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NONLINEAR SYSTEM MODELS BASED ON INTERVAL LINEARIZATION: A MEDICAL APPLICATION

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Abstract: The paper deals with an application of models based upon interval linearization in modelling human organism parameters, especially during long-term medical treatments. The generated model enables to predict patient's state as well as the impact of taken therapeutics on it. Application of such models brings about improvement of the treatment quality and helps physicians in the decision making process. *Copyright © 2003 IFAC*

Keywords: identification, interval linearization, parameters of human organism, state prediction, nonlinear systems

1. INTRODUCTION

In the medical practice there are often encountered diseases requiring a long-term treatment whereby it is almost impossible to continuously monitor the organism parameters. Very often, physicians are obliged to go repeatedly through a huge amount of data acquired from the blood, urine and other analyses, to be able to take decisions based upon the patient´s state. This process can be supported by creating a model of patient's state, based on which it is possible to take a correct decision. Therefore we focused on the identification of human organism parameters under long-term medical treatments. Results of blood tests, creation of their model and its application in the patient's state prediction have facilitated the decision making about additional interventions during the treatment, which helped to improve the whole process. For the identification and model generation we have used the interval linearization method.

2. NONLINEAR SYSTEM IDENTIFICATION

2.1. *Identification using the interval linearization method*

The interval linearization method is one of relatively new methods for nonlinear systems modelling. Basically, it differentiates from other identification and modelling approaches for such systems, one of which consists in substituting the real system by a set of nonlinear functions and relations which describe processes in the system (the human organism can be considered as a system); another possibility is substitution of the real system by a mathematical model acquired by its linearization in a chosen operating point, or it is possible to create abstract nonlinear models.

The interval linearization method offers a substantially different approach, generating a linear model created not only for one operating point but for a whole region called a linearization interval [1]. Such a model is able to include properties of the given system, whereby it requires neither to create so many models as in case of linearization in the operating point, nor to search intricate nonlinear functions which implementation is often questionable.

Identification of nonlinear dynamic systems by the interval linearization method has been invented in 1986. The method has been updated several times by improving some of their properties or the identification process itself [2] [3]. The presented method has been applied not only in nonlinear system modelling but also in designing controllers for nonlinear systems [4].

Identification of nonlinear dynamic systems consists in splitting the whole working range of the input and output variables by the limits uk_i and yk_i, respectively, into several intervals (from where the name of the method). Intersect of these intervals defines the linearization interval (Fig. 1).

Generating a system model using this method requires availability of the measured input and output data. Measurements are to be carried out during the system operation and organized in a table. Next, the limits of individual intervals for the input and output variables are to be specified. Intersect of these intervals defines the linearization section. For every nonlinear system there can be several such sections and the identification yields model of each linearization section in the following form

$$y(t) = q_0^k + \sum_{i=1}^{ny} q_i^k y(t - iT) + \sum_{j=1}^{nu} q_{ny+j}^k u(t - (j - d + 1)T) \quad (1)$$

or concisely

$$\mathbf{y}(t) = \mathbf{z}(t)\, \mathbf{q}^k \qquad k=1,2....kk \quad (2)$$

where

$$\mathbf{z}(t)=[1,y(t-1),....,y(t-ny),u(t-d-1),....,u(t-d-nu+1)] \quad (3)$$

$\mathbf{q}^k$ is vector of model coefficients in the k-th linearization section, whereby

