AUTOMATED BRAIN LESION CLASSIFICATION METHOD FOR DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGES

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AUTOMATED BRAIN LESION CLASSIFICATION METHOD FOR DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGES

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Specially dedicated to:

My parents for their priceless supports and generous prayers.

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ABSTRACT

Diffusion-weighted magnetic resonance imaging plays an increasingly important role in the diagnosis of several brain diseases by providing detailed information regarding lesion based on the diffusion of water molecules in brain tissue. Conventionally, the differential diagnosis of brain lesions is performed visually by professional neuroradiologists during a highly subjective, time-consuming process. Within this context, this study proposes a new technique for automatically detecting and classifying major brain lesions of four types: acute stroke, chronic stroke, tumor and necrosis. An analytical framework of the brain lesions consists of four stages which are pre-processing, segmentation, features extraction and classification. For segmentation process, adaptive thresholding, gray level co-occurrence matrix, region splitting and merging, semi-automatic region growing, automatic region growing and fuzzy C-means were proposed to segment the lesion region. The algorithm performance was then evaluated using Jaccard index, Dice index, and both false positive and false negative rates. Results demonstrated that automatic region growing offered the best performance for lesion segmentation while acute stroke gave the highest rate with 0.838 Dice index. Next, statistical features were extracted from the region of interest and fed into the rule-based classifier designed to the best suit to the lesion’s features. The performance of the classifier was evaluated based on overall accuracy, sensitivity and specificity. The overall accuracy for the classification was 81.3%. In conclusion, the proposed automated brain lesion classification method has the potential to diagnose and classify major brain lesions.

ABSTRAK

Pengimejan magnetik resonan pemberat-resapan memainkan peranan yang semakin penting dalam mendiagnosis beberapa penyakit otak dengan memberikan maklumat terperinci berkenaan perbezaan jelas lesi ke atas resapan molekul air di dalam tisu otak. Secara konvensional, perbezaan diagnosis lesi otak dilaksanakan secara visual oleh pakar neuroradiologi profesional dengan proses subjektif serta memakan masa yang lama. Dalam konteks ini, kajian ini mengusulkan teknik terbaru untuk mengesan dan mengkelaskan lesi otak utama yang terdiri daripada empat jenis: strok akut, strok kronik, tumor dan nekrosis. Analisis rangka kerja bagi lesi otak terdiri daripada empat peringkat iaitu pra-pemproses, pengsegmenan, pengekstrakan ciri dan pengkelasan. Untuk proses pengsegmenan, teknik ambang adaptif, matrik *gray level co-occurrence*, rantau pemisahan dan penggabungan, rantau berkembang separa automatik, rantau berkembang automatik dan *fuzzy C-means* dicadangkan untuk mensegmen rantau lesi. Prestasi algoritma kemudiannya dinilai menggunakan indeks *Jaccard*, indeks *Dice*, dan kedua-dua kadar palsu positif dan negatif. Keputusan menunjukkan teknik rantau berkembang automatik memberikan prestasi terbaik untuk pengsegmenan lesi sementara strok akut memberikan kadar indeks *Dice* tertinggi iaitu 0.838. Kemudian, ciri-ciri statistik diekstrak daripada rantau tarikan dan diinputkan kepada pengelas berasaskan peraturan yang telah direka untuk disesuaikan dengan ciri lesi. Prestasi pengelas dinilai berdasarkan kejituan keseluruhan, kepekaan dan kekhususan. Kejituan keseluruhan untuk pengkelasan adalah 81.3%. Sebagai kesimpulannya, teknik klasifikasi automatan lesi otak yang dicadangkan mempunyai potensi untuk mendiagnosis dan mengklasifikasi lesi otak utama.

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LIST OF ABBREVIATIONS

ADC	-	Apparent Diffusion Coefficient
ANFIS	-	Adaptive Network Based Fuzzy Inference System
AO	-	Area Overlap
AS	-	Acute Stroke
BG	-	Background Image
CAD	-	Computer Aided Detection and Diagnosis
CS	-	Chronic Stroke
CSF	-	Cerebral Spinal Fluid
CT	-	Computed Tomography
DICOM	-	Digital Imaging and Communications in Medicine
DWI	-	Diffusion-Weighted Imaging
FCM	-	Fuzzy C-Means
FDA	-	Food and Drug Administration
FNR	-	Fast Negative Rate
FPR	-	Fast Positive Rate
GLCM	-	Gray Level Co-Occurrence Matrix
IBSR	-	Internet Brain Segmentation Repository
kNN	-	k-Nearest Neighbors
k-SOM	-	Kohonen Self-Organizing Map
MA	-	Misclassified Error
MAPE	-	Mean Absolute Percentage Error
MLP	-	Multi-Layer Perceptron
MRI	-	Magnetic Resonance Imaging
MS	-	Mean-Shift

NC	-	Necrosis
PD	-	Proton Density
PET	-	Positron Emitted Tomography
RBF	-	Radial Basis Function
ROI	-	Region of Interest
S	-	Sensitivity
SNR	-	Signal to Noise Ratio
Sp	-	Specificity
SPM	-	Statistical Parametric Mapping
ST	-	Solid Tumor
SVM	-	Support Vector Machine
TE	-	Time Echo
TN	-	True Negative
TP	-	True Positive
TR	-	Time Repetition
WHO	-	World Health Organization
WM/GM	-	White Matter/Gray Matter

LIST OF SYMBOLS

B_0	-	Magnetic Field Strength
b	-	Diffusion Gradient
D	-	Diffusion Coefficient
E	-	Energy
eV	-	Electron Volts
Hz	-	Hertz
T	-	Tesla
r_{err}	-	Absolute Error Ratio
γ	-	Gamma
μ	-	Mean
σ	-	Standard Deviation

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CHAPTER 1

INTRODUCTION

1.1 Introduction

Diffusion-weighted magnetic resonance imaging (DW-MRI or DWI) is increasingly having an important role in the diagnosis of many brain diseases. This medical imaging technique provides higher pathologic or lesion contrast based on diffusion of water molecules in brain tissues, compared to conventional MRI. This unique information of diffusion properties plays a key role in evaluating multiple neurologic diseases, especially for stroke detection (Mukherji *et al*., 2002, Holdsworth and Bammer, 2008). It also gives additional information for cerebral diseases such as stages in neoplasm (cancer, tumor, and necrosis), infections, and others.

DWI is considered as the most sensitive technique in detecting acute infarction and is useful in giving details of the component of brain lesions (Mukherji *et al*., 2002). In DWI, image intensity and contrast only depend on the strength of diffusivity of tissue. Tissue with altered diffusion rates may appear with either hyperintense or hypointense on a pixel basis, which is absent in healthy tissue. Such information forms vital image characteristics that may lead to the classification of several brain-related diseases.

