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Water exchange in a white matter tissue phantom measured using clinically feasible diffusion exchange spectroscopy (DEXSY) MRI

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Synopsis

Studying the axons' membrane permeability at different white matter tracts could clarify the role of aquaporins. Diffusion exchange spectroscopy (DEXSY) is an assumption-free approach to measure water exchange, allowing for any number of exchange processes between any number of compartments. It has never been applied in biological MRI owing to its exceptionally long scan time requirements. Here we present a method to reduce the number of required acquisitions, making DEXSY-MRI clinically feasible for the first time. We apply this method on a nerve tissue phantom, and demonstrate that 14 acquisitions are sufficient to determine the exchange spectrum.

Introduction

During molecular exchange between microenvironments in the brain, water passes across cell membranes, either directly through the lipid bilayers or via channels, such as aquaporins (AQP).[1] AQPs represent a diverse family of membrane proteins, with AQP1 and AQP4 being the primary channels expressed in the mammalian brain.[2,3] These AQPs ability to facilitate water transport is implicated in pathological conditions such as cancer and brain.[4] Most MRI methods for determining membrane transport rates rely on trans-membrane differences in the relaxation times, and often involve the injection of contrast agents (e.g., dynamic contrast-enhanced MRI[5]). These methods all rely on biophysical models that assume there are only two microenvironments that exchange. A recent diffusion-based method to map water exchange makes the same assumption of only two exchanging compartments with slow and fast diffusion rates.[6] Avoiding such assumptions, we suggest using an assumption-free approach to measure exchange, allowing for any number of exchange processes between any number of compartments. Diffusion exchange spectroscopy (DEXSY)[7] is a 2D double pulsed-field gradient experiment that provides this functionality. As powerful as it is, it has never been applied in biological MRI owing to its exceptionally long scan time requirements. Here we present a method to vastly reduce the number of required acquisitions, making DEXSY-MRI clinically feasible for the first time.

Methods

A white matter phantom was comprised of a water-filled glass capillary array with a nominal inner diameter of 5μm, and an adjacent layer of freely diffusing water, mimicking intra- and extra-axonal spaces (Fig. 1). Water molecules in the capillaries are

free to diffuse along the symmetry axis to the free water pool, and vice versa, resulting in water exchange between restricted and unrestricted compartments. The composite phantom was put in a 15mm NMR tube and scanned using a 7T Bruker vertical wide-bore magnet with an AVANCE III MRI spectrometer. DEXSY-filtered MRI data were acquired by applying the sequence in Fig. 2 followed by a 2D spin echo MRI sequence. Diffusion gradients, G_1 and G_2, are applied in the same direction (x, see Fig. 1), and their amplitudes are varied independently with 45 linear steps (resulting in $N = 45 \times 45 = 2025$ acquisitions) in the range of 0-1346mT/m, leading to $b = \gamma^2\delta^2G^2(\Delta - \delta/3)$ in the range of 0-18180s/mm2, and τ_m=15,200,300ms. The resulting signal as a function of the applied b-values is given by

$$M(b_1, b_2) = \sum_{n=1}^{N_{D_1}} \sum_{m=1}^{N_{D_2}} \mathbf{F}(D_{1,n}, D_{2,m}) \exp(-b_1 D_1 - b_2 D_2)$$

where $\mathbf{F}(D_1, D_2)$ is the joint probability of the contribution to the signal from the initial diffusion coefficient, D_1, and the final diffusion coefficient, D_2. In this work we apply a recently proposed method[8] to stabilize the estimates of $\mathbf{F}(D_1, D_2)$ in Eq. 1, while reducing the number of acquisitions and improving accuracy, by constraining the solution according to the following relation:

$$\sum_{n=1}^{N_{D_1}} \mathbf{F}(D_1, D_{2,n}) = \sum_{n=1}^{N_{D_2}} \mathbf{F}(D_{1,n}, D_2) = F(D).$$

The 1D distribution, $F(D)$, can be separately estimated from a 1D experiment, which requires an order of magnitude less data than a conventional 2D acquisition.

