Computational simulation as a predictive tool for bioreactor design and performance

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Abstract

The biopharma industry is experiencing multiple challenges, such as cost pressure and the development of new product classes.

As a result, shorter timelines, fast scale-up, and a focus on time to market are of great importance.

In addition, process intensification, the broad use of perfusion processes, and non-mammalian expression systems put new requirements on designing high-performing, scalable, and modality-agnostic bioreactors.

In this study, we have leveraged computational fluid dynamics (CFD) to design and select the agitator and sparger for a next-generation bioreactor.

Further, we have used simulations to predict and minimize the shear stress and concentration gradients in the bioreactor.

Stages in CFD model and product development

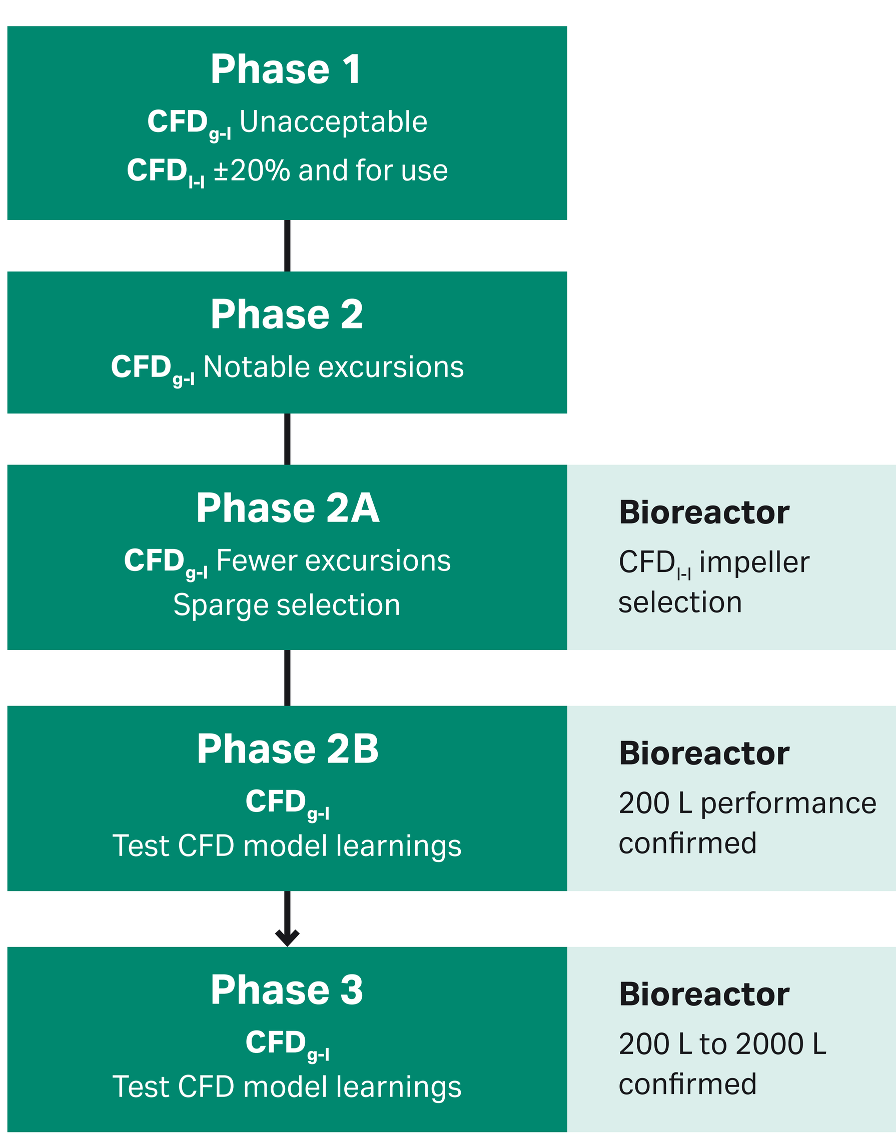

Fig 1. Outline of stages in co-development of product and CFD model.

