Bioprocess Engineering 7 (1991) 177–182

Bioprocess Engineering

Mathematical models for mixing in deep-jet bioreactors: Calculation of parameters

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Abstract. The macroscopic mathematical model based on compartments with ideal mixing zones and tanks-in series was evaluated. Based on the experimental data obtained in a 300 dm^3 pilot reactor and the dependence of mixing time on the volume of liquid phase, we have found mathematical relations between the ratio of vessel diameter to liquid level, adjustable parameters of model and the mixing time.

List of symbols

V	dm^3	total volume of bioreactor
V_g	dm^3	total volume of liquid
V_1	dm^3	volume of ideally mixed zone in the vessel
V_2	dm^3	volume of macromixer in inner circulation flows
V_3	dm^3	volume of liquid phase in the pump
V_4	dm^3	volume of liquid phase in the pipe between the vessel and the pump
V_5	dm^3	volume of liquid phase in the pipe between the pump and air input system included falling jet
V_{LT}	dm^3	volume of liquid in the tank
V_{LC}	dm^3	volume of liquid in the circulation system
F_E	dm^3/s	inner volumetric circulation flow rate across the macromixers
F_{cir}	dm^3/s	external volumetric circulation flow rate, pumping capacity
t_A	s	time interval of the pulse application
t_{AA}	s	time point of the pulse application related to the free choosen starting point of the experiment
t_m	s	mixing time
t_c	s	circulation time
t_{end}	s	end time of simulation
$C_{*,*}$	kg/m^3	concentration of tracer in the indicated compartment
C_0	kg/m^3	concentration of the tracer before the injection
C_t	kg/m^3	concentration of the tracer at the indicated time
C_∞	kg/m^3	theoretical concentration of the full mixed tracer
C_{sim}	kg/m^3	calculated concentration of tracer during numerical integration method
i	–	index of an arbitrary tank
D_T	m	diameter of bioreactor
D	1/s	dilution rate
H_L	m	level of liquid in the unaerated vessel
δ	–	vector of inhomogenities

1 Introduction

The deep-jet bioreactor is characterized by a two phase air-liquid system in the whole volume of the vessel, in pipe connections for the circulation between the tank and the pump, and in the pump compartment, too [1]. As we know, this type of bioreactor is used in the fed-batch process of yeast production by controlled feeding of substrate based on the ethanol estimation in broth and related Crabtree effect. It was reported earlier that the mixing time in this bioreactor depends on the volume of the liquid in the vessel and on the aeration rate [1, 2].

In the case of continuous flow reactors, the technique of residence time distributions is generally employed. Based on the observed residence time distributions a number of models for mixing are proposed and used to evaluate its effect upon the performance of the reactor. In fed-batch operation a fast distribution of the incoming substrate, pH corrector, dissolved oxygen as well as anti-foam effector is required. The necessity of knowing the dynamics of mixing behavior is obvious. Although all these performance depend upon flow patterns, it is not possible to use the residence time distribution model in a fed-batch fermentation, because the fluid does not flow out from the bioreactor. That means, a mathematical expression of the flow pattern for the substrate (with respect to the dependence of the mixing time and flows on the changing volume during fed-batch fermentation) could be useful in the optimization of this process.

In our previous work [3] we have presented the macroscopic model for mixing in this reactor with macromixer and micromixer region [6]. We have also assumed [3] that the fluid is circulated in the vessel continuously through a certain region, i.e. through the well-mixed compartment above the refusing plate, during two circulation loops; an external loop characterized by the pumping capacity and an inner loop achieved due to the energy dissipation of the falling jet in the vessel. The aim of this work is the testing of the previously described model (for the bioreactor with one aeration system) [3] as to its applicability in fed-batch fermentation as well as to establish simple mathematical relations between geometrical properties of the plant, the volume of the liquid in the vessel and adjustable parameters needed for calculation of the flow pattern in the simulation procedure of mixing for any volume of liquid in the deep-jet bioreactor

during fed-batch fermentation. In this work we have tried to find mathematical relations between the mixing time and the technical properties of the vessel (volume of liquid in circulation, volume of liquid in the vessel, ratio of total plant volume and volume of liquid in the vessel), which could be useful for the scale-up of deep-jet bioreactors.

