AUTOMATED PROCESSING PIPELINE FOR TEXTURE ANALYSIS OF CHILDHOOD BRAIN TUMOURS BASED ON MULTIMODAL MAGNETIC RESONANCE IMAGING

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ABSTRACT

Primary brain tumours are the most common solid tumours found in children and are an important cause of morbidity and mortality. Magnetic resonance imaging (MRI) is commonly used for non-invasive early-detection, diagnosis, delineation of tumours for treatment planning and assessment of post treatment changes. Different MRI modalities provide complementary contrast of tumour tissues, which can have varying degrees of heterogeneity and diffusivity in different tumour types. A variety of texture analysis methods have been shown to reveal tumour histological types. It is hypothesized that textural features, based on conventional and diffusion MRI modalities, would differentiate the characteristics of tumours. Tumour extraction is also a significant procedure needed to obtain a true tumour region. Semi-automated segmentation methods were applied, in comparison with the gold standard of manual segmentation. Manual segmentation is considered as a gold standard, but it is labour intensive and dependent on an operator’s expertise. Fully automatic segmentation approaches generally perform unsatisfactorily on MR-based images, because of the complexity of structures, low contrast, high noise levels or artefacts around the tumour region [3]. To address these limitations, semi-automated segmentation methods, incorporating a priori knowledge and user-guidance, have been evaluated in comparison with manual segmentation.

KEY WORDS

Brain tumours, semi-automated segmentation, diffusion and conventional MRI, texture analysis, image processing

1. Introduction

Conventional MRI is an essential part of clinical diagnosis for childhood brain tumours. It offers structural imaging of anatomical elements, which appear differently in T1-weighted (T1w), T2-weighted (T2w) and contrast-enhanced images. For example, primary malignant brain tumours appear as hypointense on T1w images and as hyperintense on T2w images. Despite its high resolution and contrast between soft tissues, conventional MRI provides insufficient functional information. Diffusion MRI, a functional imaging technique, allows examination of tissue microstructure and provides complementary structural visualization. It has been used to evaluate information on invasion, infiltration and delineation of brain tumours. For example, the apparent diffusion coefficient (ADC) has been utilised as a biomarker in various neurological studies, including the classification of brain tumours [1] and evaluation of brain tumour infiltration [2]. Diffusion tensor imaging (DTI) is widely used to study the neural tracts in the brain and various neuro-pathological diseases. Its sensitivity to subtle disturbances in white-matter tracts, due to tumour infiltration and invasion [3], could possibly provide useful information for tumour classification.

Segmentation is a primary step in brain tumour image-based classification, in order to extract tumour regions from healthy tissue. Three main approaches exist; manual, semi-automated and fully automated segmentation. Manual segmentation is considered as a gold standard, but it is labour intensive and dependent on an operator’s expertise. Fully automatic segmentation approaches generally perform unsatisfactorily on MR-based images, because of the complexity of structures, low contrast, high noise levels or artefacts around the tumour region [4]. To address these limitations, semi-automated segmentation methods, incorporating a priori knowledge and user-guidance, have been evaluated in comparison with manual segmentation.
Texture analysis provides quantification of the surface structure of an object, “for example the gray-level patterns, pixel interrelationships and the spectral properties of an image” [5]. Texture analysis has been used to differentiate heterogeneous regions of brain tumours and also identify pathological tissues [6]. The common textural features found in the literature of MR image analysis are histogram, absolute gradient, run-length, co-occurrence and wavelet energy based features. This work combines the most commonly used sets of textural features, derived from methods mentioned above, and applies them to a multi-centre multimodal MR imaging dataset of pediatric brain tumours.

