DESIGN OF EXPERIMENTS FOR NON-LINEAR MODELS

Part 2

Barbara Bogacka

Queen Mary, University of London

D - the most popular optimality criterion

The criterion, introduced by Wald (1943), is

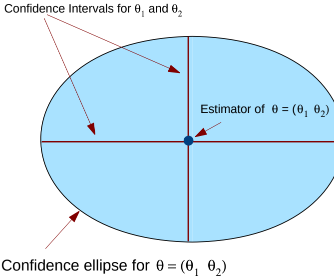
$$\Phi_D = \det(M^{-1}).$$

Properties:

- it minimises the general variance of the parameter estimator,
- it minimises the volume of the parameter confidence ellipsoid,
- it is invariant under linear transformations of the parameters,
- it is equivalent to G-optimality, what is given in so called Equivalence Theorem,
- it has at most $p(p+1)/2+1$ points of support (Carathéodory's Theorem)

D - the most popular optimality criterion

Geometrical Interpretation - volume of confidence ellipsoid



$100(1-\alpha)\%$ confidence region of for parameter estimates is

$$(\theta - \widehat{\theta})^{\mathrm{T}} M (\theta - \widehat{\theta}) \leq p s^2 F_{p,\nu,\alpha},$$

where s^2 is an estimate of σ^2, and $F_{p,\nu,\alpha}$ is $100\alpha\%$ point of the F distribution on p and ν degrees of freedom.

The volume of a p-dim. ellipsoid is proportional to $\left[\det M^{-1}\right]^{1/2}$.

D - the most popular optimality criterion

Geometrical Interpretation - design locus

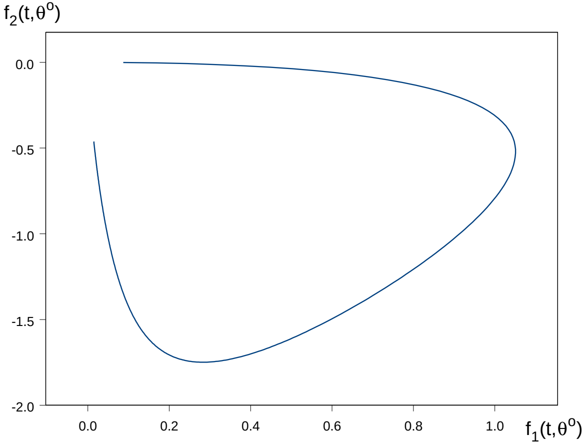
Locally optimum designs for non-linear models with p parameters usually have p support points. Then the weights are all equal to $1/p$.

Design locus is derived on the basis that the volume of a simplex in $\mathbb{R}^p$, formed by p points $x_i \in \mathbb{R}^p$ and the origin, is proportional to the determinant of the $(p \times p)$-dimensional matrix formed by these points.

So, to maximise $\det M$, we find p points in the space of derivatives, which together with the origin, form a simplex of largest volume.

D - the most popular optimality criterion

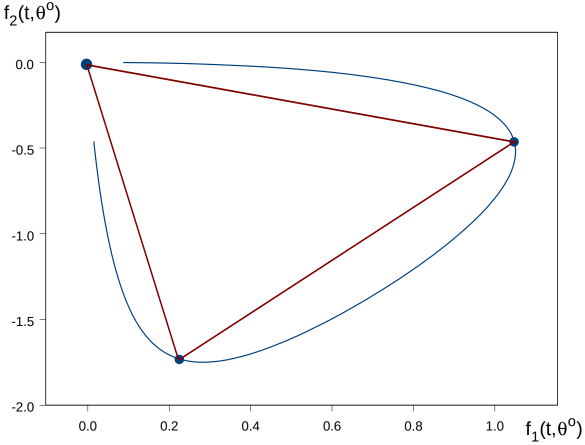
Geometrical Interpretation - design locus: PK model, $p = 2$



