TOPICAL REVIEW — Modeling and simulations for the structures and functions of proteins and nucleic acids

Quantitative modeling of bacterial quorum sensing dynamics in time and space*

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Quorum sensing (QS) refers to the cell communication through signaling molecules that regulate many important biological functions of bacteria by monitoring their population density. Although a wide spectrum of studies on the QS system mechanisms have been carried out in experiments, mathematical modeling to explore the QS system has become a powerful approach as well. In this paper, we review the research progress of network modeling in bacterial QS to capture the system's underlying mechanisms. There are four types of QS system models for bacteria: the Gram-negative QS system model, the Gram-positive QS system model, the model for both Gram-negative and Gram-positive QS system, and the synthetic QS system model. These QS system models are mostly described by the ordinary differential equations (ODE) or partial differential equations (PDE) to study the changes of signaling molecule dynamics in time and space and the cell population density variations. Besides the deterministic simulations, the stochastic modeling approaches have also been introduced to discuss the noise effects on kinetics in QS systems. Taken together, these current modeling efforts advance our understanding of the QS system by providing systematic and quantitative dynamics description, which can hardly be obtained in experiments.

Keywords: bacterial quorum sensing, signaling molecules, mathematical modeling, dynamic analysis

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1. Introduction

Bacteria can sense the concentration change of chemical signaling molecules with small molecular weight that secreted by other bacteria, thereby promoting communication between bacteria and synchronizing the behaviors of bacteria group. This phenomenon is called quorum-sensing (QS).[1,2] The signaling molecules that secreted by bacteria can regulate their own biological behaviors, called autoinducers. The concentration of QS autoinducer increases with the increase of the population of bacteria. Once a threshold concentration of autoinducer is reached, autoinducers will activate or inhibit the transcription and expression of several target genes, thereby regulating the biological population of bacteria,[3] such as bioluminescence, biofilm formation, differentiation, extracellular polysaccharides production, motility, antibiotics production, and so on.[4]

The QS system uses fatty acid derivatives as signaling molecules in Gram-negative bacteria. The signaling molecules mostly belong to the class of N-acyl-homoserine lactones (AHLs).[5] AHL is essential for the QS in *Vibrio fischeri*, which has a gene regulatory network containing two main components, LuxI and LuxR proteins. LuxI is the inducer protein that synthesizes the autoinducer AHL.[6,7] LuxR is the transcriptional regulator protein that binds AHL to form dimer, and then binds to the promoter of the protein operon on the DNA to trigger the relative genes. AHL can freely diffuse inside and outside the bacterial cells.[8] AHL concentration accumulates with the increase of cell population density. When the concentration of AHL reaches a threshold value, it binds to the LuxR protein and activates the transcription of luciferase gene, leading to luminescence of the cell.[9]

The QS system in Gram-positive bacteria mainly uses small peptides (autoinducing peptides, AIP) as signaling molecules to regulate gene expression.[10] At high cell population density, the synthesized AIP is accumulated to a certain level and can be sensed by the corresponding recognition system. The main module of this recognition system is

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the receptor molecules of the histidine kinase two-component system.[11–13] The binding of AIP to the receptors can induce the kinase activity of the two-component system and trigger a series of phosphorylation events. AIP phosphorylates the receptor and processes signals to the cytoplasmic regulator. The activated regulator further induces the transcription and expression of the related genes to produce more AIP molecules, thereby generating the behavior of QS.[14]

Another set of QS system was found in Gram-negative bacteria in the 1990s, in which autoinducer-2 (AI-2) is the signaling molecule produced by the catalyst of LuxS protein.[15,16] AI-2 was then detected in a number of Gram-positive and Gram-negative bacteria.[11] Regulators that are phosphorylated by AI-2 can induce the transcription and expression of related genes. Therefore, AI-2 can participate in the QS of both Gram-positive and Gram-negative bacteria and is believed to be a general signaling molecule for facilitating interspecies communication.[6]

QS was first observed in the marine bacterial species, which are important experimental models for exploring the underlying mechanism of the system. However, it is not convenient to directly study the QS mechanism in marine bacteria. Therefore, various synthetic QS systems have been designed and constructed for more conveniently and deeply study and programming new dynamics. *Escherichia coli* (*E. coli.*) engineered with QS systems is a typical synthetic model, which is simple and easy to perform analysis.[17,18]

