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RELIABILITY AND EFFICIENCY OF THE D, E, S, A–OPTIMAL SAMPLING SCHEDULE DESIGN

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Abstract: Due to sharp practical and ethical constraints imposed on medical measurements, the parameter estimation procedure designed for diagnosis and therapy, is often a difficult problem. When blood sampling provides the data, the number of samples and the measurement interval should be minimised. We have implemented D, E, S, A–optimal sampling schedule (OSS). These OSS have minimal size, which means that number of samples is equal to the number of model parameters that are being estimating. Setting–up the results of D, E, S and A approaches allows to compare their efficiency and usefulness. Illustrative examples are presented.

Keywords: modelling, optimal sampling schedule, various criteria

1. Introduction

Advanced mathematical modelling and identification methods are being necessary in investigation of biomedical system kinetics. Usually more or less severe limitations are imposed on the experiment conditions. The more frequent limitations concern number of input and output ports (often only blood is accessible) and the whole amount of blood allowed drawing from the object. The latter is equivalent to establishing as short measurement interval and as small number of samples as it is

possible and sufficient for model identification purpose. The above causes that optimal choice of experiment variables is of primary importance [1–3].

This paper presents minimum size OSS determined one by one by means of D, E, S and A criterion. Finally their reliability, efficiency and practical applicability is analysed and compared. In this subject literature opinions of high usefulness of the D criterion are presented, while the others are said to be less useful, difficult and complicated [2, 3]. As more powerful software and hardware is available, we have decided to verify this opinion. The questions arise:

— Do particular criterions deliver the same/similar/different optimal sampling points?

— Which of them is the most optimal and gives the best improvement of identification result?

— Which of them is most reliable and useful?

The aim of the paper is to find out an answer to the above questions.

2. System under consideration

The system under consideration is described, on a $t_0 \div T$ time interval, as follows:

$$\begin{aligned} &\dot{\mathbf{x}}(t,\mathbf{p}) = f[\mathbf{x}(t,\mathbf{p}),\mathbf{u}(t),t;\mathbf{p}], \quad \mathbf{u}(t) \geq 0, \\ &\mathbf{y}(t) = g[\mathbf{x}(t,\mathbf{p}),\mathbf{p}], \\ &\mathbf{z}(t_k) = \mathbf{y}(t_k,\mathbf{p}) + e(t_k), \quad k = 1,\ldots,N, \quad t_0 < t_k < T. \end{aligned} \tag{1}$$

We assume the model is so called a constrained structure, which means that additional independent algebraic inequality or equality, relating **x** and **p**, are imposed. These constraints are written generally as the relationship:

$$G(\mathbf{x}(t,\mathbf{p}),\mathbf{p}) \leq 0. \tag{2}$$

State vector **x** denotes measured amount or concentration of considered quantity, u is a test input, y is a measurable output, $\mathbf{z}(t_k, \mathbf{p})$ is a noisy discrete time measurement of y at time t_k and $e(t_k)$ is an additive error. We assume the error is zero–mean Gaussian noise with variance $\sigma^2(t_k)$. Functions f and g, not necessarily linear vector functions, define the particular model structure. The vector $\mathbf{p} \geq 0$ is an unknown parameter set, $i = 1, 2, \ldots, P$. N is the number of output samples.

It is assumed that the model is uniquely structurally identifiable for the designed input–output experiment and that this assumption was previously checked up. Adoption of the optimisation procedures requires a priori knowledge of unknown parameter vector **p**, which we assume is known, for example as the mean population or as the result of an intuitively designed experiment. The goal to be achieved is to get the most accurate vector **p** by intentional choice of SS. Optimal SS is the one which assures the best quality of **p** from among the others calculated for optional sampling schedule design.

3. Optimal SS design

Cramer–Rao theorem says: covariance matrix of unbiased parameter estimates $COV(\mathbf{p})$ has the inverse of the Fisher information matrix $\mathbf{M}$ as a lower bound, namely $COV(\mathbf{p}) \geq \mathbf{M}^{-1}(\mathbf{p})$. For OSS design the matrix $\mathbf{M}$ is only a function of sampling schedule $\mathbf{M}=\mathbf{M}(SS, T)$. The Fisher information matrix is a measure of the amount of information, relating unknown $\mathbf{p}$, available from the noisy data.

