Blood vessel segmentation for diabetic retinopathy

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Abstract. DR or Diabetic Eye Disease is a medical condition which causes blindness in people with diabetes. It is found to be a proceeding cause of preventable blindness. The lack of conduction of retinal screening examination on all diabetic patients has let to many undiagnosed and thereby untreated cases of DR. Timely and accurate diagnoses can reduce the rate vision loss if patients with DR are referred to an ophthalmologist for evaluation & treatment. This study aims to bring about a robust diagnostic technology in order to automate DR screening. For the automated DR detection, a data-driven deep learning algorithm was developed and evaluated as a novel diagnostic tool. Colour fundus images were processed by this algorithm and classified them as having DR or healthy, identifying medically relevant cases for referral. For further clinical review, all the learned information from the automated method was readily visualized through automatically generated abnormality heat map, which highlighted sub-regions within each input fundus image. This study enables to identify cases that should be referred to an ophthalmologist for further evaluation and treatment, with use a fully data-driven artificial intelligence based grading algorithm which can screen fundus photographs from diabetic patients. On a global basis, the implications of such algorithm can drastically aid to reduce the rate of vision loss caused by DR. The model is executed in two phases with the purpose of strengthening the framework of Diabetic Retinopathy (DR) recognition.

KEYWORDS—Diabetic Retinopathy, Proliferative Diabetic Retinopathy, Pathology, Vitrectomy.

1. INTRODUCTION

It is estimated that 415 million people are affected worldwide with diabetes that is one in every eleven adults. Diabetic Retinopathy (DR) which affects the small blood vessels in the eye is one of the leading causes of curable blindness. About half of the diabetic patients are likely to have DR but most of them may not be even aware of the disease. Therefore it is necessary that DR should be detected early and treated to prevent the loss of eyesight caused by this disease. However, the prevention of DR is not an easy task. Normally Ophthalmologist can find out the presence of DR by visual examination of the fundus and by evaluation of color photographs. But this is a time consuming and extensive method considering the number of patients affected by this diseases globally. Precise data on the diagnosis and early treatment of DR are also not available. Besides, about 75% of the of the DR patients live at places where there are no facilities for detection of DR. In spite of global programs to detect and treat retinopathy, the disease exists in such a large scale that effective individual treatment for all is not possible with the result that millions still suffer eyesight problem. To counter the problem of shortage of facilities and trained persons, automatic solutions based on screened color fundus images were proposed.
Even untrained technicians can handle the patients in that case. However, such automatic detection has some drawbacks as the algorithms are derived based on a few hundred images which may not be able to cover large scale and different types of fundus data sets collected under varying circumstances such as different fundus camera, different eye dilation method etc. Besides these algorithms depend upon the DR characteristics obtained through manual hand-tuned features to characterize anatomic structures in fundus such as optic disc, blood vessel etc. While these hand-tuned features can work on singular fundus data, this can’t be applied correctly to the fundus images obtained from different demographics. Even though features such as Speeded-up Robust Features (SURF) and Histogram of Oriented Gradient (HOG) have been found as the nonspecific method are not able to characterize subtle differences in retinopathy severity.

2. LITERATURE SURVEY

One important factor in the development of diabetic Retinopathy is vascular endothelial growth factor signaling. Recently it is found that the growth factor signaling in endothelial cells is suppressed by leukocyte cell-derived chemotaxin2. The purpose of this study is to find out serum LECT2 levels and the presence of DR. The study covers 230 people with type 2 diabetes mellitus 95 with DR and 135 without DR. It is found by multiple regression analysis that serum LECT2 level is not associated with the presence of DR[1]. In the development of DR many overlapping and connected molecular pathways are involved. The status of microglia and microglia in the process of DR is given in the study which takes into consideration the biochemical mechanisms affecting the connection among neuroretina, vessels and glial cells[2].

