

# Beyond quorum sensing: the complexities of prokaryotic parliamentary procedures

Anne K. Dunn · Eric V. Stabb

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**Abstract** Bacterial quorum-sensing regulatory systems can be summarized in a simple model wherein an autoinducer molecule accumulates in cultures and stimulates regulatory changes in gene expression upon reaching a critical threshold concentration. Although quorum sensing was originally thought to be an isolated phenomenon governing the regulation of a handful of processes in only a few bacteria, it is now considered to be a widespread mechanism for coordinating bacterial gene expression. Over decades of research, investigations of autoinducer-mediated regulation have revealed that these systems are far more complicated than originally appreciated, and such discoveries have accelerated recently with the application of molecular and genomic tools. The focus of this review is to highlight recent advances describing complexities that go beyond the simple model of quorum sensing. These complexities include the regulation of autoinducer production and degradation, the presence of multiple quorum-sensing systems in individual bacteria that regulate diverse genes, often in coordination with other regulatory elements, and the influence of interorganismal interactions on quorum sensing.

**Keywords** *Vibrio fischeri* · *Pseudomonas aeruginosa* · Acyl homoserine lactone · AI-2 · Bioluminescence

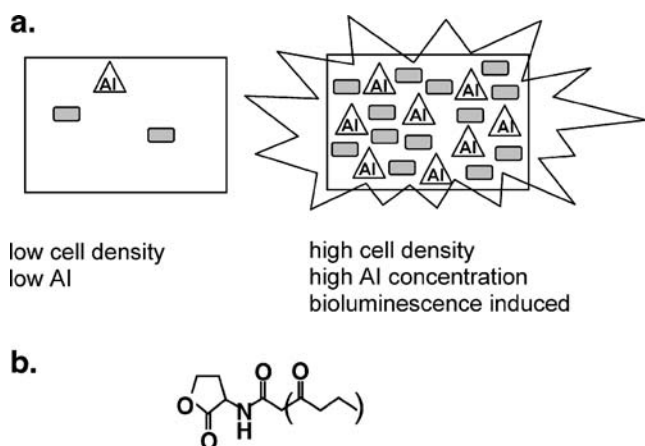
## Introduction

Studies of autoinduction or quorum sensing were initiated over forty years ago by curious investigators attempting to

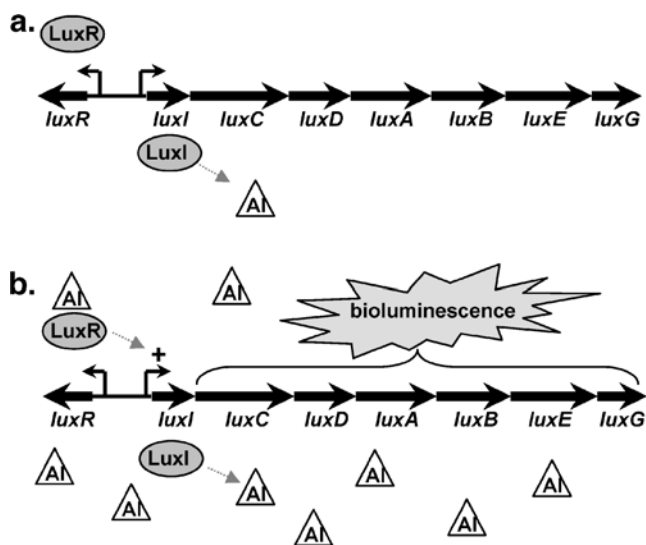
explain the pattern of light production in cultures of bioluminescent marine bacteria [1–3]. They found that these bacteria exude a bacterial pheromone or “autoinducer” that accumulates in growing cultures and stimulates bioluminescence only when it has reached a critical threshold concentration [4, 5]. The model that emerged from these studies is illustrated simplistically in Fig. 1a. Importantly, this model explained why some bacteria, such as *Vibrio fischeri*, did not produce bioluminescence when cells were dilute but glowed brightly when populations became more densely packed [5, 6]. This bioluminescence-stimulating compound of *V. fischeri* was identified over a decade later as a *N*-acylhomoserine lactone (AHL), specifically *N*-3-oxo-hexanoyl homoserine lactone (Fig. 1b) [4].