Automatic brain lesion detection and classification is necessary to implement successful therapy and treatment planning. Computer-aided detection and diagnosis system (CAD) has become a major research subject in diagnostic radiology to assist visual interpretation of the medical images. Medical imaging techniques have helped radiologists in diagnosing the brain lesions (Ain *et al*., 2010). With CAD, radiologists used the computer output as a second opinion in making the final decisions (Doi, 2007, El-Dahshan *et al*., 2014). Novel image processing techniques are allowing CAD to spread and become an indispensable tool for early diagnosis and image guided therapy.

Recently, many different techniques were used for detecting and classifying the brain lesions. Various image processing techniques such as image segmentation, feature extraction, feature selection and classification are essential in developing a brain computer aided detection methods and for the detection of various lesions in medical images. As brain imaging techniques continually evolve, new and more powerful image processing techniques are required in the CAD system to meet the challenges imposed by modern medical imaging (Ruiz-Alzola *et al*., 2013). This research work proposed an automatic lesion detection and classification system for DWI. Image analysis techniques are implemented in each stage of analysis, which aim to detect and classify the lesions.

1.2 Problem Statement

Early and accurate diagnosis of brain lesion is vital for determining accurate treatment and prognosis. However, the diagnosis is a very challenging task and can only be performed by specialists in neuroradiology. There are at least two specialists required to examine and confirm of each medical report on imaging investigations (El-Dahshan *et al*., 2014). Any difficulty may necessitate invasive tests such as biopsy and surgery. Currently, the standard lesion pathological classification is based on histological examination of tissue samples through biopsy (Barnathan *et al*., 2008). Therefore, radiologists are continuously seeking for greater diagnosis accuracy by modern medical imaging system. According to quantitative analysis of CAD, it may aid radiologists in the interpretation of the medical images. Recent studies showed that CAD can help to improve diagnostic accuracy of radiologists, lighten their increasing workload, reduce misinterpretation due to fatigue or overlooked and improve inter- and intra-reader variability (Porz *et al*., 2014, El-Dahshan *et al*., 2014). The development of automatic and accurate CAD in characterizing brain lesions are essential and it still remains an open problem (El-Dahshan *et al*., 2014) .

Lesion detection, segmentation or separation of specific ROI is an essential process for diagnosis. Computer aided surgery also requires prior analysis of lesion area inside the brain (Ain *et al*., 2010). This process is a challenging process due to the complexity and large variations in the anatomical structures of human brain tissues, the variety of the possible shapes, locations and intensities of various types of lesions. For example, brain tumor segmentations in conventional MRI performed by radiologists have approximately 14–22 % differences (Barnathan *et al*., 2008). The current manual segmentation or semi-automated frameworks have impeded the system from becoming fully automated, objective and efficient. On the other hand, computerized segmentation allows the extraction of certain regions to provide further information during other stages of quantitative assessment. Accurate segmentation is the basis for calculating important features of brain lesion such as size, density, compactness, and volume of the lesion. However, the computerized method is still evolving and far from being perfect because of the instability of the system in achieving autonomous property (Hum *et al*., 2014).

A large number of approaches have been proposed by various researchers to deal with MRI images. Commonly, the target is the detection of only one disease on a specific organ via conventional MRI (Kobatake, 2007, Fujita *et al.*, 2010). Well-known and widely used techniques are the unsupervised clustering algorithm such as fuzzy C-means (FCM) and the supervised method such as the neural network classifier (Ringenberg *et al*., 2014, Jiang *et al*., 2013, Bai *et al*., 2013). The main drawback of the supervised techniques and neural network is that it requires training each time a new data is arrived and complex computations (Ain *et al*., 2010). The commonly used unsupervised segmentation techniques can be classified into two-broad categories: (1) region-based techniques that look for the regions satisfying a given homogeneity criteria and (2) edge-based segmentation techniques that look for edges in partition regions with different characteristics (Bankman, 2008).

For the region-based segmentation category, adaptive thresholding, clustering and region growing are well known methods for segmentation (Pratt, 2007, Sonka *et al*., 2008). Inappropriate segmentation methods will produce unwanted noisy regions that will affect the subsequent processes of the system. Moreover, high sensitivity of homogeneity change in the soft tissue region surrounding the lesion may deteriorate the result (Hum *et al*., 2014). Novel segmentation and classification techniques should be able to overcome these limitations as well as be general enough to address a large class of tissue types, thus contributing to a faster performance and higher accuracy in a fully automatic system.

For instance, acute stroke and solid tumor lesions may be seen as high intensity, while chronic stroke and necrosis appear as low intensity. Visually, there might be intensity overlapping in these lesions (Koh and Padhani, 2014). The results from the quantitative analysis may be performed to detect and classify the lesions.

1.3 Objectives

From the mentioned problem statements, the specific objectives of this research are:

1. To examine image analysis techniques for DWI brain lesion detection, segmentation and classification.
2. To evaluate the performances of the analysis techniques based on DWI for lesion detection and classification.
3. To classify types of brain lesion based on DWI images.

Thus, the aim of this thesis is to provide a solution to the mentioned problems in detecting, segmenting and classifying of lesions specifically designed for the lesions from DWI images. The hypothesis of this thesis is that it is feasible to automatically detect and segment the hyperintense and hypointense lesions in DWI by using image processing and analysis techniques. Furthermore, a brain classification system can be developed based on the lesion's features in DWI.

1.4 Scope of Work

This research work is restricted to the following scopes:

1. This research analyses brain lesions based on medical image data on DWI. Acute stroke, chronic stroke, tumor and necrosis are the four types of brain lesion focused in this study. The DWI samples are using diffusion parameter of b1000. The diffusion coefficient of b0, b500 and apparent diffusion coefficient (ADC) image as well as conventional MRI such as T_1, T_2 and proton density images are not included in the analysis.
2. The main focus of this research concentrates on the automatic segmentation process of DWI lesions to accurately perform the region of interest (ROI). The techniques used are adaptive thresholding, gray level co-occurrence matrix (GLCM), region splitting and merging, semi-automatic and automatic region growing and fuzzy C-means (FCM) clustering. The best segmentation technique is identified based on similarity indices which are Jaccard and Dice indices, and error rates which are false positive rate (FPR) for over-segmentation error and false negative rate (FNR) for under-segmentation error.
3. From the ROI, features are extracted and used as input to a classifier. Determination of the type of classifier to be used is not the main focus of this study. Hence, rule-based classifier is used due to its simplicity to design a multi-class classification. The effectiveness is verified based on overall accuracy, sensitivity and specificity.

4. The analysis and simulation are done by using Matlab software. This research does not include any clinical representation, patient history, histological findings or present solution of the lesion.
5. The validation of this research is limited to small amount of samples. Therefore, thorough analysis for field testing are still needed in order to implement the system in real applications.

