

Computer-aided Analysis of Physiological Systems

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Abstract: This paper presents the recent biomedical engineering research activity of the Medical Informatics Laboratory at the Budapest University of Technology and Economics. The research projects are carried out in the fields as follows: Computer aided identification of physiological systems; Diabetic management and blood glucose control; Remote patient monitoring and diagnostic system; Automated system for analyzing cardiac ultrasound images; Single-channel hybrid ECG segmentation; Event recognition and state classification to detect brain ischemia by means of EEG signal processing; Detection of breathing disorders like apnea and hypopnea; Molecular biology studies with DNA-chips; Evaluation of the cry of normal hearing and hard of hearing infants.

Keywords: biomedical systems, physiological models, image analysis, signal processing, detection algorithms

1 Introduction

Education, research and development related to the biomedical engineering are the main activities of the Biomedical Engineering Laboratory at the Budapest University of Technology and Economics. Several research and development project has been carried out in the Lab during last fifteen years. The main research areas of the last few years are briefly presented in this article.

2 Computer-aided Identification of Physiological Systems

The computer analysis is a set of theoretical processes, allowing us to describe the behaviour of biological systems in terms of a mathematical model. Therefore, in medical-biological researches the computer analysis carries the same importance as that of the state equation in modern control theory [1].

2.1 Computer Evaluation of Measurement Data Using Compartment Analysis

The compartment model of clearance test is described generally by a linear differential equation system of the first order. Evaluation of the test consists essentially of determined parameters X_i and λ_i in Eq. (1). And then solving this system of differential equations.

$$y = \sum_{i=1}^m X_i e^{\lambda_i t} \quad (1)$$

where $\lambda_1=0$.

Thereafter, a curve of the sum of exponential terms has to be fitted to the set of measurement points bearing test results, and after having achieved an appropriate accuracy of a given degree, values of coefficients X_i and of exponents λ_i have to be printed out.

For the computer evaluation of clearance-type tests, the algorithm relying on the least squares principle, developed by D. W. Marquardt, proved excellent [2], [3].

Notation used in this chapter:

n	number of measurement data;
k	number of assessed parameters;
$t_1, \dots, t_n$	sampling times (independent variables);
$y_1, \dots, y_n$	measurement data at the time instants above;
$\hat{y}_1, \dots, \hat{y}_n$	computed assessment values;
$b_{10}, \dots, b_{k0}$	initial values of the parameters to be assessed be given.

Let us determine parameter values $b_1, \dots, b_k$ for which the sum of the square of differences between *measured data* y_i and *computed assessments* $\hat{y}_i$ is minimum, that is, minimize.

$$\Phi = \sum_{i=1}^n (y_i - \hat{y}_i)^2 \quad (2)$$

To determine assessment, let us rewrite (1):

$$\hat{y}_i = b_1 + \sum_{l=2,4,\dots}^{k-1} b_l \exp(b_{l+1} t_l) \quad (3)$$

To minimize (2) parameter vector b has to be changed stepwise, according to some convenient strategy. After some experimentation we used an **iterative computing method** [3].

In conformity with this strategy, repeating iteration steps yields the minimum for Φ . Condition of stopping the iterative computation may be defined either by specifying a given value for Φ minimum, to stop after its achievement, or by observing the rate of convergence, and to accept the result after a certain slowing down in the rate of convergence.

Namely, the rate of convergence abruptly drops after starting with very high value.

2.2 Evaluation of Liver Flow Tests

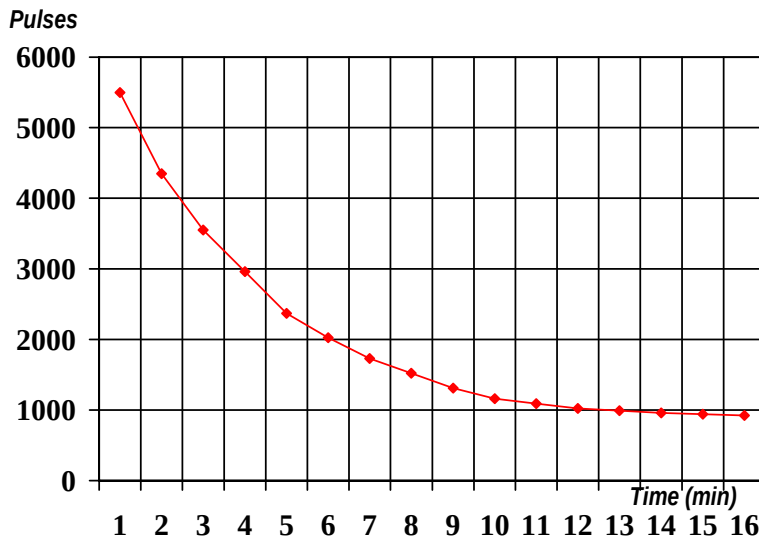


Figure 1
An example of measurement evaluation

The test relies on colloids of a given particle size being screened out from the plasma by (reticulo-endothelial system) cells of the organism. Most of these cells are found in the liver, but there are some in the spleen and the medulla.

