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Nonparametric Shape Analysis Methods in Glaucoma Detection

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Abstract

A statistical method for glaucoma detection using tomographic images is discussed. It is known that the ONH (optic-nerve-head) area contains all the relevant information on glaucoma. Mean change of the angles of the tetrahedron determined by four control points, three on the neural rim and the other one corresponding to the maximum depth of the ONH is tested for significance. Apart from Hotelling's T^2-test, a nonparametric bootstrap and permutation method are used for statistical analysis, because the assumption of normality of the data set seems clearly violated. Moreover, a projection pursuit approach based on the sign test is applied as an alternative to these nonparametric procedures. The statistical analysis is done using data from Louisiana State University, Eye Center.

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1 Introduction

Glaucoma induces a change in the shape of the tetrahedron determined by the superior aspect of the retina (S), the normal aspect of the retina (N), the temporal in the optic nerve (T), and the deepest point in the optic nerve head (V). Glaucoma detection can be based on statistical tests for shape change. Most tests employed thus far apply techniques from shape analysis (see, for instance Bhattacharya and Patrangenaru (2003), Bhattacharya and Patrangenaru (2005), Bookstein (1991), Dryden and Mardia (1998), Goodall (1991), Kendall (1984), Kent (1992), Mardia and Patrangenaru (2005)). In a recent paper Bhattacharya (2008) uses all five landmarks in the glaucoma data and reaches the same conclusion as the present authors. In this paper we propose an alternative to those tests by directly analyzing the changes in the angles of the tetrahedron. The proposed alternative method will be applied in a study involving 12 rhesus monkeys with glaucoma induced in one eye and the other kept as the control. A tetrahedron has 12 angles, 5 of which are independent. Of the latter angles 2 are in the base triangle and of no relevance for the shape change we are interested in, which means that only 3 angles for each tetrahedron will be used. The data for the paired comparison methods to be used will consist of the 12 differences of the paired 3-dimensional "angle" vectors.

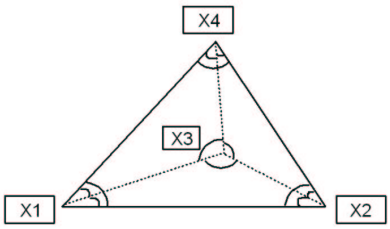
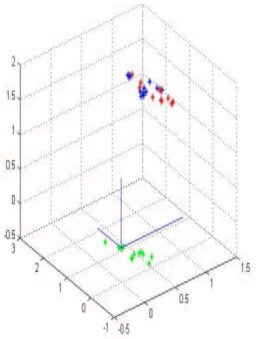


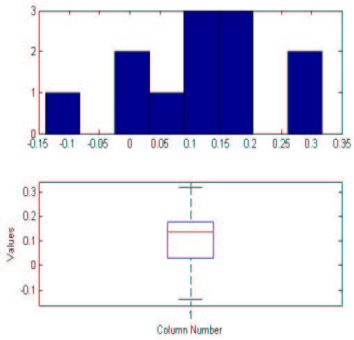
Figure 1: 12 angles of the tetrahedron

If we are willing to assume that these vectors of differences are i.i.d. and 3-dimensional normal, the hypothesis of "no change" , i.e. that the mean difference vector equals the zero vector, can be tested using Hotelling's T^2-statistic for the intrinsic mean of these multivariate circular data. The analysis of the data, using this standard procedure is briefly discussed in Section 2.

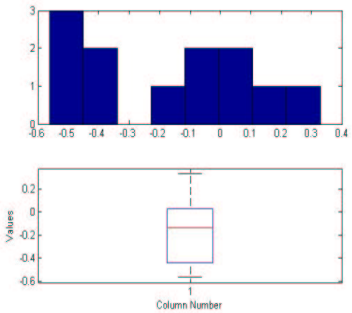
When deviations form these model assumptions are to be expected, one might resort to



