# Extravascular extracellular space fraction measurement by DSC-MRI: a theoretical study

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## Introduction:

The unclear $T_1$ and $T_2^*$ effect dominance resulting from the contrast agent (CA) leakage in dynamic susceptibility contrast (DSC)-MRI weakens linearity between $\Delta R_2^*$ and CA concentration. But endeavor has been made to measure relative cerebral blood volume (rCBV) and blood-brain barrier (BBB) permeability by DSC-MRI, such as Weisskoff model and its modified forms [1]–[4]. However, no one, to our knowledge, has discussed the relation between extravascular extracellular space (EES) fraction $V_e$ and parameters deduced from Weisskoff model. In this study, our results from simulation demonstrated that the ratio of $K_1$ and $K_2$ in Weisskoff model was linear to $V_e$, thus illustrating a potential approach to measure relative $V_e$ by DSC-MRI.

## Methods:

A simulation tool was developed in Matlab (The Mathworks Inc.) and COMSOL Multiphysics (CnTech Co.), based on approach proposed by Pannetier *at al* (2013)[5], which comprised blood flow, CA leakage, CA diffusion in EES, intrinsic and CA-induced $R_1$ and $R_2$ relaxations, magnetic field perturbations, and the diffusion of the water protons. A voxel was modeled as a 100*100μm surface with cells and vessels modeled as circles randomly distributed. The perturbation of the magnetic field was averaged over 3 orthogonal orientations [5]. The diameter of vessels was set as 4μm according to that of microvessels in grey matter [6] and distribution of cell diameters were set according to axon diameter distribution of optical nerves [7]. Arterial input function (AIF) was acquired from *in vivo* DSC data fitted to gamma-variate function and cerebral blood fraction $V_b$ was 3.8%[5]. Transfer coefficient $K_{pe}$ of vascular wall was set as 0, 0.001, 0.009, 0.016, 0.036, and 0.064, and $V_e$ was set as 0.2 to 0.8 with increment of 0.1. Both included the range reported in tumors[5][8]. And a preload of 0.01 mM was implemented. In addition, single-shot gradient echo sequence was used for simulation with TR = 1500ms, TE = 10ms, and flip angle = 90 degrees, lasting for 100s. Susceptibility maps were converted to magnetic field perturbation maps by the Fourier transform approach and MR signals were simulated by Bloch equations under 4.7 T [5]. Five simulations were conducted for each combination of the parameters. The $\Delta R_2^*$ curves of tissue and AIF were generated from MR signals by $\Delta R_2^* = \ln(S(0)/S(t))/TE$, with $V_b$ considered for AIF. Then, the curves were fitted into the Weisskoff model through Levenberg-Marquardt algorithm, and linear relationship between $V_e$ and $K_1/K_2$ was evaluated by Pearson's linear correlation coefficient.

## Results:

Fig. 1 illustrates the relationship between $K_1/K_2$ and $V_e$ for $K_{pe} = 0.001$, 0.009, 0.016, 0.036, and 0.064 respectively. Pearson's coefficients and parameters of linear regression equation $K_1/K_2 = m*V_e+b$ for each circumstance are displayed in Table 1, which manifest linear correlation between $K_1/K_2$ and $V_e$ and their stable relationship. Fig. 2 shows the magnetic field perturbation $\Delta B$ maps of $V_e = 0.2$ and $V_e = 0.8$ when $B_0$ parallels and orthogonal to the surface respectively.

## Discussion:

$T_2^*$ effect is on account of dephasing of MR spins caused by magnetic field perturbation. As shown in Fig. 2, higher $V_e$ leads to larger susceptibility interface area and thus more significant $T_2^*$ effect. On the other hand, higher $V_e$ results in a slower extravasation process and thus undermines $T_1$ effect. As a result, the absolute value of $K_1/K_2$, which is positively correlated to $T_2^*$ effect and negatively correlated to $T_1$ effect, is lower with higher $V_e$. Furthermore, the relationship between $V_e$ and $K_1/K_2$ is almost invariant for different permeability, as shown in Fig.1 and Table 1, the reason of which may be as follows. First, the CA in EES causes $T_1$ and $T_2^*$ effects at the same time, which contradict with each other, then the amount of CA may have weak relation with MR signal. Second, the integral of tissue response function in Tofts model[9] $K_{pe}*e^{-K_{pe}*t}$ on timespan of 0 to 100s varies little with a certain range of $K_{pe}$, for example, 0.907 for $K_{pe} = 0.025$, 0.969 for 0.05, and 0.951 for 0.1, effect of $K_{pe}$ therefore diminished.