1.5 Proposed System Design

In order to complete this research, there are several steps that need to be done. The proposed analysis framework consists of several stages as shown in Figure 1.1.

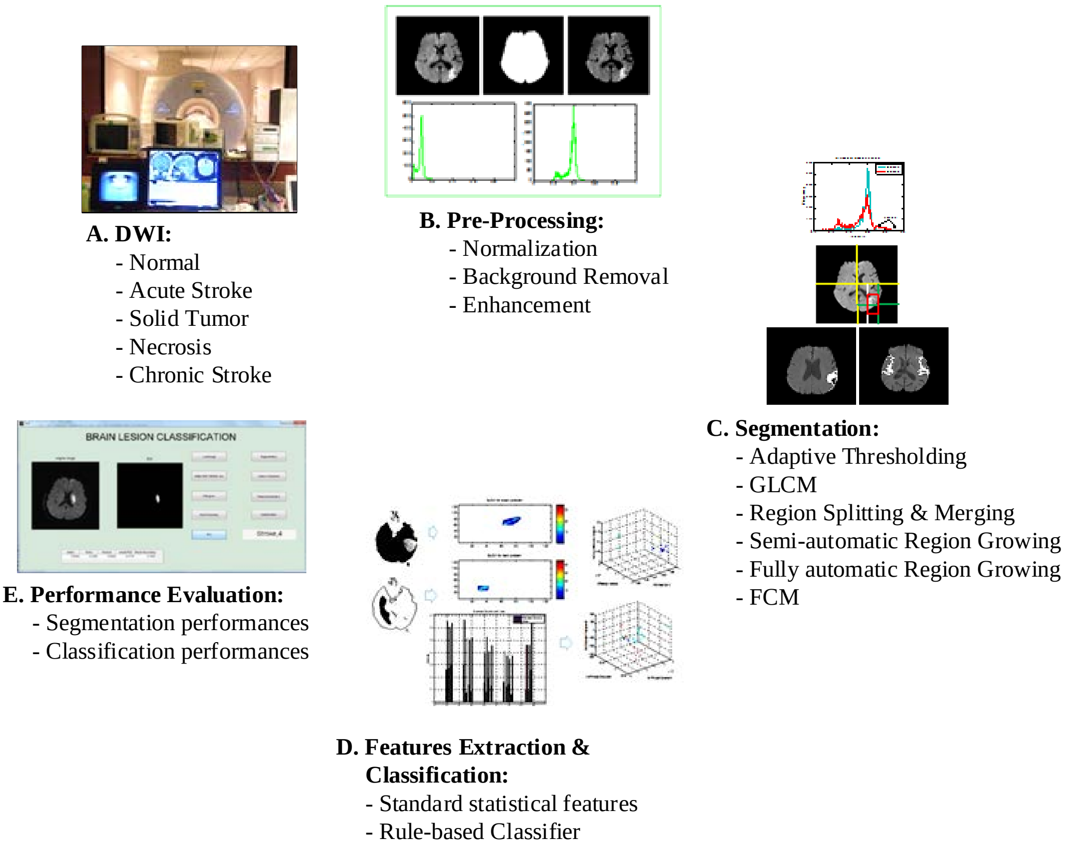

Figure 1.1 Proposed system design

Following is the list of major tasks that need to be carried out in this research:

1. DWI image acquisition: This research uses clinical DWI on real patients which is acquired at two different institutions which are Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and Kuala Lumpur General Hospital (GHKL) using 1.5 Tesla MRI scanners (Siemens Magnetom Avanto). All samples have been verified and confirmed by neuroradiologists. Images are stored in Digital Imaging and Communications in Medicine (DICOM) format. The acquisition parameters used time echo (TE), 94 ms; time repetition (TR), 3200 ms; pixel resolutions, 256×256; slice thickness, 5 mm; gap between each slice, 6.5 mm; diffusion weighting gradient known as *b* value, 1000 s/mm^2 and total number of slices, 19.
2. Visual inspection and manual reference segmentation: The ROI of brain lesions is determined by experienced neuroradiologists. This data is important as manual reference for performance evaluation for the proposed frameworks.
3. Image pre-processing stage: The original input of the DWI will go through image normalization, background removal and enhancement of the intensity.
4. Image segmentation stage: Several methods are proposed for lesion detection and segmentation. New analysis frameworks based on the available methods are designed to address a large class of lesions. The best segmentation technique is then chosen for lesion classification.
5. Features extraction stage: Basic statistical features are used to separate the lesion features into clusters.
6. Classification stage: Rule-based classifier is developed for classifying of the brain lesions into their types of neurological disorders.
7. Classification performance: Evaluation of the performance for both segmentation and classification techniques to show the efficiency of the proposed method.

1.6 Thesis Contributions

Image analysis techniques for detecting, segmenting and classifying of brain lesions from DWI is developed. This system analysed four types of brain lesion based on DWI. These are acute stroke, solid tumor, chronic stroke and necrosis. Many researchers have studied on this area but they considered only on a specific brain disease and mostly are using conventional MRI. Only few studies have been reported on DWI but currently no researchers are doing detection, separation and classification of multiple brain lesions in DWI.

The major contributions of this thesis are the development of automatic segmentation techniques for brain lesions from DWI images and classification of major brain lesions. The proposed techniques are adaptive thresholding, GLCM, region splitting and merging, semi-automatic region growing, automatic region growing and FCM incorporating with further refinement to correctly segment the lesions and eliminate noises. These techniques are designed to be fully automatic. The performance comparison of the techniques are evaluated based on Jaccard and Dice similarity indices; FPR and FNR to indicate over and under-segmentation errors and the execution processing time of the algorithms. The region from DWI hyperintensity and hypointensity lesions are segmented accurately despite the different lesion size and location in the brain. The advantage of the automatic segmentation is also its fast respond for brain region extraction. It used simpler techniques implemented to DWI.

In classifying the major lesions in DWI, rule-based classifier is designed that can provide enough information of the lesion's features and characteristics. Statistical features that characterize the mean and boundary on each lesion types is implemented. Therefore, multi-class classification is designed and the effectiveness is verified based on the accuracy on classifying of each lesions. Commonly, the existing techniques on DWI target only on a specific disease and only few studies focus on feature analysis and classification of DWI. Up to the time this thesis is written, this is the first time an image analysis and classification method has been used to classify major brain lesions of real clinical DWI scans. The results are convincing, low classification error and comparable sensitivity and specificity to the diagnosis done by neuroradiologists.

The establishment of this technique could be used to help physicians to have clear understanding of the brain lesions. Nevertheless, this is not meant that the role of physicians and neuroradiologists will be taken over by such intelligent systems. Such systems would rather serve as a compliment for clinical validation to neuroradiologists.

