

Spatial and Temporal Processing of Threshold Data for Detection of Progressive Glaucomatous Visual Field Loss

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Objective: To evaluate the effect of spatial and temporal filtering of threshold visual field data on the ability of pointwise linear regression (PLR) to detect progressive glaucomatous visual field loss.

Methods: Longitudinal visual field data (Full-Threshold Program 30-2 test point pattern) were simulated using a computer model of glaucomatous visual field progression. This approach permitted construction of a "gold standard" because matching visual field data without variability could be generated and analyzed. Four clustered progressive defects were produced, consisting of 2, 3, 9, and 18 locations, respectively, each with progression rates of -1 and -2.5 dB/y. Pointwise linear regression was used to identify progressive test locations (criterion for progression of statistically significant slope of ≤ -1 dB/y, $P < .05$). Each visual field series was analyzed after the following 3 procedures: (1) no filtering (unprocessed data), (2) Gaussian spatial processing (3×3 grid), and (3) temporal processing (2 field moving average). The effect of spatial and temporal processing on PLR discriminatory power for progression detection was quantified by comparison with the gold standard.

Results: Spatial processing reduced PLR sensitivity to levels below that achieved for analysis of unprocessed data for small progressive defects (≤ 9 locations) or at the low true progression rate (-1 dB/y). Under these conditions, spatial processing caused small PLR specificity improve-

ment. Spatial processing only improved PLR sensitivity above unprocessed levels when progressive defects were large and changing rapidly (progression rate of -2.5 dB/y). Temporal processing gave consistent PLR improvement in sensitivity for all defect sizes and true progression rates. Pointwise linear regression sensitivity gain provided by temporal processing allowed progression to be detected 2 to 3 visual fields earlier than for analysis of raw data. Specificity dropped slightly as a result of temporal processing but remained at 89% or above for all conditions studied.

Conclusions: Gaussian spatial processing reduces PLR discriminatory power with low true progression rates or small progressive defect sizes and, therefore, is of limited use for detection of progressive visual field loss. Temporal processing improves the sensitivity of PLR and reduces the number of tests required to detect progressive loss with minimal loss of specificity.

Clinical Relevance: Image processing techniques can be applied to threshold visual field data to enhance sensitivity or specificity of PLR for the determination of progressive change. This investigation demonstrates that temporal processing may assist with the detection of significant progressive visual field loss with fewer test results than unprocessed data.

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THRESHOLD VISUAL field analysis represents an essential component of the full ocular examination in glaucoma and related ocular pathologic abnormalities. Visual field assessment assists clinicians in detecting the onset of initial visual function loss and monitoring existing areas of sensitivity loss. Evaluation of visual function with threshold visual field analysis provides quantitative measures of both the spatial arrangement and magnitude of sensitivity loss present within the area examined. However, the visual field is not a stable quan-

tity and measurements of threshold sensitivity can vary physiologically over relatively short periods (minutes) or over more lengthy periods (days). This variability (or "noise") occurs in all individuals and is caused by a variety of factors including patient response fluctuations¹ and cyclic alterations of sensitivity. Variability is also dependent on the thresholding algorithm²⁻⁴ and has been shown to become greater in areas of pathologically reduced sensitivity.^{1,5-8}

The presence of variability makes identification of test locations with progressive visual loss difficult by masking the

MATERIALS AND METHODS

Longitudinal glaucomatous visual field data (Full-Threshold Program 30-2 test point pattern) were simulated using a previously described model that incorporates many aspects of visual field behavior.¹¹ This model simulates sets of full-threshold visual fields between predefined initial and final tests. Simulation permits control of many variables that affect threshold sensitivity including short- and long-term fluctuations and, therefore, allows construction of a “gold standard” because data may be simulated from the same initial and final tests without variability.

Three sizes of progressive hemifield defects were generated by simulation; small (2 and 3 horizontally adjacent test locations), medium (9 locations arranged in a 3×3 square), and large (18 clustered locations in an arcuate pattern). The spatial arrangements of these defects are shown in **Figure 1**. Two true rates of progression were used for each size of progressive defect, with each test location within the progressive area changing at –1 dB/y and –2.5 dB/y.

