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Analysis of Ophthalmic System Applications using Signal Processing

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Abstract – *The aim of this paper is to explore the potential for modern computing technology to advance clinical ophthalmology. In particular we will be investigating the potential for computer programming in the development of novel and objective measures of ophthalmic disease. Ophthalmic diseases like diabetic retinopathy, vision blur etc. have been causing issues with the society at large. Measures for evaluation are discussed in this paper. These measures could ultimately be used for clinical diagnosis or severity measures for clinical decision making. They could also be used as research tools, providing objective outcome measures to power more robust clinical trials.*

Key Words: Retinopathy, Clinical, Ophthalmology, Membrane, Hyperglycaemia, Macula.

1. INTRODUCTION

Approximately 37 million people are blind worldwide due to various eye related diseases, out of these 75% are either preventable or treatable [1]. Diabetic retinopathy (DR), a micro vascular complication in the retina due to diabetes, is one of the leading causes of adult blindness worldwide. However, it is only next to cataract, glaucoma or age-related macular degeneration (AMD) and amongst retinal degeneration; DR is the second leading cause of blindness in the working age group and accounts for 4.8% of global blindness (Fig-1). In India, 20% of the type 2 diabetes mellitus (T2DM) population is estimated to develop DR which suggests that by 2025 nearly 11.4 million adults with diabetes may develop DR [2].

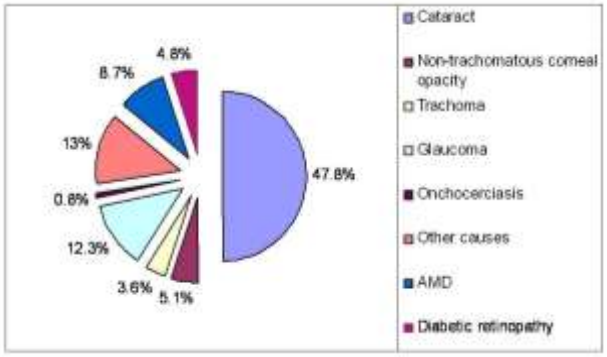

Fig-1: Major causes of worldwide blindness, 2012

DR is a progressive disease of the retina and detected clinically by the presence of retinal micro vascular lesions which are visible when examining with an ophthalmoscope. It is a sight threatening complication of diabetes if macula is involved that may result in irreversible blindness if not managed appropriately. Hyperglycaemia initiates a cascade of pathologic complications which eventually brings about devastating damages in the retina such as basement membrane thickening, loss of pericytes, blood retina barrier breakdown, etc. Clinically, DR is diagnosed by the presence of the following features (Table-1) [3]:

Table-1: Clinical features observed in DR

Clinical feature	Description
Microaneurysms	Visible out-pouching of the fragile blood vessels.
Intraretinal haemorrhage	Results from the ruptured micro aneurysms and appear as dot blots if present in the inner nuclear layer of the retina.
Soft exudates	Also known as 'cotton wool spots' formed by the swelling of nerve fibre layers due to sealing of the capillaries and ischemia.
Hard exudates	Represent protein and lipid deposits within the retina
Venous beadings	Resemble beads due to alternating thick and thin appearance of the veins
Intraretinal microvascular abnormalities (IRMA),	Distinctive aberrations that affect small blood vessels of the retina
Neovascularization	Growth of new blood vessels to compensate for the ischemia induced oxygen deficit.
Vitreous haemorrhage	Accumulation of blood in the vitreous due to more and more of leakage from the weak newly growing blood vessels

Severity of DR is determined based on the presence of one or more of these symptoms observed in an ophthalmic examination of the fundus.

Among the different systems of classification of DR, the Early Treatment Diabetic Retinopathy Study (ETDRS) is considered as the gold standard [4]. Classifications proposed by American Academy of Ophthalmology (AAO) [5], National Screening Committee (NSC) [6] and Scottish Diabetic Retinopathy Grading Scheme (SDRGS) [7] follow the ETDRS system with certain modifications. The international classification system proposed by AAO is widely used [8]

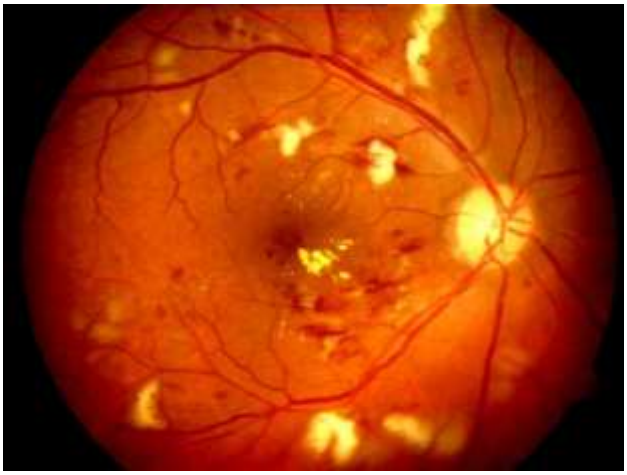

Fig-2: Fundus photograph showing features of proliferative DR with maculopathy

According to the ETDRS, retinal thickening or hard exudates at or within one third of the diameter of optic disc of the centre of the macula or retinal thickening that is greater than one optic disc area and a part of it being within one disc diameter of the centre of the macula is defined as CSME [9]. CSME may be present along with any of the severity levels of DR.

