Error Quantification in Relaxivity Rate Change (ΔR1) Due to Systematic Errors in Dynamic Contrast Enhanced MR Studies

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Target Audience: Experts and scientists working on MR contrast agent concentration measurements and pharmacokinetic modeling.

Purpose: This study investigates the bias of the longitudinal relaxation rate change profile ($\Delta R_1(t)$) in Dynamic Contrast Enhanced (DCE) studies due to the systematic errors introduced by the dynamic flip angle and the longitudinal relaxation time (T_1) estimation prior to the Contrast Agent (CA) administration. In DCE-MR studies, converting the signal intensity time course data (S_t) of dynamic study to relaxivity rate change ($\Delta R_1(t)$) is a key step for using pharmacokinetic models in DCE data processing. It is assumed that in DCE-MR studies, $\Delta R_1(t)$ is proportional to the time trace of Contrast Agent (CA) concentration[1,2]. Assessment of the propagation of systematic errors to $\Delta R_1(t)$ is critical since any bias in $\Delta R_1(t)$ generates a bias in the permeability parameters estimated in DCE analysis. Signal intensity (S_t), dynamic flip angle (θ), and resting T_1 (T_1 before CA administration) play crucial roles in construction of the $\Delta R_1(t)$ profile from T_1-Weighted or 3D Spoiled-Gradient-Echo (SPGRE) data. Resting T_1 is usually calculated from a Variable Flip Angle (VFA) pulse sequence which is acquired prior to the dynamic study. However, accurate estimation of the resting T_1 is still a challenge and is not free of error regardless of the techniques used [2,3]. Besides, the actual to nominal flip angle (θ) in dynamic studies varies due to the field inhomogeneity and coil sensitivity. Therefore, any systematic errors in resting T_1 and flip angle (θ) affect the calculation of $\Delta R_1(t)$ profiles. To the best of our knowledge, there is no study reporting direct quantification of such errors in $\Delta R_1(t)$ profiles. In this study, our goal is to investigate these systematic errors and quantify the effect of each on the $\Delta R_1(t)$ profile.

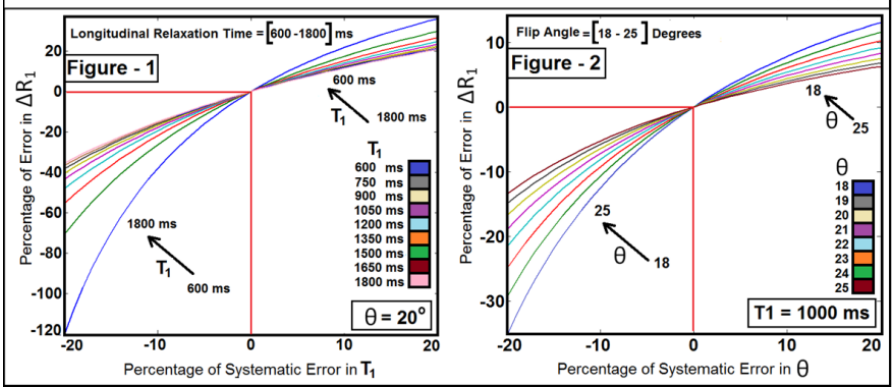
Theory: Our group has recently introduced[3] an analytical expression for calculation of $\Delta R_1(t)$ from the dynamic T1-Weighted 3D-SPGRE signal (S_t). As shown in Equations 1-4, this method recruits resting T_1 (estimated from VFA experiment prior to the CA injection) and the dynamic flip angle (θ) to estimate $\Delta R_1(t)$. In these equations, $T_1(pre)$ and S_0 represent the resting T_1 and the average of the signal intensity prior to the CA administration respectively. In all equations, T_R is the repetition time of the dynamic study and also n and m both denote starting and ending points of S_t for calculation of S_0. Equation 6 can be written by introducing a time-dependent variable, $x(t)$, which is defined as the ratio of average signal S_0 to S_t which is defined as the *"contrast-enhancement ratio"*. Assuming that the two experiments (VFA and dynamic 3D-SPGRE) are independent, the errors propagated to $\Delta R_1(t)$ profile due to the systematic errors in T_1 (estimated from VFA) and θ (associated with dynamic 3D-SPGRE) can be estimated using Equations 7, 8 and 9.

