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Quorum Sensing: Biochemical Mechanisms and Implications

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ABSTRACT: Quorum sensing (QS) is a key component of microbial communication, which controls collective behaviours in response to cellular density. Microbial organisms are mainly able to coordinate a number of physiological functions, including sporulation, motility, biofilm formation, pathogenicity, antibiotic resistance, and the synthesis of secondary metabolites, by using this complex signalling system. QS depends on the synthesis, identification, and reaction to auto-inducers; which are signalling molecules. Extensive research on the molecular principles behind QS has shown highly organized systems involving a variety of chemical signals and receptor pathways in many bacterial ecosystems. The molecular support of quorum sensing, the differences across microbial species; gram positive and gram negative, molecular mechanism of signal interference which are quorum sensing inhibition and quorum quenching and the wider applications of QS in biotechnology, microbial ecology, agriculture, and medicine are all examined in this review work.

KEYWORDS: Quorum sensing, Microbial, Biofilm, Receptor, Inducer

INTRODUCTION

The process of bacterial cell-to-cell communication known as quorum sensing (QS) entails the synthesis, identification, and reaction to extracellular signalling molecules known as auto-inducers (AIs). As the bacterial population density rises, AIs build up in the environment. Bacteria keep an eye on this data to detect changes in their cell counts and collectively modify gene expression. QS regulates genes that guide actions that are advantageous when carried out by bacterial colonies functioning in unison. Bioluminescence, sporulation, competence, antibiotic synthesis, biofilm development, and virulence factor secretion are among the processes that QS regulates (Williams and Camara, 2009; Steven and Bonnie, 2012, Samman *et al*., 2020).

Auto-inducers, also known as quorum sensing molecules (QSM), are hormone-like molecules that are continuously released and monitored. This is a key mechanism of microbial communication. When these molecules reach a certain threshold, a regulatory response is set off that result in the coordinated expression or repression of QS-dependent target genes throughout the whole bacterial group. The concentration of these molecules rises in proportion to the population of bacteria (Preda and Săndulescu, 2019). According to a thorough investigation, these auto-inducing peptides cause quorum sensing in Gram-positive bacteria. They are species and strain-specific and have been seen mostly in *Clostridium, Staphylococci*, and *Enterococci*. Another family of auto-inducers that has been extensively documented in a variety of Gram-negative bacteria, especially in *Pseudomonas, Burkholderia*, and *Acinetobacter species*, are acyl-homoserine lactones (AHLs). Numerous more varied kinds of signalling molecules such as fatty acids, ketones, epinephrine, norepinephrine, AI-2, AI-3, or quinolones have been found in bacterial species (Samman *et al*., 2020; Chigozie *et al*., 2025).

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Coordinated production of virulence factors during host infection likely provides pathogenic bacteria with a major survival advantage by increasing the likelihood of infection and immune response evasion. Furthermore, because certain quorum sensing molecules (QSMs) are toxic to host cells and/or have the ability to alter host immunity, they might be regarded as virulence factors on their own (Flemming *et al*., 2016).

Types of Quorum Sensing Signal molecules

Bacterial quorum sensing involves two kinds of signal molecules. Gram-positive bacteria usually employ peptide derivatives called Auto-inducing Peptides (AIPs), whereas Gram-negative bacteria use fatty acid derivatives called N-Acyl-homoserine Lactone (AHL). Numerous known bacterial species possess quorum sensing and a number of Gram-negative bacteria that are harmful to humans and plants, such as those belonging to the genera *Agrobacterium, Brucella, Bukholderia, Erwinia, Enterobacter, Pseudomonas, Ralstonia, Serratia, Vibrio*, and *Yersinia*, use the quorum-sensing mechanism to control the synthesis of virulence components.(Williams, 2007).

This method involving signalling molecules is used by bacteria belonging to the genera *Bacillus, Enterococcus, Staphylococcus, Streptococcus*, and *Streptomyces* to create exotoxins or antimicrobial peptides, establish genetic competence, and build biofilms (Podbielski and Kreikemeyer, 2004). Quorum sensing is used by the Rhizobium genus to fix nitrogen. Complex quorum-sensing regulatory mechanisms govern the nodulation and symbiosome formation necessary for nitrogen fixation in these symbiotic bacteria (Hoang *et al*., 2004). Additionally, quorum sensing has been found in the hyperthermophilic bacterium (*Thermotoga maritime*) (Johnson *et al*., 2005), the acidophilic bacterium (*Acidithiobacillus ferrooxidans*) (Rivas *et al*., 2007), and extremophiles like the *Haloalkaliphilic archeon*, *Natronococcus occultus* and the Halomonas genus of bacteria (Paggi *et al*., 2003; Llamas *et al*., 2005).

Mechanism of Quorum Sensing

The ability to regulate the microorganism's reaction to external stimuli is one advantage that QS provides. The biodegradation of pollutants is facilitated by the QS system, which also fortifies the biotransformation pathways (Tripathi *et al*., 2022). Quorum sensing is a population-dependent process in which the signalling molecules reach a detectable level when the concentration approaches the threshold, triggering the bacterial responses (Zhou *et al*., 2020). These QS operates on the basis of three mechanistic ideas.

I. By density-dependent action: Because there are fewer signalling molecules at low cell density (LCD), the threshold level for identifying AIs is not reached. As shown in Figure 1, there are sufficient signalling molecules at High Cell Density (HCD) to create the QS between bacterial cells.
II. A bacterial cell's cytoplasm has particular receptors that recognize these signalling molecules and cause the QS activity to start.
III. More auto-inducers would be boosted when the AIs are recognized and activated (Rutherford and Bassler, 2012).

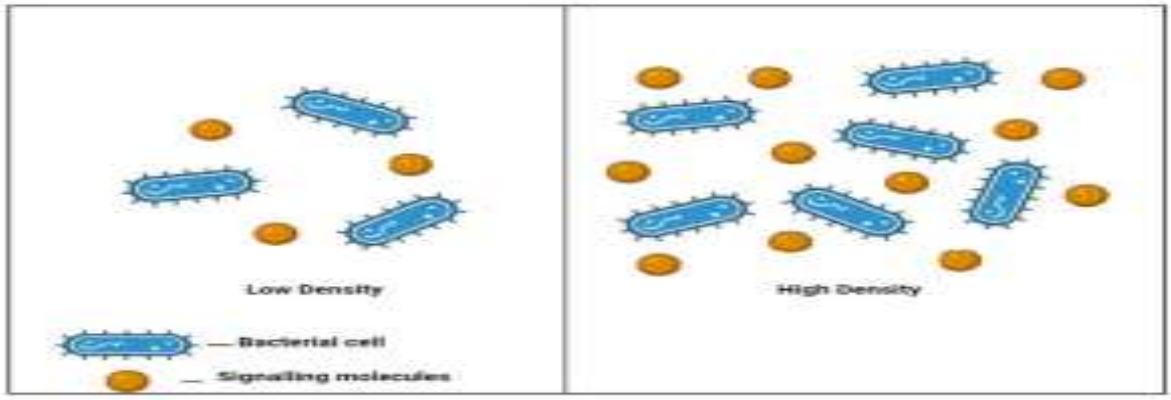


Figure 1: The signalling molecules are low and high density of the bacterial cell (Rutherford and Bassler, 2012)

Quorum sensing in Gram-negative bacteria

The LuxI (AHL synthase gene/LuxR (transcriptional regulator gene)-type quorum sensing in Gram-negative bacteria occurs through distinct operons. LuxI proteins are in charge of the biosynthesis of the signalling molecules specifically for the Homoserine lactone, while LuxR binds to the auto-inducers and activates the target gene transcription once they reach the threshold level (Figure 2). Initially, N-Acyl Homoserine Lactone (AHL) was observed in marine bacteria called *Vibrio fischeri* (Miller and Bassler, 2001).