Let us define sensitivity function matrix $\mathbf{S}_y^p$:

$$\mathbf{S}_y^p = \left[\frac{\partial y_i(p,t)}{\partial p_j}\right] = \begin{bmatrix} \frac{\partial y_1}{\partial p_1} & \cdots & \frac{\partial y_1}{\partial p_P} \\ \cdots & \cdots & \cdots \\ \frac{\partial y_N}{\partial p_1} & \cdots & \frac{\partial y_N}{\partial p_P} \end{bmatrix}. \tag{3}$$

It is the Jacobian $\mathbf{J}$ of the output with respect to the parameters and may be evaluated at some point $\mathbf{p}^*$ in the parameters space.

When the noises in the data have a zero mean unity variance and the same normal distribution at each t_k sampling point, and $e(t_k)$ are uncorrelated, then Fisher information matrix $\mathbf{M}$ is as follows:

$$\begin{aligned} &\mathbf{M}(\mathbf{p}) = [m_{ij}] = \mathbf{J}^T\mathbf{J}, \\ &[\mathrm{m_{ij}}] = \sum_{k=1}^{N}\left[\frac{\partial y(p,t_k)}{\partial p_i}\right]\left[\frac{\partial y(p,t_k)}{\partial p_j}\right]^T. \end{aligned} \tag{4}$$

When variances in each data point $\sigma^2(t_k)$ are different, then:

$$\mathbf{M}(\mathbf{p}) = \mathbf{J}^T[\mathbf{R}]^{-1}\mathbf{J}. \tag{5}$$

$\mathbf{R}$ denotes the covariance matrix of the noisy data. Particular $\sigma^2(t_k)$ form the main diagonal of the $\mathbf{R}$ matrix.

Let us define matrix $\mathbf{W}$ which generic element w_{ij} denotes relative sensitivity. It shows degree to which change ΔA_i, in parameter A_i, $i = 1, 2, \ldots, P$ being estimating, depends on change Δy_j in a measured sample y_j, $j = 1, 2, \ldots, N$:

$$\begin{bmatrix} \Delta A_1 \\ \Delta A_2 \\ \vdots \\ \Delta A_P \end{bmatrix} = \mathbf{W}\cdot\begin{bmatrix} \Delta y_1 \\ \Delta y_2 \\ \vdots \\ \Delta y_P \end{bmatrix} = \begin{bmatrix} w_{11} & w_{12} & \cdots & w_{1N} \\ w_{21} & w_{22} & \cdots & w_{2N} \\ \vdots & \vdots & \ddots & \vdots \\ w_{P1} & w_{P2} & \cdots & w_{PN} \end{bmatrix}\cdot\begin{bmatrix} \Delta y_1 \\ \Delta y_2 \\ \vdots \\ \Delta y_P \end{bmatrix}. \tag{6}$$

Matrix $\mathbf{W}$ can be expressed by means of Jacobean matrix $\mathbf{J}$ as follows:

$$\mathbf{W} = [\mathbf{J}^T\mathbf{J}]^{-1}\mathbf{J}^T. \tag{7}$$

Four objective functions for SS optimisation have been considered. Every one of them delivers a set of sampling points, which are optimal with respect to the particular criterion. The criteria being tested are:

For D–optimal SS design: $max(det\mathbf{M})$, $det\mathbf{M}$ is determinant of $\mathbf{M}$;

For E–optimal SS design: $min(max\lambda_M)$, λ_M are eigenvalues of $\mathbf{M}^{-1}$;

For S–optimal SS design: $max(\mathbf{W})$, $\mathbf{W}$ is relative sensitivity matrix;

For A–optimal SS design: $min(trace\mathbf{M}^{-1})$.

4. Constrained non–linear programming

Let us state a problem:

$$\underset{\mathbf{p}}{minimize}\ f(\mathbf{p}) \text{ subject to:}$$

$$\begin{aligned} &m_e \text{ equality constraints } G_i(\mathbf{p}) = 0,\ i = 1,\ldots,m_e, \\ &m - m_e \text{ inequality constraints } G_i(\mathbf{p}) \le 0,\ i = m_e + 1,\ldots,m, \\ &\mathbf{p}_{lb} \le \mathbf{p} \le \mathbf{p}_{ub}. \end{aligned} \tag{8}$$

A lower bound $\mathbf{p}_{lb}$ and an upper bound $\mathbf{p}_{ub}$ limit the set of designed parameters, which are optimal in some way.

