Bioautomation, 2004, vol. 1, pp. 67-82

Modelling, Optimization and Optimal Control of Small Scale Stirred Tank Bioreactors

Mitko Petrov, Tatjana Ilkova, Stoyan Tzonkov, Uldis Viesturs*

Centre of Biomedical Engineering, Bulgarian Academy of Sciences
105, Acad. G. Bonchev Str., Sofia 1113, Bulgaria
E-mail: mpetrov@clbme.bas.bg,
tanja@clbme.bas.bg,
tzonkov@clbme.bas.bg

*****Latvian State Institute of Wood Chemistry, 27 Dzerbenes Str., LV-1006 Riga, Latvia,*
E-mail: koks@edi.lv

Abstract: *Models of the mass-transfer in a stirred tank bioreactor depending on general indexes of the processes of aeration and mixing in concrete simplifications of the hydrodynamic structure of the flows are developed. The offered combined model after parameters identification is used for optimization of the parameters of the apparatus construction. The optimization problem is solved by using of the fuzzy sets theory and in this way the unspecified as a result of the model simplification are read. In conclusion an optimal control of a fed-batch fermentation process of E. Coli is completed by using Neuro-Dynamic programming. The received results after optimization show a considerable improvement of the mass-transfer indexes and the quantity indexes at the end of the process.*
Keywords: *Mass-transfer, Volumetric mass-transfer coefficient, Power input, Gas-hold up, Fuzzy sets, Neuro-dynamic programming*

Introduction

The bioreactors in that the energy is led in simultaneously in the gas and the liquid phase are appeared universals from the point of view of creating of definite intensity of the mass-transfer and the mixing. In the mechanical mixing of the middle as a result of the well-built turbulence the largest desperation of the gas in the liquid is reached. It at enough large gas hold-up creates a big relative surface of the phase contact and allows cultivation of cultural middle with components that have large density difference. This worthiness of the apparatuses with mechanical mixing brought to its wide using. The biggest application they have in the production of enzymes, amino acids, antibiotics and etc. [22,23].

The development of the new methods for analysis, modeling, control and optimization, such as neural networks [4,7,11,13-16] and fuzzy sets [1,2,5,24-26], their combination [3,6,11,12] and their successful application in the field of bioprocess engineering [4,11-14,16] shows their flexibility and possibility for their use for modeling of complex processes.

The aim of this paper is development of the mathematical models of the mass-transfer. On this base the optimization of the parameters of the bioreactor construction will be made and the optimal control of a concrete fermentation process will be made.

Modeling of mass-transfer in the bioreactor

The balance equations of the liquid and the gas phases in this case are deduced at the next basic suppositions:

1. The oxygen concentration in the gas phase is determined by a diffusion model at stationary conditions [17-20]:

$$D_L \frac{d^2 C_G}{dz^2} - W_G \frac{dC_G}{dz} - \frac{K_L a}{\varepsilon_G}\left(\frac{C_G}{m_L} - C_L\right) = 0 \qquad (1)$$

2. The liquid phase is perfect mixed [9,10]:

$$\frac{dC_L}{dt} = \frac{K_L a}{\varepsilon_L}\left(\frac{C^*}{m_L} - C_L\right) \qquad (2)$$

3. The balance concentration is determined as a mean value in the height of filling of the bioreactor:

$$L\,C^* = \int_0^L C_G(z)dz\,. \qquad (3)$$

The initial and boundary conditions have a type [9,10]:

$$t = 0:\ C_L(0) = 0;\quad C_G(z,0) = C_G^0;\quad 0 \le z \le L.$$

$$z = 0:\ W_G\, C_G^0 = W_G\, C_G - D_L \frac{dC_G}{dz};\quad z = L:\ \frac{dC_G}{dz} = 0.$$

The model equations, the initial and boundary conditions after lead in of dimensionless quantities (length and concentrations) have a type:

$$\frac{1}{Pe}\frac{d^2\overline{X}}{d\eta^2}-\frac{d\overline{X}}{d\eta}-a_3\overline{X}=-a_3\overline{Y}$$
$$X^*=\int_0^1\overline{X}(\eta)d\eta \qquad (4)$$
$$\frac{d\overline{Y}}{dt}=a_2(X^*-\overline{Y})$$
$$t=0:\overline{Y}(0)=0;\quad 0\le\eta\le 1;$$
$$\eta=0:1=\overline{X}-\frac{1}{Pe}\frac{d\overline{X}}{d\eta};\quad \eta=1:\ \frac{d\overline{X}}{d\eta}=0.$$

The solution of (4) is:

$$\overline{X}(\eta,t)=A_0\exp(r_1\eta)+B_0\exp(r_2\eta)+C_0$$
$$X^*(t)=A_0\frac{\exp(r_1)-1}{r_1}+B_0\frac{\exp(r_2)-1}{r_2}+C_0\ . \qquad (5)$$
$$\overline{Y}(t)=X^*(t)\left[1-\exp(-a_2t)\right]$$

The root of the characteristic equation $r^2\text{-}Pe_G.r\text{-}Pe_G.a_3=0$ is determined by the next dependence: $r_{1,2}=0{,}5Pe\pm\sqrt{D};\quad D=\sqrt{(Pe/2)^2+a_3Pe}$.

