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Mathematical Modeling of L-Lyzin Biosynthesis Process during Continually Cultivation

By Ivan Edissonov, Elena Nikolova & Sergei Ranchev
Institute of Mechanics, Bulgarian Academy of Sciences, Sofia, Bulgaria

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Mathematical Modeling of L-Lyzin Biosynthesis Process during Continually Cultivation

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I. Introduction

The presence of such a variety of mathematical models indicates the lack of a fundamental theory of growth and reproduction of biological objects. All the models known in the literature can only be applied for the description and analysis of some particular aspects of the growth and reproduction processes of a specific biological object. The attempts to be expanded the range of application of these models and their utilization at the development of a general theory, enter into a disagreement with the factual data usually. Moreover, in few of these works the qualitative theory of ordinary differential equations has been used as a method for state analysis of biological objects [1]. The phase analysis gives a good possibility every nonlinear system, described with ordinary differential equations to be studied qualitatively.

Mathematical models of the microorganisms cultivation processes in a bioreactor are developed, taking into account the kinetics of the final or intermediate metabolism products formation, the kinetics of biomass growth and the kinetics of sub-stratum consumption. All these models are based on different hypotheses about the acting biosynthesis mechanism: the presence of limiting substrata, inhibitors or activators of growth, and the degree of their impact on the velocity of the biomass and product formation [2].

Another peculiarity is applied of the empirical approach at the development of mathematical models. The limiting factors are many in number which influence on the cells growth. Because of that in every specific case the biomass growth velocity depending on the limiting factor concentrations is determined experimentally. In the kinetics of the "exact" microbiological systems it is assumed that the bioreactor sizes are small, and the mixing leads to an instant leveling of the concentrations of all substances into the whole volume of the bioreactor. Taking into consideration the above limits the mathematical models are obtained, which are not adequate to the actual processes. In these models it is assumed that the cultural medium of the bioreactor is homogeneous (all concentrations of biologically important substances are an even distributed). Thus, for the more precisely description of the biosynthesis processes in the bioreactor, it is necessary the diffusion processes to be reflected in the mathematical models. As a result all concentrations will be considered as functions of the time and space coordinates. The accounting of all these circumstances gives a possibility to be developed a more adequate model to the actual process. In order to solve such a problem, it is necessary to be used the qualitative theory of distributed kinetic systems.

II. Mathematical Model with Concentrated Parameters of L Lyzin Biosynthesis Process During Continually Cultivation of The Brevibacterium Flavum Type Microbial Population

The mathematical model of the L-lyzin biosynthesis process during continually cultivation of the *Brevibacterium flavum* type microbial population is obtained as a variant of the Ohno *et al.* model [3]. This model reflects the material balance of the basic components of the cultural medium and has the following form:

$$\frac{dX}{dt} = \mu_m \frac{S}{K_S + S} X - DX,$$

$$\frac{dS}{dt} = -\frac{\mu_m}{Y_{X,S}} \frac{S}{K_S + S} X + D(S^0 - S),$$

Author α σ ρ: Institute of Mechanics, Bulgarian Academy of Sciences, Sofia, Bulgaria.

$$\frac{dL}{dt} = Y_{L,X}\frac{dX}{dt} - DL, \quad (1)$$

where:

X – biomass concentration $[g/1]$;

S – sugar concentration $[g/1]$;

L – lyzin concentration $[g/1]$;

μ_m – maximum relative velocity of the biomass growth $[s^{-1}]$;

$Y_{X,S}$ = dX / dS-stoichiometry of the biomass to the sugar [–];

$Y_{L,X}$ – constant [–];

$K_S = k_{x,s} / r_{x,s}$, where $r_{x,s}$ is the velocity of the transformation of the biomass and sugar in biomass-sugar complex (XS), and $k_{x,s}$ is the velocity of the transformation of the biomass-sugar complex in biomass and sugar $[g/l]$ [4].

D – diluting velocity) $[s^{-1}]$;

S^0 – sugar concentration in the feeding medium $[g/1]$.

It is supposed that an ideal mixing is carried out in the bioreactor and all the parameters of the model are constants during the biotechnological process. As a result the proposed model (1) can be examined as a nonlinear autonomous system of ordinary differential equations with concentrated parameters.

