Mixture Model-based Clustering and Logistic Regression for Automatic Detection of Microaneurysms in Retinal Images

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ABSTRACT

Diabetic Retinopathy is one of the leading causes of blindness and vision defects in developed countries. An early detection and diagnosis is crucial to avoid visual complication. Microaneurysms are the first ocular signs of the presence of this ocular disease. Their detection is of paramount importance for the development of a computer-aided diagnosis technique which permits a prompt diagnosis of the disease. However, the detection of microaneurysms in retinal images is a difficult task due to the wide variability that these images usually present in screening programs. We propose a statistical approach based on mixture model-based clustering and logistic regression which is robust to the changes in the appearance of retinal fundus images. The method is evaluated on the public database proposed by the *Retinal Online Challenge* in order to obtain an objective performance measure and to allow a comparative study with other proposed algorithms.

Keywords: Diabetic Retinopathy, microaneurysms, mixture models, retinal images.

1. INTRODUCTION

Retinal images are widely used by ophthalmologists and primary care physicians for the screening of epidemic eye diseases, such as Diabetic Retinopathy (DR). DR is one of the leading causes of blindness and vision defects in developed countries[1]. Due to its prevalence and clinical significance the research community has attempted to improve its diagnosis and treatment by developing algorithms to perform retinal image analysis. Retinal images permit a high quality permanent record of eye fundus for detecting early signs of DR and monitoring its progression. Moreover, their digital nature allows automatic analysis to reduce the workloads of the ophthalmologists and the health costs in the screening of the disease[1].

Early detection and diagnosis of DR is crucial for the prevention of visual loss. Among the early signs of DR, Microaneurysms (MAs) are the first signs of the presence of DR[1]. Therefore, their detection is of paramount importance for the early diagnoses of DR. MAs are a small dilation of retinal capillaries due to the weakness of the vessel walls. On the retinal surface, they appear as small round dark red dots with about 10 to 100 μm in diameter.

Several techniques have been developed for MA detection in fluorescein angiographies and in color fundus images based on a variety of techniques. MAs have been detected using template matching[2] and mathematical morphology[3]. However, supervised methods, such as statistical classifiers[4-6] and k-nearest neighbor classifier[7] have been also applied. Because the brightness, contrast and color of MAs vary a lot among different patients and, therefore, different images, these methods would not work in all the images used in clinical environment.

In this work we propose a robust statistical approach based on mixture model-based clustering followed by a classification step using logistic regression. The innovative segmentation approach based on a statistical mixture model based clustering allows a robust separation of the foreground and background scenes and, specifically, a segmentation of MAS in a totally unsupervised manner. The method is robust to the changes in the appearance of retinal fundus images typically encountered in clinical environments, achieving a satisfactory MA detection performance.

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2. METHODS

The method herein presented for MA detection relies on an initial segmentation using mixture model-based clustering and a subsequent refinement stage by means of supervised classification. After preprocessing the image for background normalization, a mixture model will be fitted to pixel intensity distribution to obtain a segmentation of the image foreground in a totally unsupervised manner. The resulting pixel-cluster memberships provide a transformation of the pixels into different image regions, which are suspected of corresponding to retinal lesions. Using logistic regression techniques, a likelihood for each region will be generated based on their colour, shape and texture characteristics. A final MA classification will be obtained thresholding the probability map.

2.1 Preprocessing

There is a large variability in colour, luminosity and contrast both within and between retinal images in a clinical environment. The intrinsic characteristics of the patients, such as skin pigmentation and iris colour, cause that the colour of the fundus is typically unique for each subject. Additionally, an inadequate acquisition process can cause intra-image variations of luminosity and contrast, reducing the quality of the images. All these features have a significant impact on the diagnostic process of DR and the automatic detection of retinal lesions.

One of the main obstacles for identification of retinal lesions is the uneven illumination of the retinal images. This non-uniformity hinders absolute interpretation of the intensities in the image.

In order to obtain image normalization, the intensity variation in the background across the image is removed. This is accomplished by subtracting an estimate of the background I_{bg} from the green channel G.

$$I_{norm} = I_{bg} - G \tag{1}$$

This operation is performed on G because retinal lesions appear more contrasted in this component of the RGB colour model. I_{bg} is produced by median filtering G with a NxN mean kernel. N is selected to remove slow variations of the background while preserving the MA contrast in the retina, as it is shown in Fig. 1(b).