1.7 Thesis Outline

This thesis is organized as follows. Chapter 2 is the literature review of brain lesion detection and classification using neuroimaging techniques. Neuroimaging modalities and techniques for lesion detection and classification are reviewed in this chapter. The objective is to show the recent published techniques and state or the art of neuroimaging techniques for the human brain lesions. Computed tomography (CT), magnetic resonance imaging (MRI) and DWI analysis techniques for lesion detection and classification are briefly covered in this review.

In Chapter 3, the proposed methodology is briefly explained. A background study on each processing stage is presented. DWI data collections is discussed in this chapter. Pre-processing stage analysis is included. Segmentation methods such as thresholding, GLCM, region splitting and merging and region growing and FCM are exploit to develop new analysis frameworks that meet DWI intensity criteria. The proposed segmentation techniques are designed to be fully automatic. Methods for features extraction and classification are described in details to classify four types of lesions. The theory of the performance analysis and evaluation are also included and describe briefly in this chapter.

Chapter 4 provides result and performance analysis of the proposed techniques. The performance of the segmentation techniques are evaluated based on similarity indices and error rates. The best segmentation techniques are evaluated. The results of the lesion classification is also evaluated. Benchmarking with previous studies are compared.

Chapter 5 summarizes the thesis and the conclusions of this research works are presented. Research contributions and suggestions for future works are also provided through this chapter.

REFERENCES

Agani, N., Abu–Bakar, S. & Salleh, S. S. (2012). Application of texture analysis in echocardiography images for myocardial infarction tissue. *Jurnal Teknologi,* 46: 61–76.

Ain, Q.-U., Mehmood, I., Naqi, S. M. & Jaffar, M. A. (2010). Bayesian classification using DCT features for brain tumor detection. *Knowledge-Based and Intelligent Information and Engineering Systems.* Springer, 340-349.

American Cancer Society (2009). *Cancer Facts & Figures 2009.* Available at: http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2009/index

American Cancer Society (2014). *Cancer Facts & Figures 2014.* Available at: http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/index

Ariffanan, M. B. M. (2009). *Medical Image Classification and Symptoms Detection using Neuro Fuzzy*. Universiti Teknologi Malaysia. Master Thesis.

Avaspour, I., Saripan, M. I., Nordin, A. J. & Abdullah, R. S. A. R. (2009). Segmentation of extrapulmonary tuberculosis infection using modified automatic seeded region growing. *Biological Procedures Online,* 11: 241-252.

Bai, P. R., Liu, Q. Y., Li, L., Teng, S. H., Li, J. & Cao, M. Y. (2013). A novel region-based level set method initialized with mean shift clustering for automated medical image segmentation. *Computers in Biology and Medicine,* 43: 1827-1832.

Balafar, M. (2014). Fuzzy C-mean based brain MRI segmentation algorithms. *Artificial Intelligence Review,* 41: 441-449.

Balafar, M., Ramli, A. R., Saripan, M. I., Mahmud, R. & Mashohor, S. (2008). Medical image segmentation using fuzzy C-mean (FCM), learning vector quantization (LVQ) and user interaction. *Advanced Intelligent Computing*

Theories and Applications. With Aspects of Contemporary Intelligent Computing Techniques. Springer, 177-184.

Balafar, M. A., Ramli, A. R., Saripan, M. I. & Mashohor, S. (2010). Review of brain MRI image segmentation methods. *Artificial Intelligence Review,* 33: 261-274.

Bankman, I. (2008). *Handbook of medical image processing and analysis*. Academic Press.

Bardera, A., Boada, I., Feixas, M., Remollo, S., Blasco, G., Silva, Y. & Pedraza, S. (2009). Semi-automated method for brain hematoma and edema quantification using computed tomography. *Computerized Medical Imaging and Graphics,* 33: 304-311.

Barnathan, M., Zhang, J., Miranda, E., Megalooikonomou, V., Faro, S., Henshey, H., Del Voile, L., Khalili, K., Gordon, J. & Mohamed, F. B. (2008). A texture-based methodology for identifying tissue type in magnetic resonance images. *IEEE International Symposium on Biomedical Imaging: From Nano to Macro, ISBI 2008,* 464-467.

Bauer, S., Fejes, T., Slotboom, J., Wiest, R., Nolte Lutz-P., Reyes, M., (2012). Segmentation of brain tumor images based on integrated hierarchical classication and regularization. *Proceedings of the MICCAI Challenge on Multimodal Brain Tumor Image Segmentation, MICCAI-BRATS 2012,* 10-13.

Bhadauria, H., Singh, A. & Dewal, M. (2013). An integrated method for hemorrhage segmentation from brain CT Imaging. *Computers & Electrical Engineering,* 39: 1527-1536.

Bhanu Prakash, K., Gupta, V., Bilello, M., Beauchamp, N. J. & Nowinski, W. L. (2006). Identification, segmentation, and image property study of acute infarcts in diffusion-weighted images by using a probabilistic neural network and adaptive gaussian mixture model, *Academic Radiology,* 13: 1474-1484.

Bhanu Prakash, K., Gupta, V. & Nowinski, W. L. (2010). Segmenting Infarct from Diffusion-Weighted Imaging Volume. *U.S. Patent No. US2010/0231216 A1*. U.S. Patent and Trademark Office.

Bhat, P. & Singh, M. (2012). Classification of Stroke Using Texture Analysis on CT images. *International Journal of Soft Computing and Engineering (IJSCE),* 2: 527-530.

Bitar, R. (2006). MR Pulse Sequences: What Every Radiologist Wants to Know but Is Afraid to Ask. *RadioGraphics*, 26: 513-537.

BraTumIA (2014). *Brain Tumor Image Analysis Software*. Available at: http://www.istb.unibe.ch/content/research/medical_image_analysis/software/index_eng.html

Campbell, N. A., Reece, J. B., Taylor, M. R., Simon, E. J. & Dickey, J. (2009). *Biology: Concepts & Connections*. Pearson/Benjamin Cummings.

Cha, S. (2006). Update on brain tumor imaging: from anatomy to physiology. *American Journal of Neuroradiology*, 27: 475-487.

Chalela, J. A., Kidwell, C. S., Nentwich, L. M., Luby, M., Butman, J. A., Demchuk, A. M., Hill, M. D., Patronas, N., Latour, L. & Warach, S. (2007). Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. *The Lancet*, 369: 293-298.

Chan, T. (2007). Computer aided detection of small acute intracranial hemorrhage on computer tomography of brain. *Computerized Medical Imaging and Graphics*, 31: 285-298.

Chawla, M., Sharma, S., Sivaswamy, J. & Kishore, L. (2009). A method for automatic detection and classification of stroke from brain CT images. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2009*, 3581-3584.

Chen, P. & Pavlidis, T. (1980). Image segmentation as an estimation problem. *Computer Graphics and Image Processing*, 12: 153-172.

