

# Diffusion MR Imaging at varying of diffusion time to give more on the heterogeneous porous systems.

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**Introduction.** Recent studies have demonstrated that water diffusion in biological systems may be anomalous [1,2], due to the complexity of these high heterogeneous media. As a consequence, over the last few years, new strategies to obtain MR images representative of anomalous diffusion (AD) characteristic parameters have been developed [3,4]. AD behaviour of water in biological tissues can be observed by probing the biological systems in a large range of b-values (from 0 up to 7000 s/mm<sup>2</sup>) using a Pulse Field Gradient (PFG) sequence. There are two ways for changing b value: to vary the diffusion time  $\Delta$  or to vary the gradient strength g. In the latter case,  $\gamma$  maps are obtained from the so-called AD stretched exponential model [3,4].

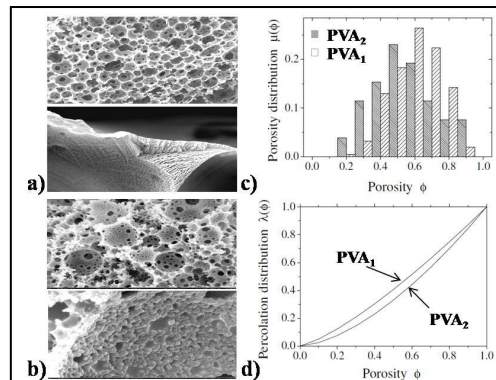
This work introduces a novel imaging method to characterize and to map AD processes of water in heterogeneous systems by means of diffusion weighted techniques at varying of the  $\Delta$ . The approach is based on the theory of the Continuous Time Random Walk [5,6] where the motion propagator (MP) is defined as the solution of fractional diffusion equations. To study sub-diffusive processes for which the mean-square displacement of diffusing particles grows sub-linearly in time, it is possible to employ the following asymptotic behavior of the Fourier Transform of the MP[5]:  $W(k,t) \propto \exp(-K_\alpha k^2 t^\alpha)$ , (Eq.1) which hold when  $k^2 \ll 1/(K_\alpha t^\alpha)$ , where  $k = 1/(2\pi)g\delta\gamma$  with  $\gamma$  the gyromagnetic ratio and  $\delta$  the pulse gradient duration. The value of the parameter  $0 < \alpha < 1$  resumes the mean behaviour of water diffusion in different compartments characterized by obstruction or trapping effects. As a consequence,  $\alpha$  index, which quantifies sub-diffusion processes, is able in principal to provide more and different information about microstructural complexity of heterogeneous media, compared to those usually obtainable from diffusion weighted imaging (DWI) experiments. Aims of this work are: 1) to obtain  $\alpha$ -maps in two phantoms characterized by different microstructural rearrangements; 2) to assess which kind of microstructural information can be derived from  $\alpha$  map and to compare it with the one provided by conventional mean diffusivity (MD).

**Materials and Methods.** Phantoms: two cylindrical scaffolds (highly porous polymeric matrices with randomly oriented interconnected pores) were prepared from a solution of polyvinyl alcohol and cetyltrimethylammonium bromide, as described in [7]. The scaffolds are characterized, in the dry state, by a void and interconnect size distribution ranging from 100 to 500  $\mu$ m and 40 to 200  $\mu$ m, respectively. The average void and interconnect diameters are approximately 220  $\mu$ m and 100  $\mu$ m, respectively. The two scaffolds differ in the roughness of the walls of their voids and interconnections: one sample is characterized by smooth walls (named PVA<sub>1</sub>, see Fig. 1a), while the other one is characterized by rough walls (named PVA<sub>2</sub>, see Fig. 1b). In a first step, the dynamic behavior of water in these water-imbibed scaffolds was characterized by means of dielectric relaxation spectroscopy (DS) [7] and subsequently it was investigated by means of DW NMR experiments. All NMR measurements were performed on a Bruker 9.4T Avance system, operating with a micro-imaging probe (10 mm internal diameter bore) and equipped with a gradient unit characterized by a maximum gradient strength of 1200 mT/m and a rise time of 100  $\mu$ s. The temperature was fixed at 293 K. An imaging version of PGSTE sequence with  $\delta=2$ ms, diffusion gradients along x, y and z axes, TE/TR=17.3/5000ms, STH=1mm, FOV=8 mm and 7 values of  $\Delta$  in the range (20-520)ms, covering a range of b-values from 400 to 6500 s/mm<sup>2</sup>, were used for collecting DW images. For each  $\Delta$  value, S(0) image with g=0 and a S(g) image with g=75mT/m were acquired. Subsequently, Eq. (1) was fitted to S(b)/S(0) data in each voxel to evaluate  $\alpha$  value for each of the diffusion gradient directions:  $(\alpha_i)_{i=x,y,z}$ . Finally, the quantity:  $Ma=1/3 \sum_{i=x,y,z} \alpha_i$ , was computed in each voxel to obtain the Ma-maps. Moreover, DW images, using a PGSTE sequence with  $\Delta\delta=40/2$  ms, TE/TR=17.3/5000ms, STH=1mm, FOV=8 mm and 5 values of b in the range (0-1500) s/mm<sup>2</sup> along x, y and z axes, were acquired to perform MD-maps.

