

Measurements of Restricted Diffusion Using an Oscillating Gradient Spin-Echo Sequence

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Received April 7, 2000; revised August 18, 2000

An oscillating gradient spin-echo (OGSE) pulse sequence was used to measure the apparent diffusion coefficient (D_{app}) of water in the short diffusion time regime in the presence of restrictions. The diffusion coefficients of water in a simple water sample and a water and oil mixture were measured to be the same for different periods of the gradient oscillation, as expected when there are no restriction effects. The D_{app} of water in the spaces between closely packed beads was also measured as a function of the gradient oscillation periods in the range 11 to 80 ms. The D_{app} of water in restricted systems varies with the period of the gradient oscillation and the dispersion depends on the scale of the restriction. For a sample of packed beads of diameter $9.1 \pm 0.7 \mu\text{m}$, the pore surface-to-volume ratio was estimated experimentally by this method to be $1.3 \pm 0.1 \mu\text{m}^{-1}$, corresponding to a mean pore diameter of $6.4 \pm 0.7 \mu\text{m}$. A Monte Carlo computer simulation of the NMR OGSE signal from the spins diffusing in a system of compartments was also implemented and the D_{app} demonstrated similar behavior with gradient oscillation periods. © 2000 Academic Press

Key Words: NMR; restricted diffusion; oscillating gradient spin echo; porous media.

INTRODUCTION

Pulsed gradient spin-echo (PGSE) methods provide information on the extent of diffusion over different time scales and thus, in principle, can directly measure the time dependence of the apparent diffusion coefficient (D_{app}) (1, 2). In practice it is difficult to determine D_{app} values in the very short diffusion time regime because such measurements require very strong gradients. These measurements are, however, of prime interest for probing the structure of media in which diffusion is restricted by closely spaced compartmental boundaries (3–7).

For example, within minutes after the onset of ischemia, the D_{app} in affected areas of the brain drops by approximately 50% (8, 9). The explanation for this change in D_{app} is not fully understood, but it might be caused partially by tortuosity changes due to cellular swelling (7). Measurements of compartment sizes and D_{app} values *in vivo* before and during ischemia might indicate what structural changes occur in the brain and provide information on the causes of the drop in D_{app} .

Since the mean squared displacement of freely diffusing

molecules is proportional to time, at very short diffusion times most molecules in media with compartments will not diffuse a distance long enough to interact with barriers separating the compartments. Thus D_{app} values measured in the very short diffusion time regime are related to the free diffusion coefficient values within each compartment (10). At slightly longer times, as molecular diffusion begins to become restricted because of interactions with the barriers, the measured D_{app} drops. At long diffusion times, molecules in all compartments experience restricted diffusion. The time characterizing the transition between the degrees of restriction can be used as an indicator of compartment sizes in the medium. The D_{app} measured at long diffusion times depends not only on compartmental sizes and volume fractions, but also on the permeability of the barriers (11). To determine compartmental sizes and unrestricted diffusion coefficients, short diffusion time measurements are needed.

Latour *et al.* (5) measured D_{app} as a function of effective diffusion times for water surrounding packed large glass beads (48 to 194 μm in diameter) using a modified pulsed gradient stimulated echo technique (PGStE). The PGStE effective diffusion times ranged from 7 to 800 ms. Coy and Callaghan (12) used q -space diffusive diffraction to measure the bead diameter and pore spacing in samples of packed beads 9.87, 14.8, and 15.8 μm in diameter. The q values used were as high as $2 \times 10^5 \text{ m}^{-1}$. The large q value experiments were repeated numerous times so that the resulting averaged signal had a large enough signal-to-noise ratio.

