

Use of Nanobubbles to Improve Mass Transfer in Bioprocesses

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Abstract: Nanobubble technology has emerged as a transformative approach in bioprocessing, significantly enhancing mass-transfer efficiency for effective microbial activity. Characterized by their nanometric size and high internal pressure, nanobubbles possess distinct properties such as prolonged stability and minimal rise velocities, allowing them to remain suspended in liquid media for extended periods. These features are particularly beneficial in bioprocesses involving aerobic strains, where they help overcome common obstacles, such as increased culture viscosity and diffusion limitations, that traditionally impede efficient mass transfer. For instance, in an experimental setup, nanobubble aeration achieved 10% higher soluble chemical oxygen demand (sCOD) removal compared to traditional aeration methods. Additionally, nanobubble-aerated systems demonstrated a 55.03% increase in caproic acid concentration when supplemented with air nanobubble water, reaching up to 15.10 g/L. These results underscore the potential of nanobubble technology for optimizing bioprocess efficiency and sustainability. This review delineates the important role of the mass-transfer coefficient (k_L) in evaluating these interactions and underscores the significance of nanobubbles in improving bioprocess efficiency. The integration of nanobubble technology in bioprocessing not only improves gas exchange and substrate utilization but also bolsters microbial growth and metabolic performance. The potential of nanobubble technology to improve the mass-transfer efficiency in biotechnological applications is supported by emerging research. However, to fully leverage these benefits, it is essential to conduct further empirical studies to specifically assess their impacts on bioprocess efficacy and scalability. Such research will provide the necessary data to validate the practical applications of nanobubbles and identify any limitations that need to be addressed in industrial settings.

Keywords: nanobubbles; bioprocesses; bioconversion; mass transfer



Citation: Silva, J.; Arias-Torres, L.; Carlesi, C.; Aroca, G. Use of Nanobubbles to Improve Mass Transfer in Bioprocesses. *Processes* **2024**, *12*, 1227. <https://doi.org/10.3390/pr12061227>

Academic Editors: Soon-Thiam Khu and Tianzhi Wang

Received: 16 May 2024

Revised: 8 June 2024

Accepted: 13 June 2024

Published: 15 June 2024



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1. Introduction

The limitations in gas mass transfer are one of the main bottlenecks in many bioprocesses. Under aerobic or anaerobic conditions, the metabolism of microorganisms depends on most of the substrates that must be provided from a gaseous to the liquid phase where it is available. The mass-transfer rate is determined by several factors, including the mass-transfer coefficient (k_L), the interfacial area between the gas and liquid phases (a), and the saturation concentration of the dissolved gas (C^*) [1]. The mass-transfer coefficient measures the rate of substance transfer between phases per unit area per concentration difference, which is crucial for process efficiency. The application of nanobubbles in several bioprocesses has attracted attention because of their properties and the potential to improve their performance. These tiny bubbles possess a defining characteristic: their diameter is typically less than 1 μm [2]. This size provides unique properties and capabilities that are increasingly valuable for various applications [3,4].

One of the defining features of nanobubbles is their exceptional stability [5]. Unlike larger bubbles, nanobubbles can remain suspended in a liquid medium for extended

periods, often lasting hours or even days [6]. This remarkable stability is due to their small size and low rising velocities, which are approximately $2.7 \text{ nm}\cdot\text{s}^{-1}$ for nanobubbles [7] with diameters of 50 nm and $272 \text{ nm}\cdot\text{s}^{-1}$ for those with diameters of 500 nm [8]. This extended lifespan in liquid media sets nanobubbles apart and positions them as compelling agents for optimizing mass transfer in bioprocesses [8]. Another important issue in this regard is that nanobubbles of air also exhibit high internal pressure (approximately 30 atm) within a typical 100 nm nanobubble in pure water [9]. This elevated internal pressure can profoundly influence the effect of its presence, particularly in improving the mass transfer and catalysis of chemical reactions [10], because it increases the solubility of the gaseous compound in the solution; the smaller the bubble, the greater the gas solubility [11]. This attribute has significant implications in bioprocesses, where microorganisms often depend on the availability of oxygen and other gases as carbon sources [12].

Nanobubbles are often associated with high zeta potential [13]. This property indicates the presence of electrical charges on their surfaces, which can affect their stability and interactions with other particles or substances in liquid media. A high absolute value of the zeta potential typically produces repulsive forces that prevent bubble coalescence and help to maintain stability [14]. Studies have investigated the relationship between zeta potential, pH, and bubble size, with pH being inversely proportional to zeta potential and bubble size [15,16].

Nanobubbles enhance mass transfer in bioprocesses, leading to faster, higher-quality production [17]. Beyond biotechnology, nanobubbles are used in various fields, such as medicine, agriculture, surface cleaning, water treatment, energy systems, microfluidic dynamics, engineering, flotation, and cosmetics [18–25]. Similarly, they have been explored in nanomedicine for imaging and drug delivery applications [19].

This review discusses the application of nanobubbles to improve mass transfer in bioprocessing. Nanobubbles, with their unique physical properties and behavior in liquid media, have not only attracted attention from a scientific point of view but also in solving bottlenecks of practical significance in environmental and industrial bioprocesses. The focus of this discussion is to elucidate how nanobubbles can overcome the traditional limitations of mass transfer, particularly in bioreactors, where gas transfer efficiency is a limitation or key phenomenon.

2. Mass-Transfer Limitations in Bioreactors

Mass transfer involves the movement of a substance from one phase to another to establish an effective and persistent contact between the different components involved in the process. The efficiency of this process is a key aspect of many bioprocesses, wherein the transport of substances between different phases is fundamental to achieving efficient bioconversion [26].

