OPTIMAL MULTICOMPARTMENTAL EXPERIMENT DESIGN

RENATA KALICKA

Technical University of Gdansk, Faculty of Electronics Telecommunications and Informatics, Department of Medical and Ecological Electronics 80-952 Gdansk, Narutowicza 11/12, Poland

Abstract: Compartmental modelling of biomedical systems, devoted to e.g. optimal therapy design, provides us with a compartmental system, the associated set of differential equations, and a number of unknown parameters. We estimate values of the unknown parameters so that we obtain a best fit of the model input-output behaviour to the experimental data. If the fit is not satisfactory, we remodel the structure of the system or/and reorganise the experiment design, and re-estimate the parameters. This is an iterative process, leading to the best model structure described with the most accurate values of its parameters. For satisfactory solution of the problem of optimal experiment design three co-operating computer programs are designed: MFIT, OSSP and OIN. MFIT enables to choose the best from any reasonable model functions. Reduced optimal sampling schedule (OSSP) and optimal input signal (OIN) allow to get the most accurate parameters' value. They operate on the basis of output files of MFIT. The final optimal experiment design is obtained by repeating the procedures.

1. Introduction

The knowledge of model parameters enables assessment of the actual state of a system using compartmental identification procedure. For satisfactory solution of the problem it is necessary to adopt the optimal experiment design.

The aim of the paper is to set up an optimal identification procedure for models of therapeutic processes. The knowledge of model parameters allows estimation of the actual state of a system. Then, it makes possible practical implementation of the adaptive therapeutic procedures, in contrast to commonly used intuitive or routine therapy. For satisfactory solution of the problem it is necessary to set up the adequate description of a system in the form of a mathematical formula expressed in model parameters. Next, the problem of „a priori" identifiability [1] has to be successfully solved out, i.e. the proper input-output pair has to be selected, in order to ensure that all the parameters could be estimated. Some input-output pairs, optimal in the above meaning, are not applicable from the clinical point of view. This is the first aspect of the experiment design. Having the „in-out" pair for which the system is structurally identifiable (SI), it is possible to carry out the experiment that allows to calculate the set of n model parameters, with an additional assumption that the number of measurements is not smaller than n. The test input, as well as the number and

the location of measurements, can be subjected to optimisation. Another experiment variable is sampling schedule (SS). After being optimised, the SS provides optimal (OSS) instead of intuitive (ISS) sampling schedule. The input signal is the next design variable. The optimal input signal (OIN) has such a form and duration that it ensures the best accuracy of parameters' estimation.

2. System under consideration

Let us assume that models under consideration are single-input, single-output (SISO), linear, dynamic and multicompartmental:

$$\begin{aligned} &\frac{dx(t)}{dt} = A(p)x(t) + Bu(t); \quad u(t) \geq 0 \\ &y(t) = C(t)x(t) \\ &z(t_k) = y(t_k, p) + e(t_k), \quad k = 1, \ldots, N; \quad t_0 < t_k < T, \end{aligned} \tag{1}$$

where x is a state vector, u is a test input, y is a measurable output $\mathbf{z}(t_k,p)$, is a measurement of y at time t_k, $e(t_k)$ is zero-mean gaussian noise with variance $s^2(t_k)$ Matrices A, B, C are the state, the input and the output matrices respectively, they are square matrices of dimension equal to the number of compartments, $\mathbf{p} \geq 0$ is an unknown parameter vector $\{p_i\}$ i=1, 2, ..., n. N is the number of samples. It is assumed, that the model is uniquely structurally identifiable (SI) for the designed experiment and that this assumption was previously checked up. The goal to be achieved is to calculate the parameter vector p. This vector has to be the most accurate one among the others calculated for optional experiment design.