The test procedure: Colloid 198 Au is administered to the patient. After the tracer has been assimilated, plasma activity (counts per minute) is determined. Theoretically, measurement points lie on an exponentially decreasing curve.

Structure of the mathematical model of the test is a so-called **mamillary system** of four compartments (Fig. 2).

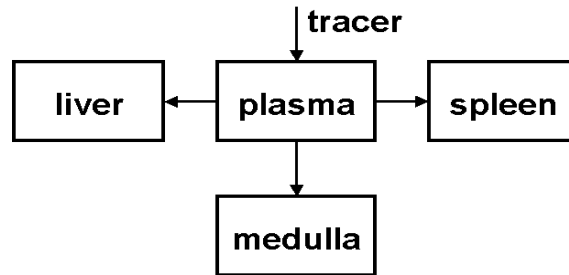


Figure 2
Mamillary system

After input of measurement data the computer program computes the parameter of the mathematical model, then physiological data much more informative for the doctors (biological halving times for liver, spleen, medulla, and blood flow in the liver as a percentage of the volume per minute of circulation).

Exponential regression outputs:

$$b_1=223, b_2=4729, b_3=-0.32, b_4=1243, b_5=-0.142, b_6=784, b_7=-0.036$$

Halving time for liver RES cells: 2.16 min.

Halving time for the spleen RES cells: 4.9 min.

Halving time for the medulla RES cells: 19.36 min.

Blood percentage flowing through the liver $V=32.03\%$

2.3 Non-Homogeneity

The concept of homogeneous compartments is fundamental to most of compartmental analysis. However, if a non-homogeneous compartment is suspected to be present, it can usually be represented by two sub-compartments [1]. One of these exchanges rapidly with the rest of the system, and the second exchanges slowly with the first. Thus the non-homogeneous compartment is divided into section 2a and 2b (Fig. 3).

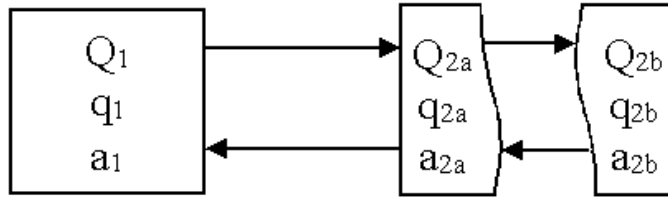


Figure 3
Non-homogenous system

For compartment 1 the amount of tracer present is given by

$$q_1 = a_1 Q_1 \quad (4)$$

For compartment 2 the total amount of tracer is

$$q_2 = q_{2a} + q_{2b} = a_{2a} Q_{2a} + a_{2b} Q_{2b} \quad (5)$$

If is the mean specific activity of the substance in compartment 2, then

$$q_2 = \bar{a}_2 Q_2 \quad (6)$$

Because a_{2a} and a_{2b} are exchanging rapidly, then a_{2a} is almost equal to a_1 , so that

$$\begin{aligned} \bar{a}_2 Q_2 &= a_1 Q_{2a} + a_{2b} Q_{2b} \\ Q_{2b} a_{2b} &= \bar{a}_2 Q_2 - a_1 Q_{2a} \end{aligned} \quad (7)$$

If $\bar{a}_2$ and a_1 are expressed as functions of time, then

$$a_{2b}(t) = \bar{a}_{2(t)} \frac{Q_2}{Q_{2b}} - a_1(t) \frac{Q_{2a}}{Q_{2b}}. \quad (8)$$

Now, if the tracer is initially added to compartment 1, $a_{2b}(0)$ will be zero. During the experiment the specific activities in compartments 1 and 2 can be determined and plotted as functions. Extrapolation of these functions to $t=0$ gives values for $\bar{a}_2(0)$ and $a_1(0)$. Thus, at $t=0$

$$\bar{a}_2(0) Q_2 - a_1(0) Q_{2a} = 0 \quad (9)$$

$$\frac{Q_{2a}}{Q_2} = \frac{\bar{a}_2(0)}{a_1(0)}. \quad (10)$$

Hence, the sizes of the sub-compartments can be calculated.