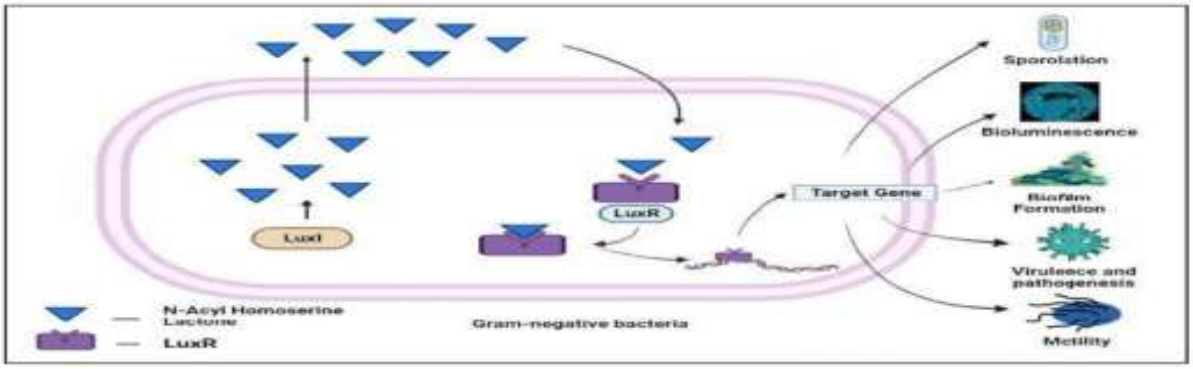


Figure 2: Quorum sensing mechanism in gram negative bacteria involves the biosynthesis of auto-inducers N-Acyl Homoserine Lactone produced from LuxI followed by the attachment of the auto-inducer on LuxR receptor which leads to target gene transcription (Miller and Bassler, 2001)

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Quorum sensing for Gram-positive bacteria

Auto-Inducing Peptides (AIPs) are the auto-inducers in Gram-positive bacteria. In their cells, Gram-positive bacteria make tiny oligopeptides. When they reach maturity, an ATP-binding cassette (ABC) transporter carries them across their cell membrane. When the AIP concentration reaches the threshold, it attaches itself to a segment of a histidine sensor kinase, which in turn triggers the kinase and histidine residue auto-phosphorylation, which then travels to a response regulator protein and triggers the expression of the gene (Figure 3) (Miller and Bassler, 2001).

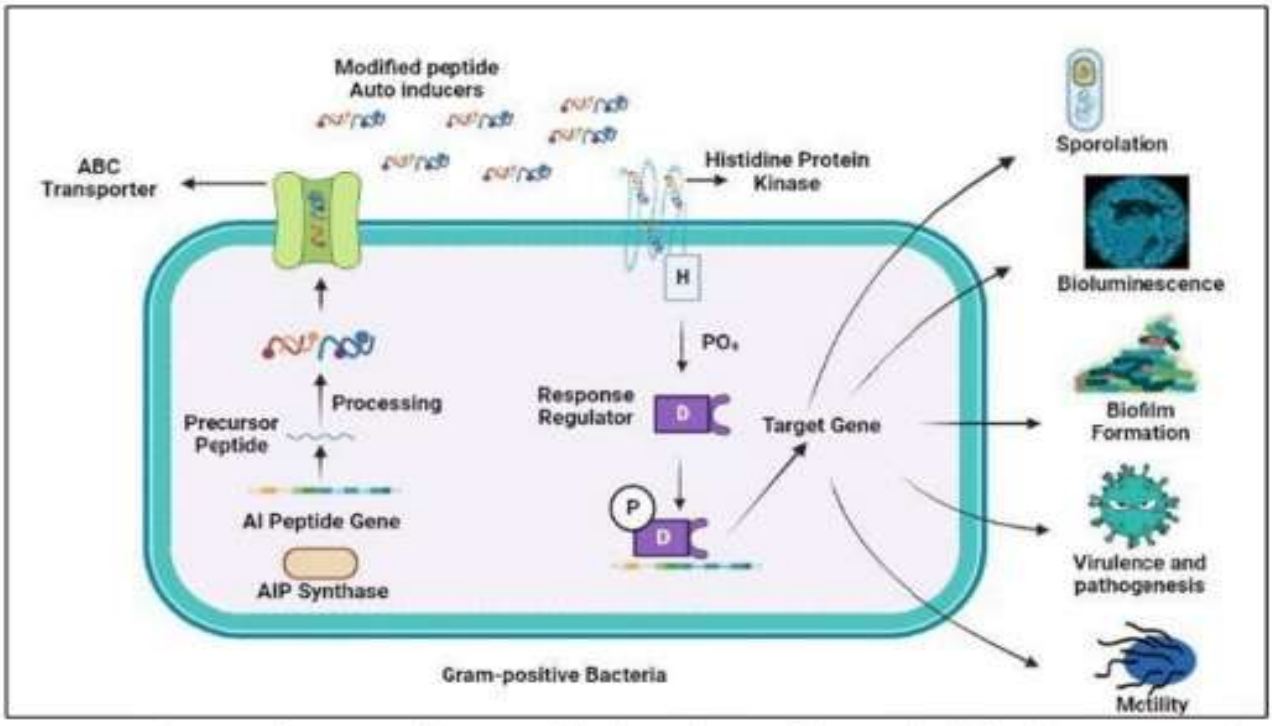


Figure 3: Quorum sensing mechanism in Gram-positive bacteria includes the production of oligopeptides (AIP) which are transported into the bacterial cell through the ABC transporter and bind to histidine sensor kinase segment. Once activated, it auto-phosphorylates and activates targeted gene expression (Miller and Bassler, 2001)

The Biochemical Basis of Quorum Sensing

Quorum Sensing in Gram-positive and Gram–negative bacteria

Gram-positive bacteria use oligopeptides as signalling molecules to form biofilms, using QS for intra-species communication. The QS system is a paramount target for the treatment of biofilm associated infections (Chen *et al*., 2016). There are at least three main types of QS systems to be distinguished: the acyl homoserine lactone QS system (AHL) in Gram negative bacteria, the auto-inducing peptide (AIP) QS system in Gram-positive bacteria and the autoinducer-2 (AI-2) system in both Gram-negative and -positive bacteria (Brackman and Coenye, 2015).

Gram-negative bacteria are the main users of the acyl homoserine lactone-dependent QS system, which is a family of significant cellular signalling molecules involved in QS. The homoserine lactone ring is shared by all AHL molecules, despite differences in length and substitutions. Interestingly, a particular cognate AHL synthetase is responsible for the synthesis of AHLs. It's interesting to note that a substantial bacterial growth was associated with an elevated AHL content (Li and Nair, 2012).

Gram-positive bacteria produce AIPs, which are signal molecules secreted by membrane transporters. When the concentration of AIPs in the environment rises, they bind to the histidine kinase sensor, phosphorylating it and changing the expression of target genes. In *Staphylococcus aureus*, quorum sensing signals are tightly controlled by the accessory gene regulator, or agr, which is linked to the secretion of AIPs (Preda and Săndulescu, 2019).

Microorganisms may perceive and translate the signals from different strains in AI-2 or auto-inducer-2 interspecific signals, which are catalysed by LuxS synthase, as part of their collaboration and communication. Additionally, LuxS has been shown to regulate the expression of hundreds of genes linked to the microbial processes of surface adherence, detachment, and toxin generation, and it is implicated in the activation of the methylation cycle (Jiang *et al*., 2019).

Molecular mechanisms messaging Quorum Sensing

Quorum sensing molecules communicate with the transcription factor receptor (ProR) and auto-inductor (ProI) proteins. It is evident that the virulence genes I and R, which are regulated by the protein complex RI, govern the message system. When there is too much ProI in the system, the transcription regulatory feedback process is enabled or disabled by the complex, *RI*, *ProR*, and *ProI* genes. The increase in AIs production is caused by the ProR transcription factor (Preda and Săndulescu, 2019).

Quorum Sensing in *Vibrio fischeri*

When the bacteria enter the tissues and build up to volume of 10^{11}ml, cephalopods become lighted. The luciferase gene is activated by the chemical produced by AHL, which results in nighttime light. LuxR is homologous to ProR, while LuxI is homologous to ProI. Together with the regulation of RI, LuxI, and LuxR of the genes involved in light generation, these two proteins were created (Figure 4), (Boban *et al*., 2023).

