

***Interim Monitoring of Clinical Trials: Decision Theory,  
Dynamic Programming and Optimal Stopping***

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## Plan of talk

1. Monitoring clinical trials
2. Sequential distribution theory
3. An optimal stopping problem
4. Numerical evaluation of stopping boundaries
5. Finding optimal group sequential designs
6. Related problems:

*Adaptive choice of group sizes*

*Testing for either superiority or non-inferiority*

*Trials with delayed response*

## **1. Monitoring clinical trials**

A clinical trial is run to compare a new treatment with an existing treatment or placebo.

As the trial progresses, a Data and Safety Monitoring Board (DSMB) monitors patient recruitment, treatment administration, and the responses observed at interim points.

The DSMB can take actions in view of safety variables or secondary endpoints, for example, to drop a treatment arm with a high dose level if this appears unsafe.

Response on the primary endpoint may indicate early termination of the study is desirable, for either a positive or negative conclusion.

## The need for special methods

Multiple looks at accumulating data can lead to over-interpretation of interim results.

Armitage et al. (*JRSS, A*, 1969) report the overall type I error rate when applying repeated significance tests at  $\alpha = 0.05$  to accumulating data:

<i>Number of tests</i>	<i>Error rate</i>
1	0.05
2	0.08
3	0.11
5	0.14
10	0.19

Clearly, a different approach is needed to avoid inflation of the type I error rate.

## Formulating the problem

Let  $\theta$  denote the “effect size”, a measure of the improvement in the new treatment over the standard.

We shall test the null hypothesis  $H_0: \theta \leq 0$  against the alternative  $\theta > 0$ .

Then, rejecting  $H_0$  allows us to conclude the new treatment is better than the standard.

We allow type I error probability  $\alpha$  for rejecting  $H_0$  when it is actually true.

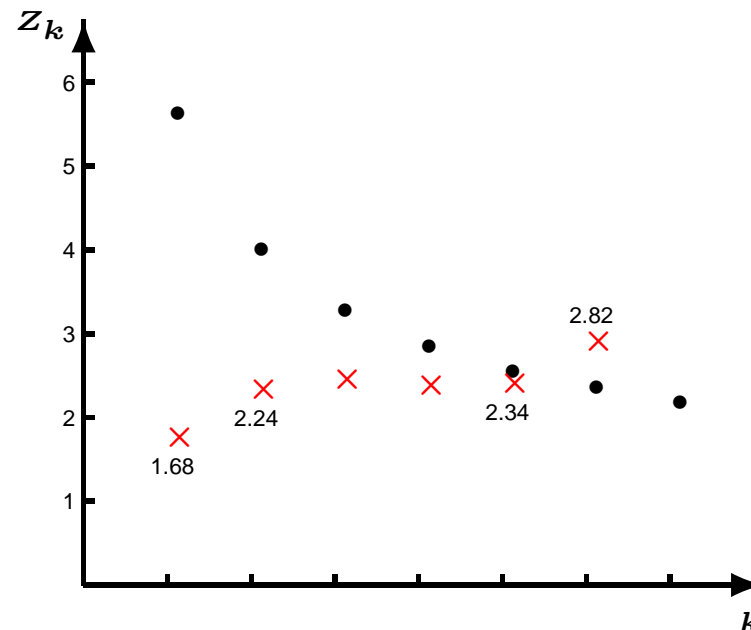
We specify power  $1 - \beta$  for the probability of (correctly) rejecting  $H_0$  when  $\theta = \delta$ . Here,  $\delta$  is, typically, the minimal clinically significant treatment difference.

The trial design, including the method of analysis and stopping rule, must be set up to attain these error rates.

## An early example: The BHAT trial

DeMets et al. (*Controlled Clinical Trials*, 1984) report on the Beta-Blocker Heart Attack Trial, which compared propranolol with placebo.

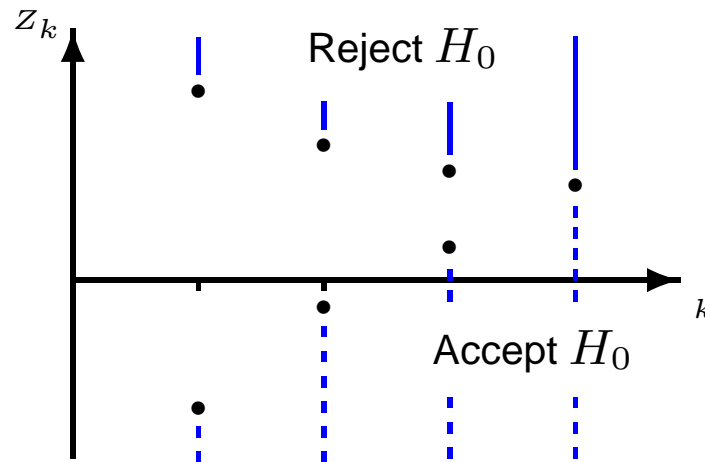
An “O’Brien and Fleming” stopping boundary was defined with overall type I error probability 0.025.



The trial stopped after the 6th of 7 planned analyses.

## Group sequential tests: Stopping for futility

Adding a lower boundary allows stopping when there is little chance of a positive conclusion.



Rosner & Tsiatis (*Statistics in Medicine*, 1989) carried out retrospective analyses of 72 cancer studies of the U.S. Eastern Co-operative Oncology Group.

If group sequential stopping rules had been applied, early stopping (mostly for futility, i.e., to accept  $H_0$ ) could have occurred in around 80% of cases.

## Requirements for clinical trial designs

Regulatory bodies recommend group sequential designs to protect subjects in a clinical trial and produce results as efficiently as possible.

We need designs which:

*Achieve specified type I error rate and power,*

*Stop early, on average, under key parameter values,*

*Can be applied to a variety of response types.*

We shall present distribution theory which shows that a common set of methods can be applied to many data types.

To define efficient tests, we shall formulate and solve an optimal stopping problem.



## 2. Sequential distribution theory

Our interest is in the parameter for the treatment effect,  $\theta$ .

Let  $\hat{\theta}_k$  denote the estimate of  $\theta$  based on data at analysis  $k$ .