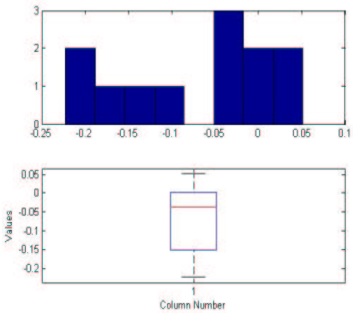
View of original angles and their differences



First coordinate of angle difference



Second coordinate of angle difference



Third coordinate of angle difference

Original data distribution

robust procedures. Since the data are differences of angles, heavy-tailed distributions will not occur, but skewness might be present. Also the differences may not all have the same distribution. Let us project the multivariate data on a line through the origin and compute the univariate student-statistics, with these projected data. Its well-known that Hotelling's statistic equals the maximum of the squares of these univariate student-statistics, when the maximum is taken over all directions. For a robust version of this test the student-statistic may be replaced with the sign-test-statistic for each direction. This collection of sign-test-statistics is a stochastic process, indexed by directions. Since the overall test statistic to be used here will not be the maximum of the squared process, but rather a squared integral norm, convergence in distribution of this process will be derived in a suitable Hilbert space. A general version of this simple but basic result is derived in Section 3.

In Section 4 we return to the analysis of the glaucoma data, exploiting the result of Section

3. In Section 4.1 the test used is based on the sum of squared sign-test-statistics over a finite number of directions. Since the direction of a possible shift is not known, the directions of the coordinate axes are included and some other directions are added for better power. In Section 4.2 the null hypothesis to be tested is modified. Rather than testing that the mean differences of the angles are exactly zero, we will test the hypothesis that their medians are approximately zero. The latter hypothesis is an instance of a neighborhood hypothesis. The idea of employing a neighborhood rather than a sharp hypothesis has already been explored in Hodges & Lehmann (1954). Recently there has been renewed interest in this type of hypothesis (Dette & Munk (1998)) that are practically relevant and usually leads to simpler asymptotics as well. Finally, Section 4.3 is devoted to a brief discussion in which in particular the results in Section 2 and Section 4 are compared.

2 The Analysis using Hotelling's Test Statistic

In Figure 1 the base triangle has two independent angles and each of the extra point creates three independent angles. All together there are 3(k-3) + 2 = 3k-7 independent angles. In our case k = 4 (see figure 5). So the dimension is reduced to 3(4)-7=5. Two of these angles are on the base triangle, thus the problem is locally reduced to a 3-dimensional multivariate circular data problem. We use the following notation for the angles considered: $G^1 = X_1X_2X_4$, $G^2 = X_1X_3X_4$, $G^3 = X_1X_4X_2$, and let G_1, G_2 be the value of (G^1, G^2, G^3) before and after inducing glaucoma. Given that the change $D = G_2 - G_1$, is small, the support of the distribution of $(exp(iD^1), exp(iD^2), exp(iD^3))$ on the torus $(S^1)^3$ is very concentrated, and we may use ordinary multivariate analysis for the vector D. The values of D are summerized in Table 1.

When we apply the Hotelling T^2 test for the data set assuming normality (Mardia *et al.* (1972))

$$H_0 : D = 0 \text{ vs. } H_1 : D \neq 0, \tag{2.1}$$

$$T^2 = \frac{(n-1)p}{n-p} F_{p,n-p}. \tag{2.2}$$

For our case $n = 12, p = 3$, $F_{cal} = 2.8798$ and the *p*-value = 0.0954. Therefore, we reject H_0 at the 0.1 level. However, Hotelling's T^2-test is based on the assumption of normality. If the assumption of normality is not acceptable, we need to look for other multivariate testing procedures. Here, we are going to discuss two such approaches, first is the so called nonparametric bootstrap approach and an approach based on the permutations. The next two subsections will show the results of the above approaches.

