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Origin and evolution of quorum quenching technology for biofouling control in MBRs for wastewater treatment

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ABSTRACT

Biofouling in membrane bioreactors (MBRs), which is defined as the unwanted accumulation of microorganisms on the membrane surface, has been intensively studied for more than two decades. However, it remains a critical limiting factor to the more widespread use of MBR for wastewater treatment. The concept of quorum sensing (QS) / quorum quenching (QQ) was proposed as an anti-fouling strategy for MBRs in 2002 and the first paper on that issue was published in 2009. Since then, many studies have demonstrated and proved the potential of QQ for biofouling control in MBR through various means. The evolution of QQ-MBR has had a run of eight years in terms of QQ-microorganisms, QQ-media, and the size of the QQ-MBRs tested. This review provides an overview on the QS/QQ studies related to the elucidation and control of biofouling in MBRs, including the identification of QS signals, the isolation of QS signal producing or degrading microorganisms, and various engineering approaches to apply enzymatic or bacterial QQ in the form of QQ-media to mitigate membrane biofouling. The challenges confronting these applications and future directions of QQ-based biofouling control strategies for MBR are discussed.

1. Introduction

Water scarcity is one of the main issues to be faced on every continent in the 21st century. Access to clean water is directly linked to human health, food, agriculture, energy, and most industrial activities. According to a report from the United Nations in 2015, the world will face a 40% global clean water deficit by 2030 [1,2]. With the increasing need for clean water, treating and recycling wastewater is inevitable. Membrane bioreactors (MBRs) offer a combination of biological treatment and membrane filtration, and are rapidly replacing conventional wastewater treatment processes due to their advantages, such as superior effluent quality and reduced footprint [3]. However, membrane biofouling causes substantial operation costs because it requires extensive aeration as well as frequent membrane cleaning and replacement. Thus, biofouling remains a critical factor limiting wider use of MBRs [4,5].

Extensive studies have been carried out to solve this membrane biofouling issue using physico-chemical and operational approaches, including physical/chemical cleaning of biofilms, new membrane materials, addition of coagulants or chemical additives, and optimization of operating conditions [6,7]. However, fully satisfactory solutions have not yet been provided.

Recently, a novel molecular biological method has been reported that effectively mitigates the attachment and growth of microorganisms on the membrane surfaces in MBRs. In 2009, Yeon et al. [8] demonstrated a positive correlation between microbial quorum sensing (QS) and membrane biofouling in an MBR for wastewater treatment. Since then, a number of studies have noted the correlation between QS and membrane biofouling, and provided development of various quorum quenching (QQ) techniques for the elucidation and control of biofouling in MBRs [9].

Since the first paper on the application of QS/QQ in membrane processes was published, eight years have already passed and the interest in this novel technology has continued to rise in academic as well as industrial sectors. Consequently, this would be the right moment to recollect the history of the QS/QQ-MBR approaches that have evolved over the last eight years. Here, we gathered and reviewed most of the QS/QQ studies, with special focus on their use in MBRs, and then monitored the evolution of QS/QQ for MBRs from their birth to their current status. This review also proposes a future direction for QS/QQ techniques for control of membrane biofouling considering the next generation membrane processes upcoming.

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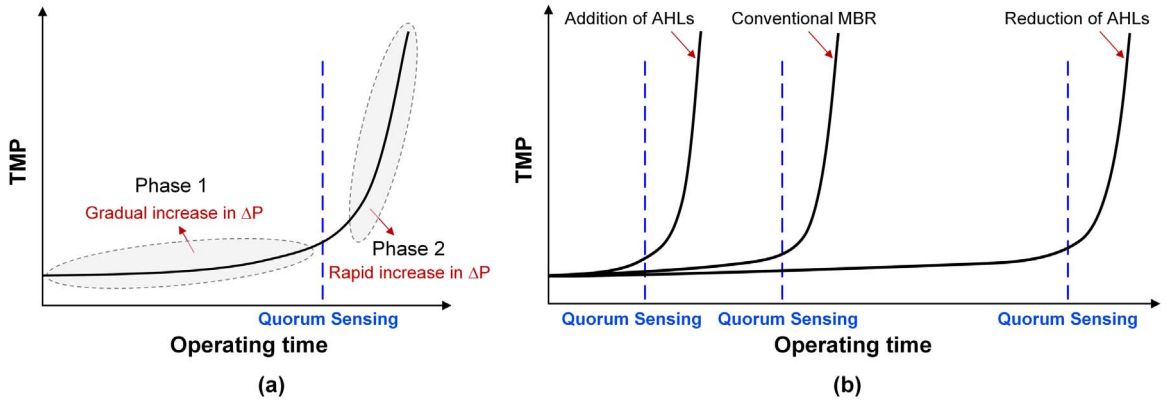

Fig. 1. (a) Typical profile of TMP increase during operation of MBRs for wastewater treatment, and (b) Change in the point of quorum sensing and TMP increase as a function of the concentration of AHL signal molecules.

2. Birth of QQ-MBR

When trans-membrane pressure (TMP) at constant flux is monitored during the operation of submerged MBRs for wastewater treatment, more often than not, two phases of TMP increase are observed [10,11]. A prolonged period of slow TMP increase (1st Phase) is followed by a sudden increase in TMP (2nd Phase) together with massive biofilm formation on the surface of the filtration membrane (i.e., membrane biofouling; Fig. 1). People involved in MBR laboratory research as well as on-site MBR operations, have taken good looks at this phenomenon. They have paid much attention to its elucidation and control because membrane biofouling is closely associated with the capital (initial investment) and operating costs of MBRs.

By the way, it is well-known that bacteria regulate their behaviors in groups, such as virulence and biofilm formation, in a cell-density-dependent way using signal molecules. This is called 'Quorum Sensing (QS)' [12,13]. In 2002, Lee's group at Seoul National University (South Korea) suspected that such a sudden TMP increase at the onset of the 2nd phase might be closely related to a threshold level of QS between microorganisms cohabiting in MBRs (Fig. 1a). Consequently, they hypothesized that the onset point of 2nd phase corresponding to a quorum level could be shifted either to the right with the reduction of signal molecules (e.g., *N*-acyl homoserine lactones: AHLs) by any means, or to the left with the intentional addition of signal molecules (Fig. 1b). Furthermore, they postulated that membrane biofouling could be alleviated through QS control (i.e., the blocking of intercellular communication by decomposing AHL signal molecules in the process called Quorum Quenching (Fig. 2). Later, Yeon et al. proved that the TMP and AHL levels of biofilms increased with very similar tendencies in MBRs [8] and demonstrated that QS-based membrane biofouling control was possible [14,15]. As a result, it turned out to be wiser to go back to nature to adequately address the biofouling problem, which is essentially an intrinsic natural phenomenon.

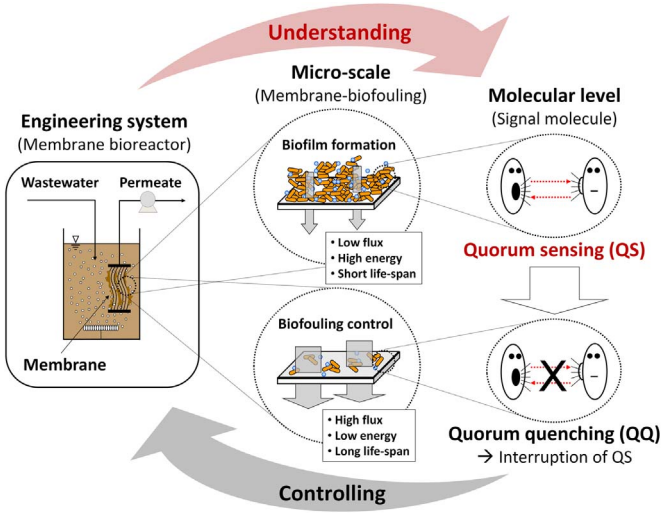

Fig. 2. Concept of QS/QQ-based biofouling control in MBRs.

3. Fundamentals of QS and QQ

3.1. QS systems

Bacteria exploit cell-to-cell communication systems to share information about their population density and to organize group behaviors accordingly. These group behaviors include virulence factor secretion, symbiosis, competence, bioluminescence, sporulation, antibiotic production, and biofilm formation [16–18]. These QS processes follow three basic steps: i) the cells in the community produce small diffusible chemical signals (i.e., autoinducers), ii) autoinducers are detected by receptors that exist in the cytoplasm or membranes of cells when the concentrations of autoinducers exceed a threshold, and iii) detection of autoinducers activates not only the expression of specific target genes but also the production of more autoinducers [17,19–21]. QS allows bacteria to convert environmental stimuli into specific gene expressions, enabling each individual cell to recognize the number of bacteria in their environment, and thus initiate collective behaviors when their number exceeds a quorum level [22]. In general, QS systems have been divided into three general classes based on the type of autoinducer signal and the apparatus used for its detection: i) *N*-acyl homoserine lactone (AHL)-type QS in Gram-negative bacteria, ii) peptide mediated QS in Gram-positive bacteria, and iii) Autoinducer-2 (AI-2) QS shared in Gram-negative and Gram-positive bacteria. In addition, several new classes of signal molecules have recently been discovered (Fig. 3).