Design Locus

D - the most popular optimality criterion

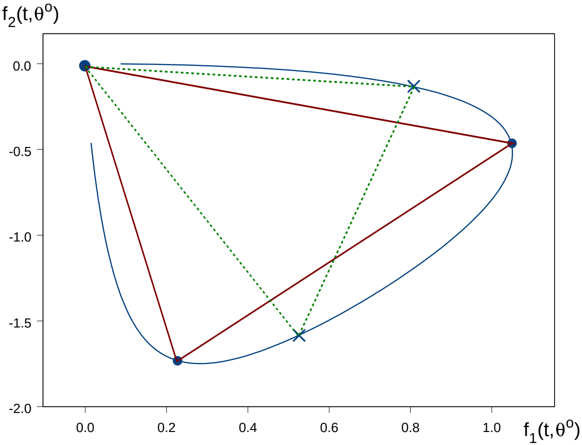
Geometrical Interpretation - design locus: PK model, $p = 2$



Design Locus, optimum points and the simplex

D - the most popular optimality criterion

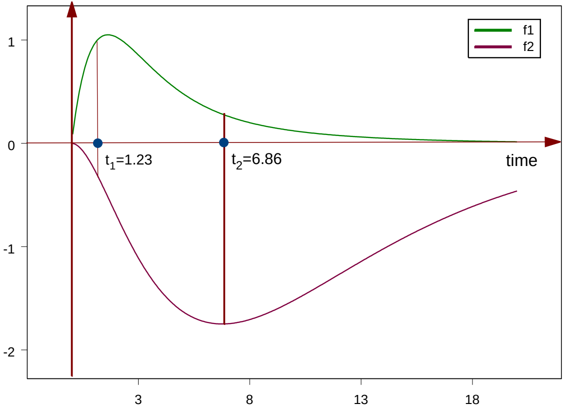
Geometrical Interpretation - design locus: PK model, $p = 2$



Design Locus, optimum and non-optimum solution

D - the most popular optimality criterion

Geometrical Interpretation - parameter sensitivities



We find t_1 and t_2 such that $\det X = f_1(t_1)f_2(t_2) - f_2(t_1)f_1(t_2)$ is maximum.

D - the most popular optimality criterion

The Equivalence Theorem

Kiefer and Wolfowitz (1960)

A design ξ^* is D-optimum if and only if it is G-optimum, that is the following conditions are equivalent:

$$\det(M^{-1}(\xi^*)) = \min_{\xi} \det(M^{-1}(\xi))$$

$$\max_{x} d(x, \xi^*) = \min_{\xi} \max_{x} d(x, \xi),$$

where $d(x, \xi) = f^{\mathrm{T}}(x) M^{-1}(\xi) f(x)$ is the variance of prediction at a point x.The third equivalent condition says

$$\max_{x} d(x, \xi^*) \leq p,$$

where p is the number of parameters.
Equality is achieved at the support points of ξ^*.

D - the most popular optimality criterion

The Equivalence Theorem, an Illustration

Let the model response be

$$\eta(x,\vartheta) = \vartheta_0 + \vartheta_1 x + \vartheta_2 x^2, \quad \text{on } [-1,\ 1].$$

Then, the D-optimum design is

$$\xi^\star = \left\{ \begin{array}{ccc} -1 & 0 & 1 \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{array} \right\}$$

The design does not depended on N, but instead on the weights.

The information matrix can then be written as

$$M(\xi^\star, \vartheta^o) = X^{\mathrm{T}} W X = \begin{pmatrix} 1 & 1 & 1 \\ -1 & 0 & 1 \\ 1 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} \frac{1}{3} & 0 & 0 \\ 0 & \frac{1}{3} & 0 \\ 0 & 0 & \frac{1}{3} \end{pmatrix} \times \begin{pmatrix} 1 & -1 & 1 \\ 1 & 0 & 0 \\ 1 & 1 & 1 \end{pmatrix}$$

