Simplifying Progress

Uses of Computational Fluid Dynamics for Evaluating the Performance of Cubical Mixers in Bioprocessing

November, 2022 | David Menahem, Myriam Lavie, Katy McLaughlin

Keywords or phrases:
Computational Fluid Dynamics, mixing performances, Flexsafe® Pro Mixer, single-use cubical mixer

SARTORIUS

Mixing in Bioprocessing

Mixing is a ubiquitous and critical part of any biomanufacturing process. Indeed, mixing equipment is needed for numerous operations such as dissolving solids and powders (media and buffer preparation), low pH adjustment (viral inactivation), resuspension, concentration (downstream intermediates), excipient preparation, and final formulation.

Proper characterization of mixing processes is especially important in modern biopharmaceutical processes since traditional mixing vessels are increasingly being replaced with single-use technologies, which have their own features and challenges. Manufacturers require reliable strategies to evaluate mixing performances across new equipment and consumables to ensure consistency across the various process steps where mixing is required.

Traditionally, the development of mixing operations largely relies on experimentation, which involves operators testing various configurations and conditions – a time-consuming and costly process. In addition, despite the seemingly simple concept of mixing, fluid dynamics in mixers is a highly challenging process to analyze: fluid flow becomes turbulent and multiphase systems emerge[1]. Reliable mixing characterization tools must be comprehensive, fast, and accurate, helping biopharmaceutical manufacturers meet the competitive demands of the industry.

In all mixing processes, product quality (especially for shear-sensitive biomolecules), reproducibility, and uniformity (i.e., homogeneity throughout the vessel) of the products are of utmost importance. One way to ensure that these product requirements are met is to perform computational fluid dynamics (CFD) simulations, which allow manufacturers to design and optimize the mixing equipment and operations without the need for time-consuming trial and error methods with different equipment configurations. Furthermore, models and simulations are particularly useful when they can be validated by a pilot process and then used for scale-up computations.

This whitepaper describes the value of CFD in determining the performance of single-use mixers during process development.

Single-Use Solutions for Mixing in Bioprocessing

The biopharma industry is increasingly moving away from traditional stainless steel equipment and reusable consumables - which require significant cleaning and validation – towards sterilized and ready-to-use single-use solutions.

Single-use mixing is appropriate for both liquid | liquid and solids | liquid applications. Single-use cubical mixers are increasingly used in bioprocessing and follow the same trend as the rest of the single-use market.

The single-use bioprocessing containers and media bags segments accounted for over 28% of the market in 2021. These segments are projected to reach over $2 million by 2026[2].

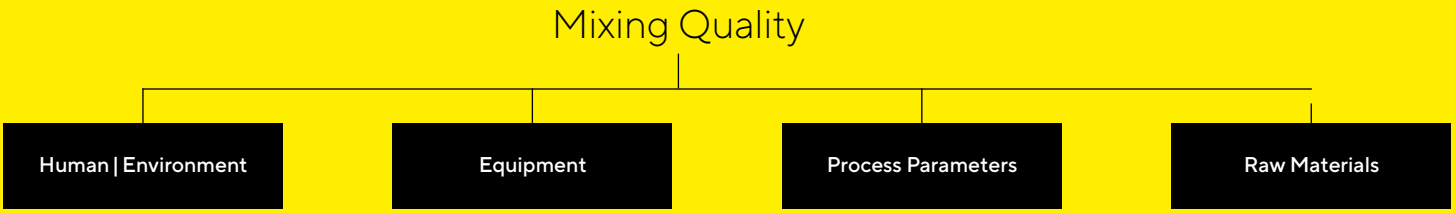
The implementation of single-use, cubical, bottom-mounted mixers is becoming increasingly common in biomanufacturing because of the minimal risk of contamination, low shear stress, and ease-of-use[3]. As discussed, the proper characterization of mixing performance is a key step in the biopharmaceutical process. Detailed behavior insights are even more critical when installing new equipment and consumables – such as single-use cubical mixers - for which prior knowledge is limited.

Characterization of Mixing Performance

Mixing is defined as the act of combining substances through the application of mechanical stirring to blend the constituents into one homogeneous mixture. Mixing in a stirred tank is influenced by many parameters.

Figure 1 summarizes the factors that influence mixing quality[4]. Raw material features include particle size, solubility, and shear sensitivity. Contributing process parameters consist of mixing time, volume, and speed. Important equipment characteristics include the tank diameter and features of the impeller. Finally, the human | environmental factors are temperature, operator and ther relative humidity[4].