Depending on the microorganisms cultivation technology for the specific process of L-lyzin biosynthesis nine replicable experiments were carried out under identical conditions in a bioreactor with volume 10 m^3. The experimental data of the biomass (X), sugar (S) and lyzin (L) concentrations are obtained under laboratory conditions by means of samples taken every four hours from the cultural medium of the bioreactor. The processing of these experimental data is accomplished by using of the fuzzy sets apparatus [5]. The smoothed experimental values for X, S and L at the different periods of time are shown in Table 1 and marked by "E ".

For this biotechnological process is speciality that the microorganisms nutrition with substratum (sugar) in the bioreactor is carried out at constant diluting velocity ($D = 0.025\ s^{-1}$). The sugar concentration in the feeding medium ($S^0 = 19\ g/1$) is also constant and equal to the initial sugar concentration in the bioreactor (S_0).

The numeric values of the parameters in system (1) μ_m, K_S, $Y_{X,S}$, $Y_{L,X}$ can be found by minimizing of the following functional:

$$J = \sum_{j=1}^{10}[(X_j^E - X_j^T)^2 + (S_j^E - S_j^T)^2 + (L_j^E - L_j^T)^2], \quad (2)$$

Where: $F_j^E = \{X_j^E, S_j^E, L_j^E\}$ is a vector of the smoothed experimental values of the biomass, sugar and lyzin concentrations at the j-th period of time (Table 1);

$F_j^T = \{X_j^T, S_j^T, L_j^T\}$ is a vector of the theoretically obtained values of the biomass, sugar and lyzin concentrations at the j - th period of time by solving of the system of ordinary differential equations (1).

Table. 1 : Obtained experimental "E" and theoretical "T"' values of the biomass, sugar, and lyzin concentrations at the different moments of time.

Time [h]	X^E [g/1]	X^T [g/1]	S^E [g/1]	S^T [g/1]	L^E [g/1]	L^T [g/1]
0	3.0	3.00	19.0	19.00	0.0	0.00
4	5.1	5.28	15.2	15.56	5.6	5.56
8	9.5	8.76	9.4	10.53	14.1	13.68
12	13.1	12.80	4.1	4.78	22.3	22.95
16	14.3	15.04	1.0	1.48	26.9	28.28
20	14.8	15.35	1.0	0.82	28.7	2936
24	15.0	15.22	1.0	0.75	29.6	29.47
28	15.1	15.07	1.0	0.75	29.9	29.47
32	15.2	14.92	1.0	0.76	30.0	29.46
36	15.2	14.79	1.0	0.76	30.1	29.45
40	15.0	14.67	1.0	0.77	30.0	29.43

System (1) can be solved by means of the Runge-Kutta method. The initial values of the parameters μ_m, K_S, $Y_{X,S}$, $Y_{L,X}$ in system (1) are determined on the basis of reference data for similar biotechnological processes, as well as taking into account the specific character of our process of the L-lyzin biosynthesis [6]. When an apriori information for the initial parameter values is lacking they are

determined randomly. In this case there exists a danger after minimizing of functional (2) such values of the parameters of the process to be obtained which are inadmissible from a physical point of view. The initial parameter values of the specific process of L-lyzin biosynthesis are presented in Table 2, line 1.

The minimum of functional (2) is found by using of an optimization method of the adaptive random search [7]. As a result of the parametrical identification, such numeric values of the parameters of the specific process of L-lyzin biosynthesis are obtained, which are physically acceptable and warrant a minimum of the root- mean-square criterion (the values of the parameters are represented in Table 2, line 2). In Table 1 the theoretical values of the biomass, sugar and lyzin concentrations at the different periods of time marked by "T" are obtained exactly for such values of the parameters whose functional (2) has a minimum.

It can be seen from Table 1 that the deviation of the smoothed experimental data from the theoretically obtained values is by a negligible margin, which suggests the conclusion that the proposed nonlinear system with concentrated parameters (1) describes the actual biotechnological process in a sufficiently accurate way.