The constants A_0, C_0 and B_0 are determined by the boundary conditions:

$$A_0=a_8B_0\,,\ C_0=1-a_9B_0,\quad B_0=\frac{1+\exp(-a_2t)}{a_9}.$$

where: $a_8=-(r_2/r_1)\exp\left(-2\sqrt{D}\right), a_9=1+a_8-(a_8r_1+r_2)/Pe$.

The coefficients have the next dependence value: $m_L=82.86$ and $Pe=1.5$.

The developed combined model of the mass-transfer will be used for optimization of the constructive bioreactor parameters.

Indexes of the hydrodynamic and the mass-transfer

The basic indexes that characterize the hydrodynamic in the bioreactor are the power input of the liquid phase and the dispersion system gas-liquid. Toward this index the kinetic energy of the flow fluctuations in characteristic points of the bioreactor volume can be supplemented. In this way the level of stirring, the presence of locally intensive and "*dead*" zones, the level of micro- and macrostirring and medium turbulization can be determined.

As basic indexes of the hydrodynamic on this stage the power input without aeration for the two-phase system gas-liquid are investigated. The power input without aeration is determined by [21]:

$$Eu = \frac{P_L}{\rho n^3 d^5} = C_0 \left(\frac{\rho n d^2}{\nu} \right)^{x_1} = C_0 \, Re^{x_1} \tag{6}$$

Including the eccentricity of the impeller respect to its axis of the rotation as new simplex of geometrical similarity leads to the next type of an equation (6):

$$Eu = C_1 \; Re^{x_2} , \quad C_1 = C_0 \left(\frac{\delta}{d} \right)^{x_3} , \tag{7}$$

The power input for the two-phase system gas-liquid is determined by [21]:

$$P_G = C_2 \left(Q_G / n d^3 \right)^{a_2} P_L^{b_2} . \tag{8}$$

As indexes of the mass-transfer in the bioreactor the volumetric oxygen mass-transfer coefficient and the gas-hold up are investigated. They are defined by the next dependence [9,10,21]:

$$K_L a = a \left(\frac{P_G}{V} \right)^b W_G^c \tag{9}$$

$$\varepsilon_G = \left(P_G / P_L \right) = C_3 \left(Q_G / n d^3 \right)^{a_3} . \tag{10}$$

In the upper dependence a new constructive parameter of the bioreactor-eccentricity of the impeller respect to its axis of the rotation is included.

Experimental investigation and identification

The experimental investigations are leaded in the elaborated laboratory bioreactor *2L-M* with disk magnetic coupling with sliding bearings with maximum volume *2L*. The basic dimensionless of bioreactor are shown in Table1.

Table 1 The basic dimensionless of bioreactor.

Number of baffle assembly	z_0	3
Number of perforation of aeration		120
High of liquid in bioreactor	L	120
High of blade of impeller	h	14
High of bioreactor	H	210
Diameter of aerator	D_a	50
Impeller diameter	d	58
Diameter of perforation of aeration	d_a	0.1
Bioreactor diameter	D	120
Wide the blades of impeller	l	12
Wide of the baffles	b_0	12
Angle of the blades of the impeller	α	90

The bioreactor is included in an automatic control system (*ACS*). The *ACS* was developed by a team from CLBA (CLBME)-BAS. It gives possibility for control of two bioreactors. *ACS* is developed as three different blocks. In block dosimeters the dosimeters for passing base, acid and foam slacked are disposed, and in block transformers- transformers for the basic measured values. The different elements of the systems can be assembled one with one or they can be divided. The system allows to be regulated the next parameters of the fermentation process: rotation speed, pO_2, pH, temperature and level of the foam in the bioreactor. In contrast to previous developments this system has possibility to be under control of a computer. The scheme of the experienced treatment is shown on Fig.1.

