Optimum Designs for the Equality of Parameters in Enzyme Inhibition Kinetic Models

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Abstract

A general model for enzyme kinetics with inhibition, the "mixed" inhibition model, simplifies to the non-competitive inhibition model when two of the parameters are equal. We reparamaterise the model and provide designs for investigating the equality of parameters, which corresponds to a scalar parameter δ being zero. For linear models T-optimum designs for discriminating between models in which δ is, and is not, equal to zero are identical to designs in which the estimate of δ has minimum variance. We show that this equality does not hold for our nonlinear model, except as δ approaches zero. We provide optimum discriminating designs for a series of parameter values. An Appendix presents analytical expressions for the D-optimum design for the four parameters of the mixed inhibition model.

Keywords: Analytical D-optimality; D_S(T)-optimality; General Equivalence Theorem; model-discriminating design; optimum design; T-optimality

1 Introduction

Establishing the equality of parameters is important in the building of the nonlinear models used for enzyme kinetic reactions with inhibition. We re-write the

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models so that testing parameter equality is identical to testing whether a parameter $\delta = 0$. We consider the problem of the optimum design of experiments for testing this hypothesis.

To test whether $\delta = 0$ we compare models in which δ is constrained to be zero with those in which it is not so constrained. For linear models the power of the resulting F test for the comparison of the two models is maximized by the T-optimum design (Atkinson and Fedorov 1975a; Atkinson et al. 2007, cap.20) which maximizes the non-centrality parameter $\delta^{\mathrm{T}} A \delta$, with A the information matrix for δ.

An alternative approach is to estimate δ as precisely as possible, by finding the $\mathrm{D_S}$-optimum design maximizing the determinant of A. Since the T criterion, unlike $\mathrm{D_S}$-optimality, depends on the value of δ, the two criteria cannot, in general, yield the same designs, the T-optimum design having higher power. However, in our application, δ is scalar ($s = 1$), so that the non-centrality parameter $\delta^{\mathrm{T}} A \delta = \delta^2 A$. Then the $\mathrm{D_1}$ and T-optimum designs coincide for linear models, since A does not depend on the values of the parameters. However, for nonlinear models, $\mathrm{D_1}$- and T-optimum designs are identical only if the models are linearized at the same nominal values of the parameters. Otherwise, for discrimination between the original (that is, nonlinearized) models, $\mathrm{D_1}$ and T-optimum designs become identical as $\delta \to 0$. See López-Fidalgo, Tommasi, and Trandafir (2008).

The two purposes of our paper are to provide a methodology yielding good designs for testing the equality of parameters and to explore the relationship between the T- and $\mathrm{D_1}$-optimum designs, with particular emphasis on the efficiency of the designs. We start in §2 with a short introduction to the optimum design criteria we shall be using. Our example, from enzyme kinetics, is introduced in §3, where we reparameterise this nonlinear model to allow for testing parameter equality. The next section describes D- and $\mathrm{D_S}$-optimum designs for this four-parameter model. We recall the analytical expressions for the D-optimum designs (Bogacka et al. 2011). Section 5 presents optimum designs for testing parameter equality for a series of values of δ and shows how the T- and $\mathrm{D_S}$-optimum designs diverge as δ increases, that is as the hypothesis of interest becomes increasingly false. Brief comments on T-optimality conclude in §6. Analytical expressions for the support points of the D-optimum design for the four-parameter mixed inhibition model are in the Appendix.

Throughout we work with the customary second-order assumptions of additive independent errors of constant variance. We are then able to use the standard theory of optimum design for regression models as described in several books including Pukelsheim (1993), Fedorov and Hackl (1997) and Atkinson, Donev, and Tobias (2007). We focus on continuous designs expressed as a probability measure ξ over a design region $\mathcal{X}$.

2 Models and Design Criteria

2.1 Linear models: D- and Ds-optimality

The linear model for observation i taken at design point x_i is

$$y_i = \psi^{\mathrm{T}} f(x_i) + \epsilon_i, \tag{1}$$

where ψ is a vector of unknown parameters, $f(.)$ is a vector of known functions and the independent errors ϵ_i are normally distributed; $\epsilon_i \sim \mathcal{N}(0, \sigma^2)$. If a simpler model may fit the data we can write

$$y_i = \psi_1^{\mathrm{T}} f_1(x_i) + \delta^{\mathrm{T}} f_2(x_i) + \epsilon_i, \tag{2}$$

where $f_1(.)$ and $f_2(.)$ are subvectors of $f(.)$ of appropriate dimension and $\psi = (\psi_1^{\mathrm{T}}, \delta^{\mathrm{T}})^{\mathrm{T}}$. We then test the significance of δ. In general, δ can be a vector of s parameters.

