DIRECTLY CALCULATED OPTIMAL SAMPLING TIMES FOR THE SUM OF EXPONENTIAL FUNCTIONS

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Abstract: The subject under investigation is the dependence of the location of the optimal sampling points on the parameters of compartmental models. A new alternative optimal sampling schedule is presented, which we have termed the "P-optimal design". The results obtained with the P-optimal design were examined and compared with the D-optimal approach. Analytical and numerical solutions are given. Illustrative examples and conclusions are presented. The traditional approach to SS optimisation requires specialised software, while the proposed new method does not. P-optimal design enables an element of experiment design to be introduced at a very early stage in the modelling.

Introduction

Biomedical models have been chosen for consideration with output $\mathbf{y}(\mathbf{p},t)$ in the form of the sum of l_{ex} exponential terms i.e. compartmental models:

$$y(\mathbf{p},t)=\sum_{r=1}^{l_{ex}} p_{2r-1}\exp(-p_{2r}t) \qquad (1)$$

The focus of interest is the optimal reduced SS design for the above function. In principle, the reduced optimal sampling schedule (OSS) consists of a number of samples n_s that is equal to the number of model parameters n, i.e. $n_s = n = 2l_{ex}$. The new criterion assumes that each parameter p_i, $i = 1,..,2l_{ex}$ has to have its representative in OSS design. Traditional criteria [1-4], for instance D, E and A-optimal design, do not provide the opportunity to fulfil this requirement. This is because the way in which they search for the OSS is not aimed at each parameter individually but at an objective function (OF). The following questions are posed:

- Is every p_i equally entitled to have its representative in a reduced OSS?
- Is it possible to form an exact, directly p_i dependent, optimal (we may refer to it as the "P-optimal") reduced OSS?
- If so, can the P-optimal reduced SS compare with and rival the *gold standard* yielded by the D-optimal criterion?

Theory

Let us consider an *r*-compartmental system. The state variable representation of MIMO (multi-input, multi-output) on a $0 \div T$ time interval is:

$$\begin{aligned}\dot{\mathbf{x}}(\mathbf{p},t) &= \mathbf{A}(\mathbf{p})\mathbf{x}(\mathbf{p},t)+\mathbf{B}\mathbf{u}(t)\\ \mathbf{y}(\mathbf{p},t) &= \mathbf{C}(\mathbf{p})\mathbf{x}(\mathbf{p},t)\\ \mathbf{p} &= [p_1, p_2, .., p_n]\end{aligned} \qquad (2)$$

where $\mathbf{p}[p_i], i = 1,2,..,n$ is the model parameter vector, $\mathbf{u}(t), \mathbf{x}(\mathbf{p},t)$ and $\mathbf{y}(\mathbf{p},t)$ are input, state and output vectors and $\mathbf{A}(\mathbf{p})$, $\mathbf{B}$ and $\mathbf{C}(\mathbf{p})$ are state, input and output matrices. Information concerning the parameters is available in the noisy data $\mathbf{z}(t)$:

$$\mathbf{z}(t) = \mathbf{y}(\mathbf{p},t)+\mathbf{e}(t) \qquad (3)$$

The output $\mathbf{y}(\mathbf{p},t)$ is measured as $\mathbf{z}(t)$, at points $t_k, k = 1,2,..,N$, with an additive error $\mathbf{e}(t)$.

To form the basis for the comparison of different experiment designs, and the SS design in particular, a measure of the *goodness* of an experiment is required [1-4], for instance a measure related to the expected accuracy of parameter estimates. The relationship between the obtainable accuracy of the parameter estimates and the amount of information available in the noisy data $\mathbf{z}(t)$ is given by Cramer-Rao inequality:

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$$\mathrm{cov}(\mathbf{p}) = E\left[(\mathbf{p}-\hat{\mathbf{p}})(\mathbf{p}-\hat{\mathbf{p}})^T\right] \geq \mathbf{M}^{-1}(\mathbf{p})$$
$$\mathbf{M}(\mathbf{p}) = E\left\{\left[\frac{\partial \log f(\mathbf{z}|\mathbf{p})}{\partial \mathbf{p}}\right]^T\left[\frac{\partial \log f(\mathbf{z}|\mathbf{p})}{\partial \mathbf{p}}\right]\right\} \qquad (4)$$

$\mathbf{M}(\mathbf{p})$ is the Fisher information matrix and $\hat{\mathbf{p}}$ is the vector of the parameter estimates. Function $f(\mathbf{z}|\mathbf{p})$ is the conditional probability density of $\mathbf{z}$ given $\mathbf{p}$ and E is the expectation operator, taken with respect to the above density function.