2. Material and Methods

2.1 Subjects

Two types of brain tumours have been considered: medulloblastoma (MB) and pilocytic astrocytoma (PA). These cases were obtained from the Children’s Cancer and Leukaemia Group (CCLG) database. Apparent Diffusion Coefficient (ADC) map reconstructed from Diffusion Weighted Imaging (DWI), Mean Diffusivity (MD) and Fractional Anisotropy (FA) map derived from Diffusion Tensor Imaging (DTI) and conventional MR images were acquired from four centres using a 1.5T GE, 1.5T Siemens, 1.5T and 3T Phillips scanners, following a common protocol defined by the CCLG Functional Imaging Group. The number of medulloblastoma and pilocytic astrocytoma cases used in this study is shown in Table 1.

Table 1 Number of cases in each MR image types

<table>
<thead>
<tr>
<th>Image type</th>
<th>MB</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWI (ADC)</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>DTI (MD)</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>DTI (FA)</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>T2w</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>T2w-FLAIR</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>T1w-post contrast</td>
<td>23</td>
<td>22</td>
</tr>
</tbody>
</table>

2.2 Data Pre-Processing

Figure 1 shows the flowchart of the processing pipeline. The standard neuro-image processing approach was adopted from FMRIIB software library (FSL) [7]-[8]:

1) Eddy current correction: distortions due to eddy currents in diffusion MR images are removed. The fieldmap unwrapping process was not included because the fieldmaps were not available in the database. However, there was no vividly large distortion in the diffusion MR images; it was assumed that the images were qualified for the study.

2) Reconstruction of diffusion MR images: Apparent Diffusion Coefficient (ADC) maps are reconstructed from the diffusion weighted images (DWI). An ADC volume is computed by collecting images with at least two different b-values, b0 and b1, as shown in equation (1).

\[ ADC = \frac{\ln S_1}{S_0} / [b_1 - b_0] \] (1)

Where \( S_1 \) and \( S_0 \) is the signal intensity with gradient having \( b_1 \) s/mm\(^2\) and without the diffusion weighting having \( b_0 = 0 \) respectively.

3) Reconstruction of DTI requires at least 6 scanning directions to form a diffusion tensor matrix. The direction and length of diffusion in DTI tensor ellipsoid is annotated by eigenvectors and eigenvalues (\( \lambda \)). Three main eigenvalues, named \( \lambda_1, \lambda_2 \) and \( \lambda_3 \), measures diffusivity along each of the three primary axes of the ellipsoid. Fractional Anisotropy (FA) and Mean Diffusivity (MD) can be calculated from these eigenvalues as follows:

\[ FA = \sqrt{\frac{\frac{1}{2} \left( \lambda_1 - \lambda_2 \right)^2 + \left( \lambda_2 - \lambda_3 \right)^2 + \left( \lambda_3 - \lambda_1 \right)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \] (2)

\[ MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \] (3)

4) Brain tissue extraction: using BET [9] to remove non-brain tissue from the whole head to enhance intermodal registration performance.

5) Registration: the FLIRT [10] is a robust multimodal MRI linear registration tool. Registering two images from the same subject, 6 DOF is used for the transformation due to a rotation and translation of the head during scanning. Based on visual inspection, normalized mutual information is selected. On T2w images, tumours appear hyperintense and show vivid boundary. T2w images are more appropriate to be segmented than other MR modality. In order to obtain the same tumour region from multimodal MR images, for each case, other MR image types are registered onto T2w images by using FLIRT tool.

6) Intensity normalization: because data were obtained from different scanners and with some varying parameter settings, which may contribute to different intensity range, the intensity of the whole image are normalized by using a linear histogram stretching technique.