D - the most popular optimality criterion

The Equivalence Theorem, an Illustration

Hence,

$$M = \frac{1}{3} \begin{pmatrix} 3 & 0 & 2 \\ 0 & 2 & 0 \\ 2 & 0 & 2 \end{pmatrix}$$

and the variance function is

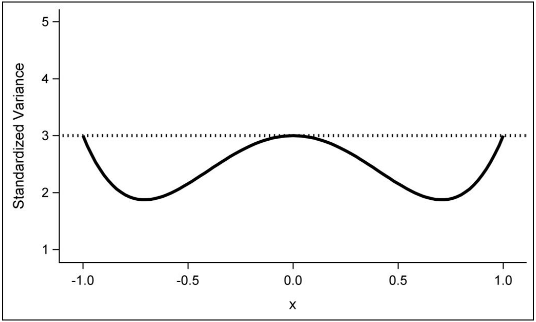
$$\begin{aligned} d(x, \xi^\star) &= f^{\mathrm{T}}(x) M^{-1} f(x) \\ &= 3(1,\ x,\ x^2) \times \begin{pmatrix} 1 & 0 & -1 \\ 0 & 0.5 & 0 \\ -1 & 0 & 1.5 \end{pmatrix} \times \begin{pmatrix} 1 \\ x \\ x^2 \end{pmatrix} \\ &= 3 - 4.5x^2 + 4.5x^4. \end{aligned}$$

Note, that $d(x, \xi^\star) = 3$ at $x = -1, 0, 1$

D - the most popular optimality criterion

The Equivalence Theorem, an Illustration

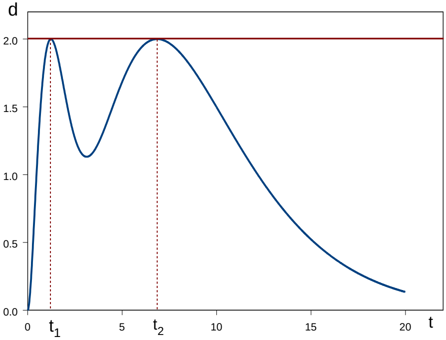
$$\xi^\star = \left\{ \begin{array}{ccc} -1 & 0 & 1 \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{array} \right\}$$



D - the most popular optimality criterion

The Equivalence Theorem - PK model

$$\xi^\star = \left\{ \begin{array}{cc} 1.23 & 6.86 \\ \frac{1}{2} & \frac{1}{2} \end{array} \right\}$$



Example 4

Enzyme Kinetics Model, $p = 2$,

In a typical enzyme kinetics reaction enzymes bind substrates and turn them into products. The binding step is reversible while the catalytic step irreversible:

$$S + E \longleftrightarrow ES \rightarrow E + P,$$

S, E and P denote substrate, enzyme and product, respectively.

Example 4

Enzyme Kinetics Model, $p = 2$,

The reaction rate is represented by the Michaelis-Menten model

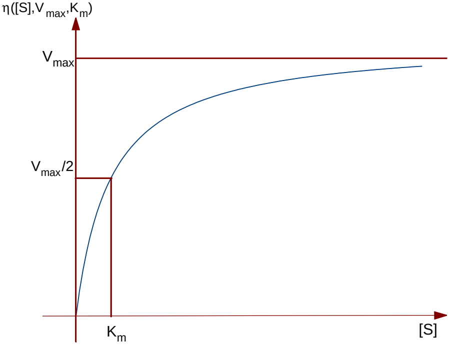
$$v = \frac{V_{max}[S]}{K_m + [S]},$$

where $[S]$ is the concentration of the substrate and V_{max} and K_m are the model parameters:

- V_{max} denotes the maximum velocity of the enzyme and
- K_m is Michaelis-Menten constant, it is the value of $[S]$ at which half of the maximum velocity V_{max} is reached.

