AM-FM Texture Image Analysis in Brain White Matter Lesions in the Progression of Multiple Sclerosis

C.P. Loizou*, *Member, IEEE*, V. Murray[+], *Member, IEEE*, M.S. Pattichis[+], *Senior Member, IEEE*, M. Pantziaris[b], C.S. Pattichis[#], *Senior Member, IEEE*

*Department of Computer Science, School of Sciences, Intercollege, P.O.Box 51604, CY-3507, Limassol, Cyprus.
E-mail: loizou.c@ lim.intercollege.ac.cy.

[+]Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, N.M., USA.
E-mails: vmurray@ieee.org; pattichis@ece.unm.edu.

[b]Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus. E-mail: pantzari@cing.ac.cy.

[#]Department of Computer Science, University of Cyprus, Nicosia, Cyprus. E-mail: pattichi@ucy.ac.cy.

***Abstract*— We present the use of multiscale Amplitude Modulation Frequency Modulation (AM-FM) methods for analyzing brain white matter lesions that are associated with disease progression. We analyze lesions and normal appearing white matter (NAWM) longitudinally (0 and 6 months) and also for progression of disease. We use the expanded disability status scale (EDSS) to assess disease progression. The findings suggest that the high-frequency scale instantaneous amplitude can be used to differentiate between lesions associated with early and advanced disease stages. The classification results using the IF information and support vector machines produced a maximum sensitivity of 0.86, specificity of 0.76 and a maximum correct classification of 0.71.**

Keywords **-** MRI, multiple sclerosis, multiscale AM-FM analysis.

I. INTRODUCTION

Multiple Sclerosis (MS) is a chronic disease that causes inflammatory demyelization of different areas of the central nervous system. It is very difficult to predict disability from standard clinical exams of MS [1]. Some of the correlating factors between MS and disability were investigated in [2]. In [3], MS disease severity was used to classify patients into subgroups.

The use of texture features for differentiating between normal and abnormal lesions was studied in [4]-[7]. Here, texture features are extracted from segmented MS brain lesions. In [7], we show the use of texture features to identify the onset of the disease. Our objective here is to investigate whether advanced disease state, as measured by the expanded disability status scale (EDSS), can be detected by the use of new multi-scale Amplitude-Modulation Frequency-Modulation (AM-FM) methods [8], [9] and standard texture features.

In [4], it was shown that texture features can reveal discriminant factors for tissue classification and image segmentation. Significant differences in texture between normal and diseased spinal cord in MS patients were found in [12] as well as the significance correlation between texture features and disability. The classification of active and non-active brain lesions in MS patients from brain MRI was investigated in [13] using texture analysis. In [14], the performance of texture analysis and tissue discrimination between MS lesions and normal appearing white matter (relates to patient group) and brain white matter (BWM which relates to normal controls) was investigated for supporting early diagnosis in MS. In [6], shape and texture features were computed on 10 subjects for differentiating between normal and abnormal lesions.

AM-FM models have been used in a variety of applications including image reconstruction, image retrieval, and video processing such as motion estimation and video analysis [8]. A theoretical framework for understanding the role of multidimensional frequency modulation was reported in [9]. In [10], for carotid plaque ultrasound images, AM-FM texture features were shown to provide better results than classical texture features.

We provide a summary of the materials and methods in Section II. Results are given in Section III. A discussion of the results is given in Section IV.

II. MATERIALS & METHODS

A. Study Group and MRI Acquisition

In agreement with the Cyprus national bioethics committee rules on clinical trials, thirty eight (17 male, and 21 female), aged 34.1±10.5 (mean age ± standard deviation), with a clinical isolated syndrome (CIS) of MS and MRI detectable brain lesions were scanned twice with an interval of 6-12 months. The images covered a field of view of 230mm at a pixel resolution of 2.226 pixels per mm. All subjects were initially untreated and remained untreated between the baseline MRI and the repeat MRI. They were also clinically examined by the MS neurologist following the MRI and at the end of the study were given an EDSS (expanded disability status scale) score [18] with 2.07±0.75 (mean EDSS ± standard deviation). Additionally, 10 healthy, age-matched (mean±SD: 30.8±7.6) volunteers (4 male, and 6 female) were scanned for image texture analysis on normal BWM.

The images used for analysis were obtained using a T2-weighted turbo spin echo pulse sequence (TR=4408ms, TE=100ms, echo spacing=10.8ms). For more details on the MRI protocol and the acquisition parameters, we refer to [7], [17].

