Multi-Scale AM-FM for lesion Phenotyping on Age-Related Macular Degeneration

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***Abstract* — Age-related macular degeneration (AMD) is the most common cause of visual loss in the United States and is a growing public health problem. The presence and severity of AMD in current epidemiological studies is detected by the grading of color stereoscopic fundus photographs. The purpose of this study was to show that a mathematical technique, amplitude-modulation frequency modulation (AM-FM) can be used to generate multi-scale features for classify pathological structures, such as druses, on a retinal image. AM-FM features were calculated for N=120 40x40 regions from 5 retinal images presenting with age-related macular degeneration. The results show that with this technique, drusen can be differenced from normal retinal structures by more than three standard deviations using the AM-FM histograms. In addition, using different color spaces perfect classification of structures of the retina is achieved. These results are the first step in the development of an automated AMD grading system.**

***Index Terms* — Macular Degeneration, AM-FM**

I. Introduction

Age-related macular degeneration (AMD) is the most common cause of visual loss in the United States and is a growing public health problem. One third of Americans will develop AMD in their lifetimes. The prevalence of AMD is expected to double over the next 25 years (CDC), due to the increase in the number of older Americans.

Over the past several years, significant progress has been made in understanding the phenotypical characteristics of AMD in order to establish those individuals at risk for progression and vision loss. Careful evaluation of the clinical features of patients has, in the past, often revealed relationships between genotype and phenotype. For example certain genetic subtypes of retinitis pigmentosa (RP) [1], glaucoma [2], and age-related macular degeneration (AMD) [3,4,5] have exhibited clinically recognizable phenotypes.

AMD is characterized by the appearance of subretinal deposits termed drusen, as well as abnormalities of the retinal pigment epithelium (RPE) consisting of depigmentation and/or increased retinal pigment [6, 7, 8]. Segmenting drusen on a retinal image is central in the classification of AMD; hence their measurement and quantification are important in research and various clinical studies. The size, density, and other characteristics of the drusen will determine the classification of the stage of the disease and serve as a basis for establishing more refined phenotypes of AMD. Currently, defining the characteristics of the drusen in a repeatable manner requires painstaking human visual analysis of the drusen size, number, area, and morphology in a number of subcategories.

In this paper, we present the results of applying amplitude modulation – frequency modulation (AM-FM) methods to characterize two different types of drusen: soft and hard, and two features of normal healthy retinas: vessels and retinal background.

AM-FM is a means for mathematically characterizing the structures within any image or signal. An image can be thought of as being composed of a multitude of sine or cosine waves with varying amplitudes and frequencies. AM-FM decomposes the image into the basic sinusoidal waves and their amplitude. For each pixel in an image, one obtains a dominant frequency and amplitude for that point. The model uses different scales and filter sets to capture the widely varying frequencies that may be present in an image.

Retinal structures are composed of spatially-varying frequencies and amplitudes that are used to characterize the image. Low frequency components are associated with soft structures such as large drusen, medium frequencies with hard drusen, and higher frequencies are associated with vessels. We expand on this idea in the methods section using examples and illustrations. AM-FM methods characterize the structures on the image in terms of the estimated instantaneous frequency (IF) and instantaneous amplitude (IA) components [9].