Assuming that the estimator used is efficient and that particular entries of the Fisher matrix give a lower bound of parameter estimate accuracy, the inequality (4) may be considered as equality: $\mathrm{cov}(\mathbf{p}) = \mathbf{M}^{-1}(\mathbf{p})$. The smaller the entry of $\mathbf{M}^{-1}(\mathbf{p})$ is, the greater the accuracy of the associated estimate. The planned formation of the entries of $\mathbf{M}^{-1}(\mathbf{p})$ is the area of optimal experiment design and of OSS design in particular. The Fisher matrix given by (4) is an uninviting expression because f may be a complicated function of $\mathbf{p}$. Assuming samples $e_k = e(t_k)$ of measurement error are zero mean, uncorrelated and have identical normal distribution at every t_k, the matrix simplifies to the form [2 - 17]:

$$\mathbf{M}(\mathbf{p}) = \left[\begin{array}{ccc|c} \sum_{k=1}^{N}\left(\frac{\partial y_k}{\partial p_1}\right)^2\frac{1}{\sigma_k^2} & \sum_{k=1}^{N}\frac{\partial y_k}{\partial p_1}\frac{\partial y_k}{\partial p_2}\frac{1}{\sigma_k^2} & & \sum_{k=1}^{N}\frac{\partial y_k}{\partial p_1}\frac{\partial y_k}{\partial p_n}\frac{1}{\sigma_k^2} \\ m_{21}=m_{12} & \sum_{k=1}^{N}\left(\frac{\partial y_k}{\partial p_2}\right)^2\frac{1}{\sigma_k^2} & & \sum_{k=1}^{N}\frac{\partial y_k}{\partial p_2}\frac{\partial y_k}{\partial p_n}\frac{1}{\sigma_k^2} \\ \hline m_{n1}=m_{1n} & m_{n2}=m_{2n} & & \sum_{k=1}^{N}\left(\frac{\partial y_k}{\partial p_n}\right)^2\frac{1}{\sigma_k^2} \end{array}\right] \qquad (5)$$

$$m_{ii} = \sum_{k=1}^{N}\left(\frac{\partial y_k}{\partial p_i}\right)^2\frac{1}{\sigma_k^2},\ i=1,2,..,n$$
$$m_{ij} = m_{ji} = \sum_{k=1}^{N}\frac{\partial y_k}{\partial p_i}\frac{\partial y_k}{\partial p_j}\frac{1}{\sigma_k^2},\ i\neq j;\ i,j=1,2,..,n \qquad (6)$$

The various criteria used for SS optimisation are based on different objective functions (*OF*). For instance [1-17], D-optimal design $OF = \max(\det \mathbf{M})$, A-optimal design $OF = \min\left(trace\mathbf{M}^{-1}\right)$ and S-optimal design $OF = \max\left(\left[\mathbf{J}^T\mathbf{J}\right]^{-1}\mathbf{J}^T\right)$, where $\mathbf{J}$ is Jacobean $\mathbf{J}\left(\frac{\mathbf{p}}{\mathbf{y}}\right)$. Special attention deserves D-optimal design, which is related to the volume of the highest probability density region for the parameters and may be considered the *gold standard* for SS design. This criterion is efficient and has a well-established reputation, although it is quite complicated numerically and requires special software.

Location of optimal samples

The dependence of optimal sample location on changes in parameter values was examined in detail. Let us follow the examination by an illustrative example, a 2-exp function $y = p_1\exp(-p_2 t) + p_3\exp(-p_4 t)$ with an initial, *true*, parameter vector $\mathbf{p} = [20\ 0.02\ 5\ 0.5]$. To show the dependence, we prepared sets of model functions for each p_i, $i = 1,..,4$. Each set consisted of 5 output functions, calculated for 5 different values of the parameter, while the other parameters were equal to their initial values. Set $y^{<1,m>}$, i.e. $y^{<1,1>}$, $y^{<1,2>}$, $y^{<1,3>}$, $y^{<1,4>}$, $y^{<1,5>}$ was for p_1 subsequently equal to 5, 10, 15, 20 and 25. Set $y^{<2,m>}$ was for p_2 equal to 0.0095, 0.0130, 0.0200, 0.0350, 0.0600, set $y^{<3,m>}$ for p_3 equal to 0.1, 2.0, 5.0, 10, 15, and set $y^{<4,m>}$ for p_4 equal to 0.035, 0.060, 0.500, 0.900, 2.000. In Figure 1, the outputs $y^{<i,m>}$, over time interval $t = 0 \div 150$ h, for $i = const$ and $m = 1 \div 5$ are shown in the same window.

