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Scientific note

A SAFE (saturate after the echo) sequence to eliminate an artefact in the measurement of T_2 in partially saturated NMR systems

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1. Introduction

^{1}H NMR relaxation times of tissues are influenced by the physicochemical environment of the protons. There is, therefore, the potential for tissue characterisation in the measurement of relaxation times. However, most pathological tissues show elevated relaxation times (Beal *et al* 1984) and simple analyses which assume mono-exponential decay are often unable to demonstrate any differences between various pathological tissues. Many tissues, however, display multi-exponential T_2 relaxation (Barnes *et al* 1986), and accurate determination of multi-exponential behaviours may give the specificity necessary for tissue characterisation.

To study multi-exponential transverse magnetisation decay with the optimum sensitivity, it is important to follow the decay up to long echo times T_E, until the signal has disappeared into the noise (i.e. $T_E \simeq 5T_2$). The naive equation often used (Mills *et al* 1984) to describe image intensity in a single-echo experiment is (for a single T_2 component and perfect radiofrequency (RF) pulses)

$$I_N = GN \exp(-T_E/T_2)[1-\exp(-T_R/T_1)] \tag{1}$$

where G is a constant describing the instrument gain, N is the spin density, T_E is the echo time and T_R is the repetition time. The slope of $\ln(I_N)$ against T_E gives T_2. However, fuller analysis reveals that the exact value of the signal intensity is (Young *et al* 1982)

$$I_E = GN \exp(-T_E/T_2)\{1-2\exp[-(T_R-T_E/2)/T_1]+\exp(-T_R/T_1)\} \tag{2}$$

in which case the slope of $\ln(I_E)$ against T_E is dependent on T_1, T_2, T_E and T_R, and T_2 cannot be determined without making a separate determination of T_1 and recourse to computer fitting techniques. T_1 could be left as a free parameter in the fit, but this increase in the number of degrees of freedom would reduce the precision with which T_2 could be determined. Measurements of T_2 are usually made using equation (1). The relative error in intensity, ε_I, caused by assuming the data follow (1) when in fact they are described by (2), is given by

$$\varepsilon_I = \frac{I_E - I_N}{I_E} = -2\frac{\exp(-T_R/T_1)[\exp(T_E/2T_1)-1]}{1-2\exp[-(T_R-T_E/2)/T_1]+\exp(-T_E/T_1)}. \tag{3}$$

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ε_1 is always negative (i.e. real data lie below the line indicated by (1)). The exact equation (2) does reduce to the naive equation (1) (i.e. $\varepsilon_1 \to 0$) under the following conditions:

$$T_E \ll T_1 \qquad \text{i.e. short echo time} \tag{4a}$$

or

$$T_R \gg T_1 \qquad \text{i.e. fully relaxed.} \tag{4b}$$

Since T_E may be as long as $5T_2$, and T_2 may be as high as $0.7T_1$ for oedema in biological systems at 0.5 T, then condition (4*a*) may not be met, in which case (1) is only correct under the fully relaxed condition (4*b*).

We investigated this artefact further, and have produced a modified spin-echo pulse sequence (SAFE—saturate after the echo) which eliminates the artefact. It retains the simplicity of equation (1), whilst working under almost any conditions of T_E and T_R. The behaviour of the sequence has been verified experimentally. The magnitude of the error caused by not using a SAFE pulse and assuming that the naive equation (1) is correct has been calculated in detail for a range of experimental parameters. The effects on data acquisition time and signal-to-noise ratio are considered, and the behaviour of multi-echo sequences is discussed. A preliminary account of the use of SAFE has been published already (Tofts *et al* 1986).

