Published in final edited form as:

NMR Biomed. 2010 January ; 23(1): 97–104. doi:10.1002/nbm.1440.

Rapid simultaneous acquisition of T(1) and T(2) mapping images using multishot double spin-echo EPI and automated variations of TR and TE (ms-DSEPI-T12)

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Abstract

A rapid method of simultaneous T_1 and T_2 measurement is presented which uses a segmented echo-planar readout with varying repetition times (TR) and echo times (TE). This method is useful in T_1 mapping for analysis of dynamic contrast enhanced MRI (DCE-MRI), where T_1 can be used to estimate contrast concentration. In the application of this method to dynamic imaging, the equilibrium magnetization is measured on pre-contrast images and incorporated into post-contrast T_1 calculations for improved accuracy. Simultaneous T_2 measurement allows correction of T_2 effects in the T_1 map which may occur at high contrast concentrations, and is performed without significant imaging time penalty. Phantom and *in vivo* results show the usefulness of this technique for analysis of contrast enhancement kinetics. Accurate rapid contrast concentration measurement may be useful for analyzing the distribution and kinetics of contrast agents or labeled pharmaceuticals.

Keywords

T_1/T_2 maps; T_1 map; T_2 map; rapid T_1/T_2 maps; simultaneous T_1/T_2 maps; multishot EPI; dynamic contrast MRI; DCE MRI

INTRODUCTIONS

Dynamic contrast enhanced MRI (DCE-MRI) has shown promise in detection and characterization of tumors (1–4). DCE-MRI may provide information about important perfusion parameters such as vessel permeability (5), microvessel density, and washout which may allow more accurate characterization of benign versus malignant neoplasms. Change in relaxation rate ΔR_1 ($R_1 = 1/T_1$) is linearly related to Gd-DTPA concentration over a range of concentrations, and can be used to estimate Gd-DTPA concentration (6).

Pharmacokinetic information can be obtained from the time-variation of $\Delta R_1(\mathbf{r})$. Change in T_2 relaxation time is not usually measured in DCE MRI, because of the extended acquisition time which conventional T_2 measurement would require. However, the change of the concentration of the gadolinium based contrast agent causes the changes in both T_1 and T_2 relaxation times (7). The change in T_2 may be negligible at low concentration, but at higher concentration T_2 shortening may introduce error in the measurement of T_1 . This effect may become significant in tumors in which contrast achieves high concentrations (8,9).

Spin echo or gradient recalled echo sequences with either inversion-recovery (IR) or saturation-recovery (SR) have been used for accurate T_1 and T_2 measurements. Their use has been limited to non-dynamic imaging because of their long imaging times. Several alternative methods for T_1 mapping have been presented including 2D singleshot-EPI (2D ss-EPI) and variants (Look-Locker EPI, IR-EPI) which achieve better simultaneous spatial and temporal resolution (10,11). However, the spatial resolution using these rapid imaging methods is limited by susceptibility artifact (12,13). A multishot spin-echo EPI (ms-SEPI) sequence may be used to trade off imaging speed with severity of susceptibility artifact. Gradient-echo imaging with flip angle variation, may be used with reasonable temporal and spatial resolutions (14). However, T_1 estimates obtained by this method are sensitive to RF inhomogeneity.

We present a rapid MR imaging method to simultaneously measure T_1 and T_2 using a ms-SEPI sequence with automated variation of TR and TE (15,16). Ms-SEPI allows flexible adjustment of echo train length to compensate for differing severity of susceptibility artifact when imaging different areas of the body. Simultaneous measurement of T_1 and T_2 allows correction of T_2 effects on T_1 measurement. Our method is able to accurately measure T_1 with high spatial and temporal resolution, making it applicable to dynamic measurement of contrast concentration for pharmacokinetic studies.