$$\mathbf{q}^k = (q_0^k, q_1^k, ..., q_{nu+ny}^k) \quad (4)$$

nu – number of samples of the input variable

ny - number of samples of the output variable

t - time

T – sampling time

d – input variable shift

k - index of the linearization interval

A total number m of linearization intervals for nu =1 and ny= 1 is

m = mu.my

and for nu> 1 and ny > 1 the number of linearization intervals is given by

$$kk = mu^{nu}.my^{ny} \tag{5}$$

The procedure for determining the index "k" of the linearization interval is as follows. If the output variable y(t-i), i=1,2....ny is from the amplitude band (yk_{s-1}, yk_s), s =1,2.....my, then this band is denoted by I_i=s. Similarly, if the variable u(t-j-d+1), j=1,2...nu is from the band $(uk_{r-1}, uk)_r$, r =1,2.....mu, the corresponding band is denoted I_{ny+j} = r. These bands notations are collected in a vector $I=(I_1, I_2...I_{nu+ny})$. The linearization interval index is calculated as follows

$$k = I_1 + \sum_{l=2}^{mu+my} (I_l - 1).\delta_l \tag{6}$$

where

$$\delta_l = my^{(l-1)} \quad \text{for } l=1,2.....ny \tag{7}$$

$$\delta_{l+ny} = my^{ny}.mu^{(l-1)} \quad \text{for } l=1,2.....nu \tag{8}$$

l – auxiliary index

For many systems, long-term operation measurements of u(t), y(t) proved, that in practice, the number of linearization intervals does not comply with their theoretical number and strongly depends on the appropriateness of chosen limits and the volume of measured data available.

Calculation of the linear model (1) or (2) for the k-th linearization interval consists in determining the vector of linearization coefficients (4) from measured samples y(t-i) and u(t-j-d+1) for i=1.....ny, j=1.....nu, within the k-th inearization interval.

The model itself is then specified from the relation $\mathbf{A}^k\mathbf{q}^k = \mathbf{b}^k$, from which we express the vector of the model $\mathbf{q}^k$ in the k-th linearization section using the least squares algorithm. To apply it, it is necessary to se tup the matrix $\mathbf{A}^k$ from measured values y(t-i) and u(t-j-d+1) and the vector b^k from measured values y(t). For the k-th row of the matrix $\mathbf{A}^k$ holds

$$a^k_{r,i-1} = y(t-i) \quad \text{for } i=1,2....ny \tag{9}$$

$$a^k_{r,j-1+ny} = u(t-j-d+1) \quad \text{for } j=1,2.....nu$$

$$a^k_1 = 1$$

The r-th entry of the vector $\mathbf{b}^k$ satisfies

$$b^k_r = y(t-0) \tag{10}$$

where r = 1,2... n : ny+nu+1 < n

The identification result is the matrix **Q**

$$\mathbf{Q} = \begin{pmatrix} q^1_0 & q^1_1 & \dots & q^1_{nu+ny} \\ \vdots & & \dots & \vdots \\ q^k_0 & q^k_1 & \dots & q^k_{nu+ny} \\ \vdots & \vdots & \dots & \vdots \\ q^m_0 & q^m_1 & \dots & q^m_{nu+ny} \end{pmatrix} \tag{9}$$