Figure 1: *Factors Affecting Mixing Quality*



Source. *Hörmann, Suzzi, & Khinast, 2011*[4]

In biopharmaceutical processes, performance evaluation is highly dependent upon the purpose of the mixing step:

1 Media | Buffer Preparation

Powerful mixing with strong turbulence within the vessel is required to dissolve powder quickly and ensure efficient mixing.

2 Mixing Sensitive Products

Low shear mixing is necessary to avoid degradation of the protein.

The mixing performance will result in mixing time, proper homogenization of the prepared solutions, and the non-degradation of the proteins.

Challenges Associated With Characterizing Mixing Performance

Performance parameters commonly used to evaluate mixing efficiency are the mixing time, the power number used to describe the power dissipation of impeller, and the flow number used to describe the pumping capacity of the impeller. The combination of these optimized parameters should ensure a proper homogenization of the prepared solution as well as the non-degradation of proteins.

Empirical correlations provide a starting point for understanding appropriate mixing conditions and scale-up. Most often, however, simple correlations cannot sufficiently capture processing complexities that impact product quality. Correlations do not adequately depict the important hydrodynamic characteristics that regulate mixing inside the vessel.

A challenge specific to single-use containers is that, while traditional stainless-steel containers (such as bioreactors) are often cylindrical shaped, typical single-use mixing containers are cubical. This makes it more challenging to characterize the mixing performances without experimentation because single-use cubical mixers do not conform to the well-defined standard.

Solutions for Characterizing Mixing Performance – Computational Fluid Dynamics (CFD)

CFD is a tool that simulates fluid motion. Powerful computers and applied mathematics are used to model fluid flow situations to provide valuable information about fluid motion, flow patterns, velocities, characteristic dimensionless numbers (e.g., Reynolds number, Power number), and specific power consumption. Numerical insights into these properties allow bioprocess engineers to optimize mixing operations[5].

With these properties, CFD provides a fundamental, process-specific understanding of hydrodynamics in mixing vessels, such as speed profile, flow patterns (Figure 2), particle dispersion and shear stress, which affect mixing performance and product quality.

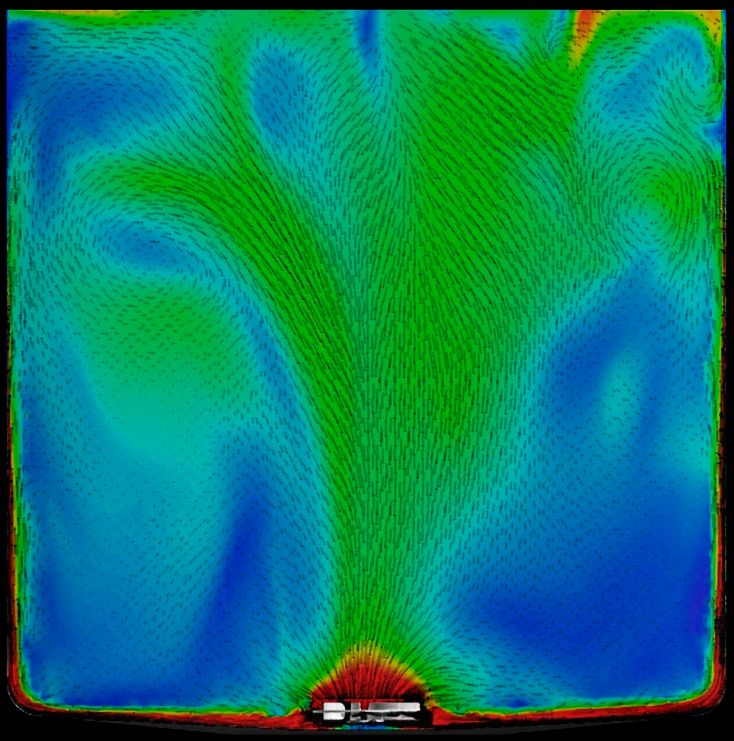
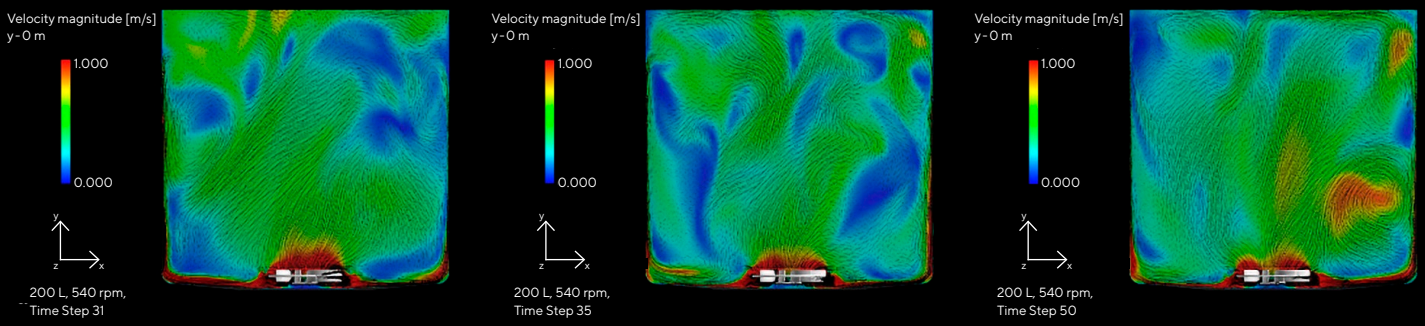


