Kybernetika

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This article describes a method for estimating biological system parameters. This method is realized in the form of hybrid programme OPTIM on the hybrid computing system EAI 690.

1. INTRODUCTION

A basic problem in biological modelling is the estimation of parameters of the model under study. As the object of biological modelling is to obtain a better knowledge of the mechanism and regulation loops involved in the metabolic and other processes in the body, we are not really confronted with the problem of the "black box" in identifying the biological system. Our problem is, as a rule, estimation of the parameters of the dynamic system as a mathematical model of the biological system, while the structure of the former is given or supposed on the basis of certain a priori information. This method is best represented by the block diagram (Fig. 1).
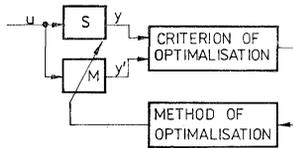

Fig. 1. Parameter estimation principle (S — system, M — model).

The task is to find parameters of the model M to obtain optimal agreement between the biological system S and model M according to the criterion selected.

The process of searching the optimal vector of parameters may be formulated as

searching such a vector of parameters $p^{opt} \in P$ for which the following inequality holds:

(1) $$F(p^{opt}) \leqq F(p) \quad \text{for all} \quad p \in P$$

where $P \subset R^r$ is the space of admissible parameters.

The space of admissible parameters P is a set of all parameter values of some significance physically and mathematically. For criterion let us suppose a weighted sum of square deviations between the output of the model $M(Y')$ and the output of the system $S(Y)$:

(2) $$F(p) = (Y - Y')^T \cdot R^{-1}(Y - Y')$$

where R is the weight matrix. To compute the respective criterion value $F(p)$ for the given vector of parameters p, it is necessary to solve the differential equations describing the multicompartmental system. We are faced, therefore, with a dynamical optimization as we do not obtain the criterion value immediately but only after completion of the dynamic response. The process of minimization of criterion $F(p)$, i.e. construction of such a sequence of vectors $p^i \in P$, $i = 0, 1, \ldots$ converging to p^{opt} irrespective of the choice of the initial estimate p^0, performs the method of optimization. The literature [2] describes many optimization methods whose applicability depends on the form of criterion $F(p)$, in this case on the mathematical model of the multicompartmental system. Despite the high number of reports there is no method permitting to find the absolute minimum. Criterion $F(p)$ has often several local minima so that we occassionaly do not find the true p^{opt} but some suboptimal value p. Therefore it is necessary to investigate the whole space of admissible parameters P by choosing several initial p^0 estimates conveniently distributed in the space P. Then, the smallest of the minima found is the absolute minimum. This method of searching absolute minimum is, however, elaborate and time consuming owing to high machine-time consumption. From the point of view of time consumption it seems therefore preferable to define the parameter subspace in which the parameters of the investigated system are to be found. This problem can be resolved by manual optimization, i.e. by defining approximate parameter values based on subjective evaluation of the agreement of the courses computed and experimentally measured by means of an analog computer. Some of the parameter values can be assessed numerically and/or graphically from the courses recorded. However, this procedure is also very time consuming and laborious for the programmer.

We have obtained very good results with the OPTIM programme. The programme is composed of two parts:

1. Global random optimization for assessing the suboptimal starting point.
2. Optimization using the method of Powell's minimization [2].

The first part performes a random search in the whole space of parameters P and determines the suboptimal vector of parameters in the vicinity of absolute minimum,

i.e. the starting point for optimization by Powell's method of minimization. The
second part of programme determines the absolute minimum of the criterion with
adequate accuracy, i.e. the optimal vector $\boldsymbol{p}^{\text{opt}}$.

