Sensitivity Analysis for Populations of Cells

Radu Dobrescu*
Eugen Iancu, Emil Petre**, Eugen Bobaşu****

**University "Politehnica" of Bucarest, 313 Splaiul Independentei Street, RO-060042, Bucharest, Romania*
(E-mail: radud@isis.pub.ro, http://www.upb.ro)
***Department of Automation, University of Craiova, 107 Decebal Street, RO-200440 Craiova, Romania*
(E-mail: Eugen.Iancu@automation.ucv.ro, http://www.ace.ucv.ro,
epetre@automation.ucv.ro, ebobasu@automation.ucv.ro)

Abstract: The system sensitivity analysis (SSA) is a mathematical method used in the behavior dynamic systems study. Simulation estimates time evolution and quantitative changes for the system variables in the case of changes in internal structure. The study of SSA for populations cells control, proves that SSA can be apply also to biological systems, it offers useful data for the medical practice and it contributes to introduce the computer assisted diagnosis in current medical assistance.

Keywords: Bioengineering, modeling and simulation, predictive control, system sensitivity analysis.

1. INTRODUCTION

Mathematical modeling and simulation are extremely effective methods, frequently used in all areas. During past years, important steps have been taken in order to involve systems theory and in the study of living organisms. Unfortunately, these attempts have not always been appreciated by biologists and medics, the main argument being the insufficient accuracy with which abstract systems model living systems. There are two objective causes that limit the performance of these models:

- The complexity of living organisms
- Difficulties met with experimental data acquisition and processing

The complexity of living systems, even in the case of inferior organisms is vastly superior to technical man-made structures. These consist of a large number of sub-systems, between which multiple connections are established. The isolation of a biological sub-system, with the purpose of studying it, is, inevitably, accompanied by altering the system's function and behavior. For this reason, experimental data differs from that corresponding to a normal functioning. In conclusion, it is recommended that the system is studied, as much as possible, in its whole. This conception means treating living systems as causal systems, deterministic or stochastic, multi-variable and ierarchy-based. The living organism is a complex of system, in a dynamic balance, permanently controlled through control loops (*feedback*). A characteristic of evolved living organisms is the robustness and adaptability to the environment. These qualities are the consequence of the control structures. Robustness is ensured by multiple control loops for each parameter, while short-term adaptability is achieved with the help of adaptive control systems, with variable structure, optimal or extreme.

Another difficulty in modeling and simulation is the non-linear character of most living systems as well as the non-stationary parameters. Data acquisition and processing raises problems technical in nature, because, structurally, a large part of the system's parameters are either inaccessible, or can not be converted into measurable units. For this reason, most of the times, the data that is available is insufficient to globally characterization the system.

From a systemic point of view, processes that take place at a cellular level (including cancerous tumors) have a strong non-linear character. Although, regarding their study and modeling remarkable progress has been made, the development and application of modern methods is slower in comparisons to other areas. This delay is caused, mainly, by two characteristics typical for bioprocesses.

- First of all, modeling these is exceptionally difficult. These systems consist of a series of interactions with other processes and, as a result, their functioning and especially their growth dynamics are, most of the times, hard to comprehend, strongly non-linear and non-stationary. Also, the repeatability of experiments is uncertain, while the lack of measurement accuracy can lead to a series of identification issues.
- Secondly, the application of monitoring strategies is confronted, in most cases, with the absence of typical instrumentations, secure and cheap, destined for the direct and/or in real time monitoring of biological and biochemical variables. Currently, the market offers few sensors capable of supplying this kind of measurements, while inaccessible or immeasurable

parameters need to be determined through off-line laboratory analysis. The cost and duration of such analysis limits their frequency and leads to an increase in overall expenses.

For the overcoming of such obstacles, it is necessary to use advanced modeling and identification techniques that use software sensors, in order to reproduce states and/or immeasurable parameters. Mathematical modeling turns the synthesis of the experimentally obtained data into a unitary system, allowing the underlining of the internal structure and the causal links between component parts and measures the weight with which every subsystem intervenes in accomplishing the system's functions. Simulation ensures the validation of concurrent theories, the understanding of physiopathological modifications and suggests relevant experiments. From what we have shown, we can tell that the modeling and simulation of living systems will be part of the modern trend of integrating obtained knowledge through inter-disciplinary collaborations.

