Bioautomation, 2008, 11, Suppl., 1-12 ISSN 1312 – 451X

Preprints of the 21st Int. Symposium Bioprocess Systems
Sofia, Bulgaria, November 4-5, 2008

Equivalent Forms of Wang-Yerusalimsky Kinetic Model and Optimal Growth Rate Control of Fed-batch Cultivation Processes

Pavlov Y.

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

Summary: In the paper is presented a control design for optimal control and stabilization of the specific growth rate of fed-batch biotechnological processes. The control design is based on a Wang-Yerusalimsky kinetic model and its equivalent Brunovsky normal form. The control is written based on information of the growth rate.

Keywords: Yerusalimsky kinetic, Wang model, Brunovsky normal form, Fed-batch, Optimal control

1. INTRODUCTION

Complicated structure and non-linearity of the comportment characterize the cultivation processes. Many mathematical investigations and models have been proposed but few of these models are used sufficiently successfully in industrial plants.

A possible way out of these difficulties is presented by the functional state modeling approach. Following the approach the cultivation process is decomposed into operation regimes. More simple mathematical models in these regimes dynamically describe the process performances [9, 10, 11, 12, 13, 15]. The control problems are decomposed into sub problems that could be described and solved separately in more constraint process state conditions. Considering an *E. coli* fed-batch cultivation process was found in CLBME, Bulgarian Academy of Sciences that good solutions are possible with Monod and Yerusalimsky models [10, 11].

The aim of this paper is an investigation of the Yerusalimsky model with a new mathematical approach based both on the differential

geometry and on the optimal control theory. This approach is developed in CLBME, Bulgarian Academy of Sciences in the previous decade. It permits new optimal control solutions for some difficult to solve optimal control problems in the field.

2. FUNCTIONAL STATE MODELING APPROACH AND WANG-YERUSALIMSKY KINETIC MODEL

The concept of functional state modeling developed by Zhang could be applied for modelling of *E. coli* cultivation [10, 15]. According to [10, 11] the whole bacteria growth process (*E. coli*) can be divided into four functional states in fed-batch cultures:

- First acetate production state (FS I);
- Mixed oxidative state (FS II);
- Complete sugar oxidative state (FS III);
- Second acetate production state (FS V).

Considering an *E. coli* fed-batch cultivation process the mathematical descriptions for the different functional states is based on Monod and Yerusalimsky kinetic models [10, 11]. That is why Wang-Monod and Wang-Yrusalimsky kinetic models could describe completely this fed-batch cultivation by a sequence of successive utilization of these models. The parameters of the models will change in the different functional sates. The Wang-Yrusalimsky kinetic model could be applied in the functional states with distinctive occurrence of an acetate inhibition effect. In the *E-coli* cultivation process the equation describing the ethanol production could be omitted [9, 10].

3. DESCRIPTION OF THE DYNAMICAL MODELS

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. Mathematical unstructured models of fed-batch process can be written based on mass balance equations [5, 12, 13, 14]. Below we shall investigate an enlarged form of the Yerusalimsky kinetic model (Wang-Yerusalimsky model):

$$\begin{aligned}
\dot{X} &= \mu X - \frac{F}{V} X, \\
\dot{S} &= -k\mu X + (So - S)\frac{F}{V}, \\
\dot{\mu} &= m(\mu_m \frac{S}{(K_S + S)} \frac{k_E}{(k_E + X)} - \mu), \\
\dot{V} &= F, \\
\dot{E} &== k_2 \mu E - \frac{F}{V} E, \\
\dot{A} &== k_3 \mu X - \frac{F}{V} A,
\end{aligned} \tag{1}$$

where X is 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 , k_3 and k_E–constant, [g/g]; m–coefficient [-]; E–the concentration of ethanol, [g/l]; A–the concentration of acetate [g/l].

We preserve the notation $U(.)$ for the criteria for optimization (*, a unimodal polynomial utility function of degree 6*). 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 [–], k_3=1/71 [–], k_E=50 [–], F_{max}= 0.19 [h^{-1}], V_{max}=1.5 [l]. The system parameters are taken from the next papers [9, 10, 11].

