Comparison of Fitting Methods and b value Sampling Strategies for Intravoxel Incoherent Motion (IVIM) in Breast Cancer

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Target Audience: Physicists and radiologists interested in intravoxel incoherent motion (IVIM) imaging, particularly in breast cancer.

Introduction: The selection of diffusion gradients or *b* values for diffusion weighted imaging (DWI) is important for protocol optimization. Currently, many DWI protocols for breast cancer subjects calculate ADC values using maximal *b* values of ~500-800 s/mm^2 [1-3]. Previous literature has shown that different ranges of *b* value selections sensitize the signal to different components of diffusion. Questions remain as to whether *b* values should be adjusted based on conditions such as tumor type. Better estimation of vascular diffusion effects can be made when sampling includes lower *b* values ($0 < b < 200$ s/mm^2). Non-Gaussian diffusion effects at higher *b* values ($b > 1000$ s/mm^2) can affect quantification even with the simple ADC model [4-6]. Consequently, quantification of DWI data with the biexponential intravoxel incoherent motion (IVIM) fitting model can be numerically nontrivial, and a variety of methods have been developed to address this challenging quantification [7-11]. Furthermore, quantitative optimization for *b* value sampling based on the minimization of analytical error propagation factors shows that an evenly distributed sampling of *b* values is not necessarily optimal for the biexponential model [10]. In this study, we employ an optimized *b* value selection for biexponential IVIM analysis of breast lesions to increase precision of the biexponential fitting of IVIM analysis. Mean diffusion parameter values of breast lesions have been shown to be comparable to values found in renal lesions. This study is therefore guided by analytical and simulation results from a renal IVIM study [10] and implements a similar optimized *b* value selection pattern of repeated acquisitions at key *b* values rather than conventionally distributed sampling. Also, the conventionally sampled dataset is analyzed with both an unconstrained least squares fit ("free"), and a 2-step constrained analysis ("segmented") approach to reduce measurement error. This fitting strategy has been used in a range of *in vivo* IVIM studies [12-15] to increase precision while making stronger assumptions about the estimated parameters' values. The motivation for these alternative techniques is to increase measurement precision, thereby increasing diagnostic differentiation between cancerous subtypes and potentially allowing more careful monitoring of response to treatment.

Methods: 14 Patients (age 48.4±14.27 years) with 14 diagnosed cancerous lesions underwent a HIPAA-compliant, IRB approved diffusion MR study. All patients were examined in a full body Siemens 3T MRI scanner using a 7-ch breast coil (Invivo Corp). Patients underwent a standard bilateral MRI breast examination using contrast enhancement along with diffusion-weighted imaging (DWI). DWI protocol used a twice-refocused, bipolar gradient single-shot turbo-spin echo (TSE) sequence (TR/TE = 2000/103 ms, 108 x 128 matrix, 18 axial slices, 2.7 x 2.7 x 4 mm voxel, single direction) with frequency-selective fat suppression and diffusion sensitization in the anterior–posterior direction applied with 2 different sets of weighting factors (*b* values) of (conventional) 0, 30, 70, 100, 150, 200, 300, 400, 500, 800 s/mm^2 and (optimized) 0 s/mm^2 plus 3 repetitions of 70, 300, 800 s/mm^2. These *b* values are close to the values optimized by a previous approach [10]. Analyses for IVIM parameters were derived from custom data analysis (Igor Pro 6, Wavemetrics). ROIs were drawn around the outer tumor border limiting IVIM analysis within the tumor region. ADC values were calculated using monoexponential fit while IVIM biomarkers (tissue diffusivity D_t, pseudodiffusivity D_p, perfusion fraction f_p) were calculated using "free" vs. "segmented" fitting for conventional *b* value selection [1] and "free" fitting for an optimized *b* value selection. Measurement precision (relative error), defined by uncertainty of each parameter measurement from least-square fitting divided by its mean value, was statistically compared between the different methods. Coefficients of variation (CV) represented the group variance of each parameter.

