

A LINEAR ALGORITHM OF THE REFERENCE REGION MODEL FOR DCE-MRI IS MORE ROBUST AND RELAXES REQUIREMENTS FOR TEMPORAL RESOLUTION

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INTRODUCTION: The Reference Region Model (RRM) can analyze Dynamic Contrast Enhancement (DCE) MRI results without requiring an Arterial Input Function (AIF) [1,2]. The RRM uses the concentration curve in a reference region (muscle) as a surrogate for the AIF in the tissue of interest (tumor) to calculate $R^{K_{trans}}$ ($K_{trans}^{TOI} / K_{trans}^{RR}$) using a Non-Linear Least Squares algorithm. However, this fitting performs poorly under low SNR and slow temporal resolution that are typical during clinical DCE-MRI [3,4]. We hypothesize that a Linear Least Squares algorithm can overcome these problems with the Non-Linear Least Squares algorithm. We have developed a new Linear RRM (LRRM) and compared its performance with the standard Non-Linear RRM (NLRRM) using simulations and pre-clinical DCE-MRI results.

METHODS: Simulations: Matlab (Mathworks, Inc.) was used to study the effect of temporal sampling, statistical noise and pharmacokinetic constants on the accuracy and precision of the LRRM and NLRRM. A series of activity curves for the tumor (TOI) and muscle (RR) were generated using the standard Tofts model with ranges of injection times, K_{trans} and k_{ep} [1]. **Animal Model:** Five mice with a MDA-MB-231 flank tumor reached an average tumor volume of 250 mm³ before initiating DCE-MRI studies. All animals were imaged at 7T on 4 consecutive days. **DCE-MRI:** Pre-contrast endogenous T_1 relaxation maps were calculated using a RARE pulse sequence with a variable TRs of 0.37, 0.75, 1.5, 3, and 6 sec. Eleven 1-mm-thick slices were acquired. DCE-MR images were acquired using the same geometry as the T_1 maps with TR=250 msec, NEX= 2, and RARE factor=2. A series of 65 image sets were acquired with a temporal resolution of 32 sec/image. After the fifth image set was acquired, 2 mmol/kg Gd-DTPA (Magnevist[®]) was injected manually through a tail vein catheter over 30 seconds. Matlab was used to analyze the DCE-MRI results pixel-wise to generate tumor parametric maps of $R^{K_{trans}}$ using LRRM and NLRRM. The same muscle ROI was used for both methods. **Temporal down-sampling:** The temporal resolution was slowed from 32 sec to 64, 96 and 128 sec by replacing 2, 3 and 4 consecutive data points with their average. All parametric maps were recalculated at each new temporal resolution, and their Spearman correlation coefficients (r) of 64, 96 and 128 sec resolution relative to 32 sec resolution were also determined (r instead of r^2 is justified for this type of statistical test).

RESULTS: Simulations: The $R^{K_{trans}}$ for NLRRM had a systematic error with different combinations of K_{trans}^{TOI} and V_e^{TOI} that was approximately twice as great as the systematic error for LRRM, and systematic errors were most severe at high K_{trans}^{TOI} and low V_e^{TOI} (Fig. 1). Simulations with clinically relevant muscle SNR and tumor SNR of ~15 and temporal resolution of 60 sec. showed that NLRRM consistently underestimates $R^{K_{trans}}$ by ~35% while LRRM had <5% systematic error (Fig. 2). **DCE-MRI:** Pixel-wise $R^{K_{trans}}$ values determined using LRRM were independent of temporal resolution ($r \geq 0.91$ for all comparisons), but $R^{K_{trans}}$ values determined using NLRRM depended on temporal resolution ($r \leq 0.80$) (Fig. 3).

DISCUSSION: The new LRRM more accurately determines $R^{K_{trans}}$ relative to the standard NLRRM especially at clinically relevant SNR and when tumor K_{trans}^{TOI} is high. The LRRM relaxes the temporal sampling limit of the Reference Region Model [4]. These results show that our LRRM algorithm is essential for robust clinical translation of RRM DCE-MRI to the clinic.

REFERENCES: 1. Tofts P., et al. *J Magn Reson Imaging* 1999, 10:223. 2) Yankeelov TE, et al. *Magn Reson Imaging* 2005, 23:519. 3) Ahearn TS, et al. *Phys Med Biol* 2005, 50:85. 4). Murase K. *Magn Reson Med* 2004, 51:858.

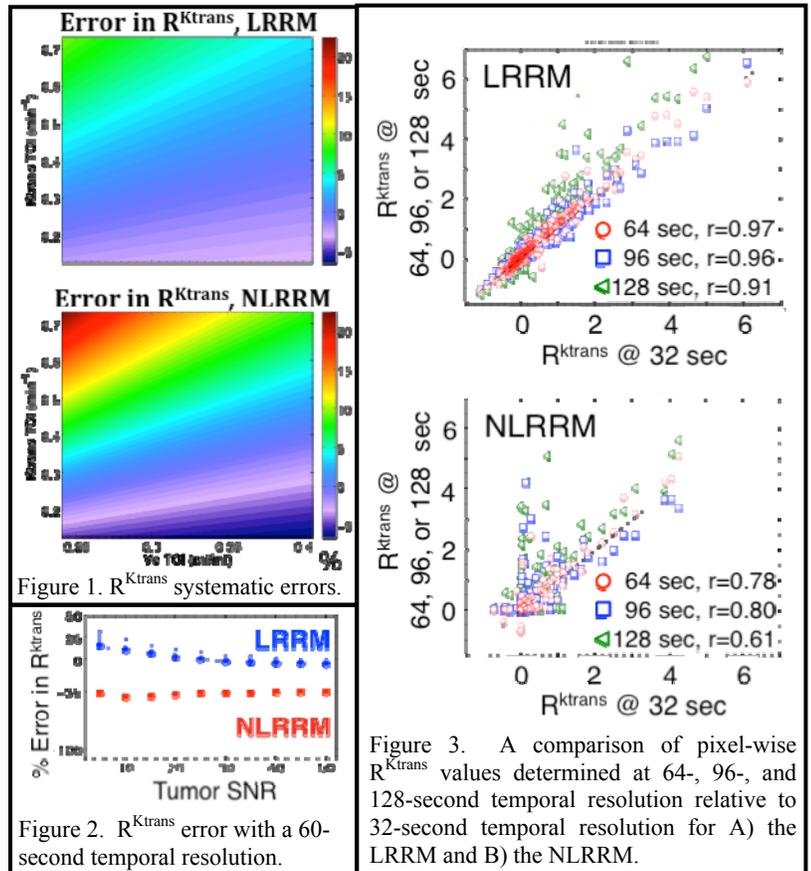


Figure 3. A comparison of pixel-wise $R^{K_{trans}}$ values determined at 64-, 96-, and 128-second temporal resolution relative to 32-second temporal resolution for A) the LRRM and B) the NLRRM.