2. The SAFE sequence

The behaviour of the z (longitudinal) component of the magnetisation, M_z, for a conventional spin-echo sequence (90°-T_E/2-180°-T_E/2-echo), with $T_1 = 1000$ ms, is shown by computer simulation in figure 1. With a short echo time ($T_E = 40$ ms) M_z starts growing at a time close to zero, from a value close to zero, and at a time T_R reaches a value of approximately $M_0[1-\exp(-T_R/T_1)]$, where M_0 is the equilibrium magnetisation. This satisfies the short echo time condition (4*a*) and hence the naive

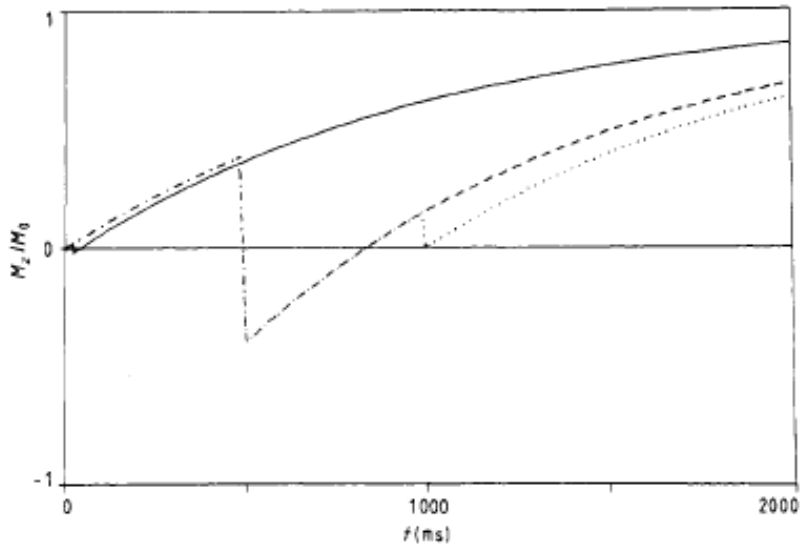

Figure 1. M_z/M_0 in conventional (——, $T_E = 40$ ms; - - -, $T_E = 1$ s) and SAFE ($T_S = 1$ s) single-echo spin-echo sequences. $T_1 = 1000$ ms. In the SAFE sequence a 90° pulse saturates M_z after the echo at $T_E = 1000$ ms.

equation (1) is correct. If the echo time is appreciable compared with T_R ($T_E = 1000$ ms in figure 1) then after the 180° pulse (i.e. at $T_E/2$) M_z starts growing from a value dependent on T_E (i.e. $-M_0[1-\exp(-T_E/2T_1)]$), for a time dependent on T_E (i.e. $T_R - T_E/2$), and to a value at T_R of $M_0\{1-2\exp[-(T_R-T_E/2)/T_1]+\exp(-T_R/T_1)\}$ which gives the exact equation (2) and has the undesirable T_E dependence.

We have removed this T_E dependence by constructing a new sequence, called SAFE. This consists of saturating (destroying) the z magnetisation after the echo, and then allowing it to recover for a fixed time T_S (the SAFE time), independent of T_E, before the next 90° pulse (figure 2). Immediately after the echo the transverse magnetisation is destroyed by the read gradient. The z magnetisation is then destroyed by applying a second (SAFE) 90° pulse, which tips M_z into the xy (transverse) plane, followed by a gradient pulse to dephase this transverse magnetisation. M_z then recovers from zero for a time T_S to $M_0[1-\exp(-T_S/T_1)]$ before the next 90° pulse at T_R. The image intensity is then

$$I = GN\exp(-T_E/T_2)[1-\exp(-T_S/T_1)] \tag{5}$$

which has the simple form of (1).

3. Validation of the SAFE sequence

Measurements were made on a 0.5 T Picker whole-body imager. Solutions in 25 mm diameter polythene bottles were imaged with 128 values of phase encoding gradient in a 15 cm field of view. The temperature was constant to within 0.5 K. Magnitude reconstruction of the image was used, with correction at low singal-to-noise ratios for Rayleigh noise in the background (Tofts and Johnson 1986). The switched attenuator in the receiver is only accurate to 0.5 dB (=6%), so it was kept at a fixed value for all measurements in a run.