CFD as a tool to capture the geometry and application of bioreactors

Cytiva agile ways of working

- Goal of co-developing the CFD with design of new bioreactor product
- Outcome expected to improve speed to market by reducing material consumption & personnel
- Intention of using CFD to screen interim bioreactor design elements (impeller, sparge, baffles)

Customer agile ways of working

- Improve selection of bioreactor for cell line needs and operational parameters
- Provide visualizations of bioreactor environments
- Present quantitative evidence of shear and turbulence for understanding of process conditions
- Reduce process development/scale-up design of experiment conditions required in wet-test

Results

CFD Phase 1: Confirmed 200 L tank geometry and CFD_{l-l} model

- Value of CFD_{l-l} model fit for immediate use in design – can use for impeller geometry screening
- Identified need for additional CFD_{g-l} model tuning – Phase 2

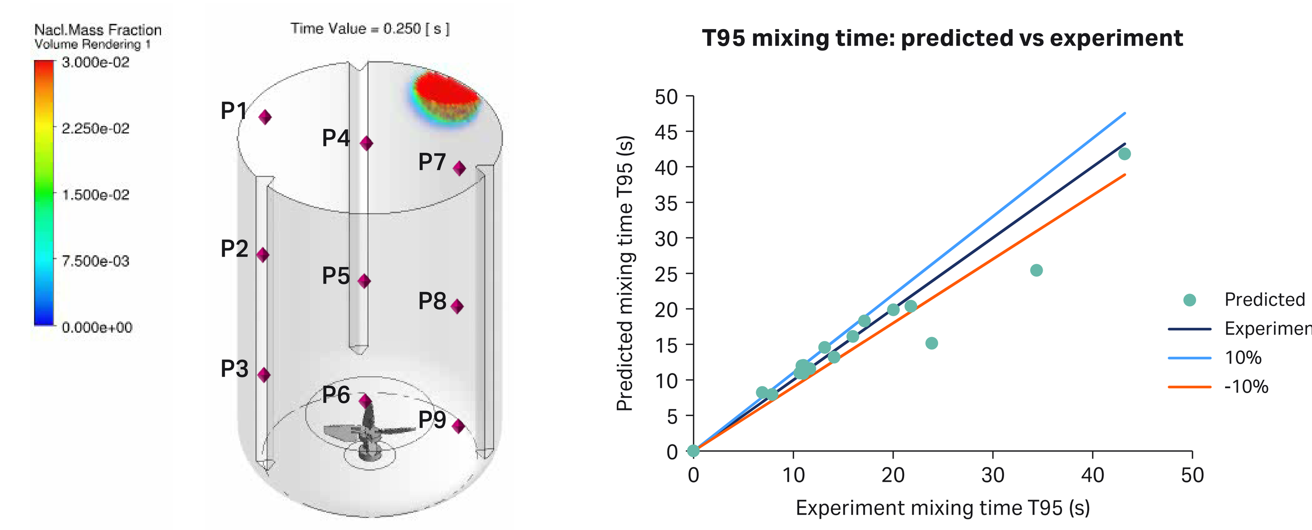

Fig 2. CFD model from Phase 1 describing the liquid-liquid mixing.

CFD Phase 2 A+B: Confirmed 200 L system performance and CFD_{g-l} model

- CFD_{g-l} model performing for torque and k_La within ± 20% of empirical for final sparge and impeller chosen with acceptable exceptions
- 200 L bioreactor design performs to design expectations for target k_La using final sparge and impeller designs

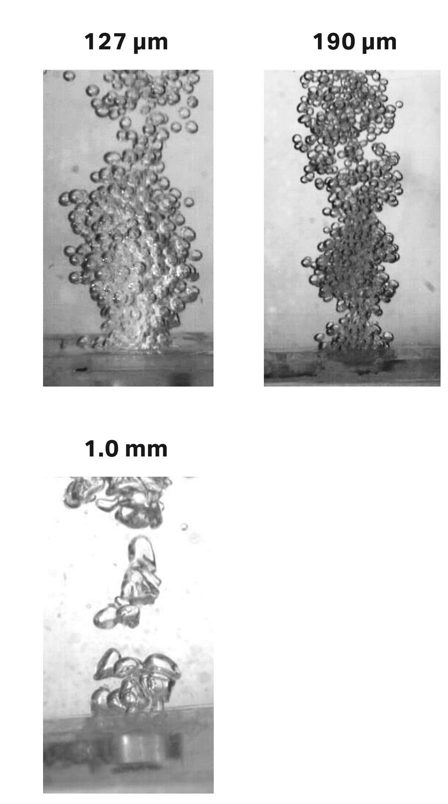

Fig 3. Bubble size analysis to assess sparge options.

