

# Multivariate Assessment of Computer Analyzed Corneal Topographers

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## Abstract

Methodological aspects of multivariate statistical models to describe and assess data from computer analyzed corneal topographers (CACT) are considered. The data generated by repeated curvature mappings of calibrated steel balls are discussed in detail with the objective of formulating the basic questions and suggesting directions to assess data from clinical applications of CACT. The interpretation of seemingly straightforward concepts such as accuracy and precision is revisited with the objective of understanding its meaning in future clinical and experimental applications of CACT. Some of the statistical problems related to the analysis of corneal astigmatism based on CACT data are also discussed.

## 1 Introduction.

This paper emphasizes the multivariate nature of computer analyzed corneal topographers (CACT) data. Section 2 revisits a number of basic CACT definitions and concepts and their corresponding multivariate expressions and includes an example of multivariate CACT data, followed by a statistical model suggested for their analysis (Section 3). Alternative multivariate models and an overview of the road ahead are included in Section 4. Technical derivations are outlined in the Appendix.

There is a considerable range of methodological issues related with the statistical assessment of CACTs. As pointed out by El Hage (Hage 1989), assessing the performance of CACTs presents a set of problems not previously encountered in keratometry. Nevertheless, assessment of CACT-related parameters such as accuracy and reproducibility (Koch, Foulks, Moran and Wakil 1989) or quite complex experimental comparisons such as CACTs against conventional keratometry (Davis and Dresner 1991) or keratometry vs photokeratoscopy vs CACTs (Hannush, Crawford, III, Gemmill, Lynn and Nizam 1989), have been documented in the literature most in the way conventional univariate data are traditionally analyzed. Univariate reductions of CACTs data have also been analyzed to correlate visual acuity with quantitative descriptors of corneal topography such as surface asymmetry and regularity indexes (Wilson and Klyce 1991) and to assess changes in keratoplasty astigmatism (Lin, Wilson, Reidy, Klyce, McDonald, Kaufman and McNeill 1990).

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Among the methodological issues there seems to be a close dependence between the end-point application of CACT and the complexity of the corresponding methodological issues, along with the need to relate the assessment of CACTs against calibrated in vitro objects with their subsequent performance against living corneas. Applications seem to range from global optometric assessments of the cornea to detailed small-area (local) postoperative assessments of the cornea's topography. The prototype stage of a new CACT requires the estimation and interpretation of certain standard specifications of the instrument, such as precision and accuracy, while a subsequent stage could require a methodology to properly assess the outcome of a clinical trial based on CACT data. The relevant statistical model to assess the performance of CACTs as a guide to laser technology in refractive surgery or to the rapid fitting of contact lenses of aspheric and astigmatic designs (Hage 1989) are bound to be different. Consequently, we should expect to have to understand and distinguish a greater number of eventually distinct methodological issues related to CACT data.

## 2 The Multivariate Nature of CACT Data

Keratometry is the measurement of corneal curvature of a small area using a sample of four reflected points of light along an annulus 3 to 4 mm in diameter, centered about the line of sight. For normal corneas this commonly approximates the apex of the cornea. Though this approach has represented the standard for corneal curvature, improved technology has permitted the quantitative analysis of a much larger area of the cornea. The fundamental principle of this technology is similar to keratometry in that the relative separation of reflected points of light are used to calculate the curvature of the measured surface. Using a pattern of rings and sampling at specific equidistant intervals, a numerical model of the measured surface may be obtained. Sampling takes place at ring-semimeridian intersections and the number of samples varies from 720 to more than 7000 depending on the instrument being used.[e.g. El (Hage 1976), (Klyce and Wilson 1989, Waring 1989)].

Let  $\mathbf{X}$  denote a random topographic map based on  $p = p_1 \times p_2$  curvatures corresponding to  $p_2$  semimeridians and  $p_1$  concentric rings. Typically  $1 \leq p_1 \leq 32$  and  $1 \leq p_2 \leq 256$ . A sample of size  $N$  is obtained from  $\mathbf{X}$  by repeatedly mapping the curvature of a given surface such as a steel ball or a living cornea. Let  $\mathbf{m} = E(\mathbf{X})$  indicate the vector of expected values of  $\mathbf{X}$ , and  $\Sigma = cov(\mathbf{X})$  indicate the matrix of variances and covariances among the components of  $\mathbf{X}$ . In contrast with univariate models, every multivariate model necessarily includes the interdependence among the components of  $\mathbf{X}$ , which is represented in  $\Sigma$ . In summary, the experimental data  $\mathbf{x}_1, \dots, \mathbf{x}_N$  constitute a sample of size  $N$  from  $\mathbf{X}$  with  $p$  components and underlying unknown parameters  $\mathbf{m}$  and  $\Sigma$ .

**Accuracy, precision and prediction.** When  $\mathbf{X}$  is observed a number of times the resulting values, in general, do not agree exactly. If the causes of disagreement between the individual values must also be causes of their differing from the true unknown value  $\mathbf{m}$ , the resulting errors are called *random* errors. Otherwise, if all of the individual values are in error by the same amount, the errors are called *systematic* or constant errors. For example, errors of calibration, personal errors, experimental conditions or imperfect techniques are among the systematic errors. In contrast, errors caused by fluctuating conditions and small disturbances are random errors. If an experiment has small random errors it is said to have high *precision*. If an experiment has small systematic errors it is said to have high *accuracy* (Beers 1957). Suppose, in the simplest univariate case ( $p=1$ ), that  $m_0$  is the true curvature at a given point, and that the experimental model for the observed

curvature  $X$  is

$$X_i = m + \epsilon, \quad i = 1, \dots, N,$$

where  $\epsilon$  represents a random component with expected value zero and variance  $\sigma^2$ . From the above definitions it follows that  $\beta = m - m_0$  is the instrument's systematic error or bias, while  $\sigma^2$  is its random error. Equivalently,  $\beta$  reflects the instrument's accuracy while  $\tau = 1/\sigma^2$  is its precision.

