Detecting Changes in Retinal Function: Analysis with Non-Stationary \textit{Weibull} Error Regression and Spatial Enhancement (\textit{ANSWERS})

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Abstract

Visual fields measured with standard automated perimetry are a benchmark test for determining retinal function in ocular pathologies such as glaucoma. Their monitoring over time is crucial in detecting change in disease course and, therefore, in prompting clinical intervention and defining endpoints in clinical trials of new therapies. However, conventional change detection methods do not take into account non-stationary measurement variability or spatial correlation present in these measures. An inferential statistical model, denoted ‘Analysis with Non-Stationary \textit{Weibull} Error Regression and Spatial enhancement’ (\textit{ANSWERS}), was proposed. In contrast to commonly used ordinary linear regression models, which assume normally distributed errors, \textit{ANSWERS} incorporates non-stationary variability modelled as a mixture of \textit{Weibull} distributions. Spatial correlation of measurements was also included into the model using a Bayesian framework. It was evaluated using a large dataset of visual field measurements acquired from electronic health records, and was compared with other widely used methods for detecting deterioration in retinal function. \textit{ANSWERS} was able to detect deterioration significantly earlier than conventional methods, at matched false positive rates. Statistical sensitivity in detecting deterioration was also significantly better, especially in short time series. Furthermore, the spatial correlation utilised in \textit{ANSWERS} was shown to improve the ability to detect deterioration, compared to equivalent models without spatial correlation, especially in short follow-up series. \textit{ANSWERS} is a new efficient method for detecting changes in retinal function. It allows for better detection of change, more efficient endpoints and can potentially shorten the time in clinical trials for new therapies.

Background and Significance

In recent years great strides have been made in understanding ocular diseases in the research laboratory and in \textit{zoo}s, leading to the elucidation of neuro-regenerative processes and even reversing blindness in some conditions.[1–4] The retina, uniquely, is an accessible and directly visible extension of the brain and, therefore, retinal research is becoming a focus for unravelling the complexity of other neurological changes such as those observed in Alzheimer’s disease,[5,6] multiple sclerosis,[7,8] and Gaucher disease.[9] The primary goal in the management of most eye conditions is preservation or improvement in visual function. An established reference test for visual function, namely the visual field, is Standard Automated Perimetry (SAP; Figure 1a). SAP measures the differential light sensitivity (DLS), across a person’s retina and the corresponding visual pathway (Figure 1b,c). Unfortunately, development of computational and statistical methods for analysing data from SAP has not kept pace with the advances in other aspects of eye-related research. Nevertheless, SAP is used extensively in eye and neurology clinics, especially in the detection and management of glaucoma, a group of chronic optic neuropathies causing progressive loss of retinal ganglion cells and their axons and resulting in loss of retinal function. This disease represents a large global health problem with about 80 million people expected to be affected by 2020.[10,11] Glaucoma stability on treatment is assessed by monitoring the visual field with SAP tests, repeated at intervals of between 2 months and 2 years over a patient’s lifetime. Computational methods are required to analyse series of SAP data to identify change; without these, even experienced clinicians have been shown to make inconsistent decisions.[12,13] Current statistical approaches typically use ordinary least squares regression over time to track changes in summary measures, regions of interest or individual visual field locations.[14–17] Other methods simply make comparisons between the most recent test(s) and baseline measurements.[18]
Current methods for detecting change in series of DLS measurements are inadequate because they do not sufficiently address the complexity of the data,[19] notably non-stationary variability and spatial correlation. SAP measurements of retinal function are indirect because of the psychophysical processes involved – a person’s response depends on the probability of perceiving and responding to a light stimulus (Figure 1d). The consequence is considerable variability that increases as DLS deteriorates with the disease progresses, eventually becoming censored in blind regions.[20–22]. For instance, when DLS is healthy at 32 dB, the repeat measurement range (90% confidence interval) is 7 dB (26 dB to 33 dB), while this range increases to 18 dB (5 dB to 27 dB) when the DLS deteriorates to 20 dB. This changing variability over time is referred to as ‘non-stationary measurement variability’. Furthermore, SAP measurements are made in a regular grid across a patient’s field of view, but this grid does not respect the anatomical arrangement of the retinal nerve fibres that transmit signals from the retina to the brain (Figure 1c).[23] The division of the grid by retinal nerve fibres results in correlation between spatially-related locations. There are prescriptions for modelling this unique spatial process,[24] but they have yet to be incorporated into analysis of series of SAP measurements over time. Therefore, without taking into account these statistical properties, detection of change in retinal function with current methods is often delayed, or requires more clinic visits than should be necessary.[25]

