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CFD: A New Challenge in Bioprocess Engineering

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Abstract

Computational Fluid Dynamics (CFD) is a powerful tool based on mathematical applications for modeling transient and spatial transport modes such as mass, momentum and heat transfer in multiphase fluids. Currently, CFD has been applied for biological engineering processes. In this paper, a review of Bioprocess engineering applications in computational fluid dynamics (CFD) is presented, including important steps such as sterilization, mixing in CSTR, mass transfer and biochemical reactions applications.

Keywords: Bioreactor, scale up, multiple reference frame (MRF), population balance model (PBM).

INTRODUCTION

Computational fluid dynamics (CFD) uses powerful computers and numerical calculations for modeling fluid situations [1], thus having multiple fields of application to solve environmental, architectural and industrial problems.

The use of numerical methods to solve complex engineering problems presents a series of very interesting advantages: (a) very complex geometries can be simulated; (b) A wide range of problems can be solved where sometimes the restrictions are quite severe; (c) it is possible to optimize process units without the need to build prototypes; (d) saving time and money [2]. However, Nowadays CFD has been applied in bioprocesses engineering even in sterilization process [1-5].

The competitive demands in bioprocess engineering requires effective and accurate tools at the shortest possible time. These requirements have been raised by the need for developing the most extensive technological systems that have a comprehensive knowledge based on relationship of synergistic models. The persistent concern for the final quality of biotechnological products generates the need to study hydrodynamics and mixing processes that take place in bioreactors. That is why CFD has become more useful due to its capacities for simulating real situations in Bioreactors. In this way, those processes can be optimized by studying different stirrers configurations and velocities without the need to build different equipment each time by trial-error methods [2]. The development of this paper is based on a Critical and Analytical perspective of the Recent Advances and Futures of Computational Fluid Dynamics (CFD) as a new challenge in Bioprocess Engineering.

ADVANTAGES BY USING CFD

The CFD went from being a solver tool for the famous Navier-Stokes equations to become a very versatile software in each of the branches of fluid dynamics. Many of CFD applications will increase development, improve product consistency and productivity in industrial plants [6]. Wanot, [7] has categorized some advantages of the CFD: I. It provides a detailed understanding of flow profile, mass and heat transfer, particle dispersions etc .; II. It makes it possible to evaluate geometric changes in less time and cost; III. It may be able to reduce problems in scale up; IV. It is particularly common in simulation conditions where detailed measurements are inadequate such as high temperatures or hazardous environments in an oven.

It is possible to make a study based on simulations either through FLUENT, FIDAP or POLYFLOW software. The latter can be applied in different scenarios for evaluating temporal and spatial behavior inside reactors using mathematical models that describe parameters such as velocity magnitude, turbulent kinetic energy, temperature, gas dispersion, bubble size for non-Newtonian fluids, etc. Based on the ideas explained before a new and extensive fluid dynamic knowledge will generate horizons towards the optimization of stirring systems used in the bioprocess industry.

Below some details about the main processes that have been studied using CFD are mentioned in this paper.

A. Sterilization

Sterilization is one of the fundamental stages to guarantee performance and productivity in a microbial culture. By means of sterilization the total absence of any unwanted growth of a contaminating microorganism is guaranteed. The thermal treatment turns out to be the most significant technique to inactivate unwanted microbial cells but its great disadvantage occurs when sterilizing culture media vulnerable to changes in its physical and chemical properties since excessive heat can denature or damage some nutrients necessary to perform a fermentative process. The CFD can be used to simulate steam flow through the interior and/or through the cooling system (jacket or helical coil) of a bioreactor. That is why, temperature and pressure profiles can be determined in the most critical point in order to avoid contamination.

Very few studies analyzed by CFD have been developed for leading thermal sterilization optimization. Abdul Ghania et

al. [8] carried out a series of experiments with CFD in culture media sterilization. They determined diffusion changes in bacteria and their transient spatial distribution during the sterilization process, simulating heat transfer by convection in a closed liquid-liquid system. However, these studies are very limited due to different types of sterilization emerged in the field of bioprocess engineering. Some assumptions have been made in CFD modeling related to mentioned works: the specific heat, thermal conductivity and volume expansion coefficient were assumed like constant values at all study carried out by Abdul Ghania et al. [3] although these parameters really depend on the temperature [1].