2.1 Bootstrap Method for the Mean Change in Angles

The pivotal statistic, under the null hypothesis that the means are equal to zero is given by $T_n(p) = n\bar{D}_n^{'} S^{-1} \bar{D}_n$. To generate the bootstrap statistic, first center the by $C_i = D_i - \bar{D}$, then

Table 1: Angle difference for twelve monkeys

$X_1X_2X_4$	$X_1X_3X_4$	$X_1X_4X_2$
0.1344	-0.4991	0.0292
0.2899	-0.4216	-0.2228
0.0002	0.1066	-0.0182
0.0389	0.0285	-0.0053
0.1722	-0.3529	-0.0415
0.1179	-0.5625	-0.0026
-0.1393	0.3291	0.0512
0.0202	0.0260	-0.0269
0.1979	-0.0216	-0.1633
0.3177	-0.4572	-0.1401
0.0955	-0.2078	-0.1185
0.1465	-0.0624	-0.1965

obtain a large number of bootstrap samples $C_1^*, C_2^*, C_3^*, ..., C_n^*$from $C_1, C_2, C_3, ..., C_n$ and the corresponding bootstrap statistics $T_n^*(p) = n\bar{C}_n^{*'} S^{*-1}\bar{C}_n^*$. To find the *p*-value calculate the proportion of the times that $T_n(p) > T_n^*(p)$. For the glaucoma dataset, it was found that $T_n(p) = 2.8796$. The *p*-value = 0.1233. The results here suggest that the nonparametric bootstrap method fails to improve the testing. However, this will lead to further investigation using more powerful nonparametric methods.

2.2 A Permutation Test Based on Hotelling's T^2

In this section a permutation test based on T^2 will be discussed. This procedure is carried out as follows: Under the null hypothesis, the vector of differences is equally likely to be either the observed vector of differences itself or the negative of the observed vector of differences. If there are *n* pairs of vectors, there are 2^n possible permutations of the pairs (each observed difference can be itself or the negative of it) and thus 2^n possible sets of difference vectors. One can compute Hotelling's T^2 on each sets of difference vectors to obtain the permutation distribution of the statistic. Based on the permutation distribution the *p*-value for the observed T^2 statistic can be calculated. When *n* is large, enumeration of all possible permutations is not feasible. In this case the test could be performed using a random sample of the permutation distribution. In our case since our sample size *n*(=12) is large enough we proceed with the latter random sample approach.

For our case the total number is a larger number (4096). We used a random sample of size 1000 for which T^2 = 10.5593 with a *p*-value of 0.1080; this clearly indicates that the

difference is marginally significant.

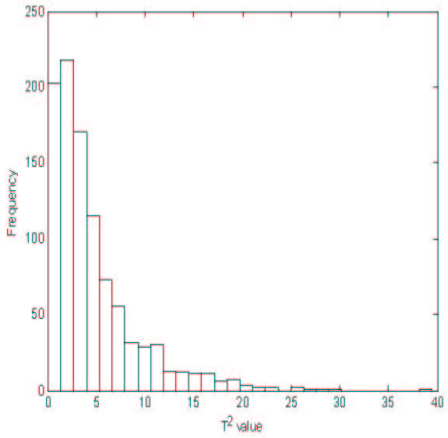


Figure 2: Histogram of the Permutations Distribution

3 The Process of Sign Test Statistics

All random elements in this section are defined on one and the same probability space $(\Omega, \mathcal{A}, \mathbb{P})$. Let $X : \Omega \to \mathbb{R}^d$ be an *d*-dimensioanl random vector, and $\mathbb{S}$ denote the unit sphere in $\mathbb{R}^d$. Introduce the real valued random variables

$$X_\theta = X^*\theta, \ \theta \in \mathbb{S}. \tag{3.1}$$

For the use of such projected data see Huber(1985). Note that

$$B_\theta = 1_{(0,\infty)}(X_\theta) = Bernoulli(p_\theta), \quad p_\theta = \mathbb{P}\{X_\theta > 0\}. \tag{3.2}$$

Let us introduce

$$m(\theta) = p_\theta - \frac{1}{2}, \qquad \theta \in \mathbb{S}. \tag{3.3}$$

Assuming that

$$\mathbb{P}\{X_\theta = 0\} = 0, \qquad \forall \theta \in \mathbb{S}, \tag{3.4}$$

we have, for each $\theta \in \mathbb{S}$,

$$m(\theta) = 0 \leftrightarrow \text{ median of } X_\theta \text{ equals } 0. \tag{3.5}$$

