POINTWISE LINEAR REGRESSION OF GLAUCOMATOUS VISUAL FIELDS
A new approach

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Abstract

Background: Pointwise linear regression is an effective technique for reliable early detection of glaucomatous visual field progression. However, if regression is always begun from the first field in a series, it is possible that a decline in sensitivity will be detected relatively late if it occurs after a period of stability. Thus, a new algorithm in which each field in a series was analyzed with those following it (rather than those preceding it) was developed.
Purpose: To compare the ability of the new algorithm to detect progression with conventional pointwise linear regression.
Methods: All the patient records that satisfied the following selection criteria were drawn from the Moorfields Eye Hospital visual field database (64,949 visual fields): more than 19 fields for either eye, age >40 years, false +ves and -ves <33%, fixation losses <20%, and macular threshold ≥30dB. If both eyes of a patient satisfied the criteria, one was chosen at random. Thus, 27 field series were studied. The first three fields in each series were ignored to obviate learning effects; the following 16 were studied. Both the conventional and new algorithms were applied to each field series. The time taken from the start of each series until progression criteria (slope worse than -1dB for inner points, -2dB for edge points, $p<0.001$) were satisfied by at least one retinal location was calculated for each algorithm.
Results: The algorithms agreed that 20 series showed progression and two were stable. Five series were detected as progressing by the new algorithm, but not by the conventional one. All series detected as progressing by the conventional algorithm were also detected as progressing by the new one. In the 20 series which both algorithms detected as progressing, the new algorithm detected progression by a mean of 0.85 years earlier ($p<0.01$, Wilcoxon signed rank test).
Conclusions: The new pointwise linear regression algorithm appears to be superior to the conventional one.

Introduction

A primary aim in the management of chronic glaucoma is early, reliable detection of deterioration of the visual field. Valid estimates of progressive glaucomatous visual

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field decay are obtained by using a linear fit, *i.e.*, postulating a constant reduction of sensitivity over time for each retinal location tested[1]. This technique, known as pointwise linear regression (PLR), has been used for several years to investigate glaucomatous visual field change[2,3], and has recently been re-examined[4-6]. PLR detects visual field progression sooner than event-type analyses (such as Statpac 2[7]), demonstrates field loss undetected by summary measures of sensitivity (such as the mean defect value), and is a good predictor of the future behavior of the field[1,8,9].

However, there are disadvantages to the conventional technique of PLR. Although test locations which show steady sustained deterioration are rapidly detected as progressing, there may be a delay in detection if the period of deterioration is preceded by a period of a different type of behavior. For example, a location which shows a long period of stability before the sensitivity begins to decline may be detected relatively late, as the stable period weights the PLR analysis in favor of a less negative slope. Similarly, a period of increased variability (long-term fluctuation[10]) before the period of steady decline may cause a delay in the detection of progression. This is especially relevant since long-term fluctuation is greater in glaucoma patients than in normals[11].

In order to address these potential problems, a new strategy for PLR that gives more weight to the recent behavior of the test location in question was developed. The present study was undertaken in order to compare this new method with conventional PLR in terms of ability to detect progression and the time taken to detect progression.

Methods

Consider a test location (x,y). For a field series F_1 to F_N, designate the sensitivity of each test location in each field as $S(x,y)_i$. Conventional PLR and new PLR ascribe a slope and *p* value to $(x,y)_i$ using different techniques.

Conventional PLR performs linear regression of $S(x,y)_1$ to $S(x,y)_i$. For example, the slope and *p* value ascribed to a location in the fourth field of a series is obtained by performing linear regression of the sensitivity values of that point in the first, second, third and fourth fields on time (the time of each field test relative to the first field). Thus, these values of slope and *p* value are fixed, and are not affected if subsequent field tests are performed.

Our technique of PLR performs linear regression of $S(x,y)_i$ to $S(x,y)_N$ on time. For example, the slope and *p* value ascribed to a location in the fourth field of a series of seven fields is obtained by performing linear regression of the sensitivity values of that point in the fourth, fifth, sixth and seventh fields on time (the time of each field test relative to the fourth field). Thus, these values of slope and *p* value are not fixed, and will be affected if subsequent field tests are performed.

This method of PLR gives more weight to relatively recent field tests. Thus, it might be expected to detect change following a period of stability (or fluctuation) sooner than conventional PLR.

