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Quantitative Assessment of Age-Related Macular Degeneration Using Parametric Modeling of the Leakage Transfer Function: Preliminary results

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Abstract

Age-related macular degeneration (AMD) is a major cause of blindness and visual impairment in older adults. The wet form of the disease is characterized by abnormal blood vessels forming a choroidal neovascular membrane (CNV), that result in destruction of normal architecture of the retina. Current evaluation and follow up of wet AMD include subjective evaluation of Fluorescein Angiograms (FA) to determine the activity of the lesion and monitor the progression or regression of the disease. However, this subjective evaluation prevents accurate monitoring of the disease progression or regression in response to a pharmacologic agent. In this work, we present a method that allows objective assessment of the activity of a CNV lesion which can be statistically compared across different patient and time points. The method is based on a hypothesis that the discrepancy in the time-intensity signals among the diseased and normal retinal areas are due to an implicit transfer function whose parameters can be used to characterize the retina. The method begins with parametric modeling of the temporal variation of the lesion and background intensities. Then, the values of the model parameters are used to evaluate the change in the activity of the disease. Preliminary results on five datasets show that the calculated parameters are highly correlated with the Visual Acuity (VA) of the patients.

Keywords:Age-related macular degeneration, Choroidal Neovascularization, Intensity Modeling, Fluorescein Angiography, quantitative assessment.

1. Introduction

Age-related macular degeneration (AMD) is a major cause of blindness and visual impairment in older adults. The wet form of the disease is characterized by abnormal blood vessels forming a Choroidal Neovascular (CNV) membrane [1]. The newly developed vessels leak blood into the macula causing the retinal surface to become uneven, resulting in a distorted central vision. This type of visual loss is potentially reversible; however, persistent blood accumulation results in loss of photoreceptors and hence, permanent visual loss [1]. The standard method for evaluating and following up the progression or regression of AMD is Fluorescein Angiography (FA) [1]-[2]. In FA, a fluorescent dye is injected into the venous system aiming to image and analyze its flow dynamics inside the retina. Immediately after injection, a retinal angiogram is obtained by acquiring a sequence of images using a fundus camera. The distribution and amount of the image intensities (or gray levels) at any time represent the amount of fluorescein leakage and thus is indication of the severity of the disease.

Estimating the amount and the extent of the leaking areas plays a significant role in monitoring the therapeutic response of newly developed drugs [3].

Currently, FA image sequences are subjectively evaluated by experienced graders. Qualitative techniques suffer from large inter- and intra- observer variability and thus does not allow accurate monitoring and following up of the disease progression or regression [2]. Therefore, there is a need for quantitative evaluation methods that can provide accurate and reliable means for evaluating the disease as well as drug development.

A number of methods attempt to quantitatively assess the CNV lesions. For example, the lesion size and the amount of leakage in the late timeframes have been used to quantify the CNV lesions [4-6]. Unfortunately, these techniques ignore the dynamic behavior of fluorescein leakage over the different timeframes. The latter has been used by Shah *et al* and was found significantly correlated with the CNV progression (or regression) [3]. Although the method was successful in providing quantitative information about the lesion, it requires acquisition of large number of images extending up to 10 minutes after dye injection. In this work, we present a novel method that allows objective assessment of the CNV lesion based on image acquisitions during the early phase (2 min after dye injection).The method is based on parametric modeling of the temporal variation of the lesion intensity. The values of the model parameters are then used to evaluate the change in the activity of the disease.

The paper is organized as follows. In Section 2, the parametric modeling of the leakage transfer function is proposed. In Section 3, results and discussion is introduced. Finally, conclusion is presented in Section 4.

2. Methods

The proposed methods comprise three main processing steps following the image acquisition. First, the image sequence is aligned to correct the shift of the images due to eye movements. Standard optical flow tracking [7] is used to estimate the non-uniform displacement field of each image pixel between the consecutive timeframes.