2. MODEL PREDICTIVE CONTROL

Model Predictive Control (MPC) has known a spectacular development in the last decade. Its success is due to good performance obtained for processes with "*difficult*" dynamics (non-minimal phase, dead-times, etc.), that lead to difficulties for classical automated control. However, predictive control methods are not generally use-able. They can only be applied to those processes for which a mathematical model and reference are known a-priori.

These two conditions basically, represent the disadvantage of predictive methods. These, however, can not be avoided, because in order to predict a process' future behavior, we need to use a process model and the use of a pre-established reference benchmark.

The main objective of MPC is to make predictions regarding a process' future actions, based on a mathematical model and to select, according to these and the imposed reference, the correct command inputs.

Types of MPC:

a) *Linear MPC*
- A linear model is used: $\dot{x} = Ax + Bu$
- A square cost function: $F = x^T Qx + u^T Ru$
- Linear restrictions: $Hx + Gu < 0$

b) *Non-linear MPC*
- A non-linear model is used: $\dot{x} = f(x,u)$
- The cost function may not be squared: $F(x,u)$
- Non-linear restrictions: $h(x,u) < 0$

All model predictive control (MPC) systems rely on the idea of generating values for process inputs as solutions of an on-line (real-time) optimization problem. That problem is constructed on the basis of a process model and a predictive algorithm. Fig. 1 shows the structure of a typical MPC system.

The whole philosophy of predictive control regarding the creation of an anticipative effect, by using explicit know-

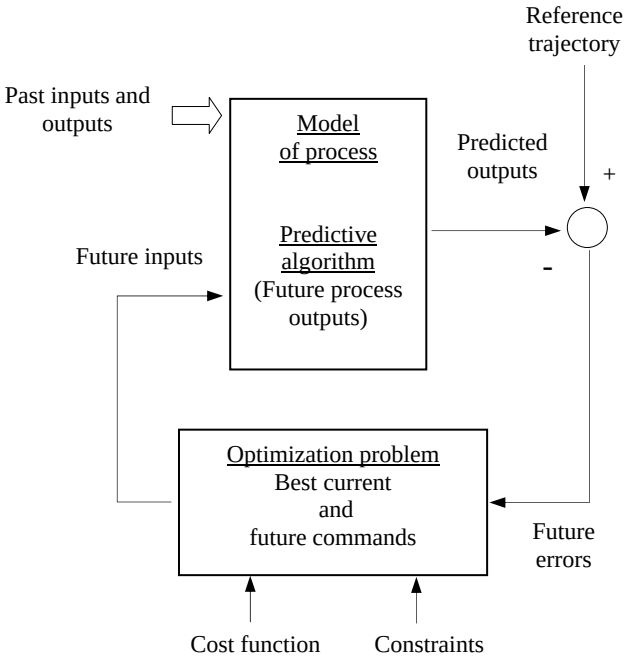

Fig. 1. Model predictive control scheme.

ledge of the future trajectory can be presented shortly as follows:

- The defining of a mathematical model of the system, in order to predict its future behavior.
- The minimizing of a square cost function on a finite horizon, by using prediction errors
- The elaboration of a future control sequence, with only the first value being applied to the system and model.
- The repeating of the entire procedure for the next sample, according to the chosen horizon.

3. SMITH PREDICTOR FOR DELAYED SYSTEMS

The more popular scheme for control processes affected by time delay was proposed by O.J Smith (Smith, 1959) and it is shown in Fig. 2. Let $P(s) = G(s)e^{-s\tau}$ be the transfer function of the process and let's indicate the setpoint with y°. This algorithm requires a minimal knowledge of the process to describe it through a transfer function (model):

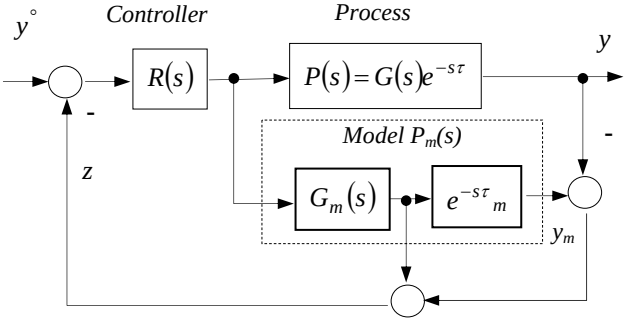

Fig. 2. The structure for Smith predictor.

$$P_m(s) = G_m(s)e^{-s\tau_m} \quad (1)$$

As shown in Fig. 2, the feedback is closed not on the process value *y*, but on the *z* variable, which has the same value that *y* had τ_m seconds earlier, and therefore it is in some ways a „*prediction*" of the measure; that is why this control architecture is called Smith „*predictor*" (Veronessi, 2003).