Example 4

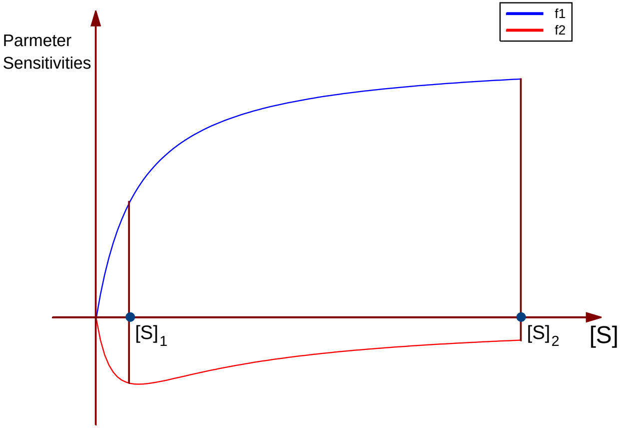
Enzyme Kinetics Model, $p = 2$,



Michaelis-Menten Model. The response function:
$\eta\big([S]; V_{max}, K_m\big)$ for the point priors $V_{max}^o = 1, K_m^o = 1$.

D optimality

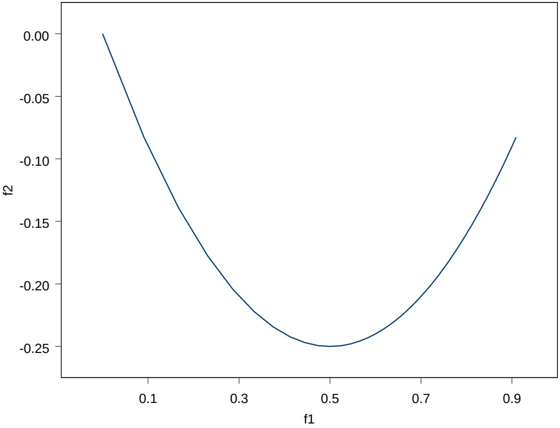
Enzyme Kinetics Model, $p = 2$, Parameter Sensitivities



f_1 does not have a proper maximum; the largest value is at the border of the design region.

D optimality

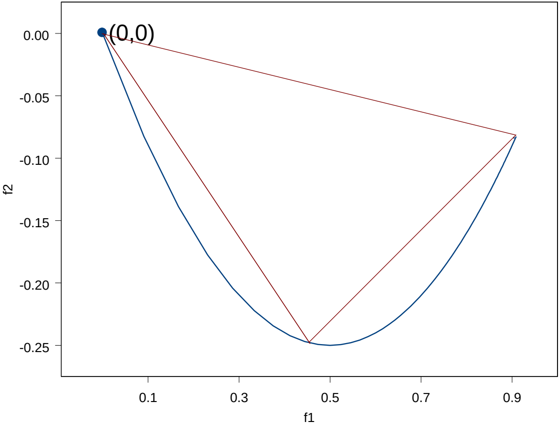
Enzyme Kinetics Model, $p = 2$, Design Locus



Design Locus does not form a loop.

D optimality

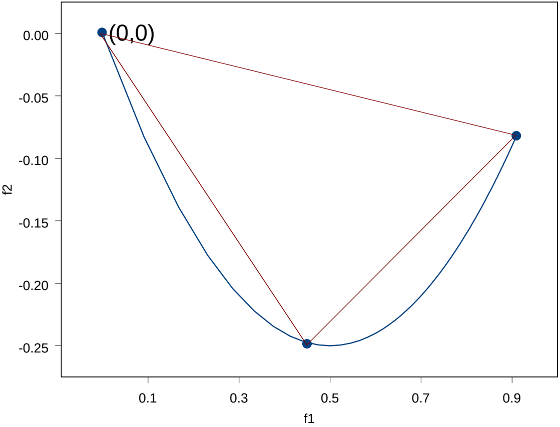
Enzyme Kinetics Model, $p = 2$, Design Locus



Design Locus: one vertex must be at the end of the locus.

D optimality

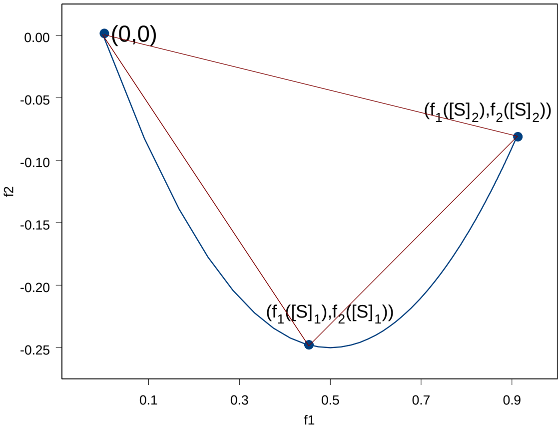
Enzyme Kinetics Model, $p = 2$, Design Locus



Design Locus: the triangle of maximum area.