Next suppose that $X_1, \ldots, X_n$ is a random sample of independent copies of X and define $X_{i,\theta}$ and $B_{i,\theta}$ in a similar way as X_θ and B_θ. A good statistic for testing $m(\theta) = 0$ is

$$\overline{B}_n(\theta) - \frac{1}{2} = \frac{1}{n}\sum_{i=1}^{n}\left(B_{i,\theta} - \frac{1}{2}\right), \tag{3.6}$$

which equals the sign-test-statistic. We will be concerned with the stochastic process

$$T_n(\theta) = \sqrt{n}\left[\left(\overline{B}_n(\theta) - \frac{1}{2}\right) - m(\theta)\right], \qquad \theta \in \mathbb{S}. \tag{3.7}$$

If μ is any finite measure on the σ-field of Borel sets $\mathcal{B}_{\mathbb{S}}$ in $\mathbb{S}$, it is immediate that T_n is a random element of the real, separable Hilbert space $L^2(\mu) = L^2(\mathbb{S}, \mathcal{B}_{\mathbb{S}}, \mu)$. In this section we will focus on convergence in distribution of the T_n in this space. For brevity, let us introduce

$$p_{\theta,\tau} = \mathbb{P}\{X_\theta > 0, X_\tau > 0\}, \quad \Sigma(\theta,\tau) = p_{\theta,\tau} - p_\theta p_\tau, \qquad \theta, \tau \in \mathbb{S}. \tag{3.8}$$

Combinations of multivariate procedures based on the projected data as in (3.1) was employed for a robust principal component analysis in Ruymgaart (1981), and for a nonparametric regression test in Buhrman & Ruymgaart(1981).

Theorem 3.1. *There exists a Gaussian random element $\mathcal{G}$ in $L^2(\mu)$ with*

$$E\mathcal{G}(\theta) = 0, \quad E\mathcal{G}(\theta)\mathcal{G}(\tau) = \Sigma(\theta,\tau), \theta, \tau \in \mathbb{S}, \tag{3.9}$$

such that

$$T_n \xrightarrow{d} \mathcal{G}, \text{ as } n \to \infty \quad \text{in } L^2(\mu). \tag{3.10}$$

Proof. The random functions

$$\theta \to (B_{i,\theta} - \frac{1}{2}) - m(\theta) = B_{i,\theta} - p_\theta, i = 1, \ldots, n, \tag{3.11}$$

are i.i.d. with

$$\mathbb{E}\int_{\mathbb{S}}(B_{i,\theta} - p_\theta)^2 d\mu(\theta) = \int_{\mathbb{S}}\Sigma(\theta,\theta)d\mu(\theta) \le \int_{\mathbb{S}} 2d\mu(\theta) < \infty, \tag{3.12}$$

Hence the conditions for applying the central limit theorem in Hilbert spaces (Laha & Rohatgi (1979)) are fulfilled. Application yields the desired result.

Let us denote inner product and norm in $L^2(\mu)$ by $< \cdot, \cdot >_\mu$ and $\| \cdot \|_\mu$ respectively. The functional

$$Q(f) = \|f\|_\mu^2, \quad f \in L^2(\mu), \tag{3.13}$$

has a Fréchet - derivative at $m \in \mathbb{S}$, given by

$$Q_m^* f = 2 < f, m >_\mu, \quad f \in L^2(\mu). \tag{3.14}$$

According to the delta-method (see, for instance, van der Vaart (1998)) in conjunction with (3.10) this yields at once the following result.

