Computer Analysis of the Optic Cup in Glaucoma

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This paper describes two complementary methods for computer analysis of the optic disc in glaucoma. The objective of both techniques is to detect and monitor changes in the optic disc through the use of digital image processing techniques that allow user intervention. In the first method, optic disc photographs from successive years are digitized, scaled and registered (aligned) with each other, and are then displayed in rapid sequence on a television monitor. Changes in the optic cup thus appear as localized movement on the display, while stable regions of the optic cup appear stationary. Both monocular and stereo photographs can be processed by this technique. In the second method, stereo optic disc photographs are digitized and processed by a new, robust, photogrammetric computer algorithm that quantifies optic cup depth information. Together, these two techniques may be valuable for both clinical and research purposes in the detection and monitoring of glaucomatous optic cupping. Invest Ophthalmol Vis Sci 26: 1759–1770, 1985

Recent studies1–12 indicate that both stereo and non–stereo photogrammetric processing of optic disc photographs can provide an objective, quantitative evaluation of the topography of the optic nerve head. This approach thus represents a potentially valuable technique for the detection and monitoring of changes in glaucomatous cupping. Portney2 and Holm et al7 found that the average volume, area, and depth of the optic cup (determined by photogrammetric techniques) were larger in glaucomatous eyes than in normal eyes. However, there was considerable overlap between the two populations, thereby limiting the diagnostic efficacy of such measurements.

In a more extensive determination of optic cup volume, area, and depth characteristics in normal, ocular hypertensive, and glaucomatous eyes, Johnson et al5 found that no single measurement parameter was able to accurately differentiate normal and glaucomatous optic cups. The most distinguishing characteristic of normal and glaucomatous eyes was the relationship between the area and depth of the optic cup. In normal eyes, a high positive correlation was found between optic cup area and depth, whereas glaucomatous eyes exhibited no correlation between the area and depth of the optic cup. These findings suggest that any single feature of the optic cup is probably not a sensitive indicator of glaucomatous cupping. Rather, glaucoma-tous alterations of the optic cup are likely to be complex, involving changes in several geometric features in localized regions of the optic cup.

The analysis of complex topographical relationships such as these can be greatly aided by the use of computer image processing techniques. In addition, manual stereophotogrammetric measurement of optic disc photographs is quite expensive and time-consuming for general clinical use. We have therefore directed our recent efforts to the development of digital image processing techniques for the quantitative evaluation of optic disc cupping in glaucoma. A previous report by Kottler, Rosenthal, and Falconer8 has described a technique for digital stereophotogrammetry of the optic disc, although the analysis is based on only a small number of normal eyes. Preliminary studies in our laboratory indicated that a number of modifications of their algorithm were necessary to process the wide variety of optic disc configurations and photographic conditions encountered in a typical clinical setting.

In this paper, we describe two techniques for performing quantitative digital image processing of optic disc photographs: the monocular sequential display and digital stereophotogrammetry. These two procedures are complementary, and provide sensitive methods for monitoring glaucomatous changes to the optic cup.

Materials and Methods

Monocular and stereo optic disc photographs on 35 mm color transparencies were obtained with either the Zeiss fundus camera (Carl Zeiss, Inc.; Oberkochen, West Germany), the Donaldson stereo fundus camera (Dr. Donaldson, Howe Labs, Harvard University, Cambridge, MA), or the Topcon (Topcon Distributors; Burlingame, CA) stereo fundus camera. Most of the photographs were from patients in our ongoing glau-
coma study at the University of California, Davis, from whom written informed consent was obtained prior to their participation. Because the study has been in effect for just 5 yr, documented progression of glaucomatous cupping and visual field loss has only been observed in a few cases. Also, each of these examples showed only small to moderate progression. In order to obtain a larger spectrum of extensive glaucomatous cupping over a longer time span, we sought the assistance of several glaucoma centers with patient populations that had been followed for many years. Monocular and stereo optic disc photographs of patients with documented glaucomatous cupping were contributed by the Bascom Palmer Eye Institute (University of Miami School of Medicine, Miami, FL), the Wilmer Eye Institute (Johns Hopkins School of Medicine, Baltimore, MD), and the Department of Ophthalmology, University of British Columbia. These examples gave us the additional benefit of evaluating the efficacy of our image processing algorithms for various fundus camera systems and photographic techniques.

