Which one is most accurate and has highest precision? - A comprehensive analysis of $T_2^{(*)}$ estimation techniques

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TARGET AUDIENCE – Researchers interested in relaxometry.

PURPOSE – MR relaxation parameters like T_1, T_2 or T_2* are often used to quantify the state of tissue and to distinguish pathological from normal conditions. The extraction of these parameters from *in vivo* MR images relies on fitting model functions to the temporal evolution of the MR data. Assuming mono-exponential decay one major complication for the parameter estimation is the presence of non-Gaussian noise. MR magnitude noise becomes non-Gaussian for signal-to-noise ratios (SNR) below a numerical value of three[1], which is difficult to analytically account for during the estimation and can introduce a serious bias toward higher or lower relaxation parameters. **Such a bias may have serious clinical consequences, e.g., when relaxation parameters are used for treatment decisions such as in liver iron overload diseases**. Several different (in part heuristic) extensions to mono-exponential fitting have been presented to account for potentially low SNR at later echo times, such as an extra constant offset parameter[2] and data truncation[3]. While it was shown that estimated relaxation rates vary substantially depending on the chosen fitting method (see e.g. **Figure 1**), a comprehensive analysis of the different approaches has not been carried out yet. **With the current contribution, we aim to give clear recommendations how to estimate relaxation rates for different experimental scenarios, such as in slow and fast relaxing tissues.** To this end, we extensively analyzed literature algorithms with respect to both accuracy and precision in two relaxation regimes and present an improved data truncation method. Numerical simulations were validated with a dedicated phantom experiment.

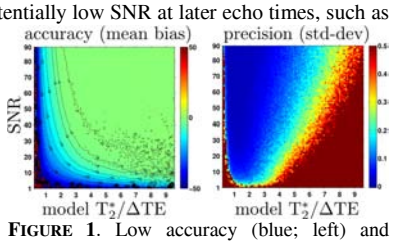

FIGURE 1. Low accuracy (blue; left) and precision (red; right) of naïve mono-exponential fitting (3 parameters; **P1-M2-T1**). Colors encode percentage deviation from the model value and absolute standard deviation of T_2*/ΔTE, respectively. For fast relaxation the technique has low accuracy; for slow relaxation the technique has low precision.

THEORY – *General*: Estimation of relaxation rates generally involves, first, preprocessing of the MR data (e.g., noise bias correction), second, choosing the fitting and optimization functions (i.e., the model) and, third, defining the data to be used for the fitting, also referred to as truncation criteria (i.e., discarding data with low SNR). *New truncation method*: We propose to, first, calculate a (rough) estimate T_2* of the relaxation time from the first two echoes and, then, use only the first T_2*/ΔTE echoes for the fitting, i.e., only echoes with TE < T_2* are used. Since truncation is generally most required for fast relaxing tissue the first two echoes usually provide the most reliable initial estimate.

METHODS – For the ease of presentation we restrict ourselves in the following to T_2* relaxation (w.l.o.g.). All results are reported in terms of relaxation rates normalized to the echo spacing (T_2*/ΔTE, TE_1=ΔTE) permitting transfer of the results to arbitrary sequence echo times. *Pre-processing techniques:* **P1**) no pre-processing, **P2**) Calculating the square of the magnitude, which makes the noise bias additive[4]. **P3**) P2 and subtracting the mean noise level[5]. *Compared fitting models:* **M1**) Linear fitting of the logarithm of the signal (two parameters; computationally most efficient)[6], **M2**) Non-linear (NL) mono-exponential (ME) fitting (two parameters; initial values from M1)[7], **M3**) NL-ME fitting with constant offset (3 parameters; initial values from M1)[2]. *Truncation criteria*: **T1**) no truncation, **T2**)[8] SNR < 2, **T3**) Based on fit quality as proposed in Ref. 9. **T4**) Cut off for TE > T2* as proposed here. *Numerical model:* A Monte Carlo simulation was used to compare the different regression techniques against a ground-truth. 92 mono-exponential decays with T_2* between 1 and 19.2 ms (uniform increment of 0.2 ms) for the *fast relaxing regime* (T_2*/ΔTE=0.2…4), and between 1 and 46.5 ms (uniform increment of 0.5) for the *slow relaxing regime* (T_2*/ΔTE=0.2…9.8), were simulated. The signal decays were sampled at seven uniformly spaced points between 4.76 and 33.32 ms (in-phase). Rician noise was added resulting in SNRs (defined as the signal magnitude at TE=0 divided by the standard deviation of the noise) between 1 and 92 (uniform spacing of 1). To mimic a region-of-interest (ROI)-based analysis with a 2D ROI of 25 x 25 voxels this procedure was repeated 625 times for each pair of T_2* and SNR value. Finally, the average of the resulting magnitude signals was calculated. To analyze the reproducibility of the fitting techniques, the whole model generation procedure was repeated 50 times resulting in 50 ROI-averaged signal decays for each T_2* constant and SNR level. Finally, all combinations of different preprocessing and fitting techniques were applied to the signal decay curves and the mean (accuracy) and standard deviation (precision) of the 50 resulting T_2* constants per model T_2* and SNR-level were calculated. *Phantom experiments*: Six samples were produced with different concentrations of Resovist (Bayer Schering Pharma AG) ranging from 766 to 3313 µmol/ml in 1% agarose. Iron concentration in the solutions was determined by performing atomic absorption spectroscopy [AAS 5 FL, Analytik Jena AG, Germany] to represent linear references for R_2*. The solutions were filled in 2 ml Eppendorf cups and MRI was conducted at 1.5 T using a loop coil and a 2D multi-echo, gradient echo sequence: TE_1/TE_7 = 2.74 ms/16.48 ms, TR=30 ms. The sequence was repeated 200 times. Eight subsets of the 200 acquisitions (2, 3, 4, 5, 10, 40, 66, and all 200) were averaged in *k*-space, mimicking different SNR levels.

