# Scale-Up on Basis of Structured Mixing Models: A New Concept

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*Received May 5, 1993/Accepted August 16, 1993*

A new scale-up concept based upon mixing models for bioreactors equipped with Rushton turbines using the tanks-in-series concept is presented. The physical mixing model includes four adjustable parameters, i.e., radial and axial circulation time, number of ideally mixed elements in one cascade, and the volume of the ideally mixed turbine region. The values of the model parameters were adjusted with the application of a modified Monte-Carlo optimization method, which fitted the simulated response function to the experimental curve. The number of cascade elements turned out to be constant ($N$ = 4). The model parameter radial circulation time is in good agreement with the one obtained by the pumping capacity. In case of remaining parameters a first or second order formal equation was developed, including four operational parameters (stirring and aeration intensity, scale, viscosity). This concept can be extended to several other types of bioreactors as well, and it seems to be a suitable tool to compare the bioprocess performance of different types of bioreactors. © 1994 John Wiley & Sons, Inc.
Key words: bioprocess • stirred tank • structured mixing model • scale-up

## INTRODUCTION

Although several scale-up studies[1,6,7,16,28,30] were published in recent years, a general scale-up principle is not known, because it is impossible to maintain total similarity of all scale-up parameters.[28] Reviews of commonly used scale-up principles are given by Oldshue,[28] Oosterhuis,[30] and Kossen.[14] Concerning the scale-up of a bioprocess from bench scale to large production scale the main aims are product yield and quality. Both requirements are "a net result from several independent, but interrelated, steps."[28] Many of these steps are closely connected to the hydrodynamics in the bioreactor.[1] The most important interactions between hydrodynamics and kinetics are oxygen and heat transfer, shear rate, $CO_2$ removal, morphology, and pH gradients,[22,28,31] of course depending on the particular fermentation. Successful scale-up and the definition of the optimal operating conditions of batch bioprocesses is still a major problem, because the optimal process variables are usually defined in small lab-scale fermentors. These bioreactors are assumed to be "pseudohomogeneous,"[22] because the corresponding time constants of the mixing and mass transport mechanisms are sufficiently small compared with those of the microbial processes.

According to Garrison,[7] eight basic mixing problems can be distinguished. Three problems, i.e., fluid blending, suspension of solids, and heat transfer, are flow controlled. Three other problems, i.e., liquid and solid dispersion and chemical reaction, are shear controlled, and the remaining two problems, i.e., gas dispersion and mass transfer, are mixed cases.

In the scale-up procedure of a bioprocess nearly all of the mentioned problems must be taken into account. In a review by Oosterhuis and Kossen,[30] all commonly used scale methods are discussed. In a fundamental method, all microbalances (mass, momentum, and heat) must be solved. In a semifundamental method, simplified balances are evaluated. The theoretical approach, called dimensional analysis, tries to obtain dimensionless numbers. In case of hydrodynamic and chemically similar systems these numbers should remain unchanged during scale-up. Because this is usually impossible, the regime analysis is a useful tool to define the rate-limiting step. The rate-limiting mechanism of the bioprocess can be determined with a comparative study of the characteristic time constants. Unfortunately, the rate-determining step might change during scale-up. They present the "scale-down" approach, concluding that probably the only safe scale-up procedure is to study all different mechanisms separately, but under conditions comparable with the ones in the production scale. They express that there is a great need for structured (gray box) models.

In a review of Joshi et al.,[12] the need for further work on the following three topics is expressed: first, there is a lack of reliable measurements carried out in large ($D_T > 1$ m) production-scale bioreactors. Second, not much work has been done concerning the behavior of viscous fermentation broths in large fermentors. Third, the influence of aeration on the mixing properties should be examined.[12,31]

Some work has already been done in the meantime; e.g., Oosterhuis[29] proved in his work that it is possible to predict the locally dissolved oxygen concentration by

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CCC 0006-3592/94/030195-12

use of a structured, five-compartment mixing model in a production-scale fermentor (19 $m^3$) equipped with two Rushton turbines. The stirrer compartment is assumed to be a torus around the stirrer, independent of stirring speed or aeration rate. The liquid exchange flow between the compartments is the pumping capacity of the turbine.

Bader,[2,3] using model simulations carried out for a 150-$m^3$ production fermentor, showed that a somewhat simple, structured model can be used as a tool to test a wide range of variables to develop general performance characteristics. He concludes that there is a rather limited knowledge base for multiturbine agitation systems, specifically, no good correlation for the liquid exchange flow between the stirrer compartments can be found in the literature.

Heinzle et al.[9] used an oxygen-sensitive *Bacillus subtilis* culture to characterize the influence of reactor parameters on the oxygen supply. For the model simulations they used three different mixing models, which were combined with a simple, structured kinetic model. The best agreement between experimental and model simulation was obtained for the three-compartment mixing model, as the simpler mixing models failed to predict the oxygen transfer coefficient correctly.

Recently, a number of scientific efforts have been directed toward the application of computational fluid dynamics (CFD) as an alternative tool.[11] The scale-up approach presented in this article for a stirred tank bioreactor equipped with three Rushton turbines is based on the physical mixing model that was described in a previous work.[20] The four adjustable mixing-model parameters (radial circulation time, $t_{c,\mathrm{RAD}}$; axial circulation time, $t_{c,AX}$; ideally mixed stirrer compartment, $V_M$, and number of tanks in each cascade, $N$) are dependent on the four most important experimental conditions (scale, viscosity, stirring speed, and aeration rate). This study is based upon approximately 400 mixing experiments, thus covering many combinations of the experimental conditions.

To describe the dependence of the performance of the particular bioprocess on oxygen transfer rate, shear rate, and the dosage of acid (base) for pH control, these process parameters shall be related to certain individual compartments according to the real conditions in the tank. This article deals with the scale-up of the mixing properties. Because it is the main goal to build an integrated bioprocess model, this study is to be seen as the basis for further work.

The mathematical formulation of the kinetics of the microorganisms must include an effect incorporating the mentioned changes in the environment caused by mixing influences. The result will be an integrated bioprocess model, capable of describing the dependence of the biological system on the physical environment. So far, only the influence of the pH control strategy was examined,[21] and further work will quantify the other influences. This integrated bioprocess model might be used for control purposes, but also to simulate the large-scale behavior of any new culture that is still in the first stage of development in the laboratory, as soon as experiments quantify the interactions between the biological and physical properties.

## MATERIALS AND METHODS

### Fermentors

Bioreactors with technical features, given in Table I, were used. All bioreactors are supplied with four baffles.

### Measurements

In case of the small (STR-3-S) and middle (STR-3-M) stirred tanks the heat pulse method[13,18,32] was used to investigate the flow properties. Six PT-100 sensors (response time $t_{90} = 0.08$ s, resolution 0.002°C) were positioned in the bioreactors[19] and their responses to the temperature pulse were recorded by means of an electronic interface connected to a personal computer. The temperature was kept in the range 22°C to 26°C.

For the largest fermentor (STR-3-L), the pH-transient method was utilized, because it was not possible to make technical changes, such as a pulse application system, in the production tank. For simplicity, the pulse of acid or base was poured on the liquid surface near the stirrer shaft. One probe (response time $t_{90} \approx 0.9$s, resolution 0.007), positioned between the middle and top turbine, recorded the distribution of the tracer (Fig. 1), the duration of the pulse injection was approximately 1.5 s. These times were fast enough compared with the homogeneity time[19] (Table II). The experimental conditions for all tests are given in Table II together with the results of the homogeneity–time analysis[19] and the adjusted model parameters.[20]

The examined liquid volumes were 0.12, 2.5, and 65 $m^3$ with tank diameters of 0.4, 1.18, and 3.5 m, respectively.

