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Medizinische Statistik
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Die diesjährige 15. Tagung über Medizinische Statistik wurde von Herrn P. Ihm (Marburg) und Herrn E. Walter (Freiburg) geleitet.

Die 33 Vorträge behandelten Themen aus den verschiedensten Bereichen der medizinischen Statistik. Die meisten Beiträge standen in Beziehung zum Generalthema "Statistische Methoden bei Krebserkrankungen".So wurden Probleme bei Screeningprogrammen und therapeutischen Versuchen,besonders Randomisierung, Stichprobengröße, Auswertung von Überlebenszeiten und Sequentialpläne eingehend behandelt. Zu diesem Themenkreis fand auch eine abendliche Diskussion mit allgemeinem Erfahrungsaustausch statt.

In zahlreichen Beiträgen wurde auf die Schwierigkeiten bei der Anwendung bekannter Methoden in der Beratungspraxis eingegangen und Lösungsmöglichkeiten erörtert.

Vortragsauszüge

K. ABT:

Non-orthogonal ANOVA as an exploratory tool in medical statistics

In medical studies very often the question arises which of a given number of factors exercise an influence upon certain variables such as a therapeutic result. Usually the combined analysis of several factors amounts to the analysis of cross-classified data structures with non-proportional cell frequencies including situations with empty cells. The appropriate method of analysis appears to be non-orthogonal ANOVA which method can play an important role as an exploratory tool in non-randomized studies of the kind described above. The aim of the paper is to outline as to which aspects non-orthogonal ANOVA and its application are of an exploratory nature and thus deviate from confirmatory methods of analysis. The version of non-orthogonal ANOVA being discussed is the one described by the author in METRICA (1967).

D. G. ALTMAN

Analysing circadian blood pressure data

Ambulatory intra-arterial blood pressure monitoring yields a continuous stream of data for 24 hours or more. The data can be analysed by looking at every beat for all or part of the day, or by considering average blood pressure over short periods (usually an hour) for 24 hours.

This paper discusses the problems in data analysis, presentation and interpretation encountered in the analysis of several hundred sets of 24 hourly mean blood pressures. The clinical questions considered include the definition of an individual's blood pressure variablility, assessing the effects of drug therapy (and placebo), validation of

automatic blood pressure analysers and studying blood pressure behaviour during sleep.

J. BERGER:

Some remarks on the proportionate mortality rate (PMR)

In occupational studies considering the association between a suspected factor and mortality one often deals only with all deaths occuring within some interval. If the index r denotes the risk group, c the control group and d_r, d_c are the numbers of cause specific deaths and D_r, D_c the total numbers of deaths, the PMR is defined as $\frac{d_r/D_r}{d_c/D_c}$ and a value > 1 is usually interpreted as an association between the risk factor and mortality.

However, the PMR is an unbiased estimator of the risk ratio (RR) only if $\frac{d_r/D_r}{d_c/D_c} = \frac{d_r/N_r}{d_c/N_c}$, where N_r, N_c denote the respective numbers of persons under risk. I.e. the PMR can be written as $PMR = \frac{D_c/N_c}{D_r/N_r} \cdot \frac{d_r/N_r}{d_c/N_c} = \lambda \cdot RR$. The expression shows that the PMR is only proportional to the RR and the factor λ depends on the overall mortality ratio.

The misleading interpretation of the PMR is demonstrated in an example concerning heart infarction and type of employment. The observed number of infarctions in the risk group was 81 out of 339 deaths and in the control 258 out of 1534 deaths yielding a PMR = 1.42. However, in this case it was possible to calculate $\lambda = 1.47$ which indicates a higher overall mortality rate in the control group. The adjusted $RR = \frac{PMR}{\lambda} = 0.97$ indicates no increased risk. This real example shows the problem behind using the PMR in risk estimation.

D. G. CLAYTON:

Multivariate life tables

Multivariate failure time data with censored observations arises in epidemiological studies of the incidence of one or more diseases in families of related individuals. A general class of models for association in such data is suggested by analogy with Cox's regression model for failure time data and with log-linear models for contingency tables.

The problems of fitting the class of models using data obtained from prospective and retrospective aetiological studies will be discussed.

