Function of quorum sensing and cell signaling in wastewater treatment systems

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ABSTRACT

Quorum sensing (QS) is a communication mode between microorganisms to regulate bacteria ecological relations and physiological behaviors, thus achieve the physiological function that single bacteria cannot complete. This phenomenon plays important roles in the formation of biofilm and granular sludge, and may be related to enhancement of some functional bacteria activity in wastewater treatment systems. There is a need to better understand bacterial QS in engineered reactors, and to assess how designs and operations might improve the removal efficiency. This article reviewed the recent advances of QS in several environmental systems and mainly analyzed the regulation mechanism of QS-based strategies for biofilm, granular sludge, functional bacteria, and biofouling control. The co-existences of multiple signal molecules in wastewater treatment (WWT) processes were also summarized, which provide basis for the future research on the QS mechanism of multiple signal molecules' interaction in WWT. This review would present some prospects and suggestions which are of practical significance for further application.

Key words | biofilm, functional bacteria, granular sludge, quorum sensing, wastewater treatment

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HIGHLIGHTS

- QS-based signal manipulation has great potential in WWT processes.
- In-depth researches on interaction of multiple signals are of practical significance.
- QS-QQ strategies regulated to certain features in WWT facilities.
- The present strategies need to be further studied to reach full-scale stage.

QUORUM SENSING

Bacteria were thought to be single-celled individuals and not related to each other in previous studies. Until the 1970s, quorum sensing (QS) was first proposed when Miller and Nealson discovered bacterial cell interactions while studying *Streptococcus pneumoniae* and *Vibrio fischeri* (Nealson & Hastins 1979; Miller & Bassler 2000). Bacterial QS refers to the bacteria release the signal molecules in the environment, and through sensing signal molecule concentration to induce the expression of related genes in the cytoplasm of bacteria. In this process, the ecological relationship of flora and physiological behavior are regulated, showing physiological functions and regulatory mechanisms that cannot be realized by a single bacterium, such as regulating the formation of biofilm, producing antibiotics and secondary metabolites, etc. (Waters & Bassler 2005; Shrout & Nerenberg 2012).

As a medium of QS, signal molecules are not only metabolites of microorganisms, but also a special 'universal' compound. They can act on communication between the same bacteria or different kinds of bacteria. According to the type of signal molecule, QS can be divided into the following categories (Swift *et al.* 2001): Gram-negative QS systems mediated by acyl-homoserine lactones (AHLs) (Fekete *et al.* 2007); QS system mediated by diester furborate (AI-2),

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which is present in Gram-negative/positive bacteria (Miller & Bassler 2000; Pereira *et al.* 2016); QS system with Gram-positive bacteria mediated by Autoinducing Peptide (AIP) (Figure 1). In addition, the researchers also found other signal molecules, e.g. diffusing signal factor (DSF), autoinducer 3 (AI-3) and diguanylate monophosphate (cyclic-di-GMP, second messenger) (Table 1). Since Gram-negative bacteria are the main bacteria in sewage and AHLs are the main signal molecules in Gram-negative bacteria, the existing researches mainly focus on AHLs-based QS.

QS-based signal regulation has been shown to play a key role in the stability of microbial community (Valle *et al.* 2004; Maddela *et al.* 2019), exoenzyme production (Chong *et al.* 2012) and the granular sludge formation (Tan *et al.* 2014; Maddela *et al.* 2019). To date, more and more researches focus on the interaction between microorganisms and QS in wastewater treatment (WWT) systems. The mechanism of human intervention QS to regulate the physiological behavior of bacteria has been gradually revealed (Shrout & Nerenberg 2012). In addition, anammox bacteria, nitrifying bacteria and other important functional bacteria in water treatment were found to be closely related to QS (Batchelor *et al.* 1997; Burton *et al.* 2005). These previous efforts would enable researchers to fill in the gaps in the knowledge base and provide detailed information for the development of WWT.

THE SIGNIFICANCE OF QS IN WWT

QS and biofilm reactor

Biofilm is a special form of bacterial existence. The development of biofilms progresses through initial attachment, irreversible attachment, maturation I and maturation II, and are influenced by a variety of factors, including hydraulics, bacterial fluidity, and protozoa-bacterial predation (Zhang & Li 2016). By secreting polysaccharide matrix, protein and other substances, bacteria wrap themselves on the surface of matrix and form a large number of highly organized membrane-like polymers. The existence of biofilms can enhance the tolerance of bacteria to environmental pressure and provide a good environment for the survival of microorganisms. The biofilm reactor produces less residual sludge and holds many kinds of microorganisms on the surface, which have more stable operation and a strong ability to remove pollutants, making it widely developed (Masic *et al.* 2010).

In the biofilm reactor, the researchers detected a variety of AHLs signaling molecules and isolated a large number of AHLs producing bacteria. When Li *et al.* used biofilm method to treat nitrobenzoic acid wastewater, two strains that produced AHLs signaling molecules and had certain membrane forming ability were isolated (Li *et al.* 2007). Harshad Lade used *Chromobacterium violaceum CV026* and *Agrobacterium tumefaciens A136* as reported strains to screen out 200 bacteria that can generate AHLs (Lade *et al.* 2014a). According to the results of 16S rRNA sequencing, it was speculated that *Aeromonas* and *Enterobacter sp.* were dominant in the system. The detection of AHLs fully indicates that QS exists in the biofilm process under natural conditions.