2.2 Mixture model-based clustering for candidate extraction

In image segmentation the image is partitioned into regions (image classes) based on the properties of pixel images. Fundus image consists of two meaningful classes: background and foreground. Retinal lesions, along with the major retinal anatomical features (optic disk, blood vessels), belong to the latter. Our purpose involves determining a suitable threshold to separate the foreground regions from the background pixels. However, the retinal illumination, anatomical features, fundus tissue reflection and lesions are quite different among images. Therefore, foreground and background scenes vary from image to image depending on the subject's anatomical characteristics, even after preprocessing stage.

We propose a flexible technique based on mixture model which is adapted to the variable characteristics of the underlying image and sets a suitable threshold depending on its statistical intrinsic structure. Mixture models are a flexible and powerful probabilistic modelling tool that provides a principled statistical approach to clustering[8]. The advantages of mixture modelling lie in its statistical basis. The flexibility and robustness in treating data with widely varying characteristics makes this approach suitable for retinal image segmentation. Besides, noise and outliers can be handled in this probabilistic approach[9].

As it is shown in Fig. 1(c), The histogram of the normalized image I_{norm} usually has a unimodal shape, heavy tailed with different weight in the tails which comprises the vast majority of the pixels in the image. The proposed method relies on the fact that the background is usually visible more frequently than any foregrounds. Therefore, the peak corresponds roughly to the natural level of variation within homogeneous regions and represents the image background. The heavy tails are caused by foreground elements varying below and above the natural level, such as vessels, the optic disk and lesions. Several pixels are characterized by grey levels far removed from the majority distribution, which are considered as outliers.