J. CUZICK:

Rank tests for association with censored data

A generalization of the proportional hazards model is presented which allows for the analysis of association between two censored time variables or for association between the (scores of the) ranks of a continuous covariate and a censored time variable. Consider the functional linear relationship $Y_1 = aZ+e_1$, $Y_2 = bZ+e_2$, where e_1, e_2 are independent error variables. Let C_1, C_2 be possibly correlated potential censoring times which are independent of Y_1, Y_2. From independent observations of $T_{ij} = \min (Y_{ij}, C_{ij})_{i=1,2,\ j=1,\ldots,N}$ and an indication of which observations were censored, a locally most powerful (with respect to an approximate likelihood) rank test for $a = 0$ is constructed. The proportional hazards model corresponds (up to monotone transformations of Y_1) to the case when e_1 has minus the extreme value distribution, i.e. $P(e_1 \leq x) = \exp(-e^x)$. The test turns out to be a simple correlation of scores based on the generalized rank vectors of the two coordinates. Basic properties of the test statistic are presented. Further details will appear in Biometrika (1982).

P. DEGENS:

Sind MLE mit inzidenten Parametern wirklich MLE?

Der erste und ein entscheidender Schritt bei der Anwendung der Statistik ist die Erstellung eines wahrscheinlichkeits-theoretischen Modells. Man kann ein bekanntes Modell verwenden, interessiert sich aber nur für einen Teilaspekt dieses Modells. Z.B. möchte man die Varianz eines Verfahrens bestimmen und hält eine Normalverteilungsannahme mit unbekannter Varianz, aber auch unbekannter Lage für akzeptabel. $(\bar{X}, S^2)$ ist hierfür eine suffiziente Statistik. Der MLE für Lage und Varianz (μ, σ^2) ist durch $(\bar{X}, \frac{1}{n} S^2)$ gegeben und die zweite Projektion liefert $\frac{1}{n} S^2$ als MLE für σ^2. Stellt man sich dagegen auf den Standpunkt, daß die Statistik $\bar{X}$ nur Information über die Lage liefert, in S^2 dagegen die volle Information über die Streuung vorhanden ist, so kann man die Verteilung von S^2 allein betrachten. Hierbei sind $\bar{X}$ und S^2 unabhängig. S^2 ist χ^2_{n-1}-verteilt, der MLE für σ^2 ist damit $\frac{1}{n-1} S^2$. Analoges gilt z.B. auch für die Exponentialverteilung mit Lage- und Skalenparameter. Bei anderen Modellannahmen ist eine solche Darstellung i.a. nicht möglich, jedoch ergeben leichte Abänderungen (Reduktionen) des Modells völlig andere MLE. Probleme dieser Art treten in der clusteranalysis, switching regression und z.B. der mathematischen Psychologie auf.

K. DIETZ:

An application of the randomized response technique

Let π_A be the proportion of individuals in a population with a sensitive attribute. If one estimates π_A by direct questioning, one is likely to get a biassed result. In order to assure anonymity to the person interviewed, Simmons proposed in 1967 the following variant of the Randomized Response Technique by Warner (1967): Select two samples. Each individual is asked either the sensitive

or an unrelated non-sensitive question depending on the outcome of a chance experiment. Only the probability P_i, $i = 1,2$ of the chance experiment in the two samples is known to the interviewer, not the outcome itself. Then $\hat{\pi}_A = [\hat{\lambda}_1(1-P_2) - \hat{\lambda}_2(1-P_1)]/(P_1-P_2)$ where $\hat{\lambda}_1$, $\hat{\lambda}_2$ are the observed proportions of "yes" answers in the two samples. An extension of this method involving several sensitive questions and its application is described where the sensitive issue is the abuse of drugs.

