was first tested using well-known optimization techniques, as a benchmark to compare how they lead to sounding results and compare the expected waiting time for further non-linear techniques. This model was tested on several slices of the images and clearly the T2 and S0 are affected by the selection as they are representing different areas of the brain. For example, slice 10 versus 26, the latter has more brain tissue while the former only has some brain parts interacting with the MR scanner. This is mainly due to the acquisition settings of the device.

The LLS algorithm outperformed the other two, beyond the ranks shown in **Table 2**, it also has inherent advantages like optimal utilization of computational resources leading to a reasonable processing time and it uses a very simple algorithm to implement. Next, the NNLS is showing fair execution times but the calculated SSD is not the best amongst the ranked techniques. Finally, as the nature of the model to fit is non-linear is expected to have the best fitting but as it can be seen in Table 2, this technique is not showing the desired results compared to LLS. In addition, it is the most expensive computationally.

Two Compartment Model

Two different settings were considered when testing these models. First, it is proposed 5 different parameters, S_0, $T2_1$, $T2_2$, v_1 and v_2. In this case, the model is said to have *free* parameters in specific for the two T2s. In addition, the *fixed* T2s model is built considering T2 times for v_1 at 20 ms and for v_2 at 200 ms. The *free* setting was good delivering lower SSD but with higher computational costs in time and processing time. In addition to the aforementioned facts, the results for the two T2s lack of interpretability when $T2_1$ values lie around a few milliseconds while $T2_2$ are estimated in hundreds or thousands.

Three Compartment Model

Similarly, for the *free* model, the set of parameters to be estimated are S_0, $T2_1$, $T2_2$, $T2_3$, v_1 and v_2. In this occasion, v_3 is just the difference between v_1 and v_2, in order to sum up 1, so it is not regarded as a free parameter. For the *fixed* model there are only 3 estimated parameters which are S_0, v_1 and v_2. For the *free* parameters model again, the values are in different ranges for different subjects in the small dataset, so inference power is affected as there is no a clear pattern on how these values are distributed across brain regions. On the other hand, having fewer parameters despite lowering accuracy (higher SSD) it is giving the additional advantages of lower computational cost and inference power. Finally, it is observed a slightly better performance of the model when considering priors as discussed in the methods section.

***Table 2**: Model Evaluation for the first dataset*

Model	*Optimization Algorithm*	*AIC*	*BIC*	*Rank*
Single Compartment	Linear Least Squares (LLS)	1.6131e+07	2.0143e+07	1
Single Compartment	Non-negative Least Squares (NNLS)	2.4580e+07	2.8592e+07	8
Single Compartment	Non-Linear fitting	1.8095e+07	2.2107e+07	2
Two Compartment – Free T2s	Non-Linear fitting	1.6201e+07	2.3864e+07	5
Two Compartment – Fixed T2s	Non-Linear fitting	1.9275e+07	2.4555e+07	7
Three Compartment – Free T2s	Non-Linear fitting	1.6763e+07	2.5516e+07	6
Three Compartment – Fixed T2s	Non-Linear fitting	1.6183e+07	2.2683e+07	4
Three Compartment – Considering Priors	Non-Linear fitting	1.6182e+07	2.2682e+07	3

3.3 Parameter precision of Tissue and Myelin Water Fraction

Considering the big data to be analyzed consisting of 2 groups of 20 people each totaling a dataset of roughly 800000 voxels per group this process took around 3 hours as a result is clear how expensive it is computationally. For term subjects the MWF confidence interval lie between 0.1918 and 0.2858 with mean value of 0.2385, while for tissue the values range is 0.5829 and 8591 with mean at 0.7210. Results for EP subjects under study show a confidence interval of MWF in the range of 0.1905 and 0.2857 with a mean value in 0.2381, in contrast for tissue fraction the range lies between 0.5520 and 0.8375 with mean around 0.714. At first sight it can be seen that no significance arise between groups as mean values and confidence intervals are very similar. In **Fig. 8** can be observed the posteriors estimated for these groups.