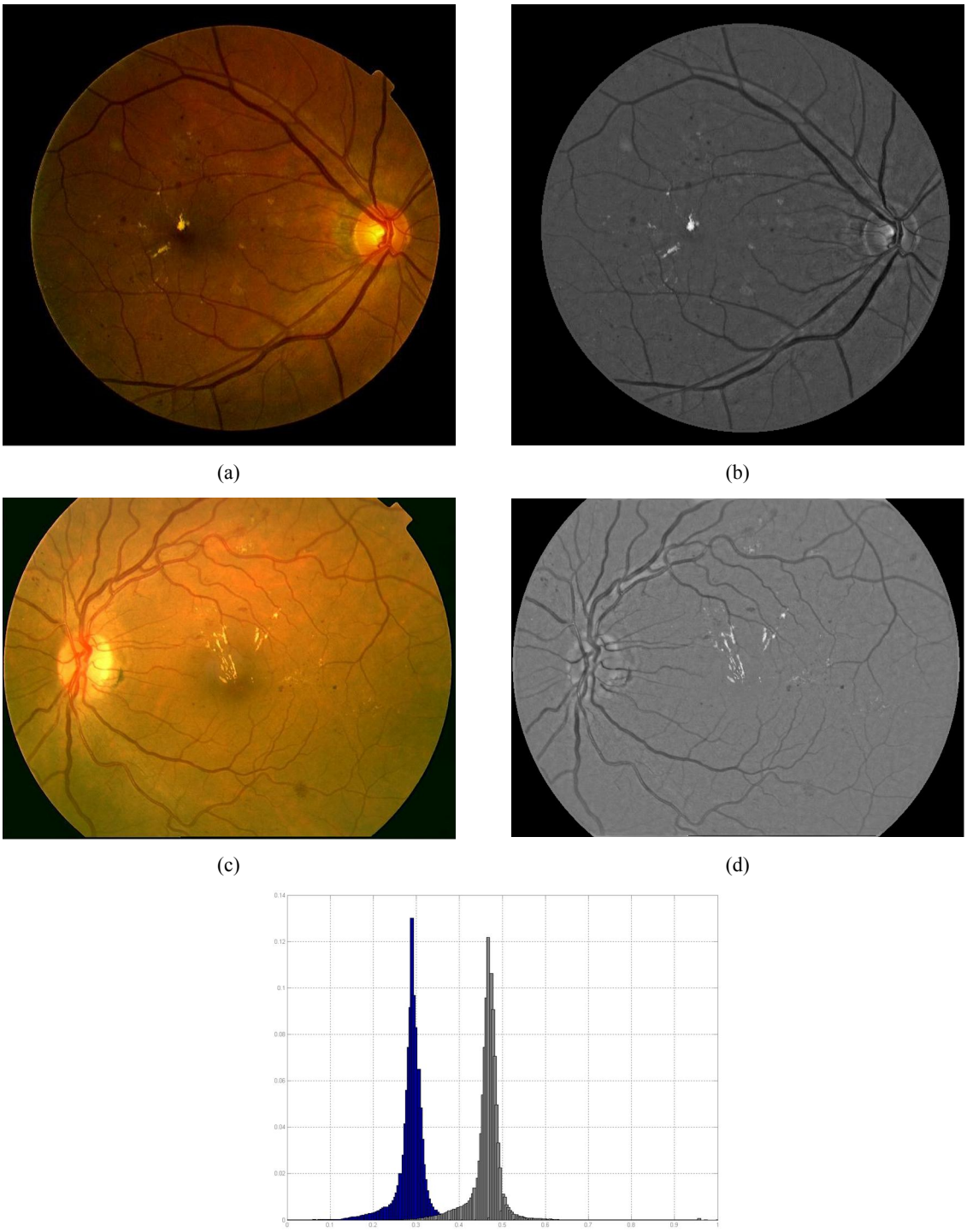

Fig. 1. Preprocessing result and histogram of the normalized images. (a,c) Original images, (b,d) normalized images after preprocessing step, (e) histogram of the normalized images.

Let $\boldsymbol{Y} = Y_1, ..., Y_n$ be a finite set of pixels from a fundus image characterized by their intensity value, Y_j, in the enhanced image I_{norm}. Suppose that a pixel comes from one of the following classes: class 1 (background elements),

class 2 (foreground elements, such as vessels, optic disk and lesions) and class 3 (outliers). Visual analysis of the histograms of several retinal images has inspired us to assume that the distribution of grey levels for each class can be modelled by a normal distribution $N(\mu_i, \sigma_i)$ with mean μ_i and variance σ_i, with $i = 1, 2, 3$. Therefore, the overall normalized histogram of the image can be estimated as a 3-component MM distribution[9]:

$$f(y_j) = \sum_{i=1}^{3} \pi_i N(y_j; \mu_i, \sigma_i^2) \tag{2}$$

The third class is introduced to obtain a robust estimation of the MM, which tries to reduce the influence of the outlying observations[9]. Applying the Expectation-Maximization (EM) algorithm[9], we can estimate the mixture parameters and fit the mixture model to the image histogram.

After the convergence of the mixture parameters (Fig. 2), the artifact component of the MM is identified by using the maximum variance criterion[9]. It presents a larger standard deviation than the others and it corresponds to grey levels that lie far away from the midline. The two remaining components correspond to the background and foreground classes. The component with higher mixing weight (π_i) is associated to the background pixels. The component with large variance represents the foreground features, such as vessels, OD and different lesions that can appear in a fundus image, such as MAs.

After the histogram modeling, we can extract a group of MA candidates thresholding the obtained model. Since the point of discontinuity on the curve represents the intersection of two overlapping distributions, we analyze the concavity of fitted model to obtain the threshold. The influence of outliers is avoided setting this threshold without considering the outlier component of the histogram model[9]. In order to get only the dark foreground elements, we set the threshold in the deepest concavity point that is found on the left tail of the model using the convex hull[10]. The final candidate objects are obtained by running a connected-components algorithm in the segmented image after automatically masking out the blood vessels.

2.3 Feature selection

A total of 28 features for each region are extracted based on region descriptions. We focused on those characteristics which correspond to the visual concepts that ophthalmologists use to distinguish lesions from the retinal background. Features based on shape, colour, brightness and contrast are included.

Significant features are identified by means of stepwise selection method. The Rao's efficient score test is evaluated for entry criterion and the likelihood ratio test for exit criterion. As the number of significant features increases with the number of example observations, a variance ratio criterion is used, along with the p-value, for variable entry criterion[11]. In that way, the stepwise procedure is repeated until the remaining features do not meet the specified level for the criterion function (p-value>0.05) or when the individual percentage of variance explained is below a specific threshold. Setting the minimum percentage of variance explained to 2.5%, we obtain an optimal trade-off between the discrimination power and the computational efficiency.

2.4 Logistic regression classification

For candidate classification, a logistic regression (LR) classifier is trained using samples in the training set characterized by the selected features. In order to robustify the design of the classifier, we remove outlying observations which do not follow the trend of the majority of the training data. To avoid the influence of these outliers, we only take into account samples contained in a 95% confidence ellipsoid, which is estimated using the Minimum Covariance Determinant approach[12].