L. EDLER:

Probleme bei der quantitativen Beschreibung eines Karzinogeneseexperiments

Ausgehend von vorliegenden Daten und bislang lediglich einfachen Modellvorstellungen der Experimentatoren werden Methoden zur quantitativen Beschreibung größerer Karzinogeneseexperimente dargestellt und an dem konkreten Fall des DIELDRIN überprüft. Dabei geht es sowohl um eine Quantifizierung der Dosisabhängigkeit der Tumorinduktionszeit als auch um eine Entscheidung darüber, ob ein Karzinogen oder ein Promotor (Co-Karzinogen) vorliegt. Druckreys Beziehung wird daraufhin diskutiert. Es wird versucht, die Dosis-Wirkungsbeziehung sowohl durch nicht-parametrische Methoden (relative Risiken, mediane Induktionszeiten, Dosis als Kovariable im Coxschen Regressionsmodell) als auch durch einen parametrischen Ansatz mit der Weibullverteilung zu quantifizieren.

K. FAILING:

Eigenschaften und Anwendungen nichtparametrischer Dichteschätzer

Nach einer kurzen Diskussion der Ziele insbesondere nichtparametrischer Dichteschätzung werden die im Vortrag betrachteten Formen des fixen und variablen Kernschätzers angegeben. Die Grundideen zum Konsistenzbeweis für den

variablen Kernschätzer schließen sich an. Danach wird die Anwendung der Kernschätzer zur Schätzung der Hazard-Rate bei unzensierten Daten demonstriert und für die Schätzung bei zensierten Daten ein "naiver" Dichte- bzw. Hazard-Rate-Schätzer angegeben. Der Vortrag endet mit Hinweisen auf weitere Verbesserungen und Anwendungen der zur Verfügung stehenden Schätzfunktionen.

U. FELDMANN:

Misclassification with tolerance regions

Statistical and heuristical tolerance intervals for measuring values of analytical methods in clinical chemistry are often used as an aid in medical decision making. Observed values lying outside the tolerance region are called positive or pathological findings. Due to the precision of a measuring method the observed value is a superposition of the actual value and a random error. A variance component model is derived in order to quantify sensitivity and specifity of the decision depending on the precision of the measuring method. The relationship between nominal and actual tolerance regions is established and quantified as a function of precision. The sensitivity of certain standard analytical methods for determining the cholesterol concentration in human serum, for example, is shown to be only 60 %.

S. M. GORE:

The statistical modelling of survival in breast cancer

The statistical modelling of survival in the Western General breast cancer series of 3922 patients is an example of non-proportional hazards. Four methodological points arise as follows:

1. the importance of the hazard function for understanding covariate effects through time

2. hazard plots allow an initial assessment of statistical models and anticipate systematic lack of fit
3. identification of prognostic factors is robust, irrespective of what model is fitted
4. the waning of covariate effects through time can be investigated in an exploratory way by fitting separate proportional hazards models in distinct follow-up intervals, for example 0-5 years, 5-10 years and 10-20 years. Little extra insight was afforded by a final (smooth) statistical model which described the decay as exponential.

Comparison of observed and expected mortality was also discussed, the 58 % excess mortality at 15-20 years after diagnosis being still highly significant.

J. D. F. HABBEMA:

Simulation models for the evaluation of mass screening for early detection of disease: advantages of simulating life-histories of individuals

Many factors together determine the impact of mass-screening on mortality and morbidity reduction. Therefore, good evaluation models should take account of all these factors (like disease-incidence, natural history of the disease, quality of the screening test, ages and frequencies of screening, attendance pattern to screening, impact of early disease detection on life-expectancy, treatment-results, costs, risk-strata etc.). When using an analytical approach by mathematical-statistical modelling, simplified assumptions have to be made, in order to make this analysis possible. Such simplifications may distort reality in a too great extent. Therefore, recently some mathematical simulation models have been proposed that indeed are able to model the screening situation quite well. The main disadvantage of these models is their problem in fitting intra-individual variation from empirical data

from screening programs. Therefore, our research group is developping another type of approach to simulating screening programs: individual life-histories are simulated according to a stochastic algorithm; first without screening, and afterwards with a screening program. The difference between these life-histories is the effect of screening. The two main advantages of using such individual life-histories are: (1) the flexibility in specifying all kinds of association between factors, indispensable in analysis in real-life screening programs (with irregular and risk-related attendance-patterns etc.). (2) the very good possibilities in assessing the model fit to empirical data (because we have after a simulation individual life-histories on file, we may count all kinds of cross-classifications for which real data are available).

