Journal of *Marine Science and Engineering*

MDPI

Review

Quorum Sensing: Unravelling the Intricacies of Microbial Communication for Biofilm Formation, Biogeochemical Cycling, and Biotechnological Applications

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Abstract: The marine environment possesses diverse and complex characteristics, representing a significant challenge for microbial survival. Therefore, bacteria must develop adaptive mechanisms to thrive in such environments. Quorum sensing (QS), a well-established phenomenon in microorganisms, involves the communication between cells through chemical signals, which is dependent on cell density. Extensive research has been conducted on this microbial ability, encompassing the early stages of understanding QS to the latest advancements in the identification and characterization of its mechanisms. This minireview comprehensively examines the role of QS in various aspects, including biofilm formation, virulence in pathogenic bacteria, such as *Vibrio* spp. And *Pseudomonas* spp., as well as its influence on biogeochemical cycling in deep-sea environments. Furthermore, future progress in the field will be achieved by combining state-of-the-art methods for observing QS in the deep sea with a deeper understanding of the underlying processes, which will facilitate the engineering of microorganisms for improved degradation of persistent environmental pollutants and other biotechnological applications.

Keywords: quorum sensing; microbial communication; biofilm formation; biogeochemical cycling; biotechnological applications; marine environment; deep-sea environment

Citation: Israel, E.; Ramganesh, S.; Abia, A.L.K.; Chikere, C.B. Quorum Sensing: Unravelling the Intricacies of Microbial Communication for Biofilm Formation, Biogeochemical Cycling, and Biotechnological Applications. *J. Mar. Sci. Eng.* **2023**, *11*, 1586. https://doi.org/10.3390/jmse11081586

Academic Editor: Azizur Rahman

Received: 11 July 2023
Revised: 1 August 2023
Accepted: 11 August 2023
Published: 13 August 2023

1. Introduction

Extensive research has significantly advanced the understanding of bacteria, particularly concerning their lifecycle. From the earliest investigations into basic phenomena, such as food fermentation, research has progressed to uncovering the presence of disease-causing pathogens in diverse ecological niches, including plant rhizosphere soil, deep ocean zones, alpine peaks, and other extreme environments [1]. Among the notable discoveries is the phenomenon of cell-to-cell communication, known as "quorum sensing," which occurs within bacterial communities, both within and between species. Traditionally, QS was understood to predominantly regulate bacterial bioluminescence. The concept of quorum sensing was first observed over 25 years ago in two marine bacterial species: *Vibrio fischeri* and *Vibrio harveyi*. In these species, quorum sensing is controlled by various genes and regulons, including Lux genes (LuxCDABEG) and their respective autoinducers. In *Vibrio*

fischeri, N-acyl homoserine lactone (AHL) acts as the autoinducer, while in *Vibrio harveyi*, autoinducer-2 (AI-2) plays QS role [2]. These autoinducers are synthesized when the bacterial population is low, but once the bacterial density reaches a threshold, these molecules bind to their respective receptor proteins, initiating a signaling cascade. This signaling alters the expression of lux genes, thus triggering the activation of bioluminescence, a phenomenon termed 'quorum sensing' [3–5]. Since this initial observation, researchers have identified homologs of these genes in various bacterial communities, which play a regulatory role in quorum sensing. This communication process has been found to influence a wide range of biological processes, including bioluminescence [6], biofilm formation [7], cell competency [8], horizontal gene transfer [9], virulence factor expression [10], symbiotic relationships [11], sporulation in fungi [12,13], pigment production [14], motility [15], toxin production [16], and even antibiotic production [17–19]. These observations highlight the intricate communication networks and coordinated behavioral patterns within bacterial communities, underscoring the complexity of microbial ecosystems. Investigations into QS have significantly enriched our understanding of the regulatory mechanisms governing bacterial interactions, thereby offering novel insights into microbial ecology and behavior. Furthermore, the study of QS has sparked interest in the potential for strategic manipulation of bacterial behavior. This field of study opens up promising avenues for application across a broad range of sectors, including healthcare for infection control, environmental management for bioremediation efforts, and various advancements in biotechnology.

To effectively engage in QS, bacteria must possess certain capabilities, including producing and secreting autoinducer signaling molecules, perceiving changes in their concentration, and respond by regulating gene transcription [20,21]. The process heavily relies on the diffusion mechanism of these signaling molecules, which are typically secreted at low concentrations by individual bacteria. These molecules may simply diffuse away from the cell in environments with low cell density. However, as cell density increases, the local concentration of signaling molecules can surpass a threshold level, triggering a shift in gene expression [22]. Numerous quorum sensing systems have been extensively studied and documented in various taxa and habitats (a PubMed keyword search for "quorum sensing" generates over 12,000 results) [23]. However, many taxa and habitats remain, including deep-sea microbes, where quorum sensing remains unidentified or poorly characterized. Further research is needed to explore and understand the prevalence and specific mechanisms of quorum sensing in these diverse environments. This ongoing investigation will enhance our knowledge of the ecological significance and evolutionary implications of quorum sensing across a broader spectrum of microbial life. This mini-review aims to discuss the phenomenon of quorum sensing in oceanic ecosystems, with a specific focus on deep-sea environments, shedding light on its implications and importance in these unique ecosystems.

