Sources of errors in pharmacokinetic analysis of DCE-MRI

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INTRODUCTION: Dynamic Contrast Enhanced MRI (DCE-MRI) is a functional imaging method whose use in oncology shows a high potential in assessing and predicting treatment response. Before it can be used in standard clinical oncology, however, it first must be validated with respect to accuracy and reliability.

One of the steps required to obtain localized quantitative PK information of tumors is the estimation of the pre-contrast relaxation time, T_{10}. To estimate this parameter, a contrast free sequence of spoiled gradient recalled echo (SPGR) with variable flip angles is used[1]. Although the effects of incorrect T_{10} on the computation of PK parameters have already been reported[2], motion between the variable flip angle volumes is still an unexplored problem which may be a relevant source of T_{10} estimation errors. In rectal tumor scans, for example, deformations are unavoidable, as, in addition to the patient's movement during the acquisitions, it is also subject to physiological motion and deformation of the organs.

This work aims to evaluate the effects of motion within the variable flip angle sequence on accuracy of the estimation of T_{10} and in subsequent Tofts[3] model PK parameter (K_{trans} and k_{ep}) estimation. Moreover, we also estimate the amount of motion present in rectal SPGR sequences. Evaluating and correcting potential sources of error in PK analysis by DCE-MRI may improve reproducibility of this procedure and increase confidence in the results from the clinical research being currently performed.

METHODS: Signal intensity (S) in T_1 MRI images is a function of the relaxation time (T_1), while relaxation time is affected by the contrast agent (CA) concentration. These relations are expressed by the following equations:

$$S = M_0 \sin(\alpha)\left[\frac{1-\exp(-TR/T_1)}{1-\cos(\alpha)\exp(-TR/T_1)}\right]$$ Equation 1: signal intensity in SPGR MRI,

$$\frac{1}{T_1} = \frac{1}{T_{10}} + r_1 C$$ Equation 2: T_1 as a function of CA concentration,

where M_0 is the magnetization, and TR and α are, respectively, the acquisition parameters of repetition time and flip angle. T_{10} is the contrast free relaxation time, r_1 is the CA's relaxivity constant and C is the CA concentration.

PK analysis by the Tofts model requires the concentration curve over time to estimate perfusion parameters (K_{trans} and k_{ep}). Thus, to extract this information from DCE-MRI volumes, the CA free relaxation time (T_{10}) needs to be estimated. This may be done by acquiring several SPGR volumes with fixed TR and variable flip angle. Using Eq. 1, for each voxel, a linear regression between the signal intensity of each volume can be performed and T_{10} and M_0 can be estimated[1]. This approach assumes physical correspondence between the voxels in these volumes, which may not be true if there is motion between these volumes. This motion can lead to misalignment and consequently inaccurate T_{10} computation, which could then compromise the PK analysis of the DCE-MRI time intensity curves.

In this work we performed tests to: (a) estimate the T_{10} error when motion is present in variable flip angle MRI sequences; (b) evaluate how this error propagates to K_{trans} and k_{ep} estimation; (c) quantify the amount of motion found in rectal SPGR variable flip angle sequences.

Estimating T_{10} error caused by motion: 21 synthetic T_{10} and M_0 volume map pairs were generated from rectal MRI volumes with a mean resolution (in mm^3 per voxel) of 0.88x0.88x4.65 and image dimensions of 180x180x26. These maps were used to generate synthetic variable flip angle SPGR sequences using Eq. 1. For each pair, a sequence of 3 or 4 SPGR volumes with flip angles 3°, 9°, 12° and/or 15° and TR=4.5ms was computed. Random (but known) B-Splines free-form deformations[4] were applied to each of these volumes with different levels of mean displacement. The motion corrupted sequences were then used to estimate T_{10} and the results were compared with the ground truth data and the mean absolute percentage error was computed (Fig. 1).

