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Glaucoma Identification on Fundus Retinal Images Using Statistical Modelling Approach

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Abstract. Glaucoma is an eye disease characterized by progressive deterioration of the optic nerve head and a broad view that can cause blindness. The Population Based Survey in 2010 indicates that glaucoma was the second leading cause of blindness after cataracts, which was about 8% of 36 million sufferers of blindness worldwide. Symptoms of glaucoma that arise usually cannot be felt directly. So it is necessary to do an eye examination to find out glaucoma, one of which is to look at the size of the optic disk in the digital fundus photo. The previous studies about glaucoma identification were done by using mathematical computation approach that have still not satisfied. Therefore, in this study we propose a new method, i.e., statistical modelling approach to identify glaucoma. In statistical modelling, there are two approaches, i.e., parametrical approach, and non-parametrical approach based on penalized spline estimator. The result of classification accuracy by using parametrical and non-parametrical approaches are 73.3% and 93.33%, respectively. Based on the result, we conclude that non-parametrical approach has better outcome so that it can be used to identify glaucoma on fundus retinal image.

1. Introduction

Glaucoma is an eye disease characterized by progressive deterioration of the optic nerve head and a board view that can cause blindness [1]. The Population Based Survey in 2010 indicates that glaucoma was the second leading cause of blindness after cataracts, which was about 8% of 36 million sufferers of blindness worldwide [2]. According to World Health Organization in 2010, an estimated 3.2 million people experience blindness due to glaucoma [3]. On other data [4] mentioned that glaucoma infects 70 million people and will increase to 79.6 million by 2020. In contrast to cataract, blindness caused by glaucoma is permanent because the large pressure on the eyeball causes clogging of the arteries leading to the eye nerve so that the eye nerve does not get enough blood supply and will eventually experience damage. So, it is necessary to do an eye examination to find out glaucoma, one of which is to look at the size of the optic disk in the digital fundus photo [5]. To detect glaucoma, we look at the size of the optical disk in a digital fundus photo. But the results of identifying fundal photos manually can produce an incorrect diagnosis. To overcome these weakness, a system that is built by using computational models to change the pixel image of the retina is needed to become a characteristic of the retina so that it can help doctors determine medical actions quickly and precisely.

Studies related to the identification of glaucoma have been done by several researchers. Research by [6] used a mathematical calculation approach namely k-nearest neighbor method and got the result



with accuracy of 50%. The study by [7] used simulation process that produces 76% classification accuracy, and [5] used adaptive thresholding and support vector machine (SVM) that got the result with accuracy of 80%. Based on these researches that have been done, the most widely used method is mathematical computing method. Other studies such as [8] used statistical region merging method that produces 97.5% accuracy. Further, according to [9], classification accuracy of cyst and tumor can be improved up to 90.91% by using statistical modeling approach based on local polynomial.

The data used in this study are categorized into two categories namely glaucoma image $Y = 0$ and normal image $Y = 1$, so that the response variable follows the Bernoulli distribution. One of the statistical methods that can be used is binary logistic regression. Logistic regression is a statistical method that is used to describe relationship between response and predictor variables, and hypotheses testing of categorical response to one or more predictor variables uses logit link function [10]. In statistical modeling, there are two approaches, i.e., parametric approach by using Generalized Linear Model (GLM) and nonparametric approach by using Generalized Additive Model (GAM). In GAM, we use penalized spline algorithm to estimate its regression function to accommodate nonparametric additive regression models whose distribution of response variables is included in an exponential family [11] whereas Bernoulli distribution included in the exponential distribution family. Some researchers, for example [12 – 15] used GAM based on local polynomial modeling, kernel, and local linear for designing growth charts of children up to five years old, and [16 – 19] used spline estimator to estimate nonparametric regression models in various cases.

Mathematical computations approaches have been used by [5] and [6] to identify glaucoma, but these approaches gave still unsatisfied accuracy. Therefore, in this paper, we propose a new method by using statistical modeling approach to identify glaucoma on fundus retinal image. The statistical models with logit link function we would be used in this study are parametric model (GLM) and nonparametric model (GAM) approaches, and then we compare the accuracy identification between GLM and GAM approaches. In addition, to validate the accuracy identification of the best model, we use Press's Q statistical testing.

2. Data and Research Method

The data used in this research are 30 retinal fundus images which are divided into 15 normal retinal images and 15 glaucoma images. The steps in this research are image processing, reducing dimension, and identify glaucoma using GLM and GAM approaches.

