Universität für Bodenkultur Wien

Optimal Design of Experiments – Theory and Application

Proceedings of the International Conference in Honor of the late Jagdish Srivastava

Satellite Conference of the 58^{th} ISI World Statistics Congress, Dublin 2011

Vienna, Austria, September $25^{th} - 30^{th}$, 2011

edited by

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Preface

The Center of Experimental Design and the Institute of Applied Statistics and Computing of the University of Natural Resources and Life Sciences, Vienna, Austria organized an international conference on experimental design from 25^{th} to 30^{th} of September 2011 with the title "Optimal Design of Experiments – Theory and Application, International Conference in Honor of the late Jagdish Srivastava". It was a satellite conference of the 58^{th} ISI World Statistics Congress 2011 in Dublin.

This conference was devoted to theoretical developments as well as practical applications of experimental design. The conference was open to researchers and practitioners. The organizers accepted papers devoted to both the development of mathematical theory and related algorithms as well as practical applications.

93 participants from 21 countries took part at this conference, the list of the participants is given at the end of the proceedings (page 216 ff.). 26 invited presentations, 31 contributed presentations and 9 poster presentations were given by the participants. We tried to publish as many contributions as possible passing the review process in this proceedings volume. Some papers could not be published due to the fact that they already had been delivered to other journals.

We want to thank all LaTeX developers and Martin Monperrus for providing the master file for the proceedings. Thanks to Thomas Emmel for the ticket package, Nicola Talbot for the datatool package and Andreas Matthias for the pdfpages package. Special thanks to Uwe Ziegenhagen for his tutorial about conference management with LaTeX.

Vienna, October 2011

The Editors.

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Contents

The Age of Maturity: Fifty Years of Methodology and Applications of Experimental Design in Russia

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Abstract: The beginning of experimental design in Russia was in 1960, when the Journal 'Progress in Chemistry' was published the review by Prof. V. Nalimov "Statistical Methods of Search the Optimal Conditions for Chemical Processes". It was some analysis of foreign sources.

The period from 1960 to 2010 we are dividing into three parts:

1) From 1960 to 1980,
2) From 1981 to 1991,
3) From 1992 to 2010.

On each part we are discuss methodological and applied aspects the investigations in area of experimental design: publications (books, review, and some articles), organizational activities (scientific councils, conferences, seminars, and so on), education, and scientometrical investigations.

The first part was connected with development of some scientific groups in chemical and metallurgical organizations. They were publication of some tens applied articles. In this time experimental design was a part of chemical cybernetics. But just in the end of 1960s was created "invisible collective (college)" under the leadership of Prof. V. Nalimov and was beginning some development of theoretical and methodological problems of building designs on the base of some criterion of optimality. There were big growth of applied publications in chemistry, metallurgy and technics. It was start of big conferences and numerous seminars. It was the beginning of educational activities in this area.

On the second part by Nalimov's school was developed logical fundamental of experimental design. Design of experiment was included in applied statistics as an independent part. In this time was published some catalogs for plans of experiments. In the beginning of 1980 was published some thousands of articles and more than 100 books with different applied problems.

On the third part scale for methodological and applied works in this area was significant smaller in connection with systematical crisis of Russian science.

In this publication we are presented first part only. We hope continue on the next conference.

Keywords: History, DOE (Design of Experiments), Russian impact.

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1 Introduction

The beginning of investigations in the area of experimental design in Russia started in 1960, when the journal «Progress in Chemistry» («Успехи химии») published the review by prof. V.V, Nalimov (1960) which descripted some foreign publications. As was pointed out in this article in 1951 Box and Wilson (1951) are introduced a new method for search the optimal conditions of chemical reactions on the base of modern mathematical statistics by experimental design and data analysis. In contrast with common methods of experimentation in this case the number of runs and those conditions were determined by special mathematical rules. Moreover all factors changed together, not one-in-time. It leads to a huge decrease of the number of runs. Experimentation gets additional information about effects of interaction which does not arise in «classical» experiment. On the last step there was building of a mathematical model. The model determines the optimal condition of the process by changing levels of factors, for example in case of change some raw materials.

For an illustration of this idea in that review a short version of one chapter from the book by Davies O.L. (1956) was translated. In another part of the review the method of search the region of optimum (near "stationary area") and experimentation in this area (the response surface methodology) was described for the case of lots of factors. In all parts there were numerical examples. Fifteen applied publications on design of experiments in the area of chemical investigations were cited. Unfortunately the method was not very popular in that time. The trouble is first of all due to the traditional system of education in which there is no information about key ideas of mathematical statistics for chemists, physicists, metallurgists, and so on.

After review V.V. Nalimov (1960) prepared a cycle of lectures about the design of experiments and organized scientific seminar in this area in the State Scientific Research Institute of rare metals and semiconductors (GIREDMET) where he was working in that time.

Up to 1964 there were published 20 applied articles: Adler, Yu., Granovsky, Yu., (1965) and only two years later the number of publications has grown by ten times: Adler, Yu., Granovsky, Yu. (1967), after 1965 some theoretical and methodological investigations have begun in our country.

2 First part (1960-1980)

2.1 Methodological investigations

Mathematical statistics implemented some methodological conceptions into the body of design of experiment. Stable frequencies, nature of statistical inference, randomization, sequential experimentation, and reduction of information, presentation of results by a set of models – are examples of such implementations. Implementation of experimental design leads to a huge decrease of the number of runs, but first of all gives much more clear conclusions of experimentations, improving his or her heuristically thinking. Mathematical theory of experiments makes clear which of ideal statistical assumptions are applicable in the real practices of experimentation V.V. Nalimov (1971).

It is important to compare active and passive experimentations. In the first case investigator has a possibility to change conditions of experiments. In the second case investigator plays a role of observer of the experiment which nature makes. In both cases it is possible to describe results by the same regression model. But in the active case observable factors always have no practical correlation

with unobservable factors and so the estimates of regression coefficients are nonbiased in contrast with the passive situation where there is strong bias between factors.

Mathematical theory of experiments expressed in the language of mathematical statistics is a methatheory with such common for all experimentations principles as decision making in the situation of uncertainty, in the design of experiments and approach to data interpretation.

«The language very suit because it lead to descriptions the response of nature on experimenters activities in frame of indeterministic system of concepts, which representation the real world with degrees of freedom for its probabilistic behavior» V.V. Nalimov (1971, p.198).

Design of experiments seems to be a part of mathematics; its inferences have a mathematical form. But in this case as well as in other parts of applied mathematics there are no structures with rigid logical content. Sometimes the structures can change the mosaic of criteria; sometimes on a mathematical language we write sentences with intuitive nature. Here there are no any syllogisms which are typical for traditional mathematical constructions.

In the experimental design the role of axioms play some criteria of optimality which are based on our intuitive understanding of a good experiment. Criteria are divided into two groups: static and dynamic. Statistic criteria determine some configurations of points in the factor space. Here the statements about the characteristics of a plan (theorems) are checking by proofing. Criteria of optimality create the mosaic of incompatible statements as a rule.

In this circumstance it is very important to compare designs which were built on the base of different criteria. It is possible to estimate by computational methods how a plan which is optimal for one criterion is optimal for another one. Sometimes it can have a sense to build a compromise decision on the base of the comparison. For it we need to have quantitative estimations of parameters of a design. Such work was done in the interfaculty laboratory of statistical methods of Moscow State University.

The comparisons of most popular for practices plans by several criteria were realized in the laboratory. Just always there are some plans with not big quantity of points with the characteristics near to optimal. On this base the first catalog of optimal designs was developed.

On computer the quasi-D-optimal designs with small quantity of points were built. Effectiveness of experiments is going up in connection with the best configurations of points in factorial space. It was clear that D-optimality is very universal criterion. For example saturated linear plans are D-optimal, such as Latin squares, Latin cubes, Greco-Latin squares and fall and fractional factorial plans V.V. Nalimov (1971), Nalimov, V.V., Golikova (1976).

Second group of criteria is dynamics criteria. They are being used for search of optimal strategy in sequential experimentation. For example by study of biological activity of big quantity of samples with strong restrictions on runs it is very actual. But in this case there is no possibility to build some mathematical theory. We have possibility to build some practical algorithm suitable for realization only.

In some cases for example in screening experiments we have a mixture of problems, when we need not only to estimate parameters of a model, but to minimize dimensions of factorial space.

So, the theory of experiments is not a result of some logical operation. It is impossible to have fully formal process of experimental investigation. Problem statement, choice of mathematical model, choice of factors and area of experimentation are nonformal stages of any investigation. Strong theory is suit for the experimental procedures which have mathematical models. The key problem is logical interpretation of goal and results. If this is clear then it is useful to discuss the problem of optimality. Design of experiments is an interdisciplinary science.

Success in the study of first group criteria leads to a change of logic in the theory of experiments. It is growing on strong formal criteria but in the same time another nonformal criteria play complementary roles. From an investigator point of view the last criteria may be very interesting: Nalimov, V.V., Golikova, T.I. (1976), Nalimov, V.V., Golikova, T.I. (1977).

Other results worth mentioning are: generalization of the theorem about equivalence of D- and G-optimality in case of linear functionals from matrix of covariation (L-optimality), and in case of convex functionals (Φ-optimality). A computational algorithm for building continual Φ-optimal designs was developed by V.V. Fedorov for any linear by parameter model in any compact area. Strong mathematical statement of problem of choice for the optimal activities for a model with non-adequate results of experiments was developed by S.M. Ermakov. There was a progress in the problem of building plans without bias with minimum points of spectrum and with minimum of random error on set plans without bias (E.V. Sedunov).

In “classical” theory of factorial design which is often used for independent variables with discrete levels new results were obtained. Strong determinations of “factorial” designs and “factorial” models were implemented. Different types of models with discrete and continuous levels of factors were analyzed. New classification of factorial designs was introduced and the methods for building effective plans of factorial models were developed (V.Z. Brodsky).

In the design of screening experiment the relationship between numbers of runs, numbers of significant effects, and numbers of “potential” effects with probability to build a plan was found by F. Satterthwaite and all such effects were determined by L.D. Meshalkin.

Different results of the theory of screening design were interpreted from common position. It was found: lower estimates for the number of runs in various statements of the screening problem, existence of plans with given points, suitable for analysis regular plans with not big number of points, simplest procedures for analysis of experiments with modest numbers of operations (M.B. Malutov): Nalimov, V.V., Golikova, T.I. (1981).

Specific problems are connected with troubles of building models which are nonlinear by parameters. Chemical kinetic is a typical example. Key problem is estimating the mechanisms of intermediate stages which are unobservable directly from experiments. It is possible by prior information to build system of differential equations for representation the mechanism of intermediate reactions and description of parameters of a model. This system we can interpret as a set of axioms for divided results of observations on components. Three kinds of troubles and uncertainties may be connected with it: 1) random error of observations, 2) ambiguity estimates of parameters of a model for very complicated processes, 3) different formalization of chemical reactions in different schools of chemists.

In such circumstances it is not possible to search one model only. More suitable is an interpretation of terms for a set of models and their geometrical representation (V.G. Gorsky): Nalimov, V.V., Golikova, T.I. (1981).

2.2 Applied investigations

If in the first review of applied papers about design of experiments (1965) there were only 15% of Russian papers, then in the next review just after two Years we have more than ten times more Russian papers, near to 25%: Adler, Yu., Granovsky, Yu. (1967), in the latter review there were not given such areas as psychological and aerobiological experiments and screening designs in biology and pharmacology.

About 250 our papers were distributed by next topics:

- Design and theoretical models of processes, kinetic and catalysis (21.2%),
- Organic chemistry and technology (18.4%),
- Nonorganic chemistry and technology (16.0%),
- Automatic, electronic, electrotechnic (15.6%),
- Mining and ore concentration (10.4%),
- Analytical chemistry (6.4%).

The rest (12%) of papers were devoted to biology, pharmacology, medicine, metallurgy, physics of metals, technology of metals, metrology, design on diagram "composition - property", and so on. Chemistry was the leader in applied studies (62%). We can see tendency to more complicated objects and methods.

In an review about design of experiment in chemistry (the end of 1970th) it was pointed that in problems of optimization and interpolation more frequently used methods are: steepest accent and fractional factorial experiment (30%), plans of second order (20%), full factorial experiment (15%), design on diagram "concentration - property" (10%). By questioning the participants of the 5th All union conference on design and automation of experiments (1976) there was found a next distribution of a number of factors in papers on design: 1-5 – 49%, 6-10 -39%, before 50 – 11%, near to 100 – 1%: Markova, E.V., Adler, Yu., Granovsky, Yu (1980).

In review by Adler, Yu., Granovsky, Yu. (1977) were presented Russian investigations in methodology and practice of experimental design for ten Years in form of books only (about 90 monographs, textbooks, and translations). The following areas were observed:

- Chemistry and chemical technology – the broadest area of applied works (37.6%),
- Metallurgy and physics of metals (14%),
- Mining and ore concentration (8.6%),
- Materials for construction (7.5%),
- Radio-electronic and automatic (5.4%).

This time DOE was working with success for research in areas of machining, electric motors and modeling of energosystems. Some works about cars testing, automatization of ship's control, cosmos study, systems of "man - machine", and from area of reliability were presented.

2.3 Education and training

V.V. Nalimov prepared a program "Statistical investigation methods in chemistry" which was approved by Ministry of higher and special education in 1961. That program was lectured in the State Institute of rare metals and semiconductors (GIREDMET), in the Moscow Institute of Chemical Technology named by D.I. Mendeleev, on Chemical Faculty of Moscow State University. Broader version of the program included 64 hours of lectures and 40 hours of exercises. Examples were from chemistry, metallurgy, and physic-technical investigations. The book by V.V. Nalimov "Application of mathematical statistics by chemical analysis" (1960) was recommended for chemists as help in study of statistics. As an experience with chemists and metallurgists demonstrated there are not any troubles with the study of statistics on the examples from analytical chemistry. For study of multifactorial designs students used the review from "Progress in chemistry" (1960) and the brochure by V.V. Nalimov "Statistical methods of description chemical and metallurgical processes" (1963).

Since 1962 mathematical theory of experiments was lectured in the Moscow Institute of Postgraduate Education in Chemistry and in Chemical Industry. During 2-4 Months people were studying special topics being away from work. The program had about 300 hours of mathematical –statistical disciplines. For 8 Years there were educated about 300 people. As a result in many cities of the country specialists who understand the ideas and methods of modern statistics have appeared. In 1979 the department "Statistical methods in management and control" chaired by Yu P. Adler was created. 3 kinds of students with different time of education: 3 Months, 2 Months, and one Month (for managers) went through this department: Markova, E.V. (2003).

At the All union scientific conference on design and automation of experiments (1970) which deals with education and training V.V. Nalimov presented the work "Problems of education of theory of experiment": Nalimov, V.V. (1970). He pointed out that a new discipline – mathematical theory of experiment – was created on the base of ideas of mathematical statistics. It implements some new ideas in experimentations thinking. The people which make experiments need to know that new conceptions for discussions with consultants. The basic ideas of the theory are possible to include into common course of higher mathematics.

The next step – it is the education of experts in the area of mathematical theory of experiment. Broad training of people is not enough for working without any assistance; experts are in need of anyway: Nalimov, V.V. (1970), Nalimov, V.V. (1999).

Professional statisticians-consultants have not being prepared by any institutions of higher education. Little quantity of our consultants is the result of self-education. We observed some attempts to prepare no mathematicians but persons with supplementary knowledge on statistics.

Small courses of design of experiment (with limited volume of information) were teaching in about 23 educational institutions in 17 cities since the beginning of 1970th (3 universities, 6 polytechnic higher schools, 4 chemicals, 2 metallurgical, 1 medical and 7l other universities). All the programs were teaching without any connections with other special or mathematical disciplines.

For example in Moscow Institute of Steel and Alloys an associated professor Novik F.S. was teaching a course of DOE firstly to students and then to postgraduate students of the faculty of upgrading qualification. In Moscow Power Institute the courses for qualification upgrade were created for engineers; the program was focused on 200 hours for three months. There was an education-consulting center under the automation laboratory of MPI (Moscow Rower Institute): Granovsky, Yu., Dragalina, I.A., Markova, E.V. (2005).

At that time V.V. Nalimov supposed to organize cross-faculty departments of DOE in 1-2 institutes. They could play the same role as statistical faculties in foreign institutes – professional preparation of statistical consultants. The problem of personnel for teaching statistics for experimenters could be solved in such way. Besides it was necessary to create programs and textbooks which could link naturally the teaching of DOE with general course of higher math: Nalimov, V.V. (1971).

But to the end of 1970 V.V. Nalimov noted that many professionals of DOE are disappointed. Everything was OK when one investigated plans for extreme designs. Box-Wilson model turned out to be typical for many situations especially in technique. Later several more typical models appeared for example for the screening problems.

The efforts should be aimed not to a choice and model construction but to all following technical activity. But many experimenters have learned to do these themselves without external assistance. Professionals in DOE should turn out to be modelers.

To teach modelers means to teach how the vague given knowledge may be presented in compact symbolic form and how to state the questioned part of the model in such way that it was in reasonable agreement with the assumptions. The art of simulation depends on a sense of measure which helps to balance our knowledge and what one wants to know: Nalimov, V.V., Golikova, T.I. (1981).

2.4 Organizational issues

At the end of 1961 during a common meeting of The Board of All-union chemical society by D. Mendeleev and The Council on cybernetics of The Academy of Science of the USSR a decision was made to create a section "Chemical cybernetics" under The Council. V.V. Nalimov became the chair of this section and E.V. Markova became its secretary. The section united the scientists and engineers working in scientific and industrial centers, universities and industry. One of the main areas of the section was design of chemical experiments.

At the first half of 1960 in the GIREDMET, MSU and MPI the scientific groups being involved into solving the problems of the design of extreme planning appeared. A workshop at the GIREDMET leaded by V. Nalimov united all investigators working in this direction. In 1962 the workshop was moved to the Council of cybernetics and became all-union: Markova, E.V., Adler, Yu. P., Preobrazhenskaya, G.B. (1976).

In 1961 a journal "Industrial laboratory" (“Заводская лаборатория”) started a section "Mathematical methods of researches" where articles on methodological and applied issues of DOE began to be published. As a result of this period the all-union meeting on DOE was held in Moscow in 1964. There were presented about 70 reports there. More than 500 persons participated.

Working in GIREDMET V.V. Nalimov proved his doctoral thesis in 1963, and in 1965 he was invited by academician A.N. Kolmogorov to work in a new cross-faculty laboratory of statistical methods

under Moscow University. Here he became a head of design of experiments department and the first deputy of the head of laboratory academician A.N. Kolmogorov. 10 years later the laboratory was closed down and Nalimov's department was moved to the biological faculty of MSU where it was named a laboratory of mathematical theory of experiment.

Among other organizations where researches were being made it is worth mentioning the Moscow chemic-technological institute by D.I. Mendeleev where in 1965 a faculty of cybernetics of chemic-technological processes was created under the leadership of corresponding member of the Academy of Science of the USSR V.V. Kafarov. There was created the teaching and methodological center there destined to upgrade qualification of chemical institutes' teachers, researchers and engineers working in the Ministry of chemical industry of the USSR and in socialistic camp countries. In 1966 due to efforts of the section «Chemical cybernetics" of the Council of cybernetics three laboratories on chemical cybernetics and DOE were created in Moscow, Kiev and Lvov universities.

The stuff of problem laboratory in MPI together with the Council of cybernetics initiated regular holdings of All-union conferences on design and automatization of experiments in scientific researches. There were held 10 conferences totally, the last one in 1992: Granovsky, Yu., Dragalina, I.A., Markova, E.V. (2005). It is worth noting that a committee of "Mathematical theory of experiment" became a section of the Council of cybernetics and Moscow workshop on DOE moved to a building "A" of Moscow University.

In 1971 in the House of Scientists of the Academy of Science of the USSR a scientific conference was held devoted to 10 year anniversary of developing DOE in this country. There V.V. Nalimov summed up the bottom line and outlined that the methods of DOE began to be applied in different areas if researches not only in chemistry, and they give a significant economic impact.

Let us pay attention to some workshops of 1970. Moscow workshop leaded by V. Nalimov became be named a workshop on DOE and data analysis. Its second leader became Dr. of physics and mathematics V.V. Fedorov. Since 1974 a workshop "Design of Experiments" has been working in Moscow house of scientific and technical propaganda leaded by Yu. Adler. The representatives from different cities of the country and from different socialistic countries participated. It was regular (6 meetings a year) and on its base 3 all-union conferences were held and proceedings of them were published. In Leningrad University S.M. Ermakov headed a workshop "Mathematical methods of DOE". In Novosibirsk' electro-technical institute a workshop "Algorithms of analysis and DOE" was working by Dr. V.I. Denisov.

In 1977 the structure of section "Mathematical theory of experiment" was radically changed. There were created 7 committees and 34 subcommittee. V.V. Nalimov stayed to be a head of the section, E.V. Markova and G.K. Krug became the deputes, E.P. Nikitina became a scientific secretary. The section united more than 500 professionals working in academic and industrial institutes, universities and industrial plants. In 1978 branch offices appeared in those towns where big groups of professionals in DOE worked and were linked with the section (Leningrad, Minsk, etc.). E.V. Markova was voted as the head of all branch offices. At the end of 1961 during a common meeting of The Board of All-union chemical society by D. Mendeleev and The Council on cybernetics of The Academy of Science of the USSR a decision was made to create a section "Chemical cybernetics" under The Council. V.V. Nalimov became the chair of this section and E.V. Markova became its

secretary. The section united the scientists and engineers working in scientific and industrial centers, universities and industry. One of the main areas of the section was design of chemical experiments.

2.5 Scientometrical researches

To analyze works of informal scientific groups there were constructed graphs of coauthors. Each author was presented as a point in the plane and two points were connected by line if two authors were coauthors even in one publication. At the end of 1963 one such graph for domestic works was created by using a work by Adler, Yu., Granovsky, Yu. (1965). Two groups were formed in the USSR. Coauthors of soviet works turned out to be connected much greater than foreign researchers. It was interpreted as greater centralization of researches. As a rule the authors of methodological works worked in cooperation with the authors of applied ones. Another graph was constructed by using a section "Mathematical methods of researches" in the journal "Industrial laboratory" over 1962-1966. This graph is highly branched; some of its vertexes are well saturated so the researchers were highly linked with each other. The most part of researchers turned out to be the coauthors of informal (invisible) collectives by V.V. Nalimov, Adler, Yu., Granovsky, Yu. (1967); Adler, Yu., Granovsky, Yu., Mul'chenko Z.M. (1969).

The structure of domestic invisible collectives on DOE was studied during 1963-1969. The membership increased from 79 in 1966 to 210 in 1969. The publications which the participants of the invisible collectives referred to were revealed. The distribution of articles on topics let to follow the idea development of the group. Almost all references of 1963-1964 are related with planning of extreme experiments. This direction stayed leading in 1965-1966 but the references on the articles about adaptive optimization, rank correlation, DOE on diagrams concentrations-property appeared. In 1967-1968 planning of extreme experiment stops being a leader in the area. New fields appeared: creation of general theory of DOE; synthesis of plans on the base of general theory; construction and development of plans of ANOVA; sequential planning of experiment for more precise estimates of constants and for discrimination of models. The contribution of invisible collectives into information flaws on DOE was about 70%.

On the base of Science Citation Index an information service on DOE was organized and several author indexes relating to 1966-1975 were published. Apart from solving only information problems this let realize the Nalimov's idea about the establishment of a feedback between an author and creative reader. By using these publications any known professional on DOE could find out when and by whom his works were cited: Granovsky, Yu., Dragalina, I.A., Markova, E.V. (2005).

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Design of a Simulation Experiment for Comparison of Shewhart Control Charts Performance

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Abstract: Control charts were introduced by W. Shewhart in 1924, and had been promoting later by E. Deming since the middle of 70th. This tool caused many discussions in literature and tremendous flow of publications. Statisticians coined many different types of charts and this induced the problem of comparison of their performance.

There are very many papers devoted to this problem, but all of them were constructed in the style of one-factor-in-time experiment. We think that it is time to use the power of DOE for this goal. That's why we built and realized the regular fraction factorial design of 2^m3^n with 36 runs.

The plan included a simulation with 10 parallel realizations in each run. On the base of this experiment we have built a regression model and are now working on its interpretation. The model included some linear effects and pair interactions. The first results are presented at this conference.

Keywords: Control Chart by Shewhart, Design of Simulation Experiments, Regular Fraction Factorial Design of 2^m3^n, Visualization of Data, Interpretation of Results.

1 Introduction

Shewhart's control charts is a power tool for managerial decision making. It divides the state of a system into two different states: "in statistical control" and "out of statistical control". These two states lead to principally different kinds of activities. In the first case one needs to change the system itself and that could be made only from the top level. Only top management has a possibility to improve the system. Moreover it is the direct responsibility of top management. In the second case the management must empower the process team for solution of current problems and the return of the system in control state. From time to time the system will go out of control because of the Second Law of Thermodynamics ("Entropy of the World strives to the maximum"). And a process team will come back to solution of current problems again and again. In such circumstances the clear determination of a moment when the system state changed plays the key role for managerial success.

Reaction of a control chart on any change in the process state depends on the working conditions. The conditions can be described in terms of a set of factors. As a measure of the reaction one can take a so-called power function. It is a natural response function measuring the probability of finding out the moment of process state change. So, we can build a simulation experiment in frame of design.

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Previous works used as a rule one-factor-in-time approach. We think that in such complicated case as a control chart is this is not enough for careful analysis of situation. The goal of this paper is an application of a regular fractional factorial design to the analysis of control chart performance.

2^m3^n plan was built and an interpolation regression model for power function depending on 9 factors was constructed and interpreted.

2 Materials and Methods

Here we discuss a behavior of a control chart of only one type, namely x-bar chart. Comparisons between different combination levels of factors give some information about the roles of each factor. It was necessary to build an experimental plan for modeling. The process included some stages.

Stage 1. The choice of response.

There were some variants for a choice of response but many traditional papers as a rule work with the power function. In connection with this we chose the same function for more clear comparisons with the previous results. One example of power function is shown in Figure 1. The red point is the response in one run of our experiment. It is the probability of one point falling outside 3 sigma limits of a chart.

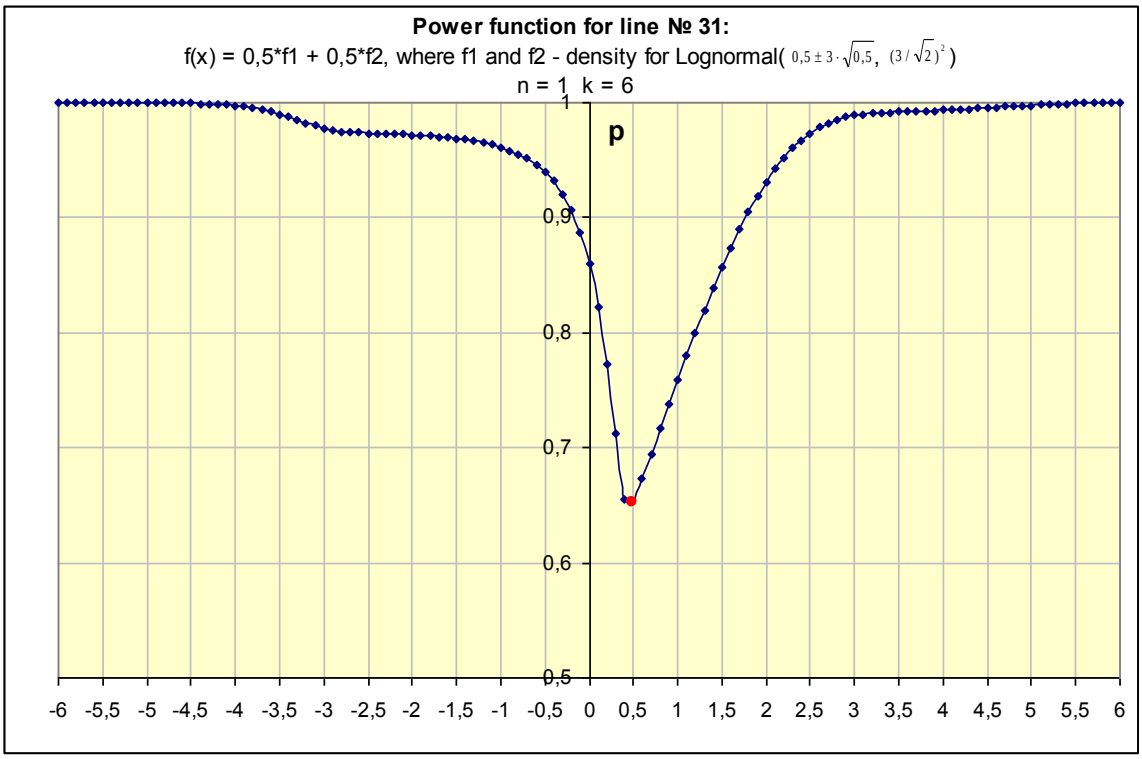


Figure 1: An example of power function (PF) with red point as response.

Stage 2. The choice of factors.

In any real situation there are many potential factors. But in our life there are a lot of restrictions. The main from them are time and money. And we need include in experiment a reasonable number of factors. We made a decision to work with 9 factors. Here there are:

X_1 – weight of intervention of distribution,

X_2 – a type of original distribution,

X_3 – a number of elements in subgroup(n),

X_4 – a type of a contaminate distribution,

X_5 – a coefficient α in the equation $\bar{x} = \alpha \cdot r$, which determines direction of a shift in "general mean",

X_6 – a coefficient β in the equation $\sigma = s^{\beta}$, which determines if σ is going up or down,

X_7 – a coefficient s in the equation $\sigma = s^{\beta}$, which determines to what times σ changed,

X_8 – number of subgroups (k),

X_9 – coefficient r in the equation $\bar{x} = \alpha \cdot r$, which determines how much the "general mean" changed

Stage 3. The choice of factorlevels.

All factors may be of two different kinds: with continual area of definition or with discrete one. In the first case we have a freedom for a choice of levels of factors which is restricted by metrological problems only. But the more number of factors we choose, the more runs we need to make. A number of levels depend on our expectations about an order of the polynomial model which suits for an approximation of the unknown real surface. Typically our expectations don't go out of linear or quadratic polynomial model. For such kind of models two or three levels of factor are enough.

In the second case we have multidimensional lattice and a choice of a number of levels depends not from a structure of a model, but from situation only. Nevertheless we made a decision to work with not more than three levels for factors of such kind. In Table 1 the results of our decisions are presented.

Table 1: Factors and those levels

Factor	X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9
High +	0.5	Lognormal	10	Lognormal	1	1	3	10	6
Zero 0		Normal	5	Normal	0	0	2	6	0.5
Low -	0	Uniform	1	Uniform	-1	-1	1	1	0

Stage 4. The choice of design matrix.

In search of a suit design matrix we took a Table (P. 1614) from the book by Taguchi, G., at al. (2005) and on the base of this matrix built an experiment with 36 runs and 9 factors. The plan is orthogonal for a linear model. The Table is given in Appendix A. It is presented in coding levels of factors. Table 1 is a "dictionary" for translating "natural" levels of factors into coding ones.

Stage 5. Experimentation.

The plan included a simulation with 10 parallel realizations in each run. Modeling was done in Statistics 7.0 in 20 runs: for each of them 1000 values were generated relative to each member of a composition distribution. This is sufficient to obtain a good estimate of the predetermined distribution parameters. Then the bootstrap simulation was applied to realize the remaining 9 replicates. So, we have 36 runs with 10 parallel realizations in each run. In the Appendix A (**D**) the vector of means responses (**Y**) is given together with design matrix.

3 Theory/Calculation

Assumptions:

1. At the first moment our data have a normal distribution with $M(X) = 0$ and $\sigma = 1$,
2. Random variables which we use for control chart are independent.
3. At unknown moment of time the distribution of data changed but we don't know how.
4. Response – power function – determinates a probability of a point to fall outside three sigma limits of the corresponding control chart.

Equation.

We calculated a saturated interpolation regression model with linear and paired interaction coefficients:

$$Y = 0.3125 + 0.2040\ X_1 + 0.0925\ X_2 + 0.1629\ X_4 + 2.4071\ X_6 + 0.4527\ X_7 + 0.0472\ X_8 + 0.3880\ X_9 + 1.0258\ X_1X_5 + 1.1086\ X_1X_6 + 1.0866\ X_1X_9 + 1.4835\ X_1X_4 + 1.8755\ X_1X_3 + 0.3215\ X_1X_8 - 0.5680\ X_5X_6 + 0.0801\ X_5X_7 + 0.3206\ X_5X_4 - 0.1109\ X_5X_3 - 0.7061\ X_5X_8 - 1.3896\ X_5X_2 + 0.0462\ X_6X_9 + 0.0951\ X_6X_7 + 0.2247\ X_6X_4 + 0.4490\ X_6X_3 - 1.0439\ X_6X_2 + 0.4994\ X_9X_4 + 0.0226\ X_9X_3 - 0.3563\ X_9X_2 - 0.0479\ X_7X_4 + 0.3424\ X_7X_3 - 0.1633\ X_7X_8 - 1.1652\ X_7X_2 + 0.8333\ X_8X_2 - 0.6846\ X_4X_2 - 0.1370\ X_3X_2 \quad (1)$$

The equation is near to saturate because only two linear coefficients are no significant: for X_3 and X_5.

Unfortunately matrix **X** for that model is not orthogonal and it is impossible to have direct interpretation of the coefficients.

Error of experiments from parallel realizations was 0.0075.

The model is adequate on the level of significance 1%.

4 Results

It is not comfortable for us to work with such complicated form of representation of results. In such case one typically works with another approach of data visualization. We made 3D or sometimes 2D sections of response surface (1). Some examples of 3D sections are shown below. The cubes in the Figures determine the area of experimentation.

(1-A)*Norm+A*Lognormal (1-A)*Norm+A*Norm (1-A)*Norm+A*Uniform

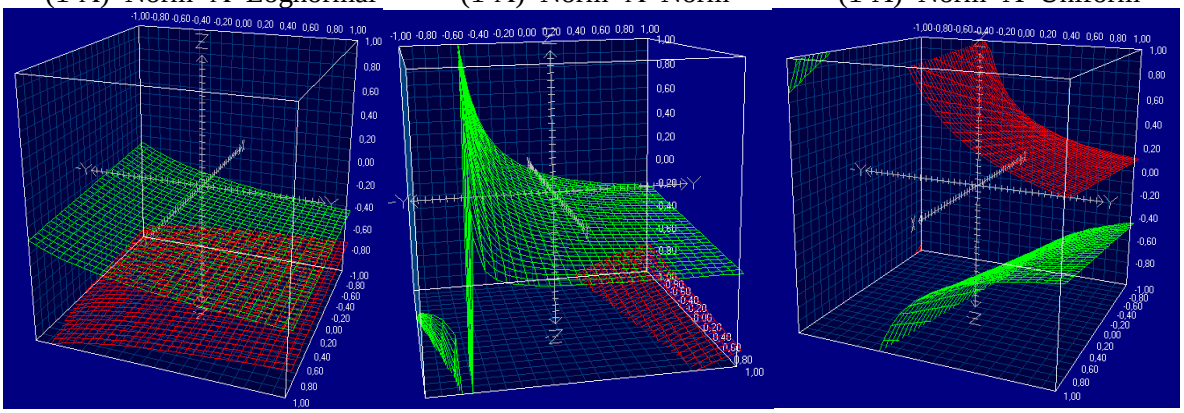
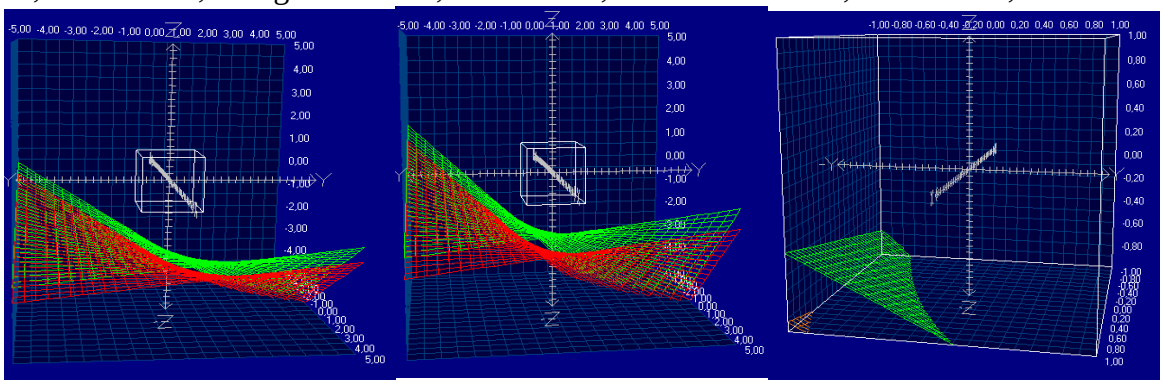


Figure 2: Examples 3D sections of response surface for $n = 5$, $\sigma \geq 1$, $\bar{x} \geq 0$

0,5*Norm + 0,5*Lognormal 0,5*Norm + 0,5*Uniform 0,5*Norm + 0,5*Norm



Lognormal Normal Uniform

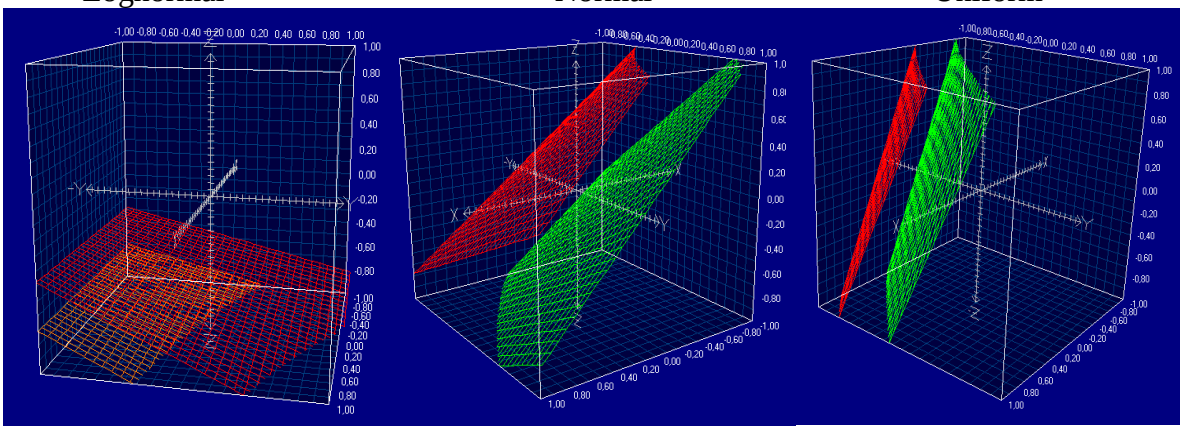


Figure 3: Examples 3D sections of response surface for $n = 1$, $\sigma \geq 1$, $\bar{x} \geq 0$.

The equal response surfaces are presented in Figures 2 and 3. Red PF- surface correspond to probability 1, green PF – surface correspond to probability 0, and orange PF – surface correspond to probability 0.5.

5 Preliminary discussion

Our model is a ten-dimensional hyperbolic paraboloid. Area of experimentation cuts some part of the surface. If the saddle point belongs to the area of experimentation then the mechanism of factor behavior changes. It leads to huge troubles in the interpretation of results. Nevertheless we have possibility to check some particular hypotheses about behavior of factors and the system as a whole in different situations. Sometimes our expectations not coincide with reality.

It is a typical situation. Control charts were introduced by Walter Shewhart in 1924: Shewhart (1931/1980), Shewhart (1939/1986) and development by Edwards Deming during practical all last century: Deming (1994).During about 90 Years were published more than 4000 works in area of control charts. Here are some examples books: Cowden, D. J. (1957), Knowler, L.A., et al. (1969), Murdoch, J. (1979), Kume, H. (1985), Rinne, H., Mittag, H.-J. (1993), Wheeler, D. J. (1993), Wheeler, D. J. (1995), Wheeler, D. J. (2006), Ott, E. R., at al. (2000), Siegel, A.F. (2000), Montgomery, D. C. (2009), and many other. And here are some articles by Woodall, W. H. one and with coauthors (1999), (2000), (2004), (2006), and many others. All the works contain a lot of contradictions. It is not wonderful that we have some troubles with interpretations of results.

Experimental design offers a new perspective for the analysis of control charts performance. First of all, multi-factorial approach leads to estimation of the interaction effects. If a one interaction is not zero than an approach of one-factor-in-time is not suitable for analysis of situation. In our case we have just the same situation. We think that we have got some base to say that many traditional investigations of control charts performance have limited value due to rather limited assumptions they are based on.

6 Conclusions

Experimental design is a natural frame for analysis of control charts performance. It gives much deeper picture of behavior of the complicate system. We have some new results about the effects of pair interactions. We are planning continue our investigations Adler, Yu., Maksimova, O., Shper, V.(2011).

Appendix A

Table A: Design matrix and means responses vector.

X_1	X_5	X_6	X_9	X_7	X_4	X_3	X_8	X_2	Y
-1	-1	-1	-1	-1	-1	-1	-1	-1	0.0000
-1	0	0	0	0	0	0	0	-1	0.0155
-1	1	1	1	1	1	1	1	-1	1.0000
-1	-1	-1	0	0	-1	-1	0	-1	0.0000
-1	0	0	1	1	0	0	1	-1	0.0198
-1	1	1	-1	-1	1	1	-1	-1	0.0000
1	0	1	1	0	-1	-1	1	-1	0.8562
1	1	-1	-1	1	0	0	-1	-1	0.0000
1	-1	0	0	-1	1	1	0	-1	0.3092

1	1	0	1	1	-1	-1	0	-1	1.0000
1	-1	1	-1	-1	0	0	1	-1	0.0320
1	0	-1	0	0	1	1	-1	-1	0.0000
-1	1	-1	1	0	0	-1	-1	0	1.0000
-1	-1	0	-1	1	1	0	0	0	0.0161
-1	0	1	0	-1	-1	1	1	0	0.0267
-1	1	0	0	-1	0	-1	1	0	0.0626
-1	-1	1	1	0	1	0	-1	0	1.0000
-1	0	-1	-1	1	-1	1	0	0	0.0000
1	-1	1	0	1	0	-1	-1	0	0.3529
1	0	-1	1	-1	1	0	0	0	0.0404
1	1	0	-1	0	-1	1	1	0	0.0045
1	0	1	-1	-1	0	-1	0	0	0.0035
1	1	-1	0	0	1	0	1	0	0.0000
1	-1	0	1	1	-1	1	-1	0	1.0000
-1	0	-1	-1	1	1	-1	1	1	0.0000
-1	1	0	0	-1	-1	0	-1	1	0.0392
-1	-1	1	1	0	0	1	0	1	1.0000
-1	0	0	1	-1	1	-1	-1	1	0.0108
-1	1	1	-1	0	-1	0	0	1	0.4402
-1	-1	-1	0	1	0	1	1	1	0.0000
1	1	1	0	1	1	-1	0	1	0.6519
1	-1	-1	1	-1	-1	0	1	1	1.0000
1	0	0	-1	0	0	1	-1	1	0.0043
1	-1	0	-1	0	1	-1	1	1	0.0777
1	0	1	0	1	-1	0	-1	1	0.2866
1	1	-1	1	-1	0	1	0	1	1.0000

Numbers of columns are result of randomization.

In the last column are given means from ten realizations.

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Advances in CUB models with application to the evaluation of natural parks in the dolomites

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Abstract: The rating problem arises very often in statistical surveys, where respondents are asked to evaluate several topics of interest (products, services, treatments, etc.). In this framework, a new approach is represented by a class of mixture models (Covariates in the mixture of Uniform and shifted Binomial distributions, CUB models), proposed by Piccolo (2003), D'Elia and Piccolo (2005) and Piccolo (2006). Together with parametric inference, a permutation solution to test for covariates effects, when a univariate response is considered, has been discussed in Bonnini *et al.* (2011), where the method has been proved to be well performing and competitive with respect to the asymptotic solution. In the present work we perform an extension of the simulation study to prove the good power behavior of the permutation solution also in other different situations. The method is also applied to real data regarding the analysis of the main reasons that drive tourists to choose Sesto/Alta Pusteria's Dolomites (an area of the Trentino Alto Adige region in Italy) as resort for their holidays.

Keywords: Permutation test, *CUB* models, rating data, power study.

1 Introduction

Analysis of ordinal data is receiving a growing interest in many fields, like marketing (studying preferences of consumers about a set of products) or clinical studies (rating treatments or drugs).

In this topic a new approach is represented by CUB models, which have been introduced by Piccolo (2003), D'Elia and Piccolo (2005) and Piccolo (2006) and then generalized by Piccolo and D'Elia (2008) and Iannario and Piccolo (2009). It assumes that the judgment process follows a psychological mechanism which is the result of a feeling towards the object under judgment and an uncertainty generated by the presence of multiple alternatives.

As only asymptotic results are available for parametric inference, nonparametric alternatives is helpful when, for instance, the sample size is not large. In Bonnini *et al.* (2011) the authors proposed a permutation solution to test for covariates effects in CUB models when conditions for asymptotic inference do not hold.

In this work we extend the simulation study presented in Bonnini *et al.* (2011) to study the performances of the permutation solution. The method is also applied to real data regarding the analysis of the main reasons that drive tourists to choose Sesto/Alta Pusteria's Dolomites (an area of the Trentino Alto Adige region in Italy) as resort for their holidays.

2 Material and methods

Within the analysis of ordinal data a new solution is represented by CUB models. In this framework the judgment process is modeled as a mixture of two distributions, which are related to a

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feeling component towards the object under judgment and an uncertainty component generated by the fact that the respondent has to choose among multiple alternatives.

When the sample size is not large non parametric alternatives can be useful in order to make inference without relying on any assumption on the asymptotic distribution of the maximum likelihood estimators. In this vein, a permutation solution is proposed in Bonnini *et al.* (2011) to test for covariates effects in CUB models when conditions for asymptotic inference do not hold.

3 Theory

CUB models are generated by a class of discrete probability distributions obtained as a mixture of a *shifted Binomial* and a *Uniform* random variable. Moreover subject (consumer or patient) and object (product or drug) characteristics can be also introduced. Assume n people are rating a definite item, hence we observe the sample $\boldsymbol{y} = (y_1, y_2, \ldots, y_n)'$; moreover let $\vec{x_i}$ and $\vec{w_i}$, with $i = 1, \ldots, n$ be subjects' covariates for explaining feeling and uncertainty respectively. Hence, the general formulation of a CUB (p, q) model (with p covariates to explain uncertainty and q covariates to explain feeling), is expressed as:

$$Pr\left(Y_i = y | \vec{x_i}, \vec{w_i}\right) = \pi_i \binom{m-1}{y-1} (1-\xi_i)^{y-1} \xi_i^{m-y} + (1-\pi_i)\left(\frac{1}{m}\right)$$

with $y = 1, 2, \ldots, m$, and the *two systematic components*:

$$\pi_i = \frac{1}{1+e^{-\vec{x_i}\,\vec{\beta}}}; \qquad \xi_i = \frac{1}{1+e^{-\vec{w_i}\,\vec{\gamma}}}$$

where $\vec{x_i}$ and $\vec{w_i}$, with $i = 1, \ldots, n$, are the covariates row-vectors for explaining π_i and ξ_i, respectively, and $\boldsymbol{\psi} = (\vec{\beta}', \vec{\gamma}')'$ the vector of parameters associated to the covariates.

Inference on CUB models has been developed nonparametrically in Bonnini *et al.* (2011). In that article the authors present a permutation solution (based on the constrained permutation of raw data) to test for the effect of covariates on the rating response. The test works according to the following steps (see Bonnini *et al.* (2011) for a more detailed description):

i. Calculate the observed value of a suitable test statistic t as function of the observed dataset (several proposals for t are done).

ii. Permute the rows of only the columns related to the tested covariates, keeping fixed the remaining elements of the dataset (perform constrained permutations within blocks, in which the non tested covariates are constant).

iii. Calculate the value of the test statistic corresponding to the permuted dataset.

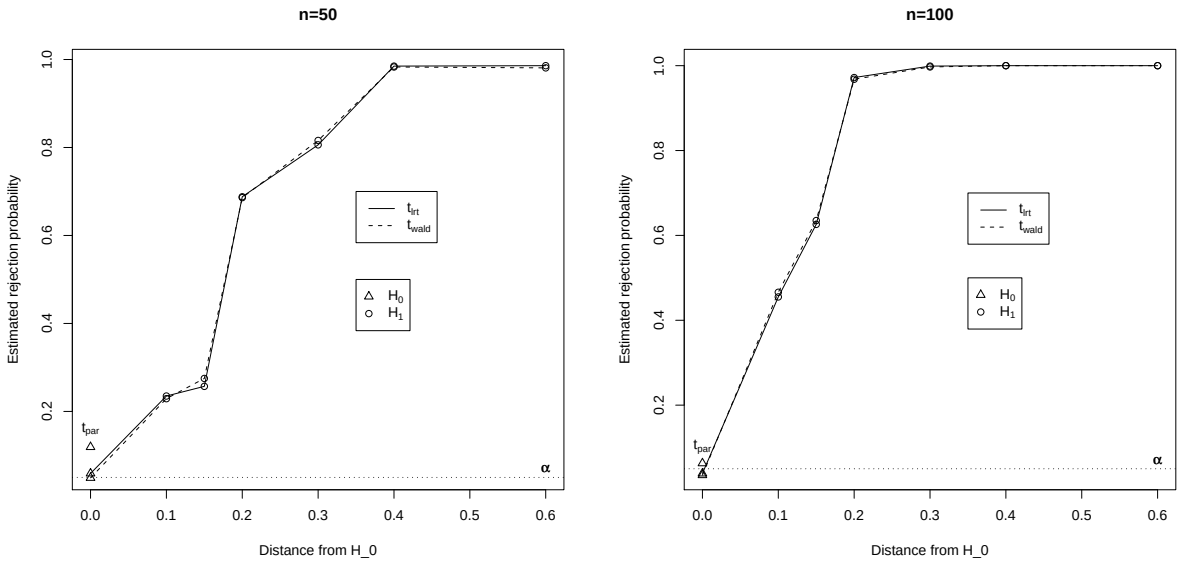
iv. Repeat Steps `ii` and `iii` B times, obtaining the permutation distribution of the test statistic.

v. Calculate the p-value λ of the test as usual according to the permutation distribution of t.

This solution is a competitive alternative to the classical parametric test when the sample size is not high.

4 Results

In Bonnini *et al.* (2011) a Monte Carlo simulation study has been carried out to study the performances of the permutation test. The power behavior of tests on the covariates of CUB $(1, 1)$, CUB $(1, 0)$ and CUB $(0, 1)$ model was studied, comparing the permutation tests with a parametric competitor. In the present work the study is extended considering more complicated CUB models under the alternative hypothesis, i.e. models with more than one covariate for π and ξ (up to the CUB $(3, 3)$ model), to study how the number of covariates affects the inferential results and the performance of the tests. As in Bonnini *et al.* (2011) we consider the case of dichotomous covariates. We compare the permutation solutions and the parametric likelihood-ratio test. The study showed how the power of all the procedures increases as we move further away from the null hypothesis and as the sample size n increases. Moreover it has to be underlined that the parametric solution does not control the type I error when the sample size is low. The results are summarized in Figure 1: the results are showed in terms of estimated rejection probability in relation to the distance of the simulated data from the null hypothesis of interest. Such distance is represented as a combination of the number of influent simulated covariates and the degree of their influence: in some sense it summarizes the differences among the values of the feeling parameter in the different populations defined by the possible combinations of levels of the covariates. The plots show the behavior of two permutation solutions t_{lrt} and t_{wald} as we move far away from the null hypothesis and as the sample size increases; the behavior of the parametric solution (t_{par}) under the null hypothesis is also indicated.



(a) (b)

Figure 1: Estimation rejection probabilities for the permutation and parametric tests on the influence of more than one covariate, for some of the settings considered in the study, with simulated sample sizes of (a) $n = 50$ and (b) $n = 100$.

The permutation solution has also been applied to real data. The Sesto Nature Survey is a study about the preferences of tourists for the facilities and offerings of the area of Dolomites of Sesto/Alta Pusteria performed in summer 2010. The respondents were asked to indicate the level of interest for different services using a rating scale from 0 to 10. In this work two particular responses, related to the interest towards equipped routes and trips by mountain-bike

(y_1 and y_2 respectively) have been considered. Moreover three covariates have been included in the analysis, all dichotomous: nationality (Italian or not), presence of below 12 aged children and presence of teenagers in the trip. For each response separately, a permutation test has been performed in order to compare the full model with the three covariates with the null model where no covariate is assumed to influence the response. In order to perform the test we used $B = 1000$ permutations. For both responses the permutation test indicates an improvement due to the inclusion of the three covariates with respect to the null model without covariates. Going backward to check which covariates influence the responses and which of the two parameters of the models are affected, we recovered the adjusted permutation p-values related to the partial Wald tests associated to the single covariate/parameter combinations. The nonparametric results are coherent with the parametric ones: the analysis suggested that the presence of teenagers in the trip affects the feeling parameter for y_1, and in particular groups with teenagers seem to be more interested in equipped routes. Moreover the nationality covariate affects the uncertainty parameter for y_2, and, although all the respondents showed low interest towards the trips by mountain-bike, in particular Italian visitors look to be more uncertain about this aspect.

5 Discussion

This paper aims to study the performances of a permutation solution to test for covariate effect in CUB models. We extended the simulation study presented in Bonnini *et al.* (2011), confirming the good behavior of the method both under the null and alternative hypotheses also with low sample sizes. We also applied the method to a real data application concerning a study about the preferences of tourists for the facilities and offerings of the area of Dolomites of Sesto/Alta Pusteria (Italy). The global influence of several covariates on some responses of interest has been tested and a backward procedure, exploiting the permutation nature of the approach, has been performed in order to check the influence of the single covariates on the outcomes, while taking care of the multiplicity issue.

6 Conclusions

We can conclude that the permutation test based on the likelihood ratio test statistic seems to be a very well performing alternative to the classical parametric counterpart when the sample size in not large. Moreover the use of nonparametric combination of permutation tests can be useful, on the other hand, if we aim to know which covariate brought to the rejection of the null hypothesis, i.e. which specific coefficients are significantly different from 0 in case of rejection of the null hypothesis, controlling the multiplicity issue. Indeed a backward analysis using a closed testing procedure can be performed in those cases.

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On exact D-optimal designes. Computational aspects.

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Abstract: Methods of D optimal experimental design construction based on Delta-square distribution simulation are discussed. The algorithms proposed earlier by the Author together with T. Misov had some disadvantages. In the paper some ways to overcome these disadvantages are presented.

Keywords: D-optimal design, global optimisation, distribution simulation.

1 Introduction

It is known that many optimal design problems are related to the search for a global extremum of functions of many variables $\Phi(X)$, where $X \in D \subset \mathbf{R^s}$ lies in the design region D. If number s of variables is high then the search problem can be very laborious. Classical problem of computational construction of the exact d-optimal designs for regression experiments is a typical example of such a problem.

Let us remind the most simple statement of the problem. Suppose the regression function $f(x)$ is defined in terms of a finite number of unknown parameters Θ_n.

$$f(x) = \sum_{k=1}^{n} \Theta_k \varphi_k(x), \quad k = 1, \ldots, n, \tag{1}$$

where $\varphi_k(x)$ – are known functions. As a result of an experiment one can measure (calculate) with random error values of f in points $X_l \in D$, $l = 1, \ldots, N$ which are defined by the experimentators

$$\xi(X_l) = f(X_l) + \epsilon_l, \quad l = 1, \ldots, N. \tag{2}$$

In the simplest case that we are discussing random values ϵ_l satisfy conditions

$$\mathrm{E}\xi(X_l) = f(X_l), \quad \mathrm{E}\left(\xi(X_l)(\xi(X_m)\right) = \begin{cases} 0, & l \neq m \\ \sigma^2, & l = m, \end{cases} \quad l, m = 1, \ldots, n. \tag{3}$$

It is also supposed that $N \geqslant n$. The well-known procedure of the method of least squares for calculation of estimates $\widehat{\Theta}_k$ of parameters Θ_k is reduced to solving system of linear algebraic equations

$$A\widehat{\Theta}_k = F. \tag{4}$$

Exact D-optimal design is named $Y^* = (X_1^*, \ldots, X_N^*)$ satisfied to equality

$$Y^* = \arg \sup_{X_1, \ldots, N} \det \left\| \sum_{m=1}^{N} \varphi_k(X_m)\varphi_l(X_m) \right\|_{k,l=1}^{n}.$$

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Solving D-optimisation problems is a difficult task, wich is mast often approached by studying continuous designs and applying the equivalence theory of Kiefer and Wolfowitz (1959). D-optimal criterion in this case is

$$\Psi(\mu) = \det \left\| \int \varphi_k(X)\varphi_m(X)\, d\mu(X) \right\|_{k,l=1}^{n}, \tag{5}$$

where μ – is normalized (probability) measure, concentrated on D. D-optimal continuous design denotes measure μ^*, which satisfies equality

$$\mu^* = \arg\max_{\mu} \Psi(\mu). \tag{6}$$

We suppose satisfaction of the conditions under which there exist Y^* and μ^*.

Methods, developed in (Fedorov 1972) and (Wynn 1970), mainly solve a problem of numerical calculation of μ^*. In some cases, especially for large values of N, μ^* that is received as a result of numerical procedures can serve as a good approximation of Y^*.

But if N is comparatively small or measure μ^* and (or) Y^* are not unique, one needs other methods for finding Y^*. It is obvious that large number of variables, complexity of function Ψ and possible lack of unique solution make ineffective general methods of finding a global extremum (including random search).

Below we will discuss special methods which use approaches developed while solving problems of distribution modeling.

2 Numerical simulation

Let λ – be a probability measure on D and $\Psi_l(X)$ – be orthonormal with respect to λ system of functions. Then

$$\Delta^2_{n,N}(Y) = \frac{(n+N)!}{n!N!}\Phi(Y)$$

is a distribution density with respect to measure

$$\lambda^N(dY) = \bigotimes_{l=1}^{N} \lambda(dX_l).$$

For proof see (Ermakov 1975).

Thus, Y^* is the mode of distribution $\Delta^2_{n,N}$. By getting computer realizations of the distribution one can estimate its mode. If a "spike" in the point of global extremum is high enough and other extremums are not too close to it, the procedure can be very effective provided the modeling algorithm is also effective. The simplest sampling method demands at the average $M|D|$ calculations of $\Psi(Y)$, where $M = \sup_{Y \in D} \Psi(Y)$. Estimation of value M is a matter of some difficulty. Normally this estimate is very over-evaluated. But even with good knowledge of M, effectiveness of the sampling method can be very low.

Author together with Misov (2005, 2009) managed to develop effective methods of modeling $\Delta^2_{n,N}$ that use its features. Methods of composition and an inversion formula were used.

Previously it was considered that for modeling $\Delta^2_{m,N}$ only the sampling method can be used. This method demands estimates of the density maximum value. For this matter, besides the well-known

case of polynomial regression on interval, one can only suggest using the Adamar inequality, which usually leads to over-evaluated result.

In this case computational complexity of the sampling method is estimated as

$$O\left(\frac{n^{n+3}}{n!}\right)\left(\max_{x\in D, i=\overline{1,n}}|\varphi_i(x)|\right)^{2n}, \qquad (N=n),$$

In papers Ermakov and Missov (2005) there were constructed methods with estimate of the complexity $O(n2^{n-1})$. This is a rather rough estimate but it shows considerable decrease of complexity, which is pointed out in the next table for specific n.

n=2	3	4	5	6	7	8	9	10	20	50
0,375	0,427	0,129	0,066	0,035	0,019	0,011	$7,1\cdot 10^{-3}$	$4\cdot 10^{-4}$	$5,6\cdot 10^{-5}$	$1,26\cdot 10^{-9}$

Specific calculations were conducted. For the case of polynomials of the third degree with two variables ($n = 10$) the ratio between average time of the suggested method and average time of the sampling method turned out to be $4 \cdot 10^{-4}$ (which coincides with the value in the table).

The use of the method for test variant of the polynomial regression on interval showed good results. In comparison with the simple random search of extremum for polynomial regression $n \leqslant 10$, it gave the gain of ≈ 3 degrees.

The following tables show results of the search for exact D-optimal designs $D = [0, 1]$ for quadratic regression with 4 points of observations

N	x_1	x_2	x_3	x_4
500	0,002942	0,503165	0,508371	0,998531
1000	0,002942	0,503165	0,508371	0,998531
2000	0,002177	0,500525	0,501087	0,999951
5000	0,000550	0,500346	0,500731	0,999992
10000	0,000014	0,500022	0,500132	0,999994

And for regression like $c_1 + c_2x + c_3e^x$.

N	x_1	x_2	x_3	x_4
500	0,006889	0,415713	0,448710	0,983057
1000	0,003014	0,524322	0,534542	0,991139
2000	0,003322	0,424577	0,505026	0,999384
5000	0,008751	0,471999	0,515507	0,998711
10000	0,000231	0,491175	0,498388	0,988331

Obviously the results can be made more precise with the use of the other methods (e. g. the gradient method).

Calculations up to $m = 15$ and n close to m in one-dimensional case show encouraging results. Some complications arise for high-dimensional regions D, when there exist a lot of points with equal global extremum, and also in case when the number of linear independent functions is substantially less than the number of points where experiment was conducted (smeared extremum). In the last case one should search for a continuous design.

Thus, the modeling method turns out to be rather robust and have the following advantages:

а) Universality — it can be applied in case of any orthonormal system φ_l and any probability measure λ.

б) It surpasses known methods of the search for a global extremum in terms of effectiveness.

3 Disadvantages and its overcoming

The next disadvantages takes plase

а) With growth of N, while n is fixed, the modeled distribution becomes more and more "diffuse" which substantially slows finding Y^*.

б) The method also works badly in case when there are a lot points that take global extremum value.

The disadvantages listed above can be overcome if one uses the Metropolis method. Preliminarily, let us point out a statement. If function $\Psi(Y)$ is non-negative, $\Psi(Y) \leqslant M$, then the following equality takes place (Ermakov 1975).

$$\lim_{m\to\infty} \frac{\Psi^m(Y)}{\int \Psi^m(Y)\lambda^N(dY)} = \chi(Z), \tag{7}$$

where $\chi(Z)$, $Z \in \mathcal{Z}$ — is the uniform distribution with respect to measure λ^N on the set $\mathcal{Z}$ of global supremums of function $\Psi(Y)$.

Obviously, if m is large enough then all realizations of the random vector Ξ with density $C\Psi^m(Y)$ will be close to points of the set $\mathcal{Z}$, and additional selection of realizations that correspond to the largest values of Ψ^m will permit to practically solve the problem, i.e. to get a number of realizations of Ξ.

As it is known, the Metropolis method generalized by Hastings consists in modeling a specially constructed Markov chain with transition density $p_i(x \to y)$ with respect to measure λ^N, which is chosen randomly to a certain degree, and in verification of the certain condition.

If the chain is in state x_i, then y_{i+1} is found as a realization of the density $p(x_i \to y)$. After that with probability a_i

$$\frac{\Psi^m(y_{i+1})p_i(y_{i+1} \to x_i)}{\Psi^m(x_i)p_i(x_i \to y_{i+1})} = a_i, \tag{8}$$

one supposes that $x_{i+1} = y_{i+1}$ and with probability $1 - a_i$ that $x_{i+1} = x_i$.

Stationary distribution of the resulting Markov chain, which has transition density

$$A_i(X \to Y) = \min(1, a_i), \tag{9}$$

is

$$\Psi^m(Y) \Big/ \int \Psi^m(Y)\lambda^N(dY).$$

Received realizations of the distribution, close to uniform on the set of extremums of $\Psi(Y)$, will permit to select exact D-optimal plans which satisfy additional conditions.

Emerging problems:

а) To check if the Markov chain exited to the steady (stationary) mode.

б) To accelerate process of the chain's exit into the stationary mode.

The suggested method can be rather complex in terms of calculation, but growing possibilities of modern computers give much prospect of its future realization for rather large values of n.

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Optimal Predictive Design Augmentation for Spatial Generalised Linear Mixed Models

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Abstract: A typical model for geostatistical data when the observations are counts is the spatial generalised linear mixed model. We present a criterion for optimal sampling design under this framework which aims to minimise the error in the prediction of the underlying spatial random effects. Our criterion is derived by performing an asymptotic expansion to the prediction variance. We perform a computational study to investigate the effect of the parameters of the model in deriving the optimal design and find that, contrary to the widely-used space-filling designs, the mean of the spatial process has a significant effect. Our results are applied to the Norway precipitation data and the rhizoctonia disease data.

Keywords: Generalised linear mixed models; Geostatistics; Predictive inference; Sampling design.

1 Introduction

One of the most frequently used model for the analysis of geostatistical count data is the spatial generalised linear mixed model (SGLMM) (Diggle *et al.* 1998). Applications of SGLMM include Diggle *et al.* (2002) which studied the risk of malaria in Gambia, Diggle *et al.* (1998) which looked into residual contamination from nuclear weapons testing and campylobacter infections in UK, Zhang (2002) which analysed a root disease in an agricultural study, and Eidsvik *et al.* (2009) which examines precipitation data for the purpose of weather forecasting and for operating hydropower plants.

In particular, this model class assumes the existence of an unobserved Gaussian random field over the region of interest and that the observations, drawn at fixed locations, are conditionally independent given the value of the random field. The distribution of the random field may depend on unknown parameters and the objective is to use the sample to predict the value of the random field at every location in the region. The "plug-in" approach is a common method for prediction in these models from a frequentist point of view (Christensen and Waagepetersen 2002; Evangelou *et al.* 2011) where in the first stage an estimate of the model parameters is obtained and in the second stage the predictive distribution of the random field is constructed conditional on the data and the parameter estimates.

The objective of *spatial predictive design* is to select the sampled locations within the region of interest in order to optimise, in some sense, the predictive capability of the sample. In summary, the strategy of optimal design comes down to developing some optimality criterion, such as the average prediction variance, and then searching over all possible sampling configurations for the optimal value of the criterion. We focus in the case where the sampling has already taken place at some locations and the data is available but either because there are more resources available or because the prediction error is too high more data is to be sampled. That is we seek to augment the current sampling scheme with new locations. The available data may be used to infer about the parameters of the random field which help decide where to sample from.

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A large part of the literature is concerned with optimal predictive designs for Gaussian models (e.g. Cressie *et al.* 1990; Martin 2001; Müller 2007; Heuvelink *et al.* 2010) which tend to be uniformly spaced while some development towards optimal SGLMM designs has been made in Diggle and Lophaven (2006) and Eidsvik *et al.* (2009). Nevertheless the field is still very new with room for further development. A drawback in applying the ideas of optimal experimental design in the context of SGLMM is that in this case the optimality criteria don't exist in closed-form. One solution is to evaluate them using Monte-Carlo approximations but this approach is too computationally intensive due to the fact that in practice the design criterion needs to be evaluated for a potentially large number of candidate designs in search for the optimal one.

Alternatively, Nychka and Saltzman (1998) and Royle and Nychka (1998) proposed a model-free approach from a wholly geometric point of view where the sampling sites are chosen in a way that the region of interest is covered uniformly and therefore there is no need of numerically evaluating the estimation and prediction error. Moreover, uniform designs tend to be very similar to Gaussian optimal designs (Royle and Nychka 1998). On the other hand, it is not clear how a uniform design performs in the context of SGLMM. The reason is that, contrary to the Gaussian model, the prediction error not only depends on the variance of the underlying process but also on its mean. Hence, it is fair to say that if the mean varies highly within the region a uniform design would not be appropriate. To support this hypothesis, let us consider the following example. Suppose that the observations are binary with probability of "success" varying from 0 to 1 across the region of interest. If a uniform design is implemented part of the sample will be associated with areas with very high or very low success probabilities; however, the data from these areas exhibit almost no variability and, in essence, are useless. We believe that, in choosing a good design, more weight should be given in areas where the probability of success is closer to half, i.e. where the variability of the data is higher.

In this article, we propose a model-based criterion for constructing optimal predictive designs based on an approximation to the predictive variance. We assume that prior data is available and the objective is to augment the given sampling network. Our strategy proceeds as follows. By fitting a SGLMM to the data we construct a prediction map for the mean and variance of the spatial random field. These estimates are used in the evaluation of the proposed design criterion and an exchange algorithm is implemented to search for the best design.

In the next section we describe the SGLMM and derive an approximation to the predictive variance which we use as our design criterion. In section 3 we present the exchange algorithm used for searching for the optimal design and in section 4 we illustrate our method through a computational study and two examples. Finally, section 5 presents a summary of the conclusions of this article.

2 An approximate predictive design criterion

2.1 Model

We assume a spatial domain $\mathbb{S}$ and an isotropic Gaussian random field $\mathcal{Z}$ defined over $\mathbb{S}$. Our objective is to predict $\mathcal{Z}$ for given observations $\boldsymbol{y} = \{y_1, \ldots, y_k\}$ drawn at k fixed, distinct locations $S = \{s_1, \ldots, s_k\} \in \mathbb{S}$ called the *sampling design*. The SGLMM assumes that the observations are conditionally independent given the value of the random field on S with distribution from the exponential family. Furthermore, each y_i corresponds to repeated sampling of size n_i from location s_i. In the binomial case n_i may be interpreted as the number of trials in a Bernoulli experiment and in the Poisson case as the length of time that the sampling is taking place.

The geostatistical approach to SGLMM assumes further that the covariance between two components of the random field, $\mathcal{Z}(s)$ and $\mathcal{Z}(s')$, at locations $s, s' \in \mathbb{S}$ is a function of the

distance $\|s - s'\|$. In particular we denote

$$\mathsf{Var}(\mathcal{Z}(s)) = \nu^2 + \tau^2$$
$$\mathsf{Cov}(\mathcal{Z}(s), \mathcal{Z}(s')) = \tau^2 c(\|s - s'\|/\rho)$$

where (ν^2, τ^2, ρ) are covariance parameters termed *nugget*, *partial sill* and *range* respectively and $c(\cdot)$ is a positive definite function defined on $(0, \infty)$ called the *correlogram*. Two particular versions of the correlogram that we make use in the examples of section 4 are the following.

- *Exponential*: $c(h) = \exp(-h)$,
- *Spherical*: $c(h) = 1 - 1.5\,h + 0.5\,h^3$ if $0 < h < 1$ and $c(h) = 0$ if $h \geq 1$.

Let $\boldsymbol{Z} = (Z_1, \ldots, Z_k)$ denote the components of the random field associated with the locations in the sampling design S and let $\boldsymbol{\lambda}$ and Σ denote the mean vector and the variance-covariance matrix respectively. Also let $f(\cdot)$ denote the probability density/mass function of its arguments so that

$$f(\boldsymbol{z}; \boldsymbol{\lambda}, \Sigma) = (2\pi)^{-\frac{k}{2}} |\Sigma|^{-\frac{1}{2}} \exp\left\{(\boldsymbol{z} - \boldsymbol{\lambda})^\intercal \Sigma^{-1} (\boldsymbol{z} - \boldsymbol{\lambda})\right\}$$

and

$$f(y_s | z_s) \propto \exp\{y_s z_s - n_s \psi(z_s)\}$$

where $\psi(\cdot)$ is a known function; for example under the binomial model with canonical link $\psi(z) = \log(1 + e^z)$ and for the Poisson model with canonical link $\psi(z) = e^z$.

2.2 Prediction variance

Consider the question of predicting $\mathcal{Z}(s)$ from $\boldsymbol{y}$ for a particular location $s \in \mathbb{S}$. A measure of the uncertainty in prediction is the *conditional prediction variance*, $\mathsf{Var}(\mathcal{Z}(s)|\boldsymbol{y}; S)$ where in the notation we make explicit the dependence of the variance on the sampling design S. The *average conditional prediction variance* over $\mathbb{S}$ for given data $\boldsymbol{y}$ is defined as

$$\frac{1}{|\mathbb{S}|} \int_{\mathbb{S}} \mathsf{Var}(\mathcal{Z}(s)|\boldsymbol{y}; S)\, \mathrm{d}s \tag{1}$$

where $|\mathbb{S}|$ denotes the volume of $\mathbb{S}$. Booth and Hobert (1998) are among those who advocate using (1) as a measure of the prediction accuracy. To that end, a suitable criterion for choosing a good sampling design is to make (1) small; however, in theory, $\mathbb{S}$ is a continuous region so prediction at all locations in it is infeasible. In practice prediction is performed over a finite, fine grid, $\bar{\mathbb{S}}$, covering $\mathbb{S}$ and the optimality criterion reduces to

$$\frac{1}{|\bar{\mathbb{S}}|} \sum_{s \in \bar{\mathbb{S}}} \mathsf{Var}(\mathcal{Z}(s)|\boldsymbol{y}; S). \tag{2}$$

The criterion in (2) has been extensively used for the derivation of sampling designs for Gaussian models (e.g. Cressie *et al.* 1990). However, for SGLMM the prediction variance is not known in closed form so exact calculation of (2) is impossible (Booth and Hobert 1998). Below we derive an approximation in closed-form to the prediction variance which will be used for defining our design criterion.

We assume increasing-domain asymptotics in the spirit of Mardia and Marshall (1984), i.e. that $k \to \infty$ and that the rows of the variance-covariance matrix Σ are absolutely summable as

$k \to \infty$. Furthermore we assume that $k/n_i \to 0$ as $k \to \infty$. These assumptions are made in order to facilitate the application of Laplace approximation to the conditional distribution of the random field given the observations.

Let $\sigma^2 = \mathsf{Var}(\mathcal{Z}(s)) = \nu^2 + \tau^2$, $\boldsymbol{c} = \mathsf{Cov}(\boldsymbol{Z}, \mathcal{Z}(s))$, and

$$\hat{\boldsymbol{z}} = \hat{\boldsymbol{z}}(\boldsymbol{y}) = \operatorname*{argmax}_{\boldsymbol{z}} f(\boldsymbol{y}, \boldsymbol{z}; \boldsymbol{\lambda}, \Sigma).$$

Then by an application of Laplace approximation (see Barndorff-Nielsen and Cox 1989) the conditional distribution of $\boldsymbol{Z}|\boldsymbol{y}$ is normal with mean $\hat{\boldsymbol{z}}$ and variance-covariance matrix $\hat{H}^{-1}$, written

$$\boldsymbol{Z}|\boldsymbol{y} \sim N(\hat{\boldsymbol{z}}, \hat{H}^{-1}), \tag{3}$$

where $\hat{H} = \hat{D}_{\boldsymbol{y}} + \Sigma^{-1}$. $\hat{D}_{\boldsymbol{y}}$ is a diagonal matrix with its ith component equal to the second order derivative of $-\log f(y_i|z_i)$ with respect to z_i evaluated at $\hat{z}_i$, namely to $n_i\psi''(\hat{z}_i)$. From (3) the prediction variance is approximately equal to (see Appendix A)

$$\mathsf{Var}(\mathcal{Z}(s)|\boldsymbol{y}; S) \approx \sigma^2 - \boldsymbol{c}^{\mathsf{T}}(\hat{D}_{\boldsymbol{y}}^{-1} + \Sigma)^{-1}\boldsymbol{c}. \tag{4}$$

The order of the approximation in (4) is $O(kn^{-2})$ where $n = \min\{n_1, \ldots, n_k\}$. (For details about the order of the approximation see Evangelou *et al.* (2011).)

