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Medical Retina

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Imaging the Retina
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Abstract
Analyzing and comparing images from the human eye fundus is a fundamental step to investigation of retinal diseases. Digital imaging and image analysis are opening new perspectives in the evaluation of retinal diseases. It is now possible to identify and quantify changes in the fundus occurring in a period of time, bringing concepts of disease activity and rate of progression. Fundus autofluorescence imaging is a new acquisition method with particular interest to follow age-related macular degeneration. Spectral domain optical coherence tomography has revolutionized our understanding of retinal diseases and allowed close monitoring of changes in the retina. All these non-invasive procedures can, finally, be combined making multimodal imaging of the retina an extremely promising tool to improve our understanding of retinal disease.

Analyzing and comparing images from the human eye fundus is a fundamental step to the investigation of retinal diseases. Both the analysis and comparison rely on the recording of the eye fundus for a particular instant in time, a way of freezing a dynamic process, registering an instant of the visible state of the human retina.

The support of this record was a photographic film, for several decades, and became nowadays a digital one, with all the advantages generally recognized, immediate storage, easy transfer and transmission, exact duplicates without information loss or original degradation, easy manipulation as filtering, digital enhancement of contrast, magnification, illumination correction, etc.

There are many advantages of using digital image analysis to quantify the extent of retinal pathology in vascular diseases, diabetic retinopathy, age-related maculopathy, and other conditions. Key benefits include the availability for immediate viewing, image management systems that allow monitoring disease progression by reviewing sequential images, and patient education. While film-based photography has a resolution of about 4,500 × 3,000 pixels, today color digital fundus images have more than 1,024 × 1,024 pixels for black-and-white digital angiography. The resolution of the newest generation of color digital photographic systems (at 3,000 × 4,000 pixels) now more closely approaches that of film. Because digital images can be displayed on a video screen as soon as they are obtained, it is possible to detect and correct any error in the photographic process at once.

Digital imaging of the retina and choroid includes color fundus photography, monochromatic fundus imaging, autofluorescence imaging, fluorescein angiography, indocyanine green angiography, retinal leakage analysis, and optical
coherence tomography. During the last decade these techniques have been improved significantly and have enabled us to improve the diagnosis and follow-up of patients with retinal and choroidal disease.

Evaluating Changes Over Time in Color Fundus Images Using the Retmarker

It is apparent, from the data available from a variety of large longitudinal studies and from clinical experience, that the evolution and progression of retinal diseases such as diabetic retinopathy vary between different individuals and does not necessarily progress in every patient to the terminal stage of proliferative retinopathy [1, 2].

Microaneurysm formation and disappearance are dynamic processes. During a 2-year follow-up of 24 type 1 diabetics with mild background diabetic retinopathy using fluorescein angiography, in 1996 Hellstedt and Immonen observed 395 new microaneurysms and the disappearance of 258 previously identified ones.

The disappearance of a microaneurysm indicates vessel closure and progressive vascular damage. Therefore, to assess progression of retinopathy, microaneurysm counting should take into account every newly developed microaneurysm identified in a new location.

A new software, the Retmarker, is able to automatically identify any changes occurring in the eye fundus image, by comparing successive visits to the reference image (any baseline chosen), based on co-registration and exact co-localization of the changes. This software shows the alterations and identifies their occurrence at each visit. It is now possible to identify automatically changes in hard exudates, hemorrhages and new microaneurysms.

Microaneurysm turnover can be calculated automatically using fundus-digitized images where the location of each microaneurysm is taken into account and registered (fig. 1, 2). In this way, in a follow-up study with repeated fundus images obtained at regular intervals, all microaneurysms in the fundus can be counted and added as they became visible in new locations in the retina [3].

Monitoring progression of retinal disease in its earlier clinical stages is fundamental to be able to characterize individual rates of progression, design appropriate management strategies and, finally, test new drug therapies. Non-invasive examination methods must be used because the examinations must be repeated at regular intervals. The two candidates for biomarkers of diabetic retinopathy progression are the determination of microaneurysms formation rates in fundus digital images assisted by appropriate software such as the Retmarker-DR and measurements of retinal thickness by optical coherence tomography (OCT).

Fundus Autofluorescence Imaging

Increased fundus autofluorescence (FAF) imaging intensities for evaluating geographic atrophy (GA) enlargement has created much interest (fig. 3). It has been shown that extension of the total area with increased FAF surrounding atrophy at baseline in eyes has a strong positive correlation with atrophy progression rate over time. In accordance with other natural history studies, the German multicenter FAM study identified a large variability of atrophy enlargement between patients, which was neither explained by baseline atrophy nor by any other risk factor (such as smoking, lens status, family history) [4].

Interestingly, the first studies using FAF imaging on patients with GA have already reported various patterns of changes in FAF in the junctional zone of GA. It was speculated that this observation might reflect heterogeneity of the underlying process.

Recently, a FAF pattern classification of patients with GA has been introduced by the FAM Study group [5].
OCT represents a major breakthrough in the diagnosis of retinal disease. As the technology allows to visualize the vitreoretinal interface, the intraretinal layers and the subretinal space together with the retinal pigment epithelial layer, many diseases can be diagnosed with a clear anatomical condition (fig. 4). The method is non-invasive and can easily be repeated at multiple time points [6].
Spectral domain OCT has a fast acquisition speed of 20,000–40,000 A-scan/s and an axial resolution of 5–7 μm. Due to the fast scanning process, the modality allows a raster scanning providing data from all locations of the retina. The complete raster scanning may be used to compose a three-dimensional image of the entire macular area. The system offers a high detail representation of anatomical changes in the single scan images.

One of the advantages of SD-OCT is the three-dimensional measurement which provides data for calculation of fluid volumes. With the high-resolution and the all location measurement of 3-D OCT in monitoring of early disease such as in age-related macular degeneration allows a clear identification of early pathogenetic mechanisms and offers parameter for measurement of disease progression. Drusen volumes and abnormal drusen areas can be quantified and their changes may be followed over time.

**Combined Retinal Imaging: Multimodal Imaging**

It is clear that no single imaging modality can capture all the information from the eye fundus. Instead, each particular aspect requires dedicated instrumentation and their associated methodologies for acquisition and analysis.

The multimodal approach becomes interesting by unifying information gathered by different instrumentation and by bringing them all into a single referential, therefore making it possible to easily establish correlations between sources of information [7].

Fundamental information to understand disease development and progression may be spread over different imaging modalities. Only the integration of these sources in a precise and reliable manner can offer a wider overview of the tiny changes provided by each independent source of information. This integration has already proved to offer new perspectives for retinal disease.

**Fig. 4.** Identification of the retinal structure using Spectral Domain OCT.

NFL: Nerve fiber layer  
ILM: Inner limiting membrane  
GCL: Ganglion cell layer  
IPL: Inner plexiform layer  
INL: inner nuclear layer  
OPL: Outer plexiform layer  
ONL: Outer nuclear layer  
ELM: External limiting membrane  
IS: Photo receptor inner segment  
OS: Photo receptor outer segment  
IS/OS: Interface between PR inner and outer segment  
OPR: Outer PR/RPE complex  
RPE: Retinal pigment epithelium + Bruch’s membrane
management and good examples is the phenotyping of nonproliferative diabetic retinopathy and the identification of markers of conversion from dry to wet AMD [8, 9].

References