**Table I.** Technical features of the bioreactors.

| Synonym | Tank volume ($m^3$) | Stirrer | Turbine diameter (m) | Max. power (kW) | Tank diameter (m) | $h_l/D$ | Liquid volume ($m^3$) |
|---|---|---|---|---|---|---|---|
| STR-3-S | 0.15 | 3 Rushton | 0.21 | 3 | 0.40 | 2.3 | 0.12 |
| STR-3-M | 3.2 | 3 Rushton | 0.51 | 26 | 1.18 | 2.3 | 2.5 |
| STR-3-L | 90.0 | 3 Rushton | 1.42 | 420 | 3.50 | 2.0 | 65.0 |

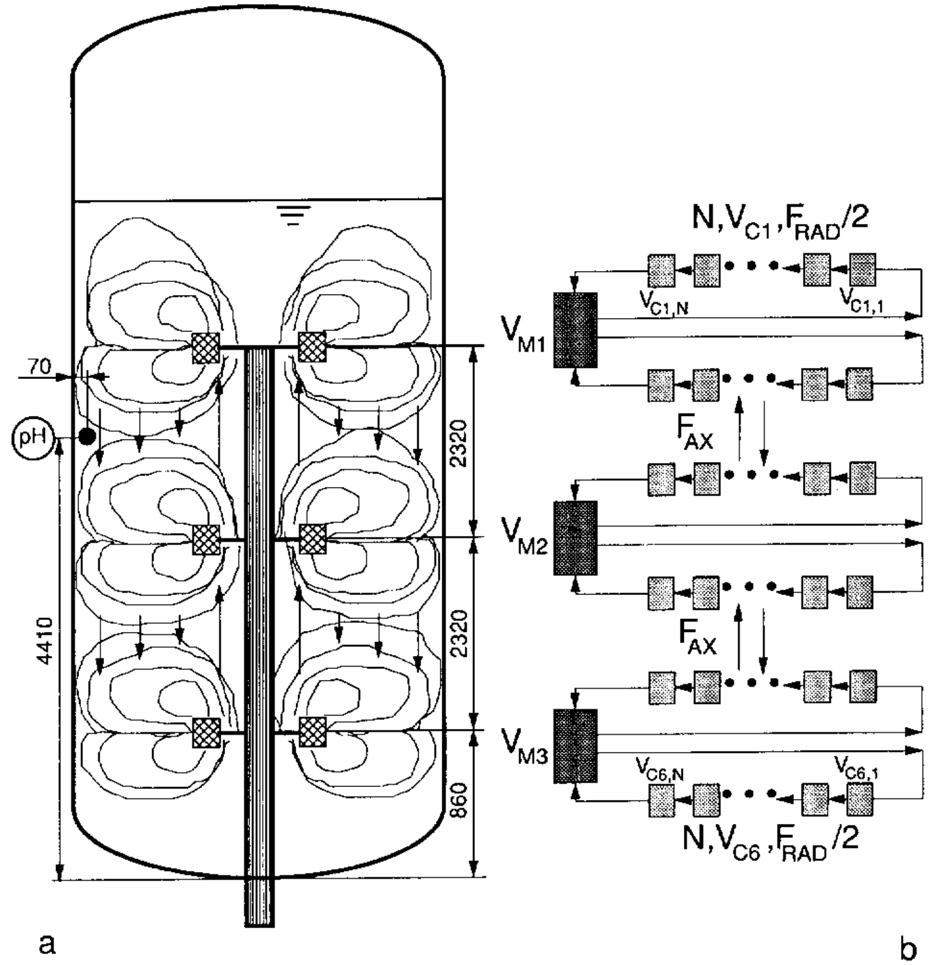


**Figure 1.** Macroscopic flow pattern (a) and physical mixing model (b) for the largest stirred tank bioreactor equipped with three Rushton turbines (STR-3-L).

The viscosity ranges from tapwater ($\eta = 0.001$ Pa · s) to a fermentation broth ($\eta = 0.7$ Pa · s). Table III shows the examined combinations of dimensionless viscosity, $\eta^*$ [Eq. (1)], and scale-up ratio, $\lambda$ [Eq. (2)]:

$$\eta^* = \eta/\eta_{\text{ref}} \qquad \eta_{\text{ref}} = 0.001 \text{ Pa} \cdot \text{s} \tag{1}$$

$$\lambda = D_T/D_{T,\text{ref}} \qquad D_{T,\text{ref}} = 1.0 \text{ m} \tag{2}$$

## Mathematical Methods

The homogeneity time method,[19] the physical mixing model,[20] used to describe the hydrodynamics, and the mathematical parameter estimation method have been presented in previous articles. The model is an extended version of one proposed by Singh et al.;[33–35] its structure and corresponding flow pattern are shown in Figure 1.

On the basis of the macroscopic flow pattern (Fig. 1a) the bioreactor can be separated into three regions. Each of them is related to one stirrer section and is characterized by an ideally mixed compartment around the stirrer and two macromixers, i.e., a cascade of tanks-in-series, describing the recirculation flow. The radial and the axial circulation times are defined according to Eqs. (3) and (4), respectively.

$$t_{c,\text{RAD}} = \frac{V_{\text{tot}}}{3 \cdot F_{\text{RAD}}} \tag{3}$$

$$t_{c,AX} = \frac{V_{\text{tot}}}{F_{AX}} \tag{4}$$

The model consists of four adjustable parameters, i.e., radial circulation time ($t_{c,\text{RAD}}$), axial circulation time ($t_{c,AX}$), ratio of ideally mixed stirrer volume to total volume ($V_M/V_{\text{tot}}$), and number of ideally mixed tanks in the recirculation cascade ($N$).

The ideally mixed stirrer compartments are equally sized ($V_{M1} = V_{M2} = V_{M3} = V_M/3$), and the same is valid for the recirculation cascades ($V_{C1} = V_{C2} = V_{C6} = V_C/6$). The position of the axial exchange flow between the top region ($V_{M1}, V_{C1}, V_{C2}$) of the vessel and the middle ($V_{M2}, V_{C3}, V_{C4}$) was assigned to the middle volume element in the adjoining cascades (i.e., $V_{C2,J}$ and $V_{C3,J}$), the interchange between the middle and the lower region is located in the middle volume of the adjoining

**Table II.** Experimental conditions, homogeneity—time[19] and results of optimization procedure for all adjustable model parameters.[20]