As an alternative approach to PGSE or PGStE for measuring diffusion in the short diffusion time regime, Gross and Kosfeld (13) proposed an oscillating gradient spin-echo (OGSE) method to probe the form of $D_{app}(T)$, where T is the period of gradient oscillation. The short period behavior of $D_{app}(T)$ reflects the behavior of the diffusing nuclei over short time intervals, and the transition of D_{app} from short to long periods can be used as an alternative indicator of restriction effects. The theoretical technique was extended by Stepisnik and colleagues, who developed a frequency spectral analysis of the data provided by experiments with oscillating gradients of different frequencies (14, 15). Minard (16) measured the pore surface-to-volume ratio and tortuosity in a water-saturated yarn

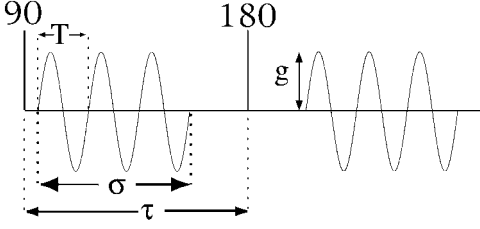


FIG. 1. Oscillating gradient spin-echo pulse sequence.

filter using OGSE, but was unable to independently verify these results because the water filter was not well characterized.

We have implemented an OGSE sequence and have used it to measure the $D_{\text{app}}(T)$ of water in samples of water and packed beads in water. Estimates of bead diameters, tortuosity, pore surface-to-volume ratio, and the free diffusion coefficient were made from the measurements of D_{app} for the bead samples. The potential of OGSE measurements to measure the characteristic dimensions of restricting compartments is demonstrated.

THEORY

The OGSE sequence is similar to a conventional PGSE pulse sequence, except that the diffusion gradient pulses are replaced by sinusoidally oscillating gradients with period T . The duration of each gradient pulse, σ , is chosen to be an integral number, n , of cycles of the oscillations. Figure 1 shows the OGSE sequence for $n = 3$. Each cycle of the oscillating gradients acts as a bipolar pulse so that there is a positive gradient lobe followed by a negative gradient lobe of equal area. After each cycle, stationary spins have their magnetic moment rephased whereas diffusing spins lose coherence. The degree of dephasing of the net transverse magnetization is proportional to the mean square displacement of the spins during the effective diffusion time, Δ_{eff} , which for the OGSE sequence is $(3/8)T$ (13).

Stepisnik and colleagues (14, 15) studied the signal dependence of OGSE experiments. In the case of no restrictions, the signal from an OGSE pulse sequence for a uniform water sample is given by (13)

$$\frac{E(\mathbf{g}, 2\tau)}{E(\mathbf{0}, 2\tau)} = \exp\left[-\gamma^2 D \frac{3\mathbf{g}^2 \sigma^3}{4\pi^2 n^2}\right] \equiv \exp[-bD], \quad [1]$$

when there are no magnetic field inhomogeneities present. b is the traditional diffusion weighting b -factor, and γ is the proton gyromagnetic ratio. This simple expression can be used to derive a D_{app} for a nonuniform system analogous to a D_{app} derived from PGSE. There is only one exponential decay for unrestricted diffusion, so the log of the decay is a straight line and the slope is used to find the diffusion coefficient. For restricted diffusion the decay might not be a simple exponential

with increasing b -factor. The log of the decay is nonetheless fit to a straight line and the slope defines D_{app} .

An inhomogeneous magnetic field, such as a background gradient, within the sample can introduce errors in the calculation of the b -factor and thus the diffusion coefficient for an OGSE sequence (13). However, by using gradient pulses with odd symmetry (17), the cross term between the applied magnetic field gradients and the background gradients vanishes.

An example of a simple system whose structural properties can be measured with the OGSE sequence is a sample of packed beads in water. In such a sample, the pore surface-to-volume ratio, S/V_p , is related to the bead diameter, d , by (5)

$$S/V_p = \frac{6(1/\epsilon - 1)}{d}, \quad [2]$$

where ϵ is the pore volume fraction. A mean pore diameter, d_p , can be defined in terms of S/V_p by (18)

$$d_p = \frac{6(1/\epsilon - 1)^{2/3}}{S/V_p}. \quad [3]$$

Latour *et al.* (5) found that the diffusion coefficient as a function of time varies as

$$D_{\text{app}}(\Delta_{\text{eff}}) = D_{\text{free}} - \left(1 - \frac{1}{\alpha}\right) D_{\text{free}} \times \frac{c \sqrt{\Delta_{\text{eff}}} + (1 - 1/\alpha) \Delta_{\text{eff}}/\theta}{(1 - 1/\alpha) + c \sqrt{\Delta_{\text{eff}}} + (1 - 1/\alpha) \Delta_{\text{eff}}/\theta}, \quad [4]$$

where α is the tortuosity of the pore space, D_{free} is the free diffusion coefficient, $\sqrt{D_{\text{free}} \theta}$ is proportional to the sphere diameter, d , and c depends on the surface-to-volume ratio, S/V , as

$$c = \frac{4}{9} \frac{S}{\sqrt{\pi}} \frac{1}{V} \sqrt{D_{\text{free}}}. \quad [5]$$

