Experimental Designs for Estimating Variance Components

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- V-class of optimality criteria
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- Discussion and further work
Example. Bioassay validation

Figure: Plates for fluorescence/ luminescence-based immuno-assays and binding assays (white, black and clear)
Example. Bioassay validation

Aim
- Set up the main study
- Estimate variance components
- Identify best conditions
- Power calculations
- Tested compounds not important!
Example. Bioassay validation

Aim

▶ Set up the main study
▶ Estimate variance components
▶ Identify best conditions
▶ Power calculations
▶ Tested compounds not important!

▶ How many plates?
▶ How many occasions?
▶ What compounds to test?
Background

- Herzberg & Cox (1969): less than 3% of the approximately 800 cited articles were classified as dealing with designs for variance components estimation
- Since then - no much change!
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- Useful reviews:
  Khuri & Sahai (1985)
  Khuri (2001)
Background

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- Common features of past research:
  - devoted to specific problems
  - fragmented

- Recognized: the optimum design depends on the unknown true values of the variance components!
Some references

- Staggered nested designs - Bainbridge, T. R. (1965)
Linear mixed effect model

Model

\[ y = X\beta + Z\gamma + \epsilon, \]

- **y** - vector of \( N \) observations
- **\epsilon** - vector of experimental errors
- **\beta** & **\gamma** - vectors of \( p \) fixed and \( r \) random effects
- **X** & **Z** - the design matrices for the fixed and the random effects
- Combining **Z\gamma + \epsilon**

\[ Z\gamma = \sum_{i=0}^{r} Z_i \gamma_i \]

where

\[ Z_0 = I_N \quad \gamma_0 = \epsilon \]
Model assumptions

\[ E(y) = X\beta, \quad E(\epsilon) = 0, \quad E(\gamma_i) = 0, \quad \text{var}(\epsilon) = \sigma_\epsilon^2 I_N \]

\[
\text{var}(\gamma) = \begin{bmatrix}
\sigma_1^2 I_{q_1} & & \\
& \sigma_2^2 I_{q_2} & \\
& & \ddots \\
& & & \sigma_r^2 I_{q_r}
\end{bmatrix}
\text{ is a block diagonal matrix}
\]

Also

\[ \text{var}(y) = V = \sum_{i=0}^{r} \sigma_i^2 Z_i Z_i^T. \]
Maximum Likelihood Estimation

► Model

\[ y \sim N_N(X\beta, V) \]

► Likelihood

\[ L = L(\beta, V|y) = \exp \left( -\frac{1}{2}(y - X\beta)^T V^{-1}(y - X\beta) \right) \]

\[ (2\pi)^{\frac{1}{2}N} |V|^{\frac{1}{2}} \]

► Log-likelihood

\[ l = \log(L) \]
Maximum Likelihood Estimation

- Fisher information matrix

\[
M \begin{bmatrix} \beta \\ \sigma^2 \end{bmatrix} = \begin{bmatrix} X^T V^{-1} X & 0 \\ 0 & \frac{1}{2} \text{tr} \left( V^{-1} Z_i Z_i^T V^{-1} Z_j Z_j^T \right) \end{bmatrix}_{i,j = 0, \ldots, r}
\]
Maximum Likelihood Estimation

- Fisher information matrix

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M \begin{bmatrix}
\beta \\
\sigma^2
\end{bmatrix} = \begin{bmatrix}
X^T V^{-1} X & 0 \\
0 & \frac{1}{2} \text{tr} \left( V^{-1} Z_i Z_i^T V^{-1} Z_j Z_j^T \right)
\end{bmatrix}
\]

- Optimizing designs for \( \beta \) and for \( \sigma^2 \) can be done independently

- Optimality of designs for \( \beta \) does not depend on \( \beta \)

- Optimality of designs for \( \sigma^2 \) does depend on \( \sigma^2 \)
Maximum Likelihood Estimation