D optimality

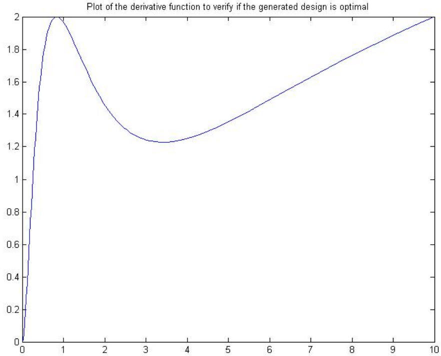
Enzyme Kinetics Model, $p = 2$, Design Locus



Design Locus: Optimum design points.

D optimality

Enzyme Kinetics Model, $p = 2$, The Equivalence Theorem



The variance function has only one proper maximum; it also reaches $p = 2$ at the border of the design region.

D optimality

Enzyme Kinetics Model, $p = 2$, COURSE-WORK 1

Obtain a locally D-optimum design points for the Michaelis-Menten model for the point prior values of the parameters equal to $V^o_{max} = 1, K^o_m = 1$.

Example 5. Two Consecutive Chemical Reactions

Model.

Atkinson and Bogacka (2002), Chemometrics

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C.$$

The kinetic differential equations for $[A], [B]$ and $[C]$, the concentrations of the chemical compounds A, B and C as functions of time t are

$$\begin{aligned} \frac{d[A]}{dt} &= -k_1[A]^{\lambda_1} \\ \frac{d[B]}{dt} &= k_1[A]^{\lambda_1} - k_2[B]^{\lambda_2} \\ \frac{d[C]}{dt} &= k_2[B]^{\lambda_2}. \end{aligned} \tag{1}$$

Interest is in estimation of the orders λ_1, λ_2 as well as of the rates k_1, k_2.

Example 5. Two Consecutive Chemical Reactions

Model

The first of the three equations can be solved analytically to give the concentration of chemical A at time t as

$$[A] = \{1 - (1-\lambda_1)k_1 t\}^{1/(1-\lambda_1)} \qquad (\lambda_1, k_1, t \geq 0; \lambda_1 \neq 1),$$

if it is assumed that the initial concentration of A is 1.

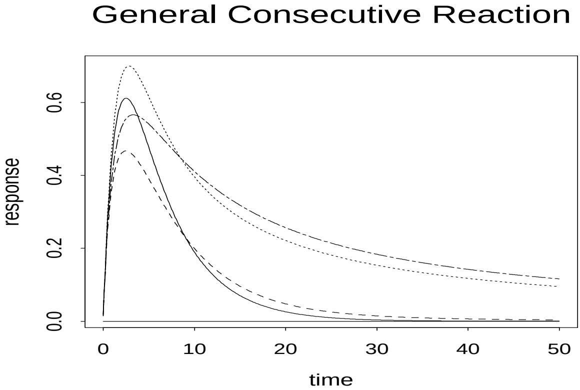
This gives the following differential equation for the concentration of the compound B

$$\frac{d[B]}{dt} = k_1\{1 - (1-\lambda_1)k_1 t\}^{\frac{\lambda_1}{1-\lambda_1}} - k_2[B]^{\lambda_2}$$

which has to be solved numerically.

