Efficient Sampling Windows for Parameter Estimation in Population Models

Barbara BOGACKA
School of Mathematical Sciences,
Queen Mary, University of London, UK
B.Bogacka@qmul.ac.uk

Maciej PATAN
Institute of Control and Computation Engineering,
University of Zielona Góra, Poland
M.Patan@issi.uz.zgora.pl

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, nj: number of observations for individual i)

\[ y_j = \psi^T \theta + \epsilon_j, \quad i = 1, \ldots, n_j, \quad k = 1, \ldots, N \]

where \( y_j \) is an observation at time \( t_i \) in \( T = [0, \infty) \), \( \psi \sim f \), \( \psi_i \sim \psi(\theta) \), where \( f \) and \( \theta \)
are known densities and \( \psi \) is known possibly nonlinear function. Vectors \( \theta \in \Theta \) are assumed to be realizations of the random vector \( \theta \) with probability density \( p(\theta) \). The function \( f \) is entirely determined by the population parameter vector \( \psi = (\psi_0, \psi_1, \ldots, \psi_k)^T \).

Efficient estimation of this vector of constant parameters \( \psi \) is of our primary interest.

3 Experimental design (N patients in G groups)
(Patan and Bogacka, 2006)

Individual level (within group): every patient follows the same design
\[ \xi_j = \begin{pmatrix} \xi_1 & \xi_2 & \cdots & \xi_{n_j} \end{pmatrix} \] \[ \sum_{i=1}^{n_j} \xi_i = 1, \quad w_i \in [0, 1], \]
where \( w_i \) denotes the proportion of observations to be taken at time instant \( t_i \).

Population level (for all G groups)
\[ \zeta \left\{ \begin{pmatrix} \psi_1 & \psi_2 & \cdots & \psi_{n_j} \end{pmatrix} \right\} := \sum_{j=1}^{G} \psi_j = 1, \quad n_j \in [0, 1], \]
where \( n_j \) denotes the proportion of the population of \( N \) subjects in group \( j \).

4 The optimum population design problem

Step 1.
\[ \zeta = \left\{ \begin{pmatrix} \psi_1 & \psi_2 & \cdots & \psi_{n_j} \end{pmatrix} \right\} : \sum_{j=1}^{G} \psi_j = 1 \]

Step 2.
\[ \psi = \left\{ \begin{pmatrix} \psi_1 & \psi_2 & \cdots & \psi_{n_j} \end{pmatrix} \right\} : \sum_{j=1}^{G} \psi_j = 1 \]

Step 3.
\[ \omega = \left\{ \begin{pmatrix} \psi_1 & \psi_2 & \cdots & \psi_{n_j} \end{pmatrix} \right\} : \sum_{j=1}^{G} \psi_j = 1 \]

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 \( \omega \) and so in \( \psi \). This information is later recovered after an optimum design \( \omega \) 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):

\[ y = \frac{D_k o_t}{(k_e - k_d)} (e^{-k_d t} - e^{-k_e t}) + \epsilon, \]

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

\[ \psi_0 = (0.06, 0.09, 100, 0.09, 0.1125, 0.1, 0.8, 0.7)^T, \quad \text{and} \quad \psi/\theta = 0.15. \]

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 \( G = 900 \).

The global D-optimum design:
\[ \omega^* = \begin{pmatrix} 0.45 & 1.86 & 9.90 \\ 0.3333 & 0.3334 & 0.3335 \end{pmatrix} \]

Fig.1. Drug concentration model
Fig.2. Variance of the response prediction \( \sigma^2(\omega^*, \psi^0) \)
The variance function \( \sigma(\omega, \psi) \) 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.

Examples of population D-optimum designs generated from \( \omega^* \):
1. Identical design (one group design), \( G = 1, n_1 = 9 \)
\[ \zeta = \left\{ \begin{pmatrix} 0.45 & 1.86 & 9.90 \end{pmatrix} \right\} : N^* = 100. \]

For each patient we have to conduct exactly three measurements at each time instant.
2. One-point population design, \( G = 3, n_1 = n_2 = n_3 = 10 \)
\[ \zeta = \left\{ \begin{pmatrix} 0.45 \end{pmatrix} \right\} \quad N^* = 90. \]

Each group consist of 30 patients, each patient in a group should have 10 replicates at the same time point.
3. Arbitrarily structural design, \( G = 3, n_1 = n_2 = n_3 = 10 \)
\[ \zeta = \left\{ \begin{pmatrix} 0.45 \end{pmatrix} \right\} : N^* = 90. \]

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 times sampled replicated 5 and 2 times, and in group 3 two times sampled replicated 6 and 4 times respectively.

6 Efficient Sampling Windows
We define an efficient sampling window population design as a design \( \psi^W \) having the D-optimum individual design weights \( \psi^W \) and numbers of observations \( w^W \) as well as the D-optimum group parameters \( \alpha_j \).

The time instants of the window design \( \psi^W \) belong to a Cartesian product of the sampling intervals obtained for the global design \( \omega^* \).

Algorithm
Step 1. Calculate a locally D-optimum global population design \( \omega^* \).
Step 2. Choose the minimum efficiency of window design (or minimal length of shortest window) and a small \( \lambda \) (\( 0, 1 \)).
Step 3. Calculate time windows solving the equation \( \psi^W, \lambda = \lambda \).
Step 4. If minimum efficiency (minimum window length) is assured then STOP, else increase \( \lambda \) and repeat Step 3.

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

PK EXAMPLE continued

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) Minimal window length subject to efficiency \( \geq 0.9 \):

(b) Minimal maximin efficiency subject to window length \( \geq 0.4 \):

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