- Fisher information matrix

\[ M \left[ \begin{array}{c} \beta \\ \sigma^2 \end{array} \right] = \begin{bmatrix} X^T V^{-1} X & 0 \\ 0 & \frac{1}{2} \text{tr} \left( V^{-1} Z_i Z_i^T V^{-1} Z_j Z_j^T \right) \end{bmatrix} \quad i, j = 0, \ldots, r. \]

- Optimizing designs for \( \beta \) and for \( \sigma^2 \) can be done independently

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Maximum Likelihood Estimation

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- Optimizing designs for \( \beta \) and for \( \sigma^2 \) can be done independently.
- Optimality of designs for \( \beta \) does not depend on \( \beta \).
- Optimality of designs for \( \sigma^2 \) does depend on \( \sigma^2 = (\sigma_\epsilon^2, \sigma_1^2, \sigma_2^2, \ldots, \sigma_r^2) \).
Maximum Likelihood Estimation

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M \begin{bmatrix} \beta \\ \sigma^2 \end{bmatrix} = \begin{bmatrix} X^T V^{-1} X & 0 \\ 0 & \frac{1}{2} \text{tr} \left( V^{-1} Z_i Z_i^T V^{-1} Z_j Z_j^T \right) \end{bmatrix} \quad i, j = 0, \ldots, r.
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- Optimizing designs for \( \beta \) and for \( \sigma^2 \) can be done independently.

- Optimality of designs for \( \beta \) does not depend on \( \beta \).

- Optimality of designs for \( \sigma^2 \) does depend on \( \sigma^2 = (\sigma^2_\epsilon, \sigma^2_1, \sigma^2_2, \ldots, \sigma^2_r) \).

- Hence, the design problem for \( \sigma^2 \) is similar to that for nonlinear models!
V class of criteria of design optimality

- Let

\[ M(\sigma^2) = \frac{1}{2} \text{tr} \left( V^{-1} Z_i Z_i^T V^{-1} Z_j Z_j^T \right) \quad i, j = 0, \ldots, r \]

- Local \( D \)-optimality requires

\[ D_V = \min \left| M^{-1}(\sigma^2) \right|_{\sigma^2 = \sigma_0^2} \]

- Bayesian \( D \)-optimality requires

\[ D_V = \min \left| M^{-1}(\sigma^2) \right|_{\sigma^2 \in \Sigma} \]
V class of criteria of design optimality

- Local $A_V$-optimality requires
  \[
  \min \ tr \ M^{-1}(\sigma^2) \bigg|_{\sigma^2=\sigma_0^2}
  \]

- Bayesian $A_V$-optimality requires
  \[
  \min \ tr \ M^{-1}(\sigma^2) \bigg|_{\sigma^2 \in \Sigma}
  \]
Similarity

- Design optimality for $\sigma^2$ does not depend on the total variability but only on the proportions of the variance components.
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- Similarity with mixtures experiments where the response depends only on the proportion of the mixture components.
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- Similarity with mixtures experiments where the response depends only on the proportion of the mixture components.
V class of criteria of design optimality

$c_V$-optimality:

Interest in functions of the model parameters $g(\hat{\sigma}^2)$. 
Example 1. Two-Way Crossed Model
(No Interaction)

The model is

\[ y_{ijk} = \mu + \alpha_i + \beta_j + e_{ijk} \]
\[ = \mu 1 + Z_1 \alpha + Z_2 \beta + Z_0 \epsilon \]

\( i = 1 \ldots a, \quad j = 1 \ldots b \)

\[ k = \begin{cases} 
1 \ldots n_{ij} & \text{Unbalanced} \\
1 \ldots n & \text{Balanced}
\end{cases} \]

\[ N = \begin{cases} 
\sum_i \sum_j n_{ij} & \text{Unbalanced} \\
abn & \text{Balanced}
\end{cases} \]
Example 1. Two-Way Crossed Model  
(No Interaction)