4. THE MODEL OF SEPSIS EVOLUTION

The cellular network is modeled as a collection of nonlinear differential equations, where reaction rates and compound concentrations are the variables (Dobrescu *et al*., 2007). Brause (2003) uses a reduced order approximation model, with three variables.

- $P(t)=P$ representing the pathogen influence, $P \in [0,1]$
- $M(t)=M$ representing the immune response, namely the macrophage action, $M \in [0,1]$, and
- $D(t)=D$ representing the percent of damaged noble cell tissue, which is destroyed in the fight between *P* and *M*, $D \in [0,1]$.

The equations of the mathematical model are Brause (2003):

$$\dot{P} = \alpha_1 P(1-P) - \alpha_2 MP\ ,\ \alpha_i > 0, i = \overline{1,2} \quad (2)$$

$$\dot{M} = -\beta_1 M + M(1-M)(\beta_2 P + \beta_3 D)\ ,\beta_i > 0, i = \overline{1,3} \quad (3)$$

$$\dot{D} = -\gamma_1 D + \gamma_2 h((M-\theta)/\gamma_3)\ ,\ \gamma_i > 0, i = \overline{1,3} \quad (4)$$

where $\theta = 0.5$ is a threshold value and

$$h(x) = 1/[1+\exp(-x)] \quad (5)$$

A typical parameter regime takes the next values:

$$\alpha_1 = 0.1; \alpha_2 = 1.0;$$
$$\beta_1 = 1.0; \beta_2 = 10.0; \beta_3 = 1.0; \quad (6)$$
$$\gamma_1 = 0.1; \gamma_2 = 0.04; \gamma_3 = 0.25;$$

The dynamical model described by equation (2, 3 and 4) reflects some basic qualitative features of the sepsis phenomenon and assume that the rate of cells damage increases also with a sigmoid function (5) of macrophages action, limited by a threshold θ.

In the application developed by the authors, we have used a linearized version of the mathematical model described in equations (7, 8 and 9), accomplishing through this, and a compatibility with the Smith predictor.

$$\dot{\Delta P} = [\alpha_1(1-2P_0) - \alpha_2 M_0]\Delta P - \alpha_2 \Delta M \quad (7)$$

$$\dot{\Delta M} = \beta_2 M_0(1-M_0)\Delta P + \\ + [(\beta_2 P_0 + \beta_3 D_0)(1-2M_0) - \beta_1]\Delta M - \beta_3 M_0 \Delta D \quad (8)$$

$$\dot{\Delta D} = \frac{\gamma_2}{\gamma_3}\exp[-(M_0-\theta)/\gamma_3]\Delta M - \gamma_1 \Delta D \quad (9)$$

where $P_0 = 0.2$, $M_0 = 0.15$ and $D_0 = 0.1$ are the steady state values calculated in Dobrescu *et al*. (2007).

Dobrescu *et al*. (2007) make an important change in the initial Brause model. They have introduced a new parameter *T* that signifies the initialization of a treatment (medication procedure) (Dobrescu *et al*., 2007). Sepsis treatment can be modeled by introducing an exogenous signal into the right hand term of (2):

$$\dot{P} = \alpha_1 P(1-P) - \alpha_2 MP - \alpha_3 T\ ,\ \alpha_i > 0, i = \overline{1,3} \quad (10)$$

Medication is carried, with the help of the circulatory system. This induces a dead-time that has to be taken into account for when, the amount of active substance, required for combating infected cells, is decided. Also, the authors have taken into consideration the existence of a dead-time between the evolution of sepsis and the body's immune response. The modified mathematical model is:

$$\dot{\Delta P}(t) = [\alpha_1(1-2P_0) - \alpha_2 M_0]\Delta P(t) - \\ - \alpha_2 \Delta M(t-\tau_1) - \alpha_3 T(t-\tau_2) \quad (11)$$

$$\dot{\Delta M}(t) = \beta_2 M_0(1-M_0)\Delta P(t) + \\ + [(\beta_2 P_0 + \beta_3 D_0)(1-2M_0) - \beta_1]\Delta M(t) - \\ - \beta_3 M_0 \Delta D(t) \quad (12)$$

$$\dot{\Delta D}(t) = \frac{\gamma_2}{\gamma_3}\exp[-(M_0-\theta)/\gamma_3]\Delta M(t-\tau_1) - \\ - \gamma_1 \Delta D(t) \quad (13)$$

5. CARDIOVASCULAR SYSTEM STRUCTURE

The anatomical structure of the cardio-vascular system is presented in Fig. 3. Due to the structure of the circulatory system, we have a time delay before the medication reaches a homogeneous concentration in the body. This dead time is put in evidence by the simplified mathematical sintetized by Minato *et al*. (see Minato *et al*., 1979; Iancu, 2000).