Under these assumptions, efficient estimation is by least squares. For the design measure ξ putting weight w_i at the design point x_i in the design region $\mathcal{X}$, the information matrix for $\hat{\psi}$ is

$$M(\xi) = \sum_{i=1}^{n} w_i f(x_i) f^{\mathrm{T}}(x_i) \tag{3}$$

for a design with n support points. With

$$M_{jk}(\xi) = \sum_{i=1}^{n} w_i f_j(x_i) f_k^{\mathrm{T}}(x_i), \tag{4}$$

the covariance matrix for the parameter of interest δ is proportional to

$$A^{-1} = \{M_{22}(\xi) - M_{21}(\xi) M_{11}^{-1}(\xi) M_{21}^{\mathrm{T}}(\xi)\}^{-1} \qquad (j, k = 1, 2). \tag{5}$$

Accordingly, the $\mathrm{D_S}$-optimum design for δ in the linear model (2) maximizes the determinant

$$|A| = |M_{22}(\xi) - M_{21}(\xi) M_{11}^{-1}(\xi) M_{21}^{\mathrm{T}}(\xi)| = |M(\xi)|/|M_{11}(\xi)|. \tag{6}$$

2.2 Linear models: T-optimality

T-optimum designs were introduced by Atkinson and Fedorov (1975a) for models that may be nonlinear. Let the two models be $\eta_t(x_i, \psi_t)$ – taken as true – and $\eta_1(x_i, \psi_1)$, where $\eta_1(.)$ need not be a special case of $\eta_t(.)$ In general the T-optimum

design depends on the value assumed for the parameter vector ψ_t. Let the parameter estimate when $\eta_1(.)$ is fitted to observations without error from $\eta_t(.)$ be $\hat{\psi}_1(\xi)$. That is

$$\hat{\psi}_1(\xi) = \arg\min_{\psi_1} \sum_{i=1}^{n} w_i \{\eta_t(x_i, \psi_t) - \eta_1(x_i, \psi_1)\}^2. \tag{7}$$

Then the T-optimum design maximizes the non-centrality parameter

$$\Delta(\xi) = \sum_{i=1}^{n} w_i \left\{\eta_t(x_i, \psi_t) - \eta_1(x_i, \hat{\psi}_1)\right\}^2. \tag{8}$$

If both models are linear and contain some terms in common, we can extend (1) and (2) and write

$$y_i = \psi^{\mathrm{T}} f(x_i) + \epsilon_i = \psi_t^{\mathrm{T}} f_t(x_i) + \delta^{\mathrm{T}} \tilde{f}_2(x_i) + \epsilon_i, \tag{9}$$

where the terms $\tilde{f}_2$ are the complement of the terms f_t in the full model f (see Atkinson et al. 2007, §20.9.1). If, as is the case in our example, $\eta_1(.)$ is nested in $\eta_t(.)$ we recover (2) and the T-optimum design maximizes the non-centrality parameter

$$\Delta(\xi) = \delta^{\mathrm{T}} \{M_{22}(\xi) - M_{21}(\xi) M_{11}^{-1}(\xi) M_{21}^{\mathrm{T}}(\xi)\} \delta. \tag{10}$$

Atkinson and Fedorov (1975a) give an example of discrimination between a quadratic polynomial in one variable and a constant. Thus $s = 2$. The T-optimum design splits trials evenly between the values of x giving the maximum and minimum of the quadratic function, the design points therefore depending on the value of ψ^0. This is distinct from the $\mathrm{D_S}$-optimum design for the two parameters, which puts one third of the trials at the ends and centre of the design region. However, for testing the quadratic against a model with linear trend, so that $s = 1$, the $\mathrm{D_S}$- and T-optimum designs are identical, putting weight 1/4 at the ends of the design region and weight 1/2 at the centre, regardless of the value of ψ^0. A curious aside is that, in the special case that the next to highest order term is missing, the designs are not unique (Dette and Titoff 2008; Atkinson 2010; Dette, Melas, and Shpilev 2011).

2.3 Nonlinear models: D-, Ds- and T-optimality

Locally D- and $\mathrm{D_S}$-optimum designs for nonlinear models are found by Taylor expansion around some prior point value ψ^0 of the parameter. The information matrix is then a function of the vector of partial derivatives

$$f(x_i, \psi^0) = \left.\frac{\partial \eta(x_i, \psi)}{\partial \psi}\right|_{\psi^0} \tag{11}$$

of the response function with respect to the parameters ψ, often called the parameter sensitivities, where ψ^0 is a prior point estimate of the parameters. See Chapter 17 of Atkinson et al. (2007).