Information matrix

\[
M \begin{bmatrix}
\hat{\sigma}_\varepsilon^2 \\
\hat{\sigma}_\alpha^2 \\
\hat{\sigma}_\beta^2
\end{bmatrix} = \frac{1}{2} \begin{bmatrix}
t_{\varepsilon\varepsilon} & t_{\alpha\alpha}/bn & t_{\beta\beta}/n \\
t_{\alpha\alpha} & abn^2/\theta_4^2 & t_{\beta\beta}
\end{bmatrix},
\]

where

\[
t_{\alpha\alpha} = b^2 n^2 \left( \frac{a - 1}{\theta_{11}^2} + \frac{1}{\theta_4^2} \right) \quad t_{\beta\beta} = a^2 n^2 \left( \frac{b - 1}{\theta_1^2} + \frac{1}{\theta_4^2} \right)
\]

\[
t_{\varepsilon\varepsilon} = \frac{abn - a - b + 1}{\theta_0^2} + \frac{a - 1}{\theta_{11}^2} + \frac{b - 1}{\theta_{12}^2} + \frac{1}{\theta_4^2}
\]

\[
\theta_0 = \sigma_\varepsilon^2 \quad \theta_{11} = \sigma_\varepsilon^2 + bn\sigma_\alpha^2
\]

\[
\theta_{12} = \sigma_\varepsilon^2 + an\sigma_\beta^2 \quad \theta_4 = \sigma_\varepsilon^2 + bn\sigma_\alpha^2 + an\sigma_\beta^2
\]
Example 2. Two-Way Nested Balanced Model

The model

\[ y_{ijk} = \mu + \alpha_i + \beta_{ij} + e_{ijk} \]
\[ = \mu 1 + Z_1 \alpha + Z_2 \beta + Z_0 \epsilon \]

\(i = 1 \ldots a, \quad j = 1 \ldots b\)

\[ k = \begin{cases} 1 \ldots n_{ij} \\ 1 \ldots n \end{cases} \quad N = \begin{cases} \sum_i \sum_j n_{ij} & \text{Unbalanced} \\ a \sum_{ab} n_{ij} & \text{Balanced} \end{cases} \]
Example 2. Two-Way Nested Balanced Model

Information matrix

\[
\mathbf{M} \begin{bmatrix}
\hat{\sigma}_\varepsilon^2 \\
\hat{\sigma}_\alpha^2 \\
\hat{\sigma}_\beta^2
\end{bmatrix} = \frac{1}{2} \begin{bmatrix}
t_{\varepsilon\varepsilon} & t_{\alpha\alpha}/bn & t_{\beta\beta}/n \\
t_{\alpha\alpha} & t_{\alpha\alpha}/b \\
t_{\beta\beta}
\end{bmatrix},
\]

where

\[
t_{\alpha\alpha} = \frac{ab^2n^2}{\theta_{11}^2} \\
t_{\beta\beta} = an^2 \left( \frac{b - 1}{\theta_1^2} + \frac{1}{\theta_{11}^2} \right) \\
t_{\varepsilon\varepsilon} = \frac{ab(n - 1)}{\theta_0^2} + \frac{a(b - 1)}{\theta_1^2} + \frac{a}{\theta_{11}^2} \\
\theta_0 = \sigma_\varepsilon^2 \\
\theta_{11} = \sigma_\varepsilon^2 + n\sigma_\beta^2 + bn\sigma_\alpha^2 \\
\theta_1 = \sigma_\varepsilon^2 + n\sigma_\beta^2
\]
Example 3. Functions of variance components: Ratios

In some applications, the interest is in functions of the variance components.

Define the ratios as

\[ \eta_i = \frac{\sigma_i^2}{\sigma^2_\epsilon}, \quad i = \alpha, \beta. \]

Then,

\[ \eta_\alpha = \frac{\sigma^2_\alpha}{\sigma^2_\epsilon}, \quad \eta_\beta = \frac{\sigma^2_\beta}{\sigma^2_\epsilon}. \]
Example 1(cont). Bioassay as a Two-Way Crossed Model

A bioassay is performed over different occasions $\Rightarrow$ days

The plates wells (exp. units) are measured in different sets of equipment $\Rightarrow$ readers

The experiment consists of taking measurements on $n$ plates, using $b$ different readers in $a$ different days.

