CFD Approach for Non-Ideally Mixed Bioreactor Modeling

L.W.T. Emily, P. Kumar and Y. Samyudia

Department of Chemical Engineering, School of Engineering & Science, Curtin University of Technology, CDT 250, 98009 Miri, Sarawak, Malaysia
emily.liew@curtin.edu.my; p.kumar@curtin.edu.my; yudi.samyudia@curtin.edu.my

Abstract **-** In this paper, we address the progress, challenges and prospect of modeling mixing in bioreactor by the utilization of Computational Fluid Dynamics (CFD). Efficient operation of bioreactor is essential in the biotechnological process, not only to ensure good yield but also to maintain consistent product quality. Process modeling technique has frequently been adopted in the bioreactor design, optimization and control as well as in scale-up process. One of the critical issues in bioreactor modeling is the need to overcome the mass and heat transfer limitations imposed on the bioreactor performance, particularly the close interaction between fluid flow and the biological reactions. CFD can be applied to overcome this obstacles by integrating the flow rates between adjacent zones, and fluid mechanical quantities, as the integration of mixing phenomena into the bioreactor modeling is considered a vital aspect in the efficient design and scale-up of bioreactor system.

Keywords: bioreactor; CFD; mixing

I. INTRODUCTION

Bioreactor has been recognized as the heart of biotechnological processes which provides the central link between the raw materials and patterns [1]. It is widely used in industrial applications for mixing and blending of viscous fluids for reaction [2]. The optimal design and operation of the bioreactor dominates the overall performance of the process [3]. Agitation produced by the rotating impeller is used for mixing of reactants, dispersion of gases or solids in liquids, distribution of energy uniformly and others. The present incomplete knowledge of hydrodynamics in a stirred tank has lead to inefficient design and optimization. Experimental studies provide empirical input to the predictive models or as validation benchmarks for simulation purposes. Most experimental studies are limited to laboratory scale mixing tanks driven by a single rotating impeller. Thus, experimental data is not sufficient for design and a computational tool is required [3].

Generally, the operation of a bioreactor is multi-scaled, whereby cellular level consists of numerous biochemical reactions catalyzed by thousands of enzymes [4]. Due to multiple steady states as a result of rapidly changing environment during the bioreactor operation, sluggish output response will be observed. Thus, it is important to have efficient operation of bioreactor to ensure good yield and to maintain consistent product quality. One of the ways to maintain product quality consistency is to ensure optimal conditions of temperature, pH, dissolved oxygen (DO) and biomass concentration to be maintained throughout the fermentation process by engaging good mixing mechanism in the bioreactor [5]. Good mixing will maintain the homogeneity of the fermentation medium throughout the fermentation process, i.e. to avoid dead zones and to overcome transport phenomena limitations. But it is of interest to note that the maintenance of good mixing is not easy to achieve, as there are certain constraints required to be taken into account, e.g. mixing of medium under high stirrer speed might cause cell damages [6] but high stirrer speed will increase mass transfer in cell cultures, supplying nutrients and oxygen to the living cells, which will eventually increase the yield and productivity of desired products [6;7]. Thus, it is of interest to investigate the hydrodynamic behavior of the cells in the bioreactor throughout the fermentation process. In order to study the hydrodynamic behavior of the cells, Computational Fluid Dynamics (CFD) could be used as tool to perform reliable 3D simulations, even for a difficult system as a stirred vessel [8]. Current methods for the improvement of multiphase bioreactors are based on empirical correlations for overall quantities, such as power consumption and mixing times [8]. Thus, a thorough understanding of fluid flow in the bioreactor is crucial before the involvement of the multiphase, multi-species, heat transfer equation and the effect of non-Newtonian fluids.

The objective of the present work is to describe the progress and challenges in CFD modeling of bioreactor. In addition, this paper highlights some of the research gaps in the current modeling approaches of mixing in bioreactor.