With the further study of QS in real WWT facilities, it was found that there is a significant correlation between AHLs production and biofilm formation (Feng *et al.* 2013). Long-term studies on the dynamics of biofilm showed that there was a high positive correlation between AHLs and biofilm formation at the growth stage (activation stage). Nevertheless, the correlation was not significant at other stages of biofilm growth (Hu *et al.* 2016). After gene

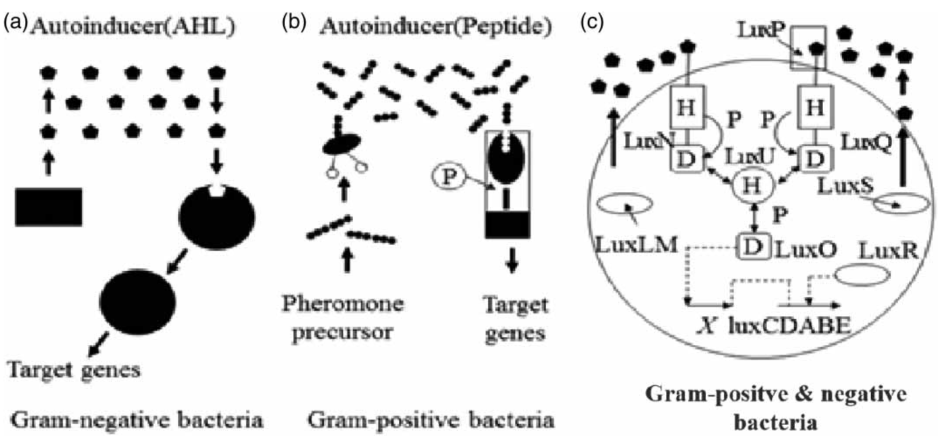
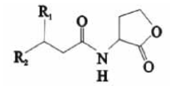
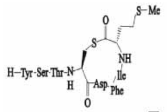
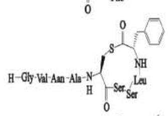
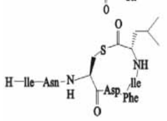
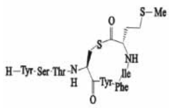
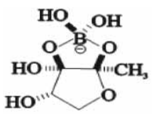
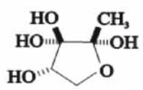
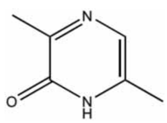
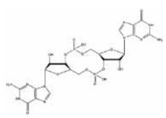


Figure 1 | Type of bacterial quorum sensing system.

Table 1 | Structure of main sensing molecules

Signal type	Structure	Source	Targets
AHLs	 R_1=–H,=O,=OH R_2=1–17C	Gram-negative bacteria, commonly produced by α-, β- and γ-*Proteobacteria*	Member of the LuxR family
Autoinducing peptides (AIPs)	   	Gram-positive bacteria	Gram-positive bacteria
Autoinducer 2 (AI-2)	 	Gram-negative & Gram-positive bacteria, commonly in *Vibrio harveyi*	Gram-negative & Gram-positive bacteria
Diffusible signal factors (DSF)		*Xanthomonas spp.*	*Xanthomonas campestris* pv. compestris
Autoinducer 3 (AI-3)		Gastrointestinal microbial flora	*Escherichia coli*
Diguanylate monophosphate (cyclic-di-GMP, second messenger)		Gram-negative and a few Gram-positive bacteria	Gram-negative and a few Gram-positive bacteria, such as some clinically important pathogens

knockout or gene silencing technology is used to process the related genes that produce signal molecules, bacteria cannot produce signal molecules, causing obvious changes in their physiological behaviors and affecting the formation of biofilms. When the bacteria lost the QS system after mutation, the biofilm formed was thinner, flat and lacked three-dimensional structure, and the mutant strain was more sensitive to biocide than the normal strain. After adding AHLs to this system, the biofilm structure was restored (Davies *et al.* 1998). In addition, it usually takes a long time to form stable biofilms in the biofilm process and at the initial stage of formation biofilm fall off easily, which seriously affects the treatment efficiency during this period. QS-based regulation can accelerate the start-up time of biofilm process, and enhance the impact resistance of the system, thereby improve the stability of the whole system (Hu *et al.* 2016). It has been known that the formation, development and functional regulation of most bacterial biofilms are mainly achieved through QS to promote the production of bacterial extracellular polymers (EPS). AHLs concentration was also closely related to EPS content, especially extracellular polysaccharide (PS) content. If EPS is inhibited, the formation of biofilm will be inhibited (Lade *et al.* 2014a). Therefore, with only a few exceptions, QS-driven EPS plays a major role in biofilm formation.

After discovering the influence of QS on biofilms formation, researchers began to pay attention to the regulation of QS on the efficiency of WWT. What's more, they tried to regulate certain functions by artificially interfering with the QS of bacteria so as to improve the treatment efficiency of the system. In the experiment of treating aquaculture wastewater with biofilm, researchers added AHLs signaling molecules (*N*-hexanoyl-homoserine lactone (C6-HSL) and *N*-3-oxo-octanoyl-homoserine-lactone (3-oxo-C8-HSL)) to the system to promote the QS (Sun 2012). The addition of AHLs significantly increased the biomass on the biofilm, and the factor analysis of the aquaculture water with SPSS software showed that the internal environment was significantly improved. According to the study of Valle *et al.*, by adding 2 μmol/L AHLs to the biofilm system for treating methanol wastewater, methanol decomposition rate increased, and the community composition, bacterial diversity and community function also changed (Valle *et al.* 2004). However, exogenous AHL signal molecules are not concentration-dependent signals. Adding a low dosage (5 nM) of mixed AHLs showed an increase in biofilm activity, which resulted in better pollutant removal performance, whereas a high dosage (50 nM and 500 nM) limited pollutant removal, especially COD and nitrogen removal. Previous studies indicated that bacterial communities can coordinate their behavior through QS and, consequently, regulate cell physiology as a feedback of population density. The high levels dosage of AHLs into the bioreactor would necessarily change the state of the bacteria, and thus potentially stimulate the activity of competing bacteria that do not contribute significantly to pollutant removal. From the above, it is not advisable to add AHLs signal molecules blindly. Introducing a parallel-system concentration of AHLs can significantly improve the activity of bacteria and the pollutant removal rate.

QS and membrane bioreactor

Membrane bio-reactor (MBR) is a type of water treatment technology which combines membrane separation unit and biological treatment unit (activated sludge). It solves the problems such as poor solid–liquid separation effect, easy loss of biomass, high yield of sludge and large occupation area (Meng *et al.* 2009; Drews 2010). However, membrane biofouling keeps restricting the wider application of MBR since its emergence (Gao *et al.* 2011).