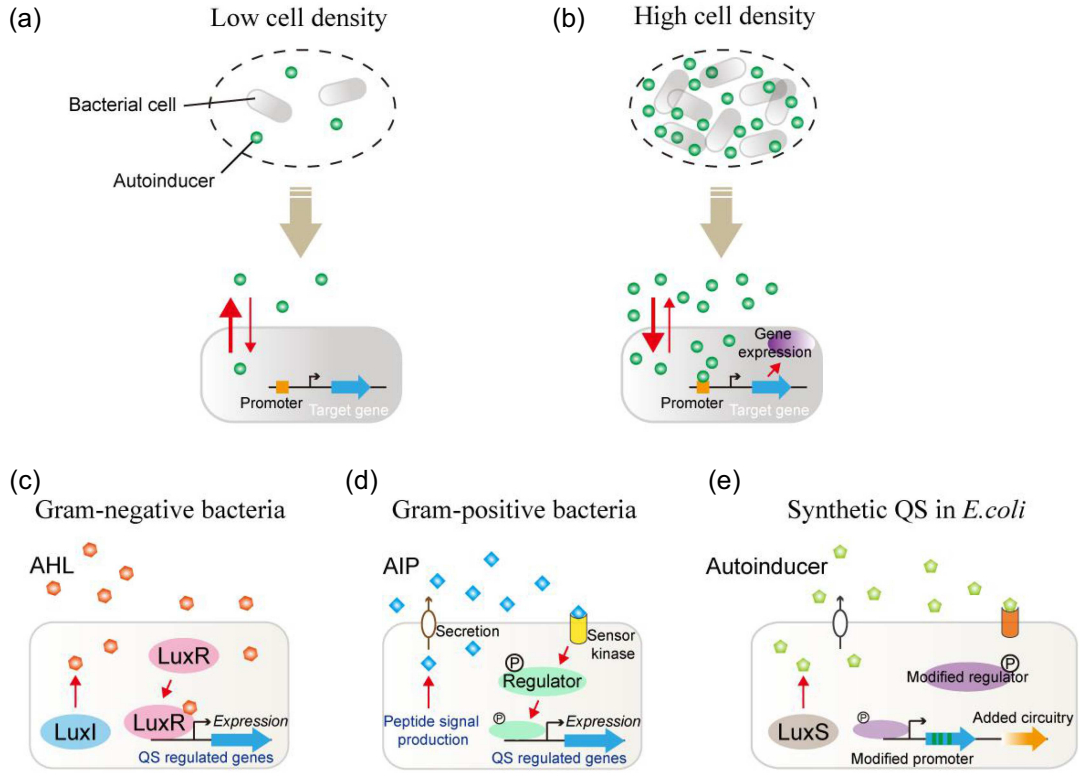

Fig. 1. An overview of the QS systems in bacterial cell. (a) At low cell density, the concentration of autoinducer is low. (b) At high cell density, the autoinducer concentration reaches a threshold to induce corresponding gene expression to trigger QS. (c) Schematic of the QS system in Gram-negative bacteria. AHL is the autoinducer in the system. (d) Schematic of the QS system in Gram-positive bacteria. AIP is the autoinducer. (e) Schematic of the synthetic QS system in *E. coli*. The synthetic strategies mainly include regulator modification, promoter modification, and circuitry addition.

Mathematical modeling is a powerful approach for dissecting the dynamic mechanisms of complex signaling networks.[19–23] For example, the link between synonymous mutation and oncogenesis has been studied with network modeling.[24] Large numbers of signaling network models have been proposed to explore the mechanisms of carcinogenesis.[25] The Myddosome assembly strategy was recently determined by using a mass spectrometer data-based modeling.[26] For the QS systems in bacteria, an increasing number of mathematical models have been developed to study the underlying control mechanisms.[27] The QS system of *agr* governs the virulence determinants of *Staphylococcus aureus*. However, how the *agr* system is activated remains unsolved in experiment. Through modeling analysis, *sarA* expression is proved to be the inducer for the transcription of *agr* operon that triggers the QS system.[28] Experimental analysis indicates that the QS system networks in *Vibrio haveyi* and *Vibrio cholerae* are topologically equivalent and have homologous components. Nevertheless, for the same experimental conditions, the two QS systems show completely different re-

sponses. Experimentalists can hardly identify the underlying mechanisms of these differences. Hunter and Keener showed that, rather than the dosage compensation mechanism that hypothesized by experimenters, the affinity of qrr and its expression play the key roles in mediating the differences.[29] Furthermore, oscillatory behavior of QS plays extremely important roles in drug deliver system for cancer therapy. Recent theoretical study proves that protein synthesis time delay can generate oscillation behavior in the QS system, which provides possible clues for efficient cancer treatment.[30]