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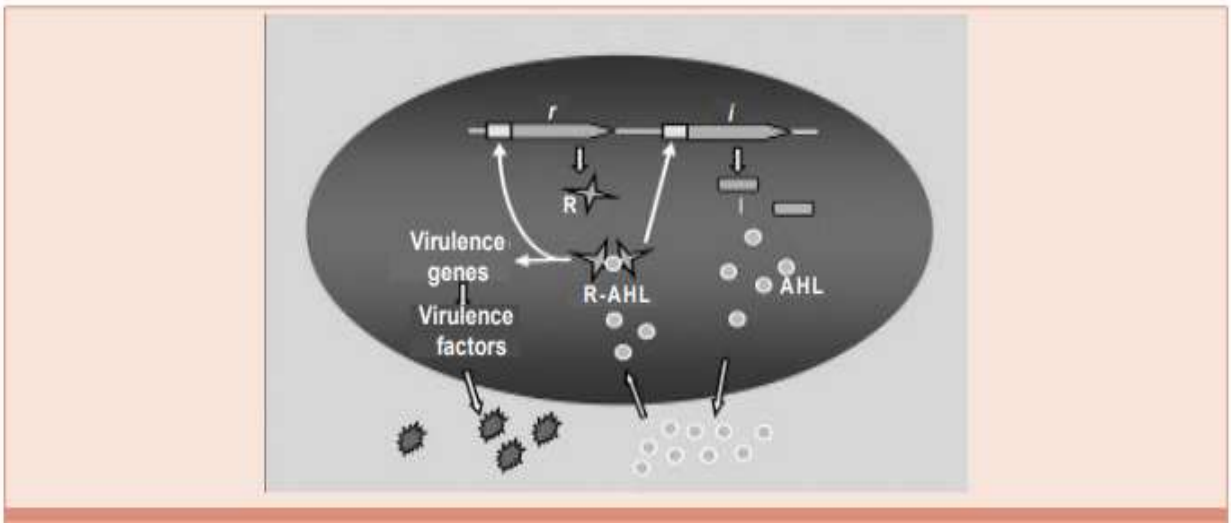


Figure 4: Molecules involve in signalling by QS (Saghi *et al*., 2015; Boban *et al*., 2023)

Quorum Sensing in *Vibrio cholera*

The production of exotoxins is how *Vibrio cholerae* causes cholera. It includes 20 genes that contribute to the pathogenicity of the bacterium, as well as genes necessary for survival in host cells and the regulation of toxin synthesis and secretion. These genes govern transcription and the cascade of *toxT*, *tcpP/I*, and *toxR* that adjusts to external conditions including temperature, pH, osmotic pressure, etc. It is now evident that QS has a role in controlling these genes (Figure 5) (Saghi *et al*., 2015).

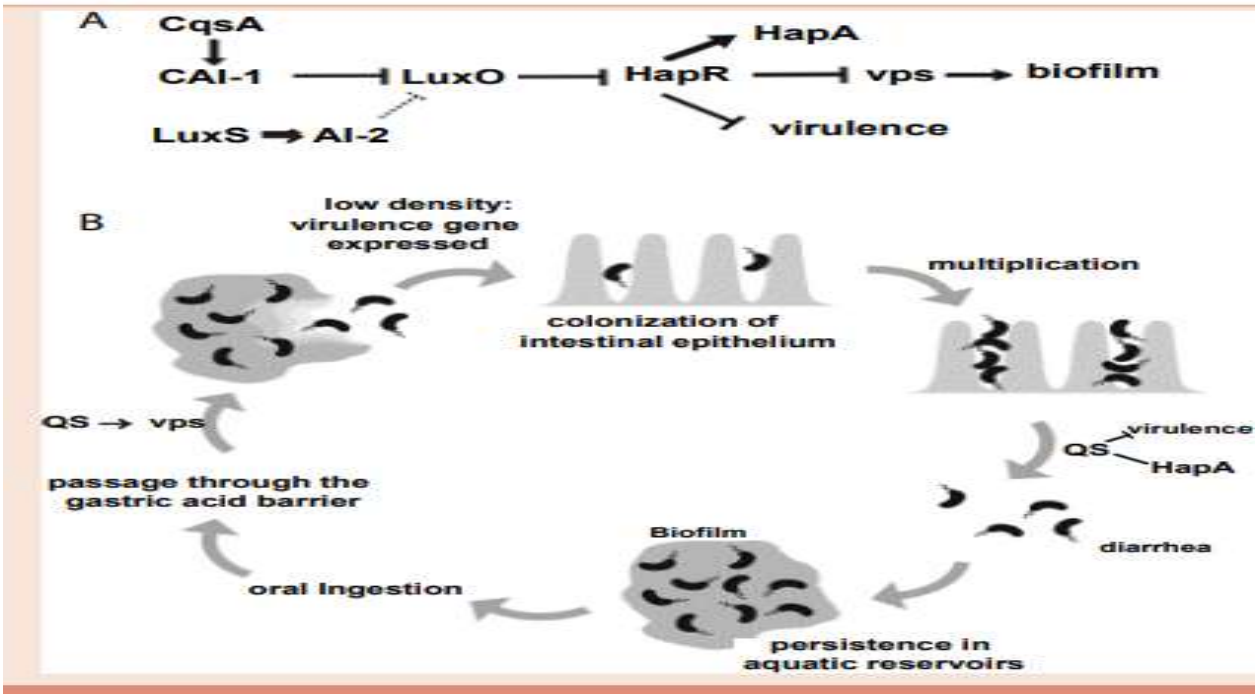


Figure 5: The role of QS in Vibrio cholera in the intestine (Saghi *et al*., 2015)

Quorum Sensing in *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a gram-negative bacterium that causes serious nosocomial infections in hospitals because of its diverse nature and strong drug resistance in biofilms. Research indicates that the bacterium is an opportunistic pathogen with over 600 genes that QS regulates. It is crucial for bacteria with strong drug resistance to produce biofilms and QS. Biofilm inhibition may result in a persistent infection and medication resistance in the bacterial solution of the above when QS and its antagonists are used. *Pseudomonas aeruginosa* RhlR/I and LasR/I are the two QS systems. Systems and controls for LasR/I, Regulon rhl pathogenicity genes *toxA*, *apr*, *lasA*, and *lasB-RhlR/I* regulates elastase synthesis (IL-2 has a breaking strength). The bacteria's capacity to live and proliferate inside cells is made possible by the system (Figure 6), (Saghi *et al*., 2015; Boban *et al*., 2023).

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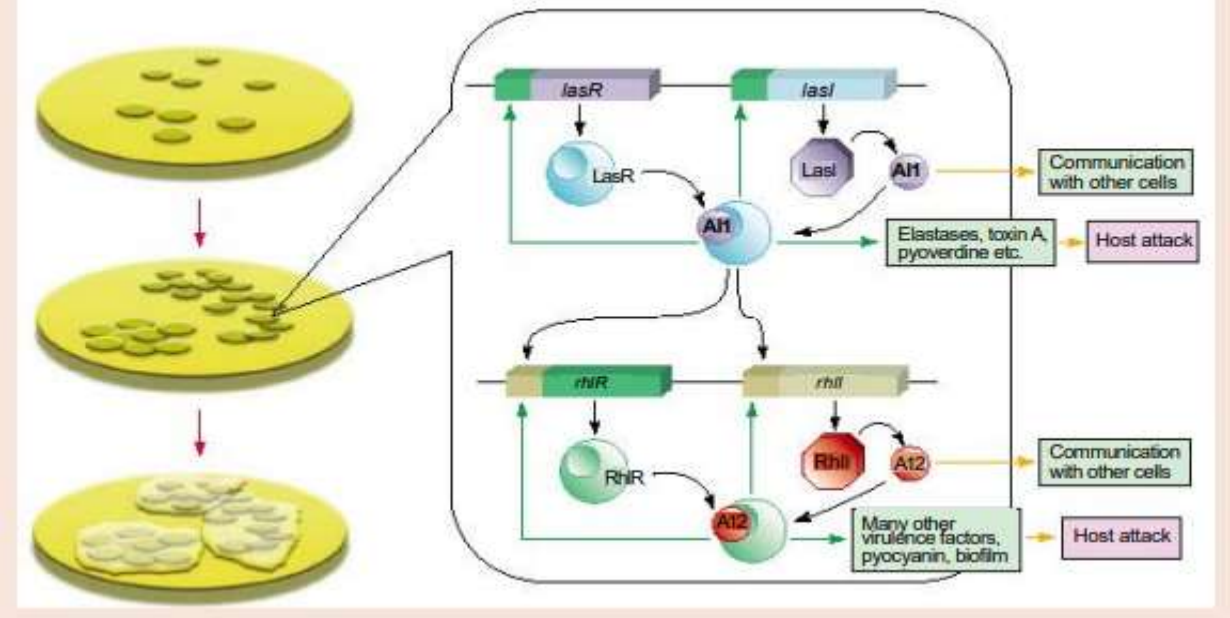


Figure 6: Activity of Pseudomonas aeruginosa QS (Saghi *et al*., 2015; Boban *et al*., 2023)

Quorum Sensing in *Staphylococcus aurous*

The General Accessory Gene Regulator (*agr*) operon contains two important genes: *AgrD* and *agrB* encoded a small peptide (QS), in contrast to the RNAIII, a promoter region of a gene responsible for the expression of RNAII gene called four *agr BDCA*. Cell density influenced the synthesis of these molecules, and RNAII and RNAIII aid in regulating gene expression (Figure 7), (Saghi *et al*., 2015).