Although the autoinduction model was initially met with skepticism, it became widely accepted after the isolation and characterization of the genes necessary for light production and regulation of luminescence expression [7, 8]. Through these studies it was discovered that the regulatory functions and enzymatic activities necessary for light production in *V. fischeri* were encoded on an 8-kb DNA fragment, consisting of the *luxICDABEG* operon and the divergently transcribed *luxR* gene (Fig. 2). The *luxCDABEG* genes encode the enzymes necessary for light production, while *luxI* encodes the AHL synthase and *luxR* the AHL receptor. From this information, a more detailed understanding of autoinduction of bioluminescence emerged, where LuxI produces the AHL molecule, which is freely diffusible across the cell membrane [9] and accumulates in the culture medium, and where AHL bound to LuxR activates transcription of the *luxICDABEG* operon, resulting in the production of light (Fig. 2). Presumably, the threshold concentration of autoinducer required to stimulate luminescence is defined by the binding affinity of LuxR for its cognate AHL.

A. K. Dunn (✉) · E. V. Stabb  
Department of Microbiology, University of Georgia,  
824 Biological Sciences Building, 1000 Cedar Street,  
Athens, GA 30602, USA  
e-mail: akdunn@uga.edu



**Fig. 1a,b** A “simple” model of autoinduction or quorum sensing in *V. fischeri*. **a** The AHL autoinducer (AI, triangle) is constitutively produced by the bacterial cells (shaded capsule). At low cell densities very little AI is present. As cell density increases, AI accumulates until a threshold level is reached that then activates the production of light. **b** Structure of the AHL autoinducer molecule produced by *V. fischeri* LuxI, *N*-3-oxo-hexanoyl homoserine lactone, also known as 3-oxo-C6-homoserine lactone. Different AHL synthases produce AHL signal molecules that vary in the length of, and substitutions on, the acyl side chain (the variable region is denoted by parentheses)



**Fig. 2a,b** Revised model of autoinduction or quorum sensing in *V. fischeri*, reflecting the identification of the genes encoding the regulatory functions and enzymatic activities necessary for light production. **a** Under low cell densities, the AHL synthase LuxI is constitutively expressed. LuxI produces autoinducer (AI or AHL), which begins to accumulate but does not reach a threshold level, and light is not produced. **b** Under high cell densities, AI accumulates to the threshold level and binds the regulator LuxR, which activates transcription of the *luxICDABEG* operon. The products of the *luxCDABEG* genes are responsible for light production. The synthesis of AI is regulated in a feedforward manner, where the activity of LuxI stimulates its expression

The general consensus at the time was that autoinduction was an obscure phenomenon present in bioluminescent marine bacteria [3], and that it was related to their dual lifestyles. Bioluminescent bacteria can be found as dilute free-living planktonic cells, but some also inhabit the light organs of squid and fish [10], where they are maintained at high densities of  $10^9$  to  $10^{10}$  cells per ml. During such dense symbiotic growth in their host, autoinducer accumulates to sufficient levels to trigger bacterial light production that is used in animal behaviors such as camouflaging by counter-illumination [11]. The density-dependent induction of bioluminescence ensures that the energetically expensive process of light production [12] is not triggered in the bacteria during free-living growth as planktonic cells in the ocean.

Although the study of autoinduction was initiated to explain a curious phenomenon in what were considered to be “unimportant” marine bacteria [3], over the years similar systems have been found in a variety of bacteria [13, 14]. AHL signals with varying acyl side chains are commonly used as autoinducers by Gram-negative bacteria [15, 16], but other autoinducer molecules such as peptides [17], quinolones [18], and 4,5-dihydroxy-2,3-pentanedione derivatives collectively known as “AI-2” [19, 20] have also been discovered. The behaviors regulated in these systems are usually those that are more productive when undertaken as groups of cells rather than as individuals, and/or behaviors that would be more profitable for cells in a diffusion-limited environment, such as the secretion of extracellular enzymes. Examples of autoinducer-triggered behaviors include secretion of proteases or virulence factors, antibiotic production, sporulation, biofilm formation, genetic competence, conjugative DNA transfer, and, as mentioned above, bioluminescence.

