Supporting Information

Supporting Figures

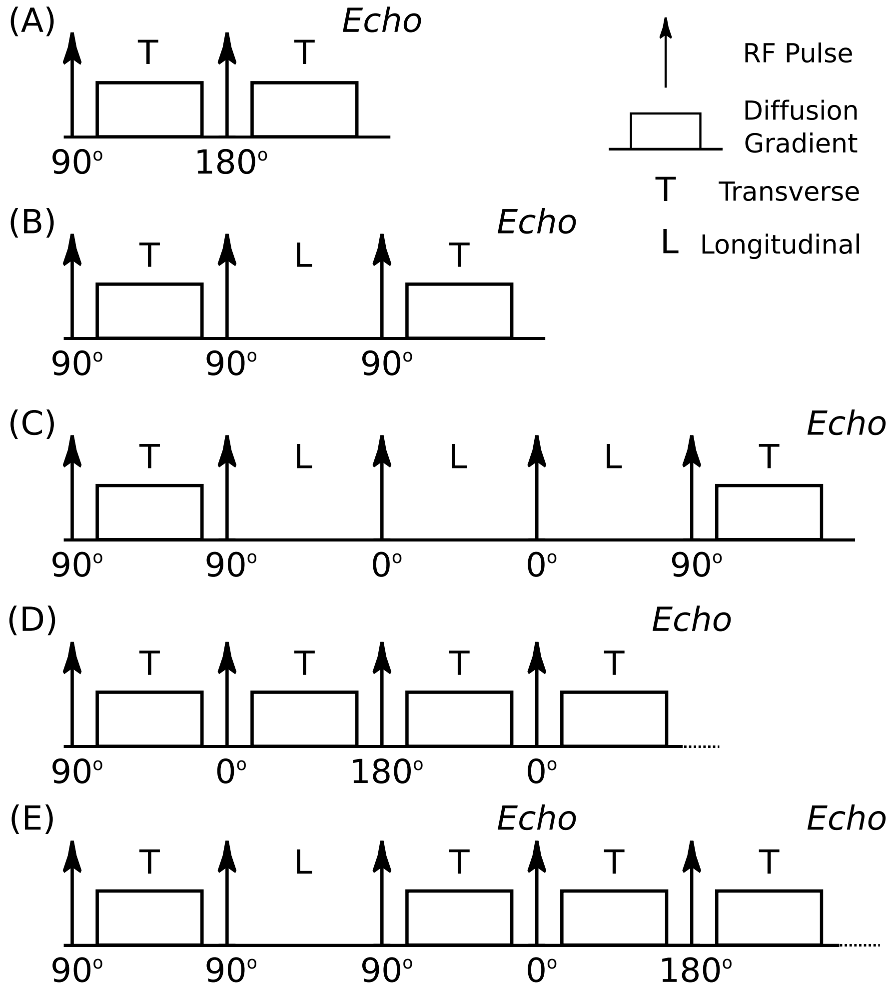

Figure S1: In DW-SSFP, repeated application of RF pulses decomposes the magnetization into a series of coherence pathways, which are sensitized to the diffusion gradient during transverse periods. Here we show 5 example coherence pathways. The spin-echo pathway (A), stimulated-echo pathway (B) and long stimulated-echo pathway (C) only survive for 2 TRs in the transverse plane, the condition for the two-transverse-period approximation (1). These pathways all experience the same q-value, but have different diffusion times, defined as $\Delta = 1 \cdot \mathrm{TR}$ (A), $2 \cdot \mathrm{TR}$ (B), and $4 \cdot \mathrm{TR}$ (C). For the full Buxton model (1), this condition is no longer required, and pathways can experience cumulative sensitization to the diffusion gradients over multiple TRs, such as the spin-echo pathway in (D), in addition to pathways that generate multiple echoes over their lifetime (E). This leads to pathways with different q-values, in addition to weighting of the signal by T_2