Figure 2: *An Example of CFD Data Showing the Flow Pattern Inside a Cubical Mixer From the Side View*

The information generated by CFD provides an improved understanding of process flow and reduces the need for empirical testing, speeding up process development and maximizing the chances of finding an effective mixing solution. Since it has such a high agreement with experimental data, CFD can act as an initial validation step before a confirmation run. CFD also enables more robust process performances and reproducible product attributes and can help avoid possible hurdles associated with scaling up.

Sartorius used CFD to study the mixing performance of the Flexsafe® Pro Mixer, a single-use mixing vessel[6,7]. The absence of permanent dead zones in Figure 3 (blue) indicates that all areas of the bag are permanently agitated during mixing operations, which is essential to creating a homogenous solution.

Figure 3: *Side Views of Velocity Profiles Inside the Flexsafe® Pro Mixer at Different Times*



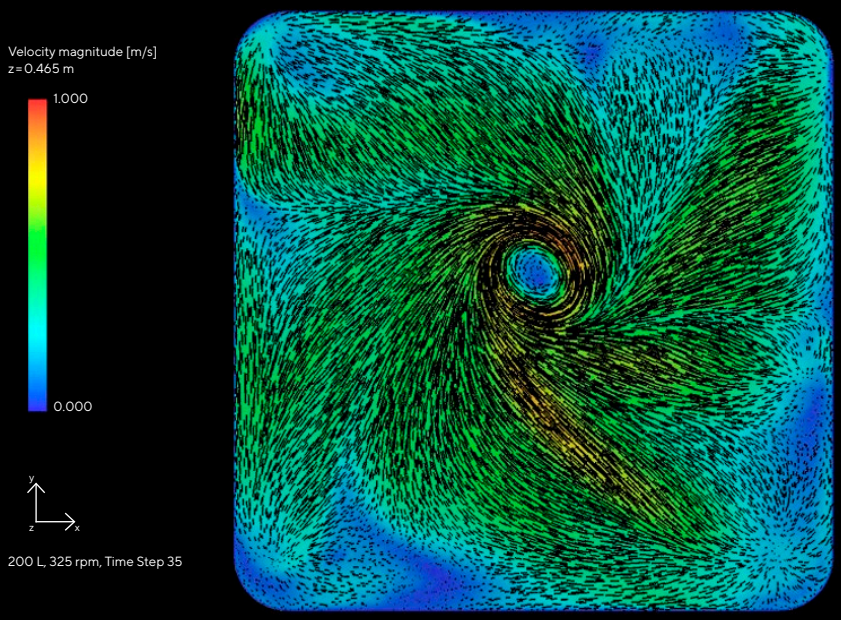
Note. Volume is 200 L and mixing speed is at 450 rpm. There are no permanent dead zones (blue).

Additionally, the CFD data indicated a moderate vortex formation (Figure 4) with both ascending and descending flows (Figure 5), which support the inclusion of powder into the liquid and dispersion throughout the solution.

The geometry of the agitator created a strong radial flow and the generation of a high turbulence zone, demonstrated through analysis of flow patterns. This enables the formation of a recirculation loop, avoiding dead zones and supporting robust mixing applications.

