REVIEW

Complex mathematical analysis of photobioreactor system

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Modeling as a tool solves extremely difficult tasks in life sciences. Recently, schemes of culturing of microalgae have received special attention because of its unique features and possible uses in many industrial applications for renewable energy production and high value products isolation. The goal of this review is to present the use of system analysis theory applied to microalgae culturing modeling and process development. The review mainly focuses on the modeling of the key steps of autotrophic growth under the integral biorefinery concept of the microalgae biomass. The system approach follows systematically a procedure showing the difficulties by modeling of sub-systems. The development of microalgae kinetics and computational fluid dynamics (CFD) studies were analyzed in details as sub-systems in advanced design of photobioreactor (PBR). This review logically follows the trends of the modeling procedure and clarifies how this approach may save time and money during the research efforts. The result of this work is a successful development of a complex PBR mathematical analysis in the frame of the integral biorefinery concept.

KEYWORDS

CO₂ sequestration, computational fluid dynamics, kinetic modeling, microalgae culturing, system analysis theory

1 | INTRODUCTION

The quantitative description of the bioreaction processes must first pass through their modeling and simulation. Nowadays, numerous knowledge database and modeling catalogs are available, on which the researcher may build his hypothesis and check it out with minimum active experiments. Having the knowledge about microalgae kinetics and microalgae physiology, the process engineer can build a complex model of the photobioreactor (PBR) and the cultivation under

autotrophic, mixotrophic or heterotrophic conditions in order to solve optimization and scale-up tasks.

During the modeling procedure, the researcher attempts to study and analyze the real complex situation, where many parallel processes (physical, chemical, biochemical, etc.) take place in the PBR vessels.

This modern mathematical approach makes it possible to distinguish between the microalgal and bacterial physiology and to evaluate them in a separate sub-system wherein the photosynthesis process depends on the hydrodynamics, mass and heat transfer under the given PBR geometry and scale. The understanding of this “photosynthesis sub-system” is crucial for comprehension and optimization of the overall process of biomass or metabolite production from microalgae under any engineering specification of unit operations and PBR design. The highly developed theory of

Abbreviations: CCM, carbon concentrating mechanism; CFD, computational fluid dynamics; FLE, flashing-light effect; FP-PBR, flat plate photobioreactor; HVP, High value products; IBC, integral biorefinery concept; MK, microalgae kinetics; PBR, photobioreactor; SGR, specific growth rate; UHDC, ultra-high-density cultures.

chemical engineering may model any sub-system such as hydrodynamics, mass and heat transfer in any innovative PBR design. Hence, we are going to present our system analysis approach and to point out how a “photosynthesis sub-system” can be modeled when light is the key state parameter in the complex PBR system including all above-mentioned sub-systems.

This usually requires simplification of the situation in an understandable physical, chemical, and biochemical analog. Hence, to solve successfully the task, the deterministic mathematical description must have physical sense through formulation using complex mathematical models. However, the application of modern and powerful tools is required to build a robust and working model. Nowadays, the application of the CFD along with the fundamental principles of mass and energy conservation allows the development of much more accurate models connected with the kinetics of “photosynthesis sub-system”. The authors have been working 30 years on the base of system analysis theory and the application of its principles in order to build a methodology for the development of working models of sophisticated systems. The theory was first published by the authors [1–3]. Our experience from Russia, Bulgaria, Brazil and the USA highlighted the milestones of the modeling procedure of biotechnological processes [4,5] as well as the wastewater treatment processes [6–13] purification of heavy metals [14], bioreactors [15–18], photobioreactors [19–22], microalgae growth kinetics [23–25], and bacterial growth kinetics [26]. As well as, different ethanol production processes were successfully modeled and analyzed in detail elsewhere [27–29]. The cited works on kinetic models’ development were extremely helpful for the creation of a multifunctional algae laboratory in West Parana State University-Toledo, Paraná, Brazil. The fundamentals of this laboratory relay on the integral biorefinery concept for complete utilization of the algae biomass with special emphasis on synthesis, isolation and identification of high value products. In this sense, any cultivation methodology was considered and implemented throughout the development procedure in the frame of the principles of the system analysis theory. This is the only fastest and robust way to save scientific efforts, time and money.

2 | SYSTEM ANALYSIS THEORY

2.1 | Model development procedure based on the principles of system analysis theory

The main stages of the system analysis theory [1–3] were successfully applied to describe step by step the procedure of kinetic model development of algae growth and complex PBR model as a system [19]. The development of an integral

biorefinery concept based on “photosynthesis sub-system” requires considering how the principles of this theory can be applied to algal kinetic model development and furthering how this theory can be extended to the PBR system:

- (i) Determination of the modeling task, choice of the criterion of optimality;
- (ii) Analysis of the bioprocess – qualitative analysis of the structure of the bio-system, decomposition of the bio-system in sub-systems; building of the sub-systems’ models; parametric identification of the sub-systems models;
- (iii) Synthesis of the system–development of the sub-systems’ complex models and their relationships; simplification and combination of all the models into a complex bioprocess kinetic model; search for optimal working conditions of the bioprocess based on the model simulations; experimental verification of the developed simple and complex models;
- (iv) Solving the modeling task–determination of the optimal structure of the kinetic model based on chosen criterion of effectiveness; solving the bioprocess scale-up problems in the frame of the developed complex kinetic model.

The applications of the principles of system analysis theory to PBR design and scale-up was analyzed and discussed in detail in our research review article published elsewhere [19].

The goal of this review was mainly to focus on key parameters of kinetics studies which were linked with hydrodynamics and directly reflect in the microalgae productivity of biomass and, consequently, in the desired metabolites with high value products. The global scheme from the work [19] can be simplified and will highlight our strategy (see Figure 1).

The topics discussed in this review follow the logic of the scheme presented in Figure 1, wherein the stepwise modeling procedure for each sub-system uses the principles of the system analysis theory.

