Efficient Sampling Windows for Parameter Estimation in Population Models

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1 Motivation

- Pharmacokinetic and toxicokinetic studies,
- Restrictiveness of conventional optimum designs,
- Lack of simple techniques of calculating sampling intervals having high efficiency and good interpretation.

2 Class of considered models

Observation equation (N - number of individuals, n_k - number of observations for individual k)

$$y_i^k = \eta(t_i^k;\theta_i^k) + \varepsilon_i^k, \quad i = 1,\dots,n_k, \quad k = 1,\dots,N \tag{1}$$

where y_i^k is an observation at time $t_i^k \in T = [0, t_{max}]$, $\varepsilon_i^k \sim f$, $y_i^k|\theta_i^k \sim g(y_i^k|\theta_i^k)$, where f and g are known densities and η is known possibly nonlinear function. Vectors $\theta_i^k \in \Theta$ are assumed to be realizations of the random vector θ with probability density $h(\theta;\psi)$. The function h is entirely determined by the population parameter vector $\psi = (\mathrm{E}(\theta), \mathrm{var}(\theta))^{\mathrm{T}} = (\psi_1,\dots,\psi_{\widetilde{p}})^{\mathrm{T}}$.
Efficient estimation of this vector of constant parameters ψ_i is of our primary interest.

3 Experimental design (N patients in G groups)

(Patan and Bogacka, 2006)

Individual level (within group j every patient follows the same design)

$$\xi_j = \begin{Bmatrix} t_1^j & \dots & t_{s_j}^j \\ w_1^j & \dots & w_{s_j}^j \end{Bmatrix}; \quad \sum_{i=1}^{s_j} w_i^j = 1; \quad w_i^j \in (0,1], \tag{2}$$

where w_i^j denotes the proportion of observations to be taken at time instant t_i^j.

Population level (for all G groups)

$$\zeta = \begin{Bmatrix} (\xi_1, n_1) & \dots & (\xi_G, n_G) \\ \alpha_1 & \dots & \alpha_G \end{Bmatrix}; \quad \sum_{j=1}^{G} \alpha_j = 1; \quad \alpha_j \in (0,1], \tag{3}$$

where α_j denotes the proportion of the population of N subjects in group j.

4 The optimum population design problem

Step 1. $\zeta = \begin{Bmatrix} (\xi_1, n_1) & \dots & (\xi_G, n_G) \\ \alpha_1 & \dots & \alpha_G \end{Bmatrix}; \ \sum_{j=1}^{G} \alpha_j = 1 \Big\}$

$$\Big\Vert \quad \beta_j = \frac{N}{N_0}\alpha_j n_j$$

Step 2. $\upsilon = \begin{Bmatrix} \xi_1 & \dots & \xi_G \\ \beta_1 & \dots & \beta_G \end{Bmatrix}; \ \sum_{j=1}^{G} \beta_j = 1 \Big\}$

$$\Big\Vert \quad q_i^j = \beta_j w_i^j$$

Step 3. $\omega = \begin{Bmatrix} t_1^1 & \dots & t_{s_j}^1 & \dots & t_1^G & \dots & t_{s_G}^G \\ q_1^1 & \dots & q_{s_j}^1 & \dots & q_1^G & \dots & q_{s_G}^G \end{Bmatrix}; \ \sum_{j=1}^{G}\sum_{i=1}^{s_j} q_i^j = 1 \Big\}$

$$\Big\Vert$$

$$\omega = \begin{Bmatrix} t_1 & \dots & t_s \\ q_1 & \dots & q_s \end{Bmatrix}; \ \sum_{k=1}^{s} q_k = 1 \Big\}$$

Comments

- Such a reformulation simplifies the problem of finding the two level hierarchical optimal population design to that of finding the equivalent one level design.
- It significantly reduce the dimensionality of the optimization problem.
- The information about groups is included in q_i^j and so in q_k. This information is later recovered after an optimum design ω has been found.

