Bioautomation, 2007, 8, Suppl. 1, 13 – 26 ISSN 1312 – 451X

Brunovsky Normal Form of Monod Kinetics Models and Growth Rate Control of a Fed-batch Cultivation Process

Pavlov Y.

Centre of Biomedical Engineering "Prof. Ivan Daskalov"
Bulgarian Academy of Sciences
105 Acad. G. Bonchev Str., Sofia 1113, Bulgaria
Phone: 979-3648
E-mail: yupavlov@clbme.bas.bg, yupavlov14@hotmail.com

Summary: A mathematical methodology that gives assistance to design of fed-batch stabilization and control is presented. The methodology is based both on Utility theory and optimal Control theory. The Utility theory deals with the expressed subjective preferences and allows for the expert preferences to be taken in consideration in complex biotechnological systems as criteria for control and optimization. The Control theory is used for parameters stabilization of a fed-batch cultivation process. The control is written based on information of the growth rate. The simulations show good efficiency of the control laws.

Keywords: Optimal Control, Brunovsky Normal Form, Utility Function, Fed-batch Fermentation.

1. INTRODUCTION

Mathematical models are used by engineers to gain advantage through applications of model based process design, control and optimization. Thus, building mathematically motivated and validated models is a key activity in bioprocesses engineering.

The specific growth rate is one of the most important parameter in biotechnological cultivation process. The relationships between the rate of growth, substrate concentration and product formation are crucial for monitoring, controlling and optimizing these processes. Therefore it is of importance to be able to model and control the specific growth rate as a function of the biomass and substrates and "vice versa" [7]. It is the opinion of some scientists that with optimal control theory can be shown a fed-batch process is likely to outperform both a continuous process and a batch process. The problem is then the determination of ***the best*** feed rate of substrate in the bioreactor as a function of the specific growth rate (and/or *the best* temperature (t^o) and *the best* acidity (pH)) [7, 10]. And since the quality of the product usually deteriorates within several hours after substrate depletion it is hence of importance to harvest in time.

The meaning of ***best*** varies from problem to problem [5, 7]. The complexity of the biotechnological cultivation processes, due to the inherent time variant properties and the lack of precise measurement make difficult the determination of the optimal (the best) process parameters. The incomplete information is compensated, some times, with participation of imprecise human estimations. The necessity of a merger of empirical knowledge with mathematical exactness causes difficulties. Possible approach for solution of these problems is the stochastic programming and the Utility theory [3, 5]. The Utility theory deals with the expressed subjective preferences. Possible criteria for "the meaning of ***best***" can be an expert (decision maker-DM) utility function [3, 5, 9].

The aim of this investigation is to demonstrate an optimization technique and the possibility to control optimally the specific growth rate of a biotechnological cultivation process. The control design is based on Monod-Wang model in Brunovsky normal form. The classical Monod form is a singular form of this model [11, 12].

2. MODELS OF THE FED-BATCH FERMENTATION PROCESS

Unstructured models take cell mass as a uniform quality without internal dynamic. The reaction rates depend only upon the macroscopic conditions in the liquid phase of the bioreactor. Unstructured models fail only when intracellular dynamics must be considered. Mathematical unstructured models of fed-batch process can be written based on mass balance equations [10]:

$$\begin{aligned} &\dot{X} = \mu X - \frac{F}{V} X, \\ &\dot{S} = -k\mu X + (So - S)\frac{F}{V}, \\ &\dot{\mu} = m(\mu_m \frac{S}{K_S + S} - \mu), \\ &\dot{V} = F, \\ &\dot{E} == k_2 \mu X - \frac{F}{V} E, \end{aligned} \qquad (1)$$

