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EUROCFD

Comparison Between Experimental Data and Computational Fluid Dynamics in Mixing Applications

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Introduction

In biomanufacturing processes, mixing is ubiquitous. Examples include buffer and media preparation, stirred tank bioreactor/fermentor operation, virus inactivation, DNA digestion, final formulation and beyond. Mixing trials are sometimes necessary to assess if a technical solution is adapted for a given process step or to optimize process parameters. However, trials may not be feasible due to various reasons:

- Product is unavailable in suitable quantities
- Product is too expensive
- Safety issues (e.g., Antibody Drug Conjugates, allergenic)
- Availability of equipment

Computational fluid dynamics (CFD) is a powerful simulation tool that can be applied to a wide range of research and engineering problems in many fields, including aerodynamics and aerospace, weather simulation, environmental engineering, biological engineering, fluid flows, and heat transfer. Typically, its use leads to an improved understanding of the process flow upon which the performance of a product relies, as well as a reduction in the amount of empirical testing required.[1] Therefore, CFD could be a complimentary or alternative solution to physical mixing trials. It could also be an initial step for validation prior to a confirmation run. To evaluate these options, we collaborated with EUROCFD on a specific study to compare empirical data with CFD results.

About EUROCFD

EUROCFD is a major player of French engineering companies dedicated to numerical simulation for industry. EUROCFD deploys its skills in many industrial sectors such as aeronautics, nuclear, oil & gas, transport, and biomanufacturing. With best-in-class resources, EUROCFD conducts research and development programs and industrial product improvements.

Background

Mixing trials are performed on a regular basis, at our M Lab™ collaboration centers. In this particular case, the objective of the trial was to determine the mixing times during the final formulation step for a mAb process. As a mock fluid for the mAb solution, a sucrose solution was used and a NaCl tracer was introduced to determine the mixing times at different fluid volumes and impeller speeds. The process conditions of this study were shared with EUROCFD to perform a CFD evaluation.

Materials and Methods

Experimental mixing trials

The Mobius® MIX single-use systems (figure 1) are particularly suited for final formulation applications as they provide gentle and low shear mixing environments. Mobius® MIX 50, 100, and 200 systems were used for this study. Sucrose and Tween® 20 were dissolved in reverse osmosis water to obtain final solutions of different viscosities. Separately, a 4 M NaCl solution was prepared to serve as a tracer. Following a Design of Experiments (DoE) (table 1), the Mobius® MIX systems were filled at specified volumes with the sucrose solutions.

System	Viscosity (cP)	Volume (L)	Speed* (rpm)
MIX 50	9.6	6; 40; 50	250
MIX 100	2; 2.9; 3.8; 9.5; 11.1	10; 15; 24; 30; 51; 54; 64; 70; 74; 110	90; 120; 150; 190; 250
MIX 200	1; 2; 2.9; 3.8; 5.5; 9.6	30; 60; 120; 130; 200; 210	60; 100; 130; 140; 150; 160; 200; 300

Table 1: Conditions tested during DoE (all combinations were not tested)

* Speed range for Mobius® MIX 50 system: 40–1000 rpm; for Mobius® MIX 100 and MIX 200 system: 40–500 rpm

Figure 1: Mobius® Mixers

A conductivity probe was installed to measure the conductivity of the solution at the surface of the liquid (figure 2). The impeller was switched on at the given speed for the test. Once the mixing steady state was achieved, the tracer was added (1 mL of tracer per liter of solution) and the conductivity of the solution was monitored. Once the conductivity was stable, a sample was taken from the bottom of the Mobius® MIX system to confirm homogeneity of the full bulk.

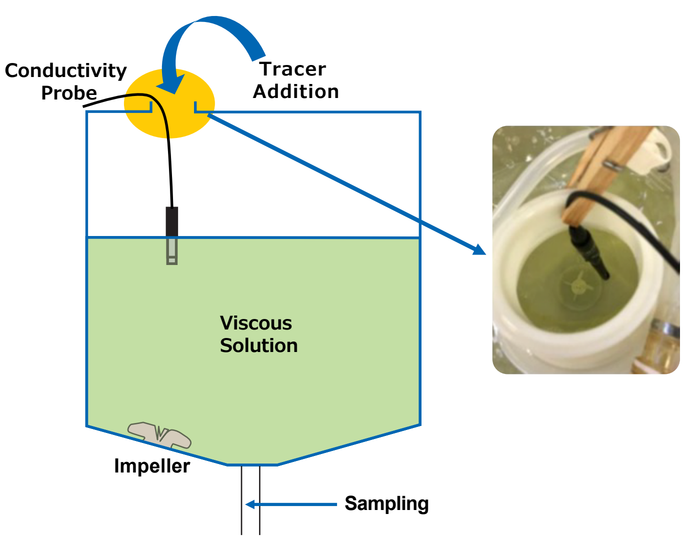

Figure 2: Experimental setup in the Mobius® MIX 100 system

The conductivity results were normalized based on the average conductivity reached at steady state. T_{95} was calculated as the mixing time corresponding to the first time for which all the following conductivity values are within the 95–105% range of the conductivity increment.

In the context of the comparison with CFD, three conditions out of approximately fifty combinations tested experimentally were selected. The conditions used for the CFD simulations are summarized in table 2.

System	Working Volume (L)	Viscosity (cP)	Impeller speed (rpm)
MIX 100	54	9.5	120
			150
	64		150

Table 2: Experimental conditions

Computational fluid dynamics study

STAR-CCM+ 2020.1 software was used by EUROCFD to perform the CFD analysis. The working volume was divided in a mesh of approximately 6 x 10^6 cells and the mesh further refined near the impeller and conductivity probe. Mixing in the tank was evaluated by injecting a virtual tracer (passive scalar) when the flow was stabilized. The evolution of the concentration of the tracer was monitored by 26 virtual sampling probes (figure 3) over 150 to 200 seconds of real time.

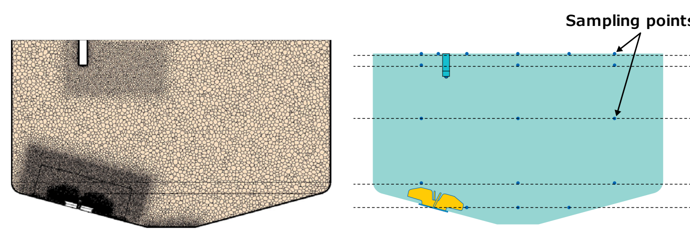

Figure 3: CFD model and mesh of the tank

Results

Physical mixing trials

The results of the experimental trials for the conditions selected for the CFD simulations are presented in table 3 and figure 4. At 54 L, a single experiment was performed at both speeds while the experiment was performed in duplicate at 64 L (T_{95} was averaged for the experiment at 64 L).

Conditions	Experimental T_{95} (s)
A: 54 L and 120 rpm	125
B: 54 L and 150 rpm	80
C: 64 L and 150 rpm	103

Table 3: Experimental results

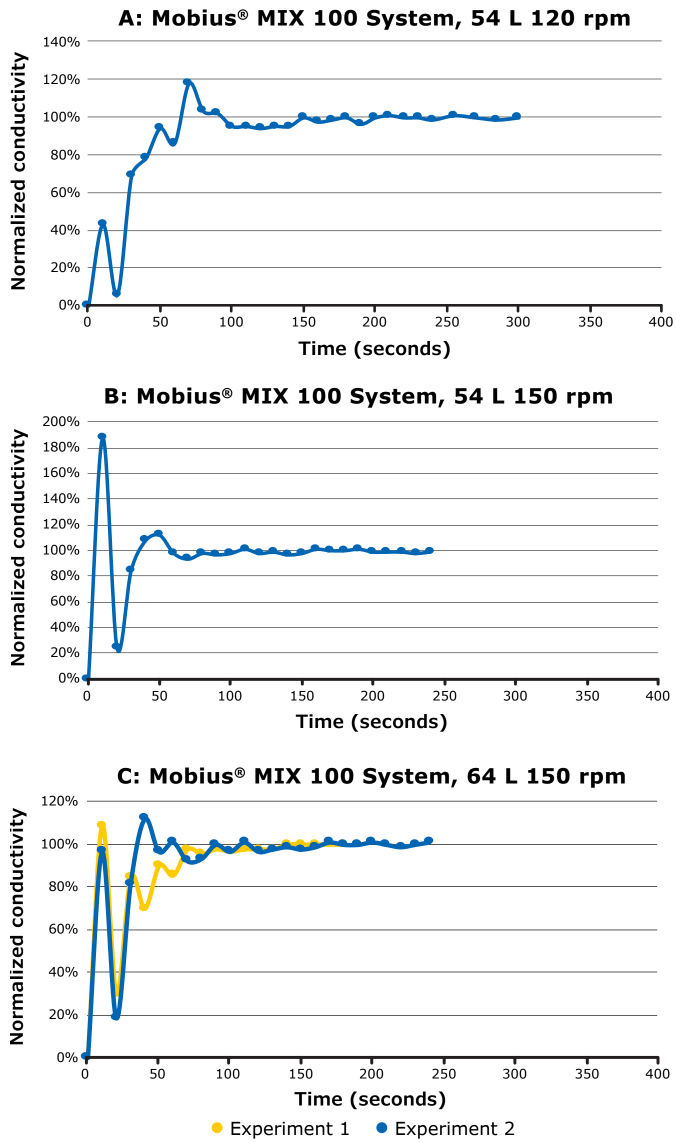

Figure 4: Conductivity curves at 54 L and 120 rpm (A), 54 L and 150 rpm (B), 64 L and 150 rpm (C)