The information for  $\theta$  at analysis  $k$  is

$$\mathcal{I}_k = \{\text{Var}(\hat{\theta}_k)\}^{-1}, \quad k = 1, \dots, K.$$

**Canonical joint distribution of  $\hat{\theta}_1, \dots, \hat{\theta}_K$**

In many situations,  $\hat{\theta}_1, \dots, \hat{\theta}_K$  are approximately multivariate normal,

$$\hat{\theta}_k \sim N(\theta, \{\mathcal{I}_k\}^{-1}), \quad k = 1, \dots, K,$$

and

$$\text{Cov}(\hat{\theta}_{k_1}, \hat{\theta}_{k_2}) = \text{Var}(\hat{\theta}_{k_2}) = \{\mathcal{I}_{k_2}\}^{-1} \quad \text{for } k_1 < k_2.$$

## Sequential distribution theory

The preceding results for the joint distribution of  $\hat{\theta}_1, \dots, \hat{\theta}_K$  can be demonstrated directly for:

*$\theta$  a single normal mean,*

*$\theta = \mu_A - \mu_B$ , comparing two normal means.*

The results also apply when  $\theta$  is a parameter in:

*a general normal linear model,*

*a general model fitted by maximum likelihood (large sample theory),*

*a Cox proportional hazards regression model for survival data.*

Thus, theory supports general comparisons, including:

*crossover studies, analysis of longitudinal data, covariate adjustment.*

## Explanation of the canonical joint distribution

The special correlation structure applies to all efficient, or asymptotically efficient, unbiased estimators.

### ***Proof***

Suppose  $\text{Var}(\hat{\theta}_2) \neq \text{Cov}(\hat{\theta}_1, \hat{\theta}_2)$ .

At the second analysis,  $\tilde{\theta}_2 = \hat{\theta}_2 + \epsilon (\hat{\theta}_2 - \hat{\theta}_1)$  has expectation  $\theta$  and variance

$$\text{Var}(\hat{\theta}_2) + 2\epsilon \text{Cov}(\hat{\theta}_2, \hat{\theta}_2 - \hat{\theta}_1) + \epsilon^2 \text{Var}(\hat{\theta}_2 - \hat{\theta}_1).$$

For small  $\epsilon$  of opposite sign to  $\text{Cov}(\hat{\theta}_2, \hat{\theta}_2 - \hat{\theta}_1) = \{\text{Var}(\hat{\theta}_2) - \text{Cov}(\hat{\theta}_1, \hat{\theta}_2)\}$ ,

$$\text{Var}(\tilde{\theta}_2) < \text{Var}(\hat{\theta}_2),$$

contradicting the assumption that  $\hat{\theta}_2$  is efficient.

(This argument is reminiscent of the proof of the Gauss-Markov theorem and, indeed, the result is essentially equivalent.)

## Canonical joint distribution of $z$ -statistics

In testing  $H_0: \theta = 0$ , the *standardised statistic* at analysis  $k$  is

$$Z_k = \frac{\hat{\theta}_k}{\sqrt{\text{Var}(\hat{\theta}_k)}} = \hat{\theta}_k \sqrt{\mathcal{I}_k}.$$

For this, the distribution theory for  $\hat{\theta}_1, \dots, \hat{\theta}_K$  implies

$(Z_1, \dots, Z_K)$  is multivariate normal,

$$Z_k \sim N(\theta \sqrt{\mathcal{I}_k}, 1), \quad k = 1, \dots, K,$$

$$\text{Cov}(Z_{k_1}, Z_{k_2}) = \sqrt{\mathcal{I}_{k_1} / \mathcal{I}_{k_2}} \quad \text{for } k_1 < k_2.$$

## Canonical joint distribution of score statistics

The general theory also implies that *score statistics*,  $S_k = Z_k \sqrt{\mathcal{I}_k}$ , are multivariate normal with

$$S_k \sim N(\theta \mathcal{I}_k, \mathcal{I}_k), \quad k = 1, \dots, K.$$

The score statistics possess the “independent increments” property,

$$\text{Cov}(S_k - S_{k-1}, S_{k'} - S_{k'-1}) = 0 \quad \text{for } k \neq k'.$$

It can be helpful to know that the score statistics behave as Brownian motion with drift  $\theta$  observed at times  $\mathcal{I}_1, \dots, \mathcal{I}_K$ .

*References:*

Jennison & Turnbull, *JASA*, 1997; Scharfstein, Tsiatis & Robins, *JASA*, 1997.

### 3. An optimal stopping problem

Consider a trial designed to test  $H_0: \theta \leq 0$  vs  $\theta > 0$ , with:

Type I error rate  $\alpha$ ,

Power  $1 - \beta$  at  $\theta = \delta$ ,

Up to  $K$  analyses.

A fixed sample test needs information

$$\mathcal{I}_{fix} = \{\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)\}^2 / \delta^2.$$

We set the maximum information to be

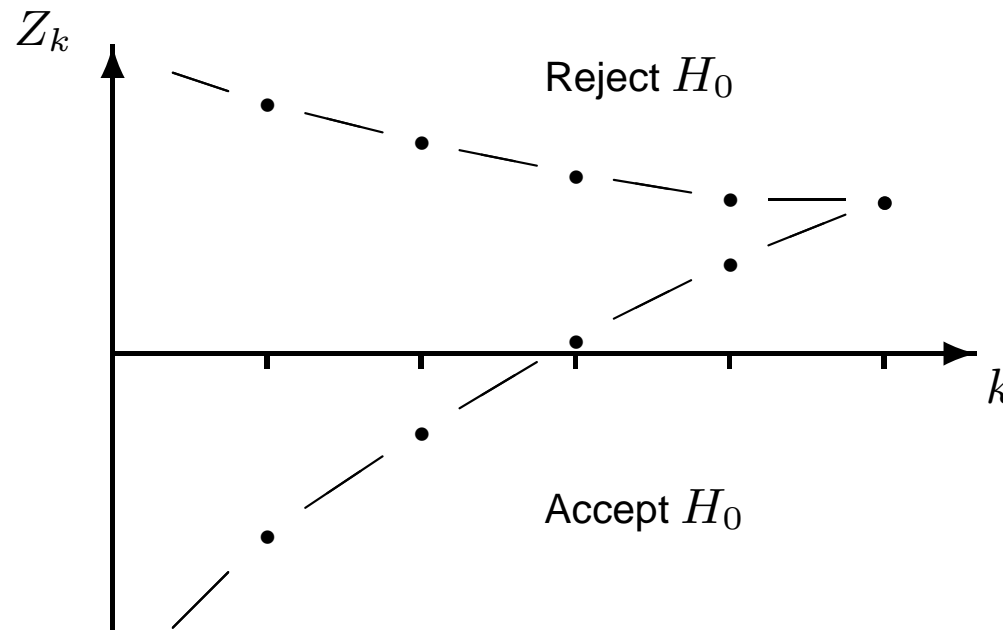
$$\mathcal{I}_{max} = R \mathcal{I}_{fix},$$