| Fermentor | Stirring (rpm) | Aeration ($m^3/h$) | Medium | Density ($kg/m^3$) | Viscosity ($Pa \cdot s$) | $t(i = 0.1)$ (s) | Optimized parameters | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | $V_m/V_{tot}$ | $N$ | $t_{c,RAD}$ | $t_{c,AX}$ | Error% |
| STR-3-L | 85 | 0 | A) | 1050 | 0.623 | 18.0 | 0.013 | 9 | 11.5 | 142.7 | 12.6 |
| | 85 | 2000 | A) | 1050 | 0.634 | 25.0 | 0.016 | 3 | 10.5 | 27.1 | 9.2 |
| | 66 | 0 | A) | 1050 | 0.759 | 32.5 | 0.027 | 3 | 6.0 | 92.6 | 9.6 |
| | 66 | 2000 | A) | 1050 | 0.751 | 29.0 | 0.023 | 4 | 7.0 | 65.3 | 9.0 |
| | 32 | 0 | A) | 1050 | 1.35 | 115.0 | 0.007 | 4 | 24.0 | 256.8 | 13.0 |
| STR-3-M | 30 | 0 | A) | 1050 | 0.04 | 49.2 | 0.009 | 2 | 13.7 | 8.7 | 17.1 |
| | 100 | 0 | A) | 1050 | 0.04 | 9.9 | 0.014 | 6 | 3.2 | 9.3 | 10.01 |
| | 200 | 0 | A) | 1050 | 0.04 | 7.0 | 0.076 | 6 | 1.6 | 6.9 | 9.0 |
| | 30 | 20 | A) | 1050 | 0.04 | 22.4 | 0.296 | 9 | 4.5 | 3.1 | 24.3 |
| | 60 | 20 | A) | 1050 | 0.04 | 18.3 | 0.005 | 6 | 7.5 | 8.5 | 14.6 |
| | 100 | 20 | A) | 1050 | 0.04 | 11.1 | 0.069 | 3 | 3.5 | 4.9 | 8.3 |
| | 150 | 20 | A) | 1050 | 0.04 | 7.9 | 0.101 | 6 | 1.5 | 8.7 | 11.2 |
| | 200 | 20 | A) | 1050 | 0.04 | 9.7 | 0.322 | 6 | 2.2 | 3.1 | 11.6 |
| | 30 | 70 | A) | 1050 | 0.04 | 14.4 | 0.143 | 2 | 4.7 | 5.8 | 44.0 |
| | 100 | 70 | A) | 1050 | 0.04 | 13.5 | 0.010 | 3 | 5.0 | 1.2 | 11.2 |
| | 150 | 70 | A) | 1050 | 0.04 | 10.2 | 0.017 | 2 | 2.9 | 1.6 | 11.4 |
| | 200 | 70 | A) | 1050 | 0.04 | 9.4 | 0.044 | 2 | 2.2 | 0.9 | 9.3 |
| STR-3-M | 60 | 0 | B) | 1218 | 0.18 | 16.1 | 0.037 | 3 | 6.0 | 11.3 | 9.7 |
| | 100 | 0 | B) | 1218 | 0.18 | 11.4 | 0.181 | 3 | 3.3 | 12.1 | 11.6 |
| | 150 | 0 | B) | 1218 | 0.18 | 7.1 | 0.256 | 2 | 2.0 | 8.4 | 10.1 |
| | 200 | 0 | B) | 1218 | 0.18 | 8.6 | 0.353 | 6 | 2.4 | 7.0 | 11.0 |
| | 60 | 20 | B) | 1218 | 0.18 | 12.5 | 0.067 | 6 | 5.8 | 2.4 | 16.7 |
| | 100 | 20 | B) | 1218 | 0.18 | 10.4 | 0.156 | 3 | 3.3 | 6.5 | 11.1 |
| | 150 | 20 | B) | 1218 | 0.18 | 8.4 | 0.069 | 3 | 2.7 | 5.5 | 8.8 |
| | 200 | 20 | B) | 1218 | 0.18 | 7.0 | 0.241 | 3 | 1.2 | 8.3 | 10.2 |
| | 60 | 40 | B) | 1218 | 0.18 | 13.3 | 0.062 | 5 | 6.2 | 2.0 | 17.3 |
| | 100 | 40 | B) | 1218 | 0.18 | 12.4 | 0.181 | 3 | 4.4 | 6.2 | 14.7 |
| | 150 | 40 | B) | 1218 | 0.18 | 8.8 | 0.325 | 2 | 2.0 | 7.9 | 11.1 |
| | 200 | 40 | B) | 1218 | 0.18 | 5.9 | 0.222 | 5 | 1.6 | 2.4 | 10.1 |
| | 250 | 40 | B) | 1218 | 0.18 | 7.5 | 0.249 | 3 | 2.6 | 0.4 | 11.7 |
| | 60 | 70 | B) | 1218 | 0.18 | 22.3 | 0.210 | 4 | 6.9 | 2.4 | 19.0 |
| | 100 | 70 | B) | 1218 | 0.18 | 11.3 | 0.049 | 3 | 4.6 | 1.9 | 11.9 |
| | 150 | 70 | B) | 1218 | 0.18 | 9.6 | 0.142 | 2 | 3.4 | 1.3 | 12.1 |
| | 200 | 70 | B) | 1218 | 0.18 | 7.2 | 0.060 | 3 | 2.8 | 1.3 | 8.8 |
| | 250 | 70 | B) | 1218 | 0.18 | 6.8 | 0.204 | 3 | 2.2 | 3.3 | 10.5 |
| | 60 | 100 | B) | 1218 | 0.18 | 13.1 | 0.118 | 4 | 5.4 | 7.1 | 14.8 |
| | 100 | 100 | B) | 1218 | 0.18 | 10.7 | 0.260 | 2 | 3.5 | 5.1 | 11.8 |
| | 150 | 100 | B) | 1218 | 0.18 | 7.9 | 0.173 | 3 | 2.1 | 8.4 | 8.4 |
| | 200 | 100 | B) | 1218 | 0.18 | 6.6 | 0.166 | 3 | 1.6 | 7.5 | 9.2 |
| | 250 | 100 | B) | 1218 | 0.18 | 7.0 | 0.278 | 6 | 2.0 | 3.0 | 12.9 |
| | 60 | 150 | B) | 1218 | 0.18 | 12.4 | 0.106 | 3 | 3.7 | 8.3 | 19.4 |
| | 100 | 150 | B) | 1218 | 0.18 | 10.3 | 0.052 | 6 | 4.8 | 1.4 | 18.2 |
| | 150 | 150 | B) | 1218 | 0.18 | 10.9 | 0.083 | 3 | 3.9 | 0.1 | 9.2 |
| | 200 | 150 | B) | 1218 | 0.18 | 11.3 | 0.144 | 3 | 3.0 | 1.3 | 9.9 |
| | 250 | 150 | B) | 1218 | 0.18 | 6.8 | 0.382 | 3 | 2.1 | 1.0 | 10.9 |
| | 60 | 200 | B) | 1218 | 0.18 | 13.2 | 0.356 | 4 | 4.9 | 2.8 | 25.4 |
| | 100 | 200 | B) | 1218 | 0.18 | 10.1 | 0.083 | 6 | 4.6 | 2.4 | 21.1 |
| | 150 | 200 | B) | 1218 | 0.18 | 13.0 | 0.070 | 3 | 4.3 | 1.2 | 11.7 |
| | 200 | 200 | B) | 1218 | 0.18 | 8.5 | 0.165 | 3 | 2.7 | 2.6 | 10.3 |
| | 250 | 200 | B) | 1218 | 0.18 | 45.1 | 0.273 | 6 | 2.7 | 0.8 | 13.8 |
| STR-3-M | 60 | 0 | C) | 998 | 0.001 | 16.3 | 0.021 | 7 | 4.9 | 6.4 | 12.1 |
| | 100 | 0 | C) | 998 | 0.001 | 8.8 | 0.176 | 9 | 2.8 | 4.8 | 12.6 |
| | 150 | 0 | C) | 998 | 0.001 | 6.8 | 0.346 | 8 | 2.0 | 5.3 | 8.3 |
| | 200 | 0 | C) | 998 | 0.001 | 6.0 | 0.481 | 3 | 1.8 | 2.5 | 8.3 |
| | 60 | 20 | C) | 998 | 0.001 | 14.8 | 0.002 | 6 | 6.4 | 4.7 | 24.4 |
| | 100 | 20 | C) | 998 | 0.001 | 9.9 | 0.030 | 2 | 4.1 | 1.2 | 10.0 |
| | 150 | 20 | C) | 998 | 0.001 | 6.2 | 0.292 | 6 | 2.3 | 2.2 | 6.8 |
| | 200 | 20 | C) | 998 | 0.001 | 5.8 | 0.381 | 6 | 1.5 | 3.4 | 8.0 |
| | 250 | 20 | C) | 998 | 0.001 | 5.8 | 0.331 | 3 | 0.6 | 6.4 | 10.1 |
| | 60 | 40 | C) | 998 | 0.001 | 14.6 | 0.010 | 6 | 7.2 | 7.8 | 25.7 |
| | 100 | 40 | C) | 998 | 0.001 | 10.5 | 0.157 | 6 | 4.3 | 2.7 | 9.0 |
| | 150 | 40 | C) | 998 | 0.001 | 7.0 | 0.183 | 6 | 2.6 | 2.2 | 7.8 |

