Maximizing Accuracy and Precision on Pharmacokinetic Parameter Estimates in DCE-MRI: What is the Optimal Flip Angle?

O. M. Girard[1], P. O. Scheibe[2], D. R. Vera[1], and R. F. Mattrey[1]
[1]Department of Radiology, University of California, San Diego, CA, United States, [2]Ixzar, Inc., Arroyo Grande, CA, United States

Purpose: Dynamic Contrast Enhanced (DCE) Magnetic Resonance Imaging (MRI) is a promising tool to investigate physiological tissue properties such as blood flow, blood volume, vessel permeability and leakage space. It has been applied in various clinical studies to assess cancer stage or response to therapy. However the accuracy and reproducibility of the method remains a subject for debate since numerous sources of error may bias the pharmacokinetic (PK) parameter estimates [1-4] regardless of the measurement protocol. The standard protocol consists of measuring baseline tissue T_1s (called T_{10}s), and then using a fast spoiled gradient echo (SPGR) sequence, time-dependent MR signal changes are measured after the bolus injection of a low molecular weight Gd-based contrast agent. Although the flip angle (FA) uncertainty can be a major source of error, especially at high field (≥ 3T) [5, 6], its impact on PK parameter estimate error has neither been studied [3] nor has the error been propagated to the PK parameter estimates [2]. Here we propose to address this issue and study the propagation of measurement noise and FA uncertainty all the way through the model to the PK parameter estimates. MR signal and PK models are implemented in this study jointly in a Monte-Carlo simulation that includes a realistic DCE-MRI extraction procedure.

Materials and Methods: PK model: The extended Tofts model [7] that includes an intravascular contribution was considered. The bolus arrival time was set to 0 (no delay between vascular and tissue enhancement). Several PK parameter sets were studied (including muscle, prostate tumor and normal prostate from [8]) and a population-averaged Arterial Input Function (AIF) was used [9] with a standard clinical dose (0.1mmol/kg). MRI model: The usual SPGR signal equation was used assuming negligible T_2 variation during the time course of the experiment, and using a single T_1 value to describe each of the two compartments (fast exchange regime). We used a 5ms repetition time (TR), a 1.4s T_{10}^{Blood}, a 1s T_{10}^{Tissue}, a 4.3mM^{-1}.s^{-1} T_1-relaxivity and a broad range of FAs (5, 15, 30, 45 and 60°). Monte Carlo simulation: The simulation was implemented on Mathematica (Wolfram Research, Inc., IL, USA). PK and MRI models were combined to synthesize time-intensity curves for both AIF and tissue. **1**/ Synthetic MRI data were sampled (6s temporal resolution) from 1min before injection and up to 14min post-injection and zero-mean uncorrelated Gaussian noise was generated and added to them. Such data simulated what could be measured in a real DCE-MRI experiment. For both AIF and tissue, pre-contrast data points were averaged and the corresponding mean was used to normalize the noisy MRI data. Resulting tissue normalized data were processed with a nonlinear least-squares fitting algorithm that combined both MRI and PK models and relied on the "measured" arterial signal to define the AIF. Three PK parameters were adjusted in the model, keeping all the others constant. **2**/ For each parameter set of both MRI and PK parameters, step 1 was repeated 1000 times. Then the corresponding mean and standard error of all three PK parameters were computed. **3**/ Step 2 was performed 5 times setting the two "supposedly known" FAs (AIF and tissue) to 0.8, 0.9, 1, 1.1 and 1.2× their actual values, in order to introduce uncertainty.

Results: Figure 1 displays the standard error and bias calculated from the normal prostate parameter set. Note that the TR and T_{10}^{Tissue} values correspond to a pre-contrast Ernst angle of ≈ 5°. As a control of the Monte Carlo simulation convergence the 30° FA case was studied additionally with 10000 iterations instead of 1000 and only marginal result differences were observed. The 5° FA case was studied (data not shown). It leads to errors higher than 20 % on average. When the actual FA is used in the fitting algorithm, the standard error is minimal at 15° FA, probably due to the high signal-to-noise (SNR) in this regime. However high error amplification occurs as soon as the uncertainty in the flip angle increases. Conversely, in the high FA regime (e.g. for 30°) the bias is reduced and the sensitivity of both bias and standard error vis-à-vis FA uncertainty decreases. However, when the FA becomes too high (e.g. for 60°) the standard error increases significantly because measurement noise becomes the major source of error in this regime. Similar behaviors were observed for all other studied parameter sets.

