

Review

Tackling Old Challenges in Microalgal Biotechnology: The Role of Photobioreactors to Advance the Technology Readiness Level

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Abstract: Microalgae biotechnology has taken the world by storm. However, despite its great potential promise, it still cannot be considered a fully consolidated technology due to a crucial challenge: the low rates of biomass productivity. To overcome this hurdle, photobioreactors have been developed as an innovative solution, promising to increase the efficiency of microalgae cultures by providing optimized conditions. However, the results obtained with these systems do not always meet initial expectations, and their large-scale implementation faces complex technical challenges. In light of this, the present review addresses the main aspects related to the design and engineering of photobioreactors, highlighting their potentialities and limitations in overcoming the critical challenges of microalgal biotechnology. Furthermore, we discuss the current technological readiness level and the commercial readiness index of microalgae-based bioproducts from the perspective of industrial-scale production.

Keywords: abiotic/biotic aspects; bioreactor parameters; commercial readiness index; microalgae-based bioproducts; technology readiness level



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1. Introduction

Industrial biotechnology has been portrayed as providing revolutionary solutions to some of the world's biggest challenges [1]. Its purposes range from mitigating climate changes to decreasing health issues, promoting renewable alternative energy sources, and developing new sustainable manufacturing routes [2]. However, biofabrication is not just about creating cheaper or more environmentally friendly materials. It is also about bringing new and innovative products to the market that surpass the best products that conventional chemistry can offer [3].

Given the widespread attention surrounding industrial biotechnology, researchers realized that microalgae could be used as a photosynthesis-powered expression chassis. Indeed, the substantial interest in microalgal biotechnology is not random. Its metabolic versatility that assimilates high carbon dioxide loads under the light, resulting in biomass with a high level of exploration, positions microalgae in a prominent place today [4]. They are emerging as new, attractive, promising, and scalable platforms for the production of various biomolecules while contributing to cleaner industrial processes. Among them, a non-exhaustive list includes some primary and secondary metabolites, such as proteins [5–7], essential fatty acids [8,9], and pigments, including carotenoids, chlorophylls, and phycocyanins [10–12]. Microalgae have gained a competitive space in the global market due to their nutritional properties, bioaccessibility, and cellular absorption [13,14]. Consequently, microalgae biotechnology has proven to be an essential strategic enabler for

marketing associated with One Health principles, resulting in an indispensable driving force for a strong and vibrant bioeconomy.

Although future market projections push decision-makers to open the doors to the industrialization of microalgae-based bioproducts, success remains doubtful. It is due to deep technical and operational hurdles that, despite their magnitude, continue to demand innovation and improvement, stemming from one of the higher bottlenecks to microalgal biotechnology: photobioreactors. Essential for large-scale operations, these devices function as the core of bioprocesses. Nevertheless, their full efficiency, which should catalyze industrial expansion, is still far from being achieved [15,16].

Given this background, the research gap to address with this publication is to examine why microalgae photobioreactors have not yet reached the greatest industrial-scale advancements despite more than 140 years of extensive and intensive investigations. Other sub-objectives of this publication consist of elucidating whether there is a combination of existing strategies in the biotechnological core that can identify these weaknesses and collectively address them to overcome these drawbacks. Also, to the best knowledge of the authors, this is the first literature review that analyzes, through concepts of technological readiness level and commercial readiness index, paths to strengthen microalgal biotechnology. Therefore, this publication is intended for all stakeholders in microalgal biotechnology, with a particular focus on addressing the pitfalls associated with the research fragmentation, development, and innovation of photobioreactors. We aim to foster a more integrative approach with industrial market players, helping to overcome past setbacks in microalgal production and positioning it as a major big win for the global community's future.

2. Biomass Production—The Death Valley of Microalgal Biotechnology

Successful technology transfer for microalgae-based processes and products depends on overcoming several hurdles. However, it is understood that the key driving force for its achievement is tied to its starting point—biomass production in cultivation systems. In this way, the consolidation of microalgae-based facilities has been limited by losses in cellular productivity, which are sharply perceived in the transition from projects on a laboratory scale to an industrial scale. Thus, biomass production has turned into a bottleneck for crowning microalgal biotechnology [17].

Scalability and trouble are terms that seem to go together. And for a long time, this has been the rule. However, for the modern researcher, although many biotechnological processes have come off the drawing board, the research and discovery pathway for large-scale production has rarely been direct and easy, especially in microalgae cultivation systems [18]. On the whole, bioprocess development occurs on three scales: laboratory, pilot, and industrial. On the laboratory scale, also known as the bench scale, the working volumes are reduced (~0.5 to 10 L), and microorganisms are inoculated for conditions and tests aimed at process optimization. Once the process parameters are established, they are only gradually transferred to larger volumes (pilot scale ~50 to 500 L) until, with all the optimal conditions determined, they can be transferred to industrial scale (>500 L), with scale factors ranging from thousands to millions (Figure 1). However, as larger work volumes are obtained, a proportional reduction in process control is observed. This is fundamentally attributed to an insufficient understanding of the principles that govern the expansion requirements [19,20].

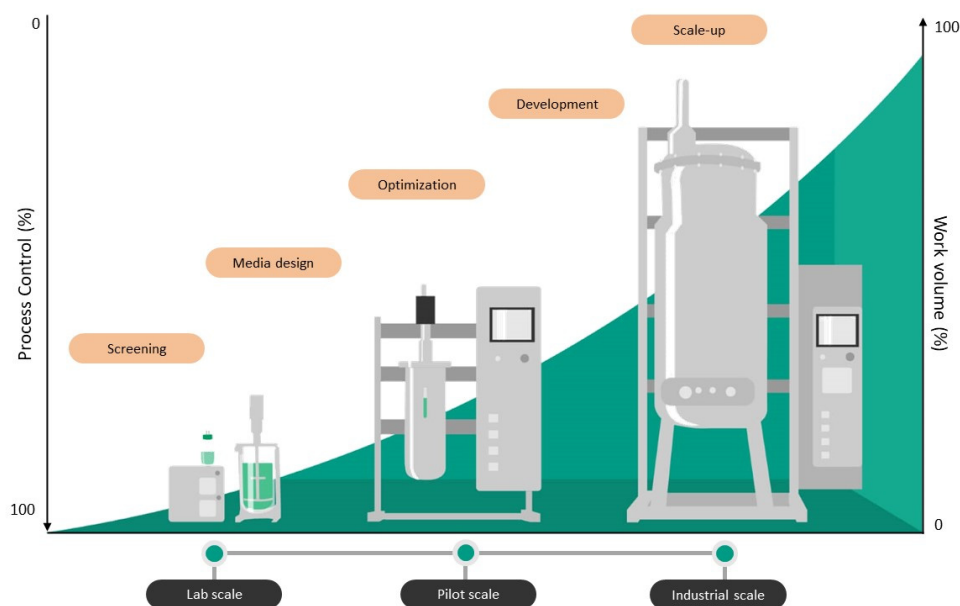


Figure 1. Tradicional principles of scale-up for microalgal bioprocesses. Note that process control is inversely proportional to the increase in the volume of work. Adapted from [21].