However, since in actual applications neither  $m$  or  $\sigma^2$  are known, any statistical statement about the instrument's accuracy  $\beta$  can only be made in terms of (the estimated value of) its own precision  $\tau$ , that is; **the instrument's accuracy is necessarily expressed in units of its own precision**. Consequently, the concept of statistical accuracy requires a word of caution in the sense that any instrument can be shown to have arbitrarily small accuracy (i.e. reject the hypothesis  $H : m = m_0$  of no systematic error), by obtaining a very small precision or increasing the number  $N$  of observations (needed to estimate  $m$  and likely to reject  $H$ ). The same caution clearly applies to comparing the accuracies of two or more instruments.

In addition, it should be pointed that the instrument's precision  $\tau$  is actually its precision to estimate or express the instrument's accuracy  $\beta$ , and needs to be distinguished from the precision to be expected or predicted from a future observation. An estimated value of  $\sigma$  equal to 0.2 Diopters only implies that in repeated experiments (of sample size  $N$ ) the instrument's estimated accuracy  $\hat{\beta} = \bar{x} - m$  is likely to be within  $0.4/\sqrt{N}$  in about 95 out of 100 trials. Note that the statement involves the parameter  $m$ , which is unknown.

This is actually a statistical prediction problem, and it is opportune to point out that the classical theory of statistical inference cannot evaluate any probabilistic statement about the next observation  $x_{N+1}$  given the past history  $x_1, \dots, x_N$  (unconditionally of  $m$  and  $\sigma^2$ ). Nevertheless, Bayesian inference shows that the predictive probability model of  $x_{N+1}$  converges to a Normal distribution with mean  $\bar{x}_N$  and variance  $\sigma^2(N+1)/N$ , where  $\bar{x}_N$  is the observed sample mean for the past  $N$  cases (Zellner 1971), (Press 1989), (Lee 1989). Consequently, in about 95 out of 100 trials, the next observation  $x_{N+1}$  is expected to be within  $2\sigma\sqrt{(N+1)/N}$  of  $\bar{x}_N$ , in contrast with the former confidence interval which is  $\sqrt{N+1}$  times **shorter** than the predictive interval. The case in which  $\sigma^2$  as well needs to be estimated from the data can be approached similarly and the exact predictive probability model and interval follow from a noncentral t distribution (Aitchison and Dunsmore 1975).

**Extreme curvatures and astigmatism.** Of particular importance is the definition and determination, in the multivariate sense, of extreme curvature values along a given concentric ring. The two extremes represent the steepest and flattest curvatures and their meridians are referred to as the *steep* and *flat* meridians or major orientations. The positive difference between steep and flat curvatures is the amount  $\alpha$  of astigmatism at that refractive aperture. The corresponding steep and flat semimeridians determine the primary meridians of astigmatism. When the amount of astigmatism and the primary meridians actually vary across the refractive aperture the eye cannot bring an image to a focal point, even with spherocylindrical spectacle correction.

Given any number  $p$  of components corresponding to a subregion  $\mathcal{G}$  defined by direction cosine vectors  $\{\theta_1, \dots, \theta_p\}$ , let  $X_{(1)}, X_{(2)}, \dots, X_{(p)}$  indicate the ordered curvatures ranked from the smallest,

flattest curvature  $X_{(1)}$  to the largest, steepest curvature  $X_{(p)}$ , with corresponding direction cosine vectors  $\theta_f$  and  $\theta_s$ . Then

$$\alpha = X_{(p)} - X_{(1)}, \quad (1)$$

is the range of the coordinates of  $\mathbf{X}$ . When  $\mathcal{G}$  includes all curvature points within a given aperture then  $\alpha$  defines the amount of astigmatism at that aperture, with major directions given by  $\theta_f$  and  $\theta_s$ . In general, however,  $\alpha$ ,  $\theta_f$  and  $\theta_s$  define the *curvature range* within the semimeridians selected. While current CACTs routinely calculate the curvature range  $\alpha$  relative to any selected subset  $\mathcal{G}$  (Hage 1989), the case in which  $\mathcal{G}$  is restricted to curvature points at orthogonal orientations is also included in the above definition, as well as the case in which  $\mathcal{G}$  is restricted to the horizontal and vertical cylindrical axes so that  $\alpha$  is either the amount of astigmatism "with the rule" or "against the rule". Regardless of the many interpretations and end-point applications, which are related only to the choice of  $\mathcal{G}$ , **the degree  $\alpha$  of astigmatism is described by the range of the components of a multivariate observation.**

The broad question underlying all interpretations of astigmatism, however, consists of measuring, estimating and testing the degree of regularity in the asphericity of the anterior corneal surface, which is described by the study of  $\alpha$ ,  $\theta_f$  and  $\theta_s$  as a function of  $\mathcal{G}$ . As pointed out early in the paper, the end-point application imposes how comprehensive the method or definition of  $\alpha$  ought to be; the study of the irregular topography and ensuing astigmatism of keratoconic corneas with the purpose of fitting ordinary contact lenses might restrict  $\mathcal{G}$  to conform more to the current technology of contact lenses than to the actual need to model the distorted cornea (Dana, Putz, Viana, Sugar and McMahon 1992). The asphericity of  $\mathbf{X}$  can be described by the spectral representation of certain quadratic forms  $\mathbf{y}'\Lambda^{-1}\mathbf{y}$  approximating the geometry of  $\mathbf{X}$ . The homogeneity of (or multiplicity among) the eigenvalues of  $\Lambda$  is related to the degree and orientation of the sphericity of  $\mathbf{X}$ , while the symmetry of  $\Lambda$  is related to the orthogonality of the major axis or meridians of  $\mathbf{X}$ .

