MATHEMATISCHES FORSCHUNGSINSTITUT OBERWOLFACH

T a g u n g s b e r i c h t 8/1989

Medical Statistics: Statistical Methods in Epidemiology

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The conference was organized by Martin Schumacher (Freiburg) and Jürgen Wahrendorf (Heidelberg). There were 37 participants from West-Germany, Canada, England, USA, Denmark, Switzerland, France, Finland and Vietnam. 29 talks were given, covering a wide range within the field of statistical methods in epidemiology.

Most of the talks could be categorized into one of the following four categories: statistical modelling, models for infectious diseases, theoretical biostatistical aspects in epidemiology, application of advanced biostatistical techniques.

In the following some of the topics of the conference are highlighted. The talks on statistical modelling comprised among others latent variable models, bootstrap-techniques for variable selection, methods for attributable risk estimation in unconditional logistic regression, considerations on the effect of misclassification in general relative risk models and models for analysing biased case-control data. A so-called cumulative damage model which stands in contrast to the multistage-model in carcinogenesis was proposed. A whole session was devoted to the mathematical approach for modelling infectious diseases (including AIDS) and analysing data statistically. There were also a number of talks of general theoretical interest such as multivariate median tests, kernel estimation methods in non-parametric survival data analysis or overdispersion in quasi-likelihood models. A series of talks addressed statistical problems in connection with on-going epidemiological studies. Among these were methods for detecting a spatial clustering of cancer cases, the determination of endpoints in a prevention study or problems in the analysis of longitudinal studies on respiratory diseases.

In an additional evening session a number of on-going epidemiological studies were presented and discussed. This evening session was generally considered to be of high value because it clearly showed the link between theoretical research and field work.

Abstracts

K. ABT:

Multivariate median tests

N-dimensional k-sample median tests are proposed on the basis of the componentwise ("arithmetic") median. For k=2, the observed frequencies of the combined sample in all 2^N rectangular subspaces - where each subspace is spanned by N half axes originating from the common median - allow the construction of N orthogonal contrasts related to the N components of the median. Under the null hypothesis of the equality of the medians of the two probability distributions, these contrasts have expectations zero and can exactly be tested by calculating N corresponding binomial probabilities. Since these probabilities originate from independent comparisons, they may be combined into one single p-value under the null hypothesis. The test is shown to be possible and exact for all k=2m, m=1,2,... For k=2m+1, m=1,2,..., a χ^2-approximation of the one-sample median test (k=1) follows in a simple way. The general procedure (k=1,2,...) has to be modified if some of the 2^N rectangular subspaces are empty.

G. ARMINGER:

Latent variable models with non-metric dependent variables

In epidemiological research not only metric data are collected but also data on behaviour (like nutritional behaviour, sport, drug use), variables on state of health and general attitudes. These variables are dichotomous or ordinally scaled. In addition those data are often only indicators for not direct observable (latent) variables. In order to analyse those data it is necessary to combine the usual regression and factoranalytic models with threshold value models (dichotomous and ordinary probits). Complex systems of variables of this kind may be estimated under use of polyserial correlation coefficients with certain maximum-likelihood methods.

P. BAUER:

Model selection in larger data sets

A multiple test procedure for inferring the dimension of a general finite parameter model is proposed which consists of individual tests of each of these parameters. If the critical limits of the individual tests are allowed to depend on the sample size in an appropriate way, the test procedure provides a really consistent estimate of the minimal "correct" subset of model parameters. The procedure is applied to a large sample of audiometric measurements in workers exposed to noise.

H. BECHER:

On the analysis of biased case-control data

Data of case-control studies are often subject of various sorts of bias. We consider the case that one has more than one control group and in a one control group some (but not all) variables are biased. The common type of analysis of case control data is conditional or unconditional logistic regression depending on whether one has a matched or an unmatched design.
Different methods of analysis of data which are biased via logistic regression are presented. It is shown that a polychotomous logistic regression model and a so-called two-stage-design analysis may be applied in the present situation.
The various methods are illustrated with data from a case-control study on lung cancer.