II. OBJECTIVES

The aims of this paper are:-
  (a) To study CFD approaches for the improvement of ethanol production through mixing mechanism in bioreactor
  (b) To review the prospects of CFD in modeling mixing mechanisms in bioreactor
  (c) To explore the key challenges and gaps in CFD modeling of mixing in bioreactor

III. CFD PROGRESS

CFD has proven to be useful in engineering fluid flow systems [9] which have been used for modeling mixing problems in recent years [10]. It is a useful tool that has become well-liked in the study of industrial fluid flow processes recently, which involves the usage of high-speed digital computer [2]. CFD codes normally facilitate the visualization of flow phenomena which is beneficial when it is impractical to position probes within the fluid domains for the measurement of parameters such as pressure and velocity [5].

A.   PREVIOUS WORK

Most of the previous works done on stirred vessels are based on steady-state analyses [11;12]. The rotating impeller is treated as a black box whereby impeller boundary conditions are required as input which needed to be determined experimentally. This application has limitations even though it is useful in predicting flow characteristics in the bulk vessel. The limitations are due to the following reasons [12]:

(a) Limitation in data availability.

(b) Could not be used to screen large number of alternative mixer configurations.

(c) Extension studies to multi-phase flow in stirred vessel are not feasible because it is impossible to obtain accurate boundary conditions at the impeller for multiphase flow from experiments.

(d) Could not capture the details of the flow between impeller blades.

Thus, in order to eliminate the above limitations, several attempts have been made to simulate flow within and outside the impeller region with the combination of moving and deforming or sliding mesh [12;13;14;15;16]. Iterative methods known as inner-outer method using rotating coordinate system have also been used [13;17]. The impeller blades are modeled as solid walls, and the flow within the impeller blades is solved using the usual transport equations. This approach showed promising results in order to view the flow characteristics in the region between the impeller blades. But at present, these methods could not be utilized due to the following considerations:

(a) The computational requirements are greater than steady-state simulations since these methods rely on solution of full time-varying flow in stirred vessels.

(b) There are restrictions on number of computational cells due to excessive computational requirements.

(c) The results obtained through these methods are yet to be sufficiently validated. Rigorous under prediction of turbulence characteristics in simulations of flow generated by a Rushton turbine was obtained using sliding mesh solution [12;13].

None of the studies have reported a qualitative comparison of the predicted flow characteristics within the impeller. It would be useful to develop an approach, which can simulate the flow generated by an impeller of any shape with as much computational requirements as that of steady-state simulations using the black-box approach, which could be utilized as a design tool for screening different alternative mixer configurations.

B.   CURRENT WORK

So far the CFD approach has been utilized to simulate single-phase and multiphase flow within relatively simple geometries and for comparison with experimental data [18;19;20;21]. Current work in modeling non-ideal mixing bioreactors is looking into the significant details of the flow within and outside the impeller which affects the hydrodynamic behavior and overall bioreactor performance [12]. Several procedures and methods are suggested by researchers to study the hydrodynamic behavior in detail.

BI.   Steady and Unsteady Computation of Impeller-Stirred Reactors

The present work in CFD approach for bioreactor simulation presents a multi-block grid-generation procedure which is applicable to general impeller-stirred tank geometry [2]. This enables users to specify various grid densities, tank and impeller dimensions, impeller type, baffles dimensions and most of any other aspects of the problem. The impellers are modeled completely, and thus no experimental measurements are required. Flows were assumed to be laminar for simplification purpose.

Two different solution methods are presented to solve the viscous flow in impeller-stirred tanks, i.e. approximate steady – state procedure and unsteady moving grid technique [2]. The approximate steady-state procedure is utilized for computation of flow generated by a rotating Rushton disk turbine at various Reynolds numbers in laminar regime. This procedure is an attractive alternative for low Reynolds number flows in tanks. Besides, this method is also beneficial for computing unsteady performances, as it is advantageous to obtain an estimated initial condition beforehand, whereby this could reduce computational cost. Thus, the parametric studies of low Reynolds number flows in impeller-stirred tanks can be performed efficiently by utilizing the approximate steady-state solution procedure. On the other hand, for high Reynolds number turbulent flows, unsteady computations might be involved to obtain realistic results by averaging solutions appropriately at a number of impeller positions relative to baffles instead of a single impeller position.

