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Analysis of mcDESPOT- and CPMG-Derived Parameter Estimates for Two-Component Nonexchanging Systems

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Abstract

Purpose—To compare the reliability and stability of the multicomponent-driven equilibrium single pulse observation of T_1 and T_2 (mcDESPOT) and Carl-Purcell-Meiboom-Gill (CPMG) approaches to parameter estimation.

Methods—The stability and reliability of mcDESPOT and CPMG-derived parameter estimates were compared through examination of energy surfaces, evaluation of model sloppiness, and Monte Carlo simulations. Comparisons were performed on an equal time basis and assuming a two-component system. Parameter estimation bias, reflecting accuracy, and dispersion, reflecting precision, were derived for a range of signal-to-noise ratios (SNRs) and relaxation parameters.

Results—The energy surfaces for parameters incorporated into the mcDESPOT signal model exhibit flatness, a complex structure of local minima, and instability to noise to a much greater extent than the corresponding surfaces for CPMG. Although both mcDESPOT and CPMG performed well at high SNR, the CPMG approach yielded parameter estimates of considerably greater accuracy and precision at lower SNR.

Conclusion—mcDESPOT and CPMG both permit high-quality parameter estimates under SNR that are clinically achievable under many circumstances, depending upon available hardware and resolution and acquisition time constraints. At moderate to high SNR, the mcDESPOT approach incorporating two-step phase increments can yield accurate parameter estimates while providing values for longitudinal relaxation times that are not available through CPMG. However, at low SNR, the CPMG approach is more stable and provides superior parameter estimates.

Keywords

mcDESPOT; CPMG; sloppiness; energy surface; accuracy; precision; quantitative MRI

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INTRODUCTION

Multicomponent driven equilibrium single pulse observation of T_1 and T_2 (mcDESPOT) was introduced by Deoni et al. (1) as a rapid approach to multicomponent relaxometry (2–5). It has been applied to map the myelin water and proteoglycan fractions in human brain and knee cartilage (3,6). Even though generally restricted to a two-compartment model, the dimensionality of parameter space for the mcDESPOT analysis remains high, with five fitting parameters even in the absence of chemical exchange. A recent study, based on Cramer-Rao lower bound (CRLB) analysis (7), demonstrated that the uncertainty in parameter estimates obtained from mcDESPOT was substantial in the presence of noise.

The mcDESPOT approach permits component characterization in terms of component fractions and longitudinal, T_1 , and transverse, T_2 , relaxation times from two independent experiments, the spoiled gradient recalled echo (SPGR) and the fully balanced steady state free precession (bSSFP), with, in both cases, imaging data acquired over multiple flip angles (FAs) with a very short repetition time (TR). This permits sufficiently rapid data acquisition to permit whole brain imaging in a feasible acquisition time, allowing, in principle, a pixel-by-pixel analysis over the entire brain. This cannot be achieved using sequences based on the classic Carl-Purcell-Meiboom-Gill (CPMG) (8–13) or gradient and spin echo (GRASE) techniques (14–16).

Zhang et al. (17) made an important in vivo comparison of parameter estimates obtained from mcDESPOT and GRASE and found that derived values differed substantially. This finding was attributed to the fact that mcDESPOT and GRASE and other multiple spin echo-based approaches such as CPMG are subject to a number of confounding factors, including diffusion, magnetization transfer, and chemical exchange, the influence of which varies among these methods. The analysis by Zhang et al. was performed in an experimental setting in which the true parameter values and signal models were unknown. We extended these results using simulations to permit a rigorous and systematic analysis of the reliability of parameter estimates under a wide range of clinically applicable experimental and physiologic conditions for the mcDESPOT and CPMG experiments.

First, we investigated the impact of finite relaxation time effects, which are omitted from the conventional signal models of both mcDESPOT and CPMG. Next, we studied the energy surface characteristics of parameter estimates and the inherent model sloppiness of mcDESPOT and CPMG (18,19). Energy surface analysis provided a clear depiction of the least squares residuals structures of estimated parameters, such as flatness and presence of local minima, as well as their behavior in the presence of noise. Sloppiness analysis was complementary to this, providing an evaluation of the degree of inherent ill-conditioning for the signal models. Finally, Monte Carlo simulations were performed to quantify the effect of noise on accuracy and precision in each parameter estimate from the two signal models. We restricted our comparison of mcDESPOT and CPMG to a two-component system without chemical exchange to highlight the main features of the analysis. We note that multicomponent CPMG analysis is more often performed using the nonnegative least squares (NNLS) algorithm in order to avoid a specific assumption regarding the number of underlying relaxation components; however, in our two-component system, we performed

the analysis with standard nonlinear least squares. Indeed, restricting the multicomponent relaxation analysis to a two-component system has been found to be a good approximation in a number of studies (20–24) and is particularly appropriate in settings of only moderate signal-to-noise ratio (SNR), such as is achievable clinically.

THEORY

mcDESPOT Signal Model

mcDESPOT is based on the use of SPGR and bSSFP datasets acquired at different FAs (1–4). Neglecting exchange between compartments, the two-component SPGR signal is given by

$$\text{SPGR}_n = S_0 \sin\theta_n \left(f_s \frac{E_{2,s}^* (1 - E_{1,s})}{1 - E_{1,s} \cos\theta_n} + (1 - f_s) \frac{E_{2,l}^* (1 - E_{1,l})}{1 - E_{1,l} \cos\theta_n} \right), \quad [1]$$

where f_s is the fraction of the short T_2^* , or rapidly relaxing, component, S_0 represents the signal amplitude at echo time (TE) = 0 ms and incorporates proton density and various machine factors, and θ_n is the n^{th} excitation FA. Here, s stands for the short T_2^* component, while l stands for the long T_2^* component. $E_{1,j} = \exp(-\text{TR}/T_{1,j})$ and $E_{2,j}^* = \exp(-\text{TE}/T_{2,j}^*)$, where $T_{1,j}$ and $T_{2,j}^*$ are the spin–lattice and the apparent spin–spin relaxation times of the j^{th} component, respectively. As noted, Equation [1] has appeared in the literature in the approximation $E_{2,s}^* = E_{2,l}^* = 1$ (1–6). This is appropriate for small TE, such as can be achieved in spectroscopy experiments (25), or equal T_2 values, but is less robust an approximation in the imaging context, for which TE is approximately 2–5 ms or more. Clearly, the two terms of Equation [1] will have different weightings in the latter case.

