Can we separate the contributions of permeability and diffusion of contrast agent? A simulation study.

C. S. Debacker[1,2], N. Pannetier[1,2], F. Mauconduit[1,2], T. Christen[1,3], and E. L. Barbier[1,2]
[1]INSERM - U836, Grenoble, France, [2]Grenoble Institut des Neurosciences, Université Joseph Fourier, Grenoble, France, [3]Department of Radiology, Stanford University, Stanford, California, United States

Introduction There is a growing interest in Dynamic Contrast Enhanced (DCE) MRI to characterize, using a contrast agent (CA), tumor perfusion and microvasculature. Current DCE approaches generally use a global parameter which concatenates two phenomena: filtration across the vascular wall (i.e. permeability) and diffusion of the CA in the interstitium [1]. These two phenomena describe two different aspects of the tumor, however. It would thus be of interest to estimate separately these two contributions. In this study, we evaluate, using a novel numerical simulation approach, an MR experiment designed for this purpose. In this MR experiment, one fills the vessels with ultra-small superparamagnetic iron oxide (USPIO) particles to generate susceptibility gradients around the vessels. These particles do not extravasate. Then, one monitors the extravasation of a Gd-chelate using a dynamic, multi-gradient-echo, sequence.

Material and methods The simulation, with a time step δt=1ms, was performed at 4.7T and is organized as follows. **Geometry**: a 70x70µm² plane, described by a 560² matrix, where 5 randomly spread capillaries (radius 3µm) occupies 3% of the plane surface (Fig.1). Capillaries are filled with a concentration of USPIO (3.3mM) constant over time. **Arterial input function** (AIF): The time evolution of Gd concentration in vessels, C_v, is described by an AIF corresponding to a slow bolus injection. For each δt and during 200s, one computes: **(i) Extravasation of Gd** from the capillaries to their peripheries (one pixel wide, concentration C_p) using Eq. (1) [1]. We used $k_{pe}=1.8\cdot10^{-3}$ s^{-1} [2] This value is denoted k_0 and is used as reference value. **(ii) Diffusion of Gd** is obtained by convolving the Gd concentration matrix, denoted [Gd], with a Gaussian kernel (Eq. (2)) [3]. We used $D_{Gd}=4.6\cdot10^{-11}$ m²·s^{-1} [4]. This value is denoted D_0 and is used as reference value. As this convolution is performed in k-space, the periodization handles edge effects and ensures matter conservation. **(iii) Magnetic field** is computed using the Fourier transform of the magnetic susceptibility matrix Δχ (Eq. (3)) to also benefit from the periodization [5][6]. At each matrix point, we considered the magnetic susceptibility in vessels – that of blood (Δχ=0.0422 ppm, for SO_2=60% and H_{ct}=40%) + that of USPIO (Δχ=0.213 ppm) – and in tissue – that of Gd (Δχ=χ_m×[Gd], with $\chi_m=3.4\cdot10^{-7}$ mM^{-1}). **(iv) Relaxation** constants T_1 and T_2 are calculated in each points of the plane based on [Gd]. **(v) Magnetization relaxation** is described by Bloch's equation (Eq. (4)). **(vi) RF excitation**: at each TR=625ms, the application of a radio-frequency pulse is described by rotating the magnetization matrix. **(vii) The MR signal** is computed at 12 TE ([1.35- 30.126]ms) by summing the complex transverse magnetizations across the plane. **Signal analysis**: to describe the signal-time curves, we used two characteristic times: the time t_{eq} for which signal intersects the pre-bolus baseline, and the time T_{min} for which the signal is minimum (Fig.2a).

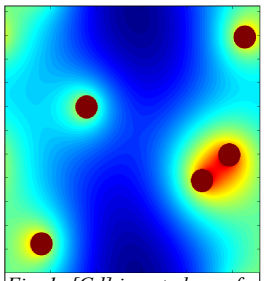

Fig. 1: [Gd] in cut plane of voxel. Gd concentrations vary between 495µM (blue) and 498µM (red).

Extravasation of CA	*Diffusion of CA*	*Magnetic field perturbation*	*Magnetization relaxation*
$\delta C_p = k_{pe}\left(C_v - C_p\right)\delta t$ (1)	$D_{xy} = \left(\frac{1}{4\pi D_{Gd}\delta t}\right) e^{-\frac{\left(x^2+y^2\right)}{4D_{Gd}\delta t}}$ (2)	$\Delta\tilde{B}_z(k) = B_0\left(\frac{1}{3} - \frac{k_y^2\sin^2\theta}{k_x^2+k_y^2}\right)\Delta\tilde{\chi}(k)$ (3)	$\begin{cases} M_\perp(t+\delta t) = M_\perp(t)\ e^{-i\gamma B(t)\delta t} e^{-\delta t/T_2(t)} \\ M_\square(t+\delta t) = \left(M_\square(t) - M_0\right)e^{-\delta t/T_1(t)} + M_0 \end{cases}$ (4)
k_{pe}: transfer constant between vessels and its peripheries (one pixel wide).	**D_{gd}**: is the apparent diffusion coefficient of Gd in brain; **x** and **y**: coordinates of matrix points in the plane.	**θ**: angle between $\overrightarrow{B_0}$ and capillary axis; **Δχ̃**: Fourier transform of the magnetic susceptibility matrix; **k_x** and **k_y**: coordinates in the Fourier domain.	**γ** = $2.68\cdot10^8$ rad.s^{-1}.T^{-1} the gyromagnetic ratio of proton; **B** = $\|\vec{B}\|$: norm of magnetic field vector.