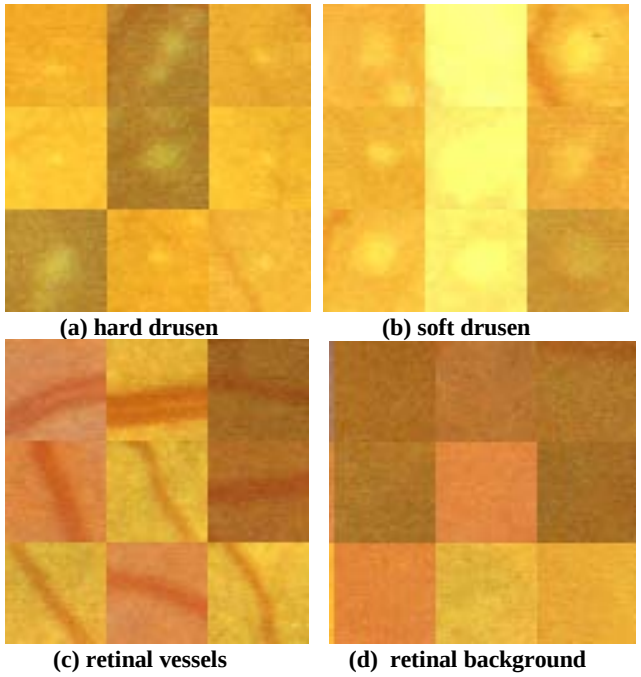
Our goal is to find a statistical measure to characterize the four different retinal structures selected for this study. For this, we first calculated the AM-FM features for each of the Age-Related Eye Disease Study (AREDS) standard images [10]. Following this calculation we extract the eleven combinations of scales (CoS) described in the methods section. These CoS allow for different spatial frequencies to be represented in our analysis by mapping their histograms.

II. METHODS

The Data

The standard high-resolution AREDS images were downloaded from the Wisconsin Fundus Photo Reading Center's website [11]. Image size is 1200x1000 pixels in TIF format. A certified ophthalmic technician (reader) selected the retinal features. For these studies, we used only areas that contain retinal background, vessels, soft drusen, and hard drusen. After the reader selected the features, regions of interest (ROI) of 40x40 pixels were extracted from the image.

Figure 1 shows the examples used for the training and testing of the AM-FM feature-based classification. Although, these were selected by a trained grader, it is clear that the two drusen classes have members which visually have characteristics that are similar.



(a) hard drusen **(b) soft drusen**

(c) retinal vessels **(d) retinal background**

Figure 1 – Samples of structures used in the AM-FM – based feature classification. (a) hard drusen, (b) soft drusen, (c) retinal vessels, and (d) retinal background

Multi-Scale AM-FM

We use (AM-FM) methods for mathematically characterizing the structures in digital images. We apply the AM-FM methods over different scales for representing an input digital image $I(k_1,k_2)$ as a sum of AM-FM components:

$$I(k_1,k_2)=\sum_n \hat{I}_{AM,n}(k_1,k_2)\hat{I}_{FM,n}(k_1,k_2) \qquad (1)$$

The AM functions characterize slowly-varying image intensity variations. For a single component, the AM function is given by the instantaneous amplitude (IA): $\hat{I}_{AM}(k_1,k_2)=a(k_1,k_2)$ whereas the FM function captures fast-changing spatial variability in the image intensity and is given by the cosine of its instantaneous phase function (IP), $\hat{I}(k_1,k_2)=\cos\varphi(k_1,k_2)$. Thus, we can approximately represent the input digital image as:

$$I(k_1,k_2)=a(k_1,k_2)\cos\varphi(k_1,k_2) \qquad (2)$$

The instantaneous frequency (IF) is defined as the vector as the gradient of the IP, $\nabla\varphi(k_1,k_2)$.

Table 1. Bandpass filters corresponding to different scales (dyadic decomposition over two quadrants).

	Scales	Range in pixels	Range in lowest frequency content
LPF	Lowpass Filter	Up to 45 – 25	$[0,\pi/16]$
VL	Very Low Frequencies	22.6 – 32	$[\pi/16,\pi/8]$
L	Low Frequencies	11.3 – 16	$[\pi/8,\pi/4]$
M	Medium Frequencies	5.7 – 8	$[\pi/4,\pi/2]$
H	High Frequencies	2.8 – 4	$[\pi/2,\pi]$

We use the IF to differentiate structures based on the gradient of the pixel-based frequency. Also, the IF models orientation variations or structures in an image region in terms of the direction of the IF vectors because of the no dependency on local image contrast or average brightness level.