Each simulated visual field set had 2 dB of short-term fluctuation and 1 dB of long-term fluctuation, typical values in patients with glaucoma who have early damage assessed with a 4-2 staircase strategy.¹⁷ Each simulated set consisted of 10 serial visual fields, equivalent to 10 years of annual testing. In this study, 20 simulation iterations were performed for each progressive defect.

Each visual field set was analyzed after (1) no processing (raw threshold data), (2) processing with a previously described Gaussian spatial filter,^{15,16} and (3) processing with a 2-field temporal filter (moving average). Gaussian spatial processing was performed using a 3×3 grid, as shown in **Figure 2A**. Each filter cell contains a different weight configured such that the grid forms a Gaussian profile from any angle. The filter is centered on a test location,

and thresholds underlying each filter cell are multiplied by the appropriate weight. The sum of these weighted threshold products is divided by the sum of the filter weights to produce a spatially processed threshold value that replaces the original central grid value. Spatial processing was performed at each test location by moving the filter across all points in the visual field. Where the grid extends over the edge of the visual field, only occupied cells are included in processing.

Temporal processing consisted of replacing the threshold at each location by the average threshold at the same location from the current and single immediately preceding test. This is equivalent to the moving average of 2 test results. Temporal processing dictates that the first field in the test set may not be processed because no prior threshold values are available. An example of temporal processing at a single test location is shown in **Figure 2B**.

Unprocessed, spatially processed, and temporally processed sets were subsequently analyzed separately using PLR analysis to identify progressive test locations. Progressive test locations were defined; those with statistically significant regression line slopes were equal to –1 dB/y ($P<.05$) or worse. This criterion for progression was based on use in previous studies of progressive visual field loss.^{9,19-21}

The ability of PLR to detect progressive test locations (sensitivity) and nonprogressive test locations (specificity) was quantified for each sequential field by comparison with gold standard data for unprocessed, spatially processed, or temporally processed threshold data for each progressive defect and true rate of progression. The gold standard consisted of visual field set generated using the same progressive defects but without glaucomatous levels of variability. This was performed for each field in each simulation iteration. Average sensitivity and specificity were calculated for each condition.

progressive change especially at gradual rates of sensitivity decline. Accordingly, many multicenter clinical trials in glaucoma have found that a large number of visual fields are needed to accurately distinguish true visual field progression from intertest variability. A variety of statistical approaches may be used to extract information on progressive loss (signal) from variability (noise), including trend analyses such as linear regression of threshold sensitivity at each test location. It has been suggested that pointwise linear regression (PLR) is advantageous because it may be able to detect low progression rates.⁹ However, previous reports have suggested that at least 8 annual test visual field results are required to detect gradually progressive test locations using this technique.^{10,11} Although more frequent testing can reduce the interval for identification of true progressive locations, this approach to reducing detection time requires more clinical resources and is also subject to diminishing returns.¹² Ideally, it would be clinically advantageous to identify progressive loss with fewer test results.

Image processing has been used within computer science to extract information by reducing noise from matrices of digital information.¹³ This processing involves

computational manipulation of the original data values with a predefined mathematical “process” or filter. Within vision science, spatial processing (or filtering) has been applied to the grid-based patterns of threshold visual field test results. This technique smoothes the visual field surface by replacing each original threshold with a weighted neighborhood average, thereby reducing the local noise produced by variability. Spatial processing of perimetric threshold sensitivity values using a Gaussian filter has been reported to be useful for quantification of local spatial variability,¹⁴ improvement of the predictive performance of future threshold values using PLR,¹⁵ and reduction of test-retest threshold variability in glaucoma.¹⁶ The latter 2 of these findings has prompted the suggestion that spatial processing of data prior to analysis for detection of change could boost the progression (signal)-variability (noise) ratio and, therefore, may enhance the ability to detect visual field change. It is also reasonable to suggest that because visual field variability occurs over time, temporal threshold averaging (temporal processing) may also be beneficial. This study evaluates and compares the effects of 2 methods of processing threshold visual field data—spatial and temporal processing—for the detection of progressive visual field loss using PLR.