2 Materials and methods

For the investigation of the flow pattern in the VB-IZ-12 deep-jet bioreactor (300 dm^3 total volume), the conductivity method with a saturated solution of NaCl as the tracer and measured data for the air-water system reported earlier [1] were used. In order to be able to evaluate the parameters of the model from measured responses to the injection of a tracer into reactor, the level of liquid quantities in the vessel were examined by the aeration rate of 1 dm^3/dm^3 min: 230, 200, 195, 185, 175, 165, 155 and 145 dm^3. For the mathematical representation of this model a system of differential equations, here presented in the vector format (Eq. 1), describing the concentration (C) of the tracer in the structural elements based on mass balance, was used.

$$\frac{d}{dt}\begin{bmatrix} C_1 \\ C_{2,1} \\ C_{2,2} \\ \vdots \\ C_{2,n_{(1)}-1} \\ C_{2,n_{(1)}} \\ C_{3,1} \\ \vdots \\ C_{3,n_{(2)}} \\ C_4 \\ C_{5,1} \\ \vdots \\ C_{5,n_{(3)}} \end{bmatrix} = A \begin{bmatrix} C_1 \\ C_{2,1} \\ C_{2,2} \\ \vdots \\ C_{2,n_{(1)}-1} \\ C_{2,n_{(1)}} \\ C_{3,1} \\ \vdots \\ C_{3,n_{(2)}} \\ C_4 \\ C_{5,1} \\ \vdots \\ C_{5,n_{(3)}} \end{bmatrix} + \begin{bmatrix} 0 \\ \vdots \\ 0 \\ \delta_{(t)} \\ 0 \\ \vdots \\ 0 \end{bmatrix} \qquad (1)$$

Matrix A contains the coefficients on the right side of Eq. (1):

	C_1	$C_{2.1}$	$C_{2.2} \cdots C_{2.n_{(1)}}$	C_3	$C_{5.1}$	$C_{5.2} \cdots C_{5.n_{(3)}}$	$C_{3.1}$	$C_{3.2} \cdots C_{3.n_{(2)}}$	
1	$\frac{-F_E+F_{cir})}{V_1}$	0	0 $\frac{F_E}{V_1}$	0	0	0 0	0	0 $\frac{F_{cir}}{V_1}$	
2.1	$\frac{F_E \cdot n_{(1)}}{V_2}$	$\frac{-(F_E \cdot n_{(1)})}{V_2}$	0 0	0	0	0 0	0	0 0	
2.2	0	$\frac{F_E \cdot n_{(1)}}{V_2}$	$\frac{-(F_E \cdot n_{(1)})}{V_2}$ 0	0	0	0 0	0	0 0	
$2.n_{(1)}$	0	0	0 $\frac{-(F_E \cdot n_{(1)})}{V_2}$	0	0	0 0	0	0 0	
3	0	0	0 0	$\frac{-F_{cir}}{V_3}$	0	0 $\frac{F_{cir}}{V_3}$	0	0 0	
5.1	$\frac{F_{cir} \cdot n_{(3)}}{V_5}$	0	0 0	0	$\frac{-(F_{cir} \cdot n_{(3)})}{V_5}$	0 0	0	0 0	$= A$
5.2	0	0	0 0	0	$\frac{F_{cir} \cdot n_{(3)}}{V_5}$	$\frac{-(F_{cir} \cdot n_{(3)})}{V_5}$ 0	0	0 0	
$5.n_{(3)}$	0	0	0 0	0	0	0 $\frac{-(F_{cir} \cdot n_{(3)})}{V_5}$	0	0 0	
3.1	0	0	0 0	$\frac{F_{cir} \cdot n_{(2)}}{V_4}$	0	0 0	$\frac{-(F_{cir} \cdot n_{(2)})}{V_4}$	0 0	
3.2	0	0	0 0	0	0	0 0	$\frac{F_{cir} \cdot n_{(2)}}{V_4}$	$\frac{-(F_{cir} \cdot n_{(2)})}{V_4}$ 0	
$3.n_{(2)}$	0	0	0 0	0	0	0 0	0	0 $\frac{-(F_{cir} \cdot n_{(2)})}{V_4}$	

