# Comparison of Stretched Exponential and Non-Negative Least Squares Fitting Methods for Multi-Exponential Diffusion Decay Curves

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**Introduction:** Fitting of multi-exponential decay curves is not trivial, and thus, numerous fitting algorithms have been proposed which provide different information about the decay. These may be useful in understanding the multi-exponential nature of the diffusion decay curve, where it has been shown that at least three diffusion rates exists – slow (D1) and intermediate (D2) rates that arise from water in the tissue and a fast (D3) rate that arises from microvascular flow [1]. In this work, we compared two methods for fitting diffusion decay curves which provide significantly different information: non-negative least squares (NNLS) [2], and a form of the stretched exponential fit proposed by Bennett *et. al.* [3]. Both methods require no *a priori* knowledge of the number of components present in the decay curve. The NNLS method produces the minimal distribution of discrete D values that best fits the decay curve. The stretched exponential fit treats the diffusion decay curve as a continuous distribution of diffusion rates. It has the form $S(b)/S_o = w * \exp(-(b*D_s)^{\alpha}) + b$, where w is a weighting factor, b is a constant, $D_s$ is the combined diffusion rates, and $\alpha$ is the stretching parameter which provides a measure of the deviation of the decay curve from mono-exponential behaviour. These fitting methods were applied to diffusion decay curves obtained from an animal tumour model both pre- and post-sacrifice of the animal.

**Hypothesis:** That NNLS and the stretched exponential fitting methods will perform equally well, while providing different ways of describing the multi-exponential nature of the decay curves, and that the fitting parameters obtained from both fitting methods will be different for the pre- and post-sacrifice decay curves.

**Methods:** Diffusion decay curves were obtained pre- and post-sacrifice from 12 mammary fat pad rat tumours (animal model as described in [1]) using a 1.5T GE CV/i MRI system, 40mT gradient strength and a quadrature surface RF coil (4cm loops) and the following protocol: single shot SE-EPI, TE/TR=90.1ms/2500ms, FOV=16x8cm, matrix=80x80, slice thickness=5.0mm, 8 averages, 18 b-values (0, 30, 61, 90, 139, 239, 366, 529, 736, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000s/mm$^2$), diffusion encoding along xz, -xz, yz, -yz, xy, -xy directions. Trace images (Tr = (X + Y + Z)/3) were calculated at each b-value, and S(b)/So was calculated pixel-by-pixel. The diffusion decay curve (S(b)/So vs b) was determined for the average signal intensities in a region of interest encompassing the entire tumour in one imaging slice. Decay curves were fit using the NNLS algorithm and then to the stretched exponential equation using the Levenberg-Marquardt algorithm. For the stretched exponential method, $D_s$ was constrained between $0.01 \times 10^{-3}$ and $50 \times 10^{-3}$ mm$^2$/s and $\alpha$, w, and b were constrained between 0 and 1. For NNLS, seventy-five logarithmically spaced values were chosen between $0.10 \times 10^{-3}$ and $50.0 \times 10^{-3}$ mm$^2$/s, and weighted means of chosen D values were calculated in the following ranges: $0.1 \times 10^{-3} \leq D1 \geq 0.08 \times 10^{-3}$, $0.08 \times 10^{-3} \leq D2 \geq 2.5 \times 10^{-3}$, and $2.5 \times 10^{-3} \leq D3 \geq 50.0 \times 10^{-3}$ mm$^2$/s. To compare the goodness-of-fits, the sum of the squares of the residuals (SSR) was calculated for both fitting methods.

**Results and Discussion:** Mean signal to noise ratio (SNR) obtained in the tumours was 313±129. Representative decay curves pre- (closed symbols) and post- (open symbols) sacrifice for one tumour are shown in Figure 1. Blue curves are the NNLS fits and red curves are the stretched exponential fits. Mean fitting parameters (± standard deviation) are in Tables 1 and 2. NNLS showed no significant difference (paired T-test, $p>0.1$) between pre- and post-sacrifice values of D1, D2, and f2, but a significant difference ($p<0.05$) in f1. Post-sacrifice, NNLS found no D3 component in all of the 12 tumours except one, so no standard deviation is reported in Table 2 for D3 and f3 post-sacrifice. Thus, NNLS yielded different D3 and f3 values pre- and post-sacrifice, as expected. While the stretched exponential method showed significant differences (paired T-test, $p<0.05$) in all fitting parameters between the pre- and post-sacrifice data, the difference in the means of $D_s$ and $\alpha$ is small. This is due to the fraction of signal that arises from the microvascular flow (f3 ranged from 0.01 to 0.17 for the NNLS method.) The stretched exponential method is heavily weighted to the signal obtained from water in the tissue, but still appears to be sensitive to small changes in the decay curve caused by the disappearance of the fast diffusion component post-sacrifice. As expected, $D_s$ decreased and $\alpha$ increased (tending more to mono-exponential decay which would give a value of 1) with the disappearance of the fast diffusion component. Figure 2 shows the mean SSR for the NNLS (blue) and stretched exponential (red) fitting algorithms for the pre- and post-sacrifice decay curves. A two-way repeated measures analysis of variance (ANOVA) was conducted between pre- and post-sacrifice decay curves and the NNLS and stretched exponential fitting methods. A significant main effect for fitting method was observed, [$F(1,11)=5.03$, $p<0.05$, power=0.534] but not for pre- versus post-sacrifice or for the pre- versus post-sacrifice by fitting method interaction. Thus, the SSR was higher for the stretched exponential fitting method in both the pre- and post-sacrifice decay curves. For this study, the NNLS fitting method provides a better fit to the diffusion decay curves.