Now suppose that we are looking to augment our sampling scheme with an additional set of l new locations $Q = \{q_1, \ldots, q_l\} \subset \mathbb{S} \setminus S$ which will result data $\boldsymbol{X}$. Consider the expected prediction variance

$$\mathsf{E}_{\boldsymbol{x}}\,\mathsf{Var}(\mathcal{Z}(s)|\boldsymbol{y}, \boldsymbol{X}; S, Q) \approx \sigma^2 - \boldsymbol{c}_{SQ}^{\mathsf{T}}\,\mathsf{E}_{\boldsymbol{x}}(\hat{D}_{\boldsymbol{yx}}^{-1} + \Sigma_{SQ})^{-1}\boldsymbol{c}_{SQ} \tag{5}$$

from (4), where $\hat{D}_{\boldsymbol{yx}} = \text{BlockDiagonal}\{\hat{D}_{\boldsymbol{y}}, \hat{D}_{\boldsymbol{x}}\}$, $\boldsymbol{c}_{SQ}$ and Σ_{SQ} denote the augmented covariance vector and variance-covariance matrix respectively, and the expectation is with respect to the conditional distribution of $\boldsymbol{X}|\boldsymbol{y}$. Exact evaluation of the expectation $\mathsf{E}_{\boldsymbol{x}}(\hat{D}_{\boldsymbol{yx}}^{-1} + \Sigma_{SQ})^{-1}$ is cumbersome unless some numerical method is used. On the other hand the elements of $\hat{D}_{\boldsymbol{yx}}^{-1}$ are of order $O(n^{-1})$ so an alternative criterion to (5) would be to replace $\mathsf{E}_{\boldsymbol{x}}(\hat{D}_{\boldsymbol{yx}}^{-1} + \Sigma_{SQ})^{-1}$ by $(\mathsf{E}_{\boldsymbol{x}}\,\hat{D}_{\boldsymbol{yx}}^{-1} + \Sigma_{SQ})^{-1}$. Furthermore $\mathsf{E}_{\boldsymbol{x}}\,\hat{D}_{\boldsymbol{yx}}^{-1} = \text{BlockDiagonal}\{\mathsf{E}_{\boldsymbol{x}}\,\hat{D}_{\boldsymbol{y}}^{-1}, \mathsf{E}_{\boldsymbol{x}}\,\hat{D}_{\boldsymbol{x}}^{-1}\}$ and we note that $\hat{D}_{\boldsymbol{yx}}$ depends on $\boldsymbol{X}$ only through $\hat{\boldsymbol{z}}(\boldsymbol{y}, \boldsymbol{X})$ so $\mathsf{E}_{\boldsymbol{x}}\,\hat{D}_{\boldsymbol{y}}^{-1} = \mathsf{E}_{\hat{\boldsymbol{z}}}\,\hat{D}_{\boldsymbol{y}}^{-1}$ and $\mathsf{E}_{\boldsymbol{x}}\,\hat{D}_{\boldsymbol{x}}^{-1} = \mathsf{E}_{\hat{\boldsymbol{z}}}\,\hat{D}_{\boldsymbol{x}}^{-1}$. By noting that $\hat{\boldsymbol{z}}(\boldsymbol{y}, \boldsymbol{X})$ is approximately equal to $\boldsymbol{Z}|\boldsymbol{y}$ we deduce that $\mathsf{E}_{\boldsymbol{x}}\,\hat{D}_{\boldsymbol{y}}^{-1} \approx \hat{D}_{\boldsymbol{y}}^{-1}$ and the ith diagonal element of $\mathsf{E}_{\boldsymbol{x}}\,\hat{D}_{\boldsymbol{x}}^{-1}$ is approximately equal to $n_i^{-1}\,\mathsf{E}_w(1/\psi''(W))$ where the expectation is taken with respect to $W \sim N(\hat{\mu}_{\boldsymbol{y}}, \hat{\sigma}_{\boldsymbol{y}}^2)$ with $\hat{\mu}_{\boldsymbol{y}}$ and $\hat{\sigma}_{\boldsymbol{y}}^2$ being the prediction mean and variance respectively of the random field at the location associated with the index i given the data $\boldsymbol{y}$.

Let $K_{\boldsymbol{x}} = \text{Diag}\{n_i^{-1}\,\mathsf{E}(1/\psi''(W))\}$ where i ranges over all locations associated with Q and $K_{\boldsymbol{yx}} = \text{BlockDiagonal}\{\hat{D}_{\boldsymbol{y}}^{-1}, K_{\boldsymbol{x}}\}$. In certain cases the expectation in $K_{\boldsymbol{x}}$ may be computed in closed form. For example for the binomial model with canonical link

$$\mathsf{E}(1/\psi''(W)) = 2 + \exp\left(-\hat{\mu}_{\boldsymbol{y}} + \frac{1}{2}\hat{\sigma}_{\boldsymbol{y}}^2\right) + \exp\left(\hat{\mu}_{\boldsymbol{y}} + \frac{1}{2}\hat{\sigma}_{\boldsymbol{y}}^2\right)$$

and for the Poisson model with canonical link

$$\mathsf{E}(1/\psi''(W)) = \exp\left(-\hat{\mu}_{\boldsymbol{y}} + \frac{1}{2}\hat{\sigma}_{\boldsymbol{y}}^2\right)$$

but alternatively a one-dimensional Gaussian quadrature method can be used.

In view of the above, the approximate expected prediction variance at location $s \in \mathbb{S}$ under the design $S \cup Q$ becomes

$$\widehat{\mathsf{Var}}(\mathcal{Z}(s)|\boldsymbol{y}; S, Q) = \sigma^2 - \boldsymbol{c}_{SQ}^{\mathsf{T}}(K_{\boldsymbol{yx}} + \Sigma_{SQ})^{-1}\boldsymbol{c}_{SQ}. \tag{6}$$

Note the dependence of (6) on the estimated mean of the random field and that fact that it is positive, as expected.

From (6) the optimal SGLMM design criterion is: Choose $Q \subset \mathbb{S} \setminus S$ to minimise

$$\sum_{s \in \bar{\mathbb{S}}} \widehat{\mathsf{Var}}(\mathcal{Z}(s)|\boldsymbol{y}; S, Q). \tag{7}$$

We note that although the criterion (7) is not exact for the expected predictive variance, we nevertheless believe that it maintains the general structure of the optimal predictive design for SGLMM and proceed by using it as the optimal design criterion.

3 The exchange algorithm

Searching for the set Q that minimises (7) can be computationally challenging. If l sites are to be selected out of N possible candidates then in theory the design criterion has to be computed N-choose-l times. Even for moderate sizes this number is too large so an alternative exchange algorithm is proposed. Royle (2002) reviews the basic exchange algorithm and some of its extensions.

The basic exchange algorithm is described as follows. For a given configuration $S \cup Q$ and a set of candidate points $(S \cup Q)^{\mathsf{c}} = \bar{\mathbb{S}} \setminus (S \cup Q)$, fix $q \in Q$ and compute the design criterion by exchanging q with each of the elements of $(S \cup Q)^{\mathsf{c}}$. If no better design is found then q remains in the design otherwise q is replaced by the element of $(S \cup Q)^{\mathsf{c}}$ with the best value of the design criterion. This process is repeated for every $q \in Q$ and iterated until no better design is found. The exchange algorithm is guaranteed to converge but it is worth pointing out that its limit is not necessarily the optimal design. Nevertheless we find that it is a good compromise between computational speed and quality of the result. Below we describe how an update of the design criterion is computed in our implementation of the exchange algorithm.

Let $A = K_{\boldsymbol{yx}} + \Sigma_{SQ}$ and suppose without loss of generality that we are looking to update the element associated with the last row and column of A. Note first that, since σ^2 is a constant, we only need to evaluate $\boldsymbol{c}_{SQ}^{\mathsf{T}} A^{-1} \boldsymbol{c}_{SQ}$.

Write $\boldsymbol{c}_{SQ}$ and A as a partitioned vector and a partitioned matrix respectively in the form

$$\boldsymbol{c}_{SQ} = \begin{pmatrix} \boldsymbol{u} \\ v \end{pmatrix} \qquad A = \begin{pmatrix} B & \boldsymbol{u} \\ \boldsymbol{u}^{\mathsf{T}} & b \end{pmatrix}.$$

Also let $\beta = b - \boldsymbol{u}^{\mathsf{T}} B^{-1} \boldsymbol{u}$. Then

$$A^{-1} = \begin{pmatrix} B & \boldsymbol{u} \\ \boldsymbol{u}^{\mathsf{T}} & b \end{pmatrix}^{-1} = \begin{pmatrix} B^{-1} & \boldsymbol{0} \\ \boldsymbol{0}^{\mathsf{T}} & 0 \end{pmatrix} + \frac{1}{\beta} \begin{pmatrix} B^{-1} \\ -1 \end{pmatrix} \begin{pmatrix} B^{-1} & -1 \end{pmatrix}$$

so

$$\boldsymbol{c}_{SQ}^{\mathsf{T}} A^{-1} \boldsymbol{c}_{SQ} = \boldsymbol{u}^{\mathsf{T}} B^{-1} \boldsymbol{u} + \frac{1}{\beta}(v - \boldsymbol{u}^{\mathsf{T}} B^{-1} \boldsymbol{u})^2$$

therefore, in the exchange of a single element we may only consider maximising the quantity

$$\sum_{s \in \bar{\mathbb{S}}} \frac{(v - \boldsymbol{u}^{\mathsf{T}} B^{-1} \boldsymbol{u})^2}{b - \boldsymbol{u}^{\mathsf{T}} B^{-1} \boldsymbol{u}}$$

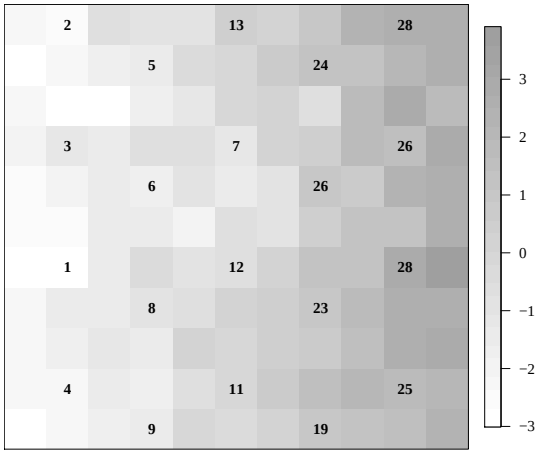

Figure 1: Simulation from the binomial SGLMM. The random field is shown by a greyscale and the binomial observations are indicated at the respective locations.

where the component $\boldsymbol{u}^\top B^{-1}\boldsymbol{u}$ is computed only once for each element of Q. In fact, by considering the block structure of B in terms of components associated with S or Q, its inverse can be computed by employing the well-known formula for the inverse of a block matrix (see Seber 2008, section 14.2). Therefore the inverse of the block associated with S is computed once for the whole execution of the algorithm and for each update the inverse of a matrix of dimension $(l-1)\times(l-1)$ is needed each time.

4 Examples

4.1 A simulated example

We consider a regularly-spaced, 11×11 square grid within $[0,1]\times[0,1]$ and a Gaussian random field having exponential covariance function with parameters $\nu^2 = 0.1$, $\tau^2 = 0.3$, and $\rho = 0.2$ corresponding to nugget, partial sill and range. We also set the mean of the random field at co-ordinate (x_1, x_2) to $-2.5 + 5.0\times x_1$, i.e. the mean increases linearly as we move from left to right from -2.5 to 2.5. The current sampling design consists of the locations indicated by a "$\circ$" in Figure 2 and the observations follow the binomial SGLMM with canonical link and the number of trials is $n = 30$ at each location.

We simulate once from the Gaussian random field and, conditionally, from the binomial model at the sampled locations. The sample is shown in Figure 1. Note that the conditional variance of the observations given the value of the random field is $n\,e^z(1+e^z)^{-2}$ and, due to the non-constant mean, the observations which are closer to the left or the right sides of the grid have very low variability while the observations that are equally far from the left and the right sides have the highest variability.

We are interested in augmenting the current sampling scheme by sampling at $l = 6$ more locations where the sample size at each location is $n = 30$. We implement an optimal SGLMM design and compare it with the space-filling design. The space-filling design suggests sampling from locations at the far left and the far right of the grid, the ones indicated by a "$\times$" in Figure 2 while the SGLMM design suggests locations from the centre of the grid, indicated by a "+". As we would expect, the locations suggested by the SGLMM-optimal design correspond to areas with higher variability while in this case the space-filling design recommends sampling from locations with very little variability. In fact a random sample from the locations suggested by the space-filling method were $1, 1, 5, 29, 29, 27$ (ordered from bottom to top and then left to

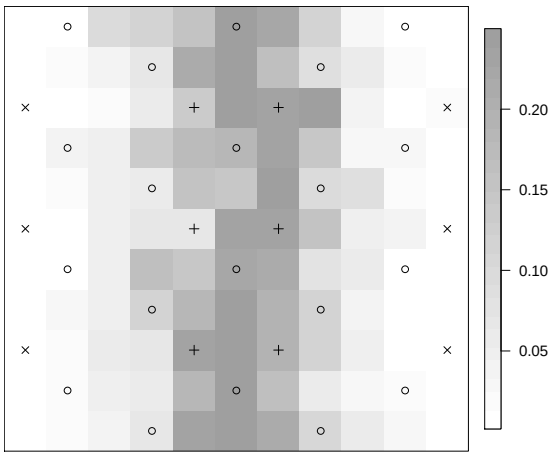

Figure 2: Predictive design for the simulated example. Showing current design (∘), space-filling augmented locations (×), and optimal SGLMM augmented locations (+). The greyscale shows the Bernoulli variance.

right) while a random sample from the locations suggested by the optimal SGLMM design gave $16, 1, 10, 19, 6, 17$. Evidently the second set of observations is far more valuable in predicting the random field than the first. In particular, the average prediction variance with the original data is 0.2986. If we augment the data with the observations from the space-filling design the average prediction variance reduces to 0.2872 (our design criterion (7) estimates this to be 0.2876) but if instead we use the data from the optimal SGLMM design the average prediction variance becomes 0.2826 (estimated to be 0.2811).

4.2 Rhizoctonia disease

The rhizoctonia root rot is a disease affecting the roots of plans and hinders the absorption of water and nutrients by them. In this study 15 plants were pulled out of each of 100 randomly chosen locations in a farm and the number of crown roots and infected crown roots were counted for each plant. The number of total roots at each location varies from 80 to 197 with an average of 138 suggesting that each plant has on average 9 crown roots.

Zhang (2002) treated the data as binomial with the random field having constant mean and spherical covariance structure. This example was also analysed by Evangelou *et al.* (2011) using approximate Laplace approximation. Figure 3 shows the prediction and prediction variance using their method. Note that, due to the assumption that the mean being constant and the fact that the variance of the spatial random effects is not very high, the variation in the predicted random field is relatively small. As a result, the regions with the highest variability tend to be the ones which are the least represented in the sampling design.

We consider the question of augmenting the current network by sampling 15 plants from each of $l = 8$ new locations ($n = 135$ at each location) chosen from a regularly-spaced, square grid of 242 points. The locations suggested by the space-filling and the SGLMM designs are shown by a "×" and a "+" respectively in Figure 4. The two designs appear very close except for two points where they are very different. This is not surprising in this case since, as we explain below, due to the large sample size at each location, the variation in the predicted random field has very little effect in the design criterion. Therefore the variability is higher at the most isolated locations which is also what the space-filling design tends to select. However consider two alternative scenarios where the available resources allow us to sample only 5 plants ($n = 45$) from each new location and in the other case only one plant ($n = 9$). The two designs are shown in Figure 4 with

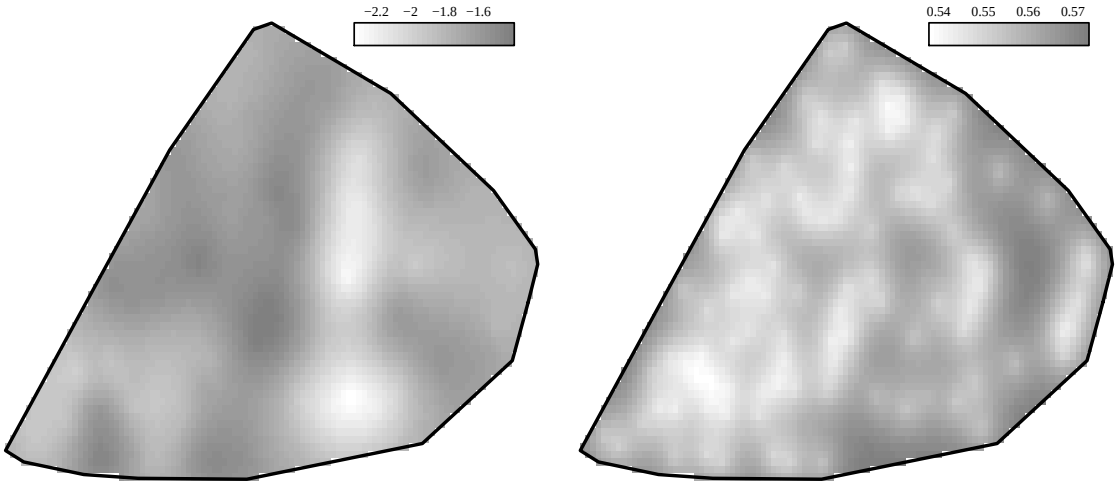

Figure 3: Prediction of the random field in the rhizoctonia example. Showing the predictive mean (left) and the predictive variance (right).

Table 1: Total prediction variance under the Optimal SGLMM and space-filling designs for different samples for the rhizoctonia example.

	15	5	1
Optimal SGLMM	136.919	137.681	139.451
Space-filling	136.952	137.750	139.574

a "V" and a "I" respectively. In the case of 5 plants there is more departure from the space-filling design and in the case of 1 plant there is a big difference. The explanation for this is because the sample size at each location enters into our design criterion as $n^{-1}e^{-\hat{z}}(1+e^{\hat{z}})^2$; therefore, when n is large the effect of the mean of the random field in the design criterion is very small so the optimal design tends to be close to the space-filling design. In the opposite case, the mean of the random field has a significant effect. This is also verified by comparing the total prediction variance under the space-filling design with the optimal SGLMM design for the different sample sizes as shown in Table 1. We observe that as the sample size increases the difference in the design criterion is reduced.

4.3 Precipitation in middle Norway

The number of rainy days for a region in the middle of Norway were recorded for a period of $n = 61$ days at 92 monitoring stations. The current monitoring network is shown in Figure 5. The data was analysed by Eidsvik *et al.* (2009) who used a binomial SGLMM with the random effect assumed to be a Gaussian random field having constant mean and exponential covariance function with no nugget effect. In their analysis the authors derived that the observations from 4 stations were outliers (circled in Figure 5) and only used data from $k = 88$ stations. Within the network there were also 6 stations not in operation (marked by a "$\diamond$") and the authors considered the improvement in prediction had data being obtained from these stations as well.

We consider prediction at a fine grid of 587 points. Using the data from the 88 locations the total prediction variance is 27.33 while assuming that data from the additional 6 stations was provided the total prediction variance from (7) reduces to 26.73.

Assuming that we have the power to place the 6 monitoring stations not in operation at different sites, the space-filling and the optimal SGLMM augmented designs were derived. These

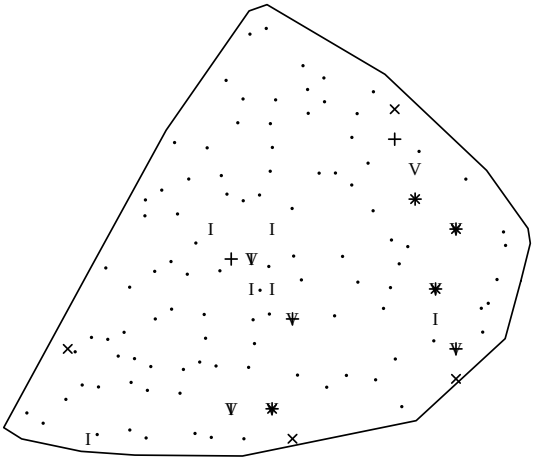

Figure 4: Predictive design for the rhizoctonia example. Showing current design (·), space-filling augmented locations (×), and optimal SGLMM augmented locations when sampling 15 plants (+), 5 plants (V), and 1 plant (I).

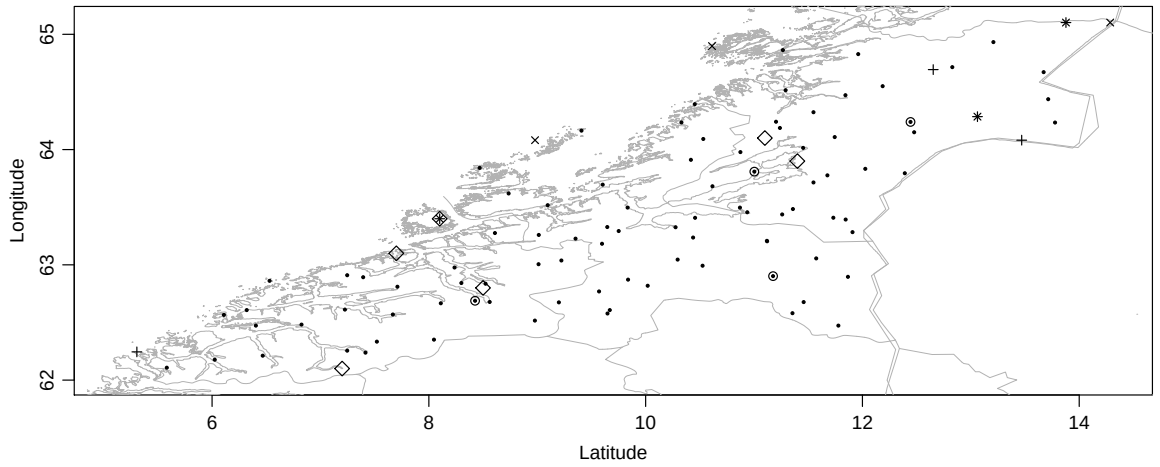

Figure 5: Norway precipitation network. Samples are obtained from locations marked by a "·" and the ones in circle are considered outliers. Al locations that did not register data are marked by a "◇". Also showing the space-filling augmented locations (×) and the optimal SGLMM augmented locations (+).

are marked by a "×" and a "+" respectively in Figure 5. All three designs agree at one location at coordinate $(8.1, 63.5)$ but apart from that there are significant differences. The total prediction variance under the space-filling design is 26.68 and for the optimal SGLMM it is 26.66. Both suggestions are an improvement compared to the current network.

5 Discussion

In this article we propose a criterion for augmenting a spatial design under the SGLMM framework when data is available. Our design criterion is derived as an approximation to the expected predictive variance of the random field and it can be evaluated with little computational cost as it avoids making use of the typical MCMC used for these models. Our approximation is based on Laplace approximation and is valid under the increasing-domain asymptotic framework.

We demonstrate theoretically and through our examples that, contrary to the more popular Gaussian model, optimal designs for SGLMM may not be regularly spaced but the level of non-uniformity depends on the structure of the conditional mean of the random field and on the sample size.

A number of issues still remain. From a computational point of view, searching for the optimal design can be very hard if the number of candidate locations is large. Questions related to the construction of predictive designs in the spirit of Smith and Zhu (2004); Zhu and Stein (2006); Zhu and Zhang (2006); Zimmerman (2006) such as how to incorporate parameter uncertainty in it or how to create a design without any available data still remain.

A Derivation of the approximate predictive variance

Here we derive the approximation to the predictive variance given in (4).

First note that by an application of the formula for matrix inversion

$$(A+B)^{-1} = A^{-1} - A^{-1}(A^{-1}+B^{-1})^{-1}A^{-1},$$

we have

$$\hat{H}^{-1} = \Sigma - \Sigma(\hat{D}_{\boldsymbol{y}}^{-1} + \Sigma)^{-1}\Sigma \tag{8}$$

Therefore if $s \in S$ the conditional variance of $\mathcal{Z}(s)$ is the corresponding diagonal element of (8) which is given by (4).

Now suppose $s \notin S$. Using the rule of iterated expectations and the fact that $\mathcal{Z}(s)|\boldsymbol{Z}, \boldsymbol{y} = \mathcal{Z}(s)|\boldsymbol{Z}$,

$$\begin{aligned}
\mathsf{Var}(\mathcal{Z}(s)|\boldsymbol{y}; S) &= \mathsf{E}\,\mathsf{Var}(\mathcal{Z}(s)|\boldsymbol{Z}, \boldsymbol{y}) + \mathsf{Var}\,\mathsf{E}(\mathcal{Z}(s)|\boldsymbol{Z}, \boldsymbol{y}) \\
&= \sigma^2 - \boldsymbol{c}^\mathsf{T}\Sigma^{-1}\boldsymbol{c} + \boldsymbol{c}^\mathsf{T}\Sigma^{-1}\hat{H}^{-1}\Sigma^{-1}\boldsymbol{c} \\
&= \sigma^2 - \boldsymbol{c}^\mathsf{T}(\hat{D}_{\boldsymbol{y}}^{-1} + \Sigma)^{-1}\boldsymbol{c}
\end{aligned}$$

by (8), as given in (4).

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Industrial Design of Experiments in *R*

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Abstract: Industrial Design of Experiments (DoE) contributes to efficient product development and improvement of production processes. This paper is about DoE in *R* in general, and in particular about implementation of the most important tools for industrial DoE, in the spirit of Montgomery (2001) or Box, Hunter and Hunter (2005). It outlines the most important aspects of a suite of *R* packages developed by the author: **DoE.base**, **FrF2**, **DoE.wrapper** and **RcmdrPlugin.DoE**. Selected aspects of the packages' strategy are discussed in more detail, and areas with potential for further improvement are pointed out.

Keywords: R package, DoE.base, FrF2, DoE.wrapper, RcmdrPlugin.DoE

1 Introduction

Industrial design of experiments (DoE) is an important contributor to data-driven product development and process improvement in various industries. Many commercial software packages offer tools for this purpose, some in direct connection to the well-known Six Sigma initiative. For example, at my former employer Ford Motor Company, the advent of Six Sigma brought access to Minitab™ (Minitab Inc 2008) and its DoE facilities to many engineers. In addition, a Ford-internal Excel tool (Grömping 1999), based on a complete catalogue of regular fractional 2-level designs by Chen, Sun and Wu (1993), supported customized planning of experiments with a VBA interface that made it easy to explore and exploit details of the confounding structure of an experimental design.

Let me now explain how I got involved in DoE *R* packages. Being no longer in industry but in academia and having come to appreciate *R* for many statistical tasks, I was still interested in Design of Experiments and played with some application problems. Trying to do simple things in *R*, I got quite frustrated by the lack of support in *R* for things that used to be easy before: I found packages **conf.design** (Venables 2000-2010), **BHH2** (Barrios 2005-2009) and **AlgDesign** (Wheeler 2004-2010) that were principally able to create regular fractional factorial 2-level plans, but there was no simple way of looking at the confounding structure of an experiment as comfortably as I was used to, and there was nothing remotely convenient that would allow specification of user requirements (like estimable 2-factor interactions) and construct a plan from there.

In the autumn of 2008, I decided to spend a sabbatical semester on implementing foundations of industrial DoE in *R*. As preparatory steps, I had started the Experimental Design Task View in February 2008, and had investigated *R* literature on the topic, in particular the "White Book" (Chambers and Hastie 1993), where functions **`fac.design`** and **`oa.design`** were mentioned which didn't exist in *R*. I decided to create software myself that should

- be close to prior work, where useful (e.g. functions **`fac.design`** and **`oa.design`** modeled after what I found in Chambers and Hastie 1993)
- allow users to specify their needs in terms as close to the problem as possible, i.e. not by doing mathematical investigations into what generators one would have to specify for

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achieving the desired behavior of the experimental plan, but by specifying estimable effects (two-factor interactions only)
- provide appropriate defaults for standard uses
- allow expert users to specifically fine-tune and deep-dive things, again emphasizing that technicalities should be done by the machine rather than by the user
- incorporate the many useful design catalogues available from the literature (cf. also Section 4.1)
- be state-of-the-art initially particularly w.r.t. fractional factorial 2-level designs
- provide at least the basic orthogonal arrays available in standard software like Minitab™
- eventually also offer response surface designs and D-optimal designs
- incorporate convenience features like exporting and re-importing designs for allowing response entry outside of *R* without error-prone cut- and paste activities
- provide a more or less self-explanatory GUI for occasional or programming-illiterate users, which should cater for inexperienced experimenters as well as for experts.

Following a benchmark of various commercial products for industrial DoE, and following a deep dive of the literature and other *R* packages, a suite of four packages for industrial DoE (with one additional auxiliary package) was implemented, cf. Section 3.

Section 2 of this paper will discuss the general development of DoE implementation on the Comprehensive *R* Archive Network CRAN (URL: http://cran.r-project.org), Section 3 will discuss some basic aspects of my suite of packages for industrial DoE, and Section 4 will look into a few mathematical aspects of these packages in more detail. An outlook to future developments with a call for contributions concludes the paper. Of course, a short paper like this can only give a rough overview. The software has an extensive online documentation, and the writing of tutorials is under way.

2 *R* embraces DoE

The growth over time in the number of *R* packages related to DoE helps to get an idea about the development of DoE in *R*; the packages from the CRAN Task View on experimental design (Grömping 2008 to 2011, status August 10, 2011) were taken as "related to DoE". Figure 1 shows development of DoE functionality in CRAN by plotting the number of current task view packages available on CRAN at the end of each year, starting in 2000 with the first and only package **conf.design** (Venables 2000-2010). The chart displays roughly exponential growth, similar to what can also be observed for *R* packages on CRAN in general (cf. Fox 2009).

Note that the above-mentioned task view has so far not considered sample size planning as DoE; it centers mainly on planning and analysis tools for multifactorial experiments. Rasch et al. (2011) offer many *R* functions for sample size planning (not yet on CRAN, therefore not in the Task View anyway); there may also be packages on CRAN with substantial functionality on sample size planning; I suspect that this functionality would be a small part of a package for other purposes, in many cases, and would therefore be very cumbersome to find and research, and I have not tried to do so.

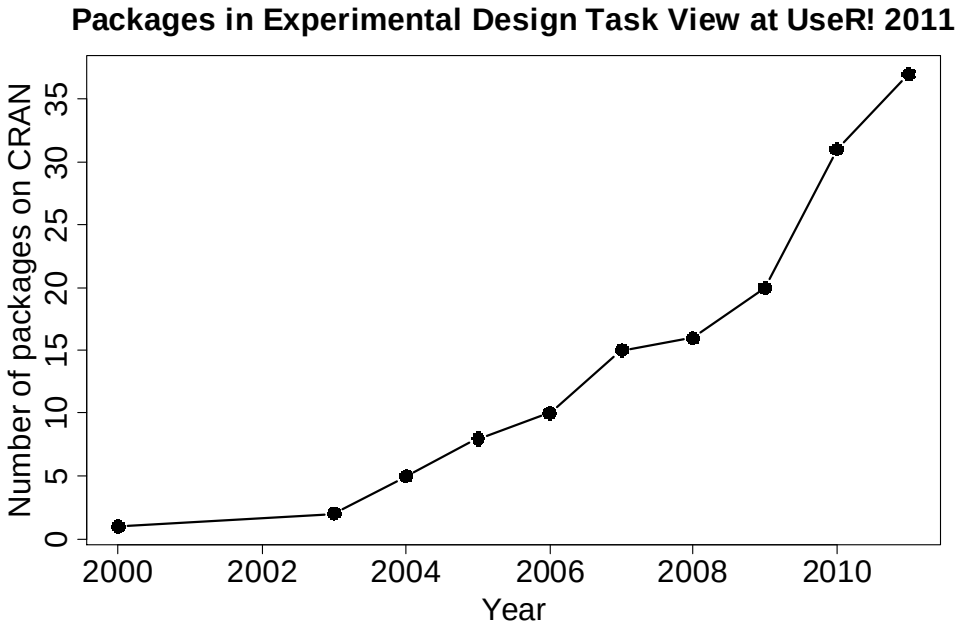

Figure 1: Number of packages already on CRAN vs. calendar year
for the 37 packages in the CRAN Task View at the time of UseR! 2011

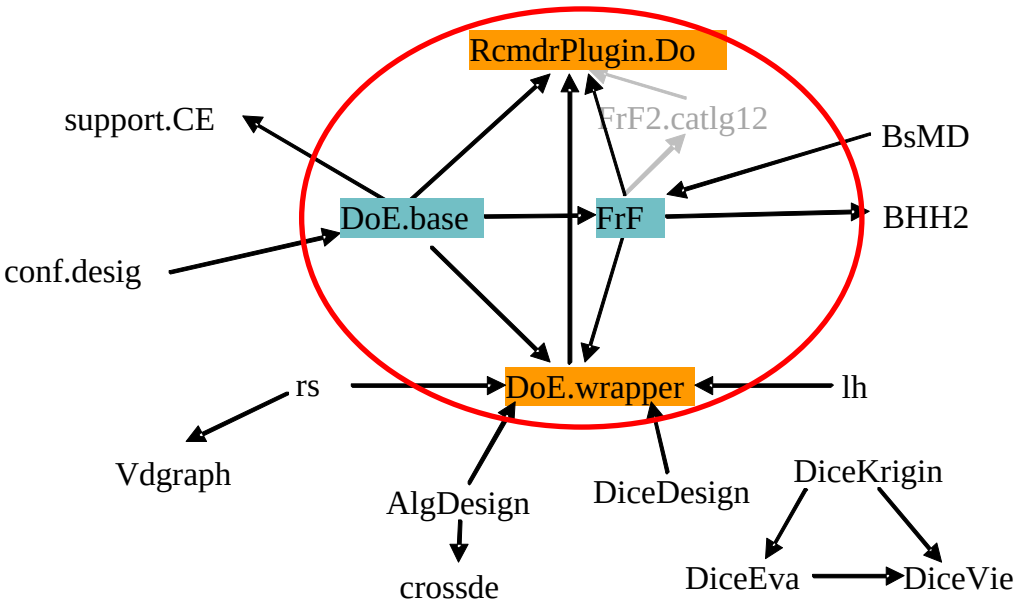

Figure 2: 18 interrelated packages from the CRAN Task View Experimental Design
Arrows indicate that the package pointed to directly depends on or suggests the pointing package, e.g. **crossdes** depends on **AlgDesign**.
The five packages enclosed in the red oval are those from the suite to be discussed below.

Among the 37 packages of the task view, only 18 are somehow related to each other; many are singletons and do not depend on or suggest any other packages from CRAN (or at least not any other DoE packages), nor are they depended on or suggested. The package suite, which will be the focus of attention for the rest of this article, is among the 18 packages that relate to each other. Figure 2 shows the direct relations.

3 *R* packages for industrial DoE

This section gives a broad overview over the suite of packages for industrial DoE. It first points out the main purposes of the four principal packages of the suite. The second sub section starts from the opposite perspective, discussing which task in industrial experimentation can be accomplished with which *R* tool, including also packages from outside the suite by the author. In the third sub section, implementation of some fundamental principles is discussed in more detail. Throughout this chapter, some aspects are illustrated using the following example: an experiment is to be conducted for investigating the dependence of sensor measurements from a system for classifying the occupant of a passenger seat on seat characteristics; the system consists of a mat equipped with sensors and placed in the passenger seat of the vehicle between foam and seat cover, together with some electronic devices and an algorithm. Seat characteristics include foam hardness (**`Foam`**), side bolster stiffness (**`Bolster`**), aged or new condition (**`Aged`**), and three further factors **`D`**, **`E`** and **`F`**, each considered at two levels. The response is a sensor activation measurement, simply denoted as **`y`**. This experiment is modeled on a real experiment conducted by an automotive supplier. Neither details nor data are available, though.

3.1 Overview of the suite of *R* packages for industrial DoE

As was mentioned before, a suite of four *R* packages plus one auxiliary package has been developed. These build on each other hierarchically, cf. Figure 3.

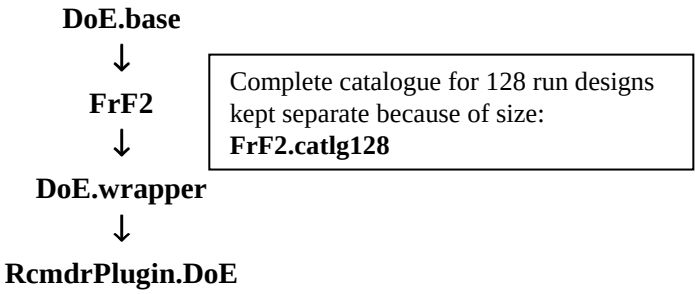

Figure 3: Suite of packages for Design of Experiments
(Grömping, 2007-2011, 2009-2011a,b,c, 2010-2011)

In brief,

- package **DoE.base** provides full factorial designs (**`fac.design`**, optionally with blocking) and general (also mixed-level) orthogonal arrays (**`oa.design`**); it also provides infrastructure like the class **`design`**, functions for printing, summarizing and plotting, for exporting and re-importing designs and for adding a response to an existing design.

Furthermore, it provides a few default analysis functions for linear models for designs with response data.

- Package **FrF2** provides regular (function **FrF2**) and non-regular (function **pb**) 2-level fractional factorial orthogonal arrays. Function **FrF2** allows blocking and split-plotting, function **pb** does not. The package also provides a few functions for effects plots.
- Package **DoE.wrapper** provides an interface for functionality from various other packages, including D-optimal designs from package **AlgDesign** (Wheeler 2004-2010), response surface designs from package **rsm** (Lenth 2009), and space-filling designs for computer experiments from packages **lhs** (Carnell 2006-2009) and **DiceDesign** (Franco, Dupuy and Roustant 2010). This would also be the place for implementing further extensions like mixture designs.
- The final package **RcmdrPlugin.DoE** provides access to a lot of the functionality (but by far not all) through a GUI based on the *R* Commander (Fox 2003-2011, 2005, 2007).

Table 1: The example design from (3) printed in standard order

```
> print(plan, std.order=TRUE)
   run.no.in.std.order run.no Foam Bolster Aged D E F
20                   1     20 soft    soft  new - - -
19                   2     19 hard    soft  new - - +
14                   3     14 soft   stiff  new - - +
25                   4     25 hard   stiff  new - - -
5                    5      5 soft    soft aged - - +
17                   6     17 hard    soft aged - - -
2                    7      2 soft   stiff aged - - -
4                    8      4 hard   stiff aged - - +
22                   9     22 soft    soft  new + - +
7                   10      7 hard    soft  new + - -
16                  11     16 soft   stiff  new + - -
12                  12     12 hard   stiff  new + - +
26                  13     26 soft    soft aged + - -
30                  14     30 hard    soft aged + - +
13                  15     13 soft   stiff aged + - +
1                   16      1 hard   stiff aged + - -
31                  17     31 soft    soft  new - + +
15                  18     15 hard    soft  new - + -
8                   19      8 soft   stiff  new - + -
24                  20     24 hard   stiff  new - + +
27                  21     27 soft    soft aged - + -
32                  22     32 hard    soft aged - + +
21                  23     21 soft   stiff aged - + +
9                   24      9 hard   stiff aged - + -
18                  25     18 soft    soft  new + + -
3                   26      3 hard    soft  new + + +
6                   27      6 soft   stiff  new + + +
10                  28     10 hard   stiff  new + + -
29                  29     29 soft    soft aged + + +
11                  30     11 hard    soft aged + + -
23                  31     23 soft   stiff aged + + -
28                  32     28 hard   stiff aged + + +
NOTE: columns run.no.in.std.order and run.no are annotation, not part of
the data frame
```

Most of the command line programming functions for design creation have at least the parameters

- **`nruns`** for the number of runs,
- **`nfactors`** for the number of factors,
- **`factor.names`** for the factor names and possible also the factor levels,
- **`randomize`** for switching off randomization, if needed
- **`seed`** for the randomization seed
- **`replications`** for the number of replications
- **`repeat.only`** for declaring that the replications are repeated measurements rather than proper replications

As a principle, the packages try to have reasonable defaults so that users can get away with very brief function calls for standard tasks. For example,

```
FrF2(32, 6)
```
(1)

creates a regular fractional factorial 2-level design with 32 runs in 6 factors – in fact the best possible such design. Alternatively, one could also ask for the smallest design with resolution at least V for 6 factors by the command

```
FrF2(nfactors=6, resolution=5)
```
(2)

Table 2: Summary of the design from Table 1

```
Call:
FrF2(32, 6, factor.names = list(Foam = c("soft", "hard"), Bolster = c("soft",
    "stiff"), Aged = c("new", "aged"), D = c("-", "+"), E = c("-",
    "+"), F = c("-", "+")), seed = 27865)

Experimental design of type  FrF2
32  runs

Factor settings (scale ends):
  Foam Bolster Aged D E F
1 soft    soft  new - - -
2 hard   stiff aged + + +

Design generating information:
$legend
[1] A=Foam    B=Bolster C=Aged    D=D       E=E       F=F

$generators
[1] F=ABCDE

Alias structure:
[[1]]
[1] no aliasing among main effects and 2fis
```

Both commands yield a randomized design with the same structure. If this design is to be used for an actual experiment, it is likely that one wants to customize it by giving some detail on the factors and making randomization reproducible by specification of a seed:

```
plan <- FrF2(32, 6, factor.names=list(Foam=c("soft","hard"),
      Bolster=c("soft","stiff"), Aged=c("new","aged"),
   D=c("-","+"), E=c("-","+"), F=c("-","+")), seed=27865)
```
(3)

All design creation packages output objects of class **`design`**, which are data frames with the three attributes **`desnum`** (a numeric matrix), **`run.order`** (a data frame with run order information for switching back and forth between standard order and randomized order) and **`design.info`** (a list with a lot of design type specific information important for post-processing). There are methods for summarizing, printing and plotting such designs. The design created by command (3) is shown in Table 1; in support of easy visibility of the experiment's structure, it has been printed in standard order, using option **`std.order=TRUE`** for the print method of class **`design`**. The summary of the design, created by the command **`summary(plan, brief=TRUE)`**, is shown in Table 2; option **`brief=TRUE`** suppresses the printout of the design itself. For preserving the class structure, it is important to not just add or delete columns but to use specific functions provided for that purpose, whenever this should be necessary, for example for adding response data (function **`add.response`**).

3.2 Tasks in industrial design of experiments

This sub section provides the broad picture of the (currently available) functionality in *R* for creating designs useful in industrial experimentation.

3.2.1 Screening

Industrial design of experiments often starts with a screening task: relatively many experimental factors are simultaneously investigated by designs that are too sparse to deep-dive interactions between factors, quadratic effects or the like. Screening tasks can be accomplished by non-regular 2-level fractional factorial designs (function **`pb`**), by low resolution regular fractional factorial designs (ideally not resolution III, but a high aberration IV may do; function **`FrF2`**), low resolution mixed level orthogonal arrays (function **`oa.design`** from package **DoE.base**, supported by function **`show.oas`** for investigating what is available), or – in case of computer experiments – by space-filling designs (packages **lhs** or **DiceDesign**, or function **`lhs.design`** from package **DoE.wrapper**). In extreme situations, even a supersaturated design may be useful for screening; packages **mkssd** or **mxkssd** (Mandal 2010-2011 and 2011) can create *k*-circulant supersaturated designs.

3.2.2 Subsequent analysis of relevant factors

In an ideal world, screening will point to a subset of important factors, and these are then explored in more depth, using a higher resolution regular fractional factorial design (**`FrF2`**), a higher resolution mixed level orthogonal array (**`oa.design`**) or a full factorial design (function **`fac.design`** of package **DoE.base**), a second order response surface design (package **rsm** or e.g. function **`ccd.design`** from package **DoE.wrapper**) or a larger space-filling design for a computer experiment. Occasionally, for example with run restrictions that prevent the running of a complete orthogonal array, one may also want to use a D-optimal design from function **`optFederov`** from package **AlgDesign** or function **`Dopt.design`** of package **DoE.wrapper**.

3.2.3 Combined arrays and augmentation

The package suite also supports creation of crossed arrays for Taguchi parameter designs and other purposes (functions **`cross.design`** and **`param.design`** in package **DoE.base**), as well as augmentation of existing designs with additional observations for sequential experimentation: Function **`fold.design`** from package **FrF2** applies fold-over to an existing fractional factorial 2-

level design created with functions **FrF2** or **pb**. Several functions from package **DoE.wrapper** allow to augment designs: **ccd.augment** augments a regular fractional factorial 2-level design (which ideally but not necessarily already has center points) by a star portion for a central composite design, functions **lhs.augment** and **Dopt.augment** add further observations to space-filling or D-optimal designs, respectively. (Functionality for combined experiments may have more bugs than other parts of the package suite, in particular the respective methods from package **DoE.base**).

3.3 Implementation of fundamental principles

This section describes how the *R* package suite implements the fundamental principles of experimental design, randomization, replication and repeated measurements, blocking and split-plotting.

3.3.1 Randomization

As randomization is very important and often neglected by practitioners, all designs are per default randomized. There have been legit user complaints about this, because users often like to get a visual impression of the structure of a design, which is of course easier from standard order designs. Therefore, the **print** method for class **design** has the option **std.order=TRUE** (default FALSE) for displaying the design in standard order, even though it is randomized (cf. also Table 1).

3.3.2 Repeated measurements and replications

If measurement accuracy is believed to be insufficient, repeated measurements can help. Note that repeated measurements and proper replications are very different concepts. Repeated measurements repeat the measurement process only, but not the complete setup of the experimental run. If there are *n* runs with *r* measurements per run, it is not permitted to simply use all *nr* measurements in an analysis of variance with just one source of error, because measurements of the same run only differ in measurement error, while measurements of different runs additionally differ in run setup variability. For the occupant classification example, a design with repeated measurements can be constructed using the options **replications** and **repeat.only** that are available with most design generating functions:

```
FrF2(32, 6, factor.names=list(Foam=c("soft","hard"),
  Bolster=c("soft","stiff"), Aged=c("new","aged"),
     D=c("-","+"), E=c("-","+"), F=c("-","+")),
   seed=27865, replications=3, repeat.only=TRUE)
```
(4)

As **repeat.only** is TRUE (default: FALSE), repeated measurement are placed directly next to each other in the design, which corresponds to the execution of an experiment with repeated measurements. The resulting design can either be analyzed with a random effect for each seat build, or, if the analysis is to be kept simple (i.e. without random effects), by analyzing the means from the repeated measurement as responses in an unreplicated design. This is supported by the software through function **aggregate.design**, which can aggregate repeated measurements after reshaping the design to wide format with function **reptowide**.

Sometimes, an unreplicated design is too small for yielding enough power. For example, observations within the experiment on seats might be expected to be so variable that 128 runs are necessary for the required estimation precision. If that were the case, it would be the best route to first

switch to a full factorial in the six factors (i.e., 64 distinct runs) and to replicate this design twice. The following command creates such a design.

```
FrF2(64, 6, factor.names=list(Foam=c("soft","hard"),
  Bolster=c("soft","stiff"), Aged=c("new","aged"),
     D=c("-","+"), E=c("-","+"), F=c("-","+")),
           seed=27865, replications=2)
```
(5)

Without specifying option **`repeat.only`** (which implies the default FALSE), these two replications are randomized in separate blocks. There may be controversy regarding the need to account for this blocking in the analysis – taking the principle "analysis follows design" literally, this would of course be necessary. My personal take on this: this is an additional chance, in case calendar time is suspected to have an influence; however, it is no more necessary to do a blocked analysis than if all 128 runs had been randomized in one go.

Note that the distinction between repeated measurements and replications is NOT an academic point only! For the real-life version of the occupant classification example, repeated measurements were conducted, placing a defined dummy on the seat and measuring, repeating that process (placing and measuring) three times for each seat build. Initially, these measurements were believed to be replications and were analyzed as such. This led to all 31 effects of the 32 run experiment being highly significant, which of course made me very suspicious and eventually led to the understanding that the seat building process used in experimentation was extremely variable (quite different from the seat building process used in production, which was believed to be stable enough to justify neglecting its variability). Re-analyzing the data as an unreplicated design based on the averages from the three repeated measurements per run removed all significances.

3.3.3 Randomization restrictions and sources of variation: blocks and split-plots

Blocking is a way to safeguard against bias in estimated effects from suspected known influences; these could be the day of experimentation or the experimentation team, a batch of material, etc. Whenever these cannot be kept constant (are not large enough for the complete experiment), one should account for their presence by including a factor for them. For the occupant classification example, blocks for two days of experimentation could be implemented as follows:

```
FrF2(32,6, factor.names=list(Foam=c("soft","hard"),
  Bolster=c("soft","stiff"), Aged=c("new","aged"),
      D=c("-","+"),E=c("-","+"),F=c("-","+")),
      seed=27865, blocks=2, block.name="Day" )
```
(6)

The package suite currently implements blocked designs for regular (fractional) factorial 2-level designs, full factorial designs and D-optimal designs. For other factorial designs, blocking can be implemented by including a block factor as one of the experimental factors. Alternatively, any design in *n* runs can be blocked into *b* blocks by crossing by conducting the following steps:

- Cross the design with a block factor at *b* levels (e.g. using function **`cross.design`** from package **DoE.base)**; this leads to a crossed design in *nb* runs.
- Use the crossed design from the previous step as the candidate design for D-optimization, requesting a design in *n* runs with estimability of the block factor main effect and all experimental effects of interest (function **`optFederov`** from package **AlgDesign** or function

Dopt.design from package **DoE.wrapper**). For achieving perfect orthogonality of blocks to experimental factors, it may be necessary to fiddle with optimization parameters.

Analysis of a blocked design can simply include the block factor as a factor with fixed effects. In case of many blocks, it may be more appropriate to treat the block factor as a factor with random effects.

Split-plotting is more complex than blocking – here, there are also two levels of units, whole plots (corresponding to blocks) and sub plots (corresponding to units within blocks). The difference to blocking is that there are some factors which change only at the whole plot level. These are called whole plot factors, while factors randomized within sub plots are called split plot factors. For all whole plot effects and all those split plot effects confounded with whole plot effects, there is less information in the experiment than for the other effects. The reason for this is analogous to the difference between replications and repeated measurements (cf. previous sub section): effects that only change between whole plots share the random setup error associated with setting up whole plot factors, while this error cancels out for split-plot effects. Within the package suite presented here, split-plotting is directly implemented for regular fractional factorial designs only (cf. example below). Indirectly, function **param.design** for Taguchi-style robustness experiments also produces a design that is usually conducted as a split-plot experiment: often all runs of the outer array are conducted together for the same run of the inner array, which is also implied by the randomization process; if this is not intended, one should use function **cross.design** for creating a fully randomized crossed design.

For a split-plot creation example, imagine (completely fictitious and probably unrealistic) that the change of factor levels for **Foam**, **Bolster** and **Aged** in the occupant classification example involves full rebuilds, while level changes are easier for the other factors. Further assume that the experiment is considered infeasible if the full rebuild has to be conducted too often. In that case, it would be appropriate to conduct the experiment as a split-plot design. If we decide on eight whole plots, the whole plot portion of the experiment can be a full factorial. The experiment can then be constructed by the command

```
FrF2(32,6, factor.names=list(Foam=c("soft","hard"),
  Bolster=c("soft","stiff"), Aged=c("new","aged"),
      D=c("-","+"),E=c("-","+"),F=c("-","+")),
           seed=27865, WPs=8, nfac.WP=3)
```
(7)

A proper analysis of split-plot designs requires a random effect for the whole plots. Effects plots like half normal plots have to treat whole plot and split-plot effects differently. The current default Daniel plot for split-plot designs at least shows whole-plot and split-plot effects in different symbols and displays an explanatory message; it also provides an output file that allows subsequent separate plotting, if this appears necessary. Likewise, the default method of function **lm** for class **design** carries out a conventional linear model analysis for split-plot designs, but indicates, which effects are whole plot effects and warns against possibly misleading p-values for these. If the setup of whole plot factors does not involve relevant variability in comparison to measurement error variability, a standard analysis of variance without an extra random effect for whole plots will work reasonably well, from a practical point of view. However, if there is substantial build variability between whole plots

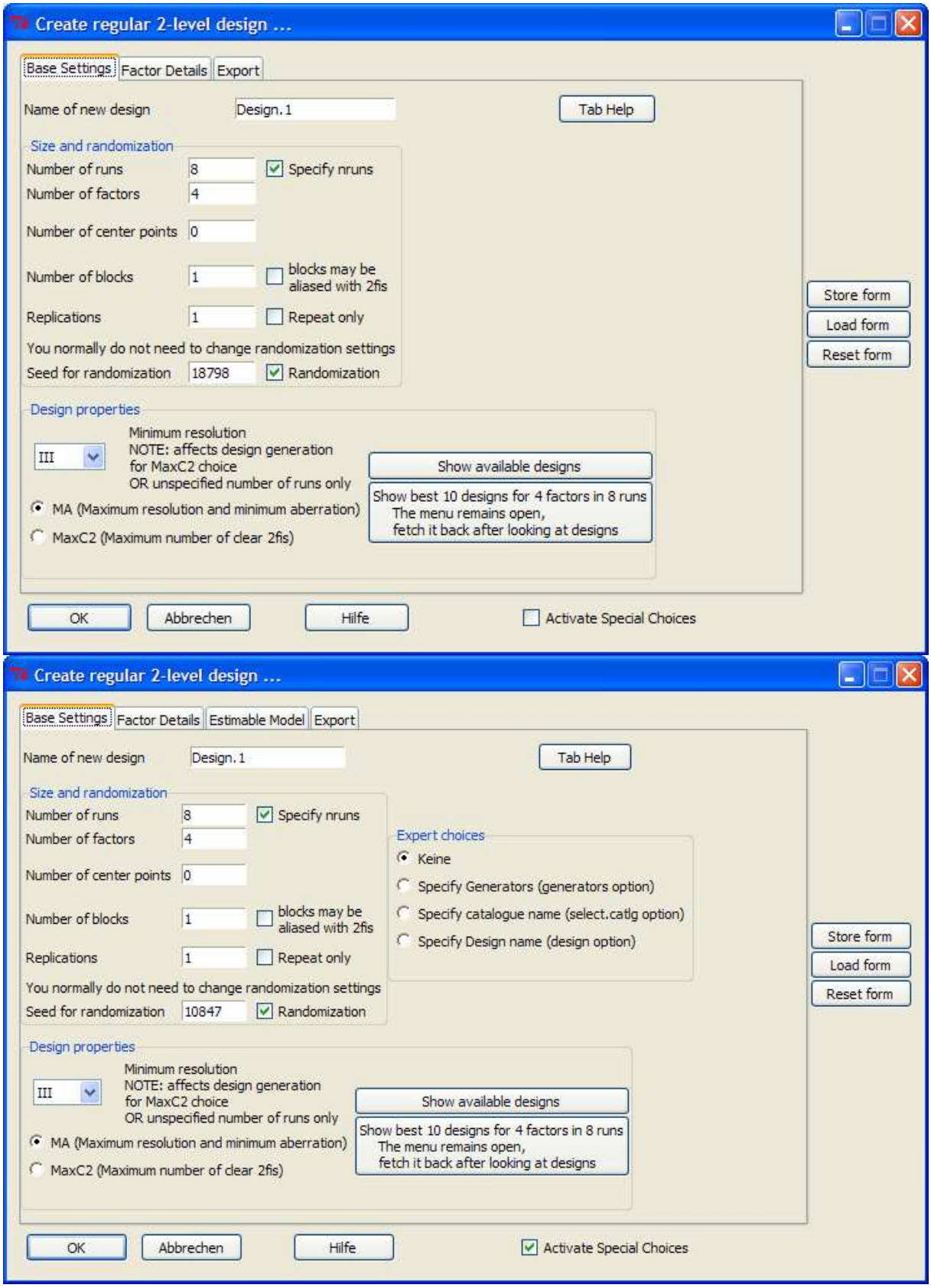

Figure 4: Dialogue for function **FrF2**, simple (top) and expert (bottom) version

(as reported for the example experiment in Section 3.3.2), standard analyses from split-plot designs can be quite misleading.

3.3.4 GUI for inexperienced users and experts

The graphical user interface is supposed to serve users who prefer to avoid command line programming. Such users can be experts or novices in Design of Experiments, and both groups should be served by the GUI. DoE novices should not be confronted with too much information at a time. Therefore, dialogs should not be too crowded. DoE experts, on the other hand, are frustrated, if they cannot access advanced functionality. The GUI therefore works with a tick box choice between simple (default) and expert version (cf. Figure 4). Furthermore, as it can take quite some time to fill in all factor details for a well-annotated version of an experiment, there are also possibilities for storing inputs for later use (note that a feature like this has been included into version 1.7-0 of the *R* Commander).

The GUI offers limited guidance not only on usage but also on statistical content. Figure 5 shows the top level menu provided by package **RcmdrPlugin.DoE**, as well as the "Create design" menu. On the top level menu, there is the content help item "Help on Experimental Design …" as well as the technical help item "Help on Using the Design Menu …". Likewise, there are four content help items on the "Create design" menu; the corresponding technical help items can be accessed from within the various design creation dialogs.

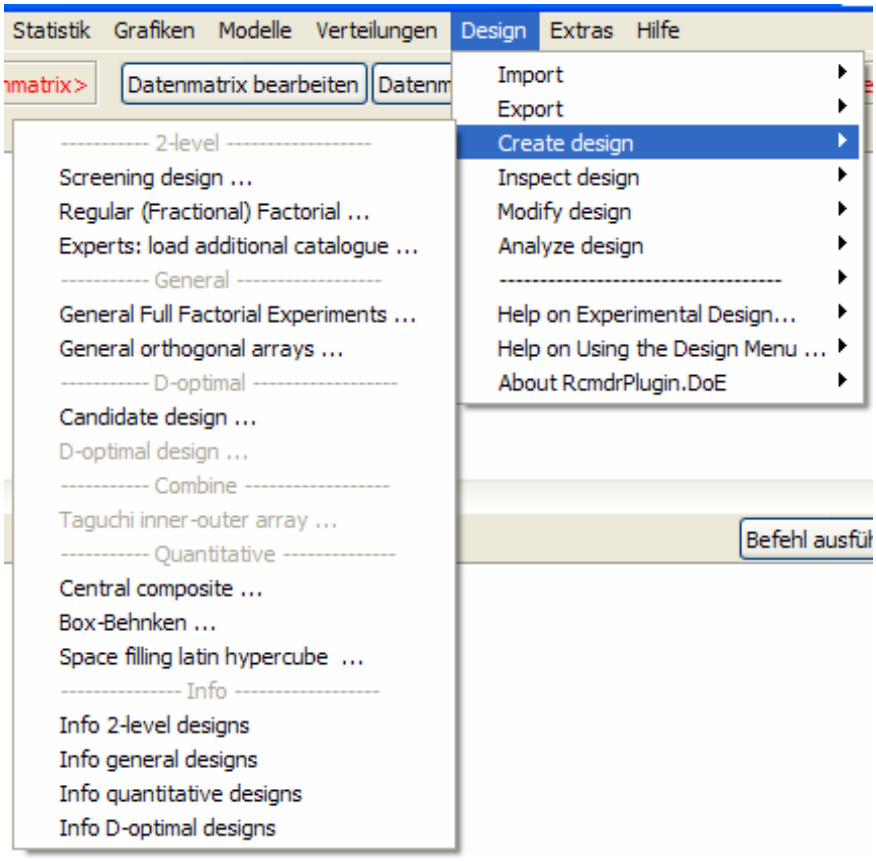

Figure 5: Menus from **RcmdrPlugin.DoE**

4 Selected mathematical aspects

4.1 Usage of design catalogues

A software of experimental designs can either construct the designs algorithmically from user inputs (like, e.g., *R* packages **AlgDesign**, Wheeler 2004-2010, or **conf.design**, Venables 2000-2010) or rely on implemented catalogues of designs, or do a combination of both. *R* packages **DoE.base** and **FrF2** use catalogues for many cases, also involving algorithmic approaches where appropriate. They thus make use of the extensive work that has been invested for many years on creation of catalogues of non-isomorphic experimental designs.

For regular fractional factorial 2-level designs, package **FrF2** uses complete catalogues of non-isomorphic designs by Chen, Sun and Wu (1993) and Xu (2009) as well as further catalogues of large designs by Block and Mee (2005) and Sanchez and Sanchez (2005). For nonregular fractional factorial 2-level designs (function **`pb`**), the package uses published individual designs (Plackett and Burman 1946; Hedayat, Sloane and Stufken 1999, Box and Tyssedal 2001). In the large catalogue of regular fractional factorial designs in package **FrF2**, the non-isomorphic designs of the same number of runs and factors are ordered from best to worst in terms of minimum aberration – thus, a search from beginning to end that takes the first hit always finds the best possible design. Usage of the catalogued design by an algorithm to find the best design for particular estimability requirements is discussed in the next sub section. Function **`FrF2`** uses algorithms to obtain block and split-plot designs with required properties from the catalogued designs.

Package **DoE.base** implements some well-known Taguchi mixed level orthogonal arrays and some large non-regular fractional factorial 2-level designs of resolution V found e.g. in Mee (2009). Furthermore, it provides the parent and child designs of the orthogonal array collection by Kuhfeld (2010, based on contributions by many others), for more general mixed level orthogonal arrays. Usage of catalogued designs in package **DoE.base** (function **`oa.design`**) is far less advanced than that of function **`FrF2`**. The available catalogue is by no means complete, and complete catalogues are very large and thus intractable under normal usage conditions. Even a search within the available smaller incomplete catalogue is non-trivial. Grömping (2011) discusses an approach at coming to grips with ranking mixed level arrays in terms of their usefulness for screening experiments. The approach is based on the seminal work on generalized minimum aberration by Xu and Wu (2001) and derivations thereof. Part of this experimental work is implemented in the package, but currently only works for moderately sized designs.

4.2 Estimable two-factor interactions

In many applications of regular fractional factorial 2-level designs, researchers have an idea about which 2-factor interactions they are interested in. Sometimes, they are also confident that these are the only active 2-factor interactions. This situation is catered for by many software products, usually by creating a D-optimal design for the requested model in terms of main effects and 2-factor interactions. The result will be a regular fractional factorial design for which all effects of interest are on distinct columns of the model matrix (therefore, called a distinct design in Grömping 2010a). Often, however, an interest in some particular interactions does not imply a conviction that other 2-factor interactions are absent. Assuming negligibility of interactions of order higher than 2, this leads to the request of a

clear design, i.e. a design for which the main effects and the 2-factor interactions of interest are clear of aliasing with each other and also with any other 2-factor interaction. There are a few software products that cater for this need, the author is aware of SAS/QC® (SAS® Institute Inc 2009) and Statistica™ (Statsoft Inc 2009) software, apart from *R* package **FrF2**. In **FrF2**, this task is addressed by a graph-based algorithm which is detailed in Grömping (2010b); package **igraph** (Csardi and Nepusz 2006) has been instrumental for the implementation. For up to 64 runs, function **`FrF2`** is guaranteed to find the best possible clear design and has been found to sometimes outperform the competition (cf. Grömping 2010a): for example, the smallest design for 10 factors requesting all interactions among the first five factors to be clear has neither been found by PROC FACTEX (SAS/QC®) nor by Statistica™. This design is a 64 run design based on the catalogued design with the ID number 10-4.3 and can be obtained from function **`FrF2`** by the command

```
FrF2(nruns=64, nfactors=10, estimable=c("AB", "AC", "AD",
       "AE", "BC", "BD", "BE", "CD", "CE", "DE"))
```
(8)

Trying the command with **`nruns=32`** will prove that 32 runs won't be sufficient.

4.3 Hard to change factors

Section 3.3.3 discussed split-plot designs, assuming for the occupant classification example that the first three factors of the experiment should not change too often. If the desire to keep changes low is even stronger than that, and hierarchically so that the first factor is the most difficult to change, the second the second most difficult and the third the third most difficult, with strong economic pressure to keep changes to a minimum, even a design with eight whole plots created by the code (7) (with three, four and five changes for first, second and third factor) may be too demanding. For such cases, it may be useful to force even fewer changes. This is possible using option **`hard`**, which gives the number of factors hard to change (the first **`hard`** factors):

```
FrF2(32,6, factor.names=list(Foam=c("soft","hard"),
  Bolster=c("soft","stiff"), Aged=c("new","aged"),
     D=c("-","+"),E=c("-","+"),F=c("-","+")),
         seed=27865, hard=3, check.hard=1)
```
(9)

Option **`check.hard`** gives the number of structurally different designs to be tried for getting better in terms of reduction of level changes. Setting this to "1" makes sure that no deterioration of resolution or aberration is accepted. Option **`hard`** causes the design to become a split-plot design, but without randomization of the whole plot factors; furthermore, the design is based on the slow-changing matrix according to Cheng, Martin and Tang (1998). For the example, factor **`Foam`** changes once, factor **`Bolster`** twice, and factor **`Aged`** four times. Of course, conducting the design with these few changes bears substantial risk: if there is relevant variation involved in these changes, the factors with fewer changes are substantially more variable than the other factors; furthermore, protection against unknown influences related to run order is insufficient. The package documentation warns the user; nevertheless, I have decided to offer this featured, because I consider it preferable that this facility is deliberately used and documented rather than run order fiddled with by users in case of urgent economic pressure to save experimental effort.

5 Final remarks

A lot of further research and development on the package suite would be of interest:

- quality of block and split-plot designs generated by the algorithm could be systematically researched vs. quality of analogous designs created by other software or catalogued designs
- mixture designs could be implemented, e.g. by incorporating function **`gen.mixture`** from package **AlgDesign** (Wheeler 2004-2010) or **`mixDesign`** from package **qualityTools** (Roth 2010-2011)
- a facility like the SAS® macros for market research by Kuhfeld (2010), which generates all kinds of intricate designs from orthogonal arrays available in package **DoE.base** could be attempted (very much effort)
- default analysis facilities could become more intricate, e.g. for split-plot designs
- the GUI package could cover more features, e.g. split-plot designs
- testing for the GUI package could be progressed more aggressively
- internationalization of the package suite is desired (but must not start too early in order to avoid double work)
- user guidance for when to use which method could be systematically provided, in terms of a simple expert system – probably very demanding
- …

Everybody can contribute by reporting bugs and wishes. Any volunteer who wants to take on a larger task than that is more than welcome.

The packages exist in an *R* environment that continues to grow and change. Many changes are positive, some are threatening. As an example for the latter, take Bob Wheeler's package **AlgDesign**: Bob is now almost 80 years old and would not mind to see this package (like probably some of his other packages) transfer into other capable hands. It is perhaps not a very rewarding task to take over maintenance of a package that someone else has programmed; it would, however, be very useful. The *R* community will have to find ways to guarantee continuity of important packages, because otherwise, the work of many people will be affected. For DoE, **AlgDesign** is such an important package. Therefore, a volunteer for taking over from Bob would be very welcome.

6 References

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Estimation of the optimal design of a nonlinear parametric regression problem via Monte Carlo experiments

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Abstract: A Monte Carlo method for estimation of the optimal design of a nonlinear parametric regression problem is presented. The basic idea is to produce via Monte Carlo values of the error of a parametric regression estimate for randomly chosen designs and randomly chosen parameters and to use nonparametric regression to estimate from this data the design for which the maximal error with respect to all possible parameter values is minimal. A theoretical result concerning consistency of this estimate of the optimal design is presented.

Keywords: Optimal design, nonparametric regression, consistency.

1 Introduction

Fatigue behaviour of materials can be described, e.g., by curves relating strain amplitudes and number of cycles till failure to each other. In corresponding experiments, for a given strain amplitude the number of cycles till failure is observed which is rather time consuming since usually strain amplitudes are used in such a region that the corresponding number of cycles achieves values up to 10^6. For an efficient estimation of such curves it is necessary to choose the used strain amplitudes (usually between 10 and 15 for one material) carefully.

Mathematically, this can be considered as a problem of determing the optimal design of a fixed design regression problem. A parametric model in this context is given by the Manson-Coffin-Basquin relation (cf., e.g., Basquin (1910), Coffin (1954), Manson (1965) and Mitchell (1996))

$$\epsilon = \frac{\sigma_f}{E} \cdot (2N)^b + \epsilon_f' \cdot (2N)^c, \tag{1}$$

which describes the dependency of the strain amplitude ϵ on the number N of cycles till failure. Here σ_f, b, ϵ_f' and c are cyclic material properties which characterize the fatigue behaviour of the material and E is a usually known parameter of the material. Since b and c are less than zero, the monotone function (**??**) has a well-defined inverse function, and it is this nonlinear model for the inverse function which describes the experiment where N is observed for given ϵ.

In el Dsoki et al. (2011) methods, which allow an estimation of these cyclic material properties given by (**??**) via artificial neural networks are presented, where the training data consist of static parameters deducted through tensile tests and corresponding cyclic parameters.

The purpose of this article is to develop a methodology which can determine values to be used in a sequence of experiments for the strain amplitudes such that by using the observed numbers till failure the above model can be estimated efficiently.

We assume that we are interested in estimation of a function r_p, where $p \in \mathcal{P}$ is some unknown parameter from a given set of parameters $\mathcal{P}$. To do this, we have to choose for fixed $N \in \mathbb{N}$ a design

$$z = (z^{(1)}, \ldots, z^{(N)}) \in D^N$$

consisting of points $z^{(i)}$ from some given set D of possible design points. For this design we generate a data set

$$\mathcal{D}_N\left(z; p\right),$$

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which we use to calculate an estimate

$$\hat{r}_N\left(\cdot, \mathcal{D}_N\left(z;p\right)\right)$$

of r_p. Its error is denoted by

$$Err\left(\hat{r}_N\left(\cdot, \mathcal{D}_N\left(z;p\right)\right), r_p\right)$$

with expected value

$$\mathbf{E}\left\{Err\left(\hat{r}_N\left(\cdot, \mathcal{D}_N\left(z;p\right)\right), r_p\right)\right\}, \tag{2}$$

where the expectation is computed with respect to the data set $\mathcal{D}_N\left(z;p\right)$.

Our aim is to choose the design $z = (z^{(1)}, \ldots, z^{(N)}) \in D^N$ such that the maximal expected error

$$\max_{p\in\mathcal{P}} \mathbf{E}\left\{Err\left(\hat{r}_N\left(\cdot, \mathcal{D}_N\left(z;p\right)\right), r_p\right)\right\}$$

is as small as possible, i.e., we want to find a design $z = (z^{(1)}, \ldots, z^{(N)}) \in D^N$ such that

$$\max_{p\in\mathcal{P}} \mathbf{E}\left\{Err\left(\hat{r}_N\left(\cdot, \mathcal{D}_N\left(z;p\right)\right), r_p\right)\right\} \approx \inf_{u\in D^N} \max_{p\in\mathcal{P}} \mathbf{E}\left\{Err\left(\hat{r}_N\left(\cdot, \mathcal{D}_N\left(u;p\right)\right), r_p\right)\right\}.$$

Our main result is that under some regularity conditions our estimated design is consistent in the sense that for this design the expected error indeed converges to the minimal possible value provided the sample size of the data used in estimation of this design converges to infinity.

1.1 Outline

The precise definition of the estimate is given in Section 2 and the main result is formulated in Section 3.

2 Definition of the estimate of the optimal design

In the sequel we assume that we have given the number $N \in \mathbb{N}$ of design points, a compact set $D \subseteq \mathbb{R}^{d_z}$ from which we have to choose the design points, and a compact set $\mathcal{P} \subseteq \mathbb{R}^{d_p}$ of possible parameters, where for each $p \in \mathcal{P}$ a function r_p is given, which has to be estimated. For a given design $z \in D^N$ and a given parameter $p \in \mathcal{P}$ we can compute a data set $\mathcal{D}_N(z;p)$, an estimate

$$\hat{r}_N(\cdot, \mathcal{D}_N(z;p))$$

of r_p and its error

$$Err\left(\hat{r}_N(\cdot, \mathcal{D}_N(z;p)), r_p\right) \geq 0.$$

Throughout this we make the following assumption:

(A1) The nonnegative function

$$(z,p) \mapsto Err\left(\hat{r}_N(\cdot, \mathcal{D}_N(z;p)), r_p\right)$$

defined on $D^N \times \mathcal{P} \subseteq \mathbb{R}^{d_z \cdot N} \times \mathbb{R}^{d_p}$ is measurable with respect to the Borel sigma-algebra.

In order to find the optimal design, for which the maximal (in view of the parameter) expected error is minimal, we choose in a first step $n \in \mathbb{N}$ and random design points $Z_1, \ldots, Z_n \in D^N$ and random parameters $P_1, \ldots, P_n \in \mathcal{P}$. Here we assume that

(A2) $Z_1, \ldots, Z_n$ are uniformly distributed on $\mathcal{D}^N$,

(A3) $P_1, \ldots, P_n$ are uniformly distributed on $\mathcal{P}$,

(A4) $Z_1, P_1, \ldots, Z_n, P_n$ are independent,

(A5) $Z_1, P_1, \ldots, Z_n, P_n$ are independent from the data $\mathcal{D}_N(z;p)$ for all $z \in \mathcal{D}^N$ and $p \in \mathcal{P}$.

In a second step we construct for each $X_i = (Z_i, P_i)$ data sets

$$\mathcal{D}_N(X_i) = \mathcal{D}_N(Z_i; P_i)$$

where for values $z_i = Z_i(\omega)$ and $p_i = P_i(\omega)$ of Z_i and P_i the data set $\mathcal{D}_N(Z_i; P_i)$ is given by $\mathcal{D}_N(z;p)$. Then we use this data set to compute $\hat{r}_N(\cdot, \mathcal{D}_N(X_i))$ and denote its error by

$$Y_i = Err\left(\hat{r}_N(\cdot, \mathcal{D}_N(X_i)), r_{P_i}\right) = Err\left(\hat{r}_N(\cdot, \mathcal{D}_N((Z_i; P_i))), r_{P_i}\right).$$

In a third step we use nonparametric regression to estimate for $x = (z,p) \in \mathcal{D}^N \times \mathcal{P}$

$$m(x) := m(z,p) := \mathbf{E}\left\{Err\left(\hat{r}_N(\cdot, \mathcal{D}_N((z;p))), r_p\right)\right\}. \tag{3}$$

Because of $(A1)$ and $(A5)$ the above term can be written as conditional expectation via

$$m(x) = m(z,p) = \mathbf{E}\left\{Y_1 | (Z_1, P_1) = (z,p)\right\} = \mathbf{E}\left\{Y_1 | X_1 = x\right\}.$$

To estimate m, we apply methods from nonparametric regression (cf., e.g., Györfi et al. (2002)). We use the data

$$(X_1, Y_1), \ldots, (X_n, Y_n)$$

to compute the so-called Nadaraya-Watson kernel regression estimate (cf., Nadaraya (1964) and Watson (1964)).

$$m_n(x) = \frac{\sum_{i=1}^n Y_i \cdot K\left(\frac{x - X_i}{\hat{h}_x}\right)}{\sum_{j=1}^n K\left(\frac{x - X_j}{\hat{h}_x}\right)}.$$

Here $K : \mathbb{R}^{N \cdot d_z + d_p} \to \mathbb{R}$ is a so-called kernel function (e.g., $K(u) = 1_{S_1(0)}$, where $S_r(z)$ denotes the (closed) ball of radius r around z in a Euclidean space) and $\hat{h}_x$ is the bandwidth of the kernel. We define the latter one depending on x and the data in such a way that the ball around x with the radius given as the bandwidth contains at least a special number of data points. More precisely, we choose $r, h_n > 0$ and set

$$\hat{h}_x = \min\left\{h \geq h_n \ : \ \mu_n(S_{r \cdot h}) \geq \frac{\log n}{n^{1/4}}\right\},$$

where

$$\mu_n(A) = \frac{1}{n} \sum_{i=1}^n 1_A(X_i)$$

is the empirical measure of $A \subseteq \mathbb{R}^{N \cdot d_z + d_p}$ corresponding to $X_1, \ldots, X_n$.

With the notation introduced above we can reformulate the aim of our procedure in the following way: Our goal is to find a design $(\hat{z}_1, \ldots, \hat{z}_N) \in D^N$ such that

$$\max_{p \in \mathcal{P}} m\left((\hat{z}_1, \ldots, \hat{z}_N), p\right) \approx \inf_{(z_1, \ldots, z_N) \in D^N} \max_{p \in \mathcal{P}} m\left((z_1, \ldots, z_N), p\right).$$

In the fourth and last step we define our estimate of the optimal design by

$$\left(\hat{z}^{(1)}, \ldots, \hat{z}^{(N)}\right) = \arg \min_{\left(\hat{u}^{(1)}, \ldots, \hat{u}^{(N)}\right) \in D^N} \max_{p \in \mathcal{P}} m_n\left(\left(\left(\hat{u}^{(1)}, \ldots, \hat{u}^{(N)}\right), p\right)\right).$$

3 Main result

Our main result is the following theorem.