In a qualitative aspect the phase portraits in the planes (X, S) and (L, S) are identical, since in the proposed model (1) a proportional dependence of the change of the L-lyzin concentration (L) from the change of the biomass concentration (X) exists. This circumstance gives a possibility the autonomous system (1) to be investigated in the phase plane (X, S) qualitatively by substituting of the obtained numerical values of the parameters μ_m, K_S, $Y_{X,S}$, $Y_{L,X}$ in it. (Tab. 2).

The nonlinear system (1) has two fixed points whose coordinates are:

$$1st-fixed\quad point \rightarrow X_1^{'}=0,\quad S_1^{'}=S^0=19$$

$$2nd-fixed\quad point \rightarrow X_2^{'}=\frac{-\mu_m K_S D^2+\mu_m^2 D S^0-\mu_m D^2 S^0}{\alpha D\mu_m-\alpha D^2}$$

$$S_2^{'}=\frac{K_S D}{\mu_m-D}=0.8432, \tag{3}$$

Table 2 : First Line – Parameters Initial Values, Second Line – Parameter Values Obtained at the Parametrical Identification.

No	μ_m	K_S	$Y_{X,S}$	$Y_{L,X}$
1.	0.1	1.0	1.0	1.0
2.	0.2333	7.0258	0.7439	2.1705

For every fixed point the local coordinates may be introduced by using of the formulae:

$$\xi_j=X-X_j^{'},\quad \eta_j=S-S_j^{'},\quad j=1\div 2,$$

i.e. every fixed point with coordinates $(X_j^{'}, S_j^{'})$ in the coordinate system (X, S) is transformed at the beginning of new coordinate system (ξ, η).

In (1) the differential equations' right-hand parts for X and S are expanded into a Taylor series in some neighbourhood of every fixed point $(X_j^{'}, S_j^{'})$ j = 1 ÷ 2. Passing to local coordinates system (1) is transformed into:

$$\begin{aligned}\frac{d\xi_j}{dt}&=\xi_j\frac{\partial F_1}{\partial X}\left(X_j^{'},S_j^{'}\right)+\eta_j\frac{\partial F_1}{\partial S}\left(X_j^{'},S_j^{'}\right)+R_1\left(\xi_j+X_j^{'}\eta_j+S_j^{'}\right)=F_1(\xi,\eta),\\ \frac{d\eta_j}{dt}&=\xi_j\frac{\partial F_2}{\partial X}\left(X_j^{'},S_j^{'}\right)+\eta_j\frac{\partial F_2}{\partial S}\left(X_j^{'},S_j^{'}\right)+R_2\left(\xi_j+X_j^{'}\eta_j+S_j^{'}\right)=F_2(\xi,\eta).\end{aligned} \tag{4}$$

In order to study system (4) qualitatively the linearization theorem should be taken into account. It reads: if the nonlinear system has a simple fixed point with coordinates $(0,0)$, then in the neighbourhood of this fixed point the phase portraits of the nonlinear system and its linearization are equivalent qualitatively only if the fixed point of the linearized system is not a centre [8].

The first requirement of the linearization theorem is executed since the matrices

Have simple fixed points (X'_j, S'_j) j = 1 ÷ 2 (further on this is seen from (5)).

After linearization of system (1) the only solution of the matrix equations, A_jY_j=0 is

$$Y_j = \begin{bmatrix} \xi_j \\ \eta_j \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}, j = 1 \div 2$$

Thus system (1) has two simple fixed points transformed at the beginning of the coordinates of the phase plane (ξ, η). In the concrete case system (1) has the following matrices $A_j, j = 1 \div 2$:

$$A_j = \left[\begin{matrix} \frac{\partial F_1}{\partial X} & \frac{\partial F_1}{\partial S} \\ \frac{\partial F_2}{\partial X} & \frac{\partial F_2}{\partial S} \end{matrix} \right]_{(X,S)=(X'_j, S'_j), j=1\div 2,}$$

$$A_1 = \begin{bmatrix} a_1 & b_1 \\ c_1 & d_1 \end{bmatrix} = \begin{bmatrix} 0.1453 & 0.0000 \\ -0.2290 & -0.0250 \end{bmatrix}, A_2 = \begin{bmatrix} a_2 & b_2 \\ c_2 & d_2 \end{bmatrix} = \begin{bmatrix} 0.0000 & 0.3576 \\ -0.0336 & -0.5056 \end{bmatrix}. \quad (5)$$

