Investigation of Bi-exponential Diffusion in Treated Brain Tumors

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Introduction: Diffusion weighted MRI has been an indispensable tool for the evaluation of tumors response to treatment. Traditionally, quantifying diffusion from MRI is typically performed using a mono-exponential model, which describes Brownian motion of water. Recent literature has shown that the actual signal attenuation due to diffusion in tissues does not follow a single exponential decay. At very high b-values (greater diffusion weighting), a slower diffusion coefficient becomes apparent, that isn't quite so obvious in the traditionally used weightings (<1500 s/mm^2). The physical reason for this bi-exponential nature, however, remains elusive. Speculations have been made that the bi-exponential attenuation could be due either to water binding or compartmentalization [1,2]. The following study investigates the bi-exponential behavior of water diffusion in a brain tumor during therapeutic treatment.

Methods and Materials: *Animal Model:* Sixteen male Fischer 344 rats (8 control, 8 treatment), weighing between 125 and 150g, were implanted, intra-cranially, with a suspension of 9L rat glioma cells. Once the tumors reached 40-80 mm^3, animals were imaged and then separated into control and treated groups. The treated group was injected intraperitoneally with 13.3 mg/kg BCNU (5 mg/mL in a 10% ethanol solution).

MRI Experiment: Each animal was imaged every three days using a 9.4T Varian *Direct Drive* system and a linear rat head RF coil (Doty Scientific, Inc.). Anatomical images were acquired using a fast spin-echo sequence with the following parameters: TR/TE = 4000/42.72 ms, field of view (FOV) = 30 mm, matrix size = 256x128, slice thickness = 1 mm, 2 averages. 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 = 4000/47 ms, field of view (FOV) = 30 mm, matrix size = 128x64, slice thickness = 1 mm, and 17 b-values ranging from 120 to 3400 s/mm^2.

Data Analysis: Image analysis was done using in-house software developed in MATLAB (The MathWorks, Inc., Natick, MA). Volumes of interest (VOI) over the tumors were drawn on the anatomical images. Diffusion VOIs were drawn using the low b-value image (120 s/mm^2), which included viable tissue while avoiding necrotic tissue areas. The bi-exponential model for diffusion was fit to the mean signal intensities from the VOIs of the 17 diffusion-weighted images. The adjustable parameters from the model were the fast and slow ADC and the fractional signal intensity. In addition, the mono-exponential model was used for calculating mean ADC. This was performed by generating ADC maps with b values 120 and 1200 s/mm^2 and calculating the mean ADC within the VOI.

Statistics: Student t-tests were used to compare control and treated groups at each time point. Animal population was stratified based on the median D_{fast}, D_{slow}, 2-pt ADC, and f_{fast}. Kaplan-Meier survival curves and the log-rank test on days 3, 6, and 9 were used to characterize and compare the groups in terms of overall survival. Significance was assessed at p-values < 0.05.

Results: Figure 1 shows representative diffusion-weighted images of a rat brain tumor at b-values of 120, 1200 and 3000 s/mm^2. The bi-exponential fit to signal intensity of healthy brain matter is presented in Figure 2. The data profile shows transitioning from the fast diffusion line (dashed) to the slower diffusion at about 1500 s/mm^2. After treatment with BCNU, both diffusion coefficients significantly increased and reached maxima on day six post-therapy (Figure 3). Figure 3 shows the mean percent change in the diffusion coefficients from pre-therapy values. The most significant increase was observed in the fast diffusion coefficient, which showed a greater increase than the two-point ADC calculation. Another interesting finding was that the fast diffusion signal fraction, f_{fast}, did not seem to change along with the diffusion coefficients. Instead, f_{fast} was found to significantly increase from pre-therapy values at day nine post-therapy (p=0.006). Survival analysis showed significance between stratified groups in f_{fast} on day 3, all four values (D_{fast}, D_{slow}, 2-pt ADC, and f_{fast}) on day 6, and all but D_{slow} on day 9 post-therapy.

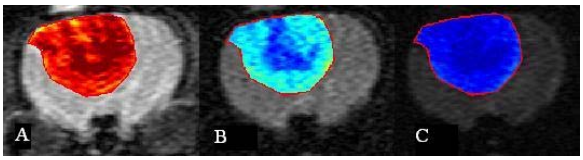

Figure 1: Representative images of a rat brain tumor at b-values of (A) 120, (B) 1200, and (C) 3000 s/mm^2.

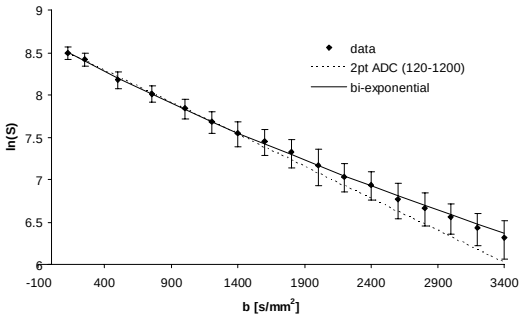

Figure 2: Plot of gray matter signal with b-value, showing both the bi-exponential fit (D_{fast}=1.22 mm^2/s, D_{slow}=0.48 mm2/s, f_{fast}=0.505) and the 2-point approximation using b-values of 120 and 1200 (ADC=0.76 mm^2/s). Data error bars show the standard deviation within the ROI.

Discussion: Our two-point ADC values correlate well with what was observed in the literature [3]. We observed a significant increase in all components of the bi-exponential model by day 6. D_{fast} showed the largest relative increase from baseline (70%), followed by D_{slow} (40%) and f_{fast} (14%). These results indicate that the therapeutic response not only involves a shift in the relative fractional volume, but also the actual diffusion rates. Survival stratification showed significance in all bi-exponential variables on day 6, but only f_{fast} was significant on day 3 post-therapy. This was very interesting since a student t-test between control and treated groups did not reveal statistical significance for f_{fast}.

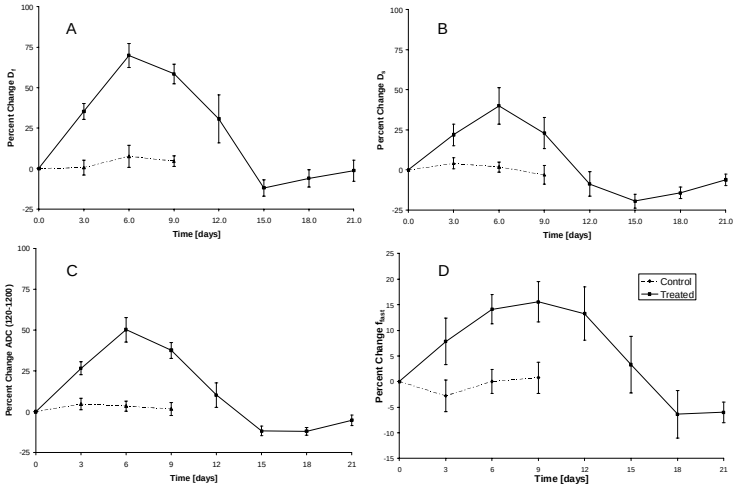

Figure 3: Average percent change (+/-SEM) in D_{fast}, D_{slow}, the 2-point ADC calculation (120-1200 s/mm^2), and f_{fast} over a period after a treatment of BCNU.

References:

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