EQUIENERGY VS EQUIDOSE INPUTS IN PHARMACOKINETIC STUDIES

R. Kalicka*, A. Pietrenko-Dąbrowska**

* Gdańsk University of Technology, Faculty of Electronics, Telecommunication and Informatics, Department of Biomedical Engineering, Gdańsk, Poland
** Gdańsk University of Technology, Faculty of Electronics, Telecommunication and Informatics, Department of Microelectronic Systems, Gdańsk, Poland

renatak@biomed.eti.pg.gda.pl, newta@eti.pg.gda.pl

Abstract: Optimal input design for parametric identification of the SISO state space compartmental models of pharmacokinetic systems is presented. The optimal input, which ensures the best accuracy of the parameter estimates, is designed on the basis of the initial parameter estimates. These estimates are calculated on the basis of the output measurements collected during the intuitive experiment. The sensitivity criterion is adopted and presented in terms of a non-linear programming problem with constraints. Two constraints imposed on the optimal input are considered and compared: the dose and the energy constraint. The two constraints define two classes of admissible inputs: the equienergy and the equidose inputs, respectively. The parameters are estimated using the prediction-error method.

Introduction

The parametric approach (*grey-box*) to the identification of pharmacokinetic systems is presented. Parametric identification consists of two steps: the formulation of the model structure and the parameter estimation. The model structure is formulated on the base of *a priori* knowledge concerning the system [1]. The model structure can be described in terms of differential equations with unknown parameters. In the estimation procedure the unknown values of the model parameters are estimated so that the best fit of the model's output to the measurements is achieved.

The choice of experiment variables in such a way that the data become maximally informative is termed "optimal experiment design" [2]. In this paper the optimised variable is the input signal u. In pharmacokinetic studies the optimal experiment design is of the greatest importance because of the severe practical constraints imposed on the experimental conditions. These constraints include the dose or energy of the signal and the signal duration. Moreover, in clinical practice usually only the central compartment (blood vascular system) is accessible both for excitation and for measurement. This paper, therefore, focuses on SISO (*Single Input Single Output*) models.

The achievable accuracy of the parameter estimates is given by the Cramer-Rao theorem [3]. The theorem claims that the lower bound of the estimate covariance matrix $\operatorname{cov}\left[\hat{\mathbf{p}}\right]_{n_k \times n_k}$ is equal to the inverse of the Fisher information matrix $\mathbf{M}_{n_k \times n_k}$

$$\operatorname{cov}\left[\hat{\mathbf{p}}\right] = E\left[\left(\hat{\mathbf{p}}-\mathbf{p}\right)\left(\hat{\mathbf{p}}-\mathbf{p}\right)^T\right] \geq \mathbf{M}^{-1}, \qquad (1)$$

where $\hat{\mathbf{p}}_{n_k \times 1}$ – parameter estimates vector and $\mathbf{p}_{n_k \times 1}$ – true parameter values vector, n_k – number of model parameters.

The elements of the Fisher information matrix $\mathbf{M}$ are described by [4]

$$\mathbf{M} = \left[m_{ij}\right] = \left[\frac{1}{R}\int_0^{T_f} \frac{\partial y(t)}{\partial p_i}\frac{\partial y(t)}{\partial p_j}dt\right],\ i, j = 1,\ldots,n_k, \quad (2)$$

where $\partial y(t)/\partial p_i$ – sensitivity of the output y with respect to the model parameter p_i, T_f – observation interval. Measurement error is assumed to be an uncorrelated, Gaussian, zero mean with a constant variance $\sigma^2 = R$, i.e. $G(0, R)$.

A result of the Cramer-Rao theorem is that the minimal covariance of parameter estimates can be achieved by maximising the Fisher information matrix. The optimality criterion is expressed as a scalar function $\Phi(\mathbf{M})$ of the Fisher information matrix. In this paper the sensitivity criterion $\Phi(\mathbf{M})$, in the form of the trace of the Fisher information matrix, is adopted [4]

$$\Phi(\mathbf{M}) = \operatorname{trace}\mathbf{M} = \sum_{i=1}^{n_k} m_{ii} = \frac{1}{R}\int_0^{T_f}\left[\sum_{i=1}^{n_k}\left(\frac{\partial y(t)}{\partial p_i}\right)^2\right]dt\ . \quad (3)$$

The main diagonal elements of the Fisher information matrix are the squares of the output sensitivity with respect to each parameter. Thus the chosen optimality criterion ensures the maximum sensitivity of the output with respect to the estimated parameters. Two optimal input design (OID) problems

ISSN: 1727-1983

were solved: the OID problem with constraint imposed on the dose D of the input signal and the OID problem with constraint imposed on the energy E of the input signal

$$D = \int_0^{T_u} u(t)\,dt\,, \tag{4}$$

$$E = \int_0^{T_u} u^2(t)\,dt\,, \tag{5}$$

where T_u denotes the duration of the input signal u.