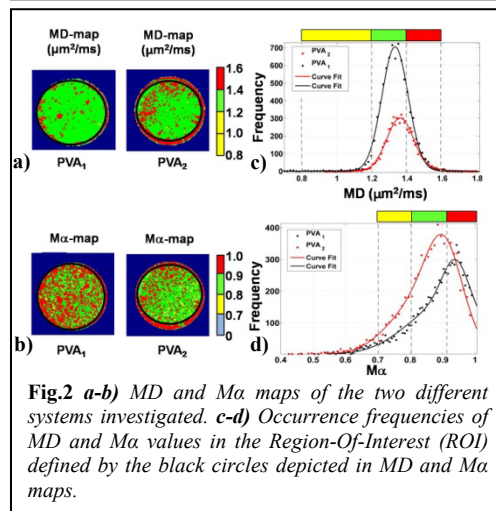
**Results and Discussion.** The local porosity distribution,  $\mu(\phi)$ , as a function of the porosity,  $\phi$ , derived from the analysis of the dielectric dispersion, measured by means of DS, is reported in Fig. 1c. As expected, the mean porosity of the rough sample (PVA<sub>2</sub>) is smaller than that of the smooth sample (PVA<sub>1</sub>), revealing an increase in the complexity of the heterogeneous morphology. Moreover, the local percolation probability,  $\lambda(\phi)$ , which measures the pore interconnectivity (Fig. 1d), corroborate the results showed in Fig. 1c. MD-maps, based on Gaussian diffusion description, and Ma-maps, representative of the spatial distribution of the anomalous sub-diffusion of water are displayed in Fig. 2a and 2b, respectively. As expected, Ma-map contrast is different from that observed in conventional MD-map. In particular, Ma-map of the smooth sample (PVA<sub>1</sub>) is quantitatively different when compared to the one of the rough sample (PVA<sub>2</sub>), showing mean Ma values equal to  $0.92 \pm 0.03$  and  $0.87 \pm 0.04$ , respectively. Conversely, MD-map of the PVA<sub>1</sub> sample is not quantitatively different from that of the PVA<sub>2</sub> sample, showing mean MD values equal to  $1.33 \pm 0.11$  and  $1.36 \pm 0.11$   $\mu$ m<sup>2</sup>/ms, respectively. To better understand information deriving from  $\alpha$  values, MD and Ma value occurrence frequency graphs are reported in Fig. 2c and 2d, respectively. The MD values measured in ROIs of the two MD-maps, marked with black circles in Fig. 2a, follow a well definite narrow Gaussian distribution, with mean value  $\mu=1.33$   $\mu$ m<sup>2</sup>/ms and standard deviation  $\sigma=0.11$   $\mu$ m<sup>2</sup>/ms, for PVA<sub>1</sub> sample (black solid line in Fig. 2c), and  $\mu=1.36$   $\mu$ m<sup>2</sup>/ms,  $\sigma=0.11$   $\mu$ m<sup>2</sup>/ms, for PVA<sub>2</sub> sample (red solid line in Fig. 2c). Conversely, a sum of two Gaussian distributions, with  $\mu_1=0.94$ ,  $\sigma_1=0.06$  and  $\mu_2=0.90$ ,  $\sigma_2=0.17$ , for PVA<sub>1</sub> sample (black solid line in Fig. 2d), and  $\mu_1=0.90$ ,  $\sigma_1=0.08$  and  $\mu_2=0.83$ ,  $\sigma_2=0.13$ , for PVA<sub>2</sub> sample (red solid line in Fig. 2d), represents the best distribution fitting to the data obtained from the ROIs of the two Ma-maps marked with black circles in Fig. 2b. In each sample, the parameters of the two Gaussian distributions characterizing the Ma values distributions allow to discriminate between two level of morphological complexity: one of these is due to the voids size distributions ( $\mu_1$  and  $\sigma_1$ ) and the other one is due to the interconnection size distribution ( $\mu_2$  and  $\sigma_2$ ). These parameters allow to discriminate the two samples, which differ only in the roughness of the walls of their voids and interconnection. Indeed,  $\mu_1$  value measured in the smooth sample (PVA<sub>1</sub>) is higher than that one measured in the rough sample (PVA<sub>2</sub>) and  $\mu_2$  value measured in PVA<sub>1</sub> is also coherently higher than that one measured in PVA<sub>2</sub>.

**Conclusion.** Here, we presented the first  $\alpha$ -maps obtained in controlled phantoms which are characterized by highly porous polymeric matrices with randomly oriented interconnected pores showing different microstructural rearrangement and morphological complexity. Our results show that  $\alpha$ -maps, based on AD description, unlike the conventional MD-maps, based on Gaussian description of diffusing water spins, are able to discriminate between two samples that differ only by the type of walls (smooth or rough) of the pores and interconnections. As a consequence, the proposed methodology may provide some additional and complementary information, compared to those of conventional MD approach, on the microstructural rearrangements of biological media in which the water diffuses.

**References:**[1] Özarslan E et al. JMR 2006;183:315. [2] J.H. Jeon et al. PRL 2011;106:048103. [3] Bennet KM et al. MRM 2006;56:235. [4] De Santis S. et al. MRM 2011;65:1043.[5] Metzler R, Klafter J. Phys Rep 2000;339:1. [6] M.Palombo et al. JCP 2011;135: 034504. [7]A. Barbetta et al. Soft Matter, 2010; 6:5213.



**Fig.1 a-b)** Scaffolds morphology as revealed by Scanning Electron Microscopy. **c-d)** Local porosity distribution,  $\mu(\phi)$ , and local percolation probability,  $\lambda(\phi)$ , as a function of the porosity,  $\phi$ , for the two different systems investigated by means of DS.



**Fig.2 a-b)** MD and Ma maps of the two different systems investigated. **c-d)** Occurrence frequencies of MD and Ma values in the Region-Of-Interest (ROI) defined by the black circles depicted in MD and Ma maps.