Experimental Designs for Estimating Variance Components

Alexander N. Donev and Sergio Loeza-Serrano

School of Mathematics
University of Manchester

E-mail for correspondence: a.n.donev@manchester.ac.uk

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Contents

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

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- Set up the main study
- Estimate variance components
- Identify best conditions
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- 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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Background

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  Khuri (2001)

- 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)
- Experimental designs for mean and variance components models - Giovagnoli, A. and Sebastiani, P. (1989)
- Computer search - Delgado, J. and Iyer, H. (1999)
- Split-factorial designs - Ankenman, B. E., Liu, H., Karr, A. F., and Picka, J. D. (2002)
- Assembled designs - Ankenman, B. E., Avilses, A. I., and Pinheiro, J. C. (2003)

Linear mixed effect model

- Model

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\boldsymbol{\gamma} + \boldsymbol{\epsilon},$$

- $\mathbf{y}$ - vector of N observations
- $\boldsymbol{\epsilon}$ - vector of experimental errors
- $\boldsymbol{\beta}$ & $\boldsymbol{\gamma}$ - vectors of p fixed and r random effects
- $\mathbf{X}$ & $\mathbf{Z}$ - the design matrices for the fixed and the random effects
- Combining $\mathbf{Z}\boldsymbol{\gamma} + \boldsymbol{\epsilon}$

$$\mathbf{Z}\boldsymbol{\gamma} = \sum_{i=0}^{r} \mathbf{Z}_i \boldsymbol{\gamma}_i$$

where

$$\mathbf{Z}_0 = \mathbf{I}_N \qquad \boldsymbol{\gamma}_0 = \boldsymbol{\epsilon}$$

Model assumptions

$$\mathrm{E}(\mathbf{y}) = \mathbf{X}\boldsymbol{\beta}, \quad \mathrm{E}(\boldsymbol{\epsilon}) = \mathbf{0}, \quad \mathrm{E}(\boldsymbol{\gamma}_i) = \mathbf{0}, \quad \mathrm{var}(\boldsymbol{\epsilon}) = \sigma_\epsilon^2 \mathbf{I}_N$$

$$\mathrm{var}(\boldsymbol{\gamma}) = \begin{bmatrix} \sigma_1^2 \mathbf{I}_{q_1} & & & \\ & \sigma_2^2 \mathbf{I}_{q_2} & & \\ & & \ddots & \\ & & & \sigma_r^2 \mathbf{I}_{q_r} \end{bmatrix} \text{ is a block diagonal matrix}$$

Also

$$\mathrm{var}(\mathbf{y}) = \mathbf{V} = \sum_{i=0}^{r} \sigma_i^2 \mathbf{Z}_i \mathbf{Z}_i^{\mathsf{T}}.$$

Maximum Likelihood Estimation

- Model

$$\mathbf{y} \sim N_N(\mathbf{X}\beta, \mathbf{V})$$

- Likelihood

$$L = L(\beta, \mathbf{V}|\mathbf{y}) = \frac{\exp\left(-\frac{1}{2}(\mathbf{y} - \mathbf{X}\beta)^{\mathsf{T}}\mathbf{V}^{-1}(\mathbf{y} - \mathbf{X}\beta)\right)}{(2\pi)^{\frac{1}{2}N}|\mathbf{V}|^{\frac{1}{2}}}$$

- Log-likelihood

$$l = \log(L)$$

Maximum Likelihood Estimation

- Fisher information matrix

$$\mathbf{M}\begin{bmatrix}\beta\\ \sigma^2\end{bmatrix} = \begin{bmatrix}\mathbf{X}^{\mathsf{T}}\mathbf{V}^{-1}\mathbf{X} & \mathbf{0}\\ \mathbf{0} & \frac{1}{2}\mathrm{tr}\left(\mathbf{V}^{-1}\mathbf{Z}_i\mathbf{Z}_i^{\mathsf{T}}\mathbf{V}^{-1}\mathbf{Z}_j\mathbf{Z}_j^{\mathsf{T}}\right)\end{bmatrix} \quad i,j = 0,\ldots,r.$$

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- Optimizing designs for $\boldsymbol{\beta}$ and for $\boldsymbol{\sigma}^2$ can be done independently

Maximum Likelihood Estimation

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- Optimizing designs for $\boldsymbol{\beta}$ and for $\boldsymbol{\sigma}^2$ can be done independently
- Optimality of designs for $\boldsymbol{\beta}$ does not depend on $\boldsymbol{\beta}$

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- Optimizing designs for $\boldsymbol{\beta}$ and for $\boldsymbol{\sigma}^2$ can be done independently
- Optimality of designs for $\boldsymbol{\beta}$ does not depend on $\boldsymbol{\beta}$
- Optimality of designs for $\boldsymbol{\sigma}^2$ does depend on $\boldsymbol{\sigma}^2 = (\sigma_\epsilon^2, \sigma_1^2, \sigma_2^2, \ldots, \sigma_r^2)$

Maximum Likelihood Estimation

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- Optimizing designs for $\boldsymbol{\beta}$ and for $\boldsymbol{\sigma}^2$ can be done independently
- Optimality of designs for $\boldsymbol{\beta}$ does not depend on $\boldsymbol{\beta}$
- Optimality of designs for $\boldsymbol{\sigma}^2$ does depend on $\boldsymbol{\sigma}^2 = (\sigma_\epsilon^2, \sigma_1^2, \sigma_2^2, \ldots, \sigma_r^2)$
- **Hence, the design problem for σ^2 is similar to that for nonlinear models!**

V class of criteria of design optimality

- Let

$$\mathbf{M}(\boldsymbol{\sigma}^{\mathbf{2}}) = \frac{1}{2}\mathrm{tr}\left(\mathbf{V}^{-1}\mathbf{Z}_i\mathbf{Z}_i^{\mathsf{T}}\mathbf{V}^{-1}\mathbf{Z}_j\mathbf{Z}_j^{\mathsf{T}}\right) \quad i,j = 0,\ldots,r$$

- Local $\mathcal{D}$-optimality requires

$$\mathcal{D}_{\mathrm{V}} = \min \left|\mathbf{M}^{-1}(\boldsymbol{\sigma}^{\mathbf{2}})\right|\Big|_{\boldsymbol{\sigma}^{\mathbf{2}}=\boldsymbol{\sigma}_0^2}$$

- Bayesian $\mathcal{D}$-optimality requires

$$\mathcal{D}_{\mathrm{V}} = \min \left|\mathbf{M}^{-1}(\boldsymbol{\sigma}^{\mathbf{2}})\right|\Big|_{\boldsymbol{\sigma}^{\mathbf{2}}\in\Sigma}$$