N. BECKER:

Cumulative Damage Models: A New Mathematical Approach in Cancer Epidemiology

Analogous to the mode of proceeding in physics, where different theoretical models have been developed for different levels of reality, a phenomenological carcinogenesis model is suggested for the macroscopic consideration of diseases - by epidemiology. Investigations indicate that "Cumulative Damage Models" (CD models) possess essential qualities desirable for such a model. This concerns theoretical qualities such as, for example, the fact that they incorporate clear concepts for exposure towards environmental factors as well as for the damage process with the respective host system and also practical qualities with regard to fitting empirical data. Important fundamental consequences for epidemiology follow from the fact that these models offer measures for the description of environment-induced damages which are not dependent upon a baseline category, linear with regard to the exposure period and additive with independent exposures. All traditional measures of epidemiology can easily be calculated with the aid of the CD model.

J. BERGER:

A comparison of populations self-selected and randomly selected for coronary risk factor screening

The comparison of one random sample with two self-selected samples shows, as expected, that self-selected samples are not representative for the target population. But in spite of this the risk profile is quite similar in all three samples. As most

people are not aware of their cholesterol level and a high cholesterol level mostly shows no symptoms it is quite unlikely that cholesterol is a self-selecting factor. Therefore the data of such screening programs may also be used to study the dependence of biological parameters on demographical and environmental factors.

M. BLETTNER:

Misclassification in general relative risk models

Misclassification is a common problem in the analysis of epidemiological data and there has been extensive work i evaluating its effect in multiplicative models.
In this paper the effect of misclassification is investigated for non multiplicative model, which have been proposed in recent years (Thomas, 1981, Breslow & Storer, 1985). Different assumption about the structur and the magnitude of the misclassification error are considered. Even more than in multiplicative models small misclassification errors can yield important biases in the estimation of the relative risk. In mixture models the mixture parameter can be seriously biased, therefore the use of the mixture parameter to distinguish between the additive and the multiplicative model should be used with caution if misclassification errors are present.

N. BRESLOW:

Overdispersion in Quasilikelihood-Models

Motivated by problems of overdispersion in Poisson regression analyses, we study simultaneous estimation of mean and variance parameters in quasilikelihood models with structured parameters in the variance function. Two versions of the standard errors and score for mean parameters are investigated, one calculated from the usual model based covariance matrix whose validity depends on correct specification of the variance function, and another usin an 'empirical' covariance matrix has a more general assymptoti justification. Monte Carlo simulations demonstrate that these procedures yield approximately unbiased estimates of regression coefficients and their standard errors and that model based Wald, score and deviance tests approximate the nominal size at the 5% level for moderate sample sizes. The empirical standard errors and score test perform adequately for larger sized samples. Various parameters are not particularly well estimated by the method of moments equations used for them and their estimated standard errors do not adequately convey the true degree of uncertainty about them. These methods have important applications in epidemiology and toxicology.

K. DIETZ:

Evaluation of vaccination strategies

In order to determine the minimum coverage necessary for reducing the transmission to zero one has to estimate the basic reproduction number (or transmission potential) R of an endemic virus disease, i.e. the number of secondary cases which one case could generate during the entire infections period if the population were completely susceptible. For the equilibrium a formula can be derived (Dietz & Schenzle, 1985) which expresses R as a function of the age-dependent infection rate. In a cross-sectional survey one only knows the age of an individual and the serological status which tells whether the individual is still susceptible or has had already the infection, i.e. one has to estimate the age-dependent infection rate based on observations which are all either left or right censored. The solution of this statistical problem is given in the contribution by Niels Keiding.

K. DRESCHER:

Attributable Risk Estimation from Case-Control Data via Logistic Regression

By fitting an 'unconditional' logistic regression model to unmatched case-control data one obtains as a by-product an estimator of the joint population attributable risk for the factors included. This estimator and its asymptotic variance can be calculated in an easy way from the estimated intercept parameter and its variance.
The method can be generalized to stratified data with large strata. In that case the strata-related intercept parameters enable the calculation of strata-specific attributive risks and the estimation of its variance.