2.1. Image Processing

The purpose of image processing is to improve the image quality for the retrieval of existing information in the image that can be processed to the next stage. Stages of image processing in this study are firstly reading process of fundus retinal image data file, secondly histogram equalization process, thirdly thresholding segmentation, and finally image resizing process. Results of image processing are shown in Figure 1.

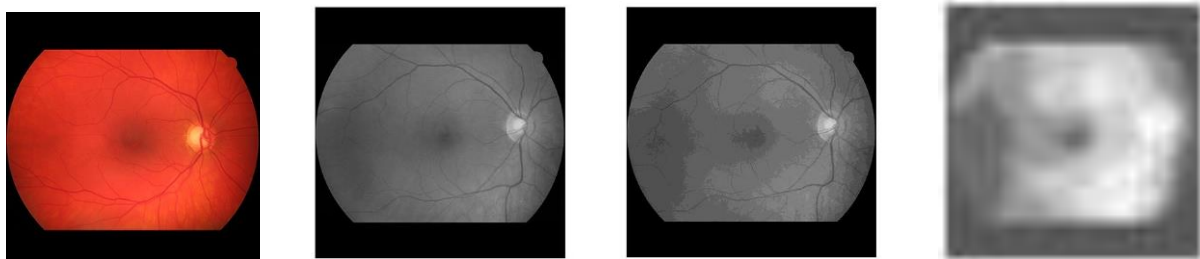


Figure 1 Glaucoma Image - Histogram – Thresholding – Resizing Image

Result of resizing size image is considered as columns and rows of matrix that are represent predictors and observations.

2.2. Reducing Dimension Using Discrete Wavelet Transform (DWT) and Principal Component Analysis (PCA)

Retinal images obtained from a doctor's examination have a very large size for each image. This can cause difficulties in calculating data. Therefore, dimensional reduction is needed until smaller dimension is obtained. Dimension reducing method used in this study is DWT which is one method that provides result close to the origin variable and can overcome high dimension of data. However, the reduction result with DWT still allows multi-collinear in modelling because there is no mathematical guarantee that the correlation between coefficients is relatively small. Then, another method namely PCA is needed to overcome multi-collinear between these variables because it produces new variables that are mutually independent.

The steps for reducing dimension are as follows:

- a. define a matrix sized $n \times q$ where $q = 2^M$ and M is a positive integer;
- b. calculate $W_{(q \times q)}$ where the matrix W is an orthogonal wavelet matrix;
- c. determine the matrix of the wavelet coefficient D by transforming W ;
- d. determine m with $m < n$ so that it gets $D^*_{(n \times m)} = X_{(n \times q)} W^T_{(q \times m)}$ by giving the value 0 in the column $m + 1$ to q ;
- e. calculate the correlation matrix of $D^*_{(n \times m)}$ to find out the colinearity;
- f. determine the variable Z from the standardization of D^* variable;
- g. determine the covariance matrix $Z^T Z$;
- h. determine the eigen value through the equation $|Z^T Z - \lambda I| = 0$;
- i. determine the value of the v_j eigenvector of each eigenvalue λ_j ;
- j. determine the main component w_j through the eigen value selection procedure, $w_j = v_{1j}Z_1 + v_{2j}Z_2 + \dots + v_{mj}Z_m$;
- k. determine the number of selected main components (k) based on described variance presentation value which closes to 100%.

In this study, by image processing, the data that contains 1024 predictor variables is reduced to 4 predictors.

2.3. Identify Glaucoma by Using GLM and GAM Approaches

To identify the data, we conduct the following steps:

1. Identify glaucoma from the result of dimension reduction data by using parametric logistic regression approach based on these following steps:
 - a. estimate binary logistic regression with logit link function;
 - b. estimate probability value on each observation with formula $\pi_i = \frac{\exp(X_i \beta)}{1 + \exp(X_i \beta)}$;
 - c. classify π_i value based on cut off probability value of 0.5;
 - d. estimate the accuracy classification based on apparent error rate (*APPER*).
2. Identify glaucoma from the result of dimension reduction data by using nonparametric logistic regression approach by creating R code based on these following steps:
 - a. estimation of f_i for each predictor with the following steps:
 - i. determine the order of the polynomial, number of knots, and the smoothing parameters (λ) based on the minimum GCV value;
 - ii. define the X_j matrix by entering the optimal polynomial order and knots point;
 - iii. define the estimation value of $\hat{\beta}_j$ by entering the optimal smoothing parameter value;
 - iv. calculate the $\hat{f}_j(X_j) = X_j(X_j^T X_j + n\lambda_j D_j)^{-1} X_j^T Y$.
 - b. iteration of local scoring and back-fitting algorithms to obtain an additive model based on the penalized spline estimator with the following steps:
 - i. define both response and predictor variables;
 - ii. determine the initial value to be used in the iteration to 0 ($h = 0$);

