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A Bayesian Model to Assess T_2 Values and their Changes Over Time in Quantitative MRI

Benoit Combès¹, Anne Kerbrat², Olivier Commowick¹, Christian Barillot¹

¹ INRIA, INSERM, VisAGeS U746 Unit/Project, F-35042 Rennes, France

² Service de Neurologie, Rennes, France

Abstract. Quantifying T_2 and T_2^* relaxation times from MRI becomes a standard tool to assess modifications of biological tissues over time or differences between populations. However, due to the relationship between the relaxation time and the associated MR signals such an analysis is subject to error. In this work, we provide a Bayesian analysis of this relationship. More specifically, we build posterior distributions relating the raw (spin or gradient echo) acquisitions and the relaxation time and its modifications over acquisitions. Such an analysis has three main merits. First, it allows to build hierarchical models including prior information and regularisations over voxels. Second, it provides many estimators of the parameters distribution including the mean and the α -credible intervals. Finally, as credible intervals are available, testing properly whether the relaxation time (or its modification) lies within a certain range with a given credible level is simple. We show the interest of this approach on synthetic datasets and on two real applications in multiple sclerosis.

1 Introduction

Relaxometry imaging provides a way to quantify modifications of biological tissues over time or differences between different populations. In this context, the problem of estimating T_2 values from echo train acquisitions is discussed in many works [10, 12, 11]. Since we deal with quantitative values, being able to then detect and assess significant differences and changes seems an important goal to achieve. However, to our knowledge, there is still a lack of statistical method to analyse such data. In this work, we focus on the analysis of the T_2 or T_2^* modification between two time-points (*e.g.* baseline versus 3 months later or pre versus post contrast agent injection) for a given subject. A naive approach to perform such a task consists in first computing the T_2 maps for the pre and post acquisitions using an optimisation algorithm and then in comparing the variation level inside a region of interest -typically multiple sclerosis lesions- to the variation inside the normal appearing white matter (NAWM). However, this solution may drive to important issues. The reproducibility error of T_2 and T_2^* maps is indeed significantly smaller in the NAWM than in regions with higher intensities. This makes the task, in the best case, complex and, in the worst, error prone with many false positive detections in the higher intensities regions.

In fact, due to the form of the relationship relating the MR signal and the relaxation time, the uncertainty of estimation increases with the relaxation time (see [7] for illustrating experiments on phantoms). In this work, we provide a Bayesian analysis of this relationship. More specifically, we build posterior distributions relating the raw (spin or gradient echo) acquisitions and the relaxation time and its modification over time. These posterior distributions extract the relevant information from the data and provide complete and coherent characterisations of the parameters distribution. Our approach has three main advantages over the existing T_2 and T_2^* estimation methods. First, it allows to build complex models including prior belief on parameters or regularisations over voxels. Second, it provides many estimators of the parameters distribution including the mean and α -credible highest posterior density (HPD) intervals. Finally, once the credible intervals estimated, testing properly whether the relaxation time (or its modification) lies to a certain range given a credible level becomes simple.

The article is organized as follows. In Section 2, we describe a set of models to analyse the T_2 and T_2^* relaxation times. More specifically, in Section 2.1, we give a posterior for the T_2 (or T_2^*) estimation. In Section 2.2, we give a procedure to assess differences of T_2 in a voxel between two time points at a given credible level. Then, in Section 2.3, we slightly modify the posterior so that the estimation is not anymore performed voxel-wise but region-wise leading to non-independent multivariate estimations and testings. In Section 2.4, we propose a prior to use the extended phase graph function instead of the exponential decay function used in the previous models. Then, in Section 3, we assess our method on synthetic data. In Section 4, we provide two examples of applications on Multiple Sclerosis data. Finally, in Section 5, we discuss this work and give perspectives.

2 Models

2.1 Bayesian analysis of T_2 relaxometry

For a given voxel in a volume, the MR signal S_i for a given echo time τ_i can be related to the two (unknown) characteristics of the observed tissue T_2 and M (where M accounts for a combination of several physical components) through:

$$S_i | T_2 = t_2, M = m, \sigma = \sigma \sim N(f_{t_2, m}(\tau_i), \sigma^2), \quad (1)$$

where $f_{t_2, m}(\tau_i) = m \cdot \exp\left(-\frac{\tau_i}{t_2}\right)$ and $N(\mu, \sigma^2)$ is the normal distribution with mean μ and variance σ^2 . The Gaussian error term allows to account for measurement noise as well as for model inadequacy (due to *e.g.* multi exponential decay of the true signal, partial volumes or misalignment). Then we consider that for all $i \neq j$ $(S_i | t_2, m, \sigma) \perp (S_j | t_2, m, \sigma)$ ($\perp$ standing for independence).