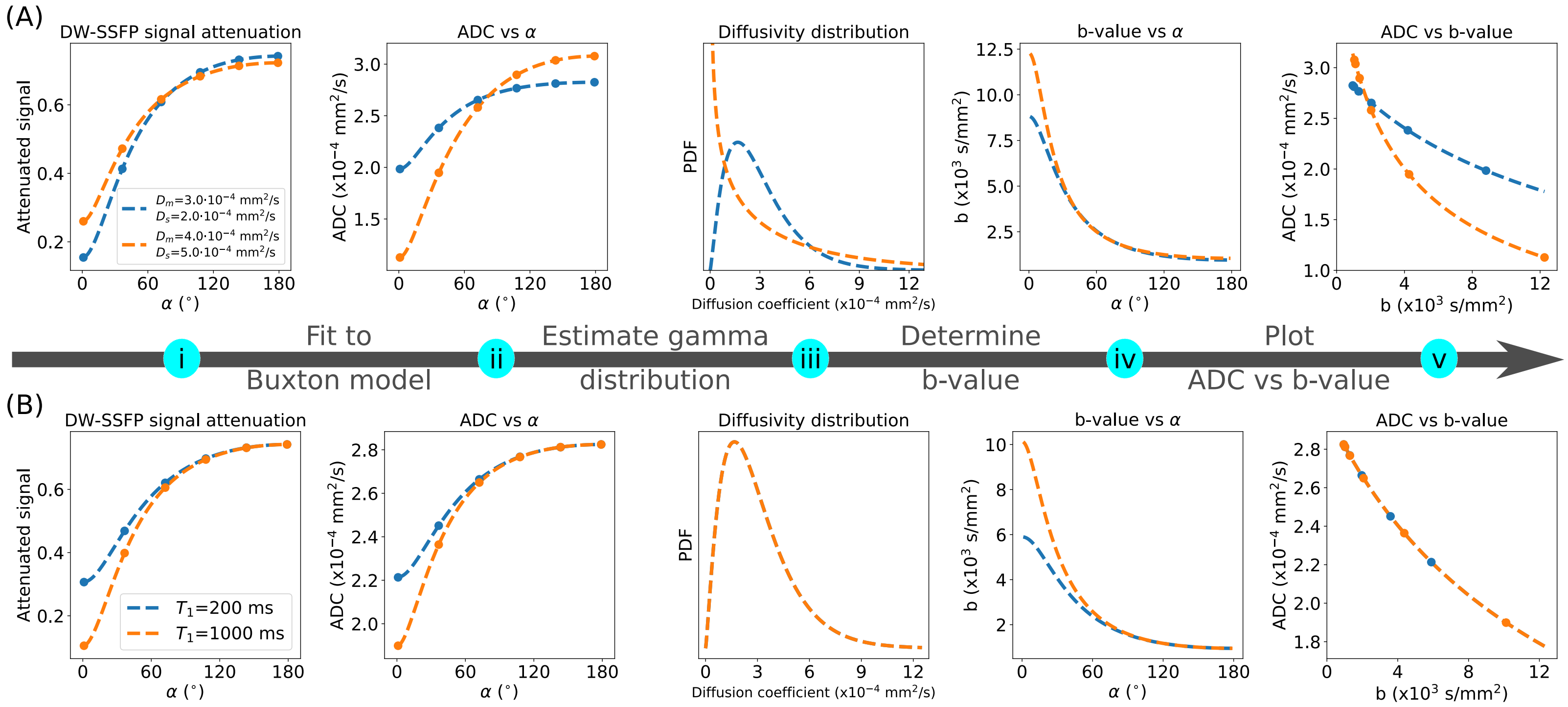

Figure S2: Processing pipeline for (A) 2 samples with different diffusion properties but identical relaxation times and (B) identical diffusion properties but different T_1 values. Experimental DW-SSFP data are acquired at multiple flip angles (i, dots) and converted into ADC estimates (ii, dots) (Equation 2, main text). To eliminate the effects of S_0, we fit to the DW-SSFP signal attenuation. The DW-SSFP signal model incorporating a gamma distribution of diffusivities (Equation 4, main text) is subsequently fit to the ADC estimates at multiple flip angles (by comparing to Equation 2, main text) to determine D_m and D_s (iii). From Equation 3 in the main text and our fitted values of D_m and D_s, we can simulate the estimated ADC with b-value for a DW-SE sequence by making comparisons with the DW-SE signal under the Stejskal-Tanner model ($S = S_0 \exp(-bD)$). From this, we can define an equivalent DW-SE b-value which gives rise to the same ADC estimate at each DW-SSFP flip angle (iv). Our ADC estimates with DW-SSFP can be subsequently plotted versus an effective b-value (v). In (A), this leads to distinct evolution of ADC with effective b-value for the 2 samples (v). However, in (B), the signal evolution is identical (v), despite having a different ADC evolution verses flip angle (ii), reflecting differences in the weighting of the different coherence pathways due to relaxation, leading to different effective b-values along the ADC curve (v, dots)