R. EDWARDS:

Spatial Clustering of Events for Inhomogeneous Populations

Some distance methods for assessing spatial clustering will be proposed, which do not require the event distribution to be uniform in the absence of clustering or the spatial intensity of the event process to be known in advance.
Instead, a group of controls are selected from the population at risk and statistics are based on whether the nearest neighbour(s) to each case is another case or a control.
The performance of these tests will be evaluated and the method applied to a dataset on the locations of cases of childhood leukaemia and lymphoma in a defined geographical area.

V. FAREWELL:

Analysis of data from a cohort of HIV^+ men

Various analyses which may be appropriate to such cohort data are explored. A mixture model is used to estimate the probability of developing AIDS after HIV infection. In addition the use of relative risk regression models is illustrated with particular attention focussed on the role of lymphaderopathy. Initial investigations of factors predictive of progression to AIDS are outlined and questions identified.

U. FELDMANN:

Assessment of adverse drug reactions during sporadic drug use and acute response

Epidemiological models are used to assess adverse drug effects. Those models generally separate the pouplation in unexposed and permanently exposed persons, but they are not applicable for drugs which are taken occasionally and repeatedly for periods of varying length. A mathematical approach is built on the distribution of the duration of individual exposures and leads to risk measures of individuals as well as to risk measures of the population. The model can consider adverse reactions during or immediately after sporadic drug use. The model is not only applicable for rare risks, and an undesired effect may occur repeatedly for an individual.
The parameters and their standard errors are estimated by the method of maximum likelihood. Statistical tests for the risk parameters are available. The model fits prospective as well as retrospective study designs, and considers confounding. The International Agranulocytosis and Aplastic Anemia Studie [1] investigated the risks of analgesics to induce the entitled diseases. It is demonstrated that the common epidemiological methods, applied to the assessment of adverse reaction, are insufficient for drugs taken sporadically.

M. GAIL:

On Strength and Weaknesses of the Method of Backcalculation for Projecting the Incidence of AIDS Cases and for Estimating Seroprevalence and Trends in Seroprevalence

This presentation represents joint work with Phil Rosenberg, Ron Brookmeyer, Robert Biggar and Tim Goedert.
The method of backcalculation permits one to estimate the infection curve (number of cases infected per unit time) from serial data in AIDS counts and from knowledge of the incubation distribution of times from infection to development of clinical AIDS. We represent the infection curve as a linear combination of known functions from "flexible families". We prefer those families because they allow recent AIDS counts to influence

estimates of the infection curve, whereas many previously used parametric forms for the infection curve are largely determined by the early AIDS count data only.
We performed a sensitivity analysis to determine how much uncertainties in our knowledge of the incubation distribution and uncertainties in AIDS counts effect our estimates of the cumulative number of AIDS cases projected through January 1993 (P93), the cumulative number infected through January, 1985 (N85), the cumulative number infected through April, 1988 (N88), and the difference between the average infection rates from January 1985 through April, 1988 and from January 1981 through January, 1983 (trends). We presented data from non-intravenous drug using homosexual men on the West Coast of United States, for whom it is thought that the rate of infection has decreased.

We estimated P93=46,000, N85=87,000, N88=93,000 and trend=-22,500 for year, which indicated a decreasing infection rate.
Taking into account both stochastic error, which derives from random variation in AIDS counts, and systematic errors that derive from misspecification of the incubation distribution or from disortion of AIDS counts from reporting delay, changing definitions of AIDS, and underreporting, we find that P93 (± 22%) and N85 (± 30%) are relatively precisely estimated, whereas uncertainty is larger for N88 (± 44%) and trend (± 84%). An increase in the hazard rate for the first two years in the incubation distribution leads to a sharp decrease in the magnitude of the trend, but trend remains negative. An increase in the hazard of the incubation distribution for years 2-8, which induces a decrease in median incubation, decreases P93, N85 and N88 substantially. An increase in AIDS counts for the years 1922-1985, where underreporting and effecting definitional changes are likely, increases estimates of the rate of infection in 1981-1983 and exaggerates the negative trend. Other perturbations produce little change, and, in particular, the right tail of the incubation distribution has little effect on these results.