3. Optimal experiment design

The essence of the optimal experiment design derives from Cramer-Rao theorem: the covariance matrix of unbiased parameter estimates COV(**p**) has the inverse of the Fisher information matrix M as a lower bound, i.e. $\mathrm{COV}(\mathbf{p}) \geq \mathbf{M}^{-1}$. The power of this theorem is based on the fact that the matrix M can be expressed by experiment design variables: M = M(u,N,SS,T,e), where: u, N, SS, T and e are respectively: input signal, number of samples, sampling schedule and measurement error. The optimisation is carried out with respect to chosen variable. The order of searching is not optional: the OSS is optimal only for a particular input but not for any input. The particular form of the variable for which M reaches maximum denotes the optimal experiment condition.

Three co-operating computer programs are designed: MFIT, OSSP and OIN. MFIT enables to choose the best from any reasonable model functions. Reduced sampling schedule (OSSP) and optimal input (OIN) are obtained on the basis of output files of MFIT. The final optimal experiment design is obtained by repeating the procedure. The design is optimal by a way of compromise between essential estimates' accuracy, reduced number of samples and the closest to the optimal, if not strict optimal, inputThe computer programs co-operate in the way shown in Fig.1

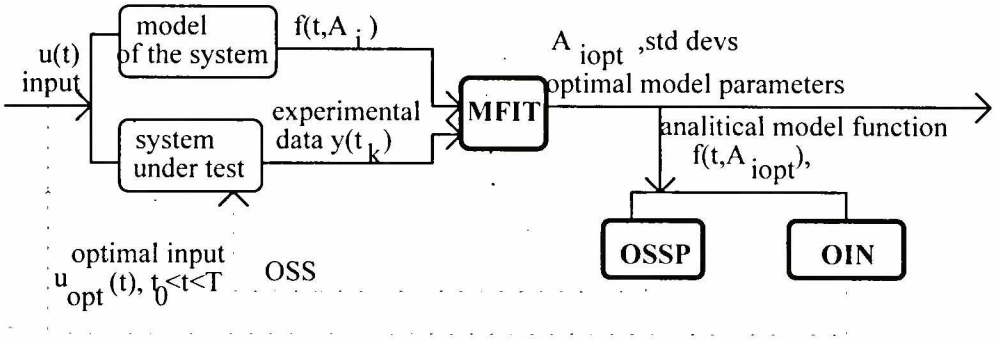


Figure 1. *Interaction of computer programs MFIT, OSSP and OIN*

3.1. Optimal input design study

An optimal input design is a necessary settlement for the optimal design of other experimental variables. The optimisation is carried out with respect to a particular form of an output signal y(t) which depends, according to the equation (1), on the particular form and duration of input signal u(t). This problem is difficult both from the theoretical and practical points of view. The optimal design problem, i.e. achieving maximal precision of parameter estimates, can be posed as a maximisation or minimisation problem of some function of the information matrix M with respect to a chosen variable. For solving the problem the A-optimisation has been adopted (after Kalaba, Spingarn, Mehra, Cobelli, Ruggeri and the others) [5, 6]. Among the consistent and unbiased estimates the best one is that having minimal variance. It gives the minimal mean square deviation of the estimate with respect to real value of the parameter. The Rao-Cramer inequality can be shown in the form:

$$COV(p) \geq \left\{ N \int_{-\infty}^{\infty} \left[\delta \ln f(\psi, \pi) / \phi \right]^2 f(y,p) dy \right\}^{-1} = \left\{ E\left[\delta \ln f(y,p) / \phi \right] \right\}^{-1} = M^{-1},$$

where f(y, p) is distribution function of y for particular value of the parameter vector p. The aim is to find such a form of input signal u(t), on stated time interval $0 < t < T_u$, for which the sensitivity is $\delta y(t)/\delta p$ maximal, therefore:

$$traceM = \sum_{i=1}^{n} m_{ii} = \sum_{i=1}^{n} \int_0^{T_u} \left(\sigma^2 \right)^{-1} \left(\delta y / \delta p_i \right)^2 dt = \int_0^{T_u} \left(\sum_{i=1}^{n} \left(\sigma^2 \right)^{-1} \left(\delta y / \delta p_i \right)^2 \right) dt = max.$$