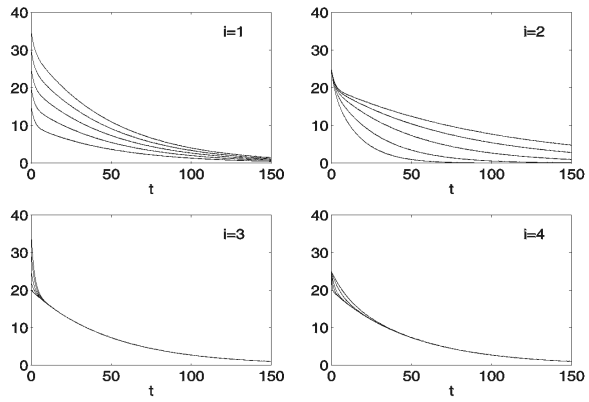

Figure 1: Output functions $y^{<i,m>}$ over t=0÷150 h, for $m = 1 \div 5$ values of $p_i, i = 1 \div 4$, while the rest of p_i are equal to their initial values.

For each parameter p_i, $i = 1,2,3,4$ and for subsequent outputs $y^{<i,m>}$, $m = 1,2,3,4,5$ optimal sampling points were calculated using D-optimal design. The results are shown in Figure 2. Interlinked circles represent optimal points for $i = const$, $m = 1 \div 5$. As shown in Figure 2, not every parameter of function (1) has equal power to produce an effect on the optimal sampling schedule. Changes in p_1 and p_3 (when p_2 and p_4 became constant) do not produce an effect on OSS location.

Surprisingly, for such different functions as those for $i = 1$, within $m = 1 \div 5$, (p_1=5,10,15,20,25) the OSSs remain the same: D-OSS=[0.0 h, 1.9 h, 9.6 h, 60.2 h].

Unlike the above, changes in p_2 and p_4 imply changes in the OSS.

D-OSS for $y^{<i,m>}$, $i = 2,4$, $m = 1,2,3,4,5$ is shown in Table 1. Outputs consisting of $l_{ex} > 2$ exponential

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functions were investigated similarly. The following conclusion is drawn:

For output functions $y(\mathbf{p},t)=\sum_{r=1}^{l_{ex}} p_{2r-1}\exp(-p_{2r}t)$ the OSS remains unchanged provided that parameters p_{2r} remain unchanged and this does not depend on the scale of the changes in p_{2r-1}.

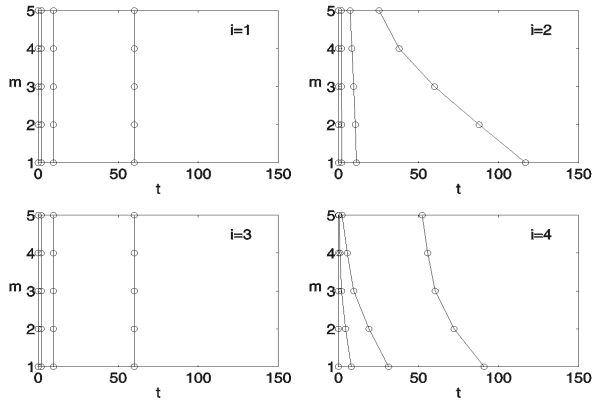

Figure 2: D-optimal time points (circles) for subsequent functions $y^{<i,m>}$. The time interval is 0÷150 h, $i=1\div4$, $m=1\div5$. The lines are drawn through the optimal points for 5 different values of 4 parameters p_i, while the other parameters are constant.

Table 1: D-optimal SS for $y^{<i,m>}$, $i=2,4$, $m=1\div5$.