Likewise, new research must be developed that takes into account the specific geometry of each sterilization system in order to minimize the idealistic assumptions that limit CFD efforts to real phenomena. Also in future studies, microorganisms that are most likely to contaminate fermentative process should be kept in mind. The latter based over-designed sterilization processes (very expensive energy requirements) due to over calculation requirement based on the most heat-resistant isolated microorganism (*Bacillus stearothermophilus*); although higher probability of contamination is expected due to fungi, enterobacteria, mycoplasma or another class of unwanted yeasts that do not require such high energy costs for their elimination.

B. Mixing Systems in Reactors

For decades there has been a concern about stirring of biotechnological processes because of its importance in bioprocess industry. However, fluid behavior is considered as one of the most difficult processes to analyze and characterize. Thus knowledge of the behavior of variables such as mixing speed or the degree of homogeneity reached in bioreactors is scarce. Another difficulty when characterizing mixing is the growing use of multiphase systems with diverse rheological behaviors. Therefore, design and optimization of stirring devices is largely reliant on experimentation [2]. CFD is considered a powerful tool to simulate the mixing processes in bioprocess engineering, as it can provide extensive information about velocity profiles and mixing times that govern a stirring system.

A Rushton turbine CFD simulation performed by Martínez, [2], it was concluded that the hydraulic efficiency increases with the Reynolds number in a laminar regime. This work allowed to conclude that 20% of energy contributed to the stirrer is lost by viscous friction. On the other hand, power lost due to viscous friction was negligible compared to power supplied by the agitator in a turbulent regime, which is why Martínez [2] stated that hydraulic efficiency in these conditions is practically 100%. Additionally, he simulated four proven turbulence models, Spallart-Allmaras, standard model k-ε, model RNG k-ε and the Realizable k-ε model together with the standard wall functions. Some irregularities were presented in that investigation, since the mesh size was not standardized. That is why the velocity profiles did not adjust well to the experimental values showing higher error than is desirable. For this reason it is considered essential to optimize the mesh size used in the modeling applied to reactors stirred by a turbulent flow turbine.

Not only specific mesh size is a requirement for bioreactors modeling but also fluid viscosity in biological processes needs to be in mind, since different biotechnological processes are operated at high viscosity levels such as biopolymer, antibiotics and biofuels from lignocellulosic substrates, which can interfere with mixing degree. Viscous fluids are lack of study in works carried out by researchers. Similarly, Krishna [4] in his master's work, developed a CFD simulation for studying the mixing degree in a 5-liters using three different stirrer geometries to model: (a) a high degree of vortex, (b) one of low vortex and (c) another with intermediate characteristics to the previous ones and he obtained data for the behavior of the degree of mixture of each geometry. Unfortunately, their simulations are only valid for very low viscosity fluids such as water, because they did not take into account the rheological characteristics of a bioprocess or the cellular morphology of mammalian eukaryotic cells raised in their research.

One of the works applied to the field of stirring biological processes was developed by Xia, et. al. [1]. They developed simulations for different devices geometries in avermectin bioinsecticide production *from Streptomyces avermitilis* taking into account the viscous effects generated during the fermentation process, becoming this the first work where systems are simulated using CFD. Xia, et. al. [1] implemented the MRF (Rotating Reference Frame) model to model the rotational flow dependent on geometries proposed in their research.

Although the MRF model offers a stationary flow approximation that allows to simulate tanks with baffles or with complex internal geometries, this shows some limitations [2]: The MRF model ignores the relative interaction between the different subdomains, and thus does not takes into account the fluid dynamic interaction between stationary and rotating components. Ideally, the flow at the interface should be relatively uniform. MRF can give erroneous results in cases where the flow passes through the rotating subdomain (the flow enters and leaves the rotating subdomain) [2]. Therefore, the MRF model should not be used if the objective is to study the design of geometries for agitation systems. For these cases, the SM (Sliding Mesh) model that is used if rotor-stator interaction is strong or when more real system results are expected. It must be borne in mind that this model requires transient simulations, requiring a much higher computational sources compared to the MRF model [2].