**Table II.** *(continued)*

| Fermentor | Stirring (rpm) | Aeration ($m^3/h$) | Medium | Density ($kg/m^3$) | Viscosity (Pa · s) | $t(i = 0.1)$ (s) | Optimized parameters | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | $V_m/V_{tot}$ | $N$ | $t_{c,RAD}$ | $t_{c,AX}$ | Error% |
| | 200 | 40 | C) | 998 | 0.001 | 6.3 | 0.239 | 3 | 1.8 | 1.5 | 7.3 |
| | 250 | 40 | C) | 998 | 0.001 | 6.3 | 0.252 | 3 | 1.7 | 0.8 | 6.8 |
| | 60 | 70 | C) | 998 | 0.001 | 9.8 | 0.019 | 7 | 5.3 | 0.6 | 24.8 |
| | 100 | 70 | C) | 998 | 0.001 | 11.6 | 0.016 | 6 | 5.4 | 2.3 | 13.1 |
| | 150 | 70 | C) | 998 | 0.001 | 9.6 | 0.103 | 6 | 3.2 | 2.5 | 10.9 |
| | 200 | 70 | C) | 998 | 0.001 | 5.4 | 0.202 | 3 | 1.9 | 1.0 | 9.4 |
| | 250 | 70 | C) | 998 | 0.001 | 6.5 | 0.218 | 3 | 2.0 | 1.5 | 7.3 |
| | 60 | 100 | C) | 998 | 0.001 | 9.9 | 0.048 | 7 | 5.2 | 2.8 | 32.5 |
| | 100 | 100 | C) | 998 | 0.001 | 11.0 | 0.024 | 6 | 5.7 | 2.3 | 20.7 |
| | 150 | 100 | C) | 998 | 0.001 | 9.0 | 0.056 | 3 | 3.6 | 0.9 | 8.8 |
| | 200 | 100 | C) | 998 | 0.001 | 6.5 | 0.151 | 6 | 2.8 | 1.1 | 11.5 |
| | 250 | 100 | C) | 998 | 0.001 | 7.5 | 0.082 | 3 | 2.7 | 0.3 | 7.7 |
| | 60 | 150 | C) | 998 | 0.001 | 15.3 | 0.076 | 7 | 4.9 | 3.1 | 27.7 |
| | 100 | 150 | C) | 998 | 0.001 | 11.7 | 0.073 | 6 | 4.8 | 1.7 | 18.1 |
| | 150 | 150 | C) | 998 | 0.001 | 10.5 | 0.179 | 6 | 3.2 | 1.3 | 10.9 |
| | 200 | 150 | C) | 998 | 0.001 | 6.0 | 0.284 | 6 | 2.1 | 0.7 | 7.3 |
| | 250 | 150 | C) | 998 | 0.001 | 6.9 | 0.133 | 3 | 2.1 | 0.6 | 8.0 |
| | 60 | 200 | C) | 998 | 0.001 | 10.5 | 0.015 | 7 | 4.6 | 1.1 | 31.8 |
| | 100 | 200 | C) | 998 | 0.001 | 10.4 | 0.026 | 6 | 5.4 | 0.9 | 23.7 |
| | 150 | 200 | C) | 998 | 0.001 | 8.2 | 0.068 | 6 | 3.7 | 1.7 | 10.8 |
| | 200 | 200 | C) | 998 | 0.001 | 7.3 | 0.052 | 3 | 3.0 | 1.0 | 7.6 |
| | 250 | 200 | C) | 998 | 0.001 | 6.3 | 0.069 | 3 | 2.6 | 1.2 | 7.1 |
| STR-3-S | 50 | 0 | B) | 1226 | 0.22 | 60.0 | 0.405 | 6 | 29.0 | 64.1 | 16.3 |
| | 100 | 0 | B) | 1226 | 0.22 | 37.5 | 0.070 | 8 | 1.7 | 47.5 | 14.6 |
| | 200 | 0 | B) | 1226 | 0.22 | 8.6 | 0.317 | 5 | 0.9 | 10.8 | 7.0 |
| | 300 | 0 | B) | 1226 | 0.22 | 5.5 | 0.555 | 6 | 0.7 | 7.4 | 7.9 |
| | 400 | 0 | B) | 1226 | 0.22 | 2.7 | 0.242 | 3 | 0.5 | 5.0 | 7.0 |
| | 50 | 2.4 | B) | 1226 | 0.22 | 17.4 | 0.400 | 7 | 7.8 | 1.0 | 23.6 |
| | 100 | 2.4 | B) | 1226 | 0.22 | 11.4 | 0.341 | 10 | 4.6 | 0.8 | 16.4 |
| | 200 | 2.4 | B) | 1226 | 0.22 | 6.9 | 0.382 | 3 | 0.8 | 11.1 | 7.3 |
| | 300 | 2.4 | B) | 1226 | 0.22 | 4.7 | 0.241 | 1 | 0.5 | 8.8 | 6.1 |
| | 400 | 2.4 | B) | 1226 | 0.22 | 3.8 | 0.618 | 1 | 0.5 | 2.6 | 10.9 |
| | 50 | 4.2 | B) | 1226 | 0.22 | 14.6 | 0.320 | 8 | 6.9 | 2.0 | 26.4 |
| | 100 | 4.2 | B) | 1226 | 0.22 | 12.5 | 0.346 | 5 | 4.0 | 2.8 | 10.2 |
| | 200 | 4.2 | B) | 1226 | 0.22 | 6.1 | 0.253 | 6 | 2.3 | 2.0 | 6.0 |
| | 300 | 4.2 | B) | 1226 | 0.22 | 6.5 | 0.395 | 6 | 1.1 | 1.9 | 5.5 |
| | 400 | 4.2 | B) | 1226 | 0.22 | 5.4 | 0.333 | 3 | 0.9 | 1.9 | 7.9 |
| | 50 | 6 | B) | 1226 | 0.22 | 11.1 | 0.352 | 10 | 5.5 | 2.7 | 17.6 |
| | 100 | 6 | B) | 1226 | 0.22 | 9.0 | 0.493 | 3 | 3.4 | 2.6 | 10.4 |
| | 200 | 6 | B) | 1226 | 0.22 | 8.7 | 0.491 | 1 | 1.9 | 2.5 | 6.9 |
| | 300 | 6 | B) | 1226 | 0.22 | 5.1 | 0.464 | 6 | 1.1 | 4.1 | 6.6 |
| | 400 | 6 | B) | 1226 | 0.22 | 6.2 | 0.583 | 6 | 0.5 | 6.4 | 6.3 |
| | 50 | 9 | B) | 1226 | 0.22 | 9.2 | 0.431 | 8 | 3.8 | 0.1 | 17.8 |
| | 100 | 9 | B) | 1226 | 0.22 | 9.2 | 0.214 | 2 | 4.3 | 0.4 | 12.0 |
| | 200 | 9 | B) | 1226 | 0.22 | 5.1 | 0.325 | 6 | 1.9 | 0.8 | 5.0 |
| | 300 | 9 | B) | 1226 | 0.22 | 4.8 | 0.327 | 8 | 1.3 | 0.4 | 5.8 |
| | 400 | 9 | B) | 1226 | 0.22 | 5.1 | 0.525 | 1 | 1.3 | 0.3 | 6.4 |
| STR-3-S | 50 | 0 | C) | 998 | 0.001 | 24.6 | 0.008 | 3 | 4.0 | 17.8 | 4.8 |
| | 100 | 0 | C) | 998 | 0.001 | 8.9 | 0.064 | 1 | 1.6 | 11.9 | 9.2 |
| | 200 | 0 | C) | 998 | 0.001 | 4.6 | 0.208 | 1 | 1.0 | 6.4 | 9.3 |
| | 300 | 0 | C) | 998 | 0.001 | 3.3 | 0.237 | 1 | 0.7 | 5.0 | 10.5 |
| | 400 | 0 | C) | 998 | 0.001 | 2.9 | 0.530 | 1 | 0.2 | 7.8 | 10.1 |
| | 50 | 2.4 | C) | 998 | 0.001 | 7.6 | 0.050 | 1 | 1.5 | 6.4 | 7.3 |
| | 100 | 2.4 | C) | 998 | 0.001 | 9.7 | 0.078 | 1 | 1.7 | 12.3 | 7.1 |
| | 200 | 2.4 | C) | 998 | 0.001 | 4.8 | 0.084 | 10 | 1.3 | 4.7 | 19.3 |
| | 300 | 2.4 | C) | 998 | 0.001 | 3.8 | 0.208 | 7 | 0.9 | 4.3 | 19.3 |
| | 400 | 2.4 | C) | 998 | 0.001 | 3.0 | 0.388 | 1 | 0.5 | 4.0 | 7.5 |
| | 50 | 4.2 | C) | 998 | 0.001 | 9.6 | 0.039 | 1 | 1.7 | 8.5 | 7.4 |
| | 100 | 4.2 | C) | 998 | 0.001 | 11.5 | 0.183 | 1 | 2.0 | 7.2 | 4.4 |
| | 200 | 4.2 | C) | 998 | 0.001 | 4.6 | 0.207 | 2 | 1.0 | 8.2 | 12.9 |
| | 300 | 4.2 | C) | 998 | 0.001 | 3.2 | 0.214 | 2 | 0.4 | 6.7 | 11.2 |
| | 50 | 6 | C) | 998 | 0.001 | 13.6 | 0.018 | 1 | 1.8 | 7.0 | 8.9 |