3 | MODELING ALGAE KINETICS

The use of mathematical models capable to describe the influence of the key operational parameters (e.g., temperature, pH, light intensity and distribution, CO₂ availability, culture medium composition) on the microalgae growth and/or components accumulation is a fundamental and helpful tool to understand the phenomena as well as to describe and predict the growth behavior. The system involves interconnected and multidisciplinary knowledge such as mass and heat transfer, kinetics, thermodynamics, amongst others. Therefore, given this complexity of the involved phenomena, not to mention the

FIGURE 1 Strategy to model a PBR system.

algae physiology, the design, optimization and scale-up of the photobioreactors still remain as one of the major drawbacks in the field. It has to be pointed out, that there is no single criterion, which is able robustly to predict and characterize the microalgae process and PBR performance. It means that any modeling of kinetics, including key state parameters and criterion such as surface-to-volume (S_f/V) ratio of PBRs, average light intensity (I_{av}), T, pH, light/dark cycles, CO_2 , O_2 concentration and their mass transfer, has to be analyzed as a part of a complex criterion which determines the objective function (OF) of the optimization procedure. Hence, an optimization procedure is applied to search for the best solutions for process development and PBRs scale-up maximizing the chosen OF. Further considerations will follow this statement and the understanding how to develop a complex model of the process/PBR capable to solve reliably scale-up tasks. The first key step in the microalgae process development is to build up a robust kinetic model of the microalgae growth.

Several mathematical models of microalgae growth in PBR have been proposed elsewhere. According to Bitog et al. [30], in order to achieve optimized conditions inside the PBR, the key factors that influence the microalgae growth (light intensity and distribution, gas injection and mixing, hydrodynamics/flow pattern) and their interdependence, must be comprehensively understood for the PBR design and scale-up.

3.1 | Criterion of cultural medium optimization

The development and optimization of a suitable culture medium for a specific microalgae species may particularly impact on the cost-effectiveness of the process [20]. Since the use of low-cost highly available nutrient sources (e.g., seawater, freshwater and wastewater, cheap nutrients and fertilizers coupled with the use of flue gas) strongly impacts on the feasibility of the culture medium, the composition of such complex sources may complicate the optimization of the culture medium.

In this sense, the medium optimization for algae culturing is a key point in overall process development. Macro- and micro-elements such as carbon, phosphorus, nitrogen, sulfur etc. are necessary for the cell in order to compose the biomass

structure [31], therefore their contents must be accordingly addressed in the culturing systems.

Traditionally, the optimization of culture medium for biomass growth and/or components accumulation (i.e. lipids, high value products etc.) is performed by using statistical experimental design methods or even trial and error procedures [32–34]. However, such procedures may be inadequate, especially for non-laboratory scale.

In this work, we have developed a robust and reliable algorithm for medium optimization. The common scheme can be presented as follows (see Figure 2). Such approach was based on the elemental composition of the algae cells and calculations by linear programming approach [21]. By using such approach, if used techno-economical criterion, not only the optimal culture medium can be obtained for the maximization of the algae biomass growth, but the desired product accumulation in the cell (e.g., lipids, carbohydrates, etc.) for the given/desired costs of the medium.

The necessity to develop such approach aroused from the technical-economic considerations of any technology. The CO_2 as a substrate represents a considerable amount of operational costs in mass production of algae. Before going any further we have to discuss some details about the optimization procedure which is in fact conditional optimization with constraints. The objective function (criterion) includes many technological and economic criteria where minimization of overall costs under given biomass/desired metabolite productivity must be the target. Hence, the minimization of these costs is crucial for its market competitiveness. Therefore, the best cost-effective choice is to use waste gases from industry as represented in Figure 2, and to build the algae plant near the source of waste gas in order to minimize the transportation costs, as well.

It must be evidenced, that for an economic feasible process, the use of wastewaters as well as flue gas for the microalgae cultivation was extensively reported [35–38]. Despite the economic advantages, the use of such nutrient sources may prejudice the microalgae growth depending on the toxic species (e.g., NO_x , SO_x , C_xH_y , CO, particulate matter, common halogens and heavy metals) and its concentration levels due to the inhibition caused by the presence of contaminants.

FIGURE 2 Common scheme of the complex theoretical approach for medium optimization of culturing microalgae on flue gas. (Adapted from Kroumov et al. [21]).

In this way, the comprehensive knowledge about the optimal culture medium composition and its dynamics, due to the use of flue gas and/or wastewaters streams in the microalgae cultivation system, is a preponderant factor in the closed PBR algae cultivation systems. Details about the use of linear programming procedure for medium optimization were discussed previously [21,23,24] and helped us in further studies [39].

3.2 | Modeling macro-nutrients dissociation–gas-liquid interface equilibrium

One of the key steps of process development is to model the algae kinetics when used waste gases. A complex approach taking into account macro-nutrients present in the liquid phase and their dissociations was presented in detail elsewhere [40]. It is worthy to mention the authors' complex approach because its robustness, which can be successfully used for process scale-up. The key macro-nutrients were targeted and their dissociation and total concentration in the liquid phase are presented in Table 1, as adapted from [40].

It must be evidenced that, by using flue gas, the speciation of nitrogen and sulfur oxides (e.g., SO_2 , NO , NO_2) cannot be neglected due to their high concentration levels. Also, depending on the water source employed for the microalgae cultivation (e.g., seawater, freshwater and wastewater, fertilizers) some of other species will be particularly relevant. Evidently, the species to be considered in the mathematical model and their consequent speciation will be strongly situational dependent.

In addition, the interaction between the different species may also take place (e.g., $Ca^{2+} + CO_3^{2-} \leftrightarrow CaCO_3$, the formation of recalcitrant calcium carbonate, associated to

the microalgae-induced calcification). Despite such phenomenon is still not completely understood, it is known that it might influence the microalgae growth providing, amongst other effects, protective shield against excessive light exposure, buffering behavior against pH rises in alkaline conditions, also changes in the carbon concentrating mechanism (CCM) [36].

The existence of ionic species as well as complexes formation as a function of the pH, element's concentration for multi-component systems can be predicted by specific software as discussed further (see Section 3.3.2).

In addition, the authors take into account the gas-liquid phase phenomena of mass transfer of CO_2 and O_2 in both phases, and the specific growth phase of algae was modeled as a function of pH and average photosynthetic light radiation I_{av} according to the works of authors [41,42]. Further, the authors built the kinetic model of *C. vulgaris* growth on 100% CO_2 concentration and by using mass balance equations of key components being able to evaluate such sophisticated system quantitatively. Especially complex in this work was the modeling of the pH for any given time as a function of ions concentrations. The algorithm involved electro-neutrality balance as well as the concentrations of cationic and anionic species in the equilibria. The main practical benefit from this work was that the system could be controlled by knowing the pH changes and its influence on microalgae growth, especially for high concentration levels of CO_2 . The theoretical achievements can be systematized in the frame of building hierarchic structure of process development and scale-up which confirmed the principles of system analysis theory.