MBR membrane biofouling is the result of the interaction between membrane and sludge. Bacteria form biofilm on the membrane surface to block the pores of membrane material, leading to the decrease of membrane flux and water yield. Therefore, membrane components need to be cleaned, but frequent cleaning will cause deterioration of membrane performance (Yeon *et al.* 2009; Feng *et al.* 2013). Based on the importance of QS system for Gram-negative bacteria, it is not surprising that some hosts or competing bacteria would benefit from inhibiting QS activity. The technique blocking QS system and inhibiting gene expression mediating bacterial behaviors is called quorum quenching (QQ), which is considered to be an ideal approach for membrane biofouling control (Malaeb *et al.* 2013). QS and QQ are two antagonistic processes that are common in WWT. The phenomenon of AHL-based QS or QQ in biological wastewater treatment can be determined by the concentration of AHL in bacteria, while the effective AHL concentration is affected by extracellular environmental factors of bacteria (Platt & Fuqua 2010; Maddela *et al.* 2019). Apparently, the environment is of great significance to the AHL-based QS and QQ in bacteria. The shorter acyl-chains of AHL signal is favorable for hydrolysis at alkaline pH, and AHL signals require at least four carbons acyl chain to keep stable under pH conditions encountered by most bacteria (Yates *et al.* 2002; Decho *et al.* 2009). AHLs with longer acyl chains (>C12) are more resistant to alkaline lysis (Decho *et al.* 2010). Studies have also demonstrated that the AHL production in the cellular environment is highly dependent on the growth temperature and accompanied by phenotypic changes (Kirwan *et al.* 2006; Kimes *et al.* 2012). In addition, operational conditions can be profoundly important for bacterial AHL-based QS. The increase of SRT in MBR would increase the QQ effect in the system, while the QS would decrease accordingly (Yu *et al.* 2016). Many bacteria have been identified to possess QS or QQ activity in biological WWT (Table 2). The QQ approach disrupts the formation of biofilm at the source, thus provides a new idea to solve the biofouling in MBRs.

In principle, interference with QQ approach is primarily achieved by three major ways (Rampioni *et al.* 2014; Zhang & Li 2016): (1) Inhibiting biosynthesis of signal molecules. (2) Simulation of signal molecules (using analogue of signal molecules to bind to receptor proteins instead of signal molecules). (3) Signal molecules are inactivated by quenching substances. These methods seem to be

Table 2 | Quorum sensing bacteria and quorum quenching bacteria present in biological wastewater treatment

Type	Bacterial genus	Signal type	QS/QQ-regulated activities	Sources	References
Quorum sensing bacteria	Acinetobacter	3-oxo-C12-HSL	Biofilm formation; biofilm development; surface motility	Activated sludge; wastewater	Jorgensen & Pauli (1995), Niu *et al.* (2008), Gaddy & Actis (2009), Clemmer *et al.* (2011)
	Aeromonas	C4-HSL, C6-HSL, AI-2	Biofilm formation; biofilm development	Activated sludge	Lynch *et al.* (2002)
	Bacillus	AI-2	Sporulation	Activated sludge	Dias & Bhat (1964), Perego & Hoch (1996)
	Comamonas	Unknown	Hormone degradation	Activated sludge	Dias & Bhat (1964), Pruneda-Paz *et al.* (2004)
	Corynebacterium	AI-2	Unknown	Activated sludge	Dias & Bhat (1964)
	Nitrobacter	Unknown	Unknown	Nitrifying-denitrifying activated sludge	Juretschko *et al.* (2002), Starkenburg *et al.* (2006)
	Nitrosomonas	C6-HSL, C8-HSL, C10-HSL	Unknown	Nitrifying-denitrifying activated sludge	Juretschko *et al.* (2002), Burton *et al.* (2005)
	Nocardia	Peptide	Antibiotic production (bacteriocins)	Activated sludge	Davidsen & Townsend (2009)
	Pseudomonas	C4-HSL, C6-HSL, oxo-C12-HSL, PQS	Biofilm formation; biofilm development; virulence factors production; EPS production; interspecies competition; denitrifification	Activated sludge	Jorgensen & Pauli (1995), Davies *et al.* (1998), Wagner *et al.* (2003)
	ingomonas	Unknown	Unknown	Activated sludge; wastewater	Jorgensen & Pauli (1995), Enya *et al.* (2007)
	Xanthomonas	DSF	EPS production	Activated sludge	He & Zhang (2008), Jorgensen & Pauli (1995)
Quorum quenching bacteria	Rhodococcus	C6-HSL, C8-HSL, C10-HSL, C12-HSL, 3-oxo-C6-HSL, 3-oxo-C8-HSL, 3-oxo-C10-HSL, 3-oxo-C12-HSL	Inhibit biofifilm formation in MBR	Activated sludge; biocake	Oh *et al.* (2012), Kim *et al.* (2013b), Oh (2013), Kim *et al.* (2015)
	Pseudomonas	C6-HSL, C8-HSL, C10-HSL, C12-HSL, 3-oxo-C8-HSL, 3-oxo-C10-HSL, 3-oxo-C12-HSL	Inhibit biofifilm formation in MBR	Activated sludge	Cheong *et al.* (2013), Ochiai *et al.* (2013), Cheong *et al.* (2014)
	Variovorax	C4-HSL, C6-HSL, C8-HSL, C10-HSL, C12-HSL, 3-oxo-C6-HSL	Degrade other species AHLs	Nitrifying-denitrifying activated sludge	Leadbetter & Greenberg (2000), Juretschko *et al.* (2002), Huang *et al.* (2003)
	Acinetobacter	C10-HSL	Unknown	Activated sludge	Ochiai *et al.* (2013, 2014)

conceptually simple approaches to block QS system and do not initiate the transcription expression of genes, inhibit the formation and growth of biofilms on the membrane surface, therefore delaying membrane biofouling. Compared with the theoretical research of QQ technology, the research of QQ substance based on QQ technology has greater engineering significance in the application of MBR. QQ substances mainly include furanone and its related structural analogues. The inhibition effect of furanones was mainly due to its similar structure with AHLs, and the biosynthetic pathway of AI-2 was also destroyed by covalent modification and inactivation of LuxS (Zhang & Li 2016). QQ substances mainly come from quenching agents extracted from plants, quenching enzymes obtained from animals and quenching sterilization from microorganisms.

