Optimal quantification of DCE-MRI data using reference tissue normalisation

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Introduction: Methods have recently been developed which enable the quantification of DCE-MRI data using a reference tissue to estimate blood plasma Gd-DTPA concentration [1,2]. By designing a spoiled gradient echo sequence with appropriate imaging parameters, signal intensity can be assumed proportional to the change in R_1 and therefore to the change in Gd-DTPA concentration. This used in conjunction with reference tissue quantification methods removes the requirement to perform potentially error-prone Gd-DTPA calibrations [3,4]. However, sequence linearity is often not exploited optimally during post-processing, as a dependence on native T_1 is introduced by the utilisation of relative enhancement (*RE*) as time-series data. In the current study two alternatives, which are independent of native T_1, are evaluated: signal difference (*SD*) and enhancement factor (*EF*). Their relative effects on subsequent quantitative analysis are also assessed.

Theory: *Relative Enhancement: RE* is the percentage increase in signal intensity ($S(x,t)$), given by $RE(x,t) = [S(x,t)-S(x,0)]*100/S(x,0)$, where x is a spatial position vector and t is time. Given the initial, theoretical sequence parameter constraints $\sin(\alpha)\sim1$, TR<<T_1 and TE<<T_2* (which we subsequently show can be relaxed in practice), signal intensity is approximately $S(x,t) = C.\rho(x).\mathrm{TR}.R_1(x,t)$ where C is a constant incorporating factors such as receiver gain, $\rho(x)$ is proton density and $R_1(x,t)$ is the longitudinal relaxation rate (=$1/T_1$). We therefore have

$$RE(x,t) \approx [T_1(x,0).100]\Delta R_1(x,t),$$

where $\Delta R_1(x,t) = R_1(x,t) - R_1(x,0)$.

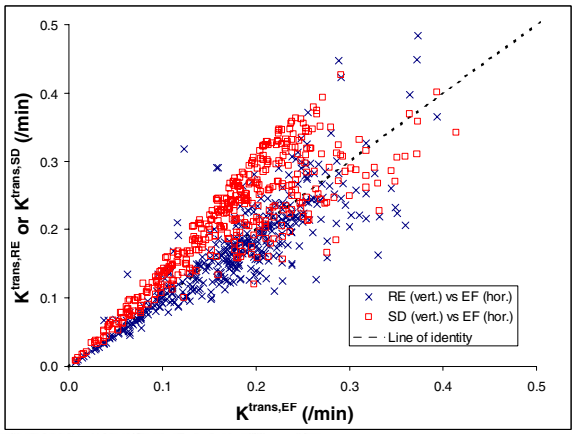
Signal Difference: SD with these sequence parameters is approximated by

$$SD(x,t) \approx [C.\mathrm{TR}.\rho(x)]\Delta R_1(x,t).$$

Enhancement Factor: As suggested by Hittmair *et al.*[5], *EF* requires the acquisition of a PD-weighted image with a small flip angle, β, such that $\sin(\beta)\sim\beta$. Under these circumstances, and keeping C, TR and TE constant, the PD-weighted image's signal intensity is $S_{PD}(x) = C.\rho(x).\beta$. Defining *EF* as $[S(x,t)-S(x,0)]/S_{PD}(x)$ we have

$$EF(x,t) \approx [\mathrm{TR}/\beta]\Delta R_1(x,t).$$

Methods and Materials: DCE-MRI data were acquired from five patients with rectal cancer, using a sliding window FLASH sequence with TR/TE/α = 30ms/6.8ms/30° for dynamic images and β=5° for PD-weighted measurements. A double dose of Gd-DTPA (0.2mMol/kg) was injected at 5ml/s and images were sampled every 0.96s for a total of 280s. ROIs corresponding to the tumour and to a region of gluteus maximus muscle were defined in each data set by a radiologist and *RE*, *SD* and *EF* were calculated. Mean uptake curves in the muscle ROI were fitted with a bi-exponential function of the form $g(t) = A.[-\exp(-m_1.t) + \exp(-m_2.t)]$ and converted to a vascular normalisation function (VNF) by rearranging the modified Kety equation [6], assuming K^{trans} = 0.07/min and v_e = 0.14 in muscle [7]. Uptake curves in the tumour were fitted with the Larsson model on a pixel-by-pixel basis using the VNFs derived from muscle and maps of K^{trans} and v_e were produced. These steps were applied to RE, SD and *EF* (giving $K^{trans,RE}$, $K^{trans,SD}$ and $K^{trans,EF}$). Native T_1 ($T_1(x,0)$) values were calculated using a lookup table calibration applied to the PDw and pre-enhancement dynamic images.