Examine whether DR is a valid predictor of coronary artery disease. The study covers 60 male patients randomly selected from diabetic and ophthalmologic clinics. Fundus examination for evaluating DR and duplex ultrasound to find out carotid intimal medial thickness was done on them. In all cases, coronary angiography was done[3]. An important cause of blindness including retinopathy of prematurity is neovascular eye diseases. Adipokines, like adiponectin which are derived from white adipose tissue, modulate metabolic responses. Evidence shows that retinal neovascularization may occur due to lack of adiponectin[4]. Retinal diseases related to inflammation are normally followed by macrophage/microglial cells activation. Human diabetic donor’s assessment of microglia polarisation in retinas was evaluated. In retinas of diabetic donors markers of activated microglia were detected[5].

Comparison of the various components of Prameha /Madhumehajanya Timer with DR and its stages. In Madhumehajanya Timer, all the three doshas with Raktadhosa and saptadhatu with four dristis petals of eye are affected. In view of the prolonged and uncontrolled hyperglycemia, Avarana and Share also have an important role in the development of DR. In pathology of DR, Agnimandya related Ama formation has a role which is similar to the oxidative theory of DR described in modern pathology[6]. The acetone or thelial agents are seen to boost visual acuity and decrease the central macular thickness of the patients. It is also found to be an effective remedy for vitrectomy. Triamcinolone is related to risks of excessive intraocular pressure and cataract[7]. In the ocular side, the fundamental remedy of diabetic macular edema, both severe non-PDR and PDR is still the laser treatment. Anti VEGF were found to be effective as an adjunct therapy[8]. Though the major method of diagnosis to detect the Microvasculature changes is fundus examination, the visual function test is considered to be an effective alternative having the potential to detect DR at early stages. Visual function components can be characterized by the electrophysiological test of the retina[9]. In cases of proliferative DR after successful vitrectomy and uneventful postoperative course, the preoperative prognostic factors contributing to the extremely poor visual outcome should be investigated. The control group was found to have creatinine level significantly lower (1.23 + _ 0.46mg/dl; p ¼ 0.003) than the study group (4.07 + 4.15mg/dl), as per multiple logistic regression analysis, chronic muscular detachment and broad fibrovascular proliferation were found to have significant associations with poor visual outcome[10].
The albuminuria and estimated glomerular filtration rate are the supposed biomarkers of DR. In Spain the prevalence of DR, its relationship with eGFR and other factors in T2DM was investigated. It resulted in 14.9% prevalence, with more prevalence (p=.0087) in women and older patients (p<0.0001)[11]. MiR-15 an in bone marrow cells and retina was found to be minimized by using a variety of tools and various technologies. The inhibition of miR-15a was found to unregulated a pro-inflammatory molecule acid sphingomyelinase (ASM). It was also found to upregulate an angiogenic molecule expression, vascular endothelial growth factor A in the retinal pigment epithelial and endothelial cells[12].

The existence of serum pro-inflammatory cytokines and acute phase reactants was examined in the patients with and without DR. The case study was conducted using a total of 36 patients divided into 3 groups. Group 1 consisted of 12 patients with diabetes mellitus and diabetic retinopathy, Group 2 had 12 diabetic patients without diabetic retinopathy and 12 healthy patients were grouped as the control group[13]. Three intravitreal injections of ranibizumab were given to a patient at monthly intervals. The new vessels were found to be completely regressed after conducting repeat angiography. The improvement was found in the perfusion of chemical areas in the retina. When compared to the normal panretinal photocoagulation, the intravitreal anti-vascular endothelial growth factor injections were found to be valuable for reversing the neovascularization[14]. Modeling approach using m-Medoids combined with a Gaussian Mixture Modeling to shape a hybrid classifier was proposed in order to improve the classification accuracy. The sensitivity, specificity, accuracy and operating characteristics of the receiver along with Databases of Fundus images are used to evaluate the proposed system[15]. The analysis was done on the visually impaired registered adults suffering from diabetic retinopathy aged 18-69 years under the National Council for the Blind of Ireland (2004-2013). The analysis revealed the need for increasing the preventive methods for microvascular complications[16]. From February 1, 2006, to February 1, 2009, a study was conducted on 2435 diabetic patients. 17.90% was found to be prevalent with DR out of which mild-moderate proliferative DR was found in 80.73%, nonproliferative DR was found in 12.16%, proliferative DR was found in 2.29% and diabetic maculopathy in 4.82%. 41 patients (1.69) had low-quality retinographies. The improvement of the circuit of communication between primary and specialist care, enabling early diagnosis and treatment are the notable benefits of tele ophthalmology[17].