R. HILGERS:

Some multi-sample extensions of grouped sequential analysis

The multi-sample extension of the model considered by POCOCK (Biometrika 1977) is treated controlling the experimentwise-error. The corresponding multivariate χ^2-distribution is given and further applied to the Kruskal-Wallis-statistic.

T. R. HOLFORD:

The estimation of age, period and cohort effects for vital rates

In the analysis of vital rates it is often of interest to consider the effects due to age, period of diagnosis and birth cohort. When estimating the effects due to age, period and cohort there is aliasing due to a linear dependence among the three factors. One solution to the dependence is to set an arbitrary constraint on the parameters, but this constraint can induce an effect on

the parameters. However, estimable functions of the parameters are invariant to the particular constraint applied. For evenly spaced intervals deviations from linear are estimable but only a linear function of the three slopes is estimable. When age and period intervals have different widths further aliasing occurs. It is assumed that the number of deaths in the numerator of the rate has a Poisson distribution. The calculations are illustrated using mortality from prostate cancer in the U.S.

L. HORBACH:

Problems of the statistical analysis of cancer risk by professional factors in the chemical industry

It was one of the main objectives of a large retrospective epidemiological study concerning professional cancer in the German heavy chemical industry (DFG Forschungsbericht Berufskrebsstudie, 1981) to provide a sound empirical base for a subsequent prospective investigation. The multivariate analysis of risk suggested by J. Cornfield (Fedn. Proc. 21, 1962) was used. Vectors of the durations of exposure to defined classes of the 1200 chemical compounds were taken into account. This statistical analysis has given plausible results with important hints for further toxicological investigation. As a desirable aim in this field a model of "epidemiological monitoring" is outlined into which the chemical and other factors of professional and private life should enter.

H. IMMICH:

Did randomization work correctly?

From the clinician's point of view each randomization method has to fulfill the following presumptions:
(1) rectangular probability, (2) constant probability, (3) impredictable assignment, (4) independency of each

assignment. Because patients enter the trial in clusters during the course of time, blocking has a lot of disadvantages and should be avoided. The aim of strata is to minimize experimental errors. As few strata as possible should be chosen. In multicenter studies the centers themselves are the most important strata. In hospital practise techniques of randomization are violated frequently. An example shows, how to check whether randomization did work correctly.

D. R. JONES:

Measuring and analysing quality of life in clinical trials of prolonged cancer therapy

Some of the problems of obtaining measurements of quality of life in patients in cancer clinical trials in which there is a prolonged survival after treatment will be discussed. The problems of analysing such data will also be discussed. Brief reviews of previous work in this field will be provided and the discussion will be illustrated with reference to the time series of quality of life data being obtained in a randomised controlled trial of neuroblastoma treatments.

Ad hoc descriptions and comparisons of quality of life patterns experienced by patients in each treatment group are straightforward if characteristic patterns (such as immediate post-treatment side effects) can be identified. Integration of measures of quality and length of survival through the use of multistate survival models (with the states corresponding to different qualities of life) and competing risk analyses (with endpoints corresponding to the onset of very poor quality of life) is reviewed.

H. KLINGER:

Zur Schärfe von Zwei-Stichproben-Tests für Verlaufskurven

Werden unter zwei Bedingungen die Werte einer Zufallsvariablen $X(t)$ zu den Zeitpunkten $0 \leq t_1 < t_2 \ldots < t_m$ jeweils n_1 bzw. n_2 mal beobachtet, so sind Zufallsvektoren $X_k^{(i)} = (X_{k1}^{(i)}, \ldots, X_{km}^{(i)})$, $k = 1, \ldots, n_i$, $i=1,2$ ein geeignetes stochastisches Modell für solche "Verlaufskurven". Unter der Voraussetzung der Unabhängigkeit der $n_1 + n_2$ Vektoren und unter geeigneten weiteren Annahmen über die zugelassenen Verteilungsfunktionen $F_k^i(x_1, \ldots, x_m)$ - z.B. $F_k^{(i)} = F^{(i)}$, $k = 1 \ldots n_i$, $i = 1,2$ - ist die Hypothese $H_o: F^{(1)} = F^{(2)}$ zu testen. χ^2 - Tests beruhen auf einer Zerlegung des Stichprobenraumes $\mathbb{R}^m = B_1 \cup B_2 \ldots \cup B_s$ und den mit Hilfe der Zufallsvariablen $Y_k^{(i)} = (1_{B_1}(X_k^{(i)}), \ldots, 1_{B_s}(X_k^{(i)}))$ durch $Z^i = \sum_{k=1}^{n_i} Y_k^{(i)}$ gegebenen multinomial-verteilten Zufallsvariablen. Nach dieser Transformation ist die Hypothese $H_o^*: p_{1j} = p_{2j}$, $j = 1 \ldots s$ mit $p_{ij} = P(X_k^{(i)} \in B_j)$, $i = 1,2$, $j = 1, \ldots, s$ gegen $H_1^* = \overline{H_o^*}$ zu testen.

