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Logic of two antagonizing intra-species quorum sensing systems in bacteria

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ABSTRACT

Bacteria release signaling molecules into the surrounding environment and sense them when present in their proximity. Using this strategy, a cell estimates the number of neighbors in its surrounding. Upon sensing a critical number of individuals, bacteria coordinate a number of cellular processes. This density-dependent control of gene expression and physiology is called quorum sensing (QS). Quorum sensing controls a wide variety of functions in bacteria, including those related to motility, growth, virulence etc. Quorum sensing has been widely observed in bacteria while the individuals of the same species or different species compete and cooperate each other. Interestingly, many species possess more than one QS system (intra-species) and these QS systems interact each other to perform quorum sensing. Thus, several logical arrangements can be possible based on the interaction among intra-species QS systems – parallel, series, antagonizing, and agonizing. In this work, we perform simulations to understand the logic of interaction between two antagonizing intra-species QS systems. In such an interaction, one QS system gets fully expressed and the other only gets partially expressed. This is found to be dictated by the interplay between autoinducer's diffusivity and antagonizing strength. In addition, we speculate an important role of the intracellular regulators (eg. LuxR) in maintaining the uniform response among the individual cells from the different localities. We also expect the interplay between the autoinducer's diffusivity and distribution of cells in fine tuning the collective response. Interestingly, in a localized niche with a heterogeneous cell distribution, the cells are expected to perform a global quorum sensing via fully expressed QS system and a local quorum sensing via partially expressed QS system.

1. Introduction

In the mid-1960s, the notion of bacterial existence as individual cells only seeking to find nutrients and multiply was revised after discovering the fact that bacteria can also communicate with each other (Kempner and Hanson, 1968; Nealson et al., 1968). From the studies on bacterial species that have followed since, we know that bacteria coordinate among themselves and respond collectively to the environmental changes (Koraimann and Wagner, 2014; Li and Tian, 2012). The idea of interaction among bacterial cells occurs in several ways that enable cells to explore a number of possibilities to estimate surrounding environment thereafter, maximize benefits in a favorable condition and chances of survival in adverse conditions.

One of the ways of interaction among bacterial cells is to release signaling molecules (also known as autoinducers) into the environment and sense molecules released by other individuals. At low cell density, these molecules are likely to simply diffuse away from the cells. However, when cell density increases, cells start sensing these molecules released by their neighbors (Fuqua et al., 1994; Miller and Bassler, 2001). In this way, a cell estimates the number of individuals in the surrounding environment. This molecule-based communication is known as quorum sensing (QS) and observed in many microbial species (Rutherford and Bassler, 2012; Waters and Bassler, 2005). Quorum sensing helps cells perform a broad range of functions, such as plastic responses to nutrients availability (Lazazzera, 2000), competition with other microorganisms for nutrients and survival (Hibbing et al., 2010), defense against toxins (Li and Tian, 2012; Rutherford and Bassler, 2012; Waters and Bassler, 2005), and establish symbiotic relationship with other species etc.

Abbreviations: QS, quorum sensing system; RA, regulator-autoinducer complex; *V. fischeri*, *Vibrio fischeri*; *V.* harveyi, *Vibrio harveyi*; *V. cholera*, *Vibrio cholera*; *V. vulnificus*, *Vibrio vulnificus*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *B. subtilis*, *Bacillus subtilis*; *E. faecalis*, *Enterococcus faecalis*; *S. typhimurium*, *Salmonella typhimurium*.

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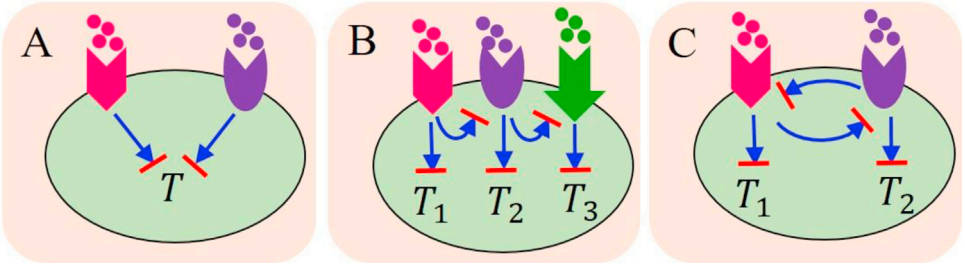

Fig. 1. A schematic showing the possibilities of interaction among intra-species QS systems in bacteria. More than one intra-species QS systems interacting each other in three different ways— **(A)** a parallel configuration, QS systems simultaneously control the same target (Eg. *V. harveyi*, *V. cholerae*, and *V. vulnificus*), **(B)** a series configuration, where the expression QS systems is induced hierarchically (Eg. *P. aeruginosa*), and **(C)** a cross interaction, where QS systems either agonize or antagonize each other (Eg. *B. subtilis* and *P. aeruginosa*).