Several limitations often arise that affect the effectiveness of mass transfer in bioreactors. Mixing is often a challenge, especially in aerobic processes, because of the notable increase in culture viscosity. Viscosity, in this context, refers to the resistance of the culture medium to flow. When elevated, it imposes a substantial constraint on mass transfer in the bioreactor. Several factors contribute to the increased viscosity of microbial cultures, such as the appearance of diffusion barriers, mainly in high-density cultures [27]. These barriers can be considered physical obstructions that hinder the movement of molecules and particles within a mixture. It is hypothesized that as these barriers accumulate, they create areas within the mixture where mass transfer becomes slower and less efficient. In practice, an increase in viscosity can create numerous operational challenges, affecting the distribution of gases and nutrients throughout the culture mixture and making it difficult for microorganisms to access these essential elements. Thus, it can hamper microbial growth and improve the efficiency of the bioconversion processes.

Diffusional limitations also arise from other factors, such as biofilm formation and the production of extracellular polymers. These elements lead to the development of a dense physical matrix that acts as a barrier for the transfer of nutrients, oxygen, or other

gaseous compounds dissolved in the medium and is required for metabolism and metabolic products. As a result, concentration gradients are created within the culture, with some areas having insufficient access to essential nutrients, whereas others may accumulate toxic byproducts. This imbalance can decrease cell growth and compromise the overall productivity of the bioprocess [28,29].

In general, diffusion limitations result in delayed reactions, which can significantly affect desired productivity. Many works have devised and implemented innovative strategies to overcome these challenges, such as:

- **Incorporating Additional Phases:** This approach introduces physical variations that can facilitate improved contact between phases, thereby expediting mass-transfer processes [30].
- **Immobilization of Microbial Cells on Solid Supports:** An alternative approach involves immobilizing microbial cells on solid supports rather than dispersing them in an aqueous phase [31]. This strategy addresses diffusion limitations by anchoring microbial cells to solid supports, thereby creating a fixed matrix that facilitates a more controlled and efficient nutrient and gas exchange [32].
- **Enhanced Design of Film Reactors:** Film reactor operation and practical design have been refined to address diffusion limitations [33], improve mass-transfer dynamics by optimizing these reactor systems, and increase their efficiency.

Despite the existing approach to improve mass transfer in bioprocesses, interest is growing in the potential of nanobubbles owing to their multiple advantages.

3. Generation and Characteristics of Nanobubbles

The generation and application of nanobubbles represents an important innovation to further enhance the efficiency and effectiveness of bioprocesses, particularly in the context of overcoming mass-transfer limitations in bioreactors. Nanobubble generation encompasses a wide range of methodologies, each of which offers specific advantages and can be used for various applications.

- **Decompression:** Controlled decompression processes that manipulate pressure within a liquid medium induce gas molecules to congregate into nanoscale bubbles, thereby presenting a method for nanobubble formation [34].
- **Solvent Substitution:** Specific alterations in the chemical properties of solvents can induce the spontaneous formation of nanobubbles under controlled conditions. Changes in solvent composition, polarity, or temperature can create a favorable environment in which dissolved gases aggregate into stable nanoscale bubbles [35].
- **Membrane Filtration:** Specialized membranes with nanoscale pores were used to generate nanobubbles in the liquids. This method allows precise control of nanobubble production [36,37].
- **Hydrodynamic Cavitation:** Nanobubbles can be produced by applying hydrodynamic forces. These forces induce rapid fluid motion and turbulence within the liquid, prompting the formation of ultrafine bubbles [38,39].
- **Electrolysis:** Nanobubbles can be precisely produced by electrolysis of water, generating both oxygen and hydrogen bubbles. The dimensions and number of bubbles depend mainly on the current density, geometry, and type of electrode used [40].
- **Other Innovative Approaches:** Various innovative techniques have broadened the scope of nanobubble generation methods, including repeated compression, vibration, manipulation of internal pressure, rotor–stator systems, and controlled compression–decompression cycles [41,42].

Table 1 presents a brief comparison of different methods.

Table 1. Comparison among the nanobubble technology generation methods.

Generation Method	Principle	Advantages	Disadvantages	Typical Applications
Hydrodynamic Cavitation	Liquid flows through constrictions, creating pressure changes that generate nanobubbles	Efficient for large-scale production	High energy consumption, potential for wear	Wastewater treatment, enhanced bioreactors
Electrolysis	Electrical current passed through water generates gas bubbles at electrodes	Simple setup, effective bubble formation	High energy use, pH changes, electrode degradation	Water treatment, oxygenation in bioprocesses
Membrane Filtration	Gas passes through a porous membrane into liquid to form nanobubbles	Precise control over bubble size	Potential membrane fouling, moderate energy use	Biotechnology, pharmaceutical

4. Mass-Transfer Mechanisms Enhanced by Nanobubbles

Nanobubbles are primarily characterized by their nanometric size, which generates a substantially higher surface-to-volume ratio than conventional bubbles. Nanometric size refers to the dimensions in the nanometer range, with typical values ranging between 1 and 100 nm, where materials exhibit unique properties owing to their small scale. In addition, their low ascent velocities allow them to remain stable in liquids for long periods until they interact with surfaces and microorganisms [43].

In the literature, it is evident that as the bubble size decreases, mass transfer improves, as shown in Table 2. This advantage is mainly due to the more extensive interactions between the phases, which promotes highly efficient mass transfer [44].

Table 2. Increase in volumetric mass-transfer coefficient inverse to bubble size.

Generation Method	Size [nm]	Volumetric Mass-Transfer Coefficient [h^{-1}]	Reference
Ceramic tubular membrane (pore size of 100 nm)	200–400	23.99	[45]
	400–700	15.59	
	35,000–85,000	2.87	
Vortex	90,000	17.82	[46]
Upper venturi sparger type	96,000	10.14	
Lower venturi	135,000	10.98	
High-speed rotation	500–5000	0.234	[47]
	500–3500	0.21	

To fully understand the factors that would increase mass transfer when using nanobubbles, their unique characteristics must be recognized.