The input is constrained to have a finite energy E: $\int_0^{T_u} u^2(t) dt \leq E$, E=const. The following performance index J is maximised:

$$J = \max_u \int_0^{T_u} \left(\sum_{i=1}^{n} \left(\sigma^2 \right)^{-1} \left(\delta y / \delta p_i \right)^2 - q u^2(t) \right) dt, \qquad (2)$$

where q is the Lagrange multiplier. The magnitude of q must be selected in such a way that the input energy constraint is satisfied. The optimal input design problem is solved utilising Pontriagin's maximum principle that involves maximising of the Hamiltonian function H. The u(t) which maximises Hamiltonian H is obtained as follows:

$$\delta H / \delta u = 0 \Rightarrow u(t) = -q^{-1} B^T \lambda(t) . \tag{3}$$

The costate vector $\lambda(t)$ is the solution of the equation $d\lambda / dt = -\delta H / \delta x$, B is the input matrix, as it was defined in the equation (1).
The computer program OIN, that determines optimal $u(t)$ (3), is designed. An optimal $u(t)$ is obtained on the basis of „a priori" estimates of the model parameters and the initial value $x(0)$ for stated q and T_u.

3.1.1 Algorithm and main procedures

The equation (3) allows to calculate the optimal input signal. The final form of the solution is derived from sensitivity equations:
where:

$$dx_p(t)/dt = Ax_p(t) + A_p x(t),$$
$$y_p(t) = Cx_p(t),$$
$$\text{where: } x_p(t) = \delta x(t) / \delta p,\ y_p(t) = \delta y(t) / \delta p,\ A_p = \delta A / \delta p.$$

Next, so called expanded state vector is defined: $X_R(t) = [x(t), x_p(t)]^T$, for which, by analogy to the above equation, the state equations are formulated:

$$dx_R(t)/dt = A_R x_R(t) + B_R u(t),$$
$$Y_R(t) = C_R x_R(t), \text{ where: } Y_R(t) = \left[y(t), y_p(t)\right]^T.$$

According to the above, the performance index J has got the following form:

$$J = \max_{u(t)} \frac{1}{2} \int_0^{T_u} \left(\sum_{i=1}^{k} X_R^T R^{-1} C_S^T C_S X_R - q u^2(t) \right) dt. \tag{4}$$

Expression (4) contains information about accuracy of measurements, the model structure, its parameters, the initial state and the optimal input u(t). This form of the performance index allows to use it in practice for optimal input calculation. For deriving this optimal input signal formula, for a system described in terms of sensitivity equations, the theory of isoperimetric calculus of variation, the method of Lagrange multiplier and Pontriagin's maximum principle are adopted. The particular expressions are as follows:

- Hamiltonian $H = \lambda_0(t)\ f_0(t) + \lambda_p(t) f_R(t)$,

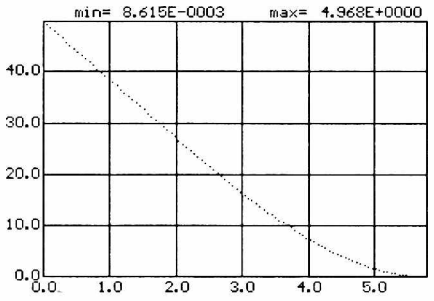
- costate vector $\lambda_0(t) = -1,\ \lambda_R(t) = [\lambda_1(t),\ldots,\lambda_{n(k+1)}(t)]$,
- additional state variable $f_0(t) = dx_0(t)/dt = dJ/dt = \frac{1}{2}[X_R^T R^{-1} C_S^T C_S X_R - qu^2]$,
- expanded state equation $f_R(t) = dX_R(t)/dt = A_R X_R(t) + B_R u(t)$,
- optimal input $u(t) = -q^{-1} B_R^T \lambda_R(t)$.