C. Mass Transfer in Bioreactors

One way to quantify oxygen mass transfer is by estimation of the volumetric mass transfer coefficient $k_L a$. The $k_L a$ depends mainly on stirring velocity and air flow. Keeping an accurate $k_L a$ for microorganisms with high oxygen demand is a difficult task at large scale and the traditional method for supplying these requirements is assure experimental $k_L a$ obtained at laboratory scale up to industrial fermentation

scale. Some researchers [5, 9-12] have performed CFD simulations based on the Eulerian model to model mass transfer in airlift and stirred tank reactors. This model considers all phases as a continuum. The Eulerian model describes an unrealistic approach if the focus is the mass transfer from the bubbles to liquid interface (Lapin, 2006) [13]. due to bubbles and microbial cells are found in a dispersed phase (not as a continuum).

In some cases, these problems have been addressed by Population balance models (PBEs) [14, 15]. Krishna [4] used this model to solve Euler limitation problem. They used a discretized bubble population for simulating oxygen transfer in 5, 10, 20 50 and 500 liters bioreactors. Unfortunately, the discretized model was not validated with experimental results, which makes it even more difficult to select a universal model to describe mass transfer in bioreactor. Krishna [4] evaluated also the mass transfer, using the velocity magnitude, the turbulent kinetic energy and the turbulent dissipation energy. They found a better fluid dynamic behavior in 50-liter bioreactor due to an accurate degree of spatial homogeneity in turbulence and superficial velocity, therefore, they concluded that parameters mentioned before may be used for scale up criteria. Niño [15], evaluated different geometries for increasing $k_L a$ in a spin filter type bioreactor: Geometry I (Figure 1), a conventional spin filter Geometry II (Figure II), a spin filter with curved bottom and centered axial blades; Geometry III (Figure 3), a spin filter with curved bottom, centered axial blades and diffuser type spider and Geometry IV (Figure 4), Spin filter with curved bottom, centered axial blades, diffuser type spider, auxiliary radial blades and modified pitch blade (separated blades). It was found that $k_L a$ is significantly increased by modifying the flat bottom design of the conventional Spin Filter by a curved bottom, four auxiliary blades and using a micro-diffuser type Spider.

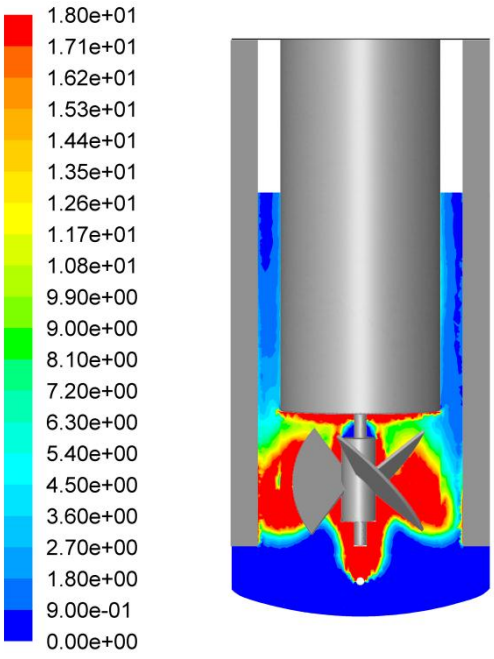

Figure 1. $k_L a$ mass transfer coefficient [1/h] calculated for the Conventional Spin filter [15].

