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Design & Analysis for Monitoring Wet Macular Degeneration by using Fluorescein Angiograms

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Abstract: **The paper presents a fully-automated approach for robust detection and classification of changes in longitudinal time-series of Fluorescein Angiograms (FA).Analysis of changes from retinal images is important in medical practice, computer-assisted reading centres, quantitative scoring of clinical trials, and in scientific research. The changes of interest here are related to the development of Choroidal Neo-Vascularization (CNV) in Wet Macular Degeneration. Retinal features including the vasculature, vessel branching locations, optic disk and location of the fovea are first segmented automatically. Specifically, the Retinal Pigment Epithelium (RPE) hypertrophic regions as well as the changes in CNV regions are detected and analyzed to study the development of disease and effect of treatment. The images are then registered to sub-pixel precision using a 12-dimensional mapping that accounts for the unknown retinal curvature and camera parameters. The changes are identified in the regions of interest and a Bayesian classifier is used to classify the changes into clinically significant classes. Spatial variations in illumination are removed using a surface fitting algorithm that exploits the segmentations of the various features.**

Keywords: **Choroidal Neo-Vascularization (CNV), Fluorescein Angiograms (FA), Retinal Pigment Epithelium (RPE), Spatial variations**

I. INTRODUCTION

The disease in which central vision lead to loss term as macular degeneration. Layer under the macula get affected in Age related macular degeneration(AMD) that called as Retinal Pigment Epithelium (RPE).Atrophic macular degeneration & /exudative macular degeneration are two types. Atrophic macular degeneration is common form in AMD. Neovascula macular degeneration is less common form but more severe than dry form. In this form development of abnormal blood vessels beneath the RPE layer of retina characteristic by Choroidal Neo-Vascularization (CNV). These vessels can bleed and cause macular scarring which cause loss of central vision. The availability of highly effective therapies that can not only stabilize neovascular AMD, but can improve vision[3]. The existing treatments on CNV is still not known interest to automatically monitor the changes & to extract quantitative measurement in these case study. It has made it more important to have patients with treatable lesions present for care as early in the disease process as possible, when vision is least affected. It has long been recognized that patient self-assessment of their vision on a daily basis offers the best hope of detecting disease progression in a timely manner. Amsler grid is used to detect changes while self monitoring their vision. A number of alternatives have been developed in an effort to either improve or replace the Amsler gird, such as Fluorescein Angiogram. This has lead to a call for making the development of a cost-effective self assessment tool for patients with macular degeneration a research priority. Image pre-processing included removal of non-retinal and noisy macular degeneration. Despite the growing interest in retinal micro vessels as early predictors for ocular and brain diseases, to date, the use of FA for the detection of micro vessel alterations is limited due to a lack of objective and acceptable quantitative analysis methods for vessel structure and function. This in turn, raises issues regarding standardization of subsequent pathology evaluation or by different experts. Establishing a quantitative, objective and reliable image analysis tool, based on readily available FA studies, may prove to be a non-invasive method for the diagnosis of retinal diseases, as well as a potential predictor for central nervous system pathologies. We have recently established a method for quantitative assessment of brain vessel permeability using FA in experimental rodent models. Based on the results obtained from such models, we were able to evaluate the accuracy of this new analysis method and apply it in a clinical setting. The objectives of the present study were to implement similar algorithms to assess vessel permeability in retinal FA examinations as part of a new platform for computer-aided diagnosis of retinal images (RetiCAD); test the method in cohorts of healthy individuals and patients diagnosed with diabetic retinopathy; and perform a preliminary evaluation for clinical significance by comparing the results obtained using RetiCAD to those of the standard examination. Future perspectives include the assessment of new treatments as well as the prediction and prevention of neurological complications in patients with small vessel diseases.

II. MACULAR DEGENERATION (MD)

MACULA

The macula or macula lutea (from Latin *macula*, "spot" + *lutea*, "yellow") is an oval-shaped highly pigmented yellow spot near the center of the retina

of the human eye. It has a diameter of around 6 mm and is often histological defined as having two or more layers of ganglion cells near its center is the fovea, a small pit that contains the largest concentration of cone cells in the eye and is responsible for central, high resolution vision. The macula also contains the par fovea and per fovea. Because the macula is yellow in color it absorbs excess blue and ultraviolet light that enter the eye, and acts as a natural sun block for this area of the retina. The yellow colour comes from its content of lutein and zeaxanthin, which are yellow xanthophylls carotenoids, derived from the diet. Zeaxanthin predominates at the macula, while lutein predominates elsewhere in the retina. There is some evidence that these carotenoids protect the pigmented region from some types of macular degenerative. Human eye cross sectional view shown in figure 1(a) & macula of retina shown in figure 1(b).

