

Quorum Sensing- Let Bacteria Talk

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Abstract

Quorum Sensing (QS), a wonderful natural method to regulate gene expressions in response to the fluctuation in the cell density of a given bacterial population and provides the key mechanism through which bacteria communicate. QS bacteria release chemical signal molecules called autoinducers that increase in concentration as a function of cell density. Lots of bacterial physiological activities including symbiosis, virulence, competence, conjugation, antibiotic production, motility, sporulation, and biofilm formation are being maintained by QS circuit. This method of QS bestows upon bacteria some of the essential qualities as that of higher organisms. The evolution of quorum sensing systems in bacteria could, probably, have been one of the early steps in the development of multicellularity. Apart from bacteria, social insects also communicate through QS.

Key words : Quorum sensing, bacterial communication, inducers, computing & robotics

Introduction

Communication- the strongest and most important gesture ever evolved by nature for every living creation. Mankind wouldn't have progressed in absence of communication. With advancement of civilization, the various means of communications have also improved tremendously and will be so in future. And the most wonderful part is, it's not only us but even the smallest living creatures- Bacteria do communicate with each other! No, they don't use any language for that. Instead the bacterial communication is carried out by different signaling molecules which are released time to time in the environment. Upon releasing the signaling molecules, bacteria are capable of measuring the exact number of molecules i.e. the concentration of the molecules in a given population.

What is quorum sensing?

'Quorum Sensing' (QS) can be described as a process through which the accumulation of

signaling molecules enable a single cell to sense the number of bacteria (cell density). In nature, many different bacteria which live together and use various classes of signaling molecules. As they employ different languages they can not talk to other bacteria present in the environment. Today, several quorum sensing systems are intensively studied in various organisms such as marine bacteria and several pathogenic bacteria.

QS helps bacteria to co-ordinate their behaviors. As environmental conditions often change rapidly, bacteria need to respond very fast in order to survive. These responses can be of different types including adaptation, nutrients availability, and defense against other microorganisms which offer competitive resistance and to get rid of the potentially dangerous toxic compounds. It is very important for pathogenic bacteria during infection of a host (e.g. humans, other animals or plants) to co-ordinate their virulence so that they can escape the host's immune responses for successful establishment of the infection. Many species of bacteria use quorum sensing

to coordinate their gene expression based on the density of their respective population. Similarly, some insects also use quorum sensing to make collective decisions about where to nest. Apart from its specialized functions in biology, quorum sensing has many other useful applications for computing and robotics. Quorum sensing occurs within a single bacterial species as well as between diverse species, and regulate a lot of different processes, essentially serving as a simple communication network. A variety of different molecules could be used as signals for the entire process of QS.

Revealing the inner mechanisms works behind QS

Bacteria using quorum sensing constantly produce and secrete certain signaling molecules known as autoinducers or pheromones. They possess specific receptors which can detect these signaling molecules. Upon binding of inducer to this receptor, it activates transcription of certain genes, including those for inducer synthesis. In order to activate gene transcriptions, a single bacterial cell must encounter signaling molecules secreted by other cells in the same environment. When only a few other similar type of bacteria are present, diffusion reduces the concentration of the inducer in the surrounding medium to almost zero, little amount of inducer molecules are synthesized. However, as the population grows the concentration of the inducer passes a threshold, causing more inducer to be produced. As a result a positive feedback loop gets formed, and the receptor becomes fully activated. Activation of the receptor

induces the up regulation of other specific genes, causing all of the cells to begin transcription at approximately the same time. This coordinated behavior of bacterial cells can be useful for a variety of different conditions. For instance, the bioluminescent luciferase produced by *V. fischeri* would not be visible if it were produced by a single cell. By using QS, to limit the synthesis of luciferase under circumstances when cell populations are large, *V. fischeri* cells make it possible to avoid wasting energy on the production of useless products.