Supporting Tables

Turbo inversion recovery (TIR) - T_1

Resolution	0.65 x 0.65 x 1.30 mm^3
TR	1000 ms
TE	12 ms
TIs	60, 120, 240, 480, 940 ms
BW	170 Hz/pixel

Turbo spin echo (TSE) - T_2

Resolution	0.65 x 0.65 x 1.30 mm^3
TR	1000 ms
TEs	11, 23, 34, 46, 57, 69 ms
BW	163 Hz/pixel

Actual flip angle imaging (AFI) - B_1

Resolution	1.50 x 1.50 x 1.50 mm^3
TRs	7, 21 ms
TE	2.6 ms
BW	263 Hz/pixel

Table S1: Acquisition protocols for the T_1, T_2 and B_1 maps. Before processing, a Gibbs ringing correction was applied to the TIR and TSE data (2). T_1 and T_2 maps were derived assuming mono-exponential signal evolution. The B_1 map was obtained using the methodology described in (3)

Supporting Derivations

The two-transverse-period approximation with a gamma distribution of diffusivities

From Equation 1 in the main text:

$$S_{\mathrm{SSFP}}(\alpha, T_1, T_2, \mathrm{TR}, q, D) = \frac{-S_0(1-E_1)E_1E_2^2\sin\alpha}{2(1-E_1\cos\alpha)}\left[\frac{1-\cos\alpha}{E_1}A_1 + \sin^2\alpha\sum_{n=1}^{\infty}(E_1\cos\alpha)^{n-1}A_1^{n+1}\right], \quad \text{[S1]}$$

where S_0 is the equilibrium magnetization, $E_1 = e^{-\frac{\mathrm{TR}}{T_1}}$, $E_2 = e^{-\frac{\mathrm{TR}}{T_2}}$, α is the flip angle, n is the number of TRs between the two transverse-periods for a given stimulated-echo, $A_1 = e^{-q^2\cdot\mathrm{TR}\cdot D}$, D is the diffusion coefficient and $q = \gamma G\tau$, where γ is the gyromagnetic ratio, G is the diffusion gradient amplitude and τ is the diffusion gradient duration. Separating this expression into spin-echo (SE) and stimulated-echo (STE) pathways:

$$S_{\mathrm{SE}} = \frac{-S_0(1-E_1)E_2^2\sin\alpha(1-\cos\alpha)}{2(1-E_1\cos\alpha)}\cdot e^{-q^2\cdot\mathrm{TR}\cdot D}, \quad \text{[S2]}$$

and:

$$S_{\mathrm{STE}} = \frac{-S_0(1-E_1)E_1E_2^2\sin\alpha}{2(1-E_1\cos\alpha)}\cdot\sin^2\alpha\cdot\sum_{n=1}^{\infty}\left[(E_1\cos\alpha)^{n-1}\cdot e^{-q^2\cdot(n+1)\cdot\mathrm{TR}\cdot D}\right]. \quad \text{[S3]}$$

SE term

Integrating over the SE term with a gamma distribution of diffusivities:

$$S_{\mathrm{SE},\Gamma} = \frac{-S_0(1-E_1)E_2^2\sin\alpha(1-\cos\alpha)}{2(1-E_1\cos\alpha)}\cdot\int_0^{\infty} e^{-q^2\cdot\mathrm{TR}\cdot D}\rho(D; D_m, D_s)dD, \quad \text{[S4]}$$

where $\rho(D; D_m, Ds)$ is the gamma distribution with mean D_m and standard deviation D_s over D. From Equation 3 in the main text:

$$\int_0^{\infty} e^{-q^2\cdot\mathrm{TR}\cdot D}\rho(D; D_m, D_s)dD = \left[\frac{D_m}{D_m + q^2\cdot\mathrm{TR}\cdot D_s^2}\right]^{\frac{D_m^2}{D_s^2}}. \quad \text{[S5]}$$