B. Interscan Intensity Normalization

Image brightness normalization was used between images (see [7] for details). We first quantified global signal characteristics by determining the average high (cerebrospinal fluid) and low intensity (air from the sinuses) values of the brain. The gray scale values of each scan were then scaled (stretched) between selected regions of interest (ROIs) representing cerebrospinal fluid and air from the sinuses based on a histogram stretching procedure.

C. Manual Delineations and Visual Perception

All detectable lesions were identified and segmented by an experienced MS neurologist and confirmed by a radiologist. The manual delineation procedure and visual perception evaluation can be found in [6] and [7]. Similarly, normal BWM areas, cerebrospinal fluid (CSF) and air from the sinuses were also segmented from the 10 healthy subjects.

D. Amplitude-Modulation Frequency-Modulation (AM-FM) Methods

Following manual lesion segmentation, we compute AM-FM features. Here, we note that AM-FM components can also reconstruct the input image using [19], [8]:

$$I(k_1,k_2) \approx \sum_{n=1}^{M} a_n(k_1,k_2)\cos\varphi_n(k_1,k_2), \qquad (1)$$

where n=1, 2,…, M denote different scales, a_n denote slowly-varying instantaneous amplitude (IA) functions and φ_n denoted the instantaneous phase functions (IP). Texture components are captured by the FM components $\cos\varphi_n$. The IA can be used to quantify the contributions from each component. The instantaneous frequency (IF) is defined in terms of the gradient of the phase.

AM-FM demodulation is applied over a dyadic filterbank after the image is filtered through an extended 2-D Hilbert filter. Let I_{AS} be $I_{AS} = I + jH_{2D}\{I\}$ where H_{2D} denotes the 2-D Hilbert operator. Also, let $\widehat{f}_{AS}$ denote the output of one of the band-pass filers. We estimate the IA and IP using [20]:

$$a(k_1,k_2) = \left|\widehat{f}_{AS}(k_1,k_2)\right| \qquad (2)$$

and

$$\varphi(k_1,k_2) = \arctan\left(\frac{imag(\widehat{f}_{AS}(k_1,k_2))}{real(\widehat{f}_{AS}(k_1,k_2))}\right). \qquad (3)$$

The IF is computed using a variable spacing, local linear phase (VS-LLP) method as described in [19], [8]:

$$\frac{d}{dk_1}\varphi(k_1,k_2) \cong \frac{1}{n_1}\cos^{-1}\left(\frac{g(k_1+n_1,k_2)+g(k_1-n_1,k_2)}{2g(k_1,k_2)}\right)$$

where $g(k_1,k_2) = \widehat{f}_{AS}(k_1,k_2)/\left|\widehat{f}_{AS}(k_1,k_2)\right|$, and similarly for the second component of the instantaneous frequency. Here, we only consider a dyadic filterbank using low, medium, and high frequency scale bands. For each lesion and each frequency scale band, we compute 32-bin histograms of the IA, IF magnitude and IF angle.

E. Statistical Analysis

The Wilcoxon rank sum test was used in order to identify if for each set of measurements a significant difference (S) or not (NS) exists between the extracted AM-FM texture features, with a confidence level of 95%. For significant differences, we require $p<0.05$. We also used the non parametric Mann-Whitney rank sum test to detect AM-FM feature differences between lesions, NAWM and normal tissue, for patients with EDSS <=2 and EDSS>2.

Classification analysis was carried out to classify lesions at 0 months for two classes: (i) lesions with EDSS<=2, and (ii) lesions with EDSS>2. We performed the classification using the Support Vector Machines (SVM) classifier and the leave-one-out cross-validation method. SVM classification was performed based on the construction of hyper planes able to separate the input data into two classes. We use a quadratic kernel [21] to solve the non-linear classification problem. This quadratic kernel function $k(x_i,x_j)$ can be expressed as $k(x_i,x_j) = (x_i \cdot x_j)^n$, where x_i and x_j are data points and $n = 2$ in this case.

We performed the classification considering three different scales: Low, Medium and High frequencies. For each scale, we performed the classification in terms of: (i) |IF| only, and (ii) |IF| and IF angle together. Also, the classification is performed using either the histograms or the 25, 50 and 75 percentiles of the estimated described features before.

