

Communication Circuits in Bacteria

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Abstract

Quorum sensing (QS) has emerged as a central mechanism by which bacteria coordinate gene expression across populations. As synthetic biology has advanced, QS has been developed into a widely exploited design layer for programming collective behaviors in living systems. At the same time, the diversity of QS chemistries and architectures discovered in natural communities suggests that microbial communication contains a much larger and more versatile design space than the classical LuxI/LuxR QS paradigms alone. These developments open the door to future applications in programmable therapies, bioprocess control, and microbiome engineering that harness QS as an internal decision-making and coordination module. In this article, we review the historical development and canonical architectures of natural QS systems, including acyl-homoserine lactones, autoinducing peptides, and AI-2 pathways. We then outline design principles that govern QS-based communication and show how they guide the construction of synthetic gene circuits. Finally, we survey engineered uses of QS, highlighting applications in synchronized gene expression, spatial pattern formation, stabilized consortia, and emerging bacterial therapeutics, and discuss how expanding QS repertoires and design frameworks could enable the next generation of programmable population-aware synthetic microbes.

Keywords: quorum sensing; synthetic biology; microbial communication; gene circuits; population dynamics; microbial consortia; engineered microbes; bacterial therapeutics; bacterial bioprocess

1. Introduction

1.1. An Overview of Bacterial Quorum Sensing

Quorum sensing (QS) is a widespread and versatile mode of microbial communication, exhibited across diverse microorganisms and now re-engineered to drive synthetic biological systems (Figure 1). QS was first described in the 1970s through pioneering studies of the bioluminescent marine bacterium *V. fischeri* [1,2]. These studies revealed the “autoinduction” mechanism driving QS, where a positive feedback loop is activated by a diffusible small molecule (Figure 2). Because the signal molecule is freely diffusible, its extracellular concentration acts as a reporter of the local population density, allowing cells to make collective gene expression decisions when coupled to signal-sensitive transcription factors (TFs). In *V. fischeri*, this mechanism is used to control bioluminescence once a sufficient number of neighbors are present, ensuring a bright bioluminescence output. Molecular



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interrogation of the bioluminescence genetic operon in *V. fischeri* identified the LuxI/LuxR proteins as the key regulators of its density-based autoinduction [3].

Quorum Sensing: From Discovery to Engineering

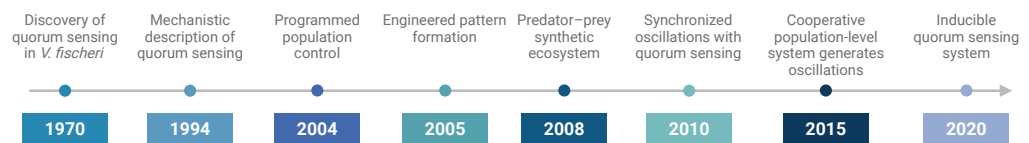


Figure 1. Timeline of quorum sensing exploration and engineering. Starting with its discovery in the naturally bioluminescent *V. fischeri* in the 1970s [1], quorum sensing has been probed, elucidated, and refined throughout the scientific literature [3]. The early 2000s saw elegant design schemes using quorum sensing for population control [4] and pattern formation [5]. From the late 2000s to the present day, groups have been employing quorum sensing in multi-strain consortia [6] and engineering spatiotemporally dynamic behaviors [7–9].

Subsequent work revealed that QS as a phenomenon is not restricted to a single species or molecular class. Homologous LuxI/LuxR-type QS systems, such as Cin, Las, and Rpa systems, were discovered in a wide range of Gram-negative bacteria where they use N-acyl homoserine lactones (AHLs) as signal molecules to regulate traits including exoenzyme secretion, motility, conjugation, and biofilm formation [10,11]. In parallel, conceptually analogous but mechanistically distinct QS systems were discovered in Gram-positive bacteria. Many of these Gram-positive QS systems instead use ribosomally encoded, post-translationally processed autoinducing peptides (AIPs) as signals [12]. AIPs are translated, processed, and then exported before diffusing in the extracellular medium. Density-dependent signaling then occurs via membrane-localized surface receptor proteins, either sensor kinases or peptide transporters. Ultimately, AIP signaling drives transcriptional activity and generates a QS response. Later, a third major signaling paradigm centered on autoinducer-2 (AI-2) was discovered by investigating *V. harveyi* mutants lacking LuxI/LuxR QS systems [13]. Together, these findings established QS as a general strategy for coordinating group behaviors in bacterial species rather than a bioluminescence-specific phenomenon in *V. fischeri*.

Early definitions emphasized QS as a mechanism by which bacteria measure and respond to cell density. Notably, small-molecule or peptide-based signals accumulate in proportion to population size, and once a critical threshold is exceeded, they trigger a coordinated change in gene expression across the population. However, subsequent studies have shown that QS responses can be graded rather than strictly thresholded and can be further modulated by additional environmental inputs such as nutrient availability and oxygen concentrations. The same QS system can control distinct phenotypes in different contexts, suggesting more nuanced behavior. The modern view therefore treats a natural QS system not as a simple cell-density sensor but as a distributed communication system that coordinates temporally and spatially organized behaviors in complex environments [7,14–16]. Autoinducers and their cognate receptors are now recognized as components of larger regulatory networks that integrate multiple information streams, including metabolic state, stress responses, and physical structure of the environment. Natural QS gene circuits act as communication modules embedded within multi-layered regulatory architectures that collectively determine when, where, and to what extent group behaviors are deployed.

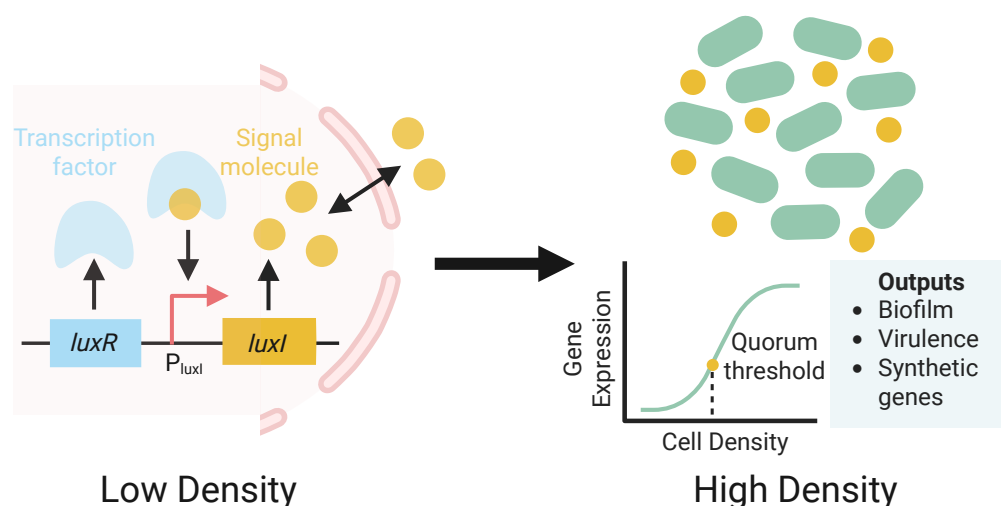


Figure 2. Canonical LuxI/LuxR-type quorum sensing mechanisms generate density-dependent behaviors. Natural LuxI/LuxR-type quorum sensing architectures consist of a membrane-diffusible signal molecule (yellow) which, when bound to its cognate transcription factor (blue), activates gene transcription along the P_{luxI} promoter (red arrow). Positive feedback, along with diffusibility, makes the signal molecule useful for generating population density-dependent outputs in both natural and synthetic gene circuits.

