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Quorum sensing based membrane biofouling control for water treatment: A review

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ABSTRACT

Exploring novel biological strategies to mitigate membrane biofouling is of significant value in order to allow sustainable performance of membrane systems for water and wastewater treatment. Quorum sensing (QS) is a bacterial communication process that involves small diffusible signalling molecules, which activate the expression of myriad genes that control a diverse array of phenotypes such as bioluminescence, virulence, biofilm formation and sporulation. Since QS is often associated with biofilm formation, inhibition of QS should be a promising strategy to control membrane biofouling. Recently, a revolutionary application of bacterial QS has been as a novel strategy for the mitigation of biofouling in membrane systems. In this review an attempt is made to correlate membrane biofouling with QS activity. Moreover, recent trends in membrane biofouling control based on QS are presented and the mechanisms by which different agents mitigate membrane biofouling based on QS are discussed. The potential impact of QS-based methods of biofilm control is assessed. Lastly, brief conclusions and future research challenges in membrane biofouling control based on QS are highlighted.

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Abbreviations: AHL, acylhomoserine lactone; AIs, autoinducers; ATCC, American type culture collection; ATP, adenosine triphosphate; CEB, cell entrapping bead; DNP, 2,4-dinitrophenol; DRR, downstream response regulator; E. coli, *Escherichia coli*; EPS, extracellular polymeric substance; Gfp, green fluorescent protein; HK, histidine kinase; HPLC, high pressure liquid chromatography; IR, infrared; kPa, kilopascal; LC, liquid chromatography; MBR, membrane bioreactor; MEC, magnetic enzyme carrier; MIC, minimum inhibitory concentration; MLSS, mixed liquor suspended solids; MS, mass spectrometry; NF, nanofiltration; NMR, nuclear magnetic resonance; PBE, piper betle extract; QS, quorum sensing; RO, reverse osmosis; SMP, soluble microbial products; TCS, tetrachlorosalicylanilide; TLC, thin layer chromatography; TMP, trans-membrane pressure.

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1. Introduction

Over the course of the last 25 years, membrane systems have become a favoured technological innovation for water and wastewater treatment [1]. Membrane systems are extensively used for wastewater treatment because they ensure improved effluent quality [2,3]. However, fouling is still a major limitation to the application of membrane bioreactor (MBR) as well as reverse osmosis and nanofiltration systems. Fouling is of various types, e.g., organic, inorganic, and biofouling [4]. Of these, "biofouling", resulting from extracellular polymeric substances (EPS) and microbial cells, presents a particular operation challenge [5,6]. Membrane biofouling decreases filtration performance owing to increased retention time caused by the deposition and growth of bacterial biofilms onto and into the membrane [7]. This major hindrance and limitation of the process has been under analysis since the early stages of membrane system development, and it is one of the most demanding obstacles to further application and enhancement of membrane technology [8].

Membrane biofouling is the adhesion, metabolism, and growth of microbial cells as a biofilm on the surface of a membrane, which is a main cause of loss of membrane permeability, and therefore, membrane flux and efficiency [9]. Biofilm formation on membrane surface is a complex process. For example, the initial adsorption of organics and suspended particles on the membrane surface form a conditioning film. This enables attachment of planktonic cells to the membrane surface, followed by the formation of microcolonies and biofilm maturation, where bacterial cells are embedded in a self-produced matrix of extracellular polymeric substances (EPS). Various biofouling control strategies have been developed through engineering and chemistry; all of these approaches have limitations [1]. Various antimicrobial compounds have been used to mitigate membrane biofouling such as silver salts, nitrofurazone, ammonium surfactants and antibacterial peptides etc. [10]. However, some anti-biofilm compounds also pollute the aquatic environment and are toxic to non-specific organisms. Moreover, killing the cells using disinfectants, as practiced in industry for example, does not always work, because it is not possible to kill 100% of the cells, leaving some viable cells to attach to solid surfaces and form a biofilm [11]. As a consequence of these limitations, there is a clear need to identify new strategies to control microbial fouling of membranes, and such strategies may be derived from an understanding of the biological process of biofilm formation. One regulatory system that has been linked to the control of biofilm formation in bacteria is the quorum sensing (QS) regulatory system [12–14]. Efforts to disrupt biofilms have enabled the identification of molecules produced by prokaryotes and eukaryotes with abilities to quench the QS system [15–19]. Thus, interfering with QS represents a 'non-disinfectant' biological alternative approach to control membrane biofouling.

Here, we review QS in membrane biofouling and an attempt is made to correlate membrane biofouling with QS activity. Recent trends in membrane biofouling control based on QS are presented and mechanisms by which different agents mitigate membrane biofouling based on QS are discussed. The potential impact of QS-based methods of biofilm control is assessed. Lastly, brief conclusions and future research challenges in membrane biofouling control based on QS are highlighted. It is expected that this review may serve as a stepping stone for further development and application of QS toward effective control of membrane biofouling. While the emphasis in this review is on biofouling control in membrane bioreactors (MBRs) the concepts are applicable to other membrane applications in the water domain.

1.1. Quorum sensing

Originally discovered in the 1970's, quorum sensing was first described as a mechanism for the coordinated expression of a phenotype, e.g., bioluminescence, at the population level [20,21]. Quorum sensing (QS) is a mechanism of cell to cell communication that is used by microbial cells to assess their local densities or diffusion gradients and control gene expression [22–25]. The mechanism of QS is based on the production, secretion and sensing of signalling molecules which, when they accumulate to a threshold concentration, trigger a change in gene expression in the population (Fig. 1) [22,26–28]. When the population density is low or when diffuse rates are high, acylhomoserine lactone (AHL) are present at low concentrations and the LuxR receptor (it is a transcriptional activator of the Lux operon that is activated when bacterial cell density is high) is quickly degraded (Fig. 1A). When the AHL concentration reaches a specific concentration, the AHL signalling molecules binds LuxR to make an AHL/LuxR complex, hence activating the receptor. AHL based signalling is predominantly found only in approximately 10% of proteobacteria (Gram-negative), although there are some exceptions. The QS systems of Gram-positive function in an analogous fashion, although the specific signal is an autoinducer peptide (AIP) (Fig. 1B). In this system, the AIP precursors are produced, are modified post-transcriptionally and secreted via specific transporters. When mature AIPs are in a high concentration, they bind to a transmembrane histidine kinase (HK) and the HK receptor is activated, which activates the downstream response regulator (DRR). This activated RR initiates transcription of specific genes.