Table 1. *Calculation for obtaining optimal input signal u(t).*

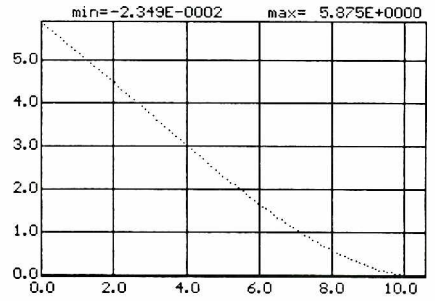
Step	*Calculations*	*on the base....*
1	matrixes A_R, B_R, C_R	structure of the model and its mean parameters
2	$X_R(t)$	measured initial values of the state variables
3	$\lambda_R(0)$	$X_R(0)$, $\lambda_R(T_u)$
4	$X_R(t)$, $\lambda_R(t)$ a two-dimensional boundary value problem	$X_R(0)$, $\lambda_R(0)$
5	optimal input u(t)	q, B_R, $\lambda_R(t)$
6	D and J(*)	optimal u(t)

(*) $D = \int_0^{T_u} u(t)\,dt$, $u(t)$ is determined in the interval $[0,T_u]$, J is equal to the actual value of performance index (4) calculated for optimal $u(t)$.

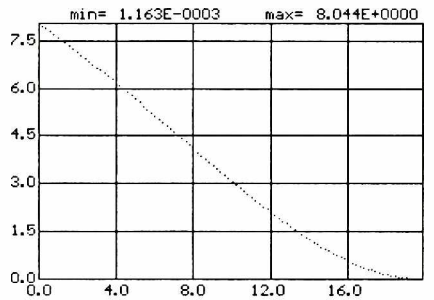
The main steps of calculation are presented in the Table 1. For stated q and given Tu, the optimal $u(t)$ has a tabular form: it is a set of the values $u(t_i)$ for particular time points $t_i \in (0, T_u)$. In the paragraph 3.2 of the paper an experiment with intranasal insulin distribution is presented. The two-compartmental model is taken into consideration. It is described by pharmacokinetics parameters k_{01}, k_{21}, k_{02}. Its two-exponential model function is shown in Table 3. For this model some exemplary optimal input candidates are presented in Fig. 2, 3 and 4. In Fig. 2 optimal inputs for estimating k_{21} are shown.



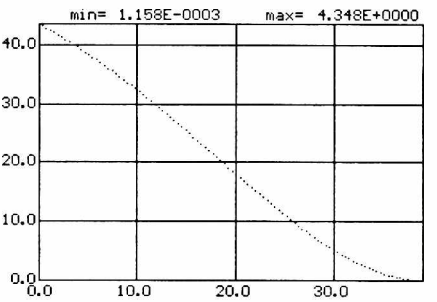
optimal input $\times 10^{-1}$, time $\times 10^{-1}$
q=0.01, D=1.1307×10^{0}, J=3.6948×10^{-2}



optimal input $\times 10^{0}$, time $\times 10^{-1}$
q=0.1, D=2.4830×10^{0}, J=9.4698×10^{-1}



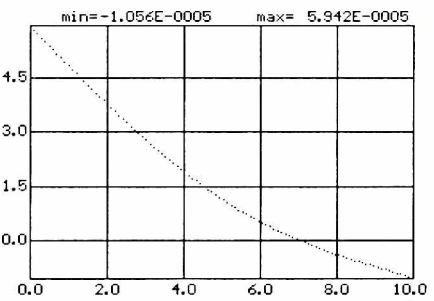
optimal input $\times 10^{0}$, time $\times 10^{-1}$
q=1, D=6.6378×10^{0}, J=3.5221×10^{1}



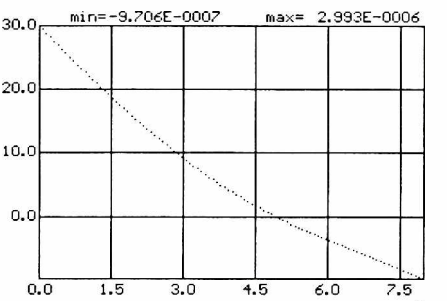
optimal input $\times 10^{-1}$, time $\times 10^{-1}$
q=10, D=7.5491×10^{0}, J=2.2411×10^{2}

Figure 2. *Optimal inputs for estimating k_{21} obtained for different T_u and q.*

All the inputs have similar shapes, convenient for implementation. Performance index J is bigger for longer T_u and the latter remark seems to be a rule. The dose D used in real experiment was $13 \cdot 10^6$ ng, which is much bigger than the above optimal inputs supply. In Fig. 3 there are two optimal inputs for estimating k_{02}. They are similar in shape to those for k_{21}, kind of decaying linear function, but the dose is far below applicable value and performance index is very low.

