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From Fluids to Pharmaceuticals: How Computational Fluid Dynamics (CFD) Transforms Drug Design

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At a Glance

Computational Fluid Dynamics (CFD) is a powerful tool that helps scientists and engineers understand how fluids behave and move, whether in the air, liquids, or biopharmaceutical manufacturing processes. This technology, which uses computer simulations to replicate real-world scenarios, plays a critical role in various industries, including medicine and drug development. By creating virtual experiments on computers, CFD allows researchers to gain insights into the interaction of biological components for drug production at different scales, from small laboratory experiments to large-scale manufacturing processes and fast-track process optimisation. The strategy and implementation of CFD for a bioreactor system has been explained in this article.

Keywords: Biopharmaceutical manufacturing, Process optimisation, Computational Fluid Dynamics.

What is Computational Fluid Dynamics?

Computational Fluid Dynamics (CFD) might sound like a complex science, but it plays a crucial role in many areas, including medicine and drug development. CFD uses computer simulations to understand how fluids, like air and liquids, move and behave. This technology helps scientists solve real-world problems by simulating them on a computer. In the realm of drug development, CFD helps to study the interaction of different components, like media (a nutrient-rich solution that is used to support the growth and maintenance of cells), cells and supplements (substances that are used to enhance the uptake of nutrients like amino acids and vitamins) that are used to make biological drugs. To create effective drugs, scientists need to know how these components behave in different situations, from small-scale to large-scale production.

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CFD applies the laws of physics (conservation of mass, momentum, and energy) to describe fluid flow. Usually, Navier-Stokes equations are used to refer to all these equations. These laws are written as mathematical equations known as Partial Differential Equations. However, these equations are so complex that they cannot be solved with traditional analytical methods. Instead, computers are used to solve them numerically. Numerical methods first convert these partial differential equations into systems of linear algebraic equations (incurring a linearisation error in this process) and then use boundary conditions and iterative solvers to solve them. Numerical methods, unlike analytical methods, produce errors due to rounding off (to save computer memory), truncations of infinite series terms, and linearisation errors. These errors, which cause an imbalance in conservation equations, are ultimately grouped into residual errors of the model and can be adjusted to achieve predefined tolerance levels of accuracy and precision.

CFD faces a big challenge when it needs to analyse large and complex flow areas, as computers have computational limits. To overcome this, CFD divides these areas into smaller parts (this step is called discretisation), reducing the equations that must be solved. However, this can introduce a new error called "discretisation error", as homogeneity of characteristics is assumed in those smaller parts. There are three main ways to divide complex areas: Finite Difference Methods (FDM), Finite Element Method (FEM), and Finite Volume Method (FVM). FDM uses a grid system that suits simple shapes. FEM breaks the area into elements and is used for a wide range of problems. FVM divides the area into volumes, particularly useful for specific fluid flow problems. However, FVM is the most used discretisation scheme in commercial software for application in fluid flow and applies conservation laws to each control volume.

Illustrating the CFD Algorithm

The CFD journey begins with pre-analysis preparations. Here, the physical problem is defined, considering the unique geometric dimensions and initial insights into the flow domain that help to define the boundaries of the problem. The boundary conditions applied to the physical problems simplify the physical problem, and this new reformulation is called the boundary-value problem. Next, the problem is transformed into a mathematical formulation that can be applied across the entire geometry. This step is like turning the real-world scenario into a language that computers can understand and work with. Before diving into numerical solutions, the geometry is discretised. In simpler terms, it is divided into manageable pieces. This segmentation lays the foundation for the numerical solution process that follows, with a defined iteration loop aimed at reducing solution errors to a specified tolerance level. Results emerge through the interpolation of data across the flow domain. Think of it as connecting the dots between known points to create a complete picture of the fluid motion. To ensure accuracy, verification and validation steps are crucial. Verification checks whether the mathematical model has been correctly solved, especially against known boundary conditions. Validation, on the other hand,

confirms that the mathematical model is not overly simplistic by comparing it to experimental data.

Achieving consistent and reliable results requires finding the right balance between computational time, convergence criteria, and mesh size used for discretisation. This equilibrium helps minimise errors in the simulations. A mesh refinement study is often conducted to fine-tune the CFD model. It ensures that the simulation accurately adapts to and resolves the specific physical problem being studied. Figure 1 provides a visual representation of the Computational Fluid Dynamics (CFD) algorithm, outlining the step-by-step process involved in solving complex fluid flow problems.