Indeed, it is well known that empirical engineering approaches based on the similarity principle and dimensional analysis for scale-up are always implemented under the general principle of keeping specific parameters constant. Among these aspects, factors such as specific energy consumption rate, mass transfer coefficient, impeller tip speed, shear forces, and mixing time and efficiency are considered, for example [22]. However, one cannot simply duplicate the scale conditions when scaling up equipment from the laboratory scale. After all, any process involving living microorganisms is unique and complex; therefore, the changes in the environment caused by a change in scale result in interactions and unforeseen responses, placing the efficiency and profitability of bioprocesses at risk [23].

Given these particularities, the scaling-up design of microalgal biotechnology begins, above all, with the numerous research efforts regarding the development of cultivation systems. Initially, large-scale cultivation was investigated in open systems led by raceway pond models due to primitive intuition compared to the way they were found in their natural habitat, as well as low installation cost [24]. However, with the need to achieve higher productivity under precisely controlled operational environments, engineering design developed closed systems known as photobioreactors. These systems are primarily designed and configured to achieve the following: (i) the highest surface-to-volume ratio; (ii) provide an adjusted level of nutrients; (iii) maintain balanced mass transfer rates; (iv) ensure appropriate photon absorption supply; and (v) sustain the ideal concentration of microalgal cells in combination with the extent of their cell multiplication phase [15].

Although a large number of photobioreactors have been investigated and have reached a somewhat satisfactory technological maturity, only detailed knowledge about hydrodynamic characteristics, mass transfer, shear stress, and scalability has not been enough to turn a silver bullet to the challenges of microalgal biotechnology [25]. Even the best-designed photobioreactor configuration requires considerable additional optimization work to achieve the necessary concentrations, rates, and yields for the adoption of these systems by industry. In this way, for the effective development of photobioreactors, your projects must integrate parameters that vary over time and on different spatial scales, considering the interaction of physical, chemical, and biological phenomena that affect microalgae cells [26]. Abiotic factors play a fundamental role in understanding how organisms interact with their physical–chemical environment, especially during the complex chemical

reactions involved in photosynthesis, which act as a cornerstone in nutrient conversion in microalgal biomass; these include (i) light supply—intensity, distribution, and spectrum quality of light, (ii) temperature, and (iii) mass transfer [27].

As is known, the light intensity that microalgae cells receive during cultivation has a substantial impact on cellular metabolism and growth since photosynthesis directly depends on the available light energy. Thus, it can be stated that the efficiency of the photobioreactors is intrinsically linked to the efficiency of the light supply, a key factor for the overall system performance [28,29]. However, one of the primary challenges associated with this principle arises from the fact that light, as it passes through the interior of photobioreactors, experiences attenuation due to absorption, scattering, and shielding effects induced by the microalgal cells. This phenomenon leads to unwanted light gradients throughout the system, thereby compromising the efficiency of photosynthesis within the photobioreactors [30]. Therefore, when managing and projecting parameters such as flow regimes within a photobioreactor configuration, it is often assumed that turbulent flows are ideal, as they favor greater homogenization of the culture, reducing light gradients and increasing uniformity of exposure to light. However, the implementation of high hydrodynamic forces can present a dilemma: while turbulent flow improves homogeneity, it can hinder the movement of the liquid between the dark zone (bottom) and the light zone (surface), limiting the exposure of cells to the light required for efficient photosynthesis. Furthermore, the resulting shear stress can become excessive, leading to increased cell mortality and decreased growth rates. This adverse effect may, therefore, reduce the effectiveness of the photosynthetic process, becoming a bottleneck in the photobioreactor performance [31].

As strategies to increase cellular exposure without rupture damage, the choice of an optimized design, such as the use of bioreactors with cylindrical or helical geometry, can help control the intensity of turbulent forces. Bioreactors with several flow zones can also be designed to dissipate excessive turbulence in certain areas, ensuring better energy distribution in the system [32]. More recently, flux and luminosity sensor use coupled with automatic control systems allows for constant monitoring and the dynamic adjustment of operating conditions. These systems can adjust the pumping speed and the rotation of the agitators or others in real time, depending on the conditions inside the photobioreactor, ensuring a balance between the efficiency of the light supply and the protection of the microalgae cells [33].

Simultaneously, light distribution efficiency can be intensified or attenuated depending on the surface-to-volume (S/V) and the height-to-diameter (H/D) ratio. The light distribution path in a photobioreactor can be divided into three zones: photo-inhibition, light-limited, and stagnation. In zones with short light paths, the light intensity is generally higher than the photosynthetic demand of the cells. It originates in a zone with the largest photo-inhibition potential, resulting in the inhibition of microalgae cell growth and, in some more extreme cases, potentially leading to cellular death. Insofar as the light path increases, the light intensity decreases, and a balance state is reached between light entry and cellular absorption at a specific point. In this position, the microalgae cells achieve their maximum growth rate. However, in zones with a longer light path, the light intensity is very low for supporting the growth of algae cells, and these, consequently, will stagnate in this area [34]. In this context, when the transition from bench photobioreactors to pilot and industrial scale occurs, the increase in work volume does not accompany the pre-established performance of the light distribution paths, and, therefore, operational problems arise in the search for illumination and space [35]. According to the literature, a height/diameter ratio suitable for the optical path to reach the reactor core without interference from cell density is set to values lower than 2. However, these configurations on an

industrial scale—today—generally present values equal to or greater than 10, as in the case of tubular photobioreactors and flat plates ($\sim 14.0 \text{ m}^2/\text{m}^3$). To try to circumvent this gap, in recent years, models of hybrid photobioreactors have been designed to provide a high work volume while maintaining an adequate height/diameter ratio ($H/D = 1.5$). For example, studies conducted by Jacob-Lopes et al. [36,37] developed a lighting platform for hybrid photobioreactors that requires only $0.22 \text{ m}^2/\text{m}^3$ since the largest reactor compartment is not dependent on light. However, these systems must be used in cultures with highly resistant strains due to the risk of contamination [38].