There are a diverse array of phenotypes that are regulated by QS, either AHL or AIP, including luminescence, virulence, motility, competence and biofilm formation. While QS is important for the expression of these phenotypes, loss of QS does not appear to be lethal to the cells. Hence, QS has been proposed to be an ideal target for microbial control since inhibition of QS does not exert a strong selection pressure. As a consequence, it has been hypothesised that bacteria are less likely to develop resistance to QS inhibitors [29–33]. Interestingly, recent publications are suggesting that despite the low apparent selection pressure, some resistance can be evolved in the laboratory [34]. None the less, it remains an interesting target to control bacteria, especially biofilm formation, which is especially relevant to the fouling of water purification membranes. QS signalling molecules are produced in a very small quantity, so these molecules cannot be commonly detected, identified and characterized via conventional techniques. A brief summary of the approaches used for detection quantification, identification and characterization are presented in Table 1.

The process of QS can be disrupted by different mechanisms [34,46]: (a) inhibiting the production of QS signalling molecules [47,48], (b) degradation of AHL [49–51], (c) reducing the activity of AHL cognate receptor protein or AHL synthase [52,53], and (d) mimicking the signal molecules primarily by synthetic compounds as analogues of signal molecules [47,48]. Given that QS plays an important role in biofilm formation by a range of bacteria as well as virulence factor expression (Table 2), there have been a

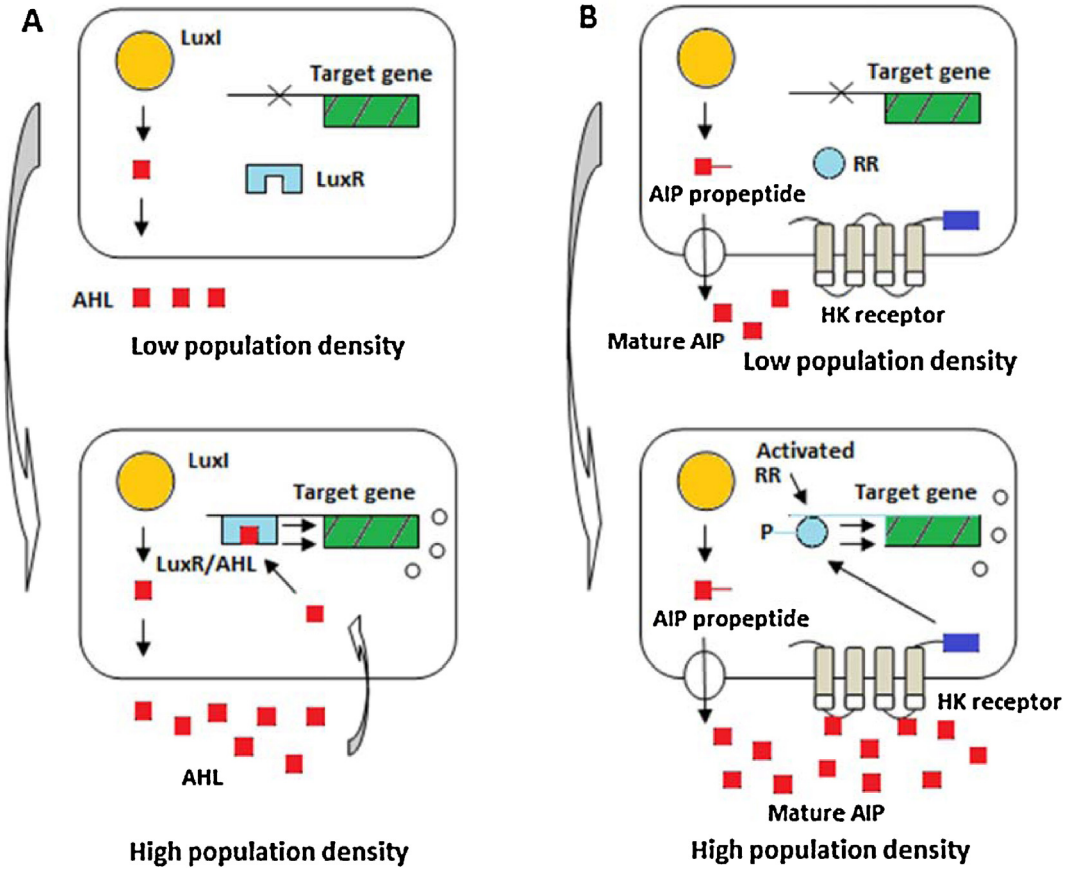

Fig. 1. Bacterial QS systems. (A) AHL mediated QS system in Gram-negative bacteria. (B) Autoinducer peptide (AIP) QS in gram-positive bacteria [22,27].

Table 1
Autoinducer detection, quantification, identification and characterization by different techniques.