- iii. determine local scoring for $(h = 0, 1, 2, \dots)$ with the following steps:
 - (1) determine the partial residual $R_j^{(h+1)} = z - \sum_{s=1}^{j-1} f_s^{(h)}(X_s) - \sum_{s=j+1}^p f_s^{(h)}(X_s)$;
 - (2) determine the smoothing function $f_j^{(h+1)} = H(\lambda_j)R_j^{(h+1)}$;
 - (3) determine the RSS value $RSS^{(h+1)} = \frac{1}{n}\{(y - \hat{\mu})^T(y - \hat{\mu})\}$;
 - (4) iterates steps (1) to (3) to obtain RSS that meets convergent criteria $|RSS^{(h+1)} - RSS^{(h)}| < \varepsilon$;
 - (5) determine vector adjusted dependent variable $z_i^{(h+1)}$, $\mu_i^{(h+1)}$, and $\eta_i^{(h+1)}$;
 - (6) determine the $W_i^{(h+1)}$ matrix;
 - (7) calculate $avg(Dev) = \frac{1}{n}\{(y_i - \mu_i)^T W_i(y_i - \mu_i)\}$;
 - (8) iterates steps (1) to (7) to obtain $avg(Dev)$ that meets the convergent criteria $|avg(Dev)^{(h+1)} - avg(Dev)^{(h)}| < \varepsilon$.
- c. analyze the results of classification accuracy with the following steps:
 - i. determine the cut off probability value as the dividing boundary between categories 0 and 1 in classifying objects;
 - ii. estimate y of each fundus image data;
 - iii. get the best cut off probability value;
 - iv. calculate the APPER value with formula $APPER = \frac{n_{12} + n_{21}}{n_{11} + n_{12} + n_{21} + n_{22}} \times 100\%$;
 - v. calculate $classification\ accuracy = 100 - APPER$;
 - vi. calculate $Press'Q = \frac{[N - (nK)]^2}{N(K-1)}$ and compare it with Chi-square value with degree of freedom 1.

3. Result and Analysis

From 30 observations, we reduce dimensions by using DWT and PCA such that produces 4 predictor variables of 1024 predictors which later will be modelled to determine the identification of glaucoma in the image.

At first we determine identification glaucoma by using parametric logistic regression model approach with logit link function. In this step, we estimate parameters, do significant testing simultaneously and individually, and calculate identification accuracy for each observation. The estimating of parameters results is given in Table 1.

Predictor	Coeff	SE Coeff	Z	P
Constant	0.115	0.551	0.21	0.835
X1	0.504	3.506	0.14	0.886
X2	168.670	83.760	2.01	0.044
X3	102.455	57.793	1.77	0.076
X4	203.080	92.206	2.20	0.028

In this study, we estimate the probability value π_i of each observation. For example, on the 16th observation by definition glaucoma image ($Y = 0$) we have the estimated probability as follows :

$$\pi_{16} = \frac{e^{(0.115+0.504(0.0294430)+168.670(-0.0128832)+102.455(-0.0195287)+203.080(-0.0110351))}}{1 + e^{(0.115+0.504(0.0294430)+168.670(-0.0128832)+102.455(-0.0195287)+203.080(-0.0110351))}} = 0.00186$$

The estimated of π_{16} is less than 0.5, so that it is identified as glaucoma image ($Y = 0$).

The next step is to determine the probability value at each observation by using the nonparametric regression model approach based on penalized spline estimator. We obtain optimal lambda for each predictor as given in Table 2.

