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Correcting Partial Volume Effect in Bi-exponential T_2 Estimation of Small Lesions

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Abstract

Purpose— T_2 mapping provides a quantitative approach for focal liver lesion characterization. For small lesions a bi-exponential model should be used to account for partial volume effects (PVE). However, conventional bi-exponential fitting suffers from large uncertainty of the fitted parameters when noise is present. The purpose of this work is to develop a more robust method to correct for PVE affecting small lesions.

Methods—We developed a ROI-based joint bi-exponential fitting (JBF) algorithm to estimate the T_2 of lesions affected by PVE. JBF takes advantage of the lesion fraction variation among voxels within an ROI. JBF is compared to conventional approaches using Cramér-Rao lower bound analysis, numerical simulations, phantom and -vivo data.

Results—JBF provides more accurate and precise T_2 estimates in the presence of PVE. Furthermore, JBF is less sensitive to ROI drawing. Phantom and in-vivo results show that JBF can be combined with a reconstruction method for highly undersampled data, enabling the characterization of small abdominal lesions from data acquired in a single breath-hold.

Conclusion—The JBF algorithm provides more accurate and stable T_2 estimates for small structures than conventional techniques when PVE is present. It should be particularly useful for the characterization of small abdominal lesions.

Keywords

T_2 estimation; MR parameter estimation; partial volume effect; lesion classification

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Introduction

T₂-weighted imaging is widely used for the characterization of lesions. In the case of focal liver lesions it is well known that the difference in signal intensities between images acquired with different T₂-weighted contrast can differentiate malignancies from the most common benign lesions (hemangiomas and cysts) (1–3). The classification based on the qualitative assessment of signal intensity, however, can be biased by partial volume effects (PVE) arising from the liver parenchyma. PVE are more pronounced as the size of the lesion decreases thus, lesions with a diameter < 1.5 cm are typically harder to classify even with the addition of Gd-enhanced imaging. These lesions could easily be misclassified (e.g. a small hemangioma or cysts can be misclassified as a malignancy) or deemed by radiologists as too-small-to-be-classified (TSTC) (4), which requires following the lesion's growth (or lack of) over extended periods of time to establish the proper diagnosis. This not only increases patient's anxiety but, more importantly, it delays the onset of treatment for malignant lesions.

Quantitative T₂ mapping has also been used for the classification of focal liver lesions (5–9). However, the incorporation of PVE in the signal equation with the goal of classifying small lesions is a task that has not been undertaken. To account for PVE in T₂ estimation a multi-exponential model is needed in order to characterize the tissue components within the voxel. However, due to the nature of the multi-exponential model for T₂ decay, there is large uncertainty of the fitted parameters and different combinations of parameters can fit the data equally well when noise is present (10). Several groups have investigated methods to improve the fitting of multi-component signals including optimization of the acquisition parameters and the stabilization of the fitting process by introducing a priori information (11–13). The effect of the Signal-to-Noise Ratio (SNR) was also investigated as a means to reduce the uncertainty. A region-fitting (RF) algorithm was proposed to obtain higher SNR by averaging signals from a homogeneous region of interest (ROI) and advantages have been shown over voxel-wise fitting (14–16). In order to achieve high SNR a non-imaging technique has also been proposed by Qin et al (17, 18) where only a specific ROI is excited by spatial selective RF pulses (19).

In this work, we present a new algorithm to estimate T₂ values of small lesions (< 1.5 cm in diameter) in the presence of partial volume effects. The algorithm is based on the assumption that for the purpose of parameter fitting the lesion and the background T₂ values can be considered homogeneous within a small ROI. The T₂ value of the lesion tissue is estimated jointly for all voxels within this ROI and the variation of the lesion fraction (*LF*) among voxels is utilized to improve T₂ estimation. We demonstrate the algorithm using simulations, phantoms and in vivo. The technique is demonstrated using fully sampled spin-echo (SE) and undersampled fast spin-echo (FSE) data. The latter is based on a radial FSE method, which allows for the acquisition of data with high spatial and temporal resolution within a breath hold (20), an important consideration for accurate T₂ mapping of small abdominal lesions.

Theory

With the assumption that the lesion and background tissue are homogeneous within a voxel, the T_2 decay signal can be modeled by a bi-exponential decay:

$$s(t) = I_l e^{-t/T_{2l}} + I_b e^{-t/T_{2b}} + \varepsilon(t), \quad [1]$$

where I_l, I_b are the initial signal intensities (i.e., signal intensity at echo time $t = 0$ ms) of the lesion and the background tissue and T_{2l}, T_{2b} are the corresponding T_2 values. The function $\varepsilon(t)$ is the noise of the given voxel at time t and the distribution of $\varepsilon(t)$ can be affected by the reconstruction technique (21, 22). When using fully sampled complex images (23, 24), images reconstructed in absorption mode (25, 26) or magnitude images with high SNR (27), $\varepsilon(t)$ can be considered as (real or complex) Gaussian distributed and spatially uncorrelated. Based on [1] we define total initial signal intensity as $I_0 = I_l + I_b$ and lesion fraction as

$$LF = \frac{|I_l|}{|I_0|}.$$

Given the signal intensities $s(t_j)$ of a voxel at J echo time points, least-square fitting can be used to estimate the parameters I_l, I_b, T_{2l}, T_{2b} :

$$\hat{I}_l, \hat{I}_b, \hat{T}_{2l}, \hat{T}_{2b} = \arg \min_{I_l, I_b, T_{2l}, T_{2b}} \left\{ \sum_{j=1}^J \| I_l e^{-t_j/T_{2l}} + I_b e^{-t_j/T_{2b}} - s(t_j) \|_2^2 \right\}. \quad [2]$$

Equation [2] represents the voxel-wise bi-exponential fitting (VBF) estimation algorithm.

