Robust estimation of changes in transverse relaxation from magnitude MRI data: Application to vessel size imaging

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Introduction: Transverse relaxation rates, R_2 and R_2* and the apparent diffusion coefficient (ADC) are all typically estimated from the exponential decay of MR signal magnitude as a function of either echo time (for R_2 and R_2*) or b-value (for ADC). Changes in R_2 and R_2* induced by ultrasmall paramagnetic iron oxide (USPIO) contrast agents, along with ADC, have recently been utilised to estimate vessel size index (VSI) in a range of contexts [1,2]. However, vessel size imaging tends to suffer from over-estimation of VSI when compared with gold-standard histological measurements [3]. In this study, a novel analysis method is described that offers a robust (accurate) approach to the estimation of ADC and of changes in R_2 and R_2* (ΔR_2 and ΔR_2*, respectively), based on the observation that noise in magnitude data is Rice-distributed [4]. This Bayesian maximum *a posteriori* (MAP) approach also offers benefits such as the provision of parameter uncertainties and estimates of the confidence that a change in R_2 or R_2* is significant, on a pixel-by-pixel basis. The approach is evaluated *in vivo* in PC3 orthotopic prostate tumours and compared with the conventional least-squares (LS) approach, which assumes noise to be normally-distributed.

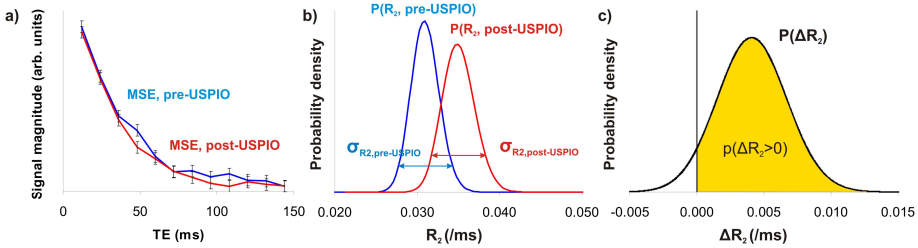

Figure 1: *a) MSE magnitude data, pre- and post-USPIO. b) Probability distributions for the data in a), given by numerically integrating the likelihood function over S_0. c) Probability distribution for ΔR_2* given by the numerical convolution of P(R_2,pre-USPIO) and P(R_2,post-USPIO). The probability that R_2 has increased is the integral of P(ΔR_2) between 0 and ∞.*

Materials and Methods:

Data acquisition: PC3 orthotopic tumours were propagated in 6 nude mice and allowed to develop for 20 days. They were scanned on a 7T Bruker MicroImaging system using a spin-echo diffusion sequence (6 b-values from 6 to 500 s/mm^2, TR=1000ms), a multi spin-echo sequence (MSE, 12 TEs ranging from 12 to 144ms, and a multi gradient-echo sequence (MGE, 8 TEs ranging from 6.2 to 28.2ms. USPIO was administered via a tail vein and allowed to circulate for two minutes prior to the acquisition of a second set of MSE and MGE data.

Data analysis: Data were fitted to a function of the form $f(x)=f_0e^{-r.x}$, where $(x,r)=(b,\text{ADC})$ for the diffusion data, $(x,r)=(\text{TE},R_2)$ for MSE data and $(x,r)=(\text{TE},R_2^*)$ for MGE data; f_0 is the signal intensity at TE or b=0 and, along with r, is a fitted parameter. Data were fitted using both a non-linear LS algorithm and a Bayesian MAP algorithm that maximised the following log-likelihood function [5]:

$$L=\sum_{i=1}^{N}\log I_0\left(\frac{f(x_i)M_i}{2\sigma}\right)-\sum_{i=1}^{N}\frac{f(x_i)^2}{2\sigma^2}-\sum_{i=1}^{N}\frac{M_i^2}{2\sigma^2}-N\log(\sigma^2)+\sum_{i=1}^{N}\log(M_i)$$

Here, I_0 is the modified Bessel function of the zeroth kind, M is the magnitude data value, σ is the standard deviation of the Rice noise and N is the number of magnitude data points. σ was estimated by fitting a Rayleigh distribution to a histogram of magnitude values from a region of background noise [3]. ΔR_2 and ΔR_2* were estimated and their posterior distributions (the probability density function for each parameter on a per pixel basis) calculated using numerical convolution. Each posterior distribution was numerically integrated from $\Delta R_2(*)$ = 0 to ∞ to produce maps defining the confidence of a positive change in $R_2(*)$ due to the presence of USPIO (see Fig. 1). Only pixels with a combined confidence of greater than 90% ($p(\Delta R_2>0)>0.9$) for both ΔR_2 and ΔR_2* were used in the subsequent analysis. The vessel size index (VSI) was estimated from the ΔR_2, ΔR_2* and ADC data, according to the approach defined by Troprès [6].