On the other hand, T-optimality, as (7) and (8) show, does not involve any linearization. When δ is scalar and the models are linear, T-optimum designs maximizing (8) are also D_1-optimum. However, for nonlinear models D_1 and T-optimum designs are not in general identical. This arises because the D_1-optimality criterion is used for discriminating between models that are linearized at $(\psi_1^{0\mathrm{T}}, 0)^{\mathrm{T}}$ and $\psi_1^{0\mathrm{T}}$, respectively, while the T-optimality criterion is applied to the original model and depends on the nominal values $(\psi_1^{0\mathrm{T}}, \delta^0)^{\mathrm{T}}$. The T-optimum design approaches the D_1-optimum design as $\delta^0 \to 0$. For a theoretical justification see López-Fidalgo et al. (2008).

Here we find two D_S-optimum designs for the nonlinear model. The first at $(\psi_1^{0\mathrm{T}}, 0)^{\mathrm{T}}$ and the second at $(\hat{\psi}_1^{\mathrm{T}}(\xi_T^*), 0)^{\mathrm{T}}$ where ξ_T^* denotes the T-optimum design. To avoid confusion, for the nonce we call this second criterion D_S(T)-optimality. Interest is in how well these two designs compare with the T-optimum design for model discrimination. We look at their properties for a series of values of δ^0.

3 Enzyme Kinetics

The models arise in the assessment of drug metabolism and drug-drug interaction. In studies of inhibition, interest may be in the effect of the drug in reducing the activity of an enzyme. An example is penicillin which inhibits the enzyme producing the cell walls of bacteria. In the study of the effect of "cocktails" of drugs, interest is in whether one drug inhibits the metabolism of another. See Segel (1993).

The models relate the velocity of reaction v to concentrations of substrate $[S]$ and of inhibitor $[I]$. Different types of binding lead to a variety of models for the reaction. Here we consider two possible models.

Mixed Inhibition. In this four-parameter model the deterministic velocity equation is:

$$v = \frac{V[S]}{K_m\left(1 + \dfrac{[I]}{K_c}\right) + [S]\left(1 + \dfrac{[I]}{K_u}\right)}, \tag{12}$$

with the parameters V, K_m, K_u and K_c to be determined experimentally. In designing experiments it is assumed that the errors in the measurements of v follow the normal assumptions of §2.

Non-competitive Inhibition. When $K_u = K_c$ the model has a specific inter-

pretation and becomes

$$v = \frac{V[S]}{(K_m + [S])\left(1 + \dfrac{[I]}{K_c}\right)}. \tag{13}$$

To obtain efficient designs for testing the equality of K_c and K_u we rewrite the model (12) in a nonlinear form analogous to (2). If we let $\theta_1 = 1/K_c$ and $\theta_2 = 1/K_u$, (12) becomes

$$v = \frac{V[S]}{K_m\,(1 + \theta_1[I]) + [S]\,(1 + \theta_2[I])}. \tag{14}$$

We now make a reparameterization and write $\theta_1 = \theta + \delta$ and $\theta_2 = \theta - \delta$, when (14) becomes

$$v = \frac{V[S]}{(K_m + [S])\,(1 + \theta[I]) + \delta[I]\,(K_m - [S])}, \tag{15}$$

which reduces to (13) when $\delta = 0$. If θ is also zero, we obtain the Michaelis-Menten model.

With $\psi = (V, K_m, \theta, \delta)^{\mathrm{T}}$ the information matrix is a function of the vector of partial derivatives (11) with $\eta = v$.

4 D- and Ds-optimum Designs

An experimental design involves the choice of concentrations $x_i = ([S]_i, [I]_i)^{\mathrm{T}}$ at which measurements are to be taken. Since (15) is nonlinear in three of the parameters, D- and $\mathrm{D_S}$-optimum designs will depend on the values of all parameters except V. In this paper we find locally optimum designs that depend on the prior value ψ^0. Chapter 18 of Atkinson et al. (2007) describes, for simpler examples, a Bayesian approach which incorporates more general prior information about ψ.

If it is known that δ is not equal to zero we require good designs for estimating all four parameters of the full model, for which D-optimality is appropriate. Bogacka et al. (2011) present D-optimum designs for the nonlinear model (12) or, equivalently, for the reparameterized form (15). When the design region is a rectangle $\mathcal{X} = \left[[S]_{\min}, [S]_{\max}\right] \times \left[[I]_{\min}, [I]_{\max}\right]$ the D-optimum design has the form

$$\xi^* = \begin{Bmatrix} ([S]_{\max}, [I]_{\min})^T & (s_2, [I]_{\min})^T & ([S]_{\max}, i_3)^T & (s_4, i_4)^T \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{Bmatrix}, \tag{16}$$

so that four settings of experimental values (s_2, s_4, i_3 and i_4) have to be calculated. Bogacka et al. (2011) present analytical expressions for these quantities as functions of the parameter values and of the boundaries of the design region.