Subjects

At the time of the study, the Glaucoma Service visual field database at Moorfields Eye

Hospital contained 64,949 automated visual field records from 9482 patients. Field series were selected for study on the basis of the following criteria:

1. The field series contained at least 19 fields.
2. The patient's age on the date of the first test of the series was at least 40 years.
3. The field series consisted of Humphrey 24-2 and Humphrey 30-2 tests using a white stimulus size III target.
4. The foveal threshold in each field of the series was greater than 30dB in order to exclude cases of frank cataract or macular disease.
5. Each test in the field series met machine-dependent reliability criteria: less than 33% false positives and false negatives and less than 20% fixation losses.
6. The first three fields in the series were ignored; this is sufficient to obviate any learning effects[12,13].
7. If both eyes of a patient satisfied the above conditions, one was chosen at random. On the basis of the foregoing criteria, 27 field series were studied.

Progression criteria

Both the conventional and new PLR algorithms used the same progression criteria. A field series was regarded as progressing if it contained at least one non-edge test location with a negative slope of 1dB per year or worse associated with $p<0.001$ for a two-tailed t test of the slope against zero (*i.e.*, the null hypothesis of no deterioration). The slope criterion of 1dB per year represents a rate of sensitivity loss approximately ten times greater than the normal age-related decline[14]. Edge points are known to be more subject to fluctuation[14], so a stricter slope criterion of 2dB per year (also with $p<0.001$) was introduced for them. These slope criteria, in combination with a less stringent slope significance criterion of $p<0.1$, have been demonstrated to compare closely with the humphrey Statpac 2 Glaucoma Change Probability analysis[9,15].

Detection time

The detection time for a given field series for a given algorithm was defined as the time interval between the initial field in the series and the field when the progression criteria for that algorithm (*vide supra*) were first satisfied.

Reliability of early detection

In order to examine whether our new PLR might diagnose spurious progression compared to conventional PLR, the two methods were compared in terms of the number of points labeled as progressing at detection time and the mean slope of the progressing points at detection time: if the new PLR consistently produced higher values of these than conventional PLR, it would suggest that our new PLR might be falsely overcalling progression.

Statistical analysis

For each field series, progression status was determined using both conventional and our new PLR. The level of agreement between the two algorithms was measured using the kappa statistic[16]. For progressing field series, detection time (*vide supra*) was

Table 1. Agreement between new and conventional PLR

New	*Conventional*	
	progressing	stable
Progressing	20	5
Stable	0	2

N = 27, K = 0.37

calculated for each algorithm. When both algorithms agreed that field series were progressing, detection times for the new PLR were compared with their correlates for conventional PLR using a non-parametric test for paired data from two related samples (Wilcoxon signed rank Z test)[17].

Statistical analysis was performed using the software package SPSS for Windows version 6.0.

Results

Agreement

Both our new and the conventional PLR classified the same 20 field series as progressing. The algorithms also agreed on the same two field series as stable. However, the new algorithm classified an additional five field series as progressing which had been reported as stable by conventional PLR. No field series that were stable according to the new PLR were found to be progressing using the conventional technique. These findings are shown as a contingency in Table 1. They are associated with a kappa value of 0.37, which corresponds to fair agreement[17].

Detection times

For the 20 field series detected as progressing by conventional PLR, the mean detection time was 3.35 years with a standard deviation of 1.73 years. The new PLR gave a mean detection time of 2.52 years with a standard deviation of 1.68 years for the 25 field series it classified as progressing. These findings are displayed in Table 2, and the individual differences between the algorithms for the 20 field series detected as progressing by both are shown as a drop-line graph in Figure 1. Conventional PLR had later detection times than the new PLR in nine of the 20 field series. In 11 of the 20 field series, both algorithms detected progression at the same time. In no field series did conventional PLR detect progression earlier than did the new PLR. These results are summarized in Table 3.

Delay

Delay in detection was calculated as the difference between the detection time for conventional PLR and that for the new PLR. The mean delay in detection associated with conventional PLR was 0.85 years, and the standard deviation was 1.40 years.