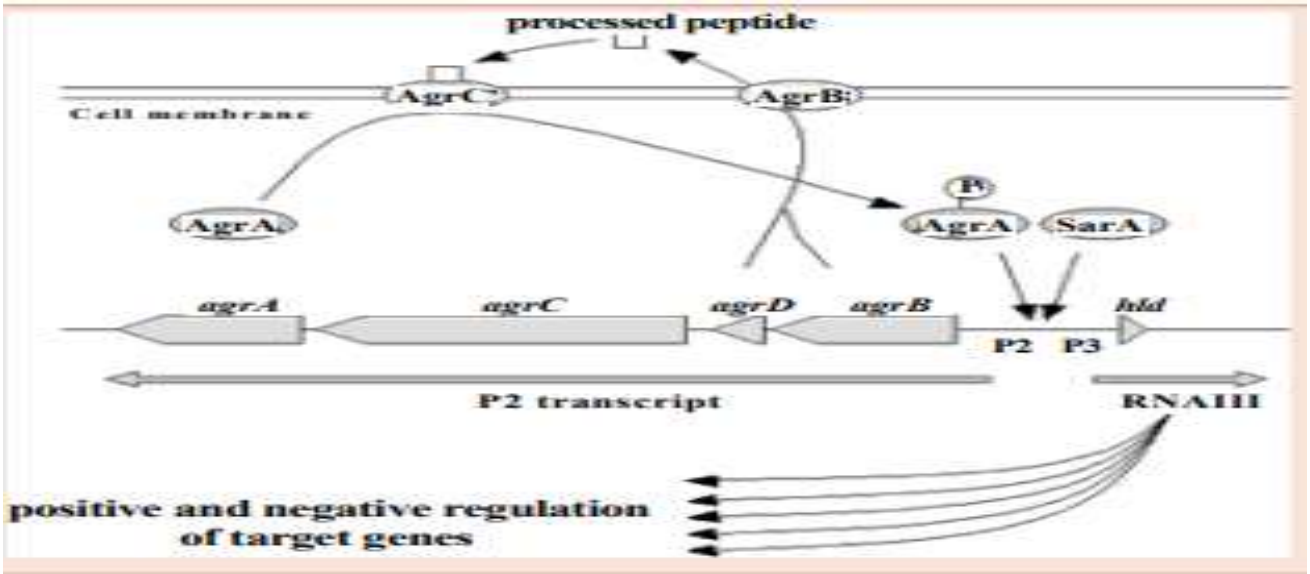


Figure 7: QS activity of *Staphylococcus aurous* (Saghi *et al*., 2015)

Biological Implication of Quorum Sensing

Biofilm and resistance mechanism

About 80% of bacteria that cause chronic infections produce bacterial biofilm, which is a crucial virulence mechanism that causes resistance to antibiotics and immune system evasion (Koo *et al*., 2017). The bacteria that produce biofilm are a diverse group of organisms, including both Gram-positive and Gram-negative bacteria, aerobic and anaerobic, motile and non-motile, to mention a few.

When biofilm-producing bacteria in an aqueous environment adhere to solid surfaces and create a network of extracellular polymeric substances (EPS), they adopt a "multicellular lifestyle" (Claessen *et al*., 2014), giving rise to biofilm, which is remarkably complex and three-dimensionally organized (Stacy *et al*., 2016). Proteins, polysaccharides, lipids, and DNA are among the components that maintain the integrity and survival of bacteria by forming a protective matrix (Coughlan *et al*., 2016). About 10–30% of the biofilm volume is made up of the bacteria. Water, which makes up around 97% of the biofilm, is what allows the nutrients needed for bacterial life to move through the biofilms (Lu and Collins, 2007; Sutherland and Sutherland, 2001). As a precursor to the production of biofilms, certain bacteria first assemble planktonic or free cells in an aqueous medium (Melaugh *et al*., 2016). One helpful adaptation that helps bacteria live in specific conditions is biofilm (Coughlan *et al*., 2016; Preda and Săndulescu, 2019).

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In general, bacteria inside the biofilm are more challenging to remove than those that are present as individual cells. The main causes of this resilience include metabolic dormancy, the extracellular network associated with biofilms, and other possible processes that influence tolerance. This kind of resistance is not primarily caused by genetic reasons; while the cells' close contact may help resistance genes spread (Flemming *et al*., 2016).

It may be extremely challenging to get rid of both Gram-positive (like *Staphylococcus aureus*) and Gram-negative (like *Pseudomonas aeruginosa*) bacteria when they develop biofilms. Biofilm development has important ramifications and is a major issue in a number of industries, such as the food sector and healthcare/clinical care. Certain bacteria, such as *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and several others, colonize tissue from individuals with chronic illnesses, implants, and/or catheters in a hospital setting (Coughlan *et al*., 2016; Preda and Săndulescu, 2019).

Microbial biofilm development is the primary cause of the majority of device-associated illnesses. Biofilm and microorganisms that produce it have the potential to change food quality and jeopardize food safety in the food business. According to Stewart and Costerton (2001), the biofilm can be found within food receivers such as vats, mixing tanks, or tools used in food preparation. Cleaning, disinfection, and surface preconditioning are examples of current biofilm management techniques that are somewhat effective and used in both hospitals and the food industry. However, biofilm-driven infections frequently recur, and they are still far from the intended impact and control (Coughlan *et al*., 2016). Therefore, new approaches to biofilm targeting are needed. Targeting the quorum sensing system is one such tactic, which interferes with conjugation, cell-to-cell communication, nutrition uptake, motility, and even the synthesis of certain metabolites (Preda and Săndulescu, 2019).

Biofilm Development

Attachment, cell-to-cell adhesion, growth, maturity, and dispersal are the stages that make up the formation of the biofilm (Figure 8) (Coughlan *et al*., 2016). Micro-colonies are created as a result of bacterial growth and are encased in a hydrogel layer that serves as a barrier between the microbial community and the outside world. Quorum sensing (QS) systems, which rely on chemical signals for communication, are used by the bacterial community's cells to exchange information. Cellular activities, population density-based pathogenesis, nutrition uptake, genetic material transfer between cells, motility, and secondary metabolite production are all influenced by communication (Preda and Săndulescu, 2019; Chigozie *et al*., 2025).

The buildup of extracellular polymeric materials occurs concurrently with the maturation of the biofilm. Bacterial strains separate from the micro-colonies in the last stage, which may result in the establishment of a new biofilm colony in a different area (Flemming *et al*., 2016). The microbial strains in the biofilms create organic extracellular molecules, which are then released into the extracellular medium as both soluble (soluble microbial products, or SMPs) and insoluble (organic extracellular polymeric substances, or EPS) materials (Aquino and Stuckey, 2004; Aquino and Stuckey, 2008). These materials come from the metabolism of the substrate and include waste and microbial leftovers as well as cellular residue from injured cells. Polysaccharides, extracellular DNA (eDNA), and/or proteins produced by strains during the formation and maintenance of biofilms are known as insoluble materials, or EPS. Usually, it is difficult to tell the difference between the molecules that are released and those that make up the microbial biofilm (Sutherland and Sutherland, 2001; Sutherland, 2001, Das *et al*., 2011).