2. DESCRIPTION OF THE METHOD OF GLOBAL OPTIMIZATION

The purpose of this part of the OPTIM programme is to determine the suboptimal
vector of parameters in the vicinity of absolute minimum of the function $F(\boldsymbol{p})$, i.e.
the starting point of the POWMIN-optimization procedure. Let

$$(3) \qquad \boldsymbol{p} = [p_1, p_2, \ldots p_n]^{\text{T}}$$

be vector of parameters and

$$(4) \qquad \bar{P} = \{\boldsymbol{p} : p_i \in \langle p_i^{\min}, p_i^{\max}\rangle, \ i = 1, 2, \ldots, n\}$$

be the set of admissible parameters. Let P be the interior of set $\bar{P}$. Thus we should
find the absolute minimum of function F, while fulfilling the limiting conditions:

$$(5) \qquad p_i^{\min} \leqq p_i \leqq p_i^{\max}, \quad i = 1, 2, \ldots, n \,.$$

The method consists of the following steps:

1. We calculate criterion value $F(\boldsymbol{p}^0)$ for starting vector of parameters $\boldsymbol{p}^0 \in P$.
2. We generate n normal random numbers $r_1, r_2, \ldots, r_n$ with zero mean and variance
   1. For random vector $\boldsymbol{r} = [r_1, r_2, \ldots, r_n]^{\text{T}}$ thus equalities

$$(6) \qquad E[\boldsymbol{r}] = 0 \,, \quad E[\boldsymbol{rr}^{\text{T}}] = \mathbf{I}$$

   hold, where E is the expectation operator and $\mathbf{I}$ is the identity matrix.

3. On the straight line determined by point $\boldsymbol{p}^0$ and vector $\boldsymbol{r}$ we choose equidistantly
   lying points

$$(7) \qquad \boldsymbol{p}^i = \boldsymbol{p}^0 + ih\boldsymbol{r} \,, \quad i = -2, -1, 0, 1, 2$$

   so that all $\boldsymbol{p}^i \in \bar{P}$. The constant $h > 0$ is the method's parameter that can be
   changed manually from the computer teletype at each successful step of optimiza-
   tion. Provided that some point $\boldsymbol{p}^i \notin \bar{P}$ we gradually reduce the parameter $h =$
   $= \frac{1}{2}, \frac{1}{2^2} \ldots, \frac{1}{2^k}$ k-times until all $\boldsymbol{p}^i \in \bar{P}$. This can be readily accomplished for an
   adequately large k since $\boldsymbol{p}^0$ is supposed to be the interior point of the set $\bar{P}$. In
   practice k should be restricted and if a point $\boldsymbol{p}^i \notin \bar{P}$ for the maximal k we return
   to step 2.
4. The value of function F is calculated in points $\boldsymbol{p}^{-2}, \boldsymbol{p}^{-1}, \boldsymbol{p}^1, \boldsymbol{p}^2$. Restriction

of function F on straight line $\boldsymbol{p}^0 + \lambda h\boldsymbol{r}$ is approximated by the Lagrange's interpolation fourth-degree polynomial

$$(8) \qquad L_4(\lambda) = A\lambda^4 + B\lambda^3 + C\lambda^2 + D\lambda + E$$

whose coefficients can be easily calculated from values of function F at points $\boldsymbol{p}^i$, $i = -2, -1, 0, 1, 2$. If $A = 0$ (in practice $|A| < \varepsilon$ where ε is an appropriate low positive number), we use Lagrange's interpolation second-degree polynomial

$$(9) \qquad L_2(\lambda) = C\lambda^2 + D\lambda + E$$

If $C = 0$ (in practice again $|C| < \varepsilon$ where ε is an appropriate low positive number) we proceed to step 6.

5. In this step we find a minimum of the interpolation polynomial. Using Cardan's formulae, we compute the real zeros of the polynomial $dL_4(\lambda)/d\lambda$ (one or three), or, if $A = 0$, we compute the zero of the polynomial $dL_2(\lambda)/d\lambda$. If polynomial $dL_4(\lambda)/d\lambda$ has three different real zeros we select that for which polynomial $L_4(\lambda)$ acquires the lowest value. In this manner we obtain a certain value λ. We compute $L_4(\lambda)$ or $L_2(\lambda)$. If we obtain $L_4(\lambda) \leqq F_0$ or $L_2(\lambda) \leqq F_0$ we determine a new point