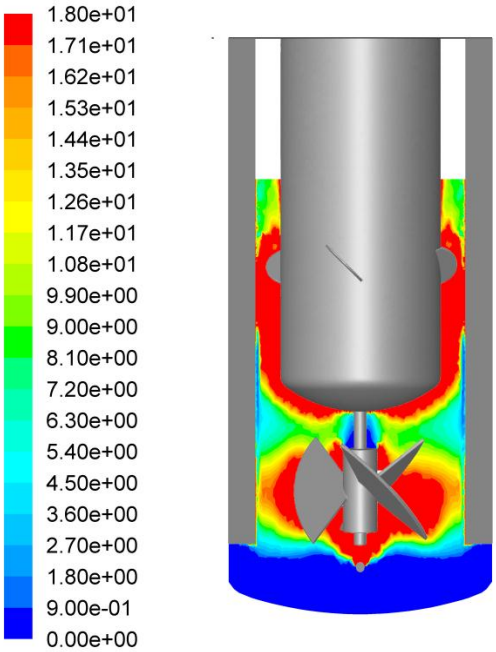

Figure 2. $k_L a$ mass transfer coefficient [1/h] calculated for the Geometry I, a micro-sparger and a curved bottom Spin filter with lateral axial blades [15].

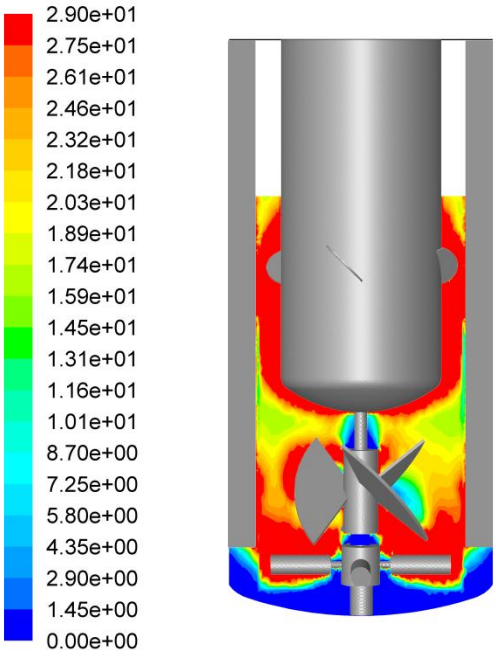

Figure 3. $k_L a$ mass transfer coefficient [1/h] calculated for the Geometry II, a diffuser type spider and a curved bottom Spin filter with lateral axial blades [15].

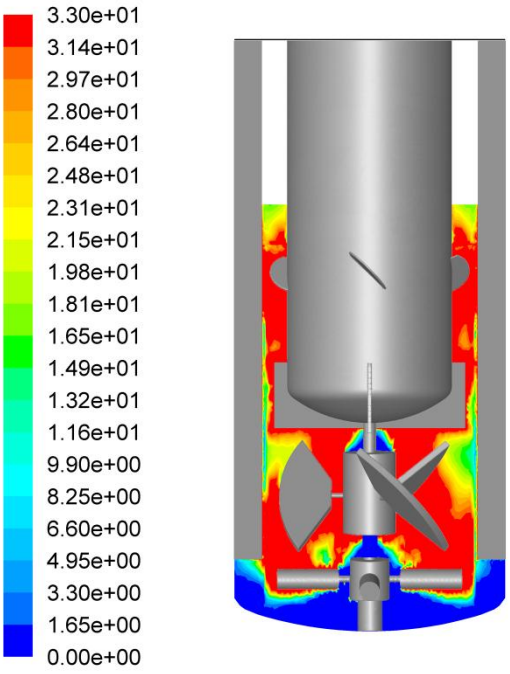

Figure 4. $k_L a$ mass transfer coefficient [1/h] calculated for the Geometry III, a hybrid model with axial and radial blades [15].

This modifications proposed could help expand the use of spin filter devices on a large scale applications. As a result these experiments, a new question has been reached: What degree of approximation would be expected by CFD based on reality of industrial processes that takes into account biological complexity and rheological changes especially if extracellular products are formed?. It is logical to affirm that $k_L a$ moves away from reality at real industrial conditions. By the way all these aspects must be specified at the moment of making a decision by setting up a validation method.