Corollary 3.1. For m as in (3.3) we have

$$\sqrt{n}\left(\left\|\overline{B}_n - \frac{1}{2}\right\|_\mu^2 - \|m\|_\mu^2\right) \xrightarrow{d} 2 < \mathcal{G}, m >_\mu, \tag{3.15}$$

where $< \mathcal{G}, m >_\mu$ has a normal distribution with

$$\mathbb{E} < \mathcal{G}, m >_\mu = 0, \quad \mathbb{V}ar < \mathcal{G}, m >_\mu = < m, \Sigma m >_\mu . \tag{3.16}$$

Remark. The directions θ and $-\theta$ generate the same one-dimensional subspace, and it is easy to verify that

$$T_n(-\theta) = -T_n(\theta), \theta \in \mathbb{S}. \tag{3.17}$$

Hence there is a redundancy in the collection of random variables $T_n(\theta)$, when considered for all $\theta \in \mathbb{S}$, as is done here. Although this redundancy doesn't need to be of any consequence, it can be eliminated by restricting the measure μ to a suitable part of $\mathbb{S}$.

4 Analyzing the Data using Robust Test Procedures

First the procedures will be described for general dimension, and will then be applied to the glaucoma data. Let us select $r \geq d$ different directions

$$\theta_1, \ldots, \theta_r \in \mathbb{R}^d. \tag{4.1}$$

For μ in (3.12) we choose the counting measure on the set of directions in (4.1), so that $\mu(\{\theta_j\}) = 1$ for $j = 1, \ldots, r$. Let us write

$$\overline{B}_{n,j} = \overline{B}_n(\theta_j), \quad m_j = m(\theta_j), \tag{4.2}$$

$$T_{n,j} = \sqrt{n}\left\{\left(\overline{B}_{n,j} - \frac{1}{2}\right) - m_j\right\}. \tag{4.3}$$

The result in (3.10) now reduces to

$$T_n = (T_{n,1}, \ldots, T_{n,r})^* \xrightarrow{d} (g_1, \ldots, g_r)^* = \mathcal{G}, \tag{4.4}$$

where $\mathcal{G}$ has an $r-$variate normal distribution with mean vector 0 and covariance matrix (see also (3.8))

$$\Sigma_{j,k} = \Sigma(\theta_j, \theta_k), \quad j = 1, \ldots, r, \quad k = 1, \ldots, r. \tag{4.5}$$

4.1 Method 1

In this subsection we will test the null hypothesis that the medians are 0 for all r directions, i.e.

$$\overline{\mathcal{H}}_0 \quad : \quad m_1 = \cdots = m_r = 0. \tag{4.6}$$

Since this hypothesis is larger than $\mathcal{H}_0$ in (2.1), the procedure will be somewhat conservative. If the matrix Σ were the same for each distribution covered by $\overline{\mathcal{H}}_0$, known, and of full rank we could employ $\left\|\Sigma^{-\frac{1}{2}}T_n\right\|^2$ as a test statistic, with approximate χ^2_r-distribution for large n. Example 4.2 below shows, however, that all these conditions are not in general satisfied, not even in the case where $\overline{\mathcal{H}}_0$ is restricted to

$$\overline{\mathcal{H}}_0' : \text{all } r\text{-variate densities that are rotationaly symmetric about the origin.} \tag{4.7}$$

Example 4.1. Let us first consider a situation in which Σ is known and of full rank, under the hypothesis (4.7). Although this hypothesis is more restrictive than (4.6) it is not an uncommon one in statistics. The matrix Σ is now in principle determined by the known positions of the θ_j. Let us illustrate this in the special case where $d = 2$, taking $r = 4$ and

$$\theta_1 = (1,0)^*, \quad \theta_2 = (\frac{1}{\sqrt{2}}, \frac{1}{\sqrt{2}})^*, \quad \theta_3 = (0,1)^*, \quad \theta_4 = (-\frac{1}{\sqrt{2}}, \frac{1}{\sqrt{2}})^*. \tag{4.8}$$

By symmetry we have

$$p_{\theta_j} = \frac{1}{2}, \quad p_{\theta_j,\theta_k} = \frac{4 - |j-k|}{8}, \tag{4.9}$$

for all j, k, which yields the matrix

$$\Sigma = \begin{bmatrix} \frac{2}{8} & \frac{1}{8} & 0 & -\frac{1}{8} \\ \frac{1}{8} & \frac{2}{8} & \frac{1}{8} & 0 \\ 0 & \frac{1}{8} & \frac{2}{8} & \frac{1}{8} \\ -\frac{1}{8} & 0 & \frac{1}{8} & \frac{2}{8} \end{bmatrix}, \tag{4.10}$$

with determinant $|\Sigma| = \frac{3}{4} > 0$.