For porous systems, c is proportional to the pore surface-to-volume ratio, S/V_p . In two-compartment systems, c is proportional to the total surface-to-volume ratio, S/V (19).

The long time diffusion coefficient can be found from Eq. [4] by taking the limit as $\Delta_{\text{eff}} \rightarrow \infty$. In this limit, the diffusion coefficient, $D_{\text{app}}(\infty)$, is related to the free diffusion coefficient by

$$\frac{D_{\text{app}}(\infty)}{D_{\text{free}}} \approx \frac{1}{\alpha}. \quad [6]$$

We can define a dimensionless parameter, η , for the beads in terms of the effective diffusion time, Δ_{eff} , the diffusion coefficient of free water, D_{free} , and the radius of the beads, r , in the sample as

$$\eta = \frac{\sqrt{2D_{\text{free}}\Delta_{\text{eff}}}}{r} = \frac{\sqrt{3D_{\text{free}}T/4}}{r}. \quad [7]$$

This parameter is the ratio of the distance free water would travel in the effective diffusion time of the OGSE sequence and the radius of the beads in the sample and can be used as a measure of the degree of restriction. When $\eta \ll 1$, there is a small degree of restriction of water diffusion. When $\eta \approx 1$ there is an intermediate degree of restriction of water diffusion, and for $\eta \gg 1$, water diffusion is highly restricted.

The D_{app} as a function of time for a sample with bead diameter d_1 , pore volume fraction, ϵ , and free diffusion coefficient, D_{free} will behave according to Eq. [4]. Another sample with beads of diameter d_2 , the same volume fraction, ϵ , and free diffusion coefficient, D_{free} will behave in the same manner as the first sample, but on a time scaled according to Einstein's relation such that

$$\Delta_{\text{eff},2} = \frac{d_2^2}{d_1^2} \Delta_{\text{eff},1}. \quad [8]$$

Thus data taken in a small time interval from bead samples of different diameters can, in principle, be combined to give the form of D_{app} at other times.

COMPUTER SIMULATION

In addition to performing experiments using an OGSE sequence, a Monte Carlo computer simulation was developed to predict and compare the results of measurements. The simulation was modified from that described by Szafer *et al.* (20) who performed a simulation of the results of PGSE sequences for spins diffusing in a system of parallel rectangular fiber compartments in a regular array with variable compartment sizes, spacing, and permeabilities. The total surface-to-volume ratio for long parallel rectangular fibers of cross section $\ell \times \ell$ on a lattice of constant a is given by

$$\frac{S}{V} = \frac{4\ell}{a^2}. \quad [9]$$

For the OGSE simulation the conventional square gradient pulses were replaced by sine wave gradient pulses. The gradients were applied perpendicular to the fibers. For each set of parameters the signal was calculated for a given gradient sine wave amplitude, g , and period, T . In the simulation at time $t_i = 0$, a random uniform distribution of $N = 10,000$ particles was placed in the system. Initially, all particles' magnetic

moments were aligned as if just tipped by a 90° RF pulse, so that particle (j) had a phase $\phi_j(0^-) = 0$ and thus a magnetic moment $m_j(0^-) = 1$.

During each step (i) before the 180° RF pulse while a gradient was applied, each particle (j) had its phase increased by

$$\delta\phi_{ij} = -x_{ij}\gamma g \sin(2\pi t_i/T)\delta t, \quad [10]$$

where t_i is the time at the beginning of time step (i), δt is the length of the time step, and x_{ij} denotes the position of particle (j) along the gradient at time t_i . For each step (i) after the 180° RF pulse while a gradient was applied, each particle (j) had its phase increased by

$$\delta\phi_{ij} = x_{ij}\gamma g \sin(2\pi(t_i - \tau)/T)\delta t. \quad [11]$$

Each particle's (j) phase at the end of the simulation was

$$\phi_j = \sum_{i=0} \delta\phi_{ij}, \quad [12]$$

and thus its magnetic moment was $m_j = \exp(i\phi_j)$.

