# Nonlinear Correction of Arterial Input Function Measured with Spoiled Gradient Echo Sequences

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**Purpose:** Accurate quantification of the arterial input function (AIF), as defined by plasma concentration of paramagnetic contrast agent, remains a challenge to efforts at quantitative kinetic analysis of dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) data. Typically, T1 relaxation time is estimated using a fast T1 sequence and the relaxivity equation in the fast exchange limit is used to infer contrast concentration.[1,2] Due to the high premium placed on temporal resolution, the quantitative T1 measurement methods used are necessarily approximate and, consequently, sensitive to measurement noise and other sources of error. Furthermore, it is commonly assumed that the relationship between signal change and contrast concentration can be modeled by a simple linear approximation.[1,2] By analysis of the

$$S = S_0 \frac{\sin\alpha\left(1-e^{-T_R/T_1}\right)e^{-T_E/T_2^*}}{1-\cos\alpha e^{-T_R/T_1}} \quad (1) \qquad \sigma = \frac{S(T_1,T_2^*)-S(T_{1,0},T_{2,0}^*)}{S(T_{1,0},T_{2,0}^*)} = \frac{e^{-r_2^* C T_E}\left(e^{(r_1 C+1/T_{1,0})T_R}-1\right)\left(\cos\alpha - e^{T_R/T_{1,0}}\right)}{\left(e^{T_R/T_{1,0}}-1\right)\left(\cos\alpha - e^{(r_1 C+1/T_{1,0})T_R}\right)} - 1 \quad (2)$$

theoretical expression for relative signal enhancement in a spoiled gradient echo (SPGR) pulse sequence, we have developed a method of directly computing contrast concentration from signal data and T10 (pre-contrast T1) which explicitly accounts for the nonlinearity of the signal vs. concentration curves, allows direct estimation of the accuracy of contrast quantification, and is insensitive to both tissue T20* values and RF receive inhomogeneity.[1,2]

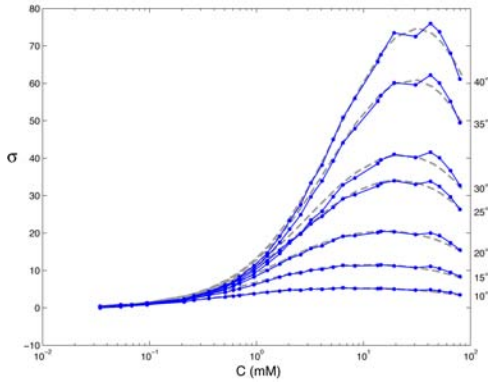


Figure 1. Measured relative SPGR signal enhancement (Eq. 2) in a Gd-DTPA phantom spanning the concentration range from 0.03-90 mM for flip angles from 10° to 40°. Measured values are indicated by the blue points. The corresponding theoretical curves for σ at the specified flip angles are plotted as gray dashed lines.

**Methods:** We used the theoretical expression for signal intensity in an SPGR pulse sequence (1) to derive an algorithm for calculation of AIF from relative signal enhancement, σ (2). Concentration is computed from the measured σ by solving Eq. 2 for C using a nonlinear root-finding algorithm (MATLAB's `fzero`). The accuracy of the method was verified in a concentration phantom made by dilution of various concentrations of Gd-DTPA in saline (Fig. 1), demonstrating excellent agreement between the theoretical curves and measured data. The method was then tested *in vivo* by measurement of AIF in a volunteer on three separate occasions (0, 1, and 45 days). Data were acquired with a 3D SPGR sequence using an 8 channel head coil on a 1.5T Siemens TIM Avanto system with TR=3.45 ms, TE=1.38 ms, α = 15°, FOV = 220×200 mm, with 0.9×0.9 mm in plane resolution, slice thickness of 5 mm, 6/8 partial phase Fourier encoding, and an acquisition time of 7.4 s per frame. Only the central 8 slices (of 16 total) were used to minimize effects due to flip angle errors at the slab boundaries. Contrast was administered intravenously through the antecubital vein at a dose of 0.1 mmol/kg; injection was performed using an autoinjector at a rate of 4 ml/s followed by a saline flush of 20 ml at 2 ml/s. AIF time curves of signal enhancement were averaged over an ROI containing approximately 150 pixels within the sigmoid sinuses; as this blood has passed through the capillary network in the brain, it will be somewhat dispersed and delayed relative to a true arterial measurement. While this could be problematic for characterization of tissue kinetics, the precise location of the AIF is unimportant for the purposes of demonstrating our method. T10 of blood was set to 1440 ms based on the literature,[3] and relaxivity values of r1 = 4/mM/s and r2 = 5/mM/s were used.

$$\sigma \approx \frac{e^{T_R/T_{1,0}}\left(e^{r_1 C T_R}-1\right)(\cos\alpha - 1)}{\left(e^{T_R/T_{1,0}}-1\right)\left(\cos\alpha - (e^{r_1 C+1/T_{1,0})T_R}\right)} \quad (3) \qquad \sigma \approx C r_1 T_{1,0} \quad (4)$$

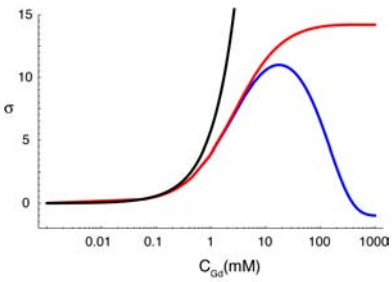


Figure 2. Concentration dependence of relative signal enhancement, σ, for equations (2) in blue, (3) in red, and (4) in black.