1.2. QS as a Communication Circuit

Given the broader functional repertoire of natural QS circuits, it is useful to explicitly frame QS systems as communication circuits. Borrowing language from communication theory and systems engineering, one can distinguish three core elements: an encoder, a channel, and a decoder [17] (Figure 3). In QS systems, the encoder corresponds to the biochemical machinery that synthesizes and exports a density-dependent signal. For LuxI/LuxR-type QS systems, this is an AHL synthase such as LuxI; for AIP QS systems, the encoder includes the prepeptide, processing enzymes, and export machinery; and for the AI-2 QS system, the encoder consists of the LuxS-dependent activated methyl cycle, in which LuxS converts S-ribosylhomocysteine into the AI-2 precursor. Regulation of gene expression, enzyme catalytic rates, substrate availability, and membrane transport properties of these encoder modules determine how cell density is translated into extracellular signals.

The channel is the extracellular medium through which signals propagate and are transformed. In a well-mixed culture, the channel may be approximated as a homogeneous volume characterized by diffusion and first-order degradation or dilution [18,19]. In other environments, channel dynamics can be shaped by flow-induced convective transport or advection, binding to surfaces or the extracellular matrix, biofilm formation, enzymatic degradation mechanisms, and spatial structures [20,21]. For example, in an open environment with boundaries, such as a bioreactor, convective flow and aeration-induced advection can facilitate quorum sensing activation, particularly between biofilm granules, which also serve as local activation hotspots [21]. In contrast, convective flow in an unbounded open environment can repress quorum sensing by diluting signals [20]. The effects of local signal gradients and time delays produced by mixing in scaled-up environments must be further studied to better understand how QS signals integrate over space and time under different channel dynamics [22]. Media composition may also affect signal stability by altering degradation kinetics. Nevertheless, QS-mediated regulation has been demonstrated in undefined media under bioprocess-relevant conditions. For example, AHL-based QS systems have enabled dynamic regulation in undefined media [6,8,23], including 3 L bioreactor studies using T12 undefined medium [24,25]. Similarly, AIP-based

regulation has been demonstrated in undefined medium in a 15 L bioreactor for vitamin K2 (MK-7) production [26]. These examples indicate that complex media do not preclude effective QS regulation, although the extent to which medium composition influences signal stability and circuit performance is likely system- and process-dependent, and warrants consideration during scale-up.

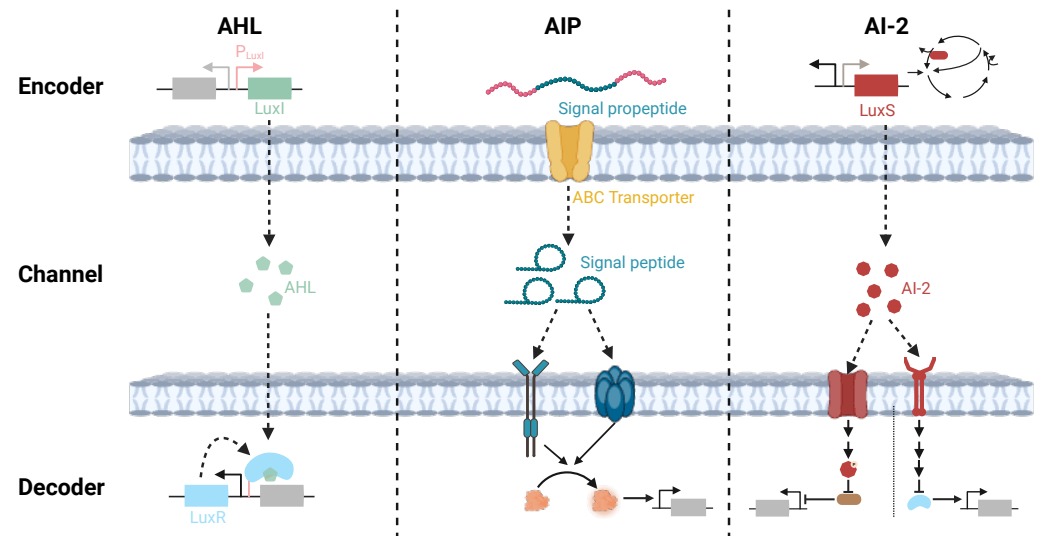


Figure 3. Types of natural quorum sensing architectures. Natural quorum sensing architectures can be understood to comprise three parts: the signal encoder, the channel through which the signal is transmitted, and the decoder which translates the signal to an output. Left, LuxI/LuxR-type QS system. Middle, AIP QS system. Right, AI-2 QS system.

The decoder layer comprises the molecular machinery that senses the signal and converts it into changes in gene expression or physiology. In LuxI/LuxR-type QS systems, the decoder is a cytoplasmic LuxR-type transcription factor whose activity on the P_{luxI} promoter is upregulated when complexed with AHL [3,27]. In AIP systems, extracellular peptides are either sensed by histidine kinases or by reimport into the cell cytosol [28,29]. In either mechanism, this information is relayed to response regulators, which, in turn, control transcriptional output. In AI-2 QS systems, AI-2 is sensed either extracellularly via periplasmic binding proteins and sensor kinases that trigger phosphorelays (e.g., LuxP/LuxQ in *Vibrio*) or intracellularly after uptake and phosphorylation [30], where phospho-AI-2 binds transcription factors such as LsrR to control gene expression [31].

Importantly, QS communication circuits are also embedded within and constrained by global regulatory networks [32,33]. Additional factors such as the nutrient-sensitive CRP, stress-response regulators, and alternative sigma factors have been discovered to modulate QS component expression and activity, influencing communication according to metabolic and stress conditions [34–36]. QS outputs can also feed back into cellular physiology and affect the global regulatory networks by altering metabolism, motility, and stress tolerance in ways that reshape the encoder (e.g., by reallocating resources toward or away from signal production), the channel (e.g., by changing biofilm matrix production), or the decoder (e.g., by altering membrane protein composition) [33].