Each 35 mm color transparency was digitized by a television video camera system connected to a digital memory (Fig. 1). A digital image of 512 by 512 pixels (picture elements) was rapidly acquired (30 ms) and stored in memory. The resolution characteristics of the digital image are approximately 50 lines/mm, or 512 by 512 pixels for a 1 cm by 1 cm region of the slide transparency. A range of 256 digital values (8 bit resolution) are used to record the luminous intensity of each pixel. To date, we have found no significant advantage offered by color processing or narrow band filtering for analysis of the optic disc. Therefore, a panchromatic black and white digital image of the color transparencies is generated and stored.

The initial registration of photographs is accomplished by establishing a "reference" digital image for each eye. For monocular fundus photographs, the reference image is the first photograph of the sequence; for stereo photographs, the reference is either the left or right photograph of a stereo pair. This photograph is placed on a uniformly illuminated light table, centered with respect to the video camera, brought into best possible focus, magnified so that the optic disc occupies approximately 80% of the effective display area, digitized and stored. All subsequent photographs for this eye are then aligned, registered, and scaled with respect to the reference image. We accomplish this by dynamically comparing the stored reference image to the new image being digitized by the video camera. By using digital subtraction and rapidly alternating (2 to 3 times per sec) the reference image and the new video camera image, misalignment of the two images will appear as global rotary or translatory apparent motion of the whole optic disc, while scaling differences appear as an apparent "zooming" (enlargement or reduction) motion of the optic disc.

Rotation and translation adjustments are then performed by means of a micrometer stage that is mounted on the light table assembly and holds the slide transparency (see Fig. 1). Scaling adjustments are performed by altering the magnification of the video camera. Once the outer region of the optic disc and the surrounding retina have been stabilized, the new image is digitized and stored. It should be noted that although the outer portion of the optic disc and the surrounding retina exhibit no movement when registration and scaling are correct, localized regions inside the optic cup will display movement for stereo pairs (due to parallax differences between the left and right photographs that
are used to interpret depth characteristics) and for sequential monocular photographs for which changes in glaucomatous cupping have occurred.

Digital refinements of the scaling and registration of the new image are also performed when necessary. However, digital scaling adjustments affect the resolution of the image, and digital rotational alignment of the image is rather time-consuming. We therefore attempt to correct the registration and scaling as much as possible prior to the digitization of the new image. All additional photographs for the same eye are also scaled and registered to the reference image in a similar manner. Both the sequential monocular display and the digital stereophotogrammetry procedures use this initial alignment and scaling process.

Results

Sequential Monocular Display

The sequential monocular display procedure is a method of determining subtle changes in the optic cup by comparing monocular fundus photographs taken at different periods of time. The sequential monocular display technique, like the use of stereophotographs, infer 3-dimensional attributes of the cup from changes in characteristics of 2-dimensional images. In the case of stereo images, we infer and estimate depth from displacement in corresponding portions of 2-dimensional photographs. In the case of the sequential monocular display technique, the change in geometry is inferred from changes in 2-dimensional images as well. Change in rim-width is interpreted as change of thickness; the changes of angle in vessels, appearance of new features in the cup, etc can all be interpreted as changes in 3-dimensional geometry. Mensuration is limited to 2-dimensional attributes, but as a method to detect change, the approach is substantially more powerful than mensuration alone would imply.

Conceptually, this approach is similar to the technique of stereochronoscopy described by Goldmann and Lotmar. The major differences are (1) stereochronoscopy displays optic changes between two photographs as a stereoscopic depth effect, while the sequential monocular display shows these differences as an apparent movement of localized regions of the optic cup; (2) stereochronoscopy compares two monocular photographs at a time, while the sequential monocular display can compare multiple photographs (up to 4 images at the present time) at once; (3) stereochronoscopy is a manual procedure that requires realignment each time that comparisons are made, while the sequential monocular display uses digital image processing. Once the photographs have been registered and scaled appropriately, they can be recalled from storage at any future time for observation or analysis without the need for realignment.