The dynamics of μ (equation 3, formulae 1) is modeled as a first order lag process with rate constant m, in response to the deviation in μ. The 5th equation describes the production of ethanol (E). The last equation describes the production of acetate (A). This equation is dynamically equivalent to the first one. We implement a simple transformation: X=(1/k_3)A. After that the first and the last equations become dynamically equivalent. The new form of the non-linear kinetic model is:

$$\begin{aligned}
\dot{X} &= \mu X - \frac{F}{V} X, \\
\dot{S} &= -k\mu X + (So - S)\frac{F}{V}, \\
\dot{\mu} &= m(\mu_m \frac{S}{(K_S + S)} \frac{k_E}{(k_E + X)} - \mu), \\
\dot{V} &= F, \\
\dot{E} &== k_2 \mu E - \frac{F}{V} E.
\end{aligned} \tag{2}$$

The initial values of the state variables are: $X_i(0)=0.99$; $S_i(0)=0.01$; $\mu_i(0)=0.1$; $E_I(0)=0.1$; $V_i(0)=0.5$. The mathematical results described in the paper have a common significance. That is why some of the parameters are taken from different sources.

4. BRUNOVSKY NORMAL FORM OF WANG-YERUSALIMSKY MODEL AND TIME MINIMIZATION OPTIMAL CONTROL

In the beginning we shall apply the mathematical approach and diffeomorfic transformations to a Wang-Yerusalimsk*y* kinetic model which describes a continuous cultivation process. After that we shall show that the time minimization optimal control of the fed-batch process has the same form as that of the continuous process. The ***continuous process*** is described dynamically by the next model:

$$\begin{aligned}
&\dot{X} = \mu X - DX,\\
&\dot{S} = -k\mu X + (So - S)D,\\
&\dot{\mu} = m(\mu_m \frac{S}{(K_S + S)} \frac{k_E}{(k_E + X)} - \mu),\\
&\dot{E} == k_2 \mu E - DE.
\end{aligned} \tag{3}$$

Here D denotes the dilution rate. We apply the next transformation to model (3):

$$\begin{aligned}
&u_1 = \frac{X}{(So - S)},\\
&u_2 = S,\\
&u_3 = \mu,\\
&u_4 = \frac{E}{(So - S)}.
\end{aligned} \tag{4}$$

The dynamical model (3) of the continuous process obtains the next equivalent form:

$$\begin{aligned}
&\dot{u}_1 = u_3 u_1 - k u_1^2 u_3,\\
&\dot{u}_2 = -k u_1 (So - u_2) u_3 + D(So - u_2),\\
&\dot{u}_3 = m(\mu_m \frac{u_2}{(K_S + u_2)} \frac{k_E}{(k_E - u_1(So - u_2))} - u_3),\\
&\dot{u}_4 = u_4 u_3 (k_2 - k u_1).
\end{aligned} \tag{5}$$

The next step is application of the GS algorithm for exact linearization to Brunovsky normal form, published by Gardner and Shadvwick in 1992 [3]. The new equivalent model of model (3) and model (5) has the form [1, 6, 7]:

$$\begin{aligned}
&\dot{Y}_1 = Y_2 \\
&\dot{Y}_2 = Y_3 \\
&\dot{Y}_3 = W \\
&\dot{Y}_4 = Y_4 Y_2 \frac{(k_2 - kY_1)}{Y_1(1-kY_1)}.
\end{aligned} \tag{6}$$

The state vector of model (6) has the next explicit extended form:

$$\begin{aligned}
&Y_1 = u_1 \\
&Y_2 = u_3(u_1 - ku_1^2) \\
&Y_3 = u_3^2(u_1 - 3ku_1^2 + 2k^2u_1^3) + m(u_1 - ku_1^2)(\mu_m \frac{u_2 k_E}{(K_S + u_2)(k_E + u_1(So - u_2))} - u_3) \\
&Y_4 = u_4.
\end{aligned} \tag{7}$$

The control input of the model (6) is W and it has the next huge analytical form:

$$\begin{aligned}
W = {} & 2u_3(u_1 - 3ku_1^2 + 2k^2u_1^3)m(\mu_m \frac{u_2}{(K_S + u_2)} \frac{k_E}{(k_E + u_1(So - u_2))} - u_3) + \\
& + u_3^3(1 - 6ku_1 + 6k^2u_1^2)(u_1 - ku_1^2) + \\
& + u_3 m(1 - 2ku_1)(u_1 - ku_1^2)(\mu_m \frac{u_2}{(K_S + u_2)} \frac{k_E}{(k_E + u_1(So - u_2))} - u_3) - \\
& - u_3 m(u_1 - ku_1^2)^2 \mu_m \frac{u_2}{(K_S + u_2)^2} \frac{k_E}{(k_E + u_1(So - u_2))^2}(So - u_2) - \\
& - m^2(u_1 - ku_1^2)(\mu_m \frac{u_2}{(K_S + u_2)} \frac{k_E}{(k_E + u_1(So - u_2))} - u_3) + \\
& + m(u_1 - ku_1^2) \times \\
& \times \frac{\mu_m k_E (K_S + u_2)(k_E + u_1(So - u_2)) - \mu_m u_2 k_E (k_E + u_1 So - K_S u_1 - 2u_1 u_2)}{(K_S + u_2)^2 (k_E + u_1(So - u_2))^2} \times \\
& \times \left[-ku_3 u_1(So - u_2) + (So - u_2)D \right]
\end{aligned} \tag{8}$$

The input D of the continuous model (3) takes part in the last mathematical expression of formula (8):

$$\begin{aligned} & f_{input}(u_1,u_2,u_3,u_4,D) = \\ & = m(u_1 - ku_1^2)\frac{\mu_u k_E((K_S+u_2)(k_E+u_1(So-u_2))-u_2(k_E+u_1So-K_Su_1-2u_1u_2))}{(K_S+u_2)^2(k_E+u_1(So-u_2))^2}\times \\ & \times(So-u_2)D = \\ & = m(u_1-ku_1^2)\frac{\mu_u k_E(K_Sk_E+K_Su_1So+u_1u_2^2)}{(K_S+u_2)^2(k_E+u_1(So-u_2))^2}(So-u_2)D \end{aligned} \tag{9}$$

The last equation of model (6) can be solved by separation of variables:

$$\dot{Y}_4 = Y_4Y_2\frac{(k_2-kY_1)}{Y_1(1-kY_1)} = Y_4\dot{Y}_1\frac{(k_2-kY_1)}{Y_1(1-kY_1)}, \tag{10}$$

$$\frac{\dot{Y}_4}{Y_4} = \dot{Y}_1\frac{(k_2-kY_1)}{Y_1(1-kY_1)} \tag{11}$$

Consecutively the variable Y_4 depend only from Y_1 and can be described analytically by Y_1. The solution of equation (11) is:

$$Y_4 = k_4Y_1^{k_2}\left|1-kY_1\right|^{(1-k_2)}, \quad k_4 \in \boldsymbol{R}. \tag{12}$$

That is why models (3), (5) and (6) are equivalent dynamically to the next Brunovsky normal form [1, 3]:

$$\begin{aligned} \dot{Y}_1 &= Y_2 \\ \dot{Y}_2 &= Y_3 \\ \dot{Y}_3 &= W \end{aligned} \tag{13}$$

It is clear that if k_2=0 or k_2=1 (formula 12) then the variables X and E in model (1) are equivalent with precision up to an affine transformation and the model is over-regulated.

We continue the investigation with a mathematical technique described in papers [6, 7, 8]. Let $U(\mu)$ be unimodal polynomial function, criteria for optimization and control. The next step is resolution of the optimal control problem [7, 8]:

$$\begin{aligned}
&\mathbf{max}(U(\mu)), \quad \mu \in [0, \mu_{\max}], \quad t \in [0,T], D \in [0, D_{\max}] \\
&\dot{X} = \mu X - DX, \\
&\dot{S} = -k\mu X + (So - S)D, \\
&\dot{\mu} = m(\mu_m \frac{S}{(K_S + S)} \frac{k_E}{(k_{E+} X)} - \mu), \\
&\dot{E} == k_2 \mu E - DE.
\end{aligned} \tag{14}$$

The input D of model (3) takes part only in the last part of the function W. According to formula (9) the solution is the same as these in papers [7, 8]. The control law is based on the application of the Brunovsky normal form and on the Pontryagin's maximum principle. The maximum principle is applied step by step for sufficiently small time periods T [4, 7]. The control law has the analytical form [8]:

$$D_{opt} = sign\left(\left(\sum_{i=1}^{6} ic_i \mu^{(i-1)}\right)(T-t)\left[\frac{(T-t)\mu(1-2kY_1)}{2} - 1\right]\right) D_{\max}, \tag{15}$$
$$where: sign(r) = 1, r > 0, \; sign(r) = 0, r \le 0.$$

The time interval T is chosen close to the step of discretization of the differential equation solver. The sum in formula (15) is the derivative of the polynomial function $U(\mu)$. It is clear that the "time-minimization" control is determined from the ***sign*** of the derivative of the function $U(\mu)$. Thus, the control 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 working point for minimal time in the case of growth rate deviations [7, 8].