Results and discussion Fig.2a shows the signal evolution for various TE. In agreement with experimental data, we can observe an initial signal fall after Gd-injection, due to T_2^* effect, followed by a signal increase above baseline as Gd extravasates due to T_1 effects. Fig.2b shows the impact of D_{gd} on the signal-time curves, for TE=11.8ms and $k_{pe}=4k_0$. Increasing D_{gd} yields an accelerate signal recovery after bolus passage. Fig.2c represents t_{eq} as a function of TE for different values of D_{Gd} and k_{pe}. We can observe an almost linear increase of t_{eq} with TE. t_{eq} increase with TE is faster for larger D_{Gd} or k_{pe} values. Moreover, t_{eq} is not sensitive to D_{Gd} at very short TE. This suggests that k_{pe} should be estimated at short TE (~ 1 − 5ms) and information on D_{Gd} could be obtained at long TE (~ 15 − 30ms). Fig.2d shows T_{min} as a function of TE for different D_{Gd} and k_{pe} values. With this AIF profile, T_{min} varies with D_{Gd} for high k_{pe} values only. With slower injection we observed that D_{Gd} impacts T_{min} for lower k_{pe} value (data not shown). For long TE, T_{min} plateaus at the time of the maximum of the AIF, i.e. the time when the magnetic field heterogeneity is the highest in ours simulations. This plateau is reached earlier for small k_{pe} and D_{Gd} values. For short TE, T_{min} is not sensitive to D_{gd}.

Conclusion We propose a new approach to simulate a DCE experiment which accounts for relaxivity and susceptibility effects, and for extravasation and diffusion of CA. Results indicate that k_{pe} estimates measured at short echo times are not sensitive to the diffusion of CA. Moreover, at long echo times, it seems that the diffusion of CA in interstitium could be characterized.

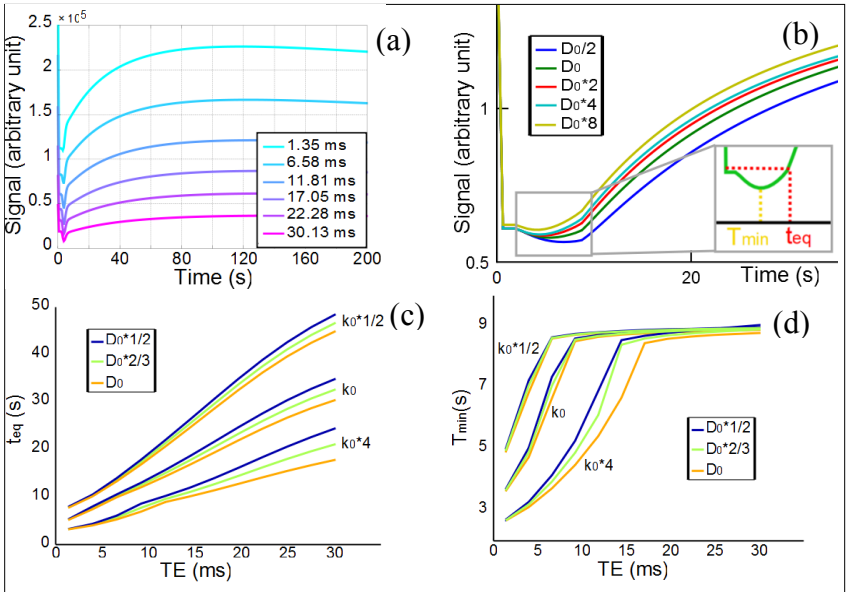

*Fig. 2 **(a)** MR signal for several values of TE with slow bolus injection of Gd. **(b)** MR signal for different values of D_{Gd}. In gray insert: Definition of t_{eq} and T_{min}. **(c)** and **(d)** Evolution of t_{eq} and T_{min} as function of TE for various values of D_{Gd} and k_{pe}.*

References [1] P S Tofts. JMRI, 1997. [2] M. Beaumont et al. Journal of Cerebral Blood Flow, 2009. [3] L. M. Klassen et al. Biophysical Journal, 2007. [4] B. Marty. ISMRM, 2010. [5] K. M. Koch et al. Physics in Medicine and Biology, 2006. [6] J. P. Marques et al. Concepts in Magnetic Resonance, 2005.