Example 4.2. Once more let us assume that (4.7) holds true, let us take $d = 3$ and $r = 3$ with directions

$$\theta_1 = (1,0,0)^*, \quad \theta_2 = (0,1,0)^*, \quad \theta_3 = (0,0,1)^*. \tag{4.11}$$

By symmetry we now have

$$p_{\theta_j} = \frac{1}{2}, \quad p_{\theta_j,\theta_k} = \frac{1}{8}. \tag{4.12}$$

for all j, k, and obtain the matrix

$$\Sigma = \begin{bmatrix} \frac{2}{8} & -\frac{1}{8} & -\frac{1}{8} \\ -\frac{1}{8} & \frac{2}{8} & -\frac{1}{8} \\ -\frac{1}{8} & -\frac{1}{8} & \frac{2}{8} \end{bmatrix}, \tag{4.13}$$

with determinant $|\Sigma| = 0$.

Let us return to the general situation. There exists an orthonormal matrix O and a diagonal matrix $\Lambda = \text{diag}(\lambda_1, \ldots, \lambda_r)$ with $\lambda_j \geq 0$ for all j, such that $\Sigma = O^* \Lambda O$. It is clear that

$$O\mathcal{G} = (\sqrt{\lambda_1} Z_1, \ldots, \sqrt{\lambda_r} Z_r)^*, \tag{4.14}$$

where $Z_1 \ldots, Z_r$ are i.i.d. standard normal random variables.

Because some of the eigenvalues may be zero, we cannot include an inverse of Λ in our procedure. We can however, employ a generalized inverse. Let us fix an arbitrary $\epsilon > 0$. As an estimator of Σ we will use

$$\hat{\Sigma}_{j,k} = \hat{p}_{j,k} - \hat{p}_j . \hat{p}_k, \tag{4.15}$$

where the estimators on the right are suggested by their population analogues in (3.8) and given by

$$\hat{p}_j = \left(\frac{1}{n} \sum_{i=1}^{n} 1_{\{X_i^* \theta_j > 0\}} \right), \tag{4.16}$$

$$\hat{p}_{j,k} = \frac{1}{n} \sum_{i=1}^{n} 1_{\{X_i^* \theta_j > 0\}} 1_{\{X_i^* \theta_k > 0\}}. \tag{4.17}$$

The estimator in (4.15) is $\sqrt{n}-$consistent.

It is immediate from the continuous mapping theorem that, under $\overline{\mathcal{H}}_0$ in (4.6),

$$\left(\epsilon I + \hat{\Sigma} \right)^{-\frac{1}{2}} T_n \xrightarrow{d} (\epsilon I + \Sigma)^{-\frac{1}{2}} \mathcal{G}, \quad \text{as} \quad n \to \infty, \tag{4.18}$$

where I is the $r \times r$ identity matrix. As a test statistic we might use the squared norm of the l.h.s of (4.15), and this statistic would have limiting distribution

$$\begin{aligned} \left\| \left(\epsilon I + \hat{\Sigma} \right)^{-\frac{1}{2}} T_n \right\|^2 &\xrightarrow{d} \left\| (\epsilon I + \Sigma)^{-\frac{1}{2}} \mathcal{G} \right\|^2 \\ &= \left\| O^* (\epsilon I + \Lambda)^{-\frac{1}{2}} O\mathcal{G} \right\|^2 \\ &= \sum_{j=1}^{r} \frac{\lambda_j}{\epsilon + \lambda_j} Z_j^2, \quad \text{as} \quad n \to \infty. \end{aligned} \tag{4.19}$$