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Similarity

- Design optimality for $\boldsymbol{\sigma}^{\mathbf{2}}$ does not depend on the total variability but only on the proportions of the variance components

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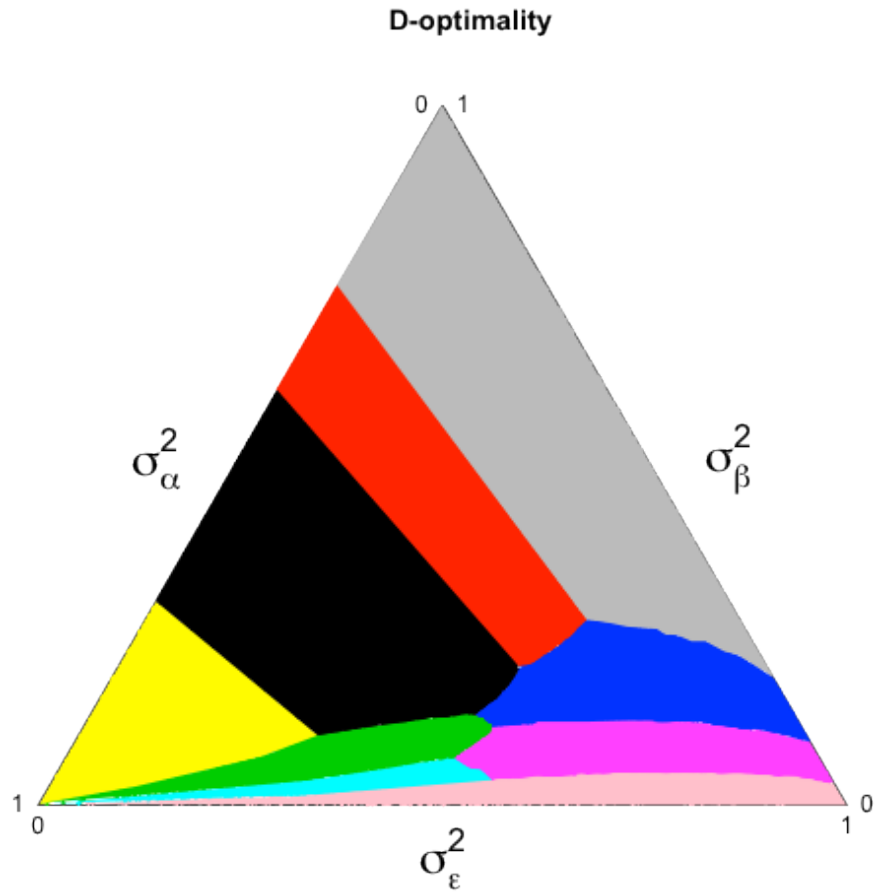

V class of criteria of design optimality

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

$$\begin{aligned} y_{ijk} &= \mu + \alpha_i + \beta_j + e_{ijk} \\ &= \mu\mathbf{1} + \mathbf{Z}_1\boldsymbol{\alpha} + \mathbf{Z}_2\boldsymbol{\beta} + \mathbf{Z}_0\boldsymbol{\epsilon} \end{aligned}$$

$i = 1 \ldots a, \qquad j = 1 \ldots b$

$$k = \begin{cases} 1 \ldots n_{ij} \\ 1 \ldots n \end{cases} \qquad N = \begin{cases} \sum_i^a \sum_j^b n_{ij} & \text{Unbalanced} \\ abn & \text{Balanced} \end{cases}$$

Example 1. Two-Way Crossed Model (No Interaction)

Information matrix

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

where

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

$$t_{\epsilon\epsilon} = \frac{abn-a-b+1}{\theta_0^2}+\frac{a-1}{\theta_{11}^2}+\frac{b-1}{\theta_{12}^2}+\frac{1}{\theta_4^2}$$

$$\theta_0 = \sigma_\epsilon^2 \qquad \theta_{11} = \sigma_\epsilon^2 + bn\sigma_\alpha^2$$

$$\theta_{12} = \sigma_\epsilon^2 + an\sigma_\beta^2 \qquad \theta_4 = \sigma_\epsilon^2 + bn\sigma_\alpha^2 + an\sigma_\beta^2$$

Example 2. Two-Way Nested Balanced Model

The model

$$\begin{aligned} y_{ijk} &= \mu + \alpha_i + \beta_{ij} + e_{ijk} \\ &= \mu\mathbf{1} + \mathbf{Z}_1\boldsymbol{\alpha} + \mathbf{Z}_2\boldsymbol{\beta} + \mathbf{Z}_0\boldsymbol{\epsilon} \end{aligned}$$

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where

$$t_{\alpha\alpha} = \frac{ab^2n^2}{\theta_{11}^2} \qquad t_{\beta\beta} = an^2\left(\frac{b-1}{\theta_1^2} + \frac{1}{\theta_{11}^2}\right)$$

$$t_{\epsilon\epsilon} = \frac{ab(n-1)}{\theta_0^2} + \frac{a(b-1)}{\theta_1^2} + \frac{a}{\theta_{11}^2}$$

$$\theta_0 = \sigma_\epsilon^2 \qquad \theta_{11} = \sigma_\epsilon^2 + n\sigma_\beta^2 + bn\sigma_\alpha^2$$

$$\theta_1 = \sigma_\epsilon^2 + n\sigma_\beta^2$$

Example 3. Functions of variance components: Ratios

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

- Define the ratios as

$$\eta_i = \frac{\sigma_i^2}{\sigma_\epsilon^2} \quad i = \alpha, \beta.$$

Then,

$$\eta_\alpha = \frac{\sigma_\alpha^2}{\sigma_\epsilon^2} \qquad \eta_\beta = \frac{\sigma_\beta^2}{\sigma_\epsilon^2}.$$

Example 1(cont). Bioassay as a Two-Way Crossed Model

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

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

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

The model is

$$\mathbf{y} = \mu\mathbf{1} + \mathbf{Z}_1\boldsymbol{\alpha} + \mathbf{Z}_2\boldsymbol{\beta} + \mathbf{Z}_0\boldsymbol{\epsilon}$$

$\mu \Longrightarrow$ overall mean $\quad \alpha \Longrightarrow$ day effects

$\epsilon \Longrightarrow$ random error $\quad \beta \Longrightarrow$ reader effects

Example 1(cont). Bioassay as a Two-Way Crossed Model

For the locally optimum designs, the space

$$\boldsymbol{\sigma^2} = \left(\sigma^2_\epsilon, \sigma^2_\alpha, \sigma^2_\beta\right)$$

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

is mapped in a fine grid.

For one design and for each of 50000 $\boldsymbol{\sigma^2}$ 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 $\boldsymbol{\sigma^2}$.