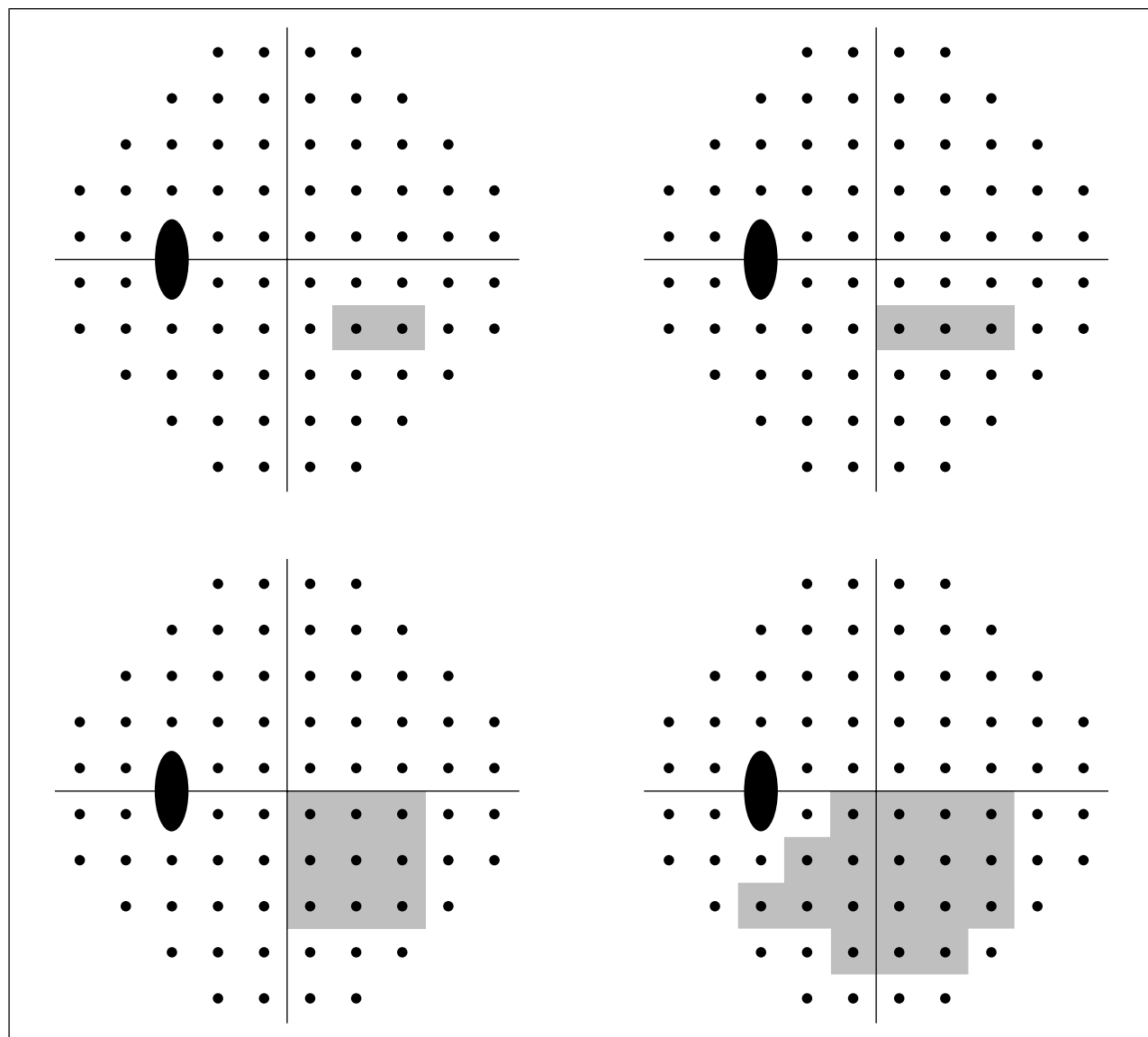


Figure 1. Four sizes of progressive defect (2, 3, 9, and 18 test locations [shaded areas]) were used for generation of progressive visual field series.

