MATHEMATISCHES FORSCHUNGSINSTITUT OBERWOLFACH

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Medizinische Statistik

24.2. bis 2.3.1985

Die von den Herren N. Keiding (Kopenhagen) und H. Klinger (Düsseldorf) geleitete Tagung stand unter dem Rahmenthema

"Growth and Repeated Measurement Designs."

Die theoretisch sehr vielschichtige und für Anwendungen wichtige Fragestellung, wie man durch wiederholte Beobachtungen an den gleichen Personen statistisch fundierte Rückschlüsse auf Abläufe in der Zeit ziehen kann, fand große Resonanz. Von den 36 Teilnehmern, davon 12 aus dem Ausland, wurden 29 Vorträge gehalten, in denen sowohl theoretische Modelle als auch praxisnahe Ansätze zum Rahmenthema und zu anderen aktuellen Fragestellungen vorgestellt wurden. Die Beiträge wurden ausführlich und teilweise bis spät in die Nacht hinein diskutiert.

Insbesondere standen Fragen, wie theoretische Konzepte in der Praxis realisiert bzw. praxisnahe Modelle formuliert werden können, immer wieder im Mittelpunkt fruchtbarer Gespräche.

Vortragsauszüge

K. ABT:

A multivariate median and a non-parametric Mahalanobis-like distance

The method of constructing non-parametric multivariate tolerance regions for continuous random variables with metric scales (ABT, Biom.Journ.1982) is applied to give an estimate $\hat{M}^*$ of an N-dimensional median which is invariant to linear transformations of the N axes. The scale independence of $\hat{M}^*$ is essential for medical applications where the axes represent variables with scalings different by nature. Since the construction process contains random decisions as to the choice of sample points for defining and cutting off "blocks", the median will be estimated by repeated construction runs.

For the population with continuous density $f(x,y)$, an analogue to the sample median $\hat{M}^*$ thus constructed may be defined, for the case of $N = 2$ dimensions, by the solution of

$$\Phi(M^*) = \int_0^{\Pi} \left| \int_{-\infty}^{\varphi(M^*)} f_\varphi(u_\varphi)\, du_\varphi - \frac{1}{2} \right| d_\varphi \overset{!}{=} \text{Min}$$

where $u_\varphi(M^*) = x_{M^*} \cos\varphi + y_{M^*} \sin\varphi$ with $M^* = (x_{M^*}, y_{M^*})$ and where $f_\varphi(u_\varphi)$ is the marginal density function of $f(x,y)$ along u_φ. $\Phi(M^*)$ can easily be interpreted as a defining function also for $N > 2$.

The connecting line between a point P_i and $\hat{M}^*$ is used to define a Mahalanobis-like scale independent distance function Q_i:

$$Q_i = \frac{|P_i - \hat{M}^*|}{|P_{io} - \hat{M}^*|}$$

where P_{io} is the intersection point of $\overrightarrow{\hat{M}^* P_i}$ with the limiting plane of the $\Pi \cdot 100\%$ tolerance region.

D.G.ALTMAN:

Problems in assessing fetal size

The similarity is noted between growth standards and the reference (or 'normal') range for a variable (often biochemical measurement) which changes with age. The problem of deriving a smooth age-specific reference range is considered and a broad strategy outlined. The use of the normal distribution approach is preferred, partly because of the ease with which one can derive a score for new individuals in standard deviation units. These scores are useful for further analysis, including the comparison of a different group of individuals with the reference group. The reference range is obtained by combining an estimate $f_1(\text{age})$ of the age-specific mean and an estimate $f_2(\text{age})$ of the age-specific standard deviation around $f_1(\text{age})$, so that a $100(1-\alpha)\%$ reference range is given by $f_1(\text{age}) \pm z_{1-\alpha/2}\, f_2(\text{age})$. The importance of careful checking of goodness-of-fit is emphasized.
Ultrasonic fetal measurement standards are discussed. These typically include a small amount of repeated measurements, but at completely irregular times. Using within-subject pairs of measurements one can get a set of estimates of growth velocity, and the methods described for modelling age-related reference ranges can be applied to derive smooth longitudinal standards. Perhaps the main problem is that cases with multiple measurements may not be a representative subset of the whole sample.