MATERIALS AND METHODS

Pulse sequence description

A multishot spin-echo EPI (ms-SEPI) sequence was used to implement the acquisition of the second echo and the automatic variations of the TR and TE on a Siemens 3T Trio clinical imaging system (Siemens Medical Solution, Erlangen, Germany). The schematic RF diagram is shown in Fig. 1. The sequence begins with a presaturation pulse, followed by a saturation recovery delay interval τ . A 90–180° RF pulse pair is then played and a spin echo is acquired with echo-planar gradients scanning a portion of the k-space of a single slice, at minimum echo time. Then a second 180° is applied at a variable second echo time TE_i , and the same portion of k-space is reacquired. The sequence is repeated with no change in sequence timing to segmentally fill in the k-space for two complete images. This procedure is repeated with different saturation recovery times τ_i to create additional images. Each of the first-echo images supplies a time point along the T_1 recovery curve for estimation of T_1 . The echo time TE_i of the second spin echo is incremented at the same time that the saturation recovery time is incremented. This creates a series of second echo images with differing T_2 weighting from which T_2 can be estimated. After a complete set of first- and second-echo images are obtained with varying recovery times τ_i and second echo times TE_i , the entire process is repeated to provide T_1 and T_2 estimates at successive time points, to allow analysis of enhancement kinetics.

The initial saturation pulse was performed with an adiabatic excitation followed by a gradient dephasing lobe. Better saturation may be obtained with a series of multiple saturation pulses and dephasing gradient lobes if needed.

Assuming that the longitudinal magnetization is completely destroyed by the saturation pulses at the beginning of the sequence, the signal equations for the first and second echoes for a given saturation recovery time τ_i and second echo time TE_i are:

$$\text{first echo: } S_1(\vec{r}, \tau_i, TE_o) = S_o(\vec{r}) \cdot \left(1 - e^{-\frac{\tau_i}{T_1(\vec{r})}}\right) \cdot e^{-\frac{TE_o}{T_2(\vec{r})}}, \quad (1)$$

$$\text{second echo: } S_2(\vec{r}, \tau_i, TE_i) = S_o(\vec{r}) \cdot \left(1 - e^{-\frac{\tau_i}{T_1(\vec{r})}}\right) \cdot e^{-\frac{TE_i}{T_2(\vec{r})}}. \quad (2)$$

A sequence of first echoes with various saturation times τ_i is used to calculate T_1 , while a sequence of second echoes with various echo times TE_i is used to calculate T_2 . Eqs. (1) and (2) can be written as:

$$S_1(\vec{r}|\tau, TE_o) = S'_o(\vec{r}) \cdot \left(1 - e^{-\frac{\tau_i}{T_1(\vec{r})}}\right), S'_o(\vec{r}) = S_o(\vec{r}) e^{-\frac{TE_o}{T_2(\vec{r})}} \quad (3)$$

$$S_2(\vec{r}|\tau_i, TE_i) = S''_o(\vec{r}) \cdot e^{-\frac{TE_i}{T_2(\vec{r})}}, S''_o(\vec{r}) = S_o(\vec{r}) \left(1 - e^{-\frac{\tau_i}{T_1(\vec{r})}}\right) \quad (4)$$

In the above equations, $S_o(\vec{r})$ represents the equilibrium longitudinal magnetization. The equilibrium signal $S_o(\vec{r})$ at a position $\vec{r}$ does not vary with T_1 and therefore does not change after administration of contrast, but depends on proton density, imaging voxel dimension, magnetic field strength, and temperature (17). $S'_o(\vec{r})$ is the signal intensity that would be obtained at the first echo time TE_o after complete saturation recovery, i.e. for $\tau_i = \infty$. $S'_o(\vec{r})$ is also independent of T_1 and can be measured once during precontrast imaging with a long recovery time τ ($\sim 5T_1$) and then used as a data point in the calculation of T_1 for each subsequent time point in the sequence of dynamic images without being measured again.

$S''_o(\vec{r})$ is the signal intensity that would be obtained for a given saturation recovery time τ_i with no T_2 decay, i.e. for $T_2 = 0$.

Calculation of T_2 using the second echoes

T_2 can be estimated from the sequence of second echoes $S_2(\tau_i, TE_i)$, each of which was obtained at a different echo time TE_i . A first echo $S_1(\tau_i, TE_o)$ can also be included in the points to be fitted for T_2 estimation. Because each second echo was obtained after a different saturation recover time τ_i , the second echo signal S_2 is dependent on T_1 . To remove this dependence, the second echo signal intensity $S_2(\tau_i, TE_i)$ is normalized by the first echo time signal $S_1(\tau_i, TE_o)$ for the same τ_i . T_2 estimation was performed with least-squares fitting of the signal intensity samples to a monoexponential decay.