RESULTS

SENSITIVITY

The effect of spatial processing on sensitivity was found to depend on both the number of progressive test locations and true rate of progression. With small progressive defects (2 or 3 progressive test locations), spatial processing (**Figure 3**, circles) caused a reduction in the sensitivity of PLR to detect progressive test locations compared with unprocessed data (squares). As shown in Figures 3A through D, this effect was found at both of the true rates of progression evaluated in this study (-1 dB/y and -2.5 dB/y), although a larger reduction in sensitivity was found for the lowest true progression rate (-1 dB/y). For this low true progression rate, the reduction in sensitivity produced by spatial filtering increased when more fields were used within the regression analysis and when analysis was based on 9 or more visual field test results, sensitivity was reduced to 0. With moderate- or

large-sized progressive defects (9 or 18 progressive locations) shown in Figure 3E through H, spatial filtering produced an improvement in sensitivity for the greatest true rate of progression examined in this study (-2.5 dB/y). For this rate of progression, the improvement in sensitivity provided by spatial filtering was maximal when 6 years of follow-up were available for analysis when unprocessed average sensitivity of around 40% was increased to more than 80% by spatial processing. With the greater numbers of available test results, the improvement in sensitivity afforded by spatial processing was reduced. At -1 dB/y of progression, spatial processing did not produce the same improvement in sensitivity. Modest improvement in sensitivity (10% maximum increase) occurred when small numbers (≤ 7) of visual field test results were available for analysis, but this improvement was lost when the number of available fields increased to 8 or more.

Temporal processing (Figure 3, triangles) produced an improvement in the ability of PLR over un-

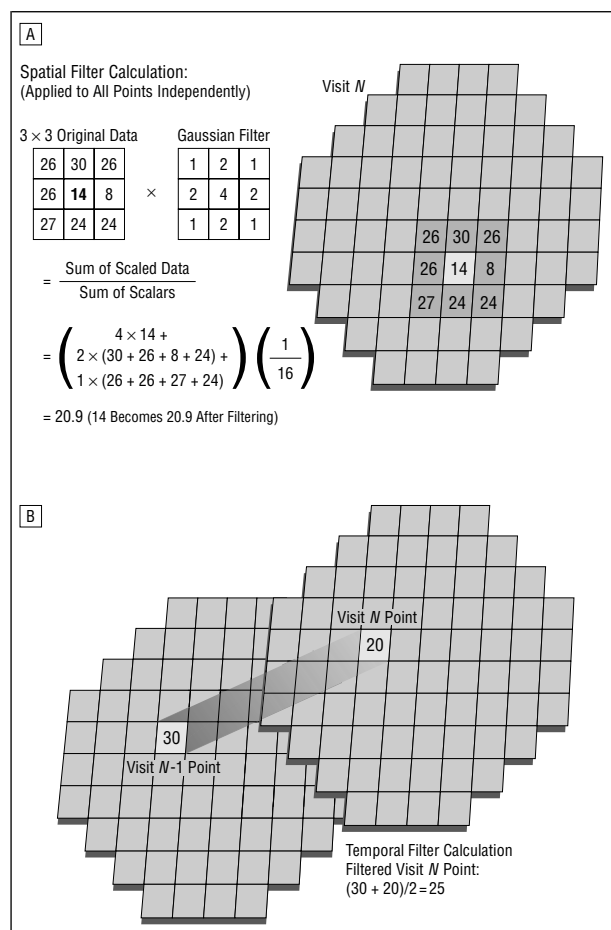


Figure 2. A, Schematic depicts the principle of spatial filtering for a single test location. This procedure was in accord with that described by Fitzke et al.^{9,16} and Crabb et al.¹⁸ B, Schematic depicts the principle of temporal processing, whereby a moving average of 2 sequential visual field test results is calculated. *N* indicates the visit number; boldface value, original threshold.

