Supplementary

Appendix 1 Forward model with cylindrical, restricted diffusivity muscle model

Following the signal equation of normalized diffusivity signal S_i from intracellular muscle $S_{M,i}$ and extracellular fluid, $S_{F,i}$ from eq. [1], $S_{M,i}$ is defined radially as an infinite cylinder with impermeable transverse boundaries and axially with Gaussian diffusivity $D_{//}$, where r is the cylinder radius, gradient vector $\vec{g}$, and the pulse width δ and mixing time Δ. By accounting for its radial gradient magnitude $g_{\perp}^2$ and axial gradient magnitude $g_{//}^2$, the natural logarithm of $S_{M,i}$ can be expressed as a summation of radial and axial terms. The radial term is derived from Neuman(30), and includes terms for the intracellular water diffusivity D_0 and α_m^2, which is the m-th root of the derivative of the Bessel function J such that $J'_1(\alpha_m^2 r)=0$:

$$\ln\left[S_{M,i}\left(r,\vec{g},\delta,\Delta\right)\right]=-2\gamma^2 g_{\perp}^2\sum_{m=1}^{\infty}\frac{2\delta/\alpha_m^2 D_0-\left(2+e^{-\alpha_m^2 D_0(\Delta-\delta)}-2e^{-\alpha_m^2 D_0\delta}-2e^{-\alpha_m^2 D_0\Delta}+e^{-\alpha_m^2 D_0(\Delta+\delta)}\right)/\left(\alpha_m^2 D_0\right)^2}{\alpha_m^2\left(\alpha_m^2 r^2-2\right)}-\gamma^2 g_{//}^2\delta^2\left(\Delta-\frac{\delta}{3}\right)D_{//} \quad [1]$$

While $S_{F,i}$ is defined as:

$$\ln\left[S_{F,i}\left(\vec{g},\delta,\Delta\right)\right]=-\gamma^2\vec{g}^2\delta^2\left(\Delta-\frac{\delta}{3}\right)D_F. \quad [2]$$

Appendix 2 Multi-compartment model

For $K_{Res}\times N_{Res}$ anisotropic, K_{Hin} isotropic, K_{Fre} isotropic and K_{Noise} isotropic tissue compartments, each with $f_{Res,j,n}$, $f_{Hin,k}$, $f_{Fre,k}$, $f_{Fat,k}$, compartment fractions, the sum of each tissue is defined by:

$$f_{Res}=\sum_{j=1}^{K_{Res}}\sum_{n=1}^{N_{Res}}f_{Res,j,n} \quad [3]$$

$$f_{Hin}=\sum_{k=1}^{K_{Hin}}f_{Hin,k} \quad [4]$$

$$f_{Fre}=\sum_{k=1}^{K_{Fre}}f_{Fre,k} \quad [5]$$

$$f_{Fat}=\sum_{k=1}^{K_{Noise}}f_{Fat,k} \quad [6]$$

Each of the anisotropic compartments has pre-defined axial/parallel and radial/orthogonal diffusivities ($\lambda_{//}$, $\lambda_{\perp}$), whereas each of the isotropic compartments has solely a mean diffusivity (λ) defined. For a maximum b-value, b and for each normalized gradient vector $\vec{q}$, radial vector $\vec{u}$ and the model's signal estimate ($\hat{s}$) is defined as

$$\begin{aligned}\hat{s}\left(b,\vec{q}\right)=&\sum_{j=1}^{K_{Res}}\sum_{n=1}^{N_{Res}}f_{Res,j,n}\exp\left(-\left(\lambda_{\parallel,j}b\left(\vec{q}^T\vec{u}_n\right)^2\right)\left(\lambda_{\perp,j}b\left(1-\left(\vec{q}^T\vec{u}_n\right)^2\right)\right)\right)\\&+\sum_{k=1}^{K_{Hin}}f_{Hin,k}\exp\left(-\lambda_{Hin,k}b\right)+\sum_{k=1}^{K_{Fre}}f_{Fre,k}\exp\left(-\lambda_{Fre,k}b\right)+\sum_{k=1}^{K_{Fat}}f_{Fat,k}\exp\left(-\lambda_{Fat,k}b\right)\end{aligned} \quad [7]$$

To adapt the method for multi-b-valued muscle diffusion, where tissue anisotropy would be less than that in the brain and where fewer diffusion-encoding directions would typically be used, a model with far fewer compartments and fewer directionalities was proposed. In multi-b-valued acquisition, b-values smaller than the maximum b-value were created by q-vectors with a squared magnitude less than one. The composition of the compartments and optimization parameter values are listed in *Table 1*. A wide range of assumed fractional anisotropy (0.11-1.00) was used in the restricted compartments to account for the wide range of FA observed in the literature.

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Appendix 3 Precision and bias error

Propagation of variance was used to convert units from each metric $M \in \{f_{Res}, f_{Hin}, f_{Fre}, f_{Fat}$, MD, AD, RD, FA$\}$ to that of r, using the derivative, $\frac{\partial M(r)}{\partial r}$. Precision error $\varepsilon_{M,n}$ for a given metric and simulation n was defined as the root-mean-square of the metric variance $\sigma^2_{M,n}(r)$ summed across all r values:

$$\varepsilon_{M,n} = \frac{\sqrt{\sum_r^{N_r} \sigma^2_{M,n}(r)}}{\sum_r^{N_r} \left| \frac{\partial M(r)}{\partial r} \right|} \quad [8]$$

The bias error, $\beta_{M,N}$, followed the same approach, except that bias was defined as the error resulting from varying one parameter, N, which was either SNR, ρ, D_0 or $D_{//}$, keeping other parameters constant. To compute bias, the metric variance, $\sigma^2_{M,N}(r)$ was defined as that from one of the parameters SNR, ρ, D_0 or $D_{//}$:

$$\beta_{M,N} = \frac{\sqrt{\sum_r^{N_r} \sigma^2_{M,N}(r)}}{\sum_r^{N_r} \left| \frac{\partial M(r)}{\partial r} \right|} \quad [9]$$

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