Table 2 Optimal Lambda Value for Each Predictor Variable

No	Predictor Variable	Order	Total Knot	Knot Point	Minimum GCV	Optimal Lambda
1	X1	2	1	-0.02891117	0.2614548	1910.5
2	X2	1	2	-0.005487012 -0.001135033	0.232447	0.1
3	X3	1	1	0.001482107	0.2676327	9999.9
4	X4	2	1	-0.001372446	0.2447572	9.2

Based on the result of local scoring algorithm iteration, the estimated parameter values are as follows:

$$\hat{\beta}_1 = [-3.281897 \quad -11.79296 \quad 110.197289 \quad -0.00000004707157]^T$$

$$\hat{\beta}_2 = [0.8645158 \quad 247.57681 \quad 63.9316688 \quad -49.1018714]^T$$

$$\hat{\beta}_3 = [0.4584386 \quad 122.4083 \quad -0.000000481857]^T$$

$$\hat{\beta}_4 = [0.4139543 \quad 293.5998284 \quad -0.3647153 \quad 1.8222798]^T$$

Therefore, the penalized spline estimators for the initial value of $\hat{f}_j(X_{ji})$ function for each predictor in each observation are as follows:

a. $\hat{f}_1(X_{1i}) = -3.281897 - 11.79296X_1 + 110.197289X_1^2 - 0.00000004707157(X_1 - (-0.02891117))^2_+$

It implies:

$$\hat{f}_1(X_{1i}) = \begin{cases} -3.281897 - 11.79296X_1 + 110.197289X_1^2 & ; X_1 < -0.02891117 \\ -3.281897 - 11.79296X_1 + 110.197289X_1^2 & ; X_1 \geq -0.02891117 \end{cases}$$

b. $\hat{f}_2(X_{2i}) = 0.8645158 + 247.57681X_2 + 63.9316688(X_2 - (-0.005487012))_+ - 49.1018714(X_2 - (-0.001135033))_+$

It implies:

$$\hat{f}_2(X_{2i}) = \begin{cases} 0.8645158 + 247.57681X_2 & ; X_2 < -0.005487012 \\ 1.21531 + 311.5084788X_2 & ; -0.005487012 \leq X_2 < -0.001135033 \\ 1.159577756 + 262.4066074X_2 & ; X_2 \geq -0.001135033 \end{cases}$$

c. $\hat{f}_3(X_{3i}) = 0.4584386 + 122.4083X_3 - 0.000000481857(X_3 - 0.001482101)_+$

It implies:

$$\hat{f}_3(X_{3i}) = \begin{cases} 0.4584386 + 122.4083X_3 & ; X_3 < 0.001482101 \\ 0.4584386 + 122.4083X_3 & ; X_3 \geq 0.001482101 \end{cases}$$

d. $\hat{f}_4(X_{4i}) = 0.4139543 + 293.5998284X_4 - 0.3647153X_4^2 + 1.82228(X_4 - (-0.001372446))^2_+$

It implies:

$$\hat{f}_4(X_{4i}) = \begin{cases} 0.4139543 + 293.5998284X_4 - 0.3647153X_4^2 & ; X_4 < -0.001372446 \\ 0.4139577325 + 293.60483179X_4 + 1.4575647X_4^2 & ; X_4 \geq -0.001372446 \end{cases}$$

Based on the optimal lambda values and the obtained order in Table 2, we determine the initial value $\hat{f}_j(X_{ji})$ for every predictor by using the penalized spline estimator. In this study, every observation has an initial value and the expected value. As an example, we discuss for the 17th observation only. The 17th observation by defining glaucoma image (Y=0) has initial values estimate as follows:

a. The first predictor variable at 17th observation equals to -0.08273. This value is included in criteria $X_1 < -0.02891117$, so the function used for $(X_{1,17})$ is

$$\begin{aligned} \hat{f}_1(X_{1,17}) &= -3.281897 - 11.79296X_1 + 110.197289X_1^2 \quad ; X_1 < -0.02891117 \text{ such that} \\ \hat{f}_1(X_{1,17}) &= -3.281897 - 11.79296(-0.08273) + 110.197289((-0.08273)^2) \\ &= -1.552 \end{aligned}$$

b. The second predictor variable at 17th observation equals to -0.00542. This value is included in criteria $-0.005487012 \leq X_2 < -0.001135033$, so the function used for $(X_{2,17})$ is

$$\begin{aligned}\hat{f}_2(X_{2,17}) &= 1.21531 + 311.5084788X_2, -0.005487012 \leq X_2 < -0.001135033 \text{ such that} \\ \hat{f}_2(X_{2,17}) &= 1.21531 + 311.5084788(-0.00542) \\ &= -0.473066\end{aligned}$$