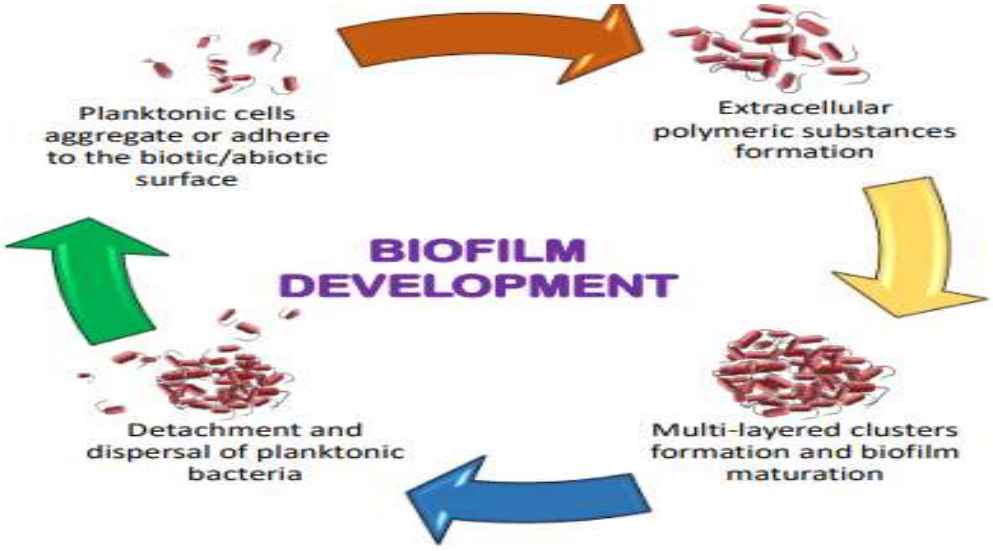


Figure 8: Biofilm Development (Coughlan *et al*., 2016; Preda and Săndulescu, 2019)

Quorum-Sensing Signals in Food Spoilage

The role that quorum-sensing signalling molecules play in food spoiling has drawn more attention in recent years. Different food systems, including milk, meat, and vegetables, have been shown to include a variety of signalling molecules, including AI-1 and AI-2 (Bruhn *et al*., 2004; Liu *et al*., 2006; Pinto *et al*., 2007). It is easy for psychrotrophic bacteria, including pseudomonads, to contaminate milk and dairy products. Extracellular proteinases, lipases, lecithinases, and glycosidases are produced by these Gram-negative bacteria (Dong *et al*., 2000; Stepaniak, 2004), and the phospholipases produced by the Gram-positive psychrotrophic aerobic *Bacillus species* cause some dairy products to deteriorate (Stepaniak, 2004). The AHL-based quorum-sensing system regulates the synthesis of extracellular lipolytic and proteolytic enzymes in *Serratia proteamaculans* strain B5a, suggesting that quorum sensing plays a role in Serratia spp.'s milk spoiling. When pasteurized milk was inoculated with wild-type *S. proteamaculans*, it spoilt after 18 hours of storage at room temperature, but not when a mutant with an inactivated *sprI* gene was employed in an

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experiment by Christensen *et al*. (2003). However, milk infected with the *sprI* mutant spoilt when 3-oxo-C6-HSL was added, suggesting that signalling molecules play a part in milk spoiling. Similarly, the psychrotrophic bacteria *Pseudomonas spp., Serratia spp., Enterobacter spp., and H. alvei* produce AHLs in both raw and pasteurized milk, suggesting that quorum sensing may be involved in the deterioration of milk and dairy products (Whitfield *et al*., 2000; Pinto *et al*., 2007).

Furthermore, the finding of furanosyl BAI-2 signals in considerable quantities in ordinary milk with a low bacterial population (102 CFU/mL) raises the possibility that interspecies communication plays a role in milk spoiling (Liu *et al*., 2006). Meat and meat products kept under aerobic cold (3 to 8 ºC) conditions are susceptible to spoiling due to *Pseudomonas spp*. Quorum sensing has been linked to the slime that forms on the surfaces of meat and the deterioration of fresh meat products kept under aerobic refrigeration, according to Jay *et al*. (2003).

QS Control of Virulence Factors in Gram-Positive Bacteria

QS in Gram-positive bacteria rely on principles common to all QS circuits: production, detection, and response to AIs. In many Gram-positive bacteria, the AIs are oligopeptide AIPs that are detected by membrane-bound two component signal transduction system. The AIPs are encoded as precursors (proAIPs) and are diverse in sequence and structure (Okada *et al*. 2005; Thoendel *et al*., 2011). Because the cell membrane is impermeable to peptides, specialized transporters are required to secrete AIPs. The AIP transporters also process the pro-AIPs. The final processed AIPs range in size from 5 to 17 amino acids, can be post-translationally modified, and can be linear or cyclized (Okada *et al*., 2005; Bouillaut *et al*. 2008). Extracellular AIPs are detected via membrane-bound two-component sensor kinases (Simon *et al*., 2007). The sensor kinases autophosphorylate at the conserved histidine when bound by the AIP. The phosphoryl group is passed from the histidine to a conserved aspartate on a cognate cytoplasmic response-regulator protein, and the phosphorylated response regulator controls expression of QS-target genes. In these Gram-positive QS circuits, the pro-AIP, transporter, histidine kinase receptor, and response regulator are typically encoded in an operon (Bouillaut *et al*., 2008). Expression of this operon is activated by the phosphorylated response regulator, resulting in an auto-inducing feed-forward loop that synchronizes the QS response. Some examples of Gram-positive QS behaviors are competence in *Streptococcus pneumonia* and *Bacillus subtilis* and sporulation in *B. subtilis* (Steven and Bonnie, 2012). QS Controls virulence factor production in Gram-positive human pathogens including *S. aureus*, *Listeria monocytogenes*, *Enterococcus faecalis*, and *Clostridium perfringens*. The well-studied system in this group of pathogens is the *S. aureus Agr* system (Thoendel *et al*., 2011; Steven and Bonnie, 2012).

S. aureus is found among the normal human skin flora. If the epithelial barrier is compromised, *S. aureus* can cause minor skin infections. These infections can lead to pneumonia, bacteremia, and sepsis (Queck *et al*. 2008). *S. aureus* is the leading cause of hospital related infections in the United States (Ansel and Jun, 2020). Its ability to cause disease depends on expression of an array of adhesion molecules, toxins, and compounds that affect the immune system. QS regulates expression of genes encoding these virulence factors. *S. aureus* uses a canonical Gram-positive two-component QS system encoded by the *agr* locus (Figure 9). The P2 promoter drives expression of a transcript (RNAII), which encodes the four components of the QS system. *agrD* encodes the pro-AIP, which is processed to the final AIP and secreted by the trans-membrane transporter protein AgrB (Thoendel *et al*., 2011).

Processes involves truncating the 45-47 residue pro-AIP to a 7-9 residues peptide, coupled with cyclization of a five-membered peptide ring via a thiolactone bond between a central cysteine residue and the carboxyl terminus. When the AIP accumulates, it binds the membrane-bound histidine kinase AgrC, which autophosphorylates at a conserved histidine and transfers the phosphate group to an aspartate on the response regulator AgrA (Steven and Bonnie, 2012). Phosphorylated AgrA binds upstream of the P2 promoter to auto-induce the *agr* operon (Thoendel *et al*., 2011). In addition to activating the P2 promoter, phosphorylated AgrA activates the divergently encoded P3 promoter. The P3 promoter controls expression of RNAIII. The 50 region of RNAIII harbors the *hld* gene, which encodes the virulence factor d-hemolysin (Steven and Bonnie, 2012). A more prominent role for RNAIII is as a regulatory RNA. RNAIII has the dual-function of activating production of a-toxin and repressing expression of rot, fibronectin binding proteins A and B, protein A, coagulase, and other surface proteins (Queck *et al*., 2008; Thoendel *et al*., 2011).

Repression of rot, which encodes a repressor of toxins, leads to de-repression of additional toxins, proteases, lipases, enterotoxins, super antigens, and urease (Queck *et al*. 2008). The net result of this QS regulatory cascade is down regulation of surface virulence factors (such as protein A), and up-regulation of secreted virulence factors (such as a-toxin). Most of the effects of QS on regulation of virulence in *S. aureus* are mediated through direct and indirect regulation by RNAIII, however, phosphorylated AgrA also directly activates at least two additional virulence genes encoding phenol-soluble modulines (Queck *et al*. 2008; Steven and Bonnie, 2012).