2.4 Study of Non-Homogeneity

Our study concerning non-homogeneity are focussed on the detection of liver diseases. The detection is based on the CLEARANCE OF COLLOID 198 Au test. Human experiments have been made at Semmelweis Medical University of Budapest, the clearance process of over 500 subjects have been identified. The detection of liver diseases has been performed using the following model (Fig. 4).

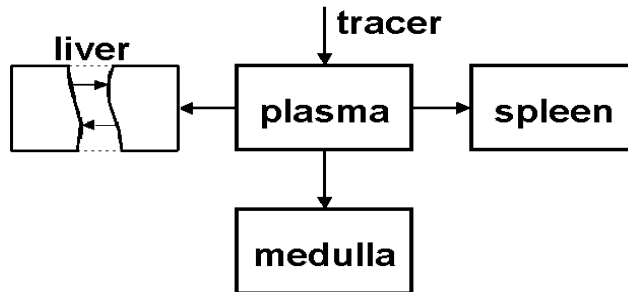


Figure 4
Non-homogenous mammary system

We have found, that in case of liver diseases the 4th exponential factors b_8 and b_9 have significant values. Among the over 500 subjects, 45 such cases have been found. To approve the real liver disease, further examinations proved to be necessary: biopsy, liver enzyme tests, etc. These further examinations lead to 42 real liver disease cases.

Consequently we can affirm, that the non-homogeneous compartment models consist a useful tool for the identification of damages in physiological systems.

With further theoretical examinations we'll hopefully be able to extend this method for other practical applications.

2.5 Use of Event Recognition Method for Determining the Illnesses of the Physiological Systems

Monitoring and quick detection of illnesses of physiological systems are of great importance. An inverse event recognition method [2] has been used for such purpose.

As a first step the parameters of a linear process model should be identified (as terminal variables). After that the monitoring of state variables and using a proper event recognition method, the outer variables (nature of illnesses) can be recalculated by an identified linear model. In this way the possible illnesses of the system can be located.

2.5.1 Linear Model

Let us consider the following linear multivariable dynamic model:

$$\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}\mathbf{u}(t) \quad (11)$$

where $\mathbf{x}(t)$ is the measurable **state deviation vector** characterising the deviation from the normal steady state, $\mathbf{u}(t)$ is the so-called **event indicator vector**. Whenever the j -th **event** takes place $u_j=1$, otherwise $u_j=0$. The elements of the $\mathbf{A}$ and $\mathbf{B}$ matrices can be identified by the "teaching" process.

2.5.2 Teaching Process

The identification of the matrices, the elements for the linear model can be accomplished by direct measurements. During this identification scheme the events to be recognised are numerically simulated one by one and the matrix elements a_{ij} and b_{ij} can be computed according to the $x(t)$ trajectories provided by the physiological hybrid model that minimises the following multi-variable non-linear function:

$$I(a_{ij}, b_{ij}) = \sum_{n=1}^N \int_0^T (\dot{x}_m^n - \mathbf{A}x_m^n - \mathbf{B}u_m^n)^2 dt \quad (12)$$

where $x_m^n(t)$ is the measured trajectory (in our case computed by the non-linear model) in the n -th experiment, when only the n -th element of the vector u differs from zero.

2.5.3 Event Recognition

The event recognition is based on the measurement of state variables and the inverse solution of (11). The solution of Eq. (11) for discrete time step ΔT in recursive form [3] is:

$$\mathbf{x}^{k+1} = \Phi(\Delta T)\mathbf{x}^k + \frac{\Delta T}{2}\mathbf{B}\mathbf{u}^{k+1} + \frac{\Delta T}{2}\Phi(\Delta T)\mathbf{B}\mathbf{u}^k \quad (13)$$

where the trapezoidal rule was used and

$$\Phi(\Delta T) = e^{\mathbf{A}\Delta T} \text{ and } \mathbf{x}^k = \mathbf{x}(t), t = k\Delta T \quad (14)$$

Reordering Eq. (13) for the event indicator-vector, we get

$$\mathbf{u}^{k+1} = \frac{2}{\Delta T}\mathbf{B}^{-1}\mathbf{x}^{k+1} - \frac{2}{\Delta T}\mathbf{B}^{-1}\Phi(\Delta T)\mathbf{x}^k - \mathbf{B}^{-1}\Phi(\Delta T)\mathbf{B}\mathbf{u}^k \quad (15)$$

In the case when disturbance of the j -th type has occurred, the state deviation vector $x(t)$ will change accordingly and the value of the event indicator computed by the recursive algorithm (15) will approach (11).

