REVIEW ARTICLE

Quorum sensing regulation methods and their effects on biofilm in biological waste treatment systems: A review

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HIGHLIGHTS

- Quorum sensing enhancement and inhibition methods are summarized.
- Effects of quorum sensing regulation on biofilm are reviewed.
- Current knowledge gaps and research challenges are proposed.

GRAPHIC ABSTRACT

ARTICLE INFO
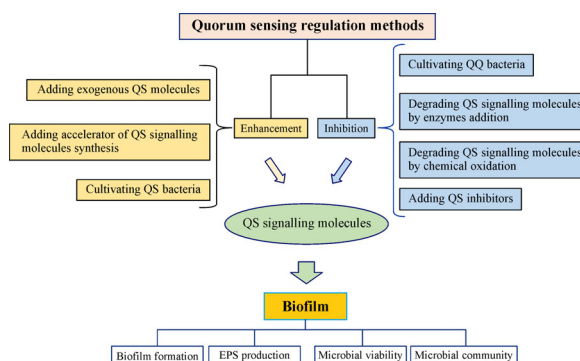
ABSTRACT

Quorum sensing (QS) plays an important role in microbial aggregation control. Recently, the optimization of biological waste treatment systems by QS regulation gained an increasing attention. The effects of QS regulation on treatment performances and biofilm were frequently investigated. To understand the state of art of QS regulation, this review summarizes the methods of QS enhancement and QS inhibition in biological waste treatment systems. Typical QS enhancement methods include adding exogenous QS molecules, adding QS accelerants and cultivating QS bacteria, while typical QS inhibition methods include additions of quorum quenching (QQ) bacteria, QS-degrading enzymes, QS-degrading oxidants, and QS inhibitors. The specific improvements after applying these QS regulation methods in different treatment systems are concluded. In addition, the effects of QS regulation methods on biofilm in biological waste treatment systems are reviewed in terms of biofilm formation, extracellular polymeric substances production, microbial viability, and microbial community. In the end, the knowledge gaps in current researches are analyzed, and the requirements for future study are suggested.

1 Introduction

The finding of quorum sensing (QS) has provided a new idea to regulate microbial growth (Sivasankar et al., 2019), and an increasing number of studies have been carried out to optimize biological waste treatment systems by QS regulation methods (Liu et al., 2015; Peng et al., 2018; Liu et al., 2020). QS signaling molecules includes N-acyl-homoserine lactones (AHLs), autoinducers-2 (AI-2), autoinducing peptides (AIPs), quinolone (PQS), etc. (Holban et al., 2016; Turan et al., 2017; Maddela et al., 2019). By different effects on QS signaling molecules, QS regulation methods can be classified into two groups: QS enhancement and QS inhibition. QS enhancement methods

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aim to increase QS signaling molecules concentrations in the systems while QS inhibition methods aim to decrease QS signaling molecules concentrations or interfering its function.

There are quite a few review articles about QS regulation in biological waste treatment systems in the literatures, covering different aspects and topics. Most of these reviews are on the roles of QS regulation and its distinctive performances in biological wastewater treatment systems (Maddela et al., 2019). Many reviews summarized the application of QS enhancement methods in specific biological wastewater treatment processes such as nitrification and denitrification, partial nitritation-anammox, granular sludge system (Huang et al., 2019; Wang et al., 2021b; Zhao et al., 2021). Besides QS enhancement, there are also some reviews targeting QS inhibition to mitigate biofouling in membrane bioreactors (MBRs) (Lade et al., 2014; Siddiqui et al., 2015). Most of the reviews focused on the effects of QS regulation on the system performance, while only a few considered the effects on biofilm formation from the microbiology perspective (Huang et al., 2016; Chen et al., 2018).

Although the reviews in the literature presented a comprehensive understanding on the development of QS regulation for wastewater treatment, there are still some questions to be answered: 1) What are the specific methods to achieve QS enhancement and inhibition in biological waste treatment systems? 2) What are the effects of QS regulation on biofilm in biological waste treatment systems? In this review, we summarized the methods of QS regulation in biological waste treatment systems. The effects of QS regulation on biofilm in terms of biofilm formation, extracellular polymeric substances (EPS) production, and microbial viability and community were also reviewed.

2 Theory of QS regulation on biofilm

The QS systems are mediated by some signaling molecules, and general signaling molecules mainly includes AHLs, AI-2, AIPs and PQS, and their mechanism to mediate QS are shown in Fig. 1.