Studies have confirmed non-toxic quenchers extracted from plants have similar structures to signal molecules, thus can replace signal molecules to bind to receptor proteins. Moreover, some quenchers could also reduce the activity of receptor proteins and therefore interfere with bacterial QS. Researchers found that tea polyphenols extracted from roses reduced the amount of bacteria biofilm (Zhang *et al.* 2014). Vanillin extracted from vanilla bean can interfere with AHLs receptor and inhibit the formation of *Aeromonas hydrophila* biofilm (Ponnusamy *et al.* 2009). In addition, quenchers were also extracted from garlic and black fungus (Choo *et al.* 2006; Li *et al.* 2012).

In recent years, QQ enzyme has been used in quenchers due to the complicated steps of extracting QQ substances from plants. At present, there are four major enzymes that have been found that can degrade AHLs: high serine cycle-lactase, high serine cycle-acyltransferase, decarboxylase hydrolyzed lactone ring and deaminase. Yeon *et al.* added high serine cycle-acyltransferase to MBR, reducing EPS concentration and QS activity, thereby delaying the formation of biofilm (Yeon *et al.* 2009). It should be noted that enzyme loss and limited service life are problems when enzymes are directly added into the reactor, which is not conducive to the continuous operation of the reactor. Enzyme immobilization appears to be a conceptually simple approach. QQ enzyme (e.g. high serine cycle-acyltransferase) was usually fixed in various carriers (e.g. sodium alginate capsule or nanofiltration membrane) and was putted into MBR reactor (Kim *et al.* 2011; Wei *et al.* 2013). This approach inhibited the formation of biofouling in MBR and changed the characteristics of sludge, resulting in better sedimentation and less EPS secreted. In the meantime, the addition of enzyme did not affect the treatment of the reactor.

In fact, previous researches have confirmed that a large number of bacteria can produce QQ enzyme. Considering the high cost of extraction and purification, as well as poor stability of enzyme, researchers intended to use interspecies QQ of bacteria as an efficient and economically feasible antibiofouling strategy, so as to maintain the stability and long-term effectiveness of QQ enzyme (Oh *et al.* 2012; Kim *et al.* 2013a; Lade *et al.* 2014b). The recombinant *Escherichia coli* that could produce QQ enzyme had been proven to be effective for inhibiting biofouling in a laboratory scale MBR, since the increase of transmembrane pressure (TMP) was delayed and the effluent index did not deteriorate (Oh *et al.* 2012). Although colony QQ bacteria is more economical and stable than enzyme addition, the invading strains may not survive well in real MBR, so more attention is focused on indigenous QQ-produced bacteria. *Rhodococcus sp.* BH4 was found in a real MBR, and the results of injecting it into the submerged MBR showed that it took about 115 h to reach the TMP of 50 kPa, which was 2.875 times longer than that of the control group without *Rhodococcus sp.* BH4 to reach the same TMP (Oh 2013). *Pseudomonas* 1A1 was also found in the batch test of MBR, which has higher QQ performance than *Rhodococcus sp.* BH4 (Cheong *et al.* 2013). The embedding of this bacteria into MBR showed that the long chain AHLs was degraded, and the QQ enzyme secreted by the bacteria could be transmitted to the outside of the cell, directly exerting the QQ effect and realizing *in situ* regulation of membrane biofouling. Considering that only soluble AHLs could diffuse into the fixed vessel and be degraded, free-moving beads that can trap the QQ bacteria exhibited better performance (Kim *et al.* 2013b, 2015). Although some achievements have been made in the regulation of MBR based on the QQ technology, the available strains, bacterial adaptability as well as its quenching effects on MBR are limited at present, so a lot of research should be studied in the future.

Membrane biofouling has always been a obstacle in MBR WWT. Since 2009, studies on the control of membrane biofouling by AHL-based QQ have shown a trend from free enzymes to immobilized enzymes, from QQ enzymes to QQ bacteria, and from pure bacteria to indigenous bacteria in wastewater. In fact, the solutions mentioned above, such as enzymatic treatments, had achieved certain results in experimental process, but had not been applied in practical engineering. Current research has shown that it is not enough to pour enzymes into the reactor and hope to alleviate biofouling. Therefore, the transformation of QQ technology in practical engineering results is an important research direction in this field.

QS and granular sludge

Granular sludge is a special form of biofilm. Most previous studies focused on the influences of changing environmental conditions and sludge physicochemical properties on EPS, surface charges, hydrophobicity and microbial communities in the granulation process. In fact, the regulation of QS on biofilm is also applicable to the granulation process of sludge (Tan *et al.* 2015; Maddela *et al.* 2019). The role of QS in the process of flocculent sludge granular was primarily positive, and mainly includes: QS can accelerate the synthesis of EPS, improve the synthesis rate of adenosine triphosphate (ATP), increase the content of EPS in the system, thus accelerating the formation of granular sludge and increasing the stability of granular sludge structure (Huang *et al.* 2019). The extracellular protein (PN)-extracellular polysaccharide (PS) framework in EPS serves as the foundational scaffold to promote bacterial adhesion and formation of granules.

The microbial community of granular sludge is composed of abundant species and has various metabolic functions, showing community level together, and signal molecules are the key connector of these communities. At present, the signal molecules in granular sludge system are mainly intraspecific (AHL), interspecific (AI-2) and diffusible signal molecule (DSF). Since the molecular weight was inversely proportional to solubility, short and medium acyl chain AHLs were mostly distributed in the aqueous or mixture phase, while long acyl chain AHLs were more likely to adhere to the surface of particles. The distribution of AI-2 in solution was relatively straightforward, with over 80% of AI-2 distributing in the aqueous phase. DSF was more likely to exist in sludge, with only less than 10% of DSF in water, indicating that DSF has better solubility in organics (Valle *et al.* 2004; Feng *et al.* 2014).