If we had simplify used the squared norm of the l.h.s of (4.4) we would have obtained

$$\|T_n\|^2 \xrightarrow{d} \sum_{j=1}^{r} \lambda_j Z_j^2. \tag{4.20}$$

We see that the limiting distribution of either statistic contains the unknown eigenvalues λ_j. Since (4.20) doesn't require the choice of an extra parameter, we will use $\|T_n\|^2$ as a test statistic for the glaucoma data. If we define

$$F_{\lambda_1,\ldots,\lambda_r}(x) = \mathbb{P}\left\{\sum_{j=1}^{r} \lambda_j Z_j^2 \leq x\right\}, x \geq 0, \tag{4.21}$$

for the actual test we will use the quantiles of the c.d.f. in (4.21) but with λ_j replaced by estimators $\hat{\lambda}_j$ obtained from $\hat{\Sigma}$ in (4.15), i.e. we use the quantiles of

$$F_{\hat{\lambda}_1,\ldots,\hat{\lambda}_r}(x), \quad x \geq 0. \tag{4.22}$$

Summerizing we have the following result.

Theorem 4.1. *The test that rejects $\overline{\mathcal{H}}_0$ in* (4.6) *for*

$$\|T_n\|^2 > F^{-1}_{\hat{\lambda}_1,\ldots,\hat{\lambda}_r}(1-\alpha), \quad 0 < \alpha < 1, \tag{4.23}$$

can be used as an approximate size-α test.

The method 1 was then used for glaucoma data with several sets of directions. This test was carried out for few different choices of ϵ including $\epsilon = 0$. The *p*-valuses produced by this method were listed on Table 1. Direction vectors on Table 1 were normalized before we used them for the calculation of *p*-values.

4.2 Method 2

An interesting alternative to the first method is based on replacing the null hypothesis $\overline{\mathcal{H}}_0$ in (4.6) by the neighbourhood hypothesis.

$$\overline{\mathcal{H}}_{0,\delta} : \sum_{j=1}^{r} m_j^2 \leq \delta^2, \quad \text{for some} \quad \delta > 0. \tag{4.24}$$

Let us assume that

$$\sigma^2 = 4\sum_{j=1}^{r}\sum_{k=1}^{r} m_j \Sigma_{j,k} m_k > 0. \tag{4.25}$$

Table 2: *p*-values produced by method 1

Directions	*p*-value		
	$\epsilon = 0$	$\epsilon = .001$	$\epsilon = .1$
$\begin{pmatrix}1\\0\\0\end{pmatrix}, \begin{pmatrix}0\\1\\0\end{pmatrix}, \begin{pmatrix}0\\0\\1\end{pmatrix}$	.000003	.00001	.0011
$\begin{pmatrix}1\\0\\0\end{pmatrix}, \begin{pmatrix}0\\1\\0\end{pmatrix}, \begin{pmatrix}0\\0\\1\end{pmatrix}, \begin{pmatrix}1\\1\\1\end{pmatrix}$	0	.00001	.0043
$\begin{pmatrix}1\\0\\0\end{pmatrix}, \begin{pmatrix}0\\1\\0\end{pmatrix}, \begin{pmatrix}0\\0\\1\end{pmatrix}, \begin{pmatrix}1\\1\\1\end{pmatrix}, \begin{pmatrix}1\\1\\-1\end{pmatrix}$	0	0	.00007
$\begin{pmatrix}1\\0\\0\end{pmatrix}, \begin{pmatrix}0\\1\\0\end{pmatrix}, \begin{pmatrix}0\\0\\1\end{pmatrix}, \begin{pmatrix}1\\1\\1\end{pmatrix}, \begin{pmatrix}1\\1\\-1\end{pmatrix}, \begin{pmatrix}1\\-1\\-1\end{pmatrix}$	0	0	.00004

This notation has already been briefly discussed in Section 1. It turns out that a natural test statistic now simply has a normal distribution. One has to decide on a suitable value for the external parameter $\delta > 0$.