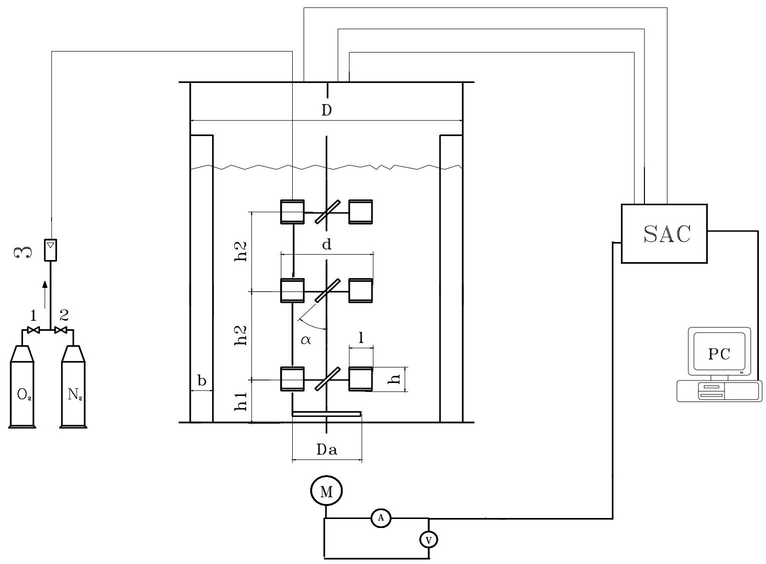

Fig. 1 The scheme of the experienced treatment.

Before determination of the coefficient of the offered models it is necessary we to choose algorithms with that its coefficients are to be defined and statistical criterions for a assessment models for adequate.

1. Methods for an assessment of the models

The determination of the coefficients in the offered models is made by different methods. The coefficients in the models (6)-(10) for modeling of the basic integral indexes of the processes of aeration and mixing are determined by nonlinear regression analysis. For this aim the subprogram *RNSSQ* for a nonlinear regression from the library *RNSSQ* of *FORTRAN* is used.

The determination of the coefficients in the mass-transfer model (5) is completed by the Nelder-Mead's method that is modification *SIMPLEX* method for optimization. This method is chosen, because it gives good and quick results at many numbers of the parameters. The Nelder-Mead's method is used to find the minimum of a multivariable function in the models:

$$SSWR = \sum_{i=1}^{N} \sum_{j=1}^{m} \frac{\Delta_{i,j}^{2}}{W_{i,j}^{2}} \quad \rightarrow \quad min\,, \tag{11}$$

where N is number of experimental data points; m-number of variables; $\Delta_{i,j} = \left(X_{i,j}^{m} - X_{i,j}^{e}\right)$; $X_{i,j}^{m}$, $X_{i,j}^{e}$ the model and experimental data points each variable respectively; $W_{i,j}$-mass of each variable, usually: $W_{i,j} = \max_{j}\left[X_{i,j}^{e},\, X_{i,j}^{e}\right]$.

The assessment of the model is made on base of following statistical criterions: Fisher's function F_E and correlation coefficient R^2.

2. Determination of the power input without aeration for the two-phase system gas-liquid

The investigations for determination of the power input for the liquid phase at different eccentricity of the impeller are implemented for Reynolds's criterion in the interval $Re=10^1 \div 10^5$. It is covered with solutions at different glycerin concentration in water.

On basis the received experimental results the curves of the power $Eu=f(Re,\delta)$ in logarithmic coordinates for different values of the eccentricity for the entire investigated interval of the Reynolds's, $Re=10^1 \div 10^5$ criterion are constructed (Fig.2).

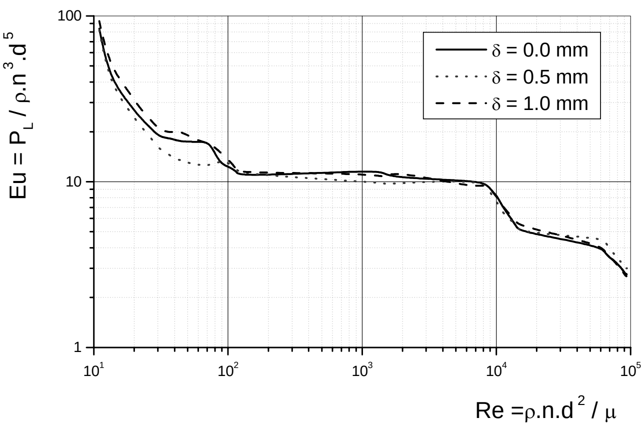

Fig. 2 Curves of the power at different eccentricity.

The model for determination of power input of the liquid at $\delta=0$ is:

$$Eu = \frac{P_L}{\rho\, n^3\, d^5} = 179.5\, Re^{-0.4}, \tag{12}$$

and for $\delta \neq 0$:

$$Eu = \frac{P_L}{\rho n^3 d^5} = 60.9 Re^{-0.18} \left(\frac{\delta}{d} \right)^{-0.23} \tag{13}$$

With correlation coefficients: $R^2_E=0.993$ and $R^2_T=0.164$, Fisher's function: $F_E=470.53$ and $F_T=2.05$. The received results show that the models are adequate.