After image alignment, we obtain a set of images $I(x, y, t_i)$ where the location (x, y) in any image represent the same location in the retina. The grader is asked to manually draw two contours enclosing a normal retinal region and an AMD region to be evaluated, fig.1. The average intensity within each region is calculated at the different times. This yields two time-intensity signals: $I_{norm}(t)$ and $I_{AMD}(t)$.

In this work, we hypothesize that the discrepancy in the time-intensity signals between the diseased and normal retinal areas are due to an implicit transfer function whose parameters can be used to characterize the retina.

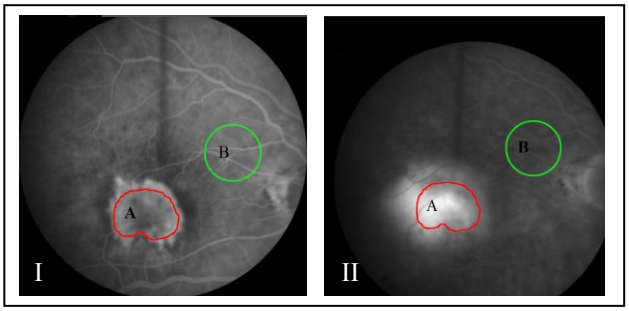

Figure1. Early (I) and Late (II) FA frames from a patient showing region (A) enclosed by the red contour which corresponds to an AMD lesion, and region (B) enclosed by the green contour representing a normal retinal region.

2.1 Modeling of the System Input/Output Signals

We propose a simple input/output linear time-invariant model to study the leakage dynamics at the different areas of the retina. That is, at a given location(x, y), the input-output relation is given by the following convolution operation,

$$I_{out}(x, y; t) = h(x, y; t) * I_{in}(x, y; t) \quad (1)$$

The input of the model is the concentration of the fluorescein at the upstream (feeding arteries of the retina).Following the derivation of the gamma-variate relationship for tracer dilution curves introduced by Robertson Davenport [8], and assuming a bolus intravenous injection of the fluorescein, the fluorescein concentration arriving at the retinal circulation can be modeled by a gamma function. That is, the input to the model at any given retinal location, $I_{in}(t)$, (the spatial variables will be dropped here for simplicity) is given by,

$$I_{in}(t) = A(t^{\propto_{in}} . e^{-\frac{t}{\beta_{in}}}) \quad (2)$$

Where $\propto_{in}$ and β_{in} are respectively the shape and scale parameters of the gamma function. Accurate estimation of $\propto_{in}$ and β_{in} requires invasive measuring procedure. Fortunately, normal retinal areas are almost transparent to the (rich) blood vessels in the underlying choroidal layer. That is, the image intensity of normal retinal areas at the different timeframes, $I_{norm}(t)$, can be used as a good approximation of the input function, $I_{in}(t)$. Levenberg-Marquardt algorithm is used to fit the function in Eq. (2) to the sampled image intensities.

At a diseased area, the output function, $I_{out}(t)$, is just the observed image intensity at the AMD lesion areas, i.e., $I_{out}(t) = I_{AMD}(t)$. A number of researchers showed that the temporal variation of image intensity during the early phase at CNV lesion sites can be accurately modeled by a gamma function [9-10]. That is,

$$I_{out}(t) = C(t^{\propto_{out}} . e^{-\frac{t}{\beta_{out}}}) \quad (3)$$

Similar to estimating the parameters in equation (2), the sampled image intensities at the AMD lesions is used to estimate the parameters $\propto_{out}$ and β_{out}.

It is worth noting that only image samples within the early phase (first pass of the fluorescein) are considered for the fitting process. This is to avoid the effect of fluorescein recirculation in the body. An iterative algorithm based on the goodness-of-fit is used to determine the number of samples that yields the best fitting accuracy. First, the first N samples are used to estimate the function parameters and the fitting error (chi-square test) is recorded. Then, the fitting is repeated using the first $N + 1$ samples and the error is recorded. The process is repeated by including more samples until reaching the minimum error (minimum value of the chi-square test), which yields set of images from time $t = 0$ to $t = \tau$.