processed data to correctly identify truly progressive test locations for all sizes of progression studied in this investigation, as shown in Figure 3A through H. The degree of benefit produced by temporal processing was found to depend on the true rate of progression and number of visual field test results available for use by regression analysis. Improvement in sensitivity was unrelated to the number of test locations that were progressive. For a true progression rate of -1 dB/y, an improvement in sensitivity of approximately 20% compared with unprocessed data was found (Figure 3A, C, E, and G). This improvement gradually decreased with 6 or more test results available for PLR and was reduced to between 5% and 10% after 10 “simulation years” of follow-up. At higher true progression rates, such as -2.5 dB/y shown in Figure 3B, D, F, and H, temporal processing provided an improvement in sensitivity of around 30% when 5 visual field test results were available, and it allowed the sensitivity of PLR to exceed 70% with as few as 6 available test results. At this rate of progression, temporal processing continued to provide benefit to PLR for up to 10 available fields. In summary, when 10 or fewer test results are available, the likely

sensitivity gain provided by temporal processing may permit PLR to detect progressive test locations up to 3 visual fields earlier than when unprocessed data are used.

SPECIFICITY

Spatial processing produced a small improvement in the ability of PLR to correctly identify nonprogressive test locations (up to 2%) compared with analysis of raw data for all sizes of progressive defect at a true progression rate of -1 dB/y (Figure 4A, C, E, and G). It should be recognized that the criterion used in this study for detection of progression (-1 dB/y [$P < .05$]) already yields high specificity levels ($\geq 95\%$) prior to processing. For the higher true progression rate of -2.5 dB/y, similar improvement occurred for progressive defect sizes of 2, 3, and 9 test locations (Figure 4B, D, and F). However, as shown in Figure 4G and H, spatial processing caused a small reduction in specificity when the size of progressive defect exceeded the spatial filter size. This reduction was small (up to 3%) and seemed to be independent of the number of visual field test results included in the regression analysis.

Figure 4 demonstrates that temporal processing had a small negative effect on the specificity of PLR, reducing specificity by up to 10% compared with unprocessed threshold data. This detrimental effect decreased with more visual field test results available for analysis. At no point was specificity below 89% by temporal processing.

COMMENT

Clinical management of glaucoma requires differentiation between cases of stable and progressive disease to determine the efficacy of treatment regimens. Currently, this determination is usually based on longitudinal series of visual field test results. Visual field progression is also a primary outcome measure for multicenter clinical trials in glaucoma. Unfortunately, the confounding effect of variability present both within and between visual field tests complicates identification of true progressive loss. This confound is such that unless threshold sensitivity reduction due to active pathologic abnormality is sufficient to exceed pathophysiologic variability, it is impossible to distinguish between progressive visual field loss and variability. This means that small but clinically important amounts of progressive loss are difficult to identify. One statistical approach that has been applied to this problem is trend analysis, whereby one or more visual field variables may be followed over time, permitting extraction of progressive signal from variability noise. One type of this technique, linear regression analysis, has been used on visual field summary (global) indices, such as mean deviation and pattern standard deviation, glaucoma hemifield test zones, and individual test locations (pointwise). For each of these, several criteria exist that can be chosen to determine acceptable levels of sensitivity and specificity. Generally, global indices have been shown to be specific but relatively insensitive to detection of early, subtle changes because small progressive regions are averaged out.²² Con-