With the discovery of many new autoinducers and population-based regulatory systems, the term “quorum sensing” (QS) was coined in the mid-1990s [21] to convey the idea that bacteria used autoinducers to census their culture density and to make certain decisions only when a critical density, a “quorum,” was present. By making the analogy to the practice of many organizations requiring a quorum of members present to conduct business, the term was readily understandable by those outside the field and it highlighted the social nature of bacteria. However, in human endeavors the rules of order are typically complex. For example, in the United States House of Representatives a quorum could be two members, one hundred members, or two hundred and eighteen members, depending on the action being taken. Moreover, a quorum is a starting point required to do business, but another tally is still necessary to make decisions, and for some group decisions multiple votes may be required, different groups may have to concur, and external forces may try to subvert the process.

It should come as no surprise that systems regulating group decisions by bacteria are at least as complex as those governing societies. Over the years it has become clear that bacterial QS systems do not respond purely to the number of cells present, and recent applications of molecular and genomic tools have accelerated the discovery of such complexities. These studies have revealed that the processes of autoinducer-mediated gene regulation are often far more complex than the simple model presented in Figs. 1a or 2. This complexity is reflected in the regulation of autoinducer production, the presence and regulation of endogenous systems for degrading autoinducers, the multiple QS systems found in individual bacteria, the coordination of QS systems with other regulatory elements, and the influence of other organisms on QS in bacteria. In this review we highlight recent advances in the QS field that have described these complex QS pathways.

#### Autoinducer accumulation: multiple levels of control

In the simplest model of QS, autoinducer is produced at a constant rate and accumulates at a constant rate. If this were true, autoinducer concentration would be a relatively straightforward reflection of bacterial numbers and autoinducer diffusion rates over time; however, quorum signaling is considerably more complicated, even in clonal cultures. Many bacteria regulate autoinducer production and some have the capacity to destroy their own autoinducers. Thus, the concentration of autoinducer actually reflects a complicated set of parameters including environmental influences.

It has been known for a long time that bacteria can regulate the production of autoinducer. Perhaps the most obvious example of this is the AHL synthase LuxI in *V. fischeri*, whose activity stimulates its own expression (see above and Fig. 2). Given the ubiquity and obvious functional logic of feedback negative regulation in biological systems, such feedforward positive regulation is striking, although not unprecedented. Interestingly, this phenomenon is not limited to *V. fischeri*, and autoinducer molecules stimulate autoinducer synthases in several bacteria, including the opportunistic pathogen *Pseudomonas aeruginosa* [22], the tumor-generating plant pathogen *Agrobacterium tumefaciens* [23], and the human pathogen *Streptococcus pneumoniae* [24]. Although such feedforward regulation means that autoinducers do not accumulate at a steady rate, it does preserve a model of QS with internal control.