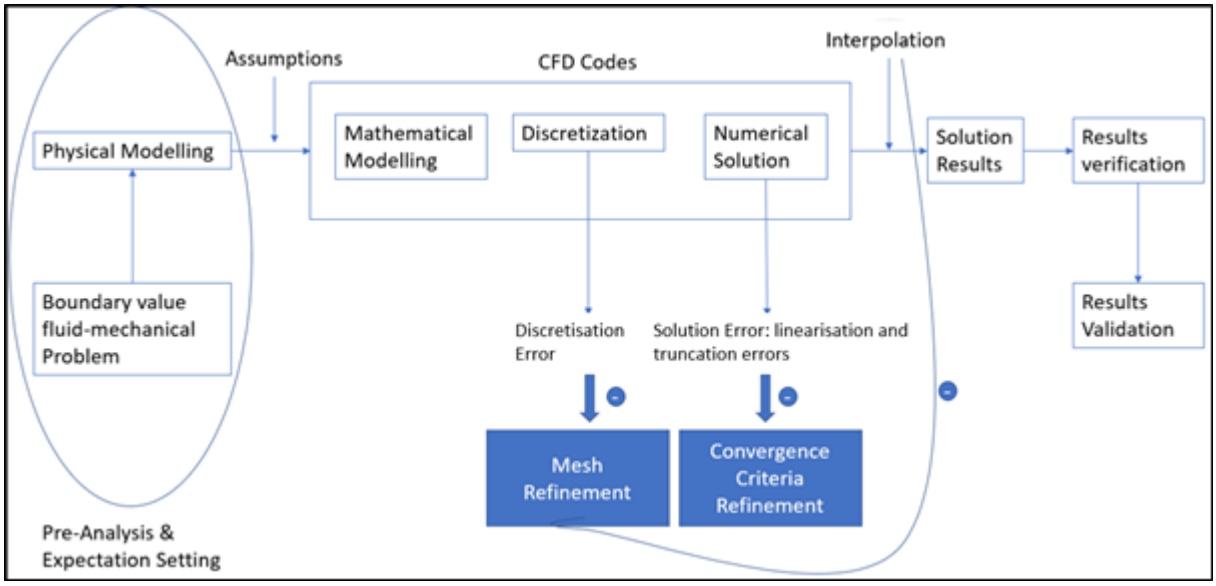


Figure 1: The strategy of CFD: Physical problem pre-analysis identifies the applicable assumptions with which the problem is specified in the CFD code for discretisation and solution. Solution data is interpolated to generate final results, which can be verified and validated

Fast-Tracking Biopharmaceutical Manufacturing using CFD

The global response to the COVID-19 pandemic has pushed the need for quicker and more adaptable biopharmaceutical production methods to unprecedented levels. Safety and quality remain top priorities, but there is an urgent demand for efficient ways to scale up and transfer technology. Significant drug development and distribution efforts have faced difficulties due to the slow process of scaling up and transferring technology. Traditionally, scaling up and optimising the manufacturing process involves a trial-and-error approach guided by practical experience. However, this method is time-consuming, causing delays that can last for months or even years. It also requires specialised skills and expensive materials. While some experimental design techniques can help, they often do not fit the unique needs of biopharmaceutical manufacturing settings or account for specific details in large-scale operations. CFD simulations allow scientists to create virtual experiments on the computer to understand how different conditions affect the manufacturing process. Unlike physical experiments, CFD is done en-

tirely on a computer. When done correctly, the results from these digital simulations can be as reliable as real-world data but at a fraction of the time and cost. CFD proves invaluable for predicting critical hydrodynamic properties such as mixing patterns, potential shear stress, and gradients of essential parameters, like temperature, pH, and nutrient concentration. This knowledge aids in designing reactors, optimising configurations, and facilitating the scale-up and scale-down of bioprocesses. Figure 2 represents application of CFD to model the velocity profile generated by the Rushton impeller (a type of agitator with flat horizontal disk, with flat, vertically-mounted blades invented by John Henry Rushton) in a bioreactor (a bioreactor is a specialised container that provides controlled conditions for growing cells to produce valuable products, like medicines, biofuels, or enzymes) using Ansys Fluent software.