Maximizing light penetration in the photobioreactor not only involves adjusting the appropriate flow regime and surface-to-volume ratio but is also closely linked to the quality of the materials used in its construction. As is known, the type of material influences the transmission, dispersion, and reflection of light and can optimize the intensity and spectrum of light that affects microalgae, directly impacting the efficiency of photosynthesis and, consequently, the microalgae growth. Furthermore, the material's durability against UV radiation and internal cooling also plays a crucial role in choosing the most suitable material for the photobioreactor [39]. Meanwhile, the advancement of this objective has been confronted with a significant additional challenge: biofouling on the internal walls of photobioreactors. Biofouling compromises the penetration of solar radiation, reduces the useful life of materials, harms the quality of culture, and amplifies the risk of contamination. As a result, frequent interruptions are necessary to carry out physical and chemical cleaning, apart from the eventual replacement of coatings, which results in an increase in operating costs [40]. In this context, choosing materials for the construction of photobioreactors must prioritize not only high transparency but also essential characteristics, such as flexibility, durability, non-toxicity, and resistance to chemicals and metabolites generated by microorganisms, as well as resistance to climatic conditions and, always if possible, low cost [41].

Currently, the traditional materials used in photobioreactor construction include glass and polymers, such as polymethylmethacrylate (PMMA) and polycarbonate (PC), which stand out for their high luminous transmittance. The common glass potential generally varies between 80–90%; however, high-quality glass, such as tempered or ultra-clear glass, can achieve more than 90% transmittance [42]. In comparison, the luminous transmittance of PMMA can vary from 90 to 92%, depending on the quality and thickness of the material [43]. Polycarbonate, in turn, has a slightly lower luminous transmittance, varying from 85 to 90%. Nevertheless, polycarbonate stands out for its greater impact resistance and better thermal performance, properties that render it especially suitable for applications demanding high mechanical durability and resistance to extreme conditions [44].

Regarding the potential for biofouling, the three materials in question have extremely smooth surfaces, which could make it difficult for microorganisms to adhere. However, considering the minimum Vogler interval ($20 < \tau_0 < 40 \text{ mJ}/\text{m}^2$), which defines the surface tension level in which surfaces are only less prone to the microorganisms' adherence, it is observed that these materials are not ideally placed in this parameter [45]. The surface tension of polymethylmethacrylate (PMMA) and polycarbonate (PC) is between 40 and 45 mJ/m^2 , while the glass presents a surface tension that varies from 50 to 70 mJ/m^2 [46]. Thus, to consider the trade-off between luminous transmittance, mechanical resistance, and biofouling potential, the optimal choice for the construction of photobioreactors seems to be polycarbonate due to its combination of high transmittance and higher resistance to biofouling in comparison with other materials.

Although light is the most studied parameter in photobioreactor design due to its impact on photosynthetic efficiency, temperature is also a crucial factor, albeit less understood and explored [47]. Each microalgae species has an optimal growth temperature that

allows the cell to photosynthesize without altering essential biochemical or physiological parameters. The temperatures that promote maximum growth rates vary between 20 and 25 °C for mesophilic species but can reach around 40 °C for thermophilic strains or reduce to around 15 °C for psychrophilic strains [48]. However, when temperatures are adjusted to these ideal conditions, the levels of cellular productivity can be affected on three levels: (i) cellular, (ii) molecular, and (iii) physical–chemical. From a cellular point of view, temperature oscillations affect enzymatic processes, mainly the kinetics of ribulose-1,5-bisphosphate adjustment (Rubisco). Rubisco is an enzyme responsible for carbon fixation and is a fundamental part of photosynthesis, catalyzing photosynthesis in two concurrent physiological pathways—photosynthesis and photorespiration—with a dual activity of carboxylase and oxygenase, respectively [49,50]. At temperatures above 30 °C, the affinity of the enzyme (Rubisco) for the substrate (carbon dioxide) is reduced, becoming a limiting factor for photosynthesis and, therefore, reducing the levels of cellular productivity. At temperatures below 15 °C, the reduced activity of Rubisco can slow down cellular metabolism, prejudging processes such as energy production and synthesis of microalgal biomass [51]. As for molecular damage, high temperatures induce protein degradation, leading to cellular mortality. Furthermore, the activation mechanisms of cellular stress strongly affect the oxygen–reactive species dynamics, causing progressive oxidative damage and, finally, cellular death. Under physical–chemical optics, temperature influences the mass transfer rates of gases, such as CO₂ and O₂, beyond affecting the gas solubility in the medium, which influences the equilibrium and the reaction kinetics [52].

It is generally known that hot and sunny regions (tropical and subtropical zones) are ideal for photobioreactor installations because they offer favorable natural conditions, such as adequate temperature and high-intensity sunlight for microalgae cultures. Most of the commercial production of microalgae is carried out in external environments with little or no humidity control over the climate [53,54]. The result of this practice is the overheating of cultures in the absorption and conversion of excess solar energy into heat. In the absence of active temperature control systems, depending on the geospatial position of the facilities, the internal temperatures of culture systems can easily reach temperatures of >50 °C, making it impossible for any mesophilic species of commercially cultivated microalgae to thrive under these conditions [55]. Therefore, temperature control becomes a vital resource for cell survival in extreme oscillations [56].

