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Multimodal Macula Mapping: A New Approach to Study Diseases of the Macula

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Abstract. Multimodal macula mapping is presented as a combination of a variety of diagnostic tools and techniques to examine the macular region in order to obtain information on its structure and function in a clinical environment. Foundations of macular mapping are reviewed and discussed. New methodologies for multimodal macula mapping based on a combination of scanning laser angiography, retinal leakage analysis, retinal thickness analysis, and visual field testing are presented, demonstrating the potential of macula mapping. Other available detection devices are briefly reviewed considering their potential to be included and utilized in future developments of multimodal macula mapping. Multimodal macula mapping appears to offer unique perspectives and insights that are expected to contribute to improved diagnosis and better understanding of macular diseases. (**Surv Ophthalmol 47:**580–589, 2002)

Key words. macula • map • multimodal • retina

The macula is the region of the retina that is located in the posterior pole of the eye and is functionally specialized. This specialization is easily inferred from the differences in the local relative concentrations of the different receptors and cells. The macula is organized for inspecting detail, containing mainly cones that are more per unit area than elsewhere, and more ganglion cells per unit area as well. Its most central zone is a circular patch that is characteristically free of major blood vessels and even capillaries. In the human eye, the extent of the cone-rich area is about 1 cm in diameter. It tends to be marked by the presence of a yellow, nonphotolabile carotenoid that gives the name to the region, macula lutea.

Any alteration of the macula will, sooner or later, affect visual acuity. Vision involving detail discrimination is particularly affected in diseases of the macula.

There are a variety of diagnostic tools and techniques that examine the macular region and obtain information on its structure and function. The different methods available offer different perspectives and fragmentary information. It has been our objective, in recent years, to combine different methodologies and to obtain maps of the alterations occurring in the macular region of the retina in health and in different stages of disease.

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Basics of Mapping

The extraordinary pace of development of new measurement devices and detectors that may be used to obtain information on the retina, and more specifically on the macula, offers unique opportunities for exploring and charting the information obtained in a multimodal macula map. Digital imaging, fluorescence measurements, and new optical devices are just a few of the possible data sources that can be integrated into a map of the macula. The treatment of this complex information requires additional instrumentation beyond that of the detector. The volume of data that can be acquired, the speed at which it is analyzed and the treatment of the signals needed for interpretation, depend on the computer.

The use of color, contours, and other visual signals to differentiate differences in thickness, visual function, capillary density, alteration in vascular permeability, and other attributes of structures or function should produce holistic views of the retina. The product should be not only informative but in many cases provocative, in that the overall patterns or relationships produced may tell a new story from that told individually.

Available maps of the macula, obtained either from digital imaging, fluorescence measurements, electrophysiological potentials, or using a variety of other optical devices, have different degrees of spatial resolution. Generally, spatial resolution has been determined by the kind of detector used to collect the data.

Increasing the field of view typically results in lower spatial resolution. Similarly, increasing the temporal resolution, by decreasing the acquisition time, results in loss of image quality due to eye movements. Maps of the macula, due to its dimensions, should include the highest spatial resolution offered by the detectors available. Spatial resolution is clearly fundamental for a useful map of the macula.

In the macula, combination of several maps obtained using different detectors in order to derive a holistic representation has tremendous potential. Maps that present correlative, multimodality, or otherwise derived data can greatly extend the map usefulness beyond that available from the individual sources alone.[1,21]

Macula and Retinal Mapping

TRANSFORMATIONS

In macula mapping, combining images across modalities and subjects for inclusion in a common map does not require the positional and shape transformations that plague brain mapping. Here we are faced with an intrinsic registration by means of anatomical landmarks.

Intrinsic registration methods are based on the image contents alone, namely, the information contained in the human eye fundus image will be used to perform the necessary registrations.

Anatomical landmarks are locatable points of the morphology in visible anatomy. In the present case, these marks are vessel bifurcations, the center of the fovea (foveola) and the center of the optic disk head. Whereas the first, vessel bifurcations, can be used to register images of the same eye, the last two can be used to register images among a group of eyes.

In the general case, projective transformations are sufficient to permit registration over the several modalities involved.[5] This transformation supercedes the affine transformation by integrating all its corrections—scale, rotation, surface dilation, translation and shearing—and adding the possibility of mapping a rectangle into a general polygon (quadrilateral).

UNIFORM DESCRIPTIVE AND MEASUREMENT SYSTEM

Coordinate systems in biological mapping are not absolute. They are based on anatomic landmarks. Their selection is crucial to the accuracy of the resulting system. These landmarks are well defined in the macula and one of the major central references is the foveola.

An important goal is the organization of a computerized stereotactic atlas in order to achieve good localization of the human retina anatomy and physiology derived from various tomographic modalities. The acceptance of a standardized nomenclature is also a critical step.

