Journal of Magnetic Resonance 207 (2010) 274–282

Contents lists available at ScienceDirect

Journal of Magnetic Resonance

journal homepage: www.elsevier.com/locate/jmr

Numerical simulations of short-mixing-time double-wave-vector diffusion-weighting experiments with multiple concatenations on whole-body MR systems

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ARTICLE INFO

Article history:
Received 12 May 2010
Revised 14 September 2010
Available online 19 September 2010

Keywords:
Double-wave-vector diffusion weighting
Multiple-wave-vector diffusion weighting
Multiple concatenations
Restricted diffusion
Cell size
Pore size

ABSTRACT

Double- or two-wave-vector diffusion-weighting experiments with short mixing times in which two diffusion-weighting periods are applied in direct succession, are a promising tool to estimate cell sizes in the living tissue. However, the underlying effect, a signal difference between parallel and antiparallel wave vector orientations, is considerably reduced for the long gradient pulses required on whole-body MR systems. Recently, it has been shown that multiple concatenations of the two wave vectors in a single acquisition can double the modulation amplitude if short gradient pulses are used. In this study, numerical simulations of such experiments were performed with parameters achievable with whole-body MR systems. It is shown that the theoretical model yields a good approximation of the signal behavior if an additional term describing free diffusion is included. More importantly, it is demonstrated that the shorter gradient pulses sufficient to achieve the desired diffusion weighting for multiple concatenations, increase the signal modulation considerably, e.g. by a factor of about five for five concatenations. Even at identical echo times, achieved by a shortened diffusion time, a moderate number of concatenations significantly improves the signal modulation. Thus, experiments on whole-body MR systems may benefit from multiple concatenations.

1. Introduction

In double-wave-vector diffusion weighting (DWV) [1–4] two diffusion-weighting periods are applied successively in a single experiment. This combination allows the investigation of the correlation of the spins' diffusion, e.g. in time or in different spatial directions. It can offer access to microscopic properties of the sample [1–4] if the additional degrees of freedom provided, the relative angle and the mixing time between the two diffusion weightings, are exploited. For long mixing times, diffusion anisotropy present on a microscopic level can be detected as a signal difference between parallel and orthogonal wave vector orientations even if the sample macroscopically appears isotropic [3–9]. At short mixing times, a signal difference is expected between a parallel and an antiparallel wave vector orientation in the presence of restricted diffusion [3], i.e. the signal amplitude differs between acquisitions with the two diffusion weightings in the same and in opposite directions. This difference has been shown to be proportional to a measure of the cell or pore size, the mean-squared radius of gyration, if the diffusion is fully restricted and short gradient pulses are assumed [3].

The signal modulation present at short mixing times has been observed experimentally in a variety of samples, e.g. water between beads [10], plant tissue [10], *ex vivo* spinal cord [10,11], and water in microcappilaries [12–14], and recently has also been reported for the cortico-spinal tract in the living human brain [15,16]. However, the signal differences present in experiments on clinical whole-body MR systems are quite small, typically only a few percent [10]. Analytical calculations [17] and numerical simulations [18] have shown that the signal difference decreases considerably for the gradient pulse duration required to achieve a sufficient diffusion weighting on whole-body MR systems. For instance, for gradient pulses of 20 ms, it is reduced by about a factor of 16 for ellipsoidal cells with an average diameter of 5 μm [18]. This decrease hampers the reliable and accurate determination of the signal difference on clinical MR systems.

Recently, an extension of the DWV experiment was presented that involves multiple concatenations of the two wave vectors [19,20], i.e. more than two diffusion weightings are applied successively and alternate between the two wave vectors. It has been shown theoretically and in numerical simulations that this

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doi:10.1016/j.jmr.2010.09.009

approach increases the modulation amplitude at short mixing times by up to a factor of two, which can help to improve the detectability of the underlying effect [19]. However, these results were obtained within the short-pulse-approximation and for long diffusion times, i.e. effectively fully restricted diffusion.

In this study, numerical simulations of DWV experiments with multiple concatenations at short mixing times were performed for gradient pulse durations and timing parameters compatible with standard whole-body MR experiments. It is shown that the derived tensor model [19,21] still yields a good approximation of the simulated data if an additional term is included. This term describes free, anisotropic diffusion and can be considered to represent spins within the fully restricted compartment that, for the finite timing parameters used, do not contribute to the signal modulation, i.e. show the signal behavior of freely diffusing spins. More importantly, it is demonstrated that the gain of the modulation amplitude obtained with multiple concatenations is considerably higher than expected if the higher diffusion-weighting efficiency of multiple concatenations is used to shorten the pulse durations. Thus, multiple concatenations may help to improve the detectability of the DWV effect at short mixing times, in particular on whole-body MR systems.

2. Theory

The tensor model presented for the generalized experiment with multiple concatenations (Fig. 1) [19] is summarized in the following paragraphs. It is based on the assumptions that the mixing time and the gradient pulse durations are short ($\tau_m, \delta \to 0$) and the diffusion time Δ is long compared to $\tau_D = \frac{a^2}{2D}$ (with the pore diameter a and the diffusion coefficient D), i.e. the time a spin typically needs to cross the pore.