**The sample size and the dimension of  $X$ .** The number  $N$  of sampled mappings is likely to be considerably smaller than the dimension of  $p$  of  $\mathbf{X}$ , which is directly related to the total number of parameters among  $\mathbf{m}$  and  $\Sigma$  to be estimated from the sample, specially when the experiment is based on living corneas. This poses a considerable problem which requires a parsimonious representation of the parameter space.

In summary, there is interest in the appropriate modelling of  $\mathbf{X}, \mathbf{m}, \Sigma$  to [a] obtain an estimate  $\widehat{\mathbf{m}}$  of  $\mathbf{m}$ , [b] estimate the covariance structure  $\Sigma$ , [c] predict a new map  $\mathbf{X}_{N+1}$  given the past  $N$  maps  $\mathbf{x}_1, \dots, \mathbf{x}_N$ , [d] derive the map predictive covariance  $cov(\mathbf{X}_{N+1} \mid \mathbf{x}_1, \dots, \mathbf{x}_N)$ , [e] derive an estimate  $\widehat{\mathcal{A}}$  of the expected curvature range  $\mathcal{A} = E(\alpha \mid \mathbf{x}_1, \dots, \mathbf{x}_N)$ , [f] model and estimate the major axis  $\theta_f, \theta_s$ , and [g] estimate  $var(\widehat{\mathcal{A}})$ . As defined above, the instrument's accuracy can be expressed in terms of  $\beta = \mathbf{m} - \widehat{\mathbf{m}}$ , while the precision in estimating  $\beta$  depends on the estimated covariance. The instrument's observed or predictive precision, however, is related to the predictive covariance, and generally needs to be distinguished from the estimated covariance of  $\mathbf{X}$  given  $\Sigma$ .

**An example of CACT data.** A topographic map  $\mathbf{X}$  consisting of  $p = 720$  curvature points is observed  $N = 10$  times in each one of two calibrated steel balls of curvatures  $42.5D$  and  $44.75D$  (in Diopters). The Optimed ECT100 Corneal Topographer (Houston, TX) was used to generate the samples. It is a 21-ring video based keratoscope where the image is digitized and corneal contour

is reconstructed using a high order polynomial equation (Hage 1976), (Hage 1989). Curvature for each of the 36 semi-meridians is calculated independently. Each observed map determines the curvature of the ball's anterior hemisphere over  $f = 20$  concentric rings at each one of  $g = 36$  equally spaced semimeridians. Figures 1 and 2 (available in the JOSA article) show in this the box plots corresponding to 10 repeated curvature mappings along ring 10 at each of 36 semimeridians from Balls 1 ( $42.5 D$ ) and 2 ( $44.75 D$ ). Univariate methods to assess similar data have clearly shown the limitations of point-by-point analyses and the necessity to understand and model the interdependence structure among observed curvature measurements (Bennett and Abrassart 1982, Wang, Rice and Klyce 1989), (Koch et al. 1989, Hannush et al. 1989), (Davis and Dresner 1991). In general, however, the available sample size  $N$  is considerably smaller than the dimension  $p$  of  $\mathbf{X}$ . Consequently, there is natural interest in modelling the parametric distribution of  $\mathbf{X}$  to efficiently equate  $N$  to the total number of parameters to be estimated.

The descriptive data of Figs. 1, 2 and similar ones have suggested that the assumption of symmetry among the components of  $\mathbf{X}$  is reasonable within certain regions  $\mathcal{G}$  of dimension  $p$  of the map  $\mathbf{X}$ . In addition, the observed sample covariance and correlation matrices associated with each subregion of  $\mathbf{X}$  seem to meet the assumptions of common correlation and common variance (Viana 1994). Consider, for example, the subregion  $\mathcal{G}$  specified by  $p = 7$  semimeridians 12, 14, 16, 18, 20, 22, 24 at the aperture corresponding to ring 10. The estimated covariance (S) and correlation (R) matrices, and the vector  $\bar{\mathbf{x}}$  of sample means based on  $N = 10$  repeated mappings are:

$$S = \begin{bmatrix} .00962 & .01203 & .00830 & .00731 & .00707 & .00929 & .01133 \\ .01203 & .01514 & .00992 & .00848 & .00824 & .01168 & .01431 \\ .00830 & .00992 & .00965 & .00912 & .00826 & .00735 & .00874 \\ .00731 & .00848 & .00912 & .00926 & .00852 & .00650 & .00751 \\ .00707 & .00824 & .00826 & .00852 & .00828 & .00645 & .00753 \\ .00929 & .01168 & .00735 & .00650 & .00645 & .00947 & .01124 \\ .01133 & .01431 & .00874 & .00751 & .00753 & .01124 & .01375 \end{bmatrix},$$