Chevrefils, C., Cheriet, F., Aubin, C.-E. & Grimard, G. (2009). Texture analysis for automatic segmentation of intervertebral disks of scoliotic spines from MR images. *IEEE Transactions on Information Technology in Biomedicine*, 13: 608-620.

Christ, M. & Parvathi, R. (2011). Segmentation of Medical Image using Clustering and Watershed Algorithms. *American Journal of Applied Sciences*, 8(12).

Deng, W., Xiao, W., Deng, H. & Liu, J. (2010). MRI brain tumor segmentation with region growing method based on the gradients and variances along and inside of the boundary curve. *3rd International IEEE Conference on Biomedical Engineering and Informatics (BMEI 2010)*, 393-396.

Doi, K. (2007). Computer-aided diagnosis in medical imaging: historical review, current status and future potential. *Computerized Medical Imaging and Graphics*, 31: 198-211.

Dubey, R., Hanmandlu, M. & Gupta, S. (2009). Region growing for MRI brain tumor volume analysis. *Indian Journal of Science and Technology,* 2: 26-31.

Duda, R. O., Hart, P. E. & Stork, D. G. (2012). *Pattern classification*. John Wiley & Sons.

El-Dahshan, E.-S. A., Hosny, T. & Salem, A.-B. M. (2010). Hybrid intelligent techniques for MRI brain images classification. *Digital Signal Processing,* 20: 433-441.

El-Dahshan, E.-S. A., Mohsen, H. M., Revett, K. & Salem, A.-B. M. (2014). Computer-aided diagnosis of human brain tumor through MRI: A survey and a new algorithm. *Expert Systems with Applications,* 41: 5526-5545.

Fazel Zarandi, M., Zarinbal, M. & Izadi, M. (2011). Systematic image processing for diagnosing brain tumors: A Type-II fuzzy expert system approach. *Applied Soft Computing,* 11: 285-294.

Fenton, J. J., Taplin, S. H., Carney, P. A., Abraham, L., Sickles, E. A., D'orsi, C., Berns, E. A., Cutter, G., Hendrick, R. E. & Barlow, W. E. (2007). Influence of computer-aided detection on performance of screening mammography. *New England Journal of Medicine,* 356: 1399-1409.

Fujita, H., Uchiyama, Y., Nakagawa, T., Fukuoka, D., Hatanaka, Y., Hara, T., Lee, G. N., Hayashi, Y., Ikedo, Y. & Gao, X. (2008). Computer-aided diagnosis: The emerging of three CAD systems induced by Japanese health care needs. *Computer Methods and Programs in Biomedicine,* 92: 238-248.

Fujita, H., You, J., Li, Q., Arimura, H., Tanaka, R., Sanada, S., Niki, N., Lee, G., Hara, T. & Fukuoka, D. (2010). State-of-the-Art of computer-aided detection/diagnosis (CAD). *Medical Biometrics.* Springer, 296-305.

Fukada, Y. (1980). Spatial clustering procedures for region analysis. *Pattern Recognition,* 12: 395-403.

Georgiadis, P., Cavouras, D., Kalatzis, I., Glotsos, D., Athanasiadis, E., Kostopoulos, S., Sifaki, K., Malamas, M., Nikiforidis, G. & Solomou, E. (2009). Enhancing the discrimination accuracy between metastases, gliomas and meningiomas on brain MRI by volumetric textural features and ensemble pattern recognition methods. *Magnetic Resonance Imaging,* 27: 120-130.

Gill, H. K., Girdhar, A. & Kaur, J. (2014). Automatic region growing segmentation for medical ultrasound images. *IEEE International Conference on Medical Imaging, m-Health and Emerging Communication Systems (MedCom 2014),* 454-457.

Gómez, F. & Romero, E. (2011). Rotation invariant texture characterization using a curvelet based descriptor. *Pattern Recognition Letters,* 32: 2178-2186.

Gonzales, R. C. & Woods, R. E. (2002). *Digital Image Processing, 2nd Edition.* Prentice Hall.

Graessner, J. (2011). Frequently Asked Questions: Diffusion-Weighted Imaging (DWI). *MAGNETOM Flash,* 1: 84-87. Available at: www.siemens.com/magnetom-world

Guy, C. & Ffytche, D. (2005). *An introduction to the principles of medical imaging*. World Scientific.

Hadjiprocopis, A., Rashid, W. & Tofts, P. S. (2005). Unbiased segmentation of diffusion-weighted magnetic resonance images of the brain using iterative clustering. *Magnetic Resonance Imaging,* 23: 877-885.

Hamamci, A., Unal, G., (2012). Multimodal brain tumor segmentation using the “tumor-cut" method on the BRATS dataset. *Proceedings of the MICCAI Challenge on Multimodal Brain Tumor Image Segmentation, MICCAI-BRATS 2012*, 19-23.

Hammer, M. D. & Wechsler, L. R. (2008). Neuroimaging in ischemia and infarction. *Seminars in Neurology*, 28: 446-452.

Han, Y., Li, E., Tian, J., Chen, J., Wang, H. & Dai, J. (2006). The application of diffusion-and perfusion-weighted magnetic resonance imaging in the diagnosis and therapy of acute cerebral infarction. *International Journal of Biomedical Imaging,* 2006:1-11.

Haralick, R. M., Shanmugam, K. & Dinstein, I. H. (1973). Textural features for image classification. *IEEE Transactions on Systems, Man and Cybernetics,* 610-621.

Hema Rajini, N. & Bhavani, R. (2013). Computer aided detection of ischemic stroke using segmentation and texture features. *Measurement,* 46: 1865-1874.

Hevia-Montiel, N., Jimenez-Alaniz, J. R., Medina-Banuelos, V., Yanez-Suarez, O., Rosso, C., Samson, Y. & Baillet, S. (2007). Robust nonparametric segmentation of infarct lesion from diffusion-weighted MR images. *29th Annual International IEEE Conference of the Engineering in Medicine and Biology Society, EMBS 2007*, 2102-2105.

Holdsworth, S. J. & Bammer, R. (2008). Magnetic resonance imaging techniques: fMRI, DWI, and PWI. *Seminars in Neurology,* 28: 395-406.

Horowitz, S. L. & Pavlidis, T. (1976). Picture segmentation by a tree traversal algorithm. *Journal of the ACM (JACM),* 23: 368-388.

Hsu, L. (2005). MR Imaging of the Central Nervous System. *Minimally Invasive Neurosurgery*. Humana Press Inc, Totowa, NJ.

Hum, Y. C., Lai, K. W., Utama, N. P., Salim, M. I. M. & Myint, Y. M. (2014). Review on Segmentation of Computer-Aided Skeletal Maturity Assessment. *Advances in Medical Diagnostic Technology*. Springer, 23-51.