Then, the signal expression for arbitrary wave vectors, pore sizes, and pore size orientation distributions and n concatenations is given by [19,21]

$$M_n(\mathbf{Q}) \propto 1 - \frac{1}{2}\mathbf{Q}^T \underline{\underline{\mathbf{T}}}_n \mathbf{Q} \tag{1}$$

with $\mathbf{Q} = (\mathbf{q}_1{}^T, \mathbf{q}_2{}^T)^T$ being composed of the two wave vectors $\mathbf{q}_i = \gamma\delta\mathbf{G}_i$ (γ: gyromagnetic ratio, $\mathbf{G}_i$: gradient amplitude). $\underline{\underline{\mathbf{T}}}_n$ is a 6×6 tensor given by [19]

$$\underline{\underline{\mathbf{T}}}_n = \begin{pmatrix} 2n\underline{\underline{\mathbf{R}}} & (2n-1)\underline{\underline{\mathbf{R}}} \\ (2n-1)\underline{\underline{\mathbf{R}}} & 2n\underline{\underline{\mathbf{R}}} \end{pmatrix} \tag{2}$$

or

$$\underline{\underline{\mathbf{T}}}_n = \begin{pmatrix} (2n'+1)\underline{\underline{\mathbf{R}}} & (2n'-1)\underline{\underline{\mathbf{R}}} \\ (2n'-1)\underline{\underline{\mathbf{R}}} & (2n'-1)\underline{\underline{\mathbf{R}}} \end{pmatrix} \tag{3}$$

for an even (Fig. 1a) and an odd number of diffusion weightings (Fig. 1b, $n' = n + \frac{1}{2}$), respectively, and is based on the elements of the 3×3 tensor $\underline{\underline{\mathbf{R}}}$. They are defined by

$$R_{ij} = \int_{\text{pore}} \rho(\mathbf{r}) r_i r_j \, d\mathbf{r} \tag{4}$$

where $\rho(\mathbf{r})$ is the spin density distribution within the pore. If only the signal difference between the parallel and antiparallel wave vector orientation is considered,

$$\Delta M(\mathbf{q}) = \mathbf{q}^T 2(2n-1)\, \underline{\underline{\mathbf{R}}}\mathbf{q} \tag{5}$$

is obtained where $q = q_1 = q_2$ was assumed. For an isotropic orientation distribution of the pores, Eq. (1) yields

$$M_{\text{iso}}(\mathbf{q}_1, \mathbf{q}_2) \propto 1 - \frac{1}{3}\rho\, q^2 \langle R^2 \rangle \, (2n + (2n-1)\cos\theta) \tag{6}$$

for $q = q_1 = q_2$ where θ is the angle between the two wave vectors and $\langle R^2 \rangle$ the mean-squared radius of gyration defined by [3]

$$\langle R^2 \rangle = \int_{\text{pore}} \rho(\mathbf{r}) r^2 d\mathbf{r} \tag{7}$$

Thus, $\langle R^2 \rangle = \sum_i R_{ii}$, i.e. it is the trace of the tensor $\underline{\underline{\mathbf{R}}}$. In case of an odd number of diffusion weightings (Fig. 1b), n in Eqs. (5) and (6) must be replaced by $n' = n + \frac{1}{2}$.

For an isotropic orientation distribution, the modulation amplitude increases with the number of concatenations, as can be seen in Eq. (6). For instance, for constant $n \cdot q^2$, i.e. a fixed diffusion weighting, the relative modulation amplitude is given by $1 - \frac{1}{2n}$. This means that it increases with the number of concatenations, but at most is doubled in the limit of large n.

In the presence of freely diffusing spins Eqs. (1) and (6) must be adapted. Eq. (5) remains valid because there is no signal difference between parallel and antiparallel wave vector orientations for free diffusion. In Eq. (6), an additional second order term $-D4nq^2\Delta$ (for $q_1 = q_2 = q$) with the free diffusion coefficient D must be added, which is obtained from the Taylor expansion of the exponential signal decay present for free diffusion. Thus, the free diffusion term, re-written as a function of $\mathbf{Q}$, is given by

$$M_{\text{free}}(\mathbf{Q}) \propto 1 - 2n\Delta D \mathbf{Q}^T \begin{pmatrix} \underline{\underline{\mathbf{1}}} & 0 \\ 0 & \underline{\underline{\mathbf{1}}} \end{pmatrix} \mathbf{Q}. \tag{8}$$

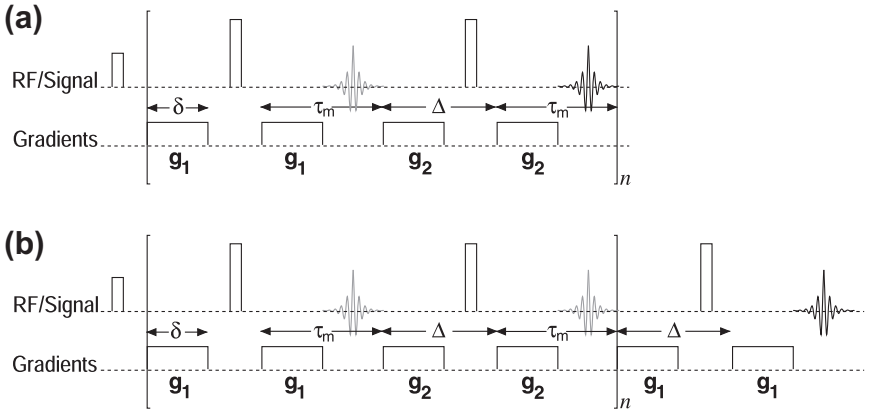

Fig. 1. Basic pulse sequences for the double-wave-vector (DWV) diffusion-weighting experiments with multiple concatenations of the two wave vectors investigated in the current study. (a) n concatenations with an even number of diffusion weightings, (b) $n' = n + \frac{1}{2}$ concatenations with an odd number of diffusion weightings, i.e. a final diffusion weighting using the first wave vector. Note that the diffusion weightings shown represent a parallel orientation of the two wave vectors according to the notation introduced in [3], i.e. the rephasing gradient of the first diffusion weighting has the same polarity as the dephasing pulse of the second one.