The temperature control systems active in photobioreactors must be designed to facilitate heat exchange and maintain a rigorous adjustment to the temperature suitable for cell development during the bioprocess [57]. The industry has developed two main control methods: (i) passive evaporative cooling and (ii) heat exchangers [58]. The operational mechanism of evaporative passive cooling consists of the utilization of water evaporated to reduce the temperature. Meanwhile, heat exchangers operate through thermal energy exchange for heat absorption by cold fluid that passes around the equipment, maintaining the equipment at temperatures around 25 °C [59]. In a decision-making process, the passive evaporative cooling method has the advantage of being a more economical device for large-scale cultures. However, from an environmental point of view, this statement is not supported. This is because the system requires the distribution and consumption of a considerable water volume: 8000 m³/ha/year of water to reduce the PBR temperature from 40 °C to 25 °C (equivalent to removing 18,000 GJ/ha/year of heat) [60]. Additionally, it is important to highlight that since all places with high solar radiation are ideal for the production of microalgae, water is a finite resource, which makes these systems economically and environmentally unsustainable. Likewise, heat exchanger systems for photobioreactors are expensive for industrial photobioreactors, especially when initial installation investments are a concern. Also, the environmental challenges regarding energy efficiency and the use

of natural resources (freshwater) are aspects that must be improved for this equipment [61]. Given the existing technological gap, significant advancements have been made in research focused on sustainable alternatives for temperature control in photobioreactors, with the aim of achieving greater energy efficiency and reducing environmental impact. Various passive approaches have already been investigated, such as thermal ground exchangers, the use of phase change materials, and light filtering [62–65]. Light filtering, for example, can use the principle of hot mirrors to selectively reflect ultraviolet (UV) and infrared (IR) radiation, which account for approximately 50% of solar energy, thus preventing system overheating. Additionally, a more innovative approach involves the use of semi-transparent photovoltaic (PV) panels placed on the optical surface of photobioreactors, which absorb and convert specific wavelengths into electricity while allowing the remaining light to pass through for microalgal cell growth. This solution not only reduces water consumption and energy needs for thermal control but also contributes to the additional production of electricity from the conversion of UV and IR radiation, improving the overall efficiency of solar light conversion and promoting the sustainable co-production of biomass and electricity [66].

Although the mass transfer characteristics are also strongly correlated with hydrodynamic parameters, such as mixing time, liquid velocity, gas ball velocity, and gas retention, the main parameter evaluated is the mass transfer coefficient [67]. Mass transfer refers to the diffusion rates of components, such as carbon dioxide, between the gas and liquid phases. In photobioreactors, bioprocesses are characterized by multiphase interactions, mainly involving gaseous exchangers for the fixation and generation of carbon dioxide and oxygen, respectively. Furthermore, it involves microalgae cell interaction in solution with substances excreted by the cells (mostly exopolymers) [68]. Likewise, improving the mass transfer coefficient between the CO₂ bubbles and the microalgae solution allows a higher rate of CO₂ fixation for microalgae and, consequently, the proliferation of microalgal biomass [69].

To better understand these aspects, it is essential to understand the reactivity of carbon dioxide in aqueous solutions. Carbon dioxide establishes various balances in its contact with water. The first equilibrium refers to the dissolution of gas in water to form carbonic acid. Carbonic acid undergoes almost instantaneous dissociation in bicarbonate and carbonate ions, with the concentration of total inorganic carbon given by total carbonic acid (H₂CO₃), bicarbonate (HCO₃[−]), and carbonate (CO₃^{2−}), which needs to be considered in the transient response [70,71]. As elucidated by Cuaresma et al. [72], how microalgae cells adapt to use CO₂ as a carbon source is related to carbon concentration mechanisms (CCMs). The photosynthetic mechanism developed by these organisms enables the transport of free CO₂ and bicarbonate ions through a thin plasma membrane after having accumulated in the cell as a carbon reserve, making it possible to assimilate inorganic carbon in the form of bicarbonate or free CO₂ [73,74]. Thus, to provide these elements efficiently throughout the process, it is necessary to understand the solubility rates of the two gases present in the system. In terms of solubility, CO₂ is much more soluble in water than O₂. However, both have low solubility at optimal cell growth temperatures of most microalgae species. To ensure a continuous supply of nutrients and high volumetric coefficients, photobioreactor projects depend mainly on the physical properties of the fluid, flow, system, and gas injector geometry. It is worth highlighting that, to improve mass transfer, reducing the size of the CO₂ bubbles leads to a faster dissolution, slower rise, and a higher surface/volume ratio, facilitating gas exchange [75].

Simultaneously with the increase in carbon dioxide fixation rates, the photosynthetic response of microalgae results in the generation of oxygen. When the gas bubbles are released during the culture process, they coalesce, forming an interface between the liquid

and gas phases and the walls of the photobioreactors. This phenomenon is mainly caused by oxygen accumulation. It is estimated that the concentration of dissolved oxygen cannot exceed 400% of the saturation value, or it leads to a reduction in the surface area available for mass transfer between the gas and the liquid [76]. Mass transfer rates can be quite prejudicial, resulting in low efficiency of the process. This inefficiency in mass transfer directly affects biomass productivity, as it can induce photorespiration and oxidative damage to cells. A high oxygen concentration favors the activity of oxygenase enzymes, which use O_2 instead of CO_2 , harming cell growth. This phenomenon is particularly common in tubular configuration photobioreactors. To mitigate this problem, many tubular photobioreactors incorporate degassing systems, which use devices based on air transport to remove excess oxygen from the air [77]. Another alternative is to manipulate secondary factors, such as activating turbulence in the system, which can increase the efficiency of the gas exchange. Furthermore, the introduction of air flows enriched with CO_2 and O_2 in controlled concentrations can optimize mass transfer, improving the efficiency of the photosynthetic process and, consequently, biomass productivity [78].

As discussed here, a deep knowledge of aspects related to the rational core of microorganisms is crucial to informing various decisions in photobioreactor project design development. However, understanding the biotic factors that influence biomass production is equally essential because, with the metabolic characteristics of strains, we can optimize growth processes, promote the production of specific metabolites, and strengthen the composition of the desired microalgal biomass [79]. Thus, biotic factors mainly involve the conditions that affect microalgae metabolism and their interactions with the environment.