In this paper, we present a comprehensive review of the currently mathematical models for wild-type and synthetic QS systems in bacteria that advance our understanding of the complex systems. The wild-type models mainly include Gram-negative, Gram-positive, and Gram-positive and -negative bacteria QS systems. We select the representative theoretical studies of the corresponding systems and classify them by different modeling methods, which give an overview of current efforts and the future challenges of modeling.

2. Mathematical modeling of the QS systems in Gram-negative bacteria

The models of QS system are mostly described by the ordinary differential equations (ODEs). In 2004, using an rhlI null mutant, Chen *et al.* evaluated the effect of auto-inducer PAI2 on the production of rhamnolipid (RL) by Pseudomonas aeruginosa.[31] They built a model to describe the RL synthesis kinetics regulated by the rhl QS system. ODEs are employed to describes the processes of PAI2 binding to the RhlR, RhlR:PAI2 complex triggering the transcription and expression of the rhlAB operon to encode rhamnosetransferase, and the enzyme catalyzing the synthesis of RL. The model fits well with the experiments and quantitatively predicts the relation between PAI2 concentrations and the enzyme synthesis. Higher PAI2 concentrations induce higher initial enzyme synthesis rates, resulting in an increase of RL. The maximum RL production rate of the culture was also quantitatively determined in this study, providing an important basis for the precise determination of the complex QS system.

Besides the positive feedback that is responsible for switching the states of QS systems, Mcintosh *et al.* found that a negative feedback is also required for state changing of the system in *Sinorhizobium meliloti*.[32] The QS system in *Sinorhizobium meliloti* is called Sin system, which mainly includes the signal molecules of AHL, SinI, SinR, and ExpR. Through an experimental data-based ODE modeling, they presented a minimal mathematical QS network model of the nitrogen-fixing bacterium. The model can correctly predict the experimental observations, particularly the relation between cell density and AHL concentration. Low cell density induces all produced AHL to leave the cells quickly. The negative feedback is the binding of ExpR/AHL to sinR promoter to inhibit sinR expression, resulting in the inhibition of sinI expression and AHL production decrease. The positive feedback was systematically discussed, which can increase AHL production when the cell density exceeds a certain value. The negative feedback switches off AHL production with higher cell density.

In 2016, Marenda *et al.* established a mathematical model to study the regulation of cell density by bacterial QS in an open boundary extension system.[33] The study demonstrates how tube height can overtake the role of producer density in triggering sensor activation, emphasizing the key role of signal diffusion and signal degradation in adjusting the effect of spatial extension on QS activation.

Bifurcation analysis approach of the QS ODE models is also widely employed to show how the steady states of the systems are modulated by the change of control parameters. An early mathematical model of the QS system in Gram-negative bacteria (*V. fischeri*) was developed by James *et al.*[34] Using bifurcation analysis, they determined how the system can create two stable states of luminescent expression and non-luminescent phenotypes. Changes in parameters of metabolic processes and extracellular signal molecule concentration can switch these two states. The study provides a quantitative analysis of the *lux* genes regulation network and further implies that lux genes can induce luminesce under the shortage of extracellular signal molecule.

The QS mechanism at the single-cell level was studied by Melke *et al.* in 2010.[35] They introduced a cell-based model of growing bacterial microcolonies, which mainly contains the components of LuxR, AHL, and LuxR-AHL. In this network, the signaling molecule AHL synthesized by LuxI protein can penetrate the cell membrane and activate LuxR protein through binding to LuxR. The activated LuxR protein can form a dimer to induce the synthesis of AHL and LuxR. Two positive feedback mechanisms are involved in this model where dimerized LuxR-AHL can activate both LuxR production and AHL synthesized by LuxI. The model predicts that the cell density-dependent behavior highly depends on local cell-clustering and the geometry of the evolution space. Bifurcation analysis finds multistability regions which are determined by the model parameters. Furthermore, the mechanisms how colony size, local clustering, and confinement affect the dynamic behaviors of the QS system are further explored in the study.