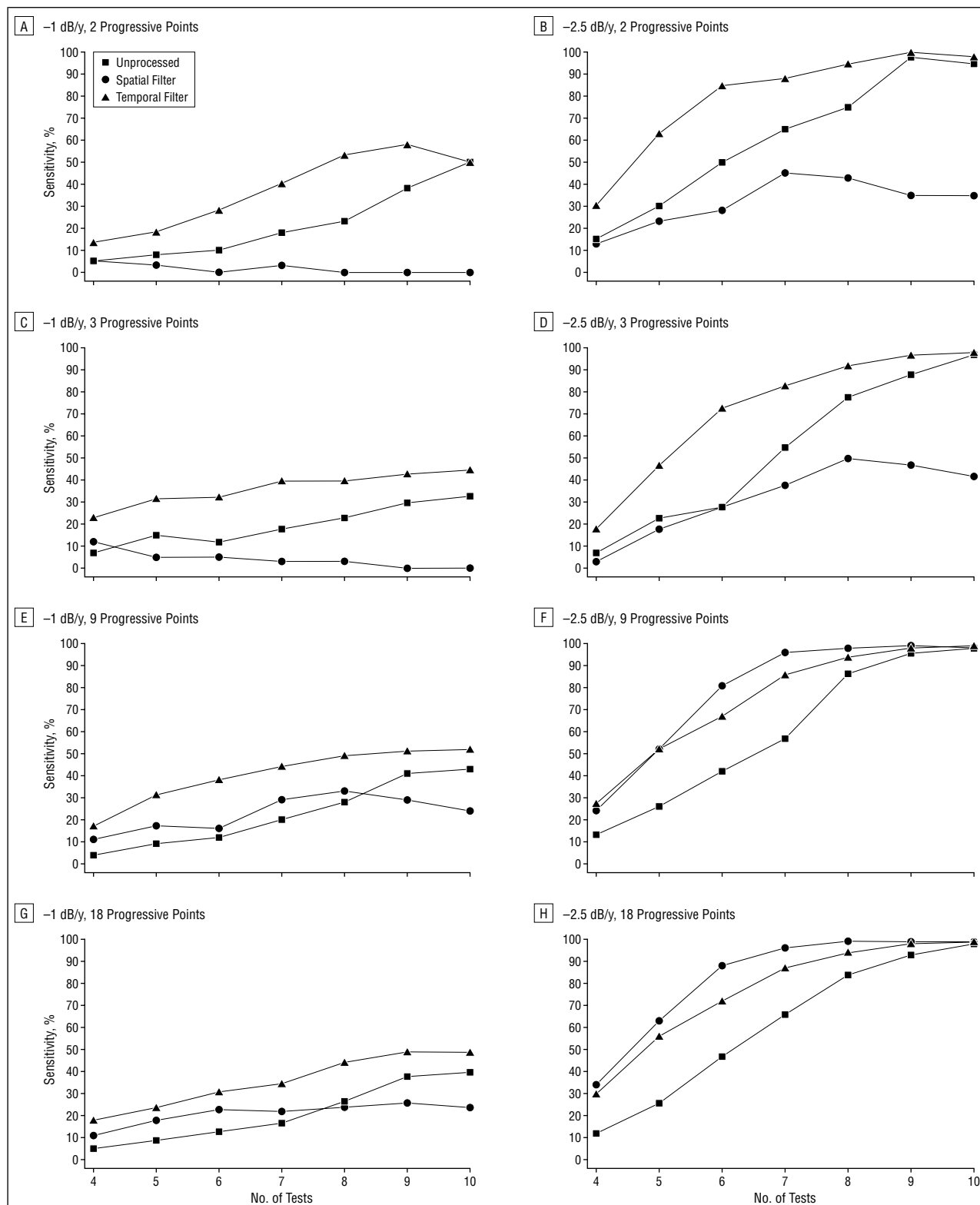


Figure 3. A through H, These show the sensitivity of pointwise linear regression using (1) unprocessed (squares), (2) spatially processed (circles), and (3) temporally filtered data (triangles). A and B, Data are from 2 progressive test locations with progression rates of -1 dB/y and -2.5 dB/y. C and D, Data are from 3 progressive test locations with progression rates of -1 dB/y and -2.5 dB/y. E and F, Data are from 9 progressive test locations with progression rates of -1 dB/y and -2.5 dB/y. G and H, Data are from 18 progressive test locations with progression rates of -1 dB/y and -2.5 dB/y.

versely, PLR may be highly sensitive to small progressive defects but may lack specificity because of the high variability present at individual test locations. The lack of

an independent reference standard to quantify the success of the methods used for the detection of progressive glaucomatous visual field loss has produced consid-