The power input of the two-phase system gas-liquid is determined by help of the subprogram *RNSSQ* for nonlinear regression from the library *IMSL* of *FORTRAN*. The next values of the coefficients are received: $C_2=0.21; a_2=-0.1$ и $b_2=0.8$. After transformation we have:

$$P_G = 0{,}21 \left(Q_G / n d^3 \right)^{-0{,}1} P_L^{0.8} \tag{14}$$

The correlation coefficient and the experimental Fisher's function have respectively the next values: $R^2_E=0.979$ *u* $F_E=22.85$. Their theoretical values are respectively: $R^2_{T(55)}=0.273$and $F_T=2.109$. Their comparison them shows the model is adequate and it can be used for determination of the power input of a two-phase system gas-liquid.

3. Identification of the model for determination of K_La gas-hold up

The influence of the power input of a dispersion systems gas-liquid and the gas linear speed under the volumetric oxygen mass-transfer coefficient are determined. For determination of the model coefficients an algorithm and a program are developed with help on subprogram *RNSSQ* for nonlinear regression from the library *IMSL* of *FORTRAN* is used. The next values of the coefficients are received: $a=52.0; b=0.38; c=0.23$. And then we have:

$$K_L a = 52 \left(\frac{P_G}{V} \right)^{0{,}38} W_G^{0{,}23} . \tag{15}$$

The calculated and the theoretical coefficients have values: $R_E^2=0.998$ *u* $R^2_{T(N-2)}=0.950$. The calculated and the theoretical Fishers' functions have respectively values: $F_E=14.00$ *u* $F_{T(3,1)}=10.12$. The analysis of the received results shows that the model is adequate.

The influence of the eccentricity under the volumetric oxygen mass-transfer coefficient for different values of the relative power input (P_G/V) is shown on Fig.3. The rotation speed is changed in interval $100\text{-}1100\ min^{-1}$, at gas flow rate $Q_G=300\ L.h^{-1}$.

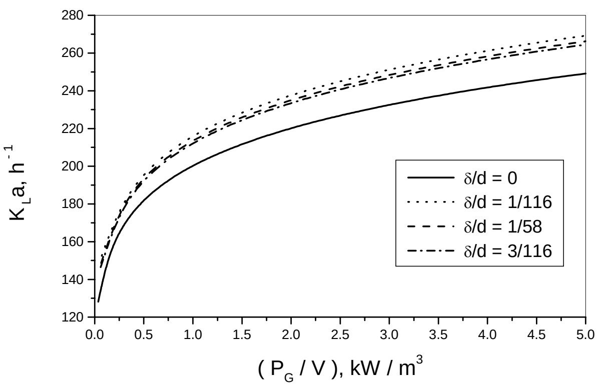

Fig. 3 Dependence between the mass-transfer coefficient on the eccentricity at different power.

The relation $\varepsilon_G=(P_G/P_L)$ is determined at change of gas flow rate in interval $Q_G \in [50 \div 350]$ *l/h*, eccentricity $\delta=0$ and temperature $T=20\ ^0C$. For determination of coefficients C_3 and a_3 the subprogram *RNSSQ* for nonlinear regression from the library *IMSL* is used. The received results are $C_3=0.53;\ a_3=-0.014$. The model for the gas-hold up has a type:

$$\varepsilon_G = 0.53\left(Q_G / nd^3\right)^{-0.014}. \tag{16}$$

The correlation coefficient and the Fisher's function have values: $R^2{}_E=0.954$ and $F_E=4.76$. Comparison with their theoretical values: $R^2{}_{T(53)}=0.233$ and $F_T=2.11$ at a error $\pm 5\%$, shows that model is adequate and it can be used for determination of the gas-hold up in the systems.

Optimization of the constructive parameters of the bioreactor

The effectiveness of the mass-transfer, aeration and mixing processes is determined by a criterion that characterizing a gas-liquid transition [27]:

$$J(\mathbf{u}) = \max_{\mathbf{u}=\mathbf{u}[x_1,x_2,x_3,x_4,D,d,L,n,Q_G]} \left[\frac{K_L a}{\rho_G\, Q_G\, \varepsilon_L} \int_0^t \int_0^\eta \left(\frac{X^*(t) - \overline{Y}(t)}{\overline{X}(\eta, t)} \right) d\eta\, dt \right]. \tag{17}$$

The volumetric coefficient is determined by the following regression model [27]:

$$\begin{aligned} K_L a = 136.5 + 8.9 x_1 + 13.1 x_3 + 7.3 x_2 x_4 + 6.1 x_3 x_4 - \\ - 7.9 x_1^2 - 34.4 x_2^2 - 9.3 x_3^2 + 23.5 x_4^2 \end{aligned} \tag{18}$$

The mass-transfer optimization of the process is done in dependence constructive and regime parameters that are shown in Table 2.

Table 2 Parameters and their intervals of change.