Finally, the maximum shear rate estimated by CFD study was found to be 9,350 s^{-1} for the Flexsafe® Pro Mixer 200 L at 450 rpm (Figure 6), which is considerably lower than the $10^7 \sim 10^8$ s^{-1} found to cause degradation of proteins[8,9].

Figure 4: *Top View of Vortex Formation in a Flexsafe® Pro Mixer*



Note. Volume is 100 L and mixing speed is at 325 rpm.

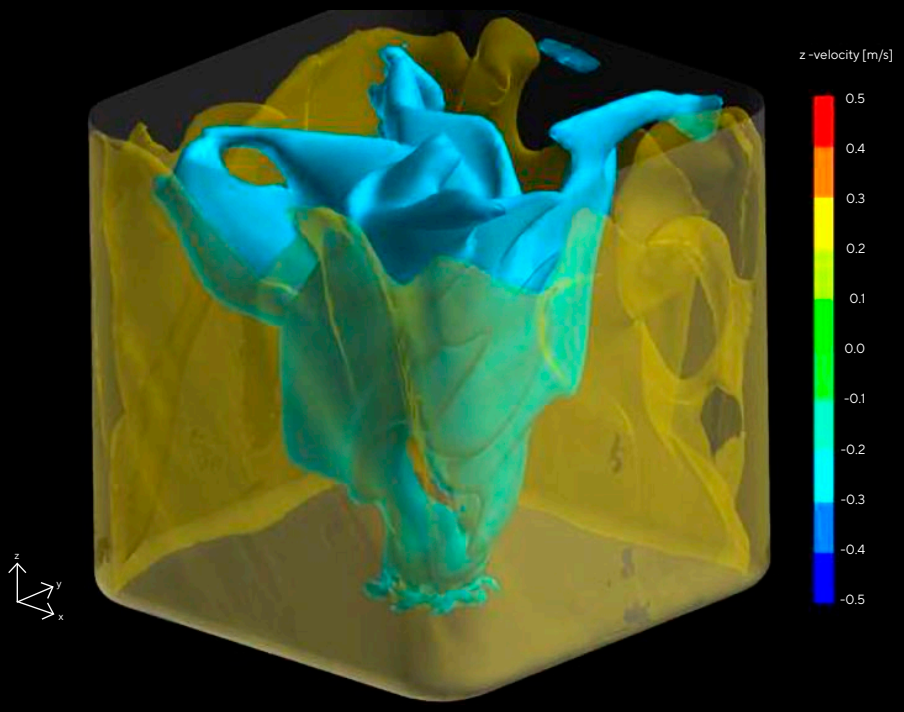


Figure 5: *Simulation of Vertical Velocity in the Flexsafe® Pro Mixer (3D View)*

Note. Volume is 1,000 L and mixing speed is at 750 rpm. Ascending (orange) and descending (blue) flows are shown. The absence of green areas indicates no stagnant areas in the z-direction.