Figure 1. Visual field measured by standard automated perimetry (SAP). (a) Contrast stimulus from SAP is projected on different locations of retina. The response from subject is captured when the stimulus is perceived. (b) SAP assesses differential light sensitivity (DLS) of the retina and corresponding visual pathway. (c) DLSs are measured at various locations (dots) on the retina. The point (0°,0°) indicates central vision that corresponds to the fovea on the retina. Optic nerve head is the anatomical blind spot. The test locations are not only correlated to their neighbours but also by the optic nerve fibres (some of which are shown as blue curves) passing through them. The whole visual field can be divided into superior and inferior hemifields on vertical and nasal and temporal regions on horizontal. (d) The DLS at a location on the retina is derived at the 50% probability of the visual system responding to a contrast stimulus and is related to the biological response to light of relay neurones in the visual pathway. (e) The DLS is measured in log scale, which in Humphrey Field Analyzer (Carl Zeiss Meditec Inc, Dublin, CA, USA) is calculated as dB = 10 log10(10000/(4 × 31.6)) where 4 is the luminance of the stimulus in apostilbs and 31.6 apostilbs is the background luminance. The DLS ranges between 0 dB (high contrast stimulus, blindness) and around 35 dB (low contrast stimulus, healthy) and is displayed as a conventional grayscale plot. Darker shading represents lower DLS. (f) Measurements of DLS over time form a complex spatial-temporal time series.

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Datasets

Two datasets collected at different centres were used in this study. The first dataset was sampled from 402,357 visual fields of 75,857 patients from electronic health records of glaucoma clinics at Moorfields Eye Hospital in London. DLS deteriorates as a result of ageing, and typically do not increase in response to standard medical treatments for glaucoma. Thus, all series in the dataset should be worsening at a rate at least equal to age-related decline. When positive rates are observed, in the case of glaucoma, this is usually due to ‘learning effects’ (patients learn to perform the visual field test) or the inherent variability of the measurement. Therefore, the first visual field of each series was discarded to reduce the impact of ‘learning effects’. If multiple visual fields were taken on the same day, the last measurement was chosen. Only series that were obtained over 6 years and contained at least 7 visual fields were included in the study. Note that the length of series is purely for evaluation purposes and is not necessitated by the proposed model. All series meeting the above criteria were selected for this study and the resulting dataset consisted of 47,483 visual field tests from 6,011 series from 6,011 eyes, representing about 2.5 million individual DLS measurements. The median (interquartile range [IQR]) time of follow up was 9.3 (7.9, 10.4) years and the median (IQR) number of visual fields in each time series was 9 (8, 11). The median (IQR) interval between visual fields was 1.0 (0.6, 1.4) years.

The second dataset was from a study examining the ‘test-retest’ variability of SAP conducted at Dalhousie University, Halifax, Canada in a cohort of glaucoma patients. Changes in retinal function are slow in glaucoma. By taking repeat measurements in a short period of time, it is possible to estimate measurement test variability, under the assumption that no measurable deterioration can occur over the observation period.[20] One eye of 30 patients was tested 12 times over a short period (maximum 8 weeks), during which no measurable deterioration may happen. The variance among visual fields in these repeat measures indicates the inherent measurement variability. Furthermore, each of these visual field series, and the same series with arbitrary reordering, represents a ‘stable’ series with no underlying deterioration. The use of randomly reordered series for estimates of measurement variability is an established method used in various studies.[28,29]

Materials and Methods

Ethics statement

Patients’ data was anonymised prior to investigation and did not contain personal or sensitive information. It was held in a secure database held at City University London. As such patients’ written consent for their data to be used in the study was not required. The study adhered to the tenets of the Declaration of Helsinki and was approved by the research governance committee of City University London, United Kingdom. The anonymised dataset can be accessed upon request.