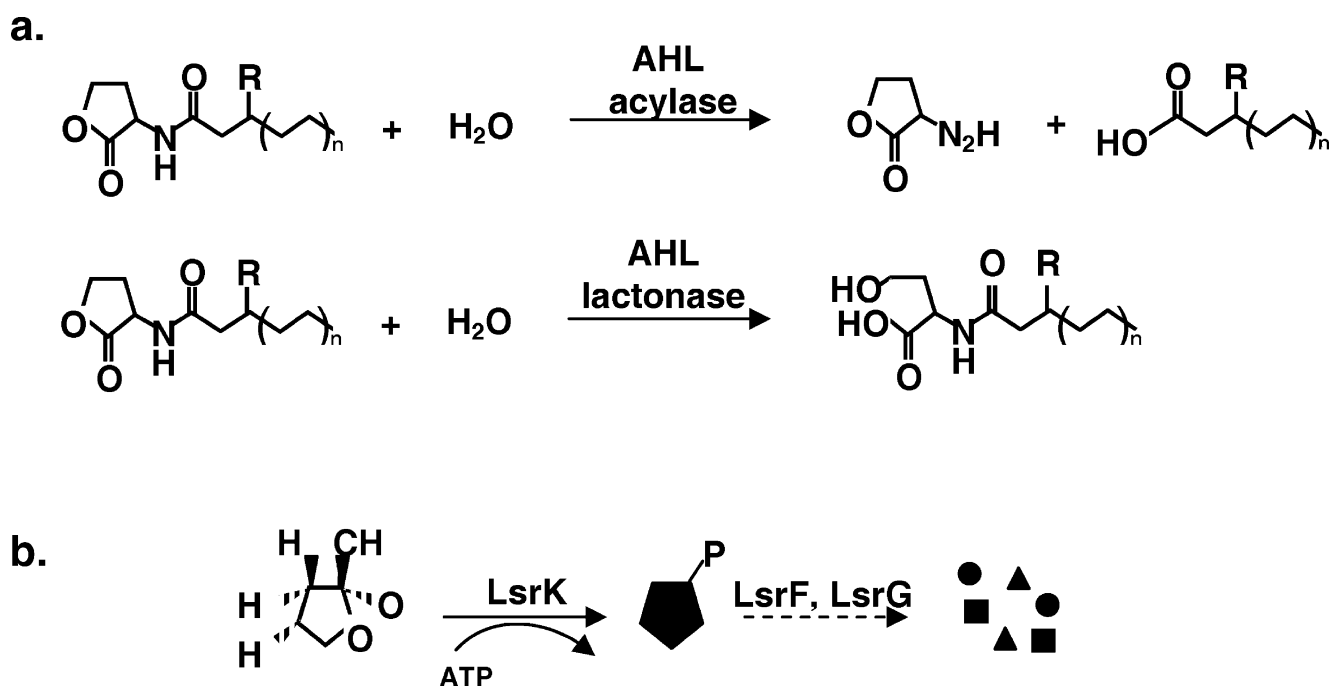
Perhaps more importantly, from an ecological perspective, regulation of autoinducer production can also respond to inputs from outside the QS systems themselves, thereby embedding QS systems in a larger, environmentally

responsive transcriptional network. Combined with the feedforward autostimulatory nature of some QS systems mentioned above, these environmental inputs can be greatly amplified. Moreover, the regulatory networks controlling QS can be quite complex. For example, the QS systems of *P. aeruginosa* are modulated by several other regulators, including VsqR, RsaL, QscR, GacA/RsmAZ, Vfr, RelA, and RpoS [25]. The precise environmental signals detected by these systems are not always clear; however, the latter two regulators respond to the nutritional/growth status of the cell. *rpoS* may also be regulated by QS, although this finding is controversial [26, 27]. This connection of QS to the availability of growth substrates represents a common, though not universal, theme in the environmental regulation of QS. For example, catabolite repressor (Crp) stimulates autoinducer synthesis in *V. fischeri* in response to growth substrates [28, 29]. By embedding quorum signaling with such regulatory systems, bacteria are able to modulate the production of autoinducers such that their concentration reflects not only cell density but also specific parameters of their environment.

Interestingly, bacteria can also control the local concentration of autoinducer by degrading signals that they have already generated. Investigation of bacteria consuming their own autoinducers has recently gained momentum, but relatively few examples have been examined and the specifics of the systems are not yet as well-understood as the synthesis of autoinducers. Both the prevalence of QS systems and the results of bioinformatic searches for homologs of known quorum-signal degraders [30] suggest that these pathways may be more widespread than has been appreciated, although their prevalence and ecological importance are still uncertain.

