6th Workshop on Quality Improvement Methods
at the Universitätskolleg Bommerholz

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Abstracts

Session 1: Applications I

Paired Comparisons in Visual Perception Studies Using Small Sizes

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Paired comparisons is a useful method for experimental design with various applications like perceived crime seriousness and measurement of health status. Industrial applications concern the relative importance of factors before including them into an experiment, consumer tests in the food industry and visual perception research. Visual perception researchers perform experiments on display systems and they ask subjects to compare or rank displays according to a specified criterion, such as brightness or sharpness. In this way, they investigate perceived differences between displays to hopefully understand these from physical specifications. A classical model for such experiments is the Thurstone model of the form -1(pAB) = a - b, where pAB is the probability that display A is preferred over display B, and a and b are scores for the two displays. It is important to estimate scores, to test differences of scores and to test the effect of factors like image content and gender of subjects. For these purposes, Generalized Linear Models (GLM) appear to be very useful.
We shall firstly embed the Thurstone model into GLM and discuss a multiple testing procedure for differences of scores, controlling the family wise error rate. Further, we present tests for factors on scores. Secondly, in a simulation study we find testing power as a function of the number of subjects. Finally, a case study will be worked out as an example and we end with some discussion points.

The Most Probable Point in Systems Engineering Uncertainty Analysis, incl. Discussion of Alternatives

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In the course of shorter development cycles and limited testing resources, the question arises, how product can be validated resource-optimal, in order to enable necessary changes in a timely manner. The usual test strategies are - due to lack of an appropriate noise factorization and sample size consideration - often times not able to assess robustness with sufficient confidence level in the required timing. One concept, that deals with this situation, is the most-probable-point (MPP) harware testing scenario. In this presentation, the MPP concept will be explained, using a small engineering example. We will then conclude with a critical discussion of shortfalls and potential alternatives.

Session 2: Microarrays

Statistical Analysis of Microarrays: How to Avoid Drowning in the Data Flood

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Microarray technology provides gene expression measurements on a genome-wide scale. To obtain valid and reliable results from microarray studies, multiple steps must be performed, including experimental design, image analysis, normalization, statistical analysis, and biological verification and interpretation. Optimal procedures depend on efficient communication and interplay between biology, statistics and computer science. We briefly describe the steps in microarray data analysis, focusing on statistical aspects.
One key issue will be discussed in more detail. Modern methods identify important biological processes or functions from gene expression data by scoring the relevance of predefined functional gene groups, for example based on the Gene Ontology (GO). We present algorithms that improve the explanatory power of this approach by integrating knowledge about the dependencies between the gene groups into the calculation of the statistical significance. In comparison with competing state-of-the-art methods, our algorithms point at additional areas in the GO graph with significant biological processes or

functions. The algorithms have been applied to several real expression data sets from prostate cancer patients.

Conflicts between Optimality Criteria in Incomplete Block-Designs for Microarray Experiments

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Microarray experiments have rekindled interest in experiments where there are only two treatments per block. When the number of blocks is the same as the number of treatments, two popular designs are the loop design and the reference design. Previous work by Kerr and Churchill (2001) and Wit, Nobile and Khanin (2005) shows that the A- and D-optimality criteria for these designs produce different rankings when there are about 10 treatments. By finding explicit formulae for the A- and D-criteria, I show that the rankings are the opposite of each other whenever there are 13 or more treatments. A heuristic method is given for avoiding this problem by using a ratio of blocks to treatments of at least 12.

Optimal Statistical Planning of 3-factorial Two-color cDNA Microarray Experiments

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With the quick growth of biotechnology during the last decades, medical research interest in genetic causes for the development of certain diseases (like diabetes, breast cancer and Parkinson's disease) gained tremendously in importance. The conduct of gene expression analyses using cDNA microarray experiments [1] is aimed at identifying candidate genes that can be made accountable for the genesis of a certain disease or the mutation of a benign into a malignant tumour. At long sight the essential findings from those experiments might be used gainfully within the development process of new drugs or therapies which are able to interrupt or modify directly the activity of those candidate genes in such a way that a benign tumour does not converge into a malignant stage or that the disease does not emerge at all. Using statistically efficient designs for cDNA microarray experiments increases the precision of the statistical analysis of the gene expression data