Humayun, J., Malik, A. S. & Kamel, N. (2011). Multilevel thresholding for segmentation of pigmented skin lesions. *IEEE International Conference on Imaging Systems and Techniques (IST 2011),* 310-314.

Hwang, J., Han, Y. & Park, H. (2007). Segmentation of brain parenchyma using bilateral filtering and region growing. *29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS 2007,* 6263-6266.

Ibrahim, S., Khalid, N. E. A. & Manaf, M. (2010). Seed-based region growing (SBRG) vs adaptive network-based inference system (ANFIS) vs fuzzy c-means (FCM): brain abnormalities segmentation. *International Journal of Electrical and Computer Engineering,* 5: 94-104.

Jafari, M. & Kasaei, S. (2011). Automatic brain tissue detection in mri images using seeded region growing segmentation and neural network classification. *Journal of Applied Sciences Research,* 7(8).

Jiang, J., Wu, Y., Huang, M., Yang, W., Chen, W. & Feng, Q. (2013). 3D brain tumor segmentation in multimodal MR images based on learning population- and patient-specific feature sets. *Computerized Medical Imaging and Graphics,* 37(7): 512-521.

Karahaliou, A., Skiadopoulos, S., Boniatis, I., Sakellaropoulos, P., Likaki, E., Panayiotakis, G. & Costaridou, L. (2014). Texture analysis of tissue surrounding microcalcifications on mammograms for breast cancer diagnosis. *The British Journal of Radiology*, 80(956).

Kassner, A. & Thornhill, R. (2010). Texture analysis: a review of neurologic MR imaging applications. *American Journal of Neuroradiology*, 31: 809-816.

Kastrup, O., Wanke, I. & Maschke, M. (2008). Neuroimaging of infections of the central nervous system. *Seminars in Neurology*, 28: 511-522.

Khalil, M. S., Muhammad, D., Khan, M. K. & Al-Nuzaili, Q. (2009) Fingerprint verification using fingerprint texture. *IEEE International Symposium on Signal Processing and Information Technology (ISSPIT 2009)*, 591-594.

Khotanlou, H., Colliot, O., Atif, J. & Bloch, I. (2009). 3D brain tumor segmentation in MRI using fuzzy classification, symmetry analysis and spatially constrained deformable models. *Fuzzy Sets and Systems*, 160: 1457-1473.

Kim, P. E. & Zee, C. S. (2007). Imaging of the cerebrum. *Neurosurgery*, (61).

Kobatake, H. (2007). Future cad in multi-dimensional medical images:–project on multi-organ, multi-disease cad system–. *Computerized Medical Imaging and Graphics*, 31: 258-266.

Koh, D.-M. & Collins, D. J. (2007). Diffusion-weighted MRI in the body: applications and challenges in oncology. *American Journal of Roentgenology*, 188: 1622-1635.

Koh, D. & Padhani, A. (2014). Diffusion-weighted MRI: a new functional clinical technique for tumour imaging. *British Journal of Radiology*, 79(2006): 633-635.

Lai, P. H., Ho, J. T., Chen, W. L., Hsu, S. S., Wang, J. S., Pan, H. B. & Yang, C. F. (2002). Brain abscess and necrotic brain tumor: discrimination with proton MR spectroscopy and diffusion-weighted imaging. *American Journal of Neuroradiology*, 23: 1369-1377.

Lauterbur, P. C. (1973). Image formation by induced local interactions: examples employing nuclear magnetic resonance. *Nature*, 242: 190-191.

Lee, J. D., Chang, T. C., Huang, C. H., Wu, S. J. & Chen, C. J. (2004). Computer-aided Diagnosis System for Acute Stroke Using Diffusion Weighted Images with Volume Calculation. *26^{th} Annual International Conference of the IEEE EMBS*, 1529-1532.

Lee, T. H., Fauzi, M. F. A., Komiya, R. & Haw, S.-C. (2008). Unsupervised abnormalities extraction and brain segmentation. *IEEE 3rd International Conference on Intelligent System and Knowledge Engineering, 2008 (ISKE 2008)*, 1185-1190.

Lee, Y., Takahashi, N., Tsai, D.-Y. & Fujita, H. (2006). Detectability improvement of early sign of acute stroke on brain CT images using an adaptive partial smoothing filter. *International Society for Optics and Photonics Medical Imaging 2006*.

Li, H., Liu, T., Young, G., Guo, L. & Wong, S. T. (2006). Brain tissue segmentation based on DWI/DTI data. *3rd IEEE International Symposium on Biomedical Imaging: Nano to Macro*, 57-60.

Liao, C.-C., Xiao, F., Wong, J.-M. & Chiang, I. (2010). Computer-aided diagnosis of intracranial hematoma with brain deformation on computed tomography. *Computerized Medical Imaging and Graphics,* 34: 563-571.

Lin, G.-C., Wang, W.-J., Kang, C.-C. & Wang, C.-M. (2012). Multispectral MR images segmentation based on fuzzy knowledge and modified seeded region growing. *Magnetic Resonance Imaging,* 30: 230-246.

Loncaric, S., Dhawan, A. P., Cosic, D., Kovacevic, D., Broderick, J. & Brott, T. (1999). Quantitative intracerebral brain hemorrhage analysis. *International Society for Optics and Photonics Medical Imaging'99,* 886-894.

Lu, C.-F., Wang, P.-S., Soong, B.-W., Chou, Y.-C., Li, H.-C. & Wu, Y.-T. (2009). Multi-tissue Classification of Diffusion-Weighted Brain Images in Multiple System Atrophy Using Expectation Maximization Algorithm Initialized by Hierarchical Clustering. *13th International Conference on Biomedical Engineering, 2009*. Springer, 722-725.

Magnets, Spins, and Resonances: An introduction to the basics of magnetic resonance. *Siemens Medical Solutions that help.* Brochure.

Mahmoodabadi, S. Z., Alirezaie, J., Babyn, P., Kassner, A. & Widjaja, E. (2011). Wavelets and fuzzy relational classifiers: A novel diffusion-weighted image analysis system for pediatric metabolic brain diseases. *Computer Methods and Programs in Biomedicine,* 103: 74-86.

Mahmoud-Ghoneim, D. (2009). Cooccurrence Histograms for characterizing brain magnetic resonance images. *IEEE International Symposium on Signal Processing and Information Technology (ISSPIT 2009)*, 1-4.

Mansfield, P. (1977). Multi-planar image formation using NMR spin echoes. *Journal of Physics C: Solid State Physics*, 10: 55.

Martel, A. L., Allder, S. J., Delay, G. S., Morgan, P. S. & Moody, A. R. (1999). Measurement of infarct volume in stroke patients using adaptive segmentation of diffusion weighted MR images. *Medical Image Computing and Computer-Assisted Intervention–MICCAI'99*, Springer, 22-31.