Approach	Uses	Advantages	Limitations	Reference
Detection				
A. tumefaciens A136	Visualize AHLs on TLC plates or on petri dishes as blue spots	Fast screening of AHLs	Cannot detect *N*-butanoyl-homoserine lactone	[35,36]
C. violacum CV026	Violacein production with a purple color for QS	Simple bioassay compared to *lux*-based reporters	Cannot detect any of the three hydroxyl derivatives	[37]
Vibrio harveyi BB170	Detect AHLs by luminescence production	Simple bioassay	Only respond to autoinducer-2 and autoinducer-1	[38,39]
A. tumefaciens NTL4	Visualize AHLs on TLC plates or on petri dishes as blue spots	Allows broad and highly sensitive AHL detections	Cannot detect *N*-butanoyl-homoserine lactone	[37,38]
Quantification				
Luminescence	Quantify AHLs by Beta-Glo Assay System (Promega, U.S.)	Simple and fast bioassay	NA	[40]
LC–MS	Quantify AHLs up to picomoles	Quantify small amount can be coupled with HPLC	NA	[40]
HPLC–MS/MS	Quantify various AHLs	Fast quantification	NA	[41]
Agar plat assay	Based on blue spots on Agar plate made of AHL biosensor	Allows fast quantification	Cannot quantify some of the AHLs	[42]
Characterization				
TLC	Partial characterization of AHLs	Easy, fast and provides preliminary information about structure	Structures cannot be assigned base on TLC alone	[37,42]
HPLC	Detect most of the AHLs	Easy and rapid technique	Cannot assign particular structure.	–
Identification				
TLC	Partially identify the structure	Rapid, cheap and easy	Cannot study structure	[38,42]
LC–MS	Capable of determining the structure of AHLs	Detect picomoles of sample	Requires chromophore, and little qualitative information	[43]
Infrared spectroscopy (IR)	Can identify functional groups	Cheap, versatile and easy to identify functional groups	Sensitive to sample preparation	[44]
NMR	Capable of elucidating the structure of AHLs	Detect fine structural components	Expensive, time consuming	[45]

Table 2
Quorum sensing signals and QS-controlled behaviors in bacteria.

QS signals	Bacteria	Signal synthase	Process controlled by QS	Reference
C4-HSL, C6-HSL	*Aeromonas Hdrophyla, A. salmonicida*	AhyI, AsaI	Biofilm formation and enzyme production	[54]
3-oxo-C6-HSL	*Vibrio fischeri*	LuxI	Light production	[21]
C4-HSL	*P. aeruginosa*	RhlI	Biofilm maturation and adhesion	[26]
3-oxo-C10-HSL	*Vibrio anguillarum*	VanI	Virulence	[30]
3-oxo-C12-HSL	*P. aeruginosa*	LasI	Virulence production	[55]
C6-HSL	*C. violacium*	CvI	Violacein, antibiotics and enzyme production	[56]
C4-HSL	*Seratia marcescens*	SwrI	Swarming	[13]
AI-2	*Vibrio harveyii* Vibrio cholerae	AI-2	bioluminescence Virulence	[57] [58]
Group I thiolactone	*Staphylococcus aereus*	AIP-1	Virulence	[59]
Hyroxy palmitic acid methyl ester	*Ralstonia solanacerum*	PhcS-PhcR	Production of polyscaccharides	[60]

Table 3
Natural and synthetic quorum sensing inhibitors.

QS inhibitor	Source of organism	Mode of action	Reference
Natural Inhibitors			
AHL-lactonase	*Bacillus cereus*	AHLs degradation	[61–63]
	Agrobacterium tumefaciens		
	Halomonas sp. strain 33	AHLs degradation	[64]
AHL-acylase	*Tenacibaculum discolor strain* 20J	AHLs degradation	[64]
	Hyphamonas sp. DG895	C4HSL and 3OC12-HSL	[64]
AHL-oxidase	*Bacillus megaterium*	C4HSL and 3OC12HSL	[65]
AHL-oxidoreductase	*Burkholderia* strain GG4	3OC6HSL	[66]
Lactones	*Streptomycetes* spp.	Mimic AHL signals	[67]
Halogenated Furanones	*Delisea pulchra*	Mimic AHL signals and inhibit gene expression	[68]
Ellagic acid (Benzoaric acid)	Fruit extract of *Terminalia chebula Retz.*	Down-regulate the expression of virulence gene in *P. aeruginosa* PAO1.	[69]
Vanillin (4-Hydroxy-3-methoxybenzaldehyde)	Vanilla beans extract (*Vanilla planifolia Andrews*)	Interfere with AHL receptors. Inhibit C4-HSL, C6-HSL, C8-HSL, 3-oxo-C8-HSL.	[70,71]
Ajoene (1-Allyldisulfanyl-3-(prop-2-ene-1-sulfinyl)-propene)	Garlic extract (*Allium sativum*)	Blocks the QS-regulated productions of rhamnolipid resulting in phagocytosis of biofilm. Targets Gac/RSM part of QS and lowers the expression of regulatory RNAs in *P. aeruginosa* PAO1	[72]
Iberin (1-Isothiocyanato-3-(methylsulfinyl) propane)	Horseradish extract (*Armoracia rusticana*)	Inhibit expression of QS-regulated *lasB-gfp* and *rhlA-gfp* genes responsible for virulence factor in *P. aeruginosa*	[73]
Piper betle	*Piper betle* extract	Inhibit QS-mediated biofilm formation in *P. aeruginosa*	[74]
Garlic	*Garlic extract*	Interferes with expression of QS-controlled virulence genes in *P. aeruginosa*	[16]
Tumonoic acids	Blennothrix cantharidosmum	Compete with QS signals	[75]
Curcumin	Turmeric	Reduction of AHL production	[76]
Synthetic inhibitors			
2-aminophenol	synthetic	QS gene expression inhibitor	[77]
Triclosan	synthetic	Inhibitor of the enoyl-ACP reductase	[78]
Furaly hydrazide	synthetic	Mimic AHL signals	[32]
Furanone F3 and F4	synthetic	Reduce 3OC12HSL dependent QscR activity	[79]
Blastmycinolactol (Lactone)	Synthetic	Mimic AHL signals	[67]

range of studies aimed at identifying compounds that disrupt QS. These QS inhibitors have been identified through a combination of natural products screening as well as screening of compound libraries to identify compounds with strong activity. For example, compounds from prokaryotic and eukaryotic organisms have been shown to disrupt QS and indeed, even synthetic compounds have been shown to inhibit QS activity. A summary of the known QS inhibitory compounds derived from plant, bacteria, fungi and synthetic compounds is provided in Table 3.