The medium's pH and the microalgae growth, as well as its metabolism, exert a narrow mutual interdependence (as

TABLE 1 Overview of relevant species from flue gas chemical equilibria in solution and total concentration of dissolved nutrients in microalgae growth medium

$CO_{2(aq)} + H_2O \xrightleftharpoons{K_{c,1}} H_2CO_3$
$CO_{2(aq)} + OH^- \xrightleftharpoons{K_{c,2}} HCO_3^-$
$H_2CO_3 \xrightleftharpoons{K_{f,1}} HCO_3^- + H^+$
$HCO_3^- \xrightleftharpoons{K_{f,2}} CO_3^{2-} + H^+$
$[C_{T,l}] = [CO_{2(aq)}] + [H_2CO_3] + [HCO_3^-] + [CO_3^{2-}]$
$NO_{(aq)} + H_2O \xrightleftharpoons{K_{N,1}} HNO_2$
$2 NO_{2(aq)} + H_2O \xrightleftharpoons{K_{N,2}} HNO_2 + HNO_3$
$3 HNO_2 \xrightleftharpoons{K_{N,3}} HNO_3 + 2 NO_{(aq)} + H_2O$
$HNO_2 \xrightleftharpoons{K_{f,N1}} NO_2^- + H^+$
$HNO_3 \xrightleftharpoons{K_{f,N2}} NO_3^- + H^+$
$[N_{T,l}] = [NO_{(aq)}] + [NO_{2(aq)}] + [HNO_2] + [HNO_3] + [NO_2^-] + [NO_3^-]$
$SO_{2(aq)} + H_2O \xrightleftharpoons{K_{s,1}} H_2SO_3$
$H_2SO_3 + SO_2 \xrightleftharpoons{K_{s,2}} H_2SO_4$
$SO_{2(aq)} + OH^- \xrightleftharpoons{K_{i,2}} HSO_3^-$
$H_2SO_4 \xrightleftharpoons{K_{f,s1}} HSO_3^- + H^+$
$HSO_3^- \xrightleftharpoons{K_{f,s2}} SO_3^{2-} + H^+$
$[S_{T,l}] = [SO_{2(aq)}] + [H_2SO_3] + [H_2SO_4] + [HSO_3^-] + [SO_3^{2-}]$
$H_3PO_4 \xrightleftharpoons{K_{p,1}} H_2PO_4^- + H^+$
$H_2PO_4^- \xrightleftharpoons{K_{p,2}} HPO_4^{2-} + H^+$
$HPO_4^{2-} \xrightleftharpoons{K_{p,3}} PO_4^{3-} + H^+$
$[P_{T,l}] = [H_3PO_4] + [H_2PO_4^-] + [HPO_4^{2-}]$
$Ca^{2+} + H_2O \xrightleftharpoons{K_{Ca,1}} CaOH^+ + H^+$
$CaOH^+ + H_2O \xrightleftharpoons{K_{Ca,2}} Ca(OH)_{2,aq} + H^+$
$[Ca_{T,l}] = [Ca^{2+}] + [CaOH^+] + [Ca(OH)_{2,aq}]$
$Mg^{2+} + H_2O \xrightleftharpoons{K_{Mg,1}} MgOH^+ + H^+$
$MgOH^+ + H_2O \xrightleftharpoons{K_{Mg,2}} Mg(OH)_{2,aq} + H^+$
$[Mg_{T,l}] = [Mg^{2+}] + [MgOH^+] + [Mg(OH)_{2,aq}]$
$[K_{T,l}] = [K^+]$
$[Cl_{T,l}] = [Cl^-]$
$H_2O \xrightleftharpoons{K_w} H^+ + OH^-$

*Adapted from Concas et al., [40].

discussed in more detail in Section 3.3.2). In fact, each algae growth metabolism (i.e., autotrophic, mixotrophic or heterotrophic) may lead to different pH changes behavior, due to the carbon sources and species consumption by the microalgae. In the fundamental books of Michael A. Borowitzka and many other books in the field [43,44], the photosynthesis processes were discussed in detail as a function of the pH and CO_2 speciation. The reader was directed to the newest achievements in the state of the art. Briefly, in

the autotrophic metabolism, since the energy source is provided by the light and the carbon source is inorganic, the consumption of the gaseous CO_2 in the bicarbonate (most often case culturing fresh and sea water algae on the particular pH medium between 7–9) form leads to a pH increase, following the stoichiometry given by Eq. (1). On the contrary, in heterotrophic metabolism the pH decreases due to the CO_2 production from organic sources according to Eq. (2). In turn, mixotrophic growth cultures tend to more stable pH behaviors, depending on the dominant metabolism [45,46].

For microalgal autotrophic cultures is assumed that the pH tolerance limits of the algae can be governed either by chemical influence on the growth medium or by metabolic effects on the cells. In addition, the maximum tolerable pH is not influenced by the availability of inorganic carbon. However, the pH plays a preponderant influence on the relative concentrations of the carbonic species in the culturing medium, therefore the pH can affect the carbon availability for the algal photosynthesis, especially for intensive cultures [47].

Note: The other critical issue of algae growth is “energetics”. It is a subject of metabolic flux analysis of the cell, starting from capturing the light and its utilization inside the cell under different forms (ATP, NADPH etc.) where different mode of cultivation take place. Most often, the theoretical yields of algae biomass on ATP decreases in the following order: heterotrophic culture > mixotrophic culture > autotrophic culture and a significant amount of the available ATP is required for maintenance processes in microalgae cells. Evaluation of major metabolic pathways in algae cell and its energy efficiency to utilize light is considered a special issue. This requires global metabolic flux analysis besides the determination of the cell components such as proteins, carbohydrates and other metabolites. Energetics gives the whole picture of energy efficiency of the algae cell and requires different modeling approach so called structural metabolic analysis of the cell.

Therefore, the energetics should not be underestimated or neglected during the optimization of PBR as a system. The results from energetics study for a particular microalgae strain of interest have to be taken into account and included in techno-economical criterion during the search of optimal cultivation condition and PBR design.

This review deals with unstructured modeling approach on a population level. Nevertheless, the modeler should be familiar in details about algae cell energetics. Fundamental experimental work on microalgae energetics can be found elsewhere [48].

3.3 | Modeling specific growth rate as a function of key parameters

Threshold type models, also known as the “minimum law”, can mathematically describe the influence of key parameters over the microalgae kinetics (MK) and specific growth rate. These models assume the hypothesis that the overall growth rate is affected by one specific limited resource amongst all requirements for cell growth. Nevertheless, the model can also consider the concept of co-limitation, taking into account all possible limiting resources for the growth. The multiplicative model, unlike the threshold model, assumes that all resources (or factors) may simultaneously contribute on the microalgae growth, as generically represented by the Eq. (3).

$$\mu = \mu_{max} \cdot \prod_i^n \hat{\mu}_i \quad (3)$$

where μ is the specific growth rate (SGR) (h^{-1}); μ_{max} is the maximum specific growth rate with respect to the most limited resource (h^{-1}); and $\hat{\mu}_i$ is a specific function for each limited resource considered in the study (e.g., $\hat{\mu}_i = f(C, N, P, \dots, pH, T, I_{av})$).