A combination of the Gaussian mixture model, support vector machine and an extension of multimodal medoid based modelling approach were used to present a hybrid classifier, in an ensemble to improve classification accuracy. The publicly available retinal image databases were used to evaluate the proposed system and was found to have higher accuracy in comparison with previously established methods[18]. Studies on various factors which are altered due the influence of endostatin’s action are being studied even though the exact mechanism of the action of endostatin is not completely known. This includes the influence of various factors such as down-regulation and activation in, on the progression of angiogenesis. Once the clinical trials show positive feedback, endostatin can be exploited as a durable agent in antiangiogenic therapy[19].

It appears that the use of some Nanoparticles assists in the growth of diabetic retinopathy symptoms, for example, retinal neovascularization. These are also debated considering the thorough management of ocular chronic disease[20].

Diabetic patients used to be directed to an ophthalmologist for frequent screening because the laser photocoagulation treatments can prevent severe vision loss. New inhibitors of vascular endothelial growth factor can provide targeted nonsurgical treatment for improving vision in diabetic retinopathy[21]. According to the recent clinical trials data, In addition to hyperglycaemia, dyslipidaemia plays an important role in the development of DR, which is often overlooked. The main aim of this article is
to show the important role of dyslipidaemia in DR progression and to underline the novel therapeutic solutions which take advantage of the vital roles played by lipid metabolism in DR progression[22].

The role of connective tissue growth factor in the pathogenesis of DR relating to extra-cellular matrix remodelling and wound healing actions are discussed. Also examined whether CTGF can be an effective novel therapeutic solution in the clinical management of initial as well as subsequent stages of DR[23]. Experiments were done to check whether the diabetic neurodegeneration (DRN) leads to DR. If it is so, the method could be used for the early detection of ocular diabetic damage. Also it could be used to surpass the vision loss by treating DR[24].

The non-dilated retinal fundus images are used to automatically examine lesion exudates. The neighborhood based segmentation technique produces low contrast images which shows the presence of exudates[25]. Inter and intraobserver variability can be determined by a computer-aided diagnosis system. The severity of the disease can be evaluated by the proposed methods of various retinal feature extraction and automated analysis. The obtained results are compared with the results obtained from the segmentation technique. The accuracy is determined and it's found to be 97.89 % and 94.76 % respectively for SVM and PNN[26]. The systematic inflammation of patients with type 2 diabetes mellitus is determined and compared. Similarly, patients having T2DM with and without diabetic retinopathy are also compared. The serum levels of inflammatory cytokines CRP, TNF-alpha, VEGF was found to be high in patients with diabetic retinopathy than those without retinopathy[27]. The retinal oxygen delivery and metabolic rates are determined to measure retinal hypoxia using visible light OCT. These techniques are used to study more about the vascular pathophysiology of diabetic retinopathy. The reliable and compatible factors to study diabetic retinopathy are to be researched[28]. Under certain conditions of PDR & severe non-proliferative diabetic retinopathy, Pan retinal scatter coagulation is very useful. It is also seen that the instant focal laser photocoagulation can minimize the risk of mediocre loss of vision by 50% in the case of macular edema. A detailed description of when and how to execute the laser treatment is given along with facts of many cases of diabetic retinopathy treatment[29].