Microalgae species selection is one of the main determinants for the success of any industrial cultivation operation. The taxonomic classification, which organizes the microalgae according to their lines and classes, offers a fundamental understanding of the biological characteristics and performance of the species, allowing the selection of the most suitable ones for different cultivation conditions and production objectives [80]. This process is crucial because each species has unique characteristics that directly influence its efficiency in growth, carbon fixation, biomass production, and added value in industrial processes. For example, species belonging to the class *Chlorophyceae*, such as *Chlorella vulgaris* and *Scenedesmus obliquus*, are widely used due to their high photosynthetic rates and high efficiency in carbon fixation. These characteristics become particularly advantageous for large-scale production, as they can reach cell productivity rates of 0.50–2.11 g/L/d and give a final biomass concentration of 3.0–20.0 g/L [81,82]. These species are frequently chosen when the main objective is to prioritize biomass, especially in controlled photobioreactors, where environmental conditions can be rigorously adjusted to optimize their growth. However, *Chlorella vulgaris* has been more prominently studied for biofuel research due to its ability to accumulate lipids (~ 0.20 g_{lipids}/L/d), whereas *Scenedesmus obliquus* is primarily investigated for carbon capture and storage (~ 0.44 g_{dioxide carbon}/L/d), with a focus on biomass utilization [83,84]. On the other hand, the species of the *Cyanophyceae* class represented by *Arthrospira platensis* (popularly known as *Spirulina*) stand out for high biomass production, especially with high protein content ($>50\%$ dry weight). This characteristic makes this microalgal species of great nutritional interest, being widely used in the food industry and the production of food supplements [85]. Thus, the identification and taxonomic classification of microalgae are essential, allowing us to select the species most suitable for specific production objectives. Species selection not only impacts the efficiency of culture productivity but also determines the economic viability and sustainability of the industrial process. Depending on the objective—whether to maximize biomass or key biocomposts—the correct species selection allied to the cultivation domain conditions is crucial for the operation's success.

Another relevant factor is the identification and management of the cell cycle of microalgal growth. In terms of life cycle, microalgae microorganisms can develop (i) vegetatively or (ii) reproductively. During the vegetative phase, these microorganisms reproduce by cell division, which results in rapid growth and is the most efficient phase for biomass production. The reproductive phase, which occurs with the gamete's formation, is generally associated with the spore's formation or resistant structures, which may be less productive in biomass [86]. Therefore, the controlled adjustment of culture parameters is important and should be used to optimize biomass production in large-scale cultures. For example, the controlled supply of nutrients, such as nitrogen and phosphorus, must be abundant in cultivation systems once we induce the vegetative phase, resulting in higher biomass production. Scarcity, on the other hand, tends to induce microorganisms to enter the reproductive phase, which may be useful, in some cases, for spore production but is not desirable for maximizing biomass [87]. This same effect induces sexual reproduction and has also been observed in conditions of environmental stress, such as intensive use in extreme light temperatures in some microalgae species, as a form of survival or resistance.

Simultaneously, certain physiological stress conditions impose microalgae microorganisms in need of environmental adaptability, which occurs through changes in their genetic expression. Some species, such as *Haematococcus pluvialis*, possess physiological mechanisms that allow them to adapt to these adverse conditions. This adaptation process can result in the production of secondary metabolites, such as astaxanthin, which have various industrial applications, especially in the pharmaceutical, food, and cosmetic industries. This is a promising alternative in the context of advances in genetic engineering, which aims to understand in more detail the metabolism and the pathways responsible for the multiplication of these microorganisms [88]. The genetic sequence not only helps in the identification of new species with exploration potential but also opens possibilities for the genetic improvement of microalgae [89]. Genetic improvement may represent a great advance for microalgae-based process consolidation, allowing the characterization of important biosynthetic pathways. An example is the chlorophyll-binding proteins, which are directly associated with the photosynthetic apparatus. The genes that encode these proteins play a crucial role in increasing microalgal biomass production [90]. Furthermore, microalgae genetic modification has been optimized for various applications, mainly in the bioenergy field, with the aim of improving lipid yields and increasing amino acid conversions. In parallel, studies focused on genetic modification during the cultivation stages have sought to increase the nutritional biocompounds, such as carotenoids [91,92].

Microalgae are subject to multiple ecological interactions that can significantly influence cell multiplication. Among them, symbiosis is one of the main mutualistic relationships in which microalgae species build with other microorganisms, such as bacteria [93]. These consortia can be beneficial once they help in essential nutrient fixation, beyond providing protective barriers against strenuous external conditions, resulting in better metabolic efficiency for cell multiplication. On the other hand, microalgae also face competition from other microalgae species or microorganisms present in the environment, which can negatively affect their productivity. When abiotic resources are limited, competition intensifies, resulting in a reduction in microalgae growth and a decrease in biomass production. This competition is especially accentuated in environments where the supply of resources is restricted, such as in intensive cultures. Likewise, microalgae are subject to the influence of pathogens and predators, which can further impact their productivity. Infections by viruses, bacteria, or fungi can reduce health and microalgae growth, negatively affecting biomass production. In open or closed systems, interactions with predators, such as zooplankton and other aquatic organisms that feed on microalgae, also represent a

challenge. These predators can directly reduce available biomass, prejudicing the success of the culture [94].

Given the current scenario, a deep understanding of abiotic factors related to the design, configuration, and operation of photobioreactors and biotic factors that regulate the physiological conditions of microalgae cells is essential to optimize microalgae cultivation. This understanding becomes even more relevant when considering the critical challenges that characterize microalgal biotechnology. In this context, a common denominator to be highlighted is that the success of industries based on microalgae intrinsically depends on the efficiency of process control systems. The relationship between process control and microalgal biomass productivity is profoundly influenced by seasonal oscillations, daily fluctuations, biotic and abiotic factors, microbiome variability, various cultivation practices, and applied regimes. These factors contribute such that the processes are, at times, highly controlled, at other times managed in an intermediary manner, and, in many situations, vulnerable to unexpected variations (Figure 2). In this way, these factors require rigorous and constant management of the cultivation parameters to ensure that ideal conditions are maintained. As reported in the literature, on bench scales, the precise control of cultivation parameters allows the productivity of some microalgae to exceed 2–5 g/L/d. However, in industrial environments, where the conditions are the most challenging, the maximum productivity of photobioreactors tends to vary between 1.5 and 2.0 g/L/d for microalgae cultures. In open systems, such as raceway ponds, with insufficient or substantially uncontrollable control, these estimates can be even more reduced (~0.5 g/L/d), seriously compromising the process viability and resulting in industrial operations with less-than-expected performance. Therefore, rigorous control and effective management of the processes represent the backbone of ensuring the stability and productivity of large-scale cultures. The dynamic implementation of control strategies, which continually adjust the operational parameters in response to changes in the growing conditions, thus becomes the main differential between industrial systems that have not yet succeeded and those that have failed to achieve their full potential.