$$(10) \qquad \boldsymbol{p} = \boldsymbol{p}^0 + \lambda h\boldsymbol{r}$$

If $\boldsymbol{p} \notin P$, we return to step 2. If $\boldsymbol{p} \in P$, we calculate value of $F(\boldsymbol{p})$. If $F(\boldsymbol{p}) < F(\boldsymbol{p}^0)$ we shift $\boldsymbol{p} \to \boldsymbol{p}^0$, $F(\boldsymbol{p}) \to F(\boldsymbol{p}^0)$ and begin again from step 1, but we need not compute value $F(\boldsymbol{p}^0)$ as it is available already. If $F(\boldsymbol{p}) \geqq F(\boldsymbol{p}^0)$ we return to step 1 without making, however, any shift (unsuccessful iteration).

6. (This step is made only when $C = 0$.) We compare values $F(\boldsymbol{p}^{-1})$, $F(\boldsymbol{p}^0)$ and $F(\boldsymbol{p}^1)$ and choose the lowest of them. If $F(\boldsymbol{p}^0)$ is the lowest we return to step 2. If $F(\boldsymbol{p}^i)$ is the lowest value, where $i = -1$ or $i = 1$, we shift $\boldsymbol{p}^i \to \boldsymbol{p}^0$, $F(\boldsymbol{p}^i) \to$ $\to F(\boldsymbol{p}^0)$ and start again at step 1, but need not compute value $F(\boldsymbol{p}^0)$ as it has already been obtained.

7. The value of function F and vector of parameters $\boldsymbol{p}$ is printed after each 20 iterations. Calculation ends after the prescribed number of iterations has been completed. One iteration covers calculation starting with step 1 and returning again to step 1. Some iterations may be unsuccessful. This algorithm was realized in the EAI-FORTRAN language as SUBROUTINE GLOBT. Flow diagram of this subroutine is in the Fig. 2. Convergence of the method from the local minimum to absolute minimum is dealt with in detail in literature [3].

3. MINIMIZATION BY POWELL'S METHOD

The object of this part of the programme is to find absolute minimum of $F(\boldsymbol{p})$, i.e. vector $\boldsymbol{p}^{\text{opt}} \in P$ for which $F(\boldsymbol{p}) \geqq F(\boldsymbol{p}^{\text{opt}})$ for all $\boldsymbol{p} \in P$. The starting point of

minimization is the optimal point obtained by SUBROUTINE GLOBT. The method has been analyzed in the literature [2]. It has been employed also in our programme and therefore there is no need to describe it in this paper.
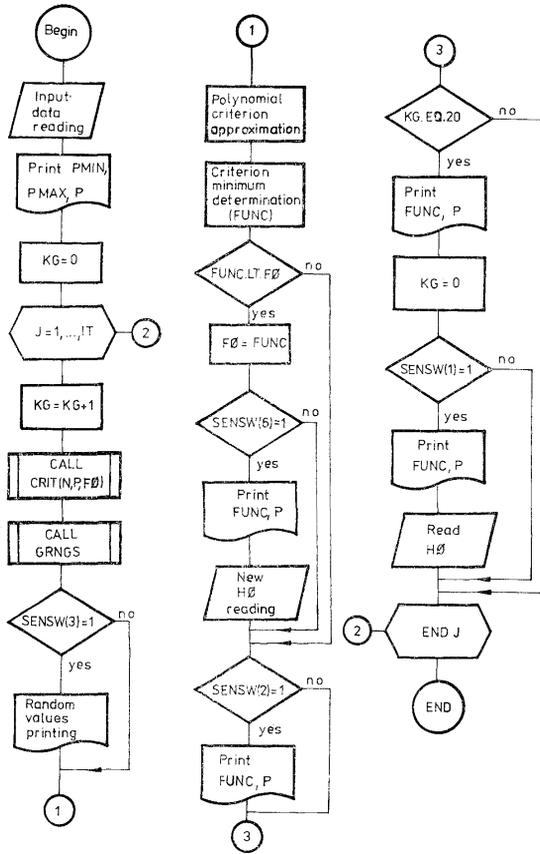
Fig. 2. Flow diagram of subroutine GLOBT.