Master molecules responsible for QS

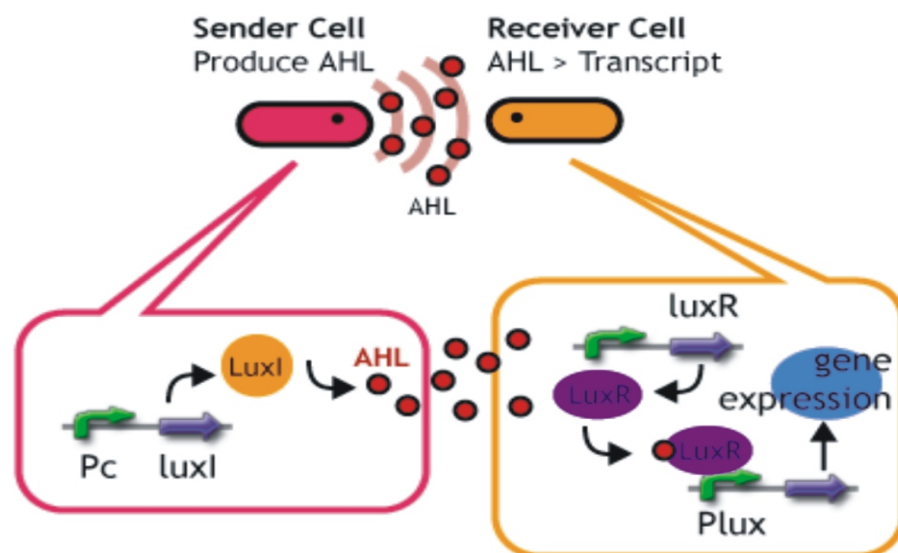


Fig 1: Mechanisms involved in bacterial QS
(Source -<http://parts.mit.edu/igem07/index.php/Chiba/Communication>)

Significant works on the three-dimensional structures of proteins involved in QS were first came into light in 2001 by determining the crystal structures of three LuxS orthologs with the help of X-ray crystallography. This was closely followed by determination of the crystal structure of the receptor LuxP of *Vibrio harveyi* with its inducer AI-2 (which is one of the few biomolecules containing boron) bound to it. AI-2 signalling is conserved among many bacterial species, including *E. coli*, the model organism. The other important molecule involved in this process is N-Acyl-Homoserine-lactones (AHLs) as they provide a wide response to environmental changes especially in Gram negative bacteria. AHLs could be highly

variable based on the acyl chain length and in terms of the different chemical structures of the radicals.

QS demonstrated by certain members of bacteria

Vibrio fischeri

Quorum sensing was first observed in *Vibrio fischeri*, a bioluminescent bacterium that lives as a mutualistic symbiont in the photophore (or light-producing organ) of the Hawaiian bobtail squid. In case of free-living *V. fischeri*, the autoinducer is at low concentration and thus cells do not luminesce. However, when they are highly concentrated in the

photophore (about 10¹¹ cells/ml) transcription of luciferase is induced, leading to prominent bioluminescence.

Pseudomonas aeruginosa

This famous opportunistic bacteria uses quorum sensing to coordinate the formation of biofilms, in terms of swarming motility, exopolysaccharide production, and cell aggregation. They can grow within a host without harming it, until they reach a certain concentration. Then these bacteria become aggressive with their numbers sufficient to overcome the defensive barriers provided by the host's immune system and form a biofilm which eventually leads to the onset of the disease. In this species, AI-2 was found to

increase expression of *sdiA*, a transcriptional regulator of promoters which promote *ftsQ* which is the part of the *ftsQAZ* operon found to be essential for cell division. Another form of gene regulation shown by this the bacteria to rapidly adapt to surrounding changes is through environmental signaling. It has been discovered recently the significant impact of anaerobiosis can on the major regulatory circuit of QS. This important link between QS and anaerobiosis ultimately leads to the production of virulence factors of this organism. It can be hoped that the therapeutic enzymatic degradation of the signaling molecules will prevent the formation of such biofilms and possibly weaken established biofilms. Disrupting the signalling process in this way is called quorum quenching.

Escherichia coli

In *Escherichia coli*, cell division is partially regulated by AI-2-mediated quorum sensing. This organism uses AI-2, which is produced and processed by a specific regulator-the *lsr* operon. Part of it encodes for an ABC transporter which imports AI-2 into the cells during the early stationary phase of growth. AI-2 is then phosphorylated by the LsrK kinase, and the newly produced phospho-AI-2 can either be internalized or used to suppress LsrR, a repressor of the *lsr* operon in order to activate the operon. Transcription of the *lsr* operon is known to be inhibited by dihydroxyacetone phosphate (DHAP) through its competitive binding to LsrR. Glyceraldehyde 3-phosphate has also been shown to inhibit the *lsr* operon through cAMP-CAPK-mediated inhibition.

Social participants of QS

Social insects which prefer to live in well constructed colonies are an excellent example of a decentralized system, because no individual is the solo in charge of making decisions for the colony. Quite a few groups of social insects have been shown to use quorum sensing once making collective decisions. Two such important examples have been explained below.

Honey bees

Honey bees (*Apis mellifera*), one of the wonderful creatures of nature, use quorum

sensing to a great extent in order to make decisions about new nest sites. Among them large colonies reproduce through budding, from which the queen leaves the hive with a portion of the workers to form a new nest elsewhere. After leaving the old nest, the workers form a swarm which hangs from a branch or any similar kind of overhanging structures. This swarm persists throughout the decision-making phase until a new nest site is chosen by them. QS plays the most important

Ants

Another classic example of social insect showing considerable amount of QS is colonies of the ant *Temnothorax albipennis* which usually nest in small crevices between rocks. When the rocks shift and the nest gets broken, these ants need to choose a new nest to move into. During the first stage of the decision-making process, a small portion of the worker ants leave the already destroyed

different suitable sites. But, because of the differences in the waiting period, the number of ants in the best nest tends to increase at the greatest rate. Eventually, the ants in this nest could sense that the rate at which they encounter other ants has exceeded a particular threshold, a strong indication that the quorum number has been reached. Once the ants sense a quorum, they return to the previous old nest and begin rapidly carrying the brood, queen, and fellow workers to the new nest. Scouts that are still tandem-running to other potential sites are also recruited to the new nest and the entire colony moves. Thus although no single worker may have visited and compared all of the available options, quorum sensing enables the colony as a whole to quickly make good decisions about where to move.