Detection Devices for Macula Mapping

Detection devices for obtaining information on macula mapping methods are numerous and varied, often complementing each other with differing degrees of invasiveness, accuracy, and object of measurement. Some chart anatomy whereas others measure an aspect of physiology. Together, they can combine structure and function.

Our research group has been developing methods to combine and integrate data from angiographic images (scanning laser ophthalmoscope, fluorescein angiography), maps of fluorescein leakage into the vitreous (scanning laser ophthalmoscope, retinal leakage analyser), maps of retinal thickness (retinal thickness analyser, Talia Technology, Mevaseret Zion, Israel) and maps of visual function (automated perimetry, Humphrey Field Analyser HFA II 750) of the macular area to achieve multimodal macula mapping.

CONFOCAL SCANNING LASER OPHTHALMOSCOPE

Confocal scanning laser ophthalmoscopy (CSLO) produces high-resolution images using much less light for illumination of the fundus than that used for conventional photography. High-contrast images of the foveal and perifoveal structures are produced with this technique, using directly reflected light.

In CSLO imaging, a laser beam illuminates an area of the eye fundus, forming a rectangular pattern (raster) on the retina. A set of moving mirrors allows the scanning of an area of interest. By illuminating a spot-sized area and not the whole retina, the scattering is reduced and the lateral resolution improves. A confocal stop placed in front of the detector rejects most of the light coming from both anterior and posterior planes. The detector captures the light reflected from each retinal point. The output of the detector determines the brilliance of the spot displayed on the monitor, which corresponds to the illuminated retinal point. The laser beam is synchronized with the electron beam, forming the monitor picture. Thus, a point-by-point video image is constructed, with each retinal point corresponding to a point on the monitor screen. CSLO, because of its monochromatic wavelength emission, minimizes scattering and chromatic aberration. This feature of CSLO increases contrast and improves visibility as compared with slit-lamp biomicroscopy and fundus photography.

CSLO can also be used to perform fluorescein angiographies (SLO.FA). In this case, we cannot speak in reflected light but in fluorescence light. The contrast of the image allows one to obtain high-quality morphological information on the retinal vasculature. A recently developed system combines CSLO with Doppler flowmetry and may provide non-invasive evaluation of regional blood flow.

We have been able to develop a method for measuring and mapping the permeability of the blood-retinal barrier based on a CSLO system.[10] The combination of two data sets, angiographic and permeability mapping, obtained simultaneously using the same instrumentation, provides a good definition of landmark references of the macula, providing both functional and morphological information, in this manner being the first step in the development of multimodal mapping.

RETINAL LEAKAGE ANALYZER

The retinal leakage analyzer (RLA) is a quantitative and reproducible method to evaluate the permeability index of the blood-retinal barrier to fluorescein.[10] Localized measurements of retinal fluorescein leakage by RLA are obtained using a modified CSLO (prototype from Carl Zeiss, Oberkochen, Germany) to perform fluorescence measurements in the vitreous, using an Argon laser source with 488 nm wavelength and 400 μW light power in the eye.

Recent developments in laser technology offer new possibilities for less cumbersome instrumentation. Compared to presently available lasers, a new solid state 488 nm laser on the market is characterized by having 98% less consumption, 90% less heat dissipation, and is 90% smaller, leading us to believe that simpler and more cost-effective systems are expected to become available in the near future. This would allow these techniques, now used only for research purposes, to become available for daily practice.

Data acquisition is performed after intravenous administration of a fluorescence dye (14 mg/kg of body weight of 20% sodium fluorescein) and pupil dilation with tropicamide (1%).

Data are collected from an area of 3.150 × 2.700 μm, along 9 confocal planes covering 2.550 μm depth, in 400 msec, with the confocal plane continuously moving. These original 9 planes are then split into 18 confocal planes due to the interlaced acquisition mode and continuous movement of the confocal plane during the acquisition.

Two types of information are obtained simultaneously: distribution of fluorescein concentration (retina and vitreous) and fundus image. This simultaneous acquisition is crucial because it allows a direct correlation to be established between the maps of permeability and the morphological information.

Two scans are necessary to quantitate the incoming fluorescein into the vitreous. The first scan is taken less than 5 minutes after the intravenous fluorescein administration and the second scan is taken 30 minutes after fluorescein administration (Fig. 1). For each pixel of the fundus image, it is possible to plot the profile of fluorescein concentration along the 18 confocal planes for each scan. After registering the two fundus images corresponding to the two scans necessary to compute the blood–retinal barrier permeability index to fluorescein, it is possible to build two profiles of fluorescein concentration for the same location. The difference between these two profiles, besides a scaling factor, is due to the fluorescein income into the vitreous. By subtracting the two profiles, after interpolation, scaling, and alignment for the retina-vitreous interface, it is possible to quantify the incoming fluorescein into the vitreous. The center of the fovea can be extracted from the morphological information collected (SLO.FA).