As shown in Fig. 1, the processes for different QS signaling molecules are quite similar. QS bacteria produce signaling molecules and secrete them to the extracellular environment. When the extracellular QS signaling molecules accumulate to a certain level in the local environment, they can enter the bacterial cell again and activate the transcription and expression of specific genes (Whiteley et al., 2017). The most widely studied QS signaling molecules are AHLs, which have been found in 25 Gram-negative bacterial species (Turan et al., 2017). The first AHLs, N-3-oxohexanoyl-l-homoserine lactone (3OC6-HSL), was found in a marine bacterium *Vibrio fischeri* in the 1980s, and controls the expression of luminescence
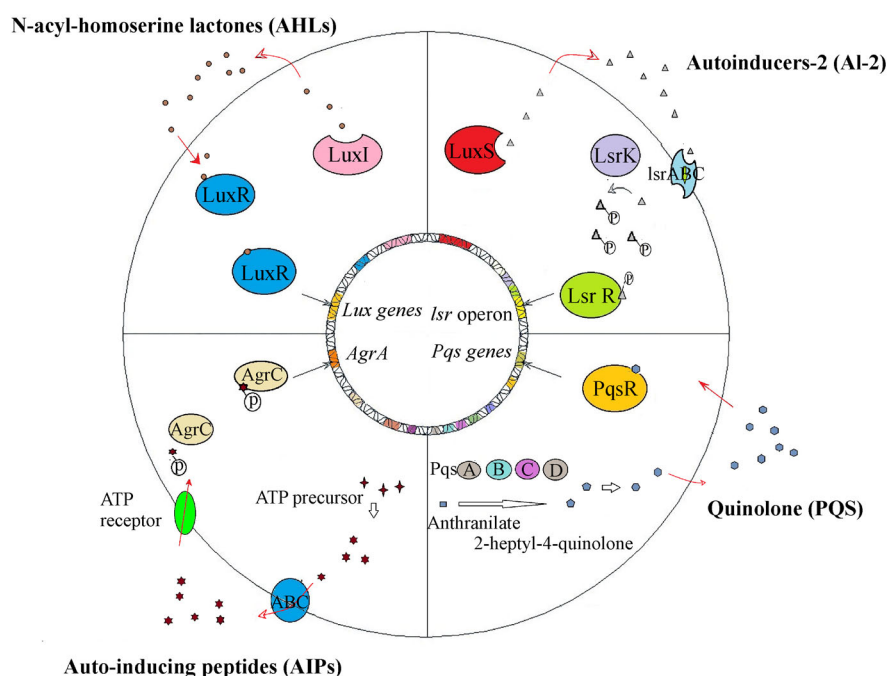

Fig. 1 Schematic diagram of QS processes for different signaling molecules.

(*lux*) genes through the LuxI/LuxR system (Eberhard et al., 1981; Engebrecht and Silverman, 1984; Whiteley et al., 2017). AHL-mediated QS affected sludge granulation and EPS production in bioreactors (Tan et al., 2014). Another important QS signaling molecule is AI-2, which was found in both Gram-positive and Gram-negative bacteria. AI-2 is produced by the participation of *lux S* gene, and can regulate biofilm adhesion (Buck et al., 2009). AIPs, always produced by Gram-positive bacteria with two-component regulatory systems, can affect the intercellular communication, biofilm formation and microbial resistance (Sturme et al., 2002; Peterson et al., 2004). PQS, belonging to the 4-quinolone (4Q) family, is produced by *Pseudomonas aeruginosa* (*P. aeruginosa*) and can regulate multicellular behaviors, denitrification and iron transport systems (Diggle et al., 2006; Fernández-Piñar et al., 2011; Maddela et al., 2019).

Quorum sensing regulation has a significant impact on biofilm formation. First, it can affect the bacterial swimming and attachment (Kjelleberg and Molin, 2002; Cui et al., 2020). For example, QS inhibition by adding porcine kidney acylase I, hampered the microbial colonization in a bioaugmented systems (Zhang et al., 2015). Second, QS signals can control the production of extracellular polysaccharide and rhamnolipid (Davey et al., 2003; Sakuragi and Kolter, 2007). The biofilm without QS signaling molecules was thin and lack of a three-dimensional structure (de Kievit and Iglewski, 2000). Finally, QS signaling molecules can regulate the activity and viability of bacterial cells (Lynch et al., 2002; Li et al., 2014). The effects of QS on biofilm have been commonly reported (Engebrecht and Silverman, 1984; Maddela et al., 2019; Zhang et al., 2021), which indicates its application in optimization of biological waste treatment systems.