3.1.1. AHL-type QS in Gram-negative bacteria

AHL, which consists of a homoserine lactone ring attached to a fatty acid side chain, is used as an autoinducer in Gram-negative bacteria. The number of carbons on the side chain varies (4–18) and the hydrogen on the third carbon can be substituted by oxo or hydroxyl group (Fig. 3) [23]. The LuxI-type protein (AHL synthase), leads to formation of an amide bond between S-adenosylmethionine (SAM) and the acyl-acyl carrier protein (acyl-ACP). Subsequently, the intermediate is lactonized with the release of methylthioadenosine to form the AHL autoinducers [12]. When the concentration of AHL is high enough, it binds to a transcription factor that is usually a member of the LuxR family of transcriptional regulators. AHL-LuxR homologue complexes induce the expression of target genes to organize specific group behaviors. There are more than 100 bacterial species that use a LuxI-LuxR

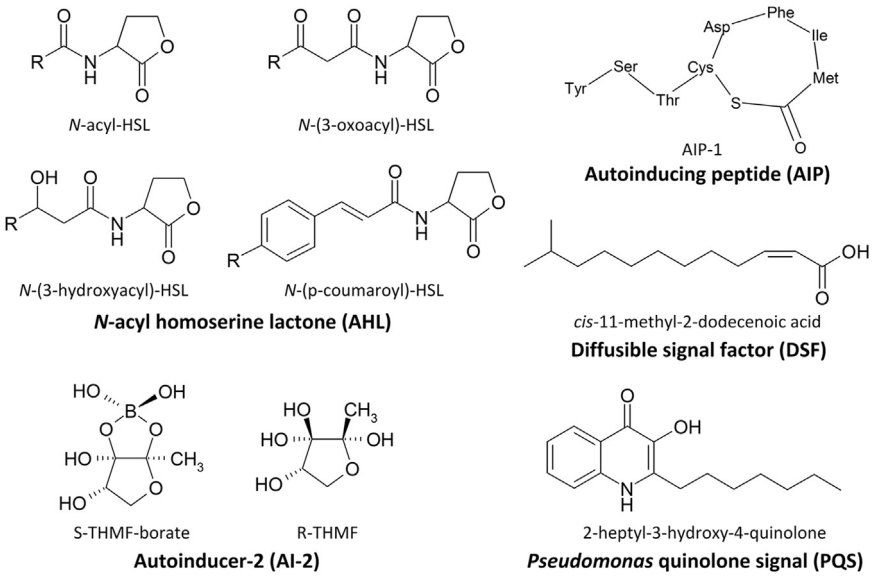

Fig. 3. Representative signal molecules involved in bacterial QS.

type circuit as their QS system [24,25]. Recent results show that LuxR solos, which are unpaired to cognate LuxI, are widespread in Proteobacteria. They play key roles in the communication within a complex community [26–29].

3.1.2. Peptide mediated QS in Gram-positive bacteria

Gram-positive bacteria also have their own QS system to regulate various gene expressions. In their system, a peptide signal precursor is translated into a precursor protein which is cleaved to produce the autoinducing peptide (AIP) (Fig. 3). In contrast to the process in Gram-negative bacteria, the peptide autoinducer does not freely diffuse out but is secreted via an ATP-binding cassette (ABC) transporter [12,30]. A membrane-bound histidine kinase and a response regulator in a two-component regulatory system are used for signal detection and specific target-gene expression. When the level of the peptide autoinducer concentration in the environment exceeds the threshold, histidine kinases sense the signals. Interaction between the histidine kinase and the peptide initiates a series of phosphorylations, which in turn phosphorylate the corresponding response regulator. Finally, the phosphorylated response regulator binds to the DNA and triggers expression of the QS-controlled target genes [12,31,32].

3.1.3. Autoinducers-2 (AI-2) QS Shared in Gram-negative and Gram-positive bacteria

AI-2 is a signaling molecule in the form of furanosyl borate diester, which has no similarity to other autoinducers (Fig. 3). The role of AI-2 in intra-species communication was first investigated through studies on bioluminescence regulation in *Vibrio harveyi* [33]. Interestingly, it was found that the *V. harveyi* QS circuit possesses characteristics similar to both Gram-negative and Gram-positive QS systems. These circuits produce and respond to AHLs like other Gram-negative bacteria, while they possess a two-component system for QS signal transduction like other Gram-positive bacteria [12,34]. *V. harveyi* use AI-2 as well as AHL (AI-1) to regulate the expression of the luciferase gene cassette luxCDABE. In *V. harveyi,* LuxS is the enzyme required for the biosynthesis of AI-2 molecules. LuxS cleaves S-ribosyl-L-homocysteine (SRH) into 4,5-dihydroxy-2,3-penanedionine (DPD) and homocysteine, followed by spontaneous conversion of DPD to AI-2 [35,36]. AI-2 and LuxS have been found in many Gram-negative and Gram-positive bacteria, and this suggested that AI-2 is involved in inter-species QS [36–39]. This concept has been extended by several observations showing that bacteria that are not able to produce AI-2 can still detect it. For example, *Pseudomonas aeruginosa*, although lacking the *luxS* gene, can recognize AI-2 synthesized by other bacteria within the oropharyngeal flora and respond with a change in its expression of virulence [40,41].

3.1.4. Other QS systems

To date, three additional QS systems have been reported in Gram-negative bacteria, including *Pseudomonas* quinolone signal (PQS), autoinducer 3 (AI-3), and diffusible signal factor (DSF). PQS regulates the expression of the elastase gene lasB together with two well-known AHL QS systems in *P. aeruginosa*: Las and Rhl systems [42]. This molecule is extremely hydrophobic, so *Pseudomonas* delivers PQS to other cells after packaging it in vesicles in aqueous environments [43]. AI-3 is known to participate in the regulation of virulence in *Escherichia coli* O157:H7. This hydrophobic signal has different chemical structure from the polar AI-2 signals, though AI-3 is associated with *luxS* homologs in *E. coli* O157:H7 [44]. DSF was discovered to be associated with a variety of phenotypes in *Xanthomonas campestris* including biofilm dispersal, toxin resistance, survival, and the production of some extracellular enzymes [45–49]. Since the chemical structure of this signaling molecule (*cis* − 11-methyl-2-dodecenoic acid) was discovered in 2004 [50], more than 13 different structures in the DSF family have been identified from various Gram-negative bacteria, including *cis* − 2-dodecenoic acid (*Burkholderia* DSF, BDSF) and *trans* − 2-decenoic acid (*Streptococcus* DSF, SDSF) [51].

3.2. Roles of QS in biofilm formation and dispersal

Biofilm has been defined as aggregates of microbial cells at an interface (usually between solid and liquid) encased in a self-generated matrix of extracellular polymeric substances (EPS) [52]. In general, biofilm development follows four stages: i) initial attachment of single cells to the surface, ii) production of EPS to provide firm adhesion to the surface and early development of the biofilm architecture, iii) maturation of the biofilm architecture, and iv) dispersion of single cells from the biofilm [53]. The mechanism of biofilm formation and dispersal is of great interest in a variety of water and wastewater treatment fields owing to its universal presence in the aquatic environment and its critical role in improving or deteriorating the performance of water and wastewater treatments.

Due to the higher cell density in biofilm than in planktonic phase, the cells in biofilm encounter elevated levels of secreted microbial by-products and secondary metabolites, including QS signal molecules.

From the idea that the concentration of bacteria in biofilm can easily exceed the threshold level to trigger QS systems, a number of studies have been carried out to identify the role of QS in biofilms [54]. Davies et al. [55] first reported he correlation between QS and biofilm in 1998, demonstrating that the lack of AHL synthase gene, *lasI,* in *P. aeruginosa* PAO1 resulted in flat, homogeneous biofilm formation that contrasted with the highly structured, heterogeneous biofilm formed by wild type PAO1. Subsequent research on *P. aeruginosa* biofilm revealed that the effect of QS on the biofilm architecture relies on the experimental conditions [56,57]. However, other apparent evidence of QS effect on biofilm maturation was reported for other bacterial species, including *Serratia liquefaciens* [58,59], *Burkholderia cepacia* H111 [60], *Aeromonas hydrophila* [61], and *Streptococcus mutans* [62]. In contrast to the maturation stage of biofilm development, a few studies showed that initial attachment of cells were hindered by QS systems. The accessory gene regulator (agr) QS system mediated by AIP in *Staphylococcus aureus* controls the production of surface adhesins including fibrinogen- and fibronectin-binding proteins [63]. The *agr* mutants attach to the surface better than the wild-type strains under certain conditions [64–66]. A *luxS* mutant of *Helicobacter pylori* was also reported to attach better than that of the wild-type strain [67].

What makes the study of biofilms more complicated is that dispersal of biofilms is also induced by QS in many bacterial species. AHL signaling is required to disperse *P. aeruginosa* and *Serratia marcescens* biofilms [68–70], and PQS induces biofilm dispersal in *P. aeruginosa* [69]. AIP was also discovered to induce dispersal of *S. aureus* biofilms [71,72], possibly mediated by upregulation of some protease expression [71]. A DSF family molecule, *cis*− 11-methyl-2-dodecenoic, was also reported to induce dispersal of *X. campestris* biofilm [46]. Another signal molecule belongs to DSF family, *cis*− 2-decenoic acid, causes biofilm dispersal in a variety of Gram-negative and -positive bacteria, including *P. aeruginosa, E. coli, Klebsiella pneumoniae, Proteus mirabilis, Streptococcus pyogenes, Bacillus subtilis, S. aureus* and the yeast *Candida albicans* [73]. It is obvious that QS plays critical roles in biofilm formation, but its role varies depending on the bacterial species and the stages of biofilm development. Therefore, careful observation and analysis are needed to determine how best to control complex community biofilms using QS-based strategy.