Test function	D-optimal SS	Test function	D-optimal SS
$y^{<2,1>}$	[0.0, 2.0, 11.2, 116.8]	$y^{<4,1>}$	[0.0, 8.1, 31.3, 90.9]
$y^{<2,2>}$	[0.0, 1.9, 10.5, 87.9]	$y^{<4,2>}$	[0.0, 4.4, 19.1, 72.2]
$y^{<2,3>}$	[0.0, 1.9, 9.5, 60.0]	$y^{<4,3>}$	[0.0, 1.9, 9.5, 60.0]
$y^{<2,4>}$	[0.0, 1.8, 8.4, 37.9]	$y^{<4,4>}$	[0.0, 1.0, 5.5, 55.7]
$y^{<2,5>}$	[0.0, 1.7, 7.3, 25.4]	$y^{<4,5>}$	[0.0, 0.3, 2.3, 52.3]

P-optimal reduced SS

The P-optimal reduced OSS is the one, which fulfils the following:

$$\max_t\left(S^y_{p_i}\right)\rightarrow P-\text{optimal SS design}$$
$$S^y_{p_i}=\frac{\partial y}{\partial p_i},\ i=1,2,..,n \qquad (7)$$

where $S^y_{p_i}$ is the sensitivity of output y with respect to parameter p_i.

Sensitivities $S^y_{p_{2r-1}}$ are:

$$S^y_{p_{2r-1}}=\frac{\partial y}{\partial p_{2r-1}}=\exp(-p_{2r}\cdot t),\ r=1,2,..,l_{ex}. \qquad (8)$$

These do not depend on parameter p_{2r-1} and change their values from $S^{MAX}_{2r-1}(t=0)=1$ to $S^{MIN}_{2r-1}(t\rightarrow\infty)=0$.

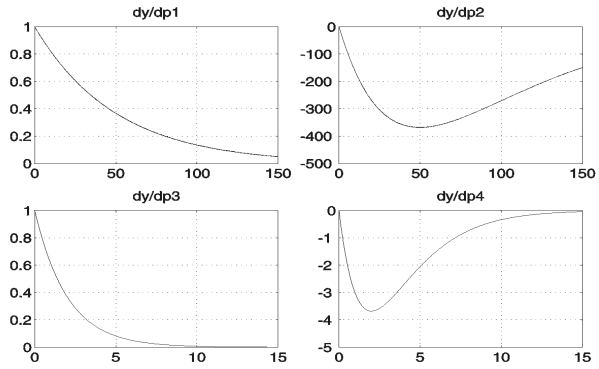

Figure 3: Sensitivities $S^y_{p_i}, i=1,2,3,4$ versus time [h].

Sensitivities $S^y_{p_{2r}}$, with respect to p_{2r}, are:

$$S^y_{p_{2r}}=\frac{\partial y}{\partial p_{2r}}=-p_{2r-1}\cdot t\cdot\exp(-p_{2r}t). \qquad (9)$$

Sensitivities $S^y_{p_{2r}}$ start from $S^y_{p_{2r}}(t=0)=0$, reach $S^{EXTR}_{p_{2r}}=S^y_{p_{2r}}\left(t=\frac{1}{p_{2r}}\right)=-\frac{p_{2r-1}}{p_{2r}}\exp(-1)$ and tend to $S^y_{p_{2r}}(t\rightarrow\infty)=0$. Figure 3 shows $S^y_{p_i}, i=1,2,3,4$ for an exemplary 2-exponential model function with an initial parameter vector $\mathbf{p}=[20\ 0.02\ 5\ 0.5]$.

The entries for the Fisher matrix (5) are the sum of products $S^y_{p_i}S^y_{p_j}$, $i,j=1,..,n=2l_{ex}$ of the respective sensitivities. These products form a matrix $\mathbf{P}=[P_{ij}]$, entries for which are plotted in Figure 4 for the exemplary model function. There are $\left(S^y_{p_i}\right)^2$ on the main diagonal of **P**. The extreme values of P_{ii} have the same time co-ordinate as the maxima of sensitivities $S^y_{p_i}$. Therefore, time points that maximise sensitivities $S^y_{p_i}$ also ensure maximal entries m_{ii} of the Fisher information matrix (5).