2. Architectures of QS Systems

Natural QS systems encompass diverse signal chemistries, receptors, and regulatory architectures, but can be grouped into a few canonical modules. In bacteria, three classes dominate: AHL-based systems in Gram-negative species, peptide-based circuits in Gram-positive species, and AI-2 and related interspecies signaling systems. Interrogation of these

systems has led to modules that can be repurposed to control distinct phenotypes, and now form a practical parts list for synthetic gene circuit design.

2.1. *LuxI/LuxR-Type Systems*

The best-studied QS architecture is the LuxI/LuxR system. LuxI/LuxR-type QS systems use *N*-acyl homoserine lactones (AHLs) as diffusible autoinducers [3,27] (Figure 3). AHLs diffuse across cell membranes and rapidly equilibrate between intra- and extracellular spaces, so the extracellular AHL concentration reports on local cell density. Canonical synthetic QS circuits are generally organized around LuxI-type synthases and LuxR-type TF. LuxI-type enzymes produce AHLs with distinct acyl-chain lengths and modifications, which influence membrane permeability, stability, and receptor affinity [37]. LuxR-type receptors are cytoplasmic TFs that bind their cognate AHLs. AHL binding stabilizes the LuxR-type receptor, promotes DNA binding, and enables regulation of target promoters [38].

A common feature of LuxI/LuxR-type QS is positive feedback. The activated TF–AHL complex often upregulates AHL synthase expression, sharply increasing AHL production. A result of this positive feedback is thresholding at a specific cell density, enabling ultrasensitive or bistable responses in appropriate dynamical contexts [39]. Other members of the LuxI/LuxR-type QS family work in reverse. For example, the EsaI/EsaR system applies negative feedback at threshold density [40]. EsaR binds to its cognate promoter and activates gene expression in the absence of its AHL. Once the AHL binds to the TF, the TF unbinds from its promoter, deactivating gene expression.

Many Gram-negative species encode multiple AHL circuits and additional signal types in parallel. *Vibrio harveyi*, for example, integrates AHLs, furanosyl borate diesters, and species-specific autoinducers through a shared phosphorelay and small-RNA regulatory hub [30]. In *Pseudomonas aeruginosa*, a broad virulence repertoire is controlled by a complex QS architecture featuring at least four interconnected systems: LasI/LasR, RhlI/RhlR, the *Pseudomonas* quinolone signal (PQS) system controlled by the transcription factor MvfR, and the Iqs system [33]. In such multiplexed architectures, distinct signals encode information about self-recognition, strain identity, or community composition, and their joint decoding allows bacteria to infer community context and coordinate context-dependent responses.

2.2. *AIP Systems*

Many Gram-positive bacteria use ribosomally encoded autoinducing peptides (AIPs) as QS signals [28]. These peptides are synthesized as precursor polypeptides, processed, and exported before acting on membrane-associated receptors. The Agr system of *Staphylococcus aureus* illustrates a canonical peptide-based QS circuit [29] (Figure 3). AgrD encodes a propeptide that is processed and cyclized by the membrane protein AgrB, which also exports the mature thiolactone AIP molecule. The extracellular AIP accumulates with cell density and binds the surface receptor AgrC, a histidine kinase that autophosphorylates and transfers phosphate to the response regulator AgrA. Phosphorylated AgrA activates transcription from P_2 (driving the *agrBDCA* operon, leading to positive feedback) and P_3 (producing RNAIII, a regulatory RNA that controls a broad virulence regulon). In other AIP QS systems such as Rgg/SHP systems, the AIP signal peptide is reimported and sensed by a cytoplasmic transcription factor to drive downstream expression [41].

The location of AIP detection creates distinct constraints for peptide-based QS systems. In surface-sensing systems, extracellular AIPs are detected by membrane-bound two-component systems, and signal transduction through phosphorylation provides a potential route for rewiring QS into other regulatory networks [15]. Because the signal remains

extracellular prior to detection, it is also exposed to environmental processes such as degradation by secreted proteases, which can alter signal persistence and the effective signaling range. By contrast, in AIP systems that rely on peptide reimport and cytoplasmic sensing, the internalized signal is no longer free to diffuse between cells and must instead be removed through intracellular degradation or dilution [42]. These differences in signal localization and clearance can therefore produce distinct constraints on the persistence, dynamics, and engineering of AIP-based communication circuits.

2.3. AI-2 Systems

Some QS signals have been proposed to act as mediators in interspecies communication. Autoinducer-2 (AI-2), a family of furanosyl borate diesters generated by LuxS in the activated methyl cycle, is the best studied [13] (Figure 3). AI-2 production in Gram-negative bacteria is tightly coupled to central metabolism, and can therefore be influenced by stress and metabolic burden, allowing it to serve as a reporter on cellular metabolic state [43,44]. In addition, AI-2 synthesis and uptake are subject to cAMP-CRP complex regulation, which indirectly influences AI-2 levels in accordance with the presence of glucose [45]. In *Vibrio harveyi*, AI-2 is recognized by the periplasmic binding protein LuxP and the sensor kinase LuxQ, which feed into a phosphorelay cascade that integrates AHL with AI-2 into density-dependent activation [30]. In many enteric bacteria, AI-2 is imported via an ABC transporter, phosphorylated in the cytoplasm, and sensed by the transcriptional regulator LsrR, which controls AI-2 uptake and downstream gene expression [31].

Because LuxS is broadly conserved across a range of bacterial genera, AI-2 was originally suggested as a universal bacterial “language”, though different species have evolved distinct niche-specific signal transduction systems [46]. However, much of the experimental evidence pointing to AI-2 as a cross-species mode of communication has focused on the presence of LuxS, while subsequent genomic and literature analyses point to an absence of known AI-2 receptors in many other bacterial species, despite harboring LuxS [47]. AI-2 production’s coupling to central metabolism suggests that evaluating the effects of LuxS presence or absence without chemical complementation experiments or identification of alternative AI-2 receptors is insufficient to deduce a role in quorum sensing distinct from its metabolic effects. Nevertheless, a cross-species QS system tied to central metabolism potentially offers a mode for coupling population-level behavior to metabolic state in microbial community design, while establishing an additional design layer that necessarily considers cell state and environmental context [48].

Beyond AI-2, additional small molecules—short-chain fatty acids, indole, and host-derived hormones—contribute to interspecies and interkingdom communication, sometimes by cross-reacting with LuxR-type receptors and sometimes via distinct sensory pathways [49]. Together, these examples broaden microbial communication beyond canonical species-specific AHL signaling.

3. Design Principles of QS Systems

QS circuits, treated as communication modules, reveal recurring design principles that govern both natural behavior and engineered applications. These principles link biochemical implementation (synthases, receptors, promoters, regulatory RNAs) to quantitative properties such as sensitivity, dynamics, and robustness.