$$R = \begin{bmatrix} 1.000 & 0.996 & 0.861 & 0.774 & 0.791 & 0.973 & 0.984 \\ 0.996 & 1.000 & 0.820 & 0.716 & 0.736 & 0.975 & 0.991 \\ 0.861 & 0.820 & 1.000 & 0.965 & 0.924 & 0.769 & 0.759 \\ 0.774 & 0.716 & 0.965 & 1.000 & 0.973 & 0.694 & 0.666 \\ 0.791 & 0.736 & 0.924 & 0.973 & 1.000 & 0.728 & 0.705 \\ 0.973 & 0.975 & 0.769 & 0.694 & 0.728 & 1.000 & 0.984 \\ 0.984 & 0.991 & 0.759 & 0.666 & 0.705 & 0.984 & 1.000 \end{bmatrix},$$

$$\bar{\mathbf{x}}' = (42.43, 42.19, 42.25, 42.28, 42.33, 42.26, 42.29).$$

We observe that  $\bar{\mathbf{x}}$  suggests the symmetry of  $\mathbf{m}$ , that there is considerable homogeneity among the correlations and among the variances.

### 3 The Equicorrelated-Symmetric Model for $\mathbf{X}$ , $\mathbf{m}$ , $\Sigma$ .

The observed symmetry of  $\mathbf{X}$  and the intrinsic symmetry of the steel ball suggests the permutation or equicorrelated-symmetric multivariate normal model in which

$$\Sigma = \sigma^2 \begin{bmatrix} 1 & \rho & \dots & \rho \\ \rho & 1 & \dots & \rho \\ \vdots & \vdots & \dots & \vdots \\ \rho & \rho & \dots & 1 \end{bmatrix}, \quad \frac{-1}{p-1} < \rho < 1, \quad \mathbf{m}' = (\mu, \mu, \dots, \mu). \quad (2)$$

When  $\rho > 0$ ,  $\mathbf{X}$  has an exchangeable normal distribution (Tong 1990). The equicorrelated-symmetric model is the simplest prototype for the purposes of this paper. In particular, the order statistics among the components of  $\mathbf{X}$  necessary to estimate the expected value of the curvature range  $\alpha$  in Eq. (1) can be directly obtained (David 1981), (Tong 1990)]. It is certainly a reasonable model for assessing the instrument in any neighborhood of a given point of the steel ball, and likely to be a valid model to the curvature of an entire ring (circularity) close enough to the apex.

**Statistical Analysis for the Equicorrelated-Symmetric Model.** Let  $\bar{\mathbf{X}} = \sum_{i=1}^N \mathbf{X}_i/N$  and  $A = \sum_{i=1}^N (\mathbf{X}_i - \bar{\mathbf{X}})(\mathbf{X}_i - \bar{\mathbf{X}})'$  indicate the vector of  $p$  sample means and the matrix of sums of squares and cross-products. The corresponding sample covariance matrix is denoted by  $S = A/N$ . Under the equicorrelated-symmetric model there are three parameters to be estimated from the data; the common mean  $\mu$ , the common standard deviation  $\sigma$  and the common correlation  $\rho$ . However, the symmetry of  $\mathbf{m}$  and  $\Sigma$  implies that the likelihood on the data can be conveniently expressed in terms of the common mean  $\mu$  and the two distinct eigenvalues  $\lambda_1 = \sigma^2[1 + (p-1)\rho]$  and  $\lambda_2 = \sigma^2(1 - \rho)$ .

**Inferences on  $\mu, \lambda_1$ .** Let  $s_{uv}$  indicate the  $(u, v)$  entry of the sample covariance matrix  $S$  and define

$$\bar{x} = \sum_{i=1}^N \sum_{j=1}^p x_{ij}/pN, \quad \bar{s} = \sum_{1 \leq u, v \leq p} s_{uv}/p^2, \quad (3)$$

so that  $\bar{x}$  is the observed overall mean curvature and  $\bar{s}$  is the observed mean covariance. Consequently, from the posterior joint distribution of  $\mu, \lambda_1$  with respect to  $p(\mu, \lambda_1) \propto \lambda_1^{-1}$ , it follows that the posterior distribution of

$$\sqrt{N-3} \frac{\mu - \bar{x}}{\sqrt{\bar{s}}} \quad (4)$$

is Student's  $t$  with  $N-3$  degrees of freedom, and the marginal posterior distribution of  $\lambda_1$  is inverted-gamma-1 distribution with parameters  $(N-1)/2$  and  $Np\bar{s}/2$ . From the predictive distribution of  $\bar{X}_{N+1}$ , the average of the  $p$  components of a subsequent observation  $\mathbf{X}_{N+1}$  with respect to past  $N$  observations, the distribution of

$$\sqrt{\frac{N-2}{N+1}} \frac{\bar{X}_{N+1} - \bar{x}}{\sqrt{\bar{s}}} \quad (5)$$

is  $t$  with  $N-2$  degrees of freedom. Consequently, credibility limits for  $\mu$  and  $\bar{X}_{N+1}$  can be obtained from tables of the  $t$  distribution, and the posterior mean and standard deviation of  $\lambda_1$  from

$$E(\lambda_1 | \mathbf{x}_1, \dots, \mathbf{x}_N) = \frac{Np\bar{s}}{N-3}, \quad var(\lambda_1 | \mathbf{x}_1, \dots, \mathbf{x}_N) = \frac{2[Np\bar{s}]^2}{(N-3)^2(N-5)}. \quad (6)$$

