Differentiating Low- and High-Grade Pediatric Brain Tumors Using a Continuous Random Walk Diffusion Model at High *b*-Values

Muge Karaman[1], Yi Sui[1,2], He Wang[3], Richard L Magin[2], Yuhua H Li[4], and Xiaohong Joe Zhou[1,5]

[1]*Center for MR Research, University of Illinois at Chicago, Chicago, IL, United States,* [2]*Bioengineering, University of Illinois at Chicago, Chicago, IL, United States,* [3]*Philips Research China, Shanghai, China,* [4]*Radiology, Xinhua Hospital, Shanghai, China,* [5]*Departments of Radiology, Neurosurgery, and Bioengineering, University of Illinois at Chicago, Chicago, IL, United States*

Introduction: Pediatric brain tumors are the second most prevalent form of childhood cancer, making up 16.6-21% of all pediatric cancers in the U.S. [1]. An accurate assessment of tumor malignancy is vital for the determination of the most effective treatment. While conventional MRI is essential for diagnosis and evaluation of brain tumors, it offers limited information for tumor grading. Diffusion-weighted imaging (DWI) has been proposed for brain tumor grading because of its ability to reveal tissue cellularity and the integrity of cellular membranes [2]. Although a mono-exponential model is widely used in quantitative diffusion MRI studies, the underlying tissue complexity and heterogeneity are better characterized using more sophisticated diffusion models, such as bi-exponential [3], stretched-exponential [4], statistical [5], q-space [6], kurtosis [7], and others. Most recently, a fractional order calculus diffusion model that is derived from the continuous time random walk (CTRW) theory was introduced [8-10]. The probabilistic perspective of the CTRW theory relaxes *a priori* distributions of waiting times (water trapping) and distance increments (jump lengths) of the water molecules, providing a more complete description of complex heterogeneous structures in biological tissues. In this study, we show that a new set of parameters estimated from the generalized solution to the fractional order diffusion equation from the CTRW theory can be used to improve diagnostic accuracy of differentiating low-grade (LG) and high-grade (HG) pediatric brain tumors.

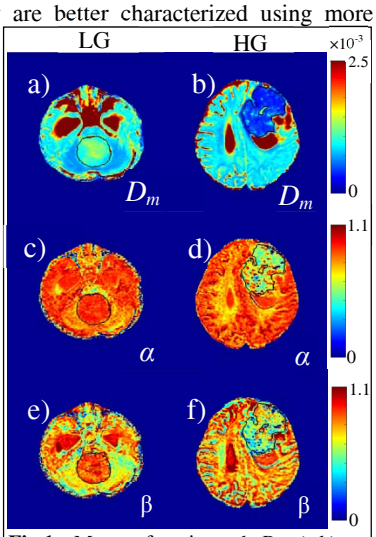

Fig.1: Maps of estimated D_m (a,b), α (c,d), and β (e,f) from patients of LG (a,c,e) and HG tumor (b,d,e).

Theory: In the context of CTRW theory, the anomalous motion of a diffusing particle in a heterogeneous tissue is described with a dual space-time fractional order diffusion equation, ${}_0^C D_t^{\alpha}\left(S(x,t)\right) = D_{\alpha,\beta}\partial^{\beta'} S(x,t)/\partial|x|^{\beta'}$, where $D_{\alpha,\beta'}$ is the effective diffusion coefficient, α and β' are the fractional time and space derivatives. The solution to the differential equation is described by a Mittag-Leffler function (MLF), E_{α}, as $s(q,\bar{\Delta}) = E_{\alpha}(-D_{1,2}(\tau^{1-\alpha}/\mu^{2-\beta'})|q|^{\beta'}\bar{\Delta}^{\alpha})$, where $b = q^2\bar{\Delta}$, $\bar{\Delta} = (\Delta - \delta/3)$, q is a q-space variable, and μ (in μm) and τ (in ms) are space and time constants [10]. To reduce the computational complexity, the MLF model can be simplified to $s(b) = E_{\alpha}(-(bD_m)^{\beta'/2})$, where $D_m{}^{\beta'/2}(\bar{\Delta}) = D_{1,2}(\tau^{1-\alpha}/\mu^{2-\beta'})\bar{\Delta}^{(\alpha-\beta'/2)}$. Replacing $\beta'/2$ with β for simplicity, the MLF model can be written as $s(b) = E_{\alpha}(-(bD_m)^{\beta})$, from which D_m, α, and β can be estimated.