The previous solution permits easy determination of the control law of ***the fed-batch process***. The control law is based on the solution of the following optimization problem:

Max($U(\mu(T_{int}))$**), *where the variable* μ *is the specific growth rate,* ($\mu \in [0, \mu_{max}]$, $F \in [0, F_{max}]$). *Here* $U(\mu)$ *is a unimodal criteria function* and *F* is the control input (**the substrate feed rate**):**

$$\begin{aligned}
&\mathbf{max}(U(\mu(T_{\text{int}}))), \mu \in [0, \mu_{\max}], t \in [0, T_{\text{int}}], F \in [0, F_{\max}] \\
&\dot{X} = \mu X - \frac{F}{V} X, \\
&\dot{S} = -k\mu X + (So - S)\frac{F}{V}, \\
&\dot{\mu} = m(\mu_m \frac{S}{(K_S + S)} \frac{k_E}{(k_{E+} X)} - \mu), \\
&\dot{V} = F, \\
&\dot{E} == k_2 \mu E - \frac{F}{V} E.
\end{aligned} \tag{16}$$

The control law ***of the fed-batch process*** has the same form (15) because $D(t)$ is replaced with $F(t)/V(t)$ in model (1). Thus, the feeding rate $F(t)$ takes $F(t)=F_{\max}$ or $F(t)=0$.

5. STABILIZATION OF THE FED-BATCH PROCESS IN THE "BEST" GROWTH RATE

We conclude that the control law (15) bring the system to the optimal specific growth rate with a" time minimization" optimal control, starting from any deviation from the set point of the optimal specific growth rate (fig. 1) [7].

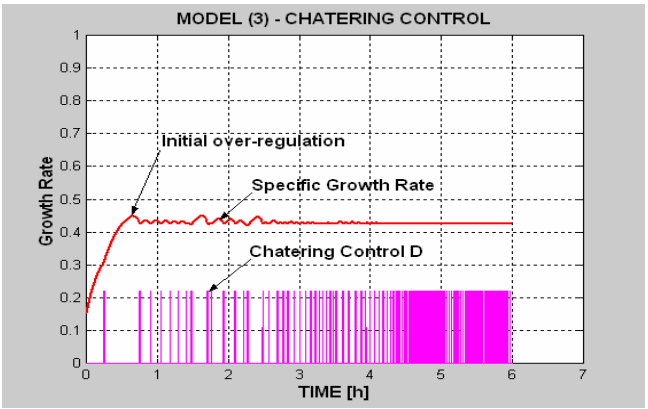

Fig. 1 Chattering control and stabilization of the specific growth rate

Thus, we design the next control law for stabilization of the fed-batch process in the "***best***" technological value of the specific growth rate [7]:

1. Time interval - [0, t_1]: the control is a **"**time-minimization**"** control (formula (15)), where $\mu(t_1)=(\mathbf{x_{30}-\varepsilon})$, $\boldsymbol{\varepsilon>0}$, $\mathbf{x_{30}}=max(U(\mu))$. The input 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 (in this investigation);
2. Time interval - [t_1, t_2]: the control is $F=0$ ($\mu(t_1)=(\mathbf{x_{30}-\varepsilon})$, $\mu(t_2)=\mathbf{x_{30}}$ and $d/dt(\mu(t_2))=0$ (to avoid an over-regulation);
3. After the moment t_2 the control is the control (15) with $F=\gamma F_{max}$, when $D=D_{max}$ (chattering control with $1\geq\gamma>0$).

The performances of the fed-batch process with this control law are shown on figure (2). The sliding mode control in figure (2) is based on the Monod kinetic models (states III, IV and V [9, 10]) [2, 7].

