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UNIVERSITY OF EDINBURGH

SEQUENTIAL METHODS IN STATISTICS

Summary of talks at
a Research Workshop
1988

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Final Report on the Research Workshop on Sequential Methods in Statistics_

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1. The purpose of the Workshop was to explore the current state of research and applications in sequential methods, and especially to bring together those concerned with theoretical developments and those involved with practical applications. Local arrangements were undertaken by Messrs. P.R. Fisk, G.R. Cohen and J. C. Duffy, and the academic programme was organized by Professor P. Armitage, Dr. K.D. Glazebrook and Dr. J.R. Whitehead.

2. The Workshop was held at the University of Edinburgh between 3 and 15 July, 1988, the last two days of which were an "Open Forum" which all professional statisticians could apply to attend at their own expense.

3. Since the scope of the Workshop covered diverse areas of application, a few participants from specific fields of application were invited to come for 2 - 3 days, so that the relevant discussions could be concentrated in time. This was a successful scheme, given the breadth of the Workshop.

4. Verbal and written comments from many participants indicate that the Workshop was regarded as being very successful. In particular, the opportunities for extended discussion, both within and outside the formal sessions, were appreciated. Many linkages across research fields were noted, and several new collaborative projects have been initiated.

5. The Open Forum complemented the closed part of the Workshop by giving an opportunity for other UK statisticians to hear about topics discussed at the Workshop, and to make their own contributions.

6. *Summary of Academic Proceedings*

   Lists of those attending the Workshop and the Open Forum, and programmes for both the Workshop and the Open Forum, are atttached. Abstracts of the talks given have been circulated to participants and are available on request.

   The Workshop had three main 'streams':

   (1) Sequential experimentation : stopping rules and clinical trials.
   (2) Sequential experimentation : treatment and resource allocation
   (3) Sequential sampling and process control.

   Stream (1) has considerable theoretical interest, as well as practical importance in clinical trials. Stream (2) was interpreted broadly to include the scheduling of research programme as well as more traditional experimental design. Stream (3) had two main topics, sequential process control (with related problems in epidemiological monitoring) and sequential methods in epidemiology.

Several discussion sessions were scheduled during the latter half of the main part of the Workshop, mainly on topics in which particular interest had been aroused earlier. Many of these revealed connections across the streams. The discussion sessions were regarded by participants as particularly successful. Four sessions were devoted to problems, descriptions of which had been circulated in advance. Not surprisingly, few of these were solved completely, but much useful discussion took place.

7. *Stream 1: Sequential experimentation : stopping rules and clinical trials*

There was considerable interaction between statisticians working on the theory of stopping rules and those concerned with the application of sequential methods in clinical trials. Results previously available in the theoretical literature were explained more simply and should be useful in practice. The theoreticians were assured that there was a market for a wide range of mathematical results.

Two particular areas are worthy of comment (as is the related topic dealt with in 11.2).

7.1 *Estimation after clinical trials*

Woodroofe, Pocock, Siegmund and Whitehead all addressed this problem in different ways. Results given by Woodroofe and by Siegmund appear to be of great potential use in practice, and collaboration will continue between them and Whitehead. The Bayesian shrinkage approach of Pocock presented a different approach. The discussions at the Workshop will have an important impact on the direction of research on this topic.

7.2 *Multiple treatment comparisons*

Bather, Jennison, Petkau and Mead all took leading roles in this debate. Classical elimination procedures and sequential χ^2 and F tests were reviewed. An important development was that of regarding orthogonal treatment contrasts as multiple comparison which could be subjected to the same kind of elimination rules.

8. *Stream 2: Sequential experimentation ; treatement and resource allocation*

A major part of the workshop considered the more radical form of sequential experimentation in which the nature of the experiment is allowed to depend upon the accumulating data. Many of the contributions here related to the planning of the early stages of new-product pharmaceutical research.

Quantitative Structure-Activity Relationships (QSAR) is the name given to the study of the relationships between the structure of chemical compounds and their biological activity. A major aim of such study is the reduction of the number of compounds to be tested before a new drug is discovered. Hence an underlying theme here concerns the sequential allocation of resources. In a particularly effective presentation by one of the chemometricians participating, Sjöstrom argued that QSAR could have been used to effect a reduction of around 30% in the amount of testing required in a published study on polypeptides. This paper exhibited an area in which there is considerable scope for increased involvement of statisticians and the more effective use of statistical methodology. In this last respect the story was similar to that revealed for other industrial situations in strong contrast with the much more satisfactory status of statistics in clinical trials (see 10).

Gittins described the CPSDAI procedure which he has developed for the sequential selection of compounds for testing. His work on what are now called Gittins indices has led to major advances in the study of sequential decision problems in general and in the analysis of stochastic models for resource allocation problems in particular. Glazebrook described much of this work and mentioned some open problems. One important question which was discussed concerned how the Gittins index rule should be modified when allocating research effort between lead compounds in pharmaceutical research, i.e. when some of these leads are directed at the same therapeutic goal. Collaboration on this topic will continue between Fay, Gittins, Glazebrook and Weber.

Complementing the above contributions was one by Bather which sought to quantify the benefits to be derived from the use of sequential methods in drug screening and phase II clinical trials - an important area with much scope for further work.

Mead described some developments of work by Box and Wilson which seem to have important implications for the design of industrial processes. In these there will often be a large number of factors involved and the overall objective is identification of the optimal combination of factor levels. The proposal was to use sequences of saturated factorial designs to reach an optimal response. There are many questions to be answered concerning how this should be done. Some theoretical insights were backed up by results of simulations. This is plainly an important area in its infancy.

9. *Stream 3; Sequential sampling and process control*

9.1 *Process control*

Discussions here revolved mainly around the need to reintroduce effective statistical process control into manufacturing industry. Wetherill and Baker stressed the importance of simple methods, but Wetherill also emphasized the complexity of modern process

industries. Cusum methods are particularly appropriate, but much research is needed, e.g. on the effect of non-iid variability such as serial correlation. Bissell, Rowlands and Rendtel presented recent results.