The associated reference prior [1] for σ and (M, T_2) in different groups writes:

$$\begin{aligned} \Pi_1(t_2, m, \sigma) &= \Pi_{T_2}(t_2) \cdot \Pi_M(m) \cdot \Pi_\sigma(\sigma) \\ &\propto \left(\frac{l_0(t_2) \cdot l_2(t_2) - l_1^2(t_2)}{t_2^2} \cdot 1_{[t_{2min}, t_{2max}]}(t_2) \right) \cdot \left(m \cdot 1_{[m_{min}, m_{max}]}(m) \right) \cdot \left(\frac{1}{\sigma} 1_{\mathbb{R}^+}(\sigma) \right), \end{aligned} \quad (2)$$

where $l_k(t_2) = \sum_i \tau_i^k \exp(-2\frac{\tau_i}{t_2})$ for $k = 0, 1, 2$ and where $1_A(x) = 1$ if $x \in A$ and 0 elsewhere. Notice that the upper limit for M and positive lower limit for T_2 in the prior support are needed to ensure posterior properness. This prior leads to invariance of the inference under reparametrisation of the exponential decay function. Moreover, as it will be shown in Section 2.1, it provides satisfying performance whatever the actual values of T_2 (so, under normal as pathological conditions). Estimators for the resulting marginal posterior $p(T_2|(s_i))$ can then be computed using a Markov Chain Monte Carlo algorithm (details in Section 3).

2.2 Bayesian analysis of T_2 modification

We are now concerned with the following question : how to assess that the T_2 value associated to a given voxel has changed between two acquisitions with a given minimal credible level. Let call X_a the random variable associated to a quantity for the pre acquisitions and X_b for the post acquisitions. We assume that the volumes are aligned and model for the pre acquisition:

$$S_{a,i}|t_2, m_a, \sigma_a \sim N(f_{t_2, m_a}(\tau_i), \sigma_a^2), \quad (3)$$

and introduce C as the T_2 modification between the two acquisitions through:

$$S_{b,i}|t_2, c, m_b, \sigma_b \sim N(f_{t_2+c, m_b}(\tau_i), \sigma_b^2), \quad (4)$$

where (additionally to above independences) for all i, j $(S_{b,i}|t_2, c, m_b, \sigma_b) \perp (S_{a,j}|t_2, m_a, \sigma_a)$. From Eq. 2 we can define the prior:

$$\Pi_2(c, t_2, m_a, m_b, \sigma_a, \sigma_b) \propto \Pi_{T_2}(t_2 + c) \Pi_{T_2}(t_2) \Pi_M(m_a) \Pi_M(m_b) \Pi_\sigma(\sigma_a) \Pi_\sigma(\sigma_b), \quad (5)$$

that defines, with Eq. 3 and 4, the marginal posterior for (among others) the T_2 modification $p(C|(s_{a,i}), (s_{b,i}))$. Then a voxel can be defined as negatively (resp. positively) altered at α level, if the α -credible HPD interval for C does not contain any positive (resp. negative) value (see [8] for a testing perspective).

The previous model of variation $T_{2b} = T_{2a} + C$ was dedicated to T_2 modification. Another important alternative model of variation states that when adding a contrast agent to a biological tissue the effect on its T_2 property is additive with the rate $1/T_2 : 1/T_{2b} = 1/T_{2a} + C_R$ and that C_R (we use this notation to distinguish it from the above C) is proportional to the contrast agent concentration. From the posterior of T_2 and C designed above, its posterior writes: $p(C_R = c_R|(s_{a,i}), (s_{b,i})) = p(\frac{-C}{T_2(C+T_2)} = c_R|(s_{a,i}), (s_{b,i}))$.

2.3 Region-wise analysis

The models proposed previously allow a voxel-wise analysis where each voxel is processed independently from others. Performing a grouped inference for all the voxels of a given region (*e.g.* lesion) can be performed by adding a supplemental layer to the model. Let us use j to index voxels, then one can replace each prior $\Pi_2(c^j)$ by for example: $\Pi_2(c^j|\mu_C, \sigma_C) = \psi_N(\mu_C - c^j, \sigma_C^2)$