The solution of this system was achieved on a personal computer by the numerical Runge-Kutta-Fehlberg method, a method with control of the relative error and with variable step of integration [4, 5]. The vector of inhomogeneities, $\delta(t)$, was applied in the compartment before the last $(n_{(1)}-1)$ in tank-in-series of macromixer, as was done in our previous work [3]. The mixing time (t_m; degree of mixing: 90%), the circulation time (t_c) and the sum of quadratic error [3] were used as criteria for the sucess of the simulation. Due to the limitation of the personal computer's memory size an optimization of the dataset of adjustable parameters was not possible. Thus, parameters evaluated in this work have been obtained by trying to minimize the sum of quadratic error [3] by repeatedly running the simulation, using different parameters. From results achieved during the above procedure the mathematical relations between adjustable parameters, the volume of the liquid phase (ratio of the tank diameter to the liquid level, respectively) and the mixing time were found. Using these relations we have calculated the new parameters and executed simulations on a PC again. Results from these simulations (expressed as mixing time) are compared with data from the first simulation procedure and with measured data.

3 Results and discussion

Simulated and measured flow patterns of the tracer in relation to the greatest and the smallest volume from the volume range examined in this work are presented in Fig. 1 and 2.

It can been observed that there is a representative difference in circulation time and mixing time between both flow patterns presented. All other simulations with respect to the liquid volume (results not shown) are in a range (with respect to the flow pattern and to t_c and t_m) between these boundary examples. Furthermore, the sum of quadratic error [3] was lower in the simulation procedure with high liquid level than with a small volume in the vessel. That means that the model used is more exact for a higher volume of liquid in the vessel. In our model [3], we have used for adinstable parameters during the simulation procedure for all examined volumes of liquid in the vessel: the volume of ideally mixed compartment in the tank (V_1, the number of tank-in-series of macromixer in the vessel $n_{(1)}$, the inner exchange flow of liquid phase across the tanks-in-series of the macromixer (F_E, and the external circulation flow across the aeration system done by the pump (F_{cir}). For the successful simulation of mixing in the whole volume range, it was necessary to change each adjustable parameter for each volume of liquid in the vessel. Parameters used in our simulations of mixing in the deep-jet reactor, are presented in Fig. 3–6 in dependence on the examined volumes, and in Fig. 7–10, in dependence on the ratio of the tank diameter to the level of unaerated liquid.

As is presented in Fig. 3, the pumping capacity (F_{cir}), as parameter in the simulation, depends linearly on the total

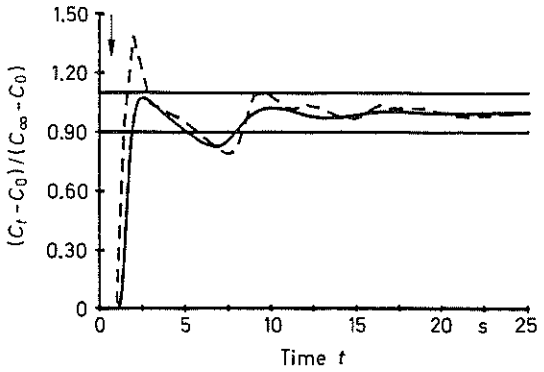

Fig. 1. Response for the injection of the tracer and the simulated data achieved using 230 dm³ of liquid in a VB-IZ-12 deep jet bioreactor. The pulse injection is indicated by an arrow