Theorem 1 *Assume that $D \subseteq \mathbb{R}^{d_z}$ and $\mathcal{P} \subseteq \mathbb{R}^{d_p}$ are compact sets, that the data is generated as in Section 2 and that the estimate is defined as in Section 2. Assume furthermore that (A_1), ..., $(A5)$ hold, that m defined by (**??**) is continuous, and that for some $L > 0$ we have with probability one*

$$0 \leq Err(\hat{r}_N(\cdot, \mathcal{D}_N(z;p)), r_p) \leq L \tag{4}$$

for all $z \in D^N$ and $p \in \mathcal{P}$. Let $\tilde{K} : \mathbb{R}_+ \to \mathbb{R}_+$ be a monotonically decreasing and left continuous function satisfying for some $R > 0$

$$\tilde{K}(+0) > 0 \quad \textit{and} \quad \tilde{K}(t) = 0 \quad \textit{for } t > R,$$

and define the kernel $K : \mathbb{R}^d \to \mathbb{R}_+$ by

$$K(u) = \tilde{K}(\|u\|) \quad (u \in \mathbb{R}^d).$$

Let $r > 0$ be such that $\tilde{K}(r) > 0$ and let the bandwidth $\hat{h}_x$ be defined as in Section 2 for some $h_n > 0$, $n \in \mathbb{N}$ satisfying

$$h_n \to 0 \quad (n \to \infty).$$

Then with probability one

$$\max_{p \in \mathcal{P}} m((\hat{z}_1, \ldots, \hat{z}_N), p) \to \inf_{(z_1,\ldots,z_N) \in D^N} \max_{p \in \mathcal{P}} m((z_1, \ldots, z_N), p)$$

as n tends to infinity.

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A Study on 3-Level Full Factorial Design with 2 Factors

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Abstract: Increasing number of cars and the growth in soil contamination have left scientists to diminish the reasons for that. The Applied Research Centre for Environmental Problems in Eskişehir has focused on soil contamination with two potential reasons (car, tramway) which might be the factors of soil contamination. Regarding to this, evaluation of the significance of a number of parameters and their interactions, as well as an obtained simple relationship which defines the response as a function of the significant factors and interactions are of interest have been taken into consideration. Three heavy metals (Cd, Zn, Pb) were recorded as pollutants and a 3^2 factorial design of experiment is considered to study the important factors, their levels and interactions between factors affecting soil contamination. In our investigation, the number of experiments is 45 with 5 times replications and 9 treatment combinations. The response surface plots of each pollutant and canonical analyses were given and interpreted in details.

Keywords: 3^2 Factorial experiments, Response surface, Heavy metals.

1 Introduction

Response surface methodology (RSM) comprises a group of statistical techniques such as statistical experimental design, regression modeling or optimization methods, for empirical model building and model exploitation (Box and Draper (2007)). It is usually refered to a process of identifying and fitting an appropriate response surface model from experimental data. Hiller and Hunter (1966) used RSM in modeling and optimization. Box and Draper (1986) worked an optimal design criterion and many studies have revealed on optimal designs as given in Khuri and Cornell (1996) and Myers and Montgomery (2002). Govaerts and Noel (2005) discussed the analysis of a designed experiment when the response is a curve, specifically the three different approaches: two-step nonlinear modeling, pointwise functional regression, and smoothed functional regression.
Concepts and techniques of RSM have been extensively used in application of engineering, especially in the chemical and manufactoring areas. The pollution studies are conducted in this field to partially contain pollutants so that higher than ambient levels of the pollutant gases can be maintained. The purpose of this paper is to evaluate the effects of the Cd, Zn and Pb contamination using a 3^2 full factorial design and to locate the stations where high level of tramway and car occur using the information obtained by the response surface models.

2 Material and methods

In this study, over the workspace in Eskişehir urban soils which were collected at some locations where high density of buildings, roads and tramways occur. Sample points within topsoil layers 0-10 cm were located at roads alongside. The coordinates of the sample locations were recorded with a GPS. All soil samples were dried for 3 h at 105^oC (to a constant weight), milled and passed through a nylon sieve ($0.5mm$). 0.5 g samples were weighed and transferred into reaction vessels. The soil contamination data were obtained from the different tramway stations in Eskişehir and

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consist of 45 observations collected from 9 different sample points: Opera, Çarşı, OGÜ, AHS, Atatürk Avenue-Çilek, AlanÖnü, Bağlar, Vişnelik, and Doktorlar. Based on 3^2 full factorial design with 5 replications, a total of 45 tests were carried out. The range of each parameter is set at three different levels, namely low, medium and high. Tramway denotes the factor x_1 and car denotes the factor x_2. Portions of the soil samples which were hold approximately 25gr were grounded in a mechanical agate grinder until fine particles ($< 200\mu m$) were obtained. The number of tramway and car at low, medium and high levels were given in Table 1.

Table 1: Factors, Low, Medium and High Values

x_1	x_2
Tramway	Car
12(-1)	174(-1)
18(0)	852(0)
24(+1)	1530(+1)

The levels of each factor were denoted by (-1), (0), and (+1) due to a computational ease. Each of the three levels of the two factors was run in all combinations for Cd, Zn and Pb.

3 Theory

RSM assumes a few number of factors are related to each other. In this study, it is assumed that some true physical relationships between the expectation of the response y and two factors (ζ_1 and ζ_2) and via physical constants λ exist. Once the important factors are investigated, next is to determine the level of these factors that affect the response in someway. In our study the surface that interested is represented by Eq. (1):

$$E(y) = f(\zeta_1, \zeta_2, \lambda) \tag{1}$$

The nature of this expectation function is unknown so that it is replaced by an approximating function as it is supposed in Eq. (2,3). Here, each X_i is a line coding of a factor ζ_i and X_i' s could be any functions, $X_i = f(\zeta_1, \zeta_2)$, i=1,2,..., of some or all of the factors which are appropriate(Box and Draper (2007)). As the shape of the response surface is unknown, RSM relates to a model which can be a first-order, second-order or higher-order with k input variables and can be formulated, respectively as

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + ... + \beta_k X_k + \epsilon \tag{2}$$

$$Y = \beta_0 + \sum_{i=1}^{k} \beta_i X_i + \sum_{i=1}^{k} \beta_{ii} X_i^2 + \sum_{i<j} \sum_{j=1}^{n} \beta_{ij} X_i X_j + \epsilon \tag{3}$$

Here, Y is the response, $X_1, X_2, ..., X_k$ are the known explanatory variables could be used to express the response, $\beta_0, \beta_1, ..., \beta_k, \beta_{11}, ..., \beta_{kk}$ are unknown parameters and ϵ is a random error. The higher-order model is upgraded by adding higher-order terms into Eq. (2). If the response is modeled by a linear function then Eq. (2) is taken into consideration, otherwise there is a curvature in the system then a polynomial or higher order should be used as given in Eq. (3).

In RSM canonical analysis is performed to determine the location and the nature of the stationary point of the second-order model. Canonical analysis of the second degree response

surface allows the investigation of the underlying nature of the response surface and whether it is a maximum, minimum, saddle, rising ridge, or stationary ridge (Myers and Montgomery (2002)).

4 Results

In this section, our approach is to develop response surfaces to characterize the contamination for Cd, Zn and Pb. The results of the analysis of variance on metal contaminations using 3^2 factorial designs are given in tables for Cd, Zn and Pb, respectively. It is used to examine the variation in heavy metals with respect to the number of tramways and cars. Moreover, *R 2.13.0* Software is used to make a detailed information related to the structure of the variation in main and interaction effect and those are divided into linear and quadratic terms (R Development Core Team (2011)). We demonstrate the 3-D surface plots of the estimated response surfaces for each heavy metal as well.

4.1 The analysis of variance

The significance of independent variables and their interactions are examined by means of the analysis of variance (ANOVA). A p level of 0.05 was used to determine the statistical significance in all analyses. Results are assessed with various descriptive statistics such as p value, F value, degrees of freedom (df), sum of squares (SS), mean sum of squares (MS) in Table 2.

Table 2: Decomposition for Cd contamination

	df	SS	MS	F	Pr(>F)	
x_1	2	0.04773	0.02387	3.8792	0.02981	*
x_1	1	0.03713	0.03713	6.0349	0.01898	*
x_1^2	1	0.0106	0.0106	1.7235	0.19756	
x_2	2	0.48709	0.24355	39.5863	8.11E-10	***
x_2	1	0.48503	0.48503	78.8367	1.34E-10	***
x_2^2	1	0.00207	0.00207	0.3359	0.5658	
x_1x_2	4	1.59105	0.39776	64.6525	6.19E-16	***
$x_1 x_2$	1	0.12002	0.12002	19.5084	8.78E-05	***
$x_1^2 x_2$	1	1.18105	1.18105	191.9681	5.34E-16	***
$x_1 x_2^2$	1	0.0015	0.0015	0.2438	0.62447	
$x_1^2 x_2^2$	1	0.28848	0.28848	46.8898	5.20E-08	***
Residuals	36	0.22148	0.00615			

*,***: significant variables

In Table 2, the main effect x_1 was statistically significant at the 1% level of probability. The individual effects of x_1 can be examined by 2 terms separately. So that, the linear effect of x_1 is significant at the same level of probability but the quadratic effect stands insignificant in contrary. In the same way, the factor x_2 is statistically significant and it is mostly the reason of the linear effect of x_2 is significant since the quadratic effect is insignificant statistically. Those would infer that β_1 and β_2 are nonzero for the corresponding model. In addition to this, the interaction effect x_1x_2 is significant that means β_{12} is in the model. For additional information the linear and quadratic components of the interaction term on the response are also examined. The individual effects of the interaction term can be examined by 4 terms separately. According to the results, the linear effect x_1x_2 is statistically significant as $x_1^2x_2$ and $x_1^2x_2^2$ is. The quadratic effect of x_2 and the linear effect of x_1 , $x_1x_2^2$ is statistically not significant. Since the interaction term

is significant fitting a second order model is considered to approximate the surface curvature's nature.

The second order response surface model (carrying the estimates to three decimals) are given in Eq. (4) and the standard error of the model is calculated as $S = 0.197$.

$$\hat{Y}(x) = 0.887 + 0.018x_1 + 0.008x_2 + 0.06x_1^2 + 0.22x_2^2 + 0.120x_1x_2 \tag{4}$$

The canonical analysis is also used to determine the optimum conditions. Since λ_1 and λ_2 are positive as $(\lambda_1, \lambda_2) = (0.240, 0.041)$ the stationary point is a minimum. The point $\mathbf{x}_0$ is located inside the experimental region since $(\mathbf{x}_0)'(\mathbf{x}_0) = 0.081 \leq 2$. The estimated Cd at $\mathbf{x}_0$ is $\hat{Y}_0 = 0.887 + (\mathbf{x}_0)'\beta/2 = 0.886$. The canonical equation of the Cd surface is given by

$$\hat{Y}_{cd} = 0.886 + 0.240w_1 + 0.041w_2 \tag{5}$$

The magnitutes of λ_i indicate the height of the surface changes faster when moving along the w_1 axis while along the w_2 axis the response increases less rapidly. Eq. (5) reveals that an increase in estimated Cd occurs upon moving away from the stationary point along the w_1 and w_2 axes.

The results of the analysis of variance for Zn contamination using a 3^2 factorial design are given in Table 3. It summarizes the main and interaction effects and gives related statistics.

Table 3: Decomposition for Zn contamination

	df	SS	MS	F	Pr(>F)	
x_1	2	42554	21277	3024.42	2.20E-16	***
x_1	1	33285	33285	4731.31	2.20E-16	***
x_1^2	1	9269	9269	1317.53	2.20E-16	***
x_2	2	18368	9184	1305.43	2.20E-16	***
x_2	1	1879	1879	267.13	2.20E-16	***
x_2^2	1	16488	16488	2343.73	2.20E-16	***
x_1x_2	4	11758	2939	417.82	2.20E-16	***
$x_1 x_2$	1	2926	2926	415.86	2.20E-16	***
$x_1^2 x_2$	1	1635	1635	232.37	2.20E-16	***
$x_1 x_2^2$	1	5965	5965	847.84	2.20E-16	***
$x_1^2 x_2^2$	1	1233	1233	175.23	2.12E-15	***
Residuals	36	253	7			

As seen in Table 3, since all terms are statistically significant and the quadratic model is highly significant.

The second order response surface model is given in Eq. (6) and the standard error of the model is calculated as $S = 33.51$.

$$E_{zn}(y) = 112.69 + 17.58x_1 - 23.44x_2 - 57.69x_1^2 - 13.71x_2^2 + 7.85x_1x_2 \tag{6}$$

According to the canonical analysis results, since λ_1 and λ_2 are positive as $(\lambda_1, \lambda_2) = (-13.361, -58.041)$ the stationary point is a maximum. The predicted value at stationary point is 123.235. The canonical equation of the Zn surface is given by

$$\hat{Y}_{zn} = 123.235 - 13.361w_1 - 58.041w_2 \tag{7}$$

The point $\mathbf{x}_0$ is located inside the experimental region since $(\mathbf{x}_0)'(\mathbf{x}_0) \leq 2$. The estimated Zn at $\mathbf{x}_0$ is $\hat{Y}_0 = 112.69 + (\mathbf{x}_0)'\beta/2 = 123.235$.

For Pb contamination, the analysis of variance results are given in Table 4.

Table 4: Decomposition for Pb contamination

	df	SS	MS	F	Pr(>F)	
x_1	2	9899.3	4949.6	295.727	<2.2e-16	***
x_1	1	681.6	681.6	40.727	2.15E-07	***
x_1^2	1	9217.6	9217.6	550.728	<2.2e-16	***
x_2	2	8880.6	4440.3	265.297	<2.2e-16	***
x_2	1	6841.3	6841.3	408.747	<2.2e-16	***
x_2^2	1	2039.4	2039.4	121.847	4.15E-13	***
x_1x_2	4	5789.1	1447.3	86.471	<2.2e-16	***
x_1x_2	1	477.9	477.9	28.552	5.24E-06	***
$x_1^2x_2$	1	4166.7	4166.7	248.949	<2.2e-16	***
$x_1x_2^2$	1	1144.6	1144.6	68.385	7.66E-10	***
$x_1^2x_2^2$	1	0	0	5.85E-07	0.999	
Residuals	36	602.5	16.7			

According to the results given in Table 4, all terms are statistically significant. The second order response surface model is shown in Eq. (8) with the corresponding standard error $S = 12.80$.

$$E_{pb}(y) = 50.313 + 17.528x_1 - 8.244x_2 - 8.256x_1^2 - 26.155x_2^2 \tag{8}$$

The canonical analysis is also applied to Pd data. Since the eigenvalues are positive as $(\lambda_1, \lambda_2) = (-8.256, -26.156)$ the stationary point is a maximum. The predicted Pb value at stationary point is 60.267.

The canonical equation of the Pb surface is given by

$$\hat{Y}_{pb} = 50.313 - 8.256w_1 - 26.156w_2 \tag{9}$$

The point $\mathbf{x}_0$ is located inside the experimental region since $(\mathbf{x}_0)'(\mathbf{x}_0) \leq 2$. The estimated Pb at $\mathbf{x}_0$ is $\hat{Y}_0 = 50.313 + (\mathbf{x}_0)'\beta/2 = 60.267$.

4.2 3-D plot of response surfaces and contour plots

In this section, all plots are generated using *package(rsm)* (Lenth (2009)). Figure 1a-b indicates a contour and three dimensional surface plot of the response Cd.

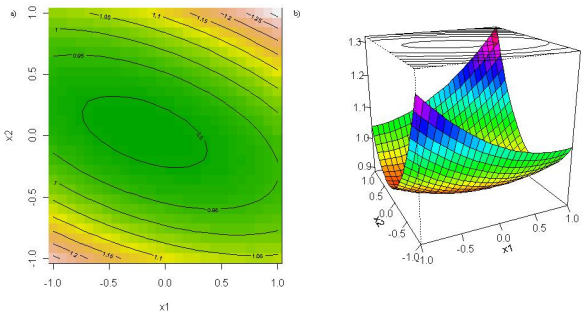

Figure 1: (a) Contour (b) Response surface plot for Cd contamination

In Figure 1-a contours are drawn whose coordinate axes represent the levels of x_1 and x_2 and the stationary point of response surface is located at $(x_1, x_2) = (-0.18, 0.03)$. In Figure 1-b the response surface shows to be a sink shaped.

In Figure 2-a, the contour plot shows to be a mount shaped. The stationary point of response surface is at $(x_1, x_2) = (0.096, -0.827)$.

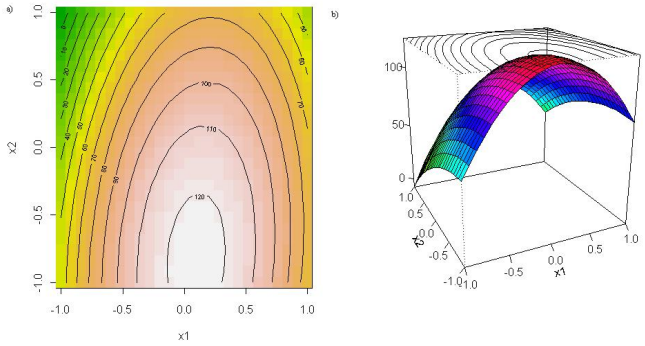

Figure 2: (a) Contour (b) Response surface plot for Zn contamination

In Figure 3-a, the contour plot shows a maximum point in the surface. The stationary point for response surface is located at the point $(x_1, x_2) = (-1.06, -0.15)$.

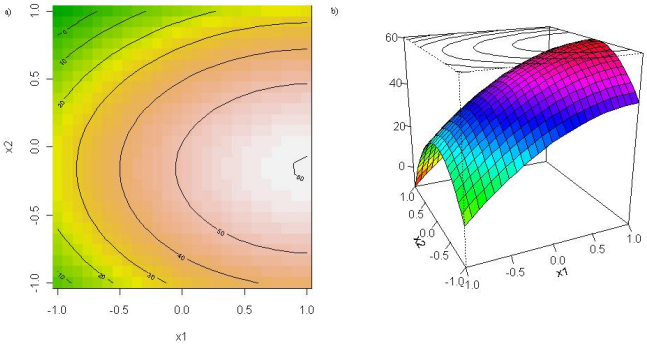

Figure 3: (a) Contour (b) Response surface plot for Pb contamination

Since one of the main interests of this research is to locate of the stations where the most contribution on soil contamination occurs, the figures are also interpreted in this way of matter. Regarding to this, the response surface of Cd contamination shows a minimum point as seen Figure 1a-b. The minimum point is nearly located at Alanönü station. When moving along the axes x_1 and x_2, an increase in response Cd is obtained, especially at Atatürk High School station for high level of tramway and car and Opera station where low level of tramway and car occur.

As seen in Figure 2a-b, the response surface of Zn contamination has a maximum point. The highest contribution on soil contamination is located at medium level of tramway and low level of car where Vişnelik station nearly is. When moving along the axes of x_1 and x_2, a decrease in Zn contamination occurs.

For Pb contamination, the peak of the mount shaped surface as seen in Figure 3a-b is located nearly at Atatürk Avenue-Çilek station where high level of tramway and medium level of car occur.

5 Conclusions

This work has demonstrated the use of a 3^2 full factorial design using the parameters namely, tramvay and car. The response variables Cd, Zn and Pb are studied effectively with a number of experiments. The class of second order response model including terms for interaction and curvature are fitted successfully for each heavy metal contamination. A measure of prediction, the root mean square error was calculated for each model and summarized in Table 5.

Table 5: RMSE for Cd, Zn and Pb model

Cd model	Zn model	Pb model
0.197	12.80	33.51

To characterise the response surface, contour plots and canonical analysis are also applied. Although the pioneering study of co-authors, a nonparametric method so called, multivariate adaptive regression splines (MARS) has been also successfully used and applied to the same datasets, it is not mentioned in the context of this paper. For further details about how to approximate the response surfaces of each heavy metal in a nonparametric way, readers are couraged to have a look at the previous papers of the authors (Kan and Yazici, 2009a,b).

6 Appendix

6.1 Datasets

Cd=(1.195 0.990 1.195 1.395 0.597 0.990 1.399 0.597 1.395 1.199 0.996 0.597 1.195 0.999 0.996 0.598 1.200 0.990 0.996 0.999 1.198 1.199 1.395 1.200 1.200 1.198 1.198 0.990 1.192 1.395 0.988 1.192 1.192 1.199 0.790 0.990 1.198 0.990 0.996 0.992 1.584 0.993 0.992 0.598 0.996)
zn=(38.408 134.402 1.200 45.835 132.920 53.586 130.722 1.200 74.030 62.710 1.200 133.610 1.198 73.436 39.403 53.187 39.801 61.711 133.120 62.310 62.773 132.621 47.828 42.057 74.228 52.789 55.500 1.198 137.278 41.658 46.433 121.230 55.300 42.057 72.910 46.337 49.086 41.284 122.222 47.129 74.096 62.972 40.088 48.490 137.478)
Pb=(1.200 21.150 76.062 10.514 21.949 11.509 21.749 42.326 41.337 41.342 29.658 16.653 9.732 28.669 41.139 76.062 41.142 9.333 8.737 1.200 1.200 40.942 49.977 16.455 9.933 1.198 1.198 10.728 76.660 28.866 10.713 11.534 11.335 12.288 71.384 46.594 97.391 10.102 24.468 10.132 9.076 48.582 6.898 47.586 25.061)

6.2 Program code

```
f.x1=factor(x1)
f.x2=factor(x2)
summary(aov(cd~f.x1+f.x1+f.x1*f.x2),split=list(f.x1=list(L=1,Q=2),f.x2=list(L=1,Q=2)))
library(rsm)
cd.rsm=rsm(cd~SO(x1,x2) )
xs=canonical(cd.rsm)$xs
contour (cd.rsm, ~ x1+x2, image = TRUE,at=xs)
persp(cd.rsm,~x1+x2,at=xs,col=rainbow(50),contours="top")
```

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Unreplicated fractional factorials, analysis with the half-normal plot and randomization of the run order

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Abstract: There is an ongoing discussion whether it is wise to randomize the run order of a factorial experiment if there is concern about a possible time trend in the experiment. It can be argued that a randomized order is not very effective because the trend inflates the error. Some authors even criticize that a randomized order will normally not be orthogonal to trend, they claim that therefore there will be bias under the randomized order. On the other hand, a systematic order will only be useful if the true trend is behaving as is predicted by the model.

The present paper investigates the properties of different run order strategies in a simulation study with unreplicated factorial designs. We check to which extend the presence of a time trend might inflate the probability of false rejection of a true null-hypothesis, and we compare the power of significance tests based on the half-normal plot under the various run order concepts.

Keywords: Half-Normal Plot, Randomization, Unreplicated factorial designs, Time trend.

1 Introduction

In the presence of a time trend, the results of an experiment depend on the sequence in which the runs are being carried out. For example, imagine a situation when there is a monotonous time trend and assume that for one factor with two levels all runs of the low level are executed before the runs with the factor at the high level. Then this factor is liable to be declared to have a significant effect on the response variable, even when in reality the factor is not active. This is due to the fact that the effect estimator in this case is highly correlated with the time trend. To avoid such situations, experimenters may want to use an appropriate run order.

Different strategies exist to deal with a possible time trend. Generally, these can be divided into two basic approaches. Firstly, one might try to avoid a bias due to the time trend, by trying to find a fixed run order which makes the estimators orthogonal or nearly orthogonal to the trend. This approach tries to find an efficient analysis and relies heavily on the appropriateness of some model assumptions. A nice overview of the arguments in favor of a fixed run order is in Mee and Romanova (2010). The second concept randomizes the order in which the runs are performed. This approach tries to derive a valid analysis which depends on model assumptions as little as possible, with the possible disadvantage that the time trend may inflate the variance of the errors. A recent publication supporting this approach for factorial designs is Adekeye and Kunert (2006).

There is an ongoing discussion, which of the two concepts should be applied. The fixed run order is criticized because it might rely too much on model assumptions. If these assumptions should be wrong in a given situation, then the systematic order might lead to strongly biassed results. On the other hand, the randomized run order is criticized because it stresses robustness against model violations too much, at the expense of a possible power loss. Correa *et al.* (2009) even doubt that a randomized run order can achieve unbiassed estimates. They claim that only

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a small fraction of the randomized orders will indeed be orthogonal to a trend. We do not think that this is a valid argument: the correlation with the trend is a random variable under randomization. A random variable can have expectation zero, even if its probability to be zero is negligible. However, as pointed out by Adekeye and Kunert (2006), there is, indeed, no proof that the randomization can validate the assumption that the errors are normally distributed for saturated factorial designs and the analysis with the half-normal plot.

In the present paper, we use a simulation study to compare the performance of a completely randomized run order on the one hand with two systematic run order strategies on the other, one suggested by Cheng and Jacroux (1988) the other by de León Adams *et al.* (2005) and Correa *et al.* (2009). We assume that the experiment is done as a saturated fractional factorial design with no degrees of freedom for the estimation of the variance. In such a case, the analysis is often done with the so-called half-normal plot, introduced by Daniel (1959), or variants thereof. We measure the performance of the run-order strategies by the probability of a false rejection and by the power. The probability of a false rejection is compared with the nominal level of significance. The power is quantified by the probability to identify truly active effects as active effects. We think that any statistical test makes sense only if the probability of a false rejection does not exceed the nominal level - calculating the power of a test which does not keep the nominal level is a fruitless exercise.

In our simulations, we introduce various forms of a time trend to see how the trend influences the performance of the different run-orders. We confine ourselves to analyzing unreplicated (fractional) factorial designs of length $n = 8$, $n = 16$ and $n = 32$ with a saturated model. All factors are at two levels and we assume that all interactions are possibly active. However, we assume that factor sparsity holds, that is, we assume that only a small number of the factors is truly active. Because there are no degrees of freedom for estimation of the variance, the designs are analyzed with the half-normal plot. For all run-orders, we use four different proposals to estimate the error variance and compare these proposals to each other.

The number of runs is denoted by n, the number of contrasts to be estimated in the model by b. We assume that

$$y_i = \mu + \sum_{j=1}^{b} x_{ij}\beta_j + e_i, \quad i \in \{1, 2, \ldots, n\},$$

where y_i is the response at run i, $x_i = [x_{i1}, \ldots, x_{ib}]^T$, with each $x_{ij} \in \{0, 1\}$, is the setting of the design at run i, $\beta = (\mu, \beta_1, \ldots, \beta_b)^T$ is the vector of parameters and e_i the ith error term. It is supposed that the errors are normally distributed with variance τ^2. The mean of the error term, however, is not zero but depends on i, to model a trend.

For the construction of trend resistant designs, it is generally assumed that the trend is linear in i, at times it is assumed to be quadratic. Adekeye and Kunert (2006) presented data from an experiment with a real time trend. This trend was neither linear nor quadratic but followed a less regular pattern. In their paper, Adekeye and Kunert (2006) compared the randomized run order with the trend-free designs constructed by Cheng and Jacroux (1988), assuming a time series model for the trend. The present paper continues this work, using linear and quadratic trends. This might help the reader to quantify how much can be gained by a systematic run order in ideal situations. Additionally, the present paper also looks at nearly trend-free systematic run orders, proposed by de León Adams *et al.* (2005) and Correa *et al.* (2009).

In each of our simulated designs, a random experiment with values $v = 1$ and $v = -1$, each with probability $1/2$, decides on the sign of the trend. We consider linear and quadratic trends. For linear trends, the ith error term follows a normal distribution with mean $v(a \cdot i)$. Here a describes the intensity, so $e_i \sim N(v(a \cdot i), \tau^2)$ with $1 \leq i \leq n$. In the presence of a quadratic trend, the error term follows a normal distribution with mean $v(c(i - \frac{n+1}{2})^2 + a \cdot i)$. Here the

intensity of the quadratic part of the trend is described by c.

The different concepts of run order are presented in Section 2. Section 3 contains a description of how half-normal plots can be applied. Finally, Section 4 presents our simulation study.

2 Concepts of run order

In Section 4 we compare three different concepts of run order. In what follows the different concepts are shortly presented, only for the case that $n = 8$ and that we have four factors, but the explanation can be adapted to the other run lengths or numbers of factors.

The designs for all three concepts are constructed by modifying a full factorial design with the desired number of runs. An example for such a design with 8 runs is given in Table 1. Each factor of the experiment is then placed on one of the columns of the full factorial design. In general, it is possible to have up to $b = n-1$ factors in a fractional factorial design. The columns left over, which are not used for factors, will be used for the estimation of interactions. We do not assume that all interactions are negligible. Hence, there will be no degrees of freedom left for the estimation of the variance.

Table 1: 8-run design with standard run order

Run	A	B	C	AB	AC	BC	ABC
1	+	+	+	+	+	+	+
2	+	+	-	+	-	-	-
3	+	-	+	-	+	-	-
4	+	-	-	-	-	+	+
5	-	+	+	-	-	+	-
6	-	+	-	-	+	-	+
7	-	-	+	+	-	-	+
8	-	-	-	+	+	+	-

Random run order

Any experimental design with standard run order can be used as a basis for a design with a random run order. Each factor is placed on one of the columns. In general, the columns are selected in such a way that we will have a good resolution of the design. For the design in Table 1, it should make sense to place factor 1 on the column A, 2 on the column B and 3 on C, while factor 4 is placed on the column ABC. This gives a resolution IV design, where the interaction (12) is confounded with (34), (13) is confounded with (24) and (23) is confounded with (14). After selecting the columns, the runs of the design are randomized, i.e. they are permuted with permutation Π, where Π is selected strictly at random among all $n!$ possible permutations. The design in Table 2 is derived from Table 1 by one random permutation of the rows.

Systematic run order

Experimental designs in which all columns are orthogonal to a linear time trend are constructed in Cheng and Jacroux (1988). With this approach, only a part of the columns of the design with standard run order can be used. It is not possible to choose a run order where all columns of a complete factorial design are orthogonal to a linear time trend.

An 8-run design with systematic run order is given in Table 3. The columns of the design in Table 3 are orthogonal to a linear time trend. This design has only four columns, so three columns of the design of Table 1 had to be given up. In general with this construction method, a 2^k-design looses k columns. In fact, from the full factorial design in standard run order, the

Table 2: Example for a 8-run design with randomized run order (RO)

Run	1	2	3	(12)	(13)	(23)	4
1	+	+	-	+	-	-	-
2	-	-	+	+	-	-	+
3	-	+	+	-	-	+	-
4	+	+	+	+	+	+	+
5	-	-	-	+	+	+	-
6	-	+	-	-	+	-	+
7	+	-	+	-	+	-	-
8	+	-	-	-	-	+	+

columns allocated with main effects have to be deleted. They are kept free and all effects of interest have to be placed on the remaining columns.

Table 3: 8-run design with systematic run order (SO)

Run	1	2	3	4
1	+	+	+	+
2	+	-	-	-
3	-	+	-	-
4	-	-	+	+
5	-	-	+	-
6	-	+	-	+
7	+	-	-	+
8	+	+	+	-

Run order with minimum bias

We call the third concept "run order with minimum bias". This was introduced by de León Adams *et al.* (2005). As opposed to the systematic run order, this concept avoids deleting columns. The columns are as orthogonal to a linear time trend as possible under the restriction that all columns are used. For several run lengths, de León Adams *et al.* (2005) and Correa *et al.* (2009) have determined sets of designs, where all columns satisfy the same maximum bias. Furthermore the number of level changes in the factors is as small as possible. In both papers, the reduction of the number of level changes is not relevant for the analysis, it is only introduced to make the experiment easier to carry out. An example is given in Table 4.

Table 4: Example for a 8-run design suggested by de León Adams *et al.* (2005) (run order with minimum bias)

Run	1	2	3	12	13	23	4
1	+	+	+	+	+	+	+
2	+	+	-	+	-	-	-
3	-	+	-	-	+	-	+
4	-	-	-	+	+	+	-
5	+	-	-	-	-	+	+
6	+	-	+	-	+	-	-
7	-	-	+	+	-	-	+
8	-	+	+	-	-	+	-

In what follows, the following abbreviations are used: RO for randomized run order, SO for systematic run order and MB for run order with minimum bias.

3 Analysis via half-normal plots

For the decision whether an effect is active, an observed test-statistic has to be compared to a critical value. Since we do not have any degrees of freedom left for the estimation of the variance, it is not possible to use a t-test. The half-normal plot makes use of the assumption that most of the effects in the model are zero. Note that the estimators for the not-active effects have expectation zero and hence their absolute value can be used to estimate the variance. For a fractional factorial design, all estimators $\hat{\beta}_j$ are uncorrelated and have the same variance $\sigma^2 = \tau^2/n$. Therefore, the sorted absolute values of the estimates $\hat{\beta}_j$ are used for an estimate for σ. In our simulations, we consider four different proposals and compare them to each other:

- Proposal 1 (Daniel, 1959):
$$\hat{\sigma}_Q = \mid \hat{\beta} \mid_{([0.683b+1])},$$
- Proposal 2 (Lenth, 1989):
$$\hat{\sigma}_M = \frac{3}{2}(\text{median} \mid \hat{\beta}_j \mid),$$
- Proposal 3 (Lenth, 1989):
$$\hat{\sigma}_{PSE} = \frac{3}{2}(\underset{|\hat{\beta}_j| \leq 2.56\hat{\sigma}_M}{\text{median}} \mid \hat{\beta}_j \mid),$$
- Proposal 4 (Dong, 1993):
$$\hat{\sigma}_{ASE} = \sqrt{\frac{1.08}{b-z} \sum_{|\hat{\beta}_j| \leq 2.56\hat{\sigma}_M} \hat{\beta}_j^2}.$$

Here b denotes the number of estimated effects and z is the number of estimates whose absolute value is less than $2.56\hat{\sigma}_M$. Kunert (1997) has shown that $\hat{\sigma}_{PSE}$ has the smallest bias, but $\hat{\sigma}_{ASE}$ has the smallest variance among these estimates.

The half-normal plot then uses the test-statistics

$$\mid T_j \mid = \mid \hat{\beta}_j/\hat{\sigma} \mid, 1 \leq j \leq b,$$

where $\hat{\sigma}$ is one of these four possibilities.

For the determination of the critical values, the distribution of

$$S := \max_j \mid T_j \mid$$

was simulated by 300,000 iterations in the situation where no effect is active. The distribution of S depends on the number of estimates and therefore on the number of columns of the experimental design which can be used. As a consequence, different critical values have to be determined for the different run order strategies presented in Section 2. In what follows, the critical values used are the simulated 95%-quantiles of the distributions of S. Some relevant critical values are given in Table 5. Hence $C(b, \alpha)$ denotes the (1-α)-quantile of the distribution of S in the presence of b columns. The distributions of the four variants are illustrated for $n = 16$ with $b = 15$ in Figure 1. Finally an example for a half-normal plot is given in Figure 2.

Table 5: Critical values for statistical tests (95%-quantiles of S)

Runs	Factors	$\hat{\sigma}_Q$	$\hat{\sigma}_M$	$\hat{\sigma}_{PSE}$	$\hat{\sigma}_{ASE}$
$n = 8$	$b = 7$	3.714	3.880	4.831	4.614
$n = 16$	$b = 11$	3.365	3.730	4.409	4.016
	$b = 15$	3.232	3.666	4.186	3.810
$n = 32$	$b = 31$	3.351	3.585	3.896	3.597

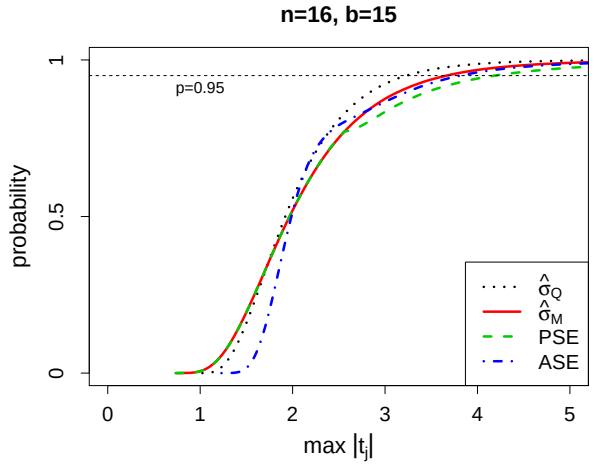

Figure 1: Distribution of S under no trend for $n = 16$ and $b = 15$. The intersections with 'p=0.95' lead to critical values for statistical tests.

4 Simulation study

In this section the performances of the three strategies of run order introduced in Section 2 are investigated in a simulation study.

In a first step, we restrict the analysis to the randomized run order and large linear trends. We consider the three run lengths 8, 16 and 32. This step is done to determine the robustness of the randomized run order: Can a randomized run order truly avoid bias due to a time trend?

In the second part of the simulation study, all concepts are researched in the situation of linear and quadratic trends. Here, we consider only the run length 16. In this part, we will compare the power loss of the three strategies in the presence of a moderate linear trend and we will compare the robustness of the three strategies to the presence of non-linear trends.

We use two criteria to evaluate the three strategies. The first one is the probability of false rejection (PFR):

$$PFR = P(\max_j \mid T_j \mid > C(b, \alpha)).$$

It gives the proportion of designs where at least one effect is declared as active, although in reality all effects are not active. This proportion is simulated in the presence of time trends with different intensities. Hence, PFR determines whether statistical tests keep the nominal level of significance under the various strategies of run-orders.

The second criterion is the probability of effect detection (PED):

$$PED = P(\min_{j:\beta_j \neq 0} \mid T_j \mid > C(b, \alpha)).$$

The probability of effect detection describes the proportion of designs, where all truly active effects are identified as active.

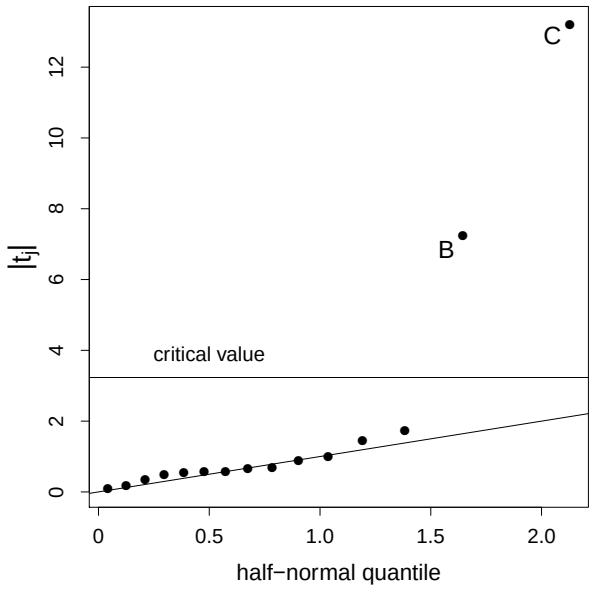

Figure 2: Example of a HNP where $\hat{\sigma}_Q$ is used to estimate the error variance. Here effects B and C would be declared as active.

The simulation study is organized as follows.

Procedure 1: Determination of PFR

(1) RO: Permute the rows of the design with standard run order.
SO: Permute the columns of the design with systematic run order.
MB: Choose at random one design out of the set of feasible designs in the catalog in de León Adams *et al.* (2005). Permute the columns of the chosen design.

(2) Create the data by equation $y_i = e_i$.

(3) Compute the test statistic max $\mid t_j \mid$.

(4) Repeat step 1 to 3, until 100,000 designs have been derived.

(5) For all three strategies and all four variants compute the respective proportion of designs where the test statistic exceeds the critical value $C(b, \alpha)$. This proportion is an estimation for the probability of false rejection.

Procedure 2: Determination of PED

(1) RO: Permute the rows of the design with standard run order.
SO: Permute the columns of the design with systematic run order.
MB: Choose at random one design out of the set of feasible designs in the catalog in de León Adams *et al.* (2005). Permute the columns of the chosen design.

(2) Create the data by equation $y_i = \mu + \sum_{j=1}^{b} x_{ij}\beta_j + e_i$.

(3) Compute the test statistic t_j.

(4) Check whether all active effects are identified as active effects, i.e. $\mid t_j \mid > C(b, \alpha)$ for all j with $\beta_j \neq 0$.

(5) Repeat step 1 to 4, until 100,000 designs have been derived.

(6) Compute for all three strategies and all four variants the respective proportion of designs where the condition in step 4 is achieved. This proportion is an estimation for the probability of effect detection.

Note that the columns are randomized for two of the strategies. The reason is that, in general, the correlation between the columns and the trend varies between the columns.

The first part of the simulation only deals with the randomized run order, with run lengths $n = 8$, $n = 16$ and $n = 32$. It only considers the scenario that there are no active factors and there is a large linear trend. The distribution of the largest contrast in the presence of the trend is then compared to the distribution that we have already derived under normally distributed errors in Section 3.

The observations in the presence of a large linear trend are simulated in the following way. The variance of the error is set equal to zero. Furthermore no effect is active and the size of the trend, a, is set to 1. Note that a can be chosen arbitrarily, because the trend is a linear component in numerator and denominator of the test statistic. This corresponds to the limiting case that the error variance is arbitrary and the trend converges to infinity. It should be the worst case for the randomized order in the presence of a time trend, because the bias according to de León Adams *et al.* (2005) then converges to infinity. As the nominal level is set to 5%, the proportion of designs that leads to a false rejection of the null hypothesis should be five percent. However, we observe for the small design with $n = 8$, in the presence of a large trend, that the largest contrast gets declared active in at least 13 percent of the cases, see Table 6. This result is also demonstrated in Figure 3 where the distribution under ideal conditions and the distribution under trend are plotted together. Obviously, the distribution under the large trend is discrete, it is far from the continuous distribution derived under normality. Hence, the randomized order does not guarantee keeping the nominal level in the presence of a linear trend for factorial designs of size 8! (This was already observed by Adekeye and Kunert (2006).)

Fortunately, this problem disappears for larger designs, when the two distributions become much more similar, see Figures 4 and 5. Here, the nominal levels are only minimally exceeded, with PFR equal to 7.6% in the maximum, see Table 6.

This indicates that, if we do an analysis with the half-normal plot, then randomization of the run-order does indeed help keeping the nominal level in the presence of a linear time trend - provided we have 16 runs or more.

Table 6: PFR of randomized run orders, strong linear trend, $\alpha = 0.05$

Runs	Factors	$\hat{\sigma}_Q$	$\hat{\sigma}_M$	$\hat{\sigma}_{PSE}$	$\hat{\sigma}_{ASE}$
n=8	b=7	0.165	0.199	0.135	0.133
n=16	b=15	0.076	0.072	0.062	0.075
n=32	b=31	0.063	0.063	0.061	0.065

In the second part of the study, we consider all three design strategies, but we restrict to the case of a 16 run design. For this case, we simulate various scenarios. The first scenario assumes that there is no active effect and tries to simulate a moderate time trend.

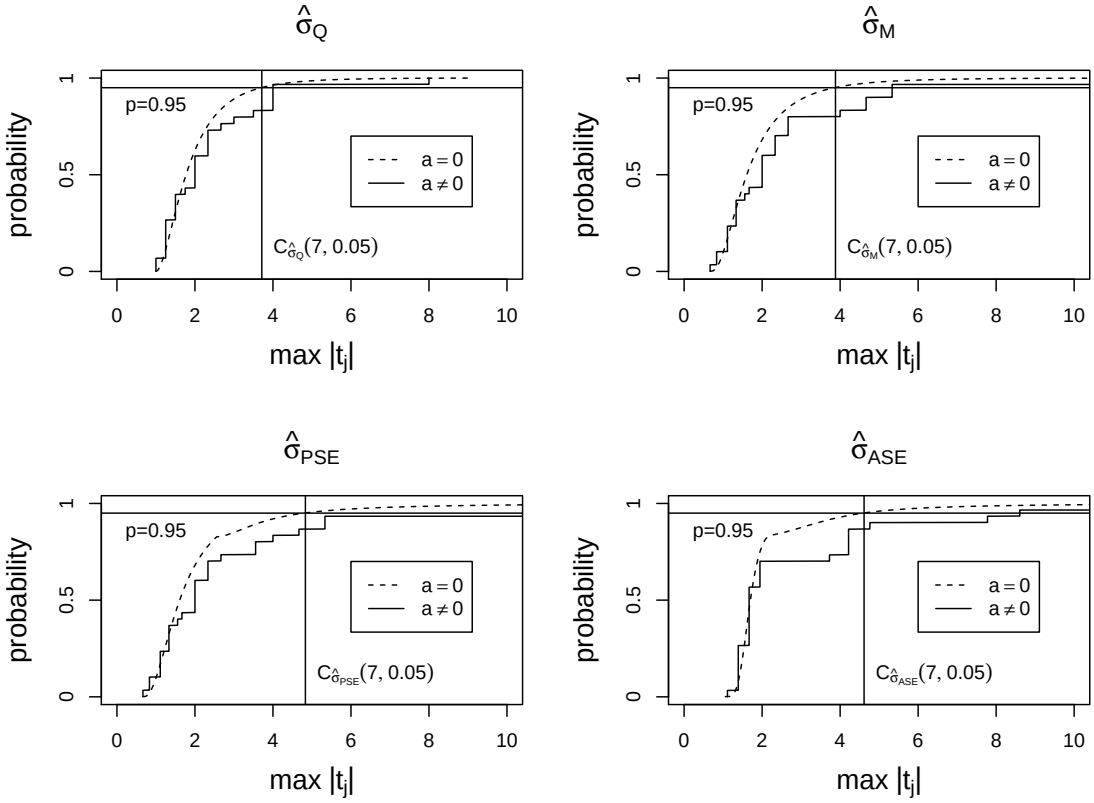

Figure 3: Distribution of max $\mid T_j \mid$ ($n = 8$, randomized run order, no active effects): Comparison of the distribution when i) there is no trend ($a = 0$) to the distribution when ii) the trend becomes infinitely large ($a \neq 0$).

We make use of the fact that, if a variable Z is standard normal, $Z \sim N(0, 1)$, then

$$E(\mid Z \mid) = \sqrt{\frac{2}{\pi}}.$$

If there is no trend and there are no active factors, then we will have for $Y_1 - Y_n$, the difference between the first and the last observation, that $Y_1 - Y_n \sim N(0, 2\sigma^2)$. Hence,

$$E(\mid Y_1 - Y_n \mid) = \sqrt{2}\sigma\sqrt{\frac{2}{\pi}} = \sqrt{\frac{4}{\pi}}\sigma.$$

This implies for our simulations that, if we set $\sigma = 1$ and the trend intensity a equal to $a = \frac{1}{15}\sqrt{\frac{4}{\pi}}$, then the expected difference between the first and 16th observation caused by the trend will be just as large as the expected difference caused by the random noise.

In this scenario, we observe that all three concepts appear to perform well, the nominal levels are approximately kept, see Table 7.

These results show that for all three design strategies a moderate linear trend does not destroy the nominal level of the half normal plot, if the design is large enough. Thus, all three strategies appear to provide valid tests in the presence of a linear trend.

In the next scenarios we compare the power of the concepts. In these settings we assume that the response of the 16-run design is influenced by one active effect of size $\beta_1 = 1$. When

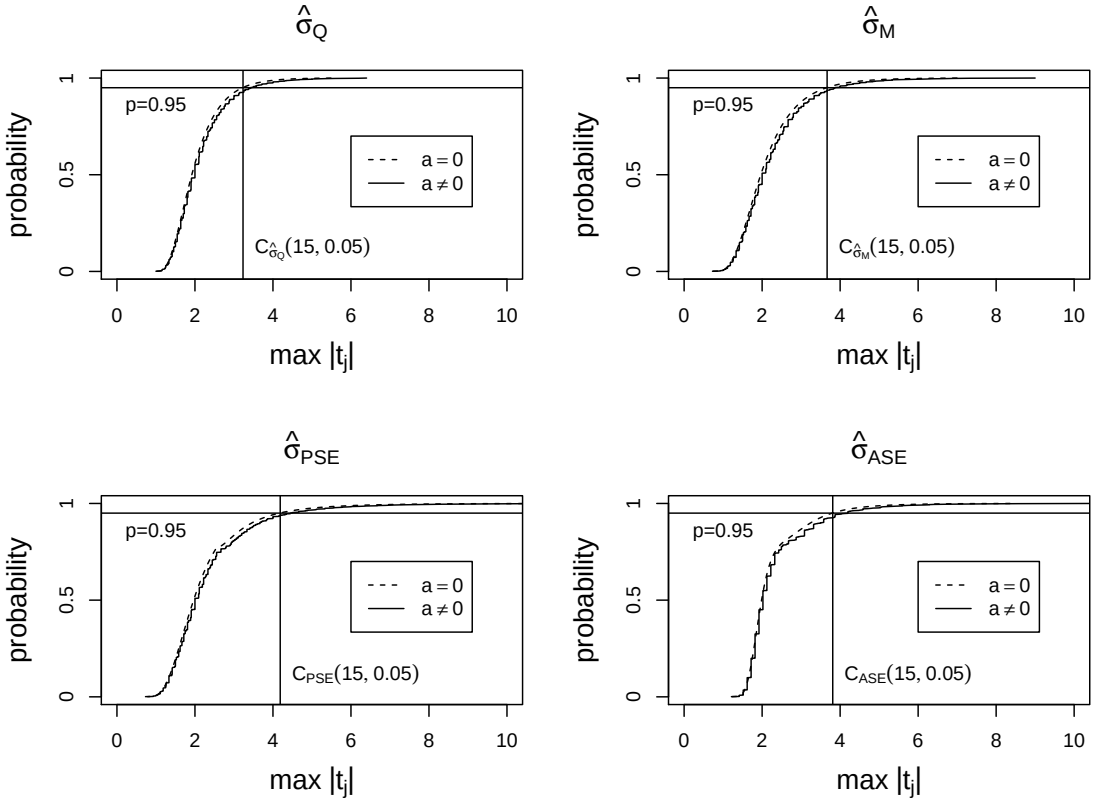

Figure 4: Distribution of max $\mid T_j \mid$ ($n = 16$, randomized run order, no active effects): Comparison of the distribution when i) there is no trend ($a = 0$) to the distribution when ii) the trend becomes infinitely large ($a \neq 0$).

Table 7: PFR of all concepts, linear trend (moderate), $\alpha = 0.05$, n=16

	RO	SO	MB
no trend	0.05	0.05	0.05
linear trend	0.05	0.05	0.05

we then simulate the moderate trend as before, it appears that all concepts perform similarly. The power of the randomized order is only slightly smaller. It should be noted, however, that the trend-free run order has a slightly lower power in a further scenario, where we assume that the trend is not present. This is due to the fact that the trend-free run order can only use a smaller number of columns. On the other hand, when we simulated the trend as large, then both the randomized run order and the run order with minimum bias experienced a dramatic loss of power, see Table 8.

As an aside, when comparing the four estimates of the variance for any given design, then in general the estimators $\hat{\sigma}_Q$ and $\hat{\sigma}_{ASE}$ lead to the highest power.

In our last scenario, we consider a quadratic trend instead of the linear one. For this scenario, the trend parameters are set to $a = 0$ and $c = 0.1$. Here we observe that only the randomized run order is able to provide a valid test that keeps the nominal level, see Table 9.

Hence, we derive from our simulations the following message: The two systematic run orders considered here, have the problem that they only work properly if the trend is truly linear. In the presence of a non-linear trend, they may fail dramatically. The randomized run order appears

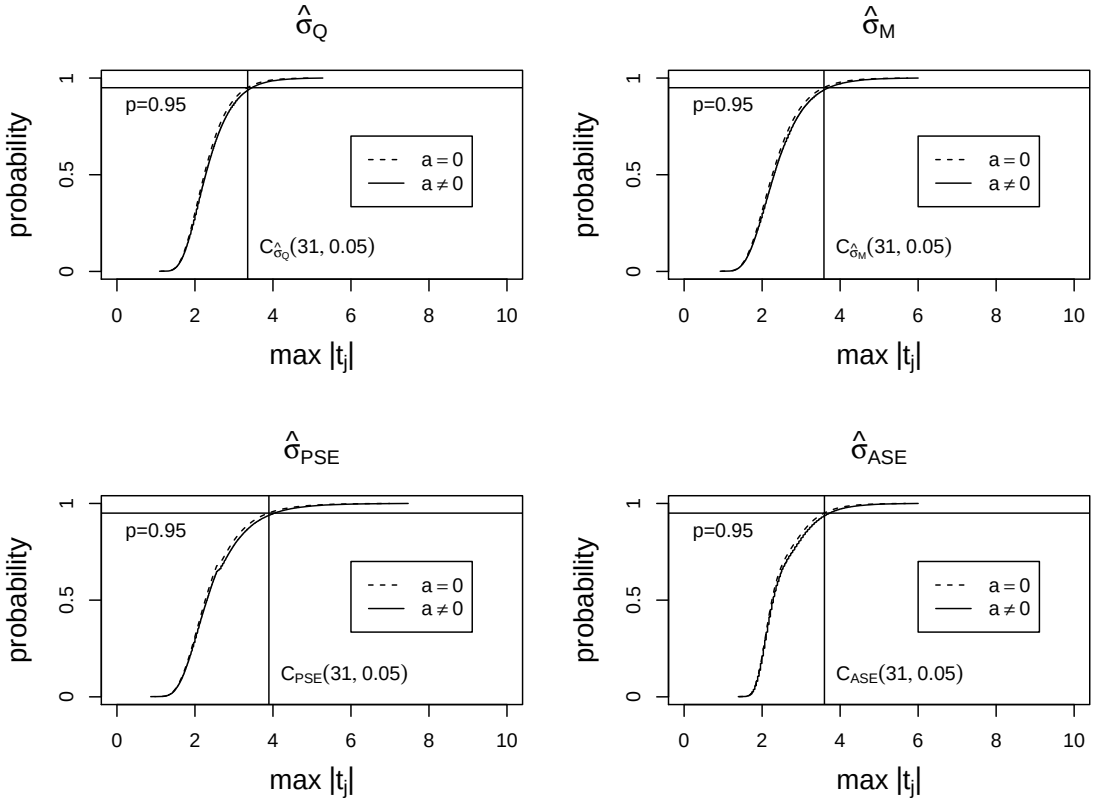

Figure 5: Distribution of max $\mid T_j \mid$ ($n = 32$, randomized run order, no active effects): Comparison of the distribution when i) there is no trend ($a = 0$) to the distribution when ii) the trend becomes infinitely large ($a \neq 0$).

to provide a valid test; it may, however, loose power if the trend gets too large.

Acknowledgment

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Table 8: PED of all concepts, linear trend (moderate/large), $\alpha = 0.05$, n=16

	RO	SO	MB	RO	SO	MB
		$\hat{\sigma}_Q$			$\hat{\sigma}_M$	
no trend	0.59	0.55	0.59	0.49	0.46	0.48
linear trend (moderate)	0.52	0.54	0.52	0.42	0.44	0.43
linear trend (large)	0.01	0.55	0.00	0.01	0.44	0.03
		$\hat{\sigma}_{PSE}$			$\hat{\sigma}_{ASE}$	
no trend	0.44	0.41	0.44	0.58	0.54	0.58
linear trend (moderate)	0.37	0.39	0.39	0.50	0.53	0.52
linear trend (large)	0.01	0.39	0.15	0.01	0.54	0.03

Table 9: PFR of randomized run orders, quadratic trend, $\alpha = 0.05$, n=16

	RO	SO	MB	RO	SO	MB
		$\hat{\sigma}_Q$			$\hat{\sigma}_M$	
quadratic trend	0.06	0.64	0.34	0.06	0.57	0.32
		$\hat{\sigma}_{PSE}$			$\hat{\sigma}_{ASE}$	
quadratic trend	0.06	0.52	0.33	0.06	0.60	0.36

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Defining the generalized dimension in the analysis of complex systems

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Abstract: The generalized dimension is a new notion that appeared about the fractal forms. The Hausdorff dimension has been defined into the beginning 20-th century and was one from the novelty entities from the modern geometry named fractal geometry. This dimension was been implied into many interesting area of applications such as medicine, biology, physics, engineering etc. Calculus for this is very important in study of the natural complex systems, there where the classical mathematical concepts proved limitary in the phenomena description.
Keywords: fractal, chaos, dimension, geometry, complexity.

1 Introduction

Fractals have practically entered every domain of interest of the human knowledge, becoming, from a simple subject of reflection, an interest theme for the uninitiated and for experts alike. From the analysis of the climatic phenomenon and to the modeling of the cancerous phenomenon, from the description of the images captured by the Hubble Space Telescope to the use of special effects in movies, fractals proved to be an inexhaustible source of ideas, solutions, tries, algorithms, on ways and directions either classical or surprisingly nonconventional.

The fractal approach on the study of cancerous tissues proved to be one of the successful themes of the systemic modeling. Thus, the medical diagnosis gained a new valence in the informational interpreting of images of the malign tissues, proportionally reducing the need to make a biopsy to take a tissue sample.

A series of fractal characteristics (i.e., specific to the Fourier spectrum of images in grey scale) were used by Heymans and his collaborators (S. Blacher, F. Rouers, G.E. Pierard). The fractal dimension quantifies here the random level of the vascular distribution also, a characteristic not easy to point out through the vascular density.

An analysis of the fractal dimension from a graphic image is useful, because the fractal dimension is a key element in studying the morpho-functional characteristics and the systemic behavior of the cancerous tissues. Searching for new methods of defining the generalized dimension for complex graphic systems leads to an inter-systemic view at the level of the perception of physical properties of the studied entities through the mathematical representation models.

2 The fractal dimension

There is a large number of methods that can be used in defining and calculating the fractal dimension of a new graphic object, which we'll call from now on *form*.

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No matter what the definition of the *dimension of a fractal form,* all ideas are derived from the Hausdorff-Besicovich dimension (HB). This dimension is a real number that can be used in characterizing the geometrical complexity of a limited subset from $\mathbf{R}^n$.

The HB dimension has a more subtle meaning that fractal dimension. One of the reasons as to why this notion is so important is that it allows comparing various "values" of sets for which the fractal dimension is the same.

In order to understand the way of defining the HB dimension, let's take the metric space $(\mathbf{R}^n, d)$. Here, n is a natural number and d notes the Euclidean metric. Let's say $A \subset \mathbf{R}^n$ is a limited domain. We can note:

$$diam\ (A) = \sup\{\ d(x, y) : x, y \in A\} \tag{1}$$

We have $0 < \varepsilon < \infty$ and $0 \le p < \infty$. We will note the set of subsets $A_i \subset A$ with Ω so that $A = \cup_{i=1}^{\infty} A_i$. Under these conditions, we can define:

$$M\ (A, p, \varepsilon) = \inf\{\ \sum_{i=1}^{\infty} (diam\ (A_i))^p : \{A_i\} \in A \wedge diam\ (A_i) < \varepsilon\} \tag{2}$$

We will use the convention that $(diam\ (A_i))^0 = 0$ when A_i is an empty set.

We notice that $M\ (A, p, \varepsilon)$ is a number included in the $[0, \infty)$ interval, finite or nonfinite. For $p \in [0, \infty)$, the value:

$$M\ (A, p) = \sup\ \{M\ (A, p, \varepsilon) : \varepsilon > 0\}$$

is called *A's p-dimensional Hausdorff value* or simpler, the *Hausdorff dimension.*

We notice that the Hausdorff dimension has a more general character than the Euclidean dimension, being able to obtain fractional values, unlike the other one. Due to this fact, we can consider it to be at the base of a special class, called the *class of generalized dimensions.* We mention that the Hausdorff dimension like it was defined before is not the only example that belongs to this class (Hambly and Jones 2003). Any other example of fractal dimension also belongs to this class.

The technique used to define the Hausdorff dimension is the one used to cover the domain A with a set of subdomains A_i, $i \in \mathbf{N}$. This technique allows us to make a deducing reasoning of the fractal dimension of self-similar forms (geometrical objects). For this, let's consider a form with the linear magnitude (after all the directions of the Euclidean space) equal with one, whose magnitude is reduced to $q < 1$ after every special direction. This way, if the initial form is self-similar, we get coverage of the form with $N(q)$ self-similar forms (figure 1).

Following the data in figure 1, we notice that:

$$N = q^{-D} \tag{3}$$

So that the dimension of the forms is determined after the relation:

$$D = \frac{\log\ N(q)}{\log\ \frac{1}{q}} \tag{4}$$

Applying this relation to a self-similar structure, we can find a value even non-integer for *D*, as value for the limit:

$$D = \lim_{q \to 0} \frac{\log N(q)}{\log \frac{1}{q}} \tag{5}$$

The (5) relation has a qualitative level, as it can be used only in numerical algorithms (Restrepo *et al.* 2004). Far more used in practice is the Mandelbrot-Richardson relation (diagram), deduced as a consequence of the Richardson effect.

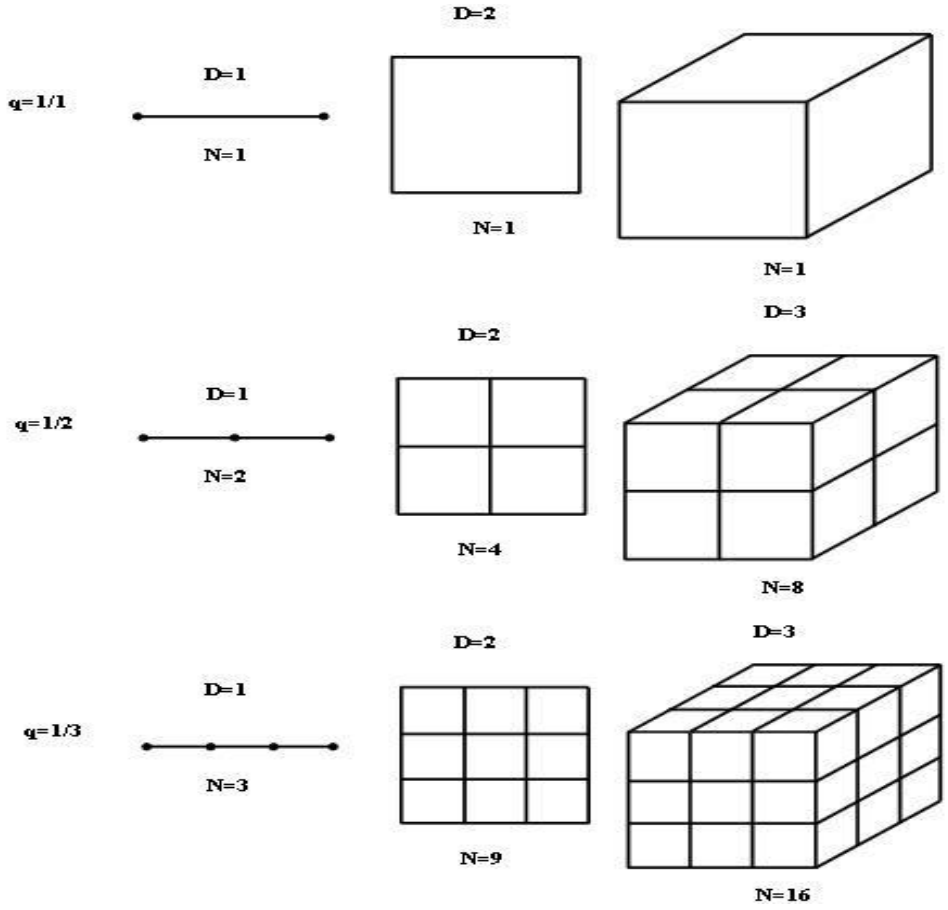

Figure 1: Defining the Euclidean topological dimension

Lewis Fry Richardson is the first one to put the question of a relation between the length of the national borders and the measurement scale. He noticed that this is a *log-log* type of relation (it can be represented in a graphic where the scale logarithm is on the abscissa and on the ordinate the logarithm of the length of the contour as a scale function).

Mandelbrot associated the $(1 - D)$ terms with inclination of the graphic, so that the function becomes:

$$\log L(s) = (1 - D) \log(s) + k \tag{6}$$

where *D* is the fractal dimension, *s* notes the reference scale, $L(s)$ is the length of the contour of the border or the coast (corresponding to the scale) and *k* is a positive constant belonging to the absolute magnitude of the length of the contour we referred to (Mosekilde *et al.* 2002).

Indeed, starting from the (4) relation and considering that:

$$k \to 0$$

$$s \leftarrow q$$

$$L(s) \leftarrow N(q)$$

we get:

$$D = 1 + \frac{\log L(s)}{\log \frac{1}{s}} \tag{7}$$

from where:

$$\log L(s) = (D-1)\log \frac{1}{s} = (1-D)\log s \tag{8}$$

which justifies the association made by Mandelbrot.

For the coast of Great Britain, Richardson found: $1 - D = -0.24$, so $D = 1.24$, meaning a fractional value. The coast line in South Africa proved to be more leveled, almost a circular arc. The estimated inclination for the Mandelbrot-Richardson diagram is very close to zero, so that we have: $D \approx 1$. Thus it is proven that this contour has the characteristics of a Euclidean geometrical form, just like it was expected to have.

3 The analysis of the generalized dimension

We will continue by making a qualitative analysis of the interpretation of a new type of geometrical dimension, different from the Euclidean topological one. We will call it *generalized dimension*, its properties being studied subsequently. In order to identify some correlations between the generalized dimension and the fractal dimension, the question of studying the existent relations between the two notions arises (Baish and Jain 2000).

Let it be a smooth, continuous curve, like the one in figure 2. In this figure, the *Ox* axis is the axis of the *x* argument and the *Oy* axis is the axis of the $y = f(x)$ function. In the particular case of the shown example, the function has the form: $f(x) = 3\sin(4x)$. The display window has been auto-dimensioned.

It is obvious that the maximum number of grid points that can be found on the grid is N^2, where N is the number of reticles is after each axis. Not all these points, though, will have this property in practice, making this number equal to $n \cdot N$, where n is the average of nods on each axis of the grid and simultaneously on the graphic. We will define the nods with this property as *active nods*, whereas the nods without this property will be called *passive nods*. The points of intersection with the graphic which are not found on the cover matrix are ignored (they are eliminated from the algorithm that determines the generalized dimension). We have in the example above three passive nods and just one active nod.

Obviously, the spread between reticular lines is arbitrary. Moreover, because the contour graphic must not represent a compulsory according with a function's graphic, the number of intersections of a contour chart with one reticle column may be greater than one. At the same time,

we will change the intersection points with intersection areas and then make a switch to limit zero for the area. In this sense, the algorithm has a routine of creating these areas.

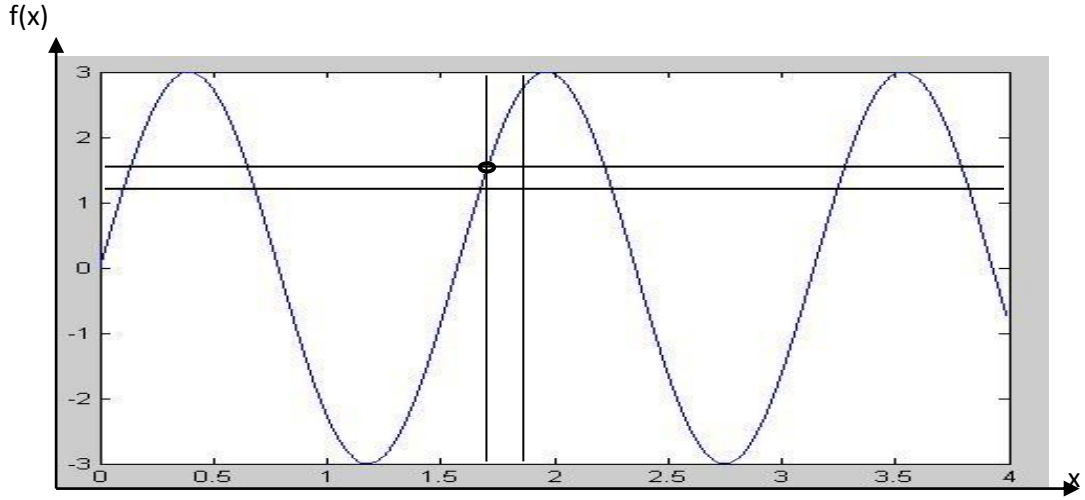

Figure 2: Defining the cover matrix

We will consider that the weight of *n*'s value in reference to *N* can vary between 0 and 1, these limits realizing, formally speaking, the *all or nothing* membership function. In other words, *n* can take values between 0 and *N*. If by modifying *N*'s value, this characteristic remains unchanged, then this is a specificity of the considered curve. Thus, we can proceed to determine the generalized dimension as a specificity index. We notice that the $\frac{n}{N}$ ratio indicates a space *factor* (or an *overlap factor*) with *active nods* (nods situated on the graphic). Due to this fact, the method used to define the generalized dimension will be called the *cover matrix method* (CMM).

To define the generalized dimension, the following formula is adopted:

$$\frac{N}{n+N} = k^{1-D} \tag{9}$$

where *n* and *N* are notions which we previously talked about, *k* is an arbitrary constant and the generalized dimension is noted with *D*.

Let us notice that, in order to norm the variation interval of the generalized dimension, we must chose $k = 2$. Truthfully, to look up the logarithm of both members from relation (9) and to choose the base of the logarithm with a value of 2, we get:

$$D = 1 + \log_2 \frac{n+N}{N} \tag{10}$$

Let us analyze relation (10). For very low values of *n* in reference to *N*, meaning for $n \to 0$, we have $D \to 1$. This fact suggests that a curve with such a characteristic is an ordinary, Euclidean curve. When $n \to N$, though, the filling of the above mentioned domain tends to be complete and relation (10) leads to $D \to 2$, indicating that the curve becomes now a special curve, with characteristics similar to those of a surface. In conclusion, the domain of variation of the generalized dimension is $\Omega = [1,2]$, the same as the variation domain of the corresponding fractal dimension.

In order to adapt the calculus necessities to the facilities offered by the various programming software, we will bring relation (10) to the form:

$$D = 1 + \frac{\ln \dfrac{n + N}{N}}{\ln 2} \tag{11}$$

where *ln* notes the *natural* or *Napierian* logarithm function.

We notice that $n \in [0, N]$, so that the following relation has meaning:

$$D = 1 + \frac{\ln(\zeta + 1)}{\ln 2} \tag{12}$$

with $\zeta = n / N$, $\zeta \in [0,1]$. We will call the ζ variable *space factor* and, when needed, we will refer to it subsequently.

We notice that the interval of possible values of the generalized dimension is $\Delta = [1,2]$, just as wanted.

Expression (12) can be brought to the form:

$$D = 1 - S \tag{13}$$

where $S = -\dfrac{\ln(\zeta + 1)}{\ln 2}$ notes the *ramp characteristic* of the cover matrix method.

However, considering the dividing method in determining the generalized dimension:

$$L(r) = r^{1-D} \tag{14}$$

and noting with L the length of the approximated curve, with *r* the length of the step, and with *D* the generalized dimension, we have (in conformity with relation (9)):

$$1 - D = \frac{\log_k L}{\log_k r} = \log_k \frac{N}{n + N} = S \tag{15}$$

In this case also the generalized dimension can be written using the ramp characteristic:

$$D = 1 - S \tag{16}$$

We notice that while *r*'s value in the dividing method is constant all through and iteration, in the case of cover matrix method, this value is a mean that takes the form:

$$r = \frac{1}{n}\sum_{i=1}^{n} \rho_i \tag{17}$$

where ρ_i is the width step from nod *i* to nod *i + 1*.

According to relation (15) and considering the notes made in relation (12), we have:

$$S = \log_k \frac{1}{\zeta + 1} \tag{18}$$

For $k = 2$ value of *S* ranges from -1 to 0 and value of *D* ranges from 1 to 2. The *D* expression is deducted in conformity with relation (16):

$$D = 1 - S = 1 - \log_k \frac{1}{\zeta + 1} \tag{19}$$

Thus, the generalized dimension in mixt method, gain expression:

$$D = 1 + \log_2 (\zeta + 1) \tag{20}$$

The relation (20) is same with relation (12). But, if we use the natural logarithm, relation (20) becomes:

$$D = 1 + \ln (\zeta + 1) \tag{21}$$

In this case *D* has a variation between 1 and $1 + \ln 2 \cong 1.69$. As ramp characteristic *S* is negative, with values between 0 and $-\ln 2 \approx -0.69$, the generalized dimension can take values in the $[0,1 - S]$ interval. To assure the same domain of affiliation for the generalized dimension like in the case of the cover matrix method, we need to renormalize:

$$D = (1 - S)^{\mu} \tag{22}$$

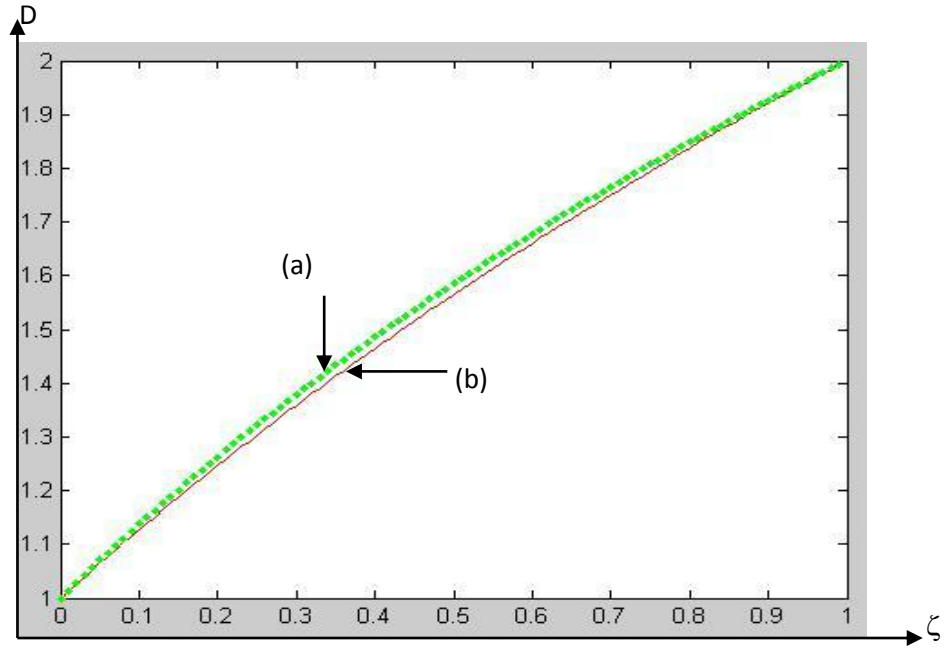

Figure 3: The Variation of the generalized dimension in relation to the space factor

(a) MA method (b) mixt method

As for $S = 0$ the value of the μ coefficient can be any number, we will evaluate this for the case when $S = -\ln 2$.

We have:

$$\mu = \frac{\ln 2}{\ln(1 + \ln 2)} \approx 1.33 \tag{23}$$

Conclusions

Relations (12) and (22) are calculation formulae of the generalized dimension within the cover matrix method (CMM) and the mixt method (MM). An analysis of this relation can signal a series of specific characteristics and can suggest some use strategies of the two methods in practical applications.

Comparing relations (12) and (22) indicates that their use leads to similar results, with very small deviations into the central area.

The result provided by the mixed method has the advantage of increased linearity. Both formulas computing facilities presents classical box-counting method above.

The computer program must create an overlap between a grid mesh and the object fractal (Armstrong 2010; Voss 2010). Determination of active nodes follows a routine that has been discussed previously.

Careful study indicates that both box-counting method and the two proposed methods leading to similar results. Each method is likely to be used practically.

According to figure 3, we notice that the deviation between the curve defined by the evolution of the generalized dimension in the case of the dividing method (the dotted curve) and the one specific to the mixt method (the continuous curve) is a small one (under 1%). Consequently, the two methods can be considered congruent, practice favoring the use of one or the other.