The objective function (3) and the constraints (4), (5) are non-linear, so both OID problems are non-linear optimisation problems with constraint. The OID problems were solved using Kuhn-Tucker necessary conditions [5]. The conditions are both necessary and sufficient conditions of the convex optimisation problem.

Equidose and equienergy inputs

The constraints (4) and (5) define two classes of admissible inputs, the equidose and equienergy class, respectively. The solution depends heavily on the constraint imposed on the input signal [4]. In pharmacokinetic studies the dose of the input signal is limited by medical considerations. Hence the equienergy class of admissible inputs is very often adopted.

Nevertheless, the constraint imposed on the energy of the input signal, which is widely used in control engineering, is applied in pharmacokinetic and metabolic studies as well [4], [6], [7]. In pharmacokinetics, the energy constraint is interpreted as limiting the rate of drug administration. The reason for adopting the energy constraint is to avoid rate-dependent side-effects, which occur for many medicines. In such cases, the medicines cannot be administered to the patient in the form of an injection or fast infusion. The medicines, whose administration rates have to be limited, belong to various groups, including cardiac medicines (*lidocaine* and *nitro-glycerine*), antibiotics (*clindamicin*, *vankomycin* and *tetracycline*) and antineoplastic medicines [8].

Let us consider the linear, continuous time, SISO system with Gaussian measurement errors $G(0,R)$. The theorem holds [9]: "Among non-negative inputs of an equidose class the impulse provides the minimum Cramer-Rao lower bound of the parameter estimates". Thus the equidose inputs are in form of the impulse input i.e. they have to be administered as an injection or short infusion. However, as stated above, the administration rate of some medicines has to be low because of the rate-dependent toxic side-effects. For these medicines, therefore, the equidose class of admissible inputs cannot be adopted. Thus the equienergy admissible inputs have to be considered instead of the equidose inputs.

The desired dose D of the energy-constrained input can be calculated on the base of the input time course $u(t)$ and its duration T_u. Better accuracy of parameter estimates is achieved for inputs of longer duration T_u. On the other hand, shorter T_u is less strenuous for the patient. In practice, the chosen input duration is usually a compromise between larger T_u, which is desirable for identification purposes, and smaller T_u, which is more sparing for the patient.

Input optimisation and parameter estimation

The continuous n-compartmental SISO model is described by the following differential equations [10]

$$\frac{d\mathbf{x}(t)}{dt} = \mathbf{A}(\mathbf{p})\cdot\mathbf{x}(t) + \mathbf{B}\cdot u(t)\,, \tag{6}$$

$$y(t) = f(t) + v(t) = \mathbf{C}\cdot\mathbf{x}(t) + v(t)\,, \tag{7}$$

where $\mathbf{x}(t) = \left[x_1(t), x_2(t), ..., x_n(t)\right]^T$ is a state vector, $u(t)$, $y(t)$, $f(t)$, $v(t)$ are the input, measured output, model output and measurement error, respectively. $\mathbf{A}(\mathbf{p})_{n\times n}$, $\mathbf{B}_{n\times 1}$, $\mathbf{C}_{1\times n}$ are the state, input and output matrix, respectively. The state x_i, $i = 1,2,...,n$, of the pharmacokinetic model denotes concentration (mass) of the substance in the i-th compartment. The parameter vector $\mathbf{p} = \left[p_1, p_2, ..., p_{n_k}\right]^T$ contains the rate constants k_{ij} and the elimination constants k_{0i}, $i, j = 1,2,...,n$. The rate constant k_{ij} describes the flow of the substance from the j-th to the i-th compartment. The elimination constant k_{0i} describes the elimination of the substance from the i-th compartment to the environment.