2. Bacterial Quorum Sensing in Oceanic Settings

Quorum sensing (QS) plays a crucial role in bacterial intercommunication, particularly in marine ecosystems. Traditionally, QS has been associated with the regulation of bacterial bioluminescence. However, a study by Tanet et al. [24] presented a challenge to this conventional understanding. The researchers analyzed the bioluminescent strain *Photobacterium phosphoreum* ANT-2200, originating from deep-sea waters of the Mediterranean, and found it exhibited higher light emission rates at lower cell densities rather than higher ones. Additionally, high hydrostatic pressure had no effect on QS gene transcription in this bacteria. Consequently, these findings suggest that in this particular strain, bioluminescence regulation may not be density-dependent and could be independent of conventional QS control mechanisms. Expanding the scope, another study by Muras et al. [25] assessed the prevalence of QS in deep-sea environments. The study found that deep-sea samples collected at a depth of 2000 meters had a comparatively low abundance of bacterial members involved in QS than surface samples from a depth of 15 meters. Paradoxically, a high prevalence of potential enzymes involved in QS was discovered in the deep-sea samples. This

finding suggests that QS activity could be an adaptive trait in bacterial strains possessing QS capabilities in an environment where QS actions potentially enhance bacterial species' fitness. Alternatively, this might also point to a scenario where the concentration of N-acyl homoserine lactones (AHLs), QS signal molecules, is high enough to regulate multiple aspects of microbial systems significantly [7]. These studies emphasize the importance of both quorum sensing and quorum quenching activities in deep-sea environments and highlight the significant role of these activities in marine systems.

Quorum sensing (QS) has been discovered in diverse bacterial species and habitats, including marine ecosystems (Table 1). *N*-acyl homoserine lactones typically serve as signaling molecules in quorum sensing for gram-negative bacteria, whereas gram-positive bacteria generally employ autoinducing peptides for intercellular communication. However, these broad categories are not all-encompassing. Numerous bacterial species are known to produce unique autoinducers, underlining the diversity and specificity inherent in bacterial communication systems [26]. In marine environments, the genera belonging to *Proteobacteria* that commonly produce autoinducers (Ais) predominantly include *Pseudoalteromonas*, *Thalassomonas*, *Pseudomonas*, *Roseobacter*, *Aeromonas*, and *Vibrio*. QS has also been identified in *Epsilonproteobacteria*, some of which are pathogens in humans. The thermal origin of this ability in mesophilic and pathogenic *Epsilonproteobacteria* has been traced back to ocean hydrothermal vents [27]. Among the different classes of signaling molecules, *N*-acyl homoserine lactones (AHLs), oligopeptides, and LuxS/autoinducer 2 (AI-2) have been extensively studied in marine environments [28]. For instance, some marine bacteria, such as *Vibrio* species, have been shown to employ multiple QS systems simultaneously, indicating a complex hierarchical organization of QS regulation that might be different from most terrestrial bacteria. Additionally, some marine bacteria are known to produce unique QS signal molecules, such as the boronated autoinducer AI-2 (BAI-2) in *Vibrio harveyi*, which is a derivative of the more common AI-2 signal and is believed to be more stable in the marine environment. *Vibrio harveyi*, a Gram-negative bacterium renowned for its bioluminescence, thrives predominantly in marine settings as a free-living organism. However, its versatility extends to engaging in both symbiotic and pathogenic relationships with diverse marine creatures [29]. The crux of *V. harveyi's* ability to interact with its hosts lies in its quorum sensing system, a regulatory mechanism controlling its bioluminescence, biofilm development, and virulence factor expression. This complex system, which encompasses multiple signaling molecules, enables *V. harveyi* to adapt and react to changes within its host environment and microbial community. In the quorum sensing (QS) network of *Vibrio harveyi*, three autoinducers (Ais) are used, which differ based on whether they are for intra-species, intra-genera, or inter-species communication [30]. Another common QS network structure is observed in the *Pseudomonas* genus, particularly in *Pseudomonas aeruginosa*. In marine ecosystems, *P. aeruginosa* has been isolated from various niches, including coastal waters, marine sediments, and marine organisms [31]. It is known for its robust biofilm formation capabilities, which can enable it to survive in challenging marine conditions. This bacterium possesses four known QS pathways that function either independently or in a coordinated manner. Two of these pathways are of the LuxI/LuxR type, specifically the LasI/LasR and RhlI/RhlR systems. Additionally, *P. aeruginosa* uses the quinolone-based QS system (PQS, which uses the 2-heptyl3-hydroxy-4-quinolone signal) and more recently identified integrated QS system (IQS, utilizing the 2-(2-hydroxyphenyl)-thiazole-4-carbaldehyde signal). These QS circuits are arranged in a hierarchical manner (Figure 1) [32]. The homologs of LuxS have been found in many species of bacteria, including *Firmicutes*, *Gamma*, and *Betaproteobacteria*. Other microbes found in deep-sea vents, such as *Epsilonbacteria* (e.g., *Sulfurovum lithotrophicum* and *Caminibacter mediatlanticus*), also express the LuxS gene and produce QS signals [27,33]. AI-2 has a precursor molecule called 4,5-dihydroxy-2,3-pentanedione (DPD), which can exist in three forms: 4-hydroxy-5-methyl-3(2H) furanone (MHF), (2R, 4S)-2-methyl-2,3,3,4-tetrahydroxy-tetrahydrofuran (R-THMF), and furanosyl borate diester (S-THMF borate). *Epsilonproteobacteria* exhibit the highest LuxS gene expression during the mid-exponential growth phase and the lowest

during the stationary phase. Conversely, bioluminescence, as detected using *Vibrio harveyi* strain BB170, is highest during the stationary phase when cell density is high, correlating with AI-2 activity [27,33].

Table 1. Quorum Sensing Activities in Various Bacterial Species and Environments, including oceanic settings.