**Table II.** *(continued)*

| Fermentor | Stirring (rpm) | Aeration ($m^3$/h) | Medium | Density (kg/$m^3$) | Viscosity (Pa · s) | $t(i = 0.1)$ (s) | Optimized parameters $V_m/V_{tot}$ | $N$ | $t_{c,RAD}$ | $t_{c,AX}$ | Error% |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 100 | 6 | C) | 998 | 0.001 | 12.1 | 0.044 | 1 | 1.6 | 8.5 | 4.7 |
| | 200 | 6 | C) | 998 | 0.001 | 5.4 | 0.085 | 3 | 0.9 | 6.0 | 6.0 |
| | 300 | 6 | C) | 998 | 0.001 | 3.5 | 0.059 | 3 | 0.8 | 4.5 | 7.9 |
| | 400 | 6 | C) | 998 | 0.001 | 2.9 | 0.070 | 7 | 0.3 | 5.8 | 12.8 |
| | 50 | 9 | C) | 998 | 0.001 | 9.1 | 0.085 | 1 | 2.0 | 0.3 | 7.9 |
| | 200 | 9 | C) | 998 | 0.001 | 6.7 | 0.074 | 2 | 1.3 | 0.7 | 11.7 |
| | 300 | 9 | C) | 998 | 0.001 | 5.3 | 0.084 | 3 | 1.2 | 2.3 | 9.3 |
| | 400 | 9 | C) | 998 | 0.001 | 3.7 | 0.153 | 7 | 1.1 | 1.5 | 20.5 |

cascades (i.e., $V_{C4,J}$ and $V_{C5,J}$). For details concerning the model structure and the parameter estimation process the reader is referred to the original work.[20] The results of the parameter estimation procedure are given in Table II.

In order to obtain mathematical relations between the adjustable model ($t_{c,RAD}, t_{c,AX}, V_M/V_{tot}, N$) and measured experimental parameters ($Fr_s, Fr_A, \eta^*, \lambda$), a surface regression method based on a Maclaurin power series of differing order, as in Eq. (5), is applied.

$$\begin{aligned} z(A,B) &= a_{00} + a_{01} \cdot B + \cdots + a_{0Y} \cdot B^Y \\ &+ a_{10} \cdot A + a_{11} \cdot A \cdot B + \cdots + a_{1Y} \cdot A \cdot B^Y \\ &+ a_{X0} \cdot A^X + a_{X1} \cdot A^X \cdot B + \cdots + a_{XY} \cdot A \cdot B^Y \end{aligned} \tag{5}$$

The total number of coefficients computed is the product $(X + 1) \cdot (Y + 1)$.

## RESULTS AND DISCUSSION

The main task of the mixing modeling efforts is to provide a reliable hydrodynamic scale-up tool. The proposed mixing model is quite low in complexity. Therefore, it can be easily used for this purpose, but also as the basis for an integrated bioprocess model. The combination with a formal kinetic model gives the chance to include local properties related to the mixing behavior in the fermentor with sufficient accuracy. In order to set up a complete bioprocess model it is necessary to define all interactions of the microbial metabolism with the local physical effects. Although such a model will be capable of describing influences of scale, viscosity, aeration, and stirring rate on the bioprocess performance it is still simple enough to be solved on a standard personal computer. Therefore, this method is especially suitable for use in industrial practice. As a first exercise, results of the effect of pH regulation[21] and dissolved oxygen concentration on a glutamic acid fermentation[25] have been presented.

The greatest advantage of this method is that the scale-up is based upon several operational and geometrical parameters. In this study, the following eight parameters are involved:

$$n,\ F_A,\ \eta,\ V_{tot},\ d_i,\ D_T,\ h_1,\ N_{turb}$$

### Hydrodynamic Scale-Up

The proposed scale-up concept derives mathematical formulae between all adjustable mixing model parameters ($V_M/V_{tot}, t_{c,RAD}, t_{c,AX}, N$) and all independent experimental variables, i.e., scale ratio ($\lambda$), dimensionless viscosity ($\eta^*$), stirrer revolutions ($n$), and aeration flow rate ($F_A$). For further evaluations, the stirrer revolutions and the aeration flow rate are transformed into dimensionless Froude numbers ($Fr_S, Fr_A$). Because of the chosen formal method all experimental conditions should be independent. This is actually not true in the case of stirring intensity and viscosity, as can be seen in the case of the largest tank, STR-3-L, with a viscous fermentation broth (Table II). To develop this scale-up method we assumed, as a working hypothesis, that the viscosity is constant at a representative value ($\eta = 0.7$ Pa · s).

**Table III.** Mean optimized and mean calculated model parameters. The error is related based upon all tested combinations of stirring intensity and aeration for each particular combination of scale and dimensionless viscosity.[a]

| Fermentor | Scale ($\lambda$) | Viscosity ($\eta^*$) | Number of tests | Mean ($t_{c,RAD}$) Opt. (s) | Calc. (s) | Error (%) | Mean ($t_{c,AX}$) Opt. (s) | Calc. (s) | Error (%) | Mean ($V_M/V_{tot}$) Opt. | Calc. | Error (%) | Mean ($N$) Opt. | Calc. | Error (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STR-3-S | 0.4 | 1 | 23 | 1.29 | 0.54 | 57.6 | 6.43 | 8.74 | 93.4 | 0.138 | 0.171 | 108 | 2.65 | 4 | 184 |
| | | 220 | 25 | 2.46 | 0.49 | 76.4 | 5.18 | 5.12 | 191 | 0.379 | 0.328 | 36.9 | 5.16 | 4 | 82.8 |
| STR-3-M | 1.18 | 1 | 34 | 3.47 | 2.91 | 26.8 | 3.16 | 5.74 | 186 | 0.141 | 0.150 | 121 | 5.21 | 4 | 37.8 |
| | | 40 | 12 | 4.38 | 4.94 | 41.6 | 5.69 | 6.86 | 112 | 0.061 | 0.163 | 519 | 4.42 | 4 | 57.4 |
| | | 180 | 33 | 3.48 | 2.96 | 24.3 | 4.78 | 7.82 | 234 | 0.174 | 0.250 | 95.5 | 3.48 | 4 | 36.6 |
| STR-3-L | 3.5 | 700 | 5 | 11.7 | 6.63 | 36.1 | 116 | 113 | 32.2 | 0.025 | 0.019 | 33.8 | 4.6 | 4 | 24.4 |

[a]See Table II.

### *Radial Circulation Time* ($t_{c,RAD}$)

The estimated values of the model parameter, "radial circulation time" ($t_{c,\mathrm{RAD}}$), is in close agreement with the value calculated ($t_{c,\mathrm{RAD,calc}}$) according to Eq. (6).[31]

$$t_{c,\mathrm{RAD,calc}} = \frac{1}{n} 0.76\left(\frac{h_T}{D_T}\right)^{0.6}\left(\frac{D_T}{d_i}\right)^{2.7}$$
$$h_T \simeq \frac{h_1}{N_{\mathrm{turb}}}, \quad N_{\mathrm{turb}} = 3 \qquad (6)$$

The mean circulation time for a system with three Rushton turbines is derived from the relation for a single turbine tank with the application of the longest circulation path concept.[31] Eq. (6) is based upon systematic experiments carried out in two different vessels (0.1 and 0.3 $m^3$). An extrapolation seems to be valid, because the optimized model parameter, "radial circulation time," correlates quite well with the values calculated according to Eq. (6). Anyhow, in Eq. (6), no dependence on aeration or viscosity is incorporated. The adequacy might be improved if these influences are included. This has not been tested so far. In the case of viscosity the effect can be neglected as long as the experiments are carried out in a turbulent regime.

Table III gives the mean value of optimized and calculated parameters and the mean error of all optimized values of $t_{c,\mathrm{RAD}}$ related on the values resulting from Eq. (6) for the several different combinations of scale ratio and viscosity. The following, Eq. (7), is used to calculate the error. The original optimized parameters are listed in Table II.

$$\mathrm{Error} = \frac{100}{p} \sum_{i=1}^{p} \frac{|t_{c,\mathrm{RAD}} - t_{c,\mathrm{RAD,calc}}|_i}{(t_{c,\mathrm{RAD}})_i} \qquad (7)$$

In order to visualize Eq. (6), the influences of the Froude numbers are illustrated in Figure 2 for a combination of viscosity ($\eta^* = 100$) and scale ratio ($\lambda = 1.8$), chosen in the center of the examined range.