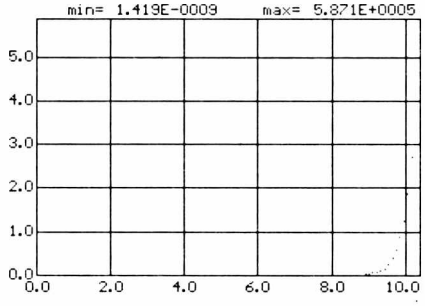


optimal input$\times 10^{-5}$, time$\times 10^{0}$
q=0.1, D=1.5933×10^{-4}, J=6.6825×10^{-10}

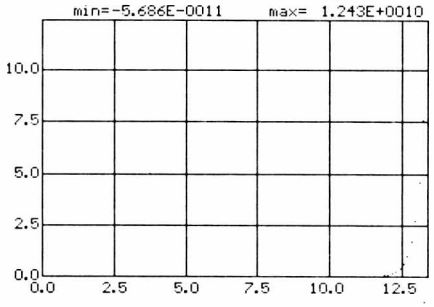


optimal input$\times 10^{-7}$, time$\times 10^{0}$
q=1, D=4.8252×10^{-6}, J=1.3185×10^{-11}

Figure 3. *Optimal inputs for estimating k_{02} obtained for different T_u and q.*



optimal inputx10^5, timex10^1
q=0.01, D=1.5807x10^6, J=4.6720x10^9



optimal inputx10^9, timex10^1
q=0.1, D=3.3358x10^{10}, J=2.0891x10^{19}

Figure 4. *Optimal inputs for estimating k01 obtained for different T_u and q.*

The inputs, optimal with respect to k_{01}, show very high performance index J. It is a very good prognosis for improving accuracy of k_{01} in case of using the optimal shape of $u(t)$. What is more, the optimal dose is close to that from the experiment. The optimal shape is not easy to produce: it has extremely flat skirt from the beginning to almost very end, where steep pulse occurs. The presented algorithm has a special property: every $u(t)$ obtained for any chosen q and T_u is theoretically optimal. It does not mean that all the obtained $u(t)$ are reasonable from practical point of view. Some of them are not applicable, for instance when the dose D<0, some are not convenient when they last too long or have too sophisticated form.

3.2. Optimal sampling schedule study

For optimal sampling schedule design the D-optimality has been chosen. D-optimality is based on maximisation of the Fisher information matrix determinant: detM with respect to SS. The generic element of M is as follows:

$$m_{ij} = \sum_{k=1}^{N} \left(\sigma^2\right)^{-1} \cdot \delta y\left(t_k\right)/\delta p_i \cdot \delta y\left(t_k\right)/\delta p_j \qquad i, j = 1, 2 \ldots, n.$$

The D-optimality is numeric robust and warrants invariability of OSS under non degenerate transformation of the model or choice of units for the parameters [4]. The computer program OSSP that determines OSS for 6 different, most useful algorithms is designed [2]. These algorithms are listed in Fig.5.

Inputs for the program, common for all algorithms, are: „a priori" estimates of the model parameters, variance of error σ^2, time interval at which samples are taken (t_0, T), and quantization step dt. An output of the program consists of a set of optimal sampling points (OSS), time points in ISS which are closest to the optimal points in *OSS*, *detM* and D-Efficiency for *OSS* [4]:

$$EFF = 100 \cdot \left(det\, M_{ISS}/det\, M_{OSS}\right)^{1/p} \cdot \left(N_{OSS}/N_{ISS}\right) [\%],$$

where: N_{ISS} and N_{OSS} are the numbers of samples in ISS and OSS, respectively. EFF is a measure of relative amount of information per unit sample size.