2. Relationship between QS activity and membrane biofouling

Membrane biofouling is a process by which microbial cells attach to the membrane surface and form a biofilm. Growing evidence suggests that these complex mixed microbial communities utilize QS to control community level behaviors, one of which may be biofilm formation. Some studies have further gone on to show that QS inhibitors either reduce membrane fouling or improve performance, e.g., water permeation, further suggesting that QS based biofilm formation plays an important role in membrane fouling [42,69].

2.1. AHL and membrane biofouling

In a laboratory scale continuous MBR, Yeon et al. [42] measured both the TMP and AHL of the biofilm and correlated these two parameters. They observed that TMP (proportional to fouling resistance) and AHL levels of the biofilm increased following similar trends, which suggests a close relationship between biofouling

and QS activity. This conclusion was further strengthened by their observation that the floccular biomass in suspension did not contain significant concentrations of the AHLs. Instead, they concluded that the AHLs detected in the membrane biofilms were a consequence of the microbial community growing on the membranes. Furthermore, Yeon et al. [80] studied use of a magnetic enzyme (acylase) carrier (MEC) to control membrane biofouling, to investigate why the addition of MEC could reduce membrane biofouling. It is understood that QS systems regulate the target gene transcription and determine the physiology of the microbial community. Therefore, it was anticipated that the addition of the MEC, which was expected to disrupt the QS signal molecules, would quench the QS process. Hopefully, this might change the microbial physiology in the bioreactor, which is now generally accepted to be closely associated with membrane biofouling [81,82]. In this context, they investigated the difference in the microbial physiological characteristics between the control and the MEC MBRs in terms of soluble microbial products (SMP) in mixed liquor and EPS in the membrane biocake, respectively. They observed low levels of EPS and SMP with the addition of MEC, which showed that production of microbial metabolites were under the control of MEC, e.g., quorum quenching. Kim et al. [83] also confirmed the significant decrease of EPS on the surface of a nanofiltration (NF) membrane, in comparison with a non-treated NF membrane, when a quorum quenching enzyme (acylase) was immobilized directly on its surface. Oh et al. [84] studied a microbial vessel containing quorum quenching bacteria (*Rhodococcus* sp. BH4) which showed the degrading activity against C8-HSL in the MBR, substantially delayed the TMP rise (i.e., membrane biofouling). Ponnusamy et al. [19] studied that treatment of *Aeromonas hydrophila* biofilms with vanillin (from vanilla beans) resulted in reduced production of AHL molecules and decreased biofilm formation on a reverse osmosis membrane. It is revealed that vanillin has varied activities against different AHLs, which shows that it also interferes with AHLs [19,85]. Furthermore, Kim et al. [38] revealed that targeting QS could be an effective method to mitigate biofilm formation and thus, to reduce biofouling of reverse osmosis (RO) membranes. Kim et al. [38] studied the presence of AHL from the fouled reverse osmosis membrane.

2.2. Autoinducer and membrane biofouling

In addition, it has been demonstrated that microorganisms regulate their group behaviors, such as biofilm formation using signal molecules, called autoinducers (AI) among which autoinducer-2 (AI-2) has been believed to coordinate cell to cell communication during biofilm formation [39,86,87]. AI-2 as a universal interspecies signaling molecule coordinates the formation of biofilm by various species [88]. Recently, Xu and Liu [39] found that bacterial biofilm on the membrane surface was positively correlated with AI-2 concentration; showing that AI-2 regulated quorum sensing might have a role in membrane biofouling.

There is evidence for QS in membrane systems, either based on testing isolates or the whole biofilm and that this correlates with fouling in many cases. This suggests that QS might be a strategy to control fouling or process failure. A brief summary of relationship between membrane biofouling and QS activity is presented in Table 4.

Table 4
Relationship between quorum sensing and biofouling.

Autoinducer	Effect on membrane biofouling	Reference
C8-HSL	AHL↑ → TMP↑, EPS↑→ biocake↑	[42]
AHL	AHL↑→ TMP↑, SMP and EPS↑→ biofouling↑	[80]
AHLs	AHLs↓→ biofouling↓	[19]
C8 HSL	AHL↓ → biofilm formation↓	[39]
AHLs	AHLs↓ → biofilm formation↓	[37]
AI-2	AI-2↓→ EPS↓→biofouling↓	[39]
AI	AI↓→ EPS↓→biofilm formation↓	[83]
AHL	AHL↓ → biofilm formation↓	[74]
C8-HSL	AHL↓ →TMP↓→ biofouling↓	[84]
C8-HSL	AHL↓ →TMP↓→ biofouling↓	[89]
AHLs	AHL →biofilm formation	[90]

↑Increase; →Leads to; ↓Decrease

3. QS based mitigation of membrane biofouling

The occurrence of QS signalling molecules in the biofilm, and the relationship of QS processes with changes in biofilm, TMP and EPS measurements, provides possible directions for research into strategies for exploiting quorum sensing to control membrane biofouling. The basic routes to target quorum sensing is already stated in Section 1.1 (Fig. 2) [46]. Hence, different strategies to mitigate membrane biofouling based on QS are discussed here.

3.1. Blockage of signal production

Blockage of signal production is a conceptually simple method for inhibiting QS pathways – no production of signal molecule, no activation of QS. However, there are relatively few reports on the inhibition of signal synthase. Compounds affecting the AHL biosynthesis or efflux pumps are likely to behave as quorum quenchers. Substrate analogs of AIs, like butyryl-Sadenosylmethionine, holoacyl carrier protein, sinefungin and L/D-S adenosylhomocysteine, can block AHL production in vitro [91]. However, in vivo experiments have not been performed, because these homologs are likely to affect the central pathways of amino acid and fatty acid metabolism [91].