III. RESULTS

We present two AM-FM decomposition examples in Fig. 1. Here, we present the low, medium, and high frequency scales IA and IF magnitude for two 51 year old males.

Table I presents statistical comparisons between NAWM and brain lesions collected at 0 and 6 months. Our primary goal here is to detect significant changes in the lesions that are also associated with advanced disease stages.

The results from Table I indicate that several AM-FM scales can be used to differentiate between early and advanced disease stages. Here, more advanced disease stages are characterized by EDSS>2.0. Earlier disease stages are characterized by EDSS<=2.0.

As an example, we discuss the case of comparing lesions after 6 months. This case is shown in the lower portion of Table I. Here, we have that the medium-frequency and high-frequency IA values can be used to differentiate between early (EDSS<=2.0) and more advanced (EDSS>2.0) cases. Unfortunately, we also have a negative result in that the medium-frequency IA shows significant differences between early cases recorded at 0 and 6 months. The combination of these findings suggests that the high-frequency IA can be used to reliably detect advanced progression of the disease.

Similarly, we can see that the medium-frequency scale IA can reliably differentiate between NAWM associated with early and advanced cases of the disease. Here, we can see that there are no significant differences between early

NAWM cases collected at 0 and 6 months. Similarly for the advanced NAWM cases.

In Table II we present the classification results for classifying lesions at 0 months for EDSS<=2.0 and for EDSS>2.0 in terms of Sensitivity (Sen.), Specificity (Spe.) and Correct Rate (CR, percentage of lesions correctly classified). We emphasize the individual results were the sensitivity values bigger than 0.7, specificity bigger than 0.5 and correct rate bigger or equal than 0.6. We can see that the best results in terms of Sensitivity is 0.86 when the complete information of the IF (both magnitude and angle) histogram is used in the Low frequencies. When the percentiles are used, the best Sensitivity results are again in the Low frequencies with the complete IF information. In terms of Specificity, the results based on percentiles are better than the results based on histograms. These results can be produced due to the smaller feature vectors describing the features. Similarly, the best CR results come from the use of the percentiles. Note that when the percentiles are used, the use of the complete IF information produces better results than the use of the IF magnitude alone. However, when the histograms are used the complete IF information produced better CR.

TABLE I. Comparison of the IA and IF (IA/IF) based on the Wilcoxon rank sum test at $p<0.05$. Table shows significant different cases for low, medium, high frequencies for EDSS lower equal than 2.0 (<=2.0) and greater than 2.0 (>2.0).

			NAWM	
			0 months	**6 months**
		EDSS	**> 2**	**≤ 2**
NAWM	**0 months**	**≤ 2**	LIA/- MIA/- HIA/-	-/- -/- -/-
	6 months	**> 2**	-/- -/- -/-	-/- MIA/- -/-

			Lesions	
			0 months	**6 months**
		EDSS	**> 2**	**≤ 2**
Lesions	**0 months**	**≤ 2**	-/- MIA/- HIA/-	-/- *MIA*/- -/-
	6 months	**> 2**	-/- -/- -/-	-/- MIA/- HIA/-

IV. CONCLUDING REMARKS

The AM-FM analysis presented in this study was performed on the normal tissue, NAWM and lesions, on 38 MR images with a CIS of MS. MRI detectable brain lesions were scanned twice with an interval of 6-12 months. The results indicate that high-frequency IA can be used to differentiate between early and advanced cases for the lesions. The classification results show that the best sensitivity is obtained when the histograms are used. However, the best specificity and CR results come from the use of percentiles. This tradeoff between increasing either the Sensitivity or both the Specificity and CR needs to be further analyzed in future work.

ACKNOWLEDGMENT

This work was funded through the project Quantitative and Qualitative Analysis of MRI Brain Images ΤΠΕ/OPIZO/0308(BIE)/15, 12/2008-12/2010, of the Program for Research and Technological Development 2007-2013, of the Research Promotion Foundation of Cyprus.

TABLE II. Classification results using the SVM classifier in terms of Sensitivity (Sen.), Specificity (Spe.) and Correct Rate (CR) in the estimation for the Low, Medium and High frequency components for differentiating lesions at 0 months for EDSS<=2 and EDSS>2. We present using bold typeface the results when sensitivity values bigger than 0.7, specificity bigger than 0.5 and correct rate bigger or equal than 0.6 (Bolded values show best performance).