What is clear is that diverse systems exist for autoinducer degradation in the bacteria that produce these signals and that these autoinducer-degrading systems are themselves regulated. For example, both *A. tumefaciens* and *P. aeruginosa* can degrade the AHL molecules that they produce, but they do so in biochemically distinct ways. *A. tumefaciens* produces a lactonase, AttM, that hydrolyzes AHLs to produce *N*-acylhomoserines [31], whereas *P. aeruginosa* encodes multiple AHL acylases, including PvdQ and QuiP, capable of cleaving the acyl side chain from homoserine lactones (Fig. 3a) [30, 32, 33]. As might be expected given the variability of AHL acyl groups, these AHL acylases display some substrate specificity; however, they do act on the signal molecules produced by *P. aeruginosa*.

Just as autoinducer synthesis is regulated, and thereby responsive to environmental inputs, so too are autoinducer degradation pathways modulated and embedded in regulatory networks. For example, the *P. aeruginosa* AHL acylase PvdQ is upregulated elevenfold in response to iron



**Fig. 3a,b** Mechanisms for enzymatic degradation of signal molecules in bacteria. **a** AHL acylases and lactonases can degrade AHL molecules with various acyl side chains. A generic AHL molecule is shown to illustrate the enzymatic processes. **b** Proposed degradation pathway for AI-2 in *Salmonella* or *E. coli* (modified from [43]). The

AI-2 molecule shown is (2*R*, 4*S*)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran or *R*-THMF, which is phosphorylated by LsrK. The phosphorylated AI-2 molecule is ultimately degraded by LsrF and LsrG. The method by which LsrF and LsrG degrade AI-2 is currently under investigation

limitation [34], and expression of the *A. tumefaciens* lactonase AttM is induced through a RelA-dependent mechanism when cells are starved of carbon or nitrogen [35]. At least superficially, these examples of autoinducer degradation being tied to nutrient availability are reminiscent of the regulation of autoinducer production. Most strikingly, autoinducer production by *P. aeruginosa* and autoinducer degradation by *A. tumefaciens* are each regulated by the starvation response regulator RelA. However, RelA activates both of these systems, so there is not a consistent pattern toward increasing or decreasing autoinducer accumulation based on starvation.

Controlled degradation of autoinducers could make for a more dynamic and responsive signaling system; however, an alternative model would be that autoinducers are degraded simply for nutrition, as sources of carbon, nitrogen, or energy. One argument against the latter model is that autoinducers generally function at very low concentrations and would not appear to be attractive growth substrates. Importantly, the autoinducer degradation systems described above catalyze AHL turnover at these low, physiologically relevant concentrations. Moreover, although *P. aeruginosa* is able to utilize AHL as a growth substrate, *A. tumefaciens* is not. Similarly, although *Salmo-*

*nella* degrade their AI-2 signal, as described below, they do not appear to use it as a carbon source [36]. When all of these factors are considered, it seems most likely that the regulation of autoinducer degradation allows bacteria to “take back” an existing signal should conditions change.

The dynamic nature of autoinducer concentration, mediated by controlled synthesis and degradation of the signal, is well-illustrated in the accumulation of AI-2 in culture. AI-2 production can be considered an offshoot, or even a by-product, of the activated methyl cycle, and not surprisingly AI-2 accumulation is connected to central metabolism [37]. The role of AI-2 as a true QS autoinducer is best understood in *Vibrio harveyi*, where recognition of AI-2 by LuxP and LuxQ initiates a regulatory phosphorylation cascade [38, 39]; however, the regulation of AI-2 accumulation is more thoroughly studied in *Escherichia coli* and *Salmonella*. In *E. coli*, the autoinducer synthase LuxS appears to be modulated by CRP based on carbon-source utilization of the cell, and in both bacteria the Pfs enzyme that presumably supplies LuxS with substrate is also transcriptionally regulated in response to the carbon source available [40, 41]. In *Salmonella*, AI-2 production correlates well with *pfs* expression [40]. Moreover, these bacteria possess an elaborate system for sequestering and

destroying the AI-2 already released in culture. The current model (Fig. 3b) proposes that LsrB binds AI-2 and shuttles it back into the cell via a transporter composed of LsrA, LsrC, and LsrD, and that AI-2 is then phosphorylated by LsrK and ultimately degraded by LsrF and LsrG [41, 42]. Like *pfs*, the *lsr* genes are themselves regulated, in part by CRP [41, 43] and also by LsrR, which derepresses most *lsr* genes in response to internalized and phosphorylated AI-2. These systems, and others regulators that are not yet fully described, function such that AI-2 accumulation is influenced by carbon source, osmolarity, pH, iron, oxygenation, redox state, various stresses, and AI-2 itself [44–46]. In contrast to the simple model of autoinducer reflecting cell numbers, AI-2 levels in batch cultures of *E. coli* and *Salmonella* usually peak and then decline.