(ψ_N being the Normal kernel). We then assume that $\forall i_1, i_2$ and $j_1 \neq j_2$, $(S_{i_1}^{j_1} | t_2^{j_1}, m^{j_1}, \sigma^{j_1}) \perp (S_{i_2}^{j_2} | t_2^{j_2}, m^{j_2}, \sigma^{j_2})$ (in particular, we consider the errors as independent between voxels). For the two hyperparameters μ_C and σ_C , we use the weakly informative priors (see [5] for details) $\mu_C \sim N(0, 10^6)$ (approximating the uniform density over $\mathbb{R}$) and $\sigma_C \sim \text{Cauchy}(x_0 = 0, \gamma = 100)I_{\mathbb{R}^+}$ (allowing σ_C to go well below 400ms), where $I_{\mathbb{R}^+}$ denotes a left-truncation. Such a model allows the set of inferences over the (C^j) to be performed not independently thus dealing in a natural way with multiple comparisons by shrinking exceptional C^j toward its estimated region-wise distribution [6] and improving the overall inference. Depending on the expected regularity of the C^j s within the regions, we can alternatively opt for a Cauchy density or/and add an informative prior for the error variances $\sigma_{a,i}^2$ and $\sigma_{b,i}^2$ to favor goodness of the fit. Parallely, a spatial Markovian regularisation can also be considered.

2.4 Using the extended phase graph

When the signals $(s_i)_{i=1:N}$ are obtained using sequences of multiple echoes spin echoes (*e.g.* CPMG sequence), the exponential decay function is only a rough approximation of the relation between T_2 and the MR signals. Some solutions to adapt it to this situation exist [10] and could be easily added to our model. In the following, we propose a broader solution that consists in replacing the exponential decay by the Extended Phase Graph function (EPG) [9] that relates the signal S_i to two other quantities (additionally to T_2 and M) so that $(S_i) = \text{EPG}(T_2, M, T_1, B_1, (\tau_i)) + \epsilon$ (T_1 being the spin-lattice relaxation time, B_1 the field inhomogeneity *i.e.* multiplicative departure from the nominal flip angle and ϵ representing the noise term of Eq. 1). This function is complicated (product of N 3x3 matrices involving non-linearly the different parameters) and derivating a dedicated reference prior would be cumbersome. Nevertheless, it consists of small departures from the exponential function and mainly depends on M and T_2 . Thus a reasonable choice consists in using the same priors as those derivated for the exponential function. Then, an informative prior is designed for B_1 . In practice, B_1 typically takes 95% of its values in $[0.4, 1.6]$ (we deliberately use this symmetric form to avoid $B_1 = 1$ to be a boundary of the prior support) so we set $B_1 \sim \text{Gamma}(k = 8.5, \theta = 0.1)$. We did the same for T_1 by choosing a gamma distribution with 95% of its density in $[20, 2000]$ ($T_1 \sim \text{Gamma}(2.3, 120)$). In practice, T_1 has a very small impact on the EPG and on the inference. Then the EPG model can be used by simply replacing $f_{t_2, m}(\tau_i)$ by $\text{EPG}(t_2, m, t_1, b_1, (\tau_i))$ (prior sensitivity analysis for T_1 and B_1 give satisfying result).

3 Results on synthetic data

3.1 Implementation, datasets and convergence diagnosis

For the sake of concision, for the previous models, we only exhibited the likelihoods, the priors and the independence assumptions. The resulting posteriors

can be obtained using the Bayes rule. Then for each marginal posterior $p(T_2|(s_i))$ (Section 2.1), $p(C|(s_{a,i}), (s_{b,i}))$ (Section 2.2) and $p((C^j)|(s_{a,i}^j), (s_{b,i}^j))$ (Section 2.3), we get its statistics using the "logarithm scaling" adaptive one variable at a time Metropolis-Hastings algorithm [13]. We used 10k samples (40k for the region-wise model) after discarding the 5k first ones (20k for the region-wise model). Convergence has been assessed using the Geweke score [2].

The data we use in this section are numerically generated T_2 spin echo acquisitions with 7 echo times τ equally spaced by 13.8ms and a repetition time of 1s. Because the function $EPG(t_2, t_1, b_1, (\tau_i))$ is time consuming and many calls are needed, it is tabulated on a fine grid for different values of t_2 , t_1 and b_1 . All the results given below are those using the EPG (for both generating data and inference), those obtained using the exponential decay are slightly better and lead to the same conclusion.

3.2 Results

T_2 estimation: We run 400 estimations for different configurations of T_2 and σ (realistic values are randomly given to T_1 , B_1 and M). Results are summarized in Table 1 and illustrate how the length of the credible intervals increases as expected with T_2 and σ . Moreover, these intervals exhibit excellent coverage properties, illustrating the interest of the derivated priors in the absence of prior information for T_2 . Notice that other choices of prior such as the reference prior with σ and M as nuisance parameters [1] do not lead us to analytical solutions.