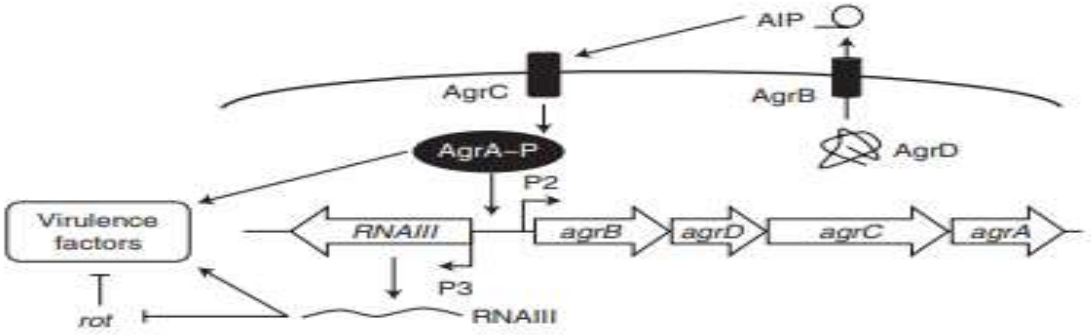


Figure 9: *S. aureus Agr* QS circuit. The auto-inducing peptide (AIP) is synthesized as a precursor from agrD. The AIP transporter AgrB processes the precursor to the mature AIP and transports it out of the cell. AIPs are detected by a two-component signal transduction pathway. AgrC is the membrane-bound histidine kinase and AgrA is the response regulator. Phosphorylated AgrA activates the P2 and P3 promoters encoding the *agr* operon (called RNAII) and the RNAIII regulatory RNA, respectively. RNAIII post-transcriptionally activates virulence factor production and represses expression of rot, the repressor of toxins, leading to further derepression of virulence factors (Steven and Bonnie, 2012)

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QS Control of Virulence Factors in Gram-Negative Bacteria

A body of work on the ecology of cholera has demonstrated that *V. cholerae* is an autochthonous aquatic organism, occupying brackish water and estuarine environments when not associated with the human host (Bouillaut *et al*. 2008), underlined by the presence of multiple adaptive strategies for persistence in aquatic reservoirs. Outside of the human host, *V. cholerae* can be found complex with marine organisms such as; *Crustacean zooplankton*. Planktonic *V. cholerae* can also respond to low temperatures or nutrient limitation by phenotypic transition to a viable but non-culturable (VBNC) state characterized by reduced cell size and minimal metabolic activity. These environmental persistence strategies have major consequences for the transition into the host gastrointestinal tract (Ansel and Jun, 2020).

Biofilm-associated *V. cholerae* is more acid resistant than planktonic cells, which aids in the transition through the low-pH environment of the stomach and ultimately into the distal small intestine, the preferred site of human colonization (Bouillaut *et al*. 2008). There, *V. cholerae* also needs to exit biofilm structures in order to disseminate into the gut mucosa. This process is aided by gut-localized environmental factors such as bile (Steven and Bonnie, 2012). As they enter the host, *V. cholerae* cells are exposed to a series of changes, such as temperature, osmolarity, oxygen concentration, and exposure of antimicrobial agents (e.g. bile salts). Given the dramatically different environmental conditions between the aquatic reservoir and the host mucosa, it is unsurprising that *V. cholerae* have evolved numerous regulatory mechanisms designed to tailor the production of factors permitting optimal host colonization (Ansel and Jun, 2020).

The ability of *V. cholerae* to colonize and cause disease in hosts requires production of a number of virulence factors during infection. The two major virulence determinants of *V. cholerae* are encoded by two separate genetic elements. Cholera toxin, which causes the diarrhea characteristic of cholera, is encoded by *ctxAB* genes on the lysogenic CTXΦ bacteriophage (Queek *et al*., 2008). *V. cholerae* also produces toxin-co-regulated pili (TCP), which are required for intestinal colonization both in animal models and in human volunteers. TCP is thought to be a polymer of the main structural subunit, TcpA, and serves as the receptor for the CTXΦ bacteriophage (Bouillaut *et al*., 2008). The genes required for TCP synthesis, including *tcpA* as well as accessory colonization factor (*acf*) genes and the genes encoding the virulence transcriptional activators ToxT and TcpP, are located on a 40-kb Vibrio pathogenicity island (Steven and Bonnie, 2012). Coordinate expression of *V. cholerae* virulence genes results from the activity of a cascading system of regulatory factors (Thoendel *et al*., 2011). The primary direct transcriptional activator of *V. cholerae* virulence genes, including *ctxAB* and *tcpA*, is ToxT, a member of the AraC/XylS-family of transcriptional regulators, members of which often bind effector molecules and/or oligomerize to affect transcriptional regulation at target promoters (Bouillaut *et al*., 2008; Steven and Bonnie, 2012). Unsaturated fatty acids can directly bind to and inhibit the activity of ToxT. To activate transcription, ToxT recognizes and binds to a degenerate 13-bp DNA sequence, the "toxbox". FadR, the master regulator of fatty acid metabolism, modulates ToxT activity at both transcriptional and posttranslational levels, suggesting that the expression of genes involved in fatty acid biosynthesis and virulence are intertwined (Ansel and Jun, 2020).

A complex regulatory pathway controls the expression of ToxT (Figure 10). The ToxR protein was identified as the first positive regulator of *V. cholerae* virulence genes; the genes involved in the transcriptional cascade resulting in *toxT* expression and consequent virulence gene activation is thus often referred to as the "ToxR regulon". Acting in conjunction with TcpP, ToxR activates the transcription of *toxT*. ToxR directly regulates the transcription of many genes, including *ompU* and *ompT*, which encode the major porins of *V. cholerae*. ToxR is a bitopic membrane protein containing a cytoplasmic DNA-binding domain, a single trans-membrane domain, and a periplasmic domain. ToxR activity requires the presence of another inner membrane protein, ToxS; deletion of toxS negatively impacts ToxR transcriptional activity, suggesting that ToxS serves as an effector of *ToxR* function by influencing the stability and/or the dimerization of *ToxR* (Ansel and Jun, 2020). Recent work has also shown that ToxR-ToxR protein– protein interactions are significantly increased in response to ToxR operators and the co-activator ToxS (Bouillaut *et al*., 2008; Ansel and Jun, 2020).

To activate the expression of *toxT*, ToxR acts with a second transcription activator, TcpP, which is also membrane-localized and contains a cytoplasmic winged helix-turn-helix (w-HTH) domain (Bouillaut *et al*., 2008). TcpP, like ToxR, requires the presence of a membrane-bound effector protein, TcpH, which interacts with TcpP (Ansel and Jun, 2020). TcpP is degraded by a protease in the absence of TcpH, and during conditions unfavourable for virulence gene activation. TcpP binds to the *toxT* promoter just upstream of the −35 element and is a direct *toxT* activator. Overexpression of TcpP alone activates *toxT* expression, but binding of ToxR to the upstream of TcpP-binding site is required for TcpP-mediated expression of *toxT* at endogenous expression levels. Two activators encoded by unlinked genes, *AphA* and *AphB*, regulate transcription of *tcpPH* (Thoendel *et al*., 2011; Ansel and Jun, 2020). AphA is a dimer with an N-terminal winged-helix DNA binding domain that is structurally similar to those of MarR family transcriptional regulators. AphA cannot activate transcription of *tcpPH* alone, but requires interaction with the LysR-type regulator AphB that binds downstream of AphA binding site. This interaction is thought to stabilize AphB binding to its recognition site and result in activation of the *tcpPH* promoter. In addition, AphB enhances the expression of *toxR*. Expression of aphA is also controlled by a quorum-sensing system, discussed in detail below. This process means that virulence gene expression declines at high cell density and is thought to contribute to the self-limiting nature of *V. cholerae* infections (Ansel and Jun, 2020).