In our example in §5 we take the design region $\mathcal{X}$ such that $[S] \in [0, 100]$ and $[I] \in [0, 100]$. With both $[I]_{\min}$ and $[S]_{\min}$ = 0, the results of Bogacka et al. (2011) simplify appreciably and we obtain the formulae given in the Appendix.

A further simplification occurs with $\delta^0 = 0$, when the design is of the form

$$\xi^* = \left\{ \begin{matrix} ([S]_{\max}, [I]_{\min})^T & (s_2, [I]_{\min})^T & ([S]_{\max}, i_3)^T & (s_2, i_3)^T \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{matrix} \right\}, \qquad (17)$$

a special case of (16) with only two unknowns. Now

$$s_2 = s_4 = \max \left\{ [S]_{\min},\ \frac{[S]_{\max} K_m}{[S]_{\max} + 2K_m} \right\},$$

$$i_3 = i_4 = \min \left\{ K_{ic} + 2[I]_{\min},\ [I]_{\max} \right\}.$$

The analytical results do not extend to D_S-optimality. In addition to the four design points we also need to find numerically the design weights w_i. When $\mathcal{X}$ is two dimensional this requires an 11-dimensional numerical search. Instead we finesse the problem, checking our results through use of the extension to D_S-optimality of the equivalence theorem for D-optimality, originally due to Kiefer and Wolfowitz (1960).

To find the D_S-optimum design for general δ^0 we assumed that this design was also of the form (16), optimization of which requires a seven-dimensional search over the weights and the values of s_2, i_3, s_4 and i_4. Again, when $\delta^0 = 0$, the problem simplifies with, as for D-optimality, just two experimental variables s_2 and i_3 needing to be found, in this case numerically. In addition numerical explorations show that the design weights simplify to

$$w_1 = 0.5 - 2p \ \ w_2 = w_3 = p \ \text{ and } \ w_4 = 0.5, \qquad (18)$$

for some $0 < p < 0.25$. In this case only a three dimensional search is required. As with all designs found in this paper, we checked optimality by using the general equivalence theorem (see Atkinson et al. 2007, §10.3 for D_S-optimality). As required for these D_S-optimum designs, the maximum over $\mathcal{X}$ of the derivative function $d_s(x, \xi)$ is one.

5 Numerical Comparison of Designs

The considerations of §2.3 provide us with four designs to be compared: those that are D-, T-, D_S- and D_S(T)-optimum. We found designs for a series of values

of δ^0. When $\delta^0 = 0$ the locally optimum designs are for the initial parameter values $(V^0, K_m^0, K_c^0, K_u^0) = (1513, 6.59, 1.35, 1.35)$, which we took from an unpublished technical report from Pfizer Ltd, Sandwich. For $\delta^0 \neq 0$, we took $\theta^0 = 1.35$ in (15). Since the value of V^0 does not affect the design it can be chosen for numerical convenience.

The D-optimum designs were calculated from the expressions in the Appendix; with four support points in the design and four parameters, the weight on each design point is 1/4. The other designs were found by numerical optimization using an unconstrained conjugate gradient algorithm, with trigonometric transformations to ensure that the design points lie in $\mathcal{X}$ and that the non-negative weights w_i sum to one (Atkinson et al. 2007, §9.5). To check the optimality of these designs we used the appropriate equivalence theorem, performing a search of derivative values over a dense grid of 1,002,001 points in $\mathcal{X}$. (Atkinson and Fedorov 1975a give the theorem for T-optimality).

Designs for three values of δ^0 and their efficiencies are detailed in Table 1. The efficiencies of further designs are in Table 2. The D-efficiency of a design ξ relative to the D-optimum design ξ^* is

$$\text{Eff}_{\text{D}}(\xi) = \{|M(\xi)|/|M(\xi^*)|\}^{1/p}. \tag{19}$$

The T-efficiency of ξ is likewise

$$\text{Eff}_{\text{T}}(\xi) = \Delta(\xi)/\Delta(\xi_T^*). \tag{20}$$

In general, our numerical results show that, as $\delta^0 \to 0$, the T-optimum design tends to the D_S-optimum design evaluated at ψ^0. However, when $\delta^0 = 0$, the T-optimum design is not defined, and there are only two designs for comparison, those that are D- and D_S-optimum. These two designs have design points that are similar, but differ radically in weights. For the D_S-optimum design the weights are approximately 1/10, 1/5, 1/5 with a weight of exactly 0.5 on the fourth design point. These weights are of the form given in (18). The D-efficiency of the D_S-optimum design is about 78%, a surprisingly high value. The T-efficiency of the D-optimum design is slightly lower at about 72%. These values are typical of those we find over a wide range of values of δ^0.