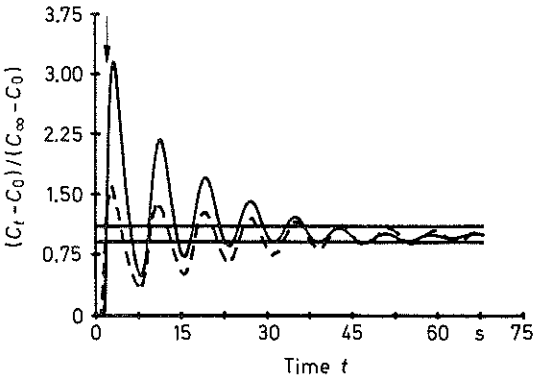

Fig. 2. Response for the injection of the tracer and the simulated data achieved using 145 dm³ of liquid in a VB-IZ-12 deep jet bioreactor. The arrow indicates the pulse injection

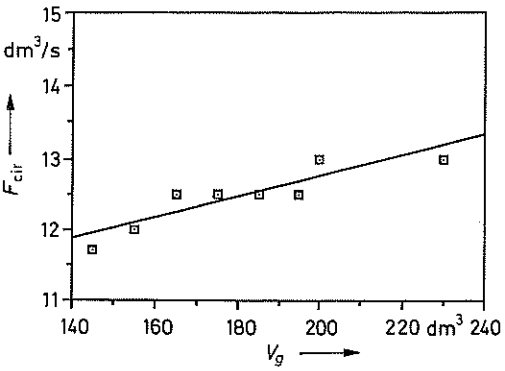

Fig. 3. Dependence of the external circulation flow (as parameter of the simulation) on the volume of liquid in the reactor

volume of the liquid. Normally, the capacity of the pump should be constant. In our case, in the reactor vessel and in the pump compartment there is not only the pure liquid, but a biphasic air-water system. Therefore, the efficiency of the pump depends on the quality of the mixing in the vessel (air dispersion) as well as on the hydrostatic pressure (liquid level) on the sucker side of the pump. Figure 7 presents the

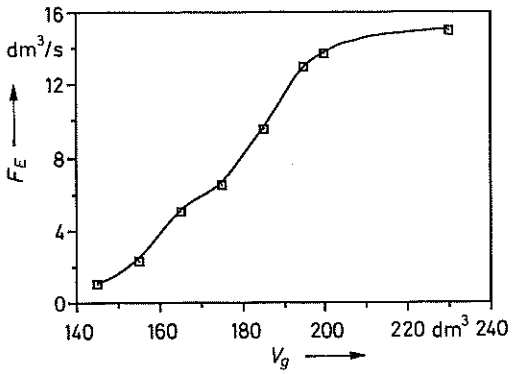

Fig. 4. Dependence of the inner circulation flow (as parameter of the simulation) on the volume of the liquid in the bioreactor

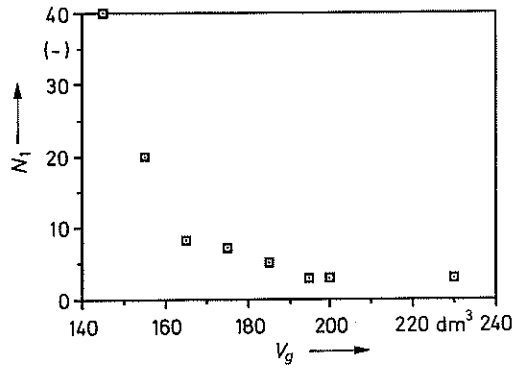

Fig. 5. Number of ideally mixed tank-in-series needed for the simulation of mixing, plotted against the volume of the liquid phase

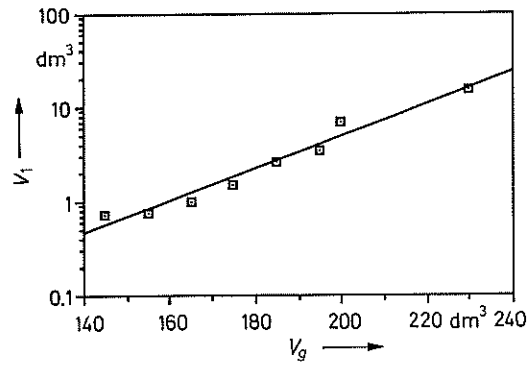

Fig. 6. Dependence of the volume of the well-mixed compartment on the total volume of liquid in the bioreactor