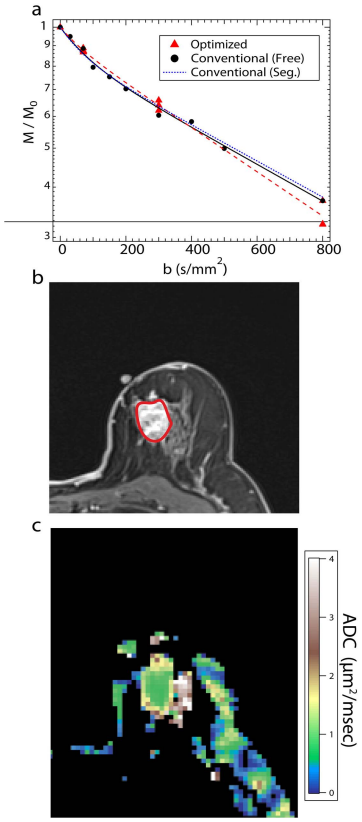

Figure 1. (a) Signal decay curves, (b) Post contrast T1w image, and (c) ADC map of a 3.5 cm invasive ductal carcinoma.

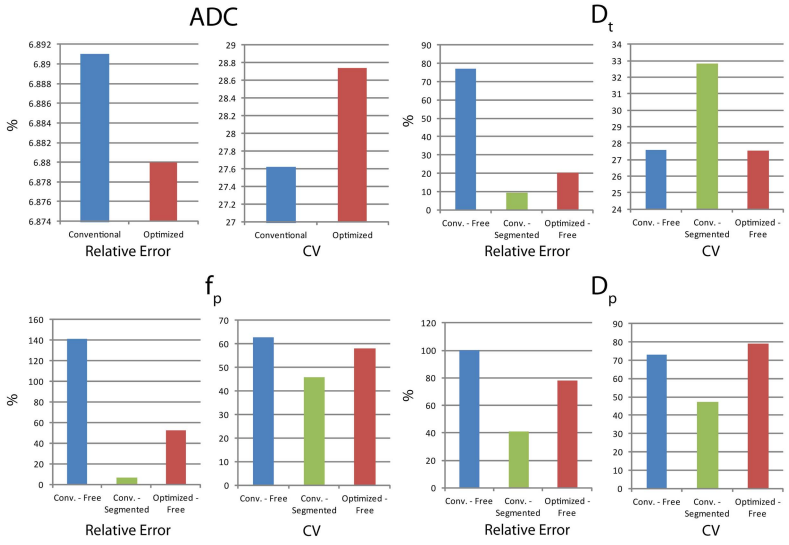

Figure 2. Average relative error (%) and CV (%) of ADC and IVIM parameters.

Results: Figure 1 shows the diffusion weighted signal decays, contrast-enhanced images, and ADC maps for a locally advanced breast cancer patient. Figure 1a shows the three different fitting methods employed, showing similar fit quality. When observed more closely, either "segmented fitting" with conventional *b* values or free fitting with optimized *b* values show significant ($p < 0.05$) improvement in precision when compared to the "free" fit method with conventional *b* value in all IVIM estimations (Figure 2). Regarding accuracy, significantly lower f_p values were estimated for conventional "segmented" approach than for the conventional "free" and optimized "free" approaches.

Discussion/Conclusion: Comparison of the different methods showed that the "segmented" analysis and the optimized *b* value selection method have higher precision when considering all parameters. The "segmented" approach estimates a lower f_p value when compared to the other two approaches, which may be due to its stronger assumptions, but offers improved precision compared to the other approaches. Interestingly, the results from the optimized *b* value selection were generally outperformed by the "segmented" approach. This may be due to the fact that *b* value selection was based on simulations from renal tissue. Limitations on the number of subjects may have also affected these results. Future simulations of precision and accuracy of these methods may clarify these findings. Future studies should explore a hybridization of both fit algorithms and *b* value selections to better define the vascular and cellular biomarkers of the IVIM model in breast cancer analysis.

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