The second requirement of the linearization theorem reads that a qualitative equivalence between the nonlinear system (1) and its linearization (4) exists only if the fixed points of the linearized system are not a centre. This requirement is executed since the matrices $A_j, j = 1 \div 2$: have different and real proper values. The fixed points can be from centre type, if the matrices Aj have complex proper values. For the nonlinear system (1) the conditions of the linearization theorem are executed, which makes possible further on at the phase analysis its linearized version (4) to be used.

After the canonization of system (4) the Jordan forms J_j of the matrices A_j are obtained in the form of:

$$J_1 = \begin{bmatrix} 0.1453 & 0.0000 \\ 0.0000 & -0.0250 \end{bmatrix}, J_2 = \begin{bmatrix} 0.0250 & 0.0000 \\ 0.0000 & -0.4806 \end{bmatrix}.$$

For the first fixed point the proper values are $\lambda_1^{(1)}$ = 0.1453 and $\lambda_2^{(1)}$ = – 0.0250 respectively. In this case the proper values have real numbers with converse signs so this fixed point generates a saddle at the beginning of the phase plane coordinates (ξ, η). For the second fixed point the proper values are negative real numbers – $\lambda_1^{(2)}$ = – 0.0250, $\lambda_2^{(2)}$ = 0.4806, and thus this fixed point generates stable node at the beginning of the phase plane coordinates (ξ, η). For the exact construction of the full phase portrait of the nonlinear system (1) it is necessary to be found the vertical (dX/dt = 0) and horizontal (dS/dt = 0) isoclinals additionally. The biomass and sugar concentrations have real positive values. As a result it is necessary to be constructed the full phase portrait of nonlinear system (1) only for the 1^{st} – quadrant of the phase plane (X, S). Passing from local coordinates (ξ, η) to real coordinates (X, S) and taking into consideration the linearization theorem.

III. Mathematical Model with Distributed Parameters of L-Lyzin Biosynthesis Process During Continually Cultivation of the Brevibacterium Flavum Type Microbial Population

At the qualitative investigation of the model with distributed parameters it is accepted that the space is one-dimensional in which the different reactions of the biosynthesis are carried out. In this special case the bioreactor is considered as long and narrow tube of which the one end is opened and through its pass substratum (sugar) with concentration ($S°$). For the model with distributed parameters it is necessary to be investigated the stability of the space similar stationary solutions (3). This investigation will be carried out taking into consideration the following limiting conditions:

$$\left.\frac{\partial X}{\partial r}\right|_{r=0} = \left.\frac{\partial X}{\partial r}\right|_{r=R}, \quad \left.\frac{\partial S}{\partial r}\right|_{r=0} = \left.\frac{\partial S}{\partial r}\right|_{r=R}, \quad (6)$$

Where r=0 and $r = R = 5\,m$ are the coordinates of the beginning and end sections of the bioreactor.

Accounting for the diffusion processes in the specific process of L-lyzin biosynthesis the model with distributed parameters has the following form:

$$\frac{dX}{dt} = \mu_m \frac{S}{K_S + S} X - DX + D_X \frac{\partial^2 X}{\partial r^2}, \quad (7)$$

$$\frac{dS}{dt} = -\frac{\mu_m}{Y_{X,S}} \frac{S}{K_S + S} X + D\left(S^0 - S\right) + D_S \frac{\partial^2 S}{\partial r^2},$$

Where D_X and D_S are coefficients of the biomass and sugar diffusions respectively.

In order to be stable the distributed system (7), it is necessary small disturbances of the forces acting upon the system to provoke small deviations

from its stationary solutions (3). The investigation of the stability is carried out on the basis of the linear distributed system analysis:

$$\frac{\partial \xi_j}{\partial t} a_j \xi_j + b_j \eta_j + D_X \frac{\partial^2 \xi_j}{\partial r^2}$$
$$\frac{\partial \eta_j}{\partial t} c_j \xi_j + d_j \eta_j + D_S \frac{\partial^2 \eta_j}{\partial r^2} \quad (8)$$

Where $\xi_j(t, r)$ and $\eta_j(t, r)$, $j = 1 \div 2$, are small deviations from the space similar solutions (X_j, S_j), and a_j, b_j, c_j, d_j, $j = 1 \div 2$, are the values of the coefficients obtained in (5).

