# Estimation of contrast agent extravasation from the tissue residue function: application to tumor perfusion Imaging

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**Purpose:** To develop a new method to estimate contrast agent (CA) extravasation directly from the tissue residue function derived from dynamic susceptibility contrast (DSC) MR imaging and to compare the method to a published method for extravasation correction in patients diagnosed with intra-axial brain tumors.

**Background:** CA extravasation is a confounding factor is DSC imaging of brain tumors since it may lead to incorrect estimation of tumor blood volume. Boxerman et al suggested a method to correct for extravasation by assuming CA relaxation to be dominated by $T_1$-shortening in the extravascular, extracellular space (EES) and then correct for leakage relative to an average first-pass response for the entire image slice [1]. This method implicitly assumes that the variation in tissue mean transit times (MTT) is small relative to the slice average MTT. MTT values which deviate significantly from the mean MTT value may, however lead to incorrect estimations of CA extravasation since this may mimic the effect of extravasation in the first-pass response. As an alternative approach, we propose to estimate extravasation directly from the tissue residue function. This approach is insensitive to variations in MTT and further provides a direct extravasation correction of both tissue flow and MTT in addition to CBV.

**Theory:** The estimated tissue CA concentration, $C_t(t)$, including terms for both flow and extravasation can be expressed as:

$C_t(t) = \int_0^t \left[F \cdot R(t-\tau) + K_1 e^{-K_2(t-\tau)}\right] C_p(\tau) d\tau$ (Eq. 1) where $C_p(t)$ is CA concentration in plasma, F is tissue flow, R(t) is the tissue residue function in absence of extravasation, $K_1$ is the rate of extravasation from plasma to (EES) and $K_2$ is rate of reflux from EES to plasma. Eq. (1) can be expressed in standard matrix notation [2] and the *apparent* residue function is then given by:

$\boldsymbol{r_a} = F[R(t_1), R(t_2)..R(t_N)]^T + K_1[e^{-K_2 t_1}, e^{-K_2 t_2}, .., e^{-K_2 t_N}]^T$

The residue function thus contains an exponential 'tail' in the presence of extravasation and the initial height of the residue function is then given by F + $K_1$. The error term in the blood volume is given by: $K_1 \int e^{-K_2 t} dt$. $K_1$ and $K_2$ can be estimated by approximating the non-leaky residue term by a Lorenzian and assuming a linear approximation to the exponential so that the residue function is fitted to the expression:

$$\boldsymbol{r_a} = \frac{F}{1+\left(\frac{t}{MTT}\right)^2} + K_1(1 - K_2 t)$$

We allowed $K_1$ to assume both positive and negative values since dominant extravascular $T_1$-effects are expected to yield negative $K_1$ values whereas $T_2$* effects are expected to yield positive values.

**Methods:** The analysis was performed retrospectively from DSC images acquired in 21 patients with confirmed gliomas and presence of contrast enhancement as seen on the post contrast $T_1$-w images. DSC imaging was performed at 1.5 T (Siemens Sonata / Avanto) using a GRE-EPI sequence (TR/TE/α=1500 ms / 40 ms/ 90 deg). $K_1$ maps were derived as described above and compared to the maps obtained using the method of Boxerman et al [1]. Deconvolution was performed using an iterative Tikhonov regularized SVD routine [3] in order to minimize oscillations in the resulting residue function. The arterial input function (AIF) was semi-automatically detected in the region of the anterior cerebral artery (ACA). Image analysis was performed in nordicICE (NordicImagingLab, Oslo, Norway). $T_1$-w post contrast images were coregistered to the $K_1$-maps and the mean (+/- SEM) of $K_1$ was calculated in the tumor as defined by the contrast enhanced volume. A histogram analysis of the resulting $K_1$-distribution was performed and the $K_1$-values were sub-divided into positive and negative values and mean ($K_1^{neg}$ , $K_1^{pos}$ ) +/- SEM was calculated.