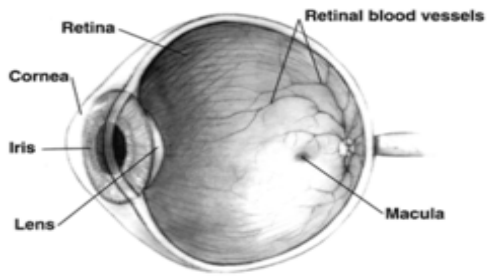


Figure.1 (a) Human eye cross sectional vie

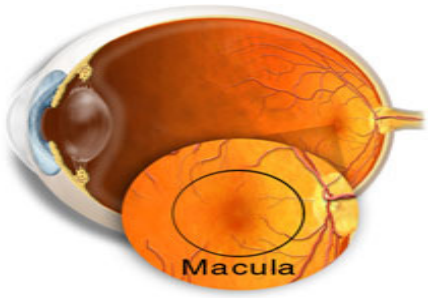
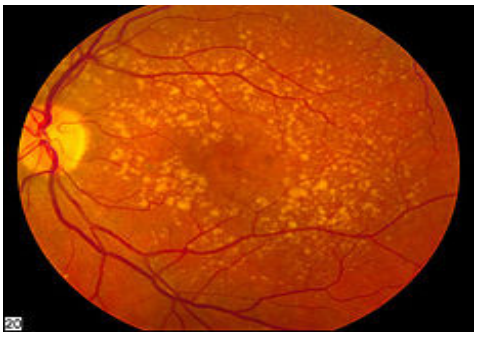


Figure.1 (b) Macula of retina

DEGENERATION

Macular degeneration MD is one of the most common sight defects, accounting for about a third of all visual impairment in this country. Usually it effects the over 50s and is therefore called age related Macular degeneration. In age related macula degeneration the highly specialised macula area has been affected. Sometimes the delicate cells of the macula become damaged and stop working. We do not know why this is, although it tends to happen when people get older. Because macula degeneration is an age-related process it usually involves both eyes, although they may not be affected at the same times Macular degeneration is a broad term describing diseases that lead to a loss of central vision. Some of these diseases affect the macula directly, while Age related Macular Degeneration (AMD) affects the layer under the macula known as the Retinal Pigment Epithelium. Age-related macular degeneration (AMD) is a medical condition which usually affects older adults and results in a loss of vision in the centre of the visual field (the macula) because of damage to the retina It occurs in "dry" and "wet" forms. It is a major cause of blindness and visual impairment in older adults (>50 years). Macular degeneration can make it difficult or impossible to read or recognize faces, although enough peripheral vision remains to allow other activities of daily life .Starting from the inside of the and going towards the outer surface, the three main layers at the back of the eye are the retina, which is light-sensitive tissue that is considered part of the central nervous system and is actually brain tissue; the choroid, which contains the blood supply; and the sclera, which is the white, outer, layer of the eye. Age-related macular degeneration begins with characteristic yellow deposits (drusen) in the macula, between the retinal pigment epithelium and choroid .Macular degeneration is revealed in figure 2..



Figuer.2 Macular Degeneration

WET MACULAR DEGENERATION

About 10-15% of macular degeneration cases are the "wet" form, in which newly-formed, immature blood vessels grow from the choroid ("choroidal neovascularization") and leak into the spaces above and below the photoreceptor cells. This process can damage the photoreceptor cells and cause permanent central vision loss. Only about 10% of patients suffering from macular degeneration have the wet type.