Brain tissues of conventional and diffusion MR images are normalized to the standard scales \( [i_{max} i_{min}] = [0.4095] \) and \( [0,1] \) respectively. The minimum and maximum robust intensity, is equivalent to 2% and 98% percentiles of the overall image intensity range, are used as threshold values. Pixels having intensity less than the robust minimum are set to 0, while pixels having intensity greater than the robust maximum is set to the maximum standard scale. Then, the rest of the pixels, having intensity greater than the robust minimum value, are scaled to:

\[ K(i - i_{min})/(i_{max} - i_{min}) \] (4)

Where \( K \) is the standard maximum intensity value, \( i \) is the original intensity.
2.3 Tumour Segmentation

One of the most simple image semi-automated segmentation methods is thresholding, where pixels are separated in different classes, depending on their gray-level. This technique still requires post processing, such as edge linking, and is not suitable for segmenting MR images of tumours, which are often heterogeneous in structure. Clustering techniques, such as the K-means method, are used to classify pixels in an extracted feature space. Nevertheless, the use of variance to measure the cluster scatter and its sensitivity to noise may not be ideal for MR images [11]. Watershed segmentation is a region-based technique. The approach uses image morphology to achieve the segmentations. It produces closed and adjacent contours, however it often presents with the problem of over-segmentation. A region merging technique has been proposed to resolve this issue; however region merging might lead to under-segmentation [12]. The gradient vector flow (GVF) deformable model or GVF snake method, as proposed by Chenyang [13], is one of the popular methods used in the field of medical image segmentation. The method relies on initial seeds, inserted by a user, as a directive boundary. The output boundary is reconstructed by initially computing an edge map of an input image and progressing contour toward a force balance condition; balance an internal force (preventing stretching and bending of contour) and external force (pull the snake towards the desired contour) to form edges. The GVF snake method is often preferred to traditional snake methods, because of its insensitivity to initialization conditions and its ability to move into concave boundary regions [14]. However, due to the structural complexity observed on MR images of brain tumours, even the initial contour of a GVF can progress towards the wrong boundary. It is usually preferable to place primary seeds close to the true boundary of the tumour region; however this could be time consuming. The multiscale normalized cut (multiscale ncut) method, as introduced by Cour et al. [15], is a recently developed graph-based segmentation technique, which uses the similarity and dissimilarity of pixels to partition an image into a “different set of patterns” [15]. Multiscale ncut adopts the normalized cut graph method [16], as a partitioning framework and enhances computational efficiency and accuracy. It computes the propagation of local cues (group of vertices formed by intensity similarity and intervening contours) across multiple ranges of spatial connections, and offers the advantage of detecting coherent regions with a faint boundary. We adopted the multiscale ncut and the GVF snake methods for tumour segmentation.

In each case, tumour images were extracted from T2w images and used as templates for segmenting other registered image types. We applied the semi-automated segmentation methods, based on a combination of the multiscale ncut and the GVF snake method, as described by the workflow discussed below:

1) We select slices displaying tumour image and crop these images to speed up processing time.
2) For each slice, we segment the tumour by using multiscale ncut method. We applied the GVF method when contour refinement is required by using the tumour boundary, which is obtained from the multiscale ncut, as initial seeds.
3) Apply the obtained ROIs to extract tumour regions of other registered images of the same case.

The semi-automated segmentation based on T2w images was evaluated against manual segmentation by calculating the percentage of overlapping volume as follows:

\[ \text{Ratio1} = \frac{(V_1 \cap V_2)}{V_1} \]  \hspace{1cm} (5)
\[ \text{Ratio2} = \frac{(V_1 \cap V_2)}{V_2} \]  \hspace{1cm} (6)
\[ \text{Dice Coefficient} = \frac{2(V_1 \cap V_2)}{(V_1 + V_2)} \]  \hspace{1cm} (7)

Where \( V_1 \) is the semi-automatic segmented volume.
\( V_2 \) is the manual segmented volume.