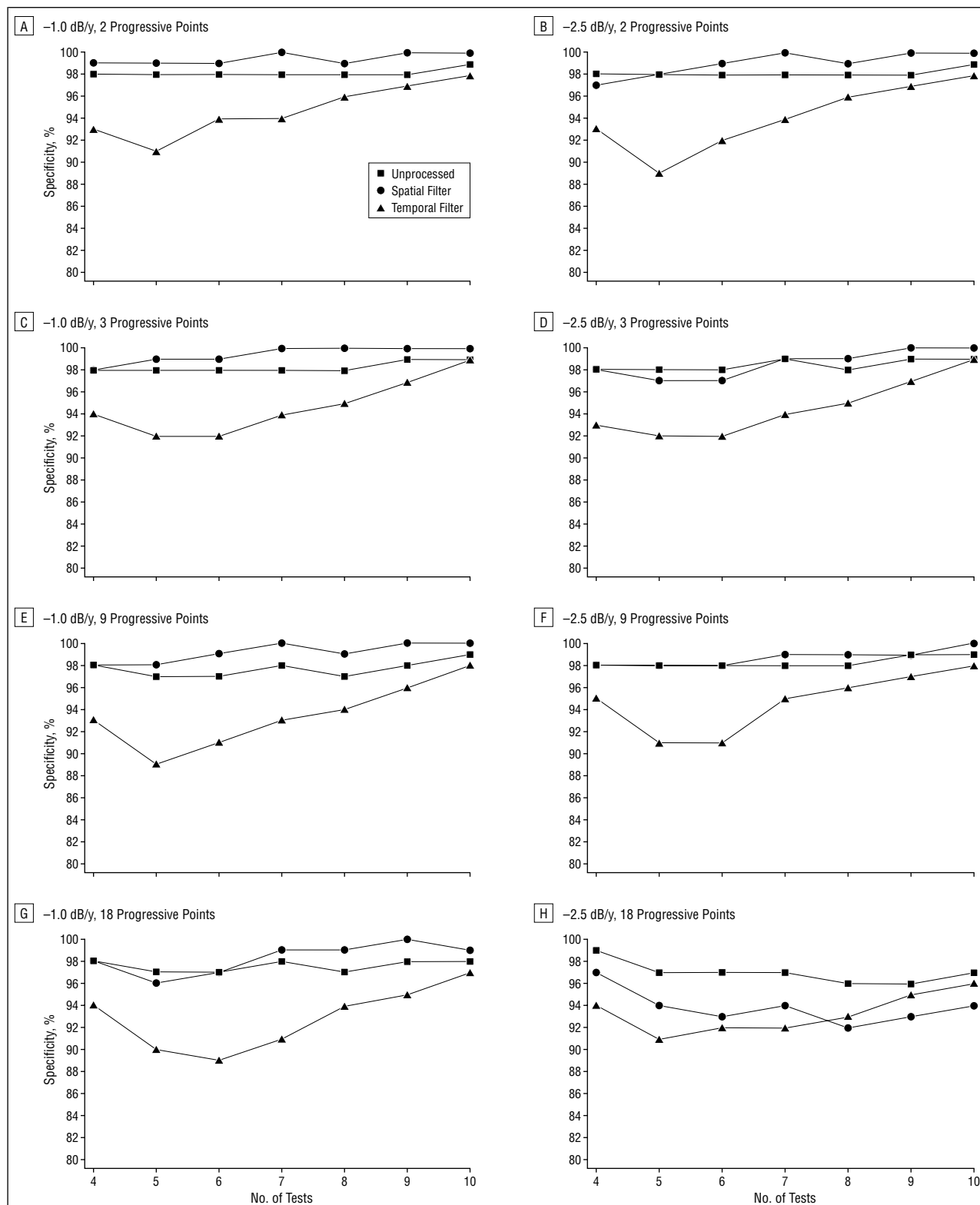


Figure 4. A through H, These show the specificity of pointwise linear regression using (1) unprocessed (squares), (2) spatially processed (circles), and (3) temporally filtered data (triangles). A and B, Data are from 2 progressive test locations with progression rates of -1 dB/y and -2.5 dB/y. C and D, Data are from 3 progressive test locations with progression rates of -1 dB/y and -2.5 dB/y. E and F, Data are from 9 progressive test locations with progression rates of -1 dB/y and -2.5 dB/y. G and H, Data are from 18 progressive test locations with progression rates of -1 dB/y and -2.5 dB/y.

erable debate concerning which variable exhibits the highest discriminatory power for detection of progressive loss when used with linear regression and on cri-

teria that should be applied to each. Each of the current multicenter clinical trials in glaucoma uses different criteria for defining progression of visual field loss.²³⁻²⁶

