Bacterial Quorum Sensing as a Networked Decision System

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Quorum sensing

Mechanism used by bacteria to coordinate collective behavior

- Antibiotic production
- Collective behaviors
- Conjugation
- Bioluminescence
- Biofilm formation
- Virulence factors

Quorum sensing

Enables bacteria to act as multicellular organisms!

- Antibiotic production
- Collective behaviors
- Bioluminescence
- Conjugation
- Biofilm formation
- Virulence factors

How does it work?

**Signaling**

**Reception**

**Activation**

**Low cell density**

**High cell density**

We do not emphasize the role of the shared communication network in this paper because our problem formulation addresses quorum sensing among a single bacterial colony. In practice, hundreds of colonies coexist in the same environment and it is known that molecular signals emitted by different colonies may interfere with each other either by causing signal destruction or cross-talk [18]. However, in order to study more than one colony, our modeling framework must reflect the interactions between colonies.

We will consider the activation of a single colony. The concentration of auto-inducers in the surrounding environment is proportional to the density of cells. The concentration is unknown to each cell and is indirectly measured by the cell, which probes the concentration of bacteria in the environment. A cell probes the surrounding environment by indirectly measuring the concentration of auto-inducers, which are then activated by the cell. Once enough auto-inducers are received, the cell expresses the gene to the corresponding exofactor.

In the context of a single colony, we assume that the population density is deterministic and that the concentration is entirely determined by the density of the colony, also known as the state-of-the-world. The concentration is defined as the number of cells in the colony, also known as the cell density/signal concentration. The global concentration of auto-inducers is proportional to the number of cells in the colony. Auto-inducers are discrete molecules. Each cell in the colony secretes auto-inducers in the environment at a basal rate and the number of auto-inducers received by a cell is distributed according to a Poisson probability mass function that the number of auto-inducers received and bound to receptors is distributed according to a Poisson probability mass function.

Remark 1: From the perspective of an individual cell, the most fundamental problem is to control the concentration, or cell density, of the colony in order to achieve a common or individual objective [16]. We argue that this framework is appropriate for modeling quorum sensing systems similar to the one considered here.

In the environment, auto-inducers are produced by bacteria as a Gamma random variable comes from the fact that the Gamma distribution subsumes many other classes of distributions on the non-negative real line as particular cases, e.g. exponential and chi-squared. Furthermore, it allows for tractable Bayesian estimation of bacterial population density under uncertainty on the density population.
Goal

Cells are decision makers

Propose a new optimization-based model for QS

Calibrate our model from experimental data
Bayesian decision system

\[ X \sim f_X \]

\[ \max_{\mathcal{P}} \mathbb{E}[U(A, X)] \]
Network decision system

Communication network
Local observations, Global actions

\[ \begin{align*}
X & \xrightarrow{C_1} Y_1 \xrightarrow{P_1} A_1 \\
X & \xrightarrow{C_2} Y_2 \xrightarrow{P_2} A_2 \\
& \vdots \\
X & \xrightarrow{C_n} Y_n \xrightarrow{P_n} A_n \\
\end{align*} \]

**Observations**  
**Actions**

\[
\text{maximize } \mathbb{E}[\mathcal{U}(A_1, \cdots, A_n, X)]
\]
The model
Density of the colony

\(X \sim \text{Gamma}(\kappa, \theta)\)


However, in order to study more colonies may interfere with each other either by causing signal and it is known that molecular signals emitted by different addresses quorum sensing among a single bacterial colony. In this paper because our problem formulation ad-

We do not emphasize the role of the shared communication measurements and under uncertainty on the density population.

the goal is to coordinate a global behavior based on local decisions with the goal of achieving a common or than the one considered here.

a recent paper by Noel et al. [15], but for a different model deterministic dynamic model in [14]. This uncertainty in the model of Heilmann et al. [14]. However, our work focuses on retic point of view [12], [13]. Among the many mathematical Mitra have studied quorum sensing from an estimation theo-

Among different colonies [11]. More recently, Michelusi and... auto-inducers at a rate) Poisson(λ)

depends on the type of bacteria
Observations

Assumptions

Given $X$: \( Y_i \perp Y_j, \; i \neq j \)

Given $X = x$: \( Y_i \sim \text{Poisson}(\lambda x) \)

Quorum size

**quorum**

*noun [C] • US /ˈkwɔːrəm, ˈkwɔːrm-/*

- the number of members who must be present at a meeting in order for decisions to be officially made