D. Biochemical Reactions

CFD would be a potential tool for modeling of biochemical reactions interact in biological systems. One example is presented by Mousave, et. al., [5] who simulated the kinetic model of ferrous biooxidation proposed by Nemati and Webb [16]. They found a considerable level of dependence of ferrous biooxidation reaction on interfacial mass transfer using an airlift bioreactor fermented with *Acidithiobacillus ferrooxidans*. Mousave, et. al. [4] applied Eulerian approach. As mentioned before, this approach has great limitations to describe real behavior not only on mass transfer but also on the spatial cell dynamics. That is why the main point are cells and interfacial mass transfer and not fluid as a whole that moves continuously.

To consider the physiological and biochemical effect in microorganisms, it is necessary to develop an approximation model that takes into account a dispersed phase where it is possible to detail the microorganism behavior. In some cases hybrid systems have been developed between multizone models and CFD simulations [17], such is the case of the research work of Bezzo [14] who applied this strategy to the production of xanthan gum in stirred tanks and combined a Eulerian approximation with a multizone model. T [15]he reactor was divided into a limited number of spatial regions, assumed as a complete and homogeneous mixture. A population balance combined with an unstructured substrate kinetic model and xanthan gum production was also proposed. The latter has a limitations since it disregards extracellular gradients, assuming a homogeneous mixing degree that really changes with the scale and geometry of the system. Recently, Lapin et al. [18] applied a combination between The Eulerian method and a Lagrangian method using segregated mathematical models. They studied the extracellular environment variation and microbial biophase metabolism with a turbulence model Chen-Kim k-ε [19-21]. They simulated the influence of extracellular glucose gradients on the intracellular changes of intermediate metabolites such as Fosfoenol pyruvate and pyruvate in E. coli bacteria. Lapin et al. [18] used kinetic parameters determined by other authors [22] to run their simulations. Therefore he obtained only indirect approximations of experimental results. However, lapin et al. [18] has developed the first research work in bioprocess engineering where physiological state of bacteria depending on extracellular gradients in a bioreactor was predicted using CFD.

Computational fluid dynamics also has some important aspects to improve. The main disadvantages associated with the use of CFD would be: (I). Errors by the calculation method; it is required to temporally and spatially model all the biochemical behavior of the microorganism of interest, which means to study the kinetic behavior considering three dimensions of both biomass and substrate, as well as final product. (II). Also, determine models to predict the heat generated by the fermentation process, models that take into account the effects of substrate inhibition, models that take into account spatial and temporal fermentation rheology, morphology, etc.; It takes experience and good criteria to build a good model, that's why, there is no turbulence model generally accepted as the best for all kinds of problems. The choice of turbulence model will depend on aspects such as the computational resources available, the amount of time available to simulate, the level of detail to be achieved, etc; it is indispensable to have a versatile computer; Some simulations (especially if simulated in transient) can last for weeks or even months [2].

E. Non-Newtonian Applications

There are several related works stirred tank reactors in gas-liquid phase using CFD forr Newtonian fluids, while references for non-Newtonian fluids are scarce.

CFD is an effective tool for researching fluid flow mixing because it is possible to obtain detailed hydrodynamics results that can hardly be analyzed by experimental evidence [15].

Currently several studies have been conducted regarding the analysis of non-Newtonian fluids hydrodynamics with Helical ribbon impeller applied for fungi cultures (Fig. 5 [27]).