2.4 Texture Analysis

Histogram and absolute gradient based texture analysis provide first-order statistical features, such as mean, variance, skewness and kurtosis. The run-length and co-occurrence method provide second-order statistical features. Galloway [17] first proposed gray level run-
length matrices (GLRLMs), which are constructed by systematically considering a number of runs on each gray-level in four main directions (see the Appendix). However, its application was not recommended by Weszka et al. [18] and Conners et al. [19] because of its inefficiency compared to other traditional features, such as co-occurrence and power spectrum features. Xiaoou [20] described a new set of GLRLMs, which improved classification accuracy over the traditional method. Haralick [21] introduced the gray-level co-occurrence matrices (GLCMs), which are constructed by considering the relationship between pixel pairs across the whole intensity range and tabulating the frequency of gray-levels. Wavelet transforms, which analyse the frequency content of an image at different scales, are often found in the medical image analysis literature, including image texture analysis software, such as the MaZda tool [22]. Wavelet transform-based techniques provide additional textural properties that may not be captured in RLMs and GLCMs.

A total of 141 textural parameters obtained from histogram, absolute gradient, run-length matrices, co-occurrence matrices and wavelet energy were extracted from segmented tumour images, based conventional and diffusion MRI. Definitions of textural features, used in this study, are described in the Appendix. In each study case; tumour images were extracted from about 2-17 sample slices, depending on the tumour size. An average of all textural features across slices was used as representative of each case. Then, each feature was scaled to the same interval range of [0, 1].

2.5 Feature Selection

Due to a large number of features generated from texture analysis and a low number of samples, these features were reduced to avoid overfitting and reduce processing time during the classification process. To select a subset of the textural features obtained from the previous step, we applied a sure independence screening (SIS) [23] method to identify the textural features having the largest discriminant indices. Given $a$ classes and $b$ features for each class, we calculate mean of each feature $1$ to $b$ in each class $1$ to $a$, and compute the mean differences of class 1 against the overall mean of the other classes ($2$ to $a$) for each feature. After accumulating the mean differences from class 1 to $a$, features are ranked according to the accumulated mean differences; a larger difference corresponds to a higher likelihood of a feature being selected.

2.6 Classification

A support vector machine is a systematic classification method and widely used in various applications, including medical image analysis. The LIBSVM [24] is one of the popular tools, which we employed for our classification. To compare the classification accuracy among MR modalities, we applied the RBF kernel function with the tuning parameters ($C = 1$ and $\gamma = 1/\text{number of feature}$) for all the modalities. The classification accuracy was evaluated by using a leave-one-out technique.

3. Results and Discussion

3.1 Tumour Segmentation

Figure 2 shows segmented pilocytic astrocytoma tumour images of diffusion and conventional MR images. Boundary of ROIs were considerably well delineated on T2w and other registered images.

The T2w image-based segmentation and the overlapping volume ratios were evaluated (see Table 2). The overlapping volume ratios show that the semi-automatic and manual segmented volumes are relatively similar. Based on the computer with the specification of CPU intel Core i5 @ 2.4 GHz and RAM 6 GB, the estimated processing time for semi-automatic segmentation is about 130±10 minutes, while the manual segmentation process is approximately 140±10 minutes. Although the semi-automatic segmentation method does not provide obvious advantages of processing time, this technique does not require an operator’s expertise and training. So it is less labouring intensive. Because the tumour structures vary from one slice to another, the segmentation procedure has been conducted based on slice by slice basis to achieve satisfactory result. In this study, the number of slices was used depending on the tumour size. It is possible that the number of slice to use for each case could be reduced to improve the processing time but still remain the useful information.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Segmentation validation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ratio 1</td>
</tr>
<tr>
<td>Mean</td>
<td>93%</td>
</tr>
<tr>
<td>Std</td>
<td>5.1</td>
</tr>
</tbody>
</table>

3.2 Texture Analysis and Feature Selection

The textural features are derived from heterogeneous tissues, composing of cystic and solid tumour, for example. The four features having the largest discriminant
The four top-ranked features of each MR modality

