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Effect of oxygen transfer on yeast growth — Growth kinetic and reactor model to estimate scale-up effects in bioreactors



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ABSTRACT

Large scale fermentations face challenges in mixing and mass transfer as well as in the design and construction of the equipment. Scale-up from laboratory and pilot scale experiments is difficult because different phenomena – such as mixing times and mass transfer conditions – scale in a different way.

We study the effect of mass transfer, reactor type and scale on the growth of *Pichia pastoris* yeast. Batch cultivation experiments monitoring the cell growth and ethanol formation are conducted in laboratory scale in two reactor types — stirred tank and an Outotec OKTOP[®] 9000 draft tube reactor. Model for the yeast growth – including respirative and fermentative metabolism and the effect of dissolved oxygen – is formed based on literature. For scale-up studies, the growth model is used along with one dimensional reactor model that accounts for liquid mixing, gas phase dynamics and local gas hold-up and mass transfer coefficient.

By using a realistic growth model along with the reactor model, the simulated effects of scale-up are presented in terms of cell yield. A decrease in yield is noticed due to oxygen depletion in gas and insufficient liquid mixing. Potential improvements are related to the gas handling capacity and liquid mixing of the reactor.

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1. Introduction

The majority of industrial microbial processes are aerobic, meaning that the cells consume oxygen for cellular respiration. Due to the low solubility of oxygen in aqueous solutions, oxygen needs to be continuously dissolved from gas to the liquid phase by introducing air or another gas containing oxygen into the reactor. Ideally, the oxygen transfer rate of the reactor is sufficient to maintain the dissolved oxygen concentration above a critical value, thus matching the oxygen uptake rate of the cells. There are complex interactions between the hydrodynamics of the reactor, mass transfer parameters, and microbial growth (Garcia-Ochoa et al., 2010; Garcia-Ochoa and Gomez, 2009).

Simple scale-up rules and related correlations are frequently discussed in the literature. One popular approach is correlations based on the mixing power per liquid volume to maintain similar values

for overall volumetric mass transfer coefficient, $k_L a$. As pointed out by Nauha et al. (2015); the exponents in the common correlations are scale-dependent which limits their applicability in scaling up industrial processes. They also pointed out issues related to hydrodynamic regimes and oxygen mass balance in industrial scale aerobic fermentations.

Gas sparged below the impeller of a stirred tank reactor forms cavities behind the low pressure areas of the impeller blades. Depending on the impeller geometry and rotation rate as well as the gas flow rate, gas is dispersed by the impeller with varying efficiency. Flow regimes at the impeller can be roughly categorized, with increasing dispersion efficiency, to flooding, loading and complete recirculation (Paul et al., 2004). However, even with sufficient gas dispersion by the impeller, high gas flow rates may cause a transition from homogeneous to heterogeneous flow regime, which is characterized by formation of large bubbles and bimodal bubble distribution. The flow in heterogeneous regime is more controlled by the gas flow rate. The transition depends mainly on the superficial gas velocity and occurs approximately at $v_s = 0.03$ m/s (Gezork et al., 2000).

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Nomenclature

a	Volumetric mass transfer area ($\text{m}^2 \text{m}^{-3}$)
c_i	Concentration of component i ($\text{g}_i \text{l}^{-1}$)
D	Dilution rate (h^{-1})
D_L	Diffusion coefficient ($\text{m}^2 \text{s}^{-1}$)
d_b	Bubble size (m)
EF_g	Exchange flow in gassed conditions ($\text{m}^3 \text{s}^{-1}$)
F	Flow rate (l h^{-1} or $\text{m}^3 \text{s}^{-1}$)
H	Height of liquid in reactor (m)
IF	Induced flow ($\text{m}^3 \text{s}^{-1}$)
k_H	Henry's constant for oxygen
k_L	Liquid side mass transfer coefficient (m s^{-1} or m h^{-1})
K_e	Saturation coefficient for ethanol uptake ($\text{g}_e \text{l}^{-1}$)
K_g	Saturation coefficient for glucose uptake ($\text{g}_g \text{l}^{-1}$)
K_i	Inhibition constant for glucose inhibition of ethanol uptake ($\text{g}_g \text{l}^{-1}$)
K_o	Saturation coefficient for oxygen uptake ($\text{g}_o \text{l}^{-1}$)
N_p	Impeller power number (-)
P	Pressure (Pa) or power (W)
p	Partial pressure (Pa)
q_i	Specific rate of component i ($\text{g}_i \text{g}_x^{-1} \text{h}^{-1}$)
V	Volume (l or m^3)
v_s	Superficial gas velocity (m s^{-1})
y	Mole fraction (-)
Y_{ij}	Yield coefficient for components i and j ($\text{g}_i \text{g}_j^{-1}$)
z	Axial coordinate of reactor ($z=0$ at the bottom) (m)

Greek letters

η	Viscosity (Pa s)
μ	Growth rate (h^{-1})
ρ	Density (kg m^{-3})
τ	Gas phase residence time (s or h)
ϕ	Gas volume fraction (-)