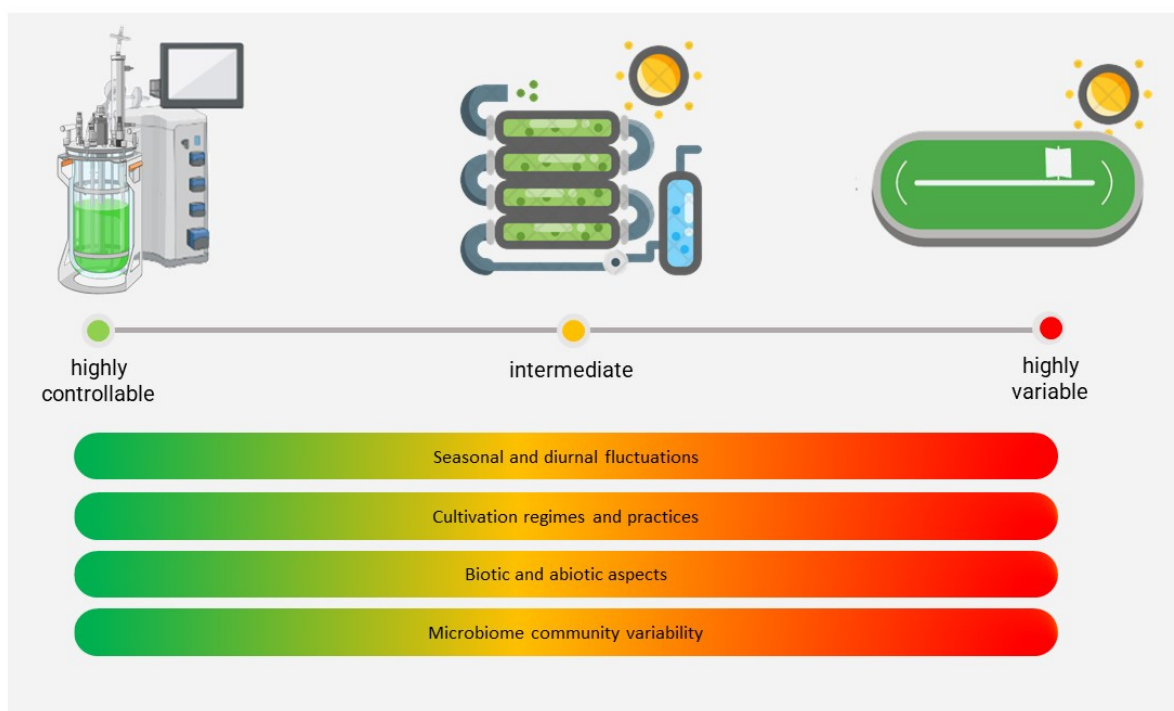


Figure 2. Relation between process control effects and microalgal biomass productivity. Adapted from [95].

3. It Takes Two to Tango: Analyzing the Technological Readiness Level and Market Demand of Microalgae-Based Bioproducts

Before any bioprocess can be implemented and raised in the laboratory on an industrial scale, it is not enough to carry out extensive research, development, and evaluation of its performance. It is also imperative to optimize and model the processes precisely and estimate the financial demands and the potential returns, in addition to deeply considering the social and environmental impacts involved [20]. Only when all these elements are meticulously aligned can the transition to large-scale production be truly feasible. Therefore, a crucial stage in the investment decision-making process for the commercialization of innovative products is to evaluate their current technological readiness level (TRL) [96]. Initially developed by NASA in the 1970s, technological readiness level is a globally recognized benchmarking tool to measure progress and support development from basic research—including blue sky research, which represents the early, exploratory phases of the innovation process—through to reaching practical implementation in real-world applications [97,98].

Structurally, the technological readiness level (TRL) scale can be divided into three major stages: (i) idea conception, (ii) death valley, and (iii) acceptance (Figure 3). The first stage, dedicated to conception and research, encompasses TRLs 1 to 3. This is technology at its most incipient stage. O TRL 1, the initial level, represents the starting point of the technological journey, where scientific research begins to transition from theory to practical application. TRL 2 marks the moment when the possibility of transforming concepts into tangible applications arises, initiating the development and the first investigations. O TRL 3 is achieved when applied research advances in laboratory experiments and the tests validate the first hypotheses, confirming the technology viability. The second phase, which encompasses TRLs 4 to 6, is characterized by intensive development and is commonly known as the death valley. At this stage, the technology begins to take shape but still faces significant challenges before reaching maturity. TRL 4 involves the integration of several components, after being individually tested, to ensure their compatibility and functionality in a controlled laboratory environment. In TRL 5, the functionality of these components begins to be validated in tangible conditions, an essential step to approximate the technology of its application potential. Upon reaching TRL 6, the technology starts to be tested in a relevant environment, bringing it closer to practical application yet still distant from large-scale production. Finally, the demonstration stage includes TRLs 7 to 9, representing the transition to commercialization and acceptance. In TRL 7, the technology consists of a crucial framework, with functional prototype implementation in a real environment that simulates and reflects the intended operating conditions. O TRL 8 denotes the final technology validity, which is now fully functional and ready to be operated within the conditions and parameters for which it was designed. Finally, TRL 9 represents the apex of the technological trajectory: full innovation commercialization, with technology fully accepted and implemented in the global market [99,100].



Figure 3. Technology readiness level (TRL) and commercial readiness index (CRI) scale. Adapted from [101].

However, for a technology to be readily available on the market, it is not enough for it to be just technically ready. It is equally crucial that there is market demand for products derived from technology [102]. Both factors—technology and market—must be aligned to ensure their commercial consolidation. Once the technology advances to the demonstration and implementation phases, a new set of variables is introduced to validate the commercial readiness of the technology [103]. The commercial readiness index (CRI), sometimes called a marketing pathway, encompasses a series of stages that enable us to identify the barriers that a given industrial sector may face. This parameter offers a rigorous structure to assess these obstacles and facilitates the financial support organization through a systematic approach, aiming to reduce risks and overcome barriers in the various phases of the marketing process [101].