For the other two prior values of δ in Table 1 there are four distinct designs. The form of the D_S- and D_S(T)-optimum designs is similar to that of the T-optimum designs. As δ^0 increases, the design points gradually spread to higher values of $[S]$ and of $[I]$, with the D_S(T)-optimum design in particular having a high T-efficiency. The weights of this design do not depend on the value of δ.

In order to illustrate the importance of optimum design, we include in our comparisons a design that is typical of those used in the subject area, consisting of a trial at each of the 121 points of a grid with spacings of ten units in each

Table 1: Enzyme kinetics: D-, T- D_S- and D_S(T)-optimum designs and efficiencies for three values of δ^0. D- and D_S-designs calculated at $\psi^0 = (V^0, K_m^0, \theta^0, \delta^0)^{\mathrm{T}}$, D_S(T) designs at $\hat{\psi}_1(\xi_T^*) = (\hat{V}, \hat{K}_m, \hat{\theta})^{\mathrm{T}}$.

	$\delta^0 = 0$					
Criterion	i	1	2	3	4	D & T efficiency %
D	$\begin{bmatrix}[S]_i\\ [I]_i\end{bmatrix}$	$\begin{bmatrix}100.\\ 0.\end{bmatrix}$	$\begin{bmatrix}5.8226\\ 0.\end{bmatrix}$	$\begin{bmatrix}100.\\ 1.35\end{bmatrix}$	$\begin{bmatrix}5.8226\\ 1.35\end{bmatrix}$	100 72.12
	w_i	1/4	1/4	1/4	1/4	
D_S	$\begin{bmatrix}[S]_i\\ [I]_i\end{bmatrix}$	$\begin{bmatrix}100.\\ 0.\end{bmatrix}$	$\begin{bmatrix}4.1877\\ 0.\end{bmatrix}$	$\begin{bmatrix}100.\\ 1.9093\end{bmatrix}$	$\begin{bmatrix}4.1877\\ 1.9093\end{bmatrix}$	78.04 100
	w_i	0.0858	0.2071	0.2071	0.5000	
	$\delta = 0.2$					
Criterion	i	1	2	3	4	D & T efficiency %
D	$\begin{bmatrix}[S]_i\\ [I]_i\end{bmatrix}$	$\begin{bmatrix}100.\\ 0.\end{bmatrix}$	$\begin{bmatrix}5.8226\\ 0.\end{bmatrix}$	$\begin{bmatrix}100.\\ 1.7684\end{bmatrix}$	$\begin{bmatrix}7.3855\\ 1.3711\end{bmatrix}$	100 71.21
	w_i	1/4	1/4	1/4	1/4	
T	$\begin{bmatrix}[S]_i\\ [I]_i\end{bmatrix}$	$\begin{bmatrix}100.\\ 0.\end{bmatrix}$	$\begin{bmatrix}4.3836\\ 0.\end{bmatrix}$	$\begin{bmatrix}100.\\ 2.3849\end{bmatrix}$	$\begin{bmatrix}5.0772\\ 2.0441\end{bmatrix}$	77.83 100
	w_i	0.0818	0.2178	0.2178	0.4826	
D_S	$\begin{bmatrix}[S]_i\\ [I]_i\end{bmatrix}$	$\begin{bmatrix}100.\\ 0.\end{bmatrix}$	$\begin{bmatrix}4.1886\\ 0.\end{bmatrix}$	$\begin{bmatrix}100.\\ 2.5007\end{bmatrix}$	$\begin{bmatrix}5.5743\\ 1.8520\end{bmatrix}$	76.14 97.89
	w_i	0.0738	0.2413	0.1832	0.5017	
D_S(T)	$\begin{bmatrix}[S]_i\\ [I]_i\end{bmatrix}$	$\begin{bmatrix}100.\\ 0.\end{bmatrix}$	$\begin{bmatrix}4.5859\\ 0.\end{bmatrix}$	$\begin{bmatrix}100.\\ 2.2743\end{bmatrix}$	$\begin{bmatrix}4.5863\\ 2.3746\end{bmatrix}$	75.94 99.15
	w_i	0.0858	0.2071	0.2071	0.5000	
	$\delta = 0.45$					
Criterion	i	1	2	3	4	D & T efficiency %
D	$\begin{bmatrix}[S]_i\\ [I]_i\end{bmatrix}$	$\begin{bmatrix}100.\\ 0.\end{bmatrix}$	$\begin{bmatrix}5.8226\\ 0.\end{bmatrix}$	$\begin{bmatrix}100.\\ 2.8870\end{bmatrix}$	$\begin{bmatrix}10.2841\\ 1.5571\end{bmatrix}$	100 68.78
	w_i	1/4	1/4	1/4	1/4	
T	$\begin{bmatrix}[S]_i\\ [I]_i\end{bmatrix}$	$\begin{bmatrix}100.\\ 0.\end{bmatrix}$	$\begin{bmatrix}4.7316\\ 0.\end{bmatrix}$	$\begin{bmatrix}100.\\ 3.5956\end{bmatrix}$	$\begin{bmatrix}6.8235\\ 2.4374\end{bmatrix}$	76.64 100
	w_i	0.0731	0.2329	0.2329	0.4611	
D_S	$\begin{bmatrix}[S]_i\\ [I]_i\end{bmatrix}$	$\begin{bmatrix}100.\\ 0.\end{bmatrix}$	$\begin{bmatrix}4.1887\\ 0.\end{bmatrix}$	$\begin{bmatrix}100.\\ 4.0838\end{bmatrix}$	$\begin{bmatrix}8.3636\\ 1.9557\end{bmatrix}$	71.64 88.01
	w_i	0.0561	0.2912	0.1517	0.5010	
D_S(T)	$\begin{bmatrix}[S]_i\\ [I]_i\end{bmatrix}$	$\begin{bmatrix}100.\\ 0.\end{bmatrix}$	$\begin{bmatrix}5.3404\\ 0.\end{bmatrix}$	$\begin{bmatrix}100.\\ 3.1634\end{bmatrix}$	$\begin{bmatrix}5.3403\\ 3.1638\end{bmatrix}$	70.64 95.02
	w_i	0.0858	0.2071	0.2071	0.5000	