As the linear model estimates the states of the non-linear process in integral or global way (see Eq. (12)), therefore using an integral (global) indicator vector $U(t)$ is more efficient [3] [4] [5].

3 Diabetic Management and Blood Glucose Control

Symbolic computation has been applied to design a procedure for blood glucose control of diabetic patients under intensive care. The used model has been verified and tested in clinical environment. From the engineering point of view, the treatment of diabetes mellitus can be represented by outer control loop to replace the partially or totally failing blood glucose control system of the human body. We have used symbolic computation to design multivariable modal control based on the space representation of a verified nonlinear model. To simulate the insulin-glucose interaction in human body, a two-compartment model was employed, which was verified by parameter estimation technique based on clinical test data. Insulin injection was given to the test person and the glucose concentration of blood has been measured in time. According to the results, the system is expected to provide a useful help to the control of blood glucose level in diabetics under intensive care, and to the optimization process of diabetic administration [10], [20].

4 Remote Patient Monitoring and Diagnostic System

The goal of this research project was to develop a patient monitoring system supporting remote access of the patient information. The traditional patient monitoring systems do not support the remote access (i.e. through internet connection) of the managed patient information. The remote access of the system makes possible the implementation several useful services:

- patients can be monitored by their doctors through the internet;
- remote diagnostic systems can be connected to the monitoring system to process the patient data.

The remote patient monitoring system is developed by the collaboration of the Department of Informatics, Széchenyi István University and the Department of Control Engineering and Information Technology, Budapest University of Technology and Economics (DCEIT-BUTE).

The structure of the system is shown in Fig 5. The system integrates a local patient monitoring system shown at the left hand side of the figure. This subsystem is responsible for the data acquisition. This a system had been developed previously at the BUTE in the framework of the INCO/Copernicus Project (INCO 960161) project with the collaboration of the University of Munich, University of Vienna, University of Prague, and University of Wroclav [11], [12].

The data is extracted from the local monitoring system by a data access server which transfers it to the data converter server. The role of the data access server is to increase the portability by isolating the other parts of the system from the local patient monitor. If somebody want to use the remote patient monitoring system with other local patient monitor only the data access server has to be modified.

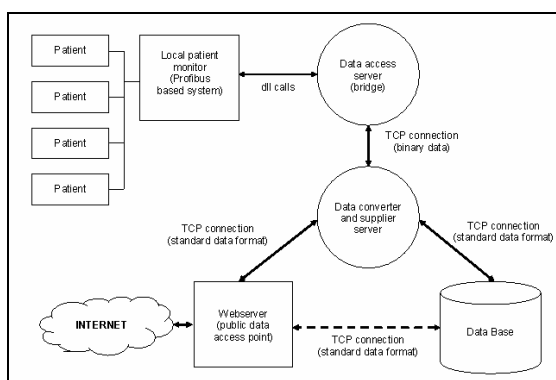


Figure 5

Structure of the remote patient monitoring and diagnostic system

The internal data representation of the system is standardized: all the system components exchange the information in the same format. The format of the internal data representation is defined based on international standards in order to make easy the interconnection of the remote patient monitor to other medical information systems such a HIS. The responsibility of the data converter server is to convert the binary data (from the data access server) to the standard internal representation.

The external interface of the system is supplied by a web server. The system stores the patient data in an SQL data base to provide access to the historical patient data as well.

Many free software components are integrated to the remote patient monitor in order to reduce the cost and the time of the development.

The core remote patient monitoring system has been already implemented. Currently we are working on the development of diagnostic systems to connect them to the remote patient monitor.

5 Automated System for Analyzing Cardiac Ultrasound Images

Ultrasound echocardiography is a widely used clinical technique, but the images obtained using the current technology, are still processed manually with semiautomated methods. In contrast to this, the newly developed system works in an automated way, first obtaining a series of long and short axes views of the heart synchronized by the ECG in real time, then processing them offline. After the detection of the internal edges of the left ventricle, the system determines the short/long axes areas, diameters, calculates the volume of the left ventricle frame by frame and, based on this, the ejection fraction for each cardiac cycle [13].