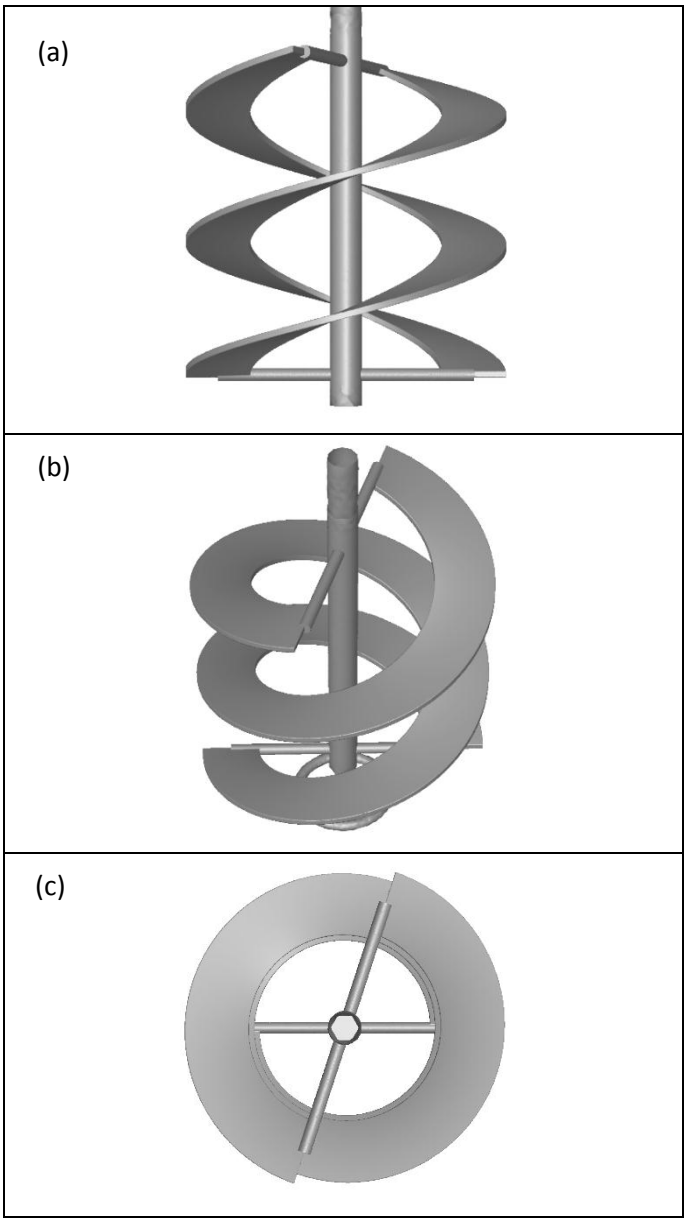

Figure 5. Helical Impeller. (a) Front View. (b) Diagonal View. (c) Cross section [27].

According to the information reported high axial upward pumping velocities adversely affect the air dispersion, and may induce an increase in bubble coalescence, generating heterogeneous zones in the bioreactor, characterized by inability to transport air to the walls of the bioreactor.

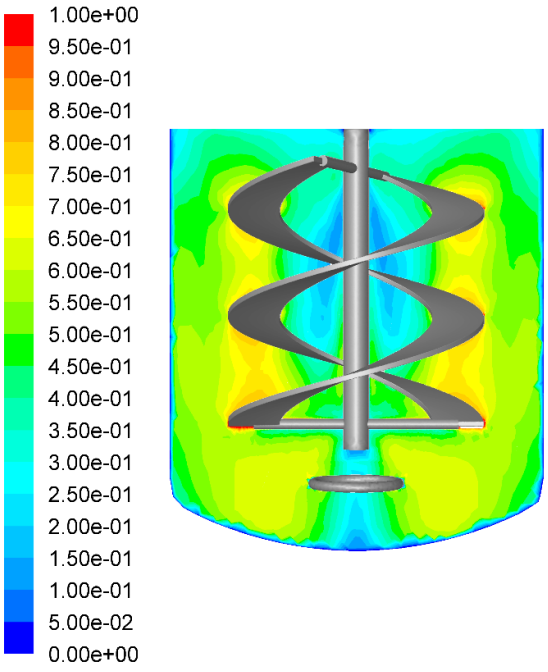

Figure 6. Velocity Magnitude contours v/vt_{ip} [-]. Helical Ribbon. N_i: 200 rpm [27].