One question relates to the shape of the mask used in Cusums (e.g. linear or parabolic). There is a close analogy here with the choice of boundaries in sequential trials, the optimal shape depending on the prior distribution of sizes of shift. Similar questions concern the types of change expected (e.g. sudden or gradual). Siegmund described the unsolved problem of allowing for unknown initial parameter values.

9.2 *Sequential methods in epidemiology*

Gail reviewed areas of epidemiology in which sequential investigation was both natural and possible. These included case-control studies for acute disease and pilot studies for large-scale investigations. Jones's open problem, about epidemiological monitoring, led to fruitful discussions about repeated confidence intervals (discussed by Jennison), stopping rules and Cusums. Collaboration between Gail and Jones is planned, leading to a review paper on the use of Cusums in epidemiology.

10. A recurrent theme was the lack of appreciation by industrial management of the potential value of even simple statistical procedures. Thus, statistical quality control was allowed to lapse in the U.K. after the war, but was exploited by Japan, and more recently the USA, to great effect. The fault was seen as partly that of management (not of the shop-floor), but some responsibility lies also with academic statisticians to provide non-technical explanations and to collaborate more readily with industry.

11. *Summary of achievements*

(1) The Workshop confirmed the practical importance of sequential procedures, in industrial process control, clinical trials, chemometrics, biological experimentation and sampling, and other areas. It confirmed also the theoretical progress made recently both in traditional branches of sequential analysis and in the broader topic of sequential resource allocation.

(2) Workers in these different fields, both theoretical and applied, were able to appreciate research possibilities over a broad canvas, and to note the many interconnections between different areas. Several collaborative projects were started some of which have been specifically identified above.

P.R. Fisk

November 1988

Workshop on Sequential Methods in Statistics

Final Programme

Sunday, 3 July 1988		
7.30 p.m.	Introduction (P. Armitage, P.R. Fisk)	
Monday, 4 July		
9.00 - 10.30	D.O. Siegmund:	Stopping rules for sequential clinical trials
11.00 - 12.30	G.B. Wetherill;	Sequential methods in statistical process control.
2.00 - 3.30	(a) P.K. Sen:	Statistical inference from a stopped clinical trial: the LIPIDS experience.
	(b) R.J. Rowlands	Sequential quality control in clinical laboratories.
4.00 - 5.15	Problem Session I	
	J.R. Whitehead:	Consumer product evaluation.
Tuesday, 5 July		
9.00 - 10.30	J.A. Bather:	A simple model for drug screening programs.
11.00 - 12.30	J.R. Whitehead:	Implementation of stopping rules in clinical trials.
2.00 - 3.30	A.F. Bissell:	Developments in the practice of quality control.
4.00 - 5.15	Problem Session II	
	K. Wallace:	*Monitoring two endpoints.*
Wednesday, 6 July		
9.00 - 10.30	M.H. Gail:	Sequential experimentation in epidemiology.
11.00 - 12.30	(a) C. Jennison:	Sequential methods for more than two treatments.
	(b) U. Rendtel:	Some generalizations of Cusum-schemes and their use in process control sequential acceptance sampling.
Thursday, 7 July		
9.00 - 9.45	R. Franke:	QSAR methods.
9.45 - 10.30	J.C. Gittins:	Sequential methods in quantitative structure activity relationships
11.00 - 12.30	D.J. Spiegelhalter and L.S. Freedman:	A comparison of Bayesian and likelihood methods with classical sequential analysis.
2.00 - 3.30	R. Mead:	The design of series of experiments.
4.00 - 5.15	Problem Session III	
	D.R. Jones:	Longitudinal studies in epidemiology.
Friday, 8 July		
9.00 - 10.00	(a) M. Woodroofe:	Very weak expansions for sequentially designed experiments in linear models
	(b) M. Sjöstrom:	QSAR methods and chemometrics.

10.00 - 10.30	Discussion Session I M.H. Gail	Sequential methods in clinical trials.
11.00 - 12.00	(a) S.J. Pocock:	Stopping rules and problems in clinical trials.
	(b) J. Tipker:	Practical experiences with QSAR methods.
12.00 - 12.30	Discussion Session II P. Armitage:	Sequential methods in clinical trials.
2.00 - 3.30	A.J. Petkau:	Optimal group sequential designs.
4.00 - 5.15	Problem Session IV D.O. Siegmund:	Sequential detection of a change in distribution when initial parameter values are unknown.

Saturday, 9 July

9.00 - 10.30	K.D. Glazebrook:	Stochastic scheduling.
11.00 - 12.15	A.G. Baker;	Have we been measuring the important risks?
12.15 - 12.45	P. Reynolds	Sequential experimentation in crystallography.

Monday, 11 July

9.00 - 9.45	H. Chernoff:	Comments on principles, old results and some current issues.
9.45 - 10.30	P.K. Sen:	Animal abundance, sequential tagging, stopping times and estimation problems.
11.00 - 11.45	S. Gilmour:	Sequential design of saturated factorial experiments.
11.45 - 12.30	J. Eales:	Optimal stopping boundaries.
2.00 - 2.45	Ramkaran Singh:	Sequential confidence interval estimation of binomial parameter.
2.45 - 3.30	C. Jennison:	Repeated confidence intervals.
4.00 - 4.40	D.N. Geary:	Sequential testing in clinical trials with repeated measurements.
4.40 - 5.15	T. Sellke:	Behaviour over time of the Kaplan-Meier estimate of probability of survival to a particular age.

Tuesday, 12 July : Discussion Sessions

9.00 - 12.45	III: M. Woodroofe:	Ordering of points on boundary for confidence intervals.
	IV: J.R. Whitehead:	Interval estimation of individual treatment means following sequential comparison of treatments.
	V: R. Mead:	Factorial designs in clinical trials
2.00 - 5.00	VI: M.H. Gail, D.R. Jones, R.J. Rowlands and D.O. Siegmund:	Monitoring routinely collected incident count data.
	VII: P. Armitage:	Adaptive treatment allocation.