Generally, PDR patients display 4 high risk characters (HRC) that are used as indicators to sight threatening levels of DR. Those who have one or two of these characters are considered to be having non-high-risk PDR, while those having 3 or 4 high risk characters are said to have high risk PDR. These PDR with HRC patients may experience peripheral tractional retinal detachment where there is no involvement of macula or tractional retinal detachment in which traction of the macula is also present.

Early stages of DR don't need any treatment and is most often prevented from progressing to severe stages through good glycaemia control and effective medical management. However, the advanced stages of the disease have to be clinically intervened through either laser photocoagulation or surgical procedures. Scatter or pan retinal laser treatment helps to shrink the abnormal blood vessels. Nearly 1,000 to 2,000 laser burns are placed on the retina away from the macula, causing the abnormal blood vessels to shrink. Although there could be a loss of side vision and slightly reduced colour vision, scatter laser treatment helps to prevent further vision loss [10]. Vitrectomy, an invasive procedure, is performed when bleeding is severe. Retinal detachments are managed through surgery.

In this paper, we have compared various systems for DR image processing, and identified the algorithms used for a given application, the next section describes the algorithms in brief. Finally, we conclude the paper with some interesting observations about the compared algorithms and proposed the future work which researchers can perform in order to further analyse these algorithms.

2. LITERATURE REVIEW

Vessel contours are identified by sharp variations of image intensities (edges). Unfortunately, the intensity variation across the edge of a typical vessel is continuous and corrupted by noise, so that the exact location of the contour becomes ambiguous. Image analysis techniques are more reliable than previous micrometric techniques in locating vessel edges [11]. Common microdensitometric techniques employ intensity profiles of a greyscale image of the fundus (Fig-2) but other methods have been used including edge detection algorithms and other curve derivatives [12].

Defining locations to measure edges: The vascular tree thins toward the periphery and vessels may also have branched before reaching any set points of measurement. The diameter of two branch vessels does not simply add up to that of the parent vessel, preventing easy solution to the problem. Furthermore it is not width but cross sectional area that is significant when combining the effective width of arteries [13]. These problems were considered as early as 2014 by Parr et al.[14]. They showed how the diameters of two branched vessels can be combined mathematically to calculate the diameter of the parent vessel and proposed a mathematical model to combine all vessel widths at a set distance from the disc in order to calculate a theoretical central retinal artery diameter equivalent. This gave less variation in calculated arterial calibre of normal eyes compared to summing artery widths or squares of artery widths [15]. The formula used was derived from information from healthy young adults [16] and equivalent algorithms for neonates have yet to be investigated. Further developments to the adult algorithms have been made by Hubbard to quantify retinal vein calibre [17], and Knudtson to improve robustness against variability, including the use of dimensionless measurements [18]. Our own team has further refined the formula for the estimation of retinal trunk arteriole/venule widths from their respective branch widths [19].

Magnification effects (camera and ocular effects): The magnification effect of the camera relates the angle emergent from the first principal point of Gullstrand's schematic eye to the image size(s) of the retinal feature, expressed as a quotient [20]. This is a constant for any particular camera system, and only needs addressing if more than one camera system is used in any individual study. Ocular magnification effect may be harder to assess. The most accurate technique is to use ray tracing [20] but because of the impracticality of gathering all of the required information, summarising formulae that make certain assumptions of the eye can be used to obtain an accurate estimate of the ocular effect of magnification. Many different techniques are available [21-23] and results of abbreviated methods [23] may differ little from

the more detailed calculations [20]. One of the simplest techniques is based solely on refraction[24]. Differences in magnification on differing images of the same patient have been corrected for, by assessing relative to disc diameter [25], but there has been less success when this approach is used for different patients with their inherent differences in disc size [26]. A move away from translating pixel measurements into corresponding estimates of 'actual' vessel width (usually in micrometres) by using summary dimensionless measurements such as by Knudtson et al.[28] may negate the effect of ocular magnification and allow inter individual differences to be measured. The degree of eccentricity of the measured object from the optical axis [23, 27] and camera-eye distance [24, 28-32] may also affect magnification. With the contact RetCam assessing posterior pole vessels these final factors should be insignificant.