2.2 Modeling of the System Transfer Function

Given the input and output functions, it is required to estimate the transfer function of the retina, $h(t)$. Because both the input and output functions are represented by gamma functions, it is intuitive to model the transfer function using a gamma function:

$$h(t) = B\left(t^{\propto_{TF}} . e^{-\frac{t}{\beta_{TF}}}\right) \quad (4)$$

Estimating the parameters is not trivial and requires a deconvolution operation that can be sensitive to noise. To avoid such ill-posed operation, we use the approximation proposed by Trevor Stewart *et al.* [11] to estimate the gamma parameters that resulting from the convolution of two gamma functions. Following this approximation, the parameters of the output gamma function can be estimated by,

$$\alpha_{out} = \frac{(\alpha_{TF}\beta_{TF} + \alpha_{in}\beta_{in})^2}{\alpha_{TF}\beta_{TF}^2 + \alpha_{in}\beta_{in}^2} \quad (4.a)$$

$$\beta_{out} = \frac{\alpha_{TF}\beta_{TF}^2 + \alpha_{in}\beta_{in}^2}{\alpha_{TF}\beta_{TF} + \alpha_{in}\beta_{in}} \quad (4.b)$$

Given the estimated parameters, $\propto_{in}$, β_{in}, $\propto_{out}$ and β_{out}, the above two nonlinear equations can be solved to estimate the parameters of the system transfer function: $\propto_{TF}$ and β_{TF}.

The estimated transfer function, h(t), can be used to characterize the lesion response to the blood flow (e.g. rate of leakage) in many ways. In this work, the area under the curve of the transfer function, AUC_{tf}, is calculated over a region of interest (ROI) and used as an indication of the disease severity as follows:

$$AUC_{tf} = \frac{1}{|ROI|}\int_{t=0}^{t=\tau}\int_{(x,y)\in ROI} I(x,y,t)\,dxdy\,dt \quad (5)$$

where $|ROI|$ is the number of pixels in the selected ROI and τ is the time of completing the first-pass of the dye determined as discussed above.

2.3 Image Acquisition

A dataset for five patients are used to test the proposed methods. Patients, with known CNV lesions, were injected with 50 ml fluorescein. Images were acquired with a fundus camera (Zeiss FF4; Carl Zeiss Meditec, Oberkochen, Germany) integrated with a digital acquisition system (MRP Systems, Boston, MA). Each frame was captured at 2000x2000 pixels. Each dataset contains a number (=20-25) of time frames spanning time intervals from 0 to 11 minutes, these data were acquired on two visits, the time interval between them is 71 days.

2.4 Testing and Validation

For the validation purpose, the results of the proposed technique are compared with those of the method introduced by Shah *et al* [3]. In Shah's method the temporal variation of the lesion intensity in the whole image sequence is modeled using a simple logarithmic model and the area under this curve, $AUC_{log}(v)$, is calculated and used as an index for the disease severity. In this work, first, the $AUC_{tf}(v)$ is calculated using Eq. (5) for the image sequences of the two visits: v = 1, 2. Then, the $AUC_{log}(v)$ is calculated using the methods described in [3]. Also, the accumulation of the fluorescein in the lesion area at the late phase of the image sequence is calculated. The difference of each area-under-curve between the different visits is calculated and used to estimate the progression of the disease between the two visits.

In addition, the area-under-curve $AUC_{tf}(v)$ difference of the transfer function is plotted against the Visual Acuity (VA) difference between the two visits.

3. Results and Discussion

Sample of the gamma fitting result of the system input taken from normal retinal region at different time frames is shown in fig.2 (A), also the fitting result of the output of this system taken from lesion area at the same time frames is shown in fig.2 (B), fig.2 (C) shows the estimated transfer function response of this system .