Wednesday, 13 July : Discussion Sessions

9.00 - 12.00	VIII:A.J. Petkau:	Sequential selection methods for more than two treatments.
	IX: A.G. Baker:	Statistics in industry.
	Summary of workshop topics (P. Armitage)	

OPEN FORUM

Thursday, 14 July

9.00 - 9.15	Introduction (P. Armitage, P.R. Fisk)	
9.15 - 10.30	D.O. Siegmund:	Tests and confidence intervals for sequential clinical trials.
11.00 - 11.30	D. Edelman:	A candidate for locally most powerful sequential t-test.
11.30 - 12.00	N. Schmitz:	New results on group sequential methods.
12.00 - 12.30	J.R. Whitehead;	Summary and discussion on stopping-rule topics.
2.00 - 3.30	J.A. Bather:	"Great expectations"
4.00 - 4.45	D.S. Coad	Outcome-dependent allocation in clinical trials with instability in the response variable.

Friday, 15 July

9.00 - 9.45	S.K. Thompson:	Sequential sampling designs: some applications in a spatial setting.
9.45 - 10.30	J.C. Gittins:	Multi-armed bandit allocation indices.
11.00 - 12.30	G.B. Wetherill:	Sequential methods in statistical process control.
12.30 - 12.45	Concluding remarks (K.D. Glazebrook)	

RESEARCH WORKSHOP ON SEQUENTIAL METHODS IN STATICS
4TH - 15TH JULY 1988.

A	Professor P. Armitage	B	Professor A.J. Petkau
F	Mr A.G. Baker	C	Professor S.J. Pocock
C	Professor J.A. Bather	B	Dr U. Rendtel
F	Dr A.F. Bissell	E	Dr R.J. Rowlands
B	Professor H. Chernoff	D	Professor Dr D.N. Schmitz
D	Professor Dr. R. Franke	D	Proessor T. Sellke
D	Dr L.S. Freedman	B	Professor P.K. Sen
B	Dr M.H. Gail	B	Professor D.O. Siegmund
E	Dr N. Geary	B	Dr Ramkaran Singh
B	Professor B.K. Ghosh	B	Dr M. Sjöström
C	Dr J.C. Gittins	C	Dr D.J. Spiegelhalter
F	Mr K. Wallace	F	Dr J. Tipker
A	Dr K.D. Glazebrook,	C	Dr R.R. Weber
C	Dr C. Jennison	C	Professor G.B. Wetherill
C	Dr D.R. Jones	A	Dr J.R. Whitehead
D	Professor Dr W. Koepcke	D	Professor M. Woodroofe
C	Professor R. Mead		

KEY TO STATUS

A	Academic Organisers	D	Important Overseas Participants
B	Essential Overseas Participants	E	Important UK Participants
C	Essential UK Participants	F	Short-stay participants

List of Ph.D. student observers (self-supporting)

Mr D.S. Coad

Mr J.D. Eales

Miss K.M. Facey

Mr N. Fay

Mr S.G. Gilmour

Mr S. Kirby

Mr P. Reynolds

LIST OF FORUM PARTICIPANTS

Dr M.K. Al-Banna

Mr L. Benkherouf

Mr A. Butler

Dr A.D. Carothers

Dr D. Edelman

Mr J.R. Ennis

Mr G. Eslava-Gomez

Dr I.B.J. Goudie

Mr K.J. Gough

Mr Salah Merad

Dr C.M. Theobald

Mr S.K. Thompson

Mr D. Waddington

Dr C.H. Zhang

Mr R. Thompson

Forword

These notes provide a summary account of the talks given at a research workshop on Sequential Methods in Statistics held at the University of Edinburgh from 4 July to 15 July 1988. The summary for each talk was supplied by the speaker and gives an outline guide to the topics discussed at the workshop. Further information can be obtained from the relevant speaker directly.

The workshop was organised by Professor P. Armitage, Dr. K.D. Glazebrook and Dr. J.R. Whitehead with local organisation by P.R. Fisk, G. Cohen and J.C. Duffy. Funds were supplied by the Science and Engineering Research Council and the U.S. Army Research, Development and Standardization Group (U.K.).

P.R. Fisk

RESEARCH WORKSHOP ON SEQUENTIAL METHODS IN STATISTICS

LIST OF SUMMARIES OF TALKS:

Tony Baker	:	Have we been measuring the important risks
J.A. Bather	:	A simple model for drug screening programs
A.F. Bissell	:	Developments in the practice of quality control
Herman Chernoff	:	Comments on principles, old results and some current issues
John Eales	:	Optimal stopping boundaries
R Franke	:	QSAR methods
M. Gail	:	Sequential experimentation in epidemiology
M.H. Gail et al	:	Monitoring routinely collected incident count data
Norman Geary	:	Sequential testing in clinical trials with repeated measurements
Steven Gilmour	:	Sequential design of saturated factorial experiments
J.C. Gittins	:	Sequential methods in quantitative structure activity relationships
K.D. Glazebrook	:	Stochastic scheduling
C. Jennison	:	Repeated confidence intervals
C. Jennison	:	Sequential methods for more than two treatments
Rodger Mead	:	Design of series of experiments
A. John Pethau	:	Optimal group sequential designs
S.J. Pocock	:	Stopping rules, estimation problems and reporting bias in clinical trials
Ulrich Rendtel	:	Some generalisations of cusum-schemes and their use in Process Control and Sequential Acceptance Sampling
Paul Reynolds	:	Sequential experimentation in crystallography
R.J. Rowlands	:	Sequential quality control in clinical laboratories
Thomas Sellke	:	Behaviour over time of the Kaplan-Meier estimate of probability of survival to a particular age
Pranab K. Sen	:	Animal abundance, sequential tagging, stopping times and estimation problems
Pranab K. Sen	:	Statistical Inference from a stopped clinical trial: the LIPIDS experience

David Siegmund	:	Stopping rules for sequential clinical trials
Ram Karan Singh	:	Sequential confidence interval estimation of binomial parameter
Michael Sjostrom	:	QSAR methods and chemometrics
D.J. Spiegelhalter and L.S. Freedman	:	A Comparison of Bayesian and likelihood methods with classical sequential analysis.
G.B. Wetherill	:	Sequential methods in statistical process control
John Whitehead	:	Implementation of stopping rules in clinical trials
Michael Woodroofe	:	Very weak expansions for sequentially designed experiments in linear models

HAVE WE BEEN MEASURING THE IMPORTANT RISKS?