Besides the ODE models, partial differential equations (PDEs) models, which can be used to follow changes in more than one independent variable, have been used to study the QS systems. In 2001, Dockery *et al.* established a mathemati-

cal model of the QS system in the Gram-negative bacterium of *Pseudomonas aeruginosa* to investigate the mechanism of how the auto-inducer can act as a signal and when this mechanism works.[36] *Pseudomonas aeruginosa* contains two regulatory QS systems of both the las system and rhl system. ODEs are employed to describe the kinetics of the system. PDEs are further involved in the model to study the inhomogeneous distributions of auto-induced factors in the extracellular spaces. With the model, they proposed that QS works through a biochemical switch between two stable steady solutions, one with low level and one with high level of auto-inducer. The steady states are highly controlled by the size and local density of cells.

In addition to the modeling of QS systems with ODE and PDE approaches, the QS system modeling based on the delay differential equations (DDEs) was also proposed. Barbarossa *et al.*[37] focused on the QS system in Gram-negative bacteria of the species *Pseudomonas putida*. The network includes a negative feedback via the degradation enzyme of auto-inducer, leading to the time delay of the system. Diverse features of the system, such as existence, uniqueness, and non-negativity are investigated. The steady state and its stability are qualitatively studied, showing that the system gives a stable switch to the delay for certain parameter values. Hopf bifurcation occurs without delay in the QS system. This study suggests that the delay system is sufficient to explain the biological observations.

3. Mathematical modeling of QS systems in Gram-positive bacteria

The Gram-positive bacteria QS systems typically use peptides as signaling molecules that are secreted by the environment and recognized by the two-component systems. In 2004, Gustafsson *et al.* developed a mathematical model to explore the Gram-positive bacteria QS system (agr system) in *Staphylococcus aureus*.[38] The model presents that the agr system can be activated by the auto-inducing peptide (AIP) at certain levels. The study indicates that altering agr activity hardly affects RNAIII levels but significantly changes the cells sensitivity to AIP. Further analysis shows that the inhibition of AIP delays the activation of the agr system.

In 2007, Karlsson *et al.* established a mathematical model of QS system referred as the ComABCDE pathway in *Streptococcus pneumoniae* to study the down-regulation of the competence-evoking network.[39] In this article, Karlsson *et al.* not only studied the QS that induces competence, but also pointed out the possible signaling molecular mechanism during the sudden shut-down of the system. Through bifurcation analysis, they found that shut-down of competence possibly occurs at the transcriptional level on the comCDE operon. Although QS in pneumococcus has been studied for many years, the negative feedback regulation mechanism has not been determined. A putative ComX-dependent repressor which inhibits the expression of comCDE and comX is predicted in the model, providing a negative control mechanism in the system. The model proves that the competence is demonstrated to appear in waves, which is supported by experimental studies in pneumococcal batch cultures.

Besides the ODE approach with bifurcation analysis, the stochastic description has also be introduced for the study of QS systems due to the intrinsically stochastic characteristics in the systems. A stochastic and a deterministic model that describe the process of endosome escape of *Staphylococcus aureus* were proposed by Koerber *et al.* in 2005.[28] This study presents the first stochastic model for bacterial QS system. The models were analyzed to study the mechanism of the production of virulence factors by *Staphylococcus aureus*, which is a Gram-positive bacterium involved in many diseases. In this network, accesory gene regulator (agr) locus provides the regulation mechanisms. AgrB is required for the processing of AgrD to generate AIP and also for the transport of AIP across the membrane of bacteria. AgrC is the acceptor of AIP and phosphorylates AgrA. Phosphorylated AgrA then interacts with SarA to promote the promoters P2 and P3 to regulate the expression of ageBDCA and RNAIII. The agr network was simplified into an encapsulated "black box" model, which assumes that all of the inherent genetic machinery is rapid. Detailed asymptotic analysis for the stochastic problem was compared with the Monte–Carlo simulation. Based on the model, they determined the biologically relevant asymptotic limit of closed-form asymptotic and numerical solutions that the up- and down-regulation rates of bacteria are rapid. The distribution of endosome escape time was also predicted.