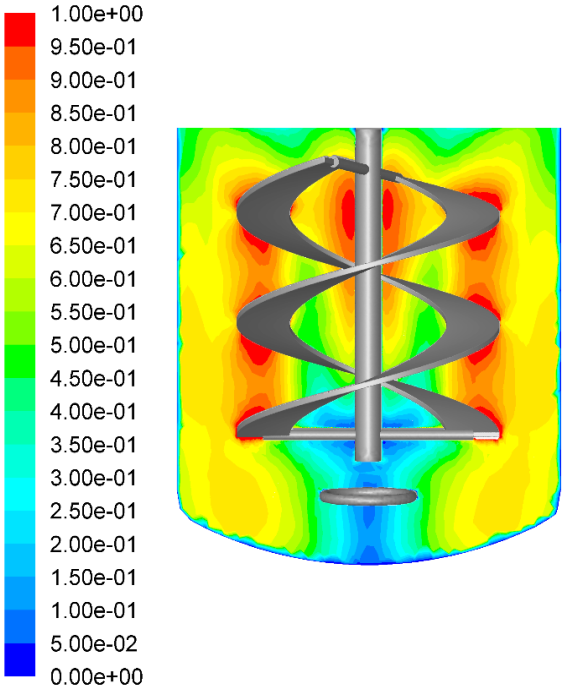

Figure. 7. Velocity Magnitude contours v/vt_{ip} [-]. Helical Ribbon. N_i: 400 rpm [27].

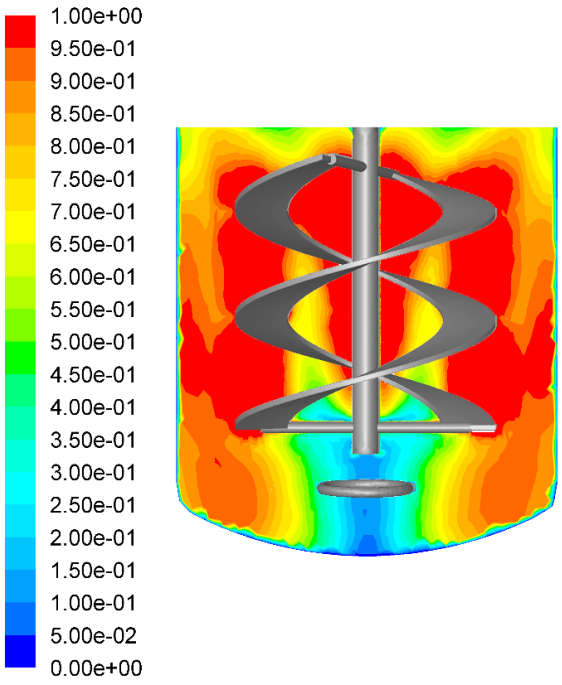

Figure. 8. Velocity Magnitude contours v/vt_{ip} [-]. Helical Ribbon. N_i: 600 rpm [27].

Advantages by using CFD Methods

Based on recent advances, it would be possible by CFD, to predict spatial and temporal microbial growth in a bioprocess where solid particles can interfere with actual measurement.

Also optimized substrate feeding point that assure a fast and efficient homogenization could be determined by CFD, as well as the design of a specific point for microbial culture aeration.

Structured models are another challenge that is hidden in the complex biochemical networks, since concentration of an enzyme or any other biological molecule could be studied in terms of increasing global productivity. Scale Up of viral particles (antiviral vaccines) is another one of the phenomenological little studied applications that could be directed to the study using CFD. So it would be very promising to determine how infection is affected in spatial and temporal terms (growth within a living cell) as the production efficiency of these particles, when they leave a living system (cell lysis), so that a greater number of viral particles a better lysis efficiency would be expected.

Continuous advances in computational machines will bring a huge change in bioreactor design and optimization bioprocesses, which will increasingly attract the use of this potential tool by scientific researchers. All of these developments will make the CFD a very powerful engineering tool that will result, increasingly, in the adoption of the use of CFD in bioprocess engineering [23].

CONCLUSIONS

This paper is based on an analytical and critical point of view related to the applications of fluid dynamics as a great challenge and a computational tool in bioprocess engineering. CFD should be a very versatile tool to predict fermentative processes, as well as helpful software to design agitation systems. In recent years there has been considerable growth in the development and application of CFD such important stages in the bioprocess engineering as sterilization, mixing, mass transfer and biochemical reactions. However, to further strengthen this broad spectrum of fluid dynamics and support the understanding of the biological system, new research is needed that concentrates biology and engineering in order to develop, through interdisciplinary knowledge, skills in the biological, chemical and computational sciences.

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