3   QS regulation methods in biological waste treatment systems

3.1   QS enhancement methods

QS enhancement methods can increase the QS signaling molecule content in biofilm and then favor the start-up and operation of biological waste treatment systems. Three QS enhancement methods were introduced in Table 1.

3.1.1   Adding exogenous QS signaling molecules

The most common method to enhance QS is direct addition of exogenous QS signaling molecules, which provides immediate and accurate control of QS level (Hu et al., 2016a). AHLs is the most commonly-used QS signaling

Table 1   QS enhancement methods and their effects on performance of biological treatment systems

QS enhancement methods	Additives	Concentration	Bioreactor	Indicators	Performance*	Reference
Adding exogenous QS signaling molecules	C8-HSL	100 nmol/L	MBBR	NH_4^+-N removal	+	Huang et al., 2020
	Mixture of AHLs (C6-, C8-, 3-OXO-C12- and C14-HSL)	1000 nmol/L	SBBR	COD removal	+ 3%	Hu et al., 2016a
	Quinolone	100 nmol/L	MFC	Power density	+ 30%	Monzon et al., 2016
	3OC6-HSL	10000 nmol/L	MEC	Current	−	Liu et al., 2015
	C6-HSL	100 nmol/L	MBBR	NH_4^+-N removal	−20%	Fan et al., 2019)
	Phenylethanol, tryptophol, tyrosol	10 μmol/L	MFC	Current density and electrons transfer	+	Christwardana et al., 2019
Adding accelerator of QS signaling molecules synthesis	Boron	60 μmol/L	BEFC	Voltage output	+ 15 mV	Cevik et al., 2020
	Fulvic acid	0.5–1 mmol/L	Anammox system	Nitrogen removal	+	Liu et al., 2020
Cultivating QS bacteria	*Pseudomonas aeruginosa, Vibrio harveyi, Xanthomonas campestris*	NA	EGSB	COD removal	+	Ding et al., 2015
	Sphingomonas rubra	10 mL bacterium solution with OD_{600} = 1.5	MBBR	COD and NH_4^+-N removal	+	Wang et al., 2019
	Centrifugation residual *Aeromonas* sp. A-L3	Strain suspension with a volume ratio of 2%	Aerobic granular sludge reactors	COD removal	+ 7%	Gao et al., 2019

Notes: * "+": Increase; "−": Decrease; "%" Absolute percentage.

molecules, and the adding concentration generally range from 10 to 10000 nmol/L. In most cases, direct addition of exogenous QS signaling molecules can promote the performance of bioreactors. For example, exogenous C6-HSL and C8-HSL were successfully used to enhance nitrogen transformation in anaerobic ammonium oxidation process and moving bed biofilm reactor (MBBR) (Zhang et al., 2019a; Huang et al., 2020). The organics removal performance of electrochemical reactors were found to be enhanced after adding QS signaling molecules. Stable increase in electron transfer and power production capacity were observed in microbial fuel cells (MFCs) and microbial electrolysis cells (MECs) (Liu et al., 2015; Monzon et al., 2016; Christwardana et al., 2019).

However, not all biological treatment systems were optimized after the addition of signaling molecules. For example, 1000-nM AHL addition decelerated approximately 7% for COD removal and 2.6% for nitrifications of the ammonia nitrogen in sequencing biofilm batch reactor (SBBR) (Hu et al., 2016a) and addition of C6-HSL during the operation period of an MBBR significantly decreased 0.44%–20.29% after 16 days on the ammonia nitrogen removal (Fan et al., 2019). One disadvantage of direct addition of exogenous QS signaling molecules is its high expense. Another disadvantage is the unstable enhancement due to the quick degradation of exogenous QS signaling molecules by some quorum quenching (QQ) bacteria (Soler et al., 2018). The concentration of C6-HSL was found to decreased by more than 70% in 15 days after 500 nM AHLs (four different AHL mixtures) was directly added into biofilm reactors (Hu et al., 2016b).

3.1.2 Adding accelerators of QS signaling molecules synthesis

Another method to enhance QS is adding accelerators in biological treatment systems to promote synthesis of QS signaling molecules. The reported accelerators include precursors of QS signaling molecules and accelerators for its release. For example, Boron is a well-known enhancer of QS signaling molecules because AI-2 will be activated with the formation of boron complexed to (R)-4,5-dihydroxy-2,3-pentanedione (DPD) as its precursor (Chen et al., 2002; Cevik et al., 2020), and the adding of boron increased potential by almost 15 mV in a bio-electrochemical fuel cells (Cevik et al., 2020). In addition, fulvic acid is one of accelerators for the AHL release, and 1 mM fulvic acid can increased total inorganic nitrogen removal rates to 1.94 mg-N/L/h from 1.27 mg-N/L/h in an anammox system (Liu et al., 2020). The advantage of adding accelerators is that the cost of accelerator is usually cheaper than those of QS signaling molecules. However, compared to directly adding exogenous QS signaling molecules, it risks failure because the synthesis processes of signaling molecules are very complex.