Calculation of T_1 using the first echoes

The sequence of first echo images $S_2(r, \tau_i, TE_o)$ traces the saturation recovery of longitudinal magnetization at various recovery times τ_i . For dynamic T_1 imaging, a limited number of saturation recovery times are measured, typically three or four, so that T_1 can be estimated in a short time to allow measurement of T_1 at multiple closely spaced time points. More saturation recovery times may be acquired during precontrast imaging. This allows accurate estimation of the fully recovered signal intensity $S'_o(\vec{r})$. This signal intensity does not

change with T_1 shortening after administration of contrast, and can be used as an additional data point for estimation of T_1 at later time points without being measured at these time points. However, $S_o'(\vec{r})$ may change from its precontrast value on postcontrast scans because of the T_2 shortening effect of contrast, causing a variable degree of T_2 decay during the fixed first echo time TE_0 . Because T_2 is being simultaneously measured by our sequence, the effect of altered T_2 on $S_o'(\vec{r})$ can be easily removed.

The calculation of T_1 and T_2 for the acquired data was performed pixel-by-pixel, using custom mapping software developed in IDL (Interactive Data Language, Boulder, CO). The non-linear Levenberg-Marquardt curve-fitting algorithm and an exponentially decaying fit were used to calculate T_1 and T_2 respectively. T_1 , T_2 , and $S_o'(\vec{r})$ of the precontrast data were calculated. For dynamic data, the spin-spin relaxation time T_2 was calculated after removing T_1 recovery effect from the second echo images. Then, this T_2 value was used to eliminate T_2 decay effect from $S_o'(\vec{r})$ that was obtained from the precontrast imaging data.

MR imaging experiments

All MR imaging experiments were performed on a clinical 3 T MRI system (Trio TIM System, Siemens Medical Solution, Erlangen, Germany). To validate the signal normalization process to remove T_1 recovery effect in T_2 measurement data, the ms-EPI T_1 and T_2 mapping sequence was performed on a phantom filled with 0.1 mMol $MnCl_2$ solution, using a transmit/receive head coil. First, the sequence was run with the following schedule of saturation recovery times τ_i : 0.2, 0.25, 0.4, 0.8, 1.4, 2.2, 3.2 and 5.0 s. The first echo time TE_0 was 11.6ms, and the schedule of second echo times was: $TE_i = (15.1 + 10i)$ ms, $i = 1, 2, \dots, 8$. This sequence was then repeated with a fixed saturation recovery time of 5.0 s, with the same schedule of TE_i 's.

To evaluate the performance and accuracy of the new method, the same phantom was used to acquire T_1 measurement data with (1) ms-EPI for T_1 and T_2 , (2) conventional inversion-recovery spin-echo (IR-SE) for T_1 , and (3) conventional turbo-spin-echo (TSE) for T_2 measurements. An echotrain length (ETL) of 7 with 75 % asymmetric sampling was used, which resulted in the actual ETL of 5. The schedule of saturation recovery times for the ms-EPI sequence was: 0.22, 0.46, 0.7, 0.94, 1.33, 1.92, 2.91 and 4.9 s, with $TE_0=10.0$ ms and $TE_i = (12.7 + 10i)$, $i = 1 \sim 8$. The inversion times TI used for the inversion-recovery sequence were 0.1, 0.4, 0.55, 0.6, 0.7, 0.8, 1.5 and 3.0 s with TR 10 s and TE 17 ms. TEs of 12, 23, 35, 47, 59, 70, 83, 94 and 105 ms were used for the TSE sequence with 5 s TR and ETL 9 to acquire T_2 maps. The imaging time for T_1 measurement was 5 min 36 s for ms-EPI measurement, while it was 16 min 39 s for IR-SE. The imaging time of T_2 measurement was 6 min 18 s for the TSE sequence.

A phantom study was performed with three phantoms that were constructed of identical glass bottles with different $MnCl_2$ concentrations of 0.1, 0.3, and 0.6 mMol. Each bottle was filled with the same amount of solution to have equal coil loading. MR imaging was separately performed on each bottle positioned at the center of the head coil, using ms-EPI with saturation recovery times 0.09, 0.16, 0.25, 0.44, 0.73, 1.52, 2.31, 5.9 s and echo times $TE_0=11$ ms, $TE_i = (13 + 10i)$ ms. After imaging the first bottle, the second and third bottles were placed in turn in the same location and separately imaged.