Large mature tumors may have necrotic cores and other structures that do not fit the homogeneity assumption. However, for small lesions it is reasonable to assume that T_{2l} and T_{2b} are homogeneous within the lesion's ROI. Thus, with VBF T_2 's are estimated independently for all M voxels within the lesion's ROI ($\hat{T}_{2l}^m, m = 1, 2, \dots, M$) and then averaged over these M voxels to obtain the final $\hat{T}_{2l}$ value for the lesion:

$$\hat{T}_{2l} = \frac{1}{M} \sum_{m=1}^M \hat{T}_{2l}^m, \quad [3]$$

or $\hat{T}_{2l}^m$ is weighted by the corresponding $\hat{I}_l^m$ and then averaged:

$$\hat{T}_{2l} = \frac{\sum_{m=1}^M \hat{I}_l^m \hat{T}_{2l}^m}{\sum_{m=1}^M \hat{I}_l^m}, \quad [4]$$

where $\hat{I}_l^m, \hat{T}_{2l}^m$ are the fitted initial signal intensity and T_2 of the lesion in the voxel m .

As an alternative to the VBF, the RF approach (16) averages the data from all the voxels within the ROI at each echo point and performs the fitting using Equation [2]. Although RF

was found to be more stable than VBF (14), it is not the optimal way to make use of all the information available. For the case of small lesions, the LF may vary significantly from voxel to voxel and this variation can be utilized to improve fitting in a bi-exponential model. Thus, we propose a T_2 estimation algorithm utilizing this variation by estimating T_{2l} and T_{2b} for all voxels jointly.

Let $I_l^1, I_l^2, \dots, I_l^M$ and $I_b^1, I_b^2, \dots, I_b^M$ be the initial signal intensities of lesion and background, respectively, for each of the M voxels within the lesion's ROI. Let $s^1(t_j), s^2(t_j), \dots, s^M(t_j)$ be the signals from these M voxels at echo time t_j . Under the assumption of homogeneity, we can constrain T_{2l}^m, T_{2b}^m to two global values T_{2l} and T_{2b} within the lesion's ROI. The proposed joint bi-exponential fitting (JBF) algorithm for T_2 estimation can be formulated as:

$$\hat{T}_{2l}, \hat{T}_{2b} = \arg \min_{\bar{T}_{2l}, \bar{T}_{2b}} \min_{I_l^1, \dots, I_l^M, I_b^1, \dots, I_b^M} \left\{ \sum_{j=1}^J \sum_{m=1}^M \| I_l^m e^{-t_j/\bar{T}_{2l}} + I_b^m e^{-t_j/\bar{T}_{2b}} - s_m(t_j) \|_2^2 \right\}. \quad [5]$$

Methods

All algorithms were implemented in Matlab (The Mathworks, Natick, MA, USA). Data were acquired on a 1.5T clinical MRI scanner (GE Signa NV-CV/I, Milwaukee, WI, USA).

Simulations

The Cramér-Rao lower bound (CRLB) analysis (28) was used to simulate the uncertainty of T_2 estimation under various conditions. Sixteen echo points from 8 ms to 128 ms equispaced by 8 ms were used in the simulation. The SNR (defined as the mean signal intensity of all pixels divided by the standard deviation of the complex Gaussian noise in complex image) at $t = 0$ was set to 60 to represent realistic SNR achieved in a clinical acquisition. The complex noise was assumed to follow a zero-mean Gaussian distribution and was added independently to the real and imaginary parts of the k-space data.

A numerical phantom representing a spherical lesion embedded in a background was used for simulations. In the numerical phantom, 16 echo images were generated for echo points equispaced by 8 ms with SNR at $t = 0$ set to 60. The in-plane resolution was 1 mm/pixel and the slice thickness was 8 mm. The lesion was placed at the center of the slice. To make the simulations more realistic small variations of T_{2l} and T_{2b} were introduced for each voxel. The variations followed a zero-mean Gaussian distribution with standard deviations for T_{2l} and T_{2b} of 3 ms and 2 ms, respectively. Independent identically distributed Gaussian noise was added to the echo images. One hundred noise realizations were used in the simulation study.

Physical Phantom

A phantom composed of four NMR tubes (Wilma Labglass, Vineland, NJ) ending in a spherical bulb was used to represent small spherical lesions. The inner diameters of the spherical bulbs were 6 mm, 8 mm, 10 mm, and 13 mm, respectively (the thickness of the

glass is approximately 1 mm). Magnevist (Bayer HealthCare Pharmaceuticals Inc., Germany) solutions with concentrations of 0.15, 0.5 and 1.5 mM were used to mimic the T_2 values of lesions found in vivo. To introduce PVE the tubes were inserted in a background bath of 4 mM Magnevist.

Phantom data were acquired with a single-echo SE pulse sequence starting at TE = 9 ms and with subsequent TE points equispaced by 9 ms. Other parameters were TR = 2 s, receiver bandwidth = ± 31.25 kHz. For each TE point, the acquisition matrix was 128×128 . The field of view (FOV) was set to 12.8 cm to achieve a 1 mm/pixel in-plane resolution. The gold standard T_2 values were obtained using the same imaging sequence and parameters with the background removed (hence no PVE). To avoid the problem caused by Rician noise, absorption mode images were reconstructed by removing the linear phase from the reconstructed phantom images for each TE image independently (25,26). Data were also acquired with a radial FSE pulse sequence (9), with Echo Train Length (ETL) = 16, TE points equispaced by 9 ms, TR = 1.2 s, receiver bandwidth = ± 31.25 kHz. Data were acquired with 256 readouts points and either 256 radial views per TE (60% sampling relative to the Nyquist condition) or 16 views per TE (4% sampling). To minimize the effects of indirect echoes (e.g. stimulated echoes) which result from imperfections in the 180° refocusing pulses mainly due to non-ideal slice profiles, we used the approach proposed by Pell et al (29) where the refocusing slice is 3 times thicker than the excitation slice (measured in full width at half maximum). The area of the crusher gradients on each side of the 180° RF pulse was adjusted to approximately 3 times the area of the refocusing slice gradient.