The net magnetization was calculated at the end of the simulation by adding the individual contribution from the N particles, so that the OGSE amplitude, E , is given by

$$E(g, T, 2\tau) = \left| \frac{1}{N} \sum_{j=1}^N m_j \right|. \quad [13]$$

At each frequency, E was calculated for the different gradient amplitudes. To obtain the D_{app} , $\log(E(g, 2\tau)/E(0, 2\tau))$ was plotted against g^2 and fitted to a straight line according to Eq. [1]. The D_{app} for that frequency was calculated from the slope, y , of this line according to

$$D_{\text{app}} = \frac{-4\pi^2 n^2}{3\gamma^2 \sigma^3} y. \quad [14]$$

MATERIALS AND METHODS

The Monte Carlo computer simulation was implemented with $\sigma = 80$ ms and n ranging from 1 to 16. For $n = 1$, or oscillation period $T = 80$ ms, g ranged from 0 to 22.5 mT/m in steps of 2.5 mT/m. For each period, $T = 80/n$ ms, gradient amplitudes increased appropriately with n to keep g^2/n^2 constant. This was done so that the same diffusion weighting was used for each gradient period, T , in order to keep the signal-to-noise ratio the same for each measurement. The simulation used $\ell = 2.7\text{-}\mu\text{m}$ -wide fibers arranged periodically on a lattice with constant $a = 3\text{ }\mu\text{m}$. The fiber system had intracellular diffusion coefficients of $1.0\text{ }\mu\text{m}^2/\text{ms}$ and extracellular diffusion

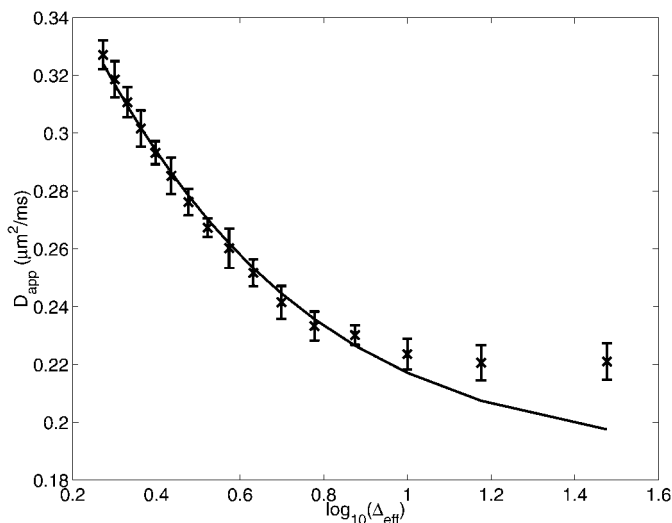


FIG. 2. Monte Carlo calculated D_{app} of water in a 2.7- μm fiber system. The data are represented by the x 's and the fit by the solid line.

coefficients of 2.5 $\mu\text{m}^2/\text{ms}$. Thus the free diffusion coefficient in the samples was calculated to be 1.3 $\mu\text{m}^2/\text{ms}$ using a weighted mean of the diffusion coefficients in the two compartments (20).