The fundus image is made up of 82 × 72 pixels while the leakage map has half the resolution (75 × 75 μm/pixel). A reference map was made using a normal population. Abnormally increased fluorescein leakage is considered when its value is above mean +2SD of the reference map. As for the map of

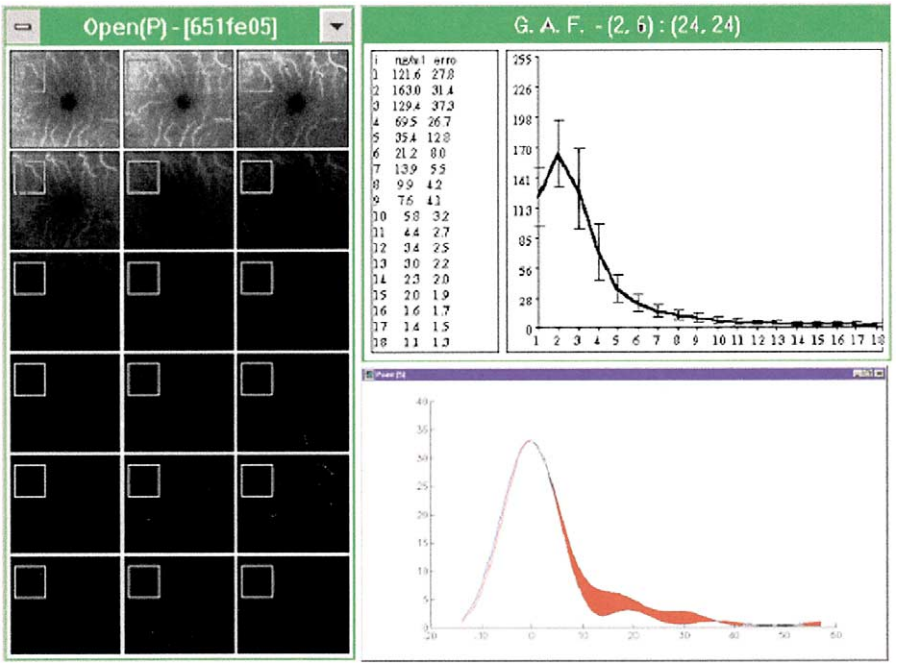

Fig. 1. Left: Scan obtained 5 minutes after injection showing 18 images. *Top right.* Fluorometric profile of the 18 images. *Bottom right.* Subtraction of 2 profiles (e.g., 30 and 5 minutes). The shaded area represents fluorescein that penetrated into the vitreous.

increased retinal leakage, and in order to establish correlations with other data sources, the chosen area for retinal leakage values is 300 × 300 μm. In areas of increased fluorescein leakage, the dominant RLA leaking sites are computed and marked in the leakage map as red squares. These leaking sites are defined as central sites of fluorescein diffusion. They are, therefore, identified as the sites showing permeability values higher than their immediate neighborhood (Fig. 2). The intravisit and intervisit reproducibility are ±10.2% and ±13%, respectively.

We have used the RLA in a series of studies performed in eyes showing initial stages of diabetic retinal disease. In eyes showing no changes on ophthalmoscopic examination, the leaking sites, identified by the RLA, appear as the most frequent alteration occurring in the retina.[8] In another study, a 2-year follow-up prospective study of eyes of patients with type 2 diabetes and only minimal retinopathy, examinations performed at 6-month intervals demonstrated a clear fluctuation in the intensity of fluorescein leakage of these RLA leaking sites. These leaking sites appeared to be not only reversible but to be directly correlated with the level of metabolic control as identified by hemoglobin A1C (HbA_{1C}) values.[9] Therefore, maps of the alterations of the blood–retinal barrier obtained with the RLA provide information of potential clinical value.

RETINAL THICKNESS ANALYZER

The retinal thickness analyzer (RTA) is a quantitative and reproducible method to evaluate retinal thickness.[25] The optical system is similar to a slit-lamp using an He-Ne laser with 543 nm wavelength shaped into a narrow slit, as an illumination source. This slit, when projected into a human retina, is 2 mm tall by 10 μm wide. The system acquires optical section images of the retina by projecting the laser into the retina at an angle, allowing the view of the reflection or scattering of the laser light from the vitreoretinal and chorioretinal interfaces. The separa-

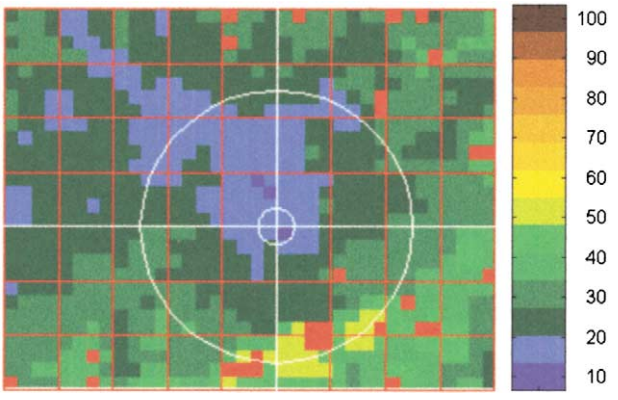

Fig. 2. Retinal leakage map. Color-coded blood–retinal barrier function. Index values of permeability can be deciphered with the aid of the color bar on the right. Units are × 10^{-7} cm · s^{-1}. Red squares represent leaking sites, defined as central sites of fluorescein diffusion. They are, therefore, identified as the sites showing permeability values higher than their immediate neighborhood. The red circles are centered on the fovea with 100- and 750-μm radii.