The calculated values for the radial circulation time [Eq. (6)] are slightly higher than the ones obtained by the optimization procedure. On the application to a bioprocess scale-up this gives a safer scale-up, because the "homogeneity time" will be overestimated. Including an aeration rate factor in Eq. (6) could improve the agreement between $t_{c,\mathrm{RAD}}$ and $t_{c,\mathrm{RAD,calc}}$.

### *Axial Circulation Time* ($t_{c,AX}$)

The axial circulation time is a measure for the mass exchange between the three turbine regions. The results of the optimization procedure (Table II)[20] show that this time is dependent on all experimental conditions. Therefore, only an approach involving all experimental variables [Eq. (8)] shows the ability to describe this model parameter correctly.

$$t_{c,Ax} = f(Fr_S, Fr_A, \eta^*, \lambda) \qquad (8)$$

In all investigated combinations of viscosity and scale ratio included in this work the influence of the aeration rate proved to be stronger than the one caused by the stirring speed. Therefore, the mathematical equation describing the correlation between these model parameters with the experimental conditions includes terms up to the second order for the aeration rate, as a linear dependence on the stirring rate is assumed.

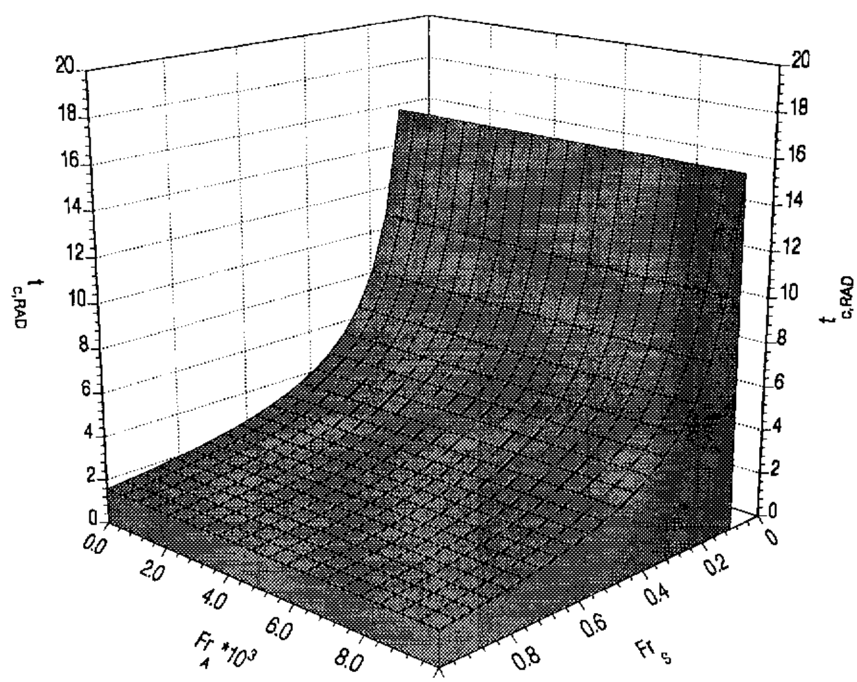


**Figure 2.** Dependence of radial circulation time ($t_{c,\mathrm{RAD}}$) on aeration and stirred Froude numbers. Simulated conditions: $\eta^* = 100$, $\lambda = 1.8$, $V_{\mathrm{tot}} = 9\ m^3$, three Rushton turbines, $d_i = 0.71$ m.

The following surface equation [Eq. (9)] is fitted to the axial circulation times for all six different investigated combinations of scale and viscosity (Table II).

$$t_{c,AX,\mathrm{calc}} = a_{00} + a_{01} \cdot Fr_A \cdot 10^3 + a_{02} \cdot (Fr_A \cdot 10^3)^2 + a_{10} \cdot Fr_S + a_{11} \cdot Fr_S \cdot Fr_A \cdot 10^3 + a_{12} \cdot Fr_S \cdot (Fr_A \cdot 10^3)^2 \quad (9)$$

Eq. 9 describes the dependence of the model parameter, $t_{c,AX}$, on both Froude numbers. The other experimental variables, i.e., dimensionless viscosity ($\eta^*$) and scale ratio ($\lambda$), are included linearly in the coefficients ($a_{00}$ to $a_{12}$). The equations for the regression coefficients are given in Eqs. (10)–(15).

$$a_{00} = 29.07 - 21.25 \cdot \lambda - 0.1066 \cdot \eta^* + 0.1759 \cdot \eta^* \cdot \lambda \quad (10)$$

$$a_{01} = -4.089 + 3.354 \cdot \lambda + 1.333 \cdot 10^{-3} \cdot \eta^* - 0.0155 \cdot \eta^* \cdot \lambda \quad (11)$$

$$a_{02} = -0.0098 - 0.0023 \cdot \lambda + 1.911 \cdot 10^{-3} \cdot \eta^* - 0.824 \cdot 10^{-3} \cdot \eta^* \cdot \lambda \quad (12)$$

$$a_{10} = -26.88 + 27.09 \cdot \lambda + 0.1487 \cdot \eta^* - 0.2272 \cdot \eta^* \cdot \lambda \quad (13)$$

$$a_{11} = 5.678 - 5.375 \cdot \lambda - 0.0207 \cdot \eta^* + 0.2988 \cdot \eta^* \cdot \lambda \quad (14)$$

$$a_{12} = -0.190 + 0.181 \cdot \lambda - 0.242 \cdot 10^{-3} \cdot \eta^* - 0.149 \cdot 10^{-3} \cdot \eta^* \cdot \lambda \quad (15)$$

Eqs. (10)–(15), for these coefficients, are obtained by use of the mentioned surface regression method [Eq. (5)]. As a first working hypothesis, linear dependencies on both parameters ($\eta^*, \lambda$) are selected. As an example, one of these surface equations (coefficient $a_{00}$) is illustrated in a 3D plot (Fig. 3).

Due to the utilized formal mathematical method, an extrapolation beyond the measured field of viscosity and scale ratio is not recommended. The valid boundaries of this field should not be exceeded and are indicated by crosshatching in Figure 4.

In Figure 5, an example of the dependence of the model parameter, "axial circulation time," on the Froude numbers is given. The relevant experimental variables are given in the caption. The same scale ratio ($\lambda = 1.8$) and viscosity ($\eta^* = 100$) were chosen again.

Very few data are available in the literature concerning the axial exchange flow rate between the stirrer sections in multiturbine stirred tanks. In spite of this lack of knowledge, flow models for these types of fermentors have been set up and used for simulations of the behavior of the bioprocess. Bader[2,3] utilized an equation [Eq. (16)] by Mandfredini[17] in his study of aerated large-scale multiturbine bioreactors (151.7 $m^3$).

$$F_{AX} = Q \cdot F_{\mathrm{PUMP}} = Q \cdot Fl \cdot n \cdot d_i^3 \quad (16)$$

Under aerated conditions, the flow rate between the stages is estimated as one fourth ($Q = 0.25$)[17] of the radial pumping capacity of the turbine ($Fl = 0.75$).[26] Under operating conditions, the resulting flow rate for the bioreactor is 0.677 $m^3/s$, thus leading to an axial circulation time of