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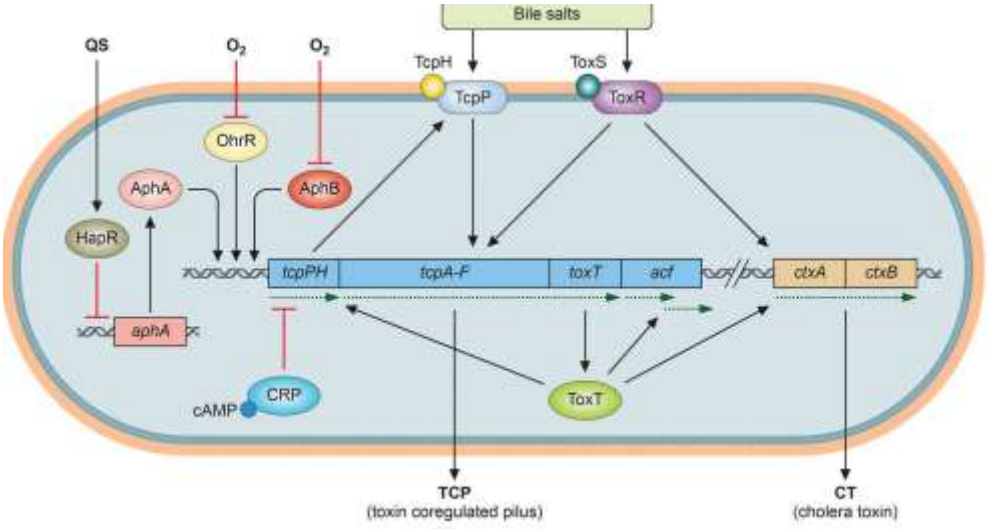


Figure 10: *V. cholerae* virulence regulatory networks. Major transcriptional regulators and their corresponding signals are shown. In particular, the master regulator ToxT activates virulence genes which products are involved in synthesis of the key virulence determinants TCP and CT. The expression of *toxT* is regulated by TcpP and ToxR. QS: quorum sensing. →: activation; repression (Ansel and Jun, 2020).

Molecular mechanisms of signal interference

Any substance that inhibits the accumulation of QS signals or the detection of QS signals by receptor proteins may inhibit the expression of bacterial QS-dependent virulence genes, as microbial QS systems depend on QS signals and the corresponding receptor proteins for gene regulation. Examples of various signal interference strategies against AHL QS systems are shown in Figure 11C. Degradation of signals is one of them. AHL-lactonase and AHL-acylase are two classes of AHL degradation enzymes that have been found in a variety of bacterial species (Zhang, 2003). AHL-lactonase hydrolyses the lactone ring of AHLs to create equivalent acyl homoserines (Figure 12), which exhibit significantly lower biological activity (Dong *et al*., 2004; Zhang and Dong, 2004). AHL-lactonase is very selective against AHLs. Fatty acids and homoserine lactone are produced when AHL-acylase breaks the amide bond of AHLs (Figure 11), however this product has little biological function (Leadbetter and Greenberg, 2000; Lin *et al*., 2003).

Signal biosynthesis inhibition is another method of signal interference. AHL production is decreased, for instance, by triclosan (Figure 12), a strong inhibitor of the enoyl-ACP reductase involved in the synthesis of acyl-ACP, one of the crucial steps in AHL biosynthesis (Zhang and Dong, 2004). Reducing the quantity of QS signal receptor proteins seems to be another intriguing strategy. The seaweed *Delisea pulchra* (Figure 12) produces halogenated furanones, which are structural counterparts of AHL signals. Treating *Vibrio fischeri* with the furanone accelerates LuxR degradation, which in turn suppresses bacterial (Manefield *et al*., 2002; Zhang and Dong, 2004; Wang *et al*., 2024).

The two-component system-based QS systems have also shown a number of signal interference processes. *S. aureus* uses auto-inducing peptide (AIP) and AgrCA, a two-component sensor and response regulator pair, to control the synthesis of virulence components. The sulphydryl group of a cysteine, the conserved amino acid at the fifth position from the C-terminal of the AIP, is connected to the carboxyl group of the C-terminal amino acid in AIPs, which are short peptides with a thiolactone structure (Lyon *et al*., 2002). Significant inter-strain sequence variation between AIP and its sensor AgrC likely explains the signal specificity. The four AIP-specificity groups interfere with one another. In other groups of *S. aureus* strains, the AIP that stimulates the development of virulence components of its own specificity group suppresses virulence expression. All four of the AIP-specificity groups of *S. aureus* strains exhibit a broad range of inhibition on virulence expression when AIP-II is shortened and lacks the N-terminal tail (Figure 11) (Zhang and Dong, 2004). The shortened AIP and its analogues interfere with AIP's ability to attach to the receptor, according to indirect evidence (Figure 11D). RWJ-49815 and closantel are two examples of phenolic inhibitors (Figure 12) that interfere with the two-component system-based QS signal transduction by altering the structure of the receptor kinase, which leads to protein aggregation (Stephenson *et al*., 2000; Zhang and Dong, 2004).

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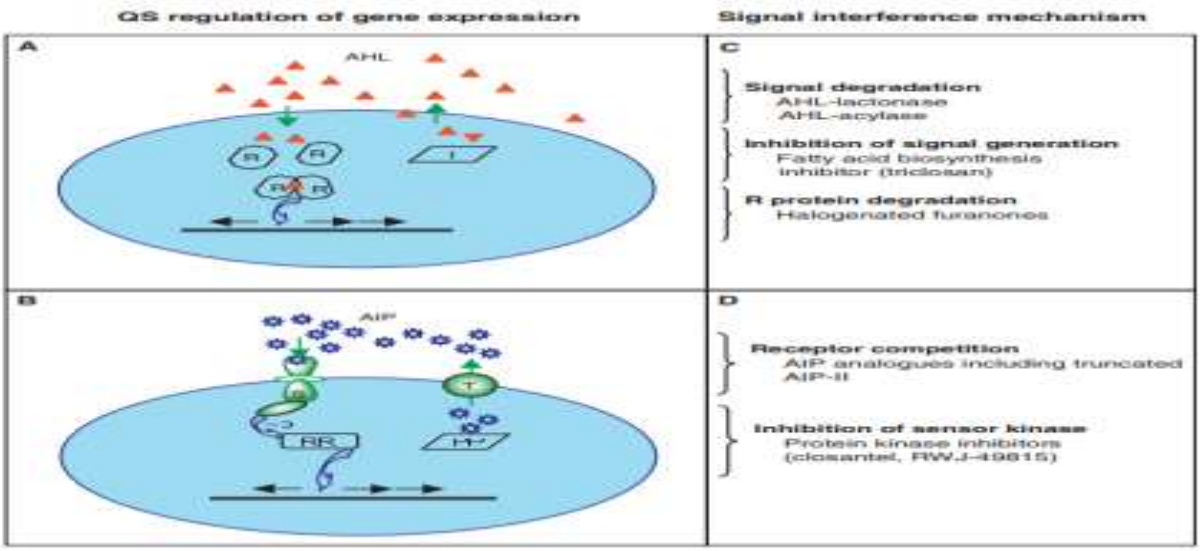


Figure 11: Quorum-sensing models and signal interference mechanisms (Zhang and Dong, 2004).

A. The LuxI protein (I) catalyses the production of AHL signals in a typical Gram-negative LuxR-type QS system. The accumulating AHL signals cause QS signalling by attaching to LuxR-type transcription factors (R) when bacterial cells multiply. Target genes are induced to express themselves via the LuxR-AHL complex.

B. An ATP-binding cassette (ABC) transporter (T) exports the modified precursor peptide (PP) and the resultant QS signals (AIP) in a typical Gram-positive AIP two component QS system. Sensor-histidine kinases (S) pick up the AIP signals, and phosphorylation relays (P) transport the sensory data to the cognate response regulator (RR), which triggers the production of the target gene.