<table>
<thead>
<tr>
<th>Feature 1</th>
<th>Feature 2</th>
<th>Feature 3</th>
<th>Feature 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC 45°</td>
<td>R - LRE 135°</td>
<td>R - LRE 90°</td>
<td>R - LRE 0°</td>
</tr>
<tr>
<td>MD 45°</td>
<td>R - SRE 0°</td>
<td>R - SRE 135°</td>
<td>R - SRE 90°</td>
</tr>
<tr>
<td>FA 0°</td>
<td>C - disi 0°</td>
<td>C - entro 45°</td>
<td>C - entro 135°</td>
</tr>
<tr>
<td>T2w 0°</td>
<td>R - RP 45°</td>
<td>R - LRE 135°</td>
<td>R - LRE 90°</td>
</tr>
<tr>
<td>T2w-FLAIR 0°</td>
<td>R - LRE 45°</td>
<td>R - LRE 90°</td>
<td>R - LRE 135°</td>
</tr>
<tr>
<td>T1w-post Variance</td>
<td>C - sosvh 135°</td>
<td>R - SRHGE 135°</td>
<td>R - SRHGE 90°</td>
</tr>
</tbody>
</table>

3.3 Classification

From the biological perspective, medulloblastoma is a highly malignant primary brain tumour that is commonly found in the cerebellum or posterior fossa. Medulloblastomas originate from embryonal cells, while pilocytic astrocytoma is the most common type of low grade glioma. These two tumours originate from different cells and their textural features can be better separated by diffusion MR images than conventional MR images (see Figure 4). The ADC maps provide relatively better prediction rate than DTI images and other modalities.
Several processes contribute to the classification performance such as the tumour segmentation, the feature selection and the classification. Alteration of ROI coverage varies textural features and the characterization result. For example, including large cystic and normal tissues, having likely less informative textural features about histological tumour type, could reduce the overall signal-to-noise ratio. The location and scanning period is another factor because the tumours used in this study are found not only from cerebellar tissues but also supratentorial region, and they can also be pre- or post-treatment dataset. The manipulation of data from multiple centres, where data might have been recorded under different parameter settings (such as magnetic strength \(B_0\), b-value and number of scanning directions for DTI images) although an effort was made for a common protocol adherence, is essential to acquire sufficient number of study and require intensity standardisation before texture analysis. In addition, the limited number of dataset; not all MR modalities are available for each case, contribute to the partial cross validation of multimodalities, particularly for DWI against DTI. However, this study provides the promising experimental results for the characterization of paediatric brain tumours based on each of MR modality.

### 4. Conclusion and Future Work

An automated processing pipeline for the characterization of childhood brain tumours, based on textural analysis, was implemented. The pipeline consists of various steps including standard neuro-image processing, tumour segmentation (and its evaluation), texture analysis, feature selection, classification (and its evaluation), respectively. Amongst all data from the various MR modalities obtained from multiple centres, textural features derived from diffusion MR images were the most promising for differentiating medulloblastomas and pilocytic astrocytomas. Ependymoma is another common histological tumour found in children. Future work will include the study of identifying texture analysis based features from MR multimodal images of ependymomas. These will be evaluated by a 3-way classification between datasets of childhood medulloblastomas, pilocytic astrocytomas and ependymomas. In addition, an application of textural features derived from the multi-scale wavelets will be investigated.

### 5. Appendix

#### 5.1 First Order Statistical based Features

Let \(x_i\) be the gray-level intensity, \(\bar{x}\) be the average of gray-level within a ROI and \(n_p\) is the number of pixels within the ROI.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>[ \frac{1}{n_p} \sum_{i=1}^{n_p} x_i ]</td>
</tr>
<tr>
<td>Variance</td>
<td>[ \frac{1}{n_p} \sum_{i=1}^{n_p} (x_i - \bar{x})^2 ]</td>
</tr>
<tr>
<td>Skewness</td>
<td>[ \frac{1}{n_p} \sum_{i=1}^{n_p} (x_i - \bar{x})^3 \left( \frac{1}{n_p} \sum_{i=1}^{n_p} (x_i - \bar{x})^2 \right)^{3/2} ]</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>[ \frac{1}{n_p} \sum_{i=1}^{n_p} (x_i - \bar{x})^4 \left( \frac{1}{n_p} \sum_{i=1}^{n_p} (x_i - \bar{x})^2 \right)^2 - 3 ]</td>
</tr>
</tbody>
</table>