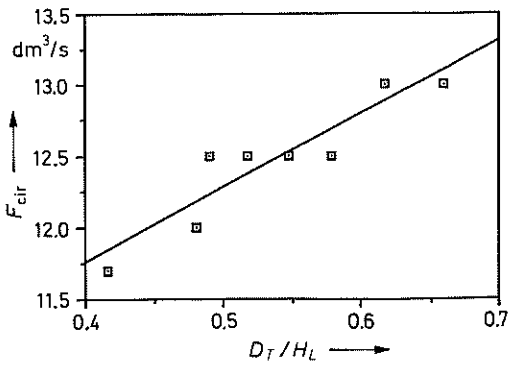

Fig. 7. External circulation flow as parameter of the simulation in its dependence on the ratio of the tank diameter to the liquid level

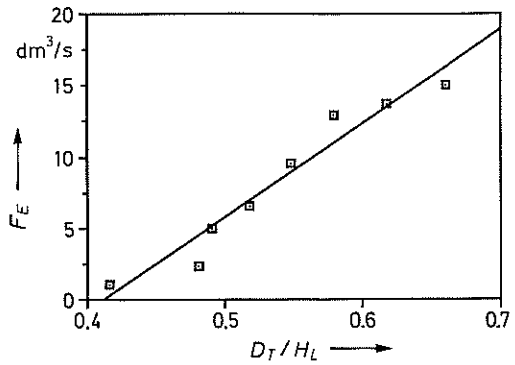

Fig. 8. Dependence of the inner circulation flow as simulation parameter on the ratio of the tank diameter to the liquid level

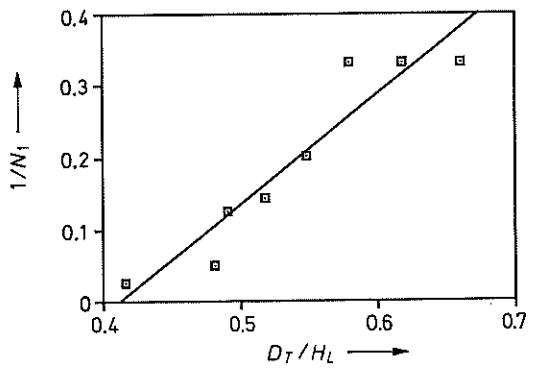

Fig. 9. Reciprocal number of ideally mixed tanks-in-series needed for the simulation of mixing, plotted against the ratio of the tank diameter to the liquid level

linear relation between the pumping capacity and the ratio of the tank diameter to the liquid level.

Comparison of Figs. 4 and 8 shows that the dependence of the inner exchange flow (F_E) on the ratio of the vessel diameter to the liquid level is more linear than the relation of this flow to the volume of the liquid. Furthermore, the number of tanks in the inner circulation flow is inversely proportional to both arguments (Figs. 5 and 9).

An interesting observation can be made in Figs. 6 and 10. The volume of the ideal mixed compartment depends exponentially on both arguments.

The relation of measured and simulated mixing time achieved by the parameters presented above is shown in Fig. 11.

Our model gives a good agreement of the simulated results for mixing times and circulation times with the experi-

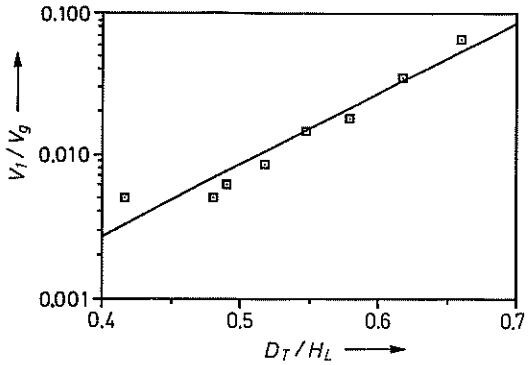

Fig. 10. Fraction of the ideally mixed compartment in the liquid volume in its dependence on the ratio of the tank diameter to the liquid level