where X presents the concentration of biomass, [g/l]; S – the concentration of substrate (glucose), [g/l]; V - bioreactor volume, [l]; F – substrate feed rate, [h^{-1}]; S_0 – substrate concentration in the feed, [g/l]; μ_{max} - maximum specific growth rate, [h^{-1}]; K_S – saturation constant, [g/l]; k, k_2 – yield coefficients, [g/g], m – rate coefficient [-]; E – the concentration of ethanol, [g/l]. We preserve the notation $U(.)$ for the DM utility function (the criteria for optimization). The system parameters are as follows: μ_m = 0.59 [h^{-1}], K_S = 0.045 [g/l], m = 3 [–], S_0 = 100 [g/l], k = 2 [–], k_2 = 3.79 [–], F_{max} = 0.19 [h^{-1}], V_{max}= 1.5 [l]. The dynamics of μ in the so called Monod-Wang model is modeled as a first order lag process with rate constant m, in response to the deviation in μ. The fifth equation describes the production of ethanol (E). This equation is equivalent dynamically to the first one. The demonstration is easy. We implement a simple transformation in the first equation:

$$X = \frac{1}{k_2}E. \tag{2}$$

After that the first and the fifth equations become equivalent. The new form of the non-linear kinetic model is:

$$\begin{aligned}
\dot{X} &= \mu X - \frac{F}{V}X, \\
\dot{S} &= -k\mu X + (So - S)\frac{F}{V}, \\
\dot{\mu} &= m(\mu_m \frac{S}{K_S + S} - \mu), \\
\dot{V} &= F.
\end{aligned} \tag{3}$$

We shall use this form of the non-linear fed-batch kinetic model in the rest of the paper. The initial values of the state variables are: $X_i(0)$ = 0.99; $S_i(0)$ = 0.01; $\mu_i(0)$ = 0.1; $V_i(0)$ = 0.5.

3. UTILITY FUNCTION AND DETERMINATION OF THE "BEST" GROWTH RATE

The complexity of the biotechnological fermentation processes makes difficult the determination of the optimal process parameters.

The incomplete information usually is compensated with the participation of imprecise human estimations. Our experience is that the human estimation of the process parameters of a cultivation process contains uncertainty at the rate of [10, 25] %. Here is used a mathematical approach for elimination of the uncertainty in the DM's preferences based both on the Utility theory and on the Stochastic programming [9]. The algorithmic approach permits evaluation of the optimal specific growth rate of the fed-batch cultivation process according to the DM point of view.

We need some mathematical formulations. Standard description of the utility function application is presented by Fig. 1. There are a variety of final results that are consequence of the expert or DM's choice and activity.

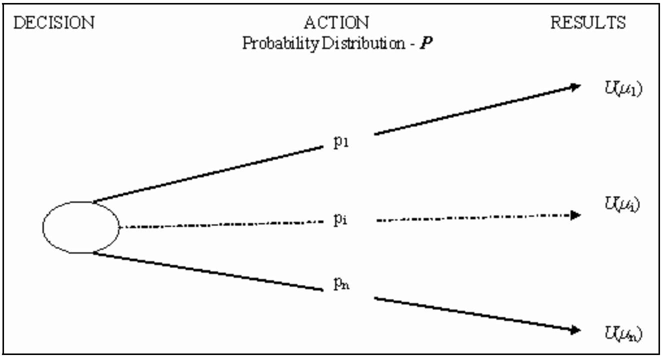

Fig. 1. Utility function application

This activity is motivated by a DM objective which possibly includes economical, social, ecological or other important process characteristics. A utility function $U(.)$ assesses each of this final results (μ_i, $i = 1 \div n$). The DM judgment of the process behavior based of the DM choice is measured quantitatively by the following formula [3, 5]:

$$U(p) = \sum_i U(\mu_i) p_i, \ where \ p = (p_1, p_2,.., p_i,..p_n), \sum_i p_i = 1. \qquad (4)$$