3.3. QS control (or QQ) strategy

In general, there are three strategies to inhibit a QS system: i) blockage of signal synthesis, ii) inactivation of signals, and iii) interference with the signal receptor. Inhibition of the best-known QS system (AHL-type) in Gram-negative bacteria, is depicted in Fig. 4.

3.3.1. Blockage of signal synthesis

The LuxI family proteins use SAM and acyl-ACP as building blocks

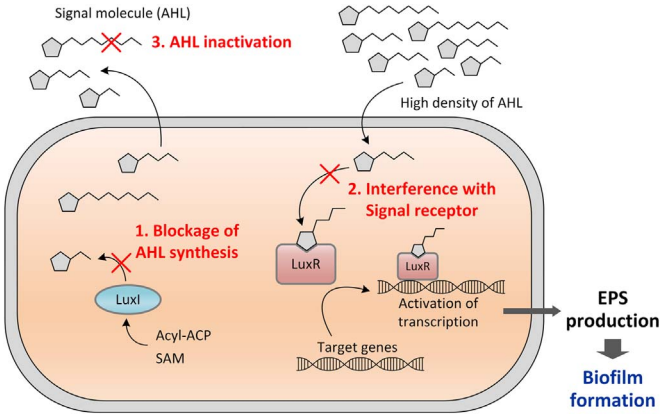

Fig. 4. Three strategies to control the AHL-type QS system of Gram-negative bacteria.

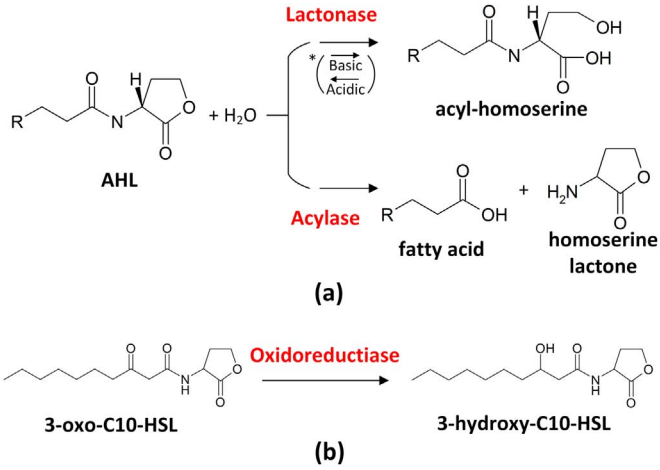

Fig. 5. Enzymatic disruption of AHL autoinducers by QQ enzymes. (a) QQ pathway by lactonase or acylase, (b) Modification of 3-oxo-C10-HSL by oxidoreductase. * Reversible reaction depending on pH.

for AHL autoinducer biosynthesis [12]. Parsek et al. [74] found that analogs of AHL building blocks such as L/D-S-adenosylhomocysteine, sinefungin, and butylryl-S-adenosylmethionine (butylryl-SAM) could inhibit AHL synthesis in vitro. Curcumin was reported to inhibit PAO1 virulence factors and biofilm formation with AHL production, but the exact inhibition mechanism was not revealed [75]. On the other hand, LuxS catalyzes the conversion of S-ribosyl homocysteine (SRH) into AI-2 and various analogs of SRH were reported to inhibit LuxS [76,77]. Brominated furanones were also shown to inhibit LuxS [78].

3.3.2. Inactivation of signal molecules

Inactivation of signal molecules is considered the most effective way to inhibit QS because this process can be carried out efficiently *ex vivo*, thus minimizing the chance of affecting other cellular functions. Among the known QS control strategies, enzymatic inactivation of signal molecules has been studied and applied the most [8,79,80]. As shown in Fig. 5, some bacteria produce 'lactonase' and 'acylase', which have enzymatic roles of hydrolyzing the cyclic ester or amide linkage of the AHL-type autoinducers and disrupting cell-to-cell communication [81–86]. In addition to these two major quorum quenching enzymes, oxidoreductase was found to modify and inactivate AHL (Fig. 5) [87].

A simpler way to inactivate the AHL signals is to increase the pH to > 7, which results in lactonolysis (ring opening of AHL; Fig. 5) [88]. A variety of higher organisms use this strategy to defend against the invasion of bacteria mediated by QS. When some plants are infected with *Erwinia carotovora*, which causes tissue maceration, the plants increase pH to attack the virulent microorganisms by inactivation of QS signal molecules and blocking the expression of QS controlled genes [89].

Meanwhile, Roy et al. [90] reported that *ex vivo* phosphorylation of AI-2 inhibits AI-2 signaling. A putative kinase LsrK is essential to switch on the *lsr* operon by intracellular phosphorylation of AI-2, but when this enzyme was added *ex vivo* to *E. coli,* the phospho-AI-2 was prevented from being transported into the cells, resulting in reduced QS response.

3.3.3. Interference with signal receptors

The QS inhibitors in this category usually have chemical structures similar to the QS signal molecules and thus are able to bind to a signal receptor, resulting in its degradation [91,92]. These QS signal-mimic compounds have been isolated from fungi, algae, and plants [93]. Penicillic acid and patulin, produced by *Penicillium* species, target the AHL receptors LasR and RhlR in *P. aeruginosa* [94]. A much-studied group of QS inhibitors, the halogenated furanone compounds, are produced by the red alga *Delisea pulchra* to avoid colonization of their surfaces by

bacteria [95]. These compounds are able to target the QS-controlled swarming phenotype of a variety of bacteria, including *S. liquefaciens* MG1, *V. fischeri, V. harveyi,* and *Serratia ficaria,* and its synthetic derivatives lacking in an acyl side chain inhibit the *las* and *rhl* QS systems in *P. aeruginosa* [59,96–100]. Vanillin, an extract from vanilla beans, interferes with receptors of AHLs, such as C4, 6, 8-HSL (homoserine lactone), and 3-oxo-C8-HSL, in *Aeromonas hydrophila* [101,102]. QS inhibitors can also be chemically synthesized by modifications in the side chain [103–106] or ring moiety [107–110] of AHLs, by increment in the length of the carbon chain of AI-2 molecules [111–113], and by truncation of AIP [114].

4. Detection and identification of AHL and AI-2 signal molecules in activated sludge

4.1. AHL signal molecules

The first trial of detecting signal molecules in activated sludge was carried out in 2005. Morgan-Sagastume et al. [115] tested eight different municipal activated sludge samples from Belgium by cross-feeding assay with two reporter strains *Agrobacterium tumefaciens* NTL4 and *Chromobacterium violaceum* CV026 to examine AHL production, and all of them showed positive results. The cross-feeding assay showed the existence of AHL producing microorganisms in the activated sludge, but was not direct evidence of AHL presence in the activated sludge. In a series of further studies, AHLs were extracted from sludge, supernatant, and biofilm to confirm the presence of AHLs in activated sludge processes.

Quantification of AHLs in activated sludge revealed that AHLs were present in sludge floc at higher concentrations than in the bulk liquid phase. The quantification has been carried out either by bioassay, using biosensor strains; or by chromatographic methods, such as high performance liquid chromatography (HPLC), ultra-performance liquid chromatography (UPLC), and gas chromatography (GC). Chong et al. [116] detected AHL molecules in activated sludge by co-culturing using a reporter strain, *Aeromonas* sp. (pBB-LuxR). The results suggested that AHLs were present at concentrations high enough to activate the LuxR transcriptional regulator in the sludge flocs, but not in the bulk liquid. Tan et al. [117], using semi-quantitative measurement of AHLs by thin layer chromatography (TLC)-bioassay, also showed that 3-oxo-C8-HSL, which was the dominant signal in a lab-scale sequencing batch reactor, was present in the sludge flocs at over 100-fold higher concentration than in the bulk liquid phase. They also used HPLC coupled with tandem mass spectrometry (MS/MS) to identify and quantify the AHLs in the sludge supernatant extracts. HPLC analysis by Feng et al. [118] showed that 3-oxo-C8-HSL was distributed more in sludge than in the bulk liquid phase of anaerobic granular sludge, whereas C4-HSL was detected equally in both phases. Meanwhile, Ding et al. [119] used UPLC-MS/MS to determine AHLs in an anaerobic granular sludge reactor.