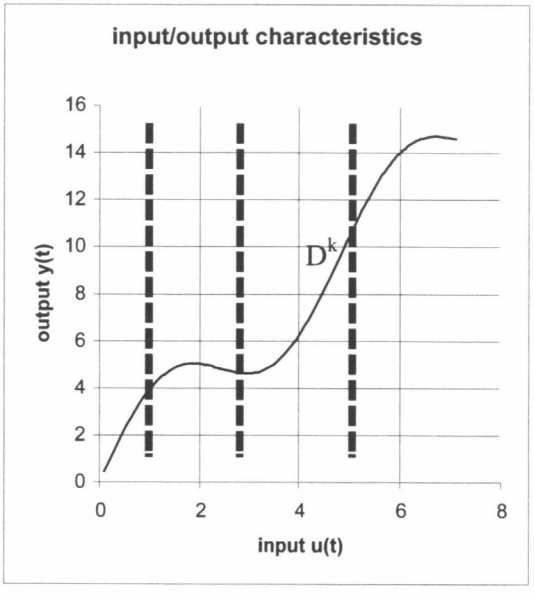

Fig.1. Input/output characterisics of the system

3. IDENTIFICATION OF BLOOD SYSTEM PARAMETERS

3.1. Data measurement

The considered method was verified in modelling leucocytes parameters for one year. During a one-year chemotherapeutic treatment blood samples were taken sporadically and individual parameters were measured. Values of individual parameters are organized in a table (Tab. 1). Input variables are values of used therapeutics (V - vincristin, CP – cysplatinum), or of certain supporting preparations (S), applied in cases when the organism parameters have decreased considerably. Output parameters are HG, Ery, HKG, LE, TR. Medicine intake is denoted by „1" in the day of application.

Tab.1. Measured values of blood parameters during the initial period

Date	N	INPUTS Cyk	V	CP	S	OUTPUTS HG	Ery	HKG	LE	TR
14.07.99	1	1	1	1	1	118	3.7	0.29	2.1	186
20.07.99	6	7				124	4.4	0.37	1.6	225
22.7.99	2	9		1		117	4.09	0.37	1.8	205
29.7.99	7	16		1		93	3.26	0.37	1.52	143
31.7.99	2	18				98	3.37	0.38	1.2	149
3.8.99	3	21				64	2.32	0.1	1	110
5.8.99	2	23				82	2.86	0.37	1.24	143
25.8.99	20	43	2	1	1	126	4.13	0.35	2.9	224
2.9.99	8	51		1		113	3.7	0.37	1.58	184
6.9.99	4	55				95	3.09	0.38	1.04	108
9.9.99	3	58		1		95	3.41	0.27	1.3	145
21.9.99	12	70				109	3.49	0.38	1.33	117
27.9.99	6	76				104	3.4	0.38	1.2	123
6.10.99	9	85				113	3.74	0.36	1.08	281
13.10.99	7	92				117	3.76	0.37	1.65	243
2.11.99	5	112				96	3.18	0.38	0.74	138
5.11.99	3	115				94	3.3	0.27	0.8	149
9.11.99	4	119				101	3.35	0.36	1.1	187

A graph of some monitored quantities is in Fig.2 whereby the leucocytes, which characterize patient's immunity are the most interesting parameter.

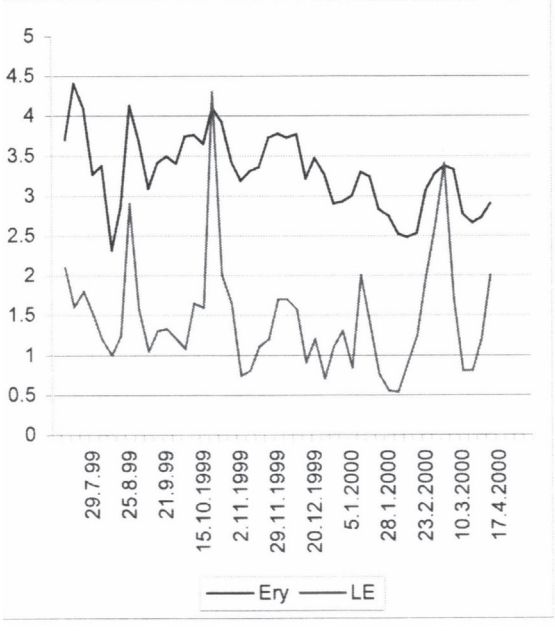

Fig.2 Measured values of some monitored quantities

3.2. Processing of measured data

As the input data were measured in various time intervals, they need to be pre-processed and appropriately adapted for next computations. Computed intervals between individual measurements and missing values have been interpolated so as to reflect in the best way the values expected in the considered time.

The simplest interpolation method is the linear interpolation. For values in individual days it substitutes the values obtained by a uniform distribution of the states between two measured values.

The quadratic interpolation method is a more advantageous one, using a quadratic approximation of values between two measurements. Though it is quite computationally demanding it follows better continuous changes of individual parameters.

