Effect of diffusion-sensitizing gradient timings on the exponential, biexponential and diffusional kurtosis model parameters: in-vivo measurements in the rat thalamus

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Abstract Object To investigate whether spacing (\(\Delta\)) and duration (\(\delta\)) of the diffusion-sensitizing gradient pulses differentially affect exponential (\(D'\)), biexponential (\(D_{\text{slow}}, D_{\text{fast}}\) and \(f_{\text{slow}}\)) and diffusional kurtosis (\(D\) and \(K\)) model parameters.

Methods Measurements were performed in the rat thalamus for \(b = 200–3,200\) s mm\(^{-2}\), sweeping \(\Delta\) between 20 and 100 ms at \(\delta = 15\) ms, and \(\delta\) between 15 and 50 ms at \(\Delta = 60\) ms. Linear regressions were performed for each model parameter vs. \(\Delta\) or \(\delta\).

Results Increasing \(\Delta\) from 20 to 100 ms increases \(D'\) (from 0.64 to 0.70 \times 10^{-3}\) mm\(^2\)s\(^{-1}\)) and \(D_{\text{slow}}\) (from 0.26 to 0.33 \times 10^{-3}\) mm\(^2\)s\(^{-1}\)), reduces \(K\) (from 0.57 to 0.53), and has no effects on \(D_{\text{fast}}, f_{\text{slow}}\) or \(D\). Increasing \(\delta\) from 15 to 50 ms increases \(D\) (from 0.80 to 0.88 \times 10^{-3}\) mm\(^2\)s\(^{-1}\)), and has no effects on the other parameters.

Conclusion The parameters of the biexponential and diffusional kurtosis models are more sensitive than the exponential model to \(\Delta\) and \(\delta\); however, observed effects are too small to account for the discrepancies found in literature.

Keywords Diffusion · Time · Exponential model · Biexponential model · Diffusional kurtosis model

Introduction

Most diffusion imaging studies adopt an exponential model to describe signal decay with increasing \(b\)-value, thereby embedding an assumption of Gaussian diffusion, which is of limited validity because in biological tissues barriers and compartments are present at multiple scales. Addressing this limitation, several models of non-Gaussian diffusion of varying complexity have been proposed, and two have emerged as potential candidates for clinical application: the biexponential and diffusional kurtosis imaging (DKI) models [1–3].

In the biexponential model, measurements are fit with

\[
s = f_{\text{slow}} \exp(-bD_{\text{slow}}) + (1 - f_{\text{slow}}) \exp(-bD_{\text{fast}})
\]

where \(s\) indicates normalized signal intensity, \(b\) diffusion weighting in s mm\(^{-2}\), \(D_{\text{slow}}\) and \(D_{\text{fast}}\) diffusivity of the slow- and fast-decaying components in mm\(^2\)s\(^{-1}\), and \(f_{\text{slow}}\) the ratio between the two components. While it is tempting to assume a correspondence with intra- and extracellular diffusion, this straightforward interpretation is inaccurate because biexponential decay can be observed in the absence of compartmentalization and the volume ratios obtained in the brain, \(f_{\text{slow}} \approx 0.2\), are incompatible with cytoarchitectonical knowledge [3,4]. Several studies have demonstrated that despite being physically meaningless, the parameters of this model provide improved sensitivity to microstructural differences and pathological change when compared to a single diffusion coefficient [3,5–7].

In the DKI model, measurements are fit with

\[
\ln(s) = -bD + \frac{1}{6}b^2D^2K
\]
where $D$ indicates the diffusion coefficient and $K$ excess kurtosis, a parameter quantifying the peakedness of the molecular displacement distribution with respect to a Gaussian one, for which $K = 0$. This model does not attempt to separate multiple components; rather, it represents deviation from free diffusion through a single parameter [2]. Recent studies suggest that excess kurtosis is more sensitive than diffusivity, especially to subtle ageing-related microstructural changes [3,8,9].

Diffusion measurements based on exponential fitting show notably good consistency across individuals and sites; by contrast, a major obstacle encountered with biexponential modelling is the observed variability. For instance, four similar studies report values differing by up to 51% for $D_{fast}$ (1.02 – 1.71 × 10−3 mm2 s−1), 76% for $D_{slow}$ (0.17 – 0.38 × 10−3 mm2 s−1) and 50% for $f_{slow}$ (0.25–0.42) in grey matter; these discrepancies, much larger than the estimated uncertainties (around 0.1 × 10−3 mm2 s−1) for $D_{fast}$, 0.04 × 10−3 mm2 s−1 for $D_{slow}$ and 0.05 for $f_{slow}$), indicate differing systematic biases across sites. They are unexplained by differences in range of $b$-values, voxel size or brain region measured [3,5–7]. As literature on the more recent DKI model is still scant, it remains to be determined whether the variability in its parameters differs from that observed for the biexponential model [3,8,9].