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Adaptive Choice of Resampling Tests for Scale in Flexible Two Stage Designs

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Abstract: The two sample scale problem is addressed within the rank framework which does not require to specify the underlying distribution. However, since the power of a rank test depends on the underlying distribution, it would be very useful for the researcher to have some information on it in order to use the possibly most suitable test. A two stage adaptive design is used with adaptive tests where the data from the first stage are used to compute a selector statistic to select the test statistic for stage two. More precisely an adaptive scale test due to Hall and Padmanabhan and its components are considered in one stage and several adaptive and non adaptive two stage procedures. A simulation study shows that the two stage test with the adaptive choice in the second stage and with Liptak combination when it is not more powerful than the corresponding one stage test shows however a quite similar power behavior. The tests procedures are illustrated using an ecological application.

Keywords: Resampling Tests, Scale, Flexible Two Stage Designs.

1 Introduction

In classical clinical trials the design features should be established in the protocol before the start of the study. However, when designing the experiment the available information might be incomplete leading to a possible misspecification of sample sizes, hypotheses, variability, test procedures, endpoints... This problem is particularly important when developing a new drug. Flexible (adaptive) study designs, by using the accumulated data, allow to modify the design features, if necessary, with the aim at improving the design (Bauer and Köhne (1994)). The central idea of adaptive designs is to conduct a sequence of experiments and analyze separately the data from each stage. The design of a stage may be changed according to the results obtained in the previous stage or stages. For example sample sizes can be adjusted using interim analysis results on variability and treatment effect (Friede and Kieser (2001)), a treatment arm can be dropped if interim analyzes show that it is toxic and/or futile (Bauer and Kieser (1999)), the test statistic can be changed (Kieser *et al.* (2002)) and one or more endpoints can be discarded (Kieser *et al.* (1999)).

Among the various possible design adaptations, in this paper we use the information on the underlying distribution obtained in an interim analysis for the selection of the test statistic for the next stage. We act within the rank framework and therefore the underlying distribution does not need to be specified. However, the power of a rank test depends on the underlying distribution and then it would be very useful for the researcher to have some information on it at her/his disposal, in order to use a more (possibly the most) suitable test statistic. We consider the two sample scale problem for a flexible two stage design (i.e. with one interim analysis) and we address it using adaptive tests where the data from the first stage are used to compute a selector statistic to select the test statistic for stage two. Acting within a flexible two stage design we assume to have no information in the planning phase about the underlying distribution. Our aim is to see whether the power of adaptive tests may be improved by using the data from the first stage to get information on the underlying distribution and in particular on its tailweight,

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and then selecting the most suitable test for the second stage according to a selector statistic. As Friede *et al.* (2003) that addressed the two sample location problem following the same point of view, we consider fixed sample sizes in the two stages without sample size re-assessment and without early stopping for futility.

In section 2 we discuss the two stage adaptive design that is considered in this paper. In section 3 we present the methods that are compared in the size/power simulation study of section 4. An application example is presented in section 5. The conclusion is in section 6.

2 The two stage adaptive design

We consider the flexible two stage design of Bauer and Köhne (1994) which is traditionally viewed in terms of p-values for testing the null hypothesis. Its central feature is to conduct an interim analysis after the first experiment stage and then a second stage with possible modification of the design at the basis of the interim analysis. We consider the problem of testing for the equality of scales of two continuous populations given iid sample $(X_{ij}\ i = 1, \ldots, n_j)$ from the jth population, $j = 1, 2$, with mean μ_j, scale σ_j and distribution function $F((x - \mu_j)/\sigma_j)$, $n = n_1 + n_2$. The function F and the constants $\mu_1, \mu_2, \sigma_1, \sigma_2$ are unknown. The system of hypotheses under testing is

$$H_0 : \sigma_1/\sigma_2 = 1 \text{ against } H_1 : \sigma_1/\sigma_2 > 1.$$

We test H_0 against H_1 using a scale test T and we reject the null hypothesis if $p_1 \leq \alpha_1$ where p_1 is the p-value of the T test in the first stage and α_1 is the nominal significance level in the first stage (early rejection of H_0). Early acceptance of H_0 occurs for $p_1 \geq \alpha_0$. If $\alpha_1 < p_1 < \alpha_0$ the trial continues, and in this case, after the first stage, we consider other two samples of sizes m_1 and m_2 respectively for the first and second population, $m = m_1 + m_2$, and we compute the p-value p_2 of the T test. Final rejection or acceptance of H_0 is based on the combination of the p-values of the two stages.

A very important aspect in this two flexible adaptive design is the allocation of the nominal significance level α to stage one and stage two. In the first stage, H_0 is tested at the $\alpha_1 < \alpha$ nominal significance level. In the second stage, H_0 is tested at a significance level $\alpha_2(p_1)$ that depends on p_1. $\alpha_2(p_1)$ is a non increasing function of p_1 because with a small (large) first stage p-value p_1 we need less (more) evidence in stage two to reject H_0. It is well known that repeated analysis might inflate the type one error rate and therefore the function $\alpha_2(p_1)$ should be chosen to maintain the desired type one error rate at α:

$$\alpha \geq Pr(p_1 \leq \alpha_1|H_0) + Pr(\alpha_1 < p_1 < \alpha_0 \cap p_2 \leq \alpha_2(p_1)|H_0) = \int_0^{\alpha_1} \mathrm{d}p_1 + \int_{\alpha_1}^{\alpha_0} \int_0^{\alpha_2(p_1)} f(p_2|p_1)\, \mathrm{d}p_2\, \mathrm{d}p_1.$$

The inequality simplifies to

$$\alpha \geq \alpha_1 + \int_{\alpha_1}^{\alpha_0} \alpha_2(p_1)\mathrm{d}p_1$$

by assuming that p_1 and p_2 under H_0 are independent and uniformly distributed between 0 and 1. By using the Fisher's product criterion H_0 is rejected if $p_1 p_2 \leq c_\alpha = \exp(-0.5\chi^2_{4,1-\alpha})$ and is accepted otherwise, where $\chi^2_{4,1-\alpha}$ is the $(1-\alpha)$th percentile of the χ^2 distribution with 4 df. In this case $\alpha_2(p_1) = c_\alpha/p_1$ and the overall type one error rate of the procedure is $\alpha_1 + c_\alpha(\ln \alpha_0 - \ln \alpha_1)$ and therefore to control the nominal significance level α under H_0 the decision boundaries for early rejection α_1 and early acceptance α_0 have to fulfill the equation $\alpha_1 + c_\alpha(\ln \alpha_0 - \ln \alpha_1) = \alpha$. A weaker condition on the conditional density of p_2 given p_1 is to assume that it is stochastically not smaller than the uniform distribution. This leads to a conservative procedure. As in Friede *et al.* (2003) we set $\alpha_0 = 1$ and then the rejection boundary is c_α both for the interim analysis

p-value p_1 and for the final analysis p-value $p_1 p_2$. In fact as $\alpha_0 \to 1$, $\alpha_1 \to c_\alpha$ (Bauer and Köhne (1994)).

As alternative p-value combination method we consider the Liptak one that leads to the rejection of H_0 if $\Phi^{-1}(1-p_1) + \Phi^{-1}(1-p_2) \geq \sqrt{2} z_{1-\alpha}$ where $z_{1-\alpha}$ is the $(1-\alpha)$th percentile of the standard normal distribution. It is important to note that the Liptak combination test does not allow for early stopping.

3 Methods

For addressing the two sample scale problem, we consider the Hall and Padmanabhan (1997) HP test because it has been found by Marozzi (2011) to perform well for detecting scale changes in a detailed study which considered fifteen different tests: it maintained the size close to the nominal significance level and showed good power for distributions ranging from symmetric to skewed, light to heavy tails, and low to high kurtosis.

To perform the HP test, firstly consider the pooled Z sample

$$\underline{Z} = (Z_{11}, ..., Z_{1n_1}, Z_{21}, ..., Z_{2n_2}) = (Z_1, ..., Z_{n_1}, Z_{n_1+1}, ..., Z_{n_1+n_2}) = (Z_i, i = 1, ..., n)$$

where $Z_{ji} = |X_{ji} - \tilde{X}_j|$ and $\tilde{X}_j$ is the median of the jth sample $j = 1, 2$, and compute the rank R_i of Z_i in $\underline{Z}$. Secondly compute $TW = (n_1 TW_1 + n_2 TW_2)/n$ where TW_j, $j = 1, 2$ is the jth sample Hogg tailweight measure. The HP statistic is defined as

$$HP = \begin{cases} HP_1 = \sum_{i=n_1+1}^{n} \Phi^{-1}((n + R_i)/(2n+1))^2 & \text{if } TW < 3 \\ HP_2 = \sum_{i=n_1+1}^{n} (1 + R_i/n)^2 & \text{if } 3 \leq TW < 5 \\ HP_3 = \sum_{i=n_1+1}^{n} (1 + R_i/n) & \text{if } TW \geq 5 \end{cases}$$

The p-value of the test is estimated via the bootstrap as $M_{HP} = \sum_{d=1}^{D} I({}_dHP \geq {}_0HP)/D$, where ${}_0HP$ is the observed value of the HP statistic and ${}_dHP$ is the value of HP in the dth couple of bootstrap samples obtained by resampling with replacement from $\underline{Z}$. Small p-values speak against H_0.

To select the test statistic for the second stage we use the weighted mean of the tailweight measure of sample 1 and sample 2 in the first stage (pooled estimator of TW). In a similar context but for testing for changes in location, Friede *et al.* (2003) along with the pooled estimator of the selector statistic, used also the one sample selector statistic (calculated by merging the first stage data over the two treatments groups), the p-value method which selects the test statistic with the minimum p-value in the first stage and a bootstrap power estimation procedure. They conclude that the pooled selector statistic method should be preferred because shows the overall best performance.

In the one stage design, with $o_1 = n_1 + m_1$ first sample size and $o_2 = n_2 + m_2$ second sample size we consider the HP test and its three components HP_1, HP_2, HP_3. For the two stage design we consider

1. the same test in both stages;
2. the adaptive test with selection of the test for the second stage according the pooled estimator of TW computed on the first stage samples.

We consider both the Fisher and Liptak methods to combine the p-values of the first and second stage.

4 Results

To assess the size and power properties of the procedures, samples of size $(n_1, n_2, m_1, m_2) = (10, 10, 10, 10), (10, 10, 20, 20), (20, 20, 10, 10), (20, 20, 20, 20)$ were simulated from a light tailed bimodal distribution (mixture of $N(-1.5, 1)$ and $N(1.5, 1)$ with equal probabilities), uniform, normal, double exponential, t with 2 df, chi squared with 8 df and exponential. All distributions but the t were re-scaled to have variance equal to one. 5000 Monte Carlo replications and 1000 bootstrap resamplings were generated. For each replication, two samples of size $n_1 + m_1$ and $n_2 + m_2$ were generated. The elements of the second sample were multiplied by $\theta_2 > \theta_1 > 1$, were θ_2 and θ_1 were chosen so that the one stage HP test had a power close to 90% and 50% respectively. Of course, with $\theta = 1$ we are simulating the null hypothesis situation. For the two stage design, the $n_1 + m_1$ elements give rise to the first sample first stage n_1 elements and to the first sample second stage m_1 elements, and so do the $n_2 + m_2$ elements for the second sample for the two stages. We consider one sided tests with $\alpha = 0.025$ and $\alpha_0 = 1$ that lead to a boundary of $c_\alpha = 0.0038$ for early and final rejection of H_0 in the two stage design.

Table 1 shows the maximum estimated significance level (MESL) of the tests. The MESL of HP and HP_1 are similar and larger than the MESL of HP_2 and HP_3. Note that HP_3 has the smallest MESL. By analyzing the MESL separately for each distribution and sample size settings we obtain the same results.

Tables 2 to 8 show the estimated significance level and power of the tests for the various distribution and sample size settings. For a fair comparison of the tests, not only their power but also their expected total sample sizes and estimated probability for rejection of the null hypothesis after the first stage for the two stage tests based on the Fisher combining function (which permits early rejection of the null hypothesis) should be considered. While the total sample size is always $o = o_1 + o_2$ for the one stage tests and the two stage tests based on the Liptak combining function, the expected total sample size of the two stage tests based on the Fisher combining function is $o - mPr(\text{early stopping})$. Both the expected total sample size and the probability for early stopping are reported in tables 2 to 8.

What is the most powerful one stage test? The HP and HP_1 test behave very similarly and are more powerful than the HP_2 and HP_3 test for the bimodal, uniform, normal, chi squared and exponential distribution. The HP_1 test is more powerful than the other ones for the double exponential distribution. The HP and HP_2 test behave very similarly and are slightly more powerful than the HP_1 and HP_3 test for the t distribution. Therefore the most powerful one stage test is the HP_1 test with the exception of the case of the t distribution where it is slightly less powerful than the HP and HP_2 test. The results do not change as the sample size setting changes.

Should the adaptive two stage design be preferred to the non adaptive two stage design? The adaptive and non adaptive two stage tests based on the Fisher combining function behave always the same. Among the two stage tests based on the Liptak combining function, the adaptation in the second stage improves the power of both the HP_2 and HP_3 test for all the distributions, although for the t distribution the improvement is less marked. On the contrary, for the HP_1 tests the adaptation using the Liptak combining function does not improve the power. Therefore the adaptation is useful only for the HP_2 and HP_3 test with the Liptak combining function.

What is the best combining function? The use of the Liptak function leads to more powerful tests compared to the use of the Fisher function. This is especially true for the HP_2 and HP_3 test, whereas for the HP and HP_1 test the difference in power is small. It is important to emphasize that the Fisher combination allows for early rejection of the null hypothesis resulting in a lower average sample size. This could be particularly important for very expensive or with ethical problem studies.

When the two stage tests are more powerful than the one stage tests? It is interesting to note that the two stage test with HP_3 in the first stage and the adaptive choice in the second stage with Liptak combination is more powerful than the one stage HP_3 test. This is true also for HP_2 under normal, chi squared and exponential distributions, and for HP_1 under the exponential distribution. The two stage test with HP_1 in the first stage and the adaptive choice in the second stage with Liptak combination is slightly less powerful than the one stage HP_1 test under normal, double exponential, t and chi squared distributions. In general, the two stage test with the adaptive choice in the second stage and with Liptak combination when it is not more powerful than the corresponding one stage test shows however a quite similar power behavior.

5 Application

As noted by Neuhäuser (2001), even if adaptive designs are particularly useful for clinical trials, they are also useful for ecological studies. Furness and Bryant (1996) studied the field metabolic rate (FMR in Kj/d) of the northern fulmars (fulmarus glacialis). The fulmarus glacialis is one of the more abundant seabirds in the northern North Pacific and it is suspected to have rather lower energy expenditures than many other seabirds and therefore it is of interest to study its FMR. Table 9 displays the FMR as a multiple of the basal metabolic rate of eight male and six female subjects.

Table 9: The FMR as a multiple of the basal metabolic rate of eight male and six female fulmars.

Male subjects							
7.85	7.03	6.37	5.73	3.53	2.3	1.42	1.4
Female subjects							
7.17	5.46	4.75	3.95	3.94	2.67	-	-

We would like to test the null hypothesis of equal variances against the one sided alternative that the variance of male FMR is greater than the variance of female FMR. For the purpose of illustrating the procedures based on the Fisher combination, this small data set is regarded as first stage data. The p-values of the tests (estimated with 1000 bootstrap resamplings) are .030, .029 and .041 for the HP_1, HP_2 and HP_3 test respectively. Since $TW = 1.65$ the adaptive test HP selects the HP_1 component. Since the p-value of the HP test is greater that $C_{.025} = .0038$ the study is not early stopped after the first stage but is continued with the second stage. To conclude that the variability of male FMR is greater than the variability of female FMR (at the nominal significance level of .025) the second stage p-value of the HP_1 test (selected at the basis of the TW result at stage one) has to be $.0038/.030 \approx .1266$ or smaller.

6 Conclusion

Flexible (adaptive) study designs allow to modify the design features, if necessary, with the aim at improving the design. Among the various possible design adaptations, in this paper we used the information on the underlying distribution obtained in an interim analysis for the selection of the test statistic for the next stage. We acted within the rank framework without the need for specifying the underlying distribution. However, the power of a rank test depends on the underlying distribution and then it would be very useful for the researcher to have some information on it, in order to use the (possibly) the most suitable test statistic. We considered the two sample scale problem for the flexible two stage design of Bauer and Köhne (1994) and we addressed it using adaptive tests where the data from the first stage are used to compute a

selector statistic to select the test statistic for stage two. Acting within a flexible two stage design we assume to have no information in the planning phase about the underlying distribution. Our aim was to see whether the power of adaptive tests may be improved by using the data from the first stage to get information on the underlying distribution and in particular on its tailweight, and then selecting the most suitable test for the second stage according to a selector statistic. For addressing the two sample scale problem, we considered the Hall and Padmanabhan (1997) HP test because it has been found to perform well for detecting scale changes under distributions ranging from symmetric to skewed, light to heavy tails, and low to high kurtosis. More precisely, in the one stage design we considered the HP test and its three components HP_1, HP_2, HP_3 and for the two stage design we considered (i) the same test in both stages and (ii) the adaptive test with selection of the test for the second stage according the pooled estimator of the Hogg tailweight measure computed on the first stage samples. We considered both the Fisher and Liptak methods to combine the p-values of the first and second stages.

After performing a Monte Carlo study to compare size and power of the different procedures, we concluded that

1. the most powerful one stage test is the HP_1 test with the exception of the case of the t distribution where it is slightly less powerful than the HP and HP_2 tests;

2. the adaptation is useful only for the HP_2 and HP_3 tests with the Liptak combining function;

3. the use of the Liptak function leads to more powerful tests compared to the use of the Fisher function;

4. the two stage test with the adaptive choice in the second stage and with Liptak combination when it is not more powerful than the corresponding one stage test shows however a quite similar power behavior.

Generalizations require caution because the results are based on simulation experiments.

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Table 1: MESL of the tests.

		Two stage			
		Fisher		Liptak	
Test	One	combination		combination	
1st stage	stage	Same	Adaptive	Same	Adaptive
		Bimodal			
HP	0.031	0.033	0.033	0.031	0.031
HP_1	0.031	0.033	0.033	0.031	0.031
HP_2	0.022	0.021	0.021	0.021	0.027
HP_3	0.021	0.018	0.019	0.020	0.025
		Uniform			
HP	0.029	0.029	0.029	0.029	0.029
HP_1	0.029	0.029	0.029	0.029	0.029
HP_2	0.024	0.019	0.020	0.022	0.026
HP_3	0.022	0.017	0.017	0.018	0.025
		Normal			
HP	0.029	0.035	0.035	0.034	0.034
HP_1	0.029	0.034	0.034	0.033	0.034
HP_2	0.026	0.023	0.023	0.023	0.029
HP_3	0.023	0.020	0.021	0.021	0.027
		DE			
HP	0.037	0.039	0.039	0.041	0.038
HP_1	0.035	0.037	0.037	0.040	0.037
HP_2	0.030	0.029	0.030	0.030	0.032
HP_3	0.027	0.025	0.025	0.027	0.030
		t_2			
HP	0.030	0.034	0.033	0.033	0.031
HP_1	0.030	0.033	0.033	0.032	0.030
HP_2	0.026	0.021	0.022	0.024	0.024
HP_3	0.026	0.020	0.020	0.021	0.023
		χ^2			
HP	0.030	0.037	0.037	0.036	0.036
HP_1	0.030	0.037	0.037	0.036	0.036
HP_2	0.029	0.028	0.029	0.029	0.028
HP_3	0.027	0.024	0.025	0.026	0.026
		Exp			
HP	0.038	0.039	0.039	0.038	0.037
HP_1	0.036	0.037	0.037	0.036	0.036
HP_2	0.030	0.027	0.027	0.029	0.034
HP_3	0.029	0.026	0.026	0.025	0.031

Table 2: Size and power for the bimodal distribution.

				Two stage				
				Fisher combination			Liptak combination	
θ	Test 1st stage	One stage	Prob (rej. 1st stage)	Average s. size	Same	Adaptive	Same	Adaptive
				$(n_1, n_2, m_1, m_2) = (10, 10, 10, 10)$				
1	HP	0.030	0.003	39.9	0.026	0.026	0.029	0.029
	HP_1	0.030	0.003	39.9	0.026	0.026	0.029	0.029
	HP_2	0.019	0.001	40.0	0.015	0.016	0.016	0.024
	HP_3	0.017	0.001	40.0	0.012	0.014	0.013	0.020
1.47	HP	0.526	0.042	39.2	0.385	0.385	0.432	0.432
	HP_1	0.526	0.042	39.2	0.385	0.385	0.432	0.432
	HP_2	0.334	0.023	39.5	0.217	0.219	0.245	0.326
	HP_3	0.285	0.018	39.6	0.172	0.175	0.193	0.296
1.95	HP	0.897	0.156	36.9	0.780	0.780	0.819	0.819
	HP_1	0.897	0.156	36.9	0.780	0.780	0.819	0.819
	HP_2	0.711	0.096	38.1	0.538	0.538	0.581	0.704
	HP_3	0.648	0.081	38.4	0.452	0.454	0.488	0.661
				$(n_1, n_2, m_1, m_2) = (10, 10, 20, 20)$				
1	HP	0.029	0.003	59.9	0.026	0.026	0.026	0.026
	HP_1	0.029	0.003	59.9	0.026	0.026	0.026	0.026
	HP_2	0.019	0.001	60.0	0.017	0.017	0.018	0.025
	HP_3	0.018	0.001	60.0	0.013	0.014	0.016	0.023
1.32	HP	0.475	0.026	59.0	0.378	0.378	0.402	0.402
	HP_1	0.475	0.026	59.0	0.378	0.378	0.402	0.402
	HP_2	0.315	0.018	59.3	0.221	0.221	0.240	0.327
	HP_3	0.277	0.015	59.4	0.176	0.176	0.196	0.304
1.65	HP	0.907	0.081	56.7	0.832	0.832	0.844	0.844
	HP_1	0.907	0.081	56.7	0.832	0.832	0.844	0.844
	HP_2	0.737	0.042	58.3	0.609	0.610	0.633	0.768
	HP_3	0.677	0.034	58.6	0.522	0.523	0.548	0.732
				$(n_1, n_2, m_1, m_2) = (20, 20, 10, 10)$				
1	HP	0.031	0.005	59.9	0.030	0.030	0.031	0.031
	HP_1	0.031	0.005	59.9	0.030	0.030	0.031	0.031
	HP_2	0.022	0.004	59.9	0.021	0.021	0.021	0.027
	HP_3	0.021	0.003	59.9	0.018	0.018	0.020	0.025
1.32	HP	0.471	0.096	58.1	0.373	0.373	0.403	0.403
	HP_1	0.471	0.096	58.1	0.373	0.373	0.403	0.403
	HP_2	0.309	0.047	59.1	0.222	0.222	0.241	0.304
	HP_3	0.266	0.036	59.3	0.178	0.179	0.194	0.277
1.65	HP	0.902	0.382	52.4	0.825	0.825	0.839	0.839
	HP_1	0.902	0.382	52.4	0.825	0.825	0.839	0.839
	HP_2	0.736	0.226	55.5	0.606	0.607	0.629	0.720
	HP_3	0.673	0.182	56.4	0.529	0.530	0.552	0.686
				$(n_1, n_2, m_1, m_2) = (20, 20, 20, 20)$				
1	HP	0.026	0.005	79.8	0.033	0.033	0.029	0.029
	HP_1	0.026	0.005	79.8	0.033	0.033	0.029	0.029
	HP_2	0.022	0.003	79.9	0.020	0.021	0.019	0.025
	HP_3	0.021	0.003	79.9	0.018	0.019	0.018	0.022
1.27	HP	0.501	0.068	77.3	0.420	0.420	0.451	0.451
	HP_1	0.501	0.068	77.3	0.420	0.420	0.451	0.451
	HP_2	0.338	0.040	78,4	0.257	0.258	0.282	0.363
	HP_3	0.291	0.032	78.7	0.221	0.221	0.239	0.339
1.52	HP	0.912	0.260	69.6	0.854	0.854	0.878	0.878
	HP_1	0.912	0.260	69.6	0.854	0.854	0.878	0.878
	HP_2	0.736	0.134	74.6	0.632	0.633	0.665	0.790
	HP_3	0.672	0.110	75.6	0.555	0.556	0.591	0.759

Table 3: Size and power for the uniform distribution.

				Two stage				
				Fisher combination			Liptak combination	
θ	Test 1st stage	One stage	Prob (rej. 1st stage)	Average s. size	Same	Adaptive	Same	Adaptive
				$(n_1, n_2, m_1, m_2) = (10, 10, 10, 10)$				
1	HP	0.024	0.004	39.9	0.024	0.024	0.022	0.022
	HP_1	0.024	0.004	39.9	0.024	0.024	0.022	0.022
	HP_2	0.021	0.002	40.0	0.014	0.014	0.015	0.019
	HP_3	0.018	0.001	40.0	0.011	0.012	0.012	0.017
1.4	HP	0.503	0.045	39.1	0.350	0.350	0.390	0.390
	HP_1	0.503	0.045	39.1	0.350	0.350	0.390	0.390
	HP_2	0.294	0.024	39.5	0.191	0.191	0.212	0.299
	HP_3	0.255	0.021	39.6	0.148	0.148	0.165	0.269
1.85	HP	0.901	0.153	36.9	0.772	0.772	0.813	0.813
	HP_1	0.901	0.153	36.9	0.772	0.772	0.813	0.813
	HP_2	0.697	0.084	38.3	0.523	0.523	0.567	0.694
	HP_3	0.627	0.064	38.7	0.432	0.432	0.477	0.651
				$(n_1, n_2, m_1, m_2) = (10, 10, 20, 20)$				
1	HP	0.029	0.003	59.9	0.029	0.029	0.029	0.029
	HP_1	0.029	0.003	59.9	0.029	0.029	0.029	0.029
	HP_2	0.024	0.002	59.9	0.019	0.019	0.022	0.024
	HP_3	0.022	0.002	59.9	0.017	0.017	0.018	0.022
1.27	HP	0.490	0.022	59.1	0.363	0.363	0.386	0.386
	HP_1	0.490	0.022	59.1	0.363	0.363	0.386	0.386
	HP_2	0.272	0.012	59.5	0.183	0.184	0.203	0.301
	HP_3	0.230	0.009	59.6	0.148	0.150	0.163	0.280
1.55	HP	0.892	0.075	57.0	0.788	0.788	0.805	0.805
	HP_1	0.892	0.075	57.0	0.788	0.788	0.805	0.805
	HP_2	0.656	0.041	58.4	0.529	0.529	0.552	0.716
	HP_3	0.592	0.033	58.7	0.448	0.448	0.470	0.683
				$(n_1, n_2, m_1, m_2) = (20, 20, 10, 10)$				
1	HP	0.028	0.006	59.9	0.028	0.028	0.025	0.025
	HP_1	0.028	0.006	59.9	0.028	0.028	0.025	0.025
	HP_2	0.021	0.003	59.9	0.019	0.020	0.018	0.024
	HP_3	0.020	0.003	59.9	0.016	0.017	0.015	0.024
1.27	HP	0.509	0.096	58.1	0.374	0.374	0.397	0.397
	HP_1	0.509	0.096	58.1	0.374	0.374	0.397	0.397
	HP_2	0.286	0.047	59.1	0.195	0.195	0.213	0.279
	HP_3	0.245	0.037	59.3	0.160	0.162	0.171	0.257
1.55	HP	0.891	0.360	52.8	0.791	0.791	0.807	0.807
	HP_1	0.891	0.360	52.8	0.791	0.791	0.807	0.807
	HP_2	0.657	0.175	56.5	0.515	0.515	0.541	0.658
	HP_3	0.590	0.137	57.3	0.430	0.430	0.454	0.611
				$(n_1, n_2, m_1, m_2) = (20, 20, 20, 20)$				
1	HP	0.028	0.004	79.8	0.026	0.026	0.027	0.027
	HP_1	0.028	0.004	79.8	0.026	0.026	0.027	0.027
	HP_2	0.023	0.003	79.9	0.018	0.018	0.021	0.026
	HP_3	0.021	0.003	79.9	0.016	0.016	0.017	0.025
1.22	HP	0.502	0.065	77.4	0.389	0.389	0.419	0.419
	HP_1	0.502	0.065	77.4	0.389	0.389	0.419	0.419
	HP_2	0.264	0.031	78.8	0.198	0.200	0.217	0.312
	HP_3	0.227	0.023	79.1	0.164	0.167	0.180	0.286
1.43	HP	0.909	0.236	70.5	0.818	0.818	0.843	0.843
	HP_1	0.909	0.236	70.5	0.818	0.818	0.843	0.843
	HP_2	0.645	0.112	75.5	0.537	0.538	0.573	0.726
	HP_3	0.573	0.087	76.5	0.461	0.462	0.496	0.691

Table 4: Size and power for the normal distribution.

				Two stage				
				Fisher combination			Liptak combination	
θ	Test 1st stage	One stage	Prob (rej. 1st stage)	Average s. size	Same	Adaptive	Same	Adaptive
				$(n_1, n_2, m_1, m_2) = (10, 10, 10, 10)$				
1	HP	0.029	0.005	39.9	0.033	0.033	0.031	0.031
	HP_1	0.029	0.005	39.9	0.033	0.033	0.031	0.031
	HP_2	0.022	0.003	39.9	0.023	0.023	0.022	0.029
	HP_3	0.020	0.003	39.9	0.019	0.019	0.019	0.025
1.65	HP	0.506	0.055	38.9	0.425	0.425	0.463	0.463
	HP_1	0.507	0.055	38.9	0.425	0.425	0.463	0.463
	HP_2	0.361	0.029	39.4	0.276	0.277	0.308	0.389
	HP_3	0.323	0.025	39.5	0.226	0.227	0.253	0.357
2.35	HP	0.900	0.193	36.1	0.827	0.827	0.857	0.857
	HP_1	0.904	0.193	36.1	0.827	0.827	0.858	0.857
	HP_2	0.775	0.109	37.8	0.655	0.655	0.693	0.778
	HP_3	0.719	0.091	38.2	0.565	0.565	0.614	0.751
				$(n_1, n_2, m_1, m_2) = (10, 10, 20, 20)$				
1	HP	0.029	0.005	59.8	0.034	0.034	0.031	0.030
	HP_1	0.028	0.005	59.8	0.033	0.033	0.030	0.030
	HP_2	0.026	0.003	59.9	0.022	0.022	0.022	0.026
	HP_3	0.023	0.002	59.9	0.019	0.021	0.020	0.024
1.45	HP	0.475	0.031	58.7	0.407	0.407	0.431	0.431
	HP_1	0.476	0.031	58.7	0.407	0.407	0.431	0.431
	HP_2	0.352	0.016	59.4	0.274	0.276	0.296	0.372
	HP_3	0.320	0.014	59.4	0.229	0.232	0.253	0.345
1.9	HP	0.891	0.098	56.1	0.835	0.835	0.850	0.853
	HP_1	0.892	0.098	56.1	0.837	0.837	0.853	0.853
	HP_2	0.758	0.053	57.9	0.658	0.658	0.685	0.790
	HP_3	0.708	0.045	58.2	0.588	0.589	0.616	0.765
				$(n_1, n_2, m_1, m_2) = (20, 20, 10, 10)$				
1	HP	0.028	0.003	59.9	0.027	0.027	0.028	0.028
	HP_1	0.028	0.003	59.9	0.028	0.027	0.027	0.028
	HP_2	0.021	0.003	59.9	0.020	0.021	0.022	0.025
	HP_3	0.021	0.002	60.0	0.018	0.019	0.020	0.024
1.45	HP	0.487	0.102	58.0	0.407	0.407	0.440	0.437
	HP_1	0.487	0.102	58.0	0.407	0.407	0.441	0.439
	HP_2	0.360	0.061	58.8	0.286	0.287	0.310	0.363
	HP_3	0.327	0.050	59.0	0.240	0.240	0.262	0.343
1.9	HP	0.885	0.364	52.7	0.827	0.827	0.841	0.838
	HP_1	0.886	0.366	52.7	0.829	0.829	0.844	0.840
	HP_2	0.749	0.233	55.3	0.646	0.647	0.680	0.755
	HP_3	0.702	0.195	56.1	0.583	0.584	0.608	0.721
				$(n_1, n_2, m_1, m_2) = (20, 20, 20, 20)$				
1	HP	0.029	0.006	79.8	0.035	0.035	0.034	0.034
	HP_1	0.029	0.006	79.8	0.034	0.034	0.033	0.034
	HP_2	0.025	0.003	79.9	0.023	0.023	0.023	0.028
	HP_3	0.023	0.002	79.9	0.020	0.020	0.021	0.027
1.4	HP	0.530	0.083	76.7	0.465	0.465	0.494	0.493
	HP_1	0.531	0.083	76.7	0.467	0.467	0.495	0.493
	HP_2	0.380	0.048	78.1	0.326	0.326	0.354	0.424
	HP_3	0.351	0.039	78.4	0.282	0.282	0.310	0.401
1.75	HP	0.907	0.272	69.1	0.861	0.861	0.881	0.880
	HP_1	0.908	0.273	69.1	0.862	0.862	0.884	0.880
	HP_2	0.782	0.166	73.4	0.716	0.716	0.741	0.822
	HP_3	0.736	0.142	74.3	0.658	0.658	0.693	0.800

Table 5: Size and power for the double exponential distribution.

				Two stage				
				Fisher combination			Liptak combination	
θ	Test 1st stage	One stage	Prob (rej. 1st stage)	Average s. size	Same	Adaptive	Same	Adaptive
				$(n_1, n_2, m_1, m_2) = (10, 10, 10, 10)$				
1	HP	0.033	0.004	39.9	0.033	0.033	0.032	0.032
	HP_1	0.031	0.004	39.9	0.033	0.033	0.032	0.032
	HP_2	0.023	0.002	40.0	0.020	0.020	0.023	0.027
	HP_3	0.023	0.002	40.0	0.017	0.017	0.017	0.025
2.1	HP	0.492	0.067	38.7	0.445	0.445	0.484	0.483
	HP_1	0.513	0.066	38.7	0.446	0.446	0.484	0.484
	HP_2	0.420	0.037	39.3	0.322	0.323	0.363	0.422
	HP_3	0.384	0.032	39.4	0.268	0.269	0.307	0.392
3.7	HP	0.891	0.246	35.1	0.881	0.881	0.901	0.900
	HP_1	0.930	0.246	35.1	0.883	0.883	0.904	0.901
	HP_2	0.851	0.143	37.1	0.751	0.751	0.791	0.855
	HP_3	0.817	0.120	37.6	0.682	0.682	0.726	0.831
				$(n_1, n_2, m_1, m_2) = (10, 10, 20, 20)$				
1	HP	0.027	0.004	59.8	0.027	0.027	0.031	0.029
	HP_1	0.025	0.004	59.8	0.026	0.026	0.029	0.029
	HP_2	0.022	0.003	59.9	0.021	0.021	0.023	0.023
	HP_3	0.021	0.002	59.9	0.020	0.021	0.019	0.021
1.8	HP	0.518	0.044	58.2	0.481	0.482	0.504	0.516
	HP_1	0.547	0.044	58.2	0.493	0.493	0.519	0.517
	HP_2	0.456	0.028	58.9	0.379	0.379	0.409	0.462
	HP_3	0.429	0.021	59.2	0.334	0.336	0.360	0.438
2.7	HP	0.919	0.164	53.4	0.903	0.903	0.917	0.930
	HP_1	0.949	0.164	53.4	0.924	0.924	0.932	0.930
	HP_2	0.898	0.097	56.1	0.839	0.839	0.858	0.901
	HP_3	0.869	0.079	56.8	0.787	0.787	0.813	0.883
				$(n_1, n_2, m_1, m_2) = (20, 20, 10, 10)$				
1	HP	0.037	0.005	59.9	0.039	0.039	0.041	0.038
	HP_1	0.035	0.005	59.9	0.037	0.037	0.040	0.037
	HP_2	0.030	0.004	59.9	0.029	0.030	0.030	0.032
	HP_3	0.027	0.004	59.9	0.025	0.025	0.027	0.030
1.8	HP	0.517	0.147	57.1	0.473	0.473	0.497	0.477
	HP_1	0.549	0.151	57.0	0.491	0.491	0.513	0.487
	HP_2	0.454	0.103	57.9	0.386	0.386	0.408	0.439
	HP_3	0.424	0.087	58.3	0.341	0.341	0.367	0.417
2.7	HP	0.922	0.486	50.3	0.906	0.907	0.917	0.898
	HP_1	0.948	0.525	49.5	0.927	0.927	0.936	0.921
	HP_2	0.901	0.403	51.9	0.841	0.841	0.860	0.879
	HP_3	0.875	0.348	53.0	0.796	0.796	0.817	0.860
				$(n_1, n_2, m_1, m_2) = (20, 20, 20, 20)$				
1	HP	0.031	0.005	79.8	0.034	0.034	0.034	0.031
	HP_1	0.031	0.004	79.8	0.031	0.031	0.032	0.031
	HP_2	0.026	0.003	79.9	0.026	0.026	0.027	0.026
	HP_3	0.025	0.002	79.9	0.023	0.023	0.024	0.026
1.62	HP	0.493	0.101	75.9	0.478	0.479	0.503	0.494
	HP_1	0.534	0.100	76.0	0.495	0.495	0.526	0.502
	HP_2	0.446	0.071	77.2	0.400	0.401	0.427	0.451
	HP_3	0.418	0.063	77.5	0.369	0.369	0.394	0.434
2.35	HP	0.888	0.327	66.9	0.880	0.880	0.896	0.888
	HP_1	0.930	0.344	66.2	0.903	0.903	0.920	0.906
	HP_2	0.869	0.249	70.0	0.826	0.827	0.850	0.873
	HP_3	0.843	0.216	71.4	0.788	0.789	0.817	0.861

Table 6: Size and power for the t_2 distribution.

				Two stage				
				Fisher combination			Liptak combination	
θ	Test 1st stage	One stage	Prob (rej. 1st stage)	Average s. size	Same	Adaptive	Same	Adaptive
				$(n_1, n_2, m_1, m_2) = (10, 10, 10, 10)$				
1	HP	0.029	0.005	39.9	0.031	0.031	0.032	0.030
	HP_1	0.027	0.005	39.9	0.028	0.028	0.030	0.029
	HP_2	0.024	0.002	40.0	0.020	0.020	0.022	0.024
	HP_3	0.023	0.002	40.0	0.016	0.016	0.017	0.022
2.1	HP	0.471	0.074	38.5	0.445	0.444	0.471	0.463
	HP_1	0.476	0.075	38.5	0.444	0.444	0.468	0.463
	HP_2	0.450	0.043	39.1	0.355	0.355	0.394	0.422
	HP_3	0.425	0.036	39.3	0.311	0.311	0.344	0.397
3.75	HP	0.906	0.274	34.5	0.874	0.874	0.891	0.884
	HP_1	0.893	0.277	34.5	0.872	0.872	0.890	0.884
	HP_2	0.902	0.174	36.5	0.806	0.806	0.840	0.860
	HP_3	0.879	0.145	37.1	0.743	0.743	0.789	0.841
				$(n_1, n_2, m_1, m_2) = (10, 10, 20, 20)$				
1	HP	0.027	0.004	59.8	0.030	0.030	0.030	0.031
	HP_1	0.025	0.004	59.8	0.030	0.030	0.030	0.030
	HP_2	0.024	0.000	60.0	0.020	0.020	0.024	0.024
	HP_3	0.023	0.001	60.0	0.018	0.018	0.021	0.021
1.85	HP	0.498	0.047	58.1	0.463	0.463	0.485	0.479
	HP_1	0.484	0.048	58.1	0.458	0.458	0.479	0.475
	HP_2	0.489	0.029	58.8	0.404	0.404	0.436	0.446
	HP_3	0.466	0.024	59.0	0.362	0.363	0.392	0.422
2.75	HP	0.897	0.147	54.1	0.852	0.852	0.859	0.856
	HP_1	0.864	0.149	54.0	0.841	0.842	0.854	0.853
	HP_2	0.895	0.092	56.3	0.826	0.826	0.849	0.845
	HP_3	0.877	0.076	56.9	0.788	0.788	0.813	0.827
				$(n_1, n_2, m_1, m_2) = (20, 20, 10, 10)$				
1	HP	0.030	0.005	59.9	0.034	0.033	0.033	0.028
	HP_1	0.030	0.006	59.9	0.032	0.032	0.032	0.028
	HP_2	0.026	0.003	59.9	0.021	0.022	0.023	0.024
	HP_3	0.024	0.003	59.9	0.018	0.018	0.019	0.023
1.85	HP	0.505	0.128	57.4	0.456	0.456	0.476	0.451
	HP_1	0.480	0.132	57.4	0.450	0.450	0.471	0.437
	HP_2	0.497	0.109	57.8	0.408	0.408	0.436	0.441
	HP_3	0.473	0.096	58.1	0.367	0.367	0.395	0.424
2.75	HP	0.899	0.413	51.7	0.855	0.855	0.866	0.853
	HP_1	0.867	0.427	51.5	0.848	0.848	0.860	0.843
	HP_2	0.899	0.378	52.4	0.827	0.827	0.849	0.849
	HP_3	0.876	0.343	53.1	0.786	0.786	0.807	0.833
				$(n_1, n_2, m_1, m_2) = (20, 20, 20, 20)$				
1	HP	0.025	0.004	79.8	0.031	0.031	0.030	0.028
	HP_1	0.029	0.004	79.8	0.033	0.033	0.032	0.027
	HP_2	0.025	0.003	79.9	0.021	0.022	0.022	0.023
	HP_3	0.026	0.002	79.9	0.020	0.020	0.020	0.021
1.65	HP	0.470	0.079	76.9	0.434	0.434	0.457	0.442
	HP_1	0.443	0.082	76.7	0.430	0.430	0.444	0.444
	HP_2	0.466	0.065	77.4	0.406	0.406	0.437	0.433
	HP_3	0.444	0.059	77.7	0.373	0.374	0.407	0.419
2.3	HP	0.881	0.277	68.9	0.850	0.850	0.867	0.861
	HP_1	0.839	0.294	68.2	0.827	0.827	0.846	0.852
	HP_2	0.880	0.250	70.0	0.834	0.834	0.858	0.858
	HP_3	0.865	0.218	71.3	0.802	0.802	0.837	0.848

Table 7: Size and power for the χ^2 distribution.

				Two stage				
				Fisher combination			Liptak combination	
θ	Test 1st stage	One stage	Prob (rej. 1st stage)	Average s. size	Same	Adaptive	Same	Adaptive
				$(n_1, n_2, m_1, m_2) = (10, 10, 10, 10)$				
1	HP	0.028	0.006	39.9	0.032	0.032	0.030	0.030
	HP_1	0.028	0.006	39.9	0.032	0.032	0.030	0.030
	HP_2	0.024	0.003	39.9	0.020	0.021	0.021	0.025
	HP_3	0.022	0.003	39.9	0.016	0.017	0.017	0.025
1.77	HP	0.515	0.035	39.3	0.436	0.436	0.478	0.478
	HP_1	0.519	0.035	39.3	0.436	0.436	0.479	0.478
	HP_2	0.380	0.018	39.6	0.264	0.264	0.316	0.400
	HP_3	0.335	0.013	39.7	0.209	0.209	0.252	0.368
2.6	HP	0.895	0.125	37.5	0.840	0.840	0.867	0.868
	HP_1	0.907	0.125	37.5	0.840	0.840	0.868	0.868
	HP_2	0.776	0.062	38.8	0.613	0.613	0.685	0.787
	HP_3	0.710	0.046	39.1	0.516	0.516	0.586	0.750
				$(n_1, n_2, m_1, m_2) = (10, 10, 20, 20)$				
1	HP	0.030	0.006	59.8	0.037	0.037	0.036	0.036
	HP_1	0.030	0.006	59.8	0.037	0.037	0.036	0.036
	HP_2	0.029	0.004	59.9	0.028	0.029	0.029	0.028
	HP_3	0.027	0.003	59.9	0.024	0.025	0.026	0.026
1.55	HP	0.496	0.024	59.0	0.433	0.433	0.461	0.461
	HP_1	0.495	0.024	59.0	0.434	0.434	0.462	0.461
	HP_2	0.379	0.010	59.6	0.288	0.297	0.319	0.397
	HP_3	0.339	0.007	59.7	0.236	0.246	0.269	0.369
2.1	HP	0.888	0.060	57.6	0.841	0.840	0.858	0.860
	HP_1	0.892	0.060	57.6	0.846	0.846	0.861	0.860
	HP_2	0.784	0.029	58.9	0.680	0.683	0.717	0.808
	HP_3	0.737	0.021	59.2	0.600	0.603	0.641	0.783
				$(n_1, n_2, m_1, m_2) = (20, 20, 10, 10)$				
1	HP	0.023	0.004	59.9	0.029	0.029	0.030	0.029
	HP_1	0.022	0.003	59.9	0.028	0.028	0.030	0.029
	HP_2	0.024	0.004	59.9	0.019	0.019	0.019	0.025
	HP_3	0.022	0.003	59.9	0.015	0.015	0.016	0.023
1.55	HP	0.503	0.119	57.6	0.447	0.447	0.474	0.471
	HP_1	0.503	0.119	57.6	0.447	0.447	0.474	0.472
	HP_2	0.383	0.053	58.9	0.291	0.291	0.331	0.398
	HP_3	0.344	0.039	59.2	0.238	0.238	0.275	0.373
2.1	HP	0.883	0.370	52.6	0.840	0.840	0.851	0.846
	HP_1	0.886	0.377	52.5	0.847	0.847	0.857	0.850
	HP_2	0.779	0.186	56.3	0.680	0.680	0.719	0.782
	HP_3	0.739	0.145	57.1	0.601	0.601	0.644	0.751
				$(n_1, n_2, m_1, m_2) = (20, 20, 20, 20)$				
1	HP	0.027	0.003	79.9	0.028	0.029	0.029	0.030
	HP_1	0.027	0.003	79.9	0.028	0.028	0.029	0.030
	HP_2	0.022	0.002	79.9	0.021	0.021	0.023	0.027
	HP_3	0.021	0.002	79.9	0.018	0.018	0.020	0.025
1.47	HP	0.510	0.081	76.8	0.469	0.469	0.499	0.498
	HP_1	0.511	0.081	76.8	0.471	0.471	0.502	0.498
	HP_2	0.392	0.040	78.4	0.334	0.335	0.373	0.427
	HP_3	0.359	0.029	78.8	0.290	0.290	0.327	0.405
1.9	HP	0.906	0.277	68.9	0.873	0.873	0.893	0.892
	HP_1	0.908	0.280	68.8	0.878	0.878	0.899	0.894
	HP_2	0.818	0.132	74.7	0.741	0.741	0.784	0.843
	HP_3	0.781	0.101	75.9	0.684	0.684	0.730	0.820

Table 8: Size and power for the exponential distribution.

				Two stage				
				Fisher combination			Liptak combination	
θ	Test 1st stage	One stage	Prob (rej. 1st stage)	Average s. size	Same	Adaptive	Same	Adaptive
				$(n_1, n_2, m_1, m_2) = (10, 10, 10, 10)$				
1	HP	0.035	0.006	39.9	0.035	0.035	0.034	0.034
	HP_1	0.032	0.006	39.9	0.034	0.035	0.034	0.034
	HP_2	0.026	0.003	39.9	0.026	0.026	0.026	0.030
	HP_3	0.025	0.003	39.9	0.021	0.021	0.022	0.028
2.1	HP	0.500	0.054	38.9	0.447	0.447	0.491	0.490
	HP_1	0.506	0.054	38.9	0.447	0.447	0.492	0.491
	HP_2	0.398	0.030	39.4	0.310	0.311	0.350	0.413
	HP_3	0.355	0.021	39.6	0.250	0.252	0.294	0.385
3.7	HP	0.907	0.158	36.8	0.875	0.875	0.897	0.896
	HP_1	0.925	0.158	36.8	0.877	0.877	0.898	0.897
	HP_2	0.837	0.099	38.0	0.718	0.719	0.776	0.847
	HP_3	0.791	0.072	38.6	0.634	0.635	0.698	0.818
				$(n_1, n_2, m_1, m_2) = (10, 10, 20, 20)$				
1	HP	0.037	0.005	59.8	0.038	0.038	0.038	0.037
	HP_1	0.036	0.005	59.8	0.037	0.037	0.036	0.036
	HP_2	0.028	0.003	59.9	0.027	0.027	0.029	0.034
	HP_3	0.025	0.002	59.9	0.023	0.023	0.025	0.031
1.8	HP	0.499	0.035	58.6	0.445	0.445	0.474	0.478
	HP_1	0.503	0.035	58.6	0.447	0.447	0.479	0.478
	HP_2	0.405	0.022	59.1	0.344	0.345	0.377	0.433
	HP_3	0.376	0.016	59.3	0.297	0.298	0.330	0.410
2.7	HP	0.894	0.094	56.2	0.859	0.859	0.871	0.873
	HP_1	0.901	0.094	56.2	0.869	0.869	0.876	0.874
	HP_2	0.819	0.057	57.7	0.752	0.752	0.775	0.834
	HP_3	0.782	0.039	58.4	0.693	0.694	0.723	0.815
				$(n_1, n_2, m_1, m_2) = (20, 20, 10, 10)$				
1	HP	0.038	0.005	59.9	0.039	0.039	0.038	0.037
	HP_1	0.034	0.004	59.9	0.037	0.037	0.035	0.035
	HP_2	0.030	0.003	59.9	0.027	0.027	0.029	0.028
	HP_3	0.029	0.002	60.0	0.022	0.022	0.024	0.027
1.8	HP	0.503	0.111	57.8	0.447	0.447	0.475	0.465
	HP_1	0.508	0.112	57.8	0.451	0.451	0.478	0.469
	HP_2	0.401	0.066	58.7	0.338	0.338	0.364	0.408
	HP_3	0.369	0.052	59.0	0.286	0.287	0.318	0.386
2.7	HP	0.885	0.366	52.7	0.841	0.841	0.858	0.849
	HP_1	0.898	0.379	52.4	0.850	0.850	0.869	0.854
	HP_2	0.805	0.242	55.2	0.731	0.731	0.759	0.802
	HP_3	0.776	0.196	56.1	0.676	0.676	0.704	0.780
				$(n_1, n_2, m_1, m_2) = (20, 20, 20, 20)$				
1	HP	0.035	0.005	79.8	0.037	0.037	0.037	0.035
	HP_1	0.034	0.005	79.8	0.035	0.034	0.034	0.034
	HP_2	0.028	0.004	79.9	0.026	0.026	0.028	0.031
	HP_3	0.027	0.003	79.9	0.026	0.026	0.025	0.029
1.62	HP	0.471	0.070	77.2	0.430	0.430	0.462	0.453
	HP_1	0.481	0.072	77.1	0.434	0.434	0.468	0.458
	HP_2	0.374	0.046	78.2	0.330	0.330	0.365	0.405
	HP_3	0.352	0.036	78.5	0.295	0.295	0.329	0.387
2.35	HP	0.894	0.272	69.1	0.866	0.866	0.885	0.880
	HP_1	0.909	0.279	68.8	0.878	0.878	0.898	0.888
	HP_2	0.823	0.181	72.7	0.781	0.782	0.814	0.847
	HP_3	0.793	0.148	74.1	0.741	0.742	0.777	0.836

Nonlinear mixed Effects models: Approximations of the Fisher Information and Design

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Abstract: The problem of the missing closed form representation of the probability density of the observations in nonlinear mixed effects models carries forward to the calculation of the Fisher information. Linearizations of the response function are often applied for approximating the underlying statistical model. The impact of different linearizations on the design of experiments will be briefly discussed in this article and an alternative motivation for an approximation of the Fisher information will be presented. The different results will be illustrated in the example of a simple population pharmacokinetic model.

Keywords: Fisher information, mixed effects models, nonlinear models, optimal design.

1 Introduction

Mixed effects models are often applied for the analysis of grouped data. The difference of observations of different groups are in these models assumed to depend on observation errors and group wise varying parameter vectors. Specially in pharmacological studies each individual can be interpreted as a single group and insight in the population behavior can be obtained by modeling the individual parameter vectors as identically distributed random variables. Nonlinear mixed effects models are in the literature often described under the assumption of normally distributed random effects. Estimators based on weighted sums of squares (e.g. Pinheiro and Bates (2000)) or on stochastic approximations (e.g. Kuhn and Lavielle (2001)) are proposed for the analysis of the population behavior, as no closed form representation of the likelihood function in these models exists. The used estimators are typically assumed to be consistent with an information matrix behaving as in linear mixed effects models or nonlinear models with heteroscedastic normal errors. However, the limitations of the stochastic behavior of some estimators were discussed on the monoexponential model by Demidenko (2005). Linearized models build the foundation for experimental designs in nonlinear mixed effects models. The different linearization approaches yield distinct information matrices, such that the approximations might have a big influence on the design of studies, as illustrated by Mielke and Schwabe (2010) in a simple example.
After introducing the mixed effects model in the second section, an alternative motivation of an approximation of the Fisher information, based on approximations of conditional moments, is presented in the third section. Designs in population studies are briefly defined in the fourth section, before an example of a pharmacokinetic model shows the influence of different approximations on the design in the fifth section.

2 Mixed effects models

In the mixed effects models, the j-th observation of the i-th individual under experimental setting $x_{ij} \in \mathcal{X}$ is with a response function η described by

$$Y_{ij} = \eta(\beta_i, x_{ij}) + \epsilon_{ij},$$

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with an individual parameter vector $\beta_i \in \mathbb{R}^p$ and real valued observation errors ϵ_{ij}. The response function η is assumed to be differentiable in β_i and continuous on the compact design space $\mathcal{X}$. The m_i dimensional observation vector Y_i is for given individual parameter vectors β_i with the exact individual design

$$\xi_i = (x_{i1}, ..., x_{im_i}) \text{ where } x_{ij} \in \mathcal{X},\ j = 1, ..., m_i$$

and the vector valued response function

$$\eta(\beta_i, \xi_i) := (\eta(\beta_i, x_{i1}), ..., \eta(\beta_i, x_{im_i}))^T,$$

assumed to be normally distributed:

$$Y_i \sim N(\eta(\beta_i, \xi_i), \sigma^2 I_{m_i}).$$

The inter-individual variation is induced by the individual wise varying parameter vectors β_i which are assumed to be realizations of normally distributed random variables:

$$\beta_i \sim N(\beta, \sigma^2 D).$$

The observation errors $\epsilon_i = (\epsilon_{i1}, ..., \epsilon_{im_i})$ and individual parameter vectors β_i are assumed to be independent and observations of different individuals are considered to be stochastically independent as well. Throughout this article we assume the variance parameter $\theta = (\sigma^2, D)$ to be known and the matrix D to be positive definite.
The likelihood of observations y_i results in integral form in

$$L(\beta; y_i, \theta) := f_{Y_i}(y_i) = \int_{\mathbb{R}^p} \phi_{Y_i|\beta_i}(y_i)\phi_{\beta_i}(\beta_i)d\beta_i,$$

where the influence of the parameters β and θ on the likelihood is contained in the normal densities

$$\begin{aligned} \phi_{Y_i|\beta_i}(y_i) &= \sqrt{2\pi\sigma^2}^{-m_i} \exp[-\frac{1}{2\sigma^2}(y_i - \eta(\beta_i, \xi_i))^T(y_i - \eta(\beta_i, \xi_i))] \\ \phi_{\beta_i}(\beta_i) &= \sqrt{2\pi\sigma^2}^{-p} \sqrt{\| D \|}^{-1} \exp[-\frac{1}{2\sigma^2}(\beta_i - \beta)^T D^{-1}(\beta_i - \beta)], \end{aligned}$$

with $\| \cdot \|$ denoting the determinant. For nonlinear response functions η, the likelihood function cannot be written in a closed from. To circumvent this problem, the model is transformed by a linearization of the response function as described by Retout and Mentré (2003). With a design matrix defined as

$$F_\beta := \frac{\partial \eta(\beta_i, \xi_i)}{\partial \beta_i^T}|_{\beta_i = \beta}$$

follows for a linearization in the true population mean β and under the assumption of negligible linearization errors:

$$Y_i = \eta(\beta, \xi_i) + F_\beta(\beta_i - \beta) + \epsilon_i.$$

The distribution assumptions on β_i and the observation error vector ϵ_i imply normally distributed vectors of observations with heteroscedastic errors:

$$Y_i \sim N(\eta(\beta, \xi_i), \sigma^2[I_{m_i} + F_\beta D F_\beta^T]).$$

Under the assumption of negligible linearization errors, a linear mixed effects model is obtained, when alternatively linearizing the response function in some point β_0:

$$Y_i \sim N(\eta(\beta_0, \xi_i) + F_{\beta_0}(\beta - \beta_0), \sigma^2[I_{m_i} + F_{\beta_0} D F_{\beta_0}^T]).$$

Both linearizations yield for linear response functions η the true linear mixed effects model, as $F_\beta = F_{\beta_0}$ is then independent of β. Note that the information matrices in heteroscedastic normal and linear mixed effects models are distinct. The linearization in the true population mean under the assumption of negligible linearization errors yields with $V_\beta := I_{m_i} + F_\beta D F_\beta^T$:

$$\mathbf{M}_{1,\beta}(\xi_i) := \frac{1}{\sigma^2} F_\beta^T V_\beta^{-1} F_\beta + \frac{1}{2} S,$$

where $S \geq 0$, with

$$S_{j,k} = \text{tr } [V_\beta^{-1} \frac{\partial V_\beta}{\partial \beta_j} V_\beta^{-1} \frac{\partial V_\beta}{\partial \beta_k}], \; j,k = 1, ..., p,$$

as approximation of the Fisher information, whereas the information resulting from a linearization in a point β_0 is of the form

$$\mathbf{M}_{2,\beta}(\xi_i) := \frac{1}{\sigma^2} F_{\beta_0}^T V_{\beta_0}^{-1} F_{\beta_0},$$

such that specially for $\beta_0 = \beta$ additional information is drawn by $\mathbf{M}_{1,\beta}$ from the variance structure of the observations. This difference in the information matrices was discussed by Mielke and Schwabe (2010) in an example with the result that the additional matrix term S in some situations might misleadingly generate information.

3 Approximation of the Fisher information

Alternatively the Fisher information can be directly computed as the covariance of the score function. The score function is obtained as in Mielke (2011) by

$$\frac{\partial l(\beta; y_i, \theta)}{\partial \beta} = \frac{1}{\sigma^2} D^{-1}(E(\beta_i | Y_i = y_i) - \beta),$$

with the log-likelihood function $l(\beta; y_i, \theta) := \log(L(\beta; y_i, \theta))$. The Fisher information can hence be written in the form

$$\begin{aligned} \mathfrak{M}_\beta(\xi_i) &= E\left(\frac{\partial l(\beta; Y_i, \theta)}{\partial \beta} \frac{\partial l(\beta; Y_i, \theta)}{\partial \beta^T}\right) \\ &= \frac{1}{\sigma^2} D^{-1} - \frac{1}{\sigma^4} D^{-1} E(Var(\beta_i | Y_i)) D^{-1}, \end{aligned}$$

since with the distributional assumptions on the individual parameter vector β_i follows

$$Var(\beta_i) = E(Var(\beta_i | Y_i)) + Var(E(\beta_i | Y_i)) = \sigma^2 D,$$

such that apporixmations of the Fisher information result as approximations of the expectation of the conditional variance. For limited numbers of possible experimental settings, small individual sample sizes m_i and low dimensional parameter vectors β, the Fisher information can then be approximated using quadrature rules or Monte-Carlo methods. Generally the computational burden for approximating the dependence of the Fisher information on the experimental settings

will already for relatively small sample sizes and small dimensions of β be very high, such that analytical approximations are of interest. Tierney and Kadane (1986) propose fully exponential Laplace approximations for approximating posterior moments. Therefor a second order Taylor approach in the minimizing argument β_i^* of the penalized least squares term

$$\tilde{l}(\beta_i; y_i, \beta, \theta) := (y_i - \eta(\beta_i, \xi_i))^T (y_i - \eta(\beta_i, \xi_i)) + (\beta_i - \beta)^T D^{-1} (\beta_i - \beta)$$

is applied for approximating the occurring integrals. The nonlinear response function η implies a nonlinear dependence of the support point β_i^* of the Taylor approach on the observation vector y_i, such that approximations of the expectation of the conditional variance cannot be obtained without yet another level of approximations. Similarly Mielke (2011) suggests the approximation of the conditional density of β_i for given observation y_i

$$f_{\beta_i|Y_i=y_i}(\beta_i) := \frac{\phi_{Y_i|\beta_i}(y_i)\phi_{\beta_i}(\beta_i)}{f_{Y_i}(y_i)} \tag{1}$$

by approximations to the denominator integral and an according approximation to the numerator with a first order Taylor approach in the response function η. In dependence of the support point $\hat{\beta}$ of the Taylor approach, the resulting density is then approximated by a normal density:

$$\begin{aligned} \beta_i|_{Y_i=y_i} &\overset{app.}{\sim} N(\mu(y_i, \hat{\beta}_i, \beta), \sigma^2 M_{\hat{\beta}_i}^{-1}), \text{ with} \\ \mu(y_i, \hat{\beta}_i, \beta) &:= M_{\hat{\beta}_i}^{-1}(F_{\hat{\beta}_i}^T (y_i - \eta(\hat{\beta}_i, \xi_i) + F_{\hat{\beta}_i}\hat{\beta}_i) + D^{-1}\beta) \text{ and} \\ M_{\hat{\beta}_i} &:= F_{\hat{\beta}_i}^T F_{\hat{\beta}_i} + D^{-1}. \end{aligned}$$

The big benefit of this approach is that approximations of the Fisher information in nonlinear mixed effects models can be directly deduced, as the approximation of the conditional variance not necessarily depends on the observations y_i. The Fisher information is in dependence of the support point of $\hat{\beta}$ with this approach approximated by

$$\mathbf{M}_{2,\beta}(\xi_i) := \frac{1}{\sigma^2} F_{\hat{\beta}}^T V_{\hat{\beta}}^{-1} F_{\hat{\beta}},$$

what corresponds for $\hat{\beta} = \beta_0$ to the linear mixed effects model approximation.

A more refined approximation of the information might however be obtained by taking the distribution of the observations into account:

$$\begin{aligned} E(Var(\beta_i|Y_i)) &= \int_{\mathbb{R}^{m_i}} Var(\beta_i|Y_i = y_i) \int_{\mathbb{R}^p} \phi_{Y_i|\beta_i}(y_i)\phi_{\beta_i}(\beta_i) d\beta_i dy_i \\ &= \int_{\mathbb{R}^p} \int_{\mathbb{R}^{m_i}} Var(\beta_i|Y_i = y_i)\phi_{Y_i|\beta_i}(y_i)\phi_{\beta_i}(\beta_i) dy_i d\beta_i \\ &\approx \int_{\mathbb{R}^p} \sigma^2 M_{\beta_i}^{-1} \phi_{\beta_i}(\beta_i) d\beta_i \\ &= \sigma^2 E(M_{\beta_i}^{-1}). \end{aligned}$$

where the approximation holds by the argument, that the solution of the penalized least squares problem should be not too far located from the true individual parameter vector, which is here β_i. Note however, that for this approximation the existence of the expectation has to be guaranteed. With similar transformations as for $\mathbf{M}_{2,\beta}$ the Fisher information can then be approximated by

$$\mathbf{M}_{3,\beta}(\xi_i) := \frac{1}{\sigma^2} E(F_{\beta_i}^T V_{\beta_i}^{-1} F_{\beta_i}).$$

Unfortunately this approximation generally cannot be written in a closed form, such that the expectation has to be calculated numerically. Note that the true Fisher information matrix is obtained for all presented approximations in the case of linear response functions η.

4 Design

The two stages of the mixed effects models carry forward to the design. Individual designs

$$\xi_i := (x_{i1}, ..., x_{im_i}) \text{ with } x_{ij} \in \mathcal{X}$$

describe the experimental settings for individuals, whereas the population designs summarize the proportions ω_i of individual designs ξ_i in the population:

$$\zeta := (\xi_1, ..., \xi_k, \omega_1, ..., \omega_k) \text{ with } \omega_i \geq 0, \ \sum_{i=1}^{k-1} \omega_i \leq 1 \ \text{ and } \ \omega_k = 1 - \sum_{i=1}^{k-1} \omega_i.$$

We here assume the numbers of observations per individual to be identical, such that $m_i = m$ for all $i = 1, ..., k$. Population designs ζ can hence be interpreted as approximate designs on the m-dimensional design space $\mathcal{X}^m$. The normalized population Fisher information matrix is with the independence of the observations of different individuals obtained as the weighted sum of the individual information matrices:

$$\mathfrak{M}_{pop,\beta}(\zeta) = \sum_{i=1}^{k} \omega_i \mathfrak{M}_\beta(\xi_i).$$

Target of the design optimization is the minimization of some real valued design criteria of the information matrix $\mathfrak{M}_{pop,\beta}$ with respect to populations designs ζ. We restrict ourselves in this article to the D-optimality criterion:

$$\Phi_D(\zeta) := -\log(\| \mathfrak{M}_{pop,\beta}(\zeta) \|),$$

as the content of the confidence ellipsoid for β is inverse proportional to the determinant of the information matrix. Results for other optimality criteria can be similarly deduced. The design optimization and the verification of optimal designs can be conducted with applications of Fedorov's equivalence theorem for designs of experiments in the case of simultaneous observations of several quantities (Fedorov (1972),p.211), yielding the sensitivity function

$$g_\zeta(\xi) \ := \ \text{tr } [\mathfrak{M}^{-1}_{pop,\beta}(\zeta)\mathfrak{M}_\beta(\xi)].$$

For the estimation of the p dimensional parameter vector β, a design ζ^* is hence D-optimal, if and only if

$$g_{\zeta^*}(\xi) \leq p \ \ \forall \xi \in \mathcal{X}^m$$

in the case of m observations per individual.

5 Example

We consider a one compartment model with first order absorption and the model structure as in Schmelter (2007), but with one observation at the time $x_i \in \mathcal{X} = [0.1, 24]$ per individual only:

$$Y_i = \frac{\beta_{1,i}}{\beta_{3,i}\beta_{1,i} - \beta_{2,i}} [\exp(-\frac{\beta_{2,i}}{\beta_{3,i}} x_i) - \exp(-\beta_{1,i} x_i)] \exp(\epsilon_i).$$

Numbers from some previous experiments were used for planning purposes for the population location parameter:

$$\beta = (\beta_1, \beta_2, \beta_3) = (0.61, 25, 88).$$

The random individual effects are here considered to enter the individual parameter vectors proportionally:

$$\beta_{j,i} = \beta_j \exp(b_{j,i}),\ j = 1,2,3 \ \text{ with } (b_{1,i}, b_{2,i}, b_{3,i}) \overset{iid}{\sim} N_3(0, \sigma^2 D),$$

with a known diagonal variance matrix $D = diag(89.3, 12.5, 9.0)$ and the observation errors ϵ_i are assumed to be normally distributed with a variance $\sigma^2 = 0.01$. The model can then be easily transformed in a nonlinear mixed effects model as introduced in the second section.

The optimal designs based on the approximations $\mathbf{M}_{1,\beta}$ and $\mathbf{M}_{2,\beta}$ were calculated with the use of the equivalence theorem:

$$\zeta_1^* = \begin{pmatrix} (3.10) & (5.18) & (24.00) \\ 0.61 & 0.08 & 0.31 \end{pmatrix} \text{ for } \mathbf{M}_{1,\beta} \text{ and}$$

$$\zeta_2^* = \begin{pmatrix} (0.10) & (4.18) & (24.00) \\ 0.33 & 0.33 & 0.33 \end{pmatrix} \text{ for } \mathbf{M}_{2,\beta}.$$

Simulations were applied in order to compute optimal designs for the approximation $\mathbf{M}_{3,\beta}$ and for the Fisher information $\mathfrak{M}_\beta$ and the dependences of the components of the information matrices on the experimental settings were approximated by using polynomial splines. Based on these approximations, the D-optimal designs:

$$\zeta_3^* = \begin{pmatrix} (2.85) & (24.00) \\ 0.59 & 0.41 \end{pmatrix} \text{ for } \mathbf{M}_{3,\beta} \text{ and}$$

$$\zeta_F^* = \begin{pmatrix} (2.32) & (6.40) & (24.00) \\ 0.61 & 0.01 & 0.38 \end{pmatrix} \text{ for } \mathfrak{M}_\beta$$

were obtained. The uniqueness of the D-optimal designs follows for the considered approximations with the structure of the sensitivity functions, which are illustrated in Figure1. Table 1

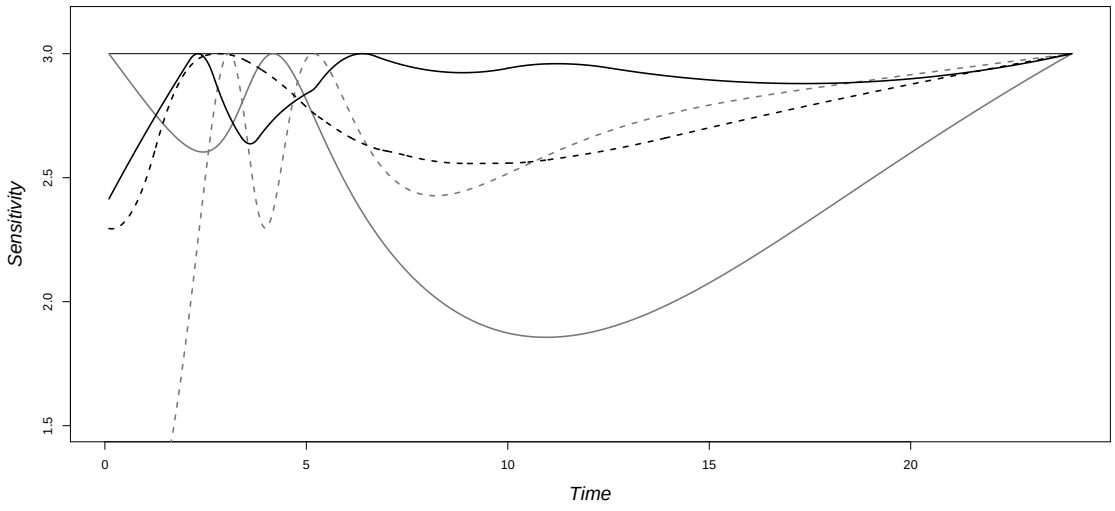

Figure 1: Sensitivity functions on the design region $\mathcal{X} = [0.1, 24]$.
Grey dashed: $\mathbf{M}_{1,\beta}$; Grey solid: $\mathbf{M}_{2,\beta}$; Black dashed: $\mathbf{M}_{3,\beta}$; Black solid: $\mathfrak{M}_\beta$.

shows the efficiency of the proposed designs for the different approximations. The efficiency of

designs is here defined by the terms

$$\delta_{\zeta_i^*}(\zeta) := \left(\frac{\| \mathbf{M}_{i,\beta}(\zeta) \|}{\| \mathbf{M}_{i,\beta}(\zeta_i^*) \|} \right)^{\frac{1}{3}}, \; i = 1, 2, 3; \quad \text{and} \quad \delta_{\zeta_F^*}(\zeta) := \left(\frac{\| \mathfrak{M}_{\beta}(\zeta) \|}{\| \mathfrak{M}_{\beta}(\zeta_F^*) \|} \right)^{\frac{1}{3}}.$$

The efficiency of all proposed designs is in relation to the simulation based approximation of the Fisher information relatively high. The similarity of the designs ζ_F^* for the Fisher information and ζ_3^* for the approximation $\mathbf{M}_{3,\beta}$ causes the high efficiency of 0.95. The efficiency of designs with respect to the often used linear mixed effects approximation $\mathbf{M}_{2,\beta}$ of the Fisher information is of special interest. The designs ζ_1^*, ζ_3^* and ζ_F^* are here relatively inefficient, what might be caused by the weights of the designs, and the missing observations on the left border of the design space. Note that the number of support points of the design ζ_3^* is smaller than the number of parameters of interest, such that the corresponding information matrix in terms of the linear mixed effects approximation is singular. The additional information of the approximation $\mathbf{M}_{1,\beta}$ was mentioned by Mielke and Schwabe (2010) and can be seen in the here presented example as well. The D-optimality criterion takes for the optimal design in the approximation $\mathbf{M}_{1,\beta}$ with respect to the different approximations the values

$$\begin{aligned} \Phi_{D;1}(\zeta_1) &= 11.81 \text{ for } \mathbf{M}_{1,\beta}; \quad \Phi_{D;2}(\zeta_1) = 15.42 \text{ for } \mathbf{M}_{2,\beta}; \\ \Phi_{D;3}(\zeta_1) &= 13.81 \text{ for } \mathbf{M}_{3,\beta}; \quad \Phi_{D;F}(\zeta_1) = 14.77 \text{ for } \mathfrak{M}_{\beta}. \end{aligned}$$

The information gain here takes place for the approximation $\mathbf{M}_{3,\beta}$ as well, as the value of the optimality criterion is smaller than the value given by the Fisher information, which is approximated by the criterion $\Phi_{D;F}(\zeta_1)$. In the present example, it can be even analytically shown that the approximation $\mathbf{M}_{1,\beta}$ suggests more information then the true Fisher information.

Table 1: Efficiency of the proposed designs

	ζ_1^*	ζ_2^*	ζ_3^*	ζ_F^*
$\delta_{\zeta_1^*}$	1.00	0.55	0.95	0.77
$\delta_{\zeta_2^*}$	0.66	1.00	0.00	0.37
$\delta_{\zeta_3^*}$	0.98	0.84	1.00	0.98
$\delta_{\zeta_F^*}$	0.88	0.83	0.95	1.00

6 Discussion

Although some new motivations propose the use of the information matrix resulting from linear mixed effects models for the design of experiments in nonlinear mixed effects models, the results for specific situations can be unsatisfactory. Designs which are obtained by analytical approximations of the Fisher information should be handled very carefully in the considered models, if the target of the design problem is the minimization of some criteria related to the Fisher information matrix. These designs can however be used as benchmarks or as starting points for the location of designs based on numeric approximations of the Fisher information. Of special interest is the optimization of designs with respect to the expected information $\mathbf{M}_{3,\beta}$. Pinheiro and Bates (2000) suggest a similar structure of the inverse of the covariance matrix for estimators of β, which are based on penalized sums of squares, such that the optimization of designs with respect to the information matrix $\mathbf{M}_{3,\beta}$ might improve the quality of estimates not only theoretically. The presented example unfortunately showed that designs with less support points than parameters of interest might result with this information matrix as optimal designs, what might

however cause new problems for the estimation. A second problem for the approximation $\mathbf{M}_{3,\beta}$ was the value of the optimality criterion, which was in the example below the bound provided by the approximated Fisher information. These points require some further investigations.

Acknowledgment

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A Comparison between D-optimality for Poisson Regression with Random Intercept and Poisson Regression with Random Slope

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Abstract: In spite of wide applications of models with random effects, there are few studies have been investigating the optimal designs for these kinds of models. Optimal designs, which can significantly enhance the perfor- mance of the models, have received increasing attention recently.In this paper, we use Quasi-likelihood approach to obtain the optimal designs for two particular categories of Poisson regression models: 1) Poisson Regression models with random Intercept; 2) Poisson Regression model with random slope. Then we empirically study the efficiency of the pro- posed optimal designs.
This work provides a framework to obtain optimal designs when the variance covariance structure of the model is a function of the mean of the observations.

Keywords: Poisson regression, Optimal designs, D-optimality, Random effect, D-efficiency.