With $1/T_{2,s}^* = 1/T_{2,s} + 1/T_2'$ and $1/T_{2,l}^* = 1/T_{2,l} + 1/T_2'$, where T_2' describes mesoscopic or macroscopic field inhomogeneities common to both relaxation components, Equation [1] can be rewritten as

$$\text{SPGR}_n = M_0 \sin\theta_n \left(f_s \frac{E_{2,s}^\dagger (1 - E_{1,s})}{1 - E_{1,s} \cos\theta_n} + (1 - f_s) \frac{E_{2,l}^\dagger (1 - E_{1,l})}{1 - E_{1,l} \cos\theta_n} \right), \quad [2]$$

where $M_0 = S_0 \exp(-\text{TE}/T_2')$ and $E_{2,j}^\dagger = \exp(-\text{TE}/T_{2,j})$ where $T_{2,j}$ is the spin–spin relaxation time of the j^{th} component. If this T_2^* -weighting is ignored (26), Equation [1] becomes

$$\text{SPGR}_n = S_0 \sin\theta_n \left(f_s \frac{1 - E_{1,s}}{1 - E_{1,s} \cos\theta_n} + (1 - f_s) \frac{1 - E_{1,l}}{1 - E_{1,l} \cos\theta_n} \right). \quad [3]$$

Similarly, the two-component bSSFP magnetization immediately preceding each radiofrequency (RF) pulse in the absence of exchange is given by (27)

$$bSSFP_n = |S_0(f_s(M_{a,s}^n + iM_{b,s}^n) + (1 - f_s)(M_{a,l}^n + iM_{b,l}^n))|, \quad [4]$$

where

$$M_{a,j}^n = \frac{E_{2,j}(1 - E_{1,j})\sin\theta_n \sin\phi}{(1 - E_{1,j}\cos\theta_n)(1 - E_{2,j}\cos\phi) - E_{2,j}(E_{1,j} - \cos\theta_n)(E_{2,j} - \cos\phi)}$$

and

$$M_{b,j}^n = \frac{E_{2,j}(1 - E_{1,j})(\cos\phi - E_{2,j})\sin\theta_n}{(1 - E_{1,j}\cos\theta_n)(1 - E_{2,j}\cos\phi) - E_{2,j}(E_{1,j} - \cos\theta_n)(E_{2,j} - \cos\phi)},$$

where $E_{2,j} = \exp(-TR/T_{2,j})$ and $\phi = \omega TR + \vartheta$, with ω as the off-resonance frequency, and ϑ the phase increment of the applied RF pulses. Unless specified otherwise, all proton pools were assumed to be on-resonance (ie, $\omega = 0$).

CPMG Signal Model

For the case of two distinct proton pools that are not exchanging and with $TR \gg TE$ or with use of appropriate spoiler gradients, the CPMG signal is given by

$$CPMG_n = S_0 \left(f_s \exp\left(-\frac{TE_n}{T_{2,s}}\right) \left(1 - \exp\left(-\frac{TR}{T_{1,s}}\right)\right) + (1 - f_s) \exp\left(-\frac{TE_n}{T_{2,l}}\right) \left(1 - \exp\left(-\frac{TR}{T_{1,l}}\right)\right) \right).$$

[5]

In the case of TR less than or on the order of $T_{1,k}$ the two terms will exhibit different T_1 -weightings; this is generally ignored in CPMG analysis (11,16,17), with the conventional signal model being taken as

$$CPMG_n = S_0 \left(f_s \exp\left(-\frac{TE_n}{T_{2,s}}\right) + (1 - f_s) \exp\left(-\frac{TE_n}{T_{2,l}}\right) \right). \quad [6]$$

METHODS

The following experimental and underlying input parameters were used in all analyses described herein. For mcDESPOT, the bSSFP signals were generated for FAs of $\theta = \{2, 6, 14, 22, 30, 38, 46, 54, 62, 70\}$ and $TR_{bSSFP} = 6.5$ ms, while the SPGR signals were generated for FAs of $\theta = \{2, 4, 6, 8, 10, 12, 14, 16, 18, 20\}$ and $TR_{SPGR} = 6.5$ ms. For

CPMG, signals were generated for 32 echoes with TE increasing linearly from 8 to 256 ms. All simulations used input parameters $T_{2,s} = 15$ ms, $T_{2,l} = 90$ ms, $T_{1,s} = 450$ ms, and $T_{1,l} = 1400$ ms; these are based on reported values from human brain imaging (1–4,7,8,16,17,24). All numerical calculations were performed using routines developed inhouse with MATLAB (MathWorks, Natick, Massachusetts, USA). Using the above values, as noted in each figure legend for ease of reference, we present results across ranges of f_s and SNR which, for typical experiments and using the definitions of SNR given herein, are in the range of 100–1000 (17).

Effects of Nonmodeled Relaxation on mcDESPOT and CPMG

Effect of Finite T_2^* on mcDESPOT—Ideal bSSFP signals were generated using Equation [4], with RF phase increments of 0° and 180° , and the SPGR signal was generated using Equation [2]. Signals were generated for values of TE_{SPGR} ranging from 0.5 to 5 ms with 0.25 ms increments, and for values of f_s ranging from 0.05 to 0.3 in increments of 0.05. These signals were then fitted simultaneously to Equations [2] and [4], explicitly accounting for T_2^* -weighting effects (corrected mcDESPOT), or to Equations [3] and [4], neglecting T_2^* -weighting (conventional mcDESPOT). Relative parameter errors were calculated as $100 * (\hat{P} - P)/P$ where $\hat{P}$ and P were the estimated and true parameter values, respectively.