5 EXAMPLE: Pharmacokinetic study

As and example we use the one-compartment model with first-order drug absorption (Jonsson et al., 1996):

$$y = \frac{Dk_a}{V(k_e - k_e)}\left(e^{-k_e t} - e^{-k_a t}\right) + \varepsilon, \tag{4}$$

where k_a and k_e are the first-order absorption and elimination rates, respectively, V is the apparent volume of distribution, D is a known dose and ε is an additive zero-mean uncorrelated Gaussian measurement noise with a constant variance. The regression parameters $\theta = (V, k_a, k_e)^{\mathrm{T}}$ are independent and normally distributed. The prior values of the population parameters are:

$$\psi_0 = \big(E(\theta), \mathrm{var}(\theta)\big)^{\mathrm{T}} = (100, 2.08, 0.1155, 0.3, 0.3, 0.03)^{\mathrm{T}} \quad \text{and} \quad \mathrm{var}(\varepsilon) = 0.15.$$

We are looking for a D-optimum population design to estimate the population parameters as precisely as possible. We assume that the concentration of the drug can be measured within the design space $T = [0.25, 12]$ scaled in hours after administration and the total number of measurements is assumed to be $C_0 = 900$.

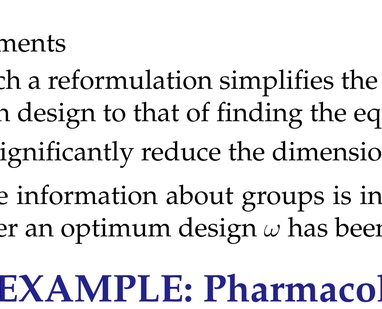


Fig.1. Drug concentration model

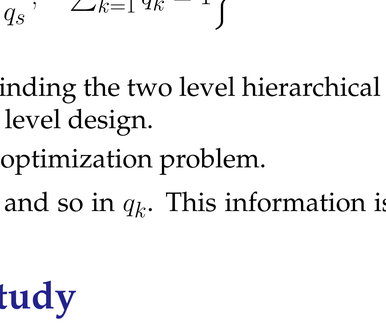


Fig.2. Variance of the response prediction $d(t, \omega^\star, \psi^0)$

The variance function $d(t, \omega^\star, \psi^0)$ reflects the behaviour of the model function: it has sharp peaks when the concentration changes fast and a flat peak at the area of slow drug elimination.

The global D-optimum design:

$$\omega^\star = \begin{Bmatrix} 0.45 & 1.86 & 9.90 \\ 0.3333 & 0.3334 & 0.3333 \end{Bmatrix}$$

Examples of population D-optimum designs generated from $\omega^\star$:

1. *Identical design (one group design)*, $G = 1$, $n_1 = 9$,

$$\zeta = \left\{ \left(\begin{Bmatrix} 0.45 & 1.86 & 9.90 \\ 0.3333 & 0.3334 & 0.3333 \end{Bmatrix}, 9 \right) \right\}; \quad N^\star = 100.$$

For each patient we have to conduct exactly three measurements at each time instant.

2. *One-point population design*, $G = 3$, $n_1 = n_2 = n_3 = 10$

$$\zeta^\star = \left\{ \begin{matrix} \left(\begin{Bmatrix} 0.45 \\ 1 \end{Bmatrix}, 10 \right) & \left(\begin{Bmatrix} 1.86 \\ 1 \end{Bmatrix}, 10 \right) & \left(\begin{Bmatrix} 9.90 \\ 1 \end{Bmatrix}, 10 \right) \\ 0.3333 & 0.3334 & 0.3333 \end{matrix} \right\}; \quad N^\star = 90$$

Each group consist of 30 patients, each patient in a group should have 10 replications at the same time point.