Example 1(cont). Bioassay as a Two-Way Crossed Model

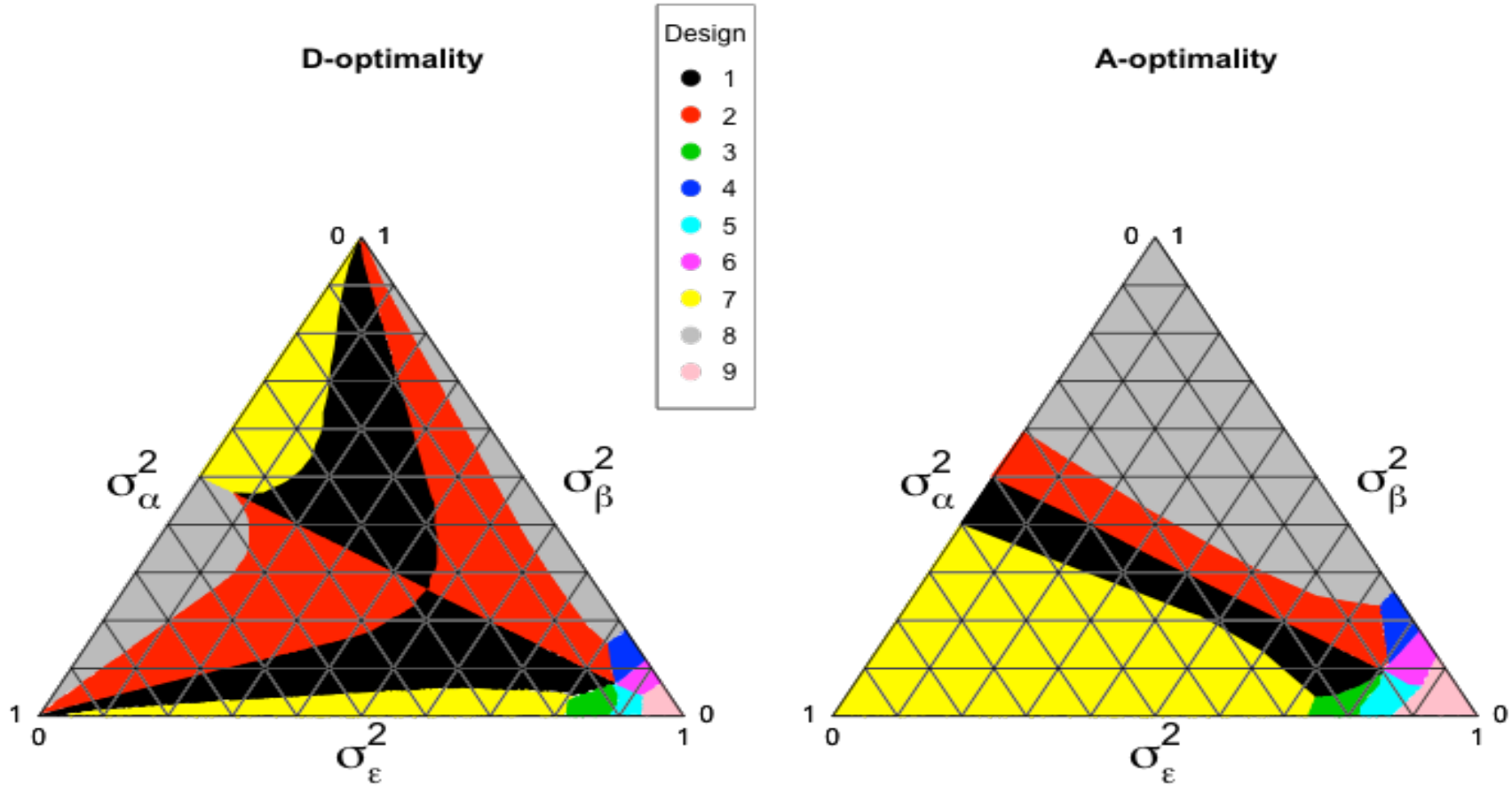
Consider a balanced design.

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

	D1	D2	D3	D4	D5	D6	D7	D8	D9
a	4	3	4	2	3	2	6	2	2
b	3	4	2	4	2	3	2	6	2
n	2	2	3	3	4	4	2	2	6

Example 1(cont). Bioassay as a Two-Way Crossed Model

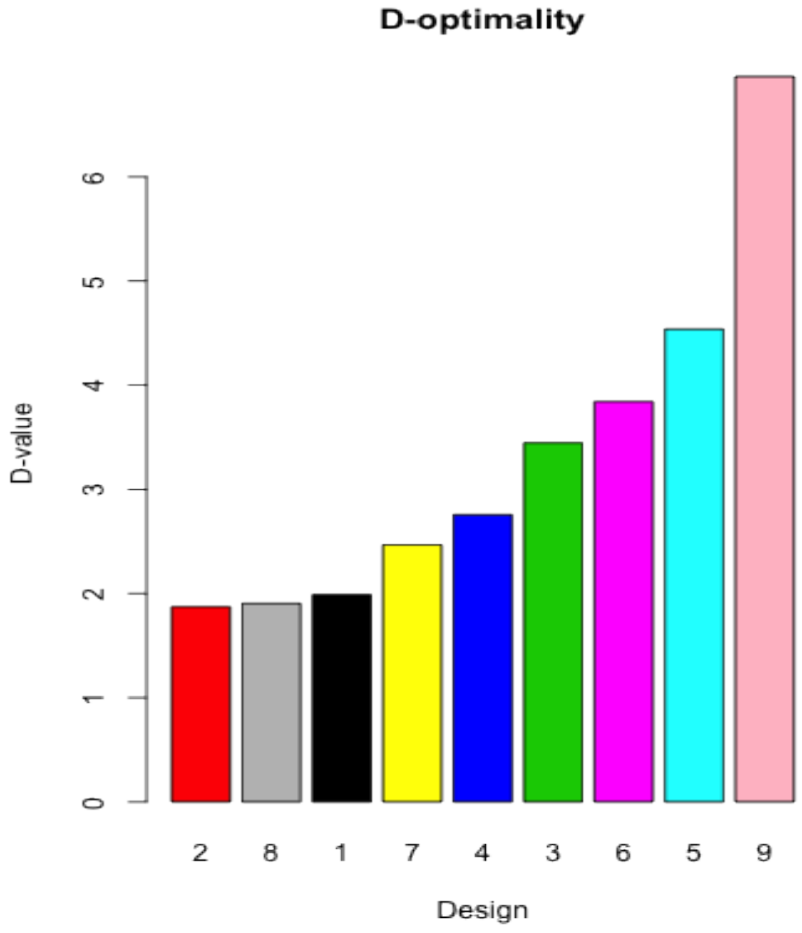
For individual variance components:

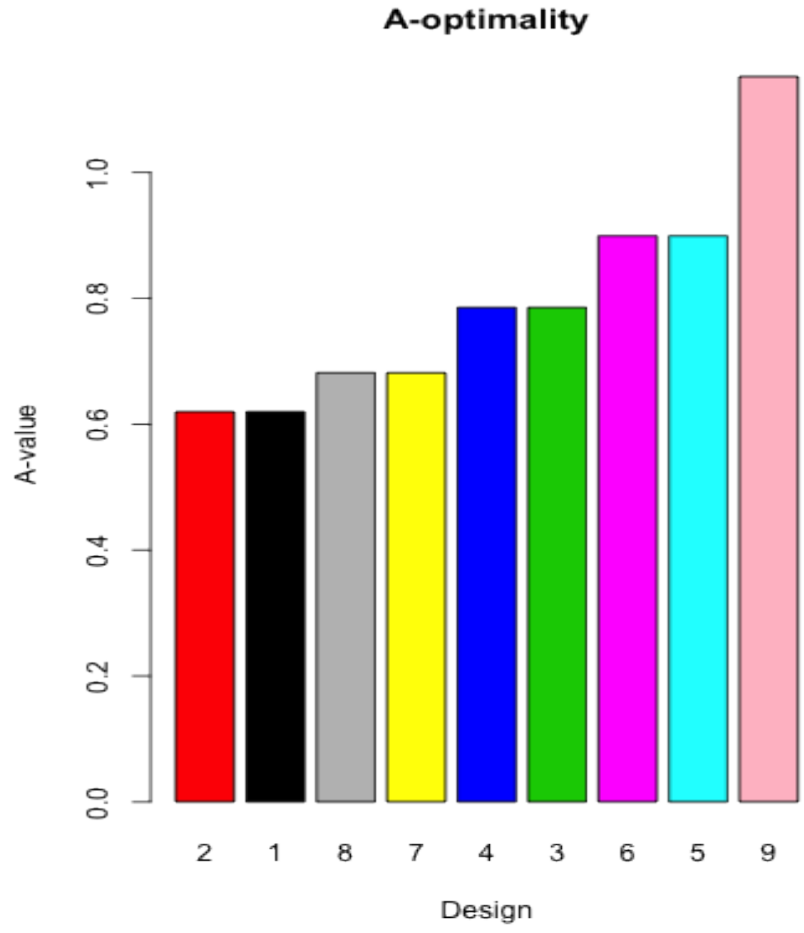


	D1	D2	D3	D4	D5	D6	D7	D8	D9
a	4	3	4	2	3	2	6	2	2
b	3	4	2	4	2	3	2	6	2
n	2	2	3	3	4	4	2	2	6

Example 1(cont). Bioassay as a Two-Way Crossed Model

Case 1: No specific information about σ^2 is available.





	D1	D2	D3	D4	D5	D6	D7	D8	D9
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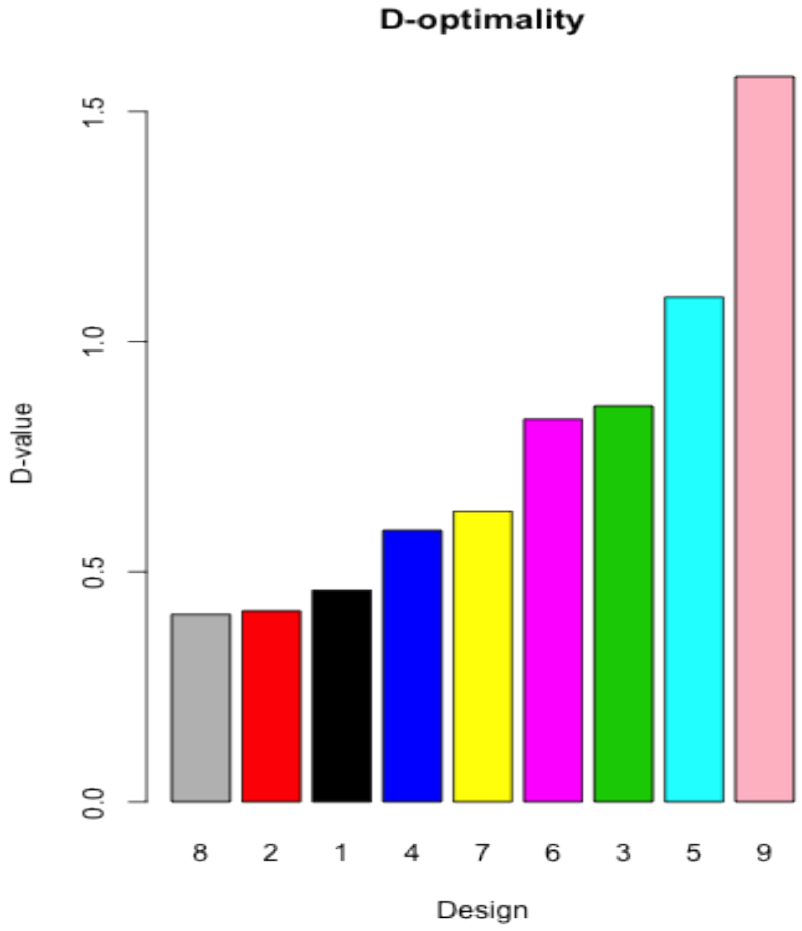
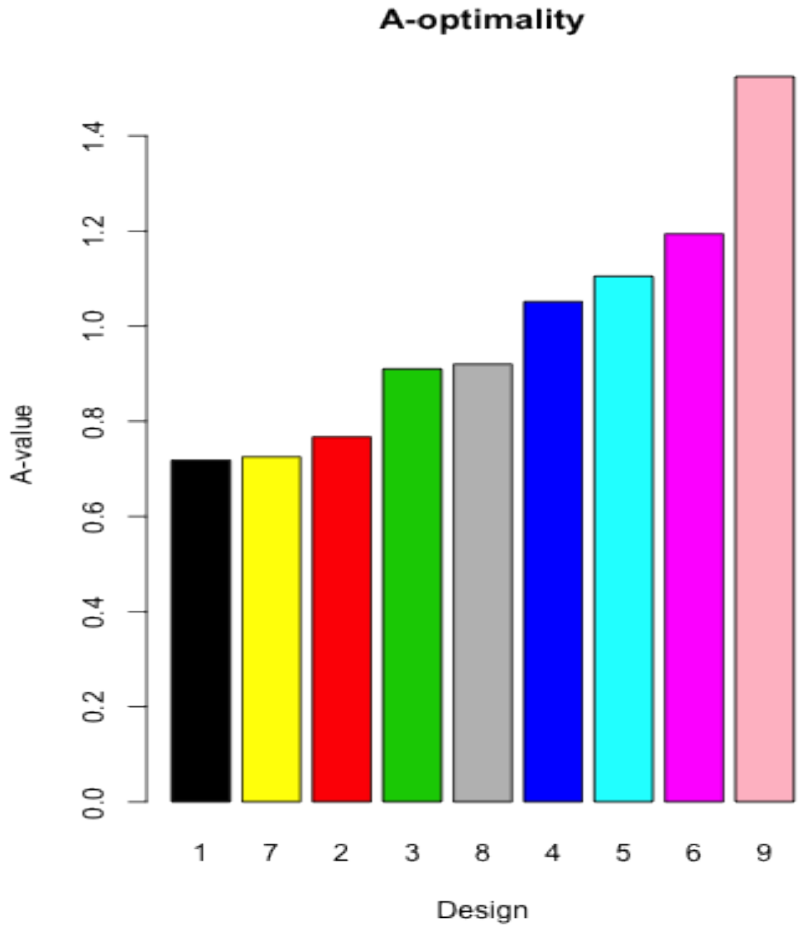
b	3	4	2	4	2	3	2	6	2
n	2	2	3	3	4	4	2	2	6