**Inferences on  $\lambda_2$ .** Let  $r$  denote the conventional estimate of the equicorrelation coefficient  $\rho$  [e.g. (Olkin 1967, Olkin and Pratt 1958, Olkin and Siotani 1964)],

$$r = \frac{2 \sum_{u < v} s_{uv}}{(p-1)trS}. \quad (7)$$

It then follows that, given the observed value  $t$  of

$$T = \frac{N}{2} \left\{ (p-1)(1-r) \frac{trS}{p} + \sum_{j=1}^p (\bar{X}_j - \bar{X})^2 \right\}, \quad (8)$$

the posterior distribution of  $\lambda_2$  with respect to  $p(\lambda_2) \propto \lambda_2^{-1}$  is inverted-gamma-1 with parameters  $(p-1)N/2$  and  $t$ . In particular

$$E(\lambda_2 | T = t) = \frac{2t}{(p-1)N-2}, \quad var(\lambda_2 | T = t) = \frac{8t^2}{[(p-1)N-2]^2[(p-1)N-4]}. \quad (9)$$

**Inferences on  $\alpha$ .** Under the equicorrelated-symmetric model the distribution of the curvature range  $\alpha = X_{(p)} - X_{(1)}$  is the distribution of  $\sigma\sqrt{1-\rho}W_p = \sqrt{\lambda_2}W_p$ , where  $W_p$  is the range of  $p$  independent standard normal variables. If  $E(W_p) = \omega_p$ , then inferences about the expected range

$$\mathcal{A} = E(\alpha | \lambda_2) = \sqrt{\lambda_2}\omega_p \quad (10)$$

can be derived from the posterior distribution of  $\lambda_2$  obtained above. In particular,

$$E(\mathcal{A} | T = t) = \omega_p E(\lambda_2^{1/2} | T = t), \quad E(\mathcal{A}^2 | T = t) = \omega_p^2 E(\lambda_2 | T = t). \quad (11)$$

$E(\lambda_2 | T = t)$  is given by Eq. (9) whereas

$$E(\lambda_2^{1/2} | T = t) = t^{1/2} \frac{\Gamma([(p-1)N-1]/2)}{\Gamma((p-1)N/2)}. \quad (12)$$

Values of  $\omega_p$  can be obtained from tables of the expected values of order statistics from  $p$  independent standard normal variables  $Z_1, \dots, Z_p$  (Beyer 1990) and the fact that  $\omega_p = 2E(Z_{(p)})$  (David 1981).

**Data Analysis.** Based on the observed covariance matrix and vector of sample means described on Section 2, the estimated mean curvature  $\bar{x}$  and mean covariance  $\bar{s}$  follow from Eq. (3), the sample equicorrelation coefficient  $r$  is obtained from Eq. (7), credibility limits  $\mu_l, \mu_u$  for  $\mu$  follow from Eq. (4) and predictive credibility limits  $\bar{x}_l, \bar{x}_u$  for a subsequent  $\bar{x}$  follow from Eq. (5). Table 1 shows the results at the aperture corresponding to ring 10 and at each one of the additional rings {11, 12, 13, 14, 15} for each one of the two calibrated steel balls. Table 2 shows the estimated mean bias  $\beta = \mu - \bar{x}$  and corresponding estimation error  $\Delta_1 = (\mu_u - \mu_l)/2$ , and estimation error  $\Delta_2 = (\bar{x}_u - \bar{x}_l)/2$  to predict  $\bar{x}$ .

The quantities  $\beta, \Delta_1, \Delta_2$  summarize the instrument's local performance within the region bounded by semimeridians 12 and 24 at each specified aperture. For example, from line 1 of Tables 1 and 2 the following statement can be made; the estimated mean bias at the aperture corresponding

Table 1: Posterior estimate  $\bar{x}$  of mean curvature,  $\bar{s}$ , equicorrelation  $r$ , 95% credibility limits  $\mu_l, \mu_u$  for  $\mu$  and predictive 95% credibility limits  $\bar{x}_l, \bar{x}_u$  for  $\bar{x}$  based on  $p = 7$  semimeridians  $\{12, 14, 16, 18, 20, 22, 24\}$  at fields 10, 11, 12, 13, 14, 15.

Ball	Ring	$\bar{x}$	$\bar{s}$	$r$	$\mu_l$	$\mu_u$	$\bar{x}_l$	$\bar{x}_u$
42.50	10	42.29	.0026	.839	42.20	42.38	42.03	42.55
42.50	11	42.30	.0113	.892	42.21	42.40	42.02	42.59
42.50	12	42.33	.0099	.900	42.25	42.42	42.06	42.60
42.50	13	42.37	.0105	.901	42.28	42.46	42.09	42.65
42.50	14	42.42	.0094	.890	42.33	42.50	42.15	42.68
42.50	15	42.45	.0101	.900	42.36	42.54	42.17	42.72
44.75	10	44.43	.0148	.811	44.53	44.53	44.10	44.76
44.75	11	44.43	.0143	.894	44.32	44.54	44.11	44.75
44.75	12	44.45	.0149	.880	44.34	44.56	44.12	44.78
44.75	13	44.47	.0152	.882	44.36	44.58	44.14	44.80
44.75	14	44.50	.0157	.861	44.39	44.62	44.16	44.84
44.75	15	44.54	.0155	.883	44.43	44.65	44.20	44.88

Table 2: Estimated mean bias  $\beta = \mu - \bar{x}$  and corresponding error  $\Delta_1 = (\mu_u - \mu_l)/2$ , and error  $\Delta_2 = (\bar{x}_u - \bar{x}_l)/2$  to predict  $\bar{x}$ , based on  $p = 7$  semimeridians  $\{12, 14, 16, 18, 20, 22, 24\}$  at fields 10, 11, 12, 13, 14, 15.