where  $R > 1$ , with equal increments between analyses, so

$$\mathcal{I}_k = (k/K) \mathcal{I}_{max}, \quad k = 1, \dots, K.$$

## Optimal group sequential tests

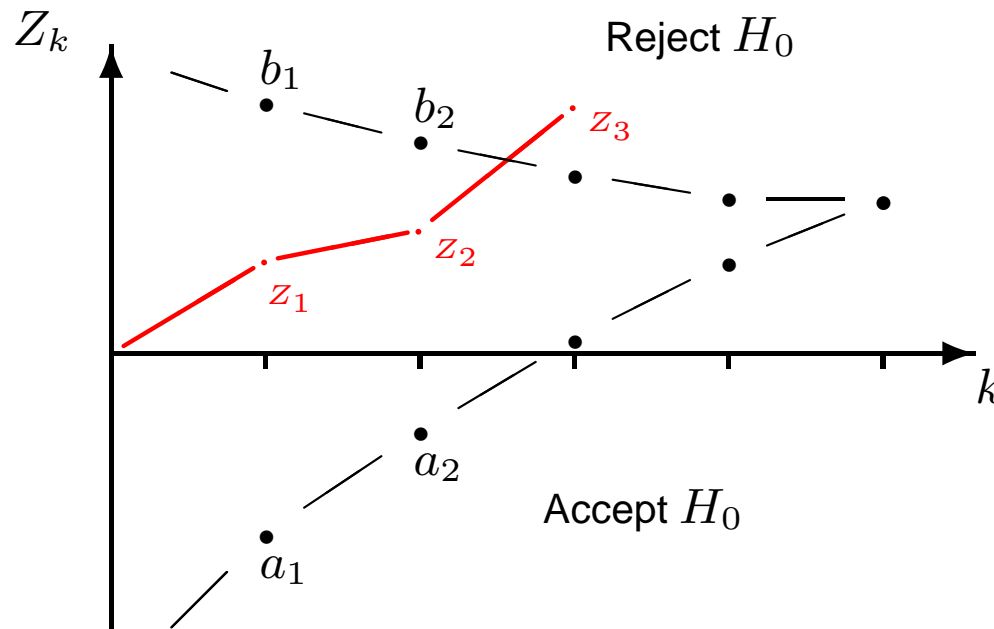
The error rates impose two constraints on the  $2K - 1$  boundary points — leaving a high dimensional space of possible boundaries.



We shall look for a boundary with an optimality property, specifically, minimising

$$\{E_0(\mathcal{I}) + E_\delta(\mathcal{I})\}/2.$$

## 4. Computations for group sequential tests



We need to be able to calculate the probabilities of basic events such as

$$a_1 < Z_1 < b_1, \quad a_2 < Z_2 < b_2, \quad Z_3 > b_3.$$

Combining such probabilities gives key properties, such as  $Pr_\theta\{\text{Reject } H_0\}$ , etc.



## Computations for group sequential tests

For a one-sided test with  $K$  analyses, define the events

$$\mathcal{A}_k = \{a_1 < Z_1 < b_1, \dots, a_{k-1} < Z_{k-1} < b_{k-1}, Z_k < a_k\}$$

and

$$\mathcal{R}_k = \{a_1 < Z_1 < b_1, \dots, a_{k-1} < Z_{k-1} < b_{k-1}, Z_k > b_k\}.$$

Then

$$Pr\{\text{Accept } H_0\} = Pr\{\mathcal{A}_1\} + \dots + Pr\{\mathcal{A}_K\},$$

$$Pr\{\text{Reject } H_0\} = Pr\{\mathcal{R}_1\} + \dots + Pr\{\mathcal{R}_K\}$$

and the observed information on termination is

$$\begin{aligned} E\{\mathcal{I}\} &= (Pr\{\mathcal{A}_1\} + Pr\{\mathcal{R}_1\}) \mathcal{I}_1 + \dots \\ &\quad + (Pr\{\mathcal{A}_K\} + Pr\{\mathcal{R}_K\}) \mathcal{I}_K. \end{aligned}$$

## Recursive formulae

Armitage, McPherson & Rowe (*JRSS, A*, 1969) present recursive formulae for densities of score statistics at interim analyses.

*On the  $Z$ -statistic scale:*

The density  $f_1(z_1)$  of  $Z_1$  is that of a  $N(\theta \sqrt{\mathcal{I}_1}, 1)$  variate.

The joint distribution of the  $Z_k$ s implies that

$$Z_2|Z_1 \sim N(\theta(\mathcal{I}_2 - \mathcal{I}_1)/\sqrt{\mathcal{I}_2} + Z_1\sqrt{(\mathcal{I}_1/\mathcal{I}_2)}, (\mathcal{I}_2 - \mathcal{I}_1)/\mathcal{I}_2).$$

Denote this conditional density by  $f_2(z_2|z_1)$ .