- Cambridge Dictionary

\[
A_i = \begin{cases} 0 & \text{if } i\text{-th cell is inactive} \\ 1 & \text{if } i\text{-th cell is active} \end{cases}
\]

Colony of \(N\) cells

**Quorum of size \(\tau N\)**

\[
\sum_{k=1}^{N} A_k \geq \tau N
\]
Public goods interpretation

Exofactor production is a **costly investment**

The **public benefit** is enjoyed by the **entire colony**

The benefit only kicks in **if a quorum is reached** (risk)
Pay-off

\[ U_i(A_i, A_{-i}, X) = \tau X \cdot 1 \left( \sum_{k=1}^{X} A_k \geq \tau X \right) - c \cdot A_i \]

**public benefit** is proportional to the **size of the colony**

utility = **growth rate of the colony**
Optimization problem

Threshold policy

\[ A_i = 1(Y_i \geq \alpha) \]

Find \( \alpha \) that maximizes the function \( \mathcal{J}_i \)

\[ \mathcal{J}_i(\alpha) \triangleq \mathbb{E}[\mathcal{U}_i(A_i, A_{-i}, X)] \]
Threshold optimization
In the economics literature, a similar phenomenon is known as the quorum ratio. Probability of not activating while establishing a quorum is visualized by fluorescence. The local activation cost which are displayed in Table I.

**A. Pay-off function and optimal thresholds**

The payoff function, it is unlikely that the optimization can be carried out directly. Consider Problem 1. The pay-off function in Eq. (11) can be explicitly computed according to the regularized incomplete Gamma function as follows. Using these two probabilities we can express the objective function, it is unlikely that the optimization can be carried out directly. Consider Problem 1. The pay-off function in Eq. (11) can be explicitly computed according to the regularized incomplete Gamma function as follows.

**Remark 3:**

Due to the intricate nature of the objective function, it is unlikely that the optimization can be carried out directly. Consider Problem 1. The pay-off function in Eq. (11) can be explicitly computed according to the regularized incomplete Gamma function as follows.

<table>
<thead>
<tr>
<th>(a)</th>
<th>(b)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

**TABLE II**

<table>
<thead>
<tr>
<th>(\tau)</th>
<th>(P_{\text{off}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>50</td>
</tr>
<tr>
<td>0.5</td>
<td>75</td>
</tr>
<tr>
<td>0.75</td>
<td>100</td>
</tr>
<tr>
<td>0.9</td>
<td>125</td>
</tr>
</tbody>
</table>

**Due to the intricate nature of the objective function, it is unlikely that the optimization can be carried out directly. Consider Problem 1. The pay-off function in Eq. (11) can be explicitly computed according to the regularized incomplete Gamma function as follows. Using these two probabilities we can express the objective function, it is unlikely that the optimization can be carried out directly.**
In the economics literature, a similar phenomenon is known and studied. The local activation cost leads to a differentiable objective function. Proposition 1: The pay-off function is unimodal and has a unique maximizer, which implies that the average concentration of cells per unit volume; the random variable $X$ is defined as $\bar{X} = \frac{X}{N}$, for different values of the quorum $c$. A cheater or free-rider is defined as a cell that doesn't activate locally but enjoys the public benefit resulting from the global activation. One of the features of our mathematical model is that it successfully captures the phenomenon of ratio $\beta$. Probability of not activating while establishing a quorum is visualized by fluorescence. The local activation cost is computed in terms of quantities previously defined in Eqs. (13) and (15). This probability can be computed in terms of quantities $\beta$ and $\alpha$. The probability of not activating while establishing a quorum is displayed in Table I. Due to the intricate nature of the objective function, it is unlikely that the optimization can be carried out exactly in closed form. However, the function $J(\alpha)$ can be explicitly computed according to Eq. (11) can be explicitly computed according to Eqs. (13) and (15).

![Quorum sensing](image-url)
Quorum sensing

\[ J \text{ is unimodal in } \alpha \]

\[ \begin{align*}
J(\alpha) & \quad \tau = 0.9 \\
& \tau = 0.75 \\
& \tau = 0.5 \\
& \tau = 0.25
\end{align*} \]

\[ \begin{align*}
J(\alpha) & \quad c = 25 \\
& \quad c = 50 \\
& \quad c = 75 \\
& \quad c = 100
\end{align*} \]
Free-riding bacteria
Free riding (cheating)

Agent that **benefits** from **public goods** but is **inactive**

\[
P_{\text{free}}(\tau) = P\left( A_i = 0 \right| \sum_{k \neq i} A_k \geq \tau X \right)
\]
In this section we discuss preliminary experimental results for several values of the local activation threshold $\tau$ in Fig. 5 for a prior distribution with parameters $\alpha = 50$, $\beta = 50$. We observe that the probability of not activating given that a quorum of ratio $\alpha$ was formed is shown in Fig. 5. Typically, the data collected in quorum sensing problems can be used to analyze the transition from unactivated to activated states of the colony. Table III shows the average concentration of cells over time. Using our Poisson measurement equations, and assuming that the cells use a threshold $\alpha$ to signal the formation of a quorum and that given $\alpha$, the optimal value of the activation threshold $\tau$ is formed, can be computed as follows.