In vivo data

All *in vivo* acquisitions were performed with Institutional Review Board approval. In vivo data were acquired during breath holding with the radial FSE pulse sequence using a phased-array body coil with ETL=16, TE points equispaced by 9 ms, TR varied between 1.2 s to 1.4 s to accommodate for the subject's ability to perform a breath hold, and receiver bandwidth = ± 31.25 kHz. Chemical shift suppression was used to reduce the signal from fat, and inferior/superior saturation bands were used to reduce the signal from flowing blood in the large abdominal vessels. Data were acquired with 256 readouts points and 16 radial views per TE (4% sampling). In all experiments the excitation slice thickness was 8 mm and the thickness of the refocusing pulse was set to 3 times thicker.

Image reconstruction from highly undersampled data

The TE images from highly undersampled data (4% sampling) were reconstructed using the REconstruction of Principal COmponent coefficient Maps (REPCOM) algorithm (20). REPCOM is a model-based reconstruction where the non-linear T_2 decay model is approximated to a linear combination of principal components to improve the fitting of highly undersampled data. In REPCOM principal component coefficient (PCC) maps are reconstructed from highly undersampled data; the PCC maps are then used to generate images at all acquired TE time points (16 for ETL=16). The PCC maps and TE images reconstructed from REPCOM are real (see Appendix A). The advantage of REPCOM over other reconstruction algorithms used for undersampled data is that it can model decays of

multiple components. REPCOM requires the generation of a training set of T_2 decay curves. The REPCOM reconstruction includes a spatial sparsity penalty term according to the compressed sensing theory. In this work, the training set curves covered T_2 values ranging between 35 ms and 300 ms. The number of principal components used in the reconstruction was set to 3 and the spatial penalty regularization parameter was 0.003. Details of the REPCOM reconstruction regarding its extension to the fitting of multiple components can be found in Appendix A.

Results

The Cramér-Rao lower bound (CRLB) analysis was first used to study the effect of varying the LF on the uncertainty of the fitted parameters. The CRLB provides the lower bound to the standard deviation (SD) for an unbiased estimator and a smaller CRLB generally indicates the potential for more precise estimates. The derivation of the CRLB for the signal model shown in Eq. [5] can be found in Appendix B. Figure 1(a) shows the CRLB results for the lesion T_2 estimate ($\hat{T}_{2l}$) according to the JBF algorithm for two voxels ($M = 2$ in Eq. [5]). In the analysis, T_{2l} was set to 180 ms (representing the T_2 of hemangiomas) and T_{2b} was set to 40 ms (representing the T_2 of the liver parenchyma) for all voxels. Each voxel had a total initial signal intensity $I_0^m = I_l^m + I_b^m = 1$ and the LF for the two voxels was varied independently from 0 to 0.9. As shown, the CRLB of $\hat{T}_{2l}$ is largest when the two voxels have the same LF and decreases as the LF difference between the voxels increases. Figure 1(b) and 1(c) show the CRLB of $\hat{T}_{2l}$ when LF of voxel 1 is fixed to (b) 0.7 and (c) 0.5, with finer steps of LF changes for voxel 2. These results indicate that the variation of LF within voxels with the same T_{2l} and T_{2b} can help reduce the ambiguity of the bi-exponential fit.

Another CRLB analysis was conducted assuming a spherical lesion embedded in a background where the lesion diameter was varied from 4 mm to 15 mm with the lesions centered in the middle of an 8 mm slice. Echo images were first generated from a LF map obtained according to the slice thickness and lesion diameter. Figure 2 shows the CRLB for $\hat{T}_{2l}$ for the JBF algorithm as a function of the lesion diameter. For comparison, the CRLB when there is no LF variation was calculated (by keeping the same number of lesion voxels but with the LF for all voxels set equal to the average LF) and shown in the figure. Although the same total amount of lesion is present in both situations, the spherical lesion distribution yields significantly lower CRLB values. This demonstrates that the LF variation can be employed to improve the accuracy of T_2 estimation.

Figure 3 shows the results of numerical simulations for lesions with various diameters and T_{2l} values (180 ms and 100 ms) representing typical benign (e.g. hemangiomas) and malignant liver lesions. The lesion radius was varied from 5 mm to 15 mm and the lesion was centered in the middle of an 8 mm slice of a background with mean $T_{2b} = 40$ ms (representing the liver parenchyma). The figure shows plots of $\hat{T}_{2l}$ vs. lesion diameter according for the VBF, RF, and JBF algorithms. It can be observed that in general, the VBF algorithm suffers from large biases (up to 20% dependent on the lesion diameter) and large uncertainty. The RF algorithm has smaller biases but still large uncertainty. In fact, some of

the error bars in Figure 3 for the RF algorithm are well out of the range of the plots and are not shown. Compared to the other two algorithms, JBF has significantly smaller standard deviations and less biased means, especially for lesion with diameters smaller than 10 mm (10 pixels). When $T_{2l}/T_{2b} < 2$ (Figure 3b), the uncertainty of the RF algorithm makes the estimate of no practical use. In Figure 3b, the standard deviations of RF estimates are all larger than 7 ms which is consistent with the observations in (15).