Tony Baker,8 Melloncroft Dr.,Caldy,Wirral L48 2JE

Summary

Statisticians,because of the limited tools available,have been limited in what they could do. For example:-
1)The literature is not very concerned about methodology for exploring the properties of the system being studied.
2)Practical tools for measuring the chances of project success are underdeveloped, though the theory of "one armed bandits" has made great strides.
Illustrative examples will be given.

Nowadays a number of very useful tools have come together which can help in the assessment of risks. Since retirement at the end of 1987,my research has been the assembling of D.I.Y. tools in the field of R&D Product Development and the Chances of Success.I am now seeing wnether the tools are of interest to R&D Departments. Such research is obviously practical. It is my view that there will have to be more practical research in statistics if the full benefit of the theoretical research is to be won. The tools are methods for :-

1) assessing the distance of a project from target.
2) assessing the chances of a project being successful.
3) aiding the communication using numbers,so that risks can more easily be discussed.
4) D.I.Y. Taguchi designs
5) extending the application of Taguchi designs so that high risk parts of a project can be tackled earlier in the project.
6) demonstrating the quality of measurements.

Computer software is increasingly taking over some of statisticians' work. It helps to reduce the cost of the statistical contribution and removes the more tedious part of the work. The trend is continuing, thus statisticians have to consider in what ways they wish their subject to develop. My view is that the important developments will be in:-

a) Risk management & quality.
b) The preparation of D.I.Y.software for specific problems e.g. a "working" data base for a given set of laboratory test protocols.
c) Decision Theory along with practical tools for using it.
d) Design of studies/projects and experiments.
e) Statisticians arguing for and designing data bases.
f) Moving away from averages to risks and patterns.

Such developments will be important in medical,social,commercial and industrial research.

Illustrative examples will be given.

ABSTRACT

A Simple Model for Drug Screening Programs.

J.A. Bather

The aim of this talk is to present some joint research with A.J. Petkau. A scenario involving a large, and continuously augmented, number of agents available for testing is relevant to designing both drug screening programs and phase II clinical trials. The objective is to identify promising agents for further study, while eliminating less promising agents with a minimum of testing. Suppose testing an agent corresponds to observing a segment of the path of a Wiener process with unknown drift and known variance. For a sequence of drift parameters with a given prior distribution and specified reward functions, the objective is a policy maximizing the infinite horizon expected average reward per unit time. The simple version of this problem with a two-point prior can be solved explicitly and provides some general insight. We suppose a reward is received whenever the final decision concerning an agent is taken, and costs are incurred for inappropriate decisions. A direct approach yields a description of the optimal fixed sample size procedure and an indirect method based on a potential reward function yields the corresponding results for sequential procedures. The performance of these sequential procedures is examined in detail.

A B S T R A C T

Developments in the Practice of Quality Control

A F Bissell

The basic techniques of Quality, centred around the control chart, are alive and well. With the enormous surge of interest in Statistical Process Control, they are now more widely used than ever before - and by more people than ever before.

Whilst most theoretical interest focuses on more sophisticated techniques, usually computer-dependent, developments in the manner of using the techniques 'on the shop floor' have also taken place and need to be recognised.

These developments include:-

(a) The use of addition rules for conventional control charts, to sharpen their detection of real anomalies albeit at higher risk of false alarms.

(b) The use of lower control limits for attribute/event control charts, to monitor for process improvement.

(c) Simplifications and adaptations to Cusum methods to widen their range of application.

(d) Simplification of ANOVA-type methods to identify and measure levels of common-cause variation.

(e) Adaptation of diagnostic tests for instability to encourage their routine use in process control.

I shall review (a), (c) and (d), offer a new form of presentation for (b) and discuss (e) in rather more detail. There is scope for theoretical consolidation in this area.

COMMENTS ON PRINCIPLES, OLD RESULTS AND SOME CURRENT ISSUES

The proper understanding of sequential procedures requires interpretation from a decision theoretic point of view with explicit consideration of reasonable approximations to costs. The explicit consideration of ethical costs in clinical trials represents a difficult problem for political reasons. Bayesian interpretations of sequential procedures are also almost essential to avoid the danger of foolish procedures.

Old results which deserve more attention in sequential experimentation than has been received in this workshop involve the use of the Rullback Leibler information in sequential experimental design.

Two technical problems mentioned here can be treated in terms of modifying the posterior risk in Bayesian analysis of optimal stopping problems. One is that of estimating an unknown mean if the terminal decision is that it is positive. The other is coping with delayed observations due to arrive after the decision to stop experimentation has been made.

Abstract of my presentation on Monday July 11, 1988

Herman Chernoff

OPTIMAL STOPPING BOUNDARIES

John Eales Bath University

We look at the problem where

$$X_1, X_2, \ldots \sim N(\theta, \sigma^2) \quad X_i\text{'s indep} \quad (\sigma^2 \text{ known})$$

We wish to test

$$H_0 : \theta = \emptyset \quad \text{vs} \quad H_1 \quad \theta \neq \emptyset$$

With error probabilities

$$P_R(\text{Accept } H_1 \mid \theta = \emptyset) = \alpha$$

$$P_R(\text{Accept } H_0 \mid \theta = \quad) =$$

We consider a group sequential test solution with a maximum of k groups each of size n.

Tests are derived which are optimal in the sense that they minimize a given objective function expected sample size under the alternative hypothesis for example.

