Reconstruction of size distribution of cellular-sized pores using DWI with clinically applicable gradients

Yaniv Katz[1], Dan Benjamini[1,2], Peter J Basser[2], and Uri Nevo[1]

[1]*Biomedical Engineering, Tel Aviv University, Ramat Aviv, Tel Aviv, Israel,* [2]*Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health, Bethesda, MD, United States*

Introduction The accurate estimation of pore morphology is of great interest in a wide range of scientific and technical fields. It is of particular importance in diffusion weighted imaging (DWI)[1], where the use of high **q**-values can accurately estimate dimensions of small pores and pore size distributions (PSD) in tissues.[2] However, there are conceptual and clinical limitations of using q-value analysis[1] for PSD estimation. Applying high gradient amplitudes is clinically infeasible, and the conventional DWI sequences violate key assumptions of the **q**-analysis. The Multiple Correlation Method (MCF) [3] first suggested by Barzykin and Grebenkov can be used to derive mathematical expressions for pulsed field gradient (PFG) restricted diffusion NMR experiments, admitting the application of finite-duration PFGs and incorporating the effects of imaging gradients. Here we present the first accurate PSD estimation that is based on clinical DWI acquisition using a well-calibrated diffusion MRI phantom.

Experiment A zero mixing-time double PFG (d-PFG) MRI acquisition was performed on a glass capillary array (GCA) phantom using a $7T$ vertical-bore Bruker AVANCE III MR microimager. The GCA consists of 6 parallel packs of water-filled monodisperse micro-capillaries, having radii of $2.5[\mu m]$, $5[\mu m]$ or $13.7[\mu m]$. Two d-PFG experimental sets were used to estimate different volume fractions (VFs). The first consisted of 90 experiments with a maximum gradient amplitude of $50[mT/m]$ in each block; the second consisted of 20 additional experiments with a maximum gradient amplitude of $80[mT/m]$. These experiments varied in gradient duration, gradient amplitude, diffusion time, and the angle between the gradients, in order to improve the estimation quality. [2]

Methods The relative intensities of each pixel inside the region of interest (ROI) were averaged to obtain a single signal per experiment. This signal depends on the NMR signals produced by the restricted motion inside each microcapillary, and weighted by the relative volume of each capillary and the NMR signal produced by the unbounded water.

Estimation PSD estimates were based on different sets of restricted diffusion NMR signals computed analytically using the MCF method. Each set was computed assuming a unique diffusion coefficient, ranging between $1500 - 2500[\mu m^2/sec]$ to account for the uncertainty in its value. For each VF estimate the set producing the smallest squared L_2-norm was selected as the optimum. The exact distribution of the GCA compartments were not provided by the manufacturer, so the VF estimate was used to determine the relative weighting of each distribution, based on some prior knowledge. The gold standard, which the relative weights were compared to, was calculated as was previously suggested by Benjamini et al. [4]

Validation Different combinations of pixels of the proton density image were selected as the ROI. Averaging the signals from these pixels produced mono- and poly-disperse VFs of different shapes, which were estimated using the two experimental sets.

Results The experiments showed promising results in the ability to differentiate between the smallest, intermediate and largest diameters, and also showed impressive ability to accurately estimate the relative weight of each compartment (Table 1), even when the diameter distribution was tri-modal. Although the **q**-values were of the order $1/20[\mu m^{-1}]$, we were still able to estimate pores sizes $< 5[\mu m]$. However, the table below shows several issues with these estimates: 1. The average pore sizes are mostly underestimated for the two smallest compartments. 2. The experimental data does not contain enough information to completely differentiate between the two smallest compartments. 3. The effect of ill-posedness[2] is more dominant in smaller pores.

Summary and Conclusions This research serves as an important proof of concept of how characterizing porous systems using NMR signals analyzed with the MCF method can be used without applying strong gradient amplitudes with short gradient durations. This research also proves that the resolution limit of PSD estimation cannot be determined using a simple inverse relation between the **q**-values and the sizes characterized. The difficulty to differentiate between the two smallest compartments arises due to the problem's ill-posedness which could have been solved by increasing the **q**-values. This could be easily done by further lengthening the gradient duration but at the expense of increased echo time (TE). **The gradients employed in this research are applicable for clinical MR scanners, thus proving the usefulness of this analysis for various clinical applications.**

Theoretical VF	Experimental Set 1		Experimental Set 2	
	Estimated VF	Estimated radii $[\mu m]$	Estimated VF	Estimated radii $[\mu m]$
1/0/0	0.89/0.11/0	1.72/4.54/-	0.88/0.12/0	2.14/4.07/-
0.42/0/0.58	0.43/0/0.57	1.40/-/14.15	0.43/0/0.57	1.40/-/14.17
0.63/0.37/0	0.75/0.25/0	1.30/5.59/-	0.75/0.25/0	1.21/5.69/-
0.50/0.15/0.35	0.52/0.13/0.35	1.86/4.51/14.19	0.53/0.12/0.35	1.55/4.87/14.22
0.21/0.22/0.57	0.20/0.23/0.57	2.46/4.35/14.16	0.21/0.22/0.57	2.39/4.41/14.16
0.34/0.18/0.48	0.35/0.17/0. 48	2.19/4.30/14.16	0.35/0.17/0. 48	1.92/4.47/14.16

Table 1: Polydisperse and monodisperse VF estimation using the two experimental sets. The relative weight and average size estimation of each compartments are shown in the following way: smallest/intermediate/largest compartment.

References **[1]** Y. Assaf *et al.* J. Mag. Res. Med. 44.5(2000): 713-722. **[2]** Y. Katz, U. Nevo. J. Chem. Phys. 140 (2014) 164201. **[3]** D. S. Grebenkov, J. Chem. Phys. 128 (2008) 134702. **[4]** D. Benjamini *et al.* J Mag. Res. 2014 (30) 246C:36-45.