Since diffusion in biological tissues is not Gaussian, measurements can depend on the timings of the diffusion-sensitizing gradient pulses, namely their spacing ($\Delta$) and duration ($\delta$). The former determines the characteristic diffusion length, and hence the scale at which water diffusion probes tissue microstructure. The latter also has an effect because, in presence of non-Gaussian diffusion, different levels of violation of the assumption of infinitesimally short $\delta$ cause deviations of the extracted diffusional parameters from those which would be obtained in the limit $\delta \to 0$ [10–14]. Uncontrolled differences in gradient timings could, therefore, be contributing to the observed discrepancies.

At present, no studies are available on the effect of gradient-pulse timings on in-vivo measurements using the biexponential and DKI models. Given their enhanced sensitivity, it could be greater for these models than exponential fitting [3]. Indeed, a study on cell cultures found that increasing $\Delta$ between 8 and 57 ms reduced $D_{fast}$ by about 20% and $D_{slow}$ by 75% [15]. Phantom measurements suggest a smaller effect for the DKI model, with kurtosis increasing by about 10% in the range $\Delta = 20–100$ ms [16].

Addressing this limitation of current literature, we performed exploratory in-vivo measurements sweeping $\Delta$ at constant $\delta$ and vice-versa, and fitting the diffusion-weighted signal from the rat thalamus using the exponential, biexponential and DKI models.

### Materials and methods

#### Image acquisition

Female Sprague–Dawley rats (150–250 g, $n = 4$) were anaesthetized with 2% Isoflurane in 40% O$_2$ and 60% N$_2$O and ventilated physiologically. Cardiac and respiratory rate were monitored, and a heated water circuit controlled through a rectal thermometer kept the body temperature at 37°C. The head was immobilized hooking the upper front teeth and through ear pins. All procedures were performed in compliance with the EEC 86/609 directive and applicable national and institutional guidelines (law 116/92). No animal was sacrificed.

The experiments were performed with a BioSpec spectrometer (Bruker BioSpin MRI GmbH, Ettlingen, DE) interfaced to a 30 cm horizontal-bore, 7-Tesla magnet equipped with 20 cm ultra-shielded gradients capable of reaching 200 mT m$^{-1}$. The $^1$H volume transmit coil and the rat head surface receiver coil were used.

Diffusion-weighted images were acquired for 1 slice using the Stejskal-Tanner spin-echo sequence and single-shot echo-planar readout, having TR = 3,000 ms, TE = 130 ms, bandwidth 250 kHz, flip angle 90°C, 96 × 96 matrix, 0.5 × 0.5 mm in-plane resolution, 2 mm thickness, 8 averages. Frequency-selective pulses suppressed fat signal. As shown in Fig. 1a, the slice was centred on the thalamus and oriented perpendicular to the encephalomyelonic axis. First- and second-order shimming and eddy-current correction were performed automatically, followed by manual refinement on $X, Y, Z$ and $Z^2$. For all combinations of $\Delta$ and $\delta$, 16 diffusion measurements were performed along the frequency- and phase-encoding directions at $b$-values always of 200, 400 ... 3, 200 s mm$^{-2}$. The signal-to-noise ratio ranged between about 85 ($b = 200$ s mm$^{-2}$) and 20 ($b = 3, 200$ s mm$^{-2}$).

Constant-$\Delta$ and constant-$\delta$ experiments were performed on two rats each. The constant-$\Delta$ measurements were performed for 9 points at $\delta = 10, 15 \ldots 50$ ms with $\Delta = 60$ ms, corresponding to diffusion times $\tau = 57, 55 \ldots 43$ ms and resulting in gradient intensities of 23.0–92.1 mT m$^{-1}$ for $\delta = 10$ ms and 5.2–20.6 mT m$^{-1}$ for $\delta = 50$ ms. The constant-$\delta$ experiments were performed for 9 points at $\Delta = 20, 30 \ldots 100$ ms with $\delta = 15$ ms, corresponding to diffusion times $\tau = 15, 25 \ldots 95$ ms and resulting in gradient intensities of 30.1–120.5 mT m$^{-1}$ for $\Delta = 20$ ms and 11.7–46.8 mT m$^{-1}$ for $\Delta = 100$ ms. Within each session, acquisition order was randomized to prevent confounding effects of potential drifts of scanning conditions. Eddy-current distortion, visually assessed by two authors through overlay and subtraction of the $b = 3,200$ s mm$^{-2}$ diffusion-weighted images comparing $\Delta = 20$ vs. 100 ms and $\delta = 10$ vs. 50 ms, was below 1 voxel.