The equidose optimal inputs were designed for one and two-compartmental models of *gonadotrophin* distribution, whereas the equienergy optimal inputs were designed for one and two-compartmental models of *tetracycline* distribution. Rapid injection of *tetracycline* causes serious cardiovascular side-effects and thus its administration rate has to be limited [11]. The models are presented in Figure 1.

The initial parameter vectors $\mathbf{p}_{init_1} = \left[k_{01}\right]$ and $\mathbf{p}_{init_2} = \left[k_{01}, k_{12}, k_{21}\right]$ of one and two-compartmental models of *gonadotrophin* and *tetracycline* distribution were calculated using the least-square method on the basis of the measurements collected during the non-optimal intuitive experiments.

ISSN: 1727-1983

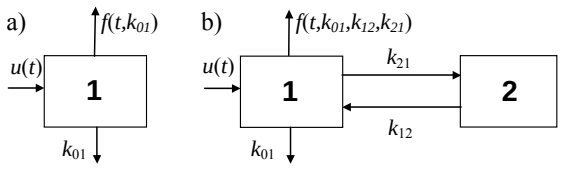

Figure 1: The one a) and two-compartmental b) model of *gonadotrophin* and *tetracycline* distribution.

The following parameter values were obtained: $k_{01} = 0.0266\ \text{min}^{-1}$ for the one-compartmental model and $k_{01} = 0.0287\ \text{min}^{-1}$, $k_{12} = 0.4270\ \text{min}^{-1}$, $k_{21} = 0.1190\ \text{min}^{-1}$ for the two-compartmental model of *gonadotrophin* distribution [12].

The parameter value obtained for the one-compartmental model of *tetracycline* distribution was $k_{01} = 0.1079\ h^{-1}$, while for the two-compartmental model of *tetracycline* distribution the following parameter values were obtained: $k_{01} = 0.0913\ h^{-1}$, $k_{12} = 0.2530\ h^{-1}$, $k_{21} = 0.0756\ h^{-1}$ [13].

In the equidose case the optimal input was designed to ensure the best accuracy of the only parameter k_{01} of the one-compartmental model of *gonadotrophin* distribution. Additionally, the optimal input was designed to ensure the best accuracy of the three parameters k_{01}, k_{12} and k_{21} of the two-compartmental model of *gonadotrophin* distribution. Likewise, two optimal inputs were designed, which ensured the best accuracy of the parameters of the one and two-compartmental models of *tetracycline* distribution.

The optimal inputs were designed on the basis of the non-optimal initial parameter vectors $\mathbf{p}_{init}$ using Matlab's *fmincon* procedure. The *fmincon* procedure adopts Kuhn-Tucker necessary conditions to solve a non-linear programming problem with constraint.

In the equidose case the duration of the optimal inputs is very short as the inputs are in the form of a short infusion. The model's output $f\left(u_{opt}, \mathbf{p}_{init}\right)$ to the optimal input u_{opt} was simulated on the observation interval $\left[0, T_{f_1}\right]$. The observation interval of $T_{f_1} = 30\,\text{min}$ is relatively long when compared with the input duration.

In the equienergy case the input duration is equal to $T_u = 0.5\,h$. The accuracy of the parameter k_{12} of the two-compartmental model of *tetracycline* distribution is very poor, as the sensitivity $\partial f\left(u_{opt}\right)/\partial k_{12}$ is smaller than the corresponding sensitivities of parameters k_{01} and k_{21} (see Figure 2). In order to improve the accuracy of the parameter estimates, the four different observation intervals were considered $T_{f_2} = 1, 1.5, 2, 2.5\,h$, as the information content in the interval $\left[T_u, T_{f_2}\right]$ is very rich [4].

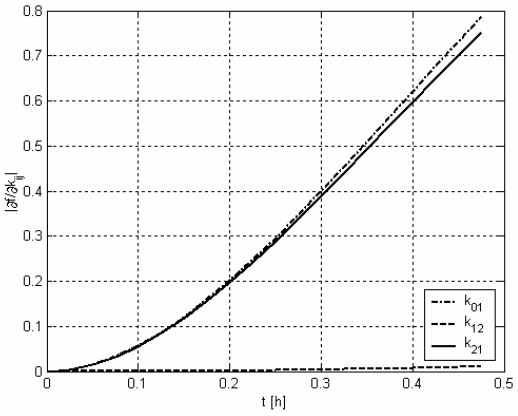

Figure 2: The sensitivity of the output of the two-compartmental model of *tetracycline* distribution with respect to parameters k_{01}, k_{12} and k_{21}.