Therefore:

$$S_{\mathrm{SE},\Gamma} = \frac{-S_0(1-E_1)E_2^2\sin\alpha(1-\cos\alpha)}{2(1-E_1\cos\alpha)}\cdot\left[\frac{D_m}{D_m + q^2\cdot\mathrm{TR}\cdot D_s^2}\right]^{\frac{D_m^2}{D_s^2}}. \quad \text{[S6]}$$

STE term

Integrating over the STE term with a gamma distribution:

$$S_{\mathrm{STE},\Gamma} = \frac{-S_0(1-E_1)E_1E_2^2\sin\alpha}{2(1-E_1\cos\alpha)} \cdot \sin^2\alpha \cdot \sum_{n=1}^{\infty}(E_1\cos\alpha)^{n-1} \cdot \int_0^{\infty} e^{-q^2\cdot(n+1)\cdot \mathrm{TR}\cdot D}\rho(D;D_m,D_s)dD. \quad \text{[S7]}$$

Evaluating the summation term, considering Equation 3 in the main text:

$$\begin{aligned}&\sum_{n=1}^{\infty}(E_1\cos\alpha)^{n-1} \cdot \int_0^{\infty} e^{-q^2\cdot(n+1)\cdot \mathrm{TR}\cdot D}\rho(D;D_m,D_s)dD \\ =&\sum_{n=1}^{\infty}(E_1\cos\alpha)^{n-1} \cdot \left[\frac{D_m}{D_m+q^2\cdot(n+1)\cdot \mathrm{TR}\cdot D_s^2}\right]^{\frac{D_m^2}{D_s^2}},\end{aligned} \quad \text{[S8]}$$

Pulling D_m from the numerator and $q^2 \cdot \mathrm{TR} \cdot D_s^2$ from the denominator :

$$= \left(\frac{D_m}{q^2\cdot \mathrm{TR}\cdot D_s^2}\right)^{\frac{D_m^2}{D_s^2}} \cdot \sum_{n=1}^{\infty} \frac{(E_1\cos\alpha)^{n-1}}{\left[\frac{D_m}{q^2\cdot \mathrm{TR}\cdot D_s^2}+(n+1)\right]^{\frac{D_m^2}{D_s^2}}}. \quad \text{[S9]}$$

Rearranging and defining $m = n - 1$:

$$= \left(\frac{D_m}{q^2\cdot \mathrm{TR}\cdot D_s^2}\right)^{\frac{D_m^2}{D_s^2}} \cdot \sum_{m=0}^{\infty} \frac{(E_1\cos\alpha)^{m}}{\left[(\frac{D_m}{q^2\cdot \mathrm{TR}\cdot D_s^2}+2)+m\right]^{\frac{D_m^2}{D_s^2}}}. \quad \text{[S10]}$$

The summation term is in an equivalent format to the the Lerch Transcendent (4), defined as:

$$\Phi(z,s,a) = \sum_{m=0}^{\infty}\frac{z^m}{(a+m)^s}, \quad \text{[S11]}$$

where $z = E_1\cos\alpha$, $s = \frac{D_m^2}{D_s^2}$ and $a = \frac{D_m}{q^2\cdot \mathrm{TR}\cdot D_s^2}+2$. Therefore:

$$S_{\mathrm{STE},\Gamma} = \frac{-S_0(1-E_1)E_1E_2^2\sin\alpha}{2(1-E_1\cos\alpha)} \cdot \sin^2\alpha \cdot \left(\frac{D_m}{q^2\cdot \mathrm{TR}\cdot D_s^2}\right)^{\frac{D_m^2}{D_s^2}} \cdot \Phi\left(E_1\cos\alpha, \frac{D_m^2}{D_s^2}, \frac{D_m}{q^2\cdot \mathrm{TR}\cdot D_s^2}+2\right). \quad \text{[S12]}$$

Total signal

Summing the SE and STE terms:

$$
\begin{aligned}
&S_{\text{SSFP},\Gamma}(\alpha, T_1, T_2, \text{TR}, q, D) = \\
&\quad \frac{-S_0(1-E_1)E_1E_2^2\sin\alpha}{2(1-E_1\cos\alpha)} \cdot \left[\frac{1-\cos\alpha}{E_1} \cdot \left(\frac{D_m}{D_m + q^2 \cdot \text{TR} \cdot D_s^2}\right)^{\frac{D_m^2}{D_s^2}} + \right. \\
&\quad \left. \sin^2\alpha \cdot \left(\frac{D_m}{q^2 \cdot \text{TR} \cdot D_s^2}\right)^{\frac{D_m^2}{D_s^2}} \cdot \Phi\left(E_1\cos\alpha, \frac{D_m^2}{D_s^2}, \frac{D_m}{q^2 \cdot \text{TR} \cdot D_s^2} + 2\right)\right].
\end{aligned} \tag{S13}
$$