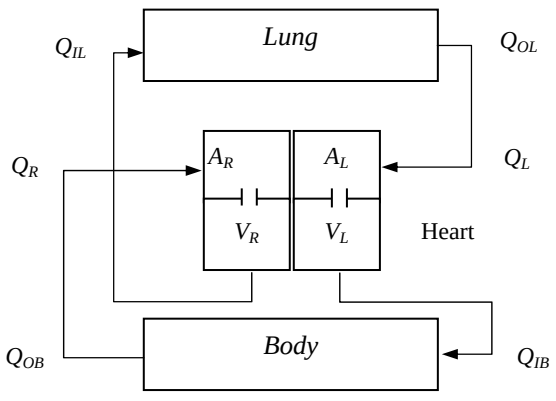

Fig. 3. The simplified structure of the cardiovascular system.

The right heart has an atrium (A_R) and a ventricle (V_R). It receives the blood from the body and pumps it in the lung. The left heart has an atrium (A_L) and a ventricle (V_L). It receives the blood from the lung and pumps it in the body. In Fig. 3 the notations have the next significances:

- Q_L – represent the blood flow input in the left heart.
- Q_{IB} - represent the blood flow input in the body.
- Q_{OB} - represent the blood flow output in the body.
- Q_R - represent the blood flow input in the right heart.
- Q_{IL} - represent the blood flow input in the lung.
- Q_{OL} - represent the blood flow output in the lung.

Also, the blood flows Q [mls^{-1}] between the different compartments are considered equals and constants.

$$Q_R = Q_{IL} = Q_{OL} = Q_L = Q_{IB} = Q_{OB} = Q = ct. \quad (14)$$

On suppose that the cardio-vascular system is working in steady state and we consider the supposition that all the involved blood volumes are constant.

- W_R [ml] - represent the blood volume in the right heart;
- W_L [ml] - represent the blood volume in the left heart;
- W_{lung} [ml] - represent the blood volume in the lung;
- W_{body} [ml] - represent the blood volume in the body.

We have modeled the injection of the pharmacological substance in a peripheral vein by the relation:

$$W_i \frac{dc_i(t)}{dt} = i(t) - Q_i c_i(t), \quad c_i(0) = 0 \quad (15)$$

where W_i represent the volume of the substance, $c_i(t)$ represent the substance concentration at the injection level and Q_i is the blood flow which receive and transport the substance. Also:

$$i(t) = \begin{cases} I / \tau_i, \text{ for } 0 \le t \le \tau_i \\ 0, \text{ for t } > \tau_i \end{cases} \quad (16)$$

where

- τ_i [s] - represents the interval of injection
- I [mg] – represents the quantity of substance in the unwashed solution.

The equation which describes the transport from the injection place to the right heart is:

$$W_R \frac{dc_R(t)}{dt} = Q_i c_i(t - \tau_i) + \\ + Qc_{body}(t - \tau_{body}) - Qc_R(t) \quad (17)$$

where τ_{body} represents the delay necessary for the transport of the injectable solution and $c_L(t),\ c_R(t),\ c_{body}(t)$ represent respectively, the substance concentrations at the left heart, right heart and at body level. Similarly, the equations for the transport in the next compartments are:

- for the lung:

$$W_{lung} \frac{dc_{lung}(t)}{dt} = Qc_R(t) - Qc_{lung}(t) \quad (18)$$

- for the left heart:

$$W_L \frac{dc_L(t)}{dt} = Qc_{lung}(t - \tau_{lung}) - Qc_L(t) \quad (19)$$

- for the body:

$$W_{body} \frac{dc_{body}(t)}{dt} = Qc_L(t) - Qc_{body}(t) \quad (20)$$

From (15), (17), (18), (19) and (20) results:

$$\dot{c}_i(t) = -\frac{1}{T_i} c_i(t) + \frac{1}{W_i} i(t) \quad (21)$$

$$\dot{c}_R(t) = \frac{1}{T_{Ri}} c_i(t - \tau_t) - \frac{1}{T_R} c_R(t) + \\ + \frac{1}{T_R} c_{body}(t - \tau_{body}) \quad (22)$$

$$\dot{c}_{lung}(t) = \frac{1}{T_{lung}} c_R(t) - \frac{1}{T_{lung}} c_{lung}(t) \quad (23)$$

$$\dot{c}_L(t) = \frac{1}{T_L} c_{lung}(t - \tau_{lung}) - \frac{1}{T_L} c_L(t) \quad (24)$$

$$\dot{c}_{body}(t) = \frac{1}{T_{body}} c_L(t) - \frac{1}{T_{body}} c_{body}(t) \quad (25)$$

where

$$T_i = W_i / Q_i, \quad T_{Ri} = W_R / Q_i,$$
$$T_R = W_R / Q, \quad T_{lung} = W_{lung} / Q,$$
$$T_L = W_L / Q, \quad T_{body} = W_{body} / Q$$

represent time constants. Using Laplace transformation (we suppose that the initial conditions are zero) it is possible to calculate the transfer function for each channel of process:

- for the injection zone:

$$H_i(s) = \frac{c_i(s)}{i(s)} = \frac{1/Q_i}{T_i s + 1} \quad (26)$$

- for the right heart:

$$c_R(s) = \frac{e^{-\tau_i s} T_R}{T_{Ri}(T_R s + 1)} c_i(s) + e^{-\tau_{body} s} \frac{1 - k}{T_R s + 1} c_{body}(s) \quad (27)$$

- for the lung:

$$H_{lung}(s) = \frac{c_{lung}(s)}{c_R(s)} = \frac{1}{T_{lung}s + 1} \quad (28)$$

- for the left heart:

$$H_L(s) = \frac{c_L(s)}{c_{body}(s)} = e^{-\tau_{body}s} \frac{1}{T_L s + 1} \quad (29)$$

- for the body:

$$H_{body}(s) = \frac{c_{body}(s)}{c_L(s)} = \frac{1}{T_{body}s + 1} \quad (30)$$

During the simulation it is possible to modify the value of concentration of the substance and time of injection. Also, we can choose physiological or pathological values for all the parameters of the cardiovascular system. So, it is possible to simulate the dilution of drugs administrated in the cardiovascular system. The results of simulation are presented in the next figures.

In the following figures we have represented:

- $P(t)$ representing the pathogen influence (Fig. 7);
- $M(t)$ representing the macrophage action (Fig. 8);
- $D(t)$ representing the percentage of damaged cell tissue, which is destroyed in the fight between P and M (Fig. 9).

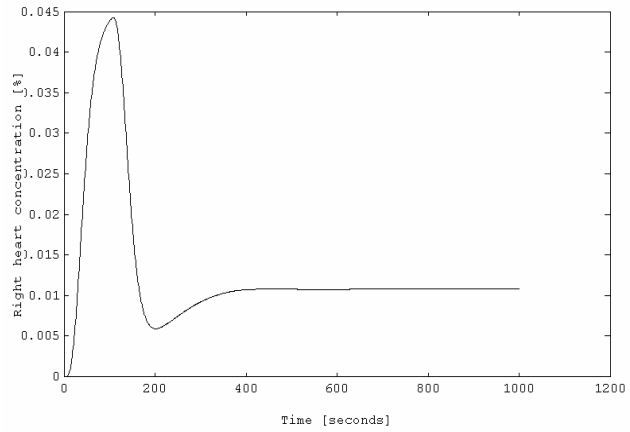

Fig. 4. The time evolution concentration at the right heart.

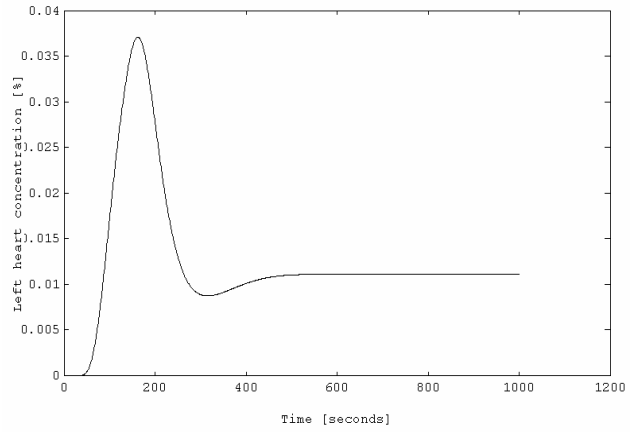

Fig. 5. The time evolution concentration at the left heart.