Computational model

Modelling measurement variability with a mixture of Weibull distributions. The variability of individual DLS measurements can be estimated by repeating visual field tests in a short period of time.[20] The test-retest dataset consisting of 1980 (300 × 2, i.e. 30 multiplied by 12-choose-2 combinations) pairs of repeated visual field tests was used to estimate the retest distributions for DLS measurements ranging from 0 dB to 35 dB. Retest distributions are generally bimodal, truncated and skewed; the shape of the distribution varies dramatically across the range of DLS measurements due to the non-stationary variability and the censored nature of the DLS measurement.[22] As the retest distribution could not be sufficiently described by a single parametric probability density function, at each integer level of DLS, it was modelled as a mixture of Weibull distributions. The Weibull distribution was chosen due to its versatility and relative simplicity. In comparison with commonly used Gaussian distribution, it is a more proper option for modelling probability distribution of non-negative variables like DLS. Its probability density function is defined by two parameters, x and β:

\[
weibull(x|\alpha, \beta) = \begin{cases} \frac{2}{\beta} \left( \frac{x}{\beta} \right)^{x-1} e^{- \left( \frac{x}{\beta} \right)^x} & x \geq 0 \\ 0 & x < 0 \end{cases} \quad (1)
\]

For K Weibull mixture components and N retest data points \( \{x_n\}_{k=1}^N \), a latent K-dimensional binary vector variable \( z \) defines to which mixture component the data point, \( x_n \), belongs. The kth element \( z_{nk} = 1 \) if \( x_n \) belongs to the kth component, otherwise \( z_{nk} = 0 \). With the prior probability,

\[
p(z_{nk} = 1) = \pi_k \quad (2)
\]

the complete likelihood of observed and latent variables becomes:

\[
p(x, Z|\pi, \alpha, \beta) = \prod_{n=1}^{N} \prod_{k=1}^{K} (\pi_k \text{weibull}(x_n|\alpha_k, \beta_k))^{z_{nk}} \quad (3)
\]

where \( \pi = \{\pi_k\}_{k=1}^{K} \) with \( \pi_k \) being the prior probability that \( x_n \) belongs to the kth mixture component so \( \sum_k \pi_k = 1 \). \( x = \{x_n\}_{n=1}^N \), \( Z = \{z_{nk}\}_{n=1}^N \), \( \alpha_k, \beta_k \) are the parameters defining the kth Weibull mixture component. Marginalising (3) over \( Z \) gives the likelihood of Weibull mixture distribution:
The maximisation of (4) does not give closed solution for parameters \( \pi, \alpha \) and \( \beta \). Therefore, an expectation-maximisation algorithm [30] was derived to iteratively optimise (4). The detailed model derivation is given in Appendix S1. Moreover, to select the number of mixture components, \( K \) was increased from 1 until the logarithm of likelihood in (4) no longer increases with statistical significance (p<1%) in cross validations.

Further, since the log Weibull distribution for the minimum DLS in visual field testing, 0 dB, is undefined, a DLS \( v \) was transformed to \( s(v) \) such that:

\[
s(v) = \begin{cases} 
  v & \text{if } v \geq 1 \\
  \exp(v-1) & \text{if } v < 1
\end{cases}
\]  

Note that \( s(v) \) is its itself except when \( v < 1 \) and the lower bound for \( s(v) \) is 0 dB. This transformation guarantees that the transformed DLS \( s(v) \) is continuous and has a first derivative, which is an important property for the optimisation of the regression model described in the next section.

For notational simplicity, the derived retest distribution (4) for DLS \( y \) will hereafter be denoted as \( R_y(\cdot) \).

