Example 5. Two Consecutive Chemical Reactions

D-optimum Designs for the Rates of Reaction

If the orders of reaction λ_1 and λ_2 are known, it makes sense to find D-optimum designs for estimating the rates k_1 and k_2.

Such designs maximise

$$\log |M_{11}(\xi, k_1^o, k_2^o)|,$$

and they have two design points, with weight 0.5 at each point.

They are listed in Table 2. The optimum points when λ^{T} = (1, 1) were originally calculated by Box and Lucas (1959).

Example 5. Two Consecutive Chemical Reactions

D-optimum Designs for the Rates of Reaction

Orders of Reaction $\lambda^{\mathrm{T}} = (\lambda_1, \lambda_2)$	Times t_1^*	t_2^*
(1,1)	1.23	6.85
(2,1)	1.01	7.70
(1,2)	1.19	7.52
(2,2)	1.06	10.09

Table 2. D-optimum designs for the rates, taking prior (k_1^o, k_2^o) = $(0.7, 0.2)$ when the orders are assumed known. The weights are 0.5 at each design point.

It is NOT surprising that the designs depend so little on the assumed values of λ_1 and λ_2.

The large values of time in Table 1 are not present in the optimum designs for the rates only.

D_s-optimum Designs

Example 5. Two Consecutive Chemical Reactions

If only a subset of s of the parameters, $\vartheta_{(2)}$, is of interest, we can calculate so-called D_s-optimum designs.

Let the parameters be partitioned as

$$\vartheta = (\vartheta_{(1)}, \vartheta_{(2)})^{\mathrm{T}}$$

with the information matrix $M(\xi, \vartheta)$ partitioned so that the information for $\vartheta_{(1)}$ is $M_{11}(\xi, \vartheta)$.

Then the D_s-optimum design for $\vartheta_{(2)}$ maximises

$$\log\left\{\frac{|M(\xi, \vartheta)|}{|M_{11}(\xi, \vartheta)|}\right\}.$$

D$_s$-optimum Designs

Example 5. Two Consecutive Chemical Reactions

The Equivalence Theorem for D$_s$-optimum designs states that, for the optimum measure ξ^*, the analogue of the standardised variance of prediction is

$$d(t,\xi^*,\vartheta) = f(t,\vartheta)^{\mathrm{T}} M^{-1}(\xi^*,\vartheta) f(t,\vartheta) - f_{(1)}(t,\vartheta)^{\mathrm{T}} M_{11}^{-1}(\xi^*,\vartheta) f_{(1)}(t,\vartheta) \leq s,$$

where $f_{(1)}(t,\vartheta)^{\mathrm{T}}$ is the vector of sensitivities for the $p-s$ parameters $\vartheta_{(1)}$.

D_s-optimum Designs

Example 5. Two Consecutive Chemical Reactions

Prior Orders of Reaction $(\lambda_1^o, \lambda_2^o)$	Times and Weights			
	t_1^* / w_1^*	t_2^* / w_2^*	t_3^* / w_3^*	t_4^* / w_4^*
(1,1)	0.54	3.13	7.48	17.61
	0.16	0.25	0.18	0.41
(2,1)	0.36	2.57	7.49	20.91
	0.22	0.22	0.17	0.39
(1,2)	0.55	3.15	8.57	50.00
	0.14	0.26	0.18	0.42
(2,2)	0.40	2.93	9.49	50.00
	0.21	0.24	0.18	0.37

Table 3. D_s-optimum designs for estimating the orders of the reaction, assuming $(k_1^o, k_2^o) = (0.7, 0.2)$. Both weights and design points have to be found numerically.

Compound Optimum Designs

Each of the three designs of the previous section is tailor-made for solving one aspect of the design problem.

We now consider the use of compound optimum designs by which the experimenter can find a single design which strikes a balance between the three objectives.