Um die Schärfe des für diese Fragestellung in Betracht kommenden χ^2-Tests für die $2 \times s$ Kontingenztafel beurteilen zu können, ist die Kenntnis der Wahrscheinlichkeiten p_{ij}, $i = 1,2$, $j = 1 \ldots s$ unter plausiblen Annahmen über die Verteilung der Zufallsvektoren $X_k^{(i)}$ unter der Alternativhypothese erforderlich. Es wurde gezeigt, daß unter der Annahme, daß die Komponenten der Zufallsvektoren $X_k^{(i)}$ unabhängig doppel-exponential, d.h. mit $P(X_{kl}^{(i)} \leq x) = \exp(-\exp(-(x-\mu_l^{(i)})))$ verteilt sind, für eine größere Klasse von üblichen Zerlegungen $(B_1 \ldots B_s)$ bequem handhabbare explizite Ausdrücke gewonnen werden können. Als Beispiel wurden das "Differenzenverfahren" (Krauth: Biom. Zeitschr. 15 (1973)) und das "Nachbarschaftsverfahren" (Immich, Sonnemann: Biometrie - Praximetrie 14 (1974)) in einem konkreten Fall verglichen und ihre Schärfen diskutiert.

W. KOEPCKE:

A comparison of the group sequential plans developped by Pocock and O'Brien-Fleming

Group sequential plans are a powerful tool for interim analyses in clinical trials not only with the aim of an early stopping but also performing only a limited number of tests (5 - 10). The plan described by Pocock (Biometrika 64 (1977)) is based on a closed sequential plan developed by Armitage et al. (J. Roy. Stat. Soc. A 132 (1969)) under the name of repeated significance testing. O'Brien and Fleming (Biometrics 35 (1979)) used the approach of Samuel-Cahn (Comm. Stat. 3 (1974)). In order to hold an overall significance level of α it is necessary to have a lower nominal significance level α_i at each analysis i. In Pocock's plan α_i is constant for all tests. In the method of O'Brien and Fleming the nominal level α_i is increasing from stage to stage. When comparing the two plans it turns out that the maximum number N needed is always higher for the Pocock-plan. On the other hand the average sample number unter H_1 ($E(N|H_1)$) is much lower for Pocock's method, if the power is greater 0.75. For a power less than 0.75 the plan of O'Brien-Fleming turns out to be better.

J. KRAUTH:

Finite tests for marginal homogeneity in square contingency tables

By Stuart (1955), Bhapkar (1966) and others asymptotic tests were derived for testing the nullhypothesis of marginal homogeneity in square contingency tables. This is of interest, e.g., in the problem of measuring observer agreement. Due to the special form of the nullhypothesis it is not possible to derive an exact distribution-free test as, e.g., in the case of the nullhypothesis of

symmetry. Therefore any distribution-free finite test must be based on the simultaneous performance of r two-sided conditional binomial tests, where r is the number of categories. The sum of the levels of these tests must not exceed a given overall level α. By Lehmacher (1980) it was proposed to choose all levels equal to α/r. Here two other approaches are discussed: Either only the test corresponding to the maximal sample size is performed with the given α, or the levels are chosen in such a way that the r tests approximately have the same power. The three procedures are compared with respect to the conditional powers for various alternatives.

