Differentiation of Low- and High-Grade Pediatric Brain Tumors Using A Non-Gaussian Diffusion Model

Muge Karaman¹, Yi Sui¹,², Frederick C. Damen¹,³, Yuhua Li⁵, and X. Joe Zhou¹-⁴

¹Center for MR Research, Departments of ²Bioengineering, ³Radiology, and ⁴Neurosurgery, University of Illinois Hospital & Health Sciences System, Chicago, IL; ⁵Department of Radiology, Xinhua Hospital, Shanghai, China
Introduction

- Pediatric brain tumors are the most common solid tumors in children.

- Differentiation between low-grade and high-grade brain tumors has prognostic significance.

- Brain biopsy may not be an option due to the inoperable location in the areas such as brain stem.

- The noninvasive diagnosis is not only desirable but also required.
Introduction

• Accurate differentiation of low-grade and high-grade brain tumors using MRI is challenging.
• Conventional T1w / T2w imaging has limited specificity.

![Image showing MRI scans of low-grade and high-grade tumors]

Low-grade
Pilocytic Astrocytoma

High-grade
Medulloblastoma
Diffusion MR Imaging for Brain Tumors

• Diffusion MR Imaging is able to reveal the cellular information of brain tissues\(^*\).
  
  • Cellularity  
  • Cell size distribution  
  • Cytoplasm ratio

• Diffusion is modeled by a random walk of the particles:
  
  • Random walk (RW) → Gaussian  
  • Continuous time random walk (CTRW) → Non-Gaussian

From RW to CTRW

- In Gaussian RW theory,
  - jump length ($\Delta x$) variance and
  - waiting time between jump lengths ($\Delta t$) are finite and Gaussian.

\[
\frac{\partial P(x,t)}{\partial t} = D \frac{\partial^2 P(x,t)}{\partial |x|^2} \quad \text{solution} \quad s(q, \bar{\Delta}) = \exp(-D_{1,2}|q|^2 \bar{\Delta})
\]

- In non-Gaussian CTRW theory,
  - jump length variance and
  - waiting time between jump lengths are not constrained by Gaussian distribution.

\[
C D_t^\alpha(P(x,t)) = D_{\alpha,\beta} \frac{\partial^{2\beta} P(x,t)}{\partial |x|^{2\beta}} \quad \text{solution} \quad s(q, \bar{\Delta}) = E_\alpha(-D_{\alpha,\beta}|q|^{2\beta} \bar{\Delta}^\alpha)
\]
ADC Approach

• Apparent Diffusion Coefficient (ADC) values are computed from the mono-exponential model.
  • Gaussian model
  • Diffusion signal is modeled by

\[
s(b) = s_0 \exp(-bD)
\]

• ADC in tumors*
  • High-grade tumors have lower ADC compared to low-grade tumors.
  • Significant overlap between groups can compromise the specificity for differential diagnosis.

Limitations of ADC Approach

- Diffusion in complex heterogeneous tissues is non-Gaussian.

- High-grade brain tumors have more complex and heterogeneous structures than low-grade ones.

- Signal attenuation in brain tissues cannot be well described by a mono-exponential decay, as predicted by the Gaussian diffusion model.

\[
s(b) = s_0 \exp(-bD)
\]

Non-Gaussian Diffusion Models

- Bi-exponential, stretched-exponential, statistical, \( q \)-space, kurtosis, continuous time random walk (CTRW) models, etc.
- CTRW model

\[
\frac{\partial}{\partial t} D_t^\alpha(P(x, t)) = D_{\alpha,\beta} \frac{\partial^{2\beta} P(x, t)}{\partial |x|^{2\beta}}
\]

\[
\text{solution} \quad s = s_0 E_{\alpha} \left[ -(bD_m)^\beta \right]
\]

- \( D_m \): diffusion coefficient, similar to ADC
- \( \alpha \): fractional power of the waiting time
- \( \beta \): fractional power of the jump length

- CTRW model has been examined on healthy fixed rat brain**, but not yet in a clinical human study.

Objective

• To investigate the feasibility of using CTRW parameters ($D_m$, $\alpha$, and $\beta$) to differentiate low- and high-grade tumors.