For instance, regarding to the SGR dependence to the CO_2 availability, the well-known Monod model [49], or inhibition effects could be considered [50], or any other model can be used as needed (e.g. Droop type models or Arrhenius – for temperature). Lee et al., [51] present a comprehensive review of growth kinetic models for microalgae cultivation as a function of multiple key parameters, such as nutrient concentration (e.g., carbon, nitrogen and phosphorus and sources), light intensity, temperature, among others.

Hence, all the effects of key process parameters on SGR can be studied independently at population level and further used for building the complex model, by coupling it to the other sub-systems (e.g., mass and heat transfer, hydrodynamics, light distribution, etc.) following the strategy of system analysis theory (see Figure 1) [19].

3.3.1 | Light intensity and penetration - S_f/V ratio

Discussing the PBRs potential for light illumination availability one has to consider as a “static” key engineering parameter surface-to-volume ratio (S_f/V) of any PBR geometry compared to the other “dynamic” key light parameters such as light/dark cycles and flashing light effect. The S_f/V ratio was discussed as a criterion of light illumination and availability of PBRs by many authors and even recently [52], but the works of Tredici M.R. can be considered as a milestone [53,54]. A modification of this idea, in order to increase S_f/V of the PBRs was proposed [55], in which a new coefficient was determined, called the photic ratio ($R_f = S_{ill}/S_{occ}$), where S_{ill} stands for the illuminated surface and S_{occ} is the

occupied by new surface of the flat plate PBR which is horizontally positioned. He suggested that this ratio considers a solar radiation dilution factor. Morita et al. [56] have worked on a new technique so called photo-redistribution effect. They improved photosynthetic productivity of *Chlorella* sp. up to $28.3 \text{ g m}^{-2} \text{ d}^{-1}$ in a special conical tubular PBR with a cone angle of 60° .

One may evaluate the simple “static” criterion S_f/V from a practical point of view and most importantly how this criterion correlates to MK and the microalgae physiology. For example, the S_f/V ratio of tubular PBR can be calculated as follows:

For a tubular PBR, based on its geometric specifications, namely, diameter (D) [m] and height (H) [m], the tubular PBR surface area and volume can be respectively determined (Eqs. (4) and (5)), as follows:

$$S_f = \pi D H \quad [\text{m}^2] \quad (4)$$

$$V = \pi H (D^2/4) \quad [\text{m}^3] \quad (5)$$

In this way, the light criterion can be defined as:

$$S_f/V = \frac{(\pi D H)}{(\pi H (D^2/4))} \therefore S_f/V = \frac{4}{D} \quad [\text{m}^{-1}] \quad (6)$$

This simple form is a key for the evaluation of light penetration and availability in the PBR. In real industrial application of tubular PBR its diameter cannot be increased or decreased outside the experimentally determined border $D = 0.01 \text{ m}$ up to 0.40 m . Diameter values below 0.01 m is not economically feasible because the PBR productivity decrease drastically which cannot be compensate by achieving even highest microalgae biomass concentration (X). In contrast, for a diameter of tubular vertical/horizontal PBR above 0.40 m , the biomass concentration which can be achieved is, usually, extremely low (not higher than $X = 0.15$ up to 0.35 g/L) for similar operational conditions. By taking the lower limit value ($D = 0.01$) and by using the above-mentioned equation for S_f/V a maximum value of the light criterion of $S_f/V = 400 \text{ m}^{-1}$ was achieved. A strong evidence of this simple analysis is presented [57], where the author analyzed many advanced industrially important closed PBR geometries on the base of S_f/V criterion and summarized them in a table where $S_f/V = 24\text{--}200 \text{ m}^{-1}$. For the researchers, a scientific challenge is how S_f/V ratio can be linked with algae physiology. Our study on this subject resulted in a kinetic model where specific growth rate (SGR) was a function of S_f/V ratio [25]. Here, we are going to describe briefly this approach and our simulation results. If microalgae biomass

growth is limited by light, one may present substrate (S) as a function of I_0 and S_f/V ratio, given by Eq. (7):

$$S = I_0 \left(\frac{S_f}{V} \right) \epsilon_x X \quad (7)$$

where, S_f is the illuminated surface area of the reactor (m^2); V is liquid volume (m^3); I_0 stands for incident light is absorbed and scattered by the algal cells and the air bubbles, creating a non-uniform distribution of light intensity inside the PBR ($\mu\text{mol m}^{-2} \text{s}^{-1}$); and ϵ_x is the extinction coefficient of the culture corrected most often hydrodynamic distribution of light inside the PBR.

Further, in our mathematical analysis (under the assumption of the model simplification) the average light intensity (I_{av}) were applied as a function of the biomass concentration (X) and the different Monod form equations in order to describe the total SGR as a function of the light criterion. In other words, the light availability is considered as the only limiting substrate (S) in the photoautotrophic growth. The SGR can be represented in a multiplicative model approach (see Eq. (3)) through Eq. (8):

$$\mu = \mu_{\max} \cdot \hat{\mu}_{S_f/V} \cdot \hat{\mu}_{I_{av}} \quad (8)$$

By using the biomass balance, the kinetic model was completed and analytically solved for this case. Simulation results for initial conditions of hot summer: $X_0 = 0.1 \text{ [kg m}^{-3}\text{]}$, $\mu_{\max} = 0.11 \text{ [h}^{-1}\text{]}$, $I_0 = 3270.0 \text{ [}\mu\text{mol m}^{-2} \text{s}^{-1}\text{]}$, time = 14 [day] and highly fast growing *Chlorella vulgaris* species were performed in the range of S_f/V between 10 and 87 m^{-1} of tubular PBR. Maximum ratio $S_f/V = 400 \text{ m}^{-1}$ was chosen as a reference point in this analysis as the upper limit of $S_f/V|_{\max}$ (i.e., lowest PBR diameter $D = 0.01 \text{ m}$). In turn, for the lower limit $S_f/V|_{\min}$ for $D = 0.4 \text{ m}$ was assumed ($S_f/V|_{\min} = 10 \text{ m}^{-1}$). The simulation results agreed with the results of others [58,59].