In order to robustify the design of the classification rules, we remove outlying observations which do not follow the trend of the majority of the training data. To avoid the influence of these outliers, we only take into account samples contained in a 95% confidence ellipsoid. This ellipsoid is defined as the set of points whose distance from the population mean is equal to $\chi^2_{p-1;0.95}$ [11]. Observations outside this tolerance ellipsoid correspond with outliers. The location and scatter of the confidence ellipsoid depends on the population mean and covariance matrix, which are extremely sensitive to outlying observations. Therefore, we apply the Minimum Covariance Determinant (MCD) estimator to obtain a robust estimation of the sample mean and covariance matrix[12]. The MCD method looks for the h observations, with $h<n$ and n

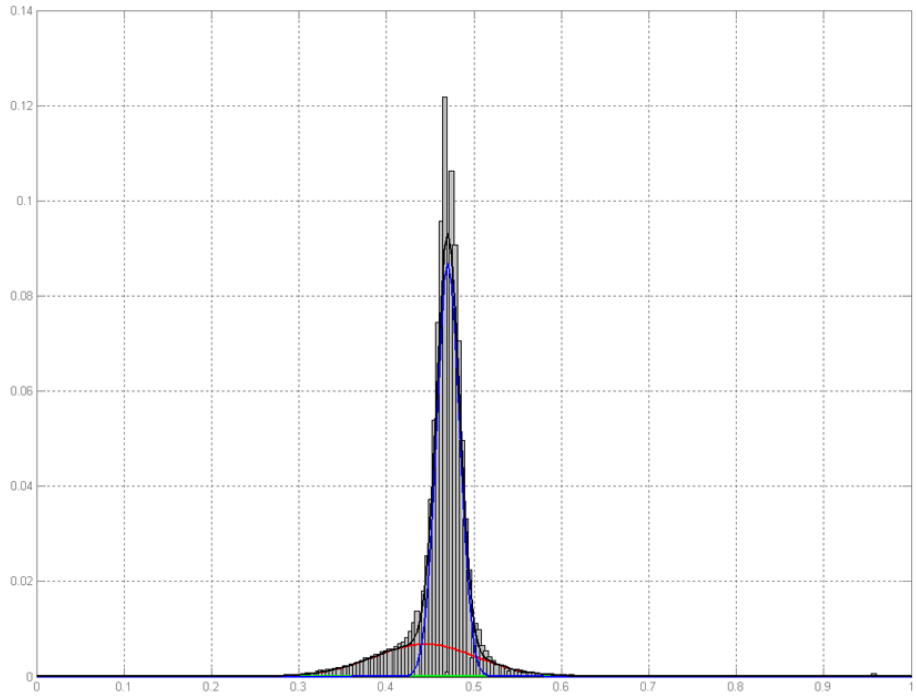

Figure 2. Convergence of the mixture model. Intensity histogram with the background, the foreground and the outlier components superimposed in blue, red and green, respectively.

is the number of training samples, whose covariance matrix has the lowest possible determinant [4]. A value for h=0.75n is highly recommended to obtain a higher finite-sample efficiency[12]. Using these h points, robust estimators for the population sample mean and covariance matrix are obtained.

After applying the robust trained LR classifier with the selected subset of features, we obtain a lesion probability map in which each candidate region is assigned a probability indicating the likelihood that it is a true MA. The final detection of retinal lesions is performed by thresholding the lesion probability map. This threshold is selected to obtain an optimum trade-off between the number of detected true lesion and the mean number of false positives. Fig. 3 shows two final classification results.

3. RESULTS

We assessed the performance of our algorithm on the retinal images proposed by the Retinal Online Challenge (http://roc.healthcare.uiowa.edu/). This dataset consists of 100 retinal images all taken from patients with diabetes without known diabetic retinopathy (at the moment of photography). The images are a random sample of all patients that were noted to have 'red lesions' from a large (> 10,000 patients) diabetic retinopathy screening program, and each image is from a different patient.

The images were acquired with Topcon NW 100, NW 200 or Canon CR5-45NM non-mydriatic cameras at the default resolution and compression settings. The set of 100 images was divided into a test and a training set both containing 50 images. The training set was used for algorithm development (i.e., to choose the value of N in the preprocessing step) and for the design of the classification rule. The expert annotations are a weighted consensus from four ophthalmologists with retinal fellowship training.

The performance of the MA detection method has been measured in a uniform and objective manner on the test set. Fig. 4 shows the Free-response Receiver Operating Characteristic (FROC) curve for MA detection using the corresponding test set, obtaining an overall score in the competition of 0.332404.