The sequential monocular display procedure is basically an extension of our alignment technique. A series of two to four images (properly scaled and aligned with each other) are presented in rapid sequence on a television monitor. Portions of the optic cup that have not changed appear to be stationary, while progression of glaucomatous optic cupping will exhibit apparent movement in a localized region of the optic cup. Differences in the intensity of the images, spurious reflections, and small focusing differences among images do not significantly affect the comparisons, since it is the appearance of localized movement of portions of the optic cup that is indicative of changes in optic cupping.

Clearly, it is not possible to demonstrate a dynamic television display technique in a written publication. However, Figures 2 and 3 provide an illustrative example of the use of the sequential monocular display. In Figure 2, digital images are shown for two monocular photographs of the same eye taken in 1974 (left panel) and 1978 (right panel), after appropriate registration and scaling of the images had been performed. The digital images still exhibit rather distinct differences in overall brightness and contrast, and minor differences in image quality. In spite of this, the registration and scaling of the images makes it quite easy to compare the thickness of the neural tissue rim around the circumference of the optic disc. This is particularly true for a dynamic sequential display, where changes in the neural tissue rim appear as movement. For illustration of this dynamic effect, Figure 3 shows outlines of the optic cup drawn for the 1974 and 1978 photographs to demonstrate the glaucomatous changes (these changes are much more prominent on the dynamic television display). The outline was obtained by interpolation of 15–20 points on the display of the optic cup using a cubic spline interpolation function—the fit matches perceptible pictures of the disc to within 1%.

Sensitivity of the sequential monocular display procedure for detection of optic cup changes were determined by evaluating sequential photographs, taken on the same day, for several patients. After registration and scaling of the images, the outline of the optic disc and optic cup were determined for each image to evaluate the variation among images, and the sequential monocular display of images was examined for movement. Over the central portion of the display, scaling and registration of the images reduced the differences to 1 or 2 pixels, with some regions exhibiting differences of less than one pixel. Outside of the optic disc, features of the surrounding retina could not be registered as accurately, with average errors of approximately 3 pixels. Thus, even with changes in camera angle and photographic artifacts, registration and scaling of photo-
Fig. 2. Example of registered and scaled photographs for the sequential monocular display. The left panel is a photograph taken in 1974, and the right panel is a photograph of the same eye in 1978.

Digital Stereophotogrammetry

We have found that extracting depth information from stereo optic disc photographs is a difficult problem for digital photogrammetry. Our experience indicates that digital stereophotogrammetric techniques similar to those described by Kottler et al. and Rosenthal et al. are able to process accurately only a small percentage of stereo fundus photographs that are free of both photographic artifacts and focusing or intensity variations between the left and right stereo pairs. Since most of the stereo fundus photographs we have analyzed (both from our laboratory and from other institutions) contain all or some of these aberrations, we have developed a series of image processing algorithms designed to eliminate or minimize the influence of these sources of error. The major problems we have had to resolve are listed below:

1. Misregistration: Accurate alignment and registration of the left and right stereo images (both translational and rotary) are essential, since residual horizontal shifts within the optic cup are interpreted by the photogrammetry algorithm as a difference in depth.

2. Focusing: For most stereo fundus photographs (regardless of the type of camera) the images are often slightly out of focus, and there are differences in the quality of focus between the left and right stereo pairs.

3. Intensity variations: In most instances, stereo fundus photographs do not have a uniform intensity distribution across the entire picture. In addition, the intensity gradient is different for the left and right stereo pairs.

4. Photographic artifacts: Many photographic artifacts exist in stereo images. These consist of spurious re-
flections, defocused dark spots (produced by the aperture stop used to eliminate the corneal reflex), and other anomalies. Often these artifacts differ between the left and right stereo pairs.