There are some studies which show reduction in signal production, but the mechanism is not clear. As the extent of microbial attachment is linked to the concentration of autoinducers in the biofilm, targeting the production of autoinducers is an alternative approach to mitigate membrane biofilm formation. In some bacteria signal production is QS regulated and the furanones have been shown to act as signal blockers, not signal synthase inhibitors. Recently, 2(5-H) furanones (non-halogenated), a commercially available compound, was found to block the production of AHL signalling molecules, and it significantly reduced biofilm formation on a fouled RO membrane. 2(5-H) furanones are believed to act as a potential quorum inhibition agent in a bacterial biofilm community [37]. However, furanone compounds are considered to be toxic and chemically unstable and therefore, these compounds are not suitable for water purification systems [37]

Some natural products from different plant sources have also been used to control membrane biofouling based on quorum sensing. A study by Ponnusamy et al. [19] revealed that exposure of *A. hydrophila* biofilms to vanillin (from vanilla beans) resulted in reduced production of AHL molecules and decreased biofilm formation on a reverse osmosis membrane. As vanillin prevents biofilm formation at very low concentrations, and it controls QS, there is no expectation that bacterial cells will develop resistance to this treatment [19,71]. Furthermore, a study by Kappachery et al. [92] demonstrated that a commercially available vanillin as a natural quorum quenching compound, considerably supressed biofilm formation on RO membrane in a CDC reactor. There was 97% reduction in biofilm, when grown in the presence of vanillin. Taken together, all of these factors, combined with its non-toxicity suggest that vanillin is a good agent to mitigate biofouling in real membrane systems. Xu and Liu [39] investigated the effect of D-tyrosine to target the QS system to reduce biofilm formation, enhance biofilm detachment and therefore, to reduce membrane biofouling. They

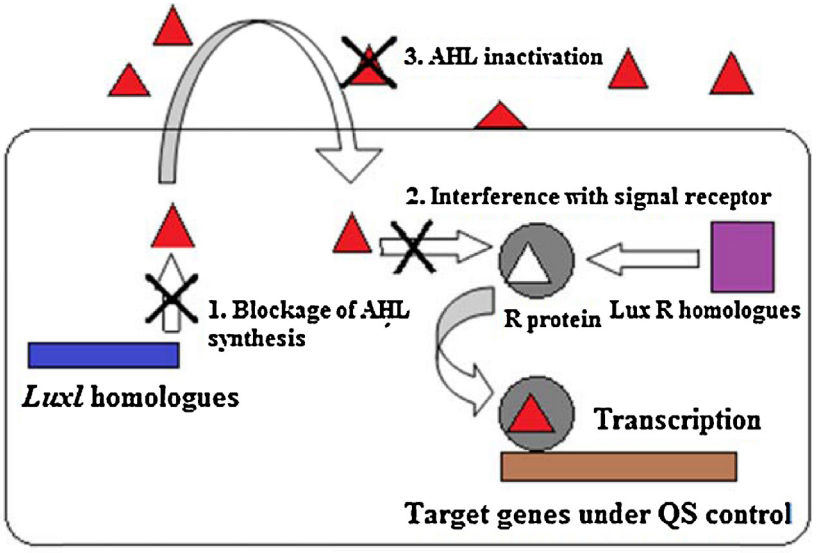

Fig. 2. Basic AHL QS control strategies; (1) blockage of AHL synthesis, (2) interference with signal receptor protein, 3. AHL inactivation [69].

found that there was significant reduction in autoinducer (AI-2) signalling molecules, which promoted biofilm detachment and mitigated membrane biofouling. These studies suggest that incorporation of natural QS inhibitor (QSI) on membrane surfaces and addition in membrane systems could be an effective strategy for control of membrane biofouling. Such artificial quorum sensing regulatory systems might help to mimic the problem of membrane biofouling without disturbing bacterial growth.

3.2. Blockage of signal receptor proteins

Besides the use of enzymes to degrade QS signalling molecules, some research efforts have focused on the use of inhibitors, which have structural similarity to the AHLs. These inhibitors block the receptor proteins and hence inhibit the activation of gene expression [93]. It has been found that halogenated furanones and their synthetic analogs have structural similarity to acylhomoserine lactone signalling molecules, and these inhibitors are known to control AHL regulated phenotypes, such as microbial attachment, biofilm formation, flagella movement and biosurfactant production [70,94,95].

Among the unicellular chlorophytes, *Chlamydomonas reinhardtii* can control QS activities by producing different compounds that mimic AHLs [96]. Some specific species of *Penicillium* grown on various media produce inhibitors of bacterial QS [97]. Patulin and penicillic acid have been used to inhibit QS as non-brominated alternatives. Different plants, such as barrel medic *Medicago truncatula* [98,99], magnolia [100], and garlic [32], have been known to inhibit bacterial QS by producing compounds that mimic AHLs. Also, *Halobacillus salinus* bacterium is able to produce phenethylamide [101] and *Streptomyces* produce lactones [67] both of which mimic AHL to inhibit bacterial QS. Many synthetic derivatives of AHLs with different structural alterations in carbon atoms in acyl side chains and lactone rings have be applied to inhibit bacterial QS [46]. Various inhibitors in gram-positive bacteria, such as closantel, alter the structure of kinase receptor which in turn inhibits bacterial QS [102]. In addition to synthetic QS AHL analogues, researchers have found that macrolides [103] and 4-nitropyridine-*N*-oxide [16] inhibits expression of genes. Recent research on QS inhibitors shows that this novel direction is in the initial stage and new inhibitors of bacterial QS might come in the future.