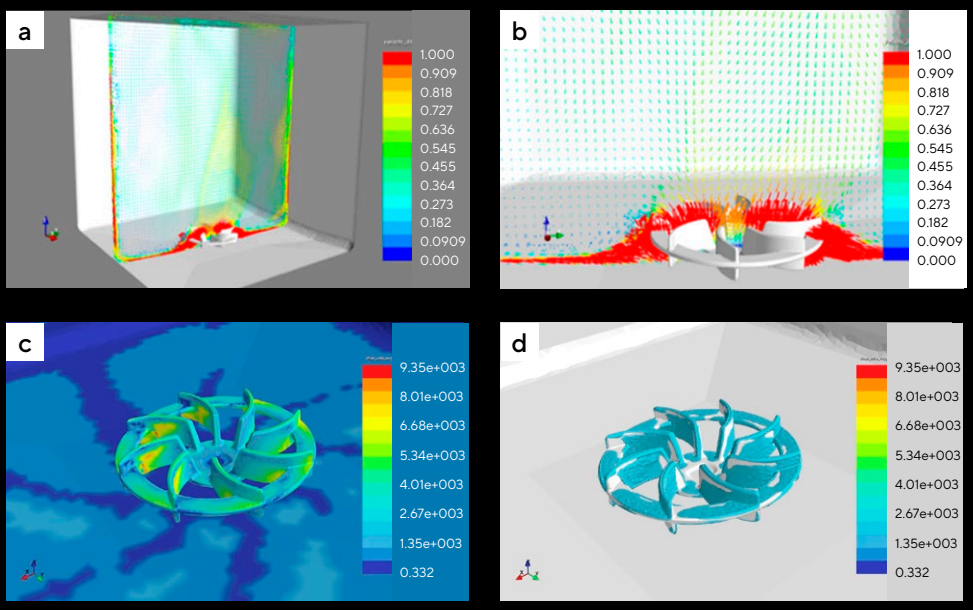


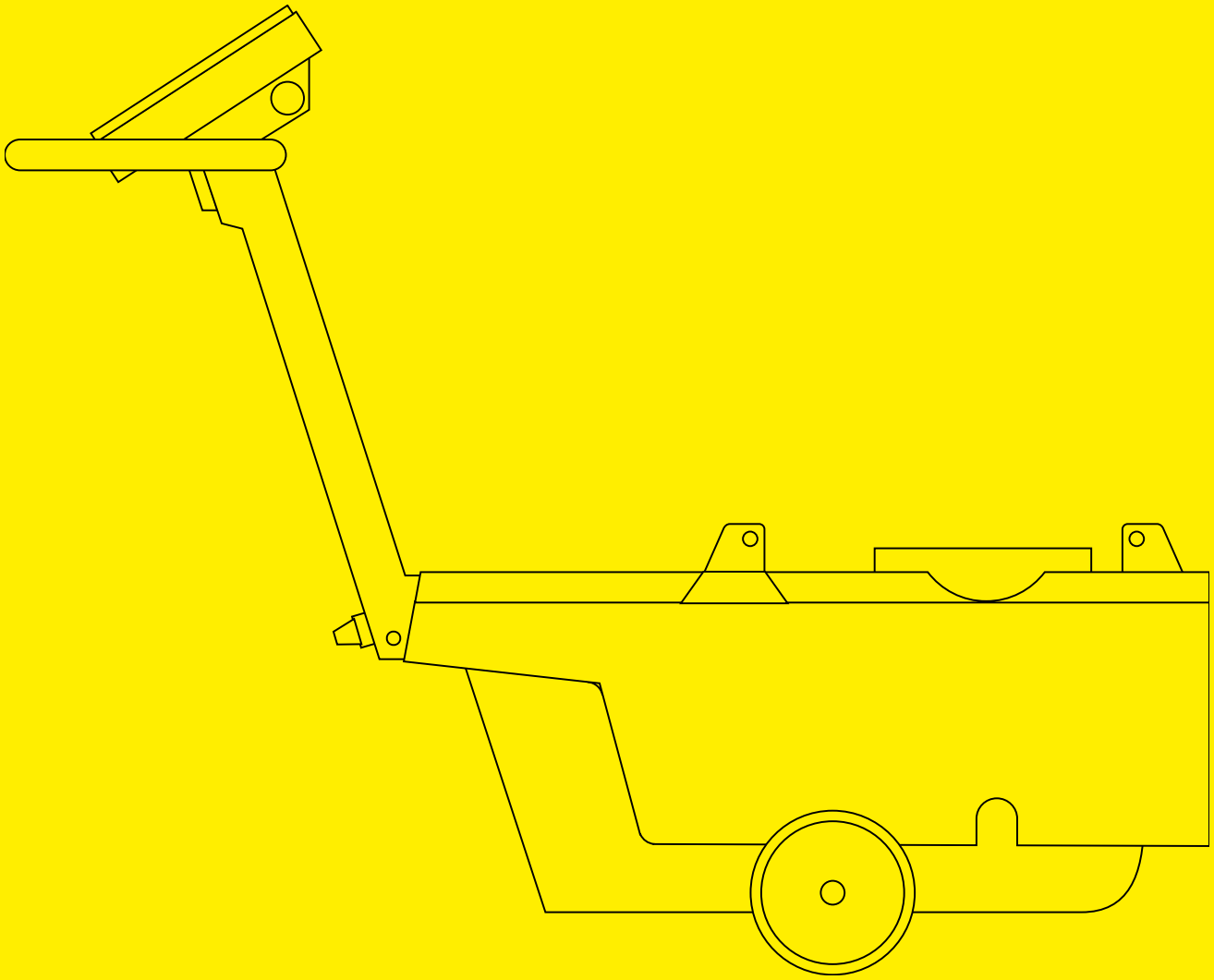
Figure 6: *CFD Data for 200 L Flexsafe® Pro Mixer at 450 rpm.*

Note. (a) 3D View (b) vector cut plane with maximal speed scale at 1 m/sec. (c) CFD simulation of the shear profile (d) Isosurface of shear rate < 25% of the maximum shear rate (2.67×10^3 s^{-1})

Conclusion

Single-use mixers are easy to use in the production of biotherapies across scales without cleaning and validation requirements. However, their implementation must be accompanied by complete characterization and understanding of their performance across scales and applications.