3.1. Modularity, Orthogonality, and Crosstalk

A central property of QS systems is their modularity. In LuxI/LuxR-type QS systems, an AHL synthase (e.g., LuxI, LasI, or CinI) defines the signal chemistry and production kinetics, a cognate LuxR-family TF (e.g., LuxR, LasR, or CinR) decodes the signal, and a

promoter with appropriate binding sites (e.g., P_{lux} , P_{las} , or P_{cin}) converts regulator activity into transcriptional output. Transplanting these components into new hosts allows QS systems to function as plug-and-play inputs that drive arbitrary output genes for engineered microbes [50]. However, crosstalk between QS systems can compromise the specificity of engineered behaviors, and orthogonality between modules is, therefore, critical for composing multiple QS systems.

QS crosstalk can occur at the promoter level via promiscuous DNA/TF-AHL complex binding, the signal level via promiscuous TF-AHL binding, or at both [50]. Crosstalk maps built from synthase–receptor panels show that some systems are nearly orthogonal to Lux or Las, whereas others exhibit strong off-target activation [50,51] (Table 1). Signal crosstalk and promoter crosstalk have different consequences. Signal crosstalk inhibits the orthogonality between the two systems when the media or culture environment is shared, such as within a synthetic consortia of multiple QS strains. Promoter crosstalk inhibits the use of two QS systems within the same cell, as the active TF-AHL complexes can bind to either promoter unit to drive expression. Both, generally, inhibit the utility of QS devices for engineering applications, but could become a useful design feature in some applications, e.g., a two-input, two-output device where one input is broadcast to both outputs.

Table 1. Summary of LuxR-type QS signal crosstalk.

System	Promoter	Receptor	Cognate AHL	Signal Crosstalk	Promoter Crosstalk
Rpa	P_{rpa}^* ¹	RpaR(W) ¹	pC-HSL	-	Lux ¹ , Las ¹
Lux	P_{lux}	LuxR	3O-C6-HSL	Tra ¹ , Las ¹	Las ¹ , Rpa ¹
Tra	P_{tra}^* ¹	TraR(W) ¹	3O-C8-HSL	Lux ¹ , Las ¹	-
Las	P_{las}	LasR	3O-C12-HSL	Tra ¹ , Cin ²	-
Cin	P_{cin}	CinR	3OH-C14-HSL	Lux ²	*

¹ Source: Scott and Hasty (2016) [50]. ² Source: Kylilis et al. (2018) [51]. * Not measured. - None observed with other QS systems present in the table.

Crosstalk can occur at different signal concentration ranges between systems. For example, the Lux QS system activates in response to its cognate AHL at a concentration an order of magnitude lower than it responds to the cognate Tra AHL, and another order of magnitude lower than it responds to the cognate Las AHL [50,51]. However, the fold change in promoter expression is similar once the Lux system has activated without regard to which AHL activated it. As a result, the simultaneous use of multiple quorum sensing systems requires careful consideration of the expected working range of each quorum sensing device and the expected concentration of AHL signals produced. For brevity, we have summarized these complications into Table 1. Signal crosstalk was identified by non-cognate AHL-induced activation (fold change) of promoter activity greater than 30% of cognate AHL activation across the range of concentrations studied in the cited works. Promoter crosstalk was identified by non-cognate receptor activation of the promoter greater than 30% of cognate receptor activation when coupled to the receptor-cognate AHL in the cited works. For example, the presence of Lux in the Rpa system promoter crosstalk column indicates that P_{rpa}^* was activated in the presence of LuxR and 3O-C6-HSL. The activation function parameters for each cognate system and any measured signal level crosstalk are given in Table 2.

Protein and promoter engineering has produced variants that reduce coupling between quorum systems for both signal and promoter crosstalk; see, for example, Meyer et al. for orthogonal Lux and Cin variants [52]. Porting QS modules in non-native hosts, such as utilizing LuxI/LuxR-type QS systems in cyanobacteria or Gram-positive bacte-

ria, typically requires further tuning of components to maintain orthogonality without compromising dynamic range [53,54]. When multiple engineered QS modules operate in the same host microbe, they also compete for shared resources like RNA polymerase and ribosomes. Strategies to mitigate these indirect couplings include reducing shared resource consumption by weakening promoters and ribosome-binding sites and distributing QS system tasks across strains in a consortium instead of stacking them within a single strain [53,55]. Of particular interest are computational models that explicitly include resource competition to predict emergent behaviors and identify parameter regimes that balance responsiveness and orthogonality [56].

Table 2. LuxR-type QS system activation functions in crosstalk studies.

System	Promoter	Receptor	AHL	EC50	Fold Change	Source
Rpa	P _{rpa}	RpaR	pC-HSL	1.14×10^{-10}	2.11	[51]
	P _{rpa} *	RpaR(W)	pC-HSL	4.99×10^{-10}	27.12 ± 0.12	[50]
Lux	P _{lux}	LuxR	3O-C6-HSL	4.54×10^{-9}	31.5 ± 0.36	[50]
			3O-C8-HSL	1.1×10^{-8}	32.5 ± 0.12	[50]
			3O-C12-HSL	4.75×10^{-7}	29.3 ± 0.03	[50]
Tra	P _{tra}	TraR	3O-C8-HSL	6.75×10^{-8}	6.97	[51]
			3O-C6-HSL	6.31×10^{-8}	7.18	[51]
			3O-C12-HSL	1.39×10^{-5}	7.53	[51]
	P _{tra} *	TraR(W)	3O-C8-HSL	3.16×10^{-8}	5.4 ± 0.06	[50]
			3O-C6-HSL	5.89×10^{-8}	5.1 ± 0.06	[50]
			3O-C12-HSL	9.65×10^{-7}	7.1 ± 0.05	[50]
Las	P _{las}	LasR	3O-C12-HSL	1.18×10^{-9}	98.7 ± 1.11	[50]
			3O-C8-HSL	5.95×10^{-7}	90.3 ± 0.52	[50]
Cin	P _{cin}	CinR	3OH-C14-HSL	3.41×10^{-6}	3.42	[51]
			3O-C6-HSL	9.18×10^{-4}	3.42	[51]
		CinR ^{AM}	3OH-C14-HSL	4.3×10^{-7}	500	[52]

3.2. Circuit Motifs and Quantitative Performance

Across AHL, AIP, and AI-2 systems, a small set of circuit motifs recurs and shapes circuit architecture [10,14,57]. Positive feedback—often via autoinduction of synthases or QS operons—amplifies small signal differences and generates ultrasensitive responses. In spatially structured environments, such feedback accentuates local signal accumulation and can support pattern formation or localized activation.

Negative feedback and gain-control mechanisms limit response amplitude and duration. Transcriptional repressors, small RNAs, proteolysis of regulators, and signal-degrading enzymes such as AHL lactonases and acylases all dampen QS responses or enforce adaptation [58]. In *Vibrio*, quorum-regulated small RNAs control master transcription factors and participate in feedback loops that tune response timing and buffer noise [59]. Feedforward loops and cascades couple QS to other sensory inputs, allowing integration of density information with metabolism, stress, or growth-phase signals.