We also looked at the effect of the lesion and background T_2 values on parameter estimation. Figure 4 shows the %error in $\hat{T}_{2l}$ as a function of the mean lesion T_2 for a simulated lesion (10 mm in diameter) with two different backgrounds (mean $T_{2b} = 40$ ms and 60 ms). Again, VBF and RF have larger biases and uncertainties than JBF. For RF many of the standard deviations are too large to be shown in the figure. The RF estimator does poorly when the ratio T_{2l}/T_{2b} is small, and starts to improve when $T_{2l}/T_{2b} > 2$. When $T_{2l} = 70$ ms with $T_{2b} = 40$ ms, the standard deviations of the RF estimates are all larger than 180 ms; when $T_{2l} = 150$ ms with $T_{2b} = 60$ ms, the standard deviations of the RF estimates are larger than 120 ms. For the VBF estimator, the bias is almost always greater than 15%, while the % error of its estimates are not as sensitive to T_{2l} changes as the RF estimator. JBF always produces the estimates with the smallest bias and standard deviation; the standard deviation of the JBF estimator becomes large only when T_{2l} is the same as, or close to, T_{2b} , which is expected since the T_2 for the two water pools become undistinguishable. The error comes from the instability of the fitting when a single exponential decay is fitted to a bi-exponential model. In practice, this situation can be identified during the fitting process (by the significantly smaller I_0 of that component or two estimated components with nearly the same T_2) and a single exponential model fitting should be used.

The previous analysis is based on using a tight ROI (an ROI which consist only of voxels containing the lesion). However, in real life situations drawing a tight ROI around a small lesion may be difficult. Under the assumption that the background voxels next to the lesion's ROI have the same T_{2b} as the background voxels within the ROI, it should be possible to obtain accurate $\hat{T}_{2l}$ even if the ROI is not tightly defined. Thus, an expanded ROI was constructed by including all immediate neighboring voxels of the tight ROI. Figure 5 shows the performances of the three algorithms with tight and expanded ROIs. The VBF estimates varied greatly when the expanded ROI was used instead of a tight ROI. The error bars of the RF algorithm overlap between the two ROIs but the variations of the bias between the two ROIs can be larger than 10% even for diameter = 10 mm. For the JBF algorithm there is a better agreement of T_2 estimation between the two ROIs. The difference of the means obtained by the tight and expanded ROIs decreases from 5% to <1% as the diameter increases from 5 mm to 15 mm. Starting from 7 mm, the difference is less than 2%. This demonstrates that the JBF algorithm is more robust to errors in ROI drawing.

Results obtained with a physical phantom (composed of 4 NMR tubes with spherical bulbs with various Magnevist concentrations embedded in a background with a different concentration) using a single spin-echo pulse sequence for T_2 mapping are summarized in Table 1. Images corresponding to 16 equispaced TE points were used (TE = 9, 18, ..., 144 ms). The table compares the % errors in $\hat{T}_{2l}$ obtained by the VBF, RF, and JBF algorithms

with respect to the gold standard (tubes without the background). In general, it can be observed that the % error in $\hat{T}_{2l}$ estimated by VBF and RF could be high and there are significant differences between the tight and expanded ROIs. The difference between the tight and expanded ROIs can be interpreted as a measure of inter-observer variation due to the fact that ROI drawing varies from observer to observer. The difference in $\hat{T}_{2l}$ between the tight and expanded ROI can be up to 78.5% for VBF. RF is less dependent on the ROI and the difference in $\hat{T}_{2l}$ between the two ROIs is under 25%. In the cases highlighted by the asterisk RF estimated a second component with a very long T_2 but low I_0 , thus failing to recognize the real second component from the decay curves. For the same phantom data, VBF recognized two components but the T_2 estimates of the background were significantly different than the gold standard. In general JBF provides better estimates across the different phantom sizes and T_2 values and results show that the algorithm is insensitive to ROI drawing; the largest observed variation between ROIs is 1%.

Table 1 demonstrated that JBF can obtain accurate lesion T_2 values from fully sampled spin-echo data. To assess the utility of the technique for breath hold applications (e.g., abdominal T_2 mapping) we evaluated JBF with data acquired with a radial FSE method developed for fast T_2 mapping (9). Data were acquired on the physical phantom to yield 16 highly undersampled TE time points (16 radial lines per TE with each radial line containing 256 samples) to mimic a breath hold acquisition for T_2 mapping. To reduce undersampling artifacts in the TE images, data were reconstructed using the principal component-based algorithm REPCOM, previously published by our group (20). The TE images obtained from the REPCOM reconstruction have high spatial resolution so that small structures can be resolved. These images were used in the JBF algorithm. As shown in Table 2, the $\hat{T}_{2l}$ obtained by JBF from highly undersampled data are similar to the gold standard. For comparison we are including in the table data acquired with a higher degree of sampling (256 radial lines per TE with each radial line containing 256 samples) and using a regular filtered back-projection reconstruction to show that the results are similar to the highly undersampled data. We are also including the $\hat{T}_{2l}$ from highly undersampled data with REPCOM but assuming a mono-exponential decay to show that $\hat{T}_{2l}$ values are increasingly underestimated as the diameter of the bulb decreases due to PVE.

We also acquired radial FSE data on three volunteers with known small liver hemangiomas. Sixteen highly undersampled TE data sets (16 radial lines per TE with each radial line containing 256 samples) were acquired in a single breath hold and reconstructed with REPCOM. T_2 maps were obtained from either JBF or using conventional single exponential fit where PVE is ignored. $\hat{T}_{2l}$ are shown in Figure 6 for the lesions highlighted with an arrow for both a tight and an expanded ROI. When a single exponential fit is used, the $\hat{T}_{2l}$ are shorter than expected T_2 values for benign lesions (based on published work on larger lesions (9)); the $\hat{T}_{2l}$ fall within the range of malignancies (false positive). This is because the PVE of the background is not taken into consideration. With JBF $\hat{T}_{2l}$ are within the range of benign lesions (true negative). Note that with JBF both the expanded and tight ROI's yield

similar values whereas when a single exponential is used the expanded ROI's have lower T_2 's due to the partial volume from the liver parenchyma.

