

# Breathing Life into Bioreactors

By Bernie Gigas, LIGHTNIN, Rochester, NY and Kumar Dhanasekharan, Fluent Inc.

Cell-culture bioreactors lie at the heart of the processes used to produce large-molecule, protein-based therapeutics. These reactors must produce an environment that is conducive to and optimizes the growth of fragile mammalian cells. Additionally, this environment must be predictable over a range of scale that can span four orders of magnitude between the laboratory and production.

Cell-culture reactors are typically aerobic bioreactors. In these reactors, oxygen is usually a limiting nutrient due to its low solubility in culture media. While blending uniformity is essential for oxygen distribution in the bioreactor, bubble size distribution is the most important factor for governing mass transfer. Bubble size dictates the available interfacial area for gas-liquid mass transfer, and is influenced by parameters such as shear rate, turbulence, and buoyancy. When bioreactors are scaled up from laboratory to production size, their design must meet both oxygen distribution and oxygen mass transfer requirements.

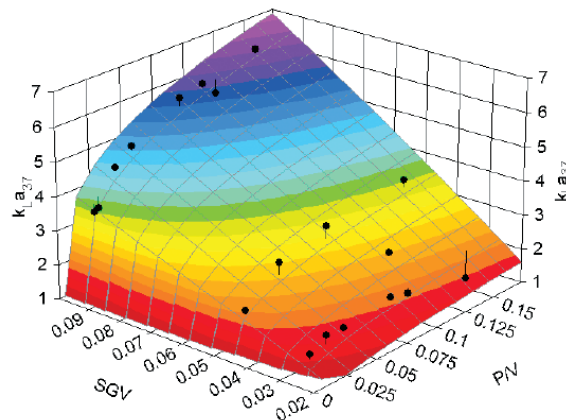
A joint project is currently underway at LIGHTNIN and Fluent to study bioreactors, with the goal of being able to identify the scale-up criteria that will satisfy these two requirements. As a first step, calculation of the mass transfer coefficient,  $k_L a$ , in a gas-liquid system has been validated. A dual-impeller, 96" diameter bioreactor was chosen for the study. It operates at low mixer power, and oxygen is injected through a sparger at a low flow rate into a water-like liquid. Experimental measurements have been compared to FLUENT calculations that make use of the Eulerian multiphase model.

A population balance approach was used to obtain the bubble size distribution for the gas phase. Birth and death terms for each size range were used to account for bubble breakup and coalescence.<sup>1</sup> The interphase drag between the gas and liquid phases was based on the Sauter mean diameter ( $d_{32}$ ), which was calculated from the bubble size distribution.

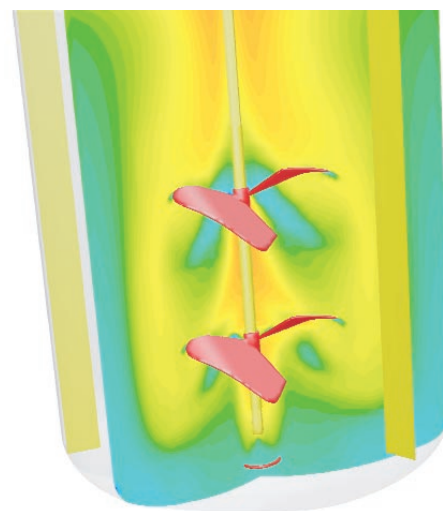
The experimental results for  $k_L a$  followed a commonly used correlation well, forming a reliable baseline for comparison with the CFD results. The correlation depends on the mixer power per unit volume and the superficial gas rise velocity. While the correlation offers a single  $k_L a$  for the entire bioreactor, the CFD results offer a spatially dependent function, derived from the flow variables. The eddy dissipation, Schmidt number, and dynamic viscosity are used to compute  $k_L$ , and the bubble size distribution is used to compute the interfacial surface area,  $a$ . The volumetric average of the resulting  $k_L a$  was found to be within an order of magnitude of the experimentally determined value for the same operating conditions.

## reference:

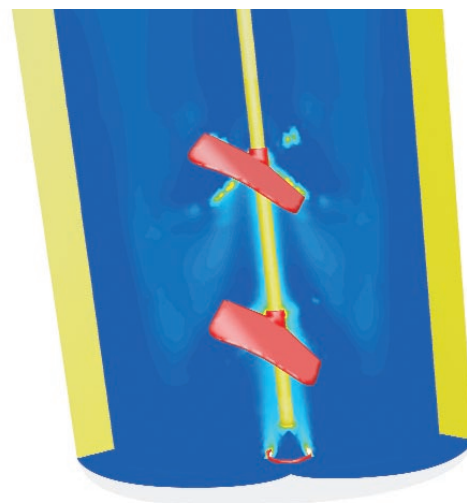
- 1 H. Luo, PhD Thesis, Department of Chemical Engineering, Trondheim, Norway, 1993.



Experimental results for  $k_L a$  (black dots) follow the contours of a popular correlation



Contours of bubble size distribution



Contours of  $k_L a$  computed from the FLUENT results