Methods: Patients: The patient group consisted of 54 children (16 females from 4 months to 9 years old, 38 males from 4 months to 13 years old) who underwent surgical biopsy or surgery with histopathology confirmation under an IRB approved protocol. According to the latest WHO guidelines, 24 patients were classified as LG (I or II) and 30 as HG (III or IV) tumors. MR Imaging: MR scans were performed on a 3T GE Signa scanner with an 8-channel head coil. The imaging protocol included FLAIR, T2, contrast- enhanced T1, and multi- *b*-value DWI sequences. DWI was performed with single-shot spin-echo EPI using 12 *b*-values (0 to 4000 sec/mm^2). The other parameters were: TR/TE=4700/100ms, slice thickness=5mm, Δ=38.6 ms, δ=32.2ms, FOV=22cm×22cm, matrix size=128×128. Trace-weighted images were obtained to reduce the effect of diffusion anisotropy. Analysis: The MLF model was used to fit to the multi-*b*-value diffusion images using a nonlinear least squares estimation. The ADC values were also computed for comparison. ROI-based analysis of the MLF parameters was performed on the tumor whose margin was determined by T1+C, T2, and FLAIR images. The mean values of D_m, α, and β were computed over the tumor ROIs for each patient, and used for differentiation of LG and HG tumors. The mean estimates were clustered into two groups in 3D space (D_m, α, β), corresponding to LG and HG, by using a *k*-means algorithm. The performance of tumor-grade differentiation was then evaluated by calculating sensitivity (SN), specificity (SP), and accuracy (AC) from the results of the cluster analysis using histopathology as the reference.

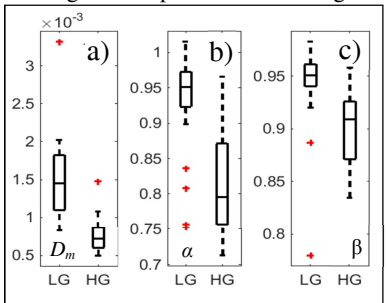

Fig. 2: Boxplots of mean values of the MLF parameters (D_m, α, and β in (a), (b), and (c), respectively) for LG and HG tumors. (Outliers: top and bottom 2.7%)

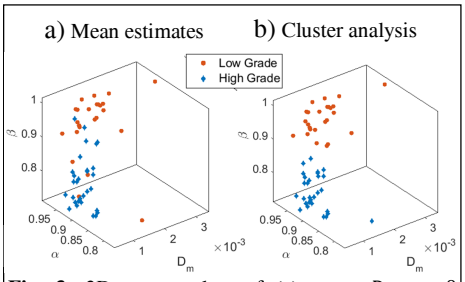

Fig. 3: 3D scatter plots of (a) mean D_m, α, β parameters, (b) *k*-means clustering analysis results from the ROIs. In (b), Clustering was performed only from parameter estimates, not using the histopathological information. (Red: LG, Blue: HG)

Results: Figure 1 shows maps of D_m, α, and β, from one representative patient in each group. Figures 2 and 3(a) are the boxplots and 3D scatter plots of the mean D_m, α, and β estimates of the tumor ROIs, respectively. Results in Figs.1-3(a) indicate that the MLF parameters exhibited a statistically significant difference between the LG and HG groups (p-values < 0.001 from t-test) when using histopathology as a gold standard. The 3D scatter plot in Fig. 3(b) illustrates that the MLF parameters can effectively separate LG tumors from HG tumors. Table 1 summarizes SN, SP, and AC values computed from the clustering analysis performed on different combinations of the MLF parameters, as well as on the ADC value. Table 1 shows that the best performance was achieved with the combination of (α,β) or (D_m,α,β). In all cases of using the MLF parameters, the specificity was considerably improved when compared to using ADC alone.

	D_m, α	D_m,β	α,β	D_m,α,β	ADC
SN	0.60	0.70	0.83	0.83	0.96
SP	0.91	0.83	0.83	0.83	0.58
AC	0.74	0.75	0.83	0.83	0.79

Table 1: Evaluation of clustering analysis from MLF parameters, and ADC values of ROIs.

Discussion and Conclusion: Our results demonstrate that the MLF parameters from LG tumors are significantly higher than those from HG ones. Using a cluster analysis, we have further demonstrated that combinations of the MLF parameters improve the specificity and accuracy for differentiation between LG and HG groups beyond that obtained using conventional ADC values. The new parameters, α and β, may lead to novel biomarkers to characterize tissue complexity and microstructure as they reflect the likelihood of water molecules to be "trapped" and to "jump" in the specific tissue environment. In conclusion, the proposed MLF diffusion model can provide valuable insights into determining pediatric brain tumor malignancy, particularly in cases where surgical biopsy is not feasible due to the tumor location.

References: [1] NCI, Snapshots, 2008. [2] Moffat et al., PNAS, 2005. [3] Niendorf et al., MRM, 1996. [4] Bennett et al., MRM, 2003. [5] Yablonskiy et al., MRM, 2003. [6] Assaf et al., MRM, 2000. [7] Jensen et al., MRM, 2005. [8] Magin et al., JMR, 2008. [9] Zhou et al., MRM, 2010. [10] Ingo et al., MRM, 2014.

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