R. Franke

QSAR Methods

The contribution will focus on the following topics:

1. Objectives and general strategy in QSAR works.
   Different situations (briefly outlined) require different method ("QSAR tool kit")

2. Multiple regression analysis
   - some aspects of variables
   - problem of collinearities and multicollinearities
   - series design
   - finding the "best" equation
   - chance correlations
   - interpretation or prediction?
   - outliers

3. Data from a battery of biological tests
   - factor and principal component analysis
   - PLS (will only briefly be mentioned since this technique will certainly be discussed in detail by Sjöström)
   - for discrete biological data: the use of information theory

4. Non-elementary discriminant analysis

5. The use of topological descriptors in QSAR work (usually logical variables directly derivable from two-dimensional chemical structures)
   - KNN method and linear learning machine (only brief discussion concentrating on the shortcommings of these methods)
   - logical procedures

6. The problem of treating drug-receptor interactions as they occur in reality and some open questions
   - what happens at a receptor
   - the role of conformation and flexibility of molecules
   - methods based on considering the volume of molecules (Simon, Hopfinger, Marshall)
   - comparing electrostatic potentials
   - DYLLOMS approach

In all cases it will be tried to outline the relative merits and, especially, problems and limitations of the various methods with the help of selected examples. The emphasis is always on application from a chemists point of view. The mathematical framework of the various methods will only briefly be mentioned and not be discussed in detail.

The following methods which also have been used in QSAR work will not be discussed: cluster analysis, non-linear mapping, canonical correlation, principal component regression, SIMCA, non-linear regression and the more special methods presented in chapter 1 of "Statistical Methods for Pharmaceutical Research Planning" (S.W. Bergman and J.C. Gittins).

M. Gail

6/27/88

Sequential Experimentation in Epidemiology

In this talk we define "epidemiologic studies" as non-experimental observational studies on humans. Formal sequential hypothesis testing has rarely been used to monitor such studies because there is no ethical imperative to end experimentation abruptly, because estimation plays a more important role than hypothesis testing, and because other scientific concerns, such as controlling for confounding and measurement errors and checking for consistency of associations across subgroups and for dose response effects, are paramount. Nonetheless, sequential data acquisition and interpretation are important: (1) for selected case-control studies of acute disease, where formal sequential hypothesis testing procedures have been proposed, (2) for the evaluation of pilot studies in determining how much additional experimentation will be required to obtained a desired amount of Fisher information, and (3) for assessing whether continued study is warranted following a major analysis. Perhaps the most effective use of sequential experimentation in epidemiology is the case-control design itself, and recent extensions, which allow one to sample covariates efficiently, based on available information on disease outcome for all members of the population.

ABSTRACT

SEQUENTIAL TESTING IN CLINICAL TRIALS WITH REPEATED MEASUREMENTS

NORMAN GEARY

Armitage, Stratton and Worthington (Biometrics, 41, 353-9, 1985) discuss how to choose appropriate intermediate significance levels when testing in clinical trials with repeated measurements. The dental clinical trial motivating their discussion is described. The trial was designed to compare two toothpaste treatments with respect to their effect on tooth decay. The number of subjects (12 year-old children) on each toothpaste was fixed at the outset of the trial, and tooth decay was measured in each subject at equally-spaced times (every year for 3 years).

A model for such repeated measurements data is described. A sequential procedure is proposed (as in Geary, Biometrika, 75, 311-8, 1988) for testing the null hypothesis of no difference in mean effect between two treatments. In this procedure, the maximum number of measurements per subject and absorption probabilities for intermediate tests are preassigned to yield a required overall significance level. The j^{th} significance test follows the j^{th} measurement on each subject, and the test depends on values of model parameters estimated from all the data available so far. Simulations show that the proposed procedure yields overall significance levels close to 5% when required, for data from a variety of models.

MONITORING ROUTINELY COLLECTED INCIDENT COUNT DATA

M.H. GAIL, D.R. JONES, R.J. ROWLANDS AND D.O. SIEGMUND

Annual incidence counts are collected and monitored to detect secular changes in rates for a variety of diseases, including cancers of various sites and congenital anomalies. We discuss some problems with using routinely collected data to detect changes in disease rates. Very unusual diseases may be obscured in routine data collection and data management.

A sudden increase in disease causing exposures may reflect itself in a gradually increasing trend in rates, rather than as a "change point". Some results based on Poisson regression will be given under the assumptions that baseline rates are known and that the origin of change is known, and other regression calculations will be given for the case when baseline rates must be estimated and when the point of origin is known with error. The major discussion will focus on Cusum techniques and their strengths and weaknesses when baseline rates must be estimated and when rates are increasing gradually, rather than at a sudden "change point".

ABSTRACT

STEVEN GILMOUR

SEQUENTIAL DESIGN OF SATURATED FACTORIAL EXPERIMENTS

The use of sequences of saturated factorial designs to reach an optimal response has been described by Professor Mead. Here, a particular case will be considered in more detail. Having performed an initial saturated fractional factorial, the possibilities for the next experiment include:

(i) taking a fractional from the same "family" to free certain effects - Davies and Hay (1950)

(ii) taking a fractional from a different family

(iii) using ideas similar to those of Daniel (1962) to break particular alias chains

(iv) holding a factor at its better level

Some simulation results will be presented.

Davies O.L., and Hay W.A., (1950): The Construction and uses of Fractional Factorial Designs in Industrial Research, Biometrics, 6, 233-249

Daniel C., (1962): Sequences of Fractional Replicates in the 2^{p-q} series, JASA, 57, 403-429

ABSTRACT

STEVEN GILMOUR

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(iv) holding a factor at its better level

Some simulation results will be presented.

Davies O.L., and Hay W.A., (1950): The Construction and uses of Fractional Factorial Designs in Industrial Research, Biometrics, 6, 233-249

Daniel C., (1962): Sequences of Fractional Replicates in the 2^{p-q} series, JASA, 57, 403-429

STOCHASTIC SCHEDULING

by

K.D. Glazebrook

ABSTRACT

By a family of alternative bandit processes is meant a cost-discounted Markov decision process with the following special features:

(a) Its state at time $t \in \mathbb{N}$ is $x(t) = \{x_1(t), x_2(t), \ldots . x_N(t)\}$ where $x_j(t) \in \Omega_j$ the (general) state space for job j, $1 \leq j \leq N$.