- **Rising Velocities:** The bubble diameter is directly proportional to the ascent rate, according to the law of Stokes [48]. Nanobubbles exhibit reduced ascent velocities, allowing them to remain suspended in liquid for prolonged periods. This prolonged suspension is important because it results in a longer surface-volume contact time than larger bubbles, as the latter rise rapidly [49].
- **Surface-to-Volume Ratio:** Nanobubbles have a larger interfacial area with the surrounding medium. Consequently, the mass-transfer efficiency was enhanced. This idea highlights the importance of the nanobubble size in improving mass transfer in various applications [50].
- **Precise Control through the Mass-Transfer Coefficient:** Nanobubbles allow precise control of the mass-transfer coefficient through various operational techniques that

optimize their applications in bioprocesses. For example, adjusting the temperature can improve the stability of nanobubbles and increase the solubility of the gases that they transport. This phenomenon occurs because the high internal pressure of nanobubbles, derived from their nanometer size, intensifies their concentration [51,52], and effective mixing strategies within the bioreactor facilitate uniform distribution of the nanobubbles without premature coalescence or breakup, thus maintaining their ability to enhance mass transfer. These strategies ensure that nanobubbles interact effectively with the medium, releasing gases in a controlled and sustained manner, which improves their availability for metabolic reactions in biological processes [53,54].

5. Determining Mass-Transfer Coefficients in Nanobubble-Enriched Systems

Understanding and quantifying the mass-transfer coefficients in systems enriched with nanobubbles involves assessing various factors and applying precise modeling techniques. This approach addresses the complex challenges faced by these systems. The key to this process is determining the optimal concentration of nanobubbles, which is influenced by specific factors that can significantly impact the system efficiency [55]:

- **Influence on Bubble Dispersion:** Bubbles dispersed in a liquid play an important role in facilitating mass transfer, particularly in processes where nano- and micro-sized particles are enriched during bubble formation and bursting [56]. It has been shown to improve mass-transfer coefficients owing to factors such as Brownian motion and increased surface area. As nanobubbles burst or dissolve, they rapidly release their contents, creating localized zones with high solute concentrations. This can enhance solute availability to the surrounding medium, improving the efficiency of reactions or metabolic processes in these applications [49]. Essentially, the increased presence and rapid dispersal of solutes enhance their interaction with biological entities or chemical reactants, which is crucial for processes requiring efficient and uniform distribution of critical components.
- **Impact on Absorption Processes:** The presence of nanobubbles can increase the mass-transfer coefficients in the bubble absorption processes. However, determining the optimal nanobubble concentration is relevant, as low concentrations could be ineffective, whereas high concentrations could lead to counterproductive effects, such as saturation or blocking of transfer interfaces [57].
- **Advances in Modeling and Simulation:** To effectively address these challenges, mass-transfer modeling in industrial and environmental settings has adopted advanced techniques, such as the Finite Element Method (FEM) and Control Volume Method (CVM). These techniques allow detailed and accurate analysis of fluid flows and mass-transfer rates in complex systems, thus enabling the optimization of processes and ensuring more efficient and sustainable results that can be used to determine the mass-transfer coefficient [58,59].

To maximize the benefits of nanobubbles in enhancing mass transfer, it is important to understand and quantify how they influence the systems in which they are incorporated. This implies not only a thorough understanding of the physicochemical properties of nanobubbles but also the ability to apply and adapt advanced modeling and simulation methodologies to predict and manage complex interactions within nanobubble-enriched systems. In this context, it is important to determine the optimal concentration of nanobubbles, which involves assessing how their dispersion affects mass transfer, especially in processes in which nano- and micro-sized particles are enriched during bubble formation and break-up. These events improve the mass-transfer coefficients due to the rapid release and localized dispersion of solutes, increasing the availability of solutes to the surrounding medium and improving the efficiency of reactions and metabolic processes.

These advances are essential for optimizing processes and ensuring more efficient and sustainable results. However, measuring the volumetric mass-transfer coefficient $k_L a$ in these systems presents additional challenges owing to the small size and high stability of nanobubbles, which require more sophisticated measurement approaches to

ensure accurate and representative data. This comprehensive understanding and advanced methodological approach are indispensable to fully exploit the capabilities of nanobubbles in improving bioprocesses and other industrial and environmental systems.

6. Effect of Internal Pressure on Solubility

Increasing the solubility of gases in liquids can be effectively achieved through the internal pressure characteristics of nanobubbles. Studies indicate that nanobubbles can maintain high internal pressures, which significantly enhance the solubility of gases [60].

The internal pressure of nanobubbles has been reported to be as high as 120–240 psi, which contributes to their stability and unique properties [61]. Molecular dynamics simulations have revealed that the gas inside nanobubbles exhibits ultrahigh density with a double-layer surface charge that counteracts the surface tension, which ultimately aids in the stabilization of nanobubbles [62]. Additionally, the high gas density and internal pressure of interfacial nanobubbles, along with their strong interfacial gas enrichment behavior, have been confirmed, further supporting the idea that nanobubbles can maintain high internal pressure [63]. Moreover, environments that confine gases to the nanoscale, such as solvents, can increase the solubility of gases such as H_2 , CH_4 , and C_2H_6 [64]. These insights underscore the potential of nanobubbles to enhance the gas solubility in various liquids by leveraging their unique internal pressures. From this perspective, certain factors governing these processes must be considered.

