# Multiexponential diffusion properties of human high grade gliomas

**T. L. Chenevert[1], S. Rohrer[1], C. I. Tsien[2], L. R. Junck[3], P. C. Sundgren[1], D. M. Gomez Hassan[1], C. R. Meyer[1], Y. Pang[1], M. K. Ivancevic[1,4], and B. D. Ross[1]**

[1]Radiology, University of Michigan, Ann Arbor, MI, United States, [2]Radiation Oncology, University of Michigan, Ann Arbor, MI, United States, [3]Neurology, University of Michigan, [4]MR, Philips Medical Systems, Cleveland, OH, United States

## Introduction

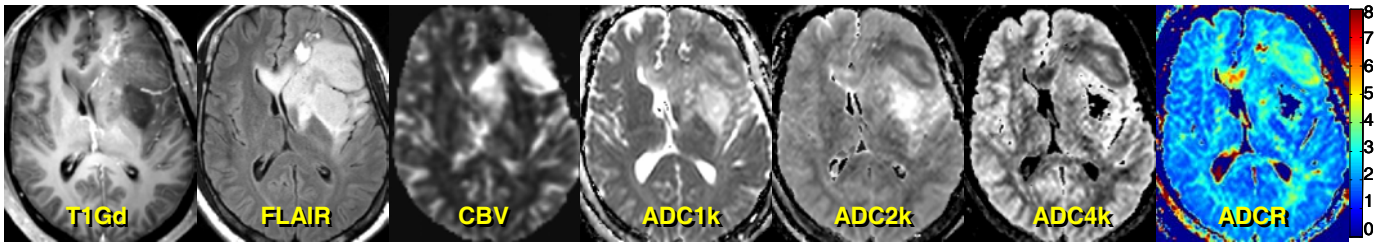
Brain tissue is known to exhibit multiexponential diffusion decay attributable to multiple compartments and inter-compartment water exchange (1-3). Nevertheless, due to SNR and acquisition time constraints, the vast majority of human diffusion studies are limited to only a few b-values in the 0 to 1000sec/mm$^2$ range yielding modest sensitivity to multiexponential behavior. Ideally, many b-values (and gradient directions) spanning much higher diffusion sensitivities are required for fits to a multicompartment/multisite exchange model to probe fundamental tissue properties, but such long scan times are prohibitive for clinical application. In this study we applied a clinically-practical high b-value DWI protocol to investigate multiexponential diffusion features in normal tissues and high grade glioma in patients with the objective to provide baseline values of landmark tissues and tumor over a wide range of b-values as prerequisites to therapy response studies.

## Materials and Methods

Thirteen high-grade glioma patients (10 GBM; 1 G3 anaplastic glioma; 1 anaplastic oligo; 1 G3 astrocytoma; 9male, 4 female; mean age 53, range 20-79) were enrolled in this IRB-approved study. Pre-therapy baseline imaging included anatomic, DWI, and perfusion imaging performed on a 3T system (Philips Achieva). DWI consisted of 3-axis isotropic weighting at diffusion sensitivities of b=0, 1000, 2000, 4000 mm$^2$/sec using SSEPI (TR/TE=8700/60ms) and parallel imaging (SENSE=3). System and 8ch head receiver coil SNR were sufficient to acquire high quality whole brain isotropic DWI at 23mm$^3$ resolution in 4'30". In lieu of multiexponential fits on so few data, apparent diffusion values were calculated from image pairs: b=0 & 1000 (ADC1k, i.e. "conventional" ADC); b=1000 & 2000 (ADC2k); and b=2000 & 4000 (ADC4k). In addition, the ratio "ADCR" ≡ {ADC1k} / {ADC4k} calculated on a pixel-by-pixel basis provided a simplistic measure of multiexponential contrast. ADCR≈1 implies mono exponential behavior independent of diffusivity, whereas higher ADCR values (e.g., ADCR>3) suggests stronger multiexponentiality. Noise thresholds were set to restrict diffusion calculation to only pixels safely above background noise to avoid ADC underestimation of high mobility tissues at high b-values. An ice-water phantom was scanned to confirm mono exponential behavior in the ADC≈1x10$^{-3}$mm$^2$/sec regime. These ADC indices were mapped on a pixel-by-pixel basis and measured on ROIs in contralateral to tumor frontal cortex WM, centrum semi ovale (CSO) WM, basal ganglia GM, and cortical GM at the CSO level. In addition, ROIs were measured in tumor extremes of hyperperfused viable tumor and hypoperfused tumor, although effort was taken to avoid surgical cysts. Anatomic, DWI, perfusion and derivative images were spatially coregistered for each patient to facilitate multimodality analyses. Perfusion values were scaled to frontal white matter which was assigned a value CBF≡50ml/100gm/min.