#### 5.2 Absolute Gradient based Feature

Absolute gradient measures an intensity change across each pixel, for example, the absolute gradient at pixel \(m\), is calculated as follows: boundary pixels are discarded; textural parameters derived from the absolute gradient are the same as the same histogram. The example of an image has pixels labelled in letters from A to Y (see Figure 5).

For 3 neighboring pixels: \(\sqrt{(H - R)^2 + (N - L)^2}\)
For 5 neighboring pixels: \(\sqrt{(C - W)^2 + (O - K)^2}\)

#### 5.3 Gray-Level Run-Length Matrix based Features

For a given image, a run-length matrix \(p(i, j)\) is defined as the number of runs with pixels of gray-level \(i\) and run length \(j\). The run-length matrix \(p(i, j)\) are obtained from four directions of 0°, 45°, 90° and 135°. Let \(N_g\) be the number of gray levels and \(N_r\) be the maximum run length. Four matrices derived from the GLRLM \(p(i, j)\) are as follows:

1. **Gray level run-length pixel number matrix:** \(p_{\text{p}}(i, j) = p(i, j) \cdot j\)
2. **Gray-level run-number vector:** \(p_{\text{g}}(i) = \sum_{j=1}^{N_r} p(i, j)\)
3. **Run-length run-number vector:** \(p_{\text{r}}(j) = \sum_{i=1}^{N_g} p(i, j)\)
4. **Gray-level run-length-one vector:** \(p_{\text{e}}(i) = p(i, 1)\)

\(n_r\) is the total number of runs and \(n_p\) is the number of pixels in the image

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>G</td>
<td>H</td>
<td>I</td>
<td>J</td>
</tr>
<tr>
<td>K</td>
<td>L</td>
<td>M</td>
<td>N</td>
<td>O</td>
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<tr>
<td>P</td>
<td>Q</td>
<td>R</td>
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</tr>
<tr>
<td>U</td>
<td>V</td>
<td>W</td>
<td>X</td>
<td>Y</td>
</tr>
</tbody>
</table>

Figure 5: An example image
5.4 Gray-Level Co-Occurrence Matrix based Features

For a given image, the GLCM is defined as follows:

- \( p(i,j) \) is the \((i,j)\)th entry in a normalised gray-tone spatial dependence matrix.
- \( p_x(i) \) is the \(i\)th entry in the marginal probability matrix obtained by summing the rows of \( p(i,j) \).
- \( p_y(j) \) is the \(j\)th entry in the marginal probability matrix obtained by summing the columns of \( p(i,j) \).

\[
\begin{align*}
p_{x+y}(k) &= \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j), \quad k = 2, 3, ..., 2N_g - 1 \\
p_{x-y}(k) &= \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j), \quad k = 0, 1, ..., N_g - 1 \\
N_g &\text{ is the number of distinct gray levels in the quantized image.}
\end{align*}
\]

\( \mu_x, \mu_y, \sigma_x, \text{ and } \sigma_y \) are the means and standard deviations of \( p_x \) and \( p_y \).

A GLCM is computed for discrete distance and in each direction of \(0^\circ, 45^\circ, 90^\circ\) and \(135^\circ\). The textural features [21], [25], [27] are defined as follows.
5.5 Wavelet Energy

For a two-dimensional wavelet decomposition, an image is decomposed into N level wavelet decomposition by using the symlet4 wavelet [26], producing four different coefficient row vectors: approximation coefficients, horizontal detail coefficients, vertical detail coefficients and diagonal detail coefficients. Four types of wavelet energy are obtained from each of these row vectors.

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