When both, $f(\mathbf{p})$ and $G(\mathbf{p})$ are linear, the above problem is called linear programming. Quadratic programming concerns quadratic objective function $f(\mathbf{p})$ and linear constraints. In non–linear programming objective function and constraints are non–linear.

Nowadays, in constrained programming problem, methods based on the Kuhn–Tucker equations solution are being used [4, 5]. These equations are necessary conditions for optimality of a constrained problem. The Kuhn–Tucker equations, referring to (8), are:

$$\begin{aligned} &f(\mathbf{p}^*) + \sum_{i=1}^{m} \lambda_i^* \nabla G_i(\mathbf{p}^*) = 0, \\ &\nabla G_i(\mathbf{p}^*) = 0,\ i = 1,\ldots,m_e, \\ &\lambda_i^* > 0,\ i = m_e + 1,\ldots,m. \end{aligned} \tag{9}$$

The first equation shows disappearance of the gradient between objective function $f(\mathbf{p})$ and the active constraints $G_i(\mathbf{p})$ at the solution point $\mathbf{p}^*$. To cancel these gradients it is necessary to match magnitude of f and ∇G. It is done by means of Lagrange multipliers λ_i.

The solution of the Kuhn–Tucker equations forms the basis of non–linear programming algorithms. From among different the algorithms the sequential quadratic programming is said to be the most efficient and accurate. Basing on (8), the sequential quadratic programming requires formulation of quadratic programming

sub–problem. It requires quadratic approximation of Lagrangian function:

$$L(\mathbf{p},\lambda) = f(\mathbf{p}) + \sum_{i=1}^{m} \lambda_i \, g_i(\mathbf{x}). \tag{10}$$

The sequential quadratic programming consists of three main stages:

— updating of the Hessian matrix of Lagrangian function,

— quadratic programming problem solution,

— line search and merit function calculation.

For solving D, E, S and A–optimal SS problem MATLAB implementation of sequential quadratic programming was used.

5. Case under study

For examination and for comparison of the D, E, S, A–optimisation methods a two–compartmental model function has been chosen:

$$y = A_1 \exp(-A_2 t) + A_3 \exp(-A_4 t) \tag{11}$$

with the parameter vector $\mathbf{p} = [A_1 \; A_2 \; A_3 \; A_4] = [19 \; 0.02 \; 6 \; 0.5]$. The exact model function, as described above, was then taken as the base for simulation yielding 1000 sets of data. Every set contains 1501 samples related to subsequent time points in time interval $t \in (0, 150)$, with step $dt = 0.1$. Simulated data are generated by adding uncertainty selected randomly from normal distributed population of values $N(0, \sqrt{0.341})$ to the exact model response.

Next, for generated data, the model parameters were reestimated. As an example parameter estimates $A_i \pm dev\ std$, $CV\%$, $i = 1, 2, 3, 4$ for 10 out of 1000 data sets are presented in Table 1. The results were obtained from fitting the model function to the particular set of simulated data.

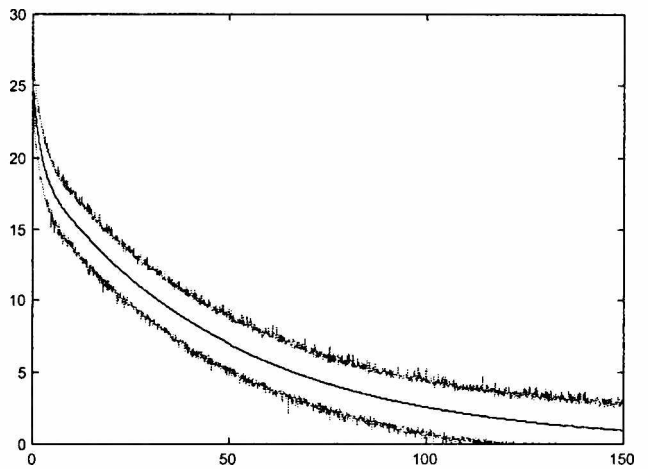


Figure1. *Exact model function (solid line) and the upper and the lower set of simulated data. The other simulated data is held within these upper and lower limits*