3.1.3 Cultivating QS bacteria

QS bacteria which can produce signaling molecules are found in natural environments and cultivation of QS bacteria is another option to economically enhance QS in biological treatment systems. Soler et al. (2018) found that 5 of 99 bacterial strains isolated from the leachates were QS bacteria. Zhang et al. (2020) added the supernatant of 7 AHL-producing strains from mature aerobic granular sludge to sequencing batch reactors, thus increasing the maximum concentrations of C6-HSL, C8-HSL, and N-(3-oxooctanoyl)-l-homoserine lactone (3OC8-HSL) by 23%, 81%, and 27%, respectively. The performances of biological treatment systems for ammonia, nitrogen, and organic carbon removal were improved by adding *P. aeruginosa*, which can serve as both AHL producers and pollutant degraders (Yong and Zhong, 2010). However, QS bacteria that promote pollutant removal always work more difficult than other methods of QS enhancement. The short-term addition of a QS strain (*Sphingomonas rubra* sp. nov.) could not significantly improve the COD and NH_4^+-N removal rates in MBBR (Wang et al., 2019). In addition, the increase of COD removal decreased to only 1% at 40-s day from 7% at seventh day after adding *Aeromonas* sp. A-L3 as an AHL-producing bacteria (Gao et al., 2019). The QS bacteria may be washed out with excess biomass or inhibited by bacteria competition in biological treatment systems.

3.2 QS inhibition methods

QS inhibition methods can suppress the effects of QS signaling molecule by degrading signaling molecule, inhibiting the signaling molecule synthesis, or interfering its functions in biological treatment systems. Typical QS inhibition methods applied in biological waste treatment systems were introduced in Table 2.

3.2.1 Cultivating QQ bacteria

One common QS inhibition method is cultivating QQ strains to degrade QS signaling molecules. Many QQ strains isolated from nature have been comprehensively studied, such as *Rhodococcus* sp. BH4, *Bacillus licheniformis* T-1, *Penicillium restrictum* CBS 367.48 and *Pseudomonas* sp. HS-18 (Oh et al., 2012; Chen et al., 2020; Maddela and Meng, 2020; Wang et al., 2020a; Fakhri et al., 2021). In particular, *Rhodococcus* sp. BH4 is one of the most popular QQ strain (Oh et al., 2012; Oh and Lee, 2018). Genetic engineering QQ strains were also constructed by plasmid transformation (Oh et al., 2017). These QQ strains can rapidly degrade QS signaling molecule. For example, 50 μM C6-HSL was completely degraded in 9 hours by a novel QQ-bacterium, *Lactobacillus* sp. SBR04MA, suspended in a solution (OD_{600} =

Table 2 QS inhibition methods and their effects on performance of biological waste treatment systems

QS inhibition methods	Additives	Bioreactor	Indicators	Performance*	Reference
Cultivating quorum quenching (QQ) strains	Recombinant *E. coli.* and *Rhodococcus* sp. BH4	MBR	Transmembrane pressure	−	Oh et al., 2012
	Rhodococcus sp. BH4	MBR	Chemical oxygen demand (COD) removal	≈	Ouyang et al., 2020
	Penicillium restrictum CBS 367.48	MBR	Sulfamethoxazole and erythromycin	+	Fakhri et al., 2021
	Lactobacillus sp. SBR04MA	MBR	COD removal	≈	Kampouris et al., 2018
	Bacillus sp. T5 and *Delftia lacustris* T6	MBR	Transmembrane pressure	−	Yavuztürk Gül and Koyuncu, 2017
Adding degrading enzymes	Acylase	MBR	COD removal	≈	Yeon et al., 2009
	Porcine kidney acylase I	MBR	Transmembrane pressure	−	Jiang et al., 2013b
	Acylase	Nanofiltration	Flux profiles	+	Kim et al., 2011
Degrading QS signaling molecules by ROS	Long-wave UV	MBR	TOC, COD, TN, TP, and NH_4^+-N removal	≈	Zhang et al., 2019b
	TiO_2 nanoparticles under UV irradiation	MBR	COD removal	+	Mehmood et al., 2021
	Electric field	EMBR	Phenol degradation rate	+	Jiang et al., 2020
Adding QS inhibitors	Vanillin	RO	Biofilm formation	−	Ponnusamy et al., 2009
	3,3′,4′,5-tetrachlorosalicylanilide	MBR	Ammonium removal	≈	Feng et al., 2020
	Piper betle extract	MBR	Transmembrane pressure	−	Siddiqui et al., 2012

Notes: * "+": Increase; "−": Decrease; "≈"No significant difference.

