33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

# Optical Coherence Tomography: health information embedded on OCT signal statistics

Rui Bernardes, *Member, IEEE*

***Abstract*—Optical coherence tomography is becoming one of the most important imaging modalities in the area of ophthalmology because of being noninvasive and by allowing to visualize 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. Following this rationale, in this work we illustrate (based on support vector machines) the possibility to discriminate between eyes from healthy volunteers, eyes from type 2 diabetic patients with no signs of diabetic retinopathy (ETDRS level 10 eyes) and eyes diagnosed with diabetic macular edema, thus confirming the presence within OCT data of information on the BRB status.**

## I. Introduction

OPTICAL Coherence Tomography (OCT) is a noninvasive imaging modality with a wide spread in ophthalmology because of its ability to image the ocular fundus in detail.

Although the primary function of OCT is to document the structure of *in vivo* human retinas, it was recently suggested ([1]-[3]) that OCT embeds information on the status of the blood-retinal barrier (BRB). In [3], it was specifically demonstrated the close link between disrupted/intact BRB status and changes in the statistics of OCT data from the human retina and its association to the retinal vascular network in retinas with diabetic retinopathy (DR).

In the work herewith presented, we propose to assess the possibility of classifying a subject's eye into one of three classes (healthy, diabetic and diabetic macular edema) solely based on OCT signal without resorting to retinal thickness. In this way, we propose to further demonstrate the presence of information on the BRB status within OCT data from the earliest stages of DR.

## II. Material and Methods

### A. Optical Coherence Tomography

In this work we resorted to Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA) for data acquisition.

Manuscript received April 7, 2011. This work was supported in part by the Fundação para a Ciência e a Tecnologia (FCT) under the project PTDC/SAU-BEB/103151/2008 and program COMPETE (FCOMP-01-0124 FEDER-010930).

R. Bernardes is with the Institute of Biomedical Research in Light and Image (IBILI), Faculty of Medicine, University of Coimbra, Coimbra, Portugal (e-mail: rmbernardes@fmed.uc.pt) and Center of New Technologies for Medicine (CNTM), AIBILI, Coimbra, Portugal (phone: +351 239480108; fax: +351 239480117; e-mail: rcb@aibili.pt).

Cirrus HD-OCT is a high-definition optical coherence tomography system, of the frequency domain type, allowing for the acquisition of 27000 A-scans per second with a depth resolution of 5 microns and a transversal resolution of 20 microns. Two scanning modes are available covering the macular area (6000x6000 square microns): a 512x128x1024 voxels protocol and a 200x200x1024 voxels protocol, the former being used in this work.

Cirrus HD-OCT automatically identifies the ILM (inner limiting membrane) and the RPE (retinal pigment epithelium), the structures limiting the retina, to compute the retinal thickness by measuring the distance ILM-RPE.

In this work, we made use of these two interfaces to segment the retina and to exclude vitreous and choroid data from our process.

Thirty-one eyes from 16 healthy volunteers, 31 eyes from 18 type 2 diabetes mellitus patients and 31 eyes diagnosed with diabetic macular edema (DME) from 22 type 2 diabetes mellitus patients were collected from the OCT database to be processed and analyzed.

### B. Data Statistics

Histograms from OCT data in between the ILM and RPE, i.e. from the retina, were built for each eye to find a Gaussian-like distribution:

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

where $\mu$ and $\sigma$ are, respectively, the average and standard deviation values of I (voxel values).

In a recent paper of Grzywacz et al. [4], authors stated that the distribution of OCT data from the human eye fundus is better defined by a stretched exponential distribution:

$$p_s(I) = k(\lambda,\beta)e^{-(I/\lambda)^\beta}, \quad (2)$$

where

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

with $\Gamma$ the gamma function.

The clear difference between these two distributions ((1) and (2)-(3)) lies in the fact that we get access to data in the logarithmic space while in [4] authors seem to have access to data in the linear space.

The logarithmic space for OCT data results from the fact that OCT real values spread in several orders of magnitude [4].

In this way, to characterize OCT data distribution as in [4] we have to revert the process by computing the exponential for each voxel value by:

$$I_{LINEAR} = K\left(10^{I_{LOG}} - 1\right), \quad (4)$$

where $I_{LINEAR}$ and $I_{LOG}$ $\left(I_{LOG} \in [0, N-1], N = 256\right)$ are, respectively, the voxel value in the linear and logarithmic spaces and $K$ a scaling factor. We then fit a stretched exponential distribution to determine parameters $\lambda$, and $\beta$ in (2)-(3).