In addition to being consumed, autoinducers may be removed from a system simply by diffusing away. Under many laboratory conditions where QS is studied, for example with cultures grown in flasks or test tubes, the concentration of autoinducer is generally not affected by local diffusion, because samples are well-mixed and the system is closed. However, in different real-world environments, the same number of cells producing and consuming autoinducer at the same rates may experience different autoinducer concentrations based on local autoinducer diffusion rates. Recently, an alternative view for the function of QS has emerged where autoinducer functions as an environmental probe to allow a bacterial cell to determine the extent of mixing and diffusion in its immediate environment [47]. It is argued that autoinducer-triggered behaviors can benefit single cells in a diffusion-limited environment, in contrast to the idea that bacteria utilize QS to act cooperatively. This raises an interesting issue as to the evolution of signaling pathways and the relation of the control of synthesis and degradation of signals to the particular environmental niche occupied by a bacterium, an area that warrants further exploration.

It is now clear that autoinducers do not necessarily accumulate at a constant rate and are therefore not purely “census-taking” molecules. Even for clonal cultures grown in shake flasks in the laboratory, the concentration of autoinducer reflects not only cell density but also the growth conditions. Environmental signals are transduced through regulatory networks that control both autoinducer synthesis and, at least in some instances, autoinducer degradation as well. Moreover, the “feedforward” nature of many QS systems can greatly amplify these environmental inputs, and the net effects on the autoinducer-to-cell ratio can be dramatic. Finally, environment-specific barriers to autoinducer diffusion may influence the local accumulation of autoinducer and QS behaviors. Thus, autoinducer concentrations are dynamic and very much context-dependent.

### Another layer of complexity: multiple QS systems in bacteria

When autoinduction or QS was first described in *V. fischeri*, it was thought that this bacterium produced a single AHL autoinducer that was produced by LuxI and detected by a single receptor protein, LuxR [7, 8]. However, it has since been found that *V. fischeri* possesses another AHL synthase, AinS, which produces a second structurally distinct AHL signal, octanoyl homoserine lactone, recognized by both LuxR and AinR, which is also called LuxN [48]. *V. fischeri* also produces an AI-2 type signaling molecule [49]. These findings actually followed the first discovery of multiple QS networks within an individual bacterium, which was described in another bioluminescent marine bacterium, *V. harveyi* [50]. The presence of multiple QS systems is now known to be a common trait in bacteria, leading to questions on the identities of the genes regulated by each system and the role(s) of multiple systems in bacterial biology.

Molecular biological tools and whole-genome analyses have been powerful tools in identifying genes belonging to QS regulons in bacteria, most notably in the opportunistic pathogen, *P. aeruginosa*. In particular, *P. aeruginosa* DNA microarray analyses have provided new insight into the complexities inherent in QS-controlled gene expression and have provided a framework for comparative studies in other organisms (reviewed in [25]). Through these analyses, it has become apparent that the multiple QS systems in *P. aeruginosa* influence the expression of a wide range of genes, and, as mentioned above, QS gene regulation is embedded in a network of regulatory pathways that respond to environmental signals.

Using microarray analysis of specific *P. aeruginosa* QS regulatory mutants, three independent groups identified hundreds of genes belonging to the two QS regulons [25, 51–53]. While many predicted suites of genes (e.g., those encoding virulence factors) were QS-regulated, these analyses also identified genes whose products are involved in “housekeeping” cell processes such as central metabolism [25], demonstrating that QS signaling can have global effects on gene expression in bacteria and can influence cell physiology. However, when comparing the three independent studies, most of the “regulated” genes were identified by only one or two of the groups, and only 102 QS-induced genes were common to all three data sets [25]. Considering the three experiments were performed in separate laboratories with differences in experimental conditions, this interesting result suggests that environmental conditions can have profound influences on QS gene regulation.