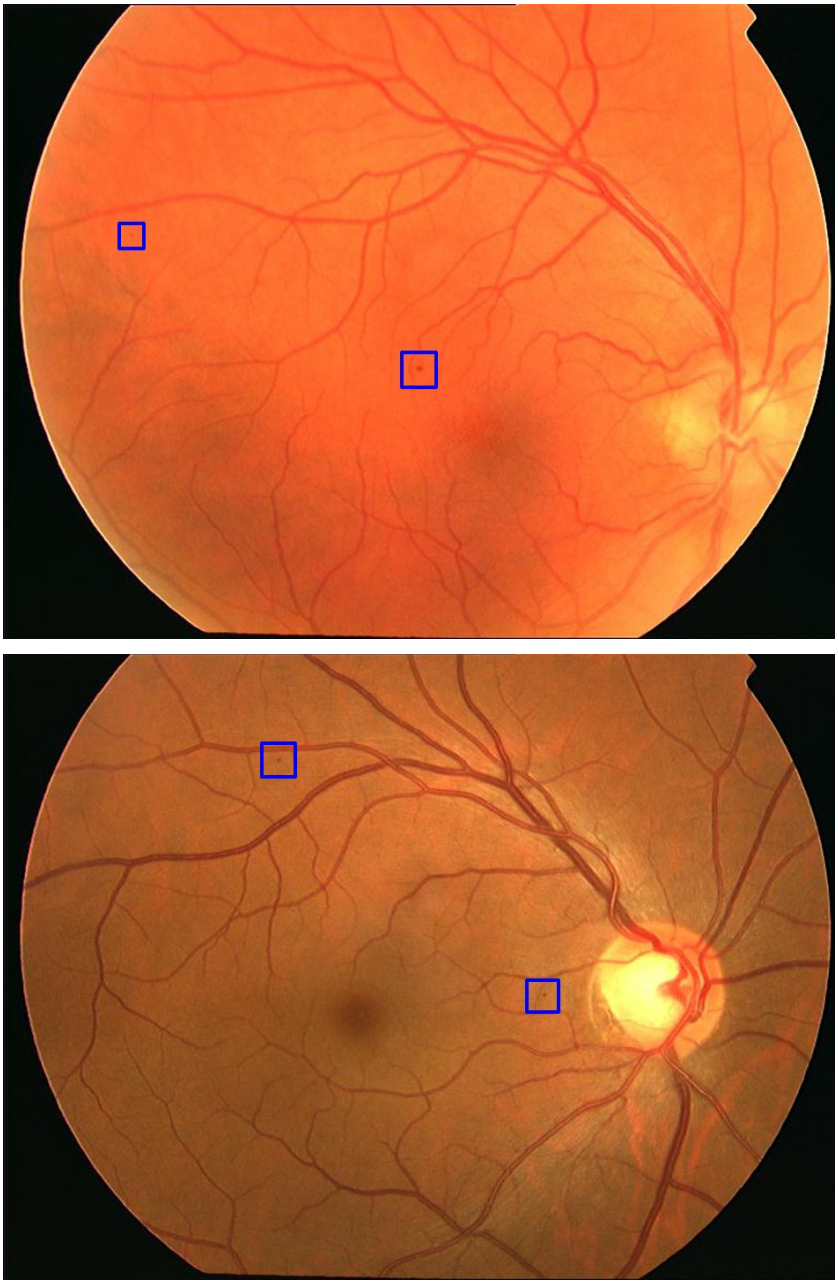

Fig. 3. Final classification results. The detected MAs are marked with a blue square.

4. DISCUSSION

An innovative algorithm based on MM based clustering and LR classifier has been proposed and evaluated for the automatic detection of MAs in retinal images.

A segmentation procedure based on MMs was first applied to divide the retinal image into foreground and background. The retinal illumination, anatomical features, fundus tissue reflection and lesion characteristics are quite