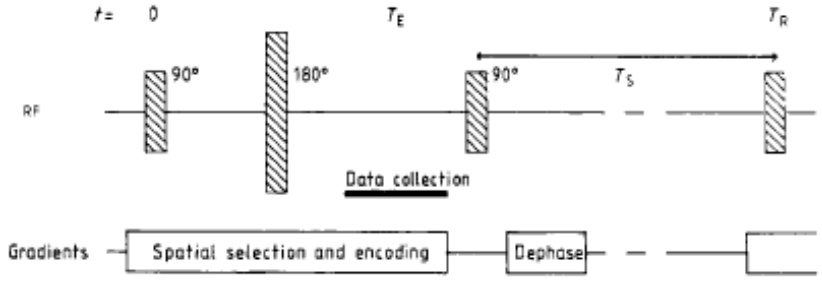

Figure 2. The SAFE spin-echo pulse sequence (single echo).

A bottle of manganese chloride solution ($T_1 = 870$ ms) was imaged with conventional single-echo sequences, with $T_R = 0.56$, 1, 2 and 5 s (i.e. fully relaxed), and with the SAFE single-echo sequence with $T_S = 1.5$ s (figure 3). Apparent T_2 values were derived by least-squares computer fit of the I against T_E data to

$$I = I_0\exp(-T_E/T_2) \tag{6}$$

and are shown in table 1.

The fitting program provides an approximate estimate of the standard error in T_2, shown as ± in table 1. The RMS residuals in I represent less than 1% of the relaxed signal at $T_E = 0$.

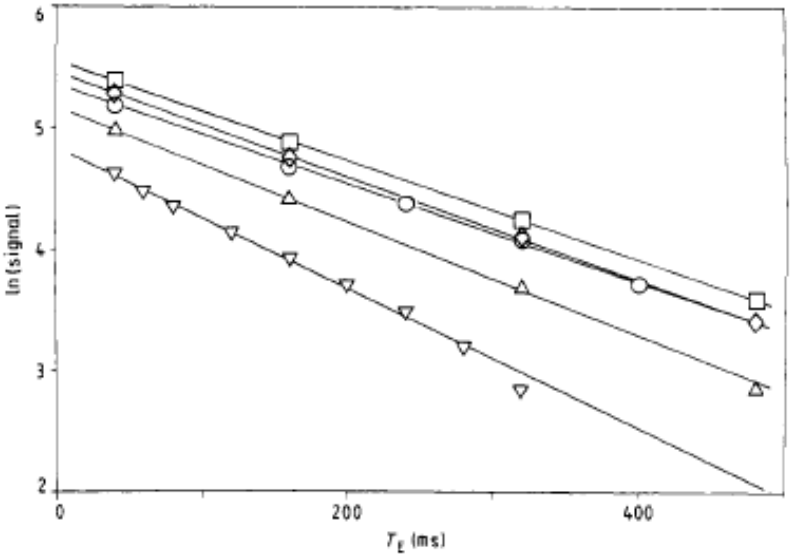

Figure 3. Conventional and SAFE single-echo sequence using $MnCl_2$ solution. ▽, conventional, $T_R = 0.56$ s; △, conventional, $T_R = 1$ s; ◇, conventional, $T_R = 2$ s; □, conventional, $T_R = 5$ s; ○, SAFE, $T_S = 1.5$ s. The $T_R = 5$ s data are relaxed. Full lines are least-squares fits from table 1.

Table 1. Validation of the SAFE single-echo sequence using $MnCl_2$ solution.

Sequence		Apparent T_2 (ms)	RMS residual
Conventional	$T_R = 0.56$ s	173 ± 4	1.6
Conventional	$T_R = 1$ s	213 ± 3	1.0
Conventional	$T_R = 2$ s	233 ± 1	0.4
Conventional†	$T_R = 5$ s	243 ± 2	0.9
SAFE	$T_S = 1.5$ s	245 ± 3	1.3

† Relaxed.

In the shortest repetition time data ($T_R = 0.56$ s) taken with the conventional sequence, the downward curve predicted by (2) at long echo times is clearly seen. Increasing the repetition time of the conventional sequence from $T_R = 1$ to $T_R = 2$ to $T_R = 5$ s (relaxed) significantly increased the measured values of T_2, although there was no obvious improvement in the fit. Thus a good fit is no guarantee of an accurate T_2, and unrelaxed sequences can give inaccurate (though misleadingly precise) values of T_2. The fully relaxed data ($T_R = 5$ s) gave the artefact-free value of T_2. The SAFE sequence gave a value of T_2 in agreement with this. The SAFE sequence took the same time as the conventional $T_R = 2$ s sequence, and therefore provides a convenient alternative to waiting for complete relaxation.