Table 2: Enzyme kinetics: T- and D-efficiencies for five design criteria over a range of values of δ^0

	T-efficiency					D-efficiency				
Criterion	$\delta^0 = 0$	0.1	0.2	0.3	0.45	$\delta^0 = 0$	0.1	0.2	0.3	0.45
D	72.12	71.77	71.21	70.43	68.78	100	100	100	100	100
T	100*	100	100	100	100	78.04*	78.00	77.83	77.51	76.64
D_S	100	99.47	97.89	95.17	88.01	78.04	77.21	76.14	74.74	71.66
D_S(T)	100*	99.79	99.15	98.00	95.02	78.04*	77.18	75.95	74.27	70.64
Grid	1.11	1.38	1.73	2.22	3.41	5.29	5.80	6.40	7.14	8.66

* values for the limiting D_S-optimum design as $\delta^0 \to 0$

concentration. The efficiencies for this and for the four optimum designs are given in Table 2.

The most noticeable feature of these efficiencies in Table 2 is the appallingly low efficiency of the grid design. The D-efficiencies range from 5.29 to 8.66%, which are unacceptably low values for estimation of all four parameters. The T-efficiencies are even lower, from 1.11 to 3.41%, showing that this design provides virtually no information for the choice of a model.

The other, unexpected, feature of Table 2 is that the D_S(T)-optimum design has very good T-efficiency and a D-efficiency only slightly lower than that of the D_S-optimum design. We accordingly use the former to illustrate convergence to the T-optimum design as $\delta^0 \to 0$.

We start our study of the effect of δ^0, that is of departure from equality of the parameters K_c and K_u, with the D-optimum design. The left-hand panel of Figure 1 shows how the design points change with δ^0. The first two design points are independent of δ^0. As δ^0 increases the values of s_4 and i_4 increase slightly. The major relative change, over the range studied, is in i_3 which increases from 1.35 to 2.887. Since we took $[I]_{\max} = 100$, the optimum design uses only a very small part of $\mathcal{X}$. This feature explains the very low efficiency of the grid-based design. Designs for polynomial models for response surfaces typically cover the whole experimental region. This example shows that the behaviour of optimum designs for nonlinear models is very different - efficient designs strongly depend, as here, on the specific nature of the nonlinear model. The results of Figure 1 also explain the slight increase of the efficiencies of the grid design with δ^0 that is a feature of Table 2; the D-optimum design spreads to higher values of the variables as δ^0 increases.