Histopathology: Hoechst 33342, a fluorescent endothelial stain, was administered via the tail vein as a terminal experiment. Using the approach of Troprès [3], measurements of vessel diameters from whole-tumour fluorescent composite images were converted to a vessel size index value equivalent to the MRI estimate, thereby enabling histological qualification.

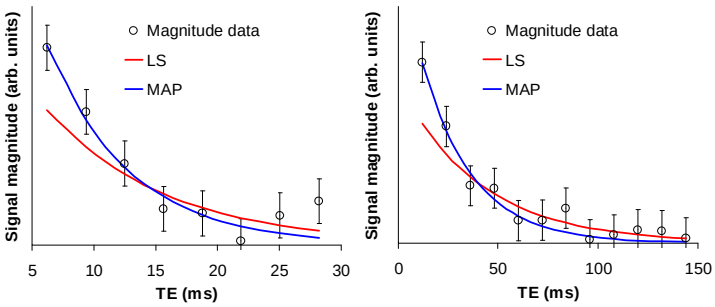

Figure 2*: Example fits to (left) MGE and (right) MSE magnitude data from a single pixel with relatively low signal-to-noise, given by the least-squares and Bayesian maximum a posteriori algorithms. Note that the LS algorithm attempts to fit the data symmetrically, whilst the MAP algorithm ignores data points with negligible signal, resulting in unbiased, larger R_2 and R_2* estimates.*

Results and Discussion: R_2, R_2* and ADC estimates from the LS algorithm were consistently lower than those from the MAP algorithm. The cause of this is illustrated in Fig. 1; the least-squares algorithm assumes normally-distributed noise, so weights high signal and low signal data points equally. The MAP approach offers a more appropriate model of the noise and as such is less weighted by low signal data points, giving more accurate parameter estimates. Figure 2 shows images from MAP R_2* analysis from an example tumour, including the first echo image and the ΔR_2* map. It is clear that ΔR_2* values are highly uncertain in regions with low initial signal intensity, although the magnitude of these was comparable with those in the rest of the imaged portion of the tumour. These were removed from the analysis along with regions with an enhancement confidence of less than 90%. Mean ΔR_2*, ΔR_2 and ADC values were significantly larger when using the MAP approach ($p<0.01$), according to Wilcoxon rank sum tests. Using these values, the mean vessel size across the cohort was 63±25µm, compared with 83±29µm from the LS approach, which were also significantly different ($p<0.01$). VSI from histological measurements was 67±6µm, which is in close agreement with the value from the MAP approach.

Conclusion: The Bayesian MAP model proposed here for estimating VSI offers a number of advantages over the standard least-squares approach, including more robust parameter estimation and the ability to segment significantly enhancing regions and regions of poor precision. This therefore allows the removal of data unsuited to the subsequent VSI calculation, thereby improving the reliability of the technique. It is suggested that this approach could offer a significant increase in parameter accuracy when used in a range of contexts, in particular, drug efficacy studies.

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References: [1] Howe et al., Int J Radiat Oncol Biol Phys, 71(5):1470-76 (2008), [2] Valable et al., NMR Biomed, EPub (2008), [3] Troprès et al, Magn Reson Med, 51(3):533-41 (2004) [4] Gudbjartsson H., *Magn Reson Med*, 34:910-4 (1995), [5] Sijbers J., Magn Reson Imaging.16(1):87-90 (1998) [6] Troprès et al, Magn Reson Med, 45:397-408 (2001).

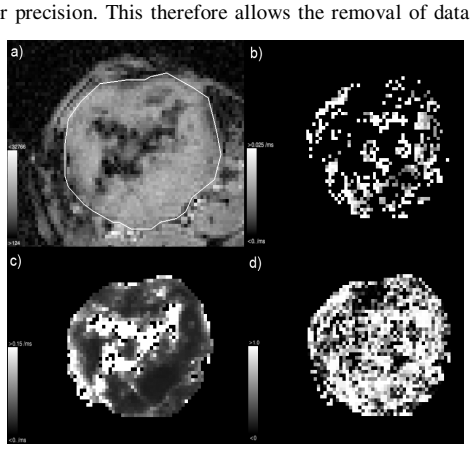

Figure 3*: Images from MAP R_2* analysis in an example tumour: a) First echo magnitude image; b) ΔR_2* image with pixels with a high uncertainty or insignificant enhancement removed; c) an R_2* uncertainty map; d) a map of the probability that the R_2* in each pixel has significantly increased following USPIO administration. Note that regions with low initial signal intensity in (a) have a high uncertainty in (c), so are of limited use in the subsequent VSI calculation and are removed.*