(b) The action space A is $\{a_1, a_2, \ldots . a_N\}$. Action a_j denotes the application of same key resource to job j. An action is taken at each time $t \in \mathbb{N}$.

(c) If action a_j is taken at time t only the j^{th} component of $x(t)$ changes. Hence $x_i(t+1) = x_i(t)$, $i \neq j$, and $x_j\{t+1\}$ is determined according to a Markovian law of motion $P_j\{x_j(t)\}$.

(d) The transition of the process under action a_j described in (c) earns a reward $a^t R_j\{x_j(t), x_j(t+1)\}$ where $0 < a < 1$. The functions $R_j : \Omega_j \times \Omega_j \to \mathbb{R}$ are assumed to be bounded.

(e) An optimal strategy is any rule for choosing actions which maximises the total expected reward.

Such decision processes have been used to model situations in which a decision-maker has to make choices among a fixed number of options (jobs), each of which evolves stochastically. Such situations arise in research planning (see, for example, Nash (1973)), search problems (Gittins (1979)) and computer scheduling (Bruno and Hofri (1975)).

Gittins and Jones (1974) demonstrated that optimal strategies for the decision process (a) - (e) are determined by a collection of Gittins' indices.

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Sequential methods for more than two treatments

by C. Jennison

University of Bath, UK

This talk will discuss several problems involving the sequential comparison of more than two treatments:

1. The selection of the Bernoulli population with the largest success probability.
2. The selection of the Normal population with the largest mean.
3. The sequential F- and χ^2- tests.

These problems would be regarded by many as "theoretical" despite their practical motivation. The concluding discussion will concern the practical requirements of procedures for comparing several treatments.

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Roger Mead

Dsg.SeriesExp'ts

The Design of Series of Experiments

In an industrial process there will usually be a large number of factors involved and the overall objective is identification of the optimal combination of factor levels. Experimentation progresses through a sequence of small sets of experimental observations (set = experiment) comprising unreplicated, treatment combinations. At each stage of the sequence there are several questions prior to the next experiment:–

(i) whether to stop

(ii) which factors to vary in the next experiment,

(iii) which levels (of each factor) to use (relevant to quantitative factors only)

(iv) which set of treatment combinations to use.

Some of the possible approaches to these questions will be considered.

A further aspect is the consideration of noise factors which are not controllable and consequently not of direct interest, but which represent some of the variation to be expressed in the environment in which the proposed optimal treatment is to be applied.

STOPPING RULES, ESTIMATION PROBLEMS AND REPORTING BIAS IN CLINICAL TRIALS

Stuart J Pocock and Michael D Hughes

Clinical Trials Research Unit,
Royal Free Hospital School of Medicine,
London NW3 2PF,
United Kingdom

SUMMARY

This paper considers some of the practical problems inherent in interim analyses and stopping rules for randomized clinical trials. Topics covered include group sequential designs, trials with unplanned interim analyses, estimation problems in trials with planned interim analyses and the balance between individual and collective ethics. Particular attention is paid to the fact that trials that stop early are prone to exaggerate the magnitude of treatment effect. Accordingly, a Bayesian "shrinkage" method of analysis is proposed to help quantify the extent to which surprisingly large point and interval estimates of treatment difference in trials that stop early should be moderated.

Keywords: Clinical trial, interim analyses, stopping rules, estimation, reporting bias.

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SOME GENERALIZATIONS OF CUSUM-SCHEMES AND THEIR USE IN PROCESS CONTROL AND SEQUENTIAL ACCEPTANCE SAMPLING

Ulrich Rendtel, Berlin, West-Germany

CUSUM-schemes may be used in situations, where a production process is expected to switch at an unknown time τ from an in-control state θ_S to an out-of-control state θ_A. As soon as one has evidence that the out-of-control state has occurred, one wishes to stop the production process to perform some corrective action. We get information about the true state θ_t of the production process at time t by observing a variable x_t with p.d.f. $f(x \mid \theta_t)$.

A CUSUM-scheme may be written in terms of likelihood ratios:

$$Q_0 = 1$$

$$Q_t = \max\left\{1,\ Q_{t-1}\frac{f(x_t \mid \theta_A)}{f(x_t \mid \theta_S)}\right\} \qquad t \geq 1$$

The production process is stopped if Q_t exceeds a preassigned value h. Running this scheme is equivalent to the performance of a sequence of SPRT's with lower bound 1 and upper bound h: The SPRT's are started at the lower bound. Each time the likelihood ratio crosses the lower decision boundary, the hypothesis is accepted that the production process is still in the in-control state θ_S and a new SPRT is started. Finally the last SPRT crosses the upper decision boundary. This leads to the assumption that the production process has reached the out-of-control state θ_A during the last SPRT.

CUSUM-schemes work at a fixed inspection level, i.e. the p.d.f. $f(\cdot \mid \theta)$ is constant over time. In quality control this means that the number of inspected items per time unit is a constant.

Now suppose that the value of Q_t is small. According to the maximum-likelihood-principle this indicates that the production is in the in-control-state. In this situation frequent inspection is unnecessary. On the other hand, a high value of Q_t indicates that production may be out-of-control. In this situation inspection should be frequent so as to give precise information about the true state of production. In order to save unnecessary inspection efforts one can introduce a decision rule based upon the last value of Q_t, which determines the next sampling interval and the sample size for the next observation.

It may be shown that there are inspection schemes with almost the same run length properties as ordinary CUSUM-Schemes, but with considerably reduced inspection efforts. Such generalized CUSUM-Schemes may be used to improve the Switching Rules of existing adaptive sampling procedures like the Military Standard 105 D.