The following result from equations (8) and (9) and Figure 3:

- Sensitivities $S^y_{p_{2r-1}}$ have a maximal value $S^{MAX}_{2r-1}(t=0)=1$ and this does not depend on the values of parameters p_{2r} and p_{2r-1}.
- Sensitivities $S^y_{p_{2r}}$ have an extreme value at $t=\frac{1}{p_{2r}}$:

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$$S_{p_{2r}}^{MAX} = S_{p_{2r}}^{y}\left(t=\frac{1}{p_{2r}}\right) = -\frac{p_{2r-1}}{p_{2r}}e^{-1}.$$

Samples taken at $t=\frac{1}{p_{2r}}$ ensure maximal sensitivities of $S_{p_{2r}}^{y}$ (that is of $S_{p_2}^{y}, S_{p_4}^{y}, S_{p_6}^{y},...$) and a sample taken at $t=0$ ensures a maximal value of $S_{p_1}^{y}, S_{p_3}^{y}, S_{p_5}^{y},...$. These imply candidates for OSS:

$$\begin{aligned} &t=0 \\ &t=\frac{1}{p_{2r}},\ r=1,2,..,l_{ex} \end{aligned} \qquad (10)$$

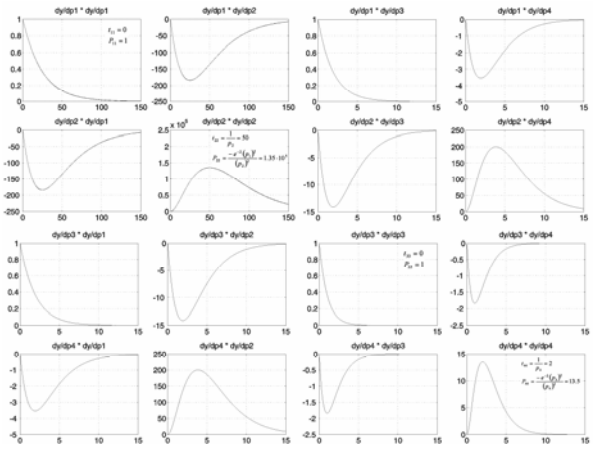

Figure 4: Products $P_{ij},\ i,j=1,2,3,4$ versus time [h]. The products are proportional to entries of the Fisher information matrix. Proportionality co-efficients $1/\sigma_y^2$ are assumed to be constant over time. On the main diagonal are given t_{ii}, P_{ii} which are the co-ordinates of the maximal values.

A reduced OSS has to consist of $2l_{ex}$ samples. For an increasing l_{ex} the consecutive time points that guarantee maximal sensitivities ($p_2 > p_4 > p_6$) are:

- $l_{ex}=1, n_s=2 \rightarrow$
  $\text{OSS}=\left[t_1=0, t_2=\frac{1}{p_2}\right]$
- $l_{ex}=2, n_s=4 \rightarrow$
  $\text{OSS}=\left[t_1=0, t_2=\frac{1}{p_2}, t_3=\underline{?}, t_4=\frac{1}{p_4}\right]$
- $l_{ex}=3, n_s=6 \rightarrow$
  $\text{OSS}=\left[t_1=0, t_2=\frac{1}{p_2}, t_3=\underline{?}, t_4=\frac{1}{p_4}, t_5=\underline{?}, t_6=\frac{1}{p_6}\right]$

For $l_{ex}=1$ (scalar case) the P-optimal points $t_1=0$ and $t_2=\frac{1}{p_2}$ are exactly the same as those given by D-OSS. For $l_{ex}>1$ there is a discrepancy between the number of optimal samples that result from analysis of $S_{p_i}^{y}$ and the number of samples necessary for identifying $n=2l_{ex}$ model parameters. The $S_{p_i}^{y}$ does not assure a sufficient number of candidates for OSS. Additional sampling points have to be chosen and the candidate has to be easily obtainable on the basis of already known parameter estimates and the optimal $t_2, t_4, t_6,...$ We examined t_c (the golden cut), t_a (the arithmetic mean), t_g (the geometric mean) and the others candidates. To choose the best candidate for an additional sample (t_c, t_a, t_g, the other?) the "leave-worst-out" method was adopted. This method has been published [18] and this can be referred to for further details. Briefly, the method uses the D-optimal criterion and allows numerous samples to be ordered from the most to the least valuable in the SS under test. We examined the P-optimal results in comparison with the D-optimal results. The comparison involved parameter estimates and their accuracy. The geometric mean t_g of two values, t_{2r} and t_{2r+2}, turned out to be the best choice as, simply, this works. Time point $t_g = t_{2r+1} = \sqrt{t_{2r}t_{2r+2}}$ ensures the best parameter estimates and their accuracy.