We use the methods developed by Murray and Pattichis [12,13] to use AM-FM components extracted from different scales. We describe the correspondence between the scales and frequency ranges in Table 1. Scales and filterbanks are important and necessary because they take into account the size variability of structures. Thus, we can relate the lengths with the corresponding frequencies. Table 1 shows the relationships between the scales and the ranges in number of pixels and frequencies, respectively.

We consider eleven different combinations of scales (CoS) for extracting the dominant AM-FM estimates from different frequencies ranges (see Table 2). From each CoS, we use the histograms of the IA, the |IF|, and the IF angle. We use those histograms to create a feature vector for encoding the characteristics related with the structure presented in the ROI image analyzed. Using histograms at different CoS (see Table 2), the information extracted with AM-FM can be analyzed to find differences among characteristics in the ROI. Using these histograms, we can discover whether certain frequencies components that encode a feature are presented at the image.

Table 2. Scale combinations used for computing the dominant AM-FM feature parameters.

Comb. #	Scales	Comb. #	Scales
1	VL, L, M, H	7	LPF, VL
2	LPF	8	VL, L
3	VL	9	L, M
4	L	10	M, H
5	M	11	H
6	LPF, VL, L, M, H		

III. RESULTS

After calculating the AM-FM histograms, we applied principal components analysis to the matrix containing histograms of the 120 ROIs (30 for each retinal structure) for three different AM-FM features: IA, |IF|, and IF Angle. PCA transforms a number of possibly correlated variables into a smaller number of uncorrelated variables called principal components. The first principal component accounts for as much of the variability in the data as possible, and each succeeding component accounts for as much of the remaining variability as possible. For our experiments, we kept the principal components that accounted for 95% of the variability of the data. Finally, the Mahalanobis distances between the different retinal structures based on PCA decomposition are calculated. These distances are shown in Table 3.

Table 3. Mahalanobis distance between retinal features: Retinal Background (RB), Hard Drusen (DRH), Soft Drusen (DRS), and Vessels.

MAX MAHALANOBIS DISTANCES

	RB	DRH	DRS	Vessels
RB		3.37	5.56	5.34
DRH			2.82	4.42
DRS				4.50
Vessels				

The numbers in Table 3 represent the standard deviations separating the histograms of the retinal structures. The entries under DRH (hard drusen) and DRS (soft drusen) show that they are significantly differentiated from other structures in the retina. A distance of 3 standard deviations represents a classification accuracy of >90%. The most interesting entry is the Mahalanobis distance between the two drusen types (2.8 standard deviations). Though still considered a high classification rate (85%), this demonstrates the challenge not only to the algorithm, but for the grader in unequivocally assigning drusen to one class or another. Figure 2 shows the examples used for the training and testing of the AM-FM feature-based classification. Although, these were selected by a trained grader, it is clear that the two drusen classes have members which visually have characteristics that are similar.

Figure 3 shows the plots of the cumulative density functions (cdf) for different retinal structures and combinations of scales in Table 2. By definition, the cdfs completely describe the probability function of a random variable, in this case the variable being the AM-FM features. Figure 1(a) shows that instantaneous frequency clearly differentiates the soft and hard drusen. The differences in their cdf are a result of the brighter cores of the soft drusen as compared to the hard drusen. (b) shows the cdf for AM-FM features that characterize the difference between hard drusen vessels. As one can see from the figures, the instantaneous amplitude is the AM-FM feature that best soft from hard drusen, while the instantaneous frequency magnitude best separates hard drusen and vessels. Similarly, (c) and (d) show that IA separates soft drusen from retinal background and the IF produces best results for separation between soft drusen and vessels.