The model is

$$ y = \mu 1 + Z_1 \alpha + Z_2 \beta + Z_0 \epsilon $$

$\mu \Rightarrow$ overall mean  \hspace{1cm} $\alpha \Rightarrow$ day effects

$\epsilon \Rightarrow$ random error  \hspace{1cm} $\beta \Rightarrow$ reader effects
Example 1 (cont). Bioassay as a Two-Way Crossed Model

For the locally optimum designs, the space

\[ \sigma^2 = (\sigma^2_\epsilon, \sigma^2_\alpha, \sigma^2_\beta) \]

\[ \sigma^2_r = [0, 1] \quad r = \epsilon, \alpha, \beta \]

is mapped in a fine grid.

For one design and for each of 50000 \( \sigma^2 \) triplets,

- the information matrix is computed
- the design optimality criterion value is calculated

The criterion values are compared across the candidate designs, and the best design is chosen for each \( \sigma^2 \).
Example 1(cont). Bioassay as a Two-Way Crossed Model

Consider a balanced design.

For $N = 24$, the triplet $(a, b, n)$ can generate 9 candidate designs

<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
<th>D8</th>
<th>D9</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4</td>
<td>3</td>
<td>4</td>
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<td>3</td>
<td>2</td>
<td>6</td>
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<td>4</td>
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Example 1 (cont.). Bioassay as a Two-Way Crossed Model

For individual variance components:

<table>
<thead>
<tr>
<th></th>
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<td>6</td>
</tr>
</tbody>
</table>
Example 1 (cont). Bioassay as a Two-Way Crossed Model

Case 1: No specific information about $\sigma^2$ is available.

<table>
<thead>
<tr>
<th>Design</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
<th>D8</th>
<th>D9</th>
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</tbody>
</table>
Example 1 (cont). Bioassay as a Two-Way Crossed Model

Case 2: $\sigma^2_\alpha > \sigma^2_\beta > \sigma^2_\epsilon$

<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
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</tr>
</tbody>
</table>
The bioassay is performed over different occasions \( \Rightarrow \) days.

Different plates are used in every experimental run.

This creates a nesting structure. Plates nested in Days.

The experiment consists of taking \( n \) measurements on \( b \) different plates in \( a \) different days.

The model is

\[
y = \mu 1 + Z_1 \alpha + Z_2 \beta + Z_0 \epsilon
\]

\( \mu \) \( \Rightarrow \) overall mean \( \alpha \) \( \Rightarrow \) day effects

\( \epsilon \) \( \Rightarrow \) random error \( \beta \) \( \Rightarrow \) plate effects in Days
Example 2 (cont). Bioassay as a Two-Way Nested Model

For individual variance components
Example 2 (cont). Bioassay as a Two-Way Nested Model

Case 1: No specific information about $\sigma^2$ is available.
Example 2 (cont). Bioassay as a Two-Way Nested Model

Case 2: $\sigma^2_\alpha > \sigma^2_\beta > \sigma^2_\epsilon$
Example 3a (cont). Variance Components Ratios in the Two-Way Crossed Model

For ratios of variances $\eta_i = \frac{\sigma_i^2}{\sigma^2_\epsilon} \quad i = 1 \ldots$
Example 3b (cont). Variance Components Ratios in the Two-Way Nested Model

For ratios of variances $\eta_i = \frac{\sigma_i^2}{\sigma^2_\epsilon}$ \(i = 1\ldots\)
Conclusions

- Methodology ready to *add* to the Optimum Design Theory
- Easy way to identify the best design
- Easy to extended to different models
- Easy interpretation
Further work

- Easy to extend for optimality of both fixed effects and variance components
- ...more types of Split-Plot designs
- ...many possible functions of the variance components
- ...variance models
- ...nonlinear model for the fixed effect
- ...