Table 1. Parameter estimates $A_i \pm$ dev std, CV%, i=1, 2, 3, 4 for 10 exemplary sets of simulated data

	$A_1 \pm$ dev std (CV %)	$A_2 \pm$ dev std (CV %)	$A_3 \pm$ dev std (CV %)	$A_4 \pm$ dev std (CV %)
1	19.08 ± 0.06951 (0.36%)	0.02014 ± 9.291e-5 (0.46%)	5.965 ± 0.2568 (4.3%)	0.5654 ± 0.04089 (7.2%)
2	19.00 ± 0.07407 (0.39%)	0.01994 ± 9.549e-5 (0.48%)	5.771 ± 0.2338 (4.1%)	0.4555 ± 0.03181 (7%)
3	18.91 ± 0.07311 (0.39%)	0.01986 ± 9.529e-5 (0.48%)	6.026 ± 0.2418 (4%)	0.4818 ± 0.03306 (6.9%)
4	19.01 ± 0.07538 (0.4%)	0.02004 ± 9.835e-5 (0.49%)	5.919 ± 0.2473 (4.2%)	0.4807 ± 0.03438 (7.2%)
5	19.04 ± 0.07118 (0.37%)	0.02006 ± 9.475e-5 (0.47%)	6.330 ± 0.2592 (4.1%)	0.5523 ± 0.03806 (6.9%)
6	18.73 ± 0.07388 (0.39%)	0.01963 ± 9.571e-5 (0.49%)	6.439 ± 0.2375 (3.7%)	0.4598 ± 0.02913 (6.3%)
7	18.95 ± 0.06923 (0.37%)	0.01984 ± 9.158e-5 (0.46%)	6.152 ± 0.2500 (4.1%)	0.5406 ± 0.03702 (6.8%)
8	19.15±0.07294 (0.38%)	0.02019 ± 9.647e-5 (0.48%)	5.791 ± 0.2579 (4.5%)	0.5337 ± 0.04019 (7.5%)
9	18.93±0.0797 (0.42%)	0.01995 ± 10.14e-5 (0.51%)	5.577 ± 0.2329 (4.2%)	0.4144 ± 0.03026 (7.3%)
10	19.09±0.07221 (0.38%)	0.01999 ± 9.438e-5 (0.47%)	5.872 ± 0.2469 (4.2%)	0.5060 ± 0.03618 (7.1%)

After 1000 simulation runs we obtained 1000 normally distributed estimates for each A_i. Calculated mean parameter estimates $\overline{A}_i$, their standard deviations $\sigma_{A_i} = std\ dev_{A_i}$ and the errors $\Delta = (A_i - \overline{A}_i)/A_i$ [%] are presented in Table 2. Percentage coefficient of variation $CV\%$ is defined as $CV\% = \sigma_{A_i}/A_i$.

Table 2. Mean parameter estimates $\overline{A}_i$, standard deviations σ_{A_i} and the errors Δ [%] obtained after 1000 simulation runs

	$\overline{A}_i$	σ_{A_i}	$\Delta[\%]$
A_1	18.99197	0.07497	0.042
A_2	0.019987	0.00009	0.065
A_3	6.008938	0.24663	0.148
A_4	0.499735	0.03522	0.053

The obtained parameter estimates $\overline{A}_i$ are very close to the initial values of parameters A_i. It validates the adopted simulation technique and assures that the simulation is not the reason for discrepancy, which may appear in results obtained through D, E, S, and A–optimal design.

6. Optimal SS

The whole process of simulation and parameter estimation, delivered 1000 simulated model functions. For each function we assigned an optimal sampling schedule OSS, consisting of 4 optimal samples $[t_1\ t_2\ t_3\ t_4]$, using one by one the D, E, S, A–optimisation criteria. In that way, we have obtained optimal sampling sets: DOSS, EOSS, SOSS and AOSS respectively for D, E, S and A–optimal design. As an example, the results obtained for 10 out of 1000 simulated sets of data

Table 3. *Optimal sampling schedules DOSS, EOSS, SOSS and AOSS respectively for D, E, S and A–optimal design for 10 exemplary simulated model functions*

