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Local gas holdup simulation and validation of industrial-scale aerated bioreactors

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HIGHLIGHTS

- An advanced numerical simulation method for large aerated bioreactors is proposed.
- Modern graphic processing units are used to increase the simulation speed.
- The simulation is fast enough to be used in the bioreactor engineering process.
- Validation is done with the measurements of a conductivity holdup sensor.
- The results of a 40 m^3 industrial-size reactor simulation are shown.

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ABSTRACT

To date, the efficiency of industrial-size bioreactors has mainly been improved based on empirical knowledge. Computer simulation may help to understand the processes that occur inside the reactor and to develop new reactor designs. Euler-Lagrange simulations of the two-phase flow in large bioreactors, which could not be performed within a timeframe suitable for engineering purposes due to the limited computation resources, were made possible by the calculation power of graphic cards. The lattice Boltzmann method is well suited for parallelization which makes it ideal for calculating the fluid field inside a reactor driven by multiple Rushton turbines on graphic processing units. The bubble movements were captured via a Lagrangian approach by solving the Newton's equations of motion. A two-way coupling between the disperse and continuous phases was applied. Break up and coalescence of the bubbles were modeled via stochastic algorithms using the approach rate of small turbulent eddies and the comparison of the contact time and film breakage time, respectively. To gather experimental data, a conductivity sensor was used to measure the local gas holdup. The rate and the duration of current drops were recorded to estimate the bubble size and the void fraction around the sensor's tip position. The sensor was used in a 150l custom-built acrylic reactor. Several flow regimes with varying gas flow rates and stirrer speeds were investigated. The experimental results were in good agreement with the simulation data, especially at low stirring and low aeration rates. To prove the applicability of the code to large-scale problems, a 40 m^3 reactor was simulated.

1. Introduction

Bioreactor, also known as fermentors, are widely used in various industrial sectors, including the (bio-)pharmaceutical industry for the production of modern drugs, such as anti-infectives, monoclonal antibodies and other protein drugs, e. g. EPO or insulin (Chu and Robinson, 2001; Jordan, 1995; Nikolai and Hu, 1992; Warnock and Al-Rubeai, 2006). Both small and large-molecule drug substances are produced in bioreactor fermentations. Reactor scales range between a few hundred milliliters on the laboratory scale to several hundred of cubic-meters at full production scale of microbial cultures. Full-scale production in cell cultures is usually carried out in smaller systems up to a few cubic-meters. Different types of bioreactors are in use today, ranging from wave reactors, shaker bottles, packed beds, airlift reactors, membrane bioreactors to stirred tanks, the latter of which are historically and still the most important systems. The mode of operation is typically fed-batch,

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Nomenclature

A_b	bubble surface, m^2
A_{fr}	frontal area of the bubble, m^2
C	stirrer height from bottom, m
c_D	drag force coefficient
c_L	lift force coefficient
C_l	turbulence correction constant
C_{SM}	Smagorinsky constant
d_b	bubble diameter, m
D	stirrer diameter, m
D_A	mass diffusivity, m^2/s
Eo	Eötvös number
$\vec{e}_a$	spatial direction
ε	turbulent energy dissipation, m^2/s^3
f_a^{eq}	equilibrium function
f_a	statistical distribution function
$f_{a'}$	statistical distribution function after the bounce-back
F	force, N
$\vec{g}$	gravitational acceleration, m/s^2
H	reactor height, m
μ	viscosity, Pa s
m_f	mass of the fluid of the same volume as the bubble, kg
m_g	bubble mass, kg
n	influence radius (mapping function, $1.5\,d_b$), m
Q	momentum flux
ρ_b	air density, kg/m^3
ρ	fluid density, kg/m^3
r^*	dimensionless radius
Re	Reynolds number
s	gas sparger height, m
Sc	Schmidt number
Sh	Sherwood number
σ	surface tension, N/m
t^*	dimensionless time
T	reactor diameter, m
τ	relaxation factor
t	time, s
$\vec{u}$	fluid velocity, m/s
$\vec{u}_b$	solid part velocity, m/s
$\vec{v}$	bubble velocity, m/s
w_a	specific weighting factor
$\vec{x}$	fluid node position (mapping function), m
$\vec{x}_p$	bubble position (mapping function), m