In the equidose case, the measurements $y_{meas}\left(u_{opt,\mathbf{p}_{init}}\right)$ were simulated by adding the Gaussian noise $v_1 \in G\left(0, R_1\right)$ to the model's output $f\left(u_{opt}, \mathbf{p}_{rees}\right)$, while in the equienergy case the measurements were obtained by adding the Gaussian noise $v_2 \in G\left(0, R_2\right)$ to the model's output $f\left(u_{opt}, \mathbf{p}_{rees}\right)$. The variances $R_1 = 0.334$ and $R_2 = 0.01$ are equal to the variances obtained in the respective real intuitive experiments [12], [13].

The parameters of one and two-compartmental models, as presented in Figure 1, were calculated using prediction-error method. The prediction-error method coincides with the least square/maximum likelihood method for equally distributed Gaussian measurement errors $G\left(0, R\right)$ **Error! Reference source not found.**. The calculations were performed using Matlab's *pem* procedure.

Results

The output $f\left(u_{opt}, \mathbf{p}_{rees}\right)$ of the one-compartmental model of *gonadotrophin* distribution, described by the re-estimated parameter vector $\mathbf{p}_{rees}$, and the simulated measurements y_{meas} are shown in Figure 3. The output of the two-compartmental model of *gonadotrophin* distribution and the measurements are presented in Figure 4.

The parameter estimates of the one and two-compartmental models of *gonadotrophin* distribution, their variances and coefficients of variation *CV*% are presented in Table 1 and Table 2, respectively. The results presented in Tables 1 and 2 were obtained for the

ISSN: 1727-1983

optimal input u_{opt} and compared to the results obtained for the non-optimal step input u_{step} of duration $T_{step} = 30\,\text{min}$.

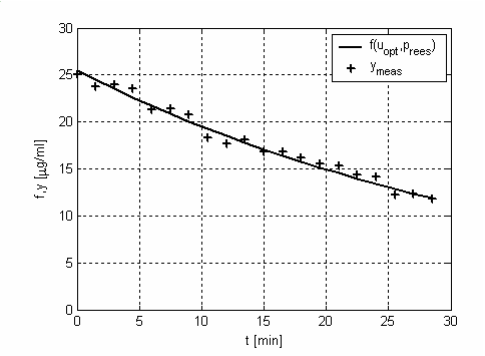

Figure 3: The output of the re-estimated one-compartmental model of *gonadotrophin* distribution $f\left(u_{opt}, \mathbf{p}_{rees}\right)$ and simulated measurements y_{meas}.

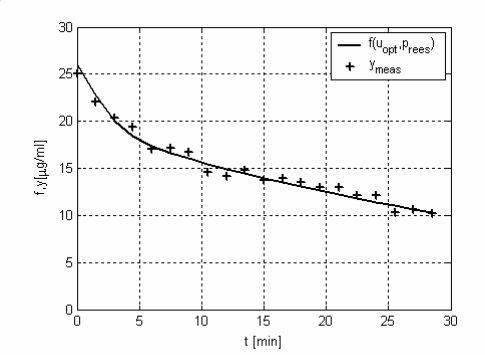

Figure 4: The output of the re-estimated two-compartmental model of *gonadotrophin* distribution $f\left(u_{opt}, \mathbf{p}_{rees}\right)$ and simulated measurements y_{meas}.

The parameter variances were calculated as the Cramer-Rao lower bound (see (1))

$$\text{var}\left(k_{ij}\right) = \left[\frac{1}{R_{rees}} \sum_{k=1}^{N} \left(\frac{\partial f_{rees}\left(t_k\right)}{\partial k_{ij}}\right)^2\right]^{-1}, \qquad (8)$$

$$R_{rees} = \frac{1}{N} \sum_{k=1}^{N} \left(y_{meas}\left(t_k\right) - f_{rees}\left(t_k\right)\right)^2, \qquad (9)$$

where $f_{rees} = f\left(\mathbf{p}_{rees}\right)$, N – number of measurements, R_{rees} – residual variance in the solution, whereas the coefficient of variation $CV\%$ is defined as follows

$$CV\% = \frac{\sqrt{\text{var}\, k_{ij}}}{k_{ij\ init}} \cdot 100\%. \qquad (10)$$

Table 1: The parameter estimates of the one-compartmental model of *gonadotrophin* distribution, their variances and coefficients of variation.