Ball	Ring	$\beta$	$\Delta_1$	$\Delta_2$
42.50	10	.209	.0860	.2602
42.50	11	.197	.0950	.2876
42.50	12	.165	.0890	.2695
42.50	13	.127	.0918	.2777
42.50	14	.082	.0869	.2630
42.50	15	.053	.0899	.2722
44.75	10	.324	.1088	.3291
44.76	11	.320	.1074	.3248
44.75	12	.304	.1092	.3303
44.75	13	.279	.1103	.3336
44.75	14	.247	.1122	.3395
44.75	15	.210	.1113	.3368

Table 3: Posterior estimates of characteristic roots  $\lambda_1, \lambda_2$ , of local astigmatism  $\mathcal{A}$  and corresponding standard deviations, based on  $p = 7$  semimeridians  $\{12, 14, 16, 18, 20, 22, 24\}$  at fields 10, 11, 12, 13, 14, 15.

Ball	Ring	$E(\lambda_1)$	$Sd(\lambda_1)$	$E(\lambda_2)$	$Sd(\lambda_2)$	$E(\mathcal{A})$	$Sd(\mathcal{A})$
42.50	10	.0925	.0585	.0075	.0014	.216	.092
42.50	11	.1132	.0715	.0045	.0008	.168	.071
42.50	12	.0993	.0628	.0027	.0005	.131	.056
42.50	13	.1055	.0667	.0021	.0004	.115	.049
42.50	14	.0945	.0598	.0023	.0004	.119	.050
42.50	15	.1013	.0640	.0024	.0004	.124	.053
44.75	10	.1481	.0936	.0093	.0017	.240	.102
44.75	11	.1442	.0912	.0055	.0010	.185	.079
44.75	12	.1492	.0943	.0047	.0008	.171	.073
44.75	13	.1522	.0962	.0063	.0012	.198	.084
44.75	14	.1576	.0996	.0084	.0015	.228	.097
44.75	15	.1552	.0981	.0080	.0015	.222	.094

to ring 10 over semimeridians  $\{12, 14, 16, 18, 20, 22, 24\}$  is  $\beta = +0.209 D$  to within  $\Delta_1 = 0.086 D$  with probability 0.95, the predictive mean curvature (over the 7 semimeridians) for a subsequent mapping is  $\bar{x} = 42.29 D$  to within  $\Delta_2 = 0.260 D$  with probability 0.95. In addition, Table 3 shows the posterior estimates of eigenvalues  $\lambda_1, \lambda_2$  and expected degree of local astigmatism  $\mathcal{A}$ , including their standard deviations. The estimated mean astigmatism at the aperture corresponding to ring 10 and bounded within semimeridians 12 and 24 is  $0.216 D$  and its estimated standard deviation is  $0.092 D$ .

## 4 Comments and the Road Ahead.

The multivariate normal equicorrelated-symmetric model has been suggested to describe the performance of computer analyzed topographers with respect to calibrated steel balls. As pointed out earlier, the proposed method has the advantage of efficiently using the relatively small sample size available, when compared with the total number of curvature points generated from each mapping. The underlying assumptions of the equicorrelated-symmetric model are likely to be met at least locally. Since, for a fixed sample size  $N$ , the relative gain with respect to the corresponding univariate analysis depend on the equicorrelation  $\rho$  and on the dimension  $p$  of  $\mathbf{X}$ , one would like to apply the model under the largest value of  $p$  and still verify the assumptions of the model. Clearly, there is a trade-off between these two objectives. To see this, first note that from Eq. (4) the estimation error

$$\Delta_1 = (\mu_u - \mu_l)/2 = \sqrt{\frac{\bar{s}}{N-3}} t_{N-3} \quad (13)$$

depends on the data only through the average covariance  $\bar{s}$ , which can be expressed [see equation (7)] as  $\bar{s} = (tr S/p)[1 + (p-1)r]/p$ , showing that  $\bar{s}$  factors into an estimate  $(tr S/p)$  of  $\sigma^2$  and the other component which estimates  $\eta = [1 + (p-1)r]/p$ . The (large sample) relative efficiency to estimate  $\mu$  under the multivariate equicorrelated-symmetric model with respect to the corresponding univariate method ( $p = 1$ ) is exactly  $\eta$ , which is an increasing function of  $\rho \in (\frac{-1}{p-1}, 1)$  and  $1/p$ . Consequently, when the sample size  $N$  and the specified credibility are held fixed, the equicorrelated-symmetric model provides for considerably narrower intervals  $(\mu_l, \mu_u)$  when  $p$  increases or  $\rho$  decreases in its range. In addition, note that the estimation error  $\Delta_2 = (\bar{x}_u - \bar{x}_l)/2$  to predict  $\bar{x}$  is the actual *precision* to be reported, and should not be interpreted as  $\Delta_1$  which refers to how well one can estimate the instrument's accuracy [e.g.  $\beta$ ]. In fact

$$\frac{\Delta_2}{\Delta_1} = \sqrt{\frac{(N+1)(N-3)}{N-2} \frac{t_{N-2}}{t_{N-3}}}, \quad (14)$$

which can be considerably greater than one. In the present case, with  $N = 10$  and 95% credibility, the above ratio is approximately equal to 3.