Identification of AHLs was also carried out for lab-scale and full-scale MBRs. The first AHL identification by Yeon et al. [8] in a lab-scale MBR using TLC-bioassay, revealed the presence of C6-HSL and C8-HSL in the membrane biofilm. Song et al. [120] visualized the presence of AHLs in sludge floc and supernatant of an MBR using green fluorescence protein (GFP) tagged reporter strain. As observed in previous studies of activated sludge in bioreactors other than MBRs, most of the AHLs were present in sludge flocs, not in the bulk liquid. However, Oh et al. [121] identified three types of AHLs (C6-HSL, C8-HSL, and C10-HSL) in the supernatant of a lab-scale MBR, which implies that a significant amount of AHLs are present in bulk-phase activated sludge, as well as in membrane biofilms and sludge flocs, in MBRs. HPLC was also used for the identification of AHLs in several MBR studies. Kim et al. [122] identified C8-HSL and 3-oxo-C8-HSL in biofilm extracts of a lab-scale MBR by HPLC analysis. More recently, Lade et al. [123] detected a variety of AHLs (C4, 6, 8, 10, 12-HSL, and 3-oxo-C8, 12, 14-HSL) in the activated sludge of an MBR plant for wastewater treatment, using TLC-bioassay and HPLC. On the other hand, Bakaraki et al. [124] used GC-MS to detect and quantify C4-HSL from MBR sludge, for which the precision of quantification was enhanced by using deuterated anthracene as the internal standard.

4.2. AI-2 signal molecules

Several researchers detected the AI-2 signal molecule, 4,5-dihydroxy-2,3-pentandione (DPD); using the luminescence of the AI-2 reporter strain *V. harveyi* BB170 [118,125–132]. However, this bioassay has the disadvantages that the measured value is highly variable depending on the sample state, and that the analytical time is rather long (5–7 h). Song et al. [133] quantitatively determined the DPD concentration in a pure culture biological sample by chromatographic determination (HPLC) of the reaction derivatives of DPD with 2,3-diaminonaphthalene (DAN). Using DAN, Lee [125] also determined quantitatively the DPD concentration in MBR fed with wastewater.

5. QS and QQ microorganisms in activated sludge

As shown in Table 1, intensive studies have been carried out on the isolation of QS or QQ microorganisms from the conventional activated sludge processes. The microbial composition in an MBR was reported to be significantly different from that in a conventional activated sludge process due to its longer solid retention time (SRT) and lower food/microorganism ratio [134–137]. However, most members of the microbial communities are commonly present in both conventional and MBR treatment systems. Therefore, studies on the QS and QQ microorganisms in conventional activated sludge processes will better our understanding of QS and QQ in MBRs.

Valle et al. [138] isolated seven proteobacterial strains producing AHL-like compounds from an industrial wastewater treatment plant (Table 1). Chong et al. [116] isolated 52 distinct isolates, and 40 isolates (77%) among them showed AHL-like activity in at least one of five different bioassays (Table 1). Kim et al. [139] also isolated 13 AHL-producing strains and 8 AHL-degrading strains in a real wastewater treatment plant. A bacterial population analysis was carried out by Ochiai et al. [140] to reveal the populations of coexisting QS and QQ-utilizing strains in seven sewage treatment plants. Among 672 total isolates from activated sludge, 107 isolates showed AHL producing activity and 46 isolates showed AHL degrading activity. The analysis of 16 S rRNA gene sequences revealed that the predominant AHL-producing and degrading isolates belonged to members of the genus *Aeromonas* and *Acinetobacter*, respectively. Tan et al. [141] also confirmed the coexistence of QS and QQ strains in activated sludge, which showed that a large proportion of floccular sludge isolates (65%) were either AHL producers or quenchers. It is noteworthy that as many as 58.1% of the total (330) isolates showed QQ activity, whereas only 9.6% of the isolates produced AHLs. These results provide an explanation for the findings by Song et al. [120] that strong AHL degradation activity was detected in the sludge extracts from MBRs. They implied that QS in activated sludge reactors had been underestimated in previous studies due to this endogenous QQ effect.

A few studies have been carried out to isolate QS signal producing strains from MBRs. Lim et al. [142] isolated an *Enterobacter cancerogenus*-like strain from a lab-scale MBR, which was found to produce AHL-type QS signals. Lade et al. [123] reported that among the 200 bacterial isolates from an activated sludge in an MBR, 32 strains were identified to produce AHL signal molecules. Analysis of the 16 S rRNA gene sequence revealed that 12 AHL producing isolates belonged to members of genus *Aeromonas* and 10 to *Enterobacter*. Waheed et al. [143] isolated 9 strains producing AHLs from the activated sludge of a semi-pilot-scale MBR.

AHL degrading strains were also isolated from a real MBR plant as well as a lab-scale MBR by enrichment culture (Table 1). Six QQ strains

Table 1
QS signal producing strains and QQ strains isolated from wastewater treatment systems.

QS signal producing isolates	Signal type	Ref.	Quorum quenching isolates	QQ signal type	Ref.
Bacteria			**Bacteria**		
Acidovorax sp., *A. facilis*	C6-HSL	[138,141]	*Acidovorax delafieldii*	3-oxo-C12-HSL	[141]
Acinetobacter sp., *A. johnsonii*	AHL	[116]	*Acinetobacter* sp., *A. bereziniae, A. junii*	C6-HSL, 3-oxo-C12-HSL, long chain AHL	[139–141,201,202]
Aeromonadaceae sp.	AHL	[116]	*Afipia* sp.	3-oxo-C6-HSL	[139]
Aeromonas sp., *A. allosaccharophila, A. hydrophila, A. jandaei, A. media, A. piscicola, A. popoffii, A. punctata, A. sobria, A. veronii*	C4, 6-HSL, 3-oxo-C6-HSL, Short and long chain AHL	[116,123,138–140]	*Bacillus firmus, B. megaterium*	C10-HSL, 3-oxo-C12-HSL	[140,141]
			Bosea thiooxidans, B. vestrisii	3-oxo-C6,8,12-HSL	[141]
			Brevibacterium aureum	3-oxo-C12-HSL	[141]
Aeromonas sp.	AI-2	[132]	*Brevundimonas diminuta, B. olei*	3-oxo-C6,8,12-HSL	[141]
Agrobacterium sp.	3-oxo-C6-HSL	[138]	*Bulkholderia multivorans*	C6-HSL	[203]
Aquaspirillum sp.	C6-HSL	[138]	*Chryseobacterium indologenes*	C10-HSL, 3-oxo-C12-HSL	[140,141]
Bulkholderia multivorans	AHL	[203]	*Cloacibacterium normanense*	3-oxo-C12-HSL	[141]
Chitinimonas taiwanensis	AHL	[116]	*Comamonas* sp.	C10-HSL	[140]
Citrobacter sp., *C. farmer, C. freundii, C. murliniae*	Short and long chain AHL	[116,123,140]	*Diaphorobacter nitroreducens*	3-oxo-C12-HSL	[141]
			Dyadobacter fermentans	3-oxo-C12-HSL	[141]
Comamonas sp.	AI-2	[126]	*Delftia tsuruhatensis*	3-oxo-C8,12-HSL	[141]
Delftia sp.	Short chain AHL	[143]	*Dokdonella* sp.	3-oxo-C12-HSL	[141]
Enterobacter sp.	AI-2	[132]	*Enterobacter ludwigii*	3-oxo-C6-HSL	[121]
Enterobacter sp., *E. cancerogenus, E. ludwiggi*	Short and long chain AHL	[123,139,140,142]	*Flavobacterium* sp., *F. banpakuense*	3-oxo-C12-HSL	[141]
			Frateuria sp.	3-oxo-C12-HSL	[141]
Enterococcus durans, E. hirae	AHL	[139]	*Klebsiella* sp.	C10-HSL	[140]
Haemophilus piscium	AHL	[139]	*Lysobacter brunescens*	3-oxo-C12-HSL	[141]
Klebsiella sp., *K. granulomatis, K. oxytoca, K. variicola*	Short and long chain AHL	[116,123,139,143]	*Mesorhizobium ciceri*	3-oxo-C12-HSL	[141]
			Microbacterium sp., *M. flavum, M. hydrocarbonoxydans, M. laevaniformans, M. oxydans*	C6-HSL, 3-oxo-C6,8,12-HSL	[139,141]
Leclercia adecarboxylata	Long chain AHL	[123]			
Lelliottia amnigene	AHL	[139]	*Micrococcus* sp., *M. luteus*	C6-HSL	[121,139]
Lysobacter brunescens	C7-HSL, 3-oxo-C6, 8, 10-HSL	[117,141]	*Novosphingobium* sp.	3-oxo-C6,8,12-HSL	[141]
Malikia spinosa	Long chain AHL	[116]	*Ochrobactrum anthropi*	3-oxo-C6,8,12-HSL	[141]
Mesorhizobium ciceri	C8-HSL	[204]	*Paenibacillus turicensis*	C6-HSL	[121]
Microbacterium sp., *M. paraoxydans*	Long chain AHL	[116]	*Pedobacter composti*	3-oxo-C12-HSL	[141]
Neisseria sp.	AHL	[116]	*Pimelobacter simplex*	3-oxo-C12-HSL	[141]
Paenibacillus sp.	Long chain AHL	[116]	*Pseudomonas* sp., *P. extremorientalis, P. koreensis, P. monteilii, P. otitidis, P. veronii*	C6,10-HSL, 3-oxo-C12-HSL	[139–141,203]
Pantoea agglomerans, P. stewartii	AHL	[116,141]			
Propioniferax-like	AI-2	[126]	*Pseudoxanthomonas* sp., *P. japonensis*	C6,8,10,12-HSL, 3-oxo-C12-HSL	[141]
Pseudomonas sp., *P. aeruginosa, P. fluorescens, P. japonica, P. kilonensis, P. koreensis, P. oryzihabitans*	C4, 6-HSL, long chain AHL	[116,123,138,140,143,203,205]	*Rheinheimera chironomi*	3-oxo-C12-HSL	[141]
			Rhizobium borbori	3-oxo-C6,8,12-HSL	[141]
			Rhodobacter sp.	3-oxo-C12-HSL	[141]
Psychrobacter sp.	AHL	[143]	*Rhodococcus* sp., *R. erythropolis, R. qingshengii*	C6,8,10,12-HSL, 3-oxo-C6,8,10,12-HSL	[121,139,141,184,203]
Raoultella ornithinolytica, R. planticola, R. terrigena	Short and long chain AHL	[116,123,139]	*Roseomonas terrae*	3-oxo-C6, 8, 12-HSL	[141]
Rhizobium sp.	AHL	[141]	*Sphingobacterium mizutaii, S. multivorum*	3-oxo-C12-HSL	[141]
Rhodobacter maris	AHL	[141]	*Sphingomonas* sp.	3-oxo-C12-HSL	[141]
Salmonella sp.	C6-HSL, 3-oxo-C6-HSL	[138]	*Staphylococcus* sp.	C10-HSL, 3-oxo-C6-HSL	[139,140]
Shigella sp.	Long chain AHL	[116]	*Stenotrophomonas* sp., *S. maltophilia, S. rhizophila*	C6,8,10-HSL, 3-oxo-C12-HSL	[140,141,203]
Shinella fusca	AHL	[141]	*Streptococcus* sp.	3-oxo-C6-HSL	[139]
Sphingomonas sp.	AHL	[141]	*Tsukamurella tyrosinosolvens*	3-oxo-C8, 12-HSL	[141]
Staphylococcus aureus	Short chain AHL	[143]	*Variovorax paradoxus*	3-oxo-C8, 12-HSL	[141]
Stenotrophomonas sp.	3-oxo-C6-HSL, 3-OH-C12-HSL	[117,138,141]	**Eukaria (Fungi)**		
Thermomonas fusca	C8-HSL	[204]	*Candida sojae, C. tropicalis*	3-oxo-C12-HSL	[141]
			Cryptococcus curvatus	3-oxo-C12-HSL	[141]
Archaea			*Meyerozyma guilliermondii*	3-oxo-C12-HSL	[141]
Methanosaeta harundinacea	*N*-carboxyl-C10, 12, 14-HSL	[206]	*Trichosporon montevideense*	3-oxo-C12-HSL	[141]