1 Introduction

There are many kind of count data in real experiments which can not modelled by a normal distribution. These data might be modelled by a Poisson Model which associates with some parameters through link function. Due to the different races, different age, etc these parameters might be changed for different individuals and hence we have random effects in the model.
Design optimality has received growing attention by statisticians over the past few decades.The main goal is to find the best experimental settings x_i, which maximize the information matrix of parameters as the inverse of variance-covariance matrix. A lot of work has been done on optimal experimental designs for binary data models and count data models in the fixed effect cases as two special cases of generalized linear models. Representative work has been done by Abdelbasit and Plackett (1983), Minkin (1987), Minkin (1993) and Yanping et al. (2006).
While the corresponding statistical analysis is well-developed for mixed effects Poisson regression models as an especial case of generalized linear mixed models, only a few results are available on optimal designs for such models.Recently Niaparast (2009) has investigated a general method to find optimal designs for the Poisson regression model with random intercept. He obtained the locally D-optimality designs for this model. An assumption in this model is that the effect of the explanatory variable is constant. This assumption might sometimes be in challenge. On the contrary of a random intercept model, random slope model allows the explanatory variable to have a different effect for each individual. In this paper we consider, as an especial case of generalized linear mixed models, Poisson regression model with random slope.
Due to the random effect in this model, a closed form of the likelihood function to estimate the fixed parameters of this model is quite intractable. So a Quasi-Likelihood approach is used to determine the information matrix for these parameters (McCullagh and Nelder (1989), chapter 9). The only assumptions on the data are those concerning the first two moments.
The outline of the paper is as follows: In the next section, we introduce the model. In section 3 we provide a short introduction to Quasi-likelihood method. In sections 4 and 5 we define two special cases and we obtain some results. Finally we outline a summary of this paper.

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2 The Model

We consider a mixed Poisson regression model. It can be written as,

$$Y_{ijk} \mid \mathbf{b}_i \overset{ind}{\sim} P(\mu_{ij}(\mathbf{b}_i)) \begin{cases} i = 1, \ldots, s & \sum_{j=1}^{t_i} m_{ij} = m_i \\ j = 1, \ldots, t_i & \\ k = 1, \ldots, m_{ij} & n = \sum_{i=1}^{s} m_i \end{cases} \tag{1}$$

where $\log(\mu_{ij}(\mathbf{b}_i)) = \mathbf{f}^T(x_{ij})\mathbf{b}_i$ is specified by a canonical link function. Here Y_{ijk} stands for the kth replication for the individual i at the experimental setting x_{ij} from the experimental region $\mathfrak{X} = [0, g]$ and can tend to infinity. Also we suppose that m_{ij} denotes the number of replications of individual i at the jth level of x. $\mathbf{b}_i$ is the random slope which varies and depends on the different individuals. We suppose that $\mathbf{b}_i$ is normally distributed with mean $\boldsymbol{\beta}$ and variance $\Sigma = \begin{pmatrix} \sigma_0^2 & 0 \\ 0 & \sigma^2 \end{pmatrix}$.
We suppose that $cov(\mathbf{b}_i, \mathbf{b}_{i'}) = 0$ for all $i \neq i'$. Note that $Var(Y_{ijk} \mid \mathbf{b}_i) = E(Y_{ijk} \mid \mathbf{b}_i) = \mu_{ij}(\mathbf{b}_i)$. For further simplification we assume $t_i = t$ and $m_i = m \, \forall i$.
We consider two special cases of the mixed Poisson regression model which are called Poisson regression model with random intercept(PRI) and Poisson regression model with random slope (PRS).

3 Quasi-information

The role played by the information matrix is very clear in the optimal design studies. This role seems apparent comes from the asymptotic relation between information matrix and variance-covariance matrix of the maximum likelihood estimator of parameters.
Suppose the $n \times 1$ random variable Y has mean $E(\mathbf{Y}) = \boldsymbol{\mu}(\boldsymbol{\beta})$ and variance-covariance matrix $Var(\mathbf{Y}) = \phi^2 V(\boldsymbol{\mu}(\boldsymbol{\beta}))$ such that the variance depends on $\boldsymbol{\beta}$ only through the mean $\boldsymbol{\mu}(\boldsymbol{\beta})$ where $V(\boldsymbol{\mu})$ is the variance function and shows the relation between the mean and the variance of $\mathbf{Y}$ (McCulloch and Searle 2001). Both are assumed to be known functions of the p-dimensional parameter vector $\boldsymbol{\beta}$ and $V(\boldsymbol{\beta})$ is positive definite.
The quasi-likelihood approach for the regression parameters $\boldsymbol{\beta}$ is defined by the quasi-score function

$$U(\boldsymbol{\beta}, \mathbf{y}) = \phi^2 D^T (V(\boldsymbol{\mu}(\boldsymbol{\beta})))^{-1} (\mathbf{y} - \boldsymbol{\mu}(\boldsymbol{\beta}))$$

$\hat{\boldsymbol{\beta}}^{(n)}$ is the quasi estimator for $\boldsymbol{\beta}$ if $U(\hat{\boldsymbol{\beta}}^{(n)}, \mathbf{y}) = 0$.
In this expression the entries of the matrix D, of order $n \times p$, are $D_{jr} = \frac{\partial \mu_j}{\partial \beta_r}$, the partial derivatives of the components of $\boldsymbol{\mu}(\boldsymbol{\beta})$, with respect to the parameters. Note that $\mathbf{D}$ also depends on $\boldsymbol{\beta}$.
Under the regularity conditions on the design, the asymptotic variance-covariance of the quasi-score function $U(\boldsymbol{\beta}, \mathbf{Y})$, which equals the negative of the expectation of $\partial U(\boldsymbol{\beta}, \mathbf{Y}) / \partial \boldsymbol{\beta}$, is

$$M(\boldsymbol{\beta}) = D^T (V(\boldsymbol{\mu}(\boldsymbol{\beta})))^{-1} D$$

(McCullagh 1983). This matrix plays the role of the Fisher information exactly in the same way as in fully parametric inference, and under the usual regularity conditions, the asymptotic variance-covariance matrix of the quasi-likelihood estimator of $\boldsymbol{\beta}$ equals $M^{-1}(\boldsymbol{\beta})$ (McCullagh 1983). For the sake of clarity we call $M(\boldsymbol{\beta})$ the quasi-information matrix.

4 PRI Model

Suppose that $\mu_{ij}(\mathbf{b}_i) = e^{b_{0i}+\beta_1 x_{ij}}$ in (1),i.e. $\sigma^2 = 0$. This model has been considered by Niaparast(2009) and hence we outline his results. Suppose that $\xi_i = \left\{ \begin{array}{ccc} x_{i1} & \cdots & x_{it} \\ p_{i1} & \cdots & p_{it} \end{array} \right\}$ be the approximate design for individual i.

- Expectation and Variance-Covariance Structure

$$\begin{aligned} E(Y_{ijk}) &= \mu(x_{ij}) = e^{\beta_0+\beta_1 x_{ijk}+\frac{1}{2}\sigma_0^2} \\ Var(Y_{ijk}) &= \mu^2(x_{ij})(e^{\sigma_0^2}-1)+\mu(x_{ij}) \\ Cov(Y_{ijk}, Y_{ij'k'}) &= (e^{\sigma_0^2}-1)\mu(x_{ij})\mu(x_{ij'}) \text{ for all } (j,k) \neq (j',k') \end{aligned}$$

  we suppose that $\mu(x_{ij})$ is an increasing function of x_{ij}

- The Quasi-information matrix to estimate $\boldsymbol{\beta}$ can be written as

$$\mathfrak{M}_{\boldsymbol{\beta}}(\xi_i) = F_i^T(A_i^{-1} + (e^{\sigma_0^2}-1)\mathbf{1}_{t_i}\mathbf{1}_{t_i}^T)^{-1}F_i \tag{2}$$

  where $A_i = diag\{m_{ij}\mu(x_{ij})\}_{j=1,\cdots,t}$, $F_i = \begin{pmatrix} \mathbf{f}^T(x_{i1}) \\ \vdots \\ \mathbf{f}^T(x_{it}) \end{pmatrix}$, the row individual design matrix neglecting the number of replications and $\mathbf{1}_t$ is an $t \times 1$ vector with all entries equal to 1.

- Optimal design can be obtained among those which are uniform across the individuals (Niaparast 2009). Thus we ignore index i.

- D-optimal design to estimate $\boldsymbol{\beta}$ has exactly two different support points.

- The D-criterion can be written as

$$\det(\mathfrak{M}_{\boldsymbol{\beta}}(\xi)) \propto \frac{p(1-p)\tilde{\mu}_1\tilde{\mu}_2(ln(\tilde{\mu}_1)-ln(\tilde{\mu}_2))^2}{1+me^{\beta_0+\frac{1}{2}\sigma_0^2}(e^{\sigma^2}-1)(p\tilde{\mu}_1+(1-p)\tilde{\mu}_2)} \tag{3}$$

  where $\tilde{\mu}_j = \frac{\mu(x_j)}{\mu(0)}$ is canonical standardized mean.

Regarding to the above statements we obtain D-optimal designs for some representative values of β_0, β_1 and σ_0^2, which are listed in table 1.

Table 1: Locally D-optimal two points designs for PRI Model

	unrestricted design domain $m = 100$, $\beta_0 = -2$ and $\beta_1 = -5$			restricted design domain $\tilde{\mu}(g) = .2$ $m = 200$, $\beta_0 = -2$ and $\beta_1 = -5$		
σ_0^2	p^*	$\tilde{\mu}_1^*$	$\tilde{\mu}_2^*$	p^*	$\tilde{\mu}_1^*$	$\tilde{\mu}_2^*$
0	0.500	0.1353	1	0.500	0.2000	1
0.5	0.7799	0.0782	1	0.6906	0.2000	1
1	0.7815	0.0777	1	0.6908	0.2000	1
2	0.7821	0.0776	1	0.6910	0.2000	1
3	0.7822	0.0775	1	0.6910	0.2000	1
4	0.7822	0.00775	1	0.6910	0.2000	1
5	0.7822	0.7755	1	0.6911	0.2000	1

Experimenters might consider a standard two points design which consists of the two end-points, i.e. $\tilde{\mu}_1 = \tilde{\mu}_g$ and $\tilde{\mu}_2 = 1$ with equal allocation, i.e. $p_1 = p_2 = \frac{1}{2}$. If we define the D-efficiency of ξ as

$$\text{D-efficiency} = \left(\frac{\det(Var(\hat{\boldsymbol{\beta}}_{\xi^*}))}{\det(Var(\hat{\boldsymbol{\beta}}_{\xi}))} \right)^{\frac{1}{2}}$$

The plots in figure 1 indicate that the efficiency of standard design increases when the design regions are more restricted.

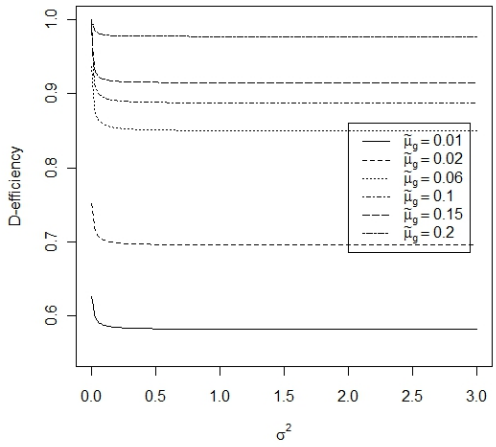

Figure 1: D-efficiency of Standard Designs for PRI Model

5 PRS Model

We consider model in the equation (1), if $\sigma_0^2 = 0$ then Model is reduced to Poisson regression with random slope. In other word $\mu_{ij}(b_i) = e^{\beta_0 + b_{1i} x_{ij}}$. We conclude the following statements:

- Expectation and Variance-Covariance Structure

$$\begin{aligned} E(Y_{ijk}) &= \mu(x_{ij}) = e^{\beta_0 + \beta_1 x_{ijk} + \frac{1}{2}\sigma^2 x_{ij}^2} && (4) \\ Var(Y_{ijk}) &= \mu^2(x_{ij})(e^{\sigma^2 x_{ij}^2} - 1) + \mu(x_{ij}) && (5) \\ Cov(Y_{ijk}, Y_{ij'k'}) &= (e^{\sigma^2 x_{ij} x_{ij'}} - 1)\mu(x_{ij})\mu(x_{ij'}) \text{ for all } (j,k) \neq (j',k') && (6) \end{aligned}$$

- If $\xi = \left\{ \begin{array}{cc} x_1 & x_2 \\ p & 1-p \end{array} \right\}$, then the Quasi-information matrix is

$$\mathfrak{M}_{\boldsymbol{\beta}}(\xi_i) = F^T (A^{-1} + B)^{-1} F \qquad (7)$$

where $B = \begin{pmatrix} e^{\sigma^2 x_1^2} - 1 & e^{\sigma^2 x_1 x_2} - 1 \\ e^{\sigma^2 x_1 x_2} - 1 & e^{\sigma^2 x_2^2} - 1 \end{pmatrix}$

- the determinant of the quasi-information matrix for $\boldsymbol{\beta}$ is as follows

$$\det(\mathfrak{M}(\xi)) = \frac{m^2\mu(0)^2 p_1(1-p_1)\tilde{\mu}(x_1)\tilde{\mu}(x_2)(x_1-x_2)^2}{1+mp_1\mu(0)\tilde{\mu}(x_1)(e^{\sigma^2 x_1^2}-1)+m(1-p_1)\mu(0)\tilde{\mu}(x_2)(e^{\sigma^2 x_2^2}-1)+m^2p_1(1-p_1)\mu(0)^2\tilde{\mu}(x_1)\tilde{\mu}(x_2)(e^{\sigma^2 x_1 x_2}-1)}$$

  where $\mu_0 = e^{\beta_0}$.

To obtain the locally D-optimal designs for some representative values of parameters we maximize $\det(\mathfrak{M}(\xi))$ and the results are listed in table 2

Table 2: Locally D-optimal two points designs for PRS Model

	unrestricted design domain $m = 100$, $\beta_0 = -2$ and $\beta_1 = -5$			restricted design domain $\tilde{\mu}(g) = .2$ $m = 200$, $\beta_0 = -2$ and $\beta_1 = -5$		
σ^2	p^*	$\tilde{\mu}_1^*$	$\tilde{\mu}_2^*$	p^*	$\tilde{\mu}_1^*$	$\tilde{\mu}_2^*$
0	0.500	0.1353	1	0.500	0.2000	1
0.5	0.482	0.1305	1	0.483	0.2000	1
1	0.462	0.1272	1	0.466	0.2000	1
2	0.422	0.1296	1	0.432	0.2000	1
3	0.384	0.1487	1	0.398	0.2000	1
4	0.354	0.1798	1	0.362	0.2000	1
5	0.331	0.2147	1	0.331	0.2147	1

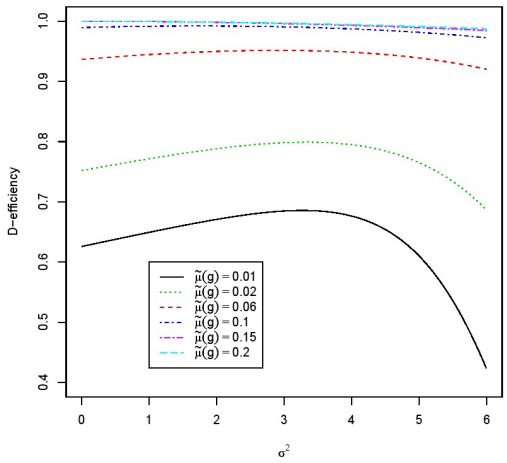

Figure 2: D-efficiency of Standard Designs for PRS Model

6 Summary

- Due to the random effects we could not use a likelihood method to find the information matrix and hence we apply a Quasi-likelihood approach. Using this method we obtain the Quasi-information matrix for $\boldsymbol{\beta}$.
- Results indicates that we have different structure of the Quasi-information matrix for $\boldsymbol{\beta}$.

- Numerical method use to maximize the determinants of the quasi-information matrices. and the results in tables 1 and 2 are completely different. In the PRI Model, the interval between two support points increases when σ^2 increases, but we have the different trend in the PRS model.
- Figures 1 and 2 indicate that both cases are not robust when g tends to infinity.

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Optimal Designs for Individual Prediction in Random Coefficient Regression Models

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Abstract: In this note we present optimal designs for the estimation of the individual response ("prediction") for the participates in a study within the framework of hierarchical linear mixed models. These optimal designs may differ substantially from those propagated in the literature so far.

Keywords: Linear Mixed Model, Random Coefficient Regression, Prediction, Individual Design.

1 Introduction

Random coefficient regression models attract an increasing popularity in many fields of applications starting from animal breeding over population pharmacokinetics to the development of individualized medicine. In random coefficient regression models interest may be either in a "typical" response described by some averaged characteristics of the population (estimation of the population parameters) or in the individual responses of the subjects involved in the study themselves (estimation of the individual parameters, "prediction"). The statistical analysis of such models has become tractable during the last years by the now available computer facilities, which pushes this field forward. However, less has been done in optimal design for such experiments. In the present note we want to develop optimal designs for the estimation of the individual response.

In their seminal paper Gladitz and Pilz (1982) established that Bayesian optimal designs are optimal for the estimation of individual responses, when the prior covariance is set equal to the covariance of the individual parameters, in the case of known population parameters, i. e. in the case of the knowledge of the "typical" response. Subsequently this last condition of known population parameters has been often overlooked, which resulted in some kind of "folklore" in the design community that all design problems have been solved related to linear mixed models. Some years later Fedorov and Hackl (1997) (section 5.2) considered design criteria for either the estimation of the population parameters or the estimation (prediction) of the individual responses under various assumptions on the knowledge of parts of the parameters. For the situation of prediction, when the population parameters are unknown, they claim that the optimal design in the corresponding model without random effects retains its optimality for the estimation of the individual parameters. This statement seems to be motivated by a conditional approach, in which the individual response is estimated by the observations of the corresponding individual only, neglecting the fact that the individual effects are assumed to be random and stem from a common population. As often the truth lies somewhere in between: As will be developed in this note the correct characterization of the mean squared error for the prediction of the individual response results in a compound criterion, which is a weighted average of the fully Bayesian criterion and the criterion related to the model without random effects.

The present paper is organized as follows: In the second section we specify the model, introduce the predictor for the individual random parameters and develop the corresponding mean squared error matrix. The third section provides some theoretical results for the determination of

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designs, which are optimal for prediction. In section 4 we illustrate these results by the example of simple straight line regression and conclude with some discussion in section 5.

2 Model Specification and Prediction

In random coefficient regression the observations are assumed to come from a hierarchical model. On the individual level the jth observation Y_{ij} of individual i is given by

$$Y_{ij} = \mathbf{f}(x_{ij})^\top \boldsymbol{\beta}_i + \varepsilon_{ij} \tag{1}$$

for $j = 1, .., m_i$ and $i = 1, .., n$, where m_i is the number of observations at individual i, n is the number of individuals, $\mathbf{f} = (f_1, .., f_p)^\top$ is a set of known regression functions, and the experimental settings x_{ij} may come from the experimental region $\mathcal{X}$. The observational errors ε_{ij} are assumed to be homoscedastic and uncorrelated with mean 0 and common variance $\sigma^2 > 0$.

On the population level the individual parameters $\boldsymbol{\beta}_i = (\beta_{i1}, .., \beta_{ip})^\top$ are assumed to come from common distribution with unknown population mean $\mathrm{E}(\boldsymbol{\beta}_i) = \boldsymbol{\beta} = (\beta_1, .., \beta_p)^\top$ and a $p \times p$ population covariance matrix $\mathrm{Cov}(\boldsymbol{\beta}_i) = \sigma^2 \mathbf{D}$. Moreover, all individual parameters $\boldsymbol{\beta}_i$ and all observational errors $\varepsilon_{i'j}$ are assumed to be uncorrelated.

To simplify the notations we will only consider random coefficient regression models throughout this note, in which all individuals get the same experimental treatments, i. e. all individuals i have the same number $m_i = m$ of observations at the same experimental settings $x_{ij} = x_j$.

To make use of the theoretical results available for the estimation of individual parameters (prediction) we will identify the above specified model as a special case of the general mixed model

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\boldsymbol{\gamma} + \boldsymbol{\varepsilon} \tag{2}$$

with a particular nice structure of the fixed effects and random effects design matrices $\mathbf{X}$ and $\mathbf{Z}$, respectively. Here $\boldsymbol{\beta}$ denotes again the fixed effect (population parameter), and $\boldsymbol{\gamma}$ are the random effects. These random effects and the observational errors $\boldsymbol{\varepsilon}$ have zero mean and are all uncorrelated with corresponding full rank covariance matrices $\mathrm{Cov}(\boldsymbol{\gamma}) = \mathbf{G}$ and $\mathrm{Cov}(\boldsymbol{\varepsilon}) = \mathbf{R}$, respectively.

Under the assumption of Gaussian normal distributions Henderson *et al.* (1959) established that the mixed model equations produce the Best Linear Unbiased Estimator $\hat{\boldsymbol{\beta}}$ and the Best Linear Unbiased Predictor $\hat{\boldsymbol{\gamma}}$ for $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ by

$$\begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\boldsymbol{\gamma}} \end{pmatrix} = \begin{pmatrix} \mathbf{X}^\top\mathbf{R}^{-1}\mathbf{X} & \mathbf{X}^\top\mathbf{R}^{-1}\mathbf{Z} \\ \mathbf{Z}^\top\mathbf{R}^{-1}\mathbf{X} & \mathbf{Z}^\top\mathbf{R}^{-1}\mathbf{Z} + \mathbf{G}^{-1} \end{pmatrix}^{-1} \begin{pmatrix} \mathbf{X}^\top\mathbf{R}^{-1}\mathbf{Y} \\ \mathbf{Z}^\top\mathbf{R}^{-1}\mathbf{Y} \end{pmatrix}, \tag{3}$$

if the fixed effects design matrix $\mathbf{X}$ has full column rank. According to Christensen (2002) the distributional assumptions can be relaxed to the moment conditions stated above.

Denote by

$$\mathbf{C} = \begin{pmatrix} \mathbf{C}_{11} & \mathbf{C}_{12} \\ \mathbf{C}_{12}^\top & \mathbf{C}_{22} \end{pmatrix} = \mathrm{Cov} \begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\boldsymbol{\gamma}} - \boldsymbol{\gamma} \end{pmatrix} \tag{4}$$

the joint mean squared error matrix for both $\hat{\boldsymbol{\beta}}$ and $\hat{\boldsymbol{\gamma}}$, which is partitioned according to these components. Then Henderson (1975) has shown that

$$\mathbf{C} = \begin{pmatrix} \mathbf{X}^\top\mathbf{R}^{-1}\mathbf{X} & \mathbf{X}^\top\mathbf{R}^{-1}\mathbf{Z} \\ \mathbf{Z}^\top\mathbf{R}^{-1}\mathbf{X} & \mathbf{Z}^\top\mathbf{R}^{-1}\mathbf{Z} + \mathbf{G}^{-1} \end{pmatrix}^{-1}. \tag{5}$$

We now adapt our model (1) to the more general model (2). First we introduce the centered random effects $\mathbf{b}_i := \boldsymbol{\beta}_i - \boldsymbol{\beta}$. Then a single observation in model (1) can be written as

$$Y_{ij} = \mathbf{f}(x_j)^\top \boldsymbol{\beta} + \mathbf{f}(x_j)^\top \mathbf{b}_i + \varepsilon_{ij}\,, \tag{6}$$

where the random effects are separated from the population mean. This results in the vector notation

$$\mathbf{Y}_i = \mathbf{F}\boldsymbol{\beta} + \mathbf{F}\mathbf{b}_i + \boldsymbol{\varepsilon}_i, \tag{7}$$

for all observations $\mathbf{Y}_i = (Y_{i1}, ..., Y_{im})^\top$ of individual i, where $\boldsymbol{\varepsilon}_i = (\varepsilon_{i1}, ..., \varepsilon_{im})^\top$ denotes the corresponding error vector and $\mathbf{F} = (\mathbf{f}(x_1), ..., \mathbf{f}(x_m))^\top$ is the individual design matrix, which coincides for all individuals under the assumptions made.

Finally, the complete observation vector $\mathbf{Y} = (\mathbf{Y}_1^\top, ..., \mathbf{Y}_n^\top)^\top$ for all individuals has the form

$$\mathbf{Y} = (\mathbf{1}_n \otimes \mathbf{F})\boldsymbol{\beta} + (\mathbf{I}_n \otimes \mathbf{F})\mathbf{b} + \boldsymbol{\varepsilon}, \tag{8}$$

where $\boldsymbol{\varepsilon} = (\boldsymbol{\varepsilon}_1^\top, ..., \boldsymbol{\varepsilon}_n^\top)^\top$ is the vector of all observational errors and $\mathbf{b} = (\mathbf{b}_1^\top, ..., \mathbf{b}_n^\top)^\top$ is the common vector of random effects. Here $\mathbf{I}_n$ is the $n \times n$ identity matrix, $\mathbf{1}_n = (1, .., 1)^\top$ is a n-dimensional vector with all entries equal to 1, and "$\otimes$" denotes the Kronecker product. Hence, model (8) attains the form of the general model (2). However, the covariance matrix $\mathrm{Cov}(\mathbf{b}) = \sigma^2\mathbf{I}_n \otimes \mathbf{D}$ may fail to be of full rank, if the population covariance matrix $\mathbf{D}$ is singular, which is the case for example for models with random intercepts (random block effects).

Therefore we have to rewrite the model (8) by reducing the dimensionality of the random effects such that the corresponding covariance matrix becomes regular: Let q be the rank of the matrix $\mathbf{D}$. Then there exists a $p \times q$ matrix $\mathbf{H}$ with $\mathbf{D} = \mathbf{H}\mathbf{H}^\top$ and $\mathrm{rank}(\mathbf{H}) = q$ such that $\mathbf{H}^\top\mathbf{H}$ is regular. Then we introduce the random variables

$$\mathbf{c}_i := (\mathbf{H}^\top\mathbf{H})^{-1}\mathbf{H}^\top\mathbf{b}_i\,, \tag{9}$$

which satisfy $\mathrm{E}(\mathbf{c}_i) = 0$, $\mathrm{Cov}(\mathbf{c}_i) = \sigma^2\mathbf{I}_q$, and $\mathbf{b}_i = \mathbf{H}\mathbf{c}_i$ almost surely. The model equation (7) can then be written as

$$\mathbf{Y}_i = \mathbf{F}\boldsymbol{\beta} + \mathbf{F}\mathbf{H}\mathbf{c}_i + \boldsymbol{\varepsilon}_i\,, \tag{10}$$

and consequently

$$\mathbf{Y} = (\mathbf{1}_n \otimes \mathbf{F})\boldsymbol{\beta} + (\mathbf{I}_n \otimes (\mathbf{F}\mathbf{H}))\mathbf{c} + \boldsymbol{\varepsilon}\,, \tag{11}$$

where $\mathbf{c} = (\mathbf{c}_1^\top, .., \mathbf{c}_n^\top)^\top$. Now with $\mathbf{X} = \mathbf{1}_n \otimes \mathbf{F}$, $\mathbf{Z} = \mathbf{I}_n \otimes (\mathbf{F}\mathbf{H})$ and $\boldsymbol{\gamma} = \mathbf{c}$ our model (11) has the form of the general model (2) with regular covariance matrices $\mathbf{R} = \sigma^2\mathbf{I}_{nm}$ and $\mathbf{G} = \sigma^2\mathbf{I}_{nq}$.

In this model the blocks of the mean squared error matrix $\mathbf{C}$ can be readily calculated as

$$\mathbf{C}_{11} = \mathrm{Cov}(\hat{\boldsymbol{\beta}}) = \frac{\sigma^2}{n}\left((\mathbf{F}^\top\mathbf{F})^{-1} + \mathbf{H}\mathbf{H}^\top\right), \tag{12}$$

$$\mathbf{C}_{22} = \mathrm{Cov}(\hat{\mathbf{c}} - \mathbf{c}) = \sigma^2\left(\frac{1}{n}\mathbf{1}_n\mathbf{1}_n^\top \otimes \mathbf{I}_q + (\mathbf{I}_n - \frac{1}{n}\mathbf{1}_n\mathbf{1}_n^\top) \otimes (\mathbf{H}^\top\mathbf{F}^\top\mathbf{F}\mathbf{H} + \mathbf{I}_q)^{-1}\right), \tag{13}$$

$$\mathbf{C}_{12} = \mathrm{cov}(\hat{\boldsymbol{\beta}}, \hat{\mathbf{c}} - \mathbf{c}) = -\frac{\sigma^2}{n}\mathbf{1}_n^\top \otimes \mathbf{H}\,. \tag{14}$$

Note that in the present case of identical design matrices $\mathbf{F}$ for all individuals the estimator $\hat{\boldsymbol{\beta}}$ for the population parameter $\boldsymbol{\beta}$ can be calculated as the ordinary least squares estimator $\hat{\boldsymbol{\beta}} = (\mathbf{F}^\top\mathbf{F})^{-1}\mathbf{F}^\top\bar{\mathbf{Y}}$, where $\bar{\mathbf{Y}} = \frac{1}{n}\sum_{i=1}^n \mathbf{Y}_i$ is the averaged response across the individuals. The estimator $\hat{\boldsymbol{\beta}}$ for the population parameter $\boldsymbol{\beta}$ can also be rewritten as the average $\hat{\boldsymbol{\beta}} = \frac{1}{n}\sum_{i=1}^n \hat{\boldsymbol{\beta}}_{i;\mathrm{ind}}$ of the individualized estimates $\hat{\boldsymbol{\beta}}_{i;\mathrm{ind}} = (\mathbf{F}^\top\mathbf{F})^{-1}\mathbf{F}^\top\mathbf{Y}_i$ of the individual parameters $\boldsymbol{\beta}_i$ based on the observations $\mathbf{Y}_i$ of subject i only (see Entholzner *et al.* (2005)).

Also the predictor $\hat{\boldsymbol{\beta}}_i = \hat{\boldsymbol{\beta}} + \hat{\mathbf{b}}_i = \hat{\boldsymbol{\beta}} + \mathbf{H}\hat{\mathbf{c}}_i$ for the individual parameter $\boldsymbol{\beta}_i$ simplifies in this situation.

Theorem 1. *In the case of identical design matrices* $\mathbf{F}$ *for all individuals the predictor*

$$\hat{\boldsymbol{\beta}}_i = \mathbf{D}((\mathbf{F}^\top\mathbf{F})^{-1} + \mathbf{D})^{-1}\hat{\boldsymbol{\beta}}_{i;\mathrm{ind}} + (\mathbf{F}^\top\mathbf{F})^{-1}((\mathbf{F}^\top\mathbf{F})^{-1} + \mathbf{D})^{-1}\hat{\boldsymbol{\beta}}, \tag{15}$$

is a weighted average of the individualized estimate $\hat{\boldsymbol{\beta}}_{i;\mathrm{ind}}$ *based on the observations of subject* i *only and the estimator* $\hat{\boldsymbol{\beta}}$ *for the population parameter.*

Consequently the corresponding covariance matrix of

$$\begin{pmatrix} \hat{\boldsymbol{\beta}}_1 - \boldsymbol{\beta}_1 \\ \vdots \\ \hat{\boldsymbol{\beta}}_n - \boldsymbol{\beta}_n \end{pmatrix} = (\mathbf{1}_n \otimes \mathbf{I}_p \mid \mathbf{I}_n \otimes \mathbf{H}) \begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\mathbf{c}} - \mathbf{c} \end{pmatrix}, \tag{16}$$

is independent of the choice of $\mathbf{H}$.

Theorem 2.

$$\begin{aligned} &\mathrm{Cov} \begin{pmatrix} \hat{\boldsymbol{\beta}}_1 - \boldsymbol{\beta}_1 \\ \vdots \\ \hat{\boldsymbol{\beta}}_n - \boldsymbol{\beta}_n \end{pmatrix} \\ &= \sigma^2 \left(\left(\mathbf{I}_n - \frac{1}{n} \mathbf{1}_n \mathbf{1}_n^\top \right) \otimes \left(\mathbf{D} - \mathbf{D}((\mathbf{F}^\top \mathbf{F})^{-1} + \mathbf{D})^{-1} \mathbf{D} \right) + \frac{1}{n} \mathbf{1}_n \mathbf{1}_n^\top \otimes (\mathbf{F}^\top \mathbf{F})^{-1} \right). \end{aligned} \tag{17}$$

If the dispersion matrix $\mathbf{D}$ is regular, the mean squared error matrix for the predictors $(\hat{\boldsymbol{\beta}}_1^\top, ..., \hat{\boldsymbol{\beta}}_n^\top)^\top$ simplifies to a weighted average of the covariance matrix $\sigma^2(\mathbf{F}^\top \mathbf{F})^{-1}$ for the fixed effects in the model without random effects ($\mathbf{D} = \mathbf{0}$) and the Bayesian covariance matrix $\sigma^2(\mathbf{F}^\top \mathbf{F} + \mathbf{D}^{-1})^{-1}$ propagated by Gladitz and Pilz (1982).

Corollary 1. *If* $\mathbf{D}$ *is regular, then*

$$\mathrm{Cov} \begin{pmatrix} \hat{\boldsymbol{\beta}}_1 - \boldsymbol{\beta}_1 \\ \vdots \\ \hat{\boldsymbol{\beta}}_n - \boldsymbol{\beta}_n \end{pmatrix} = \sigma^2 \left(\left(\mathbf{I}_\mathrm{n} - \frac{1}{\mathrm{n}} \mathbf{1}_\mathrm{n} \mathbf{1}_\mathrm{n}^\top \right) \otimes (\mathbf{F}^\top \mathbf{F} + \mathbf{D}^{-1})^{-1} + \frac{1}{\mathrm{n}} \left(\mathbf{1}_\mathrm{n} \mathbf{1}_\mathrm{n}^\top \right) \otimes (\mathbf{F}^\top \mathbf{F})^{-1} \right). \tag{18}$$

3 Optimal Design

The performance of the prediction may be measured in terms of the mean squared error matrix derived in Theorem 2 and Corollary 1 and its quality depends on the design of the experiment, i. e. on the choice of the experimental settings $x_1, ..., x_m$ for each individual. These experimental settings need not be distinct. As the performance does not depend on the order of the observations within the individuals, we may rewrite the mean squared error matrix of the predictor in terms of distinct settings $x_1, ..., x_k$, say, and their respective numbers $m_1, ..., m_k$ of replications ($\sum_{j=1}^k m_j = m$). The standardized individual design $\xi = \begin{pmatrix} x_1, ..., x_k \\ w_1, ..., w_k \end{pmatrix}$ is then introduced, where x_j are the distinct settings and $w_j = \frac{m_j}{m}$ the corresponding relative frequencies of replications, respectively, satisfying $\sum_{j=1}^k w_j = 1$. For such a standardized design ξ we denote by

$$\mathbf{M}(\xi) := \sum_{j=1}^{k} w_j \mathbf{f}(x_j) \mathbf{f}(x_j)^\top = \frac{1}{m} \mathbf{F}^\top \mathbf{F} \tag{19}$$

the standardized information matrix in the model without random effects. Further let $\boldsymbol{\Delta} = m\mathbf{D}$ be a standardized version of the dispersion matrix for the random effects.

In the present paper we will lay emphasis on the Integrated Mean Squared Error ("IMSE") criterion

$$\mathrm{IMSE}_{\mathrm{pred}}(\xi) := \int \mathrm{E}_\xi \left(\sum_{i=1}^{n} (\hat{\mu}_i(x) - \mu_i(x))^2 \right) \nu(\mathrm{d}x) = \sum_{i=1}^{n} \int \mathrm{Cov}_\xi \left(\hat{\mu}_i(x) - \mu_i(x) \right) \nu(\mathrm{d}x) \quad (20)$$

for prediction, which measures the average distance of the predicted individual response $\hat{\mu}_i(x) = \mathbf{f}(x)^\top \hat{\boldsymbol{\beta}}_i$ from the true individual response $\mu_i(x) = \mathbf{f}(x)^\top \boldsymbol{\beta}_i$. E_ξ and Cov_ξ denote the expectation and the covariance matrix, when the design ξ is used and ν is a weight distribution on the design region $\mathcal{X}$, which is typically uniform on $\mathcal{X}$ with $\nu(\mathcal{X}) = 1$.

After some rearrangements it can be seen that the IMSE-criterion for prediction is linear, and by Theorem 2 it follows that

$$\mathrm{IMSE}_{\mathrm{pred}}(\xi) = \frac{\sigma^2}{m} \operatorname{tr} \left(\left(\mathbf{M}(\xi)^{-1} + (n-1) \left(\boldsymbol{\Delta} - \boldsymbol{\Delta} (\mathbf{M}(\xi)^{-1} + \boldsymbol{\Delta})^{-1} \boldsymbol{\Delta} \right) \right) \mathbf{V} \right), \quad (21)$$

where $\mathbf{V} := \int \mathbf{f}(x) \mathbf{f}(x)^\top \nu(\mathrm{d}x)$ is the "information matrix" for the weight distribution ν in the model without random effects and "tr" denotes the trace of a matrix.

For a regular dispersion matrix $\mathbf{D}$ the criterion (21) simplifies by Corollary 1 to

$$\mathrm{IMSE}_{\mathrm{pred}}(\xi) = \frac{\sigma^2}{m} \operatorname{tr} \left(\left(\mathbf{M}(\xi)^{-1} + (n-1) (\mathbf{M}(\xi) + \boldsymbol{\Delta}^{-1})^{-1} \right) \mathbf{V} \right), \quad (22)$$

which is proportional to a weighted average of the IMSE-criterion $(\mathbf{M}(\xi)^{-1}\mathbf{V})$ in the model without random effects and the corresponding Bayesian IMSE-criterion $\operatorname{tr}\left((\mathbf{M}(\xi) + \boldsymbol{\Delta}^{-1})^{-1}\mathbf{V}\right)$. Hence the IMSE-criterion for prediction can be interpreted as a compound criterion, which could equivalently be identified with a certain constrained criterion according to Cook and Wong (1994).

If we allow for approximate designs in the sense of Kiefer (1974), then a standard equivalence theorem can be obtained, which characterizes the IMSE-optimal design, which minimizes the IMSE-criterion.

Theorem 3. *The approximate design ξ^* is IMSE-optimal for prediction, if and only if*

$$\begin{aligned} &(n-1)\, \mathbf{f}(x)^\top \mathbf{M}(\xi^*)^{-1} \left(\mathbf{M}(\xi^*)^{-1} + \boldsymbol{\Delta} \right)^{-1} \boldsymbol{\Delta} \mathbf{V} \boldsymbol{\Delta} \left(\mathbf{M}(\xi^*)^{-1} + \boldsymbol{\Delta} \right)^{-1} \mathbf{M}(\xi^*)^{-1} \mathbf{f}(x) \\ &\qquad + \mathbf{f}(x)^\top \mathbf{M}(\xi^*)^{-1} \mathbf{V} \mathbf{M}(\xi^*)^{-1} \mathbf{f}(x) \qquad (23) \\ \leq\ &(n-1) \operatorname{tr} \left(\boldsymbol{\Delta} \left(\mathbf{M}(\xi^*)^{-1} + \boldsymbol{\Delta} \right)^{-1} \mathbf{M}(\xi^*)^{-1} \left(\mathbf{M}(\xi^*)^{-1} + \boldsymbol{\Delta} \right)^{-1} \boldsymbol{\Delta} \mathbf{V} \right) + \operatorname{tr} \left(\mathbf{M}(\xi^*)^{-1} \mathbf{V} \right) \end{aligned}$$

for all $x \in \mathcal{X}$. Moreover, for any support point x_j of ξ^* with positive weight ($w_j = \xi^*(x_j) > 0$) equality holds in (23).

For regular dispersion matrices $\mathbf{D}$ condition (23) of Theorem 3 simplifies.

Corollary 2. *If $\mathbf{D}$ is regular, the approximate design ξ^* is IMSE-optimal for prediction if and only if*

$$\begin{aligned} &\mathbf{f}(x)^\top \left((n-1)(\mathbf{M}(\xi^*) + \boldsymbol{\Delta}^{-1})^{-1} \mathbf{V} (\mathbf{M}(\xi^*) + \boldsymbol{\Delta}^{-1})^{-1} + \mathbf{M}(\xi^*)^{-1} \mathbf{V} \mathbf{M}(\xi^*)^{-1} \right) \mathbf{f}(x) \\ &\quad \leq \operatorname{tr} \left(\left((n-1)(\mathbf{M}(\xi^*) + \boldsymbol{\Delta}^{-1})^{-1} \mathbf{M}(\xi^*) (\mathbf{M}(\xi^*) + \boldsymbol{\Delta}^{-1})^{-1} + \mathbf{M}(\xi^*)^{-1} \right) \mathbf{V} \right) \qquad (24) \end{aligned}$$

for all $x \in \mathcal{X}$. Moreover, for any support point x_j of ξ^* with positive weight ($w_j = \xi^*(x_j) > 0$) equality holds in (24).

Remark 1. Consider the special case of random intercepts (random block effects). There an explicit individual specific constant term is included, $f_1(x) \equiv 1$, say. The dispersion matrix $\mathbf{D} = d_1 \mathbf{e}_1 \mathbf{e}_1^\top$ has rank one, where $\mathbf{e}_1^\top = (1, 0, ..., 0)$ is the first unit vector of length p. In this situation the IMSE-criterion

$$\mathrm{IMSE}_{\mathrm{pred}}(\xi) = \sigma^2 \left(\frac{1}{m} \operatorname{tr}\left(\mathbf{M}(\xi)^{-1} \mathbf{V} \right) + \frac{(n-1) d_1}{1 + m\, d_1} \nu(\mathcal{X}) \right), \tag{25}$$

depends on the dispersion matrix only through an additive constant. Hence, the IMSE-optimal design in the fixed effects model remains IMSE-optimal for prediction in the random intercepts model.

4 Example: Straight Line Regression

For illustrative purposes we consider here the model

$$Y_{ij} = \beta_{i1} + \beta_{i2} x_j + \varepsilon_{ij}\,, \tag{26}$$

of a straight line regression on the experimental region $\mathcal{X} = [0, 1]$. The experimental setting x_j may be considered as a dosage and $x_j = 0$ yields an observation at baseline.

In the case of no random effects it is well-known that the IMSE-optimal design assigns half of the observations to the baseline and half of the observations to the maximal dose. According to Remark 1 this design retains its optimality for prediction in the case of random intercepts β_{i1}. However, this does not remain true, if we allow for random slopes β_{i2}. To keep calculations simple we assume that only the slope is random, i. e. $\beta_{i1} \equiv \beta_1$ and $\mathbf{D} = d_2 \mathbf{e}_2 \mathbf{e}_2^\top$. In view of the equivalence theorem (Theorem 1) the IMSE-optimal design ξ^* takes only observations at the baseline ($x = 0$) and at the highest dose ($x = 1$) and has hence the form $\xi^* = \begin{pmatrix} 0 & 1 \\ 1 - w^* & w^* \end{pmatrix}$, where only the optimal weight w^* at $x = 1$ has to be determined.

For numerical calculations we assume a sample size of $n = 100$ individuals and an intra-individual sample size of $m = 10$ observations per subject. For these numbers the optimal weight w^* is depicted in Figure 4 in dependence on the "intra-class correlation" $\rho = d_2/(1 + d_2)$ at $x = 1$. Here and in the following figure ρ is chosen instead of d_2 on the horizontal axis to cover the whole range of variances d_2 in a finite interval ($0 \le \rho \le 1$). The optimal weight w^* increases in d_2 from $w^* = 0.50$ for $d_2 = 0$ ($\rho = 0$, no random effects) to $w^* \approx 0.91$ for $d_2 \to \infty$ ($\rho = 1$).

To see, what may be gained by using the optimal design for prediction, we have plotted the efficiency of the IMSE-optimal design in the fixed effects model, which assigns equal weights $w = 1/2$ to both the baseline $x = 0$ and the maximal dose $x = 1$, for varying dispersions d_2 in Figure 4. Of course, for $d_2 = 0$ ($\rho = 0$, no random effects) the efficiency equals 1. The efficiency decreases, as the dispersion d_2 increases, with a limiting value 0.60 for $d_2 \to \infty$ ($\rho = 1$).

These pictures do not change much, if we introduce additionally a random intercept with small dispersion d_1, which makes $\mathbf{D}$ regular. The Bayes-optimal design in this situation, which minimizes $\operatorname{tr}\left((\mathbf{F}^\top \mathbf{F} + \mathbf{D}^{-1})^{-1} \right)$, assigns all observations to the maximal dose $x = 1$ and does, hence, not allow for prediction, as the fixed effects information $\mathbf{F}^\top \mathbf{F}$ is singular. Consequently in this situation the efficiency of the Bayes-optimal design equals zero.

5 Discussion and Conclusions

In the present note we develop the mean squared error for the estimation (prediction) of the individual responses as a performance characteristic of the design of an experiment. The resulting

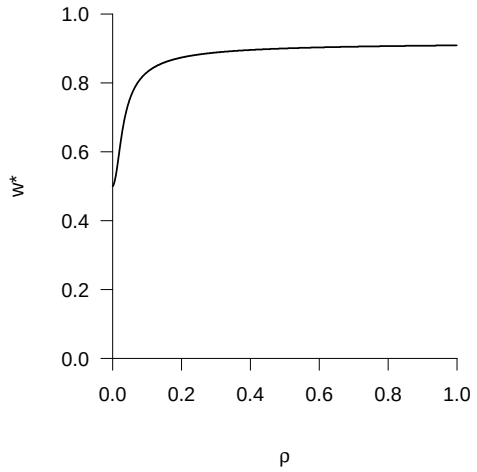

Figure 1: Optimal weight w^* in dependence of the variance parameter $\rho = d_2/(1 + d_2)$

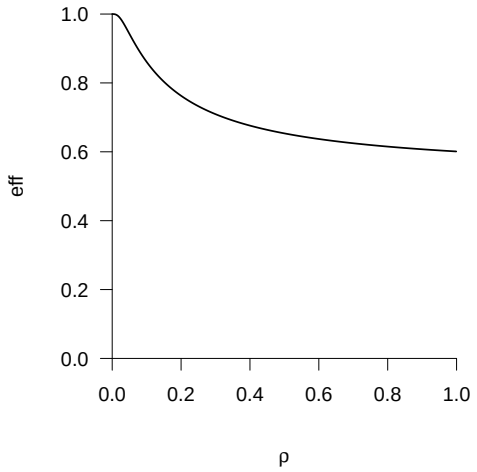

Figure 2: Efficiency of the equi-replicated design ($w = \frac{1}{2}$) in dependence of the variance parameter $\rho = d_2/(1 + d_2)$

objective function is a compromise between the Bayesian and the standard fixed effects objective function proposed so far and accounts for both the information from the observations within an individual as well as the information obtained from the other subjects within the population. In particular, the Bayesian criterion, which in a way neglects the intra-individual information and takes the population information for granted, may lead to useless designs, which do not allow for the estimation of the quantities of interest. As a specific design criterion under investigation we use here the integrated mean squared error for approximating the individual response curves over the whole design region, which is a quite natural choice. For this criterion we derive some characterizations of optimal designs, which may substantially differ from the competing designs obtained by maximizing the corresponding Bayesian or standard criteria. As a by-product we obtain that in the particular case of random intercepts the standard optimal designs retain their optimality. For computational ease we only considered approximate individual designs, which might be criticized, as typically sample sizes within individuals will be small. However these optimal approximate designs may serve well as a benchmark for candidate designs, which themselves can be derived from the optimal approximate designs by intelligent rounding. But this goes beyond the scope of the present paper. Finally we illustrate the dependence of the optimal design on the dispersion parameters as well as the efficiency of the competing designs by a simple example. This gives rise to the problem that the obtained optimal designs are only locally optimal for a specific dispersion. Robustness and sensitivity with respect to the dispersion should be investigated in the future and potentially more robust designs should be developed, which are maximin efficient or optimal with respect to some weighted ("pseudo Bayesian") criterion. Furthermore, it is to be expected that the qualitative results obtained here will carry over to other design criteria, which will be object of further investigations.

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On optimal space-time excitation structures for parameter estimation in linear partial differential equations

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Abstract: The problem of D-optimal input signals selection for parameter estimation in systems described by partial differential equations (PDE) is considered. In opposite to earlier results, the time-domain synthesis of input signals is discussed. In addition to the optimality conditions, the time-space structure of optimal input signals is derived and approximate explicit solutions are obtained for systems described by the parabolic and the hyperbolic PDE's.

Keywords: D-optimal input signals, parameter estimation, distributed-parameter systems.

1 Introduction

The problems of parameter estimation or identification in systems described by PDE's were considered in many papers, see Banks and Kunisch (1989), Banks and Kojima (1988), Chavent and Kunisch (2002), Uci nski (2005), Fleming and Moheimani (2003), Ito and Kunisch (1997), Kunisch and Nakagiri (1995), Kunisch (1988), Pierce (1979), Rafajłowicz (1984), Rafajłowicz (2000), among others. In this context the problem of sensors' allocation also received much attention, see Rafajłowicz (1978), Rafajłowicz (1981), Rafajłowicz (1987), Uci nski (2000) and interesting results on moving sensors trajectories, which are contained in Uci nski (2005).

Much less is known on optimal input signals selected for increasing the accuracy of parameter estimation in PDE's. Several results in this direction can be found in Rafajłowicz (1983), Rafajłowicz (1985), Rafajłowicz (1986), where mainly the so called frequency-domain synthesis is discussed. Partial results on the time-domain synthesis can be found in Rafajłowicz (1989). Our aim in this paper is to develop further this approach and to attain (almost) explicit solutions for important classes of PDE's. In more details, our aims include:

- providing a brief introduction to the time-domain method of selecting input signals for linear, time-invariant (LTI) dynamic systems, described by ODE's,
- indicating that new technologies of sensing and actuating in space and time can lead to new (sometimes easier) problems of input signal selection.
- discussing a new method of generating well-distributed points using space-filling curves as a way of approximating observations at every spatial point.
- focusing on input signals for parameter estimation in LTI systems with spatio-temporal dynamics.
- illustrating an interplay between spatial and time domain structure of optimal input signals,
- comparing the results obtained here with those that were presented by the first author at the Isaac Newton Institute for Mathematical Sciences, Cambridge University, UK, July 2011, that were obtained in the space-frequency domain (under different constraints),

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2 Time domain approach to optimal input signal for ODE parameter estimation

We confine to the class of systems to LTI systems, described by Green's function of an ordinary differential equation (ODE) with constant parameters. Observations are made at every $t \in (0, T)$ (the theory conveys to equidistant discrete-time observations, but formulas are less transparent). We assume that there is no feedback, i.e., input signals generated in an open loop – typical when our aim is to estimate parameters of our system, e.g. material constants.

System. Consider LTI system described by ODE

$$\frac{d^r\, y(t)}{d\, t^r} + a_{r-1}\, \frac{d^{r-1}\, y(t)}{d\, t^{r-1}} + \ldots + a_0\, y(t) = a_r\, u(t), \tag{1}$$

$t \in [0,\, T]$ with zero initial conditions (for simplicity), where T – the horizon of observations, $y(t)$ is the output, $u(t)$ is the input.

The solution $y(t;\, \bar{a})$ of (1) depends on the vector $\bar{a} = [a_0,\, a_1, \ldots,\, a_r]^{tr}$ of unknown parameters, where tr is the transposition.

Observations. Available observations:

$$Y(t) = y(t;\, \bar{a}) + \varepsilon(t), \quad t \in [0,\, T], \tag{2}$$

where $\varepsilon(t)$ is zero mean, uncorrelated, Gaussian "white noise", more precisely, $\varepsilon(t)$ is implicitly defined by:

$$d\, W(t) = \varepsilon(t)\, dt, \tag{3}$$

where $W(t)$ is the Wiener process.

It can be shown (Goodwin, Payne 70') that the Fisher information matrix (FIM) $M_T(u)$ for estimating $\bar{a}$ from (2) has the form:

$$M_T(u) = \int_0^T \nabla_a y(t;\bar{a})\, (\nabla_a y(t;\bar{a}))^{tr}\, dt \tag{4}$$

and from the Cramer-Rao inequality we know that for any estimator $\tilde{a}$ of $\bar{a}$ we have:

$$cov(\tilde{a}) \geq M_T^{-1}(u). \tag{5}$$

For LSQ estimator the equality in (5) is asymptotically attained. Thus, it is meaningful to minimize interpretable functions of $M_T^{-1}(u)$, e.g., $\min Det[M_T^{-1}(u)]$ w.r.t. $u(.)$, under certain constraints on $u(.)$. Later, we admit: $U \stackrel{def}{=} \left\{u : \int_0^T u^2(t)\, dt \leq 1\right\}$.

Nonconvexity of FIM. The problem $\min_{u\in U} Det[M_T^{-1}(u)]$ is not convex w.r.t. $u(.)$. Indeed, the sign $\underbrace{\ }$ in the formula below indicates the reason:

$$M_T(u) = \int_0^T \int_0^T H(\tau,\, \nu;\, \bar{a})\, \underbrace{u(\tau)\, u(\nu)}, d\tau\, d\nu, \tag{6}$$

$$H(\tau,\, \nu;\, \bar{a}) \stackrel{def}{=} \int_0^T \bar{k}(t-\tau;\bar{a})\, \bar{k}^{tr}(t-\nu;\bar{a})\, dt, \tag{7}$$

where $r \times 1$ vector of sensitivities $\bar{k}(t;\bar{a}) \stackrel{def}{=} \nabla_a g(t;\bar{a})$, is defined through the impulse response (Green's function) of ODE (1), denoted later by $g(t;\bar{a})$. Note that $g(t;\bar{a}) = 0$, $t < 0$.

Embedding. As a remedy to the fact that $M_T(u)$ is not linear in u, we propose the embedding of the initial problem the problem into a larger class of problems with the following matrix:

$$M_{ext}(w) = \int_0^T \int_0^T H(\tau,\, \nu;\, \bar{a})\, w(\tau,\, \nu)\, d\tau\, d\nu. \tag{8}$$

Note that if $w(\tau,\, \nu) = u(\tau)\, u(\nu)$, then $M_{ext}(w) = M_T(u)$. We also define set $\mathcal{W}$ as follows:

$$\mathcal{W} = convex\ hull\left\{w(\tau,\nu) = u(\tau)\, u(\nu) : u \in U\right\}. \tag{9}$$

Note: $w \in \mathcal{W}$ iff for certain I and $\alpha_i \geq 0$,

$$w(\tau,\nu) = \sum_{i=1}^{I} \alpha_i\, u_i(\tau)\, u_i(\nu), \qquad \sum_{i=1}^{I} \alpha_i = 1. \tag{10}$$

Lemma 1 *If $H(\tau,\, \nu; \bar{a})$ continuous in $(\tau,\, \nu) \in [0,\, T]^2$, then the set $\mathcal{M} \stackrel{def}{=} \{M_{ext}(w) :\, w \in \mathcal{W}\}$ is convex, closed and bounded.*

The proof follows the same lines as in Pazman (1986). The logic of inference under embedding is the following.

1. Observe that
$$\min_{u\in U} Det\left[M_T^{-1}(u)\right] \geq \min_{w\in\mathcal{W}} Det\left[M_{ext}^{-1}(w)\right] \tag{11}$$
2. Solve the problem:
$$w^* = \arg\ \min_{w\in\mathcal{W}} Det\left[M_{ext}^{-1}(w)\right] \tag{12}$$
3. If one can find $u^* \in U$ such that $w^*(\tau,\, \nu) = u^*(\tau)\, u^*(\nu)$, then, by (11), u^* solves our problem.

Optimality conditions. For w^* that solves (12) define a kernel:

$$ker^*(\tau,\, \nu) = trace\left[M_{ext}^{-1}(w^*)\, H(\tau,\, \nu)\right], \tag{13}$$

which is symmetric and nonnegative definite, i.e.,

$$\forall\ f \in L_2(0,T)\ \int_0^T \int_0^T ker^*(\tau,\, \nu) f(\tau)\, f(\nu) \geq 0.$$

As it is known (see, e.g., Yosida (1981)), there exists a sequence of orthonormal eigenfunctions $\phi_k^*(\tau)$ and nonnegative eigenvalues μ_k^*, $k = 1,\, 2, \ldots$ of the integral operator:

$$\mu\, \phi(\tau) = \int_0^T ker^*(\tau,\, \nu)\, \phi(\nu)\, d\nu. \tag{14}$$

One can express the optimality conditions in terms of eigenvalues of (14).

Theorem 1 (The equivalence theorem)
1) $w^* = arg\ \min_{w\in\mathcal{W}} Det\left[M_{ext}^{-1}(w)\right]$ if and only if the following cndition holds:

$$\sup_{k=1,2\ldots} \mu_k^* = r + 1 = dim(\bar{a}). \tag{15}$$

2) For w^* as in 1) there exists $\hat{w}(\tau,\nu) = \phi^*(\tau)\, \phi^*(\nu)$, which is also D-optimal and

$$M_{ext}(w^*) = M_{ext}(\hat{w}) = M_T(\phi^*),$$

where ϕ^* is the eigenfunction, corresponding to the largest eigenvalue in (15).

The scheme of the proof follows the steps of the Kiefer-Wolfowitz equivalence theorem. The main ingredients are the following:
1) $\forall w \in \mathcal{W}$ with $M_{ext}(w)$ nonsingular we have (due to (10)):

$$(r+1) = trace[M_{ext}^{-1}(w)\, M_{ext}(w)] == \int\int ker_w(\tau,\nu)\, w(\tau,\nu) \leq \mu_{max}(w)$$

where $\mu_{max}(w)$ is the largest eigenvalue of the integral operator with the kernel:

$$ker_w(\tau,\nu) = trace[M_{ext}^{-1}(w)\, H(\tau,\nu;\bar{a})]$$

2) Assume that $w^* \in \mathcal{W}$ is D-optimal and consider: $w_\alpha(\tau,\nu) = (1-\alpha)\, w^*(\tau,\nu) + \alpha\, \phi^*(\tau)\, \phi^*(\nu)$. Then, calculate: $\frac{d\, \log(Det[M_{ext}(w_\alpha)}{d\,\alpha}|_{\alpha=0+}$.

- Condition (15) allows to check the optimality of a given w rather than to infer how it looks like. It is a powerful tool for constructing algorithms for searching u^* in the spirit of the Wynn-Fedorov method.
- When one parameter is estimated, we are frequently able to derive the optimal input signal explicitly.
- The above derivations conveys to L-optimality criterions.
- $ker^*(\tau,\, \nu)$ can be interpreted as an approximation to the variance of prediction, but we skip the discussion on the relationships to G-optimality.

The curse of a priori knowledge. As in optimum experiment design for nonlinear (in parameters) regression estimation, also here the optimal u^* depends on unknown $\bar{a}$. There are well known ways of circumventing this difficulty:

1. use "the nominal" parameter values for $\bar{a}$,
2. the "worst case" analysis,
3. the Bayesian approach: use prior distribution imposed on $\bar{a}$,
4. apply "the adaptive" approach of subsequent estimation and planning stages.

Later we use the "nominal" parameter values $\bar{a}$, but the results are relevant also to other approaches.

Example 1 (1-st order system) *Consider the system:* $\dot{y}(t) + a\, y(t) = u(t)$, *where* $a > 0$ *is unknown. Then, for* $t > 0$ $g(t;\, a) = \exp(-a\, t)$ *and zero otherwise. Its sensitivity to* a *is given by* $\nabla_a\, g(t;\, a) = -t\, \exp(-a\, t), \quad t > 0$. *Thus,*

$$H(\tau,\nu;a) = (4a^3)^{-1}\, e^{a(\nu-2T+\tau)}\, C(\tau,\nu,T)$$

where $C(\tau,\nu,T)$ *is a function, which is too complicated to be worth displaying.* $H(\tau,\nu;a)$ *is intractable, but – using the first order Taylor's expansion – for small* T *we obtain:*

$$H(\tau,\nu;a) \approx T\, [\nu\, \exp(a\nu)]\, [\tau\, \exp(a\,\tau)]\,, \tag{16}$$

Hence, $ker^*(\tau,\nu) = \frac{1}{M_{ext}(w^*)}\, H(\tau,\nu;a) \approx T\, [\nu\, \exp(a\nu)]\, [\tau\, \exp(a\,\tau)]\, / M_{ext}(w^*)$ *is a degenerated kernel and it is clear that* $\phi^*(\tau) = \tau\, \exp(a\,\tau)$. *Thus,* $u^*(t) = s^{-1}\, t\, \exp(a\, t)$, $t > 0$, *where* $s \stackrel{def}{=} \frac{1}{2}\left(e^{2T}(2(T-1)T+1) - 1\right)^{\frac{1}{2}}$ *is the normalization constant. Note that* $u^*(t)$ *is a very aggressive input signal. Hence, it is reasonable to apply it on a short interval* $(0,\, T)$ *only, not only for the mathematical convenience, but also for practical reasons. Furthermore, for larger* $a \Rightarrow$ *the growth of* $u^*(t)$ *is faster.*

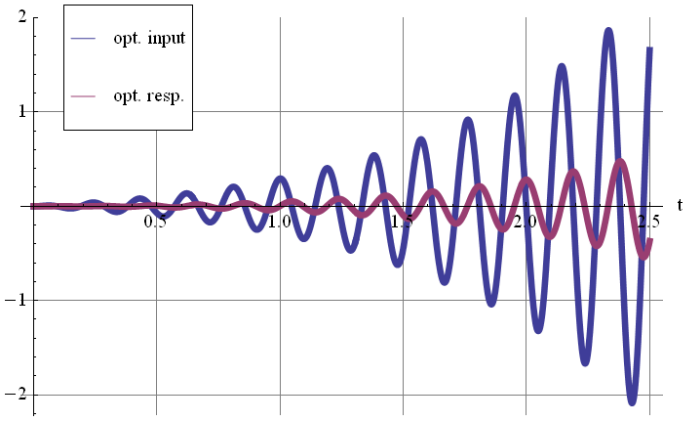

Figure 1: Optimal input and output signal in Example 2.

Example 2 (2-nd order system) *Consider 2-nd order ODE with known resonance frequency* ω_0 *and unknown damping parameter* ξ *(to be estimated).*

$$\ddot{y}(t) + 2\,\xi\,\dot{y}(t) + \omega_0^2\,y(t) = \omega_0\,u(t), \tag{17}$$

$\dot{y}(0) = 0$, $y(0) = 0$. *Its sensitivity has the form:* $k(t;\xi) = \nabla_\xi\, g(t;\xi) = -t\,\exp(-\xi\,t)\,\sin(\omega_0\,t)$. *Integrated sensitivity is so complicated that we approximate it (for small* T*) as follows:*

$$H(\tau,\nu;\xi) \approx T\,k(T-\tau;\xi)\,k(T-\nu;\xi) = T\,\mu\,\tau\,\exp(\xi\,\mu + \xi\,\tau)\,\sin(\omega_0\,\mu)\sin(\omega_0\,\tau)$$

Again, we have the degenerate kernel and it is easy to guess D-optimal input signal:

$$u^*(t) = b^{-1}\,t\,\exp(\xi\,t)\,\sin(\omega_0\,t), \tag{18}$$

where b *is the normalizing constant. This signal and the system response to it are shown in Fig. 1. As in the previous example, larger* ξ *(more dumping in a system) leads to the compensation of the sensitivity by the rapidly growing amplitude* $t\,\exp(\xi\,t)$.

We shall use the above examples as building blocks for D-opt. signals for estimating parameters in PDE's. We underline, that Thm. 1 is valid for arbitrary $T > 0$. We have used approximations for "small" T in our examples only.

3 Sensors for PDE parameter estimation

Our aim in this section is to discuss briefly availability of observations that are made at each point of a spatial domain. Firstly, we mention new devices that emerged in recent twenty years. Then, we discuss the way of generating sensors' positions, which are so well-distributed in space that we can regard observations from them as made continuously in space.

3.1 An impact of new devices

Old paradigms (from 60' of XX-th century) concerning identification of systems with spatio-temporal dynamics assumed that observations of a system state and actuators that influence our system can act at a finite number of spatial points only.

New techniques and devices – developed in last 50 years – such as industrial cameras and thermovision provide information, which can be considered as observations that are continuous in space. Also micro-mechanical and electrical measurement systems (MEMS), e.g., accelerometers, provide information, which can be treated as coming from each point in space (see below).

On the other hand, high energy lasers, acting as moving sources, microwave heating and shape changing materials (e.g., piezo- electric bonds) can be considered as acting as spatially distributed sources. Summarizing, in addition to point-wise and moving sensors and actuators, it is reasonable and useful to consider spatially distributed observations and actuators for estimating parameters of PDE's and to develop a theory for them.

3.2 Well-distributed sequences generated by SFC's as sensors' positions

Our aim is to sketch briefly the construction of well-distributed (WD) points. In this paper they serve for approximating observations as if they were made continuously in space, but they can be also useful as experiment designs for nonparametric estimation of a regression function, extending the results of Rafajłowicz and Schwabe (2006) and Rafajłowicz and Schwabe (2003).

Definition 1 (Equi-distributed sequences) *A deterministic sequence $(x_i)_{i=1}^n$ of points from the unit cube $I_d \subset \mathbb{R}^d$ is called equi-distributed (EQD) sequence in I_d if $\lim_{n\to\infty} n^{-1}\sum_{i=1}^n g(x_i) = \int_{I_d} g(x)\,dx$ holds for every g continuous on I_d.*

Formally, EQD's behave as uniformly distributed random sequences. They are also called uniformly distributed, quasi-random or quasi Monte-Carlo sequences, see, e.g., Kuipers and Niederreiter (1974), where also the following one-dimensional example of EQD sequence is discussed:

$$x_i = \text{fractional part}(i\,\theta), \quad i = 1, 2, \ldots, \tag{19}$$

where θ is an irrational number.

Definition 2 (Well-distributed sequences) *Sequence $(x_i)_{i=1}^n$ is called well distributed (WD) in I_d if $\lim_{n\to\infty} n^{-1}\sum_{i=k}^{k+n} g(x_i) = \int_{I_d} g(x)\,dx$ holds uniformly in k, for every $g \in C(I_d)$*

It is known that (19) is WD. As far as we know, multidimensional, extendable WD sequences are not known, where by extendability of WD sequence we mean that one add a new point to the sequence without the necessity of recalculating and changing positions of the previous points Niederreiter and Pillichshammer (2009).

The sequence that is proposed below is WD and extendable. Its construction is based on space-filling curves (SFC).

Definition 3 (Space-filling curve) *A space-filling curve is a mapping: $\Phi : I_1 \overset{onto}{\to} I_d$, which is a continuous function on $I_1 = [0, 1]$ and maps I_1 onto I_d.*

The Hilbert, Peano and Sierpinski are well known examples of SFCs. They can be approximated in $O\left(\frac{d}{\varepsilon}\right)$ arithmetic operations ($\varepsilon > 0$ is a desired accuracy), as it was proved by Butz (1971) and Skubalska-Rafajłowicz (2001) and Skubalska-Rafajłowicz (2003).

Our method for WD sequences runs as follows:
Step 1) Generate WD one-dimensional sequence in [0, 1]: $t_i = \text{frac}(i\,\theta), \quad i = 1, 2, \ldots,$
Step 2) Select SFC Φ and generate x_i's as $x_i = \Phi(t_i)$, $i = 1, 2, \ldots$.

Theorem 2 *If θ is irrational and SFC has the property: for all functions $g : I_d \to \mathbb{R}$*

$$\int_{I_d} g(x)\,dx = \int_0^1 g(\Phi(t))\,dt, \tag{20}$$

then our sequence x_i is not only EQD, but also well distributed.

We omit the technical proof of this result. Note that property (20) is shared by the Sierpinski, the Peano and the Hilbert SFC's. From the well known Koksma-Hlavka inequality (see, e.g., Kuipers and Niederreiter (1974)) it follows that having a WD sequence one can approximate $\int g(x)$ very accurately by $n^{-1}\sum_{i=1}^{n} g(x_i)$. As we shall see in the next section, in our derivations spatial sensors' positions appear under integrals only. Thus, we can consider observations as continuous in space, when sensors' are placed at WD points,

4 Input signals for estimating parameters in PDE's

Consider a spatio-temporal systems described by:

- $q(x,t)$ – the system state at spatial point $x \in \mathbb{R}^d$ and time t, we shall also write $q(x,t;\bar{a})$ to indicate its dependence on unknown parameters,
- $U(\chi,t)$ – an input signal at spatial point $\chi \in \Omega \subseteq \mathbb{R}^d$ and time t, where Ω is a bounded and open domain.

System description. Consider the following class of PDE:

$$\{\ddot{q}(x,t)\} + \mu\,\dot{q}(x,t) = A_x(\bar{a})\,q(x,t) + U(x,t), \tag{21}$$

$x \in \Omega$, where $\dot{q}(x,t) = \frac{\partial q(x,t)}{\partial t}$, $A_x(\bar{a})$ – an operator of the elliptic type. When the term $\ddot{q}(x,t)$ is present, we have PDE of the hyperbolic type, if not, the our PDE is classified as that of the parabolic type. (e.g., heat conduction or diffusion). Note: that we treat μ as known parameter for brevity, but it can be included also as unknown parameter. Interpretable examples of $A_x(\bar{a})$ include:

$$A_x(\bar{a})\,q(x,t) = a_1\,\frac{\partial^2 q(x,t)}{\partial x_1^2} + a_2\,\frac{\partial^2 q(x,t)}{\partial x_2^2} + a_3\,q(x,t),$$

$$A_x(\bar{a})\,q(x,t) = a_1\,\frac{\partial^4 q(x,t)}{\partial x_1^4} + a_2\,\frac{\partial^4 q(x,t)}{\partial x_2^4}, \tag{22}$$

which should be accompanied by boundary conditions that are included into the description of the domain of $A_x(\bar{a})$, denoted as $\mathcal{D}(A_x) \subset L^2(\Omega)$, where $L^2(\Omega)$ – the class of squared integrable functions with the inner product $< f, g >= \int_\Omega f(x)\,g(x)\,dx$.

More generally, we admit operators A_x of the form:

$$A_x(\bar{a})\,q(x,t) = \sum_{i=1}^{r} a_i\,P_x^{(i)}\,q(x,t), \tag{23}$$

where $P_x^{(i)}$, $i = 1,\ldots,r$ are differential operators w.r.t. spatial variables and such that:

- A_x is symmetric, i.e., $\forall f,\, g \in L_2(\Omega)$: $< A_x(\bar{a})\,f,\, g > = < f,\, A_x(\bar{a})\,g >$.
- A_x is positive definite, i.e., $\forall f, \in L_2(\Omega)\ f \neq 0 \ \Rightarrow\ < f,\, A_x(\bar{a}) f > \in \mathbb{R}^+$
- Eigenfunctions $v_1(x)$, $v_2(x),\ldots$ of $A_x(\bar{a})$ do not depend on $\bar{a}$ (it suffices that v_k's are eigenfunctions of $P_x^{(i)}$).
- This implies that the eigenvalues $\lambda_k(\bar{a})$ of $A_x(\bar{a})$ are linear functions of $\bar{a}$, i.e., $\lambda_k(\bar{a}) = \bar{b}_k^{tr}\,\bar{a}$, $A_x(\bar{a})\,v_k = -\lambda_k(\bar{a})\,v_k$ for certain (known) vectors $\bar{b}_k$, $k = 1, 2, \ldots$
- We assume that v_k, $k = 1, 2, \ldots$ form complete and orthonormal basis of $L_2(\Omega)$.

Here and later we assume that initial conditions are zero. Under these assumptions the solution of (21) is of the form:

$$q(x,t;\bar{a}) = \sum_{k=1}^{\infty} v_k(x)\, y_k(t;\bar{a}), \tag{24}$$

where $y_k(t)$'s are the solutions of

$$\{\ddot{y}_k(t;\bar{a})\} + \mu\, \dot{y}_k(t;\bar{a}) = -\lambda_k(\bar{a})\, y_k(t;\bar{a}) + u_k(t), \tag{25}$$

$u_k(t) \stackrel{def}{=} \int_\Omega U(x,t)\, v_k(x)\, dx$, $\dot{y}_k(0) = y_k(0) = 0$.

Observations of system (21) for estimating $\bar{a}$ have the form:

$$Y(x,t) = q(x,t;\bar{a}) + \varepsilon(x,t), \quad x \in \Omega, \tag{26}$$

where $\varepsilon(x,t)$ is zero mean, uncorrelated in space and time, covariance stationary, Gaussian process ($\sigma^2 = 1$). $t \in (0,\, T)$.

The Fisher information matrix is given by

$$\mathbb{M}_T(U) = \int_\Omega \int_0^T \nabla_a q(x,t;\bar{a})\, \nabla_a^{tr} q(x,t;\bar{a})\, dt\, dx. \ (**) \tag{27}$$

Problem statement: find D-optimal spatio-temporal input signal U^* such that $Det\left[\mathbb{M}_T^{-1}(U)\right]$ is minimized over all $U \in L_2(\Omega \times (0,T))$ with the constrained energy, i.e.,

$$\int_\Omega \int_0^T U^2(x,t)\, dt\, dx \ \leq\ 1. \tag{28}$$

Embedding again. The completeness and orthogonality of eigenfunctions v_k of A_x allows us to reformulate our problem. To this end, define $u_k(t) =< U(.,t), v_k >$, then constraint (28) reads as

$$\sum_{k=1}^{\infty} \int_0^T u_k^2(t)\, dt \ \leq\ 1 \tag{29}$$

while FIM can be expressed as follows:

$$\mathbb{M}_T(U) = \sum_{k=1}^{\infty} \int_0^T \nabla_a y_k(t;\bar{a})\, \nabla_a^{tr} y_k(t;\bar{a})\, dt. \tag{30}$$

Denoting by $I_k(t;\bar{a})$ the impulse response of (25), we obtain

$$\nabla_a y_k(t;\bar{a}) = \int_0^T \nabla_a I_k(t-\tau;\bar{a})\, u_k(\tau)\, d\tau. \tag{31}$$

Thus, FIM can be expressed as

$$\mathbb{M}_T(U) = \sum_{k=1}^{\infty} \int_0^T \int_0^T H_k(\tau,\nu;\bar{a})\, \underbrace{u_k(\tau) u_k(\nu)}\, d\tau\, d\nu,$$

where $\underbrace{\ }$ indicates the same source of non-convexity as in 1-D case, while

$$H_k(\tau,\nu;\bar{a}) \stackrel{def}{=} \int_0^T \nabla_a I_k(t-\tau;\bar{a})\, \nabla_a^{tr} I_k(t-\nu;\bar{a})\, dt$$

We can not select one mode and optimize its input signal, because, $H_k(\tau,\nu;\bar{a}) = \bar{b}_k\,\bar{b}_k^{tr}\,c_k(\tau,\nu;\bar{a})$ is rank one matrix, where $c_k(\tau,\nu;\bar{a}) \stackrel{def}{=} \int_0^T \rho_k(t-\tau;\bar{a})\,\rho_k(t-\nu;\bar{a})\,dt$. while

$$\ddot{\rho}_k(t;\bar{a}) + \mu\,\dot{\rho}_k(t;\bar{a}) = -\lambda_k(\bar{a})\,\rho_k(t;\bar{a}) - I_k(t), \tag{32}$$

$$\ddot{I}_k(t;\bar{a}) + \mu\,\dot{I}_k(t;\bar{a}) = -\lambda_k(\bar{a})\,I_k(t;\bar{a}) + \delta(t). \tag{33}$$

Note also that $\nabla_a I_k(t;\bar{a}) = \bar{b}_k\,\rho_k(t;\bar{a})$. We are at the position to apply the embedding trick again, but this time it is more complicated. As the optimization variables we consider sequences of the form:

$$W = [\alpha_1\,w_1(\tau,\nu),\,\alpha_2\,w_2(\tau,\nu),\ldots], \tag{34}$$

$$w_k \in \mathcal{W}, \quad \alpha_k \geq 0, \quad \sum_{k=1}^{\infty}\alpha_k \leq 1, \tag{35}$$

where $\mathcal{W}$ is the same as defined by (9). Let us denote by $\mathcal{W}_{seq}$ the set of all such sequences, which is clearly the convex set. For $W \in \mathcal{W}_{seq}$ define $\mathbb{M}_{ext}(W)$ as follows:

$$\mathbb{M}_{ext}(W) = \sum_{k=1}^{\infty}\alpha_k \int_0^T\int_0^T H_k(\tau,\nu;\bar{a})\,w_k(\tau,\nu)\,d\tau\,d\nu.$$

Then, $\log\{Det\,[\mathbb{M}_{ext}(W)]\}$ is a concave functional on $\mathcal{W}_{seq}$.