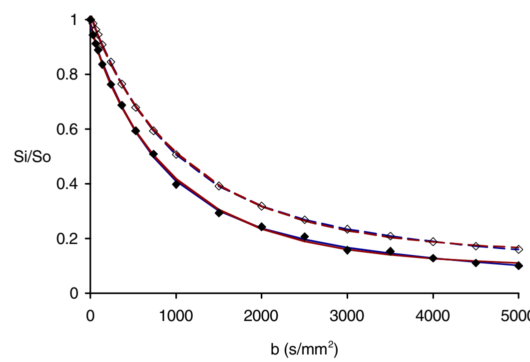


**Fig. 1:** Representative decay curves for one tumour pre- (close symbols) and post- (open symbols) sacrifice. The blue curves are the NNLS fits and the red curves are the stretched exponential fits for pre- (solid lines) and post- (dashed lines) sacrifice.

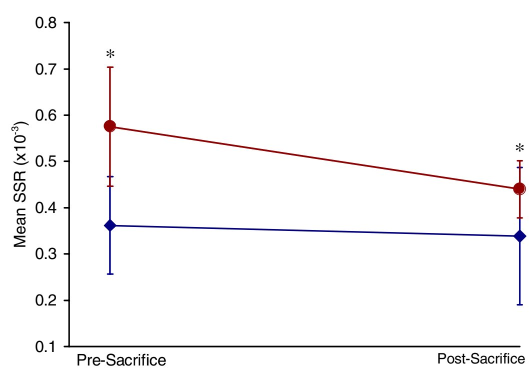


**Fig. 2:** Mean sum of the squares of the residuals (SSR) (±standard error of the mean) for NNLS (blue diamonds) and stretched exponential (red circles) methods. * SSR for the stretched exponential method was significantly higher ($p<0.05$) than NNLS for both pre- and post-sacrifice.

**Conclusions:** The NNLS fitting method yielded different pre- and post-sacrifice results in that D3 and f3 disappeared post-sacrifice. The stretched exponential method was also sensitive to the small changes in the post-sacrifice decay curves. The sum of the squares of the residuals was higher for the stretched exponential method than the NNLS method in both pre- and post-sacrifice decay curves suggesting that NNLS provides a better fit to the diffusion decay curves in this study.

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**References:** [1] Friesen Waldner, Rutt. Proc. ISMRM (2002) 635.
[2] Whittall, MacKay. J. Magn. Reson. 84:134; 1989.
[3] Bennett *et. al.* MRM 50:727; 2003.

**Table 1: Mean fitting parameters (±standard deviation) for the stretched exponential method.**

* All parameters were found to be significantly different ($p<0.05$) between pre- and post-sacrifice.

| | $D_s$ (x10$^{-3}$ mm$^2$/s) * | $\alpha$* | w * | b * |
|---|---|---|---|---|
| **Pre-sacrifice** | 0.95 ±0.16 | 0.81 ±0.04 | 0.88 ±0.04 | 0.11 ±0.03 |
| **Post-sacrifice** | 0.79 ±0.23 | 0.87 ±0.07 | 0.82 ±0.05 | 0.18 ±0.06 |

**Table 2: Mean fitting parameters (±standard deviation) for the NNLS fitting method.**

* indicates significant difference ($p<0.05$) between pre- and post-sacrifice values. # indicates no significant difference ($p>0.1$) between pre- and post-sacrifice values. Post-sacrifice, D3 and f3 values were found in only one of the twelve tumours, so N=1 and no standard deviation is reported.

| | D1 (x10$^{-3}$ mm$^2$/s) # | D2 (x10$^{-3}$ mm$^2$/s) # | D3 (x10$^{-3}$ mm$^2$/s) | f1 * | f2 # | f3 |
|---|---|---|---|---|---|---|
| **Pre-sacrifice** | 0.26 ±0.09 | 1.37 ±0.23 | 18.66 ±12.11 | 0.40 ±0.15 | 0.52 ±0.13 | 0.05 ±0.04 |
| **Post-sacrifice** | 0.24 ±0.13 | 1.28 ±0.30 | 7.27 (N=1) | 0.52 ±0.20 | 0.51 ±0.12 | 0.01 (N=1) |