BII.   General Hybrid Multizonal Approach

Multizonal or multicompartment models have been utilized in bioreactor modeling [22] to describe mixing and other fluid-flow properties as well as complex bioreactions. The non-ideal mixing behavior in a bioreactor is represented by a multizone, which divides the equipment volume into a network of interconnected zones, whereby each zone is assumed to be ideally mixed [22]. A general structure for multizonal/CFD modeling has been proposed recently, as illustrated in Fig. 1.
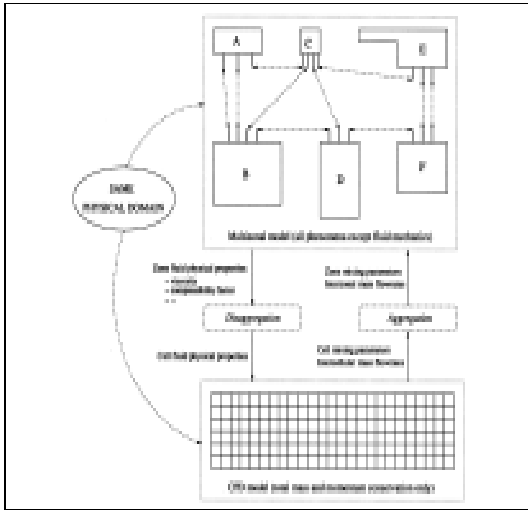
Figure 1. Architecture of the general multizonal/CFD model [22;23]

Based on Fig. 1, the spatial main interest is divided into a number of zones, which represents spatial regions in the bioreactor. Each single zone is considered to be well-mixed, whereby two zones can interact with each other via an interface that connects a port. The flow of material and energy across each interface is considered to be bidirectional. A set of differential and algebraic equations or a set of integro-partial equations in time is used to describe the transient behavior of a generic zone. The multizonal model utilizes a detailed transient modeling of all relevant physical phenomena, with the exception of fluid-flow. The dynamic behavior of the system of interest could then be determined, with the provision of the mass flowrate for each interzonal interface. Additional fluid mechanical properties such as turbulent energy dissipation rate might be required in some cases, depending on the phenomena engaged in the system of interest. Fluid-flow prediction is solely being focused by dividing the space into a relatively large number of cells and solving total mass and momentum conservation equations only. Thus, intensive properties such as composition, temperature are ignored. Based on this ignorance, fluid-flow phenomena operate on a shorter time scale than other phenomena. In order for the CFD model to be solved, the model requires information throughout the physical domain of interest such as viscosity, density, compressibility factor and coefficients for models of non-Newtonian fluids. The multizonal/CFD modeling approach opens new doors in equipment design, such as impeller design as well as process operation and control [22].

BIII. Computational Snapshot Approach

Computational snapshot approach has been proposed in order to simulate flow generated by a pitched blade turbine [11]. This approach is applicable to any impeller shapes, which is mainly governed by pressure and centrifugal forces generated due to the impeller rotation and corresponding rotating flows. The direction and characteristics of the impeller discharge stream via generated pressure forces as well as flow obstruction were mainly controlled by the impeller shape. On the other hand, impeller rotation speed controls the magnitude of centrifugal forces. Blade rotation generates pressure forces whereby these forces cause suction of fluid at the back side of the impeller blades and equivalent ejection of fluid from the front side of the blades. This phenomenon of ejection and suction is required to be modeled correctly to simulate the impeller rotation in the snapshot formulation. If these are modeled accurately, this will automatically lead to realistic rotational flow.

The blade is defined as a stationary solid, whereby a mass source is required to be defined for the cells adjacent to the front surface of the blade to simulate the displacement of fluid caused by the blade rotation. These mass sources were defined as shown below:

$$S_M = -\rho A_{bc} W_{bc} \tag{1}$$

where S_M is the mass sink; A_{bc} and W_{bc} are the computational cell surface area which is adjacent to the impeller blade and normal vector of the rotational velocity of the blade averaged for that computational cell surface.