Matesin, M., Loncaric, S. & Petravic, D. (2001). A rule-based approach to stroke lesion analysis from CT brain images. *IEEE Proceedings of the 2nd International Symposium on Image and Signal Processing and Analysis 2001, ISPA 2001*, 219-223.

Max Wintermark, Michael D. Wirt, Pratik Mukherjee, Greg Zaharchuk, Emmanuel Barbier, William P. Dillon, Birgit B. Ertl-Wagner, Claudia Rummeny, Marco Essig, Daryl C. Bergen, John M. Fagnou, Robert Sevick, E. Turgut Tali, Serap Gültekin, Sasan Karimi, Andrei I. Holodny, Mitsunori, K., Noriko Sato, Yukio Miki, Norbert Hosten, B. Zwicker, Mathias Langer, Roberto Maroldi, D. Farina, Andrea Borghesi, Elisa Botturi, Claudia Ambrosi, Hilda Stambuk & Fischbein, N. (2008). Brain, Head, and Neck. In: Reiser, M. F., Semmler, W. & Hricak, H. (eds.). *Magnetic Resonance Tomography*. Springer.

Meiera, A., Farrow, C., Harris, B. E., Kinga, G. G. & Jones, A. (2011). Application of texture analysis to ventilation SPECT/CT data. *Computerized Medical Imaging and Graphics*, 35: 438-450.

Menze, B. R., M.; Van Leemput, K. (2014). The Multimodal Brain TumorImage Segmentation Benchmark (BRATS). *IEEE Transactions on Medical Imaging*, 99: 1-33.

MICCAI Brain Tumor Segmentation (BRATS) Challenge 2012. Available at: http://www2.imm.dtu.dk/projects/BRATS2012/

Ministry Of Health Malaysia. *Health Facts 2012*. Available at: http://medicine.com.my/wp/2013/04/health-facts-malaysia-2012/

Mokji, M. M. & Abu Bakar, S. A. R. (2007). Adaptive thresholding based on co-occurrence matrix edge information. *IEEE First Asia International Conference on Modelling & Simulation, 2007 (AMS'07),* 444-450.

Moritani, T., Ekholm, S. & Westesson, P.-L. (2005). *Diffusion-Weighted MR Imaging of the Brain.* Springer.

Mujumdar, S. (2013). *Detection and Segmentation of Stroke Lesions from Diffusion Weighted MRI Data of the Brain.* International Institute of Information Technology Hyderabad. Master Thesis.

Mukherji, S. K., Chenevert, T. L. & Castillo, M. (2002). State of the Art: Diffusion-Weighted Magnetic Resonance Imaging. *Journal of Neuro-Ophtalmology,* 22: 118-122.

Nadal Desbarats, L., Herlidou, S., De Marco, G., Gondry-Jouet, C., Le Gars, D., Deramond, H. & Idy-Peretti, I. (2003). Differential MRI diagnosis between brain abscesses and necrotic or cystic brain tumors using the apparent diffusion coefficient and normalized diffusion-weighted images. *Magnetic Resonance Imaging,* 21: 645-650.

Nowinski, W. L. (2011). Introduction to Brain Anatomy. In: Miller, K. (ed.) *Biomechanics of the Brain.* Springer, 5-40.

Nowinski, W. L., Qian, G., Prakash, K. B., Volkau, I., Leong, W. K., Huang, S., Ananthasubramaniam, A., Liu, J., Ng, T. T. & Gupta, V. (2008). Stroke Suite: CAD systems for acute ischemic stroke, hemorrhagic stroke, and stroke in ER. *Medical Imaging and Informatics.* Springer, 377-386.

Ortiz, A., Gorriz, J., Ramirez, J. & Salas-Gonzalez, D. (2012). Unsupervised neural techniques applied to MR brain image segmentation. *Advances in Artificial Neural Systems,* 1-7.

Park, J. G. & Lee, C. (2009). Skull stripping based on region growing for magnetic resonance brain images. *NeuroImage,* 47: 1394-1407.

Porz, N., Bauer, S., Pica, A., Schucht, P., Beck, J., Verma, R. K., Slotboom, J., Reyes, M. & Wiest, R. (2014). Multi-Modal Glioblastoma Segmentation: Man versus Machine. *PloS one,* 9(5):e96873.

Pratt, W. K. (2007). *Digital Image Processing*. John Wiley & Sons, Inc.

Provenzale, J. M., Mukundan, S. & Barboriak, D. P. (2006). Diffusion-weighted and Perfusion MR Imaging for Brain Tumor Characterization and Assessment of Treatment Response. *Radiology,* 239: 632-649.

Przelaskowski, A., Sklinda, K., Bargieł, P., Walecki, J., Biesiadko-Matuszewska, M. & Kazubek, M. (2007). Improved early stroke detection: wavelet-based perception enhancement of computerized tomography exams. *Computers in Biology and Medicine*, 37: 524-533.

Ramírez, J., Górriz, J., Salas-Gonzalez, D., Romero, A., López, M., Álvarez, I. & Gómez-Río, M. (2013). Computer-aided diagnosis of Alzheimer's type dementia combining support vector machines and discriminant set of features. *Information Sciences,* 237: 59-72.

Rathi, Y., Malcolm, J., Michailovich, O., Goldstein, J., Seidman, L., Mccarley, R. W., Westin, C.-F. & Shenton, M. E. (2010). Biomarkers for identifying first-episode schizophrenia patients using diffusion weighted imaging. *Medical Image Computing and Computer-Assisted Intervention–MICCAI 2010.* Springer.

Ringenberg, J., Deo, M., Devabhaktuni, V., Berenfeld, O., Boyers, P. & Gold, J. (2014). Fast, accurate, and fully automatic segmentation of the right ventricle in short-axis cardiac MRI. *Computerized Medical Imaging and Graphics*, 38: 190-201.

Rivest-Hénault, D. & Cheriet, M. (2011). Unsupervised MRI segmentation of brain tissues using a local linear model and level set. *Magnetic Resonance Imaging,* 29: 243-259.

Rollin, N., Guyotat, J., Streichenberger, N., Honnorat, J., Minh, V.-A. T. & Cotton, F. (2006). Clinical relevance of diffusion and perfusion magnetic resonance imaging in assessing intra-axial brain tumors. *Neuroradiology,* 48: 150-159.

Roslan, R., Jamil, N. & Mahmud, R. (2010). Skull stripping of MRI brain images using mathematical morphology. *2010 IEEE EMBS Conference on Biomedical Engineering and Sciences (IECBES 2010)*, 26-31.

Rubin, M., Safdieh, J. E. & Netter, F. H. (2007). *Netter's Concise Neuroanatomy*. Saunders Elsevier.