Results and Discussion

The volume fraction of water that remains in the capillaries/free-water compartment after the mixing time is f_I/f_E and the volume that diffused from one space to the other and vice versa is f_{IE}/f_{EI}. Processing the 2D data using Eqs. 1&2 results in the $\mathbf{F}(D_1, D_2)$ spectra presented in Fig. 3. The distributions on the top row are obtained by using the entire dataset, and the ones on the bottom are obtained by using only 0.07% of the data. The suggested method allows for a vast reduction of required data, while yielding highly accurate results. The peaks on the diagonal of the distributions are f_I and f_E, and the off-diagonal peaks are f_{IE} and f_{EI}, which should be equal in an equilibrated system. As expected, f_I/f_E decrease and f_{IE}/f_{EI} increase as a function of τ_m. When complete exchange has occurred the off-diagonal peaks should have an intensity of 25%, a value which reflects the equilibrium probability distribution of water between the restricted and free states. Assuming an exponential process, we may estimate the exchange rate, $k_{exc} \sim 1.1$1/s, and the exchange time, $\tau_{exc} \sim 0.9$s. We showed that 14 acquisitions are sufficient to accurately determine the diffusion exchange spectrum, which is ~ 150 times less than previously thought to be needed. Combined with an EPI readout, this approach makes DEXSY MRI a clinically feasible imaging technique to measure the water exchange rate.

Conclusion

AQPs' function in the healthy brain is only partially understood, therefore studying the water exchange rate from and to axons at different white matter tracts could clarify their role. This method is not limited to any number of predetermined compartments and exchange processes, thus it can also be used to image water exchange and dynamics in gray matter.

Acknowledgements

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References

1. Agre P, King LS, Yasui M, Guggino WB, Ottersen OP, Fujiyoshi Y, Engel A, Nielsen S. Aquaporin water channels - from

atomic structure to clinical medicine. J Physiol 2002; 542: 3–16.

2. Nielsen S, Nagelhus EA, Amiry-Moghaddam M, Bourque C, Agre P, Ottersen OP. Specialized membrane domains for water transport in glial cells: high-resolution immunogold cytochemistry of aquaporin-4 in rat brain. J Neurosci. 1997;17(1):171-80.

3. Oshio K, Watanabe H, Yan D, Verkman AS, Manley GT. Impaired pain sensation in mice lacking Aquaporin-1 water channels. Biochem Biophys Res Commun. 2006;341:1022–1028.

4. Tait MJ, Saadoun S, Bell BA, Papadopoulos MC. Water movements in the brain: role of aquaporins. Trends Neurosci 2008; 31: 37–43.

5. Tofts PS, Kermode AG. Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts. Magn Reson Med. 1991;17(2):357-67.

6. Nilsson M, Lätt J, van Westen D, Brockstedt S, Lasic S, Ståhlberg F, Topgaard D. Noninvasive mapping of water diffusional exchange in the human brain using filter-exchange imaging. Magn Reson Med. 2013;69(6):1573-81.

7. Callaghan PT, Furo I. Diffusion–diffusion correlation and exchange as a signature for local order and dynamics. J Chem Phys 2004; 120: 4032–4038.

8. Benjamini D, Basser PJ, Joint radius-length distribution as a measure of anisotropic pore eccentricity: an experimental and analytical framework. J Chem Phys. 2014;141:214202.