The ms-EPI T_1 and T_2 measuring sequence was used to perform dynamic contrast enhanced T_1 measurement in mice. Female athymic nude mouse were cared for under the guidelines of a protocol approved by the University of Utah Institutional Animal Care and Use Committee. The MDA-MB-231 human breast cancer cell line was purchased from the

American Type Culture Collection (ATCC, Manassas, VA) and cultured in Leibovitz's L-15 medium with 2 mM L-glutamine and 10 % FBS at 37 °C in a humidified atmosphere of 5 % CO₂. The cells were allowed to grow to about 90 % confluence and then resuspended in DMEM medium. The cell number was adjusted to 106 cells/ml, and the cells were mixed with an equal volume of Matrigel (Becton-Dickinson, Franklin Lakes, NJ). The Matrigel mixtures, containing approximately 2×10^5 cells in 0.2 ml, were implanted subcutaneously in the flanks of the mice. Each implantation generated a tumor. Tumor size reached 0.5–1.5 cm in diameter 21 days after cell implantation.

The ms-EPI T_1 and T_2 measuring sequence was applied to acquire dynamic images in the axial plane with echotrain length of 3, imaging matrix 64×28 , inplane spatial resolution 1.0×1.0 mm², and slice thickness 2.0 mm, for 4 slices. A Siemens human wrist coil was used. Precontrast T_1 mapping data was acquired with 8 different saturation recovery times τ_i (0.25, 0.5, 0.75, 1.0, 1.4, 2.2, 3.2, and 5.0 s), first echo TE of 8ms, and second echo times of $TE_i = (9 + 10i)$ ms. Baseline relaxivity $1/T_1$ and the signal $S_o'(\vec{r})$ representing the equilibrium magnetization $M_o(\mathbf{r})$ were calculated. For post-contrast dynamic imaging, TRs of 200, 500, and 750 ms and $TE_0=8$ ms, $TE_i = (4 + 15i)$ ms were used. Slice interleaving was limited by the shortest TR, i.e., 200 ms in the current protocol.

RESULTS & DISCUSSIONS

The plots in Fig. 2 show the signal intensities of the second echoes of the fixed () and the variable (*) recovery times, and after normalization (□) by the signal intensities of the first echoes. The normalized signal intensity values (□) obtained with variable saturation recovery times τ_i match the second echo signal intensities obtained with the constant saturation recovery time of 5 s, demonstrating that the effect of varying saturation recovery time on T_2 estimation has been successfully removed.

The calculated T_1 values across the dotted line in the center of T_1 maps of a fluid phantom in Fig. 3a using ms-EPI and IR-SE are overlaid in Fig. 3b. The mean values of T_1 and T_2 in a region-of-interest at the center of the object were measured as 867.9 ± 34.1 ms and 872.0 ± 5.9 ms using ms-EPI and IR-SE, and 57.6 ± 2.0 ms and 76.1 ± 2.8 ms using ms-EPI and TSE, respectively. T_2 value measured with ms-EPI was 24.3% lower than that measured using TSE. Both methods used a similar range of echotime TE_s, 10 ~ 94 ms for ms-EPI and 12 ~ 105 ms for TSE. T_1 relaxation measured by the two methods was nearly equal, although the variance was somewhat increased in ms-EPI technique, particularly near the edge and outside of the RF coil. This was because the SNR in the source T_1 and T_2 weighted images was significantly reduced in ms-EPI images than in IR-SE images due to difference in imaging time. As in any pulse sequence, SNR decreases with shorter imaging time.

The series of three phantom studies simulates the effect of imaging a single structure with time-varying T_1 . Prescan calibration was performed only for the first bottle and transmitter and receiver gains were held constant for the remaining bottles.

T_2 was estimated for the three bottles as described above. The equilibrium signal $S_o'(\vec{r})$ for the first bottle was measured at long saturation recovery time (5.9 s). This value was then combined with the measured T_2 of each bottle to give a calculated value for the equilibrium value $S_o'(\vec{r})$ for each bottle, which was compared to the actual measured value. There was excellent agreement between the measured equilibrium values $S_o'(\vec{r})$ of the second and third bottles and the values calculated from $S_o'(\vec{r})$ of the first bottle and the T_2 of each

bottle, as shown in Table 1. This result confirms that the equilibrium value $S_o'(\vec{r})$ can be measured once in the pre-contrast phase of a dynamic contrast enhanced imaging experiment and then used to calculate $S_o'(\vec{r})$ for subsequent post-contrast time points, without actually being measured at these later time points. As demonstrated in Fig. 4, T_2 effects of increasing contrast concentration cause marked decrease in the equilibrium signal $S_o'(\vec{r})$ as well as T_1 shortening.