Since analysis 2 is only reached if  $a_1 < Z_1 < b_1$ , the sub-density for  $Z_2$  is

$$f_2(z_2) = \int_{a_1}^{b_1} f_1(z_1) f_2(z_2|z_1) dz_1.$$

## Recursive formulae

In the general recursive step, the sub-density for  $Z_k$  at analysis  $k$  is

$$f_k(z_k) = \int_{a_{k-1}}^{b_{k-1}} f_{k-1}(z_{k-1}) f_k(z_k | z_{k-1}) dz_{k-1},$$

where  $f_k(z_k | z_{k-1})$  is the density of the distribution

$$N(\theta(\mathcal{I}_k - \mathcal{I}_{k-1})/\sqrt{\mathcal{I}_k} + Z_{k-1}\sqrt{(\mathcal{I}_{k-1}/\mathcal{I}_k)}, (\mathcal{I}_k - \mathcal{I}_{k-1})/\mathcal{I}_k).$$

Numerical quadrature can be used to evaluate each of  $f_1, f_2$ , etc., in succession on a grid of points. Then, for example, one can compute

$$\begin{aligned} Pr\{a_1 < Z_1 < b_1, a_2 < Z_2 < b_2, Z_3 > b_3\} = \\ \int_{a_2}^{b_2} f_2(z_2) \Phi\left(\frac{\theta(\mathcal{I}_3 - \mathcal{I}_2) + z_2\sqrt{\mathcal{I}_2} - b_3\sqrt{\mathcal{I}_3}}{\sqrt{(\mathcal{I}_3 - \mathcal{I}_2)}}\right) dz_2. \end{aligned}$$

## Direct numerical integration

*Alternatively*, we can write probabilities as nested integrals, e.g.,

$$\Pr\{a_1 < Z_1 < b_1, a_2 < Z_2 < b_2, Z_3 > b_3\} = \\ \int_{a_1}^{b_1} \int_{a_2}^{b_2} \int_{b_3}^{\infty} f_1(z_1) f_2(z_2|z_1) f_3(z_3|z_2) dz_3 dz_2 dz_1.$$

Applying numerical integration, we replace each integral by a sum of the form

$$\int_a^b f(z) dz = \sum_{i=1}^n w(i) f(z(i)),$$

where  $z(1), \dots, z(n)$  is a grid of points from  $a$  to  $b$ .

## Direct numerical integration

Thus, we have

$$Pr\{a_1 < Z_1 < b_1, a_2 < Z_2 < b_2, Z_3 > b_3\} \approx$$

$$\sum_{i_1=1}^{n_1} \sum_{i_2=1}^{n_2} \sum_{i_3=1}^{n_3} w_1(i_1) f_1(z_1(i_1)) w_2(i_2) f_2(z_2(i_2)|z_1(i_1))$$

$$w_3(i_3) f_3(z_3(i_3)|z_2(i_2)).$$

Multiple integrations and summations will arise, e.g., for an outcome at analysis  $k$ ,

$$\sum_{i_1=1}^{n_1} \sum_{i_2=1}^{n_2} \dots \sum_{i_k=1}^{n_k} w_1(i_1) f_1(z_1(i_1)) w_2(i_2) f_2(z_2(i_2)|z_1(i_1))$$

$$\dots w_k(i_k) f_k(z_k(i_k)|z_{k-1}(i_{k-1})).$$

## Direct numerical integration

In the multiple summation

$$\sum_{i_1=1}^{n_1} \sum_{i_2=1}^{n_2} \cdots \sum_{i_k=1}^{n_k} w_1(i_1) f_1(z_1(i_1)) w_2(i_2) f_2(z_2(i_2)|z_1(i_1)) \\ \cdots w_k(i_k) f_k(z_k(i_k)|z_{k-1}(i_{k-1})),$$

the structure of the  $k$  nested summations is such that the computation required is of the order of  $k - 1$  double summations.

Using Simpson's rule with 100 to 200 grid points per integral can give accuracy to 5 or 6 decimal places.

For details of efficient sets of grid points, see Ch. 19 of *Group Sequential Methods with Applications to Clinical Trials* by Jennison and Turnbull (2000).

## 5. Finding optimal group sequential tests

Recall we wish to find a group sequential test of  $H_0: \theta \leq 0$  vs  $\theta > 0$  with

$$Pr_{\theta=0}\{\text{Reject } H_0\} = \alpha,$$

$$Pr_{\theta=\delta}\{\text{Accept } H_0\} = \beta,$$

Analyses at  $\mathcal{I}_k = (k/K) \mathcal{I}_{max}$ ,  $k = 1, \dots, K$ ,

Minimum possible value of  $\{E_0(\mathcal{I}) + E_\delta(\mathcal{I})\}/2$ .

We deal with the constraints on error rates by introducing Lagrangian multipliers, creating the *unconstrained problem* of minimising

$$\{E_0(\mathcal{I}) + E_\delta(\mathcal{I})\}/2 + \lambda_1 Pr_{\theta=0}\{\text{Reject } H_0\} + \lambda_2 Pr_{\theta=\delta}\{\text{Accept } H_0\}.$$

We shall find a pair of multipliers  $(\lambda_1, \lambda_2)$  such that the solution has type I and II error rates  $\alpha$  and  $\beta$ , then this design will solve the *constrained problem* too.

## Bayesian interpretation of the Lagrangian approach

Suppose we put a prior distribution on  $\theta$  with  $Pr\{\theta = 0\} = Pr\{\theta = \delta\} = 0.5$  and specify costs of

1 per unit of information observed,

$2\lambda_1$  for rejecting  $H_0$  when  $\theta = 0$ ,

$2\lambda_2$  for accepting  $H_0$  when  $\theta = \delta$ .

Then, the total Bayes risk is

$$\{E_0(\mathcal{I}) + E_\delta(\mathcal{I})\}/2 + \lambda_1 Pr_{\theta=0}\{\text{Reject } H_0\} + \lambda_2 Pr_{\theta=\delta}\{\text{Accept } H_0\},$$

just as in the Lagrangian problem.

The advantage of the Bayes interpretation is that it is easier to see how to solve the problem by techniques of “Dynamic Programming” or “Backwards Induction”.



## Solution by Dynamic Programming

Denote the posterior distribution of  $\theta$  given  $Z_k = z_k$  at analysis  $k$  by

$$p^{(k)}(\theta|z_k), \quad \theta = 0, \delta.$$

***At the final analysis,  $K$***

There is no further sampling cost, so compare decisions

$$\text{Reject } H_0: \quad E(\text{Cost}) = 2 \lambda_1 p^{(K)}(0|z_K),$$

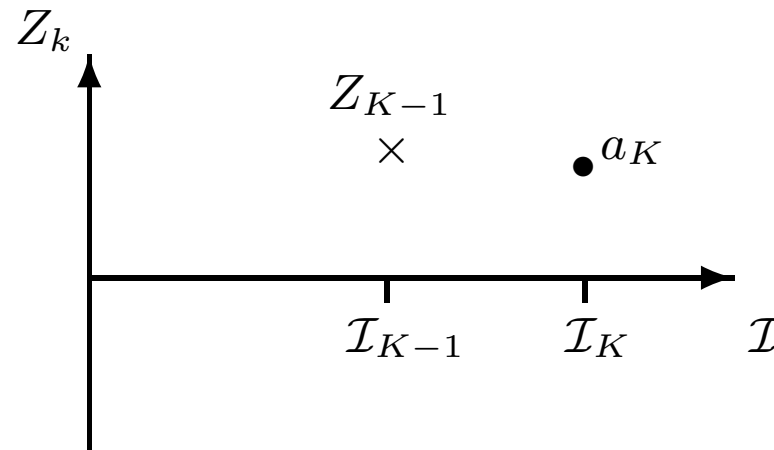
$$\text{Accept } H_0: \quad E(\text{Cost}) = 2 \lambda_2 p^{(K)}(\delta|z_K).$$

The boundary point  $a_K$  is the value of  $z_K$  where these expected losses are equal.