Experimental samples were placed in plastic tubes and stood vertically in the 2.0-T, 31-cm horizontal bore Bruker spectrometer inside a birdcage coil at 21°C. The OGSE pulse sequence was implemented with $\sigma = 80$ ms and n ranging from 1 to 7 and used the same range of g values as in the computer simulation. The exception was for $n = 7$, where the highest gradient amplitude, $g = 157.5$ mT/m, was omitted since it was above the maximum gradient amplitude obtainable with our system. Crusher gradients of 20 mT/m and 1-ms duration, separated by 2 ms and surrounding the 180° pulse, were applied orthogonal to the applied oscillating magnetic field gradient. Their effect on the diffusion weighting was calculated to be insignificant. One sample tube was filled with water. Four different samples were made by dispersing polystyrene beads [Polysciences, Warrington, PA] in water. The first contained beads with a diameter of 2.8 ± 0.1 μm , the second with 9.1 ± 0.7 μm , the third with 25 ± 3 μm , and the fourth with 46 ± 7 μm . Each sample contained beads of one nominal diameter only. All of the bead-water samples were spun in a centrifuge to pack the beads closely. The excess water was then removed from the top. The closely packed beads in water took up approximately half the volume of the small plastic tubes. To minimize susceptibility effects around the meniscus, the tube was filled with mineral oil. Since the oil is less dense than the water, the two liquids did not mix around the beads. A chemical shift difference of approximately 300 Hz was used to distinguish the water signal from the oil signal. A control sample was made with just water and mineral oil to test the effects of the oil.

To measure ϵ , the bead and water samples were placed

TABLE 1
Structural Parameters of the Monte Carlo Model

	Value from fit	Expected value
S/V	$1.3 \pm 0.3 \mu\text{m}^{-1}$	$1.2 \mu\text{m}^{-1}$
ℓ	$3.0 \pm 0.8 \mu\text{m}$	$2.7 \mu\text{m}$

together in a birdcage coil in the 2-T Bruker spectrometer. A series of 10 coronal images (matrix size 64×64 , 8-cm FOV, 5-mm slice thickness) was acquired using a spin-echo sequence ($T_R = 3$ s, echo images at $T_E = 20, 40, 60 \dots 200$ ms). By estimating and comparing the signal from a region of interest in water at $T_E = 0$ ms to the signal from an identical volume in the other samples, ϵ was measured.

RESULTS AND DISCUSSION

Values of $D_{\text{app}}(\Delta_{\text{eff}})$ were calculated for the 2.7- μm fibers using Eq. [14] and are shown in Fig. 2. The data were fitted to Eq. [4] using $D_{\text{free}} = 1.3 \mu\text{m}^2/\text{ms}$ and $1/\alpha = 0.15$ for c and θ . From c , the surface-to-volume ratio, S/V , was calculated according to Eq. [5]. The width of the fibers, ℓ , was calculated from S/V according to Eq. [9]. The results of the fit are shown in Table 1 and agree well with the expected values. When deriving Eq. [4], Latour *et al.* (5) neglected the linear term in Δ_{eff} which depends on the curvature of the system. In the case of the square fibers used in the simulation, the linear term in Δ_{eff} needs to be included at long times because of the sharp square corners. This could account for the disagreement at long times.

The diffusion coefficient, D , for pure water and for the water in the water/oil sample was the same at all gradient oscillation periods, with a mean value of $2.09 \pm 0.02 \mu\text{m}^2/\text{ms}$. Figure 3

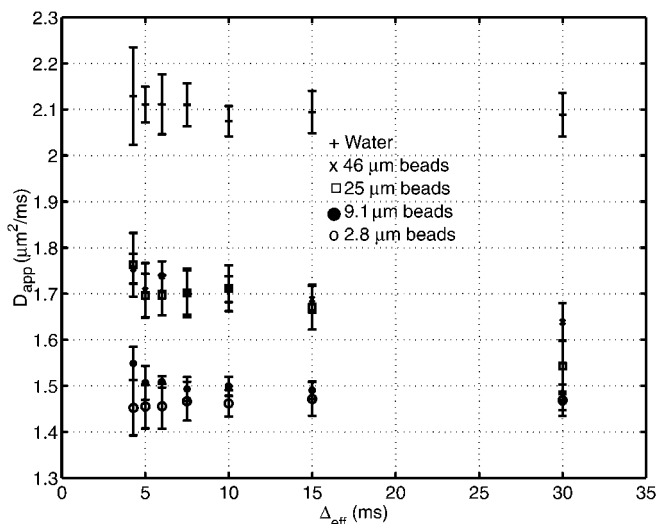


FIG. 3. D_{app} in restricted and unrestricted systems.