Computational fluid dynamics study

For the CFD study, mixing time was evaluated based on the evolution of the tracer concentration in the bulk solution. T_{95} was determined when the concentration measured at the 26 virtual sampling probes was within ± 5% from the target concentration (figures 5 and 6).

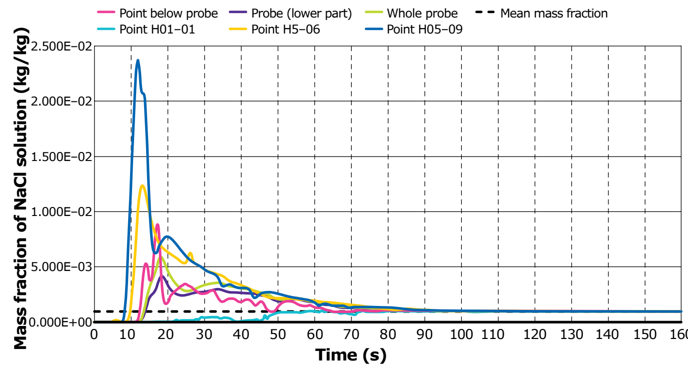

Figure 5: Evolution of the tracer concentration at 6 sampling probes

Conditions	Experimental T_{95} (s)	CFD T_{95} (s)	Difference (%)
A: 54 L and 120 rpm	125	109	12.8
B: 54 L and 150 rpm	80	80	0.0
C: 64 L and 150 rpm	103	105	1.9

Table 4: Comparison between experimental results and CFD results

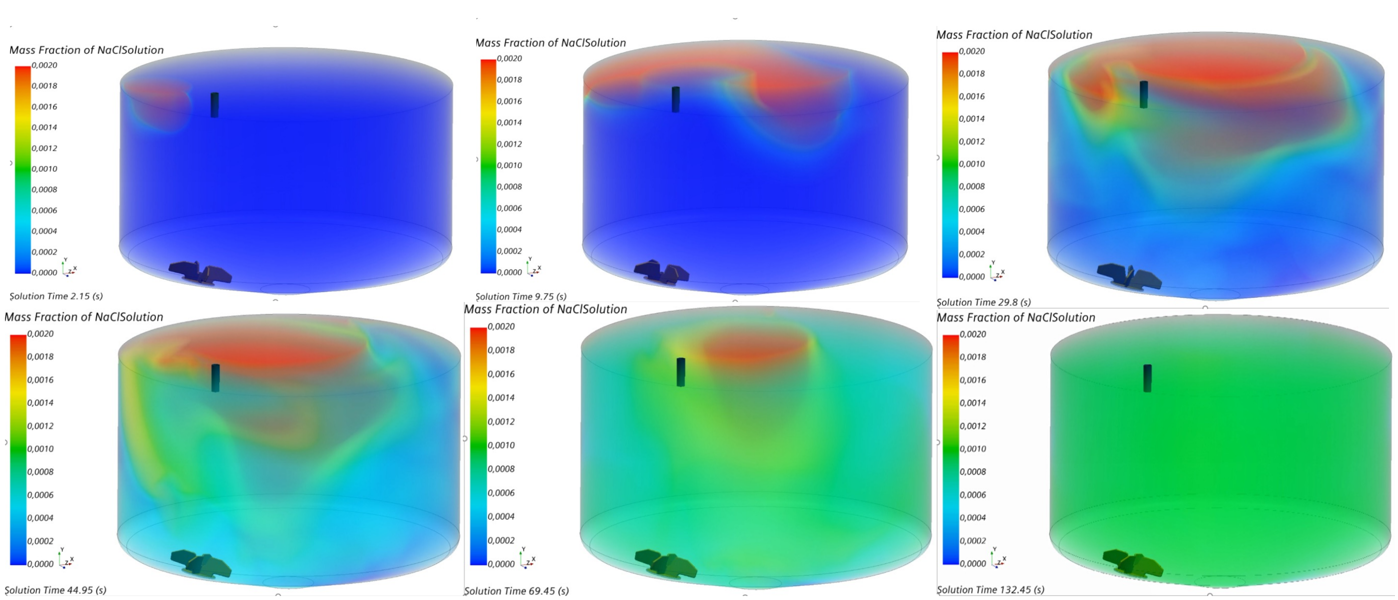

Figure 6: Tracer evolution "Volume rendering"

The comparison showed good correlation between CFD and experimental results with a mean difference of 4.9% (table 4). The model used was especially accurate for experiments at 150 rpm with a difference below 2%.