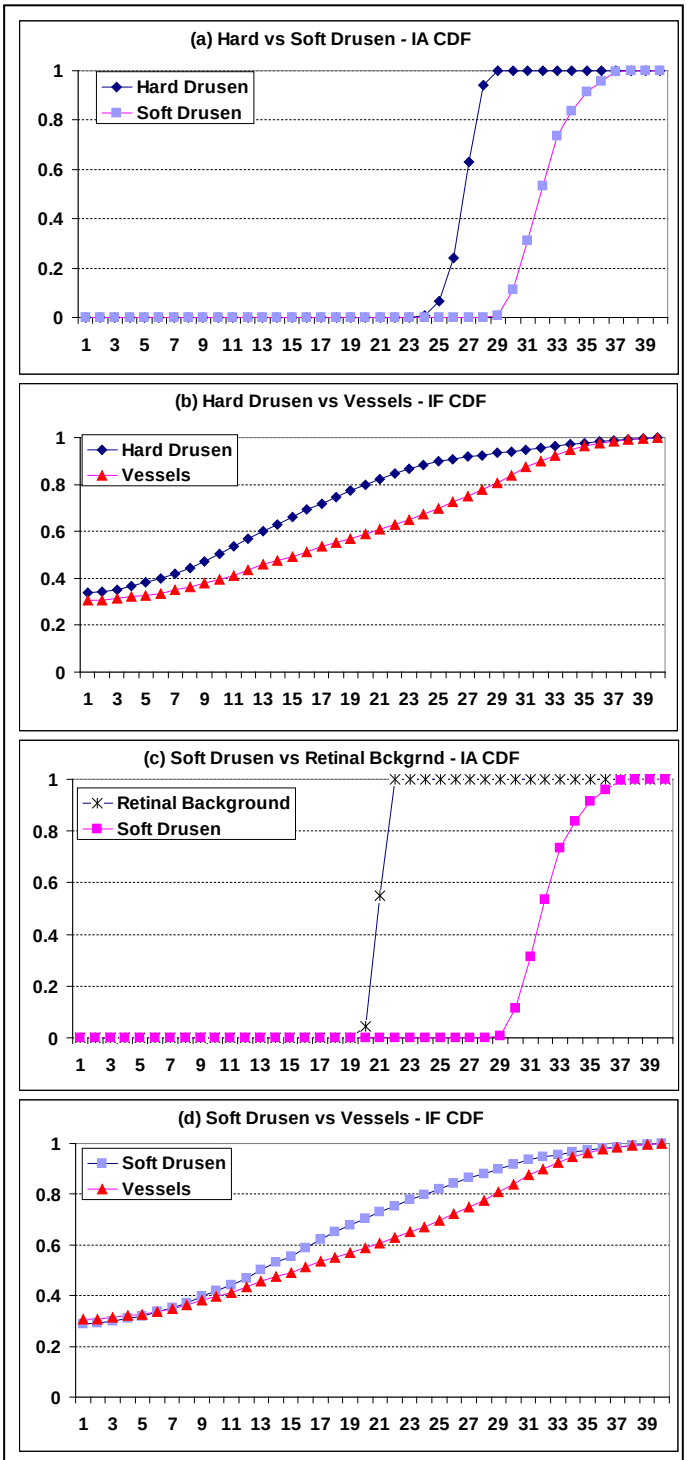


Figure 3. Cumulative Density Functions (cdfs) for drusen vs. other retinal structures. Instantaneous Amplitude (IA) cdfs clearly differenciate between hard and soft drusen (a) and between retinal background and drusen on (c). The instantaneous frequency magnitude (IF) is the feature that best differentiates drusen from retinal vessels on (b) and (d).

One can hypothesize that since in the retinal background there is low pixel-to-pixel contrast variation, its IA has low values. Conversely, retinal structures that present with larger

variations in contrast, such as drusen-background, will have higher values of IA. On the other hand, IA is not as effective at separating other structures with contrast changes such as retinal vessels. In this case, it is the instantaneous frequency magnitude that produces the largest difference in histograms because of the variations in frequencies between the structures.

Retinal Features Classification Using AM-FM and Partial Least Squares (PLS)

The original images from the database are in RGB format (Red-Green-Blue). Most of the standard image processing methods for retinal images use the Green layer only as input for the algorithms. For this study we use three different color spaces: RGB, HSV, and the Ohta [14] color space. The advantage of mapping the RGB images to different spaces is that both HSV and Ohta spaces have the property of invariance in shadows, shading, highlights, and illumination intensity [15].