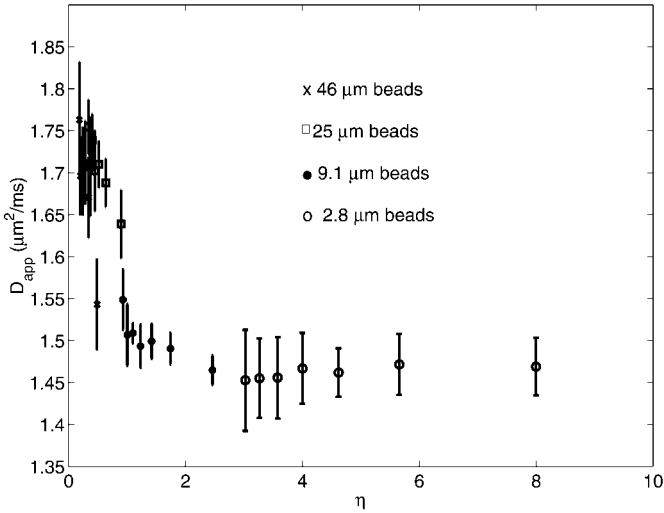


FIG. 4. D_{app} of water in restricted systems.

shows the D_{app} as a function of effective diffusion time, Δ_{eff} , for the 2.8-, 9.1-, 25-, and 46- μm -diameter bead samples, as well as for the water from the water/oil sample. The D_{app} for water in the 2.8- μm bead sample was relatively independent of frequency with mean value $1.46 \pm 0.01 \mu\text{m}^2/\text{ms}$, indicating no change in the degree of restriction. However, the D_{app} of water in the 9.1-, 25-, and 46- μm bead samples decreased with effective diffusion time by 5 ± 1 , 7 ± 1 , and $12 \pm 3\%$, respectively, over the time range measured as the diffusion of water became more restricted on the time scale $(3/8)T$.

Figure 4 shows the D_{app} of water measured in the various bead samples as a function of η . When $\eta < 1$, D_{app} varies steeply, whereas when $\eta > 1$, it remains constant. When $\eta \ll 1$, there is a small degree of restriction of water diffusion (e.g., the 46- μm bead sample): when $\eta \gg 1$, water diffusion is highly restricted (e.g., the 2.8- μm bead sample): when $\eta \approx 1$, there is an intermediate degree of restriction of water diffusion (e.g., the 9.1- and 25- μm bead samples).

Using spin-echo images of the bead samples and a water sample at different echo times, T_E , and by fitting the signals to a simple exponential decay, the data were extrapolated back to $T_E = 0$ to find M_0 . The volume fraction of water in the 9.1- μm bead sample was calculated to be $\epsilon = 0.38 \pm 0.02$. This is consistent with the range of volume fractions, 0.359 to 0.391, for a close or poured random packing of identical spheres (18).

Since the $D_{app}(\Delta_{eff})$ of water in none of the bead samples showed a large change in degree of restriction in the range of Δ_{eff} measured here, and since the D_{app} was sampled at only seven values of Δ_{eff} , a fit of the data from any one sample to Eq. [4] could not give accurate estimates of all parameters. The $D_{app}(\Delta_{eff})$ for all bead sizes were scaled in time according to Eq. [8] to give the values expected for the effective diffusion time of the 9.1- μm beads, $D_{app}(\Delta_{9.1 \mu\text{m}})$. Figure 5 shows these data. The free diffusion coefficient in these samples is expected to be that of water, $D_{free} = 2.09 \pm 0.02 \mu\text{m}^2/\text{ms}$. The tortuosity, α ,

