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# Randomised Blinding of a Phase I Trial Using Bayesian Hierarchical Optimisation

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**Abstract:** This paper presents a brief overview of Bayesian design of clinical trials from a Bayesian perspective. Hierarchical Bayesian prior adaptive designs are adopted with sampling priors. The study explores how the variances of Bayesian Gaussian priors impact the optimal design parameters in phase I. This means that the uncertainty in the prior beliefs about model parameters will be minimized using our model set up and it will determine the optimal experimental setup.

**Keywords:** Optimal designs, adaptive randomization; Bayesian designs; clinical trials.

## 1. Introduction:

The paper deals with the variance of the differences between doses, and between placebo and each dose with and without cohort effects are estimated and the results can be concluded to show that the cohort effects occur in the study and falls within a good range of clinical trial values. The design variables that are considered for optimization can include sensor locations, actuator locations, or characteristics of the excitation, such as amplitude variation and frequency content characteristics.

A stochastic optimization mcmc bugs sampler algorithm is used to solve the optimization problem within the continuous physical domain of variation of the design variables. This algorithm helps find the best experimental design. The experimental framework is applicable to both linear and nonlinear dynamical systems, making it versatile for a wide range of structural dynamics problems.

The study compares the results obtained from the proposed asymptotic approximations with those obtained from accurate but computationally expensive sampling algorithms. The goal is to demonstrate that the approximations are sufficient for practical experimental design purposes. In summary, this research focuses on using Bayesian principles and asymptotic approximations to optimize experimental designs in structural dynamics, aiming to obtain the most informative data for various applications within this field.

## 2. Methodology:

This general framework of the Lindley and Smith theorem which can be applied to find optimal designs for individual experiments and can be extended to the selection of a sequence of experiments and sequential decision making (Lindley, 1972).
The three-stage hierarchical model using Lindley and Smith Equations to find the numeric values for computation of differences between doses, and between placebo and each dose with and without a cohort effect is being fitted. The model consists of the following parameters

$\theta$ is the design matrix of the dose end points
$Y_{ij}$ is the linear response outcomes of the drug data.

$\theta_1 \sim N(A_2\theta_2, C_2)$
$\theta_2 \sim N(\mu, C_3)$
$D-1 = A^t{}_1 C_1^{-1} A_1 + (C_2 + A_2C_3A^t{}_2)^{-1}d = A^t{}_1C_1^{-1}y + (C_2 + A_2C_3A^t{}_2)^{-1}A_2\mu$

$$\begin{bmatrix} y1 \\ . \\ . \\ . \\ y32 \end{bmatrix}$$

**Prior beliefs**

Bayesian priors are set on the model to start with the vague prior information to compare the classical designs. In the Bayesian analysis the uncertainty can be expressed as prior and the posterior probabilities are updated. The Bayesian decision theoretic framework helps optimize the next given dose in the trial.

| | Mean | SD |
|---|---|---|
| dnorm(mnu,taunu) | 2.087 | 0.99 |
| dgamma(3,3) | 3.602 | 1.044 |
| dgamma(4,4) | 1.22 | 0.5429 |
| dgamma(3,3) | 1.051 | 0.5854 |
| dnorm(2,1) | 2.034 | 0.8674 |
| dgamma(3,1) | 0.9531 | 0.4916 |
| dnorm(0,0,85) | -0.01065 | 0.8906 |
| dnorm(3,2) | 1.546 | 0.8742 |
| dnorm(3,2) | 2.865 | 0.6573 |
| dgamma(4,2) | 0.9496 | 0.4343 |
| dnorm(4,1) | 4.025 | 2.013 |
| dnorm(4,1) | 3.416 | 0.8491 |
| dgamma(5,3) | 0.9454 | 0.395 |
| dnorm(5,1) | 4.976 | 2.232 |
| dnorm(5,1) | 4.146 | 0.8533 |
| dgamma(4,3) | 0.7671 | 0.3526 |
| dnorm(4,2) | 1.917 | 0.9953 |
| dnorm(5,2) | 4.509 | 0.6525 |
| dgamma(5,1) | 1.442 | 0.6645 |
| dgamma(3,2) | 1.55 | 0.8757 |
| dgamma(4,2) | 0.9507 | 0.4349 |
| dgamma(1,1) | 4.072 | 2.014 |