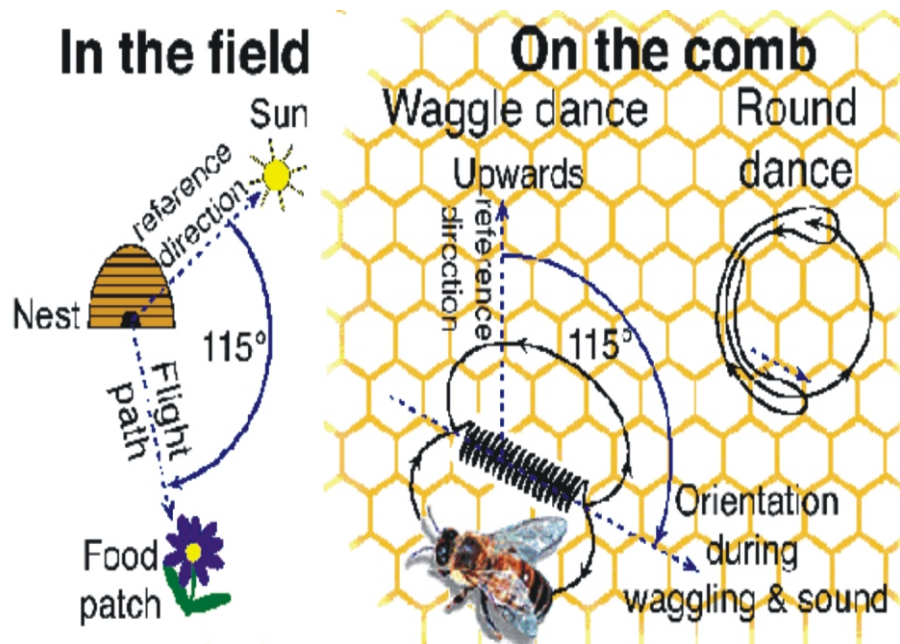


Fig 2 : QS demonstrated by honey bees (source-bees.ucr.edu/dancelanguage.html)

role in the whole process. First a small portion of the workers leave the swarm to search out suitable new nest sites, then each worker tries to assess the quality of the cavity she finds. Soon after that, the worker returns to the swarm and recruits other sincere workers to her newly found cavity using the honey bee waggle dance. Workers that found relatively poor nest sites stop dancing sooner, and can therefore be recruited to the better sites. Once the visitors to a new site sense that a quorum number (usually 10 to 20 bees) has been reached, they return to the swarm and start using another new recruitment method called piping. This vibrational signal causes the swarm to take off and fly to the new nest location. This was proved by several experimental tests that this decision-making process enabled honey bee swarms to choose the best nest site in four out of five trials.

nest and start searching for new crevices. When one of them finds a potential nest, she assesses the quality of the crevice based on various factors which include the size of the interior, the number of openings, and the presence or absence of dead ants. The worker then comes back to the deserted old nest, where she waits for a short period before recruiting other workers to follow her to the newly found nest using a process called tandem running. The waiting period is inversely related to the quality of the site- for instance a worker that has found a poor site will wait longer than a worker which has encountered a good site. Once the new recruits start visiting the potential nest site and make their own assessment of its quality, the number of ants visiting the crevice increases. During this time ants may visit many other

Other important applications of QS

Computing and robotics

QS can be applied in many other fields to achieve improved functions. One of them being computing and robotics. QS can be a potential useful tool for improving the function of self-organizing networks such as the SECOAS (Self-Organizing Collegiate Sensor) environmental monitoring system. In this system, the mode of function is that the individual nodes sense that there is a population of other nodes with similar data to report. The entire population then nominates just one node to report the data, resulting in enormous power savings. Ad-hoc wireless networks can also get benefit from QS, once it allows the system to detect and respond to network conditions. QS is also used to coordinate the behavior of autonomous robot swarms. Using a process similar to that used by *Temnothorax* ants, robots can make rapid group decisions without the direction of a specific controller.