**Analysis with non-stationary Weibull error regression and spatial enhancement (ANSWERS).** We propose a method to monitor change in measurement series, named ANSWERS. The proposed model is based on the mixture of Weibull retest distributions outlined above, and incorporates spatial correlation within the data.

Given \( Q \) visual field measurements (each with \( M \) test locations) in a time series at time \( t_i \), let \( y_{ij} \) represents a measurement at time \( t_i \) and location \( j \). To formulate the regression model in a compact notation, let \( y = \{y_{ij}\}_{j=1}^{M}, y = \{y_{ij}\}_{j=1}^{Q}, \) a column vector \( t_i = [t_i, 1]^T \) and \( t = \{t_i\}_{i=1}^{Q} \).

The regression model is defined by weight vectors \( \{w_j\}_{j=0}^{M} \) for each of the \( M \) test locations in the measurement. Each weight vector \( w_j \) contains a slope and intercept for the \( j \)th location regressed over time in the case of a linear model. For simplicity of notation, \( W = \{w_j\}_{j=0}^{M} \) was used to refer to collection of all weight vectors. The likelihood for all visual field measurements in the time series \( Y \) becomes:

\[
p(Y|W,t) = \prod_{i=1}^{Q} p(y_i|W,t_i) \\
= \prod_{i=1}^{Q} \prod_{j=1}^{M} R_{y_j}(s(y_i^t)w_j^t)
\]  

where \( R_{y_j}(\cdot) \) and \( s(\cdot) \) were defined in (4) and (5) respectively. Note that \( p(Y|W,t) \) can be factorised into the product of \( p(y_i|W,i) \) for \( i \) from 1 to \( Q \) because \( y_i \) is conditionally independent of other measurements in the series given \( W \).

To incorporate the spatial correlation among different locations in the measurement, prior distributions of slope and intercepts were defined to be multivariate normal distributions:

\[
p(w_a) = N(w_a|m_a,a\Sigma) \text{and} \\
p(w_b) = N(w_b|m_b,b\Sigma)
\]  

where \( w_a \) and \( w_b \) are the slopes and intercepts of the regression lines respectively, \( m_a \) and \( m_b \) are the means of respective normal distributions and \( \Sigma \) is the covariance matrix scaled by \( a \) and \( b \).

The unscaled covariance matrix \( \Sigma \) encodes the spatial correlation among test locations in the measurement. The element \( \Sigma_{pq} \) on the \( p \)th row and \( q \)th column represents the strength of correlation between points \( p \) and \( q \) in the visual field. For visual field DLS measurements investigated in this study, \( \Sigma_{pq} \) was defined as:

\[
\Sigma_{pq} = \begin{cases} 
  \exp\left(-\frac{1}{2}\frac{dist_{pq}^2}{\delta^2_{a}} + \frac{2}{\delta_{b}^2}\right) & \text{if } p \text{ and } q \text{ are in the same hemifield} \\
  0 & \text{otherwise}
\end{cases}
\]  

where \( dist_{pq} \) is the Euclidean distance between the points \( p \) and \( q \) in the visual field, and \( \delta_{a} = 6^\circ \) and \( \delta_{b} = 14^\circ \). Specifically, \( \delta_{a} = 6^\circ \) is the distance between two neighbouring points in the visual field and \( \delta_{b} = 14^\circ \) is the reported 95% confidence interval of population variability in the nerve fibre entrance angle into the optic nerve head.[23] Note that \( \Sigma_{pq} = 0 \) if the two points lie on different hemifields (upper or lower; Figure 1c) of the visual field due to the physiological distribution of optic nerve fibres,[23] The unscaled covariance \( \Sigma \) between each location in the visual field and all other points is illustrated in Figure 2. ANSWERS, in this study, has been specifically adapted to detect deterioration in glaucoma, so the spatial correlation \( \Sigma \) here encodes the anatomy of optic nerve fibres. To adapt ANSWERS for other types of measurement corresponding to different diseases or conditions, \( \Sigma \) should be adjusted to reflect the characteristics of the spatial correlation present in that data.