Input variables have been substituted by exponentials reaching their maximum at application time of basic therapeutics when their concentration in organism decreases successively. The exponential forgetting factor changes with each considered variable.

	V	CP
A.	1	1
D	0.3	0.04

Table 2 summarizes values of measured, and interpolated (linearly and quadratically) values. Measured values of individual variables are shown in Fig. 3. Comparison of linearly and quadratically interpolated values is depicted in Fig. 4. In measurement instants values of individual functions coincide. Leucocytes and input variable values used for modelling are shown in Fig. 5

Tab. 2. Approximation of selected parameters of the organism

days	V	CP	S	HG	Ery	HKG	LE	HG	Ery	HKG	LE
1	1	1	0	118	3.7	0.29	2.1	119	3.73	0.29	2.08
2	0.7408	0.9608	0	119	3.82	0.3	2.02	119	3.73	0.29	2.08
3	0.5488	0.9231	0	120	3.93	0.32	1.93	122	4.01	0.31	1.89
4	0.4066	0.8869	0	121	4.05	0.33	1.85	125	4.22	0.33	1.74
5	0.3012	0.8521	0	122	4.17	0.34	1.77	126	4.37	0.35	1.64
6	0.2231	0.8187	0	123	4.28	0.36	1.68	127	4.44	0.36	1.58
7	0.1653	0.7866	0	124	4.4	0.37	1.6	126	4.46	0.37	1.57
8	0.1225	0.7558	0	121	4.25	0.37	1.7	124	4.4	0.37	1.61
9	1.0907	0.7261	0	117	4.09	0.37	1.8	120	4.24	0.37	1.72
10	0.808	0.6977	0	114	3.97	0.37	1.76	116	4.07	0.37	1.81
11	0.5986	0.6703	0	110	3.85	0.37	1.72	109	3.84	0.37	1.85
12	0.4435	0.644	0	107	3.73	0.37	1.68	103	3.65	0.37	1.86
13	0.3285	0.6188	0	103	3.62	0.37	1.64	98.6	3.5	0.37	1.85
14	0.2434	0.5945	0	99.9	3.5	0.37	1.6	95.2	3.38	0.37	1.8
15	0.1803	0.5712	0	96.4	3.38	0.37	1.56	93.2	3.3	0.37	1.74
16	1.1336	0.5488	0	93	3.26	0.37	1.52	92.4	3.26	0.37	1.64
17	0.8398	0.5273	0	95.5	3.32	0.37	1.36	95.5	3.33	0.39	1.5
18	0.6221	0.5066	0	98	3.37	0.38	1.2	99.3	3.43	0.4	1.33

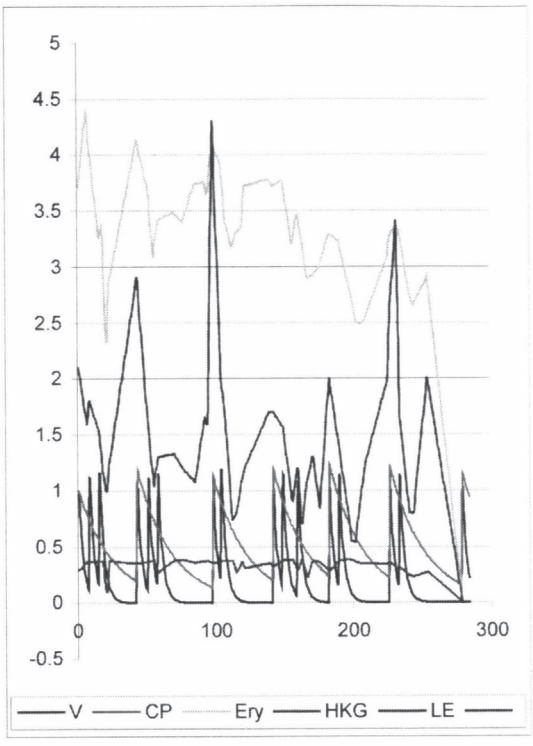

Fig. 3 Graphical representation of the linear approximation of selected organism parameters