4. Mathematical modeling of QS systems in Gram-positive and -negative bacteria

AI-2 mediates the QS systems both in Gram-negative and -positive bacteria, which is involved in interspecies communication among bacteria.[40] AI-2 is an important auto-inducer in *Vibrio harveyi* to sense cell density. At low cell density, through a phosphorylation mechanism, LuxU is phosphorylated and then phosphorylates LuxO, promoting the production of qrr sRNAs. sRNAs repress the expression of LuxR. At high cell density, AI-2 is produced with the participation of LuxS protein. Extracellular AI-2 binds to the transmembrane LuxP protein and processes signaling to the LuxQ two-component hybrid sensor kinase protein, resulting in a low production of sRNAs and a high concentration of LuxR protein to induce luminescence activation.

In 2009, Banik *et al.* established a simple model to study the luminescence regulation in the QS system of *Vibrio harveyi*.[41] Based on the experimental data of the luminescence phenotype for the wild type and for the different mutant strains, they determined the key dimensionless parameters that control system's response. Model predictions fit well with the other independent experimental results. In addition, the model predicts the change of luminescence phenotype and the effect of perturbations on the network, providing essential guidance for experimental analysis of the complex QS system.

Besides, Hunter *et al.*[29] comparatively analyzed the QS systems in *Vibrio harveyi* and *Vibrio cholerae* to facilitate a better understanding of the regulation mechanism and found that Qrr in *Vibrio cholerae* is more abundant and more sensitive to the changes in LuxO than that in *Vibrio harveyi*. Using single-cell resolution, Long *et al.*[42] quantified the integration of QS system in *Vibrio harveyi* and found that information from two distinct signals is combined strictly and additively, with precisely equal weight from each signal. Besides, Teng *et al.*[43,44] determined that the receptor ratio of LuxN and LuxPQ controls the integration and measured the copy number of the master regulators at the single cell level.

5. Mathematical modeling of synthetic QS systems in bacteria

To conveniently and deeply investigate the mechanism of bacterial QS systems, studies have also focused on constructing synthetic gene circuits that exhibit desired QS properties in synthetic biology. Several typical QS systems in bacteria have been synthesized and implanted into *E. coli* in recent years. Lee *et al.*[45] developed the first molecular mechanism-based model in a recombinant *E. coli* system to explore the effect of growth rate on the plasmid content and expression of gene production. The study clarified the advantages of model-based dynamical descriptions, which can be directly implicated for fermentation process design for recombinant bacteria.

The auto-inducer AHL is one of the most important components in bacterial and has been involved in various synthetic QS systems. Different models are developed by considering the fineness of AHL, ranging from only considering AHL inside bacteria to modeling the AHL inside and outside of the cell and then discussing the AHL on the cell membrane. In 2001, a mathematical model was developed by Nilsson *et al.* to study the concentration changes of AHL inside the cell and in the biofilm over time with growth rate, diffusion of AHL, and autoinduction rate.[46] Their study suggested that AHL inside individual cells increases rapidly at the early stage of population growth and then follows by a plateau. Then another increase of AHL concentration is observed, approaching to a second plateau. Dynamic analysis indicated that the low rate of diffusion outside the cell and the biofilm, the slow growth rate of bacteria, and the fast autoinduction can induce a high concentration of AHL inside the cell at the early stage. However, if the growth rate of bacteria is fast, the autoinduction rate is slow and the rate of diffusion is high, the high concentration plateau in stationary phase occurs. This study quantitatively explored the implications of the components for AHL regulation under different situations, suggesting that AHL-mediated phenotype can occur at relatively low cell density and low concentration of external AHL.

In 2004, You *et al.* applied the coupled gene expression of cell growth dynamics to study the QS system in *E. coli*.[47] A cell density control circuit that incorporates cell death was designed. They built a simple model and proved that the two fragments of luxI/luxR gene and target genes are closely coupled, and the cell density and gene expression can be regulated through varying the cell communication signal. They hypothesized that the cell density will have an inherent growth rate and the maximum carrying capacity of the environment without gene fragment implanted, which were experimentally validated. With the gene fragment implanted, the cell density is regulated by the lethal protein level and its increase is proportional to the level of AHL. The model predicted and verified that with implanting synthetic gene fragments, the lethal protein production rate is restricted by the synthesis of AHL. The cell density at stable steady state is proportional to the degradation rate of AHL. Further analysis implied that pH change does not affect the amount of lethal protein in cells.