| $K_{pe}$ | R | P | m | b |
|---|---|---|---|---|
| 0.001 | 0.986 | 4e-5 | 83.59 | -81.25 |
| 0.009 | 0.988 | 3e-5 | 83.04 | -81.15 |
| 0.016 | 0.987 | 4e-5 | 83.43 | -81.54 |
| 0.036 | 0.985 | 6e-5 | 84.87 | -81.85 |
| 0.064 | 0.988 | 3e-5 | 84.05 | -81.68 |

Table 1. Relationship between $V_e$ and $K_1/K_2$. R and P are Pearson's coefficients; m and b are parameters in linear regression equation.

## Conclusion:

The stable relationship between $K_1/K_2$ and $V_e$ under conditions of different permeability and cell/vessel distribution has been manifested by numeric simulation. As a consequence, Weisskoff model could be utilized for generating relative $V_e$ map by DSC-MRI and clinical data is expected to further prove the theory.

## References:

[1] R. Leigh at al, *PLoS One*, vol. 7, no. 12, 2012. [2] J. L. Boxerman at al, *AJNR Am J Neuroradiol*, vol. 27, no. 4, 2006. [3]A. Bjornerud at al *J. Cereb. Blood Flow Metab.*, vol. 31, no. 10, 2011. [4] H. L. Liu at al, *Med Phys*, vol. 38, no. 2, 2011. [5] N. A. Pannetier at al, *PLoS One*, vol. 8, no. 3, 2013. [6] A. D. and D. Boas, Neurovascular Imaging. Frontiers E-books. [7] Y. Assaf at al, *Magn. Reson. Med.*, vol. 59, no. 6, 2008. [8] A. Singh at al, *J Magn Reson Imaging*, vol. 29, no. 1, 2009. [9] P. S. Tofts at al, *J Magn Reson Imaging*, vol. 10, no. 3, 1999

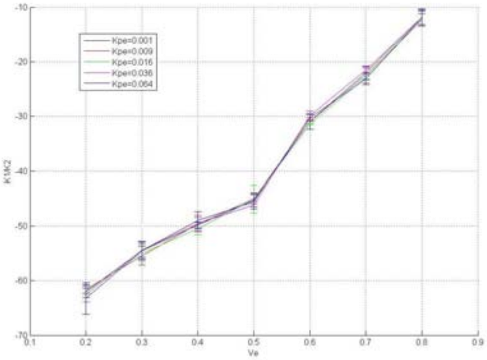

Figure 1. Relationship between $K_1/K_2$ and $V_e$ for different permeability

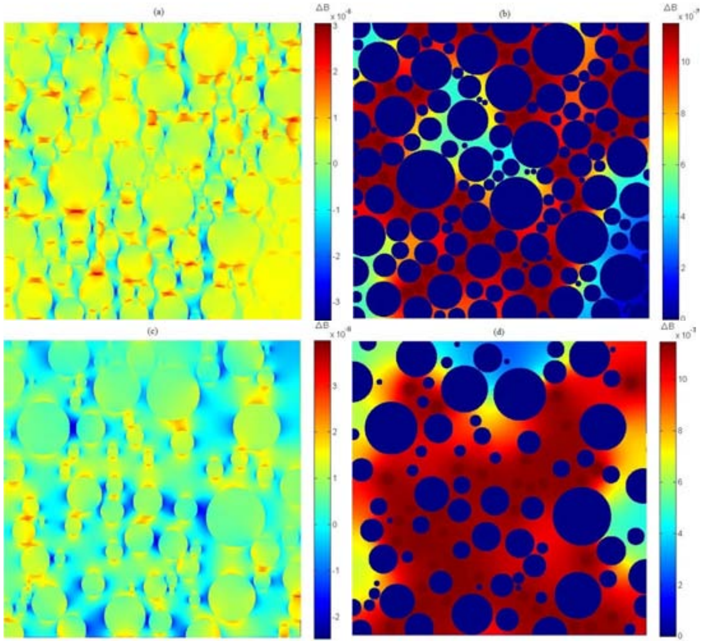

Figure 2. Magnetic field perturbation map when $K_{pe} = 0.009$. Magnetic field is parallel to surface in the left column, while orthogonal in the right. For upper row, $V_e = 0.2$; for lower row, $V_e = 0.6$. It is shown that when $V_e$ is smaller, inhomogeneity of magnetic perturbation is more severe, which leads to greater $T_2^*$ effect.