1.0) (Kampouris et al., 2018). *Betaproteobacteria* and *Firmicutes* suspensions (OD_{600} = 1.0) could remove completely 200 nM AHL in 30–60 s (Yavuztürk Gül and Koyuncu, 2017). The isolation and evaluation of those QQ strains provide a promising QS inhibition method for large-scale system.

The addition of QQ strains showed no significant effects on performance of biological waste treatment systems in many researches (Kampouris et al., 2018; Ouyang et al., 2020). For example, the addition of *Lactobacillus* sp. SBR04MA, a QQ-strain did not affect the COD removal efficiency of 95% throughout the entire operating period of an MBR. In most cases, adding QQ strains was used to control biofouling in MBRs, which was first reported in 2009 (Yeon et al., 2009). In addition, the stable operation of bioreactors after adding QQ strains indicated that the control of excessive biomass accumulation or biofouling by this QS inhibition method does not need a performance recovery period compared to other physical or chemical methods (Jiang et al., 2013b; Lee et al., 2018a; Xiao et al., 2018; Liu et al., 2021a; Wang et al., 2021a).

3.2.2 Degrading QS signaling molecules by enzymes

Another emerging method is direct addition of enzymes to degrade the QS signaling molecules in biological treatment systems. Many enzymes for QS signaling molecules

degradation have been found and studied, particularly the enzymes for AHL degradation. Lactonase, acylase, decarboxylase and deaminase were found to be four typical enzymes having AHL degradation capacity, and the pathways of AHL degradation under these enzymes are also reported (Siddiqui et al., 2015). Among the four enzymes, acylase is most frequently used and it was observed to effectively decrease the concentration of QS signaling molecules in a MBR with COD and ammonia removal efficiencies above 95% (Jiang et al., 2013b). Kim et al. (2011) also found that membrane flux of a nanofiltration system was increased by more than 30% after adding acylase. However, the enzymes also have a short lifetime in bioreactors and will loss activity easily, which limits their application.

3.2.3 Degrading QS signaling molecules by reactive oxygen species (ROS)

QS inhibition method by producing ROS including hydroxyl radicals and superoxide has gradually attracted interest in recent years (Lee et al., 2018b; Zhang et al., 2019b). For example, the ROS generated by short-time UV-TiO_2 photocatalysis inactivated AI-2 secreted from *Escherichia coli* and reduced the bacterial biomass by 42.6% (Xiao et al., 2016). Continuous UV photolysis or photocatalysis were also successfully applied to mitigate

biofouling in MBR, performing more efficiently than adding QQ bacteria (Zhang et al., 2019b; Mehmood et al., 2021). In addition, the ROS generated by an electric field (0.4 V/cm) lowered the AHLs concentrations (13–23 ng/L) compared to the control group (24–37 ng/L) in a MBR (Jiang et al., 2020). Although these new approaches showed significantly capacity to inhibit QS, their exact role and the mechanisms of QS inhibition in biological waste treatment system are still unknown.

3.2.4 Adding QS inhibitors

Besides removing QS signaling molecules, adding QS inhibitors to interfere QS receptors or inactivate signaling molecules was also applied in biological waste treatment systems (Yates et al., 2002; Teplitski et al., 2011; Kalia, 2013). Many QS inhibitors were found including 3-amino-2-oxazolidinone YXL-13, homoserine lactone-like TGK-series, ε-polysine, aporphinoid alkaloids, cladodionen, gingerol, etc (Al-Shabib et al., 2020; Alibi et al., 2020; Brown et al., 2020; Cheng et al., 2020; Di Marco et al., 2020; Li et al., 2020; Parmar et al., 2020; Qin et al., 2020; Shen et al., 2020; Wang et al., 2020b). Vanillin (4-hydroxy-3-methoxybenzaldehyde) was used as the QS inhibitor and decreased the biofilm formation by over 45% on reverse osmosis (RO) membrane (Ponnusamy et al., 2009). The inhibitor 3,3′,4′,5-tetrachlorosalicylanilide (100 μg/L) decreased the average AI-2 concentration by 30%, and reduced the biofilm in MBR by 50% (Feng et al., 2020). The addition of easily-synthesized and economic QS inhibitors can reduce the operating cost, and thus may be more cost-effective than adding QQ strains or degrading enzymes.