Bacteria	Activity Mediated by QS	Location of Occurrence	Signaling Molecules	QS System	Interaction within QS System	Reference
Staphylococcus aureus	Virulence factor production control Biofilm formation control through the agr system	Human body	Autoinducing peptides (AIPs)	Agr system	AIPs bind to the AgrC receptor, activating the AgrA response regulator, which regulates virulence factor production.	[31,32]
Bacillus cereus	Virulence factor control through the PlcR system	Various habitats, including soil and food	Cyclic peptide	PlcR system	The cyclic peptide acts as a quorum sensing signal, binding to PlcR and triggering virulence gene expression.	
Pseudomonas aeruginosa	Virulence factor control through LuxI/LuxR-type system	Various habitats, including soil, water, and plants	N-acyl homoserine lactones (AHLs)	LasR/RhlR system	AHLs bind to LasR and RhlR, initiating transcription of numerous genes, including those responsible for virulence factor production.	[33]
Vibrio fischerii	Light emission gene control through the LuxI system	Bobtail squid (Euprymna scolopes) in marine waters	N-acyl homoserine lactone (AHL)	LuxI/LuxR system	AHLs bind to LuxR, activating transcription of the luciferase operon, which is responsible for light production.	[25]
Vibrio diabolicus	Biofilm formation control	Polychaete annelid Alvinella pompejana deep-sea hydrothermal vent	Autoinducing peptides (AIPs)	Unknown QS system	Unknown	[34,35]
Escherichia coli	Regulation of biofilm formation, motility, and virulence	Various habitats, including the human gastrointestinal tract	Autoinducer-2 (AI-2)	LuxS/AI-2 system	AI-2 is internalized and binds to the LsrR repressor, leading to the de-repression of Lsr operon and other AI-2-responsive genes	[36,37]
Vibrio cholerae	Toxin production regulation and colonization of the human intestine	Hadel zones and human gastrointestinal tract	N-acyl homoserine lactones (AHLs)	LuxO/LuxR system	AHLs bind to LuxR, triggering the regulation of virulence genes, including the cholera toxin.	[38,39]

Table 1. *Cont.*

Bacteria	Activity Mediated by QS	Location of Occurrence	Signaling Molecules	QS System	Interaction within QS System	Reference
Streptococcus pneumoniae	Competence development and genetic transformation	Human respiratory tract	Peptides	ComDE system	The peptide pheromone binds to ComD, activating ComE which triggers genetic transformation and competence development	[40]
Acinetobacter baumannii	Biofilm formation and antibiotic resistance	Various environments, including hospitals and soil	Unknown	Unknown QS system	Unknown	[41,42]
Aliivibrio fischeri	Symbiotic colonization of the Hawaiian bobtail squid	Bobtail squid (Euprymna scolopes) in marine waters	N-acyl homoserine lactone (AHL)	LuxI/LuxR system	AHLs bind to LuxR, leading to changes in gene expression that allow symbiotic colonization of the bobtail squid.	[43]
Photobacterium phosphoreum	Bioluminescence control	Deep-sea waters	Autoinducer-2	LuxS/AI-2 system	AI-2 molecules are synthesized and used to modulate bioluminescence in a cell-density-dependent manner	[23]
Sulfitobacter sp.	Production of extracellular enzymes and biofilm formation	Marine environments, including surface water and sediments	Unknown	Unknown QS system	Unknown. Likely involves signaling molecules that regulate the production of extracellular enzymes and biofilm formation.	[44]
Ruegeria sp.	Biofilm formation and production of extracellular enzymes	Marine environments, including coastal seawater and sediment	N-acyl homoserine lactone (AHL)	LuxI/LuxR system	AHLs bind to LuxR, leading to changes in gene expression, including biofilm formation and the production of extracellular enzymes	[45]
Shewanella oneidensis	Regulation of biofilm formation and metal oxide reduction	Marine and freshwater environments	Unknown	Unknown QS system	Unknown	[46,47]
Colwellia psychrerythraea	Cold adaptation and biofilm formation	Cold marine environments	Unknown	Unknown QS system	Unknown	[48,49]

Table 1. *Cont.*

Bacteria	Activity Mediated by QS	Location of Occurrence	Signaling Molecules	QS System	Interaction within QS System	Reference
Psychrobacter sp.	Production of extracellular enzymes and biofilm formation	marine sediments	N-acylhomoserine lactones (AHL)	LuxI/LuxR system QS system	AHLs bind to LuxR, leading to changes in gene expression, including the production of extracellular enzymes and biofilm formation.	[50]
Marinobacter sp.	Biofilm formation and quorum quenching	Marine environments, including deep-sea sediments	Unknown	Unknown QS system	Unknown	[51]
Sulfurovum lithotrophicum	Quorum sensing in deep-sea vent bacteria	Deep-sea hydrothermal vents	Autoinducer-2 (AI-2)	LuxS/AI-2 system	AI-2 is synthesized and interacts within the LuxS/AI-2 system to regulate quorum sensing in these deep-sea vent bacteria.	[26,52]
Caminibacter mediatlanticus	Quorum sensing in deep-sea vent bacteria	Deep-sea hydrothermal vents	Autoinducer-2 (AI-2)	LuxS/AI-2 system	AI-2 is produced and interacts within the LuxS/AI-2 system to regulate quorum sensing, thus enabling these deep-sea vent bacteria to adapt and thrive in their extreme environment.	[26,52]
Thiomicrospira sp.	Symbiotic interactions and biofilm formation	Deep-sea hydrothermal vents	Unknown	Unknown QS system	Unknown	[53]