3.3. Degradation of AHL by enzymes

3.3.1. Degradation by free enzymes

AHL signal molecules can be degraded using enzymes, in a process known as quorum quenching. AHL degradation can be stimulated by four different enzymes: lactonase, acylase, decarboxylase and deaminase [104]. Of these only two types of enzymes are well known for degradation of AHLs in membrane biofouling control, namely lactonase and acylase, which can disrupt the communication between cells via cleaving the amide linkage or cyclic ester of AHL signal molecules [105,106]. Kim et al. [38] reported that biochemical control of quorum sensing could be an effective method to control biofilm formation and thus, to reduce biofouling of reverse osmosis (RO) membranes. Kim et al. [38] observed the occurrence of AHL and AI-2 from the fouled reverse osmosis membrane. Paul et al. [107] found that biofilm formation by bacterial strains *A. hydrophila* and *Pseudomonas putida* isolated from fouled RO membrane was reduced with the addition of acylase 1 at a concentration of 60 μg/ml. Paul et al. [107] further observed gradual decrease in biofilm with increasing concentration (5–60 μg/ml) of acylase 1. Recently, in a study by Kim et al. [108] showed that biofilm formation by *P. putida* (isolated from a fouled RO membrane) on the membrane was reduced by acylase as it degrades N-acylhomoserine lactone (AHL) which is a signal molecule of QS. In this study, it was shown that targeting QS by acylase with 7 U/ml (i.e., converted into about 21 mg/L) was effective for biofouling control in the bench-scale crossflow RO test unit.

In a study in a laboratory scale continuous MBR (batch MBR with total recycled mode [15 Lmh]), Yeon et al. [42] revealed that a multispecies biofilm was mitigated by degrading Acylase I (10 mg/l). Initially, they found that during early stages of reactor operation the AHL activity was low; it was observed to increase at about the time at which TMP was measured to be entering the early stages of exponential increase and was fully developed when fouling was severe. On these bases, the authors suggested the use of acylase, which can inactivate AHL via amide bond cleavage as a new approach to biofouling mitigation. Biofouling was quantified by monitoring of the TMP values, and the times taken for the recorded TMP values to exceed certain benchmark values. When applying acylase to the system and comparing with results from an untreated control experiment, ~32 h was required for the TMP to reach 40 kPa [~20 h in control] and a maximum TMP of 48 kPa was recorded after ~40 h [70 kPa at ~23 h for control], respectively

Table 5
Recent strategies to mitigate membrane biofouling based on quorum sensing.

Approach	Mode of action	Anti-biofouling capabilities	Advantages	Limitations	Reference
Acylase I	Degradation of AHL signals	Inactivating AHL by hydrolysis, ~32 h to reach 40 kPa [~20 h in control]	Low risk of bacterial resistance	Short lifetime and difficulty in recovery	[42]
Acylase I	Degradation of AHL signals	Reduced biofilm formation by *A. hydrophila* and *P. putida on* membrane (20 and 24%)	Low risk of bacterial resistance	Short lifetime and difficulty in recovery	[107]
Acylase	Degradation of AHL signals	Biofilm formation reduced by inhibiting activity of AHLs	Low risk of bacterial resistance	Short lifetime and difficulty in recovery	[108]
Magnetic Enzyme (Acylase I) carrier (MEC)	Degradation of AHL signals	Reduced biofilm and enhanced permeability; Maximum TMP 36–39 kPa [76–79 kPa in control] in 3 operation cycles (15–20 h)	Recycled use and stable in mixed liquor	Cost restricts scale up	[80]
Immobilized Acylase on membrane	Degradation of AHL signals	Prohibited biofilm formation owing to decreased production of EPS	Maintained >90% of enzyme activity over 20 cycles of reaction	High cost restricts scale up to a real MBR at present	[83]
Enzyme immobilized membrane	Degradation of AHL	Flux was maintained at more than 90% of its initial flux after a 38-h operation, whereas that with the raw NF membrane decreased to 60%	This system provided more than 90% of its initial enzyme activity	NA	[83]
Encapsulated Acylase	Degradation of AHL signals	Maximum TMP 14 kPa at ~45 h [40 kPa at 55 h in control]	No declining of treatment efficiency, no consumption of additional energy, and no production of peculiar byproducts	NA	[110]
Immobilized acylase in magnetically separable mesoporous silica	Degradation of AHL signal molecules	Increase in permeability from 6 to 14 days in treated reactor	Stabilized activity for one month	NA	[111]
Encapsulated bacteria (*Rhodococcus* sp. BH4)	AHL lactonase degrade AHL signals	Alleviated biofouling; 39 h to reach 25 kPa [28 h in control]	Longer life span and no enzyme purification	Limited mass transfer to the microbial vessel	[84]
Encapsulated bacteria (*Rhodococcus* sp. BH4)	AHL lactonase degrade AHL signals	Maximum TMP 30 kPa at 68 h [48 h in control]	Maintained QS over 100 days due to regeneration of bacteria	NA	[89]
Cell Entrapping Beads (CEBs)	Degradation of AHL signals	Time reach to TMP of 70 kPa was ten times longer than without CEBs	Controls biofouling both physical washing and quorum quenching	NA	[112]
Encapsulated bacterial (*Pseudomonas* sp. 1A1)	Degradation of AHL signals	QQ activity against quorum sensing signal molecules (AHLs)	Longer life span and no enzyme purification	Low F/M ratio compared with a mixed liquor	[113]
Encapsulated bacteria in ceramic microbial vessel	Degradation of AHL signal molecules	Reduced polysaccharides from 980 to 610 and proteins from 1840 to 1040 mg/l	Greater bacterial QQ activity through the facilitated nutrient transfer	NA	[114]
Encapsulated bacteria	Degradation of AHL signal molecules	QQ bacteria showed greater anti-biofouling capacity in continuous MBR	Maintained greater bacterial QQ activity and stability	NA	[115]
QQ Vessel	Degradation of AHL signal molecules	Stable operation of MBR without loss of permeability even at lowest aeration and it reduced 27% of specific aeration energy	Maintained the stability and lower the aeration energy	NA	[116]
Vanillin	Interfere with AHL receptors. Inhibit C4-HSL, C6-HSL, C8-and 3-oxo-C8-HSL.	Inhibit the AHL signals, leading to biofilm reduction of *Aeromonas hydrophila*	Nontoxic, inhibit different acyl chain	Require optimum conditions	[19]
Vanillin	Inhibit AHL signals	Biofilm reduction of *Aeromonas hydrophila*	Effective against all membranes tested	Not tested against mature biofilm	[85]
2(5-H) furanone	Mimics AHL signal by binding to regulatory protein	Suppressed biofilm formation	Lower toxicity, no inhibitory effect on bacterial growth	Toxic and chemically unstable and against gram negative bacteria	[37]
Piper betle Extract	Inhibit QS mediated biofilm formation in *P. aeruginosa*	Reduced membrane biofouling by targeting AHLs and EPS	Lower toxicity, no inhibitory effect on bacterial growth	NA	[74,117]

This represents a considerable enhancement of permeability in terms of TMP (compared to control MBR), and therefore, improved performance.