The values for the scale parameters \( a \) and \( b \) were chosen to produce non-informative priors for \( w_a \) and \( w_b \). To be exact, the slope prior was set as \( \delta_{a} = 60^\circ \) corresponding to a slope standard deviation of 10 dB/year. The intercept prior was set such that \( m_a = 0(0dB/year) \) with \( \delta_{b} = 10^\circ \) corresponding to an intercept standard deviation of 10 dB.

According to (6) and (7), the log of posterior probability of \( W \) can be derived as:

\[\text{Detecting Changes in Retinal Function: ANSWERS}\]
\[
\ln p(W|Y,t) = \ln \sum_{i=1}^{W} \sum_{j=1}^{M} R_{ij} \left( s\left( w_i^T t_j \right) \right) \\
- \frac{1}{2} (w_a - m_a)^T \Sigma_a (w_a - m_a)^T \\
- \frac{1}{2} (w_b - m_b)^T \Sigma_b (w_b - m_b)^T + const
\]  

(9)

where \( \Sigma_a^{-1} = \sigma^2 \Sigma \), \( \Sigma_b^{-1} = \delta \Sigma \). The terms independent of \( W \) are grouped into the constant term, \( const \).

The posterior probability (9) cannot be recognised as a known distribution because (7) is not the conjugate prior of the mixture of Weibull distributions. Although the log posterior (9) can still be maximised with regard to \( W \), it is difficult to estimate the exact variance of \( W \) without knowing the underlying distribution. Therefore, a Laplace approximation [31,32] was used to approximate \( p(W|Y,t) \) as a normal distribution centred at the mode of \( W \), as described in Appendix S1. The estimates of the slope and intercept in the Laplace method exactly match the local maximum of log posterior probability (9). However, the variance of these slopes and intercepts are approximate estimates.

For the purpose of evaluating the effects of spatial correlation, its contribution can be ‘switched off’ by setting the off-diagonal elements of \( \Sigma \) in (7) to be 0. This model without spatial enhancement is denoted as \( ANSWERS \).

\( ANSWERS \) indices: identification of change. \( ANSWERS \) estimates the slope \( w_a \) and intercept \( w_b \) with their variance approximated by the Laplace method. The distribution of the slope is of particular clinical importance because it represents the rate and certainty of change. The ‘change’ applies equally to deterioration (negative change) and improvement (positive change) in measurements. In the case of a progressive condition, such as glaucoma, the slope distribution at each location can be summarised as the ‘probability of no-deterioration’, which is quantified as the cumulative distribution of slope \( \geq 0 \, dB/year\).

The ‘probability of no-deterioration’ value will be referred to as \( P_{nd} \) hereafter. The \( P_{nd} \) value ranges between 0 and 1 where a lower value indicates a higher probability of deterioration.

In order to summarise the possibility of deterioration across all \( M \) test locations in the visual field series, a global index, the \( ANSWERS \) deterioration index \( I^\neg \), is defined as:
\[ I^- = - \sum_{j=1}^{M} \ln P_{nd_j} \]  

where \( P_{nd_j} \) is the \( P_{nd} \) value at the \( j \)th location in the measurement. \( I^- \) is the negative logarithm of the product of all \( P_{nd} \) values, thus, non-negative and larger value implies greater certainty about deterioration in the measurement series. Similarly, to evaluate the improvement in a measurement series, such as in the case of gene therapy for retinal disease,[3] the ANSWERS improvement index \( I^+ \) can be derived as \( I^+ = - \sum_{j=1}^{M} \ln (1 - P_{nd_j}) \). However, because this study illustrates the application on identifying deterioration in retinal function in glaucoma, the ANSWERS index will henceforth only refer to \( I^- \).