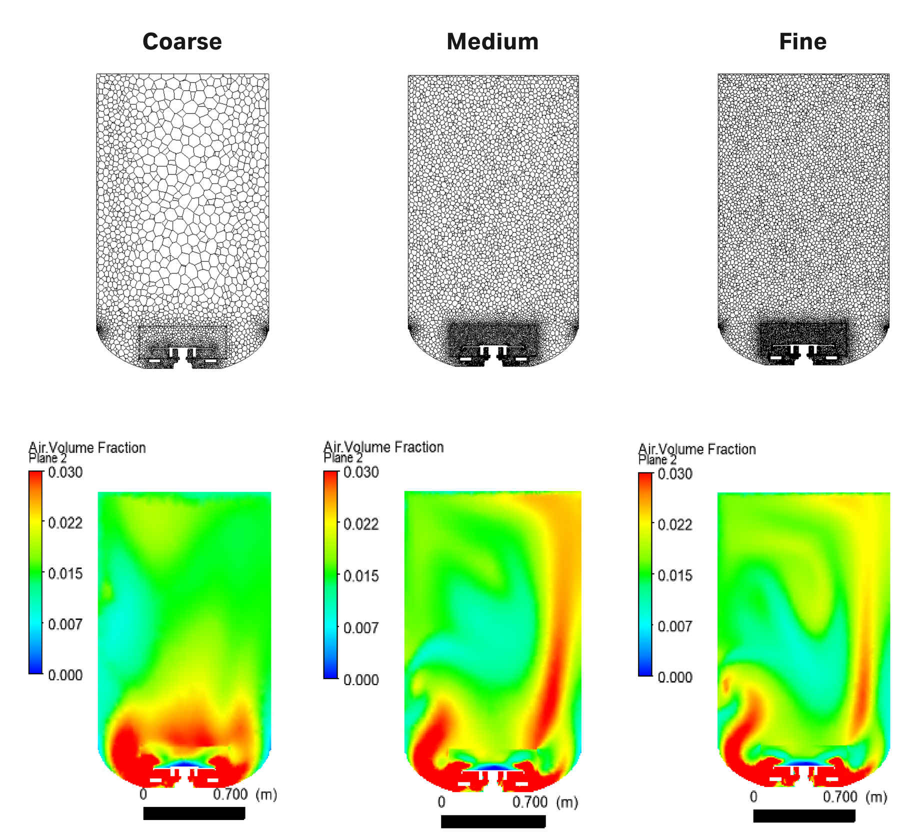

Fig 4. Model grid size impact on gas holdup distribution.

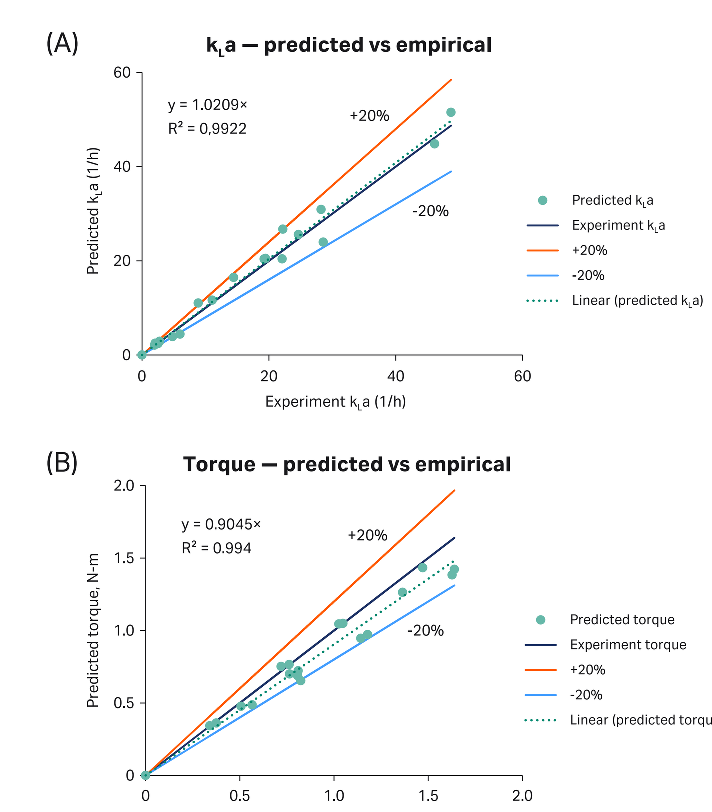

Fig 5. Confirmed 200 L system performance and CFD_{g-l} model.

