**Introduction:** T2 and T1 estimation improves characterization of various pathologies, but lengthy scan-times preclude widespread application of quantitative MRI (qMRI), so sequences have been developed for efficient 3D acquisitions. For example, 3D-QALAS utilizes an interleaved Look-Locker acquisition with a T2-preparation pulse for full brain quantification of T1 and T2. However, 3D-QALAS applies constant flip angles and reconstructs images at 5 time-points that suffer from blurring due to signal evolution during the lengthy echo-train. Summarized by Figure 1, we propose improving 3D-QALAS by: (1) incorporating subspace-based reconstruction that resolves complete temporal dynamics to eliminate blurring (2) optimizing acquisition flip angles with the Cramer-Rao-Bound (CRB) using simulation compatible with auto-differentiation, (3) and decreasing the number of total acquisitions per repetition time (TR) for reduced scan-time.

**Methods:** Subspace Reconstruction: Conventional 3D-QALAS applies T2-prep and inversion pulses and measures 5 acquisitions which each utilize an echo-train of 4-degree flips. Rather than reconstructing a volume for acquisitions in a 3D-QALAS TR (typically $A=5, E=120 \rightarrow T = 120 \times 5 = 600$ echoes/TR), where $T$ is the total number of echoes. We generate a dictionary of signal evolution to compute a low-dimensional linear basis $\Phi$ with the SVD, producing a tractable reconstruction problem $argmin_{\alpha}||y - A\Phi\alpha|| + R(\alpha)$, where $A$ represents the Fourier, coil, and sampling operators and $R$ regularization. By resolving the spatiotemporal volume with $x = \Phi\alpha$, we aim to estimate sharper quantitative maps utilizing dictionary matching with $T$ echoes.

In-vivo experiments in Figure 2 (A) showcase reduced blurring in estimated $T_2$ maps using subspaces.

**CRB Flip Angle Optimization:** We optimized flip angles in 3D-QALAS by minimizing CRB in two regimes: (1) optimizing one flip angle per echo-train (2) optimizing all flip angles in every echo-train. We initialized both optimizations with the conventional 4-degree flip angles, utilized representative tissue parameters [$T_1=700ms, T_2=700ms, M0=1$] and [$T_1=800ms, T_2=1300ms, M0=1$], and minimized the CRB-based cost function. We implemented an auto-differentiation compatible signal simulation for 3D-QALAS, enabling computation of gradients for CRB based optimization.

Reducing Acquisitions: We designed optimized sequences with $A=\{5,4,3\}$ acquisitions by removing acquisitions from the end of the TR, thus speeding up the scan.

**Experiments:** We implemented the optimized-per-echo-train 3D-QALAS sequence on the scanner and acquired data using the conventional and optimized sequence on the Mini System Phantom, Model #136 (CaliberMRI, Boulder, CO, USA) and a human subject (under IRB approval) with 3 and 5 acquisitions (1x1x1mm$^3$ resolution, R=2). We compared quantitative maps estimated with subspace reconstructions (rank = 3) and dictionary matching.

**Results:** Optimized Sequences: Figure 2 (B) plots optimized flip angles and CRB resultant CRB in comparison to the conventional sequence when applying subspace reconstruction for quantitative estimation. Optimization either reduces CRB or matches conventional 5 acquisition CRB with fewer acquisitions, potentially enabling reduced scan-time. Phantom and In-vivo: Figure 3 (A) and (B) displays estimated maps from phantom and in-vivo data where the per-ETL-flop-angle-optimized sequence with $A=5,3$ acquisitions matches constant flip angles.

**Discussion and Conclusions:** Future work will implement the all-flip-angle-optimized sequence to address the T1-bias in the prospective experiments. Combining subspace reconstruction with auto-differentiation enabled flip-angle optimization yields improved 3D-QALAS sequences with 1.75-fold reduction in scan-time.


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