Diffusion of Hyperpolarized $^{129}$Xe in Biological Systems: Effects of Chemical Exchange

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Introduction:
Xenon self-diffusion in biological systems may be a suitable NMR parameter for the characterization of different tissues by means of hyperpolarized $^{129}$Xe NMR. Chemical exchange between different compartments results in an effective diffusion coefficient $D$. Here, we present the first measurements of $^{129}$Xe diffusion in albumin solution and plasma. The results are analyzed using a straightforward extension of the random-jump model of diffusion in the presence of chemical exchange.

Materials and Methods:
Optical cells were filled with a suitable mixture of enriched $^{129}$Xe, N$_2$ and He and a small amount of Rb. The Rb vapour was optically pumped with circularly polarized light from a 120 W diode laser array.

We chose a 5% w/v solution of bovine serum albumin (BSA) in de-ionized H$_2$O, and plasma from human blood, as model systems in which xenon undergoes fast chemical exchange between the aqueous and protein-bound environments. All hyperpolarized $^{129}$Xe diffusion measurements were performed at a field of 1.5T using a pulsed-gradient spin-echo NMR sequence. This technique requires multiple experiments to determine the diffusion coefficient. Single-shot diffusion measurements using a Burst technique have been demonstrated to yield good results for xenon dissolved in various liquids [2]. However, the Burst echo train could not be refocused in the presence of chemical exchange.

Theory:
Translational diffusion of atoms or small molecules can be pictured as a succession of discrete random jumps with a small displacement $\zeta$ with a mean time $\tau_s$ between successive steps [1]. The attenuation of the NMR signal of spins that are subject to diffusion is given by the coefficient [1]

$$\exp(i\Delta \Phi) = \exp(-\frac{1}{3}\gamma^2 G^2 D t^3), \quad (1)$$

where $\gamma$ is the gyromagnetic ratio and $G$ the applied field gradient. Extending this model for two environments $A$ and $B$ characterized by diffusion coefficients $D_{A,B} = \frac{1}{3}G^2/2\tau_s$ and allowing for exchange between compartments $A$ and $B$, the NMR signal is then attenuated by

$$\exp(i\Delta \Phi) = \exp(-\frac{1}{3}\gamma^2 G^2 (p_A\sqrt{D_A} + p_B\sqrt{D_B})^3 t^3) \quad (2)$$

with $p_{A,B}$ being the fractions of atoms in compartments $A$ and $B$. In the limit of fast chemical exchange, the signal decay follows eq. 2, and the apparent diffusion coefficient $\tilde{D}$ is a weighted average of the diffusion in the two compartments:

$$\tilde{D} = (p_A\sqrt{D_A} + p_B\sqrt{D_B})^3. \quad (3)$$

Results:
The diffusion coefficient of xenon in 5% BSA solution was measured to be $1.45 \times 10^{-9} m^2 s^{-1}$, compared to $D = 1.68 \times 10^{-9} m^2 s^{-1}$ for xenon in de-ionized H$_2$O. The errors in the measurements of $D$ are < 5%. As a first approximation, we can assume that the contribution to $\tilde{D}$ of the xenon fraction bound to BSA is negligible. Therefore, eq. 3 can be used (with $D_B \approx 0$) to obtain the fractions of xenon in the aqueous phase and bound to the protein, respectively. The result $p_A = 0.93$ and $p_B = 0.07$ are in good agreement with solubility data [3], which yield fractions of $p_A = 0.96$ and $p_B = 0.04$, respectively.

In the case of plasma, the xenon diffusion coefficient is further reduced by the presence of ions [4] and other proteins. We measured a xenon diffusion coefficient of xenon in plasma of $1.0 \times 10^{-9} m^2 s^{-1}$. We also found that the xenon diffusion coefficient in a 0.9% w/v NaCl solution is $1.34 \times 10^{-9} m^2 s^{-1}$, about 20% smaller than the diffusion coefficient of xenon in de-ionized H$_2$O. Applying eq. 3 yields fractions of $p_A = 0.86$ and $p_B = 0.14$ for the dissolved and bound compartments. These results again compare favorably with the fractions $p_A = 0.87$ and $p_B = 0.13$ calculated from solubility data [3].

Conclusion:
We have extended the random-jump model to describe translational diffusion in the presence of chemical exchange. We have successfully applied this model to hyperpolarized $^{129}$Xe diffusion measurements. Both proteins and ions decrease xenon self-diffusion in solution. Typical diffusion coefficients of xenon in protein solution and plasma are on the order of $10^{-9} m^2 s^{-1}$. This is an important parameter for the understanding of in vivo hyperpolarized $^{129}$Xe dynamics in blood and tissues.

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REFERENCES: