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Single Use Bioreactors: Geometry Does Matter

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Introduction

Lonza is the leading global contract manufacturer of therapeutic proteins in mammalian cell culture with proprietary stainless steel bioreactor capacity up to 20,000 L. Lonza was also one of the earliest adopters of single use bioreactor (SUB) technology implementing rocked single use bioreactors in 2003 and single use stirred SUBs in 2008. In 2008 the SUB systems available on the market had limited geometric similarity to Lonza's proprietary stirred tank reactor (STR) geometry. Lonza's considerable experience of transferring processes between geometrically dissimilar airlift reactors (ALR) and STRs was applied to identifying culture conditions in the SUB that would match those in the STR. This strategy was successful, however, there are now more SUB venders in the market and a wider variety of vessel geometries available. Lonza is currently expanding its SUB capacity in a drive to provide an end to end single use offering. The opportunity was taken to evaluate a vessel with a geometry closer to Lonza's proprietary STR geometry. In this study the oxygen mass transfer has been characterised for two SUB geometries (SUB 1 and SUB 2) at multiple scales and the performance compared to Lonza's proprietary STR geometry. Moreover, cell culture performance has been characterised for both SUB geometries at multiple scales and in one case multiple fill volumes. Cell culture performance has been compared with performance in Lonza's laboratory scale STR and ALR geometries using principal component analysis (PCA).

Geometric Similarity

- During scale-up of bioreactors it is not possible to keep all properties identical.
- Geometric similarity keeps ratios between key bioreactor lengths constant.
  - It is still not possible to keep all vessel properties constant.
  - Examples of maintained lengths are presented in Figures 1 and 2.
- Models can be developed that generalise mass transfer across scales.
  - Different geometries usually require different models.
- Early stirred SUBs had unconventional geometries.
  - Diagonally imposed impellers.
  - Impeller position different.
  - Impeller design different.
  - No baffles.
  - Reduced sparge hole diameter.
  - Low power dissipation.
  - Designed to be operable at much lower fill volumes.

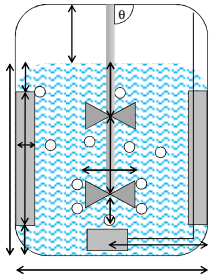


Figure 1: STR Geometry

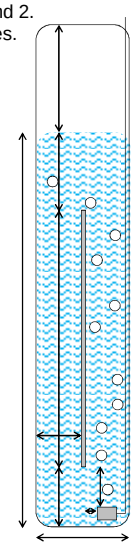
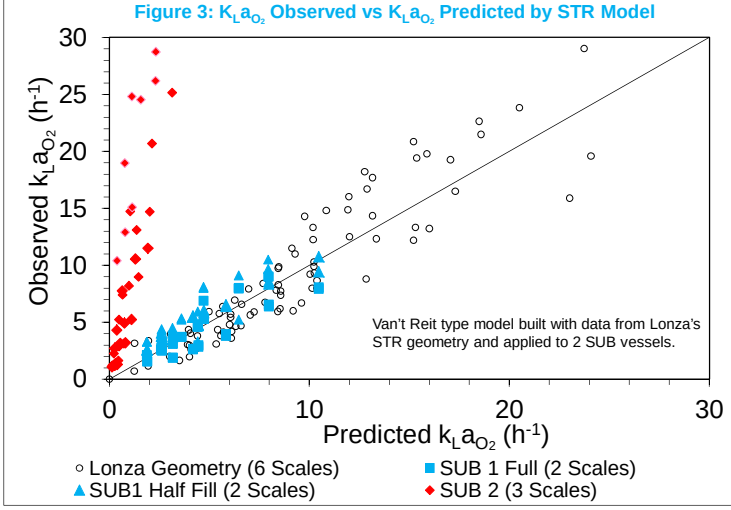


Figure 2: ALR Geometry

Matching $k_La_{O_2}$

- SUB 1's geometry is closer to Lonza's STR geometry than SUB 2.
- A scale independent $K_La_{O_2}$ model developed for Lonza's STR geometry was used to predict $K_La_{O_2}$ in both SUB geometries (Figure 3).
- The Lonza STR model was able to predict $K_La_{O_2}$ for SUB 1 but not SUB 2.
- Mass transfer characteristics of SUB 1 are closer to Lonza's STR geometry.