4. When is SAFE required?

In the introduction it was shown that the naive equation (1) is inaccurate unless the system is relaxed ($T_R \gg T_1$). The question arises of when a SAFE sequence is required in practice, and when the conventional one is adequate. The SAFE sequence is needed whenever (1) becomes inaccurate, i.e. when the difference between (1) and (2) becomes

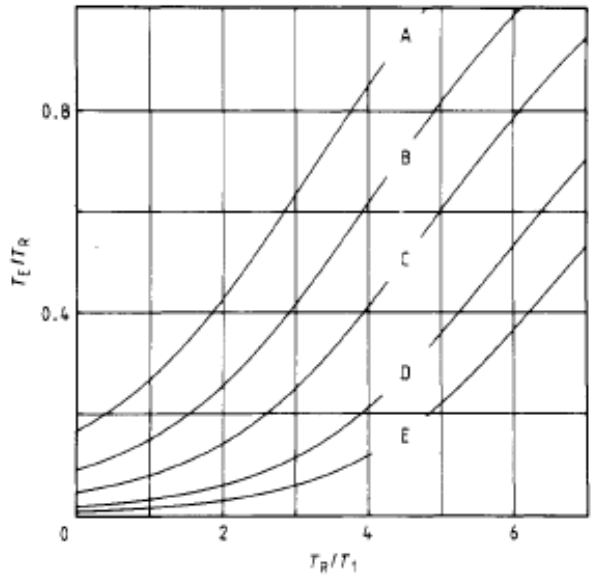

Figure 4. Error in intensity (A, −20; B, −10; C, −5; D, −2; E, −1%) using a conventional single-echo sequence. This is the difference between the *actual* intensity (equation (2)) and the intensity *assumed* (equation (1)) in calculating T_2.

significant. The fractional error in image intensity, ε_1 (equation (3)), is plotted in figure 4. To keep the error less than 1%, i.e. much less than other sources of error such as noise, we require, for example, $T_R > 5T_1$ and $T_E < 0.2T_R$. At longer T_R a longer T_E is permissible (e.g. at $T_R = 7T_1$, T_E need only be $< 0.5T_R$). These conditions are often difficult to achieve in practice. For example, in imaging experimentally induced oedema in cats, biexponential decays with approximate $T_2 = 70$ and 300 ms have been seen (Barnes *et al* 1986) with a single $T_1 = 800$ ms. Echo times up to at least 800 ms were needed to follow the longer T_2 component so to satisfy the first condition above ($T_R > 5T_1$ and $T_E < 0.2T_R$) would have required an impracticably long repetition time of about 4 s. Instead a SAFE sequence was used, with a SAFE recovery time T_S of 1.5 s, giving the same imaging time as a conventional sequence with a 2 s repetition time.

Even in the study of normal mono-exponential tissue, the conventional spin-echo sequence may be inadequate for accurate measurement of T_2. For example, human grey matter at 0.5 T has approximate relaxation times $T_1 = 600$ ms, $T_2 = 100$ ms, and is conventionally measured with a $T_R = 2$ s (Johnson *et al* 1987). At an echo time of only 200 ms (i.e. $2T_2$) there is a 1.4% error in image intensity; at 500 ms ($5T_2$) the error is 4%.

5. Signal-to-noise ratio

Since the magnetisation is destroyed after the echo by the SAFE pulse, there is a reduction in signal-to-noise ratio compared with the conventional sequence. The relative signal when using a SAFE sequence compared with a standard one (for a SAFE recovery time $T_S \simeq T_R - T_E$, when the total imaging time for each sequence is the same), R_S, is

$$R_S = \frac{1 - \exp[-(T_R - T_E)/T_1]}{1 - 2\exp[-(T_R - T_E/2)/T_1] + \exp(-T_R/T_1)}. \tag{7}$$

