# Treatment Response of Non-Monoexponential Diffusion in a Glioma Rodent Model

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**Introduction:** The apparent diffusion coefficient (ADC), as determined by diffusion-weighted imaging at low b-values, has shown increasing potential as a non-invasive imaging biomarker for the evaluation of tumors response to treatment (1). Recent literature has shown that signal attenuation deviates from a mono-exponential decay at higher diffusion weightings (2). This study investigates the utility of more complex models, utilizing a wider range of diffusion weightings, for monitoring early treatment response in rat gliomas.

**Methods and Materials:** *Animal Model:* Twenty three male Fischer 344 rats (10 controls, 13 treated) were implanted, intra-cranially, with a suspension of 1x $10^5$ 9L gliosarcoma cells. When tumors reached a volume of 40-80 $mm^3$, animals were separated into control and treated groups. The treated group was injected with a single dose of BCNU (9.98 mg/kg, i.p.) while the control group was administered the carrier solution (10% ethanol in saline). H&E stains were acquired pre and 6 days post-therapy in three BCNU treated animals.

*MRI Experiment:* Each animal was imaged in three day intervals using a 9.4T Varian *Direct Drive* system and a quadrature rat head RF coil (Doty Scientific, Inc.). Diffusion-weighted images were acquired using a spin-echo sequence, with a navigator echo and gradient waveforms sensitive to isotropic diffusion, with the following parameters: TR/TE = 4000/41 ms, field of view (FOV) = 30 mm, matrix size = 64x64, slice thickness = 2 mm, and 6 b-values: 120, 1200, 1600, 2000, 3000 and 4000 s/$mm^2$.

*Data Analysis:* Image analysis was done using in-house software developed in MATLAB (The MathWorks, Inc., Natick, MA). The tumors were contoured on the low b-value DW image. Three different diffusion models were evaluated, including a bi-exponential pixel-wise fit (3), a stretched exponential model (4), and two-point diffusion maps using low b-values (fast ADC: $ADC_{120\text{-}1200}$) and high b-values (slow ADC: $ADC_{2000\text{-}4000}$). Using the bi-exponential model, we were able to extract fast and slow diffusion coefficients ($D_f$ and $D_s$, respectively) and the signal fraction corresponding to the slow diffusion ($f_s$=1-$f_f$). From the stretched exponential model, we measured the distributed diffusion constant (DDC) and the distribution parameter, γ, which is a measure of the complexity of the diffusing environment. From the two-point analytically solution of ADC, fast and slow diffusion coefficients and the ratio between the slow and fast ADC were obtained.

*Statistics:* Student t-tests were used to compare control and treated groups at each time point as well as each time point post-therapy to its pre-treatment value. Significance was assessed at p-values < 0.05.

**Results:** Fig. 1 shows maps of the fast diffusion coefficients from the bi-exponential (A), stretched (B) and two-point (C) models pre and 6 days post-treatment. Fig. 2 shows the time course of percent change in diffusion parameter values. All fast diffusion measurements peaked at day 6 post-therapy. Though fast diffusion trends were very similar, the biexponential model resulted in the highest change (26%), followed by the stretched exponential model's DDC (23%) and the 2-point calculation (17%). All models showed a significant increase in fast ADC on days 3 and 6 post-therapy, and the biexponential $D_f$ was also significant on day 9. Slow ADC only showed a significant change on day 9 (-7%) using the 2-point calculation (Day 6: $D_s$ = 6%, $ADC_{2000\text{-}4000}$ = -2%). All dimensionless measures showed a significant change on day 6 ($f_s$: -10%, ratio: -16%, γ: -7%), and all but $f_s$ showed significance on day 9 post-therapy. H&E stains pre and 6 days post-treatment showed massive cell kill (data not shown).

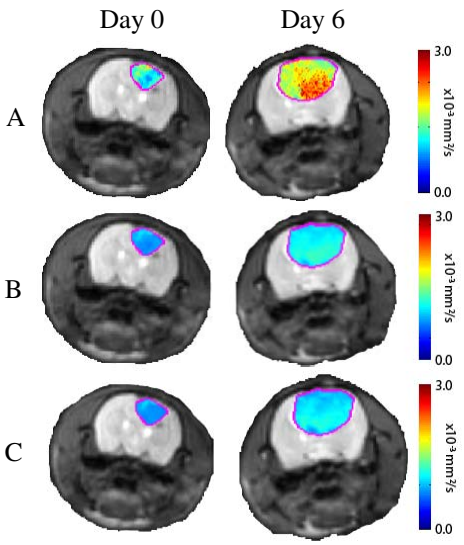


Figure 1: Representative color overlays of (A) $D_f$, (B) $ADC_{120\text{-}1200}$, and (C) DDC maps on low b-value DW images before treatment and 6 days post.

**Discussion:** All three models generated similar trends between like parameters. Most sensitive to treatment were the fast diffusion coefficients, which peaked at day 6 post-therapy (Fig. 2A). The slow diffusion coefficients from the bi-exponential and two-point models produced negligible changes from baseline (Fig. 2B). In contrast, dimensionless parameters, Fig. 2C, had changed significantly by day 6. Increase and decrease in the fast diffusion coefficient and dimensionless parameters, respectively, suggest water mobility is less hindered in the treated tumor. However, the extent of cell death in the tumor could not be fully accounted for by changes observed in $f_s$ alone. This suggests that other mechanisms, beyond simple compartmentalization of water, are involved in the non-monoexponential trend in signal intensity (2). Overall, the bi-exponential model displayed the greatest sensitivity to treatment, but at a high cost of image acquisition (~2 hours) and computational time (30-60 minutes).

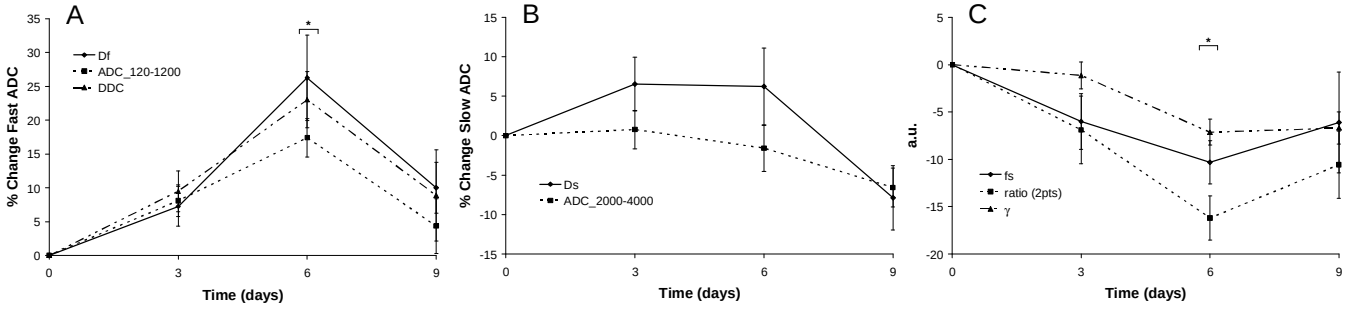


Figure 2: The percent change (mean+/- SEM) in (A) fast ADC, (B) slow ADC, and (C) dimensionless parameters from all three diffusion models. * indicates a significant change between pre- and day 6 post-therapy in all models.

**References:**

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