We denote with p_i subjective or objective probabilities which reflect the uncertainty of the final result. Let **Z** be the set of alternatives (**Z** = {specific growth rates} = [0, 0.6]) and **P** be a convex subset of discrete probability distributions over **Z** (Fig. 1). The expert "preference" relation over **P** is expressed through $(\succ)$ and this is also true for those over **Z** (**Z** $\subseteq$ **P)**. We know that the utility function is defined in the interval scale (in the proposed conditions) [3, 9]. A decision support system for subjective utility *U*(.) evaluation is used (Fig. 2). The subjective utility function *U*(.) is shown on Fig. 3. The utility *U*(.) is approximated by a polynomial:

$$U(\mu) = \sum_{i=0}^{6} c_i \mu^i \qquad (5)$$

The polynomial representation permits analytical determination of the derivative of the utility function and easy implementation in the optimization and control. The utility function in this investigation is evaluated with 64 learning DM's answers, sufficient for a primary orientation in the problem [9].

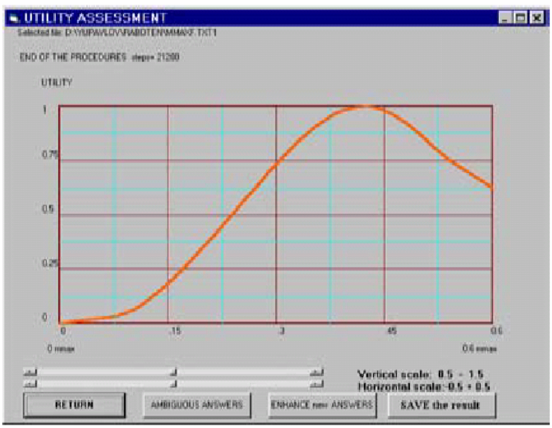

Fig. 2. Decision support system

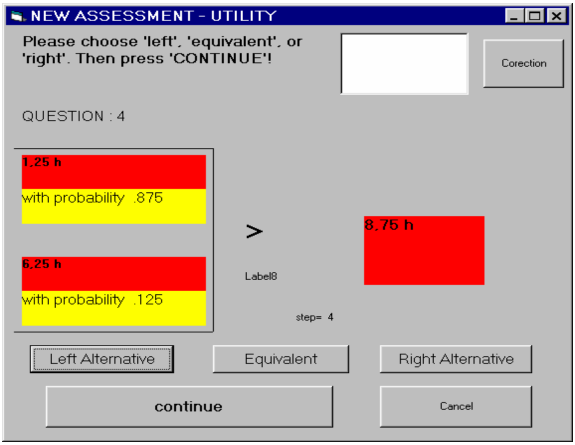

Fig. 3. Utility versus Growth rate

This utility evaluation mathematical approach is discussed in details in [9].

4. BRUNOVSKY NORMAL FORM OF MONOD-WANG MODEL, TIME MINIMIZATION CONTROL AND STABILIZATION OF THE GROWTH RATE

We preserve the notation $U(.)$ for the DM utility. The control design of the fed-batch process is based on the next subsidiary optimal control problem: **Max**($U(\mu(T_{int}))$), ***where the variable*** μ ***is the specific growth rate, (***$\mu\in[0, \mu_{max}]$***,*** $D\in[0, D_{max}]$***). Here*** $U(\mu)$ ***is an aggregation objective function (the utility function – Fig. 3*****) and** D **is the control input (the dilution rate):**

$$\max(U(\mu)),\ \mu\in[0,\mu_{\max}],\ t\in[0,T_{\text{int}}],\ D\in[0,D_{\max}]$$

$$\begin{aligned} \dot{X} &= \mu X - DX \\ \dot{S} &= -k\mu X + (So - S)D \\ \dot{\mu} &= m\left(\mu_m \frac{S}{(K_S + S)} - \mu\right) \end{aligned} \qquad (6)$$

