Optical Coherence Tomography – Automatic Retina Classification Through Support Vector Machines

Rui Bernardes,[1,2] Pedro Serranho,[3,4] Torcato Santos,[1,2] Valter Gonçalves[2] and José Cunha-Vaz[1,2]

1. Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal; 2. Institute of Biomedical Research on Light and Image, Faculty of Medicine, University of Coimbra, Coimbra, Portugal; 3. Mathematics Section, Department of Sciences and Technology, Open University, Lisbon, Portugal

Abstract

Optical coherence tomography (OCT) is becoming one of the most important imaging modalities in ophthalmology due to its non-invasiveness and by allowing the visualisation the human retina structure in detail. It was recently proposed that OCT data embeds functional information from the human retina. Specifically, it was proposed that blood–retinal barrier status information is present within OCT data from the human retina. Besides this ability, the authors present data supporting the idea of having the OCT data encoding the ageing of the retina in addition to the disease (diabetes) condition from the healthy status. The methodology followed makes use of a supervised classification procedure, the support vector machine (SVM) classifier – based solely on the statistics of the distribution of OCT data from the human retina (i.e. OCT data between the inner limiting membrane and the retinal pigment epithelium). Results achieved suggest that information on both the healthy status of the blood–retinal barrier and on the ageing process co-exist encoded within the optical properties of the human retina.

Keywords

Optical coherence tomography, support vector machines, supervised classification, retina, diabetic retinopathy, ageing

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Correspondence: Rui Bernardes, Association for Innovation and Biomedical Research on Light and Image (AIBILI), Azinhaga de Santa Comba, Celas, 3000-548 Coimbra, Portugal. E: rcb@aibili.pt

Both the ageing process and diabetes promote changes on the human retina, although not always visible through the regular eye fundus examination. The authors' research group has been focused on imaging changes within the human retina of diabetic patients aiming for better characterisation and on detection at the very early stages even when these cannot be detected in the eye fundus.

Current trends in medical imaging point to the increasing use of non-invasive techniques. In this sense, the authors started focusing our efforts in assessing the possibility of gathering information from the eye fundus through non-invasive techniques. Nevertheless, these are required to provide the same or even higher levels of information than the one currently provided. A particularly interesting non-invasive technique in use in the field of ophthalmology is the optical coherence tomography (OCT). This imaging technique is spreading quickly and, in consequence, is becoming available in multiple eye care facilities.

The authors research group has been interested in diabetic retinopathy with a special focus on the breakdown of the blood–retinal barrier (BRB) in consequence of diabetes.[1–3] The number of diabetic patients is increasing worldwide[4] and this multifactorial disease has a large social and economic impact in the active working population.[5]

Efforts made towards the assessment of the BRB function led the authors research group to the development of the retinal leakage analyser (RLA).[6,7] This imaging modality, based on the confocal imaging of the eye fundus after sodium fluorescein (NaFl) administration, led to a better characterisation of the changes occurring in the diabetic retina.[8]

Additionally, this knowledge made possible the identification of different phenotypes of diabetic retinopathy progression,[9] showing over time the significantly different rates of progression in the diabetic retina and the variability between diabetic patients. Both instruments used in Lobo et al.[6] and Bernardes et al.[7] were modified for specific purposes. The former instrument was a Carl Zeiss confocal scanning laser ophthalmoscope (CSLO) prototype (Carl Zeiss, Jena, Germany) modified for the task at hand. The latter was a CSLO (Heidelberg Retina Angiograph [HRA], Heidelberg Engineering, Heidelberg, Germany) modified to increase confocality and to use a different positioning of the confocal planes within the ocular fundus to scan through the retina and vitreous.

Besides the requirements on dedicated instrumentation, the basic principle of the technique is similar to a regular fluorescein angiography, hence the administration of sodium fluorescein into the patient's blood circulation being mandatory. This procedure prevents the widespread use of the technique by requiring the presence of medical staff in addition to a clinical environment able to cope with a potential adverse reaction. These reactions occur in 5 % of the cases while death may occur for each 220,000 cases in the first 24–48 hours after fluorescein administration.[10]

Material and Methods

Retinal Leakage Analyser

The RLA technique is based on the confocal imaging of the ocular fundus following the administration of sodium fluorescein and allows for the mapping of the BRB function into intact or disrupted BRB. It does not, however, allow to discriminate between the inner and outer BRB, the former being composed of the tight junctions of the retinal vascular network and the latter – the outer BRB – being composed of the retinal pigment epithelium (RPE).