At the limiting conditions (6) the solution of system (8) is searched in the form of:

$$\xi_j(t, r) = A_j e^{p^{(j)} t} e^{i 2\pi r/\lambda}, \quad \eta_j(t, r) = B_j e^{p^{(j)} t} e^{i 2\pi r/\lambda}, \quad (9)$$

Where A_j and B_j, $j = 1\text{-}2$, are constants.

By substituting of the solutions (9) in system (8) it is obtained:

$$\frac{d\xi_j}{dt} = \left[a_j - D_X \left(\frac{2\pi}{\lambda} \right)^2 \right] \xi_j + b_j \eta_j,$$
$$\frac{d\eta_j}{dt} = c_j \xi_j + \left[d_j - D_S \left(\frac{2\pi}{\lambda} \right)^2 \right] \eta_j, \quad (10)$$

From system (10) for the complex frequency (p) the following characteristical polynomial is obtained:

$$\left[p^{(j)} - a_j + (2\pi/\lambda)^2 D_X \right] \left[p^{(j)} - d_j + (2\pi/\lambda)^2 D_S \right] = b_j c_j, \quad (11)$$

where:

λ – wave length;

$u = (2\pi/\lambda)^2$ – wave number.

It is established experimentally that for the specific process of L-lyzin biosynthesis the diffusion coefficients have the following values: $D_X = D_S = 1$.

For the first fixed point $p^{(1)}_{1,2}$ is defined from the equality (11) by the formulae:

$$p^{(1)}_{1,2} = \frac{a_1 + d_1}{2} - (D_X + D_S)\frac{u}{2} \pm \frac{1}{2}\left[u(D_X - D_S) - (a_1 - d_1) \right],$$

where: $p_1^{(1)} = -0.0250 - u$, $p_2^{(1)} = -0.1453 - u$.

Analogous for the second fixed point $p^{(2)}_{1,2}$ has the form of:

$$p^{(2)}_{1,2} = \frac{d_2}{2} - (D_X + D_S)\frac{u}{2} \pm \frac{1}{2}\sqrt{\left[u(D_X - D_S) + d_2 \right]^2 + 4b_2 c_2},$$

where: $p_1^{(2)} = -0.4806 - u$, $p_2^{(2)} = -0.0250 - u$.

As a result the stability of system (7) at different wave lengths can be investigated by the help of the quadratic equation (11) and its solutions.

For the first fixed point the characteristical equation (11) has two real roots: $p_1^{(1)} < 0$ for all λ values, $p_2^{(1)} > 0$ for $\lambda > \lambda_2 = 16.4751$ and $u < u_2 = 0.1453$. In this case at small deviations $\xi(t, r)$ and $\eta(t, r)$ in the immediate proximity of X'_1 and S'_1 the linear distributed system have a fixed point of saddle type. The limits of wave numbers (u), at which this fixed point generates a saddle, are given with the equality:

$$u_{1,2} = \left(\frac{2\pi}{\lambda_{1,2}} \right)^2 = \frac{1}{2D_X D_S}\left[(a_1 D_S + d_1 D_X) \pm \sqrt{(a_1 D_S + d_1 D_X)^2 - 4D_X D_S (a_1 d_1 - b_1 c_1)} \right].$$

In the concrete case for $\lambda_2 = 16.4751 < \lambda \leq \infty$ and $0 \leq u < u_2 = 0.1453$ (if $\lambda_2 \to \infty$ => $u_2 = 0$) system (7) have a fixed point of saddle type, and the space periodical and independent of time solutions (dissipative structure) can arise. The stability of the stationary solution of the first fixed point has not be studied, since this fixed point can not be reached from a physical point of view. For the specific process of L-lyzin biosynthesis the biomass concentration (X) is changed from 3 to 15 [g/l], and the sugar concentration (S) – from 0.5 to 19 [g/l]. The limits of these concentrations are determined depending on the specific technology of the microorganisms cultivation.