were isolated from a real MBR plant by Oh et al. [119], while six QQ strains were isolated from a lab-scale MBR by Cheong et al. [142], respectively, in South Korea.

As mentioned above, activated sludge for wastewater treatment includes a wide variety of microorganisms including Gram-negative and Gram-positive bacteria, fungi, algae, protozoa, and metazoans. This means that there are also microorganisms that likely produce AI-2, a QS signal molecule commonly used by both Gram-negative and Gram-positive bacteria. Lee et al. [132] reported that an *Aeromonas australiensis*-like strain and *Enterobacter soli*-like strain, which produced AI-2 signaling molecule, were isolated from activated sludge. They also isolated an AI-2 inactivating strain QQ that belonged to genus *Acinetobacter,* from a real MBR plant in South Korea [125]. That *Acinetobacter* sp. inactivated AI-2 signals by releasing an active compound from its cells, which was confirmed to be hydrophilic and with a molecular weight of < 400 Da.

Recently, Jo et al. [144] analyzed microbial communities on the biofilms and activated sludge from 10 full-scale MBR plants using high-throughput sequencing (an Illumina MiSeq platform) and revealed that 11.6% and 12.1% of bacteria in biofilm and activated sludge, respectively, possessed complete QS systems of either AHL, AIP, or AI-2 types. On the other hand, the operating conditions of an MBR, such as SRT, can affect the microbial community regarding QS and QQ [145]. As SRT increased, the abundance of QQ bacteria in MBR increased, while that of QS bacteria decreased. Consequently, the AHL degradation activity of the activated sludge increased as SRT increased, whereas the concentration of AHL decreased.

6. QQ for the inhibition of biofouling in MBR

Biofilms play beneficial roles in a variety of wastewater treatment processes involving such as trickling filters, moving bed biofilm reactors, membrane biofilm reactor (MBfR), and granular sludge [25]. In contrast, biofilms are unwanted in membrane filtration processes for water treatment including such as MBRs, ultrafiltration (UF), nanofiltration (NF), and reverse osmosis (RO), because they definitely decrease the membrane permeate flux. Removal of biofilms by treatment with biocides or antibiotics may not be efficient because microorganisms within biofilms can tolerate much higher concentrations of biocides and antibiotics than their planktonic counterparts can [146,147]. Furthermore, chemical based anti-microbial treatments can cause the emergence of resistance through the mutational strategies of microorganisms [148]. Calderon et al. [149] observed that some microorganisms were resistant to sodium hypochlorite, the most commonly used chemical in membrane cleaning, and consequently, were still not removed from the membrane even after cleaning.

In contrast to antimicrobials, inhibition of microbial group behaviors such as biofilm formation or virulence by quorum quenchers could minimize the chance of generating microbial resistance because it does not affect their growth [150,151]. Since the correlation between QS signal and membrane biofouling was demonstrated in 2009 by Yeon et al. [8], various QQ strategies, including enzymatic QQ, bacterial QQ, and fungal QQ, to name a few, have been studied in membrane filtration processes as promising tools for biofouling control.

6.1. Enzymatic QQ for interrupting AHL-type QS

Porcine kidney acylase I, can deacylate the AHL signal molecule [152]. Yeon et al. [8] demonstrated that addition of porcine kidney acylase I (EC 3.5.1.14) reduced membrane biofouling in MBR without sacrificing biodegradation of organics. However, due to the short catalytic lifetime of the free enzyme, the anti-biofouling effect disappeared after one day of operation of the batch MBR [14]. In order to overcome the limitations of free acylase injection into an MBR, the researchers prepared a magnetic enzyme carrier (MEC) by immobilizing porcine kidney acylase I on magnetic particles. With addition of the MEC in a continuous MBR, they observed delay of the TMP increase reflecting slower biofilm formation on the membrane surface. This was attributed to the reduction of EPS production.

The mechanisms behind the anti-biofouling effect of the QQ enzyme (acylase I) in MBRs were further studied [153,154]. Kim et al. [153] investigated the microbial population dynamics in the mixed community of MBR with MEC using pyrosequencing. The pyrosequencing results showed that the proportion of AHL-producing bacteria (such as *Enterobacter, Pseudomonas*, and *Acinetobacter*) was reduced in the entire microbial community of mature biofilm, compared to that in the control MBR. Proteomic analysis using pure culture biofilm of the *E. cancerogenus* strain ATCC 35316, was also carried out in the study. The results from use of enzymatic QQ demonstrated possible down-regulation of protein expression related to microbial attachment to surfaces (outer membrane protein and flagellin), and the agglomeration of microorganisms (ATP synthase beta subunit). Jiang et al. [154] immobilized acylase I into sodium alginate beads for enzymatic QQ in MBRs. After its addition, better sludge settle-ability, smaller sludge-particle size, less soluble microbial products (SMP) and EPS production, lower apparent viscosity, and higher zeta potential of the mixed liquor were observed in the QQ-MBR. QQ also affected the characteristics, behavior and function of SMP and EPS, which reduced biofilm formation and enhanced membrane filterability. Interestingly, the inhibition of biofouling by QQ was found to be reversible; that is, the subsequent membrane performance returned to the original state when QQ dosing ceased.

Although it was found recently that bacteria can also evolve resistance to some QQ compounds [155–158], there has been no report yet that bacteria have successfully carried out this strategy to resist enzymatic QQ. This implies that enzymatic QQ, and bacterial QQ that utilizes QQ enzymes produced by bacteria, still remain promising for use in the inhibition of biofilm formation in membrane processes.

6.2. Bacterial QQ for interrupting AHL-type QS

Although enzymatic QQ has brought a new paradigm to membrane biofouling in MBRs, it has limitations for practical application because of the cost and stability of the QQ enzymes. As an alternative, QQ enzymes were replaced by bacteria that can produce a QQ enzyme (e.g., AHL-lactonase) [121]. Even though the activity of whole cell catalysts is not as high as that of isolated enzymes, whole cell application (i.e., live bacterial QQ) is preferred for the following reasons: i) it can be more readily and less expensively prepared, ii) it is more stable for long-term application than free enzyme because QQ enzymes inside cells are protected from the external environment, and iii) bacterial cells are easier to handle than enzymes are [159]. In addition, QQ bacteria can survive without an external supply of nutrition because wastewater has the resources needed (nutrients, dissolved oxygen, etc.). Several strategies were applied to sustain enough QQ bacteria or to protect them from other microorganisms in the activated sludge bioreactor (e.g., bioaugmentation and biostimulation).