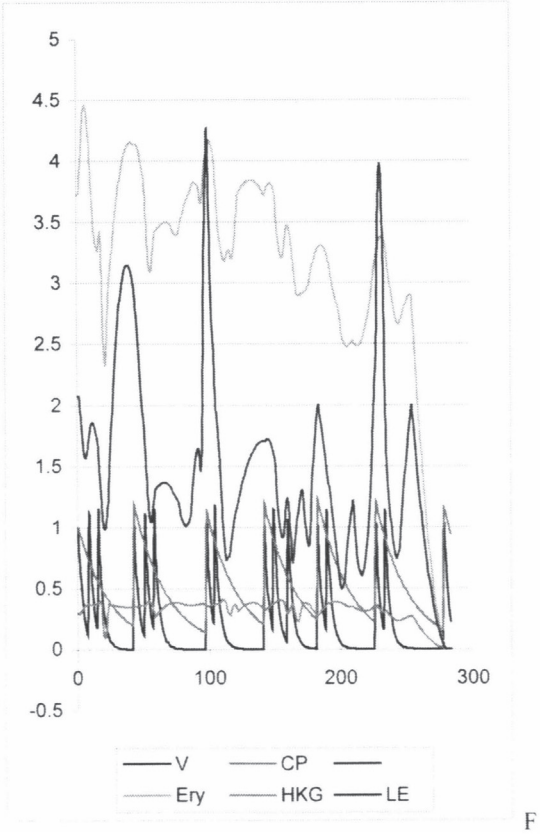

Fig. 4. Quadratic approximation of selected parameters of the organism

For modelling blood parameters we have chosen one of its most important representatives, namely the number of leucocytes indicating patient's state with respect to the possible application of chemotherapeutics. Even the state of leucocytes (along with other parameters, of course) determines whether it is possible to give the patient the therapeutics or not.

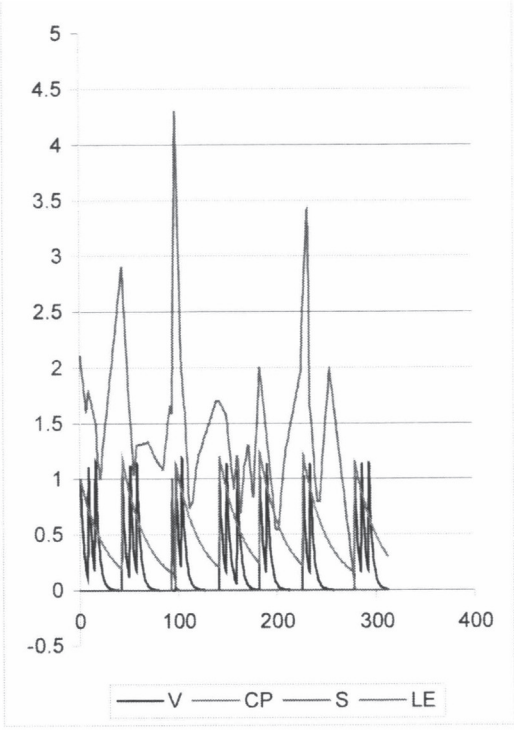

Fig. 5 Parameters of the input therapeutics and the response of the organism - leucocytes

3.3. Search of linearization intervals

A serious drawback of the described method is the search for linearization intervals, i.e. specification of limits for individual intervals. In practice this problem is being solved in various ways. As medical processes are relatively slow a stepwise changing the limits of domains and ranges of individual variables can solve this problem.