From a design standpoint, three quantitative performance metrics are central: the dynamic range, signal-to-noise ratio (SNR), and response time [60]. Dynamic range, the ratio of maximal to basal output, determines how cleanly a circuit separates “on” and “off” states. The SNR is controlled by promoter leakiness, background activation by non-cognate signals, and intrinsic noise in regulator expression. The SNR of a QS system can be improved by promoter engineering, tuning regulator expression, and adding degradation tags to limit accumulation of inactive species [61]. Response time reflects signal synthesis and diffusion, receptor folding and binding, and downstream transcription–translation–degradation.

For circuits that must synchronize dynamics across a population like oscillators, these timescales must be matched to environmental timescales such as convective flow and cell growth rate to achieve robust behavior.

3.3. Burden, Toxicity, and Evolutionary Stability

Finally, practical use of QS circuits is constrained by genetic burden and evolutionary stability. Quantifiable indications of metabolic burden as a result of QS systems typically include a reduced growth rate or final density as a result of central metabolite depletion [62]. In fact, overexpression of synthases, regulators, or toxic effectors can slow growth and select for loss-of-function mutations, especially in long-term or *in vivo* contexts [63,64]. Ruparell et al. evaluated the energy cost of producing quorum sensing signal molecules themselves, estimating approximately a 7% cost in total ATP as a result of the metabolic burden of producing AHLs [62].

Beyond reducing gene expression, toxin–antitoxin (TA) systems have been used to stabilize plasmids more generally [65,66]. Genomic integration and host optimization are also commonly employed to enhance engineered circuit stability [67–69]. More advanced concepts can be applied to stabilize genetic circuits. Division-of-labor architectures in which burdensome tasks are distributed across cells in a co-culture reduce per-cell burden and can improve the stability of individual modules [55,70]. Other stabilizing strategies include suppressing mutant emergence to promote circuit stability and reducing the advantage of mutants as a result of metabolic burden or toxicity [64]. For example, coupling circuit function to essential cellular processes using overlapping sequences can pressure cells to maintain engineered behaviors since mutation of the engineered gene would be detrimental to its essential function [71]. Finally, Liao et al. implemented a rock–paper–scissors logic, in which each population can eliminate another, allowing periodic re-seeding of the engineered strains to prevent mutant escape within a culture [72].

Recent work emphasizes that reliable QS engineering requires integrated design–build–test–learn cycles that combine gene circuit libraries, characterization, and community-level modeling [73,74]. Under this lens, natural QS architectures supply both mechanistic insight and a catalog of parts, while their design principles guide the construction of synthetic QS communication circuits.

4. Synthetic and Applied Communication Circuits

Synthetic biology has transformed quorum sensing (QS) from a natural communication strategy into a programmable wiring scheme for multicellular computation, pattern formation, and therapeutic control. These have led to the development of synthetic gene circuits that explore population control, spatiotemporal dynamics and patterns, synthetic ecosystems, and dynamic regulation in bioprocessing. In this section, we survey archetypal intra- and inter-population architectures (Figure 4) and highlight emerging work (Table 3).

4.1. Programmed Population Control

One of the earliest demonstrations showing that QS can be harnessed is the programmed population control system by You et al. (Figure 4A) [4]. In this work, *E. coli* cells were engineered so that LuxI/LuxR-dependent expression of CcdB led to cell death when population density exceeded a threshold. The circuit coupled growth to AHL density via inducible expression of LuxI from $P_{lac/ara}$. At low density, AHL levels remain below the threshold, allowing cells to grow. As density increases and AHL accumulates, LuxR activates CcdB protein expression. The result is emergent negative feedback at the population level, producing a dynamic steady state that balances growth and death below the carrying capacity of the media. The experimental system showed robust regulation of population

density over a broad range of initial conditions and parameter values, illustrating how QS-based circuits can overcome cell-to-cell heterogeneity with coordinated behavior.

Table 3. Overview of QS in select synthetic biology applications.

Operation	QS System	Brief Description	Citation
Programmed population control	LuxR/LuxI	Autonomously regulated population control using CcdB toxin	[4]
Oscillatory lysis cycles	LuxR/LuxI	Pulsatile release of genetically encoded cargo using Φ X174E	[23]
Therapeutic payload delivery	LuxR/LuxI	Pulsatile release of immunotherapeutic payload in tumor microenvironment	[75]
Population dynamics interfaced with microelectronics	LuxR/LuxI	Electrical detection of oscillatory impedance generated by population cycling	[76]
Synthetic predator–prey ecosystem	LuxR/LuxI LasR/LasI	Synthetic ecosystem with tunable predator–prey dynamics facilitated by CcdB/CcdA toxin/antitoxin system	[6]
Synthetic two-strain ecology	LuxR/LuxI RpaR/RpaI	Synthetic two-strain ‘ortholysis’ co-culture mediated by orthogonal self-lysis	[19]
Population-synchronized gene expression oscillations	LuxR/LuxI	Oscillations generated by AiiA AHL-lactonase negative feedback	[9]
Two-strain oscillatory expression	CinR/CinI RhIR/RhII	Activator upregulates gene expression in both strains and “repressor” downregulates, each by producing orthogonal signaling molecules	[8]
Synchronized DNA copy number oscillations	LuxR/LuxI	Oscillations generated by plasmid copy number regulation mediated by I-SceI endonuclease	[77]
Ring-like pattern formation	LuxR/LuxI	Sender cell produces signaling molecules that receiver cells use a band-detect network to turn on only at intermediate concentrations	[5]
Edge detection	LuxR/LuxI	Two-component genetically encoded light sensor coupled to genetic logic gate where a light and signaling molecule produces visual output	[78]
Stripe patterns	LuxR/LuxI	Density-dependent cell motility generates periodic stripes	[79]
Turing-type patterns	LasR/LasI RhIR/RhII	Activator and inhibitor molecules give rise to periodic patterns due to slower diffusion rate and positive feedback of activator molecule	[80]
Ring pattern formation independent of spatial morphogen distribution	LuxR/LuxI	Temporal pattern formation using local activation by T7 RNA polymerase and global inhibition with fast signal diffusion	[81]
Branching pattern	LuxR/LuxI	Symmetry breaking by coupling cell communication to adhesion and elongation	[82]
Out-of-phase rings	LuxR/LuxI LasR/LasI	Two-strain density-dependent reciprocal motility regulation	[83]
Distributed computation of two-input logic gates	LasR/LasI RhIR/RhII	QS sender and receiver devices spatially organized to facilitate Boolean logic gates	[84]
Autoinducing bioproduction	AI-2	Inducer-free production of recombinant proteins	[85]
Autoinducing bioproduction	LuxR/LuxI	Inducer-free production of bisabolene	[86]
Dynamic bioproduction for increased titers	EsaR/EsaI	Autonomously redirected glycolytic flux away from central metabolism to increase myo-inositol, glucaric acid, and shikimate titers	[24]
Infection biosensing	AgrQS (AIP)	Probiotic bacterial biosensor for <i>Staphylococcus aureus</i> pathogenesis	[87]
Sense and respond	AgrQS (AIP)	Bacterial biosensor to detect and eliminate <i>Staphylococcus aureus</i> infection	[88]