6.2.1. Biostimulation

Biostimulation is a process where rate limiting nutrients or electron acceptors are added to the environment to stimulate indigenous bacteria capable of bioremediation. Instead of immobilizing QQ bacteria in any kind of media, biostimulation was used to augment the population of QQ bacteria in the MBR [160]. Gamma-caprolactone (GCL), which is structurally similar to AHL, was used to stimulate QQ (AHL-degrading) bacteria specifically. When the GCL consortia were injected into MBR and GCL was continuously dosed, the secretion of EPS decreased and biofouling was effectively controlled. Quantitative real-time PCR (qPCR) revealed that the AHL-lactonase producing gene *qsdA* was augmented by the biostimulation, which resulted in the degradation of C6-HSL and C8-HSL in the MBR.

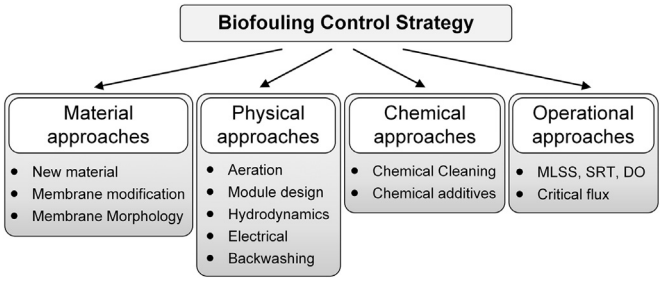

Fig. 6. Biofouling control strategies in MBRs over the last 30 years.

6.2.2. Bioaugmentation

Up to now, *Rhodococcus* sp. BH4 has mostly been used as a QQ bacterium in the operation of QQ-MBRs, although it has been limited to R & D. Actually, BH4 was isolated from a real MBR plant [121], in which its concentration was very low. Jo [161] analyzed (using MiSeq sequencing) the abundance of *Rhodococcus* in 10 real MBR plants for wastewater treatment and found that its average relative proportion was merely 0.012%. This implies that members of genus *Rhodococcus* do not compete well in MBRs, and thus the viability of BH4 is very low in MBRs. Kwon [162] substantially augmented *Rhodococcus* sp. BH4 to achieve 50 mg/L in an MBR and continually added BH4 to make up for its loss from sludge withdrawal to ensure sufficient BH4 would be present in the MBR. Despite the high concentration of QQ bacteria (BH4), membrane biofouling was not improved or became worse.

6.3. Interrupting AI-2 type QS

There have been several studies on biofouling control in MBRs by interrupting AI-2 type QS communications. While the studies on AHL-type QQ in MBRs have been focused on the degradation of signal molecules, the AI-2 QQ experiments in MBRs were conducted by inhibiting the production of signal molecules. Xu and Liu [127] reported that disrupting the energy metabolism of microorganisms inhibited membrane biofouling by suppression of AI-2 production. In a static attachment assay, 2,4-dinitrophenol (DNP), a typical uncoupler, inhibited membrane biofouling and increased biofilm dispersal from a nylon membrane. They demonstrated that suppressed ATP synthesis by DNP led to lowered AI-2 production, and further confirmed the correlation between the reduced AI-2 production and the reduced fouling resistance of nylon membranes using the standard dead-end microfiltration tests.

D-tyrosine, a typical d-amino acid, was also found to inhibit production of AI-2, EPS, and eDNA without inhibitory effect on microbial growth, substrate utilization, and synthesis of cellular ATP [128,129]. Reduction of AI-2 production in activated sludge microorganisms resulted in the reduction of microbial attachment to nylon membrane surfaces, as well as the enhancement of biofilm detachment. *Piper betle* extract (PBE), which is known as an anti-bacterial that controls the growth of many bacteria [163,164], was tested as a QQ compound [130,165] in lab-scale MBRs. When PBE was added to a submerged MBR treating synthetic dye wastewater, the production of AI-2 (as well as AHL) was reduced in the membrane biofilm, resulting in decreased EPS production and biofouling.

Most recently (2016), fungal QQ was proposed to inhibit AI-2 QS in MBR [132]. *Candida albicans*, a farnesol producing fungus, was entrapped in polymer beads and the beads were placed in the MBR to mitigate biofouling. Real-time qPCR revealed that farnesol secreted from *C. albicans* repressed the bacterial synthesis of AI-2 signals and thus suppressed their AI-2 QS, which resulted in the mitigation of biofouling in MBRs. Waheed et al. [131] entrapped an AI-2 degrading *E. coli* strain (*ΔlsrRΔluxS*) that had been engineered to degrade AI-2 signals previously [166], and the beads were placed in a lab-scale MBR with beads entrapping AHL degrading isolates. The QQ consortium reduced both AHL and AI-2 signals in the MBR and retarded membrane biofouling.

In short summary, bacterial QQ has advantages over enzymatic QQ in that it has higher QQ stability and low cost of preparation. However, despite the drawbacks of enzymatic QQ, it still has potential for preparation of anti-biofouling membrane [167,168]. On the other hand, a fungus was found to possess AI-2 QQ activity. Thus, it is worth opening all possibilities to apply enzymatic, bacterial, and fungal QQ to MBRs for biofouling control.

7. Comparison of the inhibition of biofouling between conventional- and QQ-MBRs

The mechanism of membrane biofouling in an MBR is slightly different from the biofilm development process (described in Section 3.2.). It is because the convective flow of mixed liquor caused by the permeate suction facilitates the movement of bacterial cells towards membrane surface. The main mechanisms responsible for membrane biofouling are: i) deposition of microbial cells and microbial products [169,170], ii) multiplication of microbial cells on the membrane surface, and iii) encasing cells in self-produced EPS matrix [171,172].

However, the strategy elaborated to address biofouling in conventional-MBRs is a complete contrast to that in QQ-MBRs. In conventional-MBRs, most approaches to solving biofouling (biofilm formation) are a sort of post management, i.e., dealing with the biofouling after it takes place. Whereas, in QQ-MBRs, the approach to biofouling control is a sort of preventive action, i.e., inhibiting biofouling before it is generated.

7.1. Biofouling inhibition in conventional-MBRs

Over the last 30 years, extensive studies have been carried out to solve this membrane biofouling issue in conventional-MBRs. As shown in Fig. 6, the biofouling control strategies are classified into four categories: i) material, ii) physical, iii) chemical, and iv) operational approaches. They include preparation of new membrane materials, modification of membrane surface and morphology, coarse bubble aeration, backwashing, addition of chemicals (powdered activated carbon, polymeric substances, etc.), adjustment of operational parameters (mixed liquor suspended solids [MLSS], SRT, critical flux, etc.) [6,7]. However, most of these approaches have some limitations because membrane biofouling, i.e., biofilm formation on the membrane surface, is a sort of natural phenomenon.

7.2. Biofouling inhibition in QQ-MBRs

It is well known that EPS is a key foulant and also plays a great role in biofilm formation in MBRs [5]. A QS system has been known to regulate the synthesis of EPS in various bacterial species [173–175]. Accordingly, most researchers involved in the study of QQ-MBRs anticipated that QQ would be closely associated with EPS reduction in QQ-MBRs. The reduction of EPS results in the weaker architecture of biofilm, leading to easier detachment of bacterial cells by shear stress as shown in Fig. 7.

In fact, reductions of EPS content in mixed liquors as well as in biofilm on membrane surfaces were observed in lab-scale or pilot-scale QQ-MBRs fed with synthetic or real wastewater [8,14,80,122,132,153,154,176–183]. In particular, Yeon et al. [8] reported interesting results from a batch type of MBR: the addition of acylase reduced the EPS content per unit mass of biofilm, whereas the addition of signal molecules (C8-HSL) increased it. These results showed a correlation between QS and EPS production, which led to a postulation that QQ could be used to control membrane biofouling by down-regulating the EPS production. Maqbool et al. [178] confirmed that strain BH4 entrapping QQ-bead had the anti-biofouling effect via reduced EPS production in a semi-pilot-scale MBR with effective

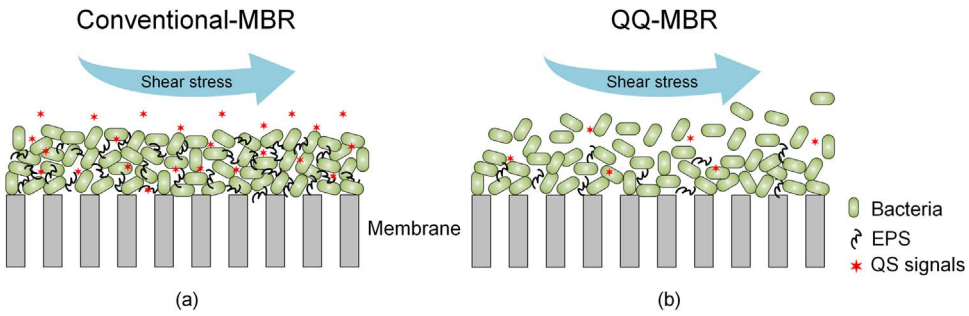

Fig. 7. Biofilm architecture in (a) Conventional-MBRs and in (b) QQ-MBRs.