Next, a model is calculated for all obtained intervals, and a simulation is carried out with the already available samples. Individual models are compared using the classical method of summing squared differences between the measured and the calculated values. Using a graphical representation of individual input variables and modified values of squared error sums for each model we can find the intervals with the least difference between the model outputs and the real values. Table 3 shows values of some limits (hr1, hr2, hr3, hr4 and the "sqe" – sum of squared errors).

Tab.3 Sum of squared errors (sqe) as a function of limits

pc	hr1	hr2	hr3	hr4	sko
1	0.1	0.5	0.7	2.4	0.39
2	0.1	0.9	0.4	2.4	0.58
3	0.1	0.5	0.7	1.4	0.71
4	0.1	0.1	1	0.4	1.08
5	0.1	0.5	1	0.8	1.38
6	0.3	0.1	0.4	0.2	2.44
7	0.1	0.5	0.7	2	25
8	0.1	0.3	0.1	0.4	97.3
9	0.1	0.7	0.1	0.4	124
10	0.1	0.3	1	1.2	282
11	0.1	0.1	1	0.6	340
13	0.1	0.7	1	0.6	388
14	0.1	0.1	1	1.2	
15	0.1	0.9	0.7	2.6	0.41
16	0.1	0.7	0.7	0.4	0.61
17	0.1	0.3	0.7	1.2	0.83
18	0.1	0.7	1	1.2	1.12
19	0.1	0.5	0.1	2	1.47

For the next analysis a model with the limits (hr1, hr2, hr3,hr4) = (0.3:0.3:0.7:0.5) has been chosen. Mathematical model and simulated data are in Fig. 6.

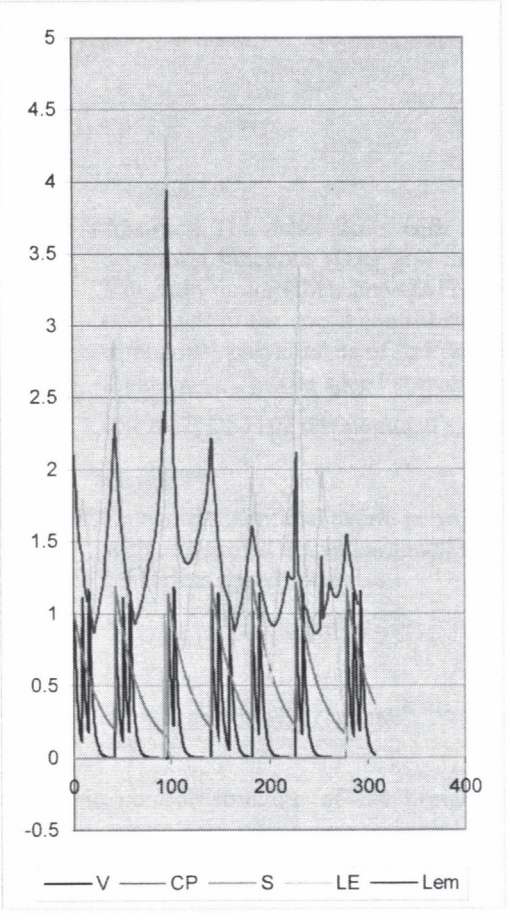

Fig. 6 Simulation of LE parameters

4. APPLICATION OF GENERATED MODELS

4.1. Problems of patient's treatment.

Application of some therapeutics may bring about a considerable worsening of some human organism parameters and thus their intake is possible only under the assumption that the patient tolerates such a treatment. One of such procedures is the application of cytostatics in curing oncogenous diseases. Application of therapeutics is possible only if the leucocytes parameters have reached some specified value (2000). To find out the patient's actual state it is necessary to take his blood, evaluate the parameters and to continue the treatment under the assumption that the state is sufficiently good. If there are low leucocytes, the blood taking has to be repeated after 1-3 days. Such frequent blood takings disturb the patient, and make him suffer. Taking into account his overall state, such a large number of blood withdrawals cannot contribute to an improved recovery. On the other hand frequent blood takings are important because it is necessary to apply the therapeutics in the specified time (necessity to keep the curative procedures) or with a least possible delay.