C. Illustrations of methods of signal interference that target LuxR-type QS systems.

D. Illustrations of signal interference techniques that target two-component QS systems in AIP.

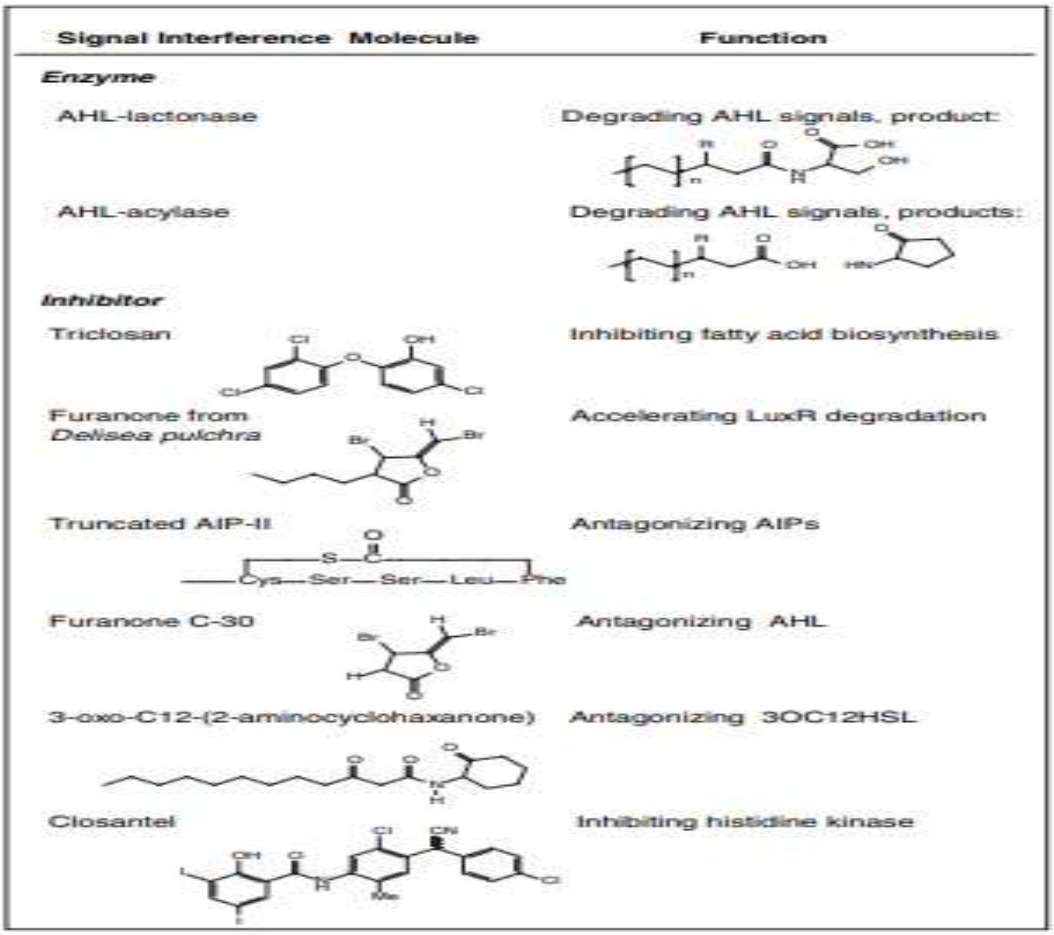


Figure 12: Examples of signal interference reagents and mode of action (Zhang and Dong, 2004).

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Quorum Sensing Inhibition

Without putting pressure on the bacteria, QS Inhibitors (QSI) work by preventing them from communicating with one another. Accordingly, QS inhibition suppresses the auto-inducer-induced QS system and interferes with cell-to-cell communication (Rémy *et al*., 2018). Bacterial virulence is decreased by QS inhibition (Jiang *et al*., 2019; Wang *et al*., 2024). Quorum-sensing inhibitory pathways can help us overcome the challenge of antimicrobial resistance, which has been a significant problem in a number of illnesses. By suppressing QS-regulated pathogenic activities such as toxin production, swimming, swarming, motility, and biofilm formation, QS-inhibiting agents reduce the capacity of bacteria to cause disease and, consequently, drug-resistant mutations (Zhao *et al*., 2020; Boban *et al*., 2023). They do not kill or stop the growth of bacteria. The following are some of the several methods of QS inhibition:

1. Inhibiting the synthesis of signalling molecules
2. Inactivation or enzymatic degradation of signalling molecules
3. Competing with signalling molecules
4. Restricting the signal receptor complex

To select effective quorum-sensing inhibitors, various factors have to be considered as follows:

1. There must be a small molecule for the adequate depletion of the QS-regulated gene expression.
2. There must be no adverse effect with a particular quorum sensing regulator.
3. It must be chemically stable and tolerant to metabolic degradation.
4. The QSI must act longer than the native AHL (Boban *et al*., 2023).

There is a wide range of Quorum sensing inhibitors like:

Prokaryotic QSIs, which are made up of different enzymes that are in charge of putting an end to quorum sensing activities, are examples of natural QSIs. For instance, *Pseudomonas aeruginosa* (*P. aeruginosa*) PAO1 has the enzyme AHL-acylase, which breaks down the lengthy chains of AHLs. *Bacillus species* and *Agrobacterium tumefaciens* also include the enzyme Lactonase, which breaks down AHL signalling molecules (Zhao *et al*., 2020). The eukaryotic host and bacterial pathogen interact in animal-based QSIs, which also function by enzymatic inhibition. For example, the fungus Penicillium, which is composed of patulin and penicillic acid, functions as a QSI by preventing *P. aeruginosa* from forming biofilm (Boban *et al*., 2023).

By having molecules similar to those of QS signals and the capacity to break down the signalling receptor, plants function as QSI. Gamma-aminobutyric acid (GABA) encourages the lactonase enzyme in *Agrobacterium tumefaciens* to degrade the AHL signal OHC8HSL (Jiang *et al*., 2019). By chemically synthesizing them, synthetic QSIs overcome the drawback of natural QSIs' lower concentration of signalling molecules. By altering the chain length, replacing the signalling molecules, altering the AHL ring moiety, and many other methods, a synthetic QSI primarily targets the biosynthetic pathway that directs the synthesis of signalling molecules according to (Boban *et al*., 2023).

Quorum Quenching

Quorum quenching (QQ) is a phenomenon that disrupts the signals involved in quorum sensing. It is mostly caused by enzymes that may break down the acyl-homoserine lactones (AHLs) signals. There are several ways to achieve this disruption of communication amongst the bacterial groups. First, the synthesis of auto-inducers may be disrupted by the tiny molecules referred to as quorum sensing inhibitors. Second, the auto-inducers can be scavenged by quorum quenching (QQ) macromolecules, such as cyclodextrins and antibodies. Moreover, enzymes can be used to hydrolyse the auto-inducers extracellularly (Remy *et al*., 2018; Wang *et al*., 2024). Numerous antagonist substances, including as polyphenols, eugenol, 5-fluorouracil (5-FU), and azithromycin, have been found in natural sources or made to quench. Some of these quorum sensing inhibitors have uncertain mechanisms of action. A few of them, including azithromycin, are primarily regarded as antibiotics due to their capacity to stop bacterial growth above a certain concentration (Jiang and Li, 2013).

CONCLUSION

A crucial regulatory mechanism that allows microbes to act strategically, collaboratively, and adaptively in a variety of settings is quorum sensing. QS is a multidisciplinary area of study due to its industrial utility, ecological significance, and biochemical complexity. Our knowledge of microbial behaviour will grow as a result of ongoing studies into QS mechanisms, signal diversity, and regulatory networks, which will also yield creative solutions for biotechnology, agriculture, and medicine.

RECOMMENDATIONS

Quorum sensing (QS) research has significant implications for various fields, including microbiology, medicine, and environmental sciences. Here are three recommendations to enhance the efficacy and scope of quorum sensing research:

1. Integration of multi-Omics approaches by utilizing genomics, transcriptomics, proteomics, and metabolomics to comprehensively understand the QS networks in different organisms. These approaches can reveal the complex interactions and regulatory mechanisms underlying QS, allowing for the identification of novel signalling molecules and pathways.
2. Development of QS inhibitors, focusing on identifying and characterizing small molecules or compounds that can effectively inhibit QS mechanisms. This is particularly important for combating antibiotic-resistant bacteria and biofilm formation. High-throughput screening and structure-activity relationship studies can play a crucial role here.
3. Exploration of environmental and ecological contexts to investigate QS in diverse ecological settings, such as natural habitats, biofilms, and mixed-species communities. Understanding how environmental factors (like nutrient availability and stress conditions) influence QS behavior can provide insights into microbial interactions and community dynamics.

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