On the other hand, the corresponding sink terms for the other variables, ϕ, for the computational cells adjacent to the back side of the impeller blades can be defined as

$$S_\phi = S_M \phi_c \tag{2}$$

where ϕ_c is the value of ϕ prevailing over the computational cell.

Considering the possibility of simulating flow within the impeller blades without excessive computations, it is worthwhile to explore the potential of this approach. Boundary conditions at the impeller swept surfaces are not necessary. The geometry and rotational speed of the impeller are required to be specified. The simulated results will be compared with experimental data for the results to be validated [11].

C. MODELING

CFD modeling is one of the most effective methods utilized in characterizing flow fields, provided that the models are corroborated by experimental velocimetry methods, such as laser Doppler anemometry (LDA) and particle-image velocimetry (PIV) [5]. These methods are too time consuming to distinguish the complete 3D fluid flow within a typical bioreactor even though these methods are dependable. Thus, much effort has been conducted in modeling stirred tanks in the last few years. The most common approach is to provide theoretical or analytical expression for the time-averaged velocity field in the immediate area of the rotating impeller and the data is used as boundary conditions for simulation purposes [2]. Mixing models are generally based on the concepts of macro-mixing, characterized by the residence time distribution, as well as micro-mixing, which is characterized by the degree of segregation intermediate between the state of complete segregation and maximum mixedness [24].

C.I. k-ε Turbulence Model

In the CFD study of bioreactor, the k- ε turbulence model is usually used in order to describe the mixing behavior and to compute turbulence in the bioreactor. Standard k- ε turbulence model is used since it is proven to be most successful in past works [3]. This model is most commonly used due to its universality as compared to other models, e.g. Reynolds-Stress Models, Large-Eddy-Simulations and Probability-Density-Function Models [9]. It is necessary for the specification of the turbulence energy distribution and the turbulence dissipation, ε, at the inflow boundary. In the case of the absence of such data, reasonable values can be used as a substitution by utilizing estimates of the local relative turbulence intensity $Tu = u'/u$, with u denoting the mean velocity and u', the velocity fluctuation [9]. An expression relating k, $ε$ and the length scale could be obtained by the equation $I = C_\mu^{3/4} k^{3/2} / \varepsilon$, where $C_\mu = 0.09$ denoted an empiric coefficient [25]. The turbulence intensity can be estimated for the flow in a tube. The energy dissipation can be expressed by

$$\varepsilon = (\Delta p F u)/m = (\Delta p u)/(x\rho) \qquad (3)$$

where Δp denotes the pressure drop, m the mass, F the tube cross-section and x the axial coordinate.

The fluid flow equations to be solved for a constant density fluid are as shown below [9]

$$div(\rho u) = 0 \text{ (Continuity Equation)} \qquad (4)$$

$$div(\rho u k) = div(\frac{\mu_{eff}}{\sigma_k} grad\_k)$$
$$+ G - \rho\varepsilon \text{ (Transport Equation 1)} \qquad (5)$$

$$div(\rho u \varepsilon) = div(\frac{\mu_{eff}}{\sigma_\varepsilon} grad\_\varepsilon)$$
$$+ (C_1 G - C_2 \rho\varepsilon)\frac{\varepsilon}{k} \text{ (Transport Equation 2)} \qquad (6)$$

$$u_T = C_\mu \rho \frac{k^2}{\varepsilon} \text{ (Eddy Viscosity)} \qquad (7)$$

whereby G is the dissipation function $\tau_{ij}\tau_{ij}/(2\mu_{eff})$; $C_\mu = 0.09$; $C_1 = 1.44$; $C_2 = 1.92$; $\sigma_k = 1.0$; $\sigma_\varepsilon = 1.3$.