Fits were performed using the stochastic region contraction (SRC) algorithm (28,29). For each iteration of the SRC algorithm, 40,000 random samples were generated within specified parameter bounds. The 50 solutions with the smallest least squares residual were used to construct bounds for the next iteration. Iterations were terminated after convergence was achieved, defined as a difference between the minimum and maximum values for all parameters of less than 1%, or after 30 iterations. The initial parameter bounds were: 0 f_s 0.5, 2 ms $T_{2,s}$ 40 ms, 50 ms $T_{2,l}$ 200 ms, 200 ms $T_{1,s}$ 700 ms, and 700 ms $T_{1,l}$ 2500 ms. To avoid the need to explicitly fit for S_0 , each dataset was normalized with respect to its mean value over the full range of FA (1,17,28).

Effect of Finite TR on CPMG—Ideal CPMG signals were generated using Equation [5] with fixed values of $T_{1,s} = 450$ ms and $T_{1,l} = 1400$ ms, and for values of TR_{CPMG} ranging from 1000 to 5000 ms in 250 ms increments and for values of f_s ranging from 0.05 to 0.3 in increments of 0.05. These signals were then fitted to Equation [5], explicitly accounting for T_1 effects (corrected CPMG), or to Equation [6], neglecting T_1 effects (conventional CPMG). Relative parameter errors were calculated as described above using the SRC algorithm described previously. To avoid the need to explicitly fit for S_0 , each dataset was again normalized with respect to its mean over echo times.

Energy Surface Structures and Sloppiness of the mcDESPOT and CPMG Signal Models

Parameter estimation in high dimensional problems, that is, those for which the number of parameters to be estimated is large, is complicated by the presence of local minima and saddle points (18,19,30,31). This problem becomes more acute with the flatness of the least squares residual (LSR) surfaces seen with increasing model complexity. To explore the structure of the energy surfaces for mcDESPOT and CPMG parameter estimation, minimum least squares residuals (MLSRs) were calculated as a function of each parameter of interest

by fixing the parameter of interest to a given value and varying all other parameters. The LSR is calculated over the entire combined multidimensional range of these variable parameter combinations for each fixed value of the parameter of interest, with the minimum calculated LSR designated as the MLSR. This process was repeated for different fixed values of the parameter of interest. Comparisons between mcDESPOT and CPMG were performed for both restricted initial parameter bounds, given by $0 \leq f_s \leq 0.5$, $2 \text{ ms} \leq T_{2,s} \leq 40 \text{ ms}$, $60 \text{ ms} \leq T_{2,l} \leq 160 \text{ ms}$, $200 \text{ ms} \leq T_{1,s} \leq 700 \text{ ms}$, and $800 \text{ ms} \leq T_{1,l} \leq 2000 \text{ ms}$ and expanded initial parameter bounds given by $0 \leq f_s \leq 1$, $2 \text{ ms} \leq T_{2,s} \leq 40 \text{ ms}$, $20 \text{ ms} \leq T_{2,l} \leq 200 \text{ ms}$, $100 \text{ ms} \leq T_{1,s} \leq 1000 \text{ ms}$, and $200 \text{ ms} \leq T_{1,l} \leq 2500 \text{ ms}$.

It is well-known that many models incorporating multiple parameters exhibit sloppiness, that is, different parameter combinations lead to virtually equivalent signal behavior (18,19). The degree of this ill-conditioning can be examined through evaluation of the eigenvalues, λ , of the Hessian matrix or its approximation, the Fisher matrix (18,19,32), of the cost function (ie, the LSRs). Sloppiness, which is manifest in sensitivity to noise, is exhibited when these eigenvalues are roughly evenly distributed over many decades. The sloppiness of the mcDESPOT and CPMG models was explored through calculation of these eigenvalues, with results presented as parameter sensitivity spectra (18).

For mcDESPOT, MLSR and sloppiness analyses were performed using three different RF phase increments (33). mcDESPOT_{PI1} is defined by using one RF phase increment of 180° in generating the bSSFP dataset. mcDESPOT_{PI2} is defined by combining mcDESPOT_{PI1} data with an additional bSSFP data incorporating a phase increment of 0° . Finally, mcDESPOT_{PI3} is defined by combining mcDESPOT_{PI2} data with an additional bSSFP dataset incorporating a phase increment of 90° . TE_{SPGR} was assumed to be very short (~ 0 ms) and TR_{CPMG} to be very long (~ 3000 ms) so that the effects of finite T_2^* and TR were negligible. Accordingly, Equations [3] and [6] were adopted for the mcDESPOT and CPMG signal models, respectively; we further assigned $f_s = 0.15$.

MLSR comparisons between mcDESPOT and CPMG were performed for both the noiseless case and for one realization of noise, with SNR as defined below for CPMG of 200, on an equal time basis, that is, under conditions of equal total experimental times. The SNR for the CPMG signal was given by $SNR_{CPMG} = S_0/\sigma$, while the SNR for mcDESPOT was given by

$$SNR_{mcDESPOT} = SNR_{CPMG} \sqrt{\frac{TR_{CPMG}}{N * TR_{SPGR} + C * M * TR_{bSSFP}}}, \text{ where } \sigma \text{ represents the standard}$$

deviation of zero-mean Gaussian noise, appropriate for our setting of relatively high SNR; N and M are the total number of SPGR and bSSFP data points, respectively; and C is the number of RF phase increments implemented in the bSSFP datasets of the mcDESPOT analysis, as appropriate for the three versions of mcDESPOT described above. For the present analysis, we neglected the incorporation of the Rician noise model, which may be more appropriate for the latter echoes, displaying lower SNR.