Quorum sensing-controlled processes are typically considered unproductive when an individual bacterium acts alone, but highly productive when a group of cells collectively launches a response (Darch et al., 2012). Thus, quorum sensing appears to obscure the distinction between unicellularity and multicellularity, and enables bacteria to act as a multicellular organism. Quorum sensing was first seen in the bioluminescent, gram-negative marine bacteria, *V. fischeri*, which live in a symbiotic relationship with seawater mollusc, the Hawaiian bobtail squid (Kempner and Hanson, 1968; Nealson et al., 1970; Ruby, 1996). This system is considered as the paradigm for many of the QS systems in gram-negative bacteria.

Two proteins, *LuxI* and *LuxR*, are involved in the control of quorum sensing dependent bioluminescence in *V. fischeri*. *LuxI*, is a synthase, which synthesizes quorum sensing autoinducers known as homoserine lactone (AHL) (Engebrecht and Silverman, 1984; Schaefer et al., 1996). Once AHL is synthesized, it freely diffuses in and out of the cell (Kaplan and Greenberg, 1985). *LuxR* is an important component of the quorum sensing system because of its dual regulatory roles – as a cytoplasmic receptor for AHL and as a transcriptional activator of the luciferase *luxICDABE* operon (Engebrecht et al., 1983; Engebrecht and Silverman, 1984). When the cell density increases, AHL starts accumulating, and gets bound by *LuxR* to form *LuxR-AHL* complex. This complex then binds to the promoter of the luciferase operon and activates the expression in order to encode subunits of luciferase, synthase, regulator, and other important proteins (Meighen, 1991; Stevens et al., 1994). The production of autoinducer depends on *LuxI* synthase, which is also controlled by the same operon. This autoinduction-dependent synthesis of *LuxI* forms a positive feedback loop, which helps the cell switch to high cell density dependent quorum sensing mode and thereby exhibiting bioluminescence.

Unlikely, gram-positive bacteria communicate using modified oligopeptides, which are relatively larger than AHL (Hense and Schuster, 2015; Lazazzera and Grossman, 1998; Miller and Bassler, 2001). Because of large size, oligopeptides do not diffuse freely through the cell membrane and therefore, the cells require two-component phosphorelay cascades to sense extracellular oligopeptides.

Initially, it was believed that the control of collective responses via quorum sensing was limited to a few bacterial species, but very soon realized that a broad range of processes, in a variety of species, is controlled via quorum sensing (De Spiegeleer et al., 2015; Pratt, 2004; Seeley and Kirk Visscher, 2004; Zhang et al., 2012). Quorum sensing is widely observed while the individuals of a single species or more than one species cooperate and compete each other. However, the interesting fact is that the presence of more than one QS system in the individuals of a same species (intra-species QS systems) allows the emergence of several types of interactions among these QS systems (Fig. 1). Therefore, the communication occurs not only between the species but also between the individuals of the same species.

The communication among the individuals of different species is observed in *V. harveyi*, *E. coli*, *S. typhimurium*, *V. cholerae*, and *E. faecalis* (Day and Maurelli, 2001; Federle and Bassler, 2003; Kolenbrander, 2000; Kolenbrander et al., 2002; Kuramitsu et al., 2007; Manefield et al., 1999; Miller et al., 2004; Prajapat et al., 2016; Xu et al., 2006). The parallel arrangement of QS systems has been reported in *V. harveyi*, *V. cholerae* and *V. vulnificus* (Fig. 1A) where it helps controlling the production of biofilm and virulence factors (Kim et al., 2003; Lilley and Bassler, 2000; Lupp and Ruby, 2005; Waters et al., 2008; Waters and Bassler, 2006). The series arrangement of QS systems is found in *P. aeruginosa* (Fig. 1B) that causes a hierarchical activation of each system and controls multiple lung adhesion factors and virulence factors (An et al., 2006; Harrison and Buckling, 2009; Kaufmann et al., 2005; Xavier et al., 2011). *B. subtilis* and *P. aeruginosa* also possess more than one QS system that antagonize each other (Fig. 1C) and only one of these systems is favored, allowing the bacterium to choose one of two alternate lifestyles (Lazazzera, 2000; Schultz et al., 2009). We assume that the existence of multiple arrangements of QS systems might play an important role in processing environment precisely and thus, dictating desired and robust collective response.

In this work, our aim was to investigate the dynamical features resulted by an interaction between two intra-species QS systems antagonizing each other (Fig. 1C). Moreover, we also focused on what factor influences the dynamics of signal processing and helps estimating environmental diversity in order to fine-tune the collective response. Towards this end, we developed a mathematical model using ordinary differential equations and studied how the parameters such as localized heterogeneous distribution of cells, antagonizing strength, diffusion of autoinducer molecules can affect the precise estimation of environment (Hense and Schuster, 2015). We highlighted a key role of the interplay between autoinducer's diffusivity and antagonizing strength in dictating the fate of interaction between two antagonizing QS systems. The intracellular regulators were found to be a key player in fine tuning the uniform response among the individual cells. We also showed that the cells were able to estimate the localized heterogeneity in their distribution and thereby, expressing two antagonizing systems differently. One of the key findings was that between the two QS systems, one that was expressed fully enabled a global quorum sensing among the cells irrespective of the local cell densities, whereas, the other system that was expressed partially exhibited a local quorum sensing among the cells within a single cell density region.