Water diffusion behavior in bone marrow

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Introduction
In biological systems, interactions with obstacles, transient binding events or molecular crowding are likely to influence the diffusion of water molecules. Complex diffusive dynamics are then observed, which lead to the failure of the Gaussian approximation. In such cases, water diffusion decay recorded by diffusion-sensitized sequences is found to deviate from the mono-exponential decay, i.e. from the conventional Stejskal-Tanner equation $S(b)=S(0)\exp(-bD)$. The solution of the diffusion equation with the proper initial conditions leads to a non linear dependence of the mean squared displacement to the diffusion time and to a stretched exponential form for the signal decay, namely $S(b)=S(0)\exp(-Ab^{\gamma})$ [1,2]. By varying the b-value, it is possible to evaluate the stretching exponent γ by means of a fitting procedure. This exponent categorizes the deviation from the ideal conditions of Gaussian diffusion and the complexity of diffusing spins excursions. It has been demonstrated that the stretching parameter shows a high sensitivity in detecting early pathological changes in tumor tissues of rat brain [3]. Other authors obtained interesting results also in human brains [2]. Bone marrow is a biological tissue which fills the bones. Human and mammalian marrow is mainly composed by water and different kinds of lipids, including saturated, unsaturated and diunsaturated fatty acids. The relative concentration of each constituent is dependent on both anatomical skeletal location and age of considered subjects [4]. This complex system is located both in diaphysis, where it is free, and in the spongy bone, where it is constrained inside the pores of a solid-bone matrix. Bone marrow may be affected by several pathologies. Recently it has been underlined that one of the main features of osteoporosis is an altered quality of the bone marrow [5]. Interesting information can be gathered about this biological network by investigating the water spins diffusion. Aim of the present work was to characterize the diffusive dynamics of water spins in calf bone marrow by means of the anomalous exponent γ at different water-to-fats ratios in both, the diaphysis and the spongy bone.

Methods and Materials
Ex-vivo spongy bone samples excised from calf distal femur were cut into pieces of about 20mm height and 7mm dept. At the same time bone marrow was removed from the femur diaphysis of calf samples. Bovines 8-36 months aged were considered and their water-to-fats ratio, as well as the specific fats composition, were assessed from the peak area of the bone marrow spectra (**Fig.1**). For each sample, a spectroscopic PGSTE sequence was applied (TR=5s, diffusion gradient pulses delay Δ=80ms, pulse gradient duration δ=4.6ms, gradient range 2-100G/cm) along x, y and z directions. All experiments were realized at 9.4T. Due to the low resolution of the bone marrow spectra, in most of the samples olefinic fat peak at 5.3ppm is overlapped to the broad water peak centred at 4.7ppm. Thus, the total signal arising from the superimposition of the two peaks was selected to perform a Levenberg-Marquard (L-M) fit. The strong difference of decay rate of water and fat as function of b values, allowed us to discriminate between the two contributions by fitting the data as a superimposition of a Stejskal-Tanner decay (fat component) and a stretched exponential decay (water component). The stretching exponent was then obtained for each gradient direction and the results were averaged to obtain the mean γ exponent. For each sample, the mean γ was then related to the water-to-fats ratio.

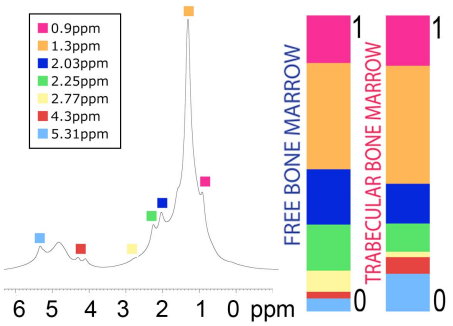

Fig. 1 Bone marrow spectrum with peaks assignment (left). Fat composition averaged across the samples, for free and trabecular bone marrow (right).

Results and Discussion
Fig.1 shows a typical bone marrow spectrum and fat composition for both free and trabecular bone marrow. No evident differences between the two systems are detectable in the specific fat compositions. In **Fig. 2** the mean γ exponent is plotted versus the water-to-fats ratio. In free bone marrow, mean γ assumes values very close to unity and its trend is constant as the water concentration increases. This means that in this system, the diffusion of water spins can be considered normal (not anomalous) and the Gaussian approximation holds. Conversely, in trabecular bone marrow, values of the mean exponent smaller than unity are obtained and an increasing trend with increasing water content is found. When the bone marrow is enclosed inside the trabeculae, the Gaussian approximation fails and anomalous dynamics appear, depending on the fat concentration. The fact that in the same concentration range the two systems, which are equivalent in fat composition, show such a different behaviour can only be explained by the presence of the solid bone matrix. The difference in magnetic susceptibility between bone and bone marrow is well known in literature due to its influence on T_2* decay. It is therefore not surprising that such a feature of the interface also affects the water diffusion spins, causing a deviation from the ideal conditions. This scenario matches with a reasonable distribution of bone marrow filling the trabecular pores, for which the water wets the surface of bone pores and the fat is rearranged principally in the centre, according to its hydrophobic nature. For very small water concentrations, the water molecules are mostly found at the bone interface. At the bone interface, internal gradients entrap water molecules and a strong effect on the diffusion decay is recorded. As the water concentration increases, only a fraction of water molecules is in contact with the pore surface and the γ exponent increases towards unity.

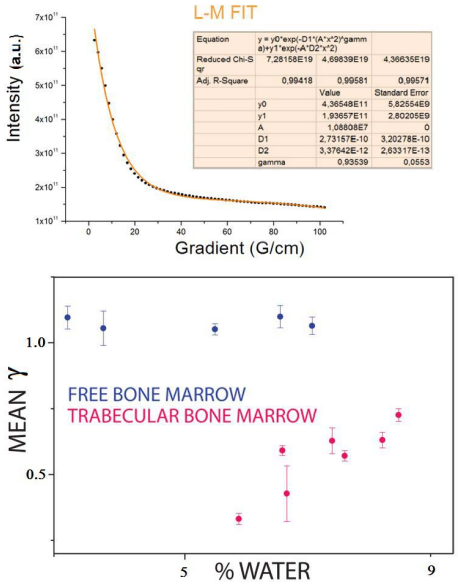

Fig. 2 Signal decay and L-M fit (up). Mean γ exponent and standard deviation versus water content for free bone marrow (blue) and trabecular bone marrow (pink) (down)

Conclusion Bone Marrow is a complex system which is found in both diaphysis, where it is free, and in spongy bone, where it fills the pores of its matrix. The diffusion of water molecules contained in the bone marrow can be investigated by means of the γ exponent, which quantifies the deviation from the ideal Gaussian diffusive conditions. The diffusion decay of water in free bone marrow samples follows conventional Stejskal-Tanner equation, i.e. γ is very close to unity. Conversely, in trabecular bone marrow the internal gradients at the interface between bone and bone marrow affect the spin diffusion causing a deviation from the Gaussian behaviour, and γ values smaller than unity are observed. Preliminary results reported here, demonstrate that non-Gaussian diffusion methods provide useful information about diffusive behaviour of water that can be related to the bone marrow quality and composition. Moreover, our findings may offer interesting perspectives for the indirect investigation of the complex bone network.

References [1] Bennett KM et al. MRM 2003;50:727-734**.** [2] Hall MG, Barrick TR., MRM 2008; 59: 447-455**.** [3] Bennett KM et al. MRM 2004;52:994-1004**.** [4] Liney GP, et al. J Magn Res Im 2007;26:787-793. [5] Yeung DKW, JMRI 2005;22:279-285.