An MR imaging experiment was performed on a fluid phantom to compare the T_1 relaxation times calculated from a data set of 8 well spaced saturation recovery times and a set with three short and one long saturation recovery times, which would represent the precontrast and the dynamic data sets of a dynamic contrast enhanced study. Post-contrast measurement at a limited number of saturation recovery times allows better temporal resolution in the T_1 estimation for dynamic imaging. Shorter saturation recovery times allow shorter TR and therefore faster imaging. The longest saturation recovery time point can be calculated from the precontrast data and the T_2 of the current acquisition, substantially shortening the required imaging time. The measured signal intensities for varying saturation recovery times τ_i are shown in Fig. 5. The solid line represents the T_1 recovery curve fit to all eight data points. The dashed line represents the T_1 recovery curve fit to only the first three data points plus the last data point. The resultant T_1 values were 445.0 ± 2.1 and 440.0 ± 3.1 ms with the full (8 τ_i 's) and the partial (3 measured τ_i 's and 1 calculated from precontrast T_1/T_2 measurements) data sets, respectively. The fractional difference between the resultant T_1 values of two methods was less than 2 %. This experiment shows that the accurate value of T_1 can be measured using only a few short τ_i 's and the semi-empirical $S_o'(\vec{r})$ for rapid dynamic MR imaging.

Phantom studies show excellent agreement in measured T_1 values measured with the current technique and with the much slower inversion recovery technique. T_2 values measured with our technique are lower than those measured with TSE sequences. Refocusing of each echo with an inversion pulse in the TSE method will result in pure T_2 weighting, while the (non-refocused) echo-planar readout of ms-EPI introduces some additional T_2^* weighting. This may account for the lower T_2 estimate obtained by ms-EPI. This effect may be related to echo train length, and may represent a tradeoff between imaging speed and accuracy of T_2 measurement.

The signal recovery plots in Fig. 6 shows the shortening of T_1 values at a point in the tumor periphery indicated by the vertical arrow in Fig. 7 at three time points after administration of contrast agent. The imaging duration for each time point was 15.0 s, during which data was measured for three different saturation recovery times τ_i .

The calculated T_1 and T_2 maps are displayed in Fig. 8 for a central slice, and their values are plotted vs. time in Fig. 8 at selected 9 pixel regions of interest at the tumor periphery, the tumor core, and in muscle. No susceptibility induced distortion was noticeable on our dynamic T_1 measurement MR images. T_2 changes with contrast administration are negligible in this experiment, but a focus of decreased T_2 is seen in the inferior periphery of the tumor, indicated by the purple arrow in Fig. 8. This may be due to the accumulation of the contrast agent with limited washout at that location.

The animal study presented shows little effect of contrast injection on T_2 . This is likely secondary to the low dose of 0.1 mM/kg of contrast agent used in this study. Phantom studies suggest that the T_2 shortening effect on the estimate of T_1 may become significant at higher contrast concentrations, which might be encountered in dynamic tumor imaging.

Phantom and in-vivo studies show the accuracy and speed of the ms-EPI technique for T_1 and T_2 mapping. This method is much faster than conventional inversion-recovery sequences for T_1 mapping, and incurs little additional imaging time penalty for the addition of simultaneous T_2 mapping. Unlike the widely used technique of fast gradient echo imaging with flip angle variation, the T_1 estimates obtained by our method are relatively insensitive to B_1 variation (14,18).

The multi-shot echo planar technique allows flexible tradeoff between imaging time and susceptibility effects such as geometric distortion. Longer echo train lengths lead to decreased imaging time and resulting improvement in time resolution of T_1 measurement, but also cause more severe artifacts from susceptibility. The increased echo trains may also result in underestimation of T_2 .