A.H. ANDERSEN:

Analysis of variance with correlated errors

The usual analysis of variance model is often inappropriate if one of the criteria of partition is the time because of serial correlations. The two-way analysis of variance model

$$X_{it} = \alpha_i + \beta_t + U_{it}$$

where the rows of the matrix $\{U_{it}\}$ are independent and identical distributed as consecutive random variables from a stationary Gaussian process was studied in Andersen, Jensen and Sahon (Internat.Statist.Review, 1981). Using the approach suggested by Welch

(Biometrika, 1937) an approximation of the distributions of the usual F-test statistics of no column and of no row effect were derived as a constant times an F-distribution with modified degrees of freedom, and the validity of the approximations as shedied. The results are extended to an one-way analysis of variance model with serial correlations within one of the n criteria of partition.

P. BAUER:

Two Stage Plans for Simultaneously Testing Main and Side Effects

In clinical trials for the comparison of two treatments it seems reasonable to stop a trial, if in the early stage either one of the treatments shows a clear tendency for being superior in the main effect, or one of the treatments appears to be clearly worse in the side effect. Two stage sampling plans for the simultaneous test of main and side effect are proposed in the situation of the normal distribution with known variances but unknown correlation. The test procedure keeps the global significance level α . A generalisation of the power function allows the choice of the maximum sample size and the individual, not necessarily equal, significance levels for the tests of main and side effect at halftime or the end of the trial, so that the probability for the detection of certain existing differences either in main or side effects can be controlled.

ULF BÖCKENHOLT:

Confidence intervals on inflection points of human growth curves

Important aspects of a fitted growth curve are commonly studied by quantifying the onset and the peak of maximum growth velocity during the pre-adolescent and the adolescent stages. These (so-called) biological parameters are defined in terms of the maxima and minima of the velocity curve, and are obtained by finding the zeros of the acceleration curve. Certain procedures for the derivation of confidence limits are discussed. By application of these methods to growth models such as those of Bock and Thissen (1980) or Preece and Baines

(1978), confidence limits are obtained that reflect the stochastic nature of the model parameter estimates as well as the flatness of the velocity curve in the neighborhood of the biological parameter estimates. This approach simplifies the interpretation of the modelled human growth process in terms of the magnitude and precision of the biological parameters.

E.BRUNNER:

Estimation problems in pre-randomized designs

The mathematical basis of Zelen's suggestion of pre-randomizing patients in a clinical trial and then asking them for their consent is investigated. First the problem of defining and estimating treatment and selection effects appears. In each sample one imagines the whole population being partitioned into subpopulations which can be considered as identical in regard of the selection. These subpopulations are unobservable in some cases. In a natural way one yields for the observable groups of subpopulations a linear model in the distinct subpopulations. By means of the theory of linear models the estimability of the effects is evaluated. Then one yields that all effects are estimable in the simple PRD, whereas additional assumptions must be made in the double or triple PRD so that interpretable effects can be estimated. Further on it will be shown that the intuitive suggestion of M.Zelen to apply the usual teststatistics is correct for the estimation of effects, if 1. linear functionals of distribution functions are considered and if 2. the effects are defined as linear constrasts of these linear functionals. Finally the problem of estimating non linear functionals will shortly be discussed.

D.G. CLAYTON:

Repeated measurements of risk factors in epidemiological aetiological studies

It is well-known that inaccuracy of measurements of risk factors in aetiological studies can result in serious bias in estimates of effects. In practice, many epidemiological studies include substudies which investigate the test-retest reliability of measurements. The paper explores the use of information from such substudies to improve inferences from the main study.

We adopt the model in which disease outcome, y, is related to the unknown true values of the risk factor, ω, by the model

$$y = \alpha + \beta\omega + \varepsilon$$

and we assume replicate measures, $\{z_i\}$, at ω are available where

$$z_i = \gamma + \delta\omega + \xi_i$$

ε and $\{\xi_i\}$ are assumed to be independent errors.

The paper explores the information available concerning β from studies in which replicate measurements are taken in a sample of individuals studied. It is concluded that even very modest reliability substudies can be very valuable.

J. CUZICK:

Semi-parametric models for accelerated growth curves

A semi-parametric model is described which can be used, among other things to model the growth of tumors subject to cytostatic treatment, drug metabolism in pharmacokinetic and bioessay problems related to drug potency. The model is of the general form

$$y = e^{\alpha z} f(e^{\beta z} x) + \text{error}$$

where z is a (vector of) covariate(s), α and β are regression parameters and f is an unknown function. Primary interest is in an estimate of α and β, and f is regarded as a nuisance parameter. Two methods of analysis are considered

1) iterative estimator of α,β by parametric methods and then f by spline functions
2) estimation of α,β by minimizing a smoothness criterion for the residuals.

