# Integrated Analysis of Bacterial Quorum Sensing Systems

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My work includes two parts: quorum-sensing simulation and bacterial growth simulation.

## 1. Quorum-sensing simulation

### 1.1 *Introduction*

The biggest contribution of quorum sensing (QS) may be that it changed our traditional thought: bacteria are just individual cells. QS, also equivalent to autoinduction or extracellular communication in some cases, makes bacteria be able to sense other bacteria in their local environment via secreting some kinds of small molecules and hence to work coordinately. It will also sure make change in our traditional research methods: to consider bacteria more physiologically and ecologically.

However, with continuous new discoveries in this field, many exceptions to previously "established" viewpoints of quorum sensing have been found. Even the name of "quorum sensing" is in danger: low-density "quorum-sensing" systems have been found. It seems only two weak properties are conserved in different species: the signal molecules are produced by bacteria and are sensed by themselves. Some eukaryote, like some higher plants, can also make use of such bacterial language. Is it possible to find some common properties, such as common gene expression regulation pattern, in this system via mathematical simulation? I tried to simulate some bacterial QS systems and did such search.

### 1.2 Vibrio fischeri *model*

*Vibrio fischeri* has a so-called best-studied QS system. For the simplicity of setting up models and well understanding of quorum sensing, I choose *V. fischeri* as the first bacterium of my QS project. However, even in such a “best-studied” system there are so many unexpected discoveries that we would begin to consider the importance and complexity of quorum sensing.

LuxR-LuxI pathway is the canonical *V. fischeri* QS pathway and also the most-studied QS system. In this pathway, a *lux* (luminescence) regulon plays the central role which includes closely located left-oriented *luxR* operon and right-oriented *luxICDABEG* operon. This pathway is subject to various positive and negative autoregulation and is also regulated by many factors outside this regulon. Besides the canonical OHHL synthesized by LuxI, another two signal molecules were also discovered: HHL also synthesized by LuxI and OHL synthesized by AinS lack of homology with LuxI family. These two signal molecules both affect LuxR-LuxI pathway. Other than canonical *lux* regulon, it was found recently that at least five other regulons are under the regulation of quorum sensing in *V. fischeri.*

For this system, I have set up a mathematical model which describing the central LuxR-LuxI pathway which has enough data to be simulated. The model was run on PC and the program was written by C language. The simulated dynamics is able to repeat some experimental observations, such as the coordination of bacterial growth and bioluminescence (Fig.1). Some more data are also possible to be integrated into the model which will be part of the future work. This will make the model more accurate and realistic, and more importantly, new properties may appear. The work will be transplanted to E-CELL later. E-CELL is a general computational simulator developed in our laboratory. The aim of E-CELL project is to develop an all-compatible, high-speed, biology-data-oriented computational simulator.

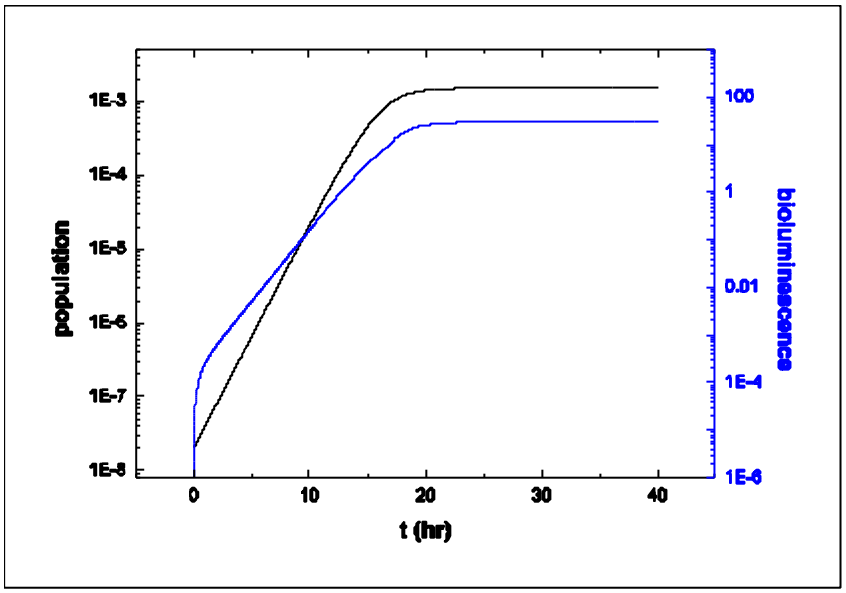


Fig.1. *Vibrio fischeri* grows coordinately with bioluminescence.

1.3 Escherichia coli *model*

To date, although many experiments have shown that probably there are many QS systems in *E. coli*, no complete QS pathway has been published yet. Quorum sensing in pathogenic *E. coli* will not be included due to our nonpathogenic purpose though it has been relatively well studied. Alternatively, we can do some cellular-level work or set up a framework model first. There are two doable such themes in *E. coli* at present: growth and motility. As part of bacterial growth control, *E. coli* growth will be discussed in some later section.

Motility in *E. coli* has been extensively studied both experimentally and theoretically. However, nobody has considered it can be related with quorum sensing. Recently, firm evidences have been provided that a novel two-component regulatory system is involved in the regulation of flagella and motility by quorum sensing. Via microarray data, it was found that, in pathogenic EHEC strain, several genes such as those encoding the expression and assembly of flagella,

motility and chemotaxis were controlled by quorum sensing. A two-component system was discovered with *qseB* encoding the response regulator and *qseC* the sensor kinase. Then it was confirmed by transcriptional fusions and mutation characterization that this system is regulated by quorum sensing. Later, it was found that *qseBC* system also exists in nonpathogenic *E. coli* K-12 and is also regulated by quorum sensing. Part of the downstream of the pathway has been explored. These discoveries will greatly facilitate our understanding of motility in *E. coli.* Since motility is such a big system which includes so many elements and sub-networks, it is hard to understand the complex regulation network merely via experimental means. Alternatively, we can resort to mathematical tools to integratedly study such a canonical system. It is hopefully this project will be collaborated with our *E. coli* two-component simulation project, *E. coli* chemotaxis simulation project and even related wet-lab projects.

1.4 *Quorum sensing in other bacteria*

Besides *V. fischeri,* some other bacteria were also comprehensively studied, such as *Agrobacterium tumefaciens*, *Erwinia carotovora*, *Pseudomonas aeruginosa*, *V. harveyi* in gram-negative bacteria and *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus pneumoniae* in gram-positive bacteria. Due to the reasons stated above, to understand QS well, it is helpfully to compare different QS mechanisms between different bacteria. And because of the complexity of biochemical network, complexity-oriented mathematical simulation is a useful means. It is hopefully to set up a QS simulation library integrating diverse QS systems and all available experimental data for this purpose. Now the work is underway.

**2. Bacterial growth simulation**

Every microbiologist knows the bacterial growth course: it includes at least four phases – lag phase, log phase, stationary phase and death phase. Many evidences showed that entering into stationary phase is not due to starvation of nutrition. So how stationary phase is achieved? The answer may be quorum sensing. It is possible that bacteria use QS to sense their local population density and control their division to promote their economical utilization of nutrition. This hypothesis has recently supported by some experiments in *E. coli*. However, as stated above, the detailed pathway information is incomplete and hence may be not proper for molecular-level simulation at present. Alternatively, we can set up models on cellular level first and gradually add molecular information. Meanwhile, it is extremely hopeful that the project can be combined with solid wet-lab experiments. A simple cellular-level model with very little molecular information has been set up. However, no ideal results have been obtained yet. The model is subject to further revision, such as parameter fine tuning or molecular information addition.