The results from the above analysis [25], can be interpreted as follows:

- For low light intensities, tubular PBRs with $D > 0.40 \text{ m}$ are not effective;
- For high light illuminations, $I_0 = 3270.0 \text{ [}\mu\text{mol m}^{-2} \text{s}^{-1}\text{]}$ tubular PBRs with $D = 0.20 \text{ m}$ are effective;
- Tubular PBRs with D between 0.05 up to 0.15 m have great potential in tropical regions;
- Ultra-high-density cultures (UHDC) $X > 20 \text{ kg m}^{-3}$ can be achieved in PBRs with very small diameters, which is unrealistic for industrial applications.

As a general conclusion of this work, it was evidenced that such a novel kinetic model, which considers S_f/V ratio, can be extremely useful in predicting limits of biomass

productivity. In addition, it can be integrated with other criteria for optimization and scale-up of the PBRs, depending on the selected species and their light-dependent behavior.

In general, the light irradiance as well as the wavelength distribution strongly affect the microalgae growth, productivity, and composition. Because both photo-inhibition and photo-limitation can be caused by inadequate irradiance [60], or even by insufficient hydrodynamics in the PBR systems.

Regarding to the light availability effect on the microalgae specific growth rate, several models have been proposed. Béchet et al. [61] present an excellent review, in which several models are categorized according to the light distribution. The authors classified from simple models, wherein the dependence of specific growth rate is a function of the incident light (I_0) or average light (I_{av}) for a well-mixed system at population level (i.e., the microalgae cells are exposed to the same light intensity and average rate of photosynthesis). Further, models that are more complex considered gradients of light intensity and photosynthesis rate. Finally, the ones that include both light gradients and short light cycles were evaluated, as well. More complex models require the knowledge of the light intensity experienced by each individual cell moving into the PBR. Hence, the hydrodynamics of the system must be determined in order to describe the flow fields inside the PBR and, consequently, the cell trajectories. In this way, the use of CFD can be an extremely useful tool to provide such information, however there is still lots of shortcomings to be overcome to provide accuracy of prediction, due to the complexity of microalgae cultivation systems (i.e., multi-phase, turbulence, etc.) [30].

3.3.2 | Carbon dioxide speciation in the culture medium and modeling pH as a state parameter

The pH of the medium is one of the main factors influencing the microalgae growth in PBR cultivation because its value shows water chemistry as a function of species dissociation, precipitation and dynamics changes of microalgae physiology during the process. Hence, this parameter can be used robustly for process monitoring and control. In microalgae cultivation, increasing supply of CO_2 and its dissolution in liquid phase decreases the pH value. On the other hand, during the algae growth, the utilization of total carbon from the cells available as $\text{CO}_{2(\text{aq})}$, HCO_3^- and CO_3^{2-} ions increases the pH value. Experimental data showed that most of the industrially used microalgae achieve optimal photosynthesis conditions within the range of pH between 6 and 10, wherein the bicarbonate species dominates [19,30].

Therefore, the pH can be used as a good (but not unique) control parameter in PBR systems because it is extremely dynamic depending on mentioned above phenomena and temperature as responsible for solubility of gases and gas-liquid interphase equilibrium conditions.

The pH of the culture medium can be controlled by adequate aeration of the PBR, wherein for elevated pH values the addition of CO₂ into the system can acidify the culture medium. However, it should be evidenced that although higher CO₂ concentration promotes higher biomass yields, the counter effect of lowering pH may affect the microalgae physiology. In addition, for lower pH levels the contamination of the system is more susceptible [30].

In this sense, pH changes influence the microalgae growth not only due to biotic factors (e.g., microalgae physiology, photosynthetic performance, etc.), but also abiotic ones (e.g., nutrient availability, due to the available species in each pH condition).

Therefore, during the cultivation, the pH oscillations and, consequently, the availability of carbonic species (e.g., CO₂, HCO₃⁻, etc.) for the photosynthesis will be affected. In general, acidic pH values lead to a predominance of CO₂, while HCO₃⁻ for alkaline ones. Following the chemical equilibrium of carbon species discussed earlier in this work.

Particularly, the CO₂ concentration in the flue gas will strongly influence the medium pH due to the elevated concentrations; therefore, the pH control is a major factor and should not be neglected in PBR modeling. Specific software may be helpful to predict the chemical components (dissociation, complexes formation, etc.) for multi-component species in aqueous solution based on thermodynamic properties, such as MINEQL+5.0 software (Chemical speciation modeling software) or Hydra plug-in from MEDUSA (Make Equilibrium Diagrams Using Sophisticated Algorithms) software [62].

Therefore, the pH can affect the distribution of CO₂ and macro- and micro-nutrients species and, consequently, its availability for the microalgae, and potentially provoke direct physiological effects [40]. Bitog et al., [30] presented an overview of CO₂ maximum tolerance and optimum CO₂ concentration of different microalgae species.

The pH also influences the enzymatic activity of several important microalgae enzymes, such as intra- and extracellular carbonic anhydrase which influences the carbon concentrating mechanism (CCM) [40,63]. More details of the CCM can be found elsewhere [63–68]. In this sense, not only the culture medium optimization but also the maintenance at optimal conditions during the algal culturing should be conducted in order to achieve efficient activities of the carbonic anhydrases for the CO₂ uptake in the photosynthetic systems.

Azov (1982) evaluated the effect of pH on the carbon uptake in autotrophic algae culturing. The author observed that pH influences the free CO₂ concentrations in the medium. In addition, other pH effects occur under higher pH values causing a decrease in the affinity of the microalgae to the free CO₂ [47].

The effect of the pH over the specific growth rate of the microalgae can be coupled to the complex model as well as the other key parameters. A relation describing the specific

growth rate as a function of the pH was proposed for bacterial growth [69,70], given by Eq. (9).

$$\hat{\mu}_{pH} = \frac{(pH - pH_{min})(pH - pH_{max})}{(pH - pH_{min})(pH - pH_{max}) - (pH - pH_{opt})^2} \quad (9)$$

In this sense, by following the system analysis theory [19], the specific growth rate pH-dependence can be linked to the kinetic model as a sub-system into the hierarchic levels of the complex model.

It must be noticed that the optimal conditions of pH as well as other parameters for the microalgae growth (i.e., biomass productivity) may diverge from the optimal conditions for specific desirable metabolites (e.g., lipids, HVPs) [71,72]. For instance, Guedes et al., [71] evaluated the antioxidant production, namely, lutein and β -carotene by microalga *Scenedesmus obliquus* and verified higher biomass productivity at pH = 6. On the other hand, the antioxidant levels were achieved at higher pH values (pH = 8). Therefore, for a robust and predictive modeling of the PBR system, the pH dynamics should be coupled with the complex kinetics model of microalgae growth.