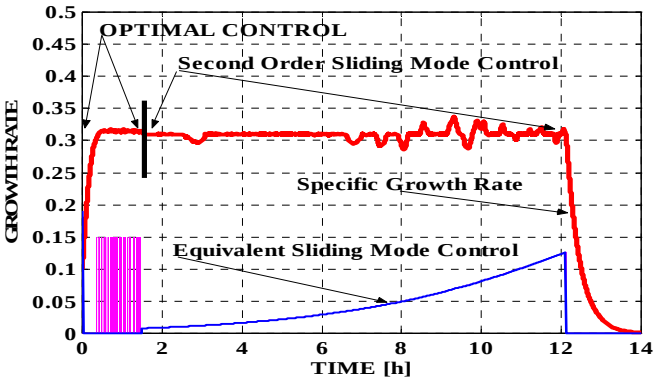

Fig. 2 Optimal profile and stabilization of the fed-batch process

The control solution without over-regulation of the growth rate is shown on figure 3 and has the same form as this in papers [7]:

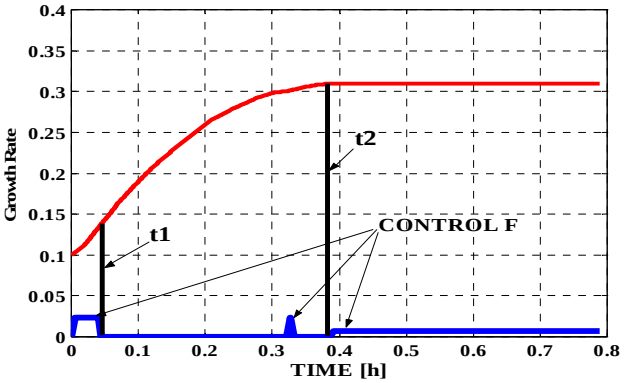

Fig. 3 Optimal profile without over- regulation of μ

The control law in time interval [0, 1] h (figures 2 and 3) is a control law based on Wang–Yerusalimsky kinetic models (model (1) and model (2)). The most difficult part of this investigation is the determination of approximations of the moments t_1 and t_2.

6. DISCUSSIONS

A manifold is determined and applied for approximation of the moments t_1 and t_2 when the fed-batch process is described by a Wang-Monod kinetic model [7, 14]. We denote with μ_e the growth rate and X_e- is the biomass concentration in steady state. The moment t_1 is determined when the state vectors of the Monod model across this manifold [7]. The moment t_2 is the moment of intersection of another manifold $(\mu=\mu_e)\cap(d\mu/dt=0)$. The solution needs determination of the substrate concentration S_e in steady states (the working point of the process): The substrate concentration S_e of the Monod model is determined by the formula:

$$\mu_e = \mu_m \frac{S_e}{K_s + S_e} \quad (\textit{optimal set} \text{ point}) \Rightarrow \quad S_e = \frac{K_s \mu_e}{\mu_m - \mu_e}. \tag{17}$$

When the Wang-Yerusalimsky kinetic model is used the situation is different. The substrate concentration S_e depends now both from the growth rate μ_e and from the biomass concentration X_e.

$$\mu_e = \mu_m \frac{S_e}{(K_S + S_e)} \frac{k_E}{(k_E + X_e)}. \quad (18)$$

The growth rate μ_e and the biomass concentration X_e are dependent on the moment of interception with the manifold. A possible way out of this situation is replacement of the biomass concentration X_e with $X(t_1)$ and calculation of the manifold in each step of the equation solver.

$$S_e \approx \frac{K_S \mu_e (k_E + X(t_1))}{(k_E \mu_m - \mu_e (k_E + X(t_1))}. \quad (19)$$

In all cases this will lead to augmentation of the calculations.

7. CONCLUSIONS

The Yerusalimsky model is discussed as a good solution for modeling of cultivation processes [11]. In the paper is presented a control design for optimal control and stabilization of the specific growth rate. The control design is based both on the Brunovsky normal form of the Wang-Yerusalimsky kinetic model and on a chattering optimal control design. The Wang-Monod kinetic model is a restricted form of this model ($k_E \rightarrow \infty$). That is why the Wang-Yerusalimsky kinetic model could be accepted as a common model in different functional state regimes for some investigations.

The ethanol concentration and the acetate concentration are determined analytically as functions of the biomass concentration, substrate concentration and the specific growth rate, regarding Wang-Yerusalimsky model.

The optimal profile and the control law for optimal control and stabilization of the specific growth rate of Wang-Yerusalimsky kinetic model remain the same as those of Wang-Monod kinetic model.

ACKNOWLEDGEMENTS

This work is partially supported from FNSF-MI-1505/2005.

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