Parameter Estimation from mcDESPOT and CPMG

The following Monte Carlo simulations were performed using computer-generated images of $60 \times 60 = 3600$ pixels. Parameter estimates were obtained using the SRC algorithm

described above. All comparisons were performed on an equal time basis as described in the previous paragraph.

Effect of RF Phase Increments on mcDESPOT-Derived Parameters—Analysis of parameter estimates was performed for mcDESPOT_{P11}, mcDESPOT_{P12}, and mcDESPOT_{P13} using SNR values of 200, 500, and 1000 with $f_s = 0.15$. Results are presented as smoothed Gaussian histograms using the MATLAB command *histfit*. The SRC fit was performed assuming the expanded initial parameter bounds defined above.

Effect of Initial Parameter Bounds on mcDESPOT_{P12}- and CPMG-Derived Parameters—The impact of the initial parameter bounds on mcDESPOT_{P12}- and CPMG-derived parameter estimates was evaluated through direct comparison of results obtained using the expanded and restricted parameter bounds defined above, with performance evaluated at SNR values of 200, 500, and 1000 and with $f_s = 0.15$. Results were again presented as smoothed Gaussian histograms.

Accuracy and Precision in Parameter Estimates Using mcDESPOT_{P12} and CPMG—Based on the results of the studies outlined above, we further evaluated the quality of mcDESPOT- and CPMG-derived parameter estimates using $TE_{SPGR} = 0$ ms and $TR_{CPMG} = 3000$ ms, mcDESPOT_{P12}, and the expanded parameter bounds. Results were obtained for values of f_s ranging between 0.05 and 0.45 in increments of 0.1 and with SNR values of 200, 500, and 1000. Relative bias, a measure of accuracy, was calculated from the difference between the mean of the estimated parameter values, $\hat{P}$, and the true value, P , by

$$100 * \left((1/L) \sum_{l=1}^L \hat{P}_l - P \right) / P,$$

where L is the total number of noise realizations, and the relative dispersion, a measure of precision, was defined by

$$100 * \sqrt{\left(1/(L-1) \right) \sum_{l=1}^L (\hat{P}_l - P)^2 / P}.$$

Effect of Imperfect FAs on mcDESPOT_{P12}- and CPMG-Derived Parameters—In the previous analyses, we assumed ideal transmit pulse FAs. However, errors are inevitable, either due to a small degree of miscalibration or due to B_1 inhomogeneities; this can result in substantial errors in parameter estimates from mcDESPOT (33). To account for this, mcDESPOT1-HIFI, incorporating an additional inversion recovery SPGR (IR-SPGR) acquisition, has been introduced by Deoni (34). By combining this with the SPGR dataset, both T_1 and B_1 may be mapped. Briefly, IR-SPGR involves the application of a 180° adiabatic inversion pulse, followed by an inversion time (TI) delay and an SPGR readout in which a train of low FA pulses, denoted by α , samples successive lines of k -space using a centric encoding. In the original paper (34), the IR-SPGR signal equation was approximated by

$$S_n \simeq S_0 \sin(B_1 \alpha) \sum_{j=1}^J f_j \exp\left(-\frac{TE_{IR-SPGR}}{T_{2,j}}\right) \quad [7]$$

$$\left(1 - 2 \exp\left(-\frac{TI_n}{T_{1,j}}\right) + \exp\left(-\frac{TE_{IR-SPGR}}{T_{1,j}}\right)\right),$$

where B_1 (unit-less) is an RF transmit scaling factor, J is the total number of components, f_j is the signal fraction of the j^{th} component, and $TR_{IR-SPGR}$ is the time between successive inversion pulses. Equation [7] corresponds to an IR spin echo signal using a 180° adiabatic inversion pulse, followed by a TI delay, a 90° RF pulse, and a 180° echo-generating pulse. However, the actual experiments described by Deoni deviated somewhat from this sequence and, rather than a 90° flip-back pulse followed by a 180° pulse, involved a sequence of small FAs, each generating a separate line in k -space. Kayvanrad (35) provided a corrected expression, showing that the IR-SPGR signal is given by

$$S_{IR-SPGR}^n \simeq S_0 \sin(B_1 \alpha) \sum_{j=1}^J f_j \exp\left(-\frac{TE_{IR-SPGR}}{T_{2,j}^*}\right) \left(1 - 2 \frac{\exp\left(-\frac{TI_n}{T_{1,j}}\right)}{1 + \exp\left(-\frac{TR_{IR-SPGR}}{T_{1,j}}\right)}\right), \quad [8]$$

resulting in T_1 values much more consistent with reference values for phantom and in vivo data. Note that Equations [7] and [6] are equivalent for $TR_{IR-SPGR} \gg T_{1,j}$. In any case, in estimating the B_1 map, both the IR-SPGR and SPGR signals are fitted to a monocomponent signal (17,34) that could in principle result in bias in the case of multicomponent systems. We investigated this by generating noisy IR-SPGR (Eq. [8]) and SPGR (Eq. [7]) signals for two-component systems with a 15% (ie, $B_1 = 0.85$) or 30% (ie, $B_1 = 0.7$) underestimate in the FAs, and deriving B_1 values from these using the monoexponential model. IR-SPGR signals were generated by assuming the following experimental parameters: $TI = 450$ ms, $TR_{IR-SPGR} = 1000$ ms, $\alpha = 8^\circ$, and $TE_{IR-SPGR} = 4$ ms. Relative bias and dispersion in the estimation of B_1 were calculated for f_s values ranging from 0.05 to 0.45 in increments of 0.1 and with SNR values of 200, 500, and 1000.