- **Laplace Law:** According to this law, the pressure inside a bubble is inversely proportional to its radius. Mathematically, this can be expressed as, $P = P_0 + 2\gamma/r$, where P is the pressure inside the bubble, P_0 is the external pressure, γ is the surface tension, and r is the bubble radius. For nanobubbles with extremely small radii, the $2\gamma/r$ term becomes significantly larger, resulting in significantly higher internal pressures than those observed for larger bubbles [65].
- **Henry's Law:** Owing to their small size, nanobubbles experience a much higher internal pressure than larger or macroscopic bubbles. This high pressure compresses the gases inside the nanobubbles, thereby increasing their molecular concentration [66]. According to Henry's law, the solubility of a gas in a liquid is directly proportional to the pressure of the gas in the liquid. In the context of nanobubbles, a high internal pressure effectively increases the partial pressure of the gases inside the bubbles, which, in turn, increases their solubility in the surrounding liquid [67].
- **Dissolution Process:** When nanobubbles encounter a liquid, the gas inside the bubble tends to dissolve into the surrounding liquid owing to the difference in gas concentrations between the inside of the bubble and the liquid. The high pressure inside the nanobubble forces more gas molecules out of the gas phase and into the solution, thereby increasing the amount of dissolved gas [68]. This phenomenon is also described by Henry's Law.

In short, the increase in gas solubility mediated by nanobubbles in liquids is a result of the high internal pressure maintained inside them, owing to their small size and associated surface tension.

7. Effects on Microbial Activity and Viability

Many authors have reported that nanobubbles enhance bioprocesses by modifying the physicochemical properties of water, which supports physiological activity and promotes cell growth. In this context, for aerobic cultures, nanobubbles allow for a constant supply of oxygen, favoring metabolic activity and growth by increasing mass transfer. W. Xiao and Xu [17] studied the use of nanobubbles in biofilters using commercial mixed cellulose aerated with nanobubbles and improved the efficiency of the oxygen supply capacity, which accelerated and expanded the size of the biofilm, demonstrating that the aeration of the nanobubbles positively modified the microbial community. The application of micro-nanobubbles for the bioconversion of CO_2 to CH_4 enhances the mass transfer of H_2 and biomass growth and significantly improves bioconversion efficiency [69]. Guo et al. [70]

reported that micro-nanobubbles could improve mass-transfer efficiency in liquids and reduce the redox potential, which is relevant for the growth and metabolism of chemoautotrophic microorganisms. W. Xiao et al. [71] found that nanobubble aeration effectively provided extra oxygen for microbial aggregates, achieving a notable improvement in the structural characteristics and performance of microbial aggregates. Furthermore, several studies have applied this technology to different microbial strains, as shown in Table 3, which is attributed to the long lifetime of nanobubbles and their high gas solubility in liquid media [72].

Table 3. Nanobubble applications and their impact on microbial growth and metabolism.

Gas	Microbial Community	Use	Results	Reference
O ₂ and H ₂	<i>Nannochloropsis oculata</i> (N. oculata) and <i>Chlorella vulgaris</i> (C. vulgaris)	Effects of gas nanobubbles on microalgae growth.	Up to 59% increase in oxygenated and hydrogenated media compared to control media.	[73]
Air, N ₂ , H ₂ , and CO ₂	<i>Lactobacillus acidophilus</i> 1028	Nanobubble-type performance of different gases in deionized water in terms of growth.	N ₂ nanobubbles showed the best performance, reaching the highest rate of increase of 51.1% after 6 h cultivation.	[74]
Air	<i>Haematococcus lacustris</i> and <i>Botryococcus braunii</i>	Effect of nanobubbles on the growth and metabolism of different microalgae.	The nanobubbles enhanced the growth of H. lacustris and B. braunii, and the highest pro-motion ratio was up to 44% and 26%, respectively.	[75]
O ₂	<i>Saccharomyces cerevisiae</i>	Increased yeast growth rate.	Stimulates the proliferation rate of yeast cells by enhancing their biomass production.	[76]

Although nanobubbles offer numerous benefits for bioprocesses, several potential limitations and drawbacks need to be considered. High concentrations of nanobubbles, especially those containing reactive oxygen species, can induce oxidative stress in cells, damaging cellular components, such as membranes, proteins, and DNA, and potentially reducing cell viability and productivity [77]. Additionally, nanobubbles formed by electrolysis may alter the pH of the solution, affecting the growth and metabolism of certain microorganisms that are sensitive to pH changes. Not all microbial strains respond positively to nanobubble aeration; some might be more sensitive to the physical and chemical properties of nanobubbles, leading to inhibited growth or metabolic activity [3]. Although nanobubbles can enhance biofilm growth in some contexts, excessive or uncontrolled biofilm formation can lead to operational issues, such as clogging and increased resistance to mass transfer [78].

In summary, the implementation of nanobubbles enhances microbial processes. Their unique properties facilitate the efficient separation of low-density particles such as algae and small flocs, offering a viable alternative to traditional sedimentation methods for algae removal from water systems. This capability is particularly effective because of the increased levels of dissolved oxygen introduced by nanobubbles at the sediment–water interface [79]. Furthermore, the enhanced oxygen supply provided by nanobubbles optimizes the circulation and functionality of microorganisms. This improved oxygenation boosts the metabolic activity of these organisms and enhances overall mass-transfer processes within the ecosystem. Nanobubbles contribute to more effective bioremediation and water treatment processes by enhancing the viability and performance of microbial communities [80].