For instance, if EFF=60% is means that the ISS wastes 40% of its sample size in comparison with OSS.

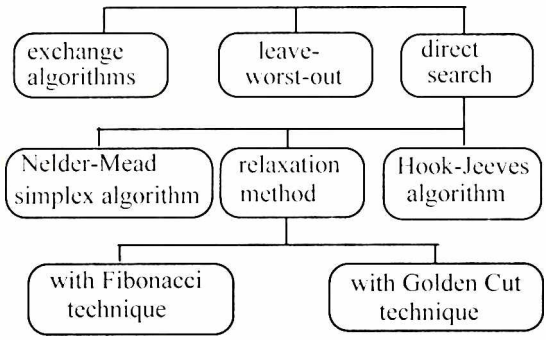


Figure 5. *Methods of optimal sampling schedule design described in the paper.*

Table 2. *Comparison of realised algorithms*

Method	*1–compartmental model*				*2–compartmental model*			
	Number of Objective Function calls			*Relative extreme*	*Number of Objective Function calls*			*Relative extreme*
	min	*mean*	*max*	*%*	*min*	*mean*	*max*	*%*
Fibonacci	131	131	131	0	298	350	423	29
Fibonacci II	111	122	125	0	293	365	639	3
Golden Cut	83	83	123	0	183	214	323	24
Golden Cut II	76	79	80	0	196	251	482	6
Hook-Jevess	62	130	180	0	314	421	610	0
Simplex	42	66	245	0	203	351	666	0.2
Exchange	3660	4964	6085	0	6180	8642	9874	0

The obtained OSS does not depend on the method. Work with the program shows evidence of replication of some samples when the number of time points in OSS was bigger than the number of the model parameters. The leave-worst-out (l-w-o) method [3] is an attempt to avoid this inconvenience. One sample, the worst among all samples, is left out in every step in the algorithm. The remaining SS is of required size. Very interesting modification, adopted in Fibonacci II and Golden Cut II methods, is not to limit searches to original sampling interval T. It allows to obtain optimal SS not for „a priori" stated interval T but globally optimal SS for a particular form of the output model function. The program is an efficient and all-purpose implement for OSS design for linear kinetic models. Two models based the same experimental data, 1-compartmental and 2-compartmental, are subjected to 1000

optimisation runs. The number of samples in OSS is fixed at 2 and 4 respectively for 1 and 2-compartmental models. Sampling interval T=117, 0, optimisation step = 0.1 are the same for all the methods. The results are shown in Table 2. Main factors used for comparison of individual algorithms are chosen : 1) necessary number of procedure calls for computation objective function -numeric complexity is the main agent which determines the whole time of optimisation process, 2) tendency to fall into relative extreme defined as the percent of the output results that are not in fact the optimal sampling points.

3.3. Fitting model to experimental data

The computer program MFIT is designed for fitting any model, linear or non-linear in its parameters, to experimental data. The program fits different models by changing a single subprogram that provides mathematical description of the model. As the criterion of the appropriateness of fit a model to data, the least square method is adopted. In this method the objective function (OF) is defined as follows:

$$OF = \sum_{k=1}^{N} \left[y_k - f\left(t_k, A_1, A_2, \ldots, A_n\right) \right]^2 = min,$$

where: is the measured response of a system at the point t_k, $f(t_k,A_1,\ldots,A_n)$ represents the value of the model response at points t_k, A_j are the model function parameters, i=1, 2, .., n. The remaining differences between model and data are called residuals. Finding the combination of parameters that minimises OF requires a sequential search of all combinations of parameters' values. In MFIT the combined algorithm is adopted: the steepest descent approach is automatically applied when it is most effective at points relatively far from the minimum, while linearization of the fitting function is made dominant as the minimum is approached. The information about the search direction is contained in both: values of the partial derivatives $\delta f(t,A)/\delta A_j$ which show how fast the OF is diminishing, as well as in results of previous steps in the search. The derivatives at the minimum are used to calculate precision of each parameter estimate. The method fails as the minimum is approached: it has tendency to search inefficiently. That is why the technique relying on linearization of fitting function, as more effective, is applied in the vicinity of the minimum. The program starts from guessed initial estimates and ends with the optimal set of model parameters when (a) the necessary accuracy of every parameter was obtained, or (b) the stated number of iterations was carried out. Residual variance for the optimum set of the parameters Aopt is used for evaluation of standard deviations std dev:

$$res\ variance = \frac{\sum_{k=1}^{N} [y_k - f(t_k, A_{opt})]^2}{degrees\ of\ freedom} \Rightarrow std\ dev = \sqrt{res\ var}.$$

