Optimal Unbiased Steady-State Relaxometry with Phase-Cycled Variable Flip Angle (PCVFA) by Automatic Computation of the Cramér-Rao Lower Bound

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Target Audience: MR scientists interested in relaxometry and ways to optimize parametric mapping protocols.

Purpose: Quantitative imaging methods seek to estimate tissue specific parameter values by repeatedly applying variations of a pulse sequence, often along only one free dimension, and fitting a signal equation to the acquired data. The Cramér-Rao lower bound (CRLB) provides a lower bound on the variance of an estimator using a given signal equation and protocol. This has been utilized in the past to not only analyze the effectiveness of mapping methods[1] but also to optimize their design by finding the protocol that minimizes the CRLB and provides the most precision per unit scan time.[2,3] However, the application of the CRLB to more complex signal behavior has been limited due to the difficulty of analytically deriving the bound. Fortunately, modern computational methods, most importantly automatic differentiation,[4] provide the ability to efficiently calculate all the necessary components of the bound to machine precision. We present a computational framework written in Python that enables the calculation of the unbiased CRLB for arbitrary signal equations with no more effort than implementing the equation under study. It is applied to the study of T1 and T2 mapping with SPGR and bSSFP steady-state sequences. These were previously used together in the DESPOT2 technique.[5] The newly derived optimal estimator, called phase-cycled variable flip angle (PCVFA), is gauged against this previous scheme.

$$(1)\quad g_{SPGR}(\alpha, TR; T1, M0) = M0\frac{\left(1-e^{-TR/T1}\right)\sin(\alpha)}{1-e^{-TR/T1}\cos(\alpha)}$$

$$(2)\quad g_{bSSFP}(\alpha, TR; T1, T2, M0) = \|\text{Eqns. [9]}+i\text{[10]}\| \text{ from Ref. 6}$$

$$(3)\quad J_{i,j} = \frac{\partial g_i^{protocol}(\theta)}{\partial \theta_j}$$

$$(4)\quad F = J^T \Sigma^{-1} J$$

$$(5)\quad \sigma_{\theta_j}^2 \geq \left(F^{-1}\right)_{jj}$$

Theory: Equations (1) and (2) give the SPGR and bSSFP signal equations. For the latter, we consider the magnitude of the signal immediately after the excitation.[6] TE is assumed small so that T2* effects are negligible. The unbiased CRLB is formulated here for simplicity with the assumption that the noise is normally distributed. This is a mild restriction that only fails in the case of extremely low signal. In Eqn. (3), $g^{protocol}(\theta)$ represents the vector of signal equations from the different sequences collected in the protocol. θ is the vector of parameters that are being estimated, e.g. T1, T2, and M0. The noise covariance matrix, Σ, incorporates the relative acquisition time fraction for each series in the protocol and is assumed diagonal for the typical case that the signals are independent. Eqn. (5) expresses the bound: the variance of the estimate of a parameter θ_i is lower bounded by the corresponding diagonal entry on the inverse of the Fisher information matrix formed in Eqn. (4) with the Jacobian matrix of the protocol and Σ.

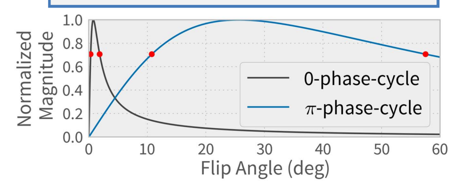

Fig. 1: The optimal PCVFA protocol using phase-cycled bSSFP, each acquired at the flip angle pairs that give 1/√2 of the maximum.