generated by those experiments. Landgrebe et al [2] proposed a gene-specific fixed effects linear model for statistical evaluation of the log-ratios calculated from the fluorescence intensity values measured in the experiments. Usually two factors are involved in the experimental setting, "dye" (red, green) and "treatment". In 3-factorial cDNA microarray experiments, in addition a third factor (f.e. the type of cell line, if the tissue samples used for the experiments are extracted from different cell lines) will be examined. Due to the block structure of these 3-factorial layouts, only balanced incomplete block designs incorporating two block factors can be realized for estimating the model parameters of the Landgrebe model [3].
In the talk we will present p-optimal designs for estimating special linear contrasts of the model parameters which are of interest in biological applications. We adopted modified versions of the generalized equivalence theorems suggested by Pukelsheim [4] in order to demonstrate optimality. With exception of some specific situations, optimality of the designs derived holds for unrestricted numbers of treatments and cell lines. The solution of the optimization problem especially resulted in A- and D-optimal designs. The independency of this solution from the optimality criterion chosen can be interpreted as robustness characteristic. For practical purposes, on grounds of the optimal 3-factorial cDNA microarray designs found in our examinations, direct recommendations on the choice of an efficient design for a concrete cDNA microarray experiment with given numbers of arrays, treatments and cell lines can be deduced.
References:

1 Brown, P.O., Botstein, D. (1999). Exploring the new world of the genome with DNA microarrays. Nature Genetics 21 (1): 10-14.

2 Landgrebe J., Bretz F., Brunner E. (2006). Efficient design and analysis of two colour factorial microarray experiments. Computational Statistics and Data Analysis 50: 499-517.

3 Stanzel, S., Hilgers, R.D. (2007). The Within-B-Swap (BS) Design is A- and D-optimal for estimating the Linear Contrast for the Treatment Effect in 3-Factorial cDNA Microarray Experiments. Proceedings of the 8th international workshop on Model-Oriented Design and Analysis. Almagro, Spain, June 4-8, 2007 (in press).

4 Pukelsheim F. (1972). Optimal Design of Experiments. Wiley, New York.

Session 3: Case-Based Reasoning

Applying Case-Based Reasoning

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Case-Based Reasoning (CBR) is a relatively new Artificial Intelligence (AI) approach inspired by human problem solving strategies which has been applied very successfully in many commercial systems during the last years. After a short introduction of the basic idea of CBR, this talk focuses on an overview of typical application scenarios where CBR has advantages compared with more traditional AI, pattern recognition and machine learning techniques. Some criteria which help to decide whether it is promising to apply CBR in a given application scenario or not will be discussed and different possibilities to adapt a CBR system to the application specific requirements will be shown.

Model Improvement by Case-Based Reasoning with Practical Experiences for Image Segmentation

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The development of image interpretation systems is concerned with tricky problems such as a limited number of observations, environmental influence, and noise. Recent systems lack robustness, accuracy, and flexibility. The introduction of case-based reasoning (CBR) strategies can help to overcome these drawbacks. The special type of information (i.e., images) and the problems mentioned above provide special requirements for CBR strategies.
One subtask when automatically interpreting an image is image segmentation. Image Segmentation is a crucial step in extracting information from a digital image. It is not easy to set up the segmentation parameter so that it fits best over the entire set of images. Most segmentation techniques contain numerous control parameters, which must be adjusted to obtain optimal segmentation performance. The parameter selection is usually done on a large enough test data set, which should represent the entire domain well enough

in order to be able to build up a general model for the segmentation. However, it is often not possible to obtain a large enough data set and therefore the segmentation model doesn't fit well to the entire data and needs to be adjusted to new data.
We propose a method for setting up and improving the model for image segmentation based on case-based reasoning. We describe the steps of the modelling process and the methods necessary to automatically perform the modelling and model improvement process. Examples are given based on an application for the determination of degenerative brain diseases in CT-images and natural images are given.

Session 4: Applications II

Optimization of Line-production Processes in Incremental Forming by Use of Statistical Methods

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Incremental forming processes like single point incremental forming, spinning, shear forming or flowforming are used to form workpieces with complex contours in a range from prototyping to mid-volume production. Due to the high complexity of the processes and the large number of possible geometries to be formed, a systematic process-design is difficult and time consuming.
In the case of model-line production with similar geometries, existing knowledge can be used to make the set-up of new processes more efficient. This can be realized by the combination of Finite-Element methods and statistical design of experiments by knowledge-based methods like the case-based reasoning.
An additional challenge in incremental forming are the often small stable regions of the parameter space. Due to this, an adaptive sequential optimization procedure has been developed, using space-filling designs and spatial regression models to overcome this limitations.
In the focus of the presentation is a discussion of the potentials and limitations of the method as well as challenges in the application of the method for industrial processes.