Information from the U.S national health and nutrition examination Surveys (NHANES) from 2005 to 2012 were used for this study. The risk of diabetic retinopathy among the HbA1c categories, modified for age, sex and hypertension were calculated from the logical regression analysis. The diagnostic cut off point of HbA1c for the dominant diabetic retinopathy was ascertained by the characteristics of receiver operation[29]. A multiple instance learning frameworks for diabetic retinopathy screening was suggested in 2-D datasets of retinal images[30]. In correlation analysis between foveal avascular zone and peripheral is a chemic index of diabetic retinopathy and the foveal avascular zone (FAZ) of the affected patients is examined by OCT angiography (OCT-A) techniques[31]. The pathophysiology of diabetic retinopathy can be supported by the mouse models. They also help in revealing and comprehending new therapeutic agents. The complete updated list of mouse diabetic and diabetic like models are reviewed[32].

A helpful effect of externally administered erythropoietin in the beginning of diabetic retinopathy is implied from the in vitro and in Vivo experiments. But, a debate in regard to the feasible use of EPO in proliferative diabetic retinopathy exists. Hence, in order to increase efficiency and reduce the side effects of EPO, non-erythropoietin EPO derived peptides are being examined during the clinical trials[33]. Identical and distinct components of Prameha, Madhumehajanya timira with diabetic retinopathy were explained the paper. Because of the resistive nature of hyperglycemia and dhatu kshaya plays a crucial role in the advancement of diabetic retinopathy. Ama formation, an embodiment of agnimandya has a role in the pathology of diabetic retinopathy of resembles the oxidation theory in modern pathology. Ojas kshaya, rakthavritta vata and pranavritta vyana are the other alternatives[34].

The disease progression can be slowed down if diabetic retinopathy is noticed. The danger of visual loss can be minimized if the sight-threatening retinopathy is diagnosed. But when the stage advances, vitrectomy operation using the modern surgical techniques enhance the condition of the patients[35].
The role of depression along with the occurrence of diabetic retinopathy amidst adults with type 2 diabetes is observed by controlling socio-demographic factors, health risk behaviors, and clinical characteristics. The severity of depression along with the patient health could estimate the severity. Logical regression was used to evaluate the risk of diabetic retinopathy and Cox proportional hazard models were used to determine the time of incident[36].

The treatment of early stage of DR using neuroprotection is given importance. The paper suggests that DR does not just depend upon blood pressures and glucose levels but also the genetic factors which need to clarify. The new methods in retinal image acquisition are useful to circulating biomarkers and personalized analysis of biological specimen could help in the research of therapy in setting of DR[37].

The complementary relationship between the sera anti-myeloperoxidase (MPO) antibody levels along with the intense level of DR is examined and studied. The study included 60 cases of type 2 diabetes mellitus (DM). It was found that a rise in serum anti-MPO was directly proportional to the rise in DR. The serum anti MPO antibody was found to be an important biological indicator for the development of retinopathy to the proliferative stage from the non-proliferative stage[38].

The circumstances of serum levels of anti-myeloperoxidase (MPO) antibody with retinal photoreceptor ellipsoid zone (EZ) disruption of the diabetic retinopathy are studied. A very noticeable deviation was noticed between the serum levels of anti-body among the various study groups (p b 0.001). It was found that in diabetic retinopathy, the increase in serum anti MPO antibody levels increases the retinal photoreceptor EZ disruption and decreases the visual acuity[39]. The ancestry and region based occurrence of diabetic retinopathy is examined and the need to emphasis the ancestry based filtering and treatment is signified[40].

The inflammatory mediators and their involvement in the early stages of DR, the ability to stop the growth of various stages of retinopathy. The knowledge was obtained from the in vivo and in vitro studies were reviewed, discussed and highlighted[41]. The thorough treatment of hyperglycemia or the standardization of glycol metabolic control was found to be the most successful technique to prevent micro vascular complications. It's done with the pancreatic and islet transplantation. The paper aims at surpassing the development of diabetic nephropathy and retinopathy[42].