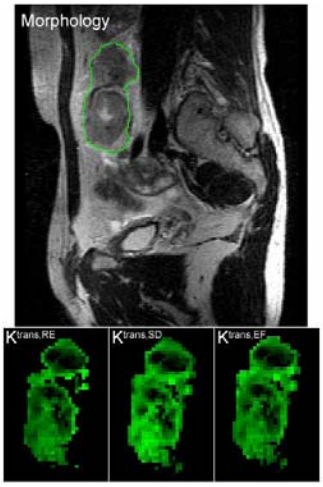


Figure 1: A*bove*) Scatter graph of $K^{trans,RE}$ and $K^{trans,SD}$ *vs* $K^{trans,EF}$ for patient #1. *Left*) Morphological image and K^{trans} maps from patient 1. Note that all K^{trans} maps have the same window levels (0 to 0.4 /min).

It is clear that the approximation $\sin(\alpha)\sim1$ does not hold for the sequence described here. Given that $\Delta S = (\partial S/\partial R_1)\Delta R_1$, it can be shown that $\Delta S = f(\mathrm{TR},T_1(x,0),\alpha).\Delta R_1$ and, for proportionality with ΔR_1, we require that f is independent of $T_1(x,0)$. This function was simulated in order to evaluate the expected error introduced into the subsequent quantitative analysis.

Results and Discussion: Table 1 shows ratios of mean native T_1 and S_{PD} in tumour ROIs to those in muscle ROIs ($\langle T_{1,t}\rangle$, $\langle T_{1,m}\rangle$, $\langle S_{PD,t}\rangle$ and $\langle S_{PD,m}\rangle$, respectively).

- $K^{trans,RE} \sim K^{trans,EF}.\langle T_{1,t}\rangle / \langle T_{1,m}\rangle$, which was as expected given the full form of the ratio $K^{trans,RE} / K^{trans,EF}$ using the Larsson model equation. As $T_{1,t} \neq \langle T_{1,m}\rangle$ in most pixels, this introduces the spread and deviation from the line of identity shown in the graph of Figure 1.
- $K^{trans,SD} \sim K^{trans,EF}.\langle S_{PD,t}\rangle / \langle S_{PD,m}\rangle$, which was also as expected. Again, Figure 1 illustrates the spread introduced due to $S_{PD,t} \neq \langle S_{PD,m}\rangle$ in most pixels.
- As a result of these mismatches, the average error introduced into the tumour $K^{trans,RE}$, relative to $K^{trans,EF}$ was 23.8 ± 8%, whereas the same measure for $K^{trans,SD}$ was 5.9 ± 6%. This difference was due to the smaller range of proton density values found in soft tissue, compared with native T_1. It should be noted that k_{ep} is identical in all methods, causing the variation in v_e to be of the same relative magnitude as that observed in K^{trans}.
- Simulations of f showed that a linear relationship between ΔS and ΔR_1 (i.e. such that f is independent of native T_1) is approximated for $\alpha > 25°$ and native $T_1 >$ 600ms. For α=30°, non-linear effects introduce a maximum of 20% error (assuming a native T_1 range of 600 to 1200ms), relative to quantification by converting to Gd-DTPA concentration directly. However, uncertainties in calculated Gd-DTPA concentrations have been shown to be of this order [8]. This non-linearity errror can be reduced by increasing α, but at the expense of signal-to-noise.

Conclusion: *RE* has a dependence on native T_1, *SD* is dependent on ρ, whilst *EF* has no dependencies other than ΔR_1. If *RE* or *SD* is used as the dynamic time-series data in a reference tissue quantification methodology, any difference in native R_1 or proton density between the ROI and the reference tissue introduces a systematic error into the value of K^{trans}. Therefore *EF* should be used for this type of quantification, if the required data are available. If not, *SD* introduces a smaller error than *RE*, as proton density is less variable in soft tissue than native T_1. Therefore, SD is a realistic alternative to calculated Gd-DTPA concentration-based methods.

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	Patient				
	#1	#2	#3	#4	#5
$\langle T_{1,t}\rangle / \langle T_{1,m}\rangle$	0.97	1.76	1.37	1.36	1.34
$\langle S_{PD,t}\rangle / \langle S_{PD,m}\rangle$	1.14	0.88	0.87	0.94	0.97
$\langle K^{trans,RE}\rangle / \langle K^{trans,EF}\rangle$	0.93	1.42	1.24	1.30	1.30
$\langle K^{trans,SD}\rangle / \langle K^{trans,EF}\rangle$	1.18	0.93	0.88	0.94	0.79

Table 1: Mean parameter ratios in each patient.