Input	u_{opt}	u_{step}
k_{01}	0.0260	0.0256
$\text{var}\, k_{01} \cdot 10^{-7}$	2.83	14.24
$CV\left[\%\right]$	2.00	4.49

Table 2: The parameter estimates of the two-compartmental model of *gonadotrophin* distribution, their variances and coefficients of variation.

Input	u_{opt}	u_{step}
k_{01}	0.0278	0.0272
$\text{var}\, k_{01} \cdot 10^{-7}$	6.09	29.96
$CV\left[\%\right]$	2.72	6.03
k_{12}	0.4605	0.4760
$\text{var}\, k_{12} \cdot 10^{-4}$	7.79	25.63
$CV\left[\%\right]$	6.54	11.86
k_{21}	0.1109	0.1074
$\text{var}\, k_{21} \cdot 10^{-5}$	4.14	10.99
$CV\left[\%\right]$	5.41	8.81

It follows from Table 1 and Table 2 that the variances and coefficients of variation $CV\%$ obtained for the optimal input are smaller than those obtained for the non-optimal, step input, both for the one and two-compartmental models of *gonadotrophin* distribution.

The parameter estimates of the one and two-compartmental models of *tetracycline* distribution, their variances and coefficients of variation $CV\%$ are presented in Table 3 and Table 4, respectively. The results presented were obtained for the optimal input u_{opt} and compared to the results obtained for the non-optimal step input u_{step} of duration $T_{step} = 0.5h$.

Table 3: The parameter estimates of the one-compartmental model of *tetracycline* distribution, their variances and coefficients of variation.

Input	u_{opt}	u_{opt}	u_{opt}	u_{opt}	u_{step}
$T_f\,[h]$	1.0	1.5	2.0	2.5	1.0
k_{01}	0.1079	0.1059	0.1115	0.1069	0.1065
$\text{var}\, k_{01} \cdot 10^{-4}$	2.42	0.61	0.26	0.14	3.65
$CV\left[\%\right]$	14.40	7.25	4.76	3.44	17.72

Four observation intervals $T_{f_2} = 1.0, 1.5, 2.0, 2.5\,h$ were considered in order to improve the accuracy of the parameter estimates.

ISSN: 1727-1983

Table 4: The parameter estimates of the two-compartmental model of *tetracycline* distribution, their variances and coefficients of variation.

Input	u_{opt}	u_{opt}	u_{opt}	u_{opt}	u_{step}
u_{opt}	1.0	1.5	2.0	2.5	1.0
k_{01}	0.0913	0.0891	0.0949	0.0904	0.0899
$\mathrm{var}\, k_{01} \cdot 10^{-4}$	2.59	0.68	0.30	0.16	3.89
$CV[\%]$	17.62	9.02	6.02	4.40	21.59
k_{12}	0.3493	0.2675	0.1638	0.2941	0.5399
$\mathrm{var}\, k_{12} \cdot 10^{-2}$	45.18	5.32	1.18	0.60	110.60
$CV[\%]$	265.64	91.17	42.84	30.59	415.64
k_{21}	0.0756	0.0727	0.0797	0.0749	0.0741
$\mathrm{var}\, k_{21} \cdot 10^{-4}$	3.04	0.87	0.43	0.25	4.48
$CV\%$	23.08	12.37	8.66	6.64	28.01

When the observation interval T_f of the optimal and non-optimal input is the same, the obtained variances and coefficients of variation $CV\%$ of all parameters are smaller for the optimal input. It follows from both Table 3 and Table 4 that the accuracy of the parameter estimates improves as the observation interval T_f increases.

Standard vs. individual therapy

In standard *tetracycline* therapy at first the saturation dose $D_{sat} = 500\,mg$ is routinely administered to the patient. Doses $D = 250\,mg$ are then administered with a repetition period of $T_{rep} = 8\,h$ [8]. However, with the standard therapy the concentration of *tetracycline* in the plasma of the patient under examination reaches the therapeutic level, equal to $4\,\mu g/ml$, only in short time intervals (see Figure 5), which is insufficient to achieve the therapeutic effect.

In the individual therapy the dose $D_{ind} = 375\,mg$ has to be administered to the patient with an individual repetition period of $T_{rep\,ind} = 6\,h$. The individual therapy ensures that the plasma concentration of tetracycline exceeds the therapeutic level. This proves the importance of the individually designed therapy.