For all λ values of the second point $p_1^{(2)} < 0$ and $p_2^{(2)} < 0$. This shows that in the immediate proximity of this fixed point (X'_2, S'_2) a stable node is generated, and at small deviations from it the stationary solution of the second fixed point for all wave length (λ) values is stable.

As a final result of the analysis two variants are possible:

a) If $\lambda > \lambda_2 = 16.4751$ then in system (7) stable or unstable space periodical and independent of time solutions (dissipative structure) can arise. This possibility is ignored since the first fixed point can not be reached from a physical point of view.
b) If $\lambda < \lambda_2 = 16.4751$ it is obviously that system (7) is stable and space periodical and independent of time solutions can not arise in it.

IV. Conclusion

In the proposed work the obtained results show that at definite conditions space periodical and independent of time solutions (dissipative structure) can arise. The carried out phase analysis gives an answer to the question for the stability of the stationary solutions of the systems with concentrated and distributed parameters. It has to be noted that the wave length ($\lambda_2 = 16.4751$ m) and the bioreactor length ($R = 5$ m) are of one and the same order. If D_X and D_S tend to zero, A_2 tends to zero too. In this case the considered nonlinear system is unstable regarding all kinds disturbances. The meaning of this fact is simple: at zero diffusion coefficients in the one-dimensional bioreactor with length (r) there is a copulation of identity cells, the symmetrical states of which are unstable [9]. When there is a diffusion the stability of the solutions describing the symmetrical states increases at small disturbances. This is naturally since the simultaneous exchange of the substratum and the product makes difficult the switching over of two neighbouring cells in different regimes. As a result the neighbouring cells are switched over in the regime of the second fixed point at the product diffusion. When the substratum concentration decreases the same cells are switched over in a converse direction at the substratum diffusion. In this way the regime of one or other cell is determined depending on the competition of two kind influences – specific (by product diffusion) and nonspecific (by substratum diffusion). If the concentration of the cells (X) becomes critical (effect of the "narrowness") it is possible to be reached to the first fixed point from a physical point of view, at the condition that the biotechnological process is not terminated. In conclusion this analysis shows that the space periodical and independent of time solutions (dissipative structure) in the distributed system can arise when there exists conditions guaranting the relaying invariant regarding time.

References Références Referencias

1. N. A. Vasilev, V. A. Ambrosov and A. A. Skladnev, *Modelirovanie protssesov microbiologicheskogo sinteza* (in russian). Moskva: Lesnaya Promishlennost (1975).
2. D. Arrowsmith and C. Place, *Ordinary Differential Equations. A Qualitative Approach with Applications.* London, New York: Chapman and Hall (1982).
3. H. Ohno, E. Nakanishi and T. Takamatsu, Optimum operating mode for a class of fermentation. *Biotechnol. Bioeng.,* 20, 625-636 (1978).
4. SH. Aiba, A. Hemphri and N. Millis, *Biochimicheskaya tehnologia i apparatura* (in russian). Moskva: Pitshevaya promishlennost (1975).
5. I. Edissonov, *Modelirane i parametrichna optimizatsia na biotechnologichni protsesi pri periodichno kultivirane* (Ph. D. Thesis in bulgarian). Sofia: Press of Sofia Technological University (1988).
6. V. V. Savenkov, M. P. Ruklisha, Algoritm poiska optimalnih upravlenii po matematicheskoi modeli biosinteza L-lizina (in russian). In: *Tehnologia mikrobnogo sinteza.* Riga: Zinatne (1978), 39-43.
7. Edissonov, The new ARSTI optimization method: Adaptive random search with translating intervals. *American Journal of Mathematical and Management Sciences,* 14 (3&4), 143-166 (1994).
8. Ph. Hartman, *Ordinary Differential Equations.* New York, London, Sydney: John Wiley and Sons, (1964).
9. Yu. Romanovskiy, N. Stepanova, D. Chernavskiy, *Mathematical Modeling in Biophysics* (in russian). Moskva: Nauka (1975).