Bioautomation, 2007, 8, Suppl. 1, 13 – 26 ISSN 1312 – 451X

When T_{int} is sufficiently small the optimization is in fact "time minimization". The differential equation in (6) describes ***a continuous fermentation process***. The model permits exact linearization to the next Brunovsky normal form (Goursat, as regard to the differential forms) [1, 8]:

$$\dot{Y}_1 = Y_2,\quad \dot{Y}_2 = Y_3,\quad \dot{Y}_3 = W. \tag{7}$$

Here W denotes the control input of the model (7). The new state vector (Y_1, Y_2, Y_3) is:

$$\begin{aligned} Y_1 &= u_1, \\ Y_2 &= u_3(u_1 - k u_1^2), \\ Y_3 &= u_3^2(u_1 - 3k u_1^2 + 2k^2 u_1^3) + m\left(\mu_m \frac{u_2}{(K_S + u_2)} - u_3\right)(u_1 - k u_1^2), \\ \begin{bmatrix} u_1(X,S,\mu) \\ u_2(X,S,\mu) \\ u_3(X,S,\mu) \end{bmatrix} &= \begin{bmatrix} \dfrac{X}{S_o - S} \\ S \\ \mu \end{bmatrix}. \end{aligned} \tag{8}$$

The derivative of the function Y_3 determines the interconnection between W-model (7) and D-model (6). The control design is a design based on the Brunovsky normal form and application of the Pontrjagin's maximum principle step by step for sufficiently small time periods T [6, 8]. The optimal control law has the analytical form [9]:

$$D_{opt} = sign\left(\left(\sum_{i=1}^{6} i c_i \mu^{(i-1)}\right)(T-t)\left[\frac{(T-t)\mu(1-2kY_1)}{2} - 1\right]\right) D_{\max}, \tag{9}$$

$$where: sign(r) = 1, r > 0,\ sign(r) = 0, r \le 0.$$

The time interval T can be the step of discretization of the differential equation solver. The sum in Eq. (10) is the derivative of the utility function $U(\mu)$. It is clear that the "time-minimization" control is determined from the ***sign*** of the utility derivative. Thus, the control input is $D = D_{max}$ or $D = 0$. The solution is a "*time-minimization*" control (if the time period T is sufficiently small). The control brings the system back to the set point for minimal time in any case of specific growth rate deviations. The demonstration is shown in [8].

The previous solution permits easy determination of the control stabilization ***of the fed-batch process***. The control law is based on the solution of the next optimization problem: **Max**$(U(\mu(T_{int})))$, ***where the variable*** μ ***is the specific growth rate,*** **(**$\mu\in$**[*0,*** μ_{max}**],** $F\in$**[*0,*** F_{max}**]). *Here*** $U(\mu)$ ***is the utility function in Fig. 3*** **and** F **is the control input** (the substrate feed rate):

$$
\begin{aligned}
&\max(U(\mu(T_{int}))),\ \mu\in[0,\mu_{max}],\ t\in[0,T_{int}],\ F\in[0,F_{max}]\\
&\dot{X} = \mu X - \frac{F}{V}X\\
&\dot{S} = -k\mu X + (So - S)\frac{F}{V}\\
&\dot{\mu} = m\left(\mu_m\frac{S}{(K_S + S)} - \mu\right)\\
&\dot{V} = F
\end{aligned}
\qquad (10)
$$

The control law ***of the fed-batch process*** has the same form (9) because $D(t)$ is replaced with $F(t)/V(t)$ in the fed-batch model. Thus, the feeding rate $F(t)$ takes $F(t) = F_{max}$ or $F(t)=0$, depending on $D(t)$ which takes $D = D_{max}$ or $D = 0$.