Multiple Imputation of Missing Values for Multivariate Analysis

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Multiple imputation is a very active field of research. While there are established text books on the method itself (Rubin 1987, Schafer 1997), there is still plenty of new literature, particularly regarding multi-level models and aspects of applying multiple imputation to data from different subject areas. This paper is based on outcomes from the EU project TRACE, a project on "TRaffic ACcidents in Europe". The sub-task "Missing value imputation methods for traffic accident data" of the task "Statistical methods for improving the usability of existing accident databases" investigates the benefits of multiple imputation for accident data bases. This includes investigations into the available software implementations of different approaches. Key competitors are the multivariate distribution-based approach (as realized in R-packages norm, cat and mix or SAS PROC MI) and the sequential-regression-based approach (as realized in R-packages mice and Hmisc (function aregImpute) and for (unrealistic) special cases also in SAS PROC MI).
After an introduction into the principles of multiple imputation and the different algorithms, the impact of using different methods for multiple imputation (or naïve complete-case analysis) is demonstrated on a showcase data analysis from the TRACE project, and results from a simulation study are outlined. These clearly point to shortfalls of current software implementations of multiple imputation (cf. also Horton and Kleinman, 2007). Nevertheless, while there are situations for which a naïve analysis is not worse or even better than a multiple imputation-based analysis, well-applied multiple imputation appears to be one of the better strategies of dealing with multivariate data that suffer from missing values.
References:
Horton, N.J. and Kleinman, K.P. (2007). Much Ado About Nothing: A Comparison of Missing Data Methods and Software to Fit Incomplete Data Regression Models. The American Statistician 61, 79-90.
Rubin, D.B. (1987). Multiple Imputation for Nonresponse in Surveys. Wiley, New York.
Schafer, J.L. (1997). Analysis of Incomplete Multivariate Data. Chapman & Hall, London.
TRACE project: http://www.trace-project.org/.

Session 5: Spectrometry

The Quality of Samples in Diagnostic Studies: the Influences of Sample Tubes and Keeping Time

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The intention of many studies in the fields of Genomics, Proteomics, Peptidomics, Metabonomics, etc is to find good new ways to diagnose diseases. To that end samples (namely: tissue, serum, plasma, urine...) are collected from patients and "controls" and high-dimensional measurements of these samples are made. Based on this data either a few one-dimensional values of these measurements or some pattern is identified that show some good potential to discriminate between patients and controls.
After the first period of hype, now, "bias will increasingly be recognized as the most important 'threat to validity' that must be adressed in the design, conduct and interpretation of such reasearch" (Ransohoff, 2005).
For mass spectrometric (MS) pattern recognition analysis sources of potential bias are the sample collection tube and the keeping time between phlebotomy and centrifugation. We will introduce a study that analyzes these influences.
Literature:
Ransohoff DF.(2005)Bias as a threat to validity of cancer molecularmarker research. Nat Rev Cancer Vol. 5, 142-149, 2005

Ion Mobility Spectrometry in Medicine: Fundamentals, Successful Applications, and Open Questions to Data Evaluation

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The primary aim of "omic-technolgies" is the non-targeted identification of all gene products (transcripts, proteins and metabolites) present in a specific biological sample. A second and more challenging aspect of the "omic-technolgies" is the refined analysis of quantitative dynamics in biological systems.
An impressive amount of data has emerged from genomics and proteomics so far, which has often served to highlight the complexity of cellular regulation