5. Lack of image detail: Overexposure and underexposure of fundus photographs will produce a restricted range of contrast for delineation of critical details of the optic cup. Also, the pallor of the optic cup provides little or no detail, except for blood vessels, making the determination of horizontal parallax quite difficult in these regions. This problem is exacerbated when the image is slightly out of focus.

We have attempted to resolve these problems by using a two-pass image processing algorithm. In the first pass, reliable but fairly coarse depth information is obtained with a standard photogrammetric analysis of horizontal parallax. The second pass provides more detailed depth information which is more prone to minor errors. A decision algorithm then combines the information from both passes to generate the best possible representation of depth information.

A general overview of our digital stereophotogrammetric procedure is presented in the flowchart shown in Figure 4. The first step consists of a linear radiometric correction of the image with the smaller range of contrast values. This brings the average intensity of the left and right stereo pairs into close approximation. Refinement of the vertical alignment of the stereo images is then performed digitally to minimize any vertical discrepancies between the two images when the absolute difference algorithm is applied to determine horizontal parallax. The absolute difference algorithm is used to process two sets of data: (1) the unskeletonized depth map value is retained. Thus, this choice algorithm attempts to optimize the sensitivity and reliability of the depth map values. The resulting composite depth map is then fitted by two dimensional polynomials to “fill-in” areas with missing data. Details of key elements of the digital photogrammetric procedure outlined in Figure 5 are described below.

**Radiometric Correction Algorithm**

Usually, the brightness and contrast of the left and right stereo photographs are not the same. A linear radiometric correction is therefore performed on the image with the smallest dynamic range of contrasts (i.e., the photograph which has the least contrast due to over- or under-exposure) to match the radiometry of the other image by using the mean, variance and dynamic range of intensities for each image. If X1 and X2 denote the intensity of the two stereo images, X2 is remapped as XX2 according to the equation:

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XX2 = (sX1/sX2)X2 + mX1 - (sX1/sX2)mX2
\]

where mX and sX denote the mean and standard deviation of the image data.

**Skeletonization Algorithm**

A high-pass filter, which removes (sets to zero or black) all uniform or slowly varying areas of intensity, is applied to both stereo images. The remaining regions, which correspond to edges and contours of the image containing fine detail, are mapped to white. The high pass filter computes the average of a 5 × 5 block of pixels and subtracts this average, after weighing, from the value of the central pixel. The weighing is such that the output of the filter is zero if all pixels have the same value in the 5 × 5 block. Following the high pass filter, a threshold is applied so that only high values are retained. All retained values are mapped to white, all others to black.

**Absolute Difference Algorithm**

Depth is determined from the stereoimages using an absolute difference method with a window size of 15
Fig. 4. Flow chart of the algorithm used for digital stereophotogrammetric assessment of stereo optic disc photographs.

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The left stereoimage is shifted with respect to the right image in the direction of horizontal parallax, and the absolute position difference between the two images is determined. Averages for each possible $15 \times 15$ pixel area are computed and stored as a function of location. This operation is repeated for different values of shift corresponding to different parallax values. The minimum of the averaged absolute difference values, for all shifts, is determined for each location. This minimum, which corresponds to the best local match of the two stereo images, is the estimate of the depth at each point. Mathematically, if we let:

$IL(x, y) = \text{pixel value of left stereoimage at location } (x, y)$

$IR(x, y) = \text{pixel value of right stereoimage at location } (x, y)$

$IL(x + k, y) = \text{pixel value of the shifted left digital stereoimage at location } (x + k, y)$

where $k$ is the number of pixels the image has been shifted,

then the absolute difference of the reference image and the shifted left image is given by

$I(x, y, k) = IL(x + k, y) - IR(x, y); \text{ for } 1 < x, y < 512.$

Averages of $I(x, y, k)$ are performed as described above. A flow chart of this algorithm is presented in Figure 6. A more detailed description of the algorithm is presented in Sasaki and Algazi.\textsuperscript{12}

An example of the digital stereophotogrammetric procedure is presented in Figure 7 for the same patient.
evaluated with the monocular sequential display. The photographs in Figure 7 consist of stereopairs taken in 1974 and 1978. Digital processing of these stereo photographs according to the algorithm previously described generated the depth maps presented in Figure 8. These depth maps indicate that the optic cup has both deepened and extended superiorly between 1974 and 1978, thereby indicating progression of glaucomatous optic cupping.