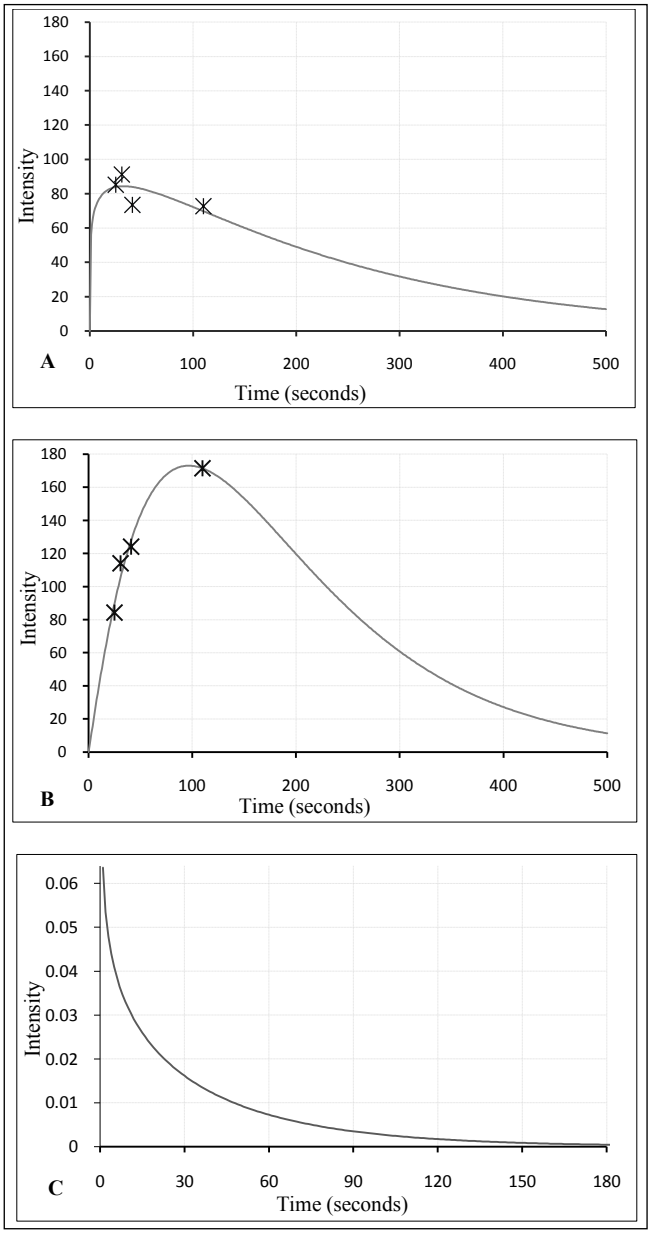

Figure2. (A) System input taken from normal retinal area, (B) System output taken from selected lesion area, (C) estimated transfer function of the system.

Fig.3 (A) shows the relation between the difference in the AUC_{tf} of the lesion transfer function response and the difference in the AUC_{log} of the logarithmic model, the correlation coefficient between them is 0.8957and the p-value of 0.039 shows the significance of this correlation.

In fig.3 (B) we can see the correlation between the difference in the AUC_{tf} of the lesion transfer function response and the change of the visual acuity (VA), which shows a high correlation coefficient value of -0.845 and p-value of 0.0714, we can notice that the decrease/increase of the AUC_{tf} value between the two visits that indicates the decrease/increase in the fluorescence accumulation in the

lesion area corresponds to the increase/decrease of the VA of the patient.

Also, the correlation between the difference in the AUC_{tf} of the lesion transfer function response and the difference of the accumulation of the fluorescein in the lesion area over the time frames of the late phase, which shows a correlation coefficient of 0.8638 and p-value of 0.0591is shown in fig3 (C).