T. HAKULINEN:

Multiplicative modelling of additive excess hazard

The hazard for a group of patients or exposed persons is often contrasted with a fixed hazard prevailing in a general population comparable with respect to, e.g., sex, age and calender time period. It may be of interest to investigate which variables are responsible for an eventual excess in the hazard and to quantify the effects. It may not always be reasonable or possible to assume that the events concerned are rare, especially when large patient materials are in question.
Estimation of various models for an increased hazard may be achieved by GLIM. For cancer patient materials, multiplicative modelling of the excess hazard is particularly advantageous in terms of interpretation and fit of the model. Results with materials from population-based cancer registries are used for illustration.

R.A. HILGERS:

How to apply an index of dental health to prehistoric populations

The scientific field of paleopathology investigates diseases and their spread in prehistoric populations. As is the case for the epidemiology of today some major aspects is the impact of socio-economic health factors. In contrast to modern epidemiologists who can properly design their investigations conclusions of paleopathologists are restricted to their findings from excavated scelets with all the practical difficulties such as missing entities.
In our paper we confine to dental health and discuss the feature of caries affection and intravital losses. With the use of a simple stochastic model and Bayes' formula we derive a meaningful index. It is a counterpart to the well-known DMFT-index (Decayed-Missed-Filled-Teeth) being widely used e.g. to evaluate the effect of dental prophylaxis. Thus the prehistoric populations may even be compared to populations of today.
The index may be presented either as the spectrum for the various types of teeth or in a condensed form for the global affection. It may be considered as estimator for the respective parameter of some distribution but must properly be adjusted for age (at time of death) which is a confounding factor of dental health.

K.-H. JÖCKEL:

The German Cardiovascular Prevention Study (GCP): Design and some related methodological problems

The GCP is a multicenter community-based intervention study for the primary prevention of ischemic heart disease and cerebrovascular diseases. Prevention measures in overlapping campaigns are aiming at modification of health behaviour and life styles with respect to cardiovascular risk factors over a period of eight years. Risk factor reduction is being assessed in three health examination surveys at the start, at mid-term and at the end of the study. Age-specific cardiovascular mortality in men and women aged 25-69 years in intervention regions shall be reduced by at least 8% as compared to the rest of the Federal Republic. Only official mortality data will be used for the final analysis of this endpoint.
After a brief description of the design and the evaluation methods two methodological problems that have occured during the course of the mortality evaluation approach will be tackled, namely the problem of determing adequate age-specific mortality rates for wider age groups and the analysis of temporal and spatial trends of cardio-vascular mortality.

J. KALDOR:

Some remarks on regression analysis and study design in epidemiology

While therapy research has resolved the problem of confounding by adoption of the randomized double blind clinical trial, etiological research in cancer has resorted to the use of multiple regression models. It is proposed that the use of these models does not provide progress in understanding the causes of cancer, and that the problems are often confounded by measurement error in risk factors. Statisticians therefore need to become more closely involved in study design, and in particular in the choice of study populations and the information of measurement error quantification. Further use of matching could also be an advantage. At the stage of analysis, more attention must be paid to correct structure. Fitting of measurement error models and stratum specific analyses are also encouraged.