Example 1(cont). Bioassay as a Two-Way Crossed Model

Case 2: $\sigma_\alpha^2 > \sigma_\beta^2 > \sigma_\epsilon^2$





	D1	D2	D3	D4	D5	D6	D7	D8	D9
a	4	3	4	2	3	2	6	2	2
b	3	4	2	4	2	3	2	6	2
n	2	2	3	3	4	4	2	2	6

Example 2(cont). Bioassay as a Two-Way Nested Model

The bioassay is performed over different occasions $\Longrightarrow$ 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

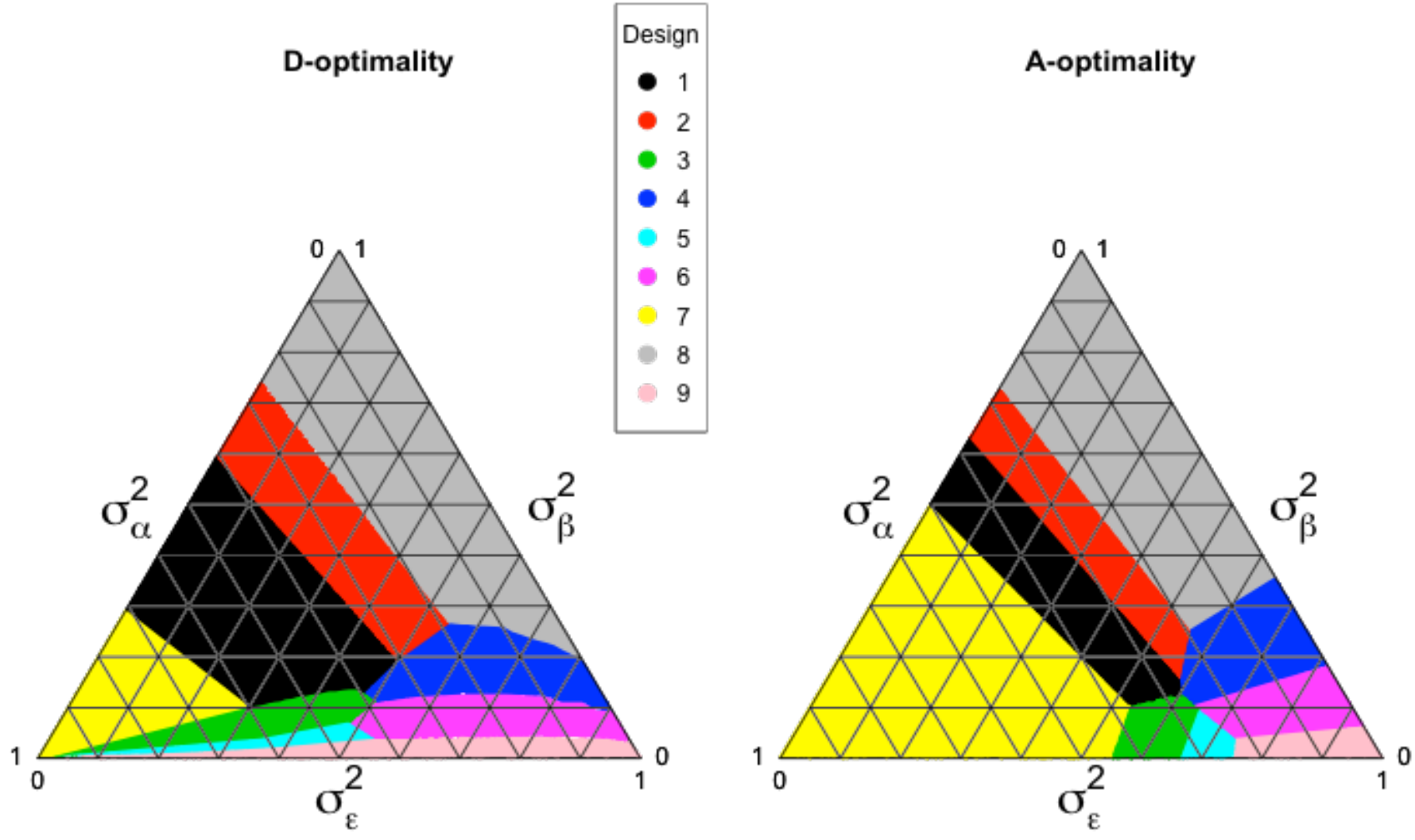
$$\mathbf{y} = \mu\mathbf{1} + \mathbf{Z}_1\boldsymbol{\alpha} + \mathbf{Z}_2\boldsymbol{\beta} + \mathbf{Z}_0\boldsymbol{\epsilon}$$

$\mu \Longrightarrow$ overall mean $\quad \alpha \Longrightarrow$ day effects

$\epsilon \Longrightarrow$ random error $\quad \beta \Longrightarrow$ plate effects in Days