Figure 3: $K_La_{O_2}$ Observed vs $K_La_{O_2}$ Predicted by STR Model



Multivariate Analysis of Cell Culture Runs

- Process set points selected to match $K_La_{O_2}$ between vessels.
- Data from 19 cultures was analysed by PCA.
  - 15 measurements for 16 days in 4 vessel geometries.
- The first 4 principal components (PC)s captured 63 % of the variance in the dataset.
  - Cross validation indicated this included all the systematic behaviour.
- Scores plots of the first 4 PCs are presented in Figures 4 and 5.

Results

- Cultures performed in Lonza's STRs form a loose cluster in both plots.
  - 95 % confidence ellipse is plotted for this cluster.
- Lonza's ALR vessels group with Lonza's STRs in PC1, PC2 and PC3.
- Cultures in SUB 1 were performed at 2 scale and two different fill volumes.
  - Cultures performed at full volume group with the STR cultures on all PCs.
  - Cultures performed at half volume group with the STR cultures only on PC4.
- Cultures in SUB 2 were performed at 3 scales with two bag materials.
  - Cultures performed in old bag material group with the STR cultures on PC4 only.
  - Culture performed in new bag material group with the STR cultures on PC2, PC3 and PC4.
- Loadings of the PCA model were inspected.
  - PC1 correlated inversely with productivity, otherwise it had no obvious structure.
  - PC2 correlated with growth and loadings for all measurements progressed from low to high over time.
  - PC3 loadings were strongly influenced by viability and productivity.
  - PC4 loadings were strongly influenced by culture metabolism.

Discussion

- Loadings for PC1 and PC2 normally track growth/culture progression and metabolism respectively.
  - Loadings for a model built with STR data alone followed this norm.
  - When expanded to include all four vessels growth/culture progression was relegated to PC2.
  - Implies the vessel is the largest cause of variance between cultures in the expanded dataset.
- ALR and STR cultures cluster well.
  - Performance can be maintained between cultures in vessels with radically different geometry.
- SUB 1 and STR cultures cluster well at full volume but not at half volume.
  - At full volume SUB 1 has a high degree of geometric similarity to Lonza's STR.
  - At half volume just 1 of these geometric parameters has been altered.
  - K_La performance was not altered (Figure 3).
  - Culture performance was radically altered.
- Half volume cultures don't form a cluster.
  - Implies inconsistent performance between scales at half volume.
- SUB 2 bag material effected culture performance.
  - Even with the new bag material SUB 2 did not group with Lonza's STRs on PC1.

Conclusion

- When moving between vessels geometry does matter, no less so in SUBs.
- Small changes in geometry can have a big impact on culture performance.
- Strategies to match physicochemical conditions aren't sufficient to correct for differences in geometry.
- Getting the geometry right matters.

Figure 4: Scores on PC1 and PC2

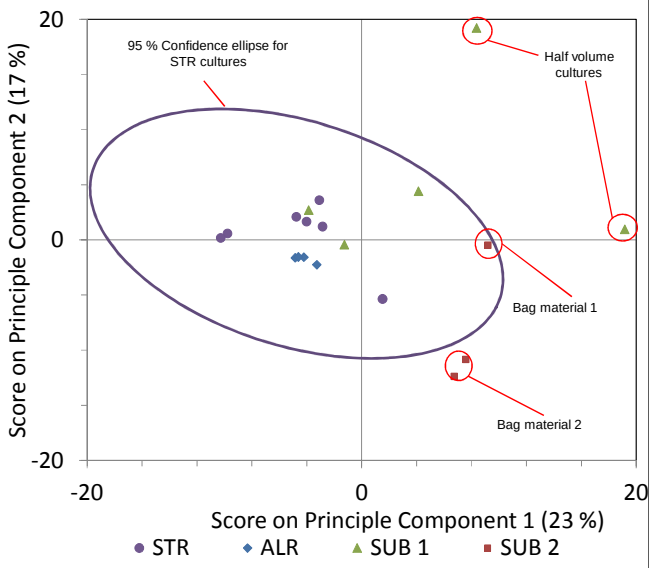


Figure 5: Scores on PC3 and PC4