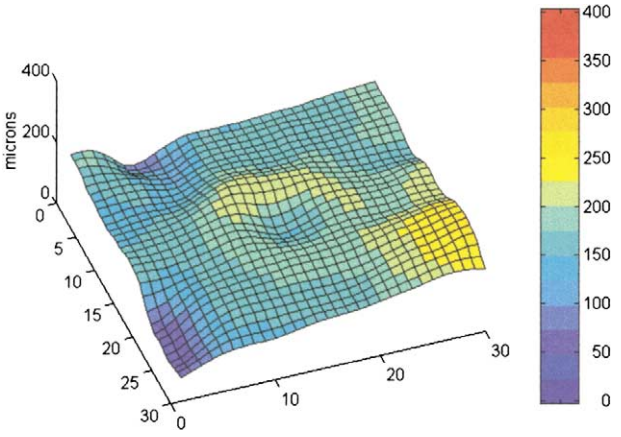

Fig. 3. Retinal thickness map. Units are μm.

tion between the reflections from these two interfaces is a measure of the retinal thickness. The laser slit is scanned across a 2 mm × 2 mm area of the fundus in 200 msec to generate 10 optical sections 200 μm apart. This process is repeated nine times using nine fixation targets covering a total area of 6 mm × 6 mm, and generating a map of thickness with 30 pixels × 30 pixels (Fig. 3). The depth resolution of the system is 50 μm and intervisit reproducibility is ±13 μm. Each pixel represents an area of 200 μm × 200 μm. Abnormally increased retinal thickness is considered when above mean +2 SD of a reference map. To compute statistical data relating RTA measures with other sources, namely the RLA, each value in the map of increased retinal thickness was chosen to cover 600 μm × 600 μm.

Increases in retinal thickness are a frequent finding in the diabetic retina, even in the earliest stages of the disease when there are no visible changes in the eye fundus, using ophthalmoscopy. The size and distribution of the areas of increase in retinal thickness, that is, retinal edema, observed in the diabetic retina, appear directly related to the location and distribution of leaking sites identified in previous examinations with the RLA.[9]

VISUAL FUNCTION/AUTOMATED PERIMETRY

Maps of visual function are obtained with the Humphrey Systems HFA II 750 (Zeiss Humphrey Systems, Dublin, CA, USA). Visual field testing allows for the determination of defects in the field of vision and tests the function of the retina, optic nerve, and optic pathways. It consists of the systematic measurement of visual field function. Although there are tests with moving targets, this one uses non-moving targets, the reason why it is called *static automated perimetry*. The test uses small non-moving targets that appear bright or dim. In this case, a specific point is chosen for examination and the stimulus is increased until it is perceived by the patient. The threshold is determined by means of an automated process. The stimulus size, which can be made different, is also of importance.

Only the abnormal values are of interest and signaled. Each value covers an area of 311 μm × 311 μm, for the "Central 10.2 Threshold Test" (Fig. 4).

FOVEAL AVASCULAR ZONE AND VASCULAR PERFUSION

Information on vascular perfusion around the foveal avascular zone is extracted from SLO angiography, at a time when the capillaries show maximal filling.

The delineation of the foveal avascular zone can be performed either automatically by the computer or manually by the user. When performed automatically, the basic procedure is to analyze the angiographic image and decide the limits of the foveal avascular zone based on the intensity levels of the image using a threshold level. This threshold can by fixed or non-fixed to accommodate for non-uniform illumination.

Multimodal Macula Mapping: Integration of Information and Representation

A map improves our representation of an object and helps to place in the right location additional information contributing to a progressive reconstruction of the same object. It is a way of organizing data, representing it, and communicating results.

The challenge of mapping, in general, and macula mapping, in particular, lies in the need for appropriate

				21 (23)	24					
			22	24	28	29	29	28		
		20 (20)	25 (25)	31 (27)	29	26	28 (26)	25	26	
		22 (28)	29	31 (33)	30	27	33 (29)	28	27	
	27	24	31	30	30	27 (23)	25 (27)	28	27	26
10										
	25	28	29	18 (20)	28	29	29	30	23 (33)	22 (24)
		24	23 (17)	33 (27)	30	23 (29)	33 (25)	28	29	
		28	29 (29)	23 (29)	23 (25)	26	26 (28)	30 (28)	25	
			32	24	26	25	29	27		
					27	18 (24)				

Fig. 4. Visual function test map. Total deviation numerical dB scale Full Threshold 10.2 test.

presentation strategies to convey the pertinent information without obscuring other data, reference systems suitable for equating the map with the real object, and a product that is compatible with its intended use.