3.3.3 | Temperature as a state parameter in the cultivation of microalgae

As previously mentioned, the microalgae growth is also temperature dependent since this parameter influences several abiotic and biotic phenomena in the cultivation system. Regarding to the abiotic ones, the temperature affects the gases solubility in the liquid phase (e.g., CO₂, O₂, NO_x, SO_x). Consequently, the mass transfer between the phases and also the dissociation of carbonic species make the carbon available for photosynthesis [30].

As previously discussed the temperature influences the gas-liquid interphase equilibrium (Eq. (10)), following the Henry's law (in this case for the carbon dioxide, the same applies to every specie from the gas in contact with the liquid phase – i.e., O₂, SO₂, etc). However, the Henry constant is also temperature-dependent described by the Van't Hoff equation [73], given by Eq. (11).

$$\frac{d \ln H_i}{d(1/T)} = -\frac{\Delta H_{sol}}{R} \quad (11)$$

where, H_i is the Henry's constant (m³ Pa mol⁻¹); T the absolute temperature (K); R the universal gas constant (J mol⁻¹ K⁻¹); and H_{sol} the enthalpy of dissolution (J mol⁻¹).

The values of Henry's constant for innumerable organic and inorganic species as well as parameters and methods to calculate the values under different temperatures are reported

elsewhere [74]. For instance, the value of Henry's constant for the carbon dioxide at the standard temperature ($T^\circ = 298.15 \text{ K}$) is $H_{\text{CO}_2}(T^\circ) = 3.3 \times 10^{-4} \text{ mol m}^{-3} \text{ Pa}^{-1}$. In addition, corrections for non-ideal behavior in the gas phase as well for dissociation in non-ideal solutions also should be considered. Weiss (1974) presented the calculations for the solubility constants as a function of temperature and salinity based on the experimental data of Murray and Riley for water and seawater.

Therefore, the CO_2 mass transfer to the liquid phase and, consequently, the availability of carbon dioxide for the CCM and microalgae photosynthesis is multi-dependent to several synergistic/antagonistic operational conditions (i.e. temperature, pH, etc.).

In addition, regarding to the temperature influence over biological factors, the activity of the biochemical enzymes (e.g., involved in the cellular reproduction process or in the photosynthesis) are extremely affected by temperature [31]. It is important to notice, that if CO_2 or light are limiting factors for the photosynthesis, the influence of temperature become a less relevant factor [30].

Obviously, for each microalgae species an intrinsic optimal temperature exist in order to achieve maximum photosynthetic efficiency [72,75]. In general, the optimal temperature values for biomass growth range between 20 and 24°C , depending on the culture medium composition and the microalgae species. Also, temperatures lower than 16°C may diminish the growth kinetics and temperature higher than 35°C can be lethal for the cells for most of the species [30].

The influence of temperature over the specific growth rate of the microalgae can be described analogously as the pH. Then, this key parameter couples with the sub-systems in the complex model. Hence, by applying such approach, the dependence of the SGR with the temperature [69,70,76], can be described by Eq. (12). In addition, Singh and Singh [77], presented a comprehensive review of temperature effect on the SGR of several microalgae species.

$$\hat{\mu}_T = \frac{(T - T_{\max})(T - T_{\min})^2}{(T_{\text{opt}} - T_{\min})(T_{\text{opt}} - T_{\min})(T - T_{\text{opt}}) - (T_{\text{opt}} - T_{\max})(T_{\text{opt}} + T_{\min} - 2T)} \quad (12)$$

Despite the optimal conditions characteristic for each strain and cultivation system, one may notice that the light incidence besides providing energy to the photosynthesis will also transfer heat to the system what will lead to a temperature increase.

Therefore, the influence of the irradiation on the temperature of the system should be addressed more carefully. According to Béchet et al., [75], the maximization of algae biomass productivity demands the maintenance of broth temperature at its optimum value, hence requires a

comprehensive understanding of how cultivation temperature is affected by environmental and process parameters. The authors presented a mechanistic modeling of temperature in column outdoor PBR systems, by applying heat balance on the liquid phase as a function of static (location, reactor geometry) and dynamic (light irradiance, air temperature, wind velocity) parameters. The authors verified that solar radiation and air convection were the main contributors to the system's temperature change, wherein temperature values above 40°C could be reached depending on the conditions (i.e., summer).

Hence, the temperature influences several phenomena and vice-versa (e.g., the temperature may affect the carbon availability in the liquid phase and can be a response to the light intensity). In fact, all the mentioned parameters are tightly interdependent. In this sense, the temperature needs to be controlled adequately in microalgae PBR cultivation systems, since it strongly influences the technical-economic feasibility and sustainability of large-scale algae biomass production.

Béchet et al., [61] state that the temperature presents different effect on the photosynthesis depending on light availability, showing that these parameters are strongly connected in the influence of photosynthetic process. Under "light-limited conditions", the rate of photosynthesis is limited by the rate of photon supply and the rate of photon capture is considered as independent of temperature. However, when the system is light saturated, the temperature affects the maximum rate wherein "dark" reactions of photosynthesis can occur and consequently the threshold for light saturation.

4 | HYDRODYNAMICS AS A SUB-SYSTEM

As previously mentioned, the movement of microalgae cells inside the reactor is of extreme importance when

developing a particular process such as new and efficient PBRs with optimized growth. One of the main reasons for that is associated to the light availability, assuring that all cells move close to the wall, absorb light, and then move back to the inner portion of the PBR (dark portion), where they can finish the photosynthesis process through the Calvin-Benson cycle. Other important points are mixing, which is important for nutrient and light availability, and CO_2 diffusion, an essential parameter that

TABLE 2 Overview of the equations commonly used for microalgae PBRs CFD studies [104–106]