N. KEIDING:

Nonparametric estimation of Dietz & Schenzle's transmission potential from current status data

In a steady-state population an immunizing infection is assumed to happen with intensity (age-dependent incidence rate) $\lambda(a)$. The age-dependent mortality $\mu(a)$ is assumed to be the same for susceptibles and infected and the age-specific vaccination rate is denoted by $\varphi(a)$. Let $\Lambda(a)$, $M(a)$ and $\Phi(a)$ denote the corresponding integrated intensities. Dietz & Schenzle (1985, J.Math.Bio. **22**, 117-120) showed that under proportionate mixing and for short infections periods, the transmission potential may be approximated by

$$R_\varphi = \int_0^\infty e^{-M(a)} \lambda^2(a) e^{-\Phi(a)} da \Big/ \int_0^\infty e^{-M(a)} \lambda^2(a) e^{-\Lambda(a)} da$$

We show how to implement modern continuous-time nonparametric survival analysis methods (see recent review by Anderson & Bongan (1985, Scand.J.Statist. **12**, 97-158)) to obtain estimates of $\lambda(a)$ and thus R_φ for given mortality patterns $\mu(a)$ and vaccination schedules $\varphi(a)$. The tools are nonparametric maximum likelihood from current-status data (Groeneboom 1987, Tech.Rep., Univ. Amsterdam) and kernel smoothing (Ramlau-Hansen 1983, Am.Statist. **11**, 453-466). The procedures are illustrated on Danish measles data and Bulgarian hepatitis A data.

W. LEHMACHER:

Two-Sample Comparisons with Multiple Endpoints Controlling the Experimentwise Error Rate

Medical trials are often concerned with the comparison of two treatment groups with multiple endpoints. As alternatives to the

commonly used methods, the T^2 test and the Bonferroni method, O'Brien (1984, *Biometrics*) proposes tests based on statistics, which are simple resp. weighted sums of the endpoints. This approach turns out to be powerful if all treatment differences are in the same direction (compare Pocock et al. (1987, *Biometrics*)). The disadvantage of these multivariate methods is that they are only suitable for demonstrating a global difference, whereas the clinician is further interested which specific endpoints or sets of endpoints actually caused this difference. It is shown here that all tests are suitable for the construction of a closed multiple test procedure which controls the experimentwise error rate. This procedure is just as powerful as the related multivariate test and furthermore it enables to detect significant differences between single endpoints or sets of endpoints.

A. MARAZZI:

Numerical algorithms for computing robust estimates
Implementation of robust methods

In classical regression, the parameters are estimated by maximum likelihood (-> least squares), taking the Gaussian distribution as error model. It is well known that this procedure is often sensitive to outlying data, especially influential points (or outliers in the covariate space). During the past two decades, estimation and testing procedures that are resistant to outliers and stable with respect to deviations from the given distributional model have been developed. These procedures are called "robust". Among these, procedures based on "M-estimates" (of Huber, Mallours and Schweffe Type) and "high-breakdown" estimates are receiving great attention. Their theory has already been partially extended to generalized linear models.
The numerical algorithms for their computation have been studied and implemented in a package called ROBETH-ROBSYS. The purpose of this talk is to give an overview of the statistical methods and algorithms included in this package.

H.G. MÜLLER

Nonparametric analysis of changes in hazard rates for censored survival data

A couple of papers were recently published on maximum likelikood analysis of the change-point of a hazard function.
The change-point was modelled there as a points of discontinuity on an otherwise constant hazard function, and the analysis was restricted to the uncensored case (Matthews, Farewell, Pyke 1985). As an alternative, we consider a smooth approximation to the hazard rate and adopt a kernel estimation approach for locating an extremum in the first derivative of this smooth approximation. Based on an i.i.d. representation due to Lo and Singh (1986), asymptotic distribution and confidence intervals are derived.

Some practical problems are discussed and the potential use of the nonparametric method for model choice is considered. Some simulations and an analysis of deaths due to treatment complications after bone marrow transplantation are reported.

R. PRENTICE:

Statistical methods for studies of diet and disease

This presentation will consider the use of linear relative risk functions to estimate the association between diet and disease based on aggregate data, as may arise in condaturial, time trend and regional studies; and analysed data, as may arise in cohort or case-control studies. Methods for testing consistency of diet and disease associations from these various types of studies will also be discusses.