- c. The third predictor variable at 17th observation equals to 0.001254. This value is included in criteria $X_3 < 0.001482101$, so the function used for $(X_{3,17})$ is

$$\begin{aligned}\hat{f}_3(X_{3,17}) &= 0.4584386 + 122.4083X_3; X_3 < 0.001482101 \text{ such that} \\ \hat{f}_3(X_{3,17}) &= 0.4584386 + 122.4083(0.001254) \\ &= 0.6119386\end{aligned}$$

- d. The fourth predictor variable at 17th observation equals to 0.004051. This value is included in criteria $X_4 \geq -0.001372446$, so the function used for $(X_{4,17})$ is

$$\begin{aligned}\hat{f}_4(X_{4,17}) &= 0.4139577325 + 293.60483179X_4 + 1.4575647X_4^2, X_4 \geq -0.001372446 \text{ such that} \\ \hat{f}_4(X_{4,17}) &= 0.4139577325 + 293.60483179(0.004051) + 1.4575647(0.004051)^2 \\ &= 1.603375\end{aligned}$$

Finally, we obtain the penalized spline estimator of 17th observation:

$$\begin{aligned}\eta_{17} &= \sum_{j=1}^4 \hat{f}_j(X_{j,17}) \\ &= \hat{f}_1(X_{1,17}) + \hat{f}_2(X_{2,17}) + \hat{f}_3(X_{3,17}) + \hat{f}_4(X_{4,17}) \\ &= -1.552 - 0.4730660 + 0.6119386 + 1.603375 \\ &= 0.1891998\end{aligned}$$

Next, by using nonparametric logistic regression approach we get the following estimated value:

$$\hat{\mu}_{17} = \frac{\exp(0.1891998)}{1 + \exp(0.1891998)} = 0.547$$

Next, we determine threshold value that is used as cut-off probability to identify glaucoma or normal images. Threshold and accuracy classification are given in Table 3 as follows:

Table 3 Threshold Values and Accuracy Classification

No	Threshold	Accuracy Classification	No	Threshold	Accuracy Classification
1	0.00	56.667	8	0.56	86.667
2	0.01	63.333	9	0.57	90.000
3	0.06	70.000	10	0.62	93.333
4	0.07	73.333	11	0.76	90.000
5	0.09	76.667	12	0.80	86.667
6	0.11	80.000	13	0.92	83.333
7	0.38	83.333	14	1	50.000

Threshold used as reference for cut-off probability of category 0 or category 1 is determined by selecting the highest classification accuracy value. If value $\hat{\mu}_i$ is greater than threshold value, then it will be classified as normal image, and vice versa. The classification result based on value $\hat{\mu}_i$ in the observations which have been analyzed by using parametric and nonparametric regression models approaches are given in Table 4.

Table 4 Classification Accuracy Using Parametric (left) and Nonparametric (right) Approaches

Observation	Prediction		Total	Observation	Prediction		Total
	Glaucoma	Normal			Glaucoma	Normal	
Glaucoma	11	4	15	Glaucoma	15	0	15
Normal	4	11	15	Normal	2	13	15
Total	15	15	30	Total	15	15	30

Next, we calculate the probability of errors by calculating APPER based on both parametric and nonparametric regression models approaches as follows:

$$APPER = \frac{4+4}{7+4+4+7} \times 100\% = 26.67\% \quad APPER = \frac{2+0}{15+0+2+13} \times 100 = 6.67\%$$

Based on APPER values, we obtain the classification accuracy values of glaucoma are 73.3% for parametric regression model approach and 93.3% for nonparametric regression model approach. It means that nonparametric regression model approach based on penalized spline estimator is better than parametric regression model approach with logit link function for determining classification accuracy value of glaucoma on fundus retinal image.

The last step, we validate the classification accuracy of nonparametric regression model approach by using Press'Q as follows:

$$Press'Q = \frac{(N - (nK))^2}{N(K - 1)} = \frac{(30 - ((28)(2)))^2}{30(2 - 1)} = 22.5333$$

The Press'Q is compared with $\chi^2_{(0.05,1)} = 3.841$. Because of the Press'Q = 22.5333 is greater than $\chi^2_{(0.05,1)} = 3.841$, so the nonparametric regression model approach based on penalized spline estimator is significantly appropriate for identifying glaucoma on fundus retinal images.

4. Conclusion

Identifying glaucoma on fundus retinal image by using nonparametric regression model approach based on penalized spline estimator is better than mathematical calculation approach namely k-nearest neighbour methods that were proposed by [6]. The use of penalized spline estimator can improve the classification accuracy of glaucoma on fundus retinal image from 50% to 93.3%.

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