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Optimum designs for the equality of parameters in enzyme inhibition kinetic models

Anthony C. Atkinson [a,*], Barbara Bogacka [b]

[a] Department of Statistics, London School of Economics, London WC2A 2AE, UK
[b] School of Mathematical Sciences, Queen Mary, University of London, London E1 4NS, UK

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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 reparameterize 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. Appendix A presents analytical expressions for the D-optimum design for the four parameters of the mixed inhibition model.

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 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 $\delta^T A \delta$, with A the information matrix for δ.

An alternative approach is to estimate δ as precisely as possible, by finding the D_s-optimum design maximizing the determinant of A, where S is the set of cardinality s of parameters to be estimated. Since the T criterion, unlike 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 $\delta^T A \delta = \delta^2 A$. Then the 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, 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, D_1 and T-optimum designs become identical as $\delta \to 0$. See López-Fidalgo et al. (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 D_1-optimum designs, with particular emphasis on the

* Corresponding author. Tel.: +44 20 7515 5716.
E-mail address: a.c.atkinson@lse.ac.uk (A.C. Atkinson).

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efficiency of the designs. We start in Section 2 with a short introduction to the optimum design criteria we shall be using. Our example, from enzyme kinetics, is introduced in Section 3, where we reparameterize this nonlinear model to allow for testing parameter equality. The next section describes D- and 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 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 Section 6. Analytical expressions for the support points of the D-optimum design for the four-parameter mixed inhibition model are in Appendix A.

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 et al. (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-, Ds- and T-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, $f(\cdot)$ 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 $f_1(\cdot)$ and $f_2(\cdot)$ are subvectors of $f(\cdot)$ 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 $M_{jk}(\xi)=\sum_{i=1}^{n} w_i f_j(x_i)f_k^{\mathrm{T}}(x_i)$ $(j,k=1,2)$ the covariance matrix for the parameter of interest δ is proportional to

$$A^{-1}=\{M_{22}(\xi)-M_{21}(\xi)M_{11}^{-1}(\xi)M_{21}^{\mathrm{T}}(\xi)\}^{-1}. \tag{4}$$

Accordingly, the D_s-optimum design for δ in the linear model (2) maximizes the determinant

$$|A|=|M_{22}(\xi)-M_{21}(\xi)M_{11}^{-1}(\xi)M_{21}^{\mathrm{T}}(\xi)|=|M(\xi)|/|M_{11}(\xi)|. \tag{5}$$

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 $\eta_1(\cdot)$ need not be a special case of $\eta_t(\cdot)$. In general the T-optimum design depends on the value assumed for the parameter vector ψ_t. Let the parameter estimate when $\eta_1(\cdot)$ is fitted to observations without error from $\eta_t(\cdot)$ be $\hat{\psi}_1(\xi)$. That is

$$\hat{\psi}_1(\xi)=\arg\min_{\psi_1}\sum_{i=1}^{n} w_i\{\eta_t(x_i,\psi_t)-\eta_1(x_i,\psi_1)\}^2. \tag{6}$$

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

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

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

$$y_i=\psi^{\mathrm{T}}f(x_i)+\epsilon_i=\psi_t^{\mathrm{T}}f_t(x_i)+\delta^{\mathrm{T}}\tilde{f}_2(x_i)+\epsilon_i, \tag{8}$$

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

$$\Delta(\xi)=\delta^{\mathrm{T}}\{M_{22}(\xi)-M_{21}(\xi)M_{11}^{-1}(\xi)M_{21}^{\mathrm{T}}(\xi)\}\delta. \tag{9}$$

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 D_s-optimum