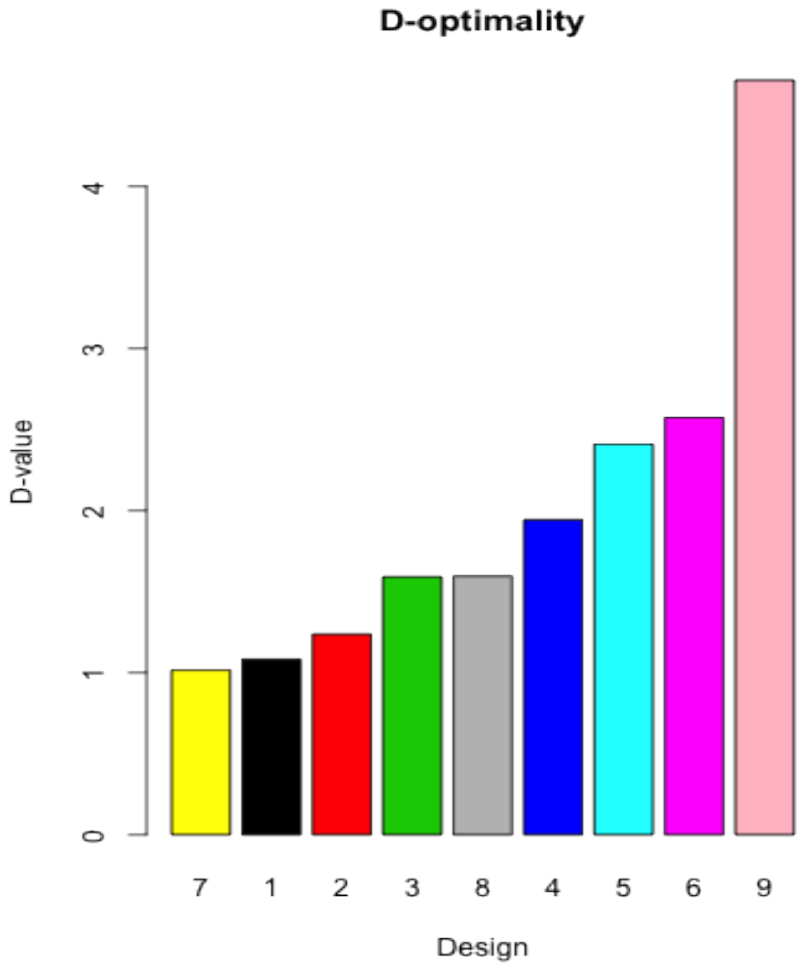
Example 2(cont). Bioassay as a Two-Way Nested Model

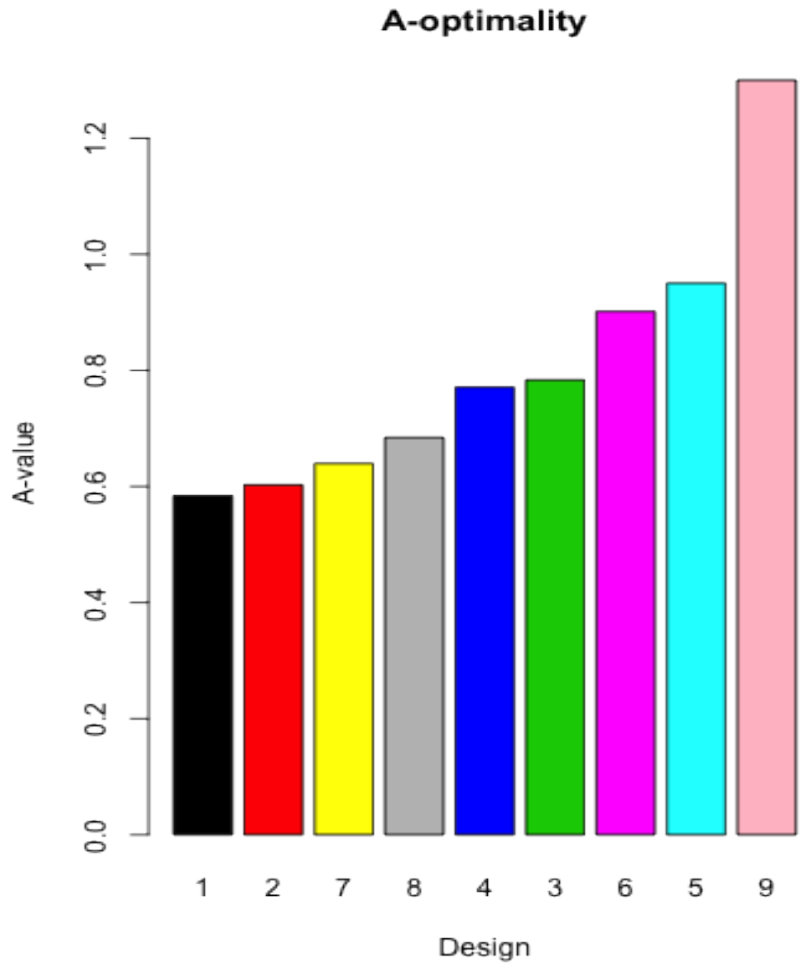
For individual variance components



Example 2(cont). Bioassay as a Two-Way Nested Model

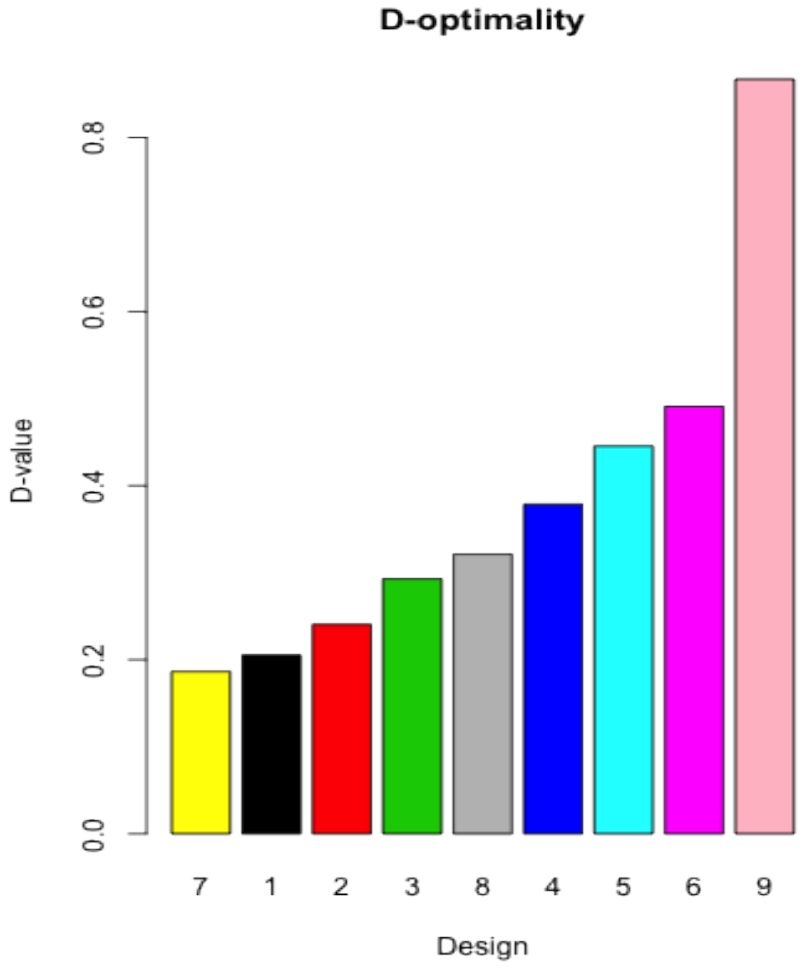
Case 1: No specific information about σ^2 is available.