Evaluation

To evaluate the utility of ANSWERS in detecting retinal function change, it is necessary to compare it to other change detection methods currently used in clinical decision making. Point-wise linear regression, the most widely used method, fits an ordinary linear regression model to a time series of measurements for each location in the visual field and assesses the significance and slope of the fit. Summary measures, such as the mean deviation from the average DLS of healthy eyes, are also utilised, but since glaucoma tends not to affect all locations to the same extent, global indices often have inadequate statistical sensitivity to detect worsening when compared with methods assessing deterioration at individual locations.[14–17] Moreover, to evaluate the benefit of taking into account non-stationary variability and spatial correlation respectively, ANSWERS without spatial enhancement (ANSWER) was also evaluated. Thus, ANSWERS was compared with three other methods: ordinary linear regression of mean deviation, point-wise linear regression and ANSWER.

Estimation of false positive rates. A false positive is a type I error where change is falsely detected in a series with no true deterioration. The false positive rate can be reliably estimated in a series of repeated measurements acquired in a period of time too short for measureable deterioration. Moreover, randomly reordering these repeated measurements produces pseudo-series where there is also no true deterioration.

The series of 12 visual fields from 30 eyes in the test-retest dataset were randomly reordered 300 times, so 90,000 pseudo-series of length between 3 and 12 were generated. It was assumed that one visual field measurement per year was taken in these pseudo series (the median test frequency in the Moorfields dataset). The false positive rate was then estimated as the proportion of series identified as deteriorating. In a clinical situation, false positives may lead to overtreatment and unnecessary cost, so methods with high false positive rates are generally considered as not clinically useful.

Different methods should be compared at equivalent false positive rates, which is dependent on the chosen change criterion and the length of the series. For ordinary linear regression of mean deviation, deterioration criteria were a negative slope and \( p \)-value lower than a set threshold. For point-wise linear regression, deterioration criteria for each test location were a negative slope and a \( p \)-value <= 1% and the visual field was worsening when at least \( n = 1, 2, 3 \) and 4 contiguous points were deteriorating. For ANSWERS and ANSWER, the criterion for deterioration was a \( I^- \) value higher than a given threshold. For each method, a set of thresholds was chosen to achieve specified false positive rates, and the performance of each method was then compared at equivalent false positive rates.

Time to detect change. The time to detect deterioration was compared between methods using the dataset from electronic health records at Moorfields Eye Hospital. In each visual field series, a subseries containing the first three visual fields was considered as the minimum series length required to detect change. The length of the subseries was then increased by incrementally adding visual fields to the subseries in chronological order. The shortest series that was flagged as deteriorating was then recorded for each method. If no deterioration was detected in any subseries of a visual field series by a method, the time was recorded as the total time span of the series. The comparison among different methods was carried out at equal false positive rates.

Hit rate of change detection. Statistical sensitivity is the measure of a method’s ability to identify true change. Ideally, the sensitivity should be evaluated as the proportion of detected change in the visual field series with true underlying deterioration. However, due to the lack of a ‘gold-standard’ and ‘ground-truth’ classification for glaucomatous deterioration,[33] the underlying worsening status of each visual field series was unknown. Therefore, the methods were compared using the ‘hit rate’, which is the proportion of series flagged as deteriorating in the Moorfields dataset. Given an unknown proportion \( p \) of truly worsening series in the dataset, the hit rate is linked to statistical sensitivity as: hit rate = \( \frac{\text{false positive rate}}{\text{true positive rate} + \text{false positive rate}} \). Note that if the false positive rate is controlled to be equivalent for all methods, a higher hit rate implies better sensitivity of a method. Therefore, hit rates of all methods were compared as a surrogate comparison for sensitivity.

Results

ANSWER was implemented in MATLAB R2013a (MathWorks Inc., Natick, MA). Analysis of a series with 10 visual fields took approximately 1.5 seconds on a 2.50 GHz Intel i7 processor. The software is freely available from the authors.

Mixture of Weibull retest distributions

At all levels of DLS, increasing the number of Weibull mixture components to be more than 2 does not significantly increase the log likelihood (4) in cross validations. Therefore, two mixture components were used to model retest distribution for sensitivities between 0 dB and 35 dB. The histograms and the derived probability density functions of the Weibull mixture at different DLSs are shown in Figure 3. Despite the non-stationary variability, each distribution can be sufficiently described by a combination of two Weibull distributions.