CFD represents a powerful engineering tool that simulates mixing processes, as it can unlock new insights about the behavior of liquid and how it influences the efficiency of a stirring system. The information generated by CFD can be used to develop optimal conditions for mixing in a bioprocess to ensure high performance, consistency, and product quality.



Author Bio

David Menahem
Product Manager Mixing
Sartorius

David Menahem has been working for Sartorius since October 2021 as Product Manager Mixing. He is graduate in biotechnology engineering at Polytech Marseille, France and in Management at Kedge Business School Marseille, France.

David started his career in infectious disease diagnostics in a global medical technology company and has held positions in sales, application support and marketing for 9 years.

Myriam Lavie
Manager Mixing Team
Fluid Management Technologies,
Sartorius

Myriam is leading a Team of Product Managers responsible for the Mixing portfolio.

In 2007, she joined Sartorius Stedim Biotech as a Process Development Engineer for Fluid Management Technologies. In 2010, she became Product Manager of the single-use mixers.

Myriam started her career in 2005 as a Process Engineer with Glaxo-SmithKline Biologicals, Belgium, and now holds more than 15 years of experience in engineering and marketing in the biopharmaceutical industry. She has been involved in many industrial projects for design, implementation and validation of single-use systems.

Katy McLaughlin
PhD, Scientific Content Writer,
Sartorius

Katy is part of the Marketing Communications team at Sartorius, where she supports the creation of a variety of written pieces, from published articles to web content.

Before joining Sartorius in 2021, Katy was employed as a Post-Doctoral Research Associate at the University of Edinburgh, where she also completed her doctoral studies. Here, she carried out research in genetics and cellular biology and began taking on writing projects, eventually entering into a career as a freelance writer for various biotech companies and agencies.

References

1. Niño, L., Peñuela, M., & Gelves, G. (2018). CFD: A New Challenge in Bioprocess Engineering. International Journal of Applied Engineering Research (Vol. 13). International Journal of Applied Engineering Research. Retrieved from http://www.ripublication.com
2. Single use Technologies for Biopharmaceuticals: Global Markets. (2022).
3. Gikanga, B., Chen, Y., Stauch, O. B., & Maa, Y. F. (2015). Mixing monoclonal antibody formulations using bottom-mounted mixers: impact of mechanism and design on drug product quality. PDA journal of pharmaceutical science and technology, 69(2), 284–296. https://doi.org/10.5731/pdajpst.2015.01031
4. Hörmann, T., Suzzi, D., & Khinast, J. G. (2011). Mixing and dissolution processes of pharmaceutical bulk materials in stirred tanks: Experimental and numerical investigations. Industrial and Engineering Chemistry Research, 50(21), 12011–12025. https://doi.org/10.1021/ie2002523
5. Xia, B., & Sun, D. W. (2002). Applications of computational fluid dynamics (CFD) in the food industry: A review. Computers and Electronics in Agriculture. https://doi.org/10.1016/S0168-1699(01)00177-6
6. Flexsafe® Pro Mixer - Computational Fluid Dynamics. (2020).
7. Flexsafe® Pro Mixer 3,000 L Filled at 80% Computational Fluid Dynamic Studies. (2021), 1–12.
8. Jaspe, J., & Hagen, S. J. (2006). Do protein molecules unfold in a simple shear flow? Biophysical Journal, 91(9), 3415–3424. https://doi.org/10.1529/biophysj.106.089367
9. Thomas, C. R., & Geer, D. (2011, March 1). Effects of shear on proteins in solution. Biotechnology Letters. Kluwer Academic Publishers. https://doi.org/10.1007/s10529-010-0469-4

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Stedim North America Inc.
565 Johnson Avenue
Bohemia, NY 11716
Toll-Free +1 800 368 7178

For more information, visit
www.sartorius.com

Status: 11 | 2022