Assessement of blood volume fraction using MRI: characterization in silico of possible bias

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Introduction

Several MR methods require a mathematical model of microvasculature to extract physiological parameters such as blood volume fraction (BV_f), vessel size index (VSI) and blood oxygen saturation. In the case of BV_f and VSI, MR estimates obtained in healthy and tumoral tissues – although well correlated with histology – seemed too large **[1]**. As tumoral development can strongly alter the geometrical characteristics of the microvascular network, the straight cylinder assumption generally made in MR simulations might become inadequate. In this study, we evaluate *in silico* how vessel density, vessel preferential orientation, vessel shape or curvature affect the MR estimate of BV_f. To obtain, *in silico*, MR estimates of BV_f from vessel networks that differed from combination of straight cylinders, we propose an original computation scheme based on **[2] [3]**.

Material and methods

The steady-state MR approach to measure BV_f was simulated **[4]**. A cube of 125µm side length was considered (spatial sampling: 0.4µm). A diffusion coefficient ($D=10^{-9}m^2s^{-1}$) and a magnetic susceptibility – that of blood or of tissue – was associated to each point, using various vessel networks (common characteristics: BV_f=3% and vessel radius=3µm, Fig. 1a). The magnetic field distribution was computed at 4.7T using a Fourier based approach **[2]** (Fig. 1b). Relaxation and diffusion of water were accounted for using a deterministic approach **[3]**. The MR signal (i.e. the gradient echo transverse magnetization as a function of echo time, Fig. 1c) was computed. In absence of contrast agent, blood and tissue susceptibility were considered as equal (i.e. the effect of O_2 on the magnetic susceptibility is neglected). In presence of contrast agent, the blood susceptibility was 0.28ppm **[4]**. $BV_{f,MR}$ was eventually computed using: $BV_{f,MR}=3/(4\pi)\ \Delta R_2^*/(\gamma\Delta\chi B_0)$, were $\Delta\chi$ represent the change in blood susceptibility and γ the magnetogyric ratio for proton.

Simulations were performed in the Matlab environment. $BV_{f,MR}$ estimates were first obtained on distributions of straight cylinders to evaluate whether our approach was able to accurately determine the BVf introduced into the simulation. Four types of simulations were then performed:

i) Vessel shape was varied stepwise from straight to curved cylinder using a distribution of 900 cylinders with random orientations (no preferential orientation).

ii) Vessel shape was varied between cylinders, ellipsoids and spheres using a distribution of 900 cylinders without preferential orientation.

iii) The distribution of vessel orientation was varied between random distribution, 3 orientations (x, y, and z axes) with no preferential orientation, one preferential orientation (either parallel or perpendicular to B_0). For the latter, the fraction of vessels with a preferential orientation (preferential orientation index, POi) was varied from perpendicular (POi=0) to parallel to B_0 (POi= infinity). POi=(number of vessels parallel to B_0) / (number of vessels perpendicular to B_0 / 2). POi=1 corresponds to the absence of preferential orientation.

iv) Vessel density was varied by increasing the inter-vessel distance from 22 to 43µm, using a distribution of 12 cylinders in the three principal orientations and without preferential orientation (POi=1).

Results

Using straight cylinders as a reference, the proposed simulation approach provides a BVf estimate with less than 2% error. Results of each simulation were: (i) Shape or curvature have minimal influence on results (<5%) except for the limit case of spherical shape (15%). (ii) Random and three direction distributions of vessel orientations (Fig. 2a) provide the same accurate estimates of BVf. A larger amount of vessels orientated perpendicularly to B_0 yields a BVf overestimation (POi<1); a larger amount of vessels orientated along B_0 (POi>1)(Fig. 2b) yields a BVf underestimation (Fig. 2c). (iv) For an intervessel distance of about 30µm (healthy gray matter value), BVf is overestimated by 20%. As intervessel distance increases from 22 to 43µm, BVf overestimation remains in the range of [23-14%] (Fig. 3c).

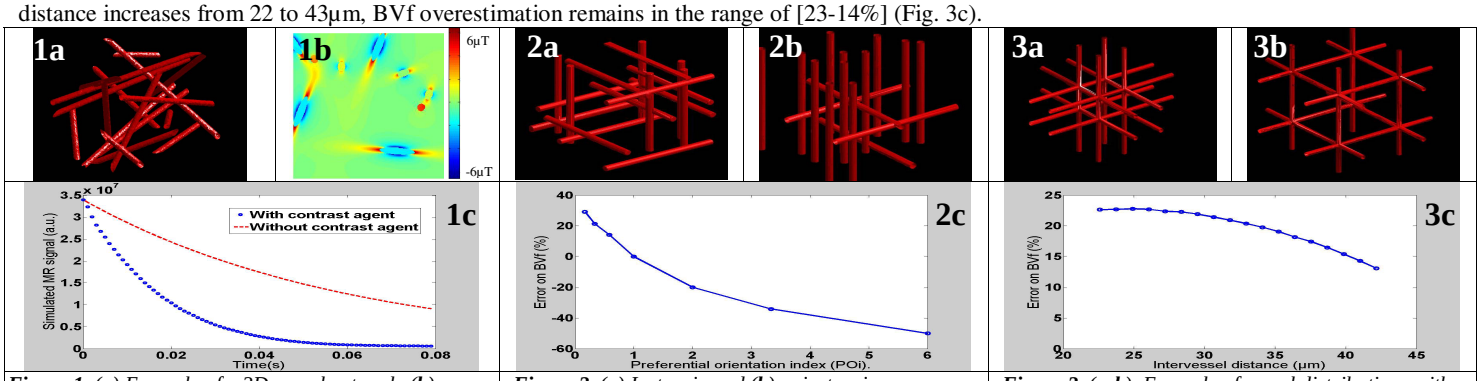

***Figure 1**. **(a)** Example of a 3D vessel network. **(b)** Simulated magnetic field intensity at 4.7T in a plane across a microvascular network. **(c)** Transverse magnetization vs. echo time with (blue) and without (red) an intravascular contrast agent ($\Delta\chi$=0.28ppm).*

***Figure 2**. **(a)** Isotropic and **(b)** anisotropic distributions of vessel orientations. **(c)** Error on BVf as a function of the preferential orientation index (POi).*

***Figure 3**. **(a-b)**. Example of vessel distributions with different intervessel distances. **(c)** Error on BVf as a function of intervessel distance.*

Conclusion

This study suggests that the proposed simulation approach can be used to obtain MR estimates of BVf *in silico*. BVf estimates do no seem to be affected by either vessel shape or vessel curvature. The impact of preferential vessel orientation the MR estimate of BVf suggests that vessel orientation should be further characterized *in vivo*, especially in pathological tissues like brain tumors. Finally, this study indicates that the MR estimate of BVf is overestimated by about 20% for normal intervessel distances. This systematic error on BVf estimate could be due to the interaction between the magnetic susceptibility gradients originating from neighbour cylinders.

References [1] S Valable et al, *NMR Biomed*, 2008. [2] J. P. Marques and R. W. Bowtell, *NMR Biomed*, 2007. [3] L. M. Klassen and R. S. Menon, *Biophys J*, 2007.[4] I Troprès et al. *Magn Reson Med*, 2001.