Conclusions

The results presented in Tables 1÷4 show that the best accuracy of the parameter estimates, of both the one and two-compartmental models, is achieved for optimal inputs (both equidose and equienergy optimal inputs). The accuracy of the parameter estimates is described by the parameter variances and the coefficients of variation.

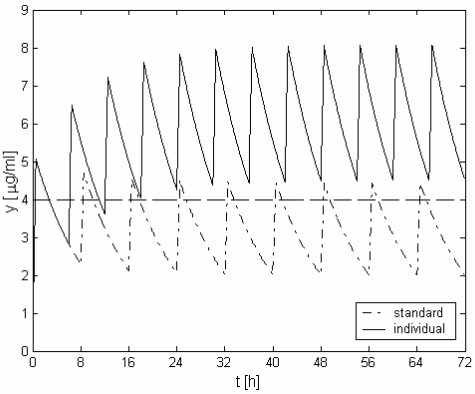

Figure 5: The concenntration of *tetracycline* in the plasma of the examined patient: individual therapy (solid line) and standar therapy (dash-dotted line).

It follows from Table 3 and Table 4 that the longer the observation interval is, the better the parameter accuracy achieved. Still, a longer observation interval is more strenuous for the patient. It is, therefore, desirable to find the length of the observation period which ensures an acceptable accuracy of the parameter estimates but which is, on the other hand, sparing for the patient.

The designed equidose optimal inputs take the form of bolus of very short duration (such as injections). This result is very convenient from the practical point of view, as injections are commonly used in clinical practice. However, the dose-constrained optimal inputs are not admissible for medicines which show rate-dependent side-effects. For these medicines the energy-constrained class of admissible inputs has to be considered. The shapes of the equienergy optimal inputs are not conventional ones and the inputs have to be administered using special volumetric pumps. These pumps are not commonly used nowadays, yet the rapid development of computer controlled volumetric pumps suggests the possibility of adopting equienergy optimal inputs for model parameter identification purposes in the future.

References

[1] KHOO, M.C.K., (2000): 'Physiological control systems', IEEE Press, New York
[2] GOODWIN, G.C., PAYNE, R.L. (1977): 'Dynamic system identification: Experiment design and data analysis', Academic Press, INC., London
[3] BRANDT, S. (1999): 'Data analysis', PWN, Warszawa
[4] COBELLI, C., RUGGERI, A., THOMASETH, K. (1985): 'Optimal input and sampling schedule for physiological system identification', in EISENFELD, J., DELISI, C. (Eds): 'Mathematics and Computer in Biomedical Applications', (Elsevier, New York), pp. 161-172

ISSN: 1727-1983

[5] FINDEISEN, W., SZYMANOWSKI J., WIERZBICKI A. (1980): 'Teoria i metody obliczeniowe optymalizacji', PWN, Warszawa
[6] MEHRA, R.K. (1974): 'Optimal inputs for linear system identification', *IEEE Trans. on Automatic Control*, **19,** pp. 192-200
[7] R. E. KALABA, K. SPRINGARN (1981): 'Optimal inputs for blood glucose regulation parameter estimation, Part 3', *J. of Optim. Theory and Applications*, **33**, pp. 267-285
[8] multi-author work, (2004): 'Pharmindex – Kompendium leków – 2004', Medimedia, Warszawa
[9] COBELLI, C., THOMASETH, K. (1988): 'On optimality of the impulse input for linear system identification', *Math. Biosci.*, **89**, pp. 127-133
[10] GODFREY, K. (1983): 'Compartmental models and their application', Academic Press, New York
[11] GYRD-HANSEN, N., RASMUSSEN, F., SMITH, M. (1981): 'Cardiovascular effects of intravenous administration of tetracycline in cattle', *J. Vet. Pharmacology and Therapeutics*, **4**, pp. 15-25
[12] KALICKA, R. (2000): 'Modelowanie procesów kinetycznych w systemach biomedycznych', Wydawnictwo Politechniki Gdańskiej, Gdańsk
[13] Univ. Of Alberta, Faculty of Pharmacy and Pharmaceutical Sciences, Internet site address: http://www.pharmacy.ualberta.ca/
[14] LJUNG, L. (1999): 'System identification - Theory for the user', Prentice-Hall, New Jersey

ISSN: 1727-1983