The examples in Figure 4 demonstrate the effect of the Weibull mixture retest distribution used by ANSWER in comparison to ordinary linear regression in series of DLSs at a single visual field location. Because only a single visual field location was considered for illustrative purposes, there is no spatial enhancement in these examples. In Figure 4a, the last measurement in the series changes suddenly due to measurement variability leading to a steep slope using ordinary linear regression. By comparison, ANSWER is less affected by the last measurement since it accounts for the large variability associated with measurements at this level of DLS, and results in a shallower slope. This property of ANSWER makes it robust to the non-stationary variability of DLS measurements and, therefore, a more reliable estimator of change rate.
Time to detect change

Despite the robustness of ANSWER, it does not compromise sensitivity to detect deterioration. In fact, by taking into account the non-stationary variability of DLS measurements, the method is able to detect significant deterioration in short time series where conventional methods cannot reach statistical significance. In Figure 4b, ordinary linear regression did not indicate significant deterioration ($p$-value $>0.05$), while ANSWER managed to ascertain with high certainty that deterioration was occurring ($P_{nd}<0.01$). This property allows ANSWER to provide better time efficiency in detecting deterioration.

Figure 5 shows the average time to first detect deterioration in the visual field series with each method at false positive rates between 0 and 15% (methods with a higher false positive rate are not clinically useful). For each method, the time to detection change was compared at the 5% false positive rate, or at the closest rate to 5% for point-wise linear regression (two contiguous points, false positive rate of 5.3%). At this false positive rate, ANSWER detected deterioration faster than point-wise linear regression ($p<0.01$ paired t-test) and linear regression of mean deviation ($p<0.01$ paired t-test). Furthermore, with spatial enhancement, ANSWERS was able to detect deterioration significantly faster than ANSWER ($p<0.01$ paired t-test). On average, ANSWERS detected deterioration 2.42 (95% confidence interval [2.35, 2.49]) years ahead of point-wise

![Figure 3. Histograms of retest differential light sensitivities at levels between 0 dB and 35 dB. The derived probability density function of the Weibull mixture is superimposed in red.](doi:10.1371/journal.pone.0085654.g003)
linear regression, 2.28 (95% confidence interval [2.20, 2.35]) years before linear regression of mean deviation, and 0.27 (95% confidence interval [0.22, 0.31]) years before ANSWER.

The hit rates of the four methods were estimated with various series lengths and at false positive rates between 0 and 15% using Moorfields dataset. Figure 6 demonstrates the hit rate with series lengths of 5, 7, 9 and 11. Only the hit rates at specified false positive rates between 0 and 15% are displayed (methods with a higher false positive rate are not clinically useful). The areas under the partial hit rate curves for different methods (Figure 6) were compared in Table 1. Because the total area with false positive rate between 0 and 15% is 0.15, the areas under the partial hit rate curves were normalised by being divided by 0.15. Because the hit rate of point-wise linear regression could not be estimated with a continuous false positive rate, the area under the partial hit rate curve was not estimated.

The methods were also compared at the 5% false positive rate, or at the closest rate to 5% for point-wise linear regression (two contiguous points criterion). The ratios of hit rates between pairs of methods are shown in Table 2 where a ratio >1 indicates a better hit rate. For instance, with series of 7 visual fields, the ratio of ANSWER against linear regression of mean deviation was 1.9, indicating that the hit rate of ANSWER is nearly twice that of the latter method.

The hit rates of ANSWER and ANSWERS were higher than linear regression of mean deviation and point-wise linear regression of DLS at all series lengths. There was particular improvement in short series. This explains the better efficiency of ANSWER and ANSWERS to detect deterioration more quickly.

The spatial enhancement included in ANSWERS also increased the hit rate compared with ANSWER, especially with short series. However, this improvement became marginal as the length of series increased.