5 Spatio-temporal structure of the solution

Theorem 3 *D-optimal input signal for parameter estimation in (21) can be expressed as follows:*

$$U^*(x,t) = \sum_{k=1}^{L}\sqrt{\alpha_k^*}\,v_k(x)\,\phi_k^*(t). \tag{36}$$

This signal is D-optimal if and only if the weights $\alpha_k^* \geq 0$, $\sum_{k=1}^L \alpha_k^* = 1$ and $\phi_k^*(t)$, $\int_0^T(\phi_k^*(t))^2\,dt = 1$ are selected so as

$$\sup_{k=1,2,\ldots}\mu_{max}^{(k)}(U^*) = dim(\bar{a}), \tag{37}$$

where $\mu_{max}^{(k)}(U^*)$ is the largest eigenvalue of the integral operator with the kernel $ker_k^*(\tau,\nu) = trace[M_T^{-1}(U^*)\,H_k(\tau,\nu;\bar{a})]$. The number of terms L in (36) can be selected $L \leq R\,(R+1)/2$, $R \stackrel{def}{=} dim(\bar{a})$.

Theorem 4 *Under the assumptions made in the previous section, $H_k(\tau,\nu;\bar{a}) = \bar{b}_k\,\bar{b}_k^{tr}\,c_k(\tau,\nu;\bar{a})$ and then one can select $\phi_k^*(t)$ as the eigenfunction, corresponding to the largest eigenvalue of the operator with kernel $c_k(\tau,\nu;\bar{a})$. In this case, α_k^*'s solve the standard D-optimal problem:*

$$\max_{\alpha_1,\alpha_2,\ldots} Det\left[\sum_{k=1}^{L}\alpha_k\,M_k\right], \tag{38}$$

over all $\alpha_k \geq 0$'s, $\sum_{k=1}^L \alpha_k = 1$, where $M_k \stackrel{def}{=} \gamma_{max}^{(k)}\,\bar{b}_k\,\bar{b}_k^{tr}$, while $\gamma_{max}^{(k)}$ is the largest eigenvalue of the operator with kernel $c_k(\tau,\nu;\bar{a})$.

Several remarks are in order concerning the above results.

- Thm. 3 reveals the structure of D-optimal signal – each spatial mode is excited by its own time domain signal. It allows to check D-optimality of a signal that was "guessed" (as the Kiefer-Wolfowitz thm.).
- Thm. 4 goes further: excitations of spatial modes are eigenfunctions of the operators with kernels $c_k(\tau,\nu;\bar{a})$ that can – in principle – be calculated (they depend only on our system). Furthermore, α_k^*'s can be calculated by solving the standard D-optimal problem (e.g., by the Wynn-Fedorov algorithm).
- These theorems are valid for arbitrary T.

If we allow T to be "small", then we can formulate a simple algorithm for approximating $U^*(x,t)$. By "small" T we mean that the following approximation is sufficiently accurate:

$$c_k(\tau,\nu;\bar{a}) = \int_0^T \rho_k(t-\tau;\bar{a})\,\rho_k(t-\nu;\bar{a})\,dt \approx T\,\rho_k(T-\tau;\bar{a})\,\rho_k(T-\nu;\bar{a}).$$

Approximating optimal solution for "small" T.

Step 1 Set $\phi_k^*(t) = n_k^{-1}\,|\rho_k(T-t;\bar{a})|$, where $n_k \stackrel{def}{=} \left[\int_0^T \rho_k^2(T-t;\bar{a})\,dt\right]^{\frac{1}{2}}$

Step 2 Solve the standard D-optimal design problem: $\max_{\alpha_1,\alpha_2,\ldots} Det\left[\sum_{k=1}^L \alpha_k\,n_k\,\bar{b}_k\,\bar{b}_k^{tr}\right]$.

Step 3 Form the approximation $\widetilde{U}(x,\,t)$ of $U^*(x,\,t)$ as follows:

$$\widetilde{U}(x,t) = \sum_{k=1}^{L} \sqrt{\alpha_k^*}\,v_k(x)\,\rho_k(T-t;\bar{a})/n_k.$$

1. Excitations of each spatial mode is based on its sensitivity function, but running backward in time. For stable systems the sensitivity functions $\rho_k(t;\bar{a})$ are decreasing in time. Thus, D-opt. excitations are rapidly growing in time.
2. Hence, allowing for "small" T is not only for mathematical convenience, but also to prevent a system from destruction.
3. $\rho_k(t;\bar{a})$ rapidly decrease with k – only several first of them is informative at all.

Example 3 (hyperbolic case) *Consider a damped spatio-temporal vibrations described by:*

$$\frac{\partial^2 q(x,t)}{\partial t^2} + 2\,\xi\,\frac{\partial q(x,t)}{\partial t} + a\,\frac{\partial^2 q(x,t)}{\partial x^2} = U(x,t),$$

$x \in (0,1)$, $q(0,t) = q(1,t) = 0$, *where a is unknown parameter. In this case it suffices to excite the first mode of the system $v_1(x) = \frac{1}{\sqrt{\pi}}\sin(\pi\,x)$ by the signal, which is proportional to $t\,exp(\xi\,t)\sin(\sqrt{a}\,t)$. Its not normalized structure is shown in Fig. 2.*

Example 4 (parabolic case) *Consider the heat transfer equation with two unknown parameters a_1, a_2:*

$$\frac{\partial q(x,t)}{\partial t} + a_1\,\frac{\partial^2 q(x,t)}{\partial x^2} + a_2\,q(x,t) = U(x,t),$$

$x \in (0,1)$, $q(0,t) = q(1,t) = 0$. *The space-time structure of the optimal input signal consists of two two modes, $v_1(x) = \frac{1}{\sqrt{\pi}}\sin(\pi\,x)$ and $v_2(x) = \frac{1}{\sqrt{\pi}}\sin(2\,\pi\,x)$, each excited by the exponentially growing function of time as it is show in Fig. 3, but the influence of the 2-nd one almost invisible.*

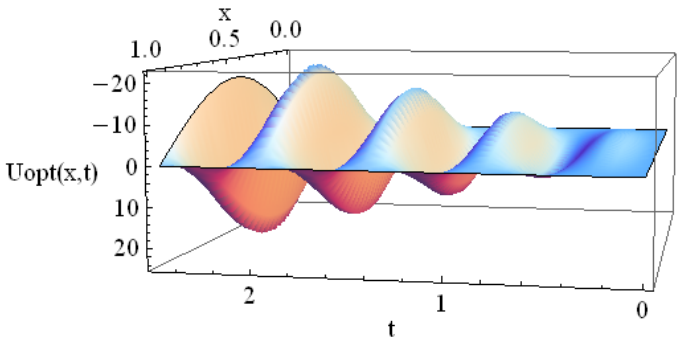

Figure 2: The space-time structure of the optimal input signal in Example 3.

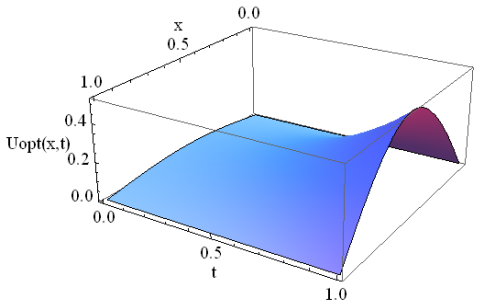

Figure 3: Optimal input signal in Example 4.

What if $U^*(x,t)$ too aggressive ?

- Use very short T. and/or add constraints on the energy of the system state.
- Change setting to the following one:

$$\lim_{T\to\infty} T^{-1} \int_\Omega \int_{-T}^{T} u^2(x,t)\,dx\,dt \le E, \tag{39}$$

where $E > 0$ is admissible input power. Applying (39) requires quite different tools to derive optimality conditions.

Conclusions

1. Under several simplifying assumptions we were able to establish pleasing results that optimal input signals are sums of excitations, which are products of natural modes in space and exponentials or exponentially growing sinusoids with natural system frequencies in time.
2. Should we apply these results in practice ? Only when we are conducting experiments in labs, with perfectly controlled conditions. Otherwise, they provide a lower bound on achievable accuracy. Add constraints to prevent your system from being destroyed.

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Determining the Size of Experiments for ANOVA Models

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Abstract: In this paper the theoretical background for determining the minimal size of an experiment that should be analyzed by analysis of variance with at least one fixed factor about which a null hypothesis has to be tested is given. Described are fixed and mixed models in cross, nested and mixed classifications. Corresponding *R*-programs are demonstrated by examples.

Keywords: Analysis of variance, sample size, non-centrality parameter

1 Introduction

The process of gaining knowledge in the empirical sciences can be considered as follows:
(i) Formulation of the problem,
(ii) Fixing the precision requirements,
(iii) Selecting the statistical model for planning and analysis,
(iv) Determining the (optimal) design of the experiment or survey,
(v) Performing the experiment or the survey,
(vi) Statistical analysis of the observed results,
(vii) Interpretation of the results.

The first four steps belong to the pre-experimental statistics whereas the two last belong to the post-experimental statistics.

The *statistical planning of an experiment* includes the construction of an optimum statistical experimental design and the determination of the *minimum sample size*, which is necessary to achieve, predetermined precision requirements in the context of a chosen statistical model for the analysis of the results.

In this paper we consider only the problem of the determination of the *minimum sample size* of an experiment for the best estimators, the in expectation shortest confidence intervals and the uniformly best unbiased tests which in linear models is sometimes different from determining the sample size.

Point Estimation:

Choose the size of the experiment (random sample) so that the variance of the best estimator is below a given bound *B*. As an example we consider the estimation of the expectation. At first we have to choose the best unbiased estimator, which is the mean of the sample. Its variance is $\frac{\sigma^2}{n}$ and from $\frac{\sigma^2}{n} \le B$ it follows $n \ge \frac{\sigma^2}{B}$ or the integer solution $n = \left\lceil \frac{\sigma^2}{B} \right\rceil$, where $\lceil x \rceil$ is the smallest integer $\ge x$.

Interval Estimation:

If the precision requirement states that the expected half-width of a confidence interval must be less than or equal to δ, then, for a given α, *n* has to be determined so that with the upper bound $\boldsymbol{u}$ and the lower bound $\boldsymbol{l}$ of the $(1-\alpha)$ - confidence interval

$$\frac{1}{2} E\left[\boldsymbol{u}(\alpha) - \boldsymbol{l}(\alpha)\right] \le \delta$$

Of course at first we have to find the $(1-\alpha)$ – confidence interval with the smallest expected length

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As an example we consider the confidence estimation of the expectation of a normal distribution (variance unknown). The shortest (in expectation) two-sided (1-α)- confidence interval is given by

$[\bar{y} - t(n-1;1-\frac{\alpha}{2})\frac{s}{\sqrt{n}} \quad ; \quad \bar{y} + t(n-1;1-\frac{\alpha}{2})\frac{s}{\sqrt{n}}]$, its half expected length is

$$E(H) = t(n-1;1-\frac{\alpha}{2})\frac{E(s)}{\sqrt{n}} = \frac{t(n-1;1-\frac{\alpha}{2})}{\sqrt{n}} \frac{\Gamma\left(\frac{n}{2}\right)\cdot\sqrt{2}}{\Gamma\left(\frac{n-1}{2}\right)\sqrt{n-1}}\sigma .$$

$E(H) \le \delta$ leads to the equation for *n*:

$$n = \left\lceil t^2(n-1;1-\frac{\alpha}{2}) \frac{2\cdot\Gamma^2\left(\frac{n}{2}\right)\cdot}{\Gamma^2\left(\frac{n-1}{2}\right)(n-1)} \frac{\sigma^2}{\delta^2} \right\rceil$$

Hypothesis Testing:

The problem of determining the size of an experiment we explain for the one-sample problem for testing an expectation, and then the size of the experiment is again the sample size.

A random sample $y_1, y_2, ..., y_n$ [1] of size *n* will be drawn from a normally distributed population with mean μ and variance σ^2, with the purpose of testing the null hypothesis:

$H_0 : \mu = \mu_0$ (μ_0 is a given constant)

against the alternative hypothesis:

$H_A : \mu \neq \mu_0$ (two-sided alternative).

The test statistic of a uniformly most powerful unbiased test is

$$t = \frac{\bar{y} - \mu_0}{s}\sqrt{n}$$

which is non-central *t*-distributed with *n* –1 *d.f.* and non-centrality parameter

$\lambda = \frac{\mu - \mu_0}{\sigma}\sqrt{n}$.

Under the null hypothesis, the distribution is central *t*.

If the Type I error probability is α , H_0 will be rejected if:

$|t| > t(n\text{-}1;1\text{-}\alpha/2)$.

Our precision requirement is given by α and the risk of the second kind β if $|\mu\text{-}\mu_0| = \delta$.

From this we have the requirement

$$t(n\text{-}1;1\text{-}\alpha/2) = t(n\text{-}1;\lambda;\beta) \qquad (1)$$

where $t(n\text{-}1;\lambda;\beta)$ is the β--quantile of the non-central *t*- distribution with $n - 1$ *d.f.* and non-centrality parameter λ.

Using the approximation $t(n\text{-}1;\lambda;\beta) = t(n\text{-}1,\beta) + \lambda$ leads to the approximate formula

$$n \approx \left\lceil \left[\left\{ t\left(n-1;1-\frac{\alpha}{2}\right) + t(n-1;1-\beta) \right\} \frac{\sigma}{\delta} \right]^2 \right\rceil .$$

Equation (1) is crucial for determining minimal sizes when testing location parameters, a generalization will be considered in the main part of the paper.

2 Tests in the Analysis of Variance about the effects of a fixed factor

For all models in the analysis of variance (ANOVA), the linear model equation has the form

$$\boldsymbol{y} = E(\boldsymbol{y}) + \boldsymbol{e}$$

In this equation the random variable $\boldsymbol{y}$ models the observed character. The observation $\boldsymbol{y}$ is the sum of the expectation (mean) $E(\boldsymbol{y})$ of $\boldsymbol{y}$ and an error term $\boldsymbol{e}$, containing observational errors with $E(\boldsymbol{e}) = 0$, $var(\boldsymbol{e}) = \sigma^2$. The variability in $E(\boldsymbol{y})$ between experimental units depends linearly on model parameters. The models for the analysis of variance differ in the number and the nature of these parameters.
The observations in an analysis of variance are allocated to at least two classes, which are determined by the levels of the factors.
Each of the models of the analysis of variance contains the general mean μ, i.e. we write $E(\boldsymbol{y})$ in the form:

$$E(\boldsymbol{y}) = \mu + EC(\boldsymbol{y})$$

where $EC(\boldsymbol{y})$ is the mean deviation from μ within the corresponding class. In the case of p factors the analysis of variance is called p-way.
It follows that the total set of the $\boldsymbol{y}$ does not constitute a random sample because not all the $\boldsymbol{y}$ have the same expectation. Furthermore in models with random factors the $\boldsymbol{y}$ within the same class are not independent.
For all the models we assume that the variance σ^2 of the error terms in the equations is the same in all subclasses and that all the random variables in the right hand side (r.h.s.) of the model equations are mutually independent and have expectation zero.
We assume that $\boldsymbol{y}$ has a normal distribution and that we have equal subclass numbers n. We then can test the following null hypothesis in all models with a fixed factor A having effects a_i, ($i = 1, \ldots, a$).

H_0: "The factor A has no effect on the dependent variable $\boldsymbol{y}$". In other words: "All the a_i are equal". If it is assumed that the sum of the a_i is zero, this is the same as "All the a_i are equal to zero".

The alternative hypothesis is:

H_A: "At least two of the a_i are different".

The test statistic for this test is a variate $\boldsymbol{F}$ that (if the null hypothesis is true) follows a (central) F-distribution with f_1 and f_2 degrees of freedom. The $(1-\alpha)$-quantile of the distribution of $F(f_1; f_2)$ is denoted by $F(f_1; f_2; 1-\alpha)$.
This test statistic is generally calculated by following the next 8 steps - here "generally" means that these steps should be used for all situations and models in this paper but also for any other ANOVA situation.

1. Define the null hypothesis.
2. Choose the appropriate model (I, II, or mixed).
3. Find the $E(\boldsymbol{MS})$ column in the ANOVA table (if there are several such columns, find the one that corresponds to your model).
4. In the same table find the row for the factor that appears in your null hypothesis.
5. Change the $E(\boldsymbol{MS})$ in this row to what it would be if the null hypothesis were true.
6. Search in the same table (in the same column) for the row, which now has the same $E(\boldsymbol{MS})$ as you found in the 5th step.
7. The F-value is now the value of the $\boldsymbol{MS}$ of the row you found in the fourth step divided by the value of the $\boldsymbol{MS}$ of the row you found in the 6-th step.
8. Note: in ANOVA with higher classifications, the 6-th step may not be successful, in which case one can use the so-called Satterthwaite approximation.

The minimum size of the experiment should be determined so that the precision requirements are fulfilled. The size of the experiment depends on the degrees of freedom (*d.f.*) of the nominator f_1 and the denominator f_2 of the *F*-statistic. f_2 depends not always on the sub-class number *n*. If we sample factor levels of random factors, the size of those samples also determines the size of the experiment.
The minimal size is determined in dependence on a lower bound δ of the difference between the maximum and the minimum of the effects to be tested for equality by an *F*-test, further on the risks α and β of the test and on a presumable value of the common residual variance.
The problem of the determination of the size of an experiment for the analysis of variance has been investigated by, among others, Tang, P. C. (1938), Lehmer (1944), Fox (1956), Tiku (1967, 1972), Das Gupta, P. (1968), Bratcher et al. (1970), Kastenbaum et al. (1970a, b), Bowman (1972, 1975), Rasch et al. (1997), Herrendörfer et al. (1997) and Rasch (1998).
The solution λ of the following equation plays a crucial role:

$$F(f_1, f_2, 0, 1-\alpha) = F(f_1, f_2, \lambda, \beta) \qquad (2)$$

where $F(f_1, f_2, 0, 1-\alpha)$ is the $(1-\alpha)$-quantile of the (central) *F*-distribution with degrees of freedom f_1 and f_2 and non-centrality parameter 0 and where $F(f_1, f_2, \lambda, \beta)$ is the β-quantile of the *F*-distribution with degrees of freedom f_1 and f_2 and non-centrality parameter λ.

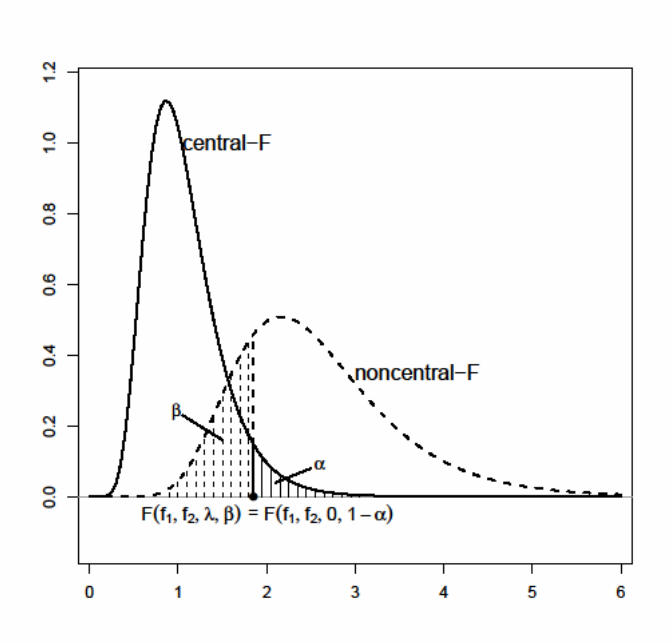

Figure 1: Demonstrating the relation of equation (2)

Figure 1 shows the relation of Equation (2) it is a generalization of equation (1).
But contrary to the *t*-test we have at least 3 expectations or effects in ANOVA models
For the null hypothesis about a fixed factor *A* having effects a_i, (i = 1, …, a) the sample size depends not only on the difference between the extreme effects but also on the position of the other effects.

Remark: The noncentrality parameter λ is proportional to $\sum_{i=1}^{a} a_i^2$ (when we assume that $\sum a_i = 0$) and from Figure 1 we see that as larger λ as smaller the minimal size needed.

The most favorable case leads to the maximum λ and the smallest minimum sample size $n_{\min}; b_{\min}, \ldots$, the *mini-min* size and the least favorable case leads to the biggest minimum sample size, the *maxi-min* size $n_{\max}; b_{\max}, \ldots$.

Lemma 1:
Without loss of generality (w.l.o.g.) we assume:
$\sum_{i=1}^{a} a_i = 0, a_1 \le a_2 \le \cdots \le a_a, a_{\min} = -\frac{\delta}{2}$, and $a_{\max} = \frac{\delta}{2}$ and further w.l.o.g. $\delta = \sigma$. We consider a Model I of ANOVA (all the factors are fixed) with a cross classification and equal sub-class numbers.

a) Under the conditions above *the* minimin size $n_{\min}$ (the most favorable case) occurs if we split the a_i into two groups of size a_{I} and a_{II} respectively with $a = a_{\mathrm{I}} + a_{\mathrm{II}}$ and $|a_I - a_{II}| \le 1$ and the a_{I} elements of the first group equal $-\frac{a_{II}}{a}\delta$ and the a_{II} remaining equal $\frac{a_I}{a}\delta$. Thus there are two solutions for odd *a* and for even *a* half of the effects are equal to $-\frac{\delta}{2}$ and half of them are equal to $\frac{\delta}{2}$. Then $\sum_{i=1}^{a} a_i^2 = \frac{\delta^2}{a}\left(a_I \cdot a_{II}\right)$ and is a maximum.

b) Under the conditions above *the* maximin size $n_{\max}$ (the least favorable case) occurs if $a_1 = -\frac{\delta}{2}$, and $a_a = \frac{\delta}{2}$ and all the other effects are zero. Then $\sum_{i=1}^{a} a_i^2 = \frac{\delta^2}{2}$ and a minimum.

c) In the singular case (two-sample problem) $a = 2$ both sizes are identical.

Proof: It is easy to see that the condition $\sum_{i=1}^{a} a_i = 0, a_1 \le a_2 \le \cdots \le a_a$ is fulfilled as well in case a) as also in case b).

a) For case a) and even *a* the statement is evident. In general we know that with $a = a_{\mathrm{I}} + a_{\mathrm{II}}$ the product $a_{\mathrm{I}}\ a_{\mathrm{II}}$ is maximum if a_{I} and a_{II} are as equal as possible. That makes $\sum_{i=1}^{a} a_i^2 = a_I \frac{a_{II}^2}{a^2}\cdot\delta^2 + a_{II}\frac{a_I^2}{a^2}\cdot\delta^2 = \frac{a}{a^2}a_I \cdot a_{II}\delta^2 = \frac{a_I \cdot a_{II}}{a}\delta^2$ a maximum if a_{I} and a_{II} differ at most by 1. In Table 1 some values of $\frac{1}{\delta^2}\sum_{i=1}^{a} a_i^2$ in the most favorable case are given.

Table 1 Values of $\frac{1}{\delta^2}\sum_{i=1}^{a} a_i^2$ for the most favourable case in dependence on a.

a	2	3	4	5	6	7	8
$\frac{1}{\delta^2}\sum_{i=1}^{a} a_i^2$	0.5	0.667	1	1.2	1.5	1.714	2

b) For even *a* the result of case b) follows from the theory of D-optimal designs in regression. For odd *a* we obtain the result by equating the partial derivatives with respect to the effects and κ of $w = x - \kappa z$ to zero. Hereby is $x = \sum_{i=1}^{a} a_i^2 = a_1^2 + \ldots + a_{a-1}^2 + \left(\delta + a_1\right)^2$ and $z = \sum_{i=1}^{a} a_i = a_1 + \ldots + a_{a-1} + \left(\delta + a_1\right)$..This completes the proof because *w* is a convex function.

We already called the mini-min size by $n_{\min}$ and the maxi-min size by $n_{\max}$. The experimenter now has to choose the number of observations *n* per factor level (class) between the lower bound n_l and the upper bound n_u:

$$n_{\min} \le n \le n_{\max}$$

All that remains to be done is to calculate the bounds $n_{\min}$ and $n_{\max}$ for different classifications and models.

3 The one-way Analysis of variance

The model equation of the one-way analysis of variance with a fixed factor *A* is written in the form:

$$\boldsymbol{y}_{ij} = \mathrm{E}(\boldsymbol{y}_{ij}) + \boldsymbol{e}_{ij} = \mu + a_i + \boldsymbol{e}_{ij} \quad (i = 1,...,a;\ j = 1,...,n\ ).$$

The α_i are the main effects of the *factor levels* A_i; they are real numbers, i.e. not random. The model is completed by the following constraints (sometimes called side conditions): the $\boldsymbol{e}_{ij}$ are mutually independent with $\mathrm{E}(\boldsymbol{e}_{ij}) = 0$ and $\mathrm{var}(\boldsymbol{e}_{ij}) = \sigma^2$ and that the sum of the a_i is zero. The pair of hypotheses:
H_0: "All the a_i are equal to zero".
H_A: "At least two of the a_i are different".
is tested with help of the test statistics

$$\boldsymbol{F} = \frac{\boldsymbol{MS}}{\boldsymbol{MS}_{res}}$$

with the mean squares from the corresponding ANOVA-Table with a-1 and $a(n$-1) degrees of freedom.
$\boldsymbol{F}$ is with these *d.f. F* distributed with the non-centrality parameter

$$\lambda = \frac{n}{a-1}\sum_{i=1}^{a} a_i^2$$

which in the most and least favorable case increases with n and decreases with a. This means that under otherwise equal conditions the necessary sample sizes and thus the size of the experiment increase with increasing number of factor levels.

Examples and *R*-Programs

To calculate the minimum sample sizes $n_{\min}$ and $n_{\max}$ we use the *R*-package **OPDOE**.

We plan to perform an experiment with four levels of a fixed factor A and measure the yield of a crop in *dt=100 kg* per ha. The four levels are four varieties of a cereal crop.
The number n of plots per variety has to be determined to satisfy the following conditions: Type I error probability α = 0.05, and Type II error probability $\beta \le$ 0.1 if $a_{max} - a_{min} \ge 2\sigma$.

```
>size_n.one_way_ model_1(0.05,0.1,2,4,"maximin")
[1]  9
>size_n.one_way_ model_1(0.05,0.1,2,4,"minimin")
[1]  5
```

This means that $n_{\min}$ = 5 and $n_{\max}$ = 9.

4 The two-way Analysis of variance

The model equation of the two-way analysis of variance with the factor A with a levels A_i and the factor B with the b levels B_j and equal number of observations in the subclasses is

$$\boldsymbol{y}_{ijk} = \mu + a_i + b_j + (ab)_{ij} + \boldsymbol{e}_{ijk}\ (i = 1, ..., a;\ j = 1, ..., b;\ k = 1, ..., n)$$

if both factors are fixed (Model I) and

$\boldsymbol{y}_{ijk} = \mu + a_i + \boldsymbol{b}_j + (\boldsymbol{ab})_{ij} + \boldsymbol{e}_{ijk}$ ($i = 1, ..., a$; $j = 1, ..., b$; $k = 1, ..., n$)

if factor A is fixed and factor B is random (mixed model).
In model I we assume in addition to the assumptions for the one-way ANOVA that the sums of the $(ab)_{ij}$ (separately over each index) all equal zero.

As in the one-way classification we like to test the pair of hypotheses:
H_0: "All the a_i are equal to zero".
H_A: "At least two of the a_i are different".
The test statistics is for Model I

$$F_A = \frac{\boldsymbol{MS}_A}{\boldsymbol{MS}_R}$$

which is *F*- distributed with $a - 1$ and $a(n\text{-}1)$ d.f. and non-centrality parameter $\lambda = \frac{bn}{a-1}\sum_{i=1}^{a} a_i^2$.

For the mixed model the test statistics is

$$\boldsymbol{F}_A = \frac{\boldsymbol{MS}_A}{\boldsymbol{MS}_{A\times B}}$$

which is *F*- distributed with $a - 1$ and $(a\text{-}1)(b\text{-}1)$ *d.f.* and non-centrality parameter $\lambda = \frac{bn}{a-1}\sum_{i=1}^{a} a_i^2$.

This means that under otherwise equal conditions the necessary sample sizes and thus the size of the experiment increases with an increasing number of levels of the factor *A* but decreases with the number of levels of the factor *B.*
For determining the minimin and the maximin size we can use Lemma 1 in both cases.

In model I we also can test a hypothesis about the interaction effects.
H_0: "All $(ab)_{ij}$ are zero"
The alternative hypothesis is:
H_A: " At least two $(ab)_{ij}$ differs from zero, respectively."
The test statistic is:

$$\boldsymbol{F}_{AB} = \boldsymbol{MS}_{A\ B} / \boldsymbol{MS}_R$$

and is under H_0 $F((a\text{-}1)(b\text{-}1); ab(n\text{-}1))$ distributed. The non-centrality parameter is

$$\lambda = \frac{n}{(a\text{-}1)(b\text{-}1)} \cdot \sum_{i,j} (ab)_{ij}^2 .$$

Before we give some examples we have to show the least and the most favorable situation for the interaction effects.

Lemma 2:
We consider a model I of the balanced two-way ANOVA or an analogue balanced multi-way ANOVA with two fixed factors A and B under the condition that the sums of the interaction effects $(ab)_{ij}$ of the two factors A and B (separately over each index) equal zero.
Further let $\max\left|(ab)_{ij}\right| - \min\left|(ab)_{ij}\right| = \delta = \sigma$ with σ^2 as the error variance of the model.

Then the minimum of $\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2$ is w.l.o.g. obtained for $(ab)_{11}=\frac{(a-1)(b-1)}{a(b-1)}\delta=\frac{a-1}{a}\delta$;

$(ab)_{i1}=-\frac{(b-1)}{a(b-1)}\delta=-\frac{1}{a}\delta; i=2,...,a$; $(ab)_{1j}=-\frac{(a-1)}{a(b-1)}\delta; j=2,...,b$;

$(ab)_{ij}=\frac{1}{a(b-1)}\delta; i=2,...,a; j=2,...,b$.

If as well *a* as also *b* are even the maximum of $\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2$ is given if half of the interaction effects equal $-\frac{1}{2}\delta$ and the remaining equal $\frac{1}{2}\delta$. Then $\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2=\frac{ab}{4}\delta^2$.

Proof:

a) We assume w.l.o.g. that $a\le b$. It is easy to see that $\sum_{i=1}^{a}(ab)_{ij}=\sum_{j=1}^{b}(ab)_{ij}=0$ and $\max\left|(ab)_{ij}\right|-\min\left|(ab)_{ij}\right|=(ab)_{11}-(ab)_{i1}=\delta$ and all side conditions are fulfilled. We now consider

$$\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2=\delta^2\left\{\begin{array}{l}\left[\frac{(a-1)(b-1)}{a(b-1)}\right]^2+(a-1)\left[\frac{(b-1)}{a(b-1)}\right]^2+(b-1)\left[\frac{(a-1)}{a(b-1)}\right]^2\\+(a-1)(b-1)\left[\frac{1}{a(b-1)}\right]^2\end{array}\right\}$$

$$=\frac{ab(a-1)(b-1)}{a^2(b-1)^2}\delta^2=\frac{b(a-1)}{a(b-1)}\delta^2\le\delta^2$$

b) The equality sign occurs if and only if *a* = *b*. This expression depends besides δ only on *a* and *b* and is invariant against permutations of rows and/or columns which all are also solutions. The solution $(ab)_{11}=(ab)_{ab}=\frac{\delta}{2};(ab)_{a1}=(ab)_{1b}=-\frac{\delta}{2}$ and all other effects equal to zero fulfills the side conditions as well but leads to a larger value of $\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2$ if *a* < *b*. This completes the proof. Thus the least favorable case is known. We give in Table 2 the value of $\frac{1}{\delta^2}\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2$ for some values of *a* and *b*.

Table 2 Values of $\frac{1}{\delta^2}\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2$ for the least favourable

	b			
a	2	3	4	5
2		0.75	0.667	0.625
3		1	0.888	0.833
4			1	0.938

case and some values of *a* and *b*.

b) under the side condition above no larger value of $\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2$ is possible.

For the most favorable case with at least one of the values *a* and *b* odd we only have a conjecture.

Conjecture.
We consider a model I of the balanced two-way ANOVA or an analogue balanced multi-way ANOVA with two fixed factors A and B under the condition that the sums of the interaction effects $(ab)_{ij}$ of the two factors A and B (separately over each index) equal zero.
Further let $\max\left|(ab)_{ij}\right| - \min\left|(ab)_{ij}\right| = \delta = \sigma$ with σ^2 as the error variance of the model.

Under the conditions above the maximum of $\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2$ is

(i) For *a* even, *b* odd
(ii) For *a* odd, *b* even
(iii) *a* and *b* both odd

obtained as the value occurring if the odd number is reduced to the next smaller even number.

The maximum of $\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2$ is for

(i) by $\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2 = \frac{a(b-1)}{4}$

(ii) by $\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2 = \frac{b(a-1)}{4}$

(iii) by $\sum_{i=1}^{a}\sum_{j=1}^{b}(ab)_{ij}^2 = \frac{(a-1)(b-1)}{4}$.

Some arguments supporting this conjecture are shown in Rasch et al. (2011).

Examples and *R*-Programs
To calculate the minimum sample sizes $n_{\min}$ and $n_{\max}$ we use the *R*-package **OPDOE**.
Assume that six wheat varieties should be compared concerning their yield. For that the varieties will be cultivated at several farms. I the model I situation four farms have been selected, for model I the farms are randomly sampled from all farms in a country. The number n of plots per variety in model I and the number of farms sampled in model II has to be determined to satisfy the following conditions: Type I error probability α = 0.05, and Type II error probability $\beta \leq$ 0.1 if $a_{max} - a_{min} \geq 2\sigma$.
The **OPDOE** programs have the following structure:

```
>size_x.two_way_cross.model_r_E(α,β,δ,a,b,q)
```

with x = n or x=b (in this case the b in the bracket is replaced by n); r = 1 or mixed, E = a or axb (when testing interaction effects) and q = "maximin" or "minimin".

Model I: Testing the main effects:

```
>size_n.two_way_cross.model_1_a(0.05,0.1,2,6,4,"maximin")
[1]  9
>size_n.two_way_cross.model_1_a(0.05,0.1,2,6,4,"minimin")
[1]  4
```

Model I: Testing the interaction effects:

```
>size_n.two_way_cross.model_1_axb(0.05,0.1,2,6,4,"maximin")
[1]  48
>size_n.two_way_cross.model_1_axb(0.05,0.1,2,6,4,"minimin")
[1]  5
```

Mixed model: Testing the main effects:
If we put n = 1 we obtain

```
>size_b.two_way_cross.mixed_model_a(0.05,0.1,2,6,1,"maximin")
[1]  35
>size_n.two_way_cross.model_1_a(0.05,0.1,2,6,4,1,"minimin")
[1]  13
```

If we put $n = 2$ we obtain

```
>size_b.two_way_cross.mixed_model_a(0.05,0.1,2,6,2,"maximin")
[1]  18
>size_n.two_way_cross.model_1_a(0.05,0.1,2,6,4,2,"minimin")
[1]  7
```

It is the product *bn* what is (up to integer rounding) constant.
For the nested classification an analogue procedure is applied. This and the different models and classification together with the R-programs can be found in Chapter 3 of Rasch et al. (2011).

5 The three-way Analysis of variance

In the three-way analysis of variance we have four classifications (cross, nested and two mixed) and several models with at least one fixed factor. For most of these cases sample size formula using the two lemmas above and the conjecture could be derived. In two cases a special approach was needed because no exact *F*-test exists and an approximate *F*-test using the Satterthwaite approximation [Satterthwaite (1946)] leads to problems with determining sample sizes – see Rasch, D, Spangl, B. and Wang, M. (2011).
Writing $F \succ G$ or $G \prec F$ if factor *G* is nested within factor *F* and GxF if both factors are cross classified and printing factor symbols in bold if a factor is random then we have the following cases:

Classification	Model equation
$A\times B\times C$	$\boldsymbol{y}_{ijkv} = \mu + a_i + b_j + c_k + (ab)_{ij} + (ac)_{ik} + (bc)_{jk} + (abc)_{ijk} + \boldsymbol{e}_{ijkv}$
$A\times B\times \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + a_i + b_j + \boldsymbol{c}_k + (ab)_{ij} + (\boldsymbol{ac})_{ik} + (\boldsymbol{bc})_{jk} + (\boldsymbol{abc})_{ijk} + \boldsymbol{e}_{ijkv}$
$A\times \boldsymbol{B}\times \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + a_i + \boldsymbol{b}_j + \boldsymbol{c}_k + (\boldsymbol{ab})_{ij} + (\boldsymbol{ac})_{ik} + (\boldsymbol{bc})_{jk} + (\boldsymbol{abc})_{ijk} + \boldsymbol{e}_{ijkv}$
$\boldsymbol{A}\times \boldsymbol{B}\times \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + \boldsymbol{a}_i + \boldsymbol{b}_j + \boldsymbol{c}_k + (\boldsymbol{ab})_{ij} + (\boldsymbol{ac})_{ik} + (\boldsymbol{bc})_{jk} + (\boldsymbol{abc})_{ijk} + \boldsymbol{e}_{ijkv}$
$A\succ B\succ C$	$\boldsymbol{y}_{ijkv} = \mu + a_i + b_{j(i)} + c_{k(ij)} + \boldsymbol{e}_{ijkv}$
$\boldsymbol{A}\succ B\succ C$	$\boldsymbol{y}_{ijkv} = \mu + \boldsymbol{a}_i + b_{j(i)} + c_{k(ij)} + \boldsymbol{e}_{ijkv}$
$A\succ \boldsymbol{B}\succ C$	$\boldsymbol{y}_{ijkv} = \mu + a_i + \boldsymbol{b}_{j(i)} + c_{k(ij)} + \boldsymbol{e}_{ijkv}$
$A\succ B\succ \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + a_i + b_{j(i)} + \boldsymbol{c}_{k(ij)} + \boldsymbol{e}_{ijkv}$
$\boldsymbol{A}\succ \boldsymbol{B}\succ C$	$\boldsymbol{y}_{ijkv} = \mu + \boldsymbol{a}_i + \boldsymbol{b}_{j(i)} + c_{k(ij)} + \boldsymbol{e}_{ijkv}$
$\boldsymbol{A}\succ B\succ \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + \boldsymbol{a}_i + b_{j(i)} + \boldsymbol{c}_{k(ij)} + \boldsymbol{e}_{ijkv}$
$A\succ \boldsymbol{B}\succ \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + a_i + \boldsymbol{b}_{j(i)} + \boldsymbol{c}_{k(ij)} + \boldsymbol{e}_{ijkv}$
$\boldsymbol{A}\succ \boldsymbol{B}\succ \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + \boldsymbol{a}_i + \boldsymbol{b}_{j(i)} + \boldsymbol{c}_{k(ij)} + \boldsymbol{e}_{ijkv}$
$(A\times B)\succ C$	$\boldsymbol{y}_{ijkv} = \mu + a_i + b_j + (ab)_{ij} + c_{k(ij)} + \boldsymbol{e}_{ijkv}$
$(A\times \boldsymbol{B})\succ C$	$\boldsymbol{y}_{ijkv} = \mu + a_i + \boldsymbol{b}_j + (\boldsymbol{ab})_{ij} + c_{k(ij)} + \boldsymbol{e}_{ijkv}$
$(\boldsymbol{A}\times \boldsymbol{B})\succ C$	$\boldsymbol{y}_{ijkv} = \mu + \boldsymbol{a}_i + \boldsymbol{b}_j + (\boldsymbol{ab})_{ij} + c_{k(ij)} + \boldsymbol{e}_{ijkv}$
$(A\times B)\succ \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + a_i + b_j + (ab)_{ij} + \boldsymbol{c}_{k(ij)} + \boldsymbol{e}_{ijkv}$
$(A\times \boldsymbol{B})\succ \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + a_i + \boldsymbol{b}_j + (\boldsymbol{ab})_{ij} + \boldsymbol{c}_{k(ij)} + \boldsymbol{e}_{ijkv}$
$(\boldsymbol{A}\times \boldsymbol{B})\succ \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + \boldsymbol{a}_i + \boldsymbol{b}_j + (\boldsymbol{ab})_{ij} + \boldsymbol{c}_{k(ij)} + \boldsymbol{e}_{ijkv}$
$(A\succ B)\times C$	$\boldsymbol{y}_{ijkv} = \mu + a_i + b_{j(i)} + c_k + (ac)_{ik} + (bc)_{j(i)k} + \boldsymbol{e}_{ijkv}$
$(\boldsymbol{A}\succ B)\times C$	$\boldsymbol{y}_{ijkv} = \mu + \boldsymbol{a}_i + b_{j(i)} + c_k + (\boldsymbol{ac})_{ik} + (bc)_{j(i)k} + \boldsymbol{e}_{ijkv}$
$(A\succ \boldsymbol{B})\times C$	$\boldsymbol{y}_{ijkv} = \mu + a_i + \boldsymbol{b}_{j(i)} + c_k + (ac)_{ik} + (\boldsymbol{bc})_{j(i)k} + \boldsymbol{e}_{ijkv}$

$(\boldsymbol{A} \succ \boldsymbol{B}) \times C$	$\boldsymbol{y}_{ijkv} = \mu + \boldsymbol{a}_i + \boldsymbol{b}_{j(i)} + c_k + (\boldsymbol{ac})_{ik} + (\boldsymbol{bc})_{j(i)k} + \boldsymbol{e}_{ijkv}$
$(A \succ B) \times \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + a_i + b_{j(i)} + \boldsymbol{c}_k + (\boldsymbol{ac})_{ik} + (\boldsymbol{bc})_{j(i)k} + \boldsymbol{e}_{ijkv}$
$(\boldsymbol{A} \succ B) \times \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + \boldsymbol{a}_i + b_{j(i)} + \boldsymbol{c}_k + (\boldsymbol{ac})_{ik} + (\boldsymbol{bc})_{j(i)k} + \boldsymbol{e}_{ijkv}$
$(A \succ \boldsymbol{B}) \times \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + a_i + \boldsymbol{b}_{j(i)} + \boldsymbol{c}_k + (\boldsymbol{ac})_{ik} + (\boldsymbol{bc})_{j(i)k} + \boldsymbol{e}_{ijkv}$
$(\boldsymbol{A} \succ \boldsymbol{B}) \times \boldsymbol{C}$	$\boldsymbol{y}_{ijkv} = \mu + \boldsymbol{a}_i + \boldsymbol{b}_{j(i)} + \boldsymbol{c}_k + (\boldsymbol{ac})_{ik} + (\boldsymbol{bc})_{j(i)k} + \boldsymbol{e}_{ijkv}$

We only show how to determine the size of the experiment for the case $(A \succ B) \times \boldsymbol{C}$
We test the null hypothesis that the factor *A* has no effect on the observed random variable.

Let us consider the case of $a = 6$ levels of *A* and $b = 5$ levels of *B* with $\alpha = 0.05$ and $\beta = 0.1$ and $\delta = 0.5\sigma$. In **OPDOE** we use the *R*-program

```
> size_c.three_way_mixed_cxbina.model_5_a(0.05, 0.1, 0.5, 6, 5,
+ 2, "maximin")
[1] 15
> size_c.three_way_mixed_cxbina.model_5_a(0.05, 0.1, 0.5, 6, 5,
+ 2, "minimin")
[1] 6
```

As result we found the minimin size 6 and the maximin size 15 for the number of levels of the random factor *C*.
We also can derive the test statistic for testing

$$H_0 : b_{j(i)} = 0 \forall j,i; H_A \text{ at least one } b_{j(i)} \neq 0$$

$\boldsymbol{F} = \dfrac{\boldsymbol{MS}_{BinA}}{\boldsymbol{MS}_{BxCinA}}$ is under H_0 $F[a(b\text{-}1); a(b\text{-}1)(c\text{-}1)]$ –distributed with a $(b\text{-}1)$ and $a(b\text{-}1)(c\text{-}1)$ degrees of freedom.
Let us again consider the case of $a = 6$ levels of *A* and $b = 5$ levels of *B* with $\alpha = 0.05$ and $\beta = 0.1$ and $\delta = 0.5\sigma$. In **OPDOE** we use the *R*-program

```
> size_c.three_way_mixed_cxbina.model_5_b(0.05, 0.1, 0.5, 6, 5,
+ 2, "maximin")
[1] 113
> size_c.three_way_mixed_cxbina.model_5_b(0.05, 0.1, 0.5, 6, 5,
+ 2, "minimin")
[1] 9
```

As result we found the minimin size 9 and the maximin size 113 for the number of levels of the random factor *C*.

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Sequential Design for Comparing Two Binary Endpoints: How to Minimize Type II Error

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Abstract: Assume that you wish to test whether the success probabilities of two binary valued random variables differ. We compare two sampling schemes. Under sequential sampling you sample one observation after another, for each sample you are allowed to determine which variable to observe next based on the previously observed outcomes. Under (simultaneous) balanced sampling each variable is sampled equally often, independently of which outcomes are generated. We compare inference under the exact randomized tests that minimize type II error. We find that if the two success probabilities are not too similar under the alternative hypothesis then balanced sampling is just as good as sequential sampling. Standard nonrandomized tests for balanced sampling perform only slightly worse in such situations, that is they perform almost as well as the theoretically best possible sequential sampling tests.

Keywords: exact testing, unavoidable type II error, sequential design.

1 Introduction

We are interested in comparing different schemes for gathering data in view of later hypothesis testing. In particular, we wish to understand the value of sequential sampling as compared to balanced sampling. Under *sequential sampling* the designer gathers data by sequentially choosing which variable to observe a realization from next given the previous observations. Under *balanced sampling*, an equal number of realizations of each variable is observed. We derive insights for the objective of comparing two binary endpoints (or binomial proportions).

To illustrate, assume that there is an even number of indistinguishable patients and two possible treatments 1 and 2 where each treatment can lead to either a success or a failure. Under balanced sampling, all patients are invited at the same time and each treatment is assigned to equally many patients. Under sequential sampling, patients are invited one by one, the next patient is only treated after the outcome of the previous treatment is known. The treatment given to the k-th patient can thus be conditioned on the previous treatments and their outcomes. So there are many different ways in which one can implement sequential sampling. Should one continue with the same treatment if it was successful? Should one sample a treatment more if there is higher variance in the outcomes? Of course one can mimic balanced sampling under sequential sampling by assigning treatments alternatingly regardless of the outcomes. So sequential sampling is weakly more powerful than balanced sampling as one can replicate balanced sampling with the sequential sampling procedure but not vice versa. We wish to investigate how much more powerful sequential sampling is from an ex-ante point of view, so for unconditional inference. This is relevant as sequential sampling is intricate and costly to implement.

How much better is sequential sampling than balanced sampling for testing if there is some difference between the two treatments?[†] As outcomes are binary valued, the value of a treatment

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[†]Our analysis will also shed light on the value of block sequential designs.

can be identified by its success probability. The value of a sampling procedure will be measured by the of the smallest possible type II error among all tests of equal success. We assume that the designer is only interested in the difference between the two success probabilities p_1 and p_2, hence we consider only alternative hypotheses that can be described in terms of the difference. Specifically, we test the null hypothesis $H_0 : p_1 \leq p_2$ against the alternative hypothesis $H_1 : p_1 \geq p_2 + d$ for some given $d > 0$.[‡]

In this paper, the value of inference of a test with type I error α is identified with its type II error for this pair of hypotheses. For each sampling scheme we search for the test that has the smallest type II error among the set of tests that have a given type I error α. We then compare the minimal type II errors of the different sampling procedures. In particular we will derive a best way to assign treatments under sequential sampling.

The result of our analysis can be considered surprising. In many situations, despite its flexibility, sequential sampling yields no better inference than balanced sampling. As long the two treatments are not too similar, so as long as d is not too small, the minimal type II error is the same under balanced sampling and under sequential sampling. In such cases, a best way to assign treatments under sequential sampling is to ignore the sequential nature and to instead apply balanced sampling.

To show this result we first characterize the smallest type II error under full information when both outcomes are observable for each patient. As this involves more information than available under balanced sampling, we obtain a lower bound on the smallest possible type II error under balanced sampling. Then we show via numerical calculations that this lower bound can be attained under balanced sampling when d is not too small. In such cases, inference is made under balanced sampling is as if there were full information. As sequential sampling provides more information than balanced sampling but less than full information sampling the result is proven.

A downside of the finding above is that it assumes that the designer uses randomized tests. What does this mean for practical testing? When comparing success probabilities based on balanced samples one typically either uses the test of Boschloo (1970) or the z test of Suissa and Shuster (1985). These tests are nonrandomized and do not achieve the minimal type II error under balanced sampling. However, their type II error is only slightly above the minimal type II error when d is not too small. Combining this with our above results shows that standard nonrandomized tests under balanced sampling perform almost as well as if both outcomes were observable for each patient. For practical testing, in terms of making inference when treatments are not too similar, we find that the advantage of sequential sampling is at most marginal.

Of course sequential sampling has its own merits. One may wish to improve inference away from the least favorable distribution. One may wish to reduce the number of treatments by stopping early when enough evidence has been gathered. One may wish to maximize the expected number of successes achieved during sampling. In these cases our investigation can be considered as a benchmark.

2 The Model

For a given set A let ΔA be the set of probability distributions that have support in A. Consider $Y = (Y_1, Y_2) \in \Delta\left(\{0,1\}^2\right)$ and let $p_i = P(Y_i = 1)$ for $i = 1, 2$. Given $d \in (0, 1)$ we wish to test the null hypothesis $H_0 : p_1 \leq p_2$ against the alternative hypothesis $H_1 : p_1 \geq p_2 + d$ under various sampling scenarios for gathering n observations where n is an even number.[§]

[‡]From this one-sided test and its mirror image one easily can construct an equi-tailed test of $H_0 : p_1 = p_2$ against $H_1 : |p_1 - p_2| \geq d$.

[§]The tests we construct are easily extended to equi-tailed tests of $H_0 : p_1 = p_2$ against $H_1 : |p_1 - p_2| \geq d$.

A test generates a recommendation for whether to reject the null hypothesis given the sample. For deriving our results we need to consider randomized tests, later we will show how to use these results when implementing nonrandomized tests. So we identify a test with the probability ϕ of rejecting the null hypothesis. The test ϕ is called *nonrandomized* if $\phi \in \{0,1\}$ for any sampled data, it is called *randomized* if it is not nonrandomized.

2.1 Full Information Sampling

Under full information sampling the test conditions on a sample of n independent realizations of Y. This is also known as matched pairs, the doctor knows the outcome of each treatment for each patient. Let $y^{(n)}$ be the observed sample where $y_{ki}^{(n)}$ is the realization of Y_i in the k-th element of the sample. A test ϕ is a mapping $\times_{k=1}^{n} \{0,1\}^2 \to [0,1]$ where $\phi\left(y^{(n)}\right)$ is the probability of rejecting H_0 given data $y^{(n)}$.

2.2 Balanced Sampling

Under balanced sampling the test conditions on a sample of $n/2$ independent realizations of Y_1 and Y_2. A test ϕ is a mapping $\{0,1\}^{n/2} \times \{0,1\}^{n/2} \to [0,1]$ where $\phi\left(y_1^{(n/2)}, y_2^{(n/2)}\right)$ is the probability of rejecting H_0 given the $n/2$ observations $y_i^{(n/2)}$ of Y_i, $i = 1,2$.

2.3 Sequential Sampling

Under sequential sampling we need to specify a sampling procedure ζ and a test ϕ. The sampling procedure specifies the variable from which the next observation is drawn conditional on the history of choices and observations. Let $h^{(k)}$ be the sequence observations up to round k such that $h_l^{(k)} \in \{1,2\} \times \{0,1\}$ is the observation made in round l in which the outcome $h_{l2}^{(k)}$ was drawn from the variable with index $h_{l1}^{(k)}$. So the sampling procedure ζ is given by the mapping $\zeta : \cup_{k=0}^{n-1} (\{1,2\} \times \{0,1\})^k \to [0,1]$ where $\zeta\left(h^{(k)}\right)$ is the probability of observing a realization from Y_1 in round $k+1$ conditional on the history $h^{(k)}$.

2.4 Testing

We recall that a test ϕ has *level* α if $E_Y \phi \leq \alpha$ for all $Y \in \Delta\left(\{0,1\}^2\right)$ such that $p_1 \leq p_2$ and has *type I error* α if $\max_Y \{E_Y \phi : p_1 \leq p_2\} = \alpha$. The type II error of ϕ is given by $\max_Y \{E_Y (1-\phi) : p_1 \geq p_2 + d\}$. Throughout our analysis α will be held fixed. The *unavoidable type II error* will refer to the smallest type II error among the tests that have level α, so it is equal to $\min_{\phi:\phi hassize\alpha} \max_Y \{E_Y (1-\phi) : p_1 \geq p_2 + d\}$. We say that a test *attains the unavoidable type II error* if its type II error is equal to the unavoidable type II error. Note that typically the unavoidable type II error is only attained by randomized tests. For nonrandomized tests we are interested in how much higher their type II error is than the unavoidable type II error, this will be called the *added type II error*.

2.5 Inference under Full Information Sampling

We start by analyzing full information sampling which will become an important benchmark. We first restrict attention to $Y \in \Delta\{(0,1),(1,0)\}$, so the set of distributions where for each patient exactly one of the two treatments yields a success. Under this restriction testing is very simple. The hypotheses can be rewritten as $H_0 : P(Y = (1,0)) \leq \frac{1}{2}$ and $H_1 : P(Y = (1,0)) \geq \frac{1}{2}(1+d)$. Consequently, the randomized binomial test attains the unavoidable type II error as

it is uniformly most powerful. This test, denoted by ϕ_R, is characterized by a unique $m \in \{0,1,..,n\}$ and the following three conditions: $\phi_R\left(y^{(n)}\right) = 1$ when $\left|\left\{k : y_k^{(n)} = (1,0)\right\}\right| > m$, $\phi_R\left(y_k^{(n)}\right) = 0$ when $\left|\left\{k : y^{(k)} = (1,0)\right\}\right| < m$ and $E_Y\phi_R = \alpha$ if $P(Y = (1,0)) = 1/2$.[¶] Note that the type II error is attained when $Y = Y^d$ where $Y^d \in \Delta\{(1,0),(0,1)\}$ is defined by $P\left(Y^d = (1,0)\right) = \frac{1}{2}(1+d)$.

Next we show how to extend ϕ_R to a test ϕ_F that attains the unavoidable type II error under full information sampling, so when $Y \in \Delta\left(\{0,1\}^2\right)$. For this we will randomly transform observations belonging to $\{0,1\}^2$ into $\{(1,0),(0,1)\}$ with the (independent) probabilistic mapping f defined by $P(f(y) = (1,0)) = 1$ if $y = (1,0)$, $= 0$ if $y = (0,1)$ and $= 1/2$ if $y \in \{(0,0),(1,1)\}$. Note that the transformation f does not change the difference in the success probabilities as $Ef(Y_1) - Ef(Y_2) = EY_1 - EY_2$. We construct the test ϕ_F by first using f to transform each observation belonging to the sample $y^{(n)}$ to generate a new sample $\left(f\left(y_k^{(n)}\right)\right)_{k=1}^n$ belonging to $\{(1,0),(0,1)\}^n$ and then applying ϕ_R. Formally, let ϕ_F be defined by $\phi_F\left(y^{(n)}\right) = E_f\phi_R\left(\left(f\left(y_k^{(n)}\right)\right)_{k=1}^n\right)$ for $y^{(n)} \in \times_{k=1}^n \{0,1\}^2$. Given Y let $Z_Y \in \Delta\{(1,0),(0,1)\}$ be defined by $P(Z_Y = (1,0)) = P(Y = (1,0)) + \frac{1}{2}P(Y \in \{(0,0),(1,1)\})$. By construction, $E_Y\phi_F = E_{Z_Y}\phi_R$. In particular,

$$\max_{Y \in \Delta\left(\{0,1\}^2\right)} \{E_Y\phi_F : p_1 = p_2\} = \max_{Y \in \Delta\left(\{0,1\}^2\right)} \{E_{Z_Y}\phi_R : p_1 = p_2\} = E_{Y^0}\phi_R = \alpha$$

and

$$\max_{Y \in \Delta\left(\{0,1\}^2\right)} \{E_Y(1-\phi_F) : p_1 \geq p_2 + d\} = \max_{Y \in \Delta\left(\{0,1\}^2\right)} \{E_{Z_Y}(1-\phi_R) : p_1 \geq p_2 + d\} = 1 - E_{Y^d}\phi_R.$$

Since ϕ_R attains the unavoidable type II error when restricting attention to $Y \in \Delta\{(0,1),(1,0)\}$ we have proven the following.

Proposition 1 *ϕ_F attains the unavoidable type II error under full information sampling, the value of the unavoidable type II error is given by*

$$1 - E_{Y^d}\phi_R.$$

The unavoidable type II error for our pair of hypotheses under full information sampling can be found in the literature if one restricts attention to unbiased tests. Lehmann and Romano (2005, p. 138) namely find that the randomized version of McNemar's test (McNemar, 1947) is uniformly most powerful among the unbiased tests. In contrast, we have not imposed unbiasedness.[‖]

2.6 Inference under Balanced and Sequential Sampling

Note that neither balanced sampling nor sequential sampling can ever generate strictly more information than full information sampling. Together with Proposition **??** this shows the following.

Proposition 2 *The unavoidable type II error under balanced sampling and under sequential sampling is bounded below by*

$$1 - E_{Y^d}\phi_R.$$

[¶] $|A|$ denotes the number of elements of the finite set A.

[‖] With a few additional arguments it is easy to show given the result above that the randomized version of McNemar's test also achieves the unavoidable type II error $(1 - E_{Y^d}\phi_R)$ among all tests.

We wish to investigate circumstances in which balanced sampling is as good (in terms of unavoidable type II error) as full information sampling, and hence as good as sequential sampling. We first derive necessary conditions. Assume that there is a test ϕ_B for balanced sampling that attains the unavoidable type II error under full information sampling. This means that

$$\max_{Y \in \Delta\left(\{0,1\}^2\right)} \left\{E_Y\left(1-\phi_B\right) : p_1 = p_2 + d\right\} = E_{Y^d}\left(1-\phi_R\right).$$

Moreover, when facing Y_d then any balanced sample contains the same information as if one had observed full information. As ϕ_B cannot outperform ϕ_R when facing Y^d we obtain that $E_{Y^d}\left(1-\phi_B\right) \geq E_{Y^d}\left(1-\phi_R\right)$. We combine these two statements.

Proposition 3 *If a test for balanced sampling attains the unavoidable type II error under full information sampling then it attains this value when $Y = Y^d$.*

So we search for a test with level α under balanced sampling that behaves like ϕ_R when facing Y^d and that has the property that its type II error equals $1 - E_{Y^d}\phi_R$. Let $\bar{y}_i$ be the number of successes observed of Y_i in the balanced sample, so $\bar{y}_i = \sum_{k=1}^{n/2} y_{ik}^{(n/2)}$. A first idea is to consider a test that rejects the null hypothesis when the number of successes observed of Y_1 exceeds those observed of Y_2 by margin $b \in \mathbb{N}$. So reject when $\bar{y}_1 > \bar{y}_2 + b$. Given that the test should exhibit the same behavior when facing Y^d as ϕ_R we obtain that $b = n/2 + m$ (so b is unique) and that there is no rejection if $\bar{y}_1 < \bar{y}_2 + b$. There are some degrees of freedom for determining behavior when $\bar{y}_1 = \bar{y}_2 + b$. The only constraint is that its type I error is equal to α. Consider some $v \in \{-1, 0, 1, .., \lfloor (n/2 - b)/2 \rfloor\}$. Let $\phi_{b,v}$ be the test with type I error equal to α that has the following additional properties when $\bar{y}_1 = \bar{y}_2 + b$: $\phi_{b,v} = 1$ if $\bar{y}_1 \leq v$ or $\bar{y}_1 \geq n/2 - v - b$ and $\phi_{b,v} = \eta$ if $v < y_1 < n/2 - v - b$. So $\phi_{b,v}$ rejects the null hypothesis on the $2(v+1)$ points closes to the boundary and rejects with constant probability otherwise. In particular, $\phi_{b,-1}$ rejects with constant probability whenever $\bar{y}_1 = \bar{y}_2 + b$. Whether or not η can be chosen when $v \neq -1$ so that the test has type I error α has to be checked numerically. Moreover, one has to check numerically whether $\phi_{b,v}$ attains its type II error when $Y = Y^d$. When both of these checks are positive we have found for the given values of v and d that the test $\phi_{b,v}$ attains the unavoidable type II error under full information sampling. One can then vary the value of the parameter v to find more values of d that satisfies these two checks, so values of d where balanced sampling is as good as full information sampling.

So we have generated a method for finding values of d where the unavoidable type II error under balanced sampling is equal to that under full information sampling (and sequential sampling). Our numerical simulations show that this works if d is not too small. Of course it is conceivable that this equality holds for a value of d where there is no value of v that makes $\phi_{b,v}$ a test with type I error α that attains this the unavoidable type II error. In fact, we do not know how to find the unavoidable type II error under balanced sampling for values of d that are below those derived by this procedure. We only know that it lies above the unavoidable type II error under full information sampling given in Proposition **??**.

In the following we report on the results of our numerical calculations. For each value of v such that $\phi_{b,v}$ has type I error α we find that there is a threshold $d(v)$ such that $\phi_{b,v}$ attains the unavoidable type II error under full sampling when $d \geq d(v)$. We search for the value of v, denoted by v^*, where $d(v)$ is smallest and let $d^* = d(v^*)$. The values are tabulated in Table 1 (Schlag, 2008).

Table 1: $\alpha = 0.05$

n	10	20	30	40	50	60	80	100	120	140
b	3	4	4	5	6	6	7	8	9	10
v^*	0	2	1	3	6	5	9	13	26	24
d^*	0.49	0.33	0.27	0.19	0.21	0.21	0.16	0.14	0.14	0.14
$1 - E_{Y^{d^*}}\phi_R$	0.52	0.56	0.55	0.67	0.56	0.52	0.58	0.6	0.56	0.51

We summarize.

Remark 1 In all numerical computations we find that the unavoidable type II error under balanced sampling is the same as it is under sequential sampling and full information sampling as long as the unavoidable type II error under full information is below 0.5, which requires that d is not too small.

2.7 Inference of Nonrandomized Tests under Balanced Sampling

Now we show how the above impacts our understanding of inference when implementing standard nonrandomized tests. For comparing two binary endpoints we find exact tests of Boschloo (1970) and Suissa and Shuster (1985). Both are uniformly more powerful than the Fisher exact test (Fisher, 1935).** These tests will typically not attain the unavoidable type II error under full information as they are, for practicality reasons, nonrandomized. We are interested in how far, for a given value of d, their type II error is from the unavoidable type II error under balanced sampling. We refer to this quantity as the *added type II error*. Following Remark **??** we can compute the unavoidable type II error under balanced sampling when this is below 0.5. In Table 2 we show for $\alpha = 0.05$ and different sample sizes the maximal added type II error where this maximum is taken over all values of d where the unavoidable type II error is below 0.5. Note from Table 2 how small the added type II errors of these two tests are. For instance, this table shows for $n = 20$ and any given value for d that there does not exist a nonrandomized test under sequential sampling (or under full information sampling) with level 0.05 that has a type II error below 0.5 that falls below that of the test of Boschloo by more than 0.031.

Table 2: Maximal Added Type II Error when $\alpha = 0.05^*$

n	20	30	40	50	60	80	100
z test	0.031	0.048	0.034	0.066	0.013	0.012	0.02
Boschloo test	0.031	0.0016	0.033	0.047	0.012	0.012	0.02

*when the unavoidable type II error is below 0.5.

Another way to evaluate tests is to consider minimal sample sizes needed to guarantee type II error to be below a given threshold. Table 3 (Schlag, 2008) shows the minimal sample size need to guarantee type II error below 0.2 for various values of d when $\alpha = 0.05$. In each case the sample size needed to ensure that the unavoidable type II error under balanced sampling is below 0.2 is the same it is under full information sampling. For instance, it shows for $d = 0.25$ and $n \leq 96$ that there is no test under sequential sampling (or full information sampling) with level 0.05 and type II error below 0.2 (we did not derive what happens for odd sample sizes). However, if $n \geq 102$ then the z test has these properties.

**While this can be proven theoretically for the test of Boschloo (1970), for the z test we have to rely on numerical evaluations of Suissa and Shuster (1985) available for $\alpha \in \{1\%, 2.5\%, 5\%\}$ and $10 \leq n/2 \leq 150$.

Table 3: Sample Sizes Needed to Guarantee Type II Error Below 0.2 when $\alpha = 0.05$

d	0.5	0.4	0.3	0.25	0.2
Minimal sample size	24	38	68	98	154
Sample size under z test	26	40	74	102	158

3 Conclusion

The results presented in this paper are more general as shown in Schlag (2008). They extend to tests of noninferiority and superiority. They also extend to nonparametric tests when allowing for distributions that can generate any outcome in $[0,1]$, so to the case where $Y \in \Delta\left([0,1]^2\right)$. The key insight is as follows. When the difference between the two treatments is not too small under the alternative hypothesis, only outcomes with two unequal components are contained in the support of the least favorable distribution. When observing one component one knows the other component. More sophisticated sampling schemes are not needed when facing this distribution.

The new insights can also be viewed in the light of counterfactual evidence. It is typically not possible to assign two treatments independently to the same patient. Yet one is interested in knowing how the two treatments compare for a given patient. While inference would be better if counterfactual evidence were available, this research shows from an ex-ante (unconditional) perspective that it is as if standard nonrandomized tests under balanced sampling use counterfactual evidence as long as treatments are not too similar whenever they are different.

The insights in this paper seem to be limited to comparing two binary endpoints. Once there are three different treatments, it is not conceivable that the outcome of one treatment will reveal the outcome of the two other treatments when facing a least favorable distribution.

Future research will look at whether our insights for comparing two treatments carry over to conditional inference where one is interested in how the two treatments compare for the patients that belong to the given sample (of size n). In this paper we considered unconditional inference, where we are interested in how they compare for a patient that does not belong to the given sample of n patients.

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The use of the 2-step procedure of Stein for sample size determination in comparisons of means with the t-test, if the variance is unknown

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Abstract: The 2-step procedure of Stein for construction of a confidence interval for the mean μ of one population or the difference Δ of the means of two independent populations is used as test procedure to test the null hypothesis $\mu \leq \mu_0$ (one sample problem) resp. $\Delta \leq \Delta_0$ (two sample problem) which preserves strictly the error probability ($p \leq \alpha$ for $\mu=\mu_0$ resp $\Delta \leq \Delta_0$) and power requirement (power $\geq 1-\beta$ for $\mu=\mu_1>\mu_0$ resp $\Delta=\Delta_1>\Delta_0$) without specification of the population variance. The power requirement is equivalent to the requirement that the $(1-\alpha)$-confidence-interval for μ resp. Δ has a specified half-length b_{opt} which does not depend on σ. At the first step a preliminary sample of size n resp. two independent samples of total size n are drawn and the sample mean resp. the means of the two samples and the sample variances are calculated. With the variance estimate(s) the sample size n_{opt} is estimated which is necessary to achieve the half length b_{opt}. If $n_{opt} \leq n$, the process is stopped. The null hypothesis is rejected, if the lower bound of the confidence interval for μ resp. Δ is greater than μ_0 resp Δ_0, otherwise accepted. The process is also stopped, if the null hypothesis can be rejected with the t-test at the level $\alpha/2$. If $n_{opt}>n$ and H_0 is not rejected, additional $n_{opt}-n$ sample values are drawn. The lower bound of the $(1-\alpha)$-confidence-interval for μ resp. Δ is computed with the mean(s) of all data and the variance estimate(s) of the preliminary sample. H_0 is rejected, if the lower bound is greater then μ_0 resp. Δ_0, otherwise accepted. By simulation studies it could be shown that this procedure preserves α and the power $1-\beta$ very well. If the size of the preliminary sample is not too small, the average sample number of the procedure can be much smaller than the sample size which is necessary for a one-step test to achieve the power requirements.

Keywords: comparison of means, sample size determination without specification of the variance, Stein's two step procedure

1 Introduction

The t-test is one of the oldest statistical tests. It was introduced 1908 by W.S. Gosset writing under the pseudonym 'Student' to test hypotheses about the means of populations (Student 1908). The test statistic t is the ratio between the deviation of the observed sample mean (one sample problem) or difference of the means of two independent samples (two samples problem) from the null hypothesis and an independent estimate of the standard error. The power of the test depends not only on the deviation of the actual population mean from the null hypothesis, but also on the variance of the population. Therefore, sample size determination at the design stage needs information about this variance. This can be avoided with the procedure proposed by C. Stein (1945) to achieve a confidence interval for the mean with given length. The use of this procedure for sample size determination and hypothesis tests is shown in the following.

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2 The procedure

2.1 One-sample

Consider a continuously distributed random variable with population mean (expected value) μ and population variance σ^2. We want to test the null hypothesis H_0 $\mu \le \mu_0$ against the alternative H_1 $\mu > \mu_0$. Given a sample of n independent realizations x_i, the test statistic is:

$$t = \frac{\bar{x} - \mu_0}{s}\sqrt{n} \tag{1}$$

with the sample mean $\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$ and standard deviation $s = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2}$. For sufficient large n, the mean $\bar{x}$ can be assumed as normal distributed with population mean μ and variance σ^2/n and s^2 as distributed like $\sigma^2\chi^2/(n-1)$ independent from $\bar{x}$, where χ^2 is a Chi^2 distributed random variable with n-1 degrees of freedom (df). With these assumptions, the test statistic t has for $\mu=\mu_0$ a central t-distribution with n-1 df (denoted by $F_{t,n-1}(\ldots)$). The null hypothesis is rejected with error probability α, if t is greater then the 1-α quantile $t_{1-\alpha,,n-1}$ of the central t-distribution with n-1 df.

As an equivalent procedure, H_0 is rejected, if the lower bound of the (1-2α)-confidence-interval for μ is greater than μ_0 (remark that the (1-2α)-confidence-interval is used because of the one-sided test):

$$\text{Re}\,ject\ H_0, if\ \ \bar{x} - t_{1-\alpha,n-1}s/\sqrt{n} > \mu_0 \tag{2}$$

The sample size n is determined by the requirement that the power for μ_1, i.e. the probability to reject Ho, if $\mu=\mu_1>\mu_0$, is 1-β:

$$Power(\mu_1) = P(rejct\ H_0 \mid \mu = \mu_1) \ge 1-\beta \tag{3}$$

The distribution of t for $\mu=\mu_1$ is the noncentral t-distribution $F_{nct,n-1,nc}(t)$ with n-1 degrees of freedom and the noncentrality parameter $nc=\sqrt{n}(\mu_1-\mu_0)/\sigma$. So we have:

$$Power(\mu_1) = 1 - F_{nct}(t_{1-\alpha}, n-1, \sqrt{n}(\mu_1-\mu_0)/\sigma) \ge 1-\beta \tag{4}$$

The necessary sample size n is the smallest natural number n which solves this inequality. The solution must be done iteratively.

Whereas the reference value μ_1 is derived by problem oriented considerations, a reasonable estimate for σ is often not or only with great uncertainty known. Therefore it would be desirable to determine the sample size n without knowledge of σ. This is possible with Stein's (1945) procedure. This is a 2-step procedure to construct a (1-α)-confidence interval for μ whose half length is not greater than a prefixed value b_{opt}. At the first step a sample of (small) size n is drawn and the statistics $\bar{x}$ and s are calculated. If the half length of the (1-α)-confidence-interval, i.e. $b_1 = t_{1-\alpha/2,n-1}s/\sqrt{n}$), is equal or less than b_{opt}, the procedure is stopped and $\bar{x} \pm t_{1-\alpha/2,n-1}s/\sqrt{n}$ is the desired interval. If $b_1 > b_{opt}$, additional n_{opt}-n sample values are drawn where n_{opt} is the smallest integer equal or greater than $t^2_{1-\alpha/2,n-1}s^2/b^2_{opt}$. The confidence interval is computed with mean $\bar{x}_{tot}$ of all n_{opt} sample values and the half length $t_{1-\alpha/2,n-1}s/\sqrt{n_{opt}}$ with s and n of the first sample. As s^2 is independent of $\bar{x}_{tot}$ and distributed like $\chi^2\sigma^2/(n-1)$, the ratio $(\bar{x}_{tot}-\mu)\sqrt{n_{opt}}/s$ has a central t-distribution with n-1 df. Therefore the interval covers μ with probability 1-α and its half length is obviously not greater than b_{opt}

To apply this procedure to sample size determination and test with the t-statistic, two points must be cleared:
1) The error probabilities α and β must be adequately spent to the two steps.
2) The half length b_{opt} which corresponds to the power requirement (3) must be evaluated

Ad 1): H_0 is rejected, if either the lower bound of the confidence interval which is calculated with the data of the first sample or that which is calculated with the mean $\overline{x}_{tot}$ of both samples and n and s of the first sample is greater than μ_0. H_0 can be falsely rejected at both steps and the error probability α must be spent adequately. An equal spending, i.e. $\alpha/2$ to both steps, seems adequate without further preferences. H_0 is rejected after the first or second step, if the lower bound of the corresponding (1-α)-confidence-interval is greater than μ_0. As at the first step acceptance of H_0 for $\mu=\mu_1$ seems very unlikely, the total error probability β is spent to the second step.

Ad 2): We consider the (1-α)-confidence-interval for μ calculated with the sample mean $\overline{x}_{tot}$ of a sample with size n' and the variance estimate s^2 calculated with the first n≤n' sample values. This estimate is independent from $\overline{x}_{tot}$ and distributed like $\chi^2\sigma^2/(n-1)$ with n-1 df. H_0 is rejected, if the lower bound of the confidence interval: $lb = \overline{x}_{tot} - t_{1-\alpha/2,n-1}s/\sqrt{n'}$ is greater than μ_0. The power requirement (3) means that for $\mu=\mu_1$ *lb* must be greater than μ_0 with probability ≥(1-β). The statistic $t = (\overline{x}_{tot} - \mu_1)\sqrt{n'}/s$ is for $\mu=\mu_1$ central t-distributed with n-1 df. Therewith we get:

$$1-\beta \le P(\overline{x}_{tot} - t_{1-\alpha/2,n-1}s/\sqrt{n'} > \mu_0 \mid \mu=\mu_1) = P(\frac{(\overline{x}_{tot}-\mu_1)\sqrt{n'}}{s} > t_{1-\alpha/2,n-1} - \frac{(\mu_1-\mu_0)\sqrt{n'}}{s} \mid \mu=\mu_1)$$

$$= F_{t,n-1}(\frac{(\mu_1-\mu_0)\sqrt{n'}}{s} - t_{1-\alpha/2,n-1}) \qquad (5)$$

From this follows: $\frac{(\mu_1-\mu_0)\sqrt{n'}}{s} \ge (t_{1-\alpha/2,n-1} + t_{1-\beta,n-1})$ or

$$n' \ge \left(s\frac{t_{1-\alpha/2,n-1} + t_{1-\beta,n-1}}{\mu_1-\mu_2} \right)^2 \qquad (6)$$

We denote the smallest integer which fits inequality (6) by n_{opt} and the half length of the (1-α)-confidence-interval derived with n_{opt} as b_{opt}. It is:

$$b_{opt} = t_{1-\alpha/2,n-1}\frac{s}{\sqrt{n_{opt}}} = \frac{t_{1-\alpha/2,n-1}}{t_{1-\alpha/2,n-1}+t_{1-\beta,n-1}}(\mu_1-\mu_0) \qquad (7)$$

The power requirement (3) is fulfilled, if H_0 is tested with a (1-α)-confidence-interval whose half length is equal or smaller than b_{opt}. Notice that b_{opt} depends on α, β, μ_1-μ_0 and the size n of the first sample, but not on σ.