8. Applications of Nanobubbles in Bioprocesses

As described previously, nanobubbles are increasingly being recognized for their unique properties and transformative potential in bioprocessing. Characterized by their microscopic size and high internal pressure, nanobubbles enhance mass-transfer efficiency and have a significant influence on the kinetics of biochemical reactions or bioconversions. Several authors have demonstrated improvements in mass transfer when implementing nanobubbles in their studies. These contributions have revealed significant advantages and have shown improvements in this type of process, such as:

- **Improvement in Mass Transfer in Several Types of Bioreactors:** Successful cases have been reported in the literature. One of them was the work of Temesgen et al. [81], where nanobubbles were applied in an aeration mechanism in a laboratory-scale semi-batch biological reactor for wastewater treatment. The oxygen utilization rate and k_{La} were doubled, increasing from 0.075 to 0.159 mg O₂ · min^{−1} and from 0.07 to 0.13, respectively. This improvement was attributed to the longer residence time of the nanobubbles in the aqueous system and their high surface-area-to-volume ratio. Consequently, the biodegradation rate of organic matter increased from 5.83 to 17.5 mg · L^{−1} h^{−1}. This resulted in a 60% reduction in the hydraulic residence time required to achieve similar levels of organic waste degradation. Oxygen nanobubbles have been used to enhance growth in various organisms, but their impact on yeast indicates that yeast cultures with oxygen nanobubbles showed higher maximum specific growth rates compared to those without nanobubble addition, indicating that oxygen nanobubbles can effectively enhance yeast growth [54]. Yaparatne et al. [82] obtained dissolved oxygen levels and improved soluble chemical oxygen demand removal by 10% compared to coarse bubble aeration with the same air input; they obtained activated sludge that was more compact, simplifying subsequent sludge handling when nanobubbles were applied. Microbial analysis revealed fewer filamentous bacteria and a lower relative abundance of floc-forming bacteria, such as *Corynebacterium*, *Pseudomonas*, and *Zoogloea*, and changes in the microbial community composition at the genus level and reduced alpha and beta diversities were observed in the nanobubble-treated sludge. Nanobubbles enhance the breakdown of hard-to-degrade organic matter [83], boost electron transfer systems in anaerobic digestion, and optimize anaerobic microbial communities. This study investigated the use of nanobubble water to increase the yield of medium-chain carboxylic acids from cow manure via chain elongation. The results indicated that air nanobubble water increased the caproic acid concentration to 15.10 g · L^{−1}, a 55.03% increase over that of the control.
- **Enhanced Aeration and Oxygen Transfer:** In water treatment, where ozone is used as a medium to oxidize organic pollutants, nanobubbles accelerate the process by increasing oxygen mass transfer, thereby providing a more efficient pollutant removal rate [84]. If this technology is strategically combined with shear stress, it can improve the performance and structure of biofilms by optimizing the amount of oxygen in the liquid medium, resulting in better stability and activity of biofilms [50]. Wu et al. [85] implemented ozone nanobubble technology and generated nanobubbles with a diameter < 200 nm for the treatment of contaminated wastewater, obtaining a performance 14 times higher compared to conventional bubbles due to the better ozonation by breaking the barrier that ozone had [86].
- **Photocatalytic Applications:** Nanobubbles have been applied in photocatalysis. Nanobubbles not only accelerate the degradation of pollutants but also enhance the overall efficiency of water treatment technologies by intensifying light-mediated reactions [87]. Wang et al. [88] demonstrated that nanobubbles with diameters ranging from 138 to 205 nm improved the removal efficiency of oxytetracycline from 45% to 98% and remained stable in the medium. Also, researchers Fan et al. [89] implemented nanobubbles with a size of 1.08 ± 0.37 μm in their study, with an efficiency of 41–141% higher than that of conventional bubbles in the hole oxidation of H₂O on TiO₂. In both studies, the effect of medium pH on nanobubble size was demonstrated [90].

- **Anaerobic Digestion and Gas Bioconversion:** Nanobubbles enhance mass transfer and methane production during anaerobic digestion and gas bioconversion [91]. Nanobubble technology has demonstrated a favorable impact on promoting methane production in the anaerobic digestion of organic waste, facilitating the transport of organic compounds from the liquid to microbial cells because of its hydrophobic attractive force and ability to adhere to solid surfaces [92]. Wang et al. [93] explored the utilization of high-mobility nanobubble water to augment methane production by enhancing hydrolysis and acidification of cellulose in anaerobic processes. The presence of nanobubbles potentially accelerates biochemical reactions, thereby boosting the efficiency of methane generation from organic waste. Similarly, Fan et al. [94] explored the resilience of anaerobic digestion processes under acidic conditions and demonstrated the mitigation of inhibitory effects using nanobubble water. Their research suggests that nanobubbles facilitate the recovery and stability of microbial communities, enhancing the overall process, even under adverse environmental conditions. Yang et al. [95] investigated the dual role of N₂-nanobubble water in promoting lignin degradation and enhancing methane production during the anaerobic co-digestion of waste-activated sludge and alkaline lignin. This study indicates that nanobubbles can significantly improve the breakdown of complex organic materials, such as lignin, thereby increasing the efficiency of gas production and enhancing the overall bioconversion process. These findings collectively underscore the potential of nanobubbles to improve mass transfer and enhance biogas production in anaerobic digestion, proving them to be a valuable addition to bioprocesses aimed at higher efficiency and sustainability in methane production and organic waste treatment. Nanobubbles also activate the anaerobic growth and metabolism of *Pseudomonas aeruginosa* by delivering essential elements and serving as a source of oxygen, thereby enhancing bacterial activity under anaerobic conditions [96]. For gas bioconversion, such as in eutrophic waters where algal blooms can cause methane emissions owing to a lack of or low oxygen concentration (anoxia/hypoxia) in the medium, the use of oxygen nanobubbles in lake sediments serves as a good supply, increasing the presence of methanotrophs and decreasing methane emissions, and serving as a substrate for subsequent biotransformation into CO₂ [97], demonstrating a possible mitigation strategy for poorly soluble gases in water.
- **Enhancing Fermentation Efficiency:** Nanobubbles provide a distinct advantage by enabling refined and controlled oxygen release, which is important for maintaining optimal conditions during fermentation. Their ability to slowly release oxygen is especially beneficial in prolonged fermentation cycles, ensuring a consistent and precise oxygen supply that contributes to higher-quality products and more stable processes [98]. The high internal pressure and durability of nanobubbles, compared to larger bubbles, enhances oxygen solubility and retention in the fermentation medium [99]. This ensures that adequate oxygen levels are maintained throughout the process. Furthermore, nanobubbles can positively affect microbial growth and metabolism, thereby influencing metabolic efficiency and improving the overall fermentation environment.
- **Minimizing Byproducts in Fermentation Using Nanobubble Technology:** Nanobubbles can enhance the quality of products in the food and beverage industry by reducing the formation of unwanted byproducts during fermentation. The key to this capability is precise control of gas levels in the fermentation environment [100]. The nanobubbles release oxygen in a controlled and sustained manner, which is crucial for preventing oxidative stress in fermenting cells. Oxidative stress often leads cells to divert their metabolic pathways towards the production of aldehydes and organic acids, which can degrade the taste and stability of the final product [101]. By maintaining a stable oxygen environment, nanobubbles ensure that fermentative cells sustain an efficient aerobic metabolism. This reduces the likelihood of secondary metabolite production, which is typically associated with oxidative stress [102]. Additionally, the enhanced oxygen solubility provided by nanobubbles optimizes substrate utilization. This