The optimum decision rule is to reject  $H_0$  for  $Z_K > a_K$ .

# Dynamic Programming

*At analysis  $K - 1$*



If the trial stops at this analysis, there is no further cost of sampling and the expected additional cost is

$$\text{Reject } H_0: \quad 2 \lambda_1 p^{(K-1)}(0|z_{K-1}),$$

$$\text{Accept } H_0: \quad 2 \lambda_2 p^{(K-1)}(\delta|z_{K-1}).$$

## At analysis $K - 1$

If the trial continues to analysis  $K$ , the expected additional cost is

$$\begin{aligned} & 1 \times (\mathcal{I}_K - \mathcal{I}_{K-1}) \\ & + 2 \lambda_1 p^{(K-1)}(0|z_{K-1}) Pr_{\theta=0}\{Z_K > a_K | Z_{K-1} = z_{K-1}\} \\ & + 2 \lambda_2 p^{(K-1)}(\delta|z_{K-1}) Pr_{\theta=\delta}\{Z_K < a_K | Z_{K-1} = z_{K-1}\}. \end{aligned}$$

We can now define the optimal boundary points:

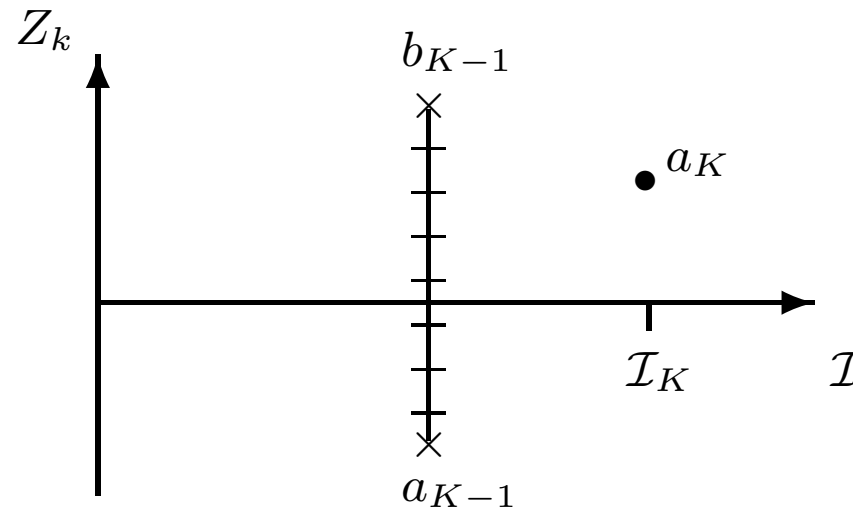
Set  $b_{K-1}$  to be the value of  $z_{K-1}$  where

$$E(\text{Cost of continuing}) = E(\text{Cost of stopping to reject } H_0),$$

Set  $a_{K-1}$  to be the value of  $z_{K-1}$  where

$$E(\text{Cost of continuing}) = E(\text{Cost of stopping to accept } H_0).$$

## At analysis $K - 1$



Before leaving analysis  $K - 1$ , we set up a grid of points for use in numerical integration over the range  $a_{K-1}$  to  $b_{K-1}$ .

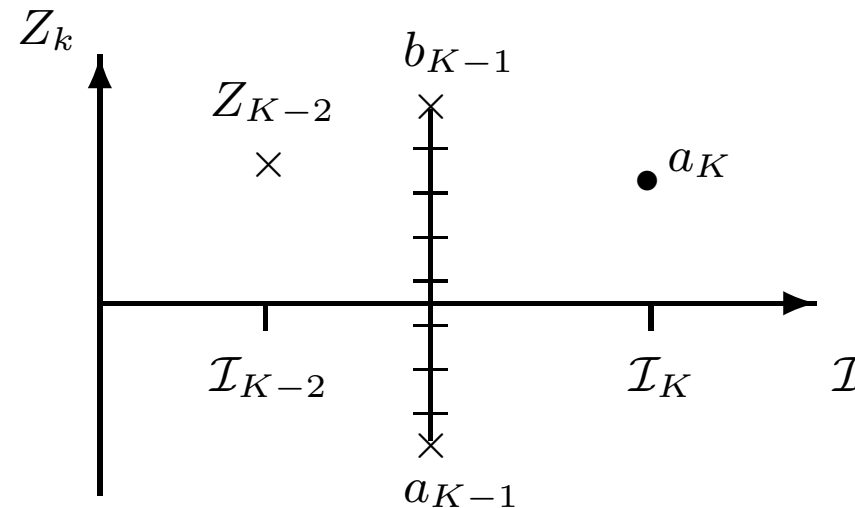
For each point, we sum over the posterior distribution of  $\theta$  to calculate

$$\beta^{(K-1)}(z_{K-1}) = E(\text{Additional cost when continuing} \mid Z_{K-1} = z_{K-1}).$$

We are now ready to move back to analysis  $K - 2$ .