Combining data into a single map compared to the option of presenting data in multiple maps has both advantages and disadvantages. The main advantage is the establishment of automatic correlations. This is clear when relating changes in blood–retinal barrier permeability with changes in retinal thickness.[8,9]

Considering the representation of data, the same situation occurs. The advantage of having two modalities in the same map offers the user the possibility of establishing direct correlations between both modalities, particularly regarding their exact location. It is important that by doing so, namely, having two modalities represented together, one modality does not hide information from the other. The best example is the plot of isolines of equal percentage of increase of retinal thickness plotted over the leakage map as shown in Fig. 5. A direct correlation is easy to establish so that there is neither disadvantage nor advantage if both are shown in different maps. The same happens for visual function and fluorescein angiography (Fig. 6).

On the other hand, it is not at all helpful to show vascular perfusion and fluorescein angiography in the same map. The information on vascular perfusion obtained with the Heidelberg Retina Flowmeter (Fig. 7) (see the section Other Available Detection Devices) would mask completely the information from the fluorescein angiography (Figs. 8 and 9). This is the reason why each information is shown in different maps (Fig. 9). Nevertheless, it is important that these two different maps show only the same area and share a common location and scaling factor.

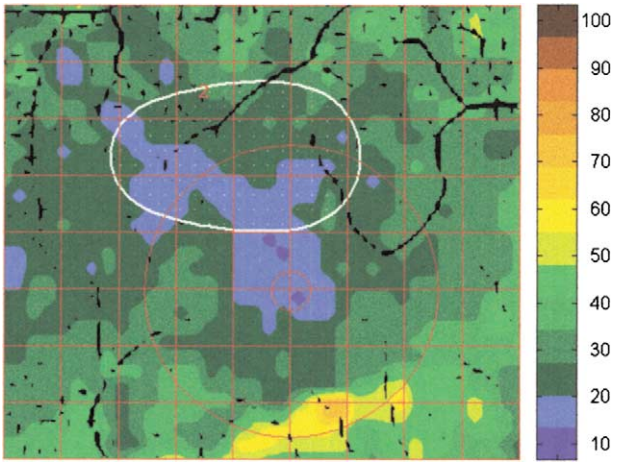

Fig. 5. First approach to multimodal macula mapping. The background represents the leakage using a false color-code. Units are $\times 10^{-7}$ cm $\cdot$ s^{-1}. Percentage of increased thickness is represented in white dots with varying density. Lines in white represent equal percentage of increase in thickness, having the corresponding value plotted in red. The red circles are centered on the fovea with 100- and 750-μm radii.

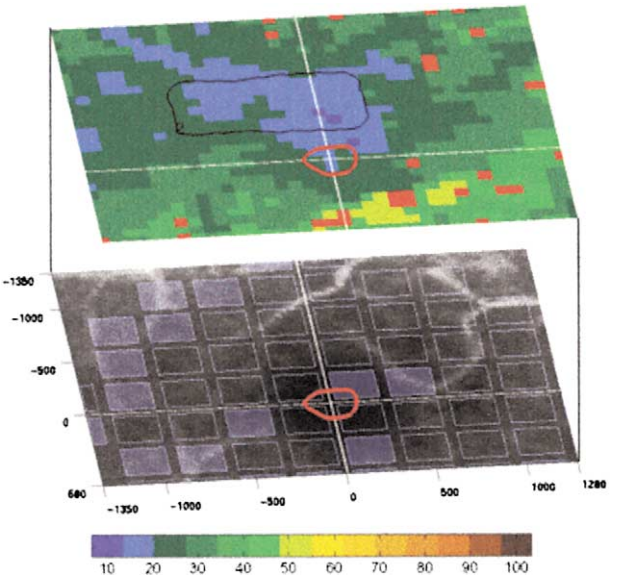

Fig. 6. This multimodal image shows the integration of morphology, thickness, leakage, and visual function data as a stack of two (multimodal) images. The red line limits the foveal avascular zone, and the intersection of the two white lines represents the center of the fovea. The top image contains information on leakage (blood–retinal barrier function), thickness, and foveal avascular zone (FAZ). Index values of permeability can be deciphered with the aid of the color-bar on the bottom. Units are $\times 10^{-7}$ cm $\cdot$ s^{-1}. Thickness is shown as lines of equal percentage of increase over a reference map. The bottom image shows the visual function represented by squares of light blue (filled on the abnormal visual field areas), the foveal avascular zone, and the morphology.