increased efficiency not only means that more of the substrate is converted into the desired product but also that less waste is produced [103]. Nanobubble technology offers a dual benefit: it enhances product quality while simultaneously reducing environmental impacts by lowering waste and byproduct formation [104,105].

9. Enhancing Bioprocessing Sustainability with Nanobubble Technology

Nanobubble technology supports sustainable bioprocessing practices by improving energy efficiency, reducing waste, and enabling innovative applications. This technology facilitates sustainable manufacturing processes by optimizing resource use and reducing environmental impact.

- **Energy Efficiency through Improved Dissolution Rates:** Nanobubbles enhance the dissolution of gases in liquids more effectively than traditional methods. This efficiency is beneficial for processes that depend on gas dissolution, such as aerobic fermentation or bioremediation, leading to reduced energy consumption [106]. The small size and high internal pressure of nanobubbles increase the surface area available for gas exchange, which accelerates reactions and reduces the energy requirements [107].
- **Minimizing Waste with Precision Delivery:** Nanobubbles can precisely deliver oxygen and other gases within bioreactors, improve the efficiency of biochemical reactions, and reduce resource overuse [108]. For example, in wastewater treatment, precise oxygen delivery optimizes pollutant breakdown, minimizes sludge production, and reduces waste [109].
- **Innovative Applications in Bio-refinement:** Nanobubbles can enhance the extraction and separation of biochemicals from biomass, improve yields under mild conditions, and preserve the functional qualities of these compounds [110]. This process efficiency contributes to resource conservation, allowing greater product extraction from fewer raw materials [111].
- **Enhancing System Longevity and Maintenance:** The stability of nanobubbles can reduce the frequency of bioprocess maintenance. Stable reaction environments reduce stress on bioreactors, extend their lifespan, and decrease maintenance needs, thereby contributing to sustainability by lowering the overall carbon footprint of the facility [112].

Integrating nanobubble technology into bioprocessing enhances operational efficiency and productivity while aligning with environmental sustainability goals. This technology plays a significant role in the sustainable advancement of the bioprocessing industry by promoting efficient and environmentally friendly manufacturing practices.

10. Economic Benefits of Nanobubble Technology in Industrial-Scale Bioreactors

The integration of nanobubble technology into industrial-scale bioreactors has demonstrated substantial economic benefits and operational efficiency. This technology is particularly valuable in environmental engineering and bioprocessing, where precision and efficiency are achieved.

- **Scale-up Considerations:** Scaling up nanobubble systems must consider the particularities of this technology and the limitations of bioprocesses. The high initial costs associated with advanced nanobubble generators and the materials required for durable, long-term operation can be mitigated through economies of scale, government subsidies, and strategic collaboration [113]. Equipment design also poses a challenge, necessitating innovations that ensure uniform bubble size and distribution in large volumes of liquid while maintaining the system [18]. Energy efficiency is key, as generating nanobubbles on a large scale typically demands a high energy input. Optimizing generation methods, integrating energy recovery systems, and employing renewable energy sources can enhance sustainability and reduce operational costs [114]. Furthermore, the integration of advanced monitoring and control systems can optimize bubble production and improve process efficiency. Real-time monitoring

and adaptive control mechanisms can ensure consistent bubble quality and process performance [115].

- **Enhancements in Membrane Bioreactors (MBRs):** Nanobubbles contribute significantly to the maintenance and efficiency of membrane bioreactors. Their unique properties help to prevent or minimize scale buildup on membranes, which typically leads to decreased efficiency and increased maintenance costs. By mitigating scale formation, nanobubbles reduce downtime and prolong the lifespan of membranes, ultimately leading to cost savings and enhanced operational efficiency [116]. The inclusion of nanobubbles increases dissolved oxygen levels, which are critical for aerobic biological processes in MBRs. This enhanced oxygenation improves the metabolic activity of microorganisms, leading to more efficient breakdown of organic pollutants and higher-quality effluent. This improvement not only meets stricter environmental discharge regulations but also reduces the need for additional chemical treatments [117].
- **Cost Reductions in Environmental Engineering:** Nanobubbles have demonstrated better efficacy in the removal of various pollutants, achieving efficiency rates significantly higher than those of traditional methods. This capability is particularly advantageous for industries facing stringent environmental compliance requirements. By employing nanobubbles, facilities can reduce their reliance on chemical treatments, which are often costly and environmentally hazardous [118].
- **Bioprocess Optimization:** The ability of nanobubbles to maintain high dissolved oxygen levels can significantly enhance the efficiency of biochemical reactions. Enhanced oxygen transfer rates lead to optimized metabolic processes, potentially reducing production times and increasing yields during processes such as fermentation [108].
- **Reduction in Byproduct Formation:** As discussed above, the controlled release of oxygen by nanobubbles minimizes oxidative stress in biological systems, which often leads to the production of undesirable byproducts. By ensuring a stable and adequate oxygen supply, nanobubbles help steer metabolic pathways toward more desirable outcomes and enhance product purity and yield. This aspect is particularly important in the manufacture of pharmaceuticals and high-grade chemicals, where product integrity is primary [119].