Methods: The Python programming language was used to create a framework that can accurately analyze this setting with SciPy for function optimization and PyAutoDiff for automatic differentiation of arbitrary functions. First, the DESPOT2 case was re-examined to verify the validity of the framework and the approach of protocol optimization by minimization of the CRLB. DESPOT2 imposes particular restrictions on the problem formulation and free variables. The optimal SPGR flip angles for T1 estimation and π-phase-cycled bSSFP flip angles for T2 estimation were found in two separate problems. For the latter, T1 was assumed known and eliminated from the bSSFP Jacobian. The acquisition time fraction was then found only between the SPGR and bSSFP portions, instead of being adjustable for all angles, by minimizing the sum of the coefficient of variations (CoV) of T1 and T2 ($\sigma_{T1}/T1+\sigma_{T2}/T2$, where σ was provided by the CRLB). Second, the unrestricted joint problem of estimating T1 and T2 simultaneously was treated with the free variables: flip angle, phase cycle, and acquisition time fraction. All protocols containing up to 6 acquisitions were searched for the best mixture of SPGRs and bSSFPs. The abovementioned was investigated for typical 3T WM (T1=1100ms, T2=60ms) and GM (T1=1645ms, T2=85ms) relaxation values.[7]

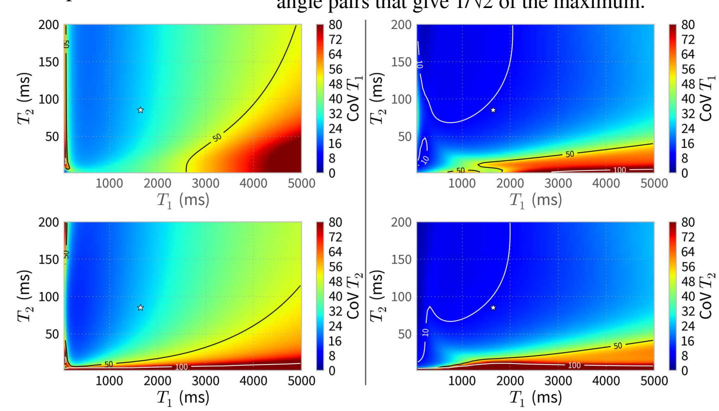

Fig. 2: T1 (top) and T2 (bottom) CoVs of the optimal GM protocols over a tissue range for columns (a) DESPOT2 and (b) PCVFA. ★denotes the target GM tissue.

Results: The framework reproduces the optimal protocol for DESPOT2 as described in [5]. In fact, it is more accurate because there are no polynomial approximations. The analysis suggests to within 5 decimal places that it is best to acquire the pairs of flip angles that attain 1/√2 of the max signal for both SPGR and π-phase-cycled bSSFP, compared to the literature value of 0.71. This has previously been established as the exact solution.[8] The framework also determines the best fraction of time to spend on the SPGR as 0.734 for WM and 0.756 for GM, which is close to the approximate value of 0.75 stated in the past.[5] These optimal DESPOT2 protocols achieve a sum of T1 and T2 CoVs of 45.7 and 53.0 for WM and GM. Solving the unrestricted joint problem, which took 2m38s on a 12-core 2.66 GHz Intel Xeon, suggests a different paradigm: only use phase-cycled bSSFP. The 0 and π phase cycles should be collected, each with a pair of flip angles that attain 1/√2 of the max signal for that phase-cycle (Fig. 1). Equal time fraction should be devoted to each of the 4 images. It achieves a sum of CoVs of 20.8 and 21.6 for WM and GM, showing more than 2.1x improvement over DESPOT2. Fig. 2 displays how the CoV in T1 (top) and T2 (bottom) varies across tissues using the optimal GM protocol of DESPOT2 (left column, a) and PCVFA (right column, b).

Discussion/Conclusion: We demonstrate using our new framework that separating SPGR and bSSFP for T1 and T2 estimation as in DESPOT2 is not the ideal approach because it conceals the effect of the T1 uncertainty on T2 precision. Our analysis takes this into account and arrives at the PCVFA solution with greater than two-fold improvement in noise performance, or effectively a four-fold scan time reduction. On-resonance, uniform B1+, and the use of magnitude images have been assumed in this work, but the alternatives can also be analyzed in this fashion. The presented framework is highly flexible and suitable to a variety of protocol optimization problems that exist in parametric mapping. It is open source and available on the web at sujason.web.stanford.edu/quantitative/.

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