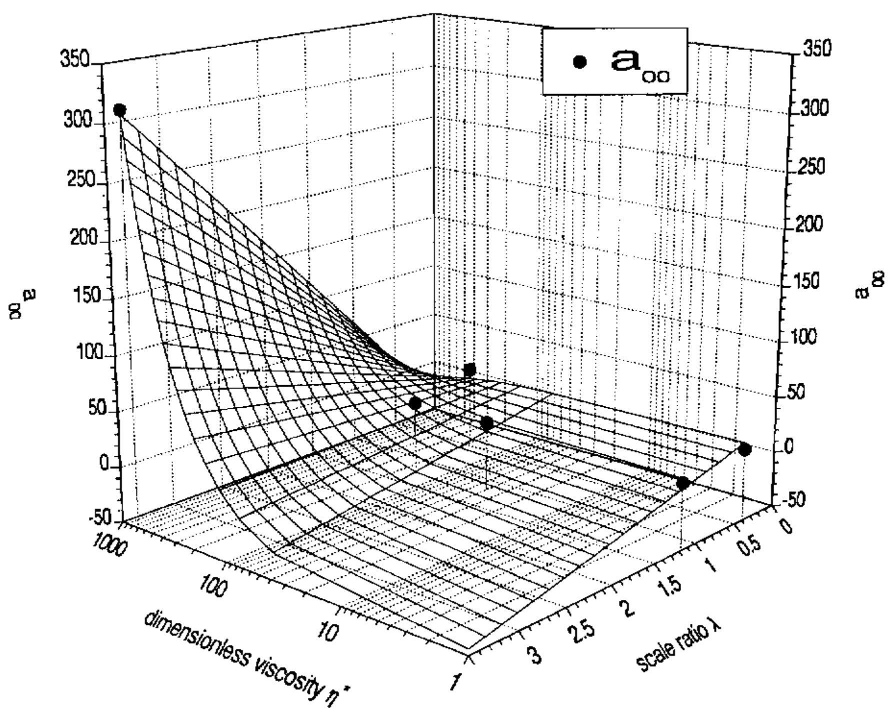


**Figure 3.** Surface regression coefficient $a_{00}$ used in Eq. (9) as a function of scale ratio and dimensionless viscosity. Each point represents one tested combination of scale and viscosity (see Table II).

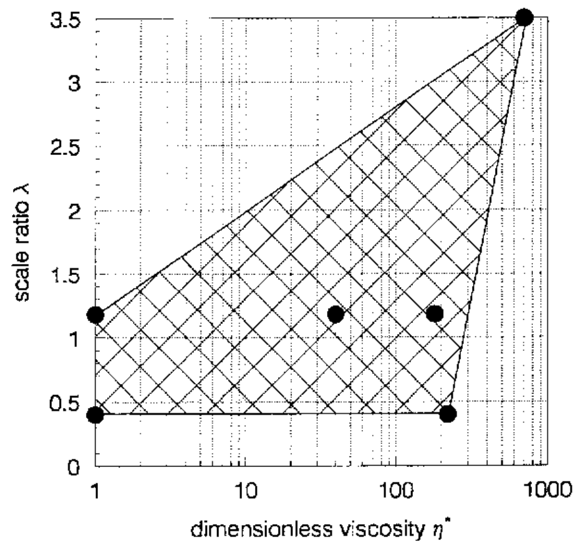


**Figure 4.** Valid boundaries for the introduced concept, valid range is marked by crosshatching.

224 s. Manfredini states that this calculation is only an approximation. This is certainly true because no influence of the most important parameter, the aeration rate, is included in this formula, but also the viscosity is not taken into account. Eq. (16) gives values lower than those of Eq. (9).

A more detailed approach to quantify the interactions between mixing and kinetic phenomena by Heinzle et al.[9] makes use of a structured three-compartment mixing model. The model calculation was carried out for three different scales, but again, the axial circulation time was just roughly estimated and the viscosity is not examined. In Table IV, the times for several bioreactors given by Heinzle et al.[9] are compared with the values calculated in Eq. (9).

Generally, the values are of the same magnitude; numbers given by Heinzle et al.[9] are seen as a special case of Eq. (9) for a defined combination of all operational parameters.

In case of the model parameter, "axial circulation time," it is concluded that there exists always a fairly good correlation between calculated and optimized values, although the range of the axial circulation time differs within two orders of magnitude.

### *Ideally Mixed Stirrer Compartment* ($V_M/V_{tot}$)

The same procedure as for the determination of the axial circulation time is applied again, except that the parameter $(V_M/V_{tot})_{calc}$ is chosen to depend with the second power on $Fr_S$ and linearly on $Fr_A$ in contradiction to $t_{c,AX,calc}$. The reason for this switch of dependencies is that the size of the ideally mixed stirrer compartment is more strongly influenced by the stirring intensity than by the aeration rate.[10,20] About 70% of the stirring energy is dissipated in the immediate vicinity of the turbine[4,5,15,27,36] as, in case of the energy input caused by the aeration, the dissipation is assumed to be rather uniform throughout the fermentor.

The surface equation describing these dependencies of the model parameter, "ideally mixed stirrer compartment," on the Froude numbers is given in Eq. (17):

$$(V_M/V_{tot})_{calc} = b_{00} + b_{01} \cdot Fr_A \cdot 10^3 + b_{10} \cdot Fr_S + b_{11} \cdot Fr_S \cdot Fr_A \cdot 10^3 + b_{20} \cdot (Fr_S)^2 + b_{21} \cdot (Fr_S)^2 \cdot Fr_A \cdot 10^3 \quad (17)$$

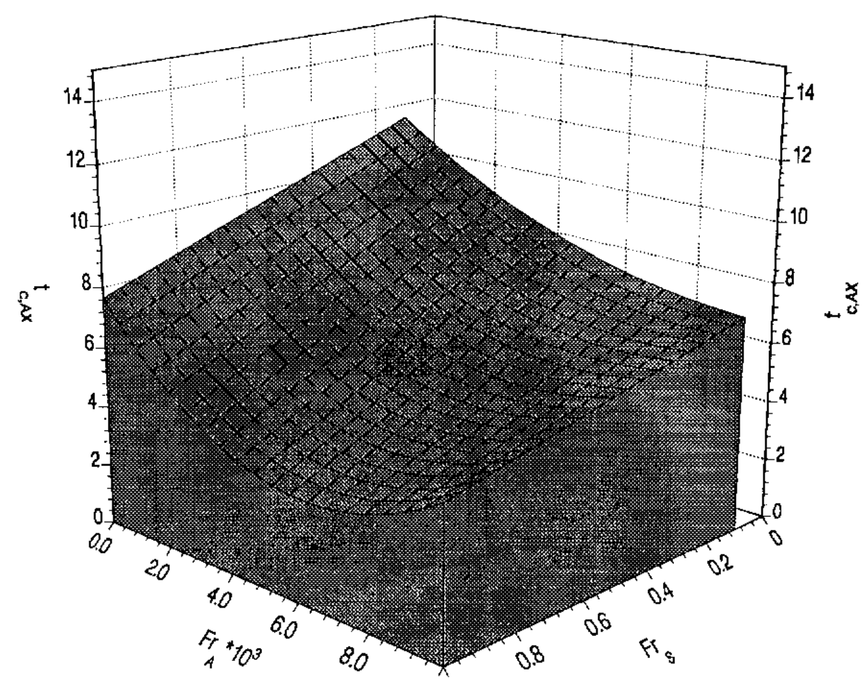


**Figure 5.** Scale-up example for axial circulation time ($t_{c,AX}$); conditions are identical to those given in Figure 2.

**Table IV.** Comparison of $t_{c,AX}$ calculated according to Eq. (8) with data cited in the literature.[9]

| $V_{tot}$ ($m^3$) | $t_{c,AX}$, Heinzle (s) | $t_{c,AX}$, Eq. (9) (s) |
|---|---|---|
| 0.025 | 2.8 | Out of valid range |
| 0.267 | 5.6 | 0.7–12 |
| 2.5 | 11.0 | 1.1–16 |

As already mentioned, the validity boundaries should not be exceeded and are indicated by crosshatching in Figure 4.

The regression coefficients ($b_{00}$ to $b_{21}$) again include the influence of scale ratio and viscosity. The equations for these coefficients are given in Eqs. (18)–(23).

$$b_{00} = 0.166 - 0.261 \cdot \lambda + 1.428 \cdot 10^{-3} \cdot \eta^* - 0.114 \cdot 10^{-3} \cdot \eta^* \cdot \lambda \quad (18)$$

$$b_{01} = -0.013 + 0.037 \cdot \lambda - 0.082 \cdot 10^{-3} \cdot \eta^* - 0.022 \cdot 10^{-3} \cdot \eta^* \cdot \lambda \quad (19)$$

$$b_{10} = -0.414 + 1.170 \cdot \lambda - 2.594 \cdot 10^{-3} \cdot \eta^* - 0.700 \cdot 10^{-3} \cdot \eta^* \cdot \lambda \quad (20)$$

$$b_{11} = 0.098 - 0.203 \cdot \lambda + 0.262 \cdot 10^{-3} \cdot \eta^* + 0.165 \cdot 10^{-3} \cdot \eta^* \cdot \lambda \quad (21)$$

$$b_{20} = 0.863 - 1.103 \cdot \lambda + 1.311 \cdot 10^{-3} \cdot \eta^* + 0.813 \cdot 10^{-3} \cdot \eta^* \cdot \lambda \quad (22)$$

$$b_{21} = -0.176 + 0.216 \cdot \lambda + 0.082 \cdot 10^{-3} \cdot \eta^* - 0.251 \cdot 10^{-3} \cdot \eta^* \cdot \lambda \quad (23)$$

In a previous work, the influence of aeration and stirring rate on $V_M/V_{tot}$ was already pointed out,[10,20] but it turned out that the scale ratio was the most important experimental variable. Besides, the viscosity showed a significant impact. As an example, the dependencies on the Froude numbers are illustrated in Figure 6. Again, the scale ratio ($\lambda = 1.8$) and the viscosity ($\eta^* = 100$) were chosen in the center of the examined validity range (Fig. 4).