	Low		Medium		High	
Feature	|IF|	|IF|-IF angle	|IF|	|IF|-IF angle	|IF|	|IF|-IF angle
	Histograms					
Sen.	**0.79**	**0.86**	0.64	0.57	0.64	0.64
Spe.	**0.62**	0.43	**0.52**	0.38	0.33	0.33
CR.	**0.69**	**0.60**	0.57	0.46	0.46	0.46
	Percentiles					
Sen.	0.64	**0.79**	0.29	0.50	0.50	0.64
Spe.	**0.76**	**0.67**	**0.57**	**0.67**	**0.57**	**0.57**
CR.	**0.71**	**0.71**	0.46	**0.60**	0.54	**0.60**

REFERENCES

[1] F. Fazekas, F. Barkof, M. Filippi, et al, "The contribution of magnetic resonance imaging to the diagnosis of multiple sclerosis", *Neurology*, vol. 53, pp. 448-456, 1999.

[2] M. Filippi, D.W. Paty, L. Kappos, F. Barkhof, D.A. Compston, A.J. Thompson, G.J. Zhao, C.M.Wiles, W.I. McDonald, and D.H. Miller, "Correlations between changes in disability and T2-weighted brain MRI activity in multiple sclerosis : a follow-up study", *Neurology*, vol. 45, pp. 255-260, 1995.

[3] J. Dehmeshki G.J. Barker, and P.S. Tofts, "Classifications of disease subgroups and correlation with disease severity using magnetic resonance imaging whole-brain histograms: Application to magnetisation transfer ratios and multiple sclerosis", *IEEE Trans. Med. Imag.*, vol. 21, no. 4, pp. 320-331, 2002.

[4] S. Herlidou-Meme, J.M. Constans, B. Carsin, D. Olivie, P.A. Eliat et al., "MRI texture analysis on texture test objects, normal brain and intracranial tumours", *Mag. Res. Imag.*, vol. 21, pp. 989-993, 2003.

[5] D.S. Meier, and C.R.G. Guttman, "Time-series analysis of MRI intensity patters in multiple sclerosis", *NeuroImage*, vol. 20, pp. 1193-1209, 2003.
[6] C.P. Loizou, C.S. Pattichis, I. Seimenis, M. Pantziaris, "Quantitative Analysis of Brain White Matter Lesions in Multiple Sclerosis Subjects", *ITAB2009-9th Int. Conf. on Inform. Techn. And Applic. in Biomed.*, Larnaca, Cyprus, pp. 1-4, Nov. 5-7, 2009.
[7] C.P. Loizou, M. Patziaris, I. Seimenis, C.S. Pattichis, "MRI intensity normalization in brain multiple sclerosis subjects", *ITAB2009-9th Int. Conf. on Inform. Techn. And Applic. in Biomed.*, Larnaca, Cyprus, pp. 1-5, Nov. 5-7, 2009.
[8] V.M. Murray Herrera, "AM-FM methods for image and video processing," Ph.D. dissertation, University of New Mexico, Sept. 2008.
[9] M.S. Pattichis, A.C. Bovik, "Analyzing image structure by multidimensional frequency modulation," *IEEE Trans. Pattern. Anal. Mach. Intellig.*, vol. 29, no. 5, pp. 753–766, 2007.
[10] C.I Christodoulou, C.S. Pattichis, V. Murray, M.S. Pattichis, A.N. Nicolaides, "AM-FM Representations for the Characterization of Carotid Plaque Ultrasound Images," *MBEC'08 4th Eur. Conf. Int. Feder. Med. Biolog. Eng.*, Antwerp, Belgium, Nov. 23-28, pp. 1-4, 2008.
[11] G. Collewet, M. Strzelecki, and F. Marriette, "Influence of MRI acquisition protocols and image intensity normalization methods on texture classification", *Magn. Reson. Imag.*, vol. 22, pp. 81-91, 2004.
[12] J.M. Mathias, P.S. Tofts, and N.A. Losseff, "Texture analysis of spinal cord pathology in multiple sclerosis", *Magn, Res. in Med.*, vol. 42, pp. 929-935, 1999.
[13] O. Yu, Y Mauss, G. Zollner, I.J. Namer, and J. Chambron, "Distinct patterns of active and non-active plaques using texture analysis of brain NMR images in multiple sclerosis patients: Preliminary results", *Magn. Reson. Imag.*, vol. 17, no. 9, pp. 1261-1267, 1999.
[14] J. Zhang, L. Wang, and L. Tong, "Feature reduction and texture classification in MRI-Texture analysis of multiple sclerosis", *IEEE/ICME 2007 Conf. Complex Med. Eng.*, pp. 752-757.
[15] A.J. Thompson, and J.C Hobart, "Multiple sclerosis: assessment of disability and disability scales", *J. Neurol.*, vol. 254, no.4, pp. 189-196, 1998.
[16] R.M. Haralick, K. Shanmugam, and I. Dinstein, "Texture Features for Image Classification", *IEEE Trans. Systems, Man., and Cybernetics*, vol. SMC-3, pp. 610-621, Nov. 1973.
[17] J.M. Mathias, P.S. Tofts, and N.A. Losseff, "Texture analysis of spinal cord pathology in multiple sclerosis", *Magn. Res. in Med.*, vol. 42, pp. 929-935, 1999.
[18] O. Yu, Y Mauss, G. Zollner, I.J. Namer, and J. Chambron, "Distinct patterns of active and non-active plaques using texture analysis of brain NMR images in multiple sclerosis patients: Preliminary results", *Magn. Reson. Imag.*, vol. 17, no. 9, pp. 1261-1267, 1999.
[19] V. Murray, P. Rodriquez, and M.S. Pattichis, "Multi-scale AM-FM demodulation and reconstruction methods with improved accuracy," to appear, *IEEE Trans. Imag. Proces.*, 2010.
[20] J.P. Havlicek, AM-FM image models. Ph.D. dissertation, The University of Texas at Austin, 1996.
[21] N. Cristianini, J. Shawe-Taylor, "An Introduction to Support Vector Machines and Other Kernel-based Learning Methods," First Edition, Cambridge: Cambridge University Press, 2000.