In light of the above, when we analyze the different models of photobioreactors and their technological maturity, the tubular photobioreactors stand out as the most advanced, with an estimated TRL between 7 and 9 (Table 1). This level reflects the technology consolidation in commercial production, especially in areas such as fine chemicals. Due to their robustness and efficiency, tubular photobioreactors have achieved success in microalgal facilities and continue to be a pillar for large-scale biotechnology applications. Models such as flat-plate photobioreactors and bubble columns (airlift), however, fall within the pilot or semi-industrial phase, with estimated TRLs ranging from 6 to 8. These systems are in

intermediate development levels, where the cultivation and scale production efficiency are still being optimized. Although these photobioreactors show great potential in light distribution and energy economy, they still face technical and economic challenges to being competitively implemented on a large scale. Moreover, hybrid photobioreactors present an estimated TRL of 5–7, indicating that they are in the initial development stage, with some prototypes still in experiments or integration tests. These systems combine different types of photobioreactors, seeking optimization of both performance and operational cost, but also need more validation to achieve full technological maturity. Finally, plastic bag photobioreactors are in the very early stages of development, with TRL estimated between 4 and 6. This application is predominantly restricted to academic research and small-scale testing due to its simple and low-cost structure but is still limited in production scale-up and energy efficiency. These systems, with promise for certain applications, need further evolution before they are considered suitable for large-scale adoption.

Table 1. Estimation of the technological readiness level for the main photobioreactor models intended for microalgae-based facilities.

Photobioreactor Design	Technological Readiness Level	Implementation Costs (kUSD/m ³)	Status	Bottlenecks
Tubular	TRL 7–9	40.0–50.0	Industrial scale	Light efficiency and nutrient distribution
Flat plate	TRL 6–8	~150.0	Pilot and semi-industrial scale	Culture maintenance and flow control
Bubble column (airlift)	TRL 6–8	5.0–10.0	Pilot and semi-industrial scale	Light efficiency and culture homogeneity
Hybrid	TRL 5–7	4.0–15.0	Pilot and semi-industrial scale	Integration between systems and operating costs
Plastic bags	TRL 4–6	1.0–3.0	Laboratory and pilot scale	Fragility of materials and temperature control

Moreover, it is important to highlight that the large-scale consolidation of the technological maturity of photobioreactors is often associated with the cost–benefit of their installation and their scalability potential. The implementation cost of photobioreactors is closely linked to the quality of materials required by each configuration, as well as the specific area requirements. As shown in Table 1, tubular photobioreactors, with the highest level of technological maturity, have implementation costs in the range of 40–50 kUSD/m³, significantly lower than flat-plate photobioreactors (~150 kUSD/m³) [104]. This substantial difference can be attributed to the amount of material required for construction, with rectangular configurations requiring more material than cylindrical tubes. Furthermore, tubular photobioreactors, which produce higher value-added products, help balance the initial investments, justifying their higher cost when compared to models with lower technological maturity [105]. In contrast, models with intermediate technological maturity, such as bubble columns and hybrid systems, have lower implementation costs but still face considerable challenges in terms of productivity and engineering setups (scale-up), hindering their full consolidation.

Additionally, when we analyze microalgal biotechnology in a broad manner, it is possible to observe that microalgal biomass exploitation for commercial purposes is not a recent idea. In fact, this field has developed consistently over the years, especially as a food source and in supplements, with technologies that have already reached levels of TRL 8–9 and CRI 4 (Figure 4). These food bioresources have been traditionally consumed across various cultures, with established markets in Asia, Europe, and North America [106]. The sustained

growth in demand for these products is closely linked to the perception of microalgae as a healthy food source, making them particularly attractive as dietary supplements due to their high protein content and overall nutritional value [107]. Additionally, fine chemical products, such as β -carotene and astaxanthin, exhibit the highest technological readiness level (TRL 8–9). These bioproducts, with CRI 6, demonstrate a high commercial readiness level, being widely recognized and distributed globally. They can be marketed under various brands, which attests to both their formal registration and proven market success. Their market leadership is further emphasized by the absence of alternative natural sources, as is the case with phycocyanin, which only has a synthetic countertype. This factor further strengthens their established position in the market [108].

Microalgae-based feeds for animal nutrition, especially for aquaculture and pets, are already a reality [109]. These bioproducts are used as essential nutrient sources, reflecting a market in the maturation process, and are classified with CRI 4. Also, although there is a growing interest in microalgae as livestock feed, this market is still in development but not as established as the aquaculture sector. While some operational trials and commercial activities are underway, they remain in an early stage (CRI 3) [110]. On the other hand, microalgae-based biofertilizers and other intermediate-volume biomaterials, such as bioplastics, are classified with TRL levels between 4 and 6, reaching CRI indices between 2 and 3. These products are in the testing and preparation phase, with a commercial adoption that is still growing but not fully consolidated [111]. In contrast, microalgae-based biofuels and bioenergy sources, recognized as potential commodities, are found in a more initial phase of development (TRL 3–5), with commercial readiness levels varying between 2 and 3. Some authors have reported TRL levels that have reached around 6 [112]. However, it is worth noting that competition with fossil fuels, especially petroleum, represents a significant challenge for full biofuel commercialization.

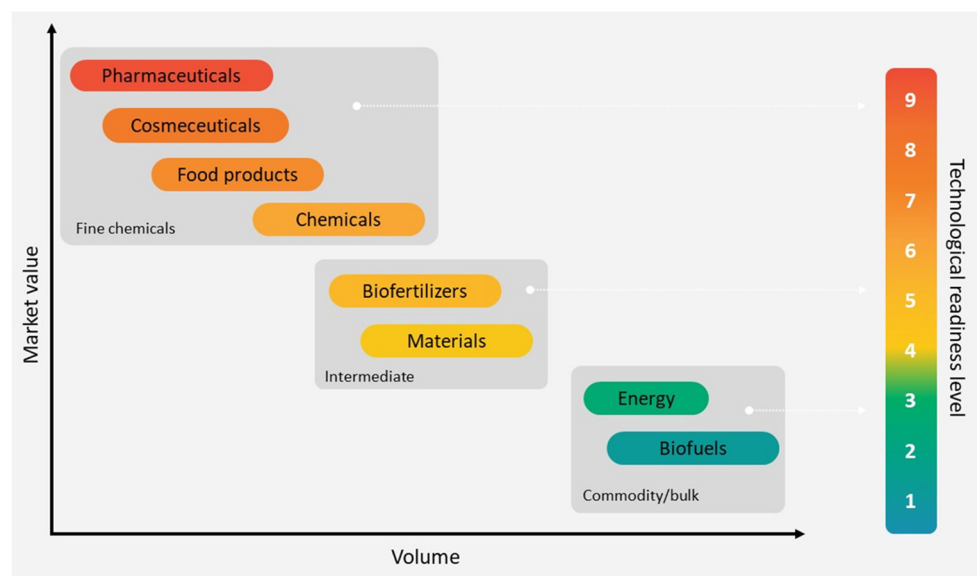


Figure 4. Technological readiness level of microalgae-based products from a market value and volume perspective. Adapted from [113].