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| dgamma(3,2) | 1.55 | 0.8757 |
| dgamma(4,2) | 0.9507 | 0.4449 |

$$\begin{pmatrix}
0.9184 & -0.8322 & -0.8322 & -0.8322 & -0.8322 & -0.0836 & -0.0836 & -0.0836 & -0.0836 \\
-0.8322 & 1.7921 & 1.6842 & 1.6842 & 1.6842 & -0.8530 & -0.8530 & -0.8530 & -0.8530 \\
-0.8822 & 1.6842 & 1.8122 & 1.0743 & 1.0743 & -0.8837 & -0.8377 & -0.8377 & -0.8530 \\
-0.8322 & 1.6842 & 1.6743 & 1.8122 & 1.6743 & -0.8377 & -0.8837 & -0.8377 & -0.8530 \\
-0.8322 & 1.6842 & 1.6743 & 1.6743 & 1.8122 & -0.8377 & -0.8377 & -0.8837 & -0.8530 \\
-0.0836 & -0.8530 & -0.8837 & -0.8377 & -0.8377 & 0.9912 & 0.9203 & 0.9203 & 0.9254 \\
-0.0836 & -0.8530 & -0.8377 & -0.8837 & -0.8377 & 0.9203 & 0.9912 & 0.9203 & 0.9254 \\
0.0836 & -0.8530 & -0.8377 & -0.8377 & -0.8837 & 0.9203 & 0.9203 & 0.9912 & 0.9254 \\
-0.0836 & -0.8530 & -0.8530 & -0.8530 & -0.8530 & 0.9254 & 0.9254 & 0.9254 & 0.9809
\end{pmatrix}$$

$$\begin{pmatrix}
0.9184 & -0.8322 & -0.8322 & -0.8322 & -0.8322 & -0.0836 & -0.0836 & -0.0836 & -0.0836 \\
-0.8322 & 1.7924 & 1.6842 & 1.6842 & 1.6842 & -0.8530 & -0.8530 & -0.8530 & -0.8530 \\
-0.8822 & 1.6842 & 1.8125 & 1.6782 & 1.6702 & -0.8838 & -0.8539 & -0.8381 & -0.8363 \\
-0.8322 & 1.6842 & 1.6782 & 1.8045 & 1.6782 & -0.8390 & -0.8671 & -0.8671 & -0.8390 \\
-0.8322 & 1.6842 & 1.6702 & 1.6782 & 1.8125 & -0.8363 & -0.8381 & -0.8539 & -0.8838 \\
-0.0836 & -0.8530 & -0.8838 & -0.8390 & -0.8363 & 0.9912 & 0.9257 & 0.9204 & 0.9198 \\
-0.0836 & -0.8530 & -0.8379 & -0.8671 & -0.8381 & 0.9257 & 0.9842 & 0.9269 & 0.9204 \\
0.0836 & -0.8530 & -0.8381 & -0.8671 & -0.8539 & 0.9204 & 0.9269 & 0.9842 & 0.9257 \\
-0.0836 & -0.8530 & -0.8363 & -0.8390 & -0.8838 & 0.9198 & 0.9204 & 0.9254 & 0.9912
\end{pmatrix}$$

The variance of the differences between the doses, and between the placebo and each dose. The above notations are to be used in the following codes using Winbugs software. Results for the Bayesian comparative study of the designs model to be fitted with and without cohort effects is applied in the estimation process.

**Design Endpoints:**

Clinical trial analysis from traditional methods that primarily compare the distributions of primary endpoints in treatment groups to a Bayesian approach that considers accumulating results and focuses on information available on individual patients.

In standard clinical trial analyses, researchers typically compare the distributions of primary endpoints (e.g., treatment outcomes) among different treatment groups. This often involves adjusting for baseline differences in patient characteristics.