Sometimes the fitting process is slow and uncertainties in some parameters are bigger than would be expected from the uncertainty in the data. The parameters are

said to be „poorly determined" and its cause is known as „parameters interaction". In the program MFIT three convenient measures of parameters' interaction are adopted: a) so called „dependence", which shows the degree to which changes in each parameter are related to changes in others, b) correlation between pairs of parameters, c) condition number, that is the ratio of the maximum to the minimum eigenvalues of latent roots of the sensitivity coefficients $\delta f(t,A)/\delta A_i$ matrix. Analysis of output results of MFIT for alternative models allows to select from the best analytical description of the process under investigation.

Considering quality coefficients of a model parameters estimation — standard deviation, „dependencies", correlation coefficients, condition number and residuals' distribution — MFIT enables to choose the best from any known reasonable model functions. Reduced optimal sampling schedule (OSSP) and optimal input (OIN) can be obtained on the base of output files of MFIT. The final optimal experiment design is achieved by repeating the procedure. It is optimal by way of compromise between essential parameters' accuracy, reduced number of samples and the closest to optimal, if not strictly optimal, input. This design gives the best, with respect to cost effectiveness, experiment which allows to follow changes in model parameters during therapy and also allows to implement individual therapy, adaptive dosing.

Numerous experiments were done and results were subjected to optimisation for getting, in the most effective way, an optimal set of a system parameters. These parameters are used for establishing an individual dosage of a medicine, or for evaluating desired progress in the therapy, or for evaluating quality of a sorption promoter. In every case the interacting programs were used. An example: Male Sprague Dawley rats 300-350 g were used in an experiment with intranasal insulin distribution. Prior to the experiment the animals were fasted for 24 hours. Rats were anaesthetised with Thiopental 125 mg/kg, Spofa Czech and allowed to stabilise for 30 minutes before insulin administration. The trachea and jugular veins were catheterised with polyethylene tubes. 30 minutes after injection of Thiopental a dose 0.3 IU of insulin with promoting substance Polyoxyethylene-9-Lauryl Ether in 20 µl solution was installed to the nasal cavity using a plastic disposable pipette tip. The 0.3 µl samples of blood were withdrawn from jugular vein in 0, 5, 10, 15, 30, 45, 60, 90, 120, 180 and 240 min and allow to clot at room temperature before centrifugation at 2400 rpm for 30 min at 4°C. D-glucose levels in serum were measured using EBIO Compact Glucometer basing on glucose oxidase method. The samples of serum for insulin determination were stored at -20°C for 2 weeks. Insulin was assayed immunologically with RIA kit, Amersham England. After thawing at 23°C, the samples from individual subjects were assayed in single batch to avoid interassay variations.

A two-compartmental model was taken into consideration. At first, for the ISS and by means of MFIT, the parameters of model function are calculated. Results are shown in Table 3.

Next, by means of OSSP (leave-worst-out method), the optimal sampling

points are fixed out. These points are shown in Table 3, together with exactly optimal points obtained with any algorithm chosen from among listed in Table 2. Finally, for OSS the parameters are reestimated. Results are shown in the right column of Table 3.

In Fig.6 there is a comparison of two model functions: one of them is drawn for the optimal parameters obtained for complete, intuitive sampling schedule, and the second is obtained for reduced to four samples, optimal sampling schedule accordingly to the l-w-o algorithm. For the latter case, the model function which has four unknown parameters, follows the four measured points very closely. Residual variance is as small as $7.58 \cdot 10^{-15}$. It causes that the errors in model parameters are far below value of importance.

