T2* measurements in myocardial iron overload: comparison of error models on optimized analysis protocol

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Introduction. Iron-induced heart failure is the main cause of death in transfusion-dependent anemia [1-3]. In the presence of tissue iron, the shortening of the relaxation time constant T2* is used for detection of cardiac iron [1]. It has been shown that patients with short T2* - corresponding with myocardial iron loading - have greater risk of systolic dysfunction. T2* measurements are performed with standardized protocols [2,3]; clinical range is 0 < T2* < 50 ms, optimized sampling range is 2 < TE < 18 ms. In the low T2* range the presence of the residual blood signal would require the addiction of a constant offset to the exponential decay [3], but a 2-parameters fit model is more robust and would avoid dangerous underestimation of T2* in the low-iron range, where 3-parameters fit overestimates the constant offset. An error estimation would help the clinical comparison of T2* measurements, especially in single patient's follow-up. In this work five different error models are compared.

Materials and Methods. All the models were applied to a 2-parameters fit model y = A e^(-x/b), where y is signal (a.u.) x is TE (ms) and b = T2* (ms). The implemented fit algorithm uses the downhill simplex method of Nelder and Mead instead of the Levenberg-Marquardt technique to compute least-squares; at low T2* the former is less influenced by high TE points (Fig. 1), which represent the residual signal, as the latter requires the choice of excluding points not to underestimate T2* in the low-T2* region [2]. Data were acquired on a PHILIPS Achieva 1.5T with multi-breathhold gradient-echo sequence at TE = 2,3,4,6,9,12,15,18 ms, TR = 21 ms. After images co-registration, a ROI was manually selected in the interventricular septum, with help of a reference Black-Blood image acquired at TE = 4 ms, to best individuate myocardial tissue. Errors occurring in T2* measurement can be divided as follows: (1) fit error - (2) ROI error - (3) signal distribution error - (4) sampling error - (5) model error - (6) calibration error. (1),(2),(3) are here under investigation as for (4),(5),(6) reference and optimized conditions were chosen. (1),(2),(3) are particularly involved in error estimation when repeated measurements of the same patient at the same site are compared. (4),(5),(6) are more involved in comparison of different iron stores (5) or of the same patients measured at different sites. ROI contouring was repeated 10 times on 10 patient uniformly distributed on iron-load range and a value of deviance was found, little varying between points in the same patient and between patients; the total mean of this value is indicated as SD_ROI and is considered a constant in the following modelling. Signal distribution into the ROI was found to be Gaussian and SD was calculated; SD(TE)/SD(2ms) was found to increase 100%:200% and relative variation of signal SD(TE)/y(TE) 100%:1000% with increasing TE.
The following error models were applied, all based on resampling:
(a) (fit) **Jackknife method**: systematically recomputes the statistic estimate leaving out one observation at a time from the sample. Simple and robust, used as reference.
(b) (fit) **Bootstrap on residuals**: uses the residuals randomly chosen (with replacement) from the least-squares fit to generate synthetic datasets. Parameters from resampling are supposed to be normally distributed, 2000 samples used.
(c) (ROI) **Gaussian distribution**: around each point a Gaussian distribution with SD_ROI sigma was created and points were resampled with Bootstrap, 2000 samples used.
(d) (ROI/signal) **Signal distribution**: method similar to (c) using F(TE) = SD(TE)/SD(TE=2ms) weighting. SD_dist = SD_ROI * SD(TE)/SD(TE=2ms)
(e) (ROI/signal) **Relative signal distribution**: method similar to (c) and (d) using F(TE) = SD(TE)/y(TE) weighting.
SD_dist = SD_ROI * [SD(TE)/y(TE)] / [SD(2ms)/y(2ms)]

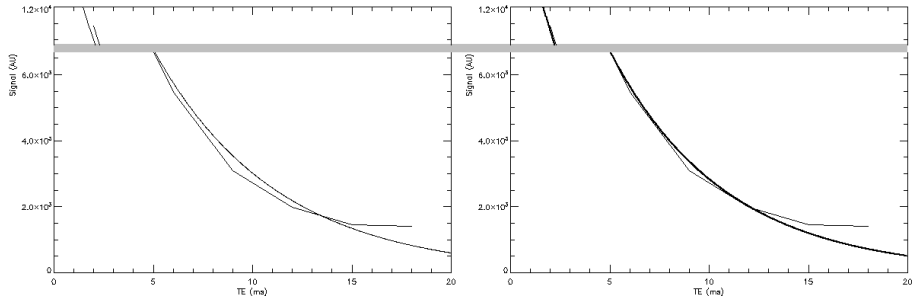

Fig. 1 - Left: Levenberg-Marquardt fit behaviour at low T2* range (<8 ms). Right: Simplex fit.

	T2* (ms)	a (ms)	a %	b (ms)	b %	c (ms)	c %	d (ms)	d %	e (ms)	e %
Case 1	**5,79**	0,11	1,9	0,25	4,3	0,14	2,4	0,29	5,0	0,63	10,9
Case 2	**10,75**	0,06	0,6	0,12	1,1	0,15	1,4	0,60	5,6	0,96	8,9
Case 3	**18,40**	0,25	1,4	0,51	2,8	0,32	1,7	1,09	5,9	0,97	5,3
Case 4	**40,30**	0,89	2,2	2,62	6,5	1,04	2,6	2,56	6,4	1,72	4,3

Table 1 - SD calculated from resampling on four representative cases with (a), (b), (c), (d), (e) approaches and related relative errors.

Results and Discussion. Measurement conditions were optimal and consequently image quality; registration by computed cross-correlation and contouring on Black-Blood reference image stabilize analysis conditions, increasing reproducibility. Deviations from exponential relaxation by water-fat shift effect were small (<1% of signal) and all points were used. Parameters from resampling were observed to be normally distributed and the mean value varied <0.7% from the original parameter. On Table 1 SD from resampling by different error models are shown, proposed as absolute error; four cases are reported, representative of four iron-loads situations and related point distributions. Absolute error increases with increasing T2*, as expected: with given sampling-range small oscillations can have relatively big effects in estimation of long T2* values. On the other hand the simplex fit gives stability to short T2* values, as on Levenberg-Marquardt fit the choice of points to be excluded would increase variability on fit value. Preliminary analysis with on Levenberg-Marquardt fit on Case 1 shows higher uncertainty if all points are included, and comparable fit value and not lower absolute error if one or two points are excluded. Absolute error increases with model complexity; fit parameters errors calculated with method (b) are bigger than with method (c), except for Case 2, which is optimally centred on the sampling-range window. Repeated analysis with new ROI contouring were found to be out of the variance computed with (b) but in all cases into the variance computed with (e); repeated measurements were all into the variance computed with (e).

Conclusions. Optimized analysis protocol is indicated, and error models are compared. Simplex fit is to be preferred if 2-parameters model is used, as it does not require observer's judgement on point distribution, and would increase robustness of the analysis. Fit parameters error is not eligible for absolute total error; error models based on weighting with signal-distribution factor can take more accurately care of relaxation model's complexity. ROI and pixel map analysis show comparable results onto the same ROI [3], but different or misregistered ROIs on pixel-wise analysis weight as F(TE) on points. F(TE) has a more rigorous formulation in method (e), which would be a more conservative approach. Error models should be applied to routine measurements and would take in account the influence of non-optimal conditions. From the present analysis it follows that in clinical comparison a minimum 5% relative error should be used if 2-parameters fit model is applied.

References

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