Aerobic granular sludge

Aerobic granular sludge (AGS) has become a hot research topic due to its excellent settling ability, good anti-shock loading capacity and treatment efficiency compared with traditional activated sludge (Pronk *et al.* 2015). In fact, activated sludge is usually used as the seed for cultivating aerobic granular sludge (Feng *et al.* 2013). Many studies have reported the fundamental characteristics and cultivation methods of AGS. However, the formation mechanisms of AGS are still unclear. There is increasing evidence that QS plays substantial roles in granules formation and stability. In the granule interior, a dense signal molecule network is exhibited by AHL, presenting good performance in inducing biofilm formation and microbial granulation (Valle *et al.* 2004). Furthermore, the concentration of QS signal molecule keeps increasing during aerobic granulation. More signal molecules are measured in mature granules than in relatively small-diameter granules (Xiong & Liu 2010; Liu *et al.* 2016). The growth rate of biofilm synthesis is greatly increased to more than 10 times the initial stage (Zhang & Tay 2015). Therefore, signal molecules are crucial to the maturation of aerobic particles. In addition, signal molecules still induce the adhesion growth and accumulation of suspended bacteria to form mature granules, which helps to maintain the stability of granule structure and accelerate the formation of granules (Liu *et al.* 2016). Exogenous addition also proved the important role of QS signal molecules in AGS. Ren *et al.* found that the increase of QS potency in the initial stage significantly promoted the formation of AGS, indicating that exgenous AHLs addition to the systems may promote the acclimation of AGS (Ren *et al.* 2010). After adding AHLs-degradation enzyme to the reactor, the stability of granular sludge was destroyed (Li *et al.* 2014; Li *et al.* 2017).

At present, researches on QS regulation behavior in AGS mainly focus on AI-2 and AHLs signaling molecules. The concentration of AI-2 was not constant in the system (Zhang *et al.* 2011). Xiong *et al.* found in the study of AGS process that there is a certain correlation between AI-2 concentration and particle size, which preliminarily proved that AI-2 could promote the maturation and maintenance of morphological integrity of AGS. As the regulators for EPS production, AI-2 can lay a foundation for the maintenance of AGS (Xiong & Liu 2012). In the process of full-scale WWT, the operating conditions are relatively complicated, therefore, the relationship between molecular content and EPS production should be studied from the perspective of alternating starvation time and organic load rate (OLRs), which is conducive to the conversion of flocculated sludge into granular sludge, so as to maintain their integrity. EPS content was positively correlated with AI-2 level during aerobic granulation and the increase of AI-2 could lead to the moderately high secretion of large molecular weight EPS during the long starvation period (Liu *et al.* 2016). Similar results were obtained under the variable OLRs condition. Sun *et al.* found that AI-2 could enhance bacterial adhesion by regulating the secretion of certain EPS by bacteria, which ultimately led to the formation of AGS. In addition, the activity of AI-2 increased significantly after adding boron in SBR reactor, which promoted the formation of AGS (Lv *et al.* 2014; Sun *et al.* 2016). Adding boron may promote the formation of 4,5-dihydroxy-2,3-pentanedione (DPD), the precursor of AI-2.

In addition to AI-2, AHL also plays an important role in AGS. The length of AHLs was mainly varies between 4 and 10 carbons (Ren *et al.* 2013). Meanwhile, the content of AHLs varied with the formation of AGS. At the initial stage of AGS formation, 3-oxo-C8-HSL dominated in the system, and then the content of *N*-butanol-hyperserine lactone (C4-HSL) and C6-HSL increased gradually, while the content of some AHLs, i.e. *N*-(b-ketocaproyl)-L-homoserine lactone (3-oxo-C6-HSL), *N*-heptanoyl-lactone homoserine (C7-HSL), *N*-Octanoyl-L-homoserine lactone (C8-HSL) and 3-oxo-C8-HSL decreased. When the particles formed steadily, the content of all AHLs increased further and the downtrend of AHLs happened when the particles began to disintegrate, AHL content began to decline (Li *et al.* 2014). AHLs content increased synchronously with the quantity and particle size of AGS (Li & Zhu 2014).

Some studies had demonstrated that EPS has a significant impact on the physical and chemical properties of microbial biomass, and can promote the formation of AGS by binding cells tightly (Shi *et al.* 2017). Therefore, the performance of EPS was an important factor to consider the role of QS in sludge granulation. Jiang *et al.* first reported that AHLs signaling molecules participate in the formation of AGS, and found a significant correlation between AHLs concentration and EPS yield (Jiang & Liu 2013). The synthesis of biosurfactants and EPS, as well as microbial surface adsorption mediated by QS, affect AGS formation. The results of Tan's study further confirm this conclusion, that is the comparatively high production of ATP and EPS based on QS may enhance the stable and integral structure of AGS (Tan *et al.* 2014; Maddela *et al.* 2019). The addition of AHLs (C6-HSL, 3-oxo-C6-HSL, 3-oxo-C8-HSL and *N*-(3-oxododecanoyl)-hyperserine lactone (3-oxo-C12-HSL)) to the system can increase the content of PS and PN, and the PS/PN ratio also increased correspondingly. However, the addition of C4-HSL accelerated PN only. According to the above, the change of AHLs content in sludge would lead to the variation of sludge system, while the influence of single AHL may not be as significant as that of mixed AHL.

QS inhibitors or QQ inhibited the function of bacterial QS, which affected the formation of AGS, proving that AHLs promoted the formation of AGS on the other hand. Lv *et al.* studied the effects of QS and extracellular proteins on the adsorption of cells to AGS (Lv *et al.* 2014). After adding vanillin and protease K to the system, the biomass adsorbed to AGS decreased significantly, and the content of AHLs and extracellular proteins were significantly reduced, revealing that the effect of AHLs on microbial adhesion to AGS was achieved by regulating extracellular proteins. When studying the role of AHLs in AGS by QQ method, the researchers found that inhibition of acyltransferase reduced the content of AHLs and thus weakened the adhesion ability of microorganisms (Li & Zhu 2014). There are multiple AHLs-produced bacteria and AHLs-quenched bacteria in AGS system, which regulate and control community behaviors *in situ*. However, in terms of physical properties, the effects of exogenous enhancement of these bacterium on the reactor during the granulation were insignificant or slighty negative.

According to existing studies, the effect of QS on the stability and treatment efficiency of AGS system was presented as follows: (1) strengthening granular sludge core; (2) influence on the morphology of granular sludge; (3) enhance biological activity; (4) increase EPS secretion and PS&PN content to promote bacterial adhesion. QS-based regulation may be a new technology to promote AGS formation and maintain granular stability. Nevertheless, there are still some challenges and knowledge gaps that warrant targeted research in the future, such as the ecological niche in AGS, the effect of multiple signals combined on transformation of sludge granulation.