In addition, and because of the expected differences in the number of voxels making part of the retina for each eye, e.g. due to edema, a probability density function (pdf) was used instead of the Gaussian distribution (in the logarithmic space) by normalizing the histogram by the number of voxels composing the retina.

Moreover, because $10^{I_{LOG}}$ in (4) will became a quite large number, (5) was used instead of (4):

$$I_{LINEAR} = 10^{\log(L)\frac{I_{LOG} - \langle I_{LOG}\rangle + N/2}{N-1}}, \quad (5)$$

were $\langle I_{LOG} \rangle$ is the average of $I_{LOG}$ and $L$ the nominal maximum for $I_{LINEAR}$.

In this way, any differences in the computed parameters from the stretched exponential distribution are solely due to the respective shape.

Consequently, a modified expression for the stretched exponential distribution in the linear space was used as defined by:

$$p_s(I) = k(\alpha, \lambda, \beta) e^{-\left((I_{LINEAR} - x_0)/\lambda\right)^{\beta}}, \quad (6)$$

where

$$k(\alpha, \lambda, \beta) = \frac{\alpha}{\lambda\, \Gamma\left((\beta+1)/\beta\right)}, \quad (7)$$

therefore adding two new parameters, $x_0$ (6) and $\alpha$ (6)-(7).

### C. Features and Support Vector Machines (SVM)

A total of 43 features were used to characterize each retina.

Four features from the logarithmic space (average, standard deviation, skewness and kurtosis), four features from the linear space ($\alpha$, $x_0$, $\lambda$ and $\beta$) and three features from the fit optimization process (goodness of fit statistics) of the stretched exponential distribution (*sse* – sum of squares due to error, *r-square* – adjusted R-square, and *exitflag* – indicating a successful or unsuccessful optimization process).

These 11 features were computed considering:

1) the entire retina (data from the ILM to the RPE);
2) the top half of the retina (from the ILM to half distance ILM-RPE);
3) the bottom half of the retina (from half distance ILM-RPE to the RPE), and;
4) the ratio between features from the top and bottom halves of the retina (except the ratio of the *exitflag*).

The rationale of splitting the retina in two halves is due to the previously demonstrated fact that particular information on the BRB function status is present on OCT data [3]. Moreover, this information is linked to the retinal vascular network, which is found in the half of the retina close to the ILM [5].

All eyes from healthy volunteers receive the classification of *0*, eyes from diabetic patients received the classification *1* and eyes with diabetic macular edema received the classification *2*.

Publicly available software, LIBSVM (Chang et al., [6]), was used. All features were scaled to the range [0,1] or [-1,1], as appropriate, and the RBF (radial basis function) kernel applied.

The optima values of $C$ (regularization margin parameter) and $\gamma$ (RBF kernel parameter) were found using the Grid-search mechanism in two steps. In the first step, the default search was used to identify optima values of $C$ and $\gamma$ from a wide range of values. After this initial step, a local search was made to fine tune $C$ and $\gamma$ values to determine a better set of parameters.

The training step of the SVM was carried out using optima values of $C$ and $\gamma$ to compute the model to be used for the classification of eyes into one of the three classes: healthy, diabetic and diabetic macular edema.

### D. SVM Data Classification

Using the entire set of data for the training of the SVM, over 80% of data was correctly classified, i.e. was classified by the SVM system receiving the same classification as the one used in the training for the establishment of the model.

A leave-one-out validation approach was applied to assess the feasibility of the system to classify OCT data not present in the training set.

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), and; DME – diabetic macular edema eyes (n=31).

## III. RESULTS AND CONCLUSIONS

Following the leave-one-out validation, over 66% (62 out of 93 eyes) were correctly classified (Table 1). On the other hand, 11 eyes were incorrectly classified as healthy from which 7 were diabetic macular edema eyes. Additionally, 6 eyes were incorrectly classified as diabetic macular edema

TABLE 2: CLASSIFICATION PERFORMANCE

| | H | Diseased |
|---|---|---|
| H | 21 (67.7%) | 10 (32.3%) |
| Diseased | 4 (13.3%) | 26 (86.7%) |

Classification performance following the leave-one-out validation. H – healthy volunteers' eyes (n=31); Diseased – diabetic patients' eyes (n=15) and diabetic macular edema eyes (n=15).

TABLE 3: CLASSIFICATION PERFORMANCE

| | D | DME |
|---|---|---|
| D | 33 (86.8%) | 5 (13.2%) |
| DME | 6 (15.8%) | 32 (84.2%) |

Classification performance following the leave-one-out validation. D – diabetic patients' eyes (n=31), and; DME – diabetic macular edema eyes (n=31).

eyes while being from the healthy volunteer group.