CFD Phase 3: CFD_{g-l} model and new bioreactor performance

Kolmogorov eddy analysis

Goal:
- Kolmogorov eddy length < 62.5 µm
- Within ≤ 5% of total volume

Early performance results:
- 200 L < 3% of total volume
- 2000 L < 3% of total volume

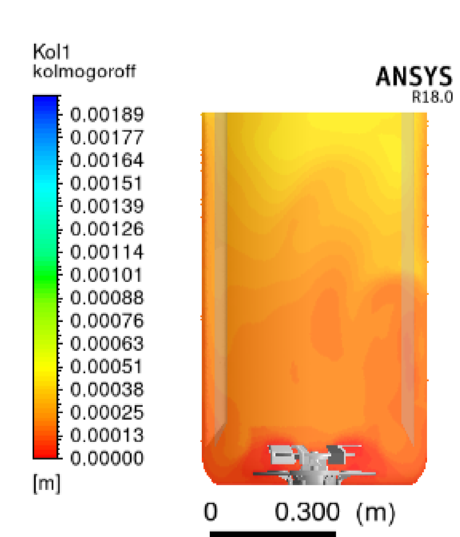

Fig 6. CFD model for Kolmogorov eddy analysis. Turbulent eddies < 62.5 µm in diameter are represented in red.

- Validated bioreactor performance for the final geometry, impeller, and spargers was within design ranges for performance for shear rate and turbulence.
- Current 200 L design will scale to 2000 L future size.

Shear rate analysis

Goal:
- < 5% of total volume with shear rate > 2000 s^{-1}

Early performance results:
- 200 L < 0.001 % of total volume
- 2000 L < 0.001 % of total volume

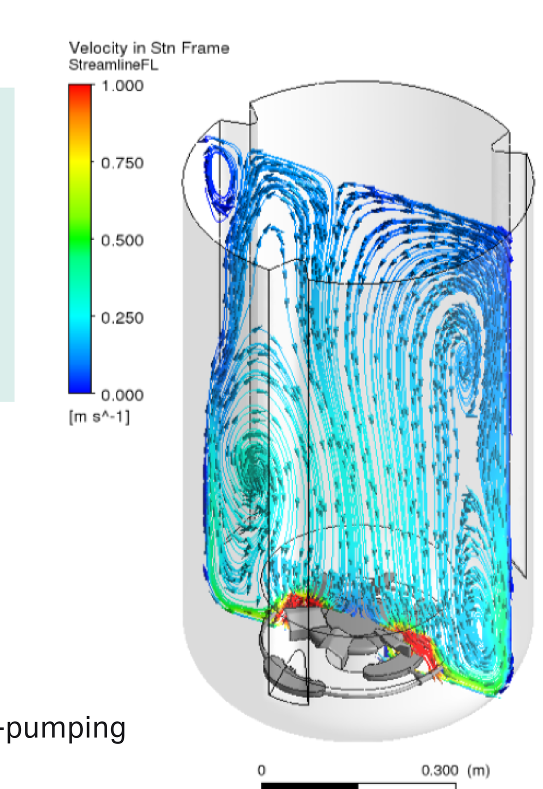

Fig 7. CFD model for shear rate analysis, here showing the velocity contours.

Note

Conditions both scales: 150 W/m^3 up-pumping with 0.2 VVM gas flow rate.

Results here are not the final performance results for the product design.

Conclusions

- The final CFD model was found to be extremely useful to accelerate bioreactor product development
- Bioreactor performance parameters optimized (k_La, shear rate, and turbulence) relevant to process applications
- Using 200 L and 2000 L sizes, CFD models and wet-test results confirm scalability
- CFD characterization provides deep understanding to inform design

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