In this study we evaluated the use of 2 image processing techniques that can be applied to threshold visual field data after collection and prior to statistical analysis for change. The aim of such procedures is to help increase the identification of progressing and stable visual fields using available data. With the aid of computers, both techniques are relatively quick and easy to apply to threshold data and are independent of thresholding strategy or perimetric instrumentation, although consistency should be maintained throughout the visual field series. Spatial processing was evaluated because previous investigators have suggested its potential role in assisting detection of progressive loss.¹⁶ Temporal processing was evaluated because such a filtering technique represents a logical approach to the temporal nature of threshold variability. Use of a validated simulation model¹¹ to generate longitudinal visual field series with and without typical glaucomatous amounts of short- and long-term fluctuations has enabled performance quantification for both processing techniques with a variety of progressive defect sizes and true progression rates.

Previously investigators have shown that spatial processing improves repeatability of full-threshold estimations.¹⁶ In this study it has been demonstrated that under most progression conditions, spatial processing does modestly improve the ability of PLR to correctly identify stable test locations. However, it was also observed that for small numbers of clustered progressive test locations (less than or equal to spatial filter size, 9 locations), or at a low true progression rate (-1 dB/y), spatial processing reduced sensitivity to a level below that achieved by analysis of raw data. It appears that although the particular Gaussian spatial processing procedure used in this study reduced the threshold variability (noise) at nonprogressive locations, thus improving specificity, it also reduced progressive loss (signal) thereby resulting in decreased sensitivity. This finding was expected given that use of spatial processing techniques in computer science assumes that pixels (or in the case of visual fields, test locations) are smaller than any of the important details,¹³ which is clearly not the case with the limited visual field matrix size. Furthermore, the negative effect of spatial filtering was greatest under the conditions at which it is most difficult to detect progression: small progressive defects or low true progression rates. It was also observed that at the largest progressive defect size (18 clustered locations) and highest true progression rate (-2.5 dB/y) combinations, spatial processing also produced a small but consistent specificity reduction. This effect can be explained by artifactual increase of thresholds of nonprogressive points directly adjacent to true progressive locations by spatial processing. Although under our experimental conditions the amount of specificity loss is negligible, it is possible that for scenarios of noncontiguous and/or more rapid rates of true progression, the resultant effect on specificity may become significant. A further interesting observation is that progressive defects consisting of 9 or 18 test locations with -1 dB/y true rates of progressive loss initially receive a sensitivity gain from spatial processing, which becomes a sensitivity reduction when 7 to 8 test results are available. It is likely that this results from the gradual re-

duction of the progression information signal by spatial processing as more information becomes available to PLR.

The effect of temporal processing on longitudinal threshold data is more predictable than spatial processing. We show that temporal processing provides consistent sensitivity gain when fewer than 10 fields are analyzed by PLR. Depending on the true rate of progression, temporal processing provides a net saving of between 1 and 3 visual fields compared with unprocessed threshold data when applied prior to PLR. As expected, the degree of benefit is reduced with more available test results. However, temporal processing also had a modest negative effect on specificity. Use of a rigorous progression criterion (significant slope of ≤ -1 dB/y) that has been shown to demonstrate high specificity ensured that specificity was not significantly compromised. It can easily be seen from Figures 3 and 4 that for fewer than 10 available visual field results, sensitivity gain always exceeds the specificity loss providing a net discriminatory power gain.

CONCLUSIONS

These data show that image processing techniques can be applied to threshold visual field data. Depending on the method of processing applied, either sensitivity or specificity can be enhanced. When few test results are available for analysis, it appears that temporal processing increases PLR sensitivity for detection of progressive visual field loss, thereby reducing the number of test results required to detect progression without significantly compromising specificity. The use of spatial processing does not seem to offer a consistent benefit over the analysis of raw data, and in some instances significantly inhibits the ability to detect small, gradual progressive changes.

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Correction

Error in Unit of Measure. In the case report titled "Late Dislocation of a LASIK Flap Caused by a Fingernail," published in the March issue of the ARCHIVES (2001;119:447-449), on page 448, lines 6 and 7, the text should have read "A -1.00DS/-1.00DC axis 135 correction improved the visual acuity to 20/20 OD."