DRY MACULAR DEGENERATION

Most cases of macular degeneration are the "dry," or "atrophic", form, distinguished by yellowish deposits of debris in the retina. Called "drusen," the material comprising these deposits is usually carried away by the same blood vessels which bring nutrients to the retina. But for reasons yet unknown, this process is diminished in macular degeneration. Some of the potential causes being studied are inflammation, inadequate blood circulation in the retina, and premature aging of the sight cells due to genetic deficiencies. In addition, environmental, behavioural, and dietary factors are thought to contribute to the progress of the disease in those who are susceptible to it. Dry AMD may occur in three stages in one or both eyes such as “Early” stage “Intermediate” stage and “Advanced dry” stage.

III. SIGNS AND SYMPTOMS

In the early stages peoples have central vision which may be blurred or distorted, with things looking an unusual size or shape. This may happen quickly or may develop over several months. People may be very sensitive to light or actually see lights that are not there. This may cause some discomfort occasionally, but otherwise macula degeneration is not painful. The macula enables you to see fine detail and people with the advanced condition will often notice a blank patch or dark spot in the centre of their sight. This makes activities like reading, writing and recognising small objects or faces very difficult. Signs and symptoms of macular degeneration includes Pigmentary alterations, Exudative changes hemorhages in the eye, hard exudates, subretinal/sub-RPE/intraretinal fluid, Visual acuity drastically decreasing (two levels or more),Trouble discerning colors, specifically dark ones from dark ones and light ones from light ones, Slow recovery of visual function after exposure tobright light, A loss in contrast sensitivity.Causes of macular degeneration includes aging effects approximately 10% of patients 66 to 74 years of age will have findings of macular degeneration. The prevalence increases to 30% in patients 75 to 85 years of age. Family history is also one cause, lifetime risk of developing late-stage macular degeneration is 50% for people who have a relative with macular degeneration, versus 12% for people who do not have relatives with macular degeneration. Macular degeneration gene is another cause The genes for the complement system proteins factor H (CFH), factor B (CFB) and factor 3 (C3) are strongly associated with a person's risk for developing AMD . Elevated cholesterol may increase the risk of AMD, Fat intake consuming high amounts of certain fats likely contributes to

Fig 3(a) Normal vision

Fig .3(b) Same view with AMD

AMD, and while mono saturated fats are potentially protective in particular w-3 fatty acid may decrease the risk of AMD. Evidence is conflicting as to whether exposure to sunlight contributes to the development of macular degeneration. A recent study on 446 subjects found it does not. Other research, however, has shown high energy visible light may contribute to AMD. Smoking tobacco increases the risk of AMD by two to three times that of someone who has never smoked, and may be the most important modifiable factor in its prevention. A review of previous studies found "the literature review confirmed a strong association between current smoking and AMD. ... Cigarette smoking is likely to have toxic effects on the retina

IV. FLUORESCEIN ANGIOGRAM

FA requires the use of a dedicated fundus camera equipped with excitation and barrier filters. Fluorescein dye is injected intravenously, usually through an antecubital vein with sufficient speed to produce high contrast images of the early phases of the angiogram. White light from a flash is passed through a blue excitation filter. Blue light (wavelength 465-490 nm) is then absorbed by unbound fluorescein molecules, and the molecules fluoresce, emitting light with a longer wavelength in the yellow-green spectrum (520-530nm). A barrier filter blocks any reflected light so that the images capture only light emitted from the fluorescein. Images are acquired immediately after injection and

continue for ten minutes depending on the pathology being imaged. The images are recorded digitally or on 35mm film. Wet and dry forms of macular degeneration is characterized by Choroidal Neo-Vascularization (CNV), the development of abnormal blood vessels beneath the RPE layer of the retina. These vessels can bleed and eventually cause macular scarring which can result in profound loss of central vision (disciform scar). Since the effect of drugs and treatments such as photo- dynamic therapy on CNV are still not well known, it is of interest to automatically monitor the changes and to extract quantitative measurements in these cases to study the effectiveness of the treatment and to track disease progression. Figure 4(a)(b) shows two FA images of the same eye captured one year apart. In the first image, the eye is starting to develop new choroidal vessels. In the second image, there is an increase in new vessels. The dark ring around the CNV is a thickening of the RPE layer believed to be the body's response to CNV and anttempt at containing the growth of new vessels. It is of interest to quantify how the new choroidal vessels (seen as the bright region in the FA), and the RPE ring (seen as the dark ring like structure), change over time.