The compound design criterion used here is a linear combination of the previous criteria

$$\begin{aligned}\Phi(\xi,\vartheta) &= (1-\alpha)\log|M_{11}(\xi,\vartheta)| + \alpha\log\{|M(\xi,\vartheta)|/|M_{11}(\xi,\vartheta)|\}\\ &= (1-2\alpha)\log|M_{11}(\xi,\vartheta)| + \alpha\log|M(\xi,\vartheta)|.\end{aligned}$$

Recall that

$$\begin{aligned}\Phi(\xi,\vartheta) &= (1-\alpha)\log|M_{11}(\xi,\vartheta)| + \alpha\log\{|M(\xi,\vartheta)|/|M_{11}(\xi,\vartheta)|\}\\ &= (1-2\alpha)\log|M_{11}(\xi,\vartheta)| + \alpha\log|M(\xi,\vartheta)|.\end{aligned}$$

Here, $0 \le \alpha \le 1$ expresses the experimenter's relative interest in determination of the parameters of the reaction:

- When $\alpha = 1$, interest is solely in order determination.
- When $\alpha = 0.5$, the criterion becomes a multiple of that for D-optimality for both orders and rates.
- When $\alpha = 0$, the criterion becomes that of D-optimality when it is assumed that the orders of reaction are known.

Compound Optimum Designs

The variance function is then the weighted linear combination of the variances for the individual criteria with the same weights.

Therefore, the optimum design ξ_c^* is such that

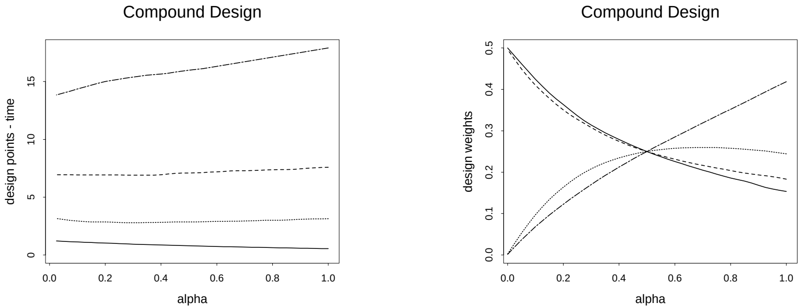
$$
\begin{aligned}
& d_c(t, \xi_c^*, \vartheta) \\
& = (1-2\alpha) f_{(1)}(t,\vartheta)^{\mathrm{T}} M_{11}^{-1}(\xi_c^*, \vartheta) f_{(1)}(t,\vartheta) + \alpha f(t,\vartheta)^{\mathrm{T}} M^{-1}(\xi_c^*, \vartheta) f(t,\vartheta) \\
& \leq (1-2\alpha) r + \alpha(r+s) = r + \alpha(s-r),
\end{aligned}
$$

where $r = p - s$.

- The bound on the variance then depends on α unless $s = r = p/2$.
- In many kinetic models, there are fewer rate constants than orders of reaction, and so we may have $r < s$.
- But, in our example, $r = s = 2$, so that the variance does not depend on α.

Compound Optimum Designs

Example 5. Two Consecutive Chemical Reactions



Support points and the weights of the compound optimum design for $\lambda_1^o = \lambda_2^o = 1$ as a function of α.

- These figures show the behaviour of the compound designs as α changes.
- To choose a value of α which yields a design reflecting the experimenter's interests requires calculation of the efficiency of a proposed design for the three specific aspects of interest.

Design Efficiency

The design efficiency is defined as

$$E(\xi) = \frac{\Phi(\xi, \vartheta^o)}{\Phi(\xi^\star, \vartheta^o)},$$

where Φ is an optimality criterion.

For D-optimality, we use

$$E(\xi) = \left\{ \frac{|M(\xi, \vartheta^o)|}{|M(\xi^\star, \vartheta^o)|} \right\}^{\frac{1}{p}}.$$

Design Efficiency

Example 5. Two Consecutive Chemical Reactions

Let the D-optimum design for estimating k_1 and k_2 be ξ_k^*. Then the efficiency of the compound design if only the rates of reaction are of interest is

$$E_k = 100\{|M_{11}(\xi_c^*, \vartheta^o)|/|M_{11}(\xi_k^*, \vartheta^o)|\}^{1/r}.$$

Likewise, if the D_s-optimum design for estimating λ_1 and λ_2 is ξ_λ^*, the relevant efficiency is