Vertical cross sections of the optic cup in 1974 and 1978 are presented in Figure 9, again showing the deepening and upward extension of the optic cup. The cross section was taken from the depth maps displayed in Figure 8. Although simultaneous stereophotographs should be preferred, non-simultaneous photography is also useful in monitoring the changes in the geometry of the optic cup. Non-simultaneous stereophotography results in uncertainty and change of stereobase. A change in stereobase will result in a global change of the scale of the geometry of the optic cup. Local changes in geometry, the most common occurrences, can still be readily measured by first performing a global change of scale correction.

Analysis and Discussion of Errors

In order to quantify and analyze the errors due to the stereophotogrammetry procedure and algorithms, a set of normal subjects (eye exams, intraocular pressure, and visual fields within normal limits) were studied under the following conditions:

(a) Stereophotographs of each subject were taken using a Topcon camera which provides simultaneous stereophotographs on a single 35 mm photographic frame.

(b) Two sets of photographs were taken 30 min apart for each subject. The clinical conditions were those routinely used for the patients of the Eye Clinic at the UC Davis Medical Center.

(c) Images were digitized at the Signal and Image Processing Laboratory at the University of California, Davis, using routine procedures developed for this project.

(d) Some photographs were discarded because of unusually poor focal or illumination. For patients, such poor images may have required that additional photographs be taken. Here we chose to discard such unusable data.

A set of 14 stereopairs for 7 different cases were analyzed in detail. The total volume and several partial volumes were computed for each optic cup, the data tabulated, and statistics generated. Figure 10 shows an example of data obtained in this study.

The following results and observations were drawn:

(a) The volumes of the optic cups are significantly different for this set of normal subjects, with the largest cup approximately three times larger than the smallest one.

(b) Relative volume errors in duplicate measurements range from a high of 12.3% to a low of 2.3%. The average volume error is 4.6%. Discarding the
smallest cup, which has a large relative error, the average volume error becomes 3.2%.

(c) The absolute volume errors show substantially fewer variations (a range of approximately 2:1).

These results can be readily explained. The measurement of depth is made on a fixed mesh which leads to an uncertainty of 2% under ideal conditions. Because of residual misalignment, additional depth errors are introduced in most cases. The resulting volumes have absolute errors of fairly constant magnitudes, and these results in large relative errors for small cups. Thus, the absolute volume changes can be monitored with a fairly constant sensitivity. Relative volume changes can be
detected if they exceed the uncertainty of 2 to 5% observed for medium to large cups. For very small cups, the errors may exceed 10%.

**Discussion**

Our results to date suggest that both the sequential monocular display and stereophotogrammetric digital image processing techniques can provide sensitive, quantitative procedures for monitoring progressive changes of the optic cup in glaucoma. However, careful analysis of more than 200 monocular and stereo optic disc photographs (both from our laboratory and from other glaucoma centers) indicates that there are several difficulties associated with these procedures. Perhaps the largest problem is related to the quality and con-
Fig. 8. Depth map of the optic cup for the 1974 (left) and 1978 (right) photographs shown in Figure 7.

Fig. 9. Vertical (90–270 deg) cross section of the depth maps shown in Figure 8. The solid line refers to the 1974 photographs, and the dotted line refers to the 1978 photographs.