# Dynamic Programming

*At analysis  $K - 2$*



If the trial stops, the expected additional cost is

$$\text{Reject } H_0: \quad 2 \lambda_1 p^{(K-2)}(0|z_{K-2}),$$

$$\text{Accept } H_0: \quad 2 \lambda_2 p^{(K-2)}(\delta|z_{K-2}).$$

## At analysis $K - 2$

If the trial continues to analysis  $K - 1$ , the expected additional cost is

$$\begin{aligned}
 & 1 \times (\mathcal{I}_{K-1} - \mathcal{I}_{K-2}) \\
 & + 2 \lambda_1 p^{(K-2)}(0|z_{K-2}) Pr_{\theta=0}\{Z_{K-1} > b_{K-1} | Z_{K-2} = z_{K-2}\} \\
 & + 2 \lambda_2 p^{(K-2)}(\delta|z_{K-2}) Pr_{\theta=\delta}\{Z_{K-1} < a_{K-1} | Z_{K-2} = z_{K-2}\} \\
 & + \int_{a_{K-1}}^{b_{K-1}} \{p^{(K-2)}(0|z_{K-2}) f_0^{(K-1)}(z_{K-1} | z_{K-2}) + \\
 & \quad p^{(K-2)}(\delta|z_{K-2}) f_\delta^{(K-1)}(z_{K-1} | z_{K-2})\} \beta^{(K-1)}(z_{K-1}) dz_{K-1},
 \end{aligned}$$

where  $f_\theta^{(K-1)}(z_{K-1} | z_{K-2})$  is the conditional density under  $\theta$  of  $Z_{K-1}$  given  $Z_{K-2} = z_{K-2}$ .

## At analysis $K - 2$

Comparing costs for stopping and continuing at values of  $z_{K-2}$ , we can now define the optimal boundary points  $a_{K-2}$  and  $b_{K-2}$ .

We then set up a grid of points for use in numerical integration over the range  $a_{K-2}$  to  $b_{K-2}$ .

For each point, we calculate

$$\beta^{(K-2)}(z_{K-2}) = E(\text{Additional cost when continuing} \mid Z_{K-2} = z_{K-2}).$$

The process now moves back to analysis  $K - 3$ , and so on all the way back to analysis 1.

*Note: We have solved an “optimal stopping problem”.*

## Solving the original problem

For any given  $(\lambda_1, \lambda_2)$  we can find the Bayes optimal design and compute its type I and II error rates.

We now add another layer above this to search for a pair  $(\lambda_1, \lambda_2)$  for which type I and type II error rates of the optimal design equal  $\alpha$  and  $\beta$  respectively.

The resulting design will be the optimal group sequential test, with the specified frequentist error rates, for our original problem.

### **Notes**

1. Since the output of the Dynamic Programming routine will be fed into another numerical algorithm, results should be of high accuracy. They should also possess the continuity properties, etc., that the higher level search algorithm expects to see.
2. The method provides an explicit demonstration that good frequentist procedures should be similar to Bayes procedures.



## Properties of optimal designs

One-sided tests,  $\alpha = 0.025$ ,  $1 - \beta = 0.9$ ,  $K$  analyses,  $\mathcal{I}_{max} = R\mathcal{I}_{fix}$ , equal group sizes, minimising  $\{E_0(\mathcal{I}) + E_\delta(\mathcal{I})\}/2$ .

*Minimum values of  $\{E_0(\mathcal{I}) + E_\delta(\mathcal{I})\}/2$ , as a percentage of  $\mathcal{I}_{fix}$*

$K$	$R$					Minimum over $R$
	1.01	1.05	1.1	1.2	1.3	
2	80.8	74.7	73.2	73.7	75.8	73.0 at $R=1.13$
3	76.2	69.3	66.6	65.1	65.2	65.0 at $R=1.23$
5	72.2	65.2	62.2	59.8	59.0	58.8 at $R=1.38$
10	69.2	62.2	59.0	56.3	55.1	54.2 at $R=1.6$
20	67.8	60.6	57.5	54.6	53.3	51.7 at $R=1.8$

Note:  $E(\mathcal{I}) \searrow$  as  $K \nearrow$  but with diminishing returns,

$E(\mathcal{I}) \searrow$  as  $R \nearrow$  up to a point.

## Role of optimal designs

The methods we have described can be applied with a variety of optimality criteria.

We can minimise general criteria of the form  $\sum_i w_i E_{\theta_i}(\mathcal{I})$ .

Or, we can optimise

$$\int f(\theta) E_{\theta}(\mathcal{I}) d\theta$$

for a normal density  $f$ .

As well as being available for direct use, optimal procedures serve as benchmarks for other methods which may have additional useful features.

They provide calibration for simple parametric boundaries or “error spending tests” which can handle uncertain information sequences.

## 6. Related problems

### *(i) Adaptive choice of group sizes in a group sequential test*

Schmitz (1993) proposed tests in which group sizes are chosen adaptively:

Initially, fix  $\mathcal{I}_1$  and observe

$$S_1 \sim N(\theta\mathcal{I}_1, \mathcal{I}_1).$$

Choose  $\mathcal{I}_2$  as a function of  $S_1$ , then observe  $S_2$  where

$$S_2 - S_1 \sim N(\theta(\mathcal{I}_2 - \mathcal{I}_1), (\mathcal{I}_2 - \mathcal{I}_1)).$$

Continue to choose  $\mathcal{I}_3$  and observe  $S_3$ , etc, etc.

The whole procedure, sampling rule and stopping rule, should achieve desired *overall* type I error rate and power, and minimise a sample size criterion.

## Examples of “Schmitz” designs

Consider designs which test  $H_0: \theta = 0$  versus  $H_1: \theta > 0$  with

*Type I error rate*  $\alpha = 0.025$ ,

*Power*  $1 - \beta = 0.9$  at  $\theta = \delta$ .

We wish to minimise

$$\int E_{\theta}(\mathcal{I}) f(\theta) d\theta,$$

where  $f(\theta)$  is the density of a  $N(\delta, \delta^2/4)$  distribution, subject to

*Maximum information*  $= 1.2 \times \mathcal{I}_{fix}$ ,

*Maximum number of analyses*  $= K$ .

Jennison & Turnbull (*Biometrika*, 2006) define and solve Bayes decision problems to find optimal Schmitz designs.

## Examples of “Schmitz” designs

Optimal average  $E(\mathcal{I})$  as a percentage of the fixed sample information.

$K$	<i>Optimal adaptive design (Schmitz)</i>	<i>Optimal non-adaptive, optimised group sizes</i>	<i>Optimal non-adaptive, equal group sizes</i>
2	72.5	73.2	74.8
3	64.8	65.6	66.1
4	61.2	62.4	62.7
5	59.2	60.5	60.9
10	55.9	57.2	57.5

The Schmitz procedures are complex and their efficiency gains are slight.