3. *Arbitrarily structured design*, $G = 3$, $n_1 = n_2 = n_3 = 10$

$$\zeta^\star = \left\{ \begin{matrix} \left(\begin{Bmatrix} 0.45 & 9.90 \\ 0.5733 & 0.4267 \end{Bmatrix}, 10 \right) & \left(\begin{Bmatrix} 0.45 & 1.86 & 9.90 \\ 0.2603 & 0.5248 & 0.2149 \end{Bmatrix}, 10 \right) & \left(\begin{Bmatrix} 1.86 & 9.90 \\ 0.6184 & 0.3816 \end{Bmatrix}, 10 \right) \\ 0.4008 & 0.3979 & 0.2013 \end{matrix} \right\}; \quad N^\star = 90.$$

After rounding of the weights there are 36 patients in groups 1 and 2 and 18 patients in group 3. Patients in group 1 have two sampling times replicated 6 and 4 times respectively, in group 2 three sampling times replicated 3, 5 and 2 times, and in group 3 two sampling times replicated 6 and 4 times, respectively.

6 Efficient Sampling Windows

We define an *efficient sampling window population design* as a design ζ^W having the D-optimum individual design weights w_i^j and numbers of observations n_i^j as well as the D-optimum group proportions α_j.

The time instants of the window design ζ^W belong to a Cartesian product of the sampling intervals obtained for the global design $\omega^\star$.

Algorithm

Step. 1. Calculate a locally D-optimum global population design $\omega^\star$.

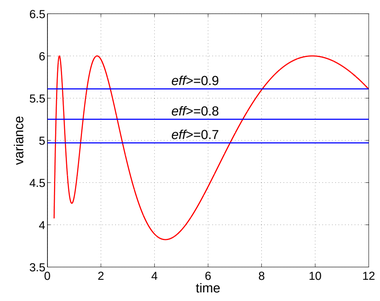
Step. 2. Choose the minimum efficiency of window design (or minimal length of shortest window) and a small $\lambda \in (0,1)$.

Step. 3. Calculate time windows solving the equation $d(t, \omega^\star, \psi^0) = \lambda$.

Step. 4. If minimum efficiency (minimum windows length) is assured then STOP, else increase λ and repeat Step. 3.

Efficient windows based on the Equivalence Theorem condition has been considered by Bogacka et al. (2006) for a fixed model.

PK EXAMPLE continued



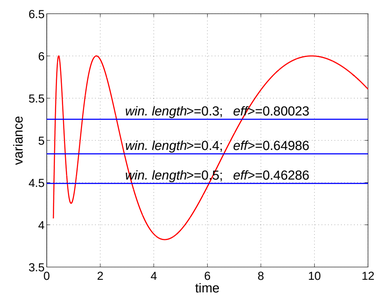


Fig.1. Time windows with guaranteed efficiency Fig.2. Time windows with guaranteed minimal length

Min. efficiency	Windows	λ
0.9	$[0.3545, 0.5635], [1.4755, 2.3505], [8.0275, 11.9915]$	5.61
0.8	$[0.3215, 0.6235], [1.3325, 2.6085], [7.2965, 12.0000]$	5.25
0.7	$[0.3015, 0.6705], [1.2395, 2.8055], [6.8225, 12.0000]$	4.97
Min. length	**Windows**	λ_p
0.5	$[0.2725, 0.7735], [1.0765, 3.1805], [6.0625, 12.0000]$	4.49
0.4	$[0.2925, 0.6945], [1.1975, 2.8995], [6.6145, 12.0000]$	4.84
0.3	$[0.3215, 0.6235], [1.3325, 2.6085], [7.2965, 12.0000]$	5.25

Due to the nature of the variance function the sampling windows are narrower when it is important to take measurements close to the optimum times and they are wider when it is less important.

Optimal maximin sampling windows:

(a) Maximized minimal window length subject to efficiency ≥ 0.9:

Min. length	Windows	Efficiency
0.2637	$[0.3318, 0.5955], [1.7977, 2.0614], [9.5657, 10.5000]$	0.9

(b) Maximized minimal efficiency subject to window length ≥ 0.4:

Min. efficiency	Windows	Win. length
0.8830	$[0.2871, 0.6871], [1.7792, 2.1792], [9.1248, 10.6065]$	0.4

7 Concluding remarks

- The variance of prediction based technique for generating efficient sampling windows for population designs is simple, assures minimum efficiency (or minimum window length), indicates the importance of accurate timing of the sampling;
- Such windows can be further improved by the maximin method.

References

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