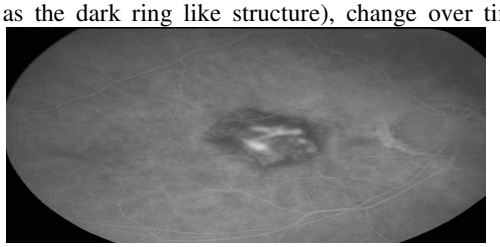


Figure. 4 (a) Eye develop CNV

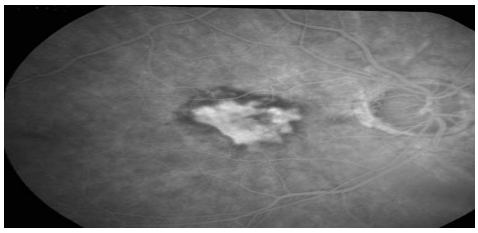


Figure. 4 (b) Eye with cordial vessel

V. SEGMENTATION OF RETINAL FEATURE

The retinal vasculature is first traced using an exploratory vessel tracing algorithm. This algorithm recursively find connected pairs of parallel edges of blood vessels using directional edge templates. The branch points are extracted from the vessel centrelines as landmarks for registration. Adaptive thresholding and template matching. Based on the location of the optic disk, the fovea is detected using an adaptation of the algorithm described by Pinz et al. The optic disk detection and fovea detection are performed on a colour image that is registered to the FA image. This is because, the optic disk appears as a bright region in the colour image and is much more distinguishable from the background in the colour image compared to the FA image. Also, the registration algorithm to be described next, accurately registers between the FA and colour images and hence helps to map the positions of the features from the colour image to the FA image precisely.

SUB PIXEL ACCURACY

REGISTRATION

We use the robust dual-bootstrap iterative closest point (ICP) algorithm to register the images. This algorithm is feature based and use the branching and cross-over points of the detected vasculature as landmarks to estimate 12 dimensional spatial transformation between the image

ROBUST ILLUMINATION

Non-uniform illumination is a well known problem in retinal imaging and is primarily caused due to a combination of different factors. When comparing images taken at different times for changes, one must compensate for the spatially non-uniform illumination. In order to remove the effect of illumination, we use an algorithm that robustly estimates the illumination and reflectance components by homomorphic filtering and robust surface fitting, leveraging extracted retinal features [1]. The observed image is modelled as the product of an illumination component, I(x,y), and a reflectance component, R(x,y), in the following form:

$$F(x,y)=I(x,y)R(x,y) \qquad (1)$$

Taking the logarithm of the observed image in equation 1, the slowly varying illumination field can be estimated by using a 4th order polynomial surface [2].

$$I(x,y)=exp(SP) \qquad (2)$$

where S is a matrix composed of powers of x and y, the pixel locations and P is a vector of the polynomial coefficients. Using the estimated illumination component, the reflectance component can be recovered up to a scale factor as:

$$R(x,y)=exp(FL(x,y)-SP) \qquad (3)$$

where FL(x,y) is the logarithm of the observed image F(x,y) Fluorescein Angiogram shows fine retinal vascular architecture which does not pass through RPE or pigment. FA does not explore

choroidal lesions well. It Confirm clinical diagnosis perfectly.

VI. Segmentation Result

Figure 5 shows sample segmentation results for eye. In order to find the region of interest for change analysis, a mask is found from the segmentation of the RPE region for each image. In cases where the RPE ring is well formed, the mask is the RPE segmentation with its interior filled in. In cases where the RPE ring is not well formed and has gaps, the mask is formed as the smallest polygon that inscribes the regions in the RPE segmentation. The logical OR of the masks from the two images is the region of interest for the change analysis. The next section describes how the changes are detected and classified.

