Towards Organ-specific b-Values for the IVIM-based Quantification of ADC: In vivo Evaluation in the Liver

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INTRODUCTION – In oncology, the apparent diffusion coefficient (ADC) has the potential to serve as early biomarker of treatment success, tumor recurrence, and treatment outcome [1-2]. However, diffusion sequences are sensitive not only to pure molecular diffusion, but also to microscopic translational motion due to blood perfusion [3]. In highly perfused organs such as the liver, the perfusion effect can lead to a significant overestimation of ADC if a conventional mono-exponential model is applied for computation [4]. The intra-voxel incoherent motion (IVIM) approach has been proposed to separate perfusion and diffusion components and has been applied successfully in the abdomen [5]. Optimal selection of b-values is an essential part of IVIM in order to (a) eliminate systematic errors (bias) due to perfusion and (b) to maximize the precision of the ADC estimates for a given scan time [6]. In this work, we applied Monte Carlo simulations to derive an optimal four b-value sampling scheme for the liver and evaluated the obtained improvements in SNR of ADC in 27 patients with respect to a standard protocol used previously in the workup of liver lesions at the clinical institution.

METHODS – The simplified IVIM model, in which the perfusion effect is modeled by a Delta function for b = 0 s/mm^2, was applied in our study [3]: $S_{IVIM}(b) = S_0 \cdot \left((1-f)\cdot \exp(-b\cdot D) + f\cdot \delta_0(b)\right)$. S_0 is the initial signal amplitude, f the perfusion fraction, and D the ADC. This extended mono-exponential model, which assumes that the perfusion term vanishes for all non-zero b-values, allows the perfusion-corrected estimation of ADC provided that the first non-zero b-value has been chosen carefully.
Following [6], Monte Carlo simulations of a bi-exponential diffusion process were performed to select a four b-value sampling scheme allowing the IVIM-based estimation of ADC with negligible bias and maximal precision, i.e. lowest noise-induced standard deviation. A total of 90 b-value combinations were compared with b_0 = 0 s/mm^2, 50 ≤ b_1 ≤ 300 s/mm^2, 300 ≤ b_2 ≤ 1000 s/mm^2 and 700 ≤ b_3 ≤ 2000 s/mm^2. To account for the in vivo variability of perfusion parameters, perfusion fraction and pseudo-diffusion coefficient (D^*) were treated in the simulations as random variables with a uniform distribution in the range of [5%-50%] for f and [10-100] 10^{-3} mm^2/s for D^*, which is different from the approach proposed in [6] where the perfusion parameters are assumed to be constant for a given organ. Gaussian noise was added to the simulated complex data. For each simulation, model parameters (S_0, D, and f) were estimated by means of a non-linear least-squares algorithm. Normalized bias and normalized standard deviation (SD) of the ADC estimates were computed on the basis of 50000 Monte Carlo samples per b-value combination.

Based on these results, the b-value combination with the lowest SD and negligible bias was selected and applied in 27 consecutive patients undergoing liver MRI on a 3T scanner (Achieva, Philips Healthcare) to assess various benign and malignant focal liver lesions. A mixed protocol consisting of the b-values originally used at the clinical institution (b = 0, 300, 500, 700 s/mm^2) and the Monte Carlo based b-values (b = 0, 150, 700, 1000 s/mm^2) was applied for each patient. ROIs were placed in normal liver tissue, taking care to avoid large vessels. Mean and SD of ADC were computed per ROI for each of the two b-value combinations, both with the IVIM model and with the widely used mono-exponential model. Differences in ADC mean and SD between the computation methods were assessed for statistical significance with paired Student's t-tests.

RESULTS – In the simulations, b-value combinations for which b_1 was below 150 s/mm^2 were characterized by a systematic overestimation of ADC due to the perfusion effect. Amongst the combinations with negligible bias (< 3%), the sampling scheme (b = 0, 150, 700, 1000 s/mm^2) had the lowest SD over the range of interest [0.5-2.0] 10^{-3} mm^2/s (Fig. 1, *top*). Note that the normalized SD for this sampling scheme was approximately constant for 1.0 ≤ ADC ≤ 2.0 10^{-3} mm^2/s and about 45% lower than for the original b-value sampling scheme (b = 0, 300, 500, 700 s/mm^2).
In the liver patients (Fig. 1, *bottom left*), no significant change of the average ADC computed with IVIM was observed between original and new protocols (1.04 and 1.01 10^{-3} mm^2/s respectively, p = 0.15). However, the computed SD was significantly lower with the new protocol (0.18 vs. 0.33 10^{-3} mm^2/s, p < 0.001), confirming the Monte Carlo predictions (Fig. 1, *bottom right*). ADC values computed with the mono-exponential model were significantly higher for both original and new protocols (1.44 and 1.21 10^{-3} mm^2/s, p < 0.001).

CONCLUSION – Careful choice of the b-values for in vivo measurements of ADC with IVIM is required to obtain non-biased ADC values with maximal precision for a given acquisition time. The proposed Monte Carlo methodology allows targeting the b-values to the organ-specific perfusion regime. Our results showed that b-value sampling schemes designed to minimize noise propagation can significantly outperform common sampling schemes such as regular distributions of b-values: In the presented study, a 77% increase in ADC SNR was observed just by modifying two b-values from the original diffusion protocol, confirming the prediction of the Monte Carlo simulations. ADC values measured with IVIM in the liver were well in agreement with previously published values [4].

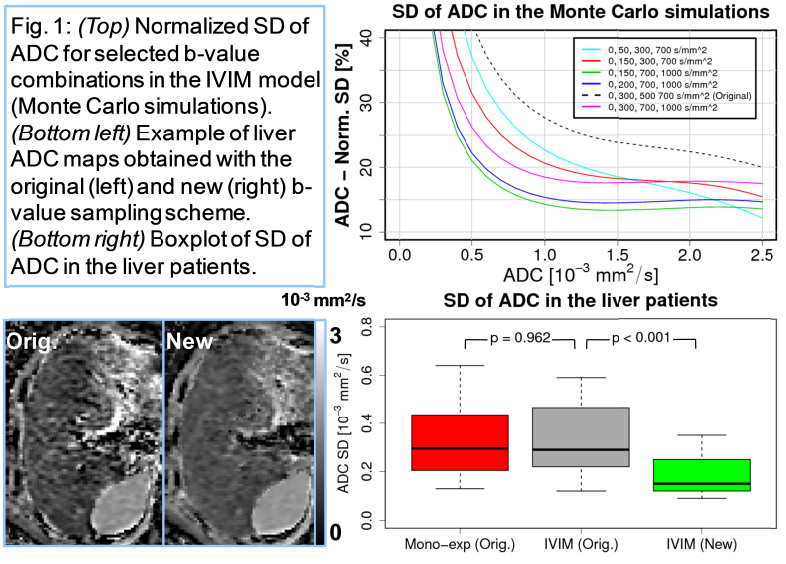

Fig. 1: *(Top)* Normalized SD of ADC for selected b-value combinations in the IVIM model (Monte Carlo simulations). *(Bottom left)* Example of liver ADC maps obtained with the original (left) and new (right) b-value sampling scheme. *(Bottom right)* Boxplot of SD of ADC in the liver patients.

REFERENCES – [1] Moffat et al, Neoplasia, 8:259-67 (2006) [2] Thoeny and Ross, JMRI, 32:2-16 (2010) [3] Le Bihan et al, Radiology, 168:497-505 (1988) [4] Luciani et al, Radiology, 249(3):891-9 (2008) [5] Lemke et al, MRM, 64:1580-5 (2010) [6] Lemke et al, MRI 29:766-76 (2011)