Equation	Application	Eq.
$\nabla \cdot (\phi_l \rho_l \vec{u}_l + \phi_g \rho_g \vec{u}_g) = 0$	Mass conservation	(13)
$\phi_l \rho_l \vec{u}_l \cdot \nabla \vec{u}_l = -\nabla p_l + \nabla \cdot [\phi_l (\mu_l + \mu_T) (\nabla \vec{u}_l + (\nabla \vec{u}_l)^T - \frac{2}{3} (\nabla \cdot \vec{u}_l) \vec{I})] + \phi_l \rho_l \vec{g} + \vec{F}$	Momentum conservation	(14)
$\nabla \cdot (\phi_g \rho_g (u_l + u_{slip})) = \nabla \cdot (\frac{\bar{\rho}_g}{\rho_l} \nabla \phi_g) - m_{gl}$	Gas phase transport	(15)
$\phi_g \nabla p = f_D$	Pressure-drag balance	(16)
$f_D = -\phi_g \frac{3}{4} \frac{C_d}{d_b} \rho_l \vec{u}_{slip} \vec{u}_{slip}$	Viscous drag force	(17)
$f_D = -\phi_g \vec{u}_{slip} C_W = 5.10^4 \text{ kg/(m}^2\text{s)}$	Viscous drag force – $1 < d_b < 10$ mm, bubbles in water	(18)
$C_d = \frac{16}{Re_b} \quad Re_b = d_b \rho_l \vec{u}_{slip} / \mu_l$	Hadamard-Rybczynski – Viscous drag coefficient – $d_b < 2$ mm	(19)
$C_d = \frac{0.622}{\frac{1}{E_0} + 0.235} \quad E_0 = \frac{g \rho_l d_b^2}{\sigma}$	Viscous drag coefficient – $d_b > 2$ mm	(20)
$\mu_T = \rho_l C_\mu \frac{k^2}{\epsilon}$	Turbulent viscosity – k- ϵ model	(21)
$\rho_l \vec{u}_l \cdot \nabla k = \nabla \cdot [(\mu + \frac{\mu_T}{\sigma_k}) \nabla k] + P_k - \rho_l \epsilon + S_k$	Turbulent kinetic energy	(22)
$\rho_l \vec{u}_l \cdot \nabla \epsilon = \nabla \cdot [(\mu + \frac{\mu_T}{\sigma_\epsilon}) \nabla \epsilon] + C_{\epsilon_1} \frac{\epsilon}{k} C_{\epsilon_1} P_k - \rho_l C_{\epsilon_2} \frac{\epsilon^2}{k} + C_{\epsilon_3} S_k \frac{\epsilon}{k}$	Turbulent energy dissipation rate	(23)
$P_k = \mu_T (\nabla \vec{u} : (\nabla \vec{u} + (\nabla \vec{u})^T) - \frac{2}{3} (\nabla \cdot \vec{u})^2) - \frac{2}{3} \rho k \nabla \cdot \vec{u}$	Productivity term from Eqs. (22) and (23)	(24)
$S_k = -C_k \phi_g \nabla p u_{slip}$	Bubble induced turbulence term from Eqs. (23) and (24)	(25)

defines inorganic carbon availability. Especially effective for the algae growth is the active control of the so-called flashing-light effect (FLE). This follows from the biochemistry and physiology of microalgae growth.

This FLE phenomenon has been proved to substantially increase cell growth by work of many authors [78–81]. The theory of photosynthetic process of CO₂ fixation was proven to be as a two-stage/phase process including light and dark cycles. The detailed description of the kinetic model representing the phenomenon was first published in 1988 [82]. Application of this knowledge to create real effective airlift PBR was achieved by authors [83].

Hence, application of an advanced tool to study and to optimize the FLE in PBRs is the powerful CFD simulator. The Euler-Euler is the most suitable approach to model bubble flux when studying CFD in cases in which the disperse phase fraction (gas fraction) is high [84], such as in microalgae PBRs. This model considers both phases (continuous-liquid and disperse-gas) as two interpenetrating continua, not accounting for each bubble, which reduces computational work while still being adequate and valid to model bubble induced multiphase flow, as pointed out by many authors [30, 85,86]. On the other hand, the Euler-Lagrange approach uses the Volume-Averaged Navier-Stokes equations to describe the motion of the liquid while tracking down each bubble, based on a balance of acting forces [87].

An overview of the equations commonly employed in computational fluid dynamic studies for microalgae growth in PBRs is presented in Table 2, also the parameters from the

equations used for CFD studies are shown in Table 3. In order to describe the movement of the fluid inside the PBR, the Euler-Euler model uses the equations of mass and momentum conservation, as shown in Eq. (13) and (14). Considering that the gas density is negligible compared to the liquid density, the motion of the gas bubbles relative to the liquid is determined by a balance between viscous drag and pressure forces, and the two phases share the same pressure field. To track the volume fraction of the bubbles, the gas phase transport equation presented by Eq. (15) can be used.

As far as the slip velocity, it is possible to be considered as zero, in a condition known as homogeneous flow. Another way to describe the slip velocity, is by reducing the momentum equation to a balance between the viscous drag force (Eqs. 17 and 18), f_D and the pressure gradient, as shown in Eq. (16). The drag coefficient can be written as shown in Eqs. (19) and (20), respectively, depending on the mean bubble diameter.

Several models account for the turbulence when modeling bubble flow. The most used one is the k- ϵ , which solves two extra transport equations for two additional variables: the turbulence kinetic energy, k (Eq. 22) and the dissipation rate of turbulent energy, ϵ (Eq. 23). In this model, the turbulent viscosity is shown in Eq. (21). The bubble induced turbulence term (S_k) and the production term (P_k) from Eqs. (22) and (23) are described in Eqs. (24) and (25), respectively.

Hence, having as a tool the CFD mathematics in the frame of system analysis theory, one is able to simulate many complex hydrodynamic conditions and coupling them with microalgae kinetics to create a new most advanced PBRs

TABLE 3 Parameters from the equations used for CFD studies

Parameter	Description	Unit
ρ	Density	kg m^{-3}
$\vec{u}$	Velocity vector	m s^{-1}
p	Pressure	Pa
μ	Dynamic viscosity	Pa s
μ_T	Turbulent dynamic viscosity	Pa s
$\vec{F}$	Volume force	N m^{-3}
k	Turbulent kinetic energy	$\text{m}^2 \text{s}^{-2}$
ε	Dissipation rate of turbulent energy	m s^{-3}
P_k	Production term	$\text{kg m}^{-1} \text{s}^{-3}$
S_k	Bubble induced turbulence term	$\text{kg m}^{-1} \text{s}^{-3}$
ϕ	Phase volume fraction	$\text{m}^3 \text{m}^{-3}$
$\tilde{\mu}$	Effective viscosity causing drift	Pa s
m_{gl}	Interfacial momentum transfer	$\text{kg m}^{-3} \text{s}^{-1}$
C_d	Viscous drag coefficient	[-]
$Eö$	Eötvös number	[-]
d_b	Bubble diameter	m
$C_\mu, C_{\varepsilon 1}, C_{\varepsilon 2}, \sigma_k, \sigma_\varepsilon$	Model constants	[-]

geometry (see Figure 1). As an excellent illustration of this approach is a work of authors [88]. Their goal was to create a most advanced flat plate PBR (FP-PBR) geometry, which will fulfill the most rigorous requirements for FP-PBR such as:

- (i) High surface area to volume ratio for the illumination;
- (ii) Achieving higher light/dark cycle frequency, preferably close to 1 Hz;
- (iii) Improving the overall hydrodynamics so that the issues of settling are overcome with minimum mixing energy.