It is immediate from (4.4) that

$$\sqrt{n}\left\{\sum_{j=1}^{r}\left(\overline{B}_{n,j}-\frac{1}{2}\right)^2-\sum_{j=1}^{r}m_j^2\right\}\xrightarrow{d}\mathcal{U},\quad \text{as}\quad n\to\infty, \tag{4.26}$$

where $\mathcal{U}$ has a normal distribution with mean 0 and variance σ^2, given by (4.25). A consistent estimator for this variance is

$$\hat{\sigma}^2 = 4\sum_{j=1}^{r}\sum_{k=1}^{r}\hat{m}_j\hat{\Sigma}_{j,k}\hat{m}_k, \tag{4.27}$$

where $\hat{\Sigma}_{j,k}$ is defined in (4.15) and where $\hat{m}_j = \hat{p}_j - \frac{1}{2}$, with $\hat{p}_j$ as in (4.16).

Let us now define

$$S_n = \sqrt{n}\left\{\sum_{j=1}^{r}\left(\overline{B}_{n,j}-\frac{1}{2}\right)^2-\delta^2\right\}/\hat{\sigma}, \tag{4.28}$$

Table 3: *p*-values produced by method 2

Directions	*p*-value		
	$\delta = .000001$	$\delta = .001$	$\delta = .1$
$\begin{pmatrix}1\\0\\0\end{pmatrix}, \begin{pmatrix}0\\1\\0\end{pmatrix}, \begin{pmatrix}0\\0\\1\end{pmatrix}$	5.9954×10^{-5}	5.9958×10^{-5}	1.1296×10^{-4}
$\begin{pmatrix}1\\0\\0\end{pmatrix}, \begin{pmatrix}0\\1\\0\end{pmatrix}, \begin{pmatrix}0\\0\\1\end{pmatrix}, \begin{pmatrix}1\\1\\1\end{pmatrix}$	1.5460×10^{-4}	1.5461×10^{-4}	2.6858×10^{-4}
$\begin{pmatrix}1\\0\\0\end{pmatrix}, \begin{pmatrix}0\\1\\0\end{pmatrix}, \begin{pmatrix}0\\0\\1\end{pmatrix}, \begin{pmatrix}1\\1\\1\end{pmatrix}, \begin{pmatrix}1\\1\\-1\end{pmatrix}$	1.3882×10^{-5}	1.3883×10^{-5}	2.494×10^{-5}
$\begin{pmatrix}1\\0\\0\end{pmatrix}, \begin{pmatrix}0\\1\\0\end{pmatrix}, \begin{pmatrix}0\\0\\1\end{pmatrix}, \begin{pmatrix}1\\1\\1\end{pmatrix}, \begin{pmatrix}1\\1\\-1\end{pmatrix}, \begin{pmatrix}1\\-1\\-1\end{pmatrix}$	1.1406×10^{-5}	1.1407×10^{-5}	1.7875×10^{-5}

and denote the c.d.f. of the standard nornal distribution as usual by Φ. The following result is clear from (4.26).

Theorem 4.2. *The test that rejects* $\overline{\mathcal{H}}_{0,\delta}$ *in* (4.24) *for*

$$S_n > \Phi^{-1}(1-\alpha), \quad 0 < \alpha < 1, \tag{4.29}$$

has the asymptotic size α*, provided* (4.25) *is fullfilled.*

It should be noted that rejection of $\overline{\mathcal{H}}_{0,\delta}$ entails rejection of $\overline{\mathcal{H}}_0$. Employing a neighbourhood hypothesis yields in fact some further protection against undue rejection of the null hypothesis of actual interest.

For the glaucoma data this test was used for several sets of directions and different values of δ. Again the *p*-values were computed: see Table 2. Again the direction vectors were normalized before we used them for the calculation of *p*-values.

5 Conclusion

The glaucoma data consist of 3-dimensional vectors with coordinates that are differences of angles. Consequently, each coordinate is a random variable with bounded range. Deviations from normality of the distribution of such a coordinate will therefore not occur in the tail behaviour. It may present itself, for instance, in the form of skewness as seems to be the case for

the current data. See Figure 2, Figure 3, Figure 4 and Figure 5. Due to this skewness, moreover, it seemed appropriate to use sign tests rather than, for instance, one-sample Wilcoxon tests, although our procedures could be easily modified so as to accomodate tests of the latter type. We see that, in general, the robust procedures yield smaller *p*-values.

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