One surprising result of these studies is that there does not appear to be a single cell density at which all QS-regulated genes are induced or repressed, and the “quorum” required for expression depends on the gene

and environmental conditions. The expression of individual QS genes is influenced by the presence and/or absence of each of the two *P. aeruginosa* AHL signals, so the cells contain distinct regulons responsive to one or both signals, each of which has its own critical threshold concentration. In addition, many QS-controlled genes do not respond to exogenously provided AHL signals until the cells reach the stationary phase of growth [25, 52], which can be explained by the requirement for the stationary-phase  $\sigma$  factor RpoS for activation of QS [26, 27, 54], or the presence of inhibitors in the culture medium [55]. These results show that QS gene regulation is not solely influenced by signal accumulation, but requires the presence of additional factors and is responsive to environmental conditions (reviewed in [25, 56]). The fact that QS gene regulation is entangled in a network of other regulatory pathways suggests that bacteria tightly control this process so that particular QS regulon genes are only expressed under the appropriate conditions. This leads to the question of the role of these complex multiple QS systems in bacterial growth in a “natural” environment, for example during host colonization.

The use of model systems such as the symbiosis between *V. fischeri* and the Hawaiian bobtail squid *Euprymna scolopes* are beginning to reveal the importance of multiple QS systems for bacteria inhabiting a natural environment. This system has been studied for over 15 years as a model for the extracellular colonization of host tissue by cooperative and pathogenic bacteria [57, 58]. As mentioned above, *V. fischeri* contains two AHL-based QS systems, LuxI/LuxR and AinS/AinR, as well as a LuxS/AI-2-based QS system, and these each influence the expression of bioluminescence [7, 8, 48]. Since luminescence is an integral part of the symbiotic relationship, the role of each system in light production and host colonization were investigated.

These studies revealed a complex picture of the involvement of each system in the regulation of light production and host colonization (reviewed in [59]). Analysis of *luxI*, *luxS* and *ainS* mutants during growth in liquid culture and during host colonization revealed a stepwise activation of the QS systems with increasing cell density [60–62]. *ainS* and *luxS* influence light production in broth cultures and are important for initiation of the symbiosis, conditions that correspond to lower cell densities. The AHL signal produced by AinS appears to be the dominant signal under these circumstances, with AI-2 playing a lesser role [49]. In contrast, the presence of *luxI* has little if any influence on luminescence in liquid culture, but is necessary for boosting luminescence during later stages of the colonization process, corresponding to the higher cell densities present in the squid light organ as compared to laboratory culture conditions. It is important to note that in certain strains of *V. fischeri*, including the

very brightly bioluminescent strains initially characterized, *luxI* does play a role in stimulating bioluminescence in culture, which explains why it was discovered early on. For reasons that are not yet clear, low expression of *luxI* in culture appears to be a hallmark of the *V. fischeri* strains isolated from *E. scolopes* [63, 64].

The involvement of *ainS* in initiation of colonization suggested that this QS system influences the expression of genes other than those responsible for light production. A *V. fischeri* DNA microarray was used to identify genes whose expression was altered in the presence of *ainS*, and this approach revealed 30 differentially regulated genes potentially involved in motility, transcriptional regulation, metabolism and biosynthesis of extracellular polysaccharides [60]. Although such detailed microarray analyses of the roles of *luxI* and *luxS* are not yet published, a proteomic approach suggested, not surprisingly, that the LuxI/LuxR system also controls several target genes involved in a variety of processes, including genes whose function are important during host colonization [65]. Thus, although the LuxI/LuxR, AinS/AinR, and AI-2 type QS systems were initially implicated in the control of bioluminescence, in-depth studies are revealing specific and distinct functions for each system in the biology of *V. fischeri* and its interactions with the squid host, and the function of autoinducer-mediated gene regulation has proven far more complex than the original model presented in Figs. 1 and 2.