It use to happen that despite numerous tests, the patient's state does not improve and in order to keep certain curative procedures it is necessary to apply supporting and stimulating pharmaceuticals.

It is especially the decision making about whether to make the patient suffer or stimulate the organism all the same, which can be facilitated by the proposed parameter model.

From Fig. 6 it is evident that in the last 250 –300 days of curing, the leucocytes (LE) number drops and at the time of therapeutics application it even does not reach the lower limit 2.

4.2. Simulation of the medical treatment

Based on the analysis of measured data and simulation of the possible patient's state (Fig. 6) it is possible to assume that the patient's state will remain on a low level for a long-time and he cannot be given the relevant therapeutics due to it.

In a standard treatment the doctor takes the blood samples several times and after having gathered long-term results he decides to skip one cycle. Some of the following facts underlie such a decision:

- on checking parameters he supposed that the patient's state will improve, however this did not happen:
- there was a possibility of helping by other means, however relatively much time has passed since then and therefore such a stimulation is already inappropriate.

Of course, there are a lot of other facts to be considered in a physician's decision making. Simulation of patient's state before starting a new curing cycle could be one possible tool for helping his decision taking. The obtained model shows that the organism parameters are relatively low and the patient is not able to create a sufficient amount of necessary sub-

stances. Should these facts be confirmed by the results from the first blood test, the physician can consider application of stimulating therapeutics, supporting this decision by a simulation on the models.
In a real situation we have first simulated the impact of the blood transfusion on other parameters. Transfusion was carried out already at about the 100th day of the curing procedure. Simulation results under stimulator application are depicted in Fig. 7. Based on obtained results (growth of the LE value above 3) correctness of such a decision could have been anticipated.

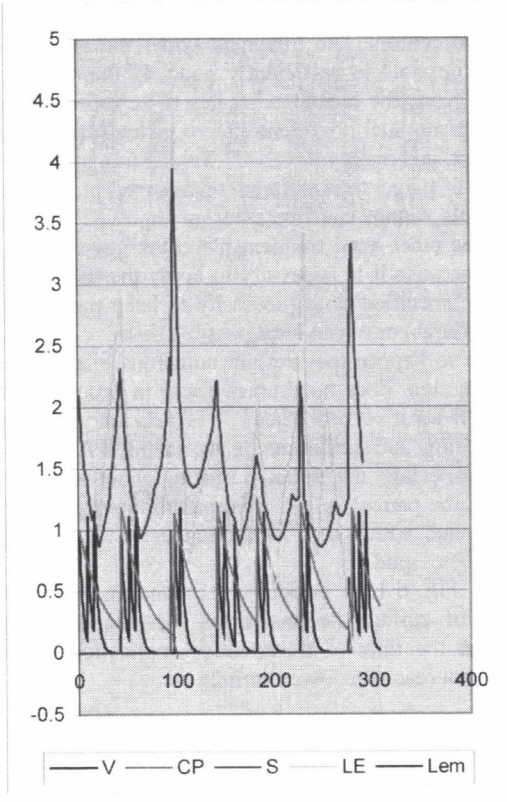

Fig.7 Simulation of LE parameters after application of a stimulator

Then the transfusion was completed and the whole curative cycle was completed successfully.
Of course, the experience of physicians played an important role in the whole treatment process as well, and the proposed model has served only as one supporting tool for the decision-making.

CONCLUSION

The aim of this paper was to present a practical application of one of the dynamic systems identification methods in medicine. At the same time we wanted to emphasize that implementation of identification, modelling, simulation and control methods in this field not only improves the treatment process but can remove lot of ache in this treatment as well, and enables a more exact decision making, often even saving the patient's life.

Certainly, the interval linearization method is not the only suitable one but hopefully it is not the last one applied in medicine, and its implementation will stimulate application of other methods as well.

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