CONCLUSIONS

We have presented a rapid method of simultaneous T_1 and T_2 mapping which is suitable for high temporal resolution measurement of T_1 for dynamic contrast enhanced MRI. Unlike conventional gradient recalled echo sequences with variable flip angle, this sequence is insensitive to B_1 inhomogeneity. Our method allows simultaneous measurement of T_2 , which allows improved accuracy in T_1 measurement by compensating for T_2 effects. Accurate precontrast T_1 measurement in association with dynamic T_2 measurement also allows more rapid post-contrast T_1 measurement by reducing the number of saturation recovery time points necessary for accurate T_1 recovery curve fitting. Resulting T_1 measurements agree experimentally with results obtained by slower inversion-recovery methods, with a fraction of the imaging time. Preliminary experiments in mice show that this method may be useful in dynamic contrast concentration MR imaging which may depict the distribution and pharmacokinetics of contrast agents or gadolinium-labeled pharmaceuticals.

Acknowledgments

This work was partly supported by NIH Grants R01CA097465 and 1R01EY015181

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Figure 1.

Pulse sequence diagram. τ_i is the saturation recovery time generating the i^{th} point on the T_1 recovery curve for estimation of T_1 . TE_i is the echo time for the second echo, which is incremented as τ is incremented to give a set of second-echo images with varying T_2 weighting for T_2 estimation. Echotrain length after each 180° refocusing pulse is determined based on the desired acquisition speed and tolerated amount of image distortion, with longer echo train lengths giving shorter imaging time but more severe distortion secondary to susceptibility shifts.. Each group of n TR's enclosed within a round bracket represents a complete k-space acquisition, giving an image for a particular recovery time τ_i (at minimum echo time TE_0) and a second image for a particular second-echo echo time TE_n . The series of TR's within the curly bracket is repeated to give T_1 and T_2 maps at different successive time points.

Figure 2. Phantom study validating correction of second echo intensity for varying saturation recovery time. Stars(*) represent uncorrected second echoes, square (□) represent second echoes normalized by first echoes to remove effects of variable saturation recovery times, and diamonds (◇) represent second echoes obtained with constant saturation time of 5 s. Normalization removes the effect of varying saturation recovery, allowing estimation of T_2 from second echoes with varying echo time.

Figure 3.

The profiles of T_1 values measured along a horizontal dotted line on T_1 maps of a phantom acquired with the ms-EPI T_1 and T_2 mapping sequence (dotted line) and IR-SE (solid line). The dotted rectangular box on the T_1 map image (a) indicates the position of the head coil.

Figure 4.

Plots of the measured signal intensities for three concentrations of MnCl_2 solutions. Increasing concentration gives faster T_1 recovery but lower equilibrium signal intensity

$S_o(\vec{r})$ because of T_2 shortening. As shown in Table 1, the last time point (5.9 s in the above plots) can be measured at one concentration and then calculated for the other concentrations, significantly shortening the required imaging time. Plot b) is an enlarged view of plot a).

Figure 5.

T_1 recovery plot of eight saturation recovery times, with T_1 recovery curve fitted to all eight points (dashed line) vs. only the first three points and the last point (dotted line). The solid line represents fitting to only the first three points without the last point, showing the necessity of the last point for accurate T_1 estimation. However, this last point does not need to be measured during post-contrast dynamic imaging but instead can be calculated from its pre-contrast value and the measured T_2 .

Figure 6.

T_1 recovery curve of a single pixel near the tumor periphery that is indicated by the vertical arrow in Fig. 8a, at different dynamic time points.

Figure 7.

a) T_1 maps with T_2 correction and b) T_2 maps precontrast and at 0.9, 5.1, and 9.9 min after the bolus administration of Gd-DTPA. The blue end of the color map indicates lower T_1 . Decreasing T_1 at the tumor periphery indicates increasing concentration of contrast agent.

Figure 8. Plots of dynamic (a) T_1 and (b) T_2 values of 3×3 pixel regions of interest indicated by the numerals in Fig. 7.

Table 1

Measured vs. calculated equilibrium signal intensity $S_o'(\vec{r})$, representing the signal intensity measured at very large saturation recovery time ($\tau_i \rightarrow \infty$). Good agreement between calculated and measured values shows that this point can be measured once and then calculated for subsequent time points from the from measured T_2 values.

Concentration (mMol)	T_2 (ms)	$S_o'(\vec{r})$ (calculated)	$S_o'(\vec{r})$ (measured)
0.1	57.1±5.5	-	2196.2±60.3
0.3	29.7±2.6	1838.6±50.5	1864.3±50.7
0.6	15.6±1.5	1315.5±36.1	1329.5±44.3