The right-hand panel of Figure 1 shows the specific dependence on δ^0 of, reading downwards, the four variable experimental levels s_4, s_2, i_3 and i_4. As the

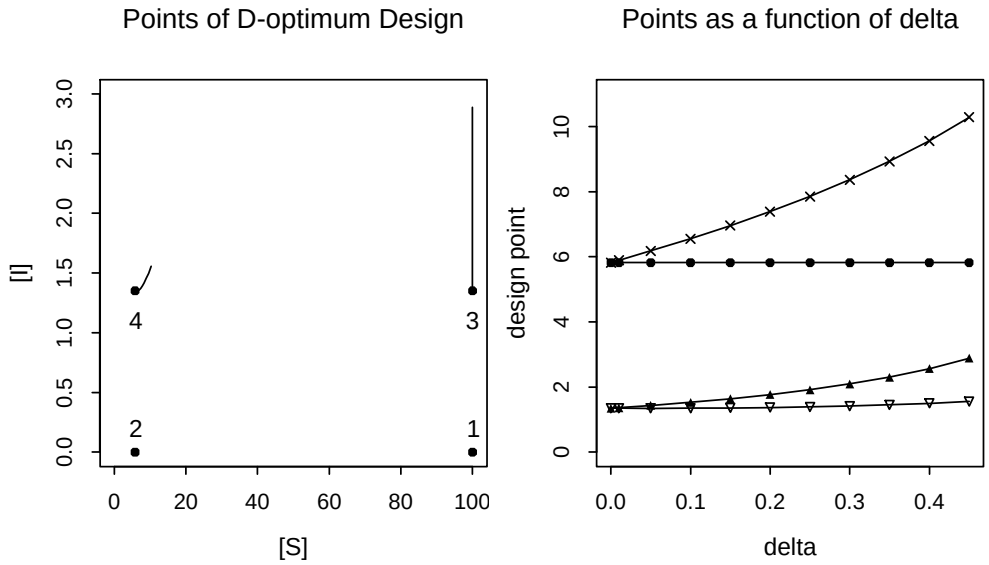

Figure 1: Enzyme kinetics: dependence of the D-optimum design on δ^0. Left-hand panel, the labelled design points in $\mathcal{X}$: $\bullet$, the points for $\delta^0 = 0$. The most noticeable change is in the value of i_3. The designs, for all values of δ^0, are concentrated in a small portion of $\mathcal{X}$ ($[I]_{\max} = 100$). Right-hand panel, design points as a function of δ^0. Reading down: s_4, s_2, i_3 and i_4.

results in the Appendix show, for this model the value of s_2 is independent of δ^0 and so remains at 5.8226 throughout.

The plots in Figure 2 illustrate the gradual divergence of the D_S(T) and the T-optimum designs as δ^0 increases. The design points are in the left-hand panel. The upper set of points are the values of s_4 and s_2. The design for the D_S(T)-optimum design has the same structure as the D-optimum design for $\delta^0 = 0$ of §4, that is $s_2 = s_4$, the value falling on the intermediate curve. Similarly, the lower triple of curves is for i_3 and i_4, which are equal in value for the D_S(T) design.

The design weights in the right-hand panel of Figure 2 show less dependence on δ^0 than do the design points; for both designs $w_2 = w_3$. The top pair of curves is for w_4 which equals 0.5 throughout for the D_S(T)-optimum design. The central pair of curves shows w_2 ($= w_3$), with w_1 forming the bottom pair. These, in particular, show only a slight divergence as the prior value of δ^0 increases.

6 Discussion

The plots quantify the relationship between the D_S(T)-optimum and T-optimum designs for the enzyme kinetic model as δ^0 increases. Unlike in linear models,