Various diabetes incited metabolites in the pathophysiology of DR such as glucose, end products of advanced glycation, protein kinase C, oxidative stress and related sources were discussed. New and operative therapies to stop and improve DR by bringing change in the biochemical and molecular levels is also discussed[43].

The proposal given in this paper classifies the exudates and non-exudates regions in the retinal images. For lesion enhancement, The Gabor filter can be used on the great scale image. Using a sequence of the statistical and geometric feature, sets are selected for each candidate. The results obtained shows an average of 0.98 AUC and 98.58% accuracy which is found to be higher than the other existing methods[44].

The potential effect of the progression of proliferative diabetic retinopathy (PDR) and vitreous hemorrhage (VH) is determined. The characteristics of initial DR and the severities are used for the prediction of PDR progression. The intra retinal micro vascular abnormalities (IRMA) is found to multiply the risk of PDR similarly the risk of VH is increased by 4Q DBHs[45].

New vessels are discovered from the retinal images by automated methods which are based on dual classification. The SVM classifier is used to perform an independent classification of each feature vector. The outputs are then combined to generate a final result which is preceded to generate 21D feature
vector by designing additional features. It is then fed to the feature selection approach which is based on the genetic algorithm to find the feature subset that will enhance the execution of the classification[46]. A date driven deep learning algorithm is created and analyzed which is used as a tool for the automatic detection of DR. The algorithm differentiates the color fundus images and groups them as healthy or having DR[47]. The difference between CVD and CVV is the swept source optical coherence (SS-OCT). Both CVD and CVV are found to decrease during the advanced stages of DR. Further discovery of the proposal of choroid vessel disease, its pathogenesis, knowledge, and treatment should be explored by the new image modalities[48].

3. PROPOSED BLOOD VESSEL SEGMENTATION ADOPTED METHODS

3.1 PROPOSED FRAMEWORK

Figure 1 depicts the proposed μcs – Ns leased DR diagnosis scheme. More precisely, it is performed under two phases, first is blood vessel segmentation and second is DR recognition. For each color fundus image, adopted vessel segmentation model is employed in three phases. 1st phase, two threshold binary images are obtained by HPF and top hat construction. The purpose of this initial step is that the areas which are found similar to the binary images are taken as major vessels and left-over pixels are merged to form a vessel sub image. At the subsequent phase the pixels found in the vessel sub image are given to a GMM classification to detect the vessel.

Fig 1. Overall architecture of the proposed framework.

3.2. SEGMENTATION PHASE

Image recognition is one of the most important stages in image processing. Its objective is to partition an input image in to regions or categories. Here input fundus image I, is subjected to blood vessel segmentation.

3.2.1 High pass filtering

High pass filters are filters that stops the passage of low frequency signals allow the passage of high frequency signals. Sharpening is basically a high pass function in the frequency domain, which seek to highlight fine details.
3.2.2 **TOP-HAT BY RECONSTRUCTION**

Arithmetical structure is a significant concept depending on ‘set theory’ and is extensively exploited in pattern recognition and optical signal processing (Soille 2003). Morphological operators are generally portrayed on the basis of the original image \( d(y; x) \) and structuring element \( O(v; u) \). \( (v; u) \) and \( (y; x) \) indicates pixel coordinates of \( O \) and \( d \), correspondingly. The fundamental morphological operator is erosion and dilation. Erosion \( \delta \) and dilation \( \delta \) of \( O(v; u) \) by \( d(y; x) \) are given by Equations (2) and (3).

\[
\delta_g(g)(y, x) = \max_{y, u}(d(y-v, x-u) + O(v, u)) \quad (2)
\]

\[
\varepsilon_g(g)(y, x) = \min_{y, u}(g(y+v, x+u) - O(v, u)) \quad (3)
\]

The geodesic dilation of the dimension \( n \) of the marker image \( d \) in terms of mask image \( g \) given by \( \delta \) is described as ‘the pixel-wise minimum between \( d \) and the dilation of \( g \) using structuring element \( O \), iteratively’, as shown by Equations (4) and (5).