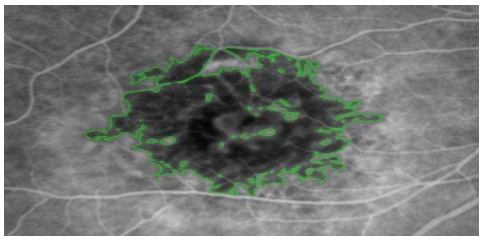


Fig.5 Sample segmetation results.(The segmented RPE hypertropic region is outlined in green)

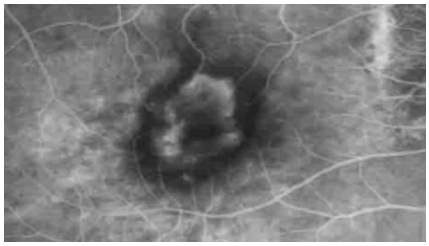
VII. Experimental Result

Data Acquisition Result

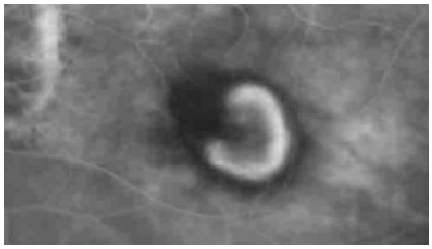
The clinical data was recorded at Northeastern Retina Specialists (Albany, NY) using a Zeiss FF450 fundus camera and MRP Imaging System. Eyes with wet AMD, and exhibiting well defind RPE ring around the choroidal neovascularization were selected for the study. Fluorescein angiography was performed for each patient and during multiple visits to the clinic. Colour images were also obtained prior to the FA examination. One frame from each FA series, collected at around one minute after dye injection were selected for further analysis. The frames were selected such that they had approximately the same brightness levels. This condition makes it possible to apply the robust illumination correction algorithm described above . A test set of 12 images from different subjects was used to evaluate the performance. Ground truth data was collected for each of the image manually outlining the region of interest. This was done by an expert observer. The automatic change analysis results were then compared with the ground truth data

Change Analysis Result

Figure 6 shows the automatically extracted changes for a patient who underwent Photo Dynamic Therapy (PDT) between the times the two images were taken. As expected, there was disappearance of CNV over some regions as well as appearance over other regions. In this case, the RPE hypertrophic layer was also seen to extend outwards a little. We are also able to relate the changes from the FA images to the colour images. Figure 3d displays this capability, where change regions are overlaid on the corresponding colour image

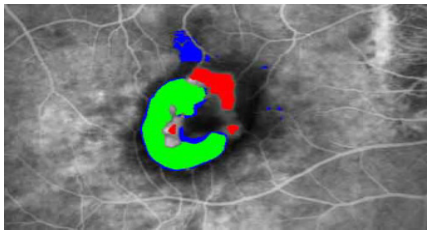


a) Eye with CNV



(b)After PDT treatment

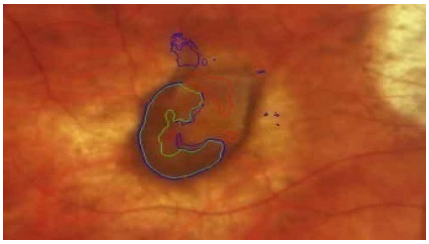
Figure.6 (a), (b) Sample change analysis result



(c) Colour coded change analysis result

VIII. Future Scope

Fluorescein Angiography plays an important role in clinical research, advancing the understanding of retinal vascular disorders and potential treatment modalities. A number of multicenter clinical trials use fluorescein angiography to investigate new treatment options to combat retinal disease. As new therapeutic modalities are developed, fluorescein



(d) The colour coded change region boundaries superimposed on the corresponding colour image

Figure. 6 Sample change analysis result

angiography will continue to play an important role in the management of common retinal conditions. In diabetic retinopathy the angiogram is useful in identifying the extent of ischemia, the location of micro aneurysms, the presence of neo vascularization and the extent of macular edema. In age-related macular degeneration, angiography is useful in identifying the presence, location and characteristic features of choroidal neo vascularization for possible treatment with laser photocoagulation, photodynamic therapy, or anti angiogenic medications.

XI. CONCLUSION

In this paper, we have extended the framework presented to analyze changes from Fluorescein Angiograms. The automated change analysis techniques described in this paper have demonstrated to be effective on the patients considered till now. In order to draw biological conclusions about the changes and their patterns, we plan to do the analysis on a bigger sample population over an extended period of time. The focus of this topic was on developing software tools for higher-level, quantitative, and highly-automated change analysis from retinal images. Reliable, illumination- invariant, and fully-automated detection and analysis of changes in retinal images can form a valuable additional diagnostic resource for the clinician and researcher by map- ping the dynamic nature of diseases.

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