• To compare the outcomes of the differentiation by CTRW parameters and the conventional ADC value.
Patient Group

- 54 patients with histopathologically proven brain tumors
  - 38 males, 16 females
  - Age range: 4 months – 13 years
  - 24 low-grade
    - 15 WHO grade I, e.g. Pilocytic Astrocytoma
    - 9 WHO grade II, e.g. Diffuse Astrocytoma
  - 30 high-grade
    - 2 WHO grade III, e.g. Anaplastic Ependymoma
    - 28 WHO grade IV, e.g. Medulloblastoma
Imaging Protocol

• Image Acquisition
  • GE 3T MR scanner
  • T1-FLAIR, T1+C, T2
    • Matrix = 256 × 256
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• Image Acquisition
  • GE 3T MR scanner

• T1-FLAIR, T1+C, T2
  • Matrix = 256 × 256

• Diffusion weighted imaging
  • 12 b-values = 0 ~ 4000 s/mm²
  • TR/TE = 4700/100 ms
  • Slice thickness = 5 mm
  • Δ = 38.6 ms, δ = 32.2 ms
  • 1 average
  • FOV = 22 cm × 22 cm
  • Matrix size = 128 × 128
  • Scan time = 3 min
Data Analysis

\[ s = s_0 E_\alpha \left[ -\left( b D_m \right)^\beta \right] \]

\[ b = \left( \frac{G_z}{D_m} \right)^2 \left( \frac{1}{3} \right) = \text{diffusion gradient duration} \]

\[ = \text{diffusion time} \quad G_z = \text{diffusion gradient amplitude} \]
Data Analysis

• Tumor ROI Determination

• Whole tumor coverage
• Guided by T1 + C, T1 FLAIR, T2 images.
• Areas of necrosis, cyst, hemorrhage, edema and calcification were avoided.
Examples of $D_m$, $\alpha$, and $\beta$ Maps

Low-grade (WHO II - 17m) Ependymoma

<table>
<thead>
<tr>
<th>T1 FLAIR</th>
<th>T1 + C</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
</tbody>
</table>

$D_m$ ($\mu m^2/\text{ms}$)  $\alpha$  $\beta$
Examples of $D_m$, $\alpha$, and $\beta$ Maps

High-grade (WHO IV - 18m)
Medulloblastoma
Mean Values of CTRW Parameters

\[
D_m (\mu m^2/ms) \quad \alpha \quad \beta
\]

<table>
<thead>
<tr>
<th>Grade</th>
<th>(D_m) ((\mu m^2/ms))</th>
<th>(\alpha)</th>
<th>(\beta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade</td>
<td>1.50±0.50</td>
<td>0.95±0.04</td>
<td>0.92±0.07</td>
</tr>
<tr>
<td>High-grade</td>
<td>0.75±0.20</td>
<td>0.90±0.03</td>
<td>0.81±0.06</td>
</tr>
</tbody>
</table>

\(p\) value*:
- <0.001
- <0.001
- <0.001

*Mann-Whitney U test
$k$-means Clustering Analysis

- Tumor grade classification
  - Low-grade vs. High-grade

- Multivariate analysis using $D_m$, $\alpha$, and $\beta$

- Partition
  - $n$ observations $\rightarrow (D_m, \alpha, \beta)$ estimates from 54 patients.
  - into $k = 2$ distinct groups $\rightarrow$ low-grade and high-grade so that observations within a group are similar.
3D Scatter Plots

Mean CTRW parameter values (using gold standard)

$k$-means clustering analysis (blind analysis)

\[ \beta \]

\[ \alpha \]

\[ D_m \]
Performance Analysis

- Analysis was performed
  - by using the tumor differentiation results from the $k$-means clustering
  - by using the histopathology as a reference.

<table>
<thead>
<tr>
<th></th>
<th>Monoexponential (ADC)</th>
<th>CTRW ($D_m$, $\alpha$, $\beta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.93</td>
<td>0.87</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.54</td>
<td>0.83</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.75</td>
<td>0.85</td>
</tr>
</tbody>
</table>
Conclusion

• CTRW parameters can be significantly different between the low-grade and high-grade pediatric brain tumors.

• The combination of CTRW parameters produced better accuracy and specificity than the ADC values obtained from the monoexponential model.

• The CTRW model can provide quantitative imaging markers to improve diagnosis of pediatric brain tumors.
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