RESULTS – Only the main findings and recommendations for practical situations are reported here due to limited space. Irrespective of the *relaxing regime* (for both *fast* and *slow*) highest accuracy and precision were obtained with **P3-M2-T1** in a homogeneous noise-level scenario. In a scenario where the noise level is non-uniform, e.g. in accelerated parallel imaging, the mean noise level is difficult to determine. In this scenario the best result was obtained with **P2-M3-T1**[10] and **P2-M2-T1** in the *fast* and *slow relaxing regimes*, respectively. A rapid calculation, e.g., for 3D mapping, can only be achieved with the log-lin calculus (**M1**). In this case the best results were obtained in the uniform noise scenario irrespective of the relaxing regime with **P3-M1-T4** (the new truncation rule) and in the non-uniform noise scenario with **P1-M1-T3** (*fast relaxing*) and **P1-M1** (*slow relaxing; all truncation criteria equivalent*)**.** However, precision was generally reduced for M1 compared to M2. Other combinations were considerable less accurate and had lower precision (e.g. **Figure 1**). In particular, precision and accuracy were generally considerably reduced in 3-parameter fits compared to 2-parameter fits. Figures 2-4 show exemplary parameter maps illustrating the results. All results were qualitatively confirmed by the phantom experiment. The performance of the different scenarios can be summarized as (decreased accuracy and precision from left to right): **P3-M2-T1 > P2-M3-T1 > P3-M1-T4 > P1-M1-T3** (*fast relaxing*) and **P3-M2-T1 > P2-M2-T1 > P3-M1-T4 > P1-M1** (*slow relaxing*)**.**

DISCUSSION – Two different scenarios need to be distinguished when performing relaxometry: A uniform noise floor, e.g., due to sum-of-squares reconstruction, and a non-uniform noise floor, e.g. due to accelerated parallel imaging. A uniform noise floor allows global correction of a pre-estimated noise bias (from a background region; **P3**) followed by a 2-parameter fit (**M1, M2**). This scenario generally turned out to yield the most reliable estimates of T_2*. Noise-bias correction in a non-uniform noise scenario requires a 3-parameter fit[10] (**M3**), which is generally less robust, resulting is excessively high std-dev values (*low precision*). In addition, it was shown that the rapid lin-log calculus (**M1**) produces accurate R_2* values, though with lower precision than non-linear regression techniques (M2, M3). **The presented results are universal (i.e. may be transferred to the *in vivo* situation), provide a guideline for future studies and enable retrospective analyses of literature studies with respect to systematic bias.**

CONCLUSION – Estimated relaxation rates depend substantially on the chosen analysis technique and may suffer from serious bias, in particular when relaxation is fast. This bias can be avoided when one of the reported optimal techniques (a combination of pre-processing, fitting routine and truncation rules) is used.

REFERENCES – [1] Gudbjartsson H and Patz S, 1995. *MRM*. 34(6):910-4. [2] Wood JC et al., 2005. *Blood*. 106(4):1460-5. [3] Yin X et al., 2010. *NMR Biomed*. 23(10):1127-36. [4] Henkelman RM, 1985. *Med Phys*. 12(2):232-3. [5] Miller AJ and Joseph PM, 1993. *Magn Reson Imaging*. 11(7):1051-6. [6] Hasan KM et al., 2011. *MRM*. 67(3):731-9. [7] Hikita T et al., 2005. *Neurosci Res*. 51(1):67-71. [8] Bonny JM et al., 1996. *MRM*. 36(2):287–93. [9] He T et al. 2013. *J Magn Reson Imag*, 37(2):479-83. [10] Feng Y et al., 2013. *MRM* (epub).

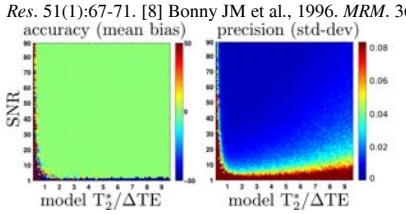

FIGURE 2. Best result over all techniques (**P3-M2-T1**; uniform noise floor)**.**

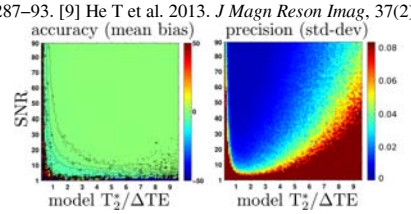

FIGURE 3. Best technique (**P2-M3-T1**) for non-uniform noise floor for the fast relaxation (T_2*/ΔTE < 4) regime.

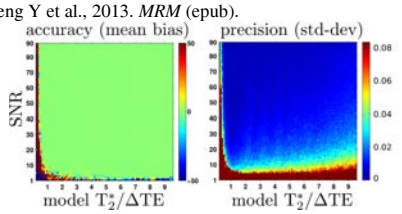

FIGURE 4. Best result with lin-log calculus (**P3-M1-T4**)**.** Accuracy and precision are comparable to the best NL-ME fitting (Fig. 2).