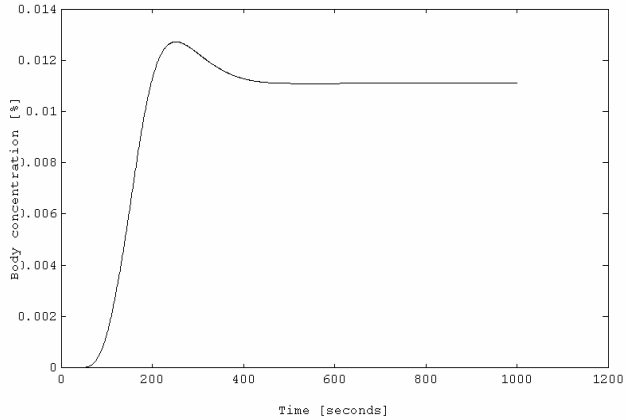

Fig. 6. The time evolution concentration at the body level.

A special situation occurs in intensive care units (ICUs), where most of the patients are not aware. Usually, sepsis represent the systemic inflammatory response syndrome (SIRS) associated with infection.

The most critical aggravation of sepsis is the septic shock. In ICUs the septic shock is a very critical situation of the patient. The diagnosis of septic shock is still made too late, because at present there are no adequate tools to predict the progression of sepsis to septic shock (Seely and Christou, 2000).

The advantage of the ICUs is the fact that medication can be fed constantly, in a controlled environment. In order to keep the concentration of active substance and control and avoid over-doses, we are proposing his use of a control structure based on the Smith predictor.

6. THE STRUCTURE PROPOSED FOR SEPSIS CONTROL

The control structure proposed by the authors takes into account dead times introduced by the cardiovascular system. Specifically, we propose that the mathematical model describing the sepsis process control is formed by the connection with the mathematical model of the cardiovascular system. The controller which will command the pump for the medication substance will be synthesized using Smith predictors. We therefore ensure a good behavior of the control system. The command required for the pump is anticipated ahead of time with a period equal with dead time. It also improves behavior in relation to disturbance. It is worth mentioning that in the synthesis of the control law, we must consider the ensuring of closed-loop stability.

7. SENSITIVITY ANALYSIS

From engineering practice is well known that a dynamic system did not respond in the same way to all external stimuli (command or disturbance). It is saying that the system is *more sensitive* to the command u_i or disturbance ζ_j. Similar, altering one or more parameters from internal structure lead to a deviation from the undisturbed trajectory and the system is more sensitive to one altering given another. All these observations lead to the necessity

of the system sensitivity analysis (SSA). Starting from these observations resulted from the engineering practice, two appearances of the system sensitivity analysis have been developed:

- Direct sensitivity analysis (*DSA*)
- Inverse sensitivity analysis (*ISA*).

7.1 Direct sensitivity analysis (DSA)

The aim of the DSA is to determine the influences of the initial state, command and parameter alterations on the time evolution of the system states and output. Conversely, the generating causes of the deviations of the state and output trajectories of the disturbed system from the undisturbed trajectories are determined through the ISA of the system, using the measurements of these deviations. Theoretical concepts presented below and which illustrates the principle of SSA are taken from speciality literature (Ungureanu, 1988; Porter and Crossley, 1972; Takamatsu et al., 1970). Ungureanu (1988) considered the following mathematical model of a dynamic system, given by the vectorial state equation:

$$\dot{x}(t) = f[x(t), u(t), p(t), t] \tag{31}$$

where $x(t)$ is the state-vector, $u(t)$ the command-vector, and $p(t)$ is parameter-vector. The trajectory of the undisturbed state is the solution of the equation (31):

$$x(t) = x[x_0, u(t), p(t), t] \tag{32}$$

where x_0 are the initial conditions. At the time moment t_1, $t_0 < t_1 < t_f$, where t_f is the final time for the system evolution, appear step modifications of the command with Δu and/or of the parameters with Δp. The disturbed state trajectory in this case is (Ungureanu, 1988):

$$x_p(t) = x[x(t_1), u(t) + \Delta u, p(t) + \Delta p], \quad t \geq t_1 \tag{33}$$

where $x_p(t)$ is the solution of the equation:

$$\dot{x}_p(t) = f[x_p(t), u(t) + \Delta u, p(t) + \Delta p, t] \tag{34}$$

The deviation of the state trajectory from the nominal trajectory is given by the relation:

$$\Delta x(t) = x_p(t) - x(t) \tag{35}$$

Using the sensitivity matrices, defined by Ungureanu (Ungureanu, 1988), we can computed directly this deviation with the relations:

$$\Delta x(t) \cong S_u^x(t)\Delta u + S_p^x(t)\Delta p \tag{36}$$

7.2 Inverse sensitivity analysis (ISA)

It can be defined the general sensitivity matrix as the matrix obtained joining the commands sensitivity matrices and parameters (Ungureanu, 1988),

$$\Delta x(t) = S_q^x(t)\Delta q \tag{37}$$

where we noted: $\Delta q = [\Delta u \ \ \Delta p]^T$. Formally, using the relation (37), *ISA* problem is resumed to solving the equation:

$$\Delta q = [S_q^x(t)]^{-1}\Delta x(t), t \in [t_0, t_f] \tag{38}$$

It can be seen that *ISA* need to know the deviation of the trajectory of the real system from the nominal trajectory. In Ungureanu (1988) it is presented an algorithm for solving *ISA* in the case of continuous systems.

The authors shall further propose a new version of the algorithm for calculating *ISA* in the discrete event systems (like as tumor growth).

One possibility to solve the problem is based on minimisation of a criteria function with two variables. The first variable is the difference Δx, that is the real state deviation. The second variable is computed using relation (37) noted Δx^*. Let it be τ the sampling period, suitable chosen. For the vectors Δx and Δx^* obtained at step e, $e=1,2,3....$ we'll use the notations:

$$[\Delta x(e\tau)]^T \overset{N}{=} [\Delta x_e]^T = [\Delta x_1^e \ \Delta x_{2e}^e \ldots \Delta x_n^e] \tag{38}$$

and respectively:

$$[\Delta x^*(e\tau)]^T \overset{N}{=} [\Delta^* x_e]^T = [\Delta(x_1^*)^e \ldots \Delta(x_n^*)^e] \tag{39}$$

We'll choose for the scalar criteria J an expression:

$$J = \sum_{e=1}^{N}[d(e\tau)]^2 = \sum_{e=1}^{N}(d_e)^2 \tag{40}$$

where d_e represents an Euclidean distance between vectors Δx_e- real deviations at the sampling moment $e\tau$ and respectively Δx^*_e - theoretically computed deviations, and $N = (t_f - t_0)/\tau$ represent the number of the samples. From (37) can be wrote:

$$\Delta x_e^* = S_q^x(e\tau)\Delta q \tag{41}$$

We'll consider the general sensitivity matrix is:

$$S_q^x(e\tau) = [s_{ij}(e\tau)]_{\substack{i=\overline{1,n} \\ j=\overline{1,k}}} = [s_{ij}^e]_{\substack{i=\overline{1,n} \\ j=\overline{1,k}}} \tag{42}$$

and relation (41) becomes:

$$\Delta x_e^* = \begin{bmatrix} \sum_{j=1}^{k} s_{1j}(e\tau)\Delta q_j \\ \ldots \\ \sum_{j=1}^{k} s_{nj}(e\tau)\Delta q_j \end{bmatrix} \overset{N}{=} \begin{bmatrix} \sum_{j=1}^{k} s^e{}_{1j}\Delta q_j \\ \ldots \\ \sum_{j=1}^{k} s^e{}_{nj}\Delta q_j \end{bmatrix} \tag{43}$$

The Euclidean distance between the two vectors is given by the relation:

$$d_e = d(\Delta x_e, \Delta x_e^*) = \left[\sum_{i=1}^{n}(\Delta x_i^e - \sum_{j=1}^{k} s_{ij}^e \Delta q_j)^2\right]^{1/2} \tag{44}$$

and criteria (40) has the general expression:

$$J = \sum_{e=1}^{N} (d_e)^2 = \sum_{e=1}^{N} \left[\sum_{i=1}^{n} (\Delta x_i^e - \sum_{j=1}^{k} s_{ij}^e \Delta q_j)^2 \right] \quad (45)$$

The minimum condition regarding the components of the vector Δq can be analytically written with the relation:

$$\frac{\partial J}{\partial(\Delta q)} = 0 \quad (46)$$

So, in the case of *ISA* it is starting from the measurement of the state trajectory and/or output trajectory deviation of the disturbed system from the ideal trajectories of an undisturbed model and it is looking to determine the causes which generate these deviations, implementing a diagnosis of the system.