N^0	Name	Symbol	Min.	Max.	Step
1	Angle of the blades of the impeller	x_1	*45*	*90*	*5*
2	Eccentricity of impeller	x_2	*0*	*1.5*	*0.1*
3	Number of impeller	x_3	*1*	*3*	*1*
4	High of the blades of impeller	x_4	*9*	*15*	*1*
5	Bioreactor diameter	D	*120*	*130*	*5*
6	Impeller diameter	d	*30*	*60*	*5*
7	High of liquid in bioreactor	L	*100*	*200*	*10*
8	Rotation speed	n	*100*	*1200*	*100*
9	Gas flow rate	Q_G	*50*	*275*	*15*

The development of a model, that reflects the influence of all impossible and parameters over the process in the bioreactor is practical impossible and inexpedient. Because of the neglecting of row of factors, that character is not stochastically, thus definite values are distinguished with the really optimums. One way to reading of this indeterminateness as a result is an application of the fuzzy sets theory [24-26]. In this paper using of a "*flexible*" model is offered [1,2], that reflects more full all possible values of the criterion and control variables. The combined mass-transfer model is examined as the most acceptable and as admissible the diversions from them are examined, but less an acceptability degree. This is presented by fuzzy sets with a membership function that has a type:

$$m_I(\mathbf{u}) = \left[1 + \varepsilon_I^2(\mathbf{u}) \right]^{-1}, \qquad (19)$$

where: **u**-vector of control variables, $\mathbf{u}=\mathbf{u}[x_1,x_2,x_3,x_4,D,d,L,n,Q_G]$; ε_I-deviation of basic model;

$$\varepsilon_1 = \overline{X} - \left[A_0 \exp(r_1 \eta) + B_0 \exp(r_2 \eta) + C_0 \right];$$

$$\varepsilon_2 = X^* - \left[A_0 \frac{\exp(r_1) - 1}{r_1} + B_0 \frac{\exp(r_2) - 1}{r_2} + C_0 \right]; \; I=1,\ldots,3.$$

$$\varepsilon_3 = \overline{Y} - \left[X^*(t) \left[1 - \exp(-a_2 t) \right] \right].$$

A fuzzy criterion is formulated from the next type: "*The optimum criterion J(***u***) to be possibility higher*"" and it is presented by the subsequent membership function:

$$m_0(\mathbf{u}) = \begin{cases} 0; & \mathbf{J}(\mathbf{u}) < \alpha \\ \dfrac{\mathbf{J}(\mathbf{u}) - \alpha}{\beta - \alpha}; & \alpha \le \mathbf{J}(\mathbf{u}) \le \beta, \\ 1; & \mathbf{J}(\mathbf{u}) > \beta \end{cases} \qquad (20)$$

where α_1 and α_2 are the fuzzy sets parameters.

The following optimization problem from the class of fuzzy mathematical programming problem is formulated:

$$J(u) \cong \frac{K_L a}{\rho_G Q_G \varepsilon_L} \int_0^t \int_0^\eta \frac{\left(X^* - \overline{Y}\right)}{\overline{X}} d\eta \, dt \quad \rightarrow \quad m\tilde{a}x, \tag{21}$$

where: "$m\tilde{a}x$" means *"in possibility maximum"*; "$\cong$" means *"is come into view approximately in following relation"*.

For determination of this problem a new approach is used [2] that generalizes the Bellman-Zadeh's method. The fuzzy set of the solution is presented with a membership function m_D, whish is conjunction of the membership functions of the fuzzy set of the criterion m_0 and the model m_I:

$$m_D(\mathbf{u}) = (1-\gamma) \prod_{I=0}^{3} m_I^{\theta_i}(\mathbf{u}) + \gamma \left\{ 1 - \prod_{I=0}^{3} \left(1 - m_I(\mathbf{u})\right)^{\theta_i} \right\}, \tag{22}$$

where: γ is a parameter that characterizing the compensation degree, θ_i-parameters, that give the m_I weights.

The fuzzy set of solution is determined from the following relations [2]:

$$\mathbf{u}^0 = \sum_{i=1}^{K} v_i \, \mathbf{u}_i, \qquad v_i = \sum_{i=1}^{K} \frac{m_{D_i}^{\theta}(\mathbf{u})}{\sum_{j=1}^{J} m_{D_j}^{\theta}(\mathbf{u})}; \; i=1, \ldots, K; \; J=K^q, \tag{23}$$

where: K is vector with dimension $\mathbf{u}$; q is number discreet values of vector $\mathbf{u}$.

An algorithm and a program are developed. The developed algorithm and program can be used for a solution of the optimization problems in different bioprocess systems field.

The optimization results of the constructive and regime bioreactor parameter are shown in Table 3. Where $\mathbf{U_0}$ are the initial values and $\mathbf{U_1}$ are the optimal values of the constructive and regime parameters.

From the presented results it shows, that the integral indexes of the mass-transfer and the aeration processes: a volumetric oxygen mass-transfer coefficient and gas-hold up in liquid phase, their values increase. The volumetric coefficient increases its value with more that twice, and the oxygen-hold up increases with *25%*.