W. SAUERBREI:

Variable selection with the bootstrap-method

In clinical and epidemiological studies we often have the problem of many correlated variables and we have to search for the "important" ones. The stepwise procedures are the mostly used methods for variable selection in regression models, although some problems are well known.
The bootstrapping method can be used as a flexible instrument for getting ideas about model stability and it may be used as a method for the selection of variables in a variety of models.
The method will be presented and some basic ideas for a selection strategy in the Cox-model will be illustrated with an example of a clinical trial.
Theoretical results will be difficult to obtain, but the first practical results show that it may be a useful tool to improve the variable selection techniques. More insight has to be gained in a simulation study.

S. SCHACH:

Methods for data distortion to improve the confidentiality of data files

Under the present law on confidentiality protection in the FRG it is almost impossible to obtain statistical data, collected by the statistical offices, in the form of data files. The reason given is that individual records in the file can be identified too easily. Some procedurers have been proposed to make the data records in such a way that the risk of reidentification becomes negligible. The talk is concerned with the statistical implications of such modifications. These methods include:

aggregation of records, coding into classes, adding random quantities, frequency imposed distortions, drawing random samples, selection of "short records", generation of synthetic records using regression techniques.

H. SCHÄFER:

Statistical procedures for the construction of a cutoff point for a quantitative diagnostic test

The paper is concerned with the problem of constructing a cutoff point for a quantitative diagnostic test from a sample of diseased and non-diseased individuals, when a prespecified specifity and sensitivity of the resulting diagnostic classification rule is required. The statistical tests proposed in the literature refer to an unknown optimal choice of the cutoff point and do not allow for confidence statements on the specifity and the sensitivity of an explicitly constructed cutoff point. We investigate the increase of the type I error when the result of such a test is incorrectly applied to a concrete cutoff point previously estimated from the same data. We propose correct statistical construction procedures. Sample size formulae are derived under the assumption of Gaussian distributions. Numerical procedures for sample size calculation in the nonparametric case are presented.

D.C. THOMAS:

Some applications of Bayesian methods in cancer epidemiology

A number of problems in epidemiology involve the estimation of many parameters, including variability in individual susceptibility, exposure measurement error, and testing multiple hypotheses. The use of empirical Bayes methods was discussed in this context. It was shown how the IP algorithm (Tanner and Wong, JASA 1987) provides a computational solution to problems that are otherwise intractable by simulating the joint posterior distribution of the parameters of interest and the hyper-parameters. The method was presented for the case of several normal means with unequal variances and a prior distribution consisting of a mixture of a normal and a spike at zero, and illustrated using data on cancer and occupational exposures (Thomas et al., Am.J.Epidemiol., 1985). More recent work on multiple regression with an exchangeable mixture distribution for the regression coefficients was described. This method seems to provide a means of selecting variables and quantifying the uncertainty in the choice of the "best model".

K. ULM:

Non-parametric analysis of dose-response-relationships

The proof of a dose-response relationship is an important criterion to establish causality. The methods widely used are the test on trend or parametric models. In all these methods the values of the variable of interest are necessary. In occupational epidemiology it is rather seldom to have measurements about the level of exposure in the past.
Under these circumstances a nonparametric approach, the isotonic regression, is proposed. The only assumption is monotonicity, which means, the response cannot decrease while the dose is increasing. Up to two variables can be considered to demonstrate either the effect of a second variable given the influence of the first one or the form of the interaction of both variables on the response.

H.E. WICHMANN:

Statistical Problems in Longitudinal Studies on Respiratory Diseases in Children

Short-term effects of air pollutants, meteorologic variables and viruses on respiratory diseases in preschool children - expecially croup syndrome - are investigated. Data from 18500 cases in different areas of the FRG, collected over 2 - 3 years, are analysed on a daily basis. Stepwise linear regression is used after data transformation.
The problem of missing or insufficient specification of confounders is discussed and correction strategies (filter techniques, dummy variables, seasonal restrictions) are introduced.
Finally, an upper and a lower approximation for air pollution effects is proposed which gives the limits in which the "real" estimates are expected.

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