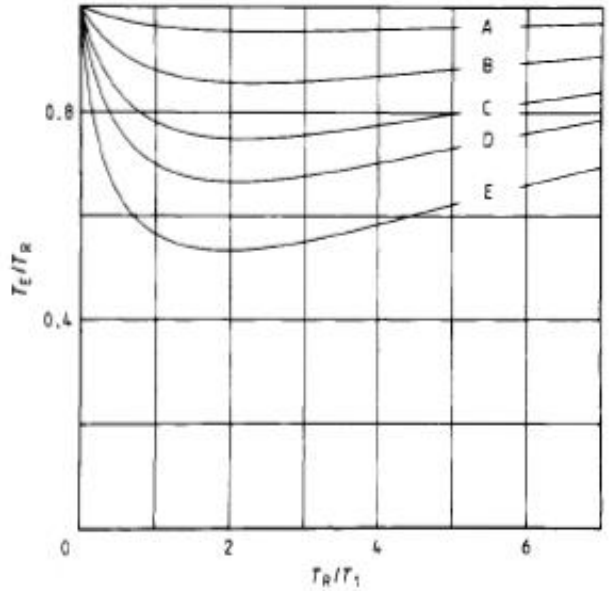

Figure 5. Signal-to-noise ratio (SNR) using a SAFE single-echo sequence compared with SNR in a conventional sequence (A, 20; B, 50; C, 70; D, 80; E, 90%). Provided $T_E < 0.5T_R$, SAFE SNR will be at least 90% of SNR in a conventional sequence.

This is shown in figure 5. (In setting $T_S = T_R - T_E$ we have ignored the small time (=15 ms) between the centre of the echo and the end of the 90° SAFE pulse. This time is required for data collection, gradient switching and the finite RF pulse duration.) Provided the SAFE recovery time is greater than the echo time (i.e. the echo time is less than half the repetition time), then the signal and signal-to-noise ratio will be at least 90% of that in the conventional sequence.

6. Multi-echo sequences

The treatment so far has been related to single-echo sequences. It is becoming increasingly common to collect imaging data using multi-echo sequences (usually CPMG) which have the benefit of speed. The exact equation for the image intensity in a conventional multi-echo sequence (analogous to (2)) can be derived but is not particularly illuminating (see, for example, Lee and Riederer 1986). However three regimes can usefully be considered (for n echos collected at intervals 2τ).

(*a*) *Echo interval* $2\tau \ll T_1$. If the change in M_z is negligible during an echo interval (i.e. $2\tau < 0.01T_1$ for a change of less than 1%), then $M_z = 0$ at the last echo and the intensity of the mth echo is

$$I_m = GN \exp(-2m\tau/T_2)\{1 - \exp[-(T_R - 2n\tau)/T_1]. \tag{8}$$

(*b*) *Fully relaxed.* If M_z has time to recover fully after the last echo (i.e. $T_R - 2n\tau > 5T_1$) then the intensity is

$$I_m = GN \exp(-2m\tau/T_2). \tag{9}$$

(c) $2\tau > 0.01T_1$ or not fully relaxed. After the last echo M_z recovers to a value dependent on the echo time and interval, described by the function f, and the intensity is

$$I_m = GN \exp(-2m\tau/T_2) f(n, \tau, T_R, T_1). \quad (10)$$

In all three regimes the data within a multi-echo set give correct values of T_2 from the slope of ln(intensity) against echo time or by fitting to equation (6). However, the standard multi-echo set on our imager can only provide data at six echo times (because of memory limitations). It is often desirable to increase the number of echo times at which the signal intensity is measured, in order to increase the precision of the fitting or to enable multi-exponential fits to be made. This can be done by combining, or 'pooling', data from several acquisitions, provided that the data all follow the same model equation, i.e. are of the form (6). Data from sets taken with different last echo times $2n\tau$ are not of the form (6), i.e. cannot be pooled unless either (i) the system is fully relaxed (equation (9)), or (ii) the echo interval is very short compared with T_1 and the repetition time is adjusted to keep the recovery time $T_R - 2n\tau$ constant (equation (8)). This latter condition ($2\tau < 0.01T_1$) is rarely met in practice. For example, at 0.5 T grey matter has $T_1 = 600$ ms and the minimum echo interval on our imager is 24 ms. In many situations neither of these two conditions is met, and data pooling is only possible by adding a 90° pulse and dephasing gradient after the last echo, to convert it to a SAFE (multi-echo) sequence. The intensity is then described by (5), and the data may be pooled.