In brief, the system computes the amount of sodium fluorescein that crosses the BRB from the retinal circulation into the human vitreous.[6,7] Since the amount of sodium fluorescein present within the vitreous is directly related to BRB permeability,[7] the amount of leakage indicates the breakdown of the BRB, being the BRB function affected by diabetes.[1–3,8,9]

A fundus reference is computed from the same data associated with the map of the BRB function status. Therefore, the fundus reference and the BRB function status are intrinsically co-registered. In consequence, regions of intact and regions of disrupted BRB can be mapped within the ocular fundus reference.

Optical Coherence Tomography

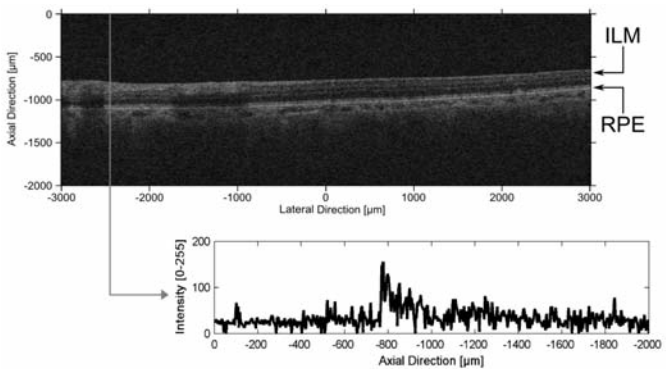
OCT is a non-invasive imaging technique able to provide cross-sectional tomograms of the retinal tissue (see *Figure 1*). The basic principle of OCT is similar to that of ultrasound, using light instead of sound waves.[12] A near-infrared light beam from a superluminescent diode is projected across the retina and images of high resolution are produced resorting to low coherence interferometry.[12]

In the work presented, the high-definition spectral domain Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, US) was used. System specifications include a 5 µm depth resolution, a 20 µm transversal resolution and a scanning speed of 27,000 A-scans per second.[13] This system allows for the scanning of the ocular fundus using two different macular cube protocols, namely the 512x128x1,024 and the 200x200x1,024, both covering the same volume of 6,000x6,000x2,000 μm^3.

Traditionally, OCT has been used (in addition to the original purpose, i.e. measuring retinal thickness) to assess structural information from the ocular fundus, allowing the identification of cyst-like structures, retinal detachments, changes in the RPE and macular holes, among other changes.[11]

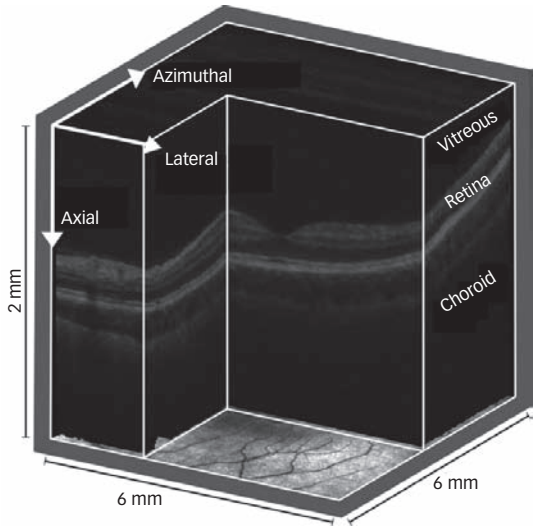
OCT readings result from reflections and/or light scattering due to refractive index changes along the light path and are therefore dependent on the content and structural organisation of the eye. Any change in those elements will consequently result in a change in OCT readings.[11]

Figure 1: Optical Coherence Tomogram (B-scan Image [Top]) and the Intensity Plot of an A-scan (Bottom)



Top: the dark upper area region of the image represents the vitreous, immediately followed by the retina (delimited by the ILM and by the RPE), the RPE and choroid. ILM = inner limiting membrane; RPE = retinal pigment epithelium. Source: Reprinted with permission from Bernardes et al., 2011.[11]

Figure 2: Optical Coherence Tomography Volumetric Data Display



The fundus image reference underneath the volume is automatically computed from the volume and corresponds to the integral (sum) along the axial direction. Reprinted with permission from Bernardes et al., 2011.[11]