To date, no AI-2 receptors have been identified in *Epsilonproteobacteria*. However, two main receptor categories, LuxP in *Vibrio* spp. And LrsB in enteric bacteria, are known. In deep-sea vents, *Epsilonproteobacteria* act as early-stage colonizers, preparing the stage for colonizing other microbes through QS signaling involving adhesive polymeric secretion. This secretion also serves as a nutrient source, promoting the recruitment of additional microbial species. The extracellular matrix of *P. aeruginosa* is composed of extracellular DNA (eDNA), which aids biofilm assemblage in a reaction with extracellular calcium by promoting bacterial association when released via QS-dependent and independent pathways. eDNA affects the RNA composition of members of the biofilm, acting as a nutrient source through the contents of the membrane vesicle in which it is enclosed, as well as modulating the expression of genes influencing acidity and antimicrobial resistance [34]. Interestingly, horizontal gene transfer has been observed between gut-dwelling *Helicobacter pylori* and *Enterococcus faecium*, explaining the successful QS responses, such as virulence, in communities of species from different taxa [27,35]. Similar gene transfers might also occur in deep-sea microbial communities, contributing to their resilience in extreme conditions. Marine environments, particularly microniches characterized by high organic matter

content (e.g., biofilm covers and biotic/abiotic surfaces), create favorable conditions for QS due to the resulting higher cell density in these habitats, leading to the accumulation of AI molecules. The primary function of QS within marine microbial communities pertains to its involvement in ecological and biogeochemical processes, including significant bioluminescence events linked to algal blooms [36]. The precise role and mechanisms of AI-2-QS, however, still require further elucidation.

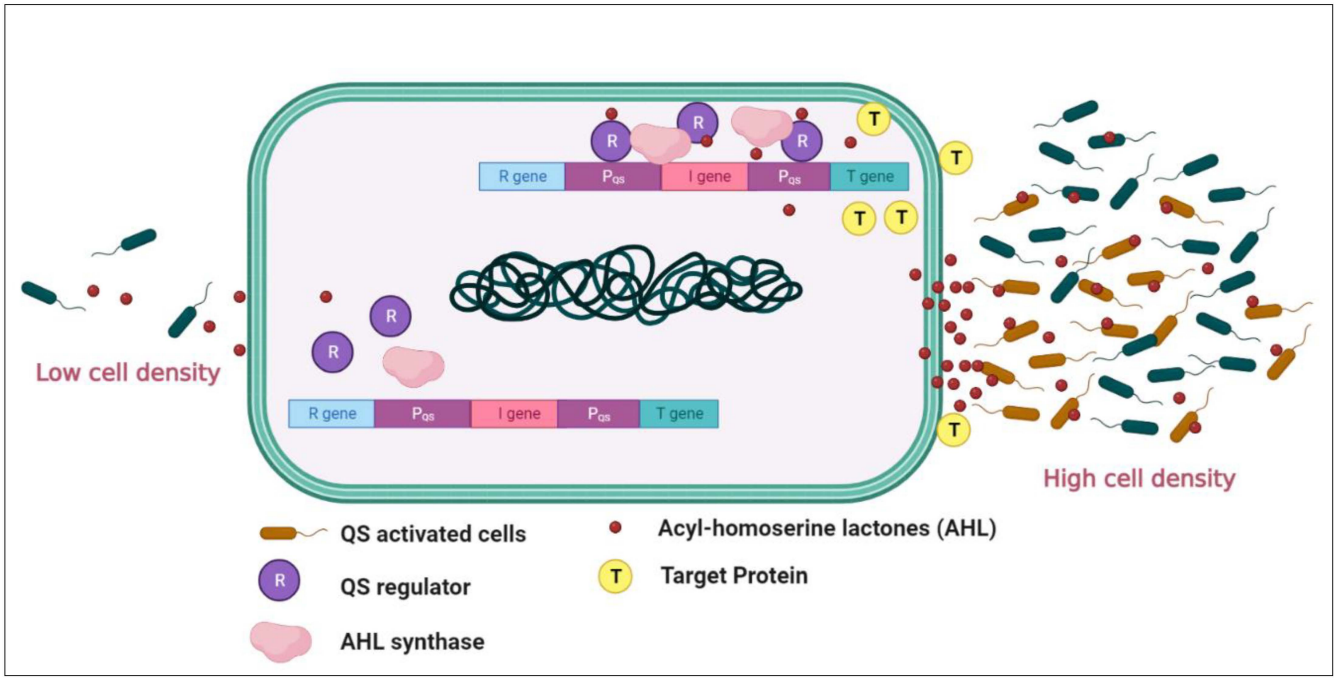

Figure 1. An illustration of the working system of the autoinducer mechanism in Gram-negative (*Pseudomonas aeruginosa*). The bacteria secrete AHLs (red dots) that, in threshold concentrations, penetrate into the cells, activate the AHL receptor, and induce the QS-regulated genes expression. 'I' represents the *LuxI* gene encoding for the enzyme that synthesizes the AHL signal, and 'R' represents the *LuxR* gene encoding for the protein that binds AHL and modulates the transcription of luciferase genes, quinolone-based QS system (Pqs). (Image created in Bio-render online platform).