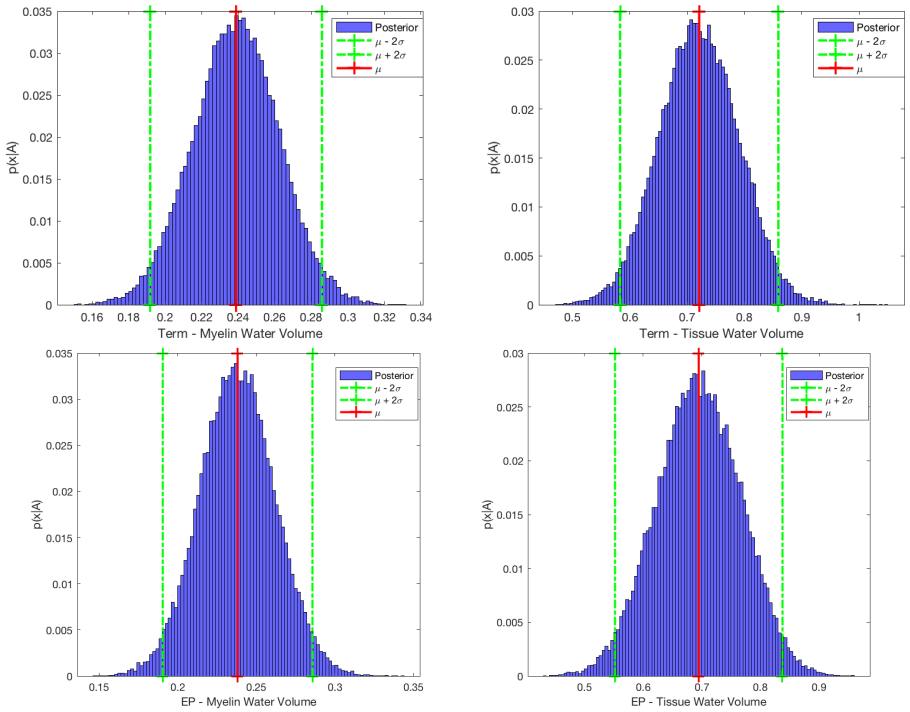
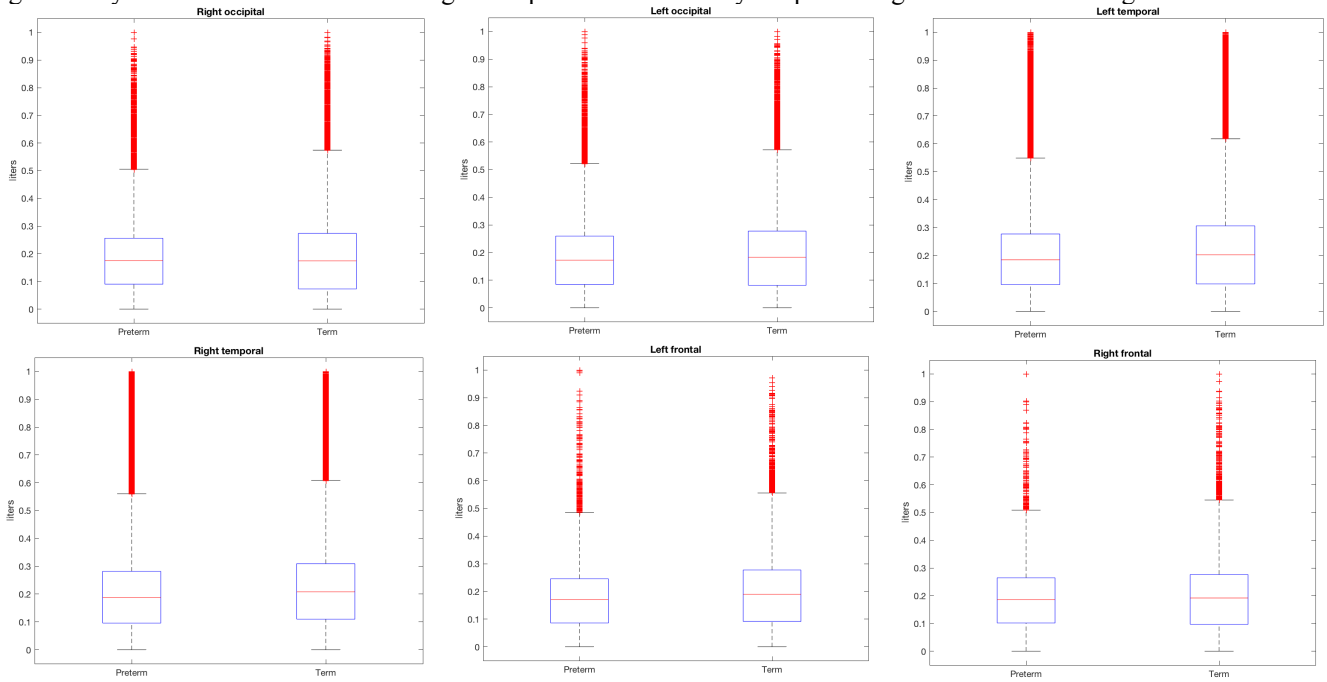