Nanobubble technology in industrial bioreactors not only produces operational improvements but also offers potential for cost savings and enhanced process efficiency across various applications. This technology supports a more sustainable approach to industrial bioprocessing by reducing chemical use, enhancing process control, and improving the overall environmental footprint [120].

11. Regulatory and Safety Aspects

Despite being an incipient technology, different countries have regulated the use of nanotechnology in some industrial fields, especially in the food and pharmaceutical sectors where nanobubbles are used. Several case studies illustrate how regulatory frameworks have been successfully adapted to these new applications. Oomen et al. [121] discussed the adaptation of risk assessment frameworks for nanomaterials and linked them to the regulatory requirements to ensure safety. Gottardo et al. [122] highlight how regulatory bodies are evolving to address the unique challenges posed by smart nanomaterials. Van Wezel et al. [123] demonstrate how risk analysis and technology assessment have been integrated into regulatory practices for nanotechnology. Stone et al. [124] outline essential elements of risk governance frameworks for nanotechnologies, illustrating modifications to incorporate specific risks and promote safe innovation. In summary, these frameworks include the following:

- **Regulatory Frameworks and Compliance:** The adoption of nanotechnologies in bioprocessing is governed by stringent regulatory frameworks, which vary significantly across jurisdictions. In the European Union, regulations such as Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) and specific guidelines under the Novel Foods Regulation ensure that any nanotechnology application,

including nanobubbles, undergo rigorous safety evaluations and meet compliance standards before they reach the market [125]. In the United States, the FDA requires similar compliance for food and pharmaceutical products utilizing nanotechnology, ensuring that they do not pose any risks to consumers [126].

- **Safety and Toxicological Assessments:** Concerns regarding the potential toxicity of nanomaterials require a thorough toxicological assessment to evaluate their impact on human health. Nanobubbles involve the analysis of their interactions with biological systems, persistence, and potential accumulation in tissues [127]. Comprehensive toxicological profiling helps understand the implications of long-term exposure to nanobubbles and is important for gaining regulatory approval [128].
- **Quality Control in Bioprocessing:** Integrating nanobubbles into bioprocessing operations must not compromise the quality or safety of the final products. Nanobubbles must be aligned with strict industrial quality standards. This includes ensuring that their use does not lead to undesirable changes in product composition or efficacy that can affect the safety or functional properties of the product [129].
- **Balancing Innovation and Regulation:** Regulators face the challenge of updating and adapting policies to keep pace with technological advances while ensuring public safety. The dynamic nature of advances in nanotechnology, such as those observed with nanobubbles, requires ongoing revisions of regulatory frameworks to adequately address new data and applications. This is necessary to foster innovation without compromising safety standards [130].
- **Consumer Transparency and Acceptance:** Ensuring consumer acceptance of nanotechnology-based products involves clear communication about benefits and risks. Labeling that indicates the use of nanobubbles or other nanotechnologies can help consumers make informed choices. Additionally, public education initiatives can demystify nanotechnology applications, alleviate concerns, and foster greater acceptance of these innovations [131].

Regulators can strike a balance between fostering innovation and ensuring public safety by implementing strategies and mechanisms. First, adopting a risk-based regulatory approach can help focus resources on the most significant risks while allowing low-risk innovations to proceed with a minimal regulatory burden. Regulatory sandboxes or pilot programs can provide controlled environments in which new technologies can be tested and evaluated under regulatory oversight prior to a full-scale implementation. Additionally, stakeholder engagement and transparent communication help build public trust and address concerns regarding new technologies. Finally, investing in regulatory science to develop new tools and methods to assess the safety of emerging technologies can contribute to making informed decisions without stifling innovation.

In summary, as the use of nanobubbles continues to increase, adherence to rigorous regulatory standards and comprehensive safety evaluations has become imperative. This ensures that, while the sectors benefit from nanotechnology advancements, consumer safety and product integrity remain uncompromised.

12. Discussion

Nanobubble technology has undergone rapid development and is being increasingly studied and applied to various bioprocesses. The unique properties of nanobubbles contribute to their ability to enhance mass transfer and improve the metabolic efficiency of microorganisms [132]. Their ability to maintain a high internal pressure, as described by Laplace's law, increases the solubility of gases, making them efficient carriers of substances such as oxygen. This property has implications for optimizing gas–liquid mass transfer, especially in aerobic fermentation processes, where a consistent gas supply is essential for microbial metabolism [133]. The stability of nanobubbles, which allows them to linger in solution for extended periods, directly contributes to prolonged interactions between the gas phase and the microorganisms. This low ascent velocity indicates that nanobubbles can enhance mass-transfer efficiency by increasing the surface contact time, particularly

with poorly soluble gases such as ozone [85]. This property makes them highly beneficial for processes in which sustained interactions are crucial, such as wastewater treatment, in which contaminants require prolonged exposure to oxidizing gases [134].

Various methods have been used to generate nanobubbles. Each method offers specific advantages, particularly in terms of scalability and efficiency, which are important considerations as applications expand to an industrial scale. Although the current generation methods are promising, their scalability is challenging. Scaling up requires the development of robust, cost-effective nanobubble generation systems that can handle high volumes without large efficiency losses [42]. The relationship between the volumetric mass-transfer coefficient and nanobubble size plays a key role in optimizing bioprocess efficiency [49]. There is a need for a better understanding of how the mass-transfer coefficient is affected at larger scales and how it can be optimized.