Figures

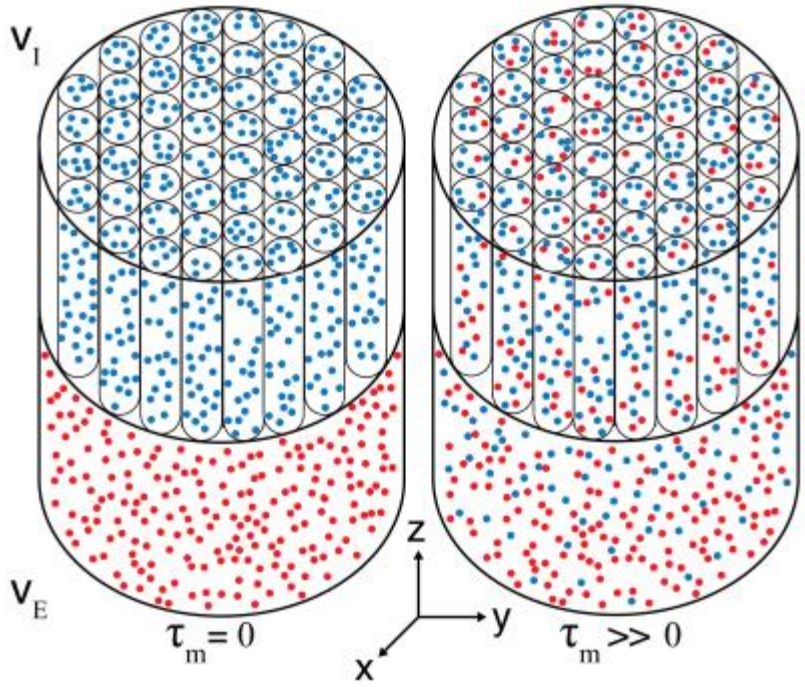

Figure 1: As τ_m is increased, the fraction of the water that resided in the capillaries during the first diffusion block and moved to the free water pool at the second diffusion block, and vice-versa, is increased as well.

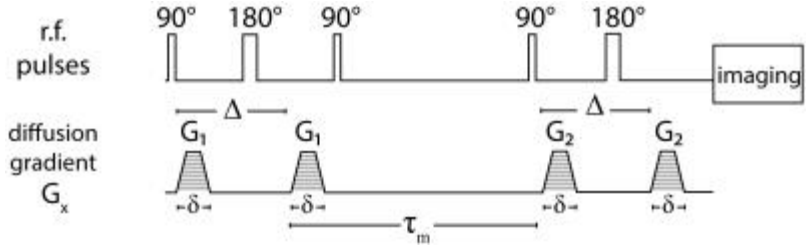

Figure 2: The DEXSY pulse sequence used here. It consists of pulsed gradient spin echo experiment in which two collinear gradient pulses pairs, G_1 and G_2 separated by a mixing time τ_m are stepped independently. Diffusion gradient duration, δ=3ms, and diffusion period Δ=15ms were used. Imaging parameters were TE/TR=7.6/3000ms, FOV=$15.5 \times 15.5 mm^2$, and an axial slice of 0.6mm.

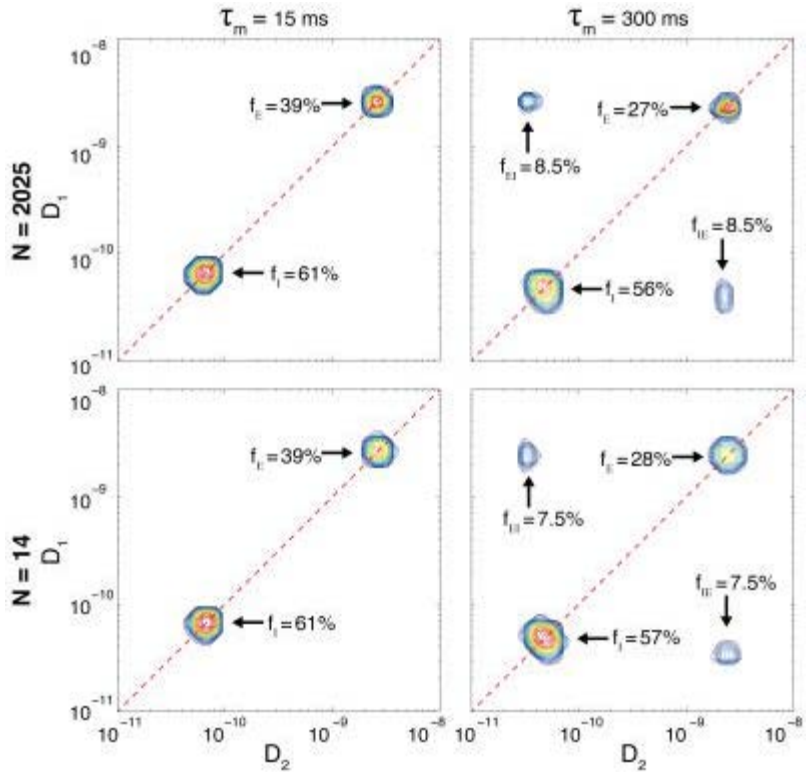

Figure 3: DEXSY spectra. The distributions on the top row were obtained by using the entire dataset (number of acquisitions $N = 2025$), and the ones on the bottom were obtained by using only $N = 14$. Left to right: increasing τ_m from 15ms to 300ms. Note the appearance of the off-diagonal peaks, representing the water volume fraction that diffused between the intra- and extra-"axonal" compartments (i.e., exchange).

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