4 Effects of QS regulation on biofilm

4.1 Biofilm formation

A quick biofilm formation is essential for the successful start-up of a biological waste treatment system (Xu et al., 2021). QS enhancement methods were applied to enhance biofilm formation in many researches. The biofilms formation in start-up phase and recovery from starvation on carriers was significantly accelerated in bioreactors in the presence of exogenous AHLs (Huang et al., 2016; Xiong et al., 2020). Besides AHLs, the exogenous PQS or some alcohol molecules (phenylethanol, tryptophol and tyrosol) also showed the positive effects on the biofilm growth in the MFC (Monzon et al., 2016; Christwardana et al., 2019). Laser scanning confocal microscopy (LSCM) is often used to observe biofilm formation in a QS enhancement system, but rarely giving quantitative results. We collected the LSCM images from some researches and calculated the pixels proportion of fluorescent biofilm with

and without QS enhancement (Huang et al., 2016; Hu et al., 2017; Wang et al., 2018; Xiong et al., 2020). The result is shown in Fig. 2. The average percentage of biofilm in QS enhancement systems was significantly increased.
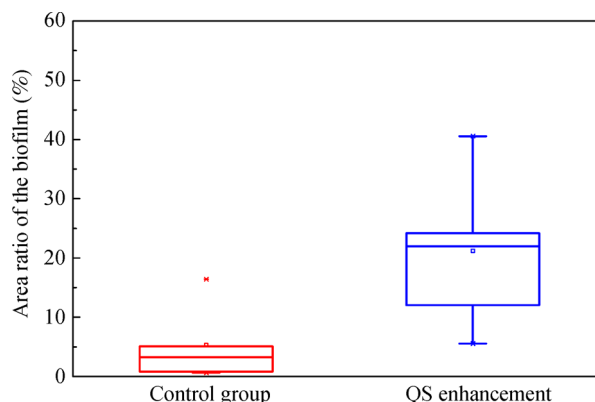

Fig. 2 Biofilm formation in QS enhanced systems observed by LSCM.

QS inhibition methods were also applied to control biofilm formation or biofouling in MBRs. Weerasekara et al. (2016) obtained LSCM images of the biofilm along the top, middle and bottom parts of the membrane fiber in a control MBR and a QS-inhibited MBR. The biofilm layer was obviously thicker and rougher in the control MBR. Similar results were observed in many other studies (Kim et al., 2011; Ergön-Can et al., 2017; Oh et al., 2017; Oh and Lee, 2018). The transmembrane pressure is the most important indicator to reflect the biofouling in MBRs. Decrease in transmembrane pressure has been frequently observed in QS-inhibited systems. In a MBR added with sodium alginate capsule-immobilized acylase to inhibit QS, the transmembrane pressure was maintained at 15 kPa, while the transmembrane pressure of control MBR was more than 40 kPa under the same conditions (Jiang et al., 2013a). Compared with adding bactericidal agents (silver salts, nitrofurazone, ammonium surfactants or antibacterial peptides), QS inhibition methods for biofouling control are much safer to the environment.

4.2 EPS production

EPS, which is dominated by polysaccharide (PS) and proteins (PN), are closely related to the microbial attachment and biofilms structure. The positive effect of AHLs on EPS production in different bioreactors such as SBBR, MBBR and MFC was the most frequently reported compared with other QS signaling molecule content (Chen et al., 2017; Fan et al., 2019). The adding of AHLs can even increase exponentially EPS production in biofilm. For example, the addition of AHLs caused increased the PS content by approximately more than 1 time during the stable operation of an MBBR (Liu et al., 2021b). Except

for AHLs, the adding Al-2 was found can promote EPS production in a bioreactor (Ding et al., 2015). However, the positive effect of QS enhancement for other QS signaling molecule content such as PQS and AIPs on EPS production is lack solid evidence. There are some QS signaling molecule such as diffusible signal factor (DSF), 3OC6-HSL, 3-oxo-C10-HSL might have no significant positive or negative effect on EPS production in biological treatment systems (Ding et al., 2015; Lv et al., 2018; Wang et al., 2018; Huang et al., 2019), and the reason why those QS signaling molecule had opposite EPS trends with increasing their content s in bioreactors is still not understood. These molecules should be avoided in similar conditions if the aim is to increase the EPS production.