The assumptions of the equicorrelated-symmetric model might not be verified when too many components are considered simultaneously, or might not be appropriate to describe the living cornea and the several possible end-point applications related to current and future CACTs. That has to be investigated. However, the equicorrelated-symmetric model is related to more general classes of models: the circular-stationary-symmetric normal model (Olkin and Press 1969),(Press 1972)] and the lagged-symmetric normal model (Press 1972). Under the circular model,  $\mathbf{X}' = (X_1, \dots, X_p)$  has a multivariate normal distribution such that  $E(X_i) = \mu$ ,  $var(X_i) = \sigma^2$  and

$$cov(X_i, X_{i+k}) = \sigma^2 \rho_k, \quad \rho_k = \rho_{p-k}, \quad (15)$$

$i = 1, \dots, p$ ;  $k = 1, \dots, p-1$ ;  $2 \leq i+k \leq p$ . Under the lagged model,  $\mathbf{X}$  has a multivariate normal distribution and  $E(X_i) = \mu$ ,  $var(X_i) = \sigma^2$ ,

$$cov(X_i, X_j) = \sigma^2 \rho_k, \quad |i-j| = k, \quad (16)$$

$i = 1, \dots, p$ ;  $k = 1, \dots, p-1$ . In particular, if  $\rho_k = 0$  for  $k \geq 2$  then  $\Sigma$  is tri-diagonal; if  $\rho_k = \rho^k$  then  $\Sigma$  is autoregressive [e.g. (Press 1972, pages 204,207)]. Both models provide more flexibility to model the covariance structure between adjacent and distant semimeridians and consequently would be able to model a subregion determined by larger number  $g$  of semimeridians. Extending  $g$ , in turn, might prove that the assumption of symmetry is no longer valid, in which case the statistical analyses related to the curvature range need to be (considerably) modified.

Concepts such as the signal-to-noise ratio  $B = m^2/\sigma^2$  (Parzen 1960) and its multivariate version  $\mathbf{m}'\Sigma^{-1}\mathbf{m}$  need to be considered as an alternative specification of CACTs, as well as inferences about the cosine directions  $\theta_f, \theta_s$  associate with the amount of astigmatism  $\alpha$ . We anticipate that standard multivariate methods of principal components can be adapted to the analysis of CACT data. These topics will be considered in another report.

To conclude, we would like to point that, in a broader sense it is opportune to keep in contrast our perception of how good a CACT ought to perform with our common expectation of how good,

for example, an ELISA test ought to screen donated blood for a certain antibody. Although an ELISA and a CACT share the broad purpose of estimating or detecting the true state of Nature based on its apparent manifestations, the language and the elements of the discourse about the diagnostic utility of such instruments contrast sharply. In fact, the clinical interpretation of the reported accuracy and precision of a CACT does not seem to find a clear analog in the corresponding clinical meaning of the sensitivity, specificity and predictive value of a diagnostic or screening test, such as an ELISA. Moreover, what is well known to be an integral part of any statement about the diagnostic utility of a clinical test, namely the prevalence of the disease under consideration, is virtually absent from our discourse and statements about the clinical utility of a CACT-based outcome (Viana and Farewell 1990, Viana, Ramakrishnan and Levy 1993).

## A Appendix.

**Posterior marginal distributions of  $\mu, \lambda_1$ .** Given  $(\mu, \sigma, \rho)$ , the distribution of  $\bar{\mathbf{X}}$  is p-variate normal  $N_p(\mathbf{m}, \Sigma/N)$  with vector of means  $\mathbf{m}$  and covariance matrix  $\Sigma/N$ , independent of the distribution of  $A$  which is p-variate Wishart with parameters  $\Sigma$  and  $n = N - 1$ . Similarly, we write:  $A \sim W_p(\Sigma, n)$ . Let  $\Gamma$  be an orthogonal  $p \times p$  matrix with first column constant and equal to  $1/\sqrt{p}$  (Press 1972). Then, conditionally,  $\bar{\mathbf{X}}^* = \Gamma' \bar{\mathbf{X}} \sim N_p(\Gamma' \mathbf{m}, D_\lambda/N)$ , independent of  $A^* = \Gamma' A \Gamma \sim W_p(D_\lambda, n)$ , where  $D_\lambda$  is a  $p \times p$  diagonal matrix with the first diagonal entry equal to  $\lambda_1 = \sigma^2[1 + (p - 1)\rho]$  and the remaining  $(p - 1)$  diagonal entries equal to  $\lambda_2 = \sigma^2(1 - \rho)$ , and  $(\Gamma' \mathbf{m})' = (\mu\sqrt{p}, 0, \dots, 0)$ . Let

$$Y_1 = \sqrt{N}(\bar{\mathbf{X}}^*)_1 = \frac{\sum_{i=1}^N \sum_{j=1}^p X_{ij}}{\sqrt{Np}}, \quad Y_j = (\bar{\mathbf{X}}^*)_j, \quad (17)$$

$$Q_1 = (A^*)_{11} = \frac{\sum_{u,v} A_{uv}}{p}, \quad Q_j = (A^*)_{jj}, \quad j = 2, \dots, p. \quad (18)$$