These results and the nature of the optimal adaptive designs shed light on recent proposals for sample size re-estimation in “adaptive” clinical trials.

## Related problems

### ***(ii) Testing for either superiority or non-inferiority***

When there is already an accepted treatment for a condition, it is not appropriate to test a new treatment against placebo.

A trial using the standard treatment as an active control has two positive outcomes:

Showing the new treatment is *superior* to the current standard,

Showing the new treatment is *non-inferior* to the standard.

Investigators may start a trial intending to show superiority, then decide to adapt to a new goal of non-inferiority if results are not as good as expected.

Having two hypotheses is not an issue as the two tests are nested:

*Superiority* — Null hypothesis:  $\theta \leq 0$ ,

*Non-inferiority* — Null hypothesis:  $\theta \leq -d$ .

## Testing for superiority and non-inferiority

### Differing sample size requirements

Wang, Hung, Tsong & Cui (*Statistics in Medicine*, 2001) note the non-inferiority margin  $d$  is often smaller than the effect size  $\delta$  at which power for declaring superiority is specified.

Thus, a larger sample size is needed to test adequately for non-inferiority.

If early data indicate that the key issue is to test for non-inferiority, one may wish to increase the overall sample size.

### ***Adaptive re-design***

Wang et al. propose a group sequential test with group size determined by the power for superiority.

They then use the adaptive method of Cui, Hung & Wang (*Biometrics*, 1999) to increase group sizes if interest shifts to proving non-inferiority.

## Testing for superiority and non-inferiority

### *A non-adaptive group sequential approach*

One can embed testing for both superiority and non-inferiority in a group sequential design.

Early stopping may be appropriate:

to reject  $H_{0,S}: \theta \leq 0$  (establishing superiority),

to accept  $H_{0,NI}: \theta \leq -d$  (failing even to show non-inferiority),

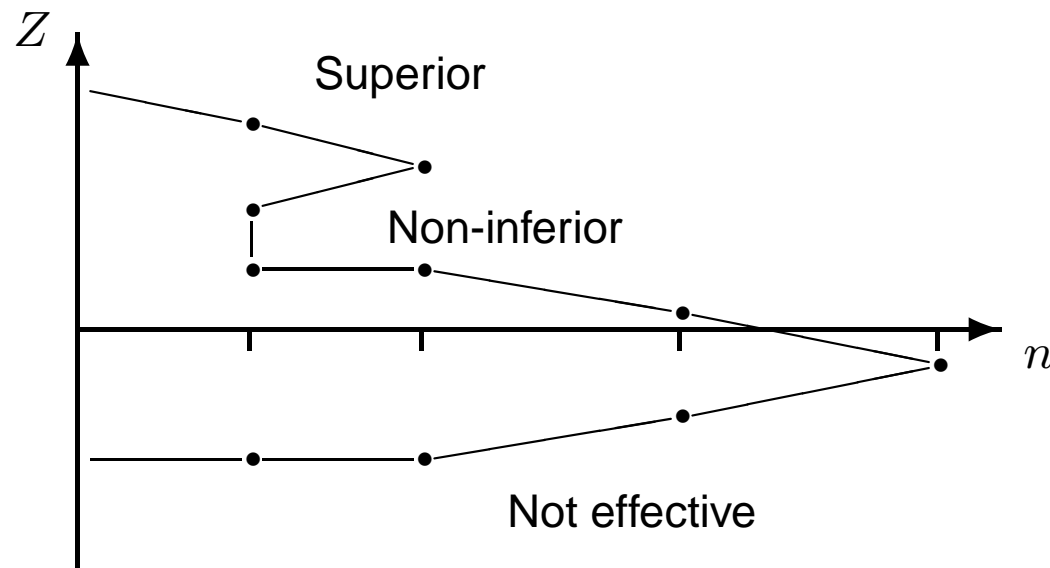
to declare non-inferiority only.

If power for declaring superiority is set at a higher effect size,  $\delta$ , than the margin of non-inferiority,  $d$ , the stopping rule for declaring superiority will be more aggressive.



## Testing for superiority and non-inferiority

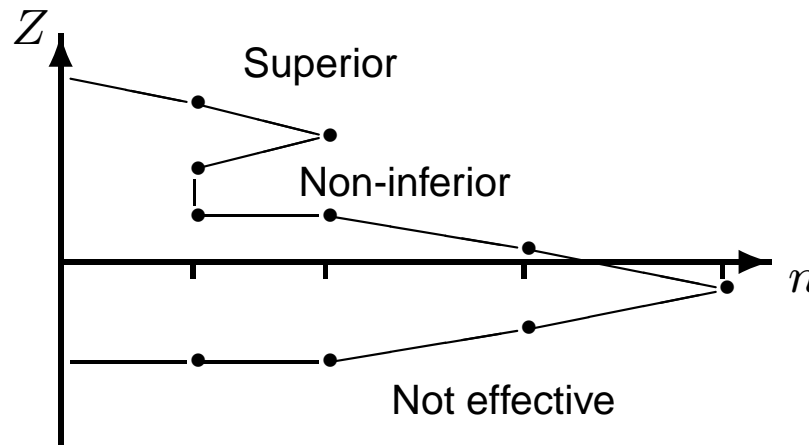
A group sequential design to test for either *Superiority* or *Non-inferiority* can have the general form:



In work with Fredrik Öhrn (*Statistics in Medicine*, 2010), we derived designs which minimise expected sample size while satisfying four error rate constraints.

Again, we define Bayes decision problems, solve these by Dynamic Programming, and search for costs such that the optimal procedure has specified error rates.

## Testing for superiority and non-inferiority



The asymmetry of these designs is important when fixed sample sizes needed for superiority and non-inferiority goals are different.

Optimal designs can be used in their own right.

They also provide a benchmark against which to judge other proposals.

The design leads to larger sample sizes when the issue is to test between inferiority and non-inferiority: there is little further benefit in choosing group sizes adaptively.

## Related problems

### ***(iii) Group sequential tests for a delayed response***

In many trials, response is measured after some period of time, e.g., change in a measurement from baseline to 4 months after treatment.

There can be further delays in validating and analysing responses.

Thus, after a group sequential test stops, one should expect additional data from “pipeline” subjects who have entered the study but not yet responded.