2.2 Two samples

In the two samples problem, hypotheses about the difference in the means of two independent populations, one with mean μ_1 and standard deviation σ_1, the second with mean μ_2 an standard deviation σ_2, are tested in two steps. Like in the one-sample problem, the one-sided null hypothesis H_0: $\Delta=\mu_1-\mu_2\leq\Delta_0$ is tested against the alternative $\Delta>\Delta_0$. The error probability to reject H_0 at the first or second step, if it holds, is restricted to $\alpha/2$ and the power to reject H_0, if $\Delta=\Delta_1$, should be $\geq 1-\beta$. The test is performed with $(1-\alpha)$-confidence-interval for Δ. The power requirement is achieved, if the sample numbers n_1 and n_2 are large enough that the half length of the $(1-\alpha)$-confidence-interval for Δ is:

$$b_{opt} = \frac{t_{1-\alpha/2,df}}{t_{1-\alpha/2,df} + t_{1-\beta,df}}(\Delta_1 - \Delta_0) \tag{8}$$

where df are the degrees of freedom of the variance estimate which is defined later. The sample numbers n_1 and n_2 can be different. The ratio $R=n_2/n_1$ is fixed in advance. If $n=n_1+n_2$, the relations: $n_1=n/(1+R)$ and $n_2=nR/(1+R)$ hold.

In the first step a sample of size n_1 is drawn from population 1 and a sample of size n_2 form population 2. The sample means $\overline{x}_1, \overline{x}_2$ and variances s_1^2, s_2^2 are calculated. The difference $\overline{x}_1 - \overline{x}_2$ is an estimate of Δ. To get an estimate for the variance of the difference, two situations must be considered.

2.2.1 The variances of the two populations are equal ($\sigma_1^2 = \sigma_2^2 = \sigma^2$):

An estimate for the common variance σ^2 is:

$$s^2 = (s_1^2(n_1 - 1) + s_2^2(n_2 - 1))/(n_1 + n_2 - 2) \tag{9}$$

This estimate is assumed to be distributed like $\sigma^2\chi^2/(n_1+n_2-2)$ with df= n_1+n_2-2. With this estimate, the lower bound of the $(1-\alpha)$-confidence-interval for Δ is

$$lb_1 = \overline{x}_1 - \overline{x}_2 - t_{1-\alpha/2,n_1+n_2-2}\, s\sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \tag{10}$$

and the half length is:

$$b_1 = t_{1-\alpha/2,n_1+n_2-2}\, s\sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \tag{11}$$

The procedure is stopped and H_0 rejected, if $lb_1>\Delta_0$. The procedure is also stopped, if $b_1\leq b_{opt.}$ H_0 is rejected, if $lb_1>\Delta_0$, otherwise accepted.

If H_0 is not rejected at step1 and $b_1>b_{opt}$, additional $n_{opt1}- n_1$ values are drawn from the first population and $n_{opt2}-n_2$ from the second population, where $n_{opt1}=n_{opt}/(1+R)$, $n_{opt2}=n_{opt}R/(1+R)$ and n_{opt} is :

$$n_{opt} = \left\lceil s^2 \frac{(1+R)^2}{R}\left(\frac{t_{1-\alpha/2,n_1+n_2-2} + t_{1-\beta,n_1+n_2-2}}{\Delta_1 - \Delta_0}\right)^2 \right\rceil \tag{12}$$

The mean $\overline{x}_{tot1}$ is calculated from all n_{opt1} values drawn from the first population, the mean $\overline{x}_{tot2}$ from the n_{opt2} values drawn from the second population and the lower bound lb_2, calculated with the estimate s of the first step, is:

$$lb_2 = \overline{x}_{tot1} - \overline{x}_{tot2} - t_{1-\alpha/2,n_1+n_2-2}\, s\sqrt{\frac{1}{n_{opt1}} + \frac{1}{n_{opt2}}} \tag{13}$$

H_0 is rejected, if $lb_2>\Delta_0$, otherwise accepted.

2.2.2 The variances of the two populations are unequal ($\sigma_1^2 \neq \sigma_2^2$):

Estimate for σ_1^2 is the sample variance s_1^2 and for σ_2^2 the sample variance s_2^2 drawn at the first step. According to the Satterthwaite-Welch approximation (Satterthwaite 1946; Welch 1947) the statistic:

$$t = \frac{\overline{x}_1 - \overline{x}_2 - \Delta_0}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}} \tag{14}$$

is assumed as central t-distributed under $\Delta=\Delta_0$ with

$$df = \frac{(s_1^2/n_1 + s_2^2/n_2)^2}{(s_1^2/n_1)^2/(n_1-1) + (s_2^2/n_2)^2/(n_2-1)} \tag{15}$$

After the first step the procedure is stopped and H_0 rejected, if

$$lb_1 = \overline{x}_1 - \overline{x}_2 - t_{1-\alpha/2.df}\sqrt{s_1^2/n_1 + s_2^2/n_2} > \Delta_0 \tag{16}$$

The process is also stopped, if $b_1 = t_{1-\beta/2,df}\sqrt{s_1^2/n_1 + s_2^2/n_2} \leq b_{opt}$; H_0 is rejected, if $lb_1>\Delta_0$, otherwise accepted.

If H_0 is not rejected at step 1 and $b_1>b_{opt}$, additional n_{opt1}-n_1 values are drawn from the first population and n_{opt2}-n_2 from the second one, where $n_{opt1}=n_{opt}/(1+R)$, $n_{opt2}=n_{opt}R/(1+R)$ and n_{opt} is :

$$n_{opt} = (1+R)(s_1^2 + s_2^2/R)\left(\frac{t_{1-\alpha/2.df} + t_{1-\beta,df}}{\Delta_1 - \Delta_0}\right)^2 \tag{17}$$

The mean $\overline{x}_{tot1}$ is calculated from all n_{opt1} values drawn from the first population, the mean $\overline{x}_{tot2}$ from all n_{opt2} values drawn from the second population and the lower bound lb_2 of the (1-α)-confidence-interval is:

$$lb_2 = \overline{x}_{tot1} - \overline{x}_{tot2} - t_{1-\alpha/2,df}\sqrt{\frac{s_1^2}{n_{opt1}} + \frac{s_2^2}{n_{opt2}}}_2 \tag{18}$$

H_0 is rejected, if $lb_2>\Delta_0$, otherwise accepted.

3 Example

In a controlled clinical study the blood-pressure-lowering effect of a new drug 1 should be compared with that of the standard drug 2 after a treatment of 4 weeks. Effect variable is the percentage reduction of blood pressure after 4 weeks. Patients are randomly and double blind assigned to the study treatments. The new drug 1 is considered as non-inferior to the standard drug, if the population mean μ_1 of the effect variable is either greater or at least 10% lower than the population mean μ_2 of the standard drug 2. Denoting with Δ the difference μ_1-μ_2, the null hypothesis H_0: $\Delta\leq$ -10% should be tested against the alternative Δ >-10% with error probability α=0.05 and power 1-β=0.95 for Δ=0%. The total sample size n_{opt} (assuming equal sample sizes for both groups: $n_{opt1}=n_{opt2}=n_{opt}/2$) is determined with the two step procedure. At the first step n_1=9 patients are treated with drug 1 and a mean $\overline{x}_1$ =15% and standard deviation s_1=8% were observed. With the standard drug 2 n_2=12 patients were treated and mean $\overline{x}_2$ =18% and standard deviation s_2=12% were observed.

Assuming equal variances ($\sigma_1^2=\sigma_2^2=\sigma^2$), b_1=9.7%, $lb_{1=}$ -12.7% and b_{opt}=5.5%. The necessary total sample size for the power requirements is n_{opt} =65. In the second step additional 44 patients (23 for treatment 1 and 21 for treatment 2) should be recruited.

Assuming unequal variances ($\sigma_1^2 \neq \sigma_2^2$), b_1=9.2%,lb_1= -12.2% and b_{opt}= 5.47%. The necessary total sample size for the power requirement is n_{opt}=61. In the second step additional 40 patients (21 for treatment 1 and 19 for treatment 2) should be recruited.

4 Simulation results

To check the feasibility of the procedure, two simulation studies with different settings of the population parameters were performed; each setting with 10 000 repetitions. In the first simulation study two independent samples of normal distributed data were generated and the two step t-test procedure applied to test the null hypothesis $\Delta \leq 0$ against the alternative hypotheses $\Delta > 0$. The error probability α to reject H_0 wrongly was set to 0.05, the error probability β to accept H_0, if $\Delta=1$, also to 0.05. The population standard deviation σ was set to 1 for both samples. The population means were set in half of the simulations to 0 for both samples (corresponds to $\Delta=0$) and in the other half in the first sample to 1 and in the second one to 0 (corresponds to $\Delta=1$). The same sample size was assumed for both samples. Simulations were performed with the sample size n ($=n_1+n_2$) at the first step which are 0.2, 0.5 and 0.8-fold of the sample size n_{fix} which is necessary to achieve the power requirement, if the t-test is performed in one step and the standard deviation σ is known. The results of the simulations are shown in table 1.

In the second simulation study the same parameter settings were used except the assumption of unequal population standard deviations (σ_1=1, σ_2=2). Correspondingly, separate variance estimates were used for the samples and the Satterthwait-Welch approximation was applied for the t-distribution. The results are shown in table 2.

The rows of the tables show:

- b_{opt} = half length of the optimal (1-α)-confidence-interval corresponding to the power requirement
- $A(n_{opt})$ = Average of the sample size n_{opt} ($=n_{pot1}+n_{opt2}$) necessary for power requirement
- $P(b_1 \leq b_{opt})$ = proportion of $b_1 \leq b_{opt}$
- P(H_0 rejected at step1, if $b_1 \leq b_{opt}$)= proportion to reject H_0 at step 1, if $b_1 \leq b_{opt}$
- P(H_0 rejected at step1, if b_1>bopt)= proportion to reject H_0 at step 1, if b_1>bopt
- P(H_0 rejected at step1, total)= proportion to reject H_0 at step 1
- P(stop at step 1) = proportion to stop at step 1
- P(H_0 rejected at step2)= proportion to reject H_0 at step 2, if this step is reached
- P(H_0 rejected at either step)= proportion to reject H_0 at step 1 or 2
- ASN = average sample number= the sum of the sample number n at step 1, multiplied with the proportion to stop at step 1 and the sample number n_{opt} multiplied with the proportion to perform step2.

The most important result of all simulations is that for all settings α and β are strictly kept. The two-step procedure is conservative. $A(n_{opt})$ and ASN are for $n=0.2n_{frix}$ much greater than for $0.5n_{fix}$ and $0.8n_{fix}$, but differ only little between $0.5n_{fix}$ and $0.8n_{fix}$. The choice $n=0.5n_{fix}$ seems optimal, if one has some idea about the population variances.

The proportion $P(b_1 \leq b_{opt})$ is very small and acceptance of H_0 at step1 for $\Delta=\Delta_1$ very seldom. Spending all error probability β to the second step is therefore justified.

ASN is smaller for $\Delta=\Delta_1$ than for $\Delta=\Delta_0$. For $n=0.5n_{fix}$ or $n=0.8n_{fix}$, ASN is even smaller than n_{fix}. This means that for not too small sample sizes n at the first step the two-step procedure is in the average advantageous against the one step t-test with known variance.

Table 1: Results of simulation study 1 (equal variances)

Simulation of 10000 normal distributed data to test $\Delta=0$ against $\Delta=1$ $\alpha=0.05$ $\beta=0.05$	$\mu_1=0$ $\mu_2=0$ $\sigma_1=1$ $\sigma2=1$ $n_{fix}=45$ n=9	$\mu_1=1$ $\mu_2=0$ $\sigma_1=1$ $\sigma2=1$ $n_{fix}=45$ n=9	$\mu_1=0$ $\mu_2=0$ $\sigma_1=1$ $\sigma2=1$ $n_{fix}=45$ n=23	$\mu_1=1$ $\mu_2=0$ $\sigma_1=1$ $\sigma_2=1$ $n_{fix}=45$ n=23	$\mu_1=0$ $\mu_2=0$ $\sigma_1=1$ $\sigma_2=1$ $n_{fix}=45$ n=36	$\mu_1=1$ $\mu_2=0$ $\sigma_1=1$ $\sigma_2=1$ $n_{fix}=45$ n=36
b_{opt}	.5552	.5552	.5472	.5472	.5458	.5458
$E(n_{opt})$	73.0360	73.5487	58.3497	58.2700	55.9531	56.1510
$P(b_1 \le b_{opt})$	.0037	.0018	.0071	.0060	.0559	.0568
$P(H_o$ rejected at step 1)						
if $b_1 \le b_{opt}$	.0015	.0015	.0016	.0053	.0039	.0528
if $b_1 > b_{opt}$	.0243	.2579	.0255	.6309	.0204	.7800
total	.00258	.2594	.0271	.6362	.0243	.8328
P(stop at set 1)	0.0280	.2597	.0326	.6369	.0763	.8368
$P(H_0$ rejected at step 2)	.01698	.9475	.0151	.8827	.0106	.7720
$P(H_0$ rejected at either step)	.0423	.9608	.0376	.9567	.0341	.9588
ASN	71.243	56.7854	57.1973	35.8065	54.4306	39.2886

Table 2: Results of simulation study 2

Simulation of 10000 normal distributed data to test $\Delta=0$ against $\Delta=1$ $\alpha=0.05$ $\beta=0.05$	$\mu_1=0$ $\mu_2=0$ $\sigma_1=1$ $\sigma2=2$ $n_{fix}=110$ n=22	$\mu_1=1$ $\mu_2=0$ $\sigma_1=1$ $\sigma2=2$ $n_{fix}=110$ n=22	$\mu_1=0$ $\mu_2=0$ $\sigma_1=1$ $\sigma2=2$ $n_{fix}=110$ n=55	$\mu_1=1$ $\mu_2=0$ $\sigma_1=1$ $\sigma_2=2$ $n_{fix}=110$ n=55	$\mu_1=0$ $\mu_2=0$ $\sigma_1=1$ $\sigma_2=2$ $n_{fix}=110$ n=88	$\mu_1=1$ $\mu_2=0$ $\sigma_1=1$ $\sigma_2=2$ $n_{fix}=110$ n=88
b_{opt}	.5488	.5488	.5456	.5456	.5448	.5448
$mean(n_{opt})$	152.9520	153.4067	138.3551	138.6208	134.7562	135.1334
$P(b_1 \le b_{opt})$	.0000	.0000	.0001	.0002	.0157	.0129
$P(H_o$ rejected at step 1)						
if $b_1 \le b_{opt}$	.0000	.0000	.0000	.0002	.0015	.0119
if $b_1 > b_{opt}$	.0263	.2867	.0250	.6311	.0226	.8219
total	.0263	.2867	.0250	.6313	.0241	.8338
P(stop at set 1)	.0263	.2867	.0251	.6313	.0383	.8348
$P(H_0$ rejected at step 2)	.0215	.9383	.0176	.8812	.0120	.7403
$P(H_0$ rejected at either step)	.0472	.9560	.0422	.9562	.0356	.9561
ASN	149.5080	115.7324	136.1522	85.8310	132.9654	95.7864

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D-Optimal Design for a Seemingly Unrelated Linear Model

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Abstract: In applications often more than one dependent variable is observed in each experimental unit. In some of these situations the explanatory variables may be adjusted separately for the components in these models. For example, if one is interested in both pharmacokinetics and pharmacodynamics, the time points need not be identical for the measurements of the two quantities within one subject. As the observations will be correlated within one unit, the data may be described by a multivariate model, which has the structure of a seemingly unrelated regression.

Keywords: multivariate linear model, seemingly unrelated regression, D-optimal design, product type design.

1 Introduction

The model of seemingly unrelated regression (SUR) has been introduced by Zellner (1962) and since then various types of it are playing an important role in many areas of science. The determination of D-optimal designs for such models, which is the aim of the present work, can be based on a multivariate equivalence theorem by Fedorov (1972) and is related to results by Kurotschka and Schwabe (1996), where design problems for multivariate experiments are reduced to their univariate counter-parts, and uses techniques concerning product type designs derived by Schwabe (1996). By this tools for SUR models, in which an intercept is included in each component, it can be shown that the D-optimal design can be generated as the product of marginal designs, which are D-optimal in the univariate marginal models for the components.

The paper is organized as follows: In the second section we specify the model and characterize optimal designs in the third section. In section 4 the results are illustrated by means of a simple example. Finally, section 5 contains some conclusions.

2 Model specification

The model contains m-dimensional multivariate observations for n individuals. The components of the multivariate observations can be heterogeneous, which means that the response can be described by different regression functions and different experimental settings, which may be chosen from different experimental regions. Then the observation of the jth component of individual i can be described by

$$Y_{ij} = \mathbf{f}_j(x_{ij})^\top \boldsymbol{\beta}_j + \varepsilon_{ij} = \sum_{l=1}^{p_j} f_{jl}(x_{ij})\beta_{jl} + \varepsilon_{ij}\,, \tag{1}$$

where $\mathbf{f}_j = (f_{j1}, ..., f_{jp_j})^\top$ are the known regression functions and $\boldsymbol{\beta}_j = (\beta_{j1}, ..., \beta_{jp_j})^\top$ the unknown parameter vectors for the jth component and the experimental setting x_{ij} may be chosen from an experimental region $\mathcal{X}_j$.

Denote by $\mathbf{Y}_i = (Y_{i1}, ..., Y_{im})^\top$ and $\boldsymbol{\varepsilon}_i = (\varepsilon_{i1}, ..., \varepsilon_{im})^\top$ the multivariate vectors of observations and error terms, respectively, for individual i and correspondingly the block diagonal multivariate

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regression function

$$\mathbf{f}(\mathbf{x}) = \operatorname{diag}\left(\mathbf{f}_j(x_j)\right)_{j=1,\ldots,m} = \begin{pmatrix} \mathbf{f}_1(x_1) & \cdots & \mathbf{0} \\ \vdots & \ddots & \vdots \\ \mathbf{0} & \cdots & \mathbf{f}_m(x_m) \end{pmatrix}$$

for the multivariate experimental setting $\mathbf{x} = (x_1, ..., x_m)^\top \in \mathcal{X} = \times_{j=1}^n \mathcal{X}_j$.

Then the individual observation vector ca be written as

$$\mathbf{Y}_i = \mathbf{f}(\mathbf{x}_i)^\top \boldsymbol{\beta} + \boldsymbol{\varepsilon}_i \,, \tag{2}$$

where $\boldsymbol{\beta} = (\boldsymbol{\beta}_1^\top, ..., \boldsymbol{\beta}_m^\top)^\top$ is the complete stacked parameter vector for all components. For the error vectors $\boldsymbol{\varepsilon}_i$ it is assumed that they have zero mean, that they are uncorrelated across the individuals and that they have a common positive definite covariance matrix $\operatorname{Cov}(\boldsymbol{\varepsilon}_i) = \boldsymbol{\Sigma}$ within the individuals.

Finally, denote by $\mathbf{Y} = (\mathbf{Y}_1^\top, ..., \mathbf{Y}_n^\top)^\top$ and $\boldsymbol{\varepsilon} = (\boldsymbol{\varepsilon}_1^\top, ..., \boldsymbol{\varepsilon}_n^\top)^\top$ the stacked vectors of all observations and all error terms, respectively. Then we can write the complete observation vector as

$$\mathbf{Y} = \mathbf{F}\boldsymbol{\beta} + \varepsilon \,, \tag{3}$$

where $\mathbf{F} = (\mathbf{f}(\mathbf{x}_1), ..., \mathbf{f}(\mathbf{x}_n))^\top$ is the complete experiment design matrix. The complete observational error $\boldsymbol{\varepsilon}$ then has the covariance matrix $\mathbf{V} = \operatorname{Cov}(\boldsymbol{\varepsilon}) = \mathbf{I}_n \otimes \boldsymbol{\Sigma}$, where $\mathbf{I}_n$ is the $n \times n$ identity matrix and "$\otimes$" denotes the Kronecker product.

If we assume the covariance matrix $\boldsymbol{\Sigma}$ and, hence $\mathbf{V}$ known, we can estimate the parameter $\boldsymbol{\beta}$ efficiently by the Gauss-Markov estimator

$$\hat{\boldsymbol{\beta}}_{\mathrm{GM}} = (\mathbf{F}^T\mathbf{V}^{-1}\mathbf{F})^{-1}\mathbf{F}^T\mathbf{V}^{-1}\mathbf{Y} \tag{4}$$

with its covariance matrix equal to the inverse of the corresponding information matrix

$$\mathbf{M} = \mathbf{F}^T\mathbf{V}^{-1}\mathbf{F} = \sum_{i=1}^{n} \mathbf{f}(\mathbf{x}_i)\boldsymbol{\Sigma}^{-1}\mathbf{f}(\mathbf{x}_i)^\top \tag{5}$$

which is the sum of the individual information

Remark 2.1 *The univariate marginal models of the components have the following form*

$$\mathbf{Y}^{(j)} = \mathbf{F}^{(j)}\boldsymbol{\beta}_j + \boldsymbol{\varepsilon}^{(j)} \,, \tag{6}$$

where $\mathbf{Y}^{(j)} = (Y_{1j}, ..., Y_{nj})^\top$ *and* $\boldsymbol{\varepsilon}^{(j)} = (\varepsilon_{1j}, ..., \varepsilon_{nj})^\top$ *are the vectors of observations and errors for the* j*th component, respectively, and* $\mathbf{F}^{(j)} = (\mathbf{f}_j(x_{1j}), ..., \mathbf{f}_j(x_{nj}))^\top$ *is the design matrix for the* j*th marginal model. The corresponding error terms are uncorrelated and homoscedastic,* $Cov(\boldsymbol{\varepsilon}^{(j)}) = \sigma_j^2\mathbf{I}_n$*, where* $\sigma_j^2 = \sigma_{jj}$ *is the* j*th diagonal entry of* $\boldsymbol{\Sigma}$*.*

3 Optimal designs

We can define an experimental design $\xi = \begin{pmatrix} \mathbf{x}_1 & \ldots & \mathbf{x}_k \\ w_1 & \ldots & w_k \end{pmatrix}$ by the set of all different experimental settings $\mathbf{x}_i = (x_{i1}, \ldots, x_{im})$, $i = 1, ..., k$, with the corresponding relative frequencies $w_i = \frac{n_i}{n}$, where n_i is the number of replications at $\mathbf{x}_i$, Then the corresponding standardized information matrix can be obtained as

$$\mathbf{M}(\xi) = \sum_{i=1}^{k} w_i \mathbf{f}(\mathbf{x}_i)\boldsymbol{\Sigma}^{-1}\mathbf{f}(\mathbf{x}_i)^\top. \tag{7}$$

For analytical purposes we consider approximate designs, for which the weights $w_i \geq 0$ need not be multiples of $\frac{1}{n}$, but only have to satisfy $\sum_{i=1}^{k} w_i = 1$. As information matrix are not necessarily comparable, we have to take some real-valued criterion function of the information matrix. In this paper we will adopt the most popular criterion of D-optimality, which aims at maximizing the determinant of the information matrix. This is equivalent to minimizing the volume of the confidence ellipsoid in the case of Gaussian noise: A design ξ^* is said to be D-optimal, if $\det \mathbf{M}(\xi^*) \geq \det \mathbf{M}(\xi)$ for all other competing designs ξ.

A useful tool for checking the performance of a given candidate design is a multivariate version of the equivalence theorem for D-optimality (see Fedorov (1972), theorem 5.2.1):

Theorem 3.1 *The approximate design ξ^* is D-optimal in the multivariate linear model if and only if*

$$\operatorname{trace}\left(\Sigma^{-1}\mathbf{f}(\mathbf{x})^\top \mathbf{M}(\xi^*)^{-1}\mathbf{f}(\mathbf{x})\right) \leq p\,, \tag{8}$$

for all $x \in \mathcal{X}$, where $p = \sum_{j=1}^{m} p_j$ is the number of parameters in the model.

The quantity $\varphi(\mathbf{x};\xi) = \operatorname{trace}\left(\Sigma^{-1}\mathbf{f}(\mathbf{x})^\top (\mathbf{M}(\xi))^{-1}\mathbf{f}(\mathbf{x})\right)$ will often be called the sensitivity function of the design ξ, which shows which experimental settings are "most informative". In particular, for an optimal design ξ^* the sensitivity function attains its maximum p at the support points.

The quality of a competing design ξ can be measured in terms of its D-efficiency

$$\operatorname{eff}_D(\xi) = \left(\frac{\det \mathbf{M}(\xi)}{\det \mathbf{M}(\xi^*)}\right)^{1/p} \tag{9}$$

compared to the D-optimal design ξ^*. The efficiency states, how much less observations are required, when the optimal design ξ^* is used instead of ξ.

To obtain a complete characterization of the D-optimal designs we have to require that all marginal models related to the components contain an intercept, $f_{j1}(\mathbf{x}) \equiv 1$, say. Then the following general result holds.

Theorem 3.2 *Let ξ_j^* be D-optimal for the jth marginal component (**??**) on the marginal design region $\mathcal{X}_j$ with an intercept included, $j = 1, ..., m$, then the product type design*

$$\xi^* = \otimes_{j=1}^{m} \xi_j^* \tag{10}$$

*is D-optimal for the SUR model (**??**) on the design region $\mathcal{X} = \times_{j=1}^{m} \mathcal{X}_j$.*
The sensitivity function φ does not depend on $\mathbf{\Sigma}$.

The proof is based on an application of the equivalence theorem **??** after an orthogonalization with respect to the constant regression functions f_{j1}. Theorem **??** may fail to hold, if the regression functions of the marginal components do not contain an intercept.

4 Example: Bivariate straight line regression

To illustrate the results we consider the SUR model with simple straight line regression models for the components,

$$Y_{ij} = \beta_{j0} + \beta_{j1} x_{ij} + \varepsilon_{ij}\,. \tag{11}$$

on the unit interval $\mathcal{X}_1 = \mathcal{X}_2 = [0, 1]$ as experimental regions. Then it is well-known that the D-optimal designs for the marginal models $\xi_1^* = \xi_2^* = \begin{pmatrix} 0 & 1 \\ 1/2 & 1/2 \end{pmatrix}$ assign equal weights to each

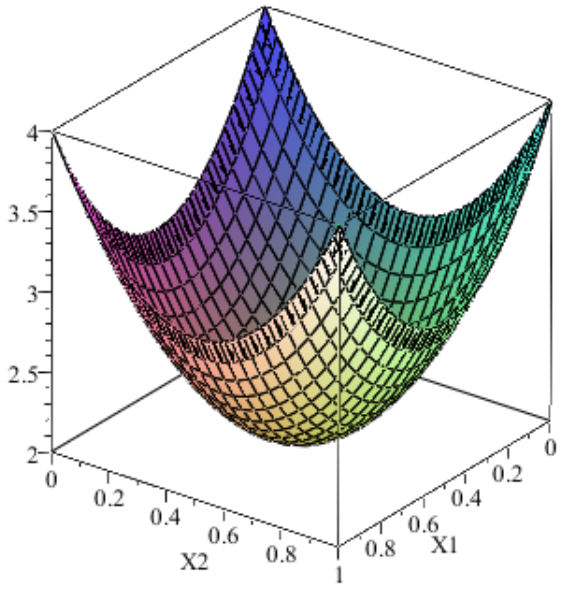

Figure 1: Sensitivity function φ for the D-optimal design $\xi_1^* \otimes \xi_2^*$

of the endpoint of the interval. By Theorem **??** the product type design

$$\xi^* = \xi_1^* \otimes \xi_2^* = \begin{pmatrix} (1,1) & (0,0) & (1,0) & (0,1) \\ 1/4 & 1/4 & 1/4 & 1/4 \end{pmatrix}$$

is D-optimal for the SUR model (**??**) on $\mathcal{X} = [0,1]^2$.

The corresponding sensitivity function

$$\varphi(\mathbf{x}; \xi^*) = \operatorname{trace}(\mathbf{\Sigma}^{-1}\mathbf{f}(\mathbf{x})^\top \mathbf{M}(\xi^*)^{-1}\mathbf{f}(\mathbf{x})) = 4 - 4x_1 + 4x_1^2 - 4x_2 + 4x_2^2 \tag{12}$$

is plotted in figure 1. It can be easily seen that the sensitivity function is independent of $\mathbf{\Sigma}$ and satisfies the condition $\varphi(\mathbf{x}; \xi^*) \leq p = 4$ for all $\mathbf{x} \in \mathcal{X}$.

An obvious alternative would be a multivariate linear regression design

$$\xi_0 = \begin{pmatrix} (1,1) & (0,0) \\ 1/2 & 1/2 \end{pmatrix},$$

where $x_1 = x_2$ is required and the corresponding marginals of ξ_0 are optimal in the marginal models. While the statistical analysis would simplify for such a design, as the Gauss-Markov estimator reduces to ordinary least squares for any $\mathbf{\Sigma}$, the D-efficiency

$$\operatorname{eff}_D(\xi) = (1 - \varrho^2)^{1/4}$$

compared to the D-optimal design ξ^* depends heavily on the correlation $\varrho = \sigma_{12}/(\sigma_1\sigma_2)$ and tends to zero as $|\varrho|$ tends to one. The corresponding behavior is depicted in figure 2.

5 Conclusions

While the data analysis is well developed for SUR models, there seemed to be no results available on design optimization in such models so far. To fill this gap we establish that under certain regularity conditions D-optimal designs for seemingly unrelated regression and related multivariate linear models can be generated as products of the D-optimal designs for the corresponding

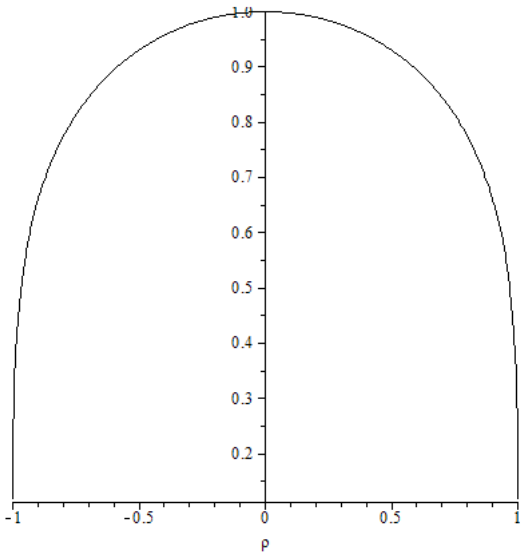

Figure 2: D-efficiency of the multivariate linear regression design ξ_0

univariate models of the single components. This construction turns out to yield optimal designs independent of the covariance structure of the components. Thus design optimization for SUR models can be reduced to univariate problems, for which the theory is well developed. In the special case that the components share the same model structure it might be tempting to simplify the design by letting the experimental settings equal across all components within each unit. Then the observations would result in a MANOVA or multivariate regression model and the analysis would be essentially facilitated. However, an example shows that the efficiency of such MANOVA designs may substantially decrease, if the correlation between the components increases.

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Integrated Design of Experiments and Analysis of Results with the offering of JMP® and SAS®

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Abstract: To reveal or model relationships between an input or factor and an output or response, the best approach is to deliberately change the first and see whether the second changes, too: Actively manipulating factors according to a pre-specified design is the best way to gain useful, new understanding. However, whenever there is more than one factor – that is, in almost all real-world situations – a design that changes just one factor at a time is essentially useless. To properly uncover how factors jointly affect the response, design of experiments (DOE) come into play, which is the focus of this conference.
JMP offers a complete library of tried and tested classical DOE designs, but also an innovative custom design capability that tailors your design to answer specific questions without wasting precious resources. Once the data has been collected, JMP and SAS streamline the analysis and model building so you can easily see the pattern of response, identify active factors and optimize responses.
This presentation shows the leading-edge JMP offering for Design of Experiments and data analysis and illustrates how SAS and JMP are integrated. See also http://www.jmp.com/applications/doe/index.shtml

Keywords: SAS, JMP, Design of Experiments, Usability, ODE, Integration

1 Introduction -- Integration of SAS and JMP

1.1 Historic Prejudices

Historically there are some prejudices about SAS, which include:

- SAS Analyses can only be executed via a complicated syntax
- SAS Graphs are hard to create, their appearance is very clumpy
- SAS Results can only be integrated into other applications with a lot of effort.

In 2011 these prejudices are wrong and outdated. SAS has fundamentally changed its appearance and its usability over time. The following subsections give a quick visual overview over the changes in the appearance of SAS.

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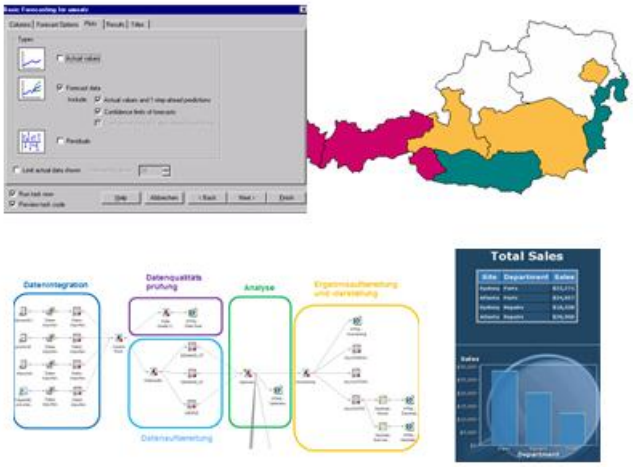

Figure 1: Year 1999 - SAS 8, Enterprise Guide, Output Delivery System, HTML, PDF, Java, Active X

Figure 2: Year 2004 – SAS 9.1 Java Front Ends, Interactive Graphs

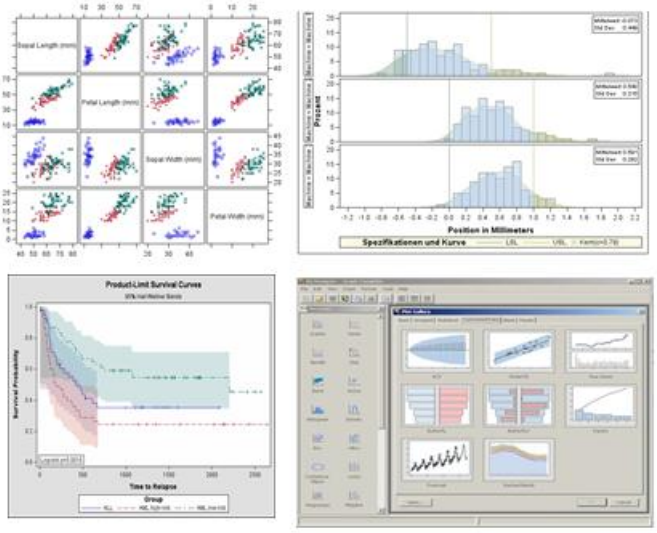

Figure 3: Year 2008 – SAS 9.2 Statistical Graphics

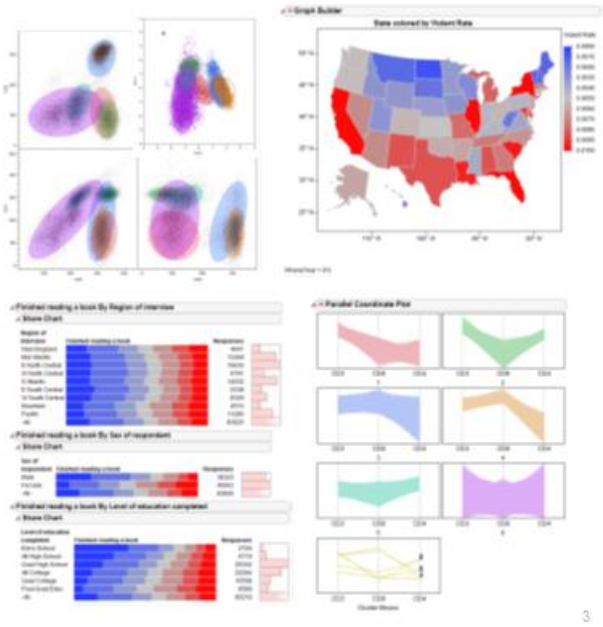

Figure 4: Year 2011 – SAS 9.3 and JMP-Integration

2 The Integration of SAS and JMP

The integration of SAS® and JMP® allows our users to benefit from the advantages of both areas:

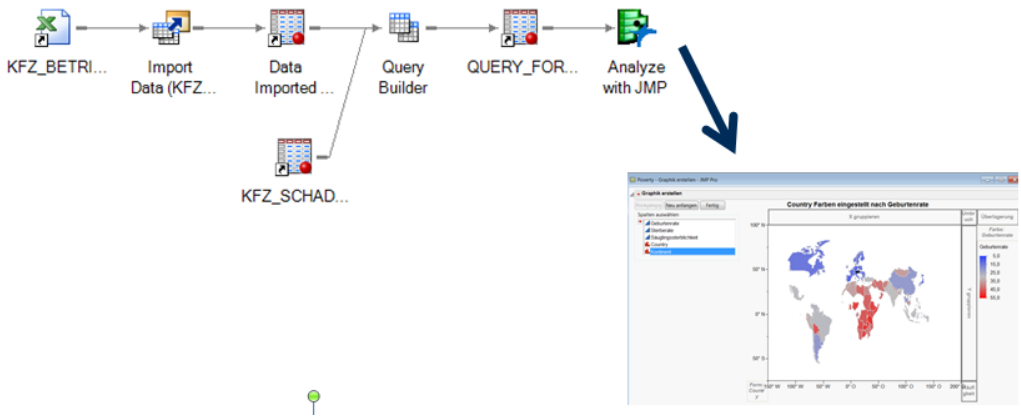

Figure 5: The integration of SAS and JMP

SAS

- Data Integration and Data Access
- Data Preparation and Data Transformations
- Data Quality Control
- Batch Processing

JMP

- Ad-hoc Analyses
- Interactive Point&Click Interfaces
- Visual representation of the results

3 Custom Designs

With two factors, a Full Factorial design explores your opportunity space by arranging points in a square. But you may already know that the area you want to explore is not square, in which case using a classical design forces you to compromise. The Custom Designer involves no compromise and always makes the best use of your experimental budget. Using its computer-generated designs allows you to tackle a much wider range of design challenges, but all within a unified framework. You can include process and mixture factors within the same design, use hard- and very hard-to-change factors for situations in which randomization is restricted, and define specific model terms to be estimable only “if possible,” building supersaturated designs that can screen for a larger number of factors than available runs. Finally, the Custom Designer allows you to perform sample size calculations to determine whether your experimental investment is likely to be worthwhile.

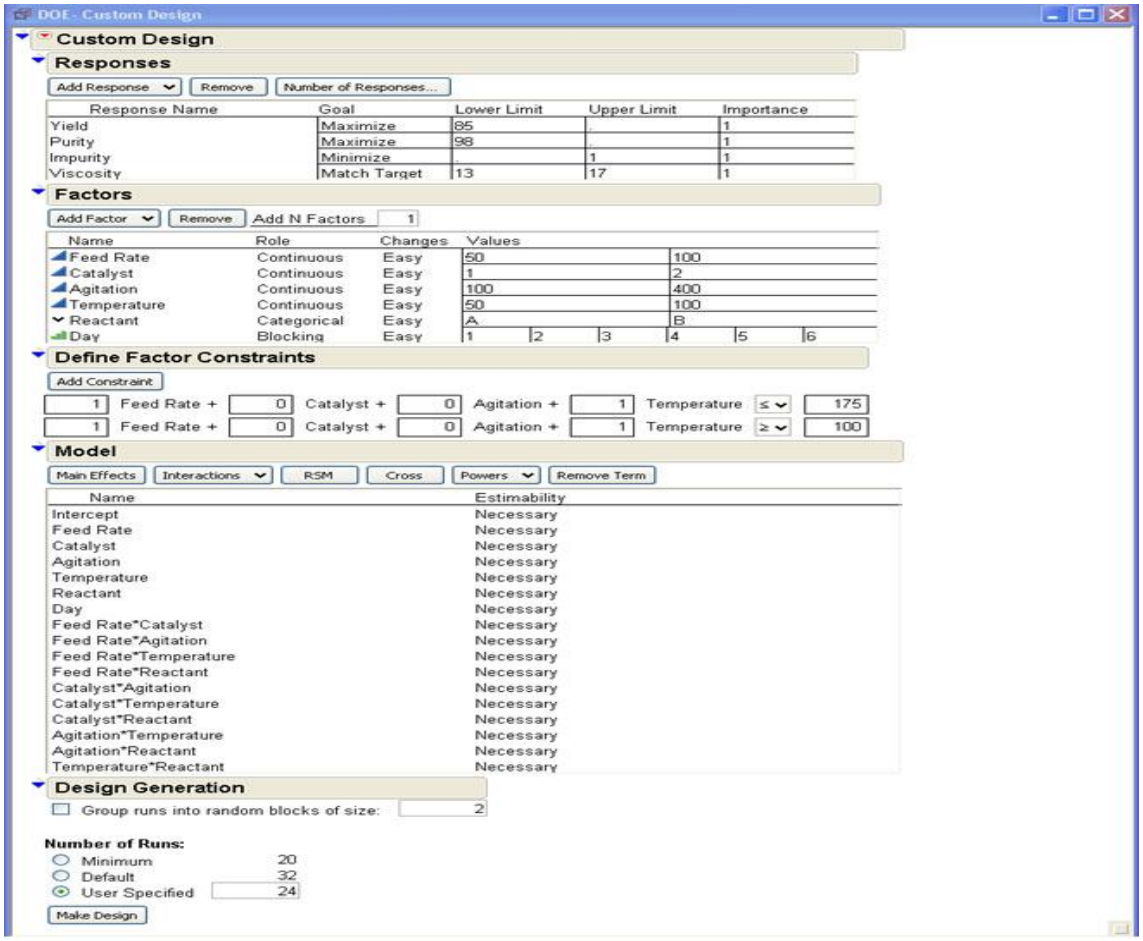

Figure 6: The power of Custom Designs is that they are model-based. So in addition to the usual specification of factors and responses, you need to input the terms that describe the expected behavior, the shape of the opportunity space you want to explore and your budget

4 Classical Designs

Ronald Fisher first introduced four enduring principles of DOE: The factorial principle, randomization, replication and blocking. But until relatively recently, generating (and then analyzing) a design to exploit these principles relied primarily on hand calculation. Despite this burden, the ingenuity of practitioners over more than 80 years has led to a series of widely applied design families adapted to meet specific situations and experimental objectives. JMP offers all of the classical design types you would expect, including Full Factorial, Screening, Response Surface, Mixture and Taguchi Array. After defining factors and responses, JMP lets you pick an appropriate design from those listed and provides various design evaluation tools, such as prediction variance profiles and FDS plots, to assess your selection before committing any resources. Once the runs have been conducted, analysis is straightforward thanks to the pre-built JMP scripts that are stored in your data table during the design process.

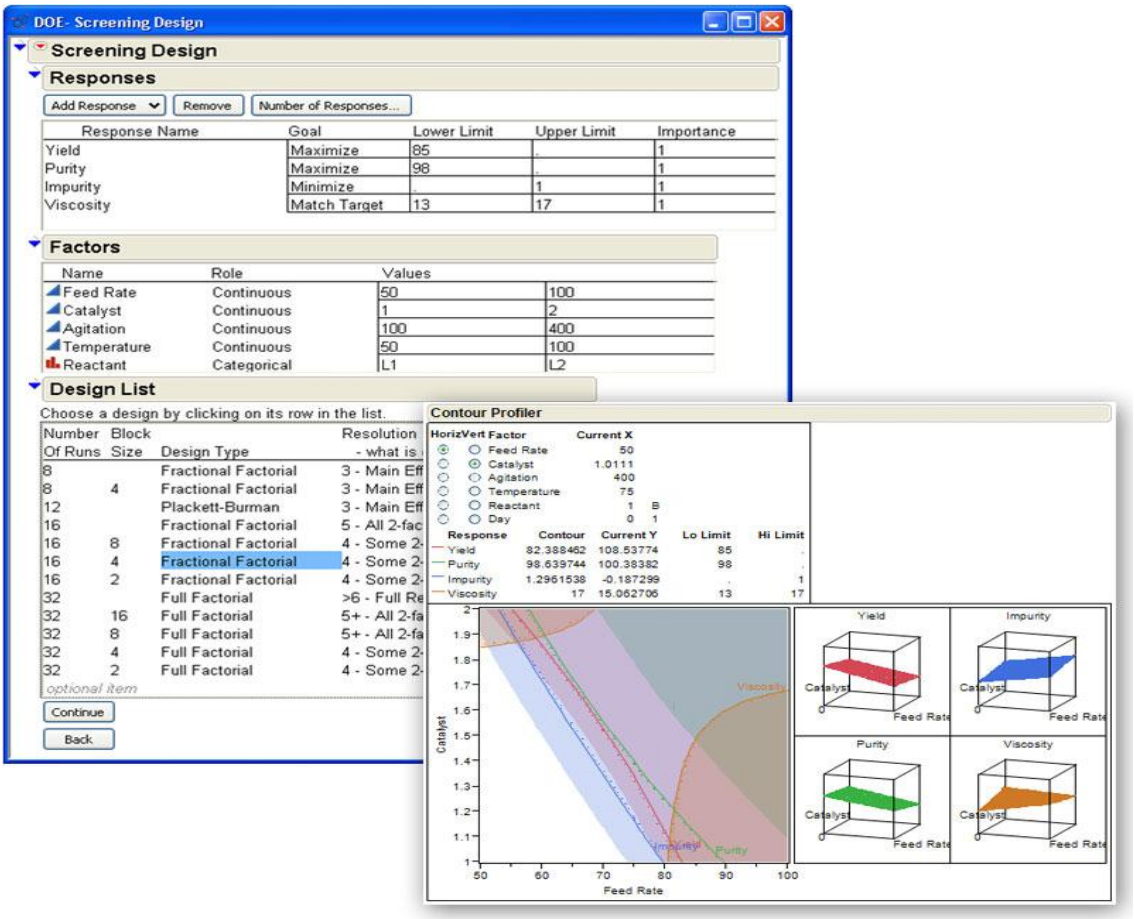

Figure 7: JMP offers all of the classical design types you would expect, including Full Factorial, Screening, Response Surface, Mixture and Taguchi Array. Whether you use a Classical, Custom or other design, you can use the Contour Profiler to interactively probe your fitted model to see patterns of variation, visually assess how factors affect your responses and find viable operating regions.

5 Other Designs

Even when there is no intrinsic variability in the response, DOE still finds application in exploring highly dimensional factor spaces efficiently. To meet this situation, JMP provides Space-Filling designs, which are typically analyzed with the Gaussian Process smoother to make a surrogate model with low prediction bias and variance. JMP can also generate and analyze Choice Designs in which consumers or users are asked to state their preferences between alternatives, including price as a factor if desired. Finally, JMP provides designs for Accelerated Life Tests and Nonlinear models. And if needed, you can add more design families to JMP through its scripting language, JSL.

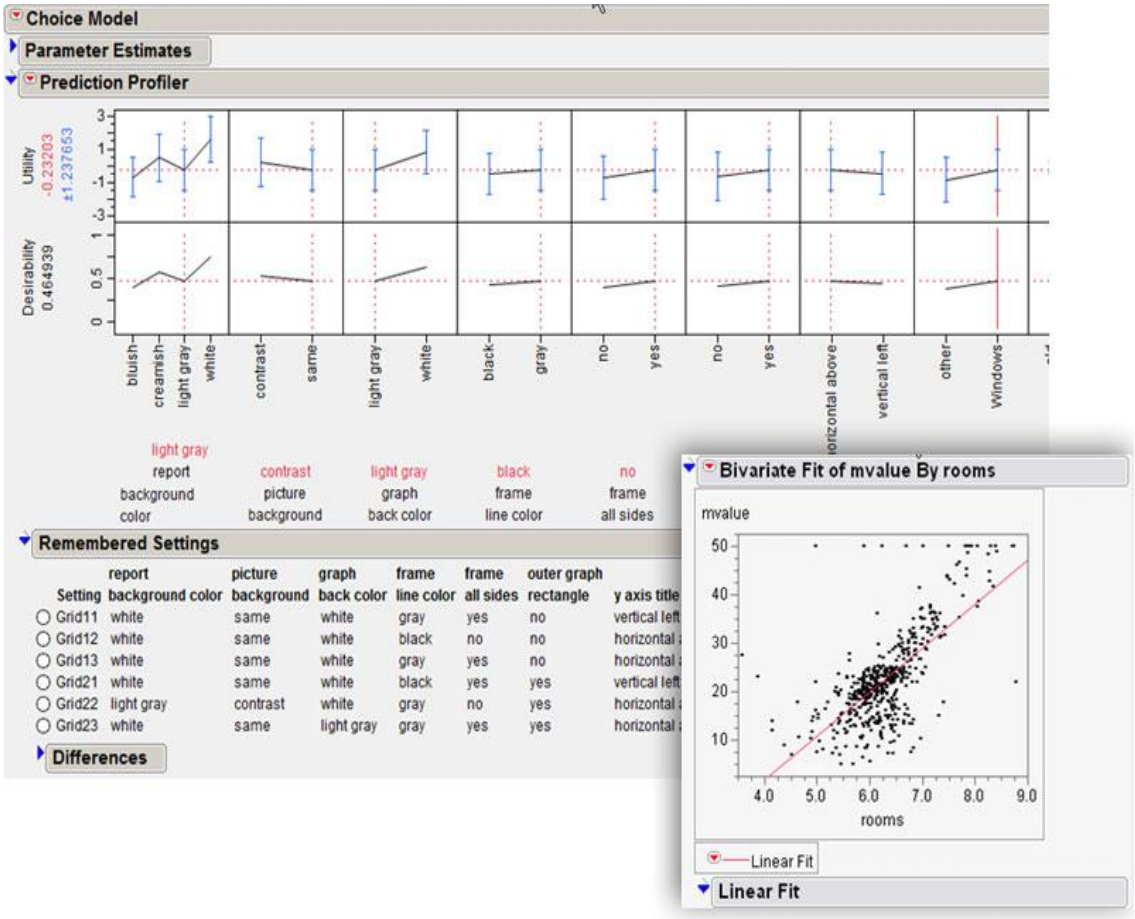

Figure 8: You can conduct visual analysis and optimization of a Choice Design using the interactive JMP Profiler

6 Optimize and Simulate

Although vital, design is only half of DOE. No matter which design you decide to use, JMP makes the subsequent analysis as easy as possible. Depending on the situation, the table containing your design will automatically contain the right script to analyze your results, usually via the Screening or Fit Model Platform. With multiple responses, you can simultaneously fit different models with Stepwise refinement using a chosen stopping rule. When you have built models you think are useful, The various Profilers in JMP allow you to interactively work with them and visually identify viable operating regimes and factor set points. No matter how complex your problem, The built-in Optimizer in JMP can perform the inevitable trade-off between responses with a single click. Once you have the sweet spot, you can then use the integrated Simulator to see how robust this is likely to be in practice.

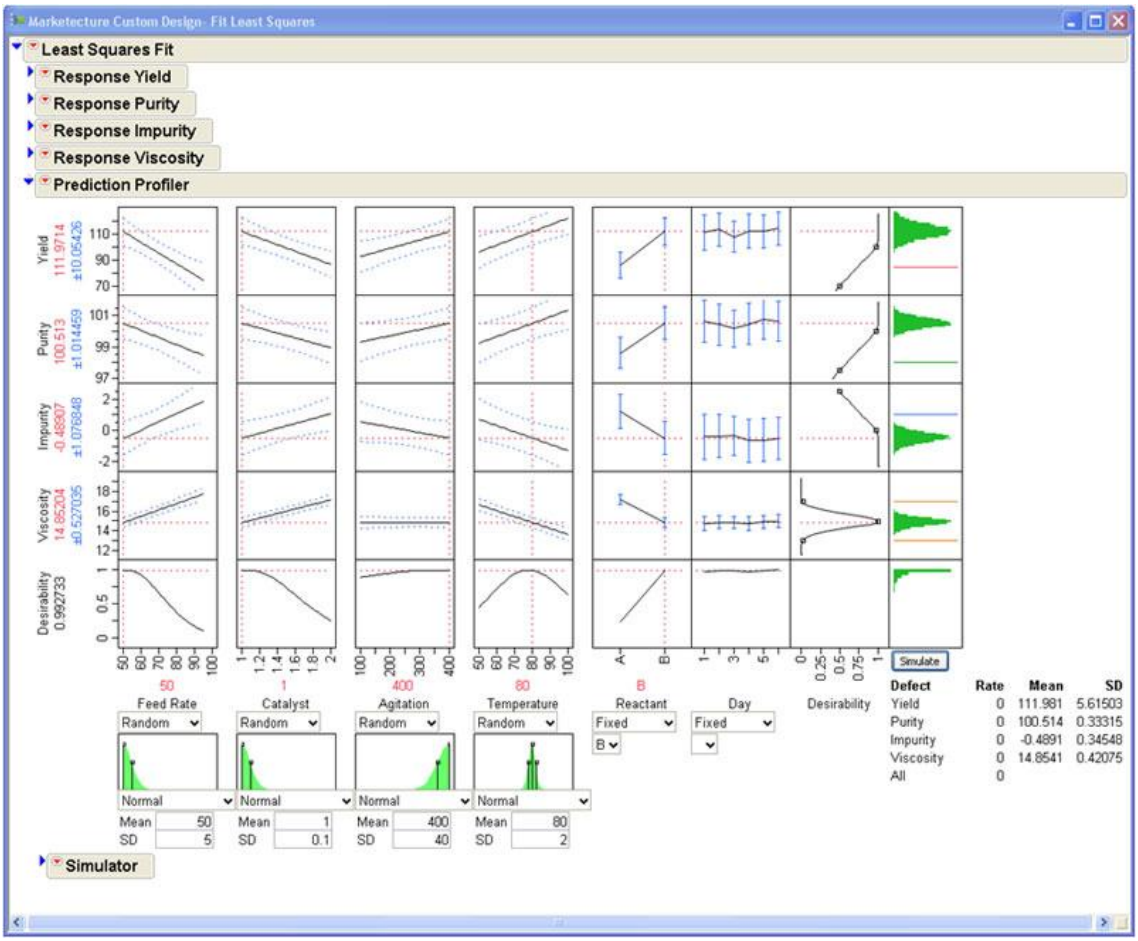

Figure 9: The Profiler allows you to interactively probe factor space, see which factors affect the responses and how, and find optimum settings for one or more responses using desirability functions. You can also use the Simulator to assess how real-world variation will be transmitted from factors into responses

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http://www.jmp.com/software/

http://www.jmp.com/applications/doe/index.shtml

A Dynamic Programming Approach to Sensor Trajectory Design for Parameter Estimation of Spatiotemporal Systems

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Abstract: A systematic procedure for planning sensor movements in a specified spatial domain in such a way as to maximize the accuracy of parameter estimation of a given spatiotemporal system is proposed. The global design criterion is a general local design criterion defined on the Fisher information matrix associated with the parameters to be identified. The approach converts the problem to an optimal control one in which the control forces of the sensors are optimized. Its solution is obtained with the use of an iterative dynamic programming algorithm capable of handling various constraints imposed on sensor motions. Some refinements to make the computational procedure more efficient are discussed. A summary of numerical performance of the resulting algorithms is given in the final part of the paper.

Keywords: D-optimum design, Moving sensors, Optimal trajectory, Dynamic programming.

1 Introduction

The importance of measurement system design for estimation of unknown coefficients in distributed parameter systems, i.e., systems modelled by partial differential equations, has been recognized for a long time, but relatively few attempts have been made at solving this problem. Moreover, most of the contributions in this area deal with the choice of stationary sensors positions (for comprehensive surveys, see (Kubrusly and Malebranche, 1985; Uciński, 2005, 1999; van de Wal and de Jager, 2001; Song *et al.*, 2009)). On the other hand, the optimal measurement problem for spatially movable sensors seems to be very attractive from the viewpoint of the degree of optimality. This is somewhat intimidating because of the complexity of the resulting optimization problem, but in recompense for such efforts a number of benefits are derived. This is due to the fact that sensors are not assigned to fixed positions which are optimal only on the average, but are capable of tracking points which provide at a given time moment best information about the parameters to be identified. Consequently, by actively reconfiguring a sensor system we can expect the minimal value of an adopted design criterion to be lower than the one for the stationary case.

It is important to note that planning techniques developed for moving sensors can prove useful in many areas of automation. A possibility of using moving observations does arise in a variety of applications, e.g., air pollutants in the environment are often measured using data gathered by monitoring cars moving in an urban area and atmospheric variables are measured using instruments carried in an aircraft. What is more, technological advances in communication systems and the growing ease in making small, low power and inexpensive mobile systems now make it feasible to deploy a group of networked vehicles in a number of environments (Zhao and Guibas, 2004; Chong and Kumar, 2003; Sinopoli *et al.*, 2003; Cassandras and Li, 2005; Bullo *et al.*, 2009). A cooperated and scalable network of vehicles, each of them equipped with a single sensor, has the potential to substantially improve the performance of the observation systems. Applications in various fields of research are being developed and interesting ongoing projects

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include extensive experimentation based on testbeds. The problem to be discussed in this paper cought our attention while working on one of such experimental platforms, namely the MAS-net lab testbed being a distributed system equipped with two-wheeled differentially driven mobile robots capable of sensing the states of DPSs described by diffusion and wave equations (Tricaud *et al.*, 2008; Uciński and Chen, 2005).

Surprisingly, few works have been reported regarding a systematic approach to mobile observer planning and the problem still waits for satisfactory solutions. Rafajłowicz (1986) considers the determinant of the Fisher Information Matrix (FIM) associated with the parameters to be estimated as a measure of the identification accuracy and looks for an optimal time-dependent measure, rather than for the trajectories themselves. On the other hand, in (Uciński, 2005, 1999, 2000; Uciński and Korbicz, 2001), apart from generalizations of Rafajłowicz's results, some computational algorithms based on the FIM were developed. The problem is reduced to a state-constrained optimal-control one for which solutions are obtained via the method of successive linearizations which is capable of handling various constraints imposed on sensor motions. In turn, the work (Uciński and Chen, 2005) was intended as an attempt to properly formulate and solve the time-optimal problem for moving sensors which observe the state of a DPS so as to estimate some of its parameters. Finally, in (Uciński and Patan, 2010) computationally efficient methods and algorithms to determine optimal trajectories of mobile sensor nodes for source identification in distributed parameter systems we developed.

One of the most difficult problems in the sensor location problem is establishing with some element of certainty that a global optimum has been obtained. The difficulty arises when the equations describing the system are highly nonlinear and a large number of local optima are present. Therefore, it is necessary to crosscheck the results, even when one is quite certain that the global optimum has been obtained. If such cross-checking is done by a totally different optimization procedure, then the confidence in accepting the result is increased. The main goal of this contribution is to show how iterative dynamic programming (Luus, 2000), which constitutes one of prospective research directions within the field of approximate dynamic programming, may be used to solve this problem encountered while configuring mobile sensor networks.

2 Sensor location problem

Consider a DPS described by the partial differential equation

$$\frac{\partial y}{\partial t} = \mathcal{L}(y,\theta) \quad \text{in } \Omega\times]0,t_f[\tag{1}$$

subject to given boundary and initial conditions, where $\Omega \subset \mathbb{R}^2$ is a fixed, bounded, open set with sufficiently smooth boundary $\partial\Omega$, $y = y(x,t;\theta)$ denotes the scalar state at a spatial point $x \in \bar{\Omega} = \Omega \cup \partial\Omega$ and time instant $t \in T = [0,t_f]$, $t_f < \infty$, and $\mathcal{L}$ signifies a (possibly nonlinear) differential operator which involves first- and second-order spatial derivatives and may include terms accounting for forcing inputs which are given *a priori*. In this description, $\theta \in \mathbb{R}^m$ represents an unknown constant parameter vector which must be estimated using observations of the system.

In what follows, we consider the observations provided by N moving pointwise sensors. Let $x^j : T \longrightarrow \Omega_{\mathrm{ad}}$ be the trajectory of the j-th sensor, where $\Omega_{\mathrm{ad}} \subset \Omega$ stands for the region where measurements can be made. The observations are assumed to be of the form

$$z(t) = y_{\mathrm{m}}(t) + \varepsilon_{\mathrm{m}}(t), \quad t \in T, \tag{2}$$

where

$$y_{\mathrm{m}}(t) = \mathrm{col}[y(x^1(t),t),\ldots,y(x^N(t),t)], \tag{3}$$

$$\varepsilon_{\mathrm{m}}(t) = \mathrm{col}[\varepsilon(x^1(t),t),\ldots,\varepsilon(x^N(t),t)], \tag{4}$$

$z(t)$ is the N-dimensional observation vector and $\varepsilon = \varepsilon(x,t)$ is a white Gaussian noise process (a formal time derivative of a Wiener process) whose statistics are

$$\begin{cases} \mathrm{E}\{\varepsilon(x,t)\} = 0, \\ \mathrm{E}\{\varepsilon(x,t)\varepsilon(x',t')\} = \sigma^2\delta(x-x')\delta(t-t'), \end{cases} \tag{5}$$

$\sigma > 0$ being the standard deviation of the measurement noise and δ the Dirac delta function concentrated at the origin. The assumption that we are in a position to observe directly the system state is made only for simplicity of presentation. The approach outlined in what follows can easily be generalized to indirect observation of state variables.

In the presented framework, the parameter identification problem is usually formulated as follows: Given the model (1) and the outcomes of the measurements z along the trajectories x^j, $j = 1,\ldots,N$, determine an estimate $\widehat{\theta} \in \Theta_{\mathrm{ad}}$ (Θ_{ad} being the set of admissible parameters) which minimizes the output least-squares fit-to-data functional given by (Banks and Kunisch, 1989; Omatu and Seinfeld, 1989)

$$\mathcal{J}(\theta) = \frac{1}{2}\int_0^{t_f} \|z(t) - \widehat{y}_{\mathrm{m}}(t;\theta)\|^2 \,\mathrm{d}t \tag{6}$$

where $\widehat{y}_{\mathrm{m}}$ is defined just as y_{m} in (3), but for y replaced by $\widehat{y} = \widehat{y}(x,t;\theta)$, the solution to (1) which corresponds to a given parameter θ ($\|\cdot\|$ stands for the Euclidean norm).

We feel, intuitively, that the parameter estimate $\widehat{\theta}$ depends on the trajectories x^j since the integrand on the right-hand side of eqn. (6) does it. This fact suggests that we may attempt to select the sensors' trajectories which lead to best estimates of the system parameters. To form a basis for the comparison of different trajectories, a quantitative measure of the 'goodness' of particular trajectories is required. A logical approach is to choose a measure related to the expected accuracy of the parameter estimates to be obtained from the data collected (note that the design is to be performed off-line, before taking any measurements). Such a measure is usually based on the concept of the *Fisher Information Matrix* (FIM) (Sun, 1994; Rafajłowicz, 1986) which is widely used in optimum experimental design theory for lumped systems (Walter and Pronzato, 1997; Fedorov and Hackl, 1997; Atkinson *et al.*, 2007). When the time horizon is large, the nonlinearity of the model with respect to its parameters is mild and the measurement errors are independently distributed and have small magnitudes, the inverse of the FIM constitutes a good approximation of the covariance matrix for the estimate of θ (Walter and Pronzato, 1997; Fedorov and Hackl, 1997; Atkinson *et al.*, 2007).

For notational convenience, introduce

$$s(t) = (x^1(t), x^2(t), \ldots, x^N(t)), \quad \forall\, t \in T \tag{7}$$

and set $n = \dim(s(t))$. The FIM has the following representation (Uciński, 2005; Quereshi *et al.*, 1980):

$$M(s) = \sum_{j=1}^{N} \int_0^{t_f} g(x^j(t),t) g^{\mathsf{T}}(x^j(t),t)\,\mathrm{d}t, \tag{8}$$

where $g(x,t) = \nabla_\theta y(x,t;\theta)\big|_{\theta=\theta^0}$ denotes the vector of the so-called *sensitivity coefficients*, θ^0 being a prior estimate to the unknown parameter vector θ (Uciński, 2000, 2005).

Optimal sensor trajectories can be found by choosing s so as to maximize some scalar function Ψ of the information matrix. The introduction of the design criterion permits to cast the sensor location problem as an optimization problem, and the criterion itself can be treated as a measure of the information content of the observations. Several choices exist for such a function (Walter and Pronzato, 1997; Fedorov and Hackl, 1997; Atkinson and Donev, 1992) and the most popular are

- The D-optimality (determinant) criterion

$$\Psi(M) = -\ln\det(M). \tag{9}$$

- The E-optimality criterion (smallest eigenvalue; $\lambda_{\max}(\,\cdot\,)$ denotes the maximum eigenvalue of its argument)

$$\Psi(M) = \lambda_{\max}(M^{-1}). \tag{10}$$

- The A-optimality (trace) criterion

$$\Psi(M) = \mathrm{tr}(M^{-1}). \tag{11}$$

3 Dynamics of sensor movments

We assume that the sensors are conveyed by vehicles whose motions are described by

$$\dot{s}(t) = f(s(t), u(t)) \quad \text{a.e. on } T, \quad s(0) = s_0 \tag{12}$$

where a given function $f : \mathbb{R}^n \times \mathbb{R}^r \to \mathbb{R}^n$ is required to be continuously differentiable, $s_0 \in \mathbb{R}^n$ defines an initial sensor configuration, and $u : T \to \mathbb{R}^r$ is a measurable control function which satisfies

$$u_l \le u(t) \le u_u \quad \text{a.e. on } T \tag{13}$$

for some constant vectors u_l and u_u.

Given any initial sensor configuration s_0 and any control function, there is a unique absolutely continuous function $s : T \to \mathbb{R}^n$ which satisfies (12) a.e. on T. In what follows, we will call it the state trajectory corresponding to s_0 and u, and make the following notational convention: if s appears without mention in a formula, it is always understood that a control u and initial condition s_0 have been specified and s is the trajectory corresponding to u and s_0 through (12).

4 Optimal control formulation

The goal in the optimal measurement problem is to determine the forces (controls) applied to each vehicle conveying a sensor, which minimize the design criterion $\Phi[\,\cdot\,]$ defined on the FIMs of the form (8), which are determined unequivocally by the corresponding trajectories, subject to the constraints (13) on the magnitude of the controls. In order to increase the degree of optimality, in our approach we will regard s_0 as a control parameter vector to be chosen in addition to the control function u. Clearly, the correctness of such a formulation necessitates some additional restrictions on the smoothness of sensitivity coefficients g. In what follows, we thus assume the continuity of g and $\partial g/\partial x$.

The above formulation can be interpreted as the following optimization problem: Find the pair (s_0, u) which minimizes

$$J(s_0, u) = \Phi[M(s)] \tag{14}$$

over the set of feasible pairs

$$\mathcal{P} = \big\{(s_0, u) \mid u : T \to \mathbb{R}^r \text{ is measurable, } u_l \le u(t) \le u_u \text{ a.e. on } T,\ s_0 \in \Omega_{\text{ad}}^N\big\}. \tag{15}$$

Evidently, its high non-linearity excludes any possibility of finding closed-form formulae for its solution. Accordingly, we must resort to numerical techniques. A number of possibilities exist in this respect (Polak, 1997; Gruver and Sachs, 1980), but before exploiting them, observe that in spite of its apparently non-classical form, the resulting optimal-control problem can be easily cast as a classical Mayer problem where the performance index is defined only via terminal values of state variables.

5 Reduction to canonical form

The aim of this section is to convert our problem into a canonical optimal control one with an endpoint cost (Polak, 1997). For notational convenience, define the function svec : $\mathbb{S}^m \to \mathbb{R}^{m(m+1)/2}$, where $\mathbb{S}^m$ denotes the subspace of all symmetric matrices in $\mathbb{R}^{m\times m}$, that takes the lower triangular part (the elements only on the main diagonal and below) of a symmetric matrix A and stacks them into a vector a:

$$a = \text{svec}(A) = \text{col}[A_{11}, A_{21}, \ldots, A_{m1}, A_{22}, A_{32}, \ldots, A_{m2}, \ldots, A_{mm}]. \tag{16}$$

Similarly, let $A = \text{Smat}(a)$ be the symmetric matrix such that $\text{svec}(\text{Smat}(a)) = a$ for any $a \in \mathbb{R}^{m(m+1)/2}$.

Consider the matrix-valued function

$$\Pi(s(t), t) = \sum_{j=1}^{N} g(x^j(t), t) g^{\mathsf{T}}(x^j(t), t). \tag{17}$$

Setting $r : T \to \mathbb{R}^{m(m+1)/2}$ as the solution of the differential equations

$$\dot{r}(t) = \text{svec}(\Pi(s(t), t)), \quad r(0) = 0, \tag{18}$$

we have

$$M(s) = \text{Smat}(r(t_f)), \tag{19}$$

i.e., minimization of $\Phi[M(s)]$ thus reduces to minimization of a function of the terminal value of the solution to (18).

Introducing the augmented state vector

$$q(t) = \begin{bmatrix} s(t) \\ r(t) \end{bmatrix}, \tag{20}$$

we obtain

$$q_0 = q(0) = \begin{bmatrix} s_0 \\ 0 \end{bmatrix}. \tag{21}$$

Then the equivalent canonical optimal control problem consists in finding a pair $(q_0, u) \in \bar{\mathcal{P}}$ which minimizes the performance index

$$\bar{J}(q_0, u) = \phi(q(t_f)) \tag{22}$$

subject to

$$\begin{cases} \dot{q}(t) = \varphi(q(t), u(t), t), \\ q(0) = q_0, \end{cases} \tag{23}$$

where

$$\bar{\mathcal{P}} = \left\{(q_0, u) \mid u : T \to \mathbb{R}^r \text{ is measurable, } u_l \le u(t) \le u_u \text{ a.e. on } T,\ s_0 \in \Omega_{\text{ad}}^N\right\}, \tag{24}$$

and

$$\varphi(q, u, t) = \begin{bmatrix} f(s(t), u(t)) \\ \text{svec}(\Pi(s(t), t)) \end{bmatrix}, \quad \phi(q(t)) = \Phi[\text{Smat}(r(t))]. \tag{25}$$

The above problem in canonical form can be solved using one of the existing packages for numerically solving dynamic optimization problems, such as **RIOTS_95** (Schwartz *et al.*, 1997), **DIRCOL** (von Stryk, 1999) or **MISER** (Jennings *et al.*, 2002). The aim of the research reported in what follows was to compare this approach with the solution based on iterative dynamic programming which offers numerous advantages regarding flexibility and prospective extensions towards parallel implementations.

6 Solution via iterative dynamic programming

Dynamic programming (DP) is an extremely powerful method for solving optimization problems (Bertsekas, 2000). It has the attractive feature of breaking up a complex optimization problem into a number of simpler problems. The solution of the simpler problems then leads to the solution of the original problem. Such stage-by-stage calculations are ideally suited for computers, and the global optimum is always obtained. However, for high-dimensional nonlinear optimal control problems with continuous state and control vectors, application of DP creates the following problems:

1. Rather fine grids for q and u are inevitable for an accurate solution.
2. When minimizing the cost-to-go function at consecutive stages, its values are needed for state vectors which are between the state grid points. They can be computed using an interpolation method which must be very accurate so as not to miss the global optimum.
3. Dense grids for state and control vectors entail unacceptable times of computations and memory requirements (the 'curse of dimensionality').

To overcome these limitations, Luus Luus (2000) developed an algorithm termed *iterative dynamic programming* (IDP). To alleviate problems with fine grids, computations are repeated for successively reduced grid sized. At first, the problem is solved by using a coarse grid. Then the midpoints of the state and control grids are set equal to the preliminary optimal state and control vectors, and the ranges of the grids are reduced. The second problem can be solved by approximating each contribution to the cost-to-go produced at a given stage by its counterpart obtained for an element of the state grid which is closest to the current state. The latter values are precomputed for the current grid and stored in computer memory. Finally, the third impediment can be surmounted by using several randomly distributed grid points.

A full description of the IDP algorithm can be found in (Luus, 2000). Since it contains quite a large number of details and heuristic improvements aimed at accelerating computations, it is omitted here.

7 Numerical example

7.1 Sensor location problem

Consider the two-dimensional diffusion equation

$$\frac{\partial y}{\partial t} = \nabla \cdot (\mu \nabla y) + F \tag{26}$$

for $x \in \Omega = (0,1)^2$ and $t \in [0,1]$, subject to homogeneous initial and Dirichlet boundary conditions, where $F(x,t) = 20\exp(-50(x_1 - t)^2)$. The assumed form of the diffusion coefficient is

$$\mu(x) = \theta_1 + \theta_2 x_1 + \theta_3 x_2. \tag{27}$$

We note that the forcing term in (26) imitates the action of a line source whose support is constantly oriented along the x_2-axis and moves with constant speed from the left to the right boundary of Ω. Given three moving sensors whose dynamics is defined by the simple model

$$\dot{s}(t) = u(t), \quad s(t_0) = s_0,$$

along with the constraints

$$|u_i(t)| \leq 0.7, \quad \forall\, t \in T, \quad i = 1, \ldots, 6$$

imposed on the controls, we are interested in designing their trajectories so as to obtain estimates of θ_1, θ_2 and θ_3 for which the confidence ellipsoid would have the smallest volume, which boils down to minimization of the D-optimality criterion. For simplicity, we assume that the initial sensor positions are fixed at

$$s_0 = (0.2, 0.1, 0.2, 0.5, 0.2, 0.8).$$

While numerically integrating the system of ODEs (18), the values of the vector of the sensitivities $g = \mathrm{col}[g_1, g_2, g_3]$ along sensor trajectories are indispensable. Assuming the nominal values $\theta_1^0 = 0.1$, $\theta_2^0 = -0.05$ and $\theta_3^0 = 0.2$, they are defined as solutions to the following system of PDEs (Uciński, 2005, 1999):

$$\begin{cases} \dfrac{\partial y}{\partial t} = \nabla \cdot (\mu \nabla y) \ + F, \\ \dfrac{\partial g_1}{\partial t} = \nabla \cdot \nabla y \quad + \nabla \cdot (\mu \nabla g_1), \\ \dfrac{\partial g_2}{\partial t} = \nabla \cdot (x_1 \nabla y) + \nabla \cdot (\mu \nabla g_2), \\ \dfrac{\partial g_3}{\partial t} = \nabla \cdot (x_2 \nabla y) + \nabla \cdot (\mu \nabla g_3), \end{cases} \tag{28}$$

in which the first equation constitutes the original state equation and the second, third and fourth equations result from its differentiation with respect to θ_1, θ_2 and θ_3, respectively. The initial and Dirichlet boundary conditions for all the four equations are homogeneous.

We numerically solved (28) using some routines of the MATLAB PDE toolbox (COMSOL AB, 1995) and stored g_1, g_2 and g_3 interpolated at the nodes of a rectangular grid in a four-dimensional array (we applied uniform partitions using 21 grid points per each spatial dimension and 31 points in time), cf. Appendix I in (Uciński, 2005) for details. Despite the impossibility of employing the graphical user interface of the toolbox (it is tailored to single PDEs, and not to systems of PDEs), we could still solve (28) using command-line functions. The GUI was applied here only to conveniently define the spatial domain Ω (which is a unit square) and then to export the resulting decomposed geometry matrix to MATLAB's workspace. Since values of g may have been required at points which were not necessarily nodes of that grid, the relevant interpolation was thus performed using cubic splines in space (to this end, MATLAB's procedure `interp2` was used) and linear splines in time. Since, additionally, the derivatives of g with respect to spatial variables and time were going to be required, these derivatives were approximated numerically using the central-difference formula.