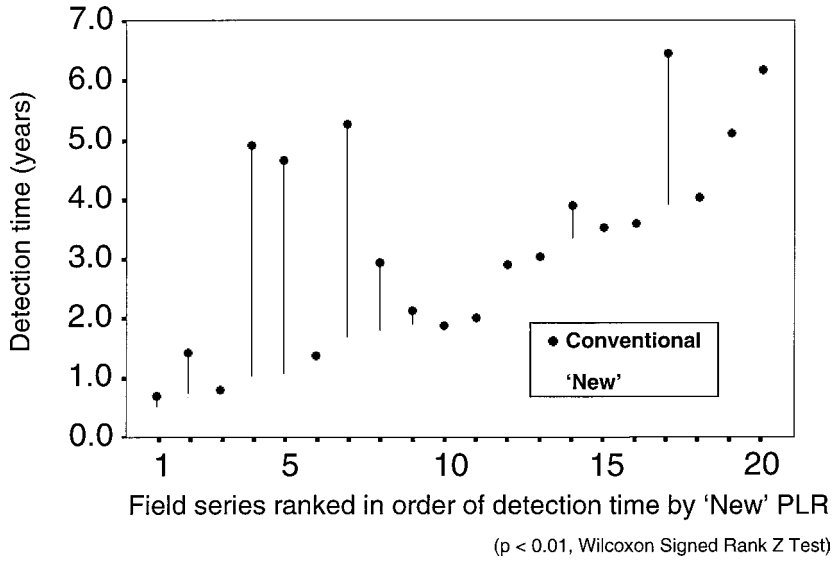

Fig. 1. Drop-line graph of detection times in years for new and conventional PLR against field series ranked in order of detection time by the new PLR.

Table 2. Detection times for new and conventional PLR

	Detection time (years)	
	mean	*SD*
Conventional	3.35	1.73
New	2.52	1.68

Table 3. Comparison of detection times between new and conventional PLR (Wilcoxon signed rank Z test)

	Cases	*Mean rank*
Negative ranks	0	0
Positive ranks	9	5
Ties	11	
Total	20	

Z = –2.6656, P = 0.0077.
Negative ranks occur when conventional PLR detects progression in a given field series earlier than our PLR. Positive ranks occur when our PLR detects progression in a given field series earlier than conventional PLR. Ties occur when both algorithms detect progression in a given field series at the same time

Reliability

For conventional PLR, the mean number of progressing points at detection time was 1.35 (SD 0.99) and the mean slope of the progressing points at detection time was –6.09dB/year (SD 5.82dB/year). For the new PLR, these figures were 1.72 (SD 1.77) and -10.16dB/year (SD 19.95dB/year), respectively. These were not significantly different.

Discussion

It is not surprising that our new and the conventional PLR show only fair agreement. This is attributable to the finding that the new PLR classified five additional fields as progressing, compared with conventional PLR. This may imply that the new PLR is more sensitive than conventional PLR, or it may mean that the new PLR is merely less specific than conventional PLR.

There is no gold standard for the identification of visual field progression in glaucoma. Thus, it is difficult to assess whether a given technique is detecting true progression, *i.e.*, to measure the specificity of the method. Some authors have used clinical impression against which to compare the performance of various algorithms[18], but this has been shown to be a largely subjective measure[19]. Others have avoided the problem entirely by not attempting to estimate the reliability of their techniques[6].

In the absence of a gold standard for glaucomatous visual field progression, the present study compared both the new and the conventional PLR with respect to the number of points labeled as progressing at detection time and the mean slope of the progressing points at detection time. The fact that the new PLR did not produce higher values of these measures than conventional PLR indicates that our new PLR is unlikely to be falsely overestimating progression. Another precaution against overestimation of progression in the present study was the use of particularly strict progression criteria compared to those in previous work[7,15]. Further support for the reliability of our new PLR is that no field series detected as progressing by conventional PLR were missed by our new PLR. Our algorithm always detected progression at least as soon as, and often sooner than, the conventional one. The high proportion of progressing field series detected by both algorithms is probably a result of the requirement for field series to be at least 19 fields long in order to be included in the study: intensity of monitoring and lengthy follow-up are both associated with progression.

In summary, this study examined the performance of a new technique of pointwise linear regression compared to the conventional technique. When both algorithms were applied to a set of field series that were not selected according to any particular progression criteria, the new algorithm was found to be more sensitive than the conventional one both in terms of the ability to detect progression and of the speed of detection. The new technique gives more weight to the recent behavior of the field, so it is theoretically suitable for the analysis of changes in the field following the conversion from ocular hypertension to glaucoma and field changes following glaucoma drainage surgery. Work is currently under way to test these hypotheses.

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