A KL-augmented design for the Hill model

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Abstract. A widely applied dose-response model is the Hill model with four parameters. In the Hill model, the measurement error may be homoscedastic or heteroscedastic. If the experimental points are fixed with the goal of identifying the right error-variance structure, then by applying the KL-criterion, we have that only two different doses are necessary. Hence, this optimum design does not enable any estimation of the parameters. From here the necessity to add some other experimental points. This work focuses on augmenting the KL-optimal design by the inclusion of two additional doses with the goal of providing an estimation of the model parameters, while guaranteeing a minimum KL-efficiency to optimally discriminate between the two variance structures.

Keywords: Augmentation design, KL-optimality, D-optimality

1 Introduction

The Hill model is widely applied in dose-response contexts, biology, enzymatic kinetics, and so on. In this work we focus on the Hill model with 4 parameters (see, for instance, [5]),

$$y = \eta(x, \boldsymbol{\beta}) + \varepsilon = \frac{(E_{con} - b) \cdot (x/IC_{50})^s}{(1 + (x/IC_{50})^s)} + b + \varepsilon, \tag{1}$$

where $\boldsymbol{\beta} = (E_{con}, b, IC_{50}, s)^T$ is the parameter vector, $x \in \mathcal{X}$ is a dose and ε is a random error term that follows a Gaussian distribution with zero mean. In Hill model, the parameters have a clear physical interpretation, being E_{con} the mean effect on the control for $x = 0$, b the asymptotic value of the response when $x \to \infty$, IC_{50} corresponds to the value for which the response would be the middle of the range $E_{con} - b$ and finally s is a shape parameter denoted slope of the response and is usually assumed $s < 0$ (note that the interpretations of E_{con} and b should be exchanged in case $s > 0$).

The error term ε may be either homoscedastic (with constant absolute error), or heteroscedastic (with constant relative error), see [5]. To decide in favour of one of the two error-variance structures, we consider the following hypothesis test:

$$\begin{cases} \mathbf{H}_0 : \ \varepsilon \sim \mathcal{N}(0, \sigma^2) \\ \mathbf{H}_1 : \ \varepsilon \sim \mathcal{N}(0, \sigma^2\, \eta(x, \boldsymbol{\beta})^2) \end{cases} \tag{2}$$

Our main goal is to choose the doses "optimally" for testing hypotheses (2). To this aim, we apply the KL-optimality criterion, see for instance [4] and [6]. From Theorem 1 in [2], we have that the KL-optimum design, say ξ_{KL}, has only two support points. Therefore, if we also want to estimate the whole parameter vector ($\boldsymbol{\beta}$) (which is a common inferential goal), then it is necessary to enrich this design by adding at least two new experimental points. Unfortunately, there is a trade off between doses which are optimal for estimation purposes or for discrimination goals (see for instance, [7]). In this work, we prove that it is always possible to add two experimental points (chosen in a specific subset of the dose domain, herein called "candidate-points region") without loosing too much in terms of KL-efficiency. For more information about augmenting-design theory, see [1] and [2] and the references therein. In Section 3 we develop a numerical example, where the additional two doses are chosen in the candidate-points region with the goal of increasing the precision of the estimates according to D-optimality. With this augmented design, we reach the double goal of discriminating between the error-variance structures and estimating the 4 parameters of the Hill model.

2 KL-augmentated designs

2.1 KL-optimality

Let ξ be a design over the dose domain $\mathcal{X}$, and f_0, f_1 be the homoscedastic and the heteroscedastic Hill models, respectively. Considering f_1 as the true completely known model, the KL-optimality criterion function is

$$\mathcal{I}(\xi, \boldsymbol{\theta}_1) = \min_{\theta_0} \int_{\mathcal{X}} \int_{\mathcal{Y}} \left[\log \frac{f_1(y; x, \boldsymbol{\theta}_1)}{f_0(y; x, \boldsymbol{\theta}_0)} \right] f_1(y; x, \boldsymbol{\theta}_1) dy \, d\xi(x), \tag{3}$$

where $\boldsymbol{\theta}_0 = (\boldsymbol{\beta}_0^T, \sigma_0^2)^T$ is the vector of unknown parameters of f_0, and $\boldsymbol{\theta}_1 = (\boldsymbol{\beta}_1^T, \sigma_1^2)^T$ is the parameter vector of f_1, assumed to be known.