These results show a good possibility of biochemical methods for more effective biofouling control when properly combined with physicochemical methods. In addition, more systematic studies are required to find out optimal conditions for effective QS inhibition including the amount and type of QS inhibitor with respect to application practices. Using enzymes to control membrane biofouling has the attractions that it should have a low risk for bacterial resistance, as it does not affect the survival of the bacteria. However, the short life time of the free enzyme and the cost of continuous treatment are possible obstacles to adoption of this technique for large-scale applications.

3.3.2. Degradation by immobilized enzymes

After verifying the quorum quenching via free enzymes in an MBR at the lab-scale, an obvious direction for development was to overcome the disadvantages of using free enzymes. Specifically, the membrane is permeable to molecules of the size of the enzyme and hence the enzyme is not retained within the reactor. This can be addressed by continuous addition of new enzyme to the reactor, but this then creates a considerable operational expense. A preferable approach is to ensure that the enzyme can be retained in the reactor, and this can be achieved by immobilising the enzyme on the surface of particles that are too large to permeate the membrane. This approach has been demonstrated in two studies using either magnetic immobilized enzyme (acylase) carriers (MECs) in the MBR [80] or by immobilizing the acylase enzyme on the surface of a Nanofiltration membrane [83]. Yeon et al. [80] observed that MEC reduced membrane biofouling in batch MBR with total recycled mode (15 Lmh). The enzyme was shown to be retained and recycled and to be stable in the mixed liquor. The maximum TMP observed was 36–39 kPa [76–79 kPa in control] in 3 operation cycles (15–20 h), however, in continuous MBR (15 Lmh), TMP of 10 kPa (30 kPa in 48 h for the control) was observed throughout the experiment. In short, degradation of AHLs using enzymes, like, Acylase I appear to have a great potential for the membrane biofouling mitigation in membrane bioreactors. There is, however, need for more effective quorum quenching methods, which can solve issues related to the stability and cost of enzymes.

3.3.3. Encapsulated enzymes

While quorum sensing controls a large number of bacterial phenotypes, it is important to understand the characteristics of sludge (i.e., settleability, viscosity and hydrophobicity) to avoid any potential adverse side effects of QS on MBR performance [109]. Furthermore, it is also worth determining the mechanism by which QS mitigates biofouling in membrane bioreactors in order to predict the possible consequences to the process if a QS control loses its efficacy. Jiang et al. [80] showed that the acylase immobilized into sodium alginate mitigated biofouling and enhanced permeability (maximum TMP 14 kPa at ~45 h, compared with 40 kPa at 55 h for the control) of the lab-scale MBR (continuous MBR, 15 Lmh). Jiang et al. [110] further revealed that QS activity was responsible for membrane biofouling control by targeting AHL and reducing EPS. QS had no obvious adverse effects on the effluent quality of bioreactor but other side effects included increased settleability of the sludge, decreased viscosity of sludge and reduced sludge hydrophobicity as well as reduced EPS production.

3.3.4. Encapsulated quorum quenching bacteria

In some of the studies, the bacteria which produce quorum quenching enzymes were contained within a hollow fiber membrane, with the result that the measured membrane biofouling was significantly reduced [84,89]. Recently, bacterial quorum quenching has been applied to the bioreactor system, which is seen to be more economical than enzymatic quorum quenching owing to the longer life span of the active agent and also because no purification step is required. As an alternative to the mitigation of membrane biofouling based on enzymatic quenching, Oh et al. [84] isolated a bacterial strain *Rhodococcus* sp. BH4, and they found that this bacterium expressed a quorum quenching enzyme. Hence, they enclosed *Rhodococcus* sp. BH4 bacterium in a microbial vessel, consisting of a hollow fibre ultrafiltration membrane. This apparatus allowed the bacteria to be physically restrained, but for transfer of solutes to occur with the MBR. They revealed that an internal continuous submerged MBR (20 Lmh) containing the microbial-vessel had a much lower biofouling propensity (39 h to reach 25 kPa) compared to an MBR without the microbial vessel (28 h to reach 25 kPa). Furthermore, Jahangir et al. [89] studied the optimum location of microbial-vessel in a submerged MBR (continuous MBR at 30 Lmh). For this purpose, they separated the membrane tank from the bioreactor of the MBR. They revealed that the QS fouling inhibition effect was more noticeable (maximum TMP 30 kPa at 68 h compared with 48 h in control) when the microbial-vessel was placed near to the membrane in the bioreactor. They also observed that the quenching effect was dependent on the recirculation rate of mixed liquor between the bioreactor and the membrane tank. Moreover, they also observed that the encapsulated *Rhodococcus* sp. BH4 retained its quorum quenching performance over 100 days of the bioreactor operation owing to the natural regeneration of the *Rhodococcus* sp. BH4 inside the microbial-vessel. In the above studies, the transfer of mass and AHLs from the mixed liquor to the microbial vessel was limited because microbial vessels were submerged in a fixed position in the MBR, so only soluble diffusible molecules, which can pass through the membranes were degraded.