In order to integrate the information which is taken from the previously mentioned detection devices for macula mapping, a common reference has to be established. The fundus image is provided by the RLA. To compute the center of the fovea, the image is compressed with a log function. This produces an image with a marked difference between the foveal avascular zone and the remaining image. A cross-correlation function is computed between the compressed image and a 2D Gaussian function. The result allows the determination of the center of the fovea, since the shift in the maximum of the cross-correlation to its center equals the shift of the center of the fovea to the center of the fundus image.

The RTA generates a thickness map and saves a fundus image to be used as reference for each of the 9 fixation targets. One should pay particular attention to the fact that the fundus reference image is

Fig. 7. Retinal flowmetry. *Left:* DC component of the Doppler effect (reflectivity). *Right:* Map obtained using the Automatic Full Field Analysis of Perfusion Images software.

collected after the 10 measures are performed for each of the nine fixation targets, that is, it is a non-simultaneous acquisition. In this way, there may be a difference between the location of the fovea on the RTA map and on the fundus reference.

For non-edematous retinas, the foveal depression may be considered a more accurate topographical reference than the one taken from the fundus image. On the other hand, in cases where edema is present, one must use the fundus image as the reference. For both cases, the fundus image provides information on rotation not available from the thickness map. In this way, foveal location is extracted from the fundus reference and not from the RTA map.

The visual field map is centered also on the fovea. To build a common reference for the maps, the location of the fovea is considered to be the origin of the axis and each map is scaled and cropped to the extent of the leakage information.

Considering the differences in scale between the retinal leakage, visual function, and retinal thickness maps, both the visual function and the retinal thickness maps are interpolated using a nearest-interpolation method for establishing automatic correlations among these modalities. In order to represent this information, the visual function uses the same interpolation, whereas for the thickness, a bilinear-interpolation method is used, producing a more informative and natural picture of the retinal changes.

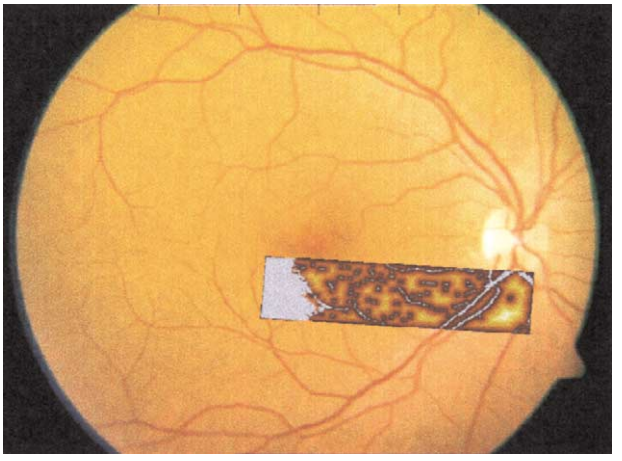

Fig. 8. Registration of the map obtained using the Automatic Full Field Analysis of Perfusion Images software over the fundus image (retinography).

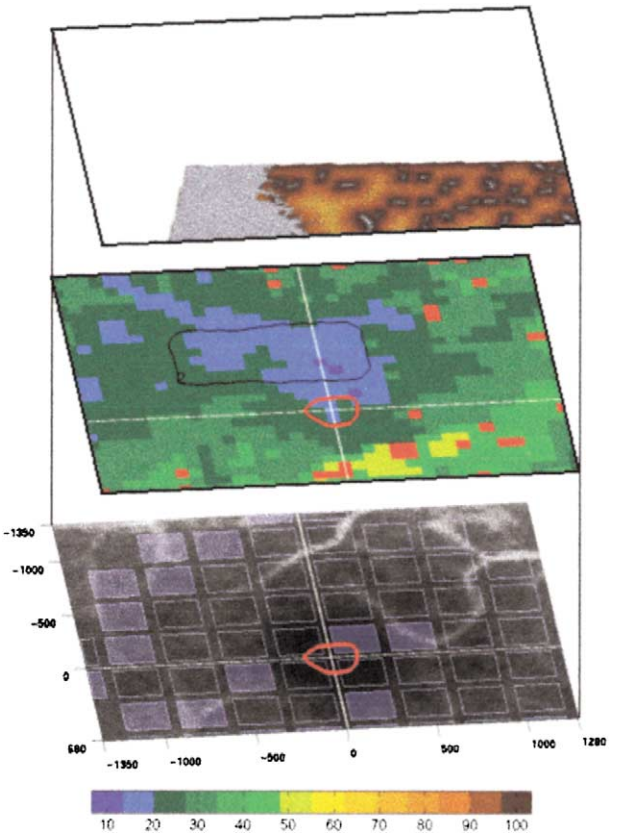

Fig. 9. The top image shows the registration of the map obtained using the Automatic Full Field Analysis of Perfusion Images software over the confocal scanning laser ophthalmoscopy angiography. For the bottom images, see legend of Fig. 6.