and the interaction mechanisms. Because of the fact that biochemical control is not strictly hierarchical, intermediary metabolism contributes to the control of the regulatory pathways.
The Department of Metabolomics at ISAS will contribute to development of the instruments, particularly different types of spectrometers, and procedures including the sampling techniques and data mining, identification of biomarkers for various diseases, and the response to therapeutic interventions. The further development of spectrometric and spectroscopic instruments as tools for high throughput analyses of the various biochemical pathways selected is crucial to the acquisition of metabolome data sets, handling procedures and data mining as well as to statistical well founded interpretation of the results obtained by analytical methods used.
Metabolomics covers the identification and quantification of intracellular and extra-cellular metabolites, including different physiological states. The subject metabonomics, defined as the study of the collection of small molecule ($< 1000\ Da$) metabolites to elucidate differences in population groups due to genetic modification, disease state and environmental stress is included dialectically in metabolomics, which is sometimes considered as corresponding or restricted to studies of single cells.
Natural scientists typically test their models against experiments by varying one parameter while keeping all the others constant, and by comparing model predictions with observations. In cells and organisms this is extremely difficult, if not impossible, to do. Changing one thing almost inevitably changes others.
Ion mobility spectrometry and mass spectrometry are used in the field of translational medicine, especially to investigate human breath as carrier of information on the metabolic processes in the human body.
Because of the fact, that early diagnosis of lung cancer and airway infections is gaining increasing importance we have examined if volatile metabolites occurring in human exhaled air can be correlated directly to different kinds of diseases. The analytical technique, which is the same basic technique used to detect explosives or chemical warfare agents, is being employed at ISAS and the lung clinic Hemer to examine hospital patients with lung cancer and airway infections. The technique is able to detect effectively metabolites in human breath down to the pptv or pg/L-region. For investigations of human breath at a comparatively high level of humidity a combination of a Multi-Capillary Column (MCC) for partly pre-separating of the analytes is used in combination with a conventional ion mobility spectrometer (IMS). An IMS coupled to a MCC allows for the identification and quantification of volatile metabolites occurring in human breath down to the ng/L- and pg/L-range of analytes within less than 500 s and without any pre-concentration. The

IMS investigations are based on different drift times of swarms of ions of metabolites formed directly in air at ambient pressure. About 10 mL of breath is necessary to carry out a full analysis.
Our procedure is based on miniaturised ion mobility spectrometers supported by mass spectrometric validations. The full procedure, including sampling, pre-separation and identification of metabolites in human exhaled air, was developed and implemented with a view to future use in hospitals. Metabolic profiling of the breath of healthy individuals and those suffering from different diseases, in particular lung cancer is considered at various lung hospitals and point-of-care centres.
The talk will discuss fundamentals of the analytical method ion mobility spectrometry and present successful applications. Finally, open questions with respect to data handling and evaluation, informatics and statistics and help needed will be considered.

Peak Detection and Characterisation for Ion Mobility Spectrometry Data

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Spectrometric methods generate a flood of data that can hardly be processed without chemoinformatics and computational statistics. In particular, regarding two-dimensional separations, an automated signal processing for the extraction of information in the form of substance peaks has to be aspired, since a manual analysis is time-consuming and sometimes also insufficient [1].
To overcome this problem, the solid two-dimensional peak detection method of 'Growing Intervall Merging' (GIM) was developed in this work for data generated by an ion mobility spectrometer [2] (IMS), coupled to a chromatographic column (GC). GIM allows to detect and distinguish peaks in a stagewise proceeding. At each stage of the GIM algorithm, data are divided into peak and non-peak groups by an intensity threshold. Afterwards, peaks are separated using a merging regions algorithm and represented by ellipses and intensity measures. Even peaks, that are not baseline-separated, can be detected by a reasonable strategy for connection of stages. By characterising measurements by a short vector of meaningful values per peak, reliable results could be obtained regarding dimensionality reduction and feature extraction. One potential application would be the utilisation of the resulting

peak data as an input for a discrimination task in a study of IMS breath measurements of lung disease patients.
Furthermore, the introduced peak detection method GIM is transmittable to other spectrometric data in two-dimensional separations, if spectra satisfy defined conditions: While a baseline-separation of peaks is not necessitated for the developed method, intensity values should vary around zero in noise areas. Data compression and denoising can accelerate computation time. Examplifying this, the GIM algorithm was successfully adjusted to data of a differential mobility spectrometer (DMS), used with pyrolysis-gas chromatography (py-GC) for measurements of bacteria cultures.
The new approach of GIM allows to directly access spectra-spanning data structures of various spectrometric methods in two-dimensional separations. On the base of the resulting peak lists, data representation and multivariate analyses for classification and discrimination are possible in a simplified manner.
References:

1 Bader, S., Urfer, W., Baumbach, J.I. (2006): Reduction of Ion Mobility Spectrometry Data by Clustering Characteristic Peak Structures. Journal of Chemometrics, 20, 128-135.

2 Baumbach, J.I., Eiceman, G.A.: Ion Mobility Spectrometry (1999): Arriving On Site and Moving Beyond a Low Profile. Applied Spectroscopy, 3, 28-37.