4. Future Directions

In order for photobioreactors to advance from their current levels of technological readiness to more advanced stages, stakeholders should adopt a comprehensive and multifaceted approach that integrates operational optimization, technological innovation, technical capacity building, infrastructure investments, and a thorough analysis of eco-

nomic and environmental feasibility. In this context, fostering collaborative research and development among academia, industry, and government is the starting point for optimizing photobioreactor designs and facilitating the transition from laboratory-scale to commercial-scale systems. Furthermore, the implementation of tax incentives for pilot-scale demonstrations is vital to assess photobioreactor performance under real operational conditions. Process optimization and standardization will significantly contribute to enhancing efficiency, reducing operational costs, and promoting broader adoption of this technology.

Precise control of parameters, such as temperature, pH, light intensity, and nutrient supply, maintains the stability and productivity of the system. The integration of real-time monitoring sensors and automated systems allows for dynamic and accurate adjustments, ensuring that the cultivation environment remains within optimal conditions. Currently, companies such as Solazyme (TerraVia) employ sophisticated computational systems, such as the SCADA system, that enable the capture of all environmental and culture parameters for data analysis while simultaneously monitoring and controlling these factors in real time, thus ensuring ideal growth conditions for their microalgae [114]. Other companies also utilize laboratory information management software to document process control and batch validation, enabling quick access and facilitating the predictive control of the photobioreactor. These technologies enable rapid research on process variables to achieve the desired production, thereby contributing to the scalability of algae-based products once environmental conditions can be instantly adjusted to maintain high productivity.

Furthermore, it is recommended to select microalgal strains with rapid growth and greater resistance to adverse environmental conditions, as this enables shorter cultivation cycles and, consequently, higher productivity. By applying advanced genetic engineering techniques, such as CRISPR, microalgal strains can be made more productive, resilient, and adaptable to various environmental conditions. Examples like those from ExxonMobil-Viridos demonstrate the success of the genetic modification of strains and optimizing the production of biofuels and other high-value compounds while simultaneously improving yield and environmental performance [115]. These technological innovations, despite requiring an expensive initial investment, must be adopted because they do not merely increase productivity but also reduce long-term operational costs, improving the robustness and efficiency of the systems and making microalgae production more economically viable.

Additionally, the efficient operation and success of photobioreactors require continuous training for staff. Training programs should focus on new technologies, data analysis, process control, and applied engineering solutions, preparing operators to manage ongoing innovations in the field. Collaboration with universities and specialized research centers is strongly recommended to enhance operational practices and ensure a qualified workforce. Through the integration of academia and industry, the adoption of risk management practices, including the development of contingency protocols for operational failures and periodic testing, will facilitate the identification of vulnerabilities, thereby promoting the continuous advancement of photobioreactors.

In economic terms, effective strategies for decision-makers involve optimizing operational costs through automation to reduce dependence on labor-intensive work. The adoption of innovative technologies, such as hybrid systems, can increase productivity and reduce land requirements, resulting in lower costs. Environmentally, it is essential to prioritize the use of renewable energy sources to power the systems, minimizing the carbon footprint. Integrating photobioreactors in locations near sources of wastewater or excess CO₂ can enhance the sustainability of the process, utilizing waste as resources and creating a closed-loop system that prevents pollutant emissions. Companies like Algenol exemplify this approach by optimizing the conversion of CO₂ into valuable products, reducing carbon emissions [116]. Solazyme (TerraVia), in turn, uses a combination of photobioreactors and

conventional bioreactors to improve process efficiency and reduce costs while also utilizing agricultural waste and by-products as nutrient sources for algae, promoting a circular economy [114]. Therefore, integrative and practical strategies like these, grounded in solid scientific principles, not only enhance economic efficiency but also promote more sustainable operations, driving photobioreactors and microalgal biotechnology to a new industrial level where innovation and sustainability intertwine synergistically. Undoubtedly, it is essential to emphasize that the initial implementation of these strategies can be substantially costly, presenting a significant challenge for their large-scale adoption. However, in the long term, these integrative approaches hold the potential to boost productivity rates, enhance efficiency in resource consumption, and optimize the overall economics of the process, paving the way for overcoming the bottlenecks in microalgal biotechnology.

5. Conclusions

Photobioreactors represent a crucial component for the advancement of microalgal biotechnology, as they are essential for maximizing cellular productivity and optimizing the use of both biotic and abiotic resources. Their capacity for customization is a determining factor, as different types of microalgae and their bioproducts require specific operational conditions. This necessitates technical innovations and sophisticated engineering to ensure process efficiency, directly influencing the scalability, viability, and competitiveness of photobioreactors.

In addition to the technical aspects, optimizing the cost–benefit ratio and aligning with market demand are key elements in ensuring that photobioreactors become competitive not only in the production of fine chemicals for the food and pharmaceutical industries but also in emerging sectors such as biofuels. In this context, the continuous improvement of these systems, with a focus on reducing operational costs and increasing productivity, will be essential for their global integration.

By overcoming the technological and economic challenges that still hinder the engineering of photobioreactors, coupled with progress in research and continuous innovations, as well as the experience gained from various photobioreactor configurations, these systems have the potential to establish themselves as robust and scalable solutions for the industrial production of microalgal-based bioproducts. Undoubtedly, photobioreactors will play a strategic role in sustainable and innovative industries, contributing decisively to a greener and more technologically advanced future.

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