We conclude that the control law (9) bring the system to the optimal point (optimal growth rate) with a" time minimization" control, starting from any deviation point of the specific growth rate (Fig. 4). Thus, we design the next control law:

1. At the interval $[0,\ t_1]$ the control is **"**time-minimization**"** control (9), where $\mu(t_1)$ = **(x$_{30}$-ε), ε > 0**, **x$_{30}$** = max**(**$U(\mu)$ (D is replaced with $F = \gamma F_{max}$, $1\geq\gamma>0$, when $D = D_{max}$, The choice of γ depends on the step of the equation solver and is not a part of the optimization (here $\gamma = 0.123$**)**;
2. At the interval $[t_1,\ t_2]$ the control is $F = 0$ ($\mu(t_1)$=(**x$_{30}$**-ε), $\mu(t_2)$ = **x$_{30}$ -** to be escaped an overregulation);

3. After this moment the control is the control (9) with $F = \gamma F_{\max}$, when $D = D_{\max}$ (chattering control with $1 \geq \gamma > 0$).

The deviation of the fed-batch process with this control is shown on Fig. 4.

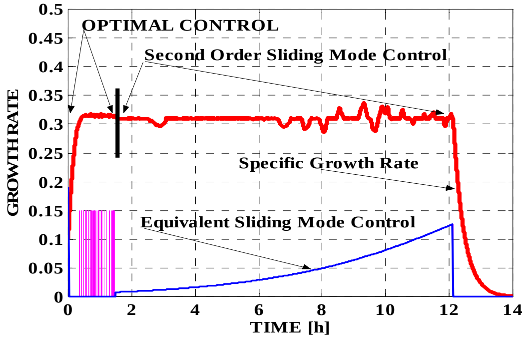

Fig. 4. Stabilization of the fed-batch process

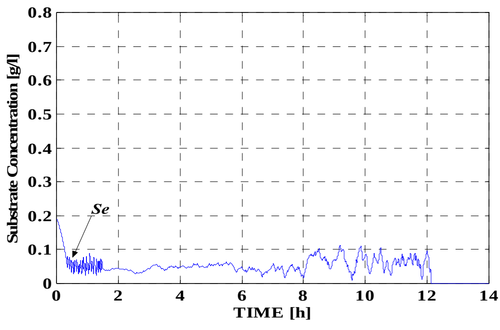

Fig. 5. Substrate concentration in the bioreactor

After the stabilization the process can be maintained around the optimal parameters with control in sliding mode (Figs. 4-5). Possible solution in sliding mode is alternation of μ_m (as a function of the temperature and the acidity in the bioreactor) or alternation of F [2].

5. OPTIMAL PROFILE AND DETERMINATION OF MOMENT t_1 AND MOMENT t_2

The solution described in the previous chapter is a chattering control. In this chapter we determine a smooth control solution for determination of the interval [t_1, t_2] - determination of the moments t_1 and t_2. Here is supposed that $\mu_i(0)<\mu_e$, $S(0)<S_e$ where:

$$x_{30} = \mu_e = \mu_m \frac{S_e}{K_s + S_e} \quad (optimal\ pont) \Rightarrow \quad S_e = \frac{K_s \mu_e}{\mu_m - \mu_e}, x_{30} = 0.31. \tag{11}$$

The optimization problem is:

$$\min\left(\int_0^{t2} |\mu_e - \mu(t)| dt\right),\ \mu \in [0, \mu_{\max}],\ t \in [0, t_2],\ F \in [0, F_{\max}],\ \mu_e = 0.31,$$

$$\begin{aligned} \dot{X} &= \mu X - \frac{F}{V} X \\ \dot{S} &= -k\mu X + (So - S)\frac{F}{V} \\ \dot{\mu} &= m\left(\mu_m \frac{S}{(K_S + S)} - \mu\right) \\ \dot{V} &= F \end{aligned} \tag{12}$$

A supplementary condition is “elimination of any overregulation” of μ. The optimal control law, according the previous solution is:

1. At the time interval [0, t_1] the control is $F(t) = \gamma F_{max}$. This is proved in [8], (γ = 0.123, this parameter is not a part of the optimization**)**;