In order to prove the usefulness of P-optimality, an experiment based on simulation was performed. The exact model function with an initial parameter vector $\mathbf{p}=[20\ 0.02\ 5\ 0.5]$ was taken as the basis for a simulation yielding 10,000 sets of data. Each set consisted of 150 samples in the time interval $0 \div 150$ h, with step $dt=0.1$ h. Simulated data were generated by adding to the exact model response uncertainty, selected randomly from a normally distributed population of values $N\left(0,\sqrt{0.341}\right)$. The parameters and measurement error $\sigma^2=0.341$ mimic a real experiment [9] on the clearance of pregnant mare gonadotrophin from the blood plasma. Intravenous injection blood samples were withdrawn and the concentration of gonadotrophin in the serum was determined. The mean parameters of the process were adopted as the *true* (mean) parameters for the simulation. Next, for simulated data, the model parameters were re-estimated on the basis of P-optimal and D-optimal designs. For each set of simulated data the same common OSS was adopted, calculated for *true* parameters. For P-optimal design this was P-OSS=[0.0 h, 2.0 h, 10.0 h, 50.0 h], while for D-optimal design it was D-OSS=[0.0 h, 1.9 h, 9.6 h, 60.2 h].

After 10,000 simulation runs 10,000 normally distributed estimates were calculated for each $p_i, i=1,..,4$ and for P-OSS and D-OSS, totalling 80,000 estimates together. Mean estimates $\overline{p}_i$, their standard deviations $\sigma_{p_i} = std\ dev_{p_i}$, coefficients of variation CV[%] and errors Δ are defined as follows:

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$$\overline{p}_i = \frac{1}{10000}\sum_{r=1}^{10000} p_i^r,$$

$$\sigma_{p_i} = std\ dev_{p_i} = \sqrt{\frac{1}{9999}\sum_{i=1}^{10000}(p_i - \overline{p}_i)^2},$$

$$\mathrm{CV} = \frac{\sigma_{p_i}}{\overline{p}_i}[\%], \Delta = \frac{p_{i\,initial} - \overline{p}_i}{p_{i\,initial}}[\%]$$

Obtained $\overline{p}_i, \sigma_{p_i}$, CV[%] and Δ for the P-optimal and for the D-optimal designs are in Table 2. Mean estimates $\overline{p}_i$, their standard deviations $\sigma_{p_i} = std\ dev_{p_i}$, CV[%] and errors Δ for p_1, p_2, p_3 are very similar for both criteria. Only for p_4, which is less accurate for P-OSS (having a larger CV[%]) do they differ to any greater extent.

We have also compared [13] features of D, E, S and A-optimal design with respect to $\overline{p}_i$, $\sigma_{p_i} = std\ dev_{p_i}$, CV[%] and Δ in a similar process of simulation and parameter estimation to that described above.

The P criterion, presented in the paper, locates with its attributes in the vicinity of the D design. To be comparable in quality to the D criterion is the highest recommendation for any OSS design. What is more, the P design does not require sophisticated software and can be immediately implemented on the basis of parameter estimates. Each optimisation criterion based on the output $y(\mathbf{p},t)$ needs an initial assessment of parameter estimates and next sophisticated software has to be designed. The D, A or S optimisation is performed for a particular function $y(\mathbf{p},t)$ and for chosen criterion. P-optimal design, when used for the output function (1), only needs estimates of parameters p_{2r}. This enables elements of optimal experiment design to be introduced at a very early stage of the investigation. Quite often the approximate values of parameters can be found in published literature or can be predicted on the basis of physiology. In this case, so-called "intuitive experiment" can, thanks to P-OSS design, be initially pre-optimised, which leads to better parameter estimates.

The same analyses and calculations were performed for $l_{ex} = 3$. The results were similar to presented for $l_{ex} = 2$. Models with $l_{ex} > 3$ are somewhat theoretical in significance.

In order to validate P-optimality, the model functions (1) were also examined with different initial parameters. The results proved the usefulness and robustness of P-optimal design. The measurement noise immunities of P and D optimality are similar. Errors $\Delta[\%]$, presented in Table 2, show the ability of both criteria to provide estimates of known parameters on the basis of erroneous measurements. For p_1, p_2 and p_3 the values of $\Delta[\%]$ for P and D optimality are almost the same. The result for p_4 is somewhat worse; $\Delta[\%]$ is greater for P-OSS than for D-OSS. This is the price to be paid for the great simplicity of P-OSS.