8. APPLICATION

To illustrate sensitivity analysis and a possible application of this to medical diagnosis we used the simplified liniarized model represented by the equations (11, 12 and 13). Be the following notations:

$$x(t) = \begin{bmatrix} \Delta P(t) \\ \Delta M(t) \\ \Delta D(t) \end{bmatrix}$$

$$A = \begin{bmatrix} [\alpha_1(1-2P_0) - \alpha_2 M_0] & -\alpha_2 & 0 \\ \beta_2 M_0(1-M_0) & [(\beta_2 P_0 + \beta_3 D_0)(1-2M_0) - \beta_1] & -\beta_3 M_0 \\ 0 & \frac{\gamma_2}{\gamma_3}\exp[-(M_0-\theta)/\gamma_3] & -\gamma_1 \end{bmatrix}$$

$$B = \begin{bmatrix} -\alpha_3 \\ 0 \\ 0 \end{bmatrix}$$

If it does not take into account the delay times, the sensitivity matrix with respect to parameter α_1 is solution of the equation (Ungureanu, 1988):

$$\dot{S}_{\alpha 1}^{x}(t) = A S_{\alpha 1}^{x}(t) + A_{\alpha 1} x(t) + B_{\alpha 1} T(t) \quad (47)$$

where

$$A_{\alpha 1} = \left[\frac{\partial a_{ij}}{\partial \alpha_1} \right] = \begin{bmatrix} 1-2P_0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad i = \overline{1,3};\ j = \overline{1,3}$$

and $B_{\alpha 1} = \left[\frac{\partial b_{il}}{\partial \alpha_1} \right] = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix} \quad i = \overline{1,3};\ l = 1$

Similarly we can calculate the other sensitivity matrices with respect to the parameters α_2, β_1, β_2, β_3, γ_1, γ_2 and γ_3.

In conclusion, using this method, it is possible to determine factors that stimulate or inhibit cell population growth. We can determine the sensitivity to treatment and we can adopt a correct therapeutic attitude.

ACKNOWLEDGMENT

This paper is part of the project *Models and morphometric techniques with applications in improving image-based diagnosis in gastrointestinal cancers and evaluating new therapies - IMAGO*, at the University of Politehnica of Bucuresti and was supported by National Center for Programme Management - CNMP, Romania.

REFERENCES

Brause, R. (2003). Adaptive modelling of biochemical pathways, *Proc. of the 15th Int. Conf. on Tools with Artificial Intelligence* – ICTAI 2003, IEEE Computer Society, 2003.

Dobrescu, R., Oltean, V.E., and Popescu D. (2007). Adaptive hybrid model of the immune system response in sepsis, *Proc. of the Int. Symposium on Systems Theory, Automation, Robotics, Computers, Informatics, Electronics and Instrumentation* SINTES 13, Craiova, ISBN 978-973-742-816-5.

Iancu, I. and Iancu, E. (2000). Mathematical Modeling in Human Physiology. Application in Diagnosis, *International Symposium on System Theory, Automation, Computers and Electronics*, SINTES 10, Craiova, Romania, pp. A38 – A41.

Minato, K., Kuwahara, M., Yonekura, Y., and Hirakawa A. (1979). Parameter Estimation of Radiocardiogram Using a Minicomputer, *Automatica*, vol.15, pp. 521 - 529.

Porter, B. and Crossley R.(1972). *Modal Control. Theory and Applications*, London, Taylor & Francis Ltd.

Seely, A. and Christou, N. (2000). Multiple Organ Dysfunction Syndrome, Exploring the Paradigm of Complex Nonlinear Systems, *Crit. Care Med*. 28(7), pp. 2193-2200.

Smith, O. J. (1959). A controller to overcame dead time, *ISA Journal*, Vol. 6, No.2, pp. 28-33.

Takamatsu, T., Hashimoto, I., and Ohno, H. (1970), Optimal Design of Large Scale Complex Systems from the Viewpoint of Sensitivity Analysis, *Ind. Eng. Chem*., 3, pp. 369-391.

Ungureanu, St. (1988). *The sensitivity of dynamics system*, Bucarest, Editura Tehnica.

Veronessi, M. (2003). Performance improvement of Smith predictor through automatic computation of dead time, *Yokogawa Technical Report*, English Edition, No. 35.