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Rendtel, U. 1987: The Use of Generalized CUSUM-Schemes to Control the Percent Defective of a Continuous Production Process, in: Lenz, Wetherill, Wilrich (eds.): Frontiers in Statistical Quality Control 3, Physica Verlag, Heidelberg.

SEQUENTIAL EXPERIMENTATION IN CRYSTALLOGRAPHY

PAUL REYNOLDS
DEPARTMENT OF STATISTICAL SCIENCE
UNIVERSITY COLLEGE LONDON

This work has developed as part of a long-standing co-operation between the Crystallography Unit of the Department of Geological Sciences and the Department of Statistical Science at University College London

Crystallography may simplistically be described as the science of 'firing X-rays at things (crystals) to see what they look like'. Less simplistically, the diffraction effects obtained when X-rays pass through a crystal may be studied in order to estimate atomic co-ordinate positions. The statistician (naturally enough) is concerned with the underlying statistics.

The basic idea is that a trial atomic configuration may be refined by including additional relevant data at each stage. In practice, a stage is suddenly reached when the structure is essentially correct, and most or all of the remaining accessible data could now be included. This immediately suggests that much of it will be redundant, and unless data collection is a zero-cost activity, data should now only be sampled rather than measured in toto.

The essential feature of sequential experimentation is that the data collection strategy is modified by information gained from data already collected. The best way to utilise this information is still very much an open problem.

BEHAVIOUR OVER TIME OF THE KAPLAN MEIER ESTIMATE OF PROBABILITY OF SURVIVAL TO A PARTICULAR AGE

PROFESSOR THOMAS SELLKE
PURDUE UNIVERSITY

Consider a staggered-entry clinical trial in which survival times are independent and identically distributed with distribution F. Suppose also that entry times and censoring times are independent of the survival times. I will state and discuss a conjectured theorem according to which, conditional on the entry times and censoring times, the Kaplan-Meier estimate of the probability of survival to a particular age (say 5 years) behaves over time approximately like a backwards Brownian motion when the estimated variance of the Kaplan-Meier estimate is used as a clock time. An analogous result should hold for the estimated difference in survival probability when two treatments are being compared. An especially interesting feature of the proposed result is that virtually no assumptions are made about the entry or censoring times beyond the assumption that they are independent of survival times.

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ANIMAL ABUNDANCE, SEQUENTIAL TAGGING, STOPPING TIMES AND ESTIMATION PROBLEMS.

Pranal K. Sen
University of North Carolina, Chapel Hill, NC27599, USA

The CMRR method is quite popular in the estimation of a finite population size. Sequential tagging schemes play a vital role in this context. Unlike the case of the classical sequential procedures, the efficacy of the sequential tagging is somewhat limited to the case of a smaller proportion of "captures". Asymptotic properties of such procedures are more conveniently studied with the help of martingale theory. In the context of asymptotically minimum risk (point) estimation and fixed-percentage width confidence intervals, different forms of stopping numbers arise, and their asymptotic theory calls for further refinements of the martingale approach. These are discussed in detail. Most of these results are adapted from
Sen (1987): REBRAPE, Vol 1, No. 2, pp. 113-130

STATISTICAL INFERENCE FROM A STOPPED CLINICAL TRIAL : THE LIPIDS EXPERIENCE

PRANAB K. SEN , University of North Carolina at Chapel Hill, USA

Because of the intricacies of an early stopping of a clinical trial (on medical as well as statistical considerations), the conventional methods of drawing statistical conclusions from the accumulated (partial) data set (prior to plausible early stopping of the trial) may not be that efficient or even properly valid in a variety of cases. For example, in a comparative clinical trial (relating to a Placebo vs. Treatment setup), when an early stopping is achieved in favor of the null hypothesis (of no effective difference between the treatment and control groups) or the alternative hypothesis (of a significant treatment effect), a convensional estimator of the treatment effect based on the stopped experimental data may be seriously biased or even be inconsistent. A more serious problem may arise when one wants to set a confidence interval for a parameter θ (of practical importance) following an early termination of a clinical trial where the stopping rule was designed to suit an hypothesis testing problem relating to the same parameter. In general, we may not have proper control over the coverage probability or the optimality (i.e., shortness) property of such an interval estimator.

As was the case with the LIPIDS Study , statistical monitoring of clinical trials is being increasingly adapted in practice (for quality control of incoming (relatively non-homogeneous) data sets from multiple clinics or centers , close watch on the toxicity or other possible side effects of the treatments, and for early termination of the study based on accumulating statistical evidence). In this context, Interim Analysis is usually done on a fixed-time interval scale or in some other unconventional group sequential manner. This raises the need for full assessment of the implications of early stopping in such a clinical trial (with respect to the validity and efficiency of statistical conclusions to be drawn from the acquired data set). The main difference between this setup and a conventional sequential case relates to the following :

(i) Violating the usual statistical considerations, often, toxicity or other side effects may dictate an early stopping of the trial, and hence, based on such a stopped trial, the conventional sequential estimation or decision rules may not be properly valid or tenable;

(ii) Generally, a clinical trial may have multiple objectives, where,of course, one or a few ones may be of primary importance, although the others are worthy of stu In such a case, an early stopping may rest on a hypothesis testing setup with respect

to a subset of the parameters, while from a stopped clinical trial one may naturall want to draw conclusions for the entire set of parameters;

(iii) A multi-center clinical trial is typically of a limited (i.e, short) time duration, and it is typically of a 'follow-up' study form. This means that the data set obtained from such a study relates only to a part of the distribution, usually censored from the right. These naturally introduce some constraints on the form of the stopping rules. Coupled with (i) and (ii), (iii) may raise serious doubts about the adequacy of the over-simplified situation based on the simple Brownian motion processes.

(iv) As was the case with the LIPIDS, simultaneous entry of the sujects into the study scheme is rarely the case. In a staggering entry plan (with possibly random entry-points) , there are some complications. First, instead of the usual one-dimensional time parameter processes, one may have two-dimensional ones. It may be possible to reduce such a process to an one-dimensional one by some reduction of data process, but such a process may be highly non-homogeneous in nature. This, in turn, may introduce further complications in the formulation of statistical analysis procedures.