The general current consensus is that most of QS inhibition significantly decreases the EPS production by from less than 10% to more than 70% (see Table 3), and many studied were carried out in MBR to control biofouling on a laboratory scale (Shi et al., 2017; Iqbal et al., 2018; Yu et al., 2018). The AHLs is the main target signaling molecule of QS inhibition because its QQ bacteria might be more easily isolated and obtained. For example, when QQ strains that degrade C6-HSL, C8-HSL, and N-decanoyl-l-homoserine lactone (C10-HSL) were added to a laboratory-scale anaerobic MBR, the EPS production decreased by 72%, 36% and 66%, respectively (Xu et al., 2020). In addition, although the decreasing EPS production reduces the amount of biofouling, it also causes excessive shedding of the biofilm that destroyed the biofilm function, which may explain why QS inhibition is rarely used to solve the biomass accumulation in bioreactors with biofilms as the functional main body.

Therefore, more accurate control of EPS production is required for widening the application scope of QS inhibition, and the quantitative relationship between EPS production and decreased content of different QS signaling molecules should be investigated more in other bioreactors, especially biofilm reactors.

4.3 Microbial viability

The positive effects of QS enhancement on microbial viability were found by semiquantitative analysis in several bioreactors. Pan et al. (2020) observed the double fluorescence stained biofilm on the anode of an MFC fed with C6-HSL and 3-OXO-C12-HSL, and they found that its microbial viability was significantly higher than that without exogenous AHLs. Similar results were also observed in a mixed-culture MFC fed with C4-HSL, C6-HSL and 3-OXO-C12-HSL and a bioelectrochemical system fed with C6-HSL and 3-OXO-C12-HSL (Chen et al., 2017; Fang et al., 2018). Although these studies directly observed the live/dead bacteria and their local distributions, they could not accurately quantify the ratio of live to dead bacteria. Therefore, we recommend the use of flow cytometry and enzyme activity assays that quantify the live/dead bacteria ratio and metabolic activity in QS-enhanced systems.

Many previous studies suggested that the microbial viability of bacteria biofilm was always decreased by the QS inhibition methods. For example, the cell viability of *Agrobacterium tumefaciens* was decreased to 77%–80% of its original level by adding the QS-degrading acylase at concentrations of 0.1–10 μg/mL, indicating that the QS

Table 3 EPS production in QS inhibited systems

Methods of QS inhibition	Target signal molecule	Bioreactor	Wastewater	Sampling time	EPS production*	Reference
QQ consortia	AHLs	MBR	Domestic	59 d	−55% (Protein) −60% (Carbohydrates)	Yu et al., 2018
Facultative QQ consortiums-C6	C6-HSL	MBR	Domestic	7 d	−72%	Xu et al., 2020
Facultative QQ consortiums-C8	C8-HSL				−36%	
Facultative QQ consortiums-C10	C10-HSL				−66%	
Rhodococcus sp. BH4	AHLs	MBR	Synthetic and municipal	100 d	−9% (Protein) −9% (Carbohydrates)	Iqbal et al., 2018
Rhodococcus sp. BH4	AHLs	MBR	Synthetic	80 d	−70% (Protein) −50% (Carbohydrates)	Weerasekara et al., 2016
Recombinant *Escherichia coli* TOP10-AiiO	AHLs	RO	Synthetic	109 h	−35% (Protein) −43% (Polysaccharides)	Oh et al., 2017
Acylase-Immobilized Nanofiltration Membrane	AHLs	Nanofiltration	Synthetic	5 d	− (Polysaccharides)	Kim et al., 2011
Rhodococcus sp. BH4	AHLs	MBR	Synthetic	30 d	−25% (Polysaccharides) −50% (Protein)	Ergön-Can et al., 2017

Notes: * "+": Increase; "−": Decrease; "%" Relative percentage.

inhibition had a negative impact on viability (Bao et al., 2020). A double mutant *P. aeruginosa* strain (Δ*lasR* Δ*rhlR* and Δ*lasI* Δ*rhlI*) showed lower survival ability than the wild-type strain (Lu et al., 2010). Interestingly, the effect of QS inhibition on microbial viability in mixed culture was opposite to that in pure culture. For example, fewer dead cells and more viable cells were observed in the biofilms in a QS-inhibited MBR by fluorescent staining method (Oh et al., 2017). The decrease in the number of dead cells was also observed in the biofilm samples in a seawater desalination RO membrane treated by AI-1 QS inhibitors (Katebian et al., 2016). Oh et al. (2017) suggested that the QS inhibition may result in slower maturation of biofilm.