Proof:

The probability of free-riding as a function of $\tau$ can be computed as follows:

$$P_{\text{free}}(\tau) = \frac{1}{1 + \frac{\alpha}{\beta} \tau}$$

where $\alpha$ and $\beta$ are the parameters of the prior distribution.

The optimal value of the activation threshold $\tau^*$ is formed when

$$P_{\text{free}}(\tau^*) = \frac{1}{1 + \frac{\alpha}{\beta} \tau^*} = \frac{1}{2}$$

for a quorum of ratio $\alpha$. This is done by knowing that for this strain of bacteria the probability of not activating is lower and $\tau^*$ is also larger, yielding a higher probability of cheating. In a dynamic problem setting where the concentration of cells and $\alpha$ change with time, this probability allows us to predict the fraction of the population that will activate within the time-interval. Another benefit of being able to compute the probability of cheating is that it is useful for estimating the value of $\tau^*$ from experimental data, as we will do in the next section.
Experimental results
Bacteria strain

**E. Coli ptd103 LuxI/R**

Threshold

Auto-inducer emission rate

\[ \alpha = 70 \text{nM} \]

\[ \lambda = 2.3 \times 10^{-9} \text{ nmol} \]
Experimental data

![Graph showing quorum sensing](image)

**Table III**

<table>
<thead>
<tr>
<th>$t$ (h)</th>
<th>$\tilde{X}$ ($10^9$ cells/L)</th>
<th>$\sigma_X$ ($10^9$ cells/L)</th>
<th>$\lambda\tilde{X}$ (nM)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0465</td>
<td>0.0140</td>
<td>0.1070</td>
<td>0</td>
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<td>1</td>
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<td>0.1503</td>
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</tr>
<tr>
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<td>0.4267</td>
<td>0.0833</td>
<td>0.9813</td>
<td>0</td>
</tr>
<tr>
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<td>0.6400</td>
<td>0.1637</td>
<td>1.4720</td>
<td>0.0135</td>
</tr>
<tr>
<td>4</td>
<td>4.0667</td>
<td>0.5033</td>
<td>9.3533</td>
<td>0.1038</td>
</tr>
<tr>
<td>5</td>
<td><strong>31.6667</strong></td>
<td><strong>13.4079</strong></td>
<td><strong>72.8333</strong></td>
<td><strong>0.8538</strong></td>
</tr>
<tr>
<td>6</td>
<td>147.3333</td>
<td>93.0017</td>
<td>338.8667</td>
<td>0.9953</td>
</tr>
<tr>
<td>7</td>
<td>262.6667</td>
<td>68.8573</td>
<td>604.1333</td>
<td>1</td>
</tr>
</tbody>
</table>

**Fig. 8.** Our experimental data was collected from microscopic images such as the ones above, where the total number of cells and the total number of...
Calibrating the model

Estimate the quorum coefficient

\[ \bar{X} = 31.6667 \]
\[ \sigma = 13.4079 \]
\[ \kappa = 5.5780 \]
\[ \theta = 5.6770 \]

\[ X \sim \text{Gamma}(\kappa, \theta) \]
Calibrating the model

Estimate the quorum coefficient

Frequency of free-riders

\[ p \approx 0.14 \]
Calibrating the model

Estimate the quorum coefficient

Frequency of free-riders

\[ p \approx 0.14 \]

\[ \hat{\tau} = 0.3 \]
Calibrating the model

Adjust the activation cost

\[ J(\alpha) \]

\[ \alpha^* = 70 \]

\[ \hat{c} \approx 20.25 \]
New decision theoretic model of Quorum Sensing

Cells are decision makers

Nature is the “system designer”

Formulate new hypothesis on the trade-offs between:

1. growth rate vs. activation cost
2. growth rate vs free-riding (cheating)
Future work

Our model does not account for dynamics

Sequential model
1. Signal accumulation/degradation
2. Population dynamics

Open questions
How do cells aggregate information?
How do bacteria avoid the “Tragedy of the Commons”?