Table 3. *Model function parameters based on ISS. Reestimated model function parameters for reduced OSS obtained with the l-w-o procedure.*

Model functionparameters $I(t)=A_1E^{-A_2t}+A_3e^{-A_4t}$	***Calculatedon the base of ISS***	***Calculated on the base of OSS l-w-o: {0.0,5.0,10.0,45.0}, D-eff=78.4% exact: {0.0,5.0,10.0,40.0}, D-eff=79.0%***
A_1	-51.4975±4.76%	-49.5432
A_2	0.36591±11.06%	0.38983
A_3	51.4679±4.47%	49.5432
A_4	0.03566±5.31%	0.03565
res var	$7.9867 \cdot 10^{-1}$	$7.58 \cdot 10^{-15}$

Making use of reduced SS gives satisfactory parameters' estimates. The appropriateness of fit of the model to data is comparable to this obtained for the complete set of measurements. Not the exactly optimal points, but the best sampling points from original ISS have been adopted. In this approach we do not know an exact, theoretically possible to achieve value of parameter and its accuracy, but it can not be worse than this obtained for the almost optimal SS delivered by the l-w-o procedure.

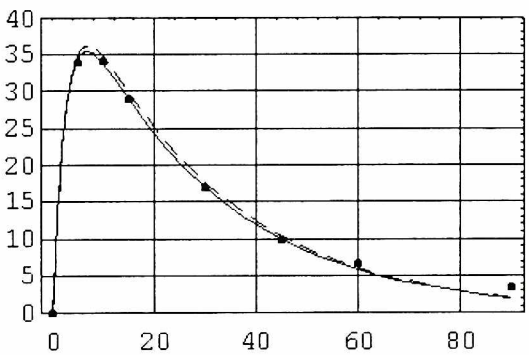


Figure 6. *Model function I(t) [ng/ml], t[min] for ISS (dashed) and for OSS with the ISS measurements (dots) in the background.*

The problem currently under development, is to what degree a displacement of the particular optimal sampling point, up and down its exact value, would affect results of estimation. Some of the optimal points are very sensitive to changes in the parameters' values and some are less sensitive. It seems to be of practical utility to have defined a measure of necessary fixedness for every optimal point with respect to expected results of estimation.

Summary

Results obtained on optimal input design show that among equienergy inputs, higher value of performance index is being achieved for longer T_u and bigger D. The pattern of optimal input is sometimes rather complex and has such a form and duration which makes it difficult to adopt, and in consequence the intended purpose, i.e. implementation of the signal for parameter estimation, is not fulfilled. Instead of that, on the basis of obtained results, an input which is closest to the optimal signal should be chosen from among routinely used inputs, such as injection or infusion. The dose of signal chosen by compromise, should be equal to the dose „carried" by exactly optimal input.

In agreement with previous experiences, an optimal sampling schedule design proved that the reduced optimal sampling schedule is necessary and sufficient for parameter estimation. In Table 3 there are results obtained on the bases of the intuitive SS. For comparison, the same parameters are calculated for the optimal SS, got by means of the leave-worst-out strategy. The results are very promising. The residual variance, which is a measure of fit goodness, is very small for the optimal SS: the model function follows very closely four optimal measurements, res var=$7.58 \cdot 10^{-15}$. The residual variance was also calculated when all the left samples from the intuitive SS were additionally included. It gave res var=$10.277 \cdot 10^{-1}$, which is bigger than this obtained for ISS but still very satisfactory. It shows the goodness of fit of the model function to original, numerous ISS and illustrates ability of the optimal reduced SS to deliver parameters suitable for describing the whole process under investigation.

Parameters' estimation is an essential part of any analytical experimentation. It requires comparison of a model function and experimental results. Unavoidable errors in measurements affect parameters values and their accuracy. The presented program MFIT delivers optimal set of model parameters basing on the least square method. The program also gives convenient measures of model quality and its parameters quality. It enables to choose the best from many alternative model functions, describing the process under investigation.

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