	DOSS $[t_1\ t_2\ t_3\ t_4]$	EOSS $[t_1\ t_2\ t_3\ t_4]$	SOSS $[t_1\ t_2\ t_3\ t_4]$	AOSS $[t_1\ t_2\ t_3\ t_4]$
1	0.0 1.7 8.7 58.8	0.2 0.4 7.7 85.3	0.0 1.7 9.3 102.1	0.0 0.8 7.8 85.3
2	0.0 2.1 10.3 61.2	0.3 0.5 9.1 86.3	0.0 2.1 11.0 104.2	0.0 0.9 9.3 86.0
3	0.0 2.0 9.9 60.9	0.3 0.5 8.7 86.1	0.0 2.0 10.6 104.2	0.0 0.8 8.9 86.4
4	0.0 2.0 9.9 60.5	0.3 0.5 8.7 85.6	0.0 2.0 10.6 103.4	0.0 0.8 8.9 85.5
5	0.0 1.7 8.9 59.2	0.2 0.4 7.9 85.6	0.0 1.7 9.5 102.6	0.0 0.8 7.9 85.6
6	0.0 2.1 10.3 61.9	0.3 0.5 9.1 87.4	0.0 2.1 11.0 105.5	0.0 0.8 9.2 87.3
7	0.0 1.8 9.0 60.0	0.2 0.4 8.0 86.5	0.0 1.8 9.6 103.6	0.0 0.8 8.1 86.6
8	0.0 1.8 9.1 59.2	0.2 0.4 8.1 85.0	0.0 1.8 9.7 102.2	0.0 0.8 8.1 85.0
9	0.0 2.3 11.1 62.1	0.4 0.6 9.7 86.1	0.0 2.3 11.9 104.8	0.0 1.0 10.0 86.1
10	0.0 1.9 9.5 60.1	0.2 0.5 8.4 85.8	0.0 1.9 10.1 103.4	0.0 0.8 8.5 85.8

are presented in Table 3.Then we have analysed scatter in t_i, $i = 1, 2, 3, 4$. Analysing bar charts, i.e. histograms of a particular t_i on 1000 simulation runs, we concluded that time points t_i are normally distributed. In Figure 2 histograms for optimal points t_i, mean optimal sampling points $\bar{t}_i$ and their standard deviations $\sigma_{t_i} = std\ dev_{t_i}$, subsequently for D, E, S and A–optimal design are presented.

7. Results

From among all simulated sampling points in every simulation run, we have chosen the samples, which were located in points previously calculated as optimal. This gave us 4000 (a 1000 for each optimisation criterion) reduced, individual optimal sampling sets $[t_1\ t_2\ t_3\ t_4]$. For every set, the model function parameters $\mathbf{p} = [A_1 A_2 A_3 A_4]$ were reestimated. Histograms presented in Figure 3 show scatter in reestimated A_i, $i = 1, 2, 3, 4$ for every considered optimisation criteria. Assuming normal distribution of A_i we have calculated $\bar{A}_i$ and σ_{A_i}. In brackets are shown deviations $\Delta = (A_i - \bar{A}_i)/A_i\,[\%]$, σ_{A_i} denotes standard deviation in a particular A_i. Calculated deviation $\Delta = (A_i - \bar{A}_i)/A_i\,[\%]$ is smaller than $CV\,\% = \sigma_{A_i}/A_i$ for each considered optimisation criteria.

Percentage fraction of whole number of SS optimisations, which did not give optimal SS but delivered a set of 4 time points is shown in Table 4. The points are not coordinates of global minimum (or maximum) value of objective function but are coordinates of a local minimum (or maximum) value of objective function.

8. Conclusions

As we can see from Table 3, different optimisation criteria, used for the same data, give different optimal SS. On 1000 optimisation runs, for each criterion, we

Table 4. Percentage fraction of the whole number 1000 of SS optimisations, which instead of OSS, delivered not optimal set of 4 time points being coordinates of a local extreme

DOSS	5.9%
EOSS	33.1%
SOSS	4.1%
AOSS	13.7%

obtained the following mean optimal sampling schedules:

DOSS = [0 1.9 9.6 60.3],
EOSS = [0.2 0.5 8.5 85.9],
SOSS = [0 1.9 10.2 103.4],
AOSS = [0 0.8 8.6 85.8].