Estimating PK parameter error from T_{10} error: CA curves were generated using the Tofts model and the Orton Arterial Input Function[5] for K_{trans} values ranging from 0.01 to 2.00 and k_{ep} values from 0.01 to 5.00. These curves were then converted into DCE-MRI sequence data using a ground truth T_{10} (1.0s), as well as TR=4.5ms and TE=2.2ms. These synthetic DCE-MRI curves (S(t)) were then used to emulate the process of estimating K_{trans} and k_{ep} with inaccurate relaxation time (T^*_{10}). Iteratively, K^*_{trans} and k^*_{ep} parameters were tested by generating a time intensity curve, which in turn was transformed into a DCE-MRI intensity curve (S*(t)) using Eq. 1 and 2 with T^*_{10}. K^*_{trans} and k^*_{ep} were optimized by finding the minimum squared error between S(t) and S*(t). This allowed the computation of the mean percentage error between the ground truth and the estimated K_{trans} and k_{ep} parameters for different degrees of T_{10} deviation (Fig. 2).

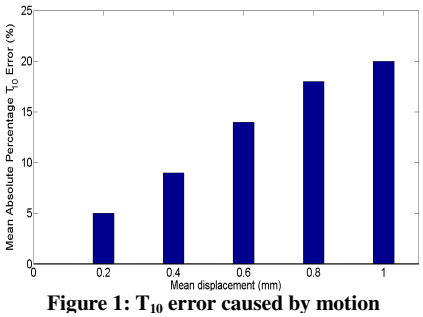

Figure 1: T_{10} error caused by motion

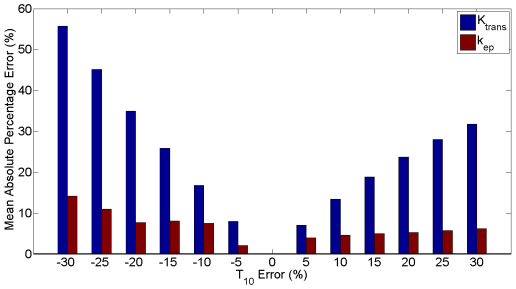

Figure 2: Error propagation from T_{10} to K_{trans} and k_{ep}

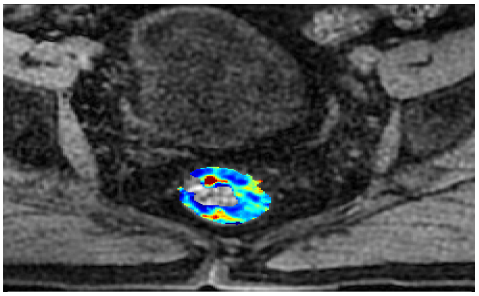

Figure 3: Rectal SPGR image and K_{trans} map

Motion estimation: 21 rectal SPGR variable flip angle sequences (Fig. 3) were used to assess the amount of motion present during acquisitions. Each sequence consisted of 3 to 4 volumes with different flip angles and TR=4.5ms, and they were cropped to a 180x180x26 cube around the rectal region with a mean resolution of 0.88x0.88x4.65mm^3. Motion was estimated by applying a groupwise rigid registration between the volumes of each sequence using a Groupwise Normalized Mutual Information similarity metric[6]. For each transformation found, the mean displacement associated with it was computed. The mean displacement between all the images from all sequences was considered to be an estimate of the amount motion found in this type of acquisitions.

RESULTS: Fig 1. shows the mean absolute T_{10} error found for different levels of displacement applied to the SPGR variable flip angle sequences. For a motion close to the in-plane voxel resolution (0.8mm), a deviation of 18% was found for T_{10}. On the second experiment, underestimated T_{10} values led to worse PK estimation than overestimated values. Moreover, the error was, on average, magnified, and a |20%| T_{10} deviation caused almost 30% K_{trans} error. It was also observed that k_{ep} was much more robust to deviations on T_{10} than K_{trans}, and the same |20%| inaccuracy was reflected by less than 10% on the k_{ep} deviation. The final experiment showed that there is an average of 0.42mm (about half the size of an in-plane voxel) mean displacement (ranging from 0.00mm to 0.90mm and a standard deviation of 0.34mm) in rectal SPGR sequences. This average motion leads to 10% T_{10} and 16% K_{trans} mean error.

CONCLUSION: This work has investigated the sources of error in PK analysis in rectal cancer DCE-MRI. These in particular stem from inaccuracies of T_{10} estimation in case of motion within variable flip angle sequences, with T_{10} estimation errors propagating and amplifying subsequent PK parameter estimations (K_{trans} and k_{ep}). It was demonstrated that even for the average motion (0.43mm) found within these volumes, this may cause more than 15% error in K_{trans} and that higher degrees of motion (of up to 0.90mm) may be present. Consequently, care should be taken to account for this source of error in PK parameter analysis.

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