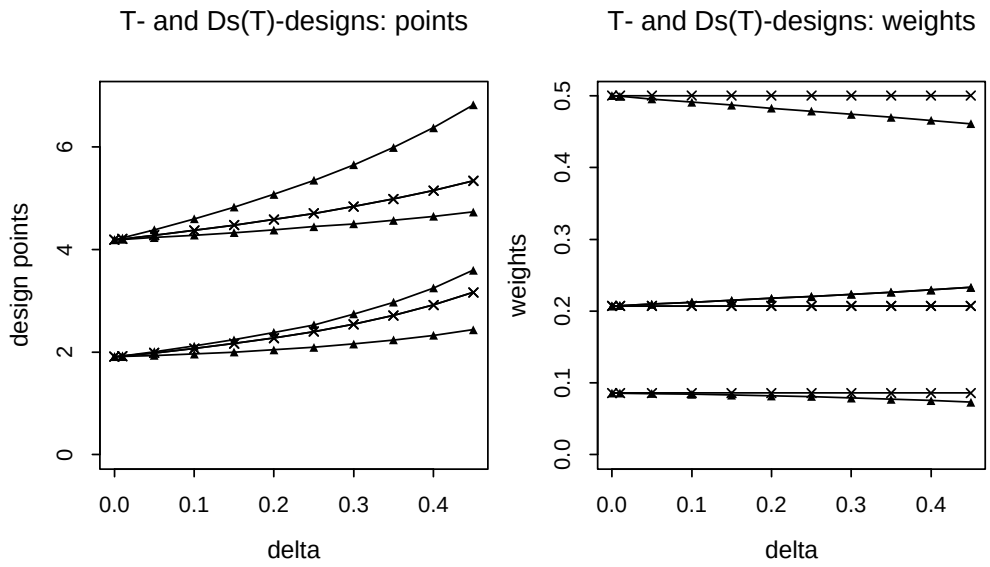

Figure 2: Enzyme kinetics: divergence of T- and D_S(T)-optimum designs as δ^0 increases: ▲ T-optimum designs, $\times$ D_S(T)-optimum designs. Left-hand panel, design points: upper triple, s_4 and s_2, equal for the D_S(T)-optimum designs; lower triple, i_3 and i_4, again equal for the D_S(T)-optimum designs. Right-hand panel, design weights: upper pair of curves, w_4; central pair, $w_2 = w_3$; bottom pair w_1.

D_S and T-optimum designs are not identical for nonlinear models, although here the differences are not large, particularly if the designs use the parameter value $\hat{\psi}_1(\xi_T^*)$ rather than ψ^0. However, as Table 2 shows, the D_S(T)-optimum design has slightly lower D- and T-efficiencies than the T-optimum design, so the T-optimum design is recommended for scientific use.

For linear models D_1- and T-optimum designs are identical. It would be interesting to investigate how the difference of the designs for nonlinear models depends not only on δ^0 but also on the parameter-effects curvature of the model (Hamilton and Watts 1985; O'Brien 1992; Bogacka and Wright 2004). There is also the possibility that there is a value of the parameter other than $\hat{\psi}_1(\xi_T^*)$ which gives a D_1-optimum design with higher efficiencies than the D_S(T)-optimum design investigated here.

We have demonstrated the relationship between D_S and T-optimality through a series of designs for prior values of $\delta > 0$. From (14) and (15) this series has $K_u = 1/(\theta - \delta) > K_c$. A similar series of designs, but with $K_c > K_u$, is obtained for negative δ.

We conclude with some comments on developments in T-optimality. T-optimum designs for three or more models are developed by Atkinson and Fedorov (1975b) and by Braess and Dette (2011). Dette and Titoff (2008) investigate the struc-

ture of T-optimum designs using results from nonlinear approximation theory and compare the power of T- and D_S-optimum designs. The investigation by López-Fidalgo et al. (2008) of some T- and D_S-optimum designs, mentioned in §2.3, is for an extension of the Michaelis-Menten model that does not include inhibition. Uciński and Bogacka (2005) extend T-optimality to designs in which the factors can be time traces of, for example, temperature in a chemical reaction. López-Fidalgo, Trandafir, and Tommasi (2007) extend T-optimality to non-normal models.

If $s > 1$, T-optimum designs typically do not contain sufficient support points to allow estimation of the parameters in the general model. Atkinson (2008) introduced compound DT-optimum designs for simultaneous parameter estimation and model discrimination. Waterhouse, Eccleston, and Duffull (2009) find approximations to DT-optimum designs based on the component optimum designs. If the prior distribution for ψ is sufficiently dispersed, the T-optimum design will have sufficient support to allow estimation of the full model. However, more efficient designs will be obtained by using a compound design incorporating all available prior information. Fast algorithms for the calculation of Bayesian designs are given by Gotwalt, Jones, and Steinberg (2009).

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Appendix: D-optimum design for the mixed inhibition model

Values of s_2, i_3, s_4 and i_4 for the D-optimum design (16) when $[I]_{\min} = [S]_{\min} = 0$.

$$s_2 = \frac{[S]_{\max} K_m}{[S]_{\max} + 2K_m}$$

$$i_3 = \min\left\{ \frac{K_c K_u ([S]_{\max} + K_m)}{K_m K_u + [S]_{\max} K_c},\ [I]_{\max} \right\}$$

$$i_4 = \min\left\{ \sqrt{\frac{K_c K_u (K_m K_c + [S]_{\max})}{K_m K_u + [S]_{\max} K_c}},\ [I]_{\max} \right\}$$

$$s_4 = \max\left\{ -K_m \frac{K_u (K_c - i_4)}{K_c (K_u - i_4)}, 0 \right\}.$$

Since s_2 is a function of neither K_c nor K_u its value does not vary with δ.

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