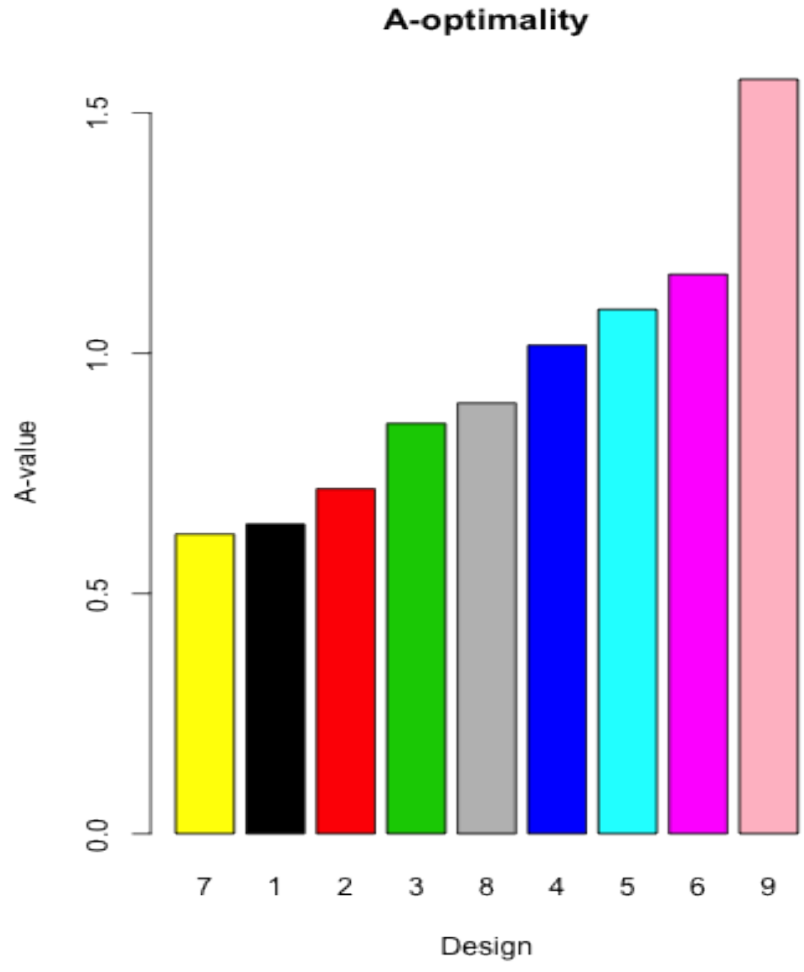




Example 2(cont). Bioassay as a Two-Way Nested Model

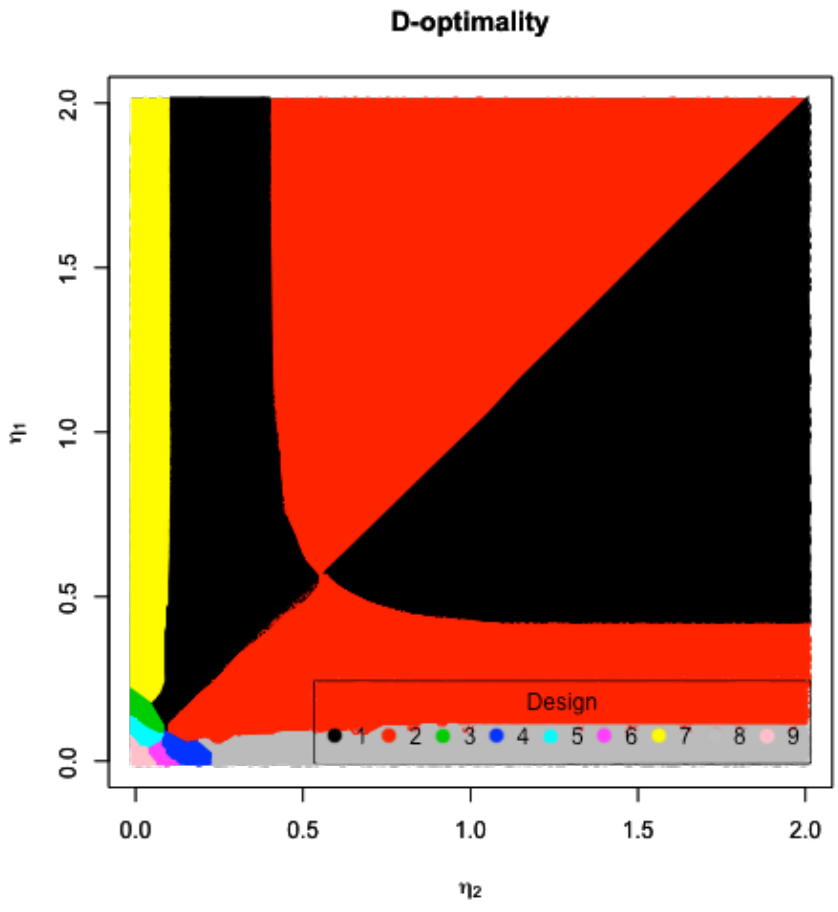
Case 2: $\sigma_\alpha^2 > \sigma_\beta^2 > \sigma_\epsilon^2$