In the experiments above we used an 8 mm thick slice which is a slice thickness typically used in vivo for abdominal imaging. In practice it is possible to tailor the slice thickness to the diameter of a particular lesion for improved results. The effect of slice thickness in terms of lesion diameter is illustrated in Figure 7 using the CRLB analysis. Since the SNR increases with slice thickness, the SNR in the simulations was set to be proportional to the slice thickness with the SNR for an 8-mm thick slice set to 60. T_{2l} and T_{2b} in the simulations were 69 ms and 40 ms, respectively. From the data in the figure, it can be concluded that for a specific lesion diameter the lower CRLB value is achieved when the slice thickness is almost the same as the lesion diameter (i.e., the thinnest slice needed to cover the entire lesion).

Discussion

Partial volume affects the qualitative and quantitative interpretation of images and in the case of small lesion characterization it has been described as the cause of lesion misclassification (6, 7). When using a quantitative approach for lesion classification PVE can be incorporated into the signal model describing the underlying contrast mechanism; for T_2 estimation involving two components this requires a bi-exponential fitting. Because parameter fitting based on a bi-exponential model is subject to ambiguity when noise is present, fitting each voxel independently as it is performed in the VBF algorithm, suffers from significant biases and uncertainty which can only be reduced by improving SNR and/or increasing the number of measurements to remove the ambiguity and resolve the two components. The RF approach, proposed to improve SNR by averaging the signal intensities over all voxels within an ROI prior to fitting, yields T_2 estimates with less biases compared to VBF but with high standard deviations. In the RF approach all voxels within the lesion are constrained to have the same T_{2l} and T_{2b} but the LF variation is ignored. In the JBF approach we take advantage of the variation in LF to reduce the ambiguity of the double exponential fit. As demonstrated above JBF yields better estimates than the VBF and RF algorithms. Compared to the latter, JBF provides estimates of the signal intensities for each tissue and for each voxel (I_l^m, I_b^m), which can be useful for other applications such as brain volume calculations. Although VBF also has the ability to provide this information, the algorithm suffers from large uncertainty and bias which makes VBF challenging to use in practice. The large estimation errors in VBF may be coming from voxels with small LF where the ambiguity of a bi-exponential system is more pronounced. JBF is able to reduce the ambiguity by enforcing the joint T_2 fitting for all voxels in the ROI.

We have also shown that JBF is more robust to ROI drawing errors and that T_{2l} estimates of a tight and expanded ROI are similar. This is not the case with the VBF or RF algorithms where the T_{2l} estimates of the expanded ROIs are affected by the T_2 of the background. This is important for small lesion classification since in practice it is difficult to define a tight ROI containing the lesion. ROI drawing has been associated with errors in small lesion classification due to inter-observer variability (30).

Because lesion classification in the abdominal cavity requires a fast imaging method we combined JBF with a method based on the acquisition of highly undersampled radial FSE data and a model-based algorithm (REPCOM) that can incorporate multiple components in the signal model used for T_2 estimation. T_2 mapping using highly undersampled radial FSE data can be performed from data acquired in a single breath hold and has been demonstrated in the context of lesion classification (9) but not in conjunction with PVE correction. We have shown that JBF applied to TE images reconstructed from radial FSE data with REPCOM can successfully estimate T_2 of small lesions in the presence of partial volume. Because radial FSE combined with REPCOM provides TE data sets with high temporal and spatial resolution (16 TE time points with in plane resolution of $\sim 1.2\text{--}1.5$ mm) from data acquired in a single breath hold the method is ideal for the classification of abdominal lesions. The method can have a significant impact in the early diagnosis of small liver malignancies by differentiating them from the more common benign lesions: cyst and hemangiomas. The early characterization of lesions will eliminate unnecessary follow up sessions and will prompt treatment when needed which in turn may result in longer survival in patients responding to therapy.

The FSE method used for fast imaging is based on echoes generated by multiple 180° refocusing pulses which give rise to indirect echoes that can confound the bi-exponential fitting. Indirect echoes are caused by the imperfect nature of the refocusing pulses due primarily to non-ideal slice profiles. In this work we reduce the effect of these secondary echoes by using a refocusing slice, which is thicker than the excitation slice. As shown by Pell et al (29), this approach suppresses indirect echoes by improving the slice profile of the refocusing pulses. Recently, approaches that incorporate the effects of indirect echoes into the signal model have been proposed for accurate T_2 estimation (31, 32); the combination of these methods with the JBF approach will be the subject of future work.

In this work, we used absorption mode TE images instead of the most commonly used magnitude images. In absorption mode (or complex) images the noise follows a Gaussian distribution whereas in magnitude images the noise distribution is Rician. The latter leads to overestimation of T_2 values because Rician noise behaves like a component with infinite T_2 . The amount of overestimation depends on SNR and other imaging parameters including ETL. Only when the SNR is high for all TEs it is possible to use magnitude images without overestimating T_2 since it has been shown that the noise distribution can be approximated to be Gaussian (27). A better approach when the noise is known to follow a Rician distribution is to perform maximum-likelihood fitting instead of least square fitting. In fact, least square is a special case of maximum-likelihood when the noise is Gaussian.

In this study we investigated lesions varying from 6 mm to 15 mm in diameter embedded in a 8 mm thick slice, which is a typical slice thickness used in abdominal imaging. As shown using the CRLB analysis it is better to have the thinnest slice that contains most of the lesion. In breath hold imaging, however, it would be beneficial to use a slice slightly thicker than the lesion due to potential patient and/or organ movement. Thus, in a clinical imaging situation it would be advisable to conduct a prior scan to assess the size of the lesion and adjust the slice thickness accordingly.