The detailed conclusions are:

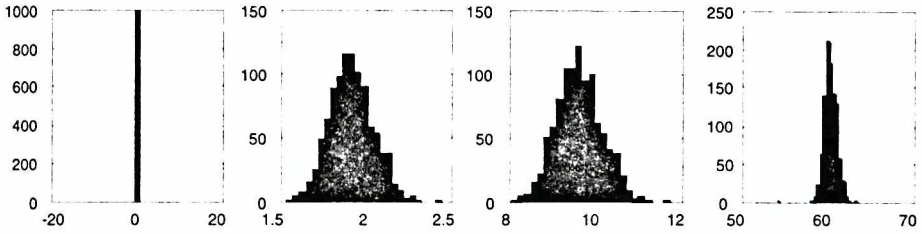
— DOSS and SOSS sets of points are very close, with the exception of the last optimal point, which for the S–optimal design is considerably bigger than for the D–optimal design.
— E–optimal design, unlike the other criteria under investigation, gives EOSS, which does not contain the point $t = 0$ as the first optimal point.
— The last two points in EOSS and AOSS are almost the same, while the first two points differ noticeably.

Before we form a judgement of superiority of one criterion over the others, let us analyse individual results. As a factor of OSS quality, one should consider ability of particular OSS to yield parameter estimates as close to their initial values A_i as possible.

As it results from Figure 3, according to the above criterion, the worst is E–optimal design. Deviation $\Delta = (A_i - \bar{A}_i)/A_i$ [%] (in brackets) is as big as 16% and 49% respectively for A_3 and A_4. This is not a satisfactory result: reduced EOSS causes considerable worsening of parameter estimates accuracy and leads to the estimates which differ noticeably from their real values.

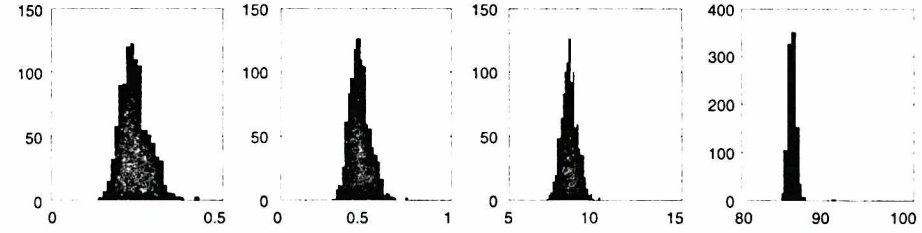
Remaining optimisation criteria give very similar results, with acceptable error levels. Deviations, for particular methods and individual parameters, are compared in Table 5. As it results from the table, for D–optimisation, deviations Δ_{A_i} of three parameters A_1, A_2, A_3 from their initial values, are smaller than for the other criteria. Deserving attention is also S–optimisation: the maximal deviation, i.e. $\Delta_{A_4} = 4.7\%$ is the smallest from among the other maximal deviations $\Delta_{A_4} = 6.2\%$ for D–optimisation and $\Delta_{A_4} = 7.2\%$ for A–optimisation. The best result for S–optimisation is due to the rule adopted: each parameter has its representative in sampling schedule being optimised, its optimal time point in the SOSS.

a)



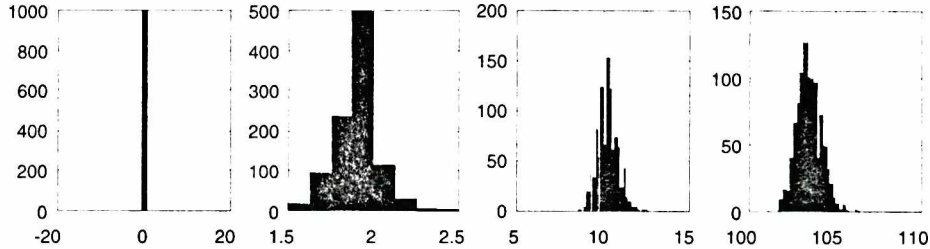
EOSS	t_1	t_2	t_3	t_4
$\bar{t}_i$	0	1.9138	9.6131	60.2844
$\sigma_{t_i} = std\ dev_{t_i}$	0	0.1294	0.5320	0.7713

b)