Similarly, B_1 inhomogeneities (36–39) lead to the generation of secondary and stimulated echoes and nonexponential decay (40) in CPMG experiments, which will affect the accuracy or precision of estimated parameters (41). This can be accounted for by using the extended phase graph (EPG) algorithm, taking into account the true B_1 value in each voxel (42). However, the incorporation of B_1 as an additional free parameter may degrade the stability of the fit. We evaluated this for the same combinations of SNR and f_s values as presented in the previous paragraph. CPMG signals were created with a 15% or 30% underestimate in the excitation and refocusing FAs, with parameter fits performed using the EPG with B_1 as an additional free parameter.

RESULTS

Effects of Nonmodeled Finite Relaxation Times on mcDESPOT and CPMG

When data were simulated with finite T_2^* (Eqs. [2] and [4]) for mcDESPOT and finite TR (Eq. [5]) for CPMG and fit with the correct models (Eqs. [2] and [4] for mcDESPOT and Eq. [5] for CPMG), all parameters were recovered with zero error (Fig. 1 a and b lower rows). This indicates the ability of the SRC fitting procedure to determine the correct least-squares minima for these multiparametric signal models at infinite SNR. Figure 1a shows the relative error in mcDESPOT-derived parameter estimates obtained by fitting data generated from Equations [2] and [4], correctly incorporating T_2^* effects with Equations [3] and [4], which omit this, for different combinations of f_s and TE. As expected, the error in the estimation of f_s , $T_{2,b}$, $T_{1,s}$, and $T_{1,l}$ increases with increasing TE; a greater value of TE permits a greater degree of nonmodeled transverse relaxation to occur with the two different time constants $T_{2,s}^*$ and $T_{2,l}^*$. In addition, the errors in $T_{2,l}$ and $T_{1,l}$ increase, and in f_s and $T_{1,s}$ decrease, with increasing f_s , while the error was negligible for $T_{2,s}$ over the entire range of TE and f_s . Figure 1b shows the relative error in CPMG-derived parameter estimates obtained by fitting data generated from Equation [5], correctly incorporating finite TR effects, with Equation [6] for different combinations of f_s and TR. As expected, the error in the estimation of f_s increases with decreasing TR or f_s , while the error remained essentially zero for $T_{2,s}$ and $T_{2,l}$ over the entire range of TR and f_s .

Energy Surface Structures and Sloppiness of mcDESPOT and CPMG Signal Models

Figure 2 shows cross-sections through the MLSR surfaces for parameters of the mcDESPOT_{P11}, mcDESPOT_{P12}, mcDESPOT_{P13}, and CPMG signal models. Results are presented for both the restricted (Fig. 2a) and expanded (Fig. 2b) parameter bounds at SNR of 200 and for the noiseless case. In the noiseless case with expanded parameter bounds, the MLSR for f_s and $T_{2,l}$ were flat for all signal models. However, the MLSR of $T_{2,s}$ showed a clear global minimum for the mcDESPOT_{P12}, mcDESPOT_{P13}, and CPMG signal models with several local minima for mcDESPOT_{P11}. mcDESPOT_{P11} demonstrates a flat MLSR for both $T_{1,s}$ and $T_{1,l}$ while the MLSR for both mcDESPOT_{P12} and mcDESPOT_{P13} showed a certain degree of improvement for $T_{1,b}$ but several local minima for $T_{1,s}$. Although the flatness of the MLSR of f_s and $T_{2,l}$ were virtually unchanged for mcDESPOT_{P11} after the restriction of the parameter bounds, the reduction in flatness for these parameters for mcDESPOT_{P12}, mcDESPOT_{P13} and CPMG was noticeable. However, no notable difference of the MLSR of $T_{1,s}$ between all investigated signal models was observed; a complex local minimum structure was seen in all cases. In contrast, the MLSR of $T_{2,s}$ and $T_{1,l}$ becomes somewhat flatter for both mcDESPOT_{P12} and mcDESPOT_{P13} after the restriction of parameter bounds. Finally, while the energy surfaces for the CPMG-derived parameters were minimally affected by noise, those for parameters derived from mcDESPOT_{P11}, mcDESPOT_{P12} and mcDESPOT_{P13} were markedly affected.

Figure 3 shows the normalized eigenvalue spectra of the Hessian cost function for all signal models as a marker of signal model sloppiness. The eigenvalues of all models were distributed over many decades, but with a smaller range for CPMG compared with all

mcDESPOT models. For the latter, the eigenvalues become less dispersed with increasing number of RF phase increments.

Parameter Estimation from mcDESPOT and CPMG

Figure 4 shows the distribution of parameter values derived from the mcDESPOT_{P11}, mcDESPOT_{P12}, and mcDESPOT_{P13} signal models over 3600 noise realizations. Results are presented for SNR values of 200, 500, and 1000. As expected, both bias and dispersion decreased with increasing SNR. It is clear that bias and dispersion in parameters derived from mcDESPOT_{P11} were much greater than those derived from mcDESPOT_{P12} or mcDESPOT_{P13}, which performed similarly.

Figure 5 shows the distribution of parameter values derived from the mcDESPOT_{P12} and CPMG signal models over 3600 noise realizations. Results are presented for both the restricted and expanded initial parameters bounds of the SRC algorithm for SNR values of 200, 500, and 1000. As expected, both bias and dispersion decreased with increasing SNR. Further, mcDESPOT_{P12}-derived parameters showed larger bias and dispersion than CPMG-derived parameters, especially at lower SNR. Finally, application of restricted parameter bounds to the SRC algorithm decreased both bias and dispersion, particularly for mcDESPOT_{P12} and at low SNR.

Figure 6 shows a comparison of the performance of mcDESPOT_{P12} and CPMG for a range of f_s and SNR. Relative bias and dispersion both increased with decreasing f_s or SNR. Overall, as in the previous results, relative bias and dispersion in parameter estimates were more favorable for CPMG than for mcDESPOT_{P12}. For CPMG, relative bias and dispersion were negligible except for small f_s and low SNR, while for mcDESPOT_{P12} they were negligible only for f_s approaching 0.5 or high SNR.