4.4 Microbial community

Many genera were found that they would be prompted with the QS enhancement in biofilm. *Pseudomonas* is one of the most common genera, and a significant increasing of its abundance has been found with AHL-mediated QS enhancement in many biological treatment reactors such as SBBR, MBBR, and MFC (Hu et al., 2017; Zhang et al., 2019a; Huang et al., 2020; Pan et al., 2020; Zhang et al., 2020), which is consistent with the results of studies on the effects of AHLs on this genus (Davies et al., 1998; Kjelleberg and Molin, 2002; Cellini et al., 2020). Meanwhile, the abundance of *Nitrosomonas*, a major class of nitrifying bacteria (Phanwilai et al., 2020; Qiu et al., 2020), increases with increasing content of signaling molecules. This trend is thought to explain (at least partly) why QS enhancement can optimize biological treatment reactors for ammonia nitrogen removal (Li et al., 2015; Hu et al., 2017; Zhang et al., 2019a). In addition, the abundance of *Methanosaeta*, which can produce methane and degrade organic matter, is commonly increased by the addition of AHLs (Lv et al., 2018; Ma et al., 2019). Directly using an electron transfer mechanism, the relative abundance of *Geoboacter* was increased in some electrochemical reactors with biofilm by adding exogenous AHLs that promoted organic matter degradation (Chen et al., 2017; Pan et al., 2020).

Some of genera with significantly decreased relative abundances were also shown in the results of high-throughput sequencing for the microbial community in QS-enhanced systems. For example, significant decreases in the relative abundance of *Pseudorhodoferax* and *Thiothrix* as the dominant bacteria were found in an SBBR with the adding AHLs and cultivating AHL-producing strains, respectively, and the growth of *Paracoccus* was inhibited in two QS-enhanced SBBRs (Hu et al., 2016a; Zhang et al., 2020). These results further indicate that QS can effectively regulate the microbial community, and QS enhancement can optimize many biological treatment systems in the start-up stage.

Two commonalities of microbial community in biofilm with QS inhibition were found. First, in studies that monitored the bacterial composition, the effects of QS inhibition on the bacterial composition tended to weaken after long running times of the reactors. This result is probably because other types of signal molecules are constantly secreted, and QS inhibition cannot decrease the levels of all of them, which results in a complex environment in the middle and late phases of the QS-inhibited system operation and weakens the effects of QS inhibition on the microbial community (Ouyang et al., 2020). Second, endogenous QS and QQ bacteria are always sensitive to decreased levels of QS signaling molecules. Ouyang et al. (2020) reported that the abundance of QQ bacteria *Comamonadaceae* increased from 24% to 29%, and that of QS bacteria *Cytophagaceae* decreased from 13% to 10% in MBRs after QS inhibition. In another study, the increased abundance of QQ bacteria *Rhodococcus* and *Stenotrophomonas* and decreased abundance of QS bacteria *Aeromonas* occurred in EMBRs as the levels of AHLs decreased (Jiang et al., 2020). Although many studies have reported decreased abundances of QS bacteria and increased abundance of QQ bacteria with QS inhibition in biological treatment systems, the mechanism of QS signaling molecules acting on QS bacteria and QQ bacteria remains unclear. Understanding the relationship between QS inhibition and the microbial community is important for optimizing biological treatment systems. It also provides an opportunity for controlling the microbial function of biofilm. The latent rules underlying the relationship between the microbial community and QS inhibition in biological treatment systems for pollutant removal hiding in previous studies need to be further excavated.

5   Conclusions and perspectives

Typical QS enhancement methods and inhibition methods employed in biological waste treatment systems are summarized in this review. The effects of QS regulation on biofilm are also introduced. Generally, QS enhancement can help to increase the biofilm formation and thus promote the pollutants removal performance of different types of bioreactors. Meanwhile, QS inhibition can help to mitigate biofouling in membrane bioreactors. Although there are great achievements in the field of QS regulation for biological waste treatment system, there are still many questions unknown and problems that should be solved. Thus, the demands for future study are listed as below:

1) The performances of different QS enhancement or inhibition methods in biological waste treatment systems should be compared. Comprehensive and quantitative evaluation on different QS regulation methods should be carried out on more types of bioreactors, such as waste gas or solid waste treatment systems.

2) The distribution, metabolism and fate of QS signaling molecules in different biological waste treatment

systems.

3) The changes in microbial community structure and functions by QS regulation should be comprehensively studied using the molecular tools such as metagenomics and metatranscriptomics analysis to understand its mechanisms.

4) Most studies on QS regulation in biological treatment systems have been conducted on laboratory scales rather than in large-scale applications. The effects and mechanisms of QS regulation in large-scale biological treatment systems should be further studied.

In the future, the QS regulation methods will function as a promising and eco-friendly options to optimize the performance of biological waste treatment systems.

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