Table 2. Mean (after 10,000 simulation runs) parameter estimates $\overline{p}_i$, σ_{p_i}, $\Delta[\%]$ and CV[%] obtained for a 2-exponential model function with an initial parameter vector $\mathbf{p} = [20.0,\ 0.02,\ 5.0,\ 0.5]$ for common P-optimal and for common D-optimal OSS.

P-OSS	$\overline{p}_i$	σ_{p_i}	Δ[%]	CV[%]
p_1	$19.81\cdot10^{0}$	$10.19\cdot10^{-1}$	0.95	5.14
p_2	$19.71\cdot10^{-3}$	$22.22\cdot10^{-4}$	1.45	11.27
p_3	$51.96\cdot10^{-1}$	$12.51\cdot10^{-1}$	3.91	24.07
p_4	$53.66\cdot10^{-2}$	$22.09\cdot10^{-2}$	7.32	41.41
D-OSS	$\overline{p}_i$	σ_{p_i}	Δ[%]	CV[%]
p_1	$19.82\cdot10^{0}$	$8.13\cdot10^{-1}$	0.90	4.10
p_2	$19.77\cdot10^{-3}$	$16.00\cdot10^{-4}$	1.15	8.09
p_3	$51.99\cdot10^{-1}$	$8.60\cdot10^{-1}$	3.81	16.54
p_4	$51.47\cdot10^{-2}$	$18.30\cdot10^{-2}$	2.94	35.55

Conclusions

The question posed was whether all parameters of model function (1) have equal power to produce an effect on reduced OSS. As shown on the basis of a 2-exponential exemplary model function, changes in p_1 and p_3 (when p_2 and p_4 are constant) produce no effect on OSS location, while changes in p_2 and p_4 imply changes in the OSS. For output function $y(\mathbf{p},t) = \sum_{r=1}^{l_{ex}} p_{2r-1}\exp(-p_{2r}t)$ the OSS remains unchanged provided that parameters p_{2r} remain unchanged.

An alternative method of sampling schedule optimisation, P-optimal design, has been presented. This optimisation criterion is based on an analysis of sensitivity. The approach presented is related, to a certain extent, to the Fisher information matrix approach. Yet for P-OSS design the Fisher matrix as a whole is not subjected to maximisation but rather its individual entries related to individual model parameters p_i.

The recipe for an easily obtained P-optimal reduced SS for model functions (1) is as follows:

1. For the biomedical process under investigation, choose the model and the parameters.
2. Perform the biomedical experiment according to intuition or standing convention, taking a sufficiently large number of measurements over the proper time interval.
3. Choose number $l_{ex} = 1,2,3$? of exponential terms.

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4. Obtain model parameter estimates $p_i, i = 1,2,..,2l_{ex}$ by comparing the measurements with the exact model function. Use a convenient objective function OF, for instance the least-square criterion.
5. If the result of step 4 for a chosen l_{ex} is satisfactory (decide if the model output function follows the measurements sufficiently closely), then proceed to step 6. If not, change l_{ex} and perform step 4 again.
6. Calculate the exact P-optimal reduced SS as follows:

$$l_{ex} = 1, \mathrm{OSS} = \left[t_1 = 0,\ \mathrm{t}_2 = \frac{1}{p_2} \right],$$

$$l_{ex} = 2,\ \mathrm{OSS} = \left[t_1 = 0, t_2 = \frac{1}{p_2}, t_3 = \frac{1}{\sqrt{p_2}}\frac{1}{\sqrt{p_4}}, t_4 = \frac{1}{p_4} \right],$$

$$l_{ex} = 3,\ \mathrm{OSS} = \begin{bmatrix} t_1 = 0, t_2 = \frac{1}{p_2}, t_3 = \frac{1}{\sqrt{p_2}}\frac{1}{\sqrt{p_4}}, t_4 = \frac{1}{p_4}, \\ t_5 = \frac{1}{\sqrt{p_4}}\frac{1}{\sqrt{p_6}}, t_6 = \frac{1}{p_6} \end{bmatrix}$$

For further examination of the biomedical system under investigation, use the P-optimal reduced SS obtained instead of the numerous intuitive SS.

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