The likelihood on the data factors into  $f(y_1 | \mu, \lambda_1)f(q_1 | \lambda_1) \prod_{j=2}^p f(y_j | \lambda_2)f(q_j | \lambda_2)$ , where  $f(\cdot | \cdot)$  indicates the respective density functions:  $Y_1$  is  $N_1(\mu\sqrt{Np}, \lambda_1)$ ,  $Y_j$  is  $N_1(0, \lambda_2/N)$ , while  $\lambda_1 Q_1$  and  $\lambda_2 Q_j$  have chi-square distributions with  $n$  degrees of freedom,  $j = 2, \dots, p$ . The marginal likelihood based on  $y_1, q_1$  leads to the posterior distribution  $g$  of  $\mu, \lambda_1$  with respect to  $p(\mu, \lambda_1) \propto \lambda_1^{-1}$ . The integration of  $g$  with respect to  $\lambda_1$  shows that the posterior distribution of  $\sqrt{n-2} (y_1 - \mu\sqrt{Np})/\sqrt{q_1}$  is Student's  $t$  with  $N - 3$  degrees of freedom. Integrating  $g$  with respect to  $y_1 - \mu\sqrt{Np}$ , which is a linear function of  $\mu$ , shows that the posterior distribution of  $\lambda_1$  is inverted-gamma-1 with parameters  $d = n/2$  and  $y = Np\bar{s}/2$ , that is (Raiffa and Schlaifer 1968):

$$f_{i\gamma 1}(\lambda_1 | d, y) = \frac{[exp - y/\lambda_1](y/\lambda_1)^{d+1}}{y\Gamma(d)} \quad \lambda_1 \geq 0, \quad d, y > 0.$$

**Posterior marginal distribution of  $\lambda_2$ .** The marginal likelihood depends only on  $Y_j, Q_j, j = 2, \dots, p$ , which, given  $\lambda_2$ , are independent. Then  $\sum_{j=2}^p Y_j^2$  and  $\sum_{j=2}^p Q_j$  are independent given  $\lambda_2$ , and because the matrix  $\Gamma$  is orthogonal, can be expressed as  $\sum_{j=1}^p (\bar{X}_j - \bar{X})^2$  and  $N(p - 1)(1 - r)trS/p$ , respectively, where  $r$  is the conventional estimate indicated in Eq. (7) of the equicorrelation coefficient  $\rho$ . Consequently,  $\lambda_2^{-1}N \sum_{j=1}^p (\bar{X}_j - \bar{X})^2$  and  $\lambda_2^{-1}N(p - 1)(1 - r)trS/p$  have chi-square

distributions with  $p - 1$  and  $(p - 1)N$  degrees of freedom, respectively, are independent given  $\lambda_2$ , and the distribution of  $2\lambda_2^{-1}T$ ; where

$$T = \frac{N}{2} \left\{ (p - 1)(1 - r) \frac{\text{tr} S}{p} + \sum_{j=1}^p (\bar{X}_j - \bar{X})^2 \right\}, \quad (19)$$

is chi-square with  $(p - 1)n$  degrees of freedom. Equivalently, the distribution of  $T$  given  $\lambda_2$  is gamma-1 with parameters  $d = (p - 1)N/2$  and  $y = 1/\lambda_2$ , that is:

$$f_{\gamma 1}(t) = \frac{[\exp - yt](yt)^{d-1}y}{\Gamma(d)}, \quad t \geq 0, \quad d, y > 0, \quad (20)$$

and it then follows that the posterior distribution of  $\lambda_2$  with respect to  $p(\lambda_2) \propto \lambda_2^{-1}$  is inverted-gamma- 1 with parameters  $d$  and  $t$ .

**Prediction of  $\bar{X}_{N+1}$ .** The predictive density function  $f$  of  $\bar{\mathbf{X}}_{N+1}$ , the average of the  $p$  components of a subsequent observation  $\mathbf{X}_{N+1}$ , conditionally independent of  $\mathbf{X}_1, \dots, \mathbf{X}_N$ , follows from

$$f(\bar{X}_{N+1} | \mathbf{x}_1, \dots, \mathbf{x}_N) = \int_{\mu} \int_{\lambda_1} f_N(\bar{x}_{N+1} | \mu\sqrt{p}, \lambda_1) g(\mu, \lambda_1 | \mathbf{x}_1, \dots, \mathbf{x}_N) d\lambda_1 d\mu. \quad (21)$$

**Posterior distribution of  $\alpha$ .** Under the equicorrelated-symmetric model with  $\rho \in [0, 1)$  the distribution of  $\mathbf{X}$  can be expressed in terms of (David 1981),(Tong 1990)

$$\sigma[\sqrt{\rho}U_0 + \sqrt{1 - \rho}U_j] + \mu, \quad j = 1, \dots, p, \quad (22)$$

where  $U_0, U_1, \dots, U_p$  are independent standard normal variables. When  $\rho \in (\frac{-1}{p-1}, 0)$  the distribution of  $\mathbf{X}$  can be expressed in terms of

$$\sigma[\sqrt{-\rho}V_0 + \sqrt{-\rho}V_j] + \mu, \quad j = 1, \dots, p, \quad (23)$$

where  $V_0, V_1, \dots, V_p$  are standard normal variables,  $V_1, \dots, V_p$  are independent, and

$$E(V_0V_j) = \frac{-\sqrt{-\rho}}{\sqrt{1 - \rho}}, \quad j = 1, \dots, p. \quad (24)$$

In either case, it then follows that the distribution of the curvature range  $\alpha = \mathbf{X}_{(p)} - \mathbf{X}_{(1)}$  is the distribution of  $\sigma\sqrt{1 - \rho} W_p = \sqrt{\lambda_2} W_p$ , where  $W_p$  is the range of  $p$  independent standard normal variables.

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