Example 5. Two Consecutive Chemical Reactions

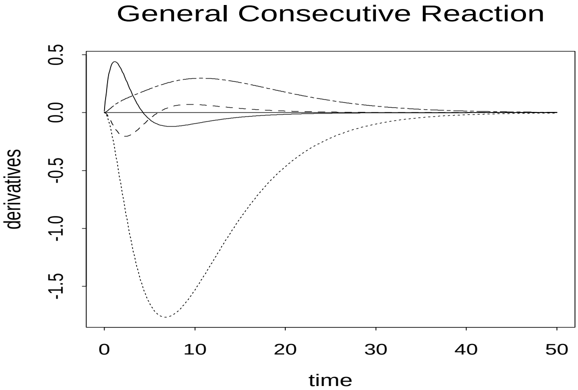
Model



Concentration of B. Reading upward at $t = 20$:
$(\lambda_1^o, \lambda_2^o) = (1, 1), (2, 1), (1, 2)$ and $(2, 2)$, $(k_1^o, k_2^o) = (0.7, 0.2)$.

Example 5. Two Consecutive Chemical Reactions

Model derivatives with respect to the parameters



Derivatives (parameter sensitivities) as a function of time. Reading upward at $t = 10$: f_2, f_1, f_3, f_4 for k_2, k_1, λ_1 and λ_2, respectively. Here $(\lambda_1^o, \lambda_2^o) = (1, 1)$, $(k_1^o, k_2^o) = (0.7, 0.2)$.

Example 5. Two Consecutive Chemical Reactions

D-optimum designs

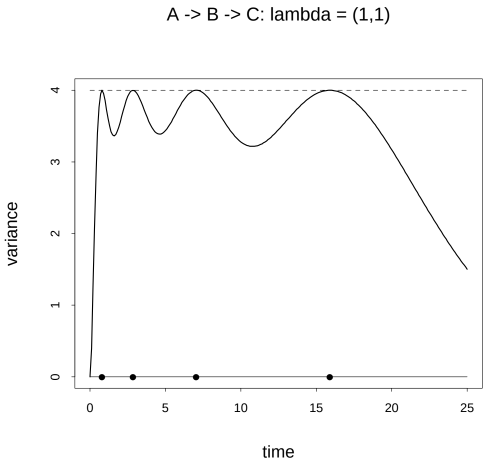
These designs were found by searching over the four continuous values of time, but with the weights held known at 0.25. The design region is $\mathcal{T}$ = [0,50].

Prior orders of reaction	time			
$(k_1^o, k_2^o, \lambda_1^o, \lambda_2^o)$	t_1^*	t_2^*	t_3^*	t_4^*
(0.7, 0.2, 1,1)	0.80	2.85	7.05	15.90
(0.7, 0.2, 2,1)	0.51	2.36	7.30	18.26
(0.7, 0.2, 1,2)	0.83	2.91	8.05	40.39
(0.7, 0.2, 2,2)	0.57	2.65	9.68	50.00

Table 1. D-optimum designs for both rate and order. The weights are 0.25 at each design point.

Example 5. Two Consecutive Chemical Reactions

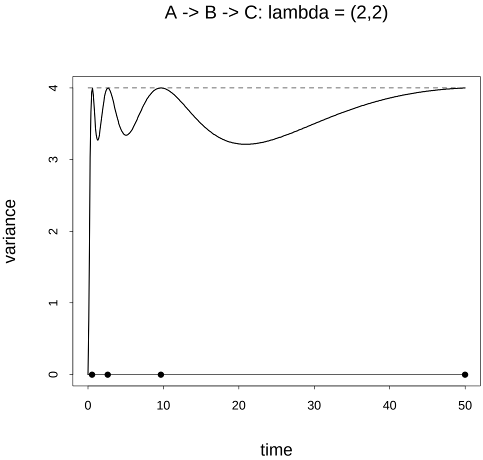
D-optimum designs



The variance of prediction $d(t, \xi^*, \vartheta)$ for prior $(k_1^o, k_2^o, \lambda_1^o, \lambda_2^o) = (0.7, 0.2, 1, 1)$.

Example 5. Two Consecutive Chemical Reactions

D-optimum designs



Responses for various priors and the variance of prediction $d(t, \xi^*, \vartheta)$ for prior $(k_1^o, k_2^o, \lambda_1^o, \lambda_2^o) = (0.7, 0.2, 2, 2)$.