3. Biofilm Formation

Biofilms play a crucial role in the adaptive strategies employed by bacteria in marine environments, including deep-sea ecosystems, as detailed in Table 2. These complex structures support bacterial survival and thriving within these environments. The unique characteristics of biofilms provide member cells with distinct advantages, such as heightened resistance against host immune responses, enhanced nutrient availability and utilization, and increased tolerance to antimicrobial agents [37]. Several studies focusing on *Vibrio fischeri*, *Vibrio anguillarum*, and *Vibrio harveyi* have demonstrated the involvement of QS in regulating bioluminescence, virulence, and biofilm formation in these species. Notably, biofilms from extreme environments exhibit the remarkable ability to rapidly transition from early colonization stages to robust production of extracellular polymeric substances (EPS) that contribute to protective mechanisms [38].

Table 2. Quorum Sensing and Biofilm Composition in Various Marine Environments.

Location	Bacteria	Biofilm Composition	Functions	Reference	Quorum Sensing Involvement
Antarctic Waters	*Marine bacteria*	Charged uronic acid moieties and sulfate groups	Plays a role in cold adaptation	[38]	QS system(s) involved
Korean yellow sea	*Bacillus* sp. *I450*	Neutral sugars and uronic acids	Exhibits antimicrobial activity	[38,52]	QS system(s) involved
Solar Saltern and Spanish Mediterranean Seaboard	*Halomonas maura & Salipiger mucosus*	Sulfated polysaccharide with high uronic acid content and fucose-rich polysaccharides	Adapted to high salinity environments and high capacity for binding cations	[53,54]	QS system(s) involved
Deep-sea hydrothermal vent	*Caminibacter mediatlanticus*	Sulfated polysaccharide high in glucosamine	Thrives in high-temperature hydrothermal vents	[27,55]	QS system(s) involved
Deep-sea hydrothermal vent	*Alteromonas infernus*	Lacking lipopolysaccha-rides (LPS)	Exhibits unique adaptations to extreme conditions, including high-pressure and high-temperature environments	[56]	QS system(s) involved
Host in deep-sea hydrothermal vent	*Vibrio diabolcus*	Large amounts of uronic acid and no sulfate groups	Forms symbiotic relationship with the host organism, the polychaete annelid Alvinella pompejana, in deep-sea hydrothermal vent ecosystems	[57]	QS system(s) involved
Antarctic Ocean	*Psychrobacter* sp.	Extracellular polysaccharides	Exhibits cold-adapted enzymatic activity and plays a role in biofilm formation under low temperatures	[58]	Not specified
Deep-sea sediments	*Marinobacter* sp.	Exopolysaccharides	Involved in sediment stabilization and biogeochemical cycling in deep-sea sediments	[59,60]	Not specified
Gulf of Mexico	*Vibrio vulnificus*	Alginate and extracellular DNA	Forms biofilms on oyster shells and contributes to oyster pathogenesis	[61]	QS system(s) involved

Table 2. *Cont.*

Location	Bacteria	Biofilm Composition	Functions	Reference	Quorum Sensing Involvement
Deep-sea hydrothermal vent	*Thiomicrospira* sp.	Extracellular sulfur and polysaccharides	Capable of sulfur oxidation and plays a role in ecosystem functioning in deep-sea hydrothermal vents	[62]	Not specified
Mariana Trench	*Pseudomonas* sp.	Exopolysaccharides	Exhibits unique adaptations to extreme pressures and low nutrient availability in the Mariana Trench	[63,64]	QS system(s) involved

In marine ecosystems, EPS production is a common trait observed among various microorganisms, including bacteria, cyanobacteria, and actinobacteria. These EPS molecules contribute to biofilms' development and structural integrity in marine environments, facilitating microbial survival and adaptation [38]. Biofilm formation mechanisms vary among different bacterial species. In dominant oceanic bacteria, such as *Vibrio* species, N-acyl homoserine lactones (AHLs) regulate the secretion of Extracellular Polymeric Substances (EPS) to construct a biofilm matrix. Specific AHLs, such as C4-HSL and C6-HSL, elevate the expression of EPS-related genes by binding to AHL receptor proteins, thereby enhancing EPS production and forming a denser biofilm matrix [39]. In contrast, *P. aeruginosa* has identified five gene clusters believed to contribute to exopolysaccharide synthesis, which include the alg biosynthetic genes, the psl and pel operons, and two additional gene clusters. Only the pel biosynthetic operon is definitively known to be subject to QS regulation [40]. The proteins encoded by the pel gene cluster (pelABCDEFG) are responsible for the production of a glucose-rich biofilm exopolysaccharide [41]. Interestingly, Las-mediated QS has been reported to inhibit the production of this exopolysaccharide [42]. Another aspect regulated by QS, specifically by AHL and PQS signaling, that plays a significant role in *P. aeruginosa* biofilm development is the production of rhamnolipids [43]. These biosurfactants were initially shown to influence a later stage of biofilm development, preserving the channels between the mushroom-shaped structures of the biofilm once they are formed. Notably, in extreme environments, such as deep-sea waters, AHLs boost bacterial adhesion to nearby solid surfaces, promoting clonal growth and hastening EPS secretion. However, when environmental conditions improve, Qrr sRNAs degrade LuxR-type AHL receptor proteins to reduce bacterial adhesion and increase their mobility [44]. This adaptation results in the migration and proliferation of the colony to more favorable environments. In addition to the physiological advantages biofilms confer in deep-sea environments, QS within these communities plays a vital role in coordinating microbial activities. It enables intercellular communication and facilitates the formation of complex multispecies biofilms commonly observed in marine ecosystems. Studies have revealed that QS regulates bioluminescence, virulence, biofilm formation, and other important processes in marine bacteria. For example, in the bacterium *Pseudomonas aeruginosa*, QS controls the production of various virulence factors, including exopolysaccharides, proteases, and toxins, contributing to its pathogenicity and colonization ability [45].