2. At the interval [t_1, t_2] the control is $F = 0$ (to be escaped any overregulation). The growth rate changes from μ_n to μ_e where $\mu(t_1) = \mu_n$, $(\mu(t_2) \wedge S(t_2) = S_e)$ and $\mu_n<\mu_e$. We effect this by determination of a manifold on the base of the problem (12) (Eq. 14). When the state vector across over this manifold the control becomes $F(t_1) = 0$. The moment t_2 is the moment of over crossing the manifold $(\mu = \mu_e) \cap (d\mu/dt=0)$;

3. After the moment t_2 the control is $F(t) = (kX(t)\mu(t)V(t)/(So-S_e)$, where $X(.)$ is the quantity of biomass in the bioreactor (if $F(t)>F_{max}$ we pose $F = F_{max}$, and here $\gamma = 1$).

The determination of moment t_1 and moment t_2 is based on the next optimal control problem:

$$\min\left(\int_{t_1}^{t_2}(\mu_e-\mu(t))dt\right),\ \mu\in[0,\mu_{max}],\ t\in[t_1,t_2],\ F\in[0,F_{max}],\ \mu_e=0.31,$$

$$\begin{aligned}
&\dot{X}=\mu X\\
&\dot{S}=-k\mu X\\
&\dot{\mu}=m\left(\mu_m\frac{S}{(K_S+S)}-\mu\right) \qquad (13)\\
&\mu(t_2)=\mu_e,\quad \dot{\mu}(t_2)=0.
\end{aligned}$$

Here is supposed that $\mu(0)<\mu_e$. We propose the next numerical solution for determination of an approximation of moment t_1:

- If $S(0)>S_n$ t_1 is equals to zero ($t_1 = 0$). In this case the initial conditions are equivalent to these of model (3). An overregulation is possible, because the process is uncontrollable from moment 0 to moment t_2;
- If $S(0)<S_n$ and $\mu(0)<\mu_e$; the moment t_1 is the moment at which the state vector of the differential Eq. (13) across over the next manifold:

$$\begin{aligned}
&Manifold\ (X,S,\mu,\mu_e,Ks)=-\mu_e+\exp(-f(t_1))\mu(t_1)+\\
&+\mu_m m\left[f(t_1)+\frac{Ksf(t_1)}{(S_e-S(t_1))}\ln\left|\frac{Ks+S(t_1)}{(Ks+S_e)}\right|\right]-\mu_m m^2\left[\frac{mf(t_1)-1}{m^2}+\frac{\exp(-f(t_1))}{m^2}\right]=0, \qquad (14)
\end{aligned}$$

$$where\ \ f(t_1)=\left[\frac{\left[\dfrac{(\mu_e-\mu(t_1))}{m}+\ln\left(\dfrac{X(t_1)+S(t_1)-S_e}{X(t_1)}\right)\right](S_e-S(t_1))}{\mu_m\left[S_e-S(t_1)+Ks\ln\left|\dfrac{Ks+S(t_1)}{(Ks+S_e)}\right|\right]}\right].$$

Bioautomation, 2007, 8, Suppl. 1, 13 – 26 ISSN 1312 – 451X

The moment t_2 is determined approximately as follows $t_2 = t_1 + f(t_1)$. The solution is shown on Fig. 6.

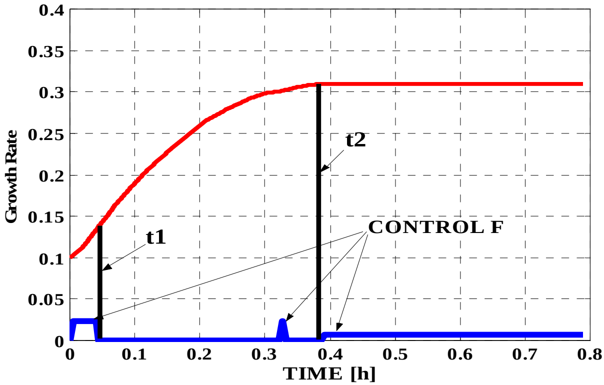

Fig. 6. Optimal profile with the manifold (14)

The optimal profile of the fed-batch cultivation, during the whole time period is shown on Fig. 7. This control law determines the same optimal solution as the chattering control (9).