We present the classification of the structures in the selected ROI images. We use the dataset described in the previous section that contains a total of 120 40x40 pixels ROI images (30 for each structure).

First, we compute the AM-FM estimates of each image using the 11 different CoS, as described in Table 2. For each ROI image (120 images total) and for each of the 11 CoS, we create a 96-bin feature vector per layer that contains the AM-FM histograms, i.e., instantaneous frequency and instantaneous amplitude at each pixel. Next, for each CoS, we apply a linear regression using PLS [16, 17] to classify the images based on the AM-FM feature vectors[13]. PLS will use the output features from the AM-FM algorithms to classify the ROIs containing different structures. This linear regression method is based on linear transition from a large number of original descriptors to a new variable space based on a *small number of orthogonal factors (latent variables)*. In other words, factors are mutually uncorrelated (orthogonal) linear combinations of original descriptors.

Table 4. Results of the classification for comparing the four types of structures. We present the results in terms of: (i) area under the receiver ROC curve (AUC), (ii) specificity (Spe), and (iii) sensitivity (Sen).

Color space	Hard drusen vs. Soft drusen			Hard drusen vs. Retinal Background		
	AUC	Spe.	Sen.	AUC	Spe.	Sen.
Green	0.99	0.93	1	0.97	0.97	1
RGB	0.99	0.97	1	1	1	1
HSV	1	0.97	1	0.97	0.97	1
Ohta	0.96	0.97	0.97	1	1	1
	Hard drusen vs. Vessels			Retinal background vs. Vessels		
	AUC	Spe.	Sen.	AUC	Spe.	Sen.
Green	0.99	1	1	1	1	1
RGB	0.99	1	0.97	1	1	1
HSV	0.95	0.97	0.97	0.99	1	1
Ohta	1	1	1	1	1	1
	Soft drusen vs. Retinal Background			Soft drusen vs. Vessels		
	AUC	Spe.	Sen.	AUC	Spe.	Sen.
Green	1	1	1	1	1	1
RGB	1	1	1	0.98	1	0.97
HSV	1	1	1	1	1	1
Ohta	1	1	1	1	1	1

In Table 4, we present the results of the classification performed in pairs. Thus, we compare: (i) hard drusen vs. soft drusen, (ii) hard drusen vs. retinal background, (iii) hard drusen vs. vessels, (iv) soft drusen vs. retinal background, (v) soft drusen vs. vessels and (vi) retinal background vs. vessels. We present the results in terms of: (i) area under the receiver operator characteristics curve (AUC), (ii) specificity, and (iii) sensitivity. Results show high values for sensitivity and specificity, meaning that our methodology has been successful in differentiating between drusen and both vessels and retinal background.

Using a dataset of 120 ROI images, the four structures in pairs (hard drusen, soft drusen, retinal background, and vessels) were compared. For each comparison (see Table 4), there is at least one color space that produced a perfect classification (AUC = 1). In the case of comparing soft drusen vs. retinal background, all the color spaces produced perfect classification.

IV. CONCLUSIONS

In this paper, we have shown two ways of characterizing phenotypes for AMD lesions. First, using multi-scale AM-FM we determined statistical distances between four different retinal structures, two normal (vessels, background) and two abnormal (hard and soft drusen). Results show separation of at least two standard deviations between the density functions that characterize these structures.

Second, using color image processing and PLS we developed a classification system to categorize the structures, obtaining 100% sensitivity and specificity. We have used 3 different color spaces. In the future we need to determine an optimum color space that has invariance under most conditions (such as illumination or over exposure) and with normalized values. This will allow us to use images from taken by different sources and using different cameras. We expect from these classifications that when we will apply the same methodology to a larger and new database, the combination of the same independent cases CoS will produce high sensitivity/specificity on the classification.

These preliminary studies demonstrate a basic element for developing an automated AMD grading system. We have shown that our approach can detect and differentiate various retinal structures and more importantly classify visually characterized structures such as hard versus soft drusen. Segmentation is a logical continuation step.

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