To cope with these limitations, Kim et al. [108] studied a different method to degrade AHLs, which was more feasible and efficient than both the microbial vessel method and the enzymatic quorum quenching method. Free moving beads were formed from alginate containing *Rhodococcus* sp. BH4., which were called cell entrapping beads (CEBs). CEBs showed reduction of biofouling that could be attributed to both quorum quenching and physical washing effects. In a bioreactor treated with CEBs, the time to reach a transmembrane pressure (TMP) of 70 kPa was ten times longer than without CEBs. This is highly significant from a practical point of view because the delay in TMP rise is closely related to reducing the energy-intensiveness of the process. The effect of CEBs is much better for the mitigation of biofouling compared to that reported by Oh et al. [84]. Oh et al. [40] demonstrated that the bacterial strain BH4 degraded AHL molecules by cleaving the lactone ring in AHLs. Moreover, they have demonstrated that lactonases from BH4 have the ability to degrade a wide range of AHLs, potentially identifying a broad-spectrum QS quenching method that may be effective against a wide range of biofilm types and compositions. It is difficult to compare the results obtained from the microbial-vessel method with the CEBS method, but it appears that CEBs show superior performance when compared with microbial vessels in terms of biofouling reduction.

These new strategies for mitigation of biofouling with cell entrapped beads and microbial vessels are vital because these strategies could provide insights, into ways that interspecies QS could be used to mitigate membrane biofouling in systems where a mixture of species is present. Table 5 lists various strategies to mitigate membrane biofouling based on quorum sensing. Thus, these studies have shown that QS disruption methods may be employed to mitigate membrane biofouling; however, the above findings have yet to be employed in practice.

4. Do QS based techniques have potential to mitigate biofouling?

Discovery of QS processes in biofilm-forming bacteria makes it an alternate target for biofilm control [16]. There is possibility that inhibition of QS may be an extensive, antimicrobial and natural biofilm control strategy [61] and biofilm can be controlled on a range of surfaces [26,86]. This QS mechanism has provided a new way to control the bacterial biofilm formation without the use of bactericidal agents like antibiotics, chemicals and disinfectants [94]. The widespread utilization of agents which suppress the growth of bacterial cells has led to formation of strains, which in turn show resistance to these agents [118]. Thus, there is a need to find other strategies for the control of biofouling. The QS interference strategies have various benefits of greater anti-biofouling effectiveness, low toxicity, eco-friendly substances and less stimulation of bacterial resistance [7]. Moreover, QS is a biochemical way to directly reduce the rate and extent of biofilm formation compared to chemical or physical ways, instead of removing the biofilm after it is already deposited [38]. Also, QS inhibitory compounds can be utilized in combination with other compounds to increase the efficiency of biofilm mitigation Paul et al. [107]. Studying different structures of quorum quenching (QQ) enzymes has led to the interpretation of protein tailoring, molecular advancement and explanations of catalytic mechanisms [118]. This shows that compounds which act as a QQ are more efficacious than bactericidal agents.

QS-based strategies are in their developmental phase and several questions should be addressed to set a roadmap for translating subsisting and new information into sustainable and efficacious control techniques. For example, can one provide enough AHL-acylase or vanillin to work? Are encapsulated enzymes truly realistic? Does a QS based strategy control all the bacteria that do not participate in QS? It may be vital to explore compounds which can control broad spectrum of bacteria. Moreover, it is important to differentiate between the QS inhibiting effect and its direct toxic effect on bacterial cells. For this purpose, it is vital to analyze the effect of a QS strategy on the viability of bacterial cells via specific controls and sensitive techniques. According to Defoirdt et al. [119], many of the results obtained in experiments that make use of QS signal molecules reporter strains may be questioned, due to the possibility that the tested compounds may be toxic to the reporter strains. Moreover, concerns about the possible emergence of resistance and adverse effects resulting from the alteration of microbiome must be properly addressed in depth [120]. Further research and development is compulsory to examine the suitability and compatibility of quorum quenchers with industrial-scale membrane systems and bioreactors for biofouling control. If they do, it will be vital to evaluate its effect on environment and living organisms in the ecosystem including both prokaryotes and eukaryotes.

5. Conclusions and future challenges in QS based strategies

In conclusion, it appears that targeting QS to mitigate membrane biofouling is a promising technology for the enhancement of efficiency and performance in membrane systems. Results from recent investigations verified the existence of a correlation between QS activity and membrane biofouling. Different strategies have been demonstrated to target QS activity, in order to mitigate membrane biofouling. However, current validation methods for QS must be improved and optimized, with its particular toxicity effects on bacterial viability. Furthermore, emergence of bacterial resistance to QS inhibitors and its adverse effects must be evaluated in depth.

Future advances in membrane biofouling mitigation based on QS can be expected from further fundamental research. According to the recent literature, future studies on membrane biofouling mitigation based on QS should take the following directions:

- Though QS-regulated pathways may be controlled by QS, it must be verified early that those vital biochemical reactions performed by the bacterial consortium in a MBR would not be affected via a specific QS approach [109,110].
- QS is a striking approach to mitigate membrane biofouling, however, further research is needed to validate its safety and effectiveness, particularly if it is to be applied in RO system for the production of drinking water.
- Understanding of the currently available range of QS methods and mechanisms, and to add elements from other QS systems, such as from Gram-positive bacteria, which may be more vital for the design of the mixed bacterial consortium.
- Focusing the basic research into the genes, their expression, and the receptors participating in bacterial quorum sensing will offer specific insights into the mechanisms of quorum sensing. This might be vital for the synthesis of new quorum sensing inhibitors.
- Much research remains to be done before we can claim to understand the quorum sensing activity in membrane systems. For example, only a few Proteobacteria have been identified to control membrane biofouling based on QS, however there are more than 100 species known to contain AHL signal genes, which could be responsible for QS based biofilm formation [121].
- It is also important to understand the eco-physiology of the bacterial cells causing biofouling for the effectiveness of a quorum quenching-based strategy.
- Almost all the above studies were carried out at lab scale; however, these findings need to be verified in practice at large scale, across the range of membrane system applications.

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