Let $\xi_{KL} = \arg\max_{\xi} \mathcal{I}(\xi, \boldsymbol{\theta}_1)$ be the KL-optimum design, the KL-efficiency:

$$0 \leq \text{eff}_{KL}(\xi, \boldsymbol{\theta}_1) = \frac{\mathcal{I}(\xi, \boldsymbol{\theta}_1)}{\mathcal{I}(\xi_{KL}, \boldsymbol{\theta}_1)} \leq 1$$

enables us to measure the "goodness" of a design ξ at performing the hypothesis test (2).

2.2 Design augmentation

Let x_1 and x_2 denote two candidate points to be added and α_1 and α_2 be the proportion of replications to be taken at these two additional doses, respectively. The weights α_j with $j = 1, 2$ are constrained to be $\alpha_1 + \alpha_2 = \alpha$, where $0 \leq \alpha \leq 1$ is the proportion of "contamination" of ξ_{KL} and is fixed in advance by the researcher. Each of the points x_1 and x_2 must be chosen from a proper candidate-points region,

$$\mathcal{R}(\xi_{KL}; \alpha, \delta) = \{x : \xi_{KL+1}^{(x)} := (1-\alpha)\xi_{KL} + \alpha\, \xi_x,\ \text{eff}_{KL}\big(\xi_{KL+1}^{(x)}\big) \geq \delta\}, \tag{4}$$

where ξ_x is a design with mass concentrated in x, $\xi_{KL+1}^{(x)}$ is a KL design with the augmentation of a point x, and $0 < \delta < 1$ is a suitable threshold for the KL-efficiency (chosen by the researcher).

Theorem 1. *Let ξ_{KL} be the KL-optimum design, which has two support points, as proven in Theorem 1 in [2]. In addition, let ξ_{x_1}, ξ_{x_2} be two designs with mass concentrated at $x_1 \in \mathcal{R}(\xi_{KL};\alpha,\delta)$ and $x_2 \in \mathcal{R}(\xi_{KL};\alpha,\delta)$, respectively. Then, the KL-augmented design*

$$\xi_{KL+2}^{(x_1,x_2)} = (1-\alpha)\xi_{KL} + \alpha_1\xi_{x_1} + \alpha_2\xi_{x_2}, \quad \alpha_1,\alpha_2 \in (0,1),\ \alpha=\alpha_1+\alpha_2 \in (0,1)$$

is such that $\mathit{eff}_{KL}\Big(\xi_{KL+2}^{(x_1,x_2)}\Big) \geq \delta$.

Proof. By the definition of KL-divergence:

$$\begin{aligned}
\mathcal{I}(\xi_{KL+2}^{(x_1,x_2)}) &= \min_{\theta_0} \int_{\mathcal{Y}}\int_{\mathcal{X}} \log\frac{f_1(y;x,\theta_1)}{f_0(y;x,\theta_0)} f_1(y;x,\theta_1)\, d\xi_{KL+2}^{(x_1,x_2)}\, dy \\
&= \min_{\theta_0}\Bigg[\int_{\mathcal{Y}}\int_{\mathcal{X}} (1-\alpha)\log\frac{f_1(y;x,\theta_1)}{f_0(y;x,\theta_0)} f_1(y;x,\theta_1)\, d\xi_{KL}\, dy \\
&\quad +\alpha_1 \textstyle\int_{\mathcal{Y}} \log\frac{f_1(y;x_1,\theta_1)}{f_0(y;x_1,\theta_0)} f_1(y;x_1,\theta_1)\,dy + \alpha_2 \int_{\mathcal{Y}} \log\frac{f_1(y;x_2,\theta_1)}{f_0(y;x_2,\theta_0)} f_1(y;x_2,\theta_1)\,dy\Bigg] \\
&= \min_{\theta_0}\Big\{ \tfrac{\alpha_1}{\alpha}\Big[\textstyle\int_{\mathcal{Y}}\int_{\mathcal{X}} (1-\alpha)\log\frac{f_1(y;x,\theta_1)}{f_0(y;x,\theta_0)} f_1(y;x,\theta_1)\,d\xi_{KL}\,dy + \int_{\mathcal{Y}} \alpha\log\frac{f_1(y;x_1,\theta_1)}{f_0(y;x_1,\theta_0)} f_1(y;x_1,\theta_1)\,dy\Big] \\
&\quad + \tfrac{\alpha_2}{\alpha}\Big[\textstyle\int_{\mathcal{Y}}\int_{\mathcal{X}} (1-\alpha)\log\frac{f_1(y;x,\theta_1)}{f_0(y;x,\theta_0)} f_1(y;x,\theta_1)\,d\xi_{KL}\,dy + \int_{\mathcal{Y}} \alpha\log\frac{f_1(y;x_2,\theta_1)}{f_0(y;x_2,\theta_0)} f_1(y;x_2,\theta_1)\,dy\Big]\Big\}
\end{aligned}$$

and by the concavity of the min:

$$\begin{aligned}
\mathcal{I}(\xi_{KL+2}^{(x_1,x_2)}) \geq \frac{\alpha_1}{\alpha}\min_{\theta_0}&\Bigg[\int_{\mathcal{Y}}\int_{\mathcal{X}} (1-\alpha)\log\frac{f_1(y;x,\theta_1)}{f_0(y;x,\theta_0)} f_1(y;x,\theta_1)\,d\xi_{KL}\,dy \\
&+\int_{\mathcal{Y}} \alpha\log\frac{f_1(y;x_1,\theta_1)}{f_0(y;x_1,\theta_0)} f_1(y;x_1,\theta_1)\,dy\Bigg] \\
+\Big(1-\frac{\alpha_1}{\alpha}\Big)\min_{\theta_0}&\Bigg[\int_{\mathcal{Y}}\int_{\mathcal{X}} (1-\alpha)\log\frac{f_1(y;x,\theta_1)}{f_0(y;x,\theta_0)} f_1(y;x,\theta_1)\,d\xi_{KL}\,dy \\
&+\int_{\mathcal{Y}} \alpha\log\frac{f_1(y;x_2,\theta_1)}{f_0(y;x_2,\theta_0)} f_1(y;x_2,\theta_1)\,dy\Bigg] \\
= \epsilon\mathcal{I}(\xi_{KL+1}^{(x_1)}) &+ (1-\epsilon)\mathcal{I}(\xi_{KL+1}^{(x_2)}),
\end{aligned} \tag{5}$$

where $\epsilon = \frac{\alpha_1}{\alpha}$ and $\xi_{KL+1}^{(x_i)} = (1-\alpha)\xi_{KL} + \alpha\xi_{x_i}$, $i=1,2$.

Dividing both sides of Equation (5) by $I(\xi_{KL}^{\star},\theta_1)$ we get

$$\mathrm{eff}_{KL}(\xi_{KL+2}^{(x_1,x_2)}) \geq \epsilon\,\mathrm{eff}_{KL}\big(\xi_{KL+1}^{(x_1)}\big) + (1-\epsilon)\,\mathrm{eff}_{KL}\big(\xi_{KL+1}^{(x_2)}\big) \geq \delta,$$

where the last inequality follows by the definition of candidate-points region given in Equation (4) and the assumption that x_1, $x_2 \in \mathcal{R}(\xi_{KL};\alpha,\delta)$.