6 Event Recognition and State Classification to Detect Brain Ischemia by Means of EEG Signal Processing

EEG is an electric signal, which is the spatial sampling of an electric field around the active neurons of the brain. In general, we observe both temporal and spatial characteristics of this signal ensemble. Due to its origin from nerve cells, it is strongly correlated with the primary component of the metabolic activity of these cells: oxygen supplied by cerebral blood flow. Physiological inputs modify the state of the brain, which is reflected in parametric changes based on the EEG. The available processing methods are automatic event recognition or state classification, or semi-quantitative human observation. Two series of animal experiments were carried out with cats and rats, where the occlusion of the middle cerebral artery was used as a model of the ischemic damage. For human registrations, data was collected during open-heart surgery and carotid endarterectomy; in these cases the observation of the neurologist served as reference. Three different methods for event recognition were developed: (1) wavelet-based semi-quantitative spectral analysis; (2) automatic detection by AR model fitting and observation of dominant frequency and peak power shifts; (3) multi-channel activity correlation method based on the eigenvalue representation of a correlation matrix [14]. On the other hand, two classification methods were developed: (1) using a distance measure derived from the Karhunen-Loève transform; (2) discriminant analysis using multi-channel autoregressive model parameters [15].

7 Single-Channel Hybrid ECG Segmentation

Our new system presents a time domain single-channel ECG segtation method based on beat type and a priori morphological information. The proposed hybrid method combines the advantages of several well-known ECG signal processing techniques with several new solutions. The denoising of the ECG signal is provided by a wavelet-based filter [16]. The R-peaks are detected on a differential basis. A new adaptive beat isolator was developed, which separates the samples belonging to individual ECG beats. The separated beats are classified by a neural network, which can currently distinguish the normal sinus rythms, ventricular and premature atrial contractions. We used a modified version of the PLA algorithm, which produced the linear approximation of the beat. The rule-based morphological segmentation is carried out by individual segmentation units specific to the beat type. The test and evaluation of the system was carried out using reference ECG databases. The segmentation precision was over 90%.

8 Detection of Breathing Disorders like Apnea and Hypopnea

The most common breathing disorder is the apnea, which means the lack of breathing for certain amount of time. Episodes of apnea can happen commonly during sleep, but also at intensively cared patients and new-born babies. Frequent episodes of apnea can disturb the normal breathing process and can cause the development of metabolic, organic and nervous disorders. The diagnosis of apnea has several standardized steps, including the detection of apnea and its milder version (hypopnea), the determination of their type (central vs. obstructive) and the calculation of frequency. The applied signal processing methods evaluate the respiration signals and provide over 80% apnea detection accuracy. The determination of event type is provided only by the off-line analysis of multi-channel signal assays (e.g. polysomnography). We developed a new neural-network based apnea/hypopnea detection method, which uses the sophisticatedly preprocessed nasal airflow signal as network input. We tested two-hour-long airflow excerpts of 16 different patients. The entire detection precision was over 90% [17].

9 Evaluation of the Cry of Normal Hearing and Hard of Hearing Infants

Is there any difference between the cry of a normal hearing and a heard of hearing infant? What is the earliest time in the infant's life when these differences are manifested? These are the questions to answer during the investigations. The recently developed technique consists of four steps: recording, pre-processing, processing, and evaluation. Recording is performed in a quiet room, at 44100 Hz sampling frequency, the distance between the microphone and the mouth of the infant was 1 meter. Pre-processing phase contains an intelligent segmentation of stationary signal parts. The processing phase consists of extracting statistic information on the strength of the speech chorus from the clarified signal. FFT is applied to obtain the spectrum of the statistical signal. In order to perform the evaluation, the fundamental frequency of the cry has to be determined. The fundamental frequency isn't the most dominant one, but the lowest useful component in the spectrum of the infant cry. This frequency differs from infant to infant, and in most cases is situated between 400 Hz and 600 Hz. The fundamental frequency is determined using the Fourier transformed spectrum called cepstrum. The diagnosis of the infant cry is based on the following criterion: the dominant frequency of the normal hearing infant is an odd multiple of its fundamental frequency, while those of hard of hearing ones are even multiples [19].

10 Molecular Biology Studies with DNA-Chips

This topic is focused on a DNA-sequencer system for translation of genetic information in to protein-structure. Several problems have been studied in this domain: (1) making electronic DNA-chips, developing new electronic hybridization and immobilization methods with polipirrol-copolymerization and with tiol-subgroups on gold-monolayer; (2) tumor development and propagation, several methodological questions, such as producing reference-RNA for microarray analysis and describing a simple recovery method of cyanine dye labeled nucleotide triphosphates; (3) Monitoring mRNA-expression changes and chromosomal aberrations in specific tumor-tissues and to build up a database. Using spotted cDNA-chips he performs Comparative Genomic Hybridization and mRNA-expression monitoring examinations on metastatic lung and hepatocellular tumors and multiplex cancers associated with sclerosis tuberosa, MEN-syndrome and adrenal gland adenomas. The main goal is to gain insights and to determine genes and pathways playing role in metastasis-development and multiplex cancer development [21].

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