Quorum-sensing control in *Staphylococci* could be a novel target for antimicrobial drug therapy

Constant urgent need for novel antibacterial drugs possesses a potential worry to the scientists as many important human pathogens have acquired multiple antibiotic

resistance factors. Among those, *Staphylococcus aureus* and *S. epidermidis* play a major role as the leading sources of nosocomial infections. Recently, it has been advised to develop new therapeutics that attack bacterial virulence rather than killing bacteria. Such drugs are called "antipathogenic" and are believed to lower the development of antibiotic resistance. Specifically, cell-density-dependent gene regulation (quorum-sensing) in bacteria has been proposed as a potential target. While promising studies exist about quorum-sensing blockers in gram-negative bacteria, the use of the staphylococcal quorum-sensing system as a drug target is now seen in an increasingly critical way. Inhibition of quorum-sensing in *Staphylococcus* has been shown to enhance biofilm formation.. The chemical nature and biological function of another proposed staphylococcal quorum-sensing inhibitor, named "RIP", are insufficiently characterized till date. Targeting quorum-sensing systems might in principle constitute a reasonable way to find novel antibacterial drugs, but being a newer approach, this requires careful investigation for every pathogen and the specific type of infection caused by it.

Conclusion

QS enables bacteria and many social insects to indulge in specific communications between themselves. This process in turn helps the total community to grow stronger. As the regulation takes place at the gene and molecular levels, this enhances the possibilities of manipulations of the original QS principle which can further be utilized for human benefits like to come up with novel antimicrobial drugs and other potential therapeutics.

Reference

- Lewis Sauer K, Camper A, Ehrlich G, Costerton J, Davies D. (2002). "Pseudomonas aeruginosa displays multiple phenotypes during development as a biofilm". *Journal of Bacteriology* 184 (4): 11401154..
- Cornelis P (editor). (2008). *Pseudomonas: Genomics and Molecular Biology*, 1st ed., Caister Academic Press. ISBN 978-1-904455-19-6.
- Lewis HA, Furlong EB, Laubert B, Eroshkina GA, Batiyenko Y, Adams JM, Bergseid MG, Marsh CD, Peat TS, Sanderson WE, Sauder JM, Buchanan SG (2001). "A structural genomics approach to the study of quorum sensing: Crystal structures of three LuxS orthologs". *Structure* 9 (6): 52737.
- Chen X, Schauder S, Potier N, Van Dorsselaer A, Pelczer I, Bassler B, Hughson F (2002). "PDF Structural identification of a bacterial quorum-sensing signal containing boron". *Nature* 415 (6871): 5459.
- Sun J, Daniel R, Wagner-Döbler I, Zeng AP (2004). "Is autoinducer-2 a universal signal for interspecies communication: a comparative genomic and phylogenetic analysis of the synthesis and signal transduction pathways". *BMC Evol. Biol.* 4: 36.
- Hense BA, Kuttler C, Müller J, Rothballer M, Hartmann A and Kreft JU (2007). "Does efficiency sensing unify diffusion and quorum sensing?". *Nature Reviews Microbiology* 5: 230239.
- Franks, N. R., A. Dornhaus, et al. (2006). "Not everything that counts can be counted: ants use multiple metrics for a single nest trait". *Proceedings of the Royal Society B-Biological Sciences* 273 (1583): 165169..
- Franks, N. R., J. Hooper, et al. (2005). "Tomb evaders: house-hunting hygiene in ants.". *Biology Letters* 1 (2): 190192.
- Mallon, E. B., S. C. Pratt, et al. (2001). "Individual and collective decision-making during nest site selection by the ant *Leptothorax albipennis*". *Behavioral Ecology and Sociobiology* 50 (4): 352359..
- Pratt, S. C. (2005). "Quorum sensing by encounter rates in the ant *Temnothorax albipennis*". *Behavioral Ecology* 16 (2): 488496.
- Seeley, T. D. and P. K. Visscher (2004). "Group decision making in nest-site selection by honey bees". *Apidologie* 35 (2): 101116..
- Seeley, T. D. and P. K. Visscher (2006). "Group decision making in honey bee swarms". *American Scientist* 94 (3): 220229..
- Britton, M, Sacks, L. (2004). "The SECOAS Project Development of a Self-Organising, Wireless Sensor Network for Environmental Monitoring". SANPA.
- Peysakhov, M., Regli, W. (2005). "Ant inspired server population management in a service based computing environment". *Swarm Intelligence Symposium, Proceedings 2005 IEEE*: 357364..
- Sahin E., Franks N. (2002). "Measurement of Space: From Ants to Robots". *Proceedings of WGW 2002: EPSRC/BBSRC International Workshop*.
- Miller.MB,Bassler BL, Quorm sensing in bacteria, *Annu Rev Microbiol*, 2001;55:165-99.
- Michael Otto, Quorum-sensing control in *Staphylococci* a target for antimicrobial drug therapy? *FEMS Microbiology Letters; volume 241 issue 2*, 135-141.

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