The high resolution and quantification available with digital image processing have revealed that optic disc photographs often have spurious reflections and unequal illumination across the picture, sometimes are marred by a defocused dark spot (the camera's aperture stop that eliminates the corneal reflex), and are seldom optimally focused. These factors, in addition to the viewing angle and size of the image, tend to vary from one year to another for sequential photographs taken of the same eye. The situation is more difficult for stereo optic disc photographs, since the left and right stereo pairs of photographs typically have different focusing, reflection, and illumination characteristics. Our experience suggests that such artifacts are present for several fundus camera systems and clinical photographic techniques, although there are differences in the magnitude and prevalence of these anomalies. These features are not usually noticed during qualitative clinical observation of photographs because the resolution requirements are not as critical, and precise alignment, scaling, and registration of sequential photographs are not necessary for qualitative judgement.

Registration and alignment of images for computer
digitization and quantification is a demanding task. Because of the necessity for extremely high accuracy, the photographs must be precisely rotated, translated, and scaled in order to compare left and right stereo pairs of photographs or a series of sequential monocular photographs. Our combined manual and automated procedures for verifying alignment and registration by utilizing image subtraction and rapid alternation of images is quite sensitive and reliable, although it is also rather time-consuming. It is possible to fully automate this procedure, but it will require a more careful, systematic analysis of all potential sources of error, including the type of slide mount employed, the flatness of the film, and the angle of the photograph with respect to the video camera.

In spite of these methodologic problems, our preliminary findings indicate that both image processing techniques described in this paper (monocular sequential display and digital stereophotogrammetry) can provide valuable quantitative information about optic cup characteristics. Even with small residual errors in registration and scaling for the monocular sequential display, an observer can readily distinguish significant localized optic cup changes (due to glaucomatous damage) from image artifacts. Similarly, the various strategies employed by our stereophotogrammetry algorithm (skeletonization, modeling, absolute difference procedure, etc) serve to minimize the influence of photographic errors and artifacts. For both techniques, it is possible to extract quantitative information for each localized region of the optic disc (e.g., nerve fiber rim thickness, surface contour of the optic cup, depth, etc).

Because of the reductions in cost and increases in availability of digital image processing equipment, it is now reasonable to assume that these techniques could be used for routine clinical evaluation of glaucomatous optic cupping. However, the current variability introduced by photographic technique and the optical artifacts produced by existing fundus camera systems (especially stereo fundus cameras), limit the sensitivity and reproducibility of these techniques. One method of approaching this problem is to upgrade the image quality of existing fundus cameras and introduce a standard photographic procedure that minimizes variations in camera viewing angle, eye-to-camera distance, and other relevant parameters. A video fundus camera attached to a digital image processing system, such as that described by McCormick and his associates,13 would be the most effective solution to this problem. Alignment, scaling, and registration of images could easily be accomplished prior to the acquisition of a photographic image, while the patient is seated at the camera. This process would certainly be more accurate than attempting to correct for such errors after the photograph has been taken. However, the video fundus camera solution would exclude the possibility of analyzing standard fundus photographs of the optic disc. Therefore, a set of image processing algorithms that is capable of correcting differences in alignment, scaling and registration, as well as spurious reflections and other photographic artifacts would be applicable to a larger group of individuals. Our present algorithms are able to perform such corrections of images, but further refinements are necessary for general application.

The algorithm developed has been the result of successive refinements to obviate the large errors introduced by “biological” elements, clinical photography, alignment and parallax, focusing, etc. The technical parts, the film shrinking, the basic photogrammetry used, and the computer analysis contribute little, per se, to errors. Substantial progress can be achieved by the use of better instruments and procedures in the clinics. As to the technical side, some improvement can be achieved by a more complete modeling and correction by computer processing of remaining errors.

We plan to pursue both of the approaches described above. Enhancements to the two procedures outlined in this paper (monocular sequential display and digital

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**Fig. 10.** Horizontal (0–180 deg) cross section of depth maps for two pairs of stereo photographs taken on the same day in the same patient.
stereophotogrammetry) may provide a sensitive, quantitative method of monitoring glaucomatous optic cupping. Additional processing of a large number of optic disc photographs will help to refine our current algorithms.

**Key words:** digital image processing, glaucomatous cupping

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