***Figure 8**: MCMC volume fraction estimation for Full term and Extremely preterm subjects.*

3.4 Myelin Water Fraction comparison on different brain regions

It was taken into account the parcellation of the brain in the following 12 parts, determined by visual inspection of the labels, Right and Left Occipital, Left and Right Temporal, Left and Right frontal, Left and Right pre-frontal lobe, Left and Right parietal, finally Left and Right limbic lobes. MWF estimation was taken for each of these regions and due to the number of voxels within the region is different for each subject, it is necessary to analyze the unbalanced sets using ANOVA. Taking the estimation values for each region and labeling according to the study group as shown in **Fig. 9**, none of the regions resulted significantly different from other according to the plots and verified by the p-values greater than the 0.5 significance level.



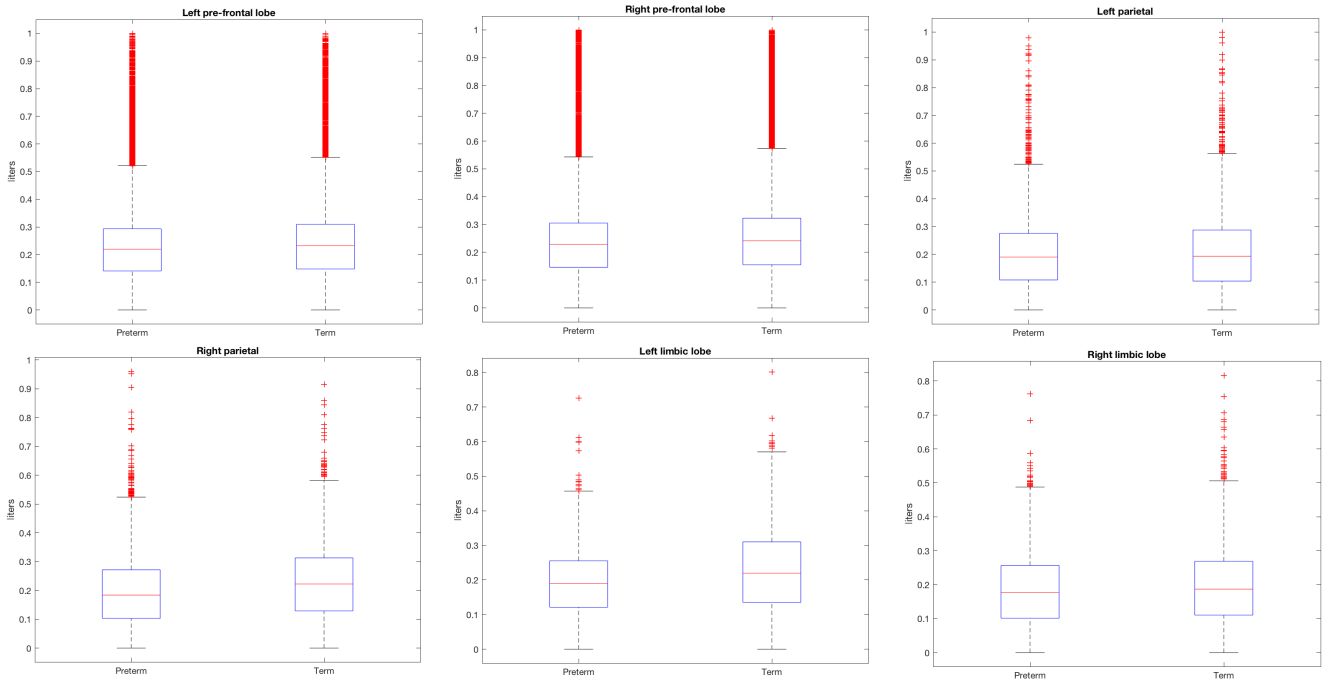
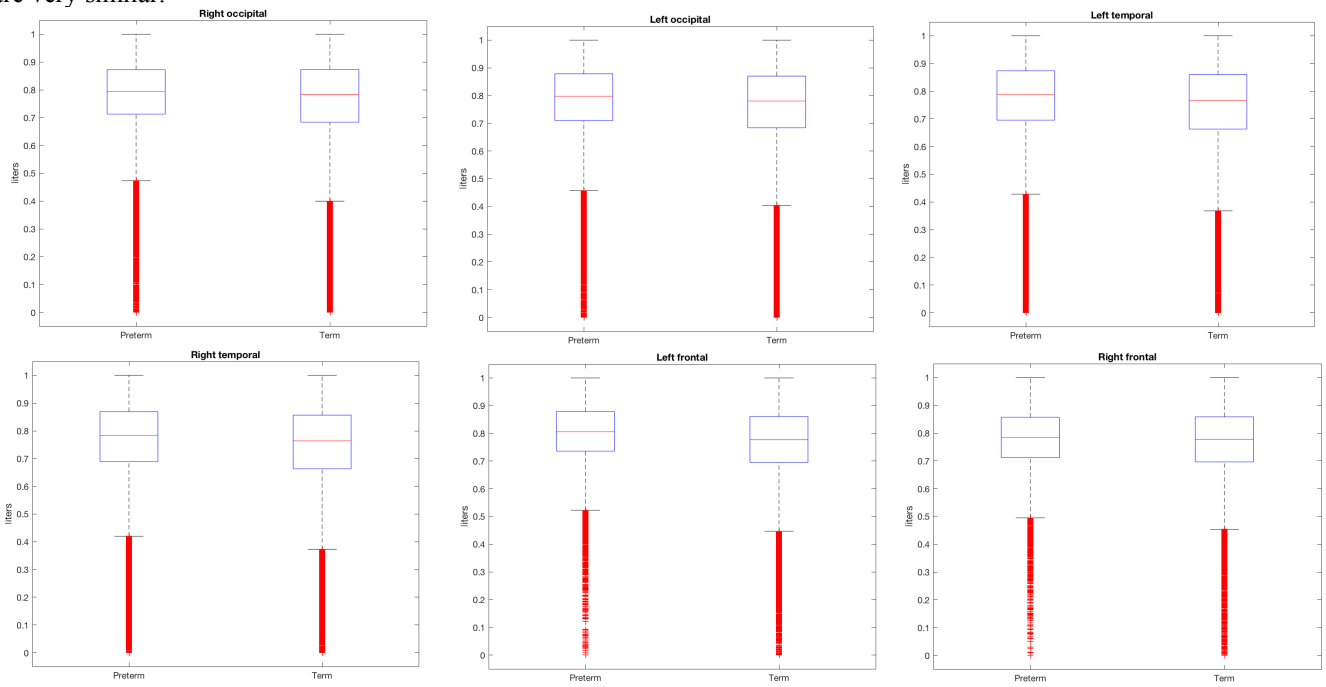