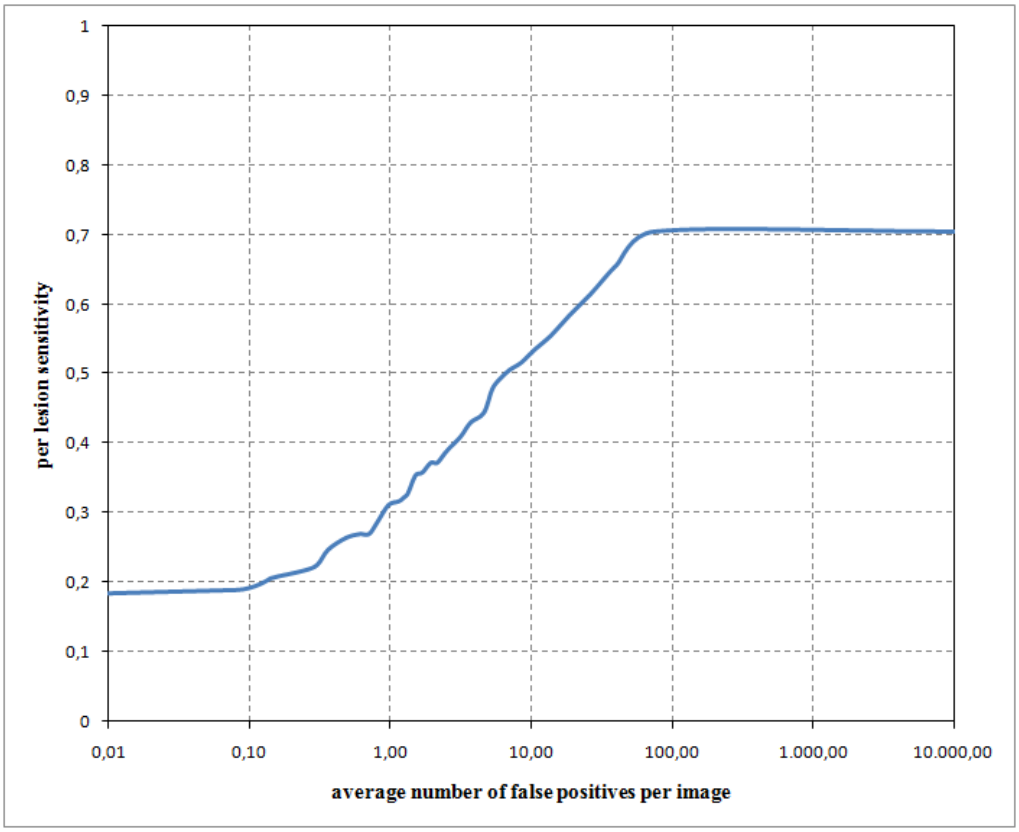

Figure 4. FROC curve for the proposed MA detection method. The horizontal axis has a logarithmic scale.

different among images. Therefore, foreground and background scenes vary from image to image depending on the subject's anatomical characteristics, even after preprocessing stage. This variability hinders the establishment of a predefined threshold or the selection of an objective training set to accurately segment foreground scene in all images. The main advantages of the proposed segmentation process relied on the use of MMs. This approach provides an unsupervised method which is adapted to the intrinsic structure of the underlying data. Additionally, it is more flexible to segment images of the same scene but with a wide variability. Finally, MMs permits a robust estimation of the data distribution to minimize the influence of outliers and undesired noise.

Several features have been proposed for the description of MAs based on visual concepts. The best subset of features was identified by means of feature selection procedures in order to find a trade-off between the discrimination power and the computational efficiency.

In order to robustify the design of the classification rules, we considered training samples included in a 95% MCD tolerance ellipsoid. Therefore, we removed outlying observations which do not follow the trend of the majority of the data and could have a strong influence on the estimation of the classification boundaries.

The complete algorithm has been evaluated using the public database proposed by the Retinal Online Challenge (http://roc.healthcare.uiowa.edu/). These images had variable characteristics and quality. In that way, the robustness and the suitability of the algorithm for a clinical environment may be investigated. Additionally, as it is a public data set, it allows a comparative study with other algorithms and retinal experts.

Despite the robustness of the segmentation process and the classification technique, the performance of the MA extraction was low. First of all, the system missed MAs adjacent to blood vessels. These elements were considered as a part of the vasculature and were masked out along with the blood vessels from the final result. The system could be improved by obtaining more accurate vessel segmentation. On the other hand, other objects were so extremely subtle that

the system failed to segment them. Finally, as MAs are usually more difficult to be distinguished from the background, a high number of false positives was also obtained.

5. CONCLUSIONS

The detection of MAs on retinal images is a difficult task due to the wide variability of images encountered in the clinical environment. This paper presents a robust statistical method adapted to the intrinsic characteristics of the images. Additionally, using the public database proposed by the Retinal Online Challenge (http://roc.healthcare.uiowa.edu/), it allows a comparative study with other algorithms and retinal experts.

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