**Results**: Various approximations to (2) may be derived. Here we consider a nonlinear equation derived in the small TE limit (3) and a linear approximation (4) which is derived by expanding (2) for small C, and TR/TE going to zero. Figure 2 shows the concentration dependence of σ determined using (2) in blue, (3) in red, and (4) in black for the imaging parameters given above. Measured time curves of σ for the three separate volunteer scans are shown in Fig. 3, and the same curves converted to absolute concentration by full nonlinear solution of (2) are shown in Fig. 4. AIF curves for scan #1 are shown in Fig. 5, with the solution to (2) plotted in blue, the solution to (3) plotted in red, and the solution to (4) plotted in black. From this plot, it is apparent that the linear approximation grossly underestimates true plasma concentrations near the first pass peak, and demonstrates a perceptible negative bias even nearly 15 minutes after bolus injection. The maximum error at the peak is ~-75%, gradually diminishing to an underestimate of ~20% in the tail. Clearly, linearization is inadequate for quantification even for plasma concentrations below 1mM. In contrast, the nonlinear approximation (red) accurately represents the AIF everywhere but at the first-pass peak, with ~15% bias at the peak rapidly decreasing to <1% in the tail.

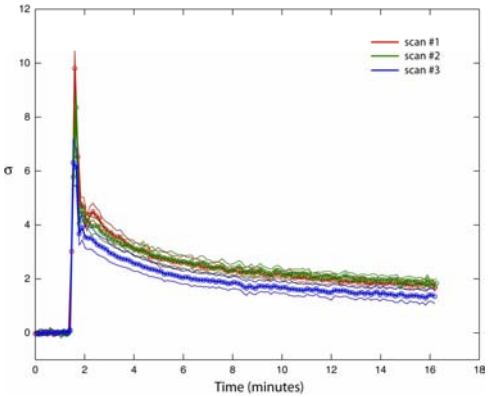


Figure 3. σ curves measured in the sigmoid sinus for three scans on the same volunteer. Figure 3. σ curves measured in the sigmoid sinus for three scans on the same volunteer.

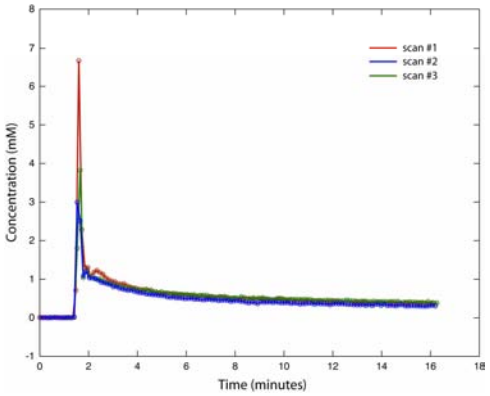


Figure 4. Concentration curves for the three scans in Fig. 3, computed using the measured values of σ from Fig. 2 and solving (2) for C.

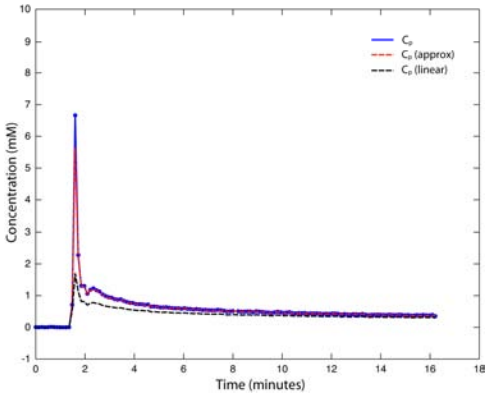


Figure 5. Comparison of concentration curves computed nonlinear solution of (2) in blue, the small TE approximation (3) in red, and the linear approximation (4) in black.

**Conclusions:** Quantification of arterial input function is essential for accurate and reproducible *in vivo* measurement of tissue kinetic parameters. We have derived a new analysis methodology for AIF determination which only requires a single pre-contrast measurement of T10, is independent of T20* and coil sensitivity variation, and explicitly accounts for the nonlinear relationship between signal enhancement and contrast concentration. Application of this method to AIFs measured in volunteers using scan parameters typical of current quantitative DCE-MRI protocols demonstrates the practicality of this approach and highlights the danger of using the linear approximation for characterization of AIF.

**References:** [1] Tofts PS JMRI **7**:91-101 (1997). [2] Roberts TPL JMRI **7**:82-90 (1997). [3] Stanisz GJ MRM **54**:507-512 (2005).