4. DESCRIPTION OF THE PROGRAMME

The above programme was realized on a hybrid computing system EAI 690. Division of the problem between the analog and digital parts of the hybrid system depends on the nature of the problem involved. The dynamic responses of model M (Fig. 1) are solved by analog part. The digital part of the system contains the own method
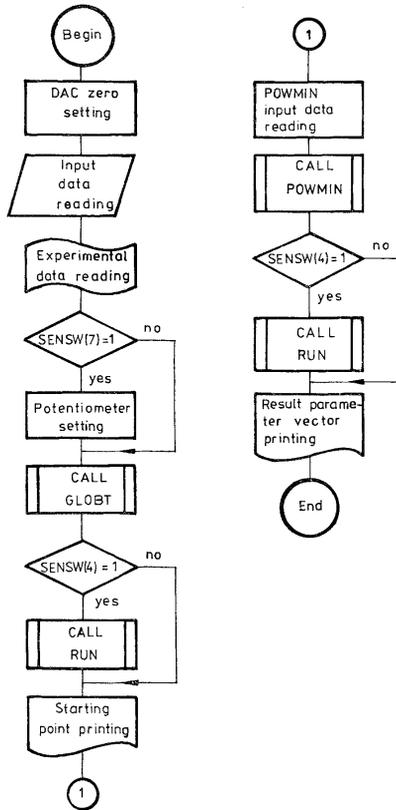

Fig. 3. Flow diagram of the OPTIM source programme.

of optimization and controls the analog computer. To determine the values of criterion $F(p)$ (SUBROUTINE RUN), we used hybrid cooperation. The particular parts of the programme are analyzed in detail in the following paragraphs.

A) *Source programme*

All digital programmes are written in the EAI FORTRAN language. The function of the programme is illustrated by the flow diagram in the Fig. 3. The source programme controls the whole process of computation. The main function of this part is to read-in the data which are necessary for appropriate cooperation between the analog and digital parts during the optimization procedure. This part also reads-in data for the VAZEB subroutine which realizes relating conditions if required by mathematical description. Further, it performs reading experimental values and stores them in two-dimensional array according to space and time coordinates. Moreover, the source programme initiates search of the starting point by calling the GLOBT subroutine and the optimization procedure by calling the POWMIN subroutine.

B) *Subroutine* RUN

This subroutine calculates the value of criterion $F(p)$. An auxiliary function of the subroutine is the printing of sampled and measured values in a table; it is done manually by means of SENSW (4). To compute values of the criterion, the analog and digital parts of the hybrid system cooperate. Synchronous cooperation of the two parts and control of the analog computer are ensured by parallel logic.

The function of subroutine RUN is illustrated by the flow diagram (Fig. 4). It involves equidistant sampling of state variables, selection of samples at time intervals obtained from the experiment and computation of the criterion $F(p)$.