Subscripts and superscripts

e	Ethanol
ferm	Fermentative pathway
g	Glucose
gas	Gas phase
o	Oxygen
ox	Oxidative pathway
sat	Saturation concentration
x	Cells

The superficial gas velocity is also present in many correlations, and it is often used to estimate the gas flow rate in different scales. If the gas flow is scaled by constant v_s , volumetric gas flow related to liquid volume, expressed as volume gas per volume liquid per minute (VVM), decreases as it scales by $V^{-1/3}$. When considering the stoichiometry in the process, maintaining constant VVM would be advantageous. However, the maximum value for v_s to maintain a homogeneous flow regime that is controlled by the agitator is considered to be about 0.03 m s^{-1} . Therefore, due to a decreased VVM-value in large reactors, gas phase residence time increases with scale, and gas phase depletion is more significant. This decreases the driving force for mass transfer, which may lead to mass transfer limited conditions.

The effect of hydrostatic pressure on the flow regime is also notable in large vessels with high aspect ratios. At higher pressure, the conditions controlling homogeneous/heterogeneous transition conditions are different, due to increased gas density. Therefore, it may be that flow in the bottom part is homogeneous and transition to heterogeneous

flow regime occurs in the higher parts of the reactor. The effect may be similar for the flooding/loading transition of the impellers (Nauha et al., 2015). The flooding regime of the impellers, however, needs to be distinguished from the homogeneous/heterogeneous flow regime, and it is affected by gas flow rate and the diameter, revolution rate and geometry of the impeller.

The applicability of stirred draft tube reactors (SDTR) on microbial fermentations has been shown in previous studies (Moo-Young et al., 1993; Pollard et al., 1997). In addition, different SDTR designs have been compared to airlift (ALR, Chisti and Jauregui-Haza, 2002) and stirred tank reactors (STR, Lueske et al., 2015) in mixing and mass transfer studies. The SDTR was found to have higher efficiency for mass transfer compared to STR but not to ALR. Recently, a scaled down model of industrial scale bottom-agitated draft tube reactor (Outotec OKTOP® 9000) was shown to perform well in mixing and mass transfer experiments and was also suitable for cell cultivations (Tervasmäki et al., 2016). This reactor type has been used in the hydrometallurgical industry for direct leaching of zinc concentrate in scales up to 1000 m^3 , which is a rather large scale for multiphase stirred tank reactor.

In this study, we further investigate the performance of different reactor types in lab-scale yeast cultivations using *Pichia pastoris* yeast. It does not exhibit glucose repression of respiration and, therefore, is suitable for batch cultivation. Furthermore, its fermentative metabolism that produces mainly ethanol is activated at oxygen limitation (Baumann et al., 2008; Carnicer et al., 2009). Therefore, the presence of ethanol can be used as an indication of oxygen limitation even if dissolved oxygen cannot be measured or if there are significant gradients, which may be the case especially in larger reactors. A kinetic model for the growth of *P. pastoris* on glucose, including the fermentative route in oxygen limited conditions and ethanol utilization, is formed based on chemostat cultivations presented in the literature. The model is qualitatively compared with batch cultivations in a laboratory-scale reactor. It is also applied in simulations along with a simple one-dimensional reactor scale model to assess the importance of scale-up effects – such as gas phase oxygen depletion, hydrostatic pressure, and liquid mixing – on oxygen transfer and cell yield during scale-up. The model is designed to be computationally light so that it can be applied also in the simulation of CFD-models developed for different reactors including the STDR, for example.

2. Materials and methods

Laboratory scale batch cultivations were carried out using *P. pastoris* X33 yeast in batch cultivations with two reactor types: OKTOP9000® and stirred tank reactor agitated with three Rushton turbines. The main geometrical parameters are presented in Fig. 1, and more information of the reactors including gas dispersion and mass transfer performance can be found from Tervasmäki et al. (2016). For the cultivation experiments, inoculum was cultivated overnight in a liquid YPD-medium in baffled shake flasks ($2 \times 500 \text{ ml}$), and the bioreactor cultivations (Biostat C-DCU, Sartorius, Germany) were carried out in a basal salt medium supplied with 4.35 ml/l PTM₁ trace salts at a temperature of 30°C (Table 1). The liquid volumes were 10 l (STR) and 12.5 l (OKTOP®), and the reactor diameter was 190 mm . Gas flow was set to 18 l/min ($v_s = 0.011 \text{ m/s}$ or $1.5\text{--}1.8 \text{ VVM}$), and the agitation rate was 450 rpm and 720 rpm for STR and OKTOP®, respectively. This corresponds to volumetric power consumption of about 500 W/m^3 . Aqueous ammonium hydroxide (25%) was used to adjust the pH between $5\text{--}5.5$; an antifoam agent (Antifoam 204, Sigma-Aldrich) was used to control the foam. Dissolved oxygen was measured from the lower (approx. 10 cm from bottom, Oxyferm FDA 120, Hamilton, Switzerland) and upper part of the reactor (approx. 10 cm from surface, Visifer, Hamilton, Switzerland). Concentrations of oxygen, carbon dioxide and hydrocarbons were measured by Innova 1313 gas analyser (LumaSense, Denmark).

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