Using the exact same set of data, a group of 31 healthy volunteers eyes and a group of 30 diseased eyes (from which 15 were diagnosed DME) were considered to test the classification into healthy or diseased eyes (table 2).

Similarly, considering diabetic patients' eyes (n=31) and eyes diagnosed with diabetic macular edema (n=31), the classification achieved is as in table 3.

In this way, using a 2-step classification system, the probability of an eye to receive the correct classification is of p=0.677, p=0.753 and p=0.730, respectively for healthy eyes, eyes from diabetic patients (non-DME) and eyes diagnosed with DME.

There are two particularly important aspects from the work herewith presented. First, diabetic patients (D eyes) included in this study were classified as level 10 from the ETDRS classification level, meaning that, although being diabetic patients, no signs of diabetic retinopathy were identified in the eye fundus.

Second, better figures could have been found should we have used additional information, e.g. retinal thickness. Nevertheless, the key issue is to demonstrate that particularly important information is present in OCT data, from the human retina, conveying more information than the simple structural one.

In addition, this study demonstrate that changes in the optical properties of the human retina (as identified through optical coherence tomography) are associated with diabetes and that these changes are present even in diabetic patients with no signs of retinal diseases (hence been classified as ETDRS level 10). Moreover, changes in the optical properties of the human retina seem to be associated with the severity of the pathology as suggested by the distinction made by the classification process between ETDRS level 10 eyes and eyes diagnosed with diabetic macular edema.

In [4], Grzywacz et al. proposed the possibility of using OCT data to discriminate between healthy and diabetic macular edema eyes, following a different approach.

While in the work herewith presented we resort to the entire retina volume, in [4] the authors resort to local data and claim the possibility to identify the location of anomalies, although at the expense of requiring to segment (four to five [4]) retinal layers, as opposed to our approach that makes use of the ILM and RPE segmentation already made available by the Cirrus HD-OCT system and most of the OCT systems commercially available.

In addition, the method herewith proposed allows to discriminate between healthy volunteers' eyes, ETDRS level 10 eyes from diabetic patients and diabetic macular edema eyes, therefore being sensitive to changes in the retina before these changes can be identified by fundoscopy.

Finally, these results suggest the possibility of identifying diabetic patients based on a noninvasive imaging modality, with a false negative rate of less than 12% (11 out of 93 cases) and to discriminate healthy eyes (non-diabetic patients' eyes) from eyes of diabetic patients with no visible signs of diabetic retinopathy within the eye fundus, i.e. ETDRS level 10 diabetic patients' eyes.

## ACKNOWLEDGMENT

The author would like to thank Dr. Melissa Horne and Carl Zeiss Meditec (Dublin, CA, USA) for their support on getting access to OCT data, Torcato Santos, Pedro Serranho, Pedro Rodrigues and Valter Gonçalves for their support and comments and AIBILI Clinical Trial Center technicians for their support in managing data, working with patients and performing scans. This study is registered at ClinicalTrials.org (ID: NCT00797524).

## REFERENCES

[1] Bernardes, R., Santos, T., and Cunha-Vaz, J.: Evaluation of Blood-Retinal Barrier Function from Fourier Domain High-Definition Optical Coherence Tomography., WC 2009, IFMBE Proceedings 25/XI, 316–319, Eds: Dössel, O., and Schlegel, W., 2009.

[2] Santos, T., Bernardes, R., Santos, A., and Cunha-Vaz, J.: Noninvasive Assessment of Blood-Retinal Barrier Function by High-Definition Optical Coherence Tomography, Technology and Medical Sciences, Proceedings of the 6th International Conference on Technology and Medical Sciences, 215–219, October 21-23, 2010, 2011.

[3] Bernardes, R., Santos, T., Serranho, P., Lobo, C., and Cunha-Vaz, J.: Noninvasive evaluation of retinal leakage using Optical Coherence Tomography, Ophthalmologica 226(2), 29–36, 2011.

[4] Grzywacz, N., Juan, J., Ferrone, C., Giannini, D., Huang, D., Koch, G., Russo, V., Tan, O., and Bruni, C.: Statistics of Optical Coherence Tomography Data From Human Retina., IEEE Trans Med Imaging 29(6), 1224–1237, June 2010.

[5] Sigelman, J., and Ozanics, V.: Ocular anatomy embryology and teratology. Retina (Chapter 15), Harper & Row, Publishers, Eds: Jakobiec, F., 1982.

[6] Chang C., and Lin C.: LIBSVM: a library for support vector machines, 2001.