***Figure 9**: Myelin Water fraction comparison per region of the brain*

3.5 Tissue density comparison results

Similarly, to the procedure for MWF, the values for tissue volume fraction is analyzed taken voxels per each parcellation labelling after splitting the subjects under study on their corresponding group. Again, results are very close to what happened with MWF as there are not significant differences, verified visually in **Fig. 10**, and also by big p-values out of the established significant value, leading to reject the null hypothesis that groups have the same mean therefore cases and controls are very similar.



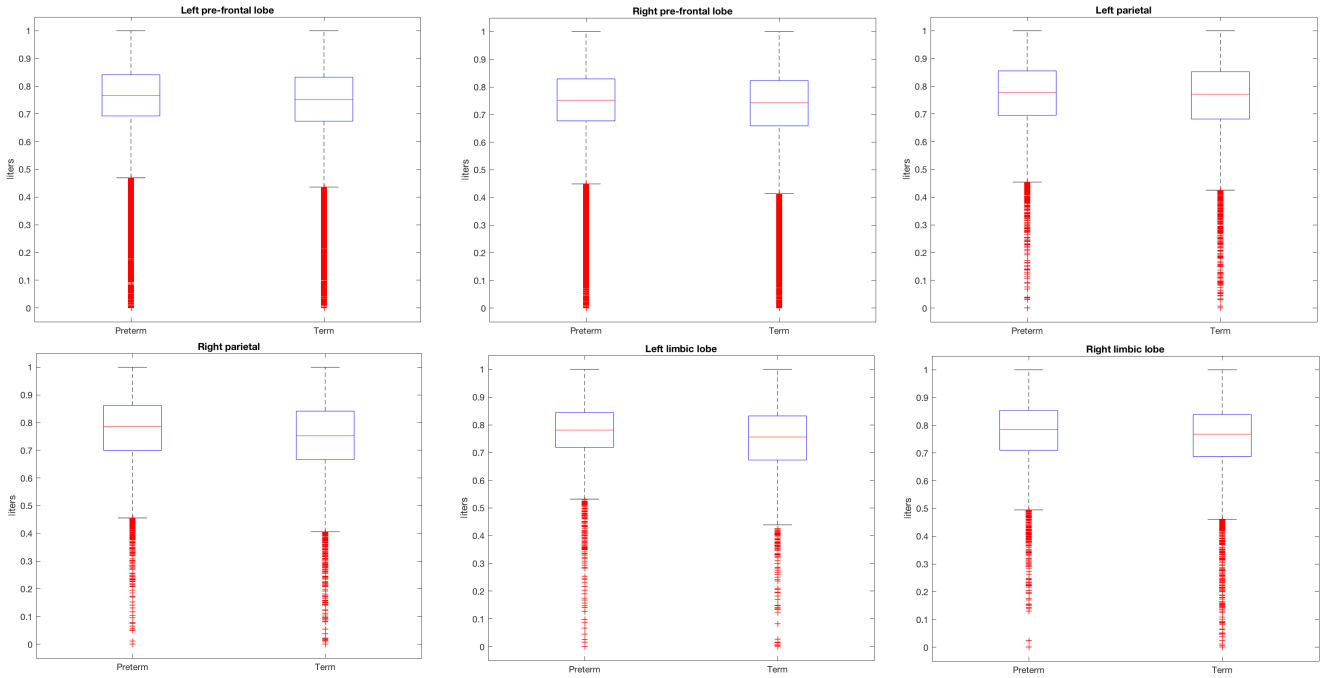


***Figure 10**: Tissue density comparison results for tissue fraction*

4. Discussion

These last numbers and figures confirm what was discovered in [8], that the brain composition is not significantly different from EP born subjects than FT born ones. Two different parameters where analyzed throughout this work and despite MWF seems to present slight differences in Left Limbic and Right Limbic lobes, statistical tests demonstrated that there is not real difference to be regarded as meaningful. On the other side tissue fraction density has shown almost homogeneous values across different regions. It has to be noted a couple of problems emerging at this point, first there is an important quantity of outliers specially in tissue fraction, regardless the status of the subject this is happening. And second, it is difficult to deal with unbalanced sample sizes which is happening with the voxels in the ROI for each parcellation. For the latter, another approach on the statistical design of the problem would have been preferred, for example doing a multi-comparison test on each subject. While for the former, it will be interesting to check in the future a different transformation restricting even more the possible values of MWF and TF given that at this point there is more evidence on which values are appropriate, in this way a different setting for a model can be done.

Results on parameter precision using MCMC is very similar to what [8] had reported, this confirms that the calculated confidence interval is good for the data which actually was fed as several hundred thousand voxels. This results together with what was said previously, can be a good option for fine-tuning model restrictions or initial point.