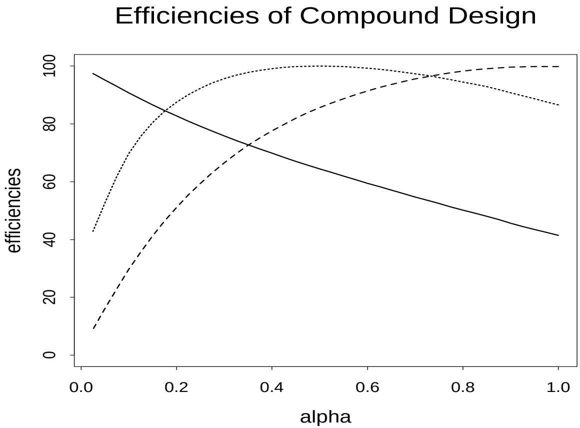
$$E_\lambda = 100\left\{\frac{|M(\xi_c^*, \vartheta^o)|/|M_{11}(\xi_c^*, \vartheta^o)|}{|M(\xi_\lambda^*, \vartheta^o)|/|M_{11}(\xi_\lambda^*, \vartheta^o)|}\right\}^{1/s}.$$

Finally, if the D-optimum design for the k s and λs is ξ_D^*, the efficiency is

$$E_D = 100\{|M(\xi_c^*, \vartheta^o)|/|M(\xi_D^*, \vartheta^o)|\}^{1/p}.$$

Design Efficiency

Example 5. Two Consecutive Chemical Reactions



Efficiencies of the compound optimum design for $\lambda_1^o = \lambda_2^o$ = 1 as a function of α. Reading upwards at $\alpha = 1$: E_k, E_D and E_λ.

Design Efficiency

Example 5. Two Consecutive Chemical Reactions

- At the boundaries of the range of α, the compound design is good for only one of the aspects of the problem:
  - either estimation of the rates of reaction, when α is close to zero, or
  - the estimation of orders with rates as nuisance parameters, when α is close to one.
- When $\alpha = 0.5$, the compound design is 100% efficient for estimation of both sets of parameters: it is D-optimum for ϑ and λ.
- An interesting choice of α is 0.73 where the curves for E_D and E_λ intersect and the efficiencies are approximately 96%.

Optimum design for a function of model parameters

c-optimality

To optimise a design for estimation of a linear combination of the parameters

$$c^{\mathrm{T}}\widehat{\vartheta},$$

where c is a p-dimensional vector of coefficients, we optimise the variance of the combination, that is,

$$\mathrm{var}(c^{\mathrm{T}}\widehat{\vartheta}) = c^{\mathrm{T}}M^{-1}(\xi)c.$$

Non-linear functions of the parameters, $g(\vartheta)$, are linearised to obtain

$$g(\vartheta) \cong \text{const} + c^{\mathrm{T}}\vartheta.$$

Then the variance is as above with

$$c^{\mathrm{T}} = \left(\frac{\partial g(\vartheta)}{\partial \vartheta_1}, \ldots, \frac{\partial g(\vartheta)}{\partial \vartheta_p}\right).$$

c-optimality

Example 6. Three-Parameter Compartmental Model

Atkinson, Donev and Tobias (2007)
The model

$$\eta(t, \vartheta) = \vartheta_3\{\exp(-\vartheta_2 t) - \exp(-\vartheta_1 t)\}, \qquad t \geq 0,$$

where $\vartheta_1 > \vartheta_2$ and all three parameters are positive, was used by Fresen (1984) to analyse the data on the concentration of theophylline in the blood of a horse. Fresen used an 18-point design.

The focus here is not whether it is possible to do better than this 18-point design.