Figure 7 shows the relative error in estimated B_1 for different combinations of SNR and f_s values. IR-SPGR (Eq. [8]) and SPGR (Eq. [1]) signals with noise were created assuming a two-component system, with the fit then performed assuming a single component. As is evident, the error in the estimation of B_1 was negligible over large ranges of SNR and f_s values and for both moderate (15%) and high (30%) errors in FAs.

Figure 8 shows relative bias and dispersion in parameter estimates obtained from CPMG signal models created with 15% or 30% errors in both excitation and refocusing FAs. Results were obtained for different combinations of f_s and SNR using the EPG algorithm. Both relative bias and dispersion increased with decreasing f_s or SNR. Comparison of Figures 6 and 8 shows that introducing B_1 as a free parameter resulted in a slight degradation of the stability of the fit but had minimal impact on the quality of parameter estimates.

DISCUSSION

Effects of Nonmodeled Finite Relaxation Times on mcDESPOT and CPMG

The impact of finite T_2^* on the derivation of parameters from mcDESPOT is minimized for very short TE (ie, TE = 0.5 ms) (Fig. 1a); while this is easily achieved in spectroscopy, it is

much more challenging in imaging experiments due to RF pulse and gradient durations. Similarly, the impact of finite TR on CPMG results is minimal for TR = 3000 ms (Fig. 1b), which, however, can lead to impracticably lengthy acquisition times for high-resolution or large-region imaging. The significance of these particular errors must be considered in comparison to the numerous experimental and physiological effects that cause received signals to deviate from ideal models; these effects include diffusion (43–50), exchange (1,25,26,28,51–53), offresonance effects (33,54–57), magnetization transfer (58–62), J-coupling (63–65), spin locking (66–68), internal gradients (69–72) and magnetization spoiling (73–75). The importance of these effects in a particular experiment will depend both on the specifics of the sample or subject under investigation and on the details of the pulse sequence, including the selection of parameters such as TE, TR, FAs, and gradient durations and amplitudes (76–79). Although a comprehensive simulation analysis of these myriad effects may be impractical, it is nevertheless clear that overall, mcDESPOT and CPMG will be influenced to substantially different degrees by these nonideal effects. Therefore, parameters derived from these two sequences may not be strictly comparable; this is supported by a recent in vivo study that showed substantial differences in parameters derived from mcDESPOT and GRASE for relaxation times and component fractions in human brain (17). As a result, we have focused on the reproducibility of the methods individually.

We have presented above the results of limited investigations into the effects of incorporating finite TE into the SPGR sequence used in mcDESPOT, and finite TR into the CPMG sequence. An additional somewhat more complex issue of potential significance is the neglect of the transverse signal decay that occurs during the time between the preceding pulse and the echo formation in bSSFP, that is, neglect of finite TE effects. This may introduce additional bias in parameter estimates. However, the focus of the present work was to rigorously compare CPMG and mcDESPOT as usually implemented.

Energy Surfaces and Sloppiness of mcDESPOT and CPMG Signal Models

The displayed energy surfaces (Fig. 2) indicate the reason that the quantitative parameter estimates from mcDESPOT were inferior to those derived from CPMG (Figs. 5 and 6). In fact, energy surfaces of mcDESPOT clearly exhibit local minima and substantial instability with respect to noise. Consistent with these observations, the eigenvalues of the Hessian matrix of the cost function of mcDESPOT were more dispersed than those of CPMG (Fig. 3), indicating the higher degree of inherent sloppiness of the mcDESPOT signal model. However, sloppiness analysis does not incorporate constraints on the parameter space underlying parameter estimation. This may explain the decreased sloppiness of mcDESPOT with increasing RF phase increments. We find that inclusion of additional nonredundant models, all of which are described by the same parameter set, results in a more constrained fit and therefore in reduced sloppiness.

Reproducibility of Parameters Derived from mcDESPOT and CPMG

We compared the quality of parameter estimates from mcDESPOT and CPMG for two-component systems on an equal-time basis, using the SRC algorithm for both restricted and expanded initial parameter bounds (Figs. 4–6). We found a substantial improvement in

accuracy and precision in parameter estimates obtained from mcDESPOT_{P12} compared with mcDESPOT_{P11}, in agreement with the results of a recent CRLB analysis (7). Consistent with this, we found that mcDESPOT_{P12} displayed more favorable energy surfaces than did mcDESPOT_{P11} in terms of both local minima and curvature (Fig. 2), as well as reduced sloppiness (Fig. 3). This improvement is again likely due to the inclusion of an additional nonredundant model described by the same parameters, resulting in a more constrained fit. No additional improvement was observed upon the addition of a third RF phase increment, which may represent a marginal further constraint over mcDESPOT_{P12} but which nevertheless requires additional acquisition time. Furthermore, we performed several additional phase increment combinations, consisted of data sets generated respectively with phase increments of 90° and 180°, as well as data sets generated with phase increments of 0° and 90°. The results were very similar to those obtained with phase increments of 0° and 180°, with a marginal superiority found for the latter combination. However, the dispersion in parameter estimates from mcDESPOT were significantly lower than those obtained through CRLB analysis; this may be attributed to the fact that CRLB analysis does not consider the constraints in parameter space (80,81).

We found that CPMG provided higher-quality parameter estimates than any of the mcDESPOT approaches, especially at low to moderate SNR (Figs. 5 and 6). The MLSR surfaces for CPMG exhibited more distinct minima, and a less complex pattern of local minima (Fig. 2). This pattern was seen over all noise realizations. Further, CPMG was less sloppy compared with any of the mcDESPOT signal models (Fig. 3).