W. LEHMACHER:

A multivariate analysis of repeated measurements in the crossover design

Wallenstein and Fisher (1977) proposed an analysis of repeated measurements (profiles) in the two-period crossover design based on an univariate parametric approach. In such methods, however, it is required that the data have an uniform covariance structure. In order to avoid this non-realistic assumption, the multivariate (over time) approach is an useful tool in the analysis of repeated measurements, see for example Morrison (1976). Here, it is suggested that multivariate statistics are used; these are the counterparts of the univariate tests proposed by Grizzle (1965) for the non-repeated case. In addition, multivariate rank tests are proposed generalizing Koch (1972) when the assumption of a normal distribution of the data is not fulfilled.

B. MAIER:

On the lead time of a screening program

Formulas for the lead time and the proportion of patients

detected by a periodic screening program as well as a device how to estimate the parameters from the findings in the initial phase of the program are presented. The preclinical state P is defined to be the interval when a patient may be detected by a screening examination before the disease becomes obvious by clinical symptoms. The lead time is the interval between detection by screening and the time point when the disease would have been diagnosed without screening. The lead time is needed e.g., if the benefit of the screening program is to be assessed by comparing the survival rates of screened and unscreened patients. Our basic assumptions are (1) constant sensitivity S throughout state P and (2) independency of subsequent screenings. Bounds for the lead time L are then given by $E(k) - \frac{1}{S} \leq L \leq E(k)$, where E(k) denotes the mean sojourn time in state P. Further, let a_i denote the number of patients detected at screen i and b_i the number of patients progressing to clinical symptoms in the interval $[i, i+1)$ without having been detected in a screen $(i = 0, 1...)$. We then obtain the following estimates $\widehat{E(k)} = \frac{a_0}{(S-1)a_0 + a_1 + b_0}$ and, if $E(k \mid 0 \leq k < 1) = 0$, also $\hat{S} = \frac{a_0 - 2a_1 + a_2}{a_0 - a_1 + b_0 - b_1}$. In the case $S = 1$ the first equation reduces to the well known relation mean sojourn time $= \frac{\text{Prevalence}}{\text{Incidence}}$ $(\widehat{E(k)} = \frac{a_0}{a_1 + b_0})$.

H. G. MÜLLER:

Analysis of human growth spurts via kernel estimates

Some mathematical details of a kernel estimation method to estimate $g^{(\nu)}$, $\nu \geq 0$, in the model $Y_i = g(t_i) + \varepsilon_i$, $i=1...n$ (fixed design regression model) are given, where Y_i are measurements of g taken at times t_i and contaminated with an error ε_i. We apply this method to longitudinal measurements of height growth from the Zürich growth

study (n = 34). For each of the 2 x 45 children we estimate g,g',g'' and then define empirical parameters according to characteristic features of these curves. These parameters enter into further statistical analysis, e.g. their distribution over the sample is investigated by kernel density estimators. Results of this analysis, which include the detection of a growth spurt at age 7 in most of the children, and some problems of the kernel approach are discussed.

H. NOWAK:

On the analysis of profiles measured at the same time

Quite often one can find graphical representations in medical publications which show time series (profiles) of different variables, e.g. blood pressure, heart rate, concentration of a drug, within one diagram - may be using different scales of the ordinate. The background for doing this might be to show some coincidence or scale-free parallelism of the profiles. Investigations using "classical" analysis of profiles are not applicable and cross correlation does not give the answer wanted. Correlation coefficients and special graphical representations give good explorative results and may even be used in a confirmatory way. Nevertheless these methods are still somewhat unsatisfactory.

S. J. POCOCK:

Practical experience of randomization in cancer trials: an international survey

The results from an international survey of 15 major cancer centres have clarified how randomization is being implemented in cancer trials. As regards the mechanics of obtaining treatment assignment for each patient a system of telephone registration to a central randomiza-

tion office was widely used. Also, we advise formal checks for patient eligibility immediately before treatment assignment and subsequent written confirmation of randomization to the investigators.