The cooperative behaviors of the QS systems with stochastic fluctuations inside and outside cells have been studied by Chen *et al.* in 2005.[48] They developed a general model of a synthetic gene network by using the luxI and luxR QS system in *Vibrio fischeri*. Hopf bifurcation theory was employed to analyze the multicellular system dynamics. The diffusion of signaling molecules is also considered in the model. The multi-system composed of synthetic QS is proposed to demonstrate the effects of noise, time delays, and the coupling on collective dynamics, which explain well that noises are essential for inducing the system cooperative behaviors.

For biological systems, if the components have very low concentrations (or amount) and slow reaction rate, due to inherent stochastic events, random fluctuations may occur, resulting in significant variation for system behaviors. In 2006, Li *et al.*[49] constructed a mathematical model with stochastic simulations to study the hierarchical organization of luxS-derived AI-2 circuitry in *E. coli*. The study indicated that in the presence of glucose, the mRNA transcription (Pfs) and protein levels of AI-2 syntheases (LuxS) cannot significantly increase the level of AI-2. An increase in metabolic flux through the synthesis pathway partially explains this difference in the presence of glucose and other biological steps were predicted

to be exist in the synthesis of AI-2, which were validated by the corresponding experiments. This work confirmed that the systems-based stochastic models can be linked to cell physiology. Tian *et al.*[50] also used stochastic models to study the QS system, suggesting that the construction of stochastic models is a powerful approach for studying noise in gene regulatory networks.

In 2013, Saeidi *et al.*[51] build a synthetic QS system model to study the regulatory mechanism in *Pseudomonas aeruginosa*. Their model described the bacterial QS mechanism in detail at gene level and modeled an example device that generates green fluorescent protein (GFP) as reporter in the presence of AHL. The model can well-reproduce the experiments quantitatively. Through parameter sensitivity analysis, not only the most sensitive reaction parameters in the system, but also the reaction parameters that have the greatest influence on the transient time to reach the equilibrium were discussed. The proposed model can be used to predict the production of GFP and applied for further control circuit design.

To subtly control bacterial cell density, Wang *et al.* built a synthetic cell–cell communication system that combined the cell death BioBricks and QS mechanism in *Vibrio fischeri*.[52] They found that the constructed ribosome binding site (RBS) of $RBS_{0.07}$, $RBS_{0.3}$, $RBS_{0.6}$, and $RBS_{1.0}$ QS circuits can successfully control the cell density through regulating the lethal gene expression. A mathematical model was further developed to validate the system dynamics and to quantitatively describe the constructed components for regulating cell density.

6. Conclusion and perspectives

QS plays an important role in cell-to-cell communication to sense their population density and to regulate corresponding gene expression. Although numerous QS systems have been discovered in experiments, little is known about their detailed control mechanisms, and quantitative analysis and circuits design are still hard to achieve. Mathematical modeling and theoretical study of the QS systems have become a powerful tool to enhance our understanding of the complex QS dynamics.[53] In this review, we classified the mathematical models of QS systems in bacteria into four categories: Gram-negative, Gram-positive, Gram-positive and -negative, and synthetic bacterial models. To comprehensively study the QS system dynamics, remarkable progresses have been made. Models were developed from only considering a few key components to constructing an integrative signaling network of QS systems, including from ignoring signaling molecules inside and outside the cells to considering the flow of molecules between cells, from developing deterministic models to building noise-involved stochastic models, and from studying the point model with ODE to discussing the effects of spatial diffusion and boundary on the system with PDE. In summary, we have elaborated a table (Table 1) to present a broad overview of the representative models of the corresponding QS system.

Based on this review, we suggest that more systematic modeling should be constructed in the future for QS system investigation. For instance, more complete signal pathways shoud be established, and the variety of genes, subtle influences, and processes involved in the QS should be considered based on the new experimental observations. Besides, the key components involved in the QS system may also participate in other biological processes in cells which can also be discussed. Although the QS system models are built at the gene level, the processes of specific inducers that act on the promoter of the gene, and the promoter that initiates the transcription and expression of genes, which have been generally simplified to only one or two equations in previous models, should be simulated in detail in order to distinguish the different functions of promoters in QS systems.