although batch and continuous operation are in use as well. Although bioreactors have been used industrially for many decades rational performance optimization remains a challenge (Rani and Rao, 1999; Roubos et al., 1999). The most critical factors in the operation of bioreactors are the (1) gas flow rate applying pressurized air that provides microorganisms or cells with oxygen, the (2) stirrer speed that largely determines the main fluid flow, gas bubble break-up and distribution, and thus, ideally the homogenous distribution of nutrients and products including the exchange with the gas phase, the (3) feed rate of nutrients and pH titration and the (4) heat transfer and thermal control of the reactor. Design factors are the reactor size and geometry, the type, position and number of stirrers (e.g. Rushton, axial pumping impellers, elephant ears, etc.), the shape and number of heat exchanges (internal vs. external), the level and number of feeding ports, the number and dimensions of baffles and the sparger type and design.

In a production setting, the gas flow rate and the stirring rate can be adjusted based on the actual demands. Often this is done based on empirical knowledge and experience applying correlation equations that are usually established for specific conditions and standard stirrers. However, for the rational design, scale-up, control and optimization of a fermentor more detailed knowledge is highly desired. Typical questions include:

- How does the impeller design impact the overall flow field, mixing time, gas dispersion and hold-up in the reactor?
- Are there inhomogenities and how can they be avoided?
- What shear rates can be expected as a function of impeller design, stirring and gassing rate?
- What is the k_La that can be obtained as a function of the design and operating parameters?
- Which flow regimes are possible and when will stirrer flooding occur?
- How does a non-Newtonian rheology impact the overall mixing pattern in the bioreactor?
- How should nutrients be fed in an optimal way, and what are the associated mixing times?
- How can a smooth scale-up be achieved, i.e., how can one design a system such that microorganisms and cells are exposed to a similar environment on the small, intermediate and production scale?

While it is difficult to answer these questions by experimentation or real-time measurements (at least on large scales), simulation tools that capture the essential phenomena can provide important insight into the processes, thus providing strategies to rationally optimize the system. However, fully-resolved multiphase simulations are rarely performed since such simulations still take months to describe only a few seconds of real operation time. This is due to the size of industrial bioreactors and the separation of scales, i.e., small scales in the order of single cells or bubbles coexist with meso- and macro-scales in the order of the stirrer or reactor diameter (Gillissen and Van den Akker, 2012; Hutmacher and Singh, 2008; Liew et al., 2008).

A recent study on the modeling of gas-liquid stirred tanks was reported by Petitti et al. (Petitti et al., 2013) who used the Eulerian multi-fluid model to simulate stirred tank reactors including coalescence, breakup and mass transfer of the gas phase. The bubble size distribution inside stirred tank reactors was predicted based on the multiple-size group model by Wang et al. (2014) and with the population-balance models by Morchain et al. (2014). The applicability of various turbulence models was evaluated by Bashiri et al. (2013). Aghbolaghy and Karimi (2014) analyzed the enzymatic production of hydrogen peroxide and combined the response surface methodology (RSM) and computational fluid dynamics (CFD) to monitor a production process online. However, well-resolved full-scale bioreactor simulations, combining stirring, bubble break-up/coalescence and mass transfer have not been addressed in the literature.

In the simulation of stirred tank bioreactors, the fluid flow field (governed by the Navier-Stokes equations) is resolved via CFD. Numerous algorithms have been developed to approximate the Navier-Stokes equations, such as the finite volume method (Patankar, 1980), the finite element method (Akira, 1986) and the finite difference method (Harlow and Welch, 1965; Richardson, 1911). Another efficient approach, which is ideally suited to be implemented on parallel-computation platforms, is the Lattice Boltzmann Method (LBM) (Chen and Doolen, 1998). The LBM is different from other CFD methods as it relies on the collective behavior of groups of "particles" forming the liquid (Yu et al., 2005). Similar to cellular automata, LBM consists of a streaming and a collision step. To enable simulating fluid flows, lattice gas