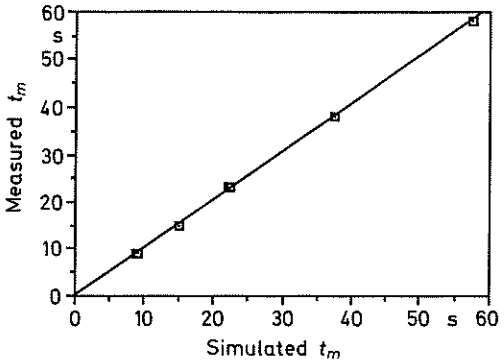

Fig. 11. Relation between measured and simulated mixing time achieved by chosen parameters for the modelling

mental data (Figs. 1, 2 and 11) for the whole range of examined volumes. In the practical use of this model for the optimization of substrate feeding in yeast fermentation, it is necessary to rapidly estimate the adjustable parameters needed for the calculation of the substrate concentration at any moment of the fermentation process, i.e. at any volume in the vessel. From the above Figs. 3–10 we also concluded that some mathematical relation must exist between the four adjustable parameters and the geometrical properties of the reactor. The following set of equations (Eqs. (2)–(6) was established:

$$F_E = -34.700 + 0.24100\ (V_g); \tag{2}$$

$$\log(V_l) = -2.72207 + 0.014487\ (V_g); \tag{3}$$

$$1/n_{(1)} = -0.0031851 + 0.023704\ (F_E); \tag{4}$$

$$F_{cir} = 9.8368 + 0.014487\ (V_g); \tag{5}$$

$$t_m = -11.907 - 40.809\ \log(1/n_{(1)}). \tag{6}$$

A similar set of equations could be established with the ratio of the tank diameter to the liquid level in the place of the total volume of liquid as the argument of eqs. (2), (3) and (5):

$$F_E = -27.128 + 65.665\ (D_T/H_L); \tag{7}$$

$$\log(V_l) = -2.72207 + 5.817\ (D_T/H_L); \tag{8}$$

$$F_{cir} = 9.6694 + 5.1821\ (D_T/H_L). \tag{9}$$

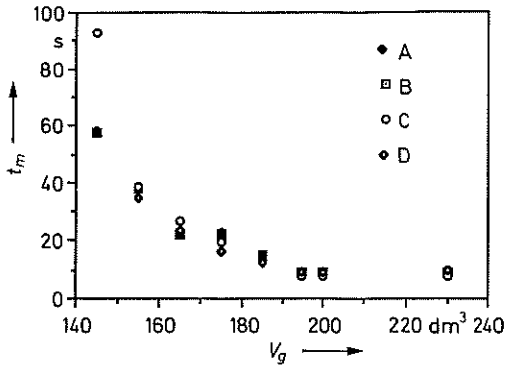

Fig. 12. The dependence of the mixing times on the volume of the liquid phase in a 300 dm^3 VB-IZ-12 bioreactor: *A* measured values; *B* simulated values; *C* calculated values from mathematical relations (see eqs. (2)–(6)); and *D* values achieved by simulations using calculated parameters from the set of equations

Two other equations which belong to this second set are Eqs. (4) and (6). This set is perhaps useful for the calculation of the model parameter in a different scale of bioreactors. According to the above set of equations we calculated the new adjustable parameters. A repeated simulation was executed using this dataset. Results from these simulations, were compared with data from the first simulation procedure with the measured data and with the calculated mixing time according to Eq. (6) and they are presented in Fig. 12.