(v) Drop-outs or withdrawals are also quite common in such clinical trials. Many a time, drop-out patterns may vary from the control to the treatment groups. As such, the usual assumption of random censoring may not be that tenable. Thus, there may be a genuine need for developing statistical methodology for stopped clinical trials accommodating more complicated censoring patterns.

(vi) As is the case with most controlled clinical trials, in the LIPID Study too, effective control was maintained by keeping track of a (moderately large) number of covariates [e.g., blood pressures, various body chemistry levels, occupation, diet, physical exercise ,sex, age etc], some of which are binary or discrete in character, and some even are time-dependent. Incorporation of such a set of covariates into the basic model appropriate for both the hypotheses testing and estimatio problems is a formidable task. The model must have simple physical interpretation and at the same time it must be enough flexible to allow the utilization of not too complicated statistical analysis systems. The proportional hazard model or the Cox-life table (regression) model is ,of course, one possible way of handling such schemes. But, the assumption of proportionality of hazard functions (under the regression setup with the covariates) may not be universally valid. In fact, often, it is found to be unsuitable (i.e., there may be cross-over hazards). Thus, it may be more appropriate to consider alternative models which allow non-proportionali of hazard functions to a greater extent and at the same time lend to more robust analysis prospects. This is a very important criterion.

(vii) What may be an optimal stopping rule for a simple testing problem (relating to a primary statistical hypothesis), may not be so for a greater perspective when multiple decisions (viz., estimation problems) are contemplated in the overall objectives of the study. This issue is particularly crucial when one encounters an estimation problem following a stopped clinical trial. The question is therefore : How to formulate optimality criteria for stopping rules in clinical trials when one may have multiple objectives and when complications [due to the causes explained in (i) through (vi)] may arise from other pertinent factors?

Based on all these considerations, it is felt that nonparametric models may workout better for such clinical trials, and in this context, some studies are reported in Chapter 11 of Sen [Sequential Nonparametrics ; Wiley, New York, 1981] and Chapter 2 of Sen [Theory and Applications of Sequential Nonparametrics; SIAM, Philadelphia, 1985]. In both these places, the main emphasis has been placed on the time-sequential testing problems. In the last few years, there has been some work on the related time-sequential estimation problems, and these will be also included in the discussion in this Workshop. For a detailed report on the main medical issues (along with some statistical points) involved in the LIPIDS Study [undertaken by the Department of Biostastistics, University of North Carolina at Chapel Hill, under contract from the National Heart, Lung and Blood Institute, N.I.H. during the active period of 1972-1984] we may refer to the article on this in the New England Journal of Medicine in 1984. Along with some further statistical comments on these findings, the main issue to be discussed would relate to the various estimation problems which are now being encountered for this stopped trial.

Sequential Confidence Interval Estimation of Binomial Parameter

Ramkaran

Lucknow University, Lucknow, India.

ABSTRACT: This paper deals with the problem of sequential confidence interval estimation of the binomial parameter p in the Bayesian decision theoretic framework. Two methods have been discussed namely (i) overall optimal procedure based on Bellman's principle of optimality and (ii) one-step optimization procedure. A conjugate prior has been assumed for the parameter p. The loss function takes into account the width of interval, non-coverage probability and the cost of sampling. The optimal design which is made up of the optimal stopping rule and optimal terminal rule has been obtained under the above loss structure. The second method gives a very satisfactory approximation of the first. It saves substantial computing time and the increase in risk due to approximation is minimal. In view of this, approximate method could be highly recommended for practical purposes.

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D2.152 28th June 1988

A COMPARISON OF BAYESIAN AND LIKELIHOOD METHODS WITH CLASSICAL SEQUENTIAL ANALYSIS

D. J. Spiegelhalter and L. S. Freedman

Abstract

We describe some problems with applying methods based on classical sequential analysis to monitoring clnical trials. A Bayesian method is develped and the boundaries are compared with frequentist schemes. For the example chosen, the Bayesian boundaries are quite similar to those obtained from Pocock and O'Brien and Fleming rules. In general the Bayesian methods provide the same desitrable features as frequentist methods, without sacrificing flexibility and simplicity of interpretation.

Key words: clinical trials, sequential methods, stopping rules, Bayesian methods.

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SEQUENTIAL METHODS IN STATISTICAL PROCESS CONTROL

G Barrie Wetherill

In this talk the basic ideas of statistical process control, including Shewhart and CuSum charts were outlined. The distinction between how this applies to component manufacturing industries and the process industries was then made. The type of process variation and possible models for process industry data were discussed.

Following this the talk outlined the theory behind current investigations into the properties of charts. Basically these reduce to Markov chain models, or integral equations for the ARL. In the light of known conditions in the process industries it turns out that there are large gaps in our knowledge. Moving average charts are of special use for the process industries, and their properties are particularly difficult to calculate.

The concept of process capability was also discussed. This particular concept also needs modification for the process industries.

In a final section, some problems needing further work were outlined.

Two bibliographies were attached to the paper, one for the Shewhart and allied charts, and one for cumulative sum charts.

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VERY WEAK EXPANSIONS FOR SEQUENTIALLY DESIGNED EXPERIMENTS IN LINEAR MODELS

By

Michael Woodroofe*

The University of Michigan

ABSTRACT

In sequentially designed experiments with linear models, each design variable may depend on previous responses. The use of such sequential designs does not affect the likelihood function or the functional form of the maximum likelihood estimator, but it may affect sampling distributions. In this paper, asymptotic expansions for sampling distributions are obtained. The expansions are very weak ones in which a confidence curve (a function of the unknown parameters) is replaced by a confidence functional defined on a class of prior distributions. The proofs use a version of Stein's Identity.

Key words and Phrases: martingale convergence theorem; maximum likelihood estimators; posterior distributions; Stein's identity.

AMS (1980) Classification: primary 62E20; secondary 62F12, 62L05

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