Case studies with ANSWERS in comparison with other methods are provided in Appendix S2.


**Discussion**

**ANSWERS** detected change in retinal function more rapidly than conventional statistical approaches without compromising false positive rates. At equivalent false positive rates, it also detected a greater number of eyes with change in retinal function when compared to the number detected by other widely used methods. The Weibull mixture retest distributions, in comparison to a normally distributed error assumed in ordinary regression models, allows **ANSWERS** to attain a high certainty about deterioration status (Figure 4b). In addition, the spatial enhancement aggregates information for adjacent locations in the visual field to ‘confirm’ the spatial deterioration pattern, further improving the method especially for short time series. This spatial element of detecting change in visual fields has rarely been considered before.[34–37] **ANSWERS** could not only aid clinical decision for prompt treatment intervention, but also define more efficient endpoints for clinical trials in eye-related research.[3]

The application and usefulness of **ANSWERS** in short series is of particular clinical interest. Current widely used methods typified by ordinary linear regression for change detection are limited in short series because they can hardly reach required statistical significance. In clinical situations, where follow-up testing is infrequent, often due to limited resources, these standard analyses may delay the detection of change in retinal function. In turn this can delay required intensification of treatment. In clinical trials, failing to pick up change in time could also lengthen the trials.

When choosing thresholds for **ANSWERS** to detect deterioration in visual field series, it is critical to consider the false positive rate for the chosen threshold of $I^-$. In this study, the threshold was estimated from the test-retest dataset at given false positive rates and for each visual field series length. However, an analytical prescription can be described theoretically and is made available in Appendix S1. Note that $I^-$ threshold does not change with series length given a constant false positive rate.

The *Laplace* method used in **ANSWERS** provides local normal approximation at the mode of the posterior slope and intercept distribution (9), so estimations of variance of these regression parameters may not capture every feature of the distribution (skewness for example). Although the true posterior distribution (9) is unknown, the estimated slope variance from the *Laplace* approximation was nonetheless demonstrated to be an effective variable in detecting change and quantifying the certainty about change relative to other current methods.

**ANSWERS** was developed with the idea that it could be adapted for other applications with similar statistical properties which are not uncommon among other medical and biological measurements. For example, serum creatinine measurement for predicting

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**Table 1.** The normalised areas under partial hit rate curves for **ANSWER**, **ANSWERS**, linear regression of mean deviation (MD).

<table>
<thead>
<tr>
<th>Series length = 5</th>
<th>Series length = 7</th>
<th>Series length = 9</th>
<th>Series length = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANSWER</strong></td>
<td>0.39</td>
<td>0.48</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>ANSWERS</strong></td>
<td>0.41</td>
<td>0.49</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>MD</strong></td>
<td>0.20</td>
<td>0.29</td>
<td>0.35</td>
</tr>
</tbody>
</table>

The comparison was carried out with series lengths of 5, 7, 9 and 11. doi:10.1371/journal.pone.0085654.t001
detecting retinal function both in terms of statistical sensitivity and in time taken to detect change. ANSWERS was shown to outperform conventional methods of detecting retinal function deterioration both in terms of statistical sensitivity, and in time taken to detect change. ANSWERS was demonstrated to detect visual field deterioration caused by glaucoma, but there is plenty of scope for its use in other measurements subject to non-stationary variability and spatial correlation.

**Supporting Information**

Appendix S1 Detailed mathematical derivation. Expectation-maximisation algorithm for Weibull mixture distribution, Laplace approximation for ANSWERS and an analytical model for calculating ANSWERS threshold given false positive rates and series lengths. (PDF)

Appendix S2 Examples illustrating ANSWERS in comparison with other methods under study. (PDF)

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**Author Contributions**

Conceived and designed the experiments: HZ DGH DC RR. Performed the experiments: HZ LS SC DGH. Analyzed the data: HZ RR LS SC DC. Wrote the paper: HZ RR LS SC DGH DC.

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Detecting Changes in Retinal Function: ANSWERS