The above equations are to be solved using the Finite Volume Method implemented in CFD code – Fluent. 3D steady-state simulations are to be carried out using segregated solver with absolute velocity formulation. The PRESTO algorithm is selected for pressure discretization whereas the SIMPLE algorithm is chosen to couple the continuity and Navier-Strokes equation. Second order upwind scheme was used to discretization of convective terms. Boundary conditions for the overlapping surfaces of inner and outer zones are defined either as pressure inlet or as pressure outlet. Periodic condition is imposed on the inner and the outer zones, which are 60° and 90° respectively [9].

C.II. Population Balance Equations (PBEs)

Fluid-particle systems could be modeled in terms of population balance equations (PBEs) due to its particle-size distribution dynamics [8]. The developed model predicts local gas fraction and bubble-size distributions for turbulent gas dispersion in a stirred vessel, with relations taken from literature for bubble coalescence and breakup derived from isotropic turbulence theory. Gas bubbles are assumed not to be significantly altering the flow field. The flow field in gassed conditions could be obtained by the scaling of the single-phase flow field with the only drop in power consumption as a parameter, provided that the flow field is in single phase. This is known as 1.5-way coupling, whereby it limits the application of this model to low gas loadings (0-5%), but it offers a more accurate method for mass-transfer rates predictions [8].

Generally, the PBE is a balance equation of the number density probability of some particle property. The particle property, x is the number density probability of particles with bubble size, d. The particle age could also be regarded as a modeled property to determine the residence time distribution.

The general form of PBE is shown below [8;26]:

$$\frac{\partial n(x,r,t)}{\partial t} + \nabla_x.\bar{x}n(x,r,t) + \nabla_r.v_p n(x,r,t)$$
$$= B(x,r,Y,t) - D(x,r,Y,t) \qquad (8)$$

where $n(x,r,t)$ is the number density probability of the property under consideration as function of the property vector, x, the physical position of the particle, r and the time t. $\bar{x}$ is the growth rate of the particle due to processes other than the interaction with other particles, and v_p is the velocity of the particle. The continuous phase variables which may affect the particle property are represented by the vector $Y(r,t)$. On the other hand, $B(x,r,Y,t)$ represents the rate of production (birth) and $D(x,r,Y,t)$, the rate of destruction (death) of particles of a particular state (x,r) at time t.

The main advantage of using PBEs is that bubble-bubble interactions are explicitly taken into account. Thus, research on mass transfer in dispersed flows can be carried out more accurately than with models with only one bubble size [8].

IV. PRELIMINARY SIMULATIONS

Preliminary CFD simulations have been conducted in order to predict and analyze flow and mixing in a stirred vessel. The bioreactor is represented by a mesh which

explicitly includes the impeller geometry, with impeller motion treated by multiple frames of reference or sliding mesh methods, whereby this method is to be applied to bioreactor tank stirred by a Rushton turbine [27]. Simulation results are compared with experimental measurements for further modeling work. The overall performance of a stirred vessel depends on three key parameters, vessel scale, impeller shape as well as dimensions and volumetric gas flowrate [28;29]. These parameters affect the gas flow regimes and mixing characteristics in the vessel. The swirling motion of fluid on the impeller boundary was assumed to be solid body rotation. Proper assumptions concerning the impeller boundary are required, thus different results are expected to be produced depending on the impeller boundary set [30].

A case study of standard Rushton turbine have been carried out for a 1.5L of water and air mixture at aeration rate of 1.5LPM and stirrer speed of 250rpm, to examine the flow pattern generated by this impeller in a 2L size bioreactor. The air speed was set at 5m/s. The tank dimensions were set according to the original tank laboratory scale dimensions, which is 12.8cm in diameter and 24cm in height. The flow generated by the standard six bladed Rushton turbine impeller, which has a diameter of 3cm, was located halfway between the liquid surface and the vessel base. The impeller blades were defined as stationary solids. The momentum transport equations in cylindrical coordinates were solved along with the standard k- ε model of turbulence using a CFD code FLUENT version 6.3.26.