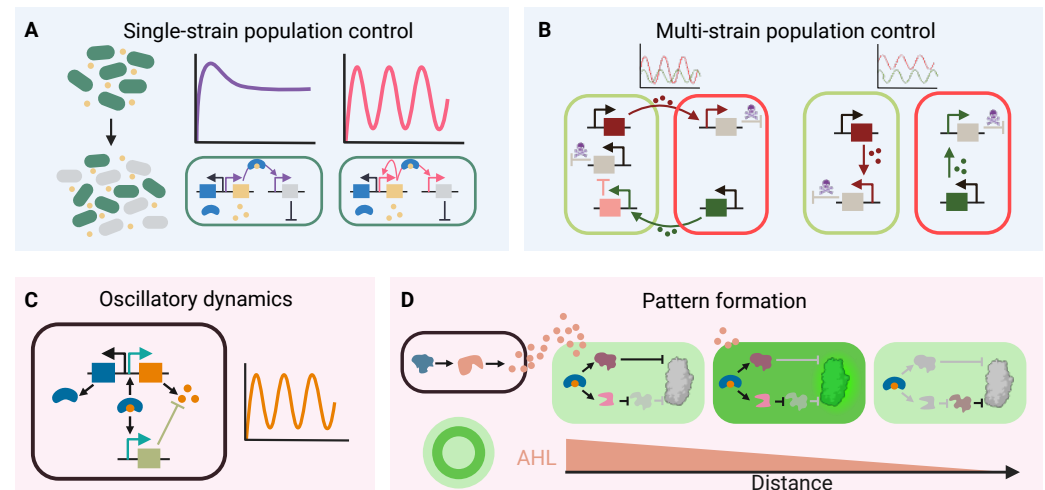


Figure 4. Applied synthetic communication circuits. **(A)** Single-strain population control using cell–cell communication (**left**) [4] and density-dependent oscillations (**right**) [23]. **(B)** Population control using multiple strains in a predator–prey relationship (**left**) [6] and a self-lysis regulatory scheme (**right**) [19]. **(C)** Oscillatory dynamics generated with negative feedback on the signal [9]. **(D)** Pattern formation resulting from a spatial AHL gradient created by a “sender” and “receiver” strain [5].

Building on this concept, QS-mediated lysis circuits have built oscillatory population gene circuits. Din et al. engineered an attenuated *Salmonella* strain to express LuxI/LuxR-regulated Φ X174 E-lysis protein and HlyE as a therapeutic payload (Figure 4A) [23]. In this system, the LuxI gene is expressed from the P_{lux} promoter, retaining the positive feedback and quorum thresholding behavior. These cells were observed to colonize tumors and exhibit QS-induced lytic release of cytotoxic agents into the tumor microenvironment. Surviving bacteria then re-seeded the population, producing oscillatory cycles of growth and lysis that maintained bacterial numbers while sustaining dosed drug release. Subsequent designs using the synchronized lysis architecture have implemented cooperative drug delivery of immunomodulating nanobodies and other therapeutic payloads for cancer therapy [75,89], improvements in stability via strain re-seeding [72], and the development of biosensors via population-coupled electrical impedance in microfluidics [76].

4.2. Synthetic Ecosystems and Stable Co-Culture

Natural multi-strain ecosystems possess complicated relationships between component strains which enable stable coexistence [90]. For the purposes of synthetic biology, often it is desirable to work within a single genetically tractable microbe. Naturally, when one strain grows faster than the other, as typically occurs when two different synthetic gene circuits are introduced to different strains, the weaker growing strain is lost in long-term co-culture [19]. To circumvent this, QS has been used as a stabilizing mechanism to constrain a culture to stably hold multiple strains for long-term co-culture.

For one, QS has also been used to implement canonical ecological motifs such as predator–prey dynamics within engineered microbial populations. Balagaddé et al. constructed a synthetic ecosystem of two *E. coli* strains in which each population regulated the survival of the other via QS-controlled expression of toxins and antitoxins (Figure 4B) [6]. The “predator” strain produces an AHL that induces toxin expression (CcdB) in the “prey” strain, killing it, while the prey produces a different AHL that activates expression of an antitoxin (CcdA) in the predator, rescuing it from its own toxin. Depending on gene circuit and flow parameters, the system exhibits extinction, coexistence, or oscillatory predator–prey cycles that closely resemble classical ecological models.

Scott et al. built a two-strain *Salmonella typhimurium* community in which each population carries a self-limiting “ortholysis” circuit driven by an orthogonal QS system (Figure 4B) [19]. One strain encodes a Lux-based lysis circuit and the other an Rpa-based circuit. In each case, accumulation of the strain’s own AHL above a threshold activates expression of the phage lysis gene Φ X174E, causing density-dependent self-killing. Introducing orthogonal QS-regulated lysis enables the strains to coexist for long durations in microfluidics despite unequal growth rates. By tuning growth and lysis parameters, the same design yields steady coexistence or distinct dynamical regimes—including phase-shifted, antiphase, and synchronized oscillations, mirroring classical coexistence-stabilizing mechanisms using synthetic QS population control.

4.3. Synchronized Oscillators and Spatiotemporal Waves

In temporal dynamics, QS can constitute the core of an oscillator whose period and coherence are set by environmental transport. Danino et al. engineered an intercellular genetic clock in *E. coli* by combining LuxI/LuxR-mediated positive feedback with QS-driven negative feedback via the AHL lactonase AiiA (Figure 4C) [9]. In their design, the P_{lux} promoter drives expression of *luxI*, *aiiA*, and a fluorescent reporter; LuxI-generated AHL diffuses between cells and, through LuxR, activates P_{lux} , reinforcing production of both LuxI and AiiA, while AiiA degrades AHL and ultimately shuts off the promoter. This coupled activate-and-degrade architecture yields relaxation-like oscillations that synchronize gene expression across thousands of cells. Using microfluidic chambers that maintain cells at quasi-constant density while imposing controlled media flow, they showed that the effective AHL dissipation rate set by flow is a key control parameter: tuning flow modulates the oscillation period and amplitude and selects between regimes with stable synchronized oscillations, damped responses, or spatial traveling waves spanning millimeter scales. Subsequent work in this field has demonstrated the generalizability of oscillatory or pulse-like behaviors from coupled QS positive and negative feedback to other QS systems with split feedback across cell subpopulations to generate spatiotemporal oscillations or pulses [8,91], negative feedback driven by coordinated cell death [23], and copy number-driven negative feedback induced by plasmid endonuclease [77].