ADC expression under the two-transverse-period approximation

Summing over Equation 1 in the main text, noting $\sum_{m=0}^{\infty} r^m = \frac{1}{1-r}$, or from (1):

$$
S_{\text{SSFP}}(\alpha, T_1, T_2, \text{TR}, q, \text{ADC}) = -\frac{S_0(1-E_1)(1+E_1A_{\text{ADC}})A_{\text{ADC}}(1-\cos\alpha)\sin\alpha}{2(1-E_1\cos\alpha)(1-A_{\text{ADC}}E_1\cos\alpha)} \cdot E_2^2. \tag{S14}
$$

Maintaining terms that depend on ADC:

$$
\begin{aligned}
\frac{(1+E_1A_{\text{ADC}})A_{\text{ADC}}}{(1-A_{\text{ADC}}E_1\cos\alpha)} &= \frac{S_{\text{SSFP}}(\alpha, T_1, T_2, \text{TR}, q, \text{ADC})}{S_{\text{SSFP}}(\alpha, T_1, T_2, \text{TR}, 0, \text{ADC})} \cdot \frac{1+E_1}{1-E_1\cos\alpha} \\
&= S'_{\text{SSFP}}.
\end{aligned} \tag{S15}
$$

$S_{\text{SSFP}}(\alpha, T_1, T_2, \text{TR}, q, \text{ADC})$ and $S_{\text{SSFP}}(\alpha, T_1, T_2, \text{TR}, 0, \text{ADC})$ can be substituted by diffusion-weighted and non diffusion-weighted data respectively. Multiplying Equation S15 by the denominator:

$$
(1+E_1A_{\text{ADC}})A_{\text{ADC}} - S'_{\text{SSFP}} \cdot (1 - A_{\text{ADC}}E_1\cos\alpha) = 0. \tag{S16}
$$

Expanding the brackets and reordering:

$$
E_1A_{\text{ADC}}^2 + (S'_{\text{SSFP}} \cdot E_1\cos\alpha + 1)A_{\text{ADC}} - S'_{\text{SSFP}} = 0. \tag{S17}
$$

This is a quadratic equation, therefore:

$$
A_{\text{ADC}} = \frac{-(S'_{\text{SSFP}} \cdot E_1\cos\alpha + 1) \pm [(S'_{\text{SSFP}} \cdot E_1\cos\alpha + 1)^2 + 4E_1 \cdot S'_{\text{SSFP}}]^{\frac{1}{2}}}{2E_1}. \tag{S18}
$$

As E_1 and S'_{SSFP} are positive, the numerator is less than 0 when we consider the negative solution. Considering $A_{\text{ADC}} = e^{-q^2 \cdot \text{TR} \cdot \text{ADC}}$, this would lead to a complex definition of ADC. Therefore:

$$
\text{ADC} = -\frac{1}{q^2\text{TR}} \cdot \ln\left[\frac{-(S'_{\text{SSFP}} \cdot E_1\cos\alpha + 1) + [(S'_{\text{SSFP}} \cdot E_1\cos\alpha + 1)^2 + 4E_1 \cdot S'_{\text{SSFP}}]^{\frac{1}{2}}}{2E_1}\right]. \tag{S19}
$$

For a Gamma distribution of diffusivities, by comparing Equation S13 to Equations S14 and S15:

$$S'_{\mathrm{SSFP},\Gamma} = \left(\frac{D_m}{D_m + q^2 \cdot \mathrm{TR} \cdot D_s^2}\right)^{\frac{D_m^2}{D_s^2}} + E_1 \cdot (1 + \cos\alpha) \cdot \left(\frac{D_m}{q^2 \cdot \mathrm{TR} \cdot D_s^2}\right)^{\frac{D_m^2}{D_s^2}} \cdot \Phi\left(E_1 \cos\alpha, \frac{D_m^2}{D_s^2}, \frac{D_m}{q^2 \cdot \mathrm{TR} \cdot D_s^2} + 2\right). \tag{S20}$$

References

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