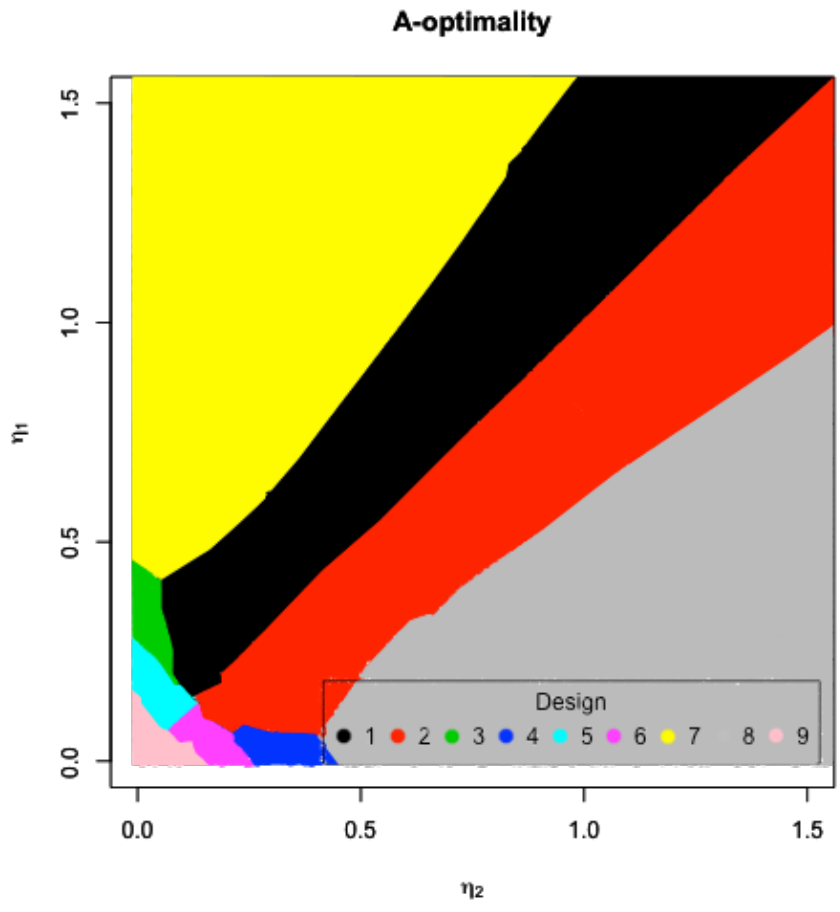




Example 3a(cont). Variance Components Ratios in the Two-Way Crossed Model

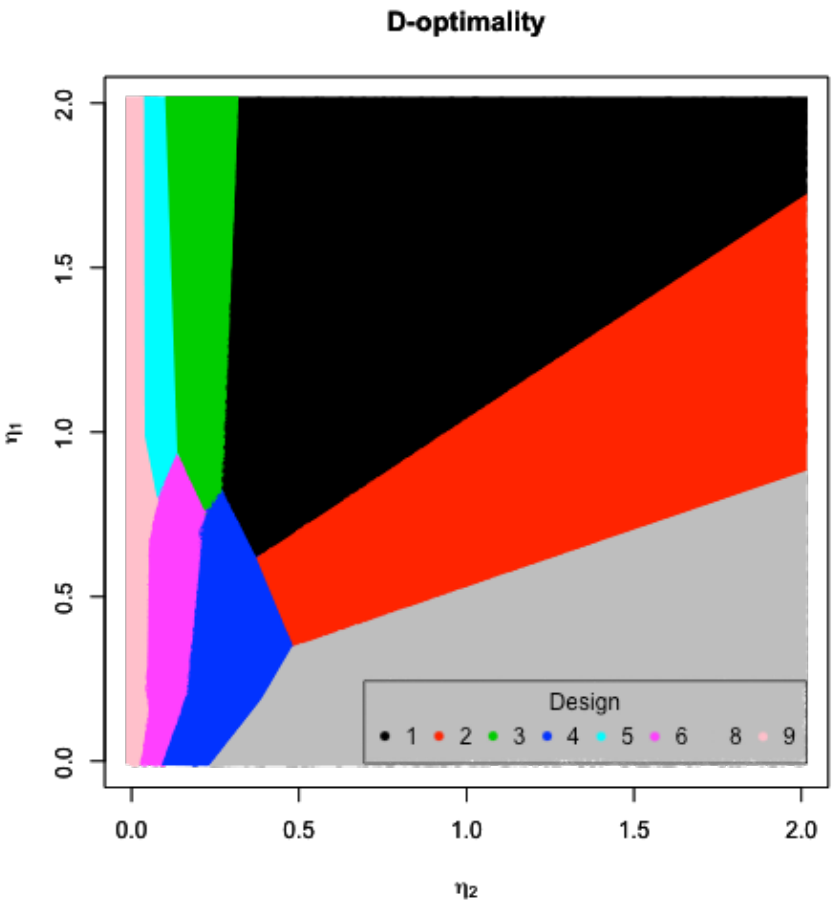
For ratios of variances $\eta_i = \frac{\sigma_i^2}{\sigma_\epsilon^2} \quad i = 1 \ldots$

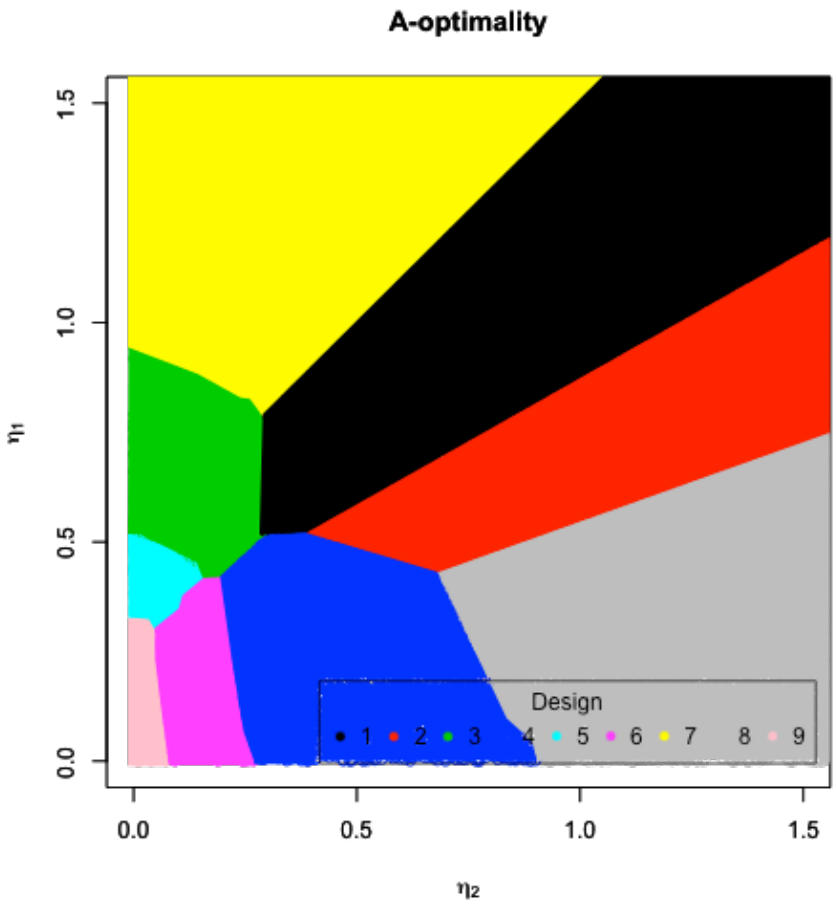




Example 3b(cont). Variance Components Ratios in the Two-Way Nested Model

For ratios of variances $\eta_i = \frac{\sigma_i^2}{\sigma_\epsilon^2} \quad i = 1 \ldots$





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
- . . .