Blood–Retinal Barrier Status from Optical Coherence Tomography

In a recent paper from the authors' research group, the authors have for the first time demonstrated the presence of BRB function status within OCT data. In brief, it was demonstrated that differences in the histograms of OCT data were significantly distinct from regions of intact to regions of disrupted BRB.[11,14] Moreover, it demonstrated the association of the differences found with the retinal vascular network through the depth discrimination within the retinal tissue. This discrimination demonstrated that the differences found were significantly different within the top 1/3 of the human retina, the location of the majority of the retinal vascular network, thus establishing a direct association between the differences found and the inner BRB.[11]

In fact, it was the first demonstration that was able to discriminate between the inner and the outer BRB *in vivo* and this work established the proof of concept that OCT data embeds information on the status of the BRB.

Table 1: Classification Performance

	H	D	DME
H	20 (64.5 %)	5 (16.1 %)	6 (19.4 %)
D	4 (12.9 %)	23 (74.2 %)	4 (12.9 %)
DME	7 (22.6 %)	5 (16.1 %)	19 (61.3 %)

Classification performance following the leave-one-out validation, with 62 out of 93 eyes (66.7 %) correctly classified. H = healthy volunteers' eyes (n=31); D = diabetic patients' eyes (n=31); DME = diabetic macular oedema eyes (n=31).[15]

Table 2: Healthy Eyes Classification Performance

	Age <46 Years Average Age (std)	Age ≥46 Years Average Age (std)	Number of Patients Average Age (std)
Age <46 years	16 (76.19 %)	5 (23.81 %)	21
	30.94 (6.85)	36.07 (5.24)	32.16 (6.76)
Age ≥46 years	7 (36.84 %)	12 (63.16 %)	19
	53.69 (4.93)	62.47 (9.30)	59.24 (8.94)

std = standard deviation (years).

Table 3: Diabetic Patients' Eyes Classification Performance

	Age <63.5 years Average Age (std)	Age ≥65.3 years Average Age (std)	Number of Patients Average Age (std)
Age <63.5 years	53 (71.62 %)	21 (28.38 %)	74
	55.24 (5.94)	58.54 (5.09)	56.17 (5.87)
Age ≥63.5 years	21 (29.17 %)	51 (70.83 %)	72
	68.56 (2.72)	68.91 (3.75)	68.80 (3.47)

std = standard deviation (years).

Table 4: Eyes Classification Performance

	Healthy Average Age (std)	Diabetic Average Age (std)	Number of Patients Average Age (std)
Healthy	22 (64.71 %)	12 (35.29 %)	34
	53.95 (11.18)	56.63 (13.52)	54.90 (11.93)
Diabetic	10 (29.41 %)	24 (70.59 %)	34
	57.83 (8.80)	54.74 (8.67)	55.65 (8.69)

std = standard deviation (years).

Healthy and Diabetic Discrimination Through Optical Coherence Tomography

Based on the above results, the hypothesis of discriminating between healthy volunteers and diabetic patients was raised as a natural consequence. In this way, the first step consists to fully characterise the OCT signal from each eye group and to establish a procedure able to discriminate it. As OCT signal spans across several orders of magnitude, OCT images are typically displayed in the logarithmic space; that is, the signal is logarithmically compressed. Therefore, one can think of the OCT data both on the logarithmic (LOG) or linear (LINEAR) spaces.

Histograms of OCT data from the human retina (i.e. from the inner limiting membrane [ILM] to the RPE) resemble the traditional Gaussian shape. Since histograms encode the number of data points used, histograms were normalised by the number of data points therefore becoming probability density functions (PDFs) while keeping the exact shape.

OCT data distribution in the logarithmic space is characterised by:

$$g(I) = G\exp\left(-\frac{(I-\mu)^2}{2\sigma^2}\right) \quad (1)$$

where μ and σ are the average and the standard deviation values of I (voxel values from the OCT volume), respectively (see *Figure 2*).