Furthermore, QS has been implicated in the regulation of motility and colonization in marine bacteria. In *Vibrio cholerae*, a pathogenic bacterium responsible for cholera, quorum sensing coordinates the expression of genes involved in flagellar motility and biofilm formation, enabling efficient colonization of aquatic environments and host surfaces [46].

Quorum sensing in marine environments is not limited to bacteria alone. Marine algae, such as diatoms, also employ QS mechanisms to coordinate their growth and reproductive processes [47]. This interkingdom communication between bacteria and algae further highlights the ecological significance of QS in marine ecosystems. The deep-sea environment presents unique challenges for microbial communities, including high pressure, low temperature, and limited nutrient availability. Quorum sensing allows bacteria to adapt to these extreme conditions by facilitating cooperative behaviors and resource sharing within biofilms. Moreover, studies have shown that deep-sea bacteria exhibit specific adaptations in their QS systems, likely influenced by the selective pressures of these environments [36,48]. Marine bacteria might adopt specific adaptations in their quorum sensing systems, including changes in signaling molecules [49], modifications of receptors [50], or alterations in downstream signal transduction pathways [51]. For example, to respond more effectively to environmental stimuli, certain deep-sea bacteria may generate specialized signaling molecules or adjust their receptor sensitivity. Alternatively, some might develop new signal transduction pathways that allow for a more efficient response to challenging conditions, such as low nutrient availability, high pressure, and cold temperatures. Nevertheless, a more in-depth examination and validation are needed to fully understand the exact adaptations in the quorum sensing systems and biofilm formation in marine bacteria. Quorum sensing plays a multifaceted role in marine environments, regulating various physiological processes in bacteria and other microorganisms. It facilitates communication and coordination within biofilms and contributes to the adaptation and survival of microbial communities in diverse marine ecosystems, including the challenging deep-sea environment.

4. Biogeochemical Cycling and Quorum Sensing

Quorum sensing mechanisms have been found to play a significant role in regulating microbial activities involved in biogeochemical cycling in the ocean. Numerous marine bacterial species participate in quorum sensing and are crucial regulators of biogeochemical cycles, including *Vibrio* sp, *Pseudomonas*, *Pseudoalteromonas*, *Marinobacter*, *Roseobacter*, and some members of *Cyanobacteria*. In marine environments, QS-mediated gene regulation influences the cycling of essential elements, such as carbon, nitrogen, phosphorous, and sulfur. For example, QS controls the production of extracellular enzymes involved in the breakdown of complex organic matter, allowing bacteria to efficiently utilize these substrates for energy and nutrient acquisition [45,46]. The coordinated expression of genes involved in enzymatic activities enhances the degradation and cycling of organic compounds in the ocean. *Vibrio* and *Pseudoalteromonas* species are associated with the carbon cycle as they have the capability to break down chitin, a highly abundant N-acetylglucosamine polymer in the ocean [65]. These bacteria play a key role in the phosphorus cycle due to their ability to produce phosphatases, enzymes that cleave phosphate groups from organic molecules, making it bioavailable for themselves and other organisms [66]. Notably, *Marinobacter*, a *Proteobacteria* genus, is often found near oil spills [67], where it aids in hydrocarbon degradation, thereby participating in the carbon cycle. Quorum sensing also influences the nitrogen cycle by regulating nitrogen fixation, nitrification, and denitrification processes. Some marine bacteria, such as the genus *Vibrio*, utilize QS to control the expression of nitrogen fixation genes, enabling them to convert atmospheric nitrogen into biologically available forms [68]. Quorum sensing also regulates the expression of genes involved in nitrification and denitrification, affecting the balance of nitrogen species in marine ecosystems. For instance, *Pseudomonas* sp. is a significant contributor to the nitrogen cycle, performing denitrification, a process that transforms nitrate into nitrogen gas under low-oxygen conditions [45,68].

Sulfur cycling in the ocean is another biogeochemical process influenced by QS. QS-controlled gene expression in sulfur-oxidizing bacteria regulates the production of enzymes involved in oxidizing reduced sulfur compounds, such as hydrogen sulfide, into sulfate [69,70]. This process is crucial for sulfur recycling in marine environments and

contributes to the global sulfur cycle. The *Roseobacter* Clade, part of the *Alphaproteobacteria*, plays a key role in the sulfur cycle by breaking down dimethylsulfoniopropionate (DMSP), a prevalent sulfur compound in the ocean, subsequently leading to the production of dimethyl sulfide (DMS), a gas that has a significant impact on the climate [71]. Additionally, *Cyanobacteria* are integral to the carbon cycle due to their photosynthetic capabilities, which involve fixing CO2 into organic matter. Certain species also contribute to the pool of biologically accessible nitrogen in the ocean by fixing nitrogen and storing phosphate in the form of polyphosphate granules [72].

Furthermore, QS-mediated biofilm formation has implications for biogeochemical cycling. Biofilms provide a structured and protected environment for microbial communities, allowing them to efficiently carry out processes, such as nutrient uptake, metabolic cooperation, and extracellular matrix production [73]. For instance, several *Vibrio* species are known to form biofilms in marine environments which can lead to localized precipitation of phosphorite minerals in a process known as biomineralization. This can particularly occur around sunken bones in the deep sea, leading to the formation of 'bone-eating' osedax worms [74]. QS coordinates the formation and maturation of biofilms, enabling microbial consortia to establish complex interactions and perform specialized functions that contribute to biogeochemical cycling.