As regards statistical methods, stratification by one or two prognostic factors (and institution in multicentre trials) is commonplace. Most centres used the standard approach of random permuted blocks within strata though some others used "dynamic" institution balancing or "minimization" methods instead. The value of stratification is more for the trial's credibility in having comparable treatment groups, rather than for statistical efficiency. One should avoid overstratification and only use reliable reported factors of known prognosis. One essential is that randomization should work in practice for every patient, so that undue complexity is to be avoided.

O. RICHTER:

Adaptive control in clinical pharmacology

It is shown, how the problem of adequate drug administration can be formulated as an optimal adaptive control problem in terms of modern control theory. Under the assumption that therapeutic and/or adverse effects are closely associated with blood levels the primary therapeutic endpoint is replaced by the secondary aim to maintain blood level within a certain range around a desired level c_d. The following notations hold: $\theta = (\theta_1,\ldots,\theta_p)$: vector for pharmacokinetic parameters; $\vec{x_N} = (x_1,\ldots,x_N)$: individual drug level measurements available before the next dosage; $f_o(\theta)$: prior density of θ (population density); $f_N(\theta \mid \vec{x_N})$: posterior density of θ; $Y(t) = g(\theta, d, t)$: blood level of the drug as a function of dose d parameter θ and time t (pharmacokinetic model); $J(Y)$: performance index. The problem of

optimal individual drug administration may be stated as follows: at each stage during the treatment, a dose d is to be determined, subject to the condition that E(J(Y)) is minimized, where the expectation is taken with respect to the posterior density f_N. This method is applied to the pharmacokinetic control problem of a 2-compartment model using the quadratic performance index $J(Y) = \frac{1}{T} \int_0^T (g(\theta, d, t) - c_d)^2 dt$, where T denotes the dosage length. A computer program is described which is able to calculate optimal individual dose precriptions.

M. SCHUMACHER:

Neue Ansätze zur Analyse von Überlebenszeiten

Bei der Analyse von Überlebenszeiten im Zweistichprobenfall bleiben die bekannten verallgemeinerten linearen Rangtests wie der Logrank- oder der Gehan-Test auf eine Anwendung in einem Modell mit proportionalen Hazardfunktionen, d.h. mit konstantem relativen Risiko beschränkt. Der Unterschied der beiden Überlebenszeitverteilungen kann im allgemeinen Fall, d.h. bei in der Zeit variierendem relativen Risiko, mit Hilfe der sogenannten "Log-Effektfunktion" beschrieben werden.

Einige Eigenschaften dieser Funktion sowie asymptotische simultane Konfidenzbänder für die Log-Effektfunktion werden hergeleitet. Abschließend werden Möglichkeiten zur Konstruktion von Zweistichprobentests und von Anpassungstests basierend auf der empirischen Log-Effektfunktion aufgezeigt.

H. J. TRAMPISCH:

Estimation of mortality rates by use of nearest neighbour estimates

For a contingency table with cells z "=" (i, j, k), $1 \leq i \leq a$, $1 \leq j \leq b$, $1 \leq k \leq c$, $1 \leq z \leq d = abc$, the nearest neighbours

of $z = (i, j, k)$ are defined by $A(z) = \{(i', j, k), (i, j', k), (i, j, k') \mid i' \neq i,\ j' \neq j,\ k' \neq k\}$. Let $N(z)$ be the cell frequencies and let $N(1), \ldots, N(d)$ be multinomially distributed with parameters $p(1), \ldots, p(d)$ and $n = \sum_z N(z)$. The number of nearest neighbours of $z = (i, j, k)$ is given by $N_1(z) = \sum_{z' \in A(z)} N(z')$. The NN-estimator of first order for $p(z)$ is defined by $\hat{p}(z) = \frac{1}{n}(\omega_0 N(z) + \omega_1 N_1(z))$, $(\omega_0, \omega_1) \in \mathbb{R}^2$. Optimal weights (ω_0, ω_1) are given such that $\sum_z E(\hat{p}(z) - p(z))^2$ is minimal. In an example the NN-estimator is applied for the estimation of mortality rates.