Anaerobic granular sludge

Compared with AGS, the quorum sensing of anaerobic granular sludge (AnGS) is more complex and has not yet formed a relatively complete regulatory mechanism. In AnGS system, the research focused on AHL, AI-2 and DSF. The main AHLs was C4-HSL, accounting for more than 95% of total AHLs, and the concentration of total AHLs was 5.72 ± 1.56 pM/L (Ding *et al.* 2015b). With the formation of AnGS, the content of C4-HSL decreased significantly. The content of AI-2 was relatively stable in the system, with relative value of 0.58 ± 0.06 (relative light unit: the intensity of the sample at 490 nm compared to that of the negative control) (Song *et al.* 2014; Servinsky *et al.* 2016; Zhao *et al.* 2018). The concentration of DSF is not stable in the system, whose initial concentration was 0.66 ± 0.06 nM/L and then increased to 1.76 ± 0.18 nM/L reaching the peaks (Wang *et al.* 2004).

The particle size of AnGS would increase under AHL-based QS regulation. AnGS with large particle size was of higher biological activity, and its internal structure was characterized by high porosity, macrovoid, low diffusivity and small diffusion area, so it could improve biogas production (Wu *et al.* 2016). However, when exogenous

AHL-producing and quenching bacteria were added to the system, the particle size of the addition groups were smaller than that of the control group (no addition), indicating that the method of directly adding AHL-producing and quenching bacteria need to be further clarified. This might be because the added strains were less competitive with native bacteria and were not dominant in the system, resulting in the destruction of the original bacterial community structure. AI-2 also promoted the granular diameter growth throughout granulation process, while the regulation of DSF tended to develop granular sludge with low particle size (Ding *et al.* 2015b). Under neutral or weakly alkaline conditions, the increase of AI-2 content and the decrease of DSF in the system will enhance the relative hydrophobicity and the strength of the granular sludge, increase the particle size of the granular sludge and facilitate the formation of granular sludge; however, under the condition of nitrogen supply imbalance, the decrease of AI-2 content and the increase of DSF content significantly reduced the hydrophobicity and particle strength of the granular sludge, and finally resulted in the degradation and particle size reduction of the granular sludge under nitrogen rich/poor conditions (Ding *et al.* 2015a, 2016).

The production of EPS and the process of granular sludge were also closely related to the type, distribution, and content of signal molecules. Ding's study further confirmed that AI-2 can promote EPS production and increase the diameter of granular sludge (Ding *et al.* 2015b). In addition, AHLs could promote the growth of Methanothrix in the upflow anaerobic sludge bed reactor (UASB), thus significantly improving the granulation of sludge and the operation efficiency of the reactor. Introducing specific AHLs can heighten the removal ability of organic matters and methanation ability in AnGS, and meanwhile, exogenous AHLs played an important role in regulating the concentration of EPS and the structure of microbial community, thereby enhancing the performance of AnGS (Li *et al.* 2015; Lv *et al.* 2018). Due to the complexity of AnGS system, no relatively complete conclusion has been drawn on the formation of AnGS in the current research. However, the discovery of QS provides a new idea to clarify the formation mechanism of AnGS, which will catch more attention in future research.

EFFECT OF QS ON FUNCTIONAL BACTERIA

At present, many QS bacteria have been identified in WWT systems, including some important functional bacteria in sewage, such as anaerobic ammonium oxidation bacteria (AnAOB), ammonia oxidizing bacteria (AOB) and nitrite oxidizing bacteria (NOB).

AnAOB

Anaerobic ammonium oxidation (anammox) process has become a new technology in WWT system due to its high efficiency and low energy consumption. The process is AnAOB directly converting nitrite into nitrogen by using ammonia nitrogen as an electron donor under anoxic condition without organic carbon source and O_2. Although many full-scale anammox installations have been built, there are bottlenecks in the practical application of anammox. On the one hand, AnAOB needs to reach the threshold of cell density to show its activity, which leads to the slow start of anammox process. On the other hand, AnAOB bacteria have a long generation cycle, making them at a disadvantage in competition, and the rapid proliferation of heterotrophic bacteria can easily lead to system collapse. The results and stability of traditional methods such as biofortification and optimization of bioreactor structure are not always satisfactory. The emergence of QS-based technology provides a new way to solve these problems.

The physiological metabolism of AnAOB is peculiar, with biological agglomeration behavior, and anammox activity can only be shown when the cell density is higher than 10^{10}–10^{11} cells/mL (Figure 2). This density-dependent effect is consistent with QS (Ni *et al.* 2010; Ding *et al.* 2012). The researchers conducted in-depth studies on the activity jump and self-aggregation characteristics of AnAOB, and proved that there are related genes encoding

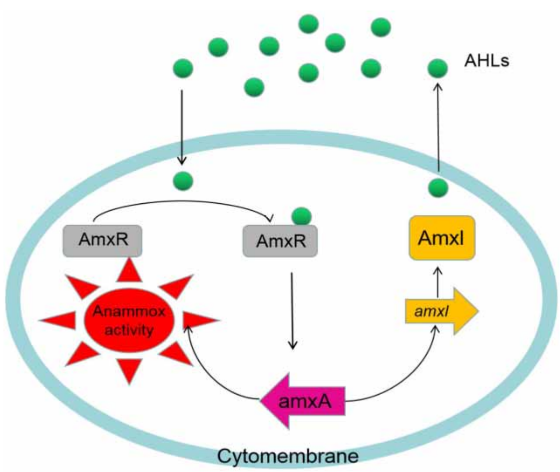


Figure 2 | Hypothetical quorum sensing system controlling the anammox activity in AnAoB.

signal molecule synthase in AnAOB from the perspective of genomics, further proving the QS mechanism in AnAOB (Strous *et al.* 2006). Subsequently, more and more signal molecules were detected, directly demonstrating the existence of QS in the anammox system. At present, the researches on QS signal molecules in anammox system focuses on AHL and second messenger molecule bis-(3′-5′)-cyclicdimeric guanosine monophosphate (c-di-GMP).