UWE FELDMANN:

A regression and discrimination model with ordered categorical response

In medicine both, diagnostics and prognostics, are of great importance. While disgnostics can be regarded as a discrimination problem to allocate a patient into one of several nominal disease categories, the mathematical modelling of prognostics has other aspects.
First there is the regression problem to estimate an ordered categorical response, for instance the degree of a future illness evoked risk, and secondly there is the decision making problem to allocate the patient into one of these ordinal categories, for instance in order to prevent the expected risk by implementing therapeutic interventions.
Regression models with ordered categorical outcome are known, however corresponding ordinal discrimination models are not available.
Using a generalized logistic regression approach, an ordinal Bayes' allocation rule is achieved and conditions of stochastic ordering are stated.
Likelihood estimates for the three common sampling designs are developped and applied to the preoperative prediction of perioperative risks.

T. GASSER:

New tools for the exploratory analysis of curve data

First, a nonparametric estimate for the residual variance in nonlinear regression is introduced. Under mild regularity conditions, strong consistency and asymptotic normality can be proved. The pseudo-residuals introduced yield also information with regard to outliers and heteroscedasticity.

Second an estimate for a sample average curve is introduced, based on the following model for the data X_{ij} (i=1,...,n:individuals; j=1,...,T:time):

$$X_{ij} = X_i(t_j) = a_i(g_i(t_j)) \cdot f(g_i(t_j)) + \varepsilon_{ij}$$

The function f (the average curve) and the individual age scale g_i and amplitude scale a_i are estimated by an iterative procedure. The starting value relies on estimating characteristic features by kernel smoothing, and the iteration procedes via correction spaces (spaces with β-spline basis with appropriate knot sequences).

W. HÄRDLE:

Bandwidth Choice in Nonparametric Regression made understandable

The bandwidth selection problem in nonparametric kernel regression is considered. Bandwidth selectors based on cross-validation, like Akaike's Information Criterion (AIC), and on other ideas are compared. It is seen that the bandwidth $\hat{h}$ selected from the cross-validation function is asymptotically optimal in the sense that

$$\frac{MISE(\hat{h})}{\inf_h MISE(h)} \longrightarrow 1 \quad a.s.$$

Other selectors (e.g. AIC etc.) are not necessarily equivalent to cross-validation. Conditions are given under which the equivalence holds and modifications are suggested which make the selectors equivalent.

R. HILGERS:

Survival Comparisons when there are responders and nonresponders

OYE & SHAPIRO, JAMA (1984), discuss the argumentation for effectiveness of chemotherapy in 80 studies on cancer treatment. In a great portion of these studies a comparison of survival between 'responders' and 'nonresponders' is performed to establish effectiveness. The authors argue that this procedure cannot yield valid results and propose to compare the pooled group of 'responders' and 'nonresponders' to a control group.
On the basis of simple stochastic models it was shown that this cannot be considered to yield valid results as well. The models are formal analogues to the ZELEN-designs, but in this connection do not give satisfactory solutions.
From a statistic-methodological as well as medicine-logical point of view the aim of research on chemotherapy of cancer has to be the identification of subpopulations e.g. general and specific responders or general nonresponders.

M.A. van 't HOF:

Interperiod covariance matrix-analysis

The calculation of the correlation matrix between all times of measurement in a repeated measurement design is often and easily be done. It is helpfull in detecting outliers and weak moments in a study. Apart from this, the structure in such a correlation (or covariance) matrix tells more about underlying parameters i.e. the measurement error and interindividual variation in growthvelocities. The analytic properties will be discussed in two developmental situations; growth during childhood and the (quasi) stationary post-menopausal period.
Interperiod covariance matrix-analysis promises to be a robust and powerful tool in longitudinal data analysis, although a complete formal statistical basis is not yet found.

PHILIP HOUGAARD:

An unbalanced random coefficient regression model for blood presure in diabetic children

The blood pressure for longitudinally followed diabetic children is analysed by a random coefficient regression model, which includes time dependent covariates (age, height, weight) and a constant covariate (age at diagnosis). The observations are twodimensional (systolic and diastolic blood pressure). Estimation, which is difficult because of the severely unbalanced design, is performed by a modified version of the two-stage procedure of Swamy (1971). This procedure is discussed and it is found that some commonly used approximations are poor. The variation between children is small compared to the variation within children. This implies that future blood pressures can be predicted only with considerable uncertainty.

KARL-HEINZ JÖCKEL:

Statistical Considerations for the Analysis of Growth Curves by RCR-Models

For the analysis of growth curves we consider linear regression models with random coefficients (so-call RCR-models). If individuals are measured at different time points, as it is usually the case in observational studies, the caculation of the 'best' linear estimator for the fixed effects (mean value parameter) involves the covariances which are unknown in practice. For this case several two-stage procedures, feasible GLS e.g., are investigated with respect to their statistical properties (finite sample and asymptotic results). Furthermore the effect of missing values due to selection is briefly discussed.