Our program implementing IDP was written using Matlab 7.6. All computations were performed using a PC equipped with an Intel Core 2 Duo 2.50 GHz processor, 4 GB RAM, running

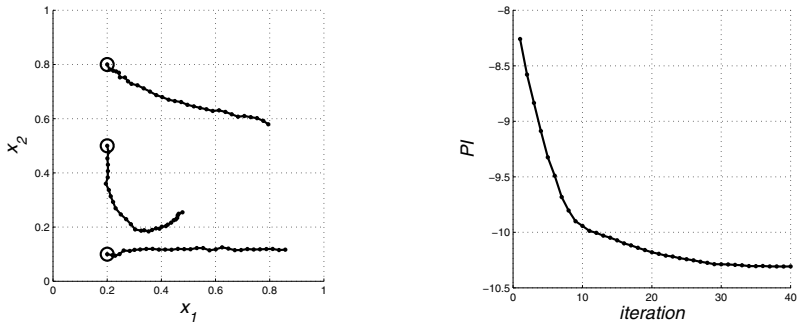


Figure 1: Results of single pass IDP computations

Table 1: Single pass IDP performance

	CPU time [h : min : s]
iteration time	15.8906
total time	636.4844

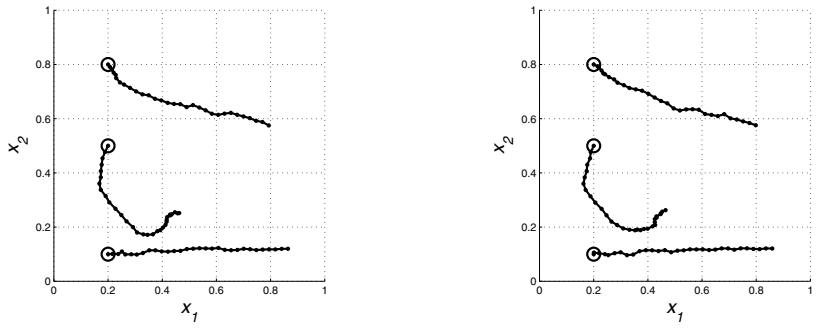
Windows Vista with SP2. The obtained results were compared with those produced by **RIOTS_95**, a high-performance **MATLAB** toolbox for solving optimal control problems (Schwartz *et al.*, 1997).

7.2 Single-Pass IDP

Figure 1 displays optimal sensor trajectories and the values of the performance index obtained by applying a single-pass IDP algorithm. Convergence to $\bar{J} = -10.3075$ was observed in 40 iterations (approximately 10 minutes of CPU time, cf. Tab. 1) using the following parameters, see (Luus, 2000) for their detailed description:

- Number of time stages: 20,
- Number of test values for the control vector: 10,
- Initial region size initial region size: 0.6,
- Region contraction factor: 0.99,
- Total number of iterations per pass: 3,
- Number of q-trajectories: 1.

In the current iteration, the best results are obtained using a single q-trajectory that has been optimal one in the previous iteration (or the initial value in the first iteration). Randomly generated multiple q-trajectories yield only minor improvements at the cost of a substantial increase in the time of computations (each additional q-trajectory approximately doubles the time spent on one iteration). A similar increase in the CPU time was observed after the number of test values for u had been increased. Moreover, even doubling this number did not significantly improve the results, since the ultimate value of $\bar{J}$ was -10.3198 (though the sensor trajectories became slightly smoother, cf. Fig. 2).



(a) (b)

Figure 2: Results of single pass IDP computations: (a) the doubled number of test values for the control vector, (b) the lack of the energy factor.

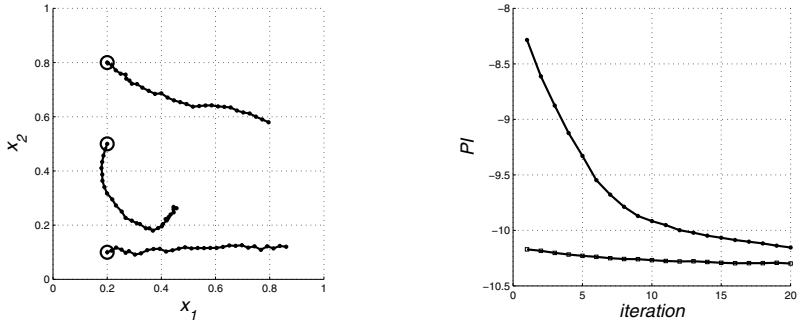


Figure 3: Results of multi-pass IDP.

For low dimensional problems it is possible to choose control candidates from an evenly spaced grid, e.g., by an exhaustive search. Systems that are much more complicated need a reduction in the number of analyzed candidates for the control profile. Consequently, the only possible way to complete calculations in a reasonable time is to use a number of control profiles that are randomly drawn from among all admissible ones. Interestingly, for high dimensional systems, the obtained results are as good (or even better) as those from evenly spaced grids.

The bottom panel of Fig. 1 presents the reduction of $\bar{J}(u)$ with successive iterations. Observe that values close to the value of the global minimum $\bar{J}$ are obtained quickly (after about 10 iterations). The rate of this convergence is strongly related to the initial region size and the contraction factor. It is clear that when the region size is big enough, satisfactory results are obtained faster. The energy saving factor is also included by adding to $\bar{J}$ a quadratic term penalizing excessive energy expense. As a result, the sensor trajectories become smoother.

7.3 Multi-Pass IDP

In our experiments, we also tested a multi-pass version of IDP, where, after a number of iterations, the region sizes were reset and the procedure was repeated. However, in our case, this alteration did not significantly improve the quality of the obtained solution. This strategy can be very useful anyway in the case of a multimodal problem for which local optima are likely to be obtained instead of the global one.

Table 2: Multi-pass IDP performance

	CPU time [h : min : s]
iteration time	15.9375
total time	639.4920

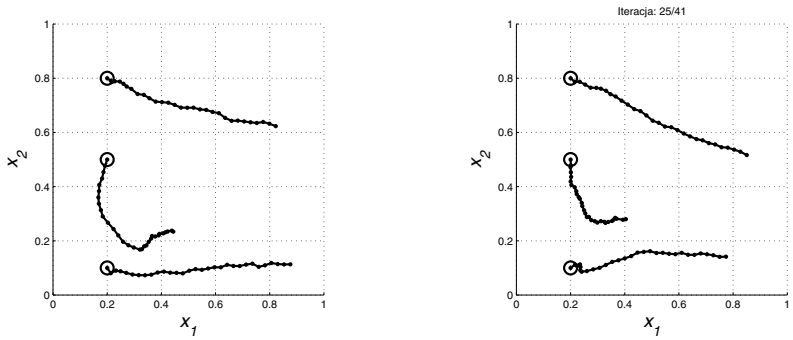


Figure 4: Results of computations for A- and E-optimality criteria (top and bottom panels, respectively).

7.4 Comparison of Optimality Criteria

Apart from the D-optimality criterion, A- and E-optimality ones were also tested. The plots of Fig. 4 reveal that the resulting trajectories are somewhat similar. More results are presented in Tab. 3. It can obe observed that D- and A-optimality criteria yield similar results, which is also noticeable in Fig. 4. The difference between the values of $\bar{J}$ obtained in both ways is less than 3%. The results for the E-optimality criterion are slightly different.

7.5 Comparison of IDP with RIOTS_95

The above results were verified using **RIOTS_95**. Figure 5 presents optimal sensors trajectories obtained using the IDP algorithm and **RIOTS_95**. The latter produced $\bar{J} = -10.3952$, which confirms that the results of IDP are close to the global optimum. The sensor trajectories

Table 3: Comparison of optimality criteria

Criterion	D	A	E
Optimal values of $\bar{J}$	−10.5350	0.2186	0.1300
Values computed using D-optimal trajectories	−10.5350	0.2251	0.1403
Loss inflicted by the use of D-optimal trajectories	0.00%	2.97%	7.92%
Values computed using A-optimal trajectories	−10.4697	0.2186	0.1341
Loss inflicted by the use of A-optimal trajectories	0.62%	0.00%	0.05%
Values computed using E-optimal trajectories	−9.9626	0.2794	0.1300
Loss inflicted by the use of E-optimal trajectories	5.43%	27.81%	0.00%

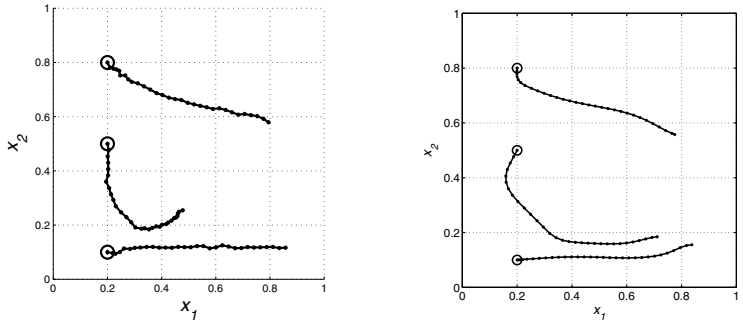


Figure 5: D-optimal trajectories produced by IDP (top) and **RIOTS_95** (bottom).

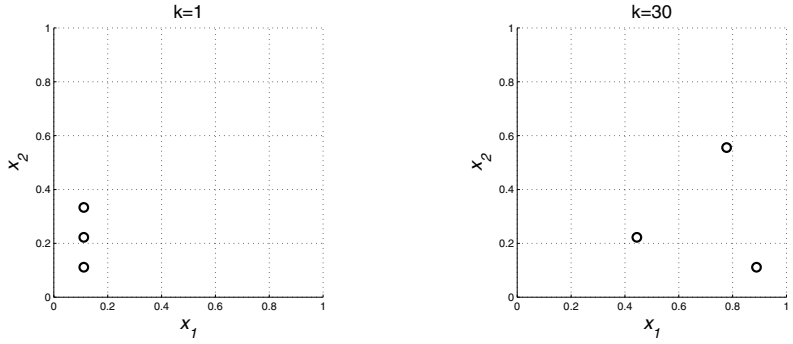


Figure 6: Results of solving the scanning sensor location problem.

are similar to each other. Decided advantages of IDP are the possibility of dealing with nondifferentiable criteria (e.g., the E-optimality one) and the flexibility regading further generalizations. In the case of high dimensional systems, finding a global optimum by **RIOTS_95** may be very time-consuming or even impossible. Moreover, **RIOTS_95** produces only local solutions.

7.6 Design for Scanning Sensors

Figure 6 presents the results produced by DP for the problem of finding optimal configurations for scanning sensors. An optimal solution was obtained after approximately 3 minutes of computations, cf. Tab. 4, using the following settings:

- a uniform 10×10 grid of allowable sensors positions,
- the time interval divided into 30 time stages.

Analyzing the obtained results, we may notice that sensor activation policies were chosen such that they follow the moving source. It could be also interpreted in terms of locating active sensors in places where the sensitivity coefficients have largest values. This numerical example can be also compared with the 'continuous scanning' discussed in previous sections. Summarizing, in the final stage the sensors were placed at positions that coincide with the corresponding ends of the trajectories produced by IDP. This constitutes another confirmation of the proposed IDP strategy.

Table 4: DP performance for scanning sensors

	CPU time [h : min : s]
time per iteration	5.8280
total time	176.0150

8 Concluding remarks

The problem of determining sensor trajectories for the purpose of more accurate parameter estimation for DPSs has been considered. Based on a local design criterion defined on the FIM, by taking the sensor velocities as the control variables, an iterative dynamic programming algorithm has been developed and applied to a simple two-dimensional diffusion equation. Extending the presented approach, some restrictions on the motions can be also considered. For example, we may impose the requirements that all sensors should stay within some admissible region Ω_{ad} or that the distances between the sensors are supposed to be less than some predefined threshold. What is more, since dynamic programming has an inherent parallel structure that makes it especially suited for parallelization, we also going to implement it on a cluster of PCs using MPI.

Further investigations in this direction also include robustification of the design. This is because the design of the sensor trajectories depends on the model parameters to be estimated, so logically the optimal design can never be found at the design stage unless prior estimate θ^0 is very close to the true paremeter vector. Generally, a sequential design procedure has to be used in which the estimated parameters are updated after some period of time and the next design is then chosen with the aid of the improved estimates. An alternative approach is the robust-design strategy which makes a design useful for all parameters in a given range, e.g. the design criterion

$$\max_{u} \min_{\theta \in \Theta_{\text{ad}}} \det(M)$$

requires to provide maximum information to a parameter vector Θ which is the most difficult to be identified in an admissible range Θ_{ad}. Here the ideas of approximated dynamic programming are going to be used (Powell, 2007).

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Planning of Equivalence and Noninferiority Trials to be Evaluated by Means of Optimal Testing Procedures

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Abstract: Optimal tests for equivalence hypotheses are comparatively complicated to carry out in practice, due to the fact that the critical constants for the test statistic must be determined from the noncentral versions of the corresponding sampling distributions (see Wellek, 2010). In this talk it is shown that as soon as efficient algorithms for computing the optimal critical constants have been made available, power and sample-size calculation is less demanding for equivalence tests than for tests of traditional one- or two-sided hypotheses, provided interest is in establishing the null alternative of no treatment effects. For a variety of practically important special cases, even explicit expressions for the required sample sizes can be given. Not surprisingly, this holds only true when the distribution of the optimal test statistic is of the continuous type. In the discrete case, testing procedures which satisfy the usual optimality criteria, involve randomized decisions between the hypotheses on the boundaries of the critical region which is rarely acceptable for real-world applications. In these settings which are also discussed in some detail powerful nonrandomized tests are required whose computation involves fairly heavy technical machinery. Exact sample-size calculation is still possible then, but no explicit formula are available.

Keywords: Chi-squared distribution, extended hypergeometric distribution, F-distribution, noncentrality parameter, sample-size formula, t-distribution.

1 Introduction

Experiments whose proper confirmatory analysis requires application of tests for equivalence or noninferiority, are conducted in an increasing number of areas, in particular in the medical sciences. Roughly speaking, experiments of the kind considered in this paper are characterized by the fact that they are run in order to establish the hypothesis that, except for practically irrelevant differences, the effects of two (or $k \geq 2$) treatments or experimental conditions are the same. Typically, the hypothesis formulation refers to some real-valued parameter θ which provides a sensible measure of the degree of dissimilarity of the probability distributions involved. For example, in the specific case of a standard parallel group design used for the purpose of testing for equivalence of two treatments A and B, an obvious choice is $\theta = \mu_1 - \mu_2$ with μ_1 and μ_2 denoting a measure of location for the distribution of the endpoint variable under A and B, respectively. The equivalence hypothesis whose compatibility with the data one wants to assess, specifies that θ is contained in a suitable neighborhood around some reference value θ_0 taken on by θ if the distributions under comparison are exactly equal.
It will be specified as an open interval throughout with endpoints denoted by $\theta_0 - \varepsilon_1$ and $\theta_0 + \varepsilon_2$, respectively, where ε_1 and ε_2 are positive constants whose numerical values must be assigned *a priori*. Specifically, in the case of the simple parallel group design with $\theta = \mu_1 - \mu_2$, the usual choice of θ_0 is $\theta_0 = 0$, and the equivalence interval is frequently chosen symmetrical about θ_0, i.e., in the form $(-\varepsilon, \varepsilon)$. Accordingly, the basis for planning a trial of this type is the power

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function of a valid statistical test at some prespecified level $\alpha \in (0,1)$ of the *null hypothesis*

$$H : \theta \leq \theta_0 - \varepsilon_1 \quad \text{or} \quad \theta \geq \theta_0 + \varepsilon_2 \tag{1.1a}$$

of nonequivalence, versus the *equivalence assumption*

$$K : \theta_0 - \varepsilon_1 < \theta < \theta_0 + \varepsilon_2 \tag{1.1b}$$

as the alternative hypothesis.

The inferential problems treated in the biostatistical literature under the heading of noninferiority assessment share with equivalence testing problems in the strict sense a basic property: The hypotheses formulation entails the introduction of a region in the space of the target distributional parameter θ within which the difference between the actual value of θ and its reference value θ_0 is considered practically irrelevant. The feature which distinguishes *noninferiority* (also called *one-sided equivalence*) from equivalence in the strict sense is that the region of tolerable discrepancies between θ and θ_0 is now bounded to below only whereas excesses in the value of θ over θ_0 of arbitrary magnitude are considered acceptable or even desirable. Formally speaking, the crucial difference between equivalence testing and testing for absence of substantial inferiority is that in the latter type of problem the right-hand boundary $\theta_0 + \varepsilon_2$ of the equivalence interval is replaced with $+\infty$ or, in cases where the parameter space Θ of θ is bounded to the right itself, by $\theta^* = \sup \Theta$. The corresponding hypothesis testing problem reads

$$H_1 : \theta \leq \theta_0 - \varepsilon \quad \text{versus} \quad K_1 : \theta > \theta_0 - \varepsilon \tag{1.2}$$

with sufficiently small $\varepsilon > 0$.

Both for equivalence and noninferiority problems, there is a fairly rich repertoire of testing procedures which satisfy rather strong optimality criteria. The construction of these tests is technically much more demanding than their counterparts being available for the traditional one- or two-sided hypotheses formulation. The reason is that in the equivalence case, the critical constants for the test statistic must generally be determined from the noncentral versions of the corresponding sampling distributions. The objective of this talk is to show that as soon as efficient algorithms for computing the optimal critical constants have been made available, power and sample-size calculation is less demanding for equivalence tests than for tests of traditional one- or two-sided hypotheses, provided interest is in establishing the *null alternative* of no treatment effects. It will turn out in the subsequent sections, that for a variety of practically important special cases, even explicit expressions for the required sample sizes can be given.

In Section 2, we start with discussing the one-sample problem with normally distributed data of known variance. Due to its simplicity, this setting is particularly well suited for describing the basic steps to be taken in planning an equivalence trial whose confirmatory analysis is to be carried out by means of an UMP testing procedure. Section 3 will be devoted to problems involving two samples from Gaussian distributions with both parameters being unknown. That part of the exposition will cover both the paired-sample case and the case of two unrelated samples. Section 4 extends the results of Section 3 to an arbitrary number k of normal distributions under comparison. Not surprisingly, the range of settings for which explicit sample-size formula exist, is restricted to cases where the distribution of the optimal test statistic is of the continuous type. In the discrete case, testing procedures which satisfy the usual optimality criteria, involve randomized decisions between the hypotheses on the boundaries of the critical region which is usually not acceptable for real-world applications. In these settings which will be discussed in some detail in Section 5, powerful nonrandomized tests are required whose computation involves fairly heavy technical machinery. Exact sample-size calculation is still possible then, but no explicit formula are available.

2 The one-sample problem with normally distributed data of known variance

Suppose that the data under analysis can be described by a vector $(X_1, \ldots, X_n)$ of mutually independent random variables having all distribution $\mathcal{N}(\theta, {\sigma_\circ}^2)$ where ${\sigma_\circ}^2 > 0$ denotes a fixed positive constant. It is easy to verify that it entails no loss of generality if we set ${\sigma_\circ}^2 = 1$, $\theta_0 - \varepsilon_1 = -\varepsilon$ and $\theta_0 + \varepsilon_2 = \varepsilon$ with arbitrarily fixed $\varepsilon > 0$. For the corresponding specific equivalence problem, a UMP level-α test exists whose critical region is given by

$$\left\{ \ |\bar{X}| < n^{-1/2} C_{\alpha;\,\sqrt{n}\varepsilon} \right\}, \tag{2.1}$$

where the critical constant $C_{\alpha;\,\sqrt{n}\varepsilon}$ admits the explicit representation

$$C_{\alpha;\,\sqrt{n}\varepsilon} = \sqrt{\chi^2_{1;\,\alpha}(n\,\varepsilon^2)} \ . \tag{2.2}$$

In this equation, the notation is as usual, which is to say that $\chi^2_{1;\,\alpha}(n\,\varepsilon^2)$ stands for the α-quantile of a χ^2-distribution with $df = 1$ and noncentrality parameter $n\varepsilon^2$.

Given the critical constant, the rejection probability of the UMP test for equivalence under any value of the target parameter θ is easily computed exactly to be

$$\beta(\theta) = \Phi\big(C_{\alpha;\,\sqrt{n}\varepsilon} - \sqrt{n}\theta\big) - \Phi\big(-C_{\alpha;\,\sqrt{n}\varepsilon} - \sqrt{n}\theta\big)\,. \tag{2.3}$$

The corresponding power curve is shown in Fig. 2.1 for a sample of size $n = 100$ with the equivalence margin being specified to be $\varepsilon = .25$. The form of the curve differs characteristically from that of the power function of a traditional one- or two-sided test. From a practical point of view, perhaps the most striking conclusion to be drawn from this picture is the following: In contrast to tests for traditional one- or two-sided problems, *equivalence tests do not admit the possibility of increasing the power to values arbitrarily close to 100% simply by selecting sufficiently extreme points in the parameter subspace corresponding to the alternative hypothesis under consideration.*

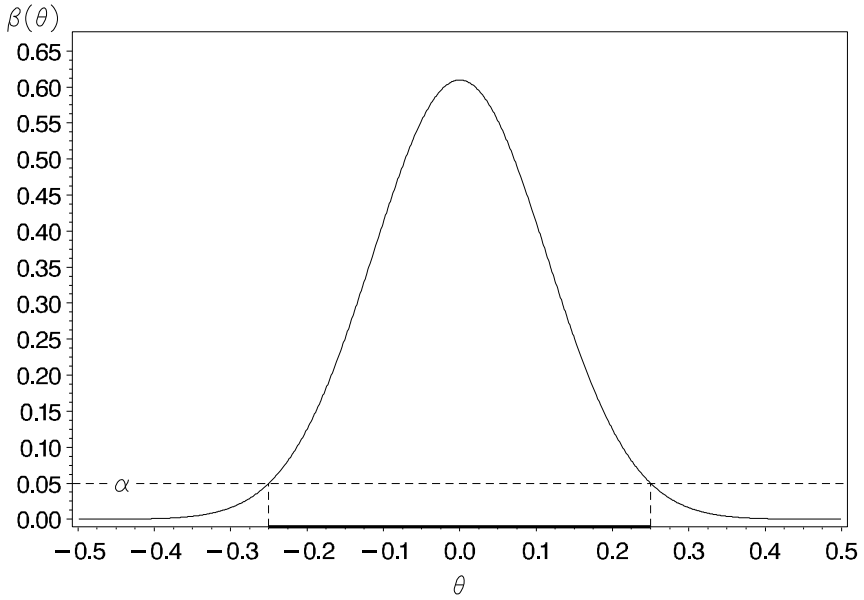

Figure 2.1 *Power function of the UMP test for equivalence at level $\alpha = 5\%$ for $|\theta| \geq .25$ vs. $|\theta| < .25$ based on $n = 100$ observations from $\mathcal{N}(\theta, 1)$. [Bold-drawn bar on horizontal coordinate axis $\leftrightarrow$ equivalence interval $(-\varepsilon, \varepsilon) = (-.25, .25)$ specified by the alternative hypothesis.]*

Sample-size planning of equivalence studies is almost exclusively done under the assumption that the null alternative $\theta = 0$ holds true implying that the true underlying distribution exactly coincides with that to be expected when no treatment effect exists. Restricting Equation (2.3) to this special case and setting the power equal to some fixed prespecified value β_0 yields

$$\beta_0 = 2\,\Phi(C_{\alpha;\,\sqrt{n}\varepsilon}) - 1 \ . \tag{2.4}$$

Keeping all other quantities fixed, this equation is easily solved for n using a simple search algorithm and a routine for calculating quantiles of noncentral chi-squared distributions. Of course, (2.4) can in particular be used for studying the relationship between the necessary sample size and the equivalence margin ε given the significance level α and the target power β_0. In Fig. 2.2, this is done for the three different choices $\beta_0 = .5$, $\beta_0 = .8$, and $\beta_0 = .9$. The (decreasing) step-functions obtained in this way show that the necessary sample size increases dramatically when the theoretical equivalence range is narrowed from, e.g., .5 to .25, with both choices being fairly frequently made in practice.

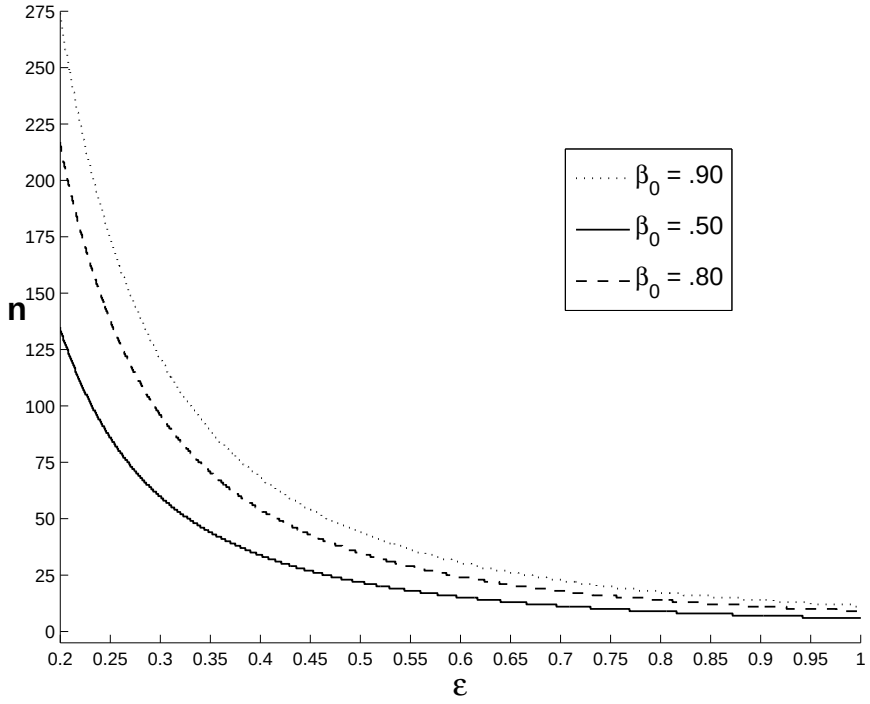

Figure 2.2 *Dependence of the minimum sample size required in the UMP test at level $\alpha = 5\%$ on the equivalence margin ε, for three different values of the target power β_0.*

Let us now direct attention to the version of the noninferiority problem (1.2) encountered when the data set under analysis consists of a single sample from $\mathcal{N}(\theta, {\sigma_\circ}^2)$ with known variance ${\sigma_\circ}^2 > 0$. Obviously, the UMP level-α test of $H_1 : \theta \leq -\varepsilon$ versus $K_1 : \theta > -\varepsilon$ rejects if it turns out that $\bar{X} > \sigma_\circ u_{1-\alpha}/\sqrt{n} - \varepsilon$. The power of this test against an arbitrarily chosen alternative $\theta > -\varepsilon$ can easiliy be computed by evaluating the expression on the right-hand side of the equation

$$\beta_1(\theta) = 1 - \Phi\big(u_{1-\alpha} - \sqrt{n}(\varepsilon + \theta)/\sigma_\circ\big) \tag{2.5}\,.$$

Except for allowing $\sigma_\circ$ to be an arbitrarily fixed positive real number, this is the direct *noninferiority analogue of (2.3).* It can be used to construct curves allowing one to read for varying values of the noninferiority margin ε and given target power β_0 the sample size required in the

test for one-sided equivalence at the same level as before (i.e., $\alpha = 5\%$) and with $\theta = 0$ as the specific alternative of interest. The graphs obtained in this way are shown in Fig. 2.3. They hold for $\sigma_\circ = 1$ and the same values of β_0 that are covered by the preceding figure. Comparing the two sets of curves enables one to assess the price which has to be paid for establishing with the same degree of certainty in terms of both error risks a hypothesis which is considerably more precise than that stated in the noninferiority problem as the alternative: Given the values of all other quantities involved, the power attainable with the same sample size in the two-sided equivalence testing scenario is substantially lower as compared with the test for noninferiority.

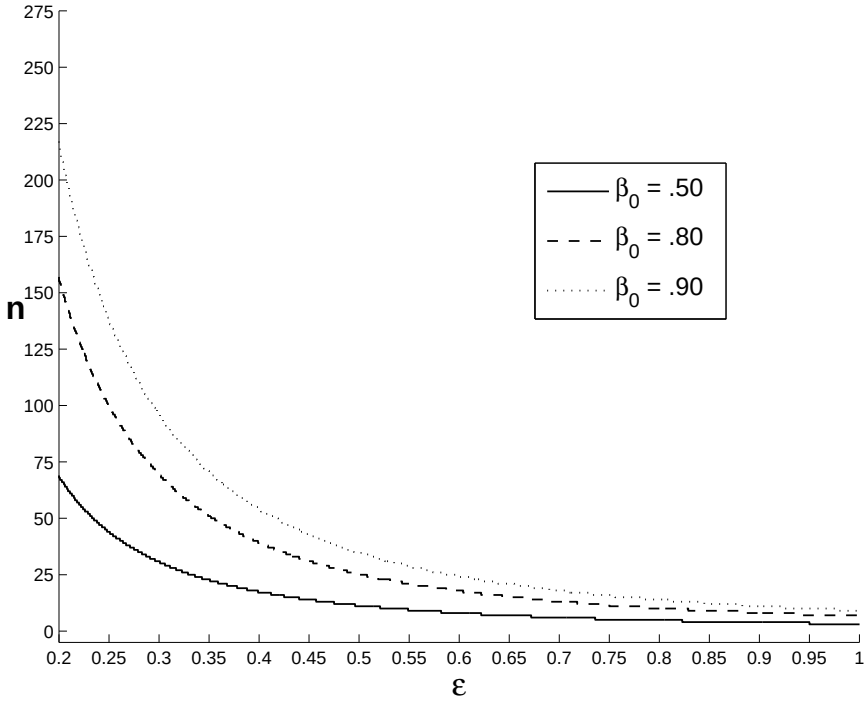

Figure 2.3 *Analogue to Fig. 2.2 for the noninferiority case.*

3 Two-sample problems involving normal distributions with both parameters being unknown

3.1 Planning of studies to be analyzed by means of the paired t-test for equivalence

In the paired-data setting, the primary observations $(X_1, Y_1), \ldots, (X_n, Y_n)$ are customarily reduced to intraindividual differences $D_i = X_i - Y_i$, $i = 1, \ldots, n$. Assuming for the moment only that the marginal distributions of the X_i and the Y_i obtained under two different treatments A and B, say, are continuous and that the same holds true for the distribution of the D_i, a reasonable criterion of equivalence can be based on the deviation of the sign-probability $p_+ \equiv P[D_i > 0]$ from $1/2$, requiring that there holds $1/2 - \varepsilon_1 < p_+ < 1/2 + \varepsilon_2$ for sufficiently small ε_1, ε_2. Upon introducing the parametric model assumption

$$D_i \sim \mathcal{N}(\delta, {\sigma_D}^2) \quad \forall\ i = 1, \ldots, n\,, \tag{3.1}$$

this hypothesis is easily shown to be equivalent to the the statement $\Phi^{-1}(1/2 - \varepsilon_1) < \delta/\sigma_D < \Phi^{-1}(1/2 + \varepsilon_2)$. Setting for brevity $\Phi^{-1}(1/2 - \varepsilon_1) = \theta_1$, $\Phi^{-1}(1/2 + \varepsilon_2) = \theta_2$, the equivalence

testing problem of interest in the paired t-test setting can thus be written

$$H : \delta/\sigma_{_D} \leq \theta_1 \vee \delta/\sigma_{_D} \geq \theta_2 \quad \text{vs.} \quad K : \theta_1 < \delta/\sigma_{_D} < \theta_2 \ . \tag{3.2}$$

Evidently, this problem remains invariant under all transformations of the sample space $\mathbb{R}^n$ of $(D_1, \ldots, D_n)$ taking the form of $(d_1, \ldots, d_n) \mapsto (cd_1, \ldots, cd_n)$, with arbitrary $c > 0$. The class of all invariant level-α tests can be shown (for details see Wellek, 2010, § 5.3) to contain a UMP element. This UMPI test is given by the critical region

$$\left\{ \tilde{C}^1_{\alpha;\, n-1}(\theta_1, \theta_2) < T < \tilde{C}^2_{\alpha;\, n-1}(\theta_1, \theta_2) \right\} \ , \tag{3.3}$$

where T denotes the usual one-sample t-statistic computed from the within-pair differences. The optimal critical bounds $\tilde{C}^{\nu}_{\alpha;\, n-1}(\theta_1, \theta_2)$ to T are uniquely determined by the equations

$$G_{\tilde{\theta}_1}(C_2) - G_{\tilde{\theta}_1}(C_1) = \alpha = G_{\tilde{\theta}_2}(C_2) - G_{\tilde{\theta}_2}(C_1) \, , \quad -\infty < C_1 < C_2 < \infty \, , \tag{3.4}$$

with

$$\begin{aligned} G_{\tilde{\theta}_\nu}(\cdot) \equiv \ & \text{cdf of noncentral } t \text{ with } df = n-1 \\ & \text{and noncentrality parameter } \tilde{\theta}_\nu = \sqrt{n}\theta_\nu \text{ for } \nu = 1, 2 \, . \end{aligned} \tag{3.5}$$

In the majority of practical applications, the equivalence interval specified under the alternative hypothesis is chosen symmetrical setting $\theta_1 = -\varepsilon$, $\theta_2 = \varepsilon$ for some $\varepsilon > 0$. In the symmetric case, the expression for the rejection region of the UMPI test can be simplified to

$$\left\{ |T| < \tilde{C}_{\alpha;\, n-1}(\varepsilon) \right\} \tag{3.6}$$

where the critical upper bound to which $|T|$ has to be compared admits the explicit representation

$$\tilde{C}_{\alpha;\, n-1}(\varepsilon) = \left[F_{1, n-1;\, \alpha}(\tilde{\varepsilon}^2) \right]^{1/2} \ , \tag{3.7}$$

with

$$\begin{aligned} F_{1, n-1;\, \cdot}(\tilde{\varepsilon}^2) \equiv \ & \text{quantile function of a } F\text{-distribution with } 1, n-1 \text{ degress} \\ & \text{of freedom and noncentrality parameter } \tilde{\varepsilon}^2 = n\varepsilon^2 \, . \end{aligned}$$

Calling (3.7) an explicit formula is justified by the fact that contemporary statistical software packages provide routines for computing with very high numerical accuracy specific quantiles of F-distributions with arbitrary numbers of degrees of freedom and values of the noncentrality parameter.

Given the values of both critical constants, the power of the UMPI test (3.3) against any specific alternative (δ, σ_D^2) can easily be computed exactly. As in the classical one- or two-sided version of the test, it depends on the pair of parameters only through δ/σ_D. More precisely speaking, we can write

$$\beta(\delta, \sigma_D^2) = G_{\sqrt{n}\delta/\sigma_D}\big(\tilde{C}^2_{\alpha;\, n-1}(\theta_1, \theta_2)\big) - G_{\sqrt{n}\delta/\sigma_D}\big(\tilde{C}^1_{\alpha;\, n-1}(\theta_1, \theta_2)\big) \, , \tag{3.8}$$

where $G_{\sqrt{n}\delta/\sigma_D}(\cdot)$ has the same meaning as in (3.5). When the equivalence margins are chosen symmetrically and interest focusses on the power β_0 against the null alternative $\delta = 0$, this equation reduces to the formula

$$\beta_0 = 2\, G_0(\tilde{C}_{\alpha;\, n-1}(\varepsilon)) - 1 \, , \tag{3.9}$$

which involves only the ordinary central t-distribution function. Keeping α and ε fixed, the expression on the right-hand side converges to that of (2.4) as $n \to \infty$. Combining (3.9) with (3.7) and denoting for any $0 < q < 1$ the qth quantile of central t with $\nu \in \mathbb{N}$ degrees of freedom by $t_{\nu;q}$ gives the following formula for the minimum sample size n_0, say, required for attaining power β_0 against $\delta = 0$ in the UMPI level-α test (3.6):

$$n_0 = \min\left\{ n \in \mathbb{N} \,|\, n \geq 2,\, F_{1,n-1;\,\alpha}(n\varepsilon^2) \geq t^2_{n-1;\,(1+\beta_0)/2} \right\}. \tag{3.10}$$

The algorithm required for determining this minimum is extremely simple, due to the fact that the function $n \mapsto F_{1,n-1;\,\alpha}(n\varepsilon^2)$ increases to $+\infty$, whereas $t^2_{n-1;\,(1+\beta_0)/2}$ decrease to $u^2_{(1+\beta_0)/2}$ as $n \to \infty$. Table 3.1 shows the sample sizes obtained from (3.10) for the usual significance level of 5% and a selection of values of β_0 and ε.

Table 3.1 *Sample sizes required for attaining power $\beta_0 \in \{.50, .75, .90, .95, .99\}$ against the null alternative in the paired t-test for equivalence at level 5% in the symmetric case $(\theta_1, \theta_2) = (-\varepsilon, \varepsilon)$, for $\varepsilon \in \{.10, .15, .20, .25, .50\}$.*

			ε =		
β_0	.10	.15	.20	.25	.50
0.50	532	237	134	86	22
0.75	782	348	196	126	32
0.90	1084	483	272	175	45
0.95	1302	580	327	210	54
0.99	1785	796	449	289	75

The modifications required for adapting the above results to the case that interest is in *testing for one-sided equivalence of two Gaussian distributions in the presence of correlated samples,* are largely straightforward. The non-inferiority version of the testing problem (3.2) reads

$$H_1 : \delta/\sigma_{_D} \leq -\varepsilon \quad \text{versus} \quad K_1 : \delta/\sigma_{_D} \geq -\varepsilon\,. \tag{3.11}$$

The same kind of argument which leads to using the critical region (3.3) for testing for two-sided equivalence with respect to $\delta/\sigma_{_D}$ shows that in order to perform a UMPI level-α test for (3.11), we have to reject the null hypothesis H_1 if and only if it turns out that

$$T > t_{n-1;1-\alpha}\big(-\sqrt{n}\varepsilon\big)\,. \tag{3.12}$$

According to this critical inequality, the standard paired-sample t-statistic has to be compared with the $(1-\alpha)$-quantile of a noncentral t-distribution with $n-1$ degrees of freedom and noncentrality parameter $-\sqrt{n}\varepsilon$. Computation of these quantiles is as easy as of the noncentral F-quantiles to be used in the equivalence version of the test with symmetric choice of the margins. Denoting the rejection probability of the UMPI level-α test (3.12) under an arbitrary parameter constellation by $\beta_1(\delta, \sigma_D^2)$, we can write

$$\beta_1(\delta, \sigma_D^2) = 1 - G_{\sqrt{n}\delta/\sigma_D}\big(t_{n-1;1-\alpha}(-\sqrt{n}\varepsilon)\big)\,. \tag{3.13}$$

[For the definition of $G_{\sqrt{n}\delta/\sigma_D}(\cdot)$, recall Eq. (3.5).] In particular, the power against the null alternative $\theta = 0 \Leftrightarrow \delta = 0$ is simply obtained by evaluating the central t-distribution function $t \mapsto G_0(t)$ at $t = -t_{n-1;1-\alpha}(-\sqrt{n}\varepsilon)$.

Exploiting these relationships, it is easy to compute the entries in Table 3.2 showing the minimum sample-sizes which are required in the paired t-test for noninferiority under the same set of constellations as were considered in Table 3.1.

Table 3.2 *Sample sizes required for attaining power* $\beta_0 \in \{.50, .75, .90, .95, .99\}$ *against the null alternative in the paired t-test for noninferiority at level 5% for the equivalence margin* ε *ranging over* $\{.10, .15, .20, .25, .50\}$.

	ε =				
β_0	.10	.15	.20	.25	.50
0.50	271	121	68	44	11
0.75	539	240	135	87	22
0.90	858	382	215	138	36
0.95	1084	483	272	175	45
0.99	1580	704	397	256	66

Elementwise comparison of the two tables clearly shows that there are marked differences between the one- and the two-sided versions of the paired t-test for equivalence: Under the same choice of the left-hand endpoint of the equivalence range specified by the alternative hypothesis, the noninferiority test provides (uniformly in n) a considerably higher chance to decide in favor of the null alternative as compared with the test for equivalence in the two-sided sense. This statement holds true despite the fact, that the lower critical bound to the t-statistic turns out to be always larger or equal in the noninferiority setting. The impact of this difference between the left-hand boundaries of the rejection regions is far overcompensated by the nonexistence of a right-hand boundary in the noninferiority case.

3.2 Two-arm trials following the parallel-group design with normally distributed data

If the trial run in order to compare the two treatments A and B follows an ordinary two-arm design, the data set to be analyzed consists of $m + n$ mutually independent observations $X_1, \ldots, X_m, Y_1, \ldots, Y_n$. The standard parametric model used for assessing the treatment effects observed in such a trial assumes that there holds

$$X_i \sim \mathcal{N}(\xi, \sigma^2) \;\; \forall\, i = 1, \ldots, m\,, \quad Y_j \sim \mathcal{N}(\eta, \sigma^2) \;\; \forall\, j = 1, \ldots, n\,, \tag{3.14}$$

with $\xi, \eta \in \mathbb{R},\ \sigma^2 \in \mathbb{R}_+$.

As in the paired-sample setting, it can be argued (cf. Wellek, 2010, § 1.6) that the most natural measure of dissimilarity of two Gaussian distributions is the standardized difference of their means. Accordingly, we define equivalence of treatments A and B through the condition that the true value of this measure falls into a sufficiently narrow interval $(-\varepsilon_1, \varepsilon_2)$ around zero. In other words, we formulate the testing problem as

$$H : (\xi - \eta)/\sigma \leq -\varepsilon_1 \text{ or } (\xi - \eta)/\sigma \geq \varepsilon_2$$
$$\text{versus } K : -\varepsilon_1 < (\xi - \eta)/\sigma < \varepsilon_2 \quad (\varepsilon_1, \varepsilon_2 > 0)\,, \tag{3.15}$$

in direct analogy to (3.2).

The construction of an optimal solution to this testing problem can be carried out along essentially the same line as leads to the paired t-test for equivalence. In the unpaired case, both hypotheses remain invariant under transformations of the form $(x_1, \ldots, x_m, y_1, \ldots, y_n) \mapsto (a + bx_1, \ldots, a + bx_m, a + by_1, \ldots, a + by_n)$ with $(a, b) \in \mathbb{R} \times \mathbb{R}_+$, applying to each coordinate of a point in the joint sample space $\mathbb{R}^N$ (with $N = m + n$) the same scale change and the same translation. Among all level-α tests for (3.15) which are invariant against this group of transformations, there is a uniformly most powerful one given by the critical region

$$\left\{ \tilde{C}^1_{\alpha;\, m,n}(-\varepsilon_1, \varepsilon_2) < T < \tilde{C}^2_{\alpha;\, m,n}(-\varepsilon_1, \varepsilon_2) \right\} . \tag{3.16}$$

Again, the test statistic T is the same as that used in the traditional one- or two-sided t-test so that it depends on the primary observations through

$$T = \sqrt{mn(N-2)/N}\,(\bar{X} - \bar{Y}) / \Big\{ \sum_{i=1}^{m} (X_i - \bar{X})^2 + \sum_{j=1}^{n} (Y_j - \bar{Y})^2 \Big\}^{1/2} . \tag{3.17}$$

The critical constants of the UMPI level-α (3.16) have to be determined by solving the equations

$$G^*_{-\tilde{\varepsilon}_1}(C_2) - G^*_{-\tilde{\varepsilon}_1}(C_1) = \alpha = G^*_{\tilde{\varepsilon}_2}(C_2) - G^*_{\tilde{\varepsilon}_2}(C_1)\,, \quad -\infty < C_1 < C_2 < \infty\,. \tag{3.18}$$

In (3.18), the superscript $*$ is added to the symbol $G_{\tilde{\varepsilon}}(\cdot)$ which has been previously used for noncentral t-distribution functions, in order to make conspicuous the change in the way the number of degrees of freedom has to be determined. Of course, in the two-sample case, the latter must be set equal to $N-2$ instead of $n-1$. Furthermore, $(-\tilde{\varepsilon}_1, \tilde{\varepsilon}_2)$ denotes the equivalence interval specified under the alternative hypothesis of (3.15) rescaled by multiplication with $\sqrt{mn/N}$.

The simplified computational scheme for determining the critical bounds to the t-statistic presented in § 3.1 for symmetrically chosen equivalence limits, has likewise its direct counterpart in the two-sample case. Actually, whenever both equivalence margins ε_1 and ε_2 are set equal to some common value $\varepsilon > 0$, the critical region (3.16) admits the representation

$$\left\{ |T| < \tilde{C}_{\alpha;\, m,n}(\varepsilon) \right\} , \tag{3.19}$$

where

$$\Big(\tilde{C}_{\alpha;\, m,n}(\varepsilon)\Big)^2 = F_{1,N-2;\,\alpha}(mn\varepsilon^2/N) \equiv \text{lower } 100\alpha \text{ percentage point of an } F\text{-distribution with } 1, N-2 \text{ degrees of freedom and noncentrality parameter } mn\varepsilon^2/N\,.$$

In view of (3.16) – (3.19), the modifications which are required in order to adapt the power formula (3.8) and (3.9) to the parallel-group design, are straightforward. The unpaired-samples analogue of Equation (3.8) reads

$$\beta(\xi, \eta, \sigma^2) = G^*_{\sqrt{mn/N}(\xi-\eta)/\sigma}\Big(\tilde{C}^2_{\alpha;\, m,n}(-\varepsilon_1, \varepsilon_2)\Big) - G^*_{\sqrt{mn/N}(\xi-\eta)/\sigma}\Big(\tilde{C}^1_{\alpha;\, m,n}(-\varepsilon_1, \varepsilon_2)\Big)\,, \tag{3.20}$$

with $G^*_{\sqrt{mn/n}(\xi-\eta)/\sigma}(\cdot)$ being defined as in (3.18). Under the symmetry restriction $\varepsilon_1 = \varepsilon_2 = \varepsilon$, the expression for the power of the UMPI test against the null alternative $\xi = \eta$ is

$$\beta_0 = 2\, G^*_0(\tilde{C}_{\alpha;\, m,n}(\varepsilon)) - 1\,, \tag{3.21}$$

which involves the t-distribution function with $N - 2$ in its central version.

Remark 3.1: It is interesting to note that, given the total sample size N, the equivalence margin ε and the significance level α, the critical upper bound $\tilde{C}_{\alpha;\,m,n}(\varepsilon)$ to which $|T|$ has to be compared in testing for equivalence in the symmetric case, is largest for $m = n = N/2$, as follows immediately from the obvious fact that the quantiles of noncentral F-distributions are increasing in the noncentrality parameter. Since, according to (3.21), β_0 increases with $\tilde{C}_{\alpha;\,m,n}(\varepsilon)$, this implies that the balanced design is also optimal when interest is in testing for equivalence of two homoskedastic normal distributions in presence of unrelated samples.

The way formula (3.21) may be used for sample-size planning of an equivalence study to be evaluated by means of the two-sample t-statistic is directly analogous to the use of (3.9) in the paired-samples setting: Provided, the equivalence interval specified under the alternative hypothesis one aims to establish is of the form $(-\varepsilon, \varepsilon)$, the minimum sample size per group required in a balanced design for attaining power β_0 against the alternative $\xi = \eta$ can be determined from

$$n_0^* = \min\left\{ n \in \mathbb{N} \,|\, n \geq 2,\; F_{1,2n-2;\,\alpha}\big((n/2)\varepsilon^2\big) \geq t^2_{2n-2;\,(1+\beta_0)/2} \right\}. \tag{3.22}$$

Table 3.3 shows the results obtained by means of this formula for the same values of ε and β_0 which appear in Table 3.1 in connection with the paired t-test for equivalence. The results directly reflect the fact that, except for negligible differences, for any $0 < q < 1$, the q-quantiles of two F-distributions with common numerator *df* and sufficiently large denominator *df*'s coincide whenever both distributions have the same noncentrality parameter. The latter is

Table 3.3 *Sample sizes required in a balanced trial to be evaluated by means of the two-sample t-test for equivalence at level 5% for attaining power* $\beta_0 \in \{.50, .75, .90, .95, .99\}$ *against the null alternative in the symmetric case* $(\theta_1, \theta_2) = (-\varepsilon, \varepsilon)$, *for* $\varepsilon \in \{.10, .15, .20, .25, .50\}$.

			ε =		
β_0	.10	.15	.20	.25	.50
0.50	1064	473	266	171	43
0.75	1563	695	391	251	63
0.90	2166	963	542	347	88
0.95	2600	1157	651	417	105
0.99	3565	1586	893	572	145

half as large in the balanced two-arm as compared with the paired-samples setting, and the reciprocal ratio holds at least approximately between homologous entries in Tables 3.3 and 3.1 throughout.

The modifications required in order to obtain an *optimum testing procedure for the noninferiority problem corresponding to (3.15)* are largely analogous to those described in § 3.1 for the case of paired observations. Replacing (3.15) with its noninferiority version yields

$$H_1 : (\xi - \eta)/\sigma \leq -\varepsilon \quad \text{vs.} \quad K_1 : (\xi - \eta)/\sigma > -\varepsilon \quad (\varepsilon > 0)\,, \tag{3.23}$$

and essentially the same arguments allowing one to establish the UMPI property of the unpaired t-test for two-sided equivalence show that the rejection region of an UMPI level-α test for this problem is given by

$$\left\{ T > t_{N-2;1-\alpha}\big(-\sqrt{mn/N}\varepsilon\big) \right\}. \tag{3.24}$$

Again [recall (3.12)], the critical lower bound has to be determined as the $(1-\alpha)$-quantile of a t-distribution with the appropriate number of degrees of freedom and the noncentrality parameter being set equal to the suitably rescaled limit of the theoretical equivalence interval. The power against any alternative (ξ, η, σ^2) with $(\xi - \eta)/\sigma = \theta > -\varepsilon$ is obtained by evaluating the survivor function $t \mapsto 1 - G^*_{\sqrt{mn/N}\theta}(t)$ of a t-distribution with $df = N - 2$ and and $nc = \sqrt{mn/N}\theta$ at $t = t_{N-2;1-\alpha}\big(-\sqrt{mn/N}\varepsilon\big)$. Thus, the parallel-group analogue of formula (3.13) is

$$\beta_1(\xi, \eta, \sigma^2) = 1 - G^*_{\sqrt{mn/N}\theta}\big(t_{N-2;1-\alpha}\big(-\sqrt{mn/N}\varepsilon\big)\big)\,. \tag{3.25}$$

If the alternative of interest specifies $\xi = \eta$, the right-hand side of Equation (3.25) can be written $G^*_0\Big(-t_{N-2;1-\alpha}\big(-\sqrt{mn/N}\varepsilon\big)\Big)$. For designing a balanced two-arm trial to be evaluated by means of the t-test for noninferiority, this yields the sample size formula

$$n_0^* = \min\Big\{n \in \mathbb{N} \,|\, n \geq 2,\, t_{2n-2;\,1-\alpha}\Big(-\sqrt{(n/2)}\varepsilon\Big) \leq t_{2n-2;\,1-\beta_0}\Big\}\,. \tag{3.26}$$

Its use is illustrated in Table 3.4 which refers to exactly the same combinations of values of the target power β_0 and the equivalence margin ε which are covered by the preceding table. Comparing these results with the entries in Table 3.2 leads to same qualitative conclusion as stated above for testing for equivalence in the strict, two-sided sense: Keeping fixed all other constants involved in sample-size planning, the number of observational units required in each group of a two-arm trial is about twice as large as the number of pairs which have to be available when the paired t-test for noninferiority is the confirmatory inferential procedure of choice.

Table 3.4 *Sample sizes required in a balanced trial to be evaluated by means of the two-sample t-test for noninferiority at level 5% for attaining power* $\beta_0 \in \{.50, .75, .90, .95, .99\}$ *against the null alternative, for* $\varepsilon \in \{.10, .15, .20, .25, .50\}$.

			ε =		
β_0	.10	.15	.20	.25	.50
0.50	542	241	136	87	22
0.75	1076	479	270	173	44
0.90	1714	762	429	275	69
0.95	2166	963	542	347	88
0.99	3156	1404	790	507	128

Remark 3.2: It is tempting to conclude from the relation $n_0^* \approx 2n_0$ with n_0^* and n_0 denoting the sample size required for the unpaired and the paired t-test for equivalence, respectively, that the paired-data design has superior efficiency. Interpreting the results presented in this section in that way would be grossly misleading, due to the fact that the equivalence hypothesis tested in the paired-data setting depends on the correlation within pairs and is not the same as that for which the unpaired test is tailored. Actually, assuming homoskedasticity in both designs, there holds $\delta/\sigma_D = (\delta/\sigma)\big/\sqrt{2(1-\varrho)}$ so that the equivalence margin which must be specified in the paired-data setting in order to obtain the same bound to the distance of δ/σ from the origin is $\varepsilon\big/\sqrt{2(1-\varrho)}$ instead of ε. For $\varrho = 0$, commensurable specifications are $\varepsilon/\sqrt{2}$ and ε, and

recalculating the entries in Tables 3.1 and 3.2 with the former specification gives approximately the same values as shown in Table 3.3 and 3.4, respectively. For large positive correlations, the equivalence condition set under the alternative hypothesis of the paired t-test admits much larger deviations of δ/σ from 0 than are compatible with the equivalence hypothesis formulated in the unpaired case. It is clear, that relaxing the equivalence criterion increases the power to decide in favor of the corresponding hypothesis.

4 Equivalence studies involving an arbitrary number $k \geq 2$ of normal distributions

The paired t-test for equivalence as discussed in the first part of § 3.1 can be generalized in a natural manner to the *problem of comparing an arbitrary number $k \geq 2$ of normal distributions from which mutually dependent samples are available.* This problem arises whenever an experimenter has to deal with k different conditions [treatments, timepoints at which some quantity is repeatedly measured, etc.] under which the observations are taken from each subject in a sample of size n, such that the marginal distributions of the corresponding k-dimensional random vectors are all of Gaussian form. We keep leaving the intraindividual correlations completely unspecified and start from the assumption that the data set consists of n mutually independent vectors $(X_{11}, \ldots, X_{k1})$, …, $(X_{1n}, \ldots, X_{kn})$ such that

$$(X_{1i}, \ldots, X_{ki}) \sim \mathcal{N}\big((\mu_1, \ldots, \mu_k),\, \boldsymbol{\Sigma}\big)\,, \quad \forall\, i = 1, \ldots, n\,, \tag{4.1}$$

where

$$\boldsymbol{\Sigma} \equiv \begin{pmatrix} \sigma_1^2 & \sigma_{12} & \ldots & \sigma_{1k} \\ \sigma_{21} & \sigma_2^2 & \ldots & \sigma_{2k} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{k1} & \sigma_{k2} & \ldots & \sigma_k^2 \end{pmatrix} \tag{4.2}$$

denotes an unknown positive definite (symmetric) matrix of order $k \times k$.

As a multivariate analogue of the distance measure $\delta^2/\sigma_D^2 = (\mu_1 - \mu_2)^2/\ (\sigma_1^2 + \sigma_2^2 - 2\sigma_{12})$ underlying the paired t-test with symmetric specification of the hypothetical equivalence range, we use the Mahalanobis distance of a set of $k-1$ contrasts $(\delta_1, \ldots, \delta_{k-1})$ in the μ's from the origin as the parametric function of interest. Of course, the covariance matrix $\boldsymbol{\Sigma}_D$, say, with respect to which this distance has to be taken, is that of the corresponding contrasts in the components of the random vectors primarily observed. For definiteness, we choose these contrasts as pairwise differences between successive components of the respective vectors, defining

$$\delta_j = \mu_{j+1} - \mu_j\,, \quad j = 1, \ldots, k-1\,. \tag{4.3}$$

Then, the entries in $\boldsymbol{\Sigma}_D$, say σ_{jl}^D, are given by

$$\sigma_{jl}^D = \sigma_{jl} + \sigma_{j+1,l+1} - \sigma_{j,l+1} - \sigma_{j+1,l}\,, \quad 1 \leq j, l \leq k-1\,. \tag{4.4}$$

The equivalence hypothesis we want to establish specifies that the true vector $\boldsymbol{\delta} = (\delta_1, \ldots, \delta_{k-1})$ of mean differences between "adjacent" components of the $\mathbf{X}_1, \ldots, \mathbf{X}_n$ is sufficiently close to $\mathbf{0}$, with distances between pairs $(\mathbf{d}_1, \mathbf{d}_2)$ of points in $\mathbb{R}^{k-1}$ measured in terms of $(\mathbf{d}_1 - \mathbf{d}_2)\boldsymbol{\Sigma}_D^{-1}(\mathbf{d}_1 - \mathbf{d}_2)'$. Accordingly, the equivalence testing problem we are now interested in reads

$$H : \boldsymbol{\delta}\boldsymbol{\Sigma}_D^{-1}\boldsymbol{\delta}' \geq \varepsilon^2 \ \text{ versus } \ K : \boldsymbol{\delta}\boldsymbol{\Sigma}_D^{-1}\boldsymbol{\delta}' < \varepsilon^2\,. \tag{4.5}$$

The first step of constructing an optimal test for the equivalence problem (4.5) consists of estimating the theoretical Mahalanobis distance through replacing $\boldsymbol{\delta}$ and $\boldsymbol{\Sigma}_D$ with

$$\bar{\boldsymbol{D}} \equiv n^{-1} \sum_{i=1}^{n} (D_{1i}, \ldots, D_{k-1,i}) \tag{4.6}$$

and

$$\boldsymbol{S}_D \equiv (n-1)^{-1} \sum_{i=1}^{n} (D_{1i} - \bar{D}_1, \ldots, D_{k-1,i} - \bar{D}_{k-1})' \\ (D_{1i} - \bar{D}_1, \ldots, D_{k-1,i} - \bar{D}_{k-1}) \,, \tag{4.7}$$

respectively. As is well-known from the classical theory of parametric multivariate inference (see, e.g., Anderson, 1984, § 5.4) the distribution of the rescaled estimated Mahalanobis distance

$$T^2 \equiv n \bar{\boldsymbol{D}} \boldsymbol{S}_D^{-1} \bar{\boldsymbol{D}}' \tag{4.8}$$

depends on $\boldsymbol{\delta}$ and $\boldsymbol{\Sigma}_D$ only through the actual value, say τ^2, of $\boldsymbol{\delta} \boldsymbol{\Sigma}_D^{-1} \boldsymbol{\delta}'$. In fact, we can write

$$T^2 \, (n-k+1) / \big((n-1)(k-1) \big) \stackrel{d}{=} \mathcal{F}_{k-1, n-k+1}(n\tau^2) \,, \tag{4.9}$$

where $\mathcal{F}_{\nu_1, \nu_2}(\psi^2)$ stands for a random variable following an F-distribution with ν_1, ν_2 degrees of freedom and noncentrality-parameter ψ^2. Consequently, an exact level-α test for (4.5) consists of checking the observed data for inclusion in the critical region

$$\big\{ T^2 < \big((n-1)(k-1)/(n-k+1) \big) \, F_{k-1, n-k+1; \, \alpha}(n\varepsilon^2) \big\} \;. \tag{4.10}$$

The test given by this critical region can be shown (cf. Wellek, 2010, § 8.1.1) to be UMPI among all level-α tests which remain invariant under arbitrary one-to-one linear transformations of the vector $\boldsymbol{D}_i$ of contrasts.

The power function of the T^2-test for equivalence of k normal distributions to be assessed on the basis of dependent samples can be evaluated exactly by means of easily accessible computational tools. Denoting its rejection probability under any parameter configuration $(\boldsymbol{\delta} \,, \boldsymbol{\Sigma}_D)$ with $\boldsymbol{\delta} \boldsymbol{\Sigma}_D^{-1} \boldsymbol{\delta}' = \tau^2 \in [0, \infty)$ by $\beta(\tau^2)$, one can write

$$\beta(\tau^2) = P\big[\mathcal{F}_{k-1, n-k+1}(n\tau^2) \leq F_{k-1, n-k+1; \, \alpha}(n\varepsilon^2) \big] \,. \tag{4.11}$$

The power against the null alternative $\tau^2 = 0$ specifying that all k population means coincide, is given by $F_0\Big(F_{k-1, n-k+1; \, \alpha}(n\varepsilon^2) \Big)$ where $F_0(\,\cdot\,)$ is a short-hand notation for the distribution function of $\mathcal{F}_{k-1, n-k+1}(0)$. Denoting for arbitrary $0 < q < 1$ the qth quantile of the latter by $F_{k-1, n-k+1; \, q}$, we obtain as a sample-size formula to be used in connection with the equivalence test (4.10)

$$n_0 = \min \Big\{ n \in \mathbb{N} \,|\, n \geq k, \, F_{k-1, n-k+1; \, \alpha}(n\varepsilon^2) \geq F_{k-1, n-k+1; \, \beta_0} \Big\} \,. \tag{4.12}$$

Of course, for given significance level and target power, n_0 is both a function of the number k of treatments under comparison, and the equivalence margin set to the theoretical Mahalanobis distance of the vector of pairwise population means from the origin. Table 4.1 shows the sample sizes calculated by means of (4.12) for a target power of 80%, the same choice of values of ε as appears in Table 3.1 and k ranging over $\{3, \ldots, 8\}$. In accordance with intuition, the entries in the table are increasing within each row. It is worth noticing that the T^2-test for equivalence of k normal distributions from which dependent samples are available, does not depend on the specific contrast between the μ_j used for assessing the degree of disparity of the distributions under comparison.

Table 4.1 *Sample sizes required for attaining power* $\beta_0 = .80$ *against the null alternative* $\mu_1 = \ldots = \mu_k$ *in the* T^2*-test for equivalence of* k *normal distributions in presence of dependent samples, for* $\alpha = .05$, $\varepsilon \in \{.10, .15, .20, .25, .50\}$ and $k = 3, \ldots, 8$.

	k =					
ε	3	4	5	6	7	8
0.10	1044	1176	1283	1375	1458	1533
0.15	465	524	572	614	651	684
0.20	262	296	323	347	368	387
0.25	169	191	208	224	237	250
0.50	44	50	55	59	63	67

A similar *extension to testing for equivalence of an arbitrary number* k *of normal distributions* is possible *when the samples taken from each distribution are mutually independent.* In order to keep within the same frame of reference as in considering the problems concerning $k = 2$ samples of normally distributed data, we assume that all distributions have a common (yet unknown) variance $\sigma^2 \in \mathbb{R}_+$. Thus we suppose that the pooled data set to be analyzed exhibits the following structure:

$$\begin{array}{lcl} X_{11}, \ldots, X_{1n_1} & \leftarrow & \text{1st sample, from } \mathcal{N}(\mu_1, \sigma^2) \\ X_{21}, \ldots, X_{2n_2} & \leftarrow & \text{2nd sample, from } \mathcal{N}(\mu_2, \sigma^2) \\ \ldots\ldots\ldots\ldots & \ldots & \ldots\ldots, \ldots\ldots\ldots\ldots \\ X_{k1}, \ldots, X_{kn_k} & \leftarrow & k\text{th sample, from } \mathcal{N}(\mu_k, \sigma^2) \end{array}$$

In the balanced case $n_1 = \ldots = n_k = n$, a natural measure of the degree to which the true underlying distributions deviate from the "ideal" of perfect pairwise coincidence is given by the squared Euclidean distance of the vector $(\mu_1/\sigma, \ldots, \mu_k/\sigma)$ from the point $(\bar{\mu}./\sigma)\,\mathbf{1}_k$, where $\bar{\mu}.$ and $\mathbf{1}_k$ denotes the ordinary arithmetic mean of the μ_i and the k-vector of ones, respectively. A useful way of extending the definition of this measure to arbitrarily unbalanced designs of the same kind consists of replacing $\bar{\mu}.$ with the sample-size–weighted mean $\tilde{\mu}.$, say, of the expected values, and the unit weight to the squared distance in the ith component with $(n_i/\bar{n})$. The resulting generalized squared Euclidean distance is then given by

$$\psi^2 = \sum_{i=1}^{k} (n_i/\bar{n})(\mu_i - \tilde{\mu}.)^2/\sigma^2\,, \tag{4.13}$$

with

$$\tilde{\mu}. = \sum_{i=1}^{k} n_i\mu_i / \sum_{i=1}^{k} n_i\,, \quad \bar{n} = \sum_{i=1}^{k} n_i/k\,. \tag{4.14}$$

Using ψ^2 as our target parameter leads to the problem of testing

$$H : \psi^2 \geq \varepsilon^2 \quad \text{versus} \quad K : \psi^2 < \varepsilon^2 \tag{4.15}$$

with suitably fixed $\varepsilon > 0$. By analogy with the construction of a test for equivalence of k normal distributions in presence of dependent samples, it is natural to replace all basic parameters by

their standard UMVU estimators and use the resulting plug-in estimator

$$\hat{\psi}^2 = \frac{\sum_{i=1}^{k}(n_i/\bar{n})(\bar{X}_i - \bar{X}_{\cdot\cdot})^2}{(N-k)^{-1}\sum_{i=1}^{k}\sum_{\nu=1}^{n_i}(X_{i\nu} - \bar{X}_i)^2} \tag{4.16}$$

of ψ^2 as the test statistic. Except for dropping the constant factor $\bar{n}/(k-1)$, this is the usual F-statistic for the one-way fixed-effects ANOVA. Hence, the distribution of $(\bar{n}/(k-1))\hat{\psi}^2$ depends on the μ_i and σ^2 only through ψ^2 and is noncentral F with $k-1, N-k$ degrees of freedom (where, as before, N stands for the total sample size $\sum_{i=1}^{k} n_i$) and noncentrality parameter $\bar{n}\psi^2$. Accordingly,

$$\left\{ \hat{\psi}^2 < ((k-1)/\bar{n}) F_{k-1,N-k;\,\alpha}(\bar{n}\varepsilon^2) \right\} \tag{4.17}$$

is the critical region of an exact level-α test for the problem (4.15). In the literature (cf. Wellek, 2010, § 7.2), the term multisample F-test for equivalence has been proposed for this testing procedure. Both the hypotheses and the critical region (4.17) are invariant under a large group of affine transformations which contains in particular arbitrary common rescalings and translations of all observations in the pooled sample. Moreover, the F-test for equivalence can be shown to be UMP among all tests remaining invariant under that group. Its rejection probability under any $\big((\mu_1, \ldots, \mu_k), \sigma^2\big)$ satisfying Equation (4.13) for some ψ^2 can be computed exactly from

$$\beta(\psi^2) = P\left[\, \mathcal{F}_{k-1,N-k}(\bar{n}\psi^2) < F_{k-1,N-k;\,\alpha}(\bar{n}\varepsilon^2) \,\right] \tag{4.18}$$

where $\mathcal{F}_{k-1,N-k}(\tilde{\psi}^2)$ denotes a random variable which has an F-distribution with $k-1, N-k$ degrees of freedom and noncentrality parameter $\tilde{\psi}^2$.

In the balanced case, (4.18) can be converted into a sample-size formula in a similar way as was done above in connection with testing for equivalence with dependent samples from normal distributions. The resulting analogue of (4.12) for the ANOVA design reads

$$n_0 = \min\left\{ n \in \mathbb{N} \,|\, n \geq k,\; F_{k-1,(n-1)k;\,\alpha}(n\varepsilon^2) \geq F_{k-1,(n-1)k;\,\beta_0} \right\}. \tag{4.19}$$

Using it for designing an equivalence trial following a one-way ANOVA layout with the same range for the number k of treatments and specifications of the equivalence margin covered by the previous table, leads to the results shown in Table 4.2. This time, in terms of the nominal values obtained for n_0 given the number of treatments under comparison, the significance level and the target power, the differences between the parallel-group design and the design involving dependent samples are small.

Remark 4.1: Except for the special case $k = 2$ [recall Remark 3.1], trying to identify that allocation of a given total N of sampling units to k different treatment groups which maximizes the power of the F-test for equivalence against the alternative $\psi^2 = 0$, makes no real sense. The reason behind this statement is that changing the pattern $(n_1, \ldots, n_k)$ of individual sample sizes changes the shape of the neighborhood of $\mathbf{0}$ specified as the equivalence region under the hypothesis one aims to establish. Thus, computing the power of the test with critical region (4.17) for different allocations of some total N of units to k subgroups yields non-commensurable quantities since they relate to tests for different pairs of hypotheses.

Table 4.2 *Sample sizes required for attaining power* $\beta_0 = .80$ *against the null alternative* $\mu_1 = \ldots = \mu_k$ *in the UMPI equivalence test at level 5% for the one-way ANOVA layout, with the number of cells ranging from 3 through 8 and the same choices of the equivalence margin as in the previous tables.*

	k =					
ε	3	4	5	6	7	8
0.10	1042	1174	1281	1372	1454	1529
0.15	464	522	570	611	647	680
0.20	261	294	321	344	364	383
0.25	168	189	206	221	234	245
0.50	43	48	52	56	59	62

5 Studies with binary outcome variables

The basic complication one encounters in any setting involving discrete data is that testing procedures which satisfy the usual optimality criteria, require to take randomized decisions between the hypotheses on the boundary of the critical region. Since decision procedures which rely on external randomization are unsuitable for most real-world applications, sample-size planning will have to be based on improved nonrandomized tests which are less conservative than those obtained by incorporating the boundary of the optimal critical region as a whole into the acceptance region. Although the computational issues encountered in constructing such modified nonrandomized tests are considerable, exact sample-size calculation is still possible. We discuss this approach for the special but practically very important case of testing for one-sided equivalence of two binomial distributions.

To fix notation, let us assume that a two-arm trial involving two treatments A and B is performed yielding data which are realizations of independent random variables X [$\leftrightarrow A$] and Y [$\leftrightarrow B$] with $X \sim \mathcal{B}(m, p_1)$] and $Y \sim \mathcal{B}(n, p_2)$. As to the parametrization of the corresponding family of joint distributions of (X, Y), we adopt the view that the odds ratio $\rho = p_1(1-p_2)/(1-p_1)p_2$ provides a more adequate measure of dissimilarity of the two distributions under comparison than the difference $\delta = p_1 - p_2$ between the responder rates in the underlying populations. Accordingly, in a noninferiority trial with binary outcome, one needs a suitable test of

$$H_1 : \rho \leq 1 - \varepsilon \quad \text{versus} \quad K_1 : \rho > 1 - \varepsilon \tag{5.1}$$

with some fixed $0 < \varepsilon < 1$.

An optimal solution to this problem can be derived by way of generalizing the construction behind the exact test of the null hypothesis of homogeneity of $\mathcal{B}(m, p_1)$ and $\mathcal{B}(n, p_2)$ usually named after R.A. Fisher (1934, § 21.02). Like the latter, the optimal [precisely: uniformly most powerful unbiased (UMPU) — see Lehmann and Romano (2005, pp. 126–127)] test for (5.1) is based on the conditional distribution of X given the realized value $s \in \{0, 1, \ldots, N\}$ of the total number $S = X + Y$ of responders [$\leftrightarrow$ first column total in a standard 2×2 contingency table]. The conditional p-value $p(x|s)$ of the number x of responders counted in treatment arm A has to

be computed by means of a probability distribution which, following Harkness (1965), is usually called extended hypergeometric distribution (cf. Johnson et al., 1992, § 6.11). In this conditional distribution, any possible value of X is an integer x such that $\max\{0, s-n\} \le x \le \min\{s, m\}$. For any such x the precise formula for the conditional p-value reads

$$p(x|s) = \sum_{j=x}^{m} \binom{m}{j} \binom{n}{s-j} (1-\varepsilon)^j \Big/ \sum_{j=\max\{0,s-n\}}^{\min\{s,m\}} \binom{m}{j} \binom{n}{s-j} (1-\varepsilon)^j \,. \tag{5.2}$$

For fixed sample sizes m, n, the power of the test based on (5.2) against an arbitrarily chosen specific alternative (p_1^*, p_2^*) equals by definition the *nonconditional* rejection probability, given the true distribution of X and Y is $\mathcal{B}(m, p_1^*)$ and $\mathcal{B}(n, p_2^*)$, respectively. In view of this, the first step of an algorithm for doing exact power computations consists of determining for each possible value $s = 0, 1, \ldots, N$ of $S = X + Y$, the critical value $k_\alpha(s)$, say. Adopting the convention that, conditional on $\{S = s\}$, the rejection region be of the form $\{X > k_\alpha(s)\}$, $k_\alpha(s)$ is obviously given as the smallest integer x such that $\max\{0, s-n\} \le x \le \min\{s, m\}$ and $p(x+1|s) \le \alpha$. Furthermore, it is essential to observe that the test holds the UMPU property only if in each conditional distribution of X the prespecified significance level $\alpha \in (0, 1)$ is exactly attained rather than only maintained in the sense of not exceeding it. In view of the discreteness of all distributions involved, this typically requires that on the boundary of the critical region $\{X > k_\alpha(s)\}$, i.e., for $X = k_\alpha(s)$ a randomized decision in favor of the alternative hypothesis is taken with probability $\gamma(s) = [\alpha - p(k_\alpha(s) + 1 \,|\, s)]/[p(k_\alpha(s) \,|\, s) - p(k_\alpha(s) + 1 \,|\, s)]$. The conditional power of this randomized test is given by

$$\beta(p_1^*, p_2^*|s) = \frac{\displaystyle\sum_{j=k_\alpha(s)+1}^{\min\{s,m\}} \binom{m}{j} \binom{n}{s-j} {\rho_*}^j + \gamma(s) \binom{m}{k_\alpha(s)} \binom{n}{s-k_\alpha(s)} {\rho_*}^{k_\alpha(s)}}{\displaystyle\sum_{j=\max\{0,s-n\}}^{\min\{s,m\}} \binom{m}{j} \binom{n}{s-j} {\rho_*}^j} \,, \tag{5.3}$$

with $\rho_* = p_1^*(1-p_2^*)/(1-p_1^*)p_2^*$. In order to compute its nonconditional power against the arbitrarily selected specific alternative (p_1^*, p_2^*), we have to integrate the function $s \mapsto \beta(p_1^*, p_2^*|s)$ with respect to the distribution of S. Unfortunately, the latter is simply of binomial form again only if (p_1^*, p_2^*) lies on the diagonal of the unit square. Whenever we select a parameter combination with $p_1^* \neq p_2^*$, the distribution of S must be computed from scratch by means of convolution. Computer programs for the implementation of this algorithms can be found among the supplementary materials provided with Wellek (2010). At the same source, tools for computing sample sizes required to achieve any given level of power in the exact UMPU test are also provided.

In practice, optimal tests based on statistics having discrete distributions are almost exclusively applied in a conservative nonrandomized version which means that the probability of taking a decision in favor of the alternative hypothesis is set equal to zero at each point of the boundary of the rejection region. One promising approach to reducing the loss of power entailed in this modification is through replacing the target significance level α with a maximally increased nominal level α^* at which the nonrandomized test can be performed. As related to testing traditional one- or two-sided hypotheses about the odds ratio ϱ, this approach goes back to Boschloo (1970). Notwithstanding the conceptual simplicity of the basic idea, determining the largest admissible value of the nominal level is computationally fairly demanding. Fortunately,

the computational burden is markedly reduced by the fact that the maximum of the rejection probability of each test carried out through comparing the conditional p-value (5.2) with some fixed upper bound over the null hypothesis of (5.1) is taken on at the boundary. This follows from a result stated by Röhmel and Mannsmann (1999a) referring to Hájek and Havránek (1978) as a primary source for a rigorous derivation. A small selection of results showing the effect of adjusting the nominal level on the sample-size planning of a balanced two-arm noninferiority trial with binary outcome is displayed in Table 5.1. The results admit the conclusion that the sample size required per group in the nonrandomized test at maximally increased nominal level typically falls distinctly left from the middle between that needed in the exact randomized test on the one hand and its conservative nonrandomized version on the other.

Table 5.1 *Sample sizes required in the exact UMPU test for one-sided equivalence of two binomial distributions and the conservative nonrandomized test to attain the same power* β_0 *as with* $n = 200$ *observations per group in the test at maximally increased nominal level* α^**. [Level of the exact test :* $\alpha = .05$*.]*

ε	α^*	p_1	p_2	β_0	n_{UMPU}	n_α
0.3333	.05974	.10	.10	.3072	179	226
0.3333	.05974	.25	.25	.5341	196	221
0.3333	.05974	.50	.50	.6368	195	219
0.5000	.05992	.10	.10	.6307	187	217
0.5000	.05992	.25	.25	.9046	198	212
0.5000	.05992	.50	.50	.9641	200	208

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