■

In the next section, to enrich ξ_{KL}, the weights α_j and the additional doses x_j (with $j = 1, 2$) will be chosen according to the D-optimality criterion, under the restrictions $\alpha_1 + \alpha_2 = \alpha$ and $x_j \in \mathcal{R}(\xi_{KL}; \alpha, \delta)$.

3 The KL-augmented design for the Hill model

From Theorem 1 in [6], the KL-optimal design for the Hill model with $\boldsymbol{\beta}_1 = (E_{con}, b, IC_{50}, s)^T = (1.70, 0.137, 111, -1.03)^T$ and design space $\mathcal{X} = [0.01, 1500]$ (the choice of β_1 and of the design space follow from [5]) is

$$\xi_{KL} = \left\{ \begin{array}{cc} 0.01 & 1500 \\ 0.23 & 0.77 \end{array} \right\},$$

that does not allow to estimate all the parameters of the model (thus, with a D-efficiency of 0%).

To make the estimation of all the model parameters possible, we can augment ξ_{KL} by choosing other two doses with a total contamination value of $\alpha = 0.3$. The candidate-points region that follows from this choice of α and a KL-efficiency threshold of $\delta = 0.8$ is

$$\mathcal{R}(\xi_{KL}; \alpha = 0.3, \delta = 0.8) = [0.01, 14.38] \cup [475.93, 1500],$$

as shown in Figure 1.

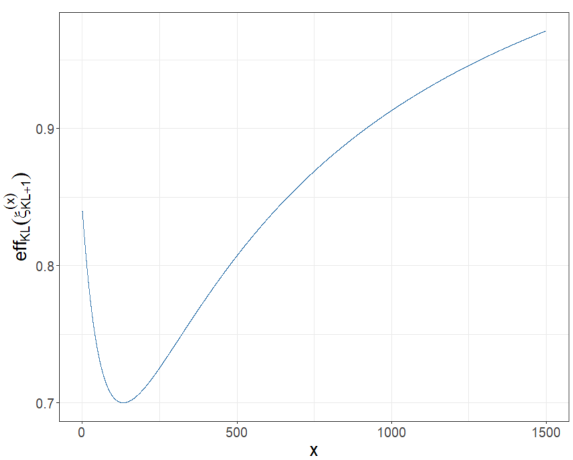

Fig. 1. Candidate-points region for $\alpha = 0.3$ and $\delta = 0.8$.

To obtain a precise estimation of the model parameters, we choose the additional doses x_1 and x_2 (within $\mathcal{R}(\xi_{KL}; 0.3, 0.8)$), and the proportions of replicates

α_1 and α_2 (with $\alpha_1+\alpha_2=\alpha$), by finding the D-optimal design $\xi^\star$ among all the designs $\xi=\left\{\begin{matrix} x_1 & x_2 \\ \frac{\alpha_1}{\alpha} & \frac{\alpha_2}{\alpha}\end{matrix}\right\}$ with 2 support points in $\mathcal{R}(\xi_{KL};0.3,0.8)$:

$$\xi^\star = \underset{\xi \text{ supported in } \mathcal{R}(\xi_{KL},0.3,0.8)}{\arg\max} |M\big((1-\alpha)\xi_{KL}+\alpha\xi\big)|^{1/4}. \qquad (6)$$

The solution is found numerically with the Wynn-Fedorov algorithm (see [3]). The resulting augmented KL-optimum design is

$$\xi_{KL+2}^{(x_1,x_2)} = (1-\alpha)\xi_{KL}+\alpha\xi^\star = \left\{\begin{matrix} 0.01 & 14.38 & 475.93 & 1500 \\ 0.16 & 0.15 & 0.15 & 0.54\end{matrix}\right\},$$

that has a KL-efficiency of 84% and a D-efficiency of 65%.

4 Conclusions

This article highlights the importance of augmenting a design that, while being the best for a certain criterion (in this case KL-optimality) is very poor for other important goals, such as parameter estimation. In the application to the Hill model, the augmented design is good enough for both aims, while ξ_{KL} is completely useless for parameter estimation.

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