The correctness of the value for $(V_M/V_{tot})_{calc}$ compared with the optimized value is demonstrated in Table III. The same way to calculate the error is used again as in the case of $t_{c,RAD}$ [Eq. (7)].

The effect of the scale ratio is extremely important in the case of the ideally mixed stirrer compartment, $V_M/V_{tot}$. The agreement between $V_M/V_{tot}$ and $(V_M/V_{tot})_{calc}$ is satisfying in most cases, but the formal correlation method might lead to incorrect physical parameters. As an example, it is impossible that $V_M/V_{tot}$ has a negative value (Fig. 6). In the case of bioprocesses this is not relevant, because this effect occurs only in an operating range with hardly any aeration ($Fr_A < 0.002$) and low stirring intensity ($Fr_S < 0.15$).

### Number of Tanks-in-Series in the Recirculation Loop (N)

No significant dependencies of this model parameter on any one of the experimental variables could be observed. The mean value of $N$ for all optimized experiments in the examined configurations equals 4.23. Because of the model structure this parameter has to be an integer, therefore, this adjustable parameter is kept constant [Eq. (24)]. The

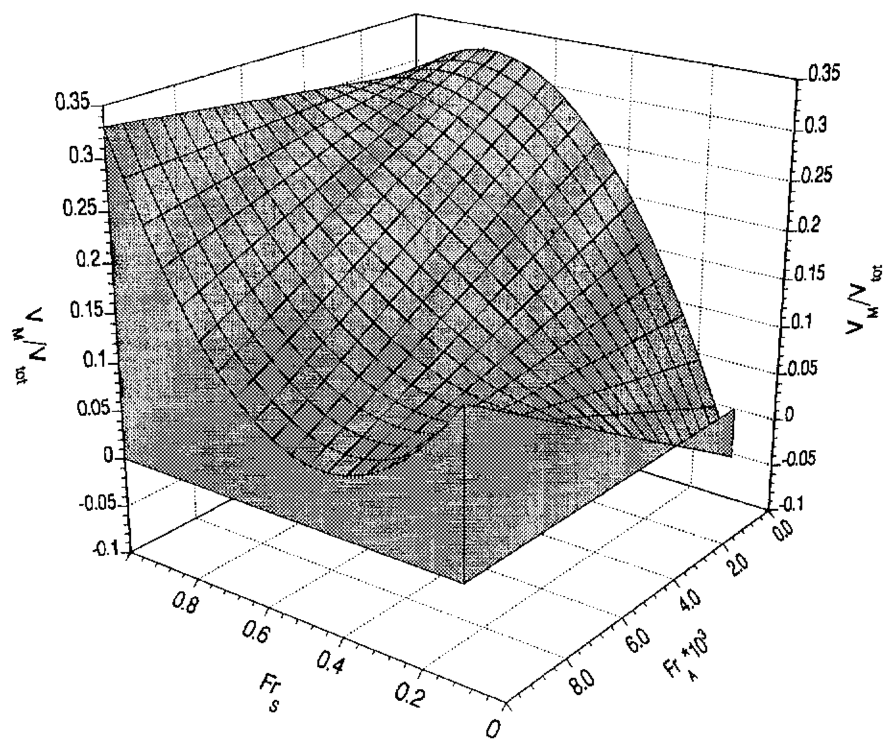


**Figure 6.** Scale-up example for ratio of ideally mixed turbine to total volume ($V_M/V_{tot}$); conditions similar as for Figure 2.

precondition is that the stirrers are operating in the turbulent regime.

$$N_{\text{calc}} = 4 \tag{24}$$

This value is actually the same number Van de Vusse[37] specified on the basis of a theoretical approach. The agreement of $N_{\text{calc}}$ with the originally optimized model parameter is listed in Table III.

## CONCLUSIONS

The proposed method of hydrodynamic scale-up is capable of describing the adjustable mixing model parameters in a wide range of bioreactor operations. This study was done in stirred tank bioreactors equipped with three Rushton turbines. The model is designed and therefore strictly valid only for this type of fermentor. The utilized mathematical correlation method was chosen as a first working hypothesis. Some problems occurring with the given formulae, which represent a formal macroapproach, were discussed previously. Mechanistic methods were not tested in this work. However, such a comparison could be executed including CFD or other pragmatic methods.[8] Therefore, all optimized model parameters and homogeneity times are given in Table II in order to provide the basis for further studies.

As a general statement it can be argued that a similar scale-up approach on the basis of structured physical mixing models can be done for all common bioreactors.[13,23,24] This gives the ability to compare the performance of a particular fermentation in different kinds of bioreactors after the screening steps in laboratory scale. The precondition is that the interactions between physical and biological parameters are known.

The scale-up method based on mixing, presented in this work, is to be regarded as an empirical approach, however, following strictly consistent scientific methods. No theoretical assumptions are needed (e.g., turbulence theory). Thus, as a consequence, extrapolation and prediction for other types of bioreactors or fluids are not recommended. On the other hand, it will be possible to improve existing mixing theories on the basis of the experimentally verified data on in situ fermentations.

This work was kindly supported by the Austrian "Ministerium für Wissenschaft und Forschung" within Project B 12, "Bioreaktorean und Bioprozesse."

## NOMENCLATURE

| | |
|---|---|
| $a_{XY}$ | surface regression coefficients used for $t_{c,AX,\text{calc}}$ (–) |
| $b_{XY}$ | surface regression coefficients used for $(V_M/V_{\text{tot}})_{\text{calc}}$(–) |
| $d_i$ | stirrer diameter (m) |
| $D_T$ | inner tank diameter (m) |
| $F_A$ | aeration flow rate ($m^3/s$) |
| $F_{AX}$ | axial flow ($m^3/s$) |
| $F_{\text{PUMP}}$ | pumping capacity ($m^3/s$) |
| $F_{\text{RAD}}$ | radial flow ($m^3/s$) |
| $Fl$ | radial flow number (–) |
| $g$ | acceleration of gravity ($m/s^2$) |
| $h_l$ | height of fluid in the tank (m) |
| $h_T$ | height of stirrer compartment (m) |
| $n$ | stirrer revolutions ($s^{-1}$) |
| $N$ | backmixing parameter, number of ideally mixed cascades in recirculation loop (–) |
| $N_{\text{turb}}$ | number of turbines (–) |
| $p$ | number of experiments (–) |
| $Q$ | axial flow number (–) |
| $t_{c,\text{RAD}}$ | radial circulation time (s) |
| $t_{c,AX}$ | axial circulation time (s) |
| $t_{90}$ | response time of the sensor (10% to 90%) (s) |
| $V_M$ | volume of ideally mixed stirrer compartment ($m^3$) |
| $V_{\text{tot}}$ | total liquid volume ($m^3$) |
| $w_0$ | superficial gas velocity (m/s) |

*Greek letters*

| | |
|---|---|
| $\lambda$ | scale ratio of tank diameters (–) |
| $\eta$ | viscosity Pa · s |
| $\eta^*$ | dimensionless viscosity (–) |

*Dimensionless numbers*

$Fr_S = n \cdot \sqrt{d_i/g}$ stirrer Froude number

$Fr_A = w_0/\sqrt{g \cdot h_l} = (F_A/V_{\text{tot}}) \cdot \sqrt{h_L/g}$ aeration Froude number

*Index*

| | |
|---|---|
| calc | calculated |

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