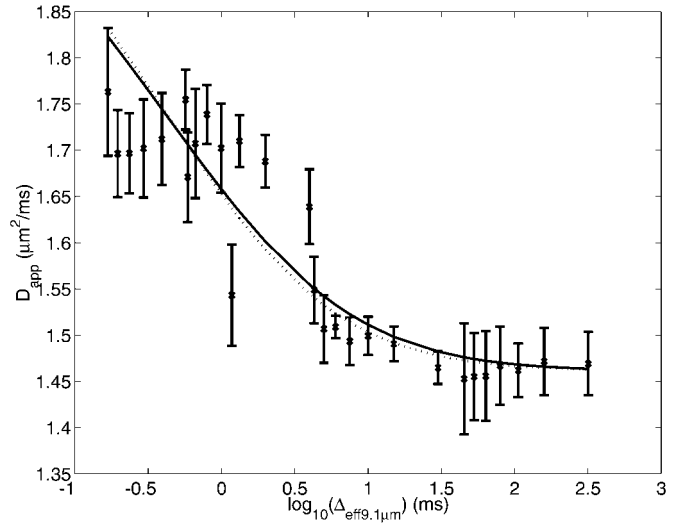


FIG. 5. D_{app} for bead data with Δ_{eff} scaled to the 9.1- μm bead Δ_{eff} . The data are represented by the x's and the fit is represented by the solid line. The dashed line represents the D_{app} values based on the expected value of $\sqrt{D_{free}\theta}/d$ and the bead diameter.

can be calculated using this value and the long time diffusion coefficient value according to Eq. [6]. The diffusion coefficient of water in the 2.8- μm bead sample was measured at all times to be in the long time regime, so $D_{app}(\Delta_{\infty})$ was taken as the mean of the 2.8- μm diffusion coefficient values, $1.46 \pm 0.01 \mu\text{m}^2/\text{ms}$. From these values $1/\alpha$ was calculated to be 0.699 ± 0.008 . The data were then fitted with a nonlinear least squares fitting function to Eq. [4] to find c and θ . The resulting fit is shown in Fig. 5 and gave $c = 0.46 \pm 0.07 \text{ ms}^{-1/2}$ and $\theta = 1.5 \pm 0.4 \text{ ms}$. Using this value of c and Eq. [5], the pore surface-to-volume ratio, S/V_p , was calculated. Using S/V_p and Eq. [2], the bead diameter, d , was found and from Eq. [3] the mean pore diameter, d_p , was determined. Table 2 summarizes the results for S/V_p , d , d_p , and $\sqrt{D_{free}\theta}/d$. The estimates from the experimental data all agree well with their expected values.

CONCLUSION

Latour *et al.* (5) measured changes in the degree of restriction of water diffusion in samples of packed beads as small as

TABLE 2
Structural Parameters of the 9.1- μm Bead Samples

	Value from fit	Expected value
S/V_p	$1.3 \pm 0.1 \mu\text{m}^{-1}$	$1.11 \pm 0.09 \mu\text{m}^{-1}$
d	$7.6 \pm 0.8 \mu\text{m}$	$9.1 \pm 0.7 \mu\text{m}$
d_p	$6.4 \pm 0.7 \mu\text{m}$	$7.6 \pm 0.8 \mu\text{m}$
$\sqrt{D_{free}\theta}/d$	0.19 ± 0.04	0.16 ± 0.02^a

^a This value is the mean and standard deviation of the values from Latour *et al.* (5) for bead samples of 48, 96, and 194 μm with volume fractions of water, $\epsilon = 0.38$.

48 μm . With the OGSE sequence, water diffusion in a packed bed of beads as small as 9 μm showed a change in degree of restriction in the effective diffusion time range measured here. The gradient amplitudes used here were approximately 10 times smaller than the gradient amplitudes used by Coy and Callaghan (12) to measure structural properties in similar-sized beads. It is likely that with moderate gradient strengths and higher frequencies, changes in the degree of restriction in smaller compartments could be detected.

The D_{app} measured as a function of time using the OGSE sequence in an unrestricted system is constant, but in restricted systems the D_{app} measured with the OGSE method changes, and the manner in which it varies with time can be used to infer cell sizes, pore surface-to-volume ratio, tortuosity, and the free diffusion coefficient. In the range we explored, the D_{app} of water in the bead samples and the fiber systems were still lower than in free water, showing that shorter periods are needed to remove all evidence of restriction. OGSE can be used to probe structural properties such as compartment sizes. It might therefore be of value in studying biological tissues, such as brain, to test whether water shifts occur in conditions similar to those after a stroke where the D_{app} drops. Thus, OGSE may provide a practical way to assess effects of restriction in tissue in the short diffusion time regime using experimental values of gradient amplitudes that can be readily implemented.

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