A common problem when dealing with several measures for the same object is to find the best representation method. Considering the presence of 3-dimensional information (RTA), it would be feasible to use stereo-images, but they are not suited for direct graphic printing. One possibility is to assume a multimodal approach, integrating a restricted number of different data in the same picture, realizing that the addition of new data may hide information already present.

A second possibility is to plot a stack of images, with the same dimension, representing the same area and showing different and complementary information for the same subject. That would allow the user to mentally establish correlations among the several images shown, given a common location and proper alignment.

A third possibility is a mix of the two previous situations: a stack of multimodal images with each one integrating data from more than one data source. This has been the chosen model to date (Fig. 6).

Up to now, the limiting factor for the area covered by the multimodal macula mapping is the RLA system. A key issue when using this technique is to have a spatial high-resolution scan on the fovea, where vision is detailed. Because each scan performed with the Zeiss CSLO system covers a given area, to compute the blood–retinal barrier permeability to fluorescein, two scans are mandatory. The final area covered by these measures depends on the amount of overlapping area for both scans.

It is realized that the covered area corresponds to a small number of visual field points. However, we consider it relevant to relate the changes mapped in the eye fundus to any alteration on the visual function.

Other Available Detection Devices

We have been able to combine in multimodal macula mapping, information on structure and function by integrating data from fluorescein angiography, retinal leakage analysis, retinal thickness analysis, and visual perimetry. Other available detection devices that may be used for macula mapping include laser Doppler retinal flowmetry[1–13,26] using the Heidelberg Retina Flowmeter (HRF from Heidelberg Engineering, Dossenheim, Germany); indocyanine green angiography (ICG);[18,19,22–24] electrophysiology (ERG);[4,20] autofluorescence mapping; [17] and optical coherence tomography[2,3] (OCT from Humphrey Systems, San Leandro, CA, USA). Each one of these methods adds more information and appears as potentially valuable tools for evaluating the structure and function of the retinal macula.

Their inclusion in a multimodal map depends on the posterior segment disease that is being considered and analyzed. Our efforts have up to now been focused on two diseases that involve the macula and contribute to the two major causes of blindness in Western Europe and USA: diabetic macular edema and age-related macular degeneration.

When examining diabetic macular edema, OCT and HRF methodologies become particularly interesting, especially when the diabetic macular edema is associated with some degree of vision loss. The HRF appears to be particularly useful and reliable to follow changes in capillary perfusion[13] in the macular area and we are examining closely its value for indicating progression of ischemia.

To integrate the HRF information data, one should pay attention to the fact that the area covered by the HRF is too small when compared with the rest of the systems being integrated. For that integration to occur, it is necessary to register each HRF scan data over the fundus reference, creating a retinal montage-like structure that permits scans, either overlapping or non-overlapping, to be integrated. The registration procedure uses the DC component image (Fig. 7 left), while the image being integrated is shown on the right resulting as shown in Fig. 8.

The integration of the data from the HRF is done in a third map overlying the previously described basic multimodal macula map (Fig. 9).

OCT is a method that uses optical reflectivity to produce high-resolution, cross-sectional images of ocular tissues. It is based on the principle of low coherence interferometry. The well-defined differences in optical reflectivity at the anterior and posterior borders of the neurosensory retina allow OCT to accurately determine retinal thickness. OCT is particularly useful in evaluating retinal architecture and in the evaluation of macular pathology. OCT identifies well the cyst-like formations in advanced stages of macular edema, by showing hyporeflectivity areas within the retina (Fig. 10). It is, however, more informative in more advanced stages of macular alterations, namely, in the presence of macular holes, vitreomacular traction, cystoid fluid accumulation within the retina, pigment epithelial detachments, epiretinal membranes, retinal trauma and dystrophies.

We have been comparing the relative performance in measuring retinal thickness using the OCT, RTA, and scanning laser ophthalmoscopy[7,14] (HRT). Our initial results suggest that the RTA is particularly sensitive to detecting minimal changes in the earliest stages of diabetic macular edema, whereas the OCT becomes more reliable and informative when increases in retinal thickness are marked and already detected by fundus photography.[6,15,16]

Measurements of retinal thickness using the scanning laser ophthalmoscope may, however, be the final choice in multimodal macula mapping because of the facility of establishing common software platforms to integrate the data using different detection devices.

Electrophysiological methods have been recently proposed for retinal mapping with the introduction of the multifocal electroretinography (mERG). The multifocal ERG technique was developed by Sutter[20] and produces 100 or more focal responses from the cone-driven retina. The display usually contains either 61 or 103 hexagons, although 241 hexagons have been used in a few experiments to obtain higher spatial resolution. With the 103 elements displayed, there is no guarantee that a hexagon will fall entirely within the optic disk. With a display of 241 elements, at least one hexagon should fall entirely within the disk if steady fixation is maintained. It is considered that mERG is actually better for peripheral disease detection. In conclusion, the mERG method offers attractive information on the electrical functions of the retina, but its spatial resolution is still limited for useful macula mapping.