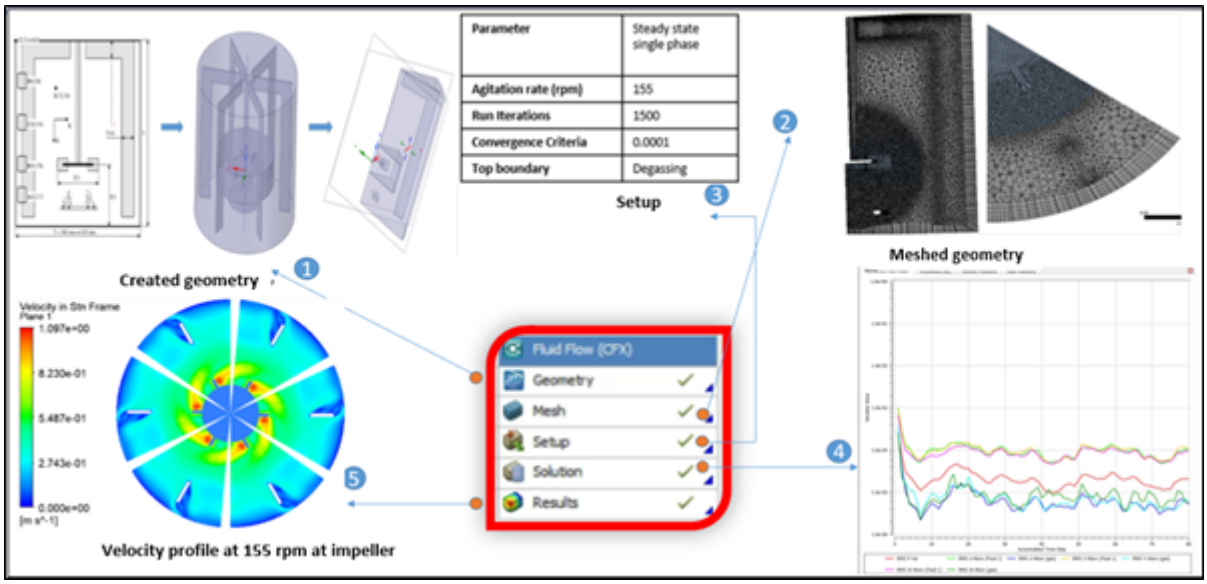


Figure 2: CFD modelling of a bioreactor system equipped with Rushton impeller at 155 rpm agitation rate using Ansys CFX: (1) Geometry: Computer-aided design of bioreactor is generated first (2) Mesh: Bioreactor is divided into small regions, called mesh (3) Setup: Initial condition and models are specified (4) Solution: Numerical solution of the model is attained (5) Results: Solution results are visualised

Several other software options are available for CFD work, including ANSYS Fluent, FloWizard, PHOENICS, Star-CCM+, and OpenFOAM. These tools serve as virtual laboratories where researchers bring their fluid dynamics experiments to life on computer screens. With advancements in computing power, modern CFD can run fully transient, time-accurate three-dimensional simulations. These simulations couple physical phenomena, like turbulence, mass transfer, and heat transfer seamlessly, allowing real-time adjustments in fluid flow based on changes in properties due to blending or bubble dispersion in a bioreactor. This new era enables the creation of time-accurate digital twins, where fluid flow, species transport, and product growth are intimately connected. Entire processes can be developed, transferred, and scaled up using these digital twins, offering a cost-effective and efficient way to simulate and optimise complex manufacturing processes.

Conclusion

Computational Fluid Dynamics (CFD) has emerged as a transformative tool that bridges the gap between theory and practice in various industries, including biopharmaceutical manufacturing. Its ability to simulate fluid motion with precision and speed has revolutionised how scientists and engineers approach real-world problems.

In the context of biopharmaceuticals, CFD has become indispensable. It allows researchers to understand gradients and dynamics of fluid flows within bioreactors, predict critical parameters, like shear stress and temperature gradients, and optimise processes for efficiency and quality. The cost savings and accelerated development timelines associated with CFD in biopharmaceutical manufacturing are substantial.

The evolution of CFD from its early days to the modern era, marked by fully transient, time-accurate simulations and the development of digital twins, has opened new horizons for innovation. As technology continues to advance, CFD will undoubtedly play an even more pivotal role in shaping the future of biopharmaceutical manufacturing, offering a pathway to faster, more cost-effective, and safer drug production.

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Declaration of Interests

I wish to confirm that there are no known conflicts of interest associated with this study.

Author Bio

Vishal is a third-year PhD student in Process and Chemical Engineering. His research focuses on bioreactor modelling using CFD and bioprocess optimisation. He is a biochemical engineer with over three years of experience in industrial upstream process development, optimisation and scale-up of therapeutic monoclonal antibodies. Vishal enjoys communicating his research and exploring interdisciplinary interactions on cell culture.