Among the different models analyzed in this project it was clear how the three-compartment model is the most suitable with regards to the hypothesis tested for several reasons. First, simplicity on the number of parameter which despite of only being solved by non-linear algorithms is less computationally expensive as a two-compartment model with 6 parameters. Second, it is more clear and intuitive to realize what the parameter values represent, which is beneficial in order to recognize where problems may happen. It would be interesting checking additional parameters for possible corrections of SNR as it was proposed by [12] but this time for multi compartment models. In regards of model selection, it is noticeable how the NNLS due to its high SSD is ranked in last position despite being reported as the most used in the literature [13]. The same factor also motivated the decision on selecting three-compartment with priors. LLS, due to its simplicity is easy to implement and it shows a very good computational performance but at the expense of being able to solve only very deterministic problems which are not common in the physical world. It might be really interesting, trying in the future plugging in the noise estimation per voxel with the weighted least-squares, giving that the estimation as shown previously seems fair enough to detect noisy signals.

There have been some attempts at reducing the effects of the SNR by using a spatially constrained Multi-Gaussian model [11]. Noise analysis has been presented over this study and is one of the stronger pointe as it is looking to individual signals in order to get a quantitative measure of how the noise is impacting and affecting the fitting by looking at its broad effects per case. It was implemented by a power law analysis over the noise distribution with the aim to get some parameter defining how good a case may be fitted. With this information at hand it will be possible in the future doing a better

preprocessing on the incoming data by looking at very troublesome images then it can be inferred a threshold on how much noise will be acceptable for a model in order to get better results or simply discard very noisy cases.

Finally, it is clear how T2 relaxometry imaging is important as an alternative for brain studies specially those for the effects of EP subjects. The necessity to detect small changes either by neuroimaging or other quantitative techniques like bioinformatics is of relevance to determine functional problems early. It was the case this time trying to get a sense on which brain regions have developed differently on the early adult EP brain. It has been important to look at how unlikely is the presence of changes despite the EP condition, but it will need a deeper research as the study group may not be big enough to capture changes. In this sense, it may be necessary to get a dataset with subjects imaged over the years in order to compare on a time line how the development of the brain is evolving to the point that we observed in this study.

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