Application Note:

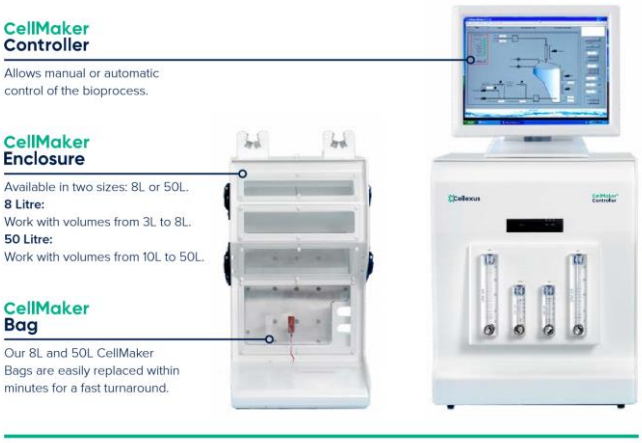
Modelling and optimisation of the CellMaker single-use bioreactor system for use with mammalian and insect cell culture.

Introduction

The CellMaker REGULAR and CellMaker PLUS are single-use bioreactor systems developed by Cellexus Limited. These robust, high quality single-use bioreactors use a disposable cell culture bag to simplify the cell culturing and fermentation processes for microbial applications. The CellMaker systems employ a unique, simple, yet effective airlift bubbling technology to improve cell culture aeration, which is scalable and inexpensive to use.

With the success of the CellMaker REGULAR and CellMaker PLUS for microbial applications, Cellexus are developing a new range of single use bioreactors using the Cellexus airlift technology to give tighter control of gas mixing in the single use cell culture bag for mammalian cell culture.

This application note describes how, with the help of Continuum Blue Ltd, a specialist multiphysics analysis company, Cellexus have utilised modelling and simulation tools to optimise their CellMaker single use bioreactor systems to ensure consistent gas bubble formation and flow to provide the ideal aeration conditions during cell culture



CellMaker single use bioreactor system

Experimental conditions

Together with Continuum Blue Ltd, Cellexus developed a full virtual model of the CellMaker system for assessment. From this, a number of selected parameters in the virtual bioreactor model were chosen for assessment and optimisation, with these being based on the ease of modification in the physical system as well as cost.

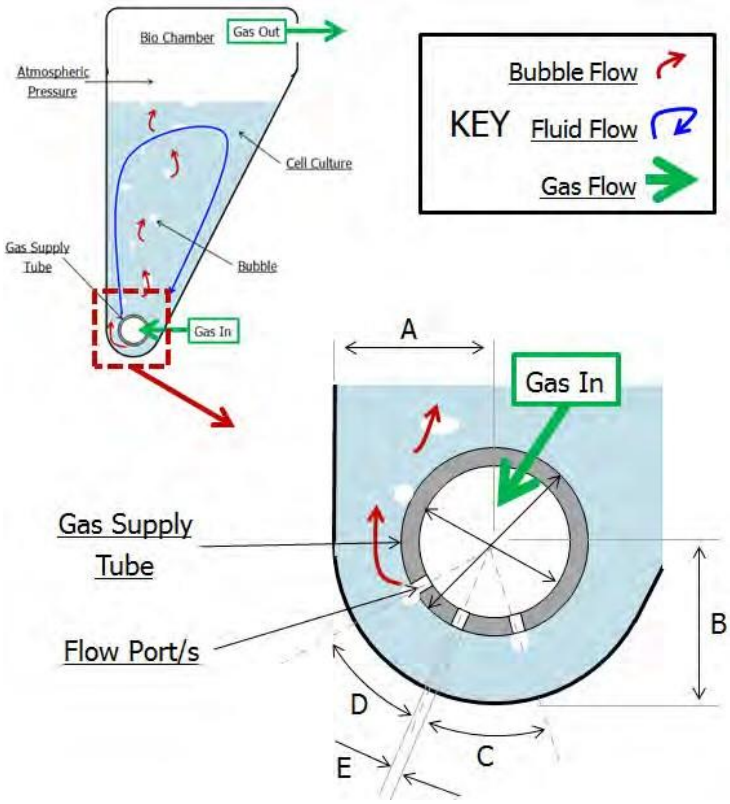
A schematic of the disposable section of the CellMaker system and a close up section of the pertinent parameters for assessment are illustrated overleaf.

The parameters chosen for scrutiny included:

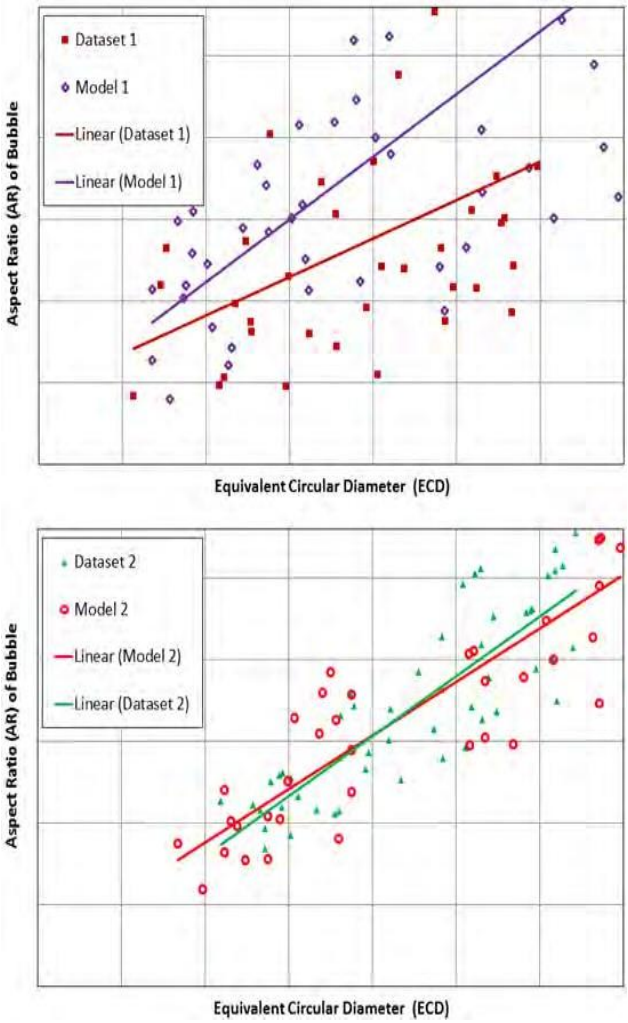
- Number of Flow Ports (n)
- Flow Rate
- Gas Mixture (% O2, CO2, & N2)
- Head (fluid height in bag chamber)
- Geometric properties (A, B, C, etc.)

Experimental conditions (continued)

Prior to assessing the influence of these various parameters and their outcomes, the virtual bioreactor model developed had to be validated against physical test data, to ensure that it was able to predict the outcomes with certainty. The virtual model was validated against physical test data of aspect ratios (AR) and equivalent circular diameters (ECD) of the bubbles formed in the bioreactor for various flow conditions and settings. The AR & ECD bubble data was obtained by taking and performing image analysis on high speed video footage of bubble formation and flow from the bioreactor for over 20 individual settings. Using the virtual model, equivalent simulations where run and AR & ECD model data collected and compared with the physical data. Figure 4 illustrates graphically the close correlations obtained from the models following validation versus the physical test data for two sets of bioreactor parameters.



Schematic of section through bioreactor bag and parameters for assessment



Comparison of bubble ECD & AR for COMSOL model versus physical test data obtained for two bioreactor settings

Application Note:

Measuring kLa values on the CellMaker PLUS
to show better performance and improved oxygen supply control.

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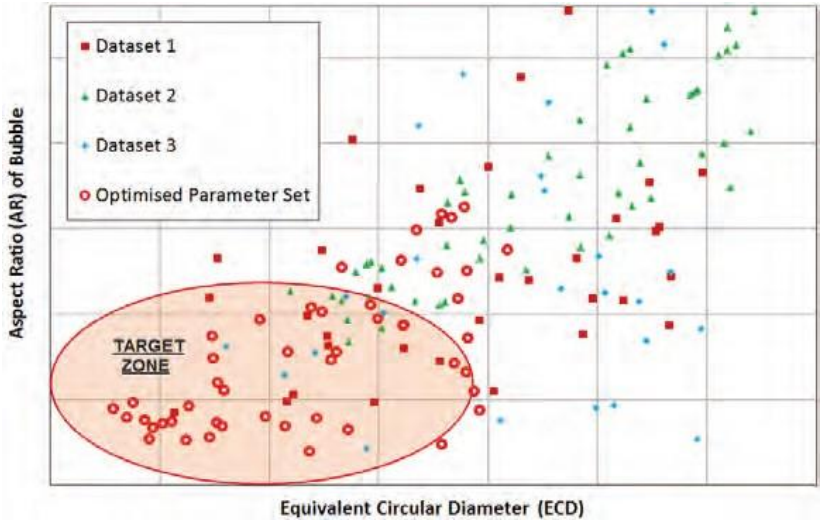
Results

Based on the work by Chisti [2000] on sparged bioreactors and the empirical equations on bubble formation frequency obtained from Goda *et al.* [2005], it was estimated that as the bubbles break the surface they should have a diameter of less than 7mm to reduce cell death in mammalian and insect cell lines. Using this target maximum bubble diameter, sweeps on the defined virtual model parameters were performed, the until model bubble ECD solutions were found to be below 7mm and the AR values obtained tended towards 1, which represents an ideal sphere. From this, several model solutions were found, and from these, a single solution was selected based on ease of production and cost. The AR and ECD values for the solution selected is illustrated below, and compares the optimized AR & ECD values to those of previously obtained physical test data.



Bubble ECD and AR values obtained from optimized solution versus three previous bioreactor settings results.

References

[1] Chisti, Animal-cell Damage in Sparged Bioreactors, Trends in Biotechnology, Vol 18, (2000)
[2] Goda et al, Empirical Equations for Bubble Formation Frequency from Downward-Facing Nozzle with and without Rotating Flow Effects, Materials Transactions, Vol. 46, No. 11 (2005)



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