Table 3 Results of the optimization of the bioreactor parameters.

Constructive and regime bioreactor parameters			Before	After
Constructive			**U_0**	**U_1**
Angle of the blades of the impeller	x_1	^{0}	90	80
Eccentricity of impeller	x_2	mm	0.00	0.83
Impeller number	x_3	numbers	1	3
Wide of the baffles	x_4	mm	12	15
Bioreactor diameter	D	mm	120	130
Impeller diameter	d	mm	58	47
High of liquid in bioreactor	L	mm	120	132
Regime			**U_0**	**U_1**
Gas flow rate	Q_G	$L.L^{-1}.h^{-1}$	60	97
Substratum floating rate	n	min^{-1}	800	565
Line gas speed	$10^3.W_G$	m/s	1.357	1.747
Criterions of the processes of aeration and mixing			**U_0**	**U_1**
Volumetric mass-transfer coefficient,	K_La,	h^{-1}	80.42	172.79
Gas-hold up,	$\varepsilon_{G,}$	%	26.53	8.00
Gas-hold up in liquid phase,	$\varepsilon_{L,}$	%	73.47	92.00
Peclet criterion,	Pe,	-	1.50	1.12
Technical-economic			**U_0**	**U_1**
Power input of the liquid phase,	$P_{L,}$	W	15.00	4.00
Power input for the two-phase system gas-liquid,	$P_{G,}$	W	13.11	3.34
Ratio,	(P/V),	W/L	9.66	1.91
Volume,	V,	L	1.36	1.75

The integral indexes, that characterizing the process of mixing-power input of the liquid and the gas phase, after determination the optimal bioreactor parameters and impeller decrease with *3.75* times for the power input in the liquid phase *3.92* times for the gas phase. The relative power input on unit volume is an important index for the mixing process. After optimization it decreases with more than 5 times and working volume increase with *28%*.

Optimal control of a fermentation process in stirred tank bioreactor

The model of the process of *E. Coli* fermentation includes the material balance of the based kinetic variables-biomass, substrate and dissolved oxygen concentration [8]:

$$
\begin{aligned}
\frac{dX}{dt} &= \mu X - \frac{F}{V}X \\
\frac{dS}{dt} &= \frac{F}{V}(S_0 - S) - \gamma X \\
\frac{dC_L}{dt} &= K_L a\left(C_L^* - C_L\right) - \alpha^{O_2} \mu X - \frac{F}{V}C_L \\
\frac{dV}{dt} &= F
\end{aligned}
\quad . \qquad (24)
$$

The initial condition for starting the simulation is: $X(0)=0.12\ g\ L^{-1}$, $S(0)=2.6\ g\ L^{-1}$, $C^{*}_{L}=C_{L}(0)=96.13\ \%$.

The specific growth rate is described function of Monod kinetics [8]: $\mu = \mu_{max} \dfrac{S}{K_S + S}$.

The specific growth rate of sugar consumption is described by the following relations [8]: $\gamma = \mu / Y_s - K_m$.

The values of the parameters of the model (26) are [8]: $\mu_{max}=0.4671\ h^{-1}$, $K_m=0.6015\ g\ g^{-1}\ h^{-1}$, $K_S=0.0742\ L^{-1}$, $Y=0.4843\ \%$, $\alpha^{O_2}=6.105\ g\ g^{-1}$.

In the paper [8] an optimal control of a fermentation process is developed. The method for optimal control is based on the contemporary and effective approach for optimal control-Neuro-Dynamic Programming (NDP). The name neuro-dynamic programming expresses the reliance of the methods of this article on both Dynamic Programming (DP) and neural network concepts and it was proposed such as one methodic for alleviation of “curse of dimensionality”.

The process of fed-batch fermentation of *E. Coli* is examined. The fermentation is leaded in a stirred tank bioreactor with mixing in mesophyle regime under indefinitely feeding up, but does not have limitation of the substrate (glucose) and using of a food mean-glucose/mineral salt.

1. Formulation of the problem on optimization

As is well-known for fermentation process, relatively little a change in the speed of feed can take process to switch over toward undesired stability state (especially steeply disturbance in *F*. The control objective is, therefore, to drive the reactor from the low biomass steady state to the desirable high biomass yield state. It may be viewed as a step change in the setpoint at time t=0 from the low biomass to the high biomass yield steady state.

2. Simulation whit using of suboptimal control

Four values of $F=[0.140\ \ 0.145\ \ 0.150\ \ 0.155]$ was examined, that can cover the possible rang of variation. For each of the parameter values, the reactor was started at three different $x(0)$

values around the low biomass yield steady state. 100 data points is obtained for each run. Thus a total of 1200 data points were obtained.