5. Methods of Monitoring Quorum Sensing

Monitoring QS in the marine environment requires using specific techniques that can capture the dynamic nature of QS interactions. Time-series methods are commonly employed to observe QS dynamics in deep-sea environments. These methods involve collecting samples at multiple time points and analyzing them using various techniques.

Omics approaches, such as metagenomics, metatranscriptomics, and metaproteomics, provide a comprehensive view of the microbial community and its gene expression patterns. These techniques enable the identification of QS-related genes, signaling molecules, and regulatory networks in the marine environment [75,76]. By analyzing the genetic information encoded in the collected samples, researchers can gain insights into the presence and activity of QS systems. Fluorescence in situ hybridization (FISH) is a microscopy-based technique that allows the visualization and identification of specific microbial populations in their natural habitat [77,78]. Using fluorescently labeled probes that target QS-related genes or specific microbial taxa, researchers can observe the spatial distribution and abundance of QS-active cells in marine samples [75]. This technique provides valuable information on the localization and dynamics of QS-mediated interactions. Bioengineered biosensors offer a powerful tool for studying QS dynamics in marine systems in real-time [79]. These biosensors are typically designed to detect and respond to specific QS signaling molecules, providing valuable information about the temporal and spatial distribution of these molecules within marine environments.

Raman microscopy is another powerful tool used in QS studies. It enables the non-destructive analysis of individual cells and their chemical composition. By detecting molecular vibrations, Raman microscopy can provide insights into cellular metabolism and QS-related molecule production in the marine environment [75,80]. Stimulated Raman Scattering (SRS) Microscopy is a technique that holds great potential for examining biofilms, especially in situ, due to its ability to swiftly provide details about the biofilm's chemical composition and structure [81]. A recent study by Aljuhani et al. [82] utilized surface-enhanced Raman scattering (SERS) in an effort to identify quorum sensing molecules, which allowed for a quantitative assessment of intrinsic marker compounds within biofilms. However, Raman spectroscopy does come with certain limitations, notably the relative weakness of Raman scattering, particularly when a low detection limit is required. This challenge can be mitigated through the use of surface-enhanced Raman scattering (SERS), which has the potential to amplify the signal. This technique can be combined with other methods to obtain a more comprehensive understanding of QS processes. To study the interactions between microorganisms in the deep sea, researchers often analyze taxonomic

data from different habitats or examine time-series samples from the same habitat. These approaches allow for identifying shifts in microbial community composition and QS-related gene expression patterns over time, providing insights into the dynamics of QS-mediated interactions [83]. Single-cell genomics is a powerful approach that involves analyzing the genetic material of individual cells in their natural environment. By targeting genes associated with QS systems, researchers can gain specific insights into the QS activity of individual cells within a microbial community [70,84,85]. This technique can provide valuable information on the diversity and functionality of QS systems in marine environments. Additional methods, such as Fluorescent Protein Tagging [86], Mass Spectrometry [87], Tandem Mass Tag (TMT) Spectrometry [88], Microfluidic Devices [89], and CRISPRi (CRISPR interference), also have a place in the study of quorum sensing [90,91]. However, it is crucial to note that these techniques each come with their own set of benefits and drawbacks when utilized in quorum sensing research (Table 3). While traditional molecular sequence-based methods, such as 16S and 18S rRNA gene sequencing, have been widely used for microbial ecology studies, they have limitations in capturing microbial communities' metabolic pathways and functional capabilities. PCR biases, mismatches, and the inability to decode metabolic pathways have limited the applicability of these methods in QS research [75,92]. Nevertheless, studies have emerged that address these limitations, using Hidden Markov Model (HMM) profiles to screen potential quorum sensing-related protein homologs in the non-redundant (NR) database. This has resulted in the creation of a specialized database rich in entries pertinent to quorum sensing, which can be directly queried for metagenomic annotations [92]. This invaluable tool facilitates the detection of potential microbial quorum sensing systems. The development of this database aids the annotation of quorum sensing-related sequences in a broad spectrum of projects, significantly augmenting our understanding of quorum sensing communication within aquatic environments, including marine systems. By combining molecular sequence-based-omics methods with isotope tracing techniques, such as FISH, researchers can better understand the metabolite flow within microbial communities. Isotope tracing allows for tracking specific metabolites and their utilization by QS-active cells, providing insights into the metabolic activities and interactions within marine microbial communities [75,88].

Table 3. Comparison of Techniques Used in Quorum Sensing Studies: Advantages and Disadvantages.

Methods	Advantages	Disadvantages	References
Time-series methods	Capture dynamics of QS over time, good for deep-sea environments.	Sample collection at multiple time points can be logistically challenging.	[93]
Molecular sequence-based methods (16S and 18S rRNA gene sequencing)	Widely used, can provide broad overview of microbial community.	PCR biases and mismatches, inability to decode metabolic pathways.	[25]
Omics approaches (Metagenomics, Metatranscriptomics, Metaproteomics)	Provide comprehensive view of microbial community, identify QS-related genes and regulatory networks.	Require high-throughput sequencing and sophisticated data analysis, potential for missing rare species or transient events.	[76]
FISH	Visualize and identify specific microbial populations, reveal spatial distribution of QS-active cells.	Difficult to correlate with metabolic activity or function.	[77,78]
Bioengineered Biosensors	Real-time analysis, designed to detect specific QS signaling molecules.	Stability and functionality can be affected by marine environment conditions.	[79]
Raman Microscopy	Non-destructive analysis of individual cells, insights into cellular metabolism.	Complex data interpretation: Equipment can be expensive.	[82]