Finally, we have shown that restricting initial parameter bounds leads to somewhat improved MLSR surfaces (Fig. 2). This was most evident at low to moderate SNR, corresponding to clinically achievable values (17). However, achieving this modest improvement may require a greater degree of a priori knowledge of possible parameter values than is available; given the experimental and physiologic variability in these experiments, appropriate results may differ substantially however from initial values based on preexisting literature.

mcDESPOT approach

We assumed no exchange in the mcDESPOT signal model for several reasons. First and foremost, our interest in the present study was with the most basic forms of CPMG and mcDESPOT, and we likewise did not incorporate exchange into the CPMG formalism (51,52,82). In addition, even with this simplification, a fit of five unknown parameters is still required for mcDESPOT. Furthermore, a recent report has suggested that the incorporation of two-site exchange has a minimal effect on the estimated values of the rapidly relaxing fraction of a two-component model (17), which is the main parameter of interest (3–6,8,9,11,17). Nevertheless, even without exchange, we found a high degree of instability in parameters derived from mcDESPOT, especially at low SNR (Figs. 4–6) due to the flatness and local minima of the MLSR surfaces (Fig. 2), as expected with higher dimensional problems and with decreasing SNR (Fig. 3) (18,19). Nevertheless, in the particular case of high SNR, mcDESPOT analysis permits high accuracy and precision in all parameter estimates, especially for mcDESPOT_{P12} and mcDESPOT_{P13} (Figs. 4–6). If this SNR requirement is met, then mcDESPOT would have the distinct advantage over CPMG of

providing longitudinal and transverse relaxation times of molecular water components; this could be of particular use when analyzing tissues by multivariate analysis (83). Furthermore, mcDESPOT is more appropriate for characterizing tissues with short T_2 , such as cartilage (6), in which case CPMG is very limited because of its prolonged TE.

Our results were consistent with previous CRLB analyses (7), which indicated the efficiency of incorporating data from two bSSFP datasets obtained with different phase increments (Fig. 4). In practice (17,28), this dataset is generated for different FAs over a large range. This general aspect of mcDESPOT is illustrated in Figure 9a, showing that the information content of the bSSFP signal obtained with 0° RF phase increment is concentrated within a narrow range of low FAs, which is also the regime of greatest SNR. Therefore, for a given number of acquisitions, improved results may be obtained by restricting the range of FAs acquired to this high-SNR regime, as indicated in Fig. 9b. However, despite these improvements, parameter estimation using CPMG remains more efficient and stable than estimation using mcDESPOT at low to moderate SNR.

To reduce the number of free parameters, B_1 values can be obtained with the DESPOT1-HIFI approach with a fit to a single component. Our results show that this strategy is very accurate in a clinical SNR regime (Fig. 7), at least for the case we have considered of negligible exchange. Further simulations and phantom and in vivo analyses would be required to explore the limits of validity of the DESPOT1-HIFI approach to B_1 mapping.

Our analyses were conducted under the assumption that all proton pools were on-resonance. However, it is well-known that bSSFP suffers from off-resonance effects (84,85) which may be included in parameter estimation (27,28,33). This is performed by incorporating an additional off-resonance parameter, ω , into the data analysis (Eq. [4]). To avoid this additional complexity, the mcDESPOT-FM approach (86) can be used to estimate ω from the bSSFP signal obtained at different RF phase increments assuming a single-component system and then used as a known parameter in the mcDESPOT analysis. In the case of multi-component systems, this may result however in biased estimates of ω . We investigated this by simulating noise-free two-component bSSFP signals (Eq. [4]) for RF phase increments of 0° and 180° and then performing a parameter fit assuming a single component system. Figure 10 shows the relative error in the estimated ω obtained from this approach for different combinations of TR , ω and f_s . As can be seen, the error in the estimation of ω was negligible over a large range for these values, so that the assumption of a single-component system still provides an accurate estimate of ω . Note that this analysis again excluded exchange between compartments and was performed at infinite SNR, and further assumed identical off-resonance frequencies for all proton pools. Further simulation analyses and experimental work would be required for a more complete exploration of the limits of validity of this approach for off-resonance mapping.

CPMG Approach

We used 32 echoes in the CPMG analyses, within the range used in clinical practice and consistent with a relatively rapid acquisition with $TR \sim T_{1,\rho}$. Although incorporating a larger number of echoes will improve the numerical results (87), this may come at the expense of a

longer TR, considerably prolonging acquisition time and rendering this technique impractical for high-resolution whole brain studies.

Our results (Fig. 8) showed that FA imperfections, analyzed through the use of the EPG algorithm, have a negligible impact on the stability of the fit. However, we did not investigate the related issue of imperfect slice profiles. Lebel and Wilman (88) provide a formalism for addressing this through incorporation of RF pulse profiles in the EPG algorithm. This method could readily be extended to multicomponent analysis.

The SRC algorithm is applied here as a particular implementation of NLLS. NLLS requires the specification of the exact model to be fit, which, in our case, consists of the sum of two exponentials, as well as initial estimates for fit parameters (89). By definition, all exponential components represented in the model are resolved and characterized by the NLLS algorithm, although the interpretation is complex if the prespecified model incorporates an incorrect number of significantly contributing components. This restriction is often avoided by performing multiexponential transverse relaxation analysis using the NNLS algorithm (8,17), which does not require any a priori assumptions about the number of relaxing components. The flexibility of the NNLS approach, however, leads to much more stringent SNR requirements for stability and accuracy compared with NLLS (90). In addition, although regularization improves the stability of NNLS analysis with respect to noise, NNLS may not appropriately resolve exponentially relaxing components in the derived histogram of T_2 values. On the other hand, an underlying distribution of T_2 relaxation times that is not comprised of distinct components, such as one that incorporates a broad distribution of relaxation times, may be more accurately represented through NNLS analysis.