QS is of great ecological significance for organisms because QS systems usually play a vital role in the rational use of resources and space in microorganisms (An *et al.* 2014; Zhao *et al.* 2019). AnAOB always coexist with other bacteria in a variety of ecosystems, competing with the symbiotic for space and substrates (Ding *et al.* 2013). QS can regulate the accumulation of AnAOB and thus occupy more resources and space, making AnAOB become the dominant bacteria. In addition, environmental factors and operational conditions profoundly affect AHL function. When studying the anammox rate of OLAND biofilms, De Clippeleir *et al.* found that adding signal molecule *N*-dodecanoyl-L-homoserine lactone (C12-HSL) could enhance the activity of AnAOB, but the effect on AOB was limited (Clippeleir *et al.* 2011). Another study detected three different kinds of signaling molecules, C6-HSL, C8-HSL and C12-HSL in AnAOB, and revealed the effect of different signaling molecules on AnAOB by adding signaling molecules into the anammox system at the same time, among which C8-HSL can significantly improve the activity of AnAOB, C6-HSL cannot only improve the activity of AnAOB, but also significantly improve its growth rate, while C12-HSL promotes the growth of heterotrophic bacteria in the community and reduces the activity of AnAOB (Tang *et al.* 2015). In these two studies, exogenous addition of C12-HSL had opposite effects on AnAOB, which may be caused by differences in system operating conditions and bacterial flora structure. Except for C12-HSL, many studies have shown that AHL-like signaling molecules have a positive effect on the anammox system (Liu *et al.* 2018; Tang *et al.* 2018). Researchers also found that QS in AnAOB is not only associated with AHL, but also with c-di-GMP which is ubiquitous in bacteria. It can interact with signal molecules secreted by QS to form a complex signal transmission network, receive extracellular signals and participate in regulating a variety of physiological functions, such as the formation of biofilms, adjusting the synthesis of EPS (Hengge 2009; Guo *et al.* 2017). These above phenomena indicate that QS of AnAOB can regulate the formation of its biological aggregates.

Quorum sensing has great potential in promoting the rapid start-up of anammox system, which is mainly reflected in the following aspects: (1) increase the growth metabolic rate of AnAOB. QS regulation of the growth metabolism of AnAOB has been confirmed in many studies, and the regulation of AnAOB was at gene level (Tang *et al.* 2015; Liu *et al.* 2018; Tang *et al.* 2018); (2) increase the activity of AnAOB. By adding 150 LM C6-HSL into UASB reactor, the activity of anammox granular sludge was increased by 16% (Zhang *et al.* 2019). Tang *et al.* Found that adding 2 μM of 3-oxo-C6-HSL, C6-HSL and C8-HSL increased special anammox activity (SAA) by approximately 10% (Tang *et al.* 2018); (3) increase the secretion of EPS. QS can regulate EPS content metabolically by mediating the synthesis of uridine diphosphate – N-acetylgalactosamine (UDP-GLcnac). The increase of EPS will promote the formation of AnAOB biofilm and particles, while the formation of granular sludge is conducive to the shortening of start-up time and stable operation of Anammox process (Guo *et al.* 2017; Tang *et al.* 2018). In addition, AI-2 signal molecules also have an impact on the anammox process. After adding boron, a AI-2 activation factor, the start-up time of the anammox process is shortened, and the synthesis of EPS is promoted, making the structure of granular sludge in the system denser.

Current research shows that QS mediated function has great potential to improve practice, although QS cannot solve all the problems of anammox process. Due to the lack of pure culture of AnAOB, the existing researches on QS signal mechanism are still insufficient. How to use QS to improve the pure culture of AnAOB, granulation of sludge and the activity and sedimentation of sludge is the focus of future research. In addition, due to the complex composition of actual wastewater, multiple signals exist in anammox systems, such as AI-2 and DSF. Through the in-depth study of QS in anammox community, it is helpful for us to better understand the relationship between AnAOB and other symbiotic bacteria, and further promote the better application of anammox process.

Nitrifying bacteria

At present, a variety of microorganisms related to nitrogen cycle have been found to be affected by QS, among which the nitrogen-fixing microorganisms living in the rhizosphere of plants in soil have been studied thoroughly (Wei & Zhang 2006). When roots, microorganisms and soil animals come into contact with each other, signaling molecules often act as intercellular signals to establish communication.

In the process of nitrogen fixation, the symbiotic interaction between rhizobia and host plants depends on the chemotaxis regulated by AHL, the production of exopolysaccharides and the symbiotic plasmid transfer.

Many nitrifying bacteria in WWT system were found to have QS, and the correlation between nitrifying bacteria and QS was confirmed by gene sequencing technology (Daims *et al.* 2015; Van Kessel *et al.* 2015). AHL has been detected in the supernatant of various nitrifying bacteria, such as *Nitrosomonas europaea* and *Nitrosospira multiformis* of ammonia-oxidizing bacteria (AOB) and *Nitrobacter Winogradskyi* of nitrite oxidizing bacteria (NOB) (Mellbye *et al.* 2015).

Nitrosomonas Europaea as one of the most studied QQ-AOB, has been detected secreting at least three types of AHLs (C6-HSL, C8-HSL, and *N*-decanoyl-homoserine lactone (C10-HSL)) (Burton *et al.* 2005). Although some nitrifying bacteria do not produce AHLs (without AHLs synthase gene, with AHLs receptor gene), they can take advantage of exogenous AHLs. Studies have shown that the biofilm formation of *Nitrosomonas europaea* is closely related to population induction, but no AHLs synthase homolog has been detected in this bacterium, suggesting that it may synthesize AHLs in another way (Burton *et al.* 2005). When *Nitrosomonas europaea* is in a starvation state, the addition of QS signal molecule can help it to restore its activity rapidly, indicating *Nitrosomonas europaea* can make use of exogenous signal molecule (Batchelor *et al.* 1997). *Nitrosospira multiformis* is also a model organism of AOB. A complete genome analysis in *Nitrosospira multiformis* had revealed that this bacterium has LuxI/R QS signal synthase and regulator, and the synthase homologous sequence is successfully expressed in the *Escherichia coli* system, which can produce C4-HSL and *N*-(3-oxotetradecanoyl)-L-homoserine lactone (3-oxo-C14-HSL) signal molecules (Norton *et al.* 2008). However, due to its own AHLs degradation system, the presence of signal molecules could not be detected in the original bacteria. At the same time, adding AHL to the system can improve the ammonia oxidation rate (Gao *et al.* 2014).