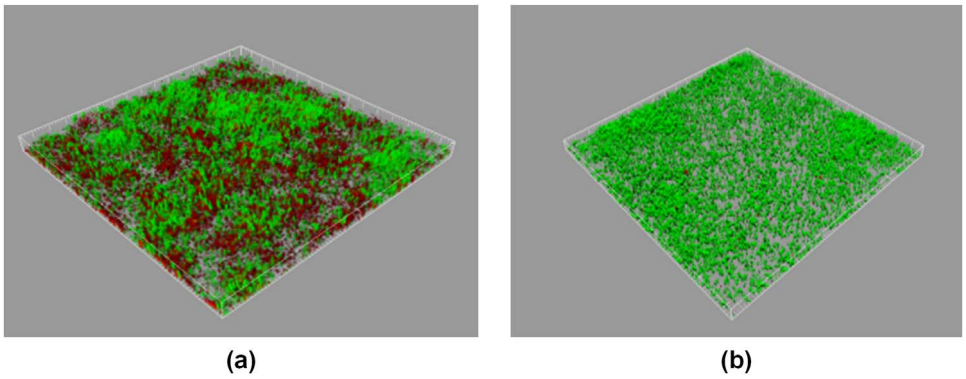

Fig. 8. Comparison of biofilm between (a) Raw NF and (b) Acylase-coated NF membranes during crossflow NF operated with microbial suspension of GFP-tagged *P. aeruginosa* PAO1. Green represents GFP and red represents EPS (polysaccharide).

volume of 35 L. The connection between QQ and EPS was clearly demonstrated by Kim et al. [80]. They immobilized QQ enzyme (porcine kidney acylase I) onto the surface of a commercial NF membrane and then visualized the spatial distribution of cells and polysaccharides on both the raw NF and acylase-immobilized NF membranes in a crossflow NF of microbial suspension with GFP-tagged *P. aeruginosa* PAO1. They observed much less EPS (polysaccharides) on the latter membrane, compared with that on the control NF membrane (Fig. 8).

The indigenous QQ strain, *Rhodococcus* sp. BH4, was investigated by Oh et al. [184] for better understanding of its biofouling mitigation by QQ mechanism, i.e., decomposition of signal molecules. They revealed that strain BH4 degraded AHL intracellularly by hydrolyzing its lactone ring through the AHL degradation testing followed by liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS) analysis. The 16 S rRNA gene sequence analysis exhibited 98.6% sequence identity of the AHL-lactonase gene in strain BH4 to *qsdA* in *R. erythropolis* W2. Moreover, strain BH4 degraded a broad range of AHLs, each with a different degradation rate.

However, the merits of QQ-MBRs do not necessarily exclude or replace entirely, conventional anti-biofouling techniques such as backflushing, coarse bubble aeration, and addition of chemicals showed in Fig. 6. Rather, combining QQ techniques with the conventional ones would maximize the efficiency of QQ techniques. Weerasekara et al. [176] investigated the combination of a QQ-vessel and physical cleaning (i.e., relaxation and air back-pulse) and demonstrated a more synergistic effect of QQ with relaxation than QQ with air back-pulse. They also reported that a combination of bacterial QQ and chemically enhanced backwashing with chlorine showed synergistic effect on the mitigation of biofouling [185]. Chlorine dosing reduced the chemically reversible filtration resistance, whereas QQ contributed to a reduction in the physically reversible resistance by mitigating biomass attachment.

8. QQ effect on the generic system of MBR

8.1. QQ effect on the generic system performance of MBR

It is worth checking the QQ effect on the generic system performance of MBR. To date, no adverse effect on the generic system performance has been reported in QQ-MBRs, indicating that only EPS production is inhibited, without sacrificing bacterial growth and effluent quality. Lee et al. [179] operated one-stage (aerobic membrane tank) and three-stage (anoxic-aerobic-membrane tanks) MBRs with or without the input of QQ bacteria. When monitoring effluent quality in terms of chemical oxygen demand (COD), total nitrogen (TN), ammonia nitrogen (NH_4-N), and nitrate nitrogen (NO_3-N), they observed no significant difference between conventional- and QQ-MBRs in both one-stage and three-stage versions. Other studies also reported no significant difference in effluent quality between conventional- and QQ-MBRs [14,121,122,153,154,176–178,186–189]. This is one remarkable advantage of QQ-MBRs.

8.2. QQ effect on the microbial community of MBR

Jo et al. [190] studied the effect of QQ bacteria on the microbial community of biofilm in MBRs. They operated two lab-scale anoxic/oxic (A/O) MBRs with or without QQ bacteria. Analysis of the microbial community on the biofilm during four consecutive cycles revealed that QQ gradually increased the diversity and evenness of the microbial community in biofilm by reducing the relative abundance of the QS bacteria. The biofilm in QQ-MBRs developed more slowly than in conventional-MBRs, and the change rate of the bacterial composition was also slower in the QQ-MBR. Proteobacteria and *Thiothrix* sp. were found to be the dominant phylum and bacterial genus in the biofilm, respectively, and both of them showed lower abundance in QQ-MBRs than in conventional-MBRs.

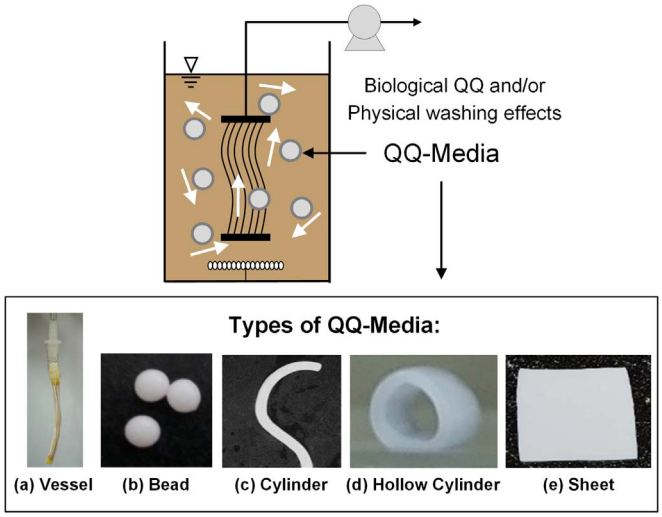

Fig. 9. Evolution of QQ-media from QQ-vessel to QQ-sheet.

9. Development and evolution of QQ-media for the application to MBRs

Both biostimulation and bioaugmentation as described in Section 6.2, are less desirable as QQ strategies in MBRs for wastewater treatment because they have trouble supplying biostimulants or QQ bacteria continuously, leading to higher operating cost. This is why immobilizing devices satisfying the following requirements should be developed so that QQ bacteria may interfere with QS continuously, effectively, and economically:

i) Good protection of QQ bacteria against other microorganisms in MBRs,
ii) Microporous structure for good mass transfer of dissolved oxygen, nutrients, substrates, etc., to promote the growth of QQ bacteria,
iii) Physical, chemical, and biological stability in harsh environments,
iv) Easy access to the surface of the filtration membrane regardless of its module type.

To fulfill the above requisites, a variety of QQ-media containing QQ bacteria were developed (Fig. 9) [191].

9.1. QQ-vessel

Oh et al. [121] encapsulated inside the lumen of microporous hollow fiber membrane, either recombinant *E. coli* or *Rhodococcus* sp. BH4 producing AHL lactonases (Fig. 9a). This QQ-medium, called a 'QQ-vessel' showed anti-biofouling effect that was maintained steadily over 100 days of MBR operation. Jahangir et al. [192] reported that the anti-biofouling QQ effect of the QQ-vessel containing BH4 was more noticeable when it was located closer to the filtration membrane (i.e., in a membrane tank rather than in a bioreactor in an external submerged MBR, in which the membrane tank is separated from the bioreactor). They also concluded that greater biofouling inhibition could be achieved with a higher recirculation rate of MLSS because this could facilitate the transport of AHLs from the biofilm into the bulk liquid, and then to the QQ-vessel.

On the other hand, extremely high density of QQ bacteria inside the QQ-vessel was pointed out as a cause of activity loss in a long-term operation due to the low food to microorganism (F/M) ratio inside the QQ-vessel [177]. A new design of QQ-vessel was suggested to solve this problem by directly supplying the MBR feed into the lumen of the QQ-vessel. The inner flow mode enabled the QQ-vessel to maintain greater bacterial QQ activity and this showed higher anti-biofouling effect than did the normal mode. A rotating QQ-vessel was devised to overcome the low F/M ratio issue of the fixed QQ-vessel [180,187]. The rotating microbial carrier frame (RMCF) was composed of a polycarbonate frame and four cubbyholes, which were covered with flat sheets of polyvinylidene fluoride (PVDF) microfiltration membrane. The RMCF showed higher anti-biofouling effect in an MBR than in the normal QQ-vessel.

9.2. QQ-bead

An alternative method of microbial QQ was devised by entrapping QQ bacteria (QQ strain BH4) within a porous microstructure of alginate or alginate/polyvinylalcohol beads (Fig. 9b) [122,132,179]. Unlike the QQ-vessel, which confines QQ bacteria in a specific place and results in low efficiency of AHL degradation, QQ-beads can circulate freely with other microbial flocs in the bulk liquid as well as contact the biofilm on the filtration membrane surface to capture AHLs in the biofilm more efficiently. Kim et al. [122] reported that the combined effect of biological QQ and physical washing (i.e., sloughing of biofilm by collision between beads and the membrane surface) provided 10 times longer to reach the same TMP compared to an MBR without beads. A novel QQ bacterium, *Bacillus methylotrophicus* sp. WY, which was isolated from a wastewater treatment plant in Beijing (China) was immobilized in alginate beads and increased membrane flux by 3–4 times in a dead-end membrane microfiltration system [193]. The strain WY showed higher degradation efficiency than *Rhodococcus* sp. BH4 and *Pseudomonas* sp. 1A1 for a wide range of AHLs. Xiao et al. [194] combined QQ strategy with powdered activated carbon (PAC) based removal of pharmaceutically active compounds (PhACs). They immobilized a QQ strain in PAC-alginate beads, which provided with both anti-biofouling effect and removal of PhACs in a lab-scale MBR.

