# Diffusion model complexity reduces repeatability in multiple b-value DWI fitting : Impact of tumour volume and fitting methodology in a phase I clinical trial setting

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**Introduction**   Diffusion Weighted Imaging with multiple b-values is being used more widely in a number of application areas, including clinical trials for assessment of novel cancer therapeutics.  Since the contrast mechanism is endogenous, a greater degree of control is in principle possible, which has the potential to give accurate quantitative measures to assess treatment effects.  A number of different models for the b-value dependent signal attenuation are appearing in the literature, and the suitability and biological interpretation of these is a matter of current debate.  In this abstract we present repeatability results for a number of different diffusion models and analysis methods obtained from multiple b-value DWI data acquired in a Phase I clinical trial setting.

**Methods**   Repeat baseline DWI data were obtained not more than 7 days apart from 22 Phase I patients with a range of pelvic and abdominal tumours and metastases.  Axial images were acquired under free-breathing on a 1.5T Siemens Avanto using a multi-slice EPI sequence: 20×5mm slices, 380mm FOV, $128^2$ matrix with 6/8 partial acquisition in the PE direction, TE = 69ms, TR = 3500ms, NSA = 6, GRAPPA factor = 2, SPAIR fat suppression, b-values = 0, 50, 100, 250, 500, 750 s/mm$^2$, 3-scan trace images, total acquisition time 6 min 51 sec.  ROIs were drawn by an experienced radiologist to segment the whole volume of the index lesion.  The four diffusion models summarised in the table below were fitted voxel-wise to these data, from which median values over each tumour volume were reported.  Model ME was fitted in two ways: 1) to all b-values, 2) to b-values $\geq 100$ s/mm$^2$, which gives a diffusion estimate insensitive to perfusion effects at low b-values.  Two parameter estimation methods were used:  1) a standard least-squares optimisation algorithm with parameter constraints listed in the table,  2) a Bayesian approach similar to that described by Neil and Bretthorst [4], where the minimum mean-squared error (MMSE) estimate (given by the mean value under the posterior distribution for each parameter) is reported.

| Code | Name | Equation $S/S_0 =$ | Parameters and limits |
|---|---|---|---|
| ME | Mono-exponential | $\exp(-bD)$ | $-10 < \log D < -4$, i.e. $4.5\times10^{-10} < D < 0.0183$ mm$^2$/s. |
| SE | Stretched-exponential [1] | $\exp(-(bD)^\alpha)$ | $D$ same as ME,  $0 < \alpha < 1$. |
| GE | Gaussian-exponential [2] | $\int p(\Delta)\exp(-b\Delta)\,\mathrm{d}\Delta$ | $p(\Delta) = N(D,\sigma^2)$, i.e. a Gaussian (Normal) distribution, $D$ same as ME, $0 < \sigma < 5\times10^{-3}$. |
| BE | Bi-exponential [3] | $f\exp(-bD^*) + (1-f)\exp(-bD)$ | $D$ same as ME,  $0 < f < 1$,  $-7 < \log D^* < 0$, i.e. $9.1\times10^{-4} < D^* < 1$ mm$^2$/s, and $D^* > D$. |

Broad prior distributions were used that were truncated at the same values as the constraints used in the least-squares estimation, and the integrals necessary for the MMSE computations were performed numerically using a fixed grid.  Bland-Altman plots and statistics of the log of the median for each parameter over the tumour volume were reviewed (except $\alpha$ for which $\log(1-\alpha)$ was used as $\alpha$ is restricted to values <1 and estimates tend to be close to 1, so this transform gives approximately normally distributed data), from which a small number of outliers were apparent.  Since outliers were observed only in the smallest tumours,  a volume threshold of 50 cm$^3$ was chosen to separate the data into large and small tumours, from which separate statistics are reported.  Tumour volumes ranged from 14 – 577 cm$^3$, 9 cases were larger than 200 cm$^3$, and six cases were under the 50cm$^3$ threshold.  The Bland-Altman 95% repeatability limits for the log values were transformed to give equivalent limits of percentage change, and results are presented in the table.

**Results and Discussion**   The least-squares and Bayesian methods have very similar repeatability limits for both ME models and the SE $D$ parameter with both tumour volume groups.  Parameters SE $\alpha$, GE $\sigma$, BE $D^*$ and BE $f$ have substantially improved repeatability with the Bayesian method in both tumour volume groups.  Restricting the analysis to large tumours improves the repeatability by around a factor of two for models ME and SE, while for models GE and BE the improvements depend on the parameter, notable cases are $D^*$ and $f$ in model BE with the least-squares estimator.   The perfusion insensitive measure ME $b \geq 100$ has slightly improved repeatability over model ME when all tumours are analysed, but there is little improvement when large tumours are analysed.

*Table showing 95% repeatability limits of percentage change between baseline estimates.*

| Model | Parameter | Tumour volume > 50 cm$^3$ (n=22) | | | | All tumours (n=16) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Least-squares | | Bayesian | | Least-squares | | Bayesian | |
| ME | $D$ | -6.65, | 6.05 | -6.58, | 6.16 | -11.6, | 11.2 | -11.3, | 10.6 |
| ME $b\geq100$ | $D$ | -6.15, | 6.60 | -6.30, | 6.81 | -11.0, | 9.59 | -10.2, | 9.43 |
| SE | $D$ | -7.07, | 6.75 | -6.81, | 7.68 | -13.1, | 12.2 | -13.2, | 13.8 |
| SE | $1-\alpha$ | -43.1 | 55.2 | -33.1 | 33.3 | -42.1 | 74.4 | -31.2 | 45.1 |
| GE | $D$ | -9.19, | 8.32 | -9.5, | 8.85 | -14.2, | 15.9 | -14.6, | 16.3 |
| GE | $\sigma$ | -35.4, | 42.1 | -16.9, | 17.4 | -36.6, | 46.8 | -20.9, | 26.5 |
| BE | $D$ | -13.8, | 16.9 | -8.79, | 10.4 | -17.0, | 16.1 | -12.6, | 12.8 |
| BE | $D^*$ | -49.1, | 102 | -25.7, | 32.6 | -67.0, | 243 | -39.8, | 65.0 |
| BE | $f$ | -42.9, | 55.6 | -24.8, | 22.1 | -49.1, | 100 | -31.3, | 41.4 |

The repeatability of all the diffusion parameters ($D$) is best for the ME models, a little worse for SE, and noticeably worse for GE and BE.  This trend is explained by the increasing complexity of these models and the consequent noise sensitivity of the estimation process.

**Conclusions**   To derive useful estimates from the more complex models (SE, GE and BE), these data suggest that only large tumours should be included and that the best repeatability is obtained using the Bayesian method.  The diffusion parameter repeatability for model SE is close to that of the simpler ME models, even though model SE has an additional parameter, and so determining the interpretation and sensitivity to change of $\alpha$ in the context of Phase I treatment response assessment is a subject of continuing work.  It should be noted that these results pertain to the diffusion protocol described, and in particular the b-value specification.

[1] Bennett et al., *Mag. Res. Med.* **50**:727-734 (2003).
[2] Yablonskiy et al., *Mag. Res. Med.* **50**:664-669 (2003).
[3] Le Bihan et al., *NMR Biomed.* **15**:431-434 (2002).
[4] Neil and Bretthorst, *Mag. Res. Med.* 29:642-647 (1993).