Ruiz-Alzola, J., Alberola-López, C. & Westin, C.-F. (2013). Advanced signal processing methods for biomedical imaging. *International Journal of Biomedical Imaging,* 1-2.

Saad, N. M., Abu-Bakar, S., Muda, S. & Mokji, M. Automated segmentation of brain lesion based on diffusion-weighted MRI using a split and merge approach. *2010 IEEE EMBS Conference on Biomedical Engineering and Sciences (IECBES 2010),* 475-480.

Santos, W. P., Assis, F. M., Souza, R. E., Filho, P. B. S. & Neto, F. B. L. (2009). Dialectical multispectral classification of diffusion-weighted magnetic resonance images as an alternative to apparent diffusion coefficients maps to perform anatomical analysis. *Computerized Medical Imaging and Graphics,* 33: 442–460.

Saraswathy, S., Sharma, S., Shanbhag, D., Patil, U. & Mullick, R. (2009). Automatic identification and segmentation of infarct lesions from diffusion weighted MR images and ADC maps. *Proceedings International Society Magnetic Resonance Medicine 2009,* 17: 2887.

Schaefer, P. W., Grant, P. E. & Gonzalez, R. G. (2000). Diffusion-weighted MR imaging of the brain. *Radiology,* 217: 331-345.

Selvanayaki, K. & Karnan, D. M. (2010). CAD System for Automatic Detection of Brain Tumor through Magnetic Resonance Image-A Review. *International Journal of Engineering Science and Technology,* 2: 5890-5901.

Shalikar, A., Ashouri, M. R. & Shahraki, M. H. N. (2014). A CAD System for Automatic Classification Of Brain Strokes in CT Images. *International Journal of Mechatronics, Electrical and Computer Technology,* 4: 67-85.

Shen, S., Szameitat, A. J. & Sterr, A. (2008). Detection of infarct lesions from single MRI modality using inconsistency between voxel intensity and spatial location—a 3-D automatic approach. *IEEE Transactions on Information Technology in Biomedicine,* 12: 532-540.

Shen, S., Szameitat, A. J. & Sterr, A. (2010). An improved lesion detection approach based on similarity measurement between fuzzy intensity segmentation and spatial probability maps. *Magnetic Resonance Imaging,* 28: 245-254.

Siemens (2010). Diffusion Weighted MRI of The Brain. *MAGNETOM Maestro Class: Siemens Medical Solutions that help.* Brochure.

Snell, R. S. (2010). *Clinical neuroanatomy*. Lippincott Williams & Wilkins.

Sokolova, M., Lapalme, G., (2009). A systematic analysis of performance measures for classification tasks. *Information Processing & Management,* 45 (4): 427-437.

Sonka, M., Hlavac, V. & Boyle, R. (2008). *Image Processing, Analysis, and Machine Vision*. Thomson Learning.

Srinivasan, A., Goyal, M., Azri, F. A. & Lum, C. (2006). State-of-the-Art Imaging of Acute Stroke. *RadioGraphics,* 26: 75-95.

Stejskal, E. & Tanner, J. (1965). Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. *The journal of chemical physics,* 42: 288-292.

Strasters, K. C. & Gerbrands, J. J. (1991). Three-dimensional image segmentation using a split, merge and group approach. *Pattern Recognition Letters,* 12: 307-325.

Sweeney, E. M., Shinohara, R. T., Shiee, N., Mateen, F. J., Chudgar, A. A., Cuzzocreo, J. L., Calabresi, P. A., Pham, D. L., Reich, D. S. & Crainiceanu, C. M. (2013). OASIS is Automated Statistical Inference for Segmentation, with applications to multiple sclerosis lesion segmentation in MRI. *NeuroImage: Clinical,* 2: 402-413.

Tang, F.-H., Ng, D. K. & Chow, D. H. (2011). An image feature approach for computer-aided detection of ischemic stroke. *Computers in Biology and Medicine,* 41: 529-536.

Termenon, M., Besga, A., Echeveste, J., Gonzalez-Pinto, A. & Graña, M. (2011). Alzheimer disease classification on diffusion weighted imaging features. *New Challenges on Bioinspired Applications.* Springer, 120-127.

Thapaliya, K., Pyun, J.-Y., Park, C.-S. & Kwon, G.-R. (2013). Level set method with automatic selective local statistics for brain tumor segmentation in MR images. *Computerized Medical Imaging and Graphics*, 37: 522-537.

Tirpude, N. & Welekar, R. (2013). Automated Detection and Extraction of Brain Tumor from MRI Images. *International Journal of Computer Applications,* 77: 26-30.

Ullrich, R. T., Kracht, L. W. & Jacobs, A. H. (2008). Neuroimaging in patients with gliomas. *Seminars in neurology*, 28: 484-494.

Ušinskas, A. (2004). Ischemic stroke segmentation on ct images using joint features. *Informatica*, 15: 283-290.

Voyvodic, J. T. (2005). *Basic Physical Principles of MRI*, Brain Imaging and Analysis Center, Duke University Medical Center: Lecture Notes.

Wang, P. & Wang, H. (2008). A modified FCM algorithm for MRI brain image segmentation. *IEEE International Seminar on Future BioMedical Information Engineering, 2008. (FBIE'08)*, 26-29.

Webster, J. G. & Wiley, J. (1999). *Wiley encyclopedia of electrical and electronics engineering*. John Wiley & Sons, Inc.

Weishaupt, D., Köchli, V. D. & Marincek, B. (2006). 7 Basic Pulse Sequences. *How Does MRI Work? An Introduction to the Physics and Function of Magnetic Resonance Imaging. 2nd Edition*. Springer Berlin Heidelberg.

Weisstein, E. W., (2014). *Pearson Mode Skewness* From MathWorld--A Wolfram Web Resource: http://mathworld.wolfram.com/PearsonModeSkewness.html.

Yang, X., Blezek, D. J., Cheng, L. T., Ryan, W. J., Kallmes, D. F. & Erickson, B. J. (2011). Computer-aided detection of intracranial aneurysms in MR angiography. *Journal of Digital Imaging*, 24: 86-95.

Zacharaki, E. I., Wang, S., Chawla, S., Yoo, D. S., Wolf, R., Melhem, E. R. & Davatzikos, C. (2009). MRI-based classification of brain tumor type and grade using SVM-RFE. *IEEE International Symposium on Biomedical Imaging: From Nano to Macro,ISBI'09*, 1035-1038.

Zaki, W. M. D. W., Fauzi, M. F. A., Besar, R. & Ahmad, W. S. H. M. W. (2011). Abnormalities detection in serial computed tomography brain images using multi-level segmentation approach. *Multimedia Tools and Applications*, 54: 321-340.

Zhang, Y. (2012). MRI texture analysis in multiple sclerosis. *Journal of Biomedical Imaging*, 2012: 1-7.