Appearance-based Approach to Extract an Age-related Biomarker from Retinal Images

Rüdiger Bock[1], Jörg Meier[1], László G. Nyúl[1], Simone Wärntges[2], Georg Michelson[2], and Joachim Hornegger[1]

[1] Institute of Pattern Recognition, University of Erlangen-Nuremberg, Martensstraße 3, 91058 Erlangen
ruediger.bock@informatik.uni-erlangen.de
[2] Department of Ophthalmology, University of Erlangen-Nuremberg, Schwabachanlage 6, 91054 Erlangen

Abstract. We present an appearance-based method that extracts a new age-related biomarker from retina images. The Principal Component Analysis is applied on intensity values of the illumination corrected green channel of fundus images. The algorithm does not use segmentation, is robust and shows a high range of reliability. It identified an age-related feature with a strong influence of the temporal parapapillary area and the optic nerve head. The feature correlates with chronological age of the participants and is significantly influenced by the appearance of cardiovascular risk factors such as smoking and hypertension, and thus it can be designated a biomarker. We extract and validate a medical parameter from retina images applying a purely data-driven approach without using any prior knowledge.

1 Introduction

1.1 Concept of Biological Age

The concept of biological age is established as a general measure to quantify the "true global state of [an] aging organism" [1]. Because of the complexity of the human body and the aging process the biological age (BA) is commonly understood as a combination of several biomarkers. A valid biomarker must correlate with age and the influence of the risk factors has to be validated.

1.2 State of the Art

One common approach to determine the BA is to combine several age-dependent biomarkers into a BA index using statistical methods [2, 3]. Age-related biomarkers obtained by multiple regression analysis, factor analysis [4], or principal component analysis (PCA) [5] were combined into a new BA index.

The aging process can also be well observed on retinal images, especially changes of the retinal tissue [6] and the cardiovascular system. As described in [7], the blood flow in the optic nerve head is significantly correlated with age. These biomarkers are mainly based on measurement of specific regions of the retina. The regions are obtained manually or by automatic segmentation.

1.3 Purpose

The purpose of the presented study is to extract and validate an age-related biomarker from retina images using a purely data-driven approach. In contrast to extensive and error-prone segmentation, this appearance-based technique [8] applies the unsupervised Principal Component Analysis (PCA) on pixel intensities [9] of digital fundus images.

2 Methods

2.1 Image Processing and Feature Extraction

As the green channel of the RGB retina image provides the highest contrast among the relevant structures, only that is used for further investigations. The images can be illuminated unequally within the sample set and mostly show inhomogeneous background. In order to eliminate illumination variations, illumination correction by mean filtering [10] is applied. The region of interest is restricted to a circular area around the papilla center with a radius of 300 pixels. For PCA calculation, the selected circular ROI is transformed to vector representation. Application of PCA on a set of input images yields multidimensional, but compact representations of these images. Each vector component of the output is considered as a feature, independently from the others.

2.2 Statistical Analysis

The SPSS software (release 13.0; SPSS Inc. Chicago, IL, USA) was used for statistical analysis. Measurement values from the transformation were standardized by subtracting the mean value from raw data and divided by the standard deviation. Correlation between a feature and age was expressed using the Spearman-Rho coefficient. The intraclass correlation coefficient of reliability was calculated by determination of Cronbach alpha at the 95 % confidence interval. The F-statistics tested wether the mean values between different subjects and between images of the same subject differed significantly. The significance between controls and subjects at cardiovascular risk was calculated using the Mann-Whitney test. All values are expressed as mean $\pm$ SD. A p-value < 0.05 was considered significant.

3 Data

The used database of the population-based screening project "TalkingEyes" [11] includes more than 45,000 pairs of retina images acquired since 2002 during a clinical non-experimental cross-sectional survey. Color images of the retina (optic nerve head centered, resolution 1216×1600, field of view $45°$) were acquired in a standardized process. They were taken with a fundus camera (KOWA, nonmyd-alpha 45, Japan) without pharmacological dilation of the pupil. Only images

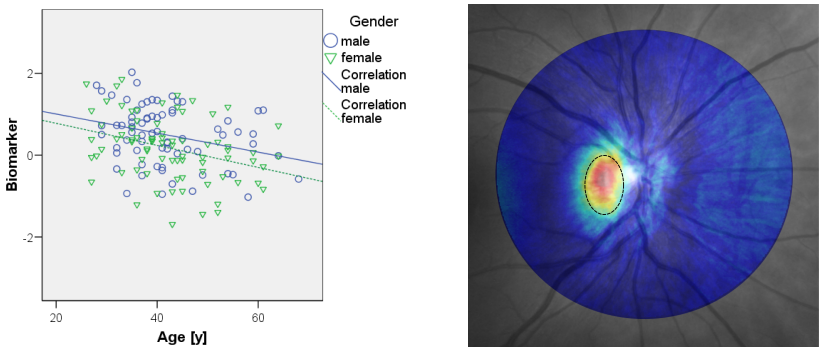

Fig. 1. Left: Age-dependency of the retinal feature in participants without cardiovascular risk factors and retinal diseases. Right: The absolute eigenimage is depicted as a overlay onto a gray-scale representation of the retina fundus image. The outlined region has a strong influence to the proposed biomarker and is located at the temporal parapapillary area and the optic nerve head.