Figure 2. Experimental Flow Pattern Observed in Laboratory Scale
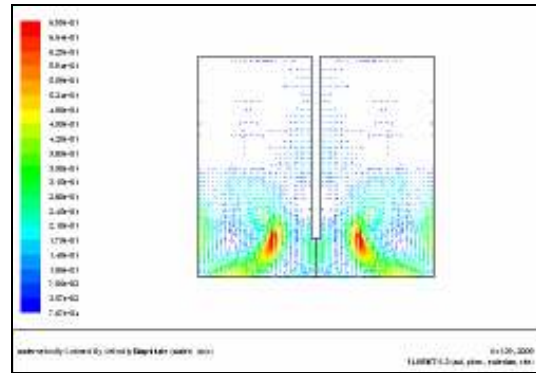
A.   RESULTS AND DISCUSSION

Figure 3. Velocity Vector of Water

In this section, results are presented for the simulation of water and air, in terms of velocity vector and magnitude. In figure 3, the maximum velocity of water computed was 0.699m/s. The water flows upwards and downwards repeatedly and forms a circular flow pattern throughout the stirred vessel. As observed, the water flow concentrated at the sides of the impeller blades, whereby the water velocity was highest at the impeller blades surrounding regions.

On the other hand, figure 4 showed the potential strength of CFD in general, whereby the internal distribution of water inside a stirred vessel could be calculated, thus the model is capable of predicting the essential features of this particular flow regime: high velocity beneath the impeller; concentration of water in the upper part of the stirred vessel; and the accumulation of water at the middle and lower part of the vessel near the vessel wall [8].

As of air, figure 5 showed the velocity vector of air, whereby the flow pattern is quite similar compared to the flow pattern of water. The flow pattern is also in a circular form, whereby the maximum air speed computed was 0.699m/s. Figure 6 showed the contours of velocity magnitude of air, which is quite similar as the contour of velocity magnitude of water as demonstrated in figure 4.
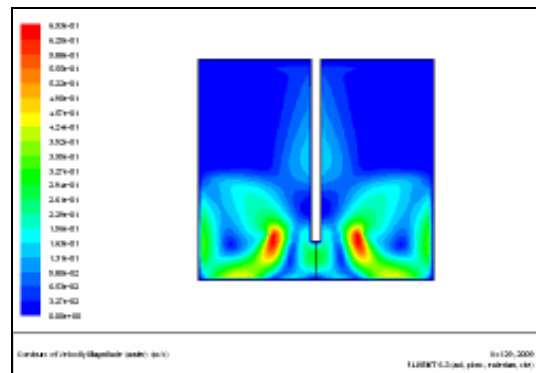

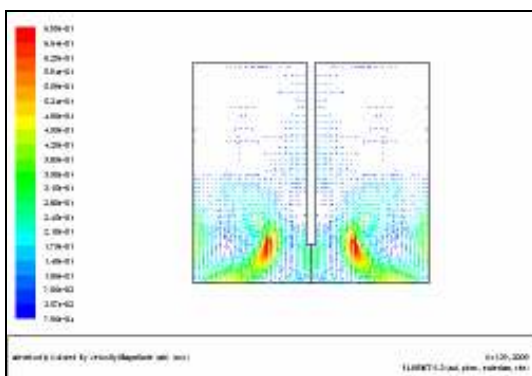Figure 4. Contours of Velocity Magnitude of Water
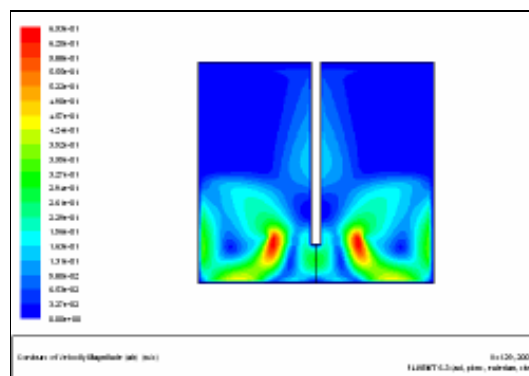
Figure 5. Velocity Vector of Air