The JBF algorithm relies on the assumption that T_{2l} and T_{2b} are the same for all voxels within the lesion's ROI and that the signal for the lesion and background follow a single exponential decay. This assumption is reasonable for hemangiomas and cysts as well as small malignant tumors, but it may not hold as malignancies become large and necrosis develops. In fact, it has been shown that the signal within the ROI of larger tumors exhibit a multi-exponential T_2 decay due to necrosis (33). Necrosis is favored in larger tumors when the core tends to die due to the lack of nutrients and other mechanisms. Our work is focused on very small lesions where necrosis is less likely to be a source of error in lesion classification based on T_2 estimation. For lesions (or background tissue) where the signal model within the ROI cannot be adequately represented by a single exponential, Eq. [5] will have to be adapted by incorporating an extra term. The proposed joint fitting approach can be extended to a tri-exponential signal model but more data and/or different a priori information may be required for accurate fitting.

The JBF algorithm applied here for the classification of small liver lesions can be extended to other parametric imaging methods based on bi-exponential fitting. Diffusion-weighted MRI, for instance, has been shown to be comparable to T_2 -weighted imaging for the characterization of liver lesions (34). However, PVE have been identified as the main problem with lesion classification when a mono-exponential approach is used to model the signal decay (35). In this work we focused on lesion T_2 estimation by utilizing the LF variation within the ROI since LF variation is naturally present for small lesions, the approach can be applied to the bi-exponential fitting of homogeneous tissue if the variation of LF can be introduced by exploiting the differences in MR characteristics between components (such as T_1 , chemical shift, etc).

Conclusions

In this work we proposed a novel algorithm to correct partial volume effects for lesion T_2 estimation. The algorithm reduces the uncertainty of T_2 estimates by exploiting the LF variation, which is naturally present in ROIs containing small lesions. We demonstrated that T_2 estimation of small lesions using the proposed joint bi-exponential fitting algorithm was considerably better than estimation with the conventional region-fitting (RF) and voxel-wise fitting (VBF) approaches. We also demonstrated that the JBF algorithm can be combined with images reconstructed from highly undersampled radial FSE data for T_2 estimation with partial volume correction from data acquired in a breath hold. The combination of these two methods should enable the improved characterization of small abdominal lesions in vivo.

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Appendix A. Properties of REPCOM

REPCOM is described in detail in ref (20). In this appendix, we provide details of the REPCOM reconstruction pertaining to the JBF algorithm.

For simplicity, if we first consider the T_2 decay to follow a single exponential, the signal s_j at the j^{th} TE (t_j , $j = 1, 2, \dots, J$) can be written as:

$$s_j = I \cdot e^{-t_j/T_2}, \quad [\text{A.1}]$$

where I is the signal intensity at $t = 0$, J is the number of TE points. Using principal component (PC) decomposition, Eq. [A.1] can be approximated as:

$$s_j = \sum_{v=1}^V C_v B_v^j, \quad [\text{A.2}]$$

where C_v is the coefficient for the v^{th} PC B_v . We have shown that the number of PCs can be less than ETL ($V \leq \text{ETL}$). The PCs are obtained from a training set designed for the expected T_2 values. Since the signal model in [A.1] is real, both C_v and B_v are real.

The algorithm to reconstruct the coefficient maps ($\mathbf{C}$) can be written as:

$$\mathbf{C} = \arg \min_{\mathbf{C}} \left\{ \sum_{l=1}^{\# \text{coils}} \sum_{j=1}^J \|FT_j(\mathbf{S}_l \mathbf{C} \hat{\mathbf{B}}_j^T) - \mathbf{K}_j\|^2 + \sum_i \lambda_i P_i(\mathbf{C}) \right\}, \quad [\text{A.3}]$$

where $\mathbf{C}$ is a $(N_x \times N_y) \times V$ matrix of PC coefficients (N_x, N_y are the dimensions of the TE images), FT_j and $\mathbf{K}_j$ are respectively the Fourier transform and measured data for all k-space locations acquired at echo time t_j , $\hat{\mathbf{B}}_j$ is the j^{th} row of the truncated PC matrix $\hat{\mathbf{B}}$ of dimension $V \times J$. For multi-coil acquisitions we include $\mathbf{S}_l$, the complex coil sensitivity map for coil l . λ_i and P_i are regularization functions and the corresponding penalties. In this work, sparsity in the Wavelet transform domain and total variation penalties were used.

The complex coil sensitivity maps $\mathbf{S}_l$ are obtained as follows: An image is reconstructed from all TE data for each coil. As sum-of-squares image is formed by combining images from all coils. Each coil image is divided by the sum-of-squares image to obtain $\mathbf{S}_l$ which consists of the object phase, phase and magnitude of the coil sensitivity map. Since the object phase is included in $\mathbf{S}_l$ and the PCs $\hat{\mathbf{B}}_j$ are real, the PC coefficients in $\mathbf{C}$ are also real. Once the PC coefficients $\mathbf{C}$ are determined using [A.3], the TE images can be reconstructed using $\hat{\mathbf{B}}_j$. Since both $\mathbf{C}$ and $\hat{\mathbf{B}}_j$ are real, the resulting TE images are real.

When two components are present in a voxel, Eq. [A.1] is replaced by a bi-exponential function:

$$s_j = I_l \cdot e^{-t_j/T_{2l}} + I_b \cdot e^{-t_j/T_{2b}}, \quad [\text{A.4}]$$

where I_l, I_b, T_{2l}, T_{2b} are the corresponding initial signal intensities and T_2 values of the two components. The bi-exponential decay can still be approximated by Eq. [A.2]:

$$I_l \cdot e^{-t_j/T_{2l}} \sim \sum_{v=1}^V C_v^l B_v^j, \quad [\text{A.5}]$$

$$I_b \cdot e^{-t_j/T_{2b}} \sim \sum_{v=1}^V C_v^b B_v^j, \quad [\text{A.6}]$$

and

$$s_j \sim \sum_{v=1}^V C_v^l B_v^j + \sum_{v=1}^V C_v^b B_v^j = \sum_{v=1}^V (C_v^l + C_v^b) B_v^j = \sum_{v=1}^V C_v' B_v^j. \quad [\text{A.7}]$$

As a result, the reconstructed signal decay curves of all pixels ($\mathbf{CB}^T$) obtained via Eq. [A.2] preserves the double exponential nature of the decay signal when there are two components in the voxel.