Table 3. *Cont.*

Methods	Advantages	Disadvantages	References
Single-cell genomics	Provides specific insights into QS activity at the single-cell level.	High sequencing cost: Data analysis can be complex.	[85]
Isotope tracing	Tracks specific metabolites and their utilization by QS-active cells, insights into metabolic activities.	Technically challenging, requires specialized equipment and expertise.	[94]
Fluorescent Protein Tagging	Visualization of protein localization and expression dynamics in real-time.	May not work for all proteins, can affect protein function.	[86]
Mass Spectrometry	Allows to identify and quantify small molecules, including QS signaling molecules.	Requires sophisticated equipment and expertise, can be expensive.	[87]
Tandem Mass Tag (TMT) Spectrometry	Allows for relative quantification of proteins in multiple samples simultaneously.	Complex data analysis, requires access to specialized equipment.	[88]
Microfluidic Devices	Allow for precise control over environment and high-resolution imaging.	Fabrication can be complex, handling and analysis require specialized knowledge.	[89]
CRISPRi (CRISPR interference)	Gene knockdown to study the function of specific genes in QS.	Requires genetic manipulation, off-target effects.	[91]

6. Biotechnological Applications

The biotechnological advancements in QS have led to the discovery and utilization of extracellular polymeric substances (EPS) produced by marine bacteria for various applications in different industries. One notable example is the EPS produced by *Vibrio diabolicus* and *Alteromonas infernus*, isolated from deep-sea hydrothermal vents, showing medicinal regenerative properties. These EPS contain glycosaminoglycans that are beneficial for tissue repair and remodeling due to their low immunogenicity. One such product derived from these EPS is Hyalurift®, which utilizes hyaluronic acid to promote tissue remodeling and aid in joint injuries and embryogenesis. The EPS consists of high molecular weight linear tetrasaccharidic repeating units of glucuronic acid and hexosamine (N-acetyl-glucosamine and N-acetyl-galactosamine), resembling a fusion of hyaluronan and non-sulfated chondroitin units [95]. *Alteromonas macleodii* subsp. Fijiensis, strain HYD657, is another species that produces EPS with protective properties for sensitive skin against chemicals and UV radiation. This EPS, marketed as Abyssine, offers potential applications in skin care products for its protective and rejuvenating effects [38].

In the food industry, EPS produced by *Labrenzia* sp. Have gained attention due to their low viscosity and antioxidant properties. These EPS can be utilized in food and pharmaceutical products, providing viscosity control and antioxidant benefits (Di Donato et al., 2016). Deep-sea bacteria have also shown the production of extremozymes, which are enzymes capable of functioning under extreme conditions. These extremozymes have significant applications in bioremediation, particularly in degrading hazardous compounds, such as crude oil, polycyclic aromatic hydrocarbons (PAHs), and heavy metals, in the environment. They offer potential solutions for environmental clean-up and mitigation of pollution [96]. Furthermore, EPS produced by *Pseudomonas aeruginosa* JP-11 have been investigated for their potential in removing toxic cadmium ions from polluted waters. This suggests the possibility of using EPS-based strategies for the remediation of heavy metal contamination [38].

Some studies applied QS in antibiotic development, where quorum sensing inhibitors (QSIs) have been explored as potential antibiotics to disrupt bacterial communication and combat biofilm formation [97]. Bioremediation processes have also benefited from quorum sensing, as it has been utilized to enhance the degradation of pollutants, such

as crude oil and heavy metals ([98,99]. In biofilm control, strategies targeting QS have been developed to prevent and disrupt biofilm formation in healthcare, water systems, and food processing industries [100–102]). Moreover, manipulating QS has improved the production of biofuels, pharmaceuticals, and enzymes in industrial fermentation processes. In agriculture, quorum sensing has shown promise for developing biocontrol agents that can target plant pathogens and reduce reliance on chemical pesticides [15,103]. Finally, synthetic quorum sensing systems have been engineered, enabling the programming of microbial cells for desired behaviors, opening up possibilities in biomedicine, biofuel production, and bioremediation. These advancements highlight the broad potential of quorum sensing in various biotechnological applications [15,97,104–106].

7. Conclusions

Studying QS in extreme environments, including deep-sea, poses unique challenges in fully comprehending its intricate systems. However, unraveling the functions, molecular components, and underlying mechanisms of QS is imperative. Deep-sea environments have served as habitats for ancestral microorganisms, making it crucial to investigate quorum sensing to gain a comprehensive understanding of its roles in microbial communities, as many of these microbes have contributed to the cultivation of various organisms observed today. In-depth studies have shed light on strategies to mitigate virulence by disrupting quorum sensing through QS techniques and enhancing therapeutic applications by inducing autoinducer molecules. It is essential to incorporate ecological considerations in microbial QS research, recognizing the influence of evolution within diverse bacterial communities across different environments. Moreover, the future exploration of synthetic communities holds promise for more effective biotechnological applications than current genetic engineering approaches. By delving deeper into these scientific realms, we can unlock the full potential of quorum sensing and its practical implications.

Author Contributions: Conceptualization, E.I. and S.R.; methodology, E.I.; software, S.R.; validation, A.L.K.A. and C.B.C.; formal analysis, A.L.K.A. and C.B.C.; data curation, S.R.; writing—original draft preparation, E.I. and S.R.; writing—review and editing, S.R., A.L.K.A. and C.B.C.; visualization, S.R., A.L.K.A. and C.B.C.; supervision, C.B.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not Applicable.

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

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