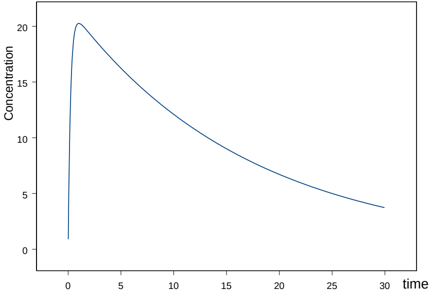
We shall be concerned with how the optimum design depends on the aspect of the model that is of interest.

c-optimality

Example 6. Three-Parameter Compartmental Model

The least squares estimates of the parameters are used as prior values:

$$\vartheta_1^0 = 4.29, \quad \vartheta_2^0 = 0.0589, \quad \vartheta_3^0 = 21.80.$$

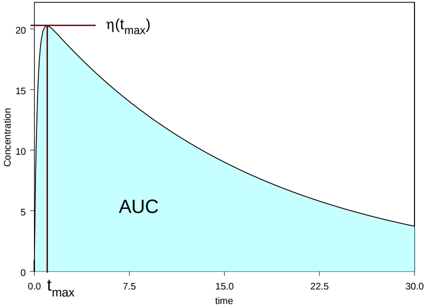


The concentration of theophylline in the blood of a horse.

c-optimality

Example 6. Three-Parameter Compartmental Model

- Area under the curve: $g_1(\vartheta) = \int_0^\infty \eta(t, \vartheta)dt$
- Time to maximum concentration: $g_2(\vartheta) = t_{max}(\vartheta)$
- The maximum concentration: $g_3(\vartheta) = \eta(t_{max}, \vartheta)$



c-optimality

Example 6. Three-Parameter Compartmental Model

The total area under the curve (AUC) is

$$g_1(\vartheta) = \int_0^\infty \eta(t, \vartheta)\mathrm{d}t = \frac{\vartheta_3}{\vartheta_2} - \frac{\vartheta_3}{\vartheta_1} = \vartheta_3 \left(\frac{1}{\vartheta_2} - \frac{1}{\vartheta_1} \right).$$

This function is linear in ϑ_3 and non-linear in ϑ_1 and ϑ_2.

The time to maximum concentration (t_{max}) is found by differentiation of $\eta(t, \vartheta)$ with respect to t to be

$$g_2(\vartheta) = \frac{\log(\vartheta_1) - \log(\vartheta_2)}{\vartheta_1 - \vartheta_2},$$

which does not depend on ϑ_3.

The maximum concentration is found by substituting t_{max} in $\eta(t, \vartheta)$:

$$g_3(\vartheta) = \eta(t_{\mathsf{max}}, \vartheta).$$

c-optimality

Example 6. Three-Parameter Compartmental Model

Criterion	Time t	Design Weight
D	0.23	1/3
	1.39	1/3
	18.45	1/3
c_{AUC}	0.23	0.0135
	17.63	0.9865
$c_{t_{max}}$	0.18	0.6061
	3.57	0.3939
$c_{\eta(t_{max})}$	1.01	1

D- and c-optimum designs

c-optimality

Example 6. Three-Parameter Compartmental Model

- The D-optimum design for this three-parameter model has three support points, each with weight 1/3. It allows estimation of the three parameters.
- The c-optimum designs, with only two points of support, or even with only one, are singular.
- In order to calculate the designs, the singularity of $M(\xi)$ was overcome by use of the ridge-type regularisation procedure in which a small quantity ϵ is added to the diagonal of $M(\xi)$ before inversion. An ϵ value of 10^{-5} was found to be adequate.
- With this regularisation, it is possible to check the equivalence theorem that, for each optimum design,

$$\{f(x)^{\mathrm{T}} M^{-1}(\xi^*) c(\vartheta)\}^2 \leq c(\vartheta)^{\mathrm{T}} M^{-1}(\xi^*) c(\vartheta)$$

for all $x \in \mathcal{X}$, the design region.

c-optimality

Example 6. Three-Parameter Compartmental Model: AUC

For the area under the curve

$$
g_1(\vartheta) = \frac{\vartheta_3}{\vartheta_2} - \frac{\vartheta_3}{\vartheta_1},
$$

$$
c(\vartheta) = \begin{pmatrix} c_1(\vartheta) \\ c_2(\vartheta) \\ c_3(\vartheta) \end{pmatrix} = \begin{pmatrix} \vartheta_3/\vartheta_1^2 \\ -\vartheta_3/\vartheta_2^2 \\ 1/\vartheta_2 - 1/\vartheta_1 \end{pmatrix}.
$$