Appendix B – Cramér-Rao lower bound of bi-exponential least square fitting

In Eq. [5], the signal equation is

$$s(t) = I_l e^{-t/T_{2l}} + I_b e^{-t/T_{2b}} + \varepsilon(t), \quad [\text{B.1}]$$

Under the assumption that the noise is independent identically distributed normal noise, the observed data at echo time t_j can be formulated as:

$$\mathbf{s}_c(t_j) = \mathbf{s}(t_j) + \varepsilon(t_j), \quad j=1, 2, \dots, J, \quad [\text{B.2}]$$

where $\varepsilon(t_j)$ is a vector with each entry drawn from $N(0, \sigma^2)$ and

$\mathbf{s}_c(t_j) = (s_c^1(t_j), s_c^2(t_j), \dots, s_c^M(t_j))^T$. $\text{SNR}_{t=0}$ is determined by σ^2 which is determined by the data noise properties.

Define a parameter vector $\boldsymbol{\theta}$ such that $\theta_1 = T_{2l}$, $\theta_2 = T_{2b}$, $\theta_{2k+1} = I_l^k$, $\theta_{2k+2} = I_b^k$, $k = 1, 2, \dots, M$. The probability distribution of the signal can be expressed as:

$$\Pr(\mathbf{s}_c(t_1), \mathbf{s}_c(t_2), \dots, \mathbf{s}_c(t_J) | \boldsymbol{\theta}) = \prod_{m=1}^M \prod_{j=1}^J \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{[\mathbf{s}_c^m(t_j) - I_l^m e^{-t_j/T_{2l}} - I_b^m e^{-t_j/T_{2b}}]^2}{2\sigma^2}}. \quad [\text{B.3}]$$

The Fisher information matrix $\mathbf{F}$ is then defined as (28):

$$F_{u,v} = - \left\langle \frac{\partial^2}{\partial \theta_u \partial \theta_v} \ln \Pr(\mathbf{s}_c(t_1), \mathbf{s}_c(t_2), \dots, \mathbf{s}_c(t_J) | \boldsymbol{\theta}) \right\rangle. \quad [\text{B.4}]$$

The expectation in Eq. [B.4] is for the given value of data.

Inserting Eq. [B.3] into Eq. [A.4] we obtain:

$$F_{1,1} = \frac{1}{\sigma^2 T_{2l}^4} \sum_{m=1}^M \sum_{j=1}^J I_l^{m2} t_j^2 e^{-2t_j/T_{2l}} \quad [\text{B.5}]$$

$$F_{2,2} = \frac{1}{\sigma^2 T_{2b}^4} \sum_{m=1}^M \sum_{j=1}^J I_b^{m2} t_j^2 e^{-2t_j/T_{2b}} \quad [\text{B.6}]$$

$$F_{2k+1,2k+1} = \frac{1}{\sigma^2} \sum_{j=1}^J e^{-2t_j/T_{2l}} \quad [\text{B.7}]$$

$$F_{2k+2,2k+2} = \frac{1}{\sigma^2} \sum_{j=1}^J e^{-2t_j/T_{2b}} \quad [\text{B.8}]$$

$$F_{1,2} = F_{2,1} = \frac{1}{\sigma^2 T_{2b}^2 T_{2l}^2} \sum_{m=1}^M \sum_{j=1}^J I_b^m I_l^m t_j^2 e^{-t_j/T_{2b}} e^{-t_j/T_{2l}} \quad [\text{B.9}]$$

$$F_{1,2k+1} = F_{2k+1,1} = \frac{I_l^m}{\sigma^2 T_{2l}^2} \sum_{j=1}^J t_j e^{-2t_j/T_{2l}} \quad [\text{B.10}]$$

$$F_{1,2k+2} = F_{2k+2,1} = \frac{I_l^m}{\sigma^2 T_{2l}^2} \sum_{j=1}^J t_j e^{-t_j/T_{2l}} e^{-t_j/T_{2b}} \quad [\text{B.11}]$$

$$F_{2,2k+1} = F_{2k+1,2} = \frac{I_b^m}{\sigma^2 T_{2b}^2} \sum_{j=1}^J t_j e^{-2t_j/T_{2b}} \quad [\text{B.12}]$$

$$F_{2,2k+2} = F_{2k+2,2} = \frac{I_b^m}{\sigma^2 T_{2b}^2} \sum_{j=1}^J t_j e^{-t_j/T_{2l}} e^{-t_j/T_{2b}} \quad [\text{B.13}]$$

$$F_{2k+1,2k+2} = F_{2k+2,2k+1} = \frac{1}{\sigma^2} \sum_{j=1}^J e^{-t_j/T_{2l}} e^{-t_j/T_{2b}} \quad [\text{B.14}]$$

where $k = 1, 2, \dots, J-1$. All other entries of $\mathbf{F}$ are 0.

CRLB for the unbiased estimator of θ_k ($\hat{\theta}_k$) can then be obtained:

$$SD(\hat{\theta}_k - \theta_k) \geq \sqrt{[\mathbf{F}^{-1}]_{k,k}}. \quad [\text{B.15}]$$

Hence,

$$SD(\hat{T}_{2l} - \bar{T}_{2l}) \geq \sqrt{[\mathbf{F}^{-1}]_{1,1}}. \quad [\text{B.16}]$$

Figure 1.