As an essential factor in controlling cell density, the cell death process that is seldom considered in previous model should be investigated for modeling in the future. During the late stage of cell growth, nutrients become lacking and toxic metabolic by-products are accumulated massively. The mechanism of which by-products lead to cell death is not particularly clear. For a model to consider such mechanisms, the kinetics of bacteria population could be accurately simulated for QS systems.

Physical properties of the environment are pivotal for the QS system. The factors, including noise, interaction between signaling molecules, spatial diffusion, boundary effects, environmental pH and temperature, etc, play important roles for QS, which should be taken into account as well. Although the effects of noise and pH on the QS system have been previously studied,[47,48] temperature and some other factors should be further considered in the future models. When encountering the slow reaction rates of gene regulation networks with very low concentrations (or amounts) of signals, random fluctuations exist due to the inherent random events and thus a stochastic model should be constructed.

Remarkable progress has been made by coupling biologists and physicists. The biological system behaviors defined by physical laws and principles provide better understanding and new insights of the complex systems, which are also the main goal for biologists. For example, a “seesaw model” that proposed by Tang *et al.* well describes the reprogramming landscape that is shaped by the interactions among various states.[54] Ouyang *et al.* found a general inverse relationship between the phase diffusion constant and free-energy dissipation in the biochemical oscillation systems.[55] Mathematical modeling not only helps to dissect the underlying control

mechanism of the complex QS systems, but also makes quantitative analysis and prediction which can provide guide for novel therapies and optimal treatment strategies. Thus, the application of more physical concepts, such as interaction landscape and free-energy dissipation, for the investigation of QS systems is a future research interest.

Overall, the current modeling studies of the QS systems are insufficient for us to systematically clarify the detailed dynamics. Considering more factors to make the modeling system more biologically realistic will provide better understanding of the underlying mechanisms in QS systems, which should be the further development for modeling study.

Table 1. Representative models of different QS systems in bacteria.

Year	Author	Method	Major conclusion
QS systems in Gram-negative bacteria			
2000	James *et al.*	ODE & bifurcation analysis	*lux* genes can induce luminesce under the shortage of extracellular signal molecule
2001	Dockery *et al.*	ODE & PDE	The high and low states of auto-inducer are highly controlled by the size and local density of cells
2004	Chen *et al.*	ODE	Providing an important basis for the precise determination of the rhl QS system
2010	Melke *et al.*	ODE & bifurcation analysis	The cell density-dependent behavior of LuxR-AHL QS system depends on local cell-clustering and the geometry of the evolution space
2013	Mcintosh *et al.*	ODE	A negative feedback is required for state changing of the QS system in Sinorhizobium meliloti
2016	Barbarossa *et al.*	DDE & bifurcation analysis	The delay QS system is sufficient to explain the biological observations
2016	Marenda *et al.*	ODE	Demonstrating how tube height overtakes the role of producer density in triggering sensor activation
QS systems in Gram-positive bacteria			
2004	Gustafsson *et al.*	ODE	Altering agr activity hardly affects RNAIII levels but changes the cells sensitivity to AIP
2005	Koerber *et al.*	ODE & Monte-Carlo	The first stochastic model for bacterial QS system
2007	Karlsson *et al.*	ODE & bifurcation analysis	A putative ComX-dependent repressor which inhibits the expression of comCDE and comX is determined
QS systems in Gram-positive and-negative bacteria			
2009	Banik *et al.*	ODE	The key dimensionless parameters that control the QS system of *Vibrio harveyi* is determined
2009	Long *et al.*	ODE	Quantifying the integration of QS system in *Vibrio harveyi*
2014	Hunter *et al.*	ODE	Qrr in *Vibrio cholerae* is more abundant and more sensitive to the changes in LuxO than *Vibrio harveyi*
Synthetic QS systems in bacteria			
2001	Nilsson *et al.*	ODE	This study quantitatively explored the implications of the components for AHL regulation under different situations
2002	Lee *et al.*	ODE	The first molecular mechanism-based model in a recombinant *E. coli* system
2004	You *et al.*	ODE	A cell density control circuit that incorporates cell death was designed.
2005	Chen *et al.*	ODE & bifurcation analysis	Noises are essential for inducing the system cooperative behaviors
2006	Li *et al.*	ODE & stochastic simulations	Biological steps were determined to be exist in the synthesis of AI-2
2013	Saeidi *et al.*	ODE	The model can be used to predict the production of GFP

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