So the c_{AUC}-optimum design is

$$
\xi^\star = \arg\min_{\xi} \mathrm{var}\left\{\widehat{g_1(\vartheta)}\right\} \cong \arg\min_{\xi} c(\vartheta)^{\mathrm{T}} M^{-1}(\xi,\vartheta) c(\vartheta).
$$

c-optimality

Example 6. Three-Parameter Compartmental Model: AUC

Here,

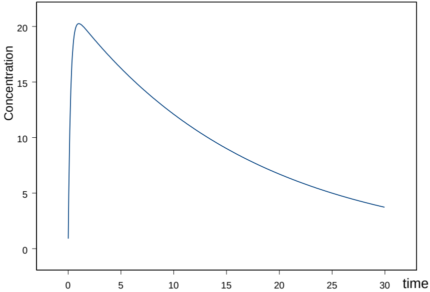
$$\xi^\star = \left\{ \begin{array}{cc} 0.23 & 17.63 \\ 0.0135 & 0.9865 \end{array} \right\}.$$

- The c_{AUC}-optimum design for estimating the AUC has only two points of support.
- This makes some sense, as the criterion is a function of the two ratios ϑ_3/ϑ_1 and ϑ_3/ϑ_2.
- The reading at the low time of 0.23 allows efficient estimation of the ratio ϑ_3/ϑ_1, whereas that at $t = 17.6$ is for the ratio ϑ_3/ϑ_2.

c-optimality

Example 6. Three-Parameter Compartmental Model: AUC

The curve rises very rapidly to the maximum at $t = 1.10$, declining slowly thereafter.



The relationship between ϑ_3 and ϑ_2 is therefore of greater importance in determining the AUC. It is reflected in the design putting over 98% of the experimental effort at the higher value of t.

c-optimality

Example 6. Three-Parameter Compartmental Model: t_{max}

Here,

$$\xi^\star = \left\{ \begin{array}{cc} 0.18 & 3.57 \\ 0.6061 & 0.3939 \end{array} \right\}.$$

- The $c_{t_{max}}$-optimum design for t_{max} again has two points of support.
- In comparison with the design for the AUC, the experimental effort is much more evenly spread over the two design points.
- In addition, these points are relatively close to the calculated time of maximum concentration.

c-optimality

Example 6. Three-Parameter Compartmental Model: $\eta(t_{max})$

This time,

$$\xi^\star = \left\{ \begin{array}{c} 1.01 \\ 1 \end{array} \right\}.$$

- The c$_{\eta(t_{max})}$-optimum design is concentrated on one point; all measurements are taken at t_{max}, the time at which the maximum is believed to occur.
- This is an extreme example of a c-optimum design for which the quantity of interest is not estimable.
- If this design were to be used, so that measurements were taken at only one point, it would be impossible to tell where, in fact, the response was a maximum.
- These results demonstrate that, whichever criterion of optimality is used, the optimum design has far fewer points of support than the 18-point design used originally.

Efficiencies of the D- and c-optimum designs

Example 6. Three-Parameter Compartmental Model

This table shows that it may be very inefficient to use a D-optimum design (or an equally-spaced design) when a function of the parameters is of interest rather than the model parameters themselves.

	Efficiency for			
Design	D-optimum	AUC	t_{max}	$\eta(t_{max})$
D-optimum	100.0	34.31	65.94	36.10
18-point	67.65	24.00	28.61	36.77

Possible remedies for the singularity problem

1. Take observations not only at the optimum points but also at some points close to the optimum ones.
   - This will lower the efficiency, but not very much if the other points are not far from the optimum ones.
2. Use a compound design criterion

$$\Psi\{M(\xi,\vartheta)\} = \sum_{j=1}^{3} \log\{c_{g_j(\vartheta)}(\xi,\vartheta)^{\mathrm{T}} M^{-1}(\xi,\vartheta) c_{g_j(\vartheta)}(\xi,\vartheta)\}.$$

   - This is a 'compromise' kind of criterion, good for all purposes but not optimum for any.
3. Use a Bayesian approach.