Table 1. Mean 0.05-credible interval length and coverage properties (*i.e.* percentage of intervals containing the true value of T_2) using 400 simulations for each configuration.

T_2/σ	50/5	80/5	120/5	200/5	300/5	50/10	80/10	120/10	200/10	300/10
mean interval length	4.95	8.63	14.54	35.85	71.17	10.08	17.40	28.27	72.30	154.89
coverage	0.97	0.96	0.98	0.95	0.96	0.96	0.97	0.96	0.97	0.98

C estimation: For different configurations of T_2 , σ and C , we analyse the specificity (denoted p^-) and sensitivity (denoted p^+) of the estimator for C modification (Section 2.2) for $\alpha=0.05$. Results are summarized in Table 2 and illustrate that for the used acquisition protocol, detecting low T_2 modifications in high values is limited with a 0.95 specificity level. Such simulations can be used to design decision rules providing an optimized specificity/sensitivity trade-off for given T_2/C values by adjusting α . We also observe that the region-wise model leads to strong improvements of the performances.

4 Two applications on real data

The present method has been developed in a clinical context including a dataset of about 50 pre-post acquisitions from relapsing-remitting multiple sclerosis patients. In this section, we exemplified applications of our method on a few data

Table 2. Specificity and sensitivity for $\alpha = 0.05$ for different $\sigma/T_2/C$ configurations (using 200 simulations). The region-wise analysis is performed with regions of 16 voxels with C values drawn from a Cauchy density (to deviate from the chosen model) with mean $1.1 \cdot C$ (C being the value for the voxel of interest) and scale parameter 10.

	T_2/σ	80/5	120/5	200/5	300/5	80/10	120/10	200/10	300/10
Voxel-wise	$C = 0, p^-$	0.96	0.97	0.96	0.94	0.93	0.96	0.97	0.95
	$C = 30, p^+$	1	1	1	0.73	1	1	0.60	0.16
	$C = 60, p^+$	1	1	1	0.93	1	1	0.90	0.23
Region-wise	$C = 0, p^-$	1	0.99	0.98	0.98	1	0.98	0.99	0.98
	$C = 30, p^+$	1	1	0.98	0.95	1	1	0.78	0.46
	$C = 60, p^+$	1	1	0.98	0.97	1	1	0.97	0.67

from this study. Data are acquired on a 3T Verio MRI scanner (Siemens Healthcare, 32-channel head coil) and consists of volumes of $192 \times 192 \times 44$ voxels of size $1.3 \times 1.3 \times 3 \text{ mm}^3$. The sequence parameters are the same as those used in Section 3. For each patient, all volumes are rigidly co-registered using a robust block-matching method [3]. No other preprocessing is applied.

4.1 Assessing USPIO enhancement in MS lesion

Ultra small superparamagnetic iron oxide (USPIO) is a contrast agent used to assess macrophagic activity that reduces the T_2 relaxation of the surrounding tissues [4]. We use, in this section, sets of pre-post injection acquisitions to detect the presence of USPIO in MS lesions using our model. Figure 1 displays detection with a 5% level for a patient acquired twice without USPIO injection and for a patient with potentially active lesions. The pre-post T_2 relaxation maps illustrate the difficulty to label the lesions as enhanced or not by simply using the point estimates. The map for the patient without USPIO injection, for which our method does not detect any voxels, highlights this point. More generally, on this data we never detected more than 5% of the voxels. For the active patient with USPIO injection, the method detects lesion 1 -for which we have independent clues that it is effectively active (*i.e.* high variation of MTR, FA and ADC values between baseline and acquisitions 3 months later)- as enhanced. By contrast, lesion 2 -for which we had no initial clue that it was actually active- is not detected as enhanced, while it shows a substantially positive pre-post signal.

4.2 Assessing T_2 recovery in an active MS lesion

In this section, we use our model to assess the evolution of the T_2 associated to a MS lesion just after its emergence (m_0) and 3 (m_3) and 6 (m_6) months after. To illustrate the interest of the credible intervals, we display the minimal plausible C values for the 0.05 level *i.e.* the lower bound of the 0.05-credible interval for $[m_3, m_0]$ (Fig 2.a) and the upper one for $[m_6, m_3]$ (Fig 2.b). Notice that, for a sake of clarity, we quantify here differences from m_3 to m_0 so that expected difference C (a decrease of the T_2 signals over time) is positive (and similarly for