CONCLUSIONS

We find that the discrepant performance of mcDESPOT and CPMG for parameter estimates in two-component systems may be accounted for by the details of the fitting characteristics of the corresponding signal models, which in turn are sensitive functions of physiologic parameters and details of the pulse sequences implemented. In general, CPMG substantially outperformed mcDESPOT in the regime of low to moderate SNR, with the complexity of the mcDESPOT signal model limiting its performance. However, at high SNR, the mcDESPOT approach incorporating two-step phase increments can yield accurate parameter estimates while providing values for longitudinal relaxation times that are not available through CPMG.

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FIG. 1.

Relative error in parameter estimates obtained from fitting simulated data with (a) conventional mcDESPOT (Eqs. [3] and [4]) and corrected mcDESPOT (Eqs. [2] and [4]) signal models for different combinations of TE_{SPGR} and f_s and (b) conventional CPMG (Eq. [6]) and corrected CPMG (Eq. [5]) signal models for different combinations of TR_{CPMG} and f_s . Analyses were performed at infinite SNR.

FIG. 2.

Minimum least squares residual (MLSR) of parameters of interest for mcDESPOT_{P11}, mcDESPOT_{P12}, mcDESPOT_{P13}, and CPMG signal models. Results were presented at infinite SNR (the noiseless case) and at SNR of 200 for (a) restricted and (b) expanded parameters bounds. True underlying parameter values were: $f_s = 0.15$, $T_{2,s} = 15$ ms, $T_{2,l} = 90$ ms, $T_{1,s} = 450$ ms, and $T_{1,l} = 1400$ ms (dashed black lines).

FIG. 3.

Eigenvalue spectra of the Hessian matrix of the cost function for mcDESPOT_{P11}, mcDESPOT_{P12}, mcDESPOT_{P13} and CPMG signal models. The evaluation was performed using the correct underlying input parameter values of $f_s = 0.15$, $T_{2,s} = 15$ ms, $T_{2,l} = 90$ ms, $T_{1,s} = 450$ ms and $T_{1,l} = 1400$ ms.

FIG. 4.

Parameter estimate distributions obtained using Monte Carlo simulations of the mcDESPOT_{PI1}, mcDESPOT_{PI2}, and mcDESPOT_{PI3} signal models using the expanded initial parameter bounds. Results were obtained at three SNRs of 200, 500, and 1000. Mean and standard deviation values for each parameter at each SNR are given at the top of the panels. True underlying parameter values were: $f_s = 0.15$, $T_{2,s} = 15$ ms, $T_{2,l} = 90$ ms, $T_{1,s} = 450$ ms, and $T_{1,l} = 1400$ ms (dashed black lines).

FIG. 5.

Parameter estimate distributions obtained using Monte Carlo simulations of mcDESPOT_{p12} and CPMG signal models. Results were obtained at three SNRs of 200, 500, and 1000 for (a) restricted and (b) expanded parameter bounds. Mean and standard deviation values for each parameter at each SNR are given at the top of the panels. True underlying parameter values were: $f_s = 0.15$, $T_{2,s} = 15$ ms, $T_{2,l} = 90$ ms, $T_{1,s} = 450$ ms, and $T_{1,l} = 1400$ ms (dashed black lines).

FIG. 6.

Relative bias and dispersion in parameter estimates obtained from mcDESPOT_{P12} and CPMG analysis using the expanded initial parameter bounds. Results were obtained for different combinations of f_s and SNR values. Values for the other input parameters were: $T_{2,s} = 15$ ms, $T_{2,l} = 90$ ms, $T_{1,s} = 450$ ms, and $T_{1,l} = 1400$ ms.

FIG. 7.

Relative error in the estimation of B_1 for different combinations of SNR and f_s values. IR-SPGR (Eq. [8]) and SPGR (Eq. [1]) signals were created assuming a two-component system, with the fit then performed assuming a single-component system. Results were obtained for FA errors of 15% and of 30%. Values for the other experimental and input parameters were: $T_{2,s} = 15$ ms, $T_{2,l} = 90$ ms, $T_{1,s} = 450$ ms, and $T_{1,l} = 1400$ ms.

FIG. 8.

Relative bias and dispersion in parameter estimates obtained from CPMG signal models generated with 15% or 30% error in both excitation and refocusing FAs using the EPG algorithm. The fit was performed using EPG with B_1 as a free parameter. Results were obtained for different combinations of f_s and SNR values. Values for the other input parameters were: $T_{2,s} = 15$ ms, $T_{2,l} = 90$ ms, $T_{1,s} = 450$ ms, and $T_{1,l} = 1400$ ms.

FIG. 9.

(a) bSSFP signal as a function of FA for three f_s values. Signals were generated for 0° (red) and for 180° (blue) RF phase increments as discussed in the text. (b) Relative bias and dispersion in parameter estimates obtained from mcDESPOT_{PI2} with a large range of FA given by {2, 6, 14, 22, 30, 38, 46, 54, 62, 70}° or with a restricted range of FA, from 2° to 29° in increments of 3°. Results were obtained for different combinations of f_s and SNR values. Other input parameter values were: $T_{2,s} = 15$ ms, $T_{2,l} = 90$ ms, $T_{1,s} = 450$ ms, and $T_{1,l} = 1400$ ms.

FIG. 10.

Relative error in the estimation of off-resonance frequency, ω , for different combinations of $TR \Delta\omega$ and f_s values. bSSFP free-noise signals (Eq. [4]) were created for RF phase increments of 0° and 180° assuming a two-component system, with the fit then performed assuming a single component. T_1 and B_1 were obtained using the corrected DESPOT-HIFI approach. The other experimental and input parameters values were: $B_1 = 0.8$, $T_{2,s} = 15$ ms, $T_{2,l} = 90$ ms, $T_{1,s} = 450$ ms, and $T_{1,l} = 1400$ ms.