R. TRAUTNER:

Histogram estimators

Denote by $\hat{F}_N$ the empirical distribution function of independent $X_1, \ldots, X_N$. Then $h_{nN}(t) = n \cdot \Delta \hat{F}_N(\frac{j}{n})$ for $\frac{j}{n} < t \leq \frac{j+1}{n}$ (where $\Delta \hat{F}_N(\frac{j}{n}) = \hat{F}_N(\frac{j+1}{n}) - \hat{F}_N(\frac{j}{n})$) is the histogram which is a crude estimator for the unknown density function. A general linear histogram estimator is defined by $\hat{f}_{nN}(t) = \sum_i \omega_{in}(t)\, n\, \Delta \hat{F}_N(\frac{j}{n})$.

It covers known smoothed histogram estimators by Wahba (1971/75), Vitale (1975), Gawronski, Stadtmüller (1980/81). It allows to construct new estimators, in particular a discrete analogue of the kernel estimator. If negative weights are admitted, undesirable boundary effects can be avoided usually occurring in the case of compact support of the density.

J. WAHRENDORF:

Estimation of the true length of broken molecules

We consider the problem of estimating the original length of molecules which have suffered partial fragmentation

and where even the unbroken molecules are subject to measurement error. A model of uniform breakage is assumed and the resulting density function, known from earlier work, is compounded with a suitable error distribution to yield reasonably tractable observed length distributions. These permit a qualitative study of the measurement error on the observed modes of the distributions. In parallel with the usual (number) densities the weight densities corresponding to length-biased sampling are developped, since some of the experimental techniques effectively produce distributions of this kind. Maximum likelihood parameter estimation is described, allowing for the truncation which results from the impossibility of accurately counting arbitrarily small fragments on an electron micrograph. This estimation method is applied to data on viral RNA.

E. WALTER:

On the size of a test for a new screening method

A new screening method (M) is justified, only if the false negative rate $\beta(M)$ is not higher than the false negative rate $\beta(A)$ of a standard method (A), and the false positive rate $\alpha(M)$ is not too high. A design is considered to get the numbers of ill persons who are "positive" by the standard method and "negative" by the new one, and vice versa "negative" by the standard and "positive" by the new one. The sign test can be used to test the difference $\beta(A) - \beta(M)$. The necessary number n lies (asymptotically) between the limits

$$\frac{(u_{\beta'} - u_{1-\alpha'/2})^2}{P|\beta(A) - \beta(M)|} \leq n \leq \frac{(u_{\beta'} - u_{1-\alpha'/2})^2 (\beta(A) + \beta(M))}{P (\beta(A) - \beta(M))^2}$$

where P is the prevalence, α' the significance level and $1-\beta'$ the power of the test. The lower (upper) limit is assumed, if $\beta(AM) = \min(\beta(A), \beta(M))$ $(\beta(AM) = 0)$.

E. WEBER:

Zum Problem der Kausalinterpretation von Indikatoren für den Zusammenhang in mehrdimensionalen Kontingenztafeln aus Beobachtungsstudien

Koller (Metrika (1963)) hat für den Korrelationskoeffizienten eine Typisierung korrelativer Zusammenhänge aufgestellt. Anhand dieser Typisierung, die weitgehend auf jedes Fachgebiet anwendbar ist, kann der jeweilige Fachwissenschaftler mühelos erkennen, ob eine kausale Korrelation auszuschließen ist.

Leider fehlen ähnliche Hilfsmittel für Indikatoren für den Zusammenhang in Kontingenztafeln. Am Beispiel eines umfangreichen Datenmaterials aus einer Klinik wird das Vorgehen demonstriert, ob ein statistisch gefundener Zusammenhang in einer Kontingenztafel dem Fachwissenschaftler auch eine kausale Interpretation ermöglicht. Im Falle ordinaler Merkmale bedient man sich des Assoziationskoeffizienten ψ (Wahrendorf (1980)).

J. WHITEHEAD:

Sequential clinical trials

This paper describes a sequential clinical trial which has recently been completed at St. Thomas's Hospital, London. The study compared two anaesthetic techniques, and patient response was classified simply as success or failure. The considerations behind the choice of stopping boundaries are discussed, and the monitoring procedure is described. The results of the analysis of the trial data, corrected for the sequential nature of the design, are presented. The wider application of these techniques is discussed.

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