4.4. Pattern-Forming Circuits and Distributed Computation

Spatial pattern formation is a natural domain for QS-mediated communication, given the diffusible nature of autoinducers. A landmark example is the synthetic multicellular system by Basu et al., in which sender cells produce an AHL that forms a concentration gradient, and receiver cells implement a band-pass response that leads to ring-like patterns of gene expression (Figure 4D) [5]. The receiver circuit uses the LuxI/LuxR system combined with activator and repressor modules such that gene expression is low at both low and high AHL concentrations but high at intermediate levels, effectively encoding a spatial “stripe detector”. Tabor et al. generalized this concept to implement a synthetic edge-detection program. In their design, engineered *E. coli* sense a projected light image, produce AHL in dark regions, and collectively compute the edges of the image via QS-mediated communication and logic gates that respond to both light and AHL inputs [78]. The population thereby performs a distributed image-processing algorithm, highlighting how QS can support spatial population-level computation. A rich body of subsequent work and reviews has expanded these ideas in synthetic pattern formation, organizing QS-based and related circuits into classes based on spatial information versus self-organized mechanisms [81,92], incorporating reaction–diffusion and Turing-type schemes [80], contact- and motility-mediated patterning [79,82,83], distributed computation [84,93], and applications in programmable “living materials” [94,95].

4.5. QS Applications in Bioprocessing

In bioproduction, quorum-sensing (QS) modules are often used to replace externally timed induction with autoinduction, so that cells grow in a low-burden state before collectively switching on costly product pathways once a signal threshold is reached. Additionally, autoinduction bypasses the use of costly inducers in bioproduction at industrial scale. Early QS-based autoinduction circuits in *E. coli* showed that such density-dependent control can simplify process operation by autonomously coordinating the transition from growth to production phases by exploiting AI-2 synthesis, since AI-2 levels peak as cells switch from exponential to a stationary phase [85]. Kim et al. systematically investigated the use and optimization of the Lux quorum system to induce production of bisabolene [86], improving product titers 1.44-fold compared to the previous IPTG induction process [96]. Additional dynamic control strategies use QS to reroute flux from biomass formation to heterologous pathways, autonomously balancing cell growth with production. For example, Gupta et al. used QS-based autoinduction to shift glycolytic flux toward heterologous production of myo-inositol by dynamically downregulating central metabolism, achieving a titer boost of up to 5.56-fold in comparison to strains without dynamic regulation [24]. Notably, this study scaled up to a 3L bioreactor, demonstrating comparable titer boosts to those achieved in shake flasks. Several QS-based dynamic regulation designs have followed suit, confirming consistent yields in liter-scale bioreactors, setting a precedent for scaling up bioprocess control with QS regulation [25,26].

QS signals have also been integrated into multi-strain consortia to partition biosynthetic tasks across specialized populations, coordinate gene expression, and support cooperative production of burdensome compounds [70,97,98]. Although QS-mediated regulation can coordinate population-dependent responses, it does not inherently prevent competitive exclusion or maintain a prescribed strain ratio. QS-independent metabolite-biosensor-assisted feedback can additionally link pathway activity or cellular selection to metabolic output. For example, biosensor-based selection pressure was dynamically tuned to improve 4-hydroxybenzoate production [99], while modular co-culture engineering combined with biosensor-assisted selection was applied to heterologous indigo biosynthesis [100]. Compared with metabolite-responsive feedback, QS can coordinate population-dependent gene expression without requiring direct sensing of the target product, but its response is agnostic to the specific target metabolite. Conversely, biosensor-assisted strategies can respond to specific metabolic signals, but their response time and operating range depend on sensor kinetics, sensitivity, dynamic range, and circuit architecture. Both approaches impose regulatory burdens that must be balanced against their benefits. Hybrid approaches applying both, such as those taken in Doong et al., may offer a pathway for synergistic benefits [25].

4.6. Beyond AHLs: Expanding the Engineered Communication Toolkit

Most *de novo* synthetic gene circuit designs above rely on LuxI/LuxR-type AHL circuits due to their tractability with *E. coli*, but emerging AIP/AI-2 systems have broadened the available communication modalities. For AIP systems, a recurring strategy is to transplant the *Staphylococcus aureus* Agr two-component module (AgrC/AgrA plus P3-like promoters) into probiotic or GRAS chassis to sense staphylococcal AIPs and actuate programmable responses. Lubkowicz et al. reprogrammed *Lactobacillus reuteri* as a biosensor for *Staphylococcus aureus* infection by wiring AgrC/AgrA and a P3-driven reporter to detect nanomolar AIP-I, yielding a living diagnostic device for virulence-associated peptides [87]. AgrQS has also been reconstructed in *Lactobacillus plantarum* WCSF1 so that exogenous AIP-I triggers a coupled induction/killing program to drive secretion of lysostaphin and selectively eliminate *Staphylococcus aureus* [88]. AI-2 systems have been exploited as non-Lux, broadly

conserved signaling modules for both microbial and interkingdom control [101]. In *E. coli*, the native LuxS/Lsr network has been rewired so that AI-2 accumulation autonomously induces recombinant protein expression from T7-based vectors via an AI-2-responsive P_{lsr} promoter, enabling unsupervised autoinduction and coupling production timing to population/metabolic state [85]. Collectively, these examples show that non-Lux QS systems provide a rapidly expanding toolkit for engineering communication, sensing, and actuation in contexts where Lux-type AHL systems are less natural.

5. Conclusions and Future Directions

5.1. Orthogonality and Evolvability

The true diversity of QS systems and chemistries is still only partially mapped. Comparative genomics and metagenomics indicate that classical AHL, AIP, and AI-2 systems are just a small subset of existing modules: large-scale *in silico* surveys of Candidate Phyla Radiation (CPR) bacteria and DPANN archaea, for example, have identified thousands of putative QS synthase and receptor variants associated with 14 distinct types of communication molecules across 69 phyla [102]. These findings suggest a vast space of ligand structures, receptor folds, and regulatory logics that has barely been sampled for engineering applications. A central quantitative question is, therefore, how many functionally distinct QS systems exist and how they are distributed across lineages and environments. Addressing this will require integrating sequence-based prediction with experimental validation—for example, by clustering synthase and receptor families using machine learning, combining metagenomic reconstruction with expression libraries to identify ligand–receptor pairs, and experimental sampling via high-throughput biosensor panels. Such efforts may reveal specialized “dialects” of communication in particular niches (e.g., host-associated or extreme environments) and begin to systematically populate this broader QS design space.