In some cases, particularly when dealing with survival as an endpoint, not all patients in the trial experience the event of interest (e.g., death) during the trial. This can make traditional analyses less informative.

Our model suggests a Bayesian approach that focuses on the accumulating results from individual patients throughout the trial. Instead of just comparing distributions, Bayesian analysis considers information about various aspects of patients' experiences, including tumor response, disease progression, patient performance status, and more.

$y_{ij} = \theta_1 + \theta_2 \log d_{ij} + s_i + \varepsilon_{ij}$

One key aspect of this Bayesian approach is the consideration of auxiliary variables or auxiliary endpoints. These are additional variables beyond the primary endpoint that provide valuable information about patients' conditions and outcomes. These auxiliary variables can include information about how early variables relate to survival.

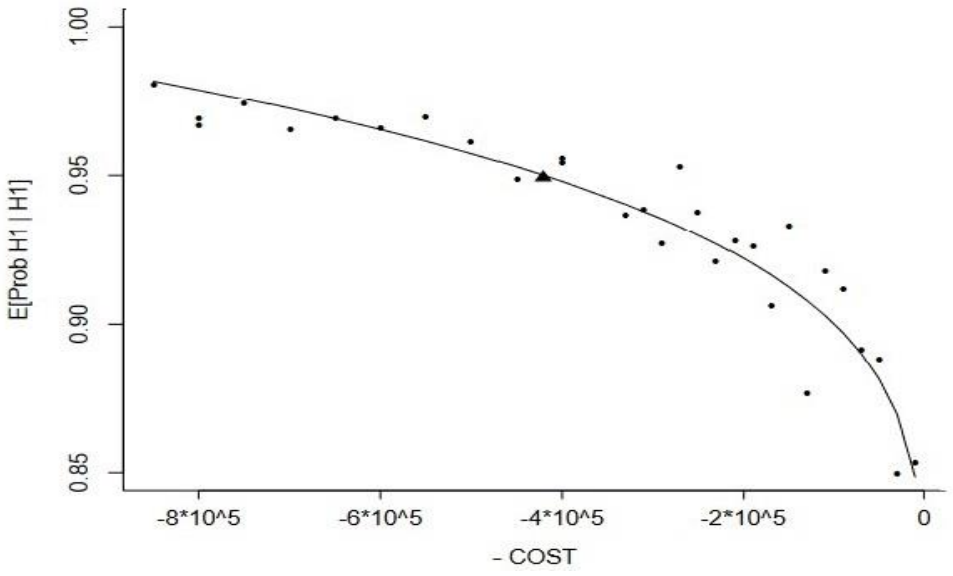
The relationships between these early variables and survival may vary between different treatment groups. This variability can be modeled within the Bayesian framework to better understand the impact of treatments on patient outcomes.

The use of auxiliary variables allows for more precise assessments of the primary endpoint. By considering how these early variables relate to the primary endpoint and incorporating this information into the analysis, researchers can potentially gain deeper insights into treatment effects.

In summary, the Bayesian approach discussed in the text emphasizes the importance of considering accumulating patient-level information, including auxiliary variables, to enhance the analysis of clinical trials, particularly when dealing with survival endpoints. This approach aims to provide more precise assessments of treatment effects and better inform decision-making in medical research.

The posterior distribution that is observe from the above results using our model forms basis for all inference from the Bayesian optimization setting which is illustrated above and to summarize it involves the:

- point and interval estimates of treatment effect.
- point and interval estimates of any function of the parameters.
- probability that treatment effect exceeds a clinically relevant value.




## 3. Conclusions

The above results give the posterior estimates with the appropriate prior assumptions taken into account in the model. Also, the sensitivity analysis observes and compares the parameters mentioned in the discussions. From the above analysis it can be concluded from the estimation of the parameters mainly monitoring for the cohort effects in the modelling that the Halving Design works best and also that the cohort effects occurred in the trial and fits within a good range of values in the designs investigated.

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