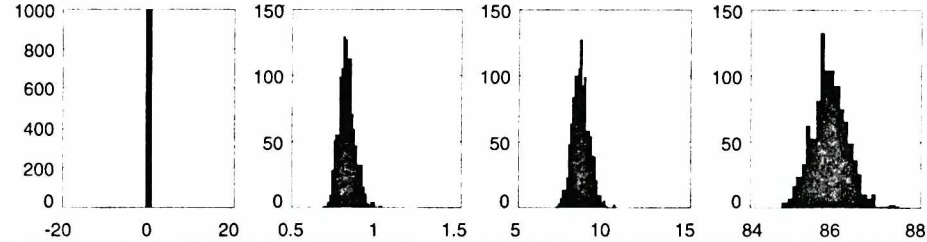
EOSS	t_1	t_2	t_3	t_4
$\bar{t}_i$	0.2435	0.4657	8.5101	85.8939
$\sigma_{t_i} = std\ dev_{t_i}$	0.0414	0.0614	0.4492	0.5731

c)



EOSS	t_1	t_2	t_3	t_4
$\bar{t}_i$	0	1.9092	10.2785	103.4664
$\sigma_{t_i} = std\ dev_{t_i}$	0	0.1376	0.5782	0.6934

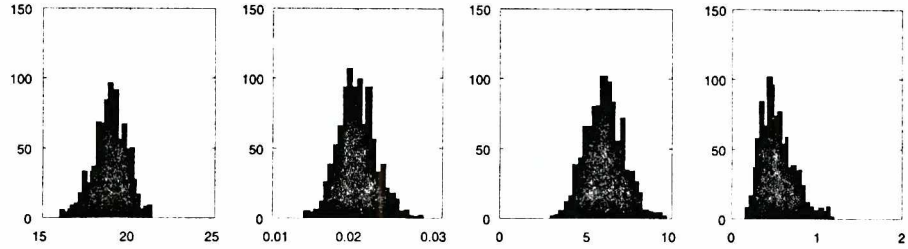
d)



EOSS	t_1	t_2	t_3	t_4
$\bar{t}_i$	0	0.8217	8.6245	85.8541
$\sigma_{t_i} = std\ dev_{t_i}$	0	0.0476	0.4940	0.4132

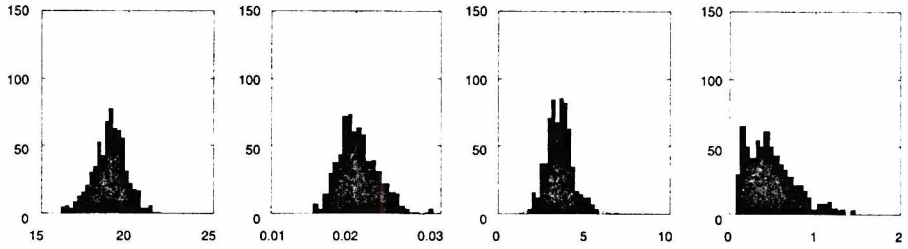
Figure 2. *Scatter in optimal sampling points OSS=[t_1 t_2 t_3 t_4], mean optimal sampling points* $\bar{t}_i = \frac{1}{1000} \cdot \sum_{r=1}^{1000} t_i^r$ *and their standard deviations* $\sigma_{t_i} = std\ dev_{t_i}$ *for D, E, S and A–optimisation*

a)



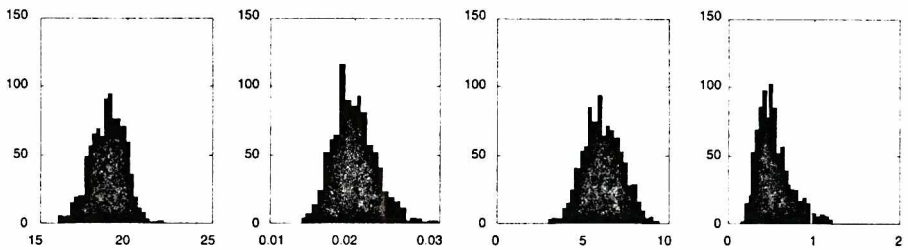
DOSS	A_1	A_2	A_3	A_4
$\overline{A_i}$	18.9093 (0.5%)	0.0199 (0.5%)	6.0920 (1.15%)	0.5333 (6.2%)
σ_{A_i}	0.9433	0.0021	1.0715	0.1905

b)