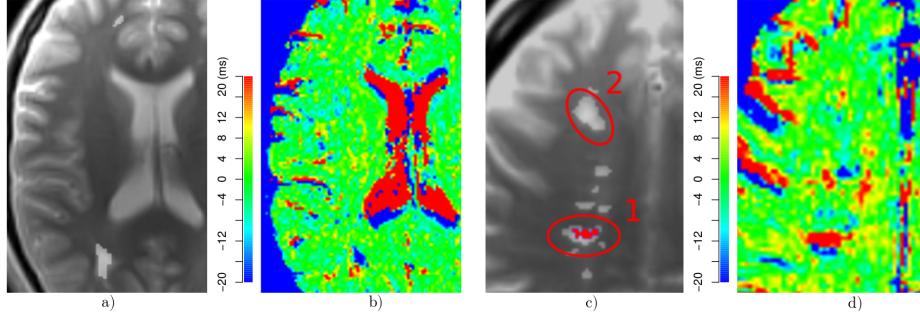


Fig. 1. Pictures a) and b): acquisitions performed without USPIO injection (so all lesions should be detected as negative). a) superposition of a T_2 weighted image, the lesion segmentation mask (white patches) and the enhanced voxels (red) for the 5% level and b) the pre-post T_2 relaxation map (using ML estimates). **Pictures c) and d): an active patient.** Same displays than for a) and b).

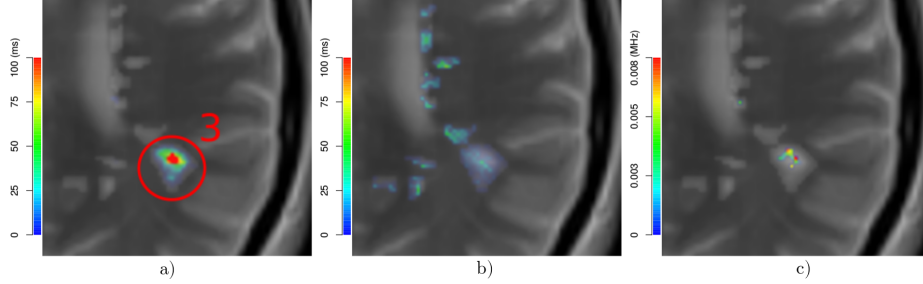


Fig. 2. Recovery assessment in MS lesions. From left to right: a) *Minimal* T_2 recovered value for $[m_3, m_0]$ (admissible with $\alpha = 0.05$), b) *Maximal* T_2 recovered value for the next time $[m_6, m_3]$ and c) *Minimal* USPIO concentration C_R at m_0 .

m_3 and m_6). These maps offer a quantitative scale to compare lesions recovery among and within patient. More precisely, for lesion 3, the minimal admissible C is positive for $[m_3, m_0]$ (thus the interval does not contain 0) demonstrating that the lesion is recovering during this period. By contrast, this is not the case for the other lesions of the slice and for lesion 3 at $[m_6, m_3]$ (not displayed) : it cannot be excluded with a 5% level that the recovering process is finished. Moreover, the *maximal* admissible value for $[m_6, m_3]$ (Fig 2.b) is far lower than the *minimal* one for $[m_3, m_0]$. We also give the *minimal* USPIO concentration *i.e.* C_R changes for the 5% level (Fig 2.c): we observe a good adequacy between USPIO concentration and T_2 change at $[m_0, m_3]$.

5 Discussion and Conclusion

In this paper, we proposed a Bayesian analysis of T_2/T_2^* relaxation time assessment and modification. Then, we showed the interesting properties of our

models on synthetic datasets. Finally, we exemplified the interest of the obtained credible intervals with two applications. As illustrated, when available, *interval* estimates can be more powerful than *point* ones to address naturally complex issues in medical imaging. Moreover, this work can be extended in several ways:

- It can be used as a base for the development of more informative hierarchical models (this is a motivation for considering a Bayesian setting). For example, the B_1^j s are correlated in space which could be accounted for adding a supplemental layer to the model (similarly to what proposed in Section 2.3). An informative prior for σ^j could also be of interest to get less conservative intervals.

- In this work, we considered the errors (modelled by the error term of Eq. 1 or Eq. 3 and 4) as not correlated between voxels and modelling correlated errors (with unknown structure) would be of interest and is a challenge to meet.

- The method is computationally intensive (about 2s per voxel for the EPG region-wise approach) and for more demanding applications, other strategies *e.g.* maximising over nuisance parameters could be investigated.

More generally, we think there is room for potential applications of interval estimation in *e.g.* T_1 or DTI and hope this work will encourage such development.

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