The mechanism of QS in NOB is mainly based on a key species, *Nitrobacter winogradskyi* Nb-255. Similar to the research strategy of AOB, the putative QS regulatory system in *Nitrobacter winogradskyi* Nb-255 was found through genome analysis. The *nwi*0626 and *nwi*0627 genes encode a functional two-component regulatory system (including the AHL synthase Nwil and the postulated AHL receptor transcriptional regulator NwiR) was shown to be cell density dependent. Two kinds of AHLs were confirmed secreting by *Nitrobacter winogradskyi* Nb-255: C10-HSL and a monounsaturated AHL with 10 carbons and a double bond between carbons 9 and 10 in acyl chain (Mellbye *et al.* 2015). The introduction of *nwiI* in *E.coli* could produce AHLs, including C7-HSL, C8-HSL, *N*-nonanoyl-lactone homoserine (C9-HSL), C10-HSL, and a new AHL signaling molecule C10:1-HSL (7, 8-trans-n-decanoyl-homoserine lactone) (Shen *et al.* 2016). Moreover, adding C10:1-HSL to the system promoted the use of nitrite and improved nitrification of the system.

Adding AHLs to autotrophic nitrifying sludge are the potential approaches for improving the nitrification effect. Studies have preliminarily explored the roles of different AHLs in bacterial adhesion, nitrification rates and sludge granulation, and found that C6-HSL and 3-oxo-C6-HSL significantly promoted bacterial adhesion and ammonia-oxidation by changing the composition of EPS (Li *et al.* 2015). In addition, exogenous AHLs was found to promote ammonia oxidation rate, as well as increased number of amoA genes at low temperature (Hu *et al.* 2017). Yu *et al.* found that adding QQ enzyme to the MBR to inhibit QS would reduce the nitrification effect (Yu *et al.* 2018). These studies indirectly proved the importance of QS to nitrification.

The current studies only preliminarily discovered the potential regulation behavior of QS and the AHL-producing ability on nitrifying bacteria. However, note that not all bacteria with LuxI/R homologs by database analysis and genome sequencing produce AHLs in pure culture. There is no in-depth study on the specific regulatory mechanism and metabolic mechanism of nitrifying bacteria. Future breakthroughs in these aspects will help overcome the bottleneck of poor competitiveness of nitrifying bacteria in the environment and thus improve the denitrification effect.

Heterotrophic denitrifiers

Understanding the roles of QS in heterotrophic denitrifiers has significant importance in the promotion of nitrogen removal, especially in the case of carbon sources insufficient. However, unlike AOB and NOB, researches on QS in heterotrophic denitrifiers are limited, and mainly focus on *Pseudomonas aeruginosa.* It was found that *P. aeruginosa* has four QS systems, which are based on Las, Rhl, quinolone-based QS and recently determined IQS-dependent system (Lee & Zhang 2015). The AHL-mediated QS systems, i.e. *las*I/R and *rhl*I/R systems, that produce and respond specifically to 3-oxo-C12-HSL and C4-HSL, respectively (Mangwani *et al.* 2015; Papenfort & Bassler 2016; Kariminik *et al.* 2017). These two systems inhibit the denitrifying activity of *P. aeruginosa* PAO1 by down-regulating denitrifying related enzymes at the transcriptional level, while the *rhl*I/R QS system dominated the denitrifying regulation of l*as*I/R QS system (Toyofuku *et al.* 2007). The quinolone-based QS system is controlled via 2-heptyl-3-hydroxy-4-quinolone, called the Pseudomonas quinolone signal (PQS), which create a global regulatory network and regulate the expression of the *P. aeruginosa* genome up to 12%. However, PQS inhibited denitrification of *P. aeruginosa* by promoting nitrite reductase activity, and the activity of nitric oxide reductase and nitrification chain was also inhibited. In addition, when iron was supplied to the medium supplemented with PQS, denitrification activity almost recovered, indicating that the iron chelating properties of PQS influenced denitrification (Masanori *et al.* 2008). This suggested that there is more than one type of QS signal molecule that affects *P. aeruginosa* function, and the coexistence of multiple signaling molecules in the system may play a synergistic or antagonistic role. More attention should be paid to investigate multiple signal molecules' interaction with QS mechanism.

Based on the current research, it is not possible to elucidate the regulation mechanism of QS in denitrification process, although the regulatory of QS on denitrification had been confirmed in *P. aeruginosa* PAO1 bacteria. More research is required to understand the presence and the role of QS in other denitrifying bacteria, so as to reveal the regulation mechanism of QS on the denitrifying process.

CONCLUSION AND PERSPECTIVE

Basic researches of AHL signal characterization and QS & QQ mechanisms have made progress. QS and QQ have been known to regulate certain features, such as EPS production, biofilm formation, development and aggregation processes, nutrient removal, organic pollutant biodegradation and biofouling control. Considering the effects of QS and QQ in biological WWT, QS-based application has great potential in the enhancement of community cooperation during WWT process, thus improving the performance of bioreactor. These results encourage us to conduct more research to discover the unknown functions of QS-regulated strategies, which are expected to elucidate other QS-driven biochemical transformations. Also, it is important to note that these strategies are insufficient to apply in full-scale processes despite their undisputed superiority. Importantly, researches on QS mainly focus on single type of signal molecules, the interation mechanisms among multiple signals are far from being understood. Thus, the future needs and possible solutions were proposed as follows:

(1) Multitype signals in WWT. Knowledge of the coexistence of multiple types of signal molecules, such as AI-2 and DSF. They may play synergistic or antagonistic roles in the system.This phenomenon exists in a variety of WWT processes, whereas their potential roles in WWT systems are limited. Therefore, in-depth researches on various types of QS signal molecules have great ecological significance.
(2) To reduce the research gap between *in situ* and *in vitro*, exploration should be done fundanmentally at genetic and community levels and tested in full-scale reactors.
(3) In the process of WWT, the QS level should be accurately estimated to eliminate the interference caused by the coexistence of QS and QQ bacteria. The disturbance of QQ may lead to the incorrect understanding of QS.
(4) Evaluate the possible risks of QS regulation, and correctly understand the effectiveness of this method. QS approach is not a master key to solving every problem, and its application may have negative impacts on the system, as it can affect the physiological behavior of bacteria and change the structure of the microbial structure.

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DATA AVAILABILITY STATEMENT

All relevant data are available from an online repository or repositories available at http://webofscience.com/.

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