The sampling alone is controlled by parallel logic whose diagram is shown in Figs 5, 6. Output of the TBD unit generates gradually the impulses A, B, C whose length has been chosen so as $A = 1$, $B = 120$, $C = 0$ (Fig. 5). Following the signal from the digital computer the CONTROL LINE OO (CL OO) obtains logical value 1 and solution begins. After completion of period B output A changes from 0 to 1 resulting in generation of blip by the differentiator DIF; the blip is extended by means of flip-flop (TT) to 1 microsecond (synchronisation frequency $f = 10^6$ Hz). Thereby CL 00 changes to 0 and analog solution is stopped. After logical interconnection of the TBD unit and the onset of period B there are blips of frequency of $f = 10$ Hz (in the NORMAL SEC regimen) at the hole marked H on the unit's jack. Each of the blips iniciates reading of the immediate value from the elected analog element transmitted to ADC convertors No. $0-4$ (each blip being extended to 1 microsecond by TT). Owing to the relatively long reading period it is necessary to preserve the immediate value of sample obtained at the time of generating the subsequent blip. This is accomplished by monostable flip-flop MS which ensures preservation of the
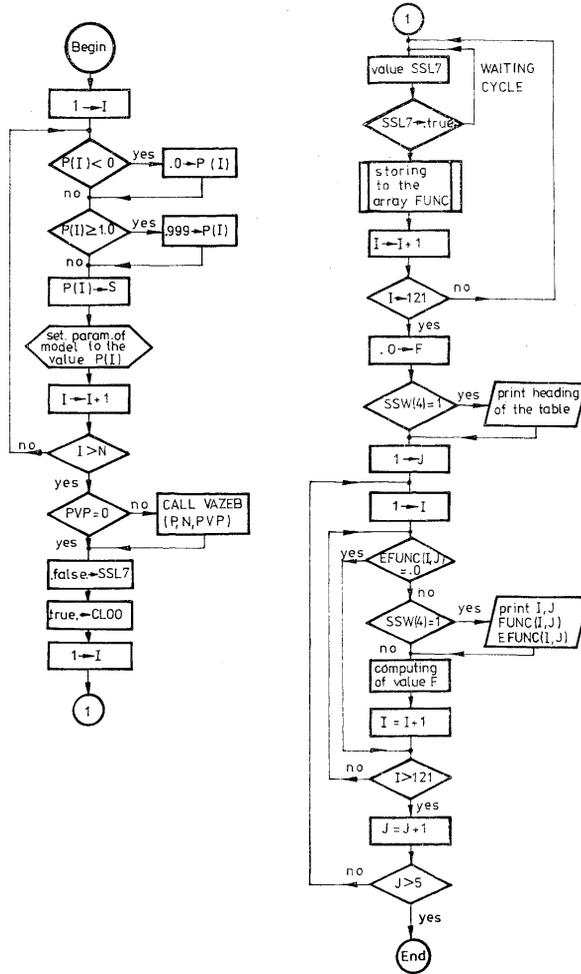
Fig. 4. Flow diagram of subroutine RUN.

value for the length of time desired (in our case $\tau = 1$ ms). The signal from negated output is used to control the analog memory SAMPLE HOLD (S) of the ADC convertors (Fig. 6). The process appears from sample time behaviour in Fig. 7.
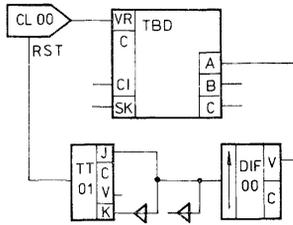

Fig. 5. Logical network generating
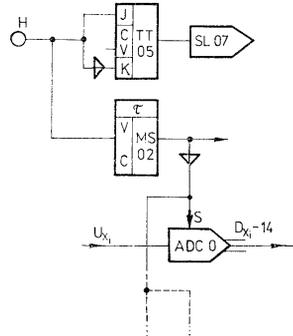logical signals A, B.

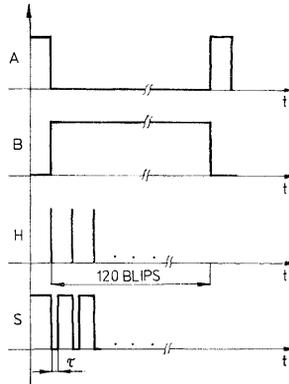Fig. 6. Logical network for sampling
instance control.

Fig. 7. Time sequences of logical signals A, B, H and S.

As shown by Figs. 4 and 7 value SLO7 = 1 iniciates the moment of reading in the ADC convertors. At the time between two reading pulses the computer waits.

This is ensured by the waiting cycle (Fig. 4) written in machine instruction to avoid delay. The communication between the analog and digital parts (i.e. reading and storing analog values, adjustment of potentiometers, digital control of the analog computer regimen and so on) is accomplished by Fortran connecting hybrid programmes from LIKAGE series.