MERETE JØRGENSEN:

Parametric an non-parametric models applied to growth data

During a seven year longitudinal study parameters concerning growth during puberty has been recorded for a number of normal boys.
Growth during puberty does not follow a simple parametric growth curve model. A way of getting around the problem is to use either non-parametric regression or a flexible parametric model with fairly many parameters.
Relation of increase in urinary content of testosterone to height growth can be performed directly using the derived curve estimate for height growth.

A. KNEIP:

On Self Modeling nonlinear regression

Assume the multivariate regression model

$$Y_{ij} = f(t_j,\theta_i) + \varepsilon_{ij} \quad (i=1,\ldots,n;j=1,\ldots,T) ,$$

where f may depend nonlinearly on the known regressors t_j and the unknown parameter vectors θ_i. If f is known exactly or to a high degree of approximation, the θ_i can be estimated by non-linear least squares. Unfortunately in many practical situations only few information about the structure of f are available.
For this case an iterative technique is proposed for simultaneous determination of estimates of $\theta_1,\ldots,\theta_n$ and f. For $\min\{n,T\} \to \infty$ conditions are established for strong consistency of the resulting estimators of θ_i and for strong uniform consistency of the resulting estimators of f. Finally results on asymptotic normality are mentioned.

JOACHIM KUNERT:

Vollständige verallgemeinerte lateinische Quadrate und Repeated Measurements Designs

Eine Methode zum Vergleich mehrerer Medikamente ist es, den einzelnen Versuchseinheiten nacheinander jedes dieser Medikamente zu geben, um so die Wirkungen an derselben Versucheinheit vergleichen zu können. Eines der einfachsten Modelle für diese Repeated Measurements Designs wertet die Messungen univariat aus und läßt lediglich einfache Nachwirkungen der Behandlungen auf die Messungen der nächsten Periode zu. In dem Fall, daß das Experiment nach einem vollständigen verallgemeinerten lateinischen Quadrat durchgeführt wurde, möchte der Vortrag die Anwendbarkeit dieses Modells untersuchen und mit Einschränkungen empfehlen.

W. LEHMACHER:

Multiple tests for marginal homogeneity of square contingency tables

For testing the marginal homogeneity of square contingency tables the STUART test is a well known procedure. Simultaneous McNEMAR tests were proposed for locating the departure from homogeneity where the α level is adjusted by the Scheffé or Bonferroni-Holm method; Fleiss and Everitt (1971), Fleiss (1981), Lehmacher (1980). Here the method of closed test procedures is applied to obtain a multiple test based on a sequence of Stuart tests. Further, an adapted and a modified Holm test version are proposed, which lead to easier calculations.

JOCHEN MAU:

Nonparametric estimation of an integrated intensity in a partially observed nonhomogeneous Markov illness-death process

Consider a nonhomogeneous Markov jump process with transient states 0 and 1 and two absorbing states 2 and 3. Assume: (i) The process starts in 0, (ii) the transition $1 \to 0$ is impossible, (iii) an observer cannot distinguish between 0 and 1, but (iv) at the time the process enters 2 or 3, or observation is discontinued on a random basis, the immediately preceding state becomes known. Though the data may be described in terms of counting processes, properties of the proposed estimator cannot be derived by the usual approach via multiplicative intensities and martingales alone. One can show unbiasedness, though only in a certain asymptotic sense, strong consistency and an approximate variance formula. Animal carcinogenicity experiments with serial sacrifice serve as an example of application.

H.G. MÜLLER:

Empirical parameters for growth curves and other longitudinal curves

The problem of estimating a zero resp. size and location of a regression function without assuming a parametric functional relation is discussed (fixed design case). As a possible approach we propose to estimate the curve or its derivatives by kernel estimators and to choose empirical zeros/extrema as zeros/extrema of the estimated curve. A.s. rates of convergence as well as limiting distributions are derived under regularity conditions. Deviations in location and size of empirical extrema are asymptotically jointly normal with diagonal covariance matrix. Application to two medical problems is discussed: (1) Empirical parametrization of the mid-growth spurt and the pubertal growth spurt; (2) Comparison of heart pacemakers based on longitudinal frequency data.