According to the results presented in Fig. 12, this procedure and system of equations gives a good agreement of simulated and calculated mixing times (according to Eq. (6)) with measured data, except in the case of the very small volume of $V_g = 145\ dm^3$. To reduce this error we assumed that the deep jet reactor is a continuously operating reactor with a dilution rate defined according to Eq. (10) concerning the circulation time period between two peeks of the tracer. In this relatively short period of time the volume of the liquid in the vessel is diluted by the falling jet:

$$D = F_{cir}/V_{LT}. \tag{10}$$

This means that a residence time distribution concept is perhaps possible, but the model must contain present recirculating plug flow in the external loop through pipes and the aeration system as well as the successive calculation for each successive time period (t_c) between two peaks. Our model was not based on this concept. Therefore, using the dimensionless product of dilution rate and mixing time, on the one hand, and the dimensionless ratio of the total plant volume to the liquid volume, on the other hand, we have tried to find the relation between the dilution rate of the liquid in the vessel and the geometrical properties of the bioreactor (Fig. 13).

The resulting relation is given in explicit form of the mixing time:

$$t_m = A \cdot \frac{1}{D} \cdot e\left(K \frac{V}{V_g}\right). \tag{11}$$

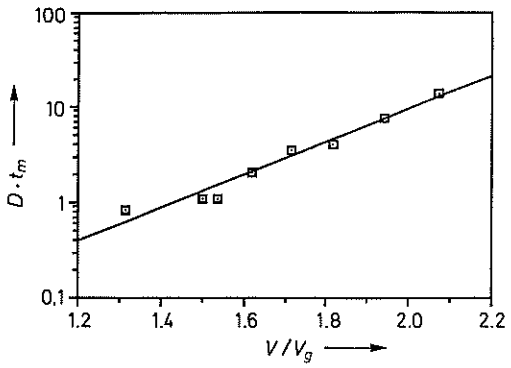

Fig. 13. Relation of the dimensionless product of dilution rate and the measured mixing times to the ratio of the total plant volume to the liquid volume in the system

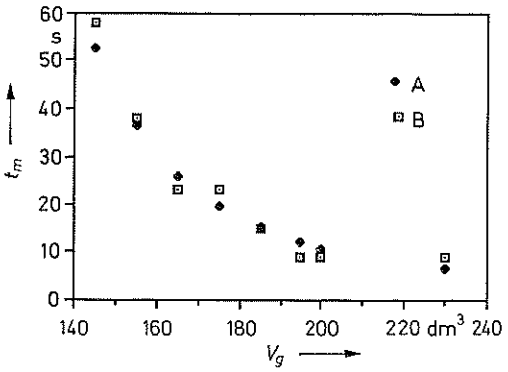

Fig. 14. Measured (*B*) and calculated (*A*) mixing times (see Eq. (14)) plotted against the volume of the liquid in the system

Inclusion of Eq. (10) in the above relation and assuming that:

$$V = V_g + V_{LC} \tag{12}$$

and that:

$$V_{LT} = V_g - V_{LC}\,, \tag{13}$$

Eq. (11) becomes:

$$t_m = A \cdot \frac{V_g - V_{LC}}{F_{cir}}\, e\left(K \frac{V_g + V_{LC}}{V_g}\right), \tag{14}$$

where A and K are the constants determined by the plant geometry, the mixing quality definition and the operating conditions. In our case, for a total plant volume of 300 dm^3 an aeration level of 1 dm^3/dm^3 min and a degree of mixing of 90%, the following values were obtained:

$A = 3.2778 \cdot 10^{-3}$

and

$K = 3.9746$.

The results of calculated mixing time according to Eq. (14) compared with measured data are presented in Fig. 14.

The results presented in Fig. 14 confirm the validity of our mathematical model for deep jet bioreactor over the whole range of the examined working volumes. In addition, the metabolism of Saccharomyces cerevisiae is extremely sensitive to changes in the concentration of the substrate in the microbial environment. For the purpose of coupling with the dynamics of substrate utilization, a relatively simple model for mixing and metabolism is required in order to permit handling of the problem within a reasonable amount of computer time. In our case, the calculation time for mixing was one minute and forty seconds. This is too long for a S. cerevisiae system. This problem can possibly be avoided by using advanced computer hardware.

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Received November 28, 1990

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