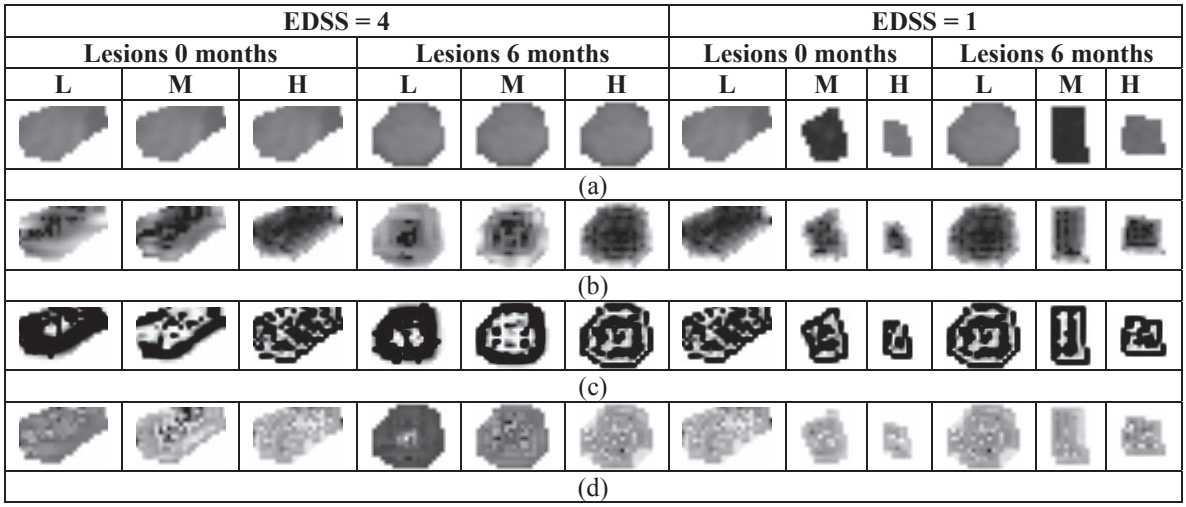

Figure 1. Multi-scale AM-FM analysis for MS brain lesions. For each column we have the Low (L), medium (M), and high frequency scales (H). Here, we have two 51-year old males with MS brain lesions (EDSS=4 and EDSS=1). Also, we present results for 0 and 6 months. (a) Original lesions. (b) Logarithm view of the IA. (c) |IF| of the lesion. (d) FM reconstruction of the lesion. Note that IF estimates with magnitudes outside the support of the low, medium, high scale passbands are presented in black.