Integrating nanobubbles into existing bioprocesses requires a detailed understanding of their interactions with the current systems. This involves studying their behavior with microbial strains and substrates to optimize productivity [26]. Additionally, process optimization should balance the number of nanobubbles generated and their sizes to maximize the mass-transfer coefficient without oversaturation or negative interactions [135].

The environmental friendliness of nanobubble technology is a significant advantage. As they do not require chemical additives, nanobubbles are ideal for use in bioprocesses in which chemical alterations can harm sensitive microbial activities. This characteristic is particularly valuable for applications that require stringent environmental compliance [129]. This makes them especially suited for applications such as water treatment and sensitive bioprocesses, where chemical changes can adversely affect microbial communities [136]. Their prolonged presence and ability to improve gas availability mean that fewer external inputs are required, contributing to resource conservation and minimizing environmental impacts. A summary of the potential drawbacks of nanobubbles used in bioprocesses is presented in Table 4.

Table 4. Potential drawbacks of nanobubble use in bioprocesses.

Issue	Description	Mitigation Strategy	Reference
Oxidative Stress	High concentrations of ROS from nanobubbles can damage cellular components	Controlled bubble concentration, use of antioxidants	[2]
pH Alterations	Electrolysis can alter pH, affecting sensitive microorganisms	Buffer systems, alternative generation methods	[3]
Energy Consumption	High energy requirements for nanobubble generation	Optimize generation methods, use renewable energy sources	[7]
Equipment Durability	Wear and tear on nanobubble generators, frequent maintenance needed	Use of durable materials, regular maintenance schedules	[69]
Economic Viability	High initial costs and potential insufficient ROI	Economies of scale, government subsidies, partnerships	[1]

Future research should focus on optimizing nanobubble generation methods, such as hydrodynamic cavitation and electrolysis, to improve efficiency, reduce energy consumption, and ensure a consistent bubble size. Long-term studies are needed to assess the impact of nanobubble exposure on cell health, process stability, and biofilm dynamics, particularly concerning the potential oxidative stress and metabolic changes. Investigating the compatibility and effects of nanobubbles on diverse microbial cultures and their community dynamics will help identify the most beneficial applications. Environmental impact assessments, regulatory compliance strategies, and pilot-scale studies will help address scalability challenges and integrate nanobubble technologies into existing industrial systems. The potential for nanobubbles extends beyond bioprocesses. Their use in

nanomedicine (e.g., drug delivery and imaging) and surface cleaning suggests a broad range of interdisciplinary applications. Research in these domains can offer insights into innovative methods for applying nanobubbles in bioprocessing. A summary of these areas is provided in Table 5.

Table 5. Research areas for nanobubble technology.

Research Area	Focus	Expected Outcome
Optimization of Generation Methods	Improving efficiency, reducing energy consumption, achieving consistent bubble size	More cost-effective and reliable nanobubble production
Long-Term Impacts on Bioprocesses	Studying effects on cell health, biofilm dynamics, and process stability over extended periods	Better understanding of nanobubble interactions and stability
Microbial Compatibility	Examining response of diverse microbial strains to nanobubble aeration	Identification of most and least compatible microorganisms
Environmental Impact Assessment	Assessing lifecycle impact and ecological effects of large-scale nanobubble use	Ensuring sustainable and eco-friendly applications
Regulatory and Safety Compliance	Developing frameworks for safe integration and handling of nanobubbles in various industries	Compliance with safety standards, fostering public trust

Nanobubbles represent a transformative approach to bioprocessing because of their exceptional mass-transfer capabilities and environmental sustainability. However, the challenges in scaling up, integrating, and understanding their full impact require comprehensive research to unlock their complete potential.

13. Conclusions

Nanobubbles offer a promising approach to overcoming the inherent limitations of mass transfer in bioreactors. Nanobubbles exhibit significantly enhanced surface-to-volume ratios owing to their small size, prolonged suspension in liquids, high inner pressure, and slow ascent speed. These properties make them highly effective for improving gas–liquid mass-transfer processes, which are critical in biotechnological applications.

Nanobubbles facilitate a more rapid and efficient exchange of gases between phases, allowing microorganisms quicker access to essential gases such as oxygen. This enhanced mass-transfer efficiency is crucial for accelerating metabolic activities and optimizing the overall process efficiency of the bioreactors.

Research has shown that nanobubbles can significantly improve the metabolic activity of microorganisms. They promote the formation and function of biofilms, which are essential for effective bioprocessing. The unique characteristics of nanobubbles help maintain an optimal environment for microbial growth, thus enhancing the stability and productivity of biofilms.

Although the benefits of nanobubbles are increasingly being recognized, the full scope of their impact on mass transfer and bioprocessing remains underexplored. Continued research is essential to deepen our understanding of how nanobubbles influence these processes at a molecular level. Studies should focus on quantifying improvements in mass-transfer coefficients and evaluating the long-term stability and scalability of nanobubble applications in industrial settings.

The promising results observed in laboratory and pilot-scale studies suggest that nanobubbles could play a crucial role in scaling up bioprocesses. Investigating their viability in large-scale industrial environments is vital to assess their potential to enhance productivity and efficiency across various sectors, including pharmaceuticals, wastewater treatment, and biochemical production.

The integration of nanobubble technology in bioprocessing aligns with global efforts to achieve more sustainable manufacturing practices. By improving efficiency and reducing reliance on chemical additives, nanobubbles contribute to creating more environmentally friendly and economically feasible processes.

Nanobubbles are transformative technologies that are used in bioprocessing. Their ability to significantly enhance mass transfer provides a pathway for efficient and sustainable bioprocesses. As technology progresses, it holds the promise of improving both the economic and environmental footprint of essential industrial operations.

Author Contributions: J.S. and L.A.-T., conceptualization, literature search, and original draft preparation; L.A.-T. and J.S., writing—review and editing; C.C. and G.A., editing and supervision. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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