The study of QS gene regulation in *P. aeruginosa* and *V. fischeri* has provided valuable insight into the complex roles of autoinducers as modulators of global regulatory systems that influence many aspects of bacterial physiology and host interactions. Moreover, these two model systems are illustrative of similar discoveries in many other bacteria. Although the initial simple model of quorum sensing (e.g., Fig. 1) requires only a single autoinducer compound to serve as a census-taker and to direct population-based regulatory decisions, it is now clear that several bacteria produce multiple autoinducers, that their cognate regulators are embedded in other regulatory networks, and that the genes they control are not always clearly connected to group behaviors. This surprising complexity and diversity of QS in bacteria is likely a reflection of the evolution of these systems in bacteria that need to respond to fluctuating and diverse conditions, particularly during the transition from life in the environment to living inside a host.

### Outside influences on bacterial quorum sensing

Bacteria that regulate gene expression through AHL-based QS are often found in mixed microbial consortia associated with plants or animals. Because QS-related behaviors such as virulence factor production, biofilm formation, and antibiotic

production often have detrimental effects on the other members of these dynamic communities, it is not surprising that plants, animals, and other microorganisms have developed methods for interfering with QS signaling processes.

The first indication that compounds from other organisms could influence QS in bacteria came with the discovery that halogenated furanones produced by the marine red alga *Delisea pulchra* acted as QS mimics that could inhibit bacterial AHL-controlled processes [66]. The mode of action of furanones is to bind to AHL receptor proteins and promote their proteolytic degradation [67, 68]. Intriguingly, *D. pulchra* is known to be remarkably free of bacterial fouling in marine environments, and the ability to disrupt bacterial QS is thought to be at least partly responsible for this characteristic. This initial report was followed by the discovery that a green alga, *Chlamydomonas reinhardtii*, and certain higher plants also secrete compounds that affect AHL-based QS regulation in bacteria [69–71]. The chemical structures of these compounds remain to be solved, but interestingly, most appear to stimulate rather than inhibit AHL-controlled gene expression.

The ability to modulate AHL-based bacterial QS is not limited to algae and plants. In addition to the AHL degradation and turnover by autoinducer producers (described above), numerous bacteria that do not produce AHL signals also inactivate AHLs enzymatically through the production of AHL acylases or lactonases (Fig. 3) [72–78]. It may be the case that interfering with QS signaling could give these bacteria a competitive advantage when occupying the same environmental niche as AHL-producing bacteria [79]. In addition, certain bacteria can not only inactivate AHLs, but also utilize them as sole carbon and/or nitrogen sources for growth [75, 78, 80], adding another potential benefit to the degradation of AHL signals. Although each specific AHL signaling molecule may not be very abundant, the total concentration of different AHLs in a microbial community could make them an attractive nutrient source, and AHL degraders may also find less competition for this substrate and thus occupy a specialized niche. Enzymatic degradation of AHL signals has also been described in certain mammalian cell types [81, 82], suggesting that host cells may be able to counteract QS signaling during bacterial infection and colonization. The studies mentioned above provide a just a sample of the ways in which other organisms can influence AHL-based QS systems, and the intense interest in this topic has resulted in several more comprehensive reviews [79, 83–85].

## Conclusions

Early studies of autoinducer-mediated gene regulation led to an intuitive and relatively simple model of QS systems as

mechanisms of censusing bacterial populations and regulating the expression of genes with roles specific to life as solitary cells or as dense groups. Over the years a much more complex picture has emerged, wherein autoinducers are dynamically controlled, individual cells produce multiple autoinducer molecules, organisms compete by disrupting QS signals, and a wide range of genes are regulated in coordination with other global regulators but not always with direct correlation to population numbers. The discovery that bacteria can use QS to regulate virulence gene expression and other medically and economically important behaviors has led to an explosion of research in this area, and with these applications in mind, future research geared toward unraveling QS in real-world environments will undoubtedly uncover more complexities inherent in these systems.

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