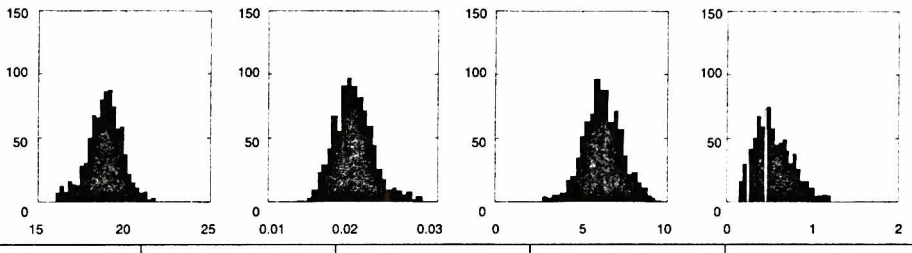
DOSS	A_1	A_2	A_3	A_4
$\overline{A_i}$	18.972 (0.14%)	0.0203 (1.4 %)	7.1488 (16 %)	0.9814 (49 %)
σ_{A_i}	0.9710	0.0023	1.5582	0.5789

c)



DOSS	A_1	A_2	A_3	A_4
$\overline{A_i}$	18.864 (0.7 %)	0.0199 (0.5 %)	6.1311 (2.1 %)	0.5248 (4.7 %)
σ_{A_i}	0.9836	0.0026	1.1103	0.1964

d)



DOSS	A_1	A_2	A_3	A_4
$\overline{A_i}$	18.820 (0.9 %)	0.0201 (0.5 %)	6.2267 (3.6 %)	0.5388 (7.2 %)
σ_{A_i}	1.0011	0.0023	1.1208	0.2202

Figure 3. *Histograms perform scatter in A_i, i=1, 2, 3, 4 calculated for 1000 simulation runs. The parameter estimates are based on individual OSS for each of the considered criteria*

Table 5. *Comparison of deviations Δ_{A_i} of parameter estimates A_i from their initial values. The shaded area refers to the worst criterion*

	DOSS	*SOSS*	*AOSS*	*EOSS*
Δ_{A_1} [%]	0.5	0.7	0.9	0.1
Δ_{A_2} [%]	0.5	0.5	0.5	1.4
Δ_{A_3} [%]	1.15	2.1	3.6	16
Δ_{A_4} [%]	6.2	4.7	7.2	49

Table 6. *Comparison of standard deviations σ_{A_i} of parameter estimates A_i. The shaded area refers to the worst criterion*

	DOSS	*SOSS*	*AOSS*	*EOSS*
σ_{A_1}	0.9533	0.9836	1.0011	0.9710
σ_{A_2}	0.0021	0.0026	0.0023	0.0023
σ_{A_3}	1.0715	1.1103	1.1208	1.5582
σ_{A_4}	0.1905	0.1964	0.2202	0.5789

In Table 6 standard deviations σ_{A_i} of parameter estimates A_i are presented. D and S–optimisations give very similar results, for A–optimisation the particular σ_{A_i} values are slightly bigger than for the latter, while E–optimisation gives the worst results.

Finally, as far as efficiency of OSS being designed is concerned, D and S–optimisations are almost equally good. The results are presented in Table 4. Percentage fraction of not optimal (locally optimal) results are 4.1% and 5.9%, respectively for S and D–optimisation. For A and E–optimisation we obtained respectively 13.7% and 33.1%. It allows forming the opinion of poorer robustness and practical usefulness of A and E–optimisations.

Let us sum up all the presented results:

— By comparison with the other criteria, D–optimisation approved their usefulness and high accuracy of reestimated parameters.

— As it turned out, S–optimisation can be considered as a very competitive choice with regard to D–optimisation. Both the methods give very similar accuracy of parameter estimates, while S–optimisation is more robust. It gives the smallest number of local extreme from among all considered methods.

— S–optimisation assures that every parameter has its representative in sampling schedule, its individual optimal point in SOSS.

— Accuracy of parameter estimates based on E–optimisation is significantly worse in comparison to the other criteria.

— A–optimisation, despite satisfactory good accuracy of parameter estimates, should not be recommended due to high rate of not globally optimal results.

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