## Results

*Mono* exponential diffusion behavior was confirmed in the ice-water phantom (in units of x10-3mm2/sec: ADC1k=1.1±0.05; ADC2k=1.1±0.04; ADC4k=1.2±0.1) with an ADCR = 0.97±0.09. The Figure illustrates a patient with a highly-perfused high grade anaplastic glioma in the left temporal lobe extending through the genu of the corpus callosum. This tumor clearly exhibits strong multiexponential properties. While ADC1k, ADC2k, ADC4k images were windowed independently to better show the relative ADC contrasts, the tumor has relatively low water mobility on each ADC which is more apparent on the ADC map derived from high b-values (i.e. ADC4k). The apparent "zero" ADC values in CSF and cyst on ADC2k and ADC4k are only a result of noise thresholding – these pixels are not included in subsequent analyses. The "ADCR" map confirms the increased degree of multiexponential contrast in white matter and particularly in this tumor exhibiting {ADC1k}/{ADC4k} ratio of ADCR ≈ 3 in the temporal lobe and ADCR ≥ 5 in the genu.




The Table summarizes measured CBF the various ADC indices for the 13 glioma patients (mean ± stdev). The "contralateral" frontal WM ADC values are slightly elevated from normal due to unavoidable peritumoral edema in this region for some of the patients. The ADCR of hyperperfused tumor was significantly greater than gray matter tissues suggesting a higher degree of multiexponentiality in tumor. Interestingly even hypoperfused tumor, presumed more necrotic, exhibits significantly higher ADCR than other tissues.

| | *Frontal WM N=13* | *CentrumSemiOvale WM N=13* | *Basal Ganglia GM N=13* | *Cortical GM N=13* | *HYPERPerfused Tumor N=9* | *HYPOPerfused Tumor N= 7* |
|---|---|---|---|---|---|---|
| ADC1k § | 0.86 ± 0.07 | 0.80 ± 0.06 | 0.76 ± 0.07 | 0.93 ± 0.07 | 1.06 ± 0.18 | 1.51 ± 0.37 |
| ADC2k § | 0.56 ± 0.05 | 0.52 ± 0.04 | 0.57 ± 0.02 | 0.61 ± 0.02 | 0.68 ± 0.10 | 0.77 ± 0.27 |
| ADC4k § | 0.29 ± 0.02 | 0.27 ± 0.02 | 0.40 ± 0.03 | 0.40 ± 0.02 | 0.35 ± 0.06 | 0.25 ± 0.07 |
| ADCR | 3.01 ± 0.21 | 2.98 ± 0.14 | 1.96 ± 0.30 | 2.39 ± 0.24 | 3.20 ± 0.78 | 5.16 ± 1.12 |
| CBF * | 50 ± 0 | 37± 8 | 121 ± 35 | 112 ± 27 | 256 ± 172 | 20 ± 9 |

**§ in units of 10$^{-3}$ mm$^2$/sec**

*** scaled relative to contralateral frontal WM assigned a value of 50ml/100gm/min**

## Conclusions

Normal brain and human glioma demonstrate substantial multiexponential diffusion decay properties observable at high b-values. Highly perfused cellular tumor, thus presumed viable, has multiexponential characteristics similar to, or greater than white matter. Hypoperfused tumor should have a greater fraction of necrosis, yet strong multiexponential behavior persists. This suggests even necrosis behaves as a complex multi-compartment or multi-viscosity diffusion system. This observation does not pertain to simple cysts or surgical voids which were excluded from this analysis.

## References

1. Clark CA, Le Bihan D. Water diffusion compartmentation and anisotropy at high b values in the human brain. Magn Reson Med 2000; 44:852-859.
2. Lee JH, et al. Effects of equilibrium exchange on diffusion-weighted NMR signals: the diffusigraphic "shutter-speed". Magn Reson Med 2003; 49:450-458.
3. Mulkern RV, et al. Multi-component apparent diffusion coefficients in human brain: relationship to spin-lattice relaxation. Magn Reson Med 2000; 44:292-300.