3. Approximation

A functional approximation relating *cost-to-go* with augmented state was obtained by using neural network with five hidden nodes, six input and one output node. The neural network showed a good fit with mean square error of 10^{-3} after training for 1000 epochs.

4. Results

The results are presented on the Fig.4-Fig.5. On the Fig.4 the optimized biomass concentration is presented with application of NDP.

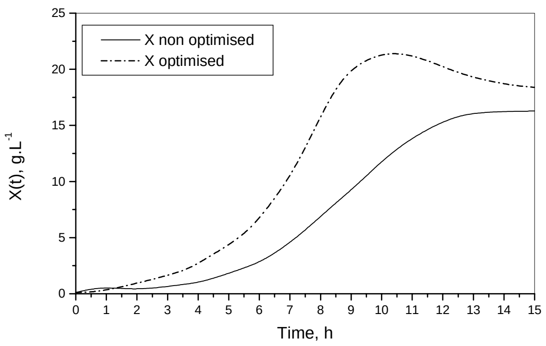

Fig. 4 Concentration of the optimized and the non optimized biomass.

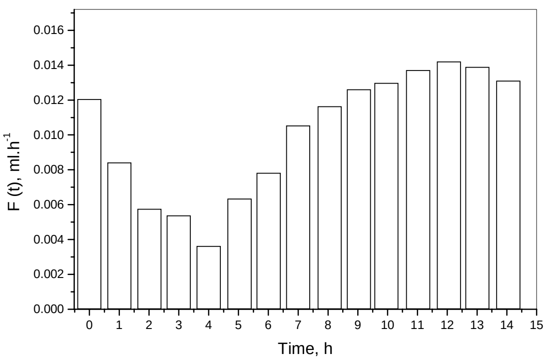

Fig.5. The received feeding rate.

In Fig.5 shows that with using this profile that is received with NDP method 40.46% increasing of biomass quantity in the end of the process.

Conclution

1. The mathematical models of the mass-transfer, aeration and mixing processes for a two-phase system gas-liquid are developed. The models give connection between the parameter of the construction and the examined processes in the bioreactor. This connection is realized by analytical and criterion dependences and not only by criterion dependence. The models successfully can be used for scale-up. In that case they can be used for one preliminary assessment of the mass-transfer indexes of the new apparatus, simultaneously can be used for apparatus projection at given effectiveness of the aeration and the mixing processes.

2. The offered models for the power input, the volumetric oxygen mass-transfer coefficient and the gas-hold up, in that a unexplored constructive parameter-eccentricity of the impeller can be used to a preliminarily calculation of the constructive and regime bioreactor parameters and they cam be used to optimization.
3. The determined optimal values of the constructive and regime parameters have allowed the elaboration of the bioreactor construction and achievement of high effectiveness of the mass-transfer and the aeration processes. In that way the effectiveness of a phase fermentation in aerobic biotechnology processes will be achieved.
4. Obtained results show, that NDP is an effective method for dynamic optimization on the fermentation processes in a stirred tank bioreactor.

Acknowledgments:

The investigations are partially supported by National Science Fund by grant N^0TH1314/2003.

Nomenclature

C_G	dissolved oxygen concentration in gas-phase,	kg m^{-3}
C_L	dissolved oxygen concentration in liquid phase,	kg m^{-3}
F	feed flow rate,	L h^{-1}
K_La	volumetric gas-liquid mass-transfer coefficient,	h^{-1}
K_m	the glucose consumption rate for the maintenance energy,	g g^{-1} h^{-1}
K_s	Monod's saturation constant for substrate,	L^{-1}
m_I	membership functions	-
m_L	Henry's law constant	-
P_G	power input in fermentation medium with aeration,	W
P_L	power input in fermentation medium without aeration,	W
Q_G	gas flow rate,	L h^{-1}
Re	Reynolds number	-
S	concentration of substrate,	g L^{-1}
S_0	initial substrate concentration,	g L^{-1}
t	time,	h
V	volume,	L
W_G	gas velocity, $W_G=4Q_G/\pi D^2$	m s^{-1},
X	concentration of the biomass,	kg m^{-3}
Y_s	yield coefficient,	g g^{-1}

Greek Letters

α^{O_2} , α^{CO_2}	kinetic constants,	g g^{-1}
δ	eccentricity of stirrer toward its rotation axis,	m
ρ	liquid density,	kg m^{-3}
γ	specific consummation rate of substrate,	h^{-1}
μ	specific grown rate of biomass,	h^{-1}
ρ	gas density,	kg m^{-3}
ε_G	gas hold-up,	%