\[
\delta_g^n(d) = \delta_g^{n+1}(\delta_g^{n-1}(d)) \quad (4)
\]

\[
\delta_g^1(d) = \min(g, \delta_g(g)(d)) \quad (5)
\]

The geodesic dilation of the dimension \( n \) of \( d \) in terms of \( g \) given by \( \varepsilon \) is described as ‘the pixel-wise maximum between \( gd \) and the dilation of \( g \) using structuring element \( O \), iteratively’ as shown by Equations (6) and (7).

\[
\varepsilon_g^n(d) = \varepsilon_g^{n+1}(\varepsilon_g^{n-1}(d)) \quad (6)
\]

\[
\varepsilon_g^1(d) = \max(g, \varepsilon_g(g)(d)) \quad (7)
\]

\( R_g \) indicates the reconstruction of \( g \) from \( d \) by dilation and it is defined as ‘the iterative geodesic dilation of \( d \) using \( g \) until the stability’ as shown by Equation (8).

\[
R_g(d) = \varepsilon_g^1(d), \quad \text{where} \quad \varepsilon_g^0(d) = \varepsilon_g^1(d) \quad (8)
\]

The reconstruction opening is defined as “the reconstruction of image \( d \) from the erosion of \( d \) using structuring element \( O \)”, which is dependent on dilation reconstruction as shown by Equation (9). In addition, reconstruction closing is defined as ‘the reconstruction of image \( d \) from the dilation of \( d \) using structuring element \( O \)’, which is dependent on erosion reconstruction as shown by Equation (10). The operators of top-hat by reconstruction, together with the black and white top-hat operators, were described as ‘the difference between the image \( d \) and the result of opening or closing by reconstruction operator’ as shown by Equations (11) and (12) correspondingly.

\[
Q_d(d) = R_d^1(c_O(d)) \quad (9)
\]

Thus, the resultant image attained by this approach is denoted by IT.

The regions common to \( IH \) and \( IT \) are taken as major vessels, while the leftover pixels in both binary images are merged to form a vessel sub-image, denoted by IV.
3.3 GAUSSIAN MIXTURE MODEL

Image is a matrix which each element is a pixel. The value of the pixel is a number that shows intensity or color of the image. In the subsequent stage, the pixels in IV are provided as input to GMM classification. GMM (Khanmohammadi and Chou 2016) is described as ‘the weighted sum of multiple Gaussian components that represent a density of a particular random variable. GMM is mainly designed to perform an efficient search for the number of mixture component.

\[
P(x; \Theta) = \sum_{i=1}^{N} w_{i} p(x | \mu_{i}, \Sigma_{i})
\]

\[
p(x | \mu_{i}, \Sigma_{i}) = \frac{1}{(2\pi)^{\frac{d}{2}} |\Sigma_{i}|^{\frac{1}{2}}} e^{-\frac{1}{2} ((x - \mu_{i})^{T} \Sigma_{i}^{-1} (x - \mu_{i}))}
\]

4. CONCLUSION

Automatic diagnosis of diabetic eye disease is feasible and achievable through the usage of well-defined image processing techniques. While many successes has been recorded in the current advances in automation of medical diagnosis, this study tends to maximize the large availability of ubiquitous devices and elicitation of past diagnostic method that is set towards providing cost-effective, easier and faster diagnosis. Future work will focus on defining and entrancing novel features, set as to improve the accuracy and also to integrate the module to risk assessment procedure. In addition, more sophisticated pattern recognition methods will be implemented. The proposed work was completed in two phases. Phase one blood vessel segmentation and phase two DR recognition. The blood vessel segmentation was further completed in three phases. In the first stage, using HPF two threshold binary images obtained and by reconstruction top-hat was obtained. The areas that looked alike in the two images were taken as the major vessels. The vessel sub-image was obtained by merging the residual pixels of the binary images.

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