from the right eye of sufficient quality were evaluated. The PCA transformation for identification of age-related image features was developed based on a randomly selected training set of 65 men (44.2 ± 11.4 years) and 60 women (48.8 ± 12.6 years) without cardiovascular risk factors and without pathological eye diagnosis. The resulting algorithm was tested on another subset of controls (70 men; 41.8 ± 9.2 years and 78 women; 42.6 ± 9.6 years) without hypertension, diabetes, hyperlipidemia, manifest ocular diseases, microaneurysms, cotton-wool spots, hard exudates, bleedings, neovascularizations, abnormalities of macular pigment epithelium and with a refractive range of -5 to +5 diopters.

3.1 Reliability

Fundus images from further six participants (four men and two women) provided a basis for assessing the reliability of the algorithm. Five fundus images were taken from the right eyes of the six healthy subjects in one minute interval by one observer.

3.2 Cardiovascular Risk Factors

For estimating the influence of cardiovascular risk factors on the biomarker, the control group was matched for age and gender to hypertensive subjects and smokers, respectively, without any other cardiovascular risk factors. Forty-four men (45.5 ± 9.3 years) and 26 women (51.2 ± 7.3 years) from the control group were opposed to the same number of hypertensive subjects (age 45.5 ± 9.4 years; hypertensive for 5.9 ± 6.7 years and age 51.2 ± 7.3 years; hypertensive for 7.9 ± 7.1 years, respectively). Fifty-seven male controls (41.7 ± 8.4 years) and 60 female controls (43.2 ± 9.4 years) were opposed to the same number of

Table 1. Biomarker values for smoking and hypertensive participants

	Hypertension			Smoking		
Gender	Risk factor	Control	Sig.	Risk factor	Control	Sig.
Male	0.10 ± 0.84	0.57 ± 0.95	0.01	-0.16 ± 1.29	0.72 ± 0.92	< 0.001
Female	-0.46 ± 1.23	0.06 ± 0.99	0.09	-0.12 ± 1.10	0.24 ± 0.98	0.048

male smokers (age 41.8 ± 8.5 years; smoking for 20.6 ± 9.8 years; 15.3 ± 8.6 cigarettes per day) and female smokers (age 43.2 ± 9.5 years; smoking for 20.1 ± 10.7 years; 13.5 ± 8.1 cigarettes per day).

4 Results

4.1 Correlation of the Retinal Biomarker with Age

The PCA generates a multidimensional and compressed representation of an image. The PCA transformation was determined using the training set. The images of the training set were compressed using this transformation and each vector component was evaluated for age correlation. One feature showed a significant correlation with age. To check the feature, the correlation was also tested on the control group. In male control subjects Spearman coefficient was -0.284, $p = 0.017$ and in female control subjects -0.374, $p = 0.001$. Figure 1 shows decreasing feature values with increasing age.

4.2 High Influence Regions of Retina to Biomarker

The PCA calculates several linear combinations that are applied to the input data. As each linear coefficient is associated to a pixel position, it can be illustrated as a so-called eigenimage.

The absolute eigenimage of the biomarker is presented in Figure 1 and allows an anatomical interpretation of image regions. The regions with the highest impact to the biomarker are located at the temporal parapapillary area and at the optic nerve head. This region is medically relevant and changes with age.

4.3 Retinal Biomarker in Subjects with Cardiovascular Risk

The biomarker in age-matched hypertensive patients and smokers differs significantly from control. As shown in Table 1, the existence of a cardiovascular risk factor like smoking or hypertension causes a significantly lower biomarker value.

4.4 Reliability

A Cronbach alpha = 0.953 indicates high reliability of the algorithm. Mean values between subjects ($df = 5$) and between the images of one subject each ($df = 4$) did not differ significantly ($F = 0.87$, $p = 0.985$).

5 Discussion

In the present study, we have established an age-related biomarker derived from retina images. The algorithm is based on fairly simple PCA and does not use segmentation. It is robust and shows a very good range of reliability. The temporal parapapillary area was identified as retinal region with the highest impact to the proposed biomarker. The validity of the biomarker was proven by the significant influence of cardiovascular risk factors such as hypertension and smoking. In conclusion, it was possible to extract and validate a medically relevant parameter by applying a purely data-driven approach without using any a priori knowledge.

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