9.3. QQ-cylinder and QQ-hollow cylinder

On the other hand, the visualization of AHLs diffused into a microbial-bead using a GFP-tagged reporter strain (*E. coli* JB525) revealed that the QQ bacteria located at the periphery of a microbial-bead carried out the degradation of AHLs mostly among the QQ bacteria in the entire bead [195]. Therefore, new designs of QQ bacteria entrapping medium, a QQ-cylinder [196] and QQ hollow cylinder (QQ-HC) [195], were proposed to maximize the surface area of the cell entrapping medium (Fig. 9c and d). QQ-HC showed higher QQ activity than did the QQ-beads, and its activity was further increased when the surface area of the QQ-HC was increased by fabricating thinner cylinder. Moreover, the geometry of the cylinder enabled the medium to collide with biofilm over a wider contact area than did the spherical shape of the QQ-beads. This led to higher efficiency of physical washing.

9.4. QQ-sheet

QQ-beads can be used without any trouble in MBRs with a flat-sheet membrane module. However, they can hardly penetrate the dense structure of hollow fiber (HF) bundles. Nahm et al. [197] developed a QQ bacteria entrapping sheet (QQ-sheet) as a new shape of QQ-media that is suitable for MBRs with HF modules (Fig. 9e). QQ-sheets showed 2.5-fold greater biological QQ activity than did QQ-beads due to their greater total surface area at a fixed volume of QQ-media.

10. Energy and cost saving of QQ applications in MBRs

Membrane fouling in MBRs is closely associated with energy consumption. Higher fouling tendency in MBRs requires more frequent and harsh membrane cleaning and a higher aeration rate, which leads to increased energy consumption and operating cost. In several studies, the reduction of energy consumption from using QQ techniques in MBRs was evaluated. Jahangir et al. [192] showed that application of QQ in an MBR could achieve reduction of aeration intensity for

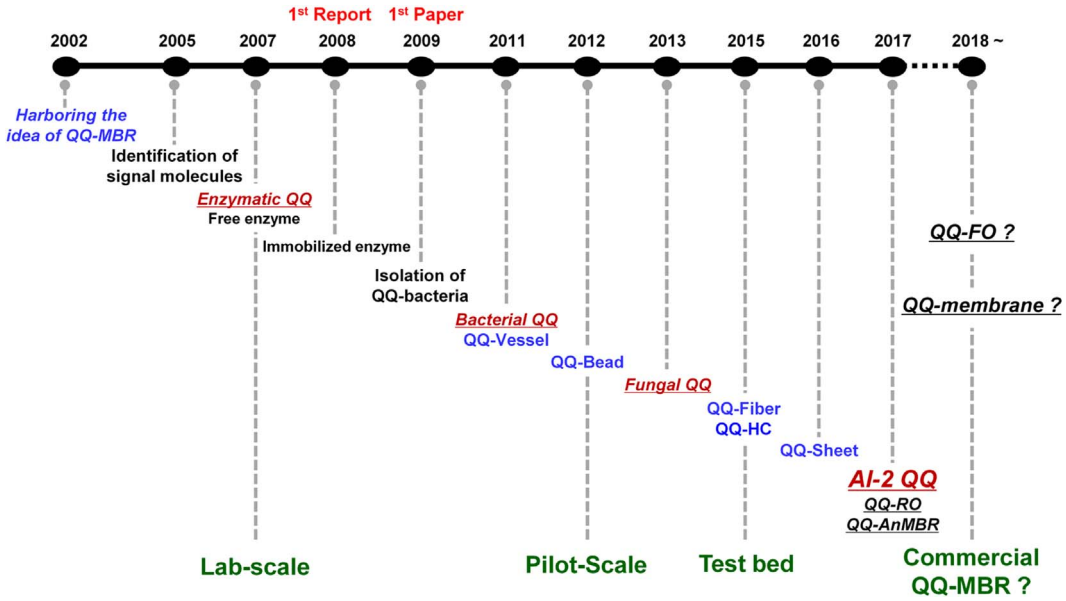

Fig. 10. Evolution of QQ-MBRs.

membrane scouring, which is the dominant factor for energy consumption in MBR operation. An energy saving equivalent to the reduction of the aeration rate by 0.5–1.0 L/min was achieved in the operation of a lab-scale MBR through the use of a QQ-vessel. Weerasekara et al. [176] also operated a lab-scale MBR with a QQ-vessel under different aeration intensity. They evaluated the specific filtration energy and specific aeration energy using TMP profiles and applied aeration intensity, respectively. The evaluation proved that either specific filtration energy or specific aeration energy could be reduced significantly by use of QQ. Köse-Mutlu et al. [187] compared the estimated cost savings by the use of QQ-beads, QQ-vessel, and RMCF. Both the QQ-beads and RMCF showed savings in operating cost of more than 10% over use of the QQ-vessel due to their physical washing effect. Taking into account the cost of the QQ-media, RMCF was the most feasible approach.

Similarly the evaluation of energy consumption was conducted in a pilot-scale MBR with QQ-beads [179]. The energy consumption for filtration and air scrubbing in the control MBR was 0.46 kWh/m^3, whereas only 0.20 kWh/m^3 was consumed in the QQ-MBR. The largest pilot-scale QQ-MBR (10 m^3/day) among those reported so far was installed in 2015 at a municipal wastewater treatment plant located in South Korea [198]. It had been run more than two years in parallel with a conventional MBR under the same operating conditions except that the QQ-beads (0.5% v/v) was put into the QQ-MBR. For both MBRs, the membrane module was flat-sheet, the aeration rate was 9 L/m^2·min, and the flux was 25.0 L/m^2·hr. Based on the results from the operation of those pilot-scale MBRs, assuming that the life span of MBR is 20 years, the total cost (construction cost + operating cost) was estimated to be saved by about 12%.

11. Confronting challenges and future directions

QQ-MBR, the revolutionary anti-biofouling strategy for use in MBRs was conceived in 2002 and opened to public use in 2009. Since then, many studies have demonstrated and proved the potential of QQ as a biofouling control in MBRs through various means. The evolution of QQ-MBR has had a run of eight years in terms of QQ-microorganisms, QQ-media, and the size of the QQ-MBRs tested. Even so, the use of QQ-MBR is still being developed (Fig. 10). Some challenges to be confronted and future directions in QQ-MBR research are as follows:

- The size of a test QQ-MBR has made progress continuously from a small lab-scale (5 L/day) fed with synthetic wastewater to a larger pilot-scale (10 m^3/day) with real municipal wastewater. The test QQ-MBRs have demonstrated excellent biofouling control and thus energy savings regardless of their sizes and installed places over the world. Furthermore, a QQ-MBR, as its present technical level, proved to be more economical in capital and operating costs than a conventional MBR. Consequently, the QQ-MBR is now approaching its final goal of practical use. However, further reduction of QQ-media production cost and further investigation to find the optimum operating conditions (e.g., the optimum concentration of QQ-media) will shorten the time required for its first commercialization.
- QQ-MBR has been developed based on knowledge of bacterial communications that had been explored not in the area of wastewater engineering, but in microbiology. Therefore, the information on the AI-2 or other signaling (AIPs) in activated sludge of MBRs was very limited and thus it was inevitable to mostly rely on AHL based QS, which was relatively easily accessible even in the area of wastewater engineering. In future, more intensive research on AI-2 or other signaling in wastewater engineering is necessary to diversify and enhance QQ-technology applicable to MBRs for wastewater treatment.
- It is also challenging to simultaneously make a target of AHL and AI-2 QS using both AHL and AI-2 QQ microorganisms to induce synergistic effect on the biofouling control in QQ-MBRs. Combination of QQ-technology with other biofilm dispersal technologies (e.g., nitric oxide or cellulolytic bacteria mediated biofilm dispersal) also has synergistic potential for the biofouling control in MBRs.
- Further study is required to investigate the optimum design and materials of QQ-media to enhance QQ activity as well as to reduce the cost of QQ-MBR. It is also worth developing new flat-sheet or hollow-fiber membrane modules in which part of sheets or fibers are replaced by QQ-sheets or QQ-fibers, respectively. Those QQ-membrane modules are expected to eliminate a process for the separation of QQ-media from activated sludge in QQ-MBR.
- Beyond the QQ-MBR, the potential of QQ-technology could be expanded to other membrane processes in aquatic environments for biofouling control, such as anaerobic MBR (AnMBR), reverse osmosis (RO), forward osmosis (FO), FO-MBR, etc. The potential of QQ-AnMBR [199] and QQ-RO [200] has already been proven in lab-scale experiments.

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