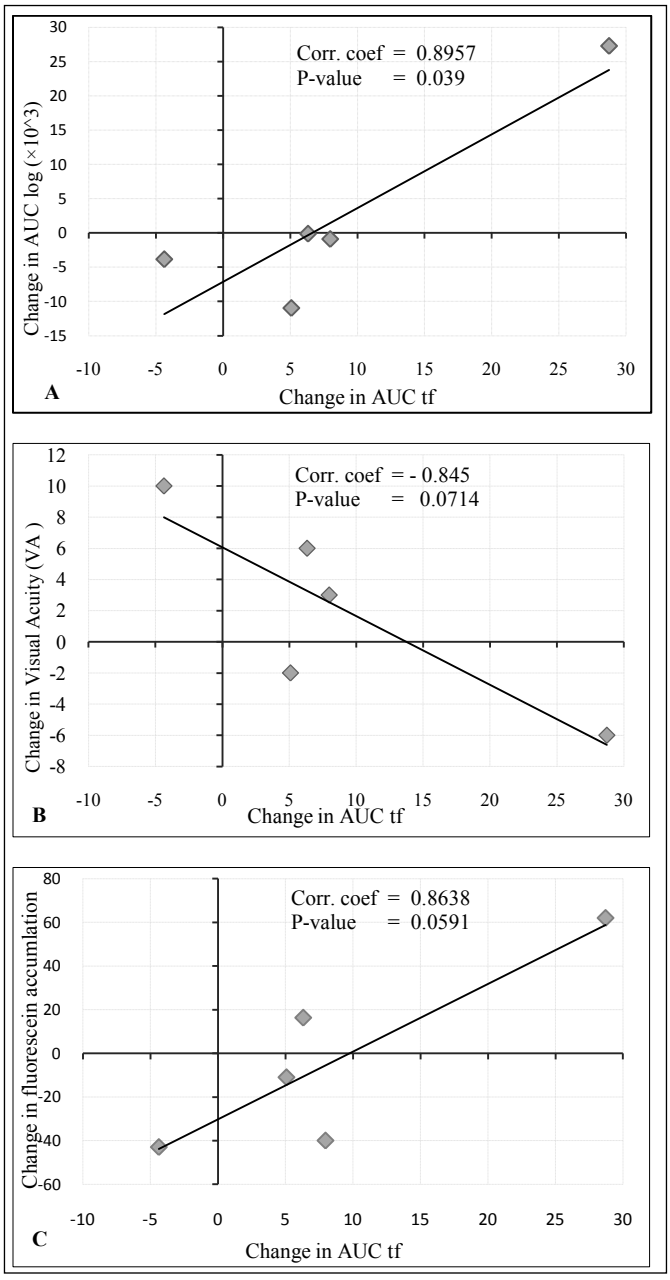

Figure3. The relation between the change in the AUC_{tf} and (A) the change in the AUC_{log} modeled by a logarithmic model, also the significance of the change of the AUC_{tf} of the lesion relative to the change in the VA can be seen in (B).
(C) The relation between the change of the AUC_{tf} of the proposed method and the change in the accumulation of the fluorescein in the lesion area at the late phase of the image sequence.

It is worth noting that the proposed method requires processing only the set of images of the early phase, whereas Shah's method requires the entire sequence of images, which might leads to reduction in the scanning time in the future.

Time taken for data fitting and analysis is four seconds for a data set that contains eight time frames representing the early phase, excluding registration phase which takes about 20 seconds per image to be aligned.

4. Conclusion

A novel technique for quantitative assessment of CNV lesions associated with AMD disease has been introduced. The technique is based on estimating the parameters of the transfer function representing the lesion response to the flow of the injected dye. The advantage of the technique is that it requires only images acquired during the early phase which might result in reducing examination time. Preliminary results on five patients show significant correlation between the proposed method and both the visual acuity and also current methods that require prolonged image acquisition times.

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