Figure 6. Contours of Velocity Magnitude of Air

As a whole, both water and air showed similar flow patterns despite having differences in their respective phases. These results showed that both phases have mixing effects within a stirred vessel embedded with impeller, as both phases showed similar flow patterns. These flow patterns were compared with flow pattern obtained during experiment (Figure 2) for validation, whereby the simulated results were quite comparable with the flow pattern attained during experiment. Thus, CFD approach for non-ideally mixed bioreactor is possible to be done, as long as the flow pattern obtained from both CFD simulation and experiments are comparable within each other. Future work will be done by implementing non-ideal mixing model in CFD simulation by including certain variables which affect the mixing mechanisms, e.g. stirrer speed and aeration rates into the non-ideal mixing model since most of the simulations done by assuming ideal mixing conditions.

V. CHALLENGES

One of the key challenges faced in process modeling today is the need to express in a quantitative manner the interaction between mixing, fluid flow and other phenomena, e.g. chemical reaction, homogeneous and heterogeneous mass transfer and phase equilibrium [22]. These interactions are important, especially for complex operations such as polymerization, crystallization and biological processes, in order to determine the quality of the product, for instance crystal sizes and shapes. Precise modeling of such processes is vital during the design stage (equipment design and scale-up without the need of extensive pilot-plant studies) and during the operational stage, e.g. derivation of optimal control strategies.

Lack of suitable models and the complexity of the bioreactor is one of the obstructions in simulations [31]. The operation of complex processes such as mixing complicates the structure of the metabolism and the mechanisms of its regulation, which are still not fully understood at the moment. Due to the overlap of the main liquid flow by turbulence fluctuations, the exact description of the fluid movement by a simple model is not possible. The situation is more complicated by the presence of two or more phases. The accurate description of the biological, chemical

and physical processes as well as their interaction in the bioreactor are thus possible and therefore abstraction is necessary.

On the other hand, many of the CFD studies for bioreactor have been reduced to a 2D flow due to the excessive computational cost of 3D calculations. The operations of complex processes require massive computational time, e.g. population balance over the possible range of cell sizes in terms of tens or hundreds of scalar quantities. Thus, it is a challenge to discover a way to solve this problem in order to lessen the computational burden [22].

Most of the mixing models used by CFD were assumed to be well-mixed and limited to simple geometries. In reality, it is difficult to maintain well-mixed condition in the bioreactor, as there are various hydrodynamic behaviors and mass transfer operations taken into account during the fermentation process. It is impossible to include all inputs in the rate expression as well as the stoichiometry of the postulated single reaction, which will change with the reaction environment in most cases. Therefore, it is interesting to come up with a non-ideally mixed bioreactor model which could be used for various geometries, such as 3D flow variations [22].

VI. PROSPECTS AND FUTURE STUDIES

Future work could involve by utilizing the approximate steady-state solution procedure, focusing on how changes in geometry affect certain tank characteristics, e.g. flow pattern, power requirements and impeller pumping capacity [2]. Further studies could be made for the hybrid multizonal/CFD approach to derive better strategies for varying agitation speed over the batch duration instead of relying on simplistic control policies [22].

The snapshot approach would be useful for optimization and scale-up of stirred vessels [12]. The optimization of the performance of the existing vessel requires screening of various mixing configurations. This would allow engineers to spend more time on evolving creative and innovative mixer configurations rather than validating and screening the established configurations [12].

The mixing problem is of great complexity. It would be a wonderful research proposal to devise an experimental investigation of the mixing pattern and to simulate the mixing/diffusion/reaction problem using CFD software and a model with proper realistic assumptions.

VII. CONCLUSION

CFD modeling provides a powerful means for enabling the full characterization of 3D flow fields in bioreactors with simple and complex geometries, as well as to allow prediction and possible design optimization, flow, nutritional and metabolic requirements of cells, without having to perform numerous and expensive bioreactor experiments, potentially saving time and resources. Experimental and computational simulations will complement with each other and will therefore lead to improved bioreactor characteristics in the future.

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