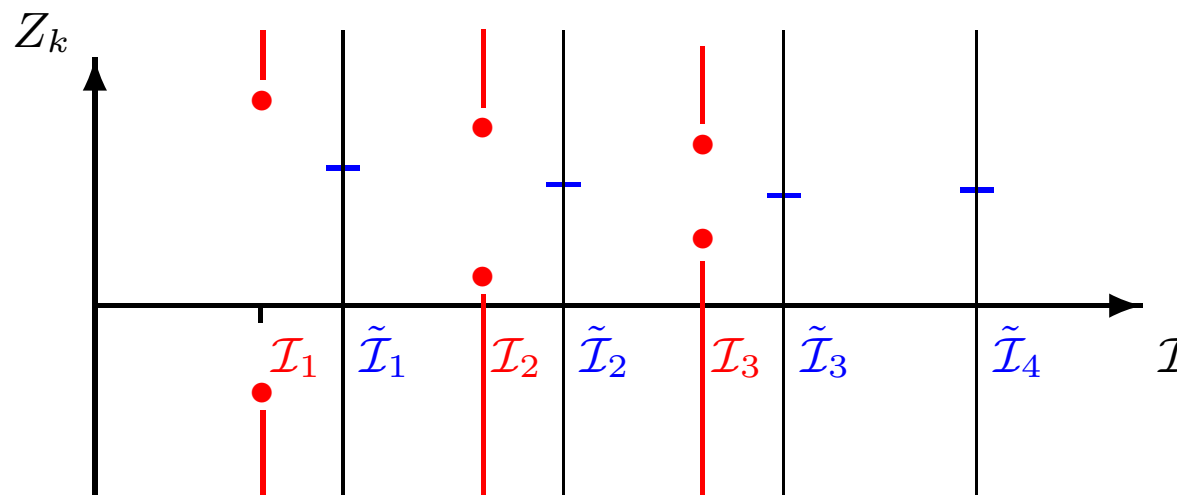
There has been some limited work on “adjusting” the final analysis of a trial to incorporate responses obtained after termination.

In recent work with Lisa Hampson (*JRSS B*, 2012), we have considered the derivation of group sequential designs which recognise there will be a delay in observing data.

## Group sequential tests for a delayed response

A formal procedure terminates the trial in two stages:

1. Cease recruitment of new patients,
2. Wait for responses from all existing subjects, then make a final decision.



Exiting the boundary upwards or downwards at  $I_k$  indicates the likely decision.

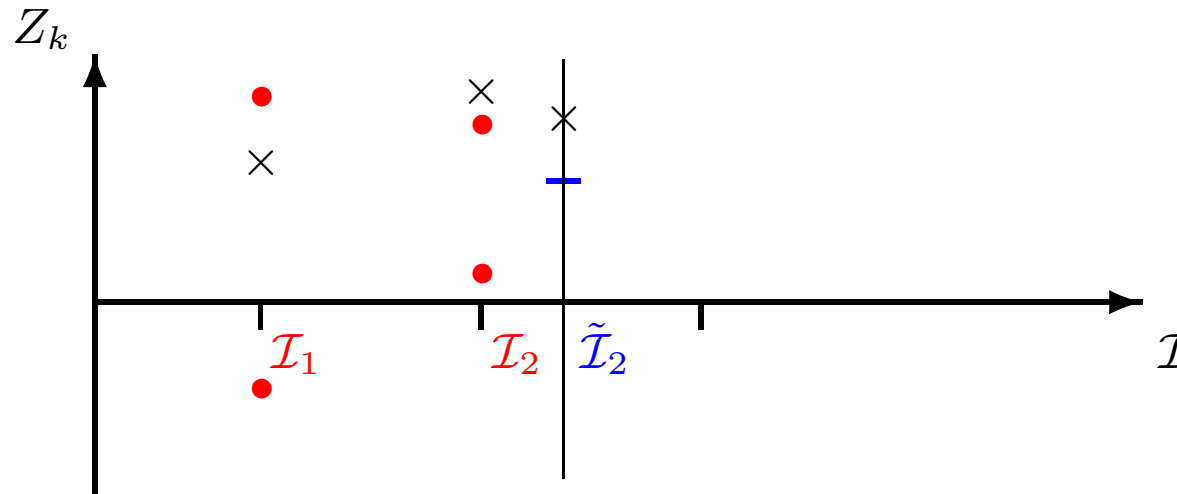
But, the full data at  $\tilde{I}_k$ , including delayed responses, determines the final outcome.

## Group sequential tests for a delayed response

For a particular sequence of observed responses, we apply boundary points at a sequence of information levels of the form

$$\mathcal{I}_1, \dots, \mathcal{I}_k, \tilde{\mathcal{I}}_k.$$

Here, recruitment ceases at the  $k$ th analysis and the final decision is made with extra “pipeline” data bringing the information up to  $\tilde{\mathcal{I}}_k$ .



## Group sequential tests for a delayed response

We have created Bayes problems and applied Dynamic Programming to find optimal delayed-response designs of this type for a variety of criteria.

### ***Brief summary of results***

Some of the benefits of group sequential tests in reducing expected sample size are lost when response is subject to delay.

The impact depends on the ratio  $r$  of the number of responses “in the pipeline” to the total fixed sample size.

Suppose a fixed sample test would need  $N = 100$  observations.

A group sequential design with 5 analyses could have  $E(N) \approx 60$ .

With  $r = 0.2$ , the optimal design has  $E(N) \approx 80$  — halving the benefits of sequential testing.

## Using a second, rapidly observed endpoint

Suppose, however, that a second endpoint can be observed more rapidly and this has a high correlation with the primary endpoint.

We can use this information and fit a model for both endpoints which incorporates this correlation.

Then, the estimate of the primary endpoint gains in accuracy and information increases.

In the previous example, with a correlation between endpoints of 0.7, we find  $E(N) \approx 70$  — so the benefits of group sequential testing are largely restored.

## 7. Conclusions

- The monitoring of clinical trials poses a range of problems of statistical inference and optimal design.
- A general distribution theory gives a basis for generic methodology.
- Using Dynamic Programming to solve specially constructed Bayes decision problems provides a route to deriving optimal designs.
- This methodology can be developed to solve a variety of additional problems of practical significance.