The authors solved a difficult task to connect equations of hydrodynamics (laminar bubbly flow) with microalgae mass balance equation for the chosen boundary conditions. The simple kinetic model of specific growth rate was used representing restriction of maximum biomass concentration and involving dead rate constant. This was their theoretical base to study 2-panel PBR and further to find the optimal configuration and operational conditions. The CFD simulations (on the platform of Comsol Multiphysics (COMSOL Inc., 2012)) were used in order to find optimal light–dark cycle. It has to be noticed, that the real FP-PBR was built after and on the base of simulation results with the developed complex model. Validation of the model was done by performing real microalgae cultivation with the strain of *Chlorella vulgaris*. The experimental results proved the effectiveness because of the optimal regime of light–dark cycle achieved in the 2-FP-PBR. In conclusion, this work highlighted the new highly effective way for development of PBR geometry of any kind. The authors' approach applied theoretical base and knowledge about

investigation of sophisticated system that fully corresponds with the principles of system analysis theory. Recently, application of very sophisticated CFD simulations was possible because of the rapidly growing computer station capabilities.

Many other works were developed by applying CFD simulations in order to achieve improved light illumination conditions for different PBR geometries, and, consequently, higher PBR biomass productivity and reduced costs for energy [80, 89,90]. These results have shown that the only way to overcome the drawbacks in the field of closed PBR development and microalgae process optimization is through complex modeling and simulation. By using catalogs of kinetic models representing different microalgae physiology phenomena and matching its requirements with key engineering state parameters (mass transfer, light availability, flow distribution, etc.).

The current state-of-the-art about microalgae cell requirements for light availability and its specific influence (light source, wavelength and intensity, light/dark cycles, FLE) on their growth and metabolism can be found elsewhere [91]. In this review article, the authors discussed and presented in deep details the mechanism of light utilization; and more precisely how the PBR design can improve light distribution. The authors discussed briefly a new technique such as “image analysis” to study the internal in the vessel light distribution. The authors cited a work, which proved that the image analysis based on trichromatic theory most likely, was more useful method than CFD to analyze light distribution because of its speed, simplicity, reliability, etc. The method is as follows: images from digital camera may be converted to gray-scaled images, filtered to remove noise, and converted to contour images for analysis of light trajectories in a PBR.

It is obvious, that any of the state-of-the-art analytical method for analysis of key state parameters of PBR should be applied if it is able to improve the search of optimal PBR design and further to help solving its scale-up problem. Of course, the application of the method has to be technically-economically feasible.

5 | THE BASIS OF THE INTEGRAL BIOREFINERY CONCEPT

The use of mathematical modeling and adequate techniques to design, optimize and control PBRs systems is fundamental. However, the feasibility of the process should be assessed in a much more comprehensive way rather than the technological factors. Nowadays, despite the great potential of microalgae the biofuels production and diversification in the energetic matrix of the human society, the economic feasibility is extremely associated with the reduction of production costs for given PBR productivity and quality of the product. Due to the other well-established fuel technologies, the microalgae-based biofuels must overcome the economic

barriers in order to achieve market competitiveness. This could be accomplished through the integral use of all microalgae products:

- (i) lipids, proteins and carbohydrates;
- (ii) added-value co-products;
- (iii) high value products (e.g., carotenoids, astaxanthin, antimicrobials, antivirals and antifungals products etc.) [20].

In this sense, an industrial-scale feasible process can be only attained by considering all possibilities and benefits of the microalgae cultivation, namely, the “biorefinery concept”, such as: carbon capturing, the production of large-scale commodities (i.e. biofuels), and HVPs. Nevertheless, the overall microalgae cultivation, aiming to reach a status of a viable feedstock to biofuels and products, involves a multidisciplinary and multistep productive chain besides the cultivation step (optimization of operational key state parameters, as previously discussed – e.g., nutrients composition, pH, temperature, light availability, hydrodynamics).

The upstream steps strongly impact on the technical-economic feasibility of the microalgae culturing, particularly, the use of CO₂ from flue gases and the development and optimization of suitable culture medium for each microalgae strain (as described in Section 3.1). It should be highlighted that logistics, preparation, and use according to the regional particularities can be a differentiator (e.g., seawater, brackish, freshwater and wastewater, cheap nutrients and fertilizers, flue gas from local sources: power-plant, cement industry, ethanol mills, biogas upgrading etc.) [20,36,38,92–99].

The downstream processes are crucial to the economics of the process development. In fact, the multiple step unit operations such as dewatering, concentration, cell disruption, purification and extraction of desirable feed stocks and end-products remain as one of the great bottlenecks in the microalgae cultivation [100–102]. However, it should be evidenced that each algae metabolite has its characteristics and requirements to provide adequate methods of isolation.

In this way, an economically feasible of microalgae biofuels production will be achieved only through the biorefinery concept by the utilization of every component of the biomass such as lipids, starch, proteins, and other metabolites. Despite the great potential of the microalgae suitability for IBC, the co-production of multiple products from microalgae remains a challenge due to the complexity of the whole productive chain [102,103]. In this way, R&D efforts still need to be directed to improve the economics of the process. For this, adequate mathematical modeling of the process is required to provide a comprehensive understanding of the involved phenomena and to allow the researcher to take rational decisions in the search for enhanced efficiency of the overall production chain. Hence, advanced optimization methods have to be used

in order to evaluate different scenarios of scheme efficiency under the space limits of the search and chosen objective functions.

6 | CONCLUSION

This review gives special attention to the mathematical tools used in the process development, PBR design and scale-up in the frame of system analysis theory. The integral biorefinery concept can be feasible only if researchers can study and verify any step of the unit operation (microalgae process development, PBR design and scale-up, and the downstream processing) for minimal time and with minimal scientific efforts. The most important element in the scheme of microalgae biomass and high value products production is the PBR design. Its effective modeling, optimization and design determine all the other steps of the process development. Hence, the review combines the current knowledge on system analysis theory and how its principles should be applied using the modern mathematical and analytical methods. In details were discussed the development of kinetic models of microalgae growth and CFD studies as sub-systems in advanced design of PBR. The recent review guides the researcher how complex efforts have to be accomplished for the successful development of complex PBR mathematical models and their validation in the frame of the integral biorefinery concept for particular industrial applications.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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