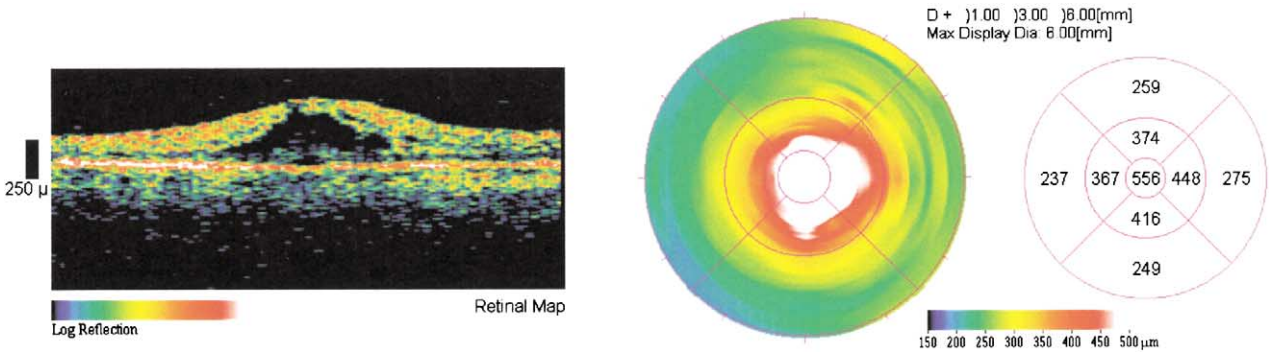

Fig. 10. Optical coherence tomography. *Left:* The log reflectivity image. *Right:* Thickness map, both in a false color-coded and with values in microns.

ICG angiography is an important and useful addition when examining age-related macular degeneration.[19] Using longer wavelengths than fluorescein angiography, it allows visualization through overlying hemorrhage, exudate, and pigment. Another advantage of ICG is that it is highly protein bound and as a result there is no early diffuse background fluorescence produced by leakage from the choriocapillaries.

These unique properties of ICG permit improved angiographic imaging of the choroidal circulation and allow detection of underlying choroidal pathology.

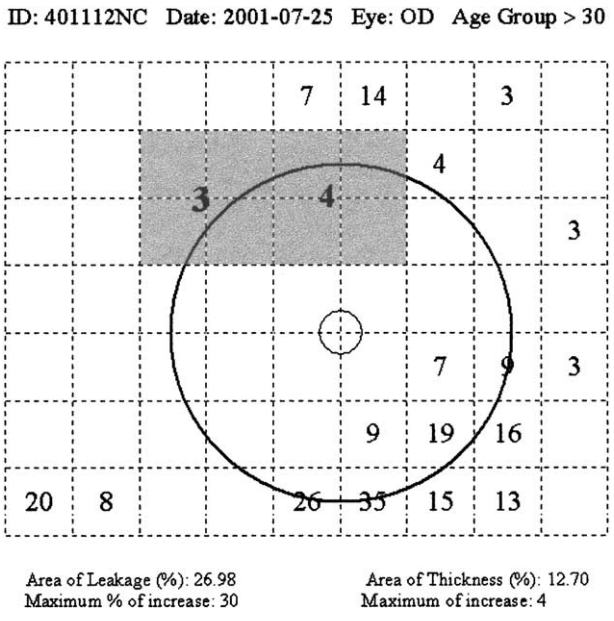

Fig. 11. The gray areas represent increased thickness. Percentages of increase are represented in bold at intersecting lines. Each value represents four adjacent squares. Percentages of increased leakage are represented by numbers in the squares. Also represented are two concentric circles of 100-µm and 750-µm radii centered on the fovea.

Finally, autofluorescence measurements[17] of the macular area and their presentation as a map offer an extremely promising piece of information. Its clinical value may lie in the characterization of the early changes occurring in age-related macular degeneration. Initial results obtained using confocal scanning laser ophthalmoscope methodologies are exciting and offer the perspective of quick integration into already available multimodal macular mapping methodologies.

Speculations About the Future

Macula mapping appears to offer unique perspectives and insights which are expected to contribute to improved diagnosis and better understanding of macular diseases. The development and refinement of different detectors, improvement in statistical representations and the combination of information from different sources will certainly increase our knowledge of the structure and function of the retinal macula in health and disease.

We believe that tabular description of the multimodal macula map describing the location, shape, and density of different measurements in numerical form may be easier to analyze in much needed prospective, follow-up clinical studies. Database and probabilistic approaches to mapping depend primarily on statistical representations. Numerical forms are particularly efficient for electronic communication and analysis. Our initial studies point in these directions (Fig. 11).

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