Subroutines HELP and VAZEB have but an auxiliary function and there is no need to analyze them.

5. VERIFICATION OF PROGRAMME FUNCTION

In this Institute the so constructed programme was used to optimize parameters of a multicompartmental biological system. The results of optimization of a model of labelled aldosteron kinetics in the human body are presented for illustration.
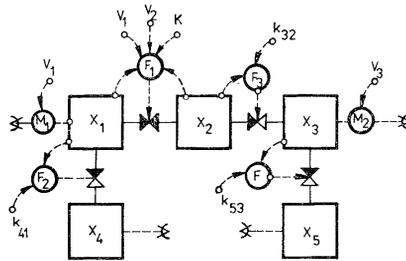

Fig. 8. Compartmental schema of the aldosterone kinetics. ($M_1 = x_1/V_1$, $M_2 = x_3/V_3$, $F_1 = k(x_1/V_1 - x_2/V_2)$, $F_2 = k_{41}x_1$, $F_3 = k_{32}x_2$, $F_4 = k_{53}x_3$).

The respective compartment diagrams of the model are depicted in Fig. 8. The diagram was drawn according to the General Method of Multicompartmental Models [5]. As shown by mathematical analysis of the model described decomposition presents no problem so that the compartment systems X_1, X_2, X_4 can be separately optimized on the basis of measurement of state quantities X_1, X_4. The results obtained by optimization can be utilized as input into the second part of the model consisting of compartments X_3 and X_5; optimization of that part of the model can again be carried out separately using the measurements of state quantities $c_3 = X_3/V_3$, X_5. The results of optimization by means of the OPTIM programme described are represented in Figs 9, 10 (9 showing the result of global optimization, i.e. the procedure of obtaining the starting point, 10 those of Powell's minimization,

Fig. 9. Results of the global optimization method. (Exp. values: $+ - x_1$, $\circ - c_3 \cdot 10$, $\square - x_5$, $* - x_4 \cdot 10$.)

NORMS:
$N_{x_1} = 100 \, [\%]$
$N_{c_3} = 10 \, [\% \, l^{-1}]$
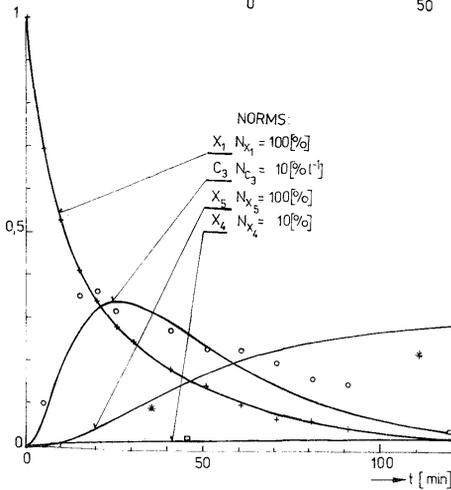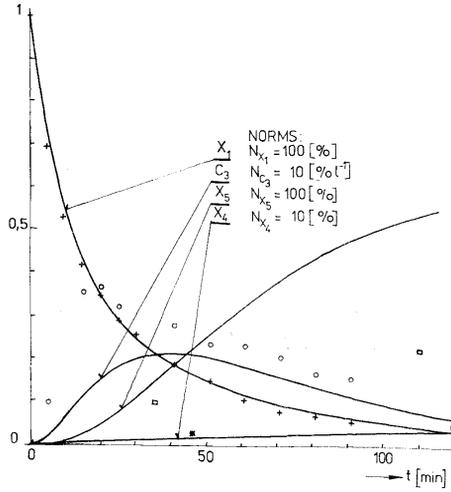$N_{x_5} = 100 \, [\%]$
$N_{x_4} = 10 \, [\%]$

Fig. 10. Results of the Powell's method with starting point obtained by the global optimization method. (Exp. values: $+ - x_1$, $\circ - c_3 \cdot 10$, $* - x_5$, $\square - x_4 \cdot 10$.)

remaining differences caused by inadequacy of structure of the metabolic part of the model).

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