ε_I	deviation from basic model	-
μ_m	maximal grown rate of biomass,	h^{-1}

Reference

1. Angelov P. (1994). A Generalized Approach to Fuzzy Optimization, International Journal of Intelligent Systems, v.9(3), pp.261–268.
2. Angelov P. (1995). An Analytical Method for Solving a Type of Fuzzy Optimization Problems, Control and Cybernetics, v.24(3), pp.363-373.
3. Berenji H. (1992) A Reinforcement Learning-Based Architecture for Fuzzy Logic Control, Int. J. of Approximate Reasoning's, **6**, 267.
4. Chtourou M., K. Najim, G. Roux, B. Dahhou (1993). Control of a Bioreactor Using a Neural Network, Bioprocess Engineering, v.8, pp. 251-254.
5. Dubois D. (1980) Prade H. Fuzzy Sets and Systems. Theory and Applications. N. Y.
6. Gupta M. (1992). Fuzzy Logic and Neural Networks, Proc. of the 2nd International Conf. on Fuzzy Logic & Neural Networks, Iizuka, Japan, pp.157-160.
7. Hornik K. (1991). Approximation Capabilities of Multilayer Feed Torward Network, Neural Network, v.4, pp. 251-257.
8. Ilkova T., St. Tzonkov (2003). Neuro-Dynamic Programming: Application to a Fermentation Process, International Symposium and Young Scientists' School "BioPS'03", November 11-13, Sofia, Bulgaria, pp. I.29-I.32.
9. Jenne M., M. Reuss (1997). Fluid dynamic modelling and simulation of gas-liquid flow in baffled stirred tank reactors. Récents Progrès en Génie des Procédés (Mixing IX: Two phase Systems), v.11, pp.201-208.
10. Jenne M., M. Reuss (1999). A Critical assessment on the use of k-e models for simulation of the turbulent liquid flow induced by a Rushton-turbine in baffled stirred tank reactors. Chem. Eng. Sci., v.54, pp.3921-3941.
11. Keler J., J. Thibault, Van Berusegen, A. Cheruy (1990). On-line Prediction of Fermentation Variables Using Neural Networks, Biotechnology & Bioinstrumentation, v.36, pp. 1041-1053.
12. Kosko B. (1992). Neural Networks and Fuzzy Systems, Prentice-Hall, Cl. Englewood Cliffs.

13. Kurtanjek Z. (1995). Bioreactor Modeling and Control by Principal Component Based Neural Network, In: Preprints of the 6-th Int. Conference on Computer Application in Biotechnology Garmish-Partenkirchen, May 14-17, Germany, pp.300-303.
14. Muralikrishnan G., M. M. Chidambaram (1995). Control of a Bioreactor Using a Neural Network Model, Bioprocess Engineering, v.12, pp.35-39.
15. Nauck D., F. Klawoon R. Kruse (1993). Combining Neural Networks and Fuzzy Controllers, Lecture Notes in Computer Science, v.35, pp.35-46.
16. Normandin A., J. Thibault, B.P. A. Grandjen (1994). Optimizing Control of a Continuous Stirred Tank Fermenter Using a Neural Network, Bioprocess Engineering, v.10, pp.109-113.
17. Reus M., R. Bajpai. (1991). Stirred tank models. Biotechnology, vl. 4 (eds. H.-J. Rehm et al), VCH Verlagsgesellschaft, Weinheim-Deerfield Beach/Florida –Basil, pp.299-348.
18. Schmalzriedt S., M. Jenne, M. Reuss (1995). Modeling of stirred tank bioreactors, In: Preprints of the 6-th Int. Conference on Computer Application in Biotechnology Garmish-Partenkirchen, May 14-17, Germany, pp.159-164.
19. Schuegerl K., K.-H. Bellgardt (2000). Bioreaction Engineering: Modeling and Control, Springer-Verlag, Berlin, Heidelberg.
20. Stenberg O., B.Andersson (1988). Gas-liquid mass transfer in Agitated Vessels I. Evaluation of the gas-liquid mass transfer coefficient from transient-Response measurement. Chem. Eng. Sci., v.43(3), pp. 719-724.
21. Strenk F. (1975). Peremeshivanie i aparatami s meshalkami, L., Himiya, in Russian
22. Viesturs U., A. Kuznetzov, V. Savenkov (1986). Sistemaj fermentacij, Riga, Zinatne, in Russian
23. Viesturs U., M. Kristapsons, E. Bilkina (1980). Kultivirovanie mikroorganizmov, M., Pishtevaya promishlenost, in Russian
24. Zadeh L. (1965). Fuzzy Sets, Information and control, .v8, pp. 338-353.
25. Zadeh L. (1999). Fuzzy Sets as a Basis for a Theory of Possibility, Fuzzy Sets and Systems, v.100, pp. 9-34
26. Zimmermann H. (1991). Fuzzy set: Theory and its Application, 2nd rev. ed. Kluwer, Boston.
27. Petrov M. (2003). Modeling and Optimization of the Parameters of the Class Bioreactors, Ph.D Thesis, Sofia, Bulgaria.