$$\Delta R_1(t) = -\frac{1}{TR} Ln\left\{\frac{(n-m+1)(1-E^{pre})S_t - (1-\cos\theta E^{pre})\sum_{t=m}^{n} S_t}{(n-m+1)(1-E^{pre})\cos\theta\, E^{pre} S_t - (1-\cos\theta E^{pre})E^{pre}\sum_{t=m}^{n} S_t}\right\} \quad (1)$$

$$S_0 = \frac{\sum_{t=m}^{n} S_t}{(n-m+1)} \quad (2), \quad S_t = \begin{cases} S_0 & t \le n \\ S_t & t > n \end{cases} \quad (3), \quad E^{pre} = e^{\frac{-T_R}{T_1(pre)}} \quad (4), \quad x(t) = \frac{S_0}{S_t} \quad (5)$$

$$\Delta R_1(t) = -\frac{1}{TR} Ln\left\{\frac{(1-E^{pre}) - (1-\cos\theta E^{pre})x(t)}{(1-E^{pre})\cos\theta\, E^{pre} - (1-\cos\theta E^{pre})E^{pre}x(t)}\right\} \quad (6)$$

$$\delta^2_{\Delta R_1(t)} = \left(\frac{\partial \Delta R_1(t)}{\partial T_1}\right)^2 \delta^2_{T_1} + \left(\frac{\partial \Delta R_1(t)}{\partial \theta}\right)^2 \delta^2_{\theta} \quad (7), \quad \delta^2_{\Delta R_1(t)}\Big]_{\theta=\text{Const.}} = \left(\frac{\partial \Delta R_1(t)}{\partial T_1}\right)^2 \delta^2_{T_1} \quad (8), \quad \delta^2_{\Delta R_1(t)}\Big]_{T_1=\text{Const}} = \left(\frac{\partial \Delta R_1(t)}{\partial \theta}\right)^2 \delta^2_{\theta} \quad (9)$$



Results: By varying the contrast enhancement ratio, $x(t)$, and using Equation 8, for a typical and constant flip angle (θ =20), the percentage of errors in ΔR_1 profile was calculated for a range of systematic errors in resting T_1. Figure 1 illustrates the range of errors in ΔR_1 (-120% to 40%) at $x(t)$=0.2 (corresponding to 5x CA enhancement due to the leakage in tissue), for a range (-20% to +20%) of systematic errors in T_1 for different values of T_1 (600 ms to 1800 ms that corresponds to reported values of T_1 in tumorous and normal tissues in 3T and 7T field strengths). This figure clearly shows that the percentage of error in ΔR_1 is not symmetric against the same level of overestimation and underestimation of resting T_1. For instance, at T_1=600 ms, ΔR_1 is underestimated by 120% for 20% underestimation of resting T_1; while it is overestimated only around 40% for 20% overestimation in resting T_1. By varying the contrast enhancement ratio, $x(t)$, and using Equation 9, for a typical resting T_1 (1000 ms), percentage of errors in ΔR_1 were calculated for a range of systematic errors in dynamic flip angle, θ. Figure 2 illustrates the range of error in ΔR_1 (-35% to 15%) at $x(t)$=0.2, due to a range (-20% to +20%) of systematic errors in θ (18 to 25 degrees that covers typical values of θ in dynamic studies done in 3T and 7T field strengths). Similar to Figure 1, this figure clearly shows that the percentage of error in ΔR_1 is not symmetric against the same level of overestimation and underestimation of dynamic flip angle (θ). As an example, for a nominal flip angle of 18° (in tissues with T_1=1000 ms), ΔR_1 is underestimated about 35% for 20% underestimation of θ (actual flip angle of ~14°corresponding to the nominal to actual value of 1.28); while it is overestimated only ~ 12% for 20% overestimation of θ.

Discussion: This study confirms that the systematic errors arising from overestimation and underestimation of the resting T_1 and dynamic flip angle (θ) do not uniformly affect the ΔR_1 profile and it suffers more when these parameters (T_1 , θ) are underestimated. As it is expected, the same trend was observed when a set of simulations were repeated for different values of the contrast enhancement ratio corresponding to different time points (t) in ΔR_1. It should be noted that all the results in this pilot study were achieved under the presumption of resting T_1 and dynamic flip angles being independent.

Conclusion: Although it was not incorporated in this study, considering the fact that the VFA experiment usually uses different (6 or more) flip angles to provide enough information for estimating the resting T_1, any systematic errors associated with different flip angles at this stage would affect the estimation of the resting T_1 value which should be taken into account for a more accurate quantification of the errors in ΔR_1 value. This fact demands calculating a variance-covariance matrix, which its off diagonal elements would explain how a systematic error in one parameter changes the bias of the other parameters and how they propagate to the ΔR_1 profile.

References:

1. Bagher-Ebadian H., et al, , *Neuroimage*, 54 Suppl 1 (2011), S176-9.
2. Tofts, P.S., *J Magn Reson Imaging* **7**, 91-101 (1997).
3. Bagher-Ebadian H., et al, *J Magn Reson Med.* 2012; 68(1):241-51.