This effect was demonstrated using a solution of $MnCl_2$. Conventional sequences with six echos separated by 40 and 160 ms intervals were used with repetition times of 6 and 1.5 s. Data were fitted to (6). The results are shown in table 2. The conventional sequences all gave the same T_2 within ±2% but only the relaxed data gave the same values of I_0 and could be pooled. SAFE sequences with $T_S = 1.5$ s gave the same T_2 as the conventional sequences, and could be pooled.

Table 2. Conventional and SAFE multi-echo sequences using $MnCl_2$ solution.

Sequence	2τ		I_0	T_2 (ms)	RMS residual
Conventional†	40 ms	$T_R = 6$ s	234 ± 1	248 ± 2	0.9
Conventional†	160 ms	$T_R = 6$ s	236 ± 1	237 ± 1	0.2
Conventional	40 ms	$T_R = 1.5$ s	181 ± 1	246 ± 1	0.4
Conventional	160 ms	$T_R = 1.5$ s	107 ± 6	244 ± 14	2.0
SAFE	40 ms	$T_S = 1.5$ s	187 ± 1	245 ± 1	0.3
SAFE	160 ms	$T_S = 1.5$ s	192 ± 2	237 ± 2	0.7

† Relaxed.

There is evidence that all the 160 ms sequences give a slightly shorter T_2 than the 40 ms sequences (237 ms compared with 246 ms), which suggests that there is a small additional source of decay in the 160 ms sequence (perhaps imperfect refocusing, or diffusion). This is the subject of further study.

7. Discussion

The single- and multi-echo data show that T_2 can be measured to great precision (≈1%) in solutions. Separate measurements using the imager as a spectrometer (with the gradients turned off) showed that imager accuracy is better than 5%, and that a

similar performance might be expected *in vivo*, provided partial volume and coil loading effects are not important (Johnson *et al* 1987). Biexponential analysis of the transverse magnetisation decay curve, collected using SAFE sequences, has yielded information on the size and T_2 of intra- and extra-cellular water compartments in oedematous lesions in cat brain (Barnes *et al* 1986) and shows great promise for elucidating the nature of pathological tissue in humans. The loss of linearity in the $\ln(I)$ against T_E plot seen at short repetition times (e.g. $T_R = 0.56$ s in figure 2) could obscure a second component with a long T_2. SAFE multi-slice clinical sequences may be possible using a selective 90° pulse to destroy the magnetisation after the echo.

The increased use of multi-echo sequences may mean that the importance of using a SAFE sequence decreases. However, there are circumstances when a multi-echo sequence is not possible, for example if (i) the radiofrequency power deposition is too great, (ii) induced gradient eddy currents distort the transverse magnetisation decay curve, (iii) imperfect 180° pulses cause parasitic echoes (Gyngell *et al* 1985) or (iv) the imager is incapable of acquiring the large amount of data produced by a many-echo multi-echo sequence.

It has been suggested that the conventional single-echo sequence can be improved by keeping $T_R - T_E$ constant, rather than T_R, for different echo times. This relies on the longitudinal magnetisation being zero at T_E. It can be seen from figure 1 (conventional $T_E = 1$ s sequence) that considerable longitudinal magnetisation may exist at T_E, and that the sequence is still in error. T_R could be measured from the zero crossing time of M_z—however this depends on there being a single known T_1.

The slice profile is known to be distorted at short repetition times (Bryant *et al* 1984). The use of a SAFE sequence removes this effect, and allows T_1 to be measured accurately at short repetition times (Waterton *et al* 1984).

Although the treatment given here is presented in the context of NMR imaging, with broad-band and selective RF pulses and pulsed gradients, it is equally applicable to any spectrometer being used to measure T_2, provided that the B_1 is reasonably homogeneous, so that the nutation angles are close to their ideal values. Thus a conventional spectrometer being used to measure T_2 will still be subject to the error shown in figure 4 unless a SAFE sequence is used. If no gradient coils are available then the magnetisation can be destroyed by a series of 90° pulses.

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