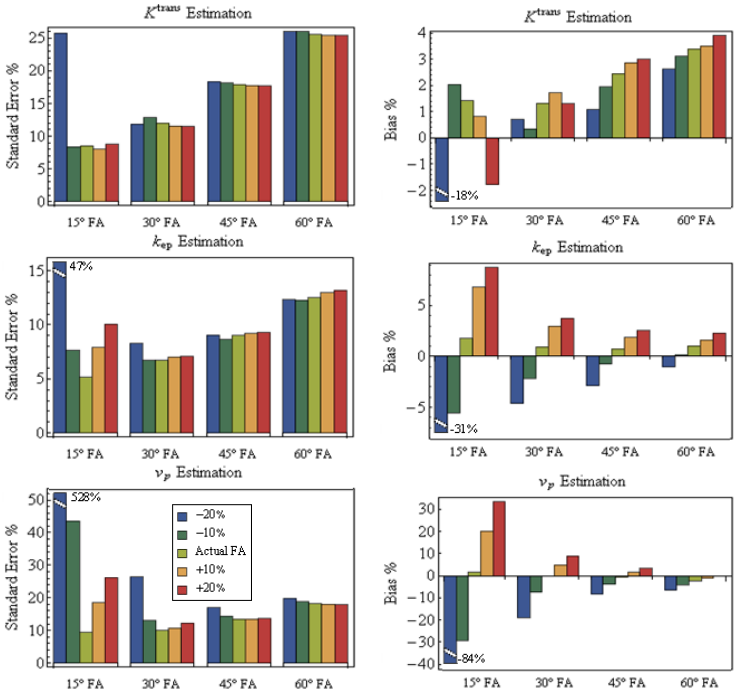

Figure 1: Standard error and bias of the PK parameter estimates as a function of nominal flip angle value (x-axis) and uncertainty (colorbars). Following parameters were considered here: K^{trans} = 0.1 min^{-1}, k_{ep} = 0.5 min^{-1}, v_p = 0.1, TR = 5ms, r_1 = 4.3 mM^{-1}.s^{-1}, T_{10}^{Blood} = 1.4s and T_{10}^{Tissue} = 1s. A SNR of 25 was used for the pre-contrast tissue signal at the Ernst angle in this simulation.

Discussion and Conclusion: Our results show that a measurement regime exists where a FA uncertainty as high as 20% leads to a much lower bias in the PK parameter estimate while keeping the standard error close to its minimum. This regime happens at an FA much higher than the pre-contrast tissue Ernst angle, consistent with the general findings from Schabel and Parker [2].

Several investigators have been working on fast FA measurement techniques to be applied in clinical setup in order to minimize errors in T_1 measurement in general, and PK parameters in particular. Reported uncertainties can be up to 10% [2]. Performing DCE-MRI in the FA regime of low error amplification will minimize the PK parameter estimate errors and could even make an FA measurement step dispensable, thus saving precious scan time.

It should be noted that a residual bias still remains in the estimates even when the actual FA is used in the fitting procedure and that the bias can even be lower using a "wrong" FA. This may be attributed to the nonlinear propagation and averaging of measurement noise or to other sources of error, such as insufficient MRI temporal resolution or the robustness of the fitting algorithm, that are induced in the whole data generation and extraction process, as it would be the case for real data. Although the present study focused on the influence of FA uncertainty on the PK parameter estimate precision and accuracy, further error sources could be easily considered in the same way, especially uncertainty in the measured pre-contrast T_{10}s.

It is not possible to derive here a general expression for the optimal flip angle to be used for all DCE-MRI protocols, since it varies with MRI and PK parameters. However for a short TR of 5ms imposed by the high temporal resolution requirement, and a realistic AIF and set of T_{10}s (1.4s for blood and 1s for tissue), our results strongly suggest that a high FA (> 30°, i.e. about 6 times the corresponding pre-contrast tissue Ernst angle) should be used to optimize accuracy while keeping reasonable precision, for a wide range of PK parameter values.

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