CFD not only allows for the determination of mixing times but is also a powerful tool to study fluid behavior. For instance, the CFD confirmed that the Mobius® MIX systems provide gentle mixing by calculating the volume corresponding to dimensionless shear rate $(^{\gamma}/_{N}) \geq 25$, 50, 75 and 100. The results for the three conditions are summarized in table 5 and show that the volumes submitted to shear forces are very limited to the zone around the impeller (figure 7).

Volume (mL) corresponding to $(^{\gamma}/_{N}) \geq 25$	Volume (mL) corresponding to $(^{\gamma}/_{N}) \geq 50$	Volume (mL) corresponding to $(^{\gamma}/_{N}) \geq 75$	Volume (mL) corresponding to $(^{\gamma}/_{N}) \geq 100$
408 to 425	137 to 140	53 to 55	28 to 30

Table 5: Volumes corresponding to a given dimensionless shear rate

Figure 7: Dimensionless shear rate (25; 100) at 54 L and 150 rpm.

The simulations also allowed us to see the velocity iso-contours on different cutting planes (figure 8) or the high velocity pumping area around the impeller (figure 9).

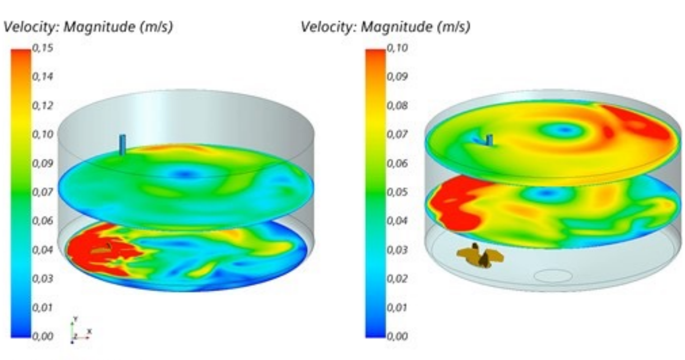

Figure 8: Velocity iso-contours at 54 L and 150 rpm.

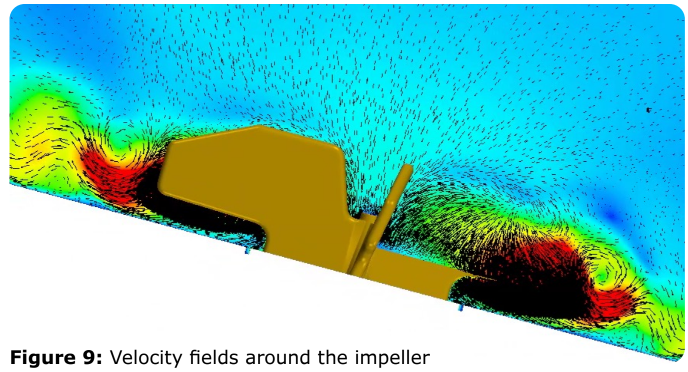

Figure 9: Velocity fields around the impeller

Finally, CFD allows determination of impeller characteristics such as the resistive torque that the fluid exerts upon the impeller, the absorbed power, the impeller power number, the pumping and circulating flow rates, and the pumping and circulating numbers. In the case of the impeller power number, the difference between the value measured experimentally and the value determined by CFD was less than 7%.

Discussion

This collaboration confirmed the benefits CFD analysis could provide for mixing applications. Experimental conditions were used as a basis for simulations and the CFD demonstrated that there is a good correlation between the experimental data and numerical analysis. In addition to mixing times, CFD could offer a great panel of fluid behavior visualizations moving from velocity fields to shear rate or path-lines. It could also provide impeller characteristics such as power and pumping numbers. Based on the overall study, CFD demonstrated that it could be a powerful tool in mixing applications either as an alternative to actual mixing trials or as a complementary solution. This study also highlights the importance of implementing safety factors in all the steps of a biomanufacturing process including adding extra filtration areas or additional mixing times to consider process variability.

REFERENCES

[1] How to - Ensure that CFD for Industrial Applications is "Fit for Purpose". NAFEMS, 2010.

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