One important limitation of current imaging systems for measuring retinal vessel widths includes the low-resolution images from the RetCam (typically 640 x 480 pixels), which will result in very low vessel widths of a few pixels in diameter. Thus, the future use of RetCam imaging in performing retinal vessel width measurement may depend on the development of higher resolution imaging devices. Other potential problems with retinal vessel width measurements include variation due to the cardiac cycle [33-35], degree of systemic autonomic nerve stimulation [36, 37] and degree of fundus pigmentation [38].

Many tortuosity measures have been proposed for blood vessels and choice of a suitable measure depends on the particular purpose of the investigation [39]. With different pathologies and anatomy (including dimension) of blood vessels, tortuosity measures currently used in adults might not be appropriate in neonates. For example, studies measuring abdominal aorta tortuosity may presume deviation from a straight line to be abnormal [40], but normal retinal vessels are significantly curved when viewed in digital images of fundi, partly due to the inherent curvature of the globe causing them to appear curved on two dimensional photographs. Indeed, traction causing straightening of vessels is a sign of severe retinopathy of prematurity [41]. However, few authors present algorithms for which vessels of constant convexity such as normal retinal vessels, would have zero tortuosity [42]. The simplest measure of vessel tortuosity is the *distance metric*, defined as the ratio of the true length of a vessel to the length of the shortest chord between the two endpoints [12, 14, 17, 35, 43, 44]. In practice, the distance metric captures how much a curve deviates from the shortest path between its endpoints. As pointed out by several authors [13, 45] the method is flawed, as vessels that bend gradually can yield the same result as vessels presenting more frequent turns [46]. More complex measures of tortuosity have been described both for ROP measurement and in other fields of study including algorithms that measure integral curvature along a vessel [47, 48] , calculating the number of curves in a segment [42, 47] or the change in angle along segments of vessels [49]. Displacements from the midline of vessels [40] have also been used as the basis of algorithms in general use for vessel tortuosity assessment [46].In adults there has been widespread acceptance of the Parr-Hubbard [45] technique of retinal vessel width measurement using central retinal vessel equivalents (CRAE/CRVE). Problems in determining an overall measure of an individual's vessel calibre that lead researchers to use central vessel equivalents should at least be acknowledged and accounted for in studies on ROP. Furthermore, with future higher resolution imaging permitting, individual vessel diameter measurement with microdensitometric techniques should be explored.

Future research might allow key factors in the pathogenesis of 'Plus disease' to be measured, such as level of ischaemia. Currently, however, the reference standard against which validity of tortuosity measures is assessed is examination by paediatric ophthalmologists. In order to progress, there needs to be clarification and incorporation of exact geometrical mathematical features that most accurately capture the essence of what paediatric specialists would regard as tortuosity.

Vascular topographical geometry, far from being a totally random network, has a tendency to minimise physical properties such as shear stress and work across the vascular network in order to reach an 'optimal' state [40-45]. Deviation away from this optimal geometrical configuration would be interesting to assess in retinal disease. Potential geometrical features that could be measured include branching coefficients (a dimensionless measure of the relation between diameters of parent and daughter vessels) [48] and the angle subtended between two branch vessels at a vascular junction [46, 47] (known to be reduced in hypertension [48], increasing age [49] and low birth weight males [40]). King et al [41] developed the length: diameter ratio as another dimensionless measure of network topography, reflecting retinal arteriolar attenuation. They found this to be increased in hypertension [41]. Finally, fractal geometry is commonly encountered in biological systems. The concept of fractals as mathematical entities to describe complex natural branching patterns, such as that present in biological systems was first considered by Mandelbrot [42, 43]. Masters and Platt [44] and Family et al.[45] were the first to introduce the use of fractal analysis to retinal vascular branching patterns in adults. It is unclear whether fractal analysis offers sensitivity to detection of pathology above and beyond established retinal geometrical features.

3. CONCLUSION

As technologies emerge, they must be harnessed by medical scientists to ensure that they are translated into improvements in patient care. Image processing and analysis represents such an opportunity for advancement of clinical assessment and research. This paper describes

the potential of image analysis in many fields and explains some of the principles and terminology used in future works.

The specific image analysis challenges presented in this paper are in assessment of posterior capsule opacification, corneal opacification and haemorrhage assessment. In posterior capsule opacification the key issue will be to determine a measure of the opacification that has relevance to visual function and at the same time is sensitive to small changes over shorter periods of time. For corneal opacification the key challenge is determine a way to obtain images that are taken quickly and are repeatable. Segmenting out unnecessary lighting artefacts is also important. For haemorrhage assessment the key challenge is in segmentation and this was never resolved in a fully automated way. Instead we relied on semi-automated segmentation by a retinal specialist to maintain validity.

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