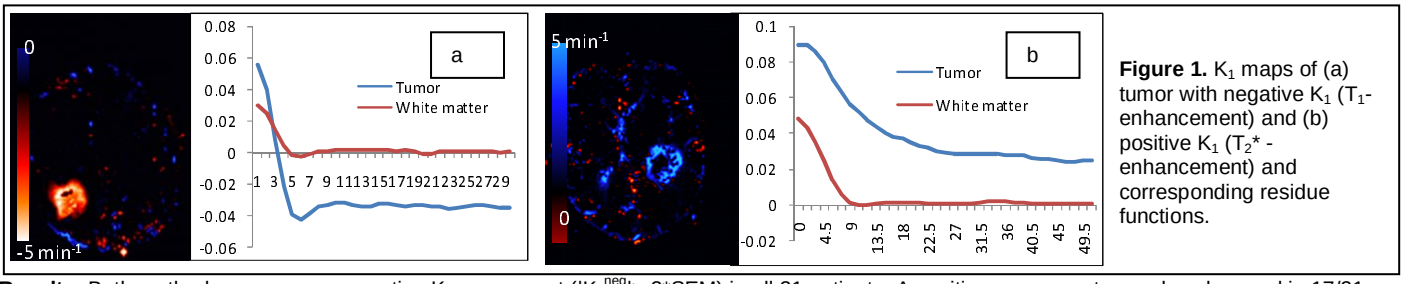


**Figure 1.** $K_1$ maps of (a) tumor with negative $K_1$ ($T_1$-enhancement) and (b) positive $K_1$ ($T_2$* -enhancement) and corresponding residue functions.

**Results:** Both method gave a mean negative $K_1$ component ($|K_1^{neg}| > 2$*SEM) in all 21 patients. A positive component was also observed in 17/21 patients using the residue function analysis and in 6/21 using the method of Boxerman et al. In all patients, venous structures gave a large positive $K_1$ value using both methods. Figure 1 shows sample $K_1$ maps and corresponding residue functions from ROIs in the tumor and unaffected white matter in a patient with (a) predominant extravascular T1 effects (negative K1) and (b) predominant T2*-effects (positive $K_1$). The leakage constant $K_1$ can be approximated by the asymptotic value of the residue function in the absence of significant reflux ($K2\Delta tN \ll 1$). Figure 2 shows the resulting quantitative CBV and MTT obtained with and without by applying the residue function correction method for the case shown in Fig.1 (a).

**Discussion:**

We propose a new method to estimate CA extravasation based on direct analysis of the tissue residue function obtained after AIF-deconvolution. The method is insensitive to variations in MTT and tissue delays and corrects both tissue flow, MTT as well as CBV according to the estimated CA extravasation effects. Both CBV and MTT can be significantly under-estimated in highly leaky gliomas unless corrected for as shown in Fig.2. The method detects both $T_1$- as well as $T_2$*- dominant extravasation effects and our results indicate that both $T_1$- and $T_2$*- effects can dominate in gliomas when CA extravasation is significant using standard T2*-weighted GRE-EPI sequences at 1.5 T. Interestingly, venous structures was found to consistently give large positive $K_1$-values and this feature was found to be useful to identify venous structure in the perfusion maps. The results warrant a proper clinical evaluation of the proposed method.

**References:**

[1] Boxerman et al. AJNR Am J Neuroradiol 2006; 27(4):859-867

[2] Ostergaard L et al, Magn Reson Med, 1996; 36:715-725

[3] Calamante et al. Magn Reson Med. 2003; 50(6):1237-1247

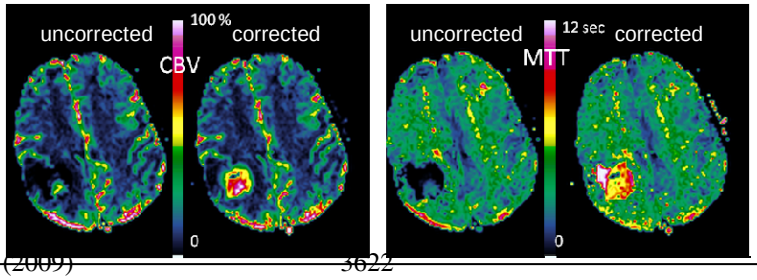


**Figure 2.** The effect of applying leakage correction from the estimated K1-values as shown in Fig 1 (a). Both CBV and MTT are significantly under-estimated in the uncorrected images.