As shown in Bernardes,[15] these same data can be characterised in the linear space by:

$$p_s(I_{LINEAR}) = k(\alpha,\lambda,\beta)\exp\left(-\left(\frac{I_{LINEAR}-x_0}{\lambda}\right)^{\gamma}\right) \quad (2)$$

where

$$k(\alpha,\lambda,\beta) = \frac{\alpha}{\lambda\,\Gamma\left(\frac{\beta+1}{\beta}\right)} \quad (3)$$

and

$$I_{LINEAR} = 10^{\log(L)\frac{I_{LOG}-\langle I_{LOG}\rangle+N/2}{N-1}} \quad (4)$$

with $I_{LOG}\in[0,N-1], N=256$, $\langle I_{LOG}\rangle$ the average of I_{LOG} and L the nominal maximum of I_{LINEAR}.

A set of features can be computed for each OCT eye scan by fitting these models to each healthy volunteer and each patient's data. A total of 43 parameters were computed in the initial approach[15] allowing for the characterisation of each scan.

A support vector machine (SVM)[16] system was used to establish a supervised classification method able to classify each eye in the healthy, diabetic or diabetic macular oedema group. A publicly available software – LIBSVM[17] – was used for the training and classification tasks resorting to the radial basis function (RBF) kernel.

The leave-one-out validation approach was applied to assess the feasibility of the system to classify OCT data not present in the training set leading to results shown in *Table 1*. As shown, over 66 % (62 out of 93 eyes) of the cases were correctly classified (i.e. received the correct classification through the SVM classification procedure).[15]

An additional set of features were recently considered, raising the number of features from the above 43 parameters to 51 parameters. To assess the dependency of the classification with age, two groups of healthy volunteers and two groups of diabetic patients were classified according to the respective age group.

Finally, an age-matched population of diabetic patients' eyes to the healthy volunteers' eyes were considered to assess the potential discrimination between these groups hence removing any potential age effect.

Results

Tables 2 and *3* summarised the achieved results regarding the discrimination between different age groups of both the healthy volunteers' and diabetic patients' eyes, respectively, following the leave-one-out approach.

Of fundamental importance is the demonstration that for both cases, healthy volunteers' and diabetic patients' eyes, there is a dependence on the age, with over 63 % of the cases correctly classified on the respective age group. Additionally, *Table 4* summarises the discrimination between age-matched healthy volunteers' eyes and diabetic patients' eyes.

These results confirm the ones previously found (see *Table 1*) and suggest the presence of two distinct levels of information on the statistics of OCT data from the human retina. In the one hand, there seems to exist information on the retinal tissue age, both on healthy and diseased (diabetes) patients' eyes and on the other hand, there seems to exist information specific to the disease process able to discriminate between age-matched healthy volunteers and diabetic patients' eyes groups.

Discussion and Conclusions

Following the authors initial proof of concept that OCT data embeds information on the BRB,[11,14] the authors went a step further demonstrating the possibility to discriminate between healthy and diseased eyes (diabetic retinopathy eyes) resorting to an automatic classification procedure widely used – the SVM classification process.[16,17]

Since the classification is based on the statistics of the OCT data only, the fact the system is able to correctly classify eyes in the proper group in over 64 % of the cases (see *Table 4*) clearly suggests the presence of this information embedded within the OCT data.

Of paramount importance is the fact that the exact same approach is able to discriminate between age groups within the healthy volunteers' eyes as well as between age groups within the diabetic patients' eyes. It suggests, therefore, the potential use of OCT data to assess the ageing process of retinal tissue. For instance, these findings suggest that the potential of OCT to embed information on degenerative diseases should also be studied. This is of particular importance if the biological tissue is similar to the retina – for instance, brain degenerative diseases. This will be a matter for future work. Moreover, it was demonstrated that the system is able to discriminate between healthy volunteers' eyes and eyes from diabetic patients even when age-matched.

This shows that OCT data embeds information both on the age of the subject and its diabetic status, namely by reflecting the possible disruption of the BRB. This opens the possibility of using a completely non-invasive technique to diagnose BRB breakdown. Moreover, since this information is contained mainly in the upper third of the retina (where retinal vessels are mainly located) as shown in Bernardes et al.,[11] this technique should be more sensible to inner BRB breakdown while the previously used RLA technique could not differentiate between inner or outer BRB breakdown. In this way the proposed technique has also the potential to allow us to distinguish between inner and outer BRB breakdown.

Finally, these findings open the possibility to use the eye as a window to changes occurring within the human brain, in a non-invasive manner, resorting to an easy to perform technique that does not even require pupil dilation and can be easily performed by a technician. ■

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