The CRLB for the estimate of lesion T_2 ($T_2(\hat{T}_{2l})$) for two voxels with varying LF . (a) The CRLB of $\hat{T}_{2l}$ when the LF of the two voxels varies independently from 0 to 0.9. The CRLB is not applicable to the blocks labeled “N/A” since there is no partial volume. (b) and (c) are plots of the CRLB of $\hat{T}_{2l}$ when the LF of voxel “1” is fixed to 0.5 and 0.7 respectively, while the LF of voxel “2” varies from 0 to 1. Some of the parameters used in the simulation are: $T_{2l} = 180$ ms, $T_{2b} = 40$ ms, SNR at $t=0$ was set to 60, 16 echo points equispaced by 8 ms with the first point = 8 ms.

Figure 2.

The CRLB of $\hat{T}_{2l}$ for lesions with varying lesion diameter. Results are shown for spherical lesions, where the LF was calculated according to the slice thickness and lesion diameter, and for the case where a uniform LF was used for all voxels and set equal to the mean LF of the corresponding spherical lesion. Some of the parameters used in the simulation are: $T_{2l} = 180$ ms, $T_{2b} = 40$ ms, SNR at $t = 0$ was set to 60, 16 echo points equispaced by 8ms with the first point = 8 ms. The lesions were centered in the middle of an 8 mm thick slice.

Figure 3.

Error bar plots of the estimated means and standard deviations of lesion T_2 vs. the diameter of lesions for the VBF, RF and JBF algorithms. Out of range error bars are not shown. T_{2l} and T_{2b} follow zero-mean Gaussian distribution with standard deviations of 3 ms and 2 ms, respectively. T_{2l} was set to (a) 180 ms and (b) 100 ms and $T_{2b} = 40$ ms. Weighted averaging was used for VBF. The simulation was performed with 16 echo points equispaced by 8ms with the first point = 8 ms. The lesions were centered in the middle of an 8 mm thick slice. The SNR at $t = 0$ was set to 60 and the in-plane resolution was 1mm/pixel. One hundred noise realizations were used in the simulations.

Figure 4.

Error in T_2 estimation of a lesion centered at the middle of the 8 mm slice with varying mean lesion T_2 (T_{2l}). Out of range error bars by RF algorithm are not shown. $T_{2b} =$ (top) 40 ms and (bottom) 60 ms, the diameter of the lesion is 10 mm. The 16 echo points are from 8 ms to 128 ms equispaced by 8 ms. The SNR at $t = 0$ is set to 60. The in-plane resolution is 1mm/pixel.

Figure 5.

Error bars of $\hat{T}_{2l}$ obtained by (left) VBF, (center) RF and (right) JBF with tight and expanded ROI. Out of range RF error bars are not shown.

Figure 6.

Abdominal images of three subjects with small focal liver lesions and the corresponding T_{2l} estimates for a tight and expanded ROI according to the JBF reconstruction, which takes into account PVE. For comparison the T_{2l} estimates from fitting the signal decay of each pixel to a single exponential (where no PVE are taken into account) are given. Data were acquired with a radial FSE method in a single breath hold with 256 readout points along the radial direction and 256 radial views. Other parameters were ETL=16 with, echo spacing= 9 ms, and TR = (left) 1.2 s, (middle) 1.3 s, (right) 1.4 s were adjusted according to each subject's breath hold capability. The FOV was (left, middle) $38 \times 38 \text{ cm}^2$ and (right) $36 \times 36 \text{ cm}^2$, thus the lesion diameters from left to right were 16 mm, 12 mm and 8 mm. The excitation slice thickness was 8 mm.

Figure 7.

The CRLB results for various slice thicknesses. $T_{2l} = 69$ ms, $T_{2b} = 40$ ms, ETL = 16, echo spacing = 8 ms, in-slice resolution is 1 mm/pixel.

Table 1

The % error of T_{2f} estimates for the physical phantom according to the VBF, RF, and JBF algorithms for tight and expanded ROIs. Data were acquired with a single spin-echo pulse sequence, where 16 TE points were measured. The SNR of the first TE image is estimated to be about 100.

Inner diameter		6 mm		8 mm		10 mm		13 mm	
ROI size		tight	expanded	tight	expanded	tight	expanded	tight	expanded
Gold standard 68.7 ms	VBF	-2.0	-9.5	-1.9	-6.6	4.4	-3.5	4.9	-6.6
	RF	-24.3 *	-31.1 *	-40.9 *	-25.8 *	-11.1 *	-22.9 *	-8.7 *	-12.7 *
	JBF	-7.9	-8.0	-2.9	-2.9	2.0	2.0	-0.1	-0.1
Gold standard 92.8 ms	VBF	8.3	-23.1	15.2	-14.0	18.5	-0.3	24.2	-9.8
	RF	-12.0	3.6	-4.2	-2.7	1.4	3.6	8.6	6.4
	JBF	-2.6	-2.6	-1.0	-1.0	0.8	0.9	2.4	2.5
Gold standard 176.2 ms	VBF	61.0	-17.5	36.7	-11.1	23.0	-18.9	38.4	3.0
	RF	55.7	78.5	-3.7	19.1	-10.3	-6.4	3.5	3.9
	JBF	-5.7	-5.3	-4.9	-4.9	-3.5	-3.1	2.4	2.5

* In addition to the value reported in the table, the RF estimator yielded a second component with very long T_2 and I_0 close to 0, which shows that the algorithm failed to distinguish the two real components.

Table 2

The T_{2l} estimates from undersampled phantom data.

		$\hat{T}_{2l}$ (ms) of spherical phantom			
		6 mm in diameter	8 mm in diameter	10 mm in diameter	13 mm in diameter
Gold standard $T_2 = 69.0$ ms	REPCOM – JBF	64.7	65.0	69.7	71.0
	Well-sampled data - JBF	64.5	66.8	70.3	69.1
	REPCOM – Single exponential	49.3	52.5	55.3	59.0
Gold standard $T_2 = 179.8$ ms	REPCOM – JBF	166.0	164.5	177.4	183.9
	Well-sampled data - JBF	168.0	168.8	172.7	184.1
	REPCOM – Single exponential	68.1	96.6	111.9	122.7