A complementary question is whether entirely new QS systems can be synthetically created, rather than merely discovered in nature. Protein engineering, directed evolution, and rational design offer routes to expand the space of ligand–receptor pairs and to tune orthogonality and dynamic range beyond what evolution has already explored. A combination of computational and combinatorial approaches has shown that LacI can be reprogrammed to respond to fucose, gentiobiose, lactitol, or sucralose as ligands [103]. Similarly, other work has shown that progesterone-responsive TFs can be designed to function in *E. coli* by utilizing molecular dynamic simulations to guide sequence design [104]. Analogous strategies could be applied to LuxR-type receptors, two-component sensor kinases, or AI-2 regulators. Computer-assisted design of sequence variants could be screened against panels of natural and synthetic ligands to map cross-reactivity matrices, identify pockets of sequence space that support high specificity, and iteratively push toward *de novo* modules. Notably, only some ligands that can freely diffuse through the cell membrane and be viably produced within the target cell can be used for quorum sensing, so targeted efforts must be made towards synthetic TF designs that are responsive to such molecules. With this, the QS repertoire of synthetic biology would not be limited to what comparative genomics reveals but can be systematically grown by designing and evolving new communication modules in the laboratory.

5.2. Communication and Control Theory Perspectives

A useful perspective for future QS engineering is to view QS networks through the complementary lenses of molecular communication and control theory. In this framework, autoinducer production can be regarded as an information-bearing process related to cellular state or population density, the extracellular environment as a potentially noisy and

lossy communication medium shaped by diffusion, flow, and degradation, and receptors as molecular decoders that convert extracellular signal concentrations into regulatory responses. Molecular communication frameworks provide mathematical tools for describing such processes, including stochastic signal production, diffusion, receptor binding, and biophysical limits on information transmission [17,105–107]. Applying these concepts quantitatively to QS systems could, in future studies, determine how much information about population density, spatial organization, or environmental state is transmitted through a given circuit and how signal-processing properties trade off against robustness, response time, and metabolic cost.

Control theory provides a complementary framework for analyzing QS-mediated feedback. Engineered microbial populations and consortia have demonstrated regulation of population dynamics [4,19,23], but formal quantities such as closed-loop stability and transfer functions have not been systematically characterized across QS architectures. Such analyses have provided insight into other synthetic gene networks [108]. Further work in applying control theory to QS architectures could connect measurable circuit parameters to system-level properties, enabling the design of more robust architectures. Improved robust and adaptive control approaches may be particularly useful for QS systems operating under uncertain host, reactor, or community conditions.

5.3. Translational Horizon

QS can be a potential design layer for bacteria-based cancer therapies. Engineered *E. coli* and *Salmonella* strains have been programmed with QS-regulated lysis and payload circuits so that therapeutic effectors (e.g., cytotoxic proteins, checkpoint inhibitors, or cytokines) are released only when bacterial populations reach a threshold density within tumors, coupling drug delivery to *in situ* growth and localization [23,89]. However, realizing the full clinical potential of these QS-guided therapies will require overcoming key hurdles, including chassis and circuit designs that reduce immunogenicity, employing biocontainment safeguards to prevent persistent colonization or horizontal gene transfer, and maintaining robust control over when and where QS thresholds are crossed. Particularly in solid tumors, an understanding of tumor colonization within the heterogeneous TME will be necessary for effective therapeutic application. Lastly, regulatory frameworks that can accommodate dynamically interacting, evolvable living medicines must be developed for clinical translation of engineered bacterial therapies.

In bioprocessing, engineered QS can underpin “self-driving” production pipelines that transition through distinct phases without external intervention using dynamic regulation and coordinated feeding, particularly with the interplay between global regulatory networks and AI-2 QS systems. QS-regulated circuits could balance burdensome heterologous pathways and biomass accumulation, initially prioritizing growth until a defined cell density threshold is reached, before flipping the culture into a production phase [24,25,85]. In multi-strain consortia, orthogonal QS systems can be used to coordinate sequential metabolic steps—one strain converting substrate to an intermediate at low density, another taking over downstream conversions once the intermediate accumulates, and a third handling detoxification or product secretion. Importantly, QS can also be used to implement safety and quality-control functions, such as density-dependent kill switches to prevent runaway growth or quorum-triggered reporter modules that signal when a batch has reached a target state. Together, these strategies suggest future bioprocesses where task allocation and fail-safes emerge automatically from QS-governed interactions rather than from purely external monitoring and control.

Finally, engineered QS offers a natural design space for microbiome engineering in both gut and soil environments, where direct external control is limited but local context

is rich. In the gut, commensal or probiotic strains could integrate the density-dependent properties of QS with endogenous sensor machinery for key metabolites or inflammatory markers, turning on therapeutic programs, such as immunomodulatory cytokine mimics or pathogen-targeting antimicrobials, only when they are stably colonized and the host is in a defined state [109]. In soil, root-associated bacteria and other rhizosphere community members could use QS to gate production of plant growth-promoting factors, biofilms, or pathogen-suppressing compounds to specific spatial niches (root tips, wounds, nutrient hotspots), or to encode “do no harm” states that prevent overgrowth or unintended community disruption [110]. Across both contexts, QS provides a programmable, density- and niche-aware design layer for tuning when and where engineered functions are expressed.

However, engineering QS systems for translational applications necessitates investigating and understanding the effects of complex physicochemical environments and ecosystems on engineered QS-based behaviors and bacterial survival. Considering the rheology of the specific environment of deployment, for example, may guide selection of QS systems. AIPs hold a slower diffusion coefficient and are inherently less stable than AHLs as they are subject to protease degradation [111]. As a result, AHLs likely hold the advantage over AIPs when scaling up bioprocesses or under environments experiencing convective flow [24,25]. Conversely, AHLs can be degraded by oxygen, which may inhibit function in certain complex environments such as soil. Other environmental factors that may influence QS processes and should be considered in translational applications include alkalinity, hydrophobicity, and hydrodynamics [111].

Taken together, natural and engineered QS circuits show how modular molecular communication systems can coordinate behavior from single cells to therapeutic consortia and biohybrid devices. Synthetic and rewired systems now span Lux-type AHLs, AIPs, AI-2, and emerging noncanonical systems, and they have been used to build oscillators, pattern-forming media, stabilized ecosystems, and context-dependent therapeutic programs. Key challenges ahead include expanding the repertoire of orthogonal signals and receptors (especially in non-model hosts), integrating QS with electrical, optical, and other orthogonal communication modalities, and developing design frameworks that link molecular implementation to ecological and clinical function [76,112,113]. As QS toolkits become more standardized and characterized, and as cell-free and microfluidic platforms accelerate prototyping, QS-based communication is poised to become core infrastructure for dynamic engineered living systems and smart therapies.

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Abbreviations

The following abbreviations are used in this manuscript:

QS	Quorum sensing
AIP	Autoinducing peptide
TF	Transcription factor
AHL	N-acyl homoserine lactone
SNR	Signal-to-noise ratio
TME	Tumor microenvironment

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