N. NEUMANN:

Pre- postmodels in pre-randomized designs

ZELEN (1979) has proposed a new method for performing clinical trials: The patients are randomized into two groups, those in the first group will receive the standard treatment A, those in the second group are asked whether they will accept the new therapy. These two groups are partitioned into two corresponding subpopulations. A linear regression model is assumed for the data in each subpopulation (post-treatment data are the variable of interest and the pre-treatment data serve as covariate). In this model the usual analysis of covariance does not work, since in the first group the subgroups are not observable. Under certain conditions the treatment effect can be estimated and tested (but not in the way suggested by Zelen). The situation is much simpler, if we assume a block-design and it can be shown that the treatment effect can be tested asymptotically by usual ANOVA.

R. REPGES:

Modeling the growth of polyglucane molecules

The process of synthetizing polyglucane molecules by the cell is modeled by a two-dimensional Markovprocess. Expressions for the probability that the length at time t is equal to n and that the degree of sulfotation S, $o \leq S \leq n$, for given length is equal to s could be derived. The distribution of the length, given t was also known by experiments, and there was a good accordance.

P. ROEBRUCK:

Remarks on permutational tests for repeated measurements

The well known distribution free tests for repeated measurements largely are based on crude transformations of the data to yield a nice distribution of the criterion. Other ones use rank procedures and their asymptotical distributions or small tables for small sample sizes. Most of all those procedures are based on permutation models and the question is, why not to use the exact permutational test.
Examples of permutational tests are presented, which partially can be performed by a quick algorithm. The following test problems are concerned: Abrupt change of level at a known timepoint or within an interval, regression, autocorrelation and correlation between time series with and without time lags, orthogonal polynomials.

M. SCHUMACHER:

Testing for proportional hazards

When comparing two samples of possibly censored survival times it is very important to assess the proportionality of the underlying hazard functions. The key idea behind the new test procedure presented is that estimates for the relative risk based on different weight functions should be very similar under the null hypothesis of proportional hazards but should be substantially different when the hazard ratio varies with time. Some properties, e.g. asymptotic normality and consistency against alternatives with monotone hazard ratio, are shown. A related graphical method, a "trend plot", is presented and recommendations for the choice of appropriate weight functions are given. The strengthes and weaknesses of the test procedure proposed are illustrated by few examples featuring various situations which are of practical importance in clinical research.

LENE THEIL SKOVGAARD:

Examples of repeated measurement designs in physiology

If the time span and sampling frequency in a repeated measurement design allow a meaningful estimation of individual time courses, the appropriate statistical analysis technique is often that of regression with random coefficients. In this case, the analysis can be decomposed into two parts, the individual curve fitting and the subsequent analysis of parameter estimates. However, the individual time courses do not always allow the fitting of reasonable parametric functions, and more ad hoc procedures must be considered instaed. For example, certain time contrasts can be of interest, or it might be appropriate to obtain estimates from nonparametric techniques. A couple of examples from anaestesiology and physiology will be used to illustrate the choice of model and some problems involved in the analyses.

H.J. TRAMPISCH:

Discriminant analysis with mixed data

The discriminant analysis problem with mixed data is treated. Quantitative and qualitative measurements are mixed. Let (X,A,G) be a random variable where X denotes the continuous and A the qualitative variable. G is the group variable where the individual on which the random variable is observed belongs to. Let $f_g(x,a) = p_g(a) \cdot h_{ga}(x)$ be the factorized density of $f(x,a)$ given $G=g$. Under the condition that the conditional distribution of x is normal $F(x \mid A=a, G=g) : N(\mu_{ga},\sigma_a^2)$ the Bayes' optimal allocation rule is determined through a linear discriminant function for each a. Methods for estimating the parameter of the so called location model are given and discussed by aid of two examples.

M. VæTH:

Treatment evaluation in chronical diseases:
a non-parametrical approach using simple scores

A non-parametrical test for comparison of treatments in chronical diseases based on observations of the stage of the disease at different timepoints is given. The test which allows for an adjustment for concomitant variables through a stratification, is based on a pairwise comparison of patients yielding scores of +1,0,-1 . The mean and the variance in the permutational distribution of the test statistic are derived and a normal approximation suggested. The method is illustrated by a material of patients with rheumatoid arthritis.

K.M. WITTKOWSKI:

On the problem of missing and uncertain data in nonparametric analysis of repeated measurement designs

Even if repeated measurements had been planned in a randomized block design, missing and uncertain data may occur e.g. if growth curves are estimated from (few) non-equidistant observations. Several generalizations of the Friedman test, consequently, have been proposed during the last few years. These approaches are generalized and corrected, resp., in two aspects: (1) From the different score weighting functions proposed, an unbiased solution is presented and implications upon interpretation of intermediate results are discussed. (2) The proposed Scheffé-type multiple comparison procedures are proven to be inconsistent, provided the global hypothesis is not true, depending on the distribution of missing cells and a corrected form is presented.

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