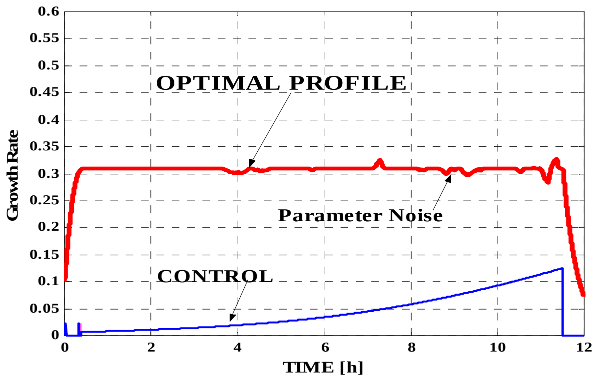

Fig. 7. Optimal profile of the growth rate

The manifold (14) is determined on the base of the optimization problems (12 and 13) with some simplification and approximation of the integral. This is a numeric solution. The moment t_2 is determined approximately. If the process do not reaches the value μ_e at the calculated time t_2 (this is a numerical solution) the step is repeated iteratively.

6. CONCLUSIONS

In the paper is presented a control design based both on the Brunovsky normal form of the Monod-Wang kinetics model and on a chattering optimal control design. The optimal profile is determined providing against the overregulation of the specific growth rate. The simulation confirms the fact that the sliding optimal solutions are robust solutions.

The evaluation of the expert utility criteria is an iterative process. This characteristic permits an iterative engineer control design and easy correction of the control law in agreement with some new changes in the technological conditions.

Acknowledgements
This work is partially supported from National Science Fund Project № MI – 1505/2005.

REFERENCES

1. Elkin V., Reduction of Non-linear Control Systems: A Differential Geometric Approach – Mathematics and its Applications, Vol. 472, Handbound, Kluwer, 1999.
2. Emelyanov S., S. Korovin and A. Levant. Higher-order Sliding Modes in Control Systems, *Differential Equations*, 29(11), 1993, 1627-1647.
3. Fishburn, P., Utility Theory for Decision-Making, Wiley, New York, 1970.
4. Gardner R., W. Shadwick, The GS algorithm for exact linearization to Brunovsky normal form, *IEEE Trans. Autom. Control*, 1992, 37(2), 224-230.

5. Keeney, R., H. Raiffa, Decision with Multiple Objectives: Preferences and Value Trade-offs, New York, 1976.
6. Krotov, V., V. Gurman, Methods and Problems in the Optimal Control, Nauka, Moscow, 1973.
7. Neeleman R., Biomass Performance: Monitoring and Control in Bio-pharmaceutical production, Thesis, Wageningen University, 2002.
8. Pavlov Y., K. Ljakova, Equivalent Models and Exact Linearization by the Optimal Control of Monod Kinetics Models, *Bioautomation*, 2004, 1, 42-56.
9. Pavlov Y., Subjective preferences, value and decision: Stochastic approximation approach, *Comptes Rendus de L'Academie Bulgare des Sciences*, 2005, 58(4), 367-372.
10. Staniskis J., D. Levisauskas, R. Simutis, U. Viestur, M Kristapsons, Automation of Biotechnological Processes. Measurements, Optimization and Control, Zinatne, Riga, 1992.
11. Tzonkov St., D. Filev, I. Simeonov, L. Vaklev, Control of Biotechnological Processes, Technika